



BLA 125388

Brentuximab vedotin (Adcetris™)

July 14, 2011

Oncologic Drugs Advisory Committee

Applicant's Proposed Indication: Treatment of patients with relapsed or refractory Hodgkin lymphoma

R. Angelo de Claro, M.D.
Medical Officer



Brentuximab Review Team

Discipline	Primary Reviewer	Team Leader
Clinical	R. Angelo de Claro (HL) Karen McGinn (ALCL)	Virginia Kwitkowski
Statistics	Kyung Lee (HL) Kallappa Koti (ALCL)	Mark Rothmann
Clinical Pharmacology	Aakanksha Khandelwal Bahru Habtemariam	Julie Bullock
Pharmacology Toxicology	Yanli Ouyang	Haleh Saber
Product Quality	Marjorie Shapiro (OBP) Francisco Borrego (OBP) Xiao Hong Chen (ONDQA) Bo Chi (OMPQ) Colleen Thomas (OMPQ)	Kathleen Clouse (OBP) Janice Brown (ONDQA) Patricia Hughes (OMPQ)
DSI	Lauren Iacono-Connors	Tejashri Purohit-Sheth
Project Manager	Lara Akinsanya	Janet Jamison

Main Points

- Brentuximab is an active drug in the treatment of patients with Hodgkin lymphoma who relapse after autologous stem cell transplant.
- Peripheral neuropathy is the main safety issue identified by the Sponsor.
- Risk-benefit assessment is limited by the single arm design.

Hodgkin Lymphoma (HL)

- Cancer of the immune system marked by the presence of CD30-expressing Reed-Sternberg cells
- Symptoms include painless enlargement of lymph nodes, spleen, or other immune tissue. Other symptoms include fever, weight loss, fatigue, and night sweats.
- Initial treatment typically includes chemotherapy and/or radiation therapy.

FDA Approvals for Hodgkin Lymphoma

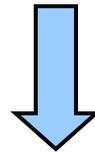
Class	Drug	Year of Approval
Alkylating agents	Carmustine (BCNU)	1977
	Lomustine (CCNU)	1976
	Dacarbazine	1975
	Procarbazine	1969
	Cyclophosphamide	1959
	Chlorambucil	1957
	Mechlorethamine	1949
Antitumor antibiotics	Doxorubicin	1974
	Bleomycin	1973
Antimicrotubule agents	Vinblastine	1965
	Vincristine	1963

ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine

BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

Treatment of Progressive Hodgkin Lymphoma

patients who relapse or do not respond
to first-line therapy



Autologous Stem Cell Transplant (ASCT)

- 40% relapse post-ASCT
- Median survival: 2 years (from time of relapse post-ASCT)



Therapy for Relapsed HL Post-ASCT Based on Literature Review

Agent (year reported)	Number treated	Prior ASCT	CR+CRu+PR	CR+CRu
Vinblastine ¹⁹⁹⁸	17	17	10 (59%)	2 (12%)
Vinorelbine ¹⁹⁹⁴	24	NS	11 (46%)	3 (13%)
Gemcitabine ²⁰⁰⁴	27	18	6 (22%)	0
Vinorelbine + Gemcitabine ²⁰⁰⁷	8	NS	6 (75%)	4 (50%)
Rituximab ²⁰⁰⁸	22	18	5 (23%)	1 (5%)
Rituximab + Gemcitabine ²⁰⁰⁸	33	18	16 (48%)	5 (15%)
Bortezomib ²⁰⁰⁶	14	13	1 (7%)	0
Bortezomib ²⁰⁰⁷	30	19	0	0
Bortezomib ²⁰⁰⁷	12	NS	0	0
Panobinostat ²⁰¹⁰	129	129	35 (27%)	5 (4%)

DISCLAIMER: Data in above table was not independently verified by FDA.

Clinical Trial: SG035-0003

Design: single arm, multicenter

Study Population:

- Relapsed or refractory HL who have **previously received ASCT**
- Age \geq 18 years (**Note:** \geq 12 years may be enrolled at US sites)
- CD30-positive disease by central review
- Measurable disease at least 1.5 cm by CT, and FDG-avid by PET
- ECOG Performance Status 0 or 1

Treatment: 1.8 mg/kg intravenously on day 1 of each 21-day cycle for up to 16 cycles, disease progression or unacceptable toxicity

Sponsor's Endpoints

- **Primary Endpoint:** Overall Response Rate (ORR) per Independent Review Facility (IRF)
- **Key Secondary Endpoints:** Duration of Response per IRF, Complete Remission Rate per IRF
- **Other Secondary Endpoints:** Progression-Free Survival per IRF, Overall Survival, Safety, Population Pharmacokinetics

Response Assessments

- Integration of FDG-PET scans based on 2007 Revised Response Criteria for Lymphoma
- Qualitative FDG-PET scans

Schedule of Response Assessments

	Baseline	C2	C4	C7	C10	C13	C16
CT	✓	✓	✓	✓	✓	✓	✓
FDG-PET	✓	Optional	✓	✓	Optional	Optional	Optional

✓ Required

Complete Remission

Sponsor's Definition

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy
- No new lesions
- However, at time points with FDG-PET scan: A residual mass of any size was permitted as long as FDG-negative.

