# Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial

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## Summary

**Background** Malignant cells of classical Hodgkin's lymphoma are characterised by genetic alterations at the 9p24.1 locus, leading to overexpression of PD-1 ligands and evasion of immune surveillance. In a phase 1b study, nivolumab, a PD-1-blocking antibody, produced a high response in patients with relapsed and refractory classical Hodgkin's lymphoma, with an acceptable safety profile. We aimed to assess the clinical benefit and safety of nivolumab monotherapy in patients with classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin.

**Methods** In this ongoing, single-arm phase 2 study, adult patients (aged ≥18 years) with recurrent classical Hodgkin's lymphoma who had failed to respond to autologous stem-cell transplantation and had either relapsed after or failed to respond to brentuximab vedotin, and with an Eastern Cooperative Oncology Group performance status score of 0 or 1, were enrolled from 34 hospitals and academic centres across Europe and North America. Patients were given nivolumab intravenously over 60 min at 3 mg/kg every 2 weeks until progression, death, unacceptable toxicity, or withdrawal from study. The primary endpoint was objective response following a prespecified minimum follow-up period of 6 months, assessed by an independent radiological review committee (IRRC). All patients who received at least one dose of nivolumab were included in the primary and safety analyses. This trial is registered with ClinicalTrials.gov, number NCT02181738.

**Findings** Among 80 treated patients recruited between Aug 26, 2014, and Feb 20, 2015, the median number of previous therapies was four (IQR 4–7). At a median follow-up of 8·9 months (IQR 7·8–9·9), 53 (66·3%, 95% CI 54·8–76·4) of 80 patients achieved an IRRC-assessed objective response. The most common drug-related adverse events (those that occurred in ≥15% of patients) included fatigue (20 [25%] patients), infusion-related reaction (16 [20%]), and rash (13 [16%]). The most common drug-related grade 3 or 4 adverse events were neutropenia (four [5%] patients) and increased lipase concentrations (four [5%]). The most common serious adverse event (any grade) was pyrexia (three [4%] patients). Three patients died during the study; none of these deaths were judged to be treatment related.

**Interpretation** Nivolumab resulted in frequent responses with an acceptable safety profile in patients with classical Hodgkin's lymphoma who progressed after autologous stem-cell transplantation and brentuximab vedotin. Therefore, nivolumab might be a new treatment option for a patient population with a high unmet need. Ongoing follow-up will help to assess the durability of response.

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## Introduction

For patients with first relapse of classical Hodgkin's lymphoma, as defined in the 2008 WHO classification,[1] the standard of care is high-dose chemotherapy followed by autologous stem-cell transplantation (ASCT).[2] In this population, only 55% of patients have been shown to be free from treatment failure at 3 years.[2] In patients who relapse after ASCT, prognosis is worse and only a small minority of patients can still be cured.[3,4] In the past 5 years, treatment with brentuximab vedotin after ASCT failure has resulted in a median overall survival of 22·4 months (95% CI 21·7–not estimable),[5] and median progression-free survival associated with the subsequent line of treatment following brentuximab vedotin is 3·5 months.[6] For patients who progress after ASCT and brentuximab vedotin, no standard treatment options exist at present. Thus, an unmet medical need for effective therapies persists in this patient population.

Classical Hodgkin's lymphoma is characterised by rare Reed–Sternberg cells,[7] which have copy number alterations involving chromosome 9p24.1, resulting in overexpression of the PD-1 ligands PD-L1 and PD-L2 on the tumour cell surface.[8–11] *JAK2* is also located on chromosome 9p24.1, and alterations in this gene increase JAK–STAT signalling, further inducing PD-L1 overexpression.[9] Under normal physiological conditions, activation of the PD-1 pathway via PD-L1 and PD-L2 engagement limits T-cell-mediated immune

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## Research in context

### Evidence before this study

To establish the role of brentuximab vedotin in treatment of classical Hodgkin's lymphoma, we searched PubMed on March 18, 2016, for all clinical trials with the terms "Hodgkin lymphoma" AND "brentuximab vedotin". We did not apply any language restrictions. Among the 16 articles we identified, brentuximab vedotin generally had clinically meaningful efficacy and acceptable tolerability in Hodgkin's lymphoma after autologous stem-cell transplantation (ASCT). Brentuximab vedotin is the only approved treatment for relapsed or refractory Hodgkin's lymphoma following failure of ASCT. In one study, responses upon re-treatment with brentuximab vedotin were reported in patients who progressed after an initial response to brentuximab vedotin; however, no studies investigated new agents for patients who did not respond to brentuximab vedotin treatment.

### Added value of this study

In this phase 2 study of nivolumab in a heavily pre-treated population who had not responded to ASCT and brentuximab vedotin, the proportion of patients achieving an objective response was high, and most patients had ongoing responses, including some durable responses that might extend with ongoing follow-up. Nivolumab was well tolerated and had an acceptable safety profile in this patient population. These results validate earlier findings from a phase 1b trial, and will hopefully contribute to research progress in an area with an unmet medical need.

### Implications of all the available evidence

Brentuximab vedotin has improved outcomes in patients with classical Hodgkin's lymphoma and is the preferred treatment for patients who have progressed after ASCT. However, many patients eventually become refractory to brentuximab vedotin and have no good therapeutic options. Duration and depth of response are important, because patients are often young and otherwise healthy. Nivolumab provides a new treatment option for patients with classical Hodgkin's lymphoma and has the potential to produce durable responses, even in heavily pre-treated patients.

responses.[12] Therefore, increased PD-L1 and PD-L2 expression by Reed–Sternberg cells might enable these cells to evade immune surveillance, suggesting that blockade of this pathway could be an effective treatment approach for patients with classical Hodgkin's lymphoma.[13]

Nivolumab, a fully human immunoglobulin G4 immune checkpoint inhibitor antibody that targets PD-1, is approved by the US Food and Drug Administration for the treatment of advanced-stage melanoma,[14] non-small-cell lung cancer,[15] and renal cell carcinoma.[16] A phase 1b study[17] assessed nivolumab in 23 patients with relapsed or refractory classical Hodgkin's lymphoma, including 15 patients who had progressed after ASCT or brentuximab vedotin treatment: the safety profile was acceptable, investigator-defined objective response was reported in 20 (87%) of 23 patients, and 86% (95% CI 62–95) of patients had progression-free survival at 24 weeks. With extended follow-up (median 20 months, range 7–25), durable responses to nivolumab have been shown: seven (35%) of 20 responders maintained a response for more than 1·5 years.[18] In all ten evaluable tumour samples, Reed–Sternberg cells had copy number alterations of chromosome 9p24.1 and increased PD-L1 and PD-L2 expression. Additionally, phosphorylated STAT3 was detected in Reed–Sternberg cell nuclei in all cases, suggesting active JAK–STAT signalling.[17] To explore the effects of PD-1 blockade in patients who relapse after treatment with approved, standard therapies, we initiated a phase 2 study, with the aim of assessing the activity and safety of nivolumab in patients with classical Hodgkin's lymphoma after failure of ASCT and brentuximab vedotin.

