Nivolumab for the Treatment of Classical Hodgkin Lymphoma

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Abstract

Objective: To review nivolumab for the treatment of classical Hodgkin lymphoma (cHL). **Data Sources:** Literature searches were conducted in Medline (1946 to May week 3 2017), EMBASE (1974 to 2017 week 22), and Google Scholar using the terms Hodgkin lymphoma AND nivolumab. **Study Selection and Data Extraction:** Two clinical trials (phase I and phase II) were identified. **Data Synthesis:** Nivolumab inhibits programmed death receptor-1 allowing for increased T-cell mediated immune surveillance of tumors. Nivolumab was evaluated in cHL patients after failure of autologous stem cell transplantation and brentuximab vedotin consolidation. Patients received nivolumab 3 mg/kg every 2 weeks. In the phase I trial, the objective response rate was 87% (95% confidence interval [CI] = 66-97) and the rate of progression-free survival (PFS) at 24 weeks was 86% (95% CI = 62-95). The most common adverse events (AE) included rash (22%) and decreased platelet count (17%). Following extended follow-up at a median of 86 weeks, 50% of the initial responders maintained a durable response. In the phase II clinical trial, 53 patients (66.3%, 95% CI = 54.8-76.4) achieved an objective response and PFS at 6 months was 76.9% (95% CI = 64.9-85.3). The common AE were fatigue (25%), infusion-related reactions (20%), and rash (16%). After further follow-up at a median of 15.4 months, 12-month overall survival was 94.9% (median overall survival not reached). **Conclusions:** Nivolumab is an effective option in treating patients with relapsed/refractory cHL with an acceptable safety profile. Further studies are needed to investigate the role of nivolumab for the treatment of cHL.

Keywords

lymphoma, pharmacology, basic, immune globulin, hematology, pharmacokinetics

Background

Hodgkin lymphoma (HL) is a hematologic malignancy that will be diagnosed in approximately 8200 patients in the United States in 2017.¹ Approximately 95% of cases will histologically be diagnosed as classical HL (cHL).² The prognosis for cHL is favorable with a 5-year survival rate of approximately 86%.¹ While responses to current first-line treatment, which consists of combination chemotherapy with or without radiation, are noteworthy, there remains a need for new modalities to manage relapsed or refractory cases. The standard of care for treating most relapsed/refractory patients is high-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT).^{2,3} Although a durable response is expected following ASCT, an estimated 40% to 50% of patients will experience disease recurrence.⁴ Prognosis following failed ASCT is poor with an estimated overall survival (OS) rate of 2.4 years.⁵

Immune checkpoint inhibitors have changed the treatment paradigm for many malignancies including non-small cell lung cancer and melanoma. These agents, particularly the programmed death receptor-1 (PD-1) inhibitors, may

also have a role in cHL. Programmed death ligands 1 and 2 (PD-L1 and PD-L2) are overexpressed on the cell surface of Reed-Sternberg cells due to genetic alterations of chromosome 9p24.1.⁶ Furthermore, chromosome 9p24.1 amplification may lead to activation of *JAK2* and thus JAK-STAT signaling, resulting in further PD-L1 expression.^{6,7}

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that inhibits PD-1.⁸ Based on the results of 2 clinical trials, the Food and Drug Administration (FDA) has granted accelerated approval of nivolumab for the treatment of cHL following ASCT and brentuximab vedotin (BV).⁹ The continued approval of nivolumab for this indication is contingent on the verification of the current results in ongoing phase III clinical trials.

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Data Sources

A literature search of Medline (1946 to May week 3 2017) and EMBASE (1974 to 2017 week 22) was conducted using the terms Hodgkin lymphoma AND nivolumab. Clinical trials conducted in humans that prospectively evaluated the use of nivolumab monotherapy for the treatment of cHL following ASCT and BV were included. Google Scholar was reviewed to identify additional relevant literature.

