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ISHL 12

COLOGNE GERMANY

OCTOBER 22-24, 2022

12th International Symposium on Hodgkin Lymphoma

ABSTRACT BOOK

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Wolters Kluwer

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Table of Contents

P036: Detection of recurrent somatic variants in cell-free DNA as a tool for disease monitoring in Hodgkin lymphoma
P037: High breadth whole exome sequencing of circulating tumor DNA identifies novel recurrent genetic alterations in Hodgkin lymphoma
P038: HLA expression patterns of Hodgkin-Reed-Sternberg cells shape a spatially arranged tumor microenvironment in classical Hodgkin lymphoma
P039: HLA expression status and prognostic impact of B-cell content in patients with early-stage unfavorable Hodgkin lymphoma
P040: LINE-1 reverse transcriptase activity in Hodgkin lymphoma cells
P041: Low percentage of T lymphocytes in Hodgkin's Lymphoma lymph nodes, measured by flow cytometry, is associated with inferior progression free survival regardless of negative interim pet scan status
P042: Metabolic regulation of adaptive response to arginine deprivation in Hodgkin Lymphoma
P043: Molecular pathogenesis of Hodgkin lymphoma
P044: PIM kinases support protumoral and immunosuppressive phenotype and functions of macrophages in classical Hodgkin Lymphoma
P045: Plasma proteome profiling of cardiotoxicity in patients with Hodgkin lymphoma
P046: Preclinical evaluation of novel repurposed drug combinations in Hodgkin lymphoma
P047: Predictive role of the Hodgkin lymphoma-associated cytokines: a prospective study of the Czech Hodgkin Study Group
P048: Predictors of risk of relapse in classic Hodgkin lymphoma by flow cytometry
P049: Reduced features of T-cell activation before and during anti-PD-1 treatment in classical Hodgkin lymphoma
P050: Reed-Sternberg cells accelerate glycolytic and mitochondrial metabolism of tumor microenvironment cells
P051: Serum procalcitonin levels in newly diagnosed classical Hodgkin Lymphoma (cHL): Correlation with other inflammatory biomarkers
P052: Targeting CSN5/JAB1 oncogene in classical Hodgkin Lymphoma (cHL)
P053: The cGAS-STING anti-tumor immune response pathway as a potential therapeutic target in classical Hodgkin Lymphoma (cHL)
P054: The Kinase CK2 is deregulated and targetable in classical Hodgkin Lymphoma
P055: Validation of the tumor cell-specific rearranged IgG-encoding circulating cell-free DNA for the treatment response monitoring in patients with classic Hodgkin lymphoma
P056: Variants of the transcription factor ONECUT2 regulate gene expression in Hodgkin Lymphoma cells
P115: Distinct signaling pathways and checkpoint molecule expression across histological subtypes of nodular lymphocyte-predominant Hodgkin lymphoma

Immunotherapy

T057: Circulating tumor DNA in classical Hodgkin lymphoma patients treated with pembrolizumab and chemotherapy: dynamic response assessment and correlation with baseline total metabolic tumor volume
T058: Safety and Dose-Expansion Study of Combination Favezelimab (anti–LAG-3) Plus Pembrolizumab in Patients With Relapsed or Refractory Classical Hodgkin Lymphoma Refractory to Anti–PD-1 Treatment
P059: Multi-effector cell targeting with half-life extended bispecific scFv in Hodgkin lymphoma
P060: Prognosis of patients with relapsed and refractory classic Hodgkin lymphoma after nivolumab discontinuation and efficacy of nivolumab retreatment
P061: Safety and Dose-Expansion Study of Combination Favezelimab (anti–LAG-3) Plus Pembrolizumab in Anti–PD-1–Naive Patients With Relapsed or Refractory Classical Hodgkin Lymphoma
P062: The efficacy and safety of nivolumab 40 mg therapy versus 3 mg/kg in patients with relapsed and refractory classic Hodgkin lymphoma
P063: Trial in Progress: Individualized Immunotherapy in Early-Stage Unfavorable Hodgkin Lymphoma - The Investigator-Initiated Phase II GHSG INDIE Trial

Living Beyond Lymphoma

T064: Doxorubicin exposure and breast cancer risk in adolescent and adult Hodgkin lymphoma survivors
T065: Reproduction patterns among Classical Hodgkin Lymphoma Survivors Treated with BEACOPP and ABVD in Sweden, Denmark, and Norway
T066: Treatment and sex-specific exposure-based risk-stratification for care of survivors of childhood Hodgkin Lymphoma: A report from the Childhood Cancer Survivor Study
P067: A pilot of lung cancer screening for survivors of Hodgkin lymphoma
P068: A Retrospective Analysis of Fertility in Female Patients with Advanced Stages of Hodgkin Lymphoma Treated with BEACOPP Escalated Chemotherapy (25 Year Experience of a Single Centre)
P069: Characterisation of influencing parameters on oocyte quality preservation in a cohort of Hodgkin lymphoma patients
P070: Design of the INSIGHT study, evaluation of long-term follow-up care for lymphoma survivors in the Netherlands: does survivorship care at the BETER clinics reduce morbidity and mortality from late effects of lymphoma treatment and associated costs?
P071: First results of cardiovascular screening in a survivorship care program for Hodgkin lymphoma survivors in the Netherlands
P072: Impact of Ageing on the Survivorship Experiences of Patients with Hodgkin Lymphoma
P073: Increased risk of colorectal cancer following treatment for Hodgkin lymphoma
P074: Long-Term Cause-Specific Mortality in Hodgkin Lymphoma Patients – A Nationwide Danish Cohort Study
P075: My Hodgkin, My Health: Feasibility of a mobile application to collect long term follow up data about Hodgkin patients
P076: Pneumococcal infection in splenectomised Hodgkin lymphoma patients: Do they pose a problem today and what is the best long-term strategy?
P077: Predicting radiotherapy dose to the heart and the risk of radiation-related cardiac toxicity for Hodgkin lymphoma patients, using pre-chemotherapy PET-CT scans
P078: Predicting the Health-Related Quality of Life of Hodgkin Lymphoma Survivors: Identification of Risk Factors
P079: PROCTCAE as a patient-reported outcome measurement (PROM) questionaire in patients with Hodgkin Lymphoma captures different adverse events profile than those reported by physicians
P080: The BETER-REFLECT Biobank: a REsource For studies on Late Effects of Cancer Treatment
P081: Treatment-related circulatory diseases and mortality in Hodgkin lymphoma patients using multi-state modelling and relative survival

Older & Frail Patients

T082: AVD - a possible golden standard in the first-line treatment of older classical Hodgkin lymphoma patients
T083: The Effect of Heart Failure on Management and Outcomes of Older Patients with Hodgkin Lymphoma
T084: Treatment patterns and outcomes for Hodgkin's Lymphoma (HL) patients (pts) aged 60 and older: a report from the Brazilian Prospective Hodgkin's lymphoma Registry
P085: Epidemiology and results of the first line therapy of HIV-related Hodgkin Lymphoma: Russian retrospective multicenter study

Pediatric HL

P086: Advancing Pediatric Hodgkin Lymphoma Research Through NODAL
T087: Brentuximab vedotin (Bv) Demonstrates Superior Event-Free Survival in Pediatric High-Risk Hodgkin Lymphoma
P088: Case series of Nodular Lymphocyte Predominant Hodgkin Lymphoma from Tanzania. A common entity in East Africa?
P089: Pembrolizumab in Pediatric and Young Adults Patients With Newly Diagnosed Classical Hodgkin Lymphoma and Slow Early Responders to Frontline Chemotherapy: The Phase 2 KEYNOTE-667 Study
P090: Staging of Lung Lesions Survey Demonstrates Continued Need for Harmonization

Radiotherapy

P091: Early analysis of the PRO-Hodgkin study: Clinical investigation of pencil beam scanning proton treatment in Hodgkin lymphoma patients
P092: Estimating the dosimetric benefit of involved-node radiotherapy in comparison to involved-field radiotherapy - implications from the GHSG HD 17 trial
P093: From involved- field to involved-node – Quality analysis of the radiation therapy in HD 17 by the expert panel of the German Hodgkin Study Group
P094: Long-term outcomes of bulky classic Hodgkin lymphoma managed with a PET-adapted approach demonstrate excellent outcomes in PET-negative cases
P095: Personalised Modelling of Quality-Adjusted Survival Benefit and Cost-Effectiveness of using Proton Beam Therapy inthe Treatment of Intermediate-Stage Hodgkin Lymphoma in England
P096: Polymorphisms in SETD7 may predispose the risk of developing late cardiac side effects after radiotherapy including the mediastinum in Hodgkin´s lymphoma
P097: The status quo of involved-field radiotherapy – Quality analysis of radiotherapy in the GHSG HD 16

Relapsed/Refractory

T098: Brentuximab Vedotin plus ESHAP (BRESHAP) versus ESHAP in Patients with Relapsed or Refractory Classical Hodgkin's Lymphoma. Interim Results of the BRESELIBET Prospective Clinical Trial
T099: High efficacy and durability of second-line therapy with pembrolizumab, gemcitabine, vinorelbine, and liposomal doxorubicin in the phase II study for relapsed and refractory Hodgkin lymphoma
T100: Long term Follow-up of a Phase I Study Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma: A trial of the ECOG-ACRIN Research Group (E4412: Arms A-I)
P101: Combination of immune checkpoint inhibitors with BeGEV in the treatment of patients with relapsed and refractory classical Hodgkin's lymphoma
P102: Comparison of Novel Salvage Regimens and Traditional salvage Chemotherapy in Relapsed and Refractory Classic Hodgkin Lymphoma
P103: Comparison of PET-derived parameters in program cell death-1 inhibitor and CD30 antibody drug conjugate-based therapies in patients with advanced stage cHL: A single center experience
P104: Consolidation Therapy with Brentuximab Vedotin after Autologous Stem Cell Transplantation for Relapsed/Refractory Hodgkin Lymphoma in the Czech Republic
P105: Decisional role of interim PET in relapsed/refractory classical Hodgkin Lymphoma treated with four begev cycles
P106: Dose intensive brentuximab vedotin for platinum resistant recurrent Hodgkin lymphoma is a feasible treatment option - a single center experience
P107: Effect of Brentuximab Vedotin Addition to Chemotherapy and Prognostic Factors in Patients with Relapsed/Refractory Hodgkin Lymphoma: a Large Multi-Trial Analysis Based on Individual Patient Data
P108: Integrating baseline circulating tumor DNA with interim PET improves outcome prediction in relapsed/refractory classical Hodgkin lymphoma
P109: One-Day Brentuximab-Bendamustine (120mg/m2) every 21 days is a feasible and safe treatment for relapsed/refractory Hodgkin lymphoma
P110: Outcome of high-dose chemotherapy (HDCT) and autologous stem cell transplant (ASCT) as first salvage treatment for relapsed or refractory classical Hodgkin Lymphoma (cHL) in the era of PET-adapted strategy among Italian centers
P111: Phase I Trial of Brentuximab Vedotin plus Cyclosporine in Relapsed/Refractory Hodgkin Lymphoma
P112: Phase II Trial of Brentuximab Vedotin plus ibrutinib in Relapsed/Refractory Hodgkin Lymphoma
P113: Promising results with anti-PD-1 therapy in primary refractory Hodgkin lymphoma: a single-centre report
P114: Very late relapses in patients with Hodgkin Lymphoma occuring ≥5 years after initial treament with chemotherapy ± radiotherapy: Treatment strategies and prognostic factors for the outcome

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Advanced Stages

T001: FDG-PET AND SERUM TARC LEVELS AFTER ONE CYCLE OF BV-AVD IN ADVANCED STAGE HODGKIN LYMPHOMA PATIENTS: RESULTS FROM THE VERY EARLY PET-RESPONSE ADAPTED EORTC-COBRA TRIAL

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The COBRA trial (EORTC-1537) is a fully enrolled, single-arm multicenter phase II study investigating the value of very early FDG-PET-response adapted Brentuximab Vedotin (BV)-based therapy for advanced stage classical Hodgkin Lymphoma (cHL). All patients received one cycle of BV, Doxorubicin, Vinblastine, and Dacarbazine (BV-AVD) followed by an early interim 18F-FDG-PET scan (iPET). Patients with a negative iPET by central assessment continued with five additional BV-AVD cycles, while iPET+ patients escalated to six cycles of BV, Etoposide, Cyclophosphamide, Doxorubicin, Dacarbazine, and Dexamethasone (BV-ECADD). The main objective of this trial is to assess whether treatment adaptation based on iPET results in improved efficacy while minimizing treatment toxicity.

We here report baseline characteristics and iPET results after one cycle of BV-AVD. Deauville scores 4 or 5 were considered positive. In addition, we used ELISA to measure serum thymus and activation regulated chemokine (TARC) levels, which have been reported to reflect cHL disease activity and correspond with treatment response. TARC levels were measured both at baseline (bTARC) and after one cycle of BV-AVD (iTARC). A serum TARC level >1000 pg/ml was considered positive for detecting active disease (PMID 22058214).

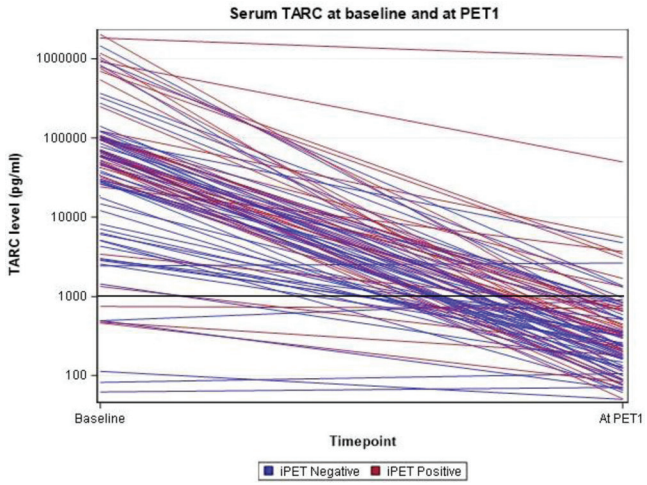

Figure 1: Serum TARC levels for 96 individual patients at baseline and after one cycle of BV-AVD.

A total of 150 patients were included in the trial. Median age at inclusion was 32 years and 46% were females. Patients presented with stage IIB (15%), III (25%) or IV (60%) disease. Bulky disease was present in 56%. bTARC levels are currently available for 96 patients and were positive in 88 (92%), with a median level of 51831 pg/ml (range: 62–2033694). There were significant differences in bTARC levels across stages (p_value=0.044, F test), with bTARC levels lower for stage IIIA, as compared to IIB, IIIB or IV, but not with regards to bulky disease, age or gender. After one cycle of BV-AVD, iPET was positive in 40% of the patients. Within the group of patients with available iTARC and positive bTARC (n=84), iPET was positive in 33 cases (39%) and iTARC was positive in 12 cases (14%). Eight out of these 12 iTARC positive cases were also iPET positive.

In conclusion, the majority of advanced stage Hodgkin patients showed a treatment response already after 1 cycle of BV-AVD, as measured by FDG-PET and serum TARC. FDG-PET quantification and tissue analysis for TARC expression are ongoing. These are preliminary data; definitive results will be presented at the symposium.

T002: TREATMENT RELATED MORBIDITY IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA: RESULTS OF THE ONGOING, RANDOMIZED PHASE III HD21 TRIAL BY THE GERMAN HODGKIN STUDY GROUP

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Introduction: PET-guided treatment of newly diagnosed advanced stage (AS) classical Hodgkin Lymphoma (cHL) patients with eBEACOPP (escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procar-bazine, prednisone) achieves outstanding survival outcomes, but also causes relevant treatment-related morbidity (TRMB). CD30-targeted therapy with brentuximab vedotin (BV) has proven high efficacy and favorable tolerability in patients with cHL. In the HD21 study, we hypothesized that using BV to remodel the eBEACOPP regimen could further decrease TRMB while maintaining its high efficacy. Here, we report the final analysis of the TRMB endpoint.

Methods: Adult patients ≤ 60 years of age with AS-cHL were included in this international randomized phase III trial. Patients were randomized

in a 1:1 ratio to PET2-guided 4–6 cycles of either standard eBEACOPP or experimental BrECADD treatment (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone). PET2 was assessed by blinded panel review (PP-2).
Reduction of TRMB was the first part of the co-primary endpoint, whereas non-inferiority of progression-free survival (PFS) was the second part. TRMB was defined as any CTCAE grade 3 or 4 organ toxicity or grade 4 hematological toxicity (anemia, thrombocytopenia, infection) during treatment. TRMB was determined using the Cochran-Mantel-Haenszel method. Stratification factors included sex, age, IPS, and location of trial site. Categorical variables were compared using fisher' s exact test. Exploratory analyses were performed for further safety outcome parameters. The trial was registered at clinicaltrials.gov (NCT02661503) and conducted according to ICH-GCP guidelines.
Results: Between July 2016 and August 2020, we enrolled 1,500 patients from 9 countries. 1,470 patients are in the intention-to-treat (ITT) population (eBEACOPP n=732, BrECADD n=738). Baseline characteristics such as sex (male=56%), age (≤45 years=79%), IPS (0–2=54%), location (Europe=92%) and stage (III/IV=84%) were well balanced between treatment arms. As recommended by PP2, 59% of patients had 4 cycles and 41% received 6 cycles of therapy, without differences between treatment groups.
TRMB was documented in 59% of patients in the eBEACOPP group (rel-risk, 1.41; 95% CI, 1.27–1.56, p<0.001) and 42% in the BrECADD group (rel-risk, 0.72; 95% CI, 0.65–0.79, p<0.001). The relative risk estimates remained stable among stratification factors. In the eBEACOPP group 52% of patients had hematological TRMB events compared to 31% in the BrECADD group (p<0.001). At least one red cell transfusion was given in 22% of patients in the eBEACOPP group and in 8% in the BrECADD group and at least one platelet transfusion in 13% and 6%, respectively. Severe leukopenia was observed in 94% and 87%, respectively. TRMB organ toxicity was documented in 17% of patients in the eBEACOPP group and 19% in the BrECADD group (p=0.455).
Conclusion: The BrECADD regimen shows a significant and clinically relevant reduction of treatment-related morbidities compared to eBEACOPP in patients with newly diagnosed AS-cHL.

P003: A RETROSPECTIVE STUDY TO EVALUATE THE RELIABILITY OF STAGING AND RISK STRATIFICATION OF ADOLESCENT AND ADULT PATIENTS WITH HODGKIN'S LYMPHOMA REGISTERED IN THE LYMPHOMA CLINIC AT TATA MEMORIAL CENTRE.

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Purpose: Risk stratification is a key factor,which depends on staging, clinical and laboratory parameters in determining the treatment in Hodgkin's lymphoma (HL). However, this is highly prone to erroneous results due to overlapping components in the staging systems and inter-observer variability.We conducted this study to assess the reliability of risk stratification performed by our clinicians at our busy multidisciplinary clinic (MDC).
Methods: A retrospective analysisof newly diagnosed HL patients from the multidisciplinary clinic database for the year 2016-18was conducted.All patients underwent an 18-FDG PET/CT scan and other evaluations as per our institutional checklist. The reliability of staging and risk stratification done during the MDC was compared with a team of independent experts (medical oncology, radiation oncology and nuclear medicine) based on a standard reference. The concordance testing was done using kappa statistic for agreement (≥ 0.8 as perfect agreement) andP <0.05 was considered significant.
Results: 120 patients were analyzed, and the baseline characteristics are described in Table 1. The patients initially underwent staging by MDC and were risk stratified into early favorable (16 patients [13.5%]), early unfavorable (29 patients [24%]) and advanced (75 patients [62.5%]). A discordance rate of 10% (12 patients) was observed in disease staging and 8.3% in risk stratification (10 patients) between the MDC and the expert team. All deviations were due to up-staging of patients by MDC, of which 9 patients in early favorable were misclassified as early unfavorable and 1 patient as advanced from early unfavorable. This resulted in 10 patients receiving higher dose of chemotherapy and radiation. However, no patients were under treated. On completion of treatment, 82%of patientshadcomplete response, 12%had partial responseand 5%had disease progression. Our results show that the discordance rates were not significantbetween the independent reviewers and MDC team with kappa score of 0.859 for stagingand 0.847 for risk stratification.
Conclusion: Despite our busy setting, the risk stratification was found to be reliable and comparable to reference standards. One reason for this would be the involvement of a multidisciplinary team in our lymphoma clinic. Yet, 8% of the patients received a more intense therapy than needed, demonstrating the need for a simpler, objective and technology driven risk stratification process.

TABLE 1: BASELINE PATIENT CHARACTERISTICS AT DIAGNOSIS

CHARACTERISTIC	No. (n=120)	%
Age, Years		
Median	28.5	
Range	15-68	
Ann Arbor Stage (MDC)		
I	17	14.2
II	29	24.2
III	24	20
IV	50	41.6
Bulky Disease	63	52.5
B Symptoms	57	47.5
Risk Group (MDC)		
Early Favorable	16	13.3
Early Unfavourable	29	24.1
Advanced	75	62.5
IPS Score (Advanced only)		
1	8	10.7
2	39	52
3	23	30.7
4	5	6.6

Table 1: Baseline characteristics

P004: ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA (CHL) PATIENTS WITH A POSITIVE INTERIM-PET (PET-2) DEAUVILLE SCORE (DS) 5 AFTER 2 ABVD CYCLES: A POOLED ANALYSIS OF INDIVIDUAL PATIENT DATA OF THREE MULTICENTER TRIALS

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Background: PET-2 is widely adopted to select patients (pt) with advanced-stage cHL, who might benefit from intensifying or de-escalating therapy. Improved PFS has been reported in PET-2 positive pt switched from ABVD to escalated BEACOPP (eBEACOPP) compared to historical controls continuing ABVD. Nevertheless, pt with a PET-2

Deauville score (DS) 5 have a dismal prognosis, with PFS from 35% to 50% at 3 years despite treatment intensification.
Aim of Study: To refine outcome prediction, we conducted a pooled analysis of individual pt data from 3 multicenter trials: HD0607 GITIL/FIL, RATHL and SWOG S0816 focusing on pt with PET-2 DS 5 after ABVD who had intensified treatment with eBEACOPP or BEACOPP-14.
Methods: The prognostic value of clinical characteristics, laboratory parameters, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) at diagnosis was evaluated. MTV was calculated with an automatic software segmentation using SUV 4.0 threshold in each pt. Predictive factors of PFS measured from the date of PET-2 until progression, relapse, death from any cause or last follow-up, and overall survival (OS) were analyzed using Cox regression. Baseline characteristics and PET MTV/TLG of pt who failed vs those who achieved CR with intensified treatment were compared.
Results: Among 2231 pt with available PET scans for review, 136 (6%) PET-2 DS 5 pt were included in the study: M 72, F 64, median age 34 yrs, Nodular Sclerosis 71%, stage IIB/III/IV 29%/ 22% /49%, B symptoms 72%, IPS >3: 31%; bulky 22%; neutrophil/lymphocyte ratio > 6: 61%. At baseline median MTV and TLG were 243 cm3 (range, 1.6–4266) and 1476cm3 (range, 7.3–29386). After a median follow-up of 41 months, 3-yr PFS and OS were 32% (95% CI, 25–42) and 82% (95% CI, 75–89), respectively. In univariate analysis no clinical or laboratory parameter nor MTV was significantly associated with PFS, whereas age ≥ 45 years, median numbers of leukocytes, lymphocytes and monocytes were significantly associated with OS. Using a threshold of 192 cm3 for MTV calculated by Youden index, 3-year PFS and OS were 35% and 87% vs 34% and 79% for pt with low vs high MTV (p=ns).
Conclusions: Pt with PET-2 DS 5 after ABVD receiving intensified treatment have similar outcomes to refractory disease with only 32% 3-yr PFS. No factors measured at diagnosis were able to detect the later failures within the DS 5 cohort. Nevertheless, pt receiving PET-guided treatment intensification can benefit from a prolonged OS.

P005: AGE, HISTOTYPE AND STAGE IV ARE ASSOCIATED WITH A SHORTER SURVIVAL IN PATIENTS WITH HODGKIN LYMPHOMA, EVEN THE PET-ADAPTED ERA. A SINGLE CENTER RETROSPECTIVE STUDY.

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Introduction: Although Hodgkin lymphoma (HL) can be cured in the majority of patients, some patients relapsed, or died due to the disease itself, second malignancies or organ failure caused by previous chemo-radiotherapy. Recently, monoclonal antibodies (mAb) targeting CD30 or PD-1 have been incorporated in the frontline treatment of patients of HL with excellent results. However, it is not clear which patients might benefit more chemo-immunotherapy rather than a traditional chemo-radiotherapy approach
Aim: In this study we aimed at identify risk factor associated with shorter survival in patients with classical Hodgkin lymphoma

	Univariate analysis		Multivariate analysis		
Variables	HR	p values	HR	p values	points
Male	2.1 (1.1-4.5)	0.0422	1.8 (0.8-3.3)	0.0836	-
Age ≥45 yy	6.2 (3.3-18.1)	<0.0001	4.3 (2.2-12.2)	<0.0001	2
not NS	2.5 (1.3-5.8)	0.0276	1.9 (1.1-3.8)	0.0432	1
B symptoms	1.4 (0.7-3.0)	0.7668	-	-	-
Bulky nodes	1.7 (0.8-4.1)	0.1728	-	-	-
Stage IV	7.5 (3.0-18.7)	<0.0001	4.2 (1.8-10.1)	<0.0001	2
iPET-therapy	1.1 (0.4-2.8)	0.8378	-	-	-

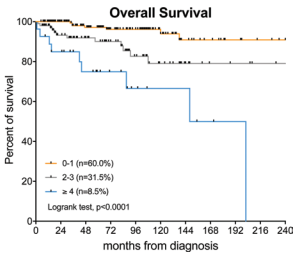

Figure 1: table 1 and Figure 1

Methods: We collected patients with HL followed at Padova university hospital from 1994 till 2020. Overall survival was calculated as months from diagnosis to death (event) or last known follow-up (censured). Survival curves were compared by the Log-rank test. P values <0.05 were considered as statistically significant
Results: Among the 383 classical HL, 313 had enough data and were included in this study. The media age at diagnosis was 37 + 16 years, 27% of patients were older than 45 years, 51% were male, 74% had a nodular sclerosis HL subtype (NSHL), 21% were at stage IV, 32% a bulky disease and 51% denied B symptoms. Ninety-seven % of patients were treated with curative intent with ABVD, ABVD-like or BEACOPP protocols. After a median follow-up of 77 months, 21% of patients relapsed and 9% died. On univariate analysis male gender, age >45 years, not NSHL subtype and stage IV were associated with a shorter OS (Tab 1). However only age >45 years, not NSHL subtype, and stage 4 maintained the independent significance in multivariate analysis (Table 1). Remarkably, a PET-adapted strategy allows to improve the progression free survival of our patients but not the OS.
By using the hard ratio half values, we assigned 1 point to male gender and 2 points to age >45 years and stage IV (Tab. 1). Combing these variables, 60% had a 0–1 point (low-risk), 31.5% 2–3 points (int. risk) and 8.5% >=4 points (high-risk). The OS decreased increasing the point scores. The 10-year OS was 94%, 79% and 67% for patients at low, intermediate and high-risk (Fig. 1). Patients at high-risk had almost 10 and 3-fold risk of death than low and intermediate risk patients
Conclusions: Despite the optimal outcome of HL with a chemo-radiotherapy approach, novel strategies incorporating anti-CD30 and/or anti-PD-1 mAb are need, in particular for adult stage IV patients.

P006: CLINICAL OUTCOME OF CLASSICAL HODGKIN LYMPHOMA PATIENTS RECEIVING SYSTEMIC ANTI-LYMPHOMA TREATMENT DURING SARS-COV-2 POSITIVITY: RESULTS FROM THE CHEMO-COVID STUDY ON BEHALF OF FONDAZIONE ITALIANA LINFOMI

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Patients (pts) affected by classical Hodgkin Lymphoma (cHL) infected by SARS-CoV-2 are at risk of protracted positivity due to immunodeficiency, and consequent delay of anti-lymphoma treatment may worsen cHL prognosis. Feasibility of chemo-therapy (CT) administration during SARS-CoV-2 infection in cHL pts has not been investigated so far. We collected data of cHL pts enrolled in Haematocovid observational trial and treated with CT while positive for SARS-CoV-2, with the aim to describe CT feasibility and to assess the risk of infection worsening. Thirteen cHL pts treated since May 2020 to May 2022 were included: median age was 39 years (17–68), 6 pts (46%) presented with advanced stage, 8 pts (62%) with B symptoms and 5 pts (38%) with bulky. Seven pts (54%) were treatment-naïve and waiting for ABVD start at time of COVID diagnosis, while in 6 pre-treated pts (46%) SARS-CoV-2 infection occurred after a median time of 18 days (1–42) from administration of the last CT cycle and the median number of prior therapeutic lines was 1 (1–4). Eight pts (62%) previously received m-RNA vaccines, while 5 pts (38%) were infected in the pre-vaccine era. At COVID onset, 6 (46%) pts were asymptomatic and 7 (54%) pauci-symptomatic, being fever (n=5) the most reported symptom; pneumonia was documented in 2 pts, but no case of respiratory failure was described. Viral variant was identified in 7 pts: 1 alpha, 1 delta and 5 omicron, while in 6 pts the presumed variant was derived from pandemic wave (3 pts alpha, 1 pt delta and 3

pts omicron). Four pts (31%) received antiviral treatment, consisting in monoclonal antibodies (n=3) and remdesivir (n=1). A median of 1 cycle of CT (1–2) after a median time of 25 days (1–45) from the first SARS-CoV-2 positivity was delivered. Ten pts (77%) received ABVD, in two cases with bleomycine omission, 1 pt (8%) received escBEACOPP and 2 pts (15%) brentuximab-vedotin. None of the pts experienced COVID worsening following CT administration. Median duration of SARS-CoV-2 positivity was 21 days (9–60). After a median follow-up of 11 months (1–61), one pt died due to cHL progressive disease while positive but asymptomatic for SARS-CoV-2. All the remaining pts were alive and negative for SARS-CoV-2 infection, and 8 pts (62%) achieved cHL complete response. In conclusion, in this preliminary analysis CT administration to high-risk cHL pts positive but asymptomatic for SARS-CoV-2 seems feasible and did not induce clinical worsening of viral infection.

P007: COMPARATIVE EFFICACY OF THE R-BEACOPP-14 AND R-CHOP REGIMENS IN THE TREATMENT OF PATIENTS WITH ADVANCED STAGES OF NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA (NLPHL) WITH THRLBCL-LIKE HISTOPATHOLOGICAL GROWTH PATTERNS IN THE TUMOR BIOPSY

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Introduction: Our data demonstrated an unfavorable prognostic value of THRLBCL-like histopathological growth patterns in the tumor substrate. Differentiated approaches of the therapy of this patients group have not been defined yet.
Objective: to evaluate the results of 1st line therapy of advanced stages NLPHL patients with THRLBCL-like histopathological growth patterns in the tumor biopsy, depending on the type of induction chemotherapy program.
Materials and methods: Results of 1st line therapy in 150 patients with NLHLP observed from 2010 to 2021 were analyzed. Growth patterns without THRLBCL-like sites was observed in 87/150 (58%) patients, of them 33 (38%) had advanced stages of the disease (AS). THRLBCL-like patterns were in 63/150 (42%), of them 55 (87%) pts with AS. Patterns with predominance of THRLBCL-like areas (more than 50% of the cut area) - 32 (21%), of them 31 (97%) pts with AS.
Results: In 33/87(38%) pts with growth patterns without THRLBCL-like areas – chemotherapy was performed in 27/33(81%) pts: R-BEACORP-14 in 17/27(63%), R-ABVD in 10/27(37%), all pts achieved complete remission (CR).
In of 55/63(87%) pts with advanced stages and with THRLBCL-like patterns, chemotherapy was underwent in 54/55(98%) pts: R-BEACORP-14–30/54(56%), of them CR - 18/ 30(60%); R-CHOP - 12/54 (21%), of them CR - 4/12 (30%); other - 12/54 (23%) pts.
In 31/32(97%) pts with advanced stages and with predominance of THRLBCL-like areas, chemotherapy received 30/31(97%) pts: R-BEACORP-14–17/30(57%), of them CR - 8/17(47%); R-CHOP - 8/30 (27%), of them CR - 2/8 (25%); other - 5/30 (17%) pts.
In pts groups with the presence and predominance of THRLBCL-like growth patterns the 5-year OS on the R-BEACOPP-14 scheme was 100% and 62%, and on the R-CHOP - 100% and 69% (p-0.02), respectively. The 3-year EFS on the R-BEACORP-14 scheme was 91% and 44%, and on the R-CHOP - 50% and 29% (p-<0.0001), respectively. Median follow-up is 34 months.
Conclusion: Induction therapy with R-BEACORP-14 allows to achieved the best overall and event-free survival in an unfavorable group of advanced stages NLPHL patients with the presence and predominance of THRLBCL-like growth patterns.

P008: IMPACT OF BONE MARROW INVOLVEMENT ON EARLY PET RESPONSE AND PROGRESSION-FREE SURVIVAL IN THE HD18 TRIAL FOR PATIENTS WITH ADVANCED-STAGE HODGKIN LYMPHOMA

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Background: The prognostic role of bone marrow (BM) involvement in advanced-stage Hodgkin lymphoma is unclear, particularly for patients receiving intensive first-line treatment. We thus retrospectively examined its impact on early response and progression-free survival (PFS) among individuals receiving escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP) in the HD18 trial.
Patients and Methods: A total of 424 individuals were suitable for analysis, of which 124 (29%) had BM involvement according to initial positron emission tomography (PET). Patient outcome was measured by PET response after 2×eBEACOPP and five-year PFS rate.
Results: After 2×eBEACOPP, 79 of the BM PET-negative individuals (26%) and 26 of the BM PET-positive patients (21%) were found to be PET-positive (odds ratio [OR] 0.74, P=0.25). The five-year PFS rate was 90.7% in BM PET-negative individuals and 91.8% for BM PET-positive patients (hazard ratio 0.82, P=0.6). In our BM PET-positive subgroup, nine (16%) of the 56 subjects with one or two sites of skeletal uptake were PET-positive after 2×eBEACOPP as compared to 17 (25%) of the 68 individuals showing three or more BM lesions (OR 1.74, P=0.23).
Conclusions: The present analysis demonstrates that BM involvement, irrespective of its extent, does not lead to increased risk for a positive interim PET result or inferior PFS in advanced-stage Hodgkin lymphoma patients undergoing eBEACOPP treatment. Skeletal lesions cannot therefore be considered as an additional prognostic marker of therapy failure or disease recurrence for individuals receiving intensive first-line treatment.

P009: IMPROVED OVERALL SURVIVAL WITH FIRST-LINE BRENTUXIMAB VEDOTIN PLUS CHEMOTHERAPY IN PATIENTS WITH ADVANCED STAGE III/IV CLASSICAL HODGKIN LYMPHOMA: AN UPDATED ANALYSIS OF ECHELON-1

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New first-line treatment strategies for classical Hodgkin lymphoma (cHL) have not improved overall survival (OS) compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Five-year data from ECHELON-1 (NCT01712490) supported long-term progression-free survival (PFS) with brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) in patients (pts) with previously untreated stage III/IV cHL vs ABVD, with a manageable long-term safety profile. We report an OS analysis from ECHELON-1 after a median of

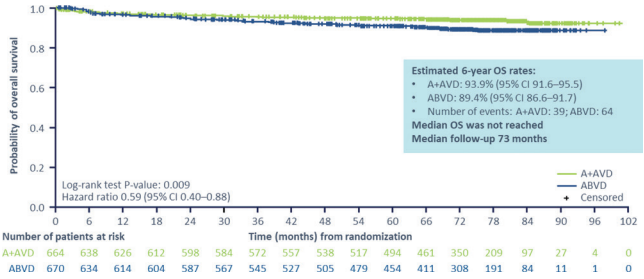

Figure 1: Overall Survival in the Intent-to-Treat Population.

6 years of follow-up (data cutoff June 1, 2021). Randomized pts (1:1) received ≤6 cycles of A+AVD (n=664) or ABVD (n=670) on days 1 and 15, every 28 days. The key secondary end point was OS (event-driven, type-1 error controlled) in the intent-to-treat population. Analysis of OS in prespecified subgroups was exploratory and not adjusted for multiplicity. PFS per investigator was reported for long-term follow-up. Deaths during follow-up, including reported causes of death per investigator, were summarized. We observed 39 OS events in the A+AVD arm vs 64 with ABVD, favoring A+AVD (hazard ratio [HR] 0.59; 95% confidence interval [CI] 0.40–0.88; p=0.009; median follow-up 73 months; Figure). OS was examined in prespecified subgroups; in a multivariable analysis adjusting for baseline demographic and disease factors, OS benefit was preserved (HR 0.53; 95% CI 0.34–0.83). PFS favored A+AVD (HR 0.68; 95% CI 0.53–0.86), consistent with prior reports. Subsequent therapy use was less frequent with A+AVD vs ABVD (135 [20%] vs 157 [24%]) including fewer autologous (44 [7%] vs 59 [9%]) and allogeneic stem cell transplants (4 [<1%] vs 12 [2%]) while use of radiation was similar (55 [8%] vs 58 [9%]), suggesting that the OS benefit was not due to undertreatment of pts in the ABVD arm. Fewer second malignancies (23 vs 32) and fewer deaths related to cHL or treatment complications (32 vs 45) or to second malignancies (1 vs 11) were reported with A+AVD vs ABVD, respectively; treatment-related deaths were comparable (8 vs 7). While fertility was not formally assessed, a total of 191 pregnancies were reported among pts and their partners (A+AVD 113; ABVD 78). More pts had peripheral neuropathy with A+AVD (443 [67%]) vs ABVD (286 [43%]), but most improved or resolved at last follow-up (379 [86%] vs 249 [87%]). To conclude, A+AVD significantly reduced risk of death vs ABVD by 41%. The long-term safety profile was manageable, consistent with prior reports.

P010: INFERIOR OUTCOMES FOR YOUNG ADULTS TREATED ON ADVANCED STAGE CLINICAL TRIALS: REPORT FROM THE HOLISTIC CONSORTIUM

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Background: Inferior outcomes have been reported for adolescents and young adults (AYAs) across several cancer types, as compared to younger pediatric or older patients (pts). While lack of access to clinical trials has been implicated, we described inferior outcomes for AYAs treated on a large US Hodgkin Lymphoma (HL) adult study (Henderson, 2018). Earlier this year, in an analysis of three US phase 3 pediatric HL trials, worse outcomes were reported for pts >15 years (yrs) compared with younger pts (Kahn, 2022). Little is known about the impact of age on outcomes from recent adult clinical trials.

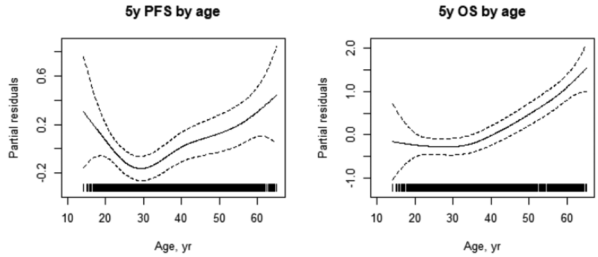
Methods: Individual patient data from eight advanced stage clinical trials (ECOG2496, SWOG0816, HD2000, HD9601, HD0607, HD0801, UK Stanford V, and RATHL), conducted from 1996–2012, were harmonized as part of the HoLISTIC Consortium. Pts with classic HL, stage IIb, III or IV disease, ages 14–65 yrs, and treated at adult centers were included. Outcomes were 5-yr progression-free survival (PFS) and 5-yr overall survival (OS), which were estimated in univariable and multivariable models. Age at diagnosis and 10 other clinical factors, were examined with multivariable adjusted plots and piecewise linear splines to identify functional forms of the relationship with PFS or OS. Multiple imputation was used for missing data.

Results: Data on 3893 HL patients were included. Across all studies, 5-year PFS was 76.5% (95% CI=75.1%, 77.9%); 5-year OS was 91.6% (95% CI=90.7%, 92.6%). Median age was 32 yrs and 41% of patients were <30 yrs at diagnosis. Associations between age (analyzed as a continuous variable) and PFS displayed a distinct piecewise linear relationship with an inflection point at age 30 (Figure A). In multivariable analyses, PFS improved from ages 14 to 30, and then declined after age 30 (Figure B). The association between age and OS was not significant <30 yrs, advancing age >30 yrs was associated with worse OS. These patterns were seen broadly across studies and not dominated by one trial.

Conclusion: The association between age and HL survival in the modern era appears to be more nuanced than the dichotomous variable of age at 45 yrs, as used in previous models. While patients under 30 yrs have worse short-term disease outcomes than age 30 yrs, 5-yr OS results suggest that younger patients may be amenable to successful salvage. Further research is needed to understand these differences to optimize outcomes.

Figure. Relationship Between Age and Risk of Progression and Death (n=3893). ***A)*** Relationship between age as a continuous variable with 5-year PFS and 5-year OS (partial residuals from the Cox model [y-axis] provide visualization of the relationship between age and outcomes, while adjusting for other clinical variables); ***B)*** Age analyses as part of univariable and multivariable modeling.

A)



B)

	Univariable[a]		Multivariable[a]	
	HR (95% CI)[b]	p-value	HR (95% CI)[b]	p-value
5-Year PFS				
Linear effect in 14 to 30 yrs	0.97 (0.95, 0.99)	<0.01	0.97 (0.95, 1.00)	0.02
Linear effect in >30 yrs	1.02 (1.01, 1.03)	<0.01	1.02 (1.01, 1.03)	<0.01
5-Year OS				
Linear effect in 14 to 30 yrs	0.97 (0.93, 1.01)	0.16	0.98 (0.94, 1.02)	0.29
Linear effect in >30 yrs	1.06 (1.04, 1.07)	<0.01	1.05 (1.04, 1.06)	<0.01

[a] Univariable and multivariable model stratified by trial; multivariable model also adjusts for total WBC (piecewise linear spline), lymphocyte count (piecewise linear spline), hemoglobin (continuous), albumin (continuous), ESR (continuous), sex, stage, histology, B symptoms, and bulk disease.

[b] HR<1 indicates improving outcomes per year of age increase for patients ages 14 to 30 years, and HR>1 indicates worsening outcomes per year of age increase for patients ages > 30 years.

Figure 1: Relationship Between Age and Risk of Progression and Death (n=3893).

P011: IPS-7 OR IPS-3 TO IDENTIFY VERY-HIGH RISK PATIENTS IN ADVANCED CLASSICAL HODGKIN'S LYMPHOMA: WHICH SCORE TO CHOOSE

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Introduction: The survival of patients (pts) with classic Hodgkin Lymphoma (cHL) has been significantly increased due to refinement of therapeutic strategies. International Prognostic Score (IPS-7) is the most used risk stratification tool for patients with advanced-stage cHL but it may have decreased prognostic value in cHL pts treated in the contemporary era. A novel scoring system, IPS-3, comprising three of the seven

IPS-7 indicators (age ≥45, stage IV, haemoglobin <105 g/L), was recently proposed to identify high-risk patients but require further validation.
Aim: To validate IPS-3 and evaluate its discriminatory power in advanced stages cHL.
Methods: Single centre retrospective analysis of adult pts with cHL diagnosed between 1990 and 2017 treated with ABVD, ABVD hybrid protocols or escalated BEACOPP. Advanced stage was defined according to the German Hodgkin Study Group classification system. Stratified models for IPS-3 and IPS-7 were compared using Akaike's information criteria (AIC) and Harrell's concordance index (C-index).
Results: We included 227 pts, with similar gender proportion; median age was 32.3 (18–80). Nodular sclerosis was the most common histologic subtype (n=176 pts; 77.5%); 90 pts (39.6%) presented stage IV; 13 pts (5.7%) had IPS-3 high risk, 12 pts (5.3%) IPS-7 high risk and 8 pts (3.5%) had both.
After a median follow-up of 123 months (m), the median overall survival (OS) was not reached. IPS-7 (HR 2.13 [95%IC 1.49–3.05]; p<0.001) and IPS-3 (HR 3.05 [95%IC 1.98–4.69]; p<0.001) identify different prognosis groups for OS, with IPS-3 (AIC 633; C-index 0.6547) providing best fit for data compared with IPS-7 (AIC 643; C-index 0.6403).
Median progression free survival (PFS) was 295.6m. IPS-7 (HR 1.43 [95%IC 1.05–1.96]; p=0.025) and IPS-3 (HR 1.72 [95%IC 1.20–2.46]; p=0.003) identified different prognostic groups for PFS, with IPS-3 (AIC 917; C-index 0.5717) providing best fit for data compared with IPS-7 (AIC 921; C-index 0.5570).
IPS-3 remained predictive for OS (HR 3.05; p<0.001) and PFS (HR 1.72; p=0.003) after adjustment for treatment protocol and had a good performance discriminating high vs intermediate/low risk for OS and PFS (HR 2.40; p=0.002 and PFS HR 3.03; p=0.001, respectively).
Conclusion: IPS-3 had better performance predicting OS and PFS compared with IPS-7, allowing a better segregation of patients with worse prognosis, which suggests its value to identify patients that will benefit more aggressive treatment protocol.

