Checkpoint Inhibition in Lymphoma

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Abstract: Checkpoint inhibition improves surveillance by the immune system and therefore outcomes in some lymphoma subtypes. In this review, we examine the available evidence regarding checkpoint inhibition in lymphoma by line of therapy. Although most published studies are in the setting of relapsed/refractory disease, several ongoing trials are looking at therapy in the upfront and second-line settings. Nivolumab and pembrolizumab have been approved for patients with relapsed or refractory Hodgkin lymphoma, whereas other programmed death 1 and programmed death ligand 1 monoclonal antibodies remain under investigation as single agents or in combination. Strategies to exploit various targets along these pathways with new forms of therapy or with traditional therapies are being developed. Amplification of chromosome 9p23-24 and other biomarkers are important correlative endpoints in several studies that could further the personalization of therapy. Immune-related adverse events are frequent, and vigilance is required for their diagnosis and treatment. The use of checkpoint inhibitors before and after allogeneic transplant can yield impressive results but can also increase the risk for graft-versus-host disease, so that mitigation strategies are needed. Overall, these agents have achieved excellent response rates with durable remissions in many lymphoma subtypes. The results of ongoing trials will yield additional options for patients.

Introduction

Tumors can evade detection and the immune response by expressing and upregulating negative costimulatory molecules. Recognition of this fact has led to various efforts to release the immune system and allow an increase in T-cell–driven antitumor activity. Inhibitory pathways, or checkpoints, are essential to normal cell function; they regulate the response to antigen exposure and prevent unbridled autoimmunity. Tumor cells overexpress the ligands of the checkpoint receptors, thereby exhausting T cells.[1-4] Antibody therapy directed against these checkpoints can revitalize the immune system, and remarkable results have been achieved in patients with heavily pretreated cancers.

There are 2 main checkpoint pathways that have been under investigation. Programmed death protein 1 (PD-1) is an inhibitory receptor expressed by activated B cells, T cells, and natural killer (NK) cells, as well as some myeloid cells. In times of chronic antigen exposure, PD-1 and its ligands, PD-L1 and PD-L2, control immune activity by causing a transient downregulation of T-cell function. The fully human immunoglobulin G4 (IgG4) monoclonal antibody nivolumab (Opdivo, Bristol-Myers Squibb) and the humanized IgG4-κ monoclonal antibody pembrolizumab (Keytruda, Merck) target PD-1 to reverse the inhibitory signal and increase antitumor activity. Similarly, monoclonal antibodies have been developed against PD-L1, including the humanized IgG1 agent atezolizumab (Tecentriq, Genentech) and the fully human IgG1 agents avelumab (Bavencio, EMD Serono/ Pfizer) and durvalumab (Imfinzi, AstraZeneca).

In normal cells, T-cell activation also leads to the upregulation of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) on the plasma membrane. This process can impair T-cell function by several mechanisms, including the induction of T-cell arrest and blockage of costimulation via competition with CD28 for the B7 ligands CD80 and CD86 on antigen-presenting cells.[5] Ipilimumab (Yervoy, Bristol-Myers Squibb) is a fully human IgG1 monoclonal antibody against CTLA-4 that stimulates the immune system to enhance T-cell–dependent cellular cytotoxicity.

In May 2016, the US Food and Drug Administration (FDA) granted accelerated approval to nivolumab for the treatment of classic Hodgkin lymphoma (HL) following relapse after autologous hematopoietic stem cell transplant (AHCT) and post-transplant brentuximab vedotin (BV; Adcetris, Seattle Genetics). In March 2017, the FDA also granted accelerated approval to pembrolizumab for the treatment of relapsed/refractory classic HL after 3 or more prior lines of therapy. Therefore, great interest is being shown in checkpoint inhibition (CPI) for the treatment of lymphoma, although many of the data are preliminary.[5-14] This review article is organized according to the timing of CPI in the disease course. Data published or presented at annual meetings through June 2017 are included, and ongoing trials and issues to be considered with the use of these agents are discussed.

First-Line Therapy

Currently, no data regarding the use of CPI in lymphoma in the upfront setting have been published. However, several trials are ongoing. Nivolumab is being studied as monotherapy for HL in CheckMate 205 (NCT02181738). In patients older than 60 years, nivolumab is being studied in combination with BV, an antibody-drug conjugate that targets CD30 (NCT02758717). It is also being combined with doxorubicin, vinblastine, and dacarbazine (AVD) for patients with early-stage unfavorable HL (NCT03004833); following ABVD (same 3 drugs plus bleomycin) for high-risk patients with advanced-stage disease who are younger than 60 years; and following AVD for patients with any-stage disease who are 60 years of age or older (NCT03033914).

For high-risk diffuse large B-cell lymphoma (DLBCL), a phase 2 study is combining durvalumab, a human IgG1 monoclonal antibody against PD-L1, either with rituximab (Rituxan, Genentech/Biogen Idec), cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or with R-CHOP plus lenalidomide (Revlimid, Celgene), depending on the cell of origin. High risk is defined as Ann Arbor stage III or IV or Ann Arbor stage II with bulky disease (at least 7.0 cm), in addition to an intermediate-high or high International Prognostic Index (IPI) score of at least 3 or a National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) score of at least 4 (NCT03003520). Pembrolizumab is also being studied in combination with R-CHOP for DLBCL and grade 3b follicular lymphoma (FL; NCT02541565). Pidilizumab is a humanized IgG1 monoclonal antibody against PD-1, although its exact mechanism of action is unclear, and it may function more as an activator of the innate immune system. It is currently under investigation as maintenance therapy to decrease relapse, with 3 doses given after induction for DLBCL (NCT02530125). Finally, Memorial Sloan Kettering Cancer Center is participating in a study of atezolizumab, a humanized IgG1 monoclonal antibody against PD-L1, in combination with R-CHOP for DLBCL and in combination with obinutuzumab (Gazyva, Genentech) and bendamustine (Treanda, Bendeka; Teva) or with obinutuzumab and CHOP for FL (NCT02596971).

Early Relapsed Disease

Pidilizumab has been tested in combination with the anti-CD20 monoclonal antibody rituximab for relapsed FL after 1 to 4 lines of therapy.[15] Although FL is not thought to respond to checkpoint blockade owing to lack of PD-L1 expression on tumor cells, the overall response rate (ORR) was 66%, with a complete remission (CR) rate of 52% and a partial remission (PR) rate of 14%. No immune-mediated or treatment-related grade 3 or 4 adverse events (AEs) were seen (Table 1).

