Brentuximab vedotin plus nivolumab after autologous haematopoietic stem-cell transplantation for adult patients with high-risk classic Hodgkin lymphoma: a multicentre, phase 2 trial

Alex F Herrera, Lu Chen, Yago Nieto, Leona Holmberg, Patrick Johnston, Matthew Mei, Leslie Popplewell, Saro Armenian, Thai Cao, Leonardo Farol, Firoozeh Sahebi, Ricardo Spielberger, Robert Chen, Auayporn Nademanee, Sandrine Puverel, Mary Nwangwu, Peter Lee, Joo Song, Alan Skarbnik, Neena Kennedy, Lacolle Peters, Steven T Rosen, Larry W Kwak, Stephen J Forman, Tatyana Feldman

Lancet Haematol 2023; 10: e14–23

Published Online November 17, 2022 https://doi.org/10.1016/S2352-3026(22)00318-0

See Comment page e2

Division of Lymphoma, Department of Hematology and Hematopoietic Cell Transplantation (A F Herrera MD, M Mei MD, L Popplewell MD, T Cao MD, L Farol MD, Prof F Sahebi MD, Prof R Spielberger MD, R Chen MD, A Nademanee MD, S Puverel PhD, N Kennedy BSN, L Peters BA, Prof S T Rosen MD, Prof L W Kwak MD, Prof S J Forman MD), **Division of Biostatistics** (L Chen PhD), **Department of Pediatrics** (Prof S Armenian DO), **Department of Immuno-Oncology** (M Nwangwu BS, Prof P Lee MD), **and Department of Pathology** (J Song MD), **City of Hope National Medical Center, Duarte, CA, USA; Department of Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX, USA** (Prof Y Nieto MD); **Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA** (Prof L Holmberg MD); **Division of Hematology, Mayo Clinic, Rochester, MN, USA** (P Johnston MD); **Department of Bone Marrow Transplant, Southern California Permanente Medical Group, Duarte, CA, USA** (T Cao, L Farol, Prof F Sahebi, Prof R Spielberger); **Lymphoma Division, Hackensack University Medical Center, Hackensack, NJ, USA** (A Skarbnik MD, T Feldman MD)

Summary

Background After autologous haematopoietic stem-cell transplantation (HSCT), consolidation with brentuximab vedotin in patients with high-risk relapsed or refractory classic Hodgkin lymphoma has been shown to improve progression-free survival compared with placebo. Brentuximab vedotin plus nivolumab is a safe and effective treatment for relapsed or refractory classic Hodgkin lymphoma; therefore, we aimed to evaluate the safety and activity of this drug combination post-autologous HSCT consolidation in patients with high-risk relapsed or refractory classic Hodgkin lymphoma.

Methods We did a multicentre phase 2 trial at five centres in the USA. Eligible patients were aged 18 years or older with high-risk relapsed or refractory classic Hodgkin lymphoma, had an ECOG performance status of 0–2, and had adequate organ and bone marrow function. Enrolled patients received brentuximab vedotin (1·8 mg/kg) and nivolumab (3 mg/kg) intravenously starting 30–60 days after autologous HSCT on day 1 of each 21-day cycle for up to 8 cycles. Nivolumab dose reduction was not allowed. Brentuximab vedotin dose reduction to 1·2 mg/kg was permitted. If one drug was discontinued because of a toxic effect, the other could be continued. The primary endpoint was 18-month progression-free survival in all treated patients. This study is registered with ClinicalTrials.gov, number NCT03057795.

Findings Between May 3, 2017, and July 13, 2019, 59 patients were enrolled and received the study therapy. Patients initiated brentuximab vedotin plus nivolumab for a median of 54 days (IQR 46–58) after autologous HSCT and received a median of 8 cycles (8–8). 34 (58%) of 59 patients were male, 29 (49%) completed 8 cycles of brentuximab vedotin plus nivolumab, and 45 (76%) completed 8 cycles of at least one drug. The median follow-up time was 29·9 months (IQR 24·6–34·8). The 18-month progression-free survival in all 59 patients was 94% (95% CI 84–98). The most common adverse events were sensory peripheral neuropathy (31 [53%] of 59) and neutropenia (25 [42%]), and immune-related adverse events requiring corticosteroids occurred in 17 (29%) of 59 patients. No treatment-related deaths were observed.

Interpretation Brentuximab vedotin plus nivolumab was highly active post-autologous HSCT consolidation for patients with high-risk relapsed or refractory classic Hodgkin lymphoma, most of whom had previous exposure to either brentuximab vedotin or PD-1 blockade. Combination immunotherapy in this setting should be further studied in patients with classic Hodgkin lymphoma with further refinement of the regimen to mitigate toxic effects, particularly in high-risk patients in whom more intensive therapy to prevent relapse is warranted.

Funding Bristol Myers Squibb, Leukemia and Lymphoma Society, Lymphoma Research Foundation, and National Cancer Institute of the National Institutes of Health.

Introduction

The standard treatment for patients with relapsed or refractory classic Hodgkin lymphoma is salvage therapy followed by autologous haematopoietic stem-cell transplantation (HSCT).[1] Autologous HSCT results in durable remission in about half of patients with relapsed or refractory classic Hodgkin lymphoma, but a majority of patients with high-risk features will relapse.[1,2] The AETHERA trial[3] showed that post-autologous HSCT consolidation with brentuximab vedotin for a planned 16 cycles prolonged progression-free survival compared with placebo in patients with high-risk relapsed or refractory classic Hodgkin lymphoma undergoing autologous HSCT. Brentuximab vedotin has been studied as initial and salvage treatment for classic Hodgkin lymphoma, and is approved for frontline use in

Research in context

Evidence before this study

At the time this study was designed, salvage treatment followed by consolidation with high-dose chemotherapy and autologous haematopoietic stem-cell transplantation (HSCT) remained the standard-of-care treatment for patients with relapsed or refractory classic Hodgkin lymphoma. The AETHERA trial showed that brentuximab vedotin consolidation following autologous HSCT significantly improved progression-free survival in patients with high-risk relapsed or refractory classic Hodgkin lymphoma compared with placebo, but opportunities for improvement remained. Brentuximab vedotin plus nivolumab had been evaluated as combination salvage therapy for patients with relapsed or refractory classic Hodgkin lymphoma and were determined to be safe and effective in this setting. On April 6, 2016, and again on Dec 15, 2016, we searched PubMed using the search terms "nivolumab", "brentuximab vedotin", "Hodgkin lymphoma", "autologous stem cell transplantation", "hematopoietic cell transplantation", and "consolidation"; we found no published evidence for the combination of brentuximab vedotin plus nivolumab. We also searched ClinicalTrials.gov with the same search terms and on the same dates and found no active clinical trials evaluating this combination as consolidation after autologous HSCT in patients with relapsed or refractory classic Hodgkin lymphoma.

