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Regulatory Issues: FDA

FDA Approval Summary: Brentuximab Vedotin in First-Line Treatment of Peripheral T-Cell Lymphoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

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Abstract

In November 2018, the U.S. Food and Drug Administration (FDA) approved brentuximab vedotin (BV) for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone (CHP). Approval was based on ECHELON-2, a randomized, double-blind, actively controlled trial that compared BV+CHP with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in 452 patients with newly diagnosed, CD30-expressing PTCL. Efficacy was based on independent review facility-assessed progression-free survival (PFS). The median PFS was 48.2 months with BV+CHP versus 20.8 months with CHOP, resulting in a hazard ratio (HR) of 0.71 (95% confidence interval [CI]: 0.54–0.93). The trial also demonstrated improvement in overall survival (HR 0.66; 95% CI: 0.46–0.95), complete response rate (68% vs. 56%), and overall response rate (83% vs. 72%) with BV+CHP. The most common adverse reactions (incidence ≥20%) observed ≥2% more with BV+CHP were nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia. Peripheral neuropathy rates were similar (52% with BV+CHP, 55% with CHOP). Through the Real-Time Oncology Review pilot program, which allows FDA early access to key data, FDA granted this approval less than 2 weeks after official submission of the application. ***The Oncologist*** 2019;24:e180–e187

Implications for Practice: This is the first U.S. Food and Drug Administration approval for treatment of patients with newly diagnosed peripheral T-cell lymphomas (PTCL). Improvement in progression-free and overall survival over cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy, which has been the standard of care for decades, is unprecedented. The new regimen represents a major advance for the frontline treatment of patients with CD30-expressing PTCL.

Introduction

Peripheral T-cell lymphoma (PTCL), which makes up approximately 10% of non-Hodgkin lymphomas in the U.S., is a heterogeneous group of lymphomas with an aggressive clinical course [1, 2]. The most common types have a predominantly nodal presentation and include anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL), and PTCL not otherwise specified. Although first-line therapy for PTCL has curative potential, the majority of patients relapse or progress. PTCLs are challenging to treat, with clinical courses often marked by advanced-stage disease at presentation and chemoresistance or relapse [1, 2].

An anthracycline-containing regimen, with or without consolidative autologous hematopoietic stem cell transplantation [3], is the usual frontline approach for most types of PTCL. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) remains the historical standard and the most widely used frontline regimen for most types of PTCL [2, 4]. Anaplastic lymphoma kinase (ALK)-positive ALCL is the only type of PTCL wherein the majority of patients achieve durable remissions with CHOP (5-year failure-free survival 60% vs. 36% with ALK-negative ALCL) [2, 5]. Anthracycline-containing regimens have otherwise had

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Table 1. Brentuximab vedotin: background information

Structure	CD30-directed ADC consisting of three components: (a) an IgG1 antibody, cAC10, specific for human CD30, (b) the microtubule disrupting agent MMAE, and (c) a protease-cleavable linker that covalently attaches MMAE to cAC10.
Mechanism of action	Binding of brentuximab vedotin to CD30-expressing cells allows internalization of the ADC-CD30 complex and release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network, inducing cell cycle arrest and apoptosis.
Pharmacokinetics	• ADC: Maximum concentrations of ADC are observed near the end of a 30-minute infusion. At a dose of 1.8 mg/kg every 3 weeks, steady state is achieved within 21 days, with minimal to no accumulation of ADC observed. • MMAE: Maximum concentrations of MMAE are observed approximately 1 to 3 days after end of infusion. At a dose of 1.8 mg/kg every 3 weeks, steady state is achieved within 21 days.
Prior approvals	Treatment of adult patients with: • cHL after failure of auto-HSCT or after failure of at least two prior multiagent chemotherapy regimens in patients who are not auto-HSCT candidates (8/2011) • systemic ALCL after failure of at least one prior multiagent chemotherapy regimen (8/2011) • cHL at high risk of relapse or progression as post-auto-HSCT consolidation (8/2015) • primary cutaneous ALCL or CD30-expressing mycosis fungoides who have received prior systemic therapy (11/2017) • previously untreated stage III or IV cHL, in combination with doxorubicin, vinblastine, and dacarbazine (3/2018)

