DOI: 10.1002/hem3.70012

HemaSphere eha

ABSTRACT BOOK

Topic: 13th International Symposium on Hodgkin Lymphoma; October 2024

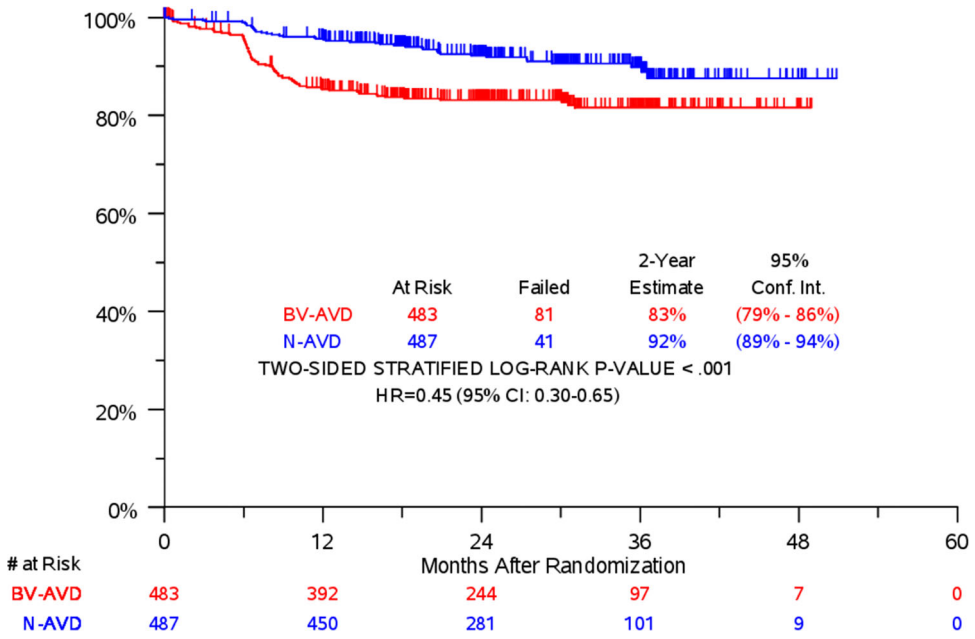
ADVANCED STAGES

T001: 2-YEAR FOLLOW-UP OF THE S1826 STUDY CONFIRMS IMPROVED PROGRESSION-FREE SURVIVAL WITH NIVOLUMAB-AVD COMPARED TO BRENTUXIMAB VEDOTIN-AVD IN ADVANCED STAGE CLASSIC HODGKIN LYMPHOMA

Alex F. Herrera[1], Michael Leblanc[2], Sharon M. Castellino[3], Hongli Li[2], Sarah Rutherford[4], Andrew Evens[5], Kelly Davison[6], Angela Punnett[7], Susan K. Parsons[8], Sairah Ahmed[9], Carla Casulo[10], Nancy L. Bartlett[11], Joseph Tuscano[12], Matthew Mei[1], Brian Hess[13], Ryan Jacobs[14], Hayder Saeed[15], Pallawi Torka[16], Boyu Hu[17], Craig H. Moskowitz[18], Supreet Kaur[19], Gaurav Goyal[20], Christopher Forlenza[16], Andrew Doan[21], Adam Lamble[22], Pankaj Kumar[23], Saeeda Chowdury[24], Brett Brinker[25], Namita Sharma[26], Avina Singh[27], Kristie Blum[28], Anamarija Perry[29], Alexandra Kovach[21], David Hodgson[30], Louis Constine[10], Lale Kostakoglu[31], Anca Prica[30], Hildy Dillon[32], Richard F. Little[33], Margaret A. Shipp[34], Michael Crump[30], Brad S. Kahl[11], John Leonard[4], Sonali Smith[35], Kara M. Kelly[36], Jonathan W. Friedberg[10]

[1]City of Hope, [2]SWOG Statistics and Data Management Center, [3]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, [4]Weill Cornell Medicine, [5]Rutgers Cancer Institute of New Jersey, [6]McGill University Health Center, [7]SickKids Hospital, [8]Tufts Medical Center, [9]MD Anderson Cancer Center, [10]University of Rochester, [11]Washington University in St. Louis, [12]UC Davis, [13]Medical University of South Carolina, [14]Levine Cancer Institute, [15]Moffitt Cancer Center, [16]Memorial Sloan Kettering Cancer Center, [17]Huntsman Cancer Institute, University of Utah, [18]University of Miami, [19]University of Texas at San Antonio, [20]University of Alabama at Birmingham, [21]Children's Hospital of Los Angeles, [22]Seattle Children's Hospital, [23]Illinois Cancer Care, [24]Prisma Health Cancer Institute, [25]Cancer & Hematology Center, [26]Geisinger Community Medical Center, [27]Fairview Ridges Hospital, [28]Emory University, Winship Cancer Institute, [29]University of Michigan, [30]Princess Margaret Cancer Centre, [31]University of Virginia, [32]SWOG Cancer Research Network, [33]National Cancer Institute, [34]Dana-Farber Cancer Institute, [35]University of Chicago, [36]Roswell Park Comprehensive Cancer Center

Figure 1: Progression-Free Survival in in Modified Intent-to-treat Analysis Set.



Background: Incorporation of brentuximab vedotin (BV) into frontline therapy of advanced stage (AS) classic Hodgkin lymphoma (cHL) has improved outcomes in pediatric and adult patients (pts). We hypothesized that introducing PD-1 blockade with nivolumab in combination with doxorubicin, vinblastine, and dacarbazine (N-AVD) would improve progression-free survival (PFS) over BV-AVD in AS cHL and evaluated this approach in the randomized, phase 3 S1826 study. Early results demonstrated a PFS advantage with N-AVD; here, we present updated data with a median follow-up of 2 years (y).

Methods: Eligible pts were ≥12 y with stage 3–4 cHL. Pts were randomized 1:1 to 6 cycles of N-AVD or BV-AVD, stratified by age, international prognostic score (IPS), and intent to use radiation (RT). G-CSF was required with BV-AVD; it was optional with N-AVD. RT to residually metabolically active lesions on end of treatment PET was allowed in pre-specified patients. Response and disease progression were assessed by investigators using 2014 Lugano Classification. The primary endpoint was PFS; secondary endpoints included safety, event-free survival (EFS), patient-reported outcomes, and overall survival.

Results: 994 pts were enrolled from 7/9/19 to 10/5/22 and randomized to N-AVD ($n = 496$) or BV-AVD ($n = 498$). 970 were eligible and comprised the modified intent-to-treat cohort. Median age was 27 y (range, 12–83 y), 56% of pts were male, 76% were white, 12% were black, and 13% were Hispanic. 24% of pts were <18 y, 10% were >60 y, and 32% had IPS 4–7. Only 7 (0.7%) pts across arms received RT. With 2.1 y median follow-up, the PFS advantage with N-AVD was sustained (HR 0.45, 95% CI 0.3–0.65, two-sided $p < 0.001$), with 2 y PFS of 92% after N-AVD compared to 83% after BV-AVD. The PFS benefit was consistent across all age, stage, IPS subgroups. EFS was also improved after N-AVD. There were 14 deaths observed after BV-AVD compared to 7 after N-AVD. Nearly all adverse events except neutropenia and arthralgia were more frequent after BV-AVD, including peripheral sensory neuropathy (any grade, 29% N vs. 56% BV). Rates of febrile neutropenia and infection were similar between arms, as were rates of pneumonitis, colitis, gastritis, and rash.

Conclusions: N-AVD was better tolerated and improved PFS versus BV-AVD in adolescent and adult pts with AS cHL. Longer follow-up confirmed the PFS benefit with N-AVD at 2 y, including pre-specified subgroups. N-AVD is a new standard of care for treatment of AS cHL.

T002: DEVELOPMENT AND APPLICATION OF A VALIDATED MRD ASSAY IN HODGKIN LYMPHOMA

Julia Mattlener[1], Jessica Schneider[1], Julia Katharina Schleifenbaum[1], Max Freihammer[1], Olivia Käsgen[1,2], Kerstin Becker[3], Hodgkin Lymphoma Mrd Consortium, Justin Ferdinandus[1,2], Helen Kaul[2], Gundolf Schneider[2], Peter Borchmann[1,2], Jan-Michel Heger[1], Sven Borchmann[1,2,4]

[1]Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, University of Cologne, Medical Faculty and University Hospital Cologne, Cologne, Germany, [2]German Hodgkin Study Group (GHSG), Cologne, Germany, [3]West German Genome Center, Cologne, Germany, [4]Liquomics GmbH, Cologne, Germany

Table 1: Sensitivity, specificity, and accuracy for different MRD levels, $n = 30–51$ repeats per MRD level.

MRD level	Sensitivity	Specificity	Accuracy
1.41×10^{-4}	100%	100%	100%
7.05×10^{-5}	100%	100%	100%
3.52×10^{-5}	100%	100%	100%
1.76×10^{-5}	73.33%	100%	86.67%

Introduction: Circulating tumor (ct)DNA sequencing in Hodgkin Lymphoma (HL) enables genotyping and minimal residual disease (MRD) assessment. However, current ctDNA MRD assays are neither validated nor optimized for HL. We designed and validated LymphoVista HL, a specialized ctDNA-based assay for HL genotyping and MRD assessment.

Methods: LymphoVista HL targets 83 kbp optimized for detecting variants of relevance and highly sensitive MRD detection in HL. First, we performed a technical validation with contrived samples to evaluate sensitivity, specificity, linearity, accuracy, limit of detection (LoD), and precision. Second, the validated assay was employed in a blinded clinical validation study using an event-enriched cohort ($n = 72$) from the GHSG HD21 trial.

Results: We validated LymphoVista HL for variant calling and MRD detection. We achieved 91.27% sensitivity for de-novo variant identification for variants with >0.5% allele frequency (AF) and >99.99% specificity. Linearity analysis showed an R-value of 0.98 confirming a linear relationship between detected AF and ground truth AF.

For MRD detection, we determined a LoD of 6.54×10^{-6}. Further validation results for MRD detection are shown in Table 1.

The precision study revealed a repeatability of 30.33% CV even at low MRD levels and good reproducibility with a low contribution of varying reagent lots, technician, and day of assay performance to variation in results.

Our clinical validation study showed the assay's strong applicability to clinical samples. In HD21 patients treated with highly effective regimens such as eBEACOPP or BrECADD, MRD assessed after 2 chemotherapy cycles was prognostic. The assay effectively distinguished between MRD-negative patients, who had excellent outcomes, and MRD-positive patients, who had a higher relapse rate. Detailed analysis, including MRD-positivity rates, outcomes for MRD-positive and -negative patients, and correlation of MRD with positron emission tomography (PET) findings, is ongoing. Detailed results will be presented at the meeting.

Conclusion: We present LymphoVista HL, a highly accurate genotyping and MRD assay for HL based on ctDNA sequencing. Our validation study confirms the assay's high accuracy, specificity, sensitivity, precision, and prognostic ability even in HL patients treated with highly effective regimen opening the way for MRD-guided clinical trials in HL.

T003: EORTC-1537-COBRA: PHASE II STUDY OF VERY EARLY FDG-PET-RESPONSE ADAPTED TARGETED THERAPY FOR ADVANCED HODGKIN LYMPHOMA. PRIMARY ANALYSIS INCLUDING VALUE OF QUANTITATIVE PET ASSESSMENT AND TARC DYNAMICS

Martin Hutchings[1,2], Sophie Teesink[3], Anna Sureda-Balari[4], Susana Carvalho[5], Andrej Vranovsky[6], Walter Noordzij[7], Annika Loft[8], Anne I. J. Aarens[9], Wendy Stevens[10], Arjan Diepstra[11], Berthe M. P. Aleman[12], Sherida Woei-A-Jin[13], Maria Viguria[14], Kirsten Saevels[15], Liane Te Boome[16], Sanne Tonino[17], Paul Meijnders[18], Eva Domingo-Domènech[19], Caroline Hasselbalch Riley[20], Sarah Nuyens[21], Cedric Mallien[21], Ward Sents[21], Emanuel Buhrer[21], Catherine Fortpied[21], Wouter J. Plattel[3]

[1]Department of Haematology, Rigshospitalet, Copenhagen, Denmark, [2]Department of Clinical Medicine, University of Copenhagen, Denmark, [3]Department of Haematology, University Medical Center Groningen, Groningen, The Netherlands, [4]Clinical Hematology Department, Institut Català d'Oncologia-L'Hospitalet, IDIBELL, Universitat de Barcelona, Spain, [5]Internal Medicine Department, Hospital da Luz Lisboa, Lisbon, Portugal, [6]Department of Haematology, National Cancer Institute, Bratislava, Slovakia, [7]Department of Nuclear Medicine & Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, [8]Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, Copenhagen, Denmark, [9]Department of Nuclear Medicine, Radboud University Medical Center, Nijmegen, The Netherlands, [10]Department of Haematology, Radboud University Medical Center, Nijmegen, The Netherlands, [11]University of Groningen, University Medical Center Groningen, the Netherlands, [12]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands, [13]Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium, [14]Hospital Universitario Donostia–Osakidetza, Spain, [15]Department of Haematology, Antwerp University Hospital, Antwerp, Belgium, [16]Haaglanden Medical Centre, The Hague, The Netherlands, [17]Department of Hematology, Amsterdam University Medical Centers, Amsterdam, The Netherlands, [18]Department of Radiation Oncology, Iridium Network, University of Antwerp, Antwerpen, Belgium, [19]Institut Catala d'Oncologia, Hospital Duran i Reynals, IDIBELL, Barcelona, Spain, [20]Department of Haematology, Rigshospitalet, Copenhagen, Denmark, [21]EORTC Headquarters, Brussels, Belgium

Background: Addition of brentuximab vedotin (BV) to conventional chemotherapy for classical Hodgkin lymphoma (cHL) improves outcomes. In cHL patients <60 years treated in the experimental arm of the ECHELON-1 study all patients received 6 x A-AVD (brentuximab vedotin, doxorubicin, vinblastine, dacarbazine) regardless of early PET results. Three-year PFS was 87.2% in PET2 negative patients and 69.2% in PET2 positive patients. The COBRA trial investigated early PET-response adapted treatment in BV-based first line therapy, by intensification to BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone) in patients PETpositive after 1 cycle of A-AVD.

Methods: The primary endpoint of this phase II study was modified progression-free survival rate at 2 years from start of treatment (2 y mPFS). All patients received 1 cycle of A-AVD followed by an early interim real-time centrally reviewed PET/CT scan (PET1). PET results were interpreted according to the Lugano criteria and Deauville scores 1–3 were defined as negative and scores 4 and 5 as positive. PET1-negative patients received an additional 5 cycles of A-AVD and PET1-positive patients switched to 6 cycles of BrECADD. Radiotherapy was applied only to PET-positive residual lesions. PET images were quantified using 3D Slicer with MUST-segmenter with SUV4 method as threshold to determine the metabolic tumour volume (TMTV). Serum TARC was analyzed before and during treatment using standardized ELISA with a pre-defined cut-off at 1000 pg/mL.

Results: Among 150 enrolled patients, PET1 was negative in 90 (60%) and positive in 60 (40%) after one cycle of A-AVD. Safety was in line with prior reports of A-AVD and BrECADD. The estimated rate of mPFS at 2 years was 89.5% (80% 2-sided exact CI: 85.7%–92.4%). Two-year mPFS was 88.3% in PET1 negative patients and 91.3% in PET1 positive patients. Quantified PET1 results showed a clear decrease in MTV in all PET1 negative patients but also in the majority of PET1 positive patients, in line with TARC1 results.

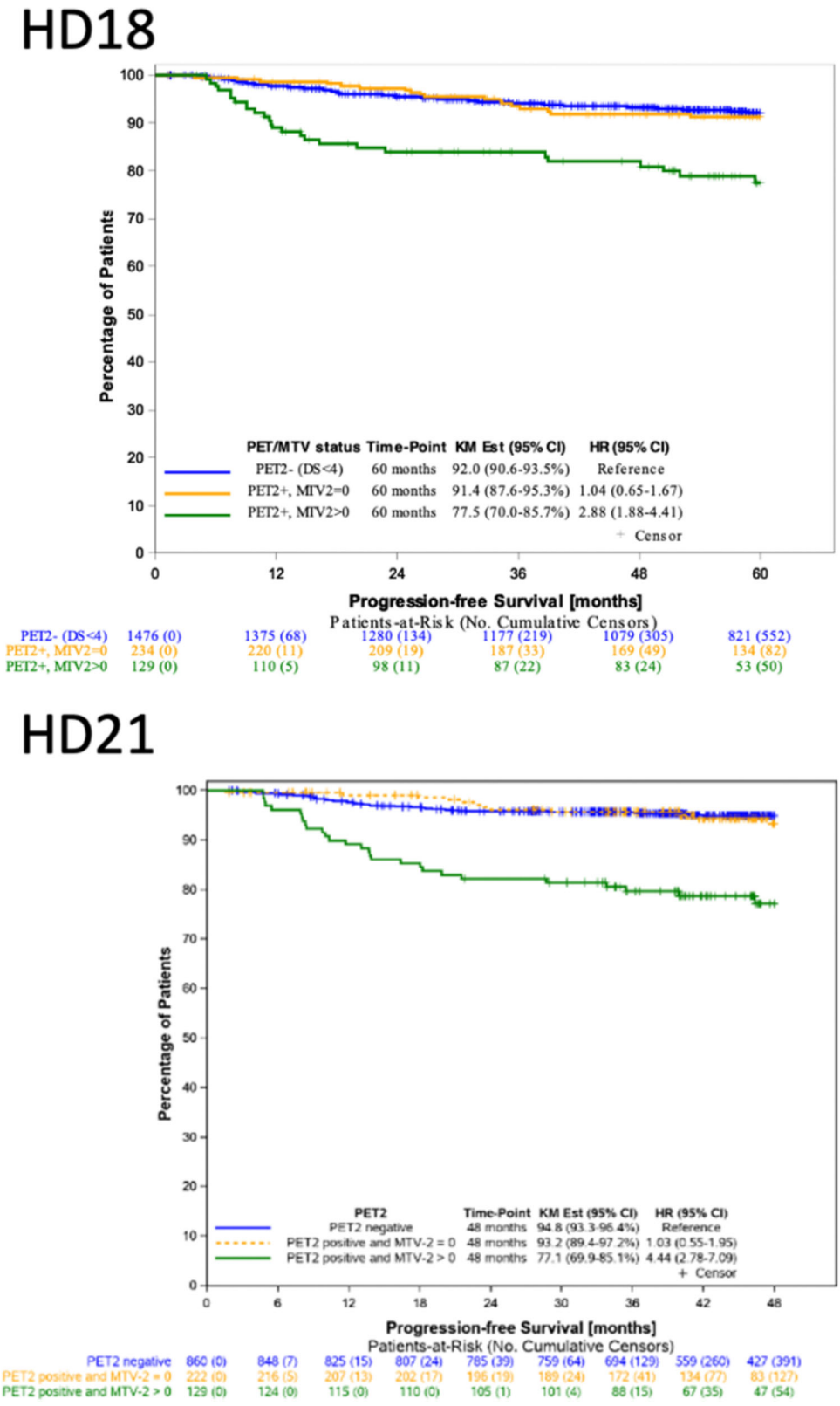
Conclusion: Treatment adaptation based on a very early FDG-PET/CT leads to very high efficacy in advanced stage HL patients receiving BV-containing first-line treatment while sparing most patients intensive chemotherapy. Semiquantitative assessment of interim PET and/or TARC analysis enhances the positive predictive value of the early response assessment and can potentially further help reduce the treatment burden.

T004: METABOLIC TUMOR VOLUME AFTER TWO CYCLES OF CHEMOTHERAPY IN PATIENTS TREATED FOR ADVANCED-STAGE HODGKIN LYMPHOMA: ANALYSIS OF THE GERMAN HODGKIN STUDY GROUP PHASE III HD18 AND HD21 TRIALS

Justin Ferdinandus[1], Helen Kaul[1], Gundolf Schneider[1], Michael Fuchs[1], Hans-Theodor Eich[2], Johannes Rosenbrock[3], Christian Baues[3], Katrin S. Roth[4], Alexander Drzezga[4], Lutz Van Heek[4], Markus Dietlein[4], Peter Borchmann[1], Carsten Kobe[4]

[1]German Hodgkin Study Group (GHSG), Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany, [2]Department of Radiotherapy, University Hospital of Münster, Münster, Germany, [3]Department of Radiotherapy, University Hospital of Cologne, Cologne, Germany, [4]Department of Nuclear Medicine, University Hospital of Cologne, Cologne, Germany

Figure 1: Association of DS and presence of measurable MTV after two cycles with PFS in HD18 and HD21.



Introduction: PET-guided treatment is standard of care to treat patients diagnosed with advanced-stage classical Hodgkin Lymphoma (AS-cHL) in several countries. Here, we investigate the role of metabolic tumor volume (MTV) for the response assessment of patients treated for AS-cHL.

Methods: The investigator-initiated phase III trials HD18 (NCT00515554) and HD21 (NCT02661503) randomized patients between 18 and 60 years with newly diagnosed AS-cHL to receive BEACOPP (HD21 standard arm, HD18) or BrECADD (HD21 experimental arm). All patients received two cycles of chemotherapy followed by response assessment after two cycles (PET-2). MTV after two cycles (MTV-2) encompassed all lymphoma tissue with standard uptake value > 4. To exclude confounding of PET-guided treatment, we first analyzed MTV-2 in patients treated in control arms of HD18 who received 6 cycles of BEACOPP irrespective of PET-2 (C6-Cohort). Cox-regression models and Kaplan Meier estimates were used to analyze impact of MTV-2 on progression-free survival (PFS). Findings were validated in the full ITT cohorts of HD18 and HD21.

Results: A total of 645 patients were included in the C6-Cohort, of these 471 (64.6%) were rated as DS1-3 in PET-2 and 569 (88.2%) had no residual MTV-2. Compared to patients with DS1-3 (5y-PFS 93.5%; CI95: 91.2–95.9), Patients with measurable MTV-2 had significantly inferior PFS (5y-PFS 77.5%; HR 3.62, CI95: 1.94–6.76), while patients without detectable MTV-2 and DS4 had similarly high PFS (5y-PFS 89.3%; HR 1.65; CI95: 0.8–3.38). In line with these results, in the analyzed ITT cohorts of HD18 (n = 1756) and HD21 (n = 1211), patients with DS4 but with completely resolved MTV-2 had similar outcomes as patients with DS1-3 (HD18: HR 1.12, CI95: 0.69–1.80; HD21: HR 1.03, CI95: 0.55–1.95), whereas patients with measurable MTV-2 featured higher risk of progression (HD18: HR 2.98, CI95: 1.92–4.64; HD21: HR 4.44, CI95: 2.78–7.09). Results were similar in both trial arms of HD21 (BEACOPP vs. BrECADD) and frequency of measurable MTV-2 was similar in HD18 post-amendment and HD21.

Conclusion: Complete resolution of MTV after two cycles of first-line chemotherapy for AS-cHL occurs in a vast majority of patients and associates with favorable prognosis, irrespective of DS. Approximately 10% had measurable MTV-2 (i.e., any lesion with SUV > 4) and face high risk of progression. Our results advocate implementation of quantitative biomarkers to refine response assessment in AS-cHL.

P005: ACCURACY OF ANN ARBOR STAGE ASSIGNMENT BASED ON PET/CT REPORTS USING A LARGE LANGUAGE MODEL IN HODGKIN LYMPHOMA PATIENTS

Conrad-Amadeus Voltin[1], Jonathan Kottlors[2], Peter Borchmann[3], Philipp Gödel[3], Alexander Drzezga[1], Markus Dietlein[1], Thomas Dratsch[2]

[1]Department of Nuclear Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany, [2]Institute for Diagnostic and Interventional Radiology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany, [3]Department of Internal Medicine I, Center for Integrated Oncology Aachen–Bonn–Cologne–Düsseldorf (CIO ABCD), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

Aim: Large language models (LLMs) have recently shown remarkable performance in solving tasks across various fields. Growing evidence suggests that they might be useful for patient self-education and the choice of diagnostic work-up. However, it remains unclear whether artificial intelligence can support complex decision processes that rely on different types of information from imaging modalities such as positron emission tomography (PET) or computed tomography (CT). Therefore, we investigated the accuracy of an advanced LLM in defining disease stages based on diagnostic reports generated for Hodgkin lymphoma patients.

Methods: Our analysis set included 70 consecutive written PET/CT reports of treatment-naïve Hodgkin lymphoma patients, which were slightly modified to remove the physicians' disease classifications. The most probable Ann Arbor stage for each patient was determined in five independent runs using GPT-4 (OpenAI, Inc., San Francisco, CA). To address potential interpretation errors arising from individual report diction, structured summaries of findings were examined as a second step. We then calculated and compared overall and per-stage accuracy for both text formats.

Results: The model's mean overall accuracy for disease extent classification was 60.0% (range, 57.1–64.3) when entering complete PET/CT reports, with a slight increase to 64.3% (range, 60.0–70.0, p = 0.08) upon presentation of structured summaries. While 37.2% of individuals were falsely assigned higher categories based on the standard texts, GPT-4 proposed lower stages in 2.9%. A notably superior mean accuracy of 93.3% (range, 86.7–100) and 98.7% (range, 93.3–100) was achieved for stage IV patients when using the complete diagnostic reports and their formatted versions, respectively.

Conclusions: Our study reveals that the accuracy of GPT-4 in Ann Arbor stage assignment based on written PET/CT reports is, so far, insufficient for clinical practice. However, its performance seems to improve slightly when using structured summaries as input. Moreover, furnishing LLMs with context-specific knowledge will presumably further increase their potential in the future.

P006: ADAPTATION OF A PET-BASED TREATMENT STRATEGY AND OUTCOMES OF PATIENTS WITH ADVANCED HODGKINS LYMPHOMA IN RESOURCE CONSTRAINED SETTINGS

Charanpreet Singh[1], K. S. Lekshmon[1], Arihant Jain[1], Alka Khadwal[1], Amanjit Bal[2], Radhika Srinivasan[3], Rajender K Basher[4], Pankaj Malhotra[1], Gaurav Prakash[1]

[1]Department of Clinical Hematology and Medical Oncology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [2]Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [3]Department of Cytology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [4]Department of Nuclear Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Table 1: Treatment response characteristics (N=167)

	De-escalation cohort (n=114)			Escalation cohort (n=51)		
	De-escalation done (n=68)	De-escalation not done (n=46)	p value	Escalation done (n=6)	Escalation not done (n=45)	p value
Therapy completed	67 (98.5%)	43 (93.4%)	0.150	6 (100%)	42 (93.3%)	0.514
End of treatment CR	59 (86.8%)	31 (73.4%)	0.056	6 (100%)	21 (52.5%)	0.027
Refractory Disease	7 (10.3%)	9 (19.6%)	0.162	0	16 (35.6%)	0.077
Relapse	3 (4.4%)	4 (8.7%)	0.349	1 (16.7%)	2 (4.4%)	0.232
4-year EFS	86.4% (78.5-95.1%)	64.3% (51.6-80.2%)	0.044	83.3% (58.3-100%)	52.3% (38.9-70.4%)	0.237
4-year OS	97.8 % (93.6-100)	89.1% (80.5-98.6%)	0.015	100% (100-100%)	88.6% (78.5-99.9%)	0.431
Death	1 (1.4%)	5 (10.9%)	0.027	0	5 (11.1%)	0.389
Therapy related toxicity leading to death	0	4/5 (80%)		0	1/5 (20%)	

Introduction: Outcomes for patients with Hodgkins Lymphoma (HL) have improved owing to the utilization of a PET based treatment strategy. However, implementation of this strategy has its challenges, especially in resource constrained settings.

Methods: This was a retrospective, single center analysis from a tertiary care hospital in India. All patients with newly-diagnosed Stage IIB-IV HL treated between January 2018 and March 2023 were included for analysis. Complete remission (CR) was defined as Deauville Score (DS) 1, 2, or 3 on PET Scan. Criteria for escalation and de-escalation was as per the RATHL study. Follow-up was censored at 31st March, 2024.

Results: Two forty-six patients with newly diagnosed advanced HL were treated at our center in the study period. Median age of the cohort was 32 years (IQR 21–45) and most patients had Stage IV disease (*n*-115, 46.7%). An interim PET (iPET) was available for only 167 patients (67.9%).

One hundred fourteen patients (68.3%) achieved a CR on iPET, while 47 (28.1%), 4 (2.4%), and 2 (1.2%) patients had a partial response, stable disease and progressive disease respectively. De-escalation and escalation of therapy was done for 59.6% (68/114) and 11.8% (6/51) of eligible patients respectively. Treatment response details, including end of therapy response, relapse and death are shown in Table 1.

In the de-escalation cohort, patients who did not have therapy de-escalated were more likely to die (10.9% vs. 1.4%; *p*-0.038). The most common cause of death in these patients was therapy related complications. The estimated 4-year Event Free Survival (EFS) and Overall Survival (OS) were statistically significantly better in patients who had therapy de-escalated (*p*-0.044 and *p*-0.015 respectively) (Table 1).

In the escalation cohort, all patients receiving escalated therapy achieved a CR. Further, no statistically significant difference in estimated 4-year EFS and OS was found between patients who did and did not receive escalated therapy (*p*-0.237 and *p*-0.431 respectively); however, this analysis is limited by the small number of patients receiving escalated therapy.

Conclusion: Adaptation of a PET based strategy is low in resource constrained settings, with approximately 2/3rd of the patients getting an iPET done and further, 60% and 12% patients receiving de-escalation and escalation respectively. In our cohort, patients who did not have therapy de-escalated had increased risk of death due to therapy related complications.

P007: ARE FOUR CYCLES OF BEACOPP ESCALATED SUFFICIENT FOR PATIENTS WITH ADVANCED HODGKIN LYMPHOMA AND PET-2 DEAUVILLE SCORE 3?

Heidi Mocikova[1], Jana Markova[1], Lubica Gaherova[1], Maria Maco[1], Eva Maule[2], Jozef Michalka[2], Andrea Janikova[2], Alice Sykorova[3], Pavla Stepankova[3], Katarina Hradska[4], Juraj Duras[4], Alexandra Kredatusova[5], Vit Prochazka[5], Zdenek Kral[2], Tomas Kozak[1]

[1]*Fakultni nemocnice Kralovske Vinohrady, Department of Haematology and Third Faculty of Medicine, Charles University, Prague, Czech Republic,* [2]*Department of Internal Medicine, Hematology and Oncology, University Hospital Brno and Faculty of Medicine, Masaryk University Brno, Brno, Czech Republic,* [3]*University Hospital and Faculty of Medicine, 4th Department of Internal Medicine– Hematology, Hradec Kralove, Czech Republic,* [4]*University Hospital and Faculty of Medicine, Department of Hemato-Oncology, Ostrava, Czech Republic,* [5]*Faculty of Medicine and Dentistry, Palacky University, Department of Haemato-Oncology, Olomouc, Czech Republic*

Background: The negative predictive value of PET-2 enabled a reduction from 6 to 4 cycles of eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses) without loss of efficacy in the GHSG HD18 trial for advanced stages of Hodgkin lymphoma (HL). Progression-free survival (PFS) of patients (pts) with PET-2 Deauville score (DS) 1–3 was comparable; however, pts with DS3 were treated with 6 to 8 cycles of eBEACOPP.

Methods: We analyzed the prognosis of pts with classical HL in advanced stages, including clinical stages IIB with massive mediastinal tumor (MMT) and/or extranodal involvement (EN), prospectively observed in the Czech Hodgkin Lymphoma Registry and treated with 6 or 4 cycles of

eBEACOPP according to interim PET-2 as defined by the Lugano classification. Overall, 441 pts (aged 18–60 years) were treated with eBEACOPP between 2014 and 2024: 136 pts received 4 cycles and 305 pts received 6 cycles. Radiotherapy was indicated in 63 (14.3%) pts.

Results: PET-2 DS1-2 was achieved in 159 pts treated with 4 (84) or 6 cycles (75). PET-2 DS3 was reported in 107 pts treated with 4 (49) or 6 cycles (58), and PET-2 DS4-5 was achieved in 64 pts treated with 4 (1) or 6 (63) cycles, respectively. Interim PET-2 was not performed in 111 pts. Median follow-up was 59.7 months. There were no significant differences in the 5-year PFS in pts with PET-2 DS1-2 and DS3 treated with 4 cycles (91% [95% CI 84–99] vs. 78% [95% CI 64–95], $p = 0.061$) or with 6 cycles (93% [95% CI 88–99] vs. 89% [95% CI 81–99], $p = 0.347$). Differences between the 5-year PFS in pts with PET-2 DS1-2 vs. DS3 treated with 4 cycles or 6 cycles were not significant in subanalyses with MMT ($p = 0.858$) and with EN disease ($p = 0.432$). The 5-year PFS in pts with PET-2 DS4-5 treated with 6 cycles was 76% (95% CI 88–99). The 5-year OS in pts with PET-2 DS1-3 was 100% regardless of the number of treatment cycles, and in DS4-5 it was 96% (95% CI 92%–100%).

Conclusion: There is a trend for 5-year PFS to be higher for PET-2 DS1-2 than for DS3 in pts treated with 4 cycles, but it has not reached statistical significance. Further evaluation is warranted. Additional data such as circulating tumor DNA (ongoing trial NCT06263530) and TARC analyses could help to better stratify pts with PET-2 DS3 into 4 or 6 cycles of eBEACOPP.

Supported by AZV NU22-03–00182 from Ministry of Health, Czech Rep., MH CZ DRO (FNOI_00098892) and Cooperatio Program Oncology and Hematology.

P008: BRENTUXIMAB VEDOTIN (BV) EXPOSURE AND LONG-TERM EFFICACY ANALYSIS IN PATIENTS WITH CLASSICAL HODGKIN'S LYMPHOMA (CHL): ANALYSIS OF PHASE 3 ECHELON-1 STUDY

Zufei Zhang[1], Daping Zhang[1], Fei Jie[1], Keenan Fenton[1], Evelyn Rustia[1], Consuelo Glenn[1], Michelle Fanale[1], Tatyana Feldman[2], Stephen M. Ansell[3], Yen-Lin Chia[1]

[1]Pfizer, Bothell, WA, USA, [2]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, [3]Mayo Clinic, Rochester, MN

Table 1: Summary of BV Exposure, Dose Adjustments, Incidence of Grade ≥2 Peripheral Neuropathy, and Survival Outcomes by BV PK Exposure Quartiles.

	A+AVD BV C_{avg} quartiles				A+AVD (n=661)	ABVD (n=659)
	Q1	Q2	Q3	Q4		
BV actual cumulative dose, median (range), mg/kg[a,b]	12.9 (1.2-15.3)	14.2 (1-15.9)	14.3 (1.2-16.5)	13.9 (1.2-15.6)	14.1 (1-16.5)	NA
BV relative dose intensity, median (range), %[a]	97.8 (39.3-107.5)	99.7 (16.7-110.2)	99.7 (45.4-114.3)	99.0 (41.7-108.5)	99.5 (16.7-114.3)	NA
Treatment duration, median (range), weeks[a,c]	25.0 (2.0-35.0)	24.6 (2.0-34.1)	24.1 (2.0-32.3)	24.0 (2.0-31.9)	24.1 (2.0-35.0)	NA
BV dose modifications, % (events/n)[a]	81.2 (134/165)	57.1 (93/163)	55.7 (93/167)	48.2 (80/166)	60.5 (400/661)	NA
BV dose discontinuation, % (events/n)[a]	13.9 (23/165)	11.7 (19/163)	6.6 (11/167)	12 (20/166)	11.0 (73/661)	NA
Time to first BV dose modification, median (range), days[a]	36.0 (1.0-163.0)	42.0 (1.0-183.0)	50.0 (1.0-170.0)	67.5 (16.0-163.0)	48.5 (1.0-183.0)	NA
Grade ≥2 PN, % (events/n)[d]	24.7 (41/166)	22.6 (37/164)	30.3 (50/165)	42.8 (71/166)	30.1 (199/661)	10.5 (69/659)
Time to onset of first grade ≥2 PN event, median (range), days[d]	79.0 (13.0-196.0)	99.0 (12.0-196.0)	102.0 (8.0-184.0)	98.0 (2.0-182.0)	91.0 (2.0-196.0)	71.0 (1.0-2053.0)
6-year OS rate (95% CI), %	92.2 (86.7-95.5)	92.0 (86.2-95.4)	96.3 (91.1-98.5)	94.9 (90.1-97.4)	93.9 (91.6-95.5)	89.4 (86.6-91.7)
6-year PFS rate (95% CI), %	82.8 (75.9-87.9)	78.1 (70.1-83.9)	85.4 (78.9-90.1)	82.5 (75.7-87.6)	82.3 (79.0-85.0)	74.5 (70.8-77.8)

A+AVD, brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD, bleomycin, doxorubicin, vinblastine, and dacarbazine; BV, brentuximab vedotin, C_{avg}, average concentration; NA, not available; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; PN, peripheral neuropathy.

[a] This analysis included all patients randomized to the A+AVD treatment arm who received ≥1 BV dose and had evaluable PK data (n=661). BV exposure quartiles were based on on-treatment C_{avg} of the BV active analyte: Q1, ≤3.14 µg/mL (n=165); Q2, >3.14 to ≤3.65 µg/mL (n=163); Q3, >3.65 to ≤4.23 µg/mL (n=167); and Q4, >4.23 µg/mL (n=166).

[b] Intended BV cumulative dose was 14.4 mg/kg.

[c] Intended treatment duration was 24 weeks, consisting of six 28-day cycles.

[d] These analyses also included all patients randomized to the A+AVD treatment arm who received ≥1 BV dose and had evaluable PK. However, time-to-event BV exposure was calculated as BV C_{avg} prior to onset of the first grade ≥2 PN event for patients who had a grade ≥2 PN event (n=199) or as on-treatment BV C_{avg} for patients who did not have a grade ≥2 PN event (n=462): Q1, ≤3.21 µg/mL (n=166); Q2, >3.21 to ≤3.73 µg/mL (n=164); Q3, <3.73 to ≤4.33 µg/mL (n=165); and Q4, >4.33 µg/mL (n=166).

Background: In the phase 3 E1 (NCT01712490) study, BV vs bleomycin in combination with doxorubicin, vinblastine, and dacarbazine (A+AVD vs ABVD) showed superior overall survival (OS; HR, 0.59; 95% CI, 0.40–0.88; $p = 0.009$) in previously untreated stage III or IV cHL. BV dose adjustments, including dose modifications (e.g., reduction) and discontinuations, were recommended for managing adverse events (AEs), including peripheral neuropathy (PN). We evaluated the impact of dose adjustments on efficacy by exploring the exposure-response (ER) relationships between BV and OS and progression-free survival (PFS).

Methods: In E1, pts were randomized 1:1 to receive A+AVD or ABVD for six 28-day cycles. Included pts had received ≥1 BV dose and had evaluable BV pharmacokinetic (PK) data ($n = 661$). Average BV concentrations (Cavg) were estimated via a validated population PK model and used for ER analyses. Incidences of dose adjustments and grade ≥2 (G≥2) PN and duration of OS and PFS were compared across exposure quartiles and with the comparator ABVD arm ($n = 659$). Univariate Cox regression analysis was used to assess ER relationships.

Results: Of 661 pts, 60.5% had BV dose modifications and 11.0% discontinued BV (Table). Median treatment duration was similar in pts with vs without BV dose modifications (25 vs. 24 wk), suggesting manageable AEs. Lower BV exposure quartiles had higher dose modification rates, but discontinuation rates were relatively similar across the quartiles. Higher G≥2 PN incidences were observed in higher BV exposure quartiles; Cavg was predictive of G≥2 PN ($p = 8 \times 10^{-6}$). A+AVD provided OS benefit in pts with ($n = 199$) and without ($n = 462$) G≥2 PN events, with estimated 6-year OS (95% CI) of 95% (91–98) and 93% (90–95), respectively, compared with 89% (87–92) with ABVD. OS and PFS benefits over ABVD were observed in all BV exposure quartiles, inclusive of dose adjustments. Average on-treatment BV exposure was not a statistically significant predictor for OS ($p = 0.091$), while higher early exposure (Cavg up to the end of cycle 2) was predictive of higher OS ($p = 0.003$).

Conclusion: At 6 years of follow-up, A+AVD provided benefit over ABVD for all BV exposure ranges, inclusive of dose adjustments for AE management. This showed that recommended dose adjustments effectively managed AEs, including G≥2 PN, while keeping most pts on treatment and subsequently maintaining survival benefits in E1. High initial BV exposure was associated with high probability of response.

P009: BRENTUXIMAB VEDOTIN PLUS CHEMOTHERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED STAGE III/IV CLASSICAL HODGKIN LYMPHOMA: SEVEN-YEAR OVERALL SURVIVAL ANALYSIS FROM ECHELON-1

Martin Hutchings[1], Stephen M. Ansell[2], David J. Straus[3], Joseph M. Connors[4], Wojciech Jurczak[5], Won-Seog Kim[6], Andrea Gallamini[7], Radhakrishnan Ramchandren[8], Jonathan W. Friedberg[9], Ranjana H. Advani[10], Andrew M. Evens[11], Kerry J. Savage[4], Hyeon-Seok Eom[12], Tatyana Feldman[13], Jeremy S. Abramson[14], Cassie Dong[15], Bipin Savani[15], Athanasios Zomas[16], Keenan Fenton[17], John Radford[18]

[1]Department of Hematology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [2]Division of Hematology, Mayo Clinic, Rochester, MN, USA, [3]Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [4]BC Cancer, Centre for Lymphoid Cancer, Vancouver, Canada, [5]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland, [6]Division of Hematology–Oncology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [7]Research and Innovation Department, Antoine-Lacassagne Cancer Center, Nice, France, [8]University of Tennessee Graduate School of Medicine, Knoxville, TN, USA, [9]Wilmot Cancer Institute, University of Rochester, Rochester, NY, USA, [10]Department of Medicine, Division of Oncology, Stanford University, Stanford, CA, USA, [11]Division of Blood Disorders, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA, [12]Department of Hematology–Oncology, Center for Hematologic Malignancy, National Cancer Center, Goyang, Republic of Korea, [13]John Theurer Cancer Center, Hackensack Meridian Health, Hackensack, NJ, US, [14]Massachusetts General Hospital, Boston, MA, USA, [15]Takeda Development Center Americas, Inc. (TDCA), Lexington, MA, USA, [16]Takeda Pharmaceuticals International AG, Zurich, Switzerland, [17]Pfizer Inc., Bothell, WA, USA, [18]University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

Table. 7-year OS rates by subgroup (ITT)

Group, % (95% CI)	A+AVD OS rate, % (95% CI) n=664	ABVD OS rate, % (95% CI) n=670	HR (95% CI) P-value
All patients	93.5 (91.1–95.2) n=664	88.8 (85.8–91.1) n=670	0.62 (0.42–0.90) 0.011
PET2 negative	95.0 (92.8–96.6) n=588	90.2 (87.2–92.5) n=577	0.57 (0.37–0.87) 0.009
PET2 positive	90.7 (72.3–97.1) n=47	74.0 (59.9–83.8) n=58	0.34 (0.11–1.03) 0.046
Stage III	92.1 (87.6–95.1) n=237	90.3 (85.3–93.7) n=246	1.01 (0.54–1.87) 0.980
Stage IV	94.2 (91.3–96.2) n=425	88.1 (84.3–91.0) n=421	0.49 (0.30–0.79) 0.003
Aged <40 years	98.2 (96.2–99.1) n=396	95.0 (91.9–96.9) n=375	0.39 (0.16–0.95) 0.032
Aged <60 years	96.4 (94.4–97.7) n=580	92.9 (90.3–94.9) n=568	0.49 (0.29–0.83) 0.007
Aged ≥60 years	72.6 (60.6–81.5) n=84	66.7 (55.9–75.5) n=102	1.01 (0.59–1.71) 0.982

Background: After 6-years' follow-up in the ECHELON-1 study (NCT01712490), patients with Stage III/IV classical Hodgkin lymphoma (cHL) treated with A+AVD (brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine) showed significant improvements in overall survival (OS) and progression-free survival (PFS) versus patients treated with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), with a comparable safety profile. We present OS and PFS data after a median follow-up of 7 years.

Methods: OS and PFS per investigator assessment were evaluated in the intent-to-treat (ITT) population (data cut-off March 11, 2023). Patients were randomized 1:1 to receive ≤6 cycles of A+AVD ($n = 664$) or ABVD ($n = 670$) on days 1 and 15, every 28 days. Positron emission tomography scan after cycle 2 (PET2) evaluation was mandatory. Long-term safety outcomes included resolution or improvement of peripheral neuropathy (PN), incidences and outcomes of pregnancies among female patients and their partners, and rates of second malignancies.

Results: At a median follow-up of 89.3 months, 7-year OS rates significantly favored A+AVD versus ABVD (93.5% [95% CI 91.1–95.2] vs. 88.8% [95% CI 85.8–91.1]; HR 0.62 [95% CI 0.42–0.90], $p = 0.011$). Consistent benefit with A+AVD over ABVD in most subgroups analyzed, including age <40 years and Stage IV disease, was observed (Table). Seven-year PFS rates with A+AVD versus ABVD were 82.3% (95% CI: 79.1–85.0) vs 74.5% (95% CI: 70.8–77.7), respectively (HR, 0.68; 95% CI: 0.53–0.86; $p = 0.001$). At the last follow-up, PN improved or resolved in most patients (A+AVD: 86.0%; ABVD: 87.1%). Median (range) time to complete resolution of PN was 16 (0–373) vs 10 (0–343) weeks with A+AVD versus ABVD; corresponding median (range) time to improvement was 42 (2–182) vs 19 (15–142) weeks. PN was ongoing in 27.5% (122/443; 11.7% grade ≥2) and 20.3% (58/286; 7.0% grade ≥2) of A+AVD- and ABVD-treated patients, respectively. Furthermore, 84/92 patients and their partners reported livebirths/pregnancies with A+AVD and 59/73 with ABVD; no stillbirths were recorded. Second malignancies were reported in 5.0% of A+AVD- and 5.9% of ABVD-treated patients.

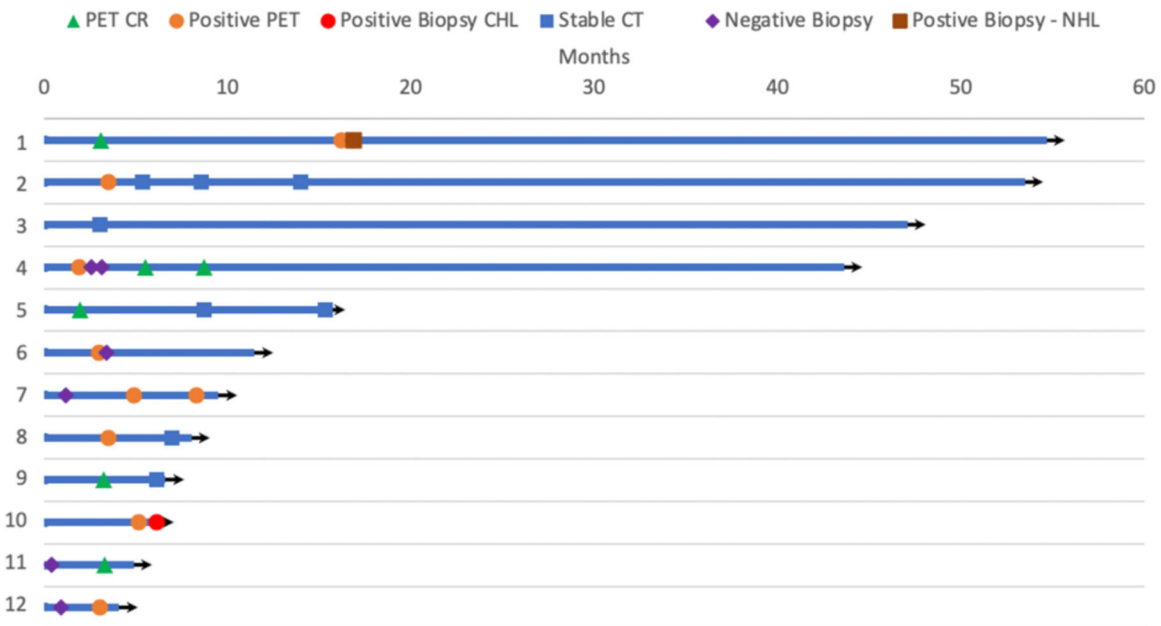
Conclusions: At a median follow-up of 7 years, patients with Stage III/IV cHL treated with A+AVD demonstrated sustained improvements in PFS and OS, compared with those treated with ABVD, with PFS rates suggesting curability. Additionally, the safety profile of A+AVD remained unchanged with no new safety signals.

P010: CLINICO-PATHOLOGICAL CORRELATION IN PATIENTS WITH POSITIVE END OF TREATMENT PET AFTER PEMBROLIZUMAB + AVD FOR UNTREATED CLASSIC HODGKIN LYMPHOMA

Ryan Lynch[1], Kikkeri Naresh[1], Ridvan Demirci[2], Delphine Chen[2], Chaitra Ujjani[1], Christina Poh[1], Edus H. Warren[1], Stephen Smith[1], Mazyar Shadman[1], Brian Till[1], Vikram M. Raghunathan[1], Yolanda Tseng[1], Ajay K. Gopal[1]

[1]*Fred Hutch Cancer Center*, [2]*University of Washington*

Figure 1: Swimmers plot of outcomes of all patients with residual FDG uptake on EOT PET (D4 or D5).



Background: Concurrent pembrolizumab with AVD chemotherapy is highly effective in the treatment of classic Hodgkin lymphoma (CHL) (Lynch et al. ASH 2023). However, this regimen and similar regimens have been associated with higher rates of residual PET positivity (PET2 CR = 61%, EOT CR = 77%) despite extremely low rates of biopsy-proven disease progression (Advani et al. ASH 2023). Additional characterization of the long-term outcomes of these patients may identify characteristics not associated with persistent lymphoma.

Methods: We examined the outcomes of patients treated with pembrolizumab+AVD (NCT03331341) who had partial metabolic response on end-of-treatment (EOT) F-18 fluorodeoxyglucose (FDG) PET. With this information, we performed a post-hoc descriptive analysis landmarked at the time of the EOT PET. In patients who had a biopsy as part of this workup, a secondary hematopathology and radiology overread was requested with additional clinical context.

Results: Among 50 patients treated in this study, 48 were evaluable with an EOT PET after completion of all therapy. Twelve (25%) had residual FDG uptake (D4 or D5) on the EOT PET. Seven (58%) patients with positive PET findings had at least one biopsy to evaluate for recurrence, of whom only one had a biopsy-proven CHL recurrence at any time.

We evaluated the eight negative biopsies. One biopsy showed normal lung tissue, but a subsequent cecal biopsy in the same patient at a new site showed diffuse large B-cell lymphoma. Two patients had biopsies that showed benign adipose tissue, one with a hyperplastic thymus, and one with inadequate sample.

Two patients had biopsies that demonstrated areas of necrosis surrounded by a histiocytic reaction. Interestingly, these pathology findings correlated with PET results that showed central necrosis with photopenia with a thin rim of peripherally intense FDG uptake at an original site of disease. In reviewing the other 5 patients who did not have any subsequent biopsy, we found one other patient also had this pattern. Other PET findings not associated with eventual recurrence included mild cervical lymph node FDG uptake (n = 5) and thymic FDG uptake (n = 3). Additional details are present in the figure below.

Conclusions: Partial metabolic response with persistent small-volume FDG positive disease on EOT PET after pembrolizumab+AVD is not associated with high rates of disease relapse. Patients can be safely followed with serial imaging and/or biopsy.

P011: DATA COLLABORATIONS ACCELERATE PEDIATRIC HODGKIN LYMPHOMA RESEARCH THROUGH NODAL

Flerlage Jamie[1], Suzi Birz[2], Sharon M. Castellino[3,4], Tara O. Henderson[2], John Lucas[5], Lindsay A. Renfro[6], Yiwang Zhou[5], Samuel Volchenboum[2], Brian Furner[2], Michael Watkins[2], Kara M. Kelly[7,8]

[1]University of Rochester, [2]University of Chicago, [3]Emory University School of Medicine, [4]Aflac Cancer and Blood Disorders Center of Children's Healthcare of Atlanta, [5]St. Jude Children's Research Hospital, [6]University of Southern California, [7]Roswell Park Comprehensive Cancer Center, [8]University at Buffalo Jacobs School of Medicine and Biomedical Sciences

Table 1: Patient case details in the NODAL database.

HISTOLOGY	
HL, NOS	79
Classical NOS	49
Lymphocyte Depletion, NOS	6
Lymphocyte-Rich	12
Mixed Cellularity, NOS	209
Nodular Lymphocyte Predominance	348
Nodular Sclerosis, NOS	1,734
ANN ARBOR STAGE	
Stage I	169
Stage II	1,274
Stage III	425
Stage IV	386

Background: Advances in pediatric oncology are in large part attributed to collaboration among international research cooperative groups. Seeking to advance collaboration and standardize aspects of diagnosis, staging, treatment, and response assessment, pediatric Hodgkin lymphoma (HL) researchers established the Hodgkin Lymphoma Data Collaboration (NODAL) consortium and partnered with the Pediatric Cancer Data Commons (PCDC) (10), led by Data for the Common Good (D4CG), to develop consensus data standards and realize a data commons for pediatric HL.

Methods: With a goal to accelerate research for pediatric HL, NODAL was founded in 2018 through the execution of a Memorandum of Understanding between the Children's Oncology Group (COG) and the Pediatric Hodgkin Consortium (PHC). Since that time, many milestones have been achieved including (a) an executive committee and a comprehensive governance structure were established, (b) NODAL members worked to formulate a harmonized data dictionary from previous clinical trials, (c) data contributor agreements were signed by each group, d) data were harmonized according to the data dictionary, and (e) the COG and PHC transferred data for collaborative research questions.

Results: As of May 2024, the HL data dictionary incudes 203 standardized elements that were used to harmonize clinical trials data on 2437 participants from six clinical trials conducted by Children's Oncology Group trials (AHOD0031, AHOD03P1) and Pediatric Hodgkin Consortium trials (HLHR13, HOD05, HOD08, HOD99). By Ann Arbor staging, the participants break down: Stage I–169, Stage II–1,274, Stage III-425, Stage IV-386 (see Table 1). Elements in the data dictionary include demographics, initial disease characteristics, therapy, response assessment, toxicity and survival status. Aggregate data can be freely explored using the publicly accessible PCDC data portal (https://portal.pedscommons.org/login).

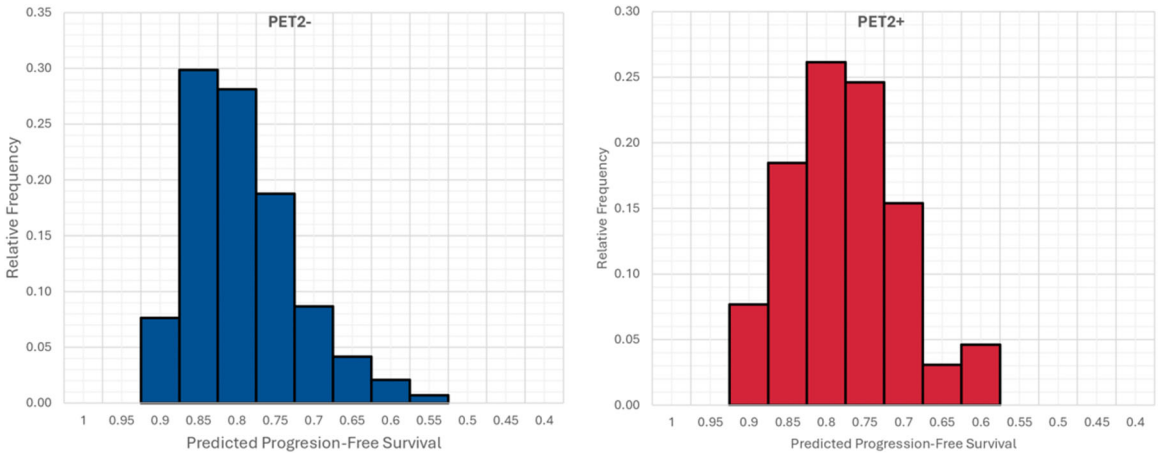
Conclusion: NODAL facilitates research and overcomes barriers to cross trial comparisons through data access via the Pediatric Cancer Data Commons. We are engaging with pediatric HL researchers around the world and invite contribution of clinical trial and registry datasets to all interested groups with complete maintenance of governance by each contributor. We also invite researchers to propose projects that use the growing Hodgkin lymphoma dataset by completing a brief project request form review by the NODAL Executive Committee.

P012: EXPLORING THE CAPABILITY OF THE ADVANCED-STAGE HODGKIN LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX TO PREDICT THE LACK OF AN EARLY COMPLETE METABOLIC RESPONSE IN A MULTICENTRIC ITALIAN COHORT

Alessandro Cellini[1], Giovanni Manfredi Assanto[2], Alessandra Romano[3], Gabriella Santuccio[3], Candida Vitale[4;5], Maria Chiara Montalbano[4;5], Chiara Adele Cavarretta[1], Francesco Angotzi[1], Valeria Ruocco[1], Andrea Serafin[1], Nicolò Danesin[1], Marta Coscia[6], Francesco Di Raimondo[3], Ilaria Del Giudice[2], Francesco Piazza[1], Livio Trentin[1], Andrea Visentin[1]

[1]Hematology Unit, Department of Medicine, University of Padova, Padova, Italy, [2]Hematology, Department of Translational and Precision Medicine, Sapienza University, Rome, Italy, [3]Hematology and BMT Unit, A.O.U. "G. Rodolico-San Marco", Catania, Italy, [4]Department of Molecular Biotechnology and Health Sciences, University of Torino, [5]Division of Hematology, A.O.U. Città della Salute e della Scienza di Torino, Torino, Italy, [6]Hematology Unit, Department of Medicine and Surgery, University of Insubria, Varese, Italy

Figure 1: Distribution of the A-HIPI predicted 5-year Progression-Free Survival in PET2− (blue) and PET2+ (red) patients.



The Advanced-Stage Hodgkin Lymphoma International Prognostic Index (A-HIPI) is a recently proposed prediction tool for classical Hodgkin Lymphoma (HL) making use of baseline prognostic factors to predict individual patient outcomes. The current therapeutic approach for HL is based on PET-guided ABVD, where the lack of an early response documented by a positive PET scan after 2 cycles (PET2) is a significant indicator of adverse risk. We therefore sought to evaluate the capability of the A-HIPI to identify patients at risk for a positive PET2 scan.

A total of 355 patients treated for advanced-stage HL (stage ≥IIB) since 2004 in 4 Italian institutions were enrolled. All subjects were treated with PET-guided ABVD, and PET2 positivity was defined as a Deauville Score >3. The A-HIPI survival estimates were calculated as previously described (Rodday et al., JCO 2022).

Median age at diagnosis was 33 years, 49% of the patients were female, 81% presented with B symptoms and 38% had a bulky disease. After a median follow-up of 63 months, 8% of the patients died and 27% experienced disease relapse, with 5 yr overall-survival (OS) and progression-free survival (PFS) being 93% and 71%, respectively. PET2 positivity was reported in 18% cases, and significant differences in both 5 yr OS (94% vs. 87%; $p = 0.03$) and 5 yr PFS (80% vs. 33%; $p < 0.001$) were documented between PET2-positive and PET2-negative patients. Regarding the A-HIPI predicted risk, PET2-positive subjects exhibited a lower mean predicted survival probability for both OS (0.90 vs. 0.92; $p = 0.048$) and PFS (0.75 vs. 0.77; $p = 0.049$). Moreover, when comparing the predicted probability of PFS of PET2-positive individuals against their peers, a significantly higher proportion ranked in the highest risk quartile (37% vs. 22%; $p = 0.017$), a finding that was also confirmed when utilising the quartile cutoff derived from the discovery dataset in the original publication (43% vs. 29%; $p = 0.039$). Furthermore, the percentage of PET2-positive patients in each quartile increased together with the predicted risk (Q1: 37%, Q2: 23%, Q3: 17%, Q4: 18%).

In conclusion, this work confirms the ability of the recently proposed A-HIPI to identify patients at higher risk of relapse, as we show that a lower predicted PFS is associated with a higher rate of PET2 positivity. In addition, the clustering of such patients into the higher risk quartile supports the usage for this cutoff in the design of future studies exploring risk-adapted strategies.

P013: HIGH RATES OF UNDETECTABLE MRD BY PHASED-SEQ ON INTERIM AND END OF TREATMENT TIMEPOINTS IN UNTREATED ADVANCED STAGE CHL TREATED WITH PEMBROLIZUMAB+AVD

Ryan Lynch[1], Stefan K. Alig[2], Chaitra Ujjani[1], Christina Poh[1], Edus H. Warren[1], Stephen Smith[1], Mazyar Shadman[1], Brian Till[1], Vikram M. Raghunathan[1], Yolanda Tseng[1], Susan Ottemiller[1], Bonnie Joy[1], Melissa Fessel[1], Hongyan Du[1], Jackie Vandermeer[1], Alyssa Kelly[1], Heather Rasmussen[1], Jenna Voutsinas[1], Ash A. Alizadeh[2], Ajay K. Gopal[1]

[1]*Fred Hutchinson Cancer Center*, [2]*Stanford University*

Figure 1: Rates of undetectable MRD (uMRD) by timepoint in patients treated with pembrolizumab + AVD.

	C2D1 uMRD	C3D1 uMRD	EOT uMRD
All patients	29/37 (78%)	36/43 (84%)	39/42 (93%)
Advanced stage	22/29 (76%)	29/35 (83%)	31/34 (91%)

Introduction: We previously reported initial (n = 30) efficacy results of a frontline study of pembrolizumab+AVD (Lynch et al. Blood 2023, ASH 2023) in classic Hodgkin lymphoma (CHL). Despite finding surprisingly high rates of positive interim and EOT PET/CT compared to historical data, observed outcomes were excellent. Herein we present updated clinical data for our full 50-patient study including interim and end of treatment (EOT) MRD testing by PhasED-Seq.

Methods: We examined additional long-term follow up pembrolizumab combined with concurrent AVD in untreated CHL as previously described (NCT03331341). Samples were analyzed for ctDNA at baseline, post cycle 1 (if available), post cycle 2, and end of treatment. ctDNA levels were quantified as haploid genome equivalents/mL plasma using PhasED-Seq (Kurtz et al., Nat Biotech 2021).

Results: 50 patients were enrolled between Feb 1, 2019, and Apr 13, 2023, with a median follow up of 3.1 years, 3-year PFS and OS were 98% and 100%, respectively. Among advanced stage patients (n = 38), 3-year PFS and OS were 97% and 100% respectively.

In patients where samples were available for analysis, baseline ctDNA was detectable in 11/12 (92%) of early-stage patients, and 36/37 (97%) of advanced stage patients. 7/8 (88%) early-stage patients had undetectable MRD (uMRD) at C3D1, and all cleared ctDNA by EOT and none have relapsed to date. Among advanced stage patients, 22/29 (76%) of samples at C2D1 and 29/35 (83%) samples at C3D1 had uMRD. In contrast, the PET CR rate at C3D1 in advanced stage patients was only 58%. At EOT, 31/34 (91%) advanced stage samples had uMRD compared to a PET CR rate of 73%. The only patient in the study to relapse had a negative interim PET but did not clear ctDNA at any timepoint. Two additional patients had minute amounts of ctDNA detectable at the end of treatment after levels dropped >20,000 fold when compared to baseline. Both patients have not relapsed 3 years and 14 months after completion of treatment, respectively. Some timepoints did not have plasma samples available, and no samples were drawn for sequencing during follow-up.

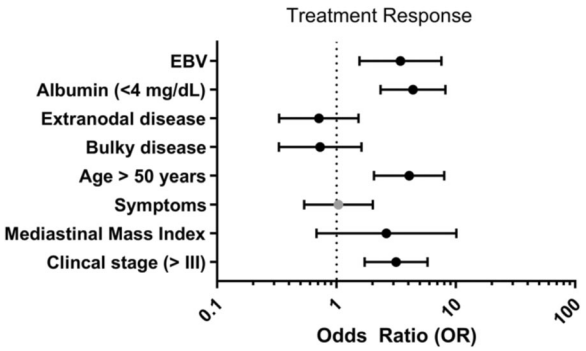
Conclusion: Pembrolizumab+AVD continues to demonstrate durable efficacy in previously untreated CHL. No patient who has cleared ctDNA as measured by PhasED-Seq has relapsed to date despite high rates of interim-PET positivity. The role of PhasED-Seq will be further examined in the upcoming Phase 2 MRD-adapted PRECISE-HL study in untreated advanced stage CHL.

P014: HODGKINS LYMPHOMA IN LATIN AMERICAN PATIENTS: TEN YEARS EXPERIENCE IN A REFERENCE CENTER IN MEXICO

Alonso Hernández Company[1], Gerardo Santiago Jiménez[1], Karen Torres Castellanos[1], Gilberto Israel Barranco Lampón[1], Juan Francisco Zazueta Pozos[1], Daniela De Jesús Pérez Sámano[1], Emmanuel Martínez Moreno[1], Adán Germán Gallardo Rodríguez[1], Carlos Martínez Murillo[1]

[1]*Hospital General de México "Dr. Eduardo Liceaga"*

Figure 1: Forest plot of the effect of clinical variables on treatment response in HL patients.



Background: Hodgkin's Lymphoma (HL) is a rare B-cell malignant neoplasm affecting more than 10,000 new patients annually in Latin America in 2022. The incidence of HL has shown an increase over the past decade. The advancements in diagnostic tools have significantly

improved the accuracy of diagnosis and subtyping. Challenges remain, including the control of treatment-related long-term side effects and the need to improve therapeutic options for those patients who fail the treatment response. This study aims to describe the HL population diagnosed and treated in a reference center in Mexico, as there is limited availability of HL data in Latin America (particularly with long-term outcomes).

Methods: A retrospective cohort using clinical records of Hodgkins Lymphoma patients treated in the Hospital de México "Dr. Eduardo Liceaga" over the past ten years. Completed clinical records of adult patients diagnosed and treated by the Hematology Department were included.

Results: The study included 207 clinical records with a median age of 35 years (range 18–87 years); 64.7% were male; 46.4% had an Advanced stage (III–IV). 17.4% were nodular sclerosis, 62.8% were mixed cellularity, 13% were lymphocytes rich, 3.4% were lymphocytic depletion and 3.4% were not classifiable according to the biopsy and the histological exam. Radiotherapy was offered to 29.5% of patients. Initial therapy outcomes were complete response, partial response, progression, and stable disease in 66.7%, 13.0%, 4.3%, and 13.5% respectively; in 2.4% response could not be evaluated. The median follow-up was 11 months and according to the disease's status at 5-year follow-up, 58.0% had a completed response and a 95.7% survivorship. Multivariate tests showed no statistical differences in clinical status at diagnosis and overall survival ($p = 0.055$), but it did show statistical significance with disease status at 5-year follow-up (OR: 2.713, 95% CI: 1.524–4.829, $p < 0.000$).

Conclusions: Despite Mexico being considered a developing country, our study showed that our population seems comparable to those presented in developed country's studies. Strikingly EBV infection was correlated with poor outcome in this patients as seen before in previous studies. Understanding the epidemiology associated with HL can contribute to personalized medicine approaches, reducing the disease burden and enhancing patient outcomes.

P015: IDENTIFICATION OF RISK CATEGORIES AND STRATIFICATION FROM THE ADVANCED-STAGE HODGKIN LYMPHOMA (AS-HL) INTERNATIONAL PROGNOSTIC INDEX (A-HIPI) MODEL

Matthew Maurer[1], Susan K. Parsons[2], Jenica Upshaw[2], Angie Mae Rodday[2], Jonathan W. Friedberg[3], Andrea Gallamini[4], Massimo Federico[5], Eliza Hawkes[6], David Hodgson[7], Peter Johnson[8], Eric Mou[9], Kerry Savage[10], Pier Luigi Zinzani[11], Andrew Evens[12]

[1]Mayo Clinic, Rochester, Minnesota, USA, [2]Tufts Medical Center, Boston, Massachusetts, USA, [3]University of Rochester Medical Center, Rochester, New York, USA, [4]Antoine Lacassagne Cancer Centre, Nice, Italy, [5]University of Modena and Reggio Emilia, Modena, Italy, [6]Department of Clinical Haematology and Medical Oncology, Austin Health, Heidelberg, Australia, [7]Princess Margaret Hospital, Toronto, Canada, [8]Southampton General Hospital School of Medicine, Southampton, UK, [9]University of Iowa Hospitals and Clinics, Iowa City, Iowa, [10]BC Cancer, Vancouver, Canada, [11]Instituto di Ematologia Seràgnoli, Bologna, Italy, [12]Rutgers Cancer Institute, New Brunswick, New Jersey, USA

Table 1: Risk groups based on "ranking" of AS-HL pts vis-a-vis the A-HIPI predictive model.

Approach 3 (Rank-Based)				
Development Cohort			*Validation Cohort*	
Increased Risk Grouping Options				
A-HIPI Patient Rank (Percentile)	**A-HIPI cutoffs**	**Observed PFS5 <cutoff**	**% of pts <cutoff**	**Observed PFS5 <cutoff**
5%	<0.646	59.3	6%	65.5
10%	<0.686	61.6	13%	65.6
25% (Quartile 1)	<0.737	66.1	27%	71.4
33% (Tertile)	<0.754	68.5	34%	72.4
50% (Median)	<0.781	71.5	49%	74.6
Decreased Risk Grouping Options				
A-HIPI Patient Rank (Percentile)	**A-HIPI cutoffs**	**Observed PFS5 >cutoff**	**% of pts >cutoff**	**Observed PFS5 >cutoff**
50% (Median)	>0.781	82.3	51%	81.7
67% (Tertile)	>0.806	83.3	35%	83.2
75% (Quartile 3)	>0.818	83.8	27%	85.8
90%	>0.844	86.0	13%	86.9
95%	>0.857	85.6	7%	88.2

Abbreviations: A-HIPI, Advanced-stage Hodgkin lymphoma International Prognostic Index; pts, patients; PFS-5, 5-year progression-free survival.

Background: Predictive modeling yields personalized risk prediction for individual patients (pt). The A-HIPI model for AS-HL (Rodday A. JCO 2023) leverages continuous variables to generate individualized probability of progression-free survival (PFS) events or death (OS) within the first 5 years (y) from diagnosis. Risk groups have clinical utility in informing the stratification of pt populations for future clinical trials. We examined approaches using the A-HIPI model to generate varied risk groups with detailed analyses of strengths & limitations.

Methods: Three approaches were examined for the generation of risk groups. Proposed cutoffs were defined using the distribution of A-HIPI risk scores & data from the clinical-trial-based development cohort. Validation was done via the A-HIPI validation cohort from cancer registries.

Results: Approach 1: Risk groups based on clinical thresholds. Clinicians provided estimates of PFS5 constituting high vs low risk. The skewed distribution of risk scores from the A-HIPI model limited this approach, as cutoffs of PFS5 < 70 and PFS > 90 only identified 15% & <1% of pts, respectively. Approach 2: Risk groups based on deviation from "average" pt. The 5 y PFS was 77% (95% CI: 76–78). We explored defining "standard risk" based on this CI with pts above or below thresholds classified as decreased or increased risk, respectively. This classified ~20% of patients into decreased and increased risk groups. Approach 3: Risk groups based on "ranking" of pts. We ranked the A-HIPI risk scores of the 4022 pts in the development cohort and used the distribution of the risk scores as a benchmark. The risk profile for a future pt was then compared to this distribution (e.g., how you rank compared to your peers). This approach allows flexibility for the user to define the tradeoff between size of the risk groups and magnitude of difference in predicted outcomes (Figure). Application of this approach also showed good alignment between the predicted model percentiles and the observed distribution of scores in the validation cohort. Additionally, this approach is more dynamic as it is agnostic to historical clinical benchmarks and allows for use of the model as treatments change.

Conclusions: We assessed 3 varied approaches to define risk groups from the A-HIPI individual risk prediction model. A flexible "rank-based" approach provided the most clinical utility, which may be leveraged for clinical trial design and AS-HL pt stratification.

P016: IMPLEMENTING BRECADD FOR THE TREATMENT OF ADULT PATIENTS WITH NEWLY DIAGNOSED ADVANCED STAGE CLASSICAL HODGKIN'S LYMPHOMA (AS-CHL). A SINGLE CENTER EXPERIENCE

Athanasios Gakopoulos[1], Chara Giatra[1], Michael Panousieris[1], Sotiris Bristogiannis[1], Athanasia Apsemidou[1], Antonia Mitkou[1], Christos Masaoutis[1], Ioannis Baltadakis[1], Maria Bouzani[1]

[1]*Evaggelismos General Hospital of Athens*

Introduction: The HD21, compared BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone) with escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) in newly diagnosed patients with AS-cHL. The final analysis showed better treatment-related morbidity and the interim results reveled a strong trend of superiority in favor of BrECADD.

Methods: To report our experience on applying BrECADD on adults, with AS-cHL. Therefore, we collected data from 11 consecutive patients, treated in our department between 2020 and 2023. PET assessment was performed after the 2nd cycle (iPET) and at the end of treatment (EoT PET).

Results: Six men and 5 women with median age of 31 years (range 24–48) were diagnosed with AS-cHL. The histologic subtype was nodular sclerosis (NS) in 8, mixed cellularity (MC) in 2 and unclassified in 1 case. The Ann Arbor stage was IIIB in 2 and IVB in 9 patients. One patient showed mediastinal bulky disease. The International Prognostic Score (IPS) was 2 in 2 subjects, 3 in 4 patients, 4 in 3 and 5 in 2 cases. All patients had ECOG score 0–2, but 2 with scores of 3 and 4. Five patients, treated before the announcement of the non inferiority results of HD21 trial, received 6 cycles of BrECADD, weather 5 patients diagnosed later received 4 cycles. One patient was lost after the 1st course. iPET was performed in 8 subjects: Five patients showed Deauville score (DS) 2 and the remaining 3 had DS1, DS3 and DS4. All patients had EoT PET. All achieved complete metabolic response: 6 showed DS1, 3 DS2, and 1 subject DS3. Radiotherapy received one patient with remaining bulky disease of 6 cm. All patients received GCSF prophylactic administration. Among them, seven (70%) showed neutropenia grade 4. In 5 (50%) neutropenia was accompanied by fever, which required hospitalization. Five cases (45%) were supported with transfusions of red blood cell concentrates. One patient manifested peripheral sensory neuropathy grade 2. With a median follow up of 11.5 months (range 0.5–49.7) all eleven patients are alive. The 10 patients who concluded treatment, all are in complete remission.

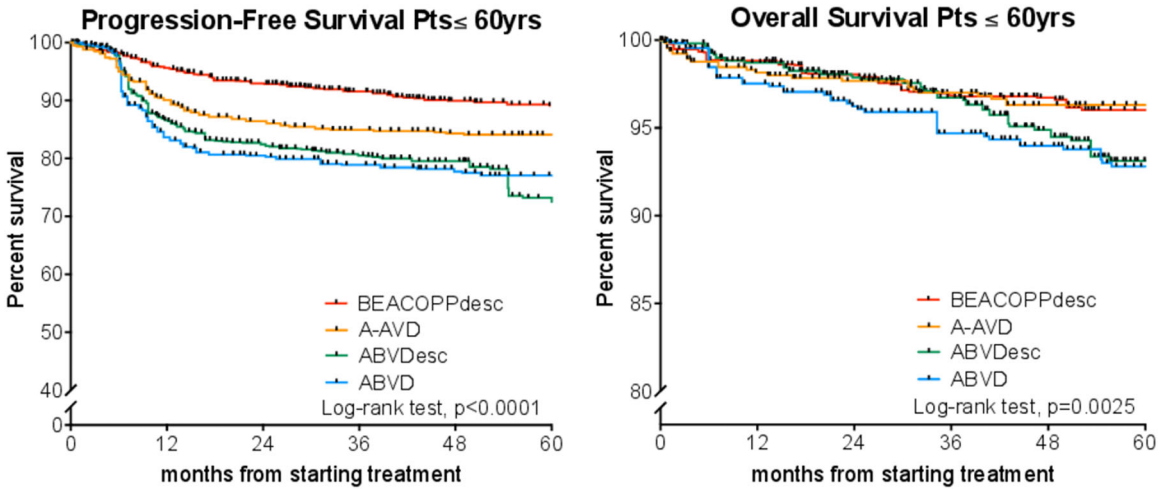
Conclusion: BrECADD regimen, showed deep complete metabolic responses with manageable toxicity. In addition, the short duration of treatment period together with the possibility of administration in an outpatient setting make the regimen very appealing for adult patients with AS-cHL.

P017: INDIRECT CLINICAL TRIALS COMPARISONS OF TREATMENTS FOR ADVANCED-STAGED HODGKIN LYMPHOMA WITH INDIVIDUAL PATIENT DATA EXTRACTION

Andrea Visentin[1], Alessandro Cellini[1], Francesco Angotzi[1], Valeria Ruocco[1], Andrea Serafin[1], Nicolò Danesin[1], Arianna Bevilacqua[1], Chiara Adele Cavarretta[1], Francesco Piazza[1], Livio Trentin[1]

[1]*Hematology Unit, Department of Medicine, University of Padova, Padova, Italy*

Figure 1: Kaplan–Meier curves of Progression-free survival and Overall survival in patients with Hodgkin lymphoma young than 60 years old across different trials.



Treatments for advanced-staged Hodgkin lymphoma (HL) include non-intensified ABVD, ABVD-based escalation with BEACOPP in case of a positive interim PET-CT (ABVDesc), BEACOPP-based de-escalation in case of a negative interim PET-CT (BEACOPPdesc) and AVD+brentuximab vedotin (A-AVD). Since a clinical trial comparing all these strategies is unlikely to be performed, alternative statistical methods should be employed.

We included data from the HD0607, RATHL, HD18, AHL2011, S0816, and ECHELON1 trials and compared the 3-year progression free survival (PFS) and overall survival (OS) of young patients. We used Liu's method (BMC Med Res Methodol 2021) to reconstruct individual patient data (IPD) from Kaplan-Meier survival curves. Comparisons of adverse events were performed.

Among the 6 included trials, the ECHELON-1 was the only one that enrolled patients >60 yr and excluded stage II patients. Since we focused on patient < =60 yr, we excluded the RATHL trial as survival curves of patients < =60 yr were not published. Among the 5,034 included patients, 11% received not-intensified ABVD, 12% A-AVD, 22% ABVDesc (S0816 and HD0607), 55% BEACOPPdesc (AHL2011 to ABVD and HD18 to less treatment cycles). The extrapolated 3 yr PFS increased from 79% with ABVD alone, to 81% with ABVDesc, 85% with A-AVD and 92% with BEACOPPdesc (Fig. 1, $p < 0.0001$).

Of note, the difference between the ABVD without or with intensification was not statistically significant (HR: 1.03, 95% CI: 0.83–1.29, $p = 0.5398$). Whereas a significant difference was identified between A-AVD vs ABVDesc (HR: 1.56, 95% CI: 1.25–1.95, $p = 0.0055$) and BEACOPPesc (HR: 0.62, 95% CI: 0.44–0.76, $p < 0.0001$). The strategy of non-intensified ABVD lead to a lower OS that the other strategies. The 3 yr OS was 95% with ABVD, 97% ABVDesc, A-AVD, and BEACOPPdesc (Fig. 1, $p < 0.0025$). In particular, no difference was observed between A-AVD vs BEACOPPdesc (HR: 1.04, 95% CI: 0.67–1.61, $p = 0.9943$) or ABVDesc (HR: 1.57, 95% CI: 0.99–2.29, $p = 0.0515$).

Regarding safety, grade > =3 cytopenia and febrile neutropenia were more common with BEACOPPdesc 90% and 27% >ABVDesc 67%–76% and 10%–32% >A-AVD 54% and 8% >ABVD 46% and 3% ($p < 0.001$). While grade 3 neuropathy was more common with A-AVD 11% >BEACOPPdesc 2–7%, ABVDesc 2% >ABVD 1% ($p < 0.001$)

In conclusion, by using indirect clinical trials comparisons with IPD extraction we demonstrated the superiority and the safety of A-AVD therapy over ABVDesc while the superimposable OS with BEACOPPesc suggest the reliability of salvage therapies after A.

P018: LOWER DOSES OF DACARBAZINE AS A SAFER STRATEGY IN HODGKIN LYMPHOMA'S INTENSIVE TREATMENT PROTOCOL (MODIFIED ESCALATED BEACODD): PRELIMINARY RETROSPECTIVE ANALYSIS OF A SINGLE AND PUBLIC CENTER IN BRAZIL

Arthur Gomes Oliveira Braga[1], Larissa Hilario Dulley[2], Guilherme Garcia Rodrigues[2], Sergio Costa Fortier[2], Carlos Sergio Chiattone[2], Talita Maira Bueno Da Silveira[1,2]

[1]*Hematology Department, A.C.Camargo Cancer Center*, [2]*Hematology Department, Irmandade de Santa Casa de Misericórdia de São Paulo*

Table 1. Characteristics of the population's groups.

	All patients n=31	500mg/m² n=17	375mg/m² n=14	p value
Age (years):	30 (14-47)	30 (16-47)	29.5 (14-41)	0.468
Gender, n (%):				0.843
Male	16 (51.6)	8 (47.1)	8 (57.1)	
Female	15 (48.4)	9 (52.9)	6 (42.9)	
Albumin (g/dL):	3.0 (2 – 4)	3.0 (2 – 4)	2.0 (2 – 4)	**0.046**
Ann Arbor, n (%):				>0.99
Stages I-III	14 (45.2)	8 (47.1)	6 (42.9)	
Stage IV	17 (54.8)	9 (52.9)	8 (57.1)	
Leukocytes (/µL x 10^3):	10.6 (3.9-41.8)	10.6 (5.6-41.8)	10.75 (3.9-41.8)	0.811
Monocytes (/µL x 10^3):	1.24 (0.386-7.6)	1.63 (0.574-7.6)	0.84 (0.386-4.0)	0.230
Lymphocytes (/µL x 10^3):	1.59 (0.014-7.6)	1.54 (0.014-7.6)	1.88 (0.318-2.5)	>0.99
IPS score, n (%):				>0.99
<3	15 (48.4)	8 (47.1)	7 (50.0)	
≥3	16 (51.6)	9 (52.9)	7 (50.0)	
B symptoms, n (%):				0.344
Absent	5 (16.1)	4 (23.5)	1 (7.1)	
Present	26 (83.9)	13 (76.5)	13 (92.9)	
Fever (>38°C), n (%):				>0.99
No	16 (51.6)	9 (52.9)	7 (50.0)	
Yes	15 (48.4)	8 (47.1)	7 (50.0)	
Weight loss (>10%), n (%):				**0.057**
No	20 (64.5)	8 (47.1)	12 (85.7)	
Yes	11 (35.5)	9 (52.9)	2 (14.3)	
Night sweats, n (%):				>0.99
No	20 (64.5)	11 (64.7)	9 (64.3)	
Yes	11 (35.5)	6 (35.3)	5 (35.7)	
Number of nodal sites:	4 (1-4)	3 (1-4)	4 (2-4)	0.769
C-reactive protein (mg/dL):	8.5 (1-95)	16 (1-95)	2 (1-19)	0.064

Table 2. Outcomes.

	All patients n=31	500mg/m² n=17	375mg/m² n=14	p value
De-escalation to ABVD, n (%):				**0.003**
No	23 (74.2)	9 (52.9)	14 (100)	
Yes	8 (25.8)	8 (47.1)	0 (0)	
First line response, n (%):				>0.84
No information	5 (16.1)	3 (17.6)	2 (14.3)	
Complete remission	23 (74.2)	13 (76.5)	10 (71.4)	
Refractory disease	3 (9.7)	1 (5.9)	2 (14.3)	
Relapse or Progression, n (%):				>0.99
No	27 (87.1)	15 (88.2)	12 (85.7)	
Yes	4 (12.9)	2 (11.8)	2 (14.3)	
Febrile Neutropenia, n (%):				>0.99
No	17 (54.8)	9 (52.9)	8 (57.1)	
Yes	14 (45.2)	8 (47.1)	6 (42.9)	
Hospitalization for Febrile Neutropenia, n (%):				0.786
No	18 (58.1)	9 (52.9)	9 (64.3)	
Yes	13 (41.9)	8 (47.1)	5 (35.7)	
Number of cycles with diagnose of febrile neutropenia, n (%):	19 (11.8)	14 (17.9)	5 (6.1)	0.004

The escalated BEACOPP (eBEACOPP) regimen represents one of the gold standard treatments for advanced-stage Hodgkin's Lymphoma (HL), as implemented by the German Hodgkin Study Group (GHSG). In Brazil, since 2008, procarbazine was replaced with dacarbazine 375 mg/m^2/cycle (eBEACOPDac protocol), due to its absence on the market. When the BRECADD (replacing bleomycin with brentuximab) phase II study was published, it was seen that the protocol used a higher dose of dacarbazine (500 mg/m^2/cycle), and this dose was incorporated into the eBEACODD regimen. After a certain period of follow-up of this increased dose of dacarbazine, it was found in our Cancer Center that we were having difficulty to continue the cycles due to toxicity related to the treatment. The aim of this investigation was to conduct a comparative analysis of the safety profiles between the two dosage regimens of the eBEACODD (375 mg/m^2/cycle vs. 500 mg/m^2/cycle) in

treating patients with advanced HL over a comparable timeframe. This retrospective study examined data from 31 patients treated at our institution from 2019 to 2021. Of these, seventeen patients received the higher dosage regimen (500-group), while 14 received the lower dosage regimen (375-group). Upon evaluating response rates at the end of treatment, both groups demonstrated comparable outcomes, with 71% of patients in the 375-group achieving complete remission (CR), compared to 76% in the 500-group. However, an analysis of the incidence of febrile neutropenia (FN) events per cycle revealed a notable discrepancy. Specifically, the 500-group exhibited a threefold higher frequency of FN events (17.9%) compared to the 375-group (6.09%), with a statistically significant *p*-value of 0.04. Furthermore, within the 500-group, 47.1% of patients necessitated a protocol switch to ABVD due to treatment-related toxicities. In contrast, among patients of the 375-group no such protocol alterations were required, suggesting a more favorable toxicity profile. In conclusion, the utilization of a modified eBEACODD regimen incorporating 375 mg/m^2 of dacarbazine per cycle represents a potentially safer therapeutic strategy for patients with advanced HL, mitigating the risk of treatment-related toxicities, particularly FN. Further investigations with larger patient cohorts and multicenter studies are warranted to validate these findings and have data about efficacy.

