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REVIEW

Emerging treatment options for the management of Hodgkin's lymphoma: clinical utility of nivolumab

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Abstract: Classical Hodgkin's lymphoma (cHL) is a B-cell malignancy comprised of pathologic Reed Sternberg cells with a surrounding immune-tolerant inflammatory milieu. RS cells evade immune recognition in part through programmed death ligand 1 (PD-L1) overexpression, which is genetically programmed through copy number alterations, polysomy, and amplification of the 9p24.1 locus encoding PD-L1. By engaging with PD-1+ T-cells, PD-L1 delivers a potent immune suppressive signal promoting immunologic escape of the tumor cell. Enhancing antitumor immune response by targeting PD-1 with the monoclonal antibody nivolumab has proved to be effective in multiple solid tumors, but the highest response rates to date have been reported in patients with cHL, with over 65% of treated patients achieving an objective clinical response. In this review, we will summarize the published evidence regarding the activity of nivolumab in cHL as well as its current place in therapy. We will review the pharmacology, mechanism of action, and side effects of nivolumab as well as the emerging data indicating possible increased risk of graft versus host disease in patients treated with PD-1 inhibitors either pre- or post-allogeneic stem cell transplant. Given the remarkable single-agent activity and safety profile of PD-1 inhibitors in heavily pretreated patients with cHL, the possibility of employing nivolumab in combination with other active agents and earlier in therapy is a promising area of active investigation, and we will briefly summarize current clinical trials.

Keywords: nivolumab, Hodgkin's lymphoma, pembrolizumab, checkpoint inhibitor therapy

Relapsed/refractory classical Hodgkin's lymphoma

Classical Hodgkin's lymphoma (cHL) is a lymphoid malignancy characterized by a small percentage of pathologic Reed Sternberg (RS) cells within a robust nodal inflammatory environment. Standard options for frontline therapy for patients with cHL depend upon stage and risk factors at diagnosis, and consist of combination chemotherapy with or without radiation therapy.[1,2] Acceptable frontline chemotherapy regimens for cHL include adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), Stanford V, as well as escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) for patients with advanced stage disease and higher risk international prognostic score.[3–9] For patients with favorable risk early-stage cHL, treatment with ABVD with or without radiation therapy is associated with 5-year progression-free survival (PFS) of ≥90%.[10,11] For unfavorable risk or bulky early-stage disease, 5 year failure-free survival rates of 85% and 79% are reported with ABVD + radiation therapy and Stanford V, respectively.[12] In patients with high-risk stage III/IV disease, frontline treatment with 6–8 cycles of ABVD leads to 5 years PFS rates ranging from 68% to 73%, while escalated BEACOPP has been

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associated with 5 year PFS rates from 81%–85% but also with significantly increased hematologic and gonadal toxicity.[13–16] While the initial management of patients with advanced-stage Hodgkin's lymphoma is beyond the scope of this review, we would refer the reader to a recent review by Vassilakopoulos and Johnson[17] for an updated and comprehensive summary of published evidence to date.

For patients with relapsed/refractory disease after initial therapy, standard treatment includes salvage chemotherapy followed by autologous stem cell transplant (ASCT).[18–23] With ASCT, 5-year PFS rates of 50%–60% can be achieved in patients with relapsed chemosensitive disease, compared with 5-year PFS rates of 40%–45% for patients with primary refractory disease.[18–20,23,24] For patients with relapsed/refractory disease following ASCT, the anti-CD30 monoclonal antibody drug conjugate brentuximab vedotin (BV) (Adcetris, Seattle Genetics, Bothell, WA, USA) demonstrated an overall response rate (ORR) of 75%, including complete response (CR) rate of 36% with a median PFS of 9.3 months in a pivotal phase II trial, leading to US Food and Drug Administration (FDA) approval in this setting.[25,26] In the phase III AETHERA trial, BV consolidation after ASCT resulted in an improvement in PFS (43 vs 24 months) compared with placebo in patients at high risk for relapse.[27]

Although there are multiple treatment options available for patients who fail ASCT and BV, historical median overall survival (OS) for these patients is about 2 years.[28] Allogeneic stem cell transplant (SCT) remains the only known curative option for this patient population, with the presence of a graft versus lymphoma effect suggested by indirect evidence such as lower relapse rates in patients that develop chronic graft-versus-host disease (GVHD).[29–31] However, despite potential for durable remissions, the historical 5-year PFS has been about 20% with a 5-year OS of 30%.[29,32] For patients who are candidates for allogeneic SCT and desire this approach, combination chemotherapy may be used for maximal disease reduction prior to transplant, albeit at the cost of significant treatment-associated toxicities.[33–35] Asymptomatic patients may be observed for a period of time or treated with radiation therapy in case of localized relapse. Palliative single-agent chemotherapy options include gemcitabine, vinorelbine, vinblastine, bendamustine, liposomal doxorubicin, or biological agents such as lenalidomide, the histone deacetylase inhibitors vorinostat and panobinostat, or the mammalian target of rapamycin inhibitor everolimus.[36–46] While there are many available options for therapy, responses are not durable, and new treatments are needed for patients with relapse following ASCT and BV.

RS cells avoid antitumor immune response by release of immunosuppressive cytokines such as interferon-gamma, TGF β, chemokine ligands 17 (CCL17) and 22 (CCL22), and interleukin 10 (IL-10) as well as expression of immune-tolerance-inducing surface molecules.[47] The identification that two of these immunomodulatory surface proteins, PD-L1 (B7H1) and PD-L2 (B7DC), that are expressed by RS cells provided the rationale for therapeutic targeting of their corresponding T-cell target, the receptor programmed death 1 (PD-1, CD279).[48] As will be discussed in this review, PD-1 inhibition with the monoclonal antibodies nivolumab and pembrolizumab have emerged as a viable treatment option for patients with cHL after ASCT failure. In this review, we will summarize the mechanism of action, pharmacology, and side effects of nivolumab, the role of PD-1 signaling in cHL, published results to date regarding treatment of cHL with nivolumab, the current role for nivolumab in the treatment of cHL, and future areas of research including ongoing trials in cHL with nivolumab and other PD-1 inhibitors.