Partial Remission

Sponsor's Definition

- $\geq 50\%$ decrease in the sum of the products of the diameters (SPD) of the index lesions
- No increase in size of other nodes, liver, or spleen
- No new lesions
- At time points with FDG-PET scan: CR or PR on CT evaluation and at least one (1) previously involved site remains FDG-positive.

Demographics

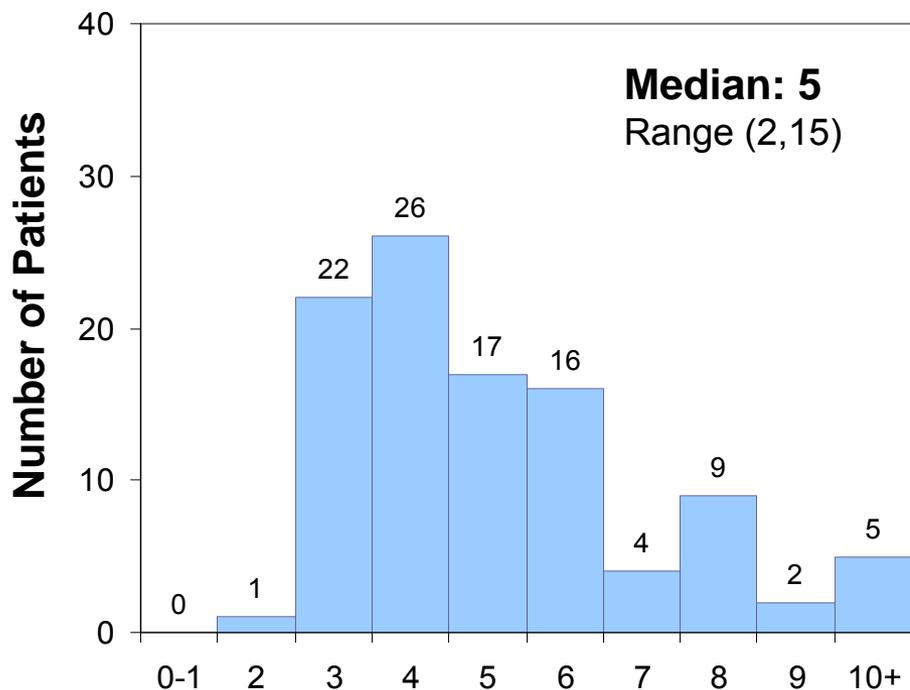
Demographic Parameter		All Subjects (N=102)
Age (years) Groups	Mean (SD)	34.1 (12.2)
	<18	1 (1%)
	18-39	76 (75%)
	40-64	22 (22%)
	≥ 65	3 (3%)
Gender	Female	54 (53%)
	Male	48 (47%)
Race	Caucasian	89 (87%)
ECOG Performance Status	0 (No symptoms)	42 (41%)
	1 (Symptomatic but fully ambulatory)	60 (59%)
Site	US	86 (84%)
	Ex-US (Canada, France, Italy)	16 (16%)

Disease Characteristics

Baseline Disease Characteristics		All Subjects (N=102)
Prior autologous stem cell transplant (ASCT)	≥ 1	102 (100%)
	2	11 (11%)
Time to relapse from ASCT	≤ 1 year	72 (71%)
	> 1 year	30 (29%)
B symptoms present		35 (34%)
Prior radiation therapy		67 (66%)

Prior Lines of Systemic Chemotherapy

Total (includes HDT/ASCT)



Example of Chemotherapy Sequence

First-line: ABVD (88%)



Mobilization: ICE* (47%)



HDT/ASCT: BEAM* (47%)



Salvage chemotherapy

None 44%

Gemcitabine 32%

Vinorelbine 18%

Median: 1

Range (0,9)

