Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial

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ABSTRACT

Purpose
Genetic alterations causing overexpression of programmed death-1 ligands are near universal in classic Hodgkin lymphoma (cHL). Nivolumab, a programmed death-1 checkpoint inhibitor, demonstrated efficacy in relapsed/refractory cHL after autologous hematopoietic cell transplantation (auto-HCT) in initial analyses of one of three cohorts from the CheckMate 205 study of nivolumab for cHL. Here, we assess safety and efficacy after extended follow-up of all three cohorts.

Methods
This multicenter, single-arm, phase II study enrolled patients with relapsed/refractory cHL after auto-HCT treatment failure into cohorts by treatment history: brentuximab vedotin (BV) naïve (cohort A), BV received after auto-HCT (cohort B), and BV received before and/or after auto-HCT (cohort C). All patients received nivolumab 3 mg/kg every 2 weeks until disease progression/unacceptable toxicity. The primary end point was objective response rate per independent radiology review committee.

Results
Overall, 243 patients were treated; 63 in cohort A, 80 in cohort B, and 100 in cohort C. After a median follow-up of 18 months, 40% continued to receive treatment. The objective response rate was 69% (95% CI, 63% to 75%) overall and 65% to 73% in each cohort. Overall, the median duration of response was 16.6 months (95% CI, 13.2 to 20.3 months), and median progression-free survival was 14.7 months (95% CI, 11.3 to 18.5 months). Of 70 patients treated past conventional disease progression, 61% of those evaluable had stable or further reduced target tumor burdens. The most common grade 3 to 4 drug-related adverse events were lipase increases (5%), neutropenia (3%), and ALT increases (3%). Twenty-nine deaths occurred; none were considered treatment related.

Conclusion
With extended follow-up, responses to nivolumab were frequent and durable. Nivolumab seems to be associated with a favorable safety profile and long-term benefits across a broad spectrum of patients with relapsed/refractory cHL.

INTRODUCTION

The prognosis of patients with relapsed/refractory classic Hodgkin lymphoma (cHL) after failure of autologous hematopoietic cell transplantation (auto-HCT) has historically been extremely poor, with a median overall survival (OS) of just over 2 years. Achieving durable responses in this population is a critical goal rarely achieved with conventional chemotherapy. Brentuximab vedotin (BV) has demonstrated efficacy after auto-HCT treatment failure, with an objective response rate (ORR) of 75% and median progression-free survival (PFS) of 5.6 months. A subset of patients who achieve complete remission (CR) with BV maintain durable responses after 5 years; however, most patients require additional treatment within 1 year. An unmet need therefore exists for therapies that provide durable disease control for patients with relapsed/refractory cHL after failure of auto-HCT.
Nivolumab for Relapsed/Refractory cHL: Full CheckMate 205 Results

Genetic alterations at 9p24.1 are almost universal in cHL, leading to overexpression of the programmed death 1 (PD-1) ligands 1 (PD-L1) and 2 (PD-L2) on the surface of tumor cells. PD-L1 and PD-L2 downregulate T-cell immune responses on binding to PD-1. Nivolumab, a fully human immunoglobulin G4 anti–PD-1 monoclonal antibody, blocks signaling through the PD-1 pathway, releasing inhibition of T cells and augmenting antitumor immune responses. Nivolumab was tested in a phase I study (ClinicalTrials.gov identifier: NCT01592370) that demonstrated objective responses in 20 of 23 heavily pretreated patients (87%) with relapsed/refractory cHL. Given these promising results, we conducted an international, multicohort, phase II clinical trial in patients with relapsed/refractory cHL after failure of auto-HCT (CheckMate 205; ClinicalTrials.gov identifier: NCT02181738). Here, we present primary efficacy and safety data after extended follow-up of three relapsed/refractory cHL cohorts. In addition, we report exploratory analyses, including results according to prior treatment sequence or refractory status, outcomes of treatment beyond progressive disease, and outcomes of allogeneic HCT (allo-HCT) after nivolumab treatment.

Fig 1. CONSORT diagram. (*) Includes seven patients who discontinued nivolumab because of persistent complete remission for 1 year. AE, adverse event.

Methods

Study Design and Participants
This multicenter, single-arm trial enrolled patients aged ≥ 18 years with biopsy-confirmed relapsed/refractory cHL after failure with auto-HCT into three independent cohorts. Complete methods for cohort B of this trial have been described, and brief methods and cohort-specific protocol differences are described here and in the Data Supplement. Patients were enrolled at 34 sites across Europe and North America; patients with no prior BV treatment were enrolled in cohort A, patients who experienced failure of post–auto-HCT BV treatment were enrolled in cohort B, and patients who were treated with BV before and/or after auto-HCT treatment failure were enrolled in cohort C. Important exclusion criteria included autoimmune disease, radiotherapy within 21 days (± 24 weeks for chest radiation) of first nivolumab dose, auto-HCT within 90 days of first nivolumab dose, and allo-HCT or checkpoint blockade at any time before nivolumab treatment.

This study was performed in accordance with the Declaration of Helsinki. Approval from the appropriate institutional review board and independent ethics committee was received for the protocol, amendments, and consent forms before initiating the study at each site. All patients provided written informed consent before trial enrollment.

Procedures
Patients received nivolumab 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity. Patients in cohort C were to discontinue nivolumab after 1 year in persistent CR and could resume treatment if they relapsed within 2 years of the last dose. A protocol amendment (July 2014) allowed patients to continue treatment beyond investigator-assessed progression (2007 International Working Group [IWG] criteria for malignant lymphoma) if protocol-predefined criteria were met, including stable performance status and deriving perceived clinical benefit. Patients treated beyond initial progression (TBP) were required to discontinue in the event of further progression (± 10% further increase in tumor burden).

Computed tomography scanning or magnetic resonance imaging was performed at screening; then at weeks 9, 17, 25, and 49 during the first year of treatment; every 16 weeks during the second year of treatment; and every 26 weeks for chest, abdominal, and pelvic imaging. 

For patients who discontinued nivolumab to proceed to transplantation, disease assessments (CR or non-CR) were performed at 100 days, 6 months, 1 year, and every year thereafter from the date of transplantation until the date of first non-CR. Transplantation date and occurrence of graft-versus-host disease (GVHD) were collected prospectively; further
outcomes after allo-HCT were collected retrospectively. Myeloablative conditioning was defined according to standard criteria.\(^\text{16}\)

### Outcomes

The primary end point was independent radiology review committee (IRC)-assessed ORR (2007 IWG criteria\(^\text{15}\)) in each cohort. Secondary end points were IRC-assessed duration of response (DOR), frequency and duration of partial remission (PR) and CR as assessed by IRC, and investigator-assessed ORR and DOR. Prespecified exploratory analyses included PFS by IRC, OS, tumor burden change with TBP, and safety. Time to next treatment (TTNT), efficacy according to BV treatment sequence or prior refractory status and efficacy in the combined three cohorts were post hoc exploratory analyses.