PD-1/PD-L signaling

PD-1 is a coinhibitory receptor of the CD28 superfamily expressed on T-cells. By interacting with its corresponding ligands (PD-L1 and PD-L2) on antigen-presenting cells (APCs), PD-1 attenuates T-cell response and promotes T-cell tolerance by inhibiting cytokine production and T-cell proliferation via suppression of Src Homology Phosphatase 2 (SHP-2) signaling within the T-cell (Figure 1).[49–52] In a healthy host, PD-1 expression is increased in activated T-cells to counter-regulate immune response to infection to prevent autoimmunity. In addition to PD-1, PD-L1 has also been shown to competitively engage CD80 (CD28 ligand), decreasing the stimulatory signal mediated by the CD80/CD28 interaction and further inhibiting T-cell proliferation and function.[53] The identification of these ligands was followed by the discovery that PD-L1 can also be expressed on tumor cells to evade antitumor immune response.[54] PD-L2 expression by tumors cells is less extensively reported, but has relevance for cHL as well as the closely related disease primary mediastinal B cell lymphoma, where it appears to be overexpressed by tumor cells due to gene amplification.[55–57]

Gain in chromosome 9p was first observed in primary mediastinal B-cell lymphoma specimens and later discovered in RS cells, distinguishing these diseases genetically from other B cell lymphomas.[55,58–61] Via high-density single-nucleotide polymorphism arrays, the 9p24.1 amplicon was shown to contain *CD274,* which encodes PD-L1, and *PDCD1LG2,* which encodes PD-L2, as well as Janus Kinase

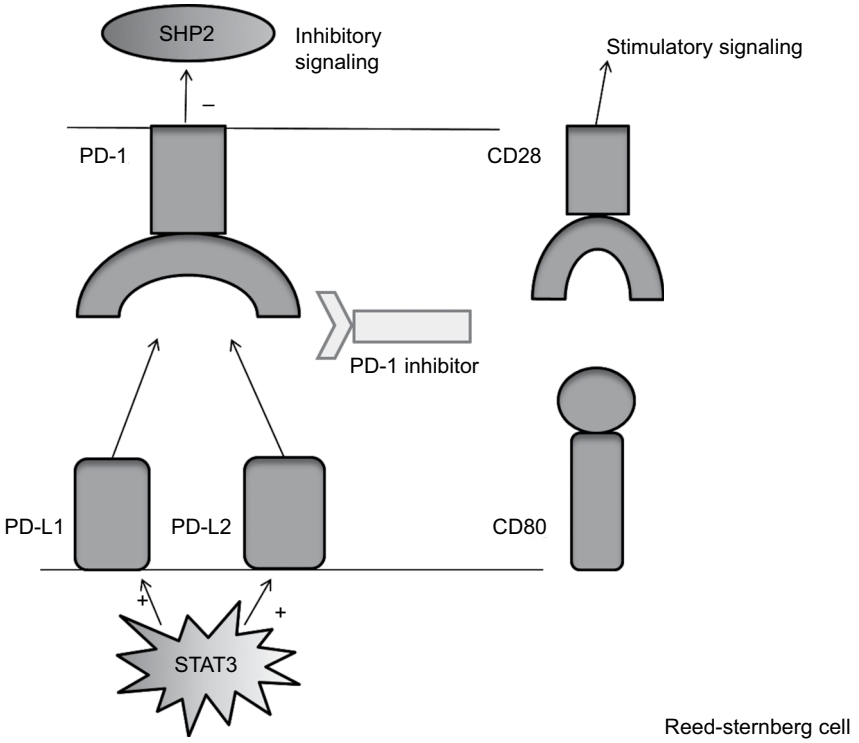

Figure 1 This figure depicts PD-L1 and PD-L2 signaling between an RS cell and a T-cell within the tumor microenvironment.
Notes: In addition to acting as a ligand for PD-1 leading to inhibitory signaling through suppression of SHP-2, PD-L1 also acts as a receptor for CD 80 on antigen presenting cells, thereby inhibiting binding of CD 80 with CD 28 on T cells. PD-1 inhibitors bind PD-1, thus attenuating PD-1 mediated T-cell exhaustion.
Abbreviations: PD-1, programmed death 1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; RS, Reed Sternberg cell; SHP-2, Src homology phosphotase 2.

2 (JAK2), which has been shown to upregulate PD-L1 and PD-L2 expression via the STAT signaling pathway.[57] This finding provided a genetic basis for the increased PD-L1 and PD-L2 expression in RS cells and suggested the importance of PD-1 signaling leading to immune evasion in this disease.[48,57] Increased PD-L1 and PD-L2 expression in RS cells has also been shown to be mediated by the *CTIIA* gene fusion[62] as well as by Epstein–Barr virus (EBV) infection.[63] Subsequent analyses of RS cells isolated from biopsy specimens in cohorts of patients with both newly diagnosed and relapsed/refractory cHL have shown almost universal genetic modification of the PD-L1 and PD-L2 loci via either polysomy of 9p or copy gain or amplification of 9p24.1.[56,64,65] In a cohort of 108 patients with newly diagnosed cHL treated with the Stanford V regimen, amplification of 9p24.1 was associated with advanced-stage disease and shorter PFS compared with polysomy or copy gain, suggesting that increased amplification of PD-L1 and PD-L2 may mediate a more aggressive clinical course.[56]

cHL is characterized by a small percentage of PD-L1+ RS cells within a robust but ineffective inflammatory and immune environment that includes PD-1 expressing T-cells.[47,66] This body of evidence, suggesting the importance of PD-L1 and PD-L2 signaling as a common pathway for immune evasion in cHL, provides the rationale for PD-1 targeting in cHL.