See Online for appendix

## Methods

### Study design and participants

This trial was a multicentre, non-comparative, multicohort, single-arm phase 2 study. In this Article, we report results from one cohort: patients with classical Hodgkin's lymphoma after failure of both ASCT and subsequent brentuximab vedotin treatment. Other study cohorts included patients after failure of ASCT who were brentuximab vedotin naive, patients after failure of ASCT who received brentuximab vedotin at any time prior to receiving the study drug, and patients with newly diagnosed advanced-stage classical Hodgkin's lymphoma. We recruited patients from 34 hospitals and academic centres across Europe, Canada, and the USA (appendix p 2). Eligible patients were aged 18 years or older and had recurrent classical Hodgkin's lymphoma after failure of ASCT and subsequent brentuximab vedotin. Patients were required to have received previous brentuximab vedotin but were not required to be refractory to brentuximab vedotin; therefore, those who responded to brentuximab vedotin and later had disease progression were eligible. At enrolment, all eligible patients had to have an Eastern Cooperative Oncology Group performance status score of 0 or 1 and either documented failure to achieve at least partial remission after the most recent treatment, or documented relapse (after complete remission) or disease progression (after partial remission or stable disease; appendix p 3). Patients also had to have had previous high-dose conditioning chemotherapy followed by ASCT as part of salvage therapy. However, those who had the following treatments or therapies were excluded: treatment with brentuximab vedotin before the first ASCT; ASCT within 90 days of the first

dose of nivolumab; previous chemotherapy within 4 weeks, nitrosoureas within 6 weeks, therapeutic anti-cancer antibodies within 4 weeks, radio-immunoconjugates or toxin immunoconjugates (excluding brentuximab vedotin) within 10 weeks, brentuximab vedotin within 4 weeks, or major surgery within 2 weeks of the first dose of nivolumab; carmustine at a dose of 600 mg/m² or more received as part of the pre-transplantation conditioning regimen; previous radiotherapy within 3 weeks or chest radiation within 24 weeks before the first dose of nivolumab; previous treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways); and previous allogeneic stem-cell transplantation. We did not restrict stem-cell transplantation (autologous and allogeneic) after discontinuation of nivolumab treatment. Patients with the following concurrent diseases were excluded from the study: active interstitial pneumonitis; any serious or uncontrolled medical disorder that might have resulted in an increased risk associated with participation in the study or study drug administration, that impaired the ability of the patient to receive nivolumab, or that interfered with the interpretation of study results; a prior malignancy active within the previous 3 years (except for locally curable cancers that have been apparently cured); active, known, or suspected autoimmune disease (except for vitiligo, type 1 diabetes, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger); or conditions requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive drugs within 14 days of nivolumab administration. Inhaled or topical steroids and adrenal replacement doses more than 10 mg daily prednisone equivalents were allowed in the absence of active autoimmune disease.

The study was done in accordance with the Declaration of Helsinki. The protocol, amendments, and patient informed consent received appropriate approval by the Institutional Review Board and the Independent Ethics Committee before study initiation at each site. Written informed consent was obtained from all patients before trial enrolment.

### Procedures

Patients received nivolumab intravenously over 60 min at 3 mg/kg every 2 weeks until disease progression, death, unacceptable toxicity, withdrawal of consent, or study end (at least 5 years of follow-up; appendix p 11). Dose reductions were not allowed; dose interruptions (any dose given >3 days after scheduled dosing date) were allowed for all drug-related adverse events until the resolution of these events, or for a maximum of 6 months. Patients who had interruptions lasting for more than 6 weeks were permanently discontinued from the study, except when dosing was interrupted to allow for prolonged steroid tapers to manage drug-related adverse events or when such interruptions due to non-drug-related reasons were approved by the study's medical monitor. A protocol amendment made on July 10, 2014, allowed patients to continue treatment beyond investigator-assessed progression in cases of atypical clinical response patterns, such as reduction in total tumour burden in spite of the appearance of a new lesion or lesions (appendix p 3). The amendment was approved by the local ethics committees at each institution and local ministries of health in each country.

Patients were assessed for tumour responses by CT (preferred) or MRI at baseline and at weeks 9, 17, 25, 37, and 49 during the first year of treatment, and then every 16 weeks until week 97, continuing every 26 weeks beyond week 97 until documented disease progression or until the patient initiated a preparative regimen for allogeneic or autologous stem-cell transplantation. $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PET was done at baseline and at weeks 17 and 25. At week 49, an $^{18}$F-FDG PET scan was required for patients who did not have two consecutive negative scans before this timepoint. A negative $^{18}$F-FDG PET scan, visually assessed by an independent radiological review committee (IRRC),[19] was required for confirmation of complete remission. For patients with bone marrow involvement at screening, a bone marrow biopsy was required to confirm complete remission. Tumour biopsy samples were obtained by excisional or incisional biopsy, or with a core needle. Submission of tumour tissue (formalin-fixed, paraffin-embedded tumour tissue block, or ten unstained slides) from a biopsy done during screening was mandatory. Archival tissue from the most recent tumour biopsy was an acceptable alternative where biopsies at screening were not possible. Quality of life was assessed every four cycles for the first 17 cycles, then every six cycles, with the EQ-5D questionnaire and the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire—Core 30 (EORTC QLQ-C30; appendix p 3).

Prespecified analyses of PD-1 ligand loci and protein expression were done at the Dana–Farber Cancer Institute (Boston, MA, USA), as previously described.[10,17] Fluorescence in-situ hybridisation was done with probes targeting *PD-L1* (*CD274*), *PD-L2* (*PDCD1LG2*; both Empire Genomics, Buffalo, NY, USA), and a centromeric region of chromosome 9 (CEP 9, control probe; Abbott Molecular, Abbott Park, IL, USA). Reed–Sternberg cells were identified by their histomorphological features and weak positive staining for PAX5 (BD Biosciences, San Jose, CA, USA); 50 Reed–Sternberg cells per patient were analysed. Nuclei with a target-to-control probe ratio of at least 3:1 were classified as being amplified, those with a probe ratio of more than 1:1 but less than 3:1 were classified as having relative copy gain, and

those with a probe ratio of 1:1 but with more than two copies of each probe were classified as polysomic for 9p24.1. Double staining of PD-L1 and PAX5 and of PD-L2 and phosphorylated STAT3 was done as previously described.[10,17] PD-L1 expression was assessed in PAX5-positive malignant Reed–Sternberg cells and in PAX5-negative cells in the tumour microenvironment (appendix p 4). The PD-L1 H score was calculated by multiplying the percentage of malignant cells with positive staining by the average intensity of positive staining.

