U.S. Food and Drug Administration Approval Summary: Brentuximab Vedotin for the Treatment of Relapsed Hodgkin Lymphoma or Relapsed Systemic Anaplastic Large Cell Lymphoma

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Abstract

The Food and Drug Administration (FDA) describes the accelerated approval of brentuximab vedotin for patients with relapsed Hodgkin lymphoma (HL) and relapsed systemic anaplastic large cell lymphoma (sALCL). FDA analyzed the results of two single-arm trials, enrolling 102 patients with HL and 58 patients with sALCL. Both trials had primary endpoints of objective response rate (ORR) and key secondary endpoints of response duration and complete response rate (CR). For patients with HL, ORR was 73% (95% CI: 65, 83); median response duration was 6.7 months, and CR was 32% (95% CI: 23, 42). For patients with sALCL, ORR was 86% (95% CI: 77, 95), median response duration was 12.6 months, and CR was 57% (95% CI: 44, 70). The most common adverse reactions were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory infection, diarrhea, pyrexia, rash, thrombocytopenia, cough and vomiting. FDA granted accelerated approval of brentuximab vedotin for the treatment of patients with HL after failure of autologous stem cell transplantation (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and for the treatment of patients with sALCL after failure of at least one prior multi-agent chemotherapy regimen.

Introduction

Classical Hodgkin lymphoma (cHL) and systemic anaplastic large cell lymphoma (sALCL) are hematologic malignancies that characteristically express the cell surface protein, CD30, a marker of lymphocyte activation.[1, 2] Both conditions typically present with symptoms of lymph node enlargement, splenomegaly, fever, weight loss, fatigue

and night sweats. Classical HL is characterized by the presence of Reed-Sternberg cells that express the CD30 antigen.

An estimated 8,830 new cases of HL are diagnosed in the United States annually.[3] Although the majority of patients achieves complete remissions with combination chemotherapy and/or radiotherapy, a small percentage do not respond to first-line therapy or will relapse. Patients with inadequate responses or those who relapse are typically evaluated for high-dose chemotherapy and autologous stem cell transplant (ASCT). However, up to 40% of patients receiving autologous stem cell transplantation eventually relapse, and the median overall survival is about two years from the time of relapse post-ASCT.[4]

Systemic ALCL is a rare type of aggressive T-cell non-Hodgkin lymphoma (NHL) with CD30 expression on tumor cells. About 1300-3500 new cases of sALCL are diagnosed annually in the United States. [3,5,6] Two subtypes of sALCL are currently recognized by immunohistochemistry testing: Anaplastic lymphoma kinase positive (ALK+) and ALK negative (ALK-).[5]

The ALK+ subtype usually affects children and young adults, and patients with ALK+ disease frequently achieve durable complete remission when treated with combination chemotherapy and/or radiotherapy. Conversely, ALK- sALCL is more commonly found in older patients and has an unfavorable prognosis. After initial chemotherapy, recurrence is expected in 40-60% of patients with sALCL, only 25-30% achieve a second complete remission with multi-agent chemotherapy, and the typical duration of second remission is less than one year[7].

There are two approval pathways for new drugs and biologics: regular approval

and accelerated approval. Regular approval is based upon substantial evidence of efficacy with acceptable safety in adequate and well-controlled trials. Oncology drugs approved under the regular approval process have shown direct evidence of clinical benefit, generally defined as an improvement in overall survival or an improvement in how a patient feels or functions.

Accelerated approval is usually based on substantial evidence for an effect on a surrogate endpoint that is considered reasonably likely to predict clinical benefit, such as a meaningful response rate with duration. Accelerated approval allows patients earlier access to promising drugs and biologics while the Applicant studies the drug further to verify and characterize the expected clinical benefit[8]. There are two considerations for what products are eligible for accelerated approval: The product must be intended to treat a serious or life-threatening illness; and the drug must provide a meaningful therapeutic benefit compared to other available therapies or provide therapy where none exists. The accelerated approval can be converted to regular approval if the required clinical trial(s) verify safety and efficacy. If confirmatory trials fail to confirm clinical benefit, the FDA can withdraw the indication(s).

In patients with advanced cancer, where there is no established alternative therapy, well-documented and durable responses of sufficient magnitude, including complete responses, obtained from single arm trials have been accepted as evidence for accelerated approval.