Introduction to nivolumab pharmacology, mode of action, and pharmacokinetics

Nivolumab (Opdivo, formerly BMS-936558 and MDX-1106; Bristol-Myers Squibb, New York, NY, USA) is a fully human monoclonal IgG4 antibody targeting PD-1. Initial studies of the safety and activity of nivolumab were performed in patients with advanced melanoma, castration resistant prostate cancer, non-small-cell lung cancer (NSCLC), renal-cell cancer (RCC), and colorectal cancer, demonstrating an acceptable safety profile and response rates ranging from 18%–28% in melanoma, NSCLC, and RCC, including durable response in a significant proportion of responders.[67,68] In these initial studies, nivolumab was given at 14 day-intervals with doses escalated from 0.1 mg/kg, 1 mg/kg to 3 mg/kg, and 10 mg/kg with no maximum tolerated dose determined.[68] A peak concentration of antibody was seen 1–4 hours after infusion, and while there was a linear correlation between dose, serum concentration, and area

under the curve at doses ranging from 0.1 to 10 mg/kg, the PD-1 receptor occupancy of peripheral blood mononuclear cells was similar at all dose levels in 65 melanoma patients (median of 64% at 0.1 mg/kg, median of 70% at 10 mg/kg).[68] Objective response rates were numerically similar at all dose levels for patients with melanoma and RCC. However, in NSCLC, all responses in the Phase I study were seen at a dose level of ≥3 mg/kg, with none of the 17 patients treated with the 1 mg/kg dose level achieving objective response. A subset of tumor samples was examined for PD-L1 expression by immunohistochemistry, and preliminary data suggested a correlation between PD-L1 expression on tumor cells and response to PD-1 blockade.[68]

Subsequent studies in melanoma, RCC, and NSCLC utilizing nivolumab at a dose of 3 mg/kg every 2 weeks validated its clinical activity in these diseases, leading to respective FDA approvals as second-line therapy.[69–72] In studies to date, the dose response rate and adverse event (AE) rate for nivolumab appears relatively flat through a wide range of doses, and the FDA cited this lack of apparent dose–response relation when changing the approved dose of nivolumab monotherapy for NSCLC, RCC, and melanoma to a non-weight-based dose of 240 mg every 2 weeks.[73] Studies to date of nivolumab as monotherapy for cHL, discussed in greater detail later, have utilized a dose of 3 mg/kg given every 2 weeks, which remains the FDA approved dose for this disease.[64,65]

Pharmacokinetic studies of 909 patients with different types of solid tumors and hematologic malignancies treated with nivolumab showed an elimination half-life of 26.7 days, mean time to steady state concentration of 12 weeks, and volume of distribution at steady state of 8.0 L.[74] Among 1,086 patients treated on 4 clinical trials of nivolumab for multiple solid tumor types, the presence of antidrug antibodies was detected in a minority of patients. This did not appear to lead to clinically meaningful loss of response, hypersensitivity reactions, or accelerated drug clearance.[75]

Activity of nivolumab in cHL

The initial evidence for the activity of nivolumab in patients with cHL comes from a phase I study of 23 patients with relapsed/refractory cHL and a phase II study of 80 patients with relapsed and refractory disease and prior treatment with both BV and ASCT (Table 1).[64,65] The genetic basis of PD-L1 expression in cHL with consequent T-cell exhaustion provided the rationale to include 23 patients with relapsed/refractory cHL as a cohort-expansion group in a phase I dose-escalation trial of single-agent nivolumab in patients with relapsed/refractory hematologic malignancies.[64] Patients were treated with nivolumab 3 mg/kg every 2 weeks until disease progression, unacceptable toxicity, or complete response.[64] Of the cHL patients included, 15/23 had received at least 4 prior lines of therapy, 78% had been previously treated with BV, and 78% had previously undergone ASCT. ORR was 87%; CRs were reported in 4 patients at time of initial publication, and 2 additional patients achieved a CR when extended follow-up was later reported at the 2015 American Society of Hematology (ASH) annual meeting.[64,76] With extended follow-up, while 10 patients were found to have durable responses to treatment, 4 of the 20 responding patients eventually developed progressive disease, 5 discontinued nivolumab while in response in order to undergo SCT (allogeneic in 4, ASCT in 1), and 1 patient discontinued nivolumab due to toxicity with response maintained off of nivolumab at 120 days follow-up.[76] In 2 of the responding patients, CR was maintained at 40 weeks after discontinuation of treatment. One patient with CR relapsed 43 weeks after cessation of nivolumab, but was able to again achieve CR when retreated with nivolumab. At the time of extended follow-up, 5 patients continued to receive nivolumab at ≥82 weeks of therapy.

Recently, the results of a multicenter, multicohort, phase II trial of nivolumab for cHL patients after failure of both ASCT and BV were reported.[65] Eighty patients enrolled across 34 medical centers in North America and Europe were treated with nivolumab every 2 weeks at a dose of 3 mg/kg and continued until unacceptable toxicity, progression, death, or withdrawal from the study. Eligible patients were required to have previously undergone ASCT followed by BV but were not required to be BV refractory. The median patient age was 37, 64% were males, and about half (49%) had received at least five prior lines of therapy. Forty three (54%) patients were refractory to BV, and 6 (8%) had received more than one prior line of BV. The ORR was 66% after review by independent radiological review committee, with 9% of patients achieving CR as defined by independent radiological review committee.[65] The investigator-assessed ORR was similar (58%), with a higher assessment (28%) of patients deemed to have achieved CR. Of the 43 patients refractory to most recent treatment with BV, 31 (72%) responded to nivolumab. Responses were seen at a median of 2.1 months from the start of treatment, although 22 of the 58 patients responding to treatment did not demonstrate response on initial follow-up scans 9 weeks after the start of treatment. At 6 months, the PFS was 77%. Updated results with a minimum of 12 months of follow-up (median follow-up 15.4 months) were presented at the 2016 ASH annual meeting with a median

