

## FDA Approval Summary: Nivolumab for the Treatment of Relapsed or Progressive Classical Hodgkin Lymphoma

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**Key Words.** Nivolumab • Hodgkin lymphoma • Programmed death-ligand 1 • Programmed cell death 1 inhibitor

### ABSTRACT

On May 17, 2016, after an expedited priority review, the U.S. Food and Drug Administration granted accelerated approval to nivolumab for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin (BV). Nivolumab in cHL had been granted breakthrough therapy designation. Accelerated approval was based on two single-arm, multicenter trials in adults with cHL. In 95 patients with relapsed or progressive cHL after autologous HSCT and post-transplantation BV, nivolumab, dosed at 3 mg/kg intravenously every 2 weeks, produced a 65% (95% confidence interval: 55%–75%) objective response rate (58% partial remission, 7% complete remission). The estimated median duration of response was 8.7 months, with 4.6-month median follow-up for response duration. The median

time to response was 2.1 (range: 0.7–5.7) months. Among 263 patients with cHL treated with nivolumab, 21% reported serious adverse reactions (ARs). The most common all-grade ARs (reported in  $\geq 20\%$ ) were fatigue, upper respiratory tract infection, cough, pyrexia, diarrhea, elevated transaminases, and cytopenias. Infusion-related reaction and hypothyroidism or thyroiditis occurred in  $>10\%$  of patients; other immune-mediated ARs, occurring in 1%–5%, included rash, pneumonitis, hepatitis, hyperthyroidism, and colitis. A new Warning and Precaution was issued for complications of allogeneic HSCT after nivolumab, including severe or hyperacute graft-versus-host disease, other immune-mediated ARs, and transplant-related mortality. Continued approval for the cHL indication may be contingent upon verification of clinical benefit in a randomized trial. *The Oncologist* 2017;22:585–591

**Implications for Practice:** Based on response rate and duration in single-arm studies, nivolumab is a new treatment option for patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed despite autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin. This was the first U.S. Food and Drug Administration marketing application for a programmed cell death 1 inhibitor in hematologic malignancies. The use of immune checkpoint blockade in cHL represents a new treatment paradigm. The safety of allogeneic HSCT after nivolumab requires further evaluation, as does the safety of nivolumab after allogeneic HSCT.

### INTRODUCTION

Autologous hematopoietic stem cell transplantation (HSCT) produces long-term progression-free survival in approximately 50% of patients with chemosensitive relapse of classical Hodgkin lymphoma (cHL) [1, 2]. Should cHL relapse despite autologous HSCT, allogeneic HSCT is potentially curative. Although allogeneic HSCT can produce durable remissions, if not cure, in a subset of patients with cHL [3, 4], it is important to first achieve disease control with salvage therapy. As in other hematologic malignancies, patients who are unable to achieve sufficient disease control are generally not considered for allogeneic HSCT, given the concern for high relapse risk.

For the treatment of cHL after failure of autologous HSCT, the U.S. Food and Drug Administration (FDA) granted brentuximab

vedotin (BV; Adcetris<sup>®</sup>, Seattle Genetics) accelerated approval in August 2011 [5] and regular approval in March 2016. BV is also approved as post-autologous HSCT consolidation for high-risk cHL and as treatment for cHL after failure of at least two multi-agent chemotherapy regimens in non-transplant candidates. Prior to nivolumab, BV was the only FDA-approved cHL therapy after failure of autologous HSCT, and there were no approved cHL therapies after failure of both autologous HSCT and BV.

Nivolumab is a humanized, IgG4 kappa monoclonal antibody against programmed death receptor-1 (PD-1) that blocks the interaction between PD-1 and its ligands, program death-ligand 1 (PD-L1) and programmed death-ligand 2. In cHL, several mechanisms lead to PD-1 ligand overexpression on Reed-

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**Table 1.** Patient and treatment characteristics of the efficacy population ( $n = 95$ )

