

Nivolumab for relapsed/refractory classical Hodgkin lymphoma: 5-year survival from the pivotal phase 2 CheckMate 205 study

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Key Points

- With 5 years of follow-up, nivolumab had lasting benefits in patients with R/R cHL after auto-HCT.
- It appears feasible to discontinue nivolumab in patients with persistent CR and reinitiate treatment upon disease progression.

Patients with relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) for whom autologous hematopoietic cell transplantation (auto-HCT) had failed experienced frequent and durable responses to nivolumab in the phase 2 CheckMate 205 trial. We present updated results (median follow-up, ~5 years). Patients with R/R cHL who were brentuximab vedotin (BV)–naïve (cohort A), received BV after auto-HCT (cohort B), or received BV before and/or after auto-HCT (cohort C) were administered with nivolumab 3 mg/kg IV every 2 weeks until progression or unacceptable toxicity. Patients in cohort C with complete remission (CR) for 1 year could discontinue nivolumab and resume upon relapse. Among 243 patients (cohort A, n = 63; B, n = 80; and C, n = 100), the objective response rate (ORR) was 71.2% (95% confidence interval [CI], 65.1-76.8); the CR rate was 21.4% (95% CI, 16.4-27.1). Median duration of response, CR, and partial remission were 18.2 (95% CI, 14.7-26.1), 30.3, and 13.5 months, respectively. Median progression-free survival was 15.1 months (95% CI, 11.3-18.5). Median overall survival (OS) was not reached; OS at 5 years was 71.4% (95% CI, 64.8-77.1). In cohort C, all 3 patients who discontinued in CR and were subsequently re-treated achieved objective response. No new or unexpected safety signals were identified. This 5-year follow-up of CheckMate 205 demonstrated favorable OS and confirmed efficacy and safety of nivolumab in R/R cHL after auto-HCT failure. Results suggest patients may discontinue treatment after persistent CR and reinitiate upon progression. This trial was registered at www.clinicaltrials.gov as #NCT02181713.

Introduction

Patients with relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL) after autologous hematopoietic cell transplantation (auto-HCT) have a poor prognosis, with a historical median overall survival

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The full-text version of this article contains a data supplement.

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(OS) of ~2 years.¹⁻⁵ Brentuximab vedotin (BV) may provide benefits in this setting, but only 10% maintain complete remission (CR) after 5 years of follow-up,^{6,7} and most patients relapse or progress after BV therapy, with few available treatment options.

Genetically driven overexpression of programmed death-1 (PD-1) ligands 1 (PD-L1) and 2 (PD-L2) are characteristic of cHL and downregulate T-cell immune responses by binding to PD-1.⁸⁻¹⁰ PD-1 immune checkpoint inhibitors have shown strong activity in patients with R/R cHL¹¹⁻¹³ and are a recommended treatment option in this setting per the clinical practice guidelines of the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology, and the Chinese Society of Clinical Oncology.¹⁴⁻¹⁶ One such inhibitor is nivolumab, a fully human immunoglobulin G4 anti-PD-1 monoclonal antibody that augments antitumor immune responses by blocking signaling through the PD-1 pathway, releasing T-cell inhibition.^{11,17} However, the long-term survival benefit of anti-PD-1 therapy and optimal treatment duration are unknown.

The pivotal, single-arm, phase 2 CheckMate 205 trial (NCT02181738) demonstrated frequent and durable responses with nivolumab in patients with R/R cHL for whom auto-HCT had failed.¹⁸⁻²⁰ A favorable objective response rate (ORR) was demonstrated after a median follow-up of 18.0 months¹⁹ and 33.0 months.²⁰ Here, we present updated efficacy and safety results from CheckMate 205 with an extended median follow-up of 58.5 months, including exploratory analyses of progression-free survival (PFS) and OS as well as CR maintenance after nivolumab discontinuation.

