

### POST-ASH Issue 1, 2015

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# **CME Information**

### **LEARNING OBJECTIVES**

- Assess the efficacy and safety of brentuximab vedotin in investigational settings, such as in combination with AVD for patients with newly diagnosed HL, as consolidation after autologous stem cell transplant or as first-line salvage therapy alone or in combination with bendamustine prior to stem cell transplant.
- Appraise recent clinical trial data on the use of immune checkpoint inhibition for patients with relapsed or refractory HL.

# **CME Information (Continued)**

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### **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:

# **CME Information (Continued)**

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POST-ASH Issue 1, 2015

Last fall, I received a set of slides submitted by Memorial Sloan Kettering's "tell it like it is" lymphoma maven Dr Craig Moskowitz for a presentation we'd asked him to give at our Year in Review regional CME meeting in Orlando, and it became instantly clear that the year's top story at ASH would be Hodgkin lymphoma (HL). What immediately grabbed my attention was a reference to 2 presentations that Craig would be giving at the upcoming Annual Meeting in



Craig Moskowitz, MD

in San Francisco. The first focused on the initial results of the much anticipated Phase III randomized **AETHERA trial** evaluating the antibody-drug conjugate brentuximab vedotin (BV) as maintenance treatment after autologous stem cell transplant (ASCT) for relapsed HL, while the second was one of a pair of very much *un*anticipated parallel presentations of Phase I studies of the anti-PD-1 monoclonal antibodies nivolumab and pembrolizumab, both of which are now approved by the FDA for metastatic melanoma.

Investigators who are about to present landmark clinical trials usually have embargoes up the wazoo, and while I couldn't squeeze many details out of Craig a month or so before ASH, there was no mistaking the enthusiasm in his voice as he told us what he could. Several weeks later when the abstracts became available it was evident why this often skeptical and conservative researcher was so genuinely excited: The 19-month jump in progression-free survival on the BV arm of AETHERA and the off-the-charts waterfall plots in the anti-PD-1 papers pretty much spoke for themselves.

After spending the last couple of months chatting with investigators (Craig among them) and general oncologists about what happened in San Francisco, we chose to profile HL on this first issue of our ASH review series, and it is interesting that the cancer that in many ways became the prototype for oncologic therapy for a generation has suddenly become the focal point of 2 of the most important innovations in the field. Unlike MOPP and its descendants, however, these newer modalities often lead to striking clinical outcomes not only in efficacy but also in tolerability. Here in a nutshell is what the justifiable fuss is all about.

#### Maintenance BV after ASCT for relapsed/refractory HL

When I met with Dr Moskowitz not long after ASH he glowed about the previously mentioned AETHERA trial, noting that it was the first ever placebocontrolled, randomized study reported in HL. Over the last few years we have learned that CD30, a transmembrane glycoprotein receptor in the tumor necrosis factor receptor superfamily, is expressed on virtually all Reed-Sternberg cells in classical HL and at notably low levels in normal cells. Thus the anti-CD30 antibody-drug conjugate BV has proved to be among the most effective agents for the disease, and this study brings that into full focus. Patients on the trial were randomly assigned to receive 16 cycles of maintenance BV or placebo every 3 weeks, and one of the most striking outcomes was that the risk of relapse at 2 years was reduced from 55% to 35%. From Craig's perspective this is likely to translate into improved cure rates because relapse after 24 to 30 months is uncommon. The bottom line is pretty much an instant change in standard of care.

### BV up front in newly diagnosed HL

As many as 25% of patients with advanced-stage HL are not cured by chemotherapy regimens such as ABVD, and many others experience long-term toxicities, particularly bleomycin-induced pulmonary damage. For these reasons there has been great interest in evaluating alternative up-front regimens, and at ASH we saw more encouraging follow-up from a **Phase I trial** that initially combined BV with ABVD but then removed the bleomycin because of unacceptable pulmonary toxicity. The findings include a 3-year failure-free survival of 92% and seem compelling enough to lead any eligible patient with newly diagnosed, advanced-stage HL to consider entering the Phase III ECHELON-1 trial comparing ABVD to AVD-BV.

### More on BV

Other key ASH BV data sets included a **Phase II trial** investigating the use of up to 4 cycles of the drug prior to ASCT in 36 patients with relapsed disease. This study demonstrated a 36% complete response rate and a 33% partial response rate, and 52% of the patients were able to proceed to transplant without additional chemotherapy.

In another **Phase II study** also evaluating patients at first relapse prior to ASCT, bendamustine was added to BV, producing outstanding efficacy outcomes, with 83% complete and 13% partial responses among 48 evaluable patients. Investigators initially observed a high rate of infusion reactions with the combination, but this problem was reportedly solved with more intensive premedication regimens.

### Anti-PD-1 antibodies in HL

The biologic story here is fascinating. It has long been known that HL tumor masses are occupied mainly by inflammatory cells with only rare cancer (Reed-Sternberg) cells. Analyses have shown that classical HL frequently harbors amplification of genetic material at the 9p24.1 locus and that these genes lead to overexpression of the PD-L1 and PD-L2 ligands. The Epstein-Barr virus — signs of which are observed in about half of patients with classical HL — is also thought to cause overexpression of PD-L1 and PD-L2, and for these and perhaps other reasons, these ligands are almost uniformly expressed on the surface of Reed-Sternberg cells. This had led to the rational hypothesis that classical HL is a tumor with a genetically determined vulnerability to PD-1 blockade.

