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Nivolumab for classical Hodgkin lymphoma after autologous stem-cell transplantation and brentuximab vedotin failure: a prospective phase 2 multi-cohort study

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Contributors

AY, AS, MS, PLZ, SA, PA, JC, GC, KJS, KK, SMP, SR, MGMR, AHL, and AE contributed to study design/conception. JK was involved in the provision of patients. AY, AS, MS, PLZ, JMT, SA, PA, MF, VR, JK, JC, GC, KJS, MT, BF, SMP, SR, MGMR, AHL, and AE contributed to data acquisition, analysis, and/or interpretation. MF performed the literature search. MS, MR, AL 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 sponsor. 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

AS, PLZ, GC, MR, and AHL declare no competing interests.

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Abstract

Background—Malignant cells of classical Hodgkin lymphoma (cHL) are characterised by genetic alterations at the 9p24·1 locus. This leads to overexpression of the programmed death 1 (PD-1) ligands and enables tumour cells to evade immune surveillance. A phase 1b study showed that nivolumab, a PD-1-blocking antibody, produced a high response rate in patients with relapsed and refractory cHL, with an acceptable safety profile. This phase 2 study assessed the clinical benefit of nivolumab monotherapy in patients with cHL after autologous stem-cell transplantation and brentuximab vedotin failure.

Methods—This ongoing phase 2 study (NCT02181738) assessed the efficacy and safety of nivolumab, administered intravenously over 60 minutes at 3 mg/kg every 2 weeks, in adult patients with cHL who had failed both autologous stem-cell transplantation and brentuximab vedotin. The primary endpoint was objective response rate by independent radiologic review committee (IRRC) assessment. Secondary and other endpoints included duration of response, safety, and assessment of *PD-L1* and *PD-L2* loci and PD-L1 and PD-L2 protein expression.

Findings—Among 80 treated patients, the median number of prior therapies was four (range 3–15). With a mean (SD) follow-up of 8·6 months (2·02), objective response rate per IRRC was 66·3% (53/80). The most common drug-related adverse events (≥15%) included fatigue, infusion-related reaction, and rash. The most common drug-related grade 3–4 adverse events were neutropenia and increased lipase levels (both n=4). The most common serious adverse event (any grade) was pyrexia (n=3).

Interpretation—Nivolumab demonstrated a high response rate and an acceptable safety profile in patients with cHL who progressed following autologous stem-cell transplantation and brentuximab vedotin. Nivolumab may therefore provide a novel 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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Keywords

Hodgkin lymphoma; immunotherapy; PD-1; PD-L1; checkpoint inhibition; nivolumab

Introduction

For patients with first relapse of classical Hodgkin lymphoma (cHL), the current standard of care is high-dose chemotherapy followed by autologous stem-cell transplantation (ASCT).[1] In this population, freedom from treatment failure at 3 years has been shown to be 55%.[1] In

patients relapsing after ASCT, prognosis is worse and only a small minority of patients can still be cured.[2,3] More recently, treatment with brentuximab vedotin has resulted in a median overall survival of 22·4 months in this setting,[4] and progression-free survival associated with the subsequent line of treatment following brentuximab vedotin is 3·5 months.[5] For patients who progress after ASCT and brentuximab vedotin, there are currently no standard treatment options. Thus, an unmet medical need for effective therapies in this patient population remains.

cHL is characterized by rare Reed-Sternberg cells,[6] which exhibit copy number alterations involving 9p24·1, resulting in overexpression of programmed death 1 (PD-1) ligands PD-L1 and PD-L2 on the tumour cell surface.[7–10] *JAK2* is also located on chromosome 9p24·1 and *JAK2* alterations increase JAK-STAT signalling, further inducing PD-L1 overexpression.[8] Under physiological conditions, activation of the PD-1 pathway via PD-L1 and PD-L2 engagement limits T-cell-mediated immune responses.[11] Therefore, increased PD-L1 and PD-L2 expression by Reed-Sternberg cells may enable them to evade immune surveillance, suggesting that blockade of this pathway could be an effective treatment approach for cHL.[12]

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,[13] non-small-cell lung cancer,[14] and renal cell carcinoma.[15] A phase 1b study (NCT01592370) evaluated nivolumab in 23 patients with relapsed/refractory cHL, including 15 patients who had progressed following ASCT or brentuximab vedotin treatment, and reported an acceptable safety profile with an investigator-defined objective response of 87%.[16] Progression-free survival was 86% at 24 weeks.[16] With extended follow-up (median 20 months), durable responses to nivolumab have been demonstrated; 7/20 responders have maintained a response for >1·5 years.[17] In all ten evaluable tumour samples, Reed-Sternberg cells exhibited copy number alterations (CNAs) of chromosome 9p24·1 and increased PD-L1 and PD-L2 expression. In addition, phosphorylated STAT3 was detected in Reed-Sternberg cell nuclei in all cases, reflecting active JAK-STAT signalling.[16] To explore the effects of PD-1 blockade in patients relapsing after approved, standard therapies, we initiated a phase 2 study to evaluate the efficacy and safety of nivolumab in a larger patient cohort with cHL after failure of ASCT and brentuximab vedotin.