Methods

Trial details have been described previously and are summarized later in the article.^{18,19}

Study design and patients

In the multicenter, multicohort, single-arm, phase 2 CheckMate 205 trial, patients aged ≥ 18 years with cHL for whom auto-HCT had failed were enrolled at 38 sites across Europe and North America. Patients were enrolled in cohort A if they had received no prior treatment with BV, cohort B if they received BV as salvage therapy after failure of auto-HCT, or cohort C if they received BV before and/or after auto-HCT. Exclusion criteria included autoimmune disease, radiation therapy within 3 weeks or chest radiation within 24 weeks of the first dose of nivolumab, auto-HCT within 90 days of the first dose of nivolumab, and allogeneic HCT (allo-HCT) or checkpoint blockade at any time before nivolumab treatment. This study was conducted in accordance with the Declaration of Helsinki. Before enrollment, all patients provided written informed consent. Before trial initiation at each site, approval from the appropriate institutional review board and independent ethics committee was obtained.

Treatment

Patients received nivolumab 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity, or patients could elect to discontinue nivolumab and proceed to receive allo-HCT. Per a protocol amendment in July 2014, patients could continue treatment after investigator-determined disease progression. Patients in cohort C who achieved CR for ≥ 1 year were to discontinue

treatment, with the option to reinstate therapy if they relapsed within 2 years.

Determination of tumor response was made by an independent review committee (IRC) using the 2007 International Working Group criteria for malignant lymphoma. Tumor assessments were performed at screening, week 9 (± 7 days) after treatment initiation, weeks 17, 25, 37, and 49, then every 16 weeks (± 14 days) up to week 97, and every 26 weeks (± 21 days) thereafter until disease progression was documented or the patient initiated a preparative regimen for auto- or allo-HCT, whichever occurred earlier.

Adverse events (AEs), serious AEs, and treatment-related AEs (TRAEs) were reported throughout the treatment period and between screening and 100 days after the last dose. Immune-mediated AEs, including specific events such as diarrhea/colitis, hepatitis, pneumonitis, nephritis and renal dysfunction, rash, and endocrine-related events, were reported within 100 days of the last dose. Late-emergent TRAEs, defined as TRAEs (including immune-mediated AEs) with an onset date >100 days after the last dose of study therapy, were also reported. AEs were coded using the Medical Dictionary for Regulatory Activities version 23.1. AEs and laboratory values were tabulated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

End points

The primary end point was IRC-assessed ORR. Secondary end points included the IRC-assessed duration of response (DOR), CR and partial remission (PR) rates, and CR and PR duration. Exploratory end points included IRC-assessed PFS according to the cohort and by best overall response (BOR), OS according to the cohort and by BOR, and safety.

Statistical analysis

The planned sample size was 60 patients each for cohorts A and B and 100 patients for cohort C. Assuming an ORR of 40%, this would provide ~93% power to reject the null hypothesis that the true ORR was $\leq 20\%$, considering a 2-sided α of 5%. The sample size for cohort C was planned to provide an 87% probability of observing at least 1 occurrence of any AE that would have occurred with 2% incidence.

All patients who received at least 1 dose of nivolumab were included in the primary efficacy and safety analyses. Primary efficacy analyses were performed independently for each cohort; safety was analyzed in the combined population. ORRs were summarized using binomial response rates, and 2-sided 95% exact confidence intervals (CIs) were calculated using the Clopper-Pearson method.

Results

Baseline patient characteristics and disposition

Between August 2014 and August 2015, a total of 276 patients were enrolled, and 243 were treated across cohorts A ($n = 63$), B ($n = 80$), and C ($n = 100$). At database lock (22 January 2021), the median follow-up was 58.5 months for all patients treated: 61.9 months for cohort A, 58.5 months for cohort B, and 53.5 months for cohort C. As reported previously,¹⁹ baseline characteristics were generally similar across cohorts (Table 1),