P019: PEMBROLIZUMAB+AVD IN CLASSIC HODGKIN LYMPHOMA: LOW RATES OF FEBRILE NEUTROPENIA DESPITE FREQUENT GRADE 4 NEUTROPENIA

Thomas Kuczmarski[1], Chaitra Ujjani[1], Christina Poh[1], Edus H. Warren[1], Stephen Smith[1], Mazyar Shadman[1], Brian Till[1], Vikram M. Raghunathan[1], Yolanda Tseng[1], Hongyan Du[1], Jackie Vandermeer[1], Alyssa Kelly[1], Heather Rasmussen[1], Jenna Voutsinas[1], Ajay K. Gopal[1], Ryan Lynch[1]

[1]*Fred Hutchinson Cancer Center*

Table 1
Rates and severity of neutropenia, febrile neutropenia, and infections in patients treated with pembrolizumab + AVD in frontline setting.

Adverse event	**Prevalence (n=50)**				
Neutropenia	Grade 4: 35 (70%) Grade 3: 7 (14%) Grade 2: 3 (6%) Grade 1: 1 (2%) No neutropenia: 4 (8%)				
Febrile neutropenia	Grade ≥3: 5 (10%)				
Infection	Grade 3-4: 4 (8%)				
Additional neutropenia-related details	**Findings**				
G-CSF use	*Primary prophylaxis:* n=7 Mean number of cycles used: 4.7 (3-6) *Secondary prophylaxis:* n=6 Mean number of cycles used: 3 (1-5)				
Grade 4 neutropenia without primary G-CSF prophylaxis	Mean number of days: 45.6 Median number of days: 21 Range of neutropenia days: 0-147				
Characteristics of those who developed FN					
Subject number	**Sex**	**Age**	**Disease stage**	**Cycle during which FN occurred**	**# of days of neutropenia prior to FN**
1	F	28	IIB	4	81
2	M	58	III	1	0
3	F	31	IV	2, 3*	15, 16*
4	F	19	IIB	5	100
5	F	49	IV	4	7

*Patient developed FN on two separate occasions.

Background: Concurrent checkpoint inhibition (CPI) and chemotherapy has demonstrated high efficacy in the frontline setting for patients with classic Hodgkin lymphoma (CHL). While historical data have supported ABVD treatment without granulocyte-colony stimulating factor (G-CSF) despite neutropenia, management in CPI-based combinations is currently undefined. In patients treated with CPI and chemotherapy, grade

≥3 neutropenia was common (47%), while febrile neutropenia rates were low (5%, Herrera et al ASCO 2023). However, there are limited data regarding the nature of febrile neutropenia (FN) episodes and correlation with other factors such as preceding neutropenia and granulocyte-colony stimulating factor (G-CSF) use.

Methods: We reviewed laboratory data for all patients enrolled in a clinical trial of 2–6 cycles of pembrolizumab and AVD (NCT03331341). We obtained clinical data, including absolute neutrophil count measured regularly throughout treatment, from the patients' electronic medical records. We evaluated the timing and severity of neutropenia for the duration of treatment. We collected additional pertinent clinical data from the electronic medical record and from the clinical trial's electronic data capture database.

Results: Baseline characteristics of this cohort ($N = 50$) have previously been reported (Lynch et al., ASH 2023). In 43 patients who did not receive G-CSF for primary prophylaxis, the mean total duration of grade 4 neutropenia was 45.6 days (range: 0–147 days), and FN occurred in 5 (12%) of patients. FN rate was 11.6% (Table 1). Of those who did not receive primary G-CSF prophylaxis, 3 (7%) patients experienced a grade ≥3 infection. FN rates for the 7 patients who received primary prophylaxis with G-CSF was 0%, though one of these patients did experience non-neutropenic sepsis due to a colonic abscess. These patients received G-CSF for a mean of 4.7 cycles of chemotherapy (87% of total chemotherapy cycles), while patients treated with G-CSF for secondary prophylaxis received G-CSF for a mean of 3 cycles. For the 5 patients who developed FN, none were previously on G-CSF, and they were neutropenic for 0 to 100 days prior to their fever. Additional data is presented in Table 1.

Conclusion: Although rates of grade 4 neutropenia were high at 70% in patients treated with pembrolizumab + AVD, febrile neutropenia and infections were uncommon despite low rates of G-CSF use and appeared similar to historical data with ABVD.

P020: REAL-LIFE EXPERIENCE WITH BV-AVD COMBINATION IN ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA: A MULTICENTER STUDY FROM GREECE

Athanasios Liaskas[1], Maria Angelopoulou[1], Pinelopi Vryttia[2], Evgenia Verrou[3], Alexia Piperidou[1], Maria-Aikaterini Lefaki[1], Angeliki Georgopoulou[1], Alexandros Machairas[1], Dionisios Stoumbos[4], Georgia Kaiafa[5], Anastasia Sioni[6], Nikolaos Kanellias[7], Maria Arapaki[1], Elianna Constantinou[1], Dimitrios Gogos[8], Marina Siakantari[1], Eirini Katodritou[3], Panayiotis Panayiotidis[1], Sotirios Papageorgiou[2], Theodoros Vassilakopoulos[1]

[1]Department of Hematology and Bone Marrow Tranplantation, National and Kapodistrian University of Athens, Laikon General Hospital, Greece, [2]2nd Propaedeutic Department of Internal Medicine, "Attikon" General Hospital, [3]Hematology Department, Theagenio Cancer Hospital, Thessaloniki, Greece, [4]Department of Hematology, "Metaxa" Anticancer Hospital, [5]1st Propaedeutic Department of Internal Medicine, University General Hospital of Thessaloniki AHEPA, Aristotle University of Thessaloniki, [6]Department of Hematology, Agios Savvas Cancer Hospital, Athens, Greece, [7]Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, [8]Department of Hematology, "Vostaneio" Hospital of Lesvos, Greece

Background: Brentuximab vedotin (BV) in combination with doxorubicin, vinblastine and dacarbazine (BV-AVD) was approved for the first-line treatment of patients with advanced stage Hodgkin lymphoma (HL), based on the results of the ECHELON-1 study initially for stage IV and subsequently for stages III and IV. We aimed to describe the real-life experience with BV-AVD in a multicenter setting in Greece.

Methods: Retrospective analysis of newly diagnosed patients with advanced HL, who received BV-AVD treatment in 8 centers in Greece. Interim PET (iPET) was evaluated according to Deauville 5-point scale and was considered as positive in cases with scores 4 or 5.

Results: 57 patients were treated with BV-AVD (2 started with a half or one cycle of ABVD, and then continued with BV-AVD). The median age was 41 years (range: 17–84; 24% of patients ≥60 years old) 57% were males, 82% had B-symptoms and 15% had bulky disease at diagnosis. By conventional staging, 71, 25 and 4% of the patients had disease stage IV, III, and IIB respectively, while 90% of the patients had stage IV disease based on baseline PET/CT. 2 deaths occurred during treatment: one due to febrile neutropenia in a 78-year old patient during the first cycle and one due to myocardial infraction in a 51-year old patient during the 6th cycle. iPET was available in 50/57 patients and was positive in 6 (12%). All iPET+ patients had DS4 (SUVmax: 4.1–7.4) and none switched to a different regimen. Among iPET+ patients, at the end of treatment (EoT): 2 patients remained PET+ with DS4 but had no evidence of disease progression and remained currently disease-free, 3 patients converted to PET- and one died due to myocardial infraction prior to EoT evaluation. Overall, there were 6 relapses, occurring between 7–43 months from treatment initiation, all derived from the iPET- population. With a median follow-up of 17 months, 2- and 3-year FFP was 88% and 82% respectively.

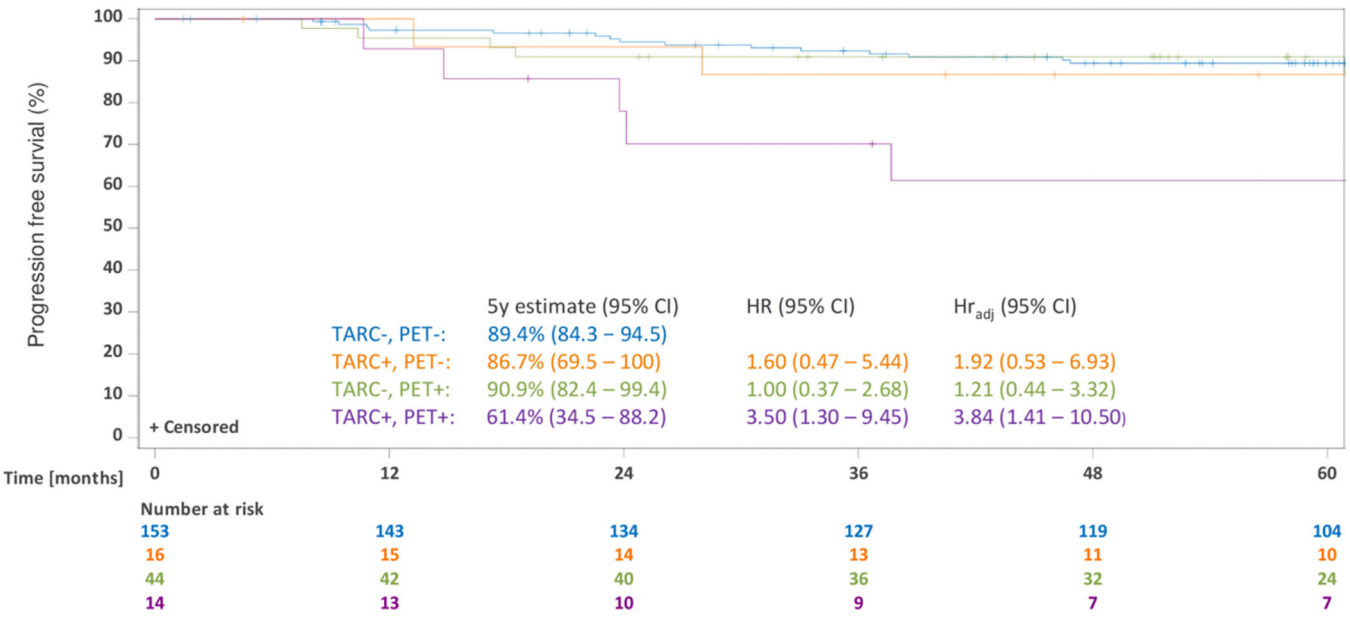
Conclusion: Our real-life study provided comparable results to ECHELON-1 regarding treatment efficacy of BV-AVD, despite the vast predominance of stage IV owing to the approved indication of BV-AVD during the study period. The rate of iPET positivity was slightly higher in our study, but a iPET+ did not compromise patients' outcome as the majority were either converted to PET- or were falsely PET+ at the EoT. All relapses occurred in iPET- patients implying that detection of prognostic factors in this subgroup of patients remains relevant.

P021: SERUM TARC COMBINED WITH FDG-PET IMAGING IMPROVES INTERIM RESPONSE EVALUATION IN CLASSIC HODGKIN LYMPHOMA: A RETROSPECTIVE ANALYSIS OF GERMAN HODGKIN STUDY GROUP HD16 AND HD18 TRIALS

Wouter J. Plattel[1], Janina Jablonski[2], Mia Lohmann[2], Bastian Von Tresckow[2], Anna Sureda[3], Michiel Pegtel[4;5], Josée M. Zijlstra[6], John Radford[7], Bart-Jan Kroesen[8], Lydia Visser[9], Michael Fuchs[2], Peter Borchmann[2], Arjan Diepstra[9], Sven Borchmann[2]

[1]Department of Hematology, University Medical Center Groningen, Groningen, The Netherlands, [2]German Hodgkin Study Group (GHSG), Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Dusseldorf, University of Cologne, Cologne, Germany, [3]Institut Català d'Oncologia, Hospital Duran i Reynals. Institut d'Investigació Biomèdica de Barcelona, Department of Hematology, Barcelona, Spain, [4]Amsterdam UMC, Location Vrije Universiteit Amsterdam, Department of Pathology, Amsterdam, The Netherlands, [5]Cancer Center Amsterdam, Imaging and Biomarkers, Amsterdam, The Netherlands, [6]Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Hematology, Amsterdam, The Netherlands, [7]Christie Hospital, Department of Medical Oncology, Manchester, UK, [8]University Medical Center Groningen, Department of Laboratory Medicine, Groningen, The Netherlands, [9]University Medical Center Groningen, Department of Pathology and Medical Biology, Groningen, The Netherlands

Figure 1: Prognostic value of PET-2 and TARC-2 combined in cHL patients in HD16 and HD18. PET-2 positive patients that are TARC-2 negative have excellent outcome, while double positive patients have significantly inferior PFS.



Background: Treatment guidance based on interim response as determined by PET imaging has become standard of care in classic Hodgkin lymphoma (cHL). However, the positive predictive value of interim PET (PET-2) is limited resulting in a significant proportion of patients being overtreated. The tumor cell specific serum biomarker Thymus and Activation Regulated Chemokine (TARC) might aid in early response assessment. The aim of the current study is to investigate the prognostic value of interim TARC (TARC-2) in patients treated in the German Hodgkin Study Group HD16 and HD18 trials.

Methods: Patients with cHL and available serum samples from HD16 and HD18 trials that were treated without PET-2 treatment adaptation were included. TARC was measured by standard ELISA and levels >1000 pg/mL were considered positive as previously defined. The primary outcome measure was progression free survival (PFS). Hazard Ratios were obtained by Cox regression analysis adjusted for age, sex, and trial if applicable. This study was performed on behalf of the consortium for minimal residual disease in cHL.

Results: A total of 278 patients with measurable disease at baseline were included (76 from HD16 and 202 from HD18). At baseline 51 (67%) of early favorable patients and 176 (87%) of advanced stage patients were TARC positive. After 2 cycles, 3 (6%) and 27 (15%) of patients in the HD16 and HD18 trial remained TARC-positive, respectively. TARC-2 was negative in 91% of PET-2 negative patients (n = 153) as well as in 76% of PET-2 positive patients (n = 44). TARC-2 positive patients had significantly worse 5y-PFS of 75% compared to 90% in TARC-2 negative patients in the entire cohort. PET-2 positive patients had a non-significant lower PFS of 84% vs 89% in PET-2 positive patients. In the combined analysis, PET-2 positive/TARC-2 negative patients had a 5-year PFS of 91%, not different from the PET-2 negative patients (Figure 1). However, PET-2 positive/TARC-2 positive patients (n = 14) had a 5-year PFS of only 61% (HR = 3.84 (1.41–10.50)).

Conclusion: We confirmed the adverse prognostic value of TARC-2 in an independent large non PET adapted cohort. Remarkably, TARC-2 could identify a subgroup of >75% of PET-2 positive patients that have excellent outcome, while at the same time identifying a group of double positive patients that are at high risk of treatment failure. The integration of TARC in response assessment can further decrease overtreatment in cHL.

P022: TREATMENT OF CLASSICAL HODGKIN'S LYMPHOMA (cHL) WITH BRENDUXIMAB VEDOTIN–DOXORUBICIN–VINBLASTINE–DACARBAZINE (BV-AVD). ONE CENTER'S EXPERIENCE

Chara Giatra[1], Andri Polyviou[1], Kyriaki Kontitsi[1], Tatiana Tzenou[1], Michael Panousieris[1], Vasiliki Babali[1], Athanasia Apsemidou[1], Sotiris Bristogiannis[1], Athanasios Gakopoulos[1], Evridiki Theodorou[1], George Kanellis[1], Ioannis Baltadakis[1], Stavros Gigantes[1], Maria Bouzani[1]

[1]*Evaggelismos General Hospital of Athens*

Backround: According to the ECHELON-1 study, administration of the combination has been widely adopted in the treatment of advanced stage HL. Additionally, other clinical trials tested the administration of this treatment in limited stage disease. Despite its effectiveness, toxicity is questionable, limiting its administration to younger patients. In our work we deposit the experience of our Center in the administration of BV-AVD.

Materials and Methods: We retrospectively collected the data of 20 consecutive patients with cHL treated in our Centre with the BV-AVD combination during the last 7 years. All but one were younger than 40 years old. We studied effectiveness as well as toxicity profile of the combination.

Results: Ten men and 10 women, with a median age of 32.4 years (range 17.3–71.6) were diagnosed with cHL between 2017 and 2023. Histological subtype was nodular sclerosis (NS) in 14 patients, mixed cellularity (MC) in 4 patients, while in 2 it was not possible to determine disease subtype due to limitations of biopsy sample. The Ann Arbor stage of the disease was I (n = 1), II (n = 8), III (n = 6), IV (n = 5). Eight (40%) patients presented with B-symptoms at diagnosis. Two patients were diagnosed with bulky disease. Three patients had limited stage disease, while 17 had advanced disease: early unfavorable n = 6, stage III–IV n = 11. Eighteen patients had performance status ECOG 0–1. All completed 6 cycles, except of 2 patients, who received 4. None received adjuvant radiotherapy. Eighteen out of 20 patients achieved metabolic remission after the 2nd cycle. Two patients had interim PET/CT assessed as Deauville Scale 4. All achieved complete metabolic response at the end of the treatment program. Progression under treatment or disease relapse was not occurred to anyone. All received prophylactic granulocyte-colony growth factor. Four patients manifested febrile neutropenia and 4 lower respiratory tract infection. Six (32%) presented with any grade peripheral neuropathy, while 2 developed grade 3. Particularly frequent (42%) were intestinal side effects: diarrhea, constipation, ileus, and 1 patient presented with pancreatitis. With a median follow-up of 48 months (range 3.2–69.6), all patients are alive and in complete remission but one, who died of a non-disease-related cause.

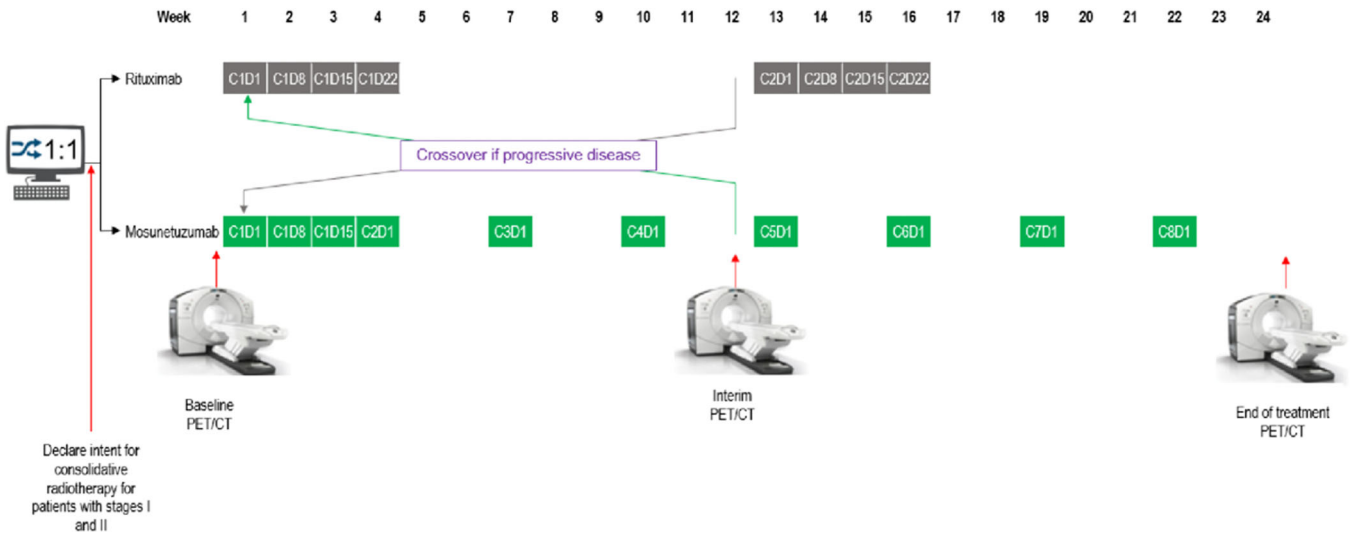
Conclusion: BV-AVD combination is effective, although accompanying toxicity limits its administration to younger patients.

P023: TRIAL IN PROGRESS: CTEP 10590, NORM: NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA PATIENTS TREATED IN A RANDOMIZED PHASE II TRIAL WITH EITHER RITUXIMAB OR MOSUNETUZUMAB

Raphael E. Steiner[1], Hun Ju Lee[2], Michael Green[2], Ruitao Lin[2], Chelsea Pinnix[2], Alison Moskowitz[1], Joachim Yahalom[1], Dai Chihara[2]

[1]*Memorial Sloan Kettering Cancer Center*, [2]*MD Anderson Cancer Center*

Figure 1: Schema of study design.



Background: NLPHL often affects young patients, who have an excellent prognosis irrespective of therapy and are frequently overtreated with cytotoxic therapies. 77% of causes of death of NLPHL patients treated in the trials HD7-HD15 with cytotoxic therapies and radiotherapy used for classical Hodgkin lymphoma (cHL) were non-NLPHL related. NLPHL expresses CD20 and is usually characterized by an indolent behavior, similar to B-cell indolent non-Hodgkin lymphomas. Mosunetuzumab is an anti-CD20/CD3 T-cell-dependent bispecific antibody with a

complete response rate of 60% in relapsed/refractory follicular lymphoma. The discovery of novel efficacious targeted therapies for NLPHL is essential to avoid overtreatment, decrease toxicities, and improve patient quality of life.

Objectives: This study aims to compare the progression-free survival (PFS), safety and antitumor activity of mosunetuzumab versus rituximab in NLPHL patients.

Methods: We are conducting a phase II, randomized multicenter trial with either rituximab or mosunetuzumab of patients 18 years or older with previously untreated NLPHL stage IB to IV and previously treated NLPHL of any stage, requiring systemic therapy. Patients with transformed NLPHL and patients previously treated with rituximab will be ineligible. Patients will receive either rituximab (375 mg/m^2 IV on Cycle 1 Day 1, followed by rituximab 1400 mg/hyaluronidase 23, 400 units SC on C1D8-C2D22, 2 cycles of weekly rituximab 4×, 8 weeks apart) or mosunetuzumab (SC with step-up dosing Cycle 1 Day 1, 8, and 15 and Day 1 of subsequent cycles (5/45/45 mg), up to 8 cycles). Consolidative XRT for patients with stages I and II is optional, to be declared prior to randomization.

The primary endpoint is the 2-year PFS for both arms. The secondary endpoints will include the response rate at the interim and EOT, landmark survival outcomes and safety. Exploratory analyses include assessing molecular response by sequencing cell-free DNA, RNAsequencing and whole exome sequencing.

We base our sample size justification on a log rank test comparing PFS between the two treatment groups with assumed 2-year PFS rates of 50% (rituximab) versus 75% (mosunetuzunab) with a one-sided type I error rate of 10% and 85% power, accrual period of 3 years and the maximum trial duration of 5 years. The expected sample size is 56 under the null hypothesis and 62 under the alternative hypothesis.

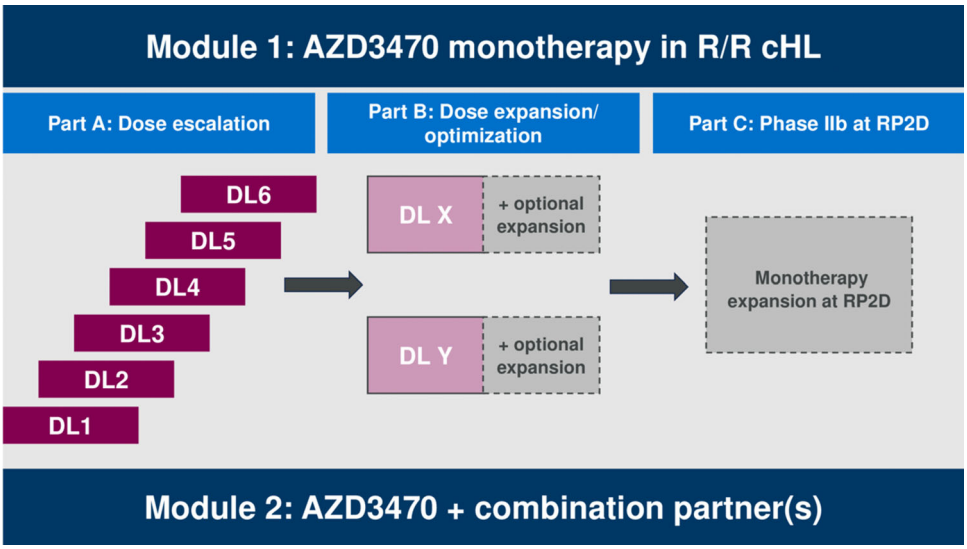
The study is open for accrual in the US and Canada since January 2024.

P024: TRIAL IN PROGRESS: PRIMAVERA: A MODULAR PHASE I/II STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF AZD3470, A PROTEIN ARGININE METHYLTRANSFERASE 5 (PRMT5) INHIBITOR, IN PARTICIPANTS WITH RELAPSED/REFRACTORY (R/R) HEMATOLOGIC MALIGNANCIES

Tae Min Kim[1], Katherine Lewis[2], Juan Alderuccio[3], Hun Ju Lee[4], Enrico Derenzini[5], Pier Luigi Zinzani[6], Marco Ladetto[7], Elizabeth H. Phillips[8], Herve Ghesquieres[9], François Lemonnier[10], Franck Morschhauser[11], Anna Sureda-Balari[12], Antonia Rodriguez Izquierdo[13], Peter Borchmann[14], Matthew Weinstock[15], Jakub Svoboda[16], Emma Dean[17], Jelena Urosevic[17], Stefanie Meyer[18], Robert Chen[19], Ting Yu[20], Ruben Reyes[18], Kaitlyn Beyfuss[21], Graham P. Collins[22]

[1]Seoul National University Hospital, Seoul, Republic of Korea, [2]Linear Clinical Research, Perth, Australia, [3]University of Miami-Sylvester Comprehensive Cancer Center, Miami, FL, USA, [4]MD Anderson Cancer Center, Houston, TX, USA, [5]IEO European Institute of Oncology, Milan, Italy, [6]Policlinico Sant'Orsola-Malpighi, University of Bologna, Bologna, Italy, [7]Ospedale Civile Ss. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy, [8]Christie NHS Foundation Trust, Manchester, and Division of Cancer Sciences, University of Manchester, Manchester, UK, [9]Hospital Lyon Sud, Lyon, France, [10]Hopital Henri Mondor, Créteil, France, [11]Centre Hospitalier Universitaire de Lille, Lille, France, [12]Instituto Catalán de Oncología - Hospital Duran i Reynals, Barcelona, Spain, [13]Hospital Universitario 12 de Octubre, Madrid, Spain, [14]Universitätsklinikum Köln, Cologne, Germany, [15]Beth Israel Deaconess Medical Center, Boston, MA, USA, [16]Hospital of the University of Pennsylvania, Philadelphia, PA, USA, [17]Oncology R & D, AstraZeneca, Cambridge, UK, [18]Hematology R & D, AstraZeneca, Boston, MA, USA, [19]Hematology R & D, AstraZeneca, Cambridge, UK, [20]Hematology R & D, AstraZeneca, San Francisco, CA, USA, [21]Hematology R & D, AstraZeneca, Mississauga, ON, Canada, [22]Oxford Cancer and Haematology Centre, Oxford, UK

Figure 1: Study design of Module 1 assessing AZD3470 monotherapy (dose escalation [Part A], dose optimization-expansion [Part B], and further expansion [Part C]) in cHL and Module 2 assessing AZD3470 + anticancer therapy combinations.



Background: PRMT5 is an enzyme that methylates arginine residues on many histone/non-histone proteins. It promotes oncogenesis through epigenetic control of gene expression, RNA splicing, and DNA repair. Methylthioadenosine phosphorylase (MTAP)-deficient tumor cells

show accumulation of methylthioadenosine (MTA), an endogenous partial inhibitor of PRMT5. AZD3470 is an MTA-cooperative PRMT5 inhibitor that preferentially targets the MTA-bound state of PRMT5, sparing its inhibition in normal cells. While MTAP homozygous deletion is found in ≈15% of advanced solid cancers, >80% of classical Hodgkin lymphoma (cHL) samples have MTAP protein loss, potentially due to epigenetic silencing (ASH 2023, Abstract 4185). Here, we describe a phase I/II trial designed to assess AZD3470 as monotherapy and in combination with anticancer agents in participants with R/R hematologic malignancies.

Methods: NCT06137144 is a first-in-human phase I/II dose escalation and expansion study. Participants ≥18 years of age with measurable R/R cHL who have received ≥3 prior lines of therapy (including brentuximab vedotin and anti-PD-1) and meet hematologic criteria (Hb ≥10 g/dL, ANC ≥ 1.5×10^9/L, platelets ≥100×10^9/L) will be enrolled. In Module 1 Part A, patients will receive daily oral AZD3470 monotherapy to evaluate its safety, tolerability, pharmacokinetics/-dynamics (PK/PD), and preliminary efficacy in a dose-escalation design. Part B dose optimization/expansion cohorts will open at selected dose level(s) to further characterize safety, PK/PD, and efficacy. An interim safety and futility analysis will be conducted in Part B and may trigger expansion of cHL at the recommended phase 2 dose (RP2D) (Part C), as well as testing of AZD3470 in combination with anticancer agents in Module 2 (Figure 1). Patients will be treated until progressive disease, unacceptable toxicity, or withdrawal of consent.

The primary objective is to assess safety/tolerability to determine the RP2D. The secondary objective is to assess preliminary efficacy (Lugano 2014 criteria). Exploratory objectives will evaluate the effect of AZD3470 on tumor biomarkers and correlation with response.

Recruitment for dose escalation (Module 1 Part A) began in January 2024 and is ongoing. The study is planning to enrol across ≈20 sites and is currently enrolling in the following countries: South Korea, Australia, France, Italy, Spain, Germany, UK, and USA.

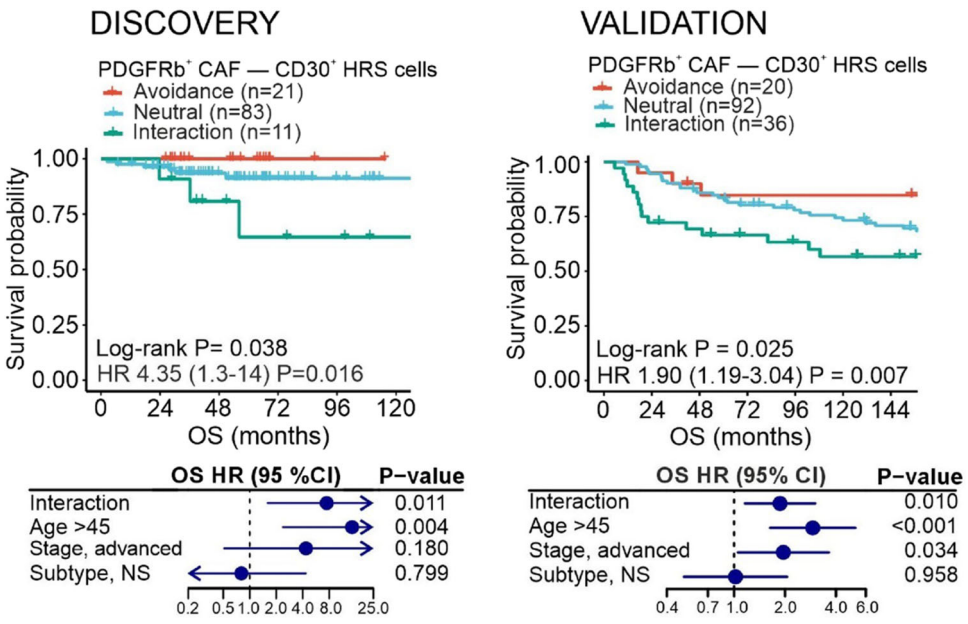
BIOLOGY AND MICROENVIRONMENT

T025: CHARACTERIZATION OF CANCER-ASSOCIATED FIBROBLASTS AND THEIR SPATIAL ARCHITECTURE REVEALS HETEROGENEITY AND SURVIVAL ASSOCIATIONS IN CLASSICAL HODGKIN LYMPHOMA

Kristiina Karihtala[1,2,3], Suvi-Katri Leivonen[1,2,3], Teijo Pellinen[4], Marja-Liisa Karjalainen-Lindsberg[5], Tomohiro Aoki[6,7], Christian Steidl[6], Sirpa M. Leppä[1,2,3]

[1]Research Programs Unit, Applied Tumor Genomics, Faculty of Medicine, University of Helsinki, Helsinki, Finland, [2]Department of Oncology, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland, [3]iCAN Digital Precision Cancer Medicine Flagship, Helsinki, Finland, [4]Institute for Molecular Medicine Finland (FIMM), Helsinki, Finland, [5]Department of Pathology, Helsinki University Hospital, Helsinki, Finland, [6]Centre for Lymphoid Cancer, BC Cancer, Vancouver British Columbia, Canada, [7]Princess Margaret Cancer Centre - University Health Network, Toronto, Ontario, Canada

Figure 1: Survival analysis showing the impact of the interactions between PDGFRb+CAFs and CD30+HRS cells on overall survival (OS) in the discovery and validation cohorts.



Background: Cancer-associated fibroblasts (CAFs) are a heterogeneous population of stromal cells, which modulate the immune system and can have both pro- and anti-tumorigenic effects. The impact of CAFs in shaping the tumor microenvironment (TME) has been recognized in solid tumors, but in classical Hodgkin lymphoma (cHL), their role has remained largely undefined. We aimed to characterize distinct CAF subsets and their interactions with other TME cells and associate the findings with clinical characteristics and outcomes of patients with primary cHL.

Methods: CAFs, macrophages, other leukocytes and Hodgkin Reed-Sternberg (HRS) cells were characterized using multiplexed immunofluorescence imaging in two independent cHL patient cohorts ($n = 131$ and $n = 166$). Image processing and quality control were performed by Ilastik and CellProfiler softwares, and a pretrained deep learning segmentation model was applied to segment the nuclei. Single cell features were extracted using histoCAT software. Phenograph clustering algorithm was utilized for cell phenotyping, and permutation tests by histoCAT and Scimap for interaction and neighborhood analysis.

Results: We identified a total of 952,099 and 2.2×10^6 single cells in the discovery and validation cohorts, respectively. These were split into distinct phenotype metaclusters spanning CAFs, macrophages, leukocytes, and HRS cells. In both cohorts, the median proportion of all CAFs was approximately 20%, being higher in nodular sclerosis (NS) compared to other subtypes. Higher proportions of all CAFs, and more specifically fibroblast activation protein (FAP)-positive CAFs, were associated with favorable outcomes independent of the histological subtype, age, and stage. In contrast, a subset of CD45+ immune cells with strong FAP-positivity, classified as macrophages, was less abundant in the NS subtype and associated with worse outcomes. Neighborhood analysis allowed for the identification of colocalization or regional exclusion of phenotypically defined cell types and recurrent cellular neighborhoods. Despite the positive impact of CAFs on survival, patients with enrichment of platelet-derived growth factor-beta (PDGFRb)-positive CAFs in the vicinity of HRS cells had worse survival in both cohorts, independent of the clinical determinants (Figure 1).

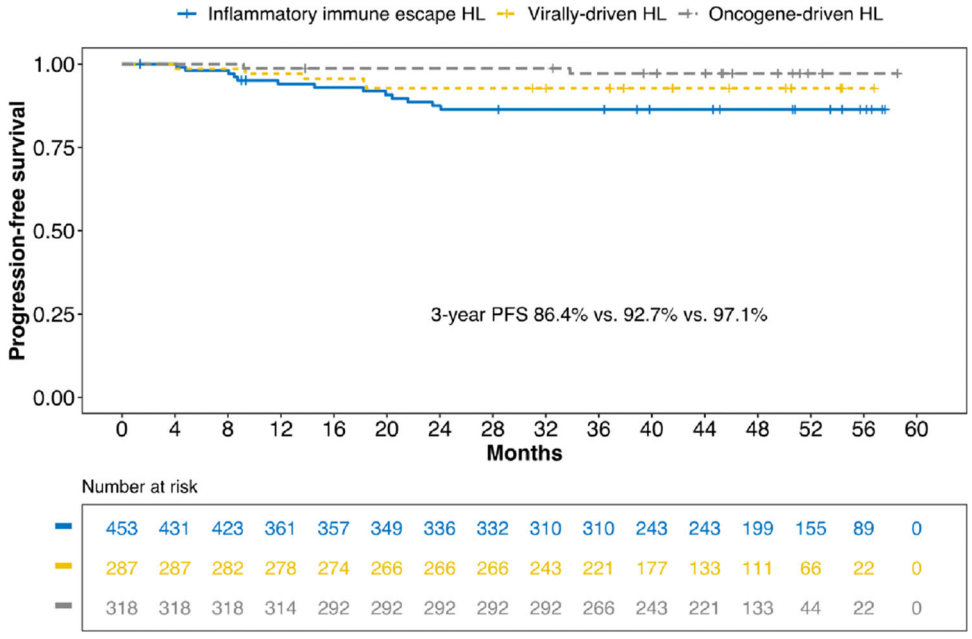
Conclusion: Our findings distinguish various subsets of CAFs and macrophages impacting survival in cHL and underscore the importance of the spatial arrangements in the TME.

T026: CIRCULATING TUMOR DNA SEQUENCING FACILITATES BIOLOGICAL CLASSIFICATION AND INDIVIDUALIZED RISK STRATIFICATION IN PATIENTS WITH HODGKIN LYMPHOMA

Jan-Michel Heger[1], Laman Mammadova[1,2], Julia Mattlener[1,2], Sophia Sobesky[2], Melita Cirillo[3], Janine Altmüller[4], Elisabeth Kirst[4], Sarah Reinke[5], Wolfram Klapper[5], Paul J. Bröckelmann[1,2], Justin Ferdinandus[1,2], Helen Kaul[2], Gundolf Schneider[2], Jessica Schneider[1], Julia Katharina Schleifenbaum[1], Roland T. Ullrich[1], Max Freihammer[1], Sabine Awerkiew[6], Mia Lohmann[7], Florian Klein[6], Peter Nürnberg[8], Michael Hallek[1], Davide Rossi[9], Christine Mauz-Körholz[10], Stefan Gattenlöhner[11], Andreas Bräuninger[11], Peter Borchmann[1,2], Bastian Von Tresckow[7,2], Sven Borchmann[1,2]

[1]Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, University of Cologne, Medical Faculty and University Hospital Cologne, Cologne, Germany, [2]German Hodgkin Study Group (GHSG), Cologne, Germany, [3]University of Western Australia and Royal Perth Hospital, Perth, Australia, [4]Technology platform genomics, Berlin Institute of Health at Charité–Universitätsmedizin Berlin and Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany, [5]Hematopathology Section and Lymph Node Registry, Department of Pathology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany, [6]Institute for Virology, University of Cologne, Cologne, Germany, [7]Department of Hematology and Stem Cell Transplantation, University Hospital Essen, University Duisburg-Essen, German Cancer Consortium (DKTK partner site Essen), Essen, Germany, [8]West German Genome Center (WGGC), University of Cologne, Cologne, Germany, [9]Division of Hematology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland, [10]Pediatric Hematology, Oncology and Immunodeficiencies, Justus-Liebig University of Giessen, Germany and Medical Faculty of the Martin-Luther-University of Halle, Wittenberg, Halle, Germany, [11]Institute for Pathology, Justus Liebig University Giessen, Giessen, Germany

Figure 1: Progression-free survival outcome analysis weighted to reflect the HD21 trial population.



Introduction: The development of biomarkers identifying high-risk Hodgkin lymphoma (HL) patients based on biological risk factors available before treatment initiation remains a high unmet medical need. We previously presented a biological classification of HL consisting of three subtypes based on plasma-derived circulating tumor (ct)DNA sequencing: Inflammatory immune escape HL is characterized by frequent copy number variations including immune escape variants such as high-level amplifications of the PD-L1 locus and an inflammatory tumor microenvironment. Virally-driven HL shows strong association with Epstein-Barr virus (EBV) and/or Human herpesvirus (HHV)6 as well as a tumor microenvironment with increased presence of cytotoxic T-cells and NK-cells. Oncogene-driven HL is defined by a high tumor mutational burden including recurrent mutations in common oncogenic drivers known in HL.

Methods: To assess clinical applicability and prognostic relevance of our classification, we performed a blinded clinical validation in an event-enriched cohort consisting of 72 patients from the GHSG HD21 trial. To increase clinical feasibility, we used a novel, validated assay in this study (LymphoVista HL, validation data presented in a separate abstract at this meeting).

Results: 64/72 (88.9%) patients were successfully assigned to one of the three subtypes. We weighted the outcome analysis to reflect the HD21 trial population. Despite the use of highly efficient treatment regimen in the HD21 trial (eBEACOPP and BrECADD), we were able to detect clinically meaningful differences in progression-free survival (PFS) between Inflammatory immune escape HL (3-year PFS 86.4%), Virally-driven HL (3-year PFS 92.7%), and Oncogene-driven HL (3-year PFS 97.1%) (Figure 1). When additionally assessing minimal residual disease using ctDNA, we were able to identify patients at very high risk of relapse within the subtypes.

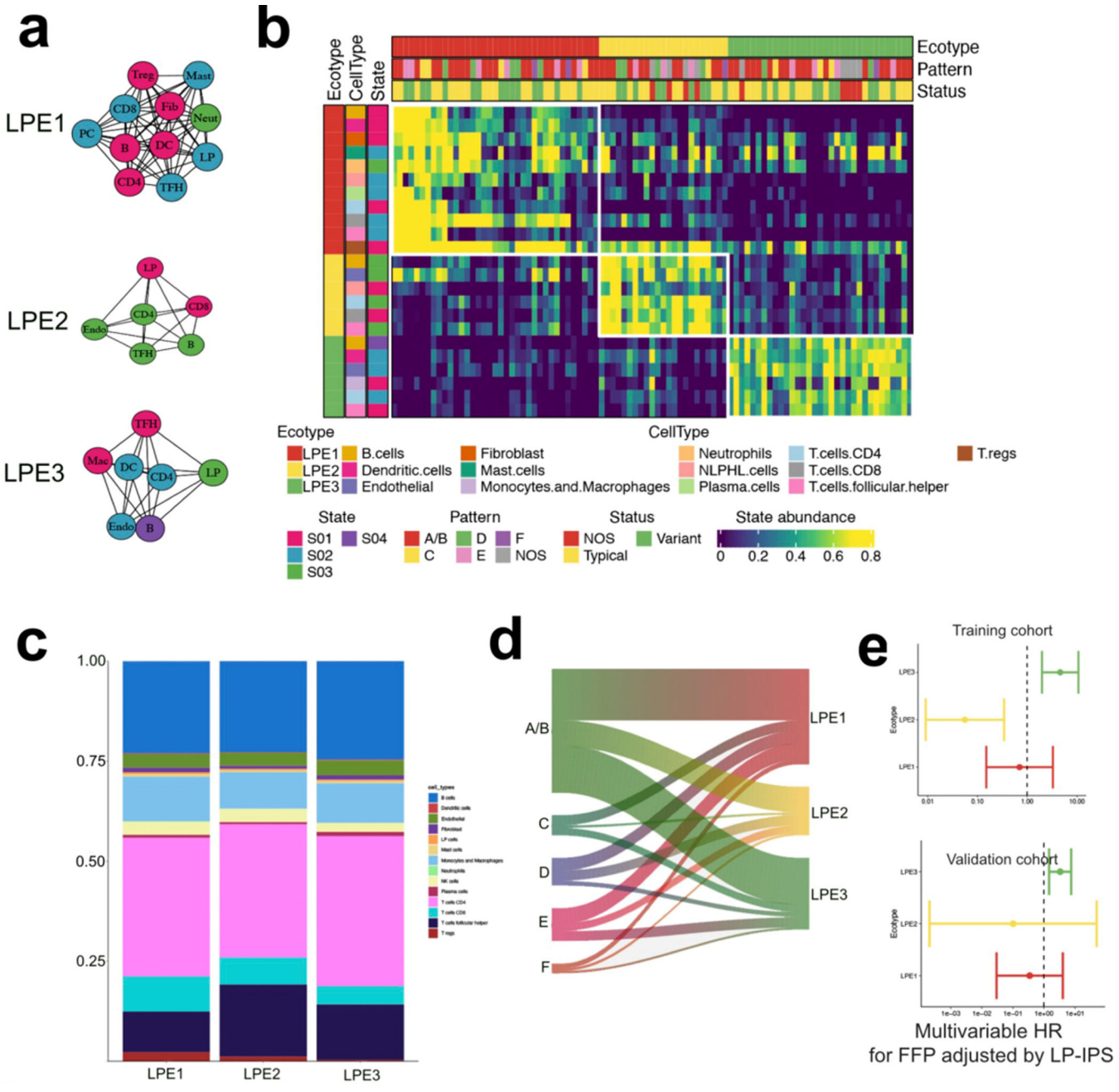
Conclusion: We propose a clinically feasible, noninvasive method for upfront individualized risk stratification in patients with HL based on ctDNA sequencing. MRD assessment during treatment using the same assay further refines risk assessment.

T027: DISTINCT CELL STATE ECOSYSTEMS FOR NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA

Ajay Subramanian[1], Shengqin Su[1], Jamie E. Flerlage[2], Stefan K. Alig[3], Sheren Younes[4], Lianna Marks[5], Chelsea Pinnix[6], Francisco Vega[7], Raphael E. Steiner[8], Priya Kumar[9], Heidi Mocikova[10], Alice Sykorova[11], Vit Prochazka[12], Cristiane Milito[13], Pamela B. Allen[14], Darina Paulino[14], Alan Ramsay[15], Timothy Flerlage[16], Monica Palese[17], Robert West[4], Chunfang Zhu[4], Joseph Schroers-Martin[3], Troy Noordenbos[3], Natalie Park[1], Anusha Kalbasi[1], Everett Moding[1], Aaron Newman[18], Ranjana H. Advani[3], Richard Hoppe[1], Maximilian Diehn[1], Yaso Natkunam[4], Ash A. Alizadeh[3], Michael Binkley[1]

[1]Department of Radiation Oncology, Stanford University, [2]Department of Pediatric Oncology, St. Jude Children's Research Hospital and University of Rochester, [3]Department of Medicine, Division of Oncology, Stanford University, [4]Department of Pathology, Stanford University, [5]Department of Pediatric Oncology, Stanford University, [6]Department of Radiation Oncology, MD Anderson Cancer Center, [7]Department of Pathology, MD Anderson Cancer Center, [8]Department of Medical Oncology, MD Anderson Cancer Center, [9]Department of Pathology, St. Jude Children's Research Hospital, [10]Department of Hematology, Fakultni nemocnice Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic, [11]th Department of Internal Medicine- Hematology, University Hospital and Faculty of Medicine, Hradec Kralove, CZE, [12]Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacky University and University Hospital Olomouc, [13]Federal University of Rio de Janeiro, [14]Department of Oncology, Emory University, [15]University College London Hospitals NHS Foundation Trust, [16]Department of Infectious Diseases, University of Rochester, [17]Department of Pediatric Oncology, University of Rochester, [18]Department of Biomedical Data Science, Stanford University

Figure 1: (a) Network plots and (b) heatmap demonstrate the EcoType defining cell states. (c) Abundance of cell types. (d) Patterns across EcoTypes. (e) Multivariable Cox regression models adjusted for the LP-IPS show LPE3 has worse freedom from progression.



Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare lymphoma, and the microenvironment is characterized by a paucity of lymphocyte-predominant (LP) cells surrounded by abundant immune cells. Few studies have explored the microenvironment, and recent single cell sequencing techniques and atlases may shed light on the cell state phenotypes and their prognostic implications for NLPHL. Here we develop a NLPHL-specific cell type gene expression signature matrix with subsequent utilization in a machine learning framework called EcoTyper to identify 34 distinct cell states across 14 cell types for 171 cases of NLPHL. We found evidence of CD8 T-cell exhaustion, M2 polarized macrophages, immune checkpoint genes expressed by follicular T-cells, and three distinct LP cell states that do not segregate with morphologic variant patterns. These cell states co-occur in 3 LP EcoTypes (LPE1 [46% of cohort], LPE2 [25%], and LPE3 [29%]) with LPE3 portending worse freedom from progression in the training ($n = 109$, HR = 2.74, $p = 0.01$) and validation cohorts ($n = 62$, HR = 2.16, $p = 0.003$) after multivariable adjustment for the LP-international prognostic score. Further, LPE3 appears predictive of worse freedom from progression after single modality but not combined modality therapy in the training and validation cohorts. Using single-nucleus RNA-seq and spatial transcriptomics, we validate the co-occurrence and co-localization of these cell states, respectively. Finally, we reconstructed the B-cell and T-cell receptor repertoires, finding lower diversity for relapse and LPE3 cases. Collectively, identify a new classification of tumor tissue for NLPHL instead of the morphologic variant patterns and show that most patients with NLPHL have a favorable prognosis with a microenvironment characterized by

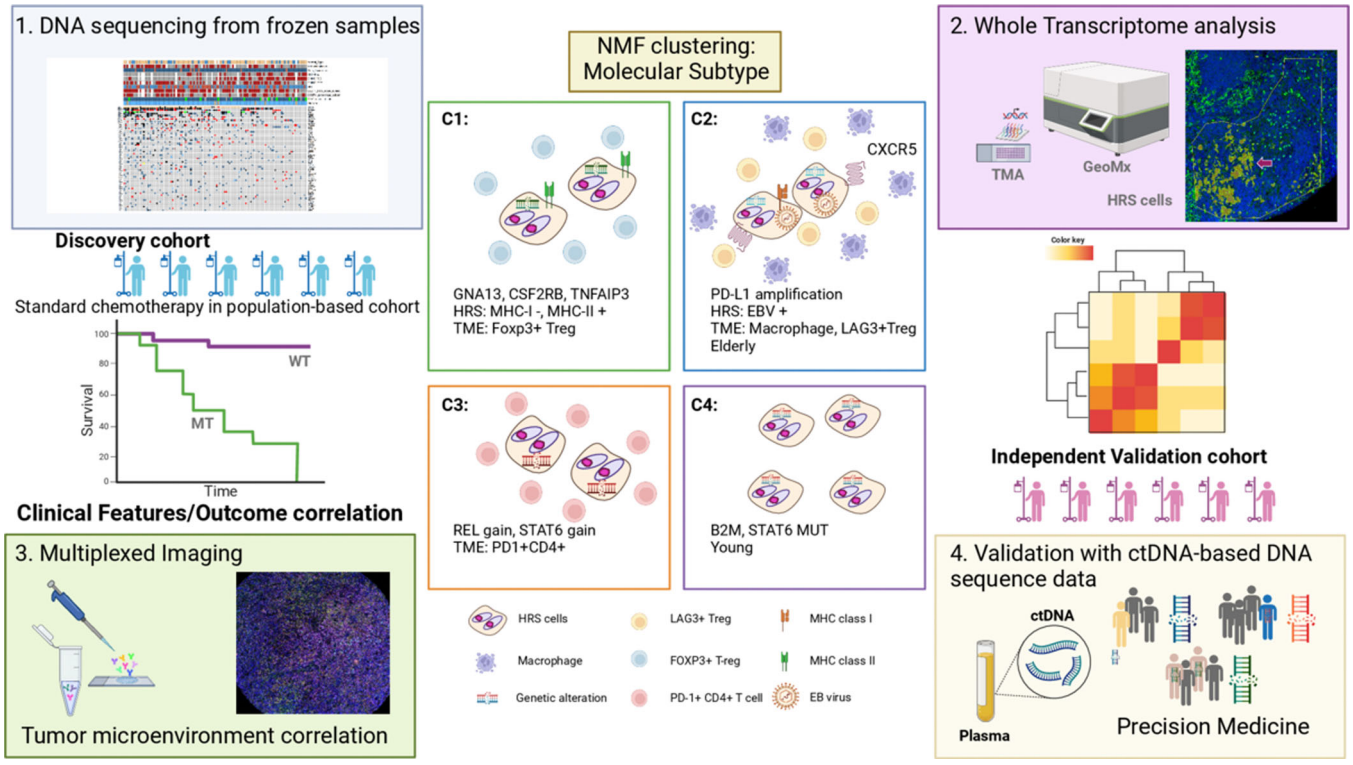
checkpoint immunosuppression and exhausted T cells supporting future trials exploring de-intensification approaches with immune checkpoint inhibitors. Conversely, patients with LPE3 may benefit from upfront combined modality therapy.

T028: MULTI-DIMENSIONAL PROFILING UNVEILS DISTINCT MOLECULAR SUBTYPES IN CLASSIC HODGKIN LYMPHOMA

Tomohiro Aoki[1,2,3], Gerben Duns[1], Shinya Rai[1], Andrew Lytle[1], Yifan Yin[1], Aixiang Jiang[1,2], Stefan K. Alig[4], Mohammad Shahrokh Esfahani[4], Clementine Sarkozy[1,5], Stacy Hung[1], Katy Milne[6], Adele Telenius[1], Makoto Kishida[1], Michael Li[1], Luke O'Brien[1], Celia Strong[6], Talia Goodyear[6], Juan Patino Rangel[3], Michael Hong[3], Shaocheng Wu[7], Katsuyoshi Takata[1,8], Tomoko Miyata-Takata[1], Merrill Boyle[1], Susana Ben-Neriah[1], Andrew P. Weng[9], Andrew Roth[7], Michael Crump[3], John Kuruvilla[3], Anca Prica[3], Robert Kridel[3], Brad H. Nelson[6], Pedro Farinha[1,2], Ash A. Alizadeh[4], Kerry J. Savage[1], David W. Scott[1], Christian Steidl[1,2]

[1]Centre for Lymphoid Cancer, BC Cancer, Vancouver, British Columbia, Canada, [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada, [3]Princess Margaret Cancer Centre-University Health Network, Toronto, Ontario, Canada, [4]Department of Medicine, Divisions of Oncology and Hematology, Stanford University, Stanford, CA, USA, [5]Hematological Department, Institut Curie, Saint Cloud, France, [6]Deeley Research Centre, BC Cancer, Victoria, British Columbia, Canada, [7]Department of Molecular Oncology, BC Cancer, Vancouver, BC, Canada, [8]Division of Molecular and Cellular Pathology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [9]Terry Fox Laboratory, BC Cancer, Vancouver, British Columbia, Canada

Figure 1: To define molecular subtypes of Hodgkin lymphoma, we performed multi-dimensional profiling; (1) DNA sequencing from fresh frozen tissue, (2) Whole Transcriptome Assay, (3) Imaging mass cytometry and (4) ctDNA-based assay in independent validation cohorts.



Introduction: Classic Hodgkin Lymphoma (CHL) is currently classified into four subtypes based on histomorphologic characteristics. However, additional molecular features might help improve disease taxonomy to guide treatment strategies and provide insights into treatment response. Here, we aimed to uncover disease heterogeneity and develop a new classification framework based on multi-dimensional profiling.

Methods: We performed whole exome/targeted sequencing on enriched HRS cells from 116 fresh-frozen CHL biopsies at BC Cancer. In addition, we constructed tissue microarrays from the same cohort and performed GeoMx® Whole Transcriptome Assay of HRS cells and imaging mass cytometry to delineate the spatial tumor microenvironment (TME) ecosystem.

Results: Mutation and copy number analyses identified known recurrent driver events including mutations and copy number changes in SOCS1, STAT6, TNFAIP3, B2M, REL, and the PDL1 locus. ZNF217 mutations was significantly associated with progression-free survival (PFS) ($p < 0.01$), and STAT6 mutation +/− amplification was the most significant feature associated with unfavorable PFS in younger patients (<45) ($p = 0.013$).

To define molecular subtypes of CHL, we applied non-negative matrix factorization consensus clustering and discovered four robust subsets of tumors (clusters) using recurrent genomic events; Cluster1 (C1): mutations in TNFAIP3 and CSF2RB, younger age and loss of MHC-I, C2: old age, EBV and upregulation of the IFN-g pathway; C3: REL and STAT6 gain, and upregulation of a DNA repair signature; and C4: mutations in STAT6 and B2M. TME analyses further identified correlations between each mutational NMF cluster and TME composition (Figure):

C1:FOXP3+Tregs, C2:LAG3+Tregs and CD68+macrophages, C3: PD1+CD4+T cells, C4 = no correlation. We then translated our mutational clustering model into a ctDNA-based classification assay using independent validation cohorts from BC Cancer/UHN ($N = 78$) and Stanford (Alig et al., Nature 2024), and validated the robustness of our model and correlations with clinical features; C2: EBV ($p = 6.30E{-}04$); and C4: younger age ($p = 0.037$).

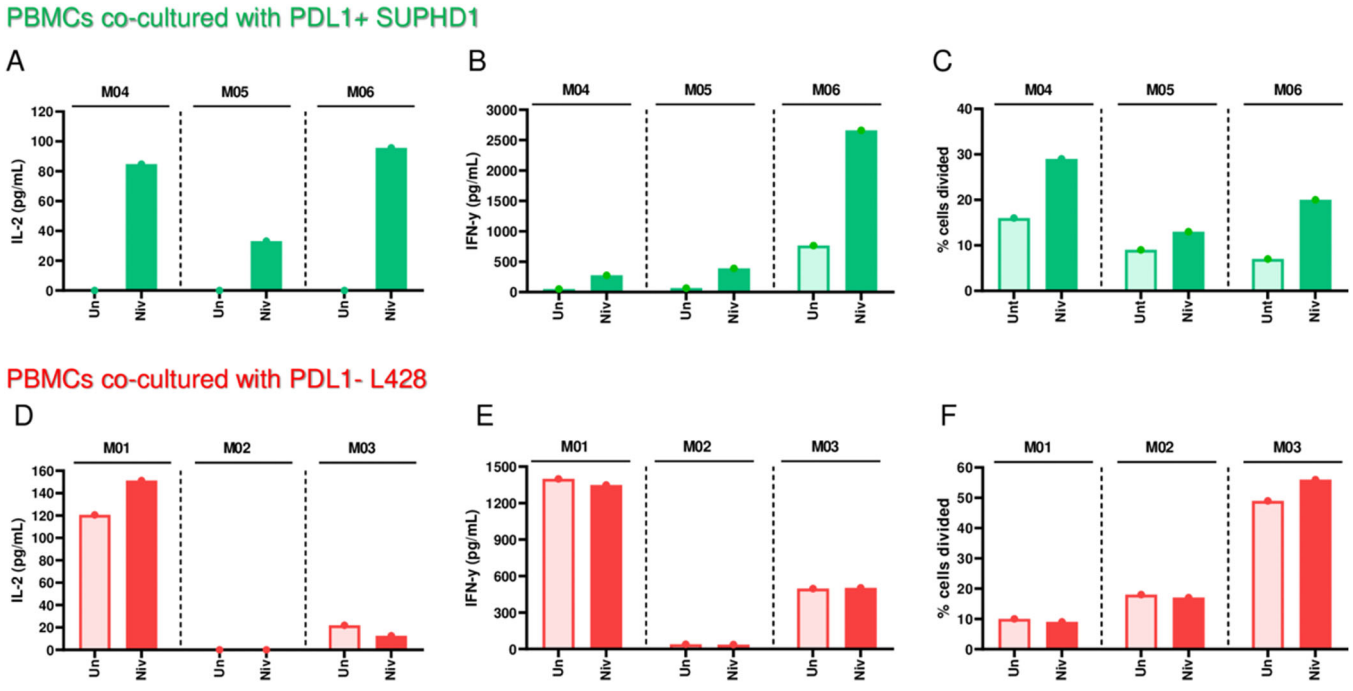
Conclusion: Our multi-dimensional profiling approach delineated molecular profiles of HRS cells linking mutational clusters to distinct TME patterns. These linkages have implications for molecular subtyping of CHL, and cellular vulnerabilities that might be therapeutically exploitable via targeting of HRS cell phenotypes and/or immune escape mechanisms.

P029: A NOVEL IN VITRO MODEL TO STUDY THE EFFECT OF PD1 INHIBITION IN HODGKIN LYMPHOMA AT A MOLECULAR LEVEL

Rodrigo Martinez Alcala[1], Yajie Lei[1], Lydia Visser[1], Arjan Diepstra[1], Johanna Veldman[2]

[1]*University Medical Center Groningen, Dept. Pathology and Medical Biology,* [2]*Netherlands Cancer Institute, Functional oncogenomics for tumor & immunotherapy*

Figure 1: Effect of nivolumab on production of IL-2 and IFNg, and cell proliferation of PBMCs in co-cultures with PDL1+ (A, B, C) and PDL1- (D, E, F) HL cell lines.



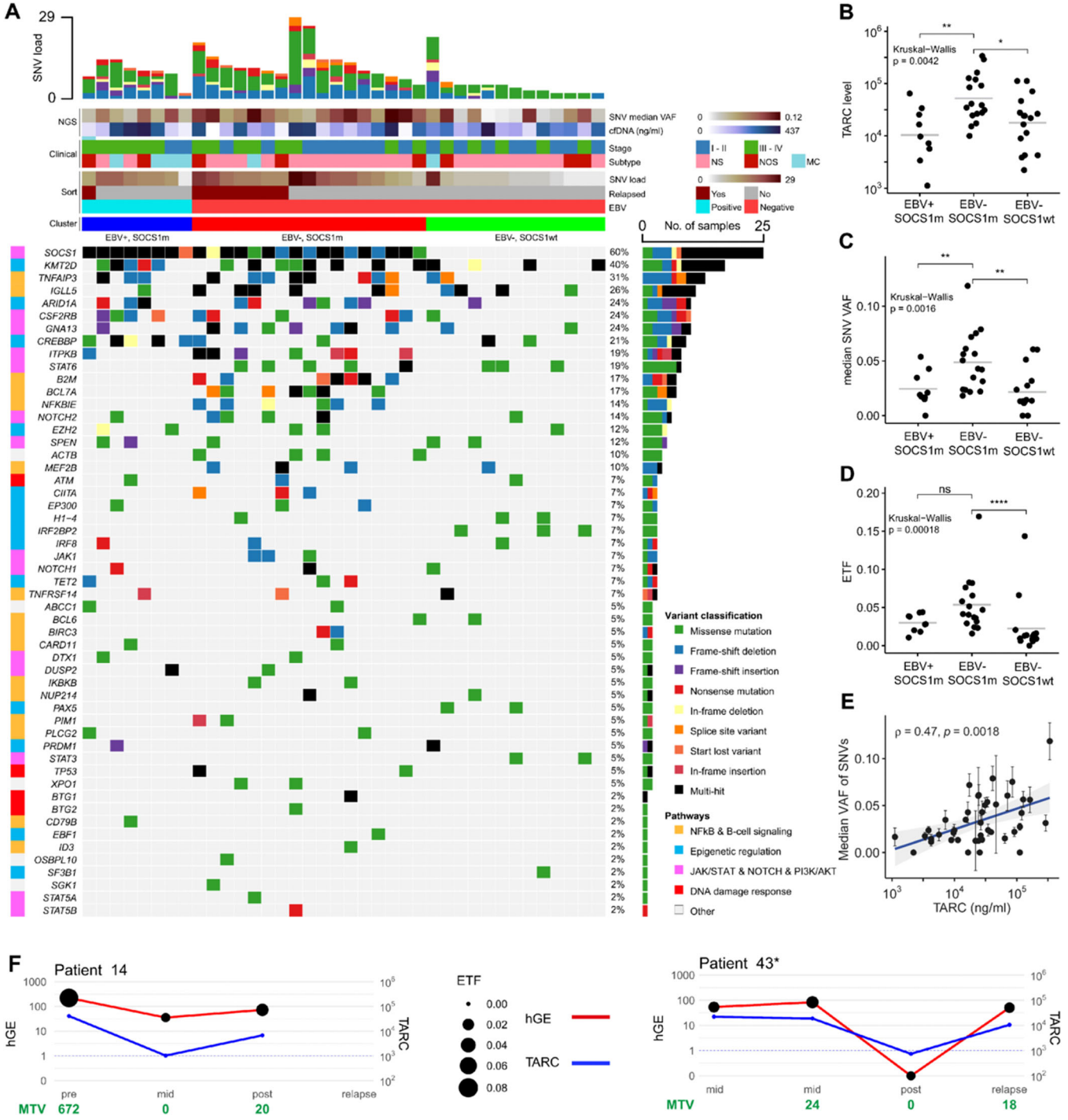
PD1 inhibition in patients with relapsed/refractory Hodgkin Lymphoma (HL) achieves high overall response rates (ORR) ranging from 69% to 80%. While this result is promising, understanding the molecular mechanisms behind this therapy is crucial for maximizing its efficacy. Currently, there is no model that captures the heterogeneous HL microenvironment (TME) to study the effects of PD1 inhibitors on the immune response. Thus, we designed an in vitro model to study the impact of nivolumab (anti-PD1) on immune response by including key aspects of the HL TME. The model consists of two phases. In the initial phase, peripheral blood mononuclear cells (PBMCs) from healthy donors are co-cultured for 7 days with irradiated HL cell lines to upregulate PD1 expression. In the second part on day 7, the PBMCs are treated with nivolumab and co-cultured for 4 more days with newly irradiated HL cell lines. Two HL cell lines with opposite PDL1 expression were used, and each HL cell line was co-cultured with PBMCs from three HLA-II matched donors. Immune activation was assessed by measuring the production of IL-2 and IFNg and monitoring cell proliferation. Nivolumab significantly increased the production of activation cytokines and cell proliferation in co-cultures with PDL1+HL cells. In untreated co-cultures, there was no IL-2 production, but nivolumab significantly increased IL-2 levels to 33–96 pg/mL. For IFNg, untreated co-cultures of two donors showed cytokine levels of 51 and 66 pg/mL, while nivolumab treatment increased levels to 276 and 390 pg/mL. The third donor's IFNg levels surged from 797 to 2660 pg/mL with treatment. Additionally, PD1+CD4 T cell proliferation increased from an average of 11% (7%–16% range) in untreated co-cultures to 21% (13%–29% range) with nivolumab. In contrast, in co-cultures with PDL1-negative HL cells, cytokine levels and PD1+CD4 T cell proliferation varied among donors, without significant differences between treated and untreated groups. In short with our model we found that nivolumab enhances PD1+CD4 T cell proliferation and stimulates the production of immune activation cytokines IL-2 and IFNg in the PDL1+TME. This model allows for further investigation into which factors block the effect of nivolumab and can be used to test other checkpoint inhibitors prior to their use in clinical trials.

P030: CELL-FREE DNA AS POTENTIAL PROGNOSTICATOR AND TRACKING TOOL IN CLASSIC HODGKIN LYMPHOMA: MOLECULAR PROFILING AND CLINICAL CORRELATIONS

Nick Veltmaat[1], Geok Wee Tan[2], Yujie Zhong[2], Sophie Teesink[1], Martijn Terpstra[2], Johanna Bult[1], Marcel Nijland[1], Joost Kluiver[2], Arjan Diepstra[2], Anke Van Den Berg[2], Wouter J. Plattel[1]

[1]*University Medical Center Groningen, Department of Hematology,* [2]*University Medical Center Groningen, Department of Pathology and Medical Biology*

Figure 1: (A) Mutational profile of 42 pre-treatment cHL samples. (B–D) TARC, median VAF of SNVs and ETF compared between the three identified clusters. (E) Median VAF of SNV correlated to TARC. (F) cfDNA dynamics compared to TARC & MTV.



Introduction: Cell-free DNA (cfDNA) analysis is a promising method to study and follow genomic aberrations in classic Hodgkin lymphoma (cHL) before and during treatment. Although TARC levels correlate with cHL disease activity with high positive predictive value, cfDNA holds the

promise to be more sensitive to detect minimal residual disease (MRD). The main goal of this study was to use plasma cfDNA as a non-invasive tool for genomic profiling and compare dynamics during treatment with established biomarkers such as TARC and metabolic tumor volume (MTV).

Methods: We analyzed 42 diagnostic plasma samples of cHL patients and a total of 20 sequential plasma samples from 8 relapsed/refractory (r/r) patients during follow-up that were enriched in our cohort. Copy number variants (CNVs) and estimated tumor fraction (ETF) were determined using low-coverage whole-genome sequencing (lcWGS) data. Single nucleotide variants (SNVs) were called using a custom pipeline on targeted NGS data, as previously described (Veltmaat et al., 2023, JHO). For disease tracking, recurring SNVs detected at baseline were tracked, and expressed as haploid genome equivalents (hGE).

Results: Targeted NGS analysis of cfDNA revealed a median of 9 SNVs per sample, with SOCS1 being the top mutated gene in 60% of cases, followed by KMT2D, TNFAIP3 and IGLL5. Clustering based on EBV status and SOCS1 mutational status resulted in three distinct clusters: EBV+ & SOCS1 mutant (m), EBV− & SOCS1m, and EBV− & SOCS1 wild type (wt). Most r/r cases were observed in the EBV− & SOCS1m cluster (Figure. 1A). This cluster also demonstrated higher TARC levels and higher median VAF of SNVs along with a higher ETF compared to the other clusters (Figure 1A–D). Median VAF of SNVs were strongly correlated with TARC levels (Figure 1E). In the sequential samples, ETF and hGE showed dynamics that were similar to TARC and MTV in most patients. Relapses as defined by MTV and TARC showed an increase in either hGE or ETF in 6/8 patients. Two examples are shown in Figure 1F.

Conclusion: In this study, we showed the feasibility of cfDNA analyses for genomic profiling at diagnosis and disease tracking during treatment. A possible increased risk of relapse in patients within the EBV− & SOCS1m cluster was observed. Improvements in sensitivity should elucidate whether cfDNA can be used as a more sensitive biomarker for MRD in cHL, offering additional information as compared to TARC and imaging.

P031: CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH HODGKINS LYMPHOMA WITH PARANEOPLASTIC MANIFESTATIONS

Charanpreet Singh[1], Lekshmon K S[1], Arihant Jain[1], Alka Khadwal[1], Amanjit Bal[1], Radhika Srinivasan[1], Rajender K Basher[1], Pankaj Malhotra[1], Gaurav Prakash[1]

[1]*Postgraduate Institute of Medical Education and Research, Chandigarh, India*

Table 1: Paraneoplastic Manifestations seen in our cohort

Hematological	8 (2 HLH, 1 AA, 3 ITP, AIHA 2)
Neurological	4 (Neuropathy 2, Cerebellar syndrome 1, NMDA encephalitis 1)
Pruritis	9
Dilated Cardiomyopathy	2
Vanishing Bile duct Syndrome	3
Miscellaneous	3 (Retroperitoneal Fibrosis 1, Ulcerative Colitis 1, Hypercalcemia (no bone disease) 1)

HLH- Hemophagocytic Lympho-Histiocytosis
AA- Aplastic Anemia
ITP- Immune Thrombocytopenia
AIHA- Autoimmune Hemolytic Anemia

Introduction: Paraneoplastic syndromes (PNS) have infrequently been reported in patients with Hodgkins Lymphoma (HL). We describe here the clinical characteristics and outcomes of patients with HL with PNS treated at our center.

Methods: This was a retrospective analysis conducted at a tertiary care center in India. All patients with HL with PNS treated at our center between January, 2018 and March, 2023 were included in the study. Details regarding the demographics, disease characteristics, PNS, treatment characteristics as well as outcomes were noted. An Event was defined as progression or relapse or death due to any cause. Follow-up was censored at 31st March, 2024.

Results: Three-hundred ten patients with newly diagnosed HL were treated at our center during the study period of whom, 29 patients (9.3%) had PNS. The majority of patients were male (n = 18, 62.1%) with a median age of 29 years (IQR 20–36.5). Twenty-three patients (79.3%) had advanced stage disease, while 5 patients (17.2%) and 1 patient (3.4%) had early unfavorable and early favorable disease respectively.

The most common PNS was pruritis (n = 9; 31.1%) followed by hematological manifestations (not due to marrow infiltration) (n = 8; 27.6%). Amongst the hematological manifestations, 3 patients had Immune thrombocytopenia, 2 patients had autoimmune hemolytic anemia, 2 patients had Hemophagocytic Lympho-Histiocytosis and 1 patient had Aplastic Anemia. The details of the PNS are given in Table 1. The majority of patients had a concurrent diagnosis of the PNS and HL (n = 25; 86.2%) and 2 patients each had a diagnosis of PNS before and after the diagnosis of HL respectively.

Twenty-one patients (72.4%) received ABVD therapy initially, 4 patients received COPP, 1 patient received GDP, while 2 patients could not get definitive therapy due to PNS and 1 patient opted against any therapy. Twenty-one patients completed therapy and 16 patients (76.2%) achieved a complete response. Six patients had refractory disease (23.1%) and 2 patients relapsed after achieving remission. The median follow-up for the cohort was 28 months (IQR 16.5–45). Nine patients (31%) died during follow-up, with the most common cause of death being disease related. The median Event Free Survival was 39 months while the median Overall Survival was not reached.

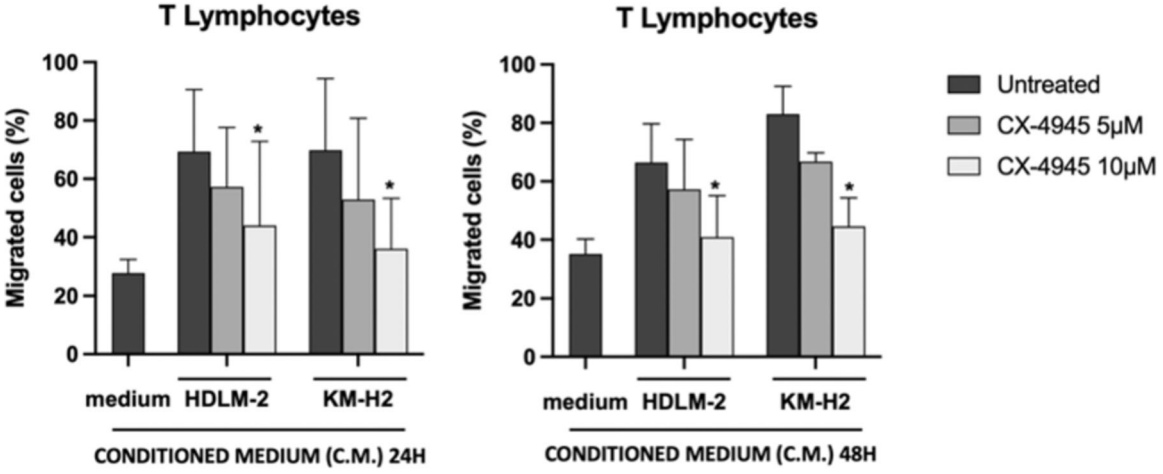
Conclusion: PNS can have a diverse presentation in patients with HL. Treatment can be a challenge given the different organ involvement which may prohibit use of different agents.

P032: CK2 FAVORS T-CELL CHEMOTAXIS THROUGHT THE RELEASE OF SOLUBLE FACTORS BY HODGKIN AND REED–STERNBERG CELLS

Andrea Visentin[1], Federica Frezzato[1], Guido Capasso[1], Nayla Mouawad[1], Maria Castronuovo[1], Alessandro Cellini[1], Francesco Angotzi[1], Andrea Serafin[1], Chiara Adele Cavarretta[1], Valeria Ruocco[1], Arianna Bevilacqua[1], Sabrina Manni[1], Monica Facco[1], Federico Scarmozzino[2], Marco Pizzi[2], Fabrizio Vianello[1], Francesco Piazza[1], Livio Trentin[1]

[1]Hematology Unit, Department of Medicine, University of Padova, Padova, Italy, [2]General Pathology & Cytopathology Unit, Department of Medicine, University of Padova, Padova, Italy

Figure 1: T lymphocyte migration after CK2 inhibition. Histograms show the percentage levels of T lymphocytes migrated across the fibronectin-coated membrane in the presence of CM collected after 24 and 48 h cell cultures.



In classical Hodgkin lymphoma (HL), Hodgkin and Reed–Sternberg (HRS) cells are surrounded by T cells. We recently identified CK2 as a key protein for the survival of HRS cells and how its inhibition triggers apoptosis. In this study, we assess the role of protein CK2 in sustaining T-cell recruitment in the tumor niche.

HL cell lines (KM-H2 and HDLM-2) were treated with 0, 5, and 10 μM of CX-4945 (CX), a CK2 inhibitor, for 24/48 h. Apoptosis was quantified by flow cytometry with the Annexin V/Propidium iodide assay. Migration assays were performed using fibronectin-coated transwells. Conditioned media (CM) from the cell lines, collected after 24/48 h treatment, was added to the bottom chamber. T-cells were purified from age-matched healthy donors. A multiplexed array was used to determine the concentration of 27 cytokines from the supernatants. CXCR3, CCR7 on T-cells, and AKT, STAT3, NF-kB on HL cells lines were assessed by western blot (WB).

In vitro CK2 inhibition by CX was not toxic for donor-derived healthy T cells after 24 or 48 h of culture as opposite to HL cells lines ($p < 0.01$). CX-treated HL cell lines generate a CM with decreased chemoattractant effects on T lymphocytes. The percentage of migrated T lymphocytes toward the CM obtained from HDLM-2 and KM-H2 cells treated with CX 5 and 10 μM for 24 and 48 h decreased by 12.1% and 18%, 25.3% and 34%, respectively, compared to untreated conditions ($p < 0.05$, Figure 1).

In vitro treatment of HL cell lines with CX caused the dephosphorylation of AKT, STAT3 and NF-kB as assessed by WB, likely interfering with production of several cytokines and chemokines. We performed an array analysis to identify CK2-related molecules. Among the tested cytokines, IL-6, M-CSF, RANTES, TARC, TGF-β1, TNF-α, and VEGF, demonstrated a significant CK2 dependence. When HL cell lines were treated with 10 μM CX, there was a significant reduction of IL-6, TARC, TGF-β1, TNF-α, and VEGF release ($p < 0.0001$) and for some molecules also at 5 μM.

We also found that CM from HL cell lines was able to modulate the expression of the T-cell surface receptor CXCR3 but not CCR7, assessed by WB ($p < 0.05$), compared the untreated condition, which was not observed with the CM derived from CX-treated HL cells.

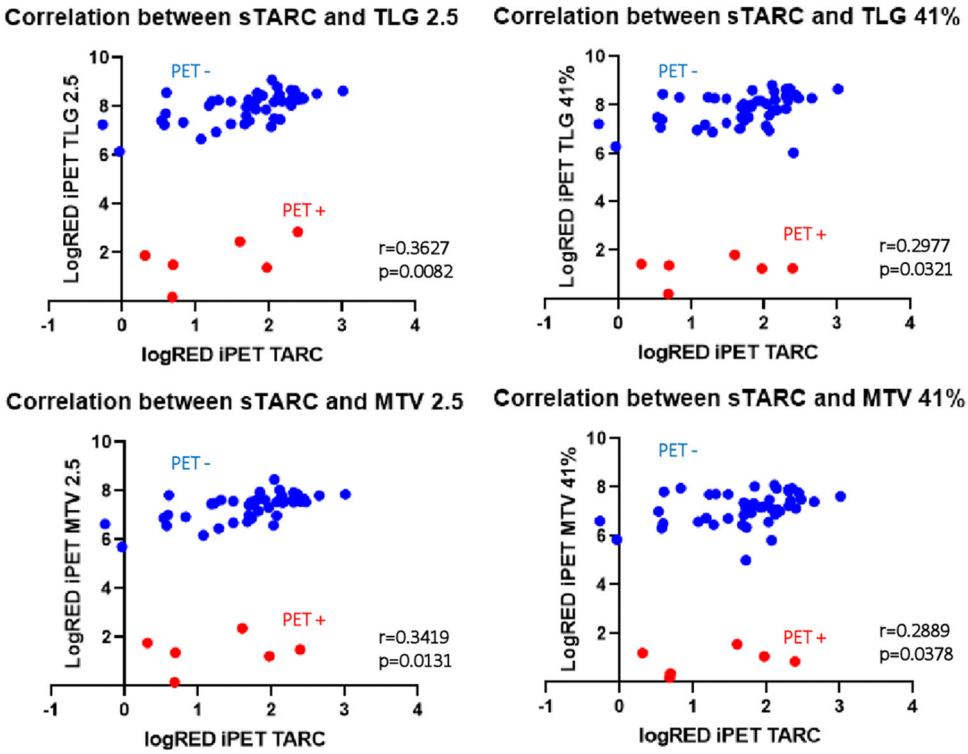
In conclusion, CK2 emerged as a novel player in the formation of HL microenvironment by modulating the release of cytokines from HRS cells molecules that are able to chemoattract and shape chemokines receptor on the surface of T cells.

P033: FINAL ANALYSIS OF CORRELATION BETWEEN SERUM TARC CONCENTRATION AND MTV,TLG IN A COHORT OF CLASSICAL HODGKIN LYMPHOMA DURING FIRST LINE TREATMENT

Benedetta Sordi[1,2], Ciceri Manuel[1,2], Leonardo Signori[1,3], Elisabetta Abenavoli[1,4], Aurora Lombardo[1,4], Ilaria Romano[1,2], Marianna Palazzo[1,2], Giacomo Coltro[1,5,3], Michela Zizza[1,3], Fabiana Pancani[1,3], Luca Nassi[5], Benedetta Puccini[5]

[1]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, [2]Division of Hematology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy, [3]Center for Research and Innovation of Myeloproliferative Neoplasms, Azienda Ospedaliero-Universitaria Careggi, Florence, [4]Department of Nuclear Medicine, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy., [5]Division of Hematology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

Figure 1: LogRED correlation between PET-variables and sTARC.



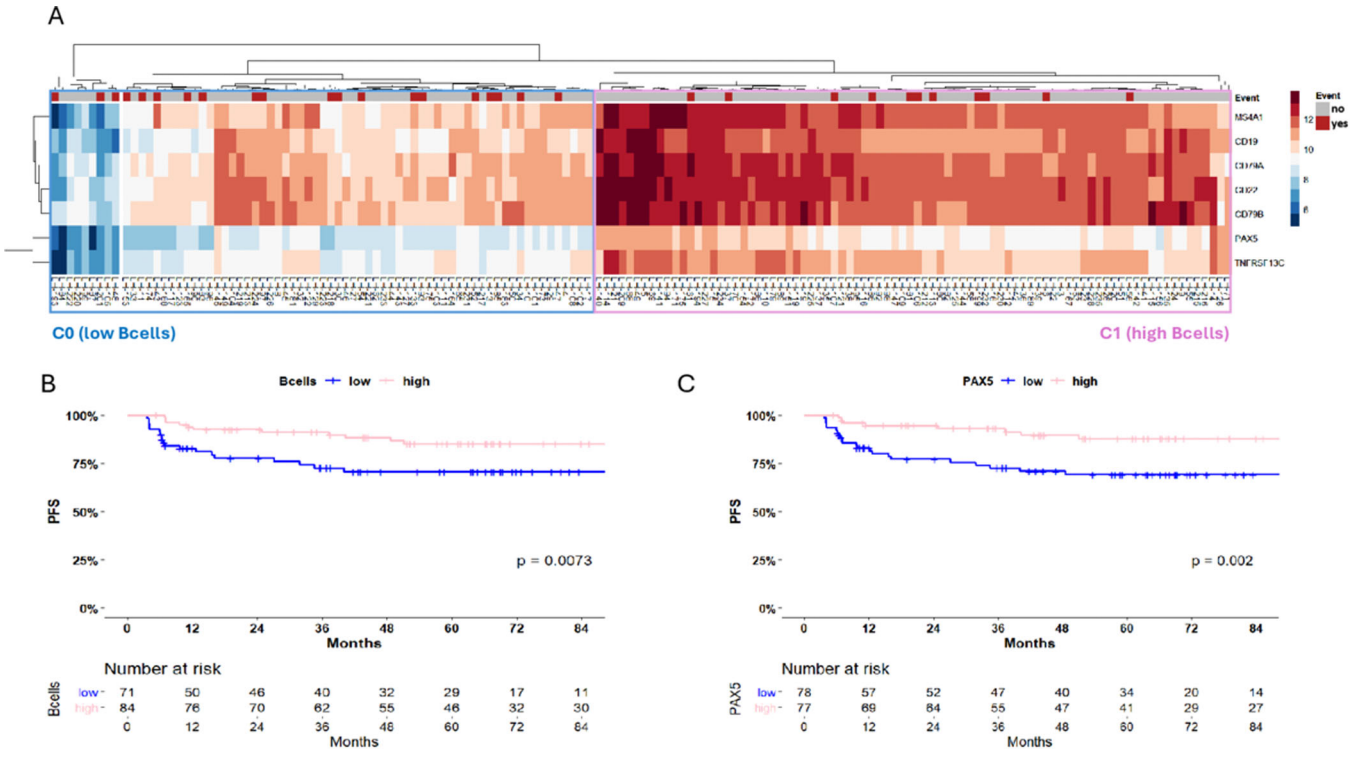
TARC (Thymus and activation-regulated chemokine) is produced by Reed-Sternberg cells in classical Hodgkin's lymphoma (cHL). Correlation between treatment response and serum TARC (sTARC) concentration has been described in several studies. The aim of this one is to evaluate correlation between sTARC and PET variables [metabolic tumour volume (MTV) and total lesion glycolysis (TLG) during first line treatment]. Plasma samples were collected from October, at baseline, after 2 cycles (corresponding with interim PET, iPET), and at the end of treatment (EOT). Thresholds used for measuring MTV and TLG were SUVmax > 2.5 and 41% of the SUVmax. To assess iPET and EOT response, variables were evaluated as logarithmic reduction (LogRED) of baseline vs iPET, and as logarithmic variation (LogΔ) of iPET and EOT. Logβ, logarithmic reduction of baseline vs EOT was added to evaluate pts receiving BV-AVD, being the role of iPET unknown. We enrolled a total of 74 cHL pts: 6 (8%) and 12 pts (16%) were excluded due to missing samples and unavailability of PET images respectively. Total evaluable pts were 56 mostly advanced stage disease (92%). 6 patients (11%) and 9 (16%) patients were iPET and EOT-PET positive. 70 pts (95%) received ABVD regimen, 4 (5%) received BV-AVD which were not evaluated for logRED and LogΔ. A total of 52 pts was evaluable for logRED, 50 and 56 for LogΔ and Logβ. LogΔ and Logβ of sTARC were significantly different in EOT+ versus EOT- pts ($p = 0.0174$ and $p = 0.0092$), but not for LogRED ($p = 0.239$). LogRED, LogΔ and Logβ of PET variables were significantly lower in iPET+ and EOT+ pts compared to iPET- and EOT- pts (LogRED $p < 0.001$; LogΔ $p = 0.0001$ and $p = 0.0003$ for MTV 2.5; Logβ $p < 0.0001$). The correlation between PET variables and sTARC showed a significant trend for LogRED using both thresholds for MTV and TLG, Figure 1. Likewise, LogΔ ($r = 0.5328$, $p < 0.0001$ TLG 2.5; $r = 0.5012$, $p = 0.0002$ for TLG 41%, $r = 0.5159$, $p < 0.0001$ for MTV 2.5 and $r = 0.4929$, $p < 0.0003$ for MTV 41%) and Logβ ($r = 0.3857$, $p = 0.0040$ TLG 2.5; $r = 0.3697$, $p = 0.0059$ for TLG 41%; 0.3783, $p = 0.0048$ for MTV 2.5 and $r = 0.3592$, $p = 0.0076$ for MTV 41%) were significantly correlated with sTARC. The current study shows the deep interconnection between PET variables and and the prognostic relevance, identifying iPET-/EOT-PET+ pts. As far as EOT PET, sTARC can be used as a useful biomarker also with BV-AVD regimen. The prognostic role of TARC should be evaluated in larger studies.