Table 1 Summary of published trials of PD-1 inhibitors for cHL

Variable	Ansell et al[64]	Younes et al[65]	Armand et al[91]	Moskowitz et al[92]
PD-1 inhibitor	Nivolumab	Nivolumab	Pembrolizumab	Pembrolizumab
Number of patients	23	80	31	210[a]
Prior BV tx	78%	100%	100%	83%[a]
Prior ASCT	78%	100%	71%	61%[a]
Overall Response Rate	87%	66%	65%	68%
CR	17%	9%	16%	22%
PR	70%	58%	48%	46%
PFS at specified timepoint	86% 24 weeks	77% 6 months	69% 24 weeks, 46% 52 weeks	NR
Subsequent allogeneic-SCT	22%	6%	10%	NR

Notes: [a]Includes 3 cohorts as described in text.
Abbreviations: BV tx, brentuximab vedotin therapy; ASCT, autologous stem cell transplant; cHL, classical Hodgkin's lymphoma; CR, complete response; PD-1, programmed death 1; PR, partial response; PFS, progression free survival; allo SCT, allogenic stem cell transplant; NR, not reported.

PFS of 14.8 months, median duration of partial response (PR) of 13.1 months, and median duration of CR not reached.[77] At updated follow-up, 37 (46%) patients had discontinued therapy, including 19 (24%) due to disease progression, 7 (9%) who proceeded to allogeneic SCT, and 5 (6%) who discontinued therapy due to AEs.[77]

Consistent with the immune-mediated mechanism of action of nivolumab, delayed responses were seen, including 1 patient with appearance of a new lesion at week 9 of therapy who went on to have 2 subsequent negative positron emission tomography scans at weeks 25 and 33.[65] By protocol definition, this patient's best response was defined as progressive disease despite the subsequent response to treatment. Given the pattern of late response and benefit beyond traditionally defined progression, the trial was amended to allow patients to continue nivolumab beyond progression at the investigator's discretion. Of 9 patients who continued nivolumab beyond progression, 5 maintained reduction in total tumor volume.[65] In an exploratory post hoc analysis, higher PD-L1 expression was associated with improved best overall response, but the majority of patients achieved at least PR even in the lowest quartile of PD-L1 expression.[65] Based on the results of this trial, on May 17, 2016, the FDA granted accelerated approval to nivolumab for the treatment of patients with cHL that has relapsed or progressed after ASCT and posttransplantation BV.

Safety and tolerability

To date, experience with nivolumab in both cHL and other malignancies shows a unique but acceptable toxicity profile when compared with conventional chemotherapy (Table 2). PD-1 functions to attenuate immune response in order to prevent autoimmunity and, as could be anticipated, patients treated with nivolumab have demonstrated autoimmune reactions following treatment, termed immune-related AEs (IRAEs).[78] These IRAEs include acute hepatitis, colitis, dermatitis, pneumonitis, pancreatitis, and autoimmune endocrine disorders, including hypophysitis and immune-related thyroid disease.[74,79,80] The combination of nivolumab with other immune checkpoint inhibitors such as the anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4) monoclonal antibody ipilumumab has been associated with more frequent incidence of high grade IRAE, but serious adverse effects are also seen in a minority of patients treated with single-agent nivolumab, leading to drug discontinuation in about 5% of cases.[67,81] Grade 3–4 IRAEs are most often treated initially with corticosteroid therapy; TNF inhibitors or other immunosuppressant therapy appears to be effective in some steroid refractory cases.[74] The management of these autoimmune toxicities is reviewed in detail separately.[74,78,82] While the side effects seen with PD-1 inhibitors have been similar across disease groups, there has been a suggestion of a higher incidence of hematologic toxicities in patients with lymphoma compared to those with solid organ malignancies.[83] The reason for this disparity is unclear, but may be in part due to the heavy pretreatment of the patients with lymphoma included in early studies.

In the first published study of nivolumab for the treatment of cHL, AEs of any grade were observed in 22 of 23 patients, with grade 3 or 4 events seen in 12 (52%) patients.[64] The most common adverse effects attributed to treatment were rash (22%), thrombocytopenia (17%), pyrexia (13%), diarrhea (13%), nausea (13%), pruritus (13%), and fatigue (13%).[64] Two patients experienced grade 3 AEs were believed to be drug related, acute pancreatitis and myelodysplastic syndrome in 1 patient each.[64] The patient with myelodysplastic syndrome was heavily pretreated with 6 lines of prior chemotherapy, radiation therapy, and ASCT. Newly diagnosed hypothyroidism was reported in 2 (9%) patients, and no other autoimmune endocrine toxicities were noted.

Table 2 Summary of common and serious AEs reported with nivolumab

Common therapy-related AEs	Incidence	Serious therapy-related AEs	Incidence
Rash	15%–22%[64,65]	Neutropenia	5%[65]
Fatigue	13%–25%[64,65]	Elevated AST/ALT	3%[65]
Infusion Reaction	9%–20%[64,65]	Elevated Lipase	3%[65]
Pyrexia	13%–14%[64,65]	Pneumonitis	3%[65]
Arthralgia	14%[65]	Autoimmune hepatitis	1%[65]
Nausea	13%[64,65]		
Diarrhea	10%–13%[64,65]		
Hypothyroidism	9%[64]		
Thrombocytopenia	1%–17%[64,65]		

Abbreviation: AEs, adverse events.