Pharmacology

The immune system plays a major role in eliminating circulating malignant cells.¹⁰ A tumor, however, can alter its microenvironment in order to evade immune system recognition and subsequent elimination.¹¹

The immune checkpoint pathway prevents overstimulation of the immune system and limits autoimmunity. In this pathway, negative regulatory molecules such as PD-1 and its ligands inhibit the function of T-cells to blunt an immune response.¹² By exploiting this pathway, an equilibrium between the tumor and the immune system develops, which ultimately limits tumor destruction and allows the tumor to progress.¹³

In the PD-1 immune checkpoint pathway, PD-L1 and PD-L2 bind to PD-1 receptors temporarily inhibiting T-cell activation and proliferation leading to failure of the T-cell-mediated immune response.¹⁴ Nivolumab is a 146-kDa IgG4 monoclonal antibody that binds to the PD-1 receptor preventing the interaction of the receptor with the ligands resulting in enhanced T-cell functioning and subsequent immunologic response resulting in tumor growth suppression.⁸

Pharmacokinetics

Population-based pharmacokinetics were established in 909 patients with solid tumors who received nivolumab in single or multiple doses ranging from 0.1 to 20 mg/kg intravenously (IV) every 2 to 3 weeks.^{8,15} Nivolumab follows a linear, 2-compartment model with first-order elimination.¹⁵ The terminal half-life is approximately 25 days with steady-state concentrations achieved by week 12 when dosed at 3 mg/kg IV every 3 weeks.⁸ Nivolumab exposure increased proportionally to the dose when administered in doses ranging from 0.1 to 10 mg/kg IV every 2 weeks.

The approximate steady state volume of distribution (VD_{ss}) and clearance (CL_{ss}) at steady state were 8 L and 9.5 mL/hour, respectively.¹⁵ Notably, age, weight, gender, race, baseline lactate dehydrogenase, PD-L1 expression, solid tumor type, and tumor size did have a significant impact on the CL_{ss} of nivolumab.^{8,15}

The impact of renal dysfunction on the CL_{ss} of nivolumab was assessed in patients with mild (estimated glomerular

filtration rate [eGFR] 60-89 mL/min/1.73 m²), moderate (eGFR 30-59 mL/min/1.73 m²), and severe (eGFR 15-29 mL/min/1.73 m²) renal dysfunction.⁸ No clinically significant changes in clearance were noted in patients with renal dysfunction compared to those with normal eGFR.

Nivolumab was studied in patients with mild hepatic impairment (total bilirubin [TB] $\leq$ the upper limit of normal [ULN] and aspartate aminotransferase [AST] $>$ ULN or TB $<$ 1-1.5 times ULN and any AST); however, its use was not investigated in patients with moderate (TB $>$ 1.5-3 times ULN and any AST) or severe impairment (TB $>$ 3 times ULN and any AST).⁸ Mild hepatic impairment did not alter the clearance of nivolumab in this evaluation.

Dosage Recommendations

The recommended dose of nivolumab for cHL is 3 mg/kg IV administered over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.⁸ No dose adjustments are required in the setting of renal insufficiency or mild hepatic impairment. Nivolumab has not been studied in patients with moderate or severe hepatic impairment; therefore, caution should be exercised when using this agent in patients with more advanced liver disease.

There are limited data on the use of nivolumab in pediatric patients. In one case series (patient ages 11, 15, and 17 years) and a single case report (patient age 7 years), nivolumab was administered at a dose of 3 mg/kg IV weeks 1 and 4 and then every 2 weeks thereafter, and 3 mg/kg IV every 2 weeks, respectively.^{16,17} At this time, the long-term safety and efficacy of nivolumab in pediatric patients is unknown, and the manufacturer does not recommend its use in this population.⁸ To date, no differences in efficacy and safety have been observed in elderly patients (≥ 65 years) compared to younger patients.

Based on the mechanism of action, nivolumab has the potential to cause fetal harm on exposure.⁸ Pregnant women should not receive nivolumab, and women of childbearing age should be counseled to use effective contraception during treatment and for a minimum of 5 months posttherapy. As with other immunoglobulins, nivolumab may enter into breast milk. Due to the potential for harm to the infant, breastfeeding is not advised while taking nivolumab.

Thyroid, liver, and renal function tests should be performed prior to administering nivolumab, and patients should be monitored occasionally during treatment.⁸ In one clinical trial, thyroid function (thyroid-stimulating hormone with reflexive free T4 and free T3) was evaluated every 6 weeks starting from the first dose of nivolumab.¹⁸ Liver function and renal function were evaluated within 72 hours prior to treatment, every other treatment cycle. Additional monitoring for immune-mediated reactions is also recommended.⁸ Dose and treatment modifications for such reactions can be found in Table 1.

