5 Minute JournalClub

POST-ASH Issue 3, 2016

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CME Information

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.

CME Information

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CME Information (Continued)

AMERICAN BOARD OF INTERNAL MEDICINE (ABIM) — MAINTENANCE OF CERTIFICATION (MOC) *continued*

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FACULTY DISCLOSURES

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

CME Information (Continued)

Michelle A Fanale, MD
Associate Professor
Department of Lymphoma and Myeloma at
The University of Texas MD Anderson Cancer Center
Houston, Texas

Consulting Agreements: Merck, Spectrum Pharmaceuticals Inc; *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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POST-ASH Issue 3, 2016

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
Research To Practice
Miami, Florida

5 Minute JournalClub

Key Papers in Hodgkin Lymphoma, Diffuse Large B-Cell Lymphoma, Mantle-Cell Lymphoma and T-Cell Lymphoma from the December 2015 American Society of Hematology (ASH) 57th Annual Meeting in Orlando, Florida

Editor: Neil Love, MD

Faculty: Michelle A Fanale, MD

Key Papers in Hodgkin Lymphoma, Diffuse Large B-Cell Lymphoma, Mantle-Cell Lymphoma and T-Cell Lymphoma from ASH 2015

Immunotherapy in HL (Abstracts 583, 584)

Brentuximab vedotin in HL (Abstracts 585, 586, 587, 519, 582)

The novel antibody-drug conjugate denintuzumab mafoditin in NHL (Abstract 182)

R-bendamustine versus R-hyper-CVAD in MCL (Abstract 518)

Consolidative radiation therapy in HL (Abstract 579)

Ibrutinib/dose-adjusted Teddi-R in CNS lymphoma (Abstract 472)

Other relevant abstracts (Abstracts 181, 813, 814, 469)

Key Papers in Hodgkin Lymphoma, Diffuse Large B-Cell Lymphoma, Mantle-Cell Lymphoma and T-Cell Lymphoma from ASH 2015

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Other relevant abstracts (Abstracts 181, 813, 814, 469)

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)[1]

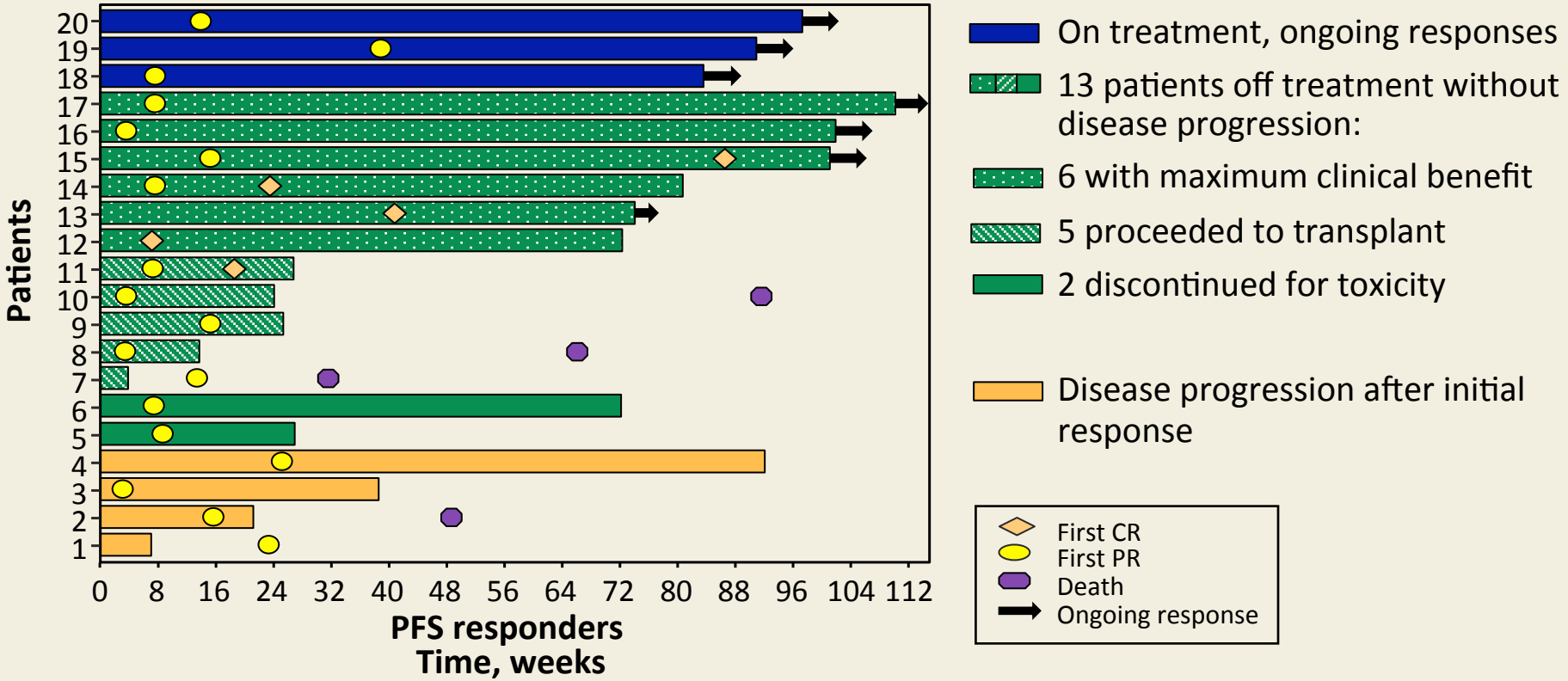
PD-1 Blockade with Pembrolizumab in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Safety, Efficacy, and Biomarker Assessment[2]

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

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

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.

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.

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 ≥24 weeks.
- Exploratory analyses suggest that pembrolizumab induces increases in T- and natural killer (NK)-cell populations and upregulation of T-cell/IFN-γ 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.

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

Key Papers in Hodgkin Lymphoma, Diffuse Large B-Cell Lymphoma, Mantle-Cell Lymphoma and T-Cell Lymphoma from ASH 2015

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- Other relevant abstracts (Abstracts 181, 813, 814, 469)

Preliminary Safety and Efficacy of the Combination of Brentuximab Vedotin and Ipilimumab in Relapsed / Refractory Hodgkin Lymphoma: A Trial of the ECOG-ACRIN Cancer Research Group (E4412)

Diefenbach CS et al.

Proc ASH 2015;Abstract 585.

