Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS
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OVERVIEW OF ACTIVITY
The treatment of hematologic cancer remains a challenge for many healthcare professionals and patients despite recent gains made in the management of this group of diseases. Determining which treatment approach is most appropriate for a given patient requires careful consideration of patient-specific characteristics, physician expertise and available health system resources. To bridge the gap between research and patient care, this issue of Hematologic Oncology Update features one-on-one discussions with leading hematology-oncology investigators. By providing information on the latest clinical developments in the context of expert perspectives, this activity assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of evidence-based and current therapeutic strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES
• Consider current and emerging clinical research data in the formulation of therapeutic recommendations for patients with newly diagnosed and relapsed/refractory (R/R) follicular, mantle cell and diffuse large B-cell lymphomas.
• Appreciate the recent FDA approvals of several novel therapies for the treatment of newly diagnosed and R/R chronic lymphocytic leukemias, and discuss how these therapies can be appropriately and safely integrated into routine clinical practice.
• Reevaluate current treatment approaches for patients with myeloproliferative disorders and acute and chronic leukemias in light of newly emerging clinical data.
• Recognize the recent FDA approvals of daratumumab, elotuzumab, ixazomib and panobinostat, and effectively identify where and how these agents should be integrated into the clinical management of relapsed or refractory multiple myeloma.
• Incorporate new therapeutic strategies into the best-practice management of newly diagnosed and R/R Hodgkin lymphoma.
• Develop an understanding of the biologic rationale for and early efficacy and toxicity data with immunotherapeutic approaches for patients with MM or various lymphoma subtypes.
• Assess the benefits of ongoing clinical trials for patients with hematologic cancers, and inform appropriately selected patients about these options for treatment.

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Tracks 1-13

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Track 2  GADOLIN trial: Overall survival benefit with the addition of obinutuzumab to bendamustine followed by obinutuzumab maintenance therapy for patients with rituximab-refractory indolent non-Hodgkin lymphoma (NHL)

Track 3  Primary results of the Phase III GALLIUM study: Obinutuzumab-based induction and maintenance therapy prolongs progression-free survival (PFS) for patients with previously untreated FL

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Track 5  Clinical experience with obinutuzumab-associated infusion reactions

Track 6  Activity of FDA-approved (idelalisib) and investigational (copanlisib) PI3K inhibitors in indolent NHL

Track 7  Response to bendamustine/obinutuzumab on a clinical trial

Track 8  **Case discussion:** A 50-year-old man with relapsed mantle cell lymphoma (MCL) receives ibrutinib

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Track 10  **Case discussion:** A 28-year-old man with Hodgkin lymphoma (HL) receives brentuximab vedotin as consolidation therapy after autologous stem cell transplant

Track 11  Results of the Phase III AETHERA trial: PFS improvement with brentuximab vedotin as consolidation therapy after autologous stem cell transplant in patients with HL at risk of relapse or progression

Track 12  Selection of first-line therapy for chronic lymphocytic leukemia (CLL)

Track 13  Integration of venetoclax into the treatment algorithm for CLL

Select Excerpts from the Interview

**Tracks 2-4**

**DR LOVE:** You were the principal investigator of the Phase III GADOLIN study investigating the role of obinutuzumab for rituximab-refractory indolent non-Hodgkin lymphoma (NHL) that was published in *The Lancet Oncology* and updated at ASH 2016 (Sehn 2016; Cheson 2016). Would you talk about the study?

**DR SEHN:** The GADOLIN trial was designed to evaluate the addition of obinutuzumab to bendamustine versus bendamustine alone for patients with rituximab-refractory indolent NHL. Most of the patients enrolled on the trial had follicular lymphoma (FL). Patients on the obinutuzumab arm whose disease did not progress received obinutuzumab maintenance for 2 years.
The trial demonstrated a significant improvement in progression-free survival (PFS) for patients who received the combination (Sehn 2016). At the ASH 2016 meeting updated results were reported demonstrating a survival advantage for the obinutuzumab/bendamustine arm (Cheson 2016; [1.1]).

DR LOVE: Would you also comment on the results of the Phase III GALLIUM trial assessing obinutuzumab-based induction and maintenance therapy for patients with newly diagnosed FL?

DR SEHN: Based on the efficacy of obinutuzumab in chronic lymphocytic leukemia (CLL) and the GADOLIN trial in FL, it was logical to investigate this agent in the front-line setting and compare it to rituximab head to head. The GALLIUM trial compared induction therapy with obinutuzumab and chemotherapy followed by maintenance obinutuzumab to rituximab with chemotherapy followed by maintenance rituximab for patients with newly diagnosed FL. The trial met its endpoint with an improvement in PFS on the obinutuzumab arm (Marcus 2016; [1.2]). Because of these results, we might find a shift in the standard up-front approach for FL.

