

# Immune checkpoint inhibitors in malignant lymphoma: Advances and perspectives

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## Abstract

Classical Hodgkin lymphoma (cHL) has been identified with universal genetic alterations of chromosome 9p24.1, which contains *PD-L1/PD-L2* genes. The amplification of 9p24.1 is associated with the increased expression of *PD-L1* and *PD-L2* on RS cells, which promotes their immune evasion, and subsequently makes cHL sensitive to PD-1 blockade. Several PD-1 inhibitors have shown significant efficacies with overall response rate (ORR) of 70%–90% in relapse/refractory (r/r) cHL and have acquired the approvals for this indication. Recently, more and more studies are conducted to investigate PD-1 blockade in earlier disease course and in combination with neo-agents or chemotherapy. Unlike cHL, non-Hodgkin lymphoma (NHL) consists of numerous subtypes harboring highly biological heterogeneity. Only a few subtypes have been shown to have genetic alteration of *9p24.1* including primary mediastinal B cell lymphoma (PMBL), gray zone lymphoma (GZL) with features intermediate between diffuse large B cell lymphoma (DLBCL) and cHL, primary central nervous system lymphoma (PCNSL) and primary testicular lymphoma (PTL). Epstein-Barr virus (EBV)-associated lymphomas have a virally mediated overexpression of PD-L1, also making them sensitive to PD-1 blockade. Therefore, PD-1 inhibitors are less effective in most r/r NHL than in r/r cHL. Further understanding of the biological features of NHL and immune checkpoint inhibitors (ICPi) combined therapy is the research focus in the future. In this review, we outlined the recent progress of ICPi in lymphoma originating from clinical studies.

**Keywords:** Immunotherapy; immune checkpoint inhibitor; PD-1 blockade; Hodgkin lymphoma; non-Hodgkin lymphoma

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## Introduction

With the development of immune checkpoint inhibitors (ICPi) and chimeric antigen receptor (CAR)-T cell therapy, immunotherapy began to play an important role in the treatment of cancer. Immune checkpoints normally help to downregulate immune response by binding to their ligands; but unfortunately, a variety of tumors use this mechanism to enhance immune escape. More recently, the

most widely investigated immune checkpoint is programmed cell death protein 1 (PD-1), which combined with its ligands, PD-L1 and PD-L2, on tumor cells, antigen-presenting cells, and T cells (1). ICPi have become one of the most active areas in cancer research, and have demonstrated encouraging results. Several ICPi, such as PD-1/PD-L1 inhibitors and cytotoxic T-lymphocyte associated protein 4 (CTLA4) inhibitors have been approved in multiple cancers for different indications,

including lung cancer, melanoma, kidney cancer and so on. Based on the excellent results from a series of phase II clinical studies, several PD-1 inhibitor products have been granted designation for relapsed/refractory classical Hodgkin lymphoma (r/r cHL) in China. More clinical trials of PD-1 and PD-L1 inhibitors are currently ongoing in lymphoma. Herein, we review the clinical applications and future direction of ICPi in classical Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma (NHL).

### ICPi in cHL

cHL accounts for approximately 95% of all HL characterized by a small percentage of tumoric Reed Sternberg (RS) cell within a cellular background rich in lymphocytes, histiocytes, plasma cells and/or eosinophils or neutrophils (2). With standard frontline chemotherapy such as ABVD or BEACOPP combined with radiotherapy indicated, the majority of cHL can be usually curable. However, 20%–30% of patients eventually experience disease relapse or have refractory disease that fails to acquire complete remission (CR) from frontline therapy, and only 45%–55% of them could be cured by salvage chemotherapy followed by high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) (3). In addition to brentuximab vedotin (BV), an antibody-drug conjugate directed against CD30 on RS cells approved in 2011, the development of PD-1 inhibitor has shown very promising results with prolonged remission or disease stabilization in many r/r cHL patients, leading the approval of nivolumab and pembrolizumab for the treatment of r/r cHL.

Universal genetic alterations of chromosome 9p24.1, which contains *PD-L1/PD-L2* genes, have been identified in cHL, supporting the possibility that PD-1 pathway plays an important role in the host immune evasion contributing to the pathogenesis of cHL. The amplification of 9p24.1 is associated with the overexpression of PD-L1 and PD-L2 on RS cells. In addition, the extended 9p24.1 amplification region contains the *JAK2* locus, and *JAK2* amplification increases *JAK2* protein expression and activity, specifically inducing the upregulation of PD-L1 transcription and expression (4,5). Furthermore, Epstein-Barr virus (EBV) infection, which is implicated in approximately 40% of cHL, has also been found as an alternative mechanism of promoting PD-L1 expression in cHL (6). The inherent genetic abnormality means that cHL may be sensitive to immunotherapy with the blockade of PD-1/PD-L1 and

PD-1/PD-L2 interaction.

### Monotherapy in r/r cHL failed after $\geq 2$ -line chemotherapy

Several PD-1 inhibitor monotherapies have been evaluated in r/r cHL and yield high activities in early phase trials. Nivolumab is an IgG4 fully human monoclonal antibody (mAb) targeting PD-1. In a phase I study (CheckMate 039) of 23 patients with r/r cHL (7), nivolumab induced an 87% overall response rate (ORR) and 17% CR rate with a progression-free survival (PFS) rate of 86% at 24 weeks. Based on the CheckMate 039 study, a phase II CheckMate 205 study of nivolumab monotherapy enrolled 243 patients with r/r cHL after ASCT failure into 3 cohorts by previous treatment: BV naïve (cohort A, n=63), BV received after ASCT (cohort B, n=80), or BV received before and/or after ASCT (cohort C, n=100). After a minimum follow-up of 31 months, 49 patients (20%) were still on treatment, and median duration of treatment was 14 months. ORR was 71% (65%, 71%, 75% in cohorts A, B, C, respectively) with a CR rate of 21% (32%, 14%, 20% in cohorts A, B, C, respectively) as assessed by an independent radiology committee (IRC). Median duration of response (DOR) was 18 months overall, and was 32 and 13 months in patients with CR and partial remission (PR), respectively. Median PFS among all patients was 15 months, and was 34.1, 15.1 and 8.3 months in patients achieving CR, PR and stable disease (SD), respectively. Median overall survival (OS) was not reached in any cohort; 24-month OS rates were 90%, 86%, and 86% in cohorts A, B, and C, respectively, and were similar among patients in CR, PR, or with SD (8-10). These data demonstrated high ORR and durable response to nivolumab regardless of BV exposure. Data from the previous two studies were the basis of the US Food and Drug Administration (FDA) approval in May 17, 2016 of nivolumab for cHL that has failed after ASCT and BV.