METHODS

Study design and participants

This was a multicentre, non-comparative, multi-cohort, single-arm phase 2 study. Herein we report the results from one cohort: patients with cHL after failure of both ASCT and subsequent brentuximab vedotin treatment. Patients were treated with nivolumab 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity (appendix p 9). Patients were enrolled from 34 study centres across Europe, Canada, and the United States. Median time between most recent brentuximab vedotin treatment and first dose of nivolumab was 0·7 years (interquartile range 0·2–1·7), and median time between high-dose conditioning chemotherapy followed by ASCT and first dose of nivolumab was 3.4 years (interquartile range 1·9–5·9).

The primary objective was to estimate the objective response rate.[18] Secondary endpoints based on IRRC assessment included duration of objective response, complete and partial remission rates, duration of complete and partial remission, and based on investigator assessment, objective response and duration of objective response. Exploratory endpoints included IRRC-assessed progression-free survival, overall survival, safety and tolerability (adverse events included events reported between first nivolumab dose and 30 days after the last dose), quality of life, and analyses of 9p24·1 alterations, and PD-1 ligand expression.

Eligible patients were ≥18 years old with recurrent cHL following failure of ASCT and subsequent brentuximab vedotin. Patients were required to have received prior brentuximab vedotin but were not required to be refractory to brentuximab vedotin; therefore, patients who responded to brentuximab vedotin and later experienced disease progression were eligible to participate in this study. At enrolment, all patients had an Eastern Cooperative Oncology Group performance-status score of 0 or 1 and either documented failure to achieve partial remission or better after the most recent treatment; or documented relapse (after complete remission) or disease progression (after partial remission or stable disease) (appendix p 3). Patients had to have had prior high-dose conditioning chemotherapy followed by ASCT as part of salvage therapy for cHL. The following treatments/therapies were prohibited: prior treatment history with brentuximab vedotin administered before first ASCT; ASCT ≤90 days prior to first dose of nivolumab; prior chemotherapy within 4 weeks, nitrosoureas within 6 weeks, therapeutic anti-cancer antibodies within 4 weeks, radio- or toxin-immunoconjugates (excluding brentuximab vedotin) within 10 weeks, and brentuximab vedotin within 4 weeks or major surgery within 2 weeks prior to the first dose of nivolumab; carmustine (BCNU) ≥600 mg/m² received as part of the pre-transplant conditioning regimen; prior radiation therapy within 3 weeks, or chest radiation ≤4 weeks prior to the first dose of nivolumab; prior 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 prior allogeneic stem-cell transplantation. Patients with the following concurrent diseases were excluded from the study: active interstitial pneumonitis; any serious/uncontrolled medical disorder that may have resulted in an increased risk associated with participating in the study or study drug administration, impaired the ability of the patient to receive nivolumab, or interfered with the interpretation of study results; prior malignancy active within the previous 3 years (except for locally curable cancers that have been apparently cured); patients with active, known or suspected autoimmune disease – patients with vitiligo, type I diabetes mellitus, 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 were permitted to enroll; or patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of nivolumab administration. Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents were permitted in the absence of active autoimmune disease. Written informed consent was obtained from all patients. The protocol, amendments, and patient informed consent received appropriate approval by the Institutional Review Board/ Independent Ethics Committee prior to initiation of the study at each site.

Procedures

Patients received nivolumab intravenously over 60 minutes at 3 mg/kg every 2 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or study end. No dose reductions were allowed; dose interruptions were allowed. Interruptions lasting >6 weeks resulted in permanent discontinuation from the study, except dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events or dosing interruptions >6 weeks that occurred due to non-drug-related reasons if approved by the study's medical monitor. A protocol amendment allowed patients to continue treatment beyond investigator-assessed progression in certain cases (appendix p 3).

On-treatment local laboratory assessments were done within 72 hours prior to dosing and included extended on-treatment local laboratory assessments during cycle 1 through cycle 5 and every alternate dose thereafter, as well as limited on-study treatment laboratory assessment, beginning at cycle 6 and every alternate dose thereafter. Extended assessments included complete blood count (CBC) with differential, blood urea nitrogen or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, chloride, amylase, lipase, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, and lactate dehydrogenase. Limited on-study treatment laboratory assessment included CBC with differential, liver function tests (ALT, AST, total bilirubin, alkaline phosphatase), and creatinine. In addition, thyroid-stimulating hormone (with reflexive free T4 and free T3) was assessed every 6 weeks (± 7 days) from first dose, regardless of dosing schedule. Toxicity assessments were continuous during the treatment phase. During the safety follow-up phase, adverse-event assessments were performed at follow-up visits 1 and 2.

Outcomes

Objective response rate was defined as the percentage of treated patients with a best overall response of complete or partial remission, per 2007 International Working Group (IWG) criteria,[18] based on independent radiologic review committee (IRRC) assessment. Best overall response was defined as best response between first dose and progression or subsequent therapy, whichever occurred first.

