5 Minute JournalClub

Key ASH Presentations

Issue 2, 2012

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CME Information

LEARNING OBJECTIVES

- Consider the inclusion of brentuximab vedotin in the treatment algorithm for relapsed/refractory Hodgkin lymphoma (HL) or systemic anaplastic large cell lymphoma (sALCL).
- Assess the benefit and toxicity resulting from prolonged treatment with brentuximab vedotin in patients with relapsed/refractory HL or sALCL.
- Evaluate the efficacy and toxicity outcomes from studies with brentuximab vedotin in combination with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) or AVD as front-line therapy for advanced HL.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES

The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Advisory Committee: Cephalon Inc, Genentech BioOncology, Seattle Genetics; *Paid Research:* Cephalon Inc, Genentech BioOncology, Lilly USA LLC, Plexxikon Inc, Seattle Genetics.

Brentuximab Vedotin in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma: A Phase 2 Study Update

Advani RH et al.

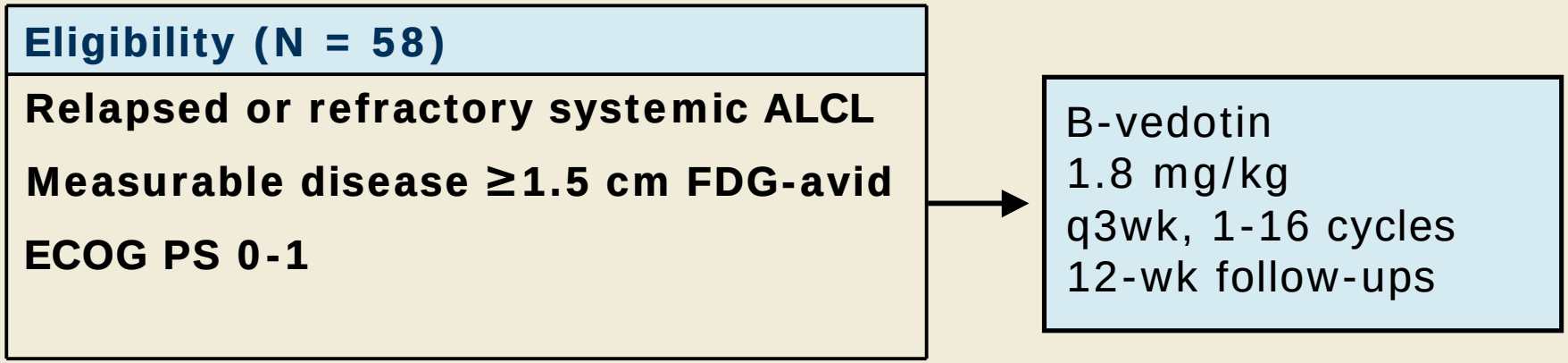
Proc ASH 2011;Abstract 443.

Background

- Systemic anaplastic large cell lymphoma (sALCL) is a CD30-positive aggressive subtype of mature T-cell lymphoma, comprising 2-5% of all NHL cases.
- 76-88% of patients achieve remission with front-line treatment. However, approximately half will experience disease relapse.
- Brentuximab vedotin (B-vedotin), a novel anti-CD30 antibody drug conjugate, selectively induces apoptotic death of $CD30^+$ cells.
- **Current Analysis Objective:** Present updated results from a Phase II, multicenter study evaluating the efficacy and safety of B-vedotin in relapsed/refractory sALCL.

Advani RH et al. *Proc ASH* 2011;Abstract 443.

Study Schema



After discontinuing treatment, 14 patients received a stem cell transplant (SCT) (7 allogeneic, 7 autologous)

Primary Endpoint: Objective response rate (ORR) by independent review facility (IRF)
Secondary Endpoints: Complete remission rate (CR), duration of response, progression-free survival (PFS), overall survival (OS), safety and tolerability

Advani RH et al. *Proc ASH* 2011;Abstract 443.

Response Results

Clinical response	**(n = 58)**
Objective response rate	86%
Complete remission rate	59%
Median duration of response	
Objective response	13.2 mo
Response in patients with CR	Not reached

Advani RH et al. *Proc ASH* 2011;Abstract 443.

Survival

Progression-free survival	B-vedotin (n = 57)	Hazard ratio*	*p*-value
Median PFS	14.5 mo	0.44	<0.001

PFS in patients with CR by subsequent transplant			
Patients with CR	**Events†**	**Median PFS**	**Median # of cycles received**
No subsequent transplant (n = 20)	9	18.4 mo	13
Subsequent allogeneic SCT (n = 7)	3	16.9 mo	8
Subsequent autologous SCT (n = 7)	1	Not reached	8

Overall survival	(n = 58)
Median OS	Not reached
Estimated OS rate at 1 year	70%
Median observation time from first dose	14.7 mo

* Versus last prior therapy (5.9 mo); † Disease progression or death

Advani RH et al. *Proc ASH* 2011;Abstract 443.