Pembrolizumab, an IgG4 fully humanized anti-PD-1 mAb, was initially evaluated in a phase Ib study (KEYNOTE-013) of 31 patients with r/r cHL who failed BV (71% with previous ASCT). The ORR was 65% with CR rate of 16% and the DOR was at least 24 weeks for 70% of responding patients at a median follow-up of 17 months. The PFS was 46% at 52 weeks (11). Following KEYNOTE-013, the phase II KEYNOTE-087 study was designed to evaluate the efficacy of pembrolizumab in 3 cohorts of patients with r/r cHL, who progressed after ASCT and subsequent BV (cohort 1, n=69), underwent salvage chemotherapy and BV, and thus, ineligible for

ASCT because of chemo-resistant disease (cohort 2, n=81), or progressed after ASCT, but without BV after ASCT (cohort 3, n=60). Patients received pembrolizumab 200 mg once every 3 weeks for 2 years or until disease progression or intolerable toxicity. After a median follow-up of 39.5 months, ORR was 71.0%, with CR rate of 27.6% in the whole group. ORR was 78.3% (CR 26.1%) in cohort 1, 64.2% (CR 25.9%) in cohort 2, and 71.7% (CR 31.7%) in cohort 3. Overall median DOR was 16.6 months, and 26.9% had a response duration  $\geq 3$  years. Median PFS was 13.7 months in all patients, not reached in patients with CR and 13.8 months in patients with PR. The 3-year OS rate was 86.4% (12-14). The results of KEYNOTE-087 led to FDA approval of pembrolizumab for adult and pediatric patients with r/r cHL who relapsed after  $\geq 3$  prior lines of therapy in March 2017. A phase III randomized KEYNOTE-204 trial (NCT02684292) was initiated in May 23, 2016, aiming to compare pembrolizumab with BV in r/r cHL, and enrolled 304 patients. Interim results will be presented in future.

Several multicenter, single-arm phase II studies were conducted in China, and all enrolled r/r cHL patients who failed at least two lines previous chemotherapy or ASCT. Sintilimab, a highly selective, fully humanized mAb against PD-1, was evaluated in ORIENT-1 study for 96 patients. Patients received sintilimab 200 mg intravenously (IV) once every 3 weeks, until disease progression, death, unacceptable toxicity, for a maximum of 24 months. The median duration of follow-up was 10.5 months, the ORR is 80.4% with CR rate of 33.7%, and the PFS at 6 months is 77.6% (15). Camrelizumab is a humanized high-affinity IgG4 mAb blocking PD-1. In the SHR-1210-II-204 study enrolling 75 patients who were treated with camrelizumab 200 mg IV every 2 weeks until disease progression, or intolerable toxicity, the ORR per IRC was 76% with 21 CR (28%). After a median follow-up of 16.9 months, the DOR at 12 months was 74.6%, and 12-month PFS was 66.5% (16). Tislelizumab, a humanized IgG4 anti-PD-1 mAb, was specifically engineered to minimize Fc $\gamma$ R binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy. In the BGB-A317-203 trial in which 70 patients received tislelizumab 200 mg IV every 3 weeks until disease progression or unacceptable toxicity, ORR is 87.1% with CR rate of 62.9%. After median follow-up of 9.8 months, the estimated 9-month PFS was 74.5% (17). The results from the former studies led to the Chinese National Medical Products

Administration (NMPA) approval of sintilimab, camrelizumab and tislelizumab for r/r cHL patients with failing after  $\geq 2$ -line system chemotherapy or ASCT.

PD-1 inhibitors have been demonstrated clinically effective, but it hasn't been established if blockade of the PD-1/PD-L1 interaction alone is sufficient for therapeutic effect. Avelumab, a fully human IgG1 mAb that selectively blocks PD-L1 rather than PD-1, was evaluated in a phase I study (JAVELIN Hodgkin) of patients with r/r cHL who had progression following either ASCT or allogeneic SCT (allo-SCT), or to be SCT-ineligible (18). Thirty-one patients were randomized into five different dosing groups, and ORR was 54.8%, with 2 CR (6.5%). Responses were observed in all dosing groups (ORR range 14.3%–83.3%). Although the ORR seemed similar to that observed with PD-1 inhibitors, due to limited data available to date, more additional studies in larger samples will be necessary to support this possibility.

#### *Combination therapy in r/r cHL failed after $\geq 2$ -line chemotherapy*

PD-1 blockade has made impressive advances in r/r cHL, however, further efforts are ongoing to optimize the efficacy, especially on improving CR rate to achieve deeper and more durable remission. The addition of other drugs in combination with PD-1 inhibitors is a possible direction to acquire higher CR. Combination of ICPi with nivolumab and ipilimumab, a fully human mAb targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), has shown superior efficacy than monotherapy in some solid tumors such as melanoma. One cohort of CheckMate 039 study (19) aimed to explore the efficacy of nivolumab and ipilimumab in hematologic malignancies. Nivolumab + ipilimumab were given at 3 mg/kg IV and 1 mg/kg IV, respectively, every 3 weeks for 4 doses, followed by nivolumab monotherapy (3 mg/kg) every 2 weeks for up to 2 years. Sixty-five patients were treated, and in 31 cHL patients ORR was 74% with 19% CR after the median follow-up of 11.4 months. The efficacy of nivolumab + ipilimumab seemed like nivolumab alone, so the benefit and possible increased risk of adding ipilimumab in this setting needs further exploration.

Given the significant efficacy of nivolumab and BV in cHL, using an ICPi to activate the immune cells in the tumor micro-environment, and concurrently targeting tumor cells with BV may overcome resistance and further improve the activity. The phase I ECOG-ACRIN E4412 study aimed to evaluate the combinations of BV (B, 1.2 or

1.8 mg/kg), ipilimumab (I, 1 or 3 mg/kg) and nivolumab (N, 3 mg/kg) in patients with r/r cHL (20). The extended follow-up results were reported at ICML in 2019 (21). Sixty-four patients were enrolled sequentially in cohorts of B-I (n=21), B-N (n=18), and B-N-I (n=22). The ORR/CR is 76%/57% (B-I), 88%/61% (B-N), and 82%/73% (B-N-I). The 1-year PFS is 60%, 68%, and 72% for B-I, B-N and B-N-I, respectively. All combinations were well tolerated; however, two grade 5 pneumonitis deaths were noted in N containing cohorts. The ORR and CR rates in the N containing cohorts seem superior to that of B-I doublet; the CR of B-N-I is higher than the other cohorts and some patients have durable responses. E4412 study is ongoing to compare the B-N doublet to the B-N-I triplet (NCT01896999), but further attention needs to be paid in the serious immune related adverse events (IRAE). A randomized phase III study (CheckMate 812, NCT03138499) was initiated to compare BV + nivolumab with BV alone in patients with r/r cHL who failed after ASCT or were ineligible for ASCT in May 16, 2017, and planned for enrollment of 340 patients. The results are worth looking forward.