The Biological License Application (BLA) for brentuximab vedotin was submitted on February 25, 2011. The application contained the final results of two single-arm clinical

Trials: SG035-0003 (HL trial)[9] and SG035-0004 (sALCL trial)[10]. The BLA was supported by safety information from a total of 357 patients who received at least a single dose of brentuximab vedotin, 160 of whom comprised the Phase 2 population.

Chemistry, Manufacturing and Controls

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30, 2) the microtubule disrupting agent MMAE (monomethyl auristatin E), and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10.[11]

Nonclinical Pharmacology and Toxicology

The anticancer activity of brentuximab vedotin is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage.[12] Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death. Brentuximab vedotin caused cell death in CD30-positive cells. MMAE not bound to antibody is toxic to cells regardless of CD30 expression status.

The cynomolgus monkey was considered an appropriate species for toxicology evaluation based on studies showing binding of the ADC to CD30-positive cells in monkeys and humans, with similar binding affinities. The main adverse findings in monkeys were related to the cytotoxic agent, MMAE, and consisted of toxicity to the hematopoietic system, including bone marrow hypocellularity, lymphoid depletion, and neutropenia.

Results of repeat-dose toxicity studies in rats indicate the potential for brentuximab

vedotin to impair fertility in males. MMAE was genotoxic, with findings consistent with the expected effect of MMAE as a microtubule disrupting agent. When administered during the period of organogenesis, brentuximab vedotin caused embryofetal lethality and teratogenicity; as a result, the product was assigned Pregnancy Category D.

Clinical Pharmacology

Pharmacokinetic data of brentuximab vedotin, total antibody, and MMAE were available from 314 patients in three phase 1 and two phase 2 trials. Brentuximab vedotin exhibited linear PK from 1.2 to 2.7 mg/kg. The half-life ranged from 4 to 6 days with minimal accumulation, and steady-state was achieved in 21 days for the ADC. The average trough concentrations of total antibody and ADC increased with increasing brentuximab vedotin doses, while the average trough concentration of MMAE flattened at doses greater than 0.8 mg/kg. Both AUC and Cmax of MMAE increased with dose. The time- to- maximum concentration of ADC ranged from approximately 1 to 3 days. Similar to the ADC, steady state MMAE was achieved within 21 days with every 3 week dosing of brentuximab vedotin. MMAE exposures decreased with continued administration of brentuximab vedotin with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses. The binding of MMAE to human plasma proteins, *in vitro,* ranged from 68-82%. MMAE is not likely to displace or to be displaced by highly protein-bound drugs. *In vitro*, MMAE was a substrate of P-glycoprotein and was not a potent inhibitor of P-gp. In humans, the mean steady state volume of distribution was approximately 6-10 L for ADC. *In vivo* data in animals and humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolized. *In vitro* data indicate that the MMAE metabolism occurs primarily via

oxidation by CYP3A4/5. *In vitro* studies using human liver microsomes indicate that MMAE inhibits CYP3A4/5 but not other CYP isoforms. MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes. MMAE appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC.

Clinical Trials

Materials and Methods

Seattle Genetics, Inc. conducted two clinical trials to support the Biologics License Application (BLA): SG035-0003 (Trial 1) and SG035-0004 (Trial 2). Both trials were single-arm, single-agent, multicenter trials. Trial 1 enrolled patients with HL who had relapsed following ASCT. Trial 2 enrolled patients with sALCL who had previously been treated with curative intent. The protocol pre-specified that CD30 positivity be confirmed by central pathology review. Key eligibility criteria common to both trials were that patients were required to have measurable disease of at least 1.5 cm by computed tomography (CT) and tumors must have been fluorodeoxyglucose (FDG) avid. In addition, Eastern Cooperative Oncology Group (ECOG) performance status was to be 0 or 1 and patients were 18 years of age or older except in the U.S. where patients were eligible if at least 12 years old.

The primary endpoint of both trials was objective response rate (ORR), defined as the sum of the complete and partial response rates (CR + PR). Response was determined by an independent review facility (IRF) using the revised response criteria for malignant lymphoma[13]. CR rate and response duration were key secondary endpoints. Patients were to be evaluated for response with CT scans at cycles 2, 4, 7, 10, 13 and 16.