Characteristic	Value
<b>Baseline parameters</b>	
Study, $n$	
CA209205 Cohort B	80 (84%)
CA209039	15 (16%)
Age, years	
Median (range)	37 (18–72)
$\geq 60$	7 (7%)
Male sex, $n$	61 (64%)
Time to autologous HSCT, years	
Median (range)	1.3 (<1–16)
<1	27 (28%)
$\geq 2$	25 (26%)
Prior systemic regimens, $n$	
Median (range)	5 (3–15)
3	22 (23%)
4	24 (25%)
$\geq 5$	49 (52%)
Time from HSCT to nivolumab, years	
Median (range)	3.5 (<1–19)
<2	27 (28%)
$\geq 2$ and <5	31 (33%)
$\geq 5$	37 (39%)
Prior radiotherapy, $n$	72 (76%)
Response to last BV regimen, $n$	
$\geq$ PR	25 (26%)
Refractory	45 (47%)
Unknown	25 (26%)
$\geq 1\%$ PD-L1 expression on RS cells, $n$	
Yes	70 (74%)
No	7 (7%)
Indeterminate	6 (6%)
Not tested	12 (13%)
<b>Nivolumab exposure</b>	
Doses, $n$	
Median (range)	17 (3–48)
Interquartile range	[12–21]
Exposure time, months, median (range)	8.3 (1.9–23.9)
Patients on treatment by month, $n$	
>6 months	69 (73%)
>9 months	36 (38%)
>12 months	8 (8%)
Relative dose intensity, mean %	93

Abbreviations: BV, brentuximab vedotin; HSCT, hematopoietic stem cell transplantation; PD-L1, programmed cell death-ligand 1; PR, partial remission; RS, Reed-Sternberg cells.

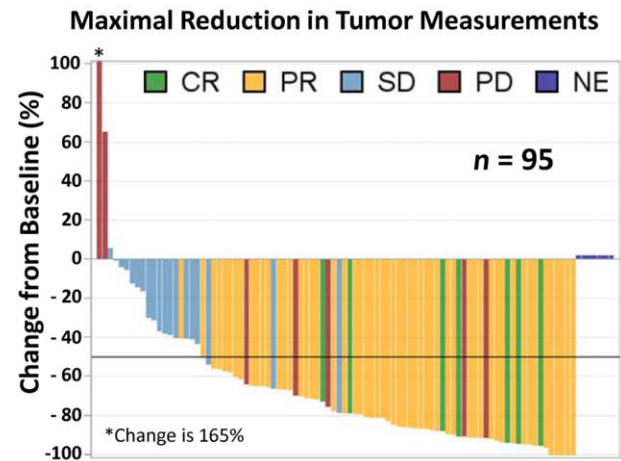
Sternberg cells [6, 7]. Thus, PD-1 blockade has the potential to inhibit tumor immune evasion, enhancing the antitumor immune response in cHL as in selected other malignancies [8, 9].

**Table 2.** Key efficacy results in classical Hodgkin lymphoma

Measures of efficacy	Result ( $n = 95$ )
Objective response <sup>a</sup> , $n$	62 (65%)
95% CI	(55–75)
Complete remission	7 (7%)
95% CI	(3–15)
Partial remission	55 (58%)
95% CI	(47–68)
Stable disease, $n$	23 (24%)
Progressive disease, $n$	7 (7%)
Not evaluable, $n$	3 (3%)
Median time to response, months (range)	2.1 (0.7–5.7)
Estimated median DOR, months (95% CI)	8.7 (6.8–NE)
Median follow-up for DOR, months <sup>b</sup> (range)	4.6 (0+ to 23.1+)
Responders still on treatment, $n$	36 (58%)

<sup>a</sup>Per 2007 revised International Working Group criteria.

<sup>b</sup>In responders, measured from the date of first objective response.

**Figure 1.** Waterfall plot of change in tumor volume with nivolumab, among patients with relapsed or progressive classical Hodgkin lymphoma after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin.

Abbreviations: CR, complete remission; NE, not evaluable; PD, progressive disease; PR, partial remission; SD, stable disease.

Nivolumab in cHL received three expedited programs of the FDA: Breakthrough Therapy Designation (May 2014), Priority Review, and Accelerated Approval [10]. On May 17, 2016, after an expedited priority review, the FDA granted accelerated approval to nivolumab (Opdivo<sup>®</sup>, Bristol-Myers Squibb) for the treatment of patients with cHL that has relapsed or progressed after autologous HSCT and post-transplantation BV. Notably, this was the first FDA application for a PD-1 inhibitor in hematologic malignancies. Herein, we provide a summary of the FDA review and approval of this marketing application.