On-treatment local laboratory assessments were done within 72 h before dosing and included extended on-treatment local laboratory assessments during cycles 1–5 and every alternate dose thereafter, as well as some on-study treatment laboratory assessments beginning at cycle 6 and every alternate dose thereafter. Extended assessments were complete blood count with differential, blood urea nitrogen or serum urea concentrations, serum creatinine, sodium, potassium, calcium, magnesium, chloride, amylase, lipase, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, and lactate dehydrogenase. From cycle 6 onwards, on-study treatment laboratory assessments were complete blood count with differential, liver function tests (ALT, AST, total bilirubin, alkaline phosphatase), and creatinine. Additionally, thyroid-stimulating hormone (with reflexive free T4 and free T3) was assessed every 6 weeks from the first dose of nivolumab, irrespective of dosing schedule. Toxicity assessments were done continuously during the treatment phase. During the safety follow-up phase, adverse events were assessed at follow-up visits 1 (35 days from the last dose) and 2 (80 days from follow-up visit 1). Adverse events were recorded between the first nivolumab dose and 30 days after the last dose, and were defined according to the US National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) and coded using the Medical Dictionary for Regulatory Activities (version 18.0).

### Outcomes

The primary outcome was the proportion of patients achieving an objective response, defined as the percentage of treated patients with a best overall response of complete or partial remission, as per the revised International Working Group (IWG) criteria for Malignant Lymphoma (2007 criteria),[19] and assessed by the IRRC. The primary analysis was done when the prespecified minimum follow-up of 6 months was met for the cohort reported here. Best overall response was defined as the best response between the first dose and progression or subsequent therapy, whichever occurred first.

Secondary endpoints assessed after a prespecified minimum follow-up of 6 months were IRRC-assessed duration of objective response (censored on the last evaluable tumour assessment visit), the proportion of patients who achieved complete and partial remission, and duration of complete and partial remission, as well as investigator-assessed objective response and duration of objective response. Exploratory endpoints included IRRC-assessed progression-free survival (defined as the time from first dosing date to the date of the first documented progression, as determined by the IRRC according to the 2007 IWG criteria,[19] or death due to any cause, whichever occurred first), overall survival (defined as the time from first dosing date to the date of death; patients who have not died were censored at last known date alive), safety and tolerability, quality of life, as well as 9p24.1 alterations, and PD-1 ligand expression.

### Statistical analysis

The planned sample size of 60 patients provided roughly 93% power to reject the null hypothesis that the true proportion of patients achieving an objective response is 20% or fewer, assuming an objective response of 40% and given a two-sided α of 5%. All patients who received at least one dose of nivolumab were included in the clinical activity and safety analyses.

We summarised IRRC-assessed objective responses using a binomial response rate and corresponding two-sided 95% exact CI as per the Clopper-Pearson method. We ascertained IRRC-assessed duration of response using the Kaplan-Meier method for patients who had achieved partial or complete remission. IRRC assessment of best change from baseline in the target lesion was assessed in all response-evaluable patients—defined as patients with a best overall response of complete or partial remission, stable disease, or disease progression of target lesions assessed at baseline, and at least one on-study timepoint with all baseline target lesions assessed. Median duration of response and two-sided 95% CIs (based on log–log transformation) were calculated. Investigator-assessed objective response and duration of objective response were summarised in a similar way. For the analysis of concordance between IRRC and investigator assessments, best overall response was cross-tabulated by assessment type (investigator *vs* IRRC). Concordance for responders was computed as the frequency with which investigator and IRRC agreed on classification of a participant as a responder or non-responder as a proportion of the total number of participants assessed. We calculated progression-free survival (IRRC assessed) and overall survival using the Kaplan-Meier method; median values and two-sided 95% CIs based on log–log transformation were calculated.

Descriptive statistics were used to evaluate mean change in quality-of-life scores (appendix p 4). QLQ-C30 and EQ-5D were analysed in all treated patients who had an assessment at baseline and at least one subsequent assessment. We did a post-hoc analysis of IRRC-assessed best overall response in patients on the basis of previous response to brentuximab vedotin

(appendix p 4). We also did a post-hoc analysis of association between best overall response and PD-L1 H score with the Kruskal-Wallis rank-sum tests for continuous data comparing two or more groups. The modified H score for PD-L1 and PD-L2 protein expression was divided into four quartiles.

All clinical activity and safety analyses were done with SAS version 9.02, and biomarker analyses were done with R version 3.2.2. This study did not have a data monitoring committee. A medical monitor and medical safety team from the funder reviewed safety data during the trial.

This study is registered with ClinicalTrials.gov, number NCT02181738.

### Role of the funding source

The funder of the study provided the study drug and worked with the investigators to design the study, and to collect, analyse, and interpret the data. All authors made the decision to submit the report for publication, and all drafts of the report were prepared by the corresponding author with input from co-authors and editorial assistance from professional medical writers (Caudex, Oxford, UK), funded by the sponsor. The corresponding author had full access to all the data and the final responsibility to submit for publication.

## Results

Between Aug 26, 2014, and Feb 20, 2015, 80 patients were recruited and enrolled into the trial, all of whom were given treatment and included in the analyses. The median age of the patients was 37 years (IQR 28–48), the median number of previous lines of therapy was four (4–7), although nearly half of patients had received five or more previous lines, and three-quarters had previous radiotherapy (table 1; appendix pp 5, 6). The median time between the most recent brentuximab vedotin treatment and the first dose of nivolumab was 0·7 years (IQR 0·2–1·7), and the median time between high-dose conditioning chemotherapy followed by ASCT and the first dose of nivolumab was 3·4 years (1·9–5·9). Five (6%) of 80 patients required infusion interruption because of hypersensitivity reaction (one patient), discomfort (one patient), infusion reaction (one patient), unspecified adverse reaction (one patient), or unspecified reasons (one patient). Cycle delay occurred in 48 (60%) patients, with 26 (33%) patients requiring more than one delay. The most common reasons for dose delay were reported as adverse events (55%) and other reasons (45%). 85% of delays lasted less than 14 days. The final patient visit date was Aug 20, 2015, and the database was locked on Oct 5, 2015.

At the time of analysis, 51 (64%) patients remained on treatment (appendix p 12). The median number of nivolumab doses received was 17 (IQR 13–20). In the 29 patients who discontinued treatment, the main reasons for treatment discontinuation were disease progression (13 [16%]), study drug toxicity (four [5%] patients: one autoimmune hepatitis, one increased ALT concentration, one increased AST concentration, and one multi-organ failure), request to withdraw (two [3%]), loss to follow-up (one [1%]), an unreported reason (one [1%]), and other reasons in eight (10%) patients (allogeneic stem-cell transplantation in five [6%], ASCT in one [1%], planned allogeneic stem-cell transplantation in one [1%], and lack of response in one [1%];

| | All patients (n=80) |
|---|---|
| **Age, years** | |
| Median (IQR) | 37 (28–48) |
| <30 | 27 (34%) |
| 30–44 | 28 (35%) |
| 45–59 | 18 (23%) |
| ≥60 | 7 (9%) |
| **Sex** | |
| Male | 51 (64%) |
| Female | 29 (36%) |
| **Eastern Cooperative Oncology Group performance status** | |
| 0 | 42 (53%) |
| 1 | 38 (48%) |
| **Disease stage at study entry** | |
| I | 1 (1%) |
| II | 11 (14%) |
| III | 14 (18%) |
| IV | 54 (68%) |
| **B symptoms at baseline*** | |
| Present | 18 (23%) |
| Absent | 62 (78%) |
| **Previous lines of therapy†** | |
| Median (IQR) | 4 (4–7) |
| Five or more lines of therapy | 39 (49%) |
| Previous radiotherapy | 59 (74%) |
| Previous autologous stem-cell transplantation | |
| One | 74 (93%) |
| Two or more | 6 (8%) |
| **Previous brentuximab vedotin therapy** | |
| After autologous stem-cell transplantation | 80 (100%) |
| More than one line of brentuximab vedotin | 6 (8%) |
| No response to previous brentuximab vedotin | 43 (54%) |
| Previous lines of brentuximab vedotin, among patients with no response to prior brentuximab vedotin | |
| One | 38/43 (88%) |
| Two | 4/43 (9%) |
| Three | 1/43 (2%) |
| **Time from completion of most recent regimen to nivolumab treatment** | |
| <3 months | 44 (55%) |
| 3–6 months | 18 (23%) |
| >6 months | 18 (23%) |