Abbreviations: ADC, antibody-drug conjugate; ALCL, anaplastic large cell lymphoma; auto-HSCT, autologous hematopoietic stem cell transplantation; cHL, classical Hodgkin lymphoma; IgG1, immunoglobulin G1; MMAE, monomethyl auristatin E.

disappointing results. In a 340-patient case series of PTCL not otherwise specified, the estimated 5-year overall survival (OS) was 32%, and the estimated 5-year failure-free survival was only 20% [1]. Only approximately 20% of patients with AITL have prolonged disease-free survival [2], and the median OS for patients with enteropathy-associated or hepatosplenic lymphoma is less than 1 year [6].

Attempts to improve upon CHOP with nontargeted agents have been largely unsuccessful [7, 8]. The low rates of complete remission (CR) and 5-year OS rates (generally <50%) associated with CHOP underscore the high unmet need. On November 16, 2018, after an expedited review, the U.S. Food and Drug Administration (FDA) approved a new regimen for the first-line treatment of selected PTCLs. Brentuximab vedotin (BV) received regular approval for the treatment of adult patients with previously untreated systemic ALCL or other CD30-expressing PTCLs, including AITL and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone (CHP). BV is a CD30-directed antibody-drug conjugate with prior approvals in Hodgkin lymphoma, previously treated ALCL (systemic and primary cutaneous), and previously treated CD30-expressing mycosis fungoides (Table 1). Herein, we summarize the FDA clinical review and basis of approval of BV+CHP as a first-line regimen for CD30-expressing PTCL.

Trial Design

The ECHELON-2 trial (SGN35-014, NCT01777152) is a phase III, randomized, double-blind, double-dummy, actively controlled trial of BV+CHP versus CHOP in adult patients with newly diagnosed, CD30-expressing PTCL [9]. The trial required CD30 expression ≥10% per immunohistochemistry (IHC) per local assessment. The trial excluded patients with primary cutaneous lymphoproliferative disorders and lymphomas, central nervous system involvement by lymphoma, or grade 2 or higher peripheral neuropathy. Requirements included an Eastern Cooperative Oncology Group performance status <2, hepatic transaminases ≤3 times the upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and serum creatinine ≤2 times ULN.

Patients were randomized 1:1 to receive BV+CHP or CHOP for six to eight cycles, as shown in Table 2. Randomization was stratified by International Prognostic Index (IPI) score and histology (ALK-positive ALCL vs. other).

The primary efficacy endpoint was progression-free survival (PFS), defined as the time from randomization to progression, death, or receipt of subsequent therapy for residual or progressive disease. The trial was designed to detect an improvement in PFS, assuming a median PFS of 24 months for BV+CHP versus 17 months for CHOP (corresponding hazard ratio [HR] = 0.69), with 80% power and a two-sided type I error rate of 0.05. The key secondary endpoints, which were tested hierarchically, were PFS in patients with systemic ALCL and, in all randomized patients, CR rate, OS, and overall response rate (ORR). PFS and response were based on independent review facility assessment.

Results

Patient and Treatment Characteristics

Of 452 patients randomized, 449 were treated (223 with BV+CHP, 226 with CHOP). The demographics and disease characteristics were balanced between treatment arms (Table 3). Of all randomized patients, the disease subtypes included systemic ALCL (70%, 22% of which were ALK positive), PTCL not otherwise specified (16%), angioimmunoblastic T-cell lymphoma (12%), adult T-cell leukemia/lymphoma (2%), and enteropathy-associated T-cell lymphoma (<1%). Most patients had stage III or IV disease (81%) and an intermediate-risk IPI (63%). Most patients (81%) had six cycles planned, with 30% receiving primary prophylaxis with granulocyte-colony stimulating factor (GCSF; Table 3).