Similarly, Nastoupil and colleagues presented early results of a phase 2 trial combining pembrolizumab and rituximab in 15 patients with relapsed FL.[16] After a median of 1 prior line of treatment (range, 1-4), the ORR was 80% (60% of patients had a CR). High-grade

Table 1. Results From Selected Studies of Checkpoint Inhibition for Lymphoma

Drug(s)	Phase	N	Lymphoma Type (n)	Median OS	Median PFS	Response Rate, ORR/CR/PR/SD/PD	Median DoR	Details
Early relapse								
Pidilizumab + rituximab[15]	2	32	FL (32)	NR	18.8 mo	66%/52%/14%	20.2 mo	NCT00904722
Pembrolizumab + rituximab[16]	2	15	FL (15)	NR	NR	80%/60%	NR	NCT02446457
Nivolumab + brentuximab vedotin[17]	1/2	62	HL (62)	NA	NA	85%/64%	NA	NCT02572167
Nivolumab + ibrutinib[18]	2	9	CLL (5), RT (4)	NA	NA	CLL: 60%/0%/60% RT: 50%/25%/25%/0/25%	NA	NCT02420912
Maintenance after AHCT								
Pidilizumab[19]	2	66	De novo DLBCL (49), Transformed DLBCL (13), PMBL (4)	84% at 16 mo	72% at 16 mo	51%/34%/17%/37%	16 mo	NCT00532259
Later relapse								
Ipilimumab[20]	1	18	FL (14), DLBCL (3), MCL (1)	NA	NA	11%/5.6%/5.6%	NA	NCT00089076
Pidilizumab[21]	1	8	CLL (3), DLBCL (2), FL (1), ALCL (1), HL (1)	NA	NA	5%/5%/—/33%	NA	
Nivolumab[22,23]	1b	23	HL (23): 78% after AHCT/BV, 83% XRT	NR	86% at 6 mo	87%/17%/70%/13%	NA	CheckMate 039, NCT01592370
Nivolumab[24]	1b	54	DLBCL (11), FL (10), Other B-cell NHL (10), MF (13) PTCL (5), Other T-cell NHL (5)	NA	NA	DLBCL: 36%/10% FL: 40%/18% MF: 15%/0% PTCL: 40%/0%	6-81.6+ wk	CheckMate 039, NCT01592370
Nivolumab + ipilimumab[25]	1	57	HL (31), DLBCL (10), FL (5), CTCL (7), PTCL (4)	HL: NR B-cell NHL: 2.9 mo T-cell NHL: 13.2 mo	HL: NR B-cell NHL: 1.5 mo T-cell NHL: 2 mo	HL: 74%/19%/55%/10% B-cell NHL: 20%/0%/20%/7% T-cell NHL: 9%/0%/9%/36%	HL: NR B-cell NHL: NR T-cell NHL: NR	Checkmate 039, NCT01592370
Nivolumab[26,28]	2	80	HL (80), 100% after AHCT and BV, 75% XRT	94.9% at 12 mo	14.8 mo, 54.6% at 12 mo	68%/8%/60%	13.1 mo	Checkmate 205, NCT02181738
Nivolumab + brentuximab[29]	1	10	HL (10)	NA	NA	100%/62.5%	NA	E4412, NCT01896999

(Table continued on next page)

Table 1. *(Continued)* Results From Selected Studies of Checkpoint Inhibition for Lymphoma

Drug(s)	Phase	N	Lymphoma Type (n)	Median OS	Median PFS	Response Rate, ORR/CR/PR/SD/PD	Median DoR	Details
Later relapse *(Continued)*								
Pembroli-zumab[31]	1b	31	HL (31), 100% after BV, 71% AHCT	NR, 90% at 1 y	11 mo, 46% at 1 y	65%/16%/48%/23%/13%	NA	KEYNOTE-013, NCT01953692
Pembroli-zumab[32]	2	210	HL (210), 61% after AHCT, 83% BV	NR, 99.5% at 6 mo	NR, 72.4% at 6 mo	69%/22%/47%/15%/14%	NR	KEYNOTE-087, NCT02453594
Pembroli-zumab[33]	1b	18	PMBL (18), 33% after AHCT, 61% XRT	NR	NR	41%/12%/29%/35%	NR	KEYNOTE-013, NCT01953692
Pembroli-zumab[34]	2	33	PMBL (33)	NA	NA	35%/13%/22%/17%/22%	NA	KEYNOTE-170, NCT02576990
Pembroli-zumab[35]	2	25	CLL (16), RT (9), 48% del17p	10.7 mo, CLL 59%, RT 73% at 6 mo	NA	CLL: 0%/0%/0%/19%/81% RT: 44%/11%/33%/33%/22%	NA	MC1485, NCT02332980
Pembroli-zumab[36]	2	24	MF/SS (24)	NR	NR, 69% at 1 y	38%/4%/33%/38%	89% ongoing at 32 wk	NCT02243579
Pembroli-zumab[37]	Retro	7	NK/T-cell (7)	NA	NA	100%/71%/29%	NA	
Avelumab[38]	1b	23	HL (23), Post AHCT (5)	NA	NA	47.8%/4%/43% Post AHCT: 20%/0%/20%	NA	NCT02603419
PD-1 + decitabine[39]	1	8	NHL (7), HL (1)	NA	NA	38%/13%/25%/63%	NA	NCT02961101
Pembrolizumab or nivolumab + azacitidine[40]	Retro	6	HL (6)	NA	NR	83%/83%	NA	Azacitidine on NCT01998035
After allogeneic transplant								
Avelumab[38]	1b	8	HL (8)	NA	NA	75%/12.5%/62.5%	NA	NCT02603419
Ipilimumab[43]	1	20	HL (14), NHL (6)	NA	NA	15%/10%/5%	NA	NCI protocol ID P6082, relapse after allo-HCT
Ipilimumab[44]	1/1b	11	HL (7), NHL (4)	NA	NA	9%/0%/9%/36%	NA	NCT01822509, relapse after allo-HCT
Nivolumab[45]	Retro	20	HL (20)	78.7% at 1 y	58.2% at 1 y	95%/42%/52%	NA	Relapse after allo-HCT
Nivolumab or pembroli-zumab[46]	Retro	31	HL (29), FL (1), FL+HL (1)	NR	591 d	77%/48%/26%/10%/13%	NA	Relapse after allo-HCT

AHCT, autologous hematopoietic stem cell transplant; ALCL, anaplastic large cell lymphoma; allo, allogeneic hematopoietic stem cell transplant; BV, brentuximab vedotin; CLL, chronic lymphocytic leukemia; CR, complete remission; CTCL, cutaneous T-cell lymphoma; d, days; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; FL, follicular lymphoma; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; MF, mycosis fungoides; mo, months; NA, not available; NCI, National Cancer Institute; NHL, non-Hodgkin lymphoma; NK, natural killer; NR, not reached; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PMBL, primary mediastinal B-cell lymphoma; PR, partial remission; PTCL, peripheral T-cell lymphoma; retro, retrospective study; RT, Richter transformation; SD, stable disease; SS, Sézary syndrome; wk, weeks; XRT, radiation therapy; y, years.

toxicities, which were rare, included nausea and infusion reaction (each in 2 patients) and aseptic meningitis and pneumonia (each in 1 patient). Immune-related (ir) AEs included grade 2 diarrhea (n=2), grade 2 pneumonitis (n=1), and grade 2 skin rash (n=1).

