A phase II study of interrupted and continuous dose lenalidomide in relapsed/refractory Hodgkin lymphoma

Newly diagnosed classical Hodgkin lymphoma (cHL) can be cured in approximately 75–85% of patients with systemic or combined-modality frontline therapy. While novel agents such as the anti-CD30 antibody drug conjugate brentuximab vedotin (BV) and immune checkpoint inhibitors (ICI; e.g., nivolumab, pembrolizumab) are highly active in cHL and now often combined with multi-agent chemotherapy,[1,2] patients with relapsed or refractory (rel/ref) disease after salvage therapy and autologous stem cell transplantation (ASCT) have few treatment options and experience 5-year median overall survival (OS) of approximately 50%.[3] Lenalidomide is an immunomodulatory agent approved for mantle cell, follicular, marginal zone, and diffuse large B-cell lymphomas, which interacts with the ubiquitin E3 ligase cereblon to degrade Ikaros family transcription factors.[4] Given multiple immunomodulatory targets in the cHL microenvironment, we hypothesized that lenalidomide would show clinical activity in rel/ref cHL. We previously reported on standard interrupted dosing of lenalidomide (25 mg/d, days 1-21, 28-day cycles) in patients with heavily pretreated rel/ref cHL.[5] In that cohort, the International Workshop Criteria (IWC) overall response rate (ORR) was 19% and the disease control rate (DCR; best response of complete response [CR] or partial response [PR], or stable disease [SD] ≥6 months) was 33%. Based on evidence in other malignancies that continuous lenalidomide dosing may increase efficacy,[6] we tested a continuous dosing schedule (25 mg/d, days 1-28, 28-day cycles until progression or intolerance) in a separate cohort of patients with rel/ref cHL (*clinicaltrials gov. Identifier: NCT00540007*). Here we report the data from the continuous dosing cohort in the context of our previously reported findings.

Collectively, 80 patients enrolled (10/2007 to 6/2011) to the two cohorts (*Online Supplementary Table S1*). Patient eligibility criteria, treatment, and response assessment were previously reported with the interrupted cohort outcomes.[5] The study was carried out in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and regulatory and country-specific requirements. Forty-two patients were assigned to the continuous cohort and received daily lenalidomide. Eight patients (2 from the interrupted cohort and 6 from the continuous cohort) were removed from study before receiving two cycles of lenalidomide due to cytopenias (n=2), increased aspartate transaminase/alanine transaminase (n=2), venous thrombosis (n=1), desquamating rash (n=1), consent withdrawal (n=1), and incarceration (n=1), thus were not response-evaluable per protocol. The median number of lenalidomide cycles administered in the interrupted and continuous cohorts was four (range, 1-48) and 3.5 (range, 1-61+), respectively. Median follow-up from enrollment was 16.0 months (range, 0.7-92.7).

Responses were assessed by positron emission tomography/computed tomography (PET/CT) in 45 patients and CT alone in 26 patients. Due to the time period of the study, international Workshop Criteria was used to assess responses, thus estimates of ORR here may be lower than expected if Lugano response criteria had been used. In 72 response-evaluable patients across both cohorts (Table 1), the ORR was 26% (95% confidence interval [CI]: 18-40), and DCR was 43% (95% CI: 34-58). In the continuous cohort (n=36), the ORR was 32% (95% CI: 20-50) and DCR was 49% (95% CI: 30-70), compared to an ORR of 19% (95% CI: 10-37) and DCR of 36% (95% CI: 24-57) in the interrupted

Table 1. Response rates for entire cohort and per protocol response-evaluable patients for interrupted and continuous cohorts.