Although PD-1 inhibitors had demonstrated high efficacy in r/r cHL, most patients would ultimately experience failure even if acquired CR. Treatment in this setting is challenging and difficult. Nivolumab and bendamustine combination was evaluated in 41 patients. The median number of previous therapy lines was 6 (3-11), and 38/41 (93%) had received monotherapy of nivolumab with the median number of 18, and one patient received 12 infusions of pembrolizumab. The previous treatment also included ASCT in 18/41 (44%), BV in 21/41 (51%) and bendamustine in 23/41 (56%) of patients. Median follow-up time was 21 months, the ORR was 80% with CR rate of 44%, and median PFS was 10 months (22). This combination showed efficacy despite the previous failure of bendamustine or PD-1 inhibitors, which provided a possible selection in clinical practice, and may be used as the bridge therapy for allo-HSCT in selected patients with r/r cHL.

Decitabine is an epigenetic modifier that inhibits DNA methyl-transferase activity. Low-dose decitabine increased tumor immunogenicity, T-cell infiltration, and antitumor response. Theoretically, decitabine could synergize with PD-1 inhibitors to restore immune-surveillance. A single center, two-arm phase II study was initiated to explore the safety and efficacy of camrelizumab + decitabine in 86 patients with r/r cHL (23). PD-1 blockade treatment-naïve

patients (cohort 1, n=61) were randomly assigned (1:2) to camrelizumab (200 mg) monotherapy or decitabine (10 mg, d 1-5) + camrelizumab (200 mg, d 8) combination therapy every 3 weeks. Patients who were previously treated with PD-1 inhibitors (cohort 2, n=25) were assigned to combination therapy. Median follow-up time is 14.9 months. In cohort 1, ORRs for monotherapy and combination were 90% and 95%, respectively. CR was 32% with monotherapy vs. 71% with combination treatment, 1-year estimated DOR was 60% vs. 89%, and 1-year PFS was 59% vs. 89%. In cohort 2, ORR was 52% with CR rate of 28%, and 1-year DOR and PFS was 81% and 59%, respectively. Camrelizumab + decitabine improved the CR and may reverse resistance to PD-1 inhibitors in patients with r/r cHL. The study is still ongoing and expands to multicenter to enroll more patients to further confirm the preliminary results.

Recently, a larger number of combination partner are being investigated, including some immune-modulatory agents like ibrutinib (NCT02950220, NCT02940301), PI3K inhibitors (NCT03471351), lenalidomide (NCT03015896, NCT02875067), histone deacetylase (HDAC) inhibitors (NCT03150329, NCT 03179930) (24,25). Other novel agents, such as AFM 13, L-NG-monomethyl arginine (L-NMMA), BMS-986016 (LAG-1 mAb) and MK-1454, are also being tested in combination with PD-1 inhibitors (26). AFM13, a bispecific anti-CD30/CD16 antibody, which was investigated in combination with pembrolizumab in a phase Ib study, produced ORR of 87% and CR of 39% per IRC in 30 patients (27). In addition, traditional chemotherapy and radiotherapy are also being trying in combination with ICPI (NCT03343652, NCT03179917, NCT03480334, NCT03495713) (24,25).

### *Salvage therapy after frontline therapy*

Since salvage chemotherapy followed by ASCT is the standard approach following frontline treatment failure in r/r cHL, how to improve the efficacy of salvage therapy, particularly in CR rate, to make more patients eligible for ASCT, is still the direction of current study. PD-1 blockade has been explored as part of first salvage therapy in transplant-eligible patients with r/r cHL. In a phase I/II study (28), patients who failed after frontline chemotherapy were treated with nivolumab (3 mg/kg) in combination with BV (1.8 mg/kg) every 3 weeks for up to 4 cycles. The updated longer follow-up data were presented at American

Society of Hematology (ASH) meeting in 2019 (29). Ninety-one patients were enrolled and 86 completed all 4 cycles of nivolumab + BV. The ORR for all-treated patients was 85%, with CR rate of 67%. Sixty-seven patients (74%) underwent ASCT, and 22 patients received additional salvage therapy after BV + nivolumab [7 progressive disease (PD), 6 PR, 5 SD and 4 CR], 17 of whom later underwent ASCT. After a median follow-up of 22.6 months, the estimated 2-year PFS in all patients was 78%, and for patients who underwent ASCT was 91%. The estimated 2-year OS was 93%. Nivolumab + BV did not impact the yield of stem cell mobilization and collection. The high CR of nivolumab + BV suggests that this combination is a promising salvage regimen after failure to frontline chemotherapy, potentially sparing patients traditional chemotherapy before ASCT and improving their life qualities. CheckMate 744 (NCT02927769) is an ongoing phase II study evaluating a risk-stratified, response-adapted approach using nivolumab, BV, and bendamustine as first salvage in patients aged 5–30 years. In the standard-risk (R2) cohort, patients received 4 cycles of nivolumab + BV, and followed by ASCT if achieving complete metabolic remission (CMR). Patients with suboptimal response after nivolumab + BV received 2–4 cycles of BV + bendamustine intensification. Forty-four patients were treated in the R2 cohort, ORR was 82% with CR rate of 59% after nivolumab + BV, and CR increased to 86% after completing BV + bendamustine prior to ASCT. The CR rates were similar for the primary refractory or pediatric patients (30).

PD-1 inhibitors have been also tested in combination with conventional chemotherapy as initial salvage regimen, especially after the frontline approval of BV. A prospective, multicenter phase II trial (31) was evaluated PET-adapted nivolumab or nivolumab + ICE (NICE) chemotherapy in this setting. Patients received 3 mg/kg nivolumab every 2 weeks for up to 6 cycles (C). After C6, patients in CR proceeded to ASCT while patients not in CR received NICE for 2 cycles. The interim results were shown at ASH meeting in 2019 (32). Thirty-nine patients were evaluable for toxicity; 37 were evaluable for response. At the end of nivolumab, the ORR was 78%, with 26 CR (70%). Seven patients were treated with NICE and all responded (100% ORR) with 6 CR (86%). At the end of treatment (nivolumab or nivolumab/NICE), the ORR was 89% with 32 CR (86%) and 1 PR (3%). Twenty-seven patients proceeded to ASCT, the median of  $4.7 \times 10^6$  CD34+ cells/kg was collected, and the median time to neutrophil and

platelet engraftment was 11 and 12 d, respectively. After a median follow-up of 10.5 months, the 1-year PFS was 79% and 1-year OS was 97%. In this small sample study, nivolumab alone seemed an effective bridge to ASCT in most patients, sparing them the toxicity of traditional salvage chemotherapy, and patients who did not achieve CR with nivolumab were effectively salvaged by nivolumab + ICE. However, this result requires larger sample studies, especially phase III controlled studies to confirm. Another phase II trial (NCT03077828) of evaluating pembrolizumab in combination with ICE in the same setting was started in April 2017 and is ongoing with planning to enroll 40 patients.