Select Adverse Events (AEs)

AEs (all grades)	
Peripheral sensory neuropathy (PN)*	45%
Fatigue	28%
Nausea	28%
Diarrhea	19%
Neutropenia	17%
Myalgia	16%
Pyrexia	14%
Vomiting	14%
Upper respiratory tract infection	12%
Rash	10%

* PN managed with dose delays and/or reductions to 1.2 mg/kg
Resolution/improvement in some or all PN events = 79%

Advani RH et al. *Proc ASH* 2011;Abstract 443.

Author Conclusions

- Durable complete remissions were achieved with B-vedotin in patients with relapsed or refractory sALCL.
- Complete remissions appear durable after completing treatment.
- Adverse events, including peripheral neuropathy, were manageable.
- Based on these results, a Phase I front-line trial is ongoing and a Phase III randomized trial for patients with ALCL and other CD30-positive mature T-cell neoplasms is planned.

Advani RH et al. *Proc ASH* 2011;Abstract 443.

Investigator Commentary: Phase II Update of B-Vedotin in Patients with Relapsed/Refractory sALCL

This is an update of a previous data set. Most of the patients were heavily pretreated, only a small percent had received a transplant. The fact that most of the patients could not get to transplant suggests their prognosis was not good.

Single agent treatment with B-vedotin resulted in a median duration of response of greater than a year, which is excellent. The median duration of response in patients who had a complete response was not reached. In baseball terms, for sALCL this is approaching a home run. This is amazing — it's changed the lives of patients with this disease.

I believe that once the B-vedotin/CHOP (B-vedotin substituting for vincristine) study is completed, it'll be a "slam dunk" and this will be standard of care for sALCL as primary therapy.

Interview with Craig Moskowitz, MD, January 11, 2012

Brentuximab Vedotin (SGN-35) Enables Successful Reduced Intensity Allogeneic Hematopoietic Cell Transplantation in Relapsed/Refractory Hodgkin Lymphoma

Chen RW et al.

Proc ASH 2011;Abstract 664.

Background

- Reduced intensity allogeneic hematopoietic transplantation (RIC allo-HCT) can induce durable remissions in some patients with relapsed/refractory Hodgkin lymphoma (HL).
- However, its use is limited by lack of disease control prior to transplantation.
- Brentuximab vedotin (B-vedotin), a novel antibody-drug conjugate, has a 75% objective response rate in this patient population (*Proc ASCO* 2011;Abstract 8031).
- **Current Analysis Objective:** To evaluate the efficacy and toxicity of allogeneic transplant after B-vedotin for patients with relapsed/refractory HL.
  - Estimate efficacy of allogeneic transplant after B-vedotin

Chen RW et al. *Proc ASH* 2011;Abstract 664.

Study Schema

- Patients with relapsed/refractory HL treated at City of Hope National Medical Center (COH) and Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance (FHCRC/SCCA) between October 2008 and October 2011 who received B-vedotin followed by RIC allo-HCT
- Eligibility:
  - PS ≥ 60% by Karnofsky scale
  - No prior allo-HCT but prior autologous transplant allowed
- Methods:
  - Thirty-one patients received B-vedotin and met the inclusion criteria
  - Eighteen of 31 underwent RIC allo-HCT (14 at COH, 4 at FHCRC/SCCA)

Chen RW et al. *Proc ASH* 2011;Abstract 664.