P034: GENE EXPRESSION SIGNATURE REVEALS A PROTECTIVE ROLE OF B-CELLS IN THE PROGRESSION OF CLASSICAL HODGKIN LYMPHOMA PATIENTS

Benedetta Donati[1], Tanja Lazic[2], Maria Elena Nizzoli[3,4], Alberto Bavieri[5], Rexhep Durmo[6], Riccardo Valli[7], Attilio Gennaro[3], Cristian Ascione[1], Alessia Ruffini[8], Stefano Pozzi[3,4], Annibale Versari[6], Francesco Merli[3], Alessia Ciarrocchi[1], Stefano Luminari[3,9]

[1]Laboratory of Translational Research, Azienda USL-IRCCS di Reggio Emilia, Italy, [2]Department of Molecular Medicine, University of Pavia, Pavia, Italy, [3]Hematology Unit, Azienda USL- IRCCS di Reggio Emilia, Reggio Emilia, Italy, [4]PhD Program in Clinical and Experimental Medicine (CEM), University of Modena and Reggio Emilia, Modena, Italy, [5]Hematology Specialization School, University of Modena and Reggio Emilia, Modena, Italy, [6]Nuclear Medicine Unit, Azienda USL-IRCCS, Reggio Emilia, Italy, [7]Pathology Unit, Azienda USL- IRCCS di Reggio Emilia, Reggio Emilia, Italy, [8]Gruppo Amici Dell'Ematologia Foundation-GrADE, Reggio Emilia, Italy, [9]Chimomo Department, University of Modena and Reggio Emilia, Reggio Emilia, Italy

Figure 1: Identification of B-cell-associated gene signature predicting progression-free survival in classical Hodgkin lymphoma patients.



Background: Classical Hodgkin Lymphoma (cHL) is considered highly treatable, but early identification of patients at risk of relapse after initial treatment remains challenging. Disease progression may involve innate features not captured by current prognostic criteria, which can be uncovered through comprehensive molecular analysis. We conducted deep gene expression analysis to identify molecular markers predictive of relapse in cHL patients.

Patients and Methods: We retrospectively reviewed local clinical records to include patients with confirmed cHL diagnosed between 2004 and 2019, aged 18–65, at any disease stage, and treated with systemic chemotherapy (e.g., ABVD or like regimens including BV-AVD). Baseline diagnostic biopsies underwent gene expression analysis using nCounter Nanostring Technology with the PanCancer Immune profiling panel. Genomic data were correlated with clinical, laboratory, and radiomic data, focusing on progression-free survival (PFS) as the primary outcome. Immunohistochemistry was used for validation purposes.

Results: We identified 185 cHL patients, with available FFPE material for 155 cases. Among them, 32% were over 45 years old, 46% had stage III-IV disease, and 10% had Bulky disease. After a median follow-up of 67 months (range, 6–171 months), 31 PFS events were observed, resulting in a 4-year PFS rate of 80.4% (95%CI 74.1–87.3). Using Cox Proportional Hazard modeling, we identified 66 genes significantly associated with PFS ($p < 0.05$). Among these, 41 genes were positively linked to improved PFS, suggesting a protective role and 25 genes were associated with reduced survival probability. Correlation analysis and gene ontology revealed a 7-gene signature related to B-cell pathways. Unsupervised clustering based on this signature identified two distinct patient clusters (Figure 1A). The low B-cell cluster (C0) had higher clinical event rates ($p = 0.03$) and lower PFS rates compared to high B-cell clusters ($p = 0.007$) (Figure 1B). Additionally, high PAX5 expression (a pivotal B-cell regulator) correlated significantly with better PFS (4-year PFS of 90%, 95%CI 82.7–97.3) compared to lower expression levels (4-year PFS: 71%, 95%CI 61.3–82.4) (Figure 1C). Evaluation of PAX5 immune staining in the tumor microenvironment supported its potential prognostic role.

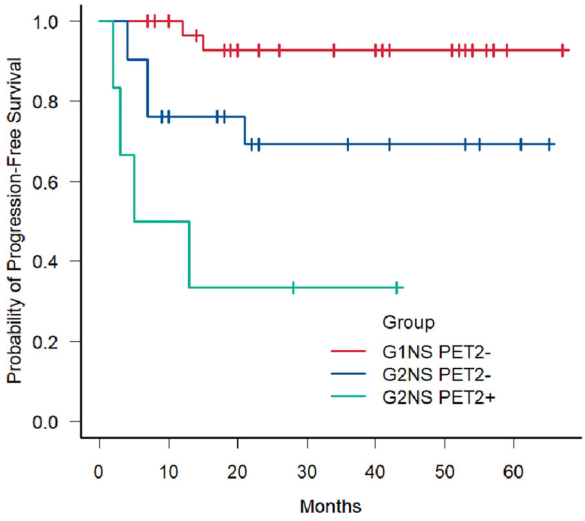
Conclusion: These results suggest gene expression analysis could aid in early relapse detection and underscore the immune-modulatory role of B-cells in cHL progression.

P035: HISTOLOGICAL GRADING IN NODULAR SCLEROSIS CLASSICAL HODGKIN LYMPHOMA IDENTIFIES A SUBGROUP OF PATIENTS WITH HIGHER EARLY RESPONSE RATES AND BETTER PROGNOSIS IN THE CONTEMPORARY TREATMENT ERA

Alessandro Cellini[1], Federico Scarmozzino[2], Chiara Adele Cavarretta[1], Francesco Angotzi[1], Valeria Ruocco[1], Andrea Serafin[1], Nicolò Danesin[1], Michele Gregianin[3], Stefania Vio[4], Filippo Crimi[5], Federica Vianello[6], Francesco Piazza[1], Marco Pizzi[2], Livio Trentin[1], Andrea Visentin[1]

[1]Hematology Unit, Department of Medicine, Padua, Italy, [2]Surgical Pathology and Cytopathology Unit, Department of Medicine, Padua, Italy, [3]Nuclear Medicine Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy, [4]Radiology Unit, Department of Medicine, University of Padua, Padua, Italy, [5]Institute of Radiology, Department of Medicine, University of Padua, Padua, Italy, [6]Radiotherapy Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

Figure 1: PFS in patients with G1 Nodular Sclerosis and a negative PET2 (red), G2 Nodular Sclerosis and a negative PET2 (blue) and G2 Nodular Sclerosis and a positive PET2 (green). PET2-positive G1 patients are not shown due to the to the low number of events.



The grading system for the Nodular Sclerosis (NS) histotype of classical Hodgkin Lymphoma (HL) was initially proposed by the British National Lymphoma Investigation (BNLI) in 1989. Since then, the therapeutic landscape for HL has been shaken by the introduction of a PET-guided approach, as well as by that of novel agents. In this new setting, the impact carried by the two NS grades has been rarely explored. We therefore sought to evaluate how the two different NS grades affected the outcomes of HL patients treated within the modern era.

Eighty-five patients treated at the University Hospital of Padova between 2016 and 2023 were enrolled. NS was graded according to the BNLI criteria, with syncytial and fibrohistiocytic variants being considered as G2. All subjects were treated with PET-adapted ABVD, with a Deauville Score >3 identifying a positive interim PET scan (PET2).

Median age at diagnosis was 33 years (range 17–77), 54% of the individuals were female, 39% presented with B symptoms and 16% had bulky disease. Stage III and IV HL were both diagnosed in 20% of patients, whereas 42% had G1 NSHL and 32% had G2 NSHL. After a median follow-up of 40 months, 22% patients experienced disease relapse, with a 3 yr PFS of 76% (65–84) and no deaths being reported.

The G1NS group had a significantly lower rate of PET2 positivity when compared to the other subjects (6% vs. 22%; $p = 0.04$), with the same trend being observed when the comparison was restricted only to the two NS grades (5% vs. 22%; $p = 0.06$).

A significant difference in survival between the two NS grades was documented, with a 3 yr PFS of 84% for G1NS and 39% for G2NS (HR 5.7 [1.9–17.5]). Such difference was more pronounced in early-stage subjects, where no relapses were documented in G1NS patients, whereas the G2NS subgroup had a 3 yr PFS of 64% ($p < 0.01$). Of note, the grading's impact on PFS remained significant after adjusting for PET2 positivity in multivariate analysis (HR 4.29 [1.15–16.07]). Moreover, a drop in 3 yr PFS was seen going from G1NS PET2- (93%) to G2NS PET2- (69%) and to G2NS PET+ (33%) subjects.

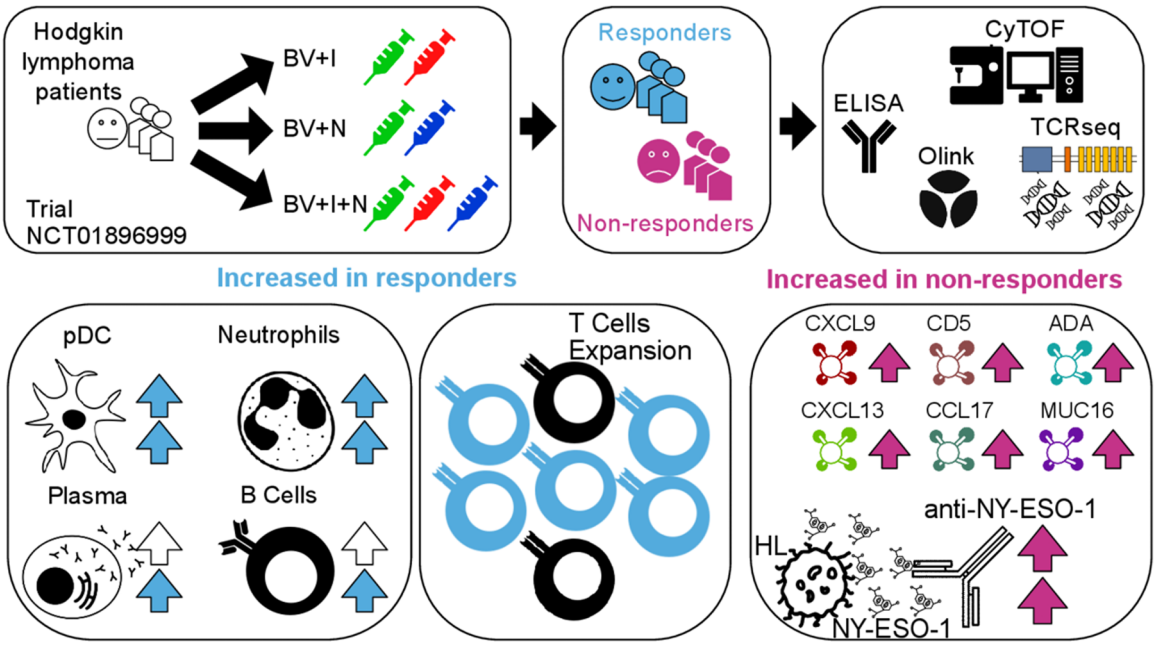
In summary, this study points out the value of NS grading in the contemporary era. While suffering from a low sample size, it shows how G1NS is associated with higher rates of early response, thus harbouring a remarkably good prognosis. Such information should be taken into account in the design of future studies, with the aim to tailor therapeutic strategies to the individual patient's risk.

P036: IMMUNE LANDSCAPE ASSOCIATED WITH RESPONSE TO BRENTUXIMAB VEDOTIN WITH IPILIMUMAB AND/OR NIVOLUMAB IN RELAPSED HODGKIN LYMPHOMA IN E4412 PHASE 1

Catherine Diefenbach[1], Edgar Gonzalez-Kozlova[2], Diane Marie Del Valle[3], Hsin-Hui Huang[4], Opeyemi Jegede[5], Vanessa Barcessat[3], Kevin Tuballes[3], Geoffrey Kelly[6], Manishkumar Patel[6], Hui Xie[6], Jocelyn Harris[6], Kimberly Argueta[6], Kai Nie[6], Radim Moravec[7], Jen Altreuter[8], Dzifa Yawa Duose[9], Brad S. Kahl[10], Stephen M. Ansell[11], Jocye Yu[5], Ethan Cerami[8], James Lindsay[8], Ignacio Wistuba[9], Seunghee Kim-Schulze[12], Sacha Gnjatic[12]

[1]Perlmutter Cancer Center at NYU Langone Health, NYU School of Medicine, New York, NY, [2]Department of Oncological Sciences, Tisch Cancer Institute, Precision Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, [3]Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, [4]Department of Population Health, Icahn School of Medicine, Mount Sinai, New York, [5]Department of Data Science, CIMAC-CIDC Network, Dana Farber Cancer Institute, Boston MA, [6]Human Immune Monitoring Center, Icahn School of Medicine at Mount Sinai, New York, [7]Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, NCI Bethesda, MD, [8]Department of Data Science, CIMAC-CIDC Network, Pipeline Development and Portal Integration, Dana Farber Cancer Institute, Boston MA, [9]Department of Translational Medical Pathology, The University of Texas, MD Anderson Cancer Center, Houston, TX, [10]Washington University School of Medicine, [11]Mayo Clinic, [12]Department of Oncological Sciences, Tisch Cancer Institute, Precision Immunology Institute, Human Immune Monitoring Center, Icahn School of Medicine at Mount Sinai, New York

Figure 1: Graphical Abstract demonstrating our methods and our primary findings.



Background: E4412 an ECOG-ACRIN sponsored phase 1/2, multicenter, open-label trial (NCT01896999) treated patients with refractory or relapsed Hodgkin lymphoma (R/R HL) with the anti-CD30 antibody-drug conjugate (ADC) brentuximab vedotin (BV) in combination with the checkpoint inhibitors targeting CTLA-4 and/or PD-1 (ipilimumab (I) and nivolumab (N). Biomarkers currently have no ability to predict which patients will maximally benefit from these therapies. We investigated the cellular and molecular mechanisms associated with these combination therapies.

Methods: Peripheral blood plasma from 54 of 61 (89%) patients evaluable for response was collected at up to 4 time points and tested for immuno-oncology soluble analytes with Olink and for antibody titers to known tumor antigens by ELISA. Matching PBMC were analyzed by CyTOF mass cytometry for major immune cell subsets and marker surface expression, and for T cell receptor diversity by Immunoseq®. Mixed effect and Cox linear models were used to identify significantly associated changes ($p < 0.05$) related to treatment longitudinally within groups and to overall response rate (ORR) between groups.

Results: NCT01896999 reported high (>75%) ORR. Posttreatment, we observed durable increase in soluble PD-1 and plasmacytoid dendritic cells as well as decreases in plasma CCL17, ANGPT2, MMP12, IL13, and CXCL13 in N-containing regimens (BV+N and BV+I+N) compared with BV+I ($p < 0.05$). Non-responders and patients with short progression free survival showed elevated CXCL9 and MUC16 at baseline and an increase of CXCL13, CD5, CCL17 and ADA post-treatment. NY-ESO-1 autoantibodies were more frequent in non-responders ($p < 0.05$), and expanded TCR clonotypes were increased in responders after one treatment cycle ($p < 0.15$).

Conclusion: This data reveals differential immune activation based on treatment modality. Our data highlights potential tumor and immune derived predictive and pharmacodynamic biomarker candidates of response. Identification of multi-omic immune markers from peripheral blood may help elucidate resistance mechanisms to checkpoint inhibitor and antibody drug conjugate combinations with potential implications for treatment decisions in relapsed HL and in earlier lines of therapy. Prospective evaluation of these biomarkers in the Phase II component of this study, a randomized comparison of BV+N vs. BV+N+I which has completed accrual, is planned.

P037: IMPACT OF CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL IN CLASSICAL HODGKIN LYMPHOMA

Caroline Hesselager[1], Peter Hollander[1], Ann-Sofie Johansson[2], Johan Linderoth[3], Gunilla Enblad[1], Simone Weström[4], Daniel Eriksson[4], Arielle R. Munters[4], Daniel Molin[1], Panagiotis Baliakas[4], Rose-Marie Amini[1]

[1]Uppsala University and Uppsala University Hospital, Department of Immunology, Genetics and Pathology, Uppsala, Sweden, [2]Umeå University, Department of Radiation Sciences, Oncology, Umeå, Sweden, [3]Lund University Hospital, Department of Oncology, Lund, Sweden, [4]Uppsala University, Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala, Sweden

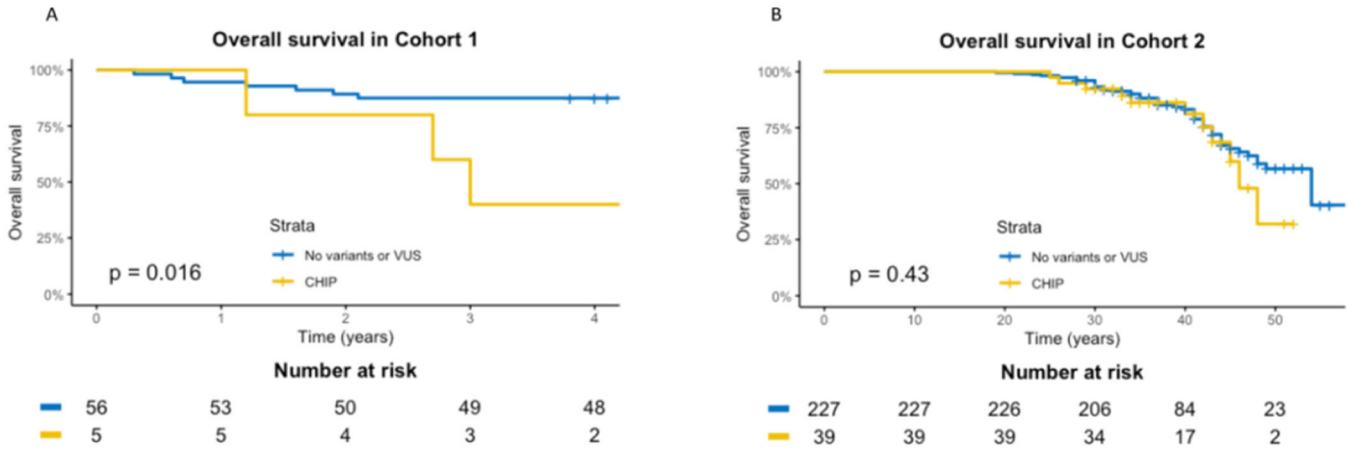


Figure 1: A. Overall survival in Cohort 1 (n=61), B. Overall survival in long-term survivors, Cohort 2 (n=266)

Background: Clonal hematopoiesis of indeterminate potential (CHIP) has been associated with an increased risk of cardiovascular diseases (CVD) in addition to developing myeloid neoplasias. Long-term survivors of classical Hodgkin lymphoma (cHL) have a risk of cardiovascular side effects. The aim of this study was to examine the prevalence and clinical impact of CHIP in patients with cHL in relation to CVD.

Materials/Methods: Blood samples were collected in cHL patients at diagnosis before treatment in a cohort diagnosed from 2010 to 2020 (n = 61) (Cohort 1) and after treatment (mean time from diagnosis 25 years) in a cohort of long-time survivors (n = 266) diagnosed between 1965 and 1995 (Cohort 2). Next generation sequencing (NGS) on DNA extracted from blood, with a targeted gene panel covering either full coding region or hotspot region of 33 genes with a sensitivity of a variant allele frequency (VAF) down to 2% was performed.

Results: Mutations classified as pathogenic (P)/likely pathogenic (LP) were detected in 39 (15%) long-term survivors compared to 5 (8%) in cHL patients in Cohort 1. An inferior overall (OS, Figure 1A) and event-free survival (EFS) was observed in cHL patients in Cohort 1 with mutations at diagnosis compared to those with no variants (n = 41) and/or variants of unknown significance (VUS) (n = 15). There were no survival differences in Cohort 2 of long-term survivors with P/LP mutations vs no variants/VUS (Figure 1B). In 111/266 (42%) long-term survivors a CVD was diagnosed (hypertension (n = 58), valvular disease (n = 44), angina pectoris (n = 31), ischemic myocardial infarction (n = 19), stroke (n = 8) and other (n = 38). There was no difference in frequencies of CVD side effects between patients with P/LP or no variants in cohort 2 of long-term survivors, whereas patients with VUS had a lower frequency (17%). The mutational landscape varied, with the most commonly mutated genes in the P/LP categories being DNMT3A (n = 12), TET2 (n = 9) and PPM1D (n = 9), and in the VUS category, ZRSR2 (n = 10), CEBPA (n = 9), KDM6A (n = 8) and ASXL1 (n = 8).

Conclusions: Detection of P/LP mutations in cHL patients at the time of diagnosis seems to affect survival. For long-time survivors, mutations detected after treatment does not affect survival and CHIP mutations does not seem to play a major role in the development of cardiovascular side effects.

P038: MOLECULAR PATHOGENESIS OF HODGKIN LYMPHOMA

Lilian Beeck[1], Bettina Budeus[1], Markus Schneider[1], Navid Farsijani[2], Julia Bein[3], Sylvia Hartmann[3], Martin-Leo Hansmann[4], Ralf Küppers[1]

[1]Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, Essen, Germany, [2]Department of Haematology, University of Duisburg-Essen, Essen, Germany, [3]Dr. Senckenberg Institute of Pathology, Goethe University of Frankfurt, Frankfurt, Germany, [4]Frankfurt Institute of Advanced Studies, 60438 Frankfurt am Main, Germany

Classical Hodgkin lymphoma (cHL) is one of the most frequent lymphomas in the Western world. Its malignant Hodgkin and Reed/Sternberg (HRS) cells are derived from pre-apoptotic germinal center B cells and only account for ca. 1% of the tumor cell mass. The surrounding inflammatory infiltrate is unable to establish an effective immune response against the HRS cells. To better understand HRS cell formation and their molecular pathogenesis, we aim to determine the mutational landscape of HRS cells. HRS cells of a total of 30 cases were isolated by microdissection or flow cytometry and subjected to exome or whole-genome sequencing. We confirmed recurrently mutated genes (e.g., SOCS1, TNFAIP3) but also found novel promising genes such as NLRC5, which is involved in MHCI expression and negative NFkB regulation. Intriguingly, mutational signatures associated with APOBEC and somatic hypermutation were identified. Moreover we analyzed the WGS samples for mutations in gene regulatory regions, miRNA binding sites and structural variants. Both WGS and WES show a wide variation in their mutational loads.

P039: NEW UNDERSTANDING OF ONCOGENIC MECHANISMS IN CLASSICAL HODGKIN LYMPHOMA

Maria Cristina Pirosa[1], Matin Salehi[1], Alessio Bruscaggin[1], Lodovico Terzi Di Bergamo[1], Federico Jauk[1], Gabriela Forestieri[1], Simone Bocchetta[1], Deborah Piffaretti[1], Riccardo Moia[2], Vanessa Cristaldi[3], Martina Di Trani[3], Georgia Alice Galimberti[1], Katia Pini[1], Valeria Spina[1], Claudia Giordano[4], Adalgisa Condoluci[1], Salvatore Annunziata[5], Fabrizio Bergesio[6], Renzo Boldorini[7], Eugenio Borsatti[8], Pietro Bulian[9], Stephane Chauvie[6], Marco Cuzzocrea[10], Bernhard Gerber[11], Michał Kurlapski[12], Luigi Maria Larocca[13], Andrea Rinaldi[14], Marcello Rodari[15],

Grzegorz Romanowicz[16], Gian Mauro Sacchetti[17], Anastasios Stathis[11], Georg Stüssi[11], Ilaria Zangrilli[18], Eleonora Calabretta[3], Francesco Corrado[3], Antonio Pinto[19], Luca Mazzucchelli[20], Valter Gattei[9], Jan Maciej Zaucha[12], Armando Santoro[21], Stefan Hohaus[18], Franco Cavalli[22], Emanuele Zucca[11], Gianluca Gaidano[2], Carmelo Carlo-stella[3], Alexandar Tzankov[23], Luca Ceriani[10], Davide Rossi[1]

[1]Laboratory of Experimental Hematology, Institute of Oncology Research, Bellinzona, Switzerland, [2]Division of Hematology, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy, [3]Department of Biomedical Sciences, Humanitas University, Milan, Italy, [4]Department of Clinical Medicine and Surgery, Federico II University Medical School, Naples, Italy, [5]UOC Medicina Nucleare, GSTeP Radiopharmacy TracerGLab, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [6]Department of Medical Physics, Santa Croce e Carle Hospital, Cuneo Italy, [7]Pathology Department, Ospedale Maggiore della Carità, University of Eastern Piedmont, Novara, Italy, [8]Nuclear Medicine, Centro di Riferimento Oncologico, Aviano, Italy, [9]Clinical and Experimental Onco Hematology Unit, Centro di Riferimento Oncologico, Aviano, Italy, [10]Clinic of Nuclear Medicine and Molecular Imaging, Imaging Institute of Southern Switzerland, Bellinzona, Switzerland, [11]Clinic of Hematology, Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland, [12]Department of Hematology and Bone Marrow Transplantation, Medical University of Gdańsk, Gdańsk, Poland, [13]Division of Pathology, Fondazione Policlinico Universitario Agostino Gemelli, Catholic University of the Sacred Heart, Rome, Italy, [14]Genomics Facility, Institute of Oncology Research, Bellinzona, Switzerland, [15]Unit of Nuclear Medicine, Humanitas Research Hospital, Milan, Italy, [16]Department of Nuclear Medicine, Medical University of Gdańsk, Gdańsk, Poland, [17]Nuclear Medicine, Ospedale Maggiore della Carità, Novara, Italy, [18]Department of diagnostic imaging, oncological radiotherapy and hematology, Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy, [19]Hematology-Oncology and Stem Cell transplantation Unit, National Cancer Institute, Fondazione "G. Pascale", Naples, Italy, [20]Division of Pathology, Ente Ospedaliero Cantonale, Bellinzona, Switzerland, [21]Department of Oncology and Hematology, Humanitas Research Hospital, Milan, Italy, [22]Fondazione per l'Istituto Oncologico di Ricerca, Bellinzona, Switzerland, [23]Pathology, Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Switzerland

Background: We leveraged advanced ctDNA analytic methods to present an in-depth overview of the genetic landscape of classic Hodgkin lymphoma (cHL) and its connection to disease pathophysiology and clinical course.

Methods: cHL cases (*N* = 297) from the IOSI-EMA003-NCT03280394 and FIL-RougeBIO-NCT05066555 studies were assessed by LyV4.0 ctDNA CAPP-seq.

Results: An expression quantitative trait locus (seQTL) of the BCL6-intragenic super-enhancer (SE) was identified in 30% of cHL, and impeded the binding of PRDM1 to BCL6. The BCL6 seQTL aligns with an area of accessible chromatin and heightened H3K27 acetylation in cHL, which was nominated a SE in cHL cell lines expressing BCL6. Notably, the BCL6 seQTL was found to co-occur with BCL6 expression in cHL cell lines and HRS cells of primary biopsies, despite the co-expression of PRDM1. BCL6 expression ranging from weak to strong was detected in the nucleus of HRS cells of 68% of primary biopsies. The core set of genes that are directly bound and regulated by BCL6 exhibited similar expression levels and chromatin accessibility in GCB cells and in BCL6 expressing cHL cell lines. BCL6 protein degradation was observed with BI-3802 in cell lines expressing BCL6. After BCL6 degradation, the core set of BCL6 genes was similarly derepressed in cHL cell lines as in DLBCL cell line. Compared to the BI-5372 control molecule, treatment with BI-3802 significantly decreased proliferation in all cell lines where BCL6 degradation was observed. Whole genome duplication (WGD) was prevalent in cHL (24%) and independently and reproducibly linked to a lower PFS after initial treatment (30-months PFS: 63% in the training and 65% in the validation cohorts). The endoreduplication-tolerance CCNE1 gene was amplified in 13% cHL and associated with WGD. Genetic clustering identified two subgroups, with C1 (32%) exhibiting a higher proportion of EBV infection, minimal STAT6 mutations, and limited aneuploidy. "Macrophage" (52%) and a "T-cell" (48%) microenvironments were deconvoluted by RNA-seq and orthogonally validated by tissue microarrays. The number of predicted MHC-I/MHC-II neoantigens was higher in patients with "macrophage" than with "T-cell" microenvironment, consistent with the selective pressures exerted by T-cells.

Conclusion: This study broadens the understanding of known oncogenic mechanisms in cHL development and identifies novel deregulated gene targets (BCL6) relevant to therapy and prognostic biomarkers (WGD).

P040: PLASMA PROTEINS AND HODGKIN'S LYMPHOMA: PROTEOME-WIDE MENDELIAN RANDOMIZATION AND COLOCALIZATION ANALYSES

Tao Pan, Jiyue Zhang, Xiaomin Wang, Yuqin Song

Exposure	deCODE		UKB-PPP		Target type
	β	*P*-value	β	*P*-value	
ADK	2.931	1.16e-05	/	/	Clinical trial Target
ADAMTSL2	1.512	4.16e-05	1.154	2.56e-03	/
DKKL1	4.717	8.46e-05	/	/	/
DBNL	-1.629	0.028	-2.107	0.022	/
BRD2	3.057	0.037	0.042	0.971	Clinical trial Target
ISOC1	-0.374	0.047	/	/	/
BTN3A1	-2.664	0.047	/	/	/
BCL2	/	/	2.891	0.034	Successful Target
CD270	/	/	-1.040	0.015	Literature-reported Target
S100P	/	/	-0.595	0.028	/

Table 1: Protein-phenotype associations identified by Mendelian randomisation.

Background: Hodgkin lymphoma (HL) is an uncommon malignancy of B-cell origin. Classical HL (cHL) and nodular lymphocyte-predominant HL are the two main types of HL. It has been reported that the proteome in blood was an important source for biomarker and therapeutic target discovery. However, up to now, few proteomes have been identified with the risk of HL.

Methods: Here, we conducted a proteome-wide Mendelian randomization (MR) study and colocalization analyses to decipher candidate protein markers and therapeutic targets for Hodgkin's lymphoma (HL). Genome-wide association studies (GWASs) on 3083 plasma proteins are derived from 54,219 UK Biobank participants (UKB-PPP) and 35,559 Icelanders (deCODE). Genetic associations with HL were obtained from the FinnGen cohort (864 cases and 324,650 controls). Additional analyses including Bayesian colocalization, protein-protein interaction, pathway enrichment analysis, and evaluation of drug targets were conducted to deepen the understanding and identify potential therapeutic targets of HL.

Results: Our research suggested that 10 candidate proteins might have a significant causal relationship with the risk of HL. Elevated levels of 5 proteins (ADK, ADAMTSL2, DKKL1, BRD2, BCL2) and decreased levels of 5 proteins (DBNL, CD270, S100P, ISOS1, BTN3A1) were associated with an increased risk of HL, in which ADK was prioritized with the most convincing evidence ($p < 1.62e{-}05$, 0.05/3083 proteins). ADAMTSL2 was supported by strong evidence of genetic co-localization. 4 proteins were found to be the targets of existing or potential drugs. BCL2 was a successful target, ADK and BRD2 were clinical trial targets, and CD270 was a literature-reported target.

Conclusions: Our study identified several important proteins that were associated with HL risk. It might shed light on protein-mediated mechanisms of HL and offer promising therapeutic targets for HL patients.

P041: PROTEOMIC PROFILE IN CLASSICAL HODGKIN LYMPHOMA PATIENTS WITH HIGH INFLAMMATION

Jeremia Collin[1], Ragnhild Risebro[1], Johan Mattsson Ulfstedt[1], Emma Pettersson[1], Mats Hellström[1], Ingrid Glimelius[1], Mattias Berglund[1], Gunilla Enblad[1], Eva Freyhult[2], Daniel Molin[1]

[1]Department of Immunology, Genetics, and Pathology, Uppsala University, Uppsala, Sweden, [2]Department of Cell and Molecular Biology, National Bioinformatics Infrastructure Sweden, Science for Life Laboratory, Uppsala University, Uppsala, Sweden.

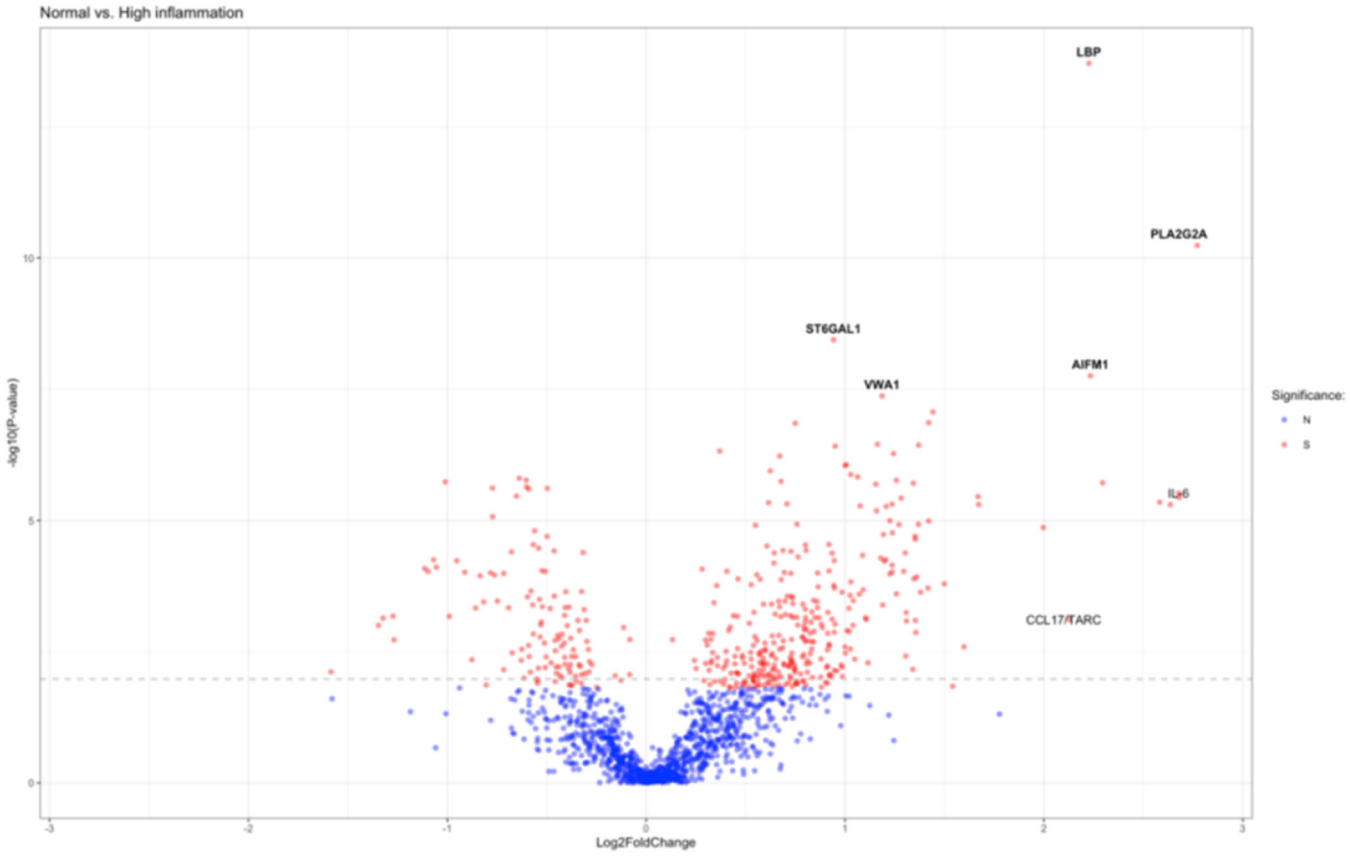


Figure 1: Differential protein expression in plasma at diagnosis of classical Hodgkin lymphoma patients without (left side), and with high inflammation, ESR>75 (right side). The x-axis represents the log2foldchange and the y-axis -log10(p-value).

Background: Classical Hodgkin lymphoma (cHL) is, in many cases, characterized by pronounced inflammation, with a very high erythrocyte sedimentation rate (ESR) and presence of B-symptoms. In contrast, a number of patients have no signs of inflammation. There is a lack of structured knowledge about the clinical characteristics of these groups as well as understanding of the biological mechanisms behind the different clinical presentations.

Method: We compared patients with a high level of inflammation (ESR > 75, $n = 25$) with a group of patients without clear signs of inflammation (normal ESR according to age and sex, $n = 32$). Clinical data was retrieved from medical records and serum samples were analyzed with comprehensive OlinkTM multiplex protein panels (Oncology, Cardiometabolic, Neurology, Inflammation, 1536 proteins in total). All patients from the regional biobank U-CAN, with clinical and proteomic data available were included. Analyses were also made with upper normal level of ESR as a cut off ($n = 60$, $n = 32$). Linear regression was made for each protein adjusted for age, sex and stage, as well as pathway analysis.

Results: No significant differences were seen between the groups regarding sex, age, stage or histology. Proteins that were most significantly overexpressed in the high inflammation groups were LBP, ST6GAL1, PLAG2A, AIFM1, and VWA1. IL-6 was also significantly elevated and IL-6 and LBP were found to be highly correlated. TARC was significantly overexpressed, but not ranked among the proteins with the lowest adjusted p-value.

Discussion: There seems to be two distinct types of cHL, characterized by no versus very high level of inflammation, that are not significantly associated to histology or other clinical characteristics. The elevated expression of LBP in the groups with high inflammation suggests it having a central role in the inflammatory response in cHL. The results also demonstrate a potential linkage with IL-6 which has been described earlier in patients with severe Covid-19 (Messner et al., 2020). PLAG2A has been associated with inflammatory diseases such as rheumatoid arthritis, as well as poor prognosis in different gastrointestinal cancers but is not previously described in cHL. Further investigations are underway to clarify the role of each protein and their interactions within the inflammatory response in cHL. The difference in protein expression supports the hypothesis of the two groups being biologically different.

P042: PROTEOMIC PROFILING IDENTIFIES CLASSIC HODGKIN LYMPHOMA PATIENTS AT RISK OF BLEOMYCIN PULMONARY TOXICITY

Maja Dam Andersen[1,2], Katharina Wolter[1], Marie Hairing Enemark[1,2], Kristina Lystlund Lauridsen[3], Stephen Jacques Hamilton-Dutoit[3], Jørn Starklint[4], Francesco D'Amore[1,2], Maja Ludvigsen[1,2], Bent Honoré[5], Peter Kamper[1,2]

[1]Department of Hematology, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, [3]Department of Pathology, Aarhus University Hospital, Aarhus, Denmark, [4]Department of Medicine, Regional hospital Goedstrup, Herning, Denmark, [5]Department of Biomedicine, Aarhus University, Aarhus Denmark

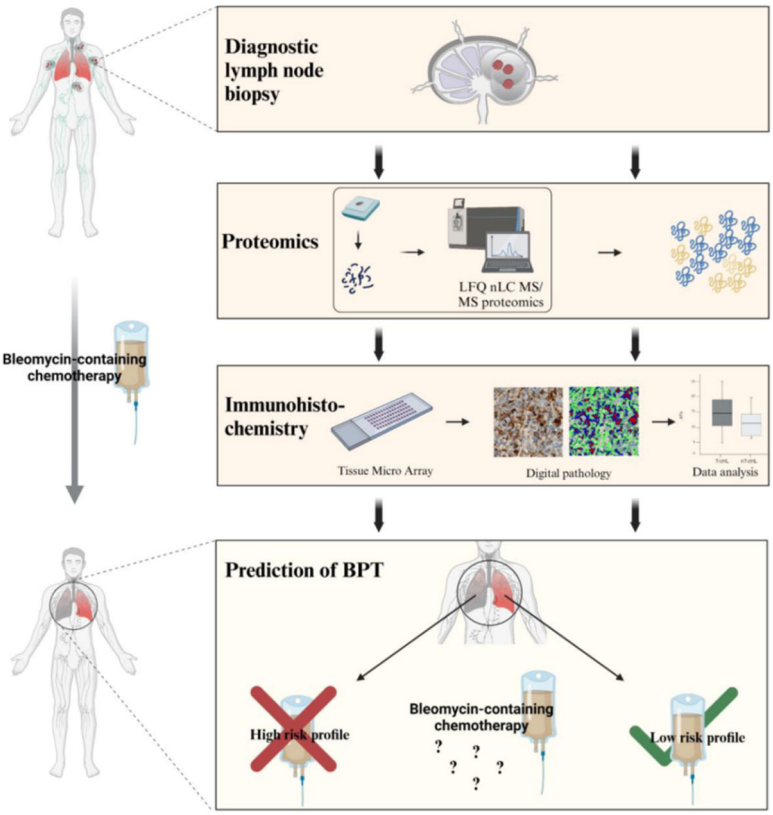


Figure 1: Study workflow. Created with Biorender.com.

Background: Advances in both chemo- and radiotherapy have notably improved cure rates in classic Hodgkin lymphoma (cHL), resulting in overall survival rates surpassing 80%. Consequently, an increasing number of long-term survivors are emerging, raising concerns about the possibility of long-term complications, notably the risk of cardiac and pulmonary toxicity. Bleomycin poses a significant risk of bleomycin-induced pulmonary toxicity (BPT), with an incidence around 10%, and a mortality ranging between 10% and 20%.

We performed proteomics as a tool for conducting a large-scale hypothesis-generating study to identify differentially expressed proteins in diagnostic cHL lymph node tumor samples from patients with and without subsequent BPT (Figure 1).

Methods: The study included patients diagnosed with cHL at Aarhus University Hospital, Denmark, during the period 2000–2018, treated with ABVD-based therapy regimens. Protein expression patterns in diagnostic lymphoma samples from patients who either developed BPT ($n = 23$; T-cHL) or did not ($n = 44$; nT-cHL), were analyzed by label-free quantification nano liquid chromatography-tandem mass spectrometry (LFQ nLC-MS/MS). Differential expressions of janus kinase 3 (JAK3), BH3 integrating domain death agonist (BID), matrix metallopeptidase 9 (MMP9), tumor protein D52 (TPD52), and phosphoinositide 3-kinase regulatory subunit 4 (PIK3R4) were further evaluated by immunohistochemistry ($n = 290$).

Results: At diagnosis, lymph node samples from T-cHL patients had significantly lower expression of TPD52 ($p < 0.001$), and PIK3R4 ($p = 0.006$), whereas JAK3 ($p = 0.003$), BID ($p = 0.003$), and MMP9 ($p = 0.006$) showed a significantly higher expression compared with samples from nT-cHL. Dividing the biomarkers into risk scores of 0 or 1, with 1 being high risk of BPT according to the individual markers, i.e. low levels of TPD52 and PIK3R4 and high levels of JAK3, BID, and MMP9, and subsequently combining the risk scores, was significantly predictive of BPT. A risk score of ≥4 markers predicted BPT with a sensitivity of 0.600 and specificity of 0.939 ($p < 0.001$).

Conclusion: Upon lymphoma diagnosis, we identified differences in protein expression in pre-treatment lymph node biopsies that could identify patients at high risk of developing BPT. Although individual protein markers offer limited predictive value for BPT development, utilizing a combination of markers can improve prediction accuracy and assist in making informed treatment decisions.

P043: SPATIAL ORGANIZATION OF THE TUMOR MICROENVIRONMENT IN NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA AND T-CELL/HISTIOCYTE-RICH LARGE B-CELL LYMPHOMA: INSIGHTS FROM A PILOT COHORT STUDY

Ilja Kalashnikov[1], Kerttu Kalander[1], Ada Junquera[2], Matias Autio[1], Suvi-Katri Leivonen[1], Johannes Dunkel[3], Anniina Färkkilä[4], Sirpa M. Leppä[5]

[1]Research Program Unit, Applied Tumor Genomics, Faculty of Medicine, University of Helsinki, Finland, [2]Research Program in Systems Oncology, University of Helsinki, [3]Department of Pathology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [4]Research Program in Systems Oncology, University of Helsinki, Finland, [5]University of Helsinki and Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland

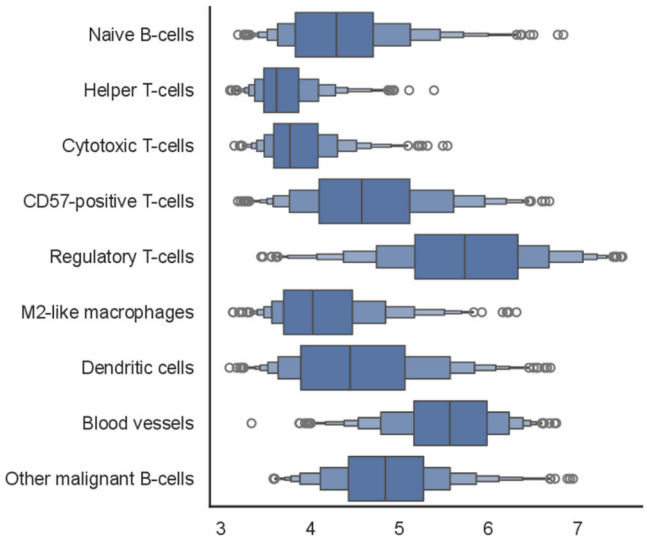


Figure 1: Average minimum distance from malignant B-cells to other cell types. X-axis represents log-scaled distance in pixels (1 pixel is equal to 0.325 micrometers).

Background: Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) and T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) are rare B-cell malignancies characterized by infrequent neoplastic cells embedded in an immunologically active tumor microenvironment (TME). NLPHL variants with T-cell infiltration, especially Fan pattern E, may resemble aggressive THRLBCL, to which NLPHL can transform. The cellular composition and spatial distribution of cells in the TME of NLPHL and THRLBCL have yet to be elucidated.

Design: In this initial pilot cohort, we collected comprehensive clinicopathological data from 11 patients with NLPHL Fan E/THRLBCL. A centralized review by an experienced hematopathologist (J.D.) ensured accurate diagnosis. We performed cyclic immunofluorescence (CycIF) on tissue microarrays (TMA) from diagnostic formalin-fixed paraffin-embedded (FFPE) tumor samples (lymph nodes). Our panel consisted of 31

markers focusing on immune cell subsets, immune checkpoint molecules, stroma, and blood vessels. We utilized the Scimap package (Python v.3.10) to enumerate the composition of tumor-infiltrating cells, with a particular emphasis on spatial distribution.

Results: All but one of the 11 patients had advanced-stage disease with bone marrow and liver or splenic involvement. All patients were treated with R-CHOP-like immunochemotherapy.

We identified a total of 108,597 single cells, with a median of 10,127 cells per patient. The cellular composition between samples varied, with the most common cell type being helper T cells (Th; 48%), followed by cytotoxic T cells (Tc; 19%) and M2-like macrophages (M2; 11%). As expected, malignant B cells were rare, constituting only 0.7% of all cells.

Th cells were closest to malignant B cells, followed by Tc cells, M2 macrophages, and nonmalignant B cells. In contrast, regulatory T cells, other malignant cells, and blood vessels were more frequently located at a greater distance.

Interaction analyses revealed that Th cells especially avoided M2 macrophages, dendritic cells, and Tc cells, but not Treg cells or malignant B cells. M2 macrophages and Th cells were less often situated next to blood vessels.

Conclusions: In this pilot cohort, we identified an organized spatial distribution of cellular composition. Malignant B cells were rare, scattered, and surrounded by T cells, positioned far from blood vessels. We have performed CycIF on over 300 TMA cores from more than 100 NLPHL and THRLBCL patients, with analyses ongoing.

P044: SULFORAPHANE, A NATURAL COMPOUND, INHIBITS CELL GROWTH AND PROMOTES NK CELL-MEDIATED ANTI-TUMOR IMMUNE RESPONSES THROUGH CGAS-STING PATHWAY IN CLASSICAL HODGKIN LYMPHOMA

Ioanna Xagoraris[1], Ying Yang[1], Erofili Bougka[1], Dora Trogrlic[1], Persa Xyderou[1], Konstantina Stathopoulou[1], Christina An Bihn Nordentoft[1], Nikolas Herold[2], Andreas Lundqvist[1], Georgios Z. Rassidakis[1]

[1]Department of Oncology-Pathology, Karolinska Institute, [2]Department of Women's and Children's Health, Karolinska Institute

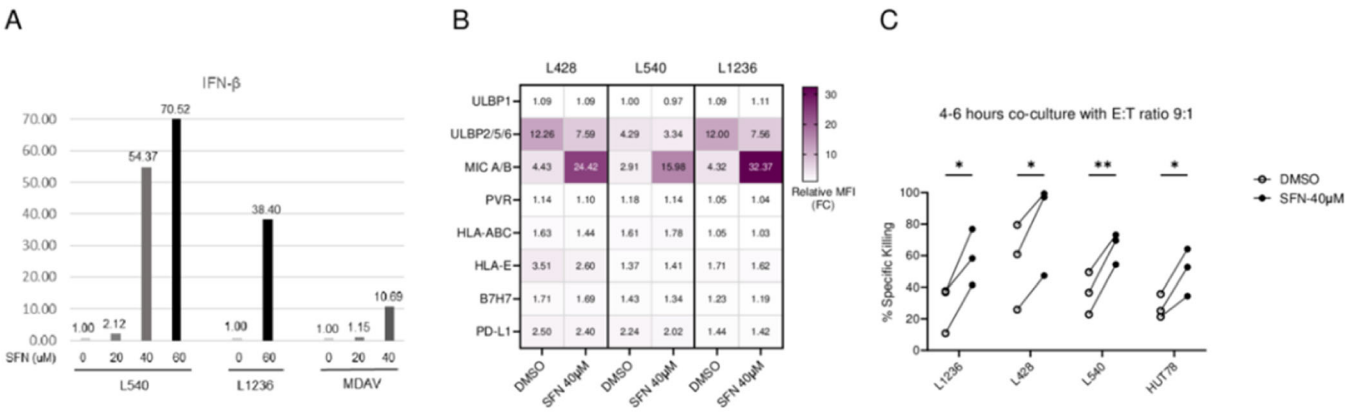


Figure 1: SFN treatment resulted in A) increased IFN-β gene expression (mRNA level) and B) overexpression of MIC A/B (NK ligand), associated with increased NK cell-mediated killing of co-cultured cHL cells.

Background: The tumor microenvironment plays a pivotal role in the pathogenesis of classical HL (cHL) because of the multiple and complex interactions of Hodgkin and Reed-Sternberg cells with inflammatory cells through numerous cytokines and chemokines. The innate immune responses can be regulated by the cGAS-STING pathway, which may be activated by cytosolic DNA in neoplastic cells. The cGAS-STING signaling, in turn, activates transcription factors IRF3 and NF-κB via kinases TBK1 and IKK, respectively. IRF3 and NF-κB can induce the expression of interferons (IFNs), cytokines and chemokines. We investigated for the first time the effects of the natural compound sulforaphane (SFN) on the cell growth and anti-tumor immune responses in cHL.

Methods: The in vitro system included 6 cHL cell lines (MDAV, L1236, L428, L540, KMH2, HDLM2) as well as HUT78 control cells. The cHL cells were treated with increasing concentrations of SFN or a STING agonist. Silencing of STING, IRF3, RelA, and RelB genes was performed using transient transfection (Nucleofector) with siRNA constructs. Expression of proteins was analyzed by western blot, and gene expression (mRNA) of type 1 IFNs, including IFN-β, CXCL10 and IFN-γ, by RT-qPCR. 51Cr-based NK cell killing, cytokine arrays and flow cytometry methods were also utilized to assess the anti-tumor immune responses.

Results: Treatment with SFN resulted in decreased cell growth and induction of IFN-β and CXCL10 gene expression, and substantially modified the cytokine profile in vitro (Figure 1). SFN treatment also led to a dramatic increase in the protein level of NK ligand MIC A/B and to a lesser degree altered expression of other NK ligand, which were associated with significant increase in functional NK cell-mediated killing of co-cultured cHL cells. MIC A/B expression is upregulated by cGAS-STING signaling, which is functional in cHL cells since stimulation with STING agonist resulted in increased gene expression of IFN-β and/or CXCL10. SFN treatment resulted in activation of the cGAS-STING pathway as

shown by phosphorylation/activation of TBK1 kinase and its downstream target IRF3. Inversely, STING gene silencing using specific siRNA constructs resulting in decreased IFN-β and CXCL10 gene expression, and altered the chemokine and cytokine profile of cHL cells in vitro.

Conclusion: SFN is a strong immunomodulatory agent that induces NK cell-mediated anti-tumor immune responses in cHL, in part through STING-dependent mechanisms.

P045: T-CELL DIVERSITY AND EXCLUSION OF BLOOD-DERIVED CLONALLY EXPANDED T-CELLS IN THE TUMOR MICROENVIRONMENT OF CLASSICAL HODGKIN LYMPHOMA

Nicole Seifert[1], Sarah Reinke[2], Johanna Grund[2], Berit Müller-Meinhard[2], Julia Richter[2], Thorsten Heilmann[3], Hans Schlößer[4], Michaela Biehl-Kotrova[5], Monika Brüggemann[5], Peter Borchmann[6], Paul J. Bröckelmann[7], Michael Altenbuchinger[1], Wolfram Klapper[2]

[1]Department of Medical Bioinformatics, University Medical Center Göttingen, Germany, [2]Department of Pathology, Hematopathology Section, University Hospital Schleswig-Holstein, Campus Kiel, Germany, [3]Franziskus-Hospital Harderberg, Münster, Germany, [4]Center of Molecular Medicine, Cologne Translational Immunology, University of Cologne, Cologne, Germany, [5]Department of Hematology and Oncology, University Hospital Schleswig-Holstein, Campus Kiel, Germany, [6]Department I of Internal Medicine, Centre for Integrated Oncology Aachen Bonn Cologne Düsseldorf (CIO ABCD), Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany German Hodgkin Study Group (GHSG), Cologne, Germany, [7]Department I of Internal Medicine, Centre for Integrated Oncology Aachen Bonn Cologne Düsseldorf (CIO ABCD), Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany German Hodgkin Study Group (GHSG), Cologne, Germany Mildred Scheel School of Oncology Aachen Bonn Cologne Düsseldorf (MSSO ABCD), Cologne, Germany Max-Planck Institute for Biology of Ageing, Cologne, Germany

The tumor microenvironment (TME) in classical Hodgkin lymphoma (HL) contains abundant immune cells and only few neoplastic Hodgkin and Reed-Sternberg cells (HRSC). We analyzed the T-cell receptor (TCR) repertoire to detect T-cell expansion in the TME and blood. In contrast to solid cancer tissue, T-cells in the TME of HL are highly polyclonal at first diagnosis and show only minor clonal expansion during anti-PD1 immune check-point blockade (ICB). At relapse and during ICB, pre-amplified T-cell populations increase in the TME of solid cancers but much less in HL. In contrast, T-cell populations in the peripheral blood of HL patients display higher clonality than healthy controls reaching clonality levels comparable to solid cancer and or CMV-infection. However, these pre-amplified blood T-cell populations show only minor additional clonal expansion during ICB. Moreover, blood-derived T-cells do not repopulate the TME of HL at relapse or during ICB to the same extent as observed in solid cancers. Thus, the T-cell repertoire in the TME of HL appears unique in its polyclonality and the exclusion of clonally expanded T-cells from the peripheral blood. Exclusion of clonally expanded tumor-specific T-cells from the TME may present a novel and potentially targetable mechanism of immune evasion in HL.

P046: TRANSCRIPTIONAL REPROGRAMMING BY MUTATED IRF4 IN LYMPHOMA

Nikolai Schleussner[1,2,3], Pierre Cauchy[4,5,6,7], Vedran Franke[8], Maciej Giefing[9,10], Oriol Fornes[11], Naveen Vankadari[12], Salam Assi[5], Mariantonia Costanza[1,2,3], Marc A. Weniger[13], Altuna Akalin[8], Ioannis Anagnostopoulos[14], Thomas Bukur[15], Marco Casarotto[16], Frederik Damm[2], Oliver Daumke[17], Benjamin Edginton-White[5], Christof Gebhardt[18], Michael Grau[19,20], Stephan Grunwald[17], Martin-Leo Hansmann[21,22], Sylvia Hartmann[23], Lionel Huber[4], Eva Kärgel[24], Simone Lusatis[1,2,3], Daniel Nörenberg[2], Nadine Obier[4,5], Ulrich Pannicke[25], Anja Pfaus[26], Anja Reisser[18], Andreas Rosenwald[14], Klaus Schwarz[25,27], Srinivasan Sundararaj[16], Andre Weilemann[20], Wiebke Winkler[1,2,3], Wendan Xu[20], Georg Lenz[20], Klaus Rajewsky[28], Wyeth Wassermann[11], Peter Cockerill[5], Claus Scheidereit[24], Reiner Siebert[10,26], Ralf Küppers[7,13], Rudolf Grosschedl[4], Martin Janz[1,2,3], Constanze Bonifer[5], Stephan Mathas[1,2,3]

[1]Biology of Malignant Lymphomas, Max-Delbrück-Center for Molecular Medicine, 13125 Berlin, Germany, [2]Hematology, Oncology, and Cancer Immunology, Charité–Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, 10117 Berlin, Germany, [3]Experimental and Clinical Research Center, a joint cooperation between Charité and MDC, [4]Max Planck Institute of Immunobiology and Epigenetics, 79108 Freiburg, Germany, [5]Institute of Cancer and Genomic Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, UK, [6]University Medical Center Freiburg, 79106 Freiburg, Germany, [7]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany, [8]Bioinformatics and Omics Data Science Platform, Berlin Institute for Medical Systems Biology, Max-Delbrück-Center, Berlin, Germany, [9]Institute of Human Genetics, Polish Academy of Sciences, Poznan, 60–479, Poland, [10]Institute of Human Genetics, Christian-Albrechts-University Kiel, 24105 Kiel, Germany, [11]Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, BC Children´s Hospital Research Institute, University of British Columbia, Vancouver, BC V5Z 4H4, Canada, [12]Department of Biochemistry and Pharmacology, Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Melbourne, Victoria 3000, Australia, [13]Institute of Cell Biology (Cancer Research), University of Duisburg-Essen, 45122 Essen, Germany, [14]Institute of Pathology, Universität Würzburg and Comprehensive Cancer Centre Mainfranken (CCCMF), Würzburg, Germany, [15]TRON gGmbH–Translationale Onkologie an der Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany, [16]Research School of Biology, The Australian National University, Canberra, ACT, Australia, [17]Structural Biology, Max-Delbrück-Center for Molecular Medicine, Berlin, Germany, [18]Department of Physics, Institute of Biophysics, Ulm University, Ulm, Germany, [19]Department of Physics, Philipps-University, 35052 Marburg, Germany, [20]Medical Department A for Hematology, Oncology and Pneumology, University Hospital Münster, Münster, Germany, [21]Frankfurt Institute of Advanced Studies, Frankfurt am Main, Germany, [22]Institute for Pharmacology and Toxicology, Goethe University, Frankfurt am Main, Germany, [23]Dr. Senckenberg Institute of Pathology, Goethe University Frankfurt, Frankfurt am Main, Germany, [24]Signal Transduction in Tumor Cells, Max-Delbrück-Center for Molecular Medicine, Berlin, Germany, [25]Institute for Transfusion Medicine, University of Ulm, Ulm Germany, [26]Institute of Human Genetics, Ulm University and Ulm University Medical Center, Ulm, 89081, Germany, [27]Institute for Clinical Transfusion Medicine and Immunogenetics Ulm, German Red Cross Blood Service Baden-Württemberg-Hessen, Ulm, Germany, [28]Immune Regulation and Cancer, Max-Delbrück-Center for Molecular Medicine, Berlin, Germany

Disease-causing mutations in genes encoding transcription factors (TFs) are a recurrent finding in hematopoietic malignancies and might involve key regulators of lineage adherence and cellular differentiation. Such mutations can affect TF-interactions with their cognate DNA-binding motifs. Whether and how TF-mutations impact upon the nature of binding to TF composite elements (CE) and influence their interaction with other TFs is unclear. Classic Hodgkin lymphoma (cHL) is characterized by perturbed B cell identity and high-level activation of various TFs, and these have been documented to centrally contribute to HL pathogenesis. Here, we report an unprecedented mechanism of TF alteration in cHL. It is caused by a recurrent somatic missense mutation c.295 T>C (p.Cys99Arg; p.C99R) targeting the center of the DNA-binding domain of

Interferon Regulatory Factor 4 (IRF4), a key TF in immune cell-differentiation and -activation. IRF4-C99R fundamentally alters IRF4 DNA-binding, with loss-of-binding to canonical IRF motifs and neomorphic gain-of-binding to canonical and non-canonical IRF composite elements (CEs), particularly those consisting of IRF and Activator Protein-1 (AP-1) motifs. Furthermore, IRF4-C99R thoroughly modifies IRF4 function, by blocking IRF4-dependent plasma cell induction, and up-regulating disease-specific genes in a non-canonical Activator Protein-1 (AP-1)-IRF-CE (AICE)-dependent manner. Among those, we identify genes essential for the microenvironment composition and genes not previously considered in cHL pathogenesis. Apart from the impact for cHL pathogenesis our data explain how a single arginine mutation creates a complex switch of TF specificity and gene regulation. These data open the possibility of designing specific inhibitors to block the neomorphic, disease-causing DNA-binding activities of a mutant transcription factor.

P047: TRIAL IN PROGRESS: EVALUATING COMBINATION OF NIVOLUMAB AND AXATILIMAB IN PATIENTS WITH RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA (NAHL)

Harsh Shah[1], Boyu Hu[1], Ken Boucher[1], Deborah Stephens[2]
[1]*HCI*, [2]*UNC*

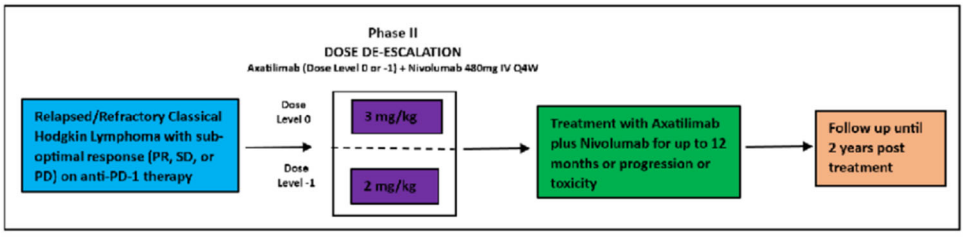


Figure 1: NAHL Trial Schema

Background: Patients with relapsed/refractory classical Hodgkin lymphoma (cHL) who have progression on anti-PD-1 therapy have 1-year median overall survival of 60% (Armand JCO 2018). Tumor Associated Macrophages (TAMs) expressing CSF1-R receptor have been implicated in resistance to anti-PD-1 therapy through (i) direct inhibition of cytotoxic T lymphocytes and (ii) phagocytosis of the anti-PD-1 antibody. Pre-clinical studies suggest that combination of anti-PD-1 and anti-CSF1-R blockade can result in upregulation of cytotoxic T lymphocytes and increased PD-L1 expression, resulting in Th1 type of type of tumor microenvironment.

Methods: We have designed a phase 2 dose de-escalation trial (Figure 1) using combination of nivolumab and axatilimab (anti-CSF1-R monoclonal antibody) in pts with R/R cHL who have sub-optimal response to anti-PD-1 therapy to determine the efficacy and safety of the drug combination (NCT05723055). Included patients must have progression on anti-PD-1 based therapy or have SD or PR after at least 4 months of treatment with anti-PD-1 based therapy. Key exclusion criteria include: (A) History of grade ≥3 immune-related adverse events (irAE) other than endocrinopathies, (B) prior exposure to anti-CSF1-R inhibitor. For the phase 2 portion, the planned sample size is 9 response-evaluable pts. The null hypothesis is a response rate of 10% and the alternative hypothesis is a response rate of 45%. The null hypothesis will be rejected if three (3) or more objective responses are observed in nine pts. Nine evaluable pts will be enrolled and receive axatilimab 3 mg/kg Q4 weeks in combination with nivolumab 480 mg Q4 weeks. If more than one DLT is observed during the DLT period (first two cycles) in the first 6 pts, the study drug dose will be reduced to 2 mg/kg and additional pts (up to 6 at 2 mg/kg dose) may be included in the study. This could result in maximum 12 pts for the entire study. The above combination will be continued until unacceptable toxicity or progression of disease (whichever comes first) for maximum of 12 months. Primary endpoint is ORR as defined by Lugano Criteria. Key secondary endpoints include frequency of AEs and serious adverse events (SAEs), PFS and ORR as measured by LYRIC criteria. Exploratory endpoints include: (i) pre-treatment and on-treatment lymph node biopsy to examine changes in tumor microenvironment, (ii) serial blood analysis including cytokine profile, circulating tumor DNA testing, and flow cytometry.

P048: TUMOR-ASSOCIATED MACROPHAGES CORRELATE WITH SKELETAL INVOLVEMENT IN CLASSIC HODGKIN LYMPHOMA

Maja Dam Andersen[1,2], Katharina Wolter[1], Marie Hairing Enemark[1,2], Mette Abildgaard Pedersen[3], Lars Christian Gormsen[3], Kristina Lystlund Lauridsen[4], Jørn Starklint[5], Stephen Jacques Hamilton-Dutoit[4], Francesco D'Amore[1,2], Maja Ludvigsen[1;2], Peter Kamper[1,2]
[1]*Department of Hematology, Aarhus University Hospital, Aarhus, Denmark*, [2]*Department of Clinical Medicine, Aarhus University, Aarhus, Denmark*, [3]*Department of Nuclear Medicine, Aarhus University Hospital, Aarhus, Denmark*, [4]*Department of Pathology, Aarhus University Hospital, Aarhus, Denmark*, [5]*Department of Medicine, Regional hospital Goedstrup, Herning, Denmark*

Background: The biology of tumors spreading to bone is poorly understood, not least in classic Hodgkin lymphoma (cHL). When cHL disseminates, the newly affected sites typically harbor both Hodgkin and Reed-Sternberg cells along with cells from the tumor microenvironment

(TME). However, whether cases presenting with bone lesions exhibit specific TME characteristics remains uncertain. We performed gene expression profiling (GEP) and immunohistochemistry (IHC) to characterize the TME of cHL with skeletal disease involvement at diagnosis.

Methods: GEP was conducted using the Nanostring nCounter Human 770 gene PanCancer Immune Profiling Panel on diagnostic lymph node biopsies from cHL patients with either no skeletal involvement (nodal only cHL, n-cHL; $n = 35$), or skeletal involvement in addition to nodal disease (s-cHL; $n = 31$). Differential protein expression of CD68, CD163, mannose receptor C-type 1 (MRC1/CD206), and CD20 were further evaluated by IHC in a larger cHL cohort ($n = 193$).

Results: GEP revealed that at the time of diagnosis, samples from patients with s-cHL were rich in macrophage markers particularly CD163, CD206, macrophage receptor with collagenous structure (MARCO), and sialic acid binding Ig like lectin 1 (SIGLEC1) compared with samples from n-cHL. In contrast to the macrophage markers, genes encoding B-cell associated markers such as CD20, CD19, paired box 5 (PAX5), and CD79A/B were downregulated in s-cHL samples compared with n-cHL.

We further evaluated the macrophage markers (CD68, CD163, and CD206) and the B cell marker CD20 at the protein level by IHC. All three macrophage markers had high expression levels in s-cHL compared with n-cHL ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively), whereas CD20 had low expression levels in s-cHL ($p < 0.001$). The three macrophage markers correlated positively with each other ($p < 0.01$) and Ann Arbor stage ($p < 0.001$), while CD20 showed a negative correlation to stage ($p < 0.001$).

Conclusion: Our data show different gene expression profiles in lymph node tumor samples from cHL with and without concomitant skeletal involvement at diagnosis. This suggests that tumors from patients with bone lesions show a unique TME molecular profile that could explain why some tumors seem to have a predisposition to disseminate to bone, and that tumor-associated macrophages and B cells could play a role in creating a pro-tumoral microenvironment facilitating the 'seed and soil' mechanism in the dissemination of disease in cHL.

LIMITED STAGES

T049: FACTORS DRIVING TREATMENT INTENSITY IN THE WHOLE COHORT OF PATIENTS WITH EARLY-STAGE FAVORABLE (I-IIA), NONBULKY HODGKIN LYMPHOMA ENROLLED IN THE RAFTING TRIAL (NCT 04866654)

Jan Maciej Zaucha[1], Marco Picardi[2], Kateryna Filonenko[1], Manuel Gotti[3], Javier Nunez[4], Andrea Rossi[5], Eva Domingo-Domènech[6], Agnieszka Giza[7], Roberto Sorasio[8], Andrea Visentin[9], Mariana Bastos[10], Ewa Paszkiewicz-Kozik[11], Ramon Garcia-Sanz[12], Caterina Patti[13], Stephane Chauvie[14], Fabrizio Bergesio[14], Luca Guerra[15], Anna Sureda[6], Andrea Gallamini[16]

[1]Hematology and Transplantology Department, Medical University of Gdańsk, Gdańsk, Poland, [2]University Hospital Federico II, Internal medicine and surgery department, Naples, Italy, [3]Hematology Department, IRCCS S. Matteo Hospital, Pavia, Italy, [4]University Hospital Marques de Valdecilla, Santander, Spain, [5]Hematology Department Papa Giovanni XXIII Hospital, Bergamo, Italy, [6]Hematology Department, Hospital Duran i Reynals, Catalan Oncology Institute IDIBELL, Barcelona, Spain., [7]Department of Hematology, Jagiellonian University Medical College, Cracow, Poland, [8]Hematology Department, S. Croce e Carle Hospital, Cuneo, Italy, [9]Internal Medicine Department, Padova Hospital, Padova, Italy, [10]Hematology Department, General University Hospital Gregorio Marañon, Madrid, Spain, [11]Hemato-Oncology Department M. Sklodowska-Curie National Institute of Oncology, Warsaw, Poland, [12]Hematology Department (CIBERONC), University Hospital, Salamanca, Spain, [13]Hematology Department Cervello Hospital, Palermo, Italy, [14]Medical Physics Department, S. Croce e Carle Hospital, Cuneo, Italy, [15]Nuclear Medicine Department, S. Gerardo University Hospital, Monza, Italy, [16]Research and Clinical innovation A. Lacassagne Cancer Center, Nice, France

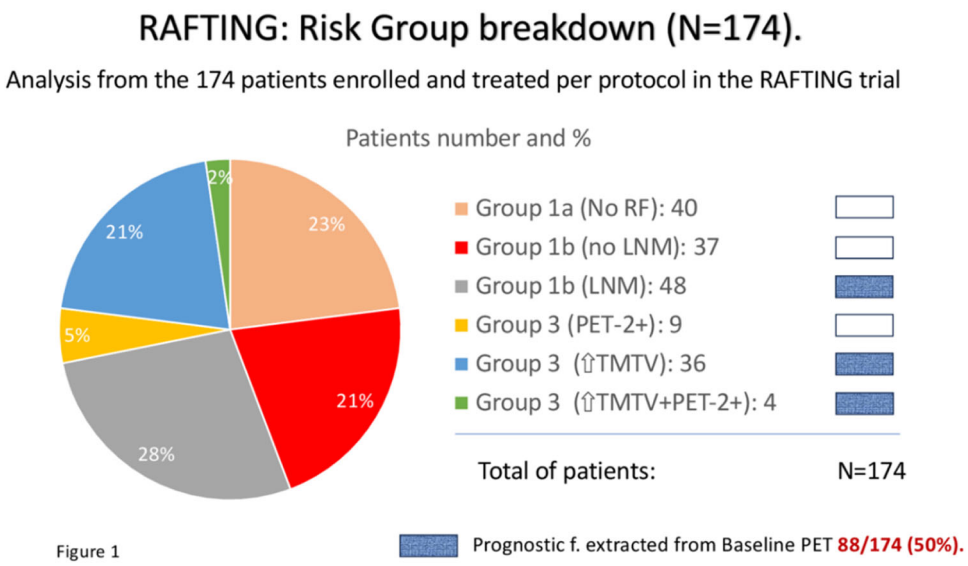


Figure 1: Patient breakdown according to risk factor and baseline PET/CT

Background: The treatment (Tx) of early-stage Hodgkin Lymphoma (eHL) with Chemotherapy plus Radiotherapy (RT) is offset by a 40-year cumulative incidence of 2nd malignancy ≥45%. RAFTING is a phase 2, prospective, clinical trial in nonbulky eHL (I-IIA) in which Tx intensity (Tx-I)

is tailored to the risk of Tx failure (Txf) in a single patient (p.), depending on: (a) presence of ≥1 of the modified EORTC criteria (m-EORTC-Cr), in which bulky is replaced by a Large Nodal Mass (LNM): a nodal mass with a diameter ≥5 cm in baseline CT/PET/CT, (b) a high Total Metabolic Tumor Volume (TMTV) at baseline, (c) a positive PET, at interim (PET-2) or after ABVD (EoC-PET). Aims: To assess the prevalence of old and new risk factors (Rf) to drive Tx-I in nonbulky eHL.

Methods: In RAFTING trial Tx-I is adapted to risk of Txf in 3 groups of p.: Gr 1 (low risk): PET-2 neg. & low TMTV p., without (Gr.1a) or with ≥1 m-EORTC-Cr (Group 1b), treated respectively with 2 or 4 ABVD cycles. After CR entry, blood samples are shipped every 3 months to Bellinzona (CH) for cell-free tumor DNA assay. Gr 2: Gr 1 p. with a post-ABVD "limited relapse".

Results: Out of 180 p. enrolled from 03.2021 till 10.2023, 174 are valuable in a per-protocol analysis: 125 (72%) in Gr 1: 40 in Gr 1a and 85 in Gr 1b. The prevalence of Rf in Gr 1b was: LNM (48), age >50 (29), ESR > 50 (23), >4 nodal areas (19). The Rf in 49 (28%) Gr 3 p. were PET-2+ (9), High TMTV (36), and both (4). Overall, after a median f-up of 380 days, 12/125 (13%) Gr 1 p. failed ABVD: 11 switched to Rt+N (per protocol), 1 to ASCT (off protocol); In Gr 3, 11/49 p. failing ABVD continued, per protocol, with Rt+N. Overall, the most frequent Rf for Txf was a LNM (13/23), and most ABVD failures occurred in EoC PET (19, with a DS score 5 in 11), or +3 months after CR entry (4).

Conclusions: In a personalized-medicine approach, LNM and TMTV at baseline were able to drive Tx-I in half (88/174) of p. (Figure 1). Triplet-T was given to 72/174 (41%) p.: in 49 (28%) as frontline Tx, while Rt+N was given to 23 (13%) as ABVD fail rescue.

T050: NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA IN THE NORDIC COUNTRIES–CHARACTERISTICS, TREATMENT AND SURVIVAL

Kossi D. Abalo[1,2], Katrin Bamdeg-Hvolbek[3], Frida Ekeblad[1], Ilja Kalashnikov[4], Johan Linderoth[5], Dennis Lund Hansen[3,6], Gunilla Enblad[7], Urban Jerlstrom[8], Christina Goldkuhl[9], Taina Reunamo[10], Marjukka Pollari[10], Martin Hutchings[11,12], Peter Kamper[13], Rasmus Bo Dahl-Sørensen[14], Ingemar Lagerlöf[7], Ann-Sofie Johansson[15], Lotta Hansson[16,17], Daniel Molin[7], Sirpa M. Leppä[4], Tarec Christoffer El-Galaly[18], Ingrid Glimelius[1]

[1]Department of Immunology, Genetics and Pathology, Cancer Precision Medicine, Uppsala University, Sweden, [2]Department of Medicine Solna, Clinical Epidemiology Division, Karolinska Institutet, Stockholm, Sweden, [3]Department of Hematology, Odense University Hospital, Denmark, [4]Research Programs Unit, Applied Tumor Genomics Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland, [5]Department of Oncology, Lund University Hospital, Lund, Sweden, [6]University of Southern Denmark, Department of Clinical Research, Denmark, [7]Department of Immunology, Genetics and Pathology, Cancer Immunotherapy, Uppsala University, Sweden, [8]Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden, [9]Department of Oncology, Faculty of Medicine and Health, Örebro University Hospital, Örebro, Sweden, [10]Department of Oncology, Tays Cancer Center, Tampere University Hospital, Tampere, Finland, [11]Department of Clinical Medicine, University of Copenhagen, Denmark, [12]Department of Hematology, Copenhagen University Hospital - Rigshospitalet, Denmark, [13]Department of Haematology, Aarhus University Hospital, Denmark, [14]Department of Hematology, Zealand University Hospital, Denmark, [15]Department of Radiation Sciences, Oncology. Umeå University, Sweden, [16]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, [17]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden, [18]Department of Hematology, Clinical Cancer Research Center, Aalborg University Hospital, Aalborg, Denmark

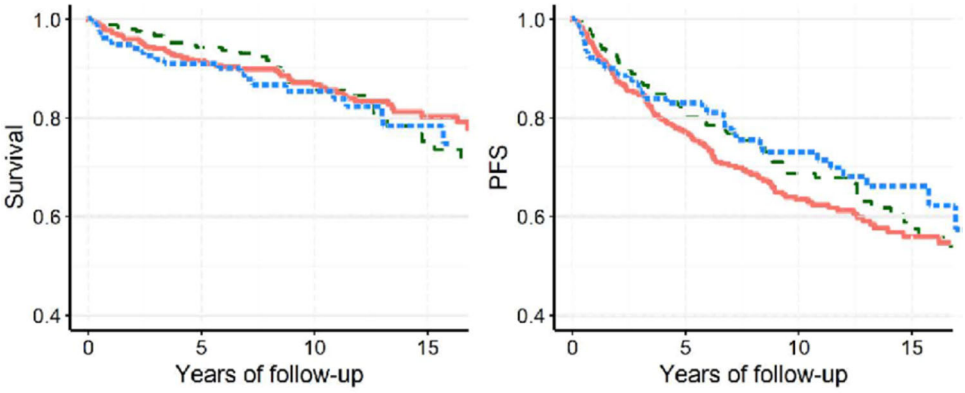


Figure 1: Overall and progression-free survival (PFS) in Denmark (dotted blue line), Finland (solid red line) and Sweden (dashed green line) in NLPHL patients diagnosed in 2000 until 2018–2022. Please note that y-axis is truncated at 0.4

Background: Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a rare cancer. While initial response to treatment is typically excellent, late relapses occur and transformation to aggressive B-cell lymphomas is a feared complication.

Aim: To investigate relapse patterns, transformation rate, and overall survival (OS) in patients diagnosed with NLPHL in Denmark, Finland, and Sweden.

Method: In each country, population-based data were identified in nationwide registers from 2000 until 2018–2022, depending on data availability. Follow-up was until 2022–2023. Data on treatment, OS, relapse- and transformation rates were collected from medical records. The Kaplan-Meier estimator was used to calculate OS, progression-free survival (PFS), and median time to first relapse.

Results: A total of 752 NLPHL patients were identified (155 Denmark, 344 Finland, and 253 Sweden). The median age at diagnosis was 46–51 years, with follow-up ranging from 8.2 to 10.0 years. A male predominance >70% was seen, and the majority >67% of patients presented with limited-stage.

The 10-year OS was 85.3%, 86.6%, 85.6%, and the 10-year PFS was 73.0%, 63.5%, and 68.7% for Denmark, Finland, and Sweden respectively (Figure 1). NLPHL progression or relapse occurred in 19% of the cohort combined with median times to first relapse rangeing from 2.9 to 4.5 years. Transformation was recorded in 4%.

Most patients were treated with radiotherapy alone, 37%, 36%, and 23% in Denmark, Finland, and Sweden respectively. Rituximab containing treatment was administered in 16%, 25%, and 51% of patients in Denmark, Finland, and Sweden, whereas combined treatment modalities (chemo-, radiotherapy, and rituximab) were given in 8%, 26%, and 16% of patients respectively. In Sweden, rituximab use increased over time with 9% receiving rituximab only. Only one patient received rituximab monotherapy in Denmark. Combined radio-chemotherapy was given to 14% in Denmark and 15% in Sweden, and radiotherapy postoperatively to 5% in Denmark. In all countries, ABVD was the most common chemotherapy used.

Conclusion: NLPHL were treated with a variety of modalities; radio- and chemotherapy above all. Rituximab use increased over time, particularly in the later periods in Sweden. Outcome in terms of OS and PFS were good and comparable across the regions. The low relapse rate (15–22%) and transformation rate (3.2%–4%) reflect population-based, long-term follow-up and indicates long-lasting remissions.

T051: SERUM TARC DYNAMICS CORRELATE WITH CLINICAL RESPONSE AND METABOLIC TUMOR VOLUME DURING ANTI-PD1-BASED FIRST-LINE HL TREATMENT IN THE GHSG PHASE II NIVAHL TRIAL

Wouter J. Plattel[1], Sophie Teesink[2], Lydia Visser[2], Conrad-Amadeus Voltin[3], Helen Kaul[4], Hans A. Schlösser[5], Bart-Jan Kroesen[6], Carsten Kobe[3], Peter Borchmann[4], Arja Diepstra[2], Paul J. Bröckelmann[4,7]

[1]Department of Hematology, University Medical Center Groningen, Groningen, The Netherlands, [2]Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, The Netherlands, [3]Department of Nuclear Medicine, University Hospital of Cologne, Cologne, Germany, [4]Department I of Internal Medicine and German Hodgkin Study Group (GHSG), University Hospital of Cologne, Cologne, Germany, [5]Department of Surgery, University Hospital of Cologne, Cologne, Germany, [6]Department of Laboratory Medicine, University Medical Center Groningen, University of Groningen, The Netherlands, [7]Max Planck Institute for Biology of Ageing, Cologne, Germany

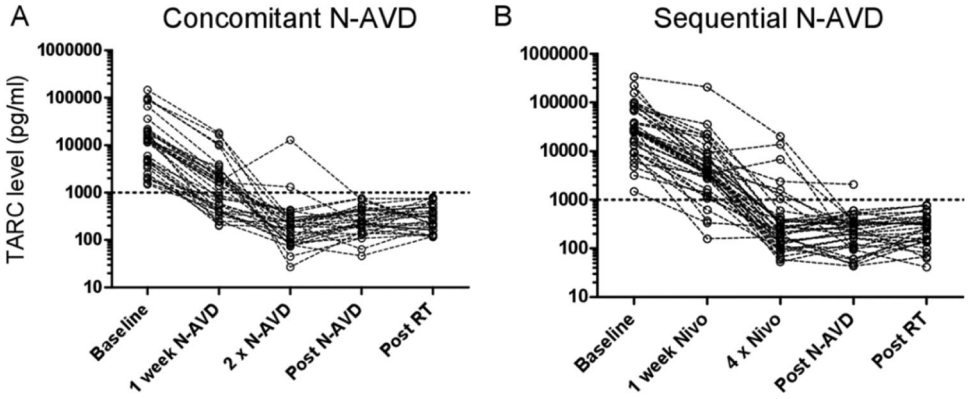


Figure 1: Serum TARC dynamics in early-stage unfavorable cHL patients treated within the phase II NIVAHL: (A) concomitant N-AVD (B) sequential nivolumab and AVD.

Background: Serum Thymus and Activation Regulated Chemokine (TARC) is a well-established tumor cell derived biomarker for monitoring early treatment response in classic Hodgkin lymphoma (cHL), offering higher positive predictive value compared to interim FDG-PET imaging. However, data on TARC in patients receiving anti-PD1-based first-line treatment is limited. To our knowledge, this is the first study correlating TARC dynamics with metabolic tumor volume (MTV) and clinical response during either sequential or concomitant nivolumab and doxorubicin, vinblastine, and dacarbazine (N-AVD) first-line treatment of early-stage unfavorable cHL patients.

Methods: Patients in the prospective randomized GHSG NIVAHL phase II trial were evaluated for early treatment response (RE2) after 2× N-AVD (arm A) or four nivolumab (N) infusions (arm B), respectively (NCT03004833). This study included all 78 NIVAHL patients with informed consent and serum samples available at baseline and at least one additional timepoint: after 1 week, at RE2, post chemotherapy and/or post 30 Gy IS-RT. TARC levels were measured using a standardized ELISA, with a predefined positivity threshold of >1000 pg/mL, while being blinded to treatment and response. For longitudinal analysis, only patients with elevated baseline TARC were included and were correlated with MTV.

Results: TARC levels were positive in 71/78 patients (91%) at baseline, with a median level of 14,830 pg/mL (range 203–339,000 pg/mL). Baseline TARC levels significantly correlated with baseline MTV (Spearman $r = 0.41$, $p = 0.007$). Already after 1 week of treatment, a sharp decline in TARC levels was observed in both treatment groups (Figure 1). At the RE2, only 3% and 19% of cases remained TARC positive in arm A (2 × N-AVD) and arm B (4 × N), respectively, demonstrating early deep responses in the vast majority of patients, including patients treated with nivolumab monotherapy. Notably, TARC negativity was observed in 12 out of 18 cases (67%) with a positive PET at RE2 and 4 out of 4 cases (100%) at end of treatment. All did not experience a relapse with a median follow-up of 41 months.

