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ORIGINAL ARTICLE

Nivolumab for relapsed or refractory Hodgkin lymphoma: real-life experience

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Background: Reed–Sternberg cells of classical Hodgkin's lymphoma (cHL) are characterized by genetic alterations at the *9p24.1 locus*, leading to over-expression of programmed death-ligand 1 and 2. In a phase 1b study, nivolumab, a PD-1-blocking antibody, produced a high response in patients with relapsed or refractory cHL, with an acceptable safety profile.

Patients and methods: We present a retrospective analysis of 82 patients (median age: 30 years; range: 18–75) with relapsed/refractory HL treated with nivolumab in a named patient program from 24 centers throughout Turkey. The median follow-up was 7 months, and the patients had a median of 5 (2–11) previous lines of therapy. Fifty-seven (70%) and 63 (77%) had been treated by stem-cell transplantation and brentuximab vedotin, respectively.

Results: Among 75 patients evaluated after 12 weeks of nivolumab treatment, the objective response rate was 64%, with 16 complete responses (CR; 22%); after 16 weeks, it was 60%, with 16 (26%) patients achieving CR. Twenty patients underwent subsequent transplantation. Among 11 patients receiving allogeneic stem-cell transplantation, 5 had CR at the time of transplantation and are currently alive with ongoing response. At the time of analysis, 41 patients remained on nivolumab treatment. Among the patients who discontinued nivolumab, the main reason was disease progression ($n = 19$). The safety profile was acceptable, with only four patients requiring cessation of nivolumab due to serious adverse events (autoimmune encephalitis, pulmonary adverse event, and two cases of graft-versus-host disease aggravation). The 6-month overall and progression-free survival rates were 91.2% (95% confidence interval: 0.83–0.96) and 77.3% (0.66–0.85), respectively. Ten patients died during the follow-up; one of these was judged to be treatment-related.

Conclusions: Nivolumab represents a novel option for patients with cHL refractory to brentuximab vedotin, and may serve as a bridge to transplantation; however, it may be associated with increased toxicity.

Key words: Hodgkin lymphoma, resistant/relapsed disease, programmed death 1 (PD-1) blocker, nivolumab

Introduction

Hodgkin's disease is a common B-cell neoplasm, the incidence of which shows regional variance; it constitutes 14.4% of lymphomas in the UK [1], 8.76% of lymphoid neoplasms in the United States [2], and 21.5% of lymphoma cases in Turkey [3]. Classical Hodgkin's lymphoma (cHL) is considered a curable disease, with sustained remission achieved in ∼80% of patients after first-line treatment. However, approximately one-third of responders relapse following first-line therapy, and 15% of patients do not respond to both first- and second-line therapies [4]. Patients relapsing following autologous stem-cell transplantation (auto-SCT) have worse prognosis, and brentuximab vedotin (BV) is an important option for these cases [5, 6]. However, the median progression-free survival (PFS) for patients refractory to BV is only 3.5 months [7].

Immune checkpoint inhibitors are emerging treatment alternatives for patients progressing following auto-SCT. The overexpression of programmed death-1 (PD-1) ligands on Reed–Sternberg cells suggests the genetic vulnerability of cHL to PD-1 blockade [8]. Accordingly, nivolumab and pembrolizumab, immunoglobulin G4 immune checkpoint inhibitors that target PD-1, have been demonstrated to show substantial response rates, with acceptable safety profiles in resistant/relapsed cHL [9–11].

This retrospective multicenter study aimed to provide information about the efficacy and safety of nivolumab in the 'real-life' setting in Turkey.

Methods

Twenty-four centers throughout Turkey participated in this study. Eligible patients included cHL patients treated with at least one course of nivolumab. The decision about inclusion of patients with organ dysfunction was made by the attending physician on an individual basis. Patients received nivolumab via a named patient program, and there was no restriction for BV- and/or transplantation-naïve cases. Nivolumab was administered as a 3 mg/kg intravenous infusion over 60 min every 2 weeks in the outpatient setting until death of any cause, unacceptable toxicity, withdrawal of consent, or the primary physician's decision. The study was approved by the local ethical committee.