Table 1. Baseline demographics and disease characteristics

Characteristic	Cohort A (BV naive) (n = 63)	Cohort B (BV after auto-HCT) (n = 80)	Cohort C (BV before and/or after auto-HCT) (n = 100)	Overall (N = 243)
Age, median (range), y	33 (18-65)	37 (18-72)	32 (19-69)	34 (18-72)
Female, n (%)	29 (46.0)	29 (36.3)	44 (44.0)	102 (42.0)
Stage at study entry, n (%)				
I	1 (1.6)	1 (1.3)	2 (2.0)	4 (1.6)
II	19 (30.2)	11 (13.8)	20 (20.0)	50 (20.6)
III	18 (28.6)	14 (17.5)	17 (17.0)	49 (20.2)
IV	24 (38.1)	54 (67.5)	61 (61.0)	139 (57.2)
Not reported	1 (1.6)	0	0	1 (0.4)
B symptoms at study entry, n (%)	10 (15.9)	18 (22.5)	25 (25.0)	53 (21.8)
Bulky disease at study entry, n (%)	10 (15.9)	17 (21.3)	22 (22.0)	49 (20.2)
Extralymphatic involvement, n (%)	24 (38.1)	36 (45.0)	45 (45.0)	105 (43.2)
Median prior lines of therapy (IQR)	2 (2-3)	4 (4-7)	4 (3-5)	4 (3-5)
Time from diagnosis to first dose of nivolumab, median (IQR), y	3.1 (2.0-7.5)	6.2 (3.3-8.3)	3.5 (2.3-6.4)	4.5 (2.4-7.6)

IQR, interquartile range.

with a median age of 34 years (range, 18-72) in the treated population.

At database lock, 7.8% of patients remained on treatment (supplemental Figure 1). The most common reason for treatment discontinuation was disease progression. Median duration of treatment was 14.3 months (95% CI, 12.7-16.3) and was similar across cohorts.

Objective response and CR

At a median follow-up of 58.5 months (range, 1.0-74.3), the IRC-assessed ORR was 71.2% (95% CI, 65.1-76.8), with a CR rate of 21.4% (95% CI, 16.4-27.1; Table 2). CR rate was the highest in patients who were naive to BV (cohort A, 31.7%) compared with those who had prior BV exposure (cohort B, 13.8%; cohort C, 21.0%). The overall population had a median time to response of 2.1 months (range, 0.8-17.9) and a median time to CR of 4.0

months (range, 1.7-34.4), both similar in all cohorts. The median DOR was 18.2 months (95% CI, 14.7-26.1; Figure 1A), and the median durations of CR and PR were 30.3 months and 13.5 months, respectively.

PFS

Median PFS was 15.1 months (95% CI, 11.3-18.5) and was the longest in patients who were naive to BV (18.3 months in cohort A, 14.8 months in cohort B, and 15.1 months in cohort C; Figure 1B). The PFS rate was 37.1% (95% CI, 30.1-44.2) at 2 years and 17.9% (95% CI, 11.6-25.3) at 5 years. When compared based on the BOR, the median PFS was highest in patients who achieved CR, at 37.4 months (95% CI, from 26.7 to not estimable; Figure 1C). For those with a BOR of PR, stable disease, and progressive disease, median PFS was 15.2 months (95% CI, 11.6-19.8), 8.3 months (95% CI, 5.7-11.3), and 2.1 months (95% CI, 1.8-2.2), respectively.

Table 2. BOR

Response	Cohort A (BV naive) (n = 63)	Cohort B (BV after auto-HCT) (n = 80)	Cohort C (BV before and/or after auto-HCT) (n = 100)	Overall (N = 243)
ORR, % (95% CI)	65.1 (52.0-76.7)	71.3 (60.0-80.8)	75.0 (65.3-83.1)	71.2 (65.1-76.8)
BOR, n (%)				
CR	20 (31.7)	11 (13.8)	21 (21.0)	52 (21.4)
PR	21 (33.3)	46 (57.5)	54 (54.0)	121 (49.8)
SD	14 (22.2)	14 (17.5)	12 (12.0)	40 (16.5)
Progressive disease	8 (12.7)	7 (8.8)	11 (11.0)	26 (10.7)
Median time to response, mo (range)	2.0 (1.5-4.6)	2.2 (1.6-11.1)	2.1 (0.8-17.9)	2.1 (0.8-17.9)
IQR	1.9-2.3	1.9-3.0	1.9-3.8	1.9-3.6
Median time to CR, mo (range)	3.9 (1.7-34.4)	4.4 (1.9-22.8)	4.2 (1.8-17.9)	4.0 (1.7-34.4)
IQR	3.7-5.2	3.7-19.1	3.7-6.5	3.7-8.3
Median DOR, mo (95% CI)	26.2 (15.2-NE)	16.6 (9.3-25.7)	18.2 (11.6-30.9)	18.2 (14.7-26.1)

NE, not evaluable; SD, stable disease.