Type of response	Entire cohort			Response-evaluable patients		
	Interrupted N=38	Continuous N=42	Combined N=80	Interrupted N=36	Continuous N=36	Combined N=72
CR*, N (%)	1 (2.6)	3 (7.2)	4 (5.0)	1 (2.8)	3 (8.3)	4 (5.5)
PR*, N (%)	6 (15.7)	9 (21.4)	15 (18.8)	6 (16.6)	9 (25.0)	15 (20.8)
SD ≥6 months*, N (%)	6 (13.2)	6 (14.3)	12 (15.0)	6 (16.6)	6 (16.7)	12 (16.7)
ORR (CR+PR)**, N (%)	7 (13.2)	12 (28.6)	19 (23.8)	7 (19.4)	12 (32.4)	19 (26.4)
Disease control rate** (CR+PR+SD ≥6 months), N (%)	13 (34.2)	18 (42.9)	31 (38.5)	13 (36.1)	18 (48.6)	31 (43.1)

*Patient response was assessed by positron emission tomography/computed tomography in 45 patients and by computed tomography alone in 26 patients. **The International Workshop Criteria were used to assess response; estimates of overall response rate from this study may be lower than would be expected if the Lugano criteria for response had been used. CR: complete response; ORR: overall response rate; PR: partial response; SD: stable disease.

cohort. Of the 13 patients achieving disease control in the continuous cohort, nine (69%) had progressed after ASCT and three (23%) were refractory to their prior therapy (*Online Supplementary Table S2*). One patient achieving PR was censored at the time of subsequent ASCT. One patient with SD for 2 months discontinued treatment due to cytopenias prior to a diagnosis of therapy-related acute myeloid leukemia. One patient withdrew due to pregnancy, and another patient achieved a PR lasting 84 months after previously discontinuing treatment due to C*ryptococcus* infection.

In the continuous cohort, median duration of response (DOR) was 8.1 months (range, 4-73), and median time-to-treatment failure (TTF) in patients achieving disease control was 8.3 months (range, 4-73) (*Online Supplementary Figure S1A*). The previously reported interrupted cohort median DOR was 6 months (range, 4-24) (*Online Supplementary Figure S1B*), and median TTF in patients achieving disease control was 15 months (range, 4-43).[5] Survival was analyzed on an intention-to-treat basis. Median progression-free survival (PFS) was 3.7 months for both the continuous (95% CI: 1.8-7.7) and interrupted cohorts (95% CI: 1.8-4.6) (Figure 1A). The median OS was 35.9 months (95% CI: 17.7-not estimated [NE]) for the continuous cohort, 19.6 months (95% CI: 15.3-29.0) for the interrupted cohort, and 23.7 months (95% CI: 17.4-35.6) for the entire study population across both cohorts (Figure 1B). Both cohorts had exceptional long-term responders. Two patients receiving interrupted lenalidomide had a TTF of 30 and 46 months. Both patients had received ≥4 prior therapies including ASCT and were refractory to their previous treatment. Two patients on continuous lenalidomide had long-term responses, one for 24 months (CR), having relapsed after three prior treatments including ASCT. The second patient (PR) remained on treatment for 73 months before discontinuation due to *Cryptococcus* infection. This patient progressed 11 months later and was subsequently treated with multiple therapies