*ICE: ifosfamide, carboplatin, etoposide

BEAM: carmustine, etoposide, cytarabine, melphalan

Prior Systemic Chemotherapy

Drug or Drug Class	Prior Chemotherapy Exposure
Doxorubicin	100%
Bleomycin	94%
Vinca alkaloids	100% received vinblastine or vincristine. (Vinblastine 94%, Vincristine 31%, Vinorelbine 33%)
Alkylating Agents*	≥2 (100%), ≥3 (99%), ≥4 (94%), ≥5 (66%)
Other	Etoposide (98%), Cytarabine (61%), Gemcitabine (51%), Rituximab (17%)

*Results based on exposure to 15 different alkylating agents

Sponsor's Definition of Refractory

- **Refractory:** response of SD or PD to most recent prior therapy
- **Primary Refractory:** failure to achieve CR or disease progression within 3 months of first-line therapy

	N	CR or PR to other lines of systemic therapy
Refractory	49	88%
Primary Refractory	72	67%

FDA Description of the Study Population in SG035-0003

Patients with Hodgkin lymphoma who relapse after autologous stem cell transplant

Response Rate and Duration of Response (Sponsor's Analysis)

ITT Population (N=102)	Response Rate (95%CI)	Median Duration of Response months (95% CI)
Complete Remission (CR) N=35	34% (25%, 44%)	20.5 (10.8, NE)
Partial Remission (PR) N=41	40% (32%, 49%)	3.5 (2.2, 4.1)
Overall Response (CR+PR) N=76	75% (65%, 83%)	6.7 (3.6, 14.8)



FDA Adjudication of Best Response

Subject ID	Adjudication	Reason
10004-0019	PR → CR	CR criteria met based on CT, FDG-PET, and clinical data review.
11002-0086	CR → PR	New 2.1 × 2.1 cm, FDG-positive, L axillary node at CR timepoint. Patient achieved PR in prior cycle.
10004-0042	CR → PR	Persistently FDG-positive non-index lesion
10011-0074	CR → PR	Persistently FDG-positive index lesion
10006-0047	PR → SD	Did not meet CT criteria for PR
39001-0070	PR → SD	Did not meet CT criteria for PR

Response Rate and Duration of Response (FDA Analysis)

ITT Population (N=102)	Response Rate (95%CI)	Median Duration of Response months (95% CI)
Complete Remission (CR) N=33	32% (23%, 42%)	20.5 (12.0, NE)
Partial Remission (PR) N=41	40% (32%, 49%)	3.5 (2.2, 4.1)
Overall Response (CR+PR) N=74	73% (64%, 80%)	6.7 (4.0, 14.8)

Not All Remissions are Durable

Best Response	N	Response Duration of Only One Assessment Period
CR	33	6/33 (18%)
PR	41	14/41 (34%)

*developed Progressive Disease (PD) at next assessment (range 39 to 92 days)

Uncertainty with Duration of Response

Example

ID 10008-0039	C2 Jul 09	C4 Sep 09	C7 Dec 09	C10 Feb 10	C13 Apr 10	C16 Jun 10	LTFU Sep 10	LTFU Dec 10	LTFU Feb 11
CT only	PR	PR	PR	PR	PR	PR	PR	PR	PR
CT+CDR	PR	PR	PR	PR	PR	PR			
CT+PET+CDR		CR	CR						
Visit response	PR	CR	CR	PR	PR	PR	PR	PR	PR

CDR, clinical data review



Duration of CR



Duration of Response

Follow-up Assessments per Period

Assessment Period	Number of patients with CT scans	Number of patients with FDG-PET scans	% with both CT and FDG-PET scans
Cycle 2	101	17	17%
Cycle 4	95	95	100%
Cycle 7	80	80	100%
Cycle 10	48	11	23%
Cycle 13	33	8	24%
Cycle 16	18	11	61%
End of Treatment	24	16	67%
Long Term Follow-up	92	26	28%