Added value of this study

Our study showed that brentuximab vedotin plus nivolumab (up to 8 cycles as opposed to 16 cycles of brentuximab vedotin in AETHERA) used as post-autologous HSCT consolidation was associated with good progression-free survival in a high-risk cohort of patients with relapsed or refractory classic Hodgkin lymphoma, a majority of whom had received previous brentuximab vedotin or PD-1 blockade without progression on therapy. The AETHERA study had only enrolled patients who were naive to brentuximab vedotin and PD-1 blockade. The safety profile of brentuximab vedotin and nivolumab in the post-autologous HSCT consolidation setting was consistent with the known safety profiles of the combination when used in other settings, although immune-related toxic effects were more frequent.

Implications of all the available evidence

This study provides evidence that a shorter, intensified course of consolidation with novel immunotherapies after autologous HSCT can yield excellent outcomes in patients with high-risk relapsed or refractory classic Hodgkin lymphoma undergoing autologous HSCT. In the modern era, brentuximab vedotin and PD-1 blockade are frequently used in earlier lines of therapy before autologous HSCT and our study suggests that post- autologous HSCT consolidation with brentuximab vedotin and nivolumab is applicable to patients who have previous exposure but did not progress while receiving novel immunotherapies. Refinement of the approach is needed, but our findings suggest that further evaluation of this combination immunotherapy as consolidation is warranted to improve outcomes in patients with high-risk relapsed or refractory classic Hodgkin lymphoma undergoing autologous HSCT.

Correspondence to:
Dr Alex F Herrera, Division of Lymphoma, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope Medical Center, Duarte, CA 91010, USA
aherrera@coh.org

advanced-stage classic Hodgkin lymphoma.[4–7] As a result, brentuximab vedotin is increasingly used before autologous HSCT and its role for consolidation in these patients is unclear since AETHERA did not include patients with previous brentuximab vedotin exposure. Moreover, the long duration of brentuximab vedotin consolidation is associated with peripheral neuropathy, which might lead to early discontinuation and decreased quality of life.[3,8]

Classic Hodgkin lymphoma exhibits genetic alteration of *PD-L1* and *PD-L2* on chromosome 9p24.1, which results in ubiquitous expression of programmed death receptor ligands (PD-L1, PD-L2) on Hodgkin Reed-Sternberg cells and have a key role in the pathogenesis of the disease.[9,10] PD-1 blockade in patients with relapsed or refractory classic Hodgkin lymphoma is safe and active, producing objective responses in a majority of patients and has been shown to be effective as part of salvage therapy.[11–13] In patients with relapsed or refractory classic Hodgkin lymphoma undergoing autologous HSCT, 8 cycles of PD-1 blockade was well tolerated and associated with promising outcomes.[14]

Brentuximab vedotin has been combined with nivolumab in patients with newly diagnosed and relapsed or refractory classic Hodgkin lymphoma with a majority of patients responding and a favourable safety profile.[15,16] We hypothesised that brentuximab vedotin plus nivolumab post-autologous HSCT consolidation in patients with relapsed or refractory classic Hodgkin lymphoma would be safe and associated with favourable progression-free survival. Our primary goal was to improve outcomes of post-HSCT consolidation by adding a PD-1 blockade to brentuximab vedotin while also minimising the cumulative toxic effects of brentuximab vedotin by using a planned 8 cycles (the previously studied duration of anti-PD-1 monotherapy post-HSCT consolidation).[14] In this Article, we report the primary analysis of brentuximab vedotin plus nivolumab consolidation after autologous HSCT in patients with high-risk relapsed or refractory classic Hodgkin lymphoma.

Methods

Study design and participants

We did a multicentre phase 2 trial at five centres in the USA (City of Hope, University of Texas MD Anderson Cancer Center, Fred Hutchinson Cancer Research Center, Mayo Clinic, and Hackensack University Medical Center; appendix p 7).

See Online for appendix

Eligible patients were 18 years or older, had histologically confirmed classic Hodgkin lymphoma, and had one or

more high-risk features, including primary refractory classic Hodgkin lymphoma, relapsed classic Hodgkin lymphoma within 1 year of completing initial therapy, extranodal involvement or B symptoms at relapse, or more than one salvage regimen used before autologous HSCT. Patients had to have reached at least stable disease by PET-CT before autologous HSCT and had to be brentuximab vedotin naive or have reached at least stable disease to previous brentuximab vedotin. Other inclusion criteria were an ECOG performance status of 0–2, recovery from autologous HSCT toxicity (outpatient status, no requirement for intravenous fluids, oral intake tolerated), absolute neutrophil count of 1000 cells per µL or more, platelet count of 50 000 cells per µL or more, haemoglobin of 8 g/dL or more, total bilirubin of 1·5×upper limit of normal (ULN) or less or 3×ULN for patients with Gilbert syndrome, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of 2·5×ULN or less, forced expiratory volume in 1 s and diffusing capacity for carbon monoxide of 50% or more of predicted, and creatinine clearance of 40 mL/min or more. Post-autologous HSCT consolidative radiation was allowed if administered before study therapy. Patients with progressive disease while receiving previous brentuximab vedotin or PD-1 blockade were excluded. Patients with grade 2 or worse peripheral neuropathy, previous allogeneic HSCT, recent live vaccination, active HIV, hepatitis B or C infection, CNS involvement by lymphoma, history of progressive multifocal leukoencephalopathy, previous pneumonitis or interstitial lung disease, autoimmune diseases, immunodeficiency, severe hypersensitivity to either brentuximab vedotin or nivolumab, other primary malignancy not in remission for at least 3 years, ongoing active infection or uncontrolled illness, or recent myocardial infarction, unstable angina, congestive heart failure, or recent cerebrovascular event were excluded. Women who were pregnant or lactating were excluded, and women of childbearing potential were required to have a negative pregnancy test because the safety of brentuximab vedotin and nivolumab in pregnancy was not established.

Patients underwent autologous HSCT according to institutional standards and had to have received less than 600 mg/m² of carmustine in the preparative regimen. All patients provided written informed consent for participation in the clinical trial. The study was approved by the Institutional Review Board and done in accordance with the principles of the Declaration of Helsinki. The study protocol is available in the appendix (pp 10–114).