Efficacy

Efficacy results are presented in Table 4. ECHELON-2 demonstrated a statistically significant improvement in PFS with

Table 2. Treatment in ECHELON-2

Variable		BV+CHP (*n* = 223 treated)	CHOP (*n* = 226 treated)
Regimen (6 to 8, 21-day cycles)			
Blinded Study Drug A[a]	BV 1.8 mg/kg IV on day 1	X	
	Placebo solution IV[b] on day 1		X
Cyclophosphamide	750 mg/m^2 IV on day 1	X	X
Doxorubicin	50 mg/m^2 IV on day 1[c]	X	X
Blinded Study Drug B	Vincristine 1.4 mg/m^2 IV on day 1[d]		X
	Placebo saline IV[b] on day 1	X	
Prednisone	100 mg orally daily on days 1–5	X	X
Treatment characteristics			
Cycles planned	6	82%	81%
	8	18%	19%
Cycles received	≤3	8%	11%
	4 or 5	4%	8%
	6	70%	62%
	7	<1%	0%
	8	18%	19%
GCSF prophylaxis	Primary	34%	27%
	Secondary	30%	29%
RDI[e], BV or vincristine	Mean (SD)	90% (20)	92% (20)
	≥90%	74%	77%
RDI, Cyclophosphamide	Mean (SD)	91% (20)	93% (18)
	≥90%	78%	85%
RDI, Doxorubicin	Mean (SD)	90% (20)	93% (18)
	≥90%	76%	85%
Dose reduction	BV or vincristine	9%	11%
	Cyclophosphamide	8%	5%
	Doxorubicin	8%	5%
Dose delay due to AR		26%	12%
Treatment cessation due to AR		6%	6%
Receipt of consolidative HSCT		22%	17%

[a]Administered within 1 hour of completing treatment with other agents administered via IV. Maximum dose of BV was 180 mg.
[b]Prepared by the site pharmacist; pharmacy blind maintained.
[c]May be administered over up to 48 hours according to institutional standards.
[d]Vincristine dose capped at 2 mg.
[e]For patients who stopped treatment early for reasons other than progressive disease, such as toxicity, the denominator for the RDI calculation was the intended number of cycles. For patients who stopped because of progressive disease, the denominator was the actual number of cycles.
Abbreviations: AR, adverse reaction; BV, brentuximab vedotin; GCSF, granulocyte-colony stimulating factor; HSCT, hematopoietic stem cell transplantation; IV, intravenous; RDI, relative dose intensity; SD, standard deviation.

BV+CHP compared with CHOP, with an HR of 0.71 (95% confidence interval [CI]: 0.54–0.93; p = .011; Fig. 1). On intention-to-treat analysis, patients in the BV+CHP arm had an estimated median PFS of 48.2 months (95% CI: 35.2 to not estimable [NE]), whereas patients in the CHOP arm had an estimated median PFS of 20.8 months (95% CI: 12.7–47.6). The difference in event rate was driven by more treatment failures on the CHOP arm. The improvement in PFS with BV+CHP translated into a statistically significant improvement in OS (HR 0.66; 95% CI: 0.46–0.95; p = .024; Fig. 1). The median OS was not reached in either treatment arm, with an estimated median follow-up of 42 months. Sensitivity analyses of PFS and OS supported the results of the primary analyses.

The CR rate and ORR at the end of treatment were likewise statistically significantly higher with BV+CHP than CHOP: 68% versus 56% (p = .007) and 83% versus 72% (p = .003), respectively (Table 4).

In the subset of patients with systemic ALCL, PFS was also statistically significantly improved on the BV+CHP arm (HR 0.59; 95% CI: 0.42–0.84; p = .003; Fig. 1). On the BV+CHP arm, 34% of patients experienced a PFS event with an estimated median PFS of 55.7 months (95% CI: 48.2 to NE). In contrast, 48% of patients on the CHOP arm experienced a PFS event with an estimated median PFS of 54.2 months (95% CI: 13.4 to NE).