The primary end point was the overall response rate (ORR); secondary end points included overall survival (OS), PFS, and safety. The response was assessed by positron-emission tomography/computed tomography (PET/CT) or CT alone. Early radiological evaluation was defined as imaging conducted at or before week 12 of treatment, whereas late radiological evaluation was defined as imaging carried out at or after week 16 of therapy. The response evaluation was carried out according to the Lugano Classification [12] and its revision regarding immunomodulatory therapy [13]. In addition, the imaging materials that could be collected from all 24 centers were re-assessed by two experienced nuclear medicine physicians in a peer-review process (supplementary Table S1, available at *Annals of Oncology* online).

OS and PFS were defined as the times from the first dose of nivolumab to death of any cause and until disease progression or death of any cause, whichever occurred first, respectively [14]. Both OS and PFS were censored at the date of last information and were estimated using the Kaplan–Meier method. Exact 95% confidence intervals (CIs) were used when appropriate. All data analyses were carried out using STATA 11.1 SE software. The safety and the tolerability were assessed before each nivolumab cycle according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 [15].

Results

From June 2015 to November 2016, 87 patients with relapsed or refractory classical HL were enrolled in a named patient program in Turkey. Five patients who had not reached the time for early radiological evaluation were excluded from the analysis. Thus, 82 patients from 24 centers were retrospectively analyzed (Figure 1). The median age of all patients was 30 (18–75) years, and there was a male predominance (58%). Most patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 (89%), and approximately half (49%) had B symptoms before the initiation of nivolumab therapy. Fifty-seven patients (70%) had undergone a previous SCT; 41, 14, and 2 patients had undergone auto-SCT alone, both auto- and allogeneic (allo-) SCT, and allo-SCT alone, respectively, before nivolumab treatment. The patients received a median of 5 (2–11) previous lines of therapy. The median exposure to nivolumab was 7 (1–22) months, and the median number of cycles was 12 (1–40). The demographic features and disease characteristics of the patients are summarized in Table 1.

At the time of analysis, 41 patients remained on nivolumab treatment. Among the remaining 41 patients who discontinued nivolumab, the main reason was disease progression ($n = 19$), followed by SCT ($n = 11$; 5 allogeneic, 2 haploidentical, 4 autologous), death due to progressive disease ($n = 4$), lack of improvement of response with subsequent nivolumab cycles [$n = 2$; one patient with partial response (PR) and one with stable disease (SD)], graft-versus-host disease (GVHD) aggravation after nivolumab ($n = 2$; one patient with acute exacerbation of chronic GVHD and one with severe acute GVHD 6 months following allo-SCT), autoimmune encephalitis following the third cycle of nivolumab treatment ($n = 1$), pulmonary serious adverse event ($n = 1$), and withdrawal of consent ($n = 1$) (Figure 1).

Efficacy evaluation

Early response assessment was carried out in 75 patients (using PET/CT and CT in 64 and 11 patients, respectively). The ORR was 64% (CR in 21% and PR in 43%; 95% CI 2.17–6.59) (Table 1). Thus, most responses to nivolumab were achieved in the first 12 weeks of the treatment course. The ORR in the late response assessment ($n = 64$; PET/CT and CT in 53 and 11 patients, respectively) was 60% (CR in 26% and PR in 34%; 95% CI 3.03–17.7) (Table 1). Thirty-four patients (63% of responders) had a response duration ≥6 months at the time of analysis.

