



*POST-ASH* Issue 3, 2016

# Phase I Studies of Nivolumab and Pembrolizumab in Relapsed/Refractory Classical Hodgkin Lymphoma

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## CME INFORMATION

### OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. These events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unmatched and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel agents and therapeutic options for the treatment of newly diagnosed and relapsed/refractory Hodgkin lymphoma (HL) and B- and T-cell lymphomas from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

### LEARNING OBJECTIVES

- Appraise emerging clinical research findings on the efficacy and safety of checkpoint inhibitors alone or in combination regimens for the treatment of relapsed/refractory HL.
- Compare the risks and benefits associated R-hyper-CVAD and bendamustine/rituximab as front-line treatment options for patients with mantle-cell lymphoma.
- Assess the activity of ibrutinib combined with a temozolomide-based regimen in CNS lymphoma.
- Recall recent data on the activity of brentuximab vedotin in novel treatment approaches, including as second-line therapy before transplant, first-line salvage therapy after transplant or incorporated with other drugs in new therapeutic combinations, for newly diagnosed or relapsed/refractory HL.
- Evaluate the efficacy and safety of everolimus combined with R-CHOP-21 in patients with newly diagnosed diffuse large B-cell lymphoma.

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

Michelle A Fanale, MD  
Associate Professor

Department of Lymphoma and Myeloma at  
The University of Texas MD Anderson Cancer Center  
Houston, Texas

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Contracted Research: Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology, Gilead Sciences Inc, MedImmune Inc, Merck, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Seattle Genetics, Takeda Oncology; Data and Safety Monitoring Board: Amgen Inc; Honoraria: Merck, Seattle Genetics, Spectrum Pharmaceuticals Inc, Takeda Oncology.

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A high-speed Internet connection  
A monitor set to 1280 x 1024 pixels or more  
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later  
Adobe Flash Player 10.2 plug-in or later  
Adobe Acrobat Reader  
(Optional) Sound card and speakers for audio

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Oncologists trained in the chemotherapy era before tyrosine kinase inhibitors, monoclonal antibodies and immunotherapy came on board learned early on about concepts like tumor cell kinetics and noncross-resistance and were told by the best minds in the field that exploiting dose and/or schedule variations of multiagent cytotoxic regimens could result in stunning cures. One only had to look at what had been achieved with Hodgkin lymphoma (HL) — perhaps the poster child of the time — to see what would soon be routine for most cancers. Or so we were told.



**Michelle A Fanale, MD**

Sadly, that vision never fully materialized, and although many patients do experience important clinical benefits and in some cases cure with chemotherapy, it largely remains a palliative treatment that is rapidly losing its place in the pecking order for many diseases to more biologically based approaches. This historical perspective is interesting to consider in light of the more recent research developments in HL, which have veered away from increasingly unexciting Phase III trials comparing variations of traditional chemotherapy regimens and taken a turn in new and exciting directions.

In particular, the rapid evolution of trials of the antibody-drug conjugate brentuximab vedotin (BV) beginning several years ago raised the notion that targeting individual biologic attributes of cancer cells could yield impressive therapeutic benefits. Even more recently, stunning early data first presented at the 2014 American Society of Hematology (ASH) meeting demonstrated that immune checkpoint inhibitors, specifically anti-PD-1 antibodies, represent another dramatic step forward, and for all the excitement about immunotherapy in solid tumors, the response rates in HL (60% to 90%) are the highest observed in any cancer type.

To gain some perspective on what new ASH data sets may tell us about current and future HL management, I met with Dr Michelle Fanale for her take on where things are and where they may be heading in this flagship hematologic cancer, and while we

were at it I asked about a number of other important lymphoma papers presented in Orlando. Here's a summary of what we discussed:



## 1. **Immune checkpoint inhibitors in HL**

One of the most discussed aspects of the extraordinary story that is sweeping across oncology is the biologic basis for why some patients benefit profoundly from these agents and others do not. There are a number of intriguing clues to this monumentally important issue — mainly from solid tumor research — many of which focus on expression of PD-L1 on tumor cells or tumor-infiltrating lymphocytes. Although there is a general correlation with treatment benefit, a plethora of compelling cases have been documented in which patients with tumors determined by the first generation of assays to be PD-L1-negative or low expressors derived extraordinary and unprecedented benefit from these agents.