Grade 1 hypersensitivity infusion reactions were noted in 2 patients (9%) not requiring treatment discontinuation. There were no deaths due to toxicity and no grade 4 AEs attributed to nivolumab.[64]

In the landmark phase II study of 80 patients with relapsed or refractory cHL following ASCT and BV treated with nivolumab, 71 (89%) patients had a reported treatment-related AE of any grade.[65] The most commonly reported treatment-related AEs were fatigue (25%), infusion-related reaction (20%), rash (15%), pyrexia (14%), arthralgia (14%), and diarrhea (10%).[65] Grade 3 AEs were reported in 17 (21%) patients, and 3 patients had reported grade 4 events (4%). Drug-related grade 3 AEs included neutropenia (5%), increased lipase (3%), increased AST/ALT (3%), abdominal pain (3%), and rash (1%).[65] Two patients discontinued treatment due to AEs believed to be drug related; 1 patient with newly diagnosed autoimmune hepatitis, and 1 patient with increased AST/ALT. One patient died from multiorgan failure and was found on autopsy to have a new diagnosis of EBV-positive T-cell lymphoma, believed to be unrelated to nivolumab therapy.[65] Pneumonitis was seen in 2 patients (1 with grade 2 and the other with grade 3), which was responsive to corticosteroids in both cases. The patient with grade 3 pneumonitis had already discontinued nivolumab due to grade 3 autoimmune hepatitis diagnosed prior to the onset of pneumonitis.[65] Most cHL patients are treated with agents with potential lung toxicity including bleomycin, radiation therapy, and BV, and therefore may be at an increased risk for pulmonary toxicity or pneumonitis. Despite this potential increased risk, the incidence of pneumonitis in published cHL trials with nivolumab has been rare and is similar to that reported in other malignancies.[64,65,78] Hypothyroidism has been seen in 5%–10% of patients treated with nivolumab to date, and clinicians should monitor thyroid function through routine thyroid-stimulating hormone measurement during treatment.[64,68–70] Although less commonly observed with PD-1 inhibitors than with CTLA-4 inhibitors, providers should be aware of the potential for autoimmune hypophysitis with checkpoint inhibition and be alert to signs and symptoms of adrenal insufficiency or central hypothyroidism.[78] New-onset type I diabetes mellitus has been reported in at least 1 instance in a patient with cHL treated with nivolumab.[84] While rare and not yet reported in patients with cHL treated with nivolumab, it is worthwhile for the clinician to be aware of the potential for life-threatening myocarditis, rhabdomyolysis, neurologic disorders including myasthenia gravis and Guillain-Barré syndrome, and skin reactions including Stevens–Johnson syndrome, bullous pemphigoid, and toxic epidermal necrolysis, which have been seen in patients following checkpoint blockade.[80,82,85–88] Despite the side effects associated with PD-1 blockade, nivolumab is relatively well tolerated overall and generally associated with fewer high-grade side effects when compared with conventional chemotherapy.[89]

Other PD-1 blocking agents, pembrolizumab

Pembrolizumab (Keytruda, formerly lambrolizumab and MK-3475, Merck Oncology, Kenilworth, NJ, USA) is a humanized monoclonal IgG4 antibody also targeting PD-1. Pembrolizumab has a higher reported affinity for PD-1, but whether this is clinically meaningful remains unclear given the wide therapeutic range seen with PD-1 inhibitors.[90]

In the Phase 1b KEYNOTE 013 trial, 31 patients with relapsed/refractory cHL were treated with pembrolizumab at a dose of 10 mg/kg every 2 weeks.[91] The patients enrolled were heavily pretreated, with over half (55%) having received at least 5 prior lines of therapy. The majority (77%) of patients had previously undergone ASCT and, by design, all patients had failed BV, including 18 (58%) patients with BV-refractory disease. Of the 31 patients, 5 (16%) patients achieved a CR and 15 (48%) patients

attained a PR for an ORR of 65%. The responses achieved appeared to be durable in many patients, with a PFS rate of 46% at 1 year. Treatment-related AEs were reported in 68% of patients including hypothyroidism (16%), diarrhea (16%), and pneumonitis (10%). Two patients were taken off therapy due to AEs; 1 with grade 2 pneumonitis and 1 with grade 3 nephrotic syndrome, both of whom responded to treatment with corticosteroids after discontinuation of pembrolizumab.[91] Grade 3 AEs not requiring treatment discontinuation were reported in 4 patients including colitis, joint swelling, back pain, axillary pain, and elevated liver aminotransferase levels.

In the phase 2 KEYNOTE-087 trial (NCT 02453594), 210 patients with relapsed/refractory cHL were enrolled across 3 cohorts, including patients with relapsed/refractory disease after ASCT and subsequent treatment with BV (cohort 1), patients ineligible for ASCT due chemo-resistant disease and BV therapy failure (cohort 2), and patients with prior ASCT without subsequent BV therapy (patients with and without exposure to BV prior to ASCT allowed) (cohort 3). Patients were treated with pembrolizumab 200 mg every 3 weeks, and response was assessed every 12 weeks. Preliminary results were reported at the 2016 ASH annual meeting: ORR was 67% (29% CR) in cohort 1, 65% (25% CR) in cohort 2, and 68% (22% CR) in cohort 3, with any degree of reduction in tumor volume from baseline seen in 94% of patients.[92] At the time of data presentation, 115 patients had an ongoing response. Reported treatment-related toxicities included pyrexia (11%), hypothyroidism (11%), diarrhea (7%), rash (6%), and nausea (6%).[92] Grade 3 treatment-related toxicities included neutropenia (1%), thrombocytopenia (1%), and diarrhea (1%), with no reported treatment-related deaths.[92] While these results both in terms of activity and safety are comparable to those reported with nivolumab in the treatment of cHL, it is unknown whether 1 agent has a superior efficacy or safety profile over the other for the treatment of cHL in the absence of a head-to-head clinical trial. On the basis of KEYNOTE 013 and 087 trials discussed above, on March 15, 2017 the US FDA granted accelerated approval to pembrolizumab for the treatment of patients with refractory cHL or patients with cHL who have relapsed after 3 or more prior lines of therapy, making it the second PD-1 inhibitor approved for the treatment of cHL.