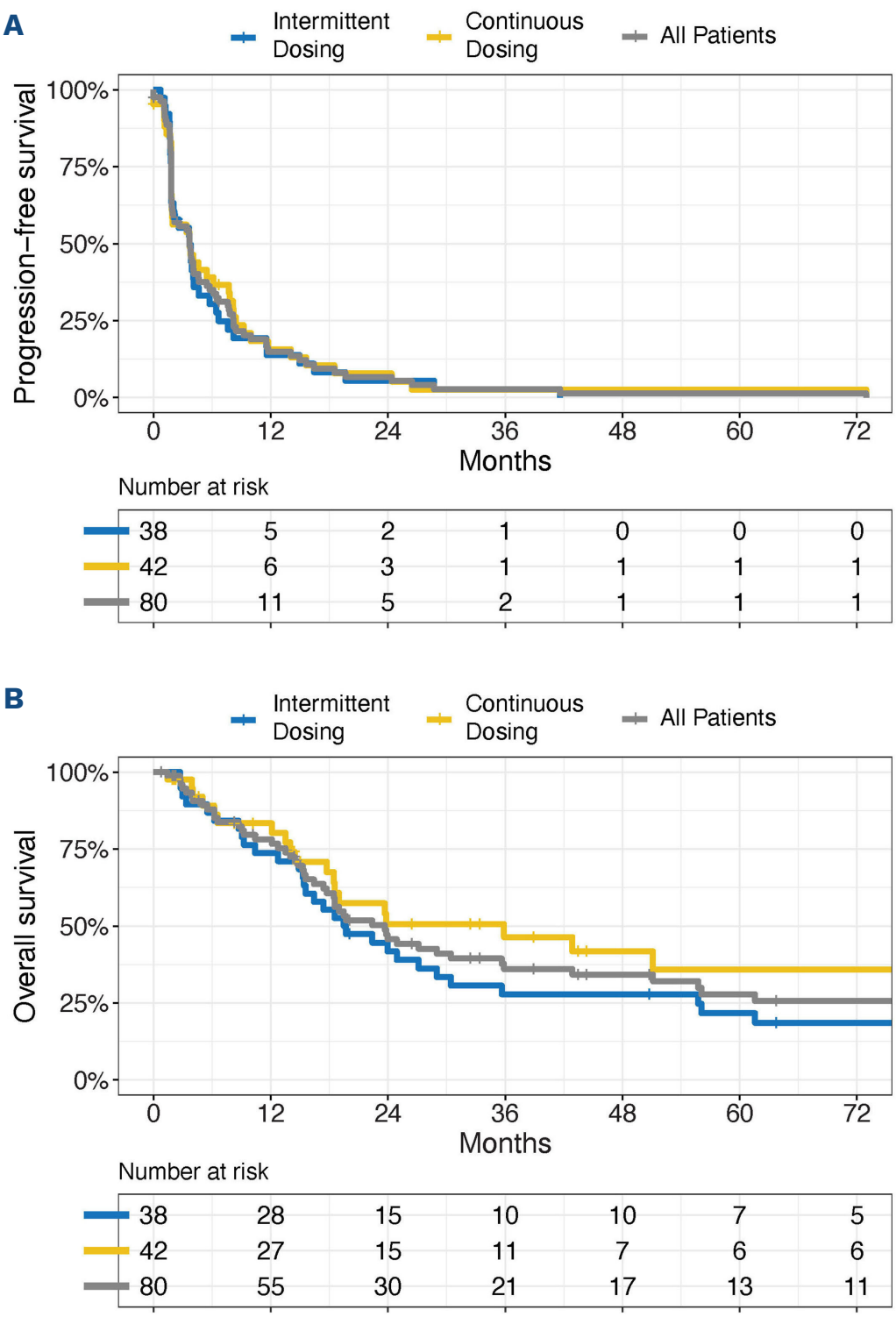

Figure 1. Intention-to-treat survival analysis by cohort. (A) Progression-free survival. (B) Overall survival.

including BV and nivolumab, all of which their disease was refractory to or relapsed again within 12 months.

Lenalidomide was generally well-tolerated with both dosing schedules. The most frequent grade 3-4 adverse events (AE) across both cohorts were neutropenia (48%), leukopenia (29%), thrombocytopenia (23%), lymphopenia (23%), and anemia (19%). Grade 3-4 AE frequencies were similar between the dosing cohorts (Table 2). In the continuous cohort, dose reductions occurred due to cytopenias (n=3) and skin ulceration (n=1). Eight patients discontinued treatment for cytopenias (n=4), vertigo (n=1), myelodysplasia (n=1), pregnancy (n=1), or rash (n=1) at a median of 5.7 months (range, 3.6-73.0). In the interrupted cohort, dose reductions (n=7) and treatment discontinuations (n=4) were previously noted.[5] The median time on therapy for patients who discontinued was 5.7 months (range, 3.6-71.5).

Prior studies in rel/ref cHL explored changes in plasma/serum levels of CCL17/TARC as a biomarker of response. In the continuous cohort, we observed a trend (P=0.07) of decreasing CCL17/TARC levels from C1D1 to C1D15 in responding patients (*Online Supplementary Figure S1C*). Data from the combined cohorts revealed significant associations between decreasing CCL17/TARC levels from C1D1 to C1D15 in responding patients (P=0.014), as well as lower CCL17/TARC levels at C1D15 in responding *versus* C1D15 in non-responding patients (P=0.017) (*Online Supplementary Figure S1D*).

