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

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Abstract:

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Title

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Running title

Nivolumab and brentuximab vedotin in 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] while 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) that 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 lab). 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 endpoints 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 endpoints included duration of response (DOR), complete response (CR), duration of CR, progression-free survival (PFS) by investigator, and overall survival (OS). This study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki; institutional board approval was obtained. All patients provided written informed consent. The Bristol Myers Squibb data sharing policy may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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 inclusion. In violation of eligibility criteria, one 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 [66.7%]; CTCL, n = 16 [55.2%]; **Table S1**). At study entry, 54.5% (n = 18) of patients with PTCL had PTCL-not otherwise specified, 30.3% (n = 10) had angioimmunoblastic T-cell lymphoma, and 15.2% (n = 5) had an unknown PTCL subtype; 82.8% (n = 24) and 17.2% (n = 5) 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) and 96.6% (n = 28) of patients had baseline PD-L1 expression of ≥ 1%, respectively; 93.3% (n = 31) and 96.4% (n = 28) of evaluable patients had tumor CD30 expression of ≥ 1% or TILs, respectively. All patients had CD30 expression ≥ 1% at local screening; however, 2 patients had CD30 expression < 1% per BMS central biomarker assessment. In the PTCL cohort, median (range) PD-L1 and CD30 expression was 60.0% (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 (March 30, 2022), all patients discontinued treatment; most commonly due to PD (PTCL, 57.6% [n = 19]; CTCL, 44.8% [n = 13]).

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) and 3.4% (n = 1) of patients achieved a CR (**Table 1**). In patients with PTCL, median DOR was 4.6 (95% CI, 2.8–12.8) months (**Figure S1**) and median PFS was 4.3 (95% CI, 1.6–5.6) months (**Figure S2**); these were 27.0 (95% CI, 2.8-not reached [NR]; **Figure S1**) and 15.6 (95% CI, 4.9–NR; **Figure S2**) months for the CTCL cohort, respectively. Median OS (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 patients experienced any-grade treatment-related adverse events (TRAEs); most commonly fatigue (24.2%, n = 8, **Table 2**). Grade 3/4 TRAEs were reported in 45.5% (n = 15) of patients, most commonly neutropenia (15.2%, n = 5); 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 patients, and grade 3/4

TEAEs occurred in 66.6% (n = 22; **Table S2**).In the CTCL cohort, 89.7% (n = 26) of patients experienced any-grade TRAEs; the most common was peripheral neuropathy (27.6%, n = 8, **Table 2**). Grade 3/4 TRAEs occurred in 44.8% (n = 13) of patients, of which 13.8% (n = 4) were skin-related; no grade 5 TRAEs were reported. Any grade TEAEs occurred in 100% (n = 29) of patients, and grade 3/4 TEAEs occurred in 58.6% (n = 17; **Table S2**). There were 26 (78.8%) and 14 (48.3%) deaths in the PTCL and CTCL cohorts, respectively, most commonly due to PD (63.6%, n = 21; 37.9%, n = 11; **Table 2**). One death was treatment-related in the PTCL cohort (grade 5 pneumonitis); none were treatment-related in the CTCL cohort.

In CheckMate 436, NBV demonstrated similar ORRs in both PTCL (45.5%) and CTCL (41.4%) 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 monotherapies (38%[21]). 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. 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 study size is 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.

This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki; institutional board approval was obtained. All patients provided written informed consent.

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AUTHOR CONTRIBUTIONS

P.L.Z and A.S. contributed to the conception and design of the study. P.L.Z., G.S., A.J.M., A.S., A.M., P.M.B., N.M-S., G.P.S., S.M.A., J.D.B., E.D-D., N.A.J., D.C., S.F., J.L., and K.S. all contributed to performing the research, collecting data, and data analysis and interpretation. N.J. contributed vital new reagents or analytical tools. All authors reviewed and revised the manuscript, provided their final approval, and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST

P.L.Z. reports honoraria from AbbVie, AstraZeneca, Beigene, Bristol Myers Squibb, Gilead, Incyte, Janssen, Kyowa Kirin, Merck Sharp & Dohme, Novartis, Roche, Sanofi, and Takeda. G.S. reports consulting fees from AbbVie, ATB Therapeutics, Bayer, Beigene, Bristol Myers Squibb/Celgene, Debiopharm, Epizyme, Genentech/Roche, Genmab, Incyte, Ipsen, Janssen, Kite/Gilead, Loxo/Lilly, Merck, Molecular Partners, Morphosys, Nordic Nanovector, Novartis, Nurix, Orna, Regeneron, and Takeda; and stock in Owkin. A.J.M. reports consulting fees from Physician Education Resource and Seattle Genetics; honoraria from Academic Medical Education, Bio Ascend, Canadian Hematology Conference, Canadian Hematology Society, Harborside Press, Medscape, New York Oncology Hematology, Physician Education Resource, Puerto Rico Hematology and Medical Oncology Association, Seagen, Seattle Genetics, SOHO Brazil, Takeda, Tessa Therapeutics, and Triangle Insights; and advisory board participation with Affimed, Janpix, Kyowa Kirin, and Seattle Genetics. A.S. reports consulting fees from Incyte and Sanofi; honoraria from AbbVie, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Eisai, Gilead, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sandoz, Servier, and Takeda; and advisory board participation with Bayer, Bristol Myers Squibb, Eisai, Gilead, Merck Sharp & Dohme, Pfizer, and Servier. A.M. reports research funding from Affimed, Celgene/Bristol Myers Squibb, fortyseven/Gilead, Incyte, I-MAB, Innate, Juno/Bristol Myers Squibb, Kite/Gilead, Merck,