Patients were evaluated for tumour responses by computed tomography or magnetic resonance imaging at baseline and weeks 9, 17, 25, 37, and 49 during the first year of treatment, then every 16 weeks to week 97, continuing every 26 weeks beyond week 97. ^{18}F-fluoro-deoxyglucose avid by positron emission tomography (FDG-PET) was performed at baseline and weeks 17 and 25. At week 49, a FDG-PET scan was required for patients who did not have two consecutive negative scans before week 49. A negative FDG-PET scan, determined by visual assessment,[18] 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. FDG-PET scans were reviewed centrally. Tumour biopsy samples were excisional, incisional, or core needle. Submission of tumour tissue (formalin-fixed, paraffin-embedded tumour tissue block, or 10 unstained slides) from a biopsy performed during screening was mandatory. Archival tissue from the most recent tumour biopsy was an acceptable alternative. Quality of life was assessed using the EQ-5D

and European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 (EORTC QLQ-C30) (appendix p 3).

Pre-specified analyses of PD-1 ligand loci and protein expression were performed at Dana–Farber Cancer Institute, Boston, MA, USA, as previously described.[9,16] Fluorescence *in situ* hybridization (FISH) was performed with probes targeting *PD-L1* (*CD274*), *PD-L2* (*PDCD1LG2*), and a centromeric region of chromosome 9 (CEP 9, control probe). Reed-Sternberg cells were identified by their histomorphological features and weak positive staining for PAX5; 50 Reed-Sternberg cells per case were analysed. Nuclei with a target: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 being polysomic for 9p24·1. Double-staining of PD-L1 and PAX5 and PD-L2 and pSTAT3 was performed as previously described.[9,16] PD-L1 expression was assessed in PAX5+ Hodgkin Reed-Sternberg cells as well as PAX5– cells in the tumour microenvironment (appendix p 4).

Statistical analysis

The planned sample size of 60 patients provided approximately 93% power to reject the null hypothesis that the true objective response rate is ≤20%, assuming an objective response rate of 40% and given a two-sided alpha of 5%. All patients who received one or more doses of nivolumab were included in the efficacy and safety analyses. The last patient last visit date was August 20, 2015 and the database lock date was October 5, 2015.

IRRC-assessed objective responses were summarised using a binomial response rate and corresponding two-sided 95% exact CI per the Clopper-Pearson method. IRRC-assessed duration of response was summarised using the Kaplan-Meier method for patients who had achieved partial or complete remission. IRRC assessment of best change from baseline in 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 lesion[s] assessed at baseline, and at least one on-study time point with all baseline target lesion[s] assessed). Median duration of response and two-sided 95% CI (based on log-log transformation) were calculated. Progression-free survival per IRRC and overall survival were summarised using the Kaplan-Meier method. Median values and two-sided 95% CIs based on log-log transformation were calculated. Investigator-assessed efficacy was similarly summarised. A sensitivity analysis was performed for IRRC-assessed objective response rate in response-evaluable patients. Duration-of-response sensitivity analysis was performed using an alternate censoring scheme. Best overall response in patients based on prior response to brentuximab vedotin was analysed post hoc per IRRC (appendix p 4). This study is registered with ClinicalTrials.gov, NCT02181738.

All efficacy and safety analyses were performed using Statistical Analysis System software v9·02, SAS Institute, North Carolina, USA. Biomarker analyses were performed using R version 3·2·2.

Rule of the funding source

The study was conducted in accordance with the Declaration of Helsinki. The sponsor (Bristol-Myers Squibb) 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, funded by the sponsor. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Patients were enrolled between August 26, 2014 and February 20, 2015. Eighty patients were enrolled, treated, and included in the analyses. No patients were deemed ineligible. Baseline characteristics are presented in table 1. Prior systemic therapies are presented in the appendix (p 5–6). Mean (SD) age of study patients was 39 years (13·0); median number of prior lines of therapy was four (range 3–15), and 49% (39/80) of patients had received ≥5 previous lines of therapy; 74% (59/80) had prior radiation therapy. Five (6%) patients required infusion interruption; reasons given were hypersensitivity reaction (n=1) and other (n=4). Cycle delay occurred in 60% (48/80) of patients, with 33% (26/80) of patients requiring more than one delay.

At the time of analysis, 51/80 patients (63·8%) remained on treatment (appendix p 10). The mean number of nivolumab doses received was 16 (range 3–25; SD 5·8). The main reasons for discontinuation were disease progression (13 patients [16%]) and allogeneic stem-cell transplantation (n=5 [6%]) and ASCT (n=1 [1%]) (appendix p 10). No responding patients received subsequent radiation therapy for curative intent.

IRRC-assessed objective response rate was 66·3% (53/80; 95% CI 54·8–76·4), with best overall responses being complete and partial remission in 8·8% (7/80) and 57·5% (46/80) of patients, respectively (table 2). All but one responder had tumour reduction of ≥50% from baseline (figure 1A). The remaining patient had a negative FDG-PET scan. Investigator-assessed objective response rate was 72·5% (58/80; 95% CI 61·4–81·9); best overall response was complete and partial remission in 27·5% (22/80) and 45·0% (36/80), respectively (table 2). Concordance between IRRC and investigator assessments was 76·3% for objective response and 53·8% for best overall response.