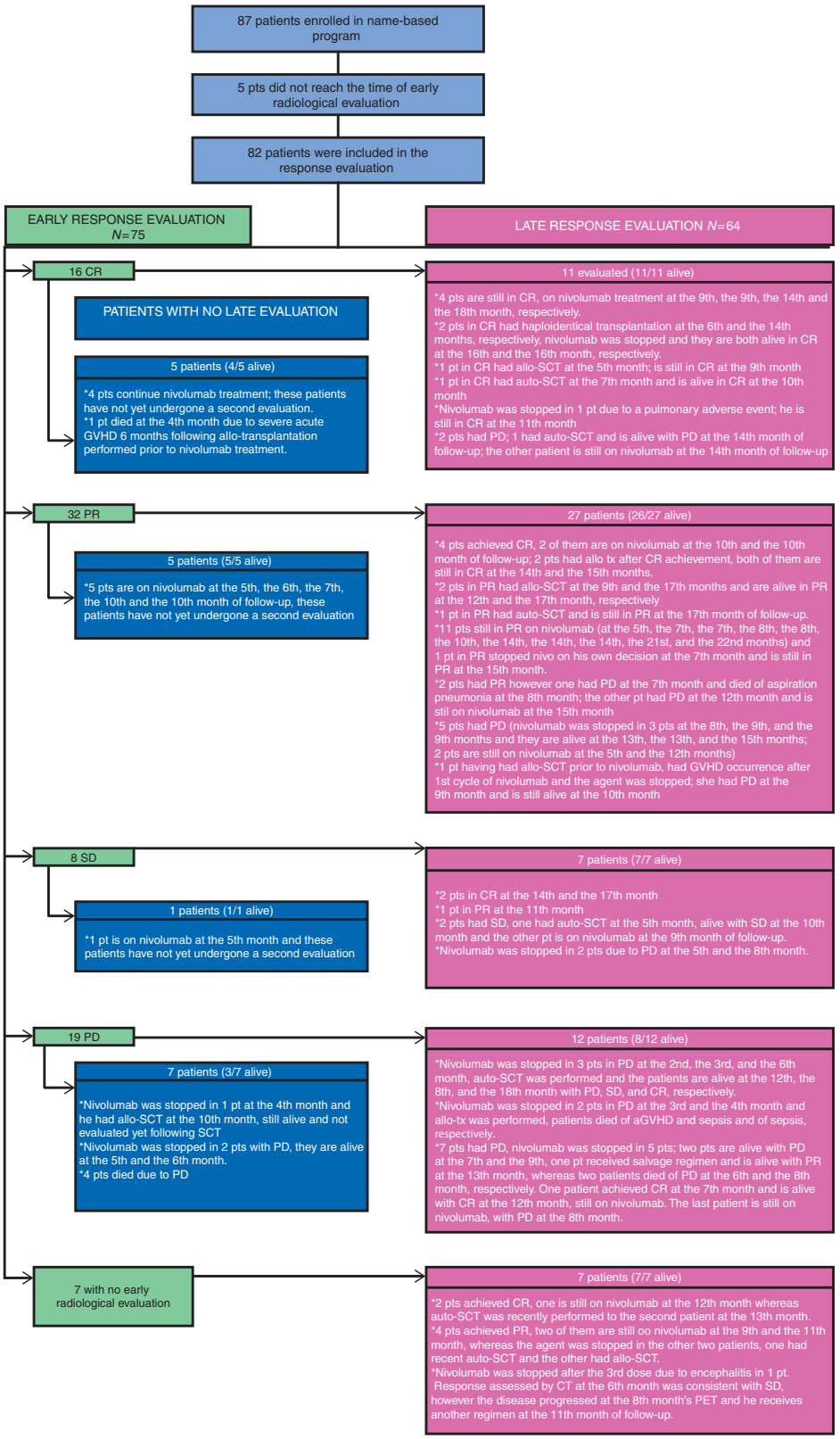

Figure 1. Results of the post-nivolumab evaluation. CR, complete response; GVHD, graft versus host disease; PR, partial response; SCT, stem cell transplantation; SD, stable disease; PD, progressive disease; pts, patients.

Table 1. Patient demographics and disease and response characteristics (n = 82)

Median age, years	30 (18–75)
Male/female	48/34
ECOG status ≤1	73 (89%)
B symptoms present	40 (49%)
Stage 3–4 disease[a]	55 (81%)
Median lines of previous therapy	5 (2–11)
5 or more lines	47 (57%)
Previous stem-cell transplantation	57 (70%)
Autologous	55 (67%)[b]
Allogeneic	16 (30%)[c]
Previous brentuximab vedotin (BV) treatment	63 (77%)
Refractory to BV[d]	40 (66%)
Median follow-up under nivolumab (months)	7 (1–22)
Median cycles of nivolumab	12 (1–40)
Early response (≤12 weeks of treatment)	
CR	16 (21%)
PR	32 (43%)
SD	8 (11%)
PD	19 (25%)
Late response (≥16 weeks of treatment)	
CR	16 (26%)
PR	21 (34%)
SD	2 (3%)
PD	23 (37%)

[a]The stage at the time of nivolumab initiation was available for 68 patients.
[b]One patient received autologous stem-cell transplantation (auto-SCT) 2 times.
[c]Fourteen patients received auto-SCT before allogeneic stem-cell transplantation.
[d]BV response data were not available in one patient, and one patient had auto-SCT after BV treatment before response evaluation.
ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Although the differences in the response assessment between investigators and independent radiological review committees are remarkable in the literature [10], our imaging materials were peer-reviewed by two experienced nuclear medicine specialists (70% of early radiological images and 48% of late radiological evaluations), and, as a result, we found that there was almost no difference between the investigators' and peer-review assessments (supplementary Table S1, available at *Annals of Oncology* online).