Pembrolizumab + GVD chemotherapy (gemcitabine, vinorelbine, liposomal doxorubicin) was also investigated in a phase II study for cHL patients following failure of first-line treatment. Treatment consists of 2–4 cycles of pembrolizumab (200 mg IV, d 1), gemcitabine (1,000 mg/m<sup>2</sup> IV, d 1, d 8), vinorelbine (20 mg/m<sup>2</sup> IV, d 1, d 8) and liposomal doxorubicin (15 mg/m<sup>2</sup>, d 1, d 8), given on 21-day cycles. Early trial results (33) showed that 18 out of a planned 39 patients enrolled, and CR is 93% (13/14) with PR of 7% after 2 cycles of treatment among the 14 evaluable patients. Three patients are proceeding to ASCT and 11 patients completed ASCT following 2 (n=10) or 4 (n=1) cycles of treatment. Median follow-up post-ASCT is 4 months and all patients remain in remission to date. An ongoing prospective phase II study is evaluating the addition of Camrelizumab to GEMOX regimen (Gemcitabine, Oxaliplatin) as first salvage strategy in patients with r/r cHL in Peking University Cancer Hospital (NCT04239170).

### ***Maintenance therapy after ASCT***

Nearly 50% of patients will eventually relapse after ASCT with poor subsequent prognosis. One way of reducing the risk of recurrence is to use maintenance therapy following ASCT especially in high-risk patients. The AETHERA trial had demonstrated that the median PFS was significantly improved in patients in the BV maintenance arm compared to the placebo arm (42.9 vs. 24.1 months,  $P=0.0013$ ) following ASCT (34). The PFS benefit sustained after 5-year follow-up, and corresponding 5-year PFS was 59% vs. 41% (35). National Comprehensive Cancer Network (NCCN) currently recommends 1 year of BV maintenance therapy following ASCT in cHL patients with a high risk of relapse. PD-1 blockade given as maintenance

therapy following ASCT has also been investigated in several phase II study. Pembrolizumab was administered at 200 mg IV every 3 weeks for up to 8 cycles, starting within 21 d of post-ASCT discharge (NCT02362997). Thirty patients were included with 90% at high risk by clinical criteria. A total of 77% of patients completed all 8 cycles. The PFS at 18 months for the 28 evaluable patients was 82%, meeting the primary end point. The 18-month OS was 100% (36). Phase II studies of nivolumab or nivolumab + BV in this maintenance setting are ongoing (NCT03436862, NCT03057795). This preliminary result supports the subsequent testing of this strategy in a randomized phase III controlled trial.

### **Frontline therapy**

Higher degrees of genetic alteration of 9p24.1 are more common in newly diagnosed advanced stage cHL and have been associated with a higher likelihood of treatment failure following standard first-line therapy (5). Given the promising efficacy of PD-1 blockade in r/r cHL, the incorporation of ICPi in frontline therapy is a current research focus. Cohort D of the CheckMate 205 study enrolled 51 patients with newly diagnosed, advanced stage cHL (defined as III–IV and IIB with unfavorable risk factors) (37). Patients received nivolumab (240 mg IV q2w) for four doses, followed by 12 doses of N-AVD every 2 weeks. Forty-nine patients completed nivolumab monotherapy and 44 patients completed N-AVD. Overall, 59% experienced a grade 3–4 treatment-related adverse event (TRAE), most commonly neutropenia (49%). Febrile neutropenia occurred in 10% of patients. The most common grade 3–4 immune-related adverse event (IRAE) was hepatitis (2 patients, 4%). Endocrine IRAE were all grade 1–2 and did not require high-dose corticosteroids; all non-endocrine IRAE resolved (most commonly, rash; 5.9%). At the end of monotherapy, ORR per IRC was 69% with CR rate of 18%; and ORR increased to 84% with 75% CMR after N-AVD. With a minimum follow-up of 24.4 months, 21-month median PFS per investigator was 80% (38).

Pembrolizumab has also been investigated in a phase II trial (39) which enrolled 30 patients with newly diagnosed cHL stages I–IV, including early-stage patients with at least one risk factor according to NCCN criteria. Patients were treated sequentially with 3 cycles of pembrolizumab at 200 mg every 3 weeks followed by 4–6 cycles of AVD chemotherapy based on initial stage. Twelve patients had

early unfavorable disease with 18 patients of advanced stage disease [13 stage IV, International Prognostic Score (IPS) score 3–4 in 7, 1–2 in 10]. The only grade 3 or 4 IRAE was the one grade 4 transaminitis that resolved with steroid administration and a delay in therapy. CR was 37% following pembrolizumab monotherapy including three with large mediastinal masses, and CR increased to 100% after 2 cycles of AVD. Another prospective, randomized phase II GHSG NIV AHL trial (NCT03004833) (40) enrolled treatment-naïve early-stage unfavorable cHL patients to evaluating nivolumab + AVD followed by 30 Gy involved-site radiotherapy (ISRT). In arm A (concomitant, n=55), patients received 240 mg nivolumab and AVD on d 1 and 15 every 28 d for a total of four cycles (4×NivoAVD). In arm B (sequential, n=54), treatment was given with 4×nivolumab in 2-weekly intervals, followed by 2×NivoAVD and 2×AVD. After 2×NivoAVD and 4×nivolumab, the ORR was 100% and 96% (49/51), with a CR rate of 85% and 53% in groups A and B, respectively. After completion of systemic therapy, ORR was 100% and 98% with a CR rate of 81% and 86%, respectively. Concomitant and sequential therapy with nivolumab and AVD was feasible with acceptable toxicity. In early-stage unfavorable cHL, concomitant Nivo-AVD seemed to induce a high early CR rate. The preliminary data showed that CR of PD-1 inhibitors alone was not ideal for the frontline treatment of cHL, and CR was significantly improved when combined with AVD. Subsequent randomized, controlled phase III studies are needed to verify whether PD-1 blockade in combination with AVD is better than ABVD.