Conclusion: Serum TARC levels correlate with MTV and treatment response in cHL patients receiving anti-PD1-based first-line treatment. Importantly, TARC negativity is achieved very early also during nivolumab monotherapy and associated with excellent outcomes despite interim or end-of-treatment PET positivity.

P052: AHOD2131: A RANDOMIZED PHASE 3 RESPONSE-ADAPTED TRIAL COMPARING STANDARD THERAPY WITH IMMUNO-ONCOLOGY THERAPY FOR CHILDREN AND ADULTS WITH NEWLY DIAGNOSED STAGE I AND II CLASSIC HODGKIN LYMPHOMA

Jennifer Seelisch[1], Boyu Hu[2], Lindsay A. Renfro[3], Frank G. Keller[4], Adam Duvall[5], Tara O. Henderson[6], Yue Wu[7], Steve Yoon-Ho Cho[8], Bradford S. Hoppe[9], Sarah Milgrom[10], Lisa Giulino Roth[11], Natalie S. Grover[12], Ann S. Lacasce[13], Justine M. Kahn[14], Song Yao[15], Susan K. Parsons[16], Niloufer Khan[17], Raymond Mailhot Vega[18], Pamela S. Hinds[19], Pamela B. Allen[20], Andrew M. Evens[21], Heiko Schoder[22], Sharon M. Castellino[4], Kara M. Kelly[23]

[1]*Children's Hospital London Health Sciences Centre, Western University, London, ON, Canada,* [2]*Huntsman Cancer Institute/University of Utah, Salt Lake City, Utah, USA,* [3]*University of Southern California and Children's Oncology Group, Los Angeles, CA, USA,* [4]*Emory University School of Medicine, Children's Healthcare of Atlanta, Atlanta, GA, USA,* [5]*University of Chicago Comprehensive Cancer Center, Chicago, IL, USA,* [6]*University of Chicago Comprehensive Cancer Center, Chicago IL, USA,* [7]*COG Data Center, University of Florida, Gainesville, FL, USA,* [8]*University of Wisconsin Hospital and Clinics, Madison, WI, USA,* [9]*Mayo Clinic Radiation Oncology, Jacksonville, FL, USA,* [10]*Children's Hospital Colorado, Aurora, CO, USA,* [11]*NYP/Weill Cornell Medical Center, New York, NY, USA,* [12]*UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA,* [13]*Dana- Farber/Harvard Cancer Center, Boston, MA, USA,* [14]*NYP/Columbia University Medical Irving Center/Herbert Irving Comprehensive Cancer Center, New York, NY, USA,* [15]*Roswell Park Cancer Institute, Buffalo, NY, USA,* [16]*Tufts Medical Center, Boston, MA, USA,* [17]*City of Hope, Duarte, CA, USA,* [18]*University of Florida, Jacksonville, FL, USA,* [19]*Children's National Medical Center, Washington, DC, USA,* [20]*Emory University Hospital/Winship Cancer Institute, Atlanta, GA, USA,* [21]*Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA,* [22]*Memorial Sloan Kettering Cancer Center, New York, NY, USA,* [23]*Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA*

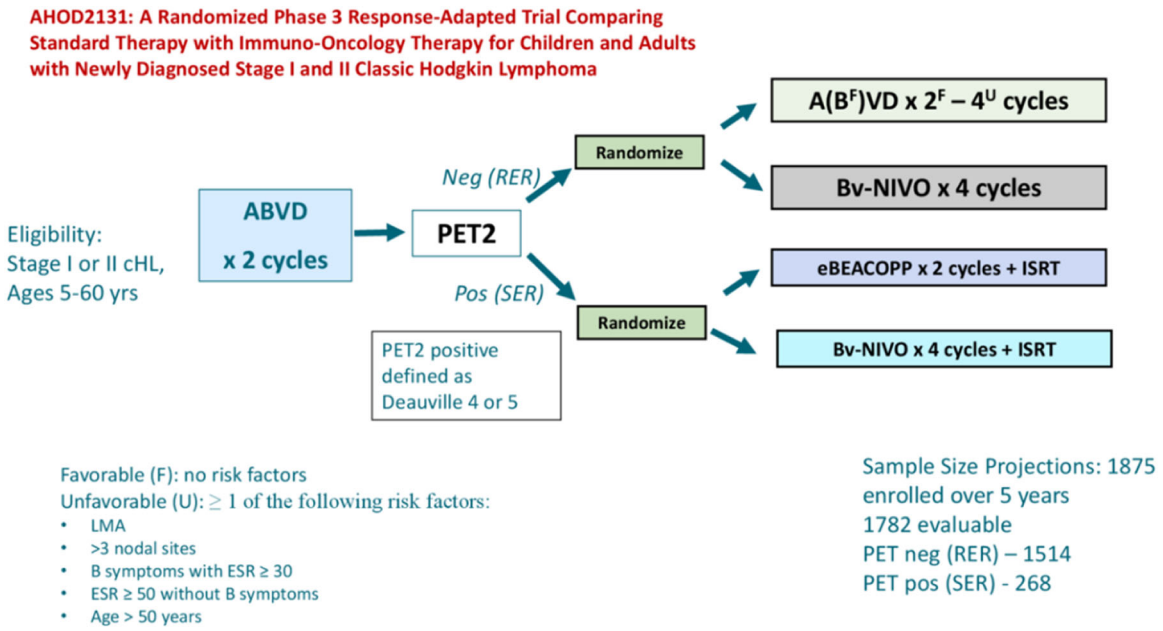


Figure 1: AHOD2131 Study Schema

*JS, BH co-first authors.

Background: Chemotherapy in combination with radiotherapy (RT) is the standard for early-stage (ES) classic Hodgkin lymphoma (cHL). Despite excellent cure rates, there is room to improve outcomes for children and adults with ES cHL. Incorporation of immunotherapy (IO) into front line treatment may improve progression-free survival (PFS) and maintain overall survival, while minimizing morbidity and mortality by reducing RT and high-dose chemotherapy.

Methods: HL leaders of the pediatric and medical oncology National Cancer Institute's National Clinical Trial Network groups, collaborated to harmonize treatment approaches for ES cHL and to reach consensus around optimal study design for incorporating IO into frontline treatment. Study champions from each North American (NA) cooperative group [Children's Oncology Group (COG), SWOG, ECOG-ACRIN, Alliance, NRG] and experts in imaging, radiation oncology, lymphoma biology and patient-reported outcomes were included. The resulting COG-led clinical trial, AHOD2131, represents the largest ES cHL trial in the history of NA cooperative groups and the first to enroll patients across the age continuum.

Results: AHOD2131 (NCT05675410; Figure) is a randomized, phase 3 trial for patients ages 5 to 60 years with newly diagnosed stage I and II cHL, investigating the addition of the CD30-antibody drug conjugate brentuximab vedotin (Bv) with PD-1 blockade (nivolumab) compared to standard chemotherapy +/− RT. As of 7 May 2024, 208 sites have activated, and 195 participants have enrolled. Target enrollment is 1875 patients over 5 years.

The primary objective is to compare the 3-year PFS of patients treated through a response-adapted, superiority design with either standard therapy or IO (BV+nivolumab). Patients will be stratified based on favorable or unfavorable risk features at enrollment. Based on response assessment by PET/CT (central review) after 2 cycles of ABVD, patients will be classified to PET2 positive (SER, defined as 5-Point Deauville Score 4 or 5) or PET2 negative (RER). Patients with SER will receive involved site RT. SER and RER patients will be randomized to standard chemotherapy vs. IO respectively. There are 11 secondary and 10 exploratory aims. 12-year OS is a key secondary aim.

Conclusion: AHOD2131 strengthens the effort between NA cooperative groups to conduct collaborative clinical trials and aims to harmonize an improved standard of care for ES cHL across the age continuum.

P053: DEVELOPMENT AND VALIDATION OF THE EARLY STAGE (ES) CLASSIC HODGKIN LYMPHOMA (CHL) INTERNATIONAL PROGNOSTICATION INDEX (E-HIPI): AN INDIVIDUALIZED PREDICTION MODEL FOR PROGRESSION-FREE SURVIVAL (PFS) UTILIZING OBJECTIVE AND CONTINOUS VARIABLES

Angie Mae Rodday[1], John Radford[2], Matthew Maurer[3], Jenica Upshaw[1], Nicholas Counsell[4], Sara Rossetti[5], Ranjana H. Advani[6], Marc Andre[7], Cheryl Chang[6], Andrea Gallamini[8], Annette Hay[9], David Hodgson[10], Richard Hoppe[6], Martin Hutchings[5], Peter Johnson[11], Eric Mou[12], Stephen Opat[13], John M.M. Raemaekers[14], Kerry Savage[15], Qingyan Xiang[1], Susan K. Parsons[1], Andrew Evens[16]

[1]Tufts Medical Center, Boston, Massachusetts, USA, [2]Christie Hospital NHS Foundation Trust, Manchester, UK, [3]Mayo Clinic, Rochester, Minnesota, USA, [4]Cancer Trials, CRUK Cancer Trials Centre, University College London, London, UK, [5]Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, [6]Stanford University Institute, Stanford, California, USA, [7]CHU UCL Namur, Yvoir, Belgium, [8]Antoine Lacassagne Cancer Centre, Nice, Italy, [9]Department of Medicine, Queen's University, Kingston, Canada, [10]Princess Margaret Hospital, Toronto, Canada, [11]Southampton General Hospital School of Medicine, Southampton, UK, [12]University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA, [13]Monash University, and Haematology Department, Monash Health, Melbourne, Australia, [14]Radboud University Nijmegen Medical Center, Nijmegen, Netherlands, [15]BC Cancer, Vancouver, Canada, [16]Rutgers Cancer Institute, New Brunswick, New Jersey, USA

	Optimism-corrected HR [b]
Female sex	**0.64**
MTD (cm) [c]	**1.08**
Hemoglobin (standardized) [d]	**0.85**
Albumin (standardized) [e]	**0.86**

[a] Stage (I vs II), number of nodal sites (analyzed at varied dichotomized cutpoints, as continuous variable, or varied anatomic locations), histology, age, white blood & lymphocyte count, and erythrocyte sedimentation rate were ***not significant*** (p>0.1). Adding B symptoms did not improve the optimism-corrected C-statistic in the development cohort (0.63).

[b] Hazard ratio (HR) <1 indicates ***better PFS***; HR>1 indicates ***worse PFS.***

[c] Continuously increasing range of maximum tumor diameter (MTD) 1.5 to 15 cm; each 1 cm increase in MTD is associated with ***worse PFS.***

[d] Continuous range of serum hemoglobin 5 to 16.5 g/dL (standardized to a mean of 13.0 g/dL and standard deviation (SD) of 1.6 g/dL); each 1 SD increase in hemoglobin is associated with ***better PFS***.

[e] Continuous range of serum albumin 2.5 to 6 g/dL (standardized to a mean of 4.2 g/dL and standard deviation (SD) 0.5 g/dL); each 1 SD increase in hemoglobin is associated with ***better PFS***.

Table 1: Optimism-corrected HRs for 2-year PFS in the final multivariable prediction model (a).

Background: ES cHL has long been classified as favorable or unfavorable by EORTC or GHSG criteria. However, these are based on dichotomized variables, and several are subjective (B symptoms) or difficult to measure (nodal sites). After integrating additional data into the HoLISTIC consortium, we further developed & validated the E-HIPI to predict 2-year (y) PFS (Evens, ASH 2023).

Methods: The model was developed in 3000 untreated patients (pts) with cHL age 18–65 y with ES (I or II) cHL from 4 phase 3 clinical trials & externally validated in 1461 pts from 4 cHL registries (using TRIPOD guidelines: Moons, Ann Int Med 2015). The primary outcome of 2 y PFS was estimated with a Cox model. Baseline candidate variables were sex, stage, histology, nodal sites, and continuous values of age, maximum tumor diameter (MTD), white blood & lymphocyte count, hemoglobin, albumin & erythrocyte sedimentation rate. Linearity was examined & missing data was multiply imputed. We used backward elimination to develop the model & internal validation to estimate optimism & correct for overfitting. The final prediction equation applied optimism correction to beta coefficients, hazard ratios & C-statistics. The C-statistic was reported for the external validation cohort. Model performance was compared to EORTC favorable/unfavorable status.

Results: Mean age in the development cohort was 34 y; 51% were female; 81% had nodular sclerosis; 77% had stage II; mean MTD was 6.5 cm. Median follow-up was 60 months (IQR = 45–75). KM estimated 2 y PFS was 93.7%. Variables retained in the model were sex, MTD, hemoglobin & albumin (Figure). The optimism-corrected C-statistic in the development cohort was 0.63. Most external validation cohort characteristics were similar besides lower 2 y PFS (90.2%) and longer median follow-up (108 months, IQR = 63–165). The external validation C-statistic was 0.63. The E-HIPI was prognostic in both favorable ($p < 0.01$) & unfavorable ($p < 0.01$) EORTC subgroups. Moreover, unfavorable status was not prognostic once E-HIPI was known ($p = 0.36$).

Conclusion: We developed & externally validated the first prediction model for ES cHL among >4400 pts, which is comprised of objective & continuous variables. Female sex and increasing hemoglobin & albumin were associated with better 2 y PFS, and increasing MTD was associated with worse PFS. The E-HIPI outperformed EORTC favorable/unfavorable status and provides more robust & biologically meaningful prediction to improve decision making.

P054: INDIVIDUALIZED IMMUNOTHERAPY IN EARLY-STAGE UNFAVORABLE HODGKIN LYMPHOMA–THE INVESTIGATOR-INITIATED PHASE II GHSG INDIE TRIAL (TRIAL IN PROGRESS)

Paul J. Bröckelmann[1], Helen Kaul[1], Michael Fuchs[1], Carsten Kobe[2], Christian Baues[3], Wolfram Klapper[4], Bastian Von Tresckow[5], Peter Borchmann[1]

[1]University Hospital of Cologne and German Hodgkin Study Group (GHSG), Cologne, Germany, [2]Department of Nuclear Medicine, University Hospital of Cologne, Cologne, Germany, [3]Department of Radiation Oncology, Klinikum Bochum, Bochum, Germany, [4]Department of Hematopathology, Campus Kiel, University Hospital of Schleswig-Holstein (UKSH), Kiel, Germany, [5]Department of Hematology and Stem Cell Transplantation, West German Cancer Center and German Cancer Consortium (DKTK partner site Essen), University Hospital Essen, University of Duisburg-Essen

Background: Immune-checkpoint inhibition targeting the programmed cell death protein 1 (PD1) axis continues to reshape the therapeutic landscape of classical Hodgkin lymphoma (HL). The randomized phase II GHSG NIVAHL trial previously investigated nivolumab-based 1st-line treatment of early-stage unfavorable HL. With either fully concomitant (4x nivo-AVD) or sequential (4x nivolumab, 2x nivo-AVD, 2x AVD) treatment, each followed by 30 Gy involved-site radiotherapy (IS-RT), good tolerability and outstanding 3-year progression-free (PFS) and overall survival (OS) of 99% and 100%, respectively, were reported (Bröckelmann PJ et al., JCO 2023). Additionally, correlative studies on tumor (re-)biopsies, longitudinal blood samples and metabolic tumor volume dynamics indicated very early complete remissions in both treatment arms. The upcoming GHSG phase II INDIE trial will investigate an individualized immunotherapy with the anti-PD1 antibody tislelizumab in this setting.

Trial design: INDIE is an investigator-sponsored open-label phase II trial conducted at 35 GHSG trial sites in Germany. Patients with newly diagnosed early-stage unfavorable HL by GHSG criteria will receive two initial infusions of tislelizumab followed by PET-based restaging. Patients in complete metabolic remission will continue treatment with four additional tislelizumab infusions. Patients with residual metabolic activity will receive concomitant treatment with four cycles of AVD and tislelizumab. In the main cohort of $N = 100$ patients aged 18–60 years, consolidative 30 Gy IS-RT will only be applied in case of PET-positive residues. In an exploratory cohort of $N = 20$ patients >60 years of age, 30 Gy IS-RT will be applied irrespective of remission status at end of systemic treatment. Primary endpoint is the 1-year PFS and 3-year PFS, OS, feasibility and safety, patient-reported outcomes and correlative studies are secondary endpoints. The trial is registered at clinicaltrials.gov (NCT04837859), financially supported by BeiGene and started recruitment in May 2024.

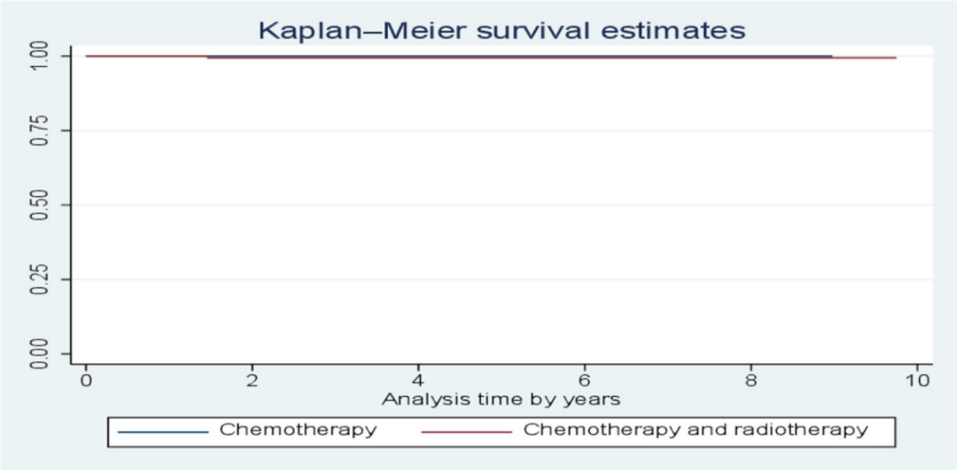
Outlook: INDIE is the first trial to investigate an individualized immunotherapy in treatment naïve early-stage unfavorable HL, potentially omitting both chemo- and radiotherapy in optimally responding patients. Together with extensive correlative studies on longitudinal tumor biopsies, blood and stool samples, this trial will generate critical insights into response-adapted 1st-line HL immunotherapy.

P055: KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

Reyad Dada[1], John Apostolidis[2], Refaei Belal Ibrahim[1], Asma Ahmed Salem[1], Mostafa Ibrahim Mahmoud[1], Hafiz Asif Iqbal[1], Tarik Boubakra[1], Hamza Ghatasheh[3], Azahr Nawaz[1], Khalid Halahleh[3]

[1]KFSHRC-Jeddah, [2]Department of Hematology & Stem Cell Transplantation, King Fahd Specialist Hospital, Kingdom of Saudi Arabia, [3]King Hussein Cancer Center, Amman, Jordan

Figure (1): Kaplan-Meier survival estimates of chemotherapy compared to chemotherapy with radiotherapy.



Introduction: The incorporation of radiotherapy (RT) into the initial treatment protocols for classical Hodgkin lymphoma (cHL) may vary across different medical institutions. Our study focuses on the outcomes of pts with classic Hodgkin lymphoma treated at three tertiary care centers in the Middle East. The retrospective analysis of collected data aims to uncover any differences between pts who underwent RT and those who did not.

Pts and Methods: Our retrospective analysis involved reviewing the medical records of pts with early-stage cHL treated between 2010 and 2021. Our analysis assessed the rates of CR and relapse.

Results: Total of 490 pts (247 female 243 males) with median age of 27 years fulfilled the inclusion criteria. Mean Follow-up time is 59 months. Most pts had nodular sclerosis subtype (68.2%) and 87.8% had stage II with 64.9% having B symptoms. In total, 57.8% of pts received RT. At the end of treatment, 87.8% of the entire cohort achieved complete remission.

46 pts of entire group relapsed: 21 pts did not receive RT, while 25 pts received RT as consolidation.

Among the pts who reached CR at first-line chemotherapy ($n = 420$), 57% proceeded with RT. Relapse rate of pts in CR who received RT as consolidation was 7.5%, compared to 7.2% ($p = 0.9$) for those who did not receive RT and reached CR at end of first-line chemotherapy.

A positive interim PET scan was documented in 25.7% of entire patient population, with 23.8% of these pts still having active disease at the end of chemotherapy. Among pts with positive interim and end-of-treatment (EOT) PET scan, 66.7% received RT, and 30% of these developed relapsed/refractory (r/r) disease. Additionally, 57.9% of pts with positive interim PET scan received RT, while 42.1% did not. Among those who did not receive RT, 15% had r/r disease, compared to 17.8% of those who did receive RT ($p = 0.8$). Ten pts with positive interim PET scan had negative EOT-PET scans and therefore did not receive RT. Among these pts, the rate of r/r disease was high, at 60%. At data cut-off (11/2022) there was no significant difference in PFS rate ($p = 0.75$) between pts who underwent radiation in comparison with the group of pts who were not irradiated. Overall survival was similar.

Conclusion: While our real-world data doesn't favor routine consolidation with RT for early-stage cHL pts with negative EOT-PET, our findings highlight RT's effectiveness in curing a substantial percentage of individuals with positive interim and EOT-PET.

P056: PEDIATRIC INFRADIAPHRAGMATIC HODGKIN'S LYMPHOMA: A UNIQUE IDENTITY

Asmaa Hamoda[1], Nashwa Ezzeldeen[1], Emad Moussa[2], Madeeha A.T. El Wakeel[1], Eman Khorshed[1], Maha Mehesen[1], Amr Elnashar[3], Sara Abdelkareem[4], Mohamed Zaghloul[1]

[1]Children Cancer Hospital of Egypt, National Cancer Institute, [2]Children Cancer Hospital of Egypt, Menoufyea University, [3]Children Cancer Hospital of Egypt, [4]Children Cancer Hospital of Egypt

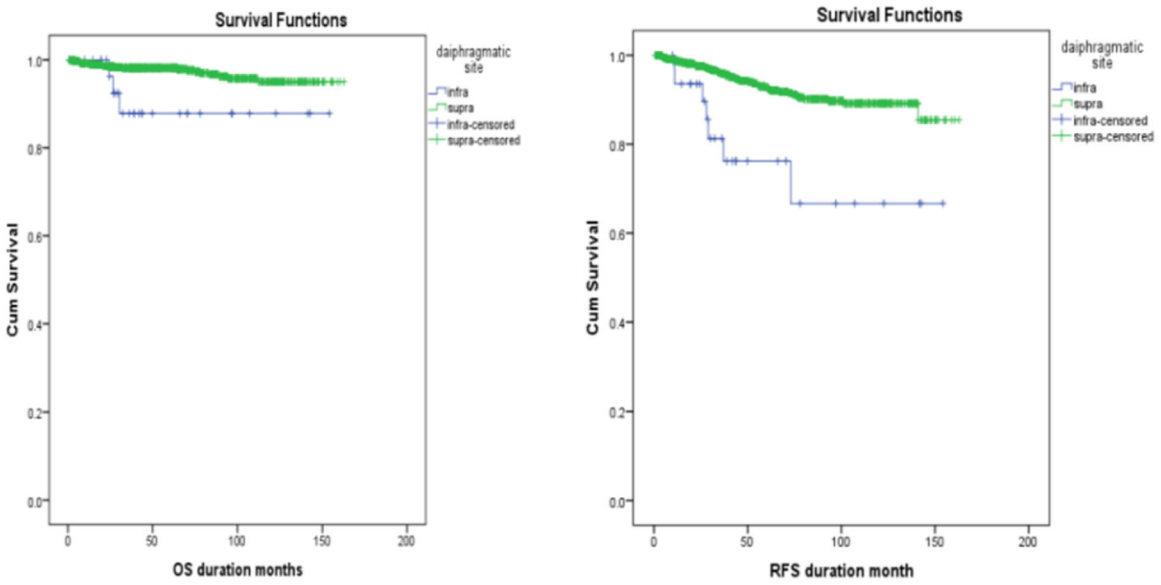


Figure 1: OS and RFS Correlation according to diaphragmatic site.

Background: Infra-diaphragmatic Hodgkin's lymphoma (IDHL) is a rare disease. The prognostic impact of infra-diaphragmatic localization of this lymphoma is controversial. We aim to evaluate the clinic- pathologic features and outcome of IDHL.

Methods: Between 2007 and 2020, all patients with histologically confirmed stage I/II IDHL were retrospectively evaluated including clinical presentation, initial lab work, radiological findings, response to initial treatment and their outcome in comparison to stage I/II supra-diaphragmatic HL (SDHL).

Results: Among 991 Hodgkin's lymphoma (HL) staged I/II, there were 35 IDHL (3.5%) patients with male to female ratio 2.5:1, median age of 10.1 years, 34.3% (12/35) of cases were histologically nodular lymphocytic predominant HL (NLPHL) while 37.1% (13/35) were classical HL (CHL) of mixed cellularity (MC) type, 34.3% (12/35) of patients presented with B symptoms. In 57% of cases erythrocyte sedimentation rate (ESR) was less than 30, 20% (7/35) of patients relapsed. Overall survival (OS) was 87.8% while relapse free survival (RFS) was 76.2% at 5 years, OS and RFS of the patients with adequate interim positron emission tomography/computed tomography (PET/CT) response were higher than those with inadequate response at 5 years ($p < 0.001$). OS according to diaphragmatic site was statistically significant ($p = 0.016$) (88.1% for infra, vs. 98.2% for supra-diaphragmatic) while RFS according to diaphragmatic site was also statistically significant ($p < 0.001$) (76.2%) for infra, versus (93%) for supra-diaphragmatic at 5 years.

Conclusions: Although IDHL cases do not carry high risk features still this category of the patients has lower OS and RFS in comparison to supra-diaphragmatic cases at initial presentation making infra- diaphragmatic site by itself a bad prognostic factor.

P057: PROTON THERAPY FOR LIMITED STAGE CLASSICAL HODGKIN LYMPHOMA PATIENTS (PRO-HODGKIN): AN INTERIM ANALYSIS OF CLINICAL OUTCOME

Christina Goldkuhl[1], Anna Bäck[2], Gunilla Enblad[3], Ingrid Glimelius[4], Lotta Hansson[5,6], Urban Jerlström[7], Ann-Sofie Johansson[8], Jenny Kahlmeter-Brandell[7], Johan Linderoth[9], Marzia Palma[5,6], Daniel Molin[3]

[1]Department of Oncology, Sahlgrenska University Hospital, Göteborg Sweden, [2]Department of Therapeutic Radiation Physics, Sahlgrenska University Hospital, Göteborg, Sweden, [3]Cancer Immunotherapy, Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden, [4]Cancer Precision Medicine, Department of Immunology, Genetics and Pathology, Uppsala, [5]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, [6]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden, [7]Department of Oncology, Faculty of Medicine and Health, Örebro University Hospital, Örebro, Sweden, [8]Department of Diagnostics and intervention, Umeå University, Sweden, [9]Department of Clinical Sciences, Division of Oncology and Pathology, Lund University, Lund, Sweden

Table 1. Patient characteristics and toxicity of proton therapy in the PRO-Hodgkin study.

Variable	Number of patients (%)		
Sex	F 30 (57), M 23(43)		
Mean age (range)	32.5 (18-60)		
Stage IA	10 (19)		
Stage IIA	42 (79)		
Stage 1B	1 (2)		
Prescribed dose, 20 Gy (RBE)	13 (25)		
Prescribed dose, 29.75 Gy (RBE)	40 (75)		
Neck target only	10 (19)		
Upper mediastinal target	38 (72)		
Lower mediastinal target	11 (21)		
Axilla only	4 (8)		
Mediastinum not involved	13 (24)		
Bulky disease (>10 cm)	12 (23)		
Deep inspiration breath hold	38 (72)		
Patients with mediastinal target treated in deep inspiration breath hold	38 (100)		
Overall survival	100%		
Progression free survival	100%		
Median follow-up from end of therapy	19 months		
Toxicity	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)
Dermatitis	32 (60)	1 (2)	1 (2)
Esophagitis	18 (34)	5 (9)	-
Pain	10 (19)	1 (2)	1 (2)
Nausea	6 (11)	-	-
Dry mouth	6 (11)	1 (2)	-
Cough	8 (15)	-	-
Mucositis	5 (9)	1 (2)	-
Pneumonitis	-	2 (4)	-
Neurological symptoms	5 (9%)		

Background: Most patients with limited stage classical Hodgkin lymphoma are cured with a short course of chemotherapy followed by radiotherapy (RT). Patients treated with RT are at risk of late side effects, particularly cardiovascular disease and second cancer. Proton therapy (PT) can reduce dose to organs at risk due to the finite range of the protons. This is a second interim analysis of the non-randomized PRO-Hodgkin study.

Methods: Since 2019, 53 patients with supradiaphragmal disease were treated with involved node/site PT with pencil beam scanning (PBS). Twenty-five patients not suitable for PT received photon therapy and were followed for comparison. Treatment was 2–4 cycles of ABVD followed by a dose of 20 Gy (RBE)/10 fractions to patients without risk factors and 29.75 Gy (RBE)/17 fractions to patients with risk factors. The median age was 32 (18–60) years. Forty-two (79%) patients were in stage IIA, 10 (19%) IA and 1 (2%) IB. All patients with mediastinal disease were treated in deep inspiration breath hold and mostly with two anterior oblique fields. Treatment plans were robustly optimized. All patients had a back-up photon plan.

Results: All patients were in complete remission (CR) after PT and none has died or relapsed at a median follow-up of 19 months from the end of therapy. Acute toxicity was generally limited apart from skin reaction in 34 (64%) patients. It was of grade 1 in 32 and grade 2–3 in 2 patients. Two patients suffered from pneumonitis grade 2 where symptoms declined after initiation of steroids (Table 1).

Five patients experienced an unforeseen neurological adverse event (AE), manifested as a hyperesthesia and/or burning sensation from the skin in a dermatomal pattern with onset 2 weeks to 5 months after end of radiotherapy. The symptoms were transient and so far, no patient has developed any long-term sequelae. However, the study was temporarily paused for investigation of the neurological AEs and during this period the eligible patients were treated with photon therapy. Some patients have also been treated with photon therapy due to dosimetric and technical reasons and due to patients choice.

Conclusion: PBS PT for Hodgkin lymphoma patients is well tolerated with good local control. Skin reaction was seen in a most patients and transient neurological AE and pneumonitis in a few. Dosimetric comparison between photon- and proton therapy plans will be analysed to evaluate which patients benefit the most from RT.

P058: REAL-LIFE DATA ON MORBIDITY AND CAUSE-SPECIFIC MORTALITY AFTER COMBINED MODALITY TREATMENT FOR CLASSICAL HODGKIN LYMPHOMA 2006–2015

Ingemar Lagerlöf[1], Per Wikman[1], Gunilla Enblad[1], Christina Goldkuhl[2], Marzia Palma[3], Helena Fohlin[4,5], Ingrid Glimelius[1], Daniel Molin[1]

[1]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden, [2]Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden, [3]Department of Haematology, Karolinska University Hospital, Stockholm, Sweden, [4]Regional Cancer Center of Southeast Sweden, [5]Department of Biomedical and Clinical Sciences, Medical Faculty, Linköping University, Linköping, Sweden

Figure 1: Relative survival of early-stage classical Hodgkin lymphoma patients, 18–65 years old, diagnosed during the years 2006–2015 in Sweden and treated with combined modality treatment.

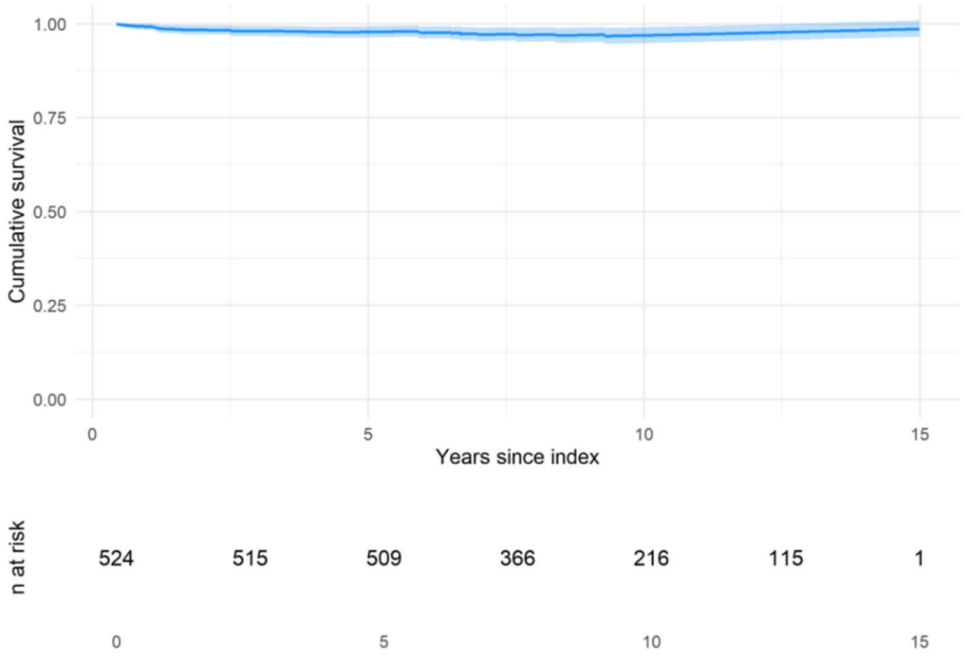


Figure 1: Relative survival of early-stage classical Hodgkin lymphoma patients, 18–65 years old, diagnosed during the years 2006–2015 in Sweden and treated with combined modality treatment.

Treating early-stage classical Hodgkin lymphoma (cHL) with a brief course of chemotherapy followed by radiotherapy (RT) results in high cure rate. In historical cohorts, RT is associated with long-term toxicity. With lower doses and smaller radiation volumes the toxicity needs to be re-evaluated. We have previously shown an absence of excess mortality (except for relapsing patients) and limited, but not eliminated, late morbidity in patients treated 1999–2005. Here, we aim to investigate the survival results and late effects in the following years.

Using a linkage of the Swedish Lymphoma Register and Swedish health registers (LymphomaBase), we identified patients aged 18–65 years, treated with 2–4 courses of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) followed by RT during the years 2006–2015 (n = 524), and matched comparators. The cohort was analysed for second cancer, diseases of the circulatory system (DCS), diseases of the respiratory system (DRS), relative survival (RS), and years of life lost, and compared with the cohort treated 1999–2005.

Hazard ratio (HR) for second cancer was not significantly elevated, for DCS it was 1.3 (95% CI, 1.0–1.8) and for the subgroup heart failure 2.6 (95% CI, 1.3–5.0). There was significant excess risk for DRS, HR 1.8 (95% CI, 1.4–2.4). There was minimal, but statistically significant, excess mortality among patients, with a RS rate of 0.98 (95% CI, 0.96–0.99) and 0.97 (95% CI, 0.95–0.99) at 5- and 10-years of follow-up, respectively. Years of life lost to cHL were in total 0.6 years/patient, but 0.90 years/patient included the first 5 years. Years of life lost to second cancer were 0.10 years/patient and 0.14 years/comparator (p = 0.85), to DCS 0.15 years/patient, and 0.06 years/comparator (p = 0.02).

Follow-up is too short to detect excess risk for second cancers. HR for DCS was roughly the same as in the preceding cohort, 1.3 compared to 1.5, while there is a trend towards lower risk for DRS, 1.8 compared with 2.6. Survival in this cohort is excellent. With minimal excess mortality, years of life lost is dominated by cHL, and the excess of years lost to CVD corresponds to only 15% of years lost to cHL. The results emphasize the importance of effective therapy to avoid relapses.

P059: SAFE RADIOTHERAPY FOR PREGNANT WOMEN WITH HODGKIN'S LYMPHOMA: MYTH OR REALITY?

Elżbieta Wojciechowska-Lampka[1], Magdalena Rosińska[1], Jacek Lampka[1], Włodzimierz Osiadacz[1], Joanna Tajer[1], Agnieszka Kuchcińska[1]

[1]*The Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Introduction: Cancer during pregnancy occurs in about 0.1% of pregnancies. Hodgkin's lymphoma is the most frequently diagnosed lymphoma in pregnant women. Diagnostic and therapeutic interventions involving ionizing radiation must ensure the best treatment for the mother while minimizing fetal risks, necessitating a multidisciplinary team. Administering radiotherapy during pregnancy involves evaluating potential fetal risks and optimizing procedures for safe treatment.

Materials and Methods: From 1990 to 2020, 162 pregnant patients with Hodgkin's lymphoma were treated at the Oncology Institute in Warsaw. This presentation highlights 23 patients (14.2%) who underwent radiotherapy during pregnancy. Two patients (8.7%) received radiotherapy in the first trimester, while 21 patients (91.3%) were treated in the second trimester. In the third trimester, none of the patients received irradiation. Gestational age and the primary location of affected areas were considered when planning the irradiation field (involved vs. mantle fields). Radiotherapy planning used 2D and 3D systems with computed tomography. Gamma radiation was administered using Cobalt 60 machines and linear accelerators with energy levels ranging from 1.25 to 4–6 MV and 15 MV. Individualized shields for the uterus and fetus, along with lead aprons, were utilized. Dosimeter positioning was monitored, with corrections based on weekly ultrasound exams of fetal and uterine fundus positions.

Results: Fetal doses during maternal irradiation ranged from 0 to 10 cGy with no observed fetal complications at higher doses. From 2018 to 2020, medical physicists conducted radiotherapeutic surveillance, verifying fetal doses multiple times. Toxicity of prenatal and postnatal radiation therapy was within grades 1–2, including skin and oral mucosal reactions, esophageal inflammation, hematologic, and cardiac disturbances. Four cases of Lhermitte's syndrome were reported. No complications required treatment interruptions or additional hospitalization.

Conclusions: Although modern principles of radiotherapy planning, techniques, equipment, and dosimetry are well-developed, the use of radiotherapy during pregnancy remains limited. Indications for radiotherapy may include significant nodal changes located above the diaphragm. Properly conducted radiotherapy is safe during pregnancy but must be applied only when appropriate planning, treatment delivery, and monitoring of fetal and uterine exposure doses are possible.

P060: TOTAL METABOLIC TUMOR VOLUME IMPAIRS THE SUCCESSFUL DETECTION OF CIRCULATING TUMOR DNA (CTDNA) IN EARLY-STAGE HODGIN LYMPHOMA PATIENTS – THE PRELIMINARY REPORT FROM THE RAFTING TRIAL

Marta Bednarek[1,2], Stephane Chauvie[3], Maria Pirosa[4,5,6], Luca Guerra[7,8], Annibale Versari[9], Michele Gregianin[10], Fabrizio Bergesio[3], Katia Pini[11], Georgia Alice Galimberti[11], Simone Bocchetta[11], Matin Salehi[11], Adam Wyszomirski[12], Alessandro Rambaldi[13], Marco Picardi[14], Kateryna Filonenko[15], Michał Kurlapski[15], Anna Sureda[16], Davide Rossi[17,5,6], Andrea Gallamini[18], Jan Maciej Zaucha[15]

[1]*2nd Division of Radiology, Medical University in Gdansk,* [2]*Department of Non-Commercial Clinical Research, Medical University in Gdansk,* [3]*Medical Physics Division, Santa Croce e Carle General Hospital, Italy,* [4]*Laboratory of Experimental Hematology, Institute of Oncology Research, Bellinzona, Switzerland,* [5]*Clinic of Hematology, Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland,* [6]*Faculty of Biomedicine, Universita'della Svizzera italiana, Lugano, Switzerland,* [7]*School of Medicine and Surgery, University of Milano Bicocca, Milan, Italy,* [8]*Nuclear Medicine Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy,* [9]*Nuclear Medicine Unit, Azienda Unità Sanitaria Locale-IRCCS of Reggio Emilia, Reggio Emilia, Italy,* [10]*Nuclear Medicine, Veneto Institute of Oncology, IOV-IRCCS, Padua, Italy,* [11]*Laboratory of Experimental Hematology, Institute of Oncology Research, Bellinzona, Switzerland,* [12]*Brain Diseases Centre, Medical University in Gdansk, Poland,* [13]*Ospedale Papa Giovanni XXIII, Bergamo,Italy,* [14]*Department of Clinical Medicine and Surgery, AOU Federico II, Naples,Italy,* [15]*Department of Hematology and Transplantology, Medical University of Gdansk and University Clinical Center, Gdansk, Poland,* [16]*Clinical Hematology Department, of Institut Català d'Oncologia–L'Hospitalet, IDIBELL, Universitat de Barcelona, Barcelona, Spain,* [17]*Experimental Hematology, Institute of Oncology Research, Bellinzona, Switzerland,* [18]*Research and Clinical Innovation Department, Lacassagne Cancer Center, Nice, France*

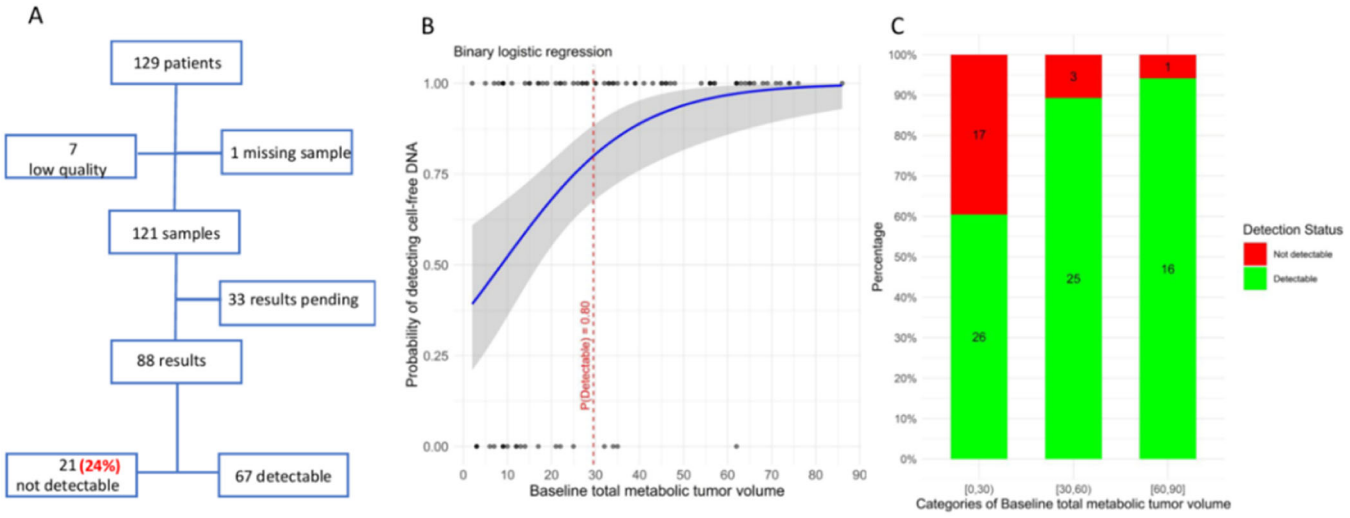


Figure 1 Panel A- the flow chart of the baseline tumor-free DNA samples, Panel B – the correlation between total metabolic tumor volume (TMTV) and detection (Yes/No) tumor-free DNA Panel C- the rate of detectable samples in three equal intervals of TMTV

Background: Liquid biopsy detects cell-free tumor-specific DNA (ctDNA) circulating in plasma. In Hodgkin Lymphoma (HL), despite the scarcity of neoplastic cells, ctDNA is detected in the plasma of 90% of patients. However, there is no data correlating the disease burden and ctDNA assay.

Methods: RAFTING trial (EudraCT 2020–002 382-33, Research financed by the Medical Research Agency, Poland, Project n° 2019/ABM/01/00060) is an example of a personalized medicine treatment in which (1) the total metabolic tumor volume at baseline (bTMTV) determines the treatment intensity and (2) ctDNA is used for monitoring HL recurrence. In RAFTING non-bulky early-stage (I-IIA) HL patients, enrolled from 37 European centers the bTMTV is centrally calculated by an Expert Panel of Nuclear Medicine physicians; low-risk patients (TMTV < 84 mL and negative interim PET2 (PET-2) are treated with ABVD alone (2 or 4 cycles) and addressed to fa watchful follow-up. ctDNA is assessed every 3 months after ABVD end for 1 year and centralized in Bellinzona (CH) for the assay. TMTV is calculated by blinded independent central review with a relative SUV threshold of 41% by three reviewers. The LyV4.0 ctDNA CAPP-seq assay (sensitivity: 0.1%) was used to qualify and quantify ctDNA. A binary logistic regression was fitted with binary cfDNA (present/absent; as the dependent variable) and the bTMTV (independent variable). In Figure 1 the vertical line indicates the bTMTV value at which the predicted probability of the binary cfDNA being detectable is 0.80. The 95% confidence interval was calculated using the bootstrap percentile method based on 1000 replicates. The relationship between cfDNA and baseline TMTV was assessed using Spearman's rank correlation coefficient.

Results: ctDNA was available for assay in 128/174p, and 7 samples resulted of low quality. So far 88/121 collected samples (73%) analyzed; (Figure Panel A). ctDNA was not detected in 21 (24%),while normal cell-free DNA (Figure 1 Panel A). The median measured TMTV value was 34 mL (3–86 mL). Upon binary logistic regression, a TMTV value < 30 mL reduced the ctDNA detection rate in plasma by 80% the detection of ctDNA below 80% (Panels B and C). The Spearman's correlation between cfDNA and bTMTV was $\rho = 0.325$ (p 0.0072).

Conclusion: In this preliminary cohort of p. enrolled in RAFTING trial ctDNA could not be monitored in one quarter (25%) of p. A TMTV value < 30 mL impairs the successful detection of ctDNA in untreated early HL.

P061: VARIATION IN THE DELIVERY OF RADIOTHERAPY AS PART OF FRONTLINE CURATIVE TREATMENT FOR HODGKIN LYMPHOMA ACROSS HEALTHCARE PROVIDERS IN ENGLAND

David Jones[1], Philip Clarke[1], Jane Wolstenholme[1], David Cutter[1], John Broggio[2]

[1]*University of Oxford*, [2]*National Cancer Registration and Analysis Service*

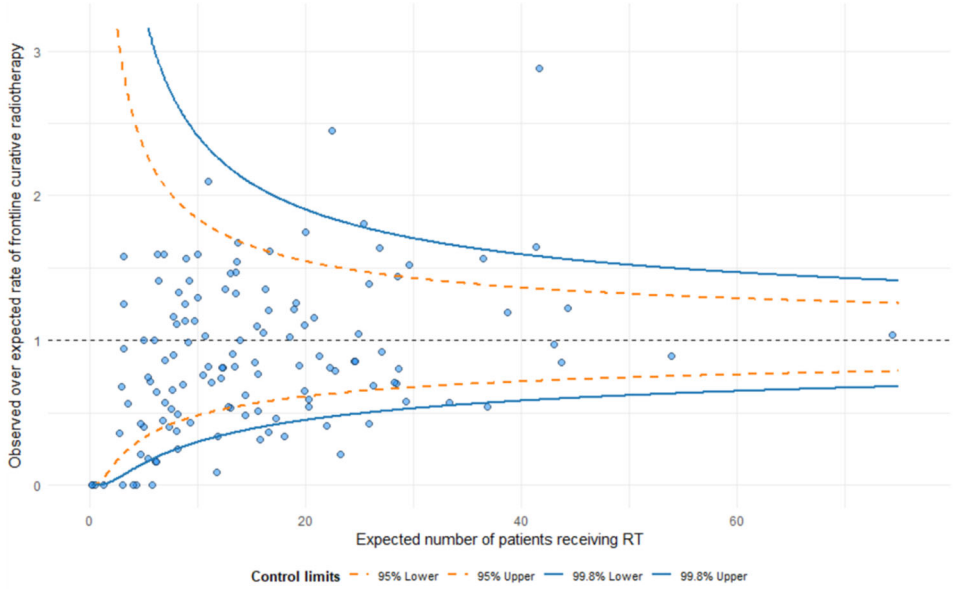


Figure 1: Funnel plot of the observed/expected radiotherapy delivery rate for each NHS Trust with 2δ and 3δ control limits

Background: The addition of radiotherapy (RT) to chemotherapy confers superior disease free-survival in limited-stage Hodgkin lymphoma (HL). However, the consequences in terms of late effects are currently unclear. Given this uncertainty, we seek to understand the extent to which receipt of frontline RT varies as a result of the provider at which a given patient receives treatment in England.

Methods: Cancer registry data was obtained for all classical HL patients diagnosed 1st Jan 2014 to 31st Dec 2020 in England. Multivariate logistic regression was used to assess associations between patient characteristics (age, sex and Index of Multiple Deprivation (IMD) quintile) and odds of receiving frontline RT. Greater than expected variation across provider (NHS Trust) in the case-mix adjusted rate of delivery was assessed via funnel plots. A hierarchal logistic regression with random intercepts for treating NHS Trust was specified and a likelihood ratio test performed to assess improvement of fit. Variation across NHS Trusts was quantified through the variance partition coefficient (VPC) and median odds ratio (MOR).

Results: 2019 of 9743 HL patients treated at 128 different NHS Trusts received frontline RT. The percentage receiving RT stayed consistent at 20% across the 7 years, ranging from 23% (2015) to 19% (2018). The case-mix adjusted rate of RT delivery was outside 2δ (95%) control limits for 33% of NHS Trusts (10 above, 32 below). Hierarchal specification led to a statistically significant increase in goodness-of-fit. Both suggestive of hospital-level effects. Being of male sex had a positive effect on the odds of receiving RT (OR = 0.122, $p = 0.095$). Similarly, patients in the least deprived IMD quintile had an increased odds of receiving RT (OR = 0.223, $p = 0.010$) compared to the most deprived. Older age at diagnosis had a non-statistically significant negative effect on the odds of receiving frontline RT (OR = −0.002, $p = 0.092$). The resulting VPC estimate suggests 10% of variation in the odds a patient receives RT is attributable to the NHS Trust-level. The increase in the MOR of receiving RT were the same patient to move from a lower-RT delivery rate NHS Trust to a higher-RT delivery rate NHS Trust was 1.405.

Conclusions: Healthcare providers had a statistically significant influence on the odds of receiving frontline RT. This effect size was greater than that of patient sex. Improved knowledge to allow optimal patient selection for RT is required.

LIVING BEYOND LYMPHOMA

T062: A PRIORI ESTIMATION OF MEDIASTINAL TOXICITIES AFTER RADIOTHERAPY FOR HODGKIN LYMPHOMA–A SECONDARY ANALYSIS OF THE HD16/17 TRIAL BY THE GERMAN HODGKIN STUDY GROUP USING NORMAL TISSUE COMPLICATION PROBABILITY CALCULATIONS

Michael Oertel[1], Priska Hölscher[1], Dominik A. Hering[1], Christopher Kittel[1], Michael Fuchs[2], Niklas B. Pepper[1], Stefan Lerch[1], Uwe Haverkamp[1], Peter Borchmann[2], Hans T. Eich[1]

[1]*Department of Radiation Oncology, University Hospital Muenster, Muenster, Germany,* [2]*Department of Internal Medicine, University Hospital of Cologne, Cologne, Germany*

Background: Treatment-associated cardiopulmonary toxicities are main causes for long-term mortality of Hodgkin lymphoma survivors. Concerning radiotherapy, disease extent, field design and setup of radiation treatment may alter the dosimetric exposure and therefore the individual risk profile. Previous works of our group could elaborate an overall low-risk profile for pulmonary toxicities which is modulated by treatment techniques. The following analysis aims at a pre-treatment estimation of relevant mediastinal toxicities after radiotherapy in modern trials for first line treatment of Hodgkin lymphoma.

Methods: Normal tissue complication probability calculations (NTCP) were used to evaluate the toxicity rates for the heart, lungs and female breast of patients undergoing radiotherapy for early-stage Hodgkin lymphoma. Overall, 45 randomly selected patients from the HD16 and HD17 trials by the German Hodgkin study group were included and risks were calculated using the Lyman–Kutcher–Burman model.

Results: Median RT doses to the heart, lungs, left breast and right breast were 6.4, 5.4, 18.4, and 16.2 Gy in the HD16 cohort, and 20.6, 11.0, 26.2, and 24.6 Gy in the HD17 cohort. Consequently, median NTCP values for pericarditis, pneumonitis and fibrosis of the left or right breast were 0.0%, 0.0%, 0.7% and 0.6% in the HD16 cohort, and 0.0%, 0.1%, 1.1%, and 1.0% in the HD17 cohort, respectively. In accordance with these numbers, none of the included patients displayed any of the evaluated toxicities during clinical follow-up. The use of higher doses (30 Gy) in the HD17 cohort led to an increase in toxicity compared to the HD16 cohort (20 Gy) concerning pneumonitis ($p < 0.01$) and breast fibrosis ($p = 0.02$ and 0.01, respectively). No significant influence of the planning target volume size or the radiation technique could be found in this study.

Conclusion: In summary, the clinically observed and NTCP-calculated toxicity rates corroborate the overall low-risk profile of radiotherapy for Hodgkin lymphoma. Further treatment individualization will be attempted in the future.

T063: CONCORDANCE BETWEEN LATE EFFECTS REPORTED BY PHYSICIANS AND PATIENTS IN A COHORT OF LONG-TERM HODGKIN LYMPHOMA SURVIVORS: AN ANALYSIS OF DATA FROM NINE CONSECUTIVE EORTC-LYSA TRIALS

Sidsel J. Juul[1], Sára Rossetti[2], Berthe M.P. Aleman[3], Flora E. Van Leeuwen[4], Marleen A.E. Van Der Kaaij[5], Francesco Giusti[6], Paul Meijnders[7], John M.M. Raemaekers[8], Hanneke C. Kluin-Nelemans[9], Michele Spina[10], Daphne Krzisch[11], Camille Bigenwald[12], Aspasia Stamatoullas[13], Marc André[14], Wouter J. Plattel[9], Martin Hutchings[2], Maja V. Maraldo[1]

[1]Department of Oncology, Copenhagen University Hospital-Rigshospitalet, Copenhagen, Denmark, [2]Department of Haematology, Copenhagen University Hospital-Rigshospitalet, Copenhagen, Denmark, [3]Department of Radiation Oncology, the Netherlands Cancer Institute, Amsterdam, the Netherlands, [4]Department of Psychosocial Research and Epidemiology, the Netherlands Cancer Institute, Amsterdam, the Netherlands., [5]Department of Internal Medicine, Amstelland Hospital, Amstelveen, The Netherlands, [6]EORTC Headquarters, Brussels, Belgium (present affiliation: Sciensano, Brussels, Belgium), [7]Department of Radiation Oncology, Iridium Network, University of Antwerp, Antwerpen, Belgium, [8]Department of Hematology, Radboud University Medical Center, Nijmegen, the Netherlands, [9]Department of Hematology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands, [10]Division of Medical Oncology and Immunerelated Tumors, IRCCS Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy, [11]AP-HP, Hôpital Saint-Louis, Hemato-oncologie, DMU DHI: Université de Paris, F-75010 Paris, France, [12]Department of Hematology, Institute Gustave Roussy, Villejuif, France, [13]Department of Haematology, Centre Henri Becquerel, Rouen, France, [14]Department of Haematology, CHU UCL NAMUR, Yvoir, Belgium

Background: Studies looking into the concordance between late effects reported by physicians vs. those reported by Hodgkin lymphoma (HL) survivors are missing.

Methods: The EORTC lymphoma group database provides extensive records of the long-term consequences of HL treatment, reported by both patients and physicians. This resource enables the correlation of information from both perspectives. In this retrospective study, survey responses from a total of 1230 long-term HL survivors with a median follow-up time of 14.3 years were included. Twenty-six disease- and treatment-related late effects from various organ systems were assessed. The concordance between physicians and survivors was systematically evaluated using percentage agreement and kappa statistics. Potential non-responder biases and associations with patient and disease characteristics were also investigated.

Results: Agreement levels (as indicated by Kappa statistics) varied from none to moderate agreement, with the highest Kappa values observed for myocardial infarction (kappa = 0.55, 95% CI: 0.43–0.66) and pulmonary embolism (kappa = 0.55, 95% CI: 0.35–0.75). The overall percentage agreement varied from 77.0% for persistent fatigue to 99.5% for bowel perforation. HL survivors consistently reported a higher prevalence of late effects compared to physicians. Notably, the prevalence of subjective symptoms such as persistent fatigue and xerostomia was repeatedly underreported by physicians. A trend towards higher concordance was observed in survivors with higher clinical stage, higher educational level, and treatment initiated at younger ages. Additionally, findings indicated that individuals who did not respond to the questionnaire regarding late effects experienced fewer late effects compared to those who did respond.

Conclusion: Substantial discrepancies were noted in the reported prevalence of late effects between survivors and physicians, especially for outcomes which are not easily quantified. However, potential biases must be considered in these findings, as individuals experiencing more late effects were more likely to respond to the survey. This may reduce some of the observed discrepancies, but our data still emphasize a group of survivors whose needs might be overlooked. It is therefore essential to integrate outcomes reported by both physicians and survivors to achieve a comprehensive assessment of the long-term consequences of HL treatment.

T064: NOVEL 3D SPECKEL TRACKING IMAGING MODALITY IN DETECTING CARDIAC TOXICITY IN ASYMPTOMATIC PEDIATRIC HL SURVIVORS

Zeinab Salah[1], Mustafa Selim[2], Nesreen Ali[3], Antoine Abdelmassih[4], Mohammed Mosaad Soliman[4], Nahla M. El Nabarawy[5], Hany Hussein[6], Doaa Mohamed Albeltagi[7], Iman Sidhom[8]

[1]Prof. Pediatrics at Faculty of Medicine, Cairo University and Senior Consultant at CCHE-57357 Hospital, Cairo, Egypt, [2]Lecture. Pediatric Oncology at NCI, Cairo University, Cairo, Egypt, [3]Associate Professor of Pediatric Oncology at National Cancer Institute, Cairo University, Egypt and Consultant at Children Cancer Hospital Egypt [CCHE-57357], [4]Assistant professor at pediatric department, Cairo University, Egypt, [5]Consultant at survival clinic at CCHE-57357 Hospital, Cairo, Egypt, [6]Prof. Pediatric Oncology at NCI, Cairo University, Egypt, [7]Clinical Research supervisor, Clinical Research Centre at CCHE-57357 Hospital, Cairo, Egypt, [8]Prof. Pediatric Oncology at NCI, Cairo University and Senior Consultant at CCHE-57357 Hospital, Cairo, Egypt

Background: Speckle tracking echocardiography (STE) is an innovative non-invasive imaging technique that can measure myocardial deformation, showing promise in identifying early subclinical myocardial damage. This study aimed to assess how STE correlates with traditional 2D echocardiographic parameters in predicting anthracycline-induced cardio-toxicity in pediatric Hodgkin Lymphoma (HL) cancer survivors.

Methods: This is a prospective study involving 116 pediatric HL survivors and 32 age- and sex-matched control cases were screened using Tissue Doppler Imaging (TDI) and 3D speckle tracking echocardiography. Data on chemotherapy cumulative doses and radiotherapy were retrieved from patient records.

Results: Chemotherapy-related cardiac dysfunction (CTRCD) was not detected using traditional 2D echocardiographic parameters for assessing left ventricular (LV) systolic function. Ejection fraction values did not significantly differ from baseline (mean 67.2+4.06 vs. 77.8+5.73 with $p > 0.05$). However, a notable distinction was observed in 3D global longitudinal strain (GLS) between the study group and controls (18.4± 3.12 vs. 18.8 ± 4.41, $p < 0.05$). Twenty-five out of 116 patients (21.5%) exhibited cardio-toxicity, showing over a 15% reduction in 3D GLS compared to the control mean. Additionally, LV diastolic function assessed by TDI was impaired in cases relative to controls, with significant differences in mitral E″/A′ and mitral septal E/E′ ratios ($p < 0.05$), indicating higher filling pressures in the study population. Systolic dysfunction as measured by 2D EF% & 3D STE GLS showed no statistical significant difference post 4–6 cycles of chemotherapy or radiotherapy ($p > 0.05$). In contrast, Mitral E/E′ ratio showed significant correlation to cumulative chemotherapy dose ($p < 0.05$).

Conclusion: Despite apparently normal LV systolic function in asymptomatic HL survivors, 3D STE, GLS values indicate impaired cardiac function in these patients. In contrast, TDI; E/E′ ratio which points to LV diastolic dysfunction which usually precedes systolic dysfunction showed significant correlation to cumulative chemotherapy dose. The aforementioned findings point to the need of regular screening of patients with HL during treatment by 3D STE, GLS is crucial for early detection of cardiac toxicity independent of treatment adjustments. Further studies are needed to explore the value of diastolic dysfunction in cancer patients.

P065: AN EXPLORATION OF PATIENT SPECIFIC AND SYSTEMIC DELAYS AS PART OF THE DIAGNOSTIC ODYSSEY IN PATIENTS WITH HODGKIN LYMPHOMA–AN ANALYSIS OF THE LYMPHOMA COALITION'S 2022 GLOBAL PATIENT SURVEY

Steve Kalloger[1,2,3], Amanda Watson[1], Shawn Sajkowski[1], Lorna Warwick[1]

[1]*Lymphoma Coalition*, [2]*Department of Pathology and Laboratory Medicine University of British Columbia*, [3]*School of Population and Public Health University of British Columbia*

Introduction: The diagnosis of classical Hodgkin lymphoma (cHL) is complex, requiring multiple immunohistochemical markers. This may require seeking care from specialist centers which translates into sequential referrals initiating from primary care physicians. This process results in one class of diagnostic delay which we will term systemic delay (SD). Conversely, individual patients may exhibit symptoms but delay seeking medical advice for up to a year or more, which we will refer to as patient delay (PD). We sought to explore the mosaic of these different types of delays and how they contribute to the diagnostic odyssey.

Methods: The Global Patient Survey on Lymphomas & CLL was conducted in 2022 to capture the experiences of patients with lymphoma. As part of this survey, patients were asked how many healthcare professionals they had to see prior to receiving their final diagnosis (Range: 1 to more than 5). Additionally, patients were asked how long they were experiencing symptoms prior to seeking medical care (Range: <1 month to ≥1 year). Results were cross-tabulated for analysis.

Results: Overall, 722 patients with cHL had valid responses to the questions used for this study with a median age of 36 [18–89]. Females comprised 68% of the study sample. Approximately half of patients (51%) sought medical care within 3 months of symptom onset while 27% waited 6 months or longer. The majority of patients (68%) received a diagnosis of cHL after seeing 1 to 3 healthcare professionals. A surprisingly large proportion of patients (19%) reported seeing 5 or more healthcare professionals before receiving their diagnosis. When looking at both SD and PD, 52% of patients receive a diagnosis within 6 months of symptom onset and with seeing 3 or fewer healthcare providers.

Conclusion: Studies have indicated that diagnostic delay has minimal adverse effect on prognosis. However, we contend that different delays may impact prognosis. Delays by the patient may indicate that symptoms are more tolerable and perhaps associated with less aggressive disease or they may be attributing symptoms to less serious diseases. Conversely, systemic delays may yield inferior outcomes, especially when coupled with delays by patient's seeking medical care. These results indicate that improved diagnostics are warranted to simplify the diagnosis of cHL and accelerate the treatment of this disease. Also, there is room for improved symptom awareness in target populations.

P066: ANALYSIS OF FETAL DOSE EXPOSURE BY MODERN RADIATION THERAPY IN PREGNANT PATIENTS WITH SUPRADIAPHRAGMATIC HODGKIN LYMPHOMA - A PHANTOM-BASED SIMULATION

Michael Oertel[1], Gina Smeets[1], Isabel Vogt[1], Heidi Wolters[1], Christopher Kittel[1], Dominik A. Hering[1], Burkhard Greve[1], Uwe Haverkamp[1], Hans T. Eich[1]

[1]*Department of Radiation Oncology, University Hospital Muenster, Muenster, Germany*

Background: Modern involved-site radiotherapy (ISRT) for Hodgkin lymphoma uses reduced field sizes and radiation doses with a subsequent low-toxicity profile. However, in the case of pregnant patients, even small doses may harm the mother and the unborn child. In lack of evidence-based data for this complicated treatment situation, we conducted a phantom-based simulation to analyze the dosimetric impact of modern cervical and mediastinal ISRT on the uterus.

Methods: Target volumes for cervical and mediastinal ISRT were contoured and used for calculation of three comparison plans (3D-CRT, IMRT and VMAT), respectively. Afterwards, dosimetric measurements were conducted using the humanoid Alderson-phantom. Thermoluminescent dosimeters (TLD) were placed at representative positions within the phantom to account for early and late stages of pregnancy, respectively. Overall, six measurements (two for every radiotherapy plan) with 38 TLD were conducted.

Results: With a RT dose of 19.8 Gy, the median total exposure to the uterus in early pregnancy was 8.8 mGy, 15.4 mGy and 9.9 mGy for 3D-CRT, IMRT and VMAT respectively. In late pregnancy, 12.6 mGy (3D-CRT), 19.7 mGy (IMRT) and 13.8 mGy (VMAT) were measured for a RT dose of 19.8 Gy and 19.5 mGy (3D-CRT), 30.4 mGy (IMRT) and 21.4 mGy (VMAT) for 30.6 Gy. By applying a tissue weighting factor of 0.05, IMRT and VMAT with 30.6 Gy exceeded an effective dose equivalent >1 mSv. In contrast, mediastinal ISRT resulted in higher uterine doses with 44 mGy, 63.8 mGy and 60.5 mGy for 3D-CRT, IMRT and VMAT respectively. In late pregnancy, 138.6 mGy (3D-CRT), 161.7 mGy (IMRT) and 161.7 mGy (VMAT) were estimated for a RT dose of 19.8 Gy, whereas 214.2 mGy (3D-conformal), 249.9 mGy (IMRT) and 249.9 mGy (VMAT) were calculated for 30.6 Gy. As a consequence, all three comparison plans resulted in an effective dose equivalent >1 mSv, both with a treatment dose of 19.8 Gy as well as 30.6 Gy.

Conclusion: The calculated RT doses at the uterus for cervical ISRT are overall low and only exceeded the legal limit of 1 mSv in the case of IMRT and VMAT (30.6 Gy). For the mediastinal ISRT, all three treatment technique exceeded the threshold of 1 mSv. Overall, the possible indication of radiotherapy in pregnant women always requires a careful risk-benefit consideration and individualized planning.

P067: EXCELLENT OUTCOMES WITH LOW INTENSITY TREATMENT BASED ON AGE AND STAGE IN CHILDREN AND ADULTS WITH NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA (NLPHL): A 10 YR RETROSPECTIVE ANALYSIS OF PATIENTS FROM 8 UK CENTRES

Thomas Jackson[1], Amy A. Kirkwood[2], Kushani Ediriwickrema[3], Satyen Gohil[3], Xiao-Yin Zhang[4], Graham P. Collins[4], Georgina Hall[5], David Hopkins[6], Pamela Mckay[6], Ananth Shankar[1], Valeria Fiaccadori[1]

[1]Children and Young People Cancer Services, University College London Hospital, London, UK, [2]Cancer Research UK & UCL Cancer Trials Centre, UCL Cancer Institute, University College London, London, UK, [3]Department of Haematology-University College London Hospital, London, UK, [4]Department of Haematology-Oxford University Hospital, Oxford, UK, [5]Department of Paediatrics, Oxford Children's Hospital, Oxford, UK, [6]Department of Haematology, Beatson West of Scotland Cancer Centre, Gartnavel Hospital, Glasgow, UK

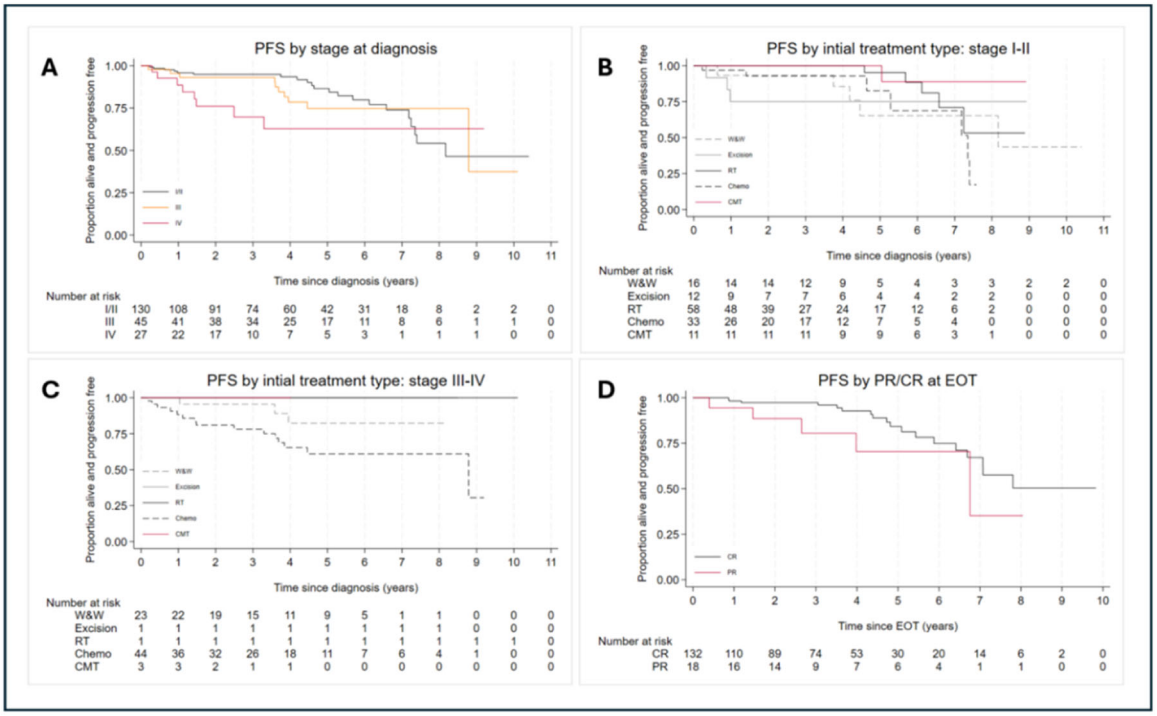


Figure 1: A: PFS by stage, B: PFS by treatment type (stage I/II), C: PFS by treatment type (stage III/IV) D: PFS by end of treatment response

Background: NLPHL is a rare subtype of Hodgkin lymphoma with no standardised treatment (trt). We performed an audit of trt and outcomes in the UK over a period of 10 years.

Methods: This is a retrospective cohort study of patients (pts) all ages diagnosed with NLPHL between 2011–2022 across 8 UK centres. PFS and OS were measured from date of diagnosis (or response) until first event.

Results: Of the total 203 pts, 144 were male (71%). Median age at diagnosis was 38 years (range 8–84); 32 pts (16%) were <18, 130 pts (64%) were stage I–II, 160 pts (83%) did not have B symptoms. A watch and wait (W & W) approach was adopted in 39 pts (19%), of whom 16 (41%) later commenced trt; at a median time of 1.7 years (IQR: 0.9–3.8), 13 pts (81%) had chemotherapy (CT) and 3 (19%) radiotherapy (RT). Of the remaining 164 pts, 13 (8%) had lymphnode excision only, 59 (36%) had RT, 78 (48%) CT and 14 (8%) had CT+RT (combined modality treatment, CMT). Age and stage influenced trt: W & W pts were older than all other groups, stage I/II pts were more likely to undergo excision or RT. W & W and RT were not used in pts<18: 5 pts (16%) had excision, 26 (81%) CT and 1(3%) CMT. For the 92 CT/CMT pts, the most common regimens were: CVP [*N* = 41 (45%); cyclophosphamide, vinca alkaloid, prednisolone] with (26; 28%), or without (15; 16%) Rituximab (R), R-CHOP [*N* = 24 (26%); rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone] and ABVD [*N* = 19 (21%); doxorubicin, bleomycin, vincristine, dacarbazine] with (6; 6%) or without (13; 14%) R. Overall response rates did not differ between CT (93%), RT (100%) and CMT (100%): $p = 0.17$. With a median follow up of 4.2 years (IQR 2.2–6.7), 5 yr PFS was 80% (95% CI: 72–86) and OS 92% (86–95) for the whole cohort. PFS by stage and initial trt is shown in Figure 1A–C. There were 16 deaths, none directly related to lymphoma, 1 related to salvage trt, 4 due to COVID-19. PFS did not differ significantly for pts in PR vs CR after first line trt [HR: 1.89 (0.70–5.12), $p = 0.21$; Figure 1D]. Transformation to high grade was reported in 8 adults (4%). Delaying trt in 16 patients in the W & W cohort who subsequently required trt did not appear to affect outcome; all are alive (median follow-up: 3.8 yrs), 13/16 (81%) showing no active disease.

Conclusions: Outcomes in NLPHL are excellent with low intensity trt based on age and stage, also in pts in PR at end of first line trt. A W & W approach prevents a proportion of pts needing trt and it does not impact negatively on survival.

P068: HODGKIN'S LYMPHOMA IN ARMENIA: DIAGNOSTIC DELAYS AND THE UNINTENDED BENEFITS OF COVID-19 SCREENING

Lusine Sahakyan[1], Diana Soghomonyan[1], Astghik Voskanyan[1], Arev Stepanyan[2], Lusine Stepanyan[2], Marina Melik-Andreasyan[1], Levon Evoyan[1], Miranush Saaryan[1]

[1]*Yeolyan Hematology and Oncology center*, [2]*National Center of Oncology after V. A. Fanarjian*

Hodgkin's Lymphoma in Armenia: Diagnostic Delays and the Unintended Benefits of COVID-19 Screening

[1]Sahakyan L.S., [1]Soghomonyan D.R., [1]Voskanyan A.A., [2]Stepanyan A.H., [2]Stepanyan L.G., [1]Melik-Andreasyan M.G., [1]Evoyan L.V., [1]Saaryan M.V.

[1]Yeolyan Hematology and Oncology Center, [2]National Center of Oncology after V. A. Fanarjian

Background: Hodgkin's lymphoma (HL) is a highly treatable malignancy, yet timely diagnosis and initiation of treatment are crucial for achieving favorable outcomes. This study examines the impact of diagnostic delays - specifically, the time from symptom onset to diagnosis and treatment initiation - on treatment success among Armenian patients with HL, with a focus on the years 2019 to 2023, a period marked by the COVID-19 pandemic.

Methods: A retrospective analysis was conducted on a cohort of Hodgkin's lymphoma patients treated at the Yeolyan Hematology and Oncology Center in Armenia between 2019 and 2023. Patient records were meticulously reviewed to collect data on demographic characteristics, presenting symptoms, duration from symptom onset to diagnosis, stage at diagnosis, treatment modalities, and treatment outcomes.

Results: Among the 368 patients analyzed (55.3% males and 44.7% females). Incidence rates of HL have stayed flat since the 2014-2023, but mortality rates have steadily declined from 14% cases in 2014-2018 to 9.5% in 2019-2023. The median duration from symptom onset to diagnosis was 2/6 weeks/months. Patients experiencing prolonged delays in diagnosis were more likely to present with advanced-stage disease compared to those with shorter diagnostic intervals. Additionally, delayed diagnosis correlated with significant delays in treatment initiation. Notably, the COVID-19 pandemic period from 2020 to 2023 contributed to a reduction in diagnostic delays, as the surge in chest CT scans due to COVID-19 led to earlier detection of HL. In 2020, this increased vigilance completely eliminated diagnostic delays in some cases. No statistically significant increase in treatment complications and mortality rates was observed in the post-COVID period compared to previous years.

Conclusion: The study highlights the critical importance of minimizing diagnostic delays in Hodgkin's lymphoma to prevent advanced disease presentation and ensure timely treatment initiation. Interestingly, the COVID-19 pandemic inadvertently facilitated earlier detection of HL in Armenia due to the widespread use of chest CT scans. This finding underscores the potential benefits of routine imaging in high-risk populations. Future efforts should focus on maintaining prompt diagnostic pathways and leveraging advancements in imaging technology to improve early detection and treatment outcomes for Hodgkin's lymphoma patients.

Keywords: *Hodgkin's lymphoma, delayed diagnosis, treatment success, time to treatment, chest CT scans, early detection, survival outcomes, Armenian patients, COVID-19.*

Figure 1: whole abstract

Background: Hodgkin's lymphoma (HL) is a highly treatable malignancy, yet timely diagnosis and initiation of treatment are crucial for achieving favorable outcomes. This study examines the impact of diagnostic delays—specifically, the time from symptom onset to diagnosis and treatment initiation—on treatment success among Armenian patients with HL, with a focus on the years 2019 to 2023, a period marked by the COVID-19 pandemic.

Methods: A retrospective analysis was conducted on a cohort of Hodgkin's lymphoma patients treated at the Yeolyan Hematology and Oncology Center in Armenia between 2019 and 2023. Patient records were meticulously reviewed to collect data on demographic characteristics, presenting symptoms, duration from symptom onset to diagnosis, stage at diagnosis, treatment modalities, and treatment outcomes.

Results: Among the 368 patients analyzed (55.3% males and 44.7% females). Incidence rates of HL have stayed flat since the 2014–2023, but mortality rates have steadily declined from 14% cases in 2014–2018 to 9.5% in 2019–2023. The median duration from symptom onset to diagnosis

was 2/6 weeks/months. Patients experiencing prolonged delays in diagnosis were more likely to present with advanced-stage disease compared to those with shorter diagnostic intervals. Additionally, delayed diagnosis correlated with significant delays in treatment initiation. Notably, the COVID-19 pandemic period from 2020 to 2023 contributed to a reduction in diagnostic delays, as the surge in chest CT scans due to COVID-19 led to earlier detection of HL. In 2020, this increased vigilance completely eliminated diagnostic delays in some cases. No statistically significant increase in treatment complications and mortality rates was observed in the post-COVID period compared to previous years.

Conclusion: The study highlights the critical importance of minimizing diagnostic delays in Hodgkin's lymphoma to prevent advanced disease presentation and ensure timely treatment initiation. Interestingly, the COVID-19 pandemic inadvertently facilitated earlier detection of HL in Armenia due to the widespread use of chest CT scans. This finding underscores the potential benefits of routine imaging in high-risk populations. Future efforts should focus on maintaining prompt diagnostic pathways and leveraging advancements in imaging technology to improve early detection and treatment outcomes for Hodgkin's lymphoma patients.

P069: MALE SEX AND LONGER TIME SINCE HODGKIN LYMPHOMA DIAGNOSIS ARE ASSOCIATED WITH NON-ATTENDANCE AT SURVIVORSHIP CLINICS

Eline M.J. Lammers[1], Berthe M.P. Aleman[2], Michael Schaapveld[1], Josée M. Zijlstra[3], Cécile P.M. Janus[4], Roel J. De Weijer[5], Maaike G.A. Schippers[6], Rinske S. Boersma[7], Saskia S. Gommers[8], Mirjam Kappert[9], Flora E. Van Leeuwen[1], Annelies Nijdam[1]

[1]Department of Epidemiology, The Netherlands Cancer Institute, Amsterdam, the Netherlands, [2]Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands, [3]Department of Haematology, Amsterdam UMC, location Vrije Universiteit, Cancer Center Amsterdam, the Netherlands, [4]Department of Radiation Oncology, Erasmus University Medical Center, Rotterdam, the Netherlands, [5]Department of Haematology, University Medical Centre Utrecht, Utrecht, the Netherlands, [6]Department Radiation Oncology, Verbeeten Institute, Tilburg, the Netherlands, [7]Department of Haematology, Amphia hospital, Breda, the Netherlands, [8]Department of Haematology, Haaglanden Medical Centre location Antoniushove, Leidschendam, the Netherlands, [9]Department of Haemotology, Gelre hospitals, Apeldoorn and Zutphen, The Netherlands

		total	attenders	non-attenders
n (%)		485 (100)	350 (72.2)	135 (27.8)
Age at clinic invitation (years) (cat.)	20-29	24 (4.9)	23 (6.6)	1 (0.7)
	30-39	92 (19.0)	74 (21.1)	18 (13.3)
	40-49	156 (32.2)	109 (31.1)	47 (34.8)
	50-59	173 (35.7)	123 (35.1)	50 (37.9)
	60-69	40 (8.2)	21 (6.0)	19 (14.1)
Time since HL diagnosis (years) (median [IQR])		20.3 [13.6, 26.3]	19.36 [11.7, 25.5]	22.3 [18.4, 26.6]
Year of HL diagnosis (cat.) (%)	1971-1980	35 (7.2)	23 (6.6)	12 (8.9)
	1981-1990	106 (21.9)	76 (21.7)	30 (22.2)
	1991-2000	176 (36.3)	126 (36.0)	50 (37.0)
	2001-2011	168 (34.6)	125 (35.7)	43 (31.9)
RT (%)	full mantle field RT	141 (29.1)	100 (28.6)	41 (30.4)
	RT to mediastinum but no full mantle field	207 (42.7)	152 (43.4)	55 (40.7)
	RT to neck but no mediastinum nor full mantle field	44 (9.1)	29 (8.3)	15 (11.1)
	other RT field	26 (5.4)	14 (4.0)	12 (8.9)
	no RT	67 (13.8)	55 (15.7)	12 (8.9)
CT (%)	procarbazine and anthracyline-containing CT	175 (36.1)	124 (35.4)	51 (37.8)
	anthracycline-containing CT only	172 (35.5)	126 (36.0)	46 (34.1)
	procarbazine-containing CT	48 (9.9)	38 (10.9)	10 (7.4)
	no CT	90 (18.6)	62 (17.7)	28 (20.7)
Splenectomy or spleen RT (%)		145 (29.9)	102 (29.1)	43 (31.9)

Abbreviations: CT = chemotherapy, HL = Hodgkin lymphoma, IQR = interquartile range, RT = radiotherapy.

Table 1: Survivor and treatment characteristics

Introduction: Participation rates in cancer survivorship programmes are suboptimal and reasons for non-attendance are poorly understood. We aimed to: (1) identify survivor and treatment characteristics associated with (non-)attendance at Dutch survivorship care clinics for Hodgkin lymphoma (HL) survivors (BETER clinics) and (2) evaluate survivor-reported reasons for non-attendance.

Methods: We assessed attendance rates at seven BETER clinics for 5-year HL survivors (n = 485) in 2013–2023. The association between sex, socio-economic status (based on zip code), age at invitation, time since HL diagnosis and treatment intensity (high: chemotherapy plus supradiaphragmatic radiotherapy, intermediate: supradiaphragmatic radiotherapy only, low: chemotherapy with subdiaphragmal radiotherapy or without radiotherapy) and non-attendance was assessed in multivariable logistic regression analysis, including a random effect for hospital. Backward selection was performed based on Akaike Information Criterion. Reasons for non-attendance were retrieved from a survey sent to all non-attenders.

Results: Seventy-two % of survivors (n = 350) attended the clinic, 28% (n = 135) did not (Table 1). Non-attenders were more often male (55% male vs. 41% of attenders), were older at invitation (median 50 years vs. 47 years among attenders) and had a longer time interval since diagnosis at invitation (median 22 years vs. 19 years among attenders). Treatment intensity was similar (non-attenders: high 65%, intermediate 18% and low 17%, attenders: high 65%, intermediate 16%, and low 19%), as well as socio-economic status score. In multivariable analysis, signification associations with non-attendance were found for male sex (OR: 2.15 [95% CI: 1.35–3.43]) and longer time since diagnosis (OR: 1.04 [95% CI: 1.02–1.07]).

Of all non-attenders, 28% (n = 39, 46% male) responded to the survey. They reported the following reasons for non-attendance: surveillance or treatment for late adverse effects outside of the BETER programme (41%), emotional burden of clinic visit (33%), insufficient time (10%), clinic too far away (13%), screened deemed not necessary (5%), could not remember the invitation or changed their mind and (now) open to visit a BETER clinic (39%) (multiple reasons per survivor possible).

Conclusion: Our findings inform attempts to improve attendance rates at Dutch survivorship clinics for HL survivors. Active involvement of (male) survivors could help to further identify barriers for attendance.

P070: MANAGEMENT AND FOLLOW-UP OF PREGNANCY IN PATIENTS DIAGNOSED WITH HODGKIN'S LYMPHOMA

Norayr Ghukasyan[1], Poghosyan Andranik[1], Gharibyan Edita[1], Danielyan Lusine[1], Sahakyan Lusine[2], Marina Melik-Andreasyan[2], Heghine Khachatryan[2]

[1]*Maternity House of Erebouni Medical Center*, [2]*Yeolyan Hematology and Oncology Center*

Background: Hodgkin's lymphoma (HL) is a rare lymphatic cancer during pregnancy, presenting significant management challenges. The overlap of HL diagnosis with pregnancy necessitates balancing optimal cancer treatment and fetal safety. This study aimed to develop management strategies and follow-up protocols for pregnant patients diagnosed with HL.

Methods: A comprehensive literature review was conducted, focusing on clinical guidelines, case reports, and recent advances in treating HL during pregnancy. Special attention was given to our experience managing HL patients.

Results: Over the past 15 years, at the Erebouni Medical Center, in collaboration with hematologists from the Yeolyan Hematology and Oncology Center, 25 successful cases of managing and delivering patients with lymphoma, including 12 with HL, were recorded. Among these, 4 patients planned pregnancies and delivered healthy children, while 8 were diagnosed with HL in the first or second trimester.

For patients planning pregnancy with a stable HL diagnosis, conception is recommended post-chemotherapy. Delivery methods depend on the patient's condition, with both cesarean and natural births considered. For those with multiparous (2a or 5.1 by Robson classification) and a stable HL condition, similar planning and delivery methods are applied. If HL is diagnosed in the first or second trimester, pregnancy continuation depends on the patient's condition, her desire, and the tumor board's decision. For multiparous women, decisions depend on HL stage and chemotherapy timing feasibility.

In case of HL relapse or necessary treatment, chemotherapy is recommended from the second trimester to avoid teratogenic effects. The risk to the fetus decreases after the first trimester, making it the optimal time to begin treatment. In the third trimester, chemotherapy can continue as in the second trimester or be postponed until delivery if HL is stable. Delivery timing is coordinated to minimize risks associated with cancer progression and treatment. Post-delivery follow-up includes continued treatment with oral contraceptives if necessary and careful monitoring of both mother and newborn health.

Conclusion: Managing HL during pregnancy requires a multidisciplinary approach to balance effective cancer treatment with fetal safety. Early diagnosis, trimester-specific treatment strategies, and careful follow-up are crucial for optimizing outcomes for both mother and child.

