Brentuximab Vedotin-Based Combination Regimens in Hodgkin and T-Cell Lymphomas
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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Miami, Florida
Brentuximab Vedotin-Based Combination Regimens in Hodgkin and T-Cell Lymphomas

Presentations discussed in this issue


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


Chen R et al. Post transplant outcome of a multicenter phase II study of brentuximab vedotin as first line salvage therapy in relapsed/refractory HL prior to AHCT. Proc ASH 2015;Abstract 519.

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

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

<table>
<thead>
<tr>
<th>Evaluatable patients</th>
<th>Overall response</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 18</td>
<td>13 (72%)</td>
<td>9 (50%)</td>
<td>4 (22%)</td>
<td>3 (17%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>

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.*

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**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

### % Reduction in Disease

Overall response rate (ORR): 31/45 evaluable (69%)

- Disease reduction with new lesions = disease progression; Data based on evaluable patients at time of presentation
- Patient with ALCL had a partial response


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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).

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

Ahmed Sawas and colleagues presented data from an international Phase I/II trial of BV/bendamustine in patients with relapsed/refractory classical HL or ALC. 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 ALC

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)

<table>
<thead>
<tr>
<th></th>
<th>BV alone (n = 26)</th>
<th>BV + DTIC (n = 21)</th>
<th>BV + Benda (n = 16)</th>
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<tbody>
<tr>
<td>ORR (CR + PR)</td>
<td>24 (92%)</td>
<td>21 (100%)</td>
<td>16 (100%)</td>
</tr>
<tr>
<td><strong>Best response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>19 (73%)</td>
<td>14 (67%)</td>
<td>13 (81%)</td>
</tr>
<tr>
<td>PR</td>
<td>5 (19%)</td>
<td>7 (33%)</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (8%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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/m² or 70 mg/m²) 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*

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

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)

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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)

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

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

### Patients evaluable for pre-ASCT response (N = 24)

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>23/24</td>
<td>96%</td>
</tr>
<tr>
<td>Metabolic CR</td>
<td>20/24</td>
<td>83%</td>
</tr>
</tbody>
</table>

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

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**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.