At ASH we saw confirmation of this theory as the very busy Dr Moskowitz unveiled results from the **Phase IB study (KEYNOTE-013)** of pembrolizumab. Among the 31 patients with relapsed or refractory HL, all demonstrated PD-L1 expression on tumors and 66% achieved objective responses. Craig noted that as has been observed with solid tumors, responses often occur early, usually in the first 12 weeks. Although more follow-up is needed, it is intriguing that to this point almost 70% of patients remain on treatment. The other major ASH anti-PD-1 HL paper came from a **Phase I trial** evaluating nivolumab for a variety of hematologic cancers. The HL cohort included 23 patients, and objective responses were observed in 87%. Analysis of pretreatment tumor specimens from 10 individuals demonstrated increased expression of both PD-L1 and PD-L2, and all 10 tumors had a genetic abnormality at 9p24.1. Note that the FDA recently bestowed breakthrough therapy designation on nivolumab in HL, although as in other tumors, including melanoma, investigators at this point can't really distinguish major differences in efficacy or tolerability of the 2 anti-PD-1 antibodies.

A related ASH data set from the same study included findings from patients with B-cell and T-cell lymphomas in addition to patients with multiple myeloma. The results were mixed: More than a third of patients with follicular and diffuse large B-cell lymphoma experienced objective responses, and the decision has been made to continue investigation of nivolumab in these diseases, either alone or combined with other therapies, including anti-CTLA4 antibodies such as ipilimumab. Fewer responses (17%) were observed in 23 patients with T-cell lymphoma and none were reported in 27 patients with multiple myeloma or 2 patients with primary mediastinal B-cell lymphoma, and for this reason this agent will not be further evaluated in these tumors.

As in prior trials of anti-PD-1 antibodies in other cancers, both nivolumab and pembrolizumab were generally well tolerated in patients with HL, with few Grade 3 or 4 adverse events. However, the spectrum of autoimmune complications with these and other checkpoint inhibitors is specific and quite different from the side effects seen with traditional anticancer systemic therapies, such as cytotoxic and

targeted treatment. In this regard Dr Moskowitz noted that while autoimmune toxicities like pneumonitis and thyroid or adrenal dysfunction are uncommon, oncologists must be vigilant in identifying and managing such complications. Similarly, during a recent interview for our audio series, lung cancer investigator Dr Julie Brahmer noted that she tells patients that "anything that ends in an 'itis''' might be observed.

BV has been around long enough for oncologists to have integrated it into their practices relatively effectively, but while checkpoint inhibitors have been used for a while in melanoma, it seems entirely possible that as early as this summer anti-PD-1 agents could be approved and used widely in non-small cell lung cancer. This development will transform the practice of oncology perhaps more than any other event in the history of the field as chemotherapy infusion rooms become, to a great extent, immunotherapy centers. Even more, this revolution will likely not be limited to melanoma and lung cancer because it seems plausible that many other, less common diseases, including HL but also bladder cancer and renal cell carcinoma, will soon incorporate checkpoint inhibitors into standard treatment algorithms and offer patients running out of options a novel approach that appears to be unique and very promising.

Next on this series we chat about multiple myeloma and a major new Phase III study (ASPIRE) that exemplifies how far we have come with this difficult disease.

Neil Love, MD Research To Practice Miami, Florida The AETHERA Trial: Results of a Randomized, Double-Blind, **Placebo-Controlled Phase 3 Study** of Brentuximab Vedotin in the **Treatment of Patients at Risk of Hodgkin Lymphoma Progression Following Autologous Stem Cell** Transplant

### Moskowitz CH et al. Proc ASH 2014;Abstract 673.

# Background

- Autologous stem cell transplant (ASCT) can achieve cure in approximately 50% of patients with relapsed or refractory Hodgkin lymphoma (HL).
- Over the past 20 years, no improvement has been shown in efficacy outcomes from randomized trials of ASCT regimens for aggressive lymphomas.
- Brentuximab vedotin (BV) is a CD30-directed therapy that has shown efficacy in patients with HL who experienced relapse or had refractory disease after prior ASCT (*J Clin Oncol* 2012;30:2183).
- <u>Study objective</u>: To assess whether BV consolidation could prevent disease progression after ASCT in patients at risk for relapse or disease progression.

Moskowitz CH et al. Proc ASH 2014; Abstract 673.

# Phase III AETHERA Study Design



Patients who experienced disease progression on the placebo arm could subsequently receive BV on another trial.

- **Primary endpoints:** Progression-free survival per independent review
- Secondary endpoints: Overall survival, safety, tolerability

Moskowitz CH et al. Proc ASH 2014; Abstract 673.

## **Progression-Free Survival**



\* Regularly scheduled CT scans; BV (n = 165), placebo (n = 164)

PFS	Per IRF		Per investigator	
Response	BV	Placebo	BV	Placebo
Median PFS	43 mo	24 mo	—	16 mo
2-y PFS rate	63%	51%	65%	45%
Hazard ratio	0.57 (p = 0.001)		0.5	5

With permission from Moskowitz CH et al. Proc ASH 2014; Abstract 673.

# Subgroup Analysis of PFS per IRF

Subgroups		Event/N
Intent-to-treat population		135/329
Response to salvage therapy pre-ASC	CT I	
Complete remission		41/123
Partial remission		51/113
Stable disease	<b></b>	43/93
HL status after frontline therapy		
Refractory		89/196
Relapse <12 months		40/107
Relapse ≥12 months		6/26
Age		
<45	<u>↓</u>	113/272
≥45		22/57
Gender		
Male	k—●—	84/173
Female		51/156
ECOG status		
0	¥¥	76/184
1		59/144
Systemic treatments pre-ASCT		
≤2	┝┿╼┥	68/180
>2		67/149
FDG negative pre-ASCT	<b>_</b>	34/113
FDG positive pre-ASCT	⊢H ·	56/115
B symptoms after frontline therapy		
Yes		38/87
No		97/239
Extranodal involvement pre-ASCT		
Yes	↓	44/107
No		91/222
0.0	313 0.125 0.5 2	8 32
	Favors Brentuximab Vedotin	Flavors Placebo

With permission from Moskowitz CH et al. Proc ASH 2014; Abstract 673.