CD30 expression is variable in PTCL subtypes other than ALCL [10–12]. Table 3 summarizes the CD30 expression

Table 3. Characteristics of efficacy population (intention to treat)

Variable	BV+CHP (*n* = 226)	CHOP (*n* = 226)
Age, years		
Median (range)	58 (18–85)	58 (18–83)
≥65, *n* (%)	69 (31)	70 (31)
Diagnosis, *n* (%)		
ALK− systemic ALCL	113 (50)	105 (46)
ALK+ systemic ALCL	49 (22)	49 (22)
PTCL not otherwise specified	29 (13)	43 (19)
Angioimmunoblastic T-cell lymphoma	30 (13)	24 (11)
Adult T-cell leukemia/lymphoma	4 (2)	3 (1)
Enteropathy-associated T-cell lymphoma	1 (<1)	2 (1)
IPI score, *n* (%)		
0–1	52 (23)	51 (23)
2–3	142 (63)	142 (62)
4–5	32 (14)	33 (15)
Stage, *n* (%)		
1–2	42 (19)	46 (20)
3	57 (25)	67 (30)
4	127 (56)	113 (50)
% CD30 expression[a], ALCL		
Mean (SD)	95 (11.0)	93 (14.3)
Range[b]	0–100	0–100
% CD30 expression[a], other histologies		
Mean (SD)	47 (30.2)	46 (31.4)
Range	5–100	0–100

[a]Percentage of cells with CD30 expression, per central review of immunohistochemistry.
[b]Three patients with ALCL had 60%–100% CD30 expression per local IHC but 0% per central review.
Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP, cyclophosphamide, doxorubicin, and prednisone; IPI, international prognostic index; PTCL, peripheral T-cell lymphoma.

profiles in ECHELON-2. Nine patients on the BV+CHP arm had CD30 expression ≤10% per central IHC, of whom seven (78%) achieved an objective response, including five (56%) CRs. Additional data from two supportive studies, SGN35-012 (NCT01421667) and 35-IST-30 (NCT02588651), included 18 patients with relapsed or refractory PTCL with CD30 expression <10% per local IHC, including 8 patients with undetectable CD30 per IHC [13]. Of the 18 patients, 8 (44%) achieved an objective response, including 4 (22%) CRs, to BV monotherapy. Of the eight patients with undetectable CD30, two achieved CR and one achieved PR.

Safety

The safety analysis considered all-cause events reported within 30 days of treatment. The arms had similar incidences of grade ≥3 and serious adverse reactions (ARs). Fatal ARs within 30 days of treatment occurred in 3% of the BV+CHP arm and 4% of the CHOP arm. The leading cause in both arms was infection, followed by acute cardiac events. The reported incidence of serious ARs was 38% with BV+CHP and 35% with CHOP. Serious ARs reported in >2% of the BV+CHP arm included febrile neutropenia (14%), pneumonia (5%), pyrexia (4%), neutropenia (4%), and sepsis (3%).

Table 5 summarizes ARs reported in ≥15% of either arm. With BV+CHP, the most common (≥20%) ARs, in order of decreasing incidence, were peripheral neuropathy, nausea, diarrhea, neutropenia, fatigue or asthenia, mucositis, constipation, alopecia, pyrexia, vomiting, and anemia. Other common ARs with BV+CHP, with incidences of 11% to 13%, included dizziness, cough, weight decrease, hypokalemia, myalgia, and insomnia. The most common ARs reported ≥2% more with BV+CHP were nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia. The largest difference was the 18% higher incidence of diarrhea with BV+CHP (38%, vs. 20% with CHOP).

The incidences and patterns of peripheral neuropathy were similar with BV+CHP and CHOP (Table 5). With BV+CHP, 52% of patients had new or worsening peripheral neuropathy, with a median time to onset of 2 months. The neuropathy was predominantly sensory (94% sensory, 16% motor) and predominantly grade 1–2. At last evaluation, 50% had complete resolution and 12% had partial improvement, with a median time to resolution or improvement of 4 months (range, 0–45).