Data are n (%) or n/N (%), unless specified otherwise. *B symptoms include unexplained weight loss of >10% in the past 6 months; unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month; or recurrent drenching night sweats during the previous month. †Salvage chemotherapy followed by high-dose preparative regimen prior to autologous stem-cell transplantation was considered a single line of therapy.

***Table 1:*** **Baseline characteristics**

| | IRRC assessed (n=80) | Investigator assessed (n=80) |
|---|---|---|
| Objective response | 53 (66·3%; 95% CI 54·8–76·4) | 58 (72·5%; 95% CI 61·4–81·9) |
| Best overall response | | |
| Complete remission | 7 (9%) | 22 (28%) |
| Partial remission | 46 (58%) | 36 (45%) |
| Stable disease | 18 (23%) | 18 (23%) |
| Progressive disease | 6 (8%) | 3 (4%) |
| Unable to determine | 3 (4%)* | 1 (1%)† |

Data are n (%), unless specified otherwise. *Two patients had no post-baseline tumour assessment available before or on the day of subsequent therapy (if any); for one patient, all post-baseline tumour assessments before or on the day of subsequent therapy (if any) were unknown. †No radiographic assessment was done after the first dose of nivolumab.

***Table 2*: Objective response and best overall response**

appendix p 12). No responding patients received subsequent radiotherapy for curative intent.

The number of patients who achieved an IRRC-assessed objective response was 53 (66·3%, 95% CI 54·8–76·4); the best overall responses were complete remission in seven (9%) patients and partial remission in 46 (58%) patients (table 2). All but one of the 53 responders had a tumour reduction of at least 50% from baseline (figure 1A); the remaining patient had a negative $^{18}$F-FDG PET scan. Investigator-assessed objective response was achieved in 58 patients (72·5%, 95% CI 61·4–81·9); the best overall responses were complete remission in 22 (28%) patients and partial remission in 36 (45%) patients (table 2). Concordance between IRRC and investigator assessments was 76·3% for objective response and 53·8% for best overall response (full data not shown). 13 of 19 investigator-assessed complete remissions were regarded at least as partial remission by the IRRC, and the proportional reduction in tumour burden was similar in the IRRC and investigator assessments (appendix p 15).

The median time to first objective response (IRRC assessed) was 2·1 months (IQR 1·9–3·0), with 31 (58%) of 53 responses achieved by the first scan at week 9. 33 (62%) responders continued to respond at the clinical data cutoff date for this analysis. Of the 33 ongoing responders, 20 had been in response for at least 4 months (figure 1B). Progressive disease after achieving an objective response was reported in 11 (21%) responders (one of seven patients with complete remission and ten of 46 with partial remission). The median follow-up duration was 8·9 months (IQR 7·8–9·9), and the median IRRC-assessed duration of objective response was 7·8 months (95% CI 6·6–not reached; figure 1C). Notably, in a post-hoc analysis of the 43 patients who had no previous response to the most recent brentuximab vedotin treatment before trial recruitment, as documented in their medical record, 31 (72%) achieved IRRC-assessed objective response after nivolumab treatment.

The median investigator-assessed duration of objective response was 9·1 months (95% CI 6·74–not available); this is an unstable estimate because of early censoring (37 of 58 responders still on treatment were censored prior to the median) and is subject to change with additional follow-up. The median duration of investigator-assessed complete remission was 8·7 months (95% CI not available); 16 (72%) of 22 patients with a complete remission were still continuing in response at the time of analysis. The median duration of investigator-assessed partial remission was 7·8 months (95% CI 6·7–7·8); 22 (61%) of 36 patients with a partial remission were still continuing in response at the time of analysis.

Several non-conventional patterns of benefit were recorded. In one patient, a new lesion was identified at week 9, followed by a negative $^{18}$F-FDG PET scan at weeks 25 and 33; the best overall response, according to the protocol-specified definition, was progressive disease. In nine patients who continued nivolumab beyond progression as per protocol amendment (appendix p 3) and investigator assessment, six maintained tumour reduction in target lesions (appendix p 13). Of these six patients, five maintained reduced tumour burden after the appearance of new lesions and the other had new lesion at the data cutoff.

At 6 months, IRRC-assessed progression-free survival was 76·9% (95% CI 64·9–85·3; figure 1D), and IRRC-assessed overall survival was 98·7% (91·0–99·8). At 12 months, 24 events (23 progression and one death) were reported, and median progression-free survival was 10·0 months (95% CI 8·41–not reached).

Our prespecified exploratory analysis showed that all 45 patients with available tumour biopsy samples had concordant alterations of the *PD-L1* and *PD-L2* loci in the malignant Reed–Sternberg cells (appendix p 14). Fluorescence in-situ hybridisation analyses of Reed–Sternberg cells revealed polysomy 9 in seven (16%) of 45 patients, copy gain of *PD-L1* and *PD-L2* in 26 (58%), and amplification of *PD-L1* and *PD-L2* in 12 (27%; appendix p 14). In the evaluable samples, there was an association between the magnitude of 9p24.1 gain and the level of PD-L1 protein expression in Reed–Sternberg cells (p=0·034, figure 2A; appendix p 14). Positive staining of phosphorylated STAT3 in the nuclei, which was indicative of active JAK–STAT signalling, was also detected in all 45 patients' tumour biopsy samples (appendix p 14).