Table 1. Recommendations for Immune-Mediated Reactions^a.

Immune-Mediated Adverse Reaction	Criteria for Dose and Treatment Modification ^a	Dose and Treatment Modification
Nephritis	Grade 2 or 3	Withhold until resolution to grade 0 or 1 and administer corticosteroids 0.5-1 mg/kg/day prednisone equivalents followed by taper; if no improvement or worsening, increase corticosteroids to 1-2 mg/kg/day prednisone equivalents followed by taper
	Grade 4	Permanently discontinue and administer corticosteroids 1-2 mg/kg/day prednisone equivalents followed by taper
Hepatitis	Grade 2	Withhold until resolution to grade 0 or 1 and administer corticosteroids 0.5-1 mg/kg/day prednisone equivalents; if resolution to grade 0 or 1 does not occur within 12 weeks, permanently discontinue
	Grade 3 or 4	Permanently discontinue and administer corticosteroids 1-2 mg/kg/day prednisone equivalents
Adrenal insufficiency	Grade 2	Withhold until resolution to grade 0 or 1
	Grade 3 or 4	Permanently discontinue therapy and administer corticosteroids 1-2 mg/kg/day prednisone equivalents
Colitis or diarrhea	Grade 2	Withhold until resolution to grade 0 or 1 and for symptoms lasting >5 days administer corticosteroids 0.5-1 mg/kg/day prednisone equivalents followed by taper; if symptoms persist or worsen increase corticosteroids to 1-2 mg/kg/day; permanently discontinue for recurrent colitis after restarting therapy
	Grade 3	Withhold until resolution to grade 0 or 1 and administer corticosteroids 1-2 mg/kg/day prednisone equivalents followed by taper; permanently discontinue for recurrent colitis after restarting therapy
	Grade 4	Permanently discontinue and administer corticosteroids 1-2 mg/kg/day prednisone equivalents followed by corticosteroid taper
Diabetes mellitus, type 1	Grade 3	Withhold until resolution to grade 0 or 1
	Grade 4	Permanently discontinue
Encephalitis	New onset, moderate to severe neurological symptoms	Withhold until resolution to grade 0 or 1 and administer corticosteroids 1-2 mg/kg/day prednisone equivalents followed by taper
	Definitive immune-mediated encephalitis	Permanently discontinue and administer corticosteroids 1-2 mg/kg/day prednisone equivalents followed by taper
Hypophysitis	Grade 2 or 3	Withhold until resolution to grade 0 or 1 and administer corticosteroids 1 mg/kg/day prednisone equivalents plus hormone replacement therapy as clinically indicated; if resolution does not occur within 12 weeks, permanently discontinue
	Grade 4	Permanently discontinue and administer corticosteroids 1 mg/kg/day prednisone equivalents plus hormone replacement therapy as clinically indicated
Hypo- or hyperthyroidism	—	Continue therapy and manage medically
Pneumonitis	Grade 2	Withhold until resolution to grade 0 or 1 and administer corticosteroids 1-2 mg/kg/day prednisone equivalents followed by taper
	Grade 3 or 4	Permanently discontinue and administer corticosteroids 1-2 mg/kg/day prednisone equivalents followed by taper
Skin	Grade 3 or suspected Steven-Johnson syndrome or toxic epidermal necrolysis	Withhold until resolution to grade 0 or 1 and administer corticosteroids 1-2 mg/kg/day prednisone equivalents followed by taper
	Grade 4 or confirmed Steven-Johnson syndrome or toxic epidermal necrolysis	Permanently discontinue and administer corticosteroids 1-2 mg/kg/day prednisone equivalents followed by taper

^aGrade based on National Cancer Institute Common Terminology Criteria for Adverse Events v.4.0.

Table 2. Most Common Adverse Reactions of Any Grade⁸.