### Statistical Analysis

The planned sample size in cohorts A (n = 60) and B (n = 60) was selected to provide 93% power to reject the null hypothesis that the true proportion of patients achieving an objective response was \(\neq 20\%\) (assuming 40% of patients achieve an objective response and a two-sided \(\alpha\) of 5%). Cohort C (n = 100) was designed to provide an 87% probability of selecting to provide 93% power to reject the null hypothesis that the true proportion of patients achieving an objective response was \(\neq 40\%\). All patients who received at least one dose of nivolumab were included in the primary safety and efficacy analyses. Primary efficacy analyses were performed independently for each cohort; safety assessments were performed for the combined population. For exploratory analyses by treatment sequence, patients from cohort C were recategorized according to the order in which they had received BV relative to auto-HCT; those receiving BV only after auto-HCT were grouped with cohort B (Appendix, online only). ORRs were summarized using binomial response rates; corresponding two-sided 95% exact CIs were calculated using the Clopper-Pearson method. For post hoc analyses, prior refractoriness was defined as the absence of objective response to a given therapy (absence of CR for first-line therapy).

TTNT was defined as the time from first nivolumab dose (or from initial disease progression in patients TBP) to next systemic therapy or death, whichever occurred first, and was calculated using the Kaplan-Meier method. Cumulative incidences of acute GVHD (aGVHD), chronic GVHD (cGVHD), disease progression, and transplant-related mortality (TRM; defined as death without disease progression) after allo-HCT were calculated using competing risks models. GVHD of unknown grade (G4) was imputed to G4; unknown dates of GVHD onset were imputed to date of transplantation. Associations between nivolumab exposure and the occurrence of G3 to G4 aGVHD or TRM were explored graphically. A previously developed population pharmacokinetic model\(^\text{17}\) was used to determine nivolumab serum concentrations at the time of allo-HCT on the basis of individual records of time lapse between last nivolumab treatment and allo-HCT.

### RESULTS

#### Patient Characteristics and Disposition

In total, 276 patients were enrolled between August 2014 and August 2015, of whom 243 were treated (Fig 1). Median age was 34 years. Baseline characteristics were generally similar across cohorts (Table 1); however, BV-naive patients (cohort A) had the fewest prior lines of therapy, and patients in cohort B (BV after auto-HCT) had the

### Table 1. Baseline Characteristics

| Characteristic                              | BV Naive: Cohort A (n = 63) | BV After Auto-HCT: Cohort B (n = 80) | BV Before and/or After Auto-HCT: Cohort C (n = 100) | Overall (N = 243) |
|--------------------------------------------|-----------------------------|-------------------------------------|---------------------------------|-------------------|
| Median age, years (IQR)                    | 33 (26-45)                  | 37 (28-48)                          | 32 (25-47)                     | 34 (26-46)        |
| \(\geq 60\)                                | 5 (8)                       | 7 (9)                               | 3 (3)                           | 15 (6)            |
| Male                                       | 34 (54)                     | 51 (64)                             | 56 (56)                         | 141 (58)          |
| ECOG PS                                    |                             |                                     |                                 |                   |
| 0                                          | 39 (62)                     | 42 (53)                             | 50 (50)                         | 131 (54)          |
| 1                                          | 24 (38)                     | 38 (48)                             | 50 (50)                         | 112 (46)          |
| Disease stage at study entry               |                             |                                     |                                 |                   |
| I                                           | 2 (1)                       | 1 (1)                               | 2 (2)                           | 4 (2)             |
| II                                          | 20 (32)                     | 11 (14)                             | 20 (20)                         | 51 (21)           |
| III                                         | 17 (27)                     | 14 (18)                             | 17 (17)                         | 48 (20)           |
| IV                                          | 24 (38)                     | 54 (68)                             | 61 (61)                         | 139 (57)          |
| Not reported                               | 2 (2)                       | 0                                   | 1 (1)                           |                   |
| B symptoms at baseline                     | 10 (16)                     | 18 (23)                             | 25 (25)                         | 53 (22)           |
| Previous lines of therapy                  |                             |                                     |                                 |                   |
| Median (IQR)                               | 2 (2-3)                     | 4 (4-7)                             | 4 (3-5)                         | 4 (3-5)           |
| 1 prior line                               | 0                           | 0                                   | 0                               | 0                 |
| \(\geq 3\) prior lines                     | 29 (46)                     | 80 (100)                            | 97 (97)                         | 206 (85)          |
| \(\geq 5\) prior lines                     | 4 (6)                       | 39 (49)                             | 30 (30)                         | 73 (30)           |
| Prior radiotherapy                         | 37 (59)                     | 59 (74)                             | 69 (69)                         | 165 (68)          |
| Prior auto-HCT                             | 63 (100)                    | 80 (100)                            | 100 (100)                       | 243 (100)         |
| Previous BV therapy                        |                             |                                     |                                 |                   |
| After auto-HCT                              | 80 (100)                    | 100 (100)                           | 180 (74)                        |                   |
| Before auto-HCT                             | 0                           | 33 (33)                             | 33 (14)                         |                   |
| Before and after auto-HCT                   | 0                           | 9 (9)                               | 9 (4)                           |                   |
| No objective response to last line of BV   | 51 (64)                     | 62 (62)                             | 113 (47)                        |                   |
| Median time from diagnosis to first dose of nivolumab, years (IQR) | 3.1 (2.0-7.5) | 6.2 (3.3-8.3) | 3.5 (2.3-6.4) | 4.5 (2.4-7.6) |
| Median time from most recent auto-HCT to first dose of nivolumab, years (IQR) | 1.0 (0.5-4.7) | 3.4 (1.9-5.9) | 1.7 (0.8-3.8) | 2.0 (0.9-4.9) |

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: auto-HCT, autologous hematopoietic cell transplantation; BV, brentuximab vedotin; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range.
longest interval between diagnosis and first nivolumab dose, and between most recent auto-HCT and first nivolumab dose. At database lock (December 2016), median follow-up was 18 months overall (interquartile range [IQR], 15 to 22 months) and 19, 23, and 16 months in cohorts A, B, and C, respectively. Overall, 40% of patients continued to receive treatment. Patients received a median of 32, 32, and 27 doses of nivolumab in cohorts A, B, and C, respectively. In cohort C, seven patients discontinued treatment because of persistent CR; none had been retreated at the time of database lock.