In a post-hoc analysis, we also assessed the associations of IRRC-assessed objective response with 9p24.1 genetic alterations and PD-L1 H score in evaluable patients (figures 2B, 2C). None of the patients with progressive disease had amplification, and none of the patients with complete remission had polysomy (figure 2B). A difference was recorded in best overall response by PD-L1 H score (p=0·013; appendix p 7). All patients who achieved complete remission had PD-L1 H scores in the third or fourth quartiles, whereas those with progressive disease had PD-L1 H scores in the first quartile

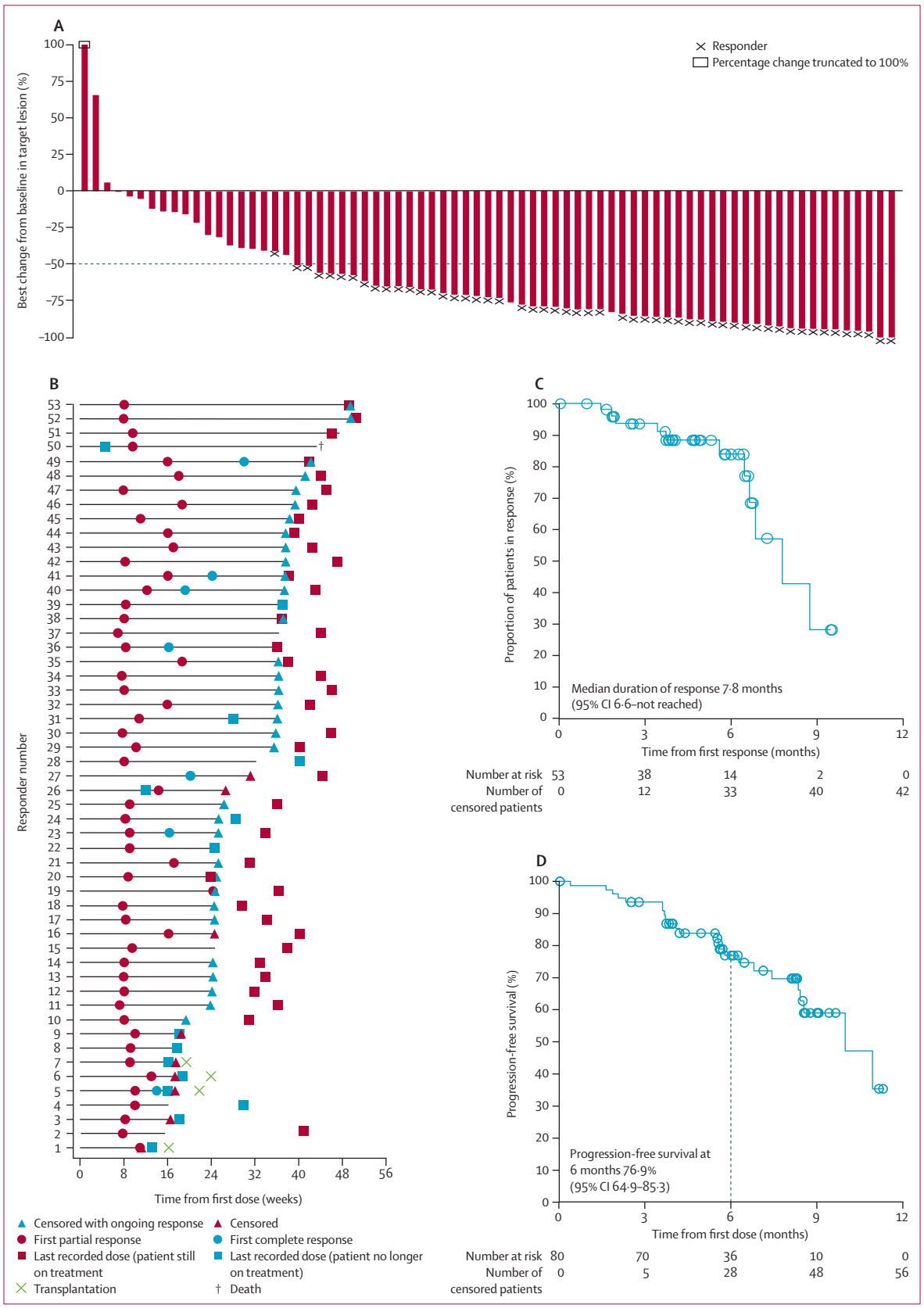


***Figure 1*: IRRC-assessed outcomes**
(A) Best change from baseline in target lesion for all response-evaluable patients. The dashed line indicates 50% reduction in target lesion. Negative values indicate maximum tumour reduction, and positive values indicate minimum tumour increase. (B) Response characteristics in all responders. (C) Duration of response. (D) Progression-free survival. IRRC=independent radiological review committee. The number of censored patients shown is cumulative.

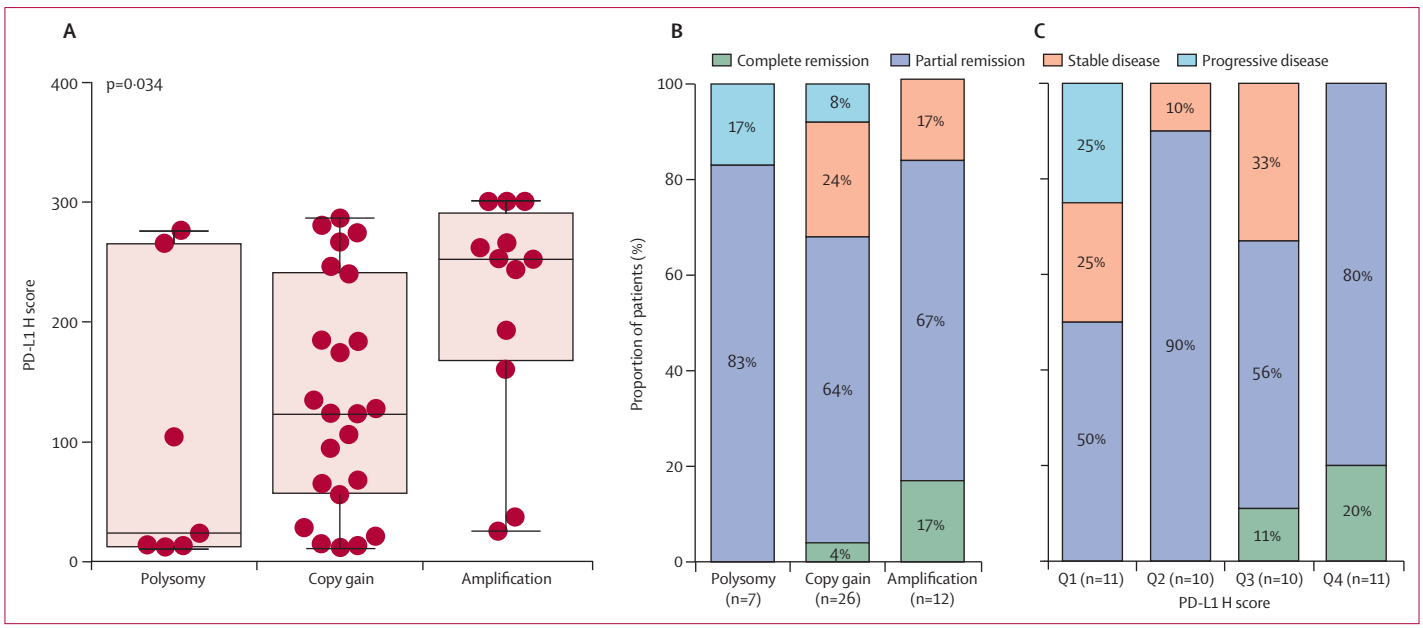


***Figure 2:*** ***PD-L1*** **and** ***PD-L2*** **alterations and PD-1 ligand expression in tumour biopsy samples from 45 patients**
(A) Distribution of PD-L1 H scores across cases with polysomy, copy gain, and amplification of 9p24.1. Three samples were not evaluable for PD-L1 immunohistochemistry. (B) Best overall responses in patients with Reed–Sternberg cells showing polysomy, copy gain, or amplification of 9p24.1. (C) Best overall responses by PD-L1 H score. Q=quartile.