Investigators from every tumor type working with us on recent CME programs have also repeatedly postulated that tumors with a higher “mutational load,” like melanoma (sun damage) and lung cancer (smoking), are more susceptible to immune checkpoint manipulation, and in non-small cell lung cancer the fascinating observation has been made that smokers are more likely to respond than nonsmokers. Viral carcinogenesis seems to be another important factor that may relate to immune checkpoint sensitivity and, for example, was thought to explain the benefits observed in human papillomavirus-associated head and neck cancer. But all of these theories have yet to be substantiated, and investigators continue to scratch their heads as they doggedly pursue the holy grail of a validated predictor of response.

Interestingly, the answer may be somewhat more apparent in HL, and while the responsiveness of the disease to checkpoint antibodies may be partially related to its connection with the Epstein-Barr virus, the classic histopathologic appearance of isolated Reed-Sternberg cells surrounded by an extensive but ineffective immune infiltrate suggests an immunologic basis to the disease. What's more, recent research has identified that Reed-Sternberg cells often exhibit amplification of 9p24.1, which is a recurrent genetic abnormality that, along with other less frequent rearrangements, leads to overexpression of the PD-L1 and PD-L2 ligands on the cell surface. It is this biology that led to the enthusiasm to evaluate checkpoint antibodies in HL.

In December at ASH we saw more follow-up from 2 HL studies in relapsed/refractory (RR) disease evaluating the anti-PD-1 antibodies nivolumab and pembrolizumab that made headlines at the previous annual meeting. Now with a mean follow-up of almost 2 years, the nivolumab study has not yet reached a median progression-free survival with a 1-year overall survival of 91%, while in the pembrolizumab trial 71% of patients with RR HL post-BV and/or autologous stem cell transplant had a response lasting for 24 weeks or more. An additional translational data set from the latter study revealed that about 90% of tumors were positive for PD-L1 and PD-L2 and treatment was associated with an expansion of circulating T-cell and NK-cell populations.

Dr Fanale, who has treated many patients with HL on immune checkpoint inhibitor trials at MD Anderson, notes that while the complete response rate (14% to 22% with pembrolizumab) with these agents is modest and probably lower than, for example, with BV, even patients who experience a partial response may experience prolonged durations of clinical benefit.

In spite of these very impressive data, neither agent is currently FDA approved in HL, but many clinicians in practice are hoping that this will soon change. Until then all should be on the lookout for ongoing and proposed trials that will examine this promising strategy in what seems to be every conceivable clinical scenario and in combination with a plethora of partners, perhaps most intriguingly BV.



## 2. [BV combined with other agents in HL](#)

Not surprisingly, a number of relevant ASH reports also assessed BV, mainly in combination with other agents. Notably, data from the Phase I ECOG/ACRIN-E4412 study evaluated the drug combined with the anti-CTLA-4 antibody ipilimumab in 23 patients with RR HL. Although the efficacy data were encouraging, with an overall response rate (ORR) of 72% and a complete response rate of 50% among 18 evaluable patients, and the regimen proved safe, all eyes are currently on the expansion cohort of the E4412 study looking at BV in combination with nivolumab and in combination with both nivolumab and ipilimumab.

Another interesting paper focused on the much discussed subset of elderly patients with HL, some of whom are not candidates for aggressive induction chemotherapy. A prior study of up-front BV in patients age 60 or older demonstrated encouraging response rates but unfortunately with disappointing durations. This year we saw data on the combination of BV with dacarbazine (DTIC) or bendamustine in the same older population. While these regimens were effective with an ORR of 100% in both cases, BV/DTIC was well tolerated whereas BV/bendamustine was not. After seeing these data Dr Fanale, who had previously participated in trials of BV up front for elderly patients and those with comorbidities, is inclined to consider the BV/DTIC combination in her next nontrial-eligible patient.



## 3. [Is consolidative radiation therapy necessary for patients with PET negativity after ABVD in advanced-stage classical HL?](#)

In short the answer is “No!” because this important retrospective study of 316 patients demonstrated a high rate of 5-year freedom from treatment failure (89% overall) even in patients with bulky disease (greater than 10 cm), and for this reason Dr Fanale generally avoids the use of consolidation radiation therapy in these cases.



