blood advances

TO THE EDITOR:

Nivolumab plus brentuximab vedotin for relapsed/refractory peripheral T-cell lymphoma and cutaneous T-cell lymphoma

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Relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL) are associated with poor survival outcomes[1-3]; therefore, there is a need for novel treatment strategies. Overexpression of programmed death ligand-1 (PD-L1) and CD30 are observed in a proportion of PTCL (15%-41%[4] and 46%-100%[5]) and CTCL (27%-73%[4] and 47%-76%[6,7]) cases, thus representing potential therapeutic targets. Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that inhibits programmed death-1 (PD-1)/PD-L1 binding,[8] whereas brentuximab vedotin (BV) is an anti-CD30 antibody–drug conjugate.[9] Limited studies have demonstrated modest activity of PD-1 inhibitor therapy in CTCL[10]; however, activity is more variable in PTCL.[11] BV was approved in CTCL based on improved efficacy in the phase 3 ALCANZA study; however, some responses were not durable.[12] Therefore, combining PD-1 inhibitors with BV may improve efficacy in patients with PTCL and CTCL. In the current analysis, we evaluated the efficacy and safety of nivolumab plus BV (NBV) in the PTCL and CTCL cohorts of the phase 2 CheckMate 436 (NCT02581631) study.

As previously described,[13,14] CheckMate 436 enrolled patients aged ≥18 years with R/R PTCL (excluding anaplastic large-cell lymphoma) or CTCL (mycosis fungoides [MF]/Sézary syndrome [SS] subtypes) who had received ≥1 prior line of therapy, had an Eastern Cooperative Oncology Group performance status of 0-1, and CD30 expression of ≥1% in the tumor or tumor-infiltrating lymphocytes (TILs; determined by immunohistochemistry at a local laboratory). Patients received nivolumab 240 mg (day 8 of cycle 1; day 1 of each subsequent 3-week cycle) plus BV 1.8 mg/kg intravenously (day 1 of all cycles) until progressive disease (PD) or unacceptable toxicity. Primary end points were investigator-assessed overall response rate (ORR) assessed by fludeoxyglucose positron emission tomography-computed tomography, or computed tomography/magnetic resonance imaging (PTCL, per Lugano classification 2014[15]; CTCL, assessed by Global Response Score per consensus statement of the International Society for Cutaneous Lymphoma)[16] and safety. Secondary end points included duration of response (DOR), complete response (CR), duration of CR, progression-free survival (PFS) by investigator, and overall survival. This study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki; institutional review board approval was obtained. All patients provided written informed consent.

Overall, 34 and 30 patients with PTCL and CTCL were enrolled, of whom 33 and 29 received treatment, respectively; 2 patients did not receive treatment due to PD and laboratory results out of range for

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inclusion. In violation of eligibility criteria, 1 patient who did not receive any prior lines of therapy was recruited to the CTCL cohort. Median (range) age was 60 (38-80) and 61 (37-77) years in PTCL and CTCL cohorts, respectively; a larger proportion of patients were male (PTCL: n = 22 of 33 [66.7%]; CTCL: n = 16 of 29 [55.2%]; supplemental Table 1). At study entry, 54.5% (n = 18 of 33) of patients with PTCL had PTCL–not otherwise specified, 30.3% (n = 10 of 33) had angioimmunoblastic T-cell lymphoma, and 15.2% (n = 5 of 33) had an unknown PTCL subtype; 82.8% (n = 24 of 29) and 17.2% (n = 5 of 29) of patients with CTCL had MF and SS subtypes, respectively. Overall, 51.5% (PTCL) and 31.0% (CTCL) of patients had stage IV disease. In the PTCL and CTCL cohorts, 78.8% (n = 26 of 33) and 96.6% (n = 28 of 29) of patients had baseline PD-L1 expression of ≥1%, respectively; 93.3% (n = 28 of 30) and 96.4% (n = 27 of 28) of evaluable patients had tumor CD30 expression ≥1% or TILs, respectively. All patients had CD30 expression ≥1% at local screening; however, 2 patients had CD30 expression <1% per Bristol Myers Squibb central biomarker assessment. In the PTCL cohort, median (range) PD-L1 and CD30 expression were 60.0% (0.0-100.0) and 35.0% (0.0-100.0), respectively; in the CTCL cohort, this was 50.0% (0.0-95.0) and 27.5% (0.0-95.0). Patients with PTCL and CTCL received a median (range) of 2 (1-5) and 3 (0-6) prior lines of systemic therapy, respectively. Patients received a median (range) of 5 (1-35) doses of nivolumab and BV in the PTCL cohort and 6 (1-73) and 7 (1-42) doses, respectively, in the CTCL cohort. At database lock (30 March 2022), all patients discontinued treatment, most commonly due to PD (PTCL, 57.6% [n = 19 of 33]; CTCL, 44.8% [n = 13 of 29]).