P071: MYHODGKIN MYHEALTH (MHMH): MOBILE APP FOR PATIENT-ENTERED DATA TO COLLECT LONG TERM FOLLOW UP (LTFU) AFTER HODGKIN LYMPHOMA (HL) TREATMENT

Nicole Wong Doo[1,2], Janlyn Falconer[1], Gajan Kailainathan[3], Patrick E. Lawrence[1], Georgia Klemm[1], Nathan Chapman[4], Judith Trotman[1,2]

[1]*Department of Haematology, Concord Repatriation General Hospital, Sydney, Australia*, [2]*Concord Clinical School, Faculty of Health & Medicine, University of Sydney, Sydney, Australia*, [3]*Blacktown Hospital, Sydney, Australia*, [4]*Pixelscope Pty Ltd.*

Background: Current methodologies for LTFU in HL include registries, cohort studies and clinical trials, each of which have limitations including provision of cross-sectional rather than longitudinal data, restriction to stereotypic patient populations and uncommon ability to follow patients for >10 years.

Aim: To assess the feasibility of a Mobile App to collect secure, patient-derived data for the LTFU of HL.

Methods: Participants using the MHMH App enter HL diagnostic and treatment details according to treatment type, dates and clinical outcomes. Follow up health data is collected under the headings: Heart Health, Lung Health, Other Cancer, Hormones, Fertility, Immune Health and Nervous System. After completing the questionnaire upon study entry, participants receive an email reminder to update information every 6 months. To protect privacy, two encrypted databases are maintained separately: one containing the identifiable participant information and the second containing responses to the health questionnaire. The databases can only be linked by application of a master code held offline by senior investigators.

Results: The MHMH App has undergone significant IT architecture changes since inception (2019), notably a change in coding language from Xamarin to ".NET MAUI" which is a cross-platform framework for App development across iOS and Android from a single shared codebase. Advantages of the change in code include improved ability for developers to make cross-platform changes, allowing for additional research questions to be added easily within MHMH.

MHMH underwent beta testing with 15 HL participants in May 2024, median age 40 (range 26–59), 40% male, who received first line treatment between 2008 and 2023, ABVD (86.7%) and escBEACOPP (13.3%). Participants tested MHMH in the context of a live webinar during which immediate feedback on user experience and questionnaire content was obtained for further development.

Conclusion: The MHMH App is now developed end-to-end, with the pilot phase of the completed App anticipated in August 2024 in the Australian HL population, with recruitment supported by clinicians, research collaboratives (Australasian Lymphoma & Leukaemia Group) and patient support groups (Lymphoma Australia). Future international rollout will follow, subsequent to implementations of improvements/learnings from the pilot phase.

P072: STUDY OF LONG-TERM SURVIVORSHIP OF LYMPHOMA PATIENTS–A MULTICENTER LONGITUDINAL STUDY OF RETURN TO WORK AND QUALITY OF LIFE (ALLY)

Ruth Elisa Eyl-Armbruster[1], Julia Wendler[1,2], Ramona Böttinger[2], Simone Neumaier[1], Antje Jensch[1], Markus Knott[1,2], Susanne Rössle[3], Nicola Giesen[4], Jessika Strentzsch[5], Veronika Schindler[6], Hans-Georg Kopp[3;4], Jochen Greiner[3;6], Claudio Denzlinger[3,5], Gerald Illerhaus[1,2,3]

[1]Stuttgart Cancer Center–Tumorzentrum Eva Mayr-Stihl, Klinikum Stuttgart, Stuttgart, Deutschland, [2]Clinic for Hematology, Oncology and Palliative Care, Klinikum Stuttgart, Stuttgart, Deutschland, [3]Department of health care research, Onkologischer Schwerpunkt Stuttgart e.V., Stuttgart, Deutschland, [4]Department of Hematology, Oncology and Palliative Medicine, Robert Bosch Hospital, Stuttgart, Deutschland, [5]Department of Hematology, Oncology and Palliative Care, Marienhospital Stuttgart, Stuttgart, Deutschland, [6]Department of Internal Medicine, Diakonie Hospital Stuttgart, Stuttgart, Deutschland

Background: Due to improving treatment options over the past decades, lymphoma long-term survivors and their ability to participate in work substantially gain in importance. However, only a few studies have identified influencing factors for their return to work process so far. Thus, this study aims to investigate the association between demographic, psychosocial, work-specific, and motivational factors in addition to medical aspects and lymphoma patients' return to work.

Methods: This longitudinal, multicenter study is planned and conducted by the Stuttgart Cancer Center and 3 other clinics of the Onkologischer Schwerpunkt Stuttgart. Patients with Hodgkin's lymphoma (HL), Mantel cell lymphoma, Follicular lymphoma, and Diffuse large B-cell lymphoma aged 18–65 years who receive systemic chemotherapy either at initial diagnosis (ID) or relapse are included in our study. Partly abbreviated standardized and validated questionnaires (e.g. COPSOQ, UWES, EORTC QLQ-C30) assess patients' work and life situation at ID as well as 6 and 12 months after the end of therapy. These parameters are correlated with clinical data (disease stage, prognosis scores, and ECOG PS). Patient recruitment started in May 2021 and is ongoing.

Result: So far 66 patients agreed to participate, including 21 (32%) patients with HL. Among patients with HL, 48% of patients were female, symptom burden was generally low (82% ECOG PS 0), 57% were married or in a permanent relationship and 42% were solely responsible for the total household income. At ID 70% of patients were working full time, 15% part time and 10% were unemployed. At 6 months 64% of respondents had returned to work. 86% of patients reported no change in their working situation and 14% of patients changed their working place. The average time of return to work was 20 weeks. Surprisingly, first analyses did not show any correlation between patients´ prognosis on their future return to work and their current work situation. However, patients who reported higher levels of fatigue and depression were less optimistic about their return to work.

P073: THE NATIONAL BREAST SCREENING AFTER RADIOTHERAPY DATASET (BARD) IDENTIFIES WOMEN IN ENGLAND AT VERY HIGH RISK (VHR) OF BREAST CANCER (BC) FOLLOWING RADIOTHERAPY (RT) AND ENSURES TIMELY REFERRAL TO THE CORRECT NATIONAL SCREENING PATHWAY

John Radford[1,2], Joanna Williams[1], Elsita Payne[3], Kirstin Roberts[3], Jacquie Jenkins[4], Anne Mackie[5], Aislinn Macklin-Doherty[6,7], Anthony Swerdlow[6], Martin Mccabe[1,2], Tanya Massey[2], Debbie Worthington[8], Natalie Yates-Bolton[8], Marianne Aznar[1], Richard Cowan[2], Sacha Howell[1,2]

[1]The University of Manchester, Manchester, UK, [2]The Christie Hospital, Manchester, UK, [3]National Disease Registration Service, [4]NHS England, [5]Department of Health and Social Care, [6]Institute of Cancer Research, London, UK, [7]The Royal Marsden Hospital, London, UK, [8]Patient representative

Background: Women receiving RT to breast tissue at a young age usually for Hodgkin lymphoma (HL) are at VHR of developing BC. English national guidelines published in 2003, advised clinician referral for annual screening starting at age 25 or 8 yrs after RT, whichever is later.

Subsequent research showed screening was effective but reach into the high-risk population was poor (Howell et al., 2009). We concluded that creating a national dataset of women at VHR of BC, removing the requirement for clinician involvement, and implementing direct referral to the national VHR NHS Breast Screening Programme (NHSBSP) would improve outcomes by ensuring all at-risk women are identified and offered screening in a timely way.

Methods: BARD was created by linking data from the National Cancer Registration Dataset, the RT dataset, RT provider treatment records, and a 2003 research database resulting from a national BC risk recall exercise. BARD, included in national VHR screening guidelines since 2020, has been operational since 2021 with women referred to NHSBSP as they become eligible. We studied screening allocation in the pre-BARD era to determine adherence to guidelines by linking BARD data with the NHSBSP dataset.

Results: 3976 women in England who received RT involving breast tissue during treatment for HL (95%) or non-HL (5%) aged 10–35 yrs between 1962 and 2013 were identified and entered on BARD. Pre-BARD, 1173/3976 (29%) had been correctly allocated to annual VHR screening, 2023 (51%) had been incorrectly allocated to three yearly screening and 780 (20%) had not been offered any screening. Using BARD, 442 women due/overdue VHR screening have been referred directly to the NHSBSP since 2021. Remedial screening has also been arranged for a sub-cohort of ~1500 diagnosed pre-2003 allocated incorrect or no screening. The remainder will be referred as they become eligible for a VHR screening appointment.

Conclusion: Although guidelines set the standard for BC screening after RT, they were not implemented reliably in England. Using pioneering linkage of national data for direct patient care, BARD was created and populated with 3976 women in England at VHR of BC after RT involving breast tissue. These are being offered annual VHR BC screening through NHSBSP in line with national guidelines and without the need for clinician referral. BARD is a model for the accurate identification and optimal screening of other cohorts at high risk of late consequences of cancer treatment.

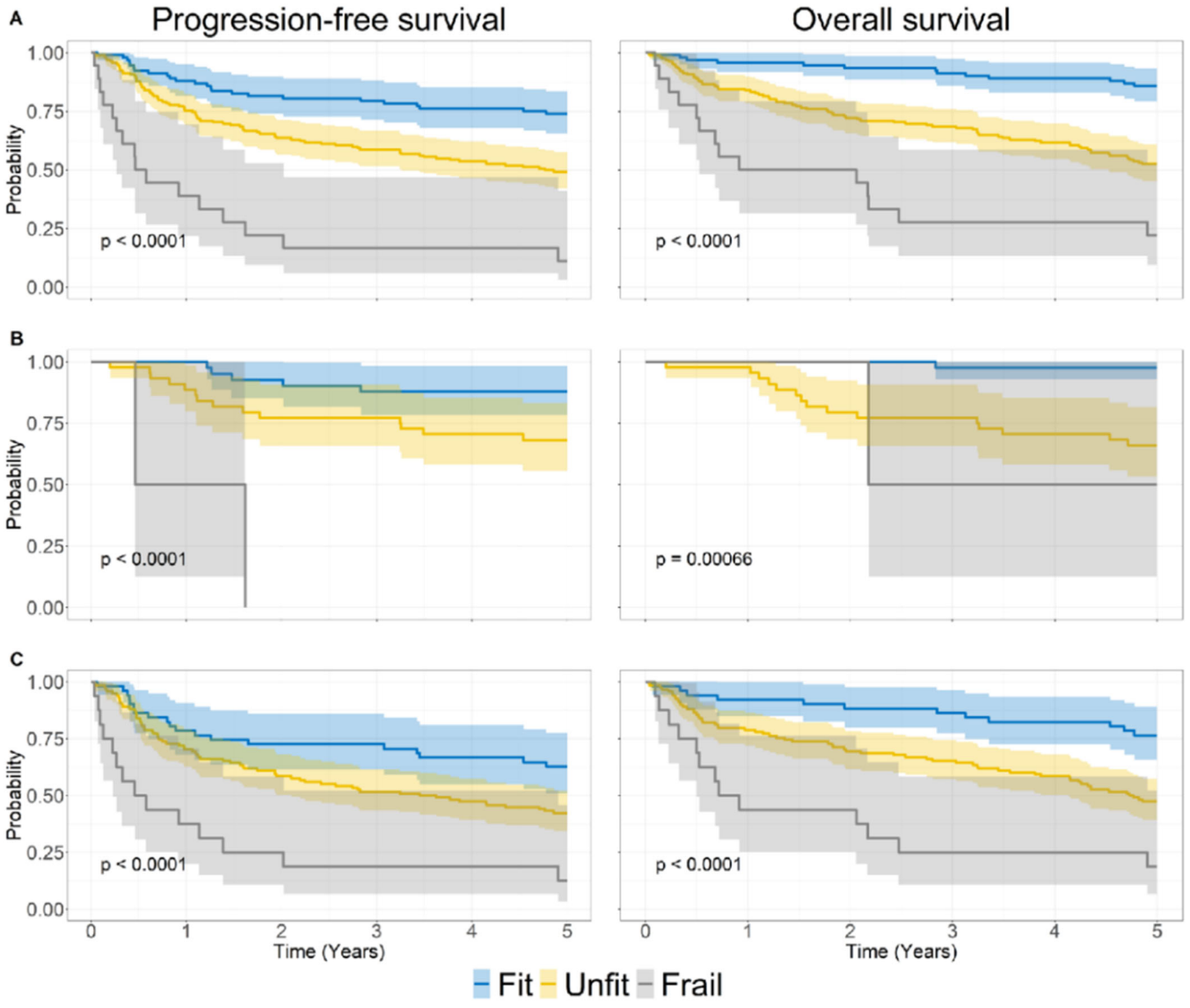
OLDER PATIENTS

T074: A SIMPLIFIED FRAILTY SCORE PREDICTS OUTCOME IN OLDER PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA TREATED WITH CURATIVE INTENT

Kjersti Lia[1,2,3], Rasmus Rask Kj[4,5], Bente L. Wold[3], øystein Fluge[6], Unn-Merete Fagerli[7,8], Hanne Bersvendsen[9], Idun B.Bø[10], Sameer Bhargava[11,12], Alexander Fosså[3,13]

[1]Department of Oncology, Bærum Hospital, Vestre Viken Hospital Trust, Gjettum, Norway, [2]Faculty of Medicine, University of Oslo, Oslo, Norway, [3]Department of Oncology, Oslo University Hospital, Oslo, Norway, [4]Clinical Cancer Research Centre, Department of Hematology, Aalborg University Hospital, Aalborg, Denmark, [5]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark, [6]Department of Oncology, Haukeland University Hospital, Bergen, Norway, [7]Department of Oncology, St. Olavs University Hospital, Trondheim, Norway, [8]Institute Clinical and Molecular Medicine (IKOM), The Norwegian University of Science and Technology (NTNU), Trondheim, Norway, [9]Department of Oncology, University Hospital of North Norway, Tromsø, Norway, [10]Department of Hematology, Stavanger University Hospital, Stavanger, Norway, [11]Cancer Registry of Norway, Norwegian Institute of Public Health, Oslo, Norway, [12]Department of Oncology, Akershus University Hospital, Lørenskog, Norway, [13]KG Jebsen Centre for B-cell Malignancies, University of Oslo, Oslo, Norway

Figure 1: Progression-free and overall survival up until 5 years according to frailty groups in all patients (A), patients with limited disease (B) and patients with advanced disease (C).



Background: Standard treatment for classical Hodgkin lymphoma (cHL) is poorly tolerated by older patients and outcomes are suboptimal. Host-related factors such as age, comorbidities and frailty are likely to impact on outcome.

Methods: We retrospectively analyzed patient and disease characteristics, treatment choices and outcomes in a population-based Norwegian cohort of cHL patients ≥60 years (ys), diagnosed 2000–2015 and treated with curative intent, defined by use of typical anthracycline-based regimens with ≥50% doxorubicin of full dose in the first cycle. Primary endpoints were overall survival (OS) and progression-free survival (PFS). We used Cox regression analysis to identify patient factors associated with OS and PFS and developed a frailty score.

Results: 279 patients (median age 69 ys, range 60–90) were included. Treatment-related mortality was 7.5% and median PFS and OS were 7.1 ys (95% CI: 5.0–9.3) and 8.7 years (95% CI: 7.0–10.4), respectively. Among disease-related parameters, advanced stage (≥IIB vs. ≤IIA; hazard ratio (HR): 2.2; 95% CI: 1.3–3.6; $p = 0.003$) and lymphocyte-rich versus nodular sclerosis histology (HR: 0.2; 95% CI: 0.1–0.7; $p = 0.009$) were independently associated with PFS. Independent associations with PFS were found for the patient-related variables age (≥70 vs. <70 years; HR: 1.7; 95% CI: 1.1–2.5; $p = 0.012$), Eastern Cooperative Oncology Group (ECOG) performance status (≥2 vs. <2; HR: 1.6; 95% CI: 1.0–2.5; $p = 0.037$) and Cumulative Illness Rating Scale Geriatrics (CIRS-G) score (≥8 vs. <8, HR 1.7; 95%CI 1.2–2.5; $p = 0.007$). A frailty index with one point each for age, ECOG status and CIRS-G score above these thresholds let us categorize patients as fit (score 0; 33.8% of all patients), unfit (1–2; 59.5%) or frail (3, 6.6%). Five-year PFS rates in fit, unfit and frail patient were 74% (95% CI: 65–83), 49% (95% CI: 42–58), and 11% (95% CI: 3–41), respectively, the score being predictive also for OS and in early and advanced stage patients separately (Figure 1). In internal 10-fold cross-validation, the C-index was 0.69 for PFS and 0.70 for OS. Nearly all fit patients received doxorubicin ≥80% of full dose in the first cycle. Unfit patients given ≥80% doxorubicin had superior 5-year PFS ($p = 0.004$) and OS ($p = 0.005$) compared to those with <80% in the first cycle.

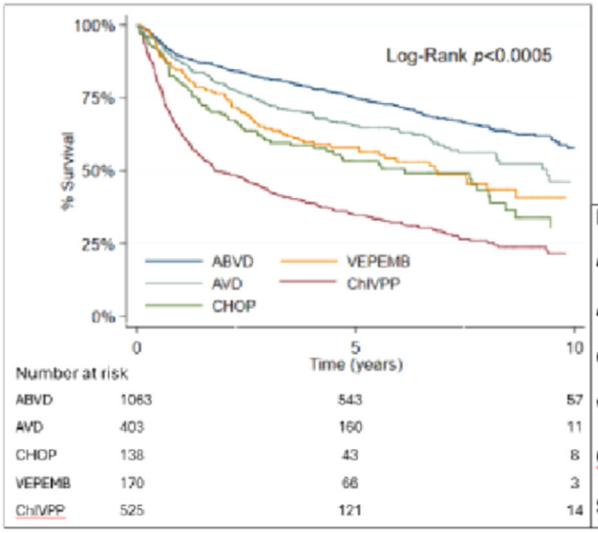
Conclusion: We developed a frailty score predicting 5-year PFS and OS in elderly cHL patients independently of disease-related findings. External validations of the frailty index are ongoing.

T075: CHARACTERISATION OF OLDER HODGKIN LYMPHOMA PATIENTS USING UK REGISTRY DATA FROM 1997–2023

Aisling Barrett[1,2], Zhe Wang[1], Andrew Challenger[1], Sarah Darby[1], John Broggio[3], David Cutter[1,2]

[1]Nuffield Department of Population Health, University of Oxford, UK, [2]Oxford Cancer and Haematology Centre, Oxford University Hospitals NHS Foundation Trust, UK, [3]National Disease Registration Service, NHS England, Birmingham, UK

Figure 1: Left panel: OS of ≥60 yo cHL patients as per the five most common first-line treatment regimens administered ($p < 0.0005$ for heterogeneity). Right panel: 2-year OS probability as per first-line treatment regimen.



Regimen Name	2-year OS probability
ABVD (n=1063)	81.5% (95% CI 79.1-83.8%)
AVD (n=403)	72.6% (95% CI 68.0-76.7%)
CHOP (n=138)	60.1% (95% CI 51.4-68.0%)
VEPEMB (n=170)	64.3% (95% CI 56.5-71.0%)
ChlVPP (n=525)	43.3% (95% CI 39.0-47.5%)
Single agent (n=80)	19.9% (95% CI 11.9-29.2%)

Introduction: Older (≥60 year old [yo]) patients with classical Hodgkin Lymphoma (cHL) have poorer survival outcomes than younger patients but data are lacking regarding the contribution of treatment-related factors.

Methods: We examined NHS England registry data regarding British patients diagnosed with cHL between 1997 and 2023 with respect to patient characteristics and chemotherapy regimens used in first-line treatment. Patients were defined on the basis of morphology and International Classification of Diseases (ICD) codes. Patients were categorised by the upfront chemotherapy regimens used, and these regimens were dichotomised into anthracycline-containing and non-anthracycline-containing as a possible surrogate for patient fitness. Survival analyses were performed using the Kaplan–Meier method with log-rank analysis performed to generate p values.

Results: The total number of patients in the survival analysis was 29,565, with 8885 (30.05%) aged ≥60 yo. Median overall survival (OS) of 18–59 yo was not reached, with a median follow up time of 8.8 years. Median OS for 60–69 yo was 9.6 years (95% CI: 9.0–10.2), 3.0 years (95% CI: 2.7–3.4) in 70-79yo and 0.8 years (95% CI: 0.7–0.9) in ≥80 yo.

First-line chemotherapy regimens were recorded in 8872 patients (30.0% of the entire cohort) of whom 2523 were ≥60 yo (28.4%). ABVD-like regimens were used in upfront treatment of 1466 (58.1%) of older cHL patients versus 5681 (89.5%) of <60 yo. Bleomycin was omitted in 37.9% of older patients receiving ABVD with significantly inferior OS seen in AVD- versus ABVD-treated patients ($p = 0.0003$). ChlVPP was used in 20.8% of older cHL patients, VEPEMB in 6.7% and CHOP-based regimens in 5.5%. Single-agent treatment was delivered to 3.2% of patients and included brentuximab vedotin, chlorambucil and vinblastine. OS for all patients receiving the most frequent combination regimens used is presented in figure 1. In anthracycline-containing regimens, significantly inferior OS was seen with CHOP-like vs ABVD/AVD regimens ($p < 0.0005$). In non-anthracycline-containing regimens, significantly inferior OS was seen with ChlVPP versus VEPEMB ($p < 0.0005$).

Discussion: Using a large English cohort we confirm that survival is poorer in older than younger cHL patients and that ABVD is associated with improved OS in comparison to other first-line regimens. Work is ongoing to explore other patient factors which may contribute to poorer survival outcomes and explain therapy-related decisions in older cHL patients.

T076: FEASIBILITY AND EFFICACY OF PET-GUIDED BRECADD IN OLDER PATIENTS WITH ADVANCED-STAGE CLASSICAL HODGKIN LYMPHOMA: THE OLDER COHORT OF THE INTERNATIONAL GHSG HD21 TRIAL

Justin Ferdinandus[1], Helen Kaul[1], Alexander Fosså[2], Andreas Hüttmann[3], Felix Keil[4], Yon-Dschun Ko[5], Felicitas Hitz[6], Stefanie Kreissl[7], Michael Fuchs[1], Dennis A. Eichenauer[1], Bastian Von Tresckow[8], Peter Borchmann[1], Paul J. Bröckelmann[1]

[1]University Hospital of Cologne and German Hodgkin Study Group (GHSG), Cologne, Germany, [2]Oslo University Hospital, Oslo, Norway, [3]University Hospital Essen, Essen, Germany, [4]Hanusch Krankenhaus, Vienna, Austria, [5]Johanniter Hospital, Bonn, Germany, [6]Kantonspital St. Gallen, St. Gallen, Switzerland, [7]Ordensklinikum Linz, Linz, Austria, [8]University Hospital Essen and German Hodgkin Study Group (GHSG), Essen, Germany

Background: PET-adapted 4–6 cycles of brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone (BrECADD) is the most effective treatment for patients aged ≤60 years with advanced-stage classical Hodgkin lymphoma (AS-cHL). Feasibility and efficacy of PET-adapted BrECADD as first-line treatment of AS-cHL in older patients >60 years are unknown.

Methods: Patients with AS-cHL aged 61–75 years were enrolled in the Older Cohort phase II single-arm extension of the international HD21 trial (NCT02661503) and received two cycles of BrECADD followed by PET restaging (PET2). PET2-negative patients (Deauville score (DS) 1–3), were given a total of four cycles, PET2-positive (DS 4) patients received a total of six cycles. Consolidation radiotherapy was recommended for PET-positive residues. The primary endpoint for this cohort was the complete response (CR) rate after completion of chemotherapy. Secondary endpoints included treatment-related morbidity (TRMB), feasibility, progression-free (PFS) and overall survival (OS). Here, we report the currently available data of the ongoing final analysis.

Results: The HD21 Older Cohort enrolled 84 predominantly male (60.7%) patients with AS-cHL. Median age was 67 years (range 61–75) and a majority had ECOG performance status ≥1 (52%, range 0–2), stage IV disease (54%) and an IPS ≥ 3 (73%). Comorbidities were reported in 87% of patients with a median CIRS-G score of 3.0; range 0–10). Three patients discontinued treatment prior to PET2 (2 because of toxicity, 1 withdrawal of consent), resulting in 81 patients eligible for central PET2 evaluation. After two cycles of BrECADD, PET2 showed CR in 59% of patients and partial response in 40%. One patient had no change (1%) and switched to off-protocol treatment. In total, 71/80 (88.8%) of patients received the planned total number of cycles according to PET2: 94% and 81% of PET2- and PET2+ patients, respectively.

Conclusions: PET-adapted BrECADD is feasible in older patients with AS-cHL and results in high metabolic CR rates at interim restaging, enabling abbreviated treatment with just four cycles in the majority of this vulnerable cohort. The final analysis of the HD21 Older Cohort is currently ongoing and the primary and secondary endpoints will be presented at the meeting.

T077: NIVOLUMAB-AVD IMPROVES 2-YEAR PROGRESSION-FREE AND OVERALL SURVIVAL COMPARED TO BV-AVD IN OLDER PATIENTS AGED ≥60 YEARS WITH ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA (CHL) ENROLLED ON SWOG S1826

Sarah Rutherford[1], Hongli Li[2], Alex F. Herrera[3], Michael Leblanc[2], Sairah Ahmed[4], Kelly Davison[5], Carla Casulo[6], Nancy L. Bartlett[7], Joseph Tuscano[8], Brian Hess[9], Pallawi Torka[10], Pankaj Kumar[11], Ryan Jacobs[12], Joo Song[3], Sharon M. Castellino[13], Brad S. Kahl[7], John Leonard[1], Sonali Smith[14], Jonathan W. Friedberg[6], Andrew Evens[15]

[1]Weill Cornell Medicine, New York, NY, [2]SWOG Statistics and Data Management Center, Seattle, WA, [3]City of Hope Comprehensive Cancer Center, Duarte, CA, [4]MD Anderson Cancer Center, Houston, TX, [5]McGill University Health Centre, Montreal, Quebec, CAN, [6]Wilmot Cancer Institute, University of Rochester, Rochester, NY, [7]Siteman Cancer Center, Washington University, St. Louis, MO, [8]UC Davis Comprehensive Cancer Center, Sacramento, CA, [9]Medical University of South Carolina, Charleston, SC, [10]Memorial Sloan Kettering Cancer Center, New York, NY, [11]Illinois CancerCare, PC, Peoria, IL, [12]Carolinas Medical Center/Levine Cancer Institute, Charlotte, NC, [13]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University Hospital/Winship Cancer Institute, Atlanta, GA, [14]University of Chicago, Chicago, IL, [15]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Figure 1: Progression-free survival (1A) and overall survival (1B) for patients aged ≥60 years enrolled on S1826.

Figure 1A: Progression-Free Survival for Patients Aged ≥60 years Enrolled on S1826.

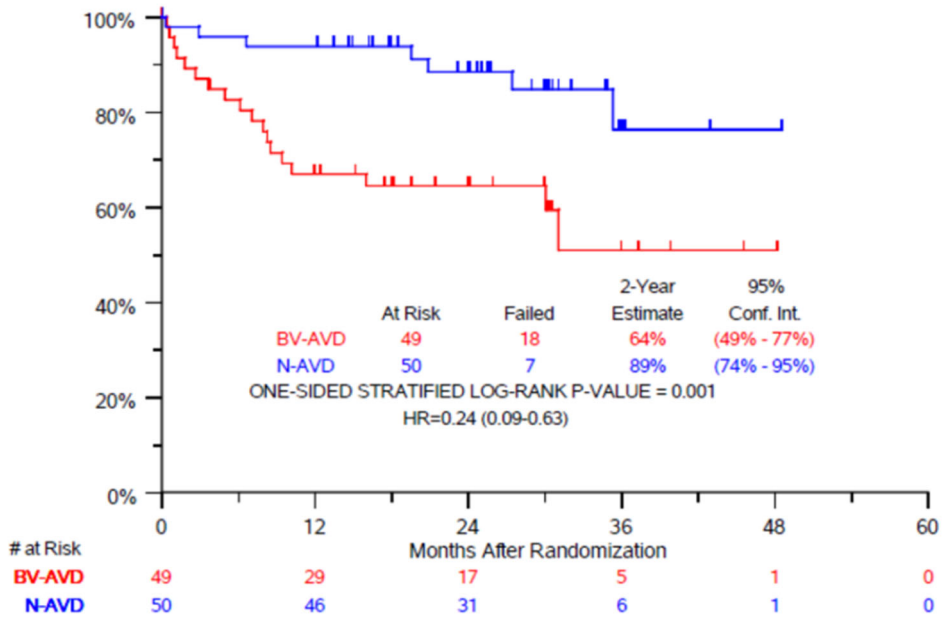
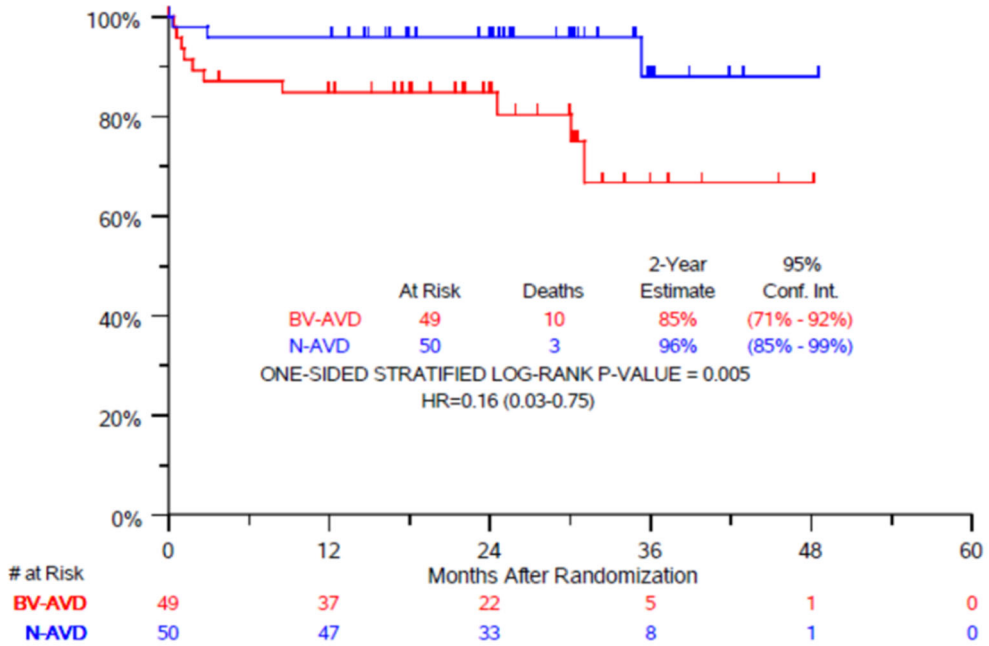


Figure 1B: Overall Survival for Patients Aged ≥60 years Enrolled on S1826.



Background: Older patients (pts) with cHL have lower survival than younger pts. We previously reported early improved efficacy and tolerability of nivolumab (N)-AVD over brentuximab vedotin (Bv)-AVD in older pts on the randomized phase 3 trial, S1826. We present 2-year (y) follow up of pts ≥60 y.

Methods: In this subset analysis, eligible pts were ≥60 y with stage 3–4 cHL. Pts were randomized 1:1 to 6 cycles of N-AVD or Bv-AVD. G-CSF was required with Bv-AVD. Response was assessed by investigators using 2014 Lugano Classification. Primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), event-free survival (EFS), and toxicity events.

Results: 103 pts ≥60 y were enrolled from 7/9/19–10/5/22; 99 were eligible and randomized to N-AVD (n = 50) or Bv-AVD (n = 49). Median age was 66 y (range, 60–83 y), 63% male, 85% white, 4% black, 9% Hispanic, 60% stage IV, 44% IPS 4–7. At 2.1 y median follow up, PFS, OS, and

EFS were superior for N-AVD over Bv-AVD in this subset analysis. For N-AVD vs Bv-AVD, 2 y PFS was 89% and 64% (HR: 0.24, 95% CI: 0.09–0.63, 1-sided stratified logrank $p = 0.001$), 2 y OS 96% and 85% (HR: 0.16, 95% CI: 0.03–0.75 stratified 1-sided logrank $p = 0.005$), and 2 y EFS 89% and 58% (HR: 0.18, 95% CI: 0.07–0.47, stratified 1-sided logrank $p < 0.001$). On N-AVD, there were 3 deaths (2 infection/sepsis, 1 hepatic failure) and 4 progressions/relapses; on Bv-AVD, there were 10 deaths (5 infection/sepsis, 2 lymphoma, 1 cardiac arrest, 1 pneumonitis, 1 s malignancy) and 9 progressions/relapses. Non-relapse mortality was 6% with N-AVD and 16% with Bv-AVD. All treatment was discontinued early in 5 pts (10%) on N-AVD and 16 (33%) on Bv-AVD. Most common reasons for discontinuation (N vs. Bv) were adverse events (AEs) (2 and 7 pts) and death (1 and 5 pts). 7 (14%) on N-AVD and 25 (51%) on Bv-AVD had any discontinuation of N and Bv, respectively. Despite more neutropenia with N-AVD, febrile neutropenia, sepsis, and infections were higher with Bv-AVD. The majority of AEs including peripheral neuropathy were more frequent with Bv-AVD. Hypothyroidism and rash were more frequent with N-AVD; other immune-related toxicity rates were similar between arms.

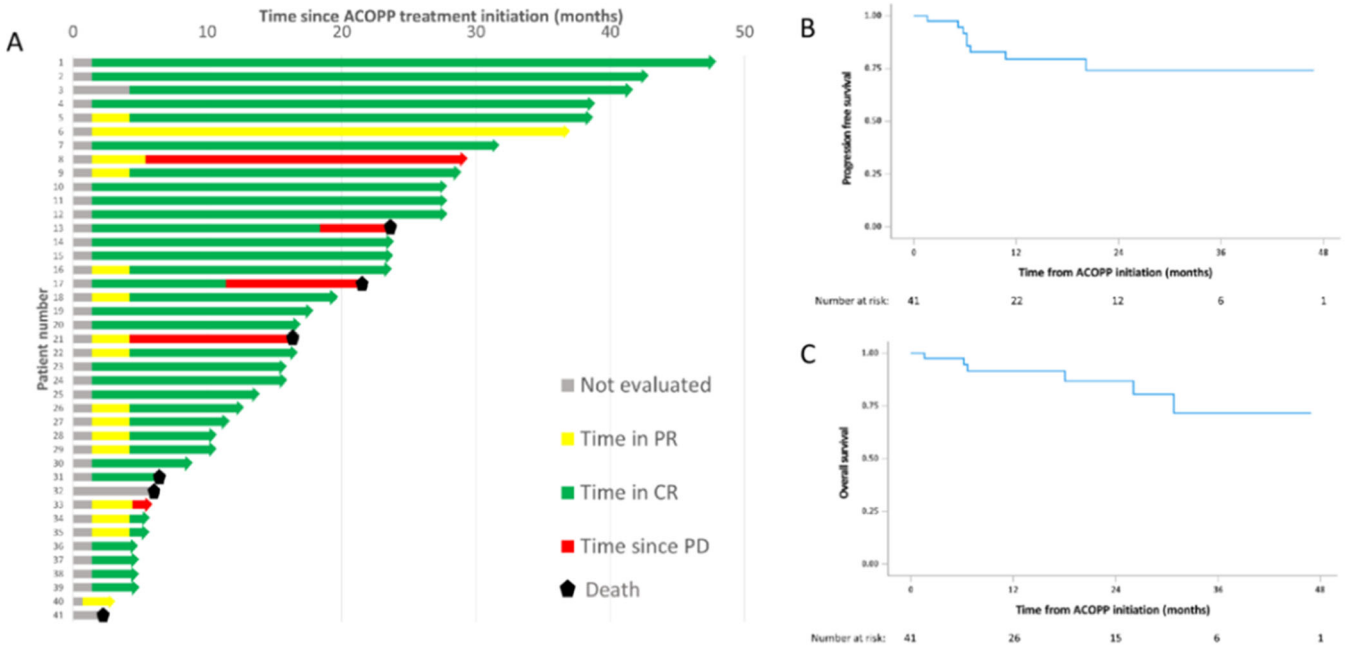
Conclusions: At 2 y follow up, N-AVD improves PFS, OS, and EFS in cHL pts ≥60 y. N-AVD is better tolerated than Bv-AVD; over half of pts discontinued Bv, primarily due to toxicity. N-AVD is a standard of care for older advanced stage pts fit for anthracycline-based combination therapy.

P078: "ACOPP" CHEMOTHERAPY FOR OLDER AND LESS FIT PATIENTS WITH HODGKIN LYMPHOMA–A MULTICENTRE, RETROSPECTIVE STUDY

Matthew Wilson[1], Euan Haynes[2], Katrina Parsons[1], David Hopkins[1], Elizabeth Robertson[3], Graeme Ferguson[1], Daire Quinn[1], Jim Murray[3], Wendy Osborne[2], Mike Leach[1], Pam Mckay[1]

[1]Beatson West of Scotland Cancer Centre, Glasgow, UK, [2]Newcastle Upon Tyne NHS Foundation Trust, Newcastle Upon Tyne, UK, [3]Royal United Hospital Bath NHS Trust, Bath, UK

Figure 1: (A) Swimmer plot of all study participants, (B) progression-free survival and (C) overall survival.



Introduction: Patients (pts) aged ≥60 years comprise 20%–30% of classical Hodgkin lymphoma (cHL) diagnoses, but are significantly underrepresented in clinical trials and outcomes for this group have not improved in line with advances seen in younger pts. Whilst anthracycline-containing regimens result in superior outcomes, older pts typically have poor tolerance of the chemotherapy regimens used in younger pts. We modified the BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) by removing bleomycin and etoposide and dose-reducing cyclophosphamide for use in older pts with co-morbidities. Here we present data from the first 41 pts treated with ACOPP across 3 UK centres.

Methods: ACOPP comprises doxorubicin 35 mg/m^2 and cyclophosphamide 650 mg/m^2 intravenous (IV) infusion day (D)1, vincristine 1.4 mg/m^2 IV injection D8, oral procarbazine 100 mg/m^2 D1-7, prednisolone 40 mg/m^2 D1-14 and subcutaneous G-CSF D9-13. Each centre retrospectively analysed consecutive patients receiving ACOPP for cHL. Medical co-morbidities were quantified using the Cumulative Illness Rating Scale-Geriatric (CIRS-G). Statistical analysis was performed using SPSS v28.0.

Results: Forty-one pts previously untreated for cHL were included, with median age 74 and median CIRS-G of 5. The majority (78%) had advanced stage disease. Six cycles of ACOPP were planned for 38/41 patients, of whom 68% completed treatment. Nine pts (22%) had dose reductions, most often with vincristine (6/9). Sixty-one percent required hospital admission during treatment, the majority having 1–2 admissions

(22/25). Grade 3+ neutropenia was seen in 34%, with a relatively low rate of febrile neutropenia (15%). Neuropathy occurred in 15 patients (37%), all grade 1–2. Six pts died during the study, only 1/41 (2%) had a direct treatment related death.

Overall response rate was 39/41 (95%), with CR in 34/41 (83%). With median follow-up of 17 months, estimated 2-year PFS and OS were 74% (95% CI: 58–90) and 87% (95% CI: 75–99) respectively.

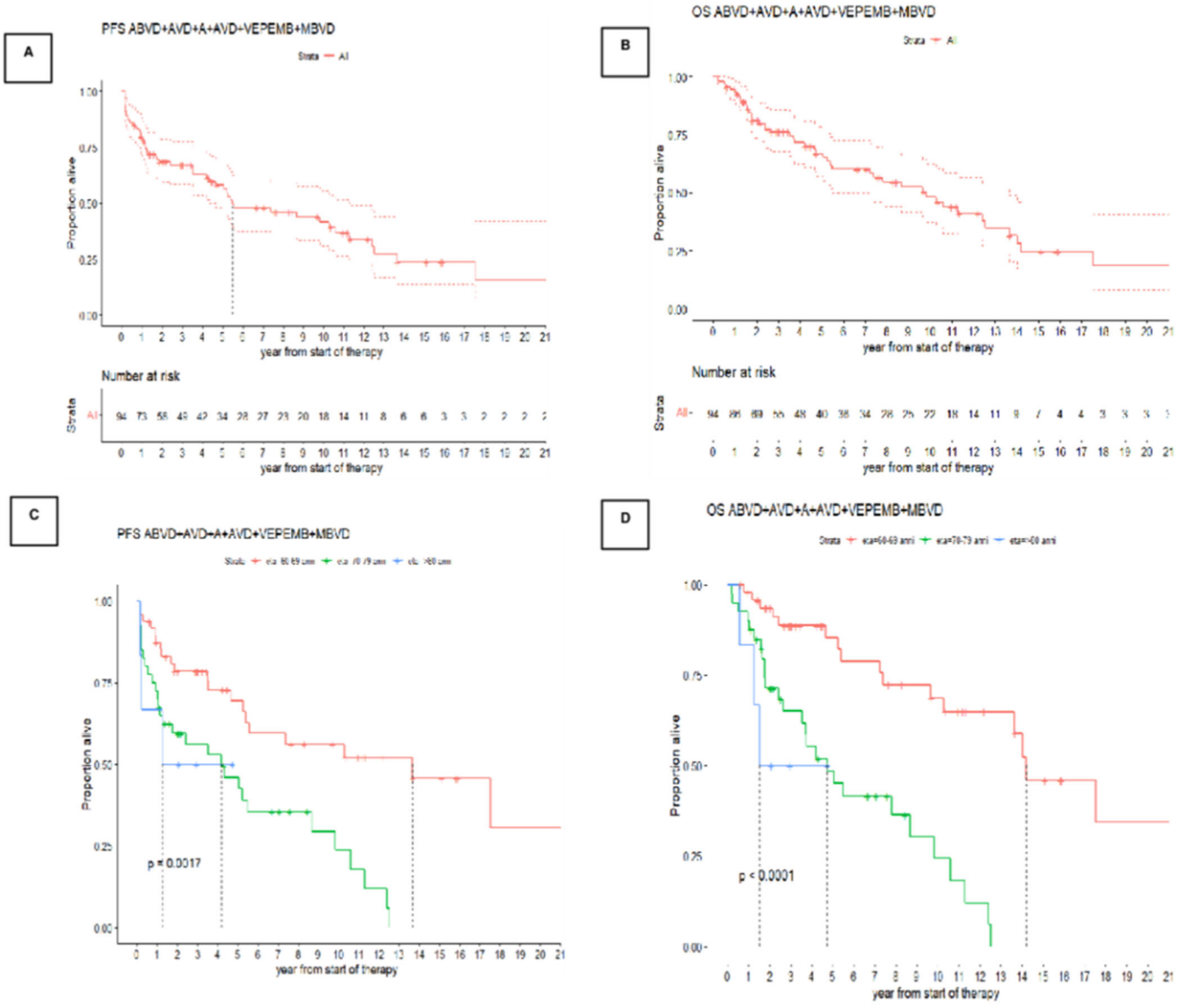
Conclusion: The ACOPP regimen can be delivered to older pts with significant co-morbidity, with a relatively favourable toxicity profile and promising efficacy. Treatment of older patients with cHL continues to be an area of unmet need. Whilst treatment in clinical trials should be considered optimal therapy, enrolment in this group remains challenging and the ACOPP regimen offers promising outcomes in a difficult to treat population.

P079: ANTHRACYCLINE-BASED THERAPY FOR ELDERLY HL PATIENTS: A RETROSPECTIVE SERIES FROM A SINGLE SOUTH ITALY CENTER

Vittoria Tarantino[1], Marika Porrazzo[1], Monica Maria Agata Leone[1], Ernesto Torretta[1], Antonino Mulè[1], Caterina Patti[1], Luca Castagna[2]

[1]*Onco-Hematology Unit, AOR Villa Sofia-Vincenzo Cervello, 90146 Palermo, Italy,* [2]*BMT Unit, AOR Villa Sofia-Vincenzo Cervello, 90146 Palermo, Italy*

Figure 1: (A, B) PFS and OS for patients treated with anthracycline-based CT; (C, D) PFS and OS according age 60–69 versus 70–79 versus over 80 years.



Background: Elderly patients account for about 20% of newly diagnosed Hodgkin lymphoma (HL) cases. For these patients, outcomes have traditionally been poor due to the negative prognostic factors associated to the disease and due the presence of comorbidities that may also make it difficult to administer anthracycline-based chemotherapy such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) with a curative intent. The aim of this study was to evaluate the treatment patterns and survival in patients aged ≥60 years treated with anthracycline-based CT.

Patients and Methods: Patients aged ≥60 years diagnosed with HL from 1995 to 2023 were retrospectively identified at Cervello Hospital in Palermo and those treated with anthracycline-based chemotherapy (CT) were included in this analysis. Anthracycline-based CT consisted of ABVD, MyocetBVD, VEPEMB, AVD, Adcetris+AVD. Data on clinical characteristics, baseline assessment including echocardiogram and spirometry, treatment response, toxicities, survival estimates were calculated.

Results: 116 HL patients were identified and 98 pts (84%) received anthracycline-based CT as follows: ABVD 46, MyBVD 4, VEPEMB 12, AVD 11, A+AVD 2. Median age was 69 years (range 60–85). At diagnosis, 18 pts (18%) had localized disease (I–IIA) and 80 (82%) an advanced stage (IIB–IVB). Before treatment, all patients performed baseline echocardiogram and spirometry. Abnormalities were reported in 8% of patients. The median number of CT cycles was 6 (range 1–8). In the advanced stage cohort, 25% of patients were not able to perform treatment schedule due PD in 11, CT toxicity in 5, UK in 4. 85 (87%) patients were evaluable for dose reduction and in 20 (24%) doses were reduced because of toxicity. The end of treatment (EOT) ORR was 83% (CR 76%, PR 7%). With a median follow-up of 4.2 years for all patients, 5-year PFS and OS were 56% and 65%, respectively. In univariate analysis, age less than 69 years predicted better PFS and OS than those aged more than 70 ($p < 0.0001$) (Figure 1).

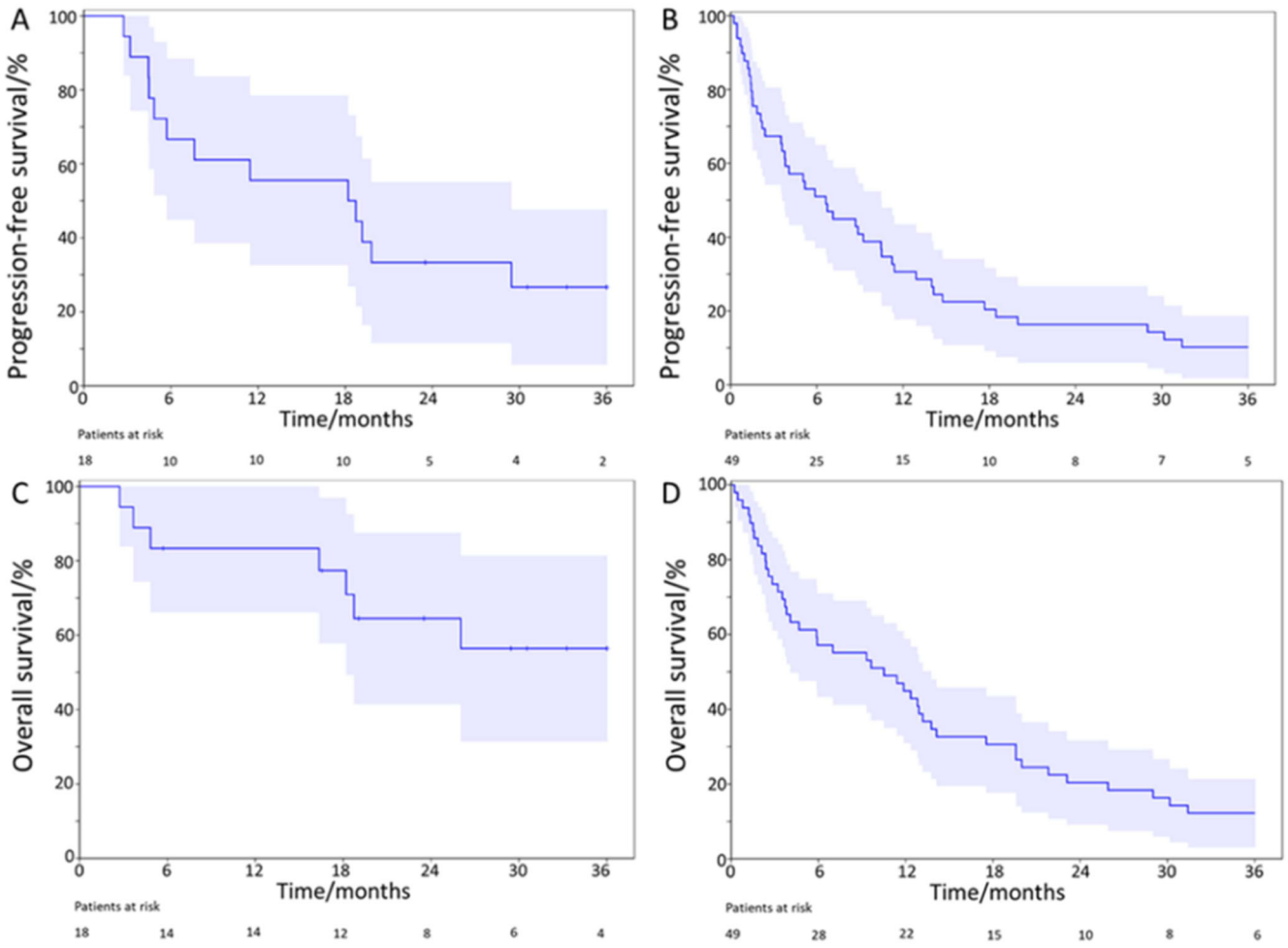
Conclusions: Our findings suggest that anthracycline-based CT is feasible in most of elderly patients, although 25% of advanced cohort was not able to complete the treatment, mainly because of lack of response. The EOT ORR was similar to that reported in younger patients. However, the survival for the whole cohort was reduced, even if better in patients aged less 70 years.

P080: BRENTUXIMAB VEDOTIN MONOTHERAPY IS A FEASIBLE AND EFFECTIVE TREATMENT IN ELDERLY AND FRAIL PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA: RESULTS OF THE PROSPECTIVE GHSG-NLG PHASE II BVB TRIAL

Alexander Fosså[1,2,3], Daniel Molin[4,2], Paul J. Bröckelmann[5,6,7], Gundolf Schneider[5,6], Ulf Schnetzke[8], Johan Linderoth[9], Peter Kamper[10,2], Sirpa M. Leppä[11,2], Julia Meissner[12], Valdete Schaub[13], Kjersti Lia[1,14], Michael Fuchs[5,6], Peter Borchmann[5,6], Boris Böll[5,6]

[1]Department of Oncology, Oslo University Hospital, Oslo, Norway, [2]Nordic Lymphoma Group, [3]KG Jebsen Centre for B-cell Malignancies, University of Oslo, Oslo, Norway, [4]Department of Immunology, Genetics and Pathology, Cancer Immunotherapy, Uppsala University, Uppsala, Sweden, [5]Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany, [6]German Hodgkin Study Group, [7]Max Planck Institute for Biology of Ageing, Cologne, Germany, [8]Department of Hematology and Medical Oncology, University of Jena, Jena, Germany, [9]Cancer Centre, Lund University Faculty of Medicine, Lund, Sweden, [10]Department of Hematology, Aarhus University Hospital, Aarhus, Denmark, [11]Comprehensive Cancer Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [12]Department of Hematology and Oncology, University of Heidelberg, Heidelberg, Germany, [13]Department II of Internal Medicine, University of Tübingen, Tübingen, Germany, [14]Department of Oncology, Bærum Hospital, Vestre Viken Hospital Trust, Gjettum, Norway

Figure 1: Progression-free and overall survival in prospective trial patients treated with brentuximab vedotin (A, C) and retrospective real-world patients treated with palliative intent (B, D). Shaded areas represent 95% confidence intervals.



Background: Standard treatment for classical Hodgkin lymphoma (HL) is poorly tolerated by older patients (pts) with comorbidities or frailty and results are disappointing.

Methods: In the international prospective phase II BVB trial (NCT02191930), we evaluated safety and efficacy of brentuximab vedotin (BV, 1.8 mg/kg every 3 weeks) in previously untreated HL patients aged ≥60 years considered unsuitable for combination chemotherapy. The primary endpoint was objective response rate (ORR) assessed by computed tomography after ≥2 cycles of BV. Secondary endpoints included toxicity, progression-free (PFS) and overall survival (OS). For comparison, we evaluated elderly HL patients from a Norwegian population-based cohort diagnosed 2000–2015.

Results: Between 2015 and 2018, we enrolled 20 pts. Nineteen pts with a median age of 82 years (range 62–88) and a median Cumulative Illness Rating Scale for Geriatrics (CIRSG) score of 8 (range 4–14) were evaluable for toxicity, whereas 18 were evaluable for response. With a median of 6 BV cycles given (range 2–16), grade (G) 3 hematological toxicity occurred in 3 pts, with no G4 reported. G3 or 4 infections were seen in 3 and 1 pts, respectively, while non-hematological G3 or 4 toxicities were noted in 7 and 3 pts, respectively. Four (22%) pts had complete and 7 (39%) had partial response (ORR: 61%, 95% CI: 31–100). One patient received radiotherapy (RT) in remission. With a median follow-up of 30 months, median PFS was 19 months (95% CI: 5–30), and median OS was not reached (Figure A+C). Three-year PFS and OS were 27% (95% CI: 6–48) and 56% (95% CI: 31–81), respectively. In the retrospective cohort, 49 pts had a median age of 81 years (range 65–92) and a median CIRSG score of 9 (range 0–25). Of these, 31 received various dose-attenuated combination regimens, mostly cyclophosphamide, vincristine and prednisolone (CVP) ± doxorubicin (CHOP), 6 oral trofosfamide and 5 received other single agent chemotherapy. Median number of cycles for intermittent schedules was 2 (range 1–8). Five pts received additional RT as part of primary treatment and 7 had limited-field RT only. ORR response rate was 47% (95% CI: 30–70) and PFS and OS at 3 years 10% (95% CI: 2–19) and 12% (95% CI: 4–21), respectively (Figure B+D).

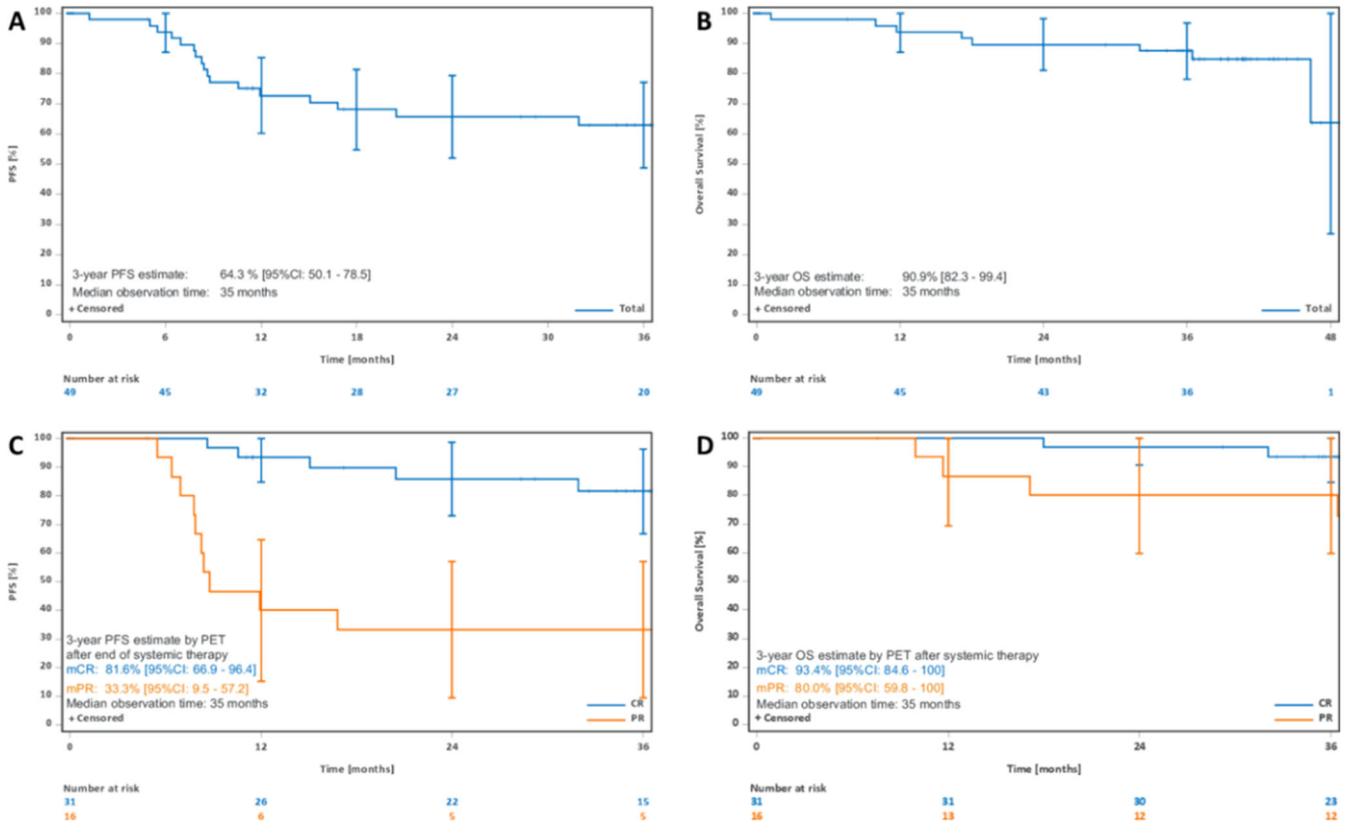
Conclusion: BV monotherapy is a tolerated and effective treatment option, and it may improve outcomes compared to conventional therapy in elderly and frail HL patients ineligible for curatively intended combination chemotherapy.

P081: BRENTUXIMAB VEDOTIN, CYCLOPHOSPHAMIDE, DOXORUBICIN AND PREDNISONE (B-CAP) FIRST-LINE TREATMENT OF ADVANCED-STAGE HODGKIN LYMPHOMA: FINAL RESULTS OF THE GHSG-NLG PHASE II BVB TRIAL

Paul J. Bröckelmann[1,2,3], Boris Böll[1,3], Daniel Molin[4], Gundolf Schneider[1], Sirpa M. Leppä[5], Julia Meissner[6], Peter Kamper[7], Martin Hutchings[8], Jacob Haaber Christensen[9], Ulf Schnetzke[10], Michael Fuchs[1], Dennis A. Eichenauer[1], Bastian Von Tresckow[11], Helen Kaul[1], Peter Borchmann[1], Alexander Fossa[12]

[1]University Hospital of Cologne and German Hodgkin Study Group (GHSG), Cologne, Germany, [2]Max Planck Institute for Biology of Ageing, Cologne, Germany, [3]Equal Contribution, [4]Uppsala, Sweden and Nordic Lymphoma Group (NLG), [5]Helsinki, Finland and NLG, [6]Heidelberg, Germany, [7]Aarhus, Denmark and NLG, [8]Copenhagen, Denmark, [9]Odense, Denmark, [10]Jena, Germany, [11]Department of Hematology and Stem Cell Transplantation, West German Cancer Center and German Cancer Consortium (DKTK partner site Essen), University Hospital Essen, University of Duisburg-Essen, [12]Oslo, Norway and NLG

Figure 1: PFS (A) and OS (B) with B-CAP in patients ≥60 with Hodgkin lymphoma. PFS (C) and OS (D) stratified by PET-based metabolic (m) remission status after systemic therapy (mCR vs. mPR).



Background: Outcomes in the growing group of older patients (pts) with advanced-stage classical Hodgkin lymphoma (cHL) are historically poor.

Methods: The international GHSG-NLG intergroup phase II BVB trial (NCT02191930) evaluated six cycles of brentuximab vedotin (1.8 mg/kg), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2) and prednisone (100 mg/day 2–6; B-CAP) as first-line treatment for advanced-stage cHL pts ≥60 years considered eligible for polychemotherapy. Primary endpoint was objective response rate (ORR) by computed tomography (CT) after at least 2 cycles. Secondary endpoints included feasibility, toxicity, progression-free (PFS) and overall survival (OS).

Results: With a median follow-up of 35 months, 49 pts with a median age of 66 years (range: 60–84) were evaluable in the intention-to-treat population. The majority presented with ECOG performance status 1 (61%, range 1–3), stage IV HL (65%), international prognostic score ≥4 (50%), and CIRS-G score 1–3 (51%, range 0–7).

Six cycles were administered in 46/49 pts (94%). Three pts terminated treatment early due to toxicity, including one infection-related death before response assessment. With G-CSF support in 98% of pts, the maximum dose level was maintained in 86% of pts, and the mean relative dose intensity was 93%. Most pts experienced hematological toxicities (any grade [G]: 92%, G3: 8%, G4: 53%); i.e., neutropenia (G3/4: 61%), anemia (G3/4: 18%) and thrombocytopenia (G3/4: 10%). Febrile neutropenia occurred in 27% and infections in 61% (G3: 29%, G4: 2%, G5: 2%) of pts, respectively. Neuropathy was mostly sensory and reported in 67% of pts (G2: 20%, no ≥G3). CT-based ORR after 2 and 6 cycles were 94% (CR: 34%) and 98% (CR: 44%, 95% CI: 90.5–100). Positron emission tomography (PET) after the last cycle showed metabolic CR in 31/48 pts (65%). Ten patients (20%) received consolidative 30 Gy radiotherapy to PET+ residues. Overall, 16 patients (33% of) experienced tumor progression or relapse and 9 (18%) died, mostly from cHL (*n* = 6, 12%). 3-year PFS and OS are 64% (95% CI: 50–79, Figure 1A+B) and 91% (95%

CI: 82–99), with improved 3-year PFS observed in patients achieving a metabolic CR (82%) compared to pts with metabolic PR (33%; Figure 1C+D).

Conclusions: B-CAP is a feasible and effective treatment option for older patients with advanced-stage cHL, with high response rates already after 2 cycles and improved 3-year PFS in patients achieving a metabolic CR

P082: ELDERLY CLASSICAL HODGKIN LYMPHOMA: CROATIAN COOPERATIVE GROUP FOR HEMATOLOGICAL DISEASES (KROHEM) EXPERIENCE

Ida Hude Dragičević[1], Ida Ivek[1], Sandra Bašić-Kinda[1], Karla Mišura Jakobac[2], Marija Ivić čikara[3], Marija Petrić[4], Vlatka Periša[5,6], Ivana Vučinić Ljubičić[7], Ivana Sušac Zrna[8], Ivan Krečak[9,10], Dina Mokwa[11], Tomislav čolak[12], Barbara Dreta[1], Dino Dujmović[1], Igor Aurer[1,13]

[1]University Hospital Center Zagreb, Zagreb, Croatia, [2]University Hospital Merkur, Zagreb, Croatia, [3]University Hospital Dubrava, Zagreb, Croatia, [4]University Hospital Center Split, Split, Croatia, [5]University Hospital Center Osijek, Osijek, Croatia, [6]Faculty of Medicine, University of Osijek, Osijek, [7]Dr. Josip Benčević General Hospital, Slavonski Brod, Croatia, [8]General Hospital Pula, Pula, Croatia, [9]General Hospital Šibenik, Šibenik, Croatia, [10]University of Rijeka School of Medicine, Rijeka, Croatia, [11]General Hospital Varaždin, Varaždin, Croatia, [12]University Clinical Hospital Mostar, Mostar, Bosnia and Herzegovina, [13]University of Zagreb School of Medicine, Zagreb, Croatia

Introduction: Classical Hodgkin lymphoma (cHL) poses unique challenges in elderly patients, necessitating tailored treatment due to age-related comorbidities and decreased tolerance to intensive therapies. This study aims to analyze the demographics, treatment modalities, and survival outcomes of elderly cHL patients treated at KroHem centers.

Methods: We identified 147 patients aged ≥60 years, diagnosed between 2011 and 2024, for retrospective analysis. We recorded patient demographics, disease characteristics, first-line treatment modalities, and treatment responses. Overall survival (OS) and event-free survival (EFS) were estimated using Kaplan-Meier methods, with comparisons between groups performed using log-rank tests.

Results: The median age of the cohort was 69 years (range 60–91), with 65% male. Patients presented with advanced stage (AS) disease in 64%, early favorable (EF) in 19%, and early unfavorable (EU) disease in 17%. Extranodal involvement was seen in 33%, and bulky disease in 12% of patients. Curative-intent anthracycline-based therapy was given to 86%, and 27% received radiotherapy. Only 24.5% received all planned treatment cycles. Of 134 patients evaluable for response assessment, 94 achieved CR, 14 PR, and 19 did not respond. Treatment-related mortality was 11.6%. After a median follow-up of 51 months, 2-year, 3-year, and 5-year OS and EFS rates were 74%, 68%, and 68%; and 62%, 52%, and 43%, respectively. Anthracycline-based treatment significantly improved median survival (86 months) compared to palliative care (11 months) ($p < 0.001$). Significant differences in OS and EFS were observed across age groups ($p < 0.001$), with mean OS and EFS decreasing from 76 and 60 months in patients aged 60–69 years to 22 and 22 months in those aged 80 years and older. Performance status and physician-evaluated frailty also significantly impacted OS and EFS, while sex, disease stage, and CIRS-G did not.

Conclusion: In this difficult-to-treat population, age, ECOG status, and frailty were significant predictors of survival, with older age groups and higher ECOG stages showing markedly reduced OS and EFS. These factors likely influenced first-line treatment choices, leading to extended survival with anthracycline-based treatment compared to less intensive regimens. Our results align with other studies on elderly cHL patients, highlighting the need for tailored treatment approaches considering patient age and frailty.

P083: HODGKIN LYMPHOMA IN OLDER PATIENTS (HOOP)–A EUROPEAN RETROSPECTIVE STUDY

Aisling Barrett[1], Amy A. Kirkwood[2], Cathy Burton[3], Ruth Clifford[4], Robert Henderson[5], Pam Mckay[6], Wendy Osborne[7], Nimish Shah[8], Graham P. Collins[1]

[1]Department of Haematology, Oxford University Hospitals NHS Foundation Trust, UK, [2]Cancer Research UK & UCL Cancer Trials Centre, University College London, UK, [3]Department of Haematology, The Leeds Teaching Hospitals NHS Trust, UK, [4]Department of Haematology, University Hospital Limerick, Republic of Ireland, [5]St James's Hospital, Dublin, Ireland, [6]Department of Haematology, Beatson West of Scotland Cancer Centre, Glasgow, UK, [7]Department of Haematology, Newcastle Upon Tyne NHS Foundation Trust, UK, [8]Department of Haematology, Norfolk and Norwich University Foundation Hospital, UK

Introduction: Older (≥60 year old (yo)) patients with classical Hodgkin Lymphoma (CHL) comprise 20% of all patients with the condition and have poorer outcomes than younger patients. Older patients far best when treated with standard doses of conventional chemotherapy but are less likely to receive this thus accurate identification of patients most likely to tolerate this approach is critically important. There is also a wide variety in treatment regimens used for older CHL patients with a paucity of specific guidance for clinicians.

Methods: HoOP (Hodgkin Lymphoma in Older Patients), a European retrospective data collection project, has been established to characterise pre-treatment comorbidities, treatment-related toxicity and survival following treatment for older CHL patients. Patients diagnosed with CHL at 60 years of age or older between the 1st of January 2010 and 31st of December 2023 will be included and data will be collected pseudo-anonymously at sites by clinicians.

The primary objective will be event-free survival of the entire group by age. Other survival objectives will include survival according to treatment initiated and diagnostic era. Toxicity objectives will include description of bleomycin use and bleomycin pulmonary toxicity (BPT), rate of unplanned hospital admissions and infections and non-relapse mortality. We will examine if there is a correlation between baseline patient characteristics and choice of chemotherapy regimen and assess outcomes from brentuximab vedotin and checkpoint inhibitors.

Characteristics of the whole population and treatment groups will be described and compared using appropriate statistical tests (chi-squared or Fisher's exact for discrete variables and t-tests or Kruskal Wallis tests for continuous variables). Statistical power to determine outcomes based on regimen used has been based on the accrual of at least 100 patients per treatment group. Any analyses comparing treatment groups will be adjusted for potential confounding factors including age and comorbidities.

Future Plans: HoOP has been adopted as an official EHA lymphoma SWG project and we are keen to engender international collaboration to maximise data accrual and allow for statistically powerful comparison of patient factors and outcomes. We plan commencement of data entry at 27 participating United Kingdom hospital trusts and 8 hospital sites in the Republic of Ireland by the 1st of July 2024 with data input ongoing until the 1st of October 2025.

P084: PATIENTS OVER THE AGE OF 60 YEARS TREATED WITH HODGKIN'S LYMPHOMA AT OUR CLINIC

Dávid Tóthfalusi[1], László Imre Pinczés[1], Boglárka Dobó[1], árpád Illés[1], Zsófia Miltényi[1]

[1]*Division of Haematology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen*

Background: Hodgkin lymphoma (HL) typically affects young adults, although there is a second peak in incidence later in life, with patients over the age of 60 years. Advanced age is known as a poor prognostic factor, that has been attributed to a variety of factors, like comorbodities, poor functional status, which may affect the toleration of treatment.

Methods: We retrospectively analyzed data of patients with HL over the age of 60 years who were diagnosed and treated between January 1, 2010, and December 31, 2023, at the Division of Haematology, University of Debrecen. The diagnostic efficiency of different independent variables was determined by Receiver Operating Characteristic (ROC) analysis and then calculated by the Youden Index. The impact of the variables on endpoints (overall survival–OS, progression-free survival–PFS) was examined using the Cox proportional hazards regression model.

Results: A total number of 35 patients over 60 years of age were treated, with a median age of 68 (range 60–88) years. 60% of patients were under the age of 70 years. 9 patients aged between 70 and 79 years, and 5 patients over the age of 80 years. The most common histological subtype (40%) was nodular sclerosis. 66% of the patients had B symptoms. 72% of the patients were in an advanced stage at the time of diagnosis. Under the age of 70 years, 86% received ABVD treatment, among 70–79 years, 56% received ABVD treatment, 60% of patients between 80 and 89 years received BV plus DTIC treatment. Almost 90% of all patients had some form of comorbidity. 26% of all patients have died. Comorbidities significantly worsened survival chances. Based on the Charlson Comorbidity Index, patients with >7 points had significantly worse 5-year PFS (93% vs. 54%, $p = 0.024$). Platelet count over 310.5 G/L and low absolute lymphocyte count (LYM# <0.47 G/L) were found to be independent risk factors for OS. Each parameter, both individually and in combination, significantly affected OS. For PFS, white blood cell count over 8.48 G/L, platelet count over 310.5 G/L and advanced age (>73.5 years) were confirmed as significant adverse prognostic factors. Each of these parameters, both individually and in combination, significantly influenced PFS.

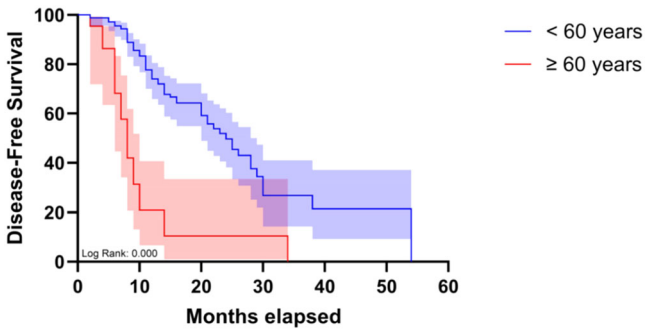
Conclusion: The survival and treatability of older HL patients are not determined significantly by their age, but by their general condition. The presence of comorbidities affects PFS. The use of innovative treatments is expected to improve survival outcomes.

P085: TREATMENT EFFICACY, OVERALL SURVIVAL, AND DISEASE-FREE SURVIVAL IN ELDERLY VERSUS YOUNGER PATIENTS WITH HODGKIN'S LYMPHOMA: A DECADE OF EXPERIENCE AT A LATIN AMERICAN REFERENCE HOSPITAL

Gerardo Santiago Jimenez[1], Alonso Hernández Company[1], Karen Torres Castellanos[1], Gilberto Israel Barranco Lampón[1], Juan Francisco Zazueta Pozos[1], Daniela De Jesús Pérez Sámano[1], Emmanuel Martínez Moreno[1], Carlos Martínez Murillo[1], Adán Germán Gallardo[2]

[1]*Hospital General de México "Dr. Eduardo Liceaga"*, [2]*Rodríguez*

Figure 1: Disease free survival in patients with Hodgkin's disease over and under 60 years old with first line treatment.



Background: Hodgkin's Lymphoma (HL) in elderly patients often manifests different biological and clinical characteristics than younger populations. Variations include tumor biology, genetic mutations, and comorbidities affecting disease prognosis and treatment efficacy (TE). Elderly patients may present more advanced stages of the disease or more aggressive symptoms, causing delays in diagnosis and treatment initiation. This study aims to evaluate TE, overall survival (OS), and disease-free survival (DFS) among elderly (≥60 years) and young (<60 years) HL patients.

Methods: A retrospective cohort using clinical records of HL patients treated in our institution over the past ten years. Completed clinical records of adult patients diagnosed and treated by the Hematology Department were included.

Results: The study analyzed 207 clinical records, including 185 patients under 60 years of age and 22 patients aged 60 years or older. Among these, 134 patients were male. The most common histopathological subtype was mixed cellularity, observed in 62.8% of the cases. In patients aged 60 years or older, there was a significant increase in Epstein-Barr Virus (EBV) positivity, ECOG scores, and clinical status compared to the younger group. Radiotherapy was administered to both groups at similar rates, with 26.5% of patients under 60 years and 22.7% of patients aged 60 years or older receiving this treatment. Multivariate analysis exhibits statistically significant differences in TE and DFS between groups (OR: 5.617, 95% CI: 2.051–15.386, $p < 0.000$ and OR: 7.470, 95% CI: 2.412–23.131, $p < 0.000$, respectively). However, the OS did not show a statistical difference ($p = 0.246$). The median OS was 11 months (range 2–54 months) for the under 60 years group and 8 months (range 2–34 months) for the 60 years or older group. Mantel-Cox analysis was made to compare OS and DFS at a 5-year follow-up, leading to a statistical difference between groups with a major and better prognosis for the under 60 years patients (Log-Rank: 0.009 and 0.000 respectively) (Figure 1).

Conclusions: Our population behaved similarly to other world study populations. There is a need to adapt treatment regimens to balance efficacy with tolerability, especially in older populations. Studying OS and DFS in elderly HL patients provides insights into the effectiveness of current treatments and helps assess long-term treatment success and the risk of relapse.

PEDIATRIC AND ADOLESCENT

T086: EFFICACY and TOLERABILITY in DECOPDAC21 versus COPDAC28 in PEDIATRIC INTERMEDIATE and ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA: INTERIM RESULTS of the EURONET-PHL-C2 RANDOMIZED STUDY

Dieter Körholz[1], Maurizio Mascarin[2], Judith Landman-Parker[3], Thierry Leblanc[4], Lars Kurch[5], Thomas W. Georgi[5], Regine Kluge[5], Dietrich Stoevesandt[6], Tanja Pelz[7], Dirk Vordermark[7], Karin Dieckmann[8], Stephen Daw[9], Ana Fernandez-Teijeiro[10], Galia Avrahami[11], Leanne Super[12,13,14], Auke Beishuizen[15], Walentyna Balwierz[16], Tomasz Klekawka[17], Anne Uyttebroeck[18], Andishe Attarbaschi[19], Michaela Cepelova[20], Francesco Ceppi[21], Alexander Fossså[22], Tim Prestidge[23], Annika Englund[24], Lisa Lyngsie Hjalgrim[25], Wolfram Klapper[26], Dirk Hasenclever[27], Christine Mauz-Körholz[28,29]

[1]Justus-Liebig-University of Giessen, Pediatric Hematology and Oncology, Giessen, Germany, [2]AYA Oncology Unit, Radiotherapy Dept, Centro di Riferimento Oncologico IRCCS, Aviano, Italy, [3]Sorbonne Université APHP Hopital Armand Trousseau, Paris, France, [4]Hopital Robert Debre, Université Paris-Cité,Paris, France, [5]University Hospital Leipzig, Department of Nuclear Medicine, Leipzig, Germany, [6]Department of Radiology, University Hospital Halle, Halle/Saale, Germany, [7]Department of Radiooncology, University Hospital Halle, Halle/Saale, Germany, [8]Medical University of Vienna, Department of Radiation Oncology, Vienna, Austria, [9]University College London Hospitals, London, UK, [10]Sociedad Española de Hematología y Oncología Pediátricas (SEHOP), Hospital Universitario Virgen Macarena, University of Sevilla, Sevilla, Spain, [11]Schneider Children's Hospital, Petah Tikvah, Israel, [12]Monash Children's Hospital, [13]Royal Children's Hospital, [14]Monash University, Melbourne, Australia, [15]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands, [16]Jagiellonian University Medical College, Krakow, Poland, [17]University Children's Hospital of Krakow, Poland, [18]Pediatric Hematology and Oncology, University Hospitals Leuven, KU Leuven, Belgium, [19]St Anna Children's Hospital, Vienna, Austria, [20]Motol University Hospital, Prague Czech Republic, [21]Pediatric Hematology-Oncology Unit, Division of Pediatrics, Department Woman-Mother-Child, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Switzerland, [22]Oslo University Hospital, Oslo, Norway, [23]Blood and Cancer Centre, Starship Hospital, Auckland, New Zealand, [24]University Hospital of Uppsala, Sweden, [25]University Hospital Copenhagen, Denmark, [26]Department of Pathology, Hematopathology Section, University Hospital Schleswig-Holstein, Kiel, Germany, [27]Institute of Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany, [28]Justus-Liebig-University of Giessen, Pediatric Hematology and Oncology, Giessen, [29]Medical Faculty of the Martin-Luther University of Halle-Wittenberg, Halle, Germany

Background: Cure rates in pediatric Hodgkin lymphoma (HL) exceed 95% with risk-adapted treatment. Involved field radiotherapy (IFRT) is still recommended in intermediate and advanced stage patients (pts) with inadequate response (IR), that is, with a positive PET at early response assessment (ERA) after 2 OEPA (vincristine, etoposide, prednisone, doxorubicin) induction cycles. The EuroNetPHL-C2 trial aimed to reduce radiotherapy (RT) by testing intensified consolidation with DECOPDAC21 (doxorubicin, etoposide, cyclophosphamide, vincristine, prednisone, dacarbazine every 21 days) against standard COPDAC28 (cyclophosphamide, vincristine, prednisone, dacarbazine every 28 days). This is the first report of the interim analysis at 36 months observation.

Methods: This international open-label, randomized phase III study included pts with HL < 25 years at diagnosis. All pts received OEPA followed by ERA. Further therapy was guided by treatment level (TL) according to risk factors of the EuroNet legacy trials, ERA and randomization arm. In intermediate (TL2) and advanced stages (TL3) either 2 or 4 COPDAC28 or DECOPDAC21 cycles were applied. PET-negative pts at ERA (adequate response, AR) received no RT. All ERA-IR pts received IFRT in the COPDAC28 arm. In DECOPDAC21 ERA-IR pts the decision on residual node RT was made at late response assessment (LRA). In case of LRA-AR, RT was completely omitted. PET thresholds for AR were Deauville scores 1–3 and qPET <1.3, both at ERA and LRA. The primary objective was event-free survival (EFS), testing for non-inferiority in IR pts and superiority in AR pts.

Results: The intention to treat (ITT) TL2 and TL3 cohort comprised 2436 pts, 2261 were randomized. Of 2249 evaluable pts, 1445 had AR and 804 had IR after induction. In the ERA-AR group, 709 pts received DECOPDAC21 and had 96.0% EFS (95% CI: 94.5%–97.5%) and 710 pts received COPDAC28 with 91.2% EFS (95% CI: 89.1%–93.4%, $p = 0.0001$). In the ERA-IR subgroup, 389 pts received DECOPDAC21 and had 85.7% EFS (95% CI: 82.2%–89.3%) and 385 pts received COPDAC28 with 88.3% EFS (95% CI: 85.1%–91.7%). In the DECOPDAC21 arms 12.8% received RT, whereas in COPDAC28, 35.6% received IFRT. In the ITT analysis 4/1445 AR pts (all COPDAC28) and 6/804 IR pts died, 2 in DECOPDAC21 and 4 in COPDAC28.

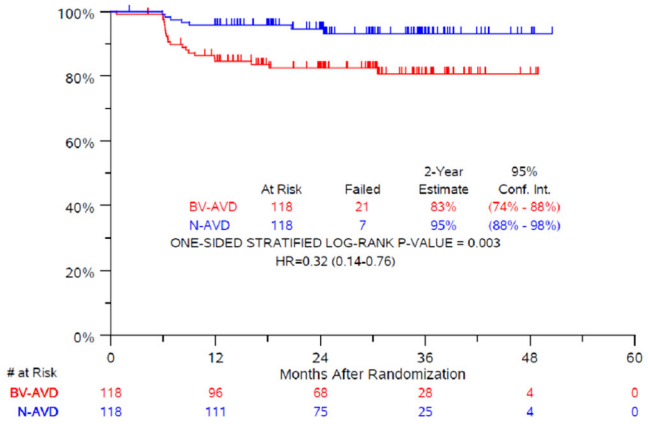
Conclusions: The novel DECOPDAC21 consolidation showed superior EFS in ERA-AR and non-inferiority in ERA-IR pts, allowing RT reduction in pediatric TL2 and TL3 pts without impacting treatment related mortality.

T087: PROGRESSION-FREE SURVIVAL (PFS) WITH NIVOLUMAB-AVD IS SUPERIOR TO BRENTUXIMAB VEDOTIN-AVD WITH 2-YEAR FOLLOW-UP OF S1826 IN ADOLESCENT ADVANCED STAGE (AS) CLASSIC HODGKIN LYMPHOMA (CHL)

Sharon M. Castellino[1,2], Hongli Li[3], Alex F. Herrera[4], Angela Punnett[5], Michael Le[3], Susan K. Parsons[6], Frank G. Keller[1,2], Richard Drachtman[7], Adam Lamble[8], Christopher J. Forlenza[9], Andrew Doan[10], Sarah Rutherford[11], Andrew Evens[7], David Hodgson[12], Richard F. Little[13], Malcom Smith[13], Hildy Dillon[14], Joo Song[4], Sonali Smith[15], Jonathan W. Friedberg[16], Kara M. Kelly[17]

[1]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, [2]Emory University, Winship Cancer Institute, Atlanta, GA, [3]SWOG Statistics and Data Management Center, Seattle, WA, [4]City of Hope Comprehensive Cancer Center, Duarte, CA, [5]SickKids Hospital, Toronto, Ontario, CAN, [6]Reid R. Sacco AYA Cancer Program, Tufts Medical Center, Boston, MA, [7]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, [8]Seattle Children's Hospital, Seattle, WA, [9]Memorial Sloan Kettering New-York, NY, [10]Children's Hospital Los Angeles, Los Angeles, CA, [11]Weill Cornell Medicine, New York, NY, [12]Princess Margaret Cancer Centre, Toronto, CAN, [13]National Cancer Institute, Cancer Therapy Evaluation Program, Bethesda, MD, [14]SWOG Cancer Research Network, [15]University of Chicago, Chicago, IL, [16]Wilmot Cancer Institute, University of Rochester, Rochester, NY, [17]Roswell Park Comprehensive Cancer Center, University at Buffalo, Buffalo, NY

Figure 1: 2 yr. PFS by Study Arm. Funding: NIH/NCI/NCTN grants U10CA180888, U10CA180819, U10CA180820, U10CA180821, U10CA180863,UG1CA189955; and Bristol-Myers Squibb. Bv provided by Seagen (Canada Only). Clinical Trial NCT03907488.



Background: While Brentuximab vedotin (BV) combined with dose-dense chemotherapy and response-based involved site radiation therapy (RT) is efficacious in pediatric patients (pts) with high-risk cHL, PD-1 inhibitors have not been evaluated in the frontline setting in adolescents with cHL. We present the 2-year (y) follow-up of adolescents treated on S1826, a randomized, phase 3 trial comparing nivolumab (N)-AVD vs. BV-AVD in newly diagnosed advanced stage (AS, Stage 3–4) cHL.

Methods: Eligible pts were randomized 1:1 to 6 cycles of N-AVD or BV-AVD. At randomization, pts were stratified based on age, international prognostic score (IPS), and intent to use RT for residual metabolically active lesions at the end of treatment. The primary endpoint was progression free survival (PFS); secondary endpoints included overall survival (OS), event-free survival (EFS), and safety.

Results: 24% ($n = 240$) of 994 pts enrolled on S1826 were 12–17 y. Among 236 eligible pts randomized to N-AVD ($n = 118$) or BV-AVD ($n = 118$) the median age was 15.6 y (12–17.9 y), 51% of pts were male, 68% were white, 15% were black, and 17% were Hispanic. 57% had Stage IV disease, 43% had bulky disease and 28% had an International Prognostic Score (IPS) score of 4–7 with no difference by study arm. At 2 y follow-up, the PFS was 95% with N-AVD and 83% in BV-AVD [HR 0.32, 95% CI 0.14–0.76] (Figure). EFS was 91% with N-AVD vs. 81% with BV-AVD ($p = 0.02$). Overall use of protocol-specified RT was 1.3% ($n = 1$ N; $n = 2$ BV). OS did not differ by treatment arm with 1 death reported at 21 days from registration in a patient on BV-AVD.

The rate of grade (gr) ≥3 neutropenia was 44% after N-AVD compared to 39% after BV-AVD; however, only 3% of pts had gr ≥3 febrile neutropenia and 1% with sepsis after either regimen. Differences in use of GCSF (64% N; 97% BV) reflected protocol mandated GCSF with BV. Overall rates of immune related adverse events (AEs) (any gr) were low. Hypo/hyperthyroidism (any gr) was more frequent after N-AVD (5%/2% N vs.1%/0%, BV). Sensory peripheral neuropathy (>gr.2) was more frequent after BV-AVD (7%, N vs. 14%, BV). 80% of adolescent pts received dexrazoxane. AE associated discontinuation of N or BV as part of therapy occurred in 4.2% and 0.8% of patients respectively.