Procedures

Patients received 1·8 mg/kg brentuximab vedotin and 3 mg/kg nivolumab intravenously on day 1 of each 21-day cycle for up to 8 planned cycles. Protocol therapy started 30–60 days after autologous HSCT, although treatment initiation was allowed as late as 75 days after autologous HSCT if extra time was needed to recover from HSCT toxicities. Nivolumab dose reduction was not allowed. Brentuximab vedotin dose reduction to 1·2 mg/kg was permitted according to protocol-specified guidelines. Post-autologous HSCT infectious prophylaxis for *Pneumocystis jirovecii* pneumonia and herpes simplex viruses was required.

Safety was monitored continuously, with toxic effects assessed using the Common Terminology Criteria for Adverse Events (version 4.03), and monitoring continuously occurred for excess unacceptable toxic effects (eg, grade ≥3 immune-related adverse events, grade 4 neutropenia without timely resolution). Laboratory assessment of blood counts, serum chemistry (including amylase and lipase) occurred on day 1 of each cycle, except thyroid function testing, which occurred every 3 cycles. PET-CT (diagnostic CT allowed if patient was in complete response before autologous HSCT) was done at least 21 days after autologous HSCT and within 28 days of enrolment, after 4 cycles of brentuximab vedotin plus nivolumab, at end of treatment after 8 cycles, and then at 12 and 18 months from start of protocol therapy. Response assessment was done by investigators according to the 2014 Lugano classification without central review.[17] Criteria for removal from the study included relapse or progression, completion of 8 cycles of treatment, unacceptable toxicity, withdrawal of consent, or a change in the participant's condition rendering them unacceptable for further treatment per investigator.

We analysed formalin-fixed paraffin-embedded tumour samples obtained at initial relapse and at relapse after study treatment using seven-colour multispectral immunofluorescence to examine the density of and spatial relationships between immune cells, immune checkpoint proteins, and tumour cells in the classic Hodgkin lymphoma tumour microenvironment (appendix pp 8–9).

Outcomes

The primary endpoint was 18-month progression-free survival; defined as the time from treatment start to relapse, progression, or death. Secondary endpoints were overall survival (defined as time from treatment start to death), cumulative incidences of relapse and progression (defined according to the 2014 Lugano classification) and non-relapse mortality (defined as the time to death without relapse and progression), the overall response rate (defined as partial or complete metabolic response) to brentuximab vedotin plus nivolumab in patients with measurable disease after autologous HSCT, and safety and tolerability. Additional non-prespecified analyses were conducted. Progression-free survival according to the number of risk factors is reported, and outcomes in patients by PET status before autologous HSCT, receipt of previous PD-1 blockade, and completion of study treatment were analysed.

Exploratory analyses were planned for the effect of brentuximab vedotin plus nivolumab on immune

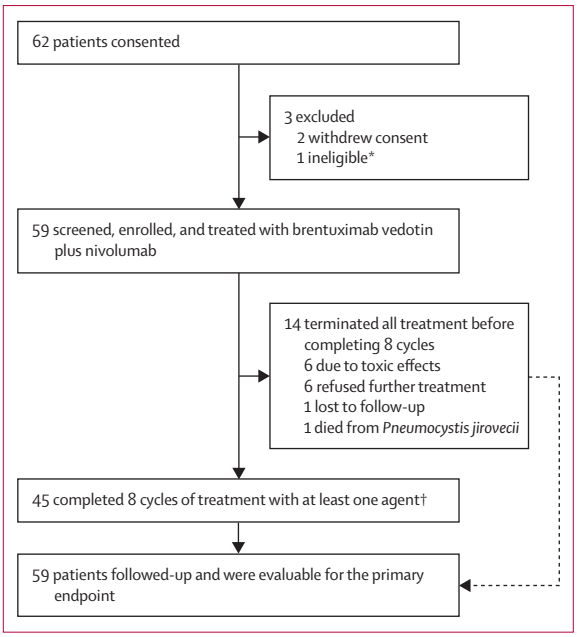

Figure 1: **Trial profile**
*Ineligible due to development of interstitial pneumonia after consent before screening. †29 (49%) of 59 patients completed 8 cycles of both brentuximab vedotin plus nivolumab.

reconstitution and the prognostic effect of peripheral blood minimal residual disease assessment, chromosome 9p24.1 abnormalities, or gene expression profiles. These exploratory analyses are not reported in this Article, as they have not been done to date either due to changes in the field (eg, methods of minimal residual disease assessment) or due to the few progression-free survival events observed that limit our statistical power and ability to draw meaningful conclusions.

Statistical analysis

Patients who received one or more doses of the protocol treatment were considered evaluable for the primary endpoint and secondary endpoints. A sample size of 59 evaluable patients was based on the provision of approximately 81% power for detecting an increase in 18-month progression-free survival from the baseline of 65% observed in the brentuximab vedotin group of AETHERA to 80% with brentuximab vedotin plus nivolumab at a one-sided type I error of 0·05 based on the exact binomial test. Brentuximab vedotin plus nivolumab consolidation would be considered promising if at least 45 (76%) of 59 evaluable participants were alive and progression free at 18 months after enrolment.

Baseline characteristics were summarised using descriptive statistics. Toxic effects were reported according to type, severity, and the probable association with the study regimen. Adverse events were deemed immune related by the treating investigator. Response rates were calculated as the percentage of evaluable patients that had an objective response by radiographic imaging.

	Brentuximab vedotin plus nivolumab (n=59)
Sex	
Male	34 (58%)
Female	25 (42%)
Age	30 (23–39)
Race and ethnicity*	
White	47 (80%)
Black or African American	3 (5%)
Asian	3 (5%)
Not disclosed or unknown	7 (12%)
Hispanic	17 (29%)
Primary refractory	19 (32%)
Relapse within 1 year	34 (58%)
Late relapse	6 (10%)
B symptoms at relapse	14 (24%)
Extranodal disease at relapse	23 (39%)
Two or more salvage regimens	15 (25%)
Stage at relapse	
I–II	32 (54%)
III–IV	27 (46%)
Disease status at HSCT	
Complete response	48 (81%)
Partial response	11 (19%)
Disease status at baseline	
Complete response	53 (90%)
Partial response	6 (10%)
Modified AETHERA risk factors†	
1	21 (36%)
2	24 (41%)
≥3	14 (24%)
Frontline regimen	
ABVD	50 (85%)
ABVD + MOPP	1 (2%)
BV + AVD	2 (3%)
ABVE + PC	6 (10%)
Previous radiation	14 (24%)
Previous brentuximab vedotin	30 (51%)
Previous PD-1 blockade	25 (42%)
HSCT conditioning regimen	
BEAM	51 (86%)
Vorinostat or GemBuMel	7 (12%)
Other	1 (2%)

