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ORIGINAL REPORT

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.

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ASSOCIATED CONTENT

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Appendix
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Data Supplement
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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.[1-3] Achieving durable responses in this population is a critical goal rarely achieved with conventional chemotherapy.[4,5] 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.[6] A subset of patients who achieve complete remission (CR) with BV maintain durable responses after 5 years[7]; 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.

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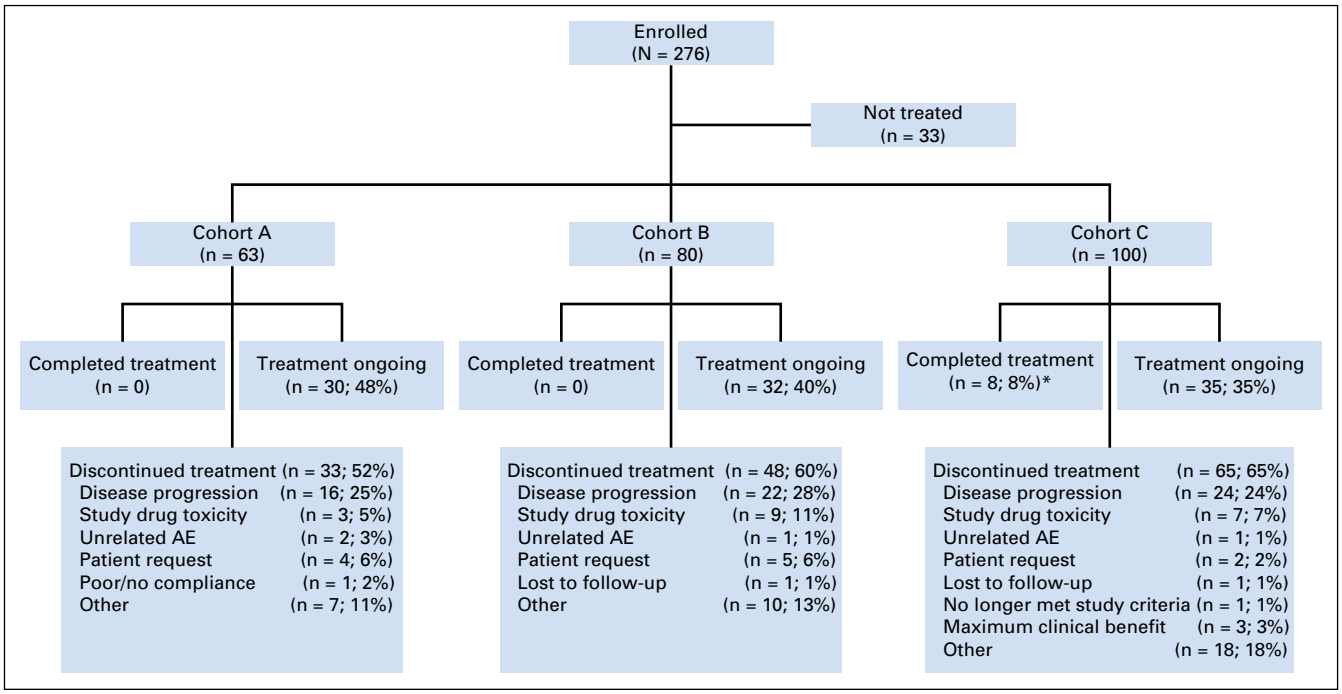

Fig 1. CONSORT diagram. (*) Includes seven patients who discontinued nivolumab because of persistent complete remission for 1 year. AE, adverse event.

Genetic alterations at 9p24.1 are almost universal in cHL,[8,9] 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.[10,11] 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.[12] 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.[13] 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).[14] 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.

METHODS

Study Design and Participants

This multicenter, single-arm trial enrolled patients aged ≥ 18 years with biopsy-confirmed relapsed/refractory cHL after treatment failure with auto-HCT into three independent cohorts. Complete methods for cohort B of this trial have been described,[14] 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[15]) 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, 37, and 49 during the first year of treatment; every 16 weeks during the second year of treatment; and every 26 weeks thereafter. [^{18}F]fluorodeoxyglucose–positron emission tomography (PET) scans were mandated at screening and weeks 17 and 25, and were also required at week 49 for patients without two consecutive negative [^{18}F]fluorodeoxyglucose–PET scans before week 49 or for confirmation of radiographic CR at other time points. Safety assessments were performed continuously.