This study represents the largest reported group of patients with rel/ref cHL treated with single-agent lenalidomide, which exhibited an ORR of 26% and DCR of 43% across 72 evaluable patients treated with either interrupted or continuous dosing. Compared to interrupted dosing, continuous dosing resulted in a modest, although not statistically significant, increase in ORR (32% *vs*. 19%) and DCR (49% *vs*. 33%). Median PFS was identical at 3.7 months. Both cohorts had exceptional long-term responders. Eleven patients had previously received BV and either progressed on or within 6 months of discontinuing BV. Three of these patients responded to lenalidomide: one PR (9.3 months) and two CR (10 and 48 months). Thus, in heavily pretreated patients, lenalidomide resulted in modest activity overall, with several exceptional responders.

Compared to interrupted dosing, continuous dosing resulted in modestly more toxicity-related discontinuations (n=8 *vs*. n=4), particularly due to cytopenias (n=4 *vs*. n=1). Despite this, there was a similar incidence of grade 3-4 AE overall. Our results indicate that lenalidomide's efficacy in rel/ref cHL is similar to that reported with other novel single-agent therapies in both the post-ASCT and post-BV setting, including panobinostat, mocetinostat, and AFM13, with lenalidomide exhibiting a favorable toxicity profile.[7] Other smaller studies have evaluated interrupted lenalidomide monotherapy in rel/ref cHL. A phase II study of 14 patients (lenalidomide 25 mg/d, days 1-21, 28-day cycles) demonstrated best responses of PR in two patients and stable disease in seven patients.[8] A lenalidomide compassionate-use program reported an ORR of 29% (1 CR, 11 PR) in 42 patients treated similarly. Two patients transitioned to continuous lenalidomide without increased toxicity.[9]

Combining lenalidomide with other therapies is also appealing, as its immunomodulatory effects may enhance partner drugs' anti-tumor activities. Several ongoing trials combine lenalidomide with chemotherapy or targeted agents. One study of AVD (4-8 cycles) and lenalidomide (5-25 mg/d) as frontline treatment in patients ≥60 years old with cHL reported an 80% ORR and 84% 3-year PFS.[10] A phase I/II study of bendamustine (60 mg/m^2, days 1/8/15) plus continuous lenalidomide (10-25 mg/d) in 15 patients with chemorefractory cHL reported a 73% ORR and 8.7-month

Table 2. Grade 3 or 4 adverse events occurring in greater than 5% of patients.

Characteristic	Grade 3			Grade 4			Grade 3-4
	Interrupted	Continuous	Combined	Interrupted	Continuous	Combined	Combined
Hematological, N (%)							
Neutropenia	13 (34)	17 (40)	30 (38)	5 (13)	3 (7)	8 (10)	38 (48)
Leukopenia	9 (24)	11 (26)	20 (25)	2 (5)	1 (2)	3 (4)	23 (29)
Lymphopenia	7 (18)	7 (17)	14 (18)	2 (5)	2 (5)	4 (5)	18 (23)
Thrombocytopenia	5 (13)	8 (19)	13 (16)	2 (5)	3 (7)	5 (6)	18 (23)
Anemia	8 (21)	5 (12)	13 (16)	2 (5)	-	2 (3)	15 (19)
Non-hematological, N (%)							
Fatigue	3 (8)	3 (7)	6 (8)	-	-	-	6 (8)
Infection without neutropenia	2 (5)	3 (7)	5 (6)	-	-	-	5 (6)
ALT	1 (3)	2 (5)	3 (4)	1 (3)	-	1 (1)	4 (5)
AST	3 (8)	1 (2)	4 (5)	-	-	-	4 (5)
Bilirubin	1 (3)	1 (2)	2 (3)	1 (3)	1 (2)	2 (3)	4 (6)
Metabolic/laboratory, N (%)							
Low potassium	2 (5)	3 (7)	5 (6)	1 (3)	-	1(1)	6 (8)
Low sodium	1 (3)	3 (7)	4 (5)	1 (3)	-	1(1)	5 (6)