Per IRRC, median time to first objective response was 2·1 months (interquartile range 1·9–3·0), with 59% (31/53) of responses achieved by the first scan at week 9. Sixty-two percent (33/53) of responders continued to respond (figure 1B). Progressive disease after achieving an objective response was reported in 11/53 responders (1/7 patients with complete remission; 10/46 with partial remission). Median duration of response was 7·8 months (95% CI 6·6–not reached), with a mean (SD) follow-up of 8·6 months (2·02; figure 1C). Of note, in the 43 patients who had no prior response to most recent prior brentuximab vedotin, as documented in patient's medical record, nivolumab treatment resulted in an IRRC-assessed objective response rate of 72·1% (31/43).

The following non-conventional patterns of benefit were observed: in one patient, a new lesion was identified at week 9, followed by a negative FDG-PET scan at weeks 25 and 33, with the best overall response determined as progressive disease, using protocol-specified definition. Among nine patients who continued nivolumab beyond progression per protocol amendment (appendix p 3), per investigator assessment, six maintained tumour reduction in target lesions (appendix p 11).

At 6 months, the progression-free survival rate was 76·9% (95% CI 64·9–85·3) (figure 1D) and the overall survival rate was 98·7% (95% CI 91·0–99·8). With 24 events (23 progression, one death), median progression-free survival was 10·0 months (95% CI 8·41–not available, upper 95% CI not reached).

Six patients elected to stop nivolumab treatment and proceeded to stem-cell transplantation (allogeneic stem-cell transplantation, n=5; autologous stem-cell transplantation, n=1). As transplantation was considered a subsequent therapy, censoring was performed at the time of transplantation. Responses at the time of transplantation referral were complete remission (n=1), partial remission (n=3), and stable disease (n=2), per IRRC. All patients who underwent transplantation following nivolumab treatment were alive at the time of analysis. Acute graft-versus-host disease (data collected per protocol) was reported in three patients (two grade 1, one grade 2). No cases of chronic graft-versus-host disease have been reported yet.

In this study, an exploratory analysis demonstrated that all 45 patients with available tumour specimens had concordant alterations of the *PD-L1* and *PD-L2* loci in the malignant Reed-Sternberg cells (figure 2 and appendix p 12). FISH analyses of Reed-Sternberg cells revealed polysomy 9 in 7/45 (16%), copy gain of *PD-L1/ PD-L2* in 26/45 (58%), and amplification of *PD-L1/PD-L2* in 12/45 (27%) of cases (appendix p 12, top panel; figure 2A). In cases with higher-level 9p24·1 genetic alterations, Reed-Sternberg cells, identified by nuclear morphological features and PAX5 staining, exhibited increased PD-L1 and PD-L2 protein expression (figure 2B and appendix p 12, middle and bottom panels). Overall, there was a significant association between increasing PD-L1 H-score (percentage malignant cells with positive staining multiplied by average intensity of positive staining) and *PD-L1/PD-L2* gain (p=0·034, Kruskal-Wallis test; figure 2B). Positive staining of nuclear pSTAT3, indicative of active JAK-STAT signalling, was also detected (appendix p 12, bottom panel).

The associations of IRRC-assessed response rates with 9p24·1 genetic alterations and PD-L1 H-score were also assessed (figures 2C and 2D). Evaluable patients with complete remission were more likely to have higher level 9p24·1 alterations, whereas those with progressive disease were more likely to have lower level 9p24·1 alterations (figure 2C and appendix p 7). In evaluable patients, there was a significant difference in best overall response by PD-L1 H-score (p=0·013, Kruskal-Wallis test; appendix p 7). All patients who achieved complete remission had PD-L1 H-scores in the third or fourth quartiles; those with progressive disease had PD-L1 H-scores in the first quartile (figure 2D and appendix p 7). Whereas PD-L1 expression on PAX5+ Hodgkin Reed-Sternberg cells was associated with response, PD-L1 expression on infiltrating PAX5– normal cells was not associated with response (data not shown).

Adverse events were reported in 79 patients (99%). The most common drug-related adverse events were fatigue (25%; 20/80), infusion-related reaction (20%; 16/80), rash (16%; 13/80), arthralgia (14%; 11/80), pyrexia (14%; 11/80), nausea (13%; 10/80), diarrhoea (10%; 8/80), and pruritus (10%; 8/80; table 3). Grade 3/4 adverse events occurred in 32/80 patients (40%), and one grade 5 event occurred (1%; multi-organ failure). The most common drug-related grade 3/4 adverse events were increased lipase and neutropenia (5% each; 4/80). Serious adverse events of any cause were reported in 20 patients (25%; 20/80), the most common being pyrexia (4%; 3/80; appendix p 8); and drug-related serious adverse events in five (6%; 5/80), the most common being infusion-related reaction (3%; 2/80). The most frequently reported select adverse events of special interest, regardless of causality, included skin (41%; 33/80), gastrointestinal (26%; 21/80), hypersensitivity/infusion-related reaction (21%; 17/80), and endocrine (18%; 14/80), hepatic (10%; 8/80), renal (5%; 4/80), and pulmonary (1%; 1/80) events. Pneumonitis (regardless of cause) was reported in two patients (3%; grade 1/2 and grade 3) between the first dose and 35 days after the last dose; both cases were considered to be drug related. One of these patients experienced grade 3 pneumonitis 35 days after the last dose of nivolumab, which was discontinued due to autoimmune hepatitis. Both cases of pneumonitis resolved with corticosteroid treatment. The majority of select adverse events reported were grade 1–2, and most were considered to be drug related by the investigator. Adverse events leading to discontinuation were autoimmune hepatitis (n=1), increased alanine aminotransferase and aspartate aminotransferase levels (n=1), and multi-organ failure (n=1). Three patients (4%) experienced a treatment-related adverse event that led to discontinuation. Abnormalities in haematology tests during treatment or within 30 days of last treatment were primarily grade 1 or 2. Grade 3 or 4 haematological abnormalities reported in >5% of patients were decreased lymphocytes (19% [15/80] grade 3, no grade 4) and decreased neutrophils (4% [3/80] grade 3, 3% [2/80] grade 4). Change from baseline in haemoglobin from grade 2–3 was reported in one patient.