## **Adverse Events\***



\* Treatment-emergent AEs regardless of relationship to Tx; incidence  $\geq$  20% on BV arm With permission from Moskowitz CH et al. *Proc ASH* 2014; Abstract 673.

# **Author Conclusions**

- Early consolidation after ASCT with BV demonstrated improved PFS per IRF in patients with HL and risk factors for relapse or disease progression (HR = 0.57, p = 0.001).
  - PFS benefit was sustained
  - Consistent benefit observed across subgroups
- Interim analysis of overall survival did not show a significant difference between treatment arms.
- Consolidation therapy was generally well tolerated.
  - Peripheral sensory neuropathy and neutropenia were common, manageable with dose reductions/delays
- BV consolidation therapy is an important therapeutic option for patients with HL who are undergoing ASCT to reduce the risk of relapse or disease progression.

Moskowitz CH et al. *Proc ASH* 2014; Abstract 673.

# Investigator Commentary: Phase III AETHERA Trial of BV in Patients at Risk of HL Progression After ASCT

This is the only placebo-controlled randomized study that has been conducted in HL. It is also the only positive trial in the HL transplant setting.

The primary endpoint of this study was PFS at 2 years. The PFS rate was 65% for patients who received BV versus 45% for those on the placebo arm by investigator analysis. In my opinion these patients who are progression free in both arms are cured because it is rare for patients to relapse 24 to 30 months after ASCT.

When the study was designed in 2009, the median survival of patients whose disease had progressed after ASCT was 26 months. In the current era with agents like BV and panobinostat, median survival is closer to 48 months. To determine if there is an overall survival benefit it will take 3 or 4 more years. I do believe that once the study has been peer reviewed there will be a window when BV therapy in this setting will become the standard.

In terms of side effects with BV, sensory and sometimes motor neuropathy was a problem. However, severe, long-term neuropathy was not common. Peripheral neuropathy was managed with dose reductions, and if there was continued toxicity, treatment was stopped.

Interview with Craig Moskowitz, MD, January 6, 2015

Brentuximab Vedotin Combined with ABVD or AVD for Patients with Newly Diagnosed Advanced Stage Hodgkin Lymphoma: Long Term Outcomes

# Background

• The ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) regimen is a common standard therapy for the front-line treatment of advanced-stage Hodgkin lymphoma (HL).

- It is curative for most patients (*JCO* 2003;21(4):607).

- Hodgkin Reed-Sternberg cells of classical HL (cHL) typically express CD30.
- In a pivotal Phase II trial, brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, induced an objective response rate (ORR) of 75% and complete response rate (CR) of 34% in patients with relapsed/refractory cHL (*JCO* 2012;30 (18):2183).
- <u>Study objective</u>: To provide long-term safety and efficacy results of a Phase I trial of BV in combination with ABVD or AVD for patients with newly diagnosed advanced-stage HL.

# **Open-Label Phase I Trial Design**



- Patients on the BV + ABVD arm received 0.6, 0.9 or 1.2 mg/kg of BV + standard doses of ABVD on days 1 and 15 of each 28-day cycle for up to 6 cycles.
- Patients on the BV + AVD arm received 1.2 mg/kg of BV with standard doses of AVD on days 1 and 15 of each 28-day cycle for up to 6 cycles.
- 80% of patients on the study had Stage III or IV disease.

# Preliminary Results from the Phase I Trial

### • CR rate

- BV + ABVD: 21/22 (95%)
- BV + AVD: 24/25 (96%)
- Adverse events were generally Grade 1 or 2.
- Pulmonary toxicity
  - An unacceptable number of patients in the BV + ABVD arm experienced pulmonary toxicity: 11/25 (44%).
  - 2 patients died of pulmonary toxicity.
  - No patient experienced pulmonary toxicity on the BV + AVD arm.
- Hence, the objective of the long-term study is to assess the durability of response and to examine the time distribution of relapses experienced by the patients.

Younes A et al. Lancet Oncol 2013;14(13):1348-56.

## **Treatment Outcomes**

- Patients who have experienced relapse: n = 5
  - BV + ABVD (n = 3): At 9, 22 and 23 months from diagnosis
  - BV + AVD (n = 2): At 7 and 22 months from diagnosis
- Follow-up for the 22 patients who received BV + ABVD and are still alive: >32 months.
- Follow-up for the 25 patients who received BV + AVD:
  >22 months.

# **Survival Outcomes**

Outcome	BV + ABVD (n = 24)*	BV + AVD (n = 26)
3-year failure-free survival (FFS)	79%	92%
3-year overall survival (OS)	92%	100%

\* One patient declined continued follow-up and so is not included.

- Number of patients alive: BV + ABVD (n = 22); AV + AVD (n = 26)
- Median follow-up: ABVD arm 45 months, AVD arm 36 months
- All 5 patients with relapsed disease have undergone autologous stem cell transplant

# **Author Conclusions**

- Brentuximab vedotin cannot safely be combined with bleomycin.
- With the BV + AVD regimen a 92% 3-year FFS, 100% 3-year OS and a 96% CR rate were observed.
  - No major unexpected toxicity was noted.
- The results strongly support the need for the currently ongoing, large, international Phase III ECHELON-1 trial comparing BV + AVD (AVD in combination with 1.2 mg/kg of brentuximab vedotin) versus standard ABVD (NCT01712490).
  - This trial may identify a new, less toxic gold standard for the treatment of advanced-stage cHL.

### Investigator Commentary: Long-Term Results from a Phase I Study of BV in Combination with ABVD or AVD in Newly Diagnosed Advanced-Stage HL

The preliminary results of this study have been published (*Lancet Oncology* 2013; 14(13):1348-56). Originally, patients received ABVD and BV, and that was found to be toxic. Two patients died of pulmonary toxicity. At that point, bleomycin was stopped and the treatment was modified to AVD and BV.