Efficacy

The overall IRC-assessed ORR was 69%, with 16% of patients achieving CR and 53% achieving PR. ORRs were 65%, 68%, and 73% in cohorts A, B, and C, respectively (Table 2). More than 95% of patients had reductions in target lesion burden (Fig 2A). Response rates were similar in patients who received BV after or only before auto-HCT (Appendix Table A1, online only) and in patients refractory to their first or last line of therapy or to BV given after auto-HCT (Table 2). Per investigator assessment, ORR was 72%, with 33% of patients achieving CR.

Median time to first objective response was 2.1 months (IQR, 1.9 to 2.7 months) overall (Appendix Fig A1, online only). Median IRC-assessed DOR was 16.6 months (95% CI, 13.2 to 20.3 months) overall and 20.3, 15.9, and 14.5 months in cohorts A, B, and C, respectively (Appendix Fig A2, online only). DOR according to best overall response is shown in Fig 2B. Median (95% CI) DOR was 16.6 months (12.8 months to not estimable [NE]) in patients refractory to their first (n = 103) or last (n = 77) line of therapy and 16.6 months (9.5 months to NE) in patients refractory to their most recent line of BV after auto-HCT (n = 51).

Median PFS was 14.7 months (95% CI, 11.3 to 18.5 months) overall and 18.3, 14.7, and 11.9 months in cohorts A, B, and C, respectively (Appendix Fig A3, online only). PFS according to best overall response is shown in Fig 2C. In recategorized analyses, median PFS was similar for patients who received BV after (11.9 months) or only before (11.5 months) auto-HCT (Appendix Table A1, online only). Median TTTNT was not reached in cohorts A and B, and was 19.4 months (95% CI, 14.8 months to NE) in cohort C. Median OS was not reached overall, in any cohort, or in patients grouped by any best overall response (Fig 2D). The 1-year OS (95% CI) rate was 92% (88% to 95%) overall, 93% (83% to 98%) in cohort A, 95% (87% to 98%) in cohort B, and 90% (82% to 94%) in cohort C; OS rates according to best overall response are shown in Fig 2D.

In total, 105 patients experienced disease progression (per investigator), of whom 70 were TBP, receiving a median of eight additional doses (IQR, 4 to 20 doses) of nivolumab, and 35 discontinued without further treatment (not TBP). Baseline characteristics of patients TBP were similar to those not TBP, although those TBP had better performance status and were less likely to have B symptoms (Appendix Table A2, online only). Patients TBP were also more likely to have new lesions as a primary cause of radiographic progression than those not TBP (67% v 37%). Before first progression, five patients TBP (7%) had achieved CR and 31 (44%) had achieved PR. Median duration of TBP was 5.2 months (minimum to maximum, 0.0 to 19.4 months), with 21 of 70 patients (30%) still on treatment at database lock. Of the 51 patients with evaluable postprogression data, 31 (61%) experienced stable or reduced target tumor burdens (Fig 3A), even after the appearance of new lesions (Fig 3B).

Patients with stable/reduced tumor burdens after TBP were more likely to have a performance status of 0 at baseline than those whose tumor burden increased (71% v 35%) and were more likely to have new lesions as a primary cause of radiographic progression (77% v 60%; Appendix Table A2, online only). Median (95% CI) time from

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Table 2. Objective and Best Overall Response per IRC

| Response                  | BV Naive: Cohort A (n = 63) | BV After Auto-HCT: Cohort B (n = 80) | BV Before and/or After Auto-HCT: Cohort C (n = 100) | All patients (N = 243) |
|---------------------------|------------------------------|--------------------------------------|-----------------------------------------------------|------------------------|
| ORR, % (95% CI)           | 65 (52-77)                   | 68 (56-78)                           | 73 (63-81)                                          | 69 (63-75)             |
| Best overall response     |                              |                                      |                                                     |                        |
| Complete remission        | 18 (29)                      | 10 (13)                              | 12 (12)                                             | 40 (16)                |
| Partial remission         | 23 (37)                      | 44 (55)                              | 61 (61)                                             | 128 (53)               |
| Stable disease            | 15 (24)                      | 17 (21)                              | 15 (15)                                             | 47 (19)                |
| Progressive disease       | 7 (11)                       | 6 (8)                                | 10 (10)                                             | 23 (9)                 |
| Unable to determine       | 0                            | 3 (4)                                | 2 (2)                                               | 5 (2)                  |

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NOTE. Data presented as No. (%) unless otherwise indicated. Best overall response was unable to be determined for five patients, all because of missing or unknown postbaseline tumor assessments.

Abbreviations: auto-HCT, autologous hematopoietic cell transplantation; BV, brentuximab vedotin; IRC, independent radiology review committee; ORR, objective response rate.
initial progression to next systemic therapy was 8.8 months (5.5 months to NE) in patients TBP and 1.5 months (0.6 to 3.3 months) in patients not TBP. Median (95% CI) OS from the date of progression was not reached for patients TBP and was 13.2 months (6.6 months to NE) for patients not TBP (Appendix Fig A4, online only); OS at 1 year was 84% (70% to 92%) and 61% (39% to 78%), respectively.
Safety

The most common drug-related AEs of any grade were fatigue (23%), diarrhea (15%), and infusion-related reactions (14%); the most common G3 to G4 drug-related AEs were lipase increases (5%), neutropenia (3%), and ALT increases (3%; Table 3). In total, 29 patients died. Causes of death were disease progression (n = 18, after allo-HCT for two patients), TRM after allo-HCT (n = 5), multiple organ failure as a result of atypical pneumonia (n = 1) or peripheral T-cell lymphoma (n = 1), sepsis (n = 1), acute hypoxic respiratory failure secondary to Pneumocystis pneumonia (n = 1), cardiac arrest (n = 1), and unknown cause (n = 1). All deaths were considered unrelated to the study drug. Seventeen patients (7%) discontinued treatment because of drug-related AEs; most commonly pneumonitis (2%) and autoimmune hepatitis (1%). Serious drug-related AEs occurred in 12% of patients; infusion-related reactions (2%), pneumonitis (1%), pneumonia (1%), pleural effusion (1%), and pyrexia (1%) were the most common. The most common immune-mediated AEs (IMAEs) by category were hypothyroidism/thyroiditis (12%; all G1 or G2) and rash (9%, including four patients with G3 AEs; Appendix Table A3, online only). Median time to onset (minimum to maximum) in these categories was 12 weeks (0 to 62 weeks) and 17 weeks (0 to 83 weeks), respectively. The majority of IMAEs resolved (Appendix Table A3, online only); however, 14 patients (6%) discontinued treatment because of IMAEs.