Adverse Reaction	Safety Population (n = 263)		Efficacy Population (n = 95)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Fatigue	32	1.1	43	1.1
Upper respiratory infection	28	0.4	48	1.1
Pyrexia	24	0.8	35	1.1
Diarrhea	23	0.8	30	1.1
Cough	22	0	35	0
Rash	19	1.5	31	3.2
Musculoskeletal pain	19	1.1	27	1.1
Pruritus	17	0	25	0
Nausea	17	0	23	0
Vomiting	15	0.8	16	1.1
Infusion-related reactions	12	0.4	18	0
Hypothyroidism	12	0	17	0
Headache	12	0.4	12	1.1
Arthralgia	11	0	21	0
Peripheral neuropathy	11	0.4	21	0
Abdominal pain	11	0.8	13	2.1
Dyspnea	10	0.8	16	2.1
Pneumonia	9	3.0	19	5.3
Hyperglycemia	9	0.4	14	1.1
Constipation	9	0.4	14	0

Drug-Drug Interactions

To date, no studies have been conducted to evaluate drug-drug interactions with nivolumab.⁸

Adverse Events

The adverse event (AE) profile was established based on a safety population consisting of 263 patients with cHL.⁸ Nivolumab 3 mg/kg IV was given every 2 weeks until disease progression, unacceptable toxicity, or maximum clinical benefit. After receiving a median of 10 doses (range = 1-48 doses) with a median duration of therapy of 4.8 months (range = 0.3-24 months), nivolumab was discontinued in 4.2% of patients secondary to AE with dose delays occurring in 23% of patients. Serious AE were reported in 21% of patients. Among patients in the efficacy population (n = 95), serious adverse reactions occurred in 27% of patients following a median of 17 doses (range not provided). AE in both the safety and efficacy populations are summarized in Table 2.

In the safety population, immune-mediated pneumonitis occurred in 9 (3.4%) patients (8 grade 2, 1 grade 3).⁸ The median onset for this reaction was 2.2 months (range = 1 day to 10.1 months). All patients were treated with corticosteroids, which resolved the event in 7 patients. One patient with a grade 2 reaction ultimately discontinued therapy while 5 patients restarted therapy. Of these 5 patients, 1

experienced a pneumonitis recurrence. Three patients experienced a dose delay secondary to this reaction. The potential for addition immune-mediated AE is possible in patients receiving nivolumab for cHL. The management of these reactions is listed in Table 1.

Clinical Trials

There are currently 2 clinical trials that have prospectively evaluated the safety and efficacy of nivolumab monotherapy in the treatment of relapsed or refractory cHL after failure of ASCT and BV.^{18,19} The first trial was a phase I study (CheckMate 039) that was conducted to assess the safety and antitumor activity of nivolumab in patients with recurrent or refractory hematologic malignancies.¹⁹ HL patients were eligible for the expansion phase of this trial that followed the dose finding phase if they were ≥18 years of age, had not received an ASCT within the previous 100 days, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were excluded if they had autoimmune disease, a history of malignancy involving the central nervous system, prior solid organ transplant, or previous allogeneic hematopoietic stem cell transplant (HSCT). Nivolumab 3 mg/kg IV was administered on week 1 and week 4, and then every 2 weeks until disease progression or a complete response (CR) was achieved or for up to 2 years. The primary outcome was safety with secondary endpoints of efficacy and PD-L1 expression.

A total of 23 patients were enrolled in the HL expansion arm.¹⁹ Eight-seven percent of patients had received 3 or more prior lines of treatment with 78% receiving prior BV and 78% having undergone ASCT. A CR was seen in 4 (17%) patients and a partial response (PR) was observed in 16 (70%) patients making the objective response rate (ORR) 87% (95% CI = 66-97). Median progression-free survival (PFS) at 24 weeks was 86% (95% CI = 62-95) and median OS had not been reached by the time the trial results were published. Median follow-up lasted 40 weeks (range = 0-75 weeks). In addition, there was an increased expression of PD-L1 and PD-L2 seen in all 10 tumor specimens evaluated for biomarkers.

