Anti–programmed cell death protein 1–based salvage therapy for relapsed/refractory Hodgkin lymphoma: a multicenter real-world analysis

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Received: August 18, 2025.
Accepted: February 18, 2026.
Early view: February 26, 2026.

https://doi.org/10.3324/haematol.2025.288996

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Abstract

In relapsed/refractory classic Hodgkin lymphoma (r/r cHL), salvage followed by high-dose chemotherapy and autologous stem cell transplantation (HD-ASCT) yields suboptimal outcomes. Programmed cell death-1 (PD-1) inhibitor-based salvage regimens have shown superior complete response (CR) rates of up to 95% (for the P-GVD regimen) with unprecedented progression-free survival (PFS) after HD-ASCT. However, immune checkpoint inhibitors are not approved by the European Medicines Agency in second-line treatment, and European data remain sparse. This retrospective, multicenter analysis included r/r cHL patients who received salvage with intent to consolidation. Responses before and after stem cell transplant consolidation, and PFS and overall survival (OS) were assessed. Forty-seven patients were included (median prior lines: of therapy 2). Salvage regimens were PD-1 monotherapy (N=10), PD-1 + chemotherapy (P-ICE/N-ICE/P-GVD) (N=34), or PD-1 + BV (brentuximab vedotin) (N=3). Overall response (OR)/CR rates were 90.9%/47.7%. OR/CR rates by salvage regimen were: PD-1 monotherapy 80%/10%; PD-1 + chemotherapy, 93.6%/61.3%; PD-1 + BV, 100%/33.3%. With a median follow-up of 16 months, 1-year PFS was 83.9% and OS was 95.6%. In the subgroup of patients who had received one prior line of therapy (N=22), 1-year PFS was 100%. In this real-world cohort, previously reported high CR rates were not reached. However, with the restriction of a limited follow-up, outcomes after HD-ASCT were excellent, supporting the role of PD-1 inhibitor-based salvage followed by consolidative HD-ASCT for r/r cHL.

Introduction

Despite classic Hodgkin lymphoma (cHL) showing high cure rates of up to 90% with first-line therapy,[1] patients with relapsed/refractory (r/r) cHL face an unfavorable prognosis with progression-free survival (PFS) rates below 50% with conventional chemotherapy.[2]

The treatment of this subgroup of patients in the past mainly

consisted of two cycles of traditional polychemotherapy-based regimens, such as ICE (ifosfamide, carboplatin and etoposide)[3] or DHAP (dexamethasone, high-dose cytarabine, and platinum),[4] followed by high-dose chemotherapy (HD) and autologous stem cell transplant (ASCT).[5] In selected cases with localized disease, radiotherapy is applied. As the prognosis of patients with r/r cHL undergoing HD-ASCT is highly dependent on the response prior to HD, the most effective salvage regimens should be used in this setting. In the last decade, immunotherapy using immune checkpoint inhibitors (ICI) has been investigated for several indications.[6] cHL shows high expression of programmed cell death 1 (PD-1) receptor ligands, caused, among other factors, by Epstein-Barr virus infection[7] and amplification of chromosome 9p24.1.[8] There have been several multicenter trials incorporating ICI, with the pivotal monotherapy trials Keynote-087 (NCT02453594)[9] and Checkmate 205 (NCT02181738)[10] showing high response rates in patients with second or higher r/r cHL (Keynote-087: overall response rate [ORR]/complete response [CR] in 69%/22.4%; Checkmate 205: ORR/CR in 69%/16%). These results have established pembrolizumab and nivolumab as effective third-line treatments in otherwise dire cases, leading to approval from both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). While Keynote-204 expanded the FDA indication for pembrolizumab to first relapse, this was not adopted by the EMA.[11] ICI are powerful agents, resulting in sensitization to chemotherapy[12] and to radiotherapy.[13] Thus, combination regimens of ICI and chemotherapy have been investigated not only as part of first-line therapy[14,15] but also incorporated in salvage regimens such as P-GVD (pembrolizumab, gemcitabine, vinorelbine, liposomal doxorubicin), N-ICE (nivolumab, ifosfamide, carboplatin, etoposide) and P-ICE (pembrolizumab, ifosfamide, carboplatin, etoposide) and tested in single-arm phase II trials. Moskowitz *et al*. included 39 patients in a phase II study with P-GVD, achieving an ORR/CR rate of 100%/95% after two to four cycles of treatment.[16] In two other phase II salvage trials, combining ICI with chemotherapy with intent to undergo HD and ASCT, similarly high ORR and CR rates were achieved (P-ICE: Bryan *et al*., N=42 patients, ORR/CR rates of 97.3%/86.5%;[17] N-ICE: Mei *et al*., N= 34, ORR/CR rate 100%/89%[18]). In addition, combination trials of the antibody-drug conjugate brentuximab vedotin with nivolumab in 91 patients showed ORR/CR rates of 85%/67%, with a 3-year PFS of 77%.[19]

More recently, a US real-world cohort study performed by Desai e*t al*. confirmed these phase II results in an analysis of 936 patients, in which 65 patients receiving ICI-based regimens prior to HD-ASCT had superior 2-year PFS (98%, compared to 68.8% with conventional chemotherapy, N=728).[20] Moreover, Merryman *et al*. had evaluated the role of ICI-based salvage followed by HD in patients with multiply r/r cHL (defined as insufficient response to proceed to ASCT after two or more treatment lines) and showed highly favorable outcomes (18-month PFS of 81% in 78 patients evaluated) in comparison to historical data with conventional salvage therapy.[21] An overview of different anti-PD-1-based salvage treatment regimens is provided in Table 1.