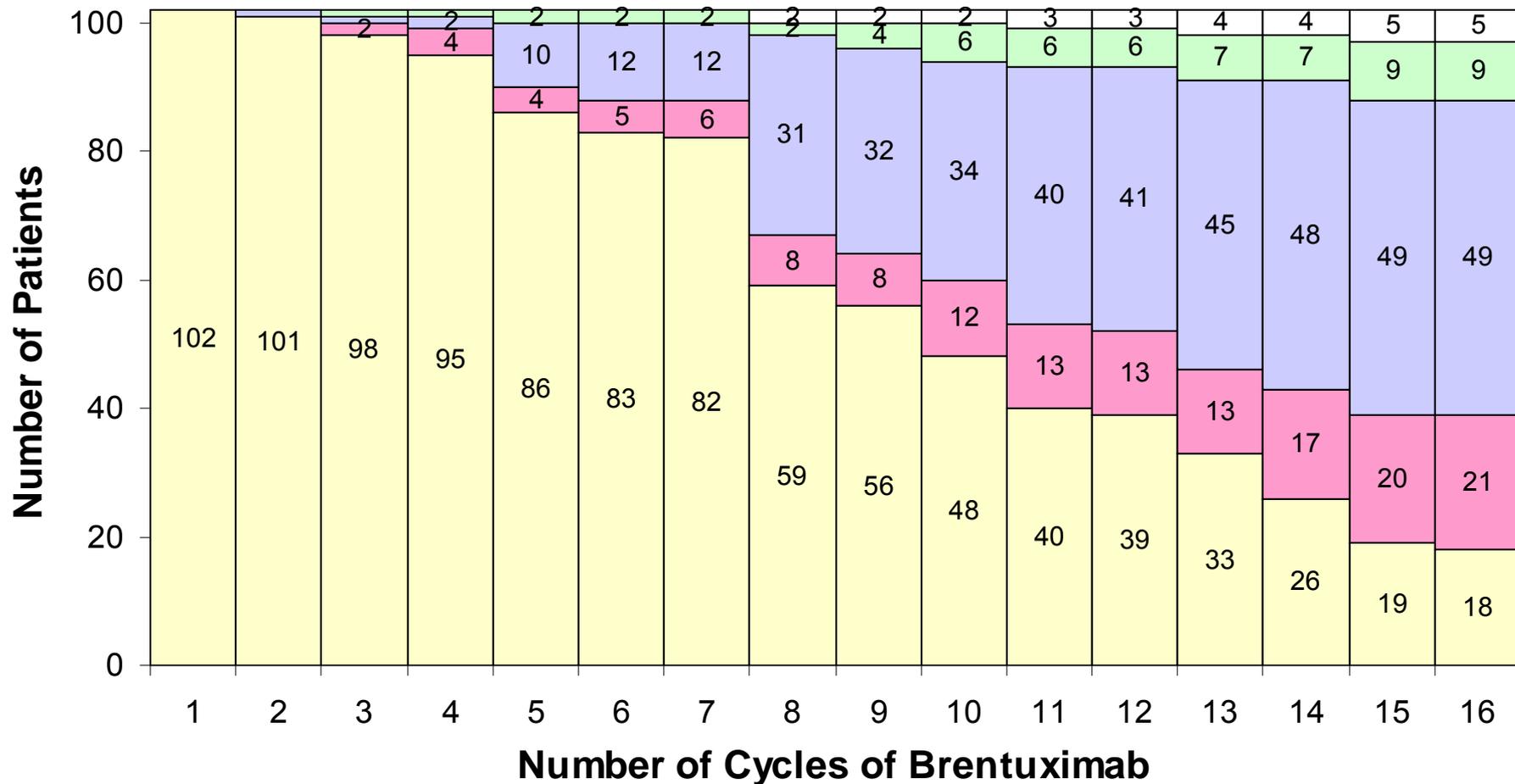
Sponsor claims efficacy in patients without prior ASCT

- **Basis of Claim:** 20 patients with relapsed Hodgkin lymphoma without prior transplant treated in two Phase 1 clinical trials
 - There were 80 patients with relapsed Hodgkin lymphoma treated in the two Phase 1 clinical trials.
- **Brentuximab dose:** 1.8 mg/kg every 3 weeks in only two patients without prior transplant

Safety Overview

Safety Population (n=102)	Number of patients (%)
Death within 30 days of last dose	0
Serious adverse events	25 (25%)
Discontinuation due to adverse event	21 (21%)
G3 or G4 Treatment-Emergent Adverse Event (TEAE)	56 (55%)
Any TEAE	100 (98%)

Patient Disposition Per Treatment Cycle



Safety Summary

	G1-4 TEAE ≥ 10%	G3-4 TEAE ≥ 2%	Serious AE
Peripheral Neuropathy			
Peripheral Sensory	51%	8%	–
Peripheral Motor	16%	4%	4%
Myelosuppression			
Neutropenia	51%	20%	–
Thrombocytopenia	27%	9%	–
Anemia	30%	6%	–
Infections	64%	7%	8%
Infusion Reactions	14%	–	–
Stevens-Johnson Syndrome	1 patient		

Peripheral Neuropathy

- Most common adverse event leading to treatment discontinuation (12 patients), and dose reductions (10 patients)
- **During Treatment***: 56 patients developed neuropathy
 - 40 sensory only, 4 motor only, 12 with both
 - Median time to onset 12.4 weeks
- **Long-term follow-up***: 26 of 56 (46%) with residual neuropathy

*Patients with pre-existing neuropathy not included, unless worse than baseline.