### **ICPi pre- and post-allo-SCT**

PD-1 blockade has shown substantial therapeutic activity and an acceptable safety profile in r/r cHL patients who did not receive allogeneic stem cell transplantation (allo-SCT). However, PD-1 blockade in a murine allo-SCT model was shown to exacerbate graft-versus-host disease (GVHD) related mortality (41,42). Thus, most clinical studies have excluded cHL patients with failure of allo-SCT due to concerns about reactivating GVHD, and there are limited data regarding the using of ICPi following allo-SCT. Less is known about the safety and efficacy of ICPi used after allo-SCT. Unfortunately, treatment options are extremely limited for patients with failure of allo-SCT (donor lymphocyte infusion with or without chemotherapy, BV, bendamustine), with discouraging results in terms of

efficacy and tolerability, and ICPi are increasingly used off-label in this setting. Recently, only a few case reports have been presented regarding PD-1 blockade in r/r cHL patients after allo-SCT. A multicenter retrospective analysis of 31 lymphoma patients was conducted to better characterize the safety and activity of PD-1 inhibitors after allo-SCT (43). Twenty-nine patients had cHL and 27 had  $\geq 1$  salvage therapy post-allo-SCT and before starting PD-1 inhibitors treatment. Median follow-up was 428 d after the first dose of PD-1 inhibitors. ORR was 79% with CR rate of 50% in 30 cHL patients. Median PFS was 591 d, and median OS was not reached because 21 of 31 patients still were alive with 8 (26%) deaths related to new-onset GVHD. Seventeen (55%) patients developed GVHD after the initiation of PD-1 inhibitors (6 acute, 4 overlap, and 7 chronic), with the median time to onset was 16, 21 and 14 d, respectively. GVHD severity was grade III–IV acute or severe chronic in 9 patients. Only 2 of these 17 patients achieved CR to GVHD treatment, and 14 of 17 required  $\geq 2$  systemic therapies.

Another retrospective study reported the safety and efficacy of nivolumab in 20 cHL patients with failure of allo-SCT (44). ORR was 95% with CR rate of 42%. After a median follow-up of 370 d, 1-year PFS was 58.2% and OS was 78.7%. Among 13 patients still in response, 6 received a single dose of nivolumab and 7 remained on nivolumab. GVHD occurred in 6 patients (30%) after nivolumab initiation who then were managed by standard treatment for acute GVHD (aGVHD). All 6 patients had prior history of aGVHD. Two patients died as a result of GVHD, 1 of PD and 1 of complications related to a second allo-SCT. PD-1 blockade in relapsed cHL allo-SCT patients appears to produce promising activity but frequently complicated by rapid onset of severe and treatment-refractory GVHD. Further studies are required to clarify the safety and efficacy in this setting.

Although PD-1 blockade has demonstrated high activities in r/r cHL and prolong the survival with the median PFS of 34.1 months in patients achieving CR (8–17), most of patients will ultimately progress on ICPi therapy. Allo-SCT may offer a possibility of cure due to its graft-versus-tumor (GVT) efficacy. This raises the challenging question about how to manage patients when acquire remission to PD-1 blockade. One option is to proceed allo-SCT to prolong the remission or even be cured. In the CheckMate 205 trial, 44 patients proceeded to allo-SCT after a median of 13 nivolumab doses. Median time from last dose to allo-SCT was 49 d, with 12 patients

receiving systemic therapy between the last dose and allo-SCT. After median follow-up after allo-SCT of 5.5 months, 6-month cumulative incidences of transplant-related mortality (TRM) and disease progression were 13% and 7%, respectively. The aGVHD occurred in 21 patients, with 10 experiencing G3 or G4 aGVHD (four patients had unknown-grade aGVHD that was imputed to G4). The estimate 6-month PFS and OS were 82% and 87%, respectively (9).

A retrospective study analyzed 39 patients with lymphoma who received prior PD-1 inhibitors, at a median time of 62 d before allo-SCT. After a median follow-up of 12 months, among the 31 patients with cHL, 1-year OS and PFS were 90% and 74%, respectively, and 1-year cumulative incidences of relapse (CIR) and nonrelapse mortality (NRM) were 16% and 10%, respectively. The 1-year cumulative incidences of grade 2–4 and grade 3–4 aGVHD were 44% and 23%, respectively, whereas the 1-year incidence of chronic GVHD (cGVHD) was 41%. There were 4 TRM (1 from hepatic sinusoidal obstruction syndrome, 3 from early aGVHD). In addition, 7 patients developed a noninfectious febrile syndrome shortly after transplant requiring prolonged courses of steroids (45). The preliminary results show that allo-SCT after PD-1 blockade appears feasible with a low rate of relapse. However, there may be an increased risk of early immune toxicity, which could reflect long-lasting immune alterations triggered by prior PD-1 blockade. Longer follow-up is required to ascertain long-term outcomes, complications, and corresponding risk factors for early toxicity about post-allo-SCT after PD-1 blockade.

The largest multicenter retrospective analysis to date was reported at ASH meeting in 2019 (46). A total of 150 cHL patients were included in the study who underwent allo-SCT after PD-1 blockade after a median of 10 (range, 1–74) doses of nivolumab (n=118), pembrolizumab (n=31), or avelumab (n=1). The median therapy was 4 (range, 2–11) lines prior to PD-1 blockade, and 138 patients had failed BV and 111 ASCT. ORR to PD-1 blockade was 78% with CR rate of 41%. Median time from last dose of PD-1 blockade to allo-SCT was 80 (range, 17–756) d. At allo-SCT, 90 patients were in CR (60%), 45 in PR (30%), 5 in SD (3%), and 10 in PD (7%). With a median follow-up for survivors of 23.8 months post-allo-SCT, the 2-year OS and PFS were 79% and 65%, respectively, while the 2-year CIR and NRM were 21% and 14%, respectively. Twenty-seven patients have died, 3 due to disease and 24 to NRM, including aGVHD (n=7) and veno-occlusive disease (VOD,



n=2). The 6-month cumulative incidences of grade 2–4, grade 3–4 and grade 4 aGVHD were 39%, 16% and 8%, respectively. Hyperacute GVHD (onset  $\leq 14$  d after allo-SCT) occurred in 4% of patients and was fatal in two patients. The 2-year cumulative incidences of cGVHD was 45%. Neither receipt of  $>10$  doses (median) of PD-(L) 1 inhibitors nor undergoing allo-SCT  $\leq 80$  d (median) was associated with PFS or OS. However, patients with a shorter time to transplant ( $\leq 80$  d) appeared to have a higher risk of severe (grade 3–4) aGVHD (6 month CumInc 24% vs. 9%,  $P=0.006$ ). From this extended follow-up of a large international cohort, allo-SCT performed after PD-1 blockade is a feasible strategy associated with a prolonged PFS and a low CIR for this disease. However, larger studies are needed to confirm this finding. ICPI should be used in the experienced centers with caution before allo-SCT and be alert to the possible increased risk of GVHD and other immunologic complications. And now, consensus guidelines for the management of PD-1 blockade in the setting of allo-SCT for cHL provide clinicians the recommendations to guide treatment decisions until more definitive data are obtained (47).