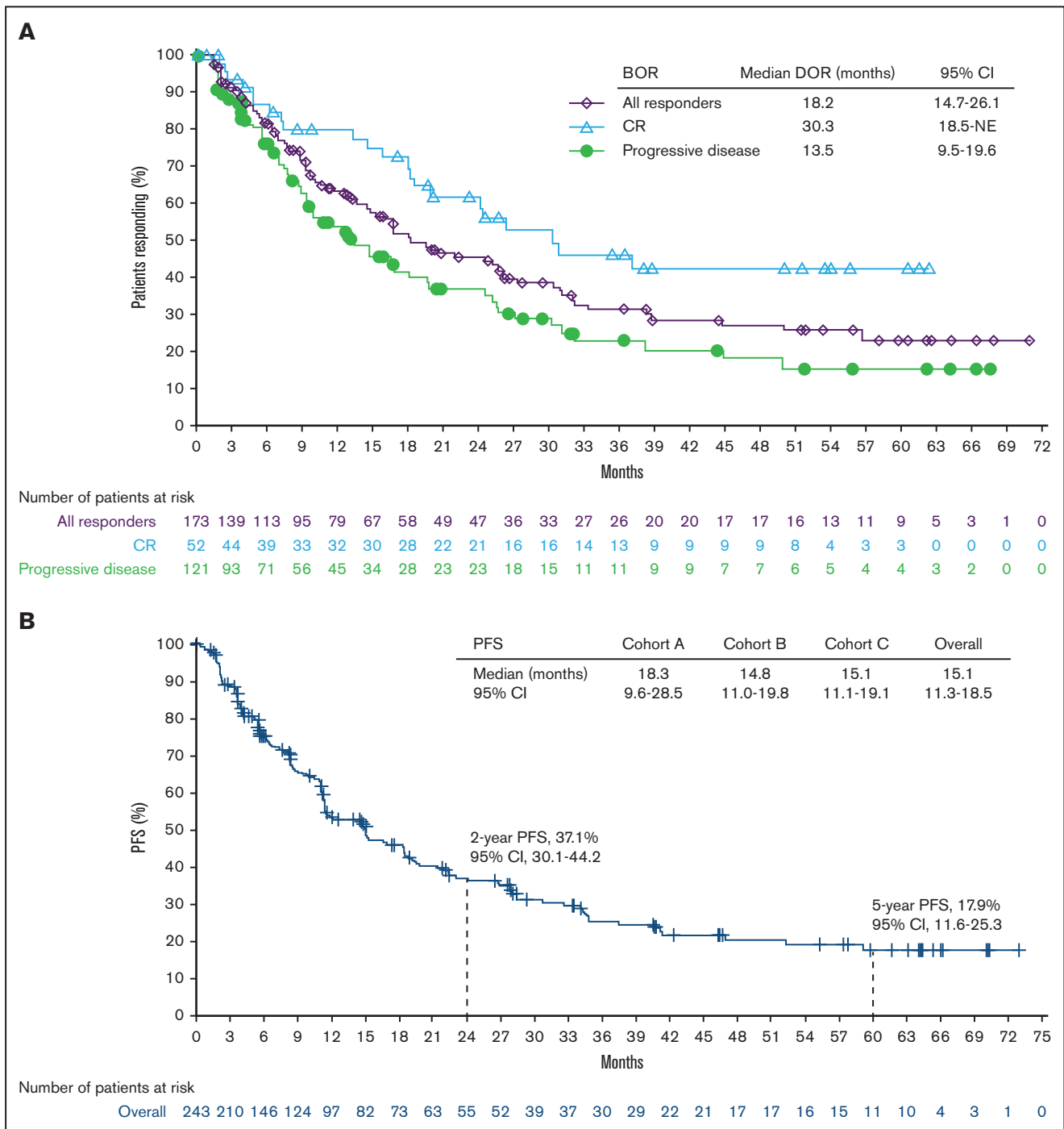


Figure 1. Efficacy endpoints: duration of response and progression-free survival. DOR according to the BOR (A), PFS according to the cohort (B), and PFS according to the BOR (C). NE, not estimable; SD, stable disease.