The bottom line is that if you exclude the 2 patients who had pulmonary toxicity, which was unfortunate, then the majority of patients have fared extremely well. Even if you count those 2 cases as events, the 3-year FFS is 79% (BV + ABVD) and 92% (BV + AVD). However, the follow-up is shorter in the group of patients who did not receive bleomycin. I believe that community physicians should be comfortable with participating if the randomized study is made available to them evaluating BV with AVD versus ABVD. The results are potentially practice changing. However, BV is quite expensive, and it is not clear how much better its addition to chemotherapy has to be for oncologists to recommend its use.

### Interview with Craig Moskowitz, MD, January 6, 2015

Results of a Phase II Trial of Brentuximab Vedotin as First Line Salvage Therapy in Relapsed/ Refractory HL Prior to AHCT

# Background

- Brentuximab vedotin (BV) is an antibody-drug conjugate that selectively induces the apoptosis of CD30-positive cells.
- A Phase II trial demonstrated an overall response rate (ORR) of 75%, with a complete response (CR) rate of 34% and a favorable toxicity profile in Hodgkin Lymphoma (HL) after autologous hematopoietic cell transplant (AHCT) (JCO 2012;30(18):2183).
- Standard first-line salvage regimens such as ICE have similar response rates but have more serious toxicities.
- **<u>Study objective</u>**: To determine the efficacy and safety of BV as first-line salvage therapy for patients with relapsed/refractory HL prior to AHCT.

# Phase II Trial Design

### Eligibility (n = 37)

Confirmed CD30+ HL at relapse Prior failure of induction treatment with ABVD or BEACOPP or ABVE-PC 1.8 mg/kg of BV (IV) Every 3 weeks Up to 4 cycles

- Radiographic assessments with CT or PET scans were done after 2 cycles.
- Patients who achieved CR, partial response (PR) or stable disease (SD) were allowed to receive 2 more cycles
  - Achievement of CR = stem cell mobilization  $\rightarrow$  transplantation
  - Achievement of PR, depending on the amount of resistant disease = transplantation or salvage therapy
- Primary endpoint: ORR
- Secondary endpoints included: Toxicity, stem cell mobilization rate, engraftment analysis and biomarker assessment
- Dose amended to 2.4 mg/kg after cycle 2 for patients not achieving CR because of risk of progression



Best response	n = 36*
ORR	69%
CR	13 (36%)
PR	12 (33%)
SD	10 (28%)
Progressive disease (PD)	1 (3%)

\* Evaluable patients

• No correlation between CD68 expression levels and response rates

## **Treatment Outcomes**

- 33/37 (89%) patients successfully proceeded to AHCT:
  - Patients who received additional chemotherapy: 16 (48%)
  - Patients who received BV only: 17 (52%)
- 13 patients with CR and 4/12 with PR went directly to AHCT.
- 73% were in CR at time of AHCT.
- 26% were in PR and 3% in SD at time of AHCT.

Chen RW et al. *Proc ASH* 2014; Abstract 501 (Abstract only).

# **Stem Cell Mobilization**

- Patients were primed with cyclophosphamide/G-CSF/ plerixafor
- Median CD34 cells collected: 5.97 x 10<sup>6</sup> (range 2.6-34.4 x 10<sup>6</sup>)
- Median number of days for collection: 2 (range 1-6)
- Median time to neutrophil engraftment: 11 days (range 10-12)
- Median time to platelet engraftment: 13 days (range 9-23)

Chen RW et al. *Proc ASH* 2014; Abstract 501 (Abstract only).

# **Select Adverse Events**

N = 37	Grade 1/2	Grade 3	Grade 4
Peripheral neuropathy	52%	0	0
Elevated AST	37%	3%	0
Elevated ALT	38%	0	0
Rash	35%	5%	0
Fatigue	30%	0	0
Anemia	19%	0	0
Neutropenia	11%	5%	0
Lymphopenia	3%	3%	3%
Thrombocytopenia	8%	0	0

 No patient required growth factor, PRBC or platelet transfusions as a result of BV

# **Author Conclusions**

- As first-line salvage therapy, BV is efficacious, well tolerated and does not hinder stem cell mobilization or engraftment.
- Eighty-nine (89%) of patients experienced an effective bridge to AHCT, and 52% went to AHCT without additional salvage chemotherapy.
- BV can be considered as first-line salvage for patients with R/R HL after induction therapy.
  - ORR = 69%
  - CR rate = 36%
- Patients not achieving a CR after 2 cycles are at risk for disease progression.

# Investigator Commentary: Results from a Phase II Study of BV as First-Line Salvage Therapy in R/R HL before AHCT

This study used standard BV administered for up to 4 cycles in patients before transplant. All patients who achieved a CR underwent AHCT. Patients who did not achieve a CR but were still PET-avid received nonuniform therapy. I believe it will be difficult to evaluate these patients.

The results are consistent with all the other studies of BV. Patients who achieved a PR after the first 2 cycles then went on to receive 2 more doses of BV. However, none of these patients' PRs were converted to a CR. If the patient does not achieve a CR early during the course of treatment with BV, perhaps the treating physician should apply a different treatment approach. In this study the choice was to escalate the dose of BV to 2.4 mg/kg for those not achieving a CR by cycle 2.

In summary, the overall response rate was high and the CR rate was pretty good. However, the absence of any conversion from PR to CR was disappointing.