Three patients died: one each from disease progression, an undetermined cause after lost follow-up, and multi-organ failure due to Epstein-Barr virus-positive T-cell lymphoma. The last event was considered unrelated to nivolumab as autopsy results showed a new diagnosis of Epstein-Barr virus-positive peripheral T-cell lymphoma, although cHL was pathologically confirmed from a biopsy during screening.

Patient-reported outcomes were an exploratory endpoint. Mean EQ-5D visual analogue scale score increased over time on treatment with nivolumab, from 62 at baseline to 80 at week 33, with a clinically meaningful improvement in health state seen by week 9 (>7-point change).[19] EORTC QLQ-C30 findings suggested a trend towards improvement from baseline across functional, symptom, and global health scores. Eighteen patients had B-symptoms present at baseline, of whom 16 had complete resolution (no B-symptoms of fever, night sweats, and weight loss) at data cut-off. The median time to resolution of symptoms was 1·9 months (interquartile range 1·9–2·1).

DISCUSSION

In this phase 2 study, nivolumab resulted in frequent responses, the majority of which were maintained through the reported follow-up period, with an acceptable safety profile in

patients with cHL after failure of ASCT and brentuximab vedotin. Reduction in target lesion tumour burden was noted in the majority of patients, with an IRRC-assessed objective response of 66% (53/80) and a similar investigator-assessed objective response rate of 72·5% (58/80). Of importance, more than two-thirds of patients, who did not respond to most recent prior brentuximab vedotin treatment, responded to nivolumab. A median duration of response of 7·8 months (95% CI 6·6–not reached) was estimated at a mean (SD) follow-up of 8·6 months (2·02). At the time of analysis, 33/53 (62%) responses were ongoing and 31/53 responders on treatment were censored prior to the median, suggesting that response durations and progression-free survival may increase with follow-up. This is encouraging and may 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 when the antibody drug conjugate brentuximab vedotin is used after ASCT failure.[20]

Discordance in complete remission between IRRC and investigator assessments was largely based on FDG-PET scan interpretation and was not considered to meaningfully impact the interpretation of clinical activity, since 13 of the 19 investigator-assessed complete remissions were assessed at least as partial remission by the IRRC, and proportional reduction in tumour burden was similarly assessed by the IRRC and investigators (appendix p 13). Notably, consistent interpretation of PET scans may be challenging,[21] and discordance might be a recurrent problem in trials designed with 2007 IWG response criteria that are being examined by independent treating clinicians/radiologists who are now familiar with more modern 2014 criteria.[22] Although standardised uptake values could aid in analysis, they were not collected as part of this study, which was designed based upon the 2007 criteria.

Although the role of allogeneic transplantation after anti-PD1 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 lymphoma, four of five patients died following complications from allogeneic stem-cell transplantation.[17] In the current study, six patients proceeded to transplantation, and at database lock all were alive.

In all evaluable biopsy specimens, Reed-Sternberg cells exhibited *PD-L1* and *PD-L2* CNAs and copy number-associated increased PD-1 ligand expression. The high frequency of 9p24·1 alterations and PD-L1 expression in the cHL biopsy specimens is in line with our recent analyses.[9] In a series of newly diagnosed patients with cHL treated with standard induction therapy, high-level *PD-L1/PD-L2* alterations (e.g. amplification) were associated with shortened progression-free survival.[9] In the current study, patients whose Hodgkin Reed-Sternberg cells exhibited *PD-L1/PD-L2* amplification and increased PD-1 ligand expression appeared more responsive to PD-1 blockade. Nonetheless, the majority of patients with 9p24·1 polysomy or PD-L1 expression in the lower quartile achieved a partial response. At this stage, the number of evaluable biopsy samples is relatively small and thus further investigations are needed.

The mechanism of action of nivolumab may contribute to the non-conventional patterns of benefit reported. In five of the nine patients treated beyond progression, tumour reduction continued even after the appearance of new lesion(s). Furthermore, negative FDG-PET scans by IRRC were reported after a new lesion appeared in one patient. These results suggest that the continued treatment beyond initial progression may be beneficial.

Nivolumab demonstrated 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 one patient who died due to Epstein-Barr virus-positive T-cell lymphoma-related multi-organ failure, a pathological biopsy report prior to initiating nivolumab therapy confirmed a diagnosis of cHL. 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.