AST: aspartate transaminase; ALT: alanine transaminase.

median PFS.[11] A study of the mTOR inhibitor temsirolimus (25 mg intravenously weekly) and lenalidomide (20 mg/d, days 1-21, 28-day cycles) in 20 patients with cHL refractory to or relapsing after BV reported an 80% ORR and 9.2-month median PFS.[12] Not all lenalidomide combinations have been as promising. A study of 25 patients with rel/ref cHL receiving lenalidomide (20 mg, days 1-21, 28-day cycles) and panobinostat (15 mg, 3 doses/week) reported a 17% ORR, lower than the expected ORR for either monotherapy,[13] as well as significant cytopenias and infections. The checkpoint inhibitors nivolumab and pembrolizumab, approved for treatment of rel/ref cHL, have similar CR rates (16-22%) and ORR (64-70%) in heavily pretreated patients,[14] but are likely to be used in first- or second-line combinations moving forward.[2,15,16] The combination of lenalidomide and nivolumab is currently under investigation.[17] Overall, lenalidomide 25 mg/d administered via interrupted (days 1-21) or continuous (days 1-28) schedule with 28-day cycles has preliminary evidence of clinical efficacy in patients with rel/ref cHL. Lenalidomide was well tolerated by the heavily pretreated patients in both cohorts, and durable responses to lenalidomide monotherapy were observed. Given the single-agent activity and observed toxicities, lenalidomide could be considered in the post-ICI/BV setting, and future studies of combination approaches including lenalidomide are warranted, especially those incorporating immunotherapy strategies.

Authors

Todd A. Fehniger,[1] Marcus P. Watkins,[1] Nkiruka Ezenwajiaku,[1] Fei Wan,[2] David D. Hurd,[3] Amanda F. Cashen,[1] Kristie A. Blum,[4] Andre Goy,[5] Timothy S. Fenske,[6] Nina D. Wagner-Johnston,[1] Kenneth Carson,[1] Marilyn J. Siegel,[7] David Russler-Germain,[1] Stephanie E. Schneider,[1] Neha Mehta-Shah,[1] Brad Kahl[1] and Nancy L. Bartlett[1]

[1]Washington University School of Medicine, Division of Oncology, St. Louis, MO; [2]Washington University School of Medicine, Division of Biostatistics, St. Louis, MO; [3]Wake Forest University School of Medicine, Section of Hematology and Oncology, Winston-Salem, NC; [4]Emory University School of Medicine, Department of Hematology and Medical Oncology, Atlanta, GA; [5]Hackensack University Medical Center, Division of Lymphoma, Hackensack, NJ; [6]Medical College of Wisconsin, Hematology and Oncology Department, Milwaukee, WI and [7]Washington University, Mallinckrodt Institute of Radiology, Alvin J. Siteman Cancer Center, St. Louis, MO, USA

Correspondence:
T.A. FEHNIGER - tfehnige@wustl.edu
N.L. BARTLETT - nbarlet@wustl.edu

https://doi.org/10.3324/haematol.2022.282246

Received: May 2, 2023.
Accepted: September 6, 2023.
Early view: September 14, 2023.

Disclosures

TAF and NLB have received research funding from Celgene for this clinical study.

Contributions

TAF and NLB developed the concept and designed the study. TAF, AFC, KAB, TSF, DDH, AG, NW-J and NLB provided study materials or patients. TAF, MJS, SES, MPW, and NE collected and assembled data. TAF, FW, MJS, SES, NLB, MPW, NE, and DR-G analyzed and interpreted data. TAF, MPW, DAR-G, NE, NLN, BK, and NM-S wrote and edited the manuscript. TAF, MPW, DAR-G, NJS, AFC, KAB, TSF, DDH, AG, FW, SES, NW-J, NLB, NE, BK, and NM-S gave the final approval of the mansucript. All authors had access to the primary clinical trial data..