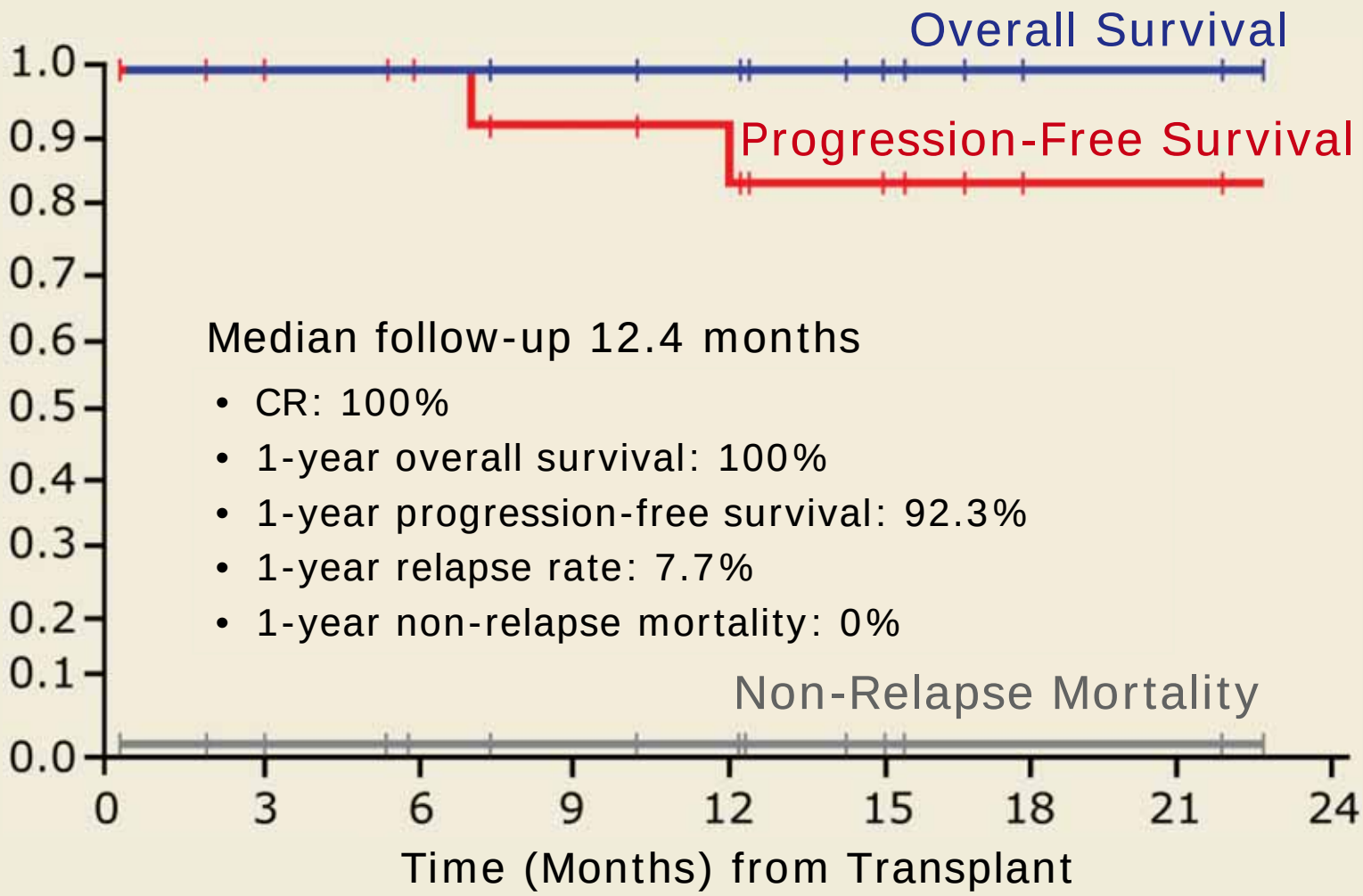
Baseline Characteristics

Characteristic	n = 18 % or median
Best response to B-vedotin	CR (39%), PR (44%), SD (11%), PD (6%)
Disease status at the end of B-vedotin therapy	CR (33%), PR (33%), SD (6%), PD (22%)
Disease status at the time of allo-HCT	CR (33%), PR (44%), SD (11%), PD (11%)
Median time from B-vedotin to allo-HCT	62 days (range: 24-276)

CR = complete response; PR = partial response; SD = stable disease;
PD = progressive disease

Chen RW et al. *Proc ASH* 2011;Abstract 664.

Survival



With permission from Chen RW et al. *Proc ASH* 2011;Abstract 664.

Transplant-Related Outcomes

Outcomes	N (%) or median (range)
Engraftment	
Days to ANC ≥ 0.5 x 10^9/L	14 (0-21)
Days to PLT > 20	12.5 (0-21)
% chimerism	>99% (day 30-209)
Acute GVHD	27.8%
Chronic GVHD	56.3%
Infectious disease	27.8%

ANC = absolute neutrophil count; PLT = platelet; GVHD = graft-versus-host disease

Chen RW et al. *Proc ASH* 2011;Abstract 664.

Bearman Toxicity Table (Patients Treated at COH)

Organ system	Bearman grade	Event incidence (n = 14)
Cardiac toxicity	I	2 (14%)
Central nervous system toxicity	I	1 (7%)
Gastrointestinal toxicity	I/II	6 (43%)
Hepatic toxicity	I/II	7 (50%)
Pulmonary toxicity	I/II	2 (14%)
Renal toxicity	I/II	7 (50%)
Stomatitis	I/II	8 (57%)

Chen RW et al. *Proc ASH* 2011;Abstract 664.

Author Conclusions

- Addition of B-vedotin prior to allogeneic transplantation does not appear to adversely affect engraftment, GVHD or survival.
- B-vedotin may provide sufficient disease control for selected patients to successfully proceed to allo-SCT.

Chen RW et al. *Proc ASH* 2011;Abstract 664.

Investigator Commentary: B-Vedotin Enables Successful RIC Allo-HCT in Relapsed/Refractory HL

To examine the impact of B-vedotin on RIC allo-HCT, the authors performed a retrospective analysis of patients with relapsed/refractory HL who received B-vedotin and then went on to receive RIC allo-HCT. Patients at COH have fared well with this approach. Following transplant, most of the patients fared well at a median follow-up of about 1 year. This is exciting because most patients with HL who receive an allo-HCT and survive up to 1 year without being adversely affected by the transplant are probably cured.

The label indication for B-vedotin is for patients for whom an autologous transplant has failed. I personally administer the agent to patients as a bridge to an allo-HCT off study. The number of doses of B-vedotin a patient should receive if the goal is to take the patient to transplant is a matter of debate. You don't have to administer B-vedotin continually. If the patient achieves remission, you can stop treatment. For a young patient who achieves remission with B-vedotin, I believe most doctors would take the patient off the agent and perform a transplant.

Interview with Craig Moskowitz, MD, January 11, 2012

Allogeneic Transplant Following Brentuximab Vedotin Treatment in Patients with Relapsed or Refractory CD30+ Lymphomas

Illidge T et al.