Conclusions: N-AVD is well tolerated in adolescents 12–17 y, with high PFS and EFS and minimal use of RT compared to prior pediatric HL studies. N-AVD is a new standard of care for adolescents with AS cHL.

T088: UPDATED RESULTS FROM THE PHASE 2 KEYNOTE-667 STUDY: PEMBROLIZUMAB (PEMBRO) IN CHILDREN AND YOUNG ADULTS WITH LOW-RISK CLASSICAL HODGKIN LYMPHOMA (CHL) AND SLOW EARLY RESPONSE (SER) TO FRONT-LINE CHEMOTHERAPY (CHEMO)

Lisa Giulino-Roth[1], Mario Melgar Toledo[2], Frank G. Keller[3], Bradford S. Hoppe[4], Christopher J. Forlenza[5], Sharon M. Castellino[3], Maitane Andion Catalan[6], Julie Krystal[7], Adam Lamble[8], Flavio Luisi[9], Fabio Molina Morales[10], Aarati V. Rao[11], Stacy Cooper[12], Oscar Gonzalez-Llano[13], Luis Juarez Villegas[14], Christine Mauz-Körholz[15], Juan Shen[16], Pallavi Pillai[16], Rushdia Yusuf[16], Kara M. Kelly[17]

[1]Weill Cornell Medicine, New York, NY, USA, [2]Unidad Nacional de Oncologia Pediatrica, Guatemala City, Guatemala, [3]Children's Healthcare of Atlanta at Egleston, Atlanta, GA, USA, [4]Mayo Clinic, Jacksonville, FL, USA, [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA, [6]Hospital Infantil Universitario Nino Jesus, Madrid, Spain, [7]Cohen Children's Medical Center of New York, Queens, NY, USA, [8]Seattle Children's Hospital, Seattle, WA, USA, [9]Instituto de Oncologia Pediatrica—GRAACC—UNIFESP, São Paulo, Brazil, [10]Oncomédica S.A.S, Monteria, Colombia, [11]Kaiser Permanente Roseville Medical Center, Roseville, CA, USA, [12]Johns Hopkins University, Baltimore, MD, USA, [13]Hospital Universitario "Dr. Jose Eleuterio Gonzalez," Monterrey, Mexico, [14]Hospital Infantil de Mexico Federico Gomez, Mexico City, Mexico, [15]Justus-Liebig University of Giessen, Giessen, and Medical Faculty of the Martin-Luther-University of Halle-Wittenberg, Halle, Germany, [16]Merck & Co., Inc., Rahway, NJ, USA, [17]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

Background: KEYNOTE-667 (NCT03407144) evaluated pembro+chemo consolidation ± involved-site radiotherapy (ISRT) followed by pembro maintenance in pts with cHL and SER to front-line chemo. Prior results for pts with low-risk cHL and SER to front-line ABVD induction showed consolidation with pembro + AVD+ISRT followed by maintenance pembro had manageable safety and resulted in 56% of pts having PET-negative disease by BICR; 67% of pts had PET-negative disease by investigator review and received a reduced dose of ISRT. We present additional follow-up of pts with low-risk cHL and SER to ABVD.

Methods: Pts aged 3–25 y with newly diagnosed stage IA, IB, or IIA cHL received 2 cycles of ABVD followed by early response assessment (PET and CT/MRI). Pts with rapid early response received nonstudy therapy. Pts with SER (ie, Deauville score [DS] 4 or 5) received consolidation with pembro 2 mg/kg up to 200 mg (3–17 y) or 200 mg (18–25 y) IV Q3W+2 cycles of AVD followed by late response assessment (LRA; PET, MRI/CT). All pts with SER received ISRT (21.6 Gy for complete PET response [i.e., DS 1–3]; 30.6–36 Gy for partial PET response [i.e., DS 4 or 5]) followed by maintenance pembro for ≤17 cycles. Primary end point: ORR by BICR per Cheson 2007 IWG criteria. Secondary end points included PET negativity after AVD and safety.

Results: 78 pts with low-risk cHL enrolled; 10 had SER to ABVD and received pembro+AVD. Median follow-up at data cutoff (Feb 29, 2024) was 19.9 mo (range, 5.6–44.8). Of 10 pts with SER, 4 completed consolidation and maintenance, 1 was ongoing, and 5 discontinued due to CR. Pts received a median of 11.5 doses of pembro (range, 5–17); median time on pembro was 7.4 mo (range, 3.5–11.3). All 10 pts who received pembro + AVD had an LRA, of whom 6 (60%) were PET negative by BICR (7 [70%] PET negative by investigator review). ORR was 100% (95% CI, 69–100; 9 CR; 1 PR). TRAEs during consolidation occurred in 8 pts (80%; grade 3 or 4 in 4 pts [40%]). No pts discontinued or died due to TRAEs. 7 pts (67%) had an AE related to pembro (grade 3 in 3 pts [30%]). 3 pts (30%) had an immune-mediated AE (all grade 1 or 2 hypothyroidism).

Conclusion: With 20 mo of follow-up, pembro+AVD consolidation followed by pembro maintenance continued to have manageable safety in pts with low-risk cHL and SER to ABVD. 60% of pts had a PET-negative response at LRA by BICR; 70% of pts had a PET-negative response by investigator review and received a reduced dose of ISRT.

P089: AN AUDIT OF COMPLIANCE WITH RECOMMENDATIONS FOR SCREENING AND MANAGEMENT OF HODKINS LYMPHOMA IN TEENAGER AND YOUNG ADULT POPULATION. RESULTS FROM A BASELINE AUDIT WITHIN THE NORTHERN HEALTH AND SOCIAL CARE TRUST

Esraa Yousif[1], Kerrie Sweeney[1], Aaron Niblock[1]

[1]Antrim Area Hospital, Bush Road, Antrim, Northern Ireland

Background/Rationale: Hodgkin's lymphoma is the most common haematopoietic tumour affecting children worldwide (Brockelman et al., 2018). Is usually presents with a supradiaphragmatic lymphadenopathy (Shanbhag et al., 2017). These patients should be staged with CT or FDG PET, biopsy is no longer needed for staging in these patients (Chosen et al., 2014). It is usually completely curable (Cabrera et al., 2019) and it is recommended to give 2 cycles of ABVD in early stages as well as 2 cycles of BEACOPP following by a PET scan and two further cycles of BEACOPP followed by 4 cycles of BEACOPP. Early-stage patients should receive radiotherapy (Brockelman et al., 2018).

Methodology: All teenagers and young adults diagnosed with Hodgkin's lymphoma since 2016 in the Northern health and social care trust were included. An audit tool was developed which was derived form the pre-existing tool set out by the Royal College of Pathologists. The audit template included criteria's such as virology bloods, staging with pet scan, whether the disease was classified as favourable or unfavourable, whether patients that received chemotherapy to the neck had regular thyroid functioning tests, the number of cycles of each chemo, the importance of thyroid function tests and the introduction of a screening checklist.

Results: Areas of good practice were identified such as pre-treatment virology bloods and education on fertility preservation as well as organ toxicity secondary cancer and fertility when formulating a treatment plan, patients educated on the need to receive irradiated blood products for life, treatment regime for favourable and unfavourable disease. These areas of good practice had an overall compliance rate of 100%. Gaps were identified in the practice such as the need to perform thyroid function tests in patients receiving radiotherapy to the neck and head (only 75% of patients received regular thyroid function tests) as well as the calculation of the IPS (only 60% of TYA's had IPS calculated),Healthcare professionals were educated on the importance of performing TFT's and calculation of the IPS.

Conclusion: Gaps were identified in meeting the recommendations for screening and management of Hodgkin's lymphoma in teenager and young adult population, early recognition of these abnormalities as well as education of healthcare professionals on the importance of these key features in the management of this subset of patients is crucial to improving outcomes.

P090: BRENTUXIMAB-ASSOCIATED ALOPECIA IN CHILDREN AND YOUNG ADULTS WITH NEWLY DIAGNOSED HODGKIN LYMPHOMA

Jonathan D. Bender[1,2], Angela T. Faulhaber[1], Robin E. Norris[1,2]

[1]Division of Oncology, Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [2]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Table 1: Cohort characteristics and alopecia details in newly diagnosed children and young adults with hodgkin lymphoma treated with brentuximab vedotin.

Table 1: Brentuximab-Associated Alopecia and Cohort Characteristics

Variable		Overall N = 23[†]	Resolution of Alopecia Post-BV: No N = 9[†]	Resolution of Alopecia Post-BV: Yes N = 14[†]	p-value
Sex	Female	15 (65%)	8 (89%)	7 (50%)	0.086
	Male	8 (35%)	1 (11%)	7 (50%)	
Age at First BV Dose		18.0 (16.8,19.9)	18.1 (16.9,19.8)	17.8 (16.3,21.3)	0.6
Chemotherapy	BV-AVD	18 (78%)	8 (89%)	10 (71%)	0.6
	BV-AVEPC	5 (22%)	1 (11%)	4 (29%)	
Cumulative BV Dose (mg/m2)		14.2 (11.2,14.4)	14.4 (13.7,14.5)	13.8 (9.2,14.3)	0.14
Peripheral Neuropathy Requiring BV Reduction		4 (17%)	2 (22%)	2 (14%)	>0.9
Days from First BV Dose to Alopecia Onset		41 (28,58)	41 (30,55)	37 (27,58)	0.7
Maximum CTCAE v5.0 Alopecia Grade	Grade 1: Hair loss of <50% normal	1 (4.3%)	0 (0%)	1 (7.1%)	>0.9
	Grade 2: Hair loss of ≥50% normal	16 (70%)	7 (78%)	9 (64%)	---
	Unable to Assess	6 (26%)	2 (22%)	4 (29%)	---
Alopecia Pattern	Diffuse	13 (57%)	7 (78%)	6 (43%)	---
	Male pattern	1 (4.3%)	1 (11%)	0 (0%)	---
	Patchy	1 (4.3%)	0 (0%)	1 (7.1%)	---
	Not reported	8 (35%)	1 (11%)	7 (50%)	---
Patient Expressed Concern		11 (48%)	8 (89%)	3 (21%)	0.003
Treatment/Referral for Alopecia		8 (35%)	8 (89%)	0 (0%)	<0.001
Treatment for Alopecia	Dermatology consultation	2 (25%)	2 (25%)	---	>0.9
	Shampoo	2 (25%)	2 (25%)	---	---
	Topical minoxidil	2 (25%)	2 (25%)	---	---
	Vitamin/Supplement	2 (25%)	2 (25%)	---	---
Alopecia Status at Last Visit	Fully resolved, no ongoing issues	14 (61%)	0 (0%)	14 (100%)	---
	Improved, thinner than baseline	9 (39%)	9 (100%)	0 (0%)	---
Days from Last BV Dose to Resolution of Alopecia		186 (117, 280)	---	186 (117, 280)	---
Years from Last BV Dose to Last Follow-up		2.2 (1.3, 3.3)	3.1 (2.1, 3.4)	2.0 (1.1, 3.1)	0.6

[†]n (%); Median (interquartile range)

Abbreviations: BV, brentuximab vedotin; BV-AVD, BV, doxorubicin, vinblastine, dacarbazine; BV-AVEPC, BV, doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide; CTCAE, Common Terminology Criteria for Adverse Events

Background: Brentuximab vedotin (BV) is an antibody-drug conjugate against CD30 used for Hodgkin lymphoma (HL). Although generally well-tolerated, BV commonly results in peripheral neuropathy, nausea, and fatigue. Prior single-agent studies of BV report alopecia as relatively uncommon; however, in practice, the prevalence and duration of alopecia in BV-treated patients seems higher. In this single-center, retrospective study, we characterize BV-associated alopecia in children and young adults with newly diagnosed HL.

Methods: Eligible patients had received ≥1 BV dose for newly diagnosed HL, had no pre-existing alopecia, and had ≥8 weeks follow-up (including information on alopecia) after last BV dose. Alopecia was graded according to CTCAE v5.0. Between-group comparisons were completed using Fisher's exact and Wilcoxon rank sum tests. Continuous variables were presented as median (interquartile range).

Results: Of 23 included patients (age: 11–34 years), 23 (100%) developed alopecia after BV. Eighteen (78%) patients were treated with BV-AVD and 5 (22%) received BV-AVEPC. Median time to alopecia onset from first BV dose was 41 (28, 58) days; among BV-AVEPC patients, time to onset trended earlier at 23 (22, 42) days as compared to BV-AVD at 45 (31, 58) days ($p = 0.3$). Seventeen (74%) patients had adequate data to grade hair loss; 16 (70%) patients experienced ≥50% hair loss from baseline. Nine (39%) patients did not have full resolution of alopecia, despite a median follow-up time of 3.1 (2.1, 3.4) years, although all have experienced some improvement in hair loss. Eight (35%) patients were referred to Dermatology and/or started treatment for alopecia. For the 14 (61%) patients with alopecia resolution, median time to resolution was 186 (117, 280) days from last BV dose. BV-AVEPC patients trended toward a shorter time to alopecia resolution of 122 (103, 149) days versus BV-AVD at 203 (140, 301) days ($p = 0.2$).

Conclusions: In this cohort, alopecia arose in all patients, tended to be severe and diffuse, and did not fully resolve in 39% of patients, despite a median follow-up of >3 years. No risk factors for prolonged alopecia were identified. Alopecia may arise and resolve more quickly in patients treated with BV-AVEPC as compared to BV-AVD, which may reflect the different BV doses and schedules in these regimens. Further research into the mechanisms and management of BV-associated alopecia is needed.

P091: CLINICAL STUDY OF IMMUNE-TARGETING COMBINED WITH ATTENUATED CHEMOTHERAPY IN THE TREATMENT OF PEDIATRIC HODGKIN LYMPHOMA

Huixia Gao[1], Yanlong Duan[1]

[1]*Beijing Children's Hospital, Capital Medical University*

Gao Huixia, Li Ying, Li Nan, Huang Shuang, Zhang Meng, Zhou Chunju, Zhang Ningning, Zhang Yiming, Yang Jing, Jin Ling, Wang Xiaoling, Peng Yaguang, Wang Tianyoug, Duan Yanlong

Abstract: Objective To explore the safety and clinical efficacy of Brentuximab Vedotin (BV) combined with Rituximab (R) and attenuated chemotherapy in the treatment of children with classic Hodgkin Lymphoma (cHL).

Methods: 40 children with newly diagnosed with intermediate-risk or high-risk cHL were enrolled from October 2022 to June 2024, who received the detection of biopsy pathological morphology and immunohistochemistry. Risk-adapted combination of immune-targeted combined with attenuated chemotherapy was given based on pre-treatment risk and early treatment response. The safety and clinical efficacy were summarized.

Results: 40 cHL children included 25 males and 15 females, with a median age of 12 years. 22 cases (55.0%) had bulky lymph nodes. 30 cases (75%) were in stage III-IV according to the Ann Arbor staging system. There were 5 intermediate-risk and 34 high-risk patients. 36 cases (90.0%) achieved Complete Metabolism Response (CMR) after 2 courses of chemotherapy. The CMR rates were 100% in middle-risk group and 88.2% in high-risk group, respectively. Five patients (12.5%) required radiotherapy. Toxicities included grade I ~ II myelosuppression, infusion reaction and mild peripheral neuropathy without dose-limiting toxicity. All the 40 patients were in continuous remission, and there were no deaths or lost to follow-up. Median follow-up was 6 months (3,13 months).

Conclusions: BV+R combined with attenuated chemotherapy and risk-adapted combination for cHL in children is effective and well tolerated, and significantly reduce radiation rate. Larger cohorts and longer follow-up will be required to confirm these preliminary findings.

P092: CNS INVOLVEMENT IN PEDIATRIC HODGKIN LYMPHOMA: A RETROSPECTIVE ANALYSIS OF AHOD1331, EURONET-PHL-C1 AND EURONET-PHL-C2 FROM SEARCH FOR CAYAHL

Reena Pabari[1], Kathleen Mccarten[2], Jamie E. Flerlage[3], Hollie Lai[4], Christine Mauz-Körholz[5], Karin Dieckmann[6], Monica Palese[3], Sue C. Kaste[7], Sharon M. Castellino[8], Kara M. Kelly[9], Dietrich Stoevesandt[10], Lars Kurch[11]

[1]*Division of Hematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada,* [2]*Diagnostic Imaging, Imaging and Radiation Oncology Core Rhode Island, Lincoln, RI, USA,* [3]*Division of Pediatric Hematology/Oncology, University of Rochester, Rochester, NY, USA,* [4]*Children's Hospital of Orange County, Orange County, CA, USA,* [5]*Department of Pediatric Hematology and Oncology, University Hospital of Giessen and Marburg, Giessen, Germany and Medical Faculty of the Martin-Luther University of Halle-Wittenberg, Halle, Germany,* [6]*Medical University of Vienna, Department of Radiation Oncology, Vienna,* [7]*Departments of Diagnostic Imaging and Oncology, St. Jude Children's Research Hospital, Memphis, TN,* [8]*Children's Hospital of Atlanta, Atlanta, GA, USA,* [9]*Roswell Park Comprehensive Cancer Center, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, USA,* [10]*University Hospital Halle, Department of Radiology, Halle, Germany,* [11]*University Hospital Leipzig, Department of Nuclear Medicine, Leipzig, Germany*

Background: Hodgkin lymphoma (HL) accounts for approximately 7% of childhood cancer, the majority of which occurs in adolescents and young adults (AYA). HL involving the central nervous system (CNS) is exceedingly rare, with an estimated incidence of <0.5%. Information regarding the presentation, management, treatment and outcome of patients with CNS HL is limited to case reports or small series.

Methods: We performed a retrospective analysis of COG AHOD1331 (NCT02166463), EuroNet-PHL-C1 (NCT00433459, EudraCT 2006–000995-33) and C2 (NCT02684708, EudraCT 2012–004053-88). Patients had morphologic (CT) and metabolic (FDG-PET) imaging at baseline, and response assessment after 2 cycles. Evaluated variables included: Ann Arbor stage, histology, symptoms at presentation, number and location of CNS lesions, anatomic description of CNS lesions, number and location of other E-lesions, FDG tracer intensity at diagnosis, metabolic and morphologic response of CNS lesions after 2 cycles, if relapse occurred and in which location. CNS involvement was defined as either: (1) lesions originating within the CNS parenchyma (intra-axial) or (2) lesions extending into the extra-axial CNS.

Results: We identified 45 HL patients with 55 CNS lesions extending into the extra-axial CNS at diagnosis from a cohort of 4995 patients; an overall incidence of 0.9%. 82.2% of patients had a single lesion in the thoracic, lumbar or sacral spine. Lesions extended into the extra-axial CNS space from adjacent soft tissue or bone, and never directly infiltrated through the dura into the brain or spinal cord. Patients with CNS involvement had a 2× greater incidence of E-lesions than previously reported cohorts without CNS involvement. 89.1% of CNS lesions demonstrated a complete metabolic response and a >75% decrease in volume after 2 cycles. Thirteen CNS lesions (23.6%) received irradiation; none were sites of disease relapse.

Conclusions: We present the largest reported cohort of pediatric and AYA HL involving the CNS at diagnosis, demonstrating that these lesions originate from surrounding tissues, extend into the extra-axial CNS space, and respond similarly to treatment as other nodal and extra-nodal disease. Our study is limited by the retrospective nature and that our cohort only includes patients enrolled on clinical trials. Despite these limitations, this study helps to describe a rare and important patient presentation.

P093: DEFINITION OF INDEPENDENT LYMPH NODE REGIONS IN PEDIATRIC HL. AN EXPERT CONSENSUS BY AN INTERNATIONAL COLLABORATION ON STAGING EVALUATION AND RESPONSE CRITERIA HARMONIZATION (SEARCH) FOR CHILDREN, ADOLESCENT, AND YOUNG ADULT HODGKIN LYMPHOMA (CAYAHL)

Dietrich Stoevesandt[1], Jonas Steglich[1], Lars Kurch[2], Jamie E. Flerlage[3], Christine Mauz-Körholz[4,5], Dieter Körholz[6], Regine Kluge[2], Dirk Vordermark[7], Bradford S. Hoppe[8], Karin Dieckmann[9], Claire Gowdy[10], Stephan Voss[11]

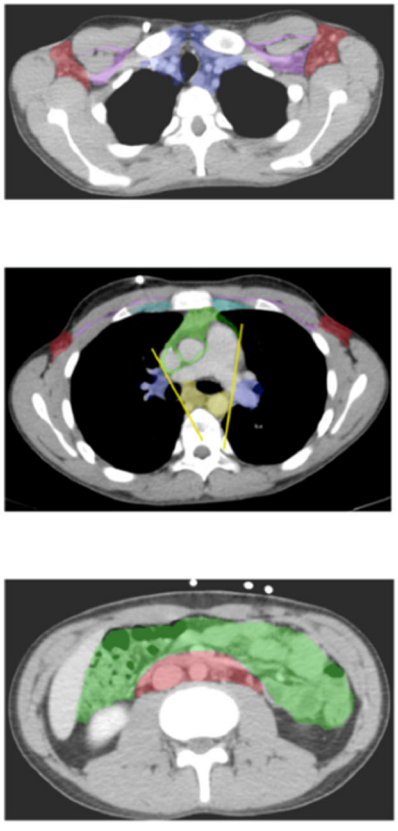
[1]Department of Radiology, University Hospital Halle, Halle/Salle, Germany, [2]Department of Nuclear Medicine, University of Leipzig, Leipzig, Germany, [3]Division of Pediatric Hematology/Oncology, University of Rochester, Rochester, NY, USA, [4]Department of Pediatric Hematology and Oncology, University Hospital Giessen-Marburg, Giessen, [5]Medical Faculty of the Martin-Luther-University of Halle-Wittenberg, Halle, Germany, [6]Department of Pediatric Hematology and Oncology, University Hospital Giessen-Marburg, Giessen, Germany, [7]Department of Radiation Oncology, Medical Faculty of the Martin-Luther-University, Halle (Saale), Germany, [8]Department of Radiation Oncology, Mayo Clinic-Jacksonville, Jacksonville, FL, USA, [9]Department of Radio-Oncology, Medical University Vienna, Vienna, Austria, [10]BC Children's Hospital, Vancouver, Canada, [11]Department of Radiology, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA

Figure 1: Supraclavicular, lower mediastinal, lower para-aortic lymph node regions and their respective boundary definitions.

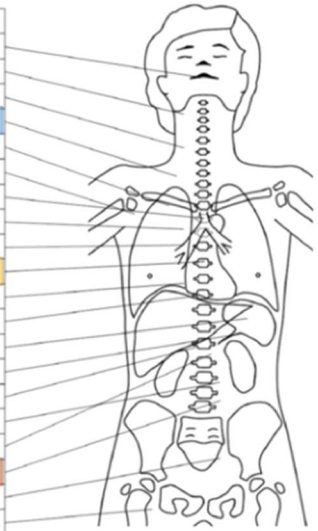
Border	Description - Supraclavicular lymph nodes (left and right)
Cranial	caudal edge of cricoid cartilage
Caudal	laterally: lower edge of clavicle / medially: cranial edge of the manubrium
Medial	midline
Lateral	medial surface of sternocleidomastoid muscle (cranially) / lateral edge of sternocleidomastoid muscle / lateral edge of scalenus muscle / trapezius muscle (caudally)
Ventral	anterior edge of the sternocleidomastoid
Dorsal	anterior edge of scalene muscles (cranially) / the prevertebral muscles / the esophagus (caudally on left side) /apex of lung, the brachiocephalic vein, the brachiocephalic trunk (right side) and the common carotid artery and subclavian artery on the left side (caudally) / anterior surface of trapezius muscle

Border	Description - Lower mediastinal lymph nodes
Cranial	carina
Caudal	diaphragm
Lateral	air–tissue interface or medial edge of either right or left hilum respectively
Ventral	imaginary horizontal line running along the posterior wall of the trachea and up to the anterior aspect of the right main bronchus (border to station 4R) or the anterior aspect of the left main bronchus (border to station 4L) or right pulmonary artery, and/or the left superior pulmonary vein; heart
Dorsal	descending aorta and the anterior aspect of the vertebral body until an imaginary horizontal line running 1 cm posterior to the anterior border of the vertebral body

Border	Description - Lower para-aortic lymph nodes
Cranial	cranial edge of the main renal artery located more caudally
Caudal	caudal edge of aortic bifurcation
Lateral	lateral edge (in the ventral aspect) of the psoas muscle
Ventral	ventral edge of superior mesenteric artery
Dorsal	lumbar spine / psoas muscle



Lymph node region
Waldeyer's ring
upper cervical
lower cervical
supraclavicular
infraclavicular / pectoral
axillary
upper mediastinal
internal mammary
hilar lymph nodes
lower mediastinal
ventral supradiaphragmatic
retrocrural / paravertebral
spleen
splenic hilar
porta hepatis
mesenteric
upper para-aortic
lower para-aortic
iliac chain
inguinal



Background/Purpose: Currently, the Ann Arbor classification and the Lugano criteria are used to stage pediatric Hodgkin lymphoma. The pattern of involvement, along with other individual risk factors, determines the treatment strategy. The increased anatomical detail provided by modern imaging modalities needs to be reflected in a consistent lexicon for lymph node level definitions. The presented atlas is intended to provide regional criteria for nodal involvement and to serve as a standardized guide for anatomic assignment of lymph node involvement.

Methods: An expert consensus from the Children's Oncology Group (COG), the European Network for Pediatric HL (EuroNet-PHL) and the Pediatric Hodgkin Consortium (PHC) defined typical involved lymph node regions in pHL using anatomic landmarks visible on modern staging CT and MRI based on other published consensus guidelines for delineating lymph node levels. These definitions were then validated in the central review process of the C2 trial.

Results: 12 regions and an additional 7 subregions were defined with their cranial, caudal, medial, lateral, ventral, and dorsal borders. The regions were then delineated on a typical neck and torso CT scan of an adolescent male patient in complete remission with no significant anatomic variations or residual tumor volume.

Also discussed are recurring situations that typically lead to questions for central review by local investigators, such as the location of axillary and infraclavicular lymph nodes in relation to arm position, inspiration-dependent assignment of lymph nodes, and the retrocrural region.

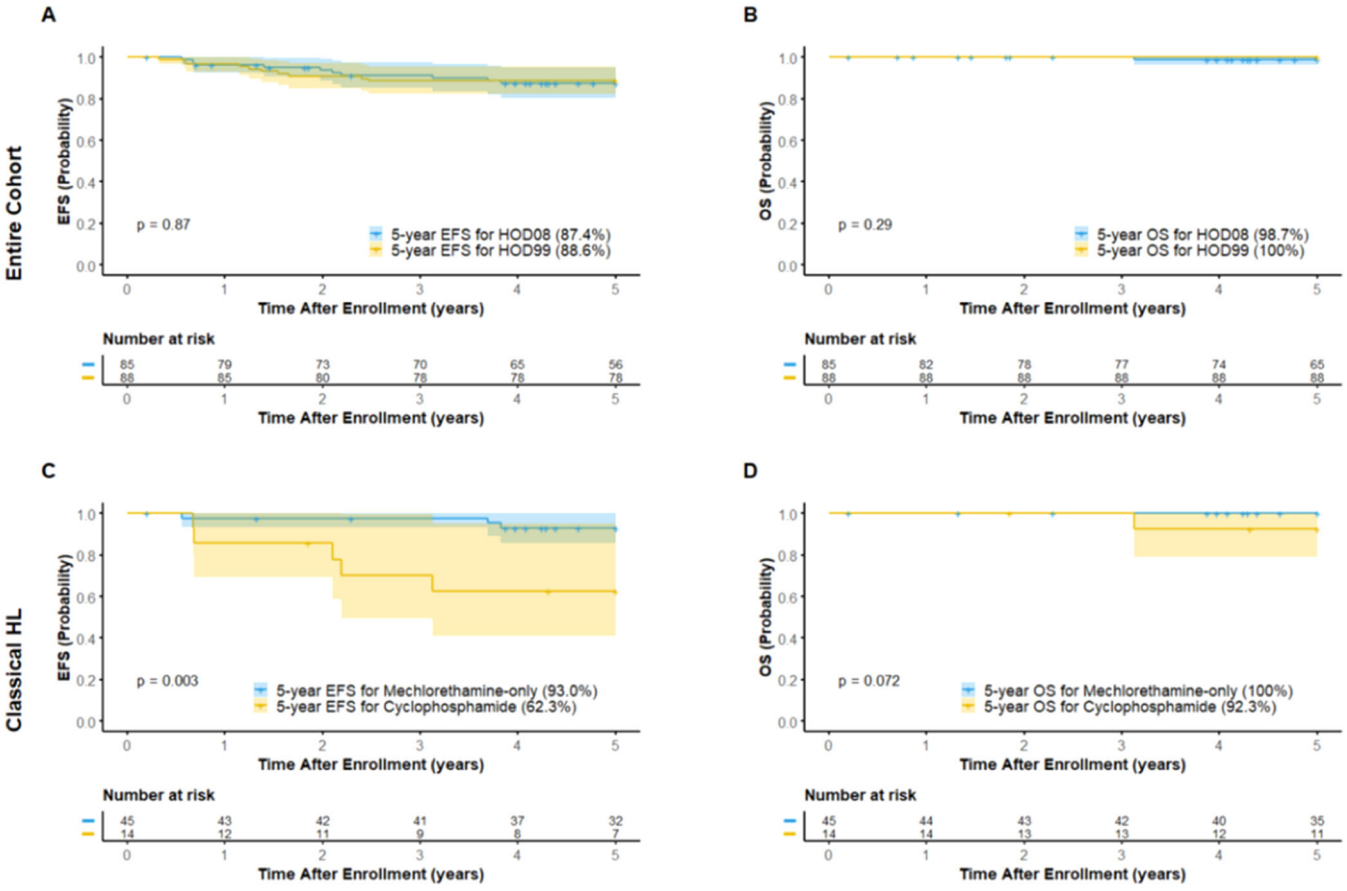
Conclusions: The atlas presented provides anatomic criteria for nodal involvement and can serve as a standardized guide to the anatomic location of lymph node involvement in pHL, which is essential for accurate and reproducible disease staging, and radiation treatment planning.

P094: DOSE-DENSE CHEMOTHERAPY ENABLES ELIMINATION OF RADIOTHERAPY FOR A MAJORITY OF PATIENTS WITH LOW-RISK PEDIATRIC HODGKIN LYMPHOMA: A REPORT ON HOD08 FROM THE PEDIATRIC HODGKIN CONSORTIUM

Jamie E. Flerlage[1,2], Angela Feraco[3], Yiwang Zhou[2], Ying Zheng[2], Lia Jiang[2], John Lucas[2], Alison Friedmann[4], Howard Weinstein[4], Torunn Yock[4], Barry Shulkin[2], Sue C. Kaste[2], Lianna Marks[5], Matthew Ehrhart[2], Stephanie Dixon[2], Scott Howard[6], Pedro De Alarcon[7,8], Sandra Luna-Fineman[9], Amy Geddis[10], Eric Larsen[11], Karen Marcus[3], Amy Billett[3], Sarah Donaldson[5], Melissa Hudson[2], Monika Metzger[12,2], Matthew Krasin[2], Michael Link[5]

[1]University of Rochester, [2]St. Jude Children's Research Hospital, [3]Dana-Farber Cancer Institute, [4]Massachusetts General Hospital, [5]Stanford University, [6]Resonance Health, [7]Children's Hospital of Illinois, [8]University of Illinois College of Medicine, [9]Children's Hospital Colorado, Anschutz, [10]Seattle Children's Hospital, [11]Maine Children's Cancer Program, [12]Médecins sans Frontières

Figure 1: Kaplan–Meier plots with risk tables of (A) event-free survival (EFS) and (B) overall survival (OS) for HOD08 and HOD99 low-risk arm; (C) EFS and (D) OS for HOD08 classical Hodgkin lymphoma, mechlorethamine treatment vs cyclophosphamide treatment.



Purpose: To increase complete response (CR) rates by ≥20% (to a goal of ≥64%) using modified Stanford V chemotherapy (8 weeks) compared to 8 weeks of VAMP (vinblastine, doxorubicin, methotrexate, and prednisone) chemotherapy in children with low-risk Hodgkin lymphoma (HL).

Methods: HOD08 (NCT00846742) was a Phase II, multicenter, investigator-initiated single-arm trial for patients ≤21 years of age with previously untreated stage IA or IIA HL without mediastinal bulk or extranodal disease extension and <3 sites of disease. Patients received a modified Stanford V regimen: two 28-day cycles (8 weeks) of chemotherapy (vinblastine 6 mg/m^2 intravenous (IV) on days 1 and 15, doxorubicin 25 mg/m^2 IV on days 1 and 15, vincristine 1.4 mg/m^2 IV on days 8 and 22 (max dose 2 mg), bleomycin 5 units/m^2 IV on days 8 and 22, mechlorethamine 6 mg/m^2 IV on day 1, etoposide 120 mg/m^2 IV on day 15, and prednisone 40 mg/m^2/day orally every other day, max dose 60 mg/day). Due to an unanticipated drug shortage, cyclophosphamide was substituted for mechlorethamine in 16 patients. Tailored field radiotherapy (25.5 Gy RT) was administered to sites of disease not in CR (defined as negative PET and ≥75% reduction in the product of 2 perpendicular dimensions by imaging) after 2 cycles of chemotherapy. The primary objective was to increase the CR rate after 8 weeks Stanford V chemotherapy by ≥20% (to a goal of 64%) compared to VAMP-treated patients on HOD99 (NCT00145600). CR rates were compared using Fisher's exact test and 5-year event-free (EFS) and overall survival (OS) rates calculated via Kaplan–Meier estimation.

Results: Among 85 enrolled patients, 66 (77.6%) achieved a CR and did not receive RT compared to 47 of 88 patients (53.4%) on HOD99 ($p = 0.001$). HOD08 5-year EFS and OS were 87.4% (95% CI: 80.4%–95.0%) and 98.7% (95% CI: 96.2%–100%). HOD99 5-year EFS and OS were 88.6% (95% CI: 82.2%–95.5%) and 100%. Of 59 patients with classical HL, 45 received mechlorethamine per protocol, while 14 received cyclophosphamide substitution. For mechlorethamine versus cyclophosphamide treatment, 5-year EFS was 93.0% (95% CI: 85.6%–100%) vs. 62.3% (95% CI: 40.9%–94.9%; $p = 0.003$) and OS 100% vs. 92.3% (95% CI: 78.9%–100%, $p = 0.07$).

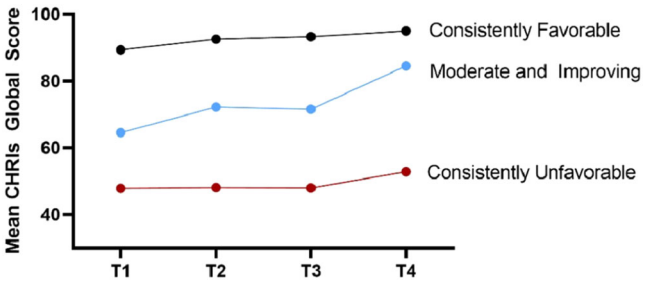
Conclusion: The modified 8-week Stanford V regimen successfully increased CR rates and thus reduced the proportion of low-risk pediatric HL patients who received RT compared to HOD99 while maintaining excellent 5-year outcomes. Cyclophosphamide substitution lacked efficacy.

P095: GROUP-BASED TRAJECTORIES OF HEALTH-RELATED QUALITY OF LIFE (HRQOL) AMONG PATIENTS WITH HIGH-RISK PEDIATRIC HODGKIN LYMPHOMA TREATED ON THE CHILDREN'S ONCOLOGY GROUP (COG) AHOD 1331 STUDY

Annalynn Williams[1], Angie Mae Rodday[2], Lindsay A. Renfro[3], Yue Wu[4], Tara O. Henderson[5], Frank G. Keller[6], Sharon M. Castellino[6], Susan K. Parsons[2]

[1]University of Rochester Medical Center, [2]Tufts Medical Center, [3]University of Southern California and Children's Oncology Group, [4]University of Florida, [5]University of Chicago Pritzker School of Medicine, [6]Emory University School of Medicine

Figure 1: Mean CHRIs-Global scores at each time point for each of three trajectory groups identified.



Background: Brentuximab vedotin (BV) with AVE-PC (Adriamycin, Vincristine, Etoposide, Prednisone, Cyclophosphamide) demonstrated superior efficacy to standard therapy (Castellino, NEJM 2022) and was associated with better HRQoL for pediatric patients with high-risk HL in the COG-led AHOD 1331 trial (Williams, JCO 2024). As mean estimates of HRQoL may not capture individual participants' heterogeneity, we aimed to identify and describe subgroups of participants with similar HRQoL trajectories over time from study entry to end of therapy.

Methods: Eligibility for AHOD1331 included previously untreated pediatric HL with stage IIB+bulk, IIIB, IVA, or IVB. 268 participants aged 11+ enrolled in a prespecified longitudinal patient-reported outcomes substudy completed the 7-item Child Health Ratings Inventories (CHRIs)–Global scale (HRQoL) prior to treatment, after cycle 2, after cycle 5, and at the end of treatment. Group-based trajectory models identified latent clusters of individuals with similar HRQoL patterns over time. The number of groups was selected based on model fit statistics, clinical interpretability, and size. Multivariate multinomial logistic regression estimated associations between a priori defined characteristics and groups. Kaplan Meier curves with log-rank tests examined differences in post-treatment progression-free survival (PT-PFS) by group.

Results: Three groups were identified (Figure 1): consistently favorable HRQoL ($n = 79$), moderate and improving HRQoL ($n = 119$), and consistently unfavorable HRQoL ($n = 70$). Older age (OR [95% CI]: 1.35 [1.10–1.66] $p = 0.005$), female sex (2.72 [1.27, 5.84] $p = 0.010$), Hispanic

ethnicity (2.65 [1.00–7.07] $p = 0.051$), and B-symptoms (2.39 [1.02–5.62] $p = 0.045$) were associated with increased odds of membership in the consistently unfavorable group vs the consistently favorable group. Age (1.25 [1.06–1.49] $p = 0.010$) and B-symptoms (2.48 [1.20–5.12] $p = 0.014$) were associated with membership in the moderate and improving trajectory group. Group membership was not associated with PT-PFS in either study arm (BV arm, $p = 0.115$) or standard arm ($p = 0.265$).

Conclusions: A subgroup of patients with high-risk pediatric HL experience persistently poor HRQoL that appears to begin at diagnosis and continue throughout therapy. Pre-treatment factors such as age, female sex, and B-symptoms were associated with worse HRQoL trajectories. These findings may help to identify patients more at risk for poor HRQoL and need intervention.

P096: INTERNATIONAL HARMONIZATION EFFORTS FOR PEDIATRIC, ADOLESCENT AND YOUNG ADULT HODGKIN LYMPHOMA: A CURRENT REPORT FROM THE SEARCH FOR CAYAHL GROUP

Jennifer Seelisch[1], Kara M. Kelly[2], Angela Punnett[3], Christine Mauz-Körholz[4], Lianna Marks[5], Monica Palese[6], Reena Pabari[7], Karin Dieckmann[8], Hollie Lai[9], Claire Gowdy[10], Jonas Steglich[11], Richard Drachtman[12], Stephan D. Voss[13], Bradford S. Hoppe[14], Kathleen Mccarten[15], Lars Kurch[16], Auke Beishuizen[17], Dietrich Stoevesandt[18], Jamie E. Flerlage[6]

[1]Children's Hospital London Health Sciences Centre, Department of Pediatrics, Division of Pediatric Hematology/Oncology, Western University, London, ON, Canada, [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA, [3]The Hospital for Sick Children and University of Toronto, Division of Haematology/Oncology, Department of Paediatrics, Toronto, ON, Canada, [4]Justus-Liebig-University of Giessen, Medical Faculty of the Martin-Luther University of Halle-Wittenberg, Pediatric Hematology and Oncology, Halle, Germany, [5]Stanford University School of Medicine, Division of Hematology/Oncology, Department of Pediatrics, Stanford, CA, USA, [6]Department of Pediatrics, Hematology and Oncology, University of Rochester Medical Center, Rochester, New York, USA, [7]The Hospital for Sick Children, Department of Paediatrics, Division of Haematology/Oncology, Toronto, Canada, [8]Medical University of Vienna, Department of Radiation Oncology, Vienna, Austria, [9]Children's Health of Orange County, Department of Radiology, Orange, CA, USA, [10]Department of Radiology, BC Children's Hospital, Vancouver, British Columbia, Canada, [11]Heart Center Leipzig, Department of Diagnostic and Interventional Radiology, Leipzig, Germany, [12]Rutgers Cancer Institute of New Jersey, Division of Pediatric Hematology Oncology, New Brunswick, NJ, USA, [13]Department of Radiology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA, [14]Mayo Clinic, Department of Radiation Oncology, Jacksonville, FL, USA, [15]Pediatric Radiology, IROCRI (Imaging and Radiation Oncology Core - Rhode Island), Lincoln, RI, USA, [16]University Hospital Leipzig, Department of Nuclear Medicine, Leipzig, Germany, [17]Princess Máxima Center for pediatric oncology, Utrecht, Netherlands, [18]Department of Radiology, University Hospital Halle, Halle/Salle, Germany

Figure 1: SEARCH for CAYAHL Publications to date.

Background: Initial evaluation and staging of patients with Hodgkin lymphoma (HL) provides the foundation for risk-adapted treatment. The Ann Arbor staging system, and subsequently the Cotswolds modification criteria, help classify patients into risk groups according to the distribution and number of anatomic sites of disease. As imaging techniques advance, ongoing refinements to staging in HL are necessary to improve prognostication and risk group assignment. Currently published staging systems are not reflective of current pediatric practices, and some elements of staging and response criteria differ across pediatric consortia. Harmonization of staging and response assessment criteria in pediatric HL is imperative to facilitate cross-trial comparison of clinical studies globally.

Methods: Established in 2011 with harmonization as its goal, the international SEARCH (Staging, Evaluation and Response Criteria Harmonization) for CAYAHL (Childhood, Adolescent and Young Adult Hodgkin Lymphoma) group is comprised of more than 40 expert members across 6 countries, with representatives from the Children's Oncology Group, European Network for Pediatric HL, Pediatric Hodgkin Consortium, and the Latin American Hemato Oncologic Pediatric Diseases Consortium. Utilizing clinical data across consortium groups where available, and delphi consensus methods where data is lacking, SEARCH has proceeded with harmonization efforts across multiple areas of HL staging and response assessment.

Results: Through SEARCH's working groups, we published harmonization projects for the involvement of liver, cortical bone, Waldeyer's Ring and E-lesions to date. In 2023/24, harmonization efforts were completed for CNS involvement and lung lesions with manuscripts in submission. A manuscript for a harmonized staging atlas for pediatric HL is also under current review.

Conclusions: We present an update on the efforts of the international SEARCH for CAYAHL group. SEARCH has successfully completed the majority of our initial harmonization projects, with next steps to include publication of a comprehensive review of current practices. The updated Lugano 2014 publication does not include pediatric patients. Given the peak age of patients with HL within the AYA spectrum and given that care is often shared between the adult and pediatric groups, there is a pressing need for pediatric oncology input and collaboration into future updates to HL staging and response assessment criteria.

P097: IS THE EVA REGIMEN (ETOPOSIDE, VINBLASTINE, DOXORUBICIN) SAFE AND EFFECTIVE FOR TREATING HODGKIN'S LYMPHOMA IN PREGNANT PATIENTS?

Elżbieta Wojciechowska-Lampka[1], Magdalena Rosińska[1], Jacek Lampka[1], Zbigniew Nowecki[1], Włodzimierz Osiadacz[1], Joanna Tajer[1], Joanna Romejko-Jarosińska[1]

[1]*The Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Introduction: Lymphomas, notably Hodgkin lymphoma, are the fourth most common cancer during pregnancy, occurring at a frequency of 1 in 1000 to 6000 pregnancies. Hodgkin lymphoma during pregnancy is documented in 3.2% of all diagnosed patients. Guidelines recommend initiating the ABVD regimen at a specific week of pregnancy or using treatments involving anthracyclines and vinca alkaloids.

Materials and Methods: The evaluation considered active treatment, encompassing both chemotherapy and radiotherapy regimens, and assessed their effects on the health of both the mother and the child. During systemic treatment administered during pregnancy, the EVA regimen (etoposide, vincristine, doxorubicin administered in cycles every 28 days) was employed in 53 patients, with an additional 5 undergoing radiotherapy. Systemic EVA therapy was predominantly administered during the second and third trimesters, with 77.4% (41 patients) receiving it during the second trimester. On average, three courses were administered, with a maximum anthracycline dose of 320 mg (median 180 mg). Most frequently, doses ranging from >120 mg to 240 mg were given, with 25 (47.2%) pregnant patients receiving them. Throughout EVA therapy, fetal status, umbilical vessels, and the placenta were monitored via ultrasound examination. Causal treatment was continued up to 3 weeks before delivery.

Results: The median follow-up duration for patients was 12.65 years. For the 53 patients treated with the EVA regimen during pregnancy: the 5-year overall survival was 88.4% (95% confidence interval [CI]: 80.1%–97.6%), and the 5-year progression-free survival was 76.8% (95% CI: 66.1%–89.3%). Out of 53 patients treated with EVA, 48 achieved complete remission before delivery. Among these, 8 experienced recurrence after 1 to 9.8 years. Growth factors were not administered to patients as part of the EVA regimen. Neutropenia was observed in some patients, as well as anemia, which did not require specific treatment.Complications around childbirth were not observed. No hematologic complications were noted in newborns except for grade 1 neutropenia in one child, which lasted for 4 days after birth. All children are developing normally.

Conclusions: The EVA regimen is a viable therapy for Hodgkin lymphoma in pregnant women. These findings support incorporating EVA therapy into clinical guidelines. Further research should address long-term outcomes and chemotherapy safety in this patient population.

P098: OMITTING RADIATION IN YOUNG ADULT FEMALES WITH HODGKIN'S DISEASE, IS THERE AN IMPACT ON OUTCOME?

Asmaa Hamoda[1], Samah Semary[2], Eman Naguib[1], Madeeha A.T. El Wakeel[1], Mohamed Zaghloul[1], Salma Abdelaziz[1], Mahmoud Hamza[3], Emad Moussa[4]

[1]*Children Cancer Hospital of Egypt and National Cancer Institute,* [2]*Children Cancer Hospital of Egypt and Beni-Suif University,* [3]*Children Cancer Hospital of Egypt,* [4]*Children Cancer Hospital of Egypt and Menofya University*

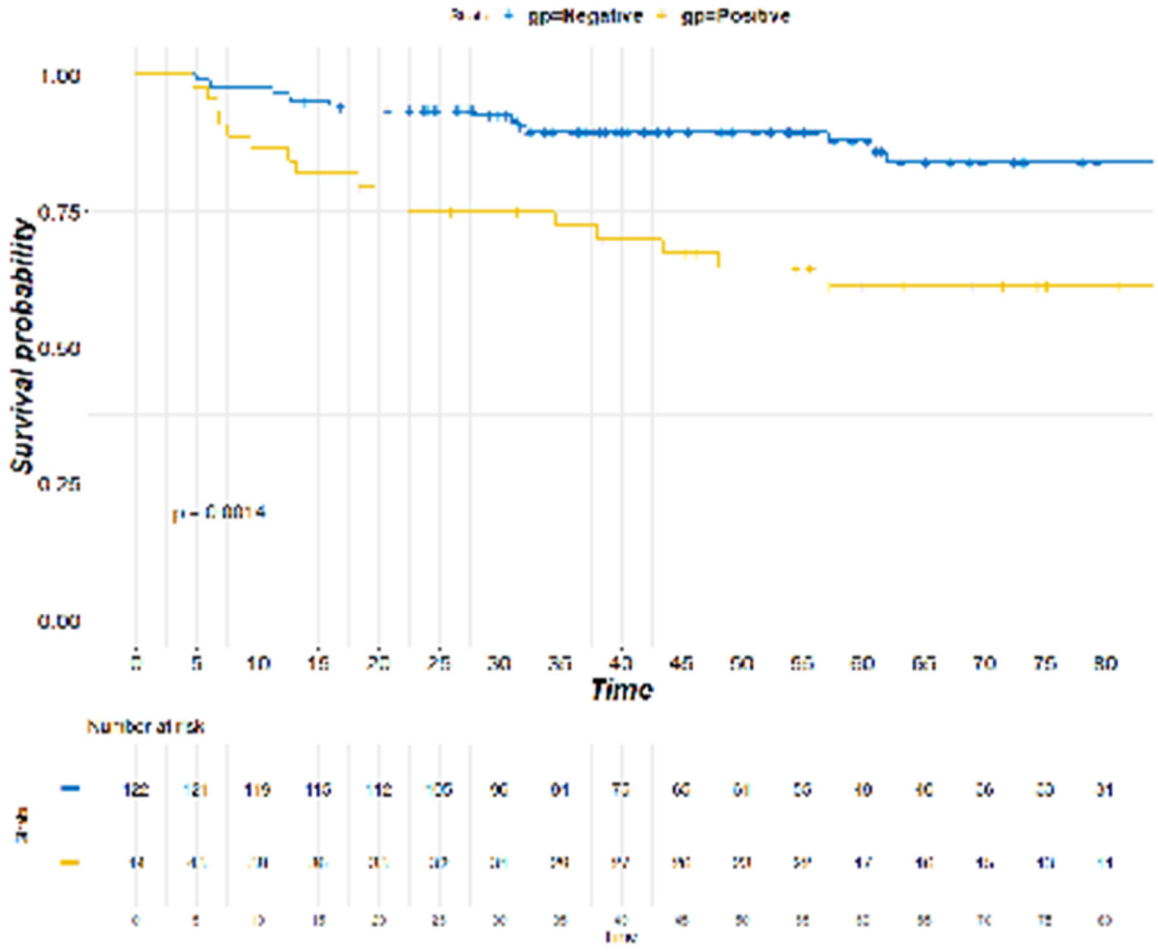


Figure 1: The three-year event-free survival among good and poor responders to chemotherapy detected by interim PET CT is 90%, and 72% respectively, and 5 years of event-free survival for them is 88%, and 61% respectively, with significant P-value 0.0014

Background: Ionizing radiation is a breast cancer risk factor. This retrospective study aims to compare the outcome of young adolescent females diagnosed and treated with classic Hodgkin lymphoma, who received chemotherapy while omitting radiotherapy, for fear of the increased risk of breast cancer, and those who received chemotherapy followed by radiotherapy. In an attempt to explore the impact of radiotherapy on the outcome, and to record the late side effects of radiotherapy as well as the incidence of breast cancer among these patients.

About 166 young adolescent females between 12 and 18 years old were diagnosed and treated with classic Hodgkin lymphoma in the Children's Cancer Hospital Egypt from July 2007 till the end of 2018, the no radiotherapy (RT) group (72 patients) received chemotherapy while omitting radiotherapy, the RT group (94 patients) received chemotherapy and radiotherapy, with 5years OS 93%, 87% respectively, and with 5 years EFS 74%, 85% respectively, with *p*-value 0.062. The initial stage and response to treatment using interim PET CT scan post-second cycle chemotherapy were documented. The outcomes were nearly identical in the no RT or RT groups. In conclusion, omitting radiation therapy did not affect the 5-year EFS; nevertheless, the existence of positive B symptoms, an advanced stage initially, or a poor response to treatment, all had an impact on the 5-year EFS.

P099: PET/CT RESPONSE ASSESSMENT IN PEDIATRIC HODGKIN LYMPHOMA. DEAUVILLE SCORE 3 DOES IT REALLY REFLECT NEGATIVITY?

Emad Moussa[1], Asmaa Hamoda[2], Samah Semary[3], Maram Salama[4], Mona Fakhry[4], Maha Mehesen[5], Madeeha Elwakeelc[6], Eman Naguib[6], Amr Elnashar[4], Asmaa Attia[6], Mohamed Sedky[7]

[1]Children Cancer Hospital of Egypt and Menoufya University, [2]Children Cancer Hospital of Egypt and National Cancer Institute, [3]Children Cancer Hospital of Egypt and Beni-Suif University, [4]Children Cancer Hospital of Egypt, [5]Children Cancer Hospital of Egypt and National Cancer Institute, [6]Children Cancer Hospital of Egypt and National Cancer Institute, [7]Children Cancer Hospital of Egypt and National Research Center

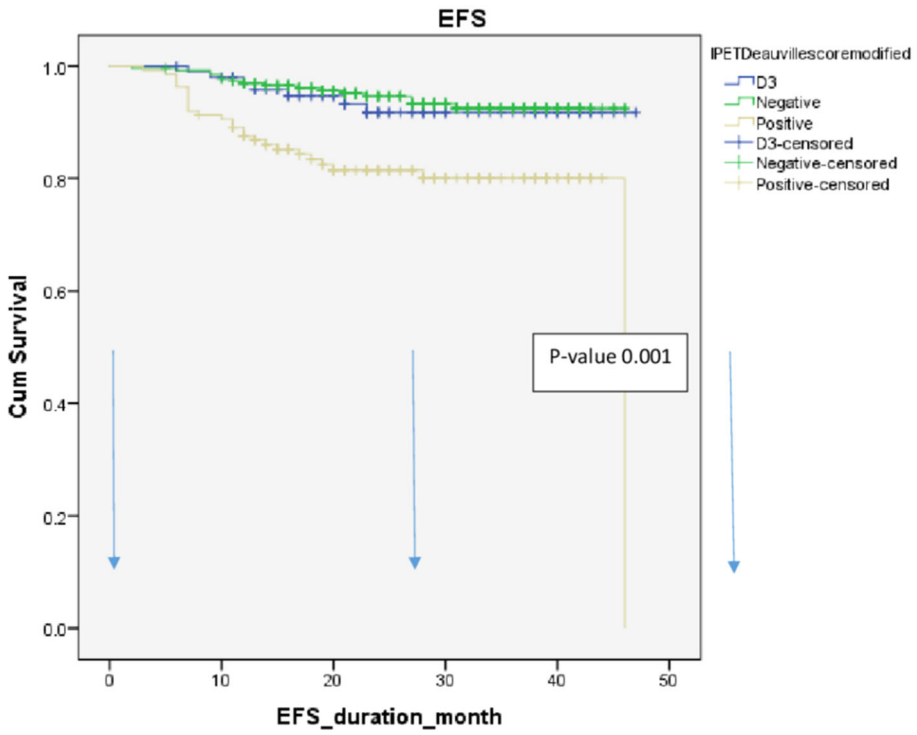


Figure : The three-years event-free survival among the DS 3 group, adequate response DS 1,2 group, and inadequate response DS 4,5 group.

Background: FDG PET is required for the staging and response evaluation of pediatric Hodgkin lymphoma. The study aims to evaluate the outcome of pediatric patients with Hodgkin's lymphoma based on interim PET CT assessments of their early response following second-cycle chemotherapy using the Deauville score (DS). To determine whether DS 3 is providing an adequate or inadequate response.

Methods: A retrospective analysis of 504 pediatric patients with classic Hodgkin lymphoma who were treated with a chemotherapy protocol based on the Euro-Net protocol at the Children Cancer Hospital Egypt from March 2019 till the end of October 2022.

Results: While adequate response DS 1/2 and DS 3 have nearly the same 3-year event-free survival (EFS) of 91.9% and 91.5%, respectively, compared to those patients with inadequate response DS 4/5, who showed an EFS of 80.4% [*p*-value, 0.001], patients with a DS 3 at interim PET evaluation were considered negative as DS 1/2.

Patients of DS 3 group who did not receive radiotherapy had a much worse 3 years EFS by the existence of positive B symptoms, an ESR > 30, or an advanced stage. Radiation therapy did not improve the 3-year EFS in patients with an inadequate response (DS4/5) and poor prognostic characteristics. They still need more advanced treatment.

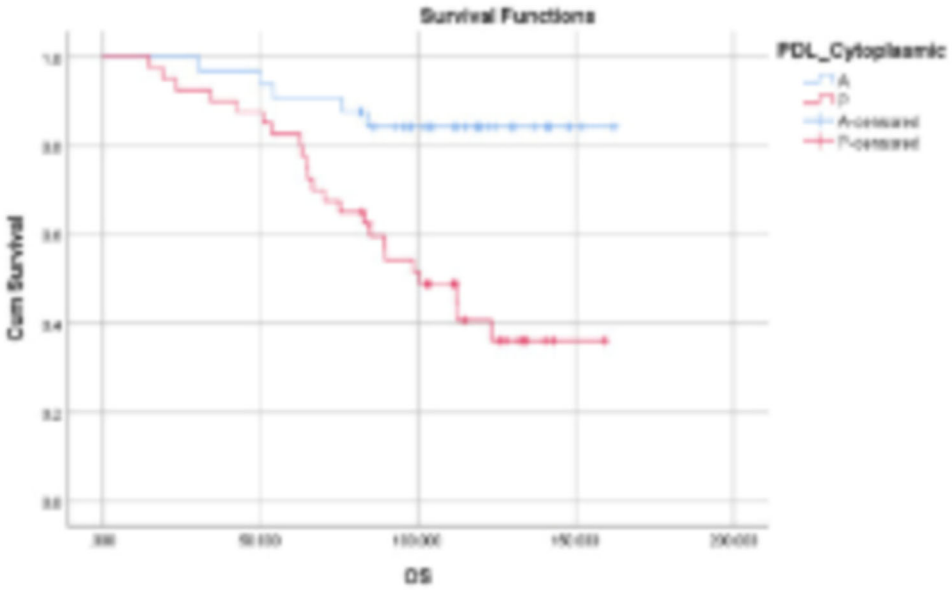
Conclusion: DS 1/2 and DS 3 had about the same 3-year EFS, which is better than the three-year EFS of patients with DS 4/5. Therefore, we can classify DS 3 as having negative FDG PET CT uptake.

P100: PROGNOSTIC SIGNIFICANCE OF PD1, PD-L1 EXPRESSION, PATHOLOGICAL SUBTYPES AND METABOLIC ACTIVITY ON 18F-FDG PET/CT IN REFRACTORY/RELAPSING PEDIATRIC HODGKIN LYMPHOMA

Reham Khedr[1], Eman Khorshed[1], Omneya Hassanein[1], Hany Abdelrahman[1], Madeeha A.T. El Wakeel[1], Mohamed Zaghloul[1], Asmaa Hamoda[1]

[1]*CHildren's cancer hospital Egypt 57357*

Figure 1: Survival.



Background: Hodgkin lymphoma (HL) is a unique disease entity both in its pathology and the young patient population that it primarily affects. Several meta-analyses have demonstrated that high PD-L1 expression levels are correlated with adverse clinical and pathologic features.

Objectives: This study aims to evaluate the correlation between the expression of PD-L1 and clinicopathological features, as well as the prognostic significance of PD-L1 expression concerning interim PET response in relapsing/refractory pediatric HL.

Methods: We measured the expression of PD-1/PD-L1 in the baseline diagnostic samples of children with relapsing/refractory classical HL. The results were correlated with the pathological subtypes and the clinical outcome.

Results: Of the 88 included patients, 77% had advanced-stage HL. PD-1 expression was detected in 50% of cases, whereas PD-L1 (membranous) was expressed by tumor cells in 60% of the cases, and strongly expressed in 16% of cases. Notably, PD-L1 (cytoplasmic) was detected in 55% of the cases. There was significant differences in the expression levels of PDL-1 between the different pathological subtypes ($p = 0.006$). OS of patients with PD-L1expression (Cytoplasmic) was 83% vs 91% in patients with absent expression ($p = 0.001$). There was no prognostic significance of PD-L1 expression with regard to PET response ($p = 0.31$).

Conclusion: Although PD-L1 expressions did not show statistical significance with well-established prognostic factors, our preliminary data indicate that pathological subtypes and cytoplasmic expression of PD-L1 may have a prognostic implication on survival in pediatric HL.

P101: TOWARDS INCORPORATION OF PEDIATRIC SPECIFIC CRITERIA IN THE REVISED LUGANO CLASSIFICATION OF HODGKIN LYMPHOMA (HL) STAGING AND RESPONSE: REPORT FROM THE ICML PEDIATRIC SUBCOMMITTEE

Kara M. Kelly[1,2], Jamie E. Flerlage[3], Bradford S. Hoppe[4], Regine Kluge[5], Christine Mauz-Körholz[6], Wilhelm Wößmann[7]

[1]Roswell Park Comprehensive Cancer Center, [2]University at Buffalo, USA, [3]University of Rochester, USA, [4]Mayo Clinic, USA, [5]Universitätsklinikum Leipzig, DE, [6]Justus-Liebig-Universität Gießen and Medical Faculty of Martin-Luther University, Halle, DE, [7]Universitätsklinikum Hamburg-Eppendorf, DE

Purpose: The Lugano Classification is the benchmark for evaluation of nodal lymphomas yet pediatric (ped) specific recommendations have not been included limiting its application to children. With increasing collaboration for AYA lymphoma clinical trials, inclusion of ped criteria is essential to allow for use of the Lugano Classification to all patients. With planned major updates to the 2014 classification, an opportunity to consider ped specific issues was identified.

Methods: 6 representatives from North America & Europe, HL & NHL, pediatric & radiation oncology & nuclear medicine convened to develop ped specific revisions. Ped-specific biomarker expertise was also obtained.

Results: The Ped Subcommittee (11 meetings between 9/2022–4/2023) recommended:

Initial Evaluation: Systematic assessment of cancer predisposition risk and referral to genetic counseling; Consider risk for underlying immunodeficiency in select cases.

Staging Criteria–Imaging: Limit lifetime exposures to radiation and anesthesia; Use measures to reduce brown fat activation to minimize PET false-positive results; reactive nodes <2 cm due to infection/inflammation are more common in children; Specific size criteria may underestimate bulk or organomegaly in children.

Staging Criteria–Biomarkers: Few validated for clinical practice; TME by nanostring, image mass cytometry, ctDNA, TARC, MTV are of research interest.

Prognostic Groups & Treatment Allocation: Risk stratification criteria vary from adult and across ped HL regimens. Most utilize low, intermediate and high-risk groups: E, bulk, & ESR/CRP elevations are used for treatment allocation regardless of stage; Age, leukocyte count, hematocrit, lymphocyte count, albumin, & number of nodal sites are not routinely used.

Assessment of Response During Treatment: New PET avid nodes should not be considered a new site of disease if original sites had adequate response, especially if history or other findings suggest infection/inflammation.

Follow Up Evaluations: False-positive findings may be related to thymic rebound or inflammation/infection; Ongoing imaging in the absence of clinical symptoms >2 years after treatment is not recommended; MRI or ultrasound are prioritized to limit lifetime radiation exposure; Lifelong follow up to monitor for late toxicities is highly encouraged.

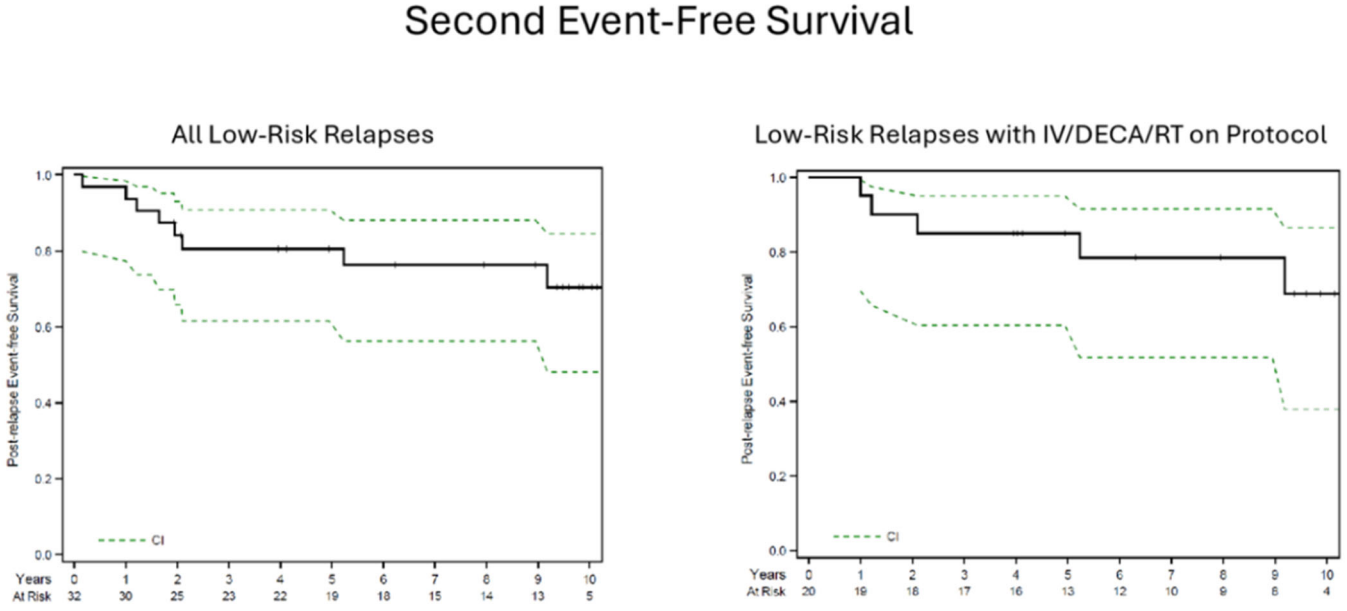
Conclusion: Inclusion of ped specific criteria for staging & response criteria is essential and will expedite advances in ped & adult lymphoma together.

P102: TRANSPLANT-FREE SALVAGE THERAPY FOR LOW-RISK RELAPSED PEDIATRIC HODGKIN LYMPHOMA: A SUB-STUDY OF CHILDREN'S ONCOLOGY GROUP AHOD0431

Bradford S. Hoppe[1], Sarah Milgrom[2], Lindsay A. Renfro[3,4], Yue Wu[4], Cindy Schwartz[5], Louis Constine[6], David Hodgson[7], Kathleen Mccarten[8], Kara M. Kelly[9], Frank G. Keller[10], Sharon M. Castellino[10]

[1]Department of Radiation Oncology, Mayo Clinic Florida, Jacksonville, FL, [2]Department of Radiation Oncology, University of Colorado, Aurora, CO, [3]Division of Biostatistics, University of Southern California, Los Angeles, CA, [4]Children's Oncology Group, Monrovia, CA, [5]Division of Pediatric Hematology, Oncology, and BMT, Medical College of Wisconsin, Milwaukee, WI, [6]Departments of Radiation Oncology and Pediatrics, University of Rochester, Rochester, NY, [7]Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, Canada, [8]Imaging and Radiation Oncology Core, Lincoln, RI, [9]Department of Pediatric Oncology, Roswell Park Comprehensive Cancer Center, and University at Buffalo Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, [10]Department of Pediatric Oncology, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, GA

Figure 1: Second event-free survival for patients on AHOD0431 with protocol-defined low-risk relapses ($n = 32$) and for the subset treated with reduced-intensity salvage therapy on study ($n = 20$).



Background: Standard treatment for relapsed/refractory classic Hodgkin lymphoma (HL) is second-line chemotherapy consolidated by high-dose therapy (HDT) with autologous stem cell transplant (ASCT); however, low-risk relapses may be salvaged effectively with conventional systemic therapy and radiation therapy (RT), without HDT/ASCT.

Methods: The prospective Children's Oncology Group AHOD0431 trial explored low-intensity first- and second-line treatment of stage IA/IIA, non-bulky HL. We report outcomes for patients on AHOD0431 who experienced protocol-defined low-risk relapses. We focus on those who received reduced-intensity salvage therapy on study that consisted of 2 cycles of ifosfamide/vinorelbine, 2 cycles of dexamethasone/etoposide/cisplatin/cytarabine, and involved-field RT (21 Gy). 2nd event-free survival (EFS) was defined as the time from the first relapse to second relapse, second cancer, or death. Overall survival (OS) was defined as the time from the first relapse to death.

Results: Of 278 patients who received first-line therapy on AHOD0431, 32 experienced low-risk relapses and 20 completed protocol-specified reduced-intensity salvage therapy. Among all 32 patients with low-risk relapses, the median follow-up time was 9.1 years, and 8 s relapses occurred at a median of 1.8 years after the first relapse (range 0.2–9.2 years). 8-year 2nd EFS was 76.3% (95% CI: 56.3%–88.0%) and OS was 100%. Five patients (15.6%) received HDT/ASCT following a second relapse. No second cancers occurred. Among the 20 patients who received reduced-intensity second-line therapy on protocol, 5 s relapses occurred at a median of 2.1 years after the first relapse (range

1.0–9.2 years). 8-year 2nd EFS was 78.5% (95% CI: 51.8%–91.4%) and OS was 100%. Three patients (15%) received HDT/ASCT following a second relapse.

Conclusions: In this cohort of patients with early-stage, favorable HL treated with minimal upfront chemotherapy, low-risk relapses were effectively salvaged using conventional chemotherapy and IFRT. 84% of patients avoided HDCT/ASCT, and OS was not compromised. These data support a role for transplant-free salvage of low-risk relapsed HL treated with modest upfront chemotherapy.

P103: UPDATED RESULTS FROM THE PHASE 2 KEYNOTE-667 STUDY: PEMBROLIZUMAB (PEMBRO) IN CHILDREN AND YOUNG ADULTS WITH HIGH-RISK CLASSICAL HODGKIN LYMPHOMA (CHL) WITH SLOW EARLY RESPONSE (SER) TO FRONT-LINE CHEMOTHERAPY (CHEMO)

Christine Mauz-Körholz[1], Luciana Vinti[2], Stephen Daw[3], Antony Ceraulo[4], Gerard Michel[5], Michaela Cepelova[6], Constantino Sabado Alvarez[7], Franca Fagioli[8], Stephane Ducassou[9], Salvatore Buffardi[10], Thierry Leblanc[11], Bradford S. Hoppe[12], Frank G. Keller[13], Kara M. Kelly[14], Lisa Giulino-Roth[15], Judith Landman-Parker[16], Juan Shen[17], Pallavi Pillai[17], Rushdia Yusuf[17], Auke Beishuizen[18]

[1]Justus-Liebig University of Giessen, Giessen, and Medical Faculty of the Martin-Luther-University of Halle-Wittenberg, Halle, Germany, [2]IRCCS Ospedale Pediatrico Bambino Gesu, Rome, Italy, [3]University College London Hospitals NHS Foundation Trust, London, UK, [4]Institut d'Hematologie-Oncologie Pediatrique (IHOPe), Lyon, France, [5]CHU de Marseille Hopital de la Timone Enfants, Marseille, France, [6]University Hospital Motol, Prague, Czech Republic, [7]Hospital Universitari Vall d'Hebron, Barcelona, Spain, [8]Ospedale Infantile Regina Margherita and University of Turin, Turin, Italy, [9]CHU de Bordeaux, Hopital Pellegrin, Bordeaux, France, [10]Azienda Ospedaliera di Rilievo Nazionale Santobono Pausilipon, Naples, Italy, [11]Hopital Universitaire Robert Debre, Paris, France, [12]Mayo Clinic, Jacksonville, FL, USA, [13]Children's Healthcare of Atlanta at Egleston, Atlanta, GA, USA, [14]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA, [15]Weill Cornell Medicine, New York, NY, USA, [16]Sorbonne Université APHP Hôpital Armand Trousseau, Paris, France, [17]Merck & Co., Inc., Rahway, NJ, USA, [18]Princess Máxima Centre, Utrecht, Netherlands

Background: KEYNOTE-667 (NCT03407144) is evaluating pembro+chemo consolidation ± involved site radiotherapy (ISRT) followed by pembro maintenance in pts with cHL and SER to front-line chemo. Prior results for pts with high-risk cHL and SER to vincristine, etoposide, prednisone/prednisolone, and doxorubicin (OEPA) induction showed consolidation with pembro+cyclophosphamide, vincristine, prednisone/prednisolone, and dacarbazine (COPDAC-28) followed by pembro maintenance had manageable safety and promising activity, and 71% had a PET-negative response per BICR (1 pt ended up receiving RT). Here, we present additional follow up of pts with high-risk cHL and SER to OEPA.

Methods: Pts aged 3–25 y with newly diagnosed stage IIEB to IVB cHL received 2 cycles of OEPA followed by early response assessment (PET and CT/MRI). Pts with rapid early response received nonstudy therapy. Pts with SER (i.e., Deauville score [DS], 4 or 5) received consolidation with pembro 2 mg/kg up to 200 mg (3–17 y) or 200 mg (18–25 y) IV Q3W+4 cycles of COPDAC-28 followed by LRA (PET, CT/MRI). Pts with PET positivity at LRA (ie, DS 4 or 5) received ISRT (28.8 Gy) to late PET-positive residua; pts with PET negativity received no ISRT. All pts received maintenance pembro ≤17 cycles. Primary end point was ORR by BICR per Cheson 2007 IWG criteria. Secondary end points included PET negativity after COPDAC-28 and safety.

Results: 84 pts with high-risk cHL and SER to OEPA were included. Median follow-up at data cutoff (Feb 29, 2024) was 24.3 mo (range, 5.7–48.4). 55 pts completed consolidation and maintenance, 20 were ongoing, and 9 discontinued. Pts received a median of 17 doses of pembro (range, 2–17); median time on pembro was 11.1 mo (range, 0.5–11.8). 80 pts (95%) had a LRA, of whom 56 (70%) were PET negative by BICR (55 [69%] PET negative by investigator). ORR in pts with a post baseline assessment (n = 80) was 99% (95% CI: 93–100; CR 57/PR 22). Treatment-related AEs (TRAEs) occurred in 61 pts (73%; grade 3 or 4 in 16 pts [19%]). 3 pts (4%) discontinued treatment due to TRAEs. No pts died due to TRAEs. 10 pts (12%) had immune-mediated AEs.

Conclusion: With median 24 mo follow-up, consolidation with pembro+COPDAC-28 ± ISRT followed by pembro maintenance continued to have manageable safety and promising activity in pts with high-risk cHL and SER to front-line OEPA. Among pts with a LRA, 70% were PET negative by BICR; 69% were PET negative by investigator review and spared RT.

RELAPSED AND REFRACTORY

T104: BRENTUXIMAB VEDOTIN - ESHAP SIGNIFICANTLY INCREASES THE METABOLIC COMPLETE REMISSION RATE VERSUS ESHAP IN RELAPSED CLASSICAL HODGKIN'S LYMPHOMA. FINAL RESULTS OF THE BRESELIBET PROSPECTIVE TRIAL

Anna Sureda[1], Javier Núñez Céspedes[2], María José Terol Casterá[3], Francisca Hernández Mohedo[4], Eva Domingo-Domènech[1], Fátima De La Cruz Vicente[5], Miriam Moreno Velázquez[6], M. Elena Amutio Díaz[7], Ana Pilar González Rodríguez[8], Raúl Córdoba[9], Carmen Martínez Muñoz[10], Samuel Romero Domínguez[11], Mariana Bastos[12], Antonia Rodríguez Izquierdo[13], Javier Briones Meijide[14], Richard Greil[15], María Casanova[16], Araceli Rubio[17], Irit Avivi[18], Raquel Del Campo García[19], Pilar Gómez[20], Theodoros Vassilakopoulos[21], Sandra Basic-Kinda[22], Sotirios Papageorgiou[23], Víctor Noriega[24], José Javier Sánchez Blanco[25], Blanca Sánchez[26], Izaskun Zeberio[27], Ramón García-Sanz[28,12]

[1]Hematology Department, Institut Català d'Oncologia-Hospitalet, IDIBELL, Universitat de Barcelona, Barcelona, Spain, [2]Hematology Department. Hospital Universitario Marqués de Valdecilla, Santander, Spain, [3]Hematology Department, Hospital Clínico Universitario, Valencia, Spain, [4]Hematology Department, Hosputal Universitario Virgen de las Nievas, Granada, Spain, [5]Hematology Department, Hospital Universitario Virgen del Rocío, Sevilla, Spain, [6]Hematology Department, Institut Català d'Oncologia-Hospital Germans Trias I Pujol, Badalona, Barcelona, Spain, [7]Hematology Department, Hospital de Cruces, Bilbao, Spain, [8]Hematology Department, Hospital Central de Asturias, Oviedo, Asturias, Spain, [9]Hematology Department, Fundación Jiménez Díaz, Madrid, Spain, [10]Hematology Department, Hospital Clínic, Barcelona, Spain, [11]Hematology Department, Hospital Universitario La Fe, Valencia, Spain, [12]Hematology Department, Hospital Universitario Gregorio Marañón, Madrid, Spain, [13]Hematology

Department, Hospital Universitario 12 de Octubre, Madrid, Spain, [14]Hematology Department, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain, [15]IIIrd Medical Department with Hematology, Medical Oncology, Hemostaseology, Infectious Diseses and Rheumatology, Oncologic Center, Paracelsus Medical University Salzburg, Austria, [16]Hematology Department, Hospital Costa del Sol, Málaga, Spain, [17]Hematology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain, [18]Hematology Department, Tel Aviv Sourasky Medical Center, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel., [19]Hematology Department, Hospital Son Llatzer, Palma de Mallorca, Spain, [20]Hematology Department, Hospital Universitario La Paz, Madrid, Spain, [21]University General Hospital Laiko, Athens, Greece, [22]University Hospital Centre Zagreb, Croacia, [23]University General Hospital Attikon, Greece, [24]Complejo Hospital Universitario A Coruña, Spain, [25]Hematology Department, Hospital General Universitario Morales Messeguer, Murcia, Spain, [26]Hematology Department, Hospital del Mar, Barcelona, Spain, [27]Hematology Department, University Hospital Donostia, San Sebastián, Spain, [28]Hematology Department, Hospital Clínico Universitario de Salamanca, Salamanca, Spain

Background: Best salvage treatment for relapsed/refractory HL (RRHL) is unknown; superiority of brentuximab vedotin (BV)+chemotherapy (CT) versus CT alone has never been tested in randomized trials. It is also unknown if consolidation with BV could eventually spare auto-HCT in good risk RRHL patients.

Objectives: BRESELIBET (ClinicalTrials.gov ID: NCT04378647) is a phase 2b prospective clinical trial that evaluates the efficacy of BRESHAP vs ESHAP in RRHL, followed by BV consolidation (13 or 16 cycles, respectively, 1.8 mg/kg iv q3wks) in patients attaining a mCR. Primary efficacy endpoint was mCR (DS 1–3) after 3 cycles.

Results: 160 adult pts with RRHL were included from 05/2020 to 10/2023 and 151 [88 (58.3%) males, median age of 39 years (18–65)] were randomized 1:1 between BRESHAP ($n = 76$) and ESHAP ($n = 75$). BRESHAP and ESHAP arms were well balanced; 53 pts (35.5%) were primary refractory, 79 pts (52.3%) had nodular sclerosis subtype, 79 (52.3%) relapsed in advanced stage (III-IV), 24 (15.9%) had >1 extranodal site, 13 (8.6%) bulky mass and 37 (24.5%), B symptoms. The primary endpoint was met: mCR was 69.7% in BRESHAP pts versus 48.0% in EHAP ($p = 0.007$). Final logistic regression model indicated that not only treatment arm (BRESHAP vs. ESHSP, $p = 0.003$) but also disease status (primary refractory vs early relapse vs. late relapse, $p = 0.007$) and extranodal disease (no vs. 1 site vs >1 site, $p < 0.001$) were independent prognostic factors for mCR. 52 treatment-related adverse events (TRAE) grade 3–4 have been reported in the BRESHAP arm versus 63 grade 3–4 TRAE in ESHAP. No cases of grade 3–4 peripheral sensory or motor neuropathy were reported. 73 pts entered into the consolidation phase and received 13 (1–16) cycles of BV; there have been 11 relapses (15%) after 5 (2–16) cycles of BV, 9 of them during the first year. No relapses have happened during the follow up and 38 patients have finished BV therapy. Ten patients discontinued consolidation due to AE (9 polyneuropathy, 1 pneumonitis) and 11 due to disease relapse. With a median follow up of 10 (1–36.5) mo after the beginning of consolidation, PFS is 79.4% (95% CI: 67.9–90.9) at 24 mo.

Conclusions: BRESELIBET trial demonstrates that the association of BV to ESHAP results in a significantly higher proportion of mCR than ESHAP alone with no additional toxicity signals; BV consolidation might eventually substitute auto-HCT in patients that achieve a mCR after salvage therapy.

T105: LONGITUDINAL CIRCULATING TUMOR DNA SEQUENCING MAY PREDICT THE RESPONSE TO PD1 BLOCKADE THERAPY IN RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA PATIENTS

Francesco Corrado[1], Eleonora Calabretta[1], Martina Di Trani[1], Martina Sollini[1], Vanessa Cristaldi[1], Lodovico Terzi Di Bergamo[2], Alessio Bruscaggin[2], Maria Cristina Pirosa[2], Marcello Viscovo[3], Stefania Bramanti[1], Arturo Chiti[1], Stefan Hohaus[3], Armando Santoro[1], Davide Rossi[2], Carmelo Carlo-stella[1]

[1]Department of Biomedical Sciences, Humanitas University, Rozzano, Milano, Italy, [2]Laboratory of Experimental Hematology, Institute of Oncology Research, Università della Svizzera Italiana, Bellinzona, Switzerland, [3]Policlinico Gemelli, Roma

Background: The introduction of immune checkpoint inhibitors (CPIs) has revolutionized the treatment of relapsed/refractory (R/R) classical Hodgkin lymphoma(cHL). However, nearly 65% fail to respond or progress after an initial response within 24 months. The evaluation of tumor-specific biomarkers of response currently requires invasive procedures, does not capture spatial tumor heterogeneity, and is not suitable for repeated evaluations. On the contrary, cell-free DNA sequencing represents a non-invasive tool for genotyping and response monitoring of several solid and hematological neoplasms. Here, we performed baseline and longitudinal liquid biopsies in 40 R/R cHL patients to identify biomarkers of response to CPIs

Methods: Peripheral blood samples were collected before treatment initiation, at each metabolic response assessment, and at the end of treatment. A targeted re-sequencing panel including the coding exons, splice sites, and Aberrant Somatic Hyper Mutation (ASHM) regions of 133 genes was designed for Cancer Personalized Profiling by deep Sequencing (CAPP-Seq). The target sequencing was performed in paired-end runs on the Nextseq. 550 platform (Illumina), allowing >2000× coverage.

Results: Baseline circulating tumor DNA (ctDNA) load positively correlated with the Total Metabolic Tumor Volume (Spearman coefficient = 0.67, $p = 0.00003$). Patients with higher levels of ctDNA showed lower overall response rates (65% vs. 100%, $p = 0.038$) and shorter Event-Free Survival [EFS] (HR: 2.0, 95% CI: [0.5–3.4], $p = 0.009$). TP53 mutation emerged as the only significant pre-treatment ctDNA mutation associated with a worse EFS (HR, 3.04; $p = 0.03$). Interestingly, after four cycles of treatment, a 1-Log reduction of the ctDNA load was associated with longer EFS (HR: 0.33, 95% CI: 0.13–0.82, $p = 0.02$). Concomitantly, the persistence of an increased percentage of baseline variants was consistently detected in CPIs non-responsive vs responsive patients (median 0 vs. 90%, $p < 0.0001$). We performed ROC analysis to assess the response classification performance of baseline ctDNA load, dynamic load reduction, and persistence of Non-Synonymous Variants. Of note, the latter feature yielded the best accuracy with an AUC of 0.95 (DeLong test $p < 0.05$).

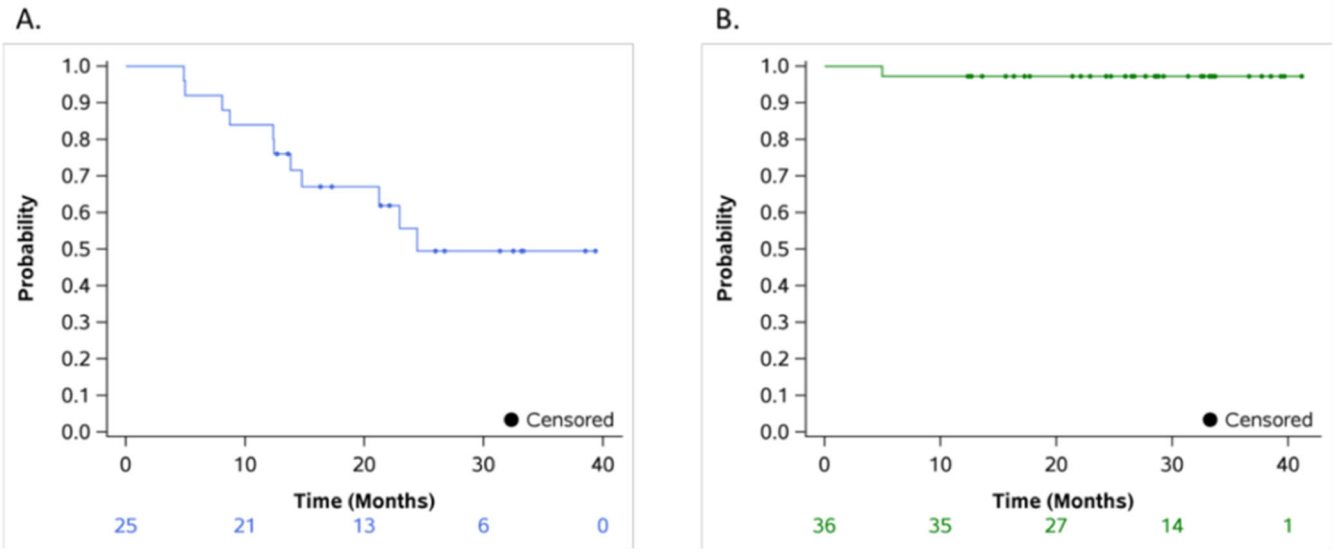
Conclusions: Taken together, these findings highlight the predictive role of baseline and longitudinal ctDNA sequencing in the early identification of R/R cHL patients at high risk of failing CPIs.