Roche/Genentech, Seattle Genetics, Takeda, and TG Therapeutics; and consulting fees from AstraZeneca, Beigene, Bristol Myers Squibb, Gilead, Incyte, Kyowa Kirin, Morphosys/Incyte, Novartis, Pharmacyclics, Seattle Genetics, and TG Therapeutics. P.M.B. has nothing to disclose. N.M-S. reports research funding from AstraZeneca, Bristol Myers Squibb/Celgene, C4 Therapeutics, Corvus, Daiichi Sankyo, Dizal, Genentech/Roche, Innate, Secura, Verastem, and Yingli; and consulting fees from AstraZeneca, C4 Therapeutics, Daiichi Sankyo, Genentech/Roche, Karyopharm, Kyowa Hakko Kirin, Ono, Secura, and Verastem. G.P.C. reports consulting fees from ADC Therapeutics, AstraZeneca, Beigene, Bristol Myers Squibb, Kite, Roche, and Takeda; honoraria from Beigene, Gilead, Incyte, Kite, Roche, and Takeda; and travel support from Roche and Takeda. S.M.A. reports research funding from ADC Therapeutics, AstraZeneca, Bristol Myers Squibb, Pfizer, Regeneron, Seagen, and Takeda. J.D.B. reports research funding from Bristol Myers Squibb and honoraria from ADC Therapeutics, Epizyme, Genentech, Merck, and Seagen. E.D-D. reports honoraria from Takeda; travel support from Celgene/Bristol Myers Squibb and Takeda; and advisory board participation with Beigene and Takeda. N.A.J. reports research funding from Gilead, Incyte, and Roche; consulting fees from AbbVie, AstraZeneca, Beigene, Gilead, Merck, and Roche; honoraria from AbbVie, AstraZeneca, and Beigene; and payment for expert testimony from Gilead. D.C. reports research funding from 4SC, Bayer, Celgene, Clovis, Leap, Lilly, MedImmune, and Roche; and advisory board participation with Ovibio. S.F. reports travel support from Beigene. J.L. reports employment and stock with Seagen. J.K. and A.A. report employment and stock with Bristol Myers Squibb. R.W. reports employment with Bristol Myers Squibb. R.C. reports employment (at time of study) and stock with Bristol Myers Squibb. K.J.S. reports consulting fees from AbbVie, Bristol Myers Squibb, Janssen, and Seagen; steering committee participation with Beigene; research funding from Bristol Myers Squibb and Roche; and Data Safety Monitoring Board participation with Regeneron.

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Tables

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), months	1.4 (1.1–5.5)	NR (0.7–10.1)
TTCR, median (range), months	2.6 (1.1–7.6)	4.8 (4.8–4.8)
DOR, median (95% CI), months	4.6 (2.8–12.8)	27.0 (2.8–NR)
DOCR, median (95% CI), months	7.4 (2.2–NR)	NR
PFS,[‖] median (95% CI), months	4.3 (1.6–5.6)	15.6 (4.9–NR)
PFS rate at 12 months, % (95% CI)	13.8 (2.9–33.0)	67.6 (43.3–83.3)
PFS rate at 24 months, % (95% CI)	6.9 (0.5–25.6)	46.4 (18.3–70.7)
OS,[‖] median (95% CI), months	11.1 (5.2–15.3)	37.2 (18.6–NR)
OS rate at 12 months, % (95% CI)	45.1 (27.7–61.0)	78.9 (58.9–89.9)
OS rate at 24 months, % (95% CI)	25.8 (12.3–41.6)	62.9 (41.7–78.1)

[*]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.
CR, complete response; CTCL, cutaneous T-cell lymphoma; DOCR, duration of complete response; DOR, duration of response; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PR, partial response; PTCL, peripheral T-cell lymphoma; SD, stable disease; TTCR, time to complete response; TTR, time to response.

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

	PTCL (n = 33)		CTCL (n = 29)	
TRAEs in ≥ 5% of patients,* n (%)	**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

*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 post-transplant 245 days after last nivolumab dose.
[‖]Patient achieved a best overall response of complete response on the study but stopped study treatment and subsequently received an allogenic transplant. No details on the cause of death are known but the patient did not have progressive disease.
CTCL, cutaneous T-cell lymphoma; GBS, group B streptococcus; MRSA, methicillin-resistant *Staphylococcus aureus*; PTCL, peripheral T-cell lymphoma; R/R, relapsed or refractory; TRAE, treatment-related adverse event.