Outcomes in Patients Who Proceeded to Allo-HCT

In total, 44 patients proceeded to allo-HCT after a median of 13 nivolumab doses (IQR, 9 to 17 doses; Appendix Table A4, online only).

Fig 2. (Continued).

Fig 3. Outcomes in patients treated beyond progression. (A) Investigator-assessed best change in target lesion tumor burden and (B, C, and D) investigator-assessed change in target lesion burden over time for patients treated beyond progression according to best overall response to nivolumab before initial progression. (A) Patients with missing postfirst progression tumor data are not included. Horizontal reference line indicates the 50% reduction consistent with a response per revised International Working Group 2007 criteria. (B, C, and D) All patients with a last available nivolumab dose date after initial investigator-assessed progression per International Working Group 2007 criteria were included, except one patient treated beyond progression who did not have an evaluable best overall response. Per protocol, patients who did not have a tumor assessment after the first dose of treatment beyond progression were censored.
Fig 3. (Continued).
Median time from last dose to allo-HCT was 49 days (IQR, 31 to 127 days), with 12 patients (27%) receiving systemic therapy between the last dose and allo-HCT (of whom nine discontinued nivolumab because of disease progression). Most patients (77%) received non-myeloablative conditioning (Appendix Table A4, online only). At database lock, median follow-up after allo-HCT was 5.5 months (IQR, 2.9 to 11.8 months). The 6-month cumulative incidences of TRM and disease progression were 13% and 7%, respectively (Fig 38). aGVHD occurred in 21 patients, with 10 experiencing G3 or G4 aGVHD (four patients had unknown-grade aGVHD that was imputed to G4). Within this small patient sample, no clear association was found between the occurrence of TRM or G3 to G4 aGVHD and estimated nivolumab plasma concentration at the time of transplantation (Appendix Fig A5, online only). In addition, univariable analysis did not identify any significant relationship between time from last dose of nivolumab to allo-HCT and TRM (P = .97) or G3 to G4 aGVHD (P = .97). AEs of special interest after allo-HCT included hyperacute GVHD (onset < 14 days after transplantation) in two patients (5%), steroid-requiring febrile syndrome in four patients (9%), encephalitis in one patient (2%), and hepatic veno-occlusive disease in one patient (2%) who received a nonmyeloablative allo-HCT. Median PFS and OS after allo-HCT were not reached, with a 6-month PFS estimate of 82% and a 6-month OS estimate of 87% (Fig 4C).

**Table 3. Adverse Events**

| Adverse Event                          | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 |
|---------------------------------------|-----------|-----------|-----------|-----------|
| All-Cause Adverse Events (n = 243)     |           |           |           |           |
| Diarrhea                              | 86 (35)   | 2 (< 1)   | 37 (15)   | 2 (< 1)   |
| Fatigue                               | 85 (35)   | 3 (1)     | 56 (23)   | 2 (< 1)   |
| Cough                                 | 83 (34)   | 0         | 15 (6)    | 0         |
| Pyrexia                                | 72 (30)   | 1 (< 1)   | 22 (9)    | 0         |
| Upper respiratory tract infection      | 53 (22)   | 2 (< 1)   | 7 (3)     | 0         |
| Nausea                                 | 52 (21)   | 0         | 25 (10)   | 0         |
| Vomiting                               | 48 (20)   | 2 (< 1)   | 21 (9)    | 1 (< 1)   |
| Nasopharyngitis                        | 48 (20)   | 0         | 2 (< 1)   | 0         |
| Pruritus                               | 47 (19)   | 0         | 25 (10)   | 0         |
| Rash                                   | 46 (19)   | 3 (1)     | 29 (12)   | 2 (< 1)   |
| Headache                               | 46 (19)   | 1 (< 1)   | 16 (7)    | 0         |
| Arthralgia                             | 44 (18)   | 1 (< 1)   | 20 (8)    | 0         |
| Abdominal pain                         | 35 (14)   | 2 (< 1)   | 18 (7)    | 2 (< 1)   |
| Constipation                           | 35 (14)   | 1 (< 1)   | 11 (5)    | 0         |
| Infusion-related reaction              | 35 (14)   | 1 (< 1)   | 34 (14)   | 1 (< 1)   |
| Dyspnea                                | 34 (14)   | 3 (1)     | 10 (4)    | 1 (< 1)   |
| Anemia                                 | 32 (13)   | 6 (2)     | 8 (3)     | 1 (< 1)   |
| Back pain                              | 30 (12)   | 1 (< 1)   | 6 (2)     | 0         |
| Oropharyngeal pain                     | 29 (12)   | 0         | 5 (2)     | 0         |
| Pneumonia                              | 27 (11)   | 6 (2)     | 5 (2)     | 3 (1)     |
| Nasal congestion                       | 27 (11)   | 0         | 2 (< 1)   | 0         |
| Myalgia                                | 26 (11)   | 0         | 12 (5)    | 0         |
| Lipase increased                       | 22 (9)    | 14 (6)    | 17 (7)    | 11 (5)    |
| Neutropenia                            | 20 (8)    | 9 (4)     | 15 (6)    | 8 (3)     |
| ALT increased                          | 19 (8)    | 8 (3)     | 18 (7)    | 8 (3)     |
| AST increased                          | 18 (7)    | 6 (2)     | 17 (7)    | 5 (2)     |
| Blood alkaline phosphatase increased   | 14 (6)    | 4 (2)     | 6 (2)     | 1 (< 1)   |
| Amylase increased                      | 13 (5)    | 5 (2)     | 11 (5)    | 5 (2)     |
| Lymphocyte count decreased             | 10 (4)    | 5 (2)     | 3 (1)     | 2 (< 1)   |
| Malignant neoplasm progression         | 5 (2)*    | 4 (2)     | 0         | 0         |

NOTE: Data presented as No. (%). Adverse events in this table are events reported in ≥ 10% of patients and grade 3 or 4 events reported in ≥ 2% of patients, occurring between first dose and 30 days after the last dose of nivolumab.

*Includes one grade 5 event. Three patients were reported as having grade 5 adverse events (multiple organ dysfunction and peripheral T-cell lymphoma in one patient, malignant neoplasm progression in one patient, and cardiac arrest in one patient); all were considered unrelated to treatment.