All of the studies mentioned were conducted in US cohorts. However, ICI are not EMA-approved for second-line treatment of cHL and published European trials in this setting are thus far lacking, leading to the absence of data in a European setting. We, therefore, aimed to investigate the efficacy of ICI-based salvage therapy in a European multicenter real-world cohort.

Methods

Data collection and inclusion criteria

This retrospective, international, multicenter cohort study

Table 1. Overview of the most important trials incorporating PD-1-based salvage.

Trial	Regimen	N	ORR, %	CRR, %	PFS
Mei *et al*.[18]	N-ICE	34	100	89	2-year PFS: 72%/94% after ASCT
Bryan *et al*.[17]	P-ICE	42	97.3	86.5	2-year PFS: 87.2%
Moskowitz *et al*.[16,30]	P-GVD	39	100	95	5-year PFS: 91% (95% CI: 82-100)
Ding *et al*.[31]*	Tislelizumab + GemOx	30	100	96.7	1-year PFS: 96% (95% CI: 74.8-99.4)
Liu *et al*.[32]	Sintilimab + ICE	44	-	61.4	Median PFS: not reached
Advani *et al*.[19]	BV-Nivo	91	85	67	3-year PFS: 77%

*Ding *et al*. did not apply high-dose chemotherapy consolidation. ORR: overall response rate; CRR: complete remission rate; PFS: progression-free survival; ASCT: autologous stem cell transplantation; 95% CI: 95% confidence interval; N-ICE: nivolumab + ifosfamide, carboplatin, etoposide; P-ICE: pembrolizumab + ifosfamide, carboplatin, etoposide; P-GVD: pembrolizumab + gemcitabine, vinorelbine, doxil; Tislelizumab + GemOx: tislelizumab + gemcitabine, oxaliplatin; Sintilimab + ICE: sintilimab + ifosfamide, carboplatin, etoposide; BV-Nivo: brentuximab vedotin + nivolumab.

Table 2. Characteristics of the whole cohort of patients.

Characteristics	Values
Age at initial diagnosis, years, median (range)	28 (17-68)
Age at start of PD-1 salvage therapy, years, median (range)	31 (19-69)
Sex, N (%)	
Male	30 (63.8)
Female	17 (36.2)
First-line treatment, N (%)	
eBEACOPP-based	19 (40.4)
eBEACOPP + ABVD-based	13 (27.7)
ABVD-based	9 (19.1)
BrECADD-based	2 (4.3)
COPP/COPDAC	2 (4.3)
BV-AVD	1 (2.1)
N-AVD	1 (2.1)
N of prior therapy lines, median (range)	2 (1-4)
N of prior therapy lines, N (%)	
1	22 (46.8)
2	20 (42.6)
3	3 (6.4)
4	2 (4.3)
Salvage regimen, N (%)	
ICI monotherapy	10 (21.3)
Nivolumab	4/10 (40)
Pembrolizumab	6/10 (60)
ICI + chemotherapy	34 (75.6)
P-GVD	30/34 (88.2)
P-ICE	3/34 (8.8)
N-ICE	1/34 (2.9)
ICI + BV	3 (6.4)
Pembrolizumab + BV	1/3 (33.3)
Nivolumab + BV	2/3 (66.7)
Consolidation, N (%)	
Allo-SCT	6 (12.8)
Prior auto-SCT	5/6 (83.3)
Auto-SCT	37 (78.7)
No SCT	4 (8.5)
Consolidating regimen (of auto/allo pts), N (%)	
BEAM	36 (83.7)
TEAM	1 (2.3)
TBI (12 Gy) + Cyclo ATG	2 (4.7)
Flu/Treo/(ATG)	4 (9.3)
Ann Arbor stage at relapse, N (%)	
II	12/34 (35.3)
III	8/34 (23.5)
IV	14/34 (41.2)
B-symptoms at relapse, N (%)	
Yes	13/32 (40.6)
No	19/32 (59.4)
ECOG at relapse, N (%)	
0	21/33 (63.6)
1	12/33 (36.4)
Bulky disease at relapse, N (%)	
Yes	11/34 (32.4)
No	23/34 (67.6)

included patients from eight large academic centers across Europe. All patients treated with anti-PD-1-based salvage for r/r cHL regardless of line of therapy (including PD-1-monotherapy or the combination with other drugs) and intent to undergo consolidation by HD-ASCT or allogeneic stem cell transplant (SCT), were included in this analysis.

This study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study and the use of anonymized data, the requirement for written informed consent was waived according to local Institutional Review Board regulations. Anonymized patients' data, including baseline characteristics such as age, sex, risk factors, and Ann Arbor stage, as well as information on prior treatment lines - including salvage and high-dose regimens - any immune-related adverse events and the status at last follow-up were collected based on a chart review by locally treating physicians.