E4412 Trial: Brentuximab Vedotin (BV) and Ipilimumab (Ipi) in Hodgkin Lymphoma (HL)

- Phase I study of BV (1.8 mg/kg) and Ipi (1 mg/kg or 3 mg/kg)
- N = 23 patients with relapsed/refractory HL
- **Primary endpoint:** Safety
- Most common treatment-related adverse events: diarrhea (Gr 1/2: 11, Gr 3: 1), rash (Gr 1/2: 9, Gr 3: 3) and peripheral neuropathy (Gr 1/2: 12, Gr 3: 1)

Evaluable patients	Overall response	Complete response	Partial response	Stable disease	Progressive disease
N = 18	13 (72%)	9 (50%)	4 (22%)	3 (17%)	2 (11%)

Diefenbach CS et al. *Proc ASH* 2015;Abstract 585.

E4412: Conclusions

- In the dose-escalation portion of the study, the combination of the checkpoint inhibitor Ipi and the CD30-targeted antibody-drug conjugate BV was well tolerated in patients with relapsed/refractory HL:
  - No Grade ≥3 infusion reactions after protocol amendment to include premedication
- Immune-related toxicities were primarily Grade 1 or 2.
- This therapy is highly active in patients with heavily pretreated HL, including those who previously received BV (4/23) or stem cell transplant (10/23).
  - More than half of the obtained complete responses occurred at the lower 1-mg/kg Ipi dose
- E4412 continues with cohorts evaluating BV + nivolumab and BV + Ipi + nivolumab.

Diefenbach CS et al. *Proc ASH* 2015;Abstract 585.

Investigator Commentary: Phase I E4412 Study of BV Combined with Ipi in Relapsed/Refractory HL

E4412 evaluated the combination of BV with the anti-CTLA-4 antibody Ipi in patients with relapsed/refractory classical HL. This trial was designed before the advent of the PD-1 inhibitor trials in classical HL. Patients received standard doses of BV and 2 escalating doses of Ipi. The regimen was well tolerated in a population of patients who had received a median of 4.1 lines of prior therapy, with immune-related adverse events being the most common toxicity. The overall response rate was 72% and the complete response rate 50%. The median progression-free survival was 1.02 years, and the median overall survival has not been reached. Further cohorts to be evaluated include BV with nivolumab and BV with nivolumab and Ipi.

Overall data to date show that Ipi might raise the complete response rate compared to that with BV alone but does not seem to increase the number of responders, perhaps because this is a population with heavily pretreated HL.

Continued

Investigator Commentary: Phase I E4412 Study of BV Combined with Ipi in Relapsed/Refractory HL

The next step will be to move this into a triplet combination with nivolumab. However, before that occurs, the doublet of BV and nivolumab will be evaluated. If the data are promising with the doublet combination, then the triplet combination will move forward. The field is moving more toward combinations of targeted treatments and less toward combinations with chemotherapy.

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

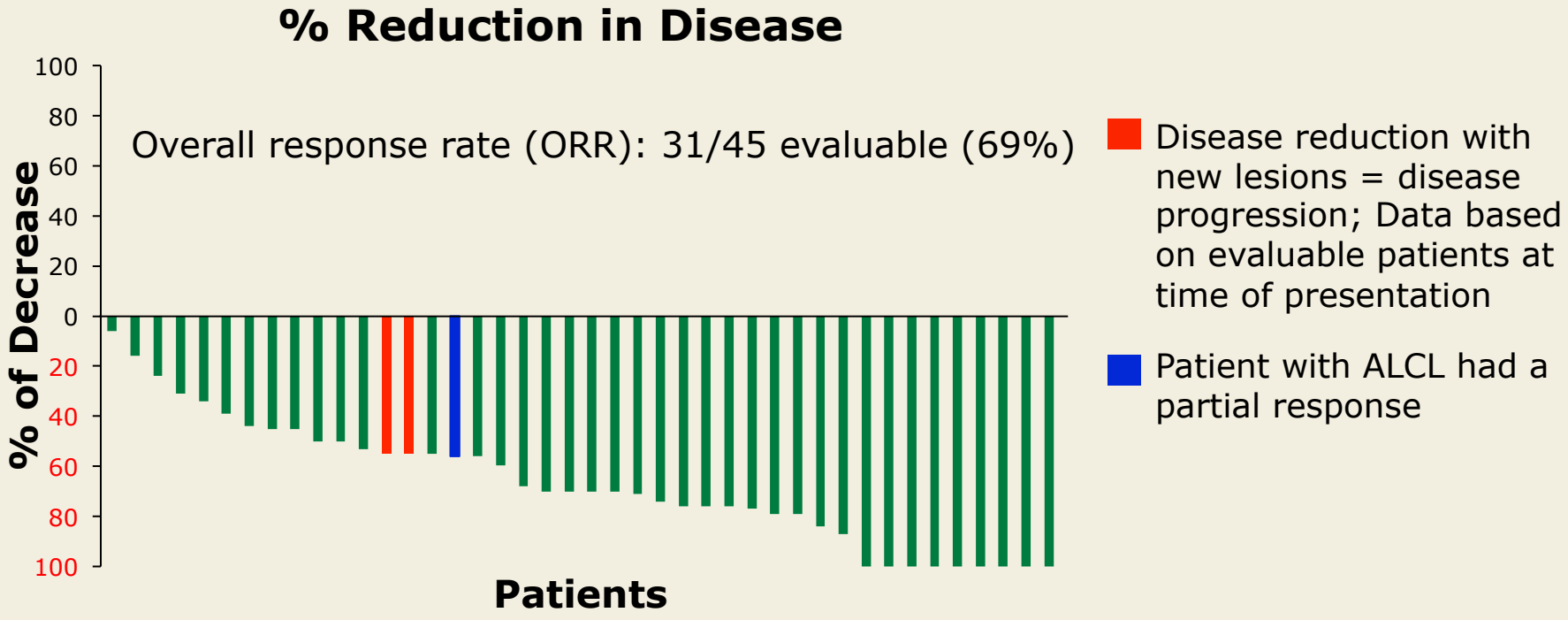
The Combination of Brentuximab Vedotin (Bv) and Bendamustine (B) Demonstrates Marked Activity in Heavily Treated Patients with Relapsed or Refractory Hodgkin Lymphoma (HL) and Anaplastic Large T-Cell Lymphoma (ALCL): Results of an International Multi Center Phase I/II Experience

Sawas A et al.

Proc ASH 2015;Abstract 586.

AAAJ5050 Trial: Brentuximab Vedotin (BV) and Bendamustine in Hodgkin Lymphoma (HL) and Anaplastic Large T-Cell Lymphoma (ALCL)

- International, multicenter Phase I/II study of BV and bendamustine
- N = 47 patients with relapsed/refractory classical HL or ALCL
- **Primary endpoints:** Activity and safety



Sawas A et al. *Proc ASH* 2015;Abstract 586.