**DISCUSSION**

On the basis of encouraging initial data, nivolumab was approved by the US Food and Drug Administration for the treatment of adults with cHL that has relapsed/progressed after auto-HCT and BV treatment or three or more prior lines of systemic therapy including auto-HCT,17 and by the European Medicines Agency for the treatment of adults with relapsed/refractory cHL after auto-HCT and BV.19 The efficacy of PD-1 blockade in relapsed/refractory cHL was further supported by positive results in a recent phase II study of pembrolizumab.20 This extended analysis of three CheckMate 205 cohorts confirms the favorable safety profile of nivolumab in relapsed/refractory cHL. After the 18-month follow-up, safety outcomes remained consistent with previous reports, and most events were G1 or G2. In addition, nivolumab led to frequent and durable responses, including in patients naive to BV, patients who received BV at differing times relative to auto-HCT, and patients refractory to prior lines of therapy.
Fig 4. Cumulative incidence of (A) transplant-related mortality (TRM) and disease progression, (B) acute graft-versus-host disease (aGVHD) and chronic graft-versus-host disease (cGVHD), and (C) overall survival (OS) and progression-free survival (PFS) after allogeneic hematopoietic cell transplantation (allo-HCT). Cumulative incidence (95% CI) at 100 days and 6 months for TRM, disease progression, and GVHD, and median (95% CI) PFS and OS are shown. Death was considered a competing risk to GVHD, and post-transplant disease progression was considered a competing event to TRM. G, grade; NA, not available; NE, not estimable.
Previous studies in cHL suggest that DOR and PFS with chemotherapeutic agents may be strongly associated with depth of response. However, durable responses with nivolumab were observed in patients with both CR and PR. Furthermore, median PFS exceeded 11 months for patients with SD, and 1-year OS rates in patients with a best response of SD (98%) were similar to those in patients with CR (100%) and PR (96%). This suggests that long-lasting clinical benefits from anti–PD-1 checkpoint inhibition are not restricted to patients with CR, and even patients who do not attain objective responses may derive clinical benefit. Median OS was not reached in any cohort, nor in patients with SD or progressive disease in the overall population, even though patients were heavily pretreated and most had received both prior auto-HCT and prior BV, further supporting the possibility of long-lasting benefits of nivolumab.

Notably, median TTNT exceeded PFS, and patients TBP often maintained disease control during the follow-up reported: 1-year OS after initial progression was higher in patients who continued to receive treatment beyond progression (84% vs 61%) and approached that from the first nivolumab dose in the overall population (92%). Time from initial progression to next systemic therapy was also high in patients TBP compared with those not TBP (8.8 vs 1.5 months). Although this may reflect a selection bias in this nonrandomized comparison, atypical patterns of response with immune checkpoint inhibitors and potential benefits of treatment past conventional progression are well described in solid tumors. According to conventional response criteria, atypical response patterns may result in patients being assessed as having progressive disease despite the potential for subsequent tumor control. Proposed updates to conventional response criteria (Lymphoma Response to Immuno-modulatory Therapy Criteria [LyRIC] and Response Evaluation Criteria in Lymphoma [RECIL]) that take this phenomenon into account may allow more accurate assessment of checkpoint inhibitor efficacy in future studies.

One limitation of this study was the discordance between IRC- and investigator-assessed CR rates. Concordance may have been improved with quantitative scoring of PET scans; however, this study was designed before the 2014 Lugano criteria and therefore used the 2007 IWG criteria.

The incidence of aGVHD and TRM after postnivolumab allo-HCT in CheckMate 205 seemed comparable to historical relapsed/refractory cHL cohorts who had received allografts without prior PD-1 blockade. Patients in this study who received allografts after nivolumab experienced low relapse rates after 6 months of follow-up, and overall outcomes (PFS and OS) seemed favorable with short follow-up. In the present cohort, we saw no clear effect of estimated nivolumab concentration or length of interval from the first nivolumab dose in the overall population (92%).

REFERENCES

1. von Tresckow B, Müller H, Eichenauer DA, et al: Outcome and risk factors of patients with Hodgkin lymphoma who relapse or progress after autologous stem cell transplant. Leuk Lymphoma 55:1922-1924, 2014

2. Crump M: Management of Hodgkin lymphoma in relapse after autologous stem cell transplant. Hematology Am Soc Hematol Educ Program 2008: 326-333, 2008

3. Moskowitz AJ, Perales MA, Keweilmann T, et al: Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol 146:158-163, 2009

4. Bartlett NL, Niedzwiecki D, Johnson JL, et al: Gemicitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin’s lymphoma: CALGB 59904. Ann Oncol 18: 1071-1079, 2007

In conclusion, to our knowledge, this is the longest phase II or III follow-up reported to date of anti–PD-1 checkpoint blockade in patients with a hematologic malignancy. Nivolumab demonstrated high response rates and led to durable responses in the majority of patients. Sustained benefits were seen across different patient populations, including patients refractory to prior therapies and patients with and without prior BV exposure, and were not dependent on achieving CR. The exploratory analyses presented here lend further support to the hypothesis that PD-1 blockade may provide durable benefit even in patients who do not achieve objective responses, including a subset of patients who experience conventional progressive disease. Altogether, the results of this study suggest that nivolumab treatment may provide long-term benefits to a broad spectrum of patients with relapsed/refractory cHL after auto-HCT.

Disclosures provided by the authors are available with this article at jco.org.

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5. Moskowitz AJ, Hamlin PA Jr, Perera MA, et al: Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol 31:456-480, 2013

6. Younes A, Gopal AK, Smith SE, et al: Results of a pivotal phase II study of brentuximab vedotin in patients with relapsed or refractory Hodgkin’s lymphoma. J Clin Oncol 30:2183-2189, 2012

7. Chen R, Gopal AK, Smith SE, et al: Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood 128:1562-1566, 2016

8. Green MR, Monti S, Rodig SJ, et al: Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin’s lymphoma and primary mediastinal large B-cell lymphoma. Blood 116:3288-3277, 2010

9. Roemer MG, Advani RH, Ligon AH, et al: PD-L1 and PD-L2 genetic alterations define classical Hodgkin lymphoma and predict outcome. J Clin Oncol 34:2690-2697, 2016

10. Freeman GJ, Long AJ, Iwai Y, et al: Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 192:1027-1034, 2000

11. Latchman Y, Wood CR, Chernova T, et al: PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2:261-268, 2001

12. Bristol-Myers Squibb: Opdivo (nivolumab) Highlights of prescribing information. http://packageinserts.bms.com/pi/pi_opdivo.pdf

13. Ansell SM, Lesokhin AM, Borrello I, et al: PD-1 blockade with nivolumab in relapsed or refractory Hodgkin’s lymphoma. N Engl J Med 372:311-319, 2015