(figure 2C; appendix p 7). Whereas PD-L1 expression on PAX5-positive malignant Reed–Sternberg cells was associated with response, PD-L1 expression on infiltrating PAX5-negative normal cells was not associated with response (data not shown).

Six patients chose to stop nivolumab treatment and proceeded to stem-cell transplantation (five allogeneic stem-cell transplantation and one ASCT). Because transplantation was regarded as a subsequent therapy, these patients were censored at the time of transplantation. IRRC-assessed best overall responses at the time of transplantation referral were complete remission in one patient, partial remission in three patients, and stable disease in two patients. All patients who had transplantation after nivolumab treatment were alive at the time of analysis. Acute graft-versus-host disease (data collected per protocol) was reported in three of these six patients (two grade 1 and one grade 2). No cases of chronic graft-versus-host disease had been reported at the time of analysis.

All-cause adverse events were reported in 79 (99%) of 80 patients: 46 (58%) had grade 1 or 2 events, 26 (33%) had grade 3 events, six (8%) had grade 4 events, and one patient (1%) died from multi-organ failure. 71 (89%) patients had drug-related adverse events, including 51 (64%) with grade 1 or 2 events, 17 (21%) with grade 3 events, and three (4%) with grade 4 events. The most common drug-related adverse events were fatigue (20 [25%] of 80 patients), infusion-related reaction (16 [20%]), rash (13 [16%]), arthralgia (11 [14%]), pyrexia (11 [14%]), nausea (10 [13%]), diarrhoea (8 [10%]), and pruritus (8 [10%]); the majority of these were grade 1–2 with the exception of one case of grade 3 rash (table 3). The most common drug-related grade 3–4 adverse events were increased lipase and neutropenia (table 3). Serious adverse events of any cause were reported in 20 (25%) of 80 patients, with the most common being pyrexia (three [4%] patients), malignant neoplasm progression (two [3%]), pneumonia (two [3%]), arrhythmia (two [3%]), meningitis (two [3%]), and infusion-related reaction (two [3%]; appendix p 8). Drug-related serious adverse events were reported in five (6%) patients, with the most common being infusion-related reaction (two [3%]). The most frequently reported adverse events of special interest, irrespective of causality, were skin abnormalities (33 patients [41%]); gastrointestinal abnormalities (21 [26%]); hypersensitivity or infusion-related reaction (17 [21%]); and endocrine (14 [18%]), hepatic (eight [10%]), renal (four [5%]), and pulmonary (one [1%]) events. Pneumonitis (irrespective of cause) was reported in two (3%) patients (one grade 2 and one grade 3) between the first dose and 35 days after the last dose; both cases were judged to be drug related and both resolved with corticosteroid treatment. One of these patients had grade 3 pneumonitis 35 days after the last dose of nivolumab, which was discontinued because of autoimmune hepatitis. Most select adverse events of special interest reported were of grades 1 or 2, and most were considered by the investigators to be drug related. Adverse events leading to discontinuation were treatment-related autoimmune hepatitis (one patient), treatment-related increased ALT and AST concentrations (one patient), and death from multi-organ failure (one patient), which was not considered treatment related. Haematological abnormalities (collected separately from adverse events) during treatment or within 30 days of last

treatment were mostly grade 1 or 2. Grade 3 or 4 haematological abnormalities reported in four (5%) or more patients were decreased lymphocyte count (grade 3 in 15 [19%] patients) and decreased neutrophil count (grade 3 in three [4%] patients and grade 4 in two [3%]). Increase from baseline in haemoglobin concentration from grade 2 to grade 3 was reported in one patient.

Three patients died during the study: one from disease progression, one from an undetermined cause after loss to follow-up, and one from multi-organ failure due to Epstein-Barr virus-positive T-cell lymphoma. The multi-organ failure was considered unrelated to nivolumab because autopsy results showed a new diagnosis of Epstein-Barr virus-positive peripheral T-cell lymphoma, although classical Hodgkin's lymphoma was pathologically confirmed during screening from a biopsy.

For patient-reported outcomes (a prespecified exploratory endpoint), mean EQ-5D visual analogue scale score (on a scale from 0 to 100) increased over time with nivolumab treatment, from 62 (SD 30) at baseline (n=76) to 80 (18) at week 33 (n=44), with a clinically meaningful improvement in health state seen by week 9 (n=62; 7·9 point change).[20] Findings from EORTC QLQ-C30 suggested improvement from baseline across functional, symptom, and global health scores (appendix pp 9–10). 18 patients had B symptoms (unexplained weight loss; unexplained, persistent, or recurrent fever; or recurrent night sweats) at baseline, of whom 16 (80%) had complete resolution at data cutoff. The median time to resolution of these symptoms was 1·9 months (IQR 1·9–2·1).

## Discussion

In this phase 2 study, nivolumab resulted in frequent responses in patients with classical Hodgkin's lymphoma after failure of ASCT and brentuximab vedotin, and most of these responses were maintained through the reported follow-up period. The safety profile was acceptable. Reduction in tumour burden in the target lesion was noted in most patients, according to both IRRC and investigator assessment. Importantly, response to nivolumab was reported in more than two-thirds of patients who did not respond to the most recent brentuximab vedotin treatment before trial enrolment. At the time of analysis, 33 (62%) of 53 responses were ongoing, and 31 responders on treatment were censored before the median duration of response, suggesting that response duration and progression-free survival might increase with follow-up. This finding is encouraging and might be related to the mechanism of action of PD-1 blockade, differentiating this approach from cytotoxic therapy. For example, the median duration of partial remission is 3·5 months (95% CI 2·2–4·1) when the antibody drug conjugate brentuximab vedotin is used after ASCT failure.[21]