Interview with Craig Moskowitz, MD, January 6, 2015

Brentuximab Vedotin in Combination with Bendamustine for Patients with Hodgkin Lymphoma Who Are Relapsed or Refractory After Frontline Therapy

LaCasce A et al. Proc ASH 2014;Abstract 293.
## Background

- Salvage chemotherapy with or without autologous stem cell transplant (ASCT) is the standard of care for patients with relapsed/refractory Hodgkin lymphoma (HL) after front-line therapy.
- Patients who achieve complete remission on salvage chemotherapy regimens prior to ASCT have improved outcomes, although the regimens are associated with significant toxicities.
- Brentuximab vedotin (B-vedotin)<sup>1</sup> and bendamustine<sup>2</sup> are highly active with manageable safety profiles as single agents for patients with HL who experience relapse after ASCT (<sup>1</sup> JCO 2012;30:2183-9; <sup>2</sup> JCO 2013;31:456-60).
- <u>Study objective</u>: Evaluate the safety and efficacy of B-vedotin in combination with bendamustine in patients with HL in first relapse.

LaCasce A et al. Proc ASH 2014; Abstract 293.

## Phase I/II Study Design

#### Eligibility Phase I: Safety (n = 10) Classical HL Bendamustine IV, 90 mg/m<sup>2\*</sup> d1,2 + B-vedotin IV, d1, Relapsed or refractory 1.8 mg/kg q3wk, up to 6 cycles after front-line therapy Phase II: Expansion (n = 40+)Bendamustine IV at selected dose + B-vedotin, 1.8 mg/kg

\* De-escalated if  $\geq 4/10$  patients had dose-limiting toxicity during cycle 1

- ASCT any time after cycle 2
- Post-transplant, B-vedotin monotherapy, up to 16 total doses

LaCasce A et al. Proc ASH 2014; Abstract 293.

#### **Adverse Events**

- No dose-limiting toxicity in cycle 1
- Main toxicities were infusion-related reactions (IRRs) dyspnea (15%), chills (13%) and flushing (13%); hypotension requiring vasopressor support also observed
- Delayed hypersensitivity reactions (n = 14, mostly rash) also noted
- Protocol amended to require premedication with corticosteroids and antihistamines
- Premedication decreased severity of IRRs



With permission from LaCasce A et al. Proc ASH 2014; Abstract 293.

#### Response

Best response	n = 48
Objective response rate	46 (96%)
Complete remission	40 (83%)
Partial remission	6 (13%)
Stable disease	1 (2%)

- Majority of complete remissions (34/40) achieved at Cycle 2 restage
- Stem cell mobilization and collection (n = 33)
  - Median CD34+ cell yield (cells/kg): 4.0 x 10<sup>6</sup> (range 1.7-11.8) in a median of 2 apheresis sessions (range 1-5)
  - Median time to platelet and neutrophil engraftment <2 weeks</li>

LaCasce A et al. Proc ASH 2014; Abstract 293.

#### **Progression-Free Survival (PFS)**



- Median PFS not reached
  - 4 progressions and 1 death subsequent to ASCT (8 events overall)
- Medians are not yet estimable for response duration

With permission from LaCasce A et al. Proc ASH 2014; Abstract 293.

## **Author Conclusions**

- B-vedotin in combination with bendamustine:
  - Induced a response rate (83% complete response rate, 96% overall response rate) that compares favorably to historical data.
  - Has a manageable safety profile with premedication for IRRs.
  - Has had no adverse impact on stem cell mobilization or engraftment.
- This combination represents a promising salvage regimen for patients with HL who have relapsed/refractory disease after front-line therapy.
- Response durability continues to be assessed.

LaCasce A et al. Proc ASH 2014; Abstract 293.

#### Investigator Commentary: B-Vedotin and Bendamustine for Relapsed/Refractory HL

Back in 2013 we published results of a Phase II evaluation of singleagent bendamustine in relapsed/refractory HL. This study by LaCasce and colleagues is an interesting one that investigated the combination of bendamustine and B-vedotin for relapsed/refractory disease.

The results of this study demonstrated a high overall response rate and complete remission rate with the combination of bendamustine and B-vedotin. Many patients who achieved a complete response after the first staging went to transplant. The number of stem cells collected was modest and lower than normal. I like the treatment, but I was not impressed by the PFS curves. At a short follow-up, the curves look fairly similar to the curves we observed in the AETHERA trial (ASH 2014;Abstract 673) investigating B-vedotin for patients at risk of relapse or disease progression after ASCT.

The combination of bendamustine and B-vedotin caused a high frequency of IRRs. Though unusual, IRRs are known to occur with bendamustine, and they may also occur with B-vedotin. However, after the protocol was amended to include corticosteroid premedication the side effects with the combination were much more manageable.

#### Interview with Craig Moskowitz, MD, January 6, 2015

PD-1 Blockade with the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients with Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure: Preliminary Results from a Phase 1b Study (KEYNOTE-013)

#### Moskowitz CH et al. Proc ASH 2014;Abstract 290.

### Background

- Binding of PD-1 to its ligands PD-L1 and PD-L2 on tumor cells inhibits T-cell activation, allowing tumors to evade the immune response.
- PD-1 has an inhibitory role on T cells in classical Hodgkin lymphoma (HL).
- Amplification of 9p24.1 is frequent in classical HL and results in overexpression of PD-L1 and PD-L2.
- Pembrolizumab, a humanized, monoclonal antibody against PD-1, mediates blockade of PD-L1 and PD-L2.
- It has demonstrated antitumor activity and durable responses in multiple tumor types (*Proc ASCO* 2014, Abstract LBA 9000; *Proc ASCO* 2014, Abstract 8020).
- <u>Study objective</u>: Evaluate the safety and efficacy of pembrolizumab in patients with classical HL after disease progression on brentuximab vedotin.

Moskowitz CH et al. *Proc ASH* 2014; Abstract 290.

## Ongoing Phase Ib KEYNOTE-013\* Trial Design

#### **Enrollment to date (n = 31)**

- Nodular sclerosing or mixed cellularity HL
- Relapsed or refractory to brentuximab vedotin
- Failure of ASCT or transplant ineligible

Pembrolizumab 10 mg/kg, IV, q2wk

- Patients who had a partial response or stable disease received treatment for 24 months or until progression or intolerable toxicity.
- Those who achieved a complete response or had progressive disease were allowed to discontinue treatment.
- **Primary endpoints:** Complete remission rate, safety
- Secondary endpoints: Overall response rate (ORR), progression-free survival, overall survival, duration of response
- \* HL cohort; ASCT = autologous stem cell transplant Moskowitz CH et al. *Proc ASH* 2014; Abstract 290.