The arms had similar incidences of treatment changes due to ARs (Table 2). In recipients of BV+CHP, ARs led to dose delays in 25% of patients, dose reduction in 9% (most often for peripheral neuropathy), and discontinuation of BV with or without the other components in 7%. The arms had similar mean exposure (relative dose intensities) for BV/vincristine, cyclophosphamide, and doxorubicin, although a numerically higher percentage of CHOP recipients had a relative dose intensity of ≥90% for cyclophosphamide and doxorubicin (Table 2).

The prescribing information for BV [13] includes warnings and precautions on progressive multifocal leukoencephalopathy (boxed warning), peripheral neuropathy, anaphylaxis and infusion reactions, hematologic toxicities, infection, tumor lysis syndrome, hepatotoxicity, pulmonary toxicity, dermatologic reactions, gastrointestinal toxicity, and embryo-fetal toxicity. The prescribing information provides dose modification guidelines for toxicity.

Discussion

BV+CHP is the first FDA-approved regimen for newly diagnosed PTCL. In patients with previously untreated, CD30-expressing PTCL, the efficacy of BV+CHP was established by progression-free and overall survival outcomes, as well as the magnitude and depth of response relative to CHOP. The recommended dose schedule of BV is 1.8 mg/kg (maximum dose, 180 mg) as an intravenous infusion over 30 minutes on day 1 of a 21-day treatment cycle, in combination with cyclophosphamide, doxorubicin, and prednisone for six to eight cycles. GCSF primary prophylaxis is advised for all recipients of BV+CHP starting with cycle 1.