### *ICPi and pseudo-progression*

Despite the promising activities of ICPI, some atypical response patterns including pseudo-progression have been observed during the treatment of ICPI and garnered the attention of physicians. Pseudo-progression is a phenomenon in which an initial increase in tumor size or in FDG uptake is observed or new lesions appear, followed by a decrease in tumor burden or FDG uptake. These changes can be confirmed by tumor biopsy or a continuous radiography scan. The exact mechanism of pseudo-progression is unclear, although it is known that enlarged lesions of pseudo-progression consist of infiltrating immune cells, hemorrhage, necrosis, and edematous tissue (48). When assessing response by conventional criteria [such as 2014 Lugano Criteria for Malignant Lymphoma (49)], this phenomenon may be misjudged as PD leading to premature discontinuation of ICPI treatment. So continuation of treatment beyond the first PD assessed by conventional criteria is permitted if the patients have no clinical deterioration and may benefit from continued treatment.

The extended follow-up of CheckMate 205 trial demonstrated the outcomes of the patients who were treated beyond progression (TBP) as defined by

conventional criteria (9,50). A total of 130 patients experienced PD, among whom 80 (62%) were TBP, receiving a median of 11 additional doses (range, 1–64) with median TBP duration of 5 months, and the other 50 patients (38%) discontinued without further treatment (non-TBP). In patients TBP vs. non-TBP, the cause of initial progression was new lesions in 50 (63%) vs. 23 (46%) patients, increased total tumor burden in 17 (21%) vs. 11 (22%) patients, and non-target lesion progression in 19 (24%) vs. 4 (8%) patients, respectively. About 55% of patients TBP (37/67 evaluable patients) had stable or reduced target lesion tumor burden. Median OS for patients TBP was not reached; 1- and 2-year OS was 94% and 87%, respectively. Median time to next treatment (TTNT) was 20 months for all patients TBP. Two (3%) patients who were TBP had treatment-related serious AEs: aspartate aminotransferase increase (n=1) and hypercalcemia (n=1). No deaths occurred in patients who were TBP. Patients who have stable performance status despite progression according to conventional criteria may derive continued clinical benefit from TBP. The precise recognition of pseudo-progression can prevent the early discontinuation of ICPI and ensure more benefit from the treatment.

### *Summary*

PD-1 inhibitors alone have demonstrated impressive activities in r/r cHL with failure of  $\geq 2$  lines chemotherapy or ASCT and have received the approval for this indication. PD-1 inhibitors in combination with new agents (such as BV, bendamustine, decitabine, CTLA-4 inhibitor) have been tested in studies to pursue higher remission and achieve more durable responses for r/r cHL. Other ICPI (such as PD-L1/CTLA-4 inhibitors) are still in earlier stages of clinical trials to make sure of their efficacy. There are also preliminary data that PD-1 inhibitors can be used earlier, such as in first-line salvage, or even frontline treatment by incorporation into chemotherapy or new agents. More clinical studies are required to figure out the exact roles of ICPI in the former setting to further improve the efficacy and reduce the long-term toxicity in the future.

### **ICPi in NHL**

NHL is a highly heterogeneous group of disease entities, and comprises multiple subtypes. Only a small number subtypes of diffuse large B-cell lymphoma (DLBCL) have



been shown to have genetic alteration of *9p24.1* including primary mediastinal B cell lymphoma (PMBL), gray zone lymphoma (GZL) with features intermediate between DLBCL and cHL, primary central nervous system lymphoma (PCNSL) and primary testicular lymphoma (PTL), which result in high expression of PD-L1 and PD-L2. EBV-associated lymphomas have a virally mediated overexpression of PD-L1 also making them sensitive to PD1 blockade. PD-L1 in general shows variable expressions on malignant T cells. Notable examples of T-NHL with PD-L1 hyper-expression are cutaneous T cell lymphoma (CTCL) and extranodal NK/T cell lymphoma (ENKTL) (25,51).

### **ICPi in PMBL**

PMBL is a rare aggressive B-cell lymphoma of putative thymic B-cell origin arising in the mediastinum, with distinctive clinical, pathologic, genotypic and molecular features. Although most of patients can be cured by frontline chemo-immunotherapy in combination with consolidative radiation, the prognosis of patients with r/r PMBL is generally poor, especially for patients who are ineligible for or failure after second-line ASCT with limited treatment options. PMBL harbors the frequent alteration of *9p24.1* and overexpression of PD-L1 and PD-L2, potentially making PMBL particularly susceptible to PD-1 blockade treatment.

One cohort of phase Ib KEYNOTE-013 study (52) enrolled patients with r/r PMBL who experienced relapse after ASCT or failed after at least 2-line chemotherapy and be ineligible for (or refused) ASCT. Pembrolizumab was given 10 mg/kg every 2 weeks in the first 10 patients, and a fixed dose of 200 mg every 3 weeks in subsequent 11 patients after a study amendment. ORR was 48% with CR rate of 33%. With a median follow-up of 29.1 months, median DOR was not reached, median PFS was 10.4 months with a median OS of 31.4 months (53). And 71% experienced TRAE of any grade with 24% of grade 3–4. The subsequent phase II KEYNOTE-170 study (53) was launched to further confirm the results of KEYNOTE-013 and to allow biomarker analyses. Fifty-three patients with r/r PMBL were treated with pembrolizumab 200 mg q3w. The ORR was 45% and CR was 21% by Lugano criteria. After a median follow-up of 12.5 months, median PFS was 5.5 months with median OS not reached. TRAE of any grade occurred in 57% of patients with 23% of grade 3–4, the most common AE was neutropenia, which occurred in

13% of patients. Among 42 evaluable patients, the magnitude of the *9p24* gene abnormality was associated with PD-L1 expression, which was itself significantly associated with PFS. Based on the data of KEYNOTE-013 and KEYNOTE-170 studies, pembrolizumab was approved by US FDA in June 2018 for r/r PMBL patients who failed after  $\geq 2$  prior line treatment.