OS

A total of 65 patients died, including 36 from disease progression. The median OS was not reached in any cohort (Figure 2A). The OS rate was 87.1% (95% CI, 82.0-90.8) at 2 years and 71.4% (95% CI, 64.8-77.1) at 5 years. The median OS was 28.8 months (95% CI, from 10.0 to not reached) in patients whose BOR was progressive disease and not reached in patients whose BOR was CR, PR, or stable disease (Figure 2B).

Patients who received subsequent allo-HCT

A total of 58 (23.9%) patients received subsequent HCT (allo-HCT, n = 57; auto-HCT, n = 1) more commonly in cohort C (n = 30) than in cohorts A (n = 13) or B (n = 14). Patients received allo-HCT at a median of 63.0 days (range, 16-716) after their last nivolumab dose. Among the patients who received allo-HCT, 29 (51%) were in CR 2 years after transplant (cohort A, n = 7; cohort B, n = 9; and cohort C, n = 13; supplemental Table 1).

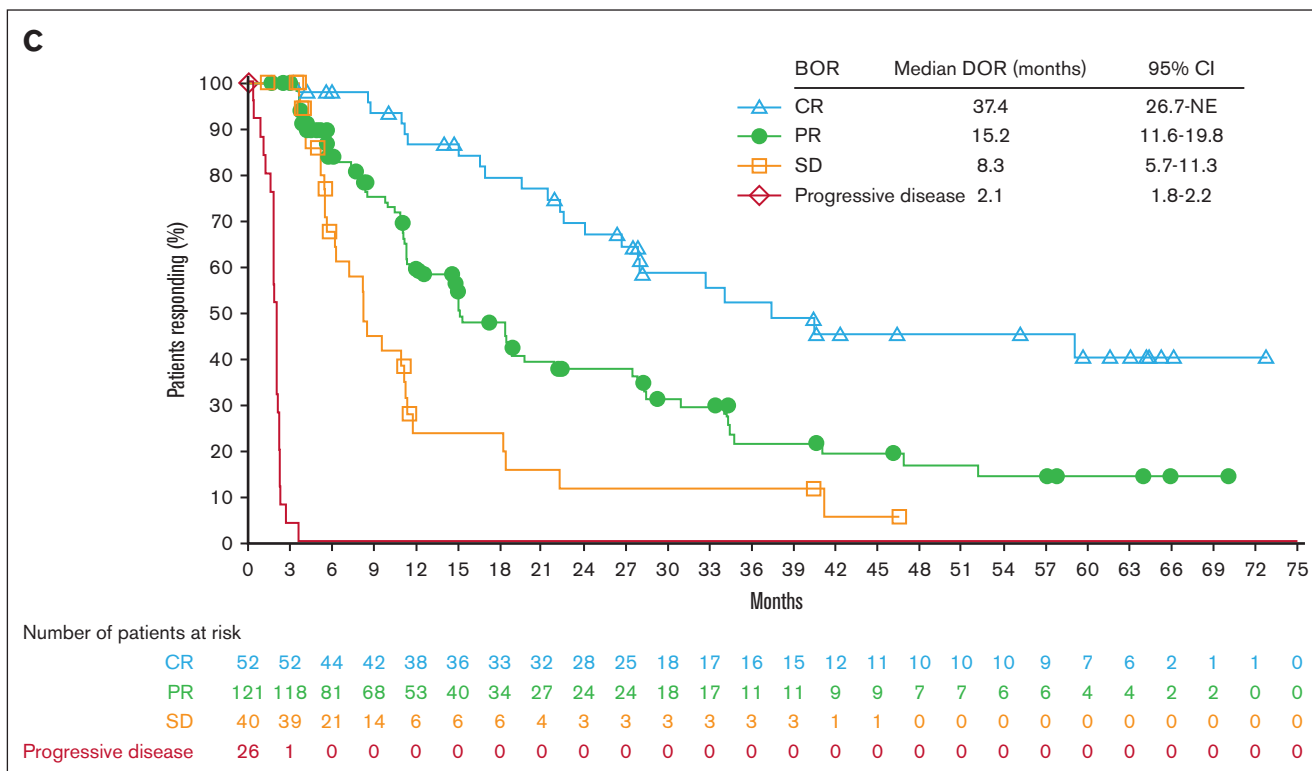


Figure 1 (continued)