Statistical analysis

The statistical analysis was conducted in SAS (version 9.4). The patients' characteristics were described including mean and minimum and maximum values. Patients were assigned to three treatment groups: (i) ICI monotherapy; (ii) ICI + chemotherapy, including any polychemotherapy; and (iii) ICI + BV. To evaluate the metabolic response, best overall response in ^{18}F- fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT) was documented by the local physicians as partial response, CR, stable disease, or progressive disease and the Deauville score was assessed.[23] PFS and OS were estimated using the Kaplan-Meier method including 95% confidence intervals (95% CI). PFS was defined as the interval from the date of starting treatment to the date of clinical or radiographic disease progression or death from any cause, whichever occurred first; patients without an event were censored at the date of last follow-up. OS was defined as the interval from the start of treatment to death of any cause. To enhance the comparability to previous phase II trials, in a subgroup analysis patients who had received only one prior line of treatment were evaluated.

eBEACOPP: escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone); ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; COPP/COPDAC: cyclophosphamide, vincristine, procarbazine, prednisone/cyclophosphamide, vincristine, prednisone, dacarbazine; BV-AVD: brentuximab vedotin + adriamycin, vinblastine, dacarbazine; N-AVD: nivolumab + adriamycin, vinblastine, dacarbazine; ICI: immune checkpoint inhibitor; BV: brentuximab vedotin; P-GVD: pembrolizumab + gemcitabine, vinorelbine, liposomal doxorubicin; P-ICE: pembrolizumab + ifosfamide, carboplatin, etoposide; N-ICE: nivolumab + ifosfamide, carboplatin, etoposide; auto-SCT: autologous stem cell transplantation; allo-SCT: allogeneic stem cell transplantation; BEAM: BCNU (carmustine), etoposide, cytarabine, melphalan; TEAM: thiotepa, etoposide, cytarabine, melphalan; TBI: total body irradiation; Cyclo: cyclophosphamide; ATG: antithymocyte globulin; Flu/Treo(/ATG): fludarabine, treosulfan (± ATG); ECOG: Eastern Cooperative Oncology Group performance status.

(Immune-related) adverse events and deaths

All immune-related adverse effects, including specific subtypes, management and engraftment syndrome, as reported by the local investigators were collected. Deaths and the causes of death were retrieved from the medical reports.

Results

In total 47 patients treated between 2017 and 2024 were included in the analysis, of whom 36.2% were female. Their median age was 31 years (range, 19-69) at the start of ICI treatment and they had received a median of two prior lines of treatment (range, 1-4). Most patients (N=32, 68%) had received first-line treatment based on eBEACOPP (+ABVD). Pembrolizumab or nivolumab was given as a monotherapy to 21.3% of cases (N=10). In the group receiving salvage with ICI + chemotherapy (75.6%, N=34), the majority (88.2%, N=30) received P-GVD. In the third group, ICI in combination with BV was administered to three patients (6.4%) (Table 2). Overall, 43 patients (91.5%) underwent consolidation, of whom the majority received HD-ASCT (78.7%, N=37) and a smaller fraction allogeneic SCT (12.8%, N=6). Four patients (8.5%) did not undergo consolidation with HD-ASCT or allogeneic SCT due to the patients' decision (4.2%, N=2), toxicity (2.1%, N=1) or death prior to consolidation (2.1%, N=1). Of the six patients undergoing allogeneic SCT (12.8%), one (16.7%) had not had a prior HD-ASCT. All 25 patients who had received more than one prior treatment line received chemotherapy-based salvage prior to reaching the anti-PD-1-based salvage line. Of all patients included, none received a second HD-ASCT during the available follow-up. A cumulative list of the number of cycles of treatment and regimens is provided in *Online Supplementary Table S1*.

Treatment response before and after high-dose chemotherapy with autologous transplantation

The ORR to anti-PD-1-based salvage was 90.9% (in 44 of 47 evaluable patients): 47.7% of patients had a CR to salvage therapy. The CR rate after salvage was highest in the ICI + chemotherapy group, with 61.3% achieving a complete remission. In contrast, the ICI monotherapy group showed a notably lower CR rate, with only one of ten patients achieving a CR. All patients showed a response to post-consolidation therapy (N=33 evaluable), of whom 97% (N=32) had a CR (Figure 1).

Progression-free and overall survival

With a median follow-up of 16 months, the 1-year PFS was 83.9% in the whole cohort (95% CI: 71.9-95.9%) and the 1-year OS was 95.6% (95% CI: 89.6-100.0%). The group treated with ICI + BV-based salvage achieved the highest 1-year PFS (100% [95% CI: 100.0-100.0%]); ICI + chemotherapy produced a 1-year PFS of 90.2% (N=34, [95% CI: 79.5-100.0%). Patients receiving consolidation SCT had a