AAAJ5050: Conclusions

- In this population of patients with heavily treated HL and ALCL, the combination of BV and bendamustine is a highly active and tolerable regimen:
  - Response rate (69% ORR, 20% complete response rate) compares favorably to historical data
  - Response rate was ≥50% for patients who received BV or bendamustine separately prior to study therapy
  - Safety profile is manageable
  - Preliminary duration of response was 4.4 months; 2 patients bridged to autologous stem cell transplant
- Phase II portion of the study is now accruing (additional 18 patients).

Sawas A et al. *Proc ASH* 2015;Abstract 586.

Investigator Commentary: Results from a Phase I/II Study of BV and Bendamustine in Relapsed/Refractory HL and ALCL

Ahmed Sawas and colleagues presented data from an international Phase I/II trial of BV/bendamustine in patients with relapsed/refractory classical HL or ALCL. These patients had heavily pretreated disease with a median of 5 prior lines of therapy. Patients received BV on day 1 and bendamustine on days 1 and 2 of a 21-day cycle for a maximum of 6 cycles.

The ORR was 69% and the complete response rate was 20%. Potentially it was because the disease was so heavily pretreated, including with BV and bendamustine, that the ORR and complete response rate were lower than one would anticipate with either agent alone. The median duration of response was short at 4.4 months but did serve to bridge 2 patients to autologous stem cell transplant.

Continued

Investigator Commentary: Results from a Phase I/II Study of BV and Bendamustine in Relapsed/Refractory HL and ALCL

I definitely believe that the combination of BV with bendamustine has a future in the second-line setting for patients with classical HL. When you look at data in the second-line setting you see ORRs of about 90% and complete response rates of about 83%. Data from the AAAJ5050 trial show that if a patient with HL experiences disease progression after achieving remission on bendamustine, if a second agent such as BV is added then one can potentially reverse the resistance to bendamustine and the patient can achieve disease remission again.

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

Brentuximab Vedotin in Combination with Dacarbazine or Bendamustine for Frontline Treatment of Hodgkin Lymphoma in Patients Aged 60 Years and Above: Interim Results of a Multi-Cohort Phase 2 Study

Yasenchak CA et al.

Proc ASH 2015;Abstract 587.

SGN35-015 Trial: Front-Line Brentuximab Vedotin (BV) and Dacarbazine (DTIC) or Bendamustine (Benda) for Hodgkin Lymphoma (HL)

- Phase II open-label study of BV alone or in combination with DTIC or Benda
- N = 60 patients ≥60 years old with HL
- **Primary endpoint:** Objective response rate (ORR)

	BV alone (n = 26)	BV + DTIC (n = 21)	BV + Benda (n = 16)
ORR (CR + PR)	24 (92%)	21 (100%)	16 (100%)
Best response			
CR	19 (73%)	14 (67%)	13 (81%)
PR	5 (19%)	7 (33%)	3 (19%)
SD	2 (8%)	0	0
PD	0	0	0

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

Yasenchak CA et al. *Proc ASH* 2015;Abstract 587.

SGN35-015: Conclusions

- BV with DTIC or Benda appears to have encouraging front-line activity in patients ≥60 years old with HL who are not candidates for standard chemotherapy.
- Preliminary data suggest superior durability of BV + DTIC (progression-free survival 66% at 12 mo) versus single-agent BV (38% at 12 mo).
  - Too early to draw conclusions for durability of BV + Benda
- BV appears well tolerated as monotherapy and with DTIC.
- Though active, BV with Benda (90 mg/m^2 or 70 mg/m^2) was not well tolerated in this elderly population with significant comorbidities:
  - Higher incidence of serious adverse events reported than on the BV + DTIC study arm
- Other BV combinations may continue to be explored in this patient population.

Yasenchak CA et al. *Proc ASH* 2015;Abstract 587.

Investigator Commentary: Interim Results from a Phase II Study of BV with DTIC or Benda as Front-Line Therapy for HL in Patients 60 Years or Older

Christopher Yasenchak and colleagues presented data from the multi-cohort Phase II trial of front-line therapy with BV in combination with DTIC or Benda for patients aged 60 years or older. The median age was 69 years in the BV/DTIC arm and 75 years in the BV/Benda arm. The ORR was 100% in both combination-therapy arms, and the CR rate was 67% with BV/DTIC and 81% with BV/Benda. BV/DTIC was well tolerated in elderly patients, but BV/Benda was not well tolerated, with a significant number of adverse events. The take-home message is that BV/DTIC combination therapy is well tolerated in this population of patients. Potentially, an elderly patient who is ineligible for chemotherapy should be able to safely tolerate front-line BV/DTIC without necessarily needing the rest of the chemotherapy components.

Continued

Investigator Commentary: Interim Results from a Phase II Study of BV with DTIC or Benda as Front-Line Therapy for Patients 60 Years or Older

Overall, however, the data support continued evaluation of non-ABVD regimens for elderly patients, including BV-based combinations. We have an ongoing clinical trial in which patients receive 2 lead-in cycles of BV before receiving chemotherapy with AVD. After completing the standard number of 6 cycles they receive additional maintenance-based therapy with BV. For chemotherapy-ineligible patients I have administered BV monotherapy. However, in light of the data from the SGN35-015 trial, I would consider administering BV/DTIC to elderly patients.

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

Post Transplant Outcome of a Multicenter Phase II Study of Brentuximab Vedotin As First Line Salvage Therapy in Relapsed/Refractory HL Prior to AHCT[1]

Evaluation of the Regimen Brentuximab Vedotin Plus ESHAP (BRESHAP) in Refractory or Relapsed Hodgkin Lymphoma Patients: Preliminary Results of a Phase I-II Trial from the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO)[2]

[1] **Chen R et al.**
Proc ASH 2015;Abstract 519.

[2] **Garcia-Sanz R et al.**
Proc ASH 2015;Abstract 582.

Post-Transplant Outcomes with Brentuximab Vedotin (BV) as First-Line Salvage Therapy Before Autologous Hematopoietic Cell Transplant (AHCT)

- Prospective, multicenter Phase II study of first-line BV salvage therapy
  - Salvage chemotherapy was allowed for patients not achieving complete response (CR) after salvage BV
- N = 37 patients with CD30+ Hodgkin lymphoma (HL) after induction failure/relapse (ABVD, BEACOPP, ABVE-PC)
- **Primary endpoint:** Overall response rate (ORR)

Endpoint	Best response to BV (n = 37)	Response to post-BV combination chemotherapy (n = 18)
ORR	25 (68%)	16 (89%)
CR	13 (35%)	10 (56%)
Partial response	12 (32%)	6 (33%)
Stable disease	10 (27%)	1 (6%)

Post-BV combination chemotherapy = ICE, DICE, IGEV or GND

Chen R et al. *Proc ASH* 2015;Abstract 519.