Acknowledgments

We thank all study site personnel as well as the patients and their families for participation in this study.

Funding

This study was supported in part by Celgene/BMS, the ASCO Foundation (to TAF), the Foundation for Barnes-Jewish Hospital Steinback Fund (to NLB), Siteman Cancer Center Team Science Award (P30 CA091842) (to TAF and BK). The authors recognize the support of the Biostatistics Core, Clinical Trials Core, Imaging Response Assessment Team, and Tissue Procurement Core of the Siteman Cancer Center (P30 CA091842) and the Clinical and Translational Science Award (CTSA) grant (UL1 TR000448).

Data-sharing statement

No shared data are available.

References

1. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med. 2018;378(4):331-344.
2. Herrera AF, LeBlanc ML, Castellino SM, et al. SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin(BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). J Clin Oncol. 2023;41(Suppl 17):LBA4-LBA4.
3. Badar T, Epperla N, Szabo A, et al. Trends in postrelapse survival in classic Hodgkin lymphoma patients after experiencing therapy failure following auto-HCT. Blood Adv. 2020;4(1):41-54.
4. Gribben JG, Fowler N, Morschhauser F. Mechanisms of action of lenalidomide in B-cell non-Hodgkin lymphoma. J Clin Oncol. 2015;33(25):2803-2811.

5. Fehniger TA, Larson S, Trinkaus K, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood. 2011;118(19):5119-5125.
6. Fehniger TA, Uy GL, Trinkaus K, et al. A phase 2 study of high-dose lenalidomide as initial therapy for older patients with acute myeloid leukemia. Blood. 2011;117(6):1828-1833.
7. Watkins MP, Fanale MA, Bartlett NL. SOHO State of the art updates and next questions: Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk. 2018;18(2):81-90.
8. Kuruvilla J, Taylor D, Wang L, Blattler C, Keating A, Crump M. Phase II trial of lenalidomide in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2008;112(11):3052.
9. Boll B, Borchmann P, Topp MS, et al. Lenalidomide in patients with refractory or multiple relapsed Hodgkin lymphoma. Br J Haematol. 2010;148(3):480-482.
10. Boll B, Plutschow A, Burkle C, et al. Doxorubicin, vinblastine, dacarbazine and lenalidomide for older Hodgkin lymphoma patients: final results of a German Hodgkin Study Group (GHSG) phase-I trial. Br J Haematol. 2019;185(1):42-52.
11. Corazzelli G, Saggese M, Pavone V, et al. A phase 1/2 study of lenalidomide and bendamustine (LEBEN) in chemorefractory Hodgkin lymphoma. J Clin Oncol. 2014;32(Suppl 15):8566.
12. Kline J, Rapoport AP, Petrich AM, et al. Phase II study of temsirolimus and lenalidomide in patients with relapsed and refractory lymphomas: final analysis of NCI 8309. Blood. 2016;128(22):4147.
13. Maly JJ, Christian BA, Zhu X, et al. A phase I/II trial of panobinostat in combination with lenalidomide in patients with relapsed or refractory Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk. 2017;17(6):347-353.
14. Armand P, Engert A, Younes A, et al. 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. J Clin Oncol. 2018;36(14):1428-1439.
15. Moskowitz A, Shah G, Schöder H, et al. Phase II trial of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin (GVD) as second-line therapy for relapsed or refractory classical Hodgkin lymphoma. J Clin Oncol. 2021;39(28):3109-3117.
16. Mei M, Palmer J, Tsai N-C, et al. Nivolumab plus ICE as first salvage therapy in high-risk relapsed/refractory Hodgkin lymphoma. Blood. 2022;140(Suppl 1):774-776.
17. Bond DA, Wei L, Yildiz V, et al. Combination of the PD-1 inhibitor nivolumab and immunomodulatory drug lenalidomide in relapsed Hodgkin and large B-cell lymphoma: results from a phase I/II study. Hematol Oncol. 2023;41(S2):597-598.