## Antitumor Activity by Investigator Review

Response	Transplant ineligible or refused <sup>*</sup> (n = 9)	Transplant failure (n = 9)	Total (n = 29)
Overall response rate	44%	75%	66%
Complete remission	22%	20%	21%
Partial remission	22%	55%	45%
Stable disease	33%	15%	21%
Clinical benefit rate	78%	90%	86%
Progressive disease	22%	10%	14%

\* Eight patients were transplant ineligible, and 1 patient refused transplant. The patient who refused transplant experienced complete remission.

Moskowitz CH et al. Proc ASH 2014; Abstract 290.

#### Treatment Exposure and Response Duration



With permission from Moskowitz CH et al. *Proc ASH* 2014; Abstract 290.

### Maximum Percentage Change from Baseline in Target Lesions



With permission from Moskowitz CH et al. Proc ASH 2014; Abstract 290.

#### **Adverse Events**

Select adverse events (any grade)	(n = 29)
Hypothyroidism	10%
Pneumonitis	10%
Diarrhea	7%
Hypercholesterolemia	7%
Hematuria	7%

- Three patients experienced 4 Grade ≥3 adverse events (axillary pain, hypoxia, joint swelling, pneumonitis)
- No Grade 4 treatment-related adverse events or deaths observed

Moskowitz CH et al. *Proc ASH* 2014; Abstract 290.

## **Author Conclusions**

- Pembrolizumab demonstrated promising antitumor activity in patients with heavily pretreated HL:
  - 21% complete remission rate, 66% ORR, 86% clinical benefit rate
- Acceptable safety and tolerability profile was observed:
  - No Grade 4 treatment-related AEs, and no single Grade
    3 treatment-related AE that occurred in >1 patient
- Among enrolled patients, PD-L1 expression was observed in 100% of the evaluable samples (data not shown).
- Results support the continued development of pembrolizumab in patients with HL.

Moskowitz CH et al. Proc ASH 2014; Abstract 290.

#### **Investigator Commentary: Phase Ib Study of Pembrolizumab in Classical HL After Disease Progression on Brentuximab Vedotin**

This study evaluated the effect of pembrolizumab in a cohort of patients with heavily pretreated HL. In the KEYNOTE-013 trial, pembrolizumab is also being investigated in patients with other hematologic cancers such as myelodysplastic syndromes. In HL, amplification of 9p24.1 and Epstein-Barr virus infection contribute to overexpression of PD-L1 and PD-L2. Also, much cross talk occurs between Reed-Sternberg cells and cells in the surrounding inflammatory infiltrate, which makes HL a tumor that is amenable to immunotherapy. Pembrolizumab, like nivolumab, causes dual blockade of both PD-L1 and PD-L2.

An interesting aspect of our study is that of the 29 patients evaluable to date, 70% are still on treatment. The median time to response to pembrolizumab was 12 weeks, which is longer than that with chemotherapy. With checkpoint inhibitors, most of the patients who achieve a complete response do so at the first restaging. However, patients' conditions improve with time — for example, stable disease can be converted to partial response with time. You don't want to stop therapy too early, provided that there are no new sites of disease.

#### Interview with Craig Moskowitz, MD, January 6, 2015

#### Investigator Commentary: Phase Ib Study of Pembrolizumab in Classical HL After Brentuximab Vedotin Failure

The data with PD-1 inhibitors in hematologic cancers, particularly HL, are exciting. The overall response rate for patients with HL treated with pembrolizumab was 66%. As you can see in the waterfall plot, a majority of the patients derive a benefit from this agent.

A number of reasons explain the significant likelihood of benefit with PD-1 inhibitors in HL. The rich inflammatory infiltrate suggests that immune cells are present. The majority of the cells in the tumor microenvironment have a Th1 phenotype, suggesting that those cells are armed and ready for action. The ligands for PD-1, namely PD-L1 and L2, are highly expressed on Reed-Sternberg cells. Alterations in the 9p24.1 chromosome that result in the overexpression of PD-L1 and L2 are commonly seen in relapsed HL. Infection with the Epstein-Barr virus may also upregulate PD-L1 and PD-L2. Even though immune cells are present, they are ineffective. When the interaction between PD-1 and its ligands is blocked, these immune cells can be reactivated and can target the malignant cells.

I believe this is a very promising approach for the future.

Interview with Stephen M Ansell, MD, PhD, January 20, 2015

### PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

## Background

- Classical Hodgkin lymphoma (cHL) is characterized by Reed-Sternberg (RS) cells surrounded by an extensive but ineffective inflammatory/immune cell infiltrate.
- RS cells have developed mechanisms that exploit the programmed death-1 (PD-1) pathway and serve to evade immune detection.
- Nivolumab, a fully human IgG4 monoclonal anti-PD-1 antibody, potentiates antitumor T-cell activity and exhibits clinical efficacy in several solid tumors.
- It is hypothesized that nivolumab would inhibit tumor immune evasion in patients with relapsed or refractory (R/R) HL.
- **Study objective:** To test the hypothesis that nivolumab may augment antitumor activity in patients with R/R cHL, including those with progressive disease on brentuximab vedotin (BV).