This study contributes to our understanding of the possible benefits of nivolumab; however, certain limitations must be acknowledged. This was a single-arm study as there is currently no appropriate, fully approved treatment for this patient population to serve as a control. FDG-PET scan interpretation did not use a scoring system such as the Deauville score, as this system was not yet recommended at the time that this study was designed, and this may account for discrepancies between the IRRC and investigator assessments. Importantly, longer-term follow-up will be required to determine the durability of responses. The rate of relapse <6 months post ASCT was not reported among the patient baseline characteristics. This was a single-arm study as there is currently no appropriate, fully approved treatment for this patient population to serve as a control.

At present, brentuximab vedotin is the only approved therapy for patients with cHL failing ASCT. There are currently no treatment options for patients who fail ASCT and brentuximab vedotin; therefore, there is a high unmet need in this patient population. In the post-brentuximab vedotin setting, this single-arm study of PD-1 blockade demonstrated a high remission rate, encouraging preliminary durability of response, including patients with both complete and partial responses (the majority of patients [62·3%; 33/53] had an ongoing response at data cut-off [mean follow-up 8·6 months]; censored prior to the calculated mean at this analysis), and acceptable safety profile. A number of factors may have contributed to the complete remission rate seen in this study. For example, patients treated with nivolumab may have attained complete remission at later time points, compared with what might be expected with traditional chemotherapy, and further complete remissions may be observed with continued follow-up. Interpretation by the Deauville criteria may facilitate more accurate reporting of complete remission rate. Additionally, ongoing host immune reactions within tumours may have contributed to persistence of FDG uptake, and thus affected the complete remission rate. Follow-up is ongoing to assess the long-term durability of nivolumab in this setting. Median progression-free survival in patients with relapsed/refractory Hodgkin lymphoma who received brentuximab vedotin treatment after ASCT was 5·6 months; therefore, based on the ongoing durability of complete and partial remission seen in the current study, our results are 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 who are either brentuximab vedotin naïve or may have received brentuximab vedotin, either prior to or after ASCT, will further define the role of nivolumab in cHL, potentially transforming the treatment landscape.

Research in context

Evidence before this study—To establish the role of treatment using brentuximab vedotin for classical Hodgkin lymphoma (cHL), we searched PubMed with the terms 'Hodgkin lymphoma' AND 'brentuximab vedotin' in clinical trials, identifying 16 articles that examined therapy in Hodgkin lymphoma. Overall, brentuximab vedotin demonstrated clinically meaningful efficacy and acceptable tolerability after autologous stem-cell transplantation (ASCT). Brentuximab vedotin is the only approved treatment for relapsed/refractory Hodgkin lymphoma following failure of ASCT. One study demonstrated responses upon re-treatment with brentuximab vedotin in patients who progressed following an initial response to brentuximab vedotin; however, there were no studies aimed at investigating new agents for patients who failed brentuximab vedotin.

Added value of this study—The results of this phase 2 study of nivolumab in a heavily pre-treated population, with ASCT failure and progression following treatment with brentuximab vedotin, demonstrated a high response rate with ongoing responses in most patients, including some durable responses that may extend with ongoing follow-up. Nivolumab was well tolerated, with an acceptable safety profile in this patient population. These results validate earlier phase 1b findings, demonstrating activity in an area of unmet medical need.