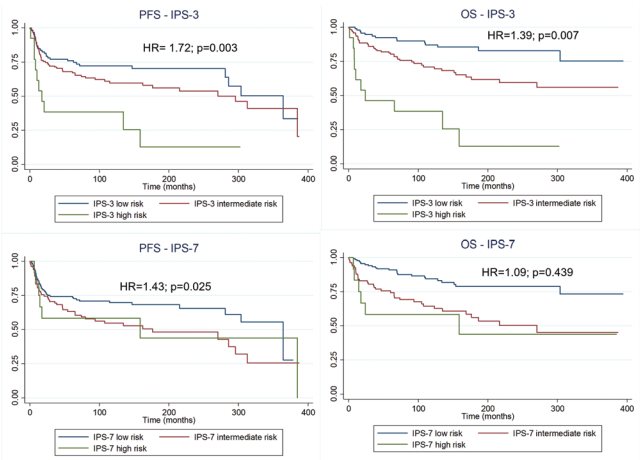

Figure 1: PFS and OS for both IPS-3 and IPS-7 scores

P012: NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA A RARE DISEASE WITH GOOD PROGNOSIS: A RETROSPECTIVE MULTICENTER EXPERIENCE

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Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare disease. It differs from Classic Hodgkin lymphoma histologically, biologically and clinically, with a more indolent course, a tendency to late relapses and transformation into high-grade B cell lymphomas. There is no consensus on the best treatment approach. The aim of this study is to characterize the clinical characteristics, first-line therapy, outcomes and prognostic factors of NLPHL in our country. We conducted a multicentric, retrospective analysis of patients (pts) with NLPHL diagnosed between 2003 and 2020 in 11 hemato-oncology centers, with a minimum follow-up (FU) of 1y. Overall and complete response rate (ORR and CRR) were defined according to Lugano criteria. Progression-free (PFS) and overall (OS) survival were analyzed using Kaplan-Meier method. Among 140 pts identified, median age at diagnosis was 40y with 69% males, 30% of pts had advanced disease (stage III-IV), 34% ≥3 nodal areas involved, 11% B symptoms and 24% increased LDH. Detailed histological characterization was available in 68 pts, most having the typical variants (A or B). In 19 pts (14%) a "watch and wait" (WW) strategy was chosen; of these, 42% required treatment after a median of 30 mo, while 58% are still under WW at last FU. In the remaining 121 pts, radiotherapy and combined modality treatment (33% and 34% respectively) were used in localized disease, while chemotherapy-only was utilized in 71% of advanced stages, mostly ABVD (42%). Rituximab was associated in 21% of pts, mainly with CHOP and CVP. ORR was 83% and CRR 81%. In localized and advanced disease ORR was 94% and 65% respectively. With a median FU of 65m (95% CI, 55–75) 17 pts relapsed and 8 transformed into high-grade B cell lymphoma. At relapse, salvage chemotherapy with ASCT and chemotherapy with rituximab were equally used. The median number of treatment lines was 1. Five-year PFS and OS were 73.8% (95% CI, 66.4–82.1) and 94.1% (95% CI, 90.0–98.5) respectively. PFS was lower in advanced stages and in pts with ≥3 nodal areas (p<0.001). At last FU 91% of patients were still alive, with 10 deaths (6 lymphoma related). Our study confirms the good outcomes and prolonged survival of NLPHL. Few pts had histological variant characterization, which is increasingly recognized as potentially contributing to better define prognosis and treatment in advanced stages. Treatment strategies should be adequately defined to optimize efficacy and minimize toxicity.

P013: OUTCOMES OF FIRST-LINE TREATMENT (FL) OF CLASSICAL HODGKIN LYMPHOMA (CHL) IN ARGENTINA: A REAL LIFE MULTICENTER RETROSPECTIVE STUDY

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Introduction: Estimated incidence of cHL in Argentina is 842 cases/year (Globocan 2018).There is no local data regarding response rates (RR) to FL. GATLA (Grupo Argentino de Tratamiento de Leucemia Aguda) reported 3 year-progression free survival (PFS) of 90% and overall survival (OS) of 98%.
Objectives: To learn the RR, PFS and OS after FL of cHL in public (PuI) and private institutions (PrI) in Argentina.
Methods: Retrospective analysis of patients (pts) with cHL diagnosis from 1–2008 to 2–2019 and available follow up (FU) data. Descriptive

statistics were used for clinical and histological variables. Survival rates were estimated with Kaplan-Meier and variables compared with log-rank test.
Results: 498 pts with cHL from 7 PuI and PrI were analyzed. Median FU: 37.4 months (m). Pts characteristics: Table 1. Median time to FL initiation: 22 days, shorter in PrI (p=0.0027). 96.5% received ABVD as FL. 17.1% required dose modifications or delays. Complete remission (CR) rate: 83.4% (higher in PrI) and partial remission (PR): 6.3%. 85.4% had negative end of treatment (EOT) PET. 70% had an interim PET (i-PET) exam, 83.8% achieved metabolic CR but only 15.5% were treated with PET-adapted strategies (6.5% deescalated to AVD). Anemia, neutropenia and thrombocytopenia were found in 28.5%, 56.4% and 7.2%, respectively. Non-hematologic toxicities were observed in 28.6% (lung toxicity in 41 pts). 51 pts had primary refractory disease and 69 relapsed. 65 pts died, due to lymphoma progression (34) and toxicity (31). 2 and 5 year OS rate: 91% and 85%. There was no difference in OS between PrI and PuI (p=0.27). 5 year PFS rate: 76%. Every day of delay in initiating FL increased 0.89 (CI95% 0.6–1.8) the risk of PR or progressive disease after FL. On univariate analysis: women, age <60, non-bulky disease, normal ESR, stage I-III, favorable prognostic disease, Charlson score <3 and absence of extranodal were associated with better outcomes. On multivariate analysis Charlson score and EOT PET scan remained independent predictors of OS with HR of 1.2 (CI95%1.1–1.7; p=0.001) and 2.3 (CI95% 1.7–3.2; p<0.0001), respectively.
Conclusions: This is one of the largest retrospective cohorts reported in cHL. ABVD is the FL regimen of choice in our country. It was well tolerated but not exempt from toxicity. Despite wide use of i-PET, only 15.5% received PET-guided treatment. The use of response-adapted strategies in our population should be strongly considered.

Variable	
Age	
Median (IQR) – yr.	34.5 (25–54)
Female gender – nº. (%)	239 (47.9)
Ann Arbor stage – %	
I	4.8
II	47.3
III	19.2
IV	28.6
Bulky disease – nº. (%)	164 (32.9)
B symptoms – nº. (%)	294 (59)
Extranodal involvement – nº. (%)	173 (34.7)
Charlson score, median (IQR)	2 (0-2)
Risk group- %	
Early favorable	15.8
Early unfavorable	36.3
Advanced favorable	15.6
Advanced unfavorable	32.3

Table 1: Characteristics of patients diagnosed with cHL treated in first line (n:498)

P014: PROGNOSTIC SIGNIFICANCE OF NUTRITIONAL INDEXES (CONUT AND PNI) IN CLASSICAL HODGKIN LYMPHOMA PATIENTS

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Background: Several recent studies have shown the clinical significance of poor nutritional status accessed by Prognostic Nutritional Index (PNI) and Controlling Nutritional status (CONUT) on patients (pts) with solid and hematological malignancies, but its impact on classical Hodgkin lymphoma (cHL) is not established.
Aim: To evaluate the prognostic value of baseline PNI and CONUT in cHL.
Methods: Retrospective analysis of adult pts with cHL, diagnosed between 1990 and 2017 and treated with curative intent with ABVD, escalated BEACOPP or ABVD hybrid regimen and with available data on all PNI variables. The cutoff point for PNI was evaluated using ROC statistics. The association between both scores and progression free survival (PFS) and overall survival (OS) was performed by Cox regression.
Results: 318pts were included, 46.2% male, with median age of 32 (18–80). Of these, 246 (77.3%) had nodular sclerosis and 213 (67%) had advanced stage cHL (GHSG classification). Information on BMI was available for 187pts (median 23.5kg/m2) and 3.2% had BMI<18.5kg/m2.
Mean baseline PNI was 47.2 (SD±8.7) and median PFS of 364 months (m). After ROC statistics, the optimal cutoff for PNI to predict 5-year (y) PFS was 47 (Sensibility 36%, Specificity 47%, AUC 0,377). PNI≥47 was significantly associated with an improved PFS (HR 0.42; p<0.001) in univariate analysis, with PFS 5y of 69% for PNI<47 and 82% for PNI≥47. In advanced stages, PNI≥47 retains its prognostic value, even after adjusting for IPS (HR 0.059; p=0.034).
After a median follow-up of 145m, median OS was not reached. PNI≥47 was significantly associated with an improved OS (HR 0.35; p<0.001) in univariate analysis but lost its significance in a multivariate model.
CONUT was calculated in 191pts (median follow-up 163m), with a median score of 2 (0–9) and most pts with normal/mild risk (86.9%). Higher values of CONUT were associated with poorer PFS (HR 1.13; p=0.040) and OS (HR 1.26; p=0.001), despite its categorization not being a significant predictor of PFS (HR 1.30; p=0.150). The four categories of CONUT were predictors for OS (HR 2.04; p=0.001).
Conclusion: In our cohort, baseline poor nutritional status, calculated with PNI or CONUT, was associated with significantly worse prognosis in cHL. Categorization of CONUT was not a significant predictor of PFS most likely due to a shorter follow-up and fewer pts included. Further external validation of theses scores in cHL is warranted.

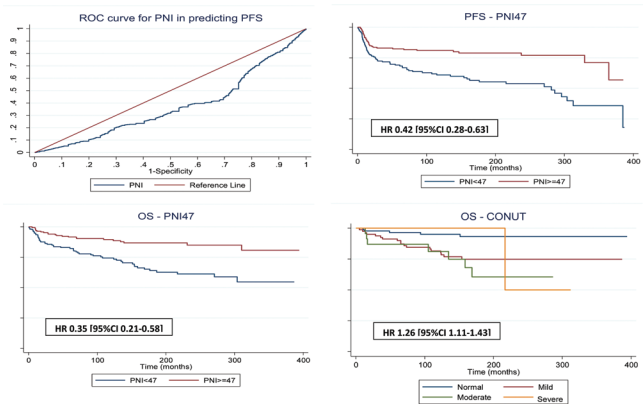

Figure 1: ROC curve for PNI in predicting progression-free survival and Overall and progression-free survival according to PNI and CONUT scores.

P015: REAL WORLD ESCALATED BEACOPDAC DELIVERS SIMILAR OUTCOMES TO ESCALATED BEACOPP WHILE POTENTIALLY REDUCING HAEMATOPOIETIC AND REPRODUCTIVE TOXICITY

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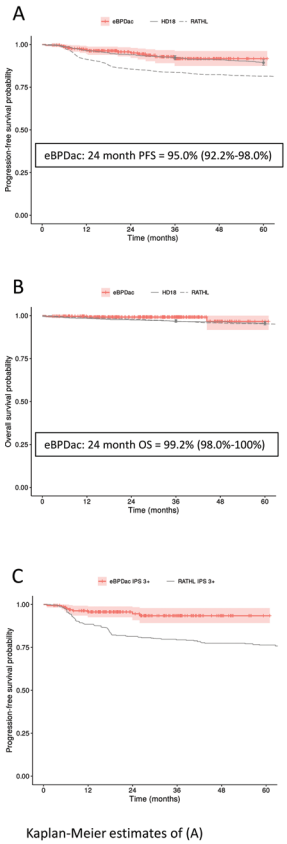
When treating advanced stage Hodgkin lymphoma, it is common UK practice to modify escalated BEACOPP (eBPP) by removing oral procarbazine and replacing it with intravenous dacarbazine (250mg/m2 D2-3). This is a retrospective study of patients treated with first line escalated BEACOPDac (eBPDac) at 23 centres updated since ASH 2021. With a median follow-up of 28 months, the 24-month progression-free survival (PFS) is 95% (CI 92.2–98.0%).

Of 268 eBPDac patients, 226 were treated as per HD18 protocol and 42 as per AHL2011. Survival outcomes were compared with 2073 eBPP patients in the HD18 trial and 1088 patients aged 18-59y in the RATHL trial. The eBPDac patients were younger than the HD18 and RATHL patients but had higher risk and more stage 4 disease. Of the eBPDac patients 76% achieved iPET Deauville score (DS) ≤3, similar to RATHL (DS≤3:83.7%) and HD18 (DS≤3:76%). One patient had primary refractory disease and twelve have relapsed at 6 to 36 months. Three patients have died of non-lymphoma causes. The eBPDac 24-month PFS is similar to HD18 3-year PFS (95% vs 92.3%) and appears superior to RATHL 5-year PFS (81.4%). The difference in PFS between eBPDac and RATHL is most marked in IPS3+ patients. The eBPDac 24-month OS estimate is 99%.

Toxicity was compared between eBPDac patients and 68 matched real-world eBPP patients over the first 4 cycles. There were no significant differences in age, sex or stage, but more eBPP patients had high risk disease (IPS3+). Mean day 8 (D8) ALT was similar between the two regimens. Mean D8 neutrophil count was lower in eBPDac patients with D9 GCSF. eBPDac patients received fewer red cell transfusions compared with eBPP patients (mean 1.88 vs 3.83 units, p<0.001) and had fewer non-elective days of inpatient care (mean 3.49 vs 5.66; p=0.021). Of the women aged <35y who completed ≥4 cycles chemotherapy, 52/52 had return of menstrual periods after eBPDac, compared to 25/28 after eBPP. eBPDac patients appeared to restart menstruation earlier post chemotherapy (mean 4.71 vs 8.89 months, p=0.002). However, eBPP patients received more cycles of chemotherapy.

To compare haematopoietic stem cell toxicity, peripheral blood mononuclear cells were isolated from 4 eBPDac, 5 eBPP and 3 ABVD patients. Haematopoietic progenitor cells were grown in culture and the colonies harvested have undergone whole genome sequencing. The data is imminent and we will present the mutation burden and mutational signatures associated with these regimens.

Figure 1



Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival of the eBPDac-treated patients compared with intention-to-treat set in the HD18 trial and 18-59y RATHL patients. (C) Kaplan-Meier estimate of progression-free survival in IPS3+ eBPDac patients compared to IPS3+ 18-59y RATHL trial patients.

Table (right) of baseline characteristics and treatment outcomes of eBPDac-treated patients and real-world eBPP patients.

Baseline Characteristics	Escalated BEACOPP N=68	Escalated BEACOPDac N=268	p-value
Median Age (range)	24 (16-57)	26 (16-62)	U=9261, p=0.836
Male sex (%)	34 (50%)	158 (59%)	Fisher, p=0.217
Stage 2B / 2X / 2XB	13 (19%)	42 (16%)	Fisher, p=0.576
3	8 (12%)	44 (16%)	
4	47 (69%)	182 (68%)	
IPS 0-2	15 (22%)	95 (36%)	
3-4	39 (57%)	134 (50%)	
5-7	14 (21%)	38 (14%)	Fisher, (0-2 vs ≥ 3) p=0.042
IPS ≥3	53 (78%)	172 (64%)	
Unknown	0	1	
Treatment Outcomes			
Total cycle number 1	1 (1%)	3 (1%)	
2	0	42 (16%)	
4	12 (18%)	150 (56%)	Fisher, (4 vs 6) p=4.64E-12
5	5 (7%)	5 (2%)	
6	49 (73%)	67 (25%)	
7	1 (1%)	0	
On treatment	1 (1%)	1 (0.3%)	
iPET Deauville score			
1- 2	16 (28%)	76 (29%)	
3	22 (39%)	125 (47%)	
4	19 (33%)	64 (24%)	Fisher, (≤3 vs 4-5) p=0.184
5	0	1 (0.4%)	
≤3	38 (67%)	201 (76%)	
No iPET	11	2	
Mean day 8 ALT (cycles 1-4) [SD]	38.7 (±30.8)	45.4 (±29.0)	t(90)=1.51 p=0.136
Mean day 8 neutrophils (cycles 1-4) [SD] (GCSF day 9)	2.74 (±1.62)	2.22 (±1.47)	t(103)=2.17 p=0.0322
(GCSF day 4)	NA	5.63 (±5.91)	
Mean days non-elective admission (cycles 1-4) [SD]	5.66 (±7.42)	3.49 (±6.39)	U=5743, p=0.021
Mean number of red cell units transfused (cycles 1-4) [SD]	3.83 (±4.01)	1.88 (±2.93)	U=4616 p=1.06E-5
Median follow-up from diagnosis in months (range)	70.0 (5.0-147)	28.1 (0.92-61.0)	U=2250, p=2.2E-16
Mean number of months for return of menstrual period post-chemotherapy [SD]	8.89 (±5.66)	4.71 (±2.64)	t(27)=3.60, p=0.00184
Mean number of cycles completed by women <35 years of age [SD]	5.76(±0.58)	4.67 (±0.94)	U=404, p=8.33E-7

Figure 1: Kaplan-Meier estimates of progression-free survival and overall survival of the eBPDac-treated patients compared with intention-to-treat set in the HD18 trial and 18-59y RATHL patients. Table of patient characteristics and treatment outcomes.

P016: REDUCED STEROID EXPOSURE IS SAFE AND DOES NOT REDUCE DISEASE CONTROL AMONG HODGKIN LYMPHOMA PATIENTS TREATED WITH ESCALATED BEACOPP (EBEACOPP)

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Background: eBEACOPP is the most effective chemotherapy regimen for younger patients with early unfavourable (EU) and advanced stage (AS) Hodgkin lymphoma (HL), but is burdened with early and late toxicities. The original 14 days of steroids contributes to side effects, including severe osteoarticular events, like avascular bone necrosis (AVN). We have been using eBEACOPP since 2009 for AS and since 2014 also for EU patients. We started reducing the length of steroid treatment to 8–10 days in 2016, primarily to reduce the risk of AVN.

Methods: We analysed outcomes of our patients, focusing on the comparison of EU and AS patients and those receiving full length and shorter steroid courses. Data was obtained retrospectively, from the hospital database.

Results: 162 patients received eBEACOPP as front-line treatment, 130 with AS and 32 with EU HL. Median age was 31 y, range 19–59; 88 (54%) were male. After a median follow-up of 58 mo, 5-y PFS of the whole cohort was 97% and OS 98%. The outcome of EU and AS patients was indistinguishable with a 5-y PFS of 95% vs. 98%, respectively (Fig). Outcome of patients receiving full-length or shorter steroid courses was also indistinguishable, with a 5 y PFS of 98% vs. 95% respectively (Fig). The incidence of AVN was numerically, but statistically insignificantly lower in patients receiving 6 cycles of eBEACOPP with a shorter steroid course (1/42 vs. 4/72, p=0.65). There were no differences in emergency hospital admissions and episodes of febrile neutropenia between the two cohorts.

Conclusion: eBEACOPP provides excellent and durable first line disease control. Our data confirms the findings of GHSG of lack of outcome differences between different prognostic groups if eBEACOPP is used as primary treatment. Reducing the duration of steroid treatment to 8 days per cycle is safe, but longer follow-up and more patients are needed to confirm that it reduces serious acute and chronic toxicities.

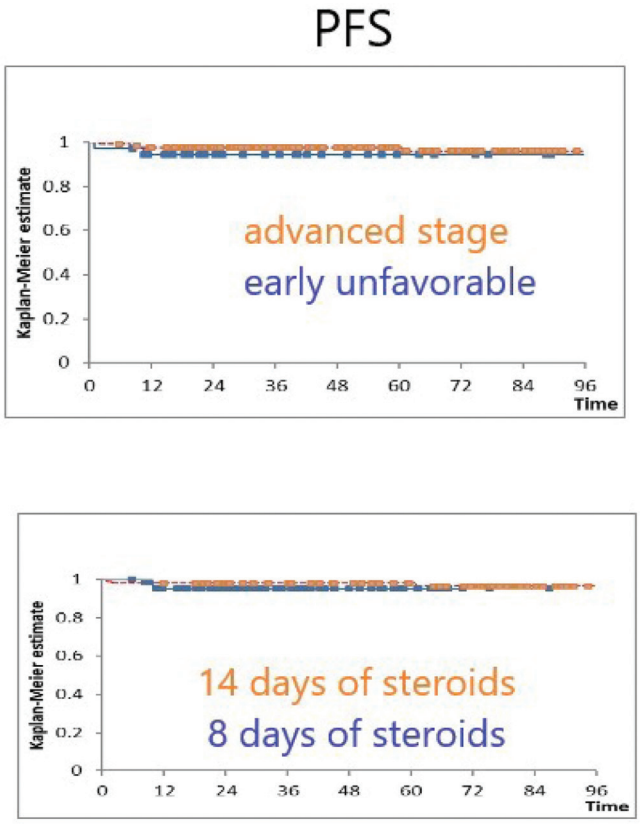

Figure 1: PFS (Kaplan-Meier curves): The outcome of EU and AS patients - 5-y PFS 95% vs. 98%, respectively. Full-length vs. shorter steroid courses - 5 y PFS 98% vs. 95%, respectively.

P017: THE ROLE OF BASELINE BULK AND DISSEMINATION MEASURES AS PREDICTORS OF PROGRESSION IN ADVANCED HODGKIN LYMPHOMA

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Introduction: Numerous clinical and FDG-PET/CT-associated models were proposed to predict treatment failure in Hodgkin's lymphoma (HL). Baseline quantitative FDG-PET metrics are emerging biomarkers showing promising prognostic value. We retrospectively analysed the impact of tumour bulk and dissemination as measured by assessing Metabolic Tumor Volume (MTV) and D max - the distance between the furthest lesions identified by FDG-PET/CT - on the probability of progression in HL patients in clinical stages II to IV.
Methods: Baseline FDG-PET/CT data of 117 patients with newly diagnosed HL from the PLRG-11 study was analysed and MTV was assessed by manual segmentation with the volume of interest (VOI) threshold of 41%SUVmax and Dmax was calculated by measuring the diameter between centroids of VOIs with SUVmax above SUVmax of the liver located furthest apart. The Median follow-up was months. The distance was measured in 3-dimensional space using Euclidean geometry. The cut-off values of MTV and Dmax were calculated with the maximally selected rank statistic method.
Results: MTV cut-off value for progression-free survival (PFS) prediction was 214 ml with PPV 0,516 and NPV of 0.848 and for Dmax

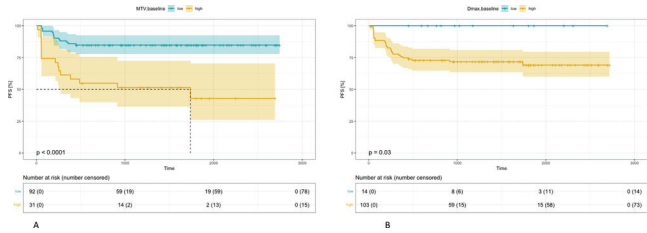

Figure 1: Probability of progression-free survival by baseline MTV (A) and Dmax (B)

was 10 cm with PPV 0.291 and NPV of 1.0. In the cohort of 69 patients with negative interim PET/CT performed post-second cycle of ABVD PFS event was reported in 0% and 17% patients with Dmax below and above 10 cm, respectively and in 6% and 36% of patients with MTV below and above threshold value of 214 ml, respectively.
Conclusion: Bulk and dissemination assessments in baseline PET/CT in Hodgkin lymphoma stage II-IV patients may help identify a population of patients with an especially good prognosis.

P018: TREATMENT OUTCOMES IN CLASSICAL HODGKIN LYMPHOMA (HL): 5-YEAR UPDATE REPORT FROM THE BRAZILIAN PROSPECTIVE REGISTRY

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Introduction: Data about HL in developing countries are scarce. In 2009, a HL prospective registry was launched in Brazil.
Methods: The first analysis was presented with patients (pts) diagnosed from 2009 to 2014. Here we present an updated analysis with pts diagnosed until 2018 and a median follow-up of 5 years.
Results: A total of 1357 pts with HIV negative classical HL were registered from January 2009 to December, 2018. 28 pts were excluded for various reasons, leaving 1329 pts for this analysis. Median age was 30 y/o (13–90). Females comprised 50%. The median time from onset of symptoms to diagnosis was 6 (0–60) months. 862 (65%) had advanced disease. Stage IVB was present in 28%, and a high-risk IPS score in 40%. Comparing pts included from 2009–2014 and 2015–2018, there was an increase in the use of PET for staging (11% vs 36%, P<.0001) and for end-of-treatment (40% vs 79%, P<.0001). ABVD was the first-line treatment in 94% of pts. 34 pts (2.6%) died during the first treatment. Radiotherapy (RT) was used in 72% of pts with limited, 59% with intermediate, and 28% with advanced disease. There was a reduction in the use of RT (44% vs 35%, P=.002) from 2009–2014 to 2015–2018. This reduction was higher in advanced disease (32% vs 24%, P=0.01). The 5-year progression-free survival (PFS) and 5-year overall survival (OS) were 70% and 86%, respectively. The 5-year PFS in limited, intermediate, and advanced disease were 97%, 82%, and 62% (P<.0001), respectively. The 5-year OS for limited, intermediate

and advanced disease were 100%, 94%, and 80% (P<.0001), respectively. The impact of socioeconomic status (SES) on outcomes was analyzed in pts treated with ABVD. The 5-year PFS in higher and lower SES were 75% and 60% (P<.0001). The 5-year OS in higher and lower SES were 90% and 77% (P<0.0001). The fatality ratio during treatment was 5.0% and 1.1% for lower and higher SES (P<0.0001). After adjustments for potential confounders, lower SES remained independently associated with poorer survival (HR 2.10 [1.52–2.90] for OS and HR 1.58 [1.26–1.99] for PFS).
Conclusions: This analysis confirmed the predominance of advanced disease and high-risk profile pts. There was an increase in the use of PET and a reduction in RT in recent years. We confirmed that the outcomes are 10–15% lower in Brazil than reported in the literature. SES was an independent factor associated with shorter survival.

P019: UNFAVORABLE PROGNOSTIC VALUE OF THE PREDOMINANCE OF THRLBCL-LIKE HISTOPATHOLOGICAL GROWTH PATTERNS IN NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA (NLPHL)

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Introduction: NLPHL is characterized by variable morphology and histopathological growth patterns of the tumor substrate. Our study demonstrated the prognostic significance of THRLBCL-like histopathological growth patterns.
Purpose: to evaluate the efficacy of 1st line therapy of NLHLP depending on THRLBCL-like histopathological growth patterns in the tumor substrate.
Materials and Methods: We analyzed the results of 1st line therapy in 150 patients with NLHLP from 2010 to 2021 yrs. Growth patterns without THRLBCL-like sites were noted in 87/150 (58%), THRLBCL-like patterns - in 63/150 (42%). Additionally, patients with a predominance of THRLBCL-like areas (more than 50% of the cut area) were identified - 32/150 (21%) pts.
Results: In 87 (58%) pts with growth patterns without THRLBCL-like areas, 30/87 (34%) pts did not receive chemotherapy; radiation therapy was applied in 20/30 (complete remission (CR) was achieved in all 20 pts); observation after surgical treatment - 10/30 pts; 5 pts - no data. Chemotherapy (R-ABVD - 44%; R-BEACOPP-14–38%; other - 17% pts) was performed in 52/87 (60%) pts; CR was achieved in 68/87 (78%).
In 63 (42%) pts with THRLBCL-like patterns, 2/63 (3%) did not receive chemotherapy; 1 patient - in CR after radiation therapy; 1 - under observation after surgical treatment; 4 patients - no data. Chemotherapy (R-ABVD - 18%; R-BEACOPP-14–54%; R-CHOP - 21%; other - 7% pts) received 57/63(90%) pts; CR was achieved in 31/63(49%) pts, partial remission (PR) - in 15/63(24%), stabilization (S) - 2(3%), progression - 4(6%) pts.
In 32 (21%) pts with predominance of THRLBCL-like areas, 30 pts underwent chemotherapy (R-ABVD - 16%; R-BEACORP-14–57%; R-CHOP- 27% pts); CR was achieved in 12 (37%), PR-10 (31%), S-1 (3%), progression - 4 (13%) pts. In 2 pts - no data.
The 5-year OS for groups with the absence, presence and predominance of THRLBCL-like patterns was 99%, 100%, 68% (p-<0.0001), respectively, the 5-year EFS was 75%, 68%, 32% (p-< 0.0001) respectively. Median follow-up is 34 months.
Conclusion: In NLHLP the group of patients with a predominance of THRLBCL-like patterns has the most unfavorable prognosis - CR achieved in 37%, 5-year OS does not exceed 68%, EFS - 32%. Therefore an intensification of first-line therapy is needed for this group of patients.

Early Stages

T020: INTERIM PET-GUIDED TREATMENT OF EARLY-STAGE NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA: A SUBGROUP ANALYSIS OF THE GHSG HD16 AND HD17 STUDIES

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Background: The optimal treatment for patients with early-stage nodular-lymphocyte predominant Hodgkin lymphoma (NLPHL) other than stage IA is undefined.
Patients and Methods: We investigated characteristics and outcomes of patients with early-stage NLPHL (favorable: 85 patients; unfavorable: 15 patients) who had treatment within the randomized GHSG HD16 and HD17 studies. Results were compared to those from patients with classical Hodgkin lymphoma (cHL) (favorable: 495 patients; unfavorable: 764 patients) treated within the same studies. Chemotherapy consisted of 2 cycles of ABVD (HD16) or 2 cycles of escalated BEACOPP plus 2 cycles of ABVD („2+2“) (HD17). In the experimental study arms, consolidation radiotherapy (RT) was applied on the basis of the result of interim positron emission tomography (PET-2). In the standard arms, consolidation RT was mandatory. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method.
Results: In the HD16 and HD17 studies, 62/85 (73%) and 13/15 (87%) NLPHL patients were male as compared to 254/495 (51%) and 337/764 (44%) cHL patients. The median age of patients with NLPHL was 37 years in the HD16 study (cHL: 36 years) and 42 years in the HD17 study (cHL: 31 years). The majority of NLPHL patients included in the HD16 and HD17 studies presented with a typical histopathological growth pattern (HD16: 66%; HD17: 70%)
The 5-year PFS for all NLPHL patients was 90.3% (cHL: 90.8%) in the HD16 study and 92.9% (cHL: 95.7%) in the HD17 study. In the HD16 study, the 5-year PFS for the subgroup of PET-2-positive NLPHL patients was 89.3% (cHL: 91.6%); PET-2-negative NLPHL patients had a 5-year PFS of 91.0% (cHL: 90.4%). For PET-2-negative NLPHL patients assigned to the chemotherapy only arm, the 5-year PFS was 83.0% (cHL: 88.2%) whereas PET-2-negative NLPHL patients treated with chemotherapy plus RT had a 5-year PFS of 100% (cHL: 92.3%) (p=0.05). Subgroup analyses according to the PET-2 result were not conducted for NLPHL patients treated within the HD17 study due to the small number of individuals with NLPHL histology included in this trial. The 5-year OS for NLPHL patients treated within the HD16 and HD17 studies was 100% (cHL: 98.6% in HD16; 99.2% in HD17).
Conclusion: Contemporary HL-directed treatment results in excellent 5-year outcomes for patients with newly diagnosed early-stage NLPHL and should thus be considered as valid approach for this patient group.

T021: RADIATION-FREE THERAPY AS THE INITIAL TREATMENT OF GOOD-PROGNOSIS EARLY NON-BULKY HODGKIN LYMPHOMA, DEFINED BY A LOW METABOLIC TUMOR VOLUME AND A NEGATIVE PET-2 - RAFTING TRIAL.

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Introduction: The efficacy of combined modality treatment (CMT) with chemotherapy (CT) and radiotherapy (RT) in early-stage Hodgkin Lymphoma (eHL) is offset by long-term morbidity, with a cumulative incidence of Second Primary Malignancy (SPM) at 40

years of 48.5% (Schaapveld 2015). The primary endpoint of the RAFTING trial is a 3-Y PFS ≥ 90% of a RT-free CT (2 or 4 ABVD cycles) in low-risk non-bulky stage I-IIA eHL with a low Metabolic Tumor Volume at baseline (bMTV) and a negative PET-2. Secondary endpoints: (a) Effectiveness of delayed Involved-node RT (In-RT) and Nivolumab maintenance, 240 mg. i.v. twice a month for one year (Nivo-m) in case of "limited" relapse (LR: stage I-II with up to 3 new nodal areas) after CT; (b) effectiveness of the triplet: ABVD x 4, InRT and Nivo-m in high-risk eHL, with either a high bMTV or a positive PET-2; (c) predictive value of tumor cell-free DNA (cfDNA) in detecting an impending relapse during follow-up of patients (p.) in CR after CT alone.

Methods: RAFTING is a prospective phase 2 multi-center, international trial, enrolling 160 non-bulky stage I-IIA eHL p. from four European countries. Treatment intensity is tailored to three classes of p. with a different risk of treatment failure, depending on (a) the modified EORTC criteria (m-EORTC), in which classical bulky is taken over by a Large Nodal Mass (LNM, defined by the largest diameter > 5 cm in CT or PET/CT scans), (b) bMTV and (c) PET-2. The risk-stratified treatment is the following: Group 1: PET-2 neg. & low bMTV p, treated with 2–4 ABVD cycles (depending on m-EORTC), addressed, once in CR, to a 3-monthly cfDNA assay; Group 2: group 1 p. relapsing with a LR, treated with delayed INRT at the dose of 36 Gy, and Nivo-m; Group 3: PET-2 positive (Group 3a), and/or a high bMTV (Group 3b) p. treated with ABVD x 4, INRT, (20 or 30 Gy), and Nivo-m. All PET/CT are centrally reviewed.

Results: out of 55 p. enrolled 52 were eligible, and 31/52 with both bMTV and PET-2 assessed were stratified for risk as follows: group 1a: 6; group 1b 17; group 3a: 2; Group 3b: 6. Three p. of group 3 are on Nivo-m, without major side effects. Updated results will be presented.

Conclusions: (a) the majority of p. enrolled so far (74%) belong to Group 1 (low risk), and most of them (74%) are treated with 4 ABVD because of mEORTC criteria (most often a LNM); (b) Most p. were attributed to Group 3 because of a high bMTV (6/8); (c) Nivo-m is feasible, safe and well-tolerated (no SAE).

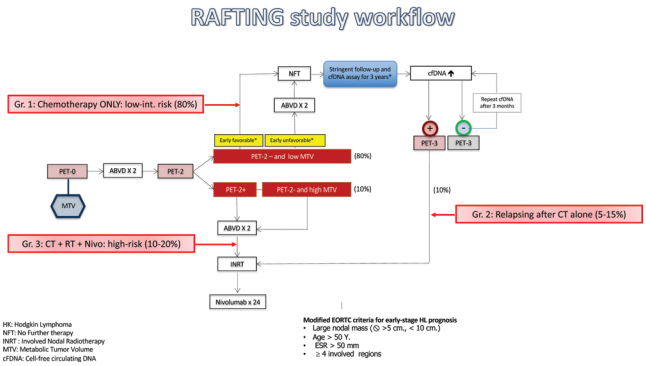

Figure 1: RAFTING Trial workflow

T022: SHARING DECISIONS REGARDING RADIOTHERAPY FOR HODGKIN LYMPHOMA: A QUALITATIVE STUDY OF THE EXPERIENCES OF PATIENTS AND CLINICIANS IN THE UK

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Background: Radiotherapy (RT) increases the chance of cure of Hodgkin lymphoma (HL) [1] but also has risks, including cardiac disease and second cancers [2]. Whilst guidelines broadly indicate which patients may benefit from RT, there are individual factors that can substantially affect the balance of benefit and risk. Little is known about how these factors are incorporated into decision-making, or patients' preferences for involvement in decisions.

This study aimed to explore the RT decision-making process, and better understand how patients' preferences are taken into account.

Methods: We conducted semi-structured interviews with 15 people treated for HL, and 12 clinicians who specialised in the treatment of HL. We used maximal variation sampling, and Braun and Clarke's thematic analysis. The study was co-designed with four people previously treated for HL and approved by the North of Scotland Ethics Committee.

Results: The decision about RT was commonly made by clinicians and presented to patients as a conclusion. Although patients acknowledged they could disagree with the clinicians' recommendation, they often perceived themselves to be in a life-threatening situation with no real choice about treatment. Patients were highly engaged and keen to receive information, but the majority felt too overwhelmed by the complexity of their illness to participate in RT decisions.

Patients and clinicians agreed that the ultimate responsibility for RT decisions lay with healthcare professionals, and that it was too challenging to lay the burden of this decision solely on the person with HL. Clinicians considered individual patient factors when recommending RT, and recognised the importance of ensuring that decisions were in line with a person's values and preferences (Figure 1).

Both patients and clinicians felt shared decision-making was hampered by the lack of easily accessible information predicting the risks of RT for an individual.

Conclusion: Decisions about RT lay mostly with clinicians, but individual patient circumstances were considered. The availability of data to understand the risks of RT for an individual would enhance the decision-making process.

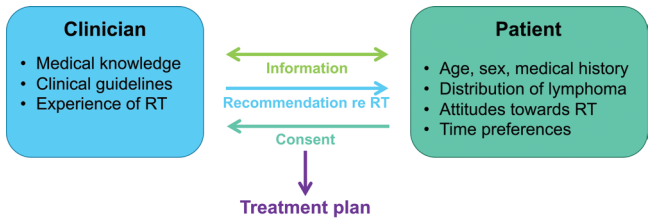

Figure 1: The radiotherapy decision-making process in current clinical practice, as described by patients and clinicians
Clinicians used their medical knowledge, experience of RT and clinical guidelines, integrated with the patients' age, sex, distribution of lymphoma, attitudes to RT and focus on short-term benefits rather than long-term risks to make a treatment recommendation for patients to consent to, resulting in a treatment plan
Abbreviations - RT: radiotherapy

Figure 1: The radiotherapy decision-making process in current clinical practice, as described by patients and clinicians

Literature

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P023: PET2-ADAPTED APPROACH AFTER 2 CYCLES OF ABVD IS COMPARABLE TO 2 CYCLES OF BEACOPP ESCALATED AND 2 CYCLES OF ABVD AND IRRADIATION IN EARLY UNFAVORABLE HODGKIN LYMPHOMA

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Background: PET2-adapted approach after 2 cycles of ABVD reduced treatment intensity in the majority of patients with early stages of classical Hodgkin lymphoma (cHL) according to EORTC H10 trial. GHSG HD17 enabled omission of radiotherapy in PET4-negative early unfavorable HL treated with 2 cycles of BEACOPP escalated and 2 cycles

of ABVD (2+2 chemotherapy). We compared PET2-adapted approach with 2+2 chemotherapy followed by 30 Gy of involved-node radiotherapy (INRT) regardless of interim PET in patients with early unfavorable cHL assessed according to the GHSG risk factors.
Methods: Overall, 224 patients with early unfavorable cHL (aged 18–60 years) prospectively observed in the Czech Hodgkin Lymphoma Study Group Registry between 2003–2021 were analyzed. Patients in clinical stage IIB with massive mediastinal tumor and/or with extranodal disease were excluded. Overall, 194 patients received 2+2+INRT chemotherapy and 30 patients were treated with PET2-adapted approach: 29 PET2-negative patients received 4 cycles of ABVD and 30 Gy of INRT and one PET2-positive patient was treated with 2 cycles of ABVD plus 2 cycles of BEACOPP escalated and 30 Gy INRT.
Results: Median age at the time of cHL diagnosis was 32 (range 18–59) years. Median follow-up was longer in the 2+2+INRT group (98.9, range 6.2–211.7) months compared to the PET2-adapted approach (30.8, range 9.8–90.4) months. The 2-year progression-free survival and 2-year overall survival did not differ between two groups (99.5% [95% CI 98.5%–100%]) and 100% [95% CI 100%–100%]), respectively. The rate of patients with neutropenia grade 3 and anemia grade 3 did not differ significantly between both groups (p=0.09 and p=0.60, respectively). Thrombocytopenia was more frequent in the 2+2+INRT group (p0.001). Grade 3 non-hematological toxicity occurred in 3 patients in the 2+2+INRT group (2 infections, 1 deep vein thrombosis).
Conclusion: This retrospective analysis indicates that there is no superiority in progression-free survival and overall survival when comparing 2+2 chemotherapy and INRT to PET2-adapted approach. The toxicity is higher in the 2+2+INRT group.
This work was supported by the following grants AZV NU22-03–00182 from the Ministry of Health of the Czech Republic and Cooperatio Program awarded by the Charles University in Prague in the Czech Republic.

P024: PREDICTIVE VALUE OF BASELINE METABOLIC TUMOR VOLUME IN EARLY-STAGE FAVORABLE HODGKIN LYMPHOMA – DATA FROM THE PROSPECTIVE, MULTICENTER PHASE III HD16 TRIAL

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Background: 18F -fluorodeoxyglucose (FDG) positron emission tomography (PET) plays an important role in the staging and response assessment of lymphoma patients. Our aim was to explore the predictive relevance of metabolic tumor volume (MTV) and total lesion glycolysis (TLG) in patients with early stage Hodgkin lymphoma treated within the German Hodgkin Study Group HD16 trial.
Methods: 18F-FDG PET/CT images were available for MTV and TLG analysis in 107 cases from the HD16 trial. We calculated MTV and TLG using three different threshold methods (SUV4.0, SUV41% and SUV140%L), and then performed receiver-operating-characteristic analysis to assess the predictive impact of these parameters in predicting an adequate therapy response with PET negativity after 2 cycles of chemotherapy.
Results: All three threshold methods analyzed for MTV and TLG calculation showed a positive correlation with the PET response after 2 cycles chemotherapy. The largest area under the curve (AUC) was observed using the fixed threshold of SUV4.0 for MTV- calculation (AUC 0.69 [95% CI 0.55–0.83]) and for TLG-calculation (AUC 0.69 [0.55–0.82]). The calculations for MTV and TLG with a relative threshold showed a lower AUC: using SUV140%L AUCs of 0.66 [0.53–0.80] for MTV and 0.67 for TLG [0.54–0.81]) were observed, while with SUV41% an AUC of 0.61 [0.45–0.76] for MTV, and an AUC 0.64 [0.49–0.80]) for TLG were seen.
Conclusions: MTV and TLG do have a predictive value after two cycles ABVD in early stage Hodgkin lymphoma, particularly when using the fixed threshold of SUV4.0 for MTV and TLG calculation.

P025: RADAR: AN INTERNATIONAL PHASE III, PET RESPONSE-ADAPTED, RANDOMISED TRIAL IN PROGRESS, COMPARING ABVD±ISRT WITH BRENTUXIMAB VEDOTIN+AVD±ISRT IN PATIENTS WITH PREVIOUSLY UNTREATED LIMITED-STAGE CLASSICAL HODGKIN LYMPHOMA

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Background: Limited-stage classical Hodgkin lymphoma (lsHL), stages I or II without B-symptoms or mediastinal bulk disease, has excellent long-term survival (≥90%) with modern treatment. Commonly used approaches, based on GSHG and EORTC trials, include 2–4 cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) plus 20 or 30

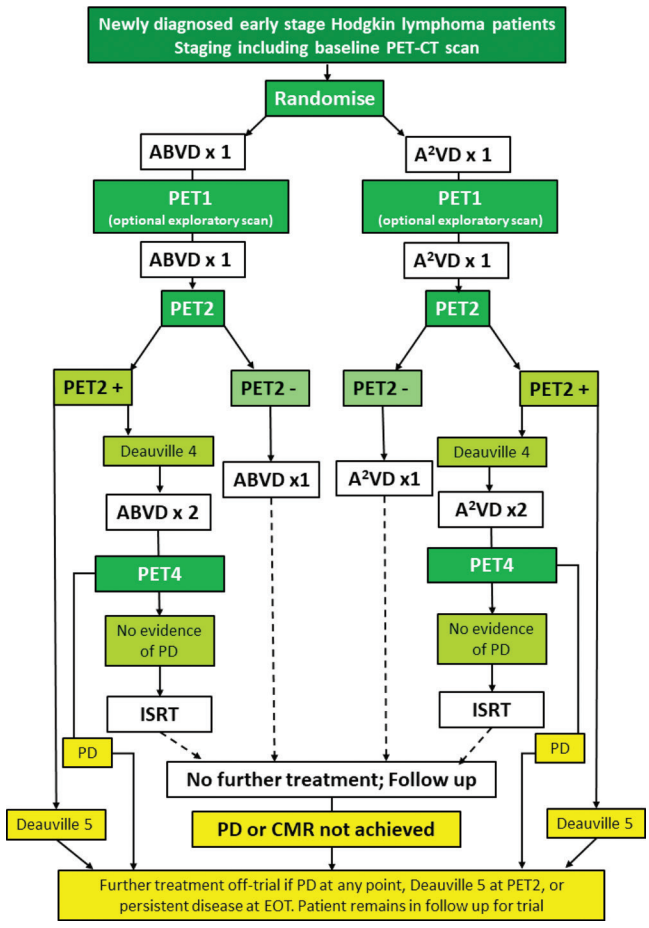

Figure 1: RADAR trial schema

Gy radiotherapy (RT), but there are concerns about the impact of using RT in all patients (pts) on the incidence of 2nd cancers and cardiovascular disease.
In the UK NCRI RAPID trial, pts who had a -ve PET scan after 3 cycles of ABVD were randomised between RT and no RT; outcomes in the no RT arm were very good but the non-inferiority margin of -7% was not achieved. The RADAR trial is building on the PET-adapted approach of RAPID but intending to make the chemotherapy more effective by replacing bleomycin with the CD30 targeted antibody drug conjugate, brentuximab vedotin (BV), in the BV+AVD regimen. Early phase trials of BV+AVD in lsHL and the phase III ECHELON-1 trial in advanced HL have demonstrated its efficacy and safety. In addition, RT will be integrated on an individualised basis to pts in RADAR who are PET -ve after initial chemotherapy but with larger nodal masses at baseline.
Methods: RADAR comprises 2 parallel identical phase III randomised multicentre trials in the UK, Europe, Australia, New Zealand (trial 1; 642 pts), Canada and the USA (trial 2; 400 pts). Eligibility: age 16–69 years, previously untreated stage IA/IIA HL above the diaphragm, any mediastinal mass ≤0.33 of internal thoracic diameter, informed consent. Pts will be randomised to receive either ABVD or BV+AVD. A centrally-reviewed PET-CT scan after cycle 2 (PET2) will determine further treatment (Deauville score (DS) 1–3: total 3 cycles +/- individualised RT; DS 4: total 4 cycles + 30 Gy ISRT; DS 5: treatment failure, subsequent treatment of clinician's choice).
1y endpoint is progression free survival (PFS) and the trial will have 85% power to show an improvement from 90 to 95% PFS at 3 years (HR of 0.49) with 2-sided 5% alpha. 2y endpoints are CMR rate at PET2, event-free survival (progression, death, PET2 DS 4–5), OS, safety and toxicity including cardiovascular disease and second cancers. Exploratory endpoints: predictive value of PET after 1 cycle, prognostic value of baseline metabolic tumour volume. Embedded translational research aims to identify biomarkers predictive of treatment failure.
RADAR opened to recruitment in April 2022.