## Ongoing Phase I Trial Design (NCT01592370)



Since August 2012, a total of 23 patients with R/R HL have been enrolled Estimated study completion date: March 2018 Database was locked for analysis on June 16, 2014

- Primary endpoint: Safety and side-effect profile of nivolumab
- Secondary endpoints include: Efficacy, assessment of PD-1 ligand loci integrity and expression of the encoded ligands

## **Baseline Characteristics (N = 23)**

Characteristic	Value
Median age (range)	35 years (20-54)
Male	52%
2 or 3 prior systemic therapies	35%
4 or 5 prior systemic therapies	30%
≥6 prior systemic therapies	35%
Prior BV	78%
Prior ASCT	78%
Prior radiation therapy	83%
Extranodal involvement	17%

#### **Best Response**

Response	All (n = 23)	Failure of both SCT and BV (n = 15)No SCT and failure of BV 		No BV (n = 5)
ORR	87%	87%	100%	80%
CR	17%	7%	0%	60%
PR	70%	80%	100%	20%
SD	13%	13%	0%	20%

ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease

#### **Survival Outcomes**

Outcome	All (n = 23)	Failure of both SCT and BV (n = 15)No SCT and failure of BV 		No BV (n = 5)
24-wk PFS	86%	85%	NC	80%
Median OS	NR	NR	R NR	
OS range at cutoff*	21-75 wk	21-75 wk	32-55 wk	30-50 wk

\* Responses are ongoing in 11 patients

PFS = progression-free survival; NC = not calculated; OS = overall survival; NR = not reached

#### Chromosome 9p24.1/PD-L1/PD-L2 Locus Integrity and Protein Expression

		PD-L1/2		Nuclear phosphorylated	
Pt	Polysomy 9p	Gain	Ampl	STAT3	
1	+	-	-	+	
2	+	-	-	+	
3	+	-	-	+	
4	+	+	-	+	
5	+	+	-	+	
6	+	+	_	+	
7	+	+	+	+	
8	+	+	+	+	
9	-	+	+	+	
10	-	-	+	+	

## Analyses of Pretreatment Tumor Specimens from 10 Patients

- There were copy-number gains in PD-L1 and PD-L2.
- Studies showed increased expression of PD-L1 and PD-L2.
- RS cells showed nuclear positivity of phosphorylated STAT3.
  - This is indicative of active JAK-STAT signaling.

#### **Select Adverse Events (AEs)**

AEs (n = 23)	Any grade	Grade 3
Rash	22%	0%
Decreased platelet count	17%	0%
Fatigue	13%	0%
Pyrexia	13%	0%
Decreased lymphocyte count	9%	4%
Increased lipase level	9%	4%
Stomatitis	9%	4%
Myelodysplastic syndromes	4%	4%
Pancreatitis	4%	4%

No Grade 4 or 5 drug-related AEs were reported.

## **Author Conclusions**

- Nivolumab exhibited substantial therapeutic activity and an acceptable safety profile in patients with R/R cHL.
- An overall response rate of 87% was achieved in patients with heavily pretreated disease.
- All studied tumors harbored genetic abnormalities at 9p24.1 leading to the overexpression of PD-1 ligands.
- cHL appears to be a tumor with genetically determined vulnerability to PD-1 blockade.
- The FDA has granted nivolumab breakthrough therapy designation in HL.
- A Phase II study is ongoing in patients with relapsed disease after ASCT (CheckMate 205).
- PD-1 blockade could become an important part of the treatment of cHL in the future.

# Investigator Commentary: Preliminary Efficacy and Safety of Nivolumab in Patients with R/R HL

This is an ongoing trial of nivolumab in patients with heavily pretreated HL that seems to be accruing well. Seventy-eight percent of patients had received prior BV or undergone ASCT. In this small study of 23 patients, the ORR is high at 87%, but the CR rate is low at 17%. The important observation is that many of the patients achieved prolonged stable disease or prolonged partial response, such that nearly half the patients are still on treatment. This is unusual in this particular patient population. Some correlative studies were conducted, evaluating chromosome 9p24.1, which is the locus for PD-L1 and PD-L2. In the 10patient study, the PD-1 ligands were overexpressed. So it makes sense that nivolumab would work in HL when the receptors are overexpressed. Notably, nivolumab is a fully human monoclonal antibody, and it causes some endocrinopathies, which can be annoying to deal with. These are easy to control, but patients on nivolumab need to be carefully monitored for thyroid and adrenal dysfunction. It is also associated with inflammation in the lungs. In my experience, this is reversible. I am somewhat concerned about prior pulmonary dysfunction in any patient receiving a checkpoint inhibitor, regardless of the disease.

Interview with Craig Moskowitz, MD, January 6, 2015

# Investigator Commentary: Preliminary Efficacy and Safety of Nivolumab in Patients with R/R HL

Results with PD-1 inhibitors in HL have been stellar, with the majority of patients who receive these agents obtaining a benefit. The response rate with nivolumab for R/R HL was about 90%, and responses are durable in many patients. I believe this a very promising approach.

The biology of HL makes it especially likely to respond to PD-1 inhibitors. Immune cells, particularly those of the Th1 phenotype, necessary to mediate the response, are present in the extensive inflammatory infiltrate. PD-L1 and L2 are highly expressed on Reed-Sternberg cells. The chromosomal alterations that contribute to overexpression of PD-L1 and PD-L2 are frequently observed in HL. Epstein-Barr virus infection also increases the expression of PD-1 ligands in this disease. Immune cells can more effectively eliminate malignant cells when the interaction between PD-1 and its ligands is inhibited.

An ongoing trial is evaluating the combination of nivolumab and ipilimumab in different hematologic cancers, including HL. It will be interesting to determine whether the combination is significantly more efficacious than nivolumab alone, given that the results with singleagent nivolumab are so promising.

Interview with Stephen M Ansell, MD, PhD, January 20, 2015

Preliminary Results of a Phase I Study of Nivolumab (BMS-936558) in Patients with Relapsed or Refractory Lymphoid Malignancies

Lesokhin AM et al. Proc ASH 2014;Abstract 291.