Data are n (%) or median (IQR). ABVD=doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine. ABVE + PC=doxorubicin (Adriamycin), bleomycin, vincristine, etoposide plus prednisone and cyclophosphamide. BEAM=carmustine, etoposide, cytarabine, and melphalan. BV + AVD=brentuximab vedotin plus doxorubicin (Adriamycin), vinblastine, and dacarbazine. GemBuMel=gemcitabine, busulfan, and melphalan. HSCT=haematopoietic stem-cell transplantation. MOPP=mechlorethamine, vincristine, procarbazine, and prednisone. *One (2%) of 59 patients reported race as White and Black or African American; therefore, the total is greater than 59 and total percentage is greater than 100. †One (2%) of 59 patients had two known risk factors and missing data for B symptoms, and is included as having two risk factors.

Table 1: **Baseline characteristics**

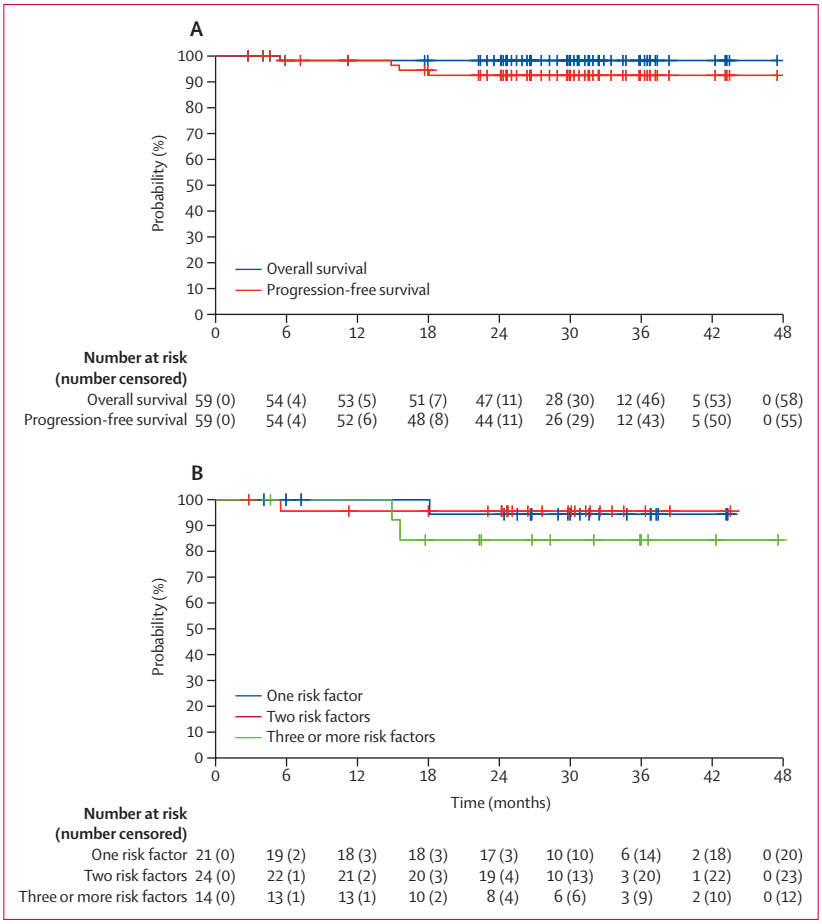

Figure 2: **Progression-free survival and overall survival outcomes**
(A) Progression-free survival and overall survival in all treated patients (n=59). (B) Progression-free survival according to number of risk factors.

Progression-free survival and overall survival were censored at the last contact for patients without failure events, except if the patient received non-protocol treatment before failure events, in which case progression-free survival was censored at the start of non-protocol treatment. Survival estimates were calculated based on the Kaplan-Meier product-limit method, 95% CIs were calculated using the log-log transformation and the Greenwood variance estimate. Cumulative incidences of relapse and progression and non-relapse mortality were estimated by the non-parametric estimators in the competing risks setting, where death and relapse and progression events were treated as competing risks.

All calculations were done using SAS (version 9.4). Trial data were locked for analysis in December 2021. This study is ongoing and is registered with ClinicalTrials.gov, number NCT03057795.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 3, 2017, and July 13, 2019, a total of 59 patients were enrolled and received the study therapy (figure 1). Baseline characteristics are presented in table 1. The median age was 30 years (IQR 23–39); 53 (90%) of 59 patients had primary refractory or early relapsed classic Hodgkin lymphoma, 48 (81%) were in complete response, and 11 (19%) patients were in partial response by PET-CT following salvage at autologous HSCT, 38 (64%) had two or more risk factors, 30 (51%) patients had received previous brentuximab vedotin, and 25 (42%) had received previous PD-1 blockade (appendix p 6). The most used salvage regimen before autologous HSCT was ifosfamide, carboplatin, and etoposide (25 [42%] of 59; appendix p 3). No patients received post-autologous HSCT consolidative radiation before brentuximab vedotin plus nivolumab. Patients initiated brentuximab vedotin plus nivolumab for a median of 54 days (IQR 46–58) after autologous HSCT. The median number of cycles received was 8 (IQR 8–8). 34 (58%) of 59 patients were male, 29 (49%) completed 8 cycles of both brentuximab vedotin and nivolumab, and 45 (76%) completed 8 cycles of at least one study drug.