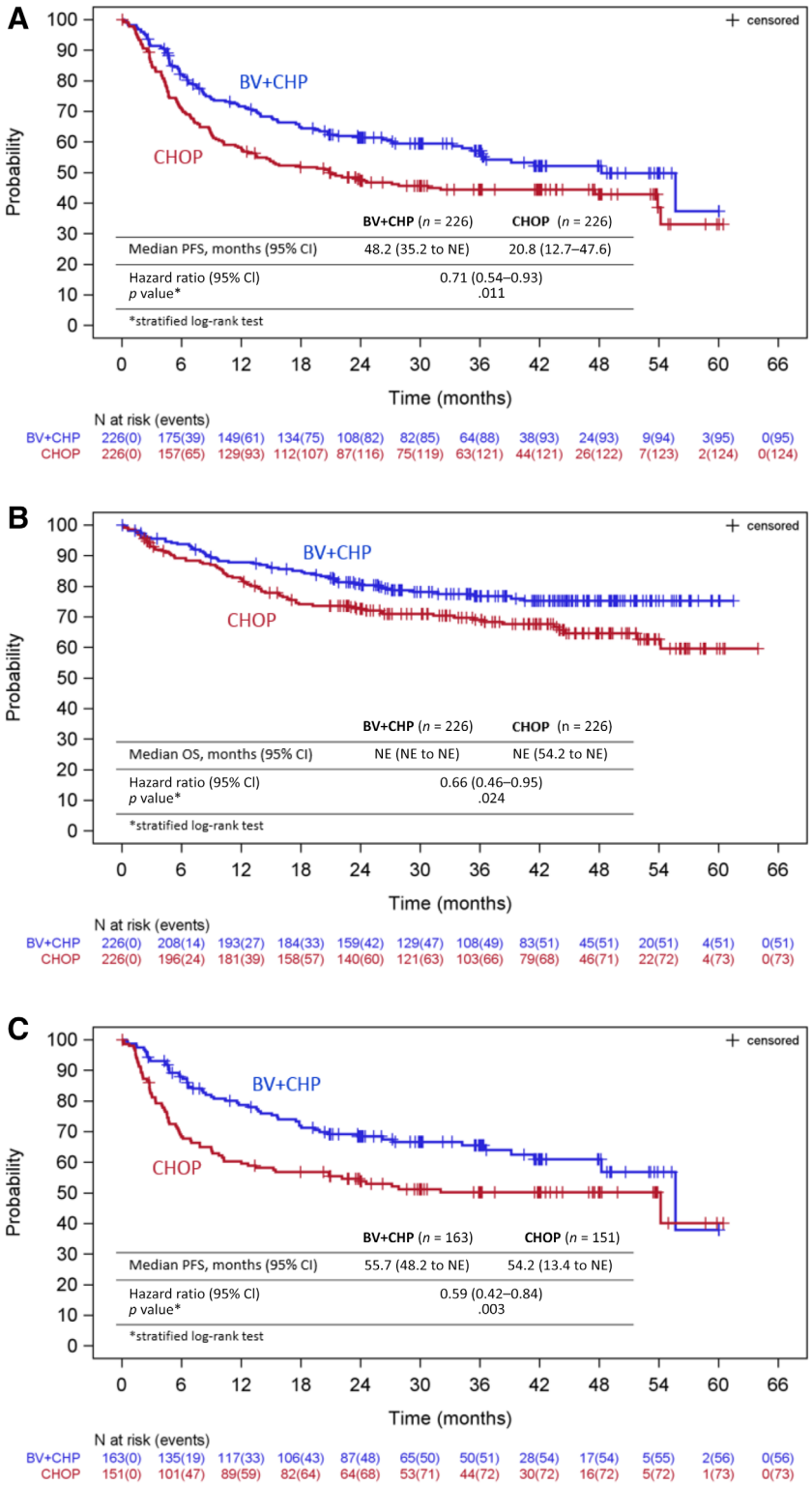

Figure 1. Progression-free and overall survival. **(A):** PFS in all patients. **(B):** Overall survival. **(C):** PFS in patients with systemic anaplastic large cell lymphoma.
Abbreviations: BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP, cyclophosphamide, doxorubicin, and prednisone; CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival.

The ECHELON-2 trial demonstrated a robust improvement in PFS and OS over CHOP chemotherapy, the decades-old standard of care for most types of PTCL. Based on these results, BV+CHP received Breakthrough Therapy Designation for its approved indication. Table 6 summarizes the FDA benefit-risk analysis. Because BV+CHP demonstrated substantial improvement in a randomized trial using established clinical endpoints, the application was selected for the Real-Time Oncology Review pilot program [14, 15]. This new program explores a more efficient review process that gives FDA

Table 4. Efficacy in ECHELON-2

Efficacy outcomes[a]	BV+CHP (*n* = 226)	CHOP (*n* = 226)
PFS in all randomized patients		
Events, *n* (%)	95 (42)	124 (55)
Progressive disease	71 (31)	86 (38)
Death	13 (6)	17 (8)
Therapy for residual or progressive disease	11 (5)	21 (9)
Median PFS, months (95% CI)[b]	48.2 (35.2 to NE)	20.8 (12.7–47.6)
Hazard ratio (95% CI)[c]	0.71 (0.54–0.93)	
p value[c]	.011	
OS		
Deaths, *n* (%)	51 (23)	73 (32)
Median OS, months (95% CI)[b]	NE (NE to NE)	NE (54.2 to NE)
Hazard ratio (95% CI)[c]	0.66 (0.46–0.95)	
p value[d]	.024	
CR rate[e]		
% (95% CI)	68 (61–74)	56 (49–62)
p value[f]	.007	
ORR[e]		
% (95% CI)	83 (78–88)	72 (66–78)
p value[f]	.003	
PFS in patients with systemic ALCL		
Patients, *n*	163	151
Events, *n* (%)	56 (34)	73 (48)
Median PFS, months (95% CI)[b]	55.7 (48.2 to NE)	54.2 (13.4 to NE)
Hazard ratio (95% CI)[c]	0.59 (0.42–0.84)	
p value[c]	.003	