### Background

- PD-1 is an immune checkpoint receptor that inhibits T-cell activation upon interaction with its ligands PD-L1 or PD-L2.
- Increased PD-L1 expression has been reported in various lymphoid cancers and may allow these tumors to circumvent host antitumor immunity.
- Nivolumab, a fully human IgG4 monoclonal antibody, potentiates T-cell activity and has clinical efficacy in various solid tumors.
- Early studies in hematologic tumors show PD-1 blockade elicits encouraging responses (*J Clin Oncol* 2013;31:4199).
- <u>Study objective</u>: To assess the safety and efficacy of nivolumab in patients with relapsed or refractory lymphoid cancers.

Lesokhin AM et al. *Proc ASH* 2014; Abstract 291.

### **Phase I Study Design**



\* B-cell lymphomas (BCL) (n = 8), CML (n = 1), multiple myeloma (n = 4) <sup>+</sup> BCL (n = 23), T-cell lymphoma (TCL) (n = 23), multiple myeloma (n = 23); patients with Hodgkin lymphoma (n = 23) are not included in this report

- Primary endpoints: Safety and tolerability
- Secondary endpoints: Include best overall response, objective response, duration of response, progression-free survival

Lesokhin AM et al. Proc ASH 2014; Abstract 291.

#### **Patient Characteristics**

N = 82*	Median age	No. of patients who underwent prior ASCT
BCL $(n = 31)^+$	—	
Follicular lymphoma (FL) (n = 10)	57 years	2 (20%)
Diffuse large B-cell lymphoma		
(DLBCL) (n = 11)	67 years	2 (18%)
Other $(n = 8)$	68 years	0 (0%)
TCL (n = 23) <sup>‡</sup>		
Mycosis fungoides (MF) (n = 13)	59 years	0 (0%)
Peripheral TCL ( $n = 5$ )	73 years	2 (40%)
Other (n = 3)	73 years	0 (0%)
Multiple myeloma (n = 27)	63 years	15 (56%)

\* CML (n = 1); <sup>+</sup> Primary mediastinal BCL (n = 2); <sup>+</sup> Other noncutaneous TCL (n = 2) Lesokhin AM et al. *Proc ASH* 2014; Abstract 291.

#### **Best Overall Response**

Response	ORR	CR	PR	SD
BCL (n = 29)	28%	7%	21%	48%
FL(n = 10)	40%	10%	30%	60%
DLBCL (n = 11)	36%	9%	27%	27%
TCL (n = 23)	17%	0%	17%	43%
MF (n = 13)	15%	0%	15%	69%
Peripheral TCL (n = 5)	40%	0%	40%	0%
Multiple myeloma (n = 27)	0%	0%	0%	67%
Primary mediastinal BCL ( $n = 2$ )	0%	0%	0%	100%

ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease

Lesokhin AM et al. Proc ASH 2014; Abstract 291.

#### **Responses in Patients with BCL**



With permission from Lesokhin AM et al. *Proc ASH* 2014; Abstract 291.

#### **Responses in Patients with TCL**



With permission from Lesokhin AM et al. *Proc ASH* 2014; Abstract 291.
# **Select Adverse Events**

N = 82	Any grade	Grade 3-5
Fatigue	13%	NR
Pneumonitis	11%	2%
Pruritus	9%	NR
Rash	9%	2%
Pyrexia	7%	NR
Anemia	6%	4%
Diarrhea	6%	NR
Leukopenia	NR	2%

NR = not reported

- Safety profile similar to other nivolumab trials
- The majority of pneumonitis was Grade 1 or 2

Lesokhin AM et al. Proc ASH 2014; Abstract 291.

# **Author Conclusions**

- In patients with relapsed or refractory hematologic cancers, nivolumab has a safety profile similar to that reported in other nivolumab trials.
- Nivolumab demonstrated activity across multiple hematologic cancers, with a 40% response rate in follicular and 36% response rate in DLBCL.
- Stable disease in the absence of objective responses were seen in multiple myeloma.
- Genetic alterations in 9p24.1 were uncommon in this small NHL series (data not shown).
- Multicenter Phase II studies are ongoing in DLBCL and follicular BCL.

Lesokhin AM et al. Proc ASH 2014; Abstract 291.

### **Investigator Commentary: A Phase I Study of Nivolumab in Relapsed or Refractory Lymphoid Cancers**

This study evaluated the effect of nivolumab in patients with BCL, TCL and multiple myeloma. The results with nivolumab in patients with Hodgkin lymphoma were presented in a separate study (*N Engl J Med* 2014;372(4):311-9). The toxicity profile of nivolumab is similar to that observed in patients with Hodgkin lymphoma. There were some cases of pneumonitis but mostly no significant side effects.

However, the responses were not robust. No responses occurred in the 27 patients with multiple myeloma. Among patients with peripheral TCL, although some partial responses were reported, the duration of response was brief. The responses in patients with FL and DLBCL should be studied further. Nivolumab is being moved forward to Phase II studies and is being investigated in combination with other agents. The goal, especially in FL, is to move toward a nonchemotherapy approach.

## Interview with Craig Moskowitz, MD, January 6, 2015

### Investigator Commentary: Phase I Study of Nivolumab in Relapsed or Refractory Lymphoid Cancers

This study evaluated the effect of nivolumab in patients with a variety of lymphoid cancers except Hodgkin lymphoma. The number of patients in each cohort was small, so the data must be interpreted with caution. It was interesting that none of the patients with multiple myeloma had a significant benefit, even though that cohort was larger.

About 40% of patients with FL and DLBCL and about 20% of patients with TCL showed a response with nivolumab. This suggests efficacy across a variety of histologies. These patients may derive a significant benefit with the addition of other agents, such as ipilimumab. An ongoing trial is investigating nivolumab in combination with ipilimumab for patients with different hematologic cancers (NCT01592370).

#### Interview with Stephen M Ansell, MD, PhD, January 20, 2015