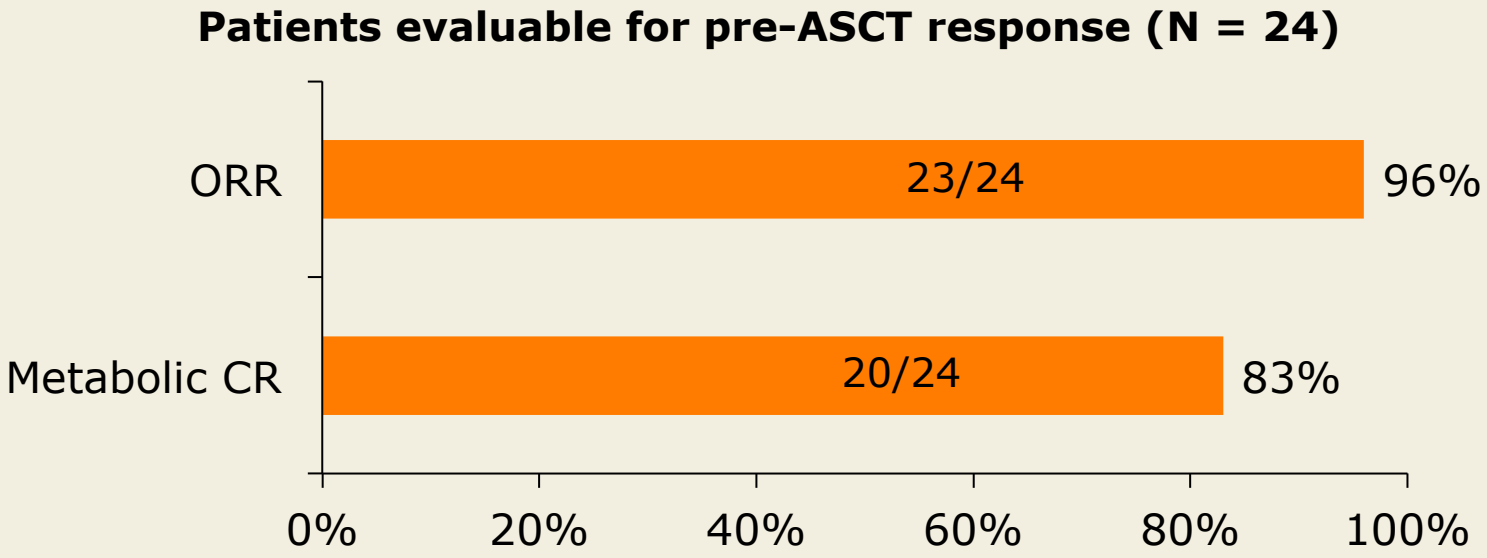
Conclusions

- BV as first-line postinduction therapy: ORR 68%, CR rate 35%
- 32/37 patients (86%) went to AHCT, 2 went to allo-HCT, 3 could not be salvaged:
  - Of the patients who underwent AHCT, 23/32 (72%) underwent transplant in CR and 15/32 (47%) received BV only.
- Stem cell mobilization, engraftment and peritransplant toxicities were not adversely affected.
- 18-month and 2-year progression-free survival/overall survival/ nonrelapse mortality are consistent with historical controls.
- Patients who underwent transplant in CR had better outcomes.
- Patients who received BV alone as salvage therapy had good outcomes after AHCT.
- Study results are consistent with Moskowitz A et al*. Lancet Oncol* 2015.
- For patients with relapsed/refractory HL after induction chemotherapy, BV can be considered as first-line salvage therapy.

Chen R et al. *Proc ASH* 2015;Abstract 519.

BRESHAP-GELTAMO.LH-2013 Trial: BV with ESHAP (BRESHAP) in Classical HL (cHL)

- Phase I/II study of BRESHAP as second-line therapy prior to autologous stem cell transplant (ASCT)
- N = 36 patients with relapsed/refractory (R/R) cHL
- **Primary endpoints:** Phase I, maximum tolerated dose (MTD); Phase II, ORR and CR



Garcia-Sanz R et al. *Proc ASH* 2015;Abstract 582.

BRESHAP-GELTAMO.LH-2013: Conclusions

- BRESHAP is a tolerable regimen as remission induction prior to transplant in patients with R/R HL:
  - No dose-limiting toxicities
  - No deaths, 1 discontinuation due to progressive disease
  - Grade 4 neutropenia (n = 2), thrombocytopenia (n = 1)
- MTD of BV when combined with ESHAP was 1.8 mg/kg every 21 days.
- No mobilization failures were reported, and stem cells were collected in all patients (N = 24).
- Pre-ASCT BRESHAP offers highly promising results (ORR 96%, metabolic CR rate 83%).

Garcia-Sanz R et al. *Proc ASH* 2015;Abstract 582.

Key Papers in Hodgkin Lymphoma, Diffuse Large B-Cell Lymphoma, Mantle-Cell Lymphoma and T-Cell Lymphoma from ASH 2015

- Immunotherapy in HL (Abstracts 583, 584)
- Brentuximab vedotin in HL (Abstracts 585, 586, 587, 519, 582)
- **The novel antibody-drug conjugate denintuzumab mafoditin in NHL (Abstract 182)**
- R-bendamustine versus R-hyper-CVAD in MCL (Abstract 518)
- Consolidative radiation therapy in HL (Abstract 579)
- Ibrutinib/dose-adjusted Teddi-R in CNS lymphoma (Abstract 472)
- Other relevant abstracts (Abstracts 181, 813, 814, 469)

A Phase 1 Study of Denintuzumab Mafodotin (SGN-CD19A) in Relapsed/Refractory B-Lineage Non-Hodgkin Lymphoma

Moskowitz CH et al.
Proc ASH 2015;Abstract 182.