[a]PFS and response are based on independent review facility assessment. Efficacy endpoints were tested at a two-sided alpha level 0.05 in the following order: PFS overall (intention-to-treat population), PFS in systemic ALCL subgroup, then in all patients, CR rate, OS, and ORR.
[b]Kaplan-Meier estimate. Median PFS follow-up was 36 months in the BV+CHP arm and 42 months in the CHOP arm; median OS follow-up was 24 months in each arm.
[c]Hazard ratio (BV+CHP/CHOP) and 95% CI based on Cox's proportional hazards regression model stratified by histology and international prognostic index score.
[d]Stratified log-rank test.
[e]Best response per 2007 International Working Group Criteria at end of treatment.
[f]Stratified Cochrane-Mantel-Haenszel test.
Abbreviations: ALCL, anaplastic large cell lymphoma; BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP, cyclophosphamide, doxorubicin, and prednisone; CI, confidence interval; CR, complete remission; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

access to key efficacy and safety data before official submission of the marketing application. Through this initiative, FDA was able to grant approval within 2 weeks of receipt of the complete application.

The safety profile of BV+CHP was consistent with the known safety profile of BV across multiple clinical trials. The arms had similar incidences of all-grade and grade ≥3 peripheral neuropathy (52% and 4%, respectively, with BV+CHP) and serious adverse reactions (BV+CHP 38%, CHOP 35%) with infection being the leading cause. Neutropenia rates in ECHELON-2 are underestimated because laboratory data were captured only at the start of each cycle (after the nadir in counts). Evaluation of the impact of GCSF was limited by the incomplete data on cytopenias and by the small number of patients who received primary prophylaxis (Table 2). Nevertheless, the review team felt that primary prophylaxis is justified with BV+CHP because (a) recipients of primary prophylaxis had a substantial reduction in grade ≥3 and grade ≥4 neutropenia events (absolute reduction 32% and 17%, respectively), (b) the febrile neutropenia rate approached or met the 20% threshold for which practice guidelines recommend prophylaxis [16], and (c) more infectious complications are expected in the general population than in a study population.

Important questions remain about the optimal patient population who might benefit from BV+CHP, including the relationship between the degree of CD30 expression and tumor response. Based on the available clinical data with BV, an optimal CD30 expression threshold remains uncertain [9, 17–20]. Because ECHELON-2 required ≥10% CD30 expression per IHC, there are no phase III data with BV+CHP in patients with CD30 expression levels of 1% to 9%. Two single-arm trials provided supportive data in patients with relapsed or refractory PTCL treated with BV monotherapy, wherein objective responses were seen in cases having <10% CD30 expression. Interestingly, three patients with 0% CD30 expression per IHC achieved objective responses to BV monotherapy, raising questions about the mechanism of action. Because the minimum CD30 expression level necessary for BV activity is not determined, the indication statements for BV do not specify a minimum CD30 expression level. Data in low-CD30-expressing PTCL remain limited, and whether the single-agent activity of BV in such cases translates into superiority of BV+CHP over CHOP is not established.

Another important limitation is the paucity of data with BV+CHP in PTCL subtypes other than ALCL. Enrollment in ECHELON-2 study was enriched for ALCL, with a prespecified target of 75%. Thus, by study design, patients with ALCL are the primary drivers of the study's outcomes. Although outcomes in the other PTCL populations were consistent with the overall study results, the data are limited, and some rare subtypes were not represented. Nevertheless, FDA granted approval of BV+CHP for CD30-expressing PTCL independent of subtype, in an effort to be as inclusive as possible because of the poor prognosis in most subtypes with frontline therapy. The broad indication statement also matches the ECHELON-2 eligibility criteria. Additional prospective trials would be helpful to characterize the activity of BV+CHP in patients with rare CD30-expressing subtypes of PTCL.

The applicability of BV regimens is limited by variability in CD30 expression. Although systemic ALCL universally expresses CD30, its expression in other types of PTCL is heterogeneous. Reported estimates of CD30 expression per IHC range from 58% to 64% in PTCL not otherwise specified, 63% to 75% in AITL, 0% to 55% in adult T-cell leukemia/lymphoma, 0% to 100% in enteropathy-associated T-cell lymphoma, and 0% to 25% in hepatosplenic T-cell lymphoma [10–12]. As a