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

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Table 1. Baseline Characteristics

Characteristic	BV Naïve: 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)
≥ 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	1 (2)	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	1 (2)	0	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
≥ 3 prior lines	29 (46)	80 (100)	97 (97)	206 (85)
≥ 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	0	80 (100)	100 (100)	180 (74)
After auto-HCT	—	80 (100)	58 (58)	138 (57)
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.

outcomes after allo-HCT were collected retrospectively. Myeloablative conditioning was defined according to standard criteria.[16]

Outcomes

The primary end point was independent radiology review committee (IRC)–assessed ORR (2007 IWG criteria[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 ≤ 20% (assuming 40% of patients achieve an objective response and a two-sided α of 5%). Cohort C (n = 100) was designed to provide an 87% probability of observing at least one occurrence of any adverse event (AE) that would occur with 2% incidence. 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 (G) 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[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-naïve patients (cohort A) had the fewest prior lines of therapy, and patients in cohort B (BV after auto-HCT) had the

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Table 2. Objective and Best Overall Response per IRC

Response	Protocol-Specified Analysis by Cohort: BV Naïve: 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)

	Exploratory Analyses by Refractory Status (all patients): To First Line (n = 142)	To Last Line (n = 114)	To BV After Auto-HCT (n = 75)
ORR	73	68	68
Best overall response			
Complete remission	25 (18)	15 (13)	5 (7)
Partial remission	78 (55)	62 (54)	46 (61)
Stable disease	25 (18)	22 (19)	13 (17)
Progressive disease	12 (8)	12 (11)	8 (11)
Unable to determine	2 (1)	3 (3)	3 (4)

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.

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, with CR in 29%, 13%, and 12% of patients, 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 TTNT 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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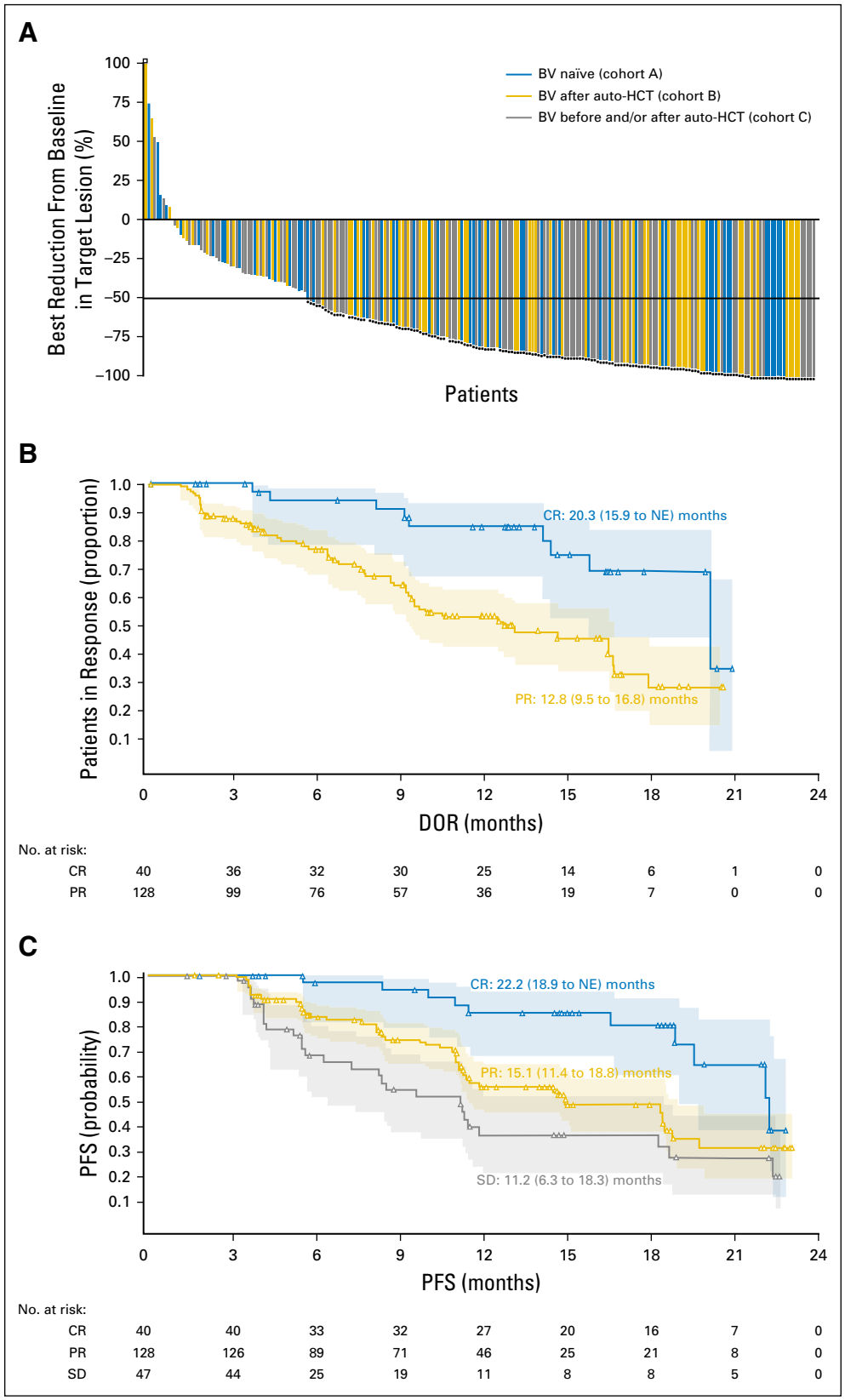