Implications of all the available evidence—Brentuximab vedotin has improved outcomes in patients with cHL and is the preferred treatment for patients who have progressed following ASCT. However, many eventually become refractory to brentuximab vedotin, with no good therapeutic options. Duration and depth of response are important, as patients are often young and otherwise healthy. Nivolumab provides a new treatment option for patients with cHL and has the potential to produce durable responses, even in heavily pre-treated patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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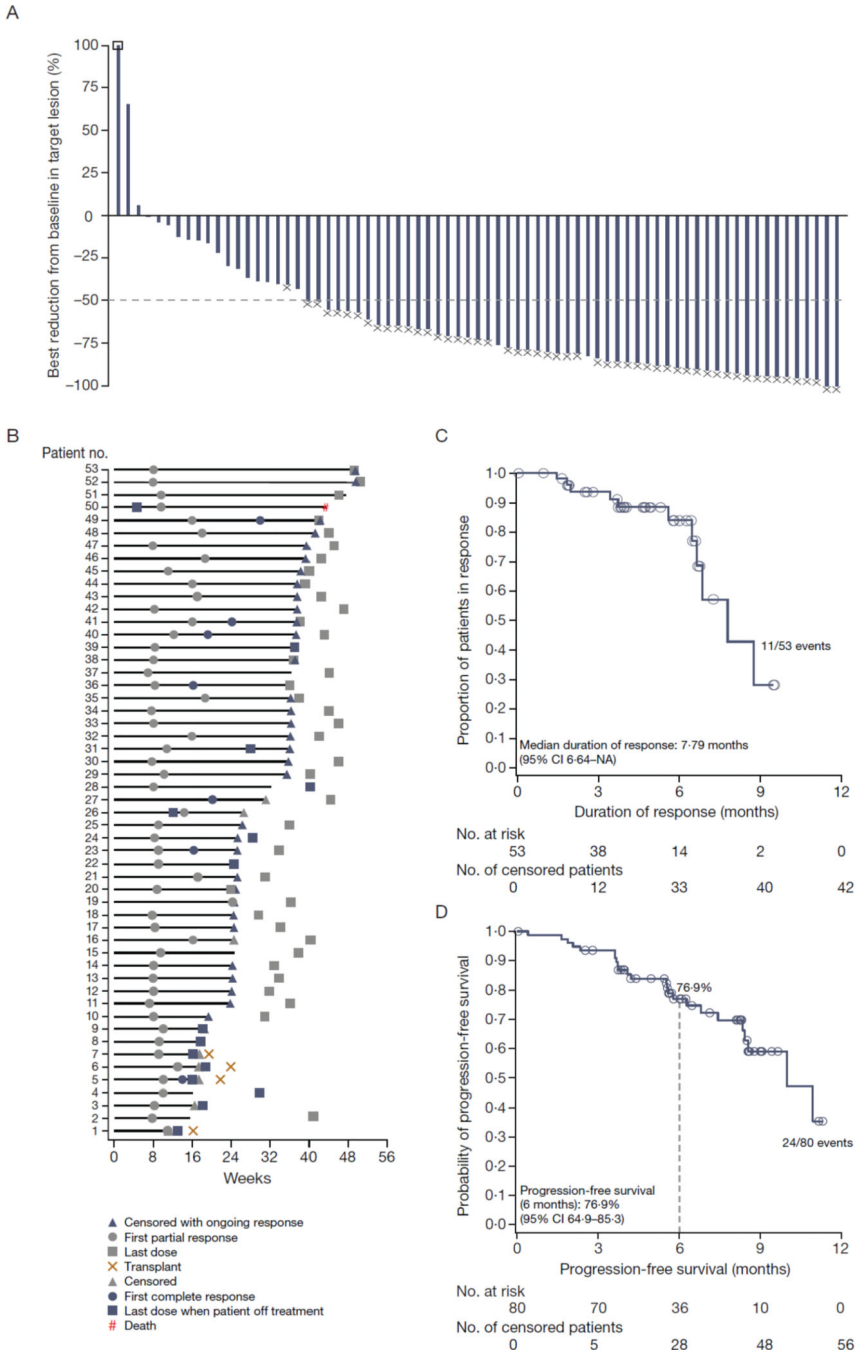

Figure 1. Efficacy outcomes per IRRC assessment

IRRC=independent radiologic review committee. Shown are the results for: Panel A – IRRC assessment of best change from baseline in target lesion for all response-evaluable patients, where crosses denote responders and the square symbol represents percentage change truncated to 100% (response evaluable was defined as patients with a best overall response of complete or partial remission, stable disease, or disease progression of target lesion[s] assessed at baseline, and at least one on-study time point with all baseline target lesion[s] assessed; negative or positive value indicates maximum tumour reduction or minimum

tumour increase); Panel B – response characteristics in all responders; Panel C – duration of response; and Panel D – progression-free survival (Panel D).