The 6-month OS and PFS rates were 91.2% (95% CI 0.83–0.96) and 77.3% (95% CI 0.66–0.85), respectively. The median OS and PFS were not reached.

Progressive disease after achieving an objective response was seen in 17% of responders ($n = 8$); 2 of 16 patients with CR and 6 of 32 patients with PR.

Bridging to transplantation

In our cohort, nine patients underwent auto-SCT; in six of these patients, this was their first auto-SCT. All four patients with an objective response before transplantation (2 CR and 2 PR) showed continuous responses at the 10th, 14th, 14th and 17th month of follow-up, respectively. One patient with SD also kept her status following SCT. One of the four patients with PD responded to the auto-SCT and is alive with CR at the 18th month of follow-up, whereas one and two patients showed SD and PD, respectively, following SCT.

Among the 11 patients receiving allo-SCT (Table 2), 8 patients had objective responses to nivolumab (5 CR and 3 PR), and, at the time of analysis, all except 2 patients with PR who both had a recent allo-SCT and were not evaluated yet, showed ongoing responses. In this group, three patients developed skin GVHD (grades 1, 2, and 4) and one patient had chronic lung GVHD. The patient with grade 4 skin GVHD and the one with chronic lung GVHD were receiving extracorporeal photopheresis at the time of analysis.

Three patients underwent allo-SCT with PD; two of them died, owing to sepsis in one case and acute grade 4 GVHD and sepsis in the other. The patient who died due to sepsis received allo-SCT in an experienced transplantation center, 15 days after the last dose of nivolumab; this patient had an atypical septic shock picture on D + 11, with no fever or hypothermia, indicating potential early immune toxicity (Figure 2).

Deaths

Among the 10 patients who died during the follow-up period of our analysis, four died before the early imaging evaluation. Two patients died due to disease progression at 6 and 8 months of follow-up, respectively. These two patients who progressed under nivolumab underwent allo-SCT and, those two patients as mentioned above, (last paragraph of efficacy evaluation) died due to sepsis, and acute GVHD and sepsis. One patient who had previously undergone allo-SCT showed CR with nivolumab; however, she died due to acute severe GVHD 6 months following allo-SCT, which was considered related to the nivolumab treatment. One patient with PR showed PD at the 7-month follow-up and died due to aspiration pneumonia.

Safety evaluation

A total of 143 adverse events (AEs) were reported in 44 patients (54%), including 13 (9%) grade 3 AEs (Table 3). The most common AEs observed were fatigue (32%), infection (12.3%), pruritus (8.7%), fever (9.7%), and rash (7.2%). Grade 2 and 3 autoimmune pneumonitis were observed in 6 and 1 patients, respectively. The treatment was discontinued in four patients due to a pulmonary AE, autoimmune encephalitis, and aggravation of GVHD in one, one, and two patients following the sixth, third, first, and ninth doses of nivolumab, respectively. Among the two patients who showed aggravation of GVHD, one patient who had already undergone allo-SCT showed CR with nivolumab; however, she died due to acute severe GVHD 6 months following allo-SCT. The other patient had PD following allo-SCT; she already had chronic GVHD and, following the first dose of nivolumab, she experienced GVHD exacerbation. As a result, nivolumab was stopped and steroid treatment was initiated. Consequently, the GVHD was ameliorated and her disease status was PR in the early evaluation; however, it progressed 9 months after the nivolumab cessation.

Table 2. Outcomes and adverse events of patients who bridged to allo-SCT

Patient number	Disease status before tx	Nivolumab cycles (*n*)	Allo-tx	Number of days between transplantation and nivolumab cessation	Adverse events	Treatment	Course
5	PR	32	Related full-match	20	None		Alive at post-transplantation D + 7
14	CR	26	Haploidentical	30	Grade 2 skin GVHD	Steroids	CR at post-transplantation+2nd month
32	PR	18	Related full-match	190	None		Alive at post-transplantation D + 21
35	PR	18	Related full-match	28	Grade 4 skin GVHD	Resistant to steroids and MMF; extracorporeal photopheresis is currently being carried out	PR at post-transplantation+2nd month
49	CR	6	Haploidentical	30	None		CR at post-transplantation+10th month
51	CR	10	Related full-match	25	Chronic lung GVHD	Extracorporeal photopheresis	CR at post-transplantation+11th month
56	CR	9	Related full-match	25	Grade 1 late occurring skin GVHD	Local steroids	CR at post-transplantation+10th month
61	CR	9	Related full-match	51	None		CR at post-transplantation+2nd month
65	PD	9	Related full-match	90	None		Alive at post-transplantation+1st month
73	PD	7	Unrelated 9/10 match	125	Grade 4 skin GVHD	Resistant to steroid	PR at + 2nd month; however, death occurred due to skin GVHD and sepsis
76	PD	5	Related full-match	15	Septic shock		Septic shock and death on D + 11