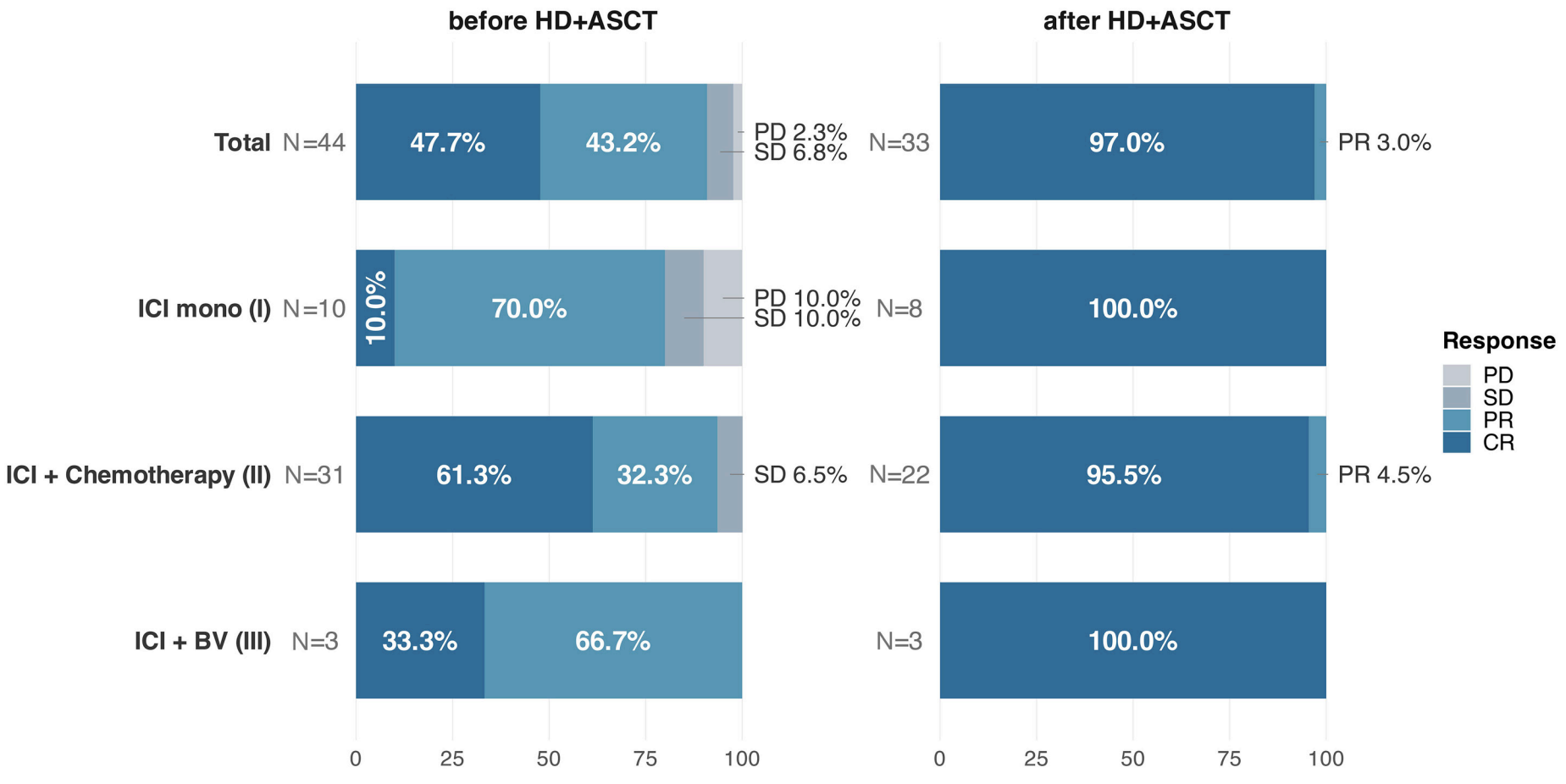


Figure 1. Best overall response to salvage therapy and subsequent consolidation, stratified by treatment subgroup. Left: response after salvage prior to high-dose chemotherapy with autologous stem cell transplantation (HD-ASCT) or allogeneic stem cell transplantation. Right: response after consolidation in patients who underwent HD-ASCT or allogeneic stem cell transplantation. ICI: immune checkpoint inhibitor; mono: monotherapy; BV: brentuximab vedotin; PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response.

higher 1-year PFS (87.7 [95% CI: 76.3-99.1%] *vs*. 37.5% [95% CI: 0.0-93.6%] without SCT) (Figure 2).

Subgroup analysis of the patients treated second line

In the cohort of patients receiving ICI in second line (N=22), there was a higher share of male patients (59.1%) and eBEACOPP (+ABVD)-based regimens in the first line (72.8%). Of the subjects in this cohort, 95% received P-GVD (Table 3). The response to treatment in this subgroup was comparable to that of the overall cohort, with an ORR prior to HD-ASCT of 95.5%, and a CR rate of 59.1% (a detailed description of response rates for all patients and a subgroup analysis can be found in *Online Supplementary Table S2*) (Figure 3). The 1-year PFS in this subgroup was excellent (100% [95% CI: 100.0-100.0%]) (Figure 4).

Immune-related adverse events and deaths

In our cohort immune-related adverse events were documented in 10.6% of cases (N=5). Two patients had an ICI-associated pneumonitis (4.3%). In one patient each, pancolitis (2.1%), thyroiditis (2.1%), and hepatitis (2.1%) were observed. All immune-related adverse events except one (thyroiditis) resolved. The patient with pancolitis was re-exposed to ICI. Two cases of engraftment syndrome (5.4%) were described