Fig 2. Best change in (A) target lesions, (B) duration of response (DOR), (C) progression-free survival (PFS), and (D) overall survival (OS), according to best overall response. (*) Indicates responders; open square indicates change truncated to 100%. (B, C, and D) Values are median (95% CI) unless stated otherwise. Shading around lines represents 95% CIs. Auto-HCT, autologous hematopoietic cell transplantation; BV, brentuximab vedotin; CR, complete remission; NA, not available; NE, not estimable; PD, progressive disease; PR, partial remission; SD, stable disease.

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.

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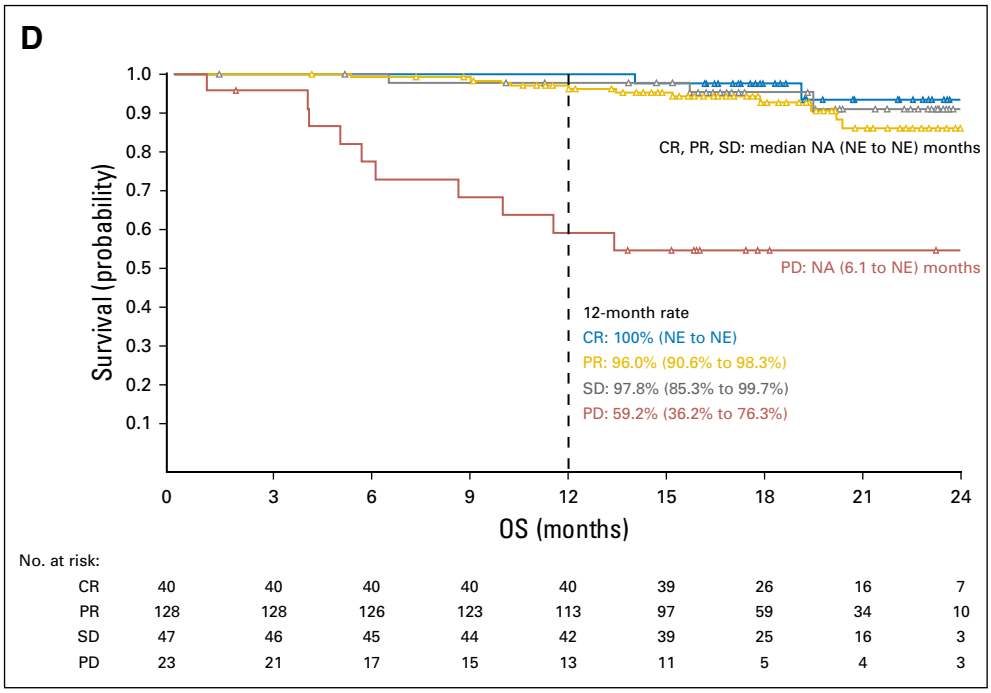

Fig 2. (Continued).

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 hypoxemic 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).

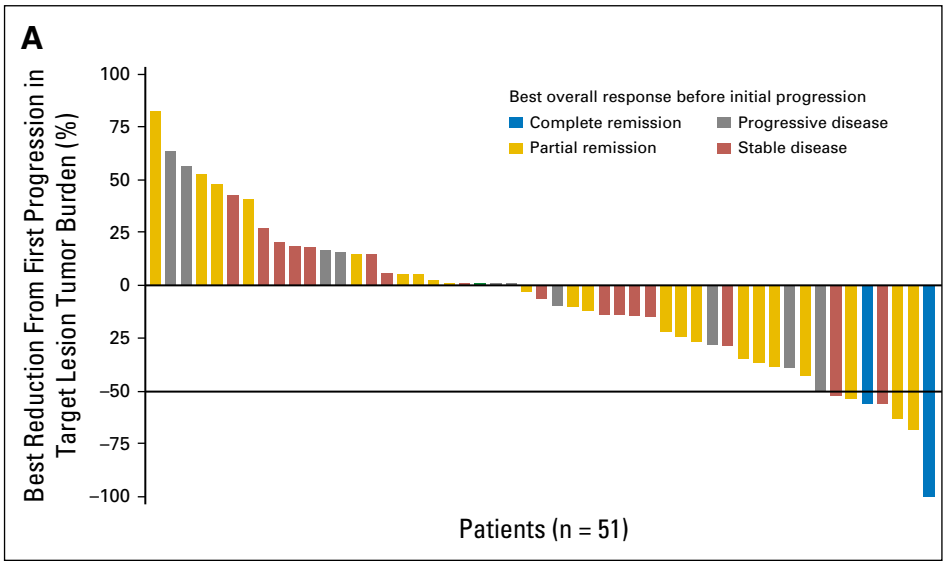

Fig 3. Outcomes in patients treated beyond progression. (A) Investigator-assessed best change in target lesion tumor burden and (B, C, and D) investigator-assessed change in target lesion burden over time for patients treated beyond progression according to best overall response to nivolumab before initial 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.