Tx, transplantation; GVHD, graft-versus-host disease; CR, complete response; PR, partial response; PD, progressive disease; MMF, mycophenolate mofetil.

Discussion

Herein, we presented the outcomes of 82 cHL patients from 24 centers throughout Turkey. This is, to our knowledge, the first real-life study on the topic. Our cohort resembles those published by Ansell et al. [9], Younes et al. [10], and Chen et al. (mainly cohort 1) [11] in terms of the patients' performance status, previous transplantation and BV treatment, and median number of previous lines of therapy. The ORR was reported to be 87%, with CR and PR rates of 17% and 70%, respectively, in Ansell's cohort [9]; it was 72.5% with a CR rate of 28% in Younes' study [10]; and 73.9% with a 21.7% CR rate in Chen's study [11]. Our response rates were comparable to these results, with early and late ORRs of 64% (95% CI 2.17–6.59; CR, 21%) and 60% (95% CI 3.03–17.7; CR, 26%; PR, 34%), respectively. Considering the finding that the ORR at our early response assessment, conducted at or before the 12th week of treatment, was 64%, we can conclude that the responses to nivolumab begin early in the treatment course. Further, PD after achieving an objective response was seen in 17% of responders, when compared with 21% of the responders in Younes' cohort [10]. Of note, in the peer-review assessment of the imaging materials collected from the centers, we found no statistical significance between the investigators' and central evaluations, which may be due to all centers having been informed about the revision of the Lugano classification regarding immunomodulatory therapy.

The PFS and OS at 6 months were 76.9% and 98.7%, respectively, in Younes' study [10]. In Chen's study, the 9-month OS and PFS rates were 97.5% and 63.4%, respectively, with 46.2% of patients being on pembrolizumab at the time of analysis [11]. In our study, the 6-month OS and PFS rates were 91.2% (95% CI 0.83–0.96) and 77.3% (95% CI 0.66–0.85), respectively. Of note, the median OS and PFS were not reached, with 50% of patients continuing nivolumab at the time of analysis. Thirty-four patients (63% of responders) had a response duration of $\geq$6 months at the time of analysis.

The main difference between our cohort and the other cohorts discussed above is that the percentage of patients who bridged to transplantation was 24% in our study, whereas it was 8% in Younes' study [10] and 7% in Chen's cohort [11]. In our cohort, 20 patients underwent SCT (9 auto- and 11 allo-SCT). Although 6 of the 23 patients in Ansell's cohort were planned to undergo SCT, there are no data regarding their outcomes [9]. To our