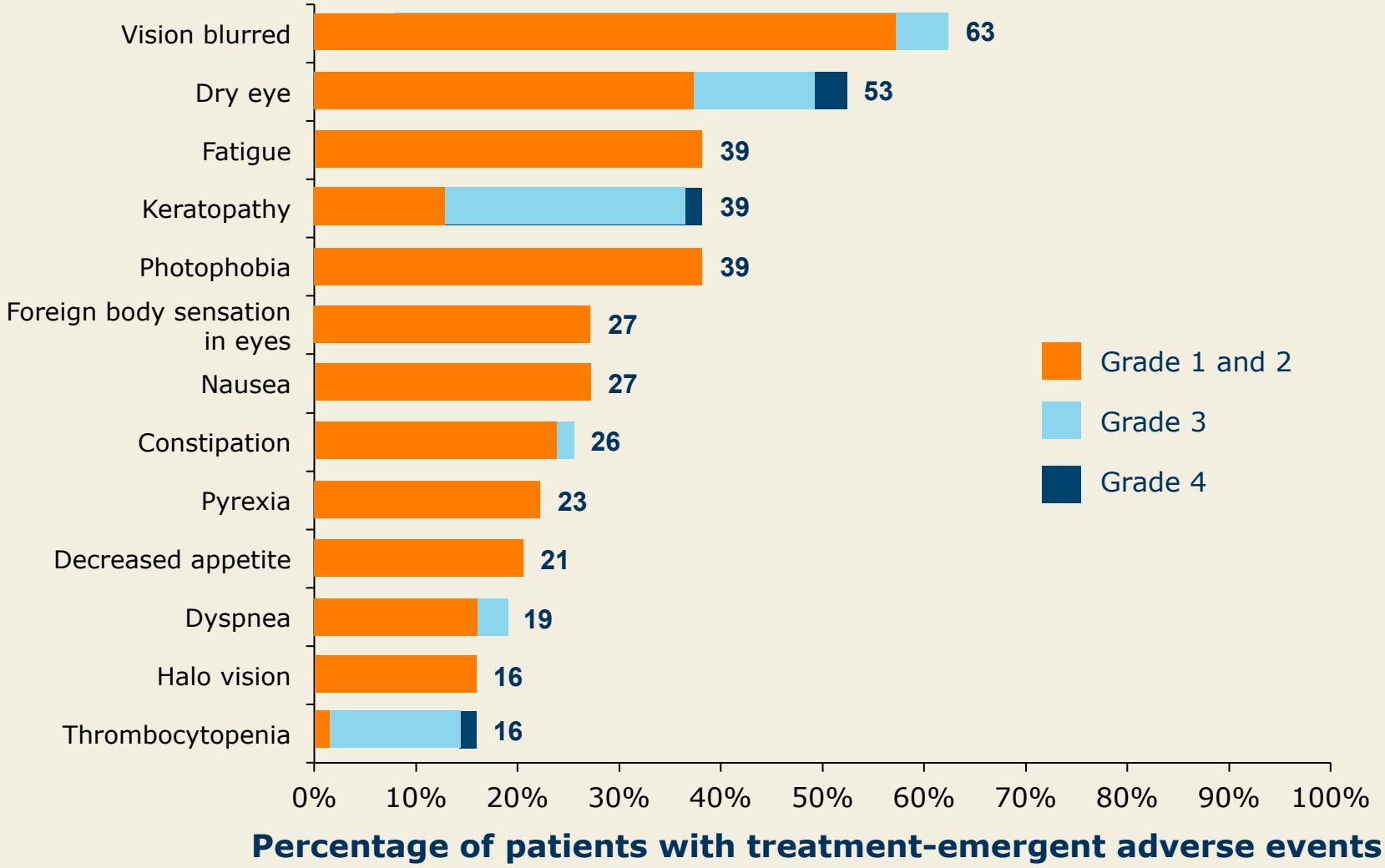
SGN19A-002 Trial: Denintuzumab Mafodotin (DM), a Novel Antibody-Drug Conjugate, in B-Lineage Non-Hodgkin Lymphoma

- Phase I, open-label, dose-escalation study of DM, an anti-CD19 monoclonal antibody conjugated to monomethyl auristatin F
- N = 62 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL, n = 54 including 16 with transformed DLBCL), mantle-cell lymphoma (n = 5) and Grade III follicular lymphoma (n = 3)
- **Primary endpoints:** Incidence of adverse events and laboratory abnormalities

Endpoint	Relapsed	Refractory
Overall response rate (ORR) (n = 25, 35)	60%	23%
Complete response (CR) (n = 25, 35)	40%	11%
Duration of response (n = 25, 35)	47.1 wk	41.1 wk
Median progression-free survival (n = 25, 37)	25.1 wk	6.1 wk
Median overall survival (n = 25, 37)	56.7 wk	29 wk

Moskowitz CH et al. *Proc ASH* 2015;Abstract 182; www.clinicaltrials.gov (NCT01786135).

SGN19A-002: Adverse Events (>15% of Patients)



Moskowitz CH et al. *Proc ASH* 2015;Abstract 182.

SGN19A-002: Conclusions

- DM demonstrated encouraging antitumor activity in patients with heavily pretreated DLBCL:
  - ORR 60%, CR 40% among patients with relapsed disease
- DM is generally well tolerated with low rates of myelosuppression and peripheral neuropathy:
  - Mild to moderate ocular symptoms secondary to keratopathy improved/resolved in the majority of patients
  - Maximum tolerated dose not exceeded at 6 mg/kg
- DM may be incorporated into novel combination regimens.
- A randomized Phase II study is evaluating R-ICE with or without DM as second-line treatment for transplant-eligible patients with DLBCL (NCT02592876).

Moskowitz CH et al. *Proc ASH* 2015;Abstract 182.

Investigator Commentary: Results of a Phase I Study of DM in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma

Craig Moskowitz and colleagues presented data with SGN-CD19A (DM) in relapsed/refractory B-cell non-Hodgkin lymphoma. DM is an antibody-drug conjugate in which an anti-CD19 monoclonal antibody is conjugated to the microtubule inhibitor monomethyl auristatin F.

Of the 62 patients who received treatment, 87% had DLBCL, 8% had mantle-cell lymphoma and 5% had Grade III follicular lymphoma. For 60% of patients the disease was refractory to their most recent therapy. The ORR was 60% with a CR rate of 40% for patients with relapsed disease and 23% with a CR rate of 11% for patients with refractory disease. The median duration of response ranged from 41.1 to 47.1 weeks, dependent on relapsed versus refractory disease status.

A unique adverse event was keratopathy, reported in 39% of patients with superficial microcystic keratopathy reported in 84%. Keratopathy was managed with steroids and improved or resolved at a median of 5 weeks.

A randomized Phase II trial of R-ICE with or without DM is under way for patients with relapsed/refractory DLBCL before autologous stem cell transplant (NCT02592876).

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

Key Papers in Hodgkin Lymphoma, Diffuse Large B-Cell Lymphoma, Mantle-Cell Lymphoma and T-Cell Lymphoma from ASH 2015

Immunotherapy in HL (Abstracts 583, 584)

Brentuximab vedotin in HL (Abstracts 585, 586, 587, 519, 582)

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R-bendamustine versus R-hyper-CVAD in MCL (Abstract 518)

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Ibrutinib/dose-adjusted Teddi-R in CNS lymphoma (Abstract 472)

Other relevant abstracts (Abstracts 181, 813, 814, 469)

Pre-Transplant R-Bendamustine Induces High Rates of Minimal Residual Disease in MCL Patients: Updated Results of S1106: US Intergroup Study of a Randomized Phase II Trial of R-HCVAD Vs. R-Bendamustine Followed By Autologous Stem Cell Transplants for Patients with Mantle Cell Lymphoma

Chen R et al.