Proc ASH 2011;Abstract 3091.

Background

- Allogeneic stem cell transplantation (allo-SCT) is an available treatment option for relapsed or refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL), though its exact role is unclear.
- Two phase II trials have evaluated brentuximab vedotin (B-vedotin), an anti-CD30 antibody-drug conjugate, in patients with relapsed or refractory CD30+ lymphomas:
  - HL: 75% ORR, 34% CR (*Proc ASCO* 2011;Abstract 8031)
  - sALCL: 86% ORR, 57% CR (*Proc ASCO* 2011;Abstract 8032)
- **Current Study Objective**: To retrospectively characterize the outcome of patients with HL and sALCL who received allo-SCTs after treatment with B-vedotin in the 2 Phase II trials.

Illidge T et al. *Proc ASH* 2011;Abstract 3091.

Baseline Characteristics

- Fifteen patients of 160 total in the 2 Phase II trials received allo-SCT as their first therapy subsequent to treatment with B-vedotin.

Characteristic	N = 15
HL	8
sALCL	7
Refractory to front-line therapy	9 (60%)
Refractory to most recent therapy	4 (27%)
Received a previous ASCT	12 (80%)
Prior chemotherapy regimens, median (range)	3 (2-5)
ALK-positive (sALCL only)	6 (40%)

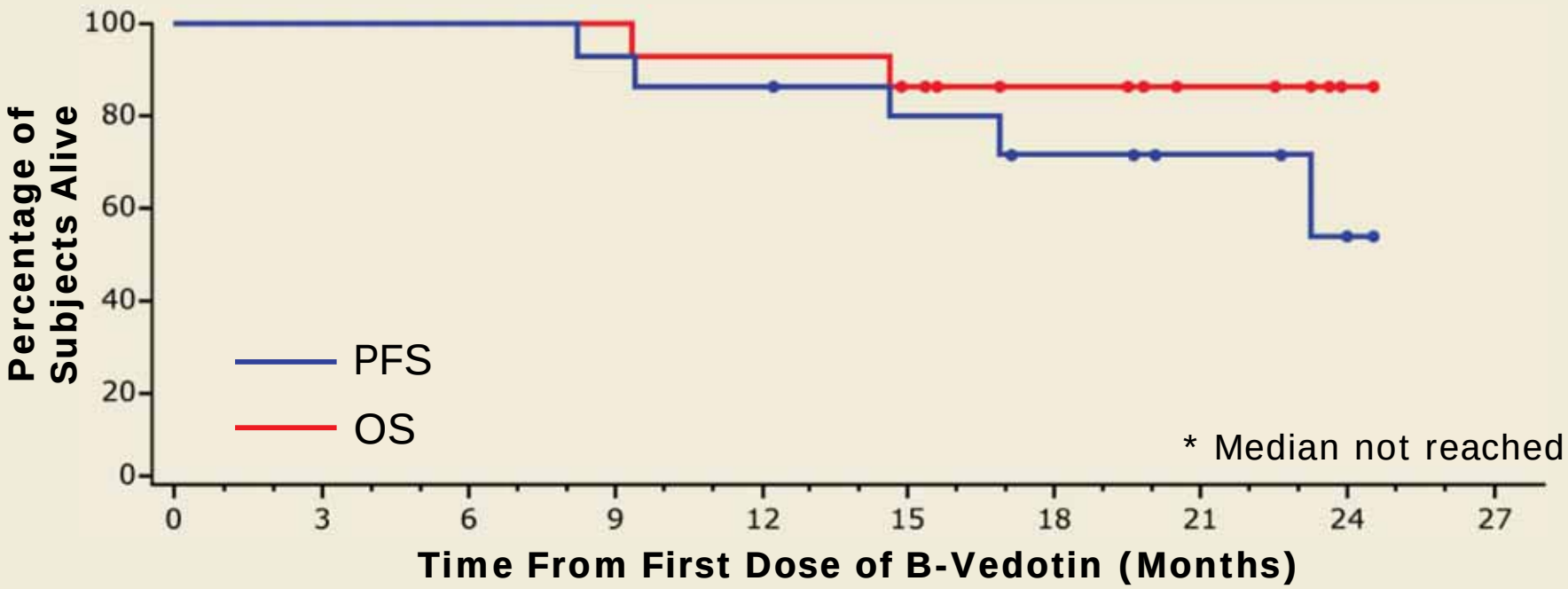
Illidge T et al. *Proc ASH* 2011;Abstract 3091.

Clinical Responses of Patients Receiving B-Vedotin and Allo-SCT

Response, n (%)	HL n = 7	sALCL n = 8	Total n = 15
Objective responses	7 (100)	8 (100)	15 (100)
Complete remission	5 (71)	7 (88)	12 (80)
Partial remission	2 (29)	1 (12)	3 (20)

Illidge T et al. *Proc ASH* 2011;Abstract 3091.