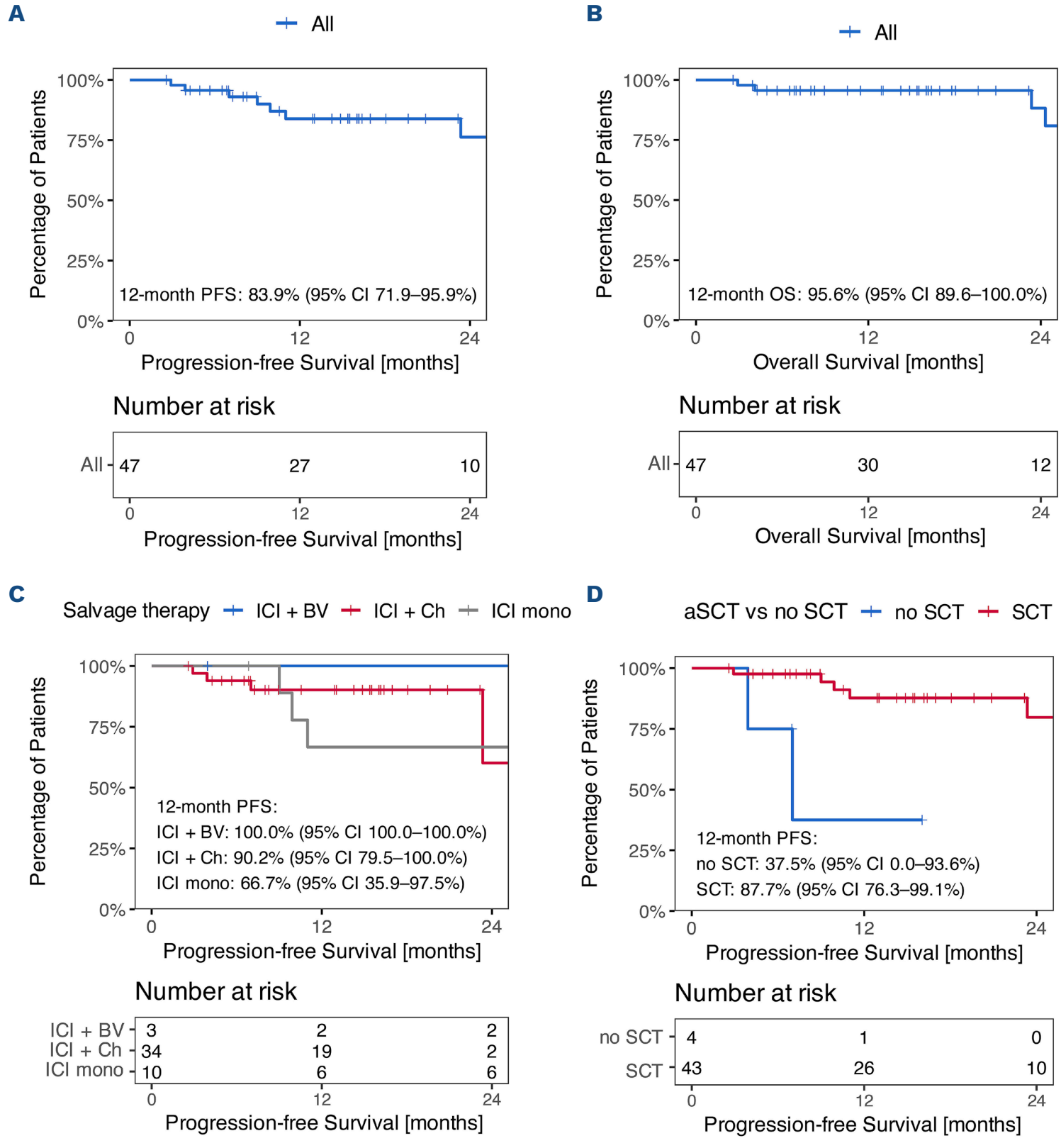


Figure 2. Kaplan–Meier plots of the survival of the entire cohort and patients stratified by treatment subgroups. (A) Progression-free (PFS) of the entire cohort. (B) Overall survival of the entire cohort. (C) PFS stratified by salvage regimen subtype: immune checkpoint inhibitor (ICI) monotherapy, ICI plus chemotherapy (ICI+Ch), and ICI plus brentuximab vedotin (ICI+BV). (D) PFS stratified by consolidation with autologous/allogeneic stem cell transplant (SCT *vs*. no SCT). 95% CI: 95% confidence interval.

in the cohort. Four deaths (8.5%) were observed (2 were related to cHL, 1 secondary acute myeloid leukemia, 1 of unknown cause) (*Online Supplementary Table S3*).

Table 3. Characteristics of the patients who had received one prior line of treatment.

Characteristics	Values
Age at initial diagnosis, years, median (range)	29 (21-67)
Age at start of PD-1 salvage therapy, years, median (range)	31 (21-68)
Sex, N (%)	
Male	13 (59.1)
Female	9 (40.9)
First-line treatment, N (%)	
eBEACOPP-based	10/22 (45.5)
eBEACOPP + ABVD-based	6/22 (27.3)
BrECADD	2/22 (9.1)
ABVD-based	2/22 (9.1)
BV-AVD	1/22 (4.5)
N-AVD	1/22 (4.5)
Salvage regimen, N (%)	
ICI monotherapy	1 (4.5)
Pembrolizumab	1/1 (100)
ICI + chemotherapy	20 (90.9)
P-ICE	1/20 (5)
P-GVD	19/20 (95)
ICI + BV	1 (4.5)
Nivolumab + BV	1/1 (100)
Consolidation, N (%)	
Allogeneic SCT	0 (0)
Autologous SCT	21 (95.5)
No SCT	1 (4.5)
Consolidating regimen (of auto/allo pts.), N (%)	
BEAM	21 (100)
Ann Arbor stage at relapse, N (%)	
II	7/19 (36.8)
III	5/19 (26.3)
IV	7/19 (36.8)
B-symptoms at relapse, N (%)	
Yes	10/19 (52.6)
No	9/19 (47.4)
ECOG at relapse, N (%)	
0	12/17 (70.6)
1	5/17 (29.4)
Bulky disease at relapse, N (%)	
Yes	3/18 (16.7)
No	15/18 (83.3)

eBEACOPP: escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone); ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; BV-AVD: brentuximab vedotin + adriamycin, vinblastine, dacarbazine; N-AVD: nivolumab + adriamycin, vinblastine, dacarbazine; ICI: immune checkpoint inhibitor; BV: brentuximab vedotin; P-ICE: pembrolizumab + ifosfamide, carboplatin, etoposide; P-GVD: pembrolizumab + gemcitabine, vinorelbine, doxil; BV: nivolumab + brentuximab vedotin; SCT: stem cell transplantation; auto/allo pts.: patients who had undergone SCT; BEAM: BCNU (carmustine), etoposide, cytarabine, melphalan; ECOG: Eastern Cooperative Oncology Group performance status.