Risk in pre- and post- allogeneic SCT

In selected cHL patients with relapsed or refractory disease after ASCT, allogeneic SCT can provide potential durable disease control with similar PFS and OS seen with either myeloablative or reduced intensity conditioning regimens.[29,93] PD-1 inhibition has been shown in preclinical models to augment acute GVHD due to T-cell disinhibition, raising concern regarding the safety of checkpoint inhibition in patients who are either being considered for allogeneic SCT or who have relapsed after allogeneic transplant.[94,95] Outcomes for 17 cHL patients treated in the phase I study (Checkmate 039) and multicohort phase II (CheckMate 205) trials of nivolumab who underwent subsequent allogeneic SCT were reported at the 2016 ASH annual meeting.[96] Of the 17 patients treated, there were 6 deaths, all due to non-relapse mortality. Five of the 6 patients died from acute GVHD after undergoing reduced-intensity transplant. Acute GVHD was seen in 82% of patients, most commonly occurring in the skin (12 patients including 4 with grade 4), GI tract (4 with grade 4), and liver (4 with grade 4). Hyper-acute GVHD occurring within 14 days of transplant was seen in 2 patients, and 2 patients developed encephalitis, including 1 patient with no infectious cause identified who recovered after treatment with corticosteroids. Hepatic sinusoidal obstruction syndrome was reported in 1 patient who died from multiorgan refractory acute GVHD. The proportion of patients experiencing acute GVHD was higher than expected following allogeneic SCT, including atypical manifestations of GVHD such as apparent autoimmune encephalitis and hyper-acute GVHD.[96]

The largest published experience to date regarding allogeneic SCT following treatment with PD-1-targeting monoclonal antibodies come from a retrospective study of 39 patients with lymphoma, including 31 patients with cHL, treated with either nivolumab (72%) or pembrolizumab (28%) across multiple studies who went on to receive allogeneic SCT.[97] Four of these patients were treated with a combination of a PD-1 inhibitor with ipilumumab, and the remainder received PD-1 inhibitor monotherapy; 49% underwent salvage therapy after treatment with PD-1 inhibitor and before SCT. Of the patients included in the analysis, 38 of 39 underwent reduced intensity conditioning, all underwent T-cell replete transplant, with a median time from last treatment with PD-1 inhibitor to SCT of 62 days.[97] Cumulative incidence of grade 3–4 acute GVHD was 23%, including 13% of patients with grade 4 acute GVHD with a median onset of 27 days. Four treatment-related deaths were reported, including 3 patients who died from acute GVHD with onset within 14 days of SCT and 1 patient who died due to sinusoidal obstruction syndrome.[97] Seven (18%) patients experienced a prolonged noninfectious febrile syndrome, which was treated with corticosteroids in all cases. Despite these toxicities, the 1-year PFS and OS rates

were 89% and 76%, respectively, with a cumulative incidence of relapse of 14% and nonrelapse mortality of 11%. A higher incidence of acute GVHD (100%) including 1 case of fatal GVHD was seen in patients treated with both ipilumumab and PD-1 inhibition in comparison to those receiving PD-1 inhibitors alone, suggesting a potential increased risk of acute GVHD with combined checkpoint inhibition prior to SCT. Correlative studies showed that, when compared to a matched control cohort, patients treated with PD-1 inhibition prior to SCT had a decreased ratio of $CD4^+$ T-regulatory cells (T-regs) to $CD4^+$ T-cells up to 1 month after transplant, as well as decreased PD-1 expression on T-cells seen up to 6 months after transplant.[97] A lower proportion of T-regs has been associated with increased incidence of acute GVHD, but may also result in enhanced graft-versus-lymphoma effect.[98] These findings suggest that the immune effects of PD-1 inhibition remain present months after cessation of PD-1 inhibitor therapy, well beyond what would be expected by pharmacokinetic models of drug clearance.[97] Clinicians should be aware of the potential risks of the combination of PD-1 blockade followed by allogeneic SCT, but based on experience to date this approach should not be considered contraindicated. More mature data from ongoing and completed trials as well as validation of these findings in a larger cohort of patients will better define the magnitude of the risk for GVHD and the risks and benefits of allogeneic SCT in patients responding to checkpoint inhibition.

Several case reports have demonstrated clinical responses with nivolumab in patients with relapsed cHL following allogeneic SCT, but there has also been 1 case reported of fatal GVHD in a patient treated for relapsed cHL with pembrolizumab who was over 18 months out from transplant.[99–105] The results from a retrospective series of 27 patients (26 with cHL) treated at 8 institutions for relapsed lymphoma following allogeneic SCT with either nivolumab or pembrolizumab were reported at the 2016 ASH annual meeting with 10 patients experiencing acute GVHD after treatment, including 3 patients with fatal GVHD.[106] The ORR in this series was 79%, including 13 patients with CR. More recently, Herbaux et al[107] reported outcomes of 20 patients with relapsed cHL following allo-SCT treated with nivolumab at the standard dose of 3 mg/kg every 2 weeks at medical centers across France. The median patient age was 33; all patients had received prior ASCT and BV. Ten (50%) patients had a history of prior acute GVHD (grade I or II) and 3 (15%) had a history of limited chronic GVHD. All patients were off of immunosuppression for ≥4 weeks prior to treatment initiation. Acute GVHD was seen during the first cycle of treatment in 6 (30%) patients, including 1 patient with febrile multiorgan dysfunction who died within 3 weeks of his first treatment and 3 patients with steroid refractory GVHD which was fatal in 1 of the 3 cases.[107] All of these 6 patients had a prior history of acute GVHD. Flare of chronic GVHD was not observed following nivolumab treatment in this cohort of patients. Other toxicities included grade 4 neutropenia and grade 3 thrombocytopenia in 1 patient and grade 2 cerebellar ataxia in a second patient, which required therapy discontinuation in both cases. The ORR was 95%, including a CR rate of 42%. After a median follow-up of 370 days, the 1-year PFS and OS rates were 58.2% and 78.7%, respectively, with 5 relapses reported at last follow-up.[107]

Interestingly, Raiola et al[108] reported an encouraging 3-year PFS and OS rate of 63% and 77%, respectively, in 26 cHL patients treated with nonmyeloablative conditioning regiment followed by a haploidentical SCT and posttransplant high-dose cyclophosphamide for GVHD prophylaxis. The incidence of grade II-IV acute GVHD and of chronic GVHD was 24% and 8%, respectively, suggesting exploration of the potential role of cyclophosphamide in reducing the incidence and the severity of checkpoint-inhibitor induced GVHD through the elimination of allo-reactive T-cells.