Genomics, Biology & Microenvironment

T026: CHARACTERIZATION OF CANCER-ASSOCIATED FIBROBLASTS IN CLASSICAL HODGKIN LYMPHOMA

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Background: Cancer-associated fibroblasts (CAFs) are a heterogeneous cell population with diverse functions. They constitute an important stromal component of the tumor microenvironment (TME), regulate immune responses and promote tumor growth. We have earlier characterized the immunoprofile of cHL and concluded that high proportions of checkpoint protein positive immune cells associated with unfavorable overall survival (OS). Here, we have characterized distinct CAF subsets and their clinical impact in cHL.
Methods: CAFs, tumor associated macrophages (TAMs), T cells and checkpoint molecules were phenotyped from the diagnostic cHL samples (n=131) using multiplex immunohistochemistry with digital image analysis. Platelet-derived growth factor receptor (PDGFR) α and β, fibroblast-activation protein (FAP) and α-smooth muscle actin (α-SMA) were utilized as CAF markers. Nanostring-based data from a 770-gene immune panel was used to correlate CAF proportions with gene expression.
Results: Median age of the patients was 30 years, 78% had nodular sclerosis subtype and 56% advanced stage. Primary treatment (85%) was mostly doxorubicin, bleomycin, vinblastine, dacarbazine, and in limited stage, in combination with radiotherapy. At the median follow-up time of 55 months, 22% of the patients relapsed and 8% died. Five-year freedom from treatment failure (FFTF) was 79% and OS 91%.
From all cells in the TME, 20% were PDGFRβ (range 0.2–92%), 19% FAP (range 0–88%), 16% α-SMA (range 2–56%), and 1% PDGFRα (range 0.1–58%) positive. High proportion of FAP+ cells associated with inferior FFTF (HR 1.25, 95%CI 1.0–1.5, P=0.020).
In a small subgroup of patients, PDGFRα and FAP were expressed on the same cells defining an PDGFRα+FAP+ double positive cHL phenotype, which translated to better outcome (5-y FFTF 100 % vs. 76%, P=0.035; 5-y OS 100% vs. 90%, P=0.270). Clinical characteristics were equally distributed between these subgroups. PDGFRα+FAP+ phenotype associated positively with high proportion of TAMs (P=0.026), but negatively with T cells (P=0.006) and checkpoint molecule indoleamine 2,3 dioxygenase 1 (IDO-1)+ cells (P=0.002). In addition, focal adhesion and extracellular matrix pathway genes were enriched in PDGFRα+FAP+ cHLs.
Conclusion: Our data identifies distinct CAF subsets in cHL and suggests that the newly characterized subset of PDGFRα+FAP+ CAFs has prognostic impact in cHL patients. Validation of the results is ongoing.

T027: HIGH SERUM LEVELS OF THYMUS AND ACTIVATION RELATED CHEMOKINE (TARC) PRECEDE HODGKIN LYMPHOMA DIAGNOSIS BY SEVERAL YEARS

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Background: Thymus and Activation Related Chemokine (TARC), also known as CCL17, is a chemokine that is highly secreted by tumor cells in classic Hodgkin lymphoma (HL). TARC levels are dramatically increased in serum samples of newly diagnosed HL patients (1).
Aim: To evaluate if and how long serum TARC levels are increased prior to a clinical diagnosis of HL.
Methods: We measured serum samples from the Department of Defense (DoD) Serum Repository that were collected over several years prior to the diagnosis of HL in the active-duty U.S. military population. Incident HL cases were diagnosed between 1990 and 1999 and included for analysis when a pre-diagnostic serum sample was available (n=101). The median age at diagnosis was 26 years and 10% were female. Pathology review revealed a normal distribution of subtypes and tumor cell EBV status was positive in 23% of cases. For each case, two matched controls were selected from the DoD Serum Repository based on age, sex, race and ethnicity, number of serum samples and sample collection date. The serum samples of these cases and controls were previously analyzed for IL-6, IL-10, soluble CD30 and total IgE (2). TARC levels were measured by a Luminex assay. Differences in log-transformed TARC levels between cases and matched controls were evaluated using mixed model analyses.

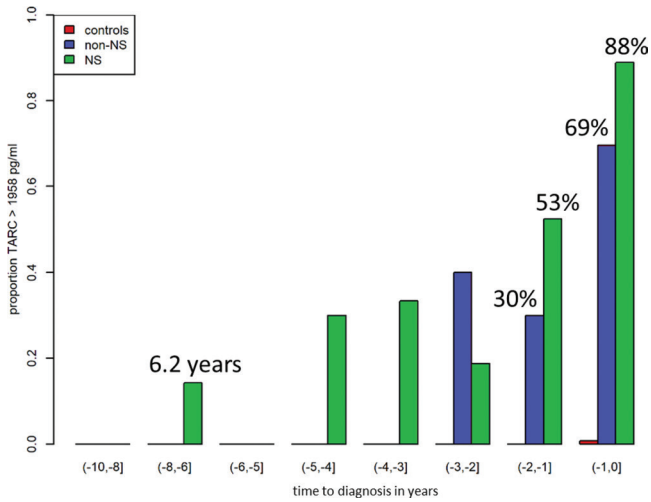

Figure 1: Proportion of individuals who can be identified as being affected in the years prior to Hodgkin lymphoma diagnosis. The cut-off is based on the mean + 1.96SD of control samples. NS, nodular sclerosis.

Results: TARC levels were measured in 211 samples from 101 patients, collected up to 9.8 years before diagnosis, and in 422 samples from matched controls. TARC levels were significantly higher in patients compared to controls (median 921 pg/ml (max. 1.6x105) vs. median 422 pg/ml (max. 3.5x102)), respectively (p=1.2x10-47 in the mixed model analysis). This effect was strongest in nodular sclerosis (NS) and EBV-negative cases, but also present in non-NS and EBV-positive cases. The longest time interval between an increased TARC level and diagnosis was 6.2 years for an individual who developed NS HL, with a logarithmic increase of TARC over time.
Conclusions: Increased serum TARC levels often precede diagnosis of classic HL by several years. This implies a long pre-diagnostic phase in which secretion of TARC and the resulting attraction of CD4+ T cells is an important mechanism in pathogenesis. In the clinical setting, serum TARC is being used as a therapy response marker(3) and its indication may be extended to diagnostic and even pre-diagnostic screening.

References
1.PMID 22058214; 2. PMID 28341757; 3. PMID 32106342

T028: SINGLE-CELL RNA SEQUENCING REVEALS THE INTERPLAY BETWEEN CIRCULATING CD4 T CELLS, B CELLS AND CANCER-ASSOCIATED MONOCYTES IN CLASSIC HODGKIN LYMPHOMA TREATED WITH PD-1 BLOCKADE

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Classic Hodgkin lymphoma (cHL) is a largely MHC class I-negative tumor with recurrent 9p24.1/ PD-L1/ PD-L2 copy gains and the highest reported response rates to PD-1 blockade. In cHL, the efficacy of PD-1 blockade is closely associated with Hodgkin and Reed-Sternberg (HRS) cell expression of MHC class II, highlighting the potential role of CD4+ T-cell effectors and additional non-MHC class I-mediated mechanisms of tumor cell killing. We utilized scRNA sequencing to characterize the peripheral immune response to PD-1 blockade and more broadly define non-CD8+ dependent mechanisms of immune evasion in cHL.
Peripheral blood mononuclear cells were obtained from 20 patients with relapsed/refractory (R/R) cHL treated with PD-1 blockade (nivolumab) on the CheckMate 205 clinical trial (cycle 1 day 1 [C1D1] and cycle 4 day 1 [C4D1]), 11 patients with newly diagnosed, previously untreated cHL and 13 healthy donors.
Unlike healthy donors, all evaluated patients with cHL had circulating IFN stimulated adaptive and innate populations, including several distinct CD4+ T-cell effectors and an NK cell subset with reduced cytotoxic potential, and decreased numbers of B cells at all stages of differentiation. Patients with the most favorable responses to PD-1 blockade had: 1) significantly increased CD4+ T-cell receptor diversity and more abundant naïve/ central memory subsets; and 2) significantly higher B-cell receptor diversity and increased numbers of circulating B cells.
The most abundant circulating CD3- population in patients with cHL was a newly identified monocyte subset with increased expression of multiple immunosuppressive and tumorigenic cytokines and chemokines, PD-L1 and SIRPa. This newly identified monocytic population was virtually absent from the blood of healthy donors. RNAscope analysis of the intact tumor microenvironment localized these tumor-infiltrating monocytes/macrophages to the immediate proximity of HRS cells. Monocytes from patients whose disease progressed following PD-1 blockade expressed significantly higher levels of immunosuppressive cytokine/chemokine signature which led to the development of a predictive transcriptional assay. We identified a comparable circulating monocyte population and transcriptional signature associated with unresponsiveness to PD-1 blockade in an additional solid tumor underscoring the broad-based significance of these findings.

P029: ARE REED-STERNBERG CELLS STUCK IN MITOSIS BY SHORT NUCLEOPLASMIC BRIDGES AS A CONSEQUENCE OF CENTROMERIC INSTABILITY?

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Background: Multinucleated giant tumor cells are frequently observed in lymph nodes of untreated lymphoma patients. Malignant Hodgkin lymphoma (HL) cells i. e. small Hodgkin and large bi- or multinucleated Reed-Sternberg (HRS) cells are characterized by genomic instability and downregulation of numerous key regulators of e.g. cell cycle, spindle apparatus, cytokinesis and cell lineage differentiation. So far, the formation of HRS cells remains obscure. We have demonstrated previously that telomere instability is involved in the proliferation of small cells into large binucleated cells. Here, we have used a collection of HL cell lines to analyze the successive steps involved in the transformation of the mononucleated into the multinucleated RS-like cells.
Materials and Methods: Seven HL cell lines and 30 HL lymph nodes were used. Cytokinesis-block micronucleus assay and telomere and centromere staining followed by the M-FISH technique were employed to analyze chromosomal instability. DNA repair pathways were investigated.
Results: We demonstrate that telomere dysfunction in HL cell lines is associated with the formation of dicentric chromosomes with both centromeres in close proximity, but also with a high rate of formation of micronuclei. Two morphologically different types of nucleoplasmic bridges (NPBs) were observed: (1) Long NPBs related to telomere dysfunction and chromosome fusions, and (2) short NPBs related to centromere breakpoints with configurations of cells looking like "stuck" together as binucleated cells. Short NPBs and binucleated cells were seen in the cultures of all HL cell lines. However, each HL cell line was characterized by an individual signature of the proportion of long and short NPBs, which correlated with centrosome amplification and formation of stable binucleated cells. Similar mechanisms were identified in HL patient lymph nodes prior to treatment, thus underscoring the biological significance of our findings in cell cultures. Transcriptome analysis confirmed the variations in the DNA repair pathways regarding the rate of large cells among the different HL cell lines.
Conclusion: The formation of dicentric chromosomes related to centromere instability, and short NPBs were associated with the emergence of binucleated cells through different mechanisms. Our findings open a novel route to understanding the transition from mononucleated cells to multinucleated cells in HL and in other B-cell lymphomas.

P030: BASELINE IGM AMOUNT CAN IDENTIFY PATIENTS WITH ADVERSE OUTCOME DESPITE A PET-2 ADAPTED TREATMENT IN CLASSICAL HODGKIN LYMPHOMA: RESULTS FROM A REAL-LIFE SINGLE-CENTER STUDY I

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Background: Hodgkin Lymphoma is characterized by an inflammatory background in which the reactive myeloid cells may exert an immune suppressive effect that advances progression of disease. Immunoglobulin M is first antibody isotype to be produced during an immune response, but it plays also an immunoregulatory role, therefore we investigated if it could have any clinical impact on prognosis.
Experimental design: In this retrospective, observational, single – center study, we evaluated 212 newly diagnosed Hodgkin Lymphoma (HL)

patients, including 132 advanced stage cases, with a median follow up of 60.3 months (range 60–204); 109 (51%) were men, with a median age of 31 years (range 15–77), 64 patients showed bulky disease, while 119 suffered from B symptoms at the onset. The median baseline values for IgM, IgA and IgG were, respectively: 86.0 (range 5.0–336.0 mg/dL), 197.5 (range 5.0–336.0 mg/dL) and 1110.00 (range 157.0–2763.0 mg/dL). 49/212 (23%) patients had a baseline IgM value lower than 50mg/dL. White blood cell count and type were determined by electrical impedance method. Nephelometry was used for immunoglobulins quantification.

Results: PFS at 60 months was 54.1% versus 81.1 % respectively in patients with IgM ≤50 mg/dL or IgM>50 mg/dL (p<0.001). A level of 50 mg/dl of IgM at baseline resulted in 84.1% sensitivity and 45.5% specificity in predicting achievement of complete response in the whole cohort (area under curve - AUC - 0.62, p=0.013). In multivariate analysis, only baseline IgM ≤50 mg/dl and presence of large nodal mass (< 7 cm) were independent baseline variables able to predict clinical outcome while after two cycles of treatment only IgM ≤50 mg/dl at baseline and PET-2 status were independent predictors of PFS. Thus, we stratified the advanced stage patients in three groups based on clinical variables available at diagnosis: low risk group was defined as absence of LNM and baseline IgM >50; standard-risk was defined by either presence of LNM or baseline IgM ≤50 mg/dL; high risk group was defined by both presence of LNM and IgM ≤50 mg/dL at baseline. The 60-months PFS estimates were significantly different among the three groups, respectively 83.5, 59.5 and 40.0%, p=<0.0001.

Conclusion: IgM amount at diagnosis is a valuable prognostic factor much earlier than PET-2 and it can also provide information in PET-2 negative patients. This can help identify at baseline different HL classes at risk of treatment failure.

P031: CD4+ T CELLS IN CLOSE PROXIMITY TO HODGKIN-REED STERNBERG CELLS ARE ANTIGEN EXPERIENCED, POLYCLONAL AND DISPLAY AN EXHAUSTED PHENOTYPE

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Introduction: Little is known about the characteristics of the CD4+ T cells residing in close proximity to the tumor cells in classical Hodgkin lymphoma (cHL). We recently established that these CD4+ T cells interact with tumor cells by binding of CD2 to CD58 and T cell receptor to HLA class II in vitro and in situ. Formation of this immunological synapse results in strong T cell activation under normal conditions, but the CD4+ T cells in cHL are only weakly activated and typically lack expression of the activation marker CD26. The aim of this study was to further characterize these T cells.

Methods: CD4+CD26- and CD4+CD26+ T cell subsets were sorted from 19 cHL lymph node derived cell suspensions (tumor cells HLA class II positive) and analyzed by RNA sequencing and T cell receptor variable gene segment usage. In addition, co-expression of genes of interest was investigated at the single cell level using previously generated single-cell RNA sequencing (scRNA-seq) data and at the protein level by immunohistochemistry.

Results: Gene set variation analysis showed an enrichment of memory Treg, Th17 and T follicular helper cell gene signatures in CD4+CD26- T cells, while naïve and Th1/17 gene cell signatures were enriched in CD4+CD26+ T cells. Although CD4+CD26- T cells displayed an antigen experienced phenotype, the T cell receptor variable gene segment usage was polyclonal and did not differ from CD4+CD26+ T cells, indicating lack of clonal expansion. Differential gene expression analysis revealed a significant enrichment of 100 genes in CD4+CD26- T cells. Seven genes (TOX, TOX2, CXCL13, CTTN, PDCD1, CD200 and NFIA) with a moderate to high expression level were chosen for subsequent co-expression analysis using scRNA-seq data. This revealed that the majority of CD4+CD26- T cells expressed TOX2 either alone or in combination with any of the other selected genes. Protein expression of TOX and TOX2, transcription factors crucial for the acquisition of an exhausted T cell phenotype, was accentuated in T cells that physically interact with tumor cells. More than 50% of these rosetting T cells were positive for TOX in 63% and TOX2 in 79% of cHL cases.

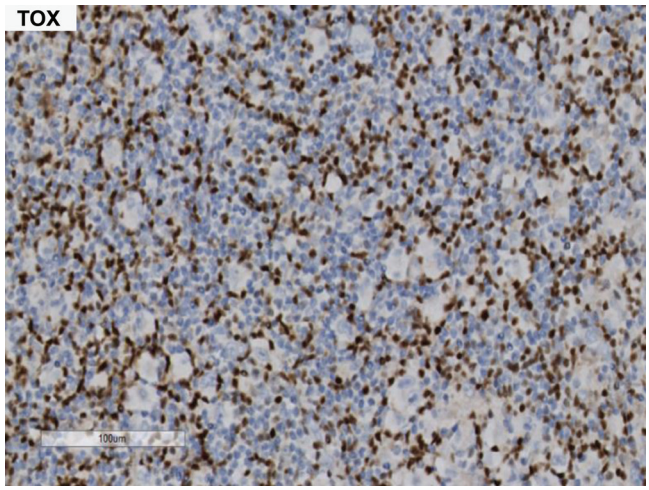

Figure 1: Immunohistochemistry for TOX in a representative case of Hodgkin lymphoma. TOX stains nuclei of T cells in close proximity to the tumor cells.

Conclusion: CD4+ T cells residing in close proximity to cHL tumor cells are polyclonal, antigen experienced and exhausted. We propose that TOX and TOX2, transcription factors known to induce expression of a variety of immune checkpoints, are attractive therapeutic targets for cHL.

P032: CIRCULATING IMMUNE BIOMARKERS IN CLASSICAL HODGKIN LYMPHOMA IN RELATION TO TUMOR BURDEN AND RESPONSE TO TREATMENT.

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Background: In classical Hodgkin lymphoma (cHL) the malignant cells represent only a small fraction of the tumor mass. Yet, they orchestrate a lymphocyte-dominated tumor microenvironment (TME) that supports their survival and growth. The systemic effects of this local immunomodulation are not fully elucidated. In this study, we aimed at characterising circulating lymphocytes and plasma proteins in cHL patients in relation to clinical parameters and treatment effect.

Methods: Peripheral blood (PB) samples were obtained from 48 consecutive patients at diagnosis (baseline, BL) and at 2 time points after primary treatment, right at the end of treatment (EoT) and at follow-up 6 months after EoT (FU). Twenty-eight patients had limited-stage (I-IIA) and 20 had advanced-stage (IIB-IV) disease. All the patients in the FU analysis were in complete remission. Twenty healthy individuals were included as controls. Cells from PB and LN were freshly analysed by flow cytometry, and plasma proteins by proximity extension assay (PEA). Concentrations of CCL17/TARC in plasma were also measured by Enzyme-Linked ImmunoSorbent Assay.

Results: At BL, the numbers of B cells were lower in both limited- and advanced-stage cHL compared to controls, while T cells were normal. Advanced-stage patients had fewer NK cells with a functionally impaired phenotype.

Compared to controls, cHL patients had higher frequencies of proliferating T cells as well as higher expression of programmed death (PD)-1 and cytotoxic T lymphocyte antigen (CTLA)-4 in circulating T cells, and lower naïve T-cell frequencies.

The plasma concentration of CCL17/TARC was elevated in both limited- and advanced-stage cHL compared to controls.
The frequencies of T and B cells positively correlated between the PB and LN compartments.
Distinct immune cellular and plasma protein biomarker profiles were observed in patients with a high tumor burden (i.e. bulky tumor and/or >2 nodal sites involved and/or stage IV) and those with high inflammation (i.e. ESR ≥50).
T-cell exhaustion and NK-cell depletion were reversed by standard first-line treatment and CCL17/TARC concentrations also dropped back to control levels.
Patients who received radiotherapy involving the mediastinum had low T-cell counts for a prolonged period.
Conclusion: The immunomodulation of lymphocytes in the TME of cHL might affect immune biomarkers in the PB. Most immunological changes are reverted after successful standard primary treatment.

P033: CLINICAL SIGNIFICANCE OF THE SEVERITY OF THRLBCL-LIKE AREAS IN NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA

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Introduction: According to the WHO 2017 the presence of sites resembling T cell/histiocyte-rich large B-cell lymphoma (THRLBCL) in nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) does not refer to transformation into THRLBCL.
Objective: To compare the severity of THRLBCL-like areas in NLPHL with the clinical course of the disease.
Materials and Methods: The study group included 59 patients with verified diagnosis (morphology, IHC) of NLPHL (2010–2017, NRCH for hematology): m/f ratio 3.4: 1, median age - 35 (range 17–68), with biopsy material of lymph node/other localization of the primary biopsy in the debut of the disease. The severity of THRLBCL-like areas was analyzed using IHC with CD20 antibodies and empirically selected cut off of these sites in 50%, compared with clinical and instrumental data.
Results: Patients with non-classical subvariants (non-A/B, n=42) were divided into 3 subgroups: 1 subgroup 0% (17/42), 2 subgroup - 0>%<50% (11/42), 3 subgroup ≥50% (14/42) THRLBCL-like areas of the area of the lymph node section. In the three analyzed subgroups, there were a significant difference in the frequency of diagnosis of stage IV of the disease (p=0.0507), bone marrow damage (p=0.0005) and spleen (p=0.0101), response to first-line therapy (p=0.0126). Table 1. In the subgroup with the presence of THRLBCL-like areas ≥50%, up to 6 affected extranodal localizations were observed: bone marrow trephine biopsies, spleen, liver, paravertebral soft tissues, bones, thyroid gland.
Conclusions: A subgroup of patients with the presence of THRLBCL-like areas ≥50% of the area of the lymph node section is characterized by the most unfavorable clinical course of the disease.

Parameter	THRLBCL-like areas			p
	0% n=17	0>%<50% n=11	≥ 50% n=14	
Clinical stage				
I	5/17 (29%)	1/11 (9%)	1/14 (7%)	
II	4/17 (24%)	2/11 (18%)	1/14 (7%)	
III	5/17 (29%)	3/11 (27%)	1/14 (7%)	
IV	3/17 (18%)	5/11 (46%)	11/14 (79%)	**0,0507**
Bone marrow lesion	1/13 (8%)	0/5 (0%)	7/9 (78%)	**0,0005**
Lesion of the spleen	2 (12%)	4/10 (40%)	9 (64%)	**0,0101**
The number of affected extranodal localizations (average value)	0,2 (0–2)	0,5 (0–1)	2,4 (0–6)	**<0,0001**
Involvement of visceral lymph nodes	8 (47%)	4/10 (40%)	8 (57%)	0,6975
Results of 1st-line therapy				
Complete remission	14/15 (93%)	7/8 (88%)	3/9 (33%)	**0,0126**
Partial remission	0/15 (0%)	1/8 (12%)	5/9 (56%)	
Progression	1/15 (7%)	0/8 (0%)	1/9 (11%)	

Table 1: Comparison of clinical parameters in 3 subgroups of patients with non-classical subvariants (non-A/B) depending on the value of THRLBCL areas (0%, 0>%<50%, ≥ 50%)

P034: CORRELATION BETWEEN MTV, TLG AND SERUM TARC CONCENTRATION IN CLASSICAL HODGKIN LYMPHOMA DURING FIRST-LINE TREATMENT

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Introduction: Positron emission tomography (PET) is an available tool to adapt treatment strategy in newly diagnosed classical Hodgkin Lymphoma (HL). However, approximately 15% of patients (pts) with negative interim PET (iPET) still experience relapse. Here, we aimed at correlating PET-variables, namely metabolic tumor volume (MTV) and total lesion glycolysis (TLG), with serum TARC (sTARC), a promising predictor of response in HL.
Methods: We prospectively collected plasma samples of 58 untreated HL pts, stratified according to GHSG risk categories and treated according to a PET-driven strategy. Samples were collected at baseline, after 2 cycles of ABVD (coinciding with iPET), and at the end of treatment (EOT). All pts underwent PET scan at the same timepoints. Thresholds used for measuring MTV and TLG were SUVmax>2.5 and 41% of the SUVmax. Deauville ≤3 defines complete remission. To assess interim response, variables were evaluated as logarithmic reduction (LogRED) of baseline vs iPET, and as logarithmic variation (LogΔ) of EOT vs iPET for EOT response.
Results: Overall, 45 out of 58 pts were evaluable. We excluded 12 pts due to unavailable PET scan at any timepoint, and 1 for missing samples. Median age was 33 years (17–58), 60% pts were male, 58% pts had

	LogRED	Median	Range		LogRED	Median	Range
iPET negative	TLG 2.5	8.19	6.15–9.09	iPET positive	TLG 2.5	1.89	0.18–2.86
	TLG 41%	8.04	6.30–8.83		TLG 41%	1.26	0.21–1.81
	MTV 2.5	7.53	5.70–8.47		MTV 2.5	1.49	0.15–2.36
	MTV 41%	7.27	5.85–8.09		MTV 41%	1.06	0.19–1.56
	sTARC	1.83	-0.04–3.12		sTARC	1.6	0.31–2.42

Table1. Median LogRED for PET-variables and sTARC

	LogΔ	Median	Range		LogΔ	Median	Range
EOT-PET negative	TLG 2.5	0.67	0–7.72	EOT-PET positive	TLG 2.5	-5.90	-7.40– -5.48
	TLG 41%	0.71	0–7.68		TLG 41%	-6.08	-6.40– -5.60
	MTV 2.5	0.64	0–7.10		MTV 2.5	-5.48	-6.86– -5.60
	MTV 41%	0.66	0–7.31		MTV 41%	-5.48	-6.0– -5.0
	sTARC	0.02	-1.46–0.44		sTARC	-1.42	-2.87– -0.26

Table 2. Median LogΔ for PET-variables and sTARC

Table 1: Median LogRED for PET-variables and sTARC
Table 2: Median LogΔ for PET-variables and sTARC

B-symptoms and 71% were diagnosed with an advanced stage (IIB, III, IV). Five (11%) pts were iPET+ and 5 (11%) were EOT-PET+.
Results of LogRED and LogΔ for TLG 2.5, TLG 41%, MTV 2.5, MTV 41% and sTARC in both iPET- and iPET+ pts are listed in Table 1 and Table 2, respectively. Overall, LogRED of PET variables were significantly lower in iPET+ compered to iPET- pts (p<.001), while no differences were observed for LogRED of sTARC (p=.4). In EOT+ pts, the LogΔ for both PET-variables and sTARC was significantly different (p<.001). The correlation between PET variables and sTARC showed a significant trend for LogRED using the 2.5 threshold for MTV and TLG (respectively, r=.333, p=.026 and r=.304, p=.042), but not for the 41% cut-off (r=.298, p=.052 and r=.268, p=.083). LogΔ between PET-variables vs sTARC were significantly correlated (r=.427, p=.004 for TLG 2.5, r=.404, p=.007 for TLG 41%, r=.427, p=.004 for MTV 2.5 and r=.401, p=.008 for MTV 41%).
Conclusion: Our findings show that the PET scan and sTARC are intercorrelated predictors in HL, with the latter potentially being a helpful marker for identifying iPET-/EOT-PET+ pts. Larger studies are needed to confirm the role of sTARC monitoring.

P035: CRISPR/CAS9-MEDIATED KNOCKOUT REVEALS AN IMPORTANT ROLE OF CD30 IN HODGKIN AND REED-STERNBERG CELLS OF CLASSICAL HODGKIN LYMPHOMA

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The malignant Hodgkin- and Reed-Sternberg (HRS) cells of classical Hodgkin lymphoma (cHL) highly and consistently express CD30 on their cell surface, which is used for its diagnosis and since recently targeted therapy with drug-conjugated CD30-specific antibodies. However, the role of CD30 in the pathogenesis of cHL is not well understood and controversially discussed. We established a CRISPR/Cas9 system in CD30-positive lymphoma cell lines and confirmed efficient knockout of CD30. Characterization of CD30-depleted cHL cell lines identified a growth disadvantage under competitive growth conditions and CD30-knockout cultures showed increased cell death, which was at least partly mediated by apoptosis. Influences of CD30 on the activity of a main signaling pathway driving cHL lymphomagenesis, i.e., NF-κB signaling, were detected. Furthermore, contribution of CD30 signaling to the high MYC activation signature of cHL cell lines was identified. These results point to an important role of CD30 expression by HRS cells for the pathobiology of cHL.

P036: DETECTION OF RECURRENT SOMATIC VARIANTS IN CELL-FREE DNA AS A TOOL FOR DISEASE MONITORING IN HODGKIN LYMPHOMA

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A major challenge in the health care management of HL is finding optimal balance between treatment efficacy and risk of toxicity. Nowadays there is no reliable and precise tool for evaluation of treatment response and MRD monitoring due to scarce presence and difficult availability of neoplastic cells. The cell-free DNA (cfDNA) in HL reflects its mutational profile and could be source for genotyping assays. We developed a specific NGS panel for analysis of 13 genes involved in pathogenesis of HL. Selected variants detected by NGS were subsequently used for MRD monitoring by droplet PCR (dPCR).
Our cohort consisted of 48 pts: 20 females/28 males; median age of dg 39.5 years. Histological subtypes: 28 pts (58%) NSCHL; 14 pts (29%) MCCHL; 1 pt (2%) NLPHL; 1 pt (2%) LRCHL (4 pts not determined). Forty four samples were obtained at dg/ 4 in relapse. CfDNA was extracted from peripheral blood plasma using QiaAmp Circulating nucleic acid kit (Qiagen). Specific NGS panel covering coding sequences (including UTRs) of 13 selected genes was designed. For library preparation we used SureSelect XT HS2 technology (Agilent Technologies) based on "target enrichment" with molecular barcodes. Sequencing was performed on a NovaSeq6000 (Illumina). Data were analyzed with the SureCall software (Agilent Technologies) with sensitivity of 1,0 %

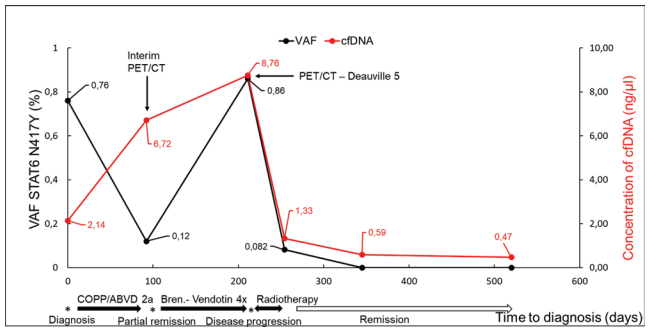

Figure 1: MRD monitoring in patient PA-1971 by dPCR using STAT6 (p.N417Y)

VAF. The detected variants were annotated using COSMIC, dbSNP, Ensembl and ClinVar. Selected variants were further monitored by dPCR (QIAcuity Digital PCR System; Qiagen) with sensitivity of 0,1 % VAF.
Mutations were detected in 22/48 (46%) pts. The most frequently mutated genes were STAT6 (12/48 pts), TNFAIP3 (10/48 pts), XPO1 (7/48 pts), SOCS1 (7/26 pts). Frameshift deletions prevailed in TNFAIP3 and SOCS1 genes. Most mutations in the STAT6 (p.N417Y/D) and XPO1 (p.E571K) genes were hotspots. We monitored levels of these variants by dPCR during the course of disease and correlate results with clinical and PET-CT data.
Fast, sensitive and noninvasive detection of mutations means an important improvement in diagnostics, prognostics, and monitoring of HL. NGS/dPCR approach would refine the evaluation of treatment response fundamentally. Correlation of mutational load with continuous PET examination would reduce the amount of false-positive results and enable us to use more precise and safe therapy de-escalation. DPCR proved to be sensitive, fast and afordable technology for MRD testing.

P037: HIGH BREADTH WHOLE EXOME SEQUENCING OF CIRCULATING TUMOR DNA IDENTIFIES NOVEL RECURRENT GENETIC ALTERATIONS IN HODGKIN LYMPHOMA

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Hodgkin lymphoma (HL) is a B-cell lymphoma with a generally favorable prognosis. However, side effects of aggressive front-line treatment and difficult-to-treat relapsed/refractory disease are still a clinical challenge. A better understanding of the biological diversity of HL at baseline might help to further individualize the treatment of patients and thus ultimately improve outcome. A broad characterization of the genetic drivers of HL is highly important to improve our understanding of the biological diversity of HL.
Here, we present the results of our study using whole-exome sequencing of circulating tumor (ct)DNA to broadly characterize the HL oncogenome in 165 patients.
After extraction of germline and cell-free DNA, WES was performed, targeting 37 Mb of the human genome. An in-house customized bioinformatic pipeline including twofold error reduction using unique molecular identifiers (UMIs) and digital error suppression was used as previously described by us (Sobesky et. al., Med, 2021).
The median ctDNA concentration per patient was 2.26 log haploid genome equivalents per milliliter (log hGE/ml) (range: 1.41–4.18 log hGE/ml) without significant correlation with clinical parameters such as sex, international prognostic score (IPS) or clinical stage. In addition to

the detection of several genetic aberrations involved in the pathogenesis of HL (such as B2M, CSF2RB, GNA13, SOCS1), we were able to detect several novel, recurrently mutated potential oncogenes and tumor suppressor genes. Among the most frequently mutated genes not previously described in HL were olfactory receptor family 10 subfamily G member 7 (OR10G7) (11.5%), Apolipoprotein B (APOB) (10.3%) and Filaggrin 2 (FLG2) (9.7%). Furthermore, several previously undescribed copy number variations (CNV) were detected (losses: 13q13.1, 1p36.13a, 6p21.33; gains: 19q13.42, 9p24, 12q12).
To decipher the detected genes' and CNVs' contribution to the biological diversity of HL, we performed non-negative matrix factorization. Furthermore, neoantigen load was assessed through human-leukocyte antigen (HLA) sequencing. Detailed results will be presented at the meeting.
In conclusion, our ctDNA based WES approach provides sufficient sensitivity to both perform genotyping in HL and detecting novel genomic aberrations potentially involved in the pathogenesis of HL.

P038: HLA EXPRESSION PATTERNS OF HODGKIN-REED-STERNBERG CELLS SHAPE A SPATIALLY ARRANGED TUMOR MICROENVIRONMENT IN CLASSICAL HODGKIN LYMPHOMA

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Introduction: Classical Hodgkin lymphoma (cHL) differs from other malignancies in its histologic architecture: Few malignant Hodgkin-Reed-Sternberg cells (HRSC) recruit an immune cell-rich tumor microenvironment (TME). Importantly, HRSC frequently show loss of human leukocyte antigen (HLA) expression potentially disturbing T-cell interactions. We aimed to understand how the expression of this key structures of HRSC-T-cell interaction affect the spatial cellular composition of the TME.
Material and Methods: 18 lymph node samples of initially diagnosed cHL patients were scored for HLA-I and -II expression. Multiplex immunofluorescence staining for CD30, CD8, CD68, FoxP3 and LAG3 was performed using Akoya Opal Polaris 7-Color Manual IHC Kit. Digital images were analyzed in three equal sized areas near (nTME; including HRSC clusters) and ≥75 µm distant (dTME) to HRSC using QuPath software (Fig. 1). We analyzed cells regarding the expression of one marker, independent of co-expressions.
Results: The content of CD68+ cells, CD8+, and LAG3+ T-cells varied in the proximity of HRSC (nTME) dependent of HLA expression of HRSC. HLA-I+ cases showed higher levels of CD68+, CD8+ and LAG3+ cells compared to HLA-I- cases. However, FoxP3+ cell content in nTME was independent of HLA-I expression. We found only slight differences in cellular composition of nTME comparing HLA-II+ with HLA-II- cases.
To illustrate spatial gradients, we compared cellular composition of nTME with dTME. Considering all cases, we found higher content of FoxP3+, LAG3+ and CD68+ cells in nTME. Of note, the enrichment of these cell types in nTME was slightly more pronounced dependent on HLA-I rather than HLA-II expression of HRSC. Interestingly, we found higher CD8+ cell content in HLA-I+ cases. This finding is consistent with bulk analyses, which showed HLA-I dependent upregulation of cytotoxic genes (see Seifert et al., ISHL12 submission).
Discussion: In line with previous publications, we demonstrate the HRSC niche to be enriched for FoxP3+, LAG3+ cells, and CD68+ macrophages. The enrichment of certain cell types in HRSC proximity seems to be a general feature of cHL independent of HLA expression, which differs in its composition depending on HLA expression of HRSC. We find that enrichment of CD68+, CD8+ and LAG3+ cells is stronger related to HLA-I than HLA-II expression on HRSC. Together with bulk gene expression data we suggest HLA-I expression of HRSC to be a key determinant of TME composition.

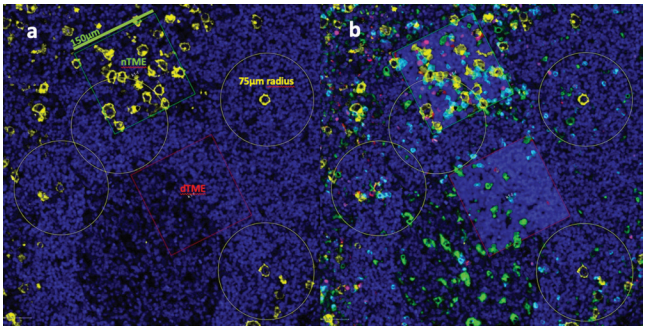

Figure 1: Example of an analysis area. a nTME (green square) within a HRSC cluster, dTME (red square) ≥75 µm (yellow circles) away from the nearest HRSC. b Cell detections for CD30 (yellow), CD68 (green), LAG3 (turquoise), FoxP3 (pink) and CD8 (red).

P039: HLA EXPRESSION STATUS AND PROGNOSTIC IMPACT OF B-CELL CONTENT IN PATIENTS WITH EARLY-STAGE UNFAVORABLE HODGKIN LYMPHOMA

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Introduction: Classical Hodgkin lymphoma (HL) is characterized by a complex, increasingly understood microenvironment which is considered crucial for survival and proliferation of the malignant Hodgkin and Reed-Sternberg cells (HRSC). HLA expression is a key component for immune cell interaction and thereby microenvironment composition. Additionally, we and others have shown that a low B-cell content is a negative prognostic factor in advanced-stage HL which can be assessed quantitatively by digital pathology using slides generated for diagnostic purposes (Jachimowicz 2021). Herein we aimed to assess HLA expression status and the prognostic relevance of B-cell content in early-stage unfavorable HL.
Patients and Methods: We analyzed primary tumor biopsies of patients with newly diagnosed early-stage unfavorable HL either treated with 4xABVD or 2xBEACOPPesc followed by 2xABVD within the GHSG HD14 trial, each consolidated by 30Gy involved-field radiotherapy (von Tresckow 2012). Our project cohort was enriched for patients suffering from disease progression or relapse (20.2% vs 6.2% in the total HD14 population). Whole-slide image

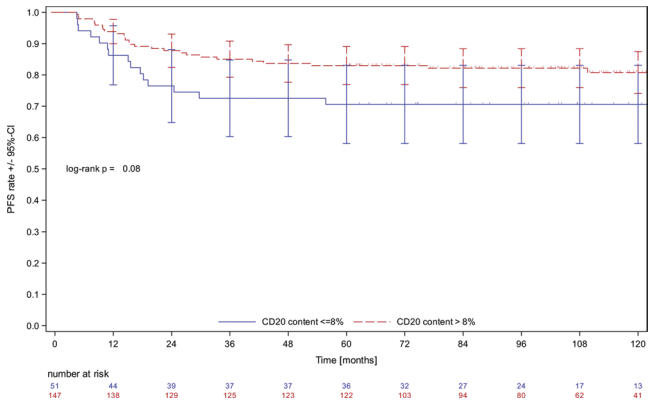

Figure 1: Kaplan-Meier Analysis of PFS according to B-cell content

analysis of CD20 staining was performed using TissueStudio 64 (Definiens) to quantify the B-cell content. Immunohistochemistry for ß-2-Microglobulin (HLA-I) and HLA-DP (HLA-II) was scored by visual inspection on HRSC.
Results: Major clinical variables such as sex, age, B-symptoms, GHSG risk factors and histological subtypes did not differ significantly between the project cohort (N=198) and HD14 trial population (N=1889). HLA-I and -II were expressed on HRSC in 13.3% and 49.1% of cases, respectively. Only 8.3% of cases showed positivity for both HLA-I and -II, while 45.8% were double-negative. Median B-cell content was lower in HLA-I negative (12.8% vs 18.5%, p=0.0168) and double-negative cases (11.5% vs 18.1% in double-positive cases, p=0.0392). A low B-cell content was associated with unfavorable outcome: 5-year PFS estimates are 70.6% and 83% for subjects with low (<=8%) or high (>8%) B-cell content (Figure 1, log-rank p=0.08). A stepwise multivariate analysis including type of treatment confirmed B-cell content as the only significant risk factor for PFS (p=0.0196).
Conclusions: HLA expression is variable in early-stage unfavorable HL and associated with B-cell content. Similarly to advanced-stage HL, a low B-cell content measured by digital pathology of routinely available diagnostic slides is associated with unfavorable outcome.

P040: LINE-1 REVERSE TRANSCRIPTASE ACTIVITY IN HODGKIN LYMPHOMA CELLS

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Background: The human genome contains a large number of repetitive elements including endogenous retroviruses and long interspersed nuclear elements (LINE). Repetitive elements have been shown to be activated and influence gene expression in Hodgkin lymphoma (HL). Some repetitive elements contain open reading frames that encode a reverse transcriptase. We analyzed RT activity and expression of reverse transcriptase sequences in HL cells.
Methods: RNA seq analysis was used for the identification of expressed putative reverse transcriptases in HL cells. Reverse transcriptase activity in HL cells was assessed using phage MS2 RNA as template for reverse transcription and amplification by quantitative polymerase chain reaction. Sensitivity of HL cells for the non-nucleoside reverse transcriptase inhibitor efavirenz was analyzed by flow cytometry. LINE-1 reverse transcriptase sequences were amplified from HL cell line L-428 by reverse transcription-polymerase chain reaction, cloned into vector pGEM-T Easy and sequenced by Sanger sequencing.
Results: HL cells showed high reverse transcriptase activity in comparison to normal blood cells. In addition, efavirenz killed HL cells in a dose dependent manner. RNA seq analysis suggested that HL cells express sequences corresponding to LINE-1 reverse transcriptase. By RT-PCR using LINE-1 reverse transcriptase specific primers, several transcripts containing open reading frames with predicted coding capacity for reverse transcriptase molecules were identified.
Conclusions: HL cells express LINE-1 reverse transcriptase sequences that might be responsible for the observed reverse transcriptase activity of these cells. LINE-1 reverse transcriptase might be interesting targets for future therapeutic developments.
Our work is supported by Mitteldeutsche Kinderkrebsforschung.

P041: LOW PERCENTAGE OF T LYMPHOCYTES IN HODGKIN'S LYMPHOMA LYMPH NODES, MEASURED BY FLOW CYTOMETRY, IS ASSOCIATED WITH INFERIOR PROGRESSION FREE SURVIVAL REGARDLESS OF NEGATIVE INTERIM PET SCAN STATUS

Laura Korin[1], Santiago Cranco[1], Lucia Fuente[1], Adriana Vitriu[1], Paola Ochoa[1], Evelina Babuin[1], Olivia Gelo[1], Luis Ayala[1], Andrea Novoa[2], Paula Tempra[2], Maria Belen Venegas[2], Anahi Vijnovich Baron[3], Norma Tartas[1], Rosario Custidiano[1], Cecilia Foncuberta[1], Julio Sanchez Avalos[1]

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Background: Tumor microenvironment (TME) can influence antitumor immunity and survival in Hodgkin lymphoma (HL) as previously published. However, most of this data has sparse clinical applicability. Flow cytometry (FC) has limited utility in HL diagnosis but its potential to assess TME has not been fully explored yet.
Aims: To determine the prognostic impact on survival of the percentage (%) of tumor infiltrating lymphocytes (TIL) and CD4/CD8 ratio in lymph nodes (LN) measured by FC.
Methods: We selected patients (pts) with HL, available LN FC data at diagnosis and i-PET scan, treated at our center from 2012–2020. FC was performed with 8-color panels according to Euroflow protocols. TIL % and CD4/CD8 ratio in LN by FC were compared to normal values reported (Battaglia, Immunology 2003) and stratified as low, normal and high. Response was assessed per Lugano recommendations. Progression free survival (PFS) was estimated with Kaplan-Meier, multivariate analysis with Cox regression, and variables were compared with log-rank test.
Results: 46 pts were included. Median age: 34 years. 24/27 with early stage had unfavorable risk and 11/19 with advanced disease had IPS≥3. 95% received ABVD. Complete response rate was 91.3%. 2 pts died. Median PFS: not reached (NR), 75th percentile 43 months (m), and median follow up: 49 m.
i-PET negative (neg) pts had significantly better PFS (median NR vs 13.7 m in i-PET positive subgroup, p:0.014). Low LN TIL % was associated with inferior PFS (median 24.4 m vs. NR in pts with normal or high TIL, p:0.024). Regarding CD4/CD8 ratio, PFS rates were 100%, 75% and 60% in normal, low and high subgroups respectively, p:0.041.
Both low TIL and positive i-PET remained independent predictors of survival on multivariate analysis with HR of 11.8 (CI 95% 1.9–72.7, p:0.021), and 7.7 (CI 95% 1.6–36.4, p:0.01) respectively.
LN TIL % could further stratify outcomes in pts with neg i-PET scans. In this subset, pts with low TIL had a median PFS of 24.4 m and PFS rates of 33.3% vs. median NR in normal and high subgroups and PFS rates of 88.9 and 87.5% respectively, p:0.006.
Conclusions: LN TIL % measured by FC showed prognostic impact in our cohort of HL pts. Pts with low TIL had inferior PFS, even in those with optimal interim response where the median was only 2 years. This finding denotes the critical role of T cells to achieve cure. Checkpoint blockade might constitute an appealing approach in these pts to restore effective antitumor immunity.