Six (10%) of 59 patients were not in complete response at baseline after autologous HSCT before starting brentuximab vedotin plus nivolumab; all six patients were in partial response by PET-CT. Following brentuximab vedotin plus nivolumab consolidation, five (83%) of the six patients not in complete response after autologous HSCT converted to complete response and one (17%) remained in partial response until experiencing progressive disease 16 months after study enrolment. The median follow-up time in all surviving patients was 29·9 months (IQR 24·6–34·8). The 18-month progression-free survival in all 59 patients was 94% (95% CI 84–98) and the study met its primary endpoint with 47 (80%) patients alive and progression free, four (7%) patients with progression-free survival events, and eight (14%) patients censored (at 19 months, based on variability of scan timing). The 24-month progression-free survival for the 59 patients was 92% (95% CI 81–97) and the 24-month overall survival was 98% (95% CI 88–100; figure 2A). The 24-month progression-free survival according to the number of risk factors was 94% (95% CI 67–99) in patients with one risk factor (n=21), 96% (73–99) in patients with two risk factors (n=24), and 85% (51–96) in patients with three or more risk factors (n=14; figure 2B). A total of four progression-free survival events were reported, including three patients with classic Hodgkin lymphoma relapse at 14·9, 15·6, and 18·1 months after enrolment, and one death due to *P jirovecii* pneumonia at 5·4 months. Two relapses were confirmed by biopsy; one relapse was not biopsy-proven (this patient was symptomatic and imaging recurrence was in the same locations [cervical, mediastinal, and lung] as previously biopsy-proven classic Hodgkin lymphoma). No significant associations were reported between PET

	Grade 1	Grade 2	Grade 3	Grade 4
Sensory peripheral neuropathy	24 (41%)	5 (8%)	2 (3%)	0
Neutrophil count decreased	3 (5%)	4 (7%)	12 (20%)	6 (10%)
Fatigue	19 (32%)	3 (5%)	0	0
Diarrhoea	13 (22%)	2 (3%)	2 (3%)	0
White blood cell decreased	8 (14%)	3 (5%)	4 (7%)	1 (2%)
Arthralgia	10 (17%)	5 (8%)	0	0
Aspartate aminotransferase increased	8 (14%)	5 (8%)	1 (2%)	0
Nausea	11 (19%)	2 (3%)	1 (2%)	0
Myalgia	9 (15%)	2 (3%)	1 (2%)	0
Alanine aminotransferase increased	7 (12%)	2 (3%)	2 (3%)	0
Dyspnoea	8 (14%)	3 (5%)	0	0
Motor peripheral neuropathy	6 (10%)	4 (7%)	1 (2%)	0
Maculopapular rash	8 (14%)	2 (3%)	1 (2%)	0
Abdominal pain	5 (8%)	5 (8%)	0	0
Lymphocyte count decreased	2 (3%)	4 (7%)	3 (5%)	0
Pneumonitis	1 (2%)	4 (7%)	4 (7%)	0
Vomiting	7 (12%)	2 (3%)	0	0
Chills	8 (14%)	0	0	0
Anaemia	6 (10%)	0	1 (2%)	0
Fever	6 (10%)	1 (2%)	0	0
Platelet count decreased	5 (8%)	0	1 (2%)	1 (2%)
Pruritus	6 (10%)	1 (2%)	0	0
Cough	6 (10%)	0	0	0
Headache	6 (10%)	0	0	0
Blood bilirubin increased	2 (3%)	0	2 (3%)	0
Lipase increased	2 (3%)	0	2 (3%)	0
Colitis	0	1 (2%)	1 (2%)	0
Cytokine release syndrome	0	0	1 (2%)	0
Eggerthella lenta pneumonia	0	0	1 (2%)	0
Hyperglycaemia	0	0	1 (2%)	0
Respiratory failure	0	0	0	1 (2%)
Syncope	0	0	1 (2%)	0

Data are n (%). Data are for all exposed patients (n=59). Grade 1 or 2 adverse events occurring in at least 10% of patients and all grade 3 or worse adverse events are shown. No treatment-related grade 5 adverse events occurred.

Table 2: **Adverse events (worse grade) with a possible or higher attribution to brentuximab vedotin or nivolumab, or both**

	Grade 1	Grade 2	Grade 3	Grade 4
Aspartate aminotransferase increased	3 (5%)	5 (8%)	1 (2%)	0
Pneumonitis	1 (2%)	4 (7%)	3 (5%)	0
Alanine aminotransferase increased	3 (5%)	2 (3%)	3 (5%)	0
Maculopapular rash	5 (8%)	1 (2%)	1 (2%)	0
Hypothyroidism	1 (2%)	3 (5%)	0	0
Blood bilirubin increased	2 (3%)	0	2 (3%)	0
Alkaline phosphatase increased	1 (2%)	0	0	0
Laryngitis	0	1 (2%)	0	0
Pharyngitis	0	1 (2%)	0	0
Viral hepatitis	0	1 (2%)	0	0
Immune-related veno-occlusive disease	0	1 (2%)	0	0
Colitis	0	0	1 (2%)	0
Diarrhoea	0	0	1 (2%)	0
Pruritus	0	1 (2%)	0	0
Increased thyroid stimulating hormone	0	1 (2%)	0	0
Cytokine release syndrome	0	0	1 (2%)	0
Respiratory failure	0	0	0	1 (2%)

Data are n (%). Data are for all exposed patients (n=59). Adverse events with identical terms in tables 2–3 were not all considered to be immune-related adverse events; therefore, numbers might differ between tables 2 and 3.

Table 3: **All immune-related adverse events (worse grade) listed in order of frequency**

status before autologous HSCT, receipt of previous PD-1 blockade, completion of all 8 cycles of both brentuximab vedotin plus nivolumab, or completion of 8 cycles of at least one drug and progression-free survival (appendix pp 1, 5). The 24-month cumulative incidence of relapse and progression was 5·7% (95% CI 1·5–14); the 24-month cumulative incidence of non-relapse mortality was 1·8% (0·14–8·4).

Complete early discontinuation of study treatment (both brentuximab vedotin and nivolumab) occurred in 14 (24%) of 59 patients after a median of 4 cycles (IQR 3–5) of treatment. The reasons for complete discontinuation included toxic effects (n=6; pneumonitis [n=3], abdominal pain [n=1], myalgia [n=1], and rash [n=1]), voluntary patient withdrawal (n=6; withdrawal after pneumonitis [n=1], logistical reasons [n=5]—eg, returning to college), lost to follow-up (n=1), and death from *P jirovecii* pneumonia (n=1; figure 1). Among patients with voluntary withdrawal or who were lost to follow-up, all intended doses of brentuximab vedotin and nivolumab had been administered until the time of discontinuation except one patient who received 3 cycles total with nivolumab discontinued after 1 cycle due to increased bilirubin. Early discontinuation of brentuximab vedotin with continuation of nivolumab occurred in eight (14%) of 59 patients after a median of 5·5 cycles (IQR 2·5–6·5), due to grade 3 peripheral neuropathy (n=2), grade 2 peripheral neuropathy (n=2), carpal tunnel syndrome (n=1), gastrointestinal adverse events (n=2), and infusion-related reaction (n=1). Of the five patients who discontinued early due to peripheral neuropathy or carpal tunnel syndrome, three (60%) received previous brentuximab vedotin. A similar proportion of patients with previous brentuximab vedotin exposure compared with brentuximab vedotin naive patients completed all 8 cycles of brentuximab vedotin (18 [60%] of 30 *vs* 18 [62%] of 29). Early discontinuation of nivolumab with continuation of brentuximab vedotin occurred in seven (12%) of 59 patients after a median of 3 cycles (IQR 1–4), due to pneumonitis (n=2), colitis (n=1), elevated bilirubin (n=1),