## 4. [Another antibody-drug conjugate](#)

Memorial’s Dr Craig Moskowitz has led a number of key studies evaluating BV in HL, including the groundbreaking AETHERA trial that paved the way to the approval of the



drug as post-transplant consolidation therapy. At ASH he was at the podium again, this time unveiling work on a new agent — denintuzumab mafodotin (DM) — in patients not with HL but rather RR B-lineage non-Hodgkin lymphoma, mostly diffuse large B-cell lymphoma (DLBCL).

In discussing this fascinating data set Dr Fanale related that while BV targets CD30, DM focuses on CD19, which is expressed on the cell surface of B-cell lymphomas. The study recorded an impressive response rate of 60% among patients with relapsed disease. Generally well tolerated, DM did produce an interesting side effect that has been seen with other antibody-drug conjugates, specifically a keratopathy that can cause blurred vision. Dr Fanale and others are eager to see the results of an ongoing randomized Phase II trial comparing R-ICE alone or with DM as second-line therapy before autologous transplant and other continuing research on this agent in patients with RR disease.



5. **Intergroup mantle-cell lymphoma (MCL) study of pretransplant R-hyper-CVAD (RH) versus bendamustine/rituximab (BR)**

This important randomized Phase II study was unfortunately closed early because of inadequate stem cell collection in the RH group, but several lessons were learned and on display at ASH. RH, which has been used extensively and championed at MD Anderson, yielded predictably high response rates of 94% as well as significant toxicity. However, many were surprised that in the other trial arm BR resulted in a somewhat comparable response rate of 83%, including conversion to minimal residual disease negativity in 8 of 9 patients, who remain in remission with more than 2 years of follow-up.

Partly because of these data, Dr Fanale believes that moving forward BR is a rational base regimen for trials with both older and younger patients with MCL. She points to the current major Phase II ECOG-E1411 trial that adds bortezomib to BR induction and lenalidomide to rituximab maintenance for older patients with previously untreated MCL and other studies evaluating ibrutinib as examples of this new model.



6. **Dose-adjusted TEDDI-R (temozolomide/etoposide/pegylated liposomal doxorubicin/dexamethasone/ibrutinib/rituximab) and ibrutinib in patients with untreated or RR primary CNS lymphoma (PCNSL)**

For the past few years our CME group has made the pilgrimage to the Society for Neuro-Oncology (SNO) Annual Meeting to host CME symposia, and in preparing for these events we have always had to look hard to find exciting or encouraging topics to discuss, not only in the management of glioblastoma multiforme but also in CNS lymphomas. At ASH an intriguing report by Dr Wyndham Wilson and his NCI colleagues raised the hope that this situation may change in the future, at least for PCNSL, which is thought to be a rare variant of the activated B-cell (ABC) subtype of DLBCL.

The idea of evaluating ibrutinib in PCNSL emanates from research suggesting a benefit from BTK inhibition with chemotherapy in ABC DLBCL and the observation that this drug and its active metabolite quickly achieve meaningful cerebrospinal fluid concentrations. This study of 14 patients confirmed those pharmacologic findings, but what Dr Fanale and others believe may be the most notable information gleaned from this fascinating trial was that during the initial 2-week window when patients received ibrutinib alone before starting chemotherapy, 10 of 11 experienced a partial response, suggesting significant activity with this agent in this subtype of the disease. Accrual continues for this important effort that is likely to be much discussed this year at the SNO meeting.

Next on this brief hem-onc review, Dr Richard Stone comments on his ASH plenary presentation of the FLT3 inhibitor midostaurin and other new data sets in AML, MDS, CML, ALL and more.