Adverse Events of Undetermined Significance to the Study Population

Serious Adverse Events (SAE)

- **Hyperglycemia:** 6 patients, 1 patient developed G4 diabetic coma
- **Gastrointestinal hemorrhage:** 2 patients
- **Grade 3-4 pneumonitis:** 2 patients
- **Pulmonary embolism:** 2 patients

Approval Mechanisms

Regular

- Public Health Service Act
 - Section 351

Accelerated

- Federal Food, Drug, and Cosmetic Act
 - Section 506
- FDA Regulations (Title 21 C.F.R.)
 - Part 601, Subpart E

Problems with Single Arm Trials

- Efficacy analysis limited to response rate and duration of response
- Time-to-event endpoints cannot be adequately interpreted (including progression-free survival and overall survival)
- Does not allow for attribution of adverse events
- If used for initial registration, no prior experience for both efficacy and safety
- Often smaller in size compared to RCT

Advice Given by FDA to Seattle Genetics

End of Phase 1 Meeting (July 2008)

A high response rate may support an accelerated approval.

Pre-BLA Meeting (November 2010)

Generally, response rate in a single-arm trial is not adequate for regular approval.

Approvals for NMEs based on Single Arm Clinical Trials, 2001 to 2011 (Malignant Hematology Indications)

Regular	Accelerated	
<p>Vorinostat (2006)* Romidepsin (2009)*</p>	<p>Alemtuzumab (2001) Imatinib (2001) Bortezomib (2003) Tositumumab (2004) Clofarabine (2004)</p>	<p>Nelarabine (2005) Dasatinib (2006) Nilotinib (2007) Pralatrexate (2009) Ofatumumab (2009)</p>

*In September 2009, ODAC recommended that FDA require randomized trials for future approvals for CTCL.

Accelerated Approval Eligibility

- “Serious or life-threatening illness”
- “Meaningful therapeutic benefit to patients over existing treatments...”
 - e.g. ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy
 - 21 CFR 601.40

Accelerated Approval Pathways

- “Surrogate endpoint reasonably likely... to predict clinical benefit”
 - 21 CFR 601.41
- “Clinical endpoint other than survival or irreversible morbidity”
 - 21 CFR 601.41

Post-Approval Clinical Trials

- Accelerated approval is given with the “requirement that the applicant study the... product further, to **verify and describe its clinical benefit.**”
- Clinical Trials
 - Must be “adequate and well-controlled”
 - Must be carried out with “due diligence”
 - Are usually underway at the time accelerated approval is granted
 - 21 CFR 601.41

Proposed Confirmatory Clinical Trials for HL

Study Design	Population	Endpoint
AETHERA trial (SGN35-005): Phase 3, double-blind, placebo-controlled, randomized trial (Post-ASCT treatment)	HL patients at high-risk* for relapse post-ASCT N = 322 patients	Primary: PFS** Secondary: OS
SGN35-009: Phase 1, dose-escalation, ABVD+brentuximab or AVD+brentuximab (First-line treatment)	Untreated HL	Safety

***Defined as at least one of the following:** (1) history of refractory HL, (2) relapsed or progressive HL that occurs <12 months from end of frontline therapy, (3) extranodal involvement at time of pre-ASCT relapse

Powered to detect a **PFS HR of 0.667, corresponding to a 6 month improvement in median PFS

FDA Concerns with the AETHERA trial

Heterogeneity of patient population

- Patients may not be in complete or partial remission at the time of randomization
- Risk-benefit assessment is different for patients who do not have active disease (i.e., CR) as compared to patients with residual disease post-transplant.

Primary endpoint

- Progression-free survival or overall survival?

Conclusions

Efficacy

- Brentuximab vedotin is an active drug in the treatment of patients with Hodgkin lymphoma who relapse after autologous stem cell transplant.
 - 73% ORR with median duration of 6.7 months
 - 32% CR rate with median duration of 20.5 months
- **Limitations:**
 - Median duration of PR is 3.5 months
 - Inter- and intra-patient variability of follow-up assessments for duration of response
 - Cannot adequately interpret progression-free survival or overall survival
 - No prior experience for efficacy
 - Small study size (N=102)

Conclusions

Safety

- The main safety issue identified by the Sponsor is peripheral neuropathy.
 - Occurred in 56% of the patients
 - 46% who developed neuropathy have persistent neuropathy
- **Limitations:**
 - Small study size (N=102)
 - Does not allow for attribution of adverse events (e.g., hyperglycemia, pneumonitis, pulmonary embolism)
 - No prior experience for safety