Nivolumab has been combined with BV in a phase 1/2 study of relapsed/refractory classic HL after frontline therapy.[17] Interim results from the 62 patients who have completed treatment demonstrated an 85% ORR (with a 64% CR rate) and 29 patients proceeding to AHCT, with no unusual post-transplant toxicities. Infusion reactions were frequent, requiring premedication. IrAEs occurred in 72% of patients, with grade 3 or higher AEs (grade 4 pneumonitis, grade 3 diarrhea, and grade 3 transaminitis) occurring in 7%. Grade 3 hypercalcemia and acute kidney injury developed in 1 patient. The combination of nivolumab and BV is also being studied in the ongoing CheckMate 436 study for CD30-positive relapsed/refractory DLBCL, primary mediastinal B-cell lymphoma (PMBL), mediastinal gray zone lymphoma, peripheral T-cell lymphoma (excluding anaplastic large cell lymphoma), or cutaneous T-cell lymphomas (mycosis fungoides/Sézary syndrome) (NCT02581631).

In an ongoing phase 2 study, nivolumab is being investigated in combination with the Bruton tyrosine kinase inhibitor ibrutinib (Imbruvica, Pharmacyclics/Janssen) for relapsed/refractory chronic lymphocytic leukemia (CLL), untreated Richter transformation, or CLL with a PR after at least 9 months of ibrutinib therapy.[18] Preliminary results showed that of 5 patients with CLL and a median of 1 prior line of therapy, 3 achieved a PR. Of the 3 patients who already had achieved a PR on the combination, all had stable disease. Of the 4 patients with untreated Richter transformation, 1 had a CR, 1 had a PR, and 1 had a transient response before disease progression.

Maintenance Therapy After Autologous Hematopoietic Stem Cell Transplant

CPI is an attractive maintenance strategy because one can intervene in cases of immune tolerance against changed tumor antigens, and the post-AHCT setting presents an ideal environment owing to the gradual immune reconstitution with lymphocyte recovery. Pidilizumab has been tested as a maintenance therapy after AHCT for DLBCL, PMBL, or transformed indolent B-cell NHL in a multicenter phase 2 trial.[19] Patients received 1.5 mg/kg every 42 days for 3 cycles beginning 30 to 90 days after AHCT. Among the 35 patients with measurable disease after AHCT, 34% achieved a CR and 17% achieved a PR. Grade 3 or 4 AEs included neutropenia (19%) and thrombocytopenia (8%). One patient died of disseminated herpes zoster 10 months after the third dose, but

this infection was considered unrelated to the treatment. At 16 months, the median overall survival (OS) rate was 84% and the median progression-free survival (PFS) rate was 72%. Although this study is believed to be the first showing a benefit of PD-1 blockade, more recently it has been thought that pidilizumab may work through other pathways.

A multicenter study evaluating pembrolizumab as maintenance therapy after AHCT for HL, DLBCL, or T-cell non-Hodgkin lymphoma (NHL) is ongoing (NCT02362997). In addition, Memorial Sloan Kettering Cancer Center will be conducting a phase 1/2 study of the PD-L1 inhibitor durvalumab with lenalidomide as maintenance after AHCT for aggressive B-cell lymphomas.

Later Relapsed Disease

The earliest trial of CPI for relapsed or refractory NHL tested ipilimumab in a phase 1 dose escalation study. Dose level 1 consisted of 3 mg/kg for the first month, then 1 mg/kg monthly for the next 3 months; dose level 2 consisted of 3 mg/kg monthly for all 4 months.[20] Although the ORR was low (11%), with 1 CR in a patient with DLBCL and 1 PR in a patient with FL, the remissions were durable: 31 and 19 months, respectively. Grade 3 adverse events were minimal; diarrhea developed in 5 patients, fatigue in 1, glucose intolerance in 1, and neutropenia in 1 patient.

Pidilizumab has also been studied for relapsed or refractory NHL, again with a low ORR, likely because of the lower rate of PD-1 expression in NHL than in HL tumors. In a phase 1 study of a variety of hematologic malignancies, 8 patients with NHL were treated with escalating doses between 0.2 and 6 mg/kg, and a CR occurred in only 1 patient, who had FL.[21]

Over the last few years, the 2 monoclonal antibodies against PD-1—nivolumab and pembrolizumab—have shown more promising results. In the phase 1b CheckMate 039 study, nivolumab was tested in patients who had a variety of relapsed or refractory lymphomas and a median of 3 prior therapies, including some after autologous transplant. In the HL cohort, 18 of 23 patients had had a relapse after autologous transplant and BV; the 6-month PFS rate was 86% and the ORR was 87% (17% CR and 70% PR rates), with responses occurring within 16 weeks after the start of therapy in 75% of patients.[22,23] Grade 3 toxicities were rare: lymphopenia in 1 patient, elevated lipase in 1, stomatitis in 1, myelodysplastic syndrome in 1, and pancreatitis in 1 patient. Grade 1 or 2 hypothyroidism was seen in 9% of patients. Objective response rates were 40%, 36%, 15%, and 40% among 10 patients with FL, 11 patients with DLBCL, 13 patients with mycosis fungoides, and 5 patients with peripheral T-cell

lymphoma, respectively.[24] High-grade toxicities again were rare and included pneumonitis, anemia, and leukopenia, each occurring in 4% of patients. A subsequent cohort was treated with nivolumab plus ipilimumab, with an ORR of 74% for HL, 20% for B-cell NHL, and 9% for T-cell NHL, although the CR rates were low.[25]

In Checkmate 205, a multicenter phase 2 study in which nivolumab was administered at 3 mg/kg every 2 weeks for HL relapsed after AHCT and BV, 58% of patients achieved a PR and 7% of patients achieved a CR, for an ORR of 66.3%.[26] The median time to response was 2.1 months (interquartile range, 1.9-3 months), and the median duration of response was 7.8 months (95% CI, 6.6-not reached). As in the phase 1 studies, grade 3 or higher AEs were rare, with 5% of patients having neutropenia or elevated lipase levels, 1 pneumonitis, and 1 autoimmune hepatitis. Grade 1 or 2 infusion reactions were seen in 20% of patients. Multiorgan failure related to a new Epstein-Barr virus (EBV)–positive T-cell lymphoma that was not thought to be related to nivolumab resulted in death in 1 patient. Quality of life, measured by the EuroQOL 5-dimension questionnaire (EQ-5D) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), improved during nivolumab treatment.[27] Updated results with a minimum of 12 months of follow-up showed an ORR of 68%, a median PFS of 14.8 months, with a 1-year PFS rate of 54.6% and a 1-year OS rate of 94.9%.[28]

The combination of nivolumab and BV with or without ipilimumab for patients with relapsed or refractory HL is being studied in the ongoing phase 1 E4421 study from the ECOG-ACRIN Cancer Research Group.[29] Preliminary data from the nivolumab and BV arms of the study demonstrate a 100% ORR with a 62.5% CR rate in a heavily pretreated population. In the second-dose cohort, 1 patient had a dose-limiting toxicity of grade 3 pneumonitis and typhlitis, which resolved. In addition, 2 other grade 3 toxicities—rash and pruritus—occurred, but no grade 4 or 5 toxicities have been seen.