AEs of any grade were experienced by 22 (96%) patients.¹⁹ AE attributed to study medication were reported in 18 (78%) patients. The most common drug-related AE included rash (n = 5 [22%]) and decreased platelet count (n = 4 [17%]). Grade 3 drug-related AE occurred in 5 (22%) patients. The most frequent grade 3 events included lymphopenia (n = 1 [4%]), stomatitis (n = 1 [4%]), and elevated lipase (n = 1 [4%]). There was no incidence of grade 4 or 5 AE in this study. Serious AE occurred in 3 patients and included grade 3 myelodysplastic syndrome (MDS), lymph-node pain, and grade 3 pancreatitis. Of the 12 (52%) patients that discontinued nivolumab, 2 (9%) discontinued due to AE (MDS with thrombocytopenia and pancreatitis). In all other patients, AE were manageable. A total of 15 (65%) patients received $\geq 90\%$ of the intended doses with dose delays occurring in 9 (39%) patients.

In an extended follow-up at a median of 86 weeks (range = 32-107 weeks), 10 (50%) of the initial 20 patients that responded had maintained a durable response.²⁰ Two patients eventually converted from a PR to a CR with continued nivolumab treatment. Time to CR ranged from 3 to 88 weeks. Seven of the 10 patients received nivolumab for over 1.5 years with an additional patient receiving therapy for over 1 year. Four of the remaining 10 responders experienced disease progression with a time-to-progression ranging from 21.4 to 92 weeks. One patient discontinued due to AE, but maintained a response for the 120-day follow-up period. The remaining 5 patients discontinued nivolumab treatment to undergo stem cell transplant (4 allogeneic, 1 autologous) once remission was achieved.

A multicenter, multi-cohort, single-arm phase II trial (CheckMate 205) evaluated the efficacy and safety of nivolumab in patients with relapsed cHL.¹⁸ Patients were eligible if they were 18 years of age or older with recurrent cHL after failure of ASCT and subsequent BV if they had an ECOG performance status of 0 or 1. Patients were excluded if they received an ASCT within the previous 90 days, had received prior allogeneic HSCT, had known or suspected autoimmune disease, or were receiving corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressant drugs. Nivolumab 3 mg/kg IV was administered every

2 weeks until death, tumor progression, or excessive toxicity. The primary outcome of the study was the number of patients achieving an objective response (OR) evaluated by an independent radiological review committee (IRRC). Secondary endpoints included duration of response (DOR) by IRRC, percentage of patients achieving a CR or PR, and OR and DOR as assessed by the trial investigators.

A total of 80 patients were enrolled in the trial.¹⁸ The median number of previous lines of therapy was 4 (interquartile range = 4-7). After a median of 8.9 months of follow-up, 53 patients (66.3%, 95% CI = 54.8-76.4) experienced an OR with 7 CR (9%) and 46 PR (58%) per-IRRC. Median DOR was 7.8 months (95% CI = 6.6-not reached) and PFS at 6 months was 76.9% (95% CI = 64.9-85.3). AE occurred in 79 (99%) patients with grade 3 events in 26 (33%) and grade 4 events in 6 (8%). Three (4%) patients died during the study; however, these were not related to the treatment. Common AE included fatigue (n = 20 [25%]), infusion reactions (n = 16 [20%]), rash (n = 13 [16%]), arthralgia, fever (n = 11 each [14%]), nausea (n = 10 [13%]), diarrhea and itching (n = 8 each [10%]). Most of these reactions were grade 1 or 2 except for 1 incidence of grade 3 rash. Neutropenia (n = 4 [5%]) and elevated lipase levels (n = 5 [6%]) were the most common drug-related grade 3 or 4 AE.

In a subsequent report of CheckMate 205, 43 (54%) patients remained on treatment after a median duration of follow-up of 15.4 months (range = 1.9-18.5).²¹ IRRC-assessed ORR was 68% (95% CI = 56-78), which comprised 8% CR (95% CI = 3-16) and 60% PR (95% CI = 48-71). The median DOR was 13.1 months (95% CI = 8.8-not reached). Median PFS was 14.8 months (95% CI = 11.3 months-not available) and 12-month OS was 94.9% (median OS not reached). Most patients that discontinued treatment stopped due to disease progression (n = 19 [24%]). Other reasons for discontinuation included allogeneic HSCT (n = 7 [9%]) and AE (n = 5 [6%]).