Discussion

Herein, we report favorable outcomes in patients treated with ICI-based salvage for r/r cHL with the intent to undergo HD-ASCT/allogeneic SCT in a real-world European setting. In a cohort of 47 patients the 1-year PFS was 83.9%, with patients receiving anti-PD-1-based salvage in second line achieving a 1-year PFS of 100%.

Previously reported high and unprecedented ORR/CR rates with anti-PD-1-chemotherapy combinations, e.g., 100/95% with two to four cycles of P-GVD by Moskowitz *et al.*, could not be confirmed in the European cohort. This observation holds true in both intensively pre-treated patients and in those with only one prior line of treatment (patients treated second-line in our analysis had ORR/CR rates of 95.5/59.1% with anti-PD-1 + chemotherapy). However, in the latter group an excellent PFS of 100% was reached, comparing favorably to what is known from historical data of r/r cHL patients treated with conventional chemotherapy salvage prior to SCT in the second line (1-year PFS of 82.3% [95% CI: 77.5-86.2%]).[2]

Anti-PD-1 treatment altogether has a favorable toxicity profile. However, immune-related adverse events during treatment and associated effects such as increased risk of graft-*versus*-host disease in patients subsequently undergoing allogeneic SCT are of concern.[24,25] Although limited by the retrospective nature of this study, immune-related adverse events were reported in 10.6% of patients, a comparable rate to in other publications.[26] In addition, a potentially elevated risk of engraftment syndrome was previously reported in patients receiving anti-PD-1-based salvage before ASCT.[25] In our study, engraftment syndrome was only observed in two of 43 patients undergoing SCT (4.6%). This was different from the trial by Moskowitz *et al.* investigating P-GVD, in which engraftment syndrome was reported in 68% of patients.[16] This was with a relatively broad definition of any of the following symptoms occurring days 8-11 after ASCT: high-grade fever (>38.5°C), skin rash covering >25% of body surface area, or diarrhea (>2 watery bowel movements in 24 hours); or hepatitis, pulmonary infiltrates, acute kidney injury, or neurological dysfunction.[16] In the study by Mei *et al.*, investigating N-ICE, 4/33 (12.1%) patients experienced engraftment syndrome (at a median of 8 days after transplant). In the phase II trial testing P-ICE by Bryan *et al.*, one patient died from respiratory failure, likely due to engraftment syndrome.[17] The different frequencies of engraftment syndrome may be explained by a lack of a widely recognized definition and reporting bias, clearly showing a need for standardized criteria for engraftment syndrome and the collection of comprehensive data in the context of ASCT after anti-PD-1-based salvage therapy.[25] In summary of our and previously published data, the addition of anti-PD-1 therapy to salvage therapy followed by consolidation seems to add only limited toxicity to the treatment strategy, further supporting its use.

The findings of this study must be interpreted within the context of its limitations. Chief among these is the retrospective study design, leading to a lower availability of structured data including grading of adverse events and a potential selection bias of patients. In addition, with a median follow-up of 16 months, the durability of the responses of anti-PD-1-based salvage followed by consolidation cannot be finally judged from our dataset. Another limitation is the small sample size, probably caused by the use of more intensive eBEACOPP-based regimens in first line and thus less frequent relapses and by the lack of approval of PD-1 inhibitors for second-line treatment in Europe. Thus, a smaller share of relapses and less frequent use of ICI as part of salvage is seen in the European treatment context and intra-cohort comparisons must be interpreted with caution due to selection bias. This may result in the application of PD-1-based salvage therapy in patients with higher-risk disease (such as those experiencing stage IV relapse or failure following prior polychemotherapy-only salvage), thereby contributing to the inclusion of a poorer prognosis cohort and thus inferior response rates. However, in addition to the actual treatment efficacy of a regimen in a specific group of patients, differences in response rates may stem from various factors, such as scanner manufacturer, scanner quality improvement over time and response assessment methodology. While the original Lugano classification relies primarily on visual assessment via Deauville scores (1–5) to determine treatment response in FDG-PET,[27] this introduces inter-observer variability, especially in borderline cases. Thus, to allow for more objective and comparable PET results, some trials use modified Lugano criteria by integrating semi-quantitative measures, specifically standardized uptake value thresholds, into the Deauville scoring system creating a heterogeneity in reported response data.[28]

Moreover, the predictive role of PET in relapsed cHL in patients treated with anti-PD-1 antibodies has been questioned.[21] The above-mentioned phase II studies combining checkpoint-inhibition and chemotherapy in relapsed cHL have reported comparably high CR rates, with assessments generally based on the Cheson 2014 criteria.[27] Different data collection time periods, heterogeneity in PET assessments and technical equipment might have contributed to differences between the CR rates in the above-mentioned phase II trials and our analysis. The comparably high ORR but lower CR rates in our analysis as well as the similar PFS results reported in phase II trials and our cohort point in this direction. Certainly, the reporting of quantitative biomarkers such as metabolic tumor volume and minimal residual disease by assessment of circulating tumor DNA is warranted in future analyses concerning anti-PD-1-therapy in r/r cHL.