Discordance in complete remission between IRRC and investigator assessments was largely based on the interpretation of $^{18}$F-FDG PET scans and was not

| | All-cause adverse events (n=80) | | | Drug-related adverse events (n=80) | | |
|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 1–2 | Grade 3 | Grade 4 |
| Fatigue | 29 (36%) | 0 | 0 | 20 (25%) | 0 | 0 |
| Pyrexia | 24 (30%) | 1 (1%) | 0 | 11 (14%) | 0 | 0 |
| Diarrhoea | 21 (26%) | 0 | 0 | 8 (10%) | 0 | 0 |
| Nausea | 19 (24%) | 0 | 0 | 10 (13%) | 0 | 0 |
| Upper respiratory tract infection | 18 (23%) | 1 (1%) | 0 | 0 | 0 | 0 |
| Pruritus | 18 (23%) | 0 | 0 | 8 (10%) | 0 | 0 |
| Rash | 15 (19%) | 2 (3%) | 0 | 12 (15%) | 1 (1%) | 0 |
| Arthralgia | 17 (21%) | 0 | 0 | 11 (14%) | 0 | 0 |
| Infusion-related reaction | 16 (20%) | 0 | 0 | 16 (20%) | 0 | 0 |
| Nasopharyngitis | 16 (20%) | 0 | 0 | 0 | 0 | 0 |
| Vomiting | 12 (15%) | 1 (1%) | 0 | 6 (8%) | 0 | 0 |
| Constipation | 12 (15%) | 0 | 0 | 5 (6%) | 0 | 0 |
| Dyspnoea | 8 (10%) | 2 (3%) | 0 | 2 (3%) | 1 (1%) | 0 |
| Peripheral neuropathy | 10 (13%) | 0 | 0 | 3 (4%) | 0 | 0 |
| Abdominal pain | 7 (9%) | 2 (3%) | 0 | 4 (5%) | 2 (3%) | 0 |
| Myalgia | 9 (11%) | 0 | 0 | 6 (8%) | 0 | 0 |
| Bronchopneumonia | 9 (11%) | 0 | 0 | 0 | 0 | 0 |
| Back pain | 8 (10%) | 1 (1%) | 0 | 2 (3%) | 0 | 0 |
| Headache | 8 (10%) | 1 (1%) | 0 | 2 (3%) | 0 | 0 |
| Anaemia | 6 (8%) | 2 (3%) | 0 | 2 (3%) | 0 | 0 |
| Hyperglycaemia | 7 (9%) | 1 (1%) | 0 | 4 (5%) | 0 | 0 |
| Increased lipase | 3 (4%) | 3 (4%) | 2 (3%) | 2 (3%) | 2 (3%) | 2 (3%) |
| Neutropenia | 3 (4%) | 4 (5%) | 0 | 3 (4%) | 4 (5%) | 0 |
| Decreased appetite | 6 (8%) | 1 (1%) | 0 | 2 (3%) | 0 | 0 |
| Increased amylase | 3 (4%) | 2 (3%) | 0 | 2 (3%) | 2 (3%) | 0 |
| Increased aspartate aminotransferase | 3 (4%) | 2 (3%) | 0 | 2 (3%) | 2 (3%) | 0 |
| Lung infection | 2 (3%) | 2 (3%) | 0 | 1 (1%) | 0 | 0 |
| Skin infection | 3 (4%) | 1 (1%) | 0 | 0 | 0 | 0 |
| Increased alanine aminotransferase | 2 (3%) | 2 (3%) | 0 | 1 (1%) | 2 (3%) | 0 |
| Increased blood alkaline phosphatase | 3 (4%) | 1 (1%) | 0 | 3 (4%) | 0 | 0 |
| Decreased weight | 3 (4%) | 1 (1%) | 0 | 0 | 0 | 0 |
| Decreased lymphocyte count | 2 (3%) | 1 (1%) | 0 | 1 (1%) | 0 | 0 |
| Leucopenia | 1 (1%) | 2 (3%) | 0 | 2 (3%) | 0 | 0 |
| Pneumonia | 1 (1%) | 2 (3%) | 0 | 0 | 1 (1%) | 0 |
| Maculo-papular rash | 2 (3%) | 1 (1%) | 0 | 2 (3%) | 1 (1%) | 0 |
| Decreased neutrophil count | 0 | 1 (1%) | 1 (1%) | 0 | 1 (1%) | 1 (1%) |
| Decreased platelet count | 1 (1%) | 1 (1%) | 0 | 1 (1%) | 0 | 0 |
| Malignant neoplasm progression | 0 | 1 (1%) | 1 (1%) | 0 | 0 | 0 |
| Arrhythmia | 1 (1%) | 1 (1%) | 0 | 0 | 0 | 0 |
| Meningitis | 1 (1%) | 1 (1%) | 0 | 1 (1%) | 0 | 0 |
| Generalised oedema | 0 | 0 | 1 (1%) | 0 | 0 | 0 |
| Pleural effusion | 0 | 1 (1%) | 0 | 0 | 0 | 0 |
| Arthritis | 0 | 1 (1%) | 0 | 0 | 1 (1%) | 0 |
| Osteonecrosis | 0 | 1 (1%) | 0 | 0 | 0 | 0 |
| Syncope | 0 | 1 (1%) | 0 | 0 | 1 (1%) | 0 |
| Hypercalcaemia | 0 | 0 | 1 (1%) | 0 | 0 | 0 |
| Febrile neutropenia | 0 | 1 (1%) | 0 | 0 | 0 | 0 |
| Gastrointestinal stromal tumour | 0 | 1 (1%) | 0 | 0 | 0 | 0 |
| Embolism | 0 | 1 (1%) | 0 | 0 | 0 | 0 |

(Table 3 continues on next page)

| | All-cause adverse events (n=80) | | | Drug-related adverse events (n=80) | | |
|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 1–2 | Grade 3 | Grade 4 |
| (Continued from previous page) | | | | | | |
| Cardiac failure | 0 | 1 (1%) | 0 | 0 | 0 | 0 |
| Left ventricular dysfunction | 0 | 1 (1%) | 0 | 0 | 0 | 0 |
| Pericardial effusion | 0 | 0 | 1 (1%) | 0 | 0 | 0 |
| Autoimmune hepatitis | 0 | 1 (1%) | 0 | 0 | 1 (1%) | 0 |

Data are n (%). Adverse events in this table include grade 1–2 events reported in ≥10% of patients, and all grade 3–4 events. One patient died as a result of multi-organ failure that was unrelated to treatment.

***Table 3:*** **Adverse events**

considered to have a meaningful effect on the interpretation of clinical activity. Notably, consistent interpretation of PET scans might be challenging,[22] and discordance might be a recurrent problem in trials designed with the 2007 IWG response criteria; these are being examined by independent treating clinicians or radiologists who are now familiar with the 2014 criteria.[23] Although standardised uptake values could help with the analysis, they were not collected as part of this study, which was designed on the basis of the 2007 criteria.

Although the role of allogeneic stem-cell transplantation after anti-PD-1 treatment in a heavily pre-treated population with few treatment options remains to be seen, it is important to note that transplantation continues to be an option for these patients. At this stage, it is too early to make any conclusions regarding the use of nivolumab as a bridge to allogeneic stem-cell transplantation. In a phase 1 study of nivolumab for classical Hodgkin's lymphoma, four of five patients died from complications of allogeneic stem-cell transplantation.[18] In our study, six patients proceeded to transplantation (five of whom had allogeneic stem-cell transplantation) and all were alive at database lock.

In all evaluable biopsy specimens, Reed–Sternberg cells had *PD-L1* and *PD-L2* copy number alterations and copy-number-associated increased PD-L1 expression. The high frequency of 9p24.1 alterations and PD-L1 expression in these specimens is consistent with our recent analyses of classical Hodgkin's lymphomas.[10] In that study,[10] high-level *PD-L1* and *PD-L2* alterations (eg, amplification) were associated with shortened progression-free survival in a series of newly diagnosed patients with classical Hodgkin's lymphoma who were given standard induction therapy. In the current study, patients whose malignant Reed–Sternberg cells had 9p24.1 amplification and increased PD-1 expression seemed more responsive to PD-L1 blockade; the association between best overall response and H score is significant (p=0·013; appendix p 8). Nonetheless, most patients with 9p24.1 polysomy or PD-L1 expression in the first quartile achieved partial remission. At this stage, the number of evaluable biopsy samples is quite small, and thus further investigations are needed.