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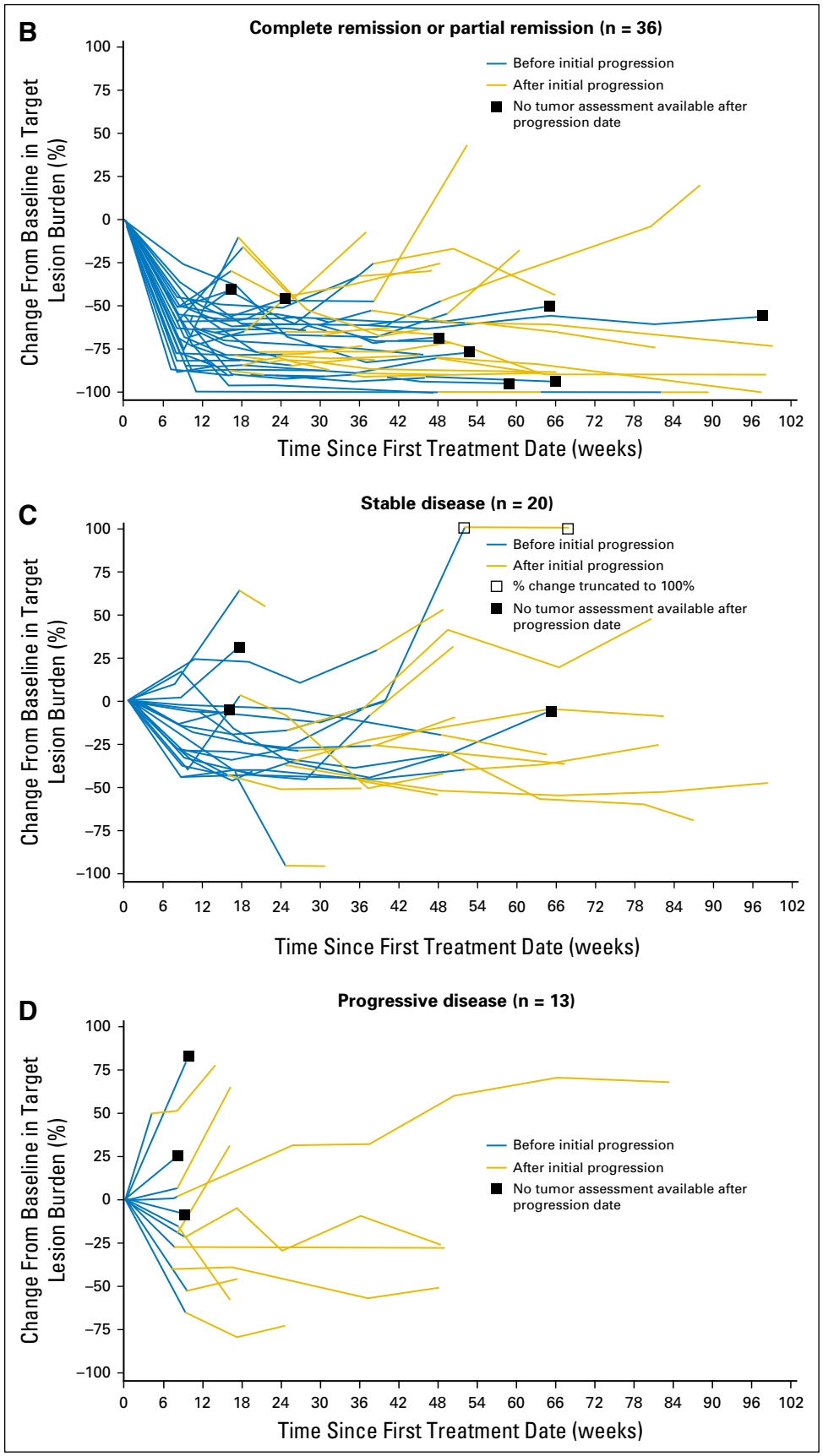

Fig 3. (Continued).

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Table 3. Adverse Events

Adverse Event	All-Cause Adverse Events (n = 243)		Drug-Related Adverse Events (n = 243)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
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.