Nevertheless, the 1-year PFS of 83.9% is remarkable given the heterogeneity of this cohort, with six patients undergoing allogeneic SCT, others receiving ICI monotherapy or ICI in combination with polychemotherapy/BV as salvage or in the third or fourth line of treatment. ICI monotherapy in particular was predominantly used in patients who had

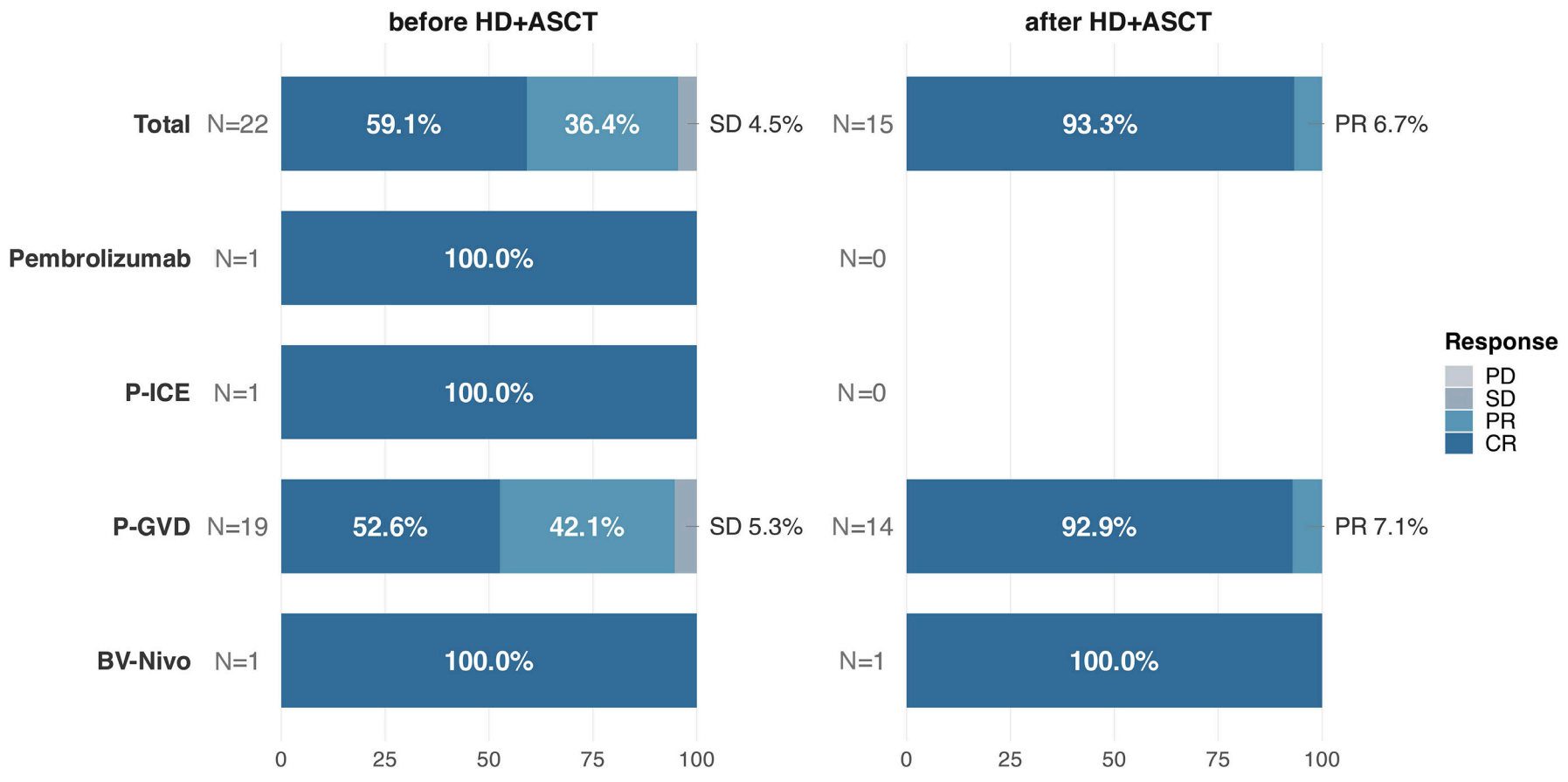


Figure 3. Best overall response to salvage therapy by exact regimen in patients who received one prior line of therapy. HD-ASCT: high-dose chemotherapy with autologous stem cell transplantation; P-GVD: pembrolizumab, gemcitabine, vinorelbine, liposomal doxorubicin; P-ICE: pembrolizumab, ifosfamide, carboplatin, etoposide; BV-Nivo: brentuximab vedotin + nivolumab; PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response.