### TRIAL DESIGN

Two single-arm, open-label, multicenter studies evaluating nivolumab in relapsed or refractory cHL comprised this application. Study CA209205 (CheckMate 205; ClinicalTrials.gov

**Table 3.** Commonly reported ( $\geq 10\%$ ) adverse reactions and laboratory abnormalities in classical Hodgkin lymphoma cohorts

Adverse reaction or laboratory abnormality <sup>a</sup>	Safety population (n = 263)		Efficacy population (n = 95)	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
<b>Adverse reaction<sup>b</sup></b>				
Fatigue	32	1	43	1
Upper respiratory tract infection	28	<1	48	1
Pyrexia	24	<1	35	1
Diarrhea	23	<1	30	1
Cough	22	0	35	0
Rash	19	2	31	3
Musculoskeletal pain	19	1	27	1
Nausea	17	0	23	0
Pruritus	17	0	25	0
Vomiting	15	<1	16	1
Infusion-related reaction	12	<1	18	0
Hypothyroidism or thyroiditis	12	0	17	0
Headache	12	<1	12	1
Peripheral neuropathy	11	<1	21	0
Arthralgia	11	0	21	0
Abdominal pain	11	<1	13	2
Dyspnea	10	<1	16	2
Pneumonia	9	3	19	5
Hyperglycemia	9	<1	14	1
Constipation	9	<1	14	0
<b>Hematology labs<sup>c</sup></b>				
Neutropenia	29	4	37	6
Thrombocytopenia	28	2	33	33
Lymphopenia	24	8	32	7
Anemia	22	3	27	2
<b>Chemistries<sup>c</sup></b>				
Increased ALT	24	2	25	2
Increased AST	23	2	32	3
Increased alkaline phosphatase	17	2	21	2
Increased lipase	16	7	28	12
Hyponatremia	14	<1	15	1
Hypokalemia	11	2	14	3
Hypocalcemia	11	<1	14	1
Hypomagnesemia	10	<1	15	1
Increased creatinine	10	0	15	0
Increased bilirubin	9	<1	10	0

<sup>a</sup>Toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4 and include events occurring up to 30 days after nivolumab completion.

<sup>b</sup>Includes grouped preferred terms.

<sup>c</sup>Represents laboratory abnormalities that are new or worsened from baseline; not all patients were evaluable.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

identifier NCT02181738) is a parallel-cohort, single-arm, open-label, multicenter phase 2 trial that evaluated nivolumab in cHL patients after failure of autologous HSCT with or without BV failure [11]. Study CA209039 (NCT01592370) is an open-label, multicenter, phase 1 trial that included relapsed cHL after at least one therapy [8]. In both trials, the dose-schedule of

nivolumab was 3 mg/kg intravenously over 60 minutes, given every 2 weeks until disease progression, maximum clinical benefit (Study CA209039), or unacceptable toxicity. A cycle consisted of one dose.

Both trials enrolled adults with biopsy-proven residual cHL, regardless of tumor PD-L1 status, and required an Eastern

**Table 4.** Allogeneic HSCT in classical Hodgkin lymphoma patients treated previously with nivolumab ( $n = 17$ )

Characteristic	Value
<b>Baseline parameters</b>	
Age at HSCT, median (range)	33 (18–56)
Prior autologous HSCT, $n$	16 (94%)
Conditioning intensity, $n$	
RIC/NMA	15 (88%)
Myeloablative	2 (12%)
Transplant type, $n$	
RIC MRD or MUD	10 (59%)
RIC haplo or MMUD	5 (29%)
Myeloablative haplo	2 (12%)
Stem cell source, $n$	
Peripheral blood	14 (82%)
Bone marrow	3 (18%)
Nivo exposure, median (range)	
Doses	9 (4–16)
Months of exposure	4.7 (2.5–7.0)
Days from nivo to HSCT <sup>a</sup>	28 (11–94)
<b>Selected events</b>	
Hyperacute GVHD <sup>b</sup> , $n$	2 (12%)
aGVHD, $n$	
Grade 2 or higher	10 (59%)
Grade 2	5 (29%)
Grade 3 or higher <sup>c</sup>	5 (29%)
Grade unknown	1 (6%)
Hepatic VOD after RIC, $n$	1 (6%)
Steroid-requiring febrile syndrome <sup>d</sup> , $n$	
Steroid responsive	5 (29%)
Steroid unresponsive	1 (6%)
Transplant-related mortality <sup>e</sup> , $n$	
aGVHD; preceded by hepatic VOD	1
aGVHD, TMA, multiorgan failure	1
aGVHD, diffuse alveolar hemorrhage	1
Sepsis; preceded by severe aGVHD	1
Lung infection; GVHD ongoing	1
Unknown; preceded by refractory lung GVHD	1

<sup>a</sup>One patient had intervening therapy between nivolumab and HSCT.