abnormal aminotransaminases (n=1), pneumonia with elevated creatinine (n=1), and hypotension with fever (n=1). Brentuximab vedotin dose reduction to 1·2 mg/kg occurred in 11 (19%) of 59 patients, due to peripheral neuropathy (n=9), neutropenia (n=1), and arthralgia (n=1). Adverse events related to brentuximab vedotin plus nivolumab consolidation are listed in table 2. The most frequent adverse events were sensory peripheral neuropathy (31 [53%] of 59), neutropenia (25 [42%]), fatigue (22 [37%]), diarrhoea (17 [29%]), arthralgia (15 [25%]), nausea (14 [24%]), elevated AST (14 [24%]), and myalgia (12 [20%]). The most frequent grade 3 or worse adverse events were neutropenia (18 [31%] of 59) and pneumonitis (four [7%]). The most common immune-related adverse events (any grade) are listed in table 3, including elevated AST (nine [15%] of 59), pneumonitis (eight [14%]), elevated ALT (eight [14%]), rash (seven [12%]), hyperbilirubinaemia (four [7%]), and hypothyroidism (four [7%]). Immune-related adverse events requiring systemic corticosteroids occurred in 17 (29%) of 59 patients (appendix p 4). Of the 25 patients with previous anti-PD-1 exposure, two (8%) had immune-related adverse events requiring corticosteroids, compared with 15 (44%) of 34 patients with no previous anti-PD-1 exposure who developed immune-related adverse events requiring steroids. Among eight patients with immune-related pneumonitis (three with grade ≥3), the median time to onset was 2·7 months (IQR 2·3–4·2) after initiating brentuximab vedotin plus nivolumab, seven patients required corticosteroids, and pneumonitis resolved in all cases. The unacceptable toxicity monitoring threshold was never met throughout the study. One death due to *P jirovecii* pneumonia was reported in the study; this patient was non-compliant with the prescribed trimethoprim plus sulfamethoxazole prophylaxis.

Of the three patients with relapse after brentuximab vedotin plus nivolumab consolidation, one (33%) patient (relapsed about 10 months after last dose of brentuximab vedotin plus nivolumab) had paired baseline and relapse tissue for evaluation. Multispectral immunofluorescence showed increased density of PD-1$^+$CD8$^+$ T-cells, CD163$^+$ macrophages, NK cells, B cells, and PD-L1$^+$ Reed-Sternberg cells, and decreased density of PD-1$^+$CD4$^+$ T-cells and plasma cells between the baseline and post-progression biopsies (appendix p 2).

Discussion

Brentuximab vedotin plus nivolumab consolidation resulted in an 18-month progression-free survival of 94% in patients with high-risk relapsed or refractory classic Hodgkin lymphoma undergoing autologous HSCT. Intensifying consolidation by adding nivolumab to brentuximab vedotin yielded promising activity despite a shorter planned duration of therapy (8 cycles *vs* 16 cycles). The overall rate of sensory peripheral neuropathy was similar to AETHERA (51% *vs* 56%), although grade 3 or worse peripheral neuropathy occurred less frequently.[3] More toxic effects were observed in our study than in those using brentuximab vedotin plus nivolumab in the pre-HSCT setting, including a higher rate of immune-related adverse events requiring systemic corticosteroids.[15,16] Notably, most patients in the study cohort had received previous brentuximab vedotin or PD-1 blockade, suggesting that these results are applicable to patients who have pervious exposure to but have not progressed on novel immunotherapies.

The randomised AETHERA study showed that brentuximab vedotin consolidation led to a sustained improvement in progression-free survival compared with placebo in patients with high-risk relapsed or refractory classic Hodgkin lymphoma, suggesting that brentuximab vedotin consolidation prevented relapses that would have occurred otherwise.[2] We built on this conceptual framework by adding nivolumab to brentuximab vedotin with the goal of further improving outcomes; our phase 2 study met its primary endpoint with efficacy that compared favourably with post- autologous HSCT outcomes in prospective or retrospective studies, including AETHERA.[2,3,18] PD-1 blockade monotherapy has also been previously studied as consolidation after autologous HSCT, with a planned 8 cycles of pembrolizumab resulting in an 18-month progression-free survival of 82% and a similar rate of immune-related toxicity (40% grade ≥2 immune-related adverse events) as our study.[14] The activity we observed after brentuximab vedotin plus nivolumab consolidation in our higher risk study cohort compares favourably with pembrolizumab consolidation.[14]

The allowance of previous exposure to brentuximab vedotin or PD-1 blockade is a key difference between our study and AETHERA, which is the only other prospective study of brentuximab vedotin consolidation and which only enrolled patients who were naive to brentuximab vedotin and PD-1 blockade.[2,3] Patients in the pembrolizumab consolidation study were allowed to have received previous novel immunotherapies, although the proportion of patients with previous brentuximab vedotin and anti-PD-1 exposure was lower (20% for each) than in our cohort.[14] In the modern era, brentuximab vedotin and PD-1 blockade are frequently used in earlier lines of therapy before autologous HSCT, which complicates the current applicability of the AETHERA results and the use of brentuximab vedotin consolidation.[4–7,15,16,19–21] A retrospective study showed favourable outcomes with brentuximab vedotin consolidation in patients with high-risk relapsed or refractory classic Hodgkin lymphoma, 70% of whom had received brentuximab vedotin as salvage therapy.[18] Also, retreatment with brentuximab vedotin or PD-1 blockade in patients with relapsed or refractory classic Hodgkin lymphoma who were previously sensitive has been shown to be effective.[22,23] The good progression-free survival we observed supports the use of consolidation with novel agents in patients who meet high-risk criteria and have not progressed on previous

brentuximab vedotin or PD-1 blockade. Therefore, a patient who responds to brentuximab vedotin or PD-1 blockade, or both, during salvage before autologous HSCT would be a reasonable candidate for post-HSCT consolidation with brentuximab vedotin plus nivolumab.