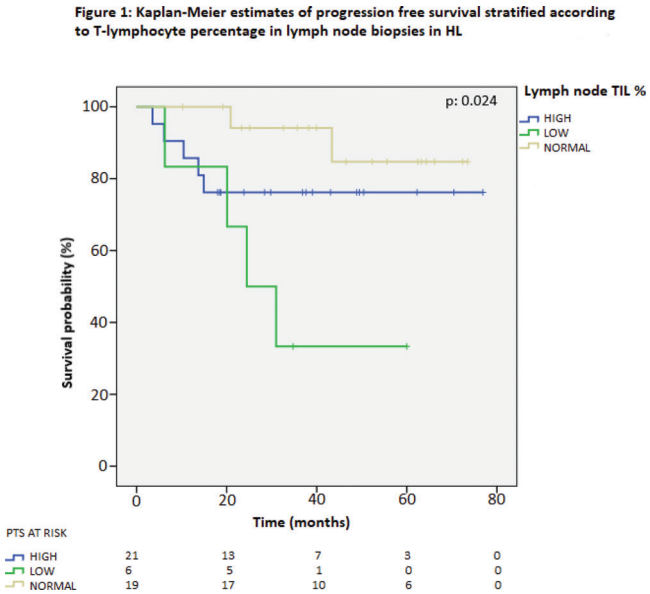

Figure 1: Kaplan-Meier estimates of progression free survival stratified according to T-lymphocyte percentage in lymph node biopsies in Hodgkin lymphoma

P042: METABOLIC REGULATION OF ADAPTIVE RESPONSE TO ARGININE DEPRIVATION IN HODGKIN LYMPHOMA

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Our group has previously shown an altered aminoacidic homeostasis in the microenvironment of classic Hodgkin`s Lymphoma (HL), due to arginine deprivation, which plays a major role in the immune-escape mechanisms and T-cell anergy induction.
To study the metabolic adaptive response to arginine deprivation in vitro, we cultured three HL human cell lines (L428, L540, KMH2) with customized complete media or lacking Arg (R0), supplemented with 10% dialyzed fetal bovine serum, in six independent experiments to collect their global metabolomic analysis by gas chromatography-mass spectrometry (GC/MS) and liquid chromatography-tandem mass spectrometry (LC/MS/MS) platforms by Metabolon Inc and transcriptome profiling by RNA-seq. Apotpostosis and mitochondrial depolarization were measured by FACS. Findings were validated by qRT-PCR and Western Blot analysis.
Gene set enrichment analysis (GSEA) showed deep transcriptome rearrangements in KMH2 and HDMYZ cell lines, involving upregulation of genes required for the unfolded protein response, p53 pathway and networks and proteosome degradation, with a minimal effect on metabolism features, except for the genes involved in lactate metabolism.
Arg deprivation caused mitochondrial distress and transcriptional reprogramming, via induction of oxidative stress, affecting the mitochondrial activity, switching from glucose-based metabolism to mitochondrial oxidation of fatty acids, requiring the transfer of fatty acids from lipid droplets to mitochondria. RNA-seq analysis showed that induction of ferroptosis key genes GPX4, TXNRD1 and ACSL4 together with reduced intracellular GSH levels and increased amount of cystine and methionine sulfoxide occurred upon arginine deprivation.
The low-energy metabolic state induced by the adaptive response to arg-deprivation posed KMH2-HL cells into a quiescence state, with elevated HMOX1 and HMOX-2 to scavenge the excess ROS with subsequent genome instability as shown by increased γHA2X+/ATM+ cells. In HDMYZ, the increased oxidative stress due to arginine deprivation induced the engagement of the UFMylation pathway.
These findings were confirmed in vivo, since in peripheral blood of HL patients we found reduced amount of GSH, glutamine and S-adenosylhomocysteine, citrate, methionine ($p<0.001$), as detected by HPLC.
Taken together, our data suggest how arginine deprivation can regulate lipid trafficking, ferroptosis and UFMylation, novel potential targets to overcome drug resistance in cHL.

P043: MOLECULAR PATHOGENESIS OF HODGKIN LYMPHOMA

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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 are currently analyzing the WGS samples for mutations in gene regulatory regions, miRNA binding sites and gains and losses. Both WGS and WES show a wide variation in their mutational loads.

P044: PIM KINASES SUPPORT PROTUMORAL AND IMMUNOSUPPRESSIVE PHENOTYPE AND FUNCTIONS OF MACROPHAGES IN CLASSICAL HODGKIN LYMPHOMA

Maciej Szydłowski[1], Filip Garbicz[1], Ewa Kurtz[1], Michał Pawlak[1], Patryk Górniak[1], Anna Szumera-Ciećkiewicz[2], Kamil Sokół.[2], Monika Kawecka[2], Daria Owczarek[2], Beata Puton[2], Monika Prochorec-Sobieszek[2], Daniela Bellarosa[3], Michał Kurlapski[4], Jan Maciej Zaucha[4], Przemysław Juszczyński[1]

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Increased abundance of tumor-associated macrophages (TAMs) predicts shortened survival of patients with classical Hodgkin lymphoma (cHL). TAMs in cHL might support growth of the malignant, Reed-Sternberg (RS) cells and due to expression of PD-L1, contribute to T-cell exhaustion. In our previous studies, we identified almost universal expression of PIM-1/2/3 kinases (PIMs) in RS cells, but also noted that they are expressed in TAMs. In RS cells, PIMs support malignant cells survival and immune privilege. However, their role in the biology of cHL-TAMs remains to be explored. Herein, using an in vitro model of cHL-TAMs (RS-conditioned macrophages, RS-M) we characterize consequences of PIM inhibition for phenotype and functions of TAMs in cHL.
THP1 cells and donor-derived monocytes were differentiated into macrophages (MΦ-0) using PMA and CSF-1 respectively. MΦ-0 were next cocultured with L428 or L1236 RS cells under conditions prohibiting direct contacts. Compared to MΦ-0, RS-M exhibited elevated expression of PIMs and genes involved in chemotaxis/immunomodulation (CCLs: 2, 5, 7, 8, 13, 17, 18 and 24), extracellular matrix organization (CD206, TGM2 and MMP-1, -7, -9 and -12), T cell exhaustion (PD-L1) and angiogenesis (VEGFA, PDGFB, CHI3L1/2). PIMs expression was also detected in primary cHL-TAMs. To assess role of PIMs in TAMs, RS-M were treated with a dual pan-PIM/FLT3 inhibitor, MEN1703, and subjected to transcriptional, biochemical and immunophenotype analyses. MEN1703 skewed gene expression profiles of RS-M toward pro-inflammatory (M1) macrophages and downregulated expression of genes associated with pro-tumoral (M2) macrophages. Consistently, PIM inhibition in RS-M downregulated expression or decreased activity of M2-associated molecules (CREB1, AKT, STAT3/6, CD163, CD206, CD209), and decreased PD-L1 levels by 32%. PIM inhibition hampered important functions of RS-M, including their ability to promote angiogenesis, matrix remodelling (collagen uptake), and eosinophil recruitment. In direct cocultures, RS-M decreased activity of T lymphocytes. This suppressive effect was alleviated in cocultures with the PIM inhibitor-treated RS-M.
Our data suggest that PIMs support pro-tumoral and immunosuppressive phenotype of cHL-TAMs. Since PIM activity is required for RS cell survival and immune escape, these kinases are rational targets for therapy in cHL.
Grant support National Science Centre, Poland 2017/26/D/NZ5/00561 and 2016/22/M/NZ5/00668

P045: PLASMA PROTEOME PROFILING OF CARDIOTOXICITY IN PATIENTS WITH HODGKIN LYMPHOMA

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Introduction: Cardiovascular toxicity is a well-known complication of both chemotherapy, especially doxorubicin (DXR), and irradiation of the mediastinum for classical Hodgkin lymphoma (cHL). Due to the excellent prognosis in cHL, the mortality rate in late toxicity historically exceeds that of cHL 15 to 20 years after diagnosis, highlighting the need for strategies to minimize toxicity. Our aim was to characterize the incidence of cardiovascular disease (CVD) in our cohort of cHL patients treated with DXR with or without radiotherapy according to standard practice, and to identify any plasma protein associations with pre-existing or emerging CVD post treatment.
Patients and Methods: We analyzed 182 different proteins in 58 biobanked plasma samples from cHL patients using Olink multiplexed panels. The analysis was complemented with separate analyses of NTpro-BNP, Troponin I and CRP. The patient samples were prospectively collected prior to, during and after treatment. Patient charts were reviewed for CVD and risk factors for CVD at diagnosis and after a median follow-up time of 7.8 years. In addition, plasma samples from 60 healthy controls, recruited from the EpiHealth survey, and health related data was collected from patient surveys.
Results: Our analysis showed a statistically significant association between the compound endpoint of heart failure and ischemic heart disease and the protein biomarkers cysteine rich protein 61 (CYR61), glycoprotein nonmetastatic melanoma protein B (GPNMB) and activated leukocyte cell adhesion molecule (ALCAM) in samples collected after treatment for cHL.
Conclusions: This study identified three possible biomarkers for cardiac damage in patients treated for cHL. We believe that optimizing treatment based on prognostic factors in this population has the potential to reduce future morbidity and mortality.

P046: PRECLINICAL EVALUATION OF NOVEL REPURPOSED DRUG COMBINATIONS IN HODGKIN LYMPHOMA

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Although the outcome of patients with Hodgkin lymphoma (HL) is comparably high, it worsens rapidly in relapsed or refractory disease. In the pursuit of improving cancer treatment and finding new therapy options, repurposing drugs has evolved as a promising strategy. This project takes a systematic look at the direct antitumor effect of 12 non-oncological, repurposed drugs in HL that survived initial screening in a broad panel of cell lines. Additionally, we consider their immunological effects and aim to decipher strategies on how to potentially use them in conjunction with immunotherapy.
Luciferase toxicity assays in different concentrations were performed with four HL cell lines, narrowing down the list of 12 to the five most toxic agents which were then tested again in three different combinations. The most effective combination was then evaluated in mouse models. To evaluate the influence of the screening survivor drugs on immune response, assays for T-cell activation, macrophage polarization and phagocytosis were conducted.
Five compounds, Albendazole (Alb), Auranofin (Aur), Disulfiram (Dis), Fluvastatin (Flu) and Propranolol (Pro) showed markedly elevated in-vitro toxicity. The three combinations Alb+Aur+Dis+Pro, Aur+Dis+Flu+Pro and a combination of all 5 drugs showed synergistic cytotoxicity in HL cell lines. Latter combination clearly reduced tumor growth in mouse models. Except for Doxycycline, which markedly repressed T-cell activation, none of the other tested 11 compounds showed negative effects on either T-cell activation, or macrophage polarization and phagocytosis. On the contrary, Eprosartan (Epro), Metformin (Met), Clofibrate (Clof) and Ornidazole (Orni) increased antibody dependent cellular phagocytosis (ADCP) in in-vitro assays.
This project shows that combinations of repurposed, non-oncological drugs at safe doses have a direct cytotoxic effect against HL and a potentially beneficial impact on key immune response mechanisms. Taken together, our results justify further evaluation of combinations of these clinically known drugs with chemotherapy or checkpoint blockade in cases of HL without other treatment options.

P047: PREDICTIVE ROLE OF THE HODGKIN LYMPHOMA-ASSOCIATED CYTOKINES: A PROSPECTIVE STUDY OF THE CZECH HODGKIN STUDY GROUP

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Background: Prognostic stratification and thus the selection of the frontline treatment in Hodgkin lymphoma (HL) is based on historical systems which only indirectly reflect lymphoma burden or cytokine activity. Analysis of the lymphoma-related soluble biomarkers offers a non-invasive tool for more precise risk stratification.
Aim: To define a prognostic significance of the pretreatment soluble cytokines levels in the newly diagnosed pts with HL treated within GHSG policy
Methods: We have conducted prospective serum sampling (2017–2021) of the unselected pts treated in three university hospitals in the Czech Republic. All samples were analysed centrally using ELISA for lymphoma cells (TARC pg/ml; sCD30, ng/ml), macrophages (sCD163, ng/ml) and inflammation-related cytokines (sIL-6, pg/ml). Clinical and laboratory data were retrieved from the national Hodgkin lymphoma registry.
Results: In total we have analysed 169 (100%) consecutive pts. Median age was 42 (19–83) yrs, with slight female predominance (52%). All but 7 pts (96%) have been diagnosed as classical HL (nodular sclerosis in 83, mixed cellularity in 58, lymphocyte-rich in 8 and lymphocyte depletion in 1, 12 not classified). Ann Arbor stages were as follows: (12%), II (37%), III (22%), IV (29%) with B-symptoms present in (56%) and extranodal disease in (32.5%) of the pts, leading to allocating of the pts into limited (18%), intermediate (24%) and advanced (58%) GHSG stages. Treatment was based on ABVD (48%), BEACOPPesc (42%), COPP/ABV (8%), or other (2%) regimen. Treatment response was assessed in 161 pts (95%), with CR in 90 % of the pts. After a median FU of 43 months the 5-y OS reached 90.4% (95% CI 0.83–0.98) and 5-y PFS 86.6% (95% CI 0.81–0.93). Lower mean pretreatment levels of 3 cytokines correlated with achieving of CR: sCD30 (70 vs 130; p=0.04), sCD163 (783 vs 1171; 0.007), sIL-6 (26 vs 130; p<0.001), TARC did not show any correlation with CR (mean 33764 vs 23702; p=0.67). Two cytokines were predictive for PFS: sCD30, cut-off 90 ng/ml (5-y PFS 79.1 vs 90.4%; p=0.044) and sIL-6, cut-off 9 pg/ml (5-y PFS 80.3 vs 92.5%; p=0.023). High levels of sCD30 and sIL-6 were associated with inferior 5-y OS of 79.3 vs 97.2% (sCD30, p=0.004) and 82.6% vs 97.4 % (sIL-6, p=0.025).
Conclusion: Pretreatment levels of soluble CD30 and IL-6 are associated with the treatment outcome and survival in the patients treated with GHSG risk-adapted policy.
Acknowledgment MZCR-RVO (FNOL, 00098892), AZV NU22-03-0018

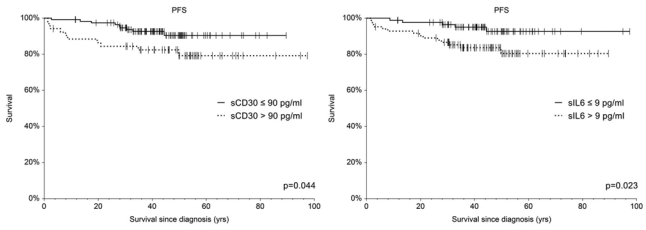


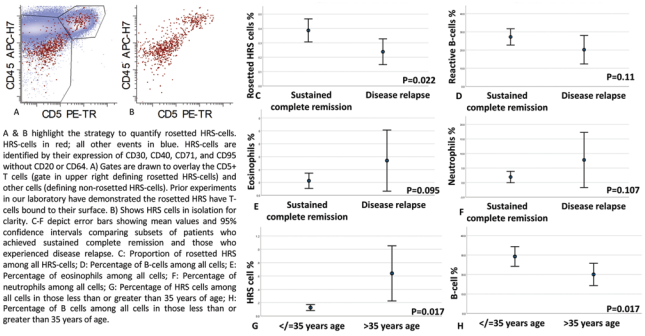
Figure 1: PFS stratified by the pretreatment levels of sCD30 (left) and sIL-6 (right)

P048: PREDICTORS OF RISK OF RELAPSE IN CLASSIC HODGKIN LYMPHOMA BY FLOW CYTOMETRY

Jonathan Fromm[1], Claire Tang[1], Kikkeri N. Naresh[2]

[1]University of Washington, [2]Fred Hutchinson Cancer Center

Figure 1



A & B highlight the strategy to quantify rosetted HRS-cells. HRS-cells in red; all other events in blue. HRS-cells are identified by their expression of CD30, CD40, CD71, and CD95 without CD20 or CD64. A) Gates are drawn to overlay the CD5+ T cells (gate in upper right defining rosetted HRS-cells) and other cells (defining non-rosetted HRS-cells). Prior experiments in our laboratory have demonstrated the rosetted HRS have T-cells bound to their surface. B) Shows HRS cells in isolation for clarity. C-F depict error bars showing mean values and 95% confidence intervals comparing subsets of patients who achieved sustained complete remission and those who experienced disease relapse. C: Proportion of rosetted HRS among all HRS-cells; D: Percentage of B-cells among all cells; E: Percentage of eosinophils among all cells; F: Percentage of neutrophils among all cells; G: Percentage of HRS cells among all cells in those less than or greater than 35 years of age; H: Percentage of B cells among all cells in those less than or greater than 35 years of age.

Background: Classic Hodgkin lymphoma (CHL) is a highly treatable lymphoid malignancy, characterized by rare neoplastic Hodgkin Reed–Sternberg cells (HRS-cells) embedded in a prominent reactive infiltrate. Despite current therapies, about 20% of patients relapse within five years of standard treatment. Identifying patients at risk of subsequent relapse will help develop novel therapeutic strategies for such high-risk patients.

Methods: Using multiparametric flow cytometric analysis, we retrospectively evaluated the impact of the proportion of HRS-cells; the proportion of HRS-cells with T-cell rosettes; proportions of T-cells, B-cells, neutrophils, and eosinophils; proportions of activated T-cells, and activated B-cells; and CD4:CD8 ratio on the likelihood of disease relapse in a cohort of 62 patients.

Results: The median follow-up period was 69.5 months. Patients >35 years of age had a significantly higher percentage of HRS-cells (P=0.017) and a significantly lower percentage of B cells (P=0.017). The nodular sclerosis subtype had a significantly higher percentage of B-cells (P=0.046) and activated B-cells (P=0.03). Patients who experienced disease relapse (DR) had a significantly lower percentage of rosetted HRS-cells as compared to patients who achieved sustained clinical remission (SCR) (P=0.022; Figure 1). Patients experiencing DR also had a marginally lower B-cell% (P=0.11), and higher neutrophil% (P=0.107) and eosinophil% (P=0.095). The proportion of SCR and DR subsets did not differ by histological subtypes, disease stage, or age-groups.

Conclusions: CHL demonstrates a prominent tumor microenvironment (TME) where HRS-cells and the TME result in HRS-cells receiving pro-survival signals and dampening the antitumor immune responses. In our study, patients who experienced DR had a lower proportion of HRS-cells rosetted by T-cells; we hypothesize that HRS-cells in biologically advanced/aggressive CHL are less dependent on its intimate contact or interactions with the T-cells for survival and growth. Likewise, a non-significant higher proportion of eosinophils and neutrophils in the TME of CHL patients who experienced DR was observed, possibly due to the ability of these cells to promote proliferation and growth of HRS-cells. Our study also identifies novel quantifiable biomarkers in CHL. Larger independent studies and multi-institutional studies are essential to validate our findings.

P049: REDUCED FEATURES OF T-CELL ACTIVATION BEFORE AND DURING ANTI-PD-1 TREATMENT IN CLASSICAL HODGKIN LYMPHOMA

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Hodgkin- and Reed-Sternberg cells (HRSC) proliferate in a presumably highly immunogenic tumor microenvironment (TME) containing abundant CD4+ and CD8+ T-cells. Even though anti-PD-1 directed treatment is clinically well established, the mechanism of action in classical Hodgkin lymphoma (cHL) is still incompletely understood. To elucidate features of a T-cell mediated immune response in cHL, we studied HRSC immunogenicity defined by human leukocyte antigen (HLA) expression, associated T-cell expansion, and TME composition.

We analyzed T-cell Receptor (TCR) repertoires, bulk gene expression levels and whole-slide images of treatment-naïve cHL patients before (n=90) and on anti-PD-1 therapy (n=4) in the NIVAHL phase II trial (Bröckelmann et al. JAMA Oncol 2020). In independent cohorts of breast cancer (n=6), benign lymph nodes (n=8) and cHL treated with chemotherapy (n=18), a biopsy both at primary diagnosis and relapse was available. To describe the proliferative activity of T-cells in the TME, we used three measures: debiased Simpson's clonality (Unbiased Clonality; UC), Percentage of Singletons (PoS), and clonal expansion.

We identified significantly lower UC and higher PoS in pre-treatment cHL compared to breast cancer specimens. Moreover, cHL showed less expansion of TCR clones in follow-up biopsies than breast cancer. A pair-wise comparison of pre- and on-anti-PD-1 treatment cHL specimens did not show a significant difference in UC or PoS. However, an analysis of primary versus relapse (after chemotherapy) biopsies of cHL showed a trend to increased UC in relapse specimens.

Next, we analyzed bulk gene expression and TCR repertoires with respect to HLA I and II status on HRSC. HLA status was not associated with UC or PoS. However, we observed a significant enrichment of CD8+ T-cells and up-regulation of cytotoxicity genes in the bulk TME of HLA I+ HRSC. This trend seems to persist for both CD8+ T-cells close and more distant to HRSC (see Müller-Meinhard et al., ISHL12 submission).

In summary, we did not observe features of a T-cell activation (UC, PoS, clonal expansion) in cHL pre- and on-anti-PD-1 treatment biopsies. Our findings suggest a cHL TME that contains a polyclonal mass of T-cells not activated early during anti-PD-1 treatment. However, our analyses cannot exclude an increased clonality in cHL at later timepoints or in relapse biopsies after conventional chemotherapy.

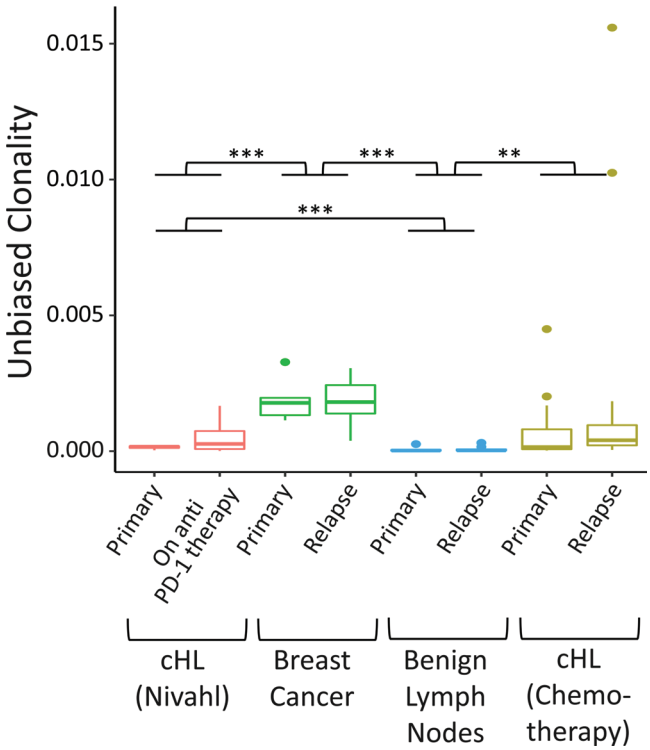

Figure 1: Unbiased Clonality by primary and follow-up biopsies of different cohorts. Stars denote a statistically significant difference in Unbiased Clonalities of two cohorts (Welch's Two Sample t-test, ** $p < 0.01$, *** $p<0.001$)

P050: REED-STERNBERG CELLS ACCELERATE GLYCOLYTIC AND MITOCHONDRIAL METABOLISM OF TUMOR MICROENVIRONMENT CELLS

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Cancer cells in Hodgkin's lymphoma [HL] account for only a few % of the tumor mass which mainly consists of normal cells of the immune system including macrophages. Macrophages may perform different functions depending on the signals they receive. Tumor-associated macrophages (TAM) are often polarized towards the M2-like phenotype - immunosuppressive phenotype, preferring oxygen metabolism, and their presence in HL is associated with a worse prognosis. HL is highly avid in positron emission tomography, which suggests that glucose (Glc) metabolism is increased in non-cancerous microenvironmental cells. Here we asked if and what type of glucose metabolism is increased in TAMs and monocytes/Cd14+ cells.
The project was conducted on the in vitro and the ex vivo model. In the in vitro model, the studied populations were THP-1 monocytic macrophages stimulated by Reed-Sternberg [RS] cells, and control macrophages that were not subjected to stimulation. In the ex vivo model, CD14+ cells were isolated, using the immunomagnetic method, from: fine-needle biopsy lymph node aspirate, peripheral blood of patients diagnosed with HL and from peripheral blood of a healthy donor. The cell's phenotype was determined by flow cytometry using CD14, CD16, CD163, CD206, CD68, CD11b, HLA-DR, PDL1 antibodies. Glc metabolism of the studied cell populations was analyzed using the Seahorse XFp analyser [by directly measuring the extracellular acidification rate (ECAR) and the oxygen consumption rate (OCR)].
The in vitro model experiment showed the intensification of Glc metabolism, in both glycolysis and oxidative phosphorylation pathways, in cells that have been stimulated by RS cells compared to control macrophages. Comparable results were obtained in the ex vivo model, which corroborates the reliability of the in vitro model. Glucose metabolism increases not only the population of cells obtained from lymph node aspirate but also from peripheral blood of patients diagnosed with HL, which may indicate both paracrine and endocrine neoplastic cells impact.
Our data indicate that RS cells stimulate Glc metabolism of tumor microenvironment and peripheral blood CD14+ cells through both glycolysis and oxidative phosphorylation pathways.

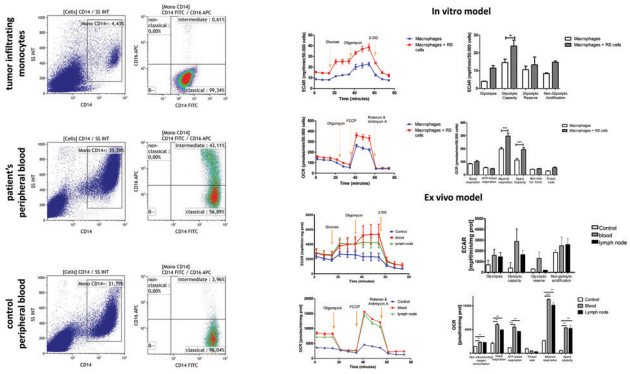

Figure 1: Phenotype of isolated from fine-needle biopsy lymph node aspirate, peripheral blood of patients diagnosed with HL and from peripheral blood of a healthy donor cells. Results of Seahorse analysis of studied cell populations.

P051: SERUM PROCALCITONIN LEVELS IN NEWLY DIAGNOSED CLASSICAL HODGKIN LYMPHOMA (CHL): CORRELATION WITH OTHER INFLAMMATORY BIOMARKERS

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Introduction: In the recent years procalcitonin (PCT) has emerged as a useful biomarker for the diagnosis of sepsis and bacterial infection. Inflammatory markers are elevated in the majority of patients with cHL, a finding that may cause diagnostic issues. Ongoing infection rarely coexists with HL at the time of diagnosis. PCT levels might be helpful in differentiating bacterial infection from non-bacterial, disease-related inflammation, which are both characterized by elevated CRP levels.
Materials and Methods: In order to assess whether and to what extent the underlying chronic inflammatory condition is associated with elevated PCT levels, we collected data on serum PCT levels and other routine inflammation markers in newly diagnosed cHL patients. Values <0.50 ng/mL were considered normal; 0.10–0.50 ng/mL were normal/detectable, while <0.10 ng/mL were normal/undetectable. Serum PCT levels were considered elevated if exceeded the cut-off of 0.50 ng/mL.
Results: Among 137 patients diagnosed with cHL between April 2010 and August 2015, 55 had B-symptoms (40%), ESR was ≥50 mm/h in 77/130 (59%) and 116 patients (85%) had elevated CRP; the median CRP was 38.1 mg/L (range;2.97–328.0). The median serum ferritin was 154.10 ng/ml (range;7-6709) and leukocytosis (WBC ≥15x109/L) was recorded in 20 (15%) patients. Serum PCT levels were normal in the vast majority of the patients [normal/undetectable 94/137(68.5%) and detectable 41/137(30%)] with median value <0.10 ng/ml (<0.10–15.90). Only 2 patients had elevated PCT levels (1.5%). Patients who had serum PCT<0.10 ng/ml had lower median CRP [25.75; range(2.97–203.0)] compared to patients with PCT ≥0.10 ng/ml who had median CRP of 92.50 mg/L(range;3.34–328.0; p<0.001). Almost all patients (40/41, 97.6%) with detectable PCT levels had also elevated CRP. Compared to patients with normal/undetectable levels, those with PCT ≥0.10 ng/ml had more frequently advanced disease (83%), B symptoms (73%), ESR≥50 (82%), anemia (81%), hypoalbuminemia (90%), leukocytosis (27%) and higher serum ferritin, haptoglobin and a2-globulin levels.
Conclusion: This is the first study showing that the inflammatory condition characterizing cHL is not associated with serum PCT elevations although CRP levels are elevated in 85% of them. Consequently, normal serum PCT levels may rule out the diagnostic possibility of occult infection, thus preventing extensive evaluation, which may further delay in treatment initiation.

P052: TARGETING CSN5/JAB1 ONCOGENE IN CLASSICAL HODGKIN LYMPHOMA (CHL)

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Background: The JAB1 (cJun activation domain binding protein1), initially discovered as a cJun coactivator, represents the fifth component of an evolutionary highly conserved 8 subunit protein complex named COP9 signalosome (CSN5). Accumulating evidence suggests that the CSN5/JAB1 gene operates as an oncogene in cancer through multiple mechanisms including cell cycle control via downregulation of CDK inhibitors. Targeting CSN5/JAB1 activity in cancer is now possible since a novel inhibitor has been developed for clinical use (CSN5i-3, Novartis). The potential role of CSN5/JAB1 in modulation of anti-tumor responses in cHL is unknown to date.
Methods: The study group included 118 previously untreated cHL patients with available tissue and clinical data. Expression of CSN5/JAB1 was assessed by immunohistochemistry and a previously validated monoclonal antibody. The in vitro system included 6 cHL cell lines (MDA-V, L1236, L428, L540, KMH2, HDLM2). Expression of proteins were analysed by Western blot and gene expression (mRNA) of type 1 interferons (IFNs), including IFN-β, CXCL10

and IFN-γ, with RT-qPCR. The cHL cell lines were treated with the CSN5i-3 at different concentrations. Silencing of CSN5/JAB1 and NFkB (p65) gene was performed using transient transfection with siRNA constructs.
Results: Using a 10% cutoff, CSN5/JAB1 was positive in the neoplastic HRS cells of cHL in 106 of 118 (90%) patients with a predominantly nuclear and weaker cytoplasmic pattern. Treatment of cHL cell lines with increasing concentrations of CSN5i-3 resulted in significant decrease in the cell growth and viability associated with upregulation of the CDK inhibitors p21, p27 and p57. Similarly, CSN5/JAB1 gene silencing resulted in decreased cell growth associated with increased expression of similar cell cycle inhibiting proteins. Inhibition of CSN5/JAB1 activity resulted in significantly increased gene expression of IFN-β, CXCL10 and IFN-γ at a variable degree among the cHL cell lines. Similarly, knocking down CSN5/JAB1 gene led to upregulation of type 1 IFNs. Silencing NFkB gene resulted in decreased levels of CSN5/JAB1 protein suggesting positive regulation of CSN5/JAB1 by NFkB.
Conclusion: The CSN5/JAB1 is overexpressed in HRS cells of most cHL patients, promotes cell growth through cell cycle control and downregulates gene expression of type 1 IFNs in vitro. These functions are sufficiently inhibited by the CSN5i-3, designed for clinical use, in preclinical models of cHL.

P053: THE CGAS-STING ANTI-TUMOR IMMUNE RESPONSE PATHWAY AS A POTENTIAL THERAPEUTIC TARGET IN CLASSICAL HODGKIN LYMPHOMA (CHL)

Ioanna Xagoraris[1], Konstantina Stathopoulou[1], Persa Xyderou[1], Marzia Palma[1], Elias Drakos[2], Theodoros P. Vassilakopoulos[3], Georgios Z. Rassidakis[1]

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Background: Cytosolic DNA of exogenous or endogenous origin triggers activation of cyclic GMP-AMP (cGAMP) synthase (cGAS), a cytosolic DNA sensor, that activates innate immune responses through production of the second messenger cGAMP and subsequently activation of the adaptor protein STING. The latter activates TBK1 and IKK kinases that, in turn, activate IRF3 and NF-κB transcription factors, which induce expression of interferons (IFNs), chemokines and cytokines involved in anti-tumor immune responses. The potential role of cGAS-STING pathway in anti-tumor immune responses in cHL remains unknown to date.
Methods: STING expression was immunohistochemically analysed in a pilot study group of 32 untreated patients with cHL and available tissue. The in vitro system included 6 cHL cell lines (MDA-V, L1236, L428, L540, HDLM2, KMH2). Gene expression (RNA level) and protein expression and activation (phosphorylation) of cGAS-STING pathway components at baseline and experimental conditions were analysed by quantitative RT-PCR (RT-qPCR) and Western blot, respectively. The cHL cell lines were treated with a STING agonist and TBK1/IKK inhibitor (Amlexanox) alone or in combination with other agents. Silencing of STING gene was performed using transient transfection with specific STING siRNA. The cGAS-STING-associated anti-tumor immune responses were evaluated by assessing the RNA levels of IFN-β, CXCL10, IFN-γ, and a control gene (GAPDH) with RT-qPCR.
Results: Using an arbitrary 10% cutoff, STING was positive in the neoplastic Hodgkin & Reed-Sternberg (HRS) cells of cHL in 20 of 32 (63%) patients with a membranous and cytoplasmic pattern. STING expression at the mRNA and protein level was substantially higher in L1236, L428 and HDLM2 compared to other cHL cell lines. Treatment with STING agonist alone stimulated gene expression of IFN-β and/or CXCL10 at a variable level depending on the cell line indicating functional cGAS-STING anti-tumor immune response pathway in cHL. Knocking down STING gene resulted in decreased CXCL10 and type 1 IFN gene expression by cHL cells. Amlexanox treatment also resulted in downregulation of IFN-β or CXCL10 gene expression in vitro.
Conclusion: STING agonists and Amlexanox modulate gene expression of type 1 IFNs in cHL with direct therapeutic implications. A large cohort of cHL patients is currently being analysed for the expression and prognostic significance of STING, and the final results will be available at the time of ISHL 2022.

P054: THE KINASE CK2 IS DEREGULATED AND TARGETABLE IN CLASSICAL HODGKIN LYMPHOMA

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Introduction: CK2 is a pleiotropic kinase consisting of 2 catalytic (a) and 2 regulatory (b) subunits, usually overexpressed, that sustains cancer signaling cascades through the activation of NF-kB, PI3K and STAT pathways. Considering that NF-kB, STAT and PI3K pathways are key players in Hodgkin lymphoma (HL), it is likely that CK2 might play a role in the pathogenesis of this disease.
Methods: Experiments were performed and replicated at least for five times employing 4 HL cell lines (L-428, L-540, KM-H2 and HDLM-1) cultured in RPMI. CK2a, CK2b, RelA-Serine (S)529, RelA, PARP, AKT-S473, AKT, STAT3-S727, STAT3, tubulin, ubiquitin expression levels were evaluated by western blot analysis (WB). Silmitasertib and bortezomib were used as CK2a and proteasome inhibitors. Apoptosis was assessed by Annexin V/Propidium iodide assay and PARP cleavage by WB. Immunohistochemistry (IHC) for CK2a and CK2b was performed on formalin fixed paraffin embedded sections of lymph-nodes from patients with HL, indolent and aggressive NHL. Chou-Talalay methods was used to calculate the combination index (C.I.) of two drugs.
Results: By WB and IF we found that all the 4 HL cell lines expressed higher levels of CK2a, but not CK2b, as compared to normal B lymphocytes ($p<0.001$). By IHC on 35 patients' lymph-nodes, we confirmed that CK2a but not CK2b was highly expressed in Reed-Sternberg cells. In addition, patients with lower levels of CK2b display a better progression-free survival ($p<0.05$). The unbalance between a and b subunits was not observed in low or high-grade NHL ($p<0.001$). Furthermore, we observed that mRNA levels of both CSNK2A and CSNK2B were similar to normal B lymphocytes, and that proteasome inhibition with bortezomib caused the upregulation of CK2b. AKT, RelA and STAT3 were constitutively phosphorylated in HL at their activatory S-residue (S473, S529, and S727 respectively). Treatment of HL cell lines with silmitasertib caused down-regulation of these phospho-serine proteins, time and dose-dependent apoptosis ($p<0.0001$). In addition, we found that silmitasertib did not modulate surface CD30 and had a synergistic anti-apoptotic effect in combination with monomethyl auristatin E (C.I.<1)
Conclusions: We demonstrated that CK2a is overexpressed, active, induced key pro-survival signals in HL, and its inhibition trigger apoptosis. CK2b is likely downregulated due to proteasome degradation. These preliminary data suggest that CK2 might be a new therapeutic target in HL.

P055: VALIDATION OF THE TUMOR CELL-SPECIFIC REARRANGED IGG-ENCODING CIRCULATING CELL-FREE DNA FOR THE TREATMENT RESPONSE MONITORING IN PATIENTS WITH CLASSIC HODGKIN LYMPHOMA

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Background: Detection and longitudinal monitoring of the cell-free circulating tumor-specific DNA (ctDNA) in plasma of cancer patients is a potent tool for treatment response assessment and detection of the early disease recurrence. There is a number of the next-generation sequencing (NGS) panels for analysis of the commonly mutated genes in tumors of classic Hodgkin lymphoma (cHL) patients, which are being validated for clinical use. The Cleveland Clinic team, in collaboration with Adaptive Biotechnologies, is exploring if longitudinal assessment of ctDNA encoding the patient- and tumor cell-specific rearranged heavy or light (kappa/lambda) chain IgG (r-IgH/r-IgK/L, could be used for the treatment response and early recurrence monitoring in cHL patients.
Methods: Enrolled are patients (9–99 y) with newly diagnosed and previously untreated cHL. First, the diagnostic biopsy specimen and the pre-treatment plasma are tested for concordant presence of dominant r-IgH/r- IgK/L ctDNA sequences. Sequence dominance and suitability for tracking is determined according to the Adaptive Biotechnologies' diagnostic algorithm validated for other B cell neoplasms. If dominant

Table 1: Clinical characteristics of patients

	Age at Dx	Sex	Histology	Stage	Therapy & Response	ID sequence / pre-Tx (count/mL)	MRD sequence (count/mL)
1	20	M	NS	IIIB	ABVD x 2; RER AVD x 4; CR1	IgH: 34.17	ND ND
2	28	F	NS	IV	AVD+NIVO x 2: RER AVD+NIVO x 4; CR1	IgH1: 30.05 IgH2: 29.3274	ND ND
3	19	F	NS	II	ABVD x 2; RER ABVD x 2; NIVO x 3; *	IgK: 4.163 IgH1: 3.341487 IgH2: 1.371	* *
4	22	M	NS	IIB	ABVD x 2; RER ABVD x 2; NIVO x 3; *	IgH: 6.552	* *

Abbreviations used: ABVD: Adriamycin, Bleomycin, Vinblastine, Dacarbazine; **CR1:** first complete remission; **ND:** not detected; **NIVO:** nivolumab; **NS:** Nodular Sclerosis; **RER:** Rapid Early Response; * Treatment response assessment pending;

Table 1: Clinical characteristics of patients

r-IgH/r-IgK/L sequence(s) is detected, the patient plasma is serially tested during and following completion of therapy.

Results: Pilot results on first 4 patients are presented. Patients' clinical characteristics are summarized in Table 1. P1 had a single dominant r-IgH ctDNA sequence; P2 had two dominant r-IgH ctDNA sequences; P3 had two r-IgH and one dominant IgK ctDNA sequences; the latter was chosen for serial tracking; P4 had a single dominant r-IgH ctDNA sequence. In P1 and P2, the concentration of ctDNA precipitously declined below detectable threshold following completion of the first two cycles of therapy, and remained undetectable through the end of treatment. These laboratory changes correlated well with the treatment response assessed by functional imaging. For P2 and P3, the in-treatment samples are in process of acquisition.

Conclusion: The preliminary results of this pilot project demonstrate feasibility of establishing trackable ctDNA sequences encoding IgG heavy or light chain, with intra- and interpatient clonotypic heterogeneity of the dominant sequences. Correlation between results of the functional imaging treatment assessment and detectable quantity of ctDNA in plasma was observed. Further testing is underway.

P056: VARIANTS OF THE TRANSCRIPTION FACTOR ONECUT2 REGULATE GENE EXPRESSION IN HODGKIN LYMPHOMA CELLS

Patricia Lein[1], Charles Gwellem Anchang[2], Ines Volkmer[1], Martin S. Staege[1]

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Background: ONECUT transcription factors are characterized by the presence of a single CUT domain and a HOX domain. ONECUT2 is involved in pathogenesis of several solid tumors and regulates proliferation, migration and differentiation of tumor cells. We identified a transcript variant of ONECUT2 in a cDNA library of the chemo-resistant Hodgkin lymphoma (HL) cell line L-1236. This variant (ONECUT2s) contains a CUT Domain without a corresponding HOX domain. To further characterize this variant, we performed over-expression and knock-down studies in diverse cell line models and studied the impact of ONECUT2 variants on gene expression.

Methods: Expression of ONECUT2 and ONECUT2s in tissue samples and cell lines was assessed by quantitative reverse transcription-polymerase chain reaction (qRT-PCR). Additional expression studies were performed using public available microarray data sets. RNA interference was used for knock-down of ONECUT2 and ONECUT2s. For over-expression studies, the different ONECUT2 variants were cloned into the doxycycline-inducible vector pRTS-1, with a bi-directional promoter, allowing simultaneous expression of the transgene and the reporter EGFP. Knock-down and over-expression was analyzed by qRT-PCR. For assessing the influence of ONECUT2 and ONECUT2s on gene expression, microarray analysis and RNA-seq analyses were performed.

Results: Gene expression analysis by qRT-PCR showed high expression of ONECUT2 and ONECUT2s in HL-cell lines and normal liver. Public available microarray data also indicated high expression of ONECUT2 in HL-cell lines and a subset of HL biopsies. The majority of the other tissues and cell lines showed only low expression of both ONECUT2 variants. Microarray and RNA-seq analyses of transgenic cells and cells after knock-down of ONECUT2 variants showed that both variants affected the global gene expression profile. However, effects of ONECUT2 were much stronger than effects of ONECUT2s. Both variants seem to regulate different sets of genes, especially for ONECUT2 these genes include genes involved in apoptosis regulation and immune response.

Conclusion: ONECUT2 acts as a transcription factors in HL-cells and both variants have different effects on gene expression. The high expression of both ONECUT2 variants in HL might qualify this transcription factor as a possible candidate for targeted therapy of HL.

Our work is supported by Mitteldeutsche Kinderkrebsforschung

P115: DISTINCT SIGNALING PATHWAYS AND CHECKPOINT MOLECULE EXPRESSION ACROSS HISTOLOGICAL SUB-TYPES OF NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA

Ilja Kalashnikov[1;2], Rachel Kositsky[3], Marja-Liisa Karjalainen-Lindsberg[4], Johannes Dunkel[4], Annika Pasanen[1;2], Cassandra Love[3], Clay Parker[5], Sarah Ondrejka[6], Eric Hsi[7], Ridas Juskevicius[8], Andrew Evans[9], Andrew G. Evans[9], Magdalena Czader[10], Lin Wang[10], Mina Xu11, Nathan Paulson[11], Mette ølgod Pedersen[12], Anne Ortved Gang12, Jean Koff[13], Chad Mccall3, Yaso Natkunam[14], Abner Louissaint15, Ong Shin Yeu[16], Raju Pillai[17], Jennifer Chapman[18], Catalina Amador[19], Amy Chadburn[20], Rashmi Goswami[21], Amir Behdad[22], Payal Sojitra[23], Eric Tse[24], Naresh Kikkeri[25], Kikkeri N. Nasresh[25], Yuri Fedoriw[26], Sandeep Dave[3], Sirpa Leppä[1;2]

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Background: Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare B-cell malignancy characterized by infrequent neoplastic cells embedded in an immunologically active tumor microenvironment (TME). The composition of the TME is known to influence the outcomes; cases with a nodular B-cell rich TME (classical histology; Fan A-B) are generally indolent, whereas increased infiltration of T-cells or diffuse growth (variant histology; Fan C-F) is associated with a more aggressive clinical course. The molecular features underlying this association remain to be discovered. To gain further insights into disease

Table 1. Patient demographics.

Characteristic	N	N=106
Agedatdiagnosis,years(median;IQR)	106	40(24.54)
Followup,months(median;IQR)	106	78(53.119)
PatientGende r,n(%)	106	
Female		29(27%)
Male		77(73%)
Splenicinvolvement,n(%)	97	
Yes		12(12%)
No		85(88%)
Unknown		9
Stage(I-IIvsII-IV),n(%)	99	
I-II		69(70%)
III-IV		30(30%)
Unknown		7
Relapse/transformationafterinitialdiagnosis,n(%)	96	
No		69(72%)
Relapse		24(25%)
Transformation		3(3.1%)
Unknown		10
Histology,n(%)	106	
Classical		63(59%)
Variant		43(41%)
10-yearOS(95%CI)	106	83%(73%,95%)
10-yearPFS(95%CI)	95	58%(46%,73%)

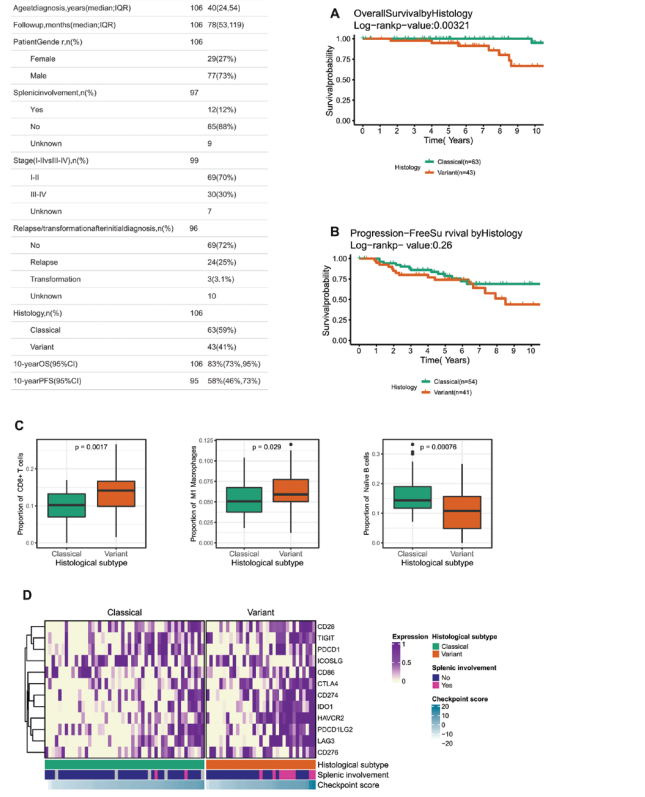

Figure 1: A. 10-year overall survival stratified by histological subtype; **B.** 10-year progression-free survival stratified by histological subtype; **C.** In silico immunophenotyping using FARDEEP with signature matrix LM22 from CIBERSORT. Boxplots comparing CD8+ T cell, macrophage M1, and naïve B-cell immune cell fractions stratified by histological subtype; **D.** Unsupervised clustering for expression of checkpoint genes stratified by histological subtype. Samples are ordered by the sum of normalized checkpoint gene expression values (checkpoint score).