Like cHL RS cells, PMBL tumor cells also express CD30, albeit at relatively lower intensities and more heterogeneous levels (54,55). In r/r PMBL, BV monotherapy in 15 patients demonstrated an extremely low activity of 13% ORR without any evidence of CR, and with DOR of 3–4 months (56). Nivolumab combined with BV has showed CR rate of 61%–67% in r/r cHL (21,29), suggesting potential synergy between these two agents. Given the common features of PMBL and cHL, the phase II CheckMate 436 study was to evaluate whether the combination of nivolumab and BV was safe and synergistically effective in patients with r/r PMBL (57). Thirty patients were treated and evaluable. At a median follow-up of 11.1 months, ORR was 70%, with a CR rate of 43% per IRC. Median DOR, PFS, and OS have not been reached, and the 6-month PFS was 63.5%. Eleven responders had consolidation with ASCT (n=5) or allo-SCT (n=6). About 83% of patients experienced TRAE, and 53% of patients had grade 3–4 TRAE, and the most common was neutropenia (30%), thrombocytopenia (10%), and peripheral neuropathy (10%). There were no treatment-related deaths. The preliminary results showed that the combination of nivolumab and BV may be synergistic and is highly active in r/r PMBL, serving as a potential bridge to other consolidative therapies of curative intent, and need to be confirmed in further studies.

### **ICPi in DLBCL**

Patients with r/r DLBCL who failed ASCT or were ineligible for ASCT have limited treatment option, and the prognosis is poor. Although CAR-T cell therapy has shown significant efficacy and improved the survival, it does not have the approval in China and is expensive. A phase I study of nivolumab monotherapy has first demonstrated that the ORR was 36% with 18% CR in 11 r/r DLBCL patients (58). The preliminary results led to a phase II study, which evaluated the efficacy and safety of nivolumab monotherapy in 121 patients with r/r DLBCL who were ineligible for ASCT (n=34) or who had relapse after ASCT (n=87) (59). After a median follow-up of 9 months in the

ASCT-failed cohort and 6 months in the ASCT-ineligible cohort, ORR were 10% and 3% per IRC, and median DOR were 11 and 8 months, respectively. Median PFS and OS were 1.9 and 12.2 months in the ASCT-failed cohort, and 1.4 and 5.8 months in the ASCT-ineligible cohort, respectively. The common TRAEs included nausea (17%), fatigue (17%), and diarrhea (10%), which were generally not severe (majority grade 1–2). TRAE of grade 3 and 4 occurred in 24% of patients. The most common grade 3–4 IRAEs were nephritis and renal dysfunction (4%), hepatitis and hepatic dysfunction (3%), diarrhea (3%), and rash (2%). Of all evaluable samples for 9p24.1 analysis, 16% exhibited low-level copy gain and 3% had amplification. Membranous PD-L1 expression was only detected in four (9%) of 46 evaluable cases. Since nivolumab monotherapy showed a low efficacy in this unselected patient, it may be useful to evaluate the approach in selective DLBCL subtype with overexpression of PD-L1 and by combination therapy.

PCNSL and PTL are rare extra-nodal large B-cell lymphomas. PCNSLs failure of high-dose methotrexate (HD-MTX) based chemotherapy or ASCT have limited treatment options. PTLs typically occur in elderly men and frequently relapse in extra-nodal sites, including the central nervous system (CNS). Treatment options are also limited for CNS recurrences of PTL. Therefore, the prognosis is poor and there are still unmet treatment needs. PCNSLs and PTLs exhibit frequent 9p24.1 alteration and associated over-expression of PD-L1 and PD-L2. Given the efficacy of PD-1 blockade in cHL and PMBL, nivolumab was also tested in 4 patients with r/r PCNSL and 1 patient with CNS relapse of PTL. Patients with PCNSL had received prior treatments, including HD-MTX-based regimens, pemetrexed, HD-cytarabine, and whole brain radiotherapy (WBRT). Patients with CNS relapse of PTL was previously treated with HD-MTX followed by thiotepa-based conditioning regimen and subsequent ASCT. All 5 patients had objective responses, including 4 CR and 1 PR. All patients were alive at a median follow-up of 17 months, and 3 patients remain progression-free at 13+ to 17+ months (60). Based on the results from this small case series, a multi-center phase II CheckMate 647 study is ongoing to explore nivolumab in r/r PCNSL and PTL patients (NCT02857426).

Maintenance therapy has proven efficacy in indolent lymphoma like follicular lymphoma, yet its role in DLBCL is an area of ongoing investigation. Studies of maintenance therapy with rituximab, enzastaurin or everolimus showed

no survival benefit following frontline chemo-immunotherapy induction (61). Pidilizumab, an anti-PD-1 humanized IgG1 mAb, was investigated in a phase II study to evaluate the outcome with DLBCL early after ASCT given as maintenance therapy. Sixty-six eligible patients, who received CT scan to exclude disease progression after ASCT, were enrolled and treated with pidilizumab 1.5 mg/kg every 6 weeks for three cycles, beginning 30–90 d from ASCT. Sixty patients completed all 3 cycles. Toxicities were mild. The 16-month PFS and OS was 72% and 85%, respectively. Among the 24 high-risk patients who remained positive PET scan after salvage chemotherapy (no CR before ASCT), the 16-month PFS was 70%. Among the 35 patients with measurable disease after ASCT, ORR was 51% with CR rate of 34% by CT assessment after pidilizumab treatment (62). Recently a phase II study is initiated to evaluate the outcome of nivolumab maintenance for 2 years in patients with high-risk aggressive B cell lymphoma acquiring CR after frontline immuno-chemotherapy (NCT03569696).

For the past two decades, R-CHOP has remained the standard choice for newly diagnosed DLBCL. Recently, neoagents, such as enzastaurin (63), bortezomib (64), ibrutinib (65) and lenalidomide (66), combined with R-CHOP (R-CHOP+X) were tried in high-risk previous untreated DLBCL, but none of which has shown a definitive benefit in activated B-cell (ABC) subgroup. Given the promising efficacy of PD-1 blockade in r/r cHL, the incorporation of ICPi in frontline therapy in DLBCL has also been explored. Durvalumab, as an anti-PD-L1 mAb, in combination with R-CHOP was investigated in previously untreated, high/high-intermediate risk DLBCL (IPI $\geq$ 3/NCCN-IPI $\geq$ 4) in a phase II study. Forty-three patients were treated with durvalumab + R-CHOP for 6–8 cycles followed by durvalumab consolidation up to 12 months from start of induction. As data cutoff at Aug 2, 2018, 30 patients had completed induction therapy, and 19 were ongoing. CR post-induction was 54%; and 68% of patients continued to consolidation therapy and were progression-free at 12 months. Grade 3/4 AEs occurred in 84% of patients (67). The role of PD-1 blockade combined with R-CHOP in untreated DLBCL needs to be verified in randomized, controlled phase III studies.