<sup>b</sup>Defined as GVHD within 14 days of HSCT.

<sup>c</sup>One with grade 3, one with grade 5, and three with at least grade 4 GVHD.

<sup>d</sup>Fever with or without other manifestations, without identified infectious source.

<sup>e</sup>Five after RIC, one after myeloablative haplo HSCT.

Abbreviations: aGVHD, acute GVHD; GVHD, graft-versus-host disease; haplo, HLA-haploidentical; HSCT, hematopoietic stem cell transplantation; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; nivo, nivolumab; NMA, non-myeloablative; RIC, reduced intensity conditioned; TMA, thrombotic microangiopathy; VOD, veno-occlusive disease.

Cooperative Oncology Group (ECOG) performance status of 0 or 1, hepatic transaminases  $\leq 3$  times upper limit of normal, total bilirubin  $\leq 1.5$ , creatinine clearance  $\geq 40$  mL/min, minimum hematologic parameters, and, in patients with prior pulmonary

toxicity, an adjusted diffusion capacity of the lungs for carbon monoxide of  $>60\%$  predicted. Patients having prior allogeneic HSCT, autologous HSCT within 90 or 100 days, autoimmune disease, active interstitial lung disease, or chest irradiation within 24 weeks were excluded. Dose delay, but not dose reduction, was permitted for toxicity. Toxicity management guidelines are available in the U.S. Prescribing Information (PI) [12].

## RESULTS

### Efficacy

Efficacy of nivolumab monotherapy was based on an integrated analysis of 95 patients with relapsed or refractory cHL after autologous HSCT and post-transplantation BV (80 from CA209205 Cohort B, 15 from CA209039). All patients had a minimum follow-up of 6 months. The primary efficacy endpoint was objective response rate (ORR), as determined by an independent radiographic review committee using revised International Working Group criteria [13].

Baseline characteristics of the efficacy population are summarized in Table 1. As is characteristic of cHL, this was a younger population (median age: 37), with approximately one-third being aged  $\leq 30$  and  $<10\%$  being aged  $\geq 60$ . Patients tended to be heavily pretreated, with a median of 5 prior systemic regimens, most had radiation therapy, and at least 47% had refractory disease to their last BV or BV-containing regimen. Despite this, all had an ECOG performance status of 0 or 1 per protocol requirement, and the majority did not have bulky disease at study baseline. Patients received a median of 17 doses of nivolumab, corresponding to a median exposure time of 8.3 months (Table 1).

Nivolumab monotherapy (3 mg/kg every 2 weeks) produced a 65% ORR (95% confidence interval [CI]: 55%–75%), with 58% partial remission (PR) and 7% complete remission (CR; Table 2). A waterfall plot is shown in Figure 1. Concordance with investigator-assessed ORR was 76%. The median time to response was 2.1 months. At the time of analysis, more than 50% of patients remained on nivolumab. The estimated median duration of response (DOR) was 8.7 (range: 0–23.1) months. This estimate is unstable due to early censoring; among patients who achieved response, the median follow-up for DOR was 4.6 months. Survival data were immature.

Exploratory subgroup analyses of efficacy were limited by sample size. ORR was nevertheless comparable across major disease subgroups ( $\geq 5$  prior systemic regimens, refractoriness to BV,  $<1$  year to autologous HSCT, bulky disease). Given the high rate of PD-L1 expression and 9p24.1 alteration, no conclusion can be made regarding the relationship between these parameters and ORR. Of the 7 patients with  $<1\%$  PD-L1 expression on Reed-Sternberg cells, 6 achieved an objective response.

### Safety

Safety was evaluated in all 263 patients with relapsed or refractory cHL who received at least one dose of nivolumab on Study CA209205 (240 patients) or CA209039 (23 patients).

### Overall Safety Outcomes

Baseline characteristics of the safety cohort were similar to those of the efficacy cohort. The median age was 34. Patients tended