Figure 1: Caption is included in the figure

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Male		77(73%)
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No		85(88%)
Unknown		9
Stage(I-IIvsIII-IV),n(%)	99	
I-II		69(70%)
III-IV		30(30%)
Unknown		7
Relapse/transformationafterinitialdiagnosis,n(%)	96	
No		69(72%)
Relapse		24(25%)
Transformation		3(3.1%)
Unknown		10
Histology,n(%)	106	
Classical		63(59%)
Variant		43(41%)
10-yearOS(95%CI)	106	83%(73%,95%)
10-yearPFS(95%CI)	95	58%(46%,73%)

biology, we recruited NLPHL cases as part of the Atlas of Blood Cancer Genomes (ABCG) initiative, a consortium consisting of 26 institutions.
Design: We collected comprehensive clinicopathological data from 106 NLPHL patients, with centralized review performed by a panel of dedicated hematopathologists to ensure accurate diagnosis. We performed RNA sequencing on formalin-fixed paraffin-embedded (FFPE) diagnostic tumor samples (n=81) and enumerated tumor-infiltrating immune cell compositions using FARDEEP with signature matrix LM22 from CIBERSORT.
Results: Patient demographics are shown in Table 1. Classical histology was associated with better survival compared to variant histology (Figure 1A-B). According to in silico immunophenotyping, NLPHLs with variant histology were characterized by a lower proportion of naïve B cells and increased proportions of CD8+ T cells and M1-macrophages compared to the classical histology (Figure 1C). Moreover, variant histology was associated with higher expression of checkpoint genes compared to classical histology (Figure 1D; P=0.019). Higher proportions of T cells and macrophages and increased expression of checkpoint genes were particularly prominent in cases with splenic involvement. Finally, we found a strong association between variant histology and gene expression related to inflammatory response (P<0.001), whereas genes related to cell cycle regulation through the E2F pathway were upregulated in NLPHLs with classical histology (P<0.001).
Conclusion: Our study represents the largest comprehensive clinical and transcriptomic analyses of NLPHL to-date. Our results indicate that TME is clinically meaningful and provide evidence for distinct signaling pathways and expression patterns of checkpoint genes across histological subtypes.

Immunotherapy

T057: CIRCULATING TUMOR DNA IN CLASSICAL HODGKIN LYMPHOMA PATIENTS TREATED WITH PEMBROLIZUMAB AND CHEMOTHERAPY: DYNAMIC RESPONSE ASSESSMENT AND CORRELATION WITH BASELINE TOTAL METABOLIC TUMOR VOLUME

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Introduction: We have previously presented early results of untreated CHL patients treated with concurrent pembrolizumab + AVD (Lynch et

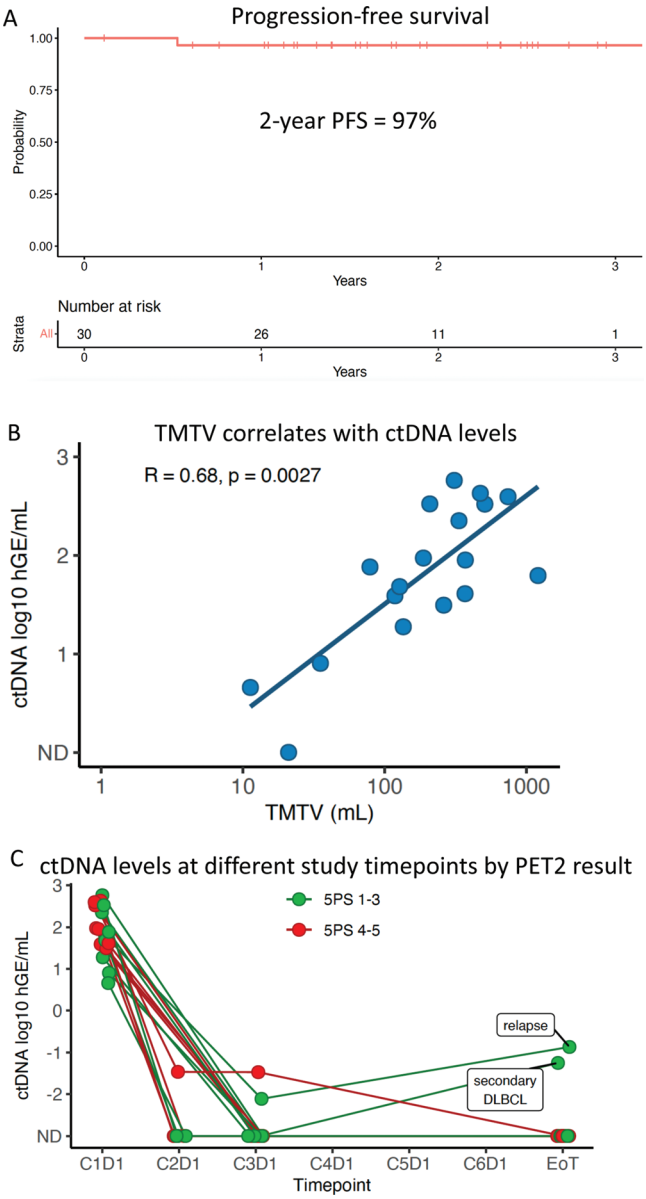

Figure 1: A: Progression-free survival; B: Scatter-plot demonstrating correlation of baseline TMTV with ctDNA levels; C: Spider-plot of ctDNA levels at various time points during the study color-coded by interim-PET results

al. ASH 2021) which had increased rates of false positive PET/CT results leading to additional scans and/or biopsies. Circulating tumor DNA (ctDNA) may represent a more sensitive and specific method of response assessment. Herein we report updated clinical results with correlation of dynamic ctDNA monitoring as well as data on total metabolic tumor volume (TMTV).

Methods: This was a single arm pilot study combining pembrolizumab with AVD in untreated CHL of any stage. Plasma 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 CAPP-Seq and PhasED-Seq (Kurtz et al. Nat Biotech 2021). Baseline, post cycle 2, and end of treatment PET/CT were analyzed for TMTV using a threshold based semiautomated technique that included any tumor with standardized uptake value (SUV) above the liver background SUVmax using MIM Encore (version 7.1.3 Cleveland, OH).

Results: Among the 30 patients enrolled, 29 are evaluable for response and/or exploratory analysis. With median follow-up of 21 months, 2-year PFS and OS were 97% and 100%, respectively. While 5 patients had residual FDG uptake at EOT, only 1 (20%) has developed recurrent lymphoma. ctDNA data was available for 18 patients. Pretreatment ctDNA levels were significantly correlated with TMTV (RS=0.68, p=0.003). 17/18 patients had detectable ctDNA at baseline and were therefore evaluable for MRD assessment. Among 8 PET2+ patients, only 1 patient had detectable ctDNA, and ctDNA became undetectable by the end of treatment. Importantly, of these 8 patients, none have relapsed. Only 1/9 (11%) patients who were PET2- had detectable ctDNA after 2 cycles, and the cancer ultimately recurred. At EOT for those who received > 2 cycles, 2/14 had detectable ctDNA (one CHL relapse, one with secondary DLBCL 11 months later). ctDNA analyses for the remaining patients are in process and will be presented at the meeting.

Conclusion: Concurrent pembrolizumab + AVD represents highly effective frontline therapy for CHL, but results in spurious PET findings in a significant proportion of patients despite most patients having undetectable ctDNA and no relapse. ctDNA may represent a more sensitive and specific response assessment tool to be studied in larger datasets.

T058: SAFETY AND DOSE-EXPANSION STUDY OF COMBINATION FAVEZELIMAB (ANTI–LAG-3) PLUS PEMBROLIZUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA REFRACTORY TO ANTI–PD-1 TREATMENT

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Background: Optimizing therapies for pts with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) after anti–PD-1 therapy failure remains of clinical interest. The multicohort phase 1/2 MK-4280–003 study (NCT03598608) evaluated the safety and efficacy of a LAG-3 inhibitor, favezelimab (MK-4280), + pembrolizumab (pembro) in pts with R/R hematologic malignancies. Cohort 2 focused on pts with R/R cHL after anti–PD-1 therapy.

Methods: Part 1 was the safety lead-in phase to determine the recommended phase 2 dose (RP2D), followed by a dose-expansion phase (part 2). Eligible pts in cohort 2 had cHL and relapsed after or were ineligible for autologous stem cell transplantation and PD after ≥2 doses of anti–PD-1 therapy. Pts in part 1 received escalating doses (per mTPI design) of pembro IV 200 mg Q3W and favezelimab IV 200 mg or 800 mg Q3W. In part 2, pts received pembro + favezelimab at RP2D for ≤35 cycles. Primary end point was safety. ORR was a secondary end point. DOR, PFS, and OS were exploratory end points. Database cutoff was March 21, 2022.

Results: Part 1 identified 1 dose-limiting toxicity (DLT; autoimmune hepatitis [grade 4]) among the first 6 pts from all cohorts at the favezelimab 200 mg dose. No DLTs were found after an additional 15 pts at the 800 mg dose; RP2D was defined as 800 mg Q3W + pembro 200 mg Q3W. 34 pts were enrolled in cohort 2; median age was 37.5 y, 62% had ECOG PS 0, and 94% had ≥4 prior lines of therapy. At database cutoff, 22/34 pts had discontinued (11 PD; 7 AEs; 2 clinical progression; 2 pt withdrawal/physician decision); 18% discontinued due to treatment-related AEs (TRAE). No deaths were treatment related. 28 pts (82%) had TRAEs; most common (≥15%) were hypothyroidism (18%) and fatigue and nausea (15%, each); 6 pts (18%) had grade 3 or 4 TRAEs. After median follow-up of 18.4 mo, ORR was 30% (95% CI,16–49; CR, 3 [9%]; PR, 7 [21%]). 25/27 (93%) pts with a postdose scan had a baseline reduction in target lesions. 70% of responders had an anti–PD-1–based regimen as most recent line of therapy at study entry. Median DOR was 19.4 mo (range, 0+ to 19.4); 4 pts (65%) had response ≥12 mo. Median PFS was 9.4 mo (range, 5.1–14.7). and median OS was 25.7 mo (range, 21.2-NR).

Conclusion: Favezelimab 800 mg + pembrolizumab 200 mg Q3W demonstrated acceptable safety and effective antitumor activity in pts with R/R cHL and PD following anti–PD-1 therapy. This combination shows potential to reinduce a response in this pt population.

P059: MULTI-EFFECTOR CELL TARGETING WITH HALF-LIFE EXTENDED BISPECIFIC SCFV IN HODGKIN LYMPHOMA

Zhiyuan Shi[1], Verena Kern[1], Max Freihammer[1], Jennifer Schitz[1], Sven Borchmann[1]

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Immunotherapy has revolutionized the treatment of many hematological cancers. One form of cancer immunotherapy is exploiting immune effector cells, for example, T-cells or NK-cells, by retargeting them to cancer-associated antigens which have been identified and validated for most hematological cancers. However, most strategies to do so employed to date suffer from disadvantages such as unfavorable pharmacokinetics and unspecific immune system activation with current bispecific antibodies, high complexity and cost with CAR T-cells or lack of efficacy with many simple monoclonal antibodies targeting tumor-associated antigens. Thus, it is highly desirable to develop new technologies that can overcome these limitations. Here, we introduce our strategy to retarget various immune effector cells simultaneously with half-life extended bispecific scFv constructs to Hodgkin lymphoma-associated antigens e.g., CD30. In doing so, we target CD3, CD16 and CD28 on immune effector cells. Half-life extension is achieved by fusing the scFv constructs to a repetitive amino acid sequence without secondary structure and immunogenicity developed by us. After optimizing the production of our constructs in mammalian protein production systems we performed functional in vitro validation. Our data shows that the designed bispecific scFv constructs can bind their targets specifically and simultaneously and facilitate the formation of an artificial immunological synapse with immune cells secreting toxic proteins such as perforin and granzymes leading to the apoptosis of the lymphoma cells. We show direct cytotoxicity towards tumor cells in vitro and a target-cell specific release of cytokines such as TNFα and IFNγ by effector cells. We are now moving some constructs into cell line xenograft mouse models for further in vivo validation.

P060: PROGNOSIS OF PATIENTS WITH RELAPSED AND REFRACTORY CLASSIC HODGKIN LYMPHOMA AFTER NIVOLUMAB DISCONTINUATION AND EFFICACY OF NIVOLUMAB RETREATMENT

Liudmila Fedorova[1], Kirill Lepik[1], Natalia Mikhailova[1], Elena Kondakova[1], Yaroslava Komarova[1], Polina Kotselyabina[1], Evgenia Borzenkova[1], Vadim Baykov[1], Ivan Moiseev[1], Alexander Kulagin[1]

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Variable	N=48
Median age, years (range)	37 (23-55)
Male/female, n (%)	12/36 (25/75)
Primary chemoresistance, n (%) Early relapse, n (%)	31 (65) 6 (13)
Prior autologous stem cell transplantation, n (%)	17 (35)
Prior brentuximab vedotin, n (%)	20 (42)
Therapy lines before Nivo therapy, n (range)	5 (2-10)
B symptoms at Nivo therapy initiation, n (%)	26 (54)
Disease stage at Nivo therapy initiation, n (%) 2 3 4	 12 (25) 3 (6) 33 (69)
Progression at Nivo therapy initiation, n (%)	36 (75)
ECOG status at Nivo therapy initiation, n (%) 0-1 2 3 4	 27 (56) 19 (40) 2 (4)
Nivo dose, n (%) 40 mg 3 mg/kg	 29 (60) 19 (40)
Number of Nivo cycles, n (range)	24 (6-30)
Status at Nivo discontinuation, n (%) CR PR	 40 (83) 8 (17)
Number of Nivo cycles before the best response achievement, n (range)	6 (6-24)

Table 1: Patient's characteristics

Background: The optimal nivolumab (N) therapy duration for patients (pts) with relapsed and refractory classic Hodgkin lymphoma (r/r cHL) has not been determined and this question remains a pressing issue. The possibility of prolonged remission after treatment discontinuation in complete response (CR) as well as the preservation of sensitivity to PD-1 inhibitors retreatment was previously demonstrated. However as the number of report regarding the problem of N discontinuation and retreatment is limited, the accumulation of additional data is required.
Aims: To analyze the survival of pts with r/r cHL after N discontinuation as well as the efficacy and safety of N retreatment.
Methods: The retrospective analysis included 48 pts with r/r cHL who were treated with N 3 mg/kg (n=29) or 40 mg (n=19). All pts discontinued N due to different reasons in CR (n=40) or partial response (PR) (n=8). In case of disease relapse the PD-1 inhibitors monotherapy was reinitiated. The response was evaluated by PET-CT using LYRIC criteria. Adverse events (AE) were analyzed by NCI CTCAE 4.0.3.
In group of N discontinuation PFS, OS were evaluated. In group of N retreatment ORR, PFS, OS and AE rate were also analyzed. PFS estimates was censored by the time of additional therapy initiation in group of N retreatment.
Results: Patient's characteristics are demonstrated in the table 1. Reasons for N discontinuation were: grade 3–4 AE in 6 (13%) pts, Russian nivolumab NPP discontinuation in 27 (56%), patient's decision in 15 (31%). Median follow up was 48 (4–65) mo. Disease relapse was occurred in 30 (63%) pts. Median PFS in group of patients who achieved CR was 24 mo (95%CI: 11.7-NA) and 4-y PFS was 43.6% (95%CI: 26.9–58.3), in group of PR all patients had disease progression: median PFS was 7.7 mo (95% CI: 5.6–16.5). Only 1 pt died due to progressive multifocal leukoencephalopathy after allo-HSCT. Median OS was not reached, 4-y OS was 92.9% (95%CI: 59.1–99).
Retreatment with mono-N was initiated in 22 pts. Median follow up was 33 (7–56) mo. ORR was 73%: CR was achieved in 9 (41%) pts, PR in 7 (32%), indeterminate response in 6 (27%). Median PFS was 24.8 mo (95%CI: 17.2-NA), 3-y PFS 26.7% (95%CI: 7.5–51). Nine (41%) pts demonstrated AE during N retreatment, 4 (18%) pts - grade 3–4 AE.
Conclusion: Patients with r/r cHL who achieved CR after N therapy may demonstrate durable remissions after N discontinuation. In case of disease relapse N retreatment is effective and safe option.

P061: SAFETY AND DOSE-EXPANSION STUDY OF COMBINATION FAVEZELIMAB (ANTI–LAG-3) PLUS PEMBROLIZUMAB IN ANTI–PD-1–NAIVE PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA

Peter Borchmann[1], Nathalie A. Johnson[2], David Lavie[3], Gareth Gregory[4], Alex F. Herrera[5], Leonard Minuk[6], Vladan Vucinic[7], Philippe Armand[8], Abraham Avigdor[9;10], Robin Gasiorowski[11], Yair Herishanu[12], Colm Keane[13], John Kuruvilla[14], John Palcza[15], Pallavi Pillai[15], Akash Nahar[15], John Timmerman[16]

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Background: PD-1 inhibitors play a key role in the treatment of relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL), yet novel strategies to enhance responses remain of clinical interest. The multicohort phase 1/2 MK-4280–003 study (NCT03598608) evaluated the safety and efficacy of a LAG-3 inhibitor, favezelimab (MK-4280), + pembrolizumab (pembro) in pts with R/R hematologic malignancies. Cohort 1 focused on anti–PD-1–naive pts with R/R cHL.
Methods: Part 1 was the safety lead-in phase to determine the recommended phase 2 dose (RP2D) followed by a dose-expansion phase (part 2). Eligible pts in cohort 1 had R/R cHL after autologous stem cell transplantation (ASCT), were ineligible for ASCT, and had no prior anti–PD-1 therapy. Part 1 included pts from all cohorts who received escalating doses (per mTPI design) of pembro IV 200 mg Q3W and favezelimab IV 200 mg or 800 mg Q3W. In part 2, pts received pembro + favezelimab at the established RP2D for ≤35 cycles. The primary end point was safety. ORR was a secondary end point. DOR, PFS, and OS were exploratory end points. Database cutoff was March 21, 2022.
Results: Part 1 identified 1 dose-limiting toxicity (DLT; autoimmune hepatitis [grade 4]) among the first 6 pts from all cohorts at the favezelimab 200 mg dose. No DLTs were found after an additional 15 pts at the 800 mg dose; RP2D was defined as 800 mg Q3W + pembro 200 mg Q3W. Of the 30 pts in cohort 1, median age was 40.5 y, 53% had ECOG PS 0, and 80% had ≤3 prior lines of therapy. At database cutoff, 12 of 30 pts had discontinued (4 AEs; 8 PD; 13% due to treatment-related AEs [TRAEs]). No deaths were treatment related. 26 pts (87%) had TRAEs; the most common (≥20%) were hypothyroidism (27%), infusion-related reactions (23%), and fatigue (20%); 7 pts (23%) had grade 3 or 4 TRAEs. After median follow-up of 14.1 mo, ORR was 73% (95% CI, 54–88; CR, 8 [27%]; PR, 14 [47%]). 28 of 29 pts (97%) who received a postdose scan had a baseline reduction in target lesions. Median DOR was not reached (NR; range, 2.6–25.9+ mo); 7 pts (55%) had response ≥12 mo. Median PFS was 19.4 mo (range, 8.5 mo-NR) and median OS was NR (range, NR-NR).
Conclusion: Favezelimab 800 mg + pembro 200 mg Q3W demonstrated acceptable safety and effective antitumor activity in anti–PD-1–naive pts with R/R cHL. Comparative studies on its activity to that of single-agent pembro would be of clinical benefit.

P062: THE EFFICACY AND SAFETY OF NIVOLUMAB 40 MG THERAPY VERSUS 3 MG/KG IN PATIENTS WITH RELAPSED AND REFRACTORY CLASSIC HODGKIN LYMPHOMA

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Background: The efficacy of nivolumab (Nivo) at a fixed dose of 40 mg in patients with relapsed and refractory classic Hodgkin lymphoma (r/r cHL) was demonstrated in previous studies. Nevertheless, comparison of the efficacy of low doses of PD1 inhibitors with standard dose 3 mg/kg is currently required.
Aims: To compare the results of Nivo 40 mg therapy versus standard dosing regimen of 3 mg/kg for patients with r/r cHL.
Methods: The Nivo40 trial (NCT03343665) expanded prospective cohort of patients (group 1, n=51) treated with Nivo 40 mg was compared with the retrospective group 2 (n=116) of patients treated with Nivo 3 mg/kg.
The response was evaluated every 3 months by PET-CT using LYRIC criteria. Adverse events (AE) were analyzed by NCI CTCAE 4.0.3.
Overall response rate (ORR), progression-free survival (PFS), overall survival (OS) were compared between group 1 and 2. During the

survival analysis the PFS was censored by the time of additional therapy initiation.

Results: Patient's characteristics are demonstrated in the table 1. Median follow up was 48 (2–60) months in group 1 and 60 (6–70) months in group 2. Median Nivo cycles was 19 (2–49) and 20 (1–32) respectively. The best response to Nivo therapy was detected at 6 (2–24) and 6 (1–27) cycles respectively.

ORR was 68% in group 1 and 67% in group 2. The structure of response in group 1 was: complete response (CR) in 40% of patients, partial response (PR) in 28%, stable disease (SD) in 6%, indeterminate response (IR) in 20% and progressive disease (PD) in 6%; in group 2: CR in 34%, PR in 33%, SD in 5%, IR in 20% and PD in 8%. Median OS was not achieved in both groups, 3-year OS was 97,9% and 96,5% respectively (p=0.243). Median PFS was 21,9 months (95%CI: 16,8–26,9) in group 1 and 18,8 months (95%CI: 13,4–24,2) in group 2, 3-year PFS was 23,6% and 27% respectively (p=0.356).

Any grade AE were detected in 65% of patients in group 1 and in 79% in group 2 (p=0.068), 3–4 grade AE were detected in 10% and 19% respectively (p=0.151).

Additional therapy after Nivo monotherapy was started in 78% of patients after Nivo 40 mg and in 84% after Nivo 3 mg/kg. Allogeneic stem cell transplantation after Nivo therapy was performed in 5 (10%) patients in group 1 and in 26 (22%) patients in group 2.

Conclusion: The efficacy of Nivo 40 mg therapy is comparable to the standard dose of 3 mg/kg in patients with r/r cHL. However, a direct comparison of different doses of Nivo in a prospective study is required.

Variable	Nivo 40 mg N=51	Nivo 3 mg/kg N=116	p
Median age, years (range)	36 (19-55)	38 (14-65)	0.19
Male/female, n (%)	18/33 (35/65)	56/60 (48/52)	0.12
Primary chemoresistance, n (%)	40 (78)	74 (64)	0.107
Early relapse, n (%)	7 (14)	14 (12)	0.766
Prior autologous stem cell transplantation, n (%)	17 (33)	44 (38)	0.57
Prior brentuximab vedotin, n (%)	18 (35)	62 (53)	0.046
Therapy lines before Nivo therapy, n (range)	4 (1-8)	5 (2-10)	<0.001
B symptoms at Nivo therapy initiation, n (%)	26 (51)	71 (61)	0.22
Disease stage at Nivo therapy initiation, n (%)			
2	9 (18)	11 (9)	0.20
3	5 (10)	7 (6)	
4	37 (72)	97 (84)	
Progression at Nivo therapy initiation, n (%)	46 (90)	92 (79)	0.19
ECOG status at Nivo therapy initiation, n (%)			
0-1	29 (63)	70 (60)	0.87
2	14 (27)	29 (25)	
3	4 (8)	14 (12)	
4	1 (2)	2 (2)	

Table 1: Patient's characteristics

P063: TRIAL IN PROGRESS: INDIVIDUALIZED IMMUNOTHERAPY IN EARLY-STAGE UNFAVORABLE HODGKIN LYMPHOMA - THE INVESTIGATOR-INITIATED PHASE II GHSG INDIE TRIAL

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Background: Immune-checkpoint blockade targeting the programmed cell death protein 1 (PD1) axis continue to reshape the therapeutic landscape of classical Hodgkin lymphoma (HL). The randomized phase II GHSG NIVAHL trial investigated nivolumab-based 1st-line treatment of early-stage unfavorable HL, either fully concomitant (4x nivo-AVD) or sequential (4x nivolumab, 2x nivo-AVD, 2x AVD) each followed by 30Gy involved-site radiotherapy (IS-RT; Bröckelmann PJ et al. JAMA Oncol 2020). The most

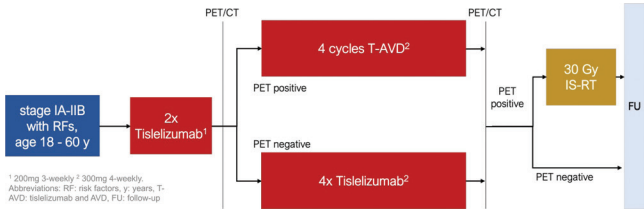

Figure 1: INDIE Trial Flowchart (Main Cohort age 18–60 years, N=100)

recent update continued to show feasibility, a favorable safety profile and outstanding efficacy with 2-year progression-free (PFS) and overall survival (OS) of 99% and 100%, respectively (Bröckelmann PJ et al. ASH 2020). 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 (200mg Q3W) followed by an FDG-PET/CT based restaging. Patients in complete metabolic remission will continue treatment with four additional tislelizumab infusions (300mg Q4W). Patients with residual metabolic activity will receive concomitant treatment with four cycles of AVD at standard dose and tislelizumab (300mg Q4W, tis-AVD). In the main cohort of N=100 patients aged 18–60 years, consolidative 30Gy IS-RT will only be applied in case of PET-positive residues (Figure 1). In an exploratory of N=20 patients >60 years of age, 30Gy IS-RT will be applied irrespective of remission status at end of systemic treatment. Primary endpoint is the 1-year PFS with 1- and 3-year OS, 3-year PFS, feasibility and safety, patient-reported outcomes and correlative studies being secondary endpoints. The trial is registered at clinicaltrials.gov (NCT04837859) and financially supported by BeiGene.

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.

Living Beyond Lymphoma

T064: DOXORUBICIN EXPOSURE AND BREAST CANCER RISK IN ADOLESCENT AND ADULT HODGKIN LYMPHOMA SURVIVORS

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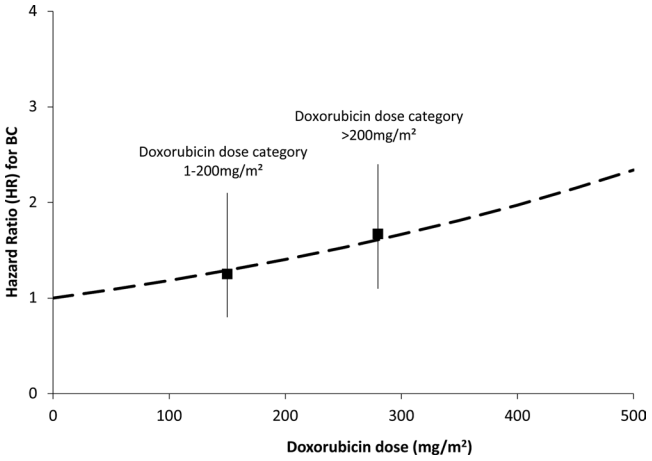

Figure 1: Doxorubicin dose-response plot. Dose-response curve for continuous doxorubicin dose and breast cancer risk, adjusted for age at HL treatment, chest radiotherapy and gonadotoxic treatment. Adjusted HRs for doxorubicin dose categories are added.

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Background: Female Hodgkin lymphoma (HL) survivors treated with chest radiotherapy at a young age have a strongly increased risk of breast cancer (BC). Recent studies in childhood cancer survivors have shown that doxorubicin may also increase BC risk. So far, the association between doxorubicin and BC risk has not been examined in cancer survivors treated at adolescent/adult ages.
Methods: We assessed BC risk in a cohort of 1964 female five year HL survivors, treated at ages 15–50 years in 20 Dutch hospitals between 1975 and 2008. Cumulative BC incidence was estimated in the presence of death as a competing risk. Treatment factors were time-dependently included in the multivariable Cox regression analysis, focusing on the effect of doxorubicin exposure on BC risk.
Results: HL survivors were treated at a median age of 27.8 years (interquartile range (IQR) 21.9–35.2 years). After a median follow-up of 18.3 years (IQR 12.9–24.7) years, 200 women had developed invasive BC (n=190) and/or ductal carcinoma in situ (n=49). The 30-year cumulative incidence was 19.4% (95% confidence Interval (CI) 16.6–22.3%). Among patients treated with chemotherapy (n=1113), receipt of doxorubicin-containing chemotherapy increased from 32.6% in 1975–1986 to 84.5% in 1998–2008. In multivariable analysis a cumulative dose of >200 mg/m2 was associated with increased BC risk (HR 1.7; 95% CI 1.1–2.4), compared to patients not treated with doxorubicin. BC risk increased 19% (HR 1.19; 95% CI 1.1–1.3) per additional 100 mg/m2 doxorubicine (ptrend=0.003). Receipt of mantle or axillary field irradiation or gonadotoxic therapy did not modify the association between doxorubicin and BC risk. Among patients who received >200 mg/m2 doxorubicin, the HR was 1.6 (95% CI 1.1–2.5) for patients treated with and 2.0 (95% CI 0.9–4.2) for patients treated without mantle or axillary field irradiation (Pinteraction=0.35). Gonadotoxic treatment (>8.4 g/m2 procarbazine or pelvic irradiation) significantly decreased the risk of BC.
Conclusion: This study shows that doxorubicin is associated with an increased BC risk among adolescent and adult HL survivors. Now that radiotherapy doses and volumes have decreased and doxorubicin increasingly forms the backbone of HL treatment, the potential association of doxorubicin with increased BC risk is an important issue.

T065: REPRODUCTION PATTERNS AMONG CLASSICAL HODGKIN LYMPHOMA SURVIVORS TREATED WITH BEACOPP AND ABVD IN SWEDEN, DENMARK, AND NORWAY

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Background: Reproduction in classical Hodgkin lymphoma (cHL) survivors has been shown to be reduced compared to the general population, likely due to multi-agent chemotherapy. Understanding if contemporary treatment protocols are associated with reduced reproduction is important as treatment guidelines shift towards more liberal use of more intensive chemotherapy.
Methods: We identified 2,937 individuals aged 18–40 years with cHL in Swedish and Danish lymphoma registers, and in the clinical database at Oslo University Hospital (OUH) between 1995 and 2019, who were linked to national medical birth registers in each country. Cox regression adjusted for stage, performance status, year and age at diagnosis was used to estimate hazard ratios (HRs) contrasting time to first childbirth by treatment groups (ABVD, 2–4 BEACOPP, 6–8 BEACOPP) up to ten years after diagnosis. Cause-specific cumulative incidence (CIF) of childbirths was further estimated using flexible parametric survival models. All analyses included an interaction between cHL treatment and sex.
Results: Overall, 71.4% of patients were treated with ABVD, 3.6% with 2–4 BEACOPP, and 10.3% with 6–8 BEACOPP. The reproduction rates (per 1,000 person-years) were 45.5 (males) and 48.2 (females) in the ABVD group, and 23.8 (males) and 39.9 (females) in the 6–8 BEACOPP group. The adjusted HR comparing reproduction rates in individuals treated with 6–8 BEACOPP to ABVD was 0.51 (95% CI 0.35–0.73) for males and 0.82 (95% CI 0.57–1.19) for females. The CIF after 10 years was 20.0% (CI: 14.7%–27.2%) for males and 33.0% (CI: 24.6%–44.3%) for females treated with 6–8 BEACOPP.
Conclusion: We found that BEACOPP treatment is associated with decreased reproduction rates compared to ABVD in male cHL patients. Infertility counselling should be prioritized for this group.
This abstract has been accepted and presented at the EHA 2022 congress.

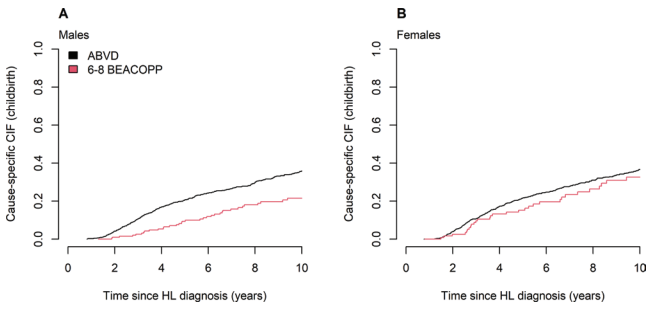

Figure 1: Aalen-Johansen estimates of the cause-specific cumulative incidence (CIF) of childbirth estimated in the presence of competing risks of death.

T066: TREATMENT AND SEX-SPECIFIC EXPOSURE-BASED RISK-STRATIFICATION FOR CARE OF SURVIVORS OF CHILDHOOD HODGKIN LYMPHOMA: A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY

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Background: Investigators from the United Kingdom (UK) have previously developed a treatment exposure-based algorithm that stratifies pediatric cancer survivors into low, medium, and high-risk groups. We sought to use the large, diverse population of the Childhood Cancer Survivor Study (CCSS) to validate risk for poor outcomes in children treated for Hodgkin Lymphoma with an emphasis on the impact of sex on long term outcomes.
Methods: Five-year survivors of childhood cancer (diagnosed between 1970–1999 at <21 years of age) were categorized into medium and high-risk groups based on treatment exposures and diagnoses. High risk was defined by receipt of transplant, doxorubicin equivalent dose ≥ 250, or direct radiation to the neck, chest, abdomen, or pelvis. The primary endpoint included cumulative incidence of grade 3–5 chronic conditions (CTCAEv4.03) conditional on reaching age 25 without the outcome. Patients were censored at age 40 and siblings used as a comparison group. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CI) of new onset grade 3–5 conditions adjusted for sex and race.
Results: A total of 2,131 survivors of Hodgkin Lymphoma met study criteria with a median follow-up of 22 years and median age of 36 at last follow-up. Using the above criteria, the final cohort included 241 medium and 1,890 high risk survivors. Among those who survived to age 25 without any grade 3–5 conditions, the risk of developing one by age 40 was 39.8% (95% CI 37.2–42.5%) for high risk patients and 27.2% (19.8–37.2%) for medium risk patients, respectively, and 8.5% (7.5–9.7%) for siblings. The risk of grade 3–5 condition by age 40 in high risk patients was substantially higher for females at 50.6% (46.9–54.6) than for males at 29.7% (26.6–33.3%). In multivariable analysis the strongest predictor of grade 3–5 conditions remained female vs. male sex (HR 1.9, 95% CI 1.6–2.3), followed by high vs. medium risk (HR 1.7, 95% CI 1.2–2.4). Toxicity was not associated with race.
Conclusions: Females treated for childhood Hodgkin Lymphoma remained at nearly double the risk of long-term high grade toxicity compared to males after adjusting for treatment exposures. Patient sex may help supplement standardized risk assessment of Hodgkin Lymphoma survivors and help inform physicians attempting to determine follow-up intervals, management, and long-term surveillance of these survivors.

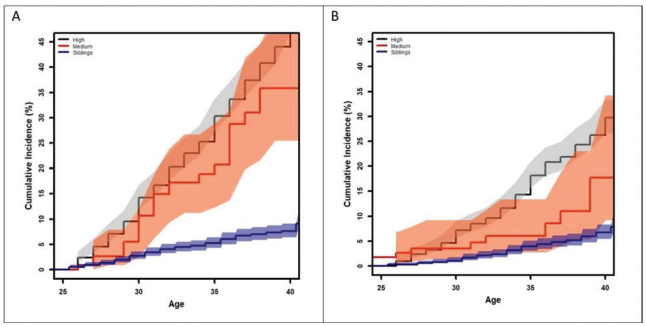

Figure 1: Cumulative grade 3–5 toxicity-free survival in A) females and B) males treated for pediatric Hodgkin Lymphoma in patients with high risk (grey line) and medium risk (red line) treatment exposures and their matched siblings (blue line).

P067: A PILOT OF LUNG CANCER SCREENING FOR SURVIVORS OF HODGKIN LYMPHOMA

Rachel Broadbent[1;2;3], Philip Crosbie[2;4], John Radford[5], Christopher J. Armitage[2;6;3], Ben Taylor[1], Joseph Mercer[1], Sean Tenant[1], Kim Linton[5]

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Background: Alkylating agents and thoracic radiation put survivors of Hodgkin lymphoma (HL) at excess risk of lung cancer (30-year cumulative incidence 6.4%). Lung cancer screening (LCS) using low-dose CT thorax (LDCT) scans reduces lung cancer mortality in ever smokers in the general population by detecting early-stage lung cancers. We ran an LCS pilot in HL survivors, who are generally ineligible for LCS programmes aimed at the general population.
Methods: 218 5+ year survivors of HL treated with mustine or procarbazine and/or thoracic radiation were identified from a follow-up database (ADAPT) hosted at The Christie NHS Foundation Trust and sent a letter of invitation. Participants underwent a baseline LDCT scan. Scans were reported as negative/indeterminate/positive in accordance with lung nodule guidelines. Indeterminate nodules required a further LDCT scan 3-months later. Participants with a positive scan were referred to lung cancer services.
Results: Of the 218 invited to the study 54% were female, median age was 53 (range 25–80), median years since treatment 21 (6–45). 12 were ineligible. 127 (59%) expressed interest in participating. The uptake among eligible responders was 83% (102/123). Participation was not influenced by age or gender. Baseline LDCT scan results in 102 participants were: 90 (88.2%) negative, 10 (9.8%) indeterminate, 2 (2.0%) positive. 3-month surveillance LDCT scan results (n=9) were: positive (2), stable (5), with 2 pending. Among 4 participants with positive baseline or 3-month scans, 1 has been diagnosed with early-stage small-cell lung cancer and treated with curative intent, 1 is undergoing tests for presumed lung cancer and 2 are undergoing further surveillance. Coronary artery calcification was detected in 36.3%. Clinically significant incidental findings including emphysema, bronchiectasis, pulmonary inflammation/infection, metastatic breast cancer and vertebral insufficiency fractures were seen in 20 (19.6%). Notably, 3/35 participants who were ever smokers met the age and risk criteria for LCS through the programme aimed at the general population.
Conclusion: LDCT scanning protocols tested in the general population are appropriate for use in the HL survivor population in a future targeted LCS programme. The feasibility of such a programme is contingent on developing methods to identify and contact long-term survivors of HL at risk of lung cancer and on investigating and addressing barriers to uptake.

P068: A RETROSPECTIVE ANALYSIS OF FERTILITY IN FEMALE PATIENTS WITH ADVANCED STAGES OF HODGKIN LYMPHOMA TREATED WITH BEACOPP ESCALATED CHEMOTHERAPY (25 YEAR EXPERIENCE OF A SINGLE CENTRE)

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On behalf of Czech Hodgkin Lymphoma Study Group The authors declared no potential conflicts of interest.

Background: BEACOPP escalated (eBEA) includes alkylating agents and its gonadal toxicity has been reported in prospective and retrospective studies. This retrospective study analyzed fertility of 119 young female patients (pts) with initial diagnosis of Hodgkin lymphoma (HL) in advanced stages treated with eBEA.
Patients and Methods: Overall 128 women aged 18–34 years (median age at diagnosis was 27 years) were treated with eBEA between 1997 and 2020. Median follow-up since the beginning of the treatment was 12.4 years. Overall 57 pts (48%) received 8 cycles of eBEA, 46 pts (39%) were treated wit 6 cycles and 16 pts (13%) received 4 cycles of eBEA. Additional radiotherapy was indicated in 36 pts (30%). Gonadotropin-releasing hormone-analogue Gosereline acetat received 68 pts (57%) and 51(43%) pts used oral contraceptives during chemotherapy to prevent gonadal toxicity. Median follow-up after the end of treatment was 12 years.
Results: Out of 119 women 45 (38%) delivered 61 babies including 18 (40%) women with 2 deliveries after treatment with eBEA. Number of

all delivered healthy babies was 59 (one baby was born with small cleft lip, other with mild renal malformation). Two pregnancies were terminated prematurely (week 20 and 22) due to congenital malformations: monozomy 45, X0 Turner syndrome and serious cleft lip). All pregnancies were spontaneous except of 6 women that underwent in vitro fertilisation (IVF) Median time from the end of terapy until the delivery of the first baby was 66 months (range 18-169m). 40 children (65%) were born in the group of pts aged 18–24 years, 16 (26%) in the group of 25–29 years and only 5 (9%) in the group of 30–34 years.
Conclusion: Our data indicate that even after eBEA 38% of young fertile women in advanced stages of HL are able to deliver babies and protection of fertility should be offered to them. Implementation of new strategies with reduction of chemotherapy cycles based on PET may further contribute to fertility preservation.

P069: CHARACTERISATION OF INFLUENCING PARAMETERS ON OOCYTE QUALITY PRESERVATION IN A COHORT OF HODGKIN LYMPHOMA PATIENTS

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Background: Hodgkin lymphoma (HL) is the most frequent lymphoma in the young population. The standard of treatment is chemotherapy including alkylating agents known to affect fertility. Fertility preservation is usually proposed before treatment with oocyte cryopreservation as a reference. In different cohorts of healthy women, some factors are well known to have an impact on oocyte quality preservation such as age, anti-Müllerian hormone (AMH), body mass index (BMI). German Hodgkin Study Group (GHSG) distinguishes 3 prognostic groups: early, intermediate, advanced stages (respectively defined GHSG I, II, III in our study). In literature, the parameters influencing fertility preservation outcomes in HL are not clear, namely HL's stage and inflammation.
In this study we evaluated the impact of HL's stage using GHSG criteria on fertility preservation outcomes.
Methods: We performed a retrospective study on 79 women, with newly diagnosed and previously untreated HL who underwent oocyte cryopreservation between 2012 and 2021. The patients were extracted from a cohort of fertility observatory in Lille University Hospital. The primary outcome was the number of metaphase 2 oocyte retrieved (M2). Estradiol level at the ovulation induction and the ratio of M2/follicles >15mm were secondary outcomes. We compared fertility outcomes between two groups: early and intermediate stage (GHSG I+II) and advanced stage (GHSG III). We evaluated in univariate and multivariate analyses the following factors: AMH, BMI, use of hormonal contraception, age and C reactive protein (CRP).
Results: The two groups (GHSG I-II and GHSG III) were comparable. In univariate analyses, AMH was the only statistically significant factor regarding the number of M2 (p<0,0001) and Estradiol level (p<0,0001). In multivariate analysis, GHSG score was not statistically significant concerning Estradiol level (p=0,5) contrary to AMH level (p<0,0001).
Conclusion: In our study, AMH level is doubtlessly a factor impacting the quality of oocyte preservation. HL's stage and inflammation do not seem to affect fertility preservation outcomes in the whole cohort. These results, based on the largest cohort of HL patients evaluating HL's risk groups provide important information about expected cryopreservation outcomes. According to this study, oocyte cryopreservation should be considered even for patients with advanced HL's stage.

P070: DESIGN OF THE INSIGHT STUDY, EVALUATION OF LONG-TERM FOLLOW-UP CARE FOR LYMPHOMA SURVIVORS IN THE NETHERLANDS: DOES SURVIVORSHIP CARE AT THE BETER CLINICS REDUCE MORBIDITY AND MORTALITY FROM LATE EFFECTS OF LYMPHOMA TREATMENT AND ASSOCIATED COSTS?

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Background: Hodgkin lymphoma (HL) survivors are at substantial risks of serious late adverse treatment effects. The BETER consortium developed a nationwide infrastructure of outpatient clinics where 5-year HL survivors are screened and treated for adverse effects of lymphoma treatment according to nationally approved screening guidelines. BETER survivorship care includes risk-based screening for and treatment of (risk factors for) cardiovascular disease (CVD), breast cancer, hypothyroidism and (functional) asplenia.
So far, evidence for the actual cost-effectiveness of structured cancer survivorship care in clinical practice is lacking. Current knowledge is based on simulation and modelling approaches and evidence from other populations (e.g. BRCA mutation carriers). In the INSIGHT study we will assess the (cost-)effectiveness of BETER survivorship care using data from clinical practice.
Methods: The first BETER clinics started in 2013–2016 and the number of centres participating in BETER is quickly expanding: several centres started/will start a BETER clinic in 2021–2024. This allows for a retrospective cohort study with a quasi-experimental design to evaluate the effectiveness of BETER survivorship care by comparing survivors who did and did not receive BETER survivorship care. Once full nationwide implementation is in place, this comparison is no longer possible.
In the INSIGHT study we will compare 450 HL survivors invited for BETER survivorship care in 2013–2016 with 450 matched survivors invited by a BETER clinic starting in 2021–2024, allowing for a median follow-up of ~8 years. The primary outcomes are burden of disease (in disability-adjusted life-years, DALYs) from CVD, breast cancer, hypothyroidism and (functional) asplenia, associated health care costs, quality of life and health-related productivity losses. Secondary outcomes are BETER clinic attendance, guideline adherence and knowledge and risk perception of late effects. In a cost-effectiveness analysis we will calculate costs/DALY and costs/QALY of BETER survivorship care.
Conclusion: BETER is an internationally unique initiative of an elaborate infrastructure for adult oncology survivorship care. To our knowledge, INSIGHT is the first evaluation of (cost-)effectiveness of cancer survivorship care in clinical practice. The results will contribute to more effective, evidence-based long-term cancer survivorship care. At ISHL12 we will present design details as well as participation rates.

P071: FIRST RESULTS OF CARDIOVASCULAR SCREENING IN A SURVIVORSHIP CARE PROGRAM FOR HODGKIN LYMPHOMA SURVIVORS IN THE NETHERLANDS

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Background: Hodgkin lymphoma (HL) survivors are at increased risk of cardiovascular diseases (CVD) due to former treatment. In 2013, we started survivorship care for 5-year HL survivors at Dutch BETER clinics, where screening for CVD and associated risk factors according to uniform guidelines was implemented. Eligibility criteria for cardiovascular screening include: 1) age at HL treatment ≤60 and current age ≤70 years 2) treatment with mediastinal radiotherapy with/without anthracyclines (irrespective of dose) or anthracycline cumulative dose equivalent to doxorubicin ≥300 mg/m2. We assessed adherence to screening guidelines and the yield of previously undiagnosed (risk factors for) CVD in the screening program.
Methods: Data on patient and treatment characteristics and cardiovascular screening were collected retrospectively from medical records for 5-year HL survivors who visited the BETER outpatient clinic at three university medical centers in 2013–2020.