Nivolumab also showed early promising results for multiply relapsed primary central nervous system (CNS) lymphoma and primary testicular lymphoma with CNS involvement. Of the 5 patients treated, 4 achieved a CR and 1 achieved a PR.[30] These results prompted an ongoing multicenter phase 2 trial (NCT02857426). Other ongoing trials with nivolumab include CheckMate 139 (NCT02038933).

Pembrolizumab was initially evaluated in the phase 1b KEYNOTE-013 study, in which patients with classic HL that had progressed after BV received the agent at 10 mg/kg every 2 weeks until disease progression.[31] The ORR was 65%, with a 16% CR rate and a 48% PR rate;

the ORR was 73% in the 22 of the 31 patients who had had a prior AHCT. Most of the responses lasted more than 24 weeks. Grade 3 AEs occurred in 16% of patients and included aspartate transaminase increase, alanine transaminase increase, axillary pain, back pain, colitis, joint swelling, and nephrotic syndrome, each seen in 1 patient. Grade 1 or 2 hypothyroidism was seen in 16%, thyroiditis in 6%, and pneumonitis in 10%. The subsequent multicenter phase 2 study, KEYNOTE-087, used a flat dose of 200 mg once every 3 weeks for up to 24 months because no exposure-response relationship had been observed for doses between 2 and 10 mg/kg across trials.[32] Patients received a median of 4 lines of therapy and were divided into 3 cohorts: progression after AHCT and BV (n=69), ineligible for AHCT owing to chemoresistant disease after salvage chemotherapy and BV (n=81), and progression after AHCT but no BV after transplant (n=60, 41% exposed pre-AHCT). The ORR for all patients was 69%, with a 22.4% CR rate and a 47% PR rate. The ORRs by cohort were 73.9%, 64.2%, and 70%, respectively. Grade 3 or higher AEs again were rare, with 5 patients having neutropenia and pyrexia, cough, fatigue, diarrhea, vomiting, hypothyroidism, arthralgias, and dyspnea each seen in 1 or 2 patients. Hypothyroidism (seen in 13.8%) was the most common immune-mediated AE. As with nivolumab treatment, net improvement in the EORTC QLQ-C30 and EQ-5D scores occurred between baseline and week 12 of therapy. At 6 months, the PFS rate was 72.4% and the OS rate was 99.5%, with the median duration of response and OS not reached in all cohorts.

PMBL, like HL, often has copy number alterations and rearrangements of 9p24.1 and so has also been evaluated in the context of CPI in the relapsed or refractory setting. As part of the KEYNOTE-013 pembrolizumab study, 18 patients were treated who had relapsed after, were ineligible for, or refused AHCT.[33] The patients had received a median of 3 prior lines of therapy, with 33% of them having had a prior AHCT and 61% having previously undergone radiation therapy. The ORR was 41%, with a 12% CR rate and a 29% PR rate. Grade 3 neutropenia developed in 1 patient and grade 4 veno-occlusive disease in 1 patient following a subsequent allogeneic transplant; both recovered. Grade 1 or 2 hypothyroidism was seen in 1 patient. Other irAEs were grade 2 diarrhea and radiation pneumonitis, each of which occurred in 1 patient. The response durations were from 2.3 to 22.5 months, with most ongoing. Recent interim results of the KEYNOTE-170 phase 2 trial included 33 patients with relapsed or refractory PMBL who received pembrolizumab and showed an ORR of 35%, with a 13% CR rate.[34]

In a phase 2 study, pembrolizumab was shown to be active in Richter transformation, but not in CLL, when given as a single agent. The ORR for Richter transforma-

tion was 44%, with 1 CR and 3 PRs. There were no CRs or PRs for CLL.[35] Drug-related AEs of grade 3 or higher occurred in 38 patients, with the most common being thrombocytopenia (21%), dyspnea (8%), and fatigue (8%). The most common irAE was liver enzyme elevation (12%, 8% grade 3), which was reversible with therapy interruption or corticosteroid therapy.

Promising activity was shown for pembrolizumab when it was used for heavily pretreated mycosis fungoides and Sézary syndrome. In a phase 2 study of 24 patients with stage IB-IV disease treated with 2 mg/kg every 3 weeks for up to 2 years, the ORR was 38%, with 1 CR and 8 PRs.[36] Interestingly, an immune-mediated skin flare reaction was seen in 6 patients with Sézary syndrome (2 patients with grade 2 and 4 patients with grade 3); other irAEs included grade 2 pneumonitis in 1 patient and grade 3 diarrhea due to corticosteroid-refractory duodenitis in 1 patient. Pembrolizumab has also been shown to be very active in patients with NK/T-cell lymphoma. Of 7 patients whose disease had progressed on L-asparaginase, 5 achieved a CR and were in remission after a median follow-up of 6 months.[37] Prospective studies are ongoing (NCT03021057).

Avelumab is currently being tested in the setting of relapsed/refractory HL in patients with progression who are not eligible for transplant or whose disease has relapsed after either AHCT or allogeneic hematopoietic stem cell transplant (allo-HCT).[38] In the phase 1 trial, JAVELIN HODGKINS (NCT02603419), 31 patients were randomly assigned to different doses and schedules, including 8 patients after allo-HCT, described below. The ORR for all patients was 54.8%, with 2 CRs (6.5%) and 15 PRs (48.4%) (Results on the 23 non–allo-HCT patients presented in Table 1). Of the 5 patients treated after AHCT, only 1 had a PR. Grade 3 or higher treatment-related AEs occurred in 36.7% of patients but were not described in detail in this early analysis.