### ***ICPi in peripheral T cell lymphoma (PTCL)***

ENKTL is an EBV-associated lymphoma and is the most common subtype of PTCL in China (68). Patients with r/r

ENKTL failing L-asparaginase have no effective salvage treatment and the prognosis is extremely poor with median OS less than 6 months. The increased expression of PD-L1 induced by EBV infection is a potential mechanism for ENKTL to avert immune surveillance, which suggesting PD-1 blockade may be effective in ENKTL. Seven patients with ENKTL failing L-asparaginase regimens were treated with pembrolizumab. All patients responded with 5 CR and 2 PR. After a median of 6 months, all five CR patients were still in remission (69). A multicenter, single-arm, phase II study (ORIENT-4) were initiated to investigate the efficacy and safety of sintilimab monotherapy in patients with r/r ENKTL failure of L-asparaginase in China. Twenty-eight patients were enrolled with 68% stage IV and 89.3% ECOG $\geq$ 1. Median duration of therapy was 14.04 months. ORR was 68%, and 1-year OS was 82.1%. Most TRAEs were G1–2 (67.9%) and no patients discontinued treatment due to AEs. Severe adverse events occurred in 21.4% of patients and none was related to sintilimab (70). CS1001, a full-length, fully human IgG4 anti-PD-L1 mAb, was also evaluated in patients with r/r ENKTL after failing prior asparaginase-based chemotherapy. As of June 17, 2019, 29 patients were enrolled and received CS1001 of 1,200 mg IV every 3 weeks for up to 2 years, until disease progression or intolerance, with 75.9% of stage IV. The median duration of treatment was 11.7 weeks. After median follow-up of 5.55 months, ORR was 44% with CR rate of 36% and median DOR was not achieved. All CR patients were still in remission. TRAEs occurred in 72.4% of patients, and the common TRAE were pyrexia (20.7%), increased thyroid stimulating hormone (13.8%), leukopenia (13.8%), and rash (10.3%). About 10.3% patients experienced TRAEs of grade  $\geq$ 3 (71). The preliminary data support further exploration of PD-1 blockade in r/r ENKTL, and the combination strategy may help to further improve the outcomes. Given the prognosis of advanced ENKTL is still poor even in the era of asparaginase, an ongoing prospective phase II study is evaluating the combination of PD-1 inhibitor with P-GEMOX for newly diagnosed advanced ENKTL (NCT04127227).

PTCL are a heterogeneous group originating from mature T-cell. They have a worse prognosis for most subtypes compared with B-NHL and are incurable. The treatment options for r/r PTCL remains limited and therefore novel effective treatment is urgently needed for PTCL. PD-1 blockade was also explored in PTCL other than ENKTL. An investigator-initiated phase II study of

nivolumab monotherapy for r/r PTCL was conducted and enrolled 12 patients, who received nivolumab of 240 mg IV every 2 weeks for 8 cycles then 480 mg IV every 4 weeks starting cycle 9. The subtype included angio-immunoblastic T-cell lymphoma (AITL, 6/12), PTCL, not otherwise specified (PTCL NOS, 3/12), and ALK negative anaplastic large cell lymphoma [ALK(-)ALCL, 1/12]. About 50% patients had received a prior ASCT. The ORR was 33% (4/12) with 2 CR and 2 PR. The median DOR, PFS and OS was 3.6, 1.9 and 7.9 months, respectively. However, hyper-progression (defined as dramatic progression within 1 cycle of treatment) occurred in 4 patients (72). Due to the high incidence of hyper-progression, the moderate activity, and short DOR, the study was halted.

Given the mild activity of PD-1 inhibitors alone in PTCL, combination therapy with target agents was investigated in this setting. Pembrolizumab in combination with romidepsin, a histone deacetylase inhibitor (HDACi) that is FDA approved for r/r PTCL and cutaneous T-cell lymphoma (CTCL), was evaluated in a phase I/II study with r/r PTCL (NCT03278782). Fifteen patients were evaluable, with ORR of 44% and CR rate of 20%. After a median follow-up of 6 months, all 3 patients with CR remained in remission >10 months. Nausea and vomiting were the most common AE (grade 1/2). Two patients experienced hyper-progression within the first 10 days after the treatment (73). Apatinib, a selective VEGFR2 tyrosine kinase inhibitor, is approved for the treatment of advanced gastric cancer in China, and its incorporation into PD-1 inhibitor has shown manageable toxicity and encouraging activity in advanced hepatocellular carcinoma (74). Since Oct 2018, a phase II study has been conducted in Peking University Cancer Hospital to evaluate Camrelizumab combined with apatinib in r/r PTCL (NCT03701022), and the preliminary result showed that 14 patients were enrolled with median prior treatment of 3 lines (1–6), including 4 PTCL NOS, 4 AITL, 2 ALK(-)ALCL and 4 ENKTL. ORR was 36.4% with CR rate of 9.1%. Two ALK(-)ALCL patients both responded to treatment (1 CR, 1 PR) and two of the three ENKTL patients achieved PR. Based on the results, the study is ongoing in multicenter. These findings reflect the distinct biologic features of PTCL, which should be considered in the study design. Further studies are developed by using ICPi in combination (rather than monotherapy) and the use of biomarkers to better predict the responders.

### Summary

PD-1 blockade has shown the preliminary efficacy both in r/r PMBL failing  $\geq 2$ -line chemotherapy or ASCT and in r/r ENKTL after previous L-asparaginase-based regimen in several phase II studies which need to be confirmed in more larger sample studies. However, except for PMBL and ENKTL, ICPI are less effective in r/r NHL than in r/r cHL, which may be attributed to the highly biological heterogeneity and clinical complexity of NHL. Based on further understanding of the biological features of each subtype, the selection of right subtype may help to improve the efficacy. What's more, choosing the right novel agents in combination with ICPI may help to extend the benefit of PD-1 blockade across the different subtype of NHL.

### Conclusions

Immunotherapy, including ICPI, has become an extremely active area in scientific and clinical study of lymphoma. PD-1 blockade by ICPI such as nivolumab, pembrolizumab, tislelizumab, camrelizumab and sintilimab, has demonstrated significant activity and superior safety, and prolonged the survival in r/r cHL. In fact, there is no evidence to support any differences among these PD-1 inhibitor products in terms of efficacy and toxicity in r/r cHL. PD-1 blockade in combined therapy, especially used in the earlier disease course (eg. first salvage, maintenance, and frontline treatment) remains in investigation, and has shown promising outcomes. Unfortunately, except for PMBL and ENKTL, PD-1 inhibitors do not perform well in the other subtypes of NHL, mostly attributing to high biological heterogeneity of NHL. Optimizing the use of ICPI in lymphoma requires further understanding of their different biological features and the selection of optimal combination strategies for different subtypes.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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