Patients in cohort C who discontinued nivolumab after CR

Another exploratory end point was to evaluate the risk and benefit of discontinuing nivolumab after persistent CR. Among the 21 patients in cohort C who achieved CR, 12 had persistent CR for at least 1 year (supplemental Table 2), discontinued treatment, and entered the observational follow-up (maximum of 2 years) and survival follow-up phases. The median follow-up period for these patients since discontinuation for persistent CR was 48.3 months (range, 36.1-54.5). Six patients (50%) completed the follow-up; 6 patients did not complete the follow-up because of progressive disease (n = 4), withdrawal of consent (n = 1), and suspicion of progression that did not meet the criteria for progressive disease (n = 1). Of the 4 patients with progressive disease, 3 were re-treated with nivolumab per protocol (the remaining patient received commercial nivolumab off-study), of whom 1 achieved and maintained CR but discontinued because of treatment-related grade 3 pneumonitis after 2.0 months, 1 achieved PR but discontinued because of disease progression (DOR, 11.1 months), and 1 achieved CR and was still receiving treatment after 35.4 months at database lock.

Safety

In the treated population, TRAEs occurred in 198 patients (81.5%) and 67 patients (27.6%) had a grade 3 or 4 TRAE (Table 3). The most common TRAEs (≥10% of patients) were fatigue (25.1%), diarrhea (16.0%), infusion-related reaction (14.0%), rash (11.9%), nausea (11.1%), and pruritus (10.3%). Thirty-two patients (13.2%)

had a serious TRAE, most commonly pneumonitis (2.1%) and infusion-related reaction (2.1%); 7.8% had a grade 3 or 4 serious TRAE. A total of 22 patients (9.1%) discontinued treatment because of a TRAE, and 13 (5.3%) discontinued because of a grade 3 or 4 TRAE. Pneumonitis was the most common TRAE leading to discontinuation (2.9%). The most common immune-mediated AEs were hypothyroidism (14.4%) and rash (11.9%). Late-onset TRAEs (>100 days after the last dose of study therapy) occurred in 1.6% of patients and included decreased lymphocyte count, increased blood glucose, hyperbilirubinemia, and autoimmune nephritis. There were no deaths related to the study treatment.

Discussion

These long-term results with 5-years of follow-up for CheckMate 205 are consistent with previous findings of median follow-ups of 18 months¹⁹ and 33 months²⁰ and confirm the durable benefit and safety of nivolumab in patients with cHL who progressed or relapsed after auto-HCT. After a median follow-up of 5 years, the observed safety profile of nivolumab was consistent with previous reports, with no newly identified late effects or unexpected safety signals.^{19,20} Additionally, in this extended follow-up study, the observed DOR (18.2 months) and duration of CR (30.3 months) indicated that responses remained durable across all 3 cohorts, particularly for patients who achieved CR. Although the median OS was not reached, the 5-year OS was highest for patients who achieved CR. The AE profile was similar to that in previous reports, with no new or unexpected safety findings.^{19,20}