Finally, synergism between the checkpoint inhibitors and epigenetic modification is under investigation. In China, the hypomethylating agent decitabine has been combined with an anti–PD-1 antibody in heavily pretreated patients with lymphoma.[39] There was a modest ORR of 37%, with 1 CR and 2 PRs. Toxicities included severe cytokine release syndrome. In a retrospective study of patients with HL who had received either pembrolizumab or nivolumab and then azacitidine within 14 months of the CPI, the CR rate was 83%. No cytokine release syndrome was seen, but high-grade toxicities included the following: infusion reaction (n=1); thrombocytopenia (n=1); grade 5 respiratory failure (n=1); myelodysplastic syndrome (n=2, pre-existent in 1 case and both evolving to fatal acute myeloid leukemia); and acute kidney injury (n=1, pre-existent).[40]

Several combination trials are ongoing in the relapsed/refractory setting. The CheckMate 812 study (NCT03138499) is a randomized phase 3 trial comparing nivolumab plus BV with BV alone for patients who have relapsed/refractory HL or are not eligible for AHCT. Similarly, KEYNOTE-204 (NCT02684292) is evaluating pembrolizumab vs BV in the relapsed/refractory HL setting. On the other hand, Javelin DLBCL (NCT02951156) is a multicenter, open-label, phase 1b study randomly assigning patients with relapsed/refractory DLBCL to rituximab/avelumab (a fully human IgG1 anti–PD-L1 antibody)/utomilumab (a 4-1BB agonist), to avelumab/azacitidine/utomilumab, or to rituximab/avelumab/bendamustine. Also for refractory DLBCL, the ZUMA-6 trial (NCT02926833) is evaluating the combination of axicabtagene ciloleucel (KTE-C19, an autologous anti-CD19 chimeric antigen receptor T cell) and atezolizumab (a fully human IgG1 anti–PD-L1 antibody) delivered sequentially. A 4-arm phase 1/2 study is evaluating a 1500-mg fixed dose of durvalumab as monotherapy or in combination with rituximab/lenalidomide, ibrutinib alone, or rituximab/bendamustine for relapsed or refractory B-cell lymphomas and CLL (NCT02733042). In PROCLAIM-CX-072 (NCT03013491), the protease-activatable anti–PD-L1 probody CX-072 will be given as monotherapy or in combination with ipilimumab for refractory lymphomas. Finally, many other phase 1 studies evaluating new anti–PD-1 or anti–PD-L1 antibodies are ongoing (NCT02836834).

Considerations With Allogeneic Transplant

Allo-HCT relies on the donor immune system to prevent the relapse or progression of lymphoma; one mechanism of failure is inadequate costimulation of T cells.[41] The goal after allo-HCT is to augment the graft-versus-tumor effect by modulating antigen-specific T-cell responses, but in this context, there may also be a possibility of initiating or worsening graft-versus-host disease (GVHD), as was seen in early mouse models.[42]

Ipilimumab was studied for relapse or progression after allo-HCT with a single dose escalated from 0.1 to 3 mg/kg after patients had been off immunosuppression for at least 4 weeks.[43] Among the 20 patients with lymphoma, a CR was achieved in 2 patients with HL and a PR in 1 patient with mantle cell lymphoma. No cases of grade 3 or 4 acute GVHD developed after ipilimumab alone, but irAEs developed in 2 patients with HL: dyspnea in 1 patient and grade 4 pneumonitis in the other after re-treatment with ipilimumab. A follow-up phase 1 study was done with escalation from 3 to 10 mg/kg, in which doses were given every 21 days for 4 courses.[44] Of the 28

patients, 11 had lymphoma (7 HL, 4 NHL), with 3 of the HL patients having stable disease and 1 NHL patient having a PR. Overall, dose-limiting toxicities included 2 cases of chronic GVHD of the liver and 1 case of grade 2 acute GVHD of the gut. These resolved with corticosteroids, but no further ipilimumab could be given.

Nivolumab has also been used off label for HL that relapsed after allo-HCT. A single-center retrospective analysis found that acute GVHD developed in 30% of the 20 patients, all of whom had had prior acute GVHD.[45] The ORR for the patients who had HL was 95%, with a 42% CR rate and a 52% PR rate, and 6 patients remained disease-free after stopping nivolumab. Corticosteroid-refractory GVHD developed in 2 patients and 2 patients died of GVHD, although the authors noted that GVHD did not develop in the patients who did not have prior GVHD after CPI and that the timing of CPI may be important.

More recently, Haverkos and colleagues collected information on 31 patients (94% with HL) at 23 centers who received CPI for relapse after allo-HCT.[46] Most had had at least 1 line of therapy after relapse before CPI (90% nivolumab, 10% pembrolizumab), but there was an ORR of 77% (15 patients with a CR and 8 with a PR). IrAEs were not frequent, but treatment-emergent GVHD occurred in 55% of patients, with 20% developing acute, 13% overlap, and 23% chronic GVHD after 1 to 2 doses. Of the 17 patients, 9 had grade 3 or higher GVHD and 14 of 17 required more than 2 GVHD therapies. Unfortunately, 8 of 10 deaths in this study were related to new-onset GVHD, 5 of them related to hepatic GVHD. The authors therefore concluded that although CPI after allo-HCT is efficacious, severe GVHD can occur, and patients should be treated in a clinical trial. In addition, the authors were not able to show the timing of CPI as a factor in the development of GVHD.

In the phase 1 JAVELIN HODGKINS study, 8 patients were treated with avelumab after allo-HCT.[38] The ORR was 75%, with 1 CR and 5 PRs. Grade 3 liver GVHD developed in 2 patients, which resolved with therapy.

Early reports noted a likelihood for increased GVHD in patients exposed to CPI before transplant, which prompted a multicenter retrospective study of 39 patients (79% HL, 5% DLBCL, 5% PMBL, 5% FL).[47] PD-1 blockade (72% nivolumab, 28% pembrolizumab) was given for a median of 62 days (range, 7-260) before allo-HCT. At 1 year, the rates of OS, PFS, cumulative incidence of relapse, and nonrelapse mortality were 89% (95% CI, 74%-96%), 76% (95% CI, 56%-87%), 14% (95% CI, 4%-29%), and 11% (95% CI, 3%-23%), respectively. Grades 2 through 4 and grade 3 or 4 acute GVHD occurred in 44% and 23% of patients, respectively, with the 1-year incidence of chronic GVHD at 41%. There

were 3 patients who died of early acute GVHD, and 1 patient died of hepatic sinusoidal obstruction syndrome. In addition, a noninfectious febrile syndrome developed in 7 patients shortly after transplant that required a prolonged course of corticosteroids. Circulating lymphocyte subsets from 17 patents showed decreased numbers of PD-1–positive T cells and decreased ratios of T-regulatory cells to conventional CD4 and CD8 T cells. The authors therefore concluded that allo-HCT after CPI is feasible and has a low rate of relapse, but that early immune toxicities may occur and should be considered.

In a study of haplo-identical and matched donor allogeneic transplants with post-transplant cyclophosphamide for GVHD prophylaxis, Schoch and colleagues concluded that the incidence and severity of GVHD were similar with and without exposure to CPI, either before or after allo-HCT.[48] Patients included in this study had a variety of diseases, including 11 with lymphoma (8 HL, 1 DLBCL, 1 PTCL, 1 mycosis fungoides), and most had previously been treated with nivolumab (n=11) or ipilimumab (n=12). Most of the patients (12/19) had received CPI more than 90 days before or more than 90 days after allo-HCT. Of the 11 patients who received CPI before allo-HCT, grade 2 acute GVHD developed in 4, stage 3 skin involvement in 3, and stage 3 skin and stage 1 liver involvement in 1 patient. In all patients, acute GVHD resolved with treatment, and chronic GVHD developed in none. Among the 9 patients with post–allo-HCT CPI, grade 2 acute GVHD with stage 3 cutaneous involvement developed in 1 after a donor lymphocyte infusion, but no other GVHD was seen.