Although the high ORR seen in these retrospective series is promising, the risk of severe and treatment-refractory acute GVHD in this setting is a concern warranting further evaluation and prospective study to better quantify the magnitude of this risk and to evaluate treatment options for GVHD in this setting. For patients with cHL relapsing after allogeneic SCT, given the limited options for inducing durable remission, checkpoint blockade is still a consideration with the awareness of the potential for life-threatening GVHD.

Nivolumab in combination

Although ORR to nivolumab in cHL has been >60%, the majority of patients achieve PR as best response and a subset of patients progress while on therapy. Whether improved response rates can be achieved with combination therapy is an area of active investigation. At the time of writing, there are 14 clinical trials of nivolumab that include patients with cHL listed on clinicaltrials.gov, 9 of which are open to enrollment (Table 3). We will briefly discuss potential rational combinations of treatment with PD-1 inhibitors including combination with alternate checkpoint inhibitors, combination with cytotoxic chemotherapy, and combination with biologic agents.

Combining multiple checkpoint inhibitors has been shown to be effective in melanoma, where the combination

Table 3 Summary of current clinical trials of nivolumab combination therapy in cHL

Trial name	Agents	Untreated or relapsed/refractory	Phase	Patient ages for eligibility (years)	Trial status
NCT 02572167	N + BV	R/R	I/II	≥18	Open
NCT 02181738 Cohort D	N + AVD	Untreated	II	≥18	Closed to accrual, ongoing
NCT 27758717	N + BV	Untreated	II	≥60[a]	Open
NCT 01896999	N + BV + ipi	R/R	I	≥18	Open
NCT 02927769	N + BV	R/R	II	≥5–30	Not yet open
NCT 02940301	N + ibrutinib	R/R	II	≥18	Open
NCT 02304458[b]	N ± ipi	R/R	I/II	12 months-30 years old	Open
NCT 02327078[b]	N + epacad	R/R	I/II	≥18	Open
NCT 01822509[b]	N or ipi	R/R post-allogeneic SCT	I	≥18	Open
NCT 01592370[b]	N + ipi or lirilumab[c]	R/R	I	≥18	Open
NCT 01716806	N + BV (Arm D)	Untreated	II	≥60	Open
NCT 03016871	N + ICE	R/R- 2nd line	II	≥15	Not yet open
NCT 03004833	N + AVD	Untreated	II	≥18–60	Not yet open
NCT 02973113[d]	N + EB-VSTS	R/R	I	All ages weighing ≥12 kg	Not yet open

Notes: [a]Also includes patients ineligible for typical therapy under age the age of 60 years; [b]Also includes other tumor types in addition to Hodgkin's lymphoma; [c]Includes alternate cohorts for patients with multiple myeloma with additional agents in combination with nivolumab; [d]Open to patients with EBV-positive lymphoma including EBV-positive cHL.
Abbreviations: N, nivolumab; AVD, doxorubicin, vinblastine, and dacarbazine; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; epacad, epacadostat; EBV, Epstein Barr virus; ICE, ifosfamide, carboplatin, and etoposide; ipi, ipilimumab; EB-VSTC, Epstein Barr virus specific T cells; R/R, relapsed/refractory.

of nivolumab with the CTLA-4 inhibitor ipilimumab lead to increased response rates, albeit with associated increased toxicity.[81] Preliminary results from the CheckMate 039 study of ipilumumab in combination with nivolumab for patients with relapsed/refractory hematologic malignancies were recently presented, with 5 of 65 (8%) patients discontinuing treatment due to AEs at a median follow-up of 11.4 months; no treatment-related deaths were reported.[109] A total of 19 (29%) patients experienced grade 3 toxicity, with the most commonly reported toxicities of any grade being pyrexia (23%), fatigue (23%), and diarrhea (18%).[109] The ORR for the 31 patients with cHL treated with ipilimumab and nivolumab was 74%, and the rate of CR was 19%.[109] Although the relatively small number of cHL patients limits interpretation of results, the response rates seen in this trial are similar to those seen with nivolumab monotherapy. The hypothesis that the combination of checkpoint inhibitors will improve response rates over a single-agent approach should be tested in future prospective clinical trials, but at the present time there is no evidence to support this approach in cHL.

Combining checkpoint inhibition with conventional chemotherapy is based on the rationale of increasing neo-antigen expression on tumor cells as a consequence of chemotherapy treatment to stimulate a T-cell-mediated antitumor response, which would be further enhanced by the addition of a checkpoint inhibitor.[110] However, the potential benefit of this approach may be limited by the immune-suppressive effects of cytotoxic agents. A phase II trial of nivolumab combined with doxorubicin, vinblastine, and dacarbazine (AVD) for previously untreated patients with cHL (NCT02181738, CheckMate205 Arm D) is currently closed to accrual, with results not yet reported as of the time of writing. Future trials are planned examining the safety and efficacy of the combination of nivolumab with cytotoxic chemotherapy in both the frontline setting and for relapsed or refractory disease (NCT03016871 and NCT03004833) that will shed further light on the feasibility and efficacy of this approach.