**Table 5.** Benefit-risk analysis for nivolumab for the treatment of cHL after autologous HSCT and brentuximab vedotin

Parameter	Summary
Disease	<ul style="list-style-type: none"> <li>cHL after failure of autologous HSCT and post-transplantation BV.</li> </ul>
Unmet medical need	<ul style="list-style-type: none"> <li>cHL is fatal if not cured, and approximately 50% of patients who receive autologous HSCT eventually relapse. Limited treatment options exist for relapsed cHL after autologous HSCT, and no drugs were previously approved for cHL after failure of both autologous HSCT and BV.</li> </ul>
Clinical benefit	<ul style="list-style-type: none"> <li>In 95 patients with cHL that failed autologous HSCT and post-transplantation BV, nivolumab (3 mg/kg every 2 weeks) produced an ORR of 65% (PR 58%), with a median time to response of 2.1 months. The estimated median response duration was 8.7 months, with 4.6-month median follow-up for response.</li> </ul>
Risks	<ul style="list-style-type: none"> <li>Among 263 patients with relapsed cHL treated with nivolumab, 21% reported serious ARs. The most common (<math>\geq 20\%</math>) all-grade ARs were fatigue, upper respiratory tract infection, fever, diarrhea, cough, elevated transaminases, and cytopenias. The immune-mediated AR profile was consistent with that previously described.</li> <li>A new Warning and Precaution was issued for complications of allogeneic HSCT after nivolumab, including hyperacute and severe acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and transplant-related mortality.</li> </ul>
Uncertainties	<ul style="list-style-type: none"> <li>Longer follow-up is necessary to characterize durability of response.</li> <li>The safety of allogeneic HSCT after nivolumab requires further evaluation, and the safety of nivolumab after allogeneic HSCT is not defined.</li> </ul>
Conclusions	<ul style="list-style-type: none"> <li>Based on response rate and duration, nivolumab has clinically meaningful activity in cHL after failure of autologous HSCT and post-transplantation BV.</li> <li>The overall safety profile of nivolumab is acceptable for patients with relapsed cHL, with a favorable benefit-risk balance.</li> </ul>

Abbreviations: AR, adverse reaction; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; ORR, objective response rate; PR, partial remission.

to be heavily pretreated, with a median of 4 (range: 2–15) prior systemic regimens, nearly all (98%) had prior autologous HSCT, and the majority had prior BV and radiation therapy. However, all had an ECOG performance status of 0 or 1 per protocol. A median of 10 (range: 1–48) doses of nivolumab was administered at the approved dose-schedule (median exposure time: 4.8 months), with treatment ongoing in 75% of patients.

Serious adverse reactions (ARs) were reported in 21% of patients overall. The most common serious ARs, reported in 1%–3% of patients, were pneumonia, pleural effusion, pneumonitis, pyrexia, infusion-related reaction, and rash. Four percent discontinued nivolumab due to ARs. Ten patients died from causes other than disease progression. Of these, 3 died within 30 days of the last nivolumab dose, 1 died from late sepsis, and 6 died after allogeneic HSCT, as discussed in the next section.

The most common (reported in  $\geq 20\%$ ) all-grade ARs were fatigue, upper respiratory tract infection, cough, pyrexia, diarrhea, elevated transaminases, and cytopenias (Table 3). Additional common ARs (reported in  $\geq 10\%$ ) included rash, pruritus, musculoskeletal pain, nausea, vomiting, abdominal pain, headache, peripheral neuropathy, arthralgia, dyspnea, infusion-related reactions, and hypothyroidism or thyroiditis (Table 3). The majority of these were grade 1–2. Other immune-mediated ARs, occurring in 1%–5% of patients, included rash, pneumonitis (3%), hepatitis, hyperthyroidism, and colitis. With the exception of endocrine events, reporting of immune-mediated ARs was limited to cases treated with a systemic immunosuppressant.

In the efficacy cohort, serious ARs (27%), all-grade ARs, and dose delays were more frequent, and ARs spanned a wider

range of toxicities compared with the overall safety cohort (Table 3). The greater percentage and range of ARs are likely attributable in part to longer exposure to nivolumab in the efficacy cohort. As most of the safety cohort had ongoing treatment, the toxicity profile might change with longer follow-up.

### Warnings and Precautions

The U.S. PI had existing Warnings and Precautions for immune-mediated ARs (pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, rash, encephalitis), infusion reactions, and embryo-fetal toxicity [12]. Based on this application, the FDA issued a new Warning and Precaution in Section 5 of the PI on complications of allogeneic HSCT after nivolumab.

As part of the review, the FDA requested information on allogeneic HSCT outcomes after nivolumab therapy. The request was based on reported clinical data [14] and concern that persisting PD-1 inhibition might stimulate alloreactive T cells, thereby increasing the risk or severity of immunologic complications such as graft-versus-host disease (GVHD) [14, 15].