Progression-Free and Overall Survival (Median Follow-Up 19.6 Months)

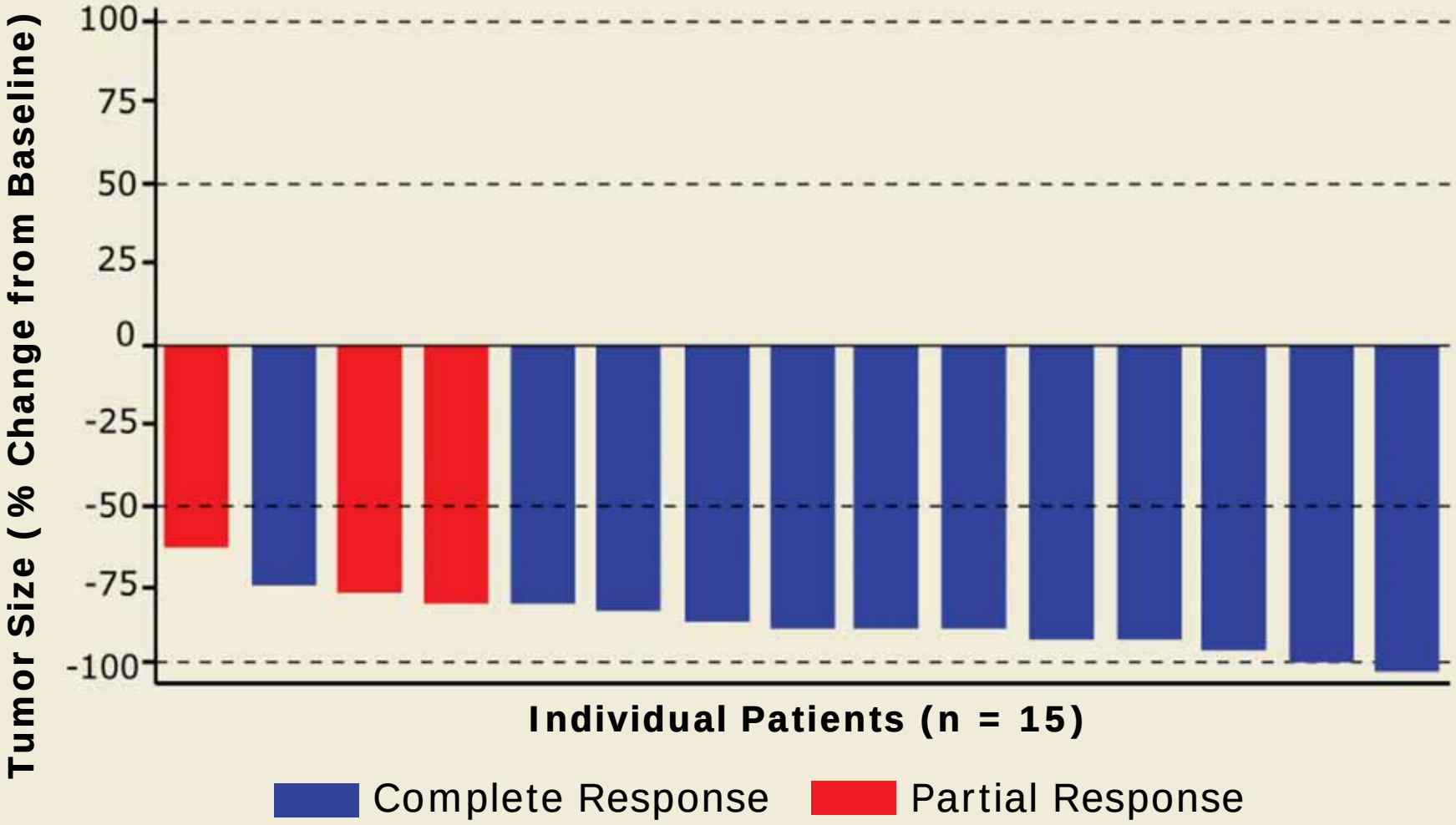


* Calculated from first dose of B-vedotin

- Five patients (1 with HL, 4 with sALCL) have progressed or died post allo-SCT.
  - Of the 2 deaths (both patients with sALCL who had a CR with B-vedotin), 1 was disease-related and the other due to transplant-related complications.

With permission from Illidge T et al. *Proc ASH* 2011;Abstract 3091.

Maximum Tumor Reduction with B-Vedotin Prior to Allo-SCT



With permission from Illidge T et al. *Proc ASH* 2011;Abstract 3091.

Adverse Events in ≥25% Patients (N = 15)

Adverse event	All grades	Grade 3
Peripheral sensory neuropathy	53%	13%
Pyrexia	53%	—
Diarrhea	47%	7%
Neutropenia	33%	7%
Nausea	33%	—
Chills	27%	—
Dyspnea	27%	7%

Other Grade 3 or 4 events in >2 patients: Anemia (20%) and thrombocytopenia (20%)

Illidge T et al. *Proc ASH* 2011;Abstract 3091.

Author Conclusions

- Treatment with B-vedotin may be an option for reducing tumor burden to facilitate a consolidative allo-SCT in patients with relapsed or refractory HL or sALCL.
- Despite adverse risk factors, 10 of 15 patients (67%) in this case series remain in remission following treatment with B-vedotin and subsequent allo-SCT.
- After a median duration of follow-up of 19.6 months, the median PFS and OS for patients who received an allo-SCT after B-vedotin treatment has not yet been reached.