14. Younes A, Santoro A, Shipp M, et al: 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. Lancet Oncol 17:1283-1294, 2016

15. Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586, 2007

16. Bredeson C, LeRademacher J, Kato K, et al: Prospective cohort study comparing intravenous busulfan to total body irradiation in hematopoietic cell transplantation. Blood 122:3871-3878, 2013

17. Bajaj G, Wang X, Agraval S, et al: Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors. CPT Pharmacometrics Syst Pharmacol 6:98-66, 2017

18. Saliba RM, de Lima M, Giralt S, et al: Hyperacute GVHD: Risk factors, outcomes, and clinical implications. Blood 109:2751-2758, 2007

19. European Medicines Agency: Annex I: Opdivo (nivolumab) Summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR-_/-Product_Information/human/003985/WC500189765.pdf

20. Chen R, Zinzani PL, Fanale MA, et al: Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol 35:2125-2132, 2017

21. Seattle Genetics: Adcetris (brentuximab vedotin) prescribing information, November 2017. http://www.seattlegenetics.com/application/files/2515/01696727/ADCRETIS_USPI_USP-BVP-2015-01625pdf.pdf

22. Hodl FS, Huvo WJ, Kefferd R, et al: Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol 34:1510-1517, 2016

23. Wolchok JD, Hoos A, O’Day S, et al: Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Cancer Res 15:7412-7420, 2009

24. Long GV, Weber JS, Larkin J, et al: Nivolumab for patients with advanced melanoma treated beyond progression: Analysis of 2 phase 3 clinical trials. JAMA Oncol 3:1511-1519, 2017

25. Cheson BD, Ansell S, Schwartz L, et al: Re-definition of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood 128:2499-2496, 2016

26. Younes A, Hilden P, Coiffier B, et al: International Working Group consensus response evaluation criteria in lymphoma (IWCIL 2017). Ann Oncol 28:1436-1447, 2017

27. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol 32:3059-3067, 2014

28. Anderlini P, Salila RM, Ledesma C, et al: Gemcitabine, fludarabine, and methylvin for reduced-intensity conditioning and autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. Biol Blood Marrow Transplant 22:1333-1337, 2016

29. Devetten MP, Hari PN, Carreras J, et al: Unrelated donor reduced-intensity allogeneic hematopoietic stem cell transplantation for relapsed and refractory Hodgkin lymphoma. Biol Blood Marrow Transplant 15:109-117, 2009

30. Marcon A, Porcher R, Robin M, et al: Impact of disease status and stem cell source on the results of reduced intensity conditioning transplant for Hodgkin’s lymphoma: A retrospective study from the French Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC). Haematologica 98:1467-1475, 2013

31. Robinson SP, Sureda A, Canals C, et al: Reduced intensity conditioning allogeneic stem cell transplantation for Hodgkin’s lymphoma: Identification of prognostic factors predicting outcome. Haematologica 94:230-238, 2009

32. Sureda A, Robinson S, Canals C, et al: Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin’s lymphoma: An analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 26:455-462, 2009

33. Merriman RW, Kim HT, Zinzani PL, et al: Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma. Blood 129:1380-1388, 2017

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Topline results from the combined CheckMate 205 cohorts were presented at the International Conference on Malignant Lymphoma, Lugano, Switzerland, June 14-17, 2017, and European Hematology Association Congress, Madrid, Spain, June 22–25, 2017. Safety outcomes after allogeneic hematopoietic cell transplantation in patients from the current study together with a phase I study of nivolumab in relapsed/refractory cHL (Study CA209-039; NCT01592370) were presented at the annual congress of the European Society for Blood and Marrow Transplantation, Marseille, France, March 26-29, 2017; however, complete results incorporating treatment beyond progression analyses and outcomes after allogeneic hematopoietic cell transplantation in CheckMate 205 are yet to be published. Initial results from cohort B were published in The Lancet Oncology in 2016.
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial

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Appendix

Methods

Additional cohort-specific eligibility criteria included:

Cohort A: No prior treatment with brentuximab vedotin (BV) and:
1. Absence of complete remission (CR) 90 days after most recent hematopoietic cell transplantation (HCT); or
2. Relapsed disease (after CR) or disease progression (after partial remission [PR] or stable disease [SD])

Cohort B: Failure of post-transplant treatment with BV, and:
1. Failure to achieve at least PR after the most recent treatment; or
2. Relapsed disease (after CR) or disease progression (after PR or SD)

Cohort C: Prior treatment with BV at any time (before and/or after autologous HCT), and:
1. Absence of CR 90 days after most recent autologous HCT; or
2. Failure to achieve at least PR after the most recent chemotherapy or radiation therapy; or
3. Relapsed disease (after CR) or disease progression (after PR or SD)
Fig A1. Response characteristics among all responders. CR, complete remission; PR, partial remission.
Nivolumab for Relapsed/Refractory cHL: Full CheckMate 205 Results

**Fig A2.** Duration of response in cohorts A, B, and C. All values are median (95% CI).

**Fig A3.** Progression-free survival (PFS) in cohorts A, B, and C. All values are median (95% CI).
Fig A4. Overall survival (OS) from date of initial disease progression in patients treated beyond initial progression (TBP) and not TBP. All values are median (95% CI). NA, not available; NE, not estimable.
Fig A5. Estimated nivolumab concentration at the time of allogeneic hematopoietic cell transplantation (µg/mL) and occurrence of (A) transplant-related mortality or (B) grade 3 to 4 acute graft-versus-host disease (GVHD). Box plots represent 25th and 75th percentiles; lines within the box plots represent median values and circles represent individual patients.
**Table A1. ORR and PFS per IRC in Patients Recategorized by BV Treatment History**

| ORR/PFS                  | BV After Auto-HCT (n = 138) | BV Only Before Auto-HCT (n = 33) | BV Naive: Cohort A (n = 63) |
|--------------------------|-----------------------------|----------------------------------|-----------------------------|
| ORR, % (95% CI)          | 71 (63 to 78)               | 70 (51 to 84)                   | 65 (52 to 77)               |
| BOR to nivolumab, No. (%)|                             |                                 |                             |
| Complete remission       | 16 (12)                     | 5 (15)                          | 18 (29)                     |
| Partial remission        | 82 (59)                     | 18 (55)                         | 23 (37)                     |
| Stable disease           | 22 (16)                     | 7 (21)                          | 15 (24)                     |
| Progressive disease      | 13 (9)                      | 3 (9)                           | 7 (11)                      |
| Unable to determine      | 5 (4)                       | 0                               | 0                           |
| Median PFS, months (95% CI) | 12 (11 to 19)             | 11 (8 to NE)                    | 18 (11 to 22)               |

**NOTE.** For these analyses, patients from cohort C were recategorized to identify those patients who received BV only after auto-HCT (grouped with cohort B), BV only before auto-HCT, or BV before and after auto-HCT.