Table 5. Adverse reactions reported in ≥15% of patients

Adverse reaction by category[a]	BV+CHP (*n* = 223), % of patients			CHOP (*n* = 226), % of patients		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Blood and lymphatic system disorders						
Anemia[b]	66	13	<1	59	12	<1
Neutropenia[b]	59	17	22	58	14	22
Lymphopenia[b]	51	18	1	57	19	2
Febrile neutropenia	19[c]	17	2	16	12	4
Thrombocytopenia[b]	17	3	3	13	3	2
Gastrointestinal disorders						
Nausea	46	2	—	39	2	—
Diarrhea	38	6	—	20	<1	—
Mucositis	30	2	<1	27	3	—
Constipation	29	<1	<1	30	1	—
Vomiting	26	<1	—	17	2	—
Abdominal pain	17	1	—	13	<1	—
Nervous system disorders						
Peripheral neuropathy	52[d,e]	3	<1	55[d]	4	—
Headache	15	<1	—	15	<1	—
Other disorders						
Fatigue or asthenia	35	2	—	29	2	—
Pyrexia	26	1	<1	19	—	—
Alopecia	26	—	—	25	1	—
Decreased appetite	17	1	—	12	1	—
Rash	16	1	<1	14	1	—
Edema	15	<1	—	12	<1	—
Dyspnea	15	2	—	11	2	—
Upper respiratory tract infection	14	<1	—	15	<1	—

[a]Includes events occurring up to 30 days after therapy completion. Toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.
[b]Derived from adverse reaction and laboratory data. Labs were reported at the start of each cycle and end of treatment.
[c]17% in recipients of primary granulocyte-colony stimulating factor prophylaxis, 20% in the remainder.
[d]With BV+CHP, 49% of patients had sensory neuropathy, 9% motor; with CHOP, 51% had sensory neuropathy, 12% motor.
[e]By maximum grade, 34% of patients had grade 1 peripheral neuropathy, 15% grade 2, 3% grade 3, <1% grade 4.
Abbreviations: BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP, cyclophosphamide, doxorubicin, and prednisone.

Table 6. U.S. Food and Drug Administration benefit-risk analysis

Parameter	Summary
Unmet medical need	Multiagent chemotherapy, with or without consolidative HSCT, is the usual first-line approach for PTCL and may be curative. However, apart from ALK+ ALCL, outcomes with CHOP-like regimens are generally disappointing.
Clinical benefit	In ECHELON-2 (*n* = 452), BV+CHP was associated with statistically significant improvements over CHOP in: • PFS (HR 0.71 [95% CI: 0.54–0.93], *p* = 0.011) • OS (HR 0.66 [95% CI: 0.46–0.95], *p* = .024) • CR rate (68% vs. 56%, *p* = .007), and • ORR (83% vs. 72%, *p* = .003).
Risks	• The BV+CHP and CHOP arms had similar incidences of fatal toxicities (≤4% per arm, most often from infection), serious ARs (BV+CHP 38%, CHOP 35%), grade ≥ 4 ARs (BV+CHP 31%, CHOP 34%), and all-grade and grade ≥3 peripheral neuropathy (52% and 4%, respectively, with BV+CHP). Rates of treatment modification and discontinuation due to ARs were also similar. • The most common ARs (≥20%) occurring ≥2% more with BV+CHP were nausea, diarrhea, fatigue or asthenia, mucositis, pyrexia, vomiting, and anemia. • With BV+CHP, febrile neutropenia rates were 17% in recipients of primary GCSF prophylaxis and 20% in patients without such prophylaxis. To reduce infection, recipients of BV+CHP should receive GCSF primary prophylaxis.

Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ARs, adverse reactions; BV, brentuximab vedotin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP, cyclophosphamide, doxorubicin, and prednisone; CI, confidence interval; CR, complete remission; GCSF, granulocyte-colony stimulating factor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma.

postmarketing commitment, FDA requested that the Sponsor develop a clinically validated in vitro diagnostic for CD30 expression, in order to inform patient selection for BV+CHP.

Conclusion

Based on improvement in progression-free as well as overall survival and a favorable benefit/risk balance, BV+CHP is a significant advance in the frontline therapy of CD30-expressing PTCL.

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Disclosures

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