Neil Love, MD

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Miami, Florida

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# Phase I Studies of Nivolumab and Pembrolizumab in Relapsed/Refractory Classical Hodgkin Lymphoma

## Presentations discussed in this issue

Ansell S et al. **Nivolumab in patients (pts) with relapsed or refractory classical Hodgkin lymphoma (R/R cHL): Clinical outcomes from extended follow-up of a phase 1 study (CA209-039).** *Proc ASH 2015*; **Abstract 583.**

Armand P et al. **PD-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: Safety, efficacy, and biomarker assessment.** *Proc ASH 2015*; **Abstract 584.**

Slides from presentations at ASH 2015 and transcribed comments from a recent interview with Michelle A Fanale, MD (2/18/16)

**Nivolumab in Patients (Pts) with Relapsed or Refractory Classical Hodgkin Lymphoma (R/R cHL): Clinical Outcomes from Extended Follow-up of a Phase 1 Study (CA209-039)<sup>1</sup>**

**PD-1 Blockade with Pembrolizumab in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Safety, Efficacy, and Biomarker Assessment<sup>2</sup>**

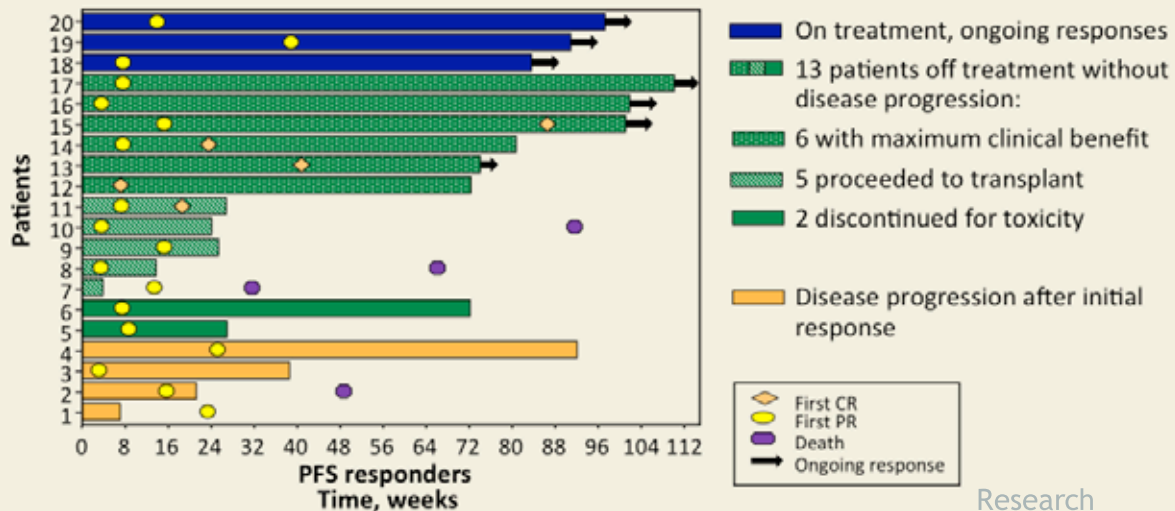
<sup>1</sup> **Ansell S et al.**  
*Proc ASH 2015*; Abstract 583.

<sup>2</sup> **Armand P et al.**  
*Proc ASH 2015*; Abstract 584.

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## CA209-039 Trial: Extended Follow-Up of Nivolumab in Classical Hodgkin Lymphoma (cHL)

- Phase I study of nivolumab 3 mg/kg at weeks 1 and 4, then every 2 weeks until confirmed complete response (CR) or up to 2 years if partial response (PR) or stable disease
- N = 23 patients with relapsed/refractory (R/R) cHL



Ansell S et al. *Proc ASH 2015*;Abstract 583.

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## CA209-039: Conclusions

- With longer follow-up, treatment of cHL with nivolumab demonstrated
  - Consistent and manageable adverse events profile
  - Durable CRs and PRs
  - In the 1 patient who received treatment after disease progression, a second response was achieved
- Long-term therapy (up to 2 y) appears feasible and is associated with durable responses and encouraging progression-free survival (PFS) and overall survival (OS):
  - Median follow-up 101 weeks; median PFS not reached
  - 1-year OS 91%; 1.5-year OS 83%
- These data support further investigation of nivolumab for cHL in a larger, ongoing Phase II study, CheckMate 205.

Ansell S et al. *Proc ASH 2015*;Abstract 583.