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 nonmyeloablative 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 4A). The five patients with TRM had transplantations 22 to 190 days from the last nivolumab dose, all from unrelated donors, and died 36 to 96 days after allo-HCT; four experienced aGVHD. Cumulative incidences of aGVHD and cGVHD are shown in Fig 4B. 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 ($P = .85$) or G3 to G4 aGVHD ($P = .97$). AEs of special interest after allo-HCT included hyperacute GVHD (onset < 14 days after transplantation[18]) 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).

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,[12] 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 naïve to BV, patients who received BV at differing times relative to auto-HCT, and patients refractory to prior lines of therapy.

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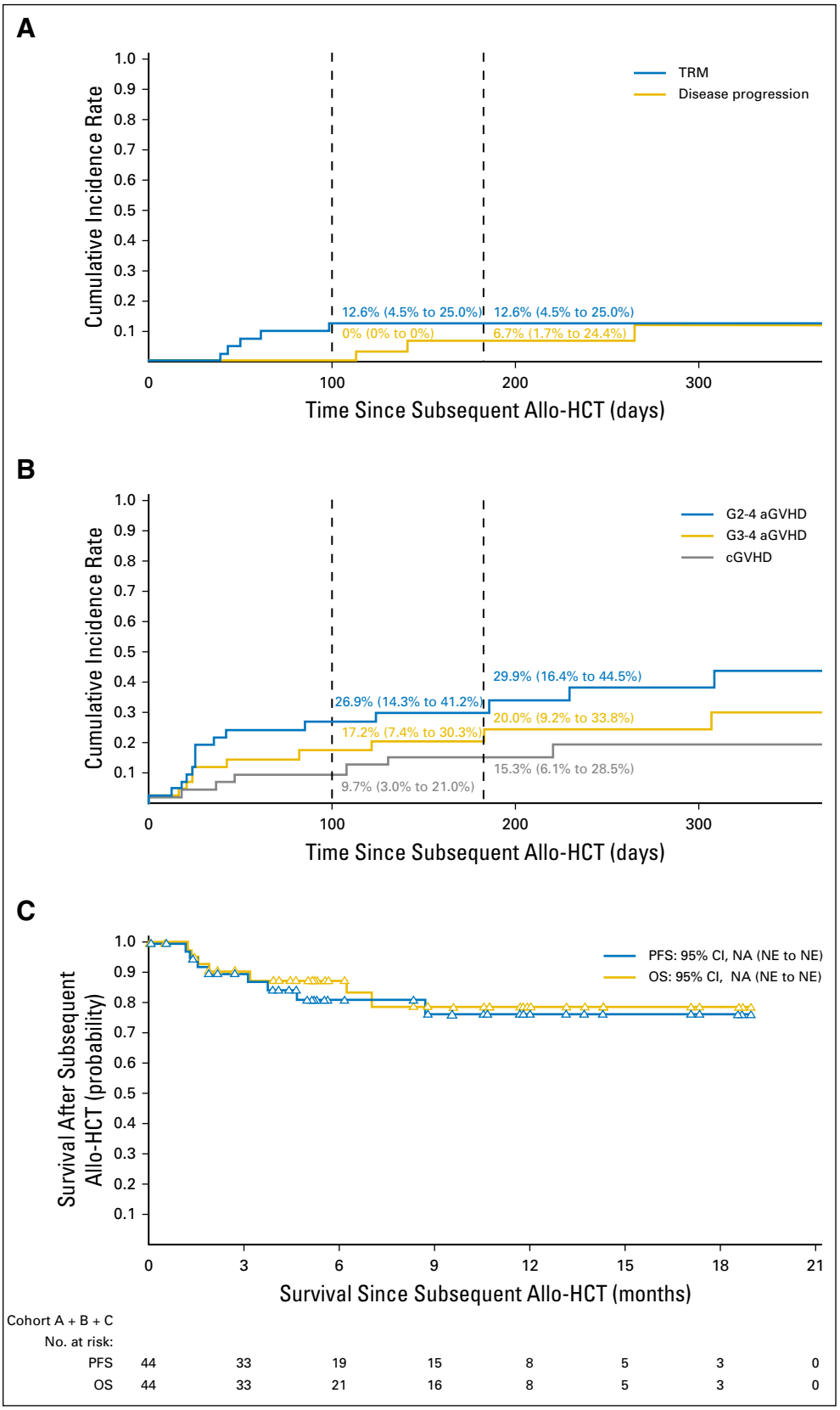

Fig 4. Cumulative incidence of (A) transplant-related mortality (TRM) and disease progression, (B) acute graft-versus-host disease (aGVHD) and chronic graft-versus-host disease (cGVHD), and (C) overall survival (OS) and progression-free survival (PFS) after allogeneic hematopoietic cell transplantation (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.