The toxicity profile of brentuximab vedotin plus nivolumab consolidation after autologous HSCT differed from what has been observed with the combination in other settings, with reduced tolerability of a full course of therapy.[15,16] Infusion-related reactions were infrequent with post- autologous HSCT consolidation, possibly due to the immunosuppression observed after myeloablative chemotherapy with autologous HSCT. A higher rate of immune-related adverse events requiring systemic corticosteroids was observed with post-autologous HSCT consolidation compared with the pre-transplantation setting, which might result from introducing PD-1 blockade while the immune system is remodelling after autologous HSCT. This finding is similar to other trials of checkpoint blockade after autologous HSCT in which immune-related adverse events were observed at similar or higher rates.[14,24] Fewer immune-related adverse events requiring corticosteroids were observed in patients with previous exposure to PD-1 blockade. However, the anti-PD-1 exposed patients were a selected population since patients with previous immune-related adverse events related to anti-PD-1 therapy were unlikely to be enrolled to the study. The rate of grade 3 or worse neutropenia (30%) was similar to AETHERA (29%) but higher than pembrolizumab post-autologous HSCT consolidation (10%). The rate of pneumonitis after brentuximab vedotin plus nivolumab consolidation was 15%, which is similar to the rate of pulmonary toxicity observed after pembrolizumab consolidation (13%) and within the range of pneumonitis incidence observed following high-dose chemotherapy regimens containing carmustine.[14,25] Although nivolumab, brentuximab vedotin, and carmustine are all associated with pneumonitis, no clear signal of increased pulmonary toxicity was observed with brentuximab vedotin plus nivolumab consolidation after BEAM (carmustine, etoposide, cytarabine, and melphalan) autologous HSCT.

45 (76%) of 59 patients completed all eight cycles of at least either brentuximab vedotin or nivolumab, but only about half of patients completed all planned cycles of brentuximab vedotin plus nivolumab. More than one-third of the patients who discontinued both brentuximab vedotin and nivolumab did so due to logistical reasons; overall it was a minority of patients who discontinued all therapy due to toxic effects. A more aggressive dose management protocol or even fewer cycles might improve tolerability in future studies. Decreasing the number of cycles would also reduce the considerable financial burden of the regimen, although the fewer planned cycles of brentuximab vedotin helps balance the cost relative to AETHERA. An advantage to using brentuximab vedotin plus nivolumab consolidation as opposed to either brentuximab vedotin or PD-1 blockade alone is the ability to discontinue one agent that is being poorly tolerated while continuing the other.

Despite the excellent outcomes we observed, our study has limitations. We designed our study using the AETHERA results as a historical comparison and, therefore, mirrored the AETHERA study eligibility criteria for our trial of brentuximab vedotin plus nivolumab. However, since these studies were done in different eras with different salvage therapies available and different response criteria used, important differences exist in the study populations that must be acknowledged. Although the inclusion of patients with previous exposure to brentuximab vedotin or PD-1 blockade is more reflective of modern practice, the exclusion of patients who had progressed while receiving brentuximab vedotin or PD-1 blockade might have excluded unfavourable patients from our study. Data with novel frontline or salvage regimens suggest such patients represent less than 20% of those treated and excluding these patients from the potential toxicity of repeating a therapy they are resistant to was logical.[4–7,15,16,19–21] By requiring only one high-risk factor to meet study eligibility in the modern era in which novel salvage regimens associated with high complete response rates are available, we enrolled 36% of patients with only one high-risk factor (AETHERA had <15%) and 64% of patients with two or more high-risk risk factors (85% in AETHERA). This difference is notable, since in AETHERA, brentuximab vedotin conferred no progression-free survival advantage in patients with one risk factor and increasing numbers of risk factors were associated with poorer progression-free survival (even among brentuximab vedotin recipients), thus our more favourable population would be expected to have better outcomes. Likewise, a high proportion of patients (81%) were in complete response by PET at autologous HSCT in our study, which again, might be related to the inclusion of novel agents in some patients' salvage treatment.[2,3] Older lymphoma response criteria[26] were used in AETHERA, which complicates direct comparison of the PET complete response rate at autologous HSCT between the patients enrolled to AETHERA and our study. For example, since patients with unknown PET status at autologous HSCT contributed to the denominator for the calculated PET-positive proportions *vs* PET-negative proportions in AETHERA, the true PET complete response rate appears higher than reported. Also, since the Deauville scores at autologous HSCT are not reported, assessment was not possible for what proportion of patients considered PET positive by the Cheson 2007 criteria in AETHERA would have been considered PET negative using the Lugano classification. Even accounting for these differences, the higher proportion of patients in PET complete response at autologous HSCT in our study, compared with AETHERA, possibly influenced the excellent post-autologous HSCT progression-free survival in our cohort, since PET status at autologous HSCT is an essential prognostic factor.[27,28] Another limitation of our study was our use of

investigator-assessed response and progression as opposed to independent or central assessment. The primary limitation of our study was a non-randomised design, which prevents us from precisely determining the effect of adding nivolumab to brentuximab vedotin consolidation. A randomised study would be the most accurate way to assess this effect and is merited based on our findings.

Similar to what was observed after pembrolizumab consolidation,[14] multispectral immunofluorescence analysis of the tumour microenvironment at relapse after brentuximab vedotin plus nivolumab identified increased PD-1 expression on $CD8^+$ T-cells and increased PD-L1 expression on Reed-Sternberg cells. Other studies have also shown increased PD-1 and PD-L1 expression at relapse following PD-1 blockade, suggesting that changes in the tumour microenvironment leading to PD-1 and PD-L1 modulation might have a role in resistance to PD-1 blockade.[14,29,30] Because our study had few relapses, we were not able to confirm this finding in a larger number of patients.

In conclusion, brentuximab vedotin plus nivolumab consolidation after autologous HSCT resulted in good outcomes in patients with high-risk relapsed or refractory classic Hodgkin lymphoma who mostly had previous exposure to either brentuximab vedotin or PD-1 blockade. On the basis of the toxic effects observed in our study, brentuximab vedotin plus nivolumab consolidation might be best suited to the highest-risk patients, wherein the balance of cost, toxicity, and efficacy might favour more intensive consolidation to prevent relapse. Our findings support further evaluation of combination immunotherapy as consolidation to improve outcomes in patients with classic Hodgkin lymphoma undergoing autologous HSCT.

Contributors

AFH, LC, and SP designed the study. AFH, LH, YN, PJ, TF, and LC had access to the raw data. AFH and LC verified and analysed the data. AFH wrote the paper and had final responsibility to submit for publication. All authors collected and interpreted the data, and edited the paper.