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## KEYNOTE-013 Trial: Pembrolizumab in cHL

- Phase Ib study of pembrolizumab 10 mg/kg every 2 weeks for up to 2 years
- N = 31 patients with cHL relapsed after or refractory to brentuximab vedotin (BV); relapsed after, ineligible for or refused autologous stem cell transplant (ASCT)
- **Primary endpoints:** Complete remission rate and safety

	BV failure		
	ASCT failure N = 22	ASCT ineligible or refused N = 9	Total N = 31
Overall response rate (ORR)	16 (73%)	4 (44%)	20 (65%)
Complete remission	3 (14%)	2 (22%)	5 (16%)
Partial remission	13 (59%)	2 (22%)	15 (48%)
Stable disease	4 (18%)	3 (33%)	7 (23%)
Progressive disease	2 (9%)	2 (22%)	4 (13%)

Armand P et al. *Proc ASH* 2015;Abstract 584.

## KEYNOTE-013: Conclusions

- Pembrolizumab has an acceptable safety profile in cHL.
- Pembrolizumab demonstrates high antitumor activity with durable responses in patients with heavily pretreated disease and BV failure:
  - 71% of patients have a duration of response  $\geq 24$  weeks.
- Exploratory analyses suggest that pembrolizumab induces increases in T- and natural killer (NK)-cell populations and upregulation of T-cell/IFN- $\gamma$  signaling pathways.
- High prevalence of PD-L1/L2 positivity in HL supports the notion of genetic vulnerability to PD-1 blockade.
- Data support further development of pembrolizumab in cHL.

Armand P et al. *Proc ASH* 2015;Abstract 584.

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### **Investigator Commentary: Phase I Studies of Nivolumab and Pembrolizumab in R/R cHL**

Dr Ansell presented updated data from the Phase I nivolumab trial previously published in 2015 in *The New England Journal of Medicine*. Enrolled patients with R/R cHL received treatment initially on weeks 1 and 4 and then every 2 weeks for up to 2 years. The study, with 23 patients, demonstrated a high ORR at 87% with a CR rate of 22%. Time to CR ranged from 3 to 88 weeks. At a median follow-up of 101 weeks, neither the median duration of response nor the median PFS had been reached. OS was 83% at 1.5 years. In comparison to BV, although the CR rate was lower, the PRs are durable. Results from a Phase II trial that enrolled patients with cHL previously treated with an ASCT who had or had not received prior BV are anticipated at ASCO this year.

Dr Armand presented data with the other PD-1 inhibitor, pembrolizumab, evaluated in a Phase I clinical trial for R/R cHL. Results were similar to those with nivolumab. For the 31 patients receiving treatment the ORR was 65% with a CR rate of 16%. Eighty percent of the responses occurred by week 12 and the PFS at 24 weeks was 69%.

*Continued*

### **Investigator Commentary: Phase I Studies of Nivolumab and Pembrolizumab in R/R cHL**

An exploratory analysis demonstrated the high prevalence of PD-L1 and PD-L2 positivity in cHL tumor cells. Immunohistochemistry of pretreatment tumor tissue showed that 94% of patients were positive for PD-L1 expression and 90% were positive for PD-L2 expression. Also, pembrolizumab was associated with an expansion of circulating T-cell and NK-cell populations. The difference between BV and the PD-1 inhibitors is that with the PD-1 inhibitors even the partial responses are durable. The partial responses could last more than 1 year, whereas with BV the partial responses generally have a duration of about 7 to 8 months.

As someone who has cared for many patients with HL on clinical trials with nivolumab or pembrolizumab, I consider these agents to be very well tolerated. Some patients might need to receive thyroid replacement therapy because of a T4 level that drops somewhat, but that is minimal. In terms of major "itis" complications like pneumonitis or pericarditis, such toxicities are also minimal.

*Continued*

## **Investigator Commentary: Phase I Studies of Nivolumab and Pembrolizumab in R/R cHL**

A Phase II 3-arm cohort trial of pembrolizumab is under way and 2 of the 3 cohorts have completed enrollment with initial results anticipated at ASCO later this year. A similar patient population was enrolled, with the exception that 1 cohort did allow patients whose disease had relapsed after treatment with or failed to respond to BV and who had not yet undergone an ASCT.

The treatment combinations that will be tested in the future are exciting. The hope is that if you could develop a highly successful combination not only in terms of high complete remission rates but also long remission durability, the potential exists for the use of these agents in the front-line setting and for a move away from standard chemotherapy options. I don't believe that we're there yet, but I believe that as each new drug is being approved we come closer and closer to that.

***Interview with Michelle A Fanale, MD, February 18, 2016***

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