Additional Abstracts of Interest in Hodgkin and Non-Hodgkin Lymphomas at ASH 2015
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:

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Hardware/Software Requirements:
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

Last review date: March 2016
Expiration date: March 2017
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.

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.

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Additional Abstracts of Interest in Hodgkin and Non-Hodgkin Lymphomas at ASH 2015

Presentations discussed in this issue


Rule S et al. Ibrutinib vs temsirolimus: Results from a phase 3, international, randomized, open-label, multicenter study in patients with previously treated mantle cell lymphoma (MCL). Proc ASH 2015;Abstract 469.

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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

<table>
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<tr>
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<th>ORR</th>
<th>CR/CRu</th>
<th>Stable disease</th>
<th>Progressive disease</th>
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<tr>
<td>11 (42%)</td>
<td>5 (19%)</td>
<td>8 (31%)</td>
<td>7 (27%)</td>
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</table>

**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


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.

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

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%

<table>
<thead>
<tr>
<th></th>
<th>CR rate</th>
<th>12-mo PFS rate</th>
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<tr>
<td>PET negative</td>
<td>69%</td>
<td>Not reported</td>
</tr>
<tr>
<td>CD30-positive</td>
<td>19/25 (76%)</td>
<td>82%</td>
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<tr>
<td>CD30-negative</td>
<td>12/19 (63%)</td>
<td>56%</td>
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PFS = progression-free survival


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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.

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

<table>
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<tr>
<th>Endpoint</th>
<th>Ibrutinib (n = 139)</th>
<th>Temsirolimus (n = 141)</th>
<th>Hazard ratio</th>
<th>p-value</th>
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<tr>
<td>Median PFS</td>
<td>14.6 mo</td>
<td>6.2 mo</td>
<td>0.43</td>
<td>&lt;0.0001</td>
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<tr>
<td>Median OS</td>
<td>Not reached</td>
<td>21.3 mo</td>
<td>0.76</td>
<td>0.13</td>
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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.

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.


Investigator Commentary: Ibrutinib 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*