Illidge T et al. *Proc ASH* 2011;Abstract 3091.

Investigator Commentary: Allogeneic Transplant Following B-Vedotin in Relapsed or Refractory CD30+ Lymphomas

In this Phase II trial that I am part of, patients with HL and sALCL who achieved a remission were allowed to be taken off study and taken to transplant. Two out of 3 patients with HL that I have treated have been cured. One patient with sALCL achieved a remission but died because of complications from the transplant. Hence, decisions must be made cautiously.

On the flip side, I treated a 62-year-old patient for whom an autologous transplant failed. She was not likely to receive an allogeneic transplant, so I started B-vedotin for her as part of the open-label study. I will keep her on B-vedotin until she has side effects. Another presentation at ASH showed no added toxicity in patients on extended treatment with B-vedotin. You can envision having a patient who responds to B-vedotin and will not be transplant eligible or does not want a transplant for whom you likely will recommend a treatment strategy by which you will administer this drug indefinitely while adjusting the dose.

Interview with Craig Moskowitz, MD, January 11, 2012

Prolonged Treatment with Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Hodgkin Lymphoma (HL) or Systemic Anaplastic Large Cell Lymphoma (sALCL)

Forero-Torres A et al.

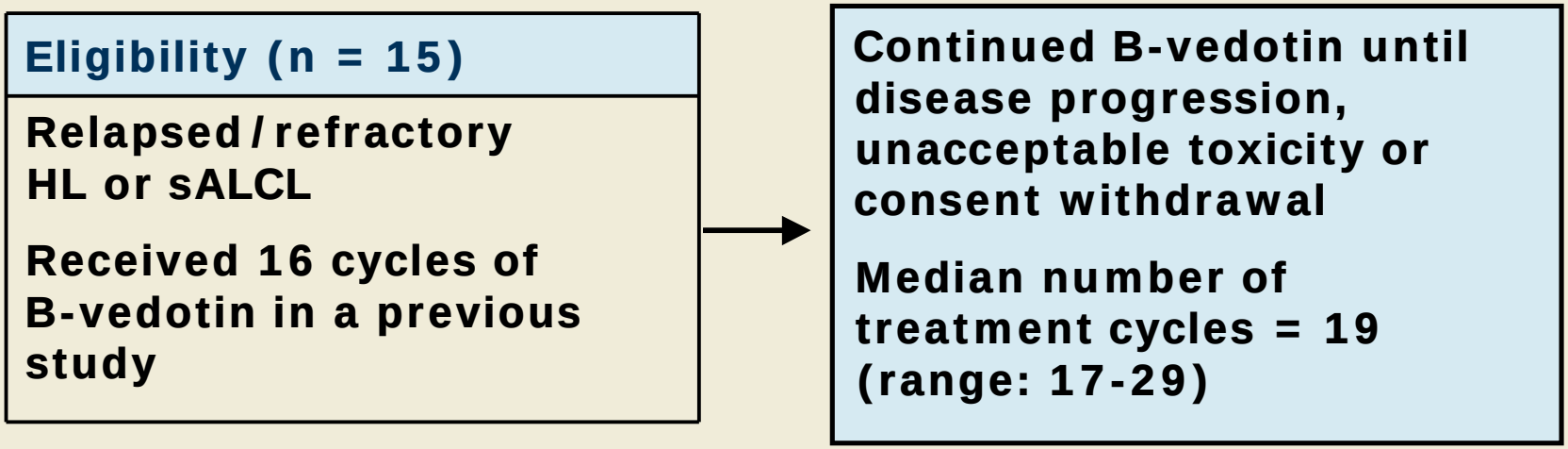
Proc ASH 2011;Abstract 3711.

Background

- Brentuximab vedotin (B-vedotin), an anti-CD30 antibody drug conjugate, induced a high rate of remission in 2 recent trials of patients with relapsed/refractory CD30+ lymphomas.
  - Patients with HL: Complete remission (CR) rate = 34%, median duration of response in patients with CR = 20.5 mo (*Proc ASCO* 2011;Abstract 8031)
  - Patients with sALCL: CR rate = 57%, median duration of response in patients with CR = 13.2 mo (*Proc ASCO* 2011;Abstract 8032)
- In both of these trials, a maximum of 16 cycles of B-vedotin was permitted (a median of 10 cycles for HL and 7 cycles for sALCL).
- **Current Analysis Objective**: To present a retrospective analysis of a subset of patients who received prolonged treatment (>16 cycles) with B-vedotin in a treatment extension study.

Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

Retrospective Analysis



Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

Baseline Characteristics (Abstract Only)

Characteristic	n = 15
Relapsed/refractory HL	10
Relapsed/refractory sALCL	5
Median age	35 years
Median number of prior therapies	3 (range 1-14)
Failed previous autologous stem cell transplant (SCT)	9*

* Two of these patients also failed allogeneic SCT

Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

Best Clinical Responses for Extended B-Vedotin Therapy (Abstract Only)

Response	(n = 15)
CR*	73.3%
Partial remission (PR)	13.3%
Stable disease	13.3%

- Median time from first dose to achievement of CR was 12 weeks (range: 5.4 to 48.9).
- Median duration of objective response has not been reached (range: 6.5+ to 21.8+ months).
- Fourteen patients were alive and free of documented disease progression at time of analysis.
- Median progression-free survival had not been reached (range: 11.8+ to 23.0+ months).