Overall, CPI in the allo-HCT setting has been effective in disease control, but the risk for GVHD must be modulated—for example, by increasing the time between CPI and allo-HCT or by using additional GVHD prophylaxis, such as post-transplant cyclophosphamide. Prospective evaluation will be important. We have included our current recommendations in Table 2.

Additional Considerations

IrAEs are particular to the CPIs, and careful monitoring for their development is required.[49-51] IrAEs can affect any organ system; the most common are cutaneous problems (primarily rashes and vitiligo) and endocrine abnormalities (hypothyroidism, hypophysitis, adrenal insufficiency, and diabetes). More serious side effects can include colitis, pneumonitis, hepatitis, and neurologic symptoms. As described previously, irAEs tend to be more frequent and severe after ipilimumab than with the PD-1 and PD-L1 inhibitors. Oral corticosteroids are the treatment of choice for mild symptoms, whereas hospitalization and intravenous corticosteroids or other

immunosuppressive agents such as mycophenolate mofetil and infliximab (Remicade, Janssen) may be needed for higher-grade irAEs. Prophylaxis for infections with organisms such as *Pneumocystis jiroveci* should be considered for patients with an expected prolonged need for corticosteroids. Mason and colleagues conducted a single-center analysis of costs related to toxicities from either nivolumab or pembrolizumab in patients with a variety of cancers; they found that the average costs of care were $640 and $4784 higher in patients treated with nivolumab and pembrolizumab, respectively, than in those without toxicities. Primary cost drivers were different; inpatient stays and radiation therapy were responsible for the difference with pembrolizumab, and outpatient visits and additional pharmacy costs were responsible for the difference with nivolumab.[52] These differences may be due to the timing of treatment and the diseases included, but it is important to keep them in consideration.

Biomarker-driven use of CPI has been an attractive proposition. In many tumor types, response rates with PD-1 inhibitors are higher in those with immunohistochemical detection of PD-L1 than in those without PD-L1 expression.[53] Increased PD-L1 expression has been found to be more common in HL, PMBL, T-cell–rich B-cell lymphoma, EBV-associated DLBCL, plasmablastic lymphoma, extranodal NK/T-cell lymphoma, human herpesvirus 8 (HHV-8)–associated primary effusion lymphoma, and post-transplant lymphoproliferative disease.[54] Genetic amplification of chromosome 9p23-24 (encoding PD-L1 and PD-L2), latent membrane protein 1 (LMP1, an EBV oncoprotein) simulated immune escape, activator protein 1 signaling, and tumor microenvironment interferon gamma production can increase the expression of PD-L1 on tumor cells.[3,55,56] Correlative studies alongside the pivotal HL trials with pembrolizumab and nivolumab have shown high degrees of PD-1 expression in tumor tissues.[26,32] Roemer and colleagues showed that all of the 96 tumor samples from the CheckMate 205 trial had genetic alterations of 9p24.1 and copy number–dependent increased expression of PD-L1 in Hodgkin Reed-Sternberg cells.[57] In extranodal NK/T-cell lymphoma, PD-L1 positivity was associated with low IPI score, normal serum lactate dehydrogenase levels, and a trend toward better OS.[58] The degree of staining required for a result to be considered positive and the effect on therapy timing and choice remain under investigation for most lymphomas.

Initial trials noted the development of a tumor flare or pseudo-progression on restaging imaging studies prompted an update of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, known as the immune-related response criteria.[59] A proposed framework incorporates the immune-related response criteria

Table 2. MSKCC Recommendations for Checkpoint Inhibition and Allogeneic Transplant for Advanced-Stage Relapsed/Refractory Hodgkin Lymphoma

For all patients at initiation of CPI, conduct HLA typing and refer for potential allogeneic stem cell transplant.
If CR on CPI, continue for 3 additional months. • If CR is maintained, stop therapy and monitor. • Restart if disease progresses and refer for consideration of allogeneic transplant.
If PR on CPI, continue therapy based on clinical situation. • Conversion to CR is still possible. • Refer for consideration of allogeneic transplant.
If stable disease on CPI, continue therapy until definitive disease progression. • CR is unlikely to occur with further treatment. • On progression, consider MOPP (or MOPP-like) chemotherapy vs clinical trial. • Refer for consideration of allogeneic transplant if PR is achieved.

CPI, checkpoint inhibition; CR, complete remission; HLA, human leukocyte antigen; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; MSKCC, Memorial Sloan Kettering Cancer Center; PR, partial remission.

into the current Lugano classification for lymphoma response.[60] The term *indeterminate response* was added to allow continuation of therapy until confirmation of actual progression, and additional prospective validation of these criteria is ongoing.

Future Directions

Radiotherapy along with CPI can enhance systemic antitumor immunity by augmenting the immune response. It works by causing tumor cell death, which leads to downstream dendritic cell activation, antigen cross-presentation, and cytotoxic T-cell activation and proliferation.[61,62] To take advantage of this combination effect, Memorial Sloan Kettering Cancer Center is conducting a clinical trial of pembrolizumab and involved-site radiation therapy (ISRT) for early-stage relapsed or primary refractory HL. The goal is to cure disease without the toxicity of either a large radiation field or additional chemotherapy and stem cell transplant (NCT03179917). Other ongoing trials include Lymvac-2, which is evaluating the use of sequential intratumoral injections of low-dose rituximab, autologous dendritic cells, pembrolizumab, and local radiotherapy for FL (NCT02677155).

The intestinal microbiome is now becoming widely studied across the medical field, especially in relation to the immune system and anticancer therapy; a higher

abundance of particular bacteria and alterations in overall diversity are associated with increased relapse risk.[63,64] Two recent studies have evaluated the effect of the microbiota in the setting of CPI and found that CTLA-4 blockade is dependent on *Bacteroides* species, and the antitumor effects of anti–PD-L1 therapy are associated with *Bifidobacterium*.[65,66] The mechanisms and therapeutic implications of these results require additional investigation.[67,68]

A multitude of alternative targets in the immune checkpoint pathways and tumor microenvironment are also under investigation.[69] Costimulatory proteins such as CD40 on antigen-presenting cells and OX40 and CD37 on T cells participate in regulating the T-cell and macrophage effector interaction. Urelumab, an anti-CD137 fully humanized IgG4 monoclonal antibody, is being tested in combination with nivolumab in relapsed/refractory B-cell NHL (NCT02253992). Dacetuzumab and lucatumumab are 2 humanized anti-CD40 monoclonal antibodies that are in early-phase testing. T-cell exhaustion has been shown to be reversed by blocking lymphocyte activation gene 3 (*LAG3*), and *LAG3* blockage is currently being studied in combination with nivolumab (NCT01968109). CA-170, a first-in-class oral small molecule that directly targets both the PD-1/PD-L1 pathway and a second checkpoint, the V-domain Ig suppressor of T-cell activation (VISTA) pathway, is in phase 1 testing (NCT02812875). Studies of an inducible T-cell costimulator (ICOS) agonist, a killer cell immunoglobulin-like receptor 3DL2 (KIR3DL2) antagonist, and a stimulator of interferon genes (STING) agonist are also under way (NCT02520791, NCT02593045, and NCT02675439). These and other combinations can provide future therapeutic options to augment the antitumor immune response.