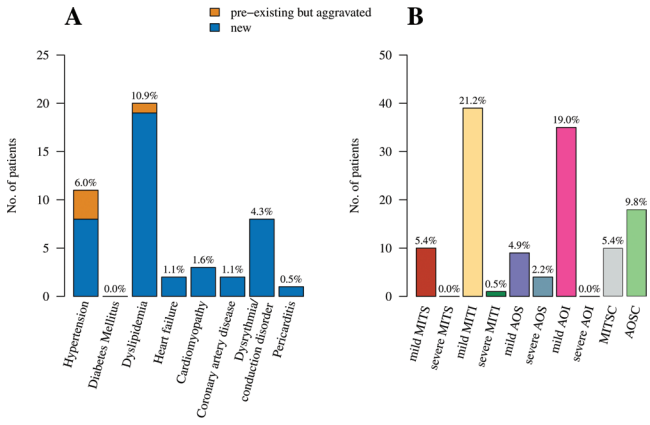

Figure 1. Diagnosed at the BETER clinic in eligible patients: A) (risk factors for) CVD B) new valve abnormalities

MITS = mitral valve stenosis, MITI = mitral valve insufficiency, AOS = aortic valve stenosis, AOI = aortic valve insufficiency, MITSC = mitral valve sclerosis, AOSC = aortic valve sclerosis

Figure 1: the figure caption is included in the figure

Results: We identified 240 patients, of whom 184 (76.7%) were eligible for cardiovascular screening (mean age at start follow-up 47.7 years).
In eligible patients, CVD screening was performed according to the guidelines: physical examination (65.8%), lipids (86.4%), (NT)proBNP (82.1%), glucose (85.3%), electrocardiogram (97.3%) and echocardiography (96.7%). Screening yielded the following new diagnoses in eligible patients (Figure 1): hypertension (4.3%), dyslipidemia (10.3%), heart failure (1.1%), cardiomyopathy (1.6%), coronary artery disease (1.1%), conduction disorder/dysrhythmia (4.3%), pericarditis (0.5%), mild aortic or mitral valve insufficiency or stenosis (31.0%) and severe aortic or mitral valve insufficiency or stenosis (2.7%). Left ventricular ejection fraction (LVEF) was available for 87 eligible patients, of whom 9 (10.3%) had a LVEF <50%.
Echocardiography was also performed in 32 out of 56 (57.1%) non-eligible patients: 21.9% had a new mild valve dysfunction, 3.1% had a new severe valve dysfunction.
Conclusion: Adherence to the screening guidelines was reasonable. A substantial number of new (risk factors for) cardiovascular conditions were diagnosed in the Dutch BETER screening program for HL survivors, also in non-eligible survivors. Future studies are needed to confirm findings in a broader population and to determine whether screening is effective in reducing burden of disease associated with late cardiovascular effects and in improving survivor's quality of life.

P072: IMPACT OF AGEING ON THE SURVIVORSHIP EXPERIENCES OF PATIENTS WITH HODGKIN LYMPHOMA

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Background: Lymphoma Coalition (LC) used its 2022 Global Patient Survey (GPS) on Lymphomas and CLL to examine the impact of ageing on the survivorship experiences of patients with Hodgkin lymphoma (HL) who were in remission.
Methods: 1,045 respondents had HL and 447 of them identified as being in remission and were included in this analysis. These patients were grouped into two age groups for analysis, based on their current age at survey time: 18-39yrs (n=248) and 40yrs+ (n=199).
Demographics of the two age groups were examined, and descriptive analyses for all questions relating to their survivorship experience were performed in IBM SPSS v27.
Results: Patients were asked which psychosocial issues they had experienced over the last 12 months because of their lymphoma. The older age group (40+) reported the lowest prevalence of every psychosocial issue listed (Table 1). The older age group (40+) also reported the highest prevalence of experiencing no psychosocial issues ('none') (19%). Fear of relapse of HL was the most prevalent psychosocial issue in both age groups (18–39- 80% and 40+- 63%) (Table 1).
Patients who reported experiencing symptoms of HL and/or side effects of treatment were asked how these symptoms and/or side effects impacted their life, including everyday activities, employment, social life, and relationships (Table 1). Both age groups differed significantly in how they experienced these impacts with the lowest prevalence for each of these impact categories being observed in the older age group (40+) (Table 1).
When asked about their transition from cancer care into survivorship, patients in both groups had similar experiences in the areas of follow-up visits, knowledge of whom to contact about health issues, and feeling supported, but differed in their knowledge regarding their personal post-treatment care plan (Table 1). About half of patients in both groups felt as supported in their survivorship experience as when they were receiving active care.
Conclusions/Summary: Compared to the older survivors, younger survivors with HL are disproportionately affected by psychosocial issues and are more impacted by the effect of their symptoms and side effects. Addressing the psychosocial and support needs of all HL survivors should be a key part of their care and it is important for health care providers to know that younger patients may require additional attention and support.

Table 1. Survivorship experience of patients with Hodgkin lymphoma

	18-39 yrs (%)	40 yrs + (%)	X^2 (p-value)
Prevalence of psychosocial issues experienced in the last 12 months			
Loss of self-esteem	34%	24%	4.21 (0.04)
Post-traumatic stress disorder	28%	15%	9.80 (0.002)
Concerns about physical appearance	49%	31%	12.85 (<0.001)
Changes in relationships	25%	18%	2.12 (0.15)
Isolation	32%	23%	4.06 (0.04)
Depression	30%	25%	1.02 (0.31)
Anxiety	55%	33%	18.58 (p<0.001)
Fear of relapse of lymphoma	80%	63%	13.11 (p<0.001)
No psychosocial issues experienced	8%	19%	11.40 (p<0.001)
Impact of lymphoma symptoms and treatment side effects	**18-39 yrs (%)***	**40 yrs + (%)***	**X^2 (p-value) ***
My symptoms and/ or side effects have negatively impacted everyday activities that people my age can usually do (e.g., exercise, shopping, household chores)	82%	75%	20.30 (0.001)
I have been unable to work/had to change my job or working pattern because of my symptoms and/or side effects	69%	57%	19.58 (0.002)
My symptoms and/or side effects have had a negative impact on my social life	73%	57%	21.46 (<0.001)
My symptoms and/or side effects have had a negative impact on my partner, children, close friends, or relatives	65%	57%	12.90 (0.02)
Healthcare changes experienced transitioning from active cancer care into survivorship	**18-39 yrs (%)***	**40 yrs + (%)***	**X^2 (p value) ***
There is a post-treatment care plan (e.g., survivorship care plan)	54%	69%	11.07 (0.03)
There are regular follow-up visits with a lymphoma/CLL care provider	93%	87%	4.7 (0.32)
I know who to contact about different health issues that may be experienced	78%	76%	1.35 (0.85)
I feel as supported now as when receiving active care for lymphoma	48%	50%	3.27 (0.51)

***Chi-square values calculated are based on the inclusion of all question response options, though only the percentages for those who 'strongly agree or agree' are displayed in the table.*

Table 1: shows various aspects of the survivorship experience of patients with HL including the prevalence of psychosocial issues, the impact of their symptoms and treatment side effects and the changes experienced transitioning into survivorship.

P073: INCREASED RISK OF COLORECTAL CANCER FOLLOWING TREATMENT FOR HODGKIN LYMPHOMA

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Purpose: Hodgkin lymphoma (HL) survivors have an increased colorectal cancer (CRC) risk, which may be related to subdiaphragmatic radiation and/or alkylating chemotherapy. While radiation dose-response relationships for breast, lung, stomach, pancreas and esophagus cancer after HL have been demonstrated, no previous studies have investigated this for CRC after HL. This study aimed to quantify CRC rate according to radiation dose to the large bowel and procarbazine dose.
Methods: We conducted a nested case-control study among 2996 five-year HL survivors treated in 1965–2000 at ages 15–50 years, who were followed for a median duration of 26.1 years. Treatment information was collected for 78 CRC cases and 238 controls, individually matched on sex, age at HL diagnosis and date of HL diagnosis. Mean radiation doses to the large bowel were estimated by reconstructing individual radiotherapy treatments on representative computed tomography datasets. Rate ratios (RRs) were estimated using conditional logistic regression. Excess rate ratios (ERRs) were modelled to evaluate the excess rate associated with each gray increase in radiation dose and effect modification by procarbazine was explored.
Results: The median age at HL diagnosis was 33.0 years and the median interval between HL and CRC was 25.7 years. Increased CRC rates were seen for patients who received subdiaphragmatic radiation (RR 2.4; 95% confidence interval (CI) 1.4–4.1) and those who received >8.4 g/m2 procarbazine (RR 2.5; 95% CI 1.3–5.0). Overall, CRC rate increased linearly with mean radiation dose to the whole large bowel and dose to the affected bowel segment. The effect of radiation dose on CRC rate was modified by cumulative procarbazine dose: the ERR/gray to the whole large bowel was 3.5% (95% CI 0.4–12.6%) for patients who did not receive procarbazine, and increased 1.19-fold (95% CI 1.06–1.33) for each g/m2 increase in procarbazine dose, with an ERR/gray of 15.0% for patients who received 8.4 g/m2 procarbazine.
Conclusion and relevance: This is the first study to demonstrate a dose-response relationship between radiation and CRC risk, and modification of this effect by procarbazine. Results enable individualized CRC risk estimations, identification of high-risk survivors and optimization of treatment strategies for future patients.

P074: LONG-TERM CAUSE-SPECIFIC MORTALITY IN HODGKIN LYMPHOMA PATIENTS – A NATIONWIDE DANISH COHORT STUDY

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Background: The documented treatment-induced excess mortality in Hodgkin lymphoma (HL) has resulted in important changes in treatment regimens over the last decades, aiming at maintaining efficacy with less toxic regimens. The aim of this study was to investigate whether these changes in treatment have had a long-term effect on patterns of mortality among HL patients in a nationwide unselected cohort.
Methods: The study included 1,348 Danish patients aged ≤40 years at time of HL diagnosis and treated in the years 1995–2015.
Cases were followed from date of diagnosis until date of emigration, death, or until study end, whichever occurred first. The primary outcome was disease specific death due to HL, with other cause specific mortality treated as competing risk. A comparison of risk of death in the study population and national background population was performed in a landmark analysis.
Results: At time of diagnosis, 66.5% of patients had Ann Arbor stage I-II; 33.5% had stage III-IV disease. After a median follow-up of 13.8 years (a total of 18,731 person-years), 139 patients (10.3%) had died with a 5-year overall survival rate of 94.6% (95% CI 93.4–95.8). Among these, 71 had died due to HL, 19 due to second malignancies, and 9 due to cardiovascular disease. Cumulative risk of death due to HL had an initial steep increase mounting to 6.1% 10 years after diagnosis, whereas the risk of death due to cardiovascular, pulmonary disease or second cancers increased at 10 years after HL diagnosis, however, only to a cumulative risk of 1.2% and 2.0%, respectively, at 20 years. By 21.6 years of follow-up risk of death due to HL was exceeded by risk of death due to other causes.
We found a 6.5-fold higher risk of mortality among HL cases compared to the background population.
Sub-analyses on overall and cause-specific mortality risk stratified by age, sex, disease stage, treatment period and exposure, will be presented.
Conclusion: Our results show a decrease in overall risk of mortality and disease-specific mortality among HL patients exposed to contemporary treatment compared to patients from earlier treatment eras. We also find a remarkable decrease in both overall and relative risk of death due to possible treatment related late-effects. So even though excess mortality among HL patients compared to the background population persists, our results suggest that the changes in treatment strategies have led to a distinct reduction in risk of fatal long-term toxicity.

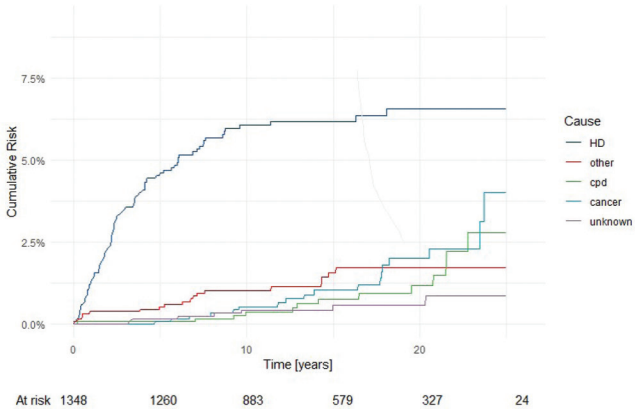

Figure 1: Aalen Johanson cumulative incidence plot demonstrating cumulative cause specific risk of death among HL patients

P075: MY HODGKIN, MY HEALTH: FEASIBILITY OF A MOBILE APPLICATION TO COLLECT LONG TERM FOLLOW UP DATA ABOUT HODGKIN PATIENTS

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Background: There is increasing utility of novel agents in the treatment of Hodgkin lymphoma (HL) and the role of radiotherapy is evolving. Whilst there is a large body of research into the long-term outcomes of HL, this data is mostly related to conventional radiotherapy and chemotherapy regimens. With the advent novel therapies, our understanding of the long-term toxicities is also undergoing a period of dynamic change. Whilst recent trials provided abundant high-level short term follow up data, they fail to provide a full picture of the long-term morbidity and mortality associated with current therapy.

The My Hodgkin, My Health (MHMH) app will be the first designed to collect patient derived data from HL patients. The purpose of this study is to demonstrate feasibility of this novel construct by meeting pre-specified recruitment and retention targets. Given the good overall survival of HL, and the paucity of long-term data in an era of novel therapies, we feel this is the ideal space in which to develop this app to capture this data conveniently and economically.

Methods: This will be a pilot study to with Initial recruitment targeted at Australian participants of the RATHL study. This is a well-defined population who are familiar with study procedures and well connected with investigators who will disseminate recruitment information. To prove feasibility, the primary outcome of this study is to recruit ≥50% of Australian RATHL study participants and retain ≥ 50% of these participants at 12 months. Secondary endpoints will include disease status and relapse rates, fertility, and other long-term sequelae from HL treatment.

Screening and consent procedures will be done electronically. Subjects complete a baseline survey including details of their treatment and disease status as well as information about any treatment complications. Subjects will be encouraged to update their data and be prompted to save or update their data every 6 months through push notifications.

If the primary endpoint is met, the project will continue with a focus on the secondary endpoints. We also envisage collaboration with international investigators and global uptake of the app. Ideally MHMH will be an invaluable database for researchers moving forward and will facilitate clinical trials aimed at optimising treatment efficacy whilst balancing quality of life and treatment sequelae.

P076: PNEUMOCOCCAL INFECTION IN SPLENECTOMISED HODGKIN LYMPHOMA PATIENTS: DO THEY POSE A PROBLEM TODAY AND WHAT IS THE BEST LONG-TERM STRATEGY?

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Purpose: Diagnostic laparotomy and splenectomy (DLS) were introduced for Hodgkin lymphoma (HL) patients in Sweden in the late 1960s/early-70s. It was soon established that splenectomised and functional hyposplenic (following irradiation) HL patients carried an increased risk of overwhelming infections, Streptococcus pneumoniae being the major causative agent. Despite this, DLS remained as a staging procedure for more than two decades. The purpose of this study was to compare incidence and outcome of pneumococcal infections between splenectomised (spl+) and non-splenectomised (spl-) HL patients.

Material and Methods: HL patients diagnosed 1973–1995 were identified in the Swedish Cancer Register. Information on splenectomies and severe pneumococcal infections was retrieved from the National Inpatient Register. Follow-up started a diagnosis and ended on date of infection, emigration, death, or December 31, 2010, whichever came first. Splenectomy was analysed as a time-varying covariate, i.e., patients were considered unexposed before the date of splenectomy and exposed after the date of splenectomy. Cox proportional hazard models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) comparing infection rates between spl+/spl- patients.

Results: A total of 4,237 HL patients were included, among whom 735 (17%) underwent a splenectomy, with a median time from splenectomy to infection of 6.8 years (range 0.1–30.8 years). The number of patients experiencing a severe pneumococcal infection was 39 (3.2 per 1,000 person-years) among spl+ and 60 (1.7 per 1,000 person-years) among spl- patients. The relative rate of severe pneumococcal infection comparing spl+/spl- HL patients was 2.43 (95% CI: 1.55–3.81), adjusted for diagnosis year, diagnosis age, and sex. The 30-day post-infection mortality proportion was 9/39 (23%) among the spl+ and 18% (11/60) among the spl- patients. Broken down by calendar period of infection, the 30-day post-infection mortality proportion among splenectomised patients was 44% (1973–1985), 23% (1986–1998), and 0% (1999–2010).

Conclusion: Severe pneumococcal disease is a serious event that is more likely to appear in splenectomised HL patients compared to non-splenectomised, possibly many years after diagnosis. However, the low proportion of deaths in later decades is reassuring, and likely a result of adequate pneumococcal vaccination together with patient and doctor education about the infection risk.

P077: PREDICTING RADIOTHERAPY DOSE TO THE HEART AND THE RISK OF RADIATION-RELATED CARDIAC TOXICITY FOR HODGKIN LYMPHOMA PATIENTS, USING PRE-CHEMOTHERAPY PET-CT SCANS

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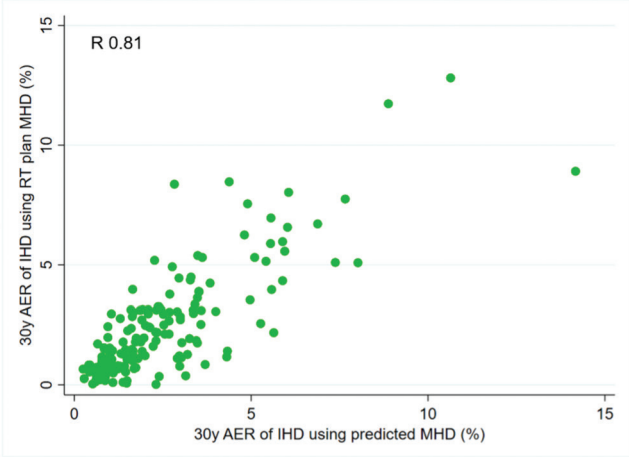

Figure 1: Scatter plot of the 30-year cumulative absolute excess risk of ischaemic heart disease calculated using the mean heart dose predicted by the model versus that calculated using the mean heart dose measured on the radiotherapy treatment plan

Abbreviations - R: correlation coefficient; y: year; AER: absolute excess risk; IHD: ischaemic heart disease; RT: radiotherapy; MHD: mean heart dose

Figure 1: Scatter plot of the 30-year cumulative absolute excess risk of ischaemic heart disease calculated using the mean heart dose predicted by the model and that calculated using the mean heart dose measured on the radiotherapy treatment plan

Background: Consolidative radiotherapy (RT) used to treat early-stage Hodgkin lymphoma (HL) reduces the chance of recurrence [1], but may cause late toxicity including cardiovascular disease (CVD) [2]. The risk of CVD can be estimated from the radiation dose received by the heart from RT, but currently this is only known once a RT plan has been produced.

The aim of this study was to develop a model to predict the dose the heart would receive, and thereby the risk of CVD, from RT using information available at the time of HL diagnosis.

Methods: The cohort was 169 patients treated with RT who had pre-chemotherapy PET-CT scans (pcPET-CT); 83% had stage 2 disease, and 91% had primary rather than relapsed HL. For each patient, the distribution of HL on the pcPET-CT was documented, and the mean heart dose (MHD) extracted from the RT plan. A multivariable linear regression model was built to predict MHD. Predicted MHDs were used in combination with a dose-response relationship for the risk of ischaemic heart disease (IHD) [3], and background IHD rates, to estimate absolute excess risk (AER) of IHD from RT.

Results: The model that best predicted MHD included the extent to which HL overlapped the heart, presence of hilar disease, width of mediastinal disease, RT delivery technique and breathing mode. The mean prediction error was 2.9 Gray (Gy) (range 0.2 to 12.1). Individual patient AER of IHD calculated using the predicted MHD were closely correlated with the AER calculated using the RT plan MHD (Figure 1). AERs calculated using the MHD from each method were not statistically significantly different (paired t-test p=0.88; mean within-patient difference 0.9%).

Conclusion: Patient-specific risks from consolidative RT can be estimated using pcPET-CT. Work is ongoing to refine this model using a larger dataset, and develop models to predict other organ doses and associated risks. If validated, such estimates could inform shared decision-making about the use of RT to treat an individual with HL.

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P078: PREDICTING THE HEALTH-RELATED QUALITY OF LIFE OF HODGKIN LYMPHOMA SURVIVORS: IDENTIFICATION OF RISK FACTORS

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Introduction: Cancer survivors are at risk of long-term impairment of their health-related quality of life (HRQoL), persisting for years after treatment. Despite the clinical importance, research is scarce and the etiology is complex. The aim of this study is to develop prediction models for different HRQoL domains of Hodgkin Lymphoma (HL) survivors. Therefore, we identify risk factors at the time of cancer diagnosis, as well as during and after therapy.
Methods: Data of N=4981 patients from diagnosis to year five of survival of the fifth study generation (HD13-15) of the German Hodgkin Study Group was analyzed. Parametric (forward stepwise regression, lasso, and all-pairs lasso) and non-parametric (bagged and boosted regression trees) machine learning algorithms were investigated to identify the relevant risk factors out of a set of 61 potential demographic, physical and psychosocial predictors. HRQoL was measured with the EORTC QLQ-C30. Assessed HRQoL domains were overall HRQoL, cancer-related fatigue, employment, and financial status, and physical, emotional, cognitive, social, and role functioning.
Results: The all-pairs lasso algorithm performed best at detecting the relevant predictors in comparison to the other methods tested. All-pairs lasso identified between six and 17 risk factors for each HRQoL domain. The risk factors included patients' age, prior HRQoL levels, specific physical risk factors, and the cancer stage. Based on the variable selection we estimated regression models to predict each HRQoL domain. Cross-validation showed that each baseline prediction model explained around 30%–33% of the variability of the corresponding outcome.
Conclusions: Our analysis reveals relevant risk factors of each HRQoL domain in HL survivors. The complex interplay between several demographic, physical and psychosocial predictors has some predictive power for the HRQoL levels after therapy. The possibility of predicting HRQoL at the time of diagnosis and during and after therapy contributes to a better understanding of HRQoL in HL survivors and informs the development of much-needed interventions.

P079: PROCTCAE AS A PATIENT-REPORTED OUTCOME MEASUREMENT (PROM) QUESTIONAIRE IN PATIENTS WITH HODGKIN LYMPHOMA CAPTURES DIFFERENT ADVERSE EVENTS PROFILE THAN THOSE REPORTED BY PHYSICIANS

Sergio Ramos-Cillan[1], Eva Castillo[1], Miriam Riesco[1], Antonio Herroro[1], Adriana Pascual[1], Alberto Lopez-Garcia[1], Maria Angeles Perez[1], Daniel Morillo[1], Alham Askari[1], Elena Prieto[1], Pilar Llamas[1], Javier Becares[1], Carla Barriocanal[2], Marta Del Olmo[2], Jorge Short[2], Javier Arcos[2], Raul Córdoba[1]

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Background and aims: Patient reported outcomes(PROs)are used in clinical trials to evaluate toxicity,effectiveness, and quality of life.A program to assess PROs was started at our hospital in2020.Here we present preliminary results about its utility in reporting symptoms and reducing visits toEmergencies and hospitalization.Patients complete a questionnaire at every cycle of treatment.
Methods: Patients(pts)with diagnosis of any type of lymphoma in need of starting therapy in our hospital between 1st Jan 2019 and 31st Dec 2021 were included in our study. Pts who started treatment in 2019 and those who refused to participate in 2020 and 2021 were considered the control arm of our study. Principal endpoint was to compare physician and patient-reported adverse events through a standardized questionnaire (PRO-CTCAE). Secondary endpoints included association between inclusion in PROMs program and reduction of hospital admissions and Emergencies visits. Here, we present the preliminary results from answers given at the beginning of treatment (as it is considered the period were most toxicity is expected).
A subgroup analysis to study patients with Hodgkin lymphoma(HL)was performed.
Results: Two-hundred and eight patients were included.Thirty-six(17,3%)were HL.Patients with HL were significantly younger (49.3vs.63.5 y.o.;p=0,029).No differences were found in terms of adherence to PROMs program between HL and NHL(52.8%vs.56.4%; p=0,69).Figure 1 shows most commonly adverse events (AEs) reported by clinicians and patients among those with diagnosis of HL and NHL. Differences were found in both groups.Differences between patients with HL and NHL were found at sexual symptoms reported by physicians(10.5%among HL and 1%among NHL; p=0,02)and tendency to statistically significant difference at oral symptoms reported by patients(36.1% among NHL and 15.1% among HL;p=0.085).
Patients included in the PROMprogram would visit Emergencies less than those in the control arm. Difference was statistically significant in the whole group(n=208)and showed tendency to significancy in the smaller group of HL(31.6%vs.58.8%;p=0,1).The same happened with unscheduled hospitalization.
Conclusions: Integration of PROs is essential to evaluate the effect of treatment. Incorporation of patients' perspective makes personalized medicine more concrete. Physicians and patients report different symptoms and intensity and those included in the program tend to use fewer unscheduled resources.

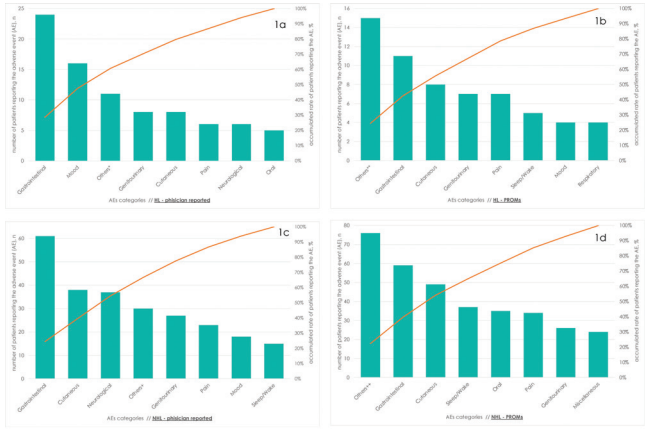

Figure 1.- Pareto charts show AEs reported by physicians (**1a and 1c**) and patients (**1b and 1d**) in patients with diagnosis of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).
** respiratory, visual/perceptual, sleep/wake, sexual, cardio/circulatory, attention/memory, miscellaneous*
***sexual, oral, visual/perceptual, miscellaneous, cardio/circulatory, neurological, attention/memory*
+oral, respiratory, cardio/circulatory, miscellaneous, visual/perceptual, attention/memory, sexual
++mood, sexual, oral, visual/perceptual, miscellaneous, cardio/circulatory, neurological, attention/memory

Figure 1: Pareto charts show AEs reported by physicians (1a and 1c) and patients (1b and 1d) in patients with diagnosis of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).

P080: THE BETER-REFLECT BIOBANK: A RESOURCE FOR STUDIES ON LATE EFFECTS OF CANCER TREATMENT

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Due to the introduction of multi-agent chemotherapy and improved radiation techniques, Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL) are now malignancies with high cure rates. While the number of long-term lymphoma survivors is increasing, their life

expectancy is compromised by late complications of chemotherapy and radiotherapy, which may emerge several decades after initial treatment. Especially second malignancies and cardiovascular diseases cause substantial excess morbidity and mortality.
Currently, knowledge about genetic susceptibility and early biomarkers for treatment-related adverse events is scarce, precluding identification of subgroups of patients at higher risk of specific treatment-related adverse events. Such knowledge would allow personalized treatment of future lymphoma patients, ultimately enabling prevention of adverse effects, as well as personalized screening for adverse events in survivors of lymphoma. Knowledge about biomarkers for treatment-related adverse events will benefit the screening program of lymphoma survivors, providing opportunities for earlier diagnosis and treatment of adverse events.
Therefore, in the 'BETER-REFLECT' project we will establish a national biobank with biospecimens of 5-year lymphoma survivors in order to facilitate research into:
- genetic susceptibility for treatment-related adverse events
- early biomarkers for adverse events
The study population consists of 5-year lymphoma survivors identified through the Dutch BETER project. The nationwide BETER consortium (Better care after (non-)Hodgkin lymphoma, Evaluation of long-term Treatment; Effects and screening Recommendations) aims to reduce the morbidity and mortality from late adverse events of treatment in lymphoma survivors. The consortium has established survivorship care for 5-year HL and DLBCL survivors, who were 15–60 years old at diagnosis. For BETER survivorship care eligible patients in 13 lymphoma treatment centers in the Netherlands are invited to participate in the BETER-REFLECT biobank project (n=3000). From participating survivors we will prospectively collect blood samples. Additionally, Formalin-Fixed Paraffin-Embedded tissue blocks of deceased individuals will be collected (n=1000). Blood samples and tissue blocks are collected to extract germline DNA to investigate genetic susceptibility; serum and plasma is collected to evaluate biomarkers for adverse events. So far, 700 samples have been collected.

P081: TREATMENT-RELATED CIRCULATORY DISEASES AND MORTALITY IN HODGKIN LYMPHOMA PATIENTS USING MULTI-STATE MODELLING AND RELATIVE SURVIVAL

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Introduction: One of the most common late effects in Hodgkin lymphoma (HL) patients are diseases of the circulatory system (DCS). How much that can be attributed to HL therapy, while accounting for the competing risk of death, remains less understood. This study aimed to assess treatment-related incidence of DCS by sex and cumulative anthracycline dose in HL patients using novel methods in multi-state modelling and relative survival.
Methods: All patients with HL registered in the Swedish Lymphoma Register 2000–2018, aged 18–80 years at diagnosis, were included. DCS was identified in the Swedish National Inpatient Register (ICD-10 codes I00-I99). Sex-, year-, and age-specific incidence rates of DCS in the general population were retrieved from public records. Patients were followed from treatment through a series of states: Alive without DCS, alive with DCS, dead without DCS, and dead after DCS. Follow-up ended on death, emigration, or December 31st, 2019. All state transitions were modelled separately using flexible parametric survival models. A relative survival model incorporating the expected DCS rates was fitted to allow for estimation of excess DCS incidence, which was defined as attributable to HL therapy. Transition probabilities were predicted for specific patient groups.
Results: A total of 1,929 HL patients were included (54% male, 49% treated with >200 mg anthracycline). The distribution of treatments was 66% ABVD, 20% CHOP-like, and 14% BEACOPP. During a median follow-up time of 7.6 years, 377 patients (20%) were diagnosed with DCS, 145 (7.5%) died without DCS, and 87 (5%) died following DCS. Females had a lower non-DCS mortality rate than men (adj. hazard ratio=0.69, 95% CI: 0.49–0.97), as did patients treated with >200mg anthracycline compared to ≤200mg (adj. hazard ratio=0.28, 95% CI: 0.18–0.44). There were no differences in excess DCS incidence rates or post-DCS all-cause mortality rates.
Figure 1a shows the predicted transition probabilities for an advanced stage patient diagnosed in 2000 at age 50, treated with ABVD including >200mg cumulative anthracycline dose, by sex. Figure 1b shows the transition probabilities for a limited stage male patient diagnosed in 2000 at age 50, treated with ABVD, by cumulative anthracycline dose (≤200mg or >200mg).
Conclusion: Across almost two decades, females experienced more excess DCS compared to men, likely due to superior survival. The same was seen for high compared to low doses of anthracycline.

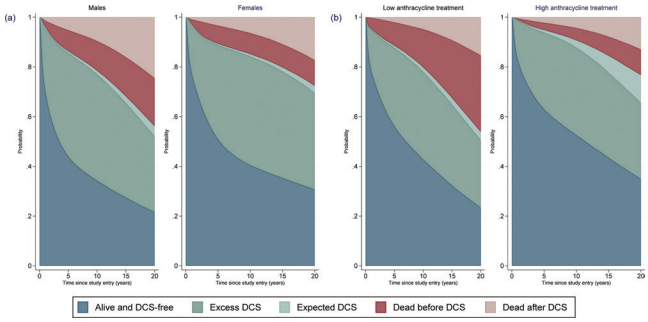

Figure 1: Probability of: Alive with DCS-free (blue), excess DCS (green), expected DCS (light green), dead without DCS (red), dead with DCS (light red). Panel (a) contrasts men versus women. Panel (b) contrasts low versus high anthracycline dose (≤200/>200mg).

Older & Frail Patients

T082: AVD - A POSSIBLE GOLDEN STANDARD IN THE FIRST-LINE TREATMENT OF OLDER CLASSICAL HODGKIN LYMPHOMA PATIENTS

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Background: First-line treatment in patients ≥60 years with classical Hodgkin lymphoma (cHL) is challenging and less well studied compared to younger patients. Although survival has improved over the past decades, older patients still have an inferior outcome and no golden standard in first-line treatment exists. These patients often have a higher comorbidity-burden and are more susceptible to acute toxicity. In addition, the ageing body and an increased incidence of more advanced disease makes curative treatment challenging.
Method: We collected patient and treatment data from Sweden, Denmark and Norway for 1554 patients aged ≥60 years at cHL diagnosis who received treatment with curative intent, diagnosed from January 1st, 2000 to December 30th, 2021 from national registries. Data was also collected from patient records. Survival was estimated using Kaplan-Meyer curves and the risk of death was estimated with both univariable and multivariable Cox regression analysis. Patients were grouped

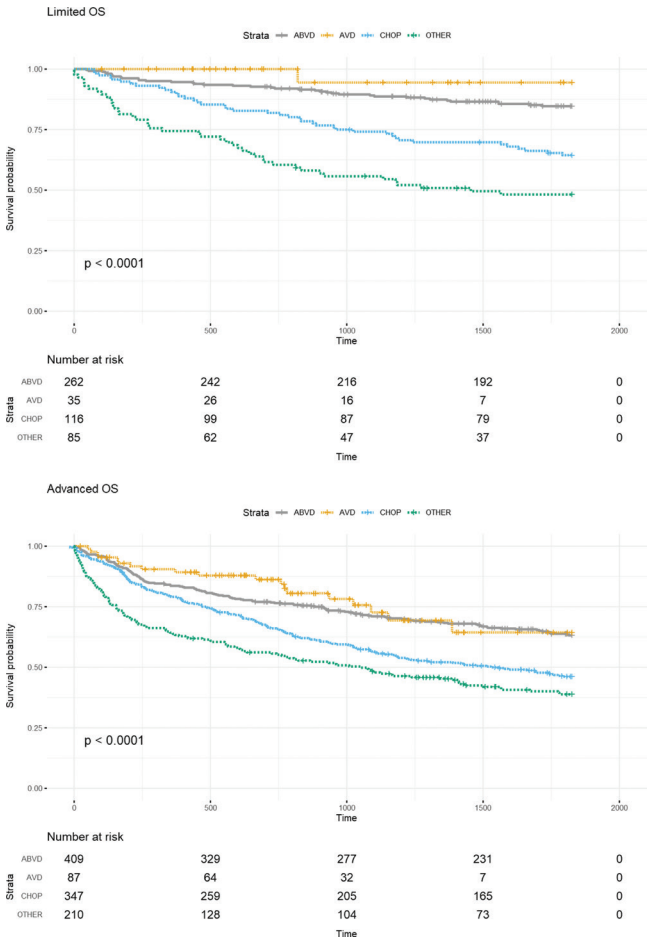

Figure 1: 5-year overall survival in cHL patients aged ≥60 years treated with curative intent in Sweden, Denmark and Norway 2000–2021. Limited stage disease (top) and advanced stage disease (bottom) stratified by first-line chemotherapy regimen.

according to first-line chemotherapy regimen; ABVD (n=671), AVD (n=122), CHOP (n=465) or "other" (n=296, single agent or combination chemotherapy).
Results: Median age was 70 years (60–94 years) for all patients and stages. In the different treatment groups the median age was 66 years (60–90), 74 years (61–86), 73 years (60–92), 73 years (60–94) for ABVD, AVD, CHOP and "other", respectively. Overall survival (OS) at 5 years for limited stage patients was 85% for the ABVD group, 94% for AVD, 64% for CHOP and 48% for patients who received "other" chemotherapy. A majority of limited stage patients also received radiotherapy. In patients with advanced stage disease 5-year OS was 63% in the ABVD group, 64% for AVD, 46% for CHOP and 39% in the "other"-group. In multivariable OS analysis patients treated with CHOP had a significantly poorer outcome than those treated with AVD, while there was no significant difference between AVD and ABVD. The majority of patients receiving AVD were treated in Sweden after 2016 and patients in the CHOP and other-group generally had poorer performance status compared to the ABVD-group. PFS data will be presented.
Conclusion: AVD is less toxic than ABVD, as bleomycin is omitted, and outcome with respect to OS was equal to ABVD and superior to CHOP in this patient group. Based on our findings AVD is a preferable treatment and should be considered as backbone in prospective studies with novel drugs.

T083: THE EFFECT OF HEART FAILURE ON MANAGEMENT AND OUTCOMES OF OLDER PATIENTS WITH HODGKIN LYMPHOMA

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Background: Anthracycline-containing regimens are recommended as first-line treatment for Hodgkin lymphoma (HL); however, the management and outcomes of patients with cardiomyopathy or heart failure (HF) at the time of lymphoma diagnosis is not known.
Methods: US Surveillance, Epidemiology, and End Results (SEER)-Medicare data from 1999–2016 were used to identify newly diagnosed HL in patients 66 years and older with one year of Medicare A and B prior to lymphoma diagnosis. Prevalent HF and comorbidities in the year prior to lymphoma diagnosis were identified using International Classification of Diseases codes. Cancer treatment, including doxorubicin and cardioprotective medications (i.e., liposomal doxorubicin and dexrazoxane) were assessed using Healthcare Common Procedure Coding Systems codes. Cause of death was defined using the SEER Cause of Death Recodes. The association between prevalent HF and cancer treatment was estimated using logistic regression with adjustment for comorbidities, social determinants of health and hospital level variables. The association between prevalent HF and cause specific mortality was evaluated using competing risk Cox proportional hazards models with sequential adjustment for comorbidities and cancer treatment.
Results: Among 3,348 individuals with newly diagnosed HL, prevalent HF was present in 13.1%. Patients with prevalent HF were less likely to be treated with an anthracycline in the first year after diagnosis (OR 0.42, 95% CI 0.29, 0.60). Among patients with HF who received an anthracycline, dexrazoxane or liposomal doxorubicin was used in only 4.5%. For those with prevalent HF, 1-year lymphoma mortality was 37.4% (95% CI 35.5, 39.5%) [Fig]. In multivariable models adjusting for clinical covariates, prevalent HF was associated with higher lymphoma mortality (HR 1.21, 95% CI 1.03, 1.41); however, the effect of prevalent HF on lymphoma mortality was no longer significant when adding cancer treatment variables to the model (HR 1.05, 95% CI 0.71, 1.56) [Fig]. Prevalent HF was also associated with cardiovascular mortality in fully adjusted models (HR 1.77, 95% CI 1.34, 2.32).
Conclusion: HF is common in older patients with HL and is associated with less anthracycline use and higher lymphoma mortality. Dexrazoxane and liposomal doxorubicin are used infrequently. Future randomized trials are needed to determine strategies to decrease lymphoma and cardiac mortality in this high-risk population.

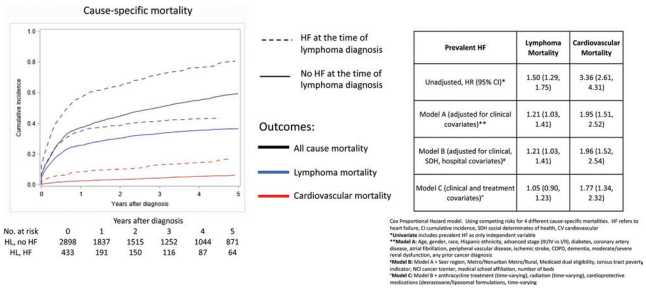

Figure 1: Cumulative incidence of lymphoma mortality (blue), cardiovascular mortality (red) and all-cause mortality (black). Dashed line represents patients with heart failure at the time of lymphoma diagnosis and solid lines patients without heart failure

T084: TREATMENT PATTERNS AND OUTCOMES FOR HODGKIN'S LYMPHOMA (HL) PATIENTS (PTS) AGED 60 AND OLDER: A REPORT FROM THE BRAZILIAN PROSPECTIVE HODGKIN'S LYMPHOMA REGISTRY

Lilian Goveia[1], Nelson Castro[2], Carmino De Souza[3], Carolina Colaço. Villarim[4], Fabiola Traina[5], Carlos Sergio Chiattone[6], Monica Praxedes[7], Cristiana Solza[8], Leila Perobelli[9], Otavio Baiocchi[10], Rafael Gaiolla[11], Carla Boquimpani[12], Valeria Buccheri[13], Caroline Bonamin, Sola[14], Roberta Oliveira De Paula E. Silva[15], Ana Carolina Ribas[16], Giovana Steffenello[17], Katia Pagnano[3],

Andrea Soares[8], Samuel Souza Medina[3], Talita Silveira[6], Karin Zattar Cecyn[9], Leonardo Carvalho Palma[5], Mariana De Oliveira Marques[10], Nelson Spector[1], Irene Biasoli[1]

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Introduction: Despite substantial progress in the treatment of HL, older pts remain an unmet treatment need.
Methods: We sought to identify the treatment patterns and outcomes in HL pts ≥ 60 y/o included in the Brazilian HL registry.
Results: A total of 141 pts with HIV negative classical HL aged ≥ 60, diagnosed from January 2009 to December 2018, were identified. Five pts were excluded, leaving 136 pts available for analysis.
The median age was 66 years old (60–90), 49% were female, PS >1 in 21%, advanced stage in 72%, anemia in 38%, high-risk IPS score in 62% and nodular sclerosis (NS) in 49%. In comparison to younger pts, pts ≥ 60 y/o were more likely to have a high-risk IPS score (63% vs 38%, P<.0001), and histopathology other than NS (51% vs 23%, P<.0001). Also, older pts were more likely to have a lower socioeconomic status (SES, 47% vs 30%, P< .0001) and a lower educational level (25% vs 3%, P<.0001).
Median follow-up was 45 months (0–144) for all pts and 64 months (14–144) for pts alive. ABVD was the first-line treatment in 96% of pts. Twenty-one pts (15%) died during the first treatment. In 18 (86%) of these pts, the cause of death was an infection or a complication of treatment. The 5-year PFS and 5-year OS were 55% and 59%. The 5-year PFS in localized and advanced disease were 72% and 47% (P=0.013). The 5-year OS in localized and advanced disease were 81% and 51% (P=0.013).
Among 131 pts treated with ABVD, 5% presented cardiac toxicity, 11% lung toxicity and 12% severe infection. 65% of pts used bleomycin for > 2 cycles and 44% for > 4 cycles. In comparison with 2009–2014, there was a decrease in the use of bleomycin for > 2 cycles in 2015–2018 (88% x 45%, P<0.0001).
The impact of (SES) on outcomes was studied in pts treated with ABVD. The fatality ratio during treatment was 9% and 21% for higher and lower SES (P=0.10). The 5-year PFS for higher and lower SES were 71% and 46% (P = .005), and the 5-year OS 72% and 55% (P = .027), respectively. After adjustments for potential confounders, lower SES remained independently associated with poorer survival (HR 2.22 [1.14–4.31] for OS and HR 2.84 [1.48–5.45] for PFS).
Conclusion: Advanced stage and poor-risk pts predominated. Inferior outcomes are in part due to advanced disease at diagnosis and to an excess of deaths during treatment. SES is an independent factor for shorter survival. The use of bleomycin remains high, despite a substantial decrease in recent years.

P085: EPIDEMIOLOGY AND RESULTS OF THE FIRST LINE THERAPY OF HIV-RELATED HODGKIN LYMPHOMA: RUSSIAN RETROSPECTIVE MULTICENTER STUDY

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Background: Patients with HIV infection have a significantly higher risk of developing cancer comparing to general population. Hodgkin lymphoma (HL) is one of the most common non-AIDS-defining malignancies. Currently, there is no unified approach to the treatment of HIV-related HL, and data on its epidemiology in the Russian Federation is limited. The ART allows treating HIV-infected patients with lymphomas with standard chemotherapy protocols.
Aim: To study epidemiology and evaluate results of the first-line therapy of HIV-related HL.
Patients and Methods: This multicenter retrospective study included 46 patients with HIV-related HL who received treatment in 9 Russian centers from 2006 to 2022. The median follow-up was 15 months (1–129). Overall survival (OS) and progression-free survival (PFS) were analyzed using the Kaplan-Meier method.
Results: The median age was 37years (25–66), men - 25 (54%), women - 21 (46%). Histological variants of HL in most cases were represented by nodular sclerosis (60%) and mixed-cell subtype (37%). The advanced stage of the disease was observed in 74% of patients, B-symptoms at the onset of the disease - 65%, extranodal involvement-52%. All patients were on ART at the start of HL therapy. The median number of CD4+ cells/μl at the onset of HL was 354 (50–727). ECOG status at the start of therapy was 0–1 in 39 (84.8%), ECOG≥2 in 7 (15.2%). As the first line of therapy, patients with early stages of HL received ABVD (79,4%) and BEACOPP therapy (20,6%), with advanced stages - ABVD (58.7%) and BEACOPP-like (41.3%). The median number of first-line therapy cycles was 4 (1–10). Radiation therapy in first-line therapy was performed on 6 patients. The structure of response to first-line therapy: complete response - 81.6%, partial response - 26.3%, disease stabilization - 2.6%, disease progression – 17.9%. 2-years OS in the study group was 85%, PFS - 49% (median PFS – 23.2 months). The level of CD4+ cells at the onset of HL less than 266.5/μl was associated with a significant worsening of 2-year OS (57% vs 100%, p=0.019). Also, ECOG-status ≥2 significantly worsened 2-year OS (71% vs 88%, p=0.033). Factors such as gender, age, stage of the disease, the presence of B-symptoms and extranodal involvement at the onset of the disease, as well as the treatment regimen did not significantly affected the results of first-line therapy.
Conclusion: The multicenter study allowed characterization of HIV-related HL and evaluation of the efficacy.