* Includes all patients with sALCL (n = 5)

Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

Adverse Events (Abstract Only)

Adverse events (in ≥30% of patients)	All grades (n = 15)
Peripheral sensory neuropathy (PSN)*	73%
Fatigue	53%
Upper respiratory tract infection	53%
Cough	40%
Alopecia	33%
Diarrhea	33%
Neutropenia†	33%
Pyrexia	33%

* Resolved or improved in 7/13 patients with a median time to resolution or improvement of 3.1 weeks (range 0.1-8); no Grade 3 or 4 PSN events observed

† Only adverse event that occurred for the first time after cycle 16 in >1 patient (n = 2)

Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

Author Conclusions

- Patients with relapsed/refractory HL or sALCL exhibited favorable responses to extended treatment with B-vedotin.
- Duration of response (11 CRs and 2 PRs) ranged from 6.5+ to 21.8+ months, with 13 patients still receiving treatment.
- The safety profile of B-vedotin did not change significantly with treatment beyond 16 cycles, with most adverse events being mild.

Forero-Torres A et al. *Proc ASH* 2011;Abstract 3711.

Investigator Commentary: Prolonged Treatment with Brentuximab Vedotin in Relapsed/Refractory HL or sALCL

This is a retrospective analysis of a subset of patients with HL or sALCL who were treated with B-vedotin until disease progression or unacceptable toxicity. Interestingly, no additional toxicity was observed in patients receiving extended maintenance with B-vedotin. So if you had a patient who was either not eligible for a transplant or who did not want a transplant, you could administer this agent indefinitely. The fear is that the patient could experience chronic severe neuropathy with indefinite use, but that didn't happen. Most patients on the study had Grade 1 or 2 neuropathy.

In my experience with this agent, I've observed little Grade 3 and 4 neuropathy. Grade 2 neuropathy is reversible, so my strategy is to delay treatment for a week. Once it resolves to Grade 1, I reduce the dose and continue.

A Phase III study (AETHERA trial) is currently evaluating the efficacy and safety of B-vedotin in patients at high risk of residual HL following autologous stem cell transplant. I've placed about 15 patients on this study and thus far it's been difficult to discern who is receiving B-vedotin versus placebo.

Interview with Craig Moskowitz, MD, January 11, 2012

Frontline Therapy with Brentuximab Vedotin Combined with ABVD or AVD in Patients with Newly Diagnosed Advanced Stage Hodgkin Lymphoma

Younes A et al.

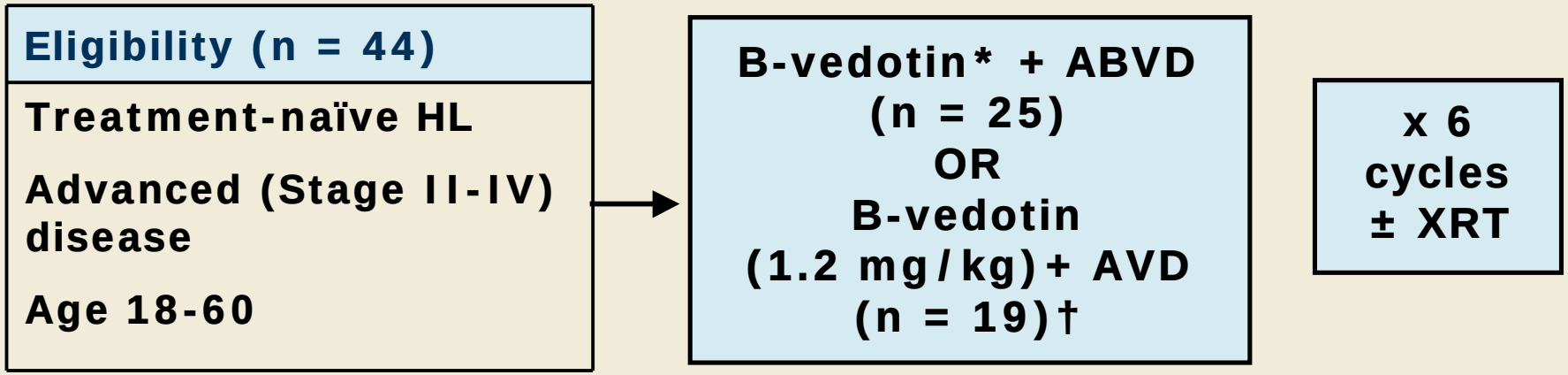
Proc ASH 2011;Abstract 955.