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Previous studies in cHL suggest that DOR and PFS with chemotherapeutic agents may be strongly associated with depth of response.[6,21] 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% *v* 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 *v* 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.[22-24] 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 Immunomodulatory Therapy Criteria [LyRIC][25] and Response Evaluation Criteria in Lymphoma [RECIL][26]) 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[27] 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.[28-32] 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 before allo-HCT on aGVHD or TRM. These results are similar to others recently published,[33] but larger studies will be needed to confirm this finding. Together, these results suggest that prior nivolumab treatment should not preclude allo-HCT. However, the possibility remains that prior PD-1 blockade may increase early post–allo-HCT toxicity, and a warning and precaution label for complications of allo-HCT is included in the prescribing information for nivolumab.[12] Additional follow-up is required to ascertain long-term outcomes post–allo-HCT after PD-1 blockade.

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.

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

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Prior Presentation

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.

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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)

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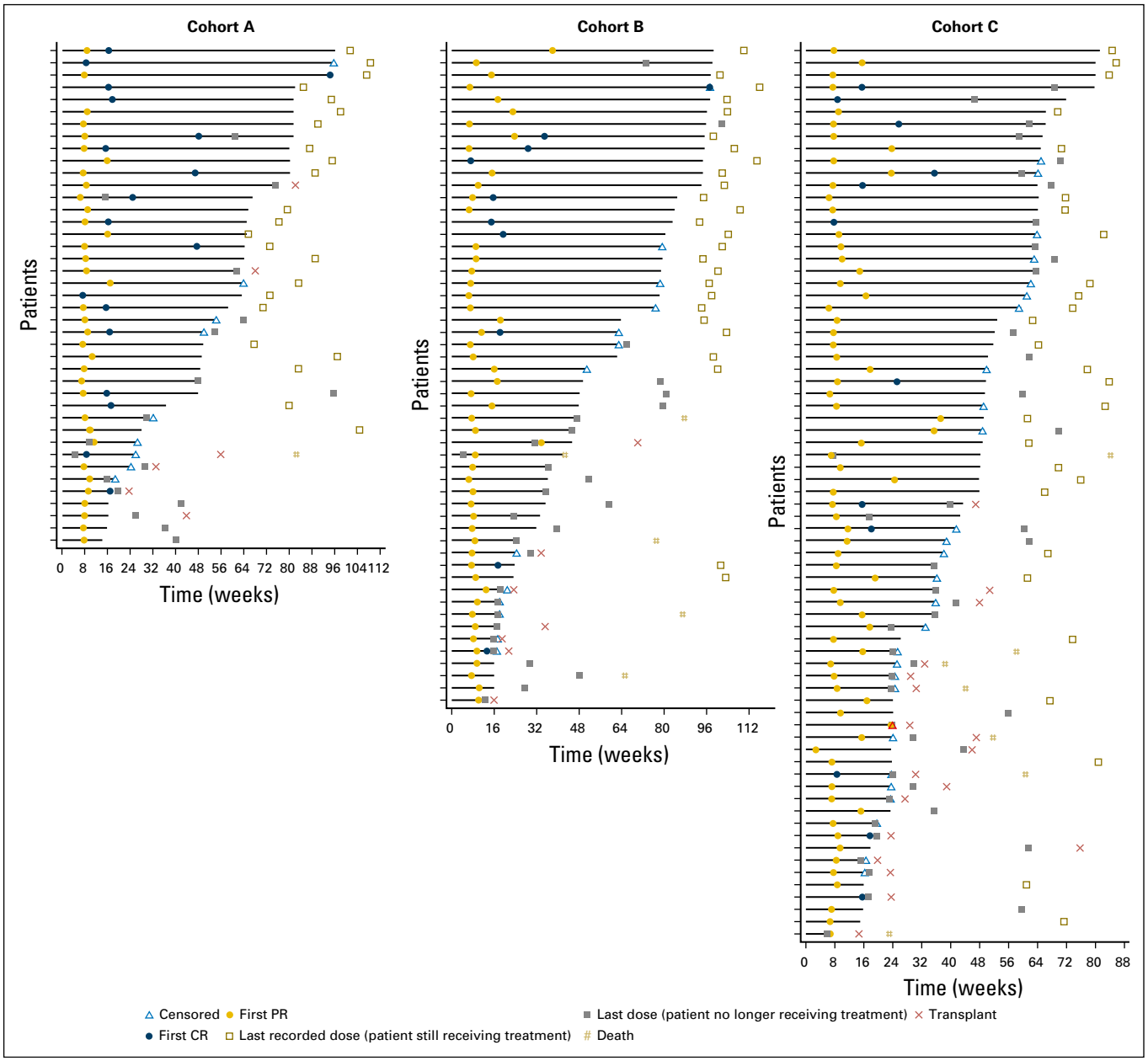

Fig A1. Response characteristics among all responders. CR, complete remission; PR, partial remission.