Pediatric HL

P086: ADVANCING PEDIATRIC HODGKIN LYMPHOMA RESEARCH THROUGH NODAL

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Background: The Pediatric Cancer Data Commons (PCDC; University of Chicago, established in 2015) has provided a robust technical infrastructure to enable harmonization and utilization of big data to answer meaningful research questions for rare diseases. Access to data is challenging and the PCDC is moving the field forward through rapid access to big data without loss of governance for each individual contributor. The HodgkiN lymphOma DatA coLlaboration (NODAL) is the next step in a longstanding collaboration between pediatric Hodgkin lymphoma (HL) consortia to help advance the field.
Methods: Our NODAL subgroup of the PCDC began in 2018 and built on the existing international working group SEARCH for

CAYAHL (Staging Evaluation and Response Criteria Harmonization for Childhood, Adolescent and Young Adult HL). The initial collaboration includes an agreement for submission of clinical trial data from COG and St. Jude-Stanford-Dana-Farber clinical trials for classic and lymphocyte predominant HL. During 2019 to 2020 NODAL members worked to harmonize case report forms from clinical trials and develop a comprehensive data dictionary. Foundational steps were made to establish an executive committee, governance structure with policies and procedures, sign a memorandum of understanding to establish the consortium, and data contributor agreements. The NODAL leadership identified research questions for which exploration would be possible with a larger data set than is currently available at any one research group. We used that information to identify working groups that would be ready to start once the data are harmonized. Data are currently being entered into NODAL and next steps will involve utilization of data of nodular lymphocyte predominant Hodgkin lymphoma patients to enable research of this rare subtype of HL previously treated on many classical HL trials.

Conclusion: NODAL is a rich resource and will provide access to large datasets from pediatric HL trials that will facilitate cross-trial comparisons and answer unmet clinical research questions in an expeditious manner. We look forward to inclusion of additional international cooperative groups and sharing this rich resource with the global community for years to come.

T087: BRENTUXIMAB VEDOTIN (BV) DEMONSTRATES SUPERIOR EVENT-FREE SURVIVAL IN PEDIATRIC HIGH-RISK HODGKIN LYMPHOMA

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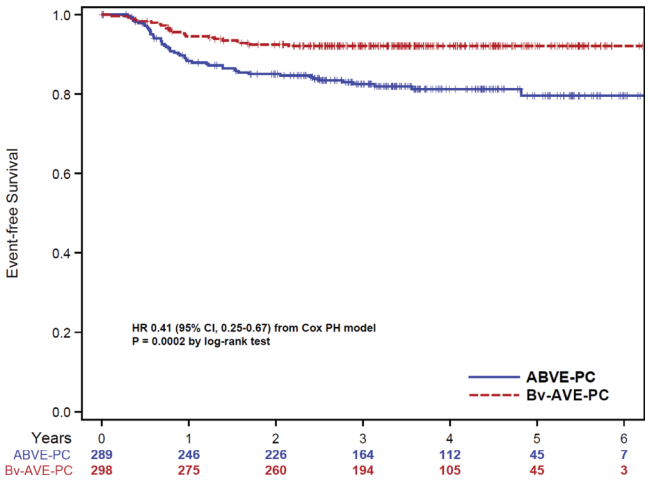

Figure 1: Event Free Survival (EFS) by study arm: The hazard for events of progression, death or second malignant neoplasm (SMN) was 0.41 (95% CI 0.25, 0.67), in favor of Bv-AVE-PC. No. of first events: Bv-AVE-PC, n=23; ABVE-PC, n=51

Background: The use of the anti-CD30 antibody drug conjugate, Brentuximab vedotin (Bv) has not been established as first line therapy for Hodgkin lymphoma (HL) in children or adolescents. We compared the efficacy and safety of Bv with doxorubicin, vincristine, etoposide, prednisone and cyclophosphamide (Bv-AVE-PC) to the standard pediatric dose intensive regimen ABVE-PC, inclusive of bleomycin.

Methods: This multicenter randomized, open-label phase 3 study enrolled patients 2–21 years (yrs) with previously untreated HL, stages IIB + bulk, IIIB, IVA, IVB (NCT02166463). Patients were randomized to 5 cycles of either ABVE-PC or Bv-AVE-PC given every 21 days with granulocyte colony-stimulating factor support. Centrally reviewed PET-CT after 2 cycles (iPET) defined slow responding lesions (SRL) by 5-point score (PS) >3. Involved site radiotherapy (ISRT) was given to bulky mediastinal adenopathy and SRL. The primary objective was EFS.

Results: 600 participants were enrolled across 153 Children's Oncology Group institutions from March 2015 to August 2019; 587 were eligible. Median age was 15.6 yrs (range 3.4–22). Patient and disease characteristics were balanced across study arms. Stage distribution: 20.6% IIB-bulk; 19.3% IIIB; 28.5% IVA; 31.7% IVB.

At a median follow-up of 42.1 mos (0.1–80.9), 3-year EFS (95%CI) by intent-to-treat analyses was 92.1% (88.4, 94.7) with Bv-AVE-PC vs. 82.5% (77.4, 86.5) with ABVE-PC (HR 0.41 (0.25, 0.67), p=0.0002). Cumulative incidence of relapse was 7% with Bv-AVE-PC and 17% following ABVE-PC. iPET+ rates were comparable (ABVE-PC 19% vs. Bv-AVE-PC 18%, p=0.8), but iPET+ patients who received Bv-AVE-PC had a significantly higher 3yr-EFS (90.7%) compared to ABVE-PC (68.3%) (HR 0.28 [0.10, 0.76]). As-treated ISRT receipt did not differ (ABVE-PC 55.7% vs. Bv-AVE-PC 52.7%, p=0.69). No difference was noted in grade 3/4 adverse events; myelosuppression, reflected in a 32% incidence of > grade 3 febrile neutropenia, did not differ by arm (p=0.67). Only 19% of patients experienced > grade 2 neuropathy by the Balis pediatric neuropathy scale, with no difference between arms (p=0.86).

Conclusion: Bv with AVE-PC in a dose intensive regimen has superior efficacy to ABVE-PC for pediatric patients with high-risk HL. A 9.6% improvement in EFS was achieved with no increase in toxicity and with fewer patients receiving RT compared to prior pediatric trials for high-risk HL.

P088: CASE SERIES OF NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA FROM TANZANIA. A COMMON ENTITY IN EAST AFRICA?

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Background: NLPHL is a rare subtype of HL and constitutes to approximately 5% of all HL, hence less than 0.5% of all lymphomas [1,2]. For Sub-Saharan Africa, publications about NLPHL are literally non existing. Due to the rarity of NLPHL, clinical trial data are limited, but NLPHL are generally associated with good prognosis [3,4]. Due to the CD20 positivity, the use of CD20-antibodies is recommended and contributes to a good treatment outcome according to publications from high income countries.

As treatment outcome and patient's characteristics from African NHLP patients have not been reported as of today, we therefore display patient's characteristics, treatment outcome and follow up from a sub-cohort of Tanzanian patients enrolled in a multi-centre study in Uganda and Tanzania focusing on EBV-driven lymphoma, the AI-REAL study [5].

Methodology: An observational descriptive case series, assessing the clinical presentation, stage, treatment and results of treatment of patient recruited through the AL-REAL [5] study at Kilimanjaro Christian Medical Centre site.

Results: Out of 55 children and young adults (between 3 to 30 years of age) who were diagnosed with lymphoma, 17 had HL and 6 out of these had NLPHL. Mean age was 19.5 years (range 3–28), sex ratio 1:1, 5 presented with B symptoms, 4 were in stage III and 2 in stage I. IHC for CD20 were available in 5 patients (all positive). In the first line therapy, 2 paediatric patients received ABVD and R-ABVD, the adult patients

received R-CHOP (2 cases), CHOP (1), and surgery only (1). For all patients receiving chemotherapy, 6 cycles were given. 5 patients achieved CR, and 1 patient progressed on 1st (ABVD) and 2nd (R-CHOEP) line and eventually died. Treatment outcome was assessed 2 weeks after the last cycle of chemotherapy (respectively surgery) by CT scan, the cumulative survival months up to June 2022 is 90 months, ranging from 10 to 24 months after finalizing therapy.
Conclusion: This case series demonstrate a high proportion of NLPHL among the study population. Further studies should evaluate the frequency of NLPHL in the Sub-Saharan setting. With 5 out of 6 patients achieving CR (1 after 2nd line), the favorable treatment outcome described in other settings can be confirmed for Tanzania.

P089: PEMBROLIZUMAB IN PEDIATRIC AND YOUNG ADULTS PATIENTS WITH NEWLY DIAGNOSED CLASSICAL HODGKIN LYMPHOMA AND SLOW EARLY RESPONDERS TO FRONTLINE CHEMOTHERAPY: THE PHASE 2 KEYNOTE-667 STUDY

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Background: Slow-early response (SER) to initial chemotherapy (chemo) and added radiotherapy (RT) exposure increases the risk for relapse and toxicity in patients (pts) with classical Hodgkin lymphoma (cHL). Pediatric and young adult pts with cHL and SER received pembrolizumab (pembro) + chemo in the open-label, phase 2 KEYNOTE-667 study (NCT03407144). We present interim data in pts with high-risk cHL (group 2) and SER to frontline chemo.
Methods: Eligible pts in group 2 were aged 3–25 y with newly diagnosed stage IIEB, IIIEA, IIIEB, IIIB, IVA, or IVB cHL. After 2 cycles of vincristine, etoposide, prednisone/prednisolone, doxorubicin (OEPA), pts with SER (Deauville score 4 or 5) received ≤17 doses of pembro 2 mg/kg to 200 mg (3–17 y) or 200 mg (18–25 y) IV Q3W + 4 cycles of cyclophosphamide, vincristine, prednisone/prednisolone, dacarbazine (COPDAC-28). After COPDAC-28 consolidation, pts with SER and were PET-positive (Deauville score 4 or 5) received RT + ≤17 doses of pembro; pts with SER and were PET-negative (Deauville score 1–3) received only pembro for ≤17 doses. Safety analyses included pts with SER who received ≥1 dose of pembro; efficacy analyses included pts who completed post-COPDAC-28 response assessment. The primary end point was ORR by blinded independent central review (BICR) per IWG 2007 criteria in pts with SER. Secondary end points included post-COPDAC-28 PET-negative rate, RT exposure details, and safety. Data cutoff was Nov 22, 2021.
Results: Group 2 included 30 pts with high-risk cHL; median age was 15 y (range, 6–19), 13 (43%) pts had bulky disease, and 19 (63%) had Ann Arbor stage IV disease. At data cutoff, 23 (77%) pts had adverse events (AEs) and 6 (20%) had AEs grade ≥3; 14 (47%) pts had treatment-related AEs (TRAE) and 2 (7%) had TRAEs grade ≥3. Serious AEs occurred in 3 (10%) pts (1 [3%] pt had grade 2 immune-mediated hypothyroidism). After 9.6 mo (range, 2.5–21.2) of median follow-up, 6 (20%) pts completed and 24 (80%) were continuing treatment; median time on treatment was 3.3 mo (range, 0–11.8). Of the 25 (83%) pts who had a post-COPDAC-28 assessment, 17 (68%) were PET-negative by BICR; 18 (72%) pts by investigator assessment.
Conclusion: Pembro + COPDAC-28 in pediatric and young adult pts with high-risk cHL and SER to frontline chemo demonstrated acceptable safety. Thus, 68% of pts with PET-negative response were spared RT after consolidation. Early data show that pembro may enhance responses to chemo in this pt population.

P090: STAGING OF LUNG LESIONS SURVEY DEMONSTRATES CONTINUED NEED FOR HARMONIZATION

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Background: Staging of lung disease in Hodgkin lymphoma (HL) has been a longstanding and controversial challenge. In 1984, a survey of 14 experts was published in the Journal of Clinical Oncology. Four case vignettes were distributed, and experts designated each vignette as either Stage IIE or Stage IV disease. Results were very divided for 2 of the 4 case vignettes, and the conclusion was a call for clear guidance and group consensus for staging of lung lesions. Despite updates to the HL staging systems at both the Cotswold (1989) and Lugano (2014) meetings, there remains today, nearly 30 years later, a perceived lack of uniformity in the approach to the staging of lung lesions even among experts in the field. The approach to each of these issues not only varies across consortium groups but among individuals within the same consortium groups. When reviewing the most recent frontline HL trials from St. Jude-Stanford-Dana Farber, EuroNet PHL, and the Children's Oncology Group, lung lesions were defined differently for each. This creates difficulty in comparing outcomes across trials and highlights the need for consensus and uniformity.
Methods: The SEARCH for CAYAHL (Staging, Evaluation and Response Criteria Harmonization for Childhood, Adolescent, and Young Adult HL) group recreated a similar survey using 7 case vignettes and distributed it to 26 internationally recognized experts in pediatric HL to establish how current world experts are staging lung lesions (see Figure 1). Of the 21 survey respondents (81% response rate), 7 were radiologists or nuclear medicine radiologists, and 14 were pediatric oncologists. While there was near consensus for some of the cases, several remained very divided, namely around the role of PET avidity in lung lesions, the number and location of lung lesions, and the concept of contiguous disease.
Conclusions: After reviewing the results of our survey, the SEARCH group acknowledges the controversy and inconsistency with which we are currently staging lung disease around the globe. We are now actively

Figure 1: Case vignettes and survey responses.

working to establish clear criteria, based on available data, and expert consensus through Delphi survey methods, and plan to have this completed in the fall of 2022.

Radiotherapy

P091: EARLY ANALYSIS OF THE PRO-HODGKIN STUDY: CLINICAL INVESTIGATION OF PENCIL BEAM SCANNING PROTON TREATMENT IN HODGKIN LYMPHOMA PATIENTS

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Background: Most stage I-IIA classical Hodgkin lymphoma (cHL) patients are cured with limited chemotherapy followed by radiotherapy (RT), with a risk of late toxicity from RT. The dose to normal tissue can be minimized with proton therapy (PT) due to the finite range in tissue and the rapid dose-drop beyond that. This study reports preliminary results of the PRO-Hodgkin study.
Method: The first 19 patients included (median age 31 (19–53)) are analysed. They received 2–4 cycles of ABVD followed by involved-node/site PT to 29.75 Gy (RBE; relative biological effectiveness)/17 fractions for patients with risk factors, and 20 Gy (RBE)/10 fractions for those without risk factors. Planning CT in deep inspiration breath hold was recommended; if not feasible, a 4DCT was performed to ensure motion amplitudes within 5 mm. Patients were typically treated by pencil beam scanning with two anterior oblique fields, sometimes with a complementary posterior field. All treatment plans were robustly optimized.
Results: All patients were in complete remission at end of therapy. Acute toxicity was generally limited and similar to photon treatment, except slightly more skin reaction, which occurred in all patients (1 grade 3, 1 grade 2 and 17 grade 1).
Surprisingly 4 patients (age 26–45), previously healthy and non-smokers, presented with skin hyperesthesia radiating from the neck or the scapula/chest wall area towards the axilla and upper arm, starting weeks or a few months after RT. The symptoms mostly resolved within a month, but one patient had symptoms gradually improving for 4 months. None of the patients had skin rash during symptoms and none had motor affection.
Analysis of the dose plans showed that the brachial nerve plexus was frequently located in or close to the target, and often had a modest overdosage (max 5% over the prescribed dose). Thoracic nerve roots and the spinal cord were usually located in the dose drop-off. Even assuming slightly higher RBE towards the end of the proton range, the dose to spinal cord/peripheral nerves was well within tolerance.
Conclusion: PT was generally well tolerated, except for an unexpected, transient neurological toxicity in 4 out of 19 patients. This could not be explained by an overdosage, and the potential mechanism has not yet been identified. Radiation- induced inflammation and cytokine release could be a possible cause. Further analyses are warranted and neurological toxicity will be reported for future patients.

P092: ESTIMATING THE DOSIMETRIC BENEFIT OF INVOLVED-NODE RADIOTHERAPY IN COMPARISON TO INVOLVED-FIELD RADIOTHERAPY - IMPLICATIONS FROM THE GHSG HD 17 TRIAL

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Question: The HD17 trial of the German Hodgkin Study Group evaluated the value of consolidative involved-node (IN)RT for patients with PET-positivity after chemotherapy and enabled a comparison between INRT and involved-field (IF)RT [1]. The present work analyzes the organs at risk (OAR) exposure of the performed RT.
Methods/Material: For dosimetric evaluation, all INRT-plans in the HD 17 trial were requested and compared to a random selection of IFRT-cases in the standard arm. Dose-volume histograms (DVH), either paper-based or digital, were analyzed using SPSS (version 28, IBM, Armonk, NY, USA). For comparisons between the two RT concepts, a two-sided t-test or a Mann-Whitney U test was used with a p-value < 0.05 considered as significant.
Results: In total, 148 DVH (INRT: 112, IFRT: 36) could be evaluated. Details on planning target volume (PTV) size and OAR exposure are shown in table 1. The introduction of INRT decreased the PTV size without reaching statistical significance. There was a consistent decrease in OAR-doses with INRT except for V5 in both lungs and V10 and Dmean in the right lung. Despite the dosimetric advantages, significant differences in favor of INRT could only be found for the spinal cord and thyroid.
Conclusion: INRT, in comparison to IFRT, decreases PTV-size and OAR exposure and may help to comply with modern dose constraints [2].

	Total cohort	IFRT	INRT	p
PTV (ml)	1265.2 (86.7-5125.3)	1438.1 (97.6-4238.0)	1181.6 (86.7-5125.3)	0.082
Lung right D_{mean} (Gy)	9.8 (0.3-20.0)	9.5 (4.0-17.8)	10.1 (0.3-20.0)	0.861
V_5 (%)	54.6 (0.0-100.0)	48.0 (0.0-98.0)	57.5 (0.0-1.0)	0.141
V_{10} (%)	37.0 (0.0-86.0)	32.0 (0.0-86.0)	38.0 (0.0-83.0)	0.538
V_{20} (%)	20.0 (0.0-48.0)	21.0 (0.0-46.0)	19.1 (0.0-48.0)	0.509
V_{25} (%)	13.0 (0.0-42.0)	16.0 (0.0-40.0)	11.9 (0.0-42.0)	0.197
V_{30} (%)	2.0 (0.0-32.0)	2.0 (0.0-30.0)	1.5 (0.0-32.0)	0.477
Lung left D_{mean}(Gy)	10.5 (0.2-26.5)	11.6 (1.0-23.5)	10.1 (0.21-26.5)	0.291
V_5 (%)	55.1 (0.0-99.0)	50.0 (0.0-99.0)	58.0 (0.0-99)	0.527
V_{10} (%)	37.8 (0.0-92.0)	39.5 (0.0-90.0)	37.5 (0.0-92.0)	0.981
V_{20} (%)	20.0 (0.0-85.0)	22.3 (0.0-70.0)	19.2 (0.0-0.85)	0.403
V_{25} (%)	13.3 (0.0-80.0)	16.0 (0.0-62.0)	12.0 (0.0-80.0)	0.136
V_{30} (%)	2.0 (0.0-60.0)	3.0 (0.0-30.0)	2.0 (0.0-60.0)	0.426
Spinal cord D_{max} (Gy)	29.6 (6.9-34.2)	31.2 (15.6-34.2)	28.8 (6.9-32.6)	**<0.001**
Esophagus D_{mean} (Gy)	21.4 (8.9-30)	23.4 (10.1-27.9)	20.5 (8.9-30.0)	0.164
Heart D_{mean} (Gy)	13.1 (0.5-30.4)	14.4 (0.62-30.4)	12.4 (0.5-26.9)	0.691
Thyroid D_{mean} (Gy)	26.5 (13.9-33.3)	31.1 (29.4-33.3)	24.2 (13.9-31.3)	**0.023**
Thyroid V_{25} (%)	49.5 (0-100)	100 (98-100)	43.6 (0-100)	**0.036**
Breast left D_{mean} (Gy)	3.6 (0.5-9.3)	3.9 (2.1-10.9)	3.5 (0.5-9.3)	0.476
Breast right D_{mean} (Gy)	3.7 (0.4-15.6)	4.3 (1.0-6.8)	3.7 (0.4-15.6)	0.935

Table 1: Size of the planning targe volume (PTV) and dose exposure to organs at risks in comparison between involved-field (IFRT) radiotherapy and involved-node radiotherapy (INRT). Gy: Gray

Literature
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2. Blood. 2019 Mar 21;133(12):1384-1385.

P093: FROM INVOLVED- FIELD TO INVOLVED-NODE – QUALITY ANALYSIS OF THE RADIATION THERAPY IN HD 17 BY THE EXPERT PANEL OF THE GERMAN HODGKIN STUDY GROUP

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Question: The use of radiotherapy (RT) for intermediate-stage Hodgkin lymphoma is discussed vividly. The HD17 trial of the German Hodgkin Study Group (GHSG) evaluated the value of consolidative involved-node (IN)RT for patients with PET-positivity after chemotherapy and enabled a comparison between INRT and involved-field (IF)RT [1]. The present work analyzes the quality of the performed RT.
Methods/Material: For quality assessment, all INRT-plans in the HD 17 trial were requested and compared to a random selection of IFRT-cases in the standard arm. The RT was assessed by experts of the radiation therapy panel of the GHSG using initial (staging) imaging, RT plans and the recommendation forms by the reference radiation oncology. Evaluation was graded as „correct", „minor deviation" or „major deviation". Statistical analyses were per-formed using a chi-square test in SPSS (version 27/28, IBM, NY, USA).
Results: In total, 178 patients (INRT: 136, IFRT: 42) were analyzed, treated with a median RT dose of 30 Gy (IFRT: 18–30.6 Gy, INRT: 14 Gy-40 Gy). The majority (76.5 %) of INRT-cases showed no deviation compared to 69.1 % of IFRT-cases. Deviations were reported for 9.6 % and 14.0 % of patients in the INRT-group compared to 11.9 % and 19.1 % in the IFRT-group for minor and major deviations, respectively. There was no significant difference between both cohorts regarding the percentage of plans with deviations (p=0.333) or the percentage of major deviations (p=0.423). The principal causes for major deviations were too narrow target volumens in the involved region (IFRT: 6 vs. INRT: 1) or incorrect RT doses (IFRT: 1, INRT: 2).
Conclusion: The performed INRT was delineated and planned correctly in most cases and reveals a high degree of quality. There has been no decline in RT-planning in comparison to IFRT. Continuous education is pivotal to enable high-quality INRT outside of clinical trials.

Literature
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P094: LONG-TERM OUTCOMES OF BULKY CLASSIC HODGKIN LYMPHOMA MANAGED WITH A PET-ADAPTED APPROACH DEMONSTRATE EXCELLENT OUTCOMES IN PET-NEGATIVE CASES

Jowon Laura Kim[1], Diego Villa[2], R. Petter Tonseth[3], Alina S. Gerrie[2], Don Wilson[3], Francois Benard[3], Chris Venner[2], Brian Skinnider[4], Pedro Farinha[4], Graham W. Slack[4], David W. Scott[2], Joseph M. Connors[2], Laurie H. Sehn[2], Kerry J. Savage[2]

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Background: With concerns of long-term complications due to radiotherapy (RT), recent studies have evaluated ABVD alone in patients (pts) with bulky classic Hodgkin lymphoma (cHL) with an end of treatment (EOT) PET-negative (neg) scan. However, variable definitions of bulky disease are used, and long-term follow-up remains limited. Since 2005, advanced stage (stage 2B/3/4, bulky (≥10cm) stage 1/2) cHL pts in British Columbia (BC) have been managed with PET-guided consolidative RT.
Methods: The BC Cancer Lymphoid Cancer Database was screened to identify all pts >16 years (y) with bulky (≥10cm) cHL treated with 6 cycles of ABVD chemotherapy. Pts with progressive disease on interim scan or at EOT were excluded. Pts with an EOT PET-positive (pos) scan received consolidative RT. PET scans assessed by the IHP criteria were re-reviewed to assign a Deauville (D) score (PET-neg=D1-3, DX; PET-pos=D4-5). Freedom from treatment failure (FFTF) was measured from diagnosis to relapse/ progression of HL, or death due to HL or treatment toxicity.
Results: From 2005–2020, 215 patients (115M, 100F) were identified. Median age was 29 years (y) (17-72y), median mass size was 11cm (10-21cm), 94% had bulky mediastinal mass, and 2%, 65%, 8%, and 25% had stage 1, 2, 3 and 4 disease, respectively. At EOT, 176 (82%) had a PET-neg scan (none received RT), and 39 (18%) had a PET-pos scan (34 received RT to residual mass; 5 were observed: false pos n=3, refused n=1, not radioencompassable n=1). With a median follow-up of 6.75y (0.8–15.75y), pts with a PET-neg scan had 5y FFTF of 94% (stage 1/2–94%, stage 3/4–96%) vs 65% with a PET-pos scan (p<0.001). Overall survival (OS) was similar in PET-neg and pos (97% vs 90%, p=0.191). The 5y FFTF was similar by D score in PET-neg cases (DX-100%; D1-90.5%; D2-97%; D3-100%, p=0.213) but inferior in D4 (58%) and D5 (42%) (p<0.001). The 5y OS was similar between PET-neg and D4 (DX-93%, D1-97%, D2-100%, D3-100%, D4-94%), but inferior in D5 cases, with 5y OS 60% (p=0.015). There were 23 relapses: 10 PET-neg (7 in what would have been the RT field (residual mass), 3 inside and outside field); 13 PET-pos (5 in field, 8 included sites outside the RT field).
Conclusion: With a median follow-up of almost 7y, bulky cHL with an EOT PET-neg scan have excellent outcomes, regardless of initial stage. A large proportion of D4 PET-pos cases are salvaged with RT and maintain an excellent OS. Both FFTF and OS are inferior in those with an EOT D5 scan.

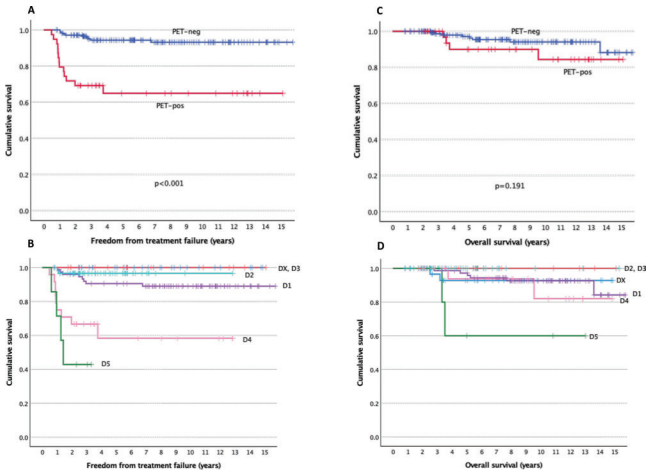

Figure 1: Freedom from treatment failure in bulky advanced stage cHL pts by post-ABVD chemotherapy PET scan (A) and Deauville score (B). Overall survival in bulky advanced stage cHL pts by post-ABVD chemotherapy PET scan (C) and Deauville score (D).

P095: PERSONALISED MODELLING OF QUALITY-ADJUSTED SURVIVAL BENEFIT AND COST-EFFECTIVENESS OF USING PROTON BEAM THERAPY INTHE TREATMENT OF INTERMEDIATE-STAGE HODGKIN LYMPHOMA IN ENGLAND

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Background: Radiotherapy (RT) for Hodgkin lymphoma leads to the incidental irradiation of organs-at-risk (OAR) which may confer excess risks of second primary cancers as well as cardiovascular disease. Comparative dosimetry studies show that proton beam therapy (PBT) may reduce OAR irradiation compared to conventional photon-RT, but the benefit in terms of risk reduction is highly heterogeneous within cohorts of comparatively planned patients. Furthermore, PBT is likely

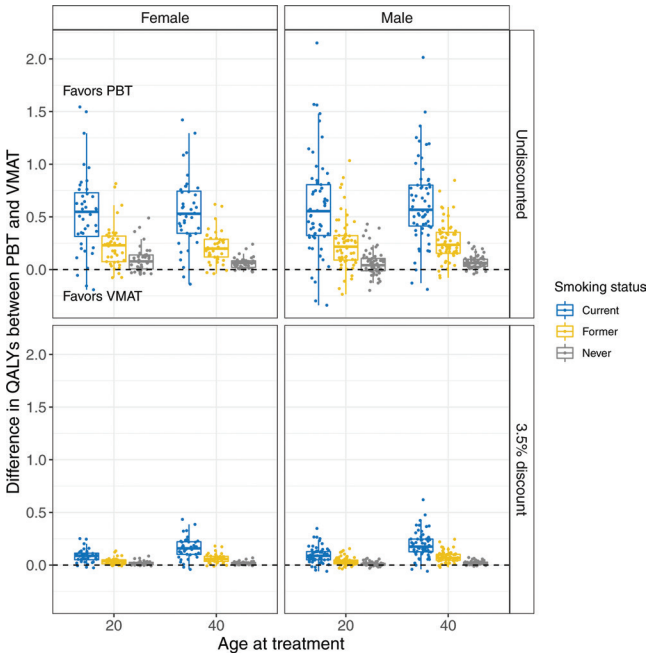

Figure 1: Box plots of the estimated difference in quality-adjusted life years between PBT and VMAT by age, sex, smoking status, and discount rate.

to be more expensive and treatment capacity is limited. In this study, we aim to inform the use of PBT for intermediate-stage Hodgkin lymphoma (ISHL) in England by modelling the life course and healthcare costs of 606 illustrative patients.

Methods: A microsimulation model simulating the life-time course of ISHL, background mortality, and incidence and mortality of late effects was used to estimate comparative quality-adjusted life years (QALYs) lived and healthcare costs after consolidative PBT or photon-RT, both in deep inspiration breath hold (DIBH). Outcomes were compared for the illustrative patients who covered a spectrum of clinical presentations, varying by two age strata (20y and 40y), sex, smoking status (never, former, and current), and 61 pairs of OAR radiation doses from a comparative planning study. Both undiscounted and discounted (3.5% annually) outcomes were estimated. We performed threshold analysis to calculate the maximum additional cost of PBT over photon-RT that might be considered cost-effective by the UK's National Institute for Health and Care Excellence (NICE).

Findings: Box plots of the estimated difference in QALYS between PBT and photon-RT by age, sex, smoking status, and discount rate are given in Figure 1. Current smokers benefited the most, averaging 0.583 undiscounted QALYs (range -0.339 to 2.151) and 0.137 discounted QALYs (range -0.059 to 0.620) whereas never smokers benefited the least, averaging 0.071 undiscounted QALYs (range -0.198 to 0.499) and 0.016 discounted QALYs (range -0.030 to 0.085). For the gain in discounted QALYs to be considered cost-effective at NICE's £30,000/per QALY threshold, PBT would have to cost, at most, £4458 more than photon-RT for current smokers and £598 for never smokers. This is likely far below the cost of PBT over conventional photon-RT.

P096: POLYMORPHISMS IN SETD7 MAY PREDISPOSE THE RISK OF DEVELOPING LATE CARDIAC SIDE EFFECTS AFTER RADIOTHERAPY INCLUDING THE MEDIASTINUM IN HODGKIN' S LYMPHOMA.

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Background: In Hodgkin's lymphoma (HL) radiation therapy including the mediastinum is known to cause long time cardiac side effects.

Method: A cohort of 183 previous HL patients who received radiotherapy involving the mediastinum during the period of 1965–1995 were dichotomized into patients with or without known cardiac complications. This was done after a separate study visit performed with a range of 13–43 years from diagnosis (median 23 years). A complication was defined as having a medical record of any of the following clinical conditions: angina, myocardial infarction, congestive heart failure or valvular disease. DNA was extracted from whole blood and analyzed using Infinum OncoArray-500K. We analyzed a set of 4341 single nucleotide polymorphisms (SNPs) representing 167 genes previously associated with late side effects of radiotherapy or associated with the normal myocyte function, ischemic heart disease, primary restrictive cardiomyopathy or valvular disease. The association between cardiac status and alterations in SNPs was examined. Forty-six of the patients had also received doxorubicin, an anthracycline associated with late cardiotoxic side effects.

Results: A SNP of SETD7 (intron), rs2725790, significantly differed between the two groups (allelic test, p = 9.2E-6, maxT permutation test p=0.024, logistic regression p=0.00013). To take prior anthracycline therapy into account, logistic regression was performed adjusting for anthracycline therapy (logistic regression p=0.00020).

Conclusion: This study indicates that constitutional differences in SETD7, a gene associated with epigenetic regulation of cardiomyogenesis and response to cardiac hypoxia may be involved in the risk of developing late cardiac side effect after radiation therapy of the mediastinum in the treatment of HL.

P097: THE STATUS QUO OF INVOLVED-FIELD RADIOTHERAPY – QUALITY ANALYSIS OF RADIOTHERAPY IN THE GHSG HD 16

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Question: The HD 16 trial of the German Hodgkin Study Group (GHSG) investigated the use of consolidative radiotherapy (RT) after 2 cycles of ABVD chemotherapy for early-stage Hodgkin lymphoma (HL) and could demonstrate the superiority of a combined modality approach [1]. The present work aims at analyzing the quality of involved-field RT used in this study.

Methods/Material: For quality assessment, 100 randomly chosen plans from the HD 16 trial were requested and analyzed. RT was assessed by experts of the radiation therapy panel of the GHSG using initial (staging) imaging, RT plans and the recommendation forms by the reference radiation oncology. Evaluation was graded as „correct", „minor deviation" or „major deviation". Statistical analyses were performed using SPSS (version 27/28, IBM, NY, USA).

Results: Radiation doses were adequate with a median of 20 Gy (19.8 Gy-21.6 Gy) in normofractionation. In the majority of radiation series, supradiaphragmatic target volumes were treated (91 %), with the regions most commonly irradiated being supraclavicular left/right (73 % each), infraclavicular left/right (73 % each) and cervical left/right (44 % and 45 %, respectively). Acute treatment toxicities were mild to moderate with only 3 cases of grade 3–4 toxicities (1 nausea/vomiting, 1 dysphagia, 1 mucositis). According to the RT panel, 84 % of cases were evaluated as „correct", 5 % as „minor deviations" and 11 % as „major deviations". Major deviations were caused by insufficient dose coverage of involved regions in most cases (10/11), predominantly in the upper mediastinum (5/10 cases). Previous GHSG studies in early-stage HL (HD 10 [2] and HD 13 [3]) showed lower rates of RT series according to protocol (38.8 % and 52 %, respectively). A χ^2-test was used to compare the number

of correct RT series in the different GHSG study generations (HD 13 vs. HD 16). No expected cell frequencies were below 5. Results reveal a significant improvement in favor of HD 16 ($\chi^2(1)=33.8$, $p<0.001$ $\Phi=-0.247$). Similar outcomes were found for the association of GHSG study generation and the absence of major deviations ($\chi^2(1)=27.4$, $p<0.001$ $\Phi=-0.222$).

Conclusion: Since its introduction in HD10, involved-field RT has evolved considerably. However, continuous efforts in RT quality assurance and training are needed in the modern era.

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Relapsed/Refractory

T098: BRENTUXIMAB VEDOTIN PLUS ESHAP (BRESHAP) VERSUS ESHAP IN PATIENTS WITH RELAPSED OR REFRACTORY CLASSICAL HODGKIN'S LYMPHOMA. INTERIM RESULTS OF THE BRESELIBET PROSPECTIVE CLINICAL TRIAL.

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Best salvage treatment for relapsed/refractory Hodgkin's lymphoma (RRHL) is still unknown; the superiority of brentuximab vedotin (BV) + chemotherapy (CT) vs CT alone has never been tested in randomized clinical trials. Consolidation with autologous transplant (auto-HCT) is the standard of care for patient (pts) with RRHL but it is unknown if consolidation with BV could spare it in a good risk group. We have conducted a phase IIb prospective clinical trial (BRESELIBET, ClinicalTrials.gov ID: NCT04378647) that evaluates the efficacy of BRESHAP vs ESHAP in RRHL, followed by BV consolidation in those who attained a mCR. 150 adult pts with RRHL were to be included and randomized 1:1 to receive either BRESHAP (x3) or ESHAP (x3). Primary efficacy endpoint was mCR [Deauville Score (DS) of 1–2, DS of 1–3 after the recent amendment of the trial]. Those pts in mCR went on to receive up to 16 doses of BV (1.8 mg/kg iv every 3 weeks). Herein we are reporting preliminary results of the first 92 pts (6 of them, screening failure). Amongst the remaining 86 pts [52 males, median age of 39 (18–64) yrs], 29 were primary refractory, 24 had had an early relapse and 33 a late relapse. 42 pts were randomized into BRESHAP and 44 into ESHAP. 58 pts completed salvage therapy and had their disease status evaluated, 3 pts were discontinued because of an adverse event (AE), 1 pt withdraw consent, 5 pts progressed under therapy and 19 pts are still under treatment. 15 out of 30 (50%) achieved a mCR in the BRESHAP group vs 15 out of 33 (45.5%) in the ESHAP group (NS) (mCR rates were 70% vs 60.6% respectively, when considering DS 1–3). Nine severe AEs were reported in 7 pts [fever (n=3), sepsis (n=2), pneumonia (n=1), pericardial effusion (n=1), diarrhea (n=1), vomiting (n=1)]. 32 pts (15 BRESHAP vs 17 ESHAP) started consolidation with BV; median number of cycles of 9 (1–16). Six pts have finished consolidation with a median follow up after treatment of 3.3 (0.1–8) months. Four pts have relapsed after 3, 3, 5 and 9 cycles of BV and two pts stopped BV after 4 and 9 cycles due to grade 2 neurological toxicity. The results of this interim analysis indicate that the mCR rate of BRESHAP is in line to what our GELTAMO group has published before (García-Sanz R, Ann Oncol 2019) and that consolidation strategies with non-HCT approaches appear to be feasible in patients achieving stringent CR assessed by PET-CT. The trial will continue until the recruitment is completed.

T099: HIGH EFFICACY AND DURABILITY OF SECOND-LINE THERAPY WITH PEMBROLIZUMAB, GEMCITABINE, VINORELBINE, AND LIPOSOMAL DOXORUBICIN IN THE PHASE II STUDY FOR RELAPSED AND REFRACTORY HODGKIN LYMPHOMA

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Introduction/Methods: The standard approach for relapsed or refractory (RR) classical Hodgkin lymphoma (cHL) following front-line treatment failure is second line therapy (SLT) aimed to achieve complete response (CR), followed by consolidation with high dose therapy and autologous hematopoietic cell transplantation (HDT/AHCT). We previously reported results from part I of a phase II study evaluating SLT with pembrolizumab, gemcitabine, vinorelbine, and liposomal doxorubicin (P-GVD) followed by HDT/AHCT (Moskowitz, et al. JCO 2021). We are now enrolling onto part II in which patients with CR after 4 cycles of P-GVD proceed to 13 cycles of pembrolizumab maintenance rather than HDT/AHCT. We

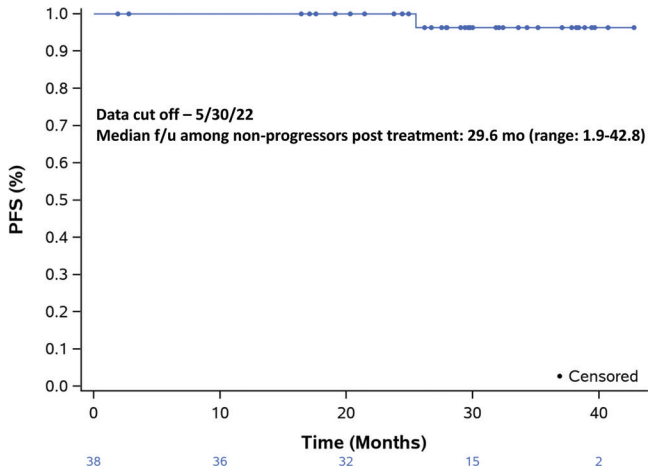

Figure 1: Progression-free survival for patients enrolled onto part I of the phase II study evaluating P-GVD followed by consideration for HDT/AHCT. 36 pts underwent HDT/AHCT. 2 pts declined transplant and were censored after 2 and 3 months.

present here extended follow-up from part I as well as updated efficacy and toxicity data for P-GVD from parts I (n=39) and II (n=33).
Results: Part I included 39 pts evaluable for toxicity and 38 evaluable for efficacy. Among 38 evaluable pts, CR and overall response rates (ORR) were 95% and 100%. 36 pts proceeded to HDT/AHCT, of whom 13 (36%) received post-transplant brentuximab vedotin (BV) (n=12) or BV plus nivolumab (bv/nivo) (n=1) maintenance. After a median follow-up of 30 (range: 2–43) months, 1 pt experienced progression 23 months after transplant. The estimated 30-month progression-free survival (PFS) is 96% (Figure 1).
To date, all 33 pts enrolled to part II are evaluable for toxicity and 30 pts for response to P-GVD. Among those, 27 (90%) achieved CR (including 2 with PET-avid findings that were biopsy negative) and 3 (10%) achieved partial response.
Among 68 pts evaluable for response from parts I and II, CR and ORR rates were 92.6% and 100%. Among 72 pts evaluable for toxicity, grade 4 or 5 events included grade 4 sepsis (n=1) and grade 5 pneumonitis (n=1, occurred after 4 cycles of P-GVD, pt enrolled on part II). Grade 3 events occurring in >1 pt included neutropenia (n=9, 12.5%), elevated AST/ALT (n=7, 10%), mucositis (n=5, 7%), anemia (n=4, 5%), lung infection (n=2, 3%), and rash (n=2, 3%).
Conclusion: Second-line therapy with P-GVD is highly effective and efficiently bridges pts with RR cHL to HDT/AHCT. With extended follow-up for transplanted pts, remissions remain durable with estimated 30-month PFS of 96%. Among 68 evaluable pts enrolled onto parts I and II, CR rate remains high at 92.6%. Enrollment onto part II, which is assessing the role of pembrolizumab maintenance as an alternative to HDT/AHCT for patients in CR, is ongoing.

T100: LONG TERM FOLLOW-UP OF A PHASE I STUDY COMBINATIONS OF IPILIMUMAB, NIVOLUMAB AND BRENTUXIMAB VEDOTIN IN PATIENTS WITH RELAPSED/ REFRACTORY HODGKIN LYMPHOMA: A TRIAL OF THE ECOG-ACRIN RESEARCH GROUP (E4412: ARMS A-I)

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Background: E4412 is a Phase 1/2 ECOG-ACRIN sponsored study of the combinations of brentuximab (BV), nivolumab (N), and ipilimumab (I) in patients with R/R HL. Here we present the long-term safety and response data on the full cohort of patients treated in Phase 1 (Arms A-I).
Methods: Patients with confirmed R/R HL were treated in sequential dose escalation cohorts using 3+3 design. Additional patients were enrolled in expansion cohorts. Dose limiting toxicity (DLT) was evaluated within the first cycle of therapy.
Results: Between March 7, 2014, and Dec 28, 2017, 64 patients were enrolled; 3 patients were excluded due to ineligibility after enrolment. Thirty-five patients (57%) were refractory to their prior therapy; twenty-one (34%) had autologous stem cell transplant (SCT), 4 (6%) had prior alloSCT. Eight patients (13%) had prior BV. Safety: All 64 enrolled patients are included in the safety analysis. The most common (>30%) treatment-related grade 1–2 AEs were: nausea, peripheral sensory neuropathy, diarrhea, fatigue, elevated liver transaminases, anemia, and rash. Grade 3+ rash was more common in BV-I, in 22% of 23 patients compared with 7% of 41 patients in the other groups. Grade 3–4 events occurred in ten (43%) patients on BV-I, three (16%) patients on BV-N, and 12 (55%) patients in the triplet group. Two (3%) patients had treatment related death, one on BV-N (pneumonitis) and one in the BV-N-I group (dyspnea).
Response: The overall response rate (ORR) was 76% for BV-I, with a complete remission (CR) rate of 57%, for BV-N the ORR was 89% with a CR rate of 61% and for BV-N-I the ORR was 82% with a CR rate of 73%. The median follow-up (Q1, Q3) for PFS and OS is 2.24 (1.67, 2.72) years and 2.98 (2.83, 3.04) years. Duration of response (DOR) is 1.32 years for BV-I responders, not reached for BV-N and BV-N-I responders (Figure 1A). The median PFS is 1.1 years, NR, and 2.49 years

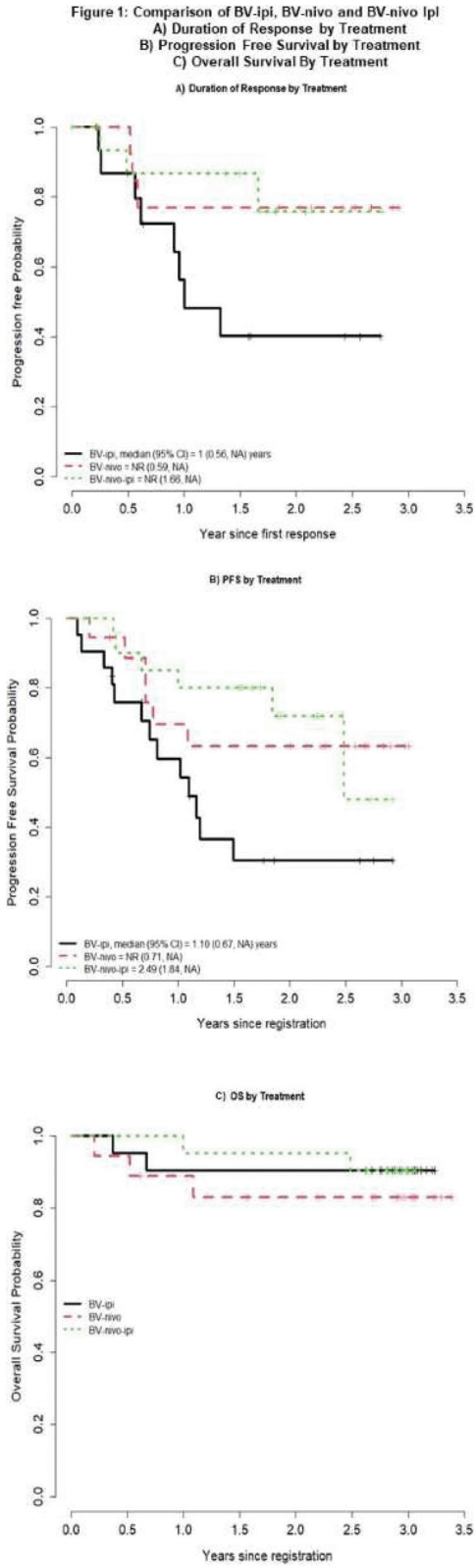

Figure 1: E4412 Response: DOR (A), PFS (B), OS (C)

for BV-I, BV-N and BV-N-I respectively (Figure 1B). The median OS has not been reached for any of the arms (Figure 1C).
Conclusion: Long term data from the Phase 1 component of E4412 shows no late safety concerns, and significant durability of response in both N containing arms with median follow-up of nearly 3 years. Analysis of the impact of transplant and depth of response will be updated by the time of the meeting. Optimization of this strategy is ongoing in E4412, now a randomized phase 2 study comparing the doublet of BV-N to the triplet of BV-N-I.