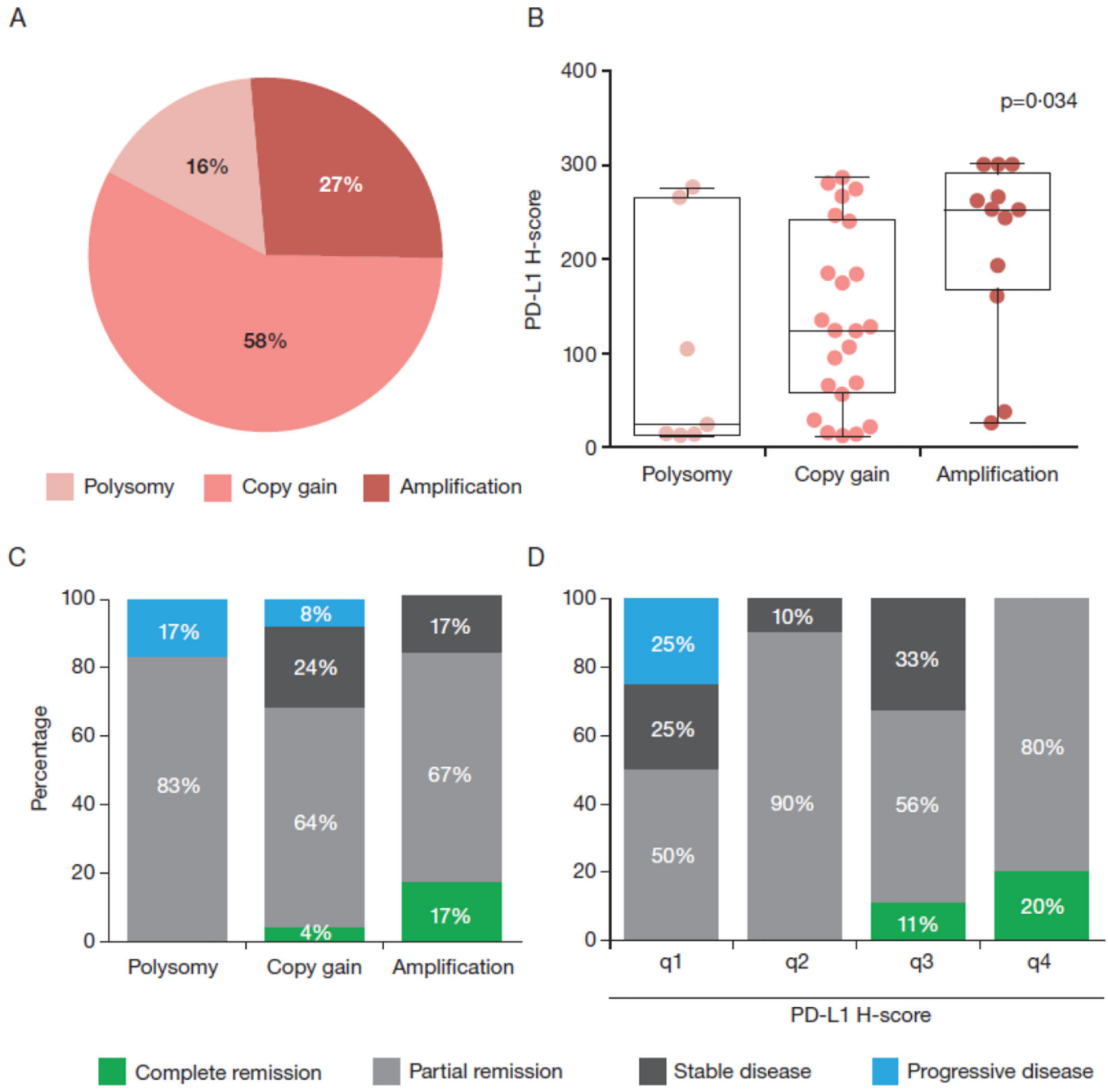

Figure 2. ***PD-L1/PD-L2*** **alterations and PD-1 ligand expression in tumour biopsies from trial patients**

Panel A: the proportion of evaluable cases with polysomy, copy gain, and amplification. Panel B: box plots showing the distribution of PD-L1 H-scores across cases with polysomy, copy gain, and amplification. There is an increase in median PD-L1 H-score with increasing 9p24·1 genetic alteration (p=0·034, Kruskal-Wallis test). Panel C: objective responses among patients with Reed-Sternberg cells exhibiting polysomy, copy gain, or amplification. Panel D: objective responses by PD-L1 H-score.

Table 1

Characteristics of the 80 patients at baseline

Characteristic	Value
Age (years) *	39 (18–72, 13)
Age ≥45–<60 years	18 (23%)
Age less than 65 years	77 (96%)
Male sex	51 (64%)
ECOG performance status	
0	42 (53%)
1	38 (48%)
Disease stage a 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 ‡	4 (4–7)
Five or more lines of therapy	39 (49%)
Previous radiation therapy	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 prior brentuximab vedotin	43 (54%)
Prior lines of brentuximab vedotin, among patients with no response to prior brentuximab vedotin	
One	38 (88%)
Two	4 (9%)
Three	1 (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 (%) unless specified otherwise.

* Mean (range, SD);

† B-symptom components: unexplained weight loss of >10% during the last 6 months; unexplained, persistent, recurrent fever with temperatures >38°*C* during the previous month, or recurrent drenching night sweats during the previous month;

‡ median (interquartile range); salvage chemotherapy followed by high-dose preparative regimen prior to autologous stem-cell transplantation was considered a single line of therapy. ECOG=Eastern Cooperative Oncology Group.

Table 2

Objective response rate as assessed by the IRRC and investigators

Response	IRRC (n=80)	Investigator (n=80)
Objective response rate *	53 (66·3%), 54·8–76·4	58 (72·5%), 61·4–81·9
Best overall response †		
Complete remission	7 (8·8%)	22 (27·5%)
Partial remission	46 (57·5%)	36 (45·0%)
Stable disease	18 (22·5%)	18 (22·5%)
Progressive disease	6 (7·5%)	3 (3·8%)
Unable to determine	3 (3·8%)‡	1 (13%)§

Data are n (%) or 95% CI. IRRC=Independent Radiologic Review Committee.

*Objective response rate was defined as the percentage of treated patients with a best overall response of complete remission or partial remission according to the revised International Working Group criteria for Malignant Lymphoma (2007 criteria[18]).

†Best overall response was defined as the best response designation recorded between the date of the first dose and the date of initial objectively documented progression per the 2007 International Working Group criteria or the date of subsequent therapy, whichever occurred first.

‡n=2, no post-baseline tumour assessment available before or on the day of subsequent therapy (if any); n=1, all post-baseline tumour assessments before or on the day of subsequent therapy (if any) are unknown.

§No radiographic assessment was performed after the first dose of nivolumab.

Table 3

Adverse events*

Event	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
Total patients with an adverse event	46 (58%)	26 (33%)	6 (8%)	51 (64%)	17 (21%)	3 (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

Event	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
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%)	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
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 (%).

* Includes adverse events reported in ≥10% of patients, and all grade 3–4 adverse events. Defined on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4·0, coded using the *Medical Dictionary for Regulatory Activities*, version 18·0. Table includes events reported between the first dose and 30 days after the last dose of nivolumab. One patient experienced a grade 5 adverse event, multi-organ failure.