The mechanism of action of nivolumab might provide an explanation for the non-conventional patterns of benefits reported. In five of the nine patients treated beyond progression, tumour reduction continued even after the appearance of new lesions. Furthermore, IRRC-assessed negative $^{18}$F-FDG PET scans were reported after a new lesion appeared in one patient. These results suggest that continued treatment beyond initial progression might be beneficial.

Nivolumab had an acceptable safety profile in this study. Adverse events were mainly grade 1 or 2, and no new safety concerns were identified. Reported events were manageable and acceptable in the context of the observed anti-tumour activity. For the patient who died because of multi-organ failure related to Epstein-Barr virus-positive T-cell lymphoma, a pathological biopsy report before initiation of nivolumab therapy confirmed a diagnosis of classical Hodgkin's lymphoma. The event of T-cell lymphoma was considered unrelated to nivolumab. Patient-reported outcomes suggest a consistent improvement in quality of life while on treatment.

Findings from this study contribute to our understanding of the possible benefits of nivolumab; however, several limitations need to be acknowledged. This was a single-arm study because no appropriate, fully approved treatment exists for this patient population to serve as a control. For PET scan interpretation, we did not use a scoring system such as the Deauville score, because this system was not yet recommended when the study was designed, which might account for discrepancies between the IRRC and investigator assessments. Importantly, long-term follow-up will be required to determine the durability of responses. Data for patients who relapsed at less than 6 months after ASCT prior to trial enrolment were not collected.

At present, brentuximab vedotin is the only approved therapy for patients with classical Hodgkin's lymphoma after ASCT failure, and no treatment options exist after failure of both ASCT and brentuximab vedotin; therefore, a high unmet need exists in this patient population. In the post-brentuximab vedotin setting, results from this single-arm study of PD-1 blockade showed frequent remissions, encouraging preliminary durability of response (including patients with both complete and partial remissions), and an acceptable safety profile. Several factors might have contributed to the complete remissions seen in this study. For example, patients treated with nivolumab might have attained complete remission at later timepoints, compared with what might be expected with traditional chemotherapy, and further complete remissions might be seen with continued follow-up. Interpretation of PET scans using standardised uptake values or the Deauville criteria might increase the accuracy of the reporting of complete remission data. Additionally, ongoing host immune reactions within tumours might have contributed to persistent $^{18}$F-FDG uptake and thus affected complete remission results.

Follow-up is ongoing to assess the long-term durability of nivolumab in this setting. Median progression-free survival in patients with relapsed or refractory classical Hodgkin's lymphoma who received brentuximab vedotin treatment after ASCT was 5·6 months (95% CI 5·0–9·0);[21] therefore, the ongoing durability of complete and partial remission seen in our study is encouraging. In this registrational study, nivolumab represents a therapeutic approach with durable responses and an acceptable safety profile, relative to standard chemotherapeutics. The inclusion of additional patient cohorts in this ongoing multi-cohort trial—eg, patients who are brentuximab vedotin naive, or patients who might have received brentuximab vedotin either before or after ASCT—will further define the role of nivolumab in classical Hodgkin's lymphoma, and could potentially contribute to transforming the treatment landscape for this disease.

#### Contributors

AY, AS, MS, PLZ, SA, PA, JBC, GC, KJS, KK, SMP, SR, MGMR, AHL, and AE contributed to study design and conception. JK was involved in patient recruitment. AY, AS, MS, PLZ, JMT, SA, PA, MF, VR, JK, JBC, GC, KJS, MT, BF, SMP, SR, MGMR, AHL, and AE contributed to data acquisition, analysis, and/or interpretation. MF did the literature search. MS, MGMR, AHL and SR provided figure 2, table S2, and figure S4. KK was responsible for operational execution and data clean-up as the medical monitor of the funder. AY, KK, BF, and SMP had full access to all the data in the study. All authors contributed to the writing of the report, reviewed it for intellectual content, and approved the submitted version.

#### Declaration of interests

AY reports receiving honoraria for consulting from Merck, Bristol-Myers Squibb, Bayer, Celgene, Incyte, Sanofi, Janssen R&D, Seattle Genetics, and Takeda Millennium; and research funding from Novartis, Johnson and Johnson, Curis, Roche, and Bristol-Myers Squibb. MS reports receiving honoraria from Bristol-Myers Squibb, Merck, Pharmacyclics, Gilead, Bayer, Sanofi, Takeda, and Cell Signaling; and research funding from Bristol-Myers Squibb, the US National Institutes of Health, Bayer, and Sanofi. JMT reports serving in a consulting or advisory role for Bristol-Myers Squibb, Seattle Genetics, and Celgene; and receipt of research funding from Bristol-Myers Squibb, Janssen, and Valor Biotherapeutics. SA reports receiving grant support from Bristol-Myers Squibb. PA reports serving in a consulting role for Bristol-Myers Squibb, Merck, and Infinity Pharmaceuticals; and research funding (institutional) from Bristol-Myers Squibb and Merck. MF reports serving in a consulting role or as an advisory board member for Bristol-Myers Squibb and Merck; and receiving honoraria from Seattle Genetics and Takeda, and research funding from Bristol-Myers Squibb, Merck, Takeda, and Seattle Genetics. VR reports receiving research funding from Bristol-Myers Squibb. JK reports receiving research funding from the Leukemia and Lymphoma Society US, the Rasch Foundation, and Roche Canada; and personal fees for consultancy or honoraria from Bristol-Myers Squibb, AbbVie, Celgene, Merck, Gilead, Janssen, Roche Canada, Seattle Genetics, and Amgen. JBC reports receiving research funding from Bristol-Myers Squibb, Novartis, Janssen, Millennium/Takeda, Lymphoma Research Foundation; and serving on advisory boards of Novartis, Celgene, Pharmacyclics, Seattle Genetics, and Millennium/Takeda. KJS reports serving as an advisory board member for and receiving honoraria from Bristol-Myers Squibb, Seattle Genetics, Merck, and Infinity. MT reports serving in a consulting or advisory role for and receiving honoraria from Roche, Gilead, Janssen, Takeda, and Celgene; and research funding from Bristol-Myers Squibb, Roche, and Celgene. KK, BF, and SMP are employees of Bristol-Myers Squibb and hold stock in the company. SR reports receiving research funding from Bristol-Myers Squibb. AE reports receiving honoraria from or serving in a consulting or advisory role for Millennium/Takeda, Bristol-Myers Squibb, Novartis, and Affimed; and receiving research funding from Millennium/Takeda, Bristol-Myers Squibb, and Affimed. AS, PLZ, GC, MGMR, and AHL declare no competing interests.

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