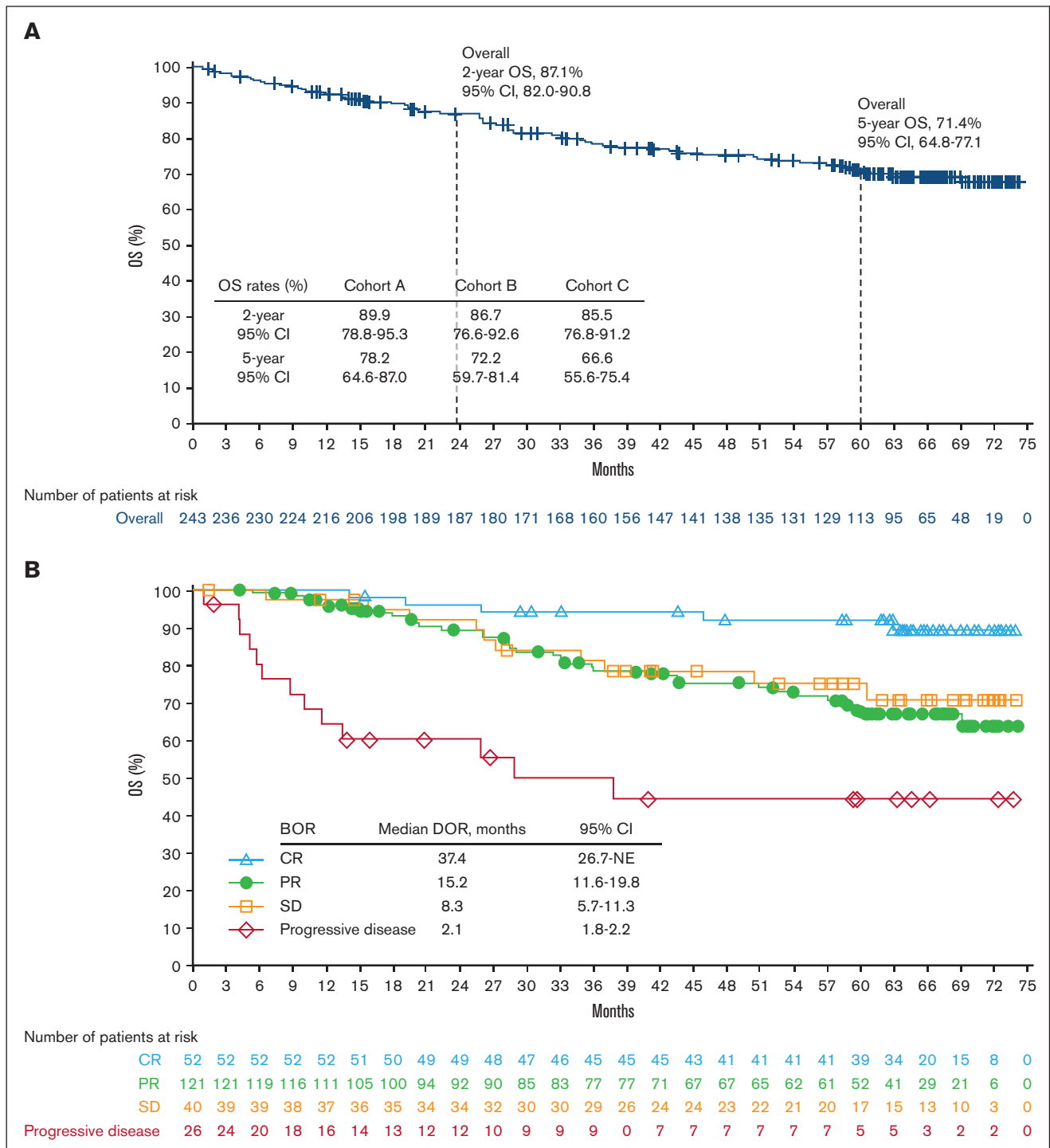


Figure 2. Efficacy endpoints: Overall survival and best overall responses. OS according to the cohort (A) and BOR (B). Of the 65 deaths, causes included disease progression (n = 36), graft-versus-host disease (n = 5), sepsis and/or septic shock (n = 3), pneumonia (n = 3), cardiac arrest (n = 2), multiple organ failure (n = 2), lung cancer (n = 1), Epstein-Barr virus-positive T-cell lymphoma with multiple organ failure (n = 1), adverse reaction to allo-HCT (n = 1), allo-HCT complicated by graft-versus-host disease (n = 1), heart failure (n = 1), post-transplant complications (n = 1), respiratory infection (n = 1), hemorrhagic cystitis (n = 1), acute hypoxemic respiratory failure secondary to pneumocystic pneumonia (n = 1), and unknown causes (n = 5).

The CR rate was numerically higher than it was at the median follow-up of 33 months²⁰; it was highest in patients who were naive to BV (cohort A) and lowest in patients who received BV after failure of auto-HCT (cohort B). The high CR rate observed in this

study in patients who were naive to BV is consistent with previous data showing that first-line nivolumab monotherapy in patients with early-stage cHL resulted in a CR rate of 51%.²¹ It should be noted, however, that patients in cohort A had only received a median of 2