Abbreviations: auto-HCT, autologous hematopoietic cell transplantation; BOR, best overall response; BV, brentuximab vedotin; IRC, independent radiology review committee; NE, not estimable; ORR, objective response rate; PFS, progression-free survival.
### Table A2. Characteristics of Patients Treated Beyond Progression

| Characteristic                                                                 | All Patients (N = 243) | TBP (n = 70) | Not TBP (n = 35) |
|--------------------------------------------------------------------------------|------------------------|--------------|------------------|
| **Age, years**                                                                 | 34 (18-72)             | 37 (18-72)   | 34 (23-63)       |
| ECOG PS, %                                                                     |                        |              |                  |
| 0                                                                              | 54                     | 61           | 34               |
| 1                                                                              | 46                     | 39           | 66               |
| **Stage IV disease at study entry, %**                                          | 57                     | 57           | 51               |
| **Previous lines of therapy, No.**                                             | 4 (2-15)               | 4 (2-15)     | 4 (2-9)          |
| **B symptoms, %**                                                              | 22                     | 20           | 34               |
| **Bulky disease, %**                                                           | 20                     | 19           | 23               |
| **Extralymphatic involvement, %**                                              | 43                     | 46           | 51               |
| Time from first dose of nivolumab to initial progression date, months         |                        |              |                  |
| Primary cause of radiographic progression (IWG 2007), No. (%)*                |                        |              |                  |
| Increase in overall tumor burden                                               |                        |              |                  |
| Nontarget lesion growth                                                        |                        |              |                  |
| New lesion                                                                     |                        |              |                  |
| Change in target lesion tumor burden at first progression from baseline (imputed)† |                        |              |                  |
| No. of patients with available data                                            | 67                     | 22           |                  |
| Median, %                                                                      | 47 (67)                | 13 (37)      |                  |
| IQR, %                                                                         | −77, −16               | −67, +15     |                  |
| Change in target lesion tumor burden at first progression from nadir (imputed)† |                        |              |                  |
| No. of patients with available data                                            | 67                     | 21           |                  |
| Median, %                                                                      | +7                     | +18          |                  |
| IQR, %                                                                         | −16, +38               | 0, +66       |                  |
| **Tumor Burden Change With Treatment Beyond Initial Progression**              |                        |              |                  |
| Age, years                                                                     | 33 (18-72)             | 33 (18-57)   | 37 (20-72)       |
| ECOG PS, %                                                                     |                        |              |                  |
| 0                                                                              | 57                     | 71           | 35               |
| 1                                                                              | 43                     | 29           | 65               |
| Stage IV disease at study entry, %                                             | 63                     | 61           | 65               |
| Previous lines of therapy                                                      | 4 (2-15)               | 4 (2-15)     | 5 (2-11)         |
| B symptoms, %                                                                  | 14                     | 13           | 15               |
| Bulky disease, %                                                               | 16                     | 13           | 20               |
| Extralymphatic involvement, %                                                  | 49                     | 52           | 45               |
| Time from first dose of nivolumab to initial progression date, months          | 6 (1-19)               | 6 (2-19)     | 6 (1-12)         |
| Primary causes of radiographic progression (IWG 2007), No. (%)*               |                        |              |                  |
| Increase in overall tumor burden                                               | 10 (20)                | 6 (19)       | 4 (20)           |
| Nontarget lesion growth                                                        | 11 (22)                | 5 (16)       | 6 (30)           |
| New lesion                                                                     | 36 (71)                | 24 (77)      | 12 (60)          |
| Median (IQR) best percent change from first progression in target lesion tumor burden† | −6 (−35, +15)         | −27 (−50, −10) | +18 (+10, +45) |

NOTE. Unless otherwise indicated, characteristics are given at baseline and values show median (range). Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; IWG, International Working Group; TBP, treated beyond progression. *Patients may have had multiple findings, and other characteristics may have been used by investigators to assess disease progression. †Missing assessments on progression date were imputed to the earliest assessment within 10 days before or after progression date. ‡Best change is defined as the maximum reduction or minimum increase in tumor burden from first progression.
Table A3. All-Cause Immune-Mediated AEs in ≥ 1 Patient by Category