FDG-PET (positron emission tomography) scans were mandatory only at baseline and at cycles 4 and 7.

For both trials, the brentuximab vedotin dosing regimen was 1.8 mg/kg, intravenously, once every 21 days.[9] Patients continued treatment until disease progression or unacceptable toxicity up to a maximum of 16 cycles.

The planned clinical trial size was 100 for Trial 1 based on the assumptions of 29% ORR and that the exact 2-sided 95% confidence interval would exclude an ORR of less than 20%. The planned clinical trial size was 55 for Trial 2 based on the assumptions of 33% ORR and that the exact 2-sided 95% confidence interval would exclude an ORR of less than 20%.

Demographics

One hundred two patients were enrolled in Trial 1 and fifty eight patients in Trial 2. Approximately 80% of the patients enrolled in Trials 1 and 2 were in the U.S and the majority were Caucasian. The median age for patients with HL was 31 years and for sALCL was 52 years. Patients in Trial 1 had a median of 5 prior therapies (including ASCT) for HL, and patients in Trial 2 had a median of 2 prior therapies for sALCL.

Efficacy Results in Hodgkin Lymphoma

The ORR for patients with HL who relapsed after ASCT was 73% (95% C.I. [65, 83]), and the CR rate was 32% (95% C.I. [23, 42]). The median duration of ORR was 6.7 months, and of CR was 20.5 months (Table 1).

Efficacy Results in Systemic Anaplastic Large Cell Lymphoma

The ORR for patients with sALCL was 86% (95% C.I. [77, 95]), and the CR rate was 57% (95% C.I. [44, 70]). The median duration of ORR was 12.6 months, and

the median duration of CR was 13.2 months (Table 1).

Safety Results

Among all 160 patients enrolled in both trials, the most frequently reported adverse reactions occurring in at least 20% of patients were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting (Table 2).

In the phase 2 trials, serious adverse reactions, regardless of causality, were reported in 31% of patients receiving brentuximab vedotin. The most common serious adverse reactions experienced by patients with HL included peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and pyrexia (2%). The most common serious adverse reactions experienced by patients with sALCL were septic shock (3%), supraventricular arrhythmia (3%), pain in extremity (3%), and urinary tract infection (3%). Other important serious adverse reactions reported included Stevens-Johnson syndrome and tumor lysis syndrome. Two cases of anaphylaxis occurred in Phase 1 trials. In the Phase 2 trials, 12% of patients experienced Grade 1 or 2 infusion-related reactions (chills, nausea, dyspnea, pruritis, pyrexia, and cough).

A fatal case of progressive multifocal leukoencephalopathy (PML) was reported in a patient while receiving brentuximab vedotin[14]. This adverse reaction was noted in the approved prescribing information (PI). Following the drug approval, two additional cases of PML were reported with brentuximab vedotin therapy, and a boxed warning for this adverse reaction has been added to the label.[14, 15]

Discussion

The response rates and duration of response in both trials, as determined by an independent review facility, provided substantial evidence of treatment effect in patients with relapsed HL following ASCT and in those with relapsed sALCL. The Office of Hematology and Oncology Products approved licensing under Accelerated Approval regulations following its own independent analysis and an Oncologic Drugs Advisory Committee (ODAC) meeting review of the trial and outcomes. The single-arm design of the two Phase 2 trials precluded reliable interpretation of the treatment effect on time- to-event endpoints, such as progression-free survival (PFS) and overall survival (OS) due to confounding effects from the natural history of the underlying disease and lack of a control group. The limited number of patients in the two trials and the single arm design also precluded a comprehensive characterization of the safety profile. The members of the ODAC voted unanimously for accelerated approval based on the high response rate and durable responses observed for both indications.