Conclusion

CPI disrupts immunologic homeostasis to re-engage the T-cell–mediated destruction of lymphomas. CPI has been shown to be very active, with high response rates and prolonged durations of remission, in certain lymphoma subtypes, especially those with a high rate of PD-L1 expression by immunohistochemistry, such as HL and PMBL. It has benefit in other lymphoma subtypes as well. Toxicities with these agents are unique and can resolve with early detection and treatment. Overall, CPI use has expanded in the approved settings, and much investigation in this field continues throughout the lymphoma disease course, with the results of ongoing trials eagerly awaited.

Disclosures
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References

1. Intlekofer AM, Thompson CB. At the bench: preclinical rationale for CTLA-4 and PD-1 blockade as cancer immunotherapy. *J Leukoc Biol*. 2013;94(1):25-39.
2. Parry RV, Chemnitz JM, Frauwirth KA, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol*. 2005;25(21):9543-9553.
3. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med*. 2002;8(8):793-800.
4. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. *Nat Rev Immunol*. 2015;15(8):486-499.
5. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol*. 2015;33(17):1974-1982.
6. Armand P. Immune checkpoint blockade in hematologic malignancies. *Blood*. 2015;125(22):3393-3400.
7. Armand P. Checkpoint blockade in lymphoma. *Hematology Am Soc Hematol Educ Program*. 2015;2015(1):69-73.
8. Galanina N, Kline J, Bishop MR. Emerging role of checkpoint blockade therapy in lymphoma. *Ther Adv Hematol*. 2017;8(2):81-90.
9. Goodman A, Patel SP, Kurzrock R. PD-1-PD-L1 immune-checkpoint blockade in B-cell lymphomas. *Nat Rev Clin Oncol*. 2017;14(4):203-220.
10. Hude I, Sasse S, Engert A, Bröckelmann PJ. The emerging role of immune checkpoint inhibition in malignant lymphoma. *Haematologica*. 2017;102(1):30-42.
11. Perales MA, Sauter CS, Armand P. Reprint of: Fast cars and no brakes: autologous stem cell transplantation as a platform for novel immunotherapies. *Biol Blood Marrow Transplant*. 2016;22(3)(suppl):S9-S14.
12. Thanarajasingam G, Thanarajasingam U, Ansell SM. Immune checkpoint blockade in lymphoid malignancies. *FEBS J*. 2016;283(12):2233-2244.
13. Villasboas JC, Ansell S. Checkpoint Inhibition: Programmed cell death 1 and programmed cell death 1 ligand inhibitors in Hodgkin lymphoma. *Cancer J*. 2016;22(1):17-22.
14. Pianko MJ, Liu Y, Bagchi S, Lesokhin AM. Immune checkpoint blockade for hematologic malignancies: a review. *Stem Cell Investig*. 2017;4:32-32.
15. Westin JR, Chu F, Zhang M, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. *Lancet Oncol*. 2014;15(1):69-77.
16. Nastoupil LJ, Westin J, Fowler N, et al. Response rates with pembrolizumab in combination with rituximab in patients with relapsed follicular lymphoma: interim results of an on open-label, phase II study [ASCO abstract 7519]. *J Clin Oncol*. 2017;35(15)(suppl).
17. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results from a phase 1/2 study of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma [ICML abstract 74]. *Hematol Oncol*. 2017;35(suppl 2):85-86.
18. Jain N, Basu S, Thompson PA, et al. Nivolumab combined with ibrutinib for CLL and Richter transformation: a phase II trial [ASH abstract 59]. *Blood*. 2016;128(22)(suppl).
19. Armand P, Nagler A, Weller EA, et al. Disabling immune tolerance by programmed death-1 blockade with pidilizumab after autologous hematopoietic stem-cell transplantation for diffuse large B-cell lymphoma: results of an international phase II trial. *J Clin Oncol*. 2013;31(33):4199-4206.
20. Ansell SM, Hurvitz SA, Koenig PA, et al. Phase I study of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with relapsed and refractory B-cell non-Hodgkin lymphoma. *Clin Cancer Res*. 2009;15(20):6446-6453.
21. Berger R, Rotem-Yehudar R, Slama G, et al. Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies. *Clin Cancer Res*. 2008;14(10):3044-3051.
22. 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(4):311-319.
23. Ansell S, Armand P, Timmerman JM, et al. Nivolumab in patients (pts) with relapsed or refractory classical Hodgkin lymphoma (R/R cHL): clinical outcomes from extended follow-up of a phase 1 study (CA209-039) [ASH abstract 583]. *Blood*. 2015;126(23)(suppl).
24. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. *J Clin Oncol*. 2016;34(23):2698-2704.
25. Ansell S, Gutierrez ME, Shipp MA, et al. A phase 1 study of nivolumab in combination with ipilimumab for relapsed or refractory hematologic malignancies (CheckMate 039) [ASH abstract 183]. *Blood*. 2016;128(22)(suppl).

26. 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(9):1283-1294.

27. Engert A, Taylor F, Bennett B, et al. Patient subgroup analysis of quality-of-life outcomes in Checkmate 205, a phase 2 study of nivolumab in patients with classical Hodgkin lymphoma [ASH abstract 1831]. *Blood.* 2016;128(22)(suppl).

28. Timmerman JM, Engert A, Younes A, et al. Checkmate 205 update with minimum 12-month follow up: a phase 2 study of nivolumab in patients with relapsed/refractory classical Hodgkin lymphoma [ASH abstract 1110]. *Blood.* 2016;128(22)(suppl).

29. Diefenbach CS, Hong F, David KA, et al. A phase I study with an expansion cohort of the combination of ipilimumab and nivolumab and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma: a trial of the ECOG-ACRIN Cancer Research Group (E4412 Arms D and E) [ASH abstract 1106]. *Blood.* 2016;128(22)(suppl).

30. Nayak L, Iwamoto F, LaCasce AS, et al. Nivolumab (anti-PD1) therapy for relapsed/refractory primary central nervous system lymphoma and primary testicular lymphoma [ASH abstract 930]. *Blood.* 2016;128(22)(suppl).

31. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure [published online June 27, 2016]. *J Clin Oncol.* doi:https://doi.org/10.1200/JCO.2016.67.3467.