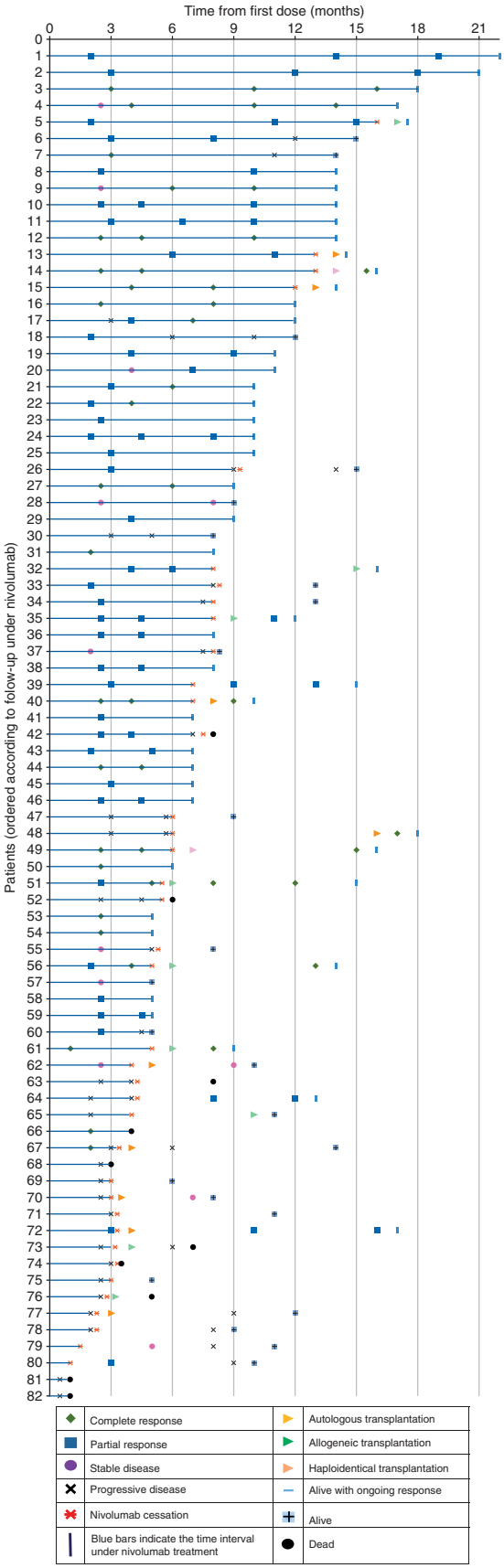

Figure 2. Descriptive graphics of the response characteristics of all patients.

Table 3. Drug-related adverse events analysis

Adverse event	Grade 1	Grade 2	Grade 3
Fatigue	20 (25%)	4 (5%)	1 (1.2%)
Pruritus	5 (6%)	2 (2.5%)	1 (1.2%)
Fever	5 (6%)	3 (3.7%)	
Rash	5 (6%)	1 (1.2%)	
Autoimmune pneumonitis		6 (7.4%)	1 (1.2%)
Anemia	5 (6%)	2 (2.5%)	
Poor appetite	3 (3.7%)	1 (1.2%)	1 (1.2%)
Nausea	4 (5%)	1 (1.2%)	
Pneumonia	5 (6%)		
Upper respiratory tract Inf	5 (6%)		
Pain (all pains included)	5 (6%)		
Stomatitis	1 (1.2%)	1 (1.2%)	2 (2.5%)
Hypothyroidism	2 (2.5%)	2 (2.5%)	
Tumor pain		1 (1.2%)	2 (2.5%)
Neutropenia	3 (3.7%)	1 (1.2%)	
Diarrhea	1 (1.2%)	2 (2.5%)	
Lymphopenia	2 (2.5%)	1 (1.2%)	
Transaminase elevation	3 (3.7%)		
Thrombocytopenia	1 (1.2%)		1 (1.2%)
Cramps	2 (2.5%)		
Creatinine elevation	2 (2.5%)		
Hypophosphatemia	2 (2.5%)		
Hypocalcemia	2 (2.5%)		
Edema	2 (2.5%)		
Encephalitis			1 (1.2%)
GVHD aggravation			2 (2.5%)
Pancreatitis			1 (1.2%)
Infusion hypersensitivity	1 (1.2%)		
Hypercalcemia	1 (1.2%)		
Scrotal pain	1 (1.2%)		
Headache	1 (1.2%)		
Abdominal pain	1 (1.2%)		
Gynecomastia	1 (1.2%)		
Visual problem	1 (1.2%)		
Peripheral neuropathy	1 (1.2%)		
Arthritis	1 (1.2%)		

knowledge, our cohort involves one of the largest patient populations having the chance to bridge to transplantation following PD-1 inhibition, and this finding is worth discussing in detail. Nine patients underwent auto-SCT, four of whom had objective responses before transplantation; these patients had continuous responses at the 10th, 14th, 14th, and 17th month of follow-up, respectively. Among the 11 patients receiving allo-SCT, 8 showed objective responses to nivolumab (5 CR and 3 PR), all of whom (excluding 2 patients with recent allo-SCT who have not yet been evaluated) had ongoing responses at the time of analysis. In our cohort, 2 of the patients who had received allo-SCT before nivolumab treatment showed GVHD aggravation following nivolumab. One of these patients died due to acute severe GVHD and subsequent sepsis 6 months following allo-SCT, whereas the other patient responded to steroid therapy for one month. Her GVHD ameliorated and her disease status was PR in the early evaluation; however, it progressed 9 months following

nivolumab cessation. This information is consistent with the fact that anti-PD-1 therapy creates a long-lasting disturbance in the composition of the circulating T-cell population [16].