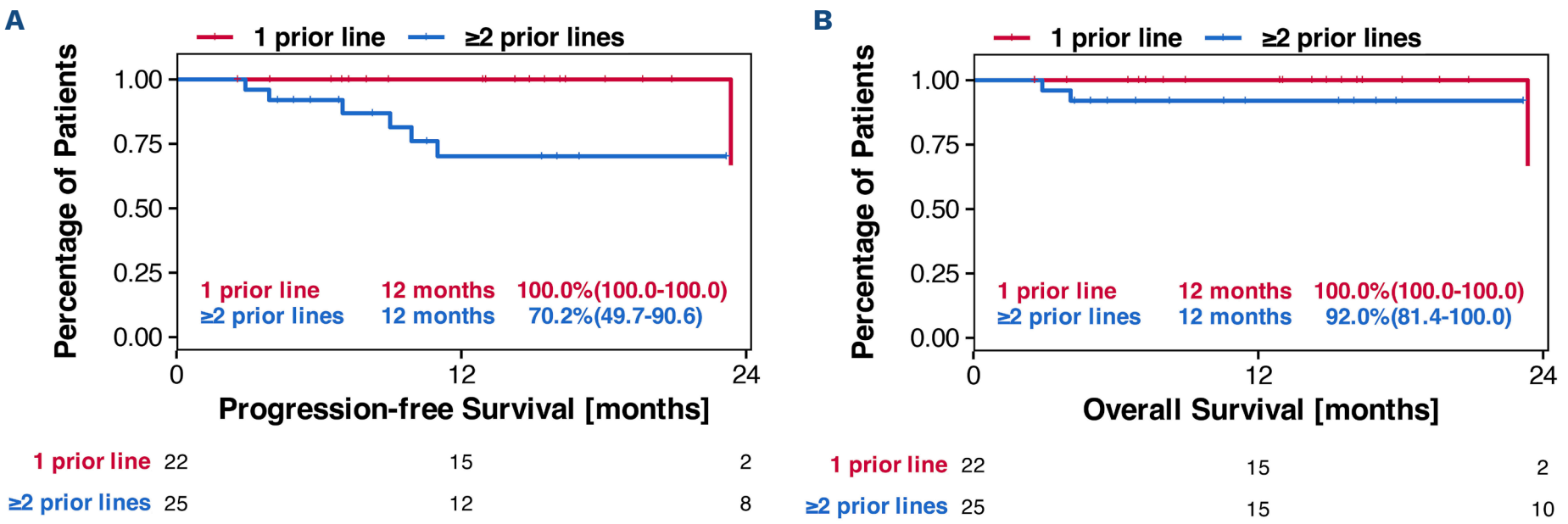


Figure 4. Kaplan–Meier survival by number of prior treatment lines. (A, B) Kaplan-Meier plots of progression-free survival (A) and overall survival (B) stratified by number of prior treatment lines (1 *vs*. >1)

undergone more intensive prior treatment; the inferior PFS is therefore likely to reflect primarily patient selection and prior treatment intensity rather than necessarily inferior biological efficacy (only 1/10 patients treated with ICI monotherapy in second line). In addition, due to this selection the high CR rates after ICI monotherapy after consolidative HD-ASCT must be interpreted with caution.

Our findings show that even after more intense prior therapy and lower CR rates to anti-PD-1-based salvage as compared to US data, the PFS after consolidation in our dataset is still excellent (87.7% after 1 year) and in the range of published US registry data.[20] However, longer follow-up is needed to confirm the durability of the responses.

ICI introduced a fundamental shift in oncology, with a particularly high impact in cHL, in which durable tumor control was achieved in a subset of patients who previously lacked effective treatment options. In retrospective evaluations since the era of the incorporation of novel agents in the salvage prior to ASCT, improvements in outcomes were observed compared to historic data, especially when PD-1 inhibitors were used as part of salvage.[29] Currently there are still trials evaluating regimens in this setting, e.g., the Canadian HD11 phase II trial is recruiting (NCT05180097) patients who are randomized to GDP (gemcitabine, dexamethasone, and cisplatin) or pembrolizumab + BV prior to ASCT.

Subject to longer follow-up of phase II data, real-world data and the results reported here confirming the durability of the high early PFS rates, anti-PD-1-based therapy seems to be the preferred salvage option before HD-ASCT. Registrational clinical trials leading to approval of anti-PD-1-based treatment in the first salvage setting in r/r cHL in Europe are highly warranted to increase patients' access to the probably most effective therapy in this difficult situation. However, if the high PFS rates with anti-PD-1-based therapy in the consolidation setting in r/r cHL hold true after longer follow-up, one might question whether a standard treatment group consisting of patients given conventional chemotherapy would still be ethically justified.

In summary, our results support the use of ICI and poly-chemotherapy-based salvage combinations in r/r cHL and likewise support the role of HD and ASCT in the treatment of r/r cHL.

Disclosures

US has received honoraria and travel support from AbbVie, AstraZeneca, Beigene, BMS, Gilead Kite, J&J, Novartis, SOBI and Takeda. TM has received honoraria from Takeda, BMS and MSD. PJB is an advisor or consultant for Hexal, Merck Sharp & Dohme (MSD), Need Inc., Stemline and Takeda; holds stock options in Need Inc.; has received honoraria from AstraZeneca, BeOne, Bristol-Myers Squibb/Celgene (BMS), Eli Lilly, MSD, Need Inc., Stemline and Takeda; and reports research funding from BeOne (to institution), BMS (to institution), MSD (to institution) and Takeda (to institution). BvT is an advisor or consultant for Allogene, Amgen, BMS/Celgene, Cerus, Gilead Kite, Incyte, IQVIA, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Miltenyi, Novartis, Noscendo, Pentixapharm, Pfizer, Pierre Fabre, Qualworld, Regeneron, Roche, Sobi and Takeda; has received honoraria from AbbVie, AstraZeneca, BMS/Celgene, Gilead Kite, Incyte, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Novartis, Roche, Serb and Takeda; reports research funding from Esteve (to institution), Merck Sharp & Dohme (to institution), Novartis (to institution), and Takeda (to institution); and reports travel support from AbbVie, AstraZeneca, Gilead Kite, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Pierre Fabre, Roche, Takeda and Novartis; and is a member of steering committees for Regeneron (institution) and Takeda.

Contributions

HT was responsible for conceptualization, methodology, validation, visualization, writing – review & editing, writ-

ing original draft, funding acquisition, investigation, and software. LMS contributed to conceptualization and data curation. IB was responsible for formal analysis and software. US, JM, MS, DB and JP contributed to data curation. JCH was involved in data curation and writing – review & editing. TZ contributed to investigation, visualization, and data curation. JF worked on methodology, investigation, and conceptualization. ES was responsible for data curation, supervision, and methodology. AK contributed to data curation. TM was responsible for visualization, writing – review & editing, and data curation. PJB contributed to visualization, writing – review & editing, and validation. CK supported writing – review & editing. PB was responsible for supervision, resources, and investigation. BvT contributed to supervision, resources, data curation, formal analysis, and project administration.

Data-sharing statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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