P101: COMBINATION OF IMMUNE CHECKPOINT INHIBITORS WITH BEGEV IN THE TREATMENT OF PATIENTS WITH RELAPSED AND REFRACTORY CLASSICAL HODGKIN'S LYMPHOMA.

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Introduction: Given the wide range of effectiveness of various high-dose chemotherapy regimens in patients with r/r HL, the lack of a unified treatment protocol, an active search is currently underway for the place and sequence of using new classes of drugs and their combination with classical chemotherapy.
Objective: Analysis of treatment effectiveness and toxicity in patients with r/r cHL according to the BeGEV regimen in combination with nivolumab at a fixed dose of 40 mg.
Materials and Methods: Since 2019 we conducted a pilot multicenter prospective study for r/r cHL patients - candidates for auto-HSCT. By 2022, 35 patients were included. The treatment protocol consisted of 2 cycles of chemotherapy according to Nivo40-BeGEV scheme (vinorelbine 20 mg/m2 on day 1, dexamethasone 20 mg/m2 on days 1–5, gemcitabine 800 mg/m2 on days 1 and 4, bendamustine 90 mg/m2 on days days 2 and 3, nivolumab 40 mg IV on day 0) with further assessment of response by PET/CT. When a complete metabolic response was achieved, an additional one course of chemotherapy Nivo40-BeGEV was performed and then auto-HSCT (BeEAM) was held. If a partial remission after 2 cycles of chemotherapy and a complete remission after 4 cycles has not been achieved, the patient was excluded from the treatment protocol.
Results: Treatment according to the Nivo40-BeGEV regimen was completed in 35 patients. All patients achieved complete remission, most after 2 cycles - 34/35 (97.1%). Effective mobilization of HSC and auto-HSCT was performed in 30/34 (85.7%) patients. Complete remission of r/r cHL is maintained in 33/35 (94.2%) patients with a follow-up of 1–34 months, and 2/35 (5.7%) patients had an early relapse of the disease. EFS and OS were 95% and 100%, respectively, with a median follow-up of 13 months. Infectious, immune complications grade III-IV were not detected. Hematological toxicity grade III-IV has been observed in 3/35 (8.5%) patients.
Conclusion: The combination of nivolumab at a fixed dose of 40 mg with chemotherapy BeGEV has demonstrated high efficacy and the absence of severe adverse eventes in patients with r/r cHL.

P102: COMPARISON OF NOVEL SALVAGE REGIMENS AND TRADITIONAL SALVAGE CHEMOTHERAPY IN RELAPSED AND REFRACTORY CLASSIC HODGKIN LYMPHOMA

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Background: Novel agents such as brentuximab vedotin (BV) and checkpoint inhibitors (CPIs) have high response rates in patients with relapsed/refractory (r/r) classical Hodgkin Lymphoma (cHL) and have recently been used as salvage regimens to induce remissions before autologous stem cell transplant (ASCT). Our aim was to compare the outcomes of pts receiving salvage chemotherapy (CT) as opposed to novel treatments (NT) for their first salvage regimen for r/r cHL since limiting data exists regarding their efficacy.
Methods: Adult pts with r/r cHL who received their first salvage regimen (SR1) between January 2018 and June 2020 were retrospectively identified. Endpoints were to compare complete response (CR), overall response rate (ORR), and event free survival (EFS) between the CT and NT cohorts.
Results: 120 pts were identified with a median age of 33 years (range 18–85). 68% had advanced disease and 13% were early stage unfavorable at diagnosis. Many pts had poor prognostic characteristics including 43% with primary refractory disease, 52% with relapse <12 months from diagnosis, 38% with extranodal disease, and 26% with B-symptoms at time of relapse (Table 1).
65% of pts (n=78) received CT and 35% (n=42) received NT for SR1. 90% of CT pts received Ifosfamide, Carboplatin, and Etoposide (ICE) as SR1. Regimens used for NT treated pts included BV + Bendamustine (43%), BV alone (36%), BV + CPI (12%), BV + CT (5%), and other CPI (4%). No significant difference was found in the ORR and CR rates according to pts treated with CT vs. NT of 67% vs. 69% and 47% vs. 55%, respectively. 88% of those who received CT for SR1 and 83% of those who received NT for SR1, eventually had ASCT. At a median follow-up of 32 months, 1-year EFS was 57% vs 69% and 2-year EFS was 56% vs 66% between CT and NT cohorts (p=0.25) (Figure 1).
All pts who progressed after CT for SR1 (n=31) received NT for SR2; whereas 73% (n=11) of those progressing after NT for SR1 received CT for SR2. ORR for CT in SR2 was 91% vs 70% for NT (p=.48). 79% vs 89% remained progression-free post-ASCT at their last follow-up after receiving CT vs. NT at last salvage before ASCT respectively (p=0.15).

Table 1: Baseline Characteristics		All Patients		Chemotherapy for SR1		Novel Agents for SR1		
		N	%	N	%	N	%	p
		120		78	65%	42	35.0%	
Age	<45	85	70.8%	61	78.2%	24	57.1%	0.015
	>45	35	29.2%	17	21.8%	18	42.9%	
Primary Refractory Disease		52	43.3%	33	42.3%	19	45.2%	0.453
Relapse w/in 12 months		62	51.7%	41	52.6%	21	50.0%	0.469
Extranodal Sites at relapse		45	37.5%	29	37.2%	16	38.1%	0.537
ORR (CR+PR)		81	67.5%	52	66.7%	29	69.0%	0.478
CR		60	50.0%	37	47.4%	23	54.8%	0.809
2-year EFS		120	60.0%	78	56.0%	42	66.0%	0.251
Salvage Lines Received	1	74	61.7%	47	60.3%	27	64.3%	0.59
	>/=2	46	38.3%	31	39.7%	15	35.7%	
ASCT		104	86.7%	69	88.5%	35	83.3%	0.671
Response Before ASCT*								
	CR	77	74.0%	40	70.2%	37	78.7%	0.281
	<CR	27	26%	17	30%	10	21%	
* Based on last salvage before transplant								

Table 1: Baseline Characteristics of CT and NT cohorts

Figure 1:

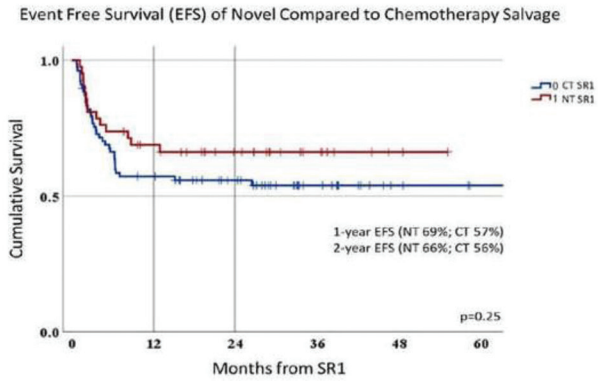

Figure 1: Comparison of EFS between CT and NT cohorts

Conclusion: There was a numerical trend towards better CR and EFS for novel therapy compared to traditional chemotherapy for first salvage, however the outcomes were not statistically significant, demonstrating that chemotherapy is still a valid option for salvage before ASCT.

P103: COMPARISON OF PET-DERIVED PARAMETERS IN PROGRAM CELL DEATH-1 INHIBITOR AND CD30 ANTIBODY DRUG CONJUGATE-BASED THERAPIES IN PATIENTS WITH ADVANCED STAGE CHL: A SINGLE CENTER EXPERIENCE.

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Background: Advanced-stage classical Hodgkin's lymphoma (cHL) is a curable malignancy, however up to 25% of patients may relapse following frontline multiagent-chemotherapy. Novel treatment options such as PD-1 inhibitors and antibody-drug conjugates (ADC) have demonstrated high efficacy with favorable safety profiles in frontline and relapsed cHL. Early reduction in volumetric and metabolic PET parameters have been reported as effective predictors of outcome in cHL. Here, we describe the changes in metabolic tumor volume (MTV), total lesion glycolysis (TLG), and maximum standardized uptake value (SUVmax) after two cycles of therapies containing nivolumab, brentuximab vedotin (Bv), or both in advanced cHL.
Methods: We retrospectively enrolled subjects with newly diagnosed, advanced stage cHL who received therapy in three protocols: Bv-nivolumab-AD, Bv-AVD, or nivolumab-AVD. All protocols did not allow for radiation consolidation. Baseline (PET0) and interim PET after two cycles (PET2) were analyzed and cHL lesions were segmented using a threshold of 41% of the SUVmax. MTV, TLG, and SUVmax were recorded at both time-points and percentage changes were calculated as ΔMTV, ΔTLG, and ΔSUVmax, respectively. Summary statistics were reported, and Kurskal-Wallis test was used to compare PET-parameters among the groups with $P<0.05$ considered statistically significant.
Results: A total of 27 subjects were included in the final analysis. Subjects were treated with Bv-nivolumab-AD (n=16), Bv-AVD (n=5) and nivolumab-AVD (n=6). The distribution of MTV, TLG, and SUVmax values at PET0 and PET2 were not significantly different across the three groups. The median (IQR) ΔMTV of all study subjects was 100% (99.2%–100%), ΔTLG 100% (99.69%–100%) and ΔSUVmax 100% (68.1%–100%). Initial observation suggested that subjects receiving nivolumab-AVD had less tumor burden reduction rate compared to Bv-nivolumab-AD and Bv-AVD groups. However, this difference was not statistically significant (P=0.10) (Table 1)

Table 1: Patient characteristics and PET-derived parameters

A) Patient characteristics			
Therapy group	Bv-nivolumab-AD (16/27) †	Bv-AVD (5/27) §	Nivolumab-AVD (6/27) ¶
Age median (range, y)	36 (19-56)	33.8(20-50)	40 (21-50)
Gender (M, F)	7,9	1,4	4,2
Stage (n)	IIB (11), III (1), IV (4)	IV (5)	IIB (3), IV (3)

B) Median (interquartile range) for PET-derived parameters across therapy groups				
Therapy group	Bv-nivolumab-AD (16)	Bv-AVD (5)	Nivolumab-AVD (6)	P-value
MTV0	100.4 (46.19-136.1)	201.22 (124.8-239.24)	143.8 (103.5-233.4)	0.12
TLG0	787.3 (339.65-1177.22)	1457.53 (633.66-1891.2)	1123.54 (736.28)	0.12
SUVmax0	15.62 (12.73-18.52)	15.42 (12.8-16.5)	18.01 (14.02-20.17)	0.53
Δ MTV %	100 (99.95-100)	99.34 (99.22-100)	99.72 (75.1-100)	0.36
Δ TLG %	100 (99.97-100)	99.71 (99.69-100)	99.88 (90-100)	0.36
Δ SUVmax %	100 (92.6-100)	68 (64.85-100)	88.69 (20.38-100)	0.18

AVD: Doxorubicin, Vinblastine, and Dacarbazine, Bv: Brentuximab vedotin, IPS: International prognostic score, MTV: Metabolic tumor volume, SUV: standardized uptake value, TLG: total lesion glycolysis.
§ Subjects on the brentuximab-AVD were treated as per Echelon 1 protocol for 6 cycles with a growth factor. ¶ Subjects on nivolumab AVD were treated on Checkmate 205D protocol. † Subjects on nivolumab brentuximab AD were given nivolumab 240 mg and brentuximab 1.2 mg per m2 with AD every 2 weeks

Table 1: Patient characteristics and PET-derived parameters

Conclusion: This is the first report to describe PET-derived metabolic changes in advanced stage cHL patients receiving nivolumab and/or Bv-based regimens. Our initial results suggest a significant and comparable reduction in MTV, TLG, and SUVmax among the three treatment groups. The limited sample size did not confirm an initial observation of higher reductions in patients receiving Bv-based strategies. Future studies are needed to further explore and validate these findings.

P104: CONSOLIDATION THERAPY WITH BRENTUXIMAB VEDOTIN AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA IN THE CZECH REPUBLIC.

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Introduction: Consolidation therapy with brentuximab vedotin (BV) following autologous stem cell transplantation (ASCT) has demonstrated improved progression-free survival (PFS) in high-risk patients (pts) with relapsed/refractory classic Hodgkin lymphoma (cHL) in the AETHERA trial. We have analysed data from seven centres of intensive haematological care in the Czech Republic between January 2015 and December 2021 based on real-life experience with the treatment. The primary goals included basic statistical decription, assessment of the PFS and toxicity of the treatment.
Patients and Methods: All of the pts were treated with high-dose chemotherapy and ASCT in the first relapse, all had at least one of the risk factors as per AETHERA and no previous treatment with BV. We have analysed 39 pts treated with BV 1.8 mg/kg i.v. every 3 weeks for a maximum of 16 cycles.
Results: Median age was 37 years (range 19–65) at the time of the first dose of BV. Nearly 80% of pts were initially treated as advanced stage cHL and eBEACOPP was administered in 59% of pts in the frontline setting. Primary refractory or early relapsed (within 12 months after the frontline therapy) cHL pts represented 69% of the analysed cohort. Two different salvage regimens were administered in 30.8% and failure to achieve a complete response (CR) after salvage chemotherapies prior ASCT was seen in 64% of pts. The median number of BV administered was 8 (1–16), with 16 completed cycles in 20.5% pts. Main reasons for early discontinuation were neuropathy and relapsed or

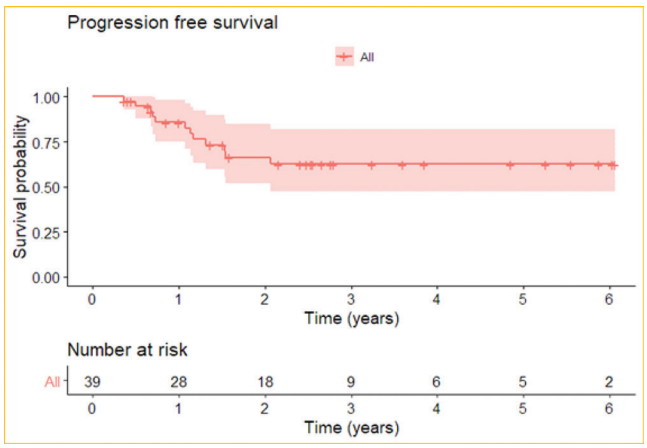

Figure 1: Progression-free survival figure, N=39 pts

progressive disease, both in 15.4%. Overall, 82% of pts achieved CR during the treatment. With a median follow-up 28 months the 2-year PFS was 66.2% (95% CI 0.52–0.85) and the 2-year overall survival was 95% (95% CI 0.82–1.00). Two pts died, one of progressive lymphoma and one of severe bacterial infection. Peripheral sensory neuropathy occurred in 38.5% (grade 3–4 in 10.3%), neutropenia in 28.2% (grade 3–4 in 17.9%) and respiratory infections in 28.5% (grade 3–4 in 2.6%).
Discussion: Despite some differences in the analysed groups, our results are comparable with a few real-world data published lately and support the notion that BV consolidation improves PFS in patients with at least one risk factor for subsequent relapse of cHL and has a feasible and manageable toxicity.

Supported by following grants

MH CZ – DRO (FNOl, 00098892)
AZV NU22-03-00182

P105: DECISIONAL ROLE OF INTERIM PET IN RELAPSED/ REFRACTORY CLASSICAL HODGKIN LYMPHOMA TREATED WITH FOUR BEGEV CYCLES

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Achievement of complete response (CR) before autologous stem cell transplantation (ASCT) is one of the main predictive factors of outcome in patients (pts) affected by relapsed/refractory (R/R) classical Hodgkin Lymphoma (cHL) eligible to high-dose chemotherapy. The predictive role of interim PET during salvage treatment has not been investigated in pts receiving BEGEV (Bendamustine, Gemcitabine and Vinorelbine) as first salvage treatment. With the aim to investigate the predictive value of PET after 2 cycles of BEGEV (PET2) in terms of CR rate and survival in pts who completed 4 BEGEV courses followed by ASCT, we retrospectively collected data of 90 consecutive R/R cHL pts eligible to ASCT treated from 2011 to 2021 in 3 Italian centres. Eleven out of 90 pts were excluded due to BEGEV discontinuation for progressive disease (PD) before or at PET2. Seventy-nine pts who completed the planned 4 BEGEV cycles were analysed: median age at relapse was 37 years (range: 18–70), 39 pts (49%) were in stage III-IV, 13 pts (16%) had B symptoms and 23 pts (29%) had extranodal involvement (EI). Thirty-eight pts (48%) were primary refractory, 21 pts (27%) had an early and 20 pts (25%) a late relapse. PET2 was negative [Deauville Score (DS) 1–3] in 61 (77%) and positive in 18 pts (23%) (DS 4 in 15 pts, DS 5 in 3 pts). Adverse risk factors at relapse (EI, B symptoms and time to relapse) did not correlate with PET2 positivity. At evaluation after 4 BEGEV cycles, CR was achieved in 62 (78%), partial response in 6 (8%) and PD in 11 (14%) pts. Complete response after 4 BEGEV was obtained in 55/61 (90%) PET2 negative pts and 7/18 (39%) PET2 positive pts (OR=14.4, 95% CI 3.8–45.2, p<0.0001). Autologous SCT was performed in 73 pts, following BEGEV in 59 pts (75%) and after further salvage treatments in 14 pts (18%). With a median follow-up of 36 (range: 5–100) months, 3-years overall survival (OS), progression-free survival (PFS) and event-free survival (EFS) for the whole study population were 93%, 72% and 63%. No significant differences in OS and PFS were detected according to PET2 result. Conversely, 3-years EFS was significantly superior in PET2 negative vs PET2 positive pts [71% vs 32%, OR 13.66 (95% CI 3.4–62.1) p<0.0001] (Fig.1). In conclusion, R/R cHL pts with PET2 positive during BEGEV salvage treatment had a significantly inferior probability to achieve CR after 2 additional BEGEV cycles and could benefit from early exposure to new therapeutic strategies before ASCT.

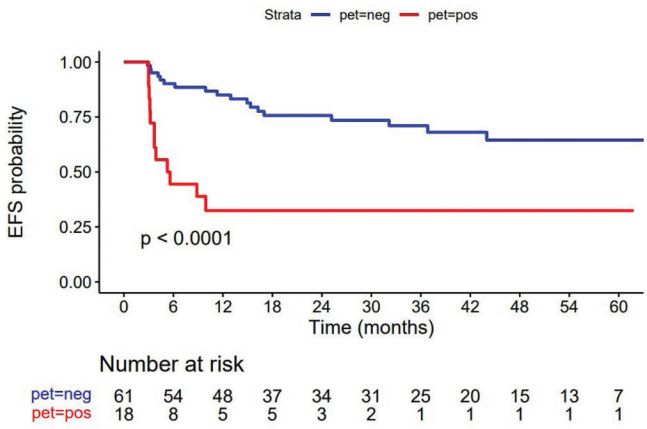

Figure 1: Event-free survival according to PET2 result

P106: DOSE INTENSIVE BRENTUXIMAB VEDOTIN FOR PLATINUM RESISTANT RECURRENT HODGKIN LYMPHOMA IS A FEASIBLE TREATMENT OPTION - A SINGLE CENTER EXPERIENCE

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Since 2013, mainly before the introduction of PD-1 inhibitors, we treated Hodgkin lymphoma (HL) patients failing to respond with a complete metabolic remission (CR) after first salvage treatment with a dose intense regimen of 1.2 mg/kg brentuximab vedotin (BV) given days 1, 8, 15 in a 28-day cycle. Patients achieving CR after one cycle received another cycle and proceeded to high dose chemotherapy (HDCT) with autologous stem cell transplant. Patients not reaching metabolic CR received other treatments.
Ten patients were treated with dose intense BV, five patients with primary refractory disesease/early relapse and five patients with later relapses. First salvage regimens were IME x 2 (1 patient), DHAP 2–4 cycles (5 patients), IME x 2 + 2–4 cycles DHAP (2 patients) and ICE x 2–4 (2 patients).
Of the five patients with refractory disease/early relapse, four patients had satisfactory responses and proceeded to HDCT. One patient progressed and received radiotherapy instead.
Four patients of five with later recurrent disease had satisfactory responses and proceeded to HDCT. For one patient with insufficient response, bendamustine was added to BV 1.8 mg/kg and given in further three cycles before HDCT. One patient with PET-positive disease after ICE x 2 and possibly concurrent tuberculosis was for this reason treated with a PD1-inhibitor for 9 months, progressed, received dose intense BV with good effect and proceeded to HDCT.
In total 8/10 (80 %) responded satisfactorily to dose intense BV.
The patient who was not treated with HDCT later succumbed to the disease, and two patients with late relapses have had new relapses. The rest of the patients are free of recurrence. Consolidative treatment after HDCT was given with radiotherapy in two cases and maintenance BV in another two cases. Median follow up is 67 months after ASCT.
Side effects have been mild, mostly grade 1 neuropathy. For one patient with grade 1–2 neuropathies already on primary treatment with ABVD, dose reduction was made to 90 % in the second cycle of induction BV and to 66% for the six cycles of maintenance BV given. For another patient maintenance BV was stopped after 4 cycles due to grade 2 neuropathy.
Conclusion: According to our experience dose intense BV is an effective and feasible treatment option for HL patients with platinum resistant recurrent disease.
We suggest that this way of using BV should be studied in the context of insufficient response to PD-1 inhibitors pre-HDCT.

P107: EFFECT OF BRENTUXIMAB VEDOTIN ADDITION TO CHEMOTHERAPY AND PROGNOSTIC FACTORS IN PATIENTS WITH RELAPSED/REFRACTORY HODGKIN LYMPHOMA: A LARGE MULTI-TRIAL ANALYSIS BASED ON INDIVIDUAL PATIENT DATA

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Background: The aims of this study were to investigate the effect of brentuximab vedotin (BV) addition to salvage chemotherapy compared to chemotherapy alone on progression free survival (PFS), overall survival (OS) and complete metabolic response (CMR) rate prior to autologous stem-cell transplant (ASCT), and to identify prognostic factors in patients with a first relapse or primary refractory classical Hodgkin lymphoma (R/R cHL).
Methods: We collected individual patient data of 770 transplant eligible R/R cHL patients treated in prospective clinical trials, of whom n=386 were treated with BV and chemotherapy (BV-cohort), and n=384 with chemotherapy alone (Chemo-cohort), followed by ASCT [Fig1A]. The BV- and Chemo-cohorts were matched by propensity scores on baseline characteristics (i.e. relapsed/refractory, bulky disease, extranodal disease, stage I-II/III-IV, B symptoms and first-line treatment with BEACOPP). Matching was repeated 2000 times as internal validation and mean results are presented. Primary refractory disease was defined as no complete response on first-line treatment.
Results: After matching, there were no statistically significant differences in baseline characteristics between the cohorts [Fig1B]. The 3-year PFS was 73% (95%CI: 67–79%) in the BV-cohort compared to 67% (61–74%) in the Chemo-cohort (p=0.14) [Fig1C] and the 3-year OS was 93% (89–96%) versus 80% (75–86%) (p<0.001), respectively [Fig1D]. Primary refractory patients did not show any difference in PFS between the BV- and Chemo-cohorts (p=0.78), while patients with relapsed disease showed a significantly higher PFS in the BV-cohort (p=0.037) [Fig1E+F]. Logistic regression showed a significantly higher CMR rate for the BV-cohort compared to the CMR rate after BeGEV or ICE only (71.2% versus 63.1%; p=0.021), but there was no significant difference when compared to ICE-GVD (71.2% versus 76.4%; p=0.43). Cox regression for 3-year PFS showed high prognostic value for not achieving a CMR pre-ASCT (HR 2.0; p=0.002), stage III/IV (HR 2.0; p<0.001), B-symptoms (HR 1.8; p<0.001) and primary refractory disease (HR 1.7; p<0.001).
Conclusions: The addition of BV to salvage chemotherapy followed by ASCT seems to increase PFS in relapsed, but not in primary refractory cHL patients. This suggests that in patients who are chemotherapy resistant other treatment modalities, such as checkpoint inhibitors (CPI), should be considered.

A)

Cohort	Study	N	Regimen
BV (n=386)	Kersten, 2020	65	BV-DHAP
	Garcia-Sanz, 2019	66	BV-ESHAP
	Broccoli, 2019	40	BV-Benda
	LaCasce, 2018	55	BV-Benda
	Cole, 2018	39	BV-Gem
	Herrera, 2017	57	BV-ICE (seq)
	Moskowitz, 2017	64	BV-ICE (seq)
Chemo (n=384)	Moskowitz, 2012	98	ICE-GVD (seq)
	Jostings, 2010	227	DHAP
	Santoro, 2016	59	BeGEV

B)

	BV (N=240)	CHEMO (N=240)	Total (N=480)	P val
Female sex	53%	55%	54%	0.58
Age, median (range)	31 (5-66)	33 (18-72)	32 (5-72)	0.10
Primary refractory	32%	32%	32%	1.00
Extranodal disease	42%	41%	41%	0.93
Primary treatment = BEACOPP	6%	8%	7%	0.46
B symptoms	29%	23%	26%	0.20
Stage III/IV	52%	53%	53%	0.98
Bulky disease	41%)	38%	39%	0.47

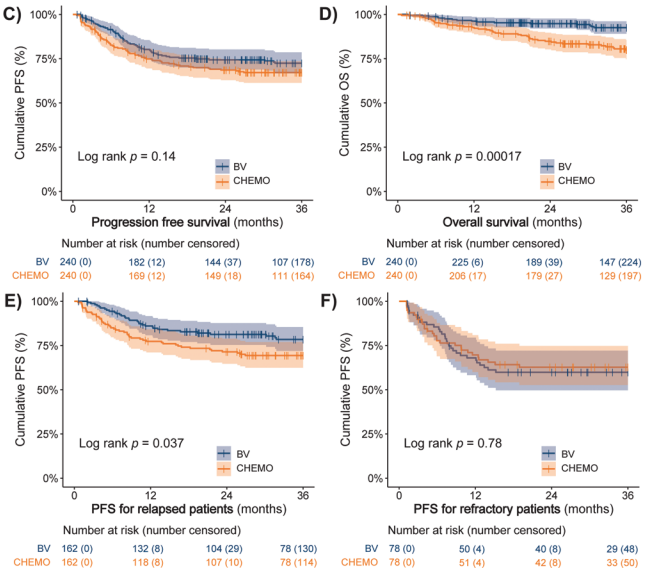

Figure 1: Overview of included studies, patient characteristics of the matched cohort and Kaplan-Meier results of progression free survival and overall survival analysis in the matched cohort.

P108: INTEGRATING BASELINE CIRCULATING TUMOR DNA WITH INTERIM PET IMPROVES OUTCOME PREDICTION IN RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA

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Background: Reliable biomarkers for early identification of treatment failure for relapsed/refractory (r/r) cHL are lacking. In this scenario, circulating tumor DNA (ctDNA) profiling may guide rational treatment choice.

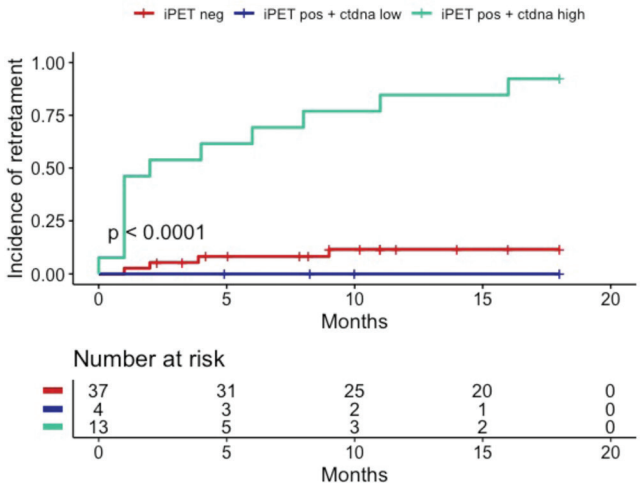

Figure 1: Cumulative event rate of retreatment according to partitioning analysis categories.

Aim: We performed a retrospective analysis in r/r cHL patients treated with the BEGEV regimen to assess the predictive efficacy of baseline ctDNA quantification. Additionally, we evaluated whether integrating ctDNA genotyping with interim positron emission tomography (iPET) may improve outcome prediction.
Methods: 54 patients with r/r cHL treated with 4 cycles of BEGEV followed by autologous (auto) or allogeneic (allo) stem cell transplantation (SCT) were included in the study. Response was assessed by iPET after 2 cycles; complete response was defined as a Deauville Score (DS) of 1–3. Blood samples collected at baseline were profiled by CAPP-Seq. We performed partitioning analysis to evaluate the predictive value of baseline ctDNA load combined with iPET, assessed by need for further therapy within 18 months from BEGEV initiation.
Results: In response to first-line therapy, 65% of patients were refractory. BEGEV was administered as second-line therapy in 61% of patients whereas 39% received BEGEV beyond second line. After induction, 54% of patients underwent auto-SCT and 24% proceeded to allo-SCT. The median baseline ctDNA value reported as haploid genome equivalent per ml (hGE/ml) was 39 (range, 4–5086), with ctDNA detected in PD patients being significantly higher as compared to CR patients (P=.0002). 31% of patients were iPET positive (DS 4/5), while 69% were negative. Baseline ctDNA predicted need for retreatment with an accuracy rate of 81% (sensitivity 63%, specificity 89%). iPET predicted the need for retreatment with similar accuracy rate (83%) and specificity (87%), but with a higher sensitivity (75%). Integrating baseline ctDNA and iPET resulted in an increased predictive value (accuracy rate 89%, sensitivity 75%, specificity 95%). Based on the results of the partitioning analysis, patients with positive iPET and high baseline ctDNA (>31 hGE/ml) showed a significantly inferior 18-months treatment-free survival with 92,3% (95% CI 84.9–99.7) of patients in this category requiring additional treatment (p<0.0001) (Fig 1).
Conclusion: Patients with high baseline ctDNA and positive iPET have a limited benefit from completing the BEGEV regimen. Early switch to non-chemotherapeutic agents should be evaluated in prospective trials.

P109: ONE-DAY BRENTUXIMAB-BENDAMUSTINE (120MG/M2) EVERY 21 DAYS IS A FEASIBLE AND SAFE TREATMENT FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA

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Brentuximab(1.8 mg/kg day 1) plus Bendamustine (90mg/m2 day 1 and 2) every 28 days is a new therapeutic combination for relapsed/refractory (R/R) Hodgkin lymphoma (HL), mainly as salvage therapy and bridge to autologous stem-cell transplantation (ASCT) but is associated to high toxicity. We conducted a retrospective study in St Louis Hospital in Paris between 2015 and 2021 to assess the feasibility and tolerance of one-day Brentuximab-Bendamustine (120mg/m2) every 21 days for R/R HL.
All patients for whom one-day Brentuximab-Bendamustine (120mg/m2) every 21 days was prescribed between 2015 and 2021 were identified from the Chimioweb platform and medical data were collected from Middlecare software. Characteristics of population were detailed. Feasibility and toxicities were reported. Progression-free survival (PFS) and overall survival (OS) were calculated.
Three patients were excluded (one in complete response at beginning, one who refused therapy and one lost to follow-up with second cancer). Forty-three patients were included, with a median age of 45 years old (19 to 76) at time of treatment. Relapse or progression was of advanced stage for 63% of patients and occurred after a median of 2 former lines. Sixteen patients (37%) had only one line before. Eleven (26%) patients already had an ASCT and 2 (5%) an allogenic stem cell transplantation. Twenty-seven patients (63%) and 12 (28%) had respectively a relapsed or refractory HL. Four patients (9%) had a secondary HL.
A median of 5 cycles was administered. For 32 patients (74,4% [95%CI, 74 to 74,8]) treatment was conducted until its end and did not need any adaptation for toxicity. Main causes of adaptation were anaphylaxis (7%), neutropenia (2%), infection (2%) and peripheral neuropathy (2%). Anaphylactic reactions occurred in 16 patients (37%), of which one was grade 3 and no grade 4. For 8 of these patients (50%), reaction was resolved after prescription of pre-medication.
Grade 3–4 neutropenia and thrombocytopenia occurred in respectively 3 (7%) and 2 (5%) patients. Only one febrile neutropenia was reported.
After treatment, overall response rate was of 84%, with 31 (72%) complete responses, 5 (12%) partial responses, 1 (2%) stable disease and 5 (12%) progressive diseases.
We suggest that one-day Brentuximab-Bendamustine (120mg/m2) ever 21 days is a safe and feasible treatment for R/R HL. Main limiting toxicity was anaphylactic reaction, which was well managed with premedication.

P110: OUTCOME OF HIGH-DOSE CHEMOTHERAPY (HDCT) AND AUTOLOGOUS STEM CELL TRANSPLANT (ASCT) AS FIRST SALVAGE TREATMENT FOR RELAPSED OR REFRACTORY CLASSICAL HODGKIN LYMPHOMA (CHL) IN THE ERA OF PET-ADAPTED STRATEGY AMONG ITALIAN CENTERS

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Background: HDCT+ASCT is still considered the standard of care for patients (pt) with cHL failing first-line treatment(FT). However data on the efficacy of HDCT+ASCT in the era of PET-driven strategy are limited.
Aim of study: To evaluate the outcome and prognostic factors of ASCT as first salvage treatment in pt failing or relapsing after FT.
Methods: We performed a retrospective observational multicenter study on individual data of pt who underwent ASCT from 2009 to

Figure 1: 3-year Progression-free Survival according to response to front-line therapy

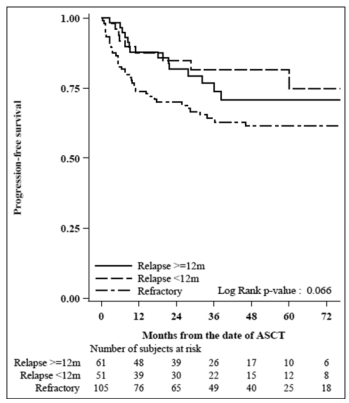

Figure 1: According to response to FT, patients with late relapse vs early relapse vs refractory disease had 3-yr PFS of 77% (95%CI, 63–86) vs 82% i(95%CI, 66–91) vs 64% (95%CI, 54–73)

2021 at 11 participating centers in Italy. Study endpoints were: clinical characteristics at relapse or failure, overall response rate (ORR) and complete remission (CR) to first salvage therapy (ST), number of ST before ASCT, disease-status at ASCT, 3-yr progression-free survival (PFS) and overall survival (OS) calculated from the date of ASCT, factors associated with ASCT outcome evaluated by univariate and multivariate analysis.
Results: 217 evaluable pt were enrolled; 32% of them had a positive PET-2 (PET2+) after the firs 2 cycles of ABVD and 66% switched from ABVD to intensified therapy. Main pt characteristics at relapse or progression after FT were: median age 34 years (range, 18–68), stage III/IV 46%, B symptoms 25%, bulky 4%, extranodal disease 29%, anemia 13%, ECOG PS ≥2: 9%; refractory disease (failure to achieve CR with FT or relapse ≤3 months) 48%, early relapse (< 12 months from FT end) 24%, late relapse (≥12 months from FT end) 28%. Before ASCT, 53% pt received 1, 31% 2 and 16% received ≥3 ST lines. After first ST line, ORR was 65% and mCR 45%. Overall, 67% pt underwent ASCT in CR (98% of them in mCR), 22% in partial response (PR) and 11% with stable or progressive disease. After a median follow up of 42 months (IQR,24–66) 3-yr PFS and OS were 72 (95%CI, 65–77) and 90% (95% CI, 84–93), respectively. Figure 1 shows 3-yr PFS according to response to FT. According to disease status at ASCT and number of ST lines, 3-yr PFS was significantly better for pt in CR compared to their counterpart (HR 1.79, p=.039), and for pt receiving ≤ 2 vs > 2 lines ST (HR 2.52; p=.002). PET2+ during FT was associated with a higher risk of salvage ASCT failure (HR 2.43, p=.002).
Conclusions: HDCT+ASCT is an effective salvage approach for pt failing a PET-guided FT, even for those with primary refractory disease. Receiving ≤2 ST lines and being in CR at ASCT confers the most favorable outcome, whereas a PET2+ in the FT seems an early unfavorable redictor for subsequent salvage ASCT procedures.

P111: PHASE I TRIAL OF BRENTUXIMAB VEDOTIN PLUS CYCLOSPORINE IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA

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Treatment of relapsed/refractory (R/R) Hodgkin lymphoma (HL) following failure of brentuximab vedotin (BV) and PD-1 blockade is a major unmet need. Resistance to BV is associated with multidrug resistance gene 1 (MDR1) overexpression. MDR1 inhibitors cyclosporine (CsA) or verapamil (VRP) can re-sensitize cHL to BV. We previously reported preliminary results of a phase I study of BV combined with CsA in R/R HL. Here we report the final results of the completed study.
This is a single center, open-label phase I study. The dose finding portion followed a 3+3 design with 4 planned dose levels (DL). BV was given at 1.2 mg/kg (DL1) or 1.8 mg/kg (DL2-4) intravenously every 3 weeks. Planned dose of CsA was 5 mg/kg (DL1-2) or 7.5 mg/kg (DL3-4) orally twice daily on days 1–5. Planned dose of VRP was 120 mg orally four times daily on days 1–5 (DL4). Each cycle was 3 weeks. Once the maximum tolerated dose (MTD) was determined, BV-refractory pts were enrolled in an expansion cohort at the MTD. Primary objective was to determine the MTD and safety of the combination. Secondary objectives were overall response rate (ORR), complete response (CR) rate, response duration (DOR), overall survival (OS), and progression-free survival (PFS).
29 pts (14 dose-finding, 15 dose-expansion) were enrolled. Median age was 36 (20–69) and pts had a median of 5 (3–12) prior lines of therapy. All had prior BV (only 2 BV-sensitive) and 27 had prior PD-1 blockade. Four pts were treated on DL1, 22 on DL2, 3 on DL3. MTD was DL2. DLTs observed were: DL1 10-day CsA (n=1) grade (Gr) 3 hyperbilirubinemia, abdominal pain, and hypertension, DL2 (n=1) Gr3 abdominal pain and Gr3-4 neutropenia, DL3 (n=2) Gr3 bone pain/constipation/Gr4 lymphopenia (n=1) and Gr3 hyperglycemia (n=1). Median duration of treatment was 3 (1–16) cycles. Most frequent adverse events (AEs) were nausea (90%), hypertension (90%), anemia (86%), fatigue (76%), neutropenia (76%), and leukopenia (76%). All pts had Gr3+ AEs with most frequent being neutropenia (62%). Reasons for treatment discontinuation included death (n=4), disease progression (n=10), and toxicity (n=2). Treatment-related death occurred in 3 pts (pneumonitis at DL1, respiratory failure and hypotension at DL2). The ORR/CR was 62%/24%. The median DOR and PFS was 5 months and median OS was not reached.
BV + CsA was effective in BV-refractory R/R HL but was also associated with toxicity leading to early study termination.

P112: PHASE II TRIAL OF BRENTUXIMAB VEDOTIN PLUS IBRUTINIB IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA

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Background: Brentuximab vedotin (BV) is an antibody-drug conjugate and is highly effective in relapsed/refractory (r/r) Hodgkin lymphoma (HL). Although most patients respond to BV, only a minority will obtain a complete response (CR), and almost all patients eventually progress.
Ibrutinib (Ibr) is a Bruton tyrosine kinase (BTK) inhibitor active in multiple subtypes of non-Hodgkin lymphoma. Limited data exist regarding its use in HL, but malignant Reed-Sternberg cells can express BTK. Ibr also inhibits IL-2-inducible kinase (ITK) with Th1 based responses which may promote immunogenic cell death in combination with BV. As we previously observed preclinical synergy between Ibr and BV, we hypothesized Ibr may enhance the antitumor activity of BV in HL. We conducted a phase II trial of Ibr plus BV in patients with r/r HL and report here the final primary analysis of safety and efficacy.
Methods: This was a multicenter phase II trial with a 6 patient safety lead-in cohort of BV and Ibr in patients with r/r HL. Eligibility included age > 15 years with r/r HL after at least one prior line of therapy. Prior BV was allowed if patients were not refractory. Treatment consisted of 1.8 mg/kg BV intravenously every 3 weeks and Ibr 560 mg oral daily (420 mg in the lead-in cohort). The primary endpoint was CR rate according to Lugano 2014. Secondary endpoints included toxicity, overall response rate (ORR), and duration of response (DOR).
Results: 39 patients were enrolled; 67% were male and median age was 33. At initial diagnosis 40% had stage III-IV disease and 38% had extranodal disease. 51% were refractory to most recent therapy, and 21% had prior BV. Of 36 evaluable patients, CR rate was 33%, ORR 64%, and median DOR 25.5 months (range); median number of cycles received was 5. Most common adverse events of any grade were nausea (67%), diarrhea (59%), peripheral neuropathy (62%), fatigue (46%), thrombocytopenia (46%), headache (41%), rash (41%), elevated ALT (38%), anemia (36%), vomiting (36%), abdominal pain (33%), fever (33%), and hypertension (33%). 6 (%) patients experienced unacceptable toxicity, defined as Gr 3/4 non-hematologic toxicity or non-resolving Gr 3/4 hematologic toxicity including one patient who died of sepsis during cycle 1.
Discussion: The combination of BV and Ibr had similar efficacy to BV monotherapy in patients with r/r HL, but with additional toxicity compared to BV alone.

P113: PROMISING RESULTS WITH ANTI-PD-1 THERAPY IN PRIMARY REFRACTORY HODGKIN LYMPHOMA: A SINGLE-CENTRE REPORT

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Background: Salvage chemotherapy (CHT) followed by autologous stem cell transplant (ASCT) is considered the standard of care for classical Hodgkin lymphoma (cHL) patients who are primary refractory (PrRef) to first line treatment. However, among the few studies based solely on PrRef cHL cases, it has been reported that this strategy leads to a sustained complete response (CR) in almost a half of PrRef patients (pts). Furthermore, Horning et al. reported an overall survival (OS) of 50% at a median follow up of 42 months in a cohort of 29 PrRef pts. Although it is conventionally believed that chemorefractory pts are poor ASCT candidates, recent studies reported promising results in terms of response rate and survival among PrRef cases receiving anti-PD-1 salvage treatment and subsequent ASCT.
Methods: We retrospectively collected 9 consecutive PrRef cHL pts who did not respond to salvage CHT and brentuximab-vedotin (BV) and were treated with pembrolizumab monotherapy as fourth-line. Pts defined as PrRef were those who did not achieve a durable (>90 days) CR at the end of first line therapy or those with a Deauville score of 5 (DS 5) at interim PET (PET-2).
Results: The majority of pts were male (67%). Systemic symptoms were reported in 56% of cases. Stage at the onset was 2 in 5 cases and 3 and 4 in 2 pts each. An unfavourable prognostic score was seen in 75% of pts. Nodular sclerosis was the predominant histological variant (67%); LMP-1 was positive in 2 out of 7 evaluable cases. The median number of cycles of pembrolizumab administered was 6 (range, 2 to 9). After anti-PD-1 therapy, 75% pts obtained a CR and 25% a partial response (PR). Seven pts underwent ASCT subsequently to pembrolizumab: among these, 87% pts achieved a metabolic CR and 14% a PR at the pre-ASCT PET scan. Disease evaluation after ASCT showed a CR in 100% of cases. After a median follow-up time of 40.3 months (interquartile range: 20.4–54.7 months) from first-line treatment failure, all pts still maintain a CR.
Conclusion: If compared to similar series of PrRef cases reported in literature, our experience using pembrolizumab before ASCT resulted in successful outcomes in terms of quality and duration of response in this difficult-to-treat subset of cHL pts.

P114: VERY LATE RELAPSES IN PATIENTS WITH HODGKIN LYMPHOMA OCCURING ≥5 YEARS AFTER INITIAL TREAMENT WITH CHEMOTHERAPY ± RADIOTHERAPY: TREATMENT STRATEGIES AND PROGNOSTIC FACTORS FOR THE OUTCOME

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Background: Despite the excellent long-term outcome of patients with Hodgkin Lymphoma (HL) some patients will eventually relapse, mainly within the initial 2 years from diagnosis. Typically the disease is considered cured after a 5-year continuous first complete remission. However, Very Late Relapses (VLRs), occurring≥5 years after treatment initiation, are non-negligible and possibly consist a patient subgroup with unique characteristics.
Aim: To describe the treatment strategies adopted for patients with VLRs as well as their outcome and search for relevant prognostic factors.
Methods: Patients with HL who experienced VLRs≥5 years after treatment initiation with chemotherapy±radiotherapy, were identified retrospectively from the databases of 6 referral centers. Statistical endpoints were the estimation of Freedom From Second Progression (FF2P), Overall Survival after Failure (O2S) and Disease Specific Survival after Failure (DS2S).
Results: Overall, 137 patients with VLRs were identified. The median age was 49 years (19–82), 69% were males and 19% were ≥65 years old at the time of relapse. In 21% of the patients,relapse occurred >15 years after the initial diagnosis. Reinduction with the same regimen was given in 24% of the patients, and 25% proceeded or were treated with second-line regimen with the intention to proceed to high-dose therapy and autologous stem cell transplantation (HDT/ASCT). The 5- and 10-year FF2P were 57% and 52% respectively, the 10-year O2S was 57% and the 10-year DS2S was 75%. Among 50 deaths, only 28 were disease-related, whereas 22 were attributed to secondary malignancies or unrelated causes. Reinduction with the same regimen did not significantly affect FF2P and O2S. Despite the numerical difference in 5-year FF2P for patients <65 years old who received HDT/ASCT (75% vs 60%), there was no difference at 10 years. In multivariate analysis anemia, extranodal disease and age ≥65 were independent prognostic factors for FF2P, O2S and DS2S. Patients combining 2–3 adverse characteristics had significantly compromised outcome.
Conclusion: The outcome of VLRs does not appear favorable, however a considerable proportion of patients were ≥65 years old at the time of VLR when treatment options are limited and also, many patients succumb to disease-unrelated causes. Treatment approaches were heterogenous and HDT/ASCT was rather underused. In our study anemia,extranodal disease and age≥65 were the most relevant adverse prognostic factors.

Index of Authors