In the study recently published by Merryman et al., 39 patients (31 with HL) were reported to have undergone allo-SCT following nivolumab treatment [16]. Within the first year of their follow-up, grade 3 and 4 GVHD was seen in 23% of patients, and four patients died due to treatment-related complications (one hepatic obstructive syndrome, three acute GVHD). Forty-nine percent of this cohort received intervening salvage therapy before allo-SCT, and the median time between nivolumab cessation and transplantation was 62 days. Our cases of allo-SCT differ in that our patients received their transplantation at a median of 30 days after treatment, without any intervening salvage therapy. The median number of cycles of nivolumab before transplantation was nine and the median follow-up time (2 months) following transplantation was short in our study. In Merryman's study, the median number of nivolumab cycles before transplantation was eight, with a median post-transplantation follow-up time of 1 year. The rate of acute GVHD was 36% (4 of 11 patients) in the present study. One of our patients underwent allo-SCT 15 days of the last dose of nivolumab and died due to an atypical septic shock on D + 11, with no fever or hypothermia, indicating early immune toxicity. Taken together, these data suggest that bridging to allo-SCT is feasible and encouraging with nivolumab; however, it may be associated with increased early toxicity. Determination of the optimal bridging conditions is needed by further analyses with a longer follow-up.

The safety profile of our cohort with nivolumab usage is comparable with that in other studies of PD-1 blocking agents in Hodgkin's disease. We encountered manageable side-effects, with only four cases of AEs leading to discontinuation of the agent. Considering our heavily pre-treated, relapsed or refractory cHL population, we had a low rate of discontinuation due to AEs and an acceptable safety profile.

There are some limitations in this study, including its retrospective nature and the short duration of follow-up, precluding accurate estimations of the OS and PFS. A longer follow-up is needed and we continue to follow our cohort to better assess the survival data and the durability of the responses.

In conclusion, considering the prognosis of patients refractory to BV and/or SCT, PD-1 blockers represent candidate treatments for heavily pretreated cHL, and they may serve as a bridge to transplantation, albeit with an increased risk of toxicity.

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Disclosure

The authors have declared no conflicts of interest.

References

1. Smith A, Crouch S, Lax S et al. Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological Malignancy Research Network. Br J Cancer 2015; 112: 1575–1584.
2. Morton LM, Wang SS, Devesa SS et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. Blood 2006; 107: 265–276.
3. Üner A, Esin E, Sağlam Ayhan A et al. Lenfoma Vakalarının Klinikopatolojik Değerlendirmesi Hacettepe Üniversitesi Verileri (Clinicopathological Evaluation of Lymphoma Cases: Hacettepe University Data). In 6. Türk Tıbbi Onkoloji Kongresi (6th Turkish Medical Oncology Congress), Antalya/TURKEY, 2016.
4. Skarbnik AP, Pro B. Heads or tails? Choosing a salvage therapy for relapsed/refractory Hodgkin lymphoma. Expert Rev Hematol 2013; 6: 1–3.
5. Younes A, Gopal AK, Smith SE et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 2012; 30: 2183–2189.
6. Salihoglu A, Elverdi T, Karadogan I et al. Brentuximab vedotin for relapsed or refractory Hodgkin lymphoma: experience in Turkey. Ann Hematol 2015; 94: 415–420.
7. Cheah CY, Chihara D, Horowitz S et al. Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes. Ann Oncol 2016; 27: 1317–1323.
8. Roemer MG, Advani RH, Ligon AH et al. PD-L1 and PD-L2 genetic alterations define classical Hodgkin lymphoma and predict outcome. J Clin Oncol 2016; 34: 2690–2697.
9. Ansell SM, Lesokhin AM, Borrello I et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015; 372: 311–319.
10. Younes A, Santoro A, Shipp M et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol 2016; 17: 1283–1294.
11. Chen R, Zinzani PL, Fanale MA et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol 2017; JCO2016721316.
12. Cheson BD, Fisher RI, Barrington SF et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Omcol 2014; 32: 3059–3068.
13. Cheson BD, Ansell S, Schwartz L et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood 2016; 128: 2489–2496.
14. Cheson BD, Pfistner B, Juweid ME et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007; 25: 579–586.
15. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. In Edition U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health National Cancer Institute June 14, 2010.
16. Merryman RW, Kim HT, Zinzani PL et al. Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/refractory lymphoma. Blood 2017; 129: 1380–1388.