T106: PEMBROLIZUMAB MAINTENANCE INSTEAD OF AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION FOR PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA IN COMPLETE RESPONSE AFTER PEMBROLIZUMAB, GEMCITABINE, VINORELBINE, AND LIPOSOMAL DOXORUBICIN

Alison Moskowitz[1], Gunjan Shah[1], Nivetha Ganesan[1], Helen Hancock[1], Theresa Davey[1], Tiffany Chang[1], Brittney Munayirji[1], Monifa Douglas[1], Alayna M. Santarosa[1], Alexander Boardman[1], Philip Caron[1], Kevin David[1], Zachary Epstein-Peterson[1], Lorenzo Falchi[1], Paola Ghione[1], Andrew Intlekofer[1], Paul Hamlin[1], Steven Horwitz[1], William Johnson[1], Anita Kumar[1], Jennifer Lue[1], Efrat Luttwak[1], Ariela Noy[1], Colette Owens[1], Maria Palomba[1], Gilles Salles[1], Raphael E. Steiner[1], Robert Stuver[1], Pallawi Torka[1], Santosha Vardhana[1], Andrew Zelenetz[1], Joachim Yahalom[1], Ahmet Dogan[1], Heiko Schoder[1], Craig H. Moskowitz[2]

[1]*Memorial Sloan Kettering Cancer Center*, [2]*University of Miami, Sylvester Cancer Center*

Figure 1: (A) Progression-free survival after P-GVD and pembrolizumab maintenance (B) Freedom from third relapse for all 36 patients with CR after P-GVD.



Introduction: In our phase II study evaluating pembrolizumab, gemcitabine, vinorelbine, and liposomal doxorubicin (P-GVD) followed by high dose therapy and autologous hematopoietic cell transplantation (AHCT) (Moskowitz et al. JCO 2021) for relapsed or refractory (RR) Hodgkin lymphoma (HL), 95% of pts achieved complete response (CR) and 96% are progression-free at 30 months. Building upon these results, we explored whether pts achieving CR after P-GVD could avoid AHCT.

Methods: After 1-line of therapy, RR HL pts received 4 cycles of P-GVD and those who achieved CR proceeded to 13 cycles of pembrolizumab maintenance (PM). Primary endpoint was 2-year progression free survival (PFS) after PM.

Results: Among 40 patients enrolled, median age was 36 (range 19–76), 18 (45%) were male, 17 (43%) had primary refractory disease, 18 (45%) had extranodal disease, 16 (40%) had stage IV disease, and 7 (18%) had B symptoms at enrollment. All pts responded to P-GVD, including 36 (90%) with CR and 4 (10%) with PR. Of 36 pts with CR, 5 elected to proceed to AHCT, 4 were referred to AHCT by treating physician due to treatment-related toxicity (1 pt with G4 immune thrombocytopenia and G2 pneumonitis; 1 with G1 pneumonitis, 1 with G2 rash, 1 with G3 PJP pneumonia), 2 elected to come off study and receive no further treatment. Among 25 patients who proceeded to PM, 11 events occurred, including 1 death from pneumonitis (after 4 cycles of P-GVD) and 10 progressions. After a median follow-up of 26 mos for PM pts, 2-year PFS was 56% (95% CI: 38–82) (Figure 1A). Stage IV disease at enrollment had a trend towards higher risk for progression (PFS 36% vs. 65%, $p = 0.07$). Nine of the 10 pts who progressed successfully proceeded with AHCT and remain in remission after a median of 12.7 months (range: 3.8–24.4) post-transplant (Figure 1B). One patient with progression was not eligible for transplant due to comorbidities and is receiving palliative treatment with pembrolizumab plus gemcitabine.

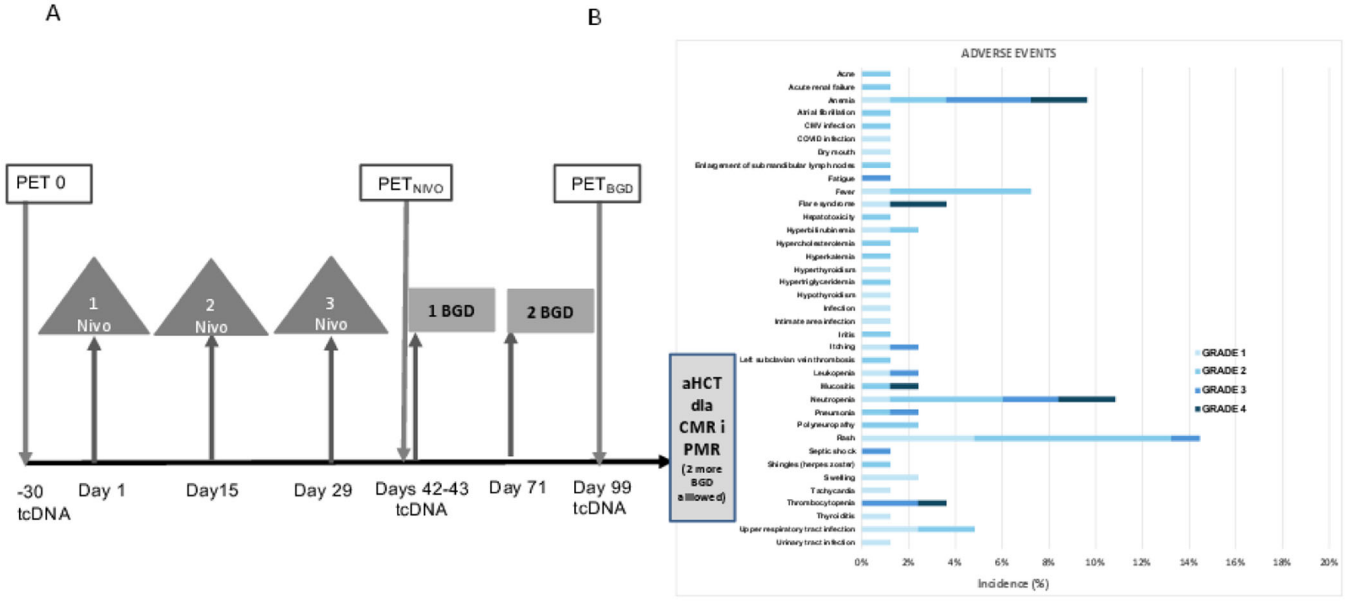
Conclusion: After a median follow-up of 26 mos, 56% of pts with RR HL treated with P-GVD followed by PM are progression free. Furthermore, pts who relapse during or after PM can be salvaged with third-line therapy and AHCT. Patients with stage IV disease are more likely to need ASCT. A randomized study evaluating AHCT versus PM for patients with RR stage I-III HL who achieve CR to P-GVD is underway.

P107: A SHORT COURSE OF NIVOLUMAB (N) FOLLOWED BY CHEMOTHERAPY BGD AND AUTOLOGOUS TRANSPLANTATION (AHCT) AS THE SALVAGE TREATMENT FOR RELAPSED/REFRACTORY (R/R) HODGKIN LYMPHOMA (CHL) PATIENTS–THE PRELIMINARY RESULTS OF THE N-BURGUND TRIAL OF PLRG

Jan Maciej Zaucha[1], Ewa Paszkiewicz-Kozik[2], Bogdan Małkowski[3], Michał Taszner[1], Justyna Rybka[4], Karolina Chromik[5], Agnieszka Kołkowska-Leśniak[6], Edyta Subocz[7], łukasz Targoński[2], Paulina Ceklarz[8], Magdalena Witkowska[9], Katarzyna Domańska-Czyż[2], Agnieszka Giza[8], Małgorzata Kobylecka[10], Conrad-Amadeus Voltin[11], Joanna Romejko-Jarosińska[2], Beata Ostrowska[2], Monika świerkowska[2], Agnieszka Druzd-Sitek[2], Michał Kurlapski[1], Marta Bednarek[12], Grzegorz Romanowicz[13], Ryszard Swoboda[14], Joanna Góra-Tybor[9], Janusz Hałka[7], Tomasz Wróbel[4], Sebastian Giebel[14], Grzegorz Helbig[5], Ewa Lech-Marańda[9]

[1]Department of Hematology and Transplantology, Medical University of Gdańsk and University Clinical Center, Gdańsk, Poland, [2]Department of Lymphoid Malignancies, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland, [3]Department of Nuclear Medicine, Oncology Center, Bydgoszcz, Poland, [4]Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Poland, [5]Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia, Katowice, Poland, [6]Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland, [7]Department of Hematology and BMT, Clinical Hospital of the Ministry of Internal Affairs and Administration with the Warmia-Mazury Oncology Centre in Olsztyn and University of Warmia and Mazury in Olsztyn, [8]Department of Hematology, Jagiellonian University Medical College, Krakow, Poland, [9]Department of Hematology, Medical University of Lodz, Lodz, Poland, [10]Department of Nuclear Medicine, Medical University of Warsaw, Poland, [11]Department of Nuclear Medicine, University Hospital of Cologne, Cologne, Germany, [12]Department of Radiology and Department of Non-Commercial Clinical Research, Medical University, Medical University of Gdańsk, Gdańsk, Poland, [13]Department of Nuclear Medicine, Medical University of Gdańsk, Gdańsk, Poland, [14]Department of Bone Marrow Transplantation and Oncohematology, Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland

Figure 1: (A) The schema of the N-BURGUND trial run by the Polish Lymphoma Research Group (ct DNA- circulating tumor DNA), (B) The incidence of adverse events.



Introduction: Achieving complete metabolic remission (CMR) before aHCT in patients with r/r HL improves their long-term outcomes. BGD induces CMR in about 50%–65% of r/r HL pts (Swoboda T et al. Ann Hematol 2021). The phase 2 N-BURGUND trial (EudraCT 2021–002630-17) evaluates the efficacy and safety of a short course of Nivolumab (N) (3 cycles) followed by 2 (max. 4) cycles of BGD in r/r HL pts before aHCT having hypothesized that addition of N will improve the response to BGD. We present the preliminary analysis of efficacy and safety in enrolled pts.

Methods: Patients aged ≥18 years with r/r advanced stage (IIB-IV) HL after first-line treatment received N 240 mg IV Q2W for 3 cycles followed by PETNIV and 2–4 cycles of BGD (bendamustine 90 mg/m^2 D1,2; gemcitabine 800 mg/m^2 on D1,4; dexamethasone 40 mg on D1–4.) combined with CD34+ cell mobilization followed by PET2BGD. Patients achieving CMR (Deauville score 1–3 assessed by the Central Reviewer Panel) are subjected to aHCT. The primary endpoint for this analysis is centrally assessed PETBGD-negativity response in patients who completed at least 2 cycles of BGD. The secondary end-point is PETNIVO response and the results of tumor-free DNA assessment at the time of PET examinations.

Results: At a date cut-off (May 20, 2024), 59 pts with r/r cHL were enrolled from 9 centers affiliated with the PLRG. Median (range) age was 32,5 years (19–65); 83% of patients received ABVD, and 17% BEACOPPesc in the first line. 54% of pts were primary refractory; 34% pts had an early relapse (<12 months) whereas the remaining (12%) had a late relapse. So far, 37 pts have completed 3 × N and 2 × BGD. The PETBGD negativity rate was 86%, whereas the PETNIVO negativity rate was 40,5%. BGD improved response in 17(46%) pts. One patient required two more BGD cycles to achieve CMR. Grade ≥3 adverse events (AEs) (26.5% of all AEs) occurred in 13 pts (22% of all pts). Drug-related grade 4 AEs included: flare syndrome and anemia caused by pure red cell aplasia, which resolved after 6 months of treatment with steroids, rituximab, and

bortezomib. Immune-mediated AEs (3,6% of all AEs) occurred in 5% of patients who received nivolumab. The most common AE was rash (14.5%) (Figure 1). There were no deaths.

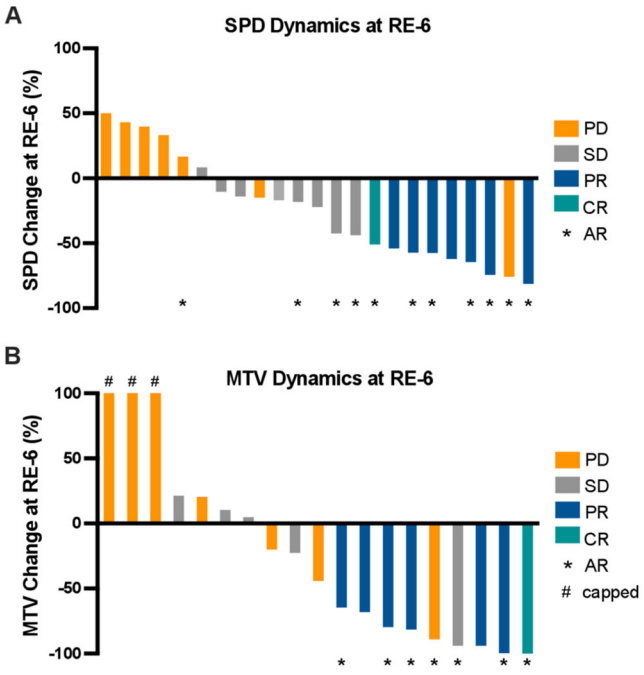
Conclusion: A short Nivolumab induction followed by standard second-line BGD chemotherapy is well tolerated in pts with r/r HL, improving the response to BGD to 86% PET negativity. There were no new safety issues, and the study is ongoing.

P108: ABSCOPAL EFFECT OF RADIOTHERAPY AND NIVOLUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA: RESULTS OF THE INTERNATIONAL GHSG PHASE II AERN TRIAL

Paul J. Bröckelmann[1], Ina Bühnen[1], Josée M. Zijlstra[2], Stephan Mathas[3], Katrin S. Roth[4], Maria Garcia-Marquez[5], Christian Sillaber[6], Julia Meissner[7], Alexander Fossså[8], Richard Greil[9], Karolin Trautmann-Grill[10], Johannes Rosenbrock[11], Wouter J. Plattel[12], Hans A. Schlösser[5], Carsten Kobe[4], Michael Fuchs[1], Peter Borchmann[1], Christian Baues[13]

[1]University Hospital of Cologne and German Hodgkin Study Group (GHSG), Cologne, Germany, [2]Amsterdam, The Netherlands, [3]Berlin, Germany, [4]Department of Nuclear Medicine, University Hospital of Cologne, Cologne, Germany, [5]CMMC and University of Cologne, Cologne, Germany, [6]Vienna, Austria, [7]Heidelberg, Germany, [8]Oslo, Norway, [9]Salzburg, Austria, [10]University Hospital Carl-Gustav Carus, Technical University Dresden, Dresden, Germany, [11]Department of Radiation Oncology, University Hospital of Cologne, Cologne, Germany, [12]Groningen, The Netherlands, [13]Department of Radiation Oncology, Klinikum Bochum, Bochum, Germany

Figure 1: (A) Relative SPD change at first restaging (RE-6) and(B) Relative MTV change at RE-6 in patients with MTV-evaluable PET/CT scans.



Background: Failure of anti-PD1 treatment (aPD1) in patients (pts) with relapsed or refractory classical Hodgkin lymphoma (rrHL) is a clear unmet need. Whether the addition of local radiotherapy (RT) to aPD1 is effective and able to induce a systemic ("abscopal") response (AR) in this setting is unknown.

Methods: The international GHSG phase II AERN trial (NCT03480334) enrolled rrHL pts with aPD1 failure as last line of therapy. They had to be enrolled latest 4 weeks after the last aPD1 dose without any intermittent therapy. In AERN, pts received 240 mg nivolumab at 2-weekly intervals. Administration of 20 Gy RT in 2 Gy fractions to a single lesion started on day 6 after the first nivolumab dose on trial. The primary endpoint was AR, determined by the central review panel at first restaging after 6x nivolumab (RE-6). AR was defined as an objective response in ≥1 rrHL lesion ≥5 cm distant and outside the 10% isodose of the RT field. Nivolumab continued until progression, toxicity or a maximum of 18 months. Secondary endpoints included toxicity, objective response rate (ORR), progression-free (PFS) and overall survival (OS).

Results: A total of 25 pts (40% female) were enrolled with a median age of 37 years (range: 25–90) that had received a median of 4 (range 2–15) prior lines of therapy and predominantly presented with stage III/IV HL (88%). Prior to enrollment, 72% had received autologous stem-cell transplantation, 72% brentuximab vedotin and 72% prior RT. All pts failed aPD1 (nivolumab: 60%, pembrolizumab: 40%) as last line of therapy and 96% experienced progressive disease immediately before enrollment. Of the 24 pts evaluable at RE-6, 11 (45.8%, 95% CI: 35.8%–71.8%) achieved an AR, meeting the predefined efficacy endpoint. ORR was 33.4% (1 complete, 7 partial response) and 7 pts had stable disease (29.2%), for a disease control rate of 62.6%. Figure 1 summarizes changes in sum of product of diameters (SPD) and metabolic tumor volume (MTV) in evaluable pts. Ongoing analyses of longitudinal blood samples show significant associations of T- and NK-cell subsets with AR at RE-6 and additionally indicate a correlation between TARC dynamics and response.

Conclusions: The addition of local RT to aPD1 is feasible and effective in rrHL pts failing aPD1 treatment. It results in a systemic effect with AR, and overall complete or partial responses were observed. The final analysis of the AERN trial is currently ongoing and updated data will be presented at the meeti.

P109: ARE REFRACTORY/RELAPSED HODGKIN LYMPHOMA PATIENTS CAN BE RECOGNIZED EARLIER?

Boglárka Dobó[1], Dávid Tóthfalusi[1], László Imre Pinczés[1], Zsófia Miltényi[1], Árpád Illés[1]

[1]*Division os Haematology, Department of Internal Medicine, Facultaty of Medicine, University of Debrecen*

Introduction: Hodgkin lymphoma (HL) is highly curable malignant disease, 10%–30% of the patients are relapsed or refractory (R/R) to the first-line treatment. Early diagnosis and effective treatment of these patients are essential for the subsequent recovery.

Patients and Methods: HL patients (<60 years) who were treated in our department between 01.01.2010 and 2023.03.30 were examined using a retrospective method.

We compared the clinical characteristics and laboratory parameters of R/R HL patients with patients remaining in complete remission (CR). We also analyzed these datas in terms of therapeutic changes and survival.

Results: All in all 171 patients (82 women and 89 men) datas were processed. The median age was 32 (17–59). According to histological subtype, nodular sclerosis was dominant (56%). About 90% of the patients received ABVD treatment as first-line therapy. Among the patients, 38 were in the R/R group (17 women and 21 men), and 133 were in the CR group (65 women and 68 men). In our R/R group, 81% of the patients received only chemotherapy (CT), and 16% received chemoradiotherapy (CRT). Among our patients in CR, 67% received CT, and 32% received CRT. There is no significant difference between the groups in treatment. We examined the prognostic role of the laboratory results which were taken at the time of the diagnosis and after two complete cycles of treatment. Prognostic value was found in the platelet/monocyte ratio, LDH/hemoglobin ratio, and the combination of the two ratios. At the time of staging, the platelet/monocyte ratio (>987.5) and LDH/hemoglobin ratio (>3.22) are unfavorably influenced survival. We created a risk classification from these parameters (low risk: 0 points, high risk: 1–2 points), due to this score the 5-year OS was 95% vs. 82% ($p < 0.001$), and the 5-year PFS was 84.4% vs. 64.3% ($p = 0.001$). We also compared the results of interim PET/CT scan. There were significantly more PET positive (Deauville score 4–5)t patients in the R/R group $p = 0.043$).

Conclusion: Independently, clinical characteristics do not help in the early identification of R/R patients. We would like to use further biomarker studies (e.g., ctDNA, TARC) combined with the interim PET/CT result to represent a significant advancement.

P110: AUTOLOGOUS STEM CELL TRANSPLANTATION IN RELAPSED/REFRACTORY CLASSIC HODGKIN LYMPHOMA AFTER PD-1 INHIBITORS SALVAGE REGIMENS IS EFFECTIVE IN THIRD- OR FOURTH-LINE THERAPY

Polina Kotselyabina[1], Evgenia Borzenkova[1], Andrey Chekalov[1], Kirill Lepik[1], Liudmila Fedorova[1], Artem Ivanov[1], Elena Lepik[1], Elena Kondakova[1], Ivan Moiseev[1], Natalia Mikhailova[1], Alexander Kulagin[1]

[1]*Raisa Gorbacheva Memorial Research Institute for Pediatric Oncology, Hematology and Transplantation, Saint Petersburg, Russia*

Table 1: Patients characteristics.

	Group 1 n=27 (2-line)	Group 2 n=24 (3/4-line)	p
Median age of patients at the time of auto-HSCT, years (range)	36 (22-65)	37 (21-62)	0.89
Primary refractory disease, n (%)	20 (74)	12 (50)	0.075
Early relapse, n (%)	8 (30)	7 (29)	0.57

Backgrounds: Autologous hematopoietic stem cell transplantation (auto-HSCT) is the standard for relapsed/refractory classic Hodgkin lymphoma (r/r cHL) after first salvage therapy. With PD-1 inhibitors (CPI) successfully used to achieve responses before auto-HSCT, idea of delaying auto-HSCT to third- or fourth-line therapy is emerging. However, data on the impact of this shift is limited. This study aims to evaluate whether delaying auto-HSCT to the third or fourth line affects patient prognosis compared to second-line auto-HSCT after CPI.

Methods: This study included adult patients (pts) with histologically confirmed r/r cHL who underwent auto-HSCT after nivolumab-containing therapy: second-line (group 1, $n = 27$) and third- or fourth-line (group 2, $n = 24$). Group 1 was composed from a multicenter phase II study of nivolumab at the fixed dose 40 mg (nivo 40), followed by PET-CT assessment, and those with less than CR received two cycles of a combination therapy of nivo, ifosfamide, carboplatin, and etoposide (NICE-40, NCT04981899) before subsequent auto-HSCT. Group 2 consisted of a retrospective cohort who underwent auto-HSCT in a third- or fourth-line therapy after nivo due to either response non-achievement after

first salvage therapy (58%, *n* = 14) or patient/physician decision (42%, *n* = 10). We hypothesized that the two groups would have similar 1-year overall and progression-free survival (1y-OS,1y-PFS) with nivo salvage regimens.

Results: A total of 51 pts were included. In group 1 (*n* = 27), nivo 40 mg was given in all pts, with 41% (*n* = 11) receiving nivo monotherapy and 59% (*n* = 16) nivo followed by combination with ICE. Group 2 (*n* = 24) received nivo at reduced dosage (40 mg and 1 mg/kg) in 71% (*n* = 17), while 29% (*n* = 7) received 3 mg/kg. In group 2, 50% (*n* = 12) received nivo combined with chemotherapy. Pre-HSCT response assessment (by LYRIC criteria) showed an objective response in 82% (CR - 63%, *n* = 17; PR - 19%, *n* = 5) of group 1 and 100% (CR - 96%, *n* = 23; PR - 4%, *n* = 1) of group 2. With a median follow-up of 11 months (1–63), survival did not differ between the groups despite a trend towards better pre-HSCT responses in group 2 (Table 1). Thus, 1y-PFS was 75% (95% CI: 55%–99%) in group 1 and 80% (95% CI: 64%–100%) in group 2 (*p* = 0.3), and 1y-OS was 91% (95% CI: 79%–100%) in group 1 and 92% (95% CI: 82%–100%) in group 2 (*p* = 0.9).

Conclusion: CPI in salvage regimens may enable auto-HSCT to be performed in the third or fourth line without affecting prognosis in terms of OS and PFS.

P111: C-MOPP CHEMOTHERAPY IS A HIGHLY EFFICACIOUS REGIMEN FOR PATIENTS WITH RELAPSED CLASSICAL HODGKIN LYMPHOMA FOLLOWING PD-1 INHIBITOR TREATMENT FAILURE

Stephen Ma[1,2], Shahla Vilcassim[1,3], Pasquale Fedele[1,3], George Grigoriadis[3,2], Michael Low[1,3], Gareth P. Gregory[1,3], Stephen Opat[1,3], Michael Gilbertson[1,3,4]

[1]Monash Haematology, Monash Health, [2]Department of Haematology, Alfred Health, [3]School of Clinical Sciences at Monash Health, Monash University, [4]Dept. of Haematology and Oncology, Western Health

Introduction: Despite excellent outcomes of initial chemotherapy for patients treated with classical Hodgkin lymphoma (cHL), unfortunately up to one third of patients will relapse, and of these, 50% will not respond to high dose chemotherapy/autologous stem cell transplantation. Checkpoint inhibitors (CPI) have shown high response rates in patients with relapsed cHL by restoring the programmed death pathway, though the complete response rates are low and most patients treated with single agent CPI will relapse. The optimal treatment approach for patients who lose response to CPI is not clearly defined, though some investigators have identified that prior CPI therapy may re-sensitise patients to standard chemotherapy.

Aim: To assess the safety and efficacy of C-MOPP (prednisolone 60 mg/m^2 daily D1-14, procarbazine 100 mg/m^2 daily D1-14, vincristine 1.4 mg/m^2 2 D1, 8 and cyclophosphamide 650 mg/m^2 D1 and 8 of a 28 day cycle) chemotherapy in patients with cHL who have lost response to CPI therapy.

Methods: Retrospective analysis of patients with relapsed cHL treated at Monash Health with C-MOPP chemotherapy after CPI therapy.

Results: A total of 4 patients received a median of 3 cycles (range 2–6) of C-MOPP chemotherapy. The median age was 29 years (range 23–48 years). All 4 patients had been treated with ABVD, then a range of subsequent therapies including brentuximab vedotin and autologous stem cell transplant (2 patients) prior to CPI therapy.

All 4 patients treated with C-MOPP achieved a complete metabolic response, allowing 3 patients to proceed to allogeneic bone marrow transplant.

At a median follow-up of 1.8 years (range 0.2–2.7), one patient (who did not receive allogeneic bone marrow transplant) relapsed, however all other patients remained in complete response.

C-MOPP was generally well tolerated with nausea and haematological toxicity being the main adverse effects identified.

Conclusion: C-MOPP chemotherapy is a well-tolerated and highly efficacious chemotherapy regimen in patients with cHL who are refractory to CPI therapy and should be considered in this challenging patient cohort.

P112: COFORMULATED FAVEZELIMAB AND PEMBROLIZUMAB (PEMBRO) VERSUS CHEMOTHERAPY (CHEMO) IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) CLASSICAL HODGKIN LYMPHOMA (CHL) REFRACTORY TO ANTI–PD-1 THERAPY: THE PHASE 3 KEYFORM-008 STUDY

David Lavie[1], John Timmerman[2], Ramón García-Sanz[3], Won-Seog Kim[4], Tae Min Kim[5], Abraham Avigdor[6], Daan Dierickx[7], Deepa Jagadeesh[8], Daniel Molin[9], Muhit Ozcan[10], Omur Gokmen Sevindik[11], Hayder Saeed[12], Yulia Sidi[13], Pallavi Pillai[13], Rushdia Yusuf[13], Alex F. Herrera[14]

[1]Hadassah Medical Center, Jerusalem, Israel, [2]UCLA Medical Center, Los Angeles, CA, USA, [3]University Hospital of Salamanca, Salamanca, Spain, [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, [5]Seoul National University Hospital, Seoul, Republic of Korea, [6]Sheba Medical Center, Ramat Gan, and School of Medicine, Tel Aviv University, Tel Aviv, Israel, [7]University Hospitals Leuven, Leuven, Belgium, [8]Cleveland Clinic, Cleveland, OH, USA, [9]Uppsala University, Uppsala, Sweden, [10]Ankara University School of Medicine, Ankara, Türkiye, [11]Istanbul Medipol University, International School of Medicine, Istanbul, Türkiye, [12]Moffitt Cancer Center, Tampa, FL, USA, [13]Merck & Co., Inc., Rahway, NJ, USA, [14]City of Hope, Duarte, CA, USA

Background: Anti–PD-1 therapies such as pembro are a standard-of-care option for R/R cHL, but effective treatments for pts with disease progression on or after anti–PD-1–based therapy are limited. Lymphocyte-activation gene 3 (LAG-3) is an inhibitory checkpoint receptor thought to contribute to anti–PD-1 resistance. In a phase 1/2 study, combination therapy with the humanized IgG4 anti–LAG3 antibody favezelimab + pembro demonstrated manageable safety and promising antitumor activity in pts with R/R cHL whose disease had progressed after anti–PD-1

therapy. The randomized, open-label, phase 3 KEYFORM-008 study (NCT05508867) will evaluate efficacy and safety of a coformulated favezelimab/pembro in pts with anti–PD-1–refractory R/R cHL.

Methods: Eligible pts are ≥18 yrs old with histologically confirmed R/R cHL who have progressed on anti–PD-1–based therapy and exhausted all other available treatment options with known clinical benefit and are ineligible for or failed autologous stem cell transplantation (ASCT). Pts must also have been ineligible for brentuximab vedotin (BV), relapsed on or whose disease failed to respond to BV, or discontinued BV due to toxicity. Approximately 360 pts will be enrolled and randomly assigned 1:1 to receive coformulated favezelimab 800 mg/pembrolizumab 200 mg IV Q3W or physician's choice of chemo (gemcitabine, 800–1200 mg/m2 IV or bendamustine, 90–120 mg/m2 IV). Randomization will be stratified by prior ASCT (yes vs no) and ECOG PS (0 or 1 vs. 2). Treatment will continue for ≤35 cycles of coformulated favezelimab/pembro or ≤6 cycles for chemo or until progressive disease (PD), unacceptable toxicity, or withdrawal. Pts in the chemo with PD confirmed by BICR per Lugano criteria may be eligible to cross over to coformulated favezelimab/pembrolizumab. Primary end point is PFS by BICR per Lugano criteria. Secondary end points are OS, ORR and DOR by BICR per Lugano criteria, and safety. Exploratory end points include PFS on subsequent anticancer therapy and HRQoL.

Results: Recruitment is ongoing at sites in Asia, Australia, Europe and North and South America.

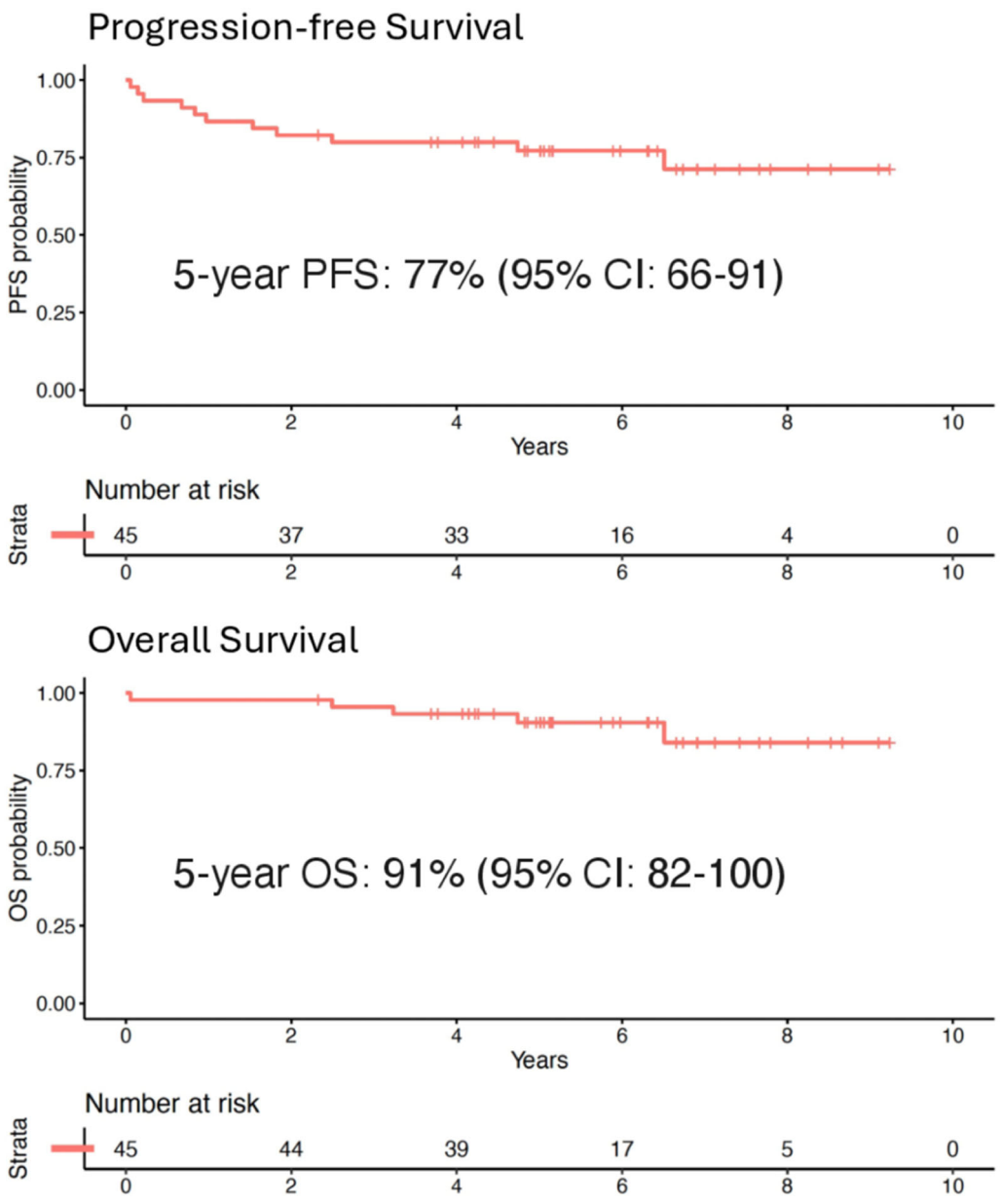
Conclusion: Results of KEYFORM-008 will provide clarity on the efficacy and safety of coformulated favezelimab/pembro versus chemo in pts with anti–PD-1–refractory R/R cHL.

P113: DOSE-DENSE BRENTUXIMAB VEDOTIN PLUS IFOSFAMIDE, CARBOPLATIN, AND ETOPOSIDE (ICE) IN SECOND LINE TREATMENT OF RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA: 5-YEAR LONG TERM FOLLOW UP

Ryan Lynch[1], Ryan Cassaday[1], Stephen Smith[1], Andrew Cowan[1], Edus H. Warren[1], Mazyar Shadman[1], Brian Till[1], Chaitra Ujjani[1], Karolyn Morris[1], Heather Rasmussen[1], Jenna Voutsinas[1], Ajay K. Gopal[1]

[1]*Fred Hutchinson Cancer Center*

Figure 1: Progression-free and overall survival analyses.



Background: Classical Hodgkin lymphoma (CHL) patients (pts) requiring second line therapy may still be cured with multiagent salvage chemotherapy followed by autologous stem cell transplant (ASCT). We previously published results of a phase I/II clinical trial which showed that dose-dense brentuximab vedotin (Bv) combined with ICE was highly active in this setting (Lynch RC et al, Lancet Haematology 2021) We present 5-year long term follow-up from this study (#NCT02227199).

Methods: Pts ≥18 years old with first relapse or primary refractory CD30+CHL were eligible. Treatment details were previously published. Once MTD of Bv with ICE was established, subsequent pts were treated at this dose. Two 21-day cycles were given with G-CSF support. PET was performed after Cycle 2, with response assigned per Cheson 2007. The primary endpoint was to estimate the MTD and CR rate after 2 cycles. Secondary endpoints included PFS and OS.

Results: All 45 pts have enrolled and completed study treatment, including 42 pts who received treatment at the MTD of 1.5 mg/kg on day 1 and 8 of each cycle. Median age was 31 (range, 21–61). 43 pts were evaluable for efficacy. Overall response rate (ORR) and CR for all enrolled pts were 91% and 74% respectively. Among primary refractory pts, ORR and CR were and 86% and 68% respectively. Thity-seven pts proceeded with ASCT. Only 2 pts did not proceed with ASCT due to inadequate response to salvage therapy.

With an updated median follow up of 5.2 years, 5-year PFS was 77% (95% CI 66–91), and 5-year OS was 91% (82–100).

Two pts had PD post study treatment and never received an ASCT (one lost to follow up, other died after declining therapy for chronic phase CML). Five pts relapsed post ASCT, two of whom subsequently had an allogeneic transplant and are in CR. Three pts remain alive after relapse with ongoing therapy.

Five pts developed secondary malignancies, two of which were excised skin cancers (basal cell carcinoma, melanoma). Three pts developed non-skin cancers (lung adenocarcinoma, myelodysplastic syndrome, chronic phase CML) and all have succumbed to their disease.

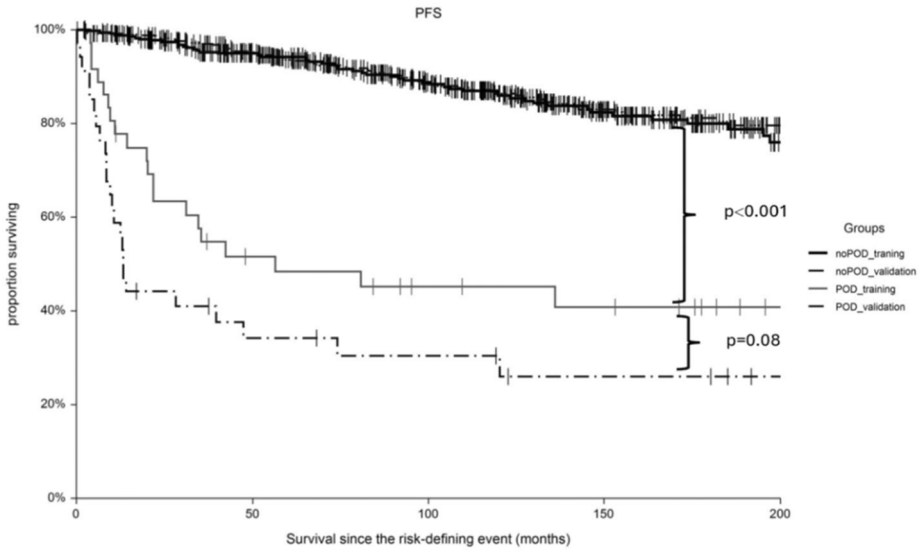
Overall, five pts have died since enrollment on the study due to secondary cancers (3), study treatment (1), or complications of ASCT (1).

Conclusions: As the field of CHL shifts to incorporate PD1-inhibitors in the front-line setting, the Bv-ICE regimen may provide primary refractory patients a novel, effective treatment option.

P114: EARLY PROGRESSION OF DISEASE PREDICTS POOR SURVIVAL IN PATIENTS WITH CLASSIC HODGKIN LYMPHOMA: CZECH HODGKIN LYMPHOMA STUDY GROUP ANALYSIS

Vít Procházka[1], Alice Sýkorová[2], Alexandra Kredátusová[1], Marie Lukášová[1], Pavla Štěpánková[2], Tomáš Papajík[1]

[1]Dept. of Hemato-Oncology, University Hospital Olomouc, [2]th Department of Internal Medicine– Hematology, Hradec Kralove, Czech Republic, University Hospital and Faculty of Medicine



	Pts (all)	PFS 5y	PFS 10y	OS 5y	OS 10y	POD24 pts*	POD24 (n, %)	Post-risk defining event 5-y survival
training	418	79.2%	73.0%	89.2%	83.0%	403	36; 8.9%	48.1 vs 94.2 %
validation	488	82.5%	74.7%	87.7%	80.3%	468	38; 8.1%	34% vs 93.2 %

*excluded cases with deaths without progression within 24 months.

Background: Early progression within 24 months (POD24) of initial immunochemotherapy is associated with poor survival in non-Hodgkin lymphomas, identifying a high-risk subgroup with different lymphoma biology. Little is known about the incidence and impact of POD24 in Hodgkin lymphoma patients (pts), as current prognostic systems (aHIPI) use longer (5-year) survival endpoints.

Methods: We analyzed pts with classic HL (cHL) treated at two academic institutions: Olomouc (training-T) and Hradec Králové (validation-V), enrolled in the Czech Hodgkin Lymphoma Study Group database (NCT06263530) between 2000 and 2020. An early event was defined as progression, relapse, or death related to progressive HL within 24 months after the date of diagnosis. Overall survival (OS) and progression-free survival (PFS) were calculated from the date of diagnosis. To evaluate the association between early POD and OS from a risk-defining event, survival was calculated from the time of POD for early progressors (POD24) or from 2 years after diagnosis for the reference group (noPOD24). Patients with early death (<24 months) without recorded disease progression were excluded from the POD24 analysis.

Results: The analyzed cohort consisted of 906 pts (418 in T and 488 in the V cohort). There was no significant difference in terms of age (median age 35 vs. 34 years, $p = 0.52$), clinical stages distribution (CS III/IV in 41.6% vs. 44.8%, $p = 0.64$), induction therapy given (BEACOPP in 57% vs. 52%, p = ns), and treatment response (CRR 88.4% vs. 90.7%, $p = 0.52$). There was a significant difference in the cHL subtypes distribution with MC in 35% versus 6% and NS in 53% versus 82% in the T and V cohorts, respectively ($p = 0.01$). After a median follow-up of surviving pts of 118 versus 126 months ($p = 0.07$), 72 pts relapsed or progressed in the T group and 62 in the V group. The POD24-event occurred in 36 pts (8.9%) in the T group and 38 pts (8.1%) in the V group. There was no difference in terms of PFS ($p = 0.1$) or OS ($p = 0.88$) between the T and V groups. The 5-year OS since the risk-defining event was 48.1% and 34% versus 94.2% and 93.2% in the POD-T, POD-V, noPOD-T, and noPOD-V groups, respectively (Figure 1).

Conclusions: Early progression of the disease is rare but catastrophic event in HL, resulting in high risk of death. Further exploration is ongoing to contextualize POD24 with prognostic indices (aHIPI), PET metrics, and ctDNA analyses.

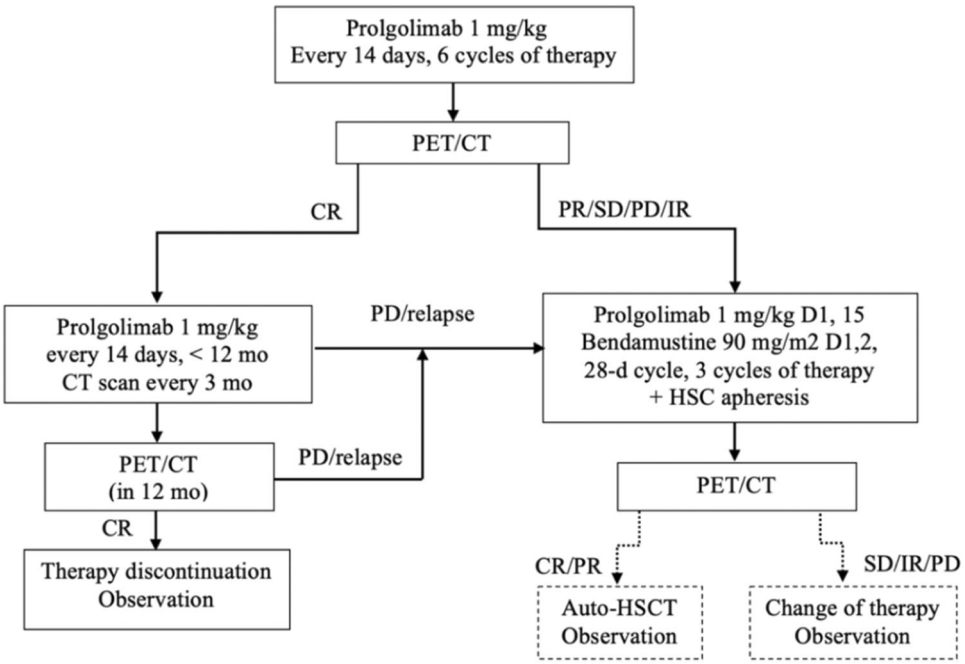
Acknowledgements: Supported by MH CZ – DRO (FNOL, 00098892), AZV NU22-03–00182.

P115: EFFICACY AND SAFETY OF PROLGOLIMAB MONOTHERAPY OR IN COMBINATION WITH BENDAMUSTINE IN SECOND-LINE THERAPY FOR R/R CLASSIC HODGKIN LYMPHOMA: TRIAL IN PROGRESS (PROLGO-HL)

Liudmila Fedorova[1], Kirill Lepik[1], Polina Kotselyabina[1], Anastasia Semenova[2], Valerie Shpirko[2], Stanislav Volchenkov[3], Vladislav Markelov[1], Andrey Chekalov[1], Ilya Zyuzgin[3], Gayane Tumyan[2], Natalia Mikhailova[1], Alexander Kulagin[1]

[1]RM Gorbacheva Research Institute, Pavlov University, [2]National Medical Research Center of Oncology named after N.N. Blokhin, [3]The N.N. Petrov National Medicine Research Center of oncology

Figure 1: The study protocol (Prolgo-HL).



Backgrounds: Prolgolimab (Prolgo), an anti-PD-1 inhibitor, has proven effective and safe for melanoma treatment. Expected efficacy extends to classic Hodgkin lymphoma (cHL). Incorporating Prolgo into PET-adapted second-line therapy may achieve extended remission or cure in cHL patients, sparing autologous stem cell transplantation (auto-HSCT).

Methods: This prospective, multicenter, single-arm, phase 2 trial includes adult patients with histologically confirmed relapsed or refractory (r/r) cHL after first-line therapy without history of PD-1 inhibitor therapy (NCT05757466). The study protocol is outlined in Figure 1. Response assessments performed every 3 months by PET-CT or CT, using LYRIC and Lugano criteria. Adverse events (AE) were assessed using NCI CTCAE v5.0.

The primary endpoint was overall response rate: complete response (CR) and partial response (PR). Secondary endpoints included the frequency of AE, overall survival (OS), progression-free survival (PFS), and duration of response (DOR). We performed intention-to-treat (ITT) analysis for safety and per-protocol (PPA) analysis for efficacy, due to deviation from protocol in 3 patients in one study center.

Results: A total of 20 pts with r/r cHL were enrolled between April 2023 and April 2024. The PPA included 17 pts. Fourteen pts (82%) completed all 6 cycles of Prolgo. Five pts (36%) achieved CR and 6 (43%) - PR. Among those achieving CR and completing 24 cycles, all responses were maintained at the end of treatment ($n = 2$, 14%). One patient each demonstrated indeterminate response, stable disease, and disease progression. Eight patients (47%) were switched to the Prolgo-bendamustine arm. All patients who completed combined therapy achieved an objective response (CR $n = 4$, PR $n = 1$), and in two cases, auto-HSCT was performed.

With a median follow-up of 7 months (2–11), all pts were alive. In the safety ITT analysis ($n = 20$), the rate of grade (gr) 1–2 AE was 55% ($n = 11$), and gr 3 AE - 20% ($n = 4$: rash, diabetes mellitus onset, pneumonia, and renal colic).

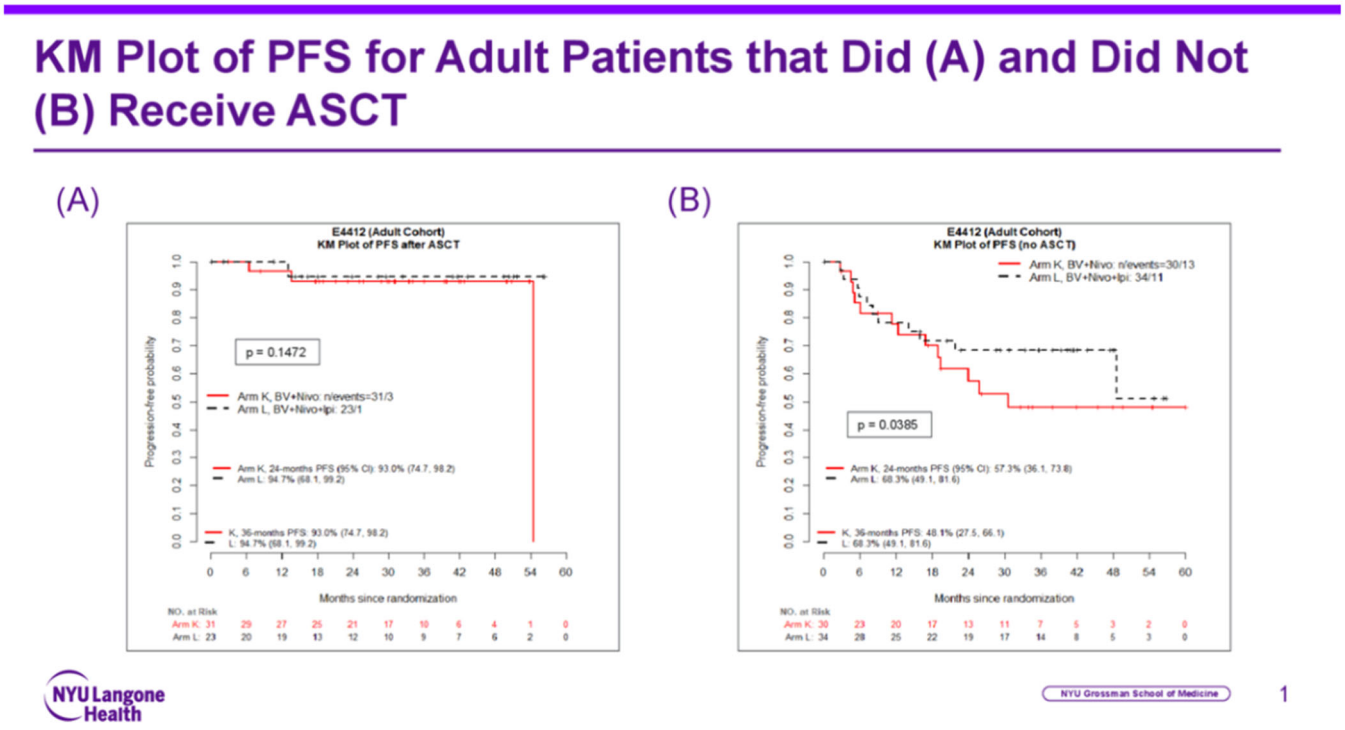
Conclusion: This study is the first to assess Prolgo efficacy and safety as second-line therapy for cHL, aiming to avoid auto-HSCT in early CR patients. Preliminary data demonstrate an anticipated toxicity profile and promising efficacy with the potential for chemotherapy and auto-HSCT avoidance.

P116: EXTENDED FOLLOW-UP FROM AN INTERGROUP RANDOMIZED PHASE II STUDY OF THE COMBINATIONS OF IPILIMUMAB, NIVOLUMAB AND BRENTUXIMAB VEDOTIN IN PATIENTS WITH RELAPSED/REFRACTORY CLASSIC HODGKIN LYMPHOMA: A TRIAL OF THE ECOG-ACRIN RESEARCH GROUP (E4412)

Catherine Diefenbach[1], Opeyemi Jegede[2], Stephen M. Ansell[3], Christian Steidl[4], Yasodha Natkunam[5], David W. Scott[4], Neha Mehta-Shah[6], Jennnifer E. Amengual[7], Christopher J. Forlenza[8], Peter Cole[9], Nancy L. Bartlett[6], Kevin David[9], Ranjana H. Advani[5], Richard F. Ambinder[10], Sachdev P. Thomas[11], Sami Ibrahimi[12], Brad S. Kahl[6]

[1]*Perlmutter Cancer Center at NYU Langone Health, NYU School of Medicine, New York, NY,* [2]*Dana Farber Cancer Institute-ECOG ACRIN Biostatistics Center,* [3]*Mayo Clinic,* [4]*BCCA Vancouver Cancer Center,* [5]*Stanford Cancer Institute,* [6]*Washington University School of Medicine,* [7]*Columbia University Medical Center,* [8]*Memorial Sloan-Kettering Cancer Center,* [9]*Rutgers Ca. Institute of New Jersey, Robert Wood Johnson University Hospital,* [10]*John Hopkins-Sidney Kimmel Cancer Center,* [11]*Kaiser Permanente-Vallejo,* [12]*University of Oklahoma Health Sciences Center*

Figure 1: KM plot of progression free survival (PFS) for adult patients that did (A) and did not (B) receive ASCT.



Background: The Phase 1/2 ECOG-ACRIN sponsored intergroup trial E4412 (NCT01896999) investigated brentuximab vedotin (BV) combined with the checkpoint inhibitors nivolumab (N) and ipilimumab (I) in patients with relapsed or refractory Hodgkin lymphoma (R/R HL); here we present the Phase 2 efficacy and safety data for the combined adult and pediatric patients with extended follow-up for the adult population.

Methods: R/R HL patients were equally randomized between the doublet of BV/N and the triplet of BV/N/I. With 140 eligible & treated patients, there was 87% power to detect a 20% increase in complete response (CR) rate from 40% expected in BV/N to 60% in BV/N/I using a Fisher's exact test with a 15% alpha (one-sided). Results: A total of 147 patients were randomized, 133 adults and 14 pediatric. Sixteen (12%) adult patients and no pediatric patients had prior BV.

Response: One hundred thirty-two patients are evaluable for response: 68 BV/N and 64 BV/N/I, with a CR rate of 64.7% (44 of 68) compared to 70.3% (45 of 64) ($p = 0.287$); ORR was 89% in both arms. The median (Q1, Q3) survival follow-up is 38.0 months (32.6, 48.1). We compared PFS in response eligible adult patients by autologous stem cell transplant (SCT) status in a post-hoc comparison. Fifty-four of 118 (46%) patients received SCT; there is no difference in 36-month PFS: 93.0% for BV/N and 94.7% BV/N/I ($p = 0.1472$). Baseline characteristics were balanced for the 64 adult patients that did not receive SCT (30 BV/N and 34 BV/N/I) in terms of prior BV and prior SCT. For patients who did not have SCT the 36-month PFS for BV/N was 48.1 months compared to 68.3 months for BV/N/I ($p = 0.0385$).

Safety: 65 (BV/N) and 61 (BV/N/I) patients in the adult safety cohort received at least 1 cycle of therapy. The rate of treatment-related grade 3+ toxicities, excluding rash, is similar between both arms, 38.5% (25/65) BV/N and 39.3% (24/61) BV/N/I; there was a higher amount of grade 3 rash in BV/N/I 24.6% (15/61) vs 9.2% (6/65). There was no grade 4 rash. There were no grade 5 toxicities in either arm.

Conclusion: The experimental arm of BV/N/I did not significantly improve CR rate and led to a higher incidence of grade 3 rash. In a post-hoc analysis for patients receiving SCT 36-month PFS was > 90% in both arms, but for patients who did not undergo SCT there was a significant improvement 36-month PFS with BV/N/I.

P117: FREQUENCY AND INDICATORS OF PRIMARY REFRACTORINESS IN LOW-RISK NON-BULKY EARLY-STAGE HODGKIN'S LYMPHOMA PATIENTS AND NEGATIVE INTERIM PET – REPORT FROM THE RAFTING TRIAL

Kateryna Filonenko[1], Eva Domingo-Domènech[2], Javier Nunez[3], Cecilia Carpio[4], Alessandra Romano[5], Corrado Tarella[6], Antonia Rodríguez Izquierdo[7], Ramon Garcia[8], Livio Trentin[9], Manuel Gotti[10], Michał Kurlapski[11], Marta Bednarek[11], Andrea Gallamini[12], Jan Maciej Zaucha[11]

[1]University Clinical Center, Gdansk, Poland, [2]Institut Català d'Oncologia, Barcelona, Spain, [3]Hospital Universitario Marques de Valdecilla, Santander, Spain, [4]Hospital Universitario Vall d'Hebron, Barcelona, Spain, [5]Catania-Policlinico Melacrino e Morelli, Reggio di Calabria, Italy, [6]Istituto Europeo di Oncologia, Milan, Italy, [7]Hospital Universitario 12 de Octubre, Madrid, Spain, [8]Hospital Universitario de Salamanca, Salamanka, Spain, [9]Azienda Ospedaliera di Padova, Padova, Italy, [10]IRCCS Policlinico San Matteo, Pavia, Italy, [11]Medical University of Gdansk, Gdansk, Poland, [12]Antoine Lacassagne Cancer Centre, Nice, France

Table 1: Patients' characteristics.

Characteristic	Patients with inadequate response in EOC PET, n=15	Patients with CR in EOC PET, n=113	p
Age: median (range), years	38 (18-69)	38 (19-65)	0.907
Gender: male/female, n(%)	7 (47)/8 (53)	49 (43)/64 (57)	0.502
mEORTC risk factors:			
LNM, n(%)	9 (60)	41 (37)	0.087
Number of NA, n(%)	6 (40)	21 (19)	0.072
Age >50 yo, n(%)	2 (13)	27 (24)	0.343
ESR, n(%)	2 (13)	24 (23)	0.476
Combination of LNM and number of NA, n(%)	3 (20)	10 (9)	0.189
2 and more risk factors, n(%)	5 (33)	28 (25)	0.503
Baseline MTV, median (range), cm^3	30 (2-74)	34 (9-74)	0.962
Baseline TLG, median (range)	200 (47-720)	201 (5-720)	0.598

Introduction: The RAFTING trial is a phase 2, multicenter, international prospective study investigating risk-adapted treatment strategy in non-bulky early-stage Hodgkin's lymphoma (eHL) pts. Around 10% of the pts from low-risk (LR) group in the RAFTING trial showed inadequate end-of-chemotherapy (EOC) response (non-CR), that fulfill the definition of primary refractoriness (PrR). Research financed by the Medical Research Agency, Poland, Project number 2019/ABM/01/00060.

Methods: Pts from low-risk group in the RAFTING trial were defined by low (<84 mL) baseline metabolic tumor volume (MTV) and negative interim PET after 2 ABVD cycles. Within the LR group the pts without any risk factors according to modified EORTC (mEORTC) criteria (largest nodal mass (LNM) 5–10 cm, age >50 yo, ESR >50 mm/h, ≥4 nodal areas (NA)) (group 1a) were treated with 2 ABVD cycles only whereas pts with at least 1 risk factor (group 1b)–with 4 ABVD cycles. Additional PET was performed after the end of the 4 ABVD cycle in group 1b or in case of relapse suspicion 3 months in group 1a. Pts with CR or non-CR in the EOC-PET were compared by demographic and clinical characteristics (age, gender, age >50 yo, LNM, ESR > 50 mm/h, ≥4 NA, >2 risk factors according to mEORTC, combination of LNM and ≥4 NA, total lesion glycolysis (TLG) and MTV measurement).

Results: Up to May 2024 all 128 enrolled pts (56 males and 72 females) with a mean age of 38 (18–69) years from the LR group completed CT. In 15 cases (11%), primary refractoriness was observed at the EOC PET. Complete information on risk factors was available for 90% of pts at the data cut-off. Patients' characteristics are presented in the table 1. The most common risk factors among pts with primary refractoriness were LNM (9 pts, 64%), ≥4 NA (6 pts, 43%); and more than 1 risk factor had 5 pts, (36%). In the univariate analysis, the only risk factor that significantly increased the risk of refractoriness ($p = 0.048$) was the number of "NA." A trend was also observed for the presence of LNM ($p = 0.087$). Similar results were shown in logistic regression model: the presence of ≥4 NA was the most important risk factor with OR 14.9 ($p = 0.012$), followed by LNM with OR 6.9 ($p = 0.07$).

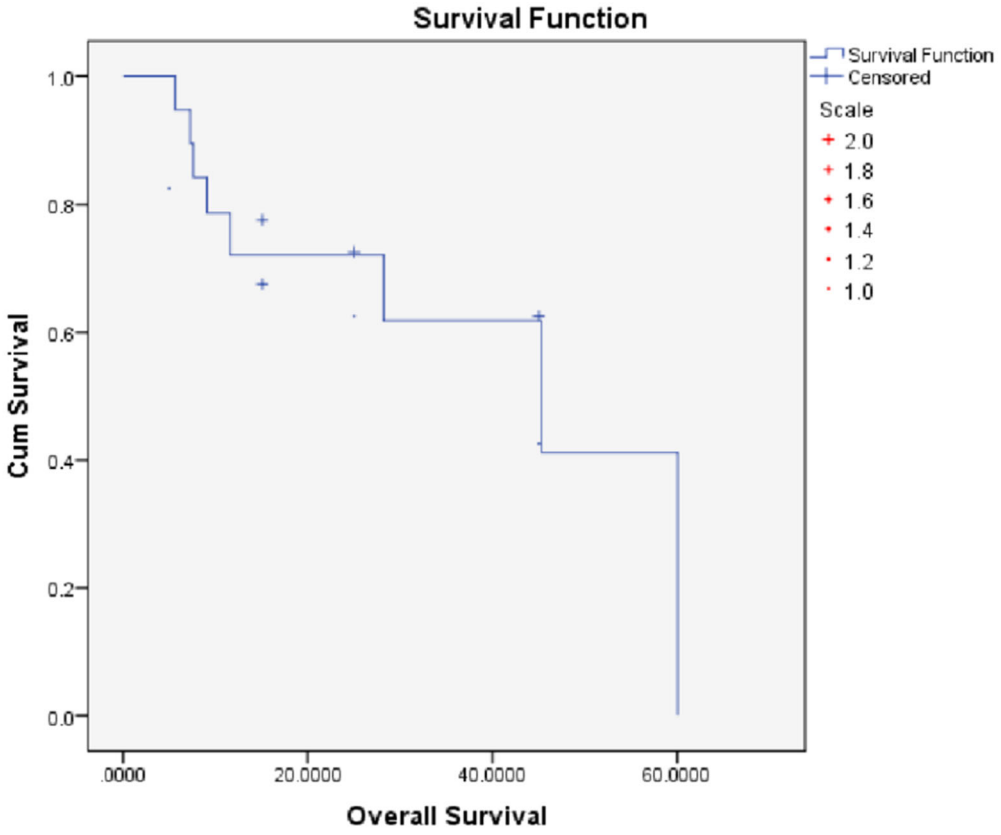
Conclusion: The frequency of primary refractoriness to CT in the low-risk (low TMTV and negative iPET) eHL pts enrolled in the RAFTING TRIAL is 11%. The most important risk factor of primary refractoriness is the number of NA, followed by LNM.

P118: GEMCITABINE AND VINORELBINE AS 3RD LINE CHEMOTHERAPY FOR PRIMARY REFRACTORY/RELAPSING HODGKIN LYMPHOMA-OUTCOME AND TOXICITY PROFILE

Asmaa Hamoda[1], Reham Khedr[1], Hany Abdelrahman[2], Naglaa Elkinaii[1], Iman Zaki[1], Engy Mohamed[3]

[1]Children Cancer Hospital of Egypt and National Cancer Institute, [2]Children Cancer Hospital of Egypt and National Cancer Institute, [3]Children Cancer Hospital of Egypt

Figure 1: 2 years overall survival for responding patients was 87.5%.



Case Processing Summary

Total N	N of Events	Censored	
		N	Percent
19	8	11	57.9%

2 years overall survival for responding patients was 87.5%

For patients with relapsed or primary refractory Hodgkin's disease, the potential for cure remains approximately 50% with current therapies including high-dose chemotherapy and autologous hematopoietic stem cell transplantation (AHSCT).The aim of our study is to report the response rate and toxicity profile of the 3rd line chemotherapy Gemcitabine/Vinorelbine in primary refractory/relapsing HL.

Patients and Methods: A retrospective analysis including all patients who received Gemcitabine/Vinorelbine as 3rd line salvage chemotherapy following ABVD ± radiotherapy as 1st line, and ICE as 2nd lines chemotherapy diagnosed and treated at the Children Cancer Hospital Egypt during 10 years period.

Results: Out of 700 patients registered between July 2007 and end of December 2017 116 patients relapsed or had a progressive disease (16.5%). Ninety-eight patients received ICE as second line chemotherapy. Thirty patients out of 116 failed second line and received third line, 4 patients were excluded from analysis as they received other type of chemotherapy (Navelbine/Ifosfamide), while 32 patients received Gemcitabine/Vinorelbine and were included in our study. They were 21 males (65.6%), and 11 females (34.4%). Mean age was 10.71 years, range 4.5–17.4 with standard deviation 3.69 years. The most common pathologic subtype was nodular sclerosis (62.5%), followed by mixed cellularity (21.9%). According to Ann Arbor staging, 1 patient (3.1%) was stage I, while 6 (18.7%) were stage II, 10 stage III (31.3%), and 15 (46.9%) stage IV. High risk patients were 21 (65.6%), intermediate risk 5 (15.6%), and low risk 6 (18.8%). Sixteen patients (50%) had late relapse (>1 year), 8 (25%) early relapse (3 months–1 year), and 8 (25%) were progressive/refractory (less than 3 months). Chemotherapy cycles varied from 1 to 6 with a mean of 3 cycles. Thirteen patients (40.6%) were responders to Gemzar/Navelbine and underwent hematopoietic stem cell transplantation, while (59.4%) progressed and continued treatment on palliative basis. Eight patients (42.1%) died, 5 of them (62.5%) due to disease progression, and 3 (37.5%) out of chemotherapy toxicity. The 2 years overall survival for responding patients was 87.5%, for non-responders was 72%. Multivariate analysis included sex, risk stratification, type of relapse, stage and showed no significant association.Conclusion:Gemzar/Navelbine is safe to be given as 3rd line chemotherapy for relapsing or primary refractory HL.

P119: INCLUSION OF BRENTUXIMAB VEDOTIN IN SALVAGE REGIMENS BEFORE TRANSPLANT BENEFITS RELAPSED/REFRACTORY HODGKIN LYMPHOMA PATIENTS IN A REAL-WORLD SETTING - A MULTICENTER STUDY IN PORTUGAL

Pedro Santos[1], Sara Tavares[1], Catarina Costa[2], Miguel Neto[3], Isabel Paulos Mesquita[4], Catarina Silva[4], Filipe R. Pinto[5], Ana Tomé[6], Rita Gerivaz[6], Alexandra Monteiro[6], Rita Coutinho[2], Adriana Roque[7], Ana Luísa Pinto[3], Margarida Badior[3], Teresa Ribeiro[8], Marco Dias[8], Ana Vagos Mata[4], Tatiana Mendes[9], Francisca Miranda[9], Filipa Mousinho[9], Renata Cabral[5], Sofia Ramalheira[10], Mafalda Alpoim[10], Bruno Mesquita[11], Francesca Pierdomenico[1], Maria Gomes Da Silva[1]

[1]Instituto Português de Oncologia de Lisboa Francisco Gentil, [2]Instituto Português de Oncologia do Porto Francisco Gentil, [3]Unidade Local de Saúde de São João, [4]Hospital Universitário Santa Maria, Unidade Local de Saúde Santa Maria, [5]Centro Hospitalar Universitário do Porto, [6]Hospital de Santo António dos Capuchos, [7]Centro Hospitalar e Universitário de Coimbra, [8]Hospital de Braga, [9]Centro Hospitalar de Lisboa Ocidental, [10]Centro Hospitalar De Vila Nova De Gaia/Espinho, [11]Centro Hospitalar de Trás-Os-Montes e Alto Douro

Table 1: Baseline characteristics of all patients and relapse characteristics by salvage regimen.

At Diagnosis	All (n=149)	CHT 1st Salvage (n=118)	BV-Based 1st Salvage (n=31)	BV 2nd Salvage (n=20)	BV+CHT 2nd Salvage (n=34)	CPI-Based 2nd Salvage (n=15)	p value
Age - Median | Min-Max	**36** 20-68	**38** 20-68	**32** 23-62	**33** 24-67	**32** 20-67	**34** 22-61	NS
Male - n | %	**88** 59,1	**73** 61,9	**15** 48,4	**33** 61,0	**22** 64,7	**10** 66,7	NS
B Symptoms - n | %	**84** 56,4						
Bulky - n | %	**60** 40,3						
Extra-Nodal involvment - n | %	**71** 47,7						
GHSG Risk Group							
Early Stage - n | %	**9** 6,0						
Intermediate Stage - n | %	**38** 25,5						
Advanced Stage - n | %	**102** 68,5						
At Relapse/Refractory							
B Symptoms - n | %	**29** 19,5	***27** 22,9	***2** 6,5	**4** 21,1	**5** 14,7	**1** 6,7	***0,038**
Bulky - n | %	**19** 12,8	**16** 13,6	**3** 9,7	**2** 10,5	**5** 14,7	**3** 20,0	NS
Extra-Nodal involvment - n | %	**68** 45,6	**51** 43,2	**17** 54,8	**11** 57,9	***13** 38,2	***12** 80,0	***0,021**
Advanced Stage - n | %	**89** 59,7	**69** 58,5	**20** 64,5	**14** 70,0	**18** 59,9	**13** 86,7	NS
Primary Refractory - n | %	**79** 53,0	**60** 50,8	**19** 61,3	**18** 90,0	**22** 64,7	**9** 60,0	NS
Early Relapse <12M - n | %	**27** 18,1	**17** 14,4	**9** 29,0	**1** 5,0	**5** 14,7	**4** 26,7	NS
Chemotherapy - n | %		**118** 100,0	**28** 90,3	- -	**34** 100,0	**4** 26,6	
Platinum based		**91** 77,1	**22** 70,9	- -	**2** 5,9	**1** 6,7	
GVD		**27** 22,9	**1** 3,2	- -	**8** 23,5	**3** 20,0	
Bendamustine		- -	**5** 16,1	- -	**24** 70,6	- -	
None		- -	**3** 9,7	- -	- -	**11** 73,3	
ASCT[1] - n | %	**125** 83,9	**59** 50,0	**15** 48,4	***7** 35,0	***23** 67,0	***5** 33,3	***0,021**
Evaluable Responses							
Complete Response - n | %		**54** 45,8	**12** 38,7	**7** 35,0	**20** 58,8	**7** 46,7	NS
Partial Response - n | %		**23** 19,5	**9** 29,0	**2** 10,0	**6** 17,6	**1** 6,7	NS
PD/NR - n | %		**41** 34,7	**10** 32,3	**10** 50,0	**8** 23,5	**7** 46,7	NS

Footnote: ASCT - Autologous Stem Cell Transplantation. PD/NR - Progressive Disease/No Response. NS - Non Significant

[1] Referes to the number of patients who did not receive further salvage regimens until undergoing ASCT.

Background: Hodgkin lymphoma (HL) is curable with frontline therapy in 70%–80% of patients (pts). Nonetheless, in those who relapse or are primary refractory (PRD), the best salvage regimen to allow autologous stem cell transplantation (ASCT) in the era of checkpoint inhibitors (CPI) and brentuximab vedotin (BV) is not well defined.

Methods: We performed a retrospective multicenter study in a cohort of pts with relapsed/refractory HL (r/r HL) from 11 centers receiving salvage therapy between 2019 and 2022 with intention to proceed to ASCT. Data were collected from pt records. The primary endpoint was event-free survival (EFS) measured from the beginning of each salvage: EFS1 for the 1st and EFS2 for the 2nd salvage. Secondary endpoints were the proportion of transplanted pts, response rate (according to Lugano criteria) and overall survival (OS). Outcomes were accessed according to different salvage regimens including chemotherapy (CHT), BV-based [BV monotherapy, BV + chemotherapy (BV-CHT)] and CPI based regimens. Kaplan-Meier estimates were used to describe time-to-event endpoints and groups compared by the log rank test. Cox regression models were applied to assess survival associations.

Results: We included 149 pts [median age 36 years (20–68), 59% males, 53% PRD]–Table 1. At first salvage, 118 pts received CHT and 31 received BV-based regimens (90.3% with CHT). When adjusting for the presence of B-symptoms, PRD, extra-nodal disease and ASCT, median EFS1 was significantly longer for pts treated with BV-based regimens compared to CHT (12 vs. 8 months, respectively; HR: 0.47, 95% CI: 0.288–0.814, $p = 0.007$). Half of the pts in each group proceeded to ASCT. PRD pts had a significant benefit from BV-based compared with CHT (median EFS1 12 months vs. 5 months, $p = 0.045$). Sixty-nine pts needed a 2nd salvage therapy: 20 received BV, 34 BV-CHT and 15 CPI-based regimens. There was no difference in EFS2 between these groups. However, BV-CHT doubled the proportion of pts proceeding to ASCT compared to BV alone and CPI-based regimens (67% vs. 35% vs. 33% respectively, $p = 0.021$). There was 1 toxic death in BV-CHT group (infection-related) and 1 in the CPI-based group (myocarditis).

Conclusion: In this cohort of r/r HL pts, BV-based regimens as 1st salvage, led to a significant improvement in EFS1 compared with CHT. This benefit was greater in high-risk PRD pts. Comparative trials are needed to clarify the most adequate salvage regimens in this highly curable tumor.

P120: KEYNOTE-B68: UPDATED EFFICACY AND SAFETY OF PEMBROLIZUMAB EVERY SIX WEEKS IN RELAPSED/REFRACTORY (R/R) CLASSICAL HODGKIN LYMPHOMA (CHL) OR PRIMARY MEDIASTINAL B-CELL LYMPHOMA (PMBCL)

Andrew Mcdonald[1], Estelle Verburgh[2], Manuel Gotti[3], Antonio Pinto[4], Jan Maciej Zaucha[5], Vladimir Ivanov[6], Vladimir Melnichenko[7], Heidi Mocikova[8], Muhit Ozcan[9], Caterina Patti[10], João Farias[11], Iara Goncalves[12], Olha Kuchkova[13], Jiri Mayer[14], Güray Saydam[15], Sarah Tomassetti[16], Kumudu Pathiraja[17], Katherine Ryland[17], Rushdia Yusuf[17], Wojciech Jurczak[18]

[1]Alberts Cellular Therapy, Netcare Pretoria east Hospital, Pretoria, South Africa, [2]Department of Medicine, Division of Clinical Haematology, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa, [3]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [4]Hematology-Oncology and Stem Cell Transplantation Unit, Istituto Nazionale Tumori, Fondazione G. Pascale, IRCCS, Naples, Italy, [5]Department of Haematology and Transplantology, Medical University of Gdańsk, Smoluchowskiego, Gdańsk, Poland, [6]Almazov National Medical Research Center, Saint Petersburg, Russia, [7]Pirogov National Medical Surgical Center, Moscow, Russia, [8]Department of Clinical Hematology, University Hospital Kralovske Vinohrady, Prague, Czech Republic, [9]Department of Hematology, School of Medicine, Ankara University, Ankara, Turkey, [10]Onco-Hematology Unit, Azienda Ospedaliera Riunita Villa Sofia-Vincenzo Cervello, Palermo, Italy, [11]Hospital Erasto Gaertner, Curitiba, Brazil, [12]Fundação Pio XII-Hospital de Câncer de Barretos, São Paulo, Brazil, [13]Kharkiv National Medical University, Kharkiv, Ukraine, [14]University Hospital Brno, and Masaryk University, Brno, Czech Republic, [15]Department of Internal Diseases, Division of Hematology, Ege University Medical Faculty Hospital, Izmir, Turkey, [16]Division of Hematology and Oncology Harbor-UCLA Medical Center, [17]Merck & Co., Inc., Rahway, NJ, USA, [18]MSC National Research Institute of Oncology, Kraków, Poland

Table 1: Antitumor activity of pembrolizumab 400 mg Q6W in patients with R/R cHL and R/R PMBCL.

Table. Antitumor activity

	R/R cHL N = 60	R/R PMBCL N = 6
ORR, n (%) [95% CI]	40 (66.7) [53.3-78.3]	3 (50.0) [11.8-88.2]
CR	21 (35.0)	2 (33.3)
PR	19 (31.7)	1 (16.7)
Median* DOR mo (range)	16.6 (1.6-17.0+)	9.7 (2.6-9.7)
9-mo DOR rate, %	53.1	66.7
Median OS mo (95% CI)*	NR (NR to NR)	NR (0.1 to NR)
12-mo OS rate, %	89.0	66.7
Median PFS mo (95% CI)*	8.3 (5.6-19.3)	4.1 (0.1 to NR)
12-mo PFS rate, %	38.3	33.3

NR = Not reached; *Kaplan-Meier estimates; "+" no progressive disease at time of last assessment

Background: Pembrolizumab (pembro) 200 mg Q3W is approved by the FDA to treat R/R cHL and R/R PMBCL. Recently, the FDA gave accelerated approval of pembro 400 mg Q6W in all approved indications based on data in solid tumors. The Phase 2 KEYNOTE-B68 trial (NCT04875195) evaluates efficacy and safety of pembro 400 mg Q6W in patients (pts) with R/R cHL or R/R PMBCL. We previously reported ORR of 65% in R/R cHL, and 50% in R/R PMBCL with approximately 9 months (mo) of follow-up. Here we present data from 66 pts with approximately 16 mo of follow-up.

Methods: In this nonrandomized trial, pts aged ≥18 years with anti-PD-1/PD-L1 naïve R/R cHL or R/R PMBCL received 400 mg pembro Q6W for ≤18 cycles, until progression, toxicity, or withdrawal. Eligible pts with cHL must have relapsed or failed to respond after ≥1 prior lines of therapy (LOT), or relapsed or failed to respond after ≥1 prior multiagent LOT, or autologous stem cell transplant (ASCT). Eligible pts with PMBCL must have relapsed or failed to respond after ≥2 prior LOT including rituximab, and relapsed or failed to respond to or were ineligible for ASCT. Primary endpoint was ORR (Lugano by INV). Secondary endpoints were DOR (Lugano by INV) and safety. Exploratory endpoints were PFS (Lugano by INV) and OS.

Results: At data cut-off (May 15, 2023), 66 pts (60 R/R cHL, 6 R/R PMBCL) were enrolled. Median follow-up was 15.7 mo for R/R cHL and 17.5 mo for R/R PMBCL. ORR was 66.7% (95% CI: 53.3–78.3 [35.0% CR: 31.7% PR]) for R/R cHL, and 50% (95% CI: 11.8–88.2 [33.3% CR: 16.7% PR]) for R/R PMBCL. Median DOR was 16.6 mo for R/R cHL and 9.7 mo for R/R PMBCL (Table). Treatment-related AEs occurred in 26 pts with R/R cHL and 2 with R/R PMBCL. Grade 3–4 treatment-related AEs occurred in 3 (5%) pts with R/R cHL and 1 (17%) with R/R PMBCL. Immune-mediated AEs occurred in 14 (23%) pts with R/R cHL and 1 (17%) with R/R PMBCL. Grade 3 infusion-related reactions and immune-mediated AEs occurred in 2 (3%) pts and 1 (2%) pt, respectively, with R/R cHL. No grade ≥4 immune-mediated AEs occurred in pts with R/R cHL and no grade ≥3 immune-mediated AEs occurred in pts with R/R PMBCL.

Conclusions: With approximately 16 mo of follow-up, ORR and PFS in pts with R/R cHL increased, further highlighting the consistency to pembro 200 mg Q3W. No new safety concerns occurred in pts with cHL or PMBCL. This trial further demonstrates the continued antitumor activity in pts and confirms the acceptability of Q6W dosing in heme indications.

P121: NIVOLUMAB BASED SALVAGE IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA: EXPERIENCE FROM A TERTIARY CARE HOSPITAL IN NORTH INDIA

Sanjeev Sanjeev[1], Deep Gala[1], Sauvik Saha[1], Manish Kumar Singh[1], Aftab Nazar[1], Manish Ora[1], Dinesh Chandra[1], Khaliqur Rahman[1], Ruchi Gupta[1], Rajesh Kashyap[1]

[1]*SGPGI, Lucknow*

Background: Nivolumab (anti PD-1 antibody), is an immune check point inhibitor, that restores effective anti-tumor immune response and is effective in patients with relapsed/refractory HL. Combining Nivolumab with chemotherapy (eg. Ifosfamide+Carboplatin+Etoposide) is an effective salvage therapy in relapsed/refractory HL and serves as a bridge to autologous stem cell transplant in these patients.

Objective: To assess the effectiveness of Nivolumab based salvage therapy in patients with relapsed/refractory Hodgkin lymphoma.

Methods: This is a retrospective analysis wherein hospital records of patients with biopsy proven relapsed/refractory Hodgkin lymphoma treated with nivolumab based salvage regimen were reviewed.

Results: From December 2020 till June 2023, a total of 15 patients received Nivolumab based therapy for relapsed/refractory Hodgkin lymphoma. Median age was 28 years (range 7–52), 80% were male and 20% were female, 47% (7 out of 15) had primary refractory disease and 53% had relapsed disease (20% had early relapse while 33% had late relapse); at baseline 93% had stage 4 disease, 60% had bulky disease and 60% had extra nodal involvement. 73% (11 out of 15) patients received Nivo-ICE regimen while 13.3% received Nivo-AVD and 6.7% received Nivo-BV and Nivo monotherapy each. Mean dose of Nivolumab was 2.3 mg/kg. Majority of the patients (67%) received nivolumab as a part of their third line salvage regimens. The adverse events observed were Febrile neutropenia (40%), immunologic events (27%) (skin rash, arthralgias), transaminitis (27%), autoimmune thyroiditis (6.7%). With nivolumab based salvage therapy, Overall response rate of 67% (10 out of 15) was observed, Complete metabolic response (CMR) and partial metabolic response (PMR) was observed in 40% and 27% patients respectively. 20% (3 out of 15) patients had progressive disease after receiving 3 cycles of nivolumab based salvage, while 2 patients expired after first cycle of Nivo-ICE, cause of death being gram negative sepsis in both patients. Out of 10 who achieved remission, 7 (70%) proceeded for autologous hematopoietic stem cell transplant. All transplanted patients but one remain in CR with a median follow up time of 20 months (range 5–34 months). Post transplant relapse was observed in 1 patient after a progression free survival of 34.

Conclusion: Nivolumab based salvage therapy is highly effective across all age groups and serves as a bridge to transplant thereby prolonging the PFS.

P122: OPEN-LABEL PHASE 1 STUDY TO EVALUATE THE SAFETY OF SGN-35T IN PATIENTS WITH RELAPSED/REFRACTORY CD30-EXPRESSING LYMPHOID MALIGNANCIES (SGN35T-001; TRIAL IN PROGRESS)

Tatyana Feldman[1], Radhakrishnan Ramchandren[2], Hun Ju Lee[3], Gizelle Popradi[4], Graham P. Collins[5], Daniel Morillo[6], Mingjin Yan[7], Tara L. Chen[7], Youn H. Kim[8]

[1]*Hackensack University Medical Center, Hackensack, NJ, USA,* [2]*University of Tennessee Medical Center, Knoxville, TN, USA,* [3]*The University of Texas MD Anderson Cancer Center, Houston, TX, USA,* [4]*McGill University Health Centre, Montreal, Quebec, Canada,* [5]*Oxford University Hospitals, Oxford, UK,* [6]*START Madrid - Fundacion Jimenez Diaz, Madrid, Spain,* [7]*Pfizer Inc., Bothell, WA, USA,* [8]*Stanford Cancer Center, Stanford, CA, USA*

Patients (pts) with relapsed/refractory (R/R) lymphomas have limited treatment options and poor mortality rates versus pts with non-R/R disease. CD30 is an established therapeutic target in R/R lymphoid malignancies. Brentuximab vedotin (BV), a CD30-directed antibody-drug conjugate (ADC), has demonstrated clinical benefit in cHL and PTCL.

SGN-35T is an investigational ADC comprised of an anti-CD30 monoclonal antibody, conjugated to monomethyl auristatin E (MMAE) via a novel protease-cleavable tripeptide linker with a drug-to-antibody ratio of approximately 4. SGN-35T has the same antibody backbone as BV; however, the tripeptide linker is designed to preferentially release MMAE in target cells to improve tolerability.

Preclinically, SGN-35T elicits antitumor activity through MMAE-mediated direct cytotoxicity, CD30+ regulatory T-cell depletion, bystander effect, and immunogenic cell death, providing rationale to clinically develop SGN-35T.

SGN35T-001 (NCT06120504) is a first-in-human, open-label, global, multicenter, dose-escalation and dose-expansion study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and antitumor activity of SGN-35T in pts with R/R CD30-expressing lymphoid malignancies.

Pts will be enrolled into dose-escalation (Part A), optional dose-optimization (Part B), dose-expansion (Part C), and optional biology cohorts. Pts in Part A will receive SGN-35T intravenously at various doses. Part B dosing may evaluate doses from Part A; Part C and biology cohort dosing will occur at the recommended dose from Parts A/B.

For Parts A/B, pts must have histologically confirmed R/R lymphoid malignancy with no standard therapy available. CD30 expression must be ≥1% in tumor tissue from the most recent biopsy or obtained at or after relapse, as determined by local pathology except in diagnoses where CD30 is universally expressed. For Part C, pts are eligible irrespective of CD30 expression and must provide tumor tissue for evaluation; the

number of prior therapies permitted is dependent on histologic subtype. Enrolled pts must be ≥18 years of age, have measurable disease, and ECOG PS ≤ 1.

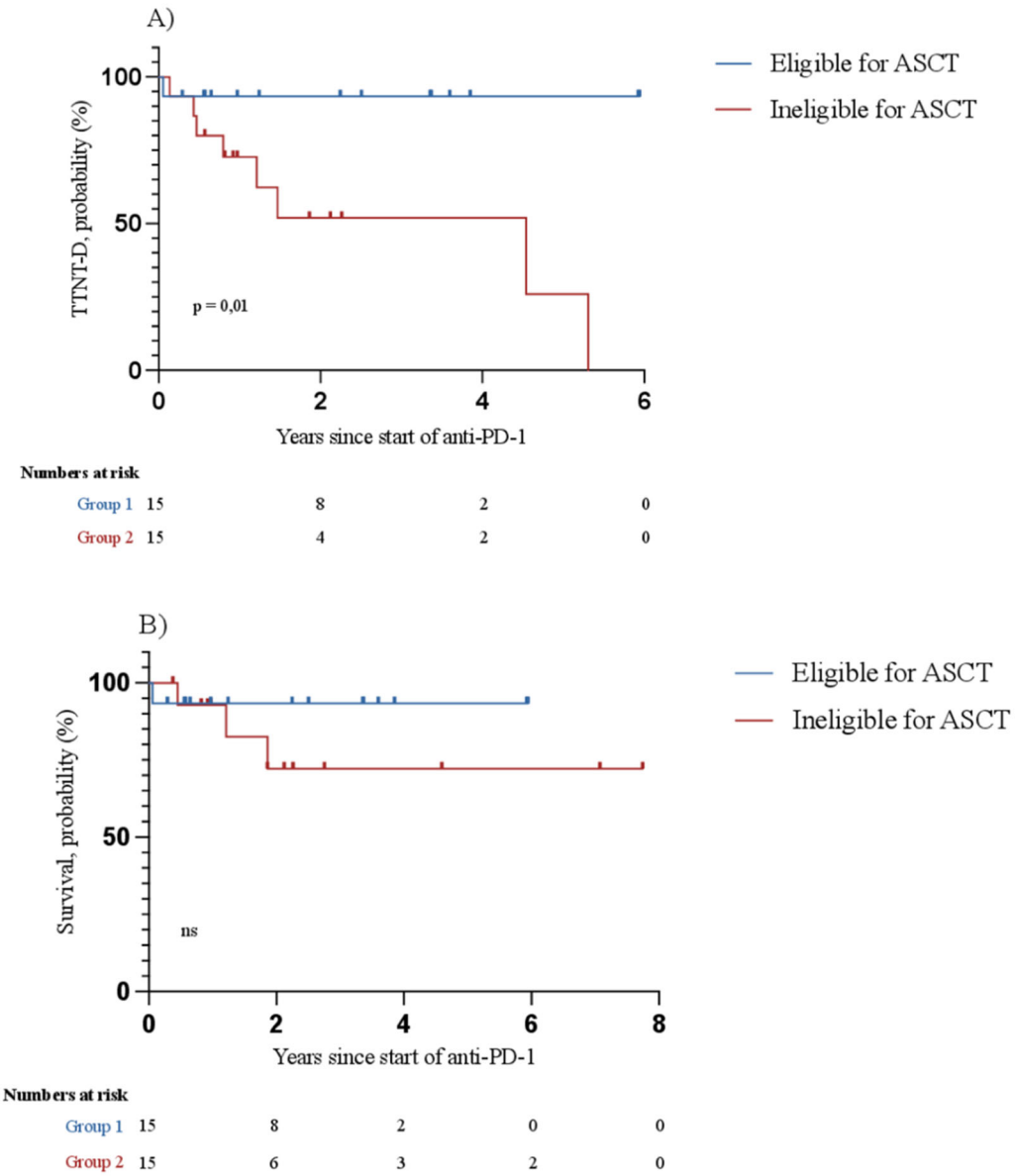
Primary endpoints include incidence and severity of adverse events and laboratory abnormalities, frequency of dose modifications, and incidence of dose-limiting toxicities. Secondary endpoints include PK parameters, objective response rate, duration of response, and complete response rate. Enrollment is ongoing in the US and planned globally.