Proc ASH 2015;Abstract 518.

S1106 Trial: R-hyper-CVAD (RH) versus Bendamustine/Rituximab (BR) Followed by Autologous Stem Cell Transplant (ASCT)

- Phase II randomized study of RH versus BR
- N = 52 evaluable out of a planned 160 patients aged 18 to 65 years with untreated mantle-cell lymphoma (MCL) eligible for ASCT
- **Primary endpoint:** 2-year progression-free survival (PFS)

Endpoint	BR (n = 35)	RH (n = 17)
Two-year PFS	81%	82%
Two-year overall survival	87%	88%
Overall response rate	83%	94%
Complete response rate	40%	35%

Chen R et al. *Proc ASH* 2015;Abstract 518.

S1106: Conclusions

- RH is not an ideal platform for future transplant trials in MCL because of stem cell mobilization failures:
  - Only 4 of 17 patients who received RH and 21 of 35 who received BR underwent ASCT.
- PFS rate at 2 years with BR was 81%, higher than the planned target of 75%.
  - Minimal residual disease (MRD) negativity rate with BR was 89% for all the paired samples tested.
  - All patients with MRD-negative status remain in remission, with some not having undergone ASCT.
- Low complete response rate with BR could be due to lack of mandatory PET.
- Premature closure of the study limited the sample size and the precision of PFS estimates and MRD assessment.
- However, this analysis suggests that BR can effect deep remissions and could be a platform for future trials in MCL.

Chen R et al. *Proc ASH* 2015;Abstract 518.

Investigator Commentary: Updated Results of the Phase II S1106 Trial of RH versus BR followed by ASCT in MCL

Rob Chen and colleagues presented data from the S1106 Intergroup Phase II trial evaluating RH versus BR followed by ASCT for patients with MCL. Data were reported on MRD status, for which negative status has been previously demonstrated to predict improved long-term outcomes, and 2-year PFS and overall survival. A total of 53 patients were accrued out of the planned 160 because the study arm alternating RH with R-MTX/Ara-C was closed early owing to stem cell collection failures.

Overall, the ORR was 94% with RH and 83% with BR and the complete response rates were generally comparable at 35% and 40%. Interestingly, the complete response rate for the RH arm was actually lower than what has been typically observed in the past with this regimen. This may be because some of the patients came off treatment earlier than planned owing to potential tolerability issues in comparison to the BR approach. So the investigators concluded that the complete response rates for both arms were about equal.

Continued

Investigator Commentary: Updated Results of the Phase II S1106 Trial of RH versus BR followed by ASCT in MCL

Also, the 2-year PFS and overall survival overlapped for both treatment arms at 81% and 87%, respectively. BR achieved a high MRD negativity rate of 89%, and all patients with negative status remain without disease relapse independent of whether they underwent ASCT.

These data support the transition of BR to the front-line setting for MCL management as a platform for therapy given its high effectiveness, including high MRD negativity rates and overall good tolerability.

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

Key Papers in Hodgkin Lymphoma, Diffuse Large B-Cell Lymphoma, Mantle-Cell Lymphoma and T-Cell Lymphoma from ASH 2015

Immunotherapy in HL (Abstracts 583, 584)

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Ibrutinib/dose-adjusted Teddi-R in CNS lymphoma (Abstract 472)

Other relevant abstracts (Abstracts 181, 813, 814, 469)

Advanced Stage Classical Hodgkin Lymphoma Patients with a Negative PET-Scan Following Treatment with ABVD Have Excellent Outcomes without the Need for Consolidative Radiotherapy Regardless of Disease Bulk at Presentation

Savage KJ et al.
Proc ASH 2015;Abstract 579.

Outcomes in Advanced-Stage Classical Hodgkin Lymphoma (cHL) with a Negative PET Scan After ABVD

- Retrospective study from British Columbia Cancer Agency Centre comparing outcomes after ABVD (doxorubicin/bleomycin/vinblastine/dacarbazine) by PET status
- N = 316 patients with advanced-stage cHL (Stage I bulky [>10 cm], Stage II with B symptoms and/or bulky disease and all Stage III/IV) treated with curative intent using ABVD who underwent a restaging PET scan at the end of treatment
- **Primary endpoint:** Freedom from treatment failure (FFTF)

	PET negative (n =261)	**PET positive (n = 49)**	***p*-value**
Five-year FFTF	89.0%	53.0%	<0.0001
	PET negative		
	Bulky (n = 112)	**Nonbulky (n = 152)**	***p*-value**
Five-year FFTF	89.0%	88.5%	0.5

Savage KJ et al. *Proc ASH* 2015;Abstract 579.

British Columbia Cancer Agency Study: Conclusions

- Patients with advanced-stage cHL, including those with bulky disease, who have a negative PET scan after ABVD chemotherapy have excellent outcomes without additional consolidative radiation therapy (RT), thus potentially avoiding long-term effects.
- RT may be useful for select responding patients with PET-positive residual uptake:
  - For those who were able to receive consolidative RT (n = 41), the 5-y FFTF was 60% and the 5-y overall survival was 94%.
  - For those with mediastinal PET-positive disease who received RT (n = 29, 72% with bulky disease at diagnosis), the 5-y FFTF was 69.5%.
- With a PET-guided approach, the need for RT has been significantly reduced.

Savage KJ et al. *Proc ASH* 2015;Abstract 579.

Investigator Commentary: Clinical Outcomes for Patients with Advanced cHL with a Negative PET Scan After ABVD

Kerry Savage and colleagues presented data from a retrospective trial conducted by the British Columbia Cancer Agency evaluating the need for consolidative RT for patients who have negative PET scans after treatment with ABVD. Patients with a PET-negative scan after completion of chemotherapy had a 5-year FFTF rate of 89%, and the rate was 53% for patients with a PET-positive scan after completion of chemotherapy. Among the patients with PET-negative scans, no difference was observed in the 5-year FFTF rate between patients who presented with bulky disease and those who presented with nonbulky disease. The 5-year overall survival rate was 94.5% for the entire study cohort, and only 2 patients out of 261 with PET-negative status after chemotherapy received consolidative RT.

Continued

Investigator Commentary: Clinical Outcomes for Patients with Advanced cHL with a Negative PET Scan After ABVD

Thus, outcomes were good for patients with advanced-stage disease and negative PET scans after chemotherapy. Also, disease bulk did not influence these outcomes. These results support an ongoing CALGB/ Alliance study designed to evaluate treatment with ABVD alone in patients with early-stage, bulky mediastinal, PET-negative cHL. Data from this study will be important in answering the question, is radiation therapy really needed in all cases for patients with bulky mediastinal disease?