At a median (range) follow-up (defined as time from first dose to last known date alive or death) of 9.6 (0.7-52.1) and 24.4 (0.6-61.0) months in patients with PTCL and CTCL, respectively, the ORR (95% confidence interval [CI]) was 45.5% (28.1-63.6) and 41.4% (23.5-61.1); 33.3% (n = 11 of 33) and 3.4% (n = 1 of 29) of patients achieved a CR (Table 1). In patients with PTCL, median DOR was 4.6 (95% CI, 2.8-12.8) months (supplemental Figure 1) and median PFS was 4.3 (95% CI, 1.6-5.6) months (supplemental Figure 2); these were 27.0 (95% CI, 2.8-not reached [NR]; supplemental Figure 1) and 15.6 (95% CI, 4.9-NR; supplemental Figure 2) months for the CTCL cohort, respectively. Median overall survival (95% CI) was 11.1 (5.2-15.3) and 37.2 (18.6-NR) months for PTCL and CTCL, respectively.

In the PTCL cohort, 84.8% (n = 28 of 33) of patients experienced any-grade treatment-related adverse events (TRAEs); most commonly fatigue (24.2%, n = 8 of 33, Table 2). Grade 3/4 TRAEs were reported in 45.5% (n = 15 of 33) of patients, most commonly neutropenia (15.2%, n = 5 of 33); 1 patient experienced grade 5 treatment–related pneumonitis (no prior chest radiation therapy; treated with levafloxacin, steroids, and mycophenolate mofetil). Any-grade treatment-emergent adverse events (TEAEs) occurred in 100% (n = 33 of 33) of patients, and grade 3/4 TEAEs occurred in 66.6% (n = 22 of 33; supplemental Table 2). In the CTCL cohort, 89.7% (n = 26 of 29) of patients experienced any-grade TRAEs; the most common was peripheral neuropathy (27.6%, n = 8 of 29; Table 2). Grade 3/4 TRAEs occurred in 44.8% (n = 13 of 29) of patients, of which 13.8% (n = 4 of 29) were skin-related; no grade 5 TRAEs were reported. Any-grade TEAEs occurred in 100% (n = 29 of 29) of patients, and grade 3/4 TEAEs occurred in 58.6% (n = 17 of 29; supplemental Table 2). Overall, 78.8% (26 of 33) and 48.3% (14 of 29) of patients died in the PTCL and CTCL cohorts, respectively, most commonly due to PD (63.6%, n = 21 of 33; 37.9%, n = 11 of 29; Table 2). One death was treatment-related in the PTCL cohort (grade 5 pneumonitis); none were treatment-related in the CTCL cohort.

Table 1. Efficacy results (ORR, DOR, PFS, OS)

Efficacy	PTCL (n = 33)	CTCL (n = 29)
ORR,* n (%)	15 (45.5)	12 (41.4)
80% CI, %	33.3-58.0	28.8-55.0
95% CI, %	28.1-63.6	23.5-61.1
Best overall response,† n (%)		
CR	11 (33.3)‡	1 (3.4)
PR	4 (12.1)‡	11 (37.9)
SD	6 (18.2)	11 (37.9)§
PD	10 (30.3)	1 (3.4)
Unable to determine	2 (6.1)	5 (17.2)
TTR, median (range), mo	1.4 (1.1-5.5)	NR (0.7-10.1)
TTCR, median (range), mo	2.6 (1.1-7.6)	4.8 (4.8-4.8)
DOR, median (95% CI), mo	4.6 (2.8-12.8)	27.0 (2.8-NR)
DOCR, median (95% CI), mo	7.4 (2.2-NR)	NR
PFS‖, median (95% CI), mo	4.3 (1.6-5.6)	15.6 (4.9-NR)
PFS rate at 12 mo, % (95% CI)	13.8 (2.9-33.0)	67.6 (43.3-83.3)
PFS rate at 24 mo, % (95% CI)	6.9 (0.5-25.6)	46.4 (18.3-70.7)
OS‖, median (95% CI), mo	11.1 (5.2-15.3)	37.2 (18.6-NR)
OS rate at 12 mo, % (95% CI)	45.1 (27.7-61.0)	78.9 (58.9-89.9)
OS rate at 24 mo, % (95% CI)	25.8 (12.3-41.6)	62.9 (41.7-78.1)

DOCR, duration of CR; OS, overall survival; PR, partial response; SD, stable disease; TTCR, time to CR; TTR, time to response.
*CIs based on the Clopper-Pearson method.
†Based on Lugano Classification 2014.[15]
‡There were 3 patients with baseline PD-L1 < 1% in the PTCL cohort; 2 achieved a CR and 1 a PR.
§There was 1 patient with baseline PD-L1 < 1% in the CTCL cohort; this patient achieved SD.
‖Median and rates calculated using Kaplan-Meier method.