32. Chen R, Zinzani PL, Fanale MA, et al; KEYNOTE-087. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. *J Clin Oncol.* 2017;35(19):2125-2132.

33. Zinzani PL, Ribrag V, Moskowitz CH, et al. Safety and tolerability of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. *Blood.* 2017;130(3):267-270.

34. Zinzani P, Thieblemont C, Melnichenko V, et al. Efficacy and safety of pembrolizumab in relapsed/refractory primary mediastinal large B-cell lymphoma (rrPMBCL): interim analysis of the KEYNOTE-170 phase 2 trial. *Hematol Oncol.* 2017;35(S2):62-63.

35. Ding W, Le-Rademacher J, Call TG, et al. PD-1 blockade with pembrolizumab in relapsed CLL including Richter's transformation: an updated report from a phase 2 trial (MC1485) [ASH abstract 4392]. *Blood.* 2016;128(22)(suppl).

36. Khodadoust M, Rook AH, Porcu P, et al. Pembrolizumab for treatment of relapsed/refractory mycosis fungoides and Sezary syndrome: clinical efficacy in a CITN multicenter phase 2 study [ASH abstract 181]. *Blood.* 2016;128(22)(suppl).

37. Kwong Y-L, Chan TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. *Blood.* 2017;129(17):2437-2442.

38. Chen R, Gibb AL, Collins GP, et al. Blockade of the PD-1 checkpoint with anti-PD-L1 antibody avelumab is sufficient for clinical activity in relapsed/refractory classical Hodgkin lymphoma (CHL) [ICML abstract 67]. *Hematol Oncol.* 2017;35(suppl 2).

39. Wang C, Liu W, Zhang W, et al. Phase I study of anti-PD1 in combination with low-dose decitabine in patients with advanced and untreated malignancies [ASCO abstract e14555]. *J Clin Oncol.* 2017;35(15)(suppl).

40. Falchi L, Sawas A, Deng C, et al. PD-1 blockade after epigenetic therapy in patients with relapsed or refractory Hodgkin lymphoma: higher-than-expected rate of complete responses [ASH abstract 2999]. *Blood.* 2016;128(22)(suppl).

41. Merryman RW, Armand P. Immune checkpoint blockade and hematopoietic stem cell transplant. *Curr Hematol Malig Rep.* 2017;12(1):44-50.

42. Blazar BR, Taylor PA, Boyer MW, Panoskaltsis-Mortari A, Allison JP, Vallera DA. CD28/B7 interactions are required for sustaining the graft-versus-leukemia effect of delayed post-bone marrow transplantation splenocyte infusion in murine recipients of myeloid or lymphoid leukemia cells. *J Immunol.* 1997;159(7):3460-3473.

43. Bashey A, Medina B, Corringham S, et al. CTLA4 blockade with ipilimumab to treat relapse of malignancy after allogeneic hematopoietic cell transplantation. *Blood.* 2009;113(7):1581-1588.

44. Davids MS, Kim HT, Bachireddy P, et al; Leukemia and Lymphoma Society Blood Cancer Research Partnership. Ipilimumab for patients with relapse after allogeneic transplantation. *N Engl J Med.* 2016;375(2):143-153.

45. Herbaux C, Gauthier J, Brice P, et al. Efficacy and tolerability of nivolumab after allogeneic transplantation for relapsed Hodgkin lymphoma. *Blood.* 2017;129(18):2471-2478.

46. Haverkos BM, Abbott D, Hamadani M, et al. PD-1 blockade for relapsed lymphoma post-allogeneic hematopoietic cell transplant: high response rate but frequent GVHD. *Blood.* 2017;130(2):221-228.

47. 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(10):1380-1388.

48. Schoch LK, Borrello I, Fuchs EJ, et al. Checkpoint inhibitor therapy and graft versus host disease in allogeneic bone marrow transplant recipients of haploidentical and matched products with post-transplant cyclophosphamide [ASH abstract 4571]. *Blood.* 2016;128(22)(suppl).

49. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer.* 2016;54:139-148.

50. Eigentler TK, Hassel JC, Berking C, et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. *Cancer Treat Rev.* 2016;45:7-18.

51. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev.* 2016;44:51-60.

52. Mason N, Antonia S, Khushalani N, McLeod H. Comparison of incidence and average cost per toxicity in patients treated with nivolumab and pembrolizumab [ASCO abstract e18292]. *J Clin Oncol.* 2017;35(15)(suppl).

53. Taube JM, Klein A, Brahmer JR, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. *Clin Cancer Res.* 2014;20(19):5064-5074.

54. Chen BJ, Chapuy B, Ouyang J, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. *Clin Cancer Res.* 2013;19(13):3462-3473.

55. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood.* 2010;116(17):3268-3277.

56. Green MR, Rodig S, Juszczynski P, et al. Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative disorders: implications for targeted therapy. *Clin Cancer Res.* 2012;18(6):1611-1618.

57. Roemer MGM, Ligon AH, Engert A, et al. Chromosome 9p24.1/PD-L1/PD-L2 alterations and PD-L1 expression and treatment outcomes in patients with classical Hodgkin lymphoma treated with nivolumab (PD-1 blockade). *Blood.* 2016;128(22):2923.

58. Jo JC, Kim M, Choi Y, et al. Expression of programmed cell death 1 and programmed cell death ligand 1 in extranodal NK/T-cell lymphoma, nasal type. *Ann Hematol.* 2017;96(1):25-31.

59. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res.* 2009;15(23):7412-7420.

60. 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(21):2489-2496.

61. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. *J Natl Cancer Inst.* 2013;105(4):256-265.

62. Sharabi AB, Lim M, DeWeese TL, Drake CG. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *Lancet Oncol.* 2015;16(13):e498-e509.

63. Peled JU, Devlin SM, Staffas A, et al. Intestinal microbiota and relapse after hematopoietic-cell transplantation. *J Clin Oncol.* 2017;35(15):1650-1659.

64. Peled JU, Hanash AM, Jenq RR. Role of the intestinal mucosa in acute gastrointestinal GVHD. *Blood.* 2016;128(20):2395-2402.

65. Vétizou M, Pitt JM, Daillère R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science.* 2015;350(6264):1079-1084.

66. Sivan A, Corrales L, Hubert N, et al. Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science.* 2015;350(6264):1084-1089.

67. Firwana B, Avaritt N, Shields B, et al. Do checkpoint inhibitors rely on gut microbiota to fight cancer? *J Oncol Pharm Pract.* 2017;107815521771590(June):1078155217715903.

68. Cozen W, Yu G, Gail MH, et al. Fecal microbiota diversity in survivors of adolescent/young adult Hodgkin lymphoma: a study of twins. *Br J Cancer.* 2013;108(5):1163-1167.

69. Smyth MJ, Ngiow SF, Ribas A, Teng MWL. Combination cancer immunotherapies tailored to the tumour microenvironment. *Nat Rev Clin Oncol.* 2016;13(3):143-158.