Declaration of interests

AFH reports research funding from Bristol Myers Squibb (BMS), Merck, Genentech, F Hoffmann-La Roche, Gilead Sciences, Seattle Genetics, AstraZeneca, and ADC Therapeutics; and consultancy for BMS, Merck, Genentech, F Hoffmann-La Roche, Kite Pharma/Gilead, Seattle Genetics, Karyopharm, Takeda, Tubulis, AstraZeneca, Genmab, Pfizer, Caribou, Adicet Bio, Abbvie, and Regeneron. MM reports research funding from TG therapeutics, Epizyme, and BMS; and consultancy for Morphosys and Glaxosmithkline. AS reports honoraria for consultancy or speakers bureau from Abbvie, AstraZeneca, ADC Therapeutics, BeiGene, BMS, Celgene, Epizyme, Genentech, GenMab, Janssen, Jazz Pharmaceuticals, Kite Pharma, Novartis, MorphoSys, Pharmacyclics, and TG Therapeutics. All other authors declare no competing interests.

Data sharing

Data collected for the study, including individual deidentified participant data and a data dictionary defining each field in the set, can be requested by email to the corresponding author.

Acknowledgments

Research funding and nivolumab were provided by Bristol Myers Squibb. AFH was supported by the Emmet and Toni Stephenson Leukemia and Lymphoma Society Scholar Award, and the Lymphoma Research Foundation Larry and Denise Mason Clinical Investigator Career Development Award. Research reported in this Article included work done in the Biostatistics and Mathematical Oncology Core supported by the National Cancer Institute of the National Institutes of Health, under award number P30CA033572.

References

1 Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet* 2002; **359:** 2065–71.

2 Moskowitz CH, Walewski J, Nademanee A, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. *Blood* 2018; **132:** 2639–42.

3 Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015; **385:** 1853–62.

4 Moskowitz AJ, Schoder H, Yahalom J, et al. PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study. *Lancet Oncol* 2015; **16:** 284–92.

5 Herrera AF, Palmer J, Martin P, et al. Autologous stem-cell transplantation after second-line brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. *Ann Oncol* 2018; **29:** 724–30.

6 LaCasce AS, Bociek RG, Sawas A, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. *Blood* 2018; **132:** 40–48.

7 Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med* 2018; **378:** 331–44.

8 Ramsey SD, Nademanee A, Masszi T, et al. Quality of life results from a phase 3 study of brentuximab vedotin consolidation following autologous haematopoietic stem cell transplant for persons with Hodgkin lymphoma. *Br J Haematol* 2016; **175:** 860–67.

9 Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood* 2010; **116:** 3268–77.

10 Roemer MG, Advani RH, Ligon AH, et al. PD-L1 and PD-L2 genetic alterations define classical Hodgkin lymphoma and predict outcome. *J Clin Oncol* 2016; **34:** 2690–97.

11 Armand P, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 Trial. *J Clin Oncol* 2018; **36:** 1428–39.

12 Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol* 2017; **35:** 2125–32.

13 Moskowitz AJ, Shah G, Schoder H, et al. Phase II trial of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin as second-line therapy for relapsed or refractory classical Hodgkin lymphoma. *J Clin Oncol* 2021; **39:** 3109–17.

14 Armand P, Chen YB, Redd RA, et al. PD-1 blockade with pembrolizumab for classical Hodgkin lymphoma after autologous stem cell transplantation. *Blood* 2019; **134:** 22–29.

15 Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. *Blood* 2018; **131:** 1183–94.

16 Cheson BD, Bartlett NL, LaPlant B, et al. Brentuximab vedotin plus nivolumab as first-line therapy in older or chemotherapy-ineligible patients with Hodgkin lymphoma (ACCRU): a multicentre, single-arm, phase 2 trial. *Lancet Haematol* 2020; **7:** e808–15.

17 Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32:** 3059–68.

18 Marouf A, Cottereau AS, Kanoun S, et al. Outcomes of refractory or relapsed Hodgkin lymphoma patients with post autologous stem cell transplantation brentuximab vedotin maintenance: a French multicenter observational cohort study. *Haematologica* 2022; **107:** 1681–86.

19 Allen PB, Savas H, Evens AM, et al. Pembrolizumab followed by AVD in untreated early unfavorable and advanced-stage classical Hodgkin lymphoma. *Blood* 2021; **137:** 1318–26.

20 Bröckelmann PJ, Goergen H, Keller U, et al. Efficacy of nivolumab and AVD in early-stage unfavorable classic Hodgkin lymphoma: the randomized phase 2 German Hodgkin study group NIVAHL trial. *JAMA Oncol* 2020; **6:** 872–80.

21 Kumar A, Casulo C, Advani RH, et al. Brentuximab vedotin combined with chemotherapy in patients with newly diagnosed early-stage, unfavorable-risk Hodgkin lymphoma. *J Clin Oncol* 2021; **39:** 2257–65.

22 Fedorova L, Lepik K, Mikhailova N, et al. Retreatment with nivolumab in patients with R/R classical Hodgkin lymphoma after discontinuation of the therapy with immune checkpoint inhibitors. *Hematol Oncol* 2019; **37:** 496–97.

23 Bartlett NL, Chen R, Fanale MA, et al. Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. *J Hematol Oncol* 2014; **7:** 24.

24 Skarbnik AP, Donato ML, Feinman R, et al. Safety and efficacy of consolidation therapy with ipilimumab plus nivolumab after autologous stem cell transplantation. *Transplant Cell Ther* 2021; **27:** 391–403.

25 Lane AA, Armand P, Feng Y, et al. Risk factors for development of pneumonitis after high-dose chemotherapy with cyclophosphamide, BCNU and etoposide followed by autologous stem cell transplant. *Leuk Lymphoma* 2012; **53:** 1130–36.

26 Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; **25:** 579–86.

27 Moskowitz AJ, Yahalom J, Kewalramani T, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. *Blood* 2010; **116:** 4934–37.

28 Moskowitz CH, Matasar MJ, Zelenetz AD, et al. Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. *Blood* 2012; **119:** 1665–70.

29 Sasse S, Reddemann K, Diepstra A, et al. Programmed cell death protein-1 (PD-1)-expression in the microenvironment of classical Hodgkin lymphoma at relapse during anti-PD-1-treatment. *Haematologica* 2019; **104:** e21–24.

30 Hollander P, Amini RM, Ginman B, Molin D, Enblad G, Glimelius I. Expression of PD-1 and PD-L1 increase in consecutive biopsies in patients with classical Hodgkin lymphoma. *PLoS One* 2018; **13:** e0204870.