In the cHL safety cohort, 17 patients had received post-nivolumab allogeneic HSCT (Table 4). As expected, most transplants (88%) used reduced-intensity conditioning (RIC) given its lower risks of transplant-related mortality (approximately 10% at 1 year) and morbidity [16]. However, 6 patients (35%), median age 32, had transplant-related deaths, with 5 occurring after RIC and 5 preceded or accompanied by GVHD (Table 4).

Retrospectively, hyperacute GVHD was reported in 12% of patients, grade 2 or higher acute GVHD in approximately 60%, and grade 3 or higher acute GVHD in approximately 30% (Table 4). With the limitations of the data in mind, the incidences of



severe GVHD and transplant-related mortality seem excessive. Data on chronic GVHD were limited. Other atypical complications included steroid-requiring febrile syndromes, a case of hepatic veno-occlusive disease after RIC transplantation, and a case of grade 3 lymphocytic encephalitis.

## DISCUSSION

On May 17, 2016, the FDA granted accelerated approval to nivolumab for the treatment of patients with cHL that has relapsed or progressed after autologous HSCT and post-transplantation BV. The application was approved in 2.5 months, more than 3 months ahead of the Prescription Drug User Fee Act goal date of September 1, 2016. This was the first FDA application and approval for a PD-1 inhibitor as treatment for hematologic malignancies. The recommended dose-schedule of nivolumab is 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Table 5 summarizes the FDA benefit-risk analysis.

The integrated efficacy and safety data support the current nivolumab labeling for the treatment of patients with relapsed or refractory cHL. Continued marketing approval for the cHL indication may be contingent upon verification of clinical benefit in a randomized trial. As a postmarketing requirement, FDA requested a randomized phase 3 clinical trial that verifies and isolates the clinical benefit of nivolumab for patients with cHL.

Data to inform the optimal duration of nivolumab, or transition to a reduced dose-schedule upon achievement of maximal response, are not available. Due to early censoring, longer follow-up is also necessary to establish the durability of overall response, as well as the durability of partial versus complete remission. In an updated analysis of CA209205 Cohort B with minimum 12-month follow-up in all patients, the reported median DOR was 13.1 (range: 0+ to 14.2+ months) [17]. Refinements to lymphoma response criteria in the setting of immunomodulatory agents such as PD-1 inhibitors were recently proposed [18].

The toxicity profile of nivolumab, including immune-mediated ARs, was generally consistent with that established previously in other malignancies. It is, however, important to note the key exclusion criteria for these studies. Safety in cHL patients who are older, have poorer functional status, or have significant comorbidities, including pulmonary dysfunction, has not been defined. With immune-activating therapies, a

potential concern in cHL patients is pneumonitis, because first-line regimens standardly include bleomycin (received by 97% of the safety cohort), mediastinal radiation therapy may be given, and pulmonary toxicity can occur from HSCT. However, the reported incidence of immune-mediated pneumonitis was 3%. Notably, the studies excluded recipients of prior allogeneic HSCT.

Recipients of allogeneic HSCT after nivolumab should be followed closely for early evidence of transplant-related complications, including hyperacute GVHD, grade 3–4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated ARs. The limited retrospective data, coupled with the heterogeneity of transplant regimens, preclude an accurate assessment of post-transplantation toxicities. With continued follow-up and larger numbers, the post-transplantation toxicity profile may change. As a condition of continued approval, FDA mandated a postmarketing study to further characterize the safety of allogeneic HSCT after nivolumab.

## CONCLUSION

Patients with relapsed or refractory cHL, particularly after autologous HSCT, have unmet medical needs. The composite results of trials CA209039 and CA209205 demonstrate clinically meaningful activity of nivolumab, based on overall response and response duration, in cHL patients after failure of autologous HSCT and post-transplantation BV, with an overall favorable benefit-risk balance. Based on the magnitude and durability of response after autologous HSCT and BV failure, coupled with the acceptable safety profile, nivolumab is a potentially important option in a setting in which there was previously no approved treatment.

## AUTHOR CONTRIBUTIONS

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## DISCLOSURES

The authors indicated no financial relationships.

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#### For Further Reading:

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#### Implications for Practice:

Brentuximab vedotin was approved in the European Union for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma or systemic anaplastic large cell lymphoma. For Hodgkin lymphoma, brentuximab vedotin should only be used after autologous stem cell transplantation or following at least two prior therapies when transplantation or multiagent chemotherapy is not a treatment option. In two studies involving 160 patients, partial or complete responses were observed in the majority of patients. Although there was no information on the survival of patients treated in the studies at the time of approval, the responses were considered a clinically relevant benefit.