Conversion from accelerated to regular approval is contingent upon satisfactory completion of clinical trials to verify and describe the clinical benefit of brentuximab vedotin. The applicant has agreed to conduct a randomized controlled trial of CHOP (cyclophosphamide,doxorubicin, vincristine, and prednisone) alone versus brentuximab vedotin in combination with CHP (cyclophosphamide, doxorubicin, and prednisone) as first-line treatment in patients with newly diagnosed CD30-positive mature T- and NK-cell lymphoma. The applicant also has agreed to conduct a randomized controlled trial of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) alone versus brentuximab vedotin in combination with AVD (doxorubicin, vinblastine, and dacarbazine) as first-

line treatment in patients with advanced HL. Bleomycin was removed from the ABVD combination with brentuximab following preliminary results of a trial of the combination that reported excessive pulmonary toxicity. Pulmonary toxicity occurred in 40 percent of patients who received the combination, and manifested as interstitial infiltration and/or inflammation observed on radiographs and computed tomography of the chest. The PI has been revised to contraindicate the combination of brentuximab vedotin with bleomycin.[15]

PFS was considered an acceptable endpoint for confirmation of clinical benefit for these disease settings because an OS endpoint would not likely be attained within a reasonable time frame. Both trials are designed to show superiority on the primary endpoint of PFS, as determined by an independent, blinded review facility. OS is a key secondary endpoint for each trial.

FDA did not require a validated CD30 *in-vitro* diagnostic at the time of accelerated approval for brentuximab vedotin since CD30 positivity is present in nearly 100% of the malignant cells in both conditions. For Trial 1, although the enrollment criteria did not specifically exclude nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), patients with NLPHL were not enrolled due to the absence of CD30 expression[16].

The brentuximab vedotin BLA represented the first application submitted to the Agency that used the 2007 response criteria for lymphoma, which included the integration of FDG-PET scans in the response assessments. The performance of FDG-PET scans during response assessments only after cycles 4 and 7 led to difficulties in the interpretation of best response and response duration. To address this limitation, the FDA conducted sensitivity analyses using the 1999 response criteria that demonstrated results consistent

with the 2007 response criteria.

On August 19, 2011, FDA granted accelerated approval to brentuximab vedotin for the following indications: for the treatment of patients with HL after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and for the treatment of patients with sALCL after failure of at least one prior multi-agent chemotherapy regimen. The FDA analysis of the two trials concluded that the response rates, durations, and the observed toxicities of the therapy supported a favorable benefit-risk outcome in each condition. Post-approval randomized clinical trials are in progress to address the requirement to verify clinical benefit.

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Table 1. Efficacy Results for Phase 2 Clinical Trials of Brentuximab Vedotin

Clinical Trial Population	Response Rate (95% CI)	Median Duration of Response (months) (95% CI)
Relapsed HL after ASCT (ITT population N=102)		
CR (n=33)	32% (23%, 42%)	20.5 (12.0, NE)
PR (n=41)	40% (32%, 49%)	3.5 (2.2, 4.1)
ORR (n=74)	73% (65%, 83%)	6.7 (4.0, 14.8)
Relapsed sALCL (ITT population N=58)		
CR (n=33)	57% (44%, 70%)	13.2 (10.8, NE)
PR (n=17)	29% (18%, 41%)	2.1 (1.3, 5.7)
ORR (n=50)	86% (77%, 95%)	12.6 (5.7, NE)

CI, confidence interval; ITT, intent-to-treat; CR, complete response; PR, partial response; ORR, overall response rate; NE, not estimable

Table 2. Most Commonly Reported Adverse Reactions (≥20%) in Phase 2 Clinical Trials of Brentuximab Vedotin

	HL Total N = 102 % of patients			sALCL Total N = 58 % of patients		
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Blood and lymphatic system disorders						
Neutropenia	54	15	6	55	12	9
Anemia	33	8	2	52	2	-
Thrombocytopenia	28	7	2	16	5	5
Nervous system disorders						
Peripheral sensory neuropathy	52	8	-	53	10	-
General disorders and administration site conditions						
Fatigue	49	3	-	41	2	2
Pyrexia	29	2	-	38	2	-
Pain	7	-	-	28	-	5
Infections and infestations						
Upper respiratory tract infection	47	-	-	12	-	-
Gastrointestinal disorders						
Nausea	42	-	-	38	2	-
Diarrhea	36	1	-	29	3	-
Abdominal pain	25	2	1	9	2	-
Vomiting	22	-	-	17	3	-
Skin and subcutaneous tissue disorders						
Rash	27	-	-	31	-	-
Respiratory, thoracic and mediastinal disorders						
Cough	25	-	-	17	-	-

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