Background

- Hodgkin lymphoma (HL) is characterized by the presence of $CD30^+$ Hodgkin Reed-Sternberg cells.
- Brentuximab vedotin (B-vedotin), a novel anti-CD30 antibody-drug conjugate, selectively induces apoptosis of $CD30^+$ cells.
- A previous Phase II study reported a 75% overall response rate and 34% durable complete remission rate for patients with treatment-refractory HL treated with single-agent B-vedotin (*Proc ASCO* 2011;Abstract 8031).
- **Current Study Aim:** To evaluate the efficacy and safety of brentuximab vedotin in combination with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) or AVD in patients with newly diagnosed, advanced HL.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Phase I Study Design



* Dose expansion cohorts:

Cohort 1 (n = 6): 0.6 mg/kg
Cohort 2 (n = 13): 0.9 mg/kg
Cohort 3 (n = 6): 1.2 mg/kg

† Thirteen patients in this cohort are still receiving treatment.

XRT = radiation therapy

Younes A et al. *Proc ASH* 2011;Abstract 955.

Baseline Patient Characteristics

Characteristic	(n = 44)
Age (median)	32.5 years
Male	75%
ECOG performance status*	
0	45%
1	52%
IPS score ≥4	23%
Stage	
IIA bulky	5%
IIB	16%
IIIA	18%
IIIB	16%
IV	45%

* One patient in the AVD cohort is missing baseline ECOG performance status.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Response Results After Completion of Therapy with B-Vedotin + ABVD

Response	ABVD cohorts (n)
Complete response	15
Partial response	0
Stable disease	0
Progressive disease	0
Not evaluable	5

- Fifteen of the 25 patients in the ABVD cohorts have completed front-line therapy on study and have response results.
- Five patients withdrew prior to completion of 6 cycles of front-line therapy due to adverse events (peripheral sensory neuropathy, dyspnea or hyponatremia) and did not have an end-of-treatment response on study.
- End-of-treatment response results are not yet available for the AVD cohorts.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Cycle 2 FDG-PET Results

	Total N (%)
PET negative	36 (97%)
PET positive	1 (3%)

- Cycle 2 FDG-PET results were completed for 37 patients:
  - FDG-PET interpretation for cycle 2 performed by a central review per Deauville criteria with uptake above liver background considered positive
- Of these 37 patients, 36 had a negative interim PET scan:
  - B-vedotin with ABVD cohorts: 22 of 22 negative (100%)
  - B-vedotin with AVD cohorts: 14 of 15 negative (93%)
- Prognostic value of interim PET in these regimens is not yet established.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Most Common Adverse Events

Adverse event	Any grade* (n = 44)
Neutropenia	77%
Nausea	66%
Peripheral sensory neuropathy	48%
Fatigue	43%
Vomiting	43%
Constipation	36%
Alopecia	32%
Pyrexia	32%
Cough	30%
Insomnia	30%
Decreased appetite	25%

* Events occurring in ≥25% of patients

Younes A et al. *Proc ASH* 2011;Abstract 955.

Grade 3 or 4 Adverse Events

Adverse event	Grade 3 or 4* (n = 44)
Neutropenia	77%
Anemia	14%
Febrile neutropenia	11%
Pulmonary toxicity†	11%
Dyspnea	9%
Syncope	9%
Pulmonary embolism	7%
Leukopenia	5%

* Events occurring in ≥5% of patients

† Forty percent of patients in the ABVD cohort experienced pulmonary toxicity; none observed in the AVD cohort. Toxicity resembling that of bleomycin alone led to its discontinuation in 10 patients. Seven of these 10 patients continued treatment with AVD and B-vedotin.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Author Conclusions

- Preliminary results suggest that AVD combined with B-vedotin is generally well tolerated with manageable adverse events.
- Combination of bleomycin and B-vedotin is not recommended:
  - Increased incidence of pulmonary adverse events relative to historical observations of ABVD
  - No pulmonary toxicity events observed in the AVD cohort at current analysis
- No dose-limiting toxicity was observed in any cohort at the maximum planned dose of 1.2 mg/kg (data not shown).
- To date, all patients in the ABVD cohorts who completed front-line therapy on study achieved complete remission.
- A Phase III study is planned to assess front-line treatment with B-vedotin in combination with AVD as compared to ABVD alone.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Investigator Commentary: Front-Line Therapy with B-Vedotin and ABVD or AVD in Newly Diagnosed Advanced Hodgkin Lymphoma

In this study, interim PET scanning was performed after 2 cycles of therapy and all the patients whose PET results were negative have fared well. Unfortunately, the protocol had to be amended because of a 40% incidence of pulmonary toxicity of B-vedotin with ABVD. Patients were switched from the ABVD to the AVD regimen. Going forward, B-vedotin will have to be administered with AVD.

We know that B-vedotin alone doesn't cause pulmonary toxicity. Bleomycin does cause pulmonary toxicity but not a 40% rate. So the combination of B-vedotin and bleomycin was toxic. We already know that B-vedotin can't be combined with gemcitabine. We do not know how patients with Hodgkin lymphoma will fare with B-vedotin and radiation therapy. I believe those will have to be administered sequentially and will be tolerated.

We're performing a study in which we administer B-vedotin weekly at 1.2 mg with a 3 weeks on, 1 week off protocol. We administer chemotherapy sequentially with B-vedotin, not concomitantly. Patients who experience a response go on to transplant without any salvage chemotherapy.

Interview with Craig Moskowitz, MD, January 11, 2012