The combination of BV with nivolumab is of particular interest given the high response rates with both drugs as monotherapy.[25,65] Preliminary results from 2 early-phase studies of the combination of BV and nivolumab were recently reported at the 2016 ASH annual meeting.[111,112] The first is a phase 1/2 study (NCT02572167) of 25 cHL patients treated with BV dosed at 1.8 mg/kg in combination with nivolumab dosed at 3 mg/kg, both given on day 1, except for cycle 1 where nivolumab was given on day 8, of a 21-day cycle for up to 4 cycles after failure of frontline therapy and prior to ASCT.[111] Of the 25 patients enrolled, 16 (64%) had relapsed and 9 (36%) had refractory disease after frontline treatment. Toxicity was acceptable, with 3 (15%) patients experiencing grade 3 toxicity, but no grade 4 toxicity or toxicity leading to discontinuation of treatment reported.[111] An increased incidence of infusion reactions were noted with BV and nivolumab when the 2 drugs were administered together, but this was improved with the addition of hydrocortisone and antihistamine premedication. Six patients had completed treatment at the time of the presentation with an ORR of 100%, including 3 patients with complete metabolic

response.[111] Results from the phase I ECOG-ACRIN Cancer Research Group E4412 trial with 10 relapsed/refractory cHL patients treated with BV at a dose of 1.2 mg/kg or 1.8 mg/kg combined with nivolumab at a dose of 3 mg/kg given every 21 days for 16 cycles were also reported at the same meeting.[112] Grade 3 toxicity was observed in 2 of 10 patients including 1 patient treated with BV at a dose of 1.8 mg/kg who discontinued treatment due to grade 3 pneumonitis and grade 3 typhlitis.[112] No grade 4 toxicities were observed, and the remaining 9 patients were able to complete treatment. Of 8 patients who were evaluable for response at the time of presentation, 5/8 achieved CR and the remaining 3 achieved PR.

Finally, the use of biological agents in combination with PD-1 inhibition is another potential future approach to combination therapy. DNA methyltransferase inhibitors were shown in a preclinical ovarian cancer model to upregulate PD-L1 expression, suggesting a potential role for DNA methyltransferase inhibitors in priming patients for sensitization to checkpoint inhibitor therapy.[113] In support of this role for epigenetic therapy, in a small single-institution case series of patients treated with either pembrolizumab or nivolumab, 5 cHL patients who were previously treated with azacitidine in combination with romidepsin on a prior clinical trial all achieved a CR to PD-1 inhibitor therapy.[114] While this higher-than-expected rate of CR is provocative, results from future prospective clinical trials are needed to further evaluate this potential combination therapy.

The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (Imbruvica, Phamacyclics, and Janssen) has been successfully employed in the treatment of chronic lymphocytic leukemia as well as subtypes of non-Hodgkin's lymphoma, including mantle cell lymphoma and Waldenström's macroglobulinemia.[115–121] While B-cell non-Hodgkin lymphoma cells exhibit nearly universal BTK expression, BTK expression by RS cells has been reported in only a minority (22%) of cHL biopsy specimens.[122] Moreover, RS cells lack several components of the B cell receptor signaling pathway, and, to our knowledge, there is no published evidence that this pathway is constitutively activated in cHL. However, in addition to targeting BTK signaling, ibrutinib has been shown to irreversibly inhibit interleukin-2-inducible kinase (ITK), promoting a shift to Th-1-dominant signaling, thereby enhancing T-cell response to antigenic stimuli.[123] In a published case report, 2 patients with cHL with relapsed disease following allogeneic SCT were treated with ibrutinib. One achieved a PR with subsequent progression 4 months later, and 1 achieved CR and remained in CR at 6 months follow-up.[124] In 1 of these patients, expression of interferon-inducible-protein 10 was reported in serum samples after treatment, suggesting shift to Th-1 signaling and a potential immune modulatory effect of ibrutinib mediated by its activity on ITK.[124] The hypothesis that ibrutinib may enhance the immune effect of checkpoint inhibition in cHL warrants exploration in clinical trials, with a current phase II trial open to enrollment (NCT 02940301).

At this time, until results from these and future studies are available, the use of nivolumab in combination with other agents for the treatment of cHL remains investigational.

Patient-focused perspectives

As discussed previously, the side effects seen to this point with nivolumab in clinical practice are distinct from the side effect profile seen with cytotoxic agents that remain the mainstay of treatment for patients with cHL in the frontline setting and at first disease relapse. The long-term effects of PD-1 blockade are unknown, and this as well as the durability of response will be an important question for patients as outcomes mature.

Given the wide therapeutic index seen in trials utilizing nivolumab in other disease groups, 1 question for patients is the necessity of an every 2 week dosing schedule. As discussed previously, the elimination half-life of nivolumab is 26.7 days, and ongoing prospective trials of combination therapy with nivolumab in cHL and other diseases are utilizing an every 3-week dosing schedule. As patients with clinical response to nivolumab may remain on therapy for months and even years, the question of whether the dosing schedule can be switched to an every 3-week schedule and whether nivolumab can be safely stopped at any point is relevant to the quality of life for patients benefitting from this therapy. Results from ongoing prospective trials with nivolumab will help in answering this important question in the coming years.

Conclusion and future directions

Nivolumab has demonstrated impressive response rates and in some cases durable remissions in patients with cHL. Given the excellent response rates and acceptable side effect profile, nivolumab received FDA approval for cHL patients who have progressed following both prior ASCT and BV therapy. The long-term durability of response and the magnitude of benefit and risk of allogeneic SCT in patients who have responded to nivolumab will be better elucidated with long-term follow-up from completed trials of nivolumab monotherapy and potential future prospective investigation. Preliminary results suggest that administration of pembrolizumab results in similarly impressive responses in this patient population; whether a clinical meaningful difference between these 2 PD-1 inhibitors exists would be best answered in a phase III, head-to-head clinical trial.

Given the high response rates seen with nivolumab, whether it can be incorporated into earlier lines of therapy remains to be seen in future trials, including ongoing trials of the combination of nivolumab with AVD chemotherapy in untreated patients (NCT 02181738) and the combination of nivolumab with BV in patients aged ≥60 years (NCT 27758717). Incorporating nivolumab into earlier lines of therapy offers the potential to reduce exposure to cytotoxic therapy and the associated risks and toxicities and abrogates the potential immunosuppressive effect of prior lines of therapy. While the ultimate role of nivolumab in the treatment of cHL remains to be seen, it is already an established part of treatment in the relapsed and refractory setting and represents a success story in the rational application of genomic-guided cancer therapy.

Author contributions

DAB and LA contributed toward literature review, analysis, drafting, and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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