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

Key Papers in Hodgkin Lymphoma, Diffuse Large B-Cell Lymphoma, Mantle-Cell Lymphoma and T-Cell Lymphoma from ASH 2015

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Ibrutinib/dose-adjusted Teddi-R in CNS lymphoma (Abstract 472)

Other relevant abstracts (Abstracts 181, 813, 814, 469)

Phase I Study of Dose-Adjusted-Teddi-R with Ibrutinib in Untreated and Relapsed/ Refractory Primary CNS Lymphoma

Dunleavy K et al.
Proc ASH 2015;Abstract 472.

Dose-Adjusted (DA) TEDDI-R and Ibrutinib for Primary CNS Lymphoma (PCNSL)

- Phase I study of DA-TEDDI-R (temozolomide/etoposide/pegylated liposomal doxorubicin/dexamethasone/ibrutinib/rituximab)
- N = 14 patients with untreated or relapsed or refractory (R/R) PCNSL
- Ibrutinib and its active metabolite achieved meaningful cerebrospinal fluid (CSF) concentrations >IC_{50} for 2 to 10 hours:
  - The higher the dose, the higher the time above IC_{50}.
- Of 11 evaluable patients, 10 achieved partial response to ibrutinib alone before cycle 1.
- Of 14 patients, 9 achieved complete response (CR) by month 3:
  - R/R PCNSL (n = 6): 3 maintained CR for >8 months and 1 for >15 months
  - Untreated (n = 3): 1 experienced relapse at 6 months

Dunleavy K et al. *Proc ASH* 2015;Abstract 472.

DA-TEDDI-R with Ibrutinib: Conclusions

- DA-TEDDI-R is a promising novel treatment strategy for patients with PCNSL:
  - It leverages molecular and therapeutic principles developed for the curative treatment of ABC DLBCL.
- Results suggest that ibrutinib may effect significant CNS penetration with meaningful therapeutic activity in PCNSL:
  - The higher the dose of ibrutinib, the longer the time above IC_{50}.
- Future analysis of ibrutinib dose escalation to augment CSF exposure is planned.

Dunleavy K et al. *Proc ASH* 2015;Abstract 472.

Investigator Commentary: DA-TEDDI-R and Ibrutinib for PCNSL

This is the first major study to be presented in a long time that adds further evidence for alternative treatment approaches beyond a high-dose methotrexate-based treatment strategy. This study evaluated the DA-TEDDI-R combination, and patients also underwent a "window" approach by which they received ibrutinib alone for approximately 14 days as a lead-in. This was a small study, and of the 14 patients who received treatment approximately half had previously received other therapies such as high-dose methotrexate and the other half were newly diagnosed. Of the 14 patients, 9 achieved complete remission by month 3. The longest follow-up was more than 15 months, and 1 patient was still in remission at that point. So this is definitely a promising potential treatment. Additionally, the study investigators were able to observe ibrutinib in the CSF in most patients, so it appears that ibrutinib can cross the blood-brain barrier.

Continued

Investigator Commentary: DA-TEDDI-R and Ibrutinib for PCNSL

If not on a clinical trial, patients would often receive a modified DeAngelis-based regimen as initial front-line therapy, by which modification they would not receive the radiation therapy component. If the disease relapsed, often these patients would receive whole brain radiation therapy, or sometimes they would circle back to the DeAngelis regimen if they experienced remission for a while. Then they might also receive temozolomide with or without rituximab. Beyond that our therapeutic options are extremely limited.

Interview with Michelle A Fanale, MD, February 23, 2016

Other Relevant Abstracts

Lenalidomide in relapsed adult T-cell leukemia-lymphoma (Abstract 181)

R-CHOP/everolimus in diffuse large B-cell lymphoma (Abstract 813)

Brentuximab vedotin/R-CHOP in diffuse large B-cell lymphoma (Abstract 814)

Ibrutinib in mantle-cell lymphoma (Abstract 469)

Multicenter Phase II Study of Lenalidomide in Patients with Relapsed Adult T-Cell Leukemia-Lymphoma

Fujiwara H et al.
Proc ASH 2015;Abstract 181.

ATLL-002 Trial: Lenalidomide in Adult T-Cell Leukemia/Lymphoma (ATL)

- Multicenter Phase II study of lenalidomide 25 mg/d continuously
- N = 26 patients with relapsed or recurrent ATL
- **Primary endpoint:** Overall response rate (ORR) by central review

ORR	CR/CRu	Stable disease	Progressive disease
11 (42%)	5 (19%)	8 (31%)	7 (27%)

Survival analyses	
Median PFS	3.8 mo
Median OS	20.3 mo

CR = complete response; CRu = unconfirmed CR; PFS = progression-free survival; OS = overall survival

Fujiwara H et al. *Proc ASH* 2015;Abstract 181.

ATLL-002: Conclusions

- In this multicenter Phase II study, single-agent lenalidomide was associated with a 42% ORR (including a 19% CR/CRu rate) for Japanese patients with relapsed/recurrent ATL.
- Median OS of 20.3 months is the longest reported for this patient population to date.
- Adverse events were primarily hematologic and consistent with those reported with lenalidomide in other studies:
  - Grade ≥3: Neutropenia (65%), leukopenia (39%), lymphopenia (39%), thrombocytopenia (23%), anemia (19%) and hypokalemia (12%)
- These results support the potential for lenalidomide as a treatment option for patients with relapsed/recurrent ATL.

Fujiwara H et al. *Proc ASH* 2015;Abstract 181.

Other Relevant Abstracts

Lenalidomide in relapsed adult T-cell leukemia-lymphoma (Abstract 181)

R-CHOP/everolimus in diffuse large B-cell lymphoma (Abstract 813)

Brentuximab vedotin/R-CHOP in diffuse large B-cell lymphoma (Abstract 814)

Ibrutinib in mantle-cell lymphoma (Abstract 469)

Everolimus Plus RCHOP-21 Is Safe and Highly Effective for New Untreated Diffuse Large B-Cell Lymphoma (DLBCL): Results of the Phase I Trial NCCTG1085 (Alliance)

Johnston PB et al.
Proc ASH 2015;Abstract 813.

NCCTG-N1085 Trial: Everolimus and R-CHOP-21 in Diffuse Large B-Cell Lymphoma (DLBCL)

- Phase I study of everolimus/R-CHOP-21
- N = 24 evaluable patients with newly diagnosed DLBCL
- **Primary endpoints:** Maximum tolerated dose and safety
  - Previously reported recommended dose of everolimus: 10 mg/d on days 1 to 14
- Overall response rate: 23/24 (96%); 23 patients attained functional complete response by PET/CT
- Median follow-up: 16.8 months
  - No deaths
  - No DLBCL relapses
- Most common Grade 3 or 4 toxicity: Hematologic, even with prophylactic pegfilgrastim (Grade 4: 71%)
  - Febrile neutropenia 5/24 (21%)
  - Grade 3 hyperglycemia (n = 1), Grade 3 hypertriglyceridemia (n = 3)

Longer follow-up and a larger trial will be necessary to confirm the benefits of this novel combination.