Table 3. TRAEs

TRAEs (N = 243)	Any grade	Grade 3 or 4
Patients with TRAEs, n (%)	198 (81.5)	67 (27.6)
TRAEs occurring in ≥10% of patients, n (%)		
Fatigue	61 (25.1)	2 (0.8)
Diarrhea	39 (16.0)	2 (0.8)
Infusion-related reaction	34 (14.0)	1 (0.4)
Rash	29 (11.9)	2 (0.8)
Nausea	27 (11.1)	0
Pruritus	25 (10.3)	0
Immune-mediated AEs within 100 d of last dose		
Hypothyroidism/thyroiditis	35 (14.4)	0
Rash	29 (11.9)	4 (1.6)
Hepatitis	15 (6.2)	12 (4.9)
Pneumonitis	15 (6.2)	2 (0.8)
Hypersensitivity/infusion reactions	13 (5.3)	2 (0.8)
Diarrhea/colitis	6 (2.5)	5 (2.1)
Hyperthyroidism	6 (2.5)	0
Nephritis and renal dysfunction	3 (1.2)	1 (0.4)
Diabetes mellitus	2 (0.8)	1 (0.4)
Adrenal insufficiency	1 (0.4)	0

prior lines of therapy, whereas patients in cohorts B and C had received a median of 4 prior lines of therapy. The OS was favorable in all cohorts and all patients who did not experience progressive disease as a BOR to nivolumab. Recent data support the superiority of PD-1 inhibitors over BV in this setting,¹² and this study supports the earlier use of PD-1 inhibitors in R/R cHL.

The optimal duration of PD-1 inhibitor therapy in R/R cHL remains unknown. Discontinuation of nivolumab in patients who achieved CR for at least 1 year was explored, and although patient numbers were limited, all patients responded to re-treatment, suggesting that this approach may be feasible. A larger sample size is necessary, however, to understand the frequency, depth, and durability of responses in this setting.

A limitation of this study was the absence of quantitative scoring of positron emission tomography scans because of the use of 2007 International Working Group criteria, because it was designed before the availability of the 2014 Lugano criteria.²²

The results presented herein confirm data from previous studies reporting the efficacy of PD-1 pathway inhibition in R/R cHL for which auto-HCT had failed. In the phase 3 KEYNOTE-204 trial in patients with R/R cHL ineligible for auto-HCT or for whom auto-HCT had failed, pembrolizumab, the only other PD-1 inhibitor approved in the United States for the treatment of R/R cHL,²³ significantly improved PFS compared with BV, with up to a 2-year follow-up.¹² Additionally, the phase 2 KEYNOTE-087 and phase 1 KEYNOTE-013 trials demonstrated comparably favorable ORR and CR rates in patients with R/R cHL at median follow-ups of 2 years and 4 years, respectively.^{13,24} To our knowledge, these analyses represent the longest phase 2 or 3 study follow-up of anti-PD-1 blockade in patients with cHL.

Recent studies have shown excellent results with the combination of PD-1 blockade and chemotherapy before auto-HCT in R/R cHL.²⁵⁻²⁷ There is also increasing evidence that PD-1 blockade combined with chemotherapy may be beneficial as first-line therapy.^{28,29} The increased use of PD-1 blockade in either setting could affect its efficacy and role after a failure of auto-HCT. For patients who achieve PR with nivolumab, subsequent chemotherapy or allo-HCT may be beneficial, because evidence suggests that both are effective after PD-1 blockade.³⁰⁻³³

In conclusion, this 5-year follow-up of CheckMate 205 confirmed durable responses, particularly a long duration of CR and favorable OS with nivolumab in patients with R/R cHL for whom auto-HCT had failed, irrespective of prior BV treatment. These results also suggest that it may be feasible for patients to discontinue treatment after 1 year of CR and reinitiate treatment upon disease progression. Recent and ongoing trials including NCT03004833, NCT03016871, and NCT01100502 are examining the benefits of nivolumab in earlier lines of therapy.

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Authorship

Contribution: S.M.A., P.J.B., G.v.K., H.J.L., A.S., P.L.Z., G.P.C., J.B.C., J.P.d.B., J.K., K.J.S., M.T., M.P., U.J., W.W., M.A.S., A.E., and P.A. conceptualized and designed the study and collected and assembled data; P.J.B. was responsible for the provision of study materials or for patients; and all authors analyzed, interpreted, and approved the data, wrote the manuscript, provided the final approval for the manuscript, and are accountable for all aspects of the work.

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