P123: OUTCOME OF TREATMENT WITH THE ANTI-PD-1 MONOCLONAL ANTIBODIES NIVOLUMAB AND PEMBROLIZUMAB IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA—A RETROSPECTIVE ANALYSIS ON CONSECUTIVE PATIENTS FROM A WELL-DEFINED REGION

Zaid Mansur[1,2], Elin Lundin[1], Lotta Hansson[1,2], Björn Engelbrekt Wahlin[3,2], Marzia Palma[1,2]

[1]Immune and Gene Therapy Laboratory, Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, [2]Lymphoma, Medical Unit Hematology, Karolinska University Hospital, Stockholm, Sweden, [3]Hematology, Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden

Figure 1: Kaplan–Meier curves of TTNT-D (A) and OS (B). Dots on the curves represent censored subjects.



Background: In the past years, PD-1 blockade for relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) has increased in clinical practice, both as salvage therapy prior to autologous stem-cell transplantation (ASCT) and for patients (pts) who are ineligible or have relapsed after ASCT.

The aim here was to describe the clinical outcome with the PD-1 inhibitors nivolumab and pembrolizumab in a cohort of consecutive pts with R/R cHL.

Methods: Clinical data from pts with cHL treated with anti-PD-1 therapy at the Hematology Dept. at Karolinska University Hospital during the years of 2017–2023 was gathered from medical records. Considering that clinical benefit was often achieved despite radiological progression, time to next treatment or death (TTNT-D) was used as a marker of clinical outcome whilst overall response rate (ORR) was calculated based on best objective radiological response.

Results: Thirty pts with R/R cHL who received ≥1 dose of either nivolumab or pembrolizumab were included. Median age at start of treatment was 48.5 years (range 18–89) and 67% of the pts were men.

Two groups were considered for further analysis: Group 1 (n = 15) received anti-PD-1 alone or in combination with chemotherapy with the intention to proceed to ASCT and Group 2 (n = 15) were ineligible for or had progressed after ASCT.

In Group 1, ORR was 93%; 10 CR and 2 PR before proceeding to ASCT, 2 achieved CR but were later deemed ineligible for ASCT and 1 died due to PD. At a median follow-up of 28 months (range 3–71), 87% remain in CR and the estimated OS and proportion of pts with remaining clinical benefit at 2 years were both 93% (Figure A and B).

Group 2 showed an ORR of 67% (5 CR and 5 PR). At a median follow-up of 24 months (range 4–92), 3 are treatment-free in CR, 2 pts died due to PD and 1 died due to complications following allogeneic SCT. Among the pts still in CR, 2 were treated with concomitant RT and 1 received additional treatment following relapse. At 2 years, the estimated OS and proportion of pts with remaining clinical benefit was 72% and 52%, respectively (Figure A and B).

At the end of the study period, 5 pts remain on treatment. Excluding planned discontinuations, the main causes for discontinuation were PD in 5 pts (17%) and adverse events in 3 (10%).

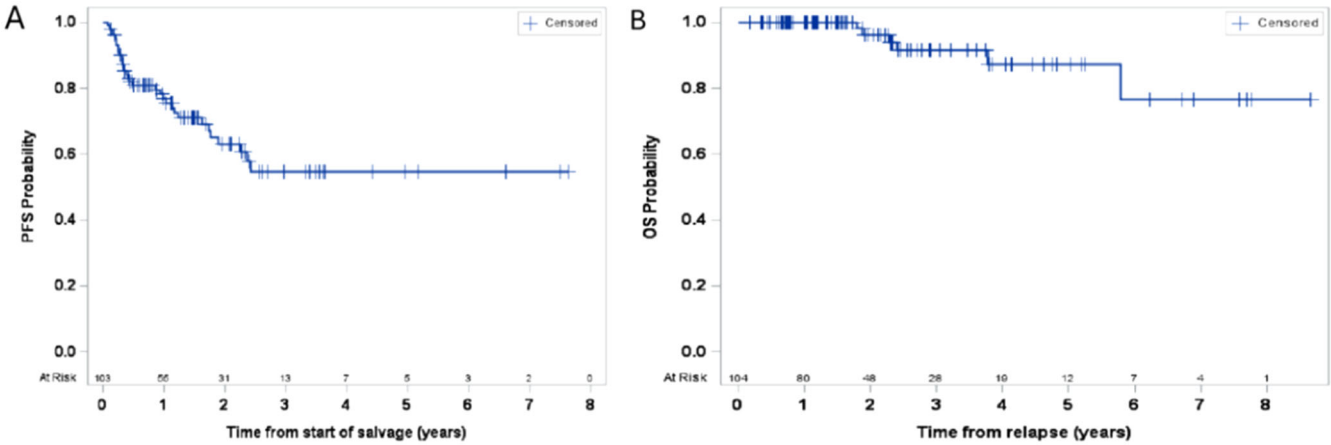
Conclusion: We conclude that anti-PD-1 therapy is an effective and well tolerated treatment for R/R cHL as well as an effective addition to salvage chemotherapy preceding ASCT in a real-world setting.

P124: OUTCOMES IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA AFTER FAILURE FOLLOWING FRONTLINE BRENTUXIMAB VEDOTIN-BASED TREATMENT

Shin Yeu Ong[1,2], Lu Chen[1], Reid Merryman[3], Harsh Shah[4], Robert Stuver[5], Ann S. Lacasce[3], Ayo Falade[6,7], Kelsey Baron[4], Nivetha Ganesan[5], Tiffany Chang[5], Urshila Durani[1], Tamer Othman[1], Philippe Armand[3], Matthew Mei[1], Alison J. Moskowitz[5], Alex F. Herrera[1]

[1]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, California, USA, [2]Department of Haematology, Singapore General Hospital, Singapore, [3]Dana-Faber Cancer institute, Harvard Medical School, Boston, USA, [4]Division of Hematology and Hematologic Malignancies, Department of Internal Medicine, University of Utah, Salt Lake City, UT, USA, [5]Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [6]Department of Medicine, Mass General Brigham Salem Hospital, Salem, MA, [7]Department of Hematology/Oncology, Mayo Clinic, Rochester, MN

Figure 1: (A) Progression-free survival (PFS) post first salvage treatment; (B) Overall survival (OS) post relapse after frontline treatment with BV-based treatment.



Background: Brentuximab vedotin (BV) combined with AVD chemotherapy is a standard of care for treatment (tx) of advanced stage classic Hodgkin lymphoma (cHL) based on improved progression-free survival (PFS) and overall survival (OS) compared to ABVD. Available data regarding outcomes of patients (pts) with relapsed or refractory (RR) cHL is primarily derived from pts who received ABVD, with limited data from pts progressing after BV-based frontline regimens. We performed a multicenter retrospective analysis to assess outcomes in pts with RR cHL after BV-based initial tx.

Methods: Consecutive patients with RR cHL after BV-containing frontline tx were identified at each institution. Descriptive statistics were used to describe the patient population. Response to tx was assessed by the treating MD based on response criteria at time of assessment.

Results: 105 pts treated between Dec 2015 and Nov 2023 were included. Most pts received BV-AVD (76%) as their initial tx, 16% received ABVD/BV-AVD, 8% received BV in other combinations. The median age at first relapse was 35 years (y, range 18–82), and 52% were male. 56% had primary refractory disease, 28% relapsed within 12 months of completing initial tx, and 15% had late relapse. At relapse, 57% pts presented with stage III/IV disease, 17% had B symptoms, and 18% had bulk ≥5 cm.

The most frequently used salvage regimens were anti-PD1+chemotherapy combinations (55%), followed by chemotherapy alone (29%), BV +nivolumab (8%), anti-PD1 monotherapy (7%), and RT only (1%). In all pts, the overall response rate (ORR) to first salvage tx was 88%, the complete response (CR) rate was 66%. First salvage tx that included PD-1 blockade ($n = 73$) led to an ORR of 96% with 72% CR versus ORR 84% and 61% CR for chemotherapy-only salvage ($n = 31$). Eighty seven pts (83%) underwent autologous stem cell transplantation (ASCT). Among these pts, 29% of pts received >1 line of salvage tx and 6% required ≥ 3 lines. Overall, 79% of pts received PD-1 blockade as part of salvage tx. 13% received peri-ASCT RT, and 8 (10%) received post-ASCT maintenance tx. At a median follow-up of 20 months, the 2 y PFS from the start of 1st salvage was 63% and the 2 y OS was 96%.

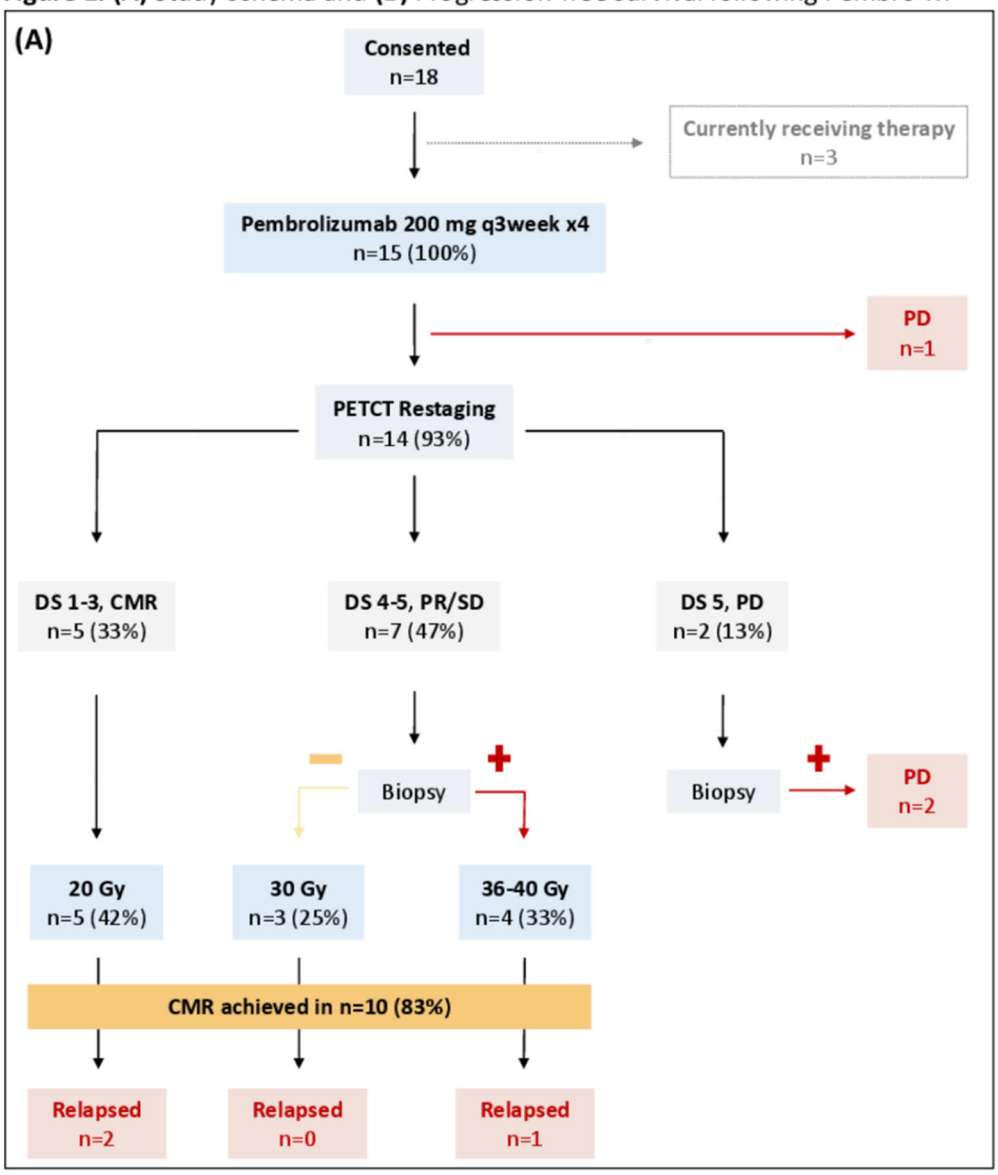
Conclusions: In this cohort of pts with RR cHL after BV-containing frontline tx, a majority of pts achieved CR and proceeded to ASCT. Despite most receiving novel salvage regimens, PFS may be lower than expected compared to available data regarding outcomes after novel salvage tx.

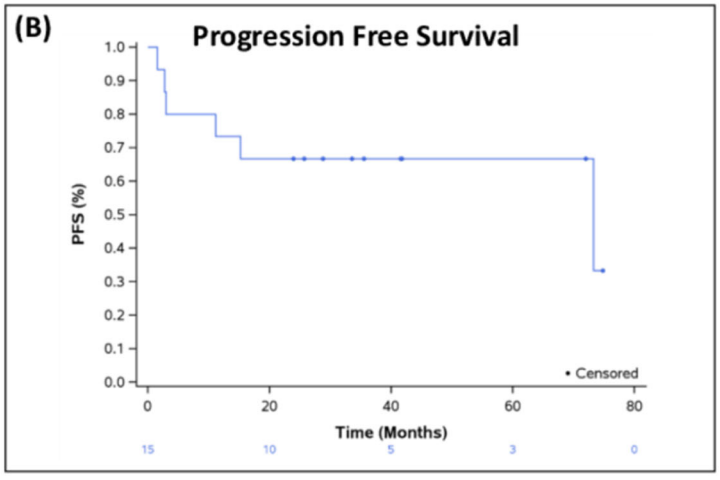
P125: PEMBROLIZUMAB AND INVOLVED SITE RADIATION THERAPY ALONE AS AN ALTERNATIVE TO TRANSPLANT IN PATIENTS WITH LOCALIZED FAILURE FOLLOWING CHEMOTHERAPY FOR HODGKIN LYMPHOMA: A PROSPECTIVE MULTICENTER PHASE II STUDY

Alexandra Dreyfuss[1], Nivetha Ganesan[2], Alvaro Alencar[3], Alexander Boardman[2], Philip Caron[2], Tiffany Chang[2], Theresa Davey[2], Kevin David[2], Ahmet Dogan[4], Zachary Epstein-Peterson[2], Lorenzo Falchi[2], Beatrice Fregonese[1], Paola Ghione[2], Paul Hamlin[2], Steven Horwitz[2], Brandon Imber[1], Andrew Intlekofer[2], Derek Isrow[3], Erel Joffe[2], William Johnson[2], Anita Kumar[2], Michael Lariviere[5], Jennifer Lue[2], Efrat Luttwak[2], Michael Mcnicholas[6], Zachary Moore[1], Brittney Munayirji[2], Ariela Noy[2], Colette Owens[2], Lia Palomba[2], Jaldhi Patel[6], John Plastaras[5], Alayna M. Santarosa[2], Heiko Schöder[7], Gunjan Shah[2], Raphael E. Steiner[2], Robert Stuver[2], Jakub Svoboda[6], Pallawi Torka[2], Santosha Vardhana[2], Andrew Zelenetz[2], Gilles Salles[2], Joachim Yahalom[1], Craig H. Moskowitz[3], Alison Moskowitz[2]

[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, [2]Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, [3]Division of Hematology, Department of Medicine, Sylvester Comprehensive Cancer Center, University of Miami, Miller School of Medicine, [4]Department of Pathology, Memorial Sloan Kettering Cancer Center, [5]Department of Radiation Oncology, University of Pennsylvania, [6]Department of Medicine, Lymphoma Service, University of Pennsylvania, [7]Department of Radiology, Memorial Sloan Kettering Cancer Center

Figure 1. (A) Study schema and **(B)** Progression-free survival following Pembro-RT





Background: Chemotherapy (chemo) followed by stem cell transplant (SCT) is standard of care for relapsed/refractory (RR) Hodgkin Lymphoma (HL). In a phase II study, we evaluated pembrolizumab (pembro) with involved site radiation therapy (ISRT) as an alternative salvage approach for localized favorable relapse.

Methods: Patients (pts) with RR stage IA/IIA, non-bulky (<10 cm) HL after 1 line of therapy received PETCT simulation followed by pembro 200 mg IV every 21 days for 4 cycles and PETCT simulation 2–3 weeks later. Pts then received ISRT per response as follows: (1) 20 Gy for complete metabolic response (CMR) defined by Deauville Score (DS) 1–3; (2) 30 Gy for partial metabolic response (PMR) or stable disease (SD) (DS 4–5) and negative biopsy; or (3) 36–40 Gy for PMR/SD and positive biopsy. Pts who progressed (PD) were taken off study. PETCT was done 4–6 weeks after ISRT to document response. The primary endpoint was CMR rate after pembro-RT. Secondary endpoints were response to single agent pembro, 2-year progression free survival (PFS2), and toxicity.

Results: 18 of planned 22 pts enrolled so far, with median age 37 (range 22–66). 3 (17%) had stage I, 14 (78%) stage II, and 1 had an unspecified limited stage at initial diagnosis. Frontline therapy was chemo alone in 15 (83%) and combined modality in 3 (17%). 16 (89%) received ABVD, 12 (67%) with <6 cycles. 13 (72%) had relapsed and 5 (28%) had refractory disease.

Of the 15 evaluable pts (3 still on therapy), 5 (33%) had CMR after pembro, 3 (20%) had PMR/SD with negative biopsy, 4 (27%) had PMR with positive biopsy, and 3 (20%) had PD. 12 pts proceeded to ISRT, of whom 5 (42%) with CMR received 20 Gy, 3 (25%) with PMR/SD and negative biopsy received 30 Gy, and 4 (33%) with PMR/SD and positive biopsy received 36–40 Gy. 10 (83% of these pts, 67% overall) achieved CMR. After median follow up of 42 months (3–82), PFS2 was 67% (95% CI: 47–95).

3 pts had PD on pembro and 3 had HL relapse at median 12 months (7–70) post-pembro-RT. Among them, 3 are in remission following pembro+chemo or brentuximab vedotin (BV)+nivolumab and SCT, or BV+RT. 3 have unknown status.

Immune-related toxicities were 3 grade 1 rash, and 2 grade 2 hypo/hyperthyroidism. Grade >2 toxicities were 1 grade 3 headache and 1 grade 4 lipase elevation.

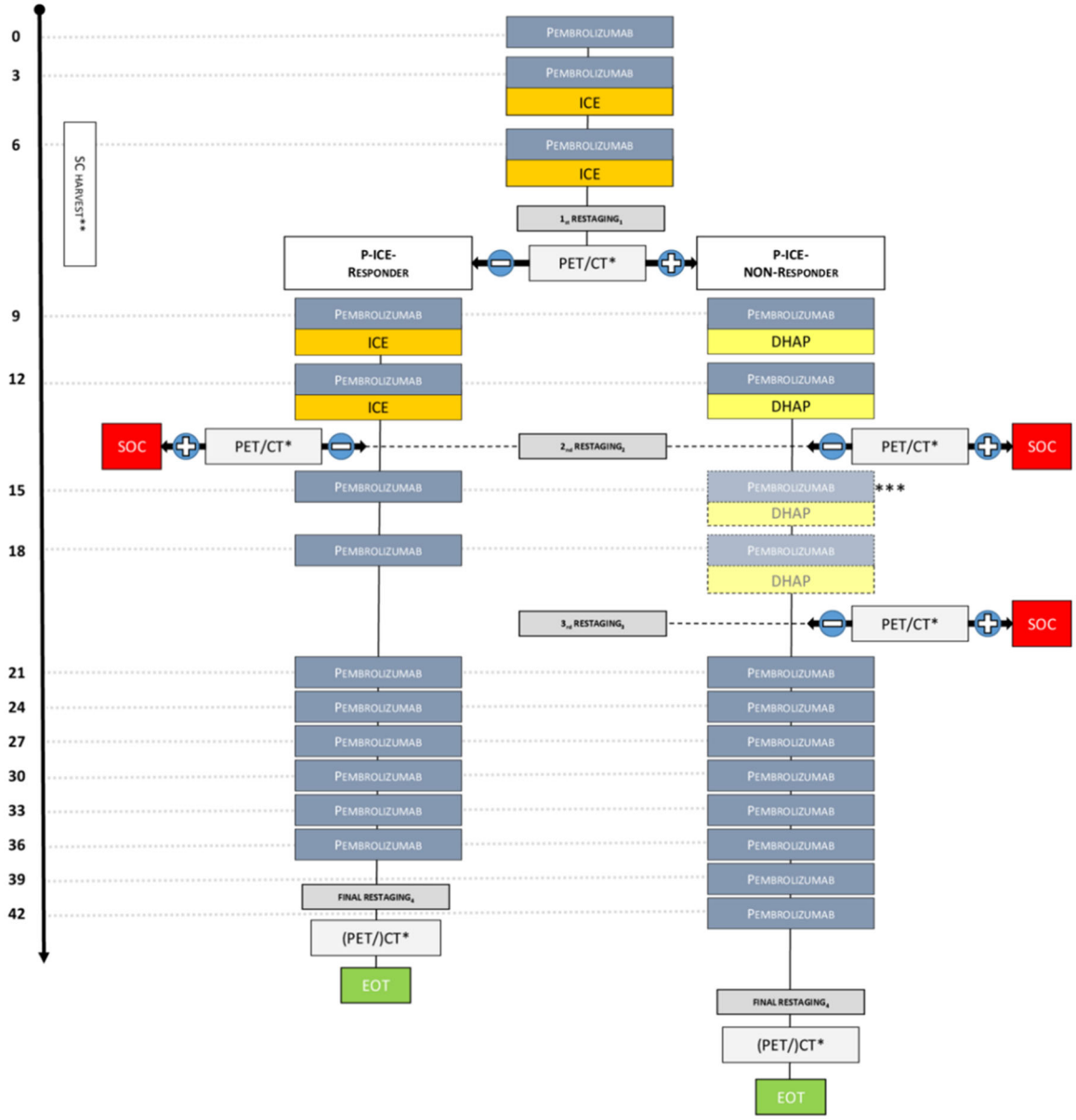
Conclusion: Pembro-RT yielded excellent CMR rates and minimal toxicity, suggesting pembro-RT as a potential alternative to SCT in localized, favorable RR HL. Study enrollment continues.

P126: PEMBROLIZUMAB IN COMBINATION WITH SALVAGE CHEMOTHERAPY FOR FIRST-RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA: THE MULTICENTER PHASE II PEMBRO-CORE STUDY (TRIAL IN PROGRESS)

Hishan Tharmaseelan[1], Sarah Gillessen[1], Ina Bühnen[1], Helen Kaul[1], Carsten Kobe[2], Wolfram Klapper[3], Michael Fuchs[1], Sven Borchmann[1], Paul J. Bröckelmann[1], Peter Borchmann[1], Bastian Von Tresckow[4]

[1]University of Cologne, Faculty of Medicine and University Hospital of Cologne, Department I of Internal Medicine, and Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf (CIO ABCD), and German Hodgkin Study Group (GHSG), Cologne, Germany, [2]Department of Nuclear Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany, [3]Hematopathology Section and Lymph Node Registry, Department of Pathology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany, [4]Department of Hematology and Stem Cell Transplantation, West German Cancer Center and German Cancer Consortium (DKTK partner site Essen), University Hospital Essen, University of Duisburg-Essen, Essen, Germany

Figure 1: Flowchart of the PET-guided Pembro-CORE study for patients with first-relapsed or refractory classical Hodgkin's lymphoma.



Background: Despite high efficacy of first-line therapies for classical Hodgkin lymphoma (cHL), treatment for patients with relapse has been only moderately successful. The current standard of care (SOC) in most cases includes salvage chemotherapy followed by high-dose chemotherapy (HD-CT) and autologous stem cell transplant. This approach only achieves long-term remission in about half of patients without proven significant benefit in overall survival. Moreover, patients suffer from high treatment associated toxicity and severe short- and long-term side effects. Recent studies emphasize the potential of immunotherapy-based approaches in treating cHL, with PD-1 based salvage regimens like P-GVD, P-ICE, and N-ICE achieving response rates of up to 95%.

Objective: The Pembro-CORE trial is investigating a HD-CT-free treatment for patients with first relapse of cHL by combining Pembrolizumab with salvage chemotherapy. This multicentric phase II study, initiated in March 2024, has thus far recruited three patients. According to protocol, patients receive one cycle of Pembrolizumab and two cycles of P-ICE (Pembrolizumab, Ifosfamide, Carboplatin, Etoposide). After PET restaging, responders receive two cycles of P-ICE. Non-responders switch to two cycles of P-DHAP (Pembrolizumab, Dexamethasone, High-Dose Cytarabine, Cisplatin). A second PET restaging after five cycles determines further treatment; PET-positive cases are treated outside the study according to SOC. Non-responders in the P-ICE arm may receive two additional cycles of P-DHAP followed by a third restaging. If they remain PET-positive, they will also be treated according to SOC. Treatment concludes with consolidating Pembrolizumab until final staging. Complete metabolic response rate, defined as the proportion of patients with a Deauville score of 1–3 in restaging after treatment with 1x Pembrolizumab+4 cycles of Pembrolizumab and chemotherapy (4x P-ICE or 2x P-ICE+2x P-DHAP) is the primary endpoint. This is the proportion of patients that can be spared from HD-CT. Secondary endpoints include PFS, OS and patient reported outcomes. The trial is complemented by a scientific side program.

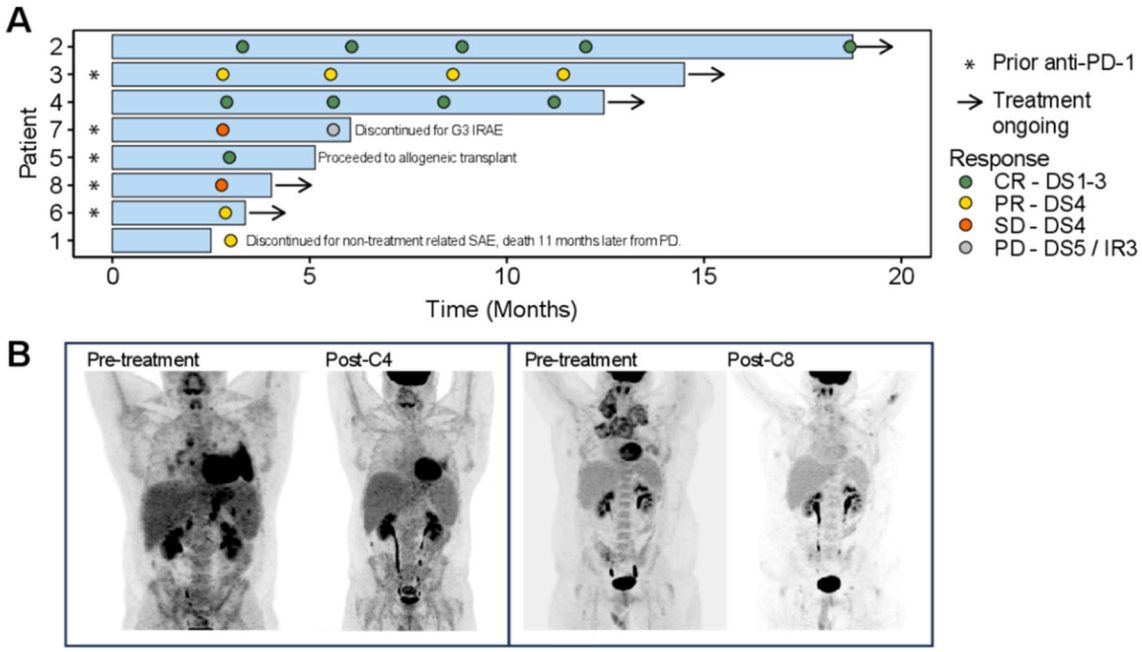
Outlook: The Pembro-CORE trial investigates a novel approach to treatment of first relapsed or refractory classical Hodgkin's lymphoma by combining Pembrolizumab with PET-guided salvage chemotherapy. If succesful, the trial might contribute to the omission of HD-CT in patients with relapsed HL.

P127: PHASE II TRIAL EVALUATING THE ANTI-CD47 ANTIBODY MAGROLIMAB IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY CLASSIC HODGKIN LYMPHOMA

Joseph Schroers-Martin[1], Michael Spinner[2], Reid Merryman[3], Cheryl Chang[1], Austin Yeung[1], Chandley Silin[1], May Powell[1], Philippe Armand[3], Margaret A. Shipp[3], Ranjana H. Advani[1]

[1]*Stanford University*, [2]*University of California San Francisco*, [3]*Dana Farber Cancer Institute*

Figure 1: (A) Swimmer plot depicting responses with magrolimab & pembrolizumab. (B) Responses in patients with prior anti-PD-1 exposure. Left, CR (DS3) in patient #5. Right, PR (DS4) in patient #3 with bulky cervical and pulmonary disease.



Supported in part by research grants from the Investigator-Initiated Studies Program of Merck Sharp & Dohme LLC and from Gilead Sciences, Inc.
The opinions expressed are those of the authors and do not necessarily represent those of Merck Sharp & Dohme LLC or Gilead Sciences, Inc.

Background: Programmed death-1 (PD-1) inhibitors are effective in relapsed/refractory classic Hodgkin lymphoma (R/R cHL) with monotherapy CRR 16%–28% and median PFS 14–15 months. Hodgkin Reed Sternberg (HRS) cells exhibit near-universal chromosome 9p24.1/CD274 (PD-L1) copy gains, a genetic basis for sensitivity to PD-1 blockade. We recently found that tumor-associated macrophages in proximity to HRS cells express SIRP-alpha, the CD47 ligand. Additionally, HRS cells express CD47, which limits macrophage-mediated phagocytosis following SIRP-alpha engagement ("don't eat me signal"). These findings provide a preclinical rationale for dual targeting of the PD-1 & CD47 immune checkpoints. In this phase II trial we assessed safety & preliminary efficacy of the anti-CD47 antibody magrolimab with pembrolizumab in R/R cHL.

Methods: Eligible patients had R/R cHL with ECOG PS0-1 & ≥2 prior therapies. Prior anti-PD-1 was permitted if ≥6 months prior. Prior allo-SCT & systemic autoimmune disease were excluded. Patients received magrolimab ramp-up during C1/C2, 45 mg/kg from C3, & pembrolizumab 200 mg each 21-day cycle. Response was assessed with PET/CT by Lugano & LYRIC criteria. Treatment continued up to 24 months or until progression, toxicity, or transplant.

Results: 8 patients have been enrolled at 2 centers. Median age was 34 years (25–59) & median prior lines of therapy were 2 (2–18). All patients were post auto-SCT. 5/8 received prior PD-1 with 40% refractory to last CPi. The ORR (3 CR, 3 PR) was 75% and 2 with SD. For PD-1 exposed patients the ORR was 60% (1 CR, 2 PR). At a median follow-up of 13 months, treatment is ongoing in 5 patients. Therapy was discontinued in 3 patients: (1) worsening radiotherapy-related mucositis, (2) G3 hepatotoxicity attributed to pembrolizumab, (3) allo-SCT in CR. Transient anemia occurred in 75% of patients (G1-2 62.5%, G3 12.5%). Other G ≥ 3 TRAEs included lymphopenia (n = 2) & increased ALT & bilirubin (n = 1). An interim safety analysis after the first 6 patients found no DLTs. There were no fatal AEs, G ≥ 3 infectious AEs, or treatment-related deaths. One patient died off study due to PD.

Conclusions: Magrolimab with pembrolizumab is well tolerated and demonstrates promising response rates in patients with R/R cHL, supporting preclinical translational data. The combination of anti-PD-1 & CD47-directed therapies warrants further investigation in R/R cHL. Correlative studies (ctDNA, tumor microenvironment) are planned.

P128: PRELIMINARY RESULTS OF THE PHASE 2 STUDY EVALUATING THE SAFETY AND EFFICACY OF PEMBROLIZUMAB (KEYTRUDA) WITH BENDAMUSTINE (TREANDA) IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA (KESTREL-01, NCT04510636)

Chathuri Abeyakoon[1], Semira Sheikh[1], Lisa Wang[1], Tomohiro Aoki[1], Sita Bhella[1], Robert Kridel[1], Vishal Kukreti[1], Anca Prica[1], Abi Vijenthira[1], Rob Laister[1], Michael Crump[1], John Kuruvilla[1]

[1]*Princess Margaret Cancer Centre*

Background: Single agent strategies have not demonstrated deep and durable responses for the majority of patients with relapsed and refractory cHL (RR-cHL) and therefore effective and well tolerated combination therapies are needed. Both pembrolizumab and bendamustine have demonstrated single agent efficacy in RR-cHL with no overlapping toxicity.

Aims: The ongoing investigator-initiated phase 2 KEsTREL-01 study aims to evaluate response, survival rates and safety of the combination of pembrolizumab and bendamustine (PB). The primary endpoint is ORR (CR and PR) and PET-CR rate for PB. Secondary endpoints include safety, tolerability and 2-year PFS and OS.

Methods: Eligible patients (pts) are >18 years with RR-cHL after standard first-line therapy containing an anthracycline, have subsequently progressed after or are not candidates for ASCT, adequate organ function and ECOG PS 0–1. Prior pembrolizumab exposure is permitted, but not prior bendamustine therapy. Treatment regimen includes pembrolizumab 200 mg IV (day 1) and bendamustine 90 mg/m^2 IV (days 1 & 2) every 21 days for up to 6 cycles. Patients achieving at least SD continue pembrolizumab monotherapy for 35 doses in total. Response is investigator-assessed by using Lugano 2014.

Results: As of 31 May 2024, 21 pts have been enrolled: median age 36 (range 18–77), ECOG PS; 0 in 16 and 1 in 5 patients, median number of prior therapies 2 (range 1–6); 2 pts prior BV, 3 pts prior pembrolizumab; 6 pts had received prior radiation. Median number of treatment cycles received was 2 (range 2–34). 15 pts have discontinued treatment; 9 to receive alternative treatment, 3 for AEs, 2 for PD and one death on study (pulmonary infection). 10 pts proceeded to ASCT (1 patient taken off study due to AE proceeded to ASCT once AE resolved). For the first 20 pts, Grade 3+ treatment-related AEs included 1 each of: hypomagnesemia, hypocalcemia, anemia, dyspnea, lung infection, pneumonitis, neutropenia, acute kidney injury, hypotension, LV systolic dysfunction, sinus bradycardia and pain. The ORR in 20 evaluable patients was 100%, with CR 70% (14) and PR 30% (6). With a median follow-up of 7 months (range 0.7–26), estimated median PFS is 16.7 months (4 events) and median OS has not been reached (3 events).

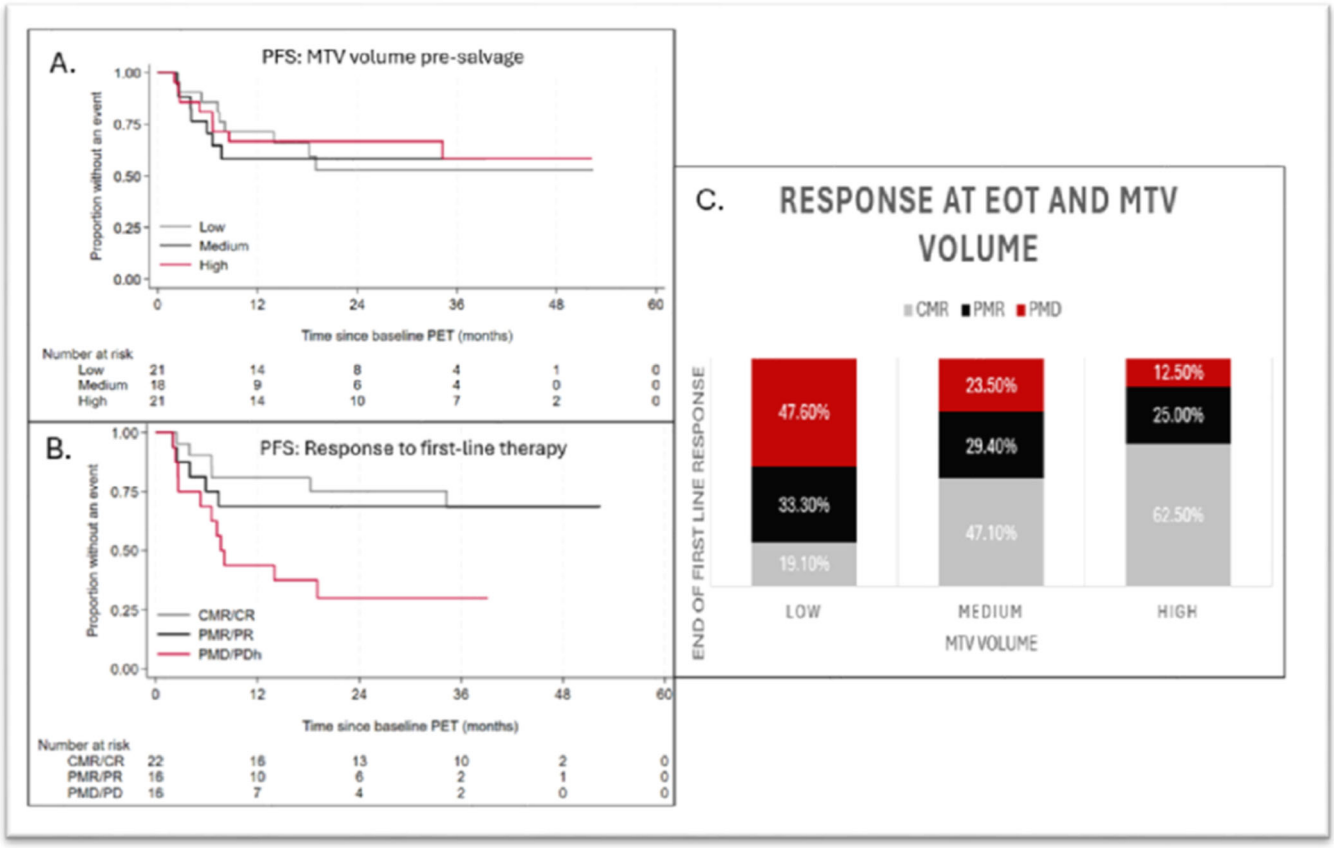
Conclusion: Preliminary results of the phase 2 KEsTREL-01 study demonstrate an encouraging CR rate and acceptable toxicity for combination PB in RR-cHL, which can successfully bridge patients to ASCT. Accrual is ongoing.

P129: RADIOMIC AND BIOLOGICAL BIOMARKERS IN RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA: AN ANALYSIS FROM THE ANIMATE STUDY

Aisling Barrett[1], Amy A. Kirkwood[2], Maria Micaela Vidal[3], Victoria Warbey[3], Cathy Burton[4], Sharon Barrans[5], Tracey Mell[6], Reuben Tooze[6], John R. Davies[6], David Westhead[6], Charlotte Tyson[2], Emma Lawrie[2], Laura Clifton-Hadley[2], Fiona Miall[7], Rifca Ledieu[8], Elizabeth H. Phillips[9], Wendy Osborne[10], Dominic Culligan[11], Nimish Shah[12], Bryson Pottinger[13], David Cunningham[14], Ruth Pettengell[15], Nicolas Martinez-Calle[16], Peter Johnson[17], Eve Gallop-Evans[18], Karl Peggs[19], Stephen Booth[20], Arzhang Ardavan[21], Sally F. Barrington[3], Graham P. Collins[1]

[1]*Oxford Cancer and Haematology Centre, Oxford, UK,* [2]*Cancer Research UK & UCL Cancer Trials Centre, University College London, UK,* [3]*King's College London and Guy's and St Thomas' PET Centre, School of Biomedical Engineering and Imaging Sciences, King's College London, UK,* [4]*Leeds Teaching Hospital NHS Trust, UK,* [5]*Haematological Malignancy Diagnostic Service, St James's Institute of Oncology, Leeds, UK,* [6]*Leeds Institute of Medical Research, University of Leeds, UK,* [7]*University of Leicester Hospitals NHS Trust, UK,* [8]*St Bartholomew's Hospital, London, UK,* [9]*Manchester University and the Christie NHS Trust, UK,* [10]*Newcastle Upon Tyne Hospitals NHS Foundation Trust, UK,* [11]*Aberdeen Royal Infirmary, UK,* [12]*Norfolk and Norwich University Hospitals UK,* [13]*Royal Cornwall Hospitals NHS Trust, UK,* [14]*Royal Marsden Hospital, Sutton, UK,* [15]*St George's Healthcare NHS Trust, London, UK,* [16]*Nottingham University Hospitals, UK,* [17]*University of Southampton, UK,* [18]*Velindre Cancer Centre, Cardiff, UK,* [19]*University College London, UK,* [20]*Royal Berkshire Hospital, Reading, UK,* [21]*Department of Physics, University of Oxford, UK*

Figure 1: (A) PFS does not correlate with MTV volume before salvage treatment. (B) PFS correlates with response to first-line therapy as determined by the end of treatment scan. (C) MTV volume as per response to first-line therapy.



Background: The ANIMATE study was a single arm phase II trial in classical Hodgkin lymphoma (cHL) patients fit for transplantation. It was designed to assess response to single-agent nivolumab in patients responding incompletely to first-line relapse chemotherapy. Patients were registered at start of salvage therapy ($n = 78$), with 50% achieving complete metabolic response (CMR) and 31 incomplete responders receiving nivolumab. The overall response (partial metabolic response (PMR) and CMR) to 4–8 doses of nivolumab was 41.9% (80% CI: 29.7%–55%).

Traditionally, prediction of prognosis at cHL relapse has relied on baseline clinical and laboratory features as well as positron emission tomography (PET) response to initial salvage therapy. In newly diagnosed cHL functional radiomic markers are associated with survival. We assessed radiological and biological biomarkers in ANIMATE with the aim of refining these tools in the era of checkpoint inhibition.

Methods: PET radiomic features (metabolic tumour volume [MTV], total lesion glycolysis and disease dissemination) were assessed at first progression or relapse. Association with PET response and 2-year progression-free survival (PFS) was explored using Logistic regression, Kaplan-Meier survival analysis, Cox regression and survival ROC.

Results: PET features at first progression were neither significantly associated with response nor PFS including MTV pre-salvage (ROC AUC 0.41). We explored this further by assessing patients by PET response after first-line treatment. Patients with CMR or PMR at end of first-line treatment had a better PFS from the time of relapse than patients with progressive metabolic disease ($p = 0.013$ for trend) but responding patients also had higher MTV ($p = 0.019$), probably due to later detection of relapse. This unanticipated finding of higher MTV in patients with better PFS suggests that MTV as a prognostic factor must be considered carefully in the context of relapsed/refractory (R/R) studies.

Radiomic analysis of PET0 for nivolumab-treated patients did not reveal any predictive value for response to nivolumab or PFS albeit with small patient numbers ($n = 30$).

Data will be presented on the association of PDL1 expression and 9p24 copy number with response to salvage chemotherapy and nivolumab.

Conclusion: Increased MTV is not associated with poorer outcomes in this cohort of R/R cHL patients. Further analysis of radiomics in R/R patients including those treated with checkpoint inhibitors is warr

P130: RESPONSE AND SURVIVAL RESULTS FROM A PHASE II TRIAL OF PEMBROLIZUMAB AND ENTINOSTAT IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA

Robert Stuver[1], Santosha Vardhana[1], Nivetha Ganesan[1], Neena Mahajan[1], Alexander Boardman[1], Philip Caron[1], Kevin David[1], Zachary Epstein-Peterson[1], Lorenzo Falchi[1], Paola Ghione[1], Paul Hamlin[1], Francisco Hernandez-Ilizaliturri[2], Steven Horwitz[1], Andrew Intlekofer[1], William Johnson[1], Reem Karmali[3], Anita Kumar[1], Jennifer Lue[1], Efrat Luttwak[1], Ariela Noy[1], Colette Owens[1], Maria Palomba[1], Gilles Salles[1], Heiko Schoder[1], David Sermer[4], Raphael E. Steiner[1], Pallawi Torka[1], Andrew Zelenetz[1], Gottfried Von Keudell[5], Alison Moskowitz[1]

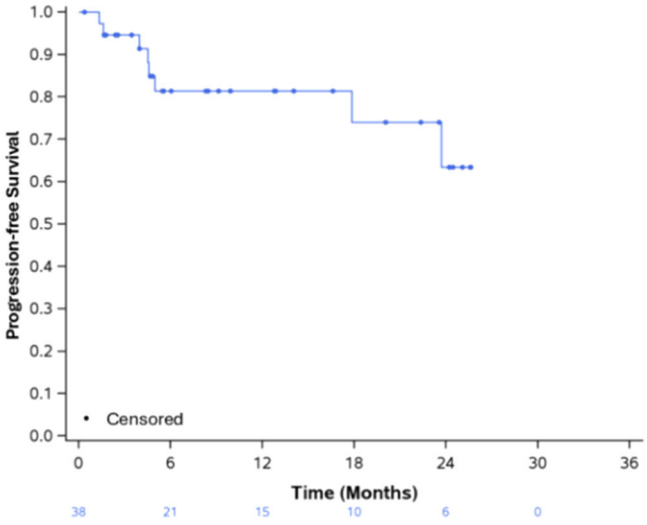
[1]Memorial Sloan Kettering Cancer Center, [2]Roswell Park Cancer Institute, [3]Northwestern, [4]AstraZeneca, [5]Beth Israel Deaconess Medical Center

Figure 1: At left, response rates stratified by prior anti-PD1 exposure and sensitivity. At right, progression-free survival for the entire cohort.

Response to pembrolizumab-entinostat.

Cohort	N	CR rate	ORR
Total population	38[1]	47%	63%
Anti-PD1 exposure			
Prior anti-PD1	28	36%	50%
Anti-PD1 naïve	10	80%	100%
Prior anti-PD1 response[2]			
Sensitive	5	40%	40%
POD	22	36%	55%
POD as last line	16	31%	44%

CR, complete response; ORR, objective response rate; POD, progression of disease; PD1, programmed cell death protein 1; POD, progression of disease.
[1]Note that 39 patients enrolled. 1 patient was not evaluable for efficacy.
[2]Note that 1 patient with prior unknown response to anti-PD1 therapy is omitted.



Introduction: Targeting PD-1 is a highly effective strategy in HL and is rapidly being incorporated into upfront regimens. Strategies for relapsed or refractory (R/R) disease remains an unmet need, especially in those with prior anti-PD1 exposure. We tested whether histone deacetylase (HDAC) inhibition could restore anti-PD-1 sensitivity.

Methods: Patients with R/R HL after ≥2 systemic therapies were eligible. Prior therapy with an HDAC inhibitor and/or anti-PD1 therapy was allowed. Treatment was pembrolizumab 200 mg every 21 days plus entinostat 5–7 mg on days 1, 8 and 15 of each 21-day cycle. Treatment was continued until progression, unacceptable toxicity, or death, for a max of 35 cycles. If one of the study drugs was discontinued, the other could be continued. The primary endpoint was 12-month progression-free survival (PFS). PFS was measured from treatment initiation to progression or death, with censoring if patients completed treatment (without progression), received transplant or radiation, or stopped treatment due to an adverse event or clinical decision. The null hypothesis was a 12-month PFS of 40% versus a 12-month PFS of 60%.

Results: Thirty-nine patients enrolled. The median number of prior therapies was 5 (range: 2–18). Prior therapies included brentuximab vedotin (82%), anti-PD1 (74%), HDAC inhibitor (10%), and/or autoHCT (67%). Twenty-two patients (56%) had prior progression of disease (POD) to anti-PD1, including 16 (41%) with POD to anti-PD1 as the last line of therapy prior to enrollment.

Of 38 evaluable patients, the complete response rate (CRR)/ORR was 47% and 63%, respectively. Stratifying patients by prior exposure and response to anti-PD1, CRR/ORR was as follows: (1) prior anti-PD1 at any timepoint: 36% (10/28)/50% (14/28); (2) anti-PD1 naïve: 80% (8/10)/100% (10/10); (3) anti-PD1 sensitive: 40% (2/5)/40% (2/5); (4) prior POD to anti-PD1: 36% (8/22)/55% (12/22), (5) POD to anti-PD1 as last line of therapy: 31% (5/16)/44% (7/16). The 12-month PFS was 81% (95% CI 69–96) (Figure). The median PFS was not reached. The median duration of response was 24 months (95% CI 10-NR).

Adverse events (AE) of ≥ grade 3 occurred in 30 (77%) patients. The most common AEs of ≥ grade 3 were neutropenia (n = 17, 44%) and thrombocytopenia (n = 11, 28%).

Conclusions: Pembrolizumab and entinostat showed high response rates and encouraging PFS in R/R HL, including in patients with prior anti-PD1 antibody exposure.

P131: RESULTS OF ALLOGENEIC STEM CELL TRANSPLANTATION IN HODGKIN LYMPHOMA–LONG TERM EXPERIENCE

Zuzana Rusináková[1], Andrej Vranovský[1], Miriam Ladická[1], Silvia Cingeľová[1], Ladislav Sopko[2], Eva Bojtárová[2], Eva Mikušková[1], ľuboš Drgoňa[1]

[1]Department of Oncohematology, National Cancer Institute and Faculty of Medicine, Comenius University, Bratislava, Slovakia, [2]Department of Hematology and Transfusiology, University Hospital Bratislava and Faculty of Medicine, Comenius University Bratislava, Slovakia

Goal: Retrospective analysis of allogeneic stem cell transplantation (allo-SCT) in relapsed/refractory Hodgkin lymphoma (R/R HL).

Methods: Retrospective analysis of patients who underwent allo-SCT between the years 2013–2023 at 2 transplant centers. Data were calculated using NCSS software. The probabilities of OS and PFS were estimated using the Kaplan–Meier method and Cox regression analysis.

Results: Among 32 patients with a median age of 42 years (22–52) were 19 men (60%) and 13 (40%) women. The median time from diagnosis to transplantation was 904 days. All patients received prior autologous transplant and brentuximab vedotin, 8 patients also nivolumab. Ten (31%) patients were in complete remission (CR) at the time of transplant. Twelve patients underwent matched related allo-SCT and 20 matched unrelated transplant. The preferred conditioning regimen was fludarabine and melphalan ±ATG (29 patients). The median time to neutrophil engraftment was 18 days, 13 days for platelets. All patients achieved complete chimerism at day 30. NRM at day 100 was 3%. The cumulative incidence of acute GVHD was 59%; 2 patients had grade III–IV acute GVHD. Fifteen out of 30 evaluated patients developed chronic GVHD. According to the NIH scoring system 3 had NIH I, 7 NIH II and 5 NIH III. CR was achieved in 23 patients at day 100 after allo-SCT. Fourteen (43%) of them are in ongoing CR (median duration of follow-up 7.2 years; 0.7–8.7 years). One patient in remission died due to infectious complications. Eight patients relapsed after transplant. Nine patients did not achieve remission after allo-SCT. Of 17 relapsed/refractory patients after allo-SCT, 9 died due to the progression of the disease, 1 is alive with active lymphoma, and 7 are in remission after the following treatments: 3x nivolumab, 1x brentuximab vedotin+bendamustine, 1x radiotherapy,1x anti-CD20 monoclonal antibody, 1x 2nd haplo SCT). With a median duration follow-up of 6 years, 22 patients are alive (20 in ongoing CR). Five-year PFS is 49% with a median of 4,5 years and 5-year OS is 69%, the median was not reached. The donor type (related vs. unrelated) had no impact on PFS ($p = 0.5827$) and OS ($p = 0.0983$). The presence of cGVHD was not associated with worse OS ($p = 0.7217$). CR before ($p = 0.0062$) and after transplant ($p = 0.0000$) was statistically significant for better OS.

Conclusion: R/R HL remains a therapeutic challenge despite the newer treatment options. Anal

P132: RICHTER TRANSFORMATION OF CLL TO HODGKIN LYMPHOMA

Mária Maco[1], Heidi Mocikova[1], Markéta Kalinová[2], Zuzana Prouzová[3], Patrik Flodr[4], Anna Panovská[5], Tomáš Arpáš[5], Martin šimkovič[6], Tomáš Kozák[7]

[1]University Hospital Kralovske Vinohrady-Department of Haematology, Third Faculty of Medicine, Charles University Prague, [2]University Hospital Kralovske Vinohrady-Department of Molecular Biology and Genetics, Third Faculty of Medicine, Charles University Prague, [3]University Hospital Kralovske Vinohrady-Department of Pathology, Third Faculty of Medicine, Charles University Prague, [4]University Hospital and Faculty of Medicine Palacky University, Department of Clinical and Molecular Pathology, Olomouc, [5]Department of Internal Medicine, Haematology and Oncology, University Hospital Brno and Faculty of Medicine, Masaryk University Brno, [6]University Hospital and Faculty of Medicine, 4th Department of Internal Medicine–Haematology, Hradec Kralove, [7]University Hospital Kralovske Vinohrady- Department of Haematology, Third Faculty of Medicine, Charles University Prague

Background: Richter transformation of chronic lymphocytic leukemia (CLL) to Hodgkin lymphoma (HL) is a very rare phenomenon which accounts for less than 1% of all cases of transformation of CLL to high-grade lymphomas. Particularly challenging is the question, whether we are dealing with the clonal evolution of one disease or two distinct lymphomas. The answer lies in assessment of clonality by determining the specific IgHV rearrangement of the CLL cells and then comparing it with the DNA from the isolated HRS cells in the aim of finding the identical rearrangement. The goal of the study was to assess clonality of CLL transformed to HL in our cohort of patients.

Methods: The DNA isolated from the CLL cells was obtained either from the lymph node biopsies, trephine biopsies or peripheral blood. The Hodgkin and Reed-Sternberg cells (HRS) from HL biopsies were isolated by technique of laser microdissection. The screening of clonal Ig rearrangement was performed by a PCR method according to the certified protocol Biomed-2. The protocol enables detection of IgH, IgK and IgL clonality and the methodology has a detection threshold the presence of at least 10%–15% of clonal cells in a polyclonal background. In the case of detection of a clonal rearrangement, we sequenced the given rearrangement in order to determine the exact sequence composition.

Results: We identified 29 patients with Richter transformation of CLL to HL between 2008 and 2024 and data of IgH clonality re-arrangement on 20 patients will be presented.

At initial diagnosis of CLL patients 0 had TP53 mutation or del 17p and 4 had unmutated IgHV. Out of 29 patients 6 had mixed cellularity histology and 4 had nodular sclerosis histology. EBV positivity was proved in 1 patient. Currently, out of 13 patients with completed analysis we detected identical IgH rearrangement in two patients and thus proved clonal relation between CLL and HL. Clonality analysis is ongoing in seven patients. Quality and quantity of available DNA either from CLL or HRS cells vary significantly based on the source of histology, preservation medium, time duration since the date of diagnosis and obtaining sufficient DNA material from scarce HRS cells.

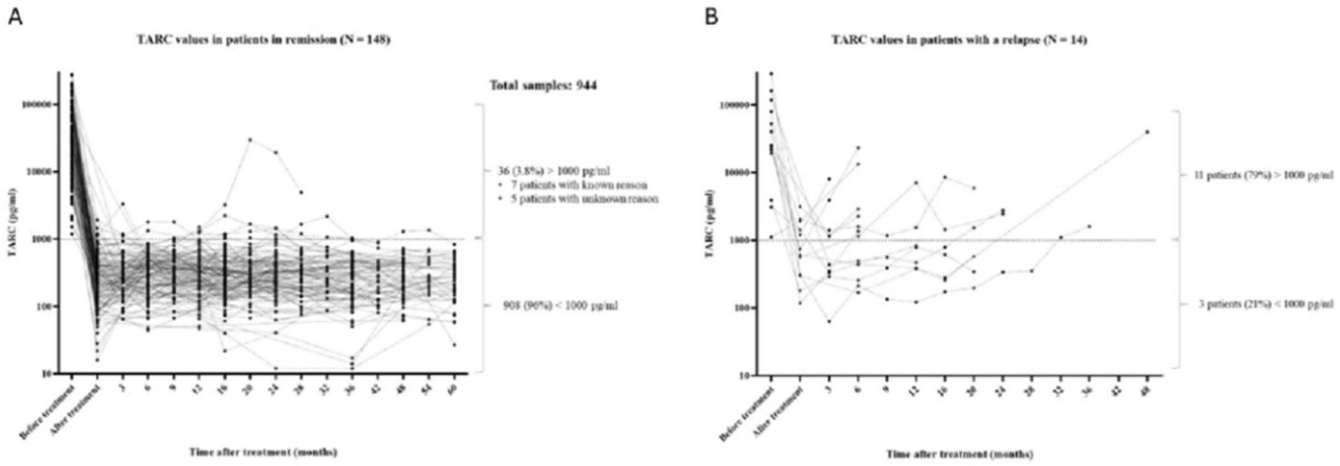
Conclusion: Understanding the biology of Richter transformation to Hodgkin lymphoma is crucial to personalize the treatment and improve patient's survival.

P133: SERUM TARC MONITORING DURING ROUTINE FOLLOW-UP LEADS TO EARLY DIAGNOSIS OF RELAPSE IN CLASSIC HODGKIN LYMPHOMA

Sophie Teesink[1], Lydia Visser[1], Kylie Keijzer[2], Bart-Jan Kroesen[2], Marcel Nijland[2], Anke Van Den Berg[1], Arjan Diepstra[1], Wouter J. Plattel[2]

[1]Department of Pathology and Medical Biology, University Medical Center Groningen, [2]Department of Hematology, University Medical Center Groningen

Figure 1: (A) TARC values in patients in remission (*N* = 148). (B) TARC values in patients with a relapse (*N* = 14). Last timepoint represent time of relapse diagnosis.



Background: Thymus and Activation Regulated Chemokine (TARC, or CCL-17) is a chemokine that is specifically excreted by Hodgkin Reed-Sternberg cells in classic Hodgkin lymphoma (cHL). TARC is excreted in extremely high quantities that result in elevated serum levels in ~90% of cHL patients at diagnosis. TARC levels correlate with metabolic tumour volume (MTV) and elevated levels can precede clinical symptoms and diagnosis up to 6 years. The aim of the current study was to evaluate whether serial serum TARC measurements during routine follow-up of cHL patients achieving a complete response after first-line treatment enables early detection of relapse.

Methods: Our cohort included 162 patients with cHL who were treated at the University Medical Centre Groningen between 2005 and 2022 and who achieved a complete metabolic response. Serum samples were collected before, during and at the end of treatment and during routine follow-up every 3–6 months for up to 5 years post-treatment. TARC levels were analysed either retrospectively (blinded to disease status) or prospectively using routine diagnostic procedures by ELISA. TARC levels >1000 pg/mL were defined as positive, as previously described. MTV was quantified on FDG-PET scans at relapse using 3D Slicer with MUST-segmenter and SUV4.0 as threshold and was correlated with TARC.

Results: At a median follow-up of 36 months, 148/162 patients (91%) remained in remission. A total of 944 samples were collected of these patients. 96% of these samples were TARC negative, while 3.8% were elevated (Figure 1A). Most of these were single time-point elevations and were related to eczema or other recognizable immune conditions. Of the 14 patients that were diagnosed with a histologically confirmed relapse, 11 patients (79%) had elevated TARC levels. TARC elevation preceded clinical symptoms and was the first sign of relapse in 9/11 (82%) of these cases. (Figure 1B). Sensitivity, specificity, positive and negative predictive value of TARC for cHL relapse were 79%, 92%, 48% and 98% respectively. At relapse, TARC levels strongly correlated with MTV (Spearman $r = 0.70$, $p = 0.025$).

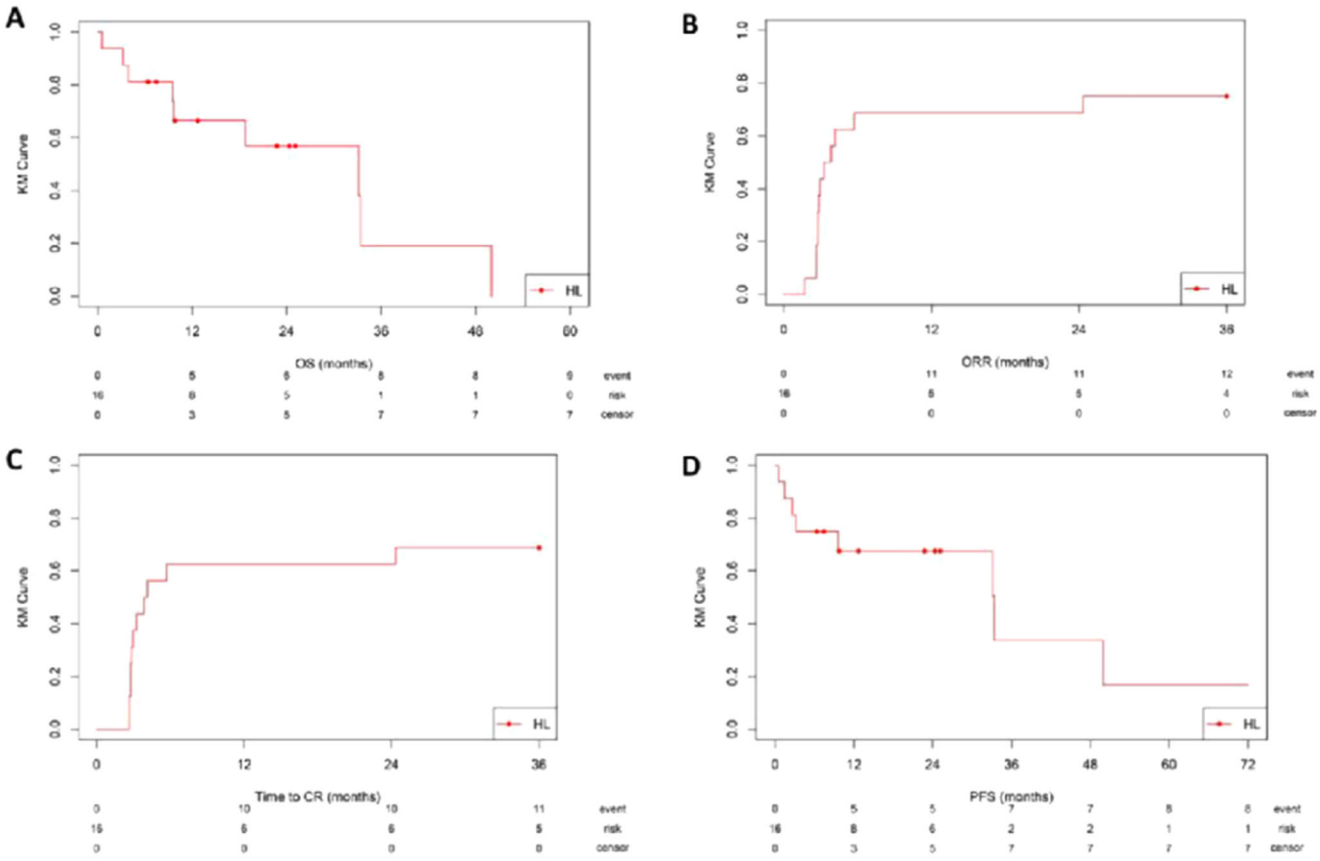
Conclusion: In conclusion, integrating serum TARC monitoring into routine follow-up results in biochemical detection of relapse in 79% of cases, often preceding clinical symptoms. TARC levels at relapse strongly correlate with MTV. We suggest integrating serum TARC monitoring during routine follow-up of cHL patients to enable early detection of relapse.

P134: THE BELIEVE STUDY: EFFECTIVENESS AND SAFETY FOR RE-TREATMENT WITH BRENTUXIMAB-VEDOTIN IN RELAPSED/REFRACTORY (R/R) HODGKIN LYMPHOMA: A RETROSPECTIVE MEDICAL CHART REVIEW IN SPAIN. NCT:04 998 331

Anna Sureda-Balari[1], Ramón García-Sanz[2], Eva Domingo-Domènech[1], Francisco J. Capote[3], Antonio Gutierrez[4], Antonia Rodríguez Izquierdo[5], Marta Grande[6,7], Lourdes Baeza-Montañez[6]

[1]Institut Catala D'oncologia, Hospital Duran i Reynals. IDIBELL. L'Hospitalet de Llobregat, Barcelona, Spain, [2]Hospital Universitario Gregorio Marañon, Madrid, Spain, [3]Hospital Universitario Puerta del Mar, Cádiz, Spain, [4]Hospital Son Espases IdISBa, Palma de Mallorca, Spain, [5]Hospital Universitario 12 de Octubre, Madrid, Spain, [6]Medical Department, Takeda Farmacéutica España S.A, Madrid, Spain, [7]Universidad de Alcalá, Alcalá de Henares, Madrid, Spain

Figure 1: Kaplan–Meier estimates of (A) Overall Survival, (B) time to OR, (C) CR and (D)PFS in cHL patients at retreatment with Brentuximab vedotin.



Introduction: Brentuximab vedotin (BV) is a CD30-directed antibody-drug conjugate. The efficacy and clinical benefit of BV in patients with CD30+ R/R malignancies has been shown in pivotal studies. The aim of this study was to describe effectiveness/safety of BV retreatment in R/R CD30+ patients in Spain.

Methods: A noninterventional, retrospective chart review was conducted in 30 Spanish sites (collection: 2014–2022). Adult patients with CD30+ malignancies who were treated with BV (evidence of objective response, OR), and having received ≥2 doses of BV as retreatment were included. Patients were followed up to ≥6 months, treatment discontinuation due to death, or toxicity. The primary objectives: to assess the safety and effectiveness of BV retreatment. In this communication we will present the data related to cHL patients.

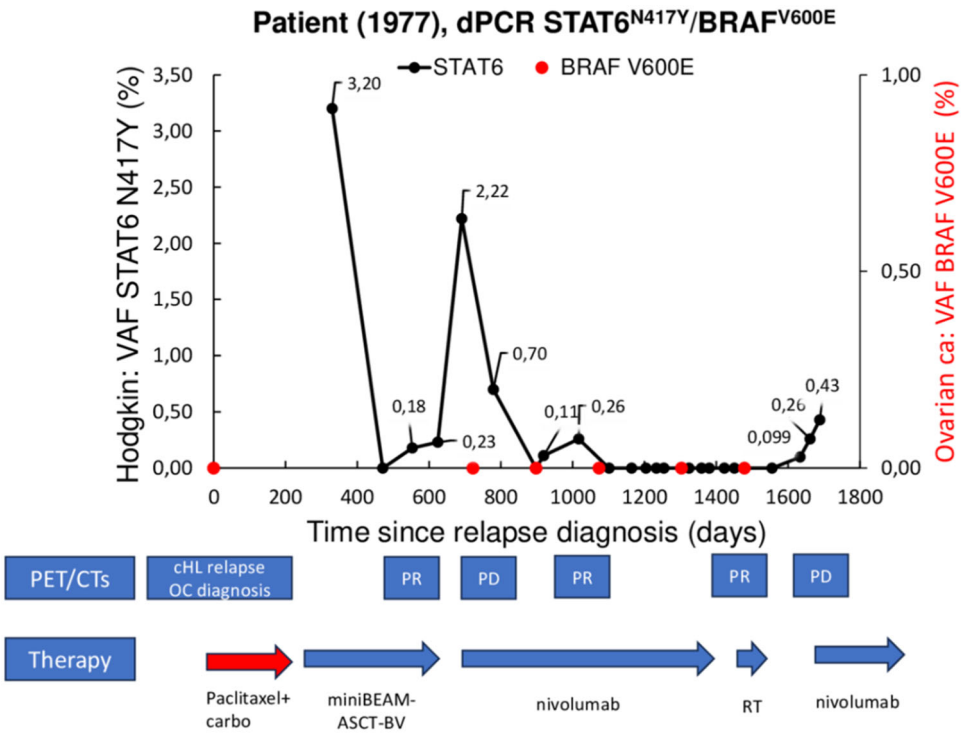
Results: Of 43 patients included, 16 were cHL. At BV retreatment more than 50% of patients had advanced disease (2 Stage III, and 5 Stage IV). The median age was 36 (18–62) years, 56.2% males, and 90% had ECOG PS, grade 0–1. Most patients, 13 (81.2%), received treatments between the first course of BV and BV retreatment with a median number of lines: 1 (1–5). After the first treatment with BV: 4 patients underwent an autologous transplant, 1 underwent 2 autologous in tandem and 2 patients had an allogenic. After retreatment 4 patients underwent 1 allogenic. ORR was 75%; 68.8% CR, 1 (6.2%) achieved PR and progression was observed in 2 patients (12.5%). Median time to achieve CR: 3 months. The median PFS: 9.6 months (0.5–77.5) and median OS was 33.1 (0.5–50) months. 9 (56%) patients died mainly due to progression (Figure 1). The median number of cycles during the first treatment with Bv: 4 (2–16) and during retreatment: 4.5 (2–18). Seven (53.8%) experienced adverse events (AEs) related to BV retreatment, mainly peripheral sensory neuropathy. Severe AEs were reported in 2 patients (12.5%), peripheral motor and sensory neuropathy. No Grade 5 events were reported during retreatment.

Conclusions: The BELIEVE study is the first real word evidence study in Spain that assesses the role of BV as retreatment. Safety results were manageable with dose modification or interruption. BV retreatment seems to be a promising and tolerable treatment alternative for cHL patients.

P135: THE COINCIDENCE OF RELAPSED HODGKIN LYMPHOMA AND OVARIAN CARCINOMA AS A ROLE-MODEL FOR CTDNA MRD MONITORING

Veronika Hanáčková[1], Jan Grohmann[1], Patrik Flodr[2], Tomáš Papajík[1], Jana Navrátilová[1], Vít Procházka[1]

[1]*Dept. of Hemato-Oncology, University Hosp Olomouc,* [2]*Department of Clinical and Molecular Pathology, Palacký University Olomouc and University Hospital Olomouc*



Background: The co-occurrence of classic Hodgkin lymphoma (cHL) with gynecologic neoplasms is a rare event that can pose challenges for diagnosis, management, and treatment monitoring. We present a case of a woman who was simultaneously diagnosed with relapsed cHL and ovarian carcinoma, proving the usefulness of the long-term ctDNA monitoring of both malignancies in routine practice.

Case Summary: A 42-year-old woman in remission from intermediate-stage nodular-sclerosis cHL for 7 years was referred in August 2019 with enlarged axillary lymph nodes (LNs). PET/CT surprisingly detected an asymptomatic pelvic tumor mass. Extensive surgical tumor resection revealed an advanced serous OC (FIGO IIIA, pT3aN0M0R0). Concurrently, axillary LNs biopsy confirmed cHL relapse. NGS panel identified MRD markers from the paraffin-embedded tissues from the OC (BRAF V600E mutation) and the cHL (STAT6 gene, N417Y/N421S). Those targets were followed using ctDNA throughout the disease course (Figure 1).

The diagnosis of OC has been prioritized, and the patient received adjuvant chemotherapy with 4 cycles of paclitaxel with carboplatine out of planned 6 (terminated early in January 2020 for intolerance). The patient achieved CR of OC with persistent supradiaphragmatic lymph node enlargement and skeletal involvement (July 2020, cHL CS IVEA). The patient was given 2 cycles of miniBEAM and subsequent autologous stem cell rescue, with very good PR (December 2020), followed by the maintenance therapy of brentuximab-vedotin. After 8 cycles of BV (July 2021), pt progressed and started nivolumab (flat dose of 240 mg) a month later. PET/CT scan after 12 doses of nivolumab proved PR; next PET/CT scan performed after one year of nivolumab showed residual inguinal and axillar LNs - involved-site RT (30 Gy) of the inguinal LNs was indicated for possible abscopal effect in October 2022. Following PET/CT scan in March 2023, regression in all localities except the axillary nodes was found. Nivolumab (36th dose) was terminated on August 2023, and the patient was indicated to be PET-guided IF RT (36 Gy) of the small axillary LNs. She remained in the CR of OC.

Conclusion: In our case, we discussed the co-occurrence of two clonally unrelated malignancies in a single patient being eventually treated with the same drug (nivolumab) and followed using cell-free DNA.

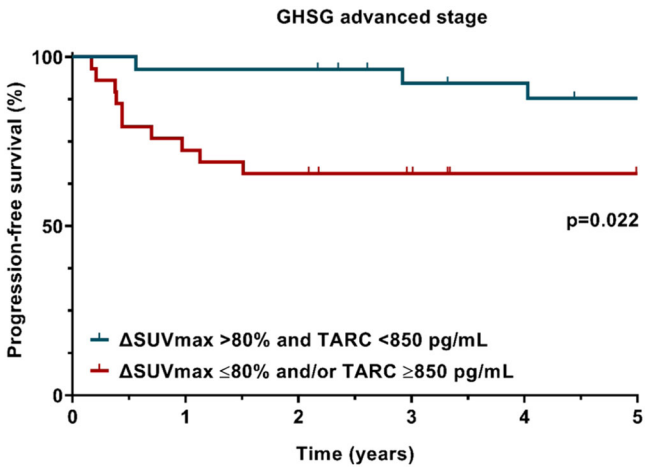
Acknowledgement: Supported by MZ ČR – RVO (FNOl, 00 098 892), AZV NU22-03–0018.

P136: THE PROGNOSTIC VALUE OF ΔSUVMAX AND TARC IN THE FIRST-LINE TREATMENT OF CLASSICAL HODGKIN LYMPHOMA

László Imre Pinczés[1], Dávid Tóthfalusi[1], Boglárka Dobó[1], Sándor Barna[2], Bence Farkas[2], Ildikó Garai[2], Zsolt Fejes[3], Béla Nagy Jr.[3], árpád Illés[1], Zsófia Miltényi[1]

[1]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, [2]Division of Nuclear Medicine and Translational Imaging, Department of Medical Imaging, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, [3]Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

Figure 1: PFS of patients with advanced stage disease (GHSG), with separate biomarker and PET/CT profile.



Background: In classical Hodgkin lymphoma (cHL), early risk stratification and response assessment are the cornerstones of therapy. The advanced interpretation of positron emission tomography/computed tomography (PET/CT) results and the inclusion of other biomarkers may provide a unique approach to the response assessment in cHL.

Aim: Our aim was to investigate the prognostic value of the change in standardized uptake value (ΔSUVmax) and thymus and activation-regulated chemokine (TARC) to predict disease progression during the first-line treatment of cHL.

Methods: We retrospectively analysed adult patients with cHL, treated with a curative intent, standard therapy. The analysed PET/CT assessments were performed at baseline and after 2 cycles of first-line therapy. ΔSUVmax was calculated with the following formula: (baseline SUVmax–interim SUVmax)/baseline SUVmax × 100. TARC levels were measured by an immunoassay. Cut-off values were determined by the receiver operating characteristics (ROC) analysis. Survival analysis was performed by the Kaplan–Meier method via the log-rank test.

Results: Altogether, 81 patients had sufficient data for analysis. The presence of a ΔSUVmax of >80%, and a TARC level of ≤850 pg/mL after 2 cycles of therapy were independent prognostic factors for longer progression-free survival (PFS) ($p = 0.045$ and $p = 0.017$, respectively). The PFS of patients without any of these two risk factors differed from the patients positive for one or both parameters ($p = 0.03$). According to the German Hodgkin Study Group's (GSHG) risk group classification system, patients with an advanced stage cHL had a better PFS if none of the risk factors were present ($p = 0.019$). There was no difference in PFS between patients with a Deauville Score (DS) of 1–2, with the presence of any of the risk factors, and patients with DS 3. This group of patients experienced an inferior PFS compared to DS 1–2 patients without any risk factors ($p = 0.04$) and a superior PFS versus patients with a DS of 4–5 ($p = 0.003$).

Conclusion: Interim PET/CT response should be discussed in the light of ΔSUVmax and TARC values. Determining patient populations at elevated risk of shorter PFS should be addressed adequately in everyday practice. Our results can draw attention to patients requiring more rigorous monitoring.

P137: UPDATED ANALYSIS OF A PHASE 1/2 STUDY EVALUATING PEMBROLIZUMAB (PEMBRO) PLUS THE ANTI–LYMPHOCYTE-ACTIVATION GENE 3 (LAG-3) ANTIBODY FAVEZELIMAB FOR ANTI–PD-1–NAIVE RELAPSED OR REFRACTORY (R/R) CLASSICAL HODGKIN LYMPHOMA (CHL)

Nathalie A. Johnson[1], David Lavie[2], Peter Borchmann[3], Gareth P. Gregory[4], Alex F. Herrera[5], Leonard Minuk[6], Vladan Vucinic[7], Philippe Armand[8], Abraham Avigdor[9], Robin Gasiorowski[10], Yair Herishanu[11], Colm Keane[12], John Kuruvilla[13], Rachel Marceau West[14], Pallavi Pillai[14], Rushdia Yusuf[14], John Timmerman[15]

[1]Jewish General Hospital, Montréal, QC, Canada, [2]Hadassah Medical Center, Jerusalem, Israel, [3]University Hospital Cologne, Cologne, Germany, [4]School of Clinical Sciences at Monash Health, Monash University, Melbourne, VIC, Australia, [5]City of Hope, Duarte, CA, USA, [6]CancerCare Manitoba and University of Manitoba, Winnipeg, MB, Canada, [7]Leipzig University Medical Center, Clinic and Polyclinic for Hematology, Cell Therapy and Hemostaseology, Leipzig, Germany, [8]Dana-Farber Cancer Institute, Boston, MA, USA, [9]Sheba Medical Center, Ramat Gan, and School of Medicine, Tel Aviv University, Tel Aviv, Israel, [10]Concord Hospital, University of Sydney, Concord, NSW, Australia, [11]Tel Aviv Sourasky Medical Center, Tel Aviv-Yafo, Israel, [12]Princess Alexandra Hospital, Brisbane, QLD, Australia, [13]Princess Margaret Cancer Centre, Toronto, ON, Canada, [14]Merck & Co., Inc., Rahway, NJ, USA, [15]UCLA Medical Center, Los Angeles, CA, USA

Background: Dual blockade of PD-1 and the immune checkpoint receptor LAG-3 shows promise as a treatment option for patients (pts) with R/R cHL. In a multicohort phase 1/2 study (NCT03598608), pembro + the anti–LAG-3 antibody favezelimab demonstrated acceptable safety and sustained antitumor activity in pts with R/R cHL who were previously naïve to PD-1 inhibitor therapy (cohort 1). Here, we present updated results with additional follow-up for pts from cohort 1.

Methods: Eligible pts (aged ≥18 y) had R/R cHL and were ineligible for autologous stem cell transplantation (ASCT), whose disease failed to respond to or progressed after ASCT, or who did not respond to salvage chemotherapy. Pts in cohort 1 were naïve to prior PD-1 inhibitor therapy. The study comprised a safety lead-in to determine the recommended phase 2 dose (RP2D) followed by an efficacy expansion phase. In

safety lead-in, all pts received pembro 200 mg IV Q3W+favezelimab 200 mg starting dose with escalation to 800 mg IV Q3W per a modified toxicity probability interval method. In efficacy expansion, all pts received pembro 200 mg Q3W+favezelimab at the RP2D of 800 mg Q3W for ≤35 cycles. Primary end point: safety and tolerability. ORR per IWG 2007 criteria by investigator review was a secondary end point. Exploratory end points included DOR and PFS per IWG 2007 criteria by investigator review and OS. Data cutoff was February 22, 2024.

Results: Cohort 1 included 30 pts. Median time from first dose to data cutoff was 43.2 mo (range, 35.7–54.9). Treatment-related adverse events (TRAEs) occurred in 27 pts (90%; grade 3 or 4 in 7 pts [23%]). TRAEs led to treatment discontinuation in 5 pts (17%). No pts died due to TRAEs. AEs of clinical interest occurred in 20 pts (67%); 3 pts (10%) had grade 3 events (colitis, pneumonitis, severe skin reaction); 1 pt (3%) had grade 4 hepatitis. ORR was 83% (95% CI: 65%–94%; 11 CR; 14 PR). Median DOR was 17.0 mo (range, 2.6–33.3+). Median PFS was 19.4 mo (95% CI: 9.5–28.5); median OS was not reached (95% CI: 46.9 mo to not reached).

Conclusion: With additional follow-up, pembro+favezelimab continued to demonstrate manageable safety and sustained antitumor activity in pts with anti–PD-1–naive R/R cHL. These findings support further investigation of pembro + favezelimab.

P138: UPDATED ANALYSIS OF A PHASE 1/2 STUDY EVALUATING PEMBROLIZUMAB (PEMBRO) PLUS THE ANTI–LYMPHOCYTE-ACTIVATION GENE 3 (LAG-3) ANTIBODY FAVEZELIMAB FOR HEAVILY PRETREATED ANTI–PD-1–REFRACTORY CLASSICAL HODGKIN LYMPHOMA (CHL)

John Timmerman[1], David Lavie[2], Nathalie A. Johnson[3], Abraham Avigdor[4], Peter Borchmann[5], Charalambos Andreadis[6], Ali Bazargan[7,8], Gareth P. Gregory[9], Colm Keane[10], Inna Tzoran[11], Vladan Vucinic[12], Pier Luigi Zinzani[13,14], Rachel Marceau West[15], Pallavi Pillai[15], Rushdia Yusuf[15], Alex F. Herrera[16]

[1]UCLA Medical Center, Los Angeles, CA, USA, [2]Hadassah Medical Center, Jerusalem, Israel, [3]Jewish General Hospital, Montréal, QC, Canada, [4]Sheba Medical Center, Ramat Gan, and School of Medicine, Tel Aviv University, Tel Aviv, Israel, [5]University Hospital Cologne, Cologne, Germany, [6]UCSF, San Francisco, CA, USA, [7]University of Melbourne, Melbourne, VIC, Australia, [8]St Vincent's Hospital, Fitzroy, VIC, Australia, [9]School of Clinical Sciences at Monash Health, Monash University, Melbourne, VIC, Australia, [10]Princess Alexandra Hospital, Brisbane, QLD, Australia, [11]Rambam Health Care Campus, Haifa, Israel, [12]Leipzig University Medical Center, Clinic and Polyclinic for Hematology, Cell Therapy and Hemostaseology, Leipzig, Germany, [13]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli," Bologna, Italy, [14]Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy, [15]Merck & Co., Inc., Rahway, NJ, USA, [16]City of Hope, Duarte, CA, USA

Background: The immune checkpoint receptor LAG-3 may contribute to anti–PD-1 resistance in patients (pts) with relapsed or refractory (R/R) cHL. In a multicohort phase 1/2 study (NCT03598608), pembro + the anti–LAG-3 antibody favezelimab demonstrated manageable safety and promising antitumor activity in pts with heavily pretreated cHL whose disease progressed on or after anti–PD-1 therapy (cohort 2). Updated results with additional follow-up from cohort 2 are presented.

Methods: Eligible pts (aged ≥18 y) had R/R cHL and had no response to or whose disease progressed after autologous stem cell transplantation (ASCT), were ineligible for ASCT, or had no response to salvage chemotherapy. Pts in cohort 2 had disease progression after ≥2 doses of anti–PD-1–based therapy and within 12 wks of last dose. Study comprised a safety lead-in followed by efficacy expansion. In safety lead-in, all pts received pembro 200 mg IV Q3W+favezelimab 200 mg starting dose with escalation to 800 mg IV Q3W per a modified toxicity probability interval design. In efficacy expansion, pts received pembro 200 mg Q3W+favezelimab at the RP2D of 800 mg Q3W for ≤35 cycles. Primary end point: safety. ORR per IWG 2007 criteria by investigator review was a secondary end point. Exploratory end points included DOR and PFS per IWG 2007 criteria by investigator review and OS. Data cutoff was February 22, 2024.

Results: Cohort 2 included 34 pts. Median time from first dose to data cutoff was 47.0 mo (range, 26.7–61.1). Treatment-related adverse events (TRAEs) occurred in 28 pts (82%; grade 3 or 4 in 6 pts [18%]). TRAEs led to treatment discontinuation in 6 pts (18%). No pts died due to TRAEs. AEs of clinical interest occurred in 17 pts (50%); 2 (6%) had grade 3 events (encephalitis, hepatitis) and 1 (3%) had grade 4 type 1 diabetes mellitus. ORR was 29% (95% CI: 15–48%; 3 CR; 7 PR). Median DOR was 21.9 mo (range, 0.0+ to 26.1+). Median PFS was 9.7 mo (95% CI: 5.1–14.7) and median OS was not reached (95% CI: 27.9–not reached).

Conclusion: With additional follow-up, pembro plus favezelimab continued to demonstrate manageable safety and sustained antitumor activity in pts with heavily pretreated anti–PD-1–refractory R/R cHL. A coformulation of favezelimab and pembro is being evaluated (KEYFORM-008; NCT05508867).