Johnston PB et al. *Proc ASH* 2015;Abstract 813.

Investigator Commentary: Efficacy and Safety of Everolimus and R-CHOP-21 for Patients with Newly Diagnosed DLBCL

Patrick Johnston and colleagues presented data from the Alliance-sponsored Phase I study of the mTOR inhibitor everolimus administered on days 1 to 10 or 1 to 14 in combination with R-CHOP-21. The dosing of everolimus at 10 mg on days 1 to 14 was recommended on the basis of earlier safety data. Twenty-six patients were enrolled. The most common Grade 3 or 4 adverse events were hematologic, including a 21% febrile neutropenia rate despite prophylactic pegfilgrastim. However, the complete response rate was outstanding at 96%, and results were similar in germinal center B-cell (GCB) and non-GCB DLBCL. No patient at a follow-up of 16.8 months has experienced relapse of DLBCL. A larger subsequent trial would be needed to confirm these findings.

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

Other Relevant Abstracts

Lenalidomide in relapsed adult T-cell leukemia-lymphoma (Abstract 181)

R-CHOP/everolimus in diffuse large B-cell lymphoma (Abstract 813)

Brentuximab vedotin/R-CHOP in diffuse large B-cell lymphoma (Abstract 814)

Ibrutinib in mantle-cell lymphoma (Abstract 469)

Brentuximab Vedotin with RCHOP As Frontline Therapy in Patients with High-Intermediate/High-Risk Diffuse Large B Cell Lymphoma (DLBCL): Results from an Ongoing Phase 2 Study

Yasenchak CA et al.
Proc ASH 2015;Abstract 814.

SGN35-017 Trial: Brentuximab Vedotin (BV) and R-CHOP in Diffuse Large B-Cell Lymphoma (DLBCL)

- Phase II study of front-line BV with R-CHOP
- N = 51 patients with high intermediate/high-risk (IPI score 3 to 5) or age-adjusted IPI score 2 to 3, untreated DLBCL regardless of CD30 expression
- **Primary endpoints:** Tolerability and complete response (CR) rate
- Grade ≥3 adverse events occurred in 76% of patients:
  - Neutropenia 33%
  - Febrile neutropenia 31%

	CR rate	12-mo PFS rate
PET negative	69%	Not reported
CD30-positive	19/25 (76%)	82%
CD30-negative	12/19 (63%)	56%

PFS = progression-free survival

Yasenchak CA et al. *Proc ASH* 2015;Abstract 814.

SGN35-017: Conclusions

- Interim results demonstrate that adding BV to R-CHOP results in a high rate of CR in this population of patients with IPI 3 to 5 DLBCL.
- CD30-positive disease appears to be associated with a higher CR rate and fewer early progression events than CD30-negative DLBCL.
- Subsets of patients who have a particularly poor prognosis (CD30+ ABC subtype and EBV+ DLBCL) appeared to have favorable outcomes with BV + R-CHOP.
- Higher frequencies of infiltrating CD3-positive cells were observed in the CR group, suggesting possible immunologic correlates of response.
  - However, CD30 expression appears to have greater prognostic significance.
- These results merit further testing in a randomized trial.

Yasenchak CA et al. *Proc ASH* 2015;Abstract 814.

Other Relevant Abstracts

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R-CHOP/everolimus in diffuse large B-cell lymphoma (Abstract 813)

Brentuximab vedotin/R-CHOP in diffuse large B-cell lymphoma (Abstract 814)

Ibrutinib in mantle-cell lymphoma (Abstract 469)

Ibrutinib Vs Temsirolimus: Results from a Phase 3, International, Randomized, Open-Label, Multicenter Study in Patients with Previously Treated Mantle Cell Lymphoma (MCL)

Rule S et al.
Proc ASH 2015;Abstract 469.

RAY (MCL3001) Trial: Ibrutinib versus Temsirolimus in Mantle-Cell Lymphoma (MCL)

- Phase III open-label study of ibrutinib versus temsirolimus
- N = 280 patients with relapsed or refractory MCL who received ≥1 prior rituximab-containing therapy
- **Primary endpoint:** Progression-free survival (PFS) by independent review

Endpoint	Ibrutinib (n = 139)	Temsirolimus (n = 141)	Hazard ratio	*p*-value
Median PFS	14.6 mo	6.2 mo	0.43	<0.0001
Median OS	Not reached	21.3 mo	0.76	0.13

OS = overall survival

The overall and complete response rates were higher for ibrutinib (n = 100; 72% and 19%) than for temsirolimus (n = 57; 40% and 1%); 23% of patients who received temsirolimus crossed over to ibrutinib at disease progression.

Rule S et al. *Proc ASH* 2015;Abstract 469; Dreyling M et al. *Lancet* 2016;387(10020):770-8.

RAY (MCL3001): Conclusions

- Ibrutinib is superior to temsirolimus for PFS and overall response rate in previously treated MCL.
- Ibrutinib showed preferable tolerability with the incidence of treatment-emergent adverse events consistently lower than with temsirolimus.
- The results of this Phase III trial confirm the efficacy and favorable safety profile of ibrutinib shown in Phase II studies.
- Future concepts will investigate ibrutinib-based combination approaches for patients with relapsed or refractory MCL.

Rule S et al. *Proc ASH* 2015;Abstract 469; Dreyling M et al. *Lancet* 2016;387(10020):770-8.

Investigator Commentary: Ibrutunib versus Temsirolimus for Patients with Previously Treated MCL

Simon Rule and colleagues presented data from a randomized, international Phase III trial for patients with relapsed/refractory MCL who received the BTK inhibitor ibrutinib versus the mTOR inhibitor temsirolimus. Overall 280 patients with a median age of 68 and a median of 2 prior therapies received treatment. At the designated landmark of 2 years the PFS with ibrutinib was 41% and with temsirolimus 7%. The overall response and complete response rates also, as anticipated, were higher with ibrutinib compared to temsirolimus at respectively 72% versus 40% and 19% versus 1%. Median OS was not reached with ibrutinib but was 21.3 months with temsirolimus.

Ibrutinib clearly surpassed temsirolimus in terms of being a selected agent in its use in relapsed or refractory MCL. This study confirms data from single-arm Phase II trials and further supports the exploration of combinations with ibrutinib in MCL.

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