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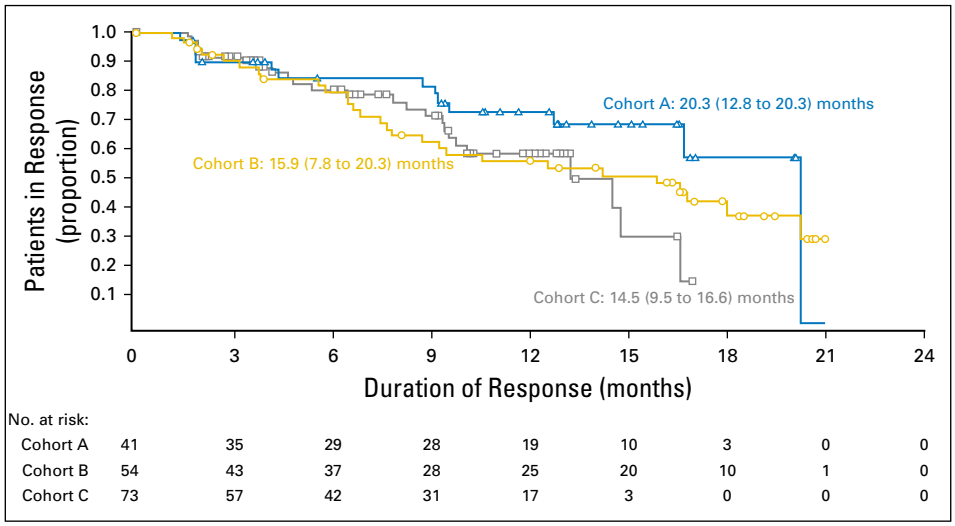

Fig A2. Duration of response in cohorts A, B, and C. All values are median (95% CI).

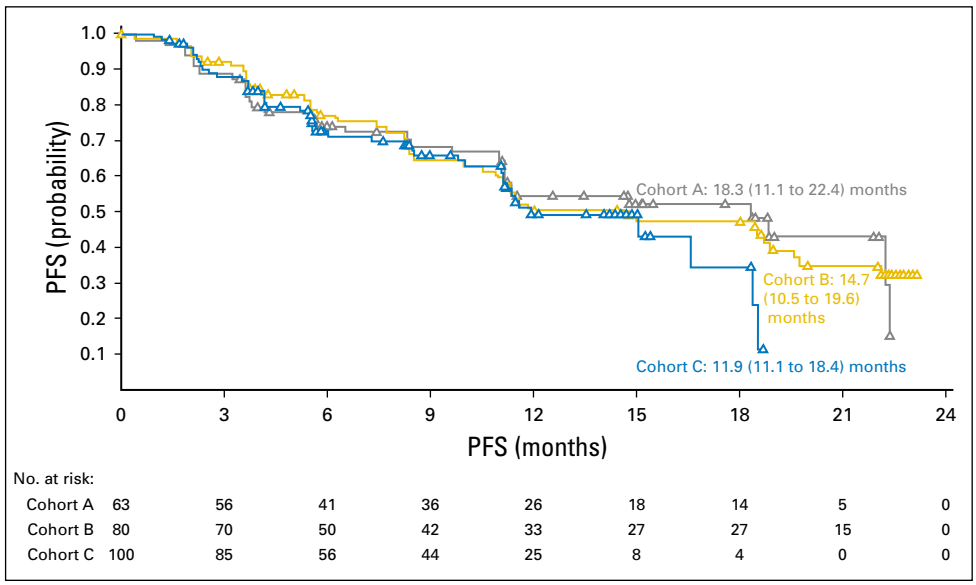

Fig A3. Progression-free survival (PFS) in cohorts A, B, and C. All values are median (95% CI).

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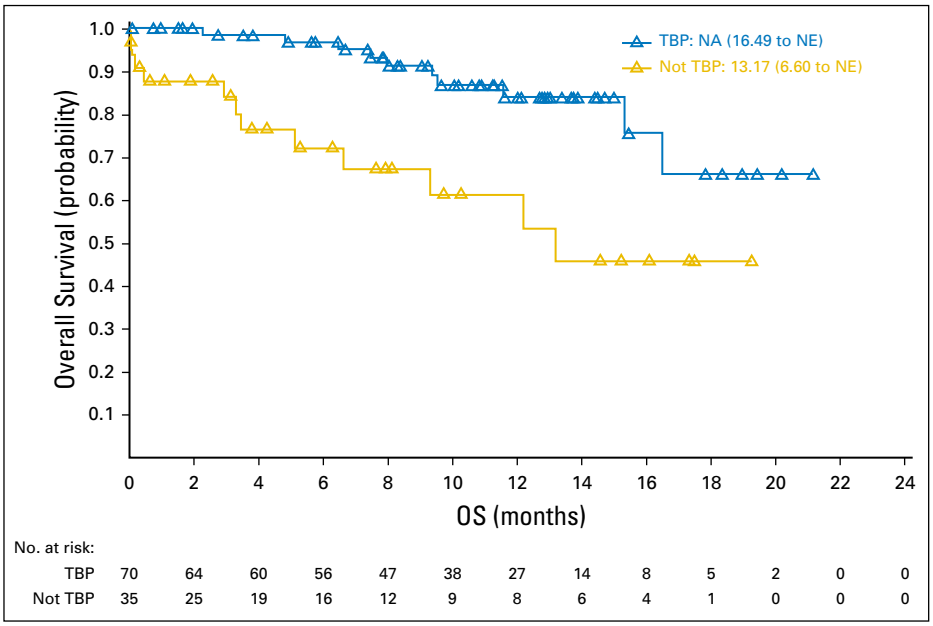