Discussion

The management of patients with relapsed/refractory cHL is highly individualized. For most patients, HDCT followed by ASCT is the preferred option.^{2,3} This treatment approach has demonstrated an improvement in PFS compared to conventional chemotherapy in clinical trials.^{22,23} Long-term follow-up data suggest that approximately 50% of patients treated with HDCT followed by ASCT can be cured.^{24,25} BV was approved by the FDA in 2015 for post-ASCT consolidation in patients at high risk of relapse.²⁶ In a phase III trial, 1 year of BV following ASCT improved PFS by 18.8 months compared to placebo in a high-risk population (42.9 months [95% CI = 30.4-42.9] BV group vs 24.1 months [95% CI 11.5-not estimable] placebo group).²⁷ For individuals that do not respond to ASCT with or without BV consolidation, options are limited and prognosis is poor.²⁸

At this time, there is no standard treatment option for patients that fail ASCT. Treatment options that have been evaluated include bendamustine, bendamustine plus BV, BV monotherapy, anti-PD-1 monoclonal antibodies, and allogeneic HSCT.^{18,19,29-33} None of these treatments have been compared head-to-head; therefore, treatment decisions must be based on individual patient characteristics.

In addition to nivolumab, pembrolizumab was FDA approved in March of 2017 for adult and pediatric patients with refractory cHL or for those with disease that has relapsed after ≥ 3 lines of therapy.³⁴ The approval was based on a multicenter, open-label trial that evaluated pembrolizumab in 210 patients with relapsed/refractory cHL.³¹ After a median of 9.4 months of follow-up, the ORR was 69% (95% CI = 62-75) with 22% of patients experiencing a CR and 47% experiencing a PR. Median DOR was 11 months (range = 0.0-11.1).

Based on the differences in FDA approval between nivolumab and pembrolizumab, different populations may be eligible for one antibody over the other. Nivolumab, at this time, is approved only for relapse post-ASCT and BV.⁹ Pembrolizumab, on the other hand, may be given to a broader spectrum of patients including those that have relapsed post-ASCT and subsequent BV, those with chemotherapy-resistant disease that are ineligible for ASCT, as well as those that have received ASCT without BV consolidation.^{31,34} Data regarding nivolumab in these other populations is currently pending. These clinical trial results as well as other emerging data will further confirm the role of these drugs in the relapsed/refractory and upfront arenas.

Additional considerations in selection of these agents includes the dosing schedule and cost. The average wholesale price (AWP) for a 240 mg dose of nivolumab is \$6108.36 while a 200 mg dose of pembrolizumab is \$9026.40.³⁵ The AWP, however, does not reflect the full cost of treatment as associated fees and insurance coverage will differ. In addition, given that nivolumab is administered every 2 weeks and pembrolizumab is administered every 3 weeks, costs associated with administration and lost productivity will differ.^{8,31} A full pharmacoeconomic evaluation is needed to determine the cost-effectiveness of one treatment compared to the other. Patient preference for administration schedule should also be considered.

Another concern is the potential for the patient to proceed to allogeneic HSCT. At this time, the FDA is requiring additional data on the outcomes of patients that receive a PD-1 inhibitor prior to allogeneic HSCT.^{9,34} This request is based on an increase in complications, including some fatal events, observed in this population.^{8,31,36} The manufacturers recommend close monitoring for hyperacute and acute graft-versus-host disease, venoocclusive disease, steroid-requiring febrile syndrome, and other immune-mediated reactions in patients that received either agent prior to allogeneic HSCT.

There may be a role for these agents in managing relapse following allogeneic HSCT. Several case reports and case series as well as 2 retrospective studies have described the use of nivolumab following allogeneic HSCT failure.³⁷⁻⁴³ Although these reports have demonstrated the relative safety and efficacy of PD-1 inhibitors, the rate of acute graft-versus-host disease was 30% in one retrospective analysis and 37% in the other.^{42,43} Prospective data are needed to confirm the role of PD-1 blockade after allogeneic HSCT.

Conclusion

Nivolumab has shown significant activity and a manageable toxicity profile in heavily pretreated patients with relapsed/refractory cHL. The novelty of this agent comes from its ability to inhibit the interaction between PD-L1 and PD-1 resulting in improved T-cell mediated immune surveillance, resulting in tumor growth suppression. Multiple clinical trials are currently ongoing to evaluate nivolumab as monotherapy or in combination with other treatments for the initial management or for the treatment of relapsed or refractory cHL.

Declaration of Conflicting Interests

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