In CheckMate 436, NBV demonstrated similar ORRs in both PTCL (45.5%; 15 of 33) and CTCL (41.4%; 12 of 29) cohorts and safety was similar to previous reports.[9,11,17] ORRs in patients with PTCL were generally comparable with previous studies investigating PD-1 inhibitor monotherapy (nivolumab, 33%[18]; pembrolizumab, 33%[10]) and BV (41%[19]). Compared with studies that included patients with SS, ORR in patients with CTCL in CheckMate 436 was higher compared with nivolumab monotherapy (15%[11]), and similar to tislelizumab (45.5%[20]) and pembrolizumab (38%[21]) monotherapies. Additionally, ORR was lower compared with BV monotherapy in patients with CTCL excluding SS (65.6%[12]). Median DOR in PTCL (4.6 months) with NBV was comparable to nivolumab monotherapy (3.6 months)[18]; in patients with CTCL, median DOR was higher (27.0 months) than previously reported in one study (8.6 months) in patients with MF-CTCL.[11] Similar durable remissions were observed with tislelizumab monotherapy in patients with R/R CTCL (11.3 months [95% CI, 2.8-11.3]; n = 11).[20]

Hyperprogression has previously been observed in PTCL treated with nivolumab monotherapy[18] and romidepsin plus pembrolizumab[22]; however, no cases were reported in this study.

Table 2. Safety data in patients with R/R PTCL and CTCL

TRAEs in ≥5% of patients,* n (%)	PTCL (n = 33)		CTCL (n = 29)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
All TRAEs	28 (84.8)	15 (45.5)	26 (89.7)	13 (44.8)
Fatigue	8 (24.2)	2 (6.1)	4 (13.8)	0
Nausea	6 (18.2)	0	6 (20.7)	0
Pyrexia	6 (18.2)	0	5 (17.2)	0
Neutropenia	5 (15.2)	5 (15.2)	0	0
Peripheral neuropathy	5 (15.2)	1 (3.0)	8 (27.6)	0
Diarrhea	5 (15.2)	1 (3.0)	6 (20.7)	1 (3.4)
Anemia	5 (15.2)	1 (3.0)	1 (3.4)	0
Increased aspartate aminotransferase	5 (15.2)	0	3 (10.3)	1 (3.4)
Paresthesia	5 (15.2)	0	1 (3.4)	0
Thrombocytopenia	4 (12.1)	2 (6.1)	1 (3.4)	1 (3.4)
Peripheral sensory neuropathy	4 (12.1)	1 (3.0)	2 (6.9)	0
Infusion-related reaction	4 (12.1)	0	6 (20.7)	1 (3.4)
Pruritis	4 (12.1)	0	2 (6.9)	0
Arthralgia	4 (12.1)	0	1 (3.4)	0
Rash	3 (9.1)	0	4 (13.8)	2 (6.9)
Increased alanine aminotransferase	2 (6.1)	0	2 (6.9)	0
Pneumonitis†	2 (6.1)	0	1 (3.4)‡	1 (3.4)‡
Increased blood alkaline phosphatase	2 (6.1)	0	0	0
Rash maculo-papular	1 (3.0)	0	2 (6.9)	1 (3.4)
Dermatitis exfoliative generalized	0	0	4 (13.8)	2 (6.9)
Rash macular	0	0	2 (6.9)	0

	PTCL (n = 33)	CTCL (n = 29)
Deaths, n (%)	26 (78.8)	14 (48.3)
Disease	21 (63.6)	11 (37.9)
Graft-versus-host disease§	1 (3.0)	0
Pneumonia	1 (3.0)	0
Pneumonitis	1 (3.0)	0
Respiratory	1 (3.0)	0
Infection due to leg amputation	0	1 (3.4)
MRSA and GBS bacteremia	0	1 (3.4)
Septic shock	0	1 (3.4)
Unknown	1 (3.0)‖	0

GBS, group B *Streptococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*.
*Up to 30 days following last dose.
†One instance of pneumonitis in the PTCL cohort was grade 5.
‡Incidence was classed as hypersensitivity pneumonitis.
§Death from graft-versus-host disease occurred 245 days posttransplant after last nivolumab dose.
‖Patient achieved a best overall response of CR on the study but stopped study treatment and subsequently received an allogeneic transplant. No details on the cause of death are known but the patient did not have PD.

Further research is needed to determine if PD-1 inhibitors increase hyperprogression risk. Incidence of infusion-related reactions in CheckMate 436 was low, despite high incidence previously reported in patients with classical Hodgkin lymphoma treated with NBV.[23] Although the study size was limited, given the modest ORRs observed with NBV compared with individual monotherapies, NBV is not supported in patients with PTCL and CTCL. Given disease heterogeneity, further evaluation is needed to determine which disease subtypes may benefit from this combination.

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