Fig A4. Overall survival (OS) from date of initial disease progression in patients treated beyond initial progression (TBP) and not TBP. All values are median (95% CI). NA, not available; NE, not estimable.

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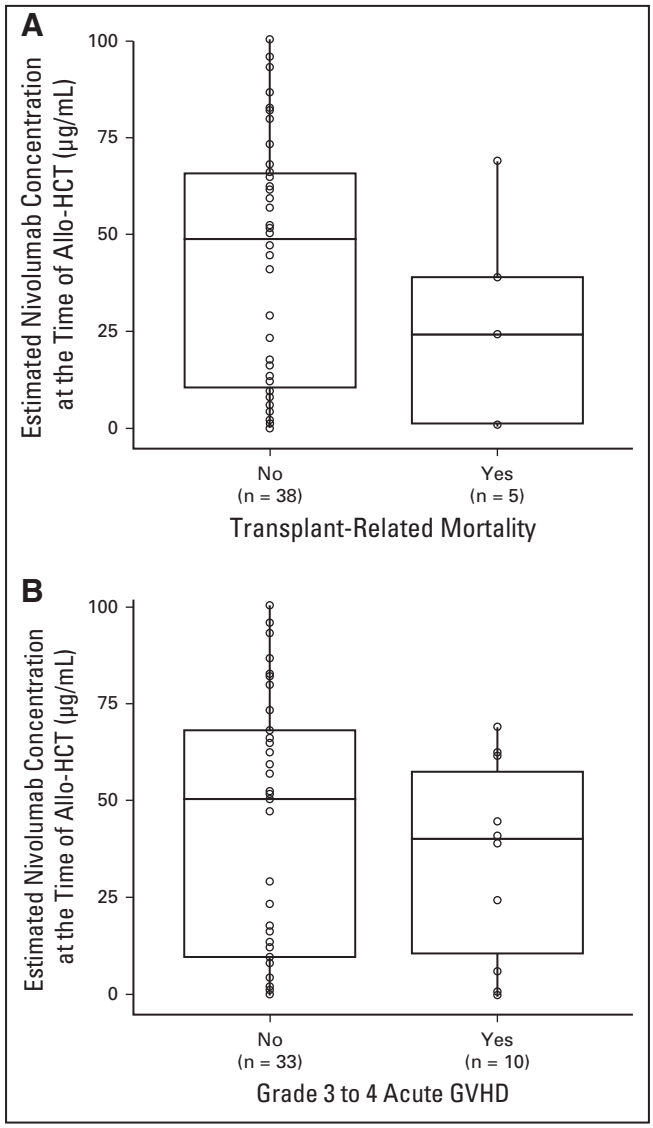

Fig A5. Estimated nivolumab concentration at the time of allogeneic hematopoietic cell transplantation (µg/mL) and occurrence of (A) transplant-related mortality or (B) grade 3 to 4 acute graft-versus-host disease (GVHD). Box plots represent 25th and 75th percentiles; lines within the box plots represent median values and circles represent individual patients.

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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 Naïve: 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.

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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	—	6 (1-22)	7 (1-22)
Primary cause of radiographic progression (IWG 2007), No. (%)*			
Increase in overall tumor burden	—	13 (19)	7 (20)
Nontarget lesion growth	—	17 (24)	2 (6)
New lesion	—	47 (67)	13 (37)
Change in target lesion tumor burden at first progression from baseline (imputed)†			
No. of patients with available data	—	67	22
Median, %	—	−44	−38
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	
	All Evaluable Patients (n = 51)	Reduction or No Change (n = 31)	Increase (n = 20)
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.

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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		Received High-Dose Corticosteroids, by Category	
			Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hypothyroidism/thyroiditis	29 (12)	0	10 (34)	—	0	—
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	17 (7)	3 (1)				
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)	6 (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.

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Table A4. Characteristics of Patients Who Proceeded to Allo-HCT and Characteristics of Allo-HCT

Characteristic	BV Naïve: 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.

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