| All-Cause Immune-Mediated AEs (n = 243) | Any Grade | Grade 3-4 | Resolution by Category | Any Grade | Grade 3-4 | Received High-Dose Corticosteroids, by Category | Any Grade | Grade 3-4 |
|----------------------------------------|-----------|-----------|------------------------|-----------|-----------|-----------------------------------------------|-----------|-----------|
| Hypothyroidism/thyroiditis             | 29 (12)   | 0         | 10 (34)                | —         | —         | —                                             | —         | —         |
| Hypothyroidism                         | 21 (9)    | 0         |                        | —         | —         | —                                             | —         | —         |
| Hypothyroidism, primary                | 7 (3)     | 0         |                        | —         | —         | —                                             | —         | —         |
| Thyroiditis                            | 2 (< 1)   | 0         |                        | —         | —         | —                                             | —         | —         |
| Rash                                   | 21 (9)    | 4 (2)     | 20 (95)                | 4 (100)   | 4 (19)    | 2 (50)                                         | —         | —         |
| Rash maculopapular                     | 3 (1)     | 1 (< 1)   |                        | —         | —         | —                                             | —         | —         |
| Dermatitis                             | 1 (< 1)   | 0         |                        | —         | —         | —                                             | —         | —         |
| Rash pruritic                          | 1 (< 1)   | 0         |                        | —         | —         | —                                             | —         | —         |
| Hypothyroidism                         | 21 (9)    | 4 (2)     | 20 (95)                | 4 (100)   | 4 (19)    | 2 (50)                                         | —         | —         |
| Hypothyroidism                         | 7 (3)     | 3 (1)     |                        | —         | —         | —                                             | —         | —         |
| Hypothyroidism, primary                | 7 (3)     | 3 (1)     |                        | —         | —         | —                                             | —         | —         |
| Thyroiditis                            | 2 (< 1)   | 0         |                        | —         | —         | —                                             | —         | —         |
| Rash                                   | 21 (9)    | 4 (2)     | 20 (95)                | 4 (100)   | 4 (19)    | 2 (50)                                         | —         | —         |
| Rash maculopapular                     | 3 (1)     | 1 (< 1)   |                        | —         | —         | —                                             | —         | —         |
| Dermatitis                             | 1 (< 1)   | 0         |                        | —         | —         | —                                             | —         | —         |
| Rash pruritic                          | 1 (< 1)   | 0         |                        | —         | —         | —                                             | —         | —         |
| Hepatitis                              | 12 (5)    | 10 (4)    | 9 (75)                 | 7 (70)    | 12 (100)  | 9 (90)                                         | —         | —         |
| Alanine aminotransferase increased     | 7 (3)     | 5 (2)     |                        | —         | —         | —                                             | —         | —         |
| Aspartate aminotransferase increased   | 4 (2)     | 3 (1)     |                        | —         | —         | —                                             | —         | —         |
| Autoimmune hepatitis                   | 3 (1)     | 3 (1)     |                        | —         | —         | —                                             | —         | —         |
| Hepatitis                              | 1 (< 1)   | 1 (< 1)   |                        | —         | —         | —                                             | —         | —         |
| Hepatotoxicity                         | 1 (< 1)   | 0         |                        | —         | —         | —                                             | —         | —         |
| Hyperbilirubinemia                     | 1 (< 1)   | 1 (< 1)   |                        | —         | —         | —                                             | —         | —         |
| Hypersensitivity                       | 12 (5)    | 2 (< 1)   | 11 (92)                | 2 (100)   | 9 (75)    | 1 (50)                                         | —         | —         |
| Infusion-related reaction              | 10 (4)    | 0         |                        | —         | —         | —                                             | —         | —         |
| Anaphylactic reaction                  | 1 (< 1)   | 1 (< 1)   |                        | —         | —         | —                                             | —         | —         |
| Hypersensitivity                       | 1 (< 1)   | 1 (< 1)   |                        | —         | —         | —                                             | —         | —         |
| Pneumonitis                            | 10 (4)    | 0         | 10 (100)               | —         | 9 (90)    | —                                             | —         | —         |
| Diarrhea/colitis                       | 6 (2)     | 5 (2)     | 8 (100)                | 5 (100)   | 5 (83)    | 4 (80)                                         | —         | —         |
| Diarrhea                               | 4 (2)     | 2 (< 1)   |                        | —         | —         | —                                             | —         | —         |
| Colitis                                | 3 (1)     | 3 (1)     |                        | —         | —         | —                                             | —         | —         |
| Autoimmune colitis                     | 1 (< 1)   | 0         |                        | —         | —         | —                                             | —         | —         |
| Hyperthyroidism                        | 6 (2)     | 0         | 4 (67)                 | —         | 1 (17)    | —                                             | —         | —         |
| Diabetes                               | 2 (< 1)   | 1 (< 1)   | 1 (50)                 | 1 (100)   | 0         | 0                                             | —         | —         |
| Diabetes mellitus                      | 1 (< 1)   | 0         |                        | —         | —         | —                                             | —         | —         |
| Diabetes ketoacidosis                   | 1 (< 1)   | 1 (< 1)   |                        | —         | —         | —                                             | —         | —         |
| Adrenal insufficiency                  | 1 (< 1)   | 0         | 1 (100)                | —         | 0         | —                                             | —         | —         |
| Nephritis and renal dysfunction        | 1 (< 1)   | 1 (< 1)   | 1 (100)                | 1 (100)   | 1 (100)   | 1 (100)                                        | —         | —         |
| Autoimmune nephritis                   | 1 (< 1)   | 1 (< 1)   |                        | —         | —         | —                                             | —         | —         |

NOTE. Data presented as No. (%). Includes events defined as AEs (regardless of causality) that required immune-modulating medication (with the exception of those of endocrine origin) and were reported up to 100 days after the last dose. High-dose corticosteroids defined as a dose equivalent to ≥ 40 mg prednisone.

Abbreviation: AE, adverse event.
### Table A4. Characteristics of Patients Who Proceeded to Allo-HCT and Characteristics of Allo-HCT

| Characteristic | BV Naive: Cohort A (n = 9) | BV After Auto-HCT: Cohort B (n = 14) | BV Before and/or After Auto-HCT: Cohort C (n = 21) |
|---------------|---------------------------|-------------------------------------|-----------------------------------------------|
| **Characteristics of patients who proceeded to allo-HCT** | | | |
| Median nivolumab doses received (IQR) | 11 (8–14) | 10 (8–17) | 13 (10–16) |
| BOR to nivolumab | | | |
| Complete remission | 2 (22) | 1 (7) | 4 (19) |
| Partial remission | 4 (44) | 6 (43) | 14 (67) |
| Stable disease | 1 (11) | 7 (50) | 2 (10) |
| Progressive disease | 2 (22) | 0 | 1 (5) |
| Discontinued nivolumab as a result of disease progression | 3 (33) | 5 (36) | 2 (10) |
| Therapeutic intervention after nivolumab and before allo-HCT | 4 (44) | 6 (43) | 2 (10) |
| Median time from last nivolumab dose to allo-HCT, months (IQR) | 4.2 (1.6–6.2) | 1.4 (1.0–4.2) | 1.5 (1.2–3.3) |
| Disease status at allo-HCT | | | |
| Complete remission | 4 (44) | 7 (50) | 10 (48) |
| Partial remission | 4 (44) | 6 (43) | 9 (43) |
| UTD/not reported | 1 (11) | 1 (7) | 2 (10) |
| **Allo-HCT characteristics** | | | |
| HCT source | | | |
| Peripheral blood | 8 (89) | 10 (71) | 14 (67) |
| Bone marrow | 0 | 3 (21) | 6 (29) |
| Unknown/not reported | 1 (11) | 1 (7) | 1 (5) |
| Donor type | | | |
| HLA-identical relative | 2 (22) | 2 (14) | 5 (24) |
| ≥ 2 HLA-mismatched haploidentical relative | 2 (22) | 3 (21) | 7 (33) |
| Unrelated | 4 (44) | 8 (57) | 9 (43) |
| Unknown | 1 (11) | 1 (7) | 0 |
| Preparative regimen | | | |
| MAC | 1 (11) | 1 (7) | 0 |
| Non-MAC | 5 (56) | 10 (71) | 19 (90) |
| Unknown/not reported | 3 (33) | 3 (21) | 22 (10) |

**NOTE:** Data presented as No. (%) unless otherwise indicated.

**Abbreviations:** allo-HCT, allogeneic hematopoietic cell transplantation; auto-HCT, autologous hematopoietic cell transplantation; BOR, best overall response; BV, brentuximab vedotin; HLA, human leukocyte antigen; IQR, interquartile range; MAC, myeloablative conditioning; UTD, unable to determine.