DR LOVE: What is the mechanism of action of obinutuzumab, and how would you compare its efficacy to that of rituximab across the various hematologic histologies?

DR SEHN: Obinutuzumab is classified as a Type II anti-CD20 monoclonal antibody. Its primary advantage compared to rituximab is its enhanced ability to stimulate direct cell death and antibody-dependent cellular cytotoxicity. It has a different mechanism of action from that of rituximab and may be superior, depending on tumor histology. A big advantage relative to rituximab was observed in the GALLIUM trial in FL and...
in the CLL11 trial in CLL (Goede 2014). However, the GOYA trial for patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) did not show an advantage with obinutuzumab (Vitolo 2016).

Track 9

DR LOVE: How do you approach sequencing treatment for patients with mantle cell lymphoma (MCL)?

DR SEHN: The management of MCL is complicated with all the available options. Ideally, we want to administer the agents that are most effective and least toxic in the earlier settings. It is likely that novel compounds like ibrutinib and possibly lenalidomide may move into the front-line setting because they have a better toxicity profile than our current therapies.

Currently chemoimmunotherapy is still the standard for up-front treatment. For younger patients, autologous stem cell transplant (ASCT) is recommended. I would offer patients ibrutinib in the second line because it is highly effective. After ibrutinib I would recommend bendamustine or bendamustine/rituximab (BR). Lenalidomide either alone or with rituximab is also an option, but I believe it is not as effective as ibrutinib, so I would consider it in a later-line setting. Venetoclax is one of the exciting agents in development for MCL, but we must await further data with this agent.

All of these options will likely be used because we don’t have a cure for this disease. We do not have a right or wrong sequence, and in my practice I consider the patient’s clinical condition, choose the agent with the highest efficacy and balance that with the toxicity.
DR LOVE: What is your approach to newly diagnosed CLL?

DR SEHN: In my practice in Canada my recommendations are partly dependent on funding. Currently purine analogue-based therapy, like FCR (fludarabine/cyclophosphamide/rituximab), is usually the front-line choice for most patients. In my clinic I generally offer patients fludarabine/rituximab. BR has been shown to be as effective as FCR and has better tolerability, so for many patients BR is a reasonable standard.

We are excited about targeted agents like ibrutinib, which have lower toxicity. Ibrutinib is now a mainstay of therapy in the relapsed setting and may be considered for elderly patients for whom we want to avoid chemotherapy. For patients with 17p deletion chemotherapy is not highly effective and ibrutinib has now become the standard therapy. In my practice we can access ibrutinib for patients with 17p deletion, but it’s much more difficult for us to access for elderly patients.

The obinutuzumab/chlorambucil combination is effective for older patients for whom toxicity is an additional concern. In the future I believe we will move away from the more toxic, high-intensity therapies. Novel targeted agents are going to make their way into the front-line setting.

DR LOVE: What is your clinical experience with venetoclax in the management of CLL?

DR SEHN: Venetoclax is on the verge of approval in Canada, and I’ve only had access to it in my clinic in the context of clinical trials. For patients with CLL, tumor lysis syndrome (TLS) is a definite risk. As venetoclax is starting to be used more commonly, oncologists will need a strategy for identifying and monitoring patients at high risk for TLS and managing care accordingly. TLS is generally a risk only at the initiation of treatment.

Tools and guidelines are available for physicians to aid in the care of these patients. Some patients may need to be admitted to a hospital or receive treatment in centers where sequential laboratory investigations can be obtained to monitor for TLS. We’re currently trying to create algorithms and management strategies that allow us to better identify patients at high risk.

SELECT PUBLICATIONS


Vitolo U et al. Obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma: Final results from an open-label, randomized phase 3 study (GOYA). Proc ASH 2016; Abstract 470.
### Tracks 1-14

**Track 1**  Management of high-risk multiple myeloma (MM)

**Track 2**  Trials of immune checkpoint inhibitors and immunomodulatory drugs for MM

**Track 3**  Emergence of ixazomib as a component of maintenance therapy for high-risk MM

**Track 4**  **Case discussion:** A 62-year-old man with high-risk MM experiences disease progression on maintenance lenalidomide and receives pomalidomide with daratumumab

**Track 5**  Early versus delayed autologous transplant after induction therapy for MM

**Track 6**  Activity of daratumumab and management of associated infusion reactions

**Track 7**  Biologic rationale for combining daratumumab with immunomodulatory drugs or immune checkpoint inhibitors

**Track 8**  Carfilzomib- versus bortezomib-based induction therapy for patients with MM

**Track 9**  **Case discussion:** A 75-year-old man with relapsed/refractory (R/R) MM receives elotuzumab/lenalidomide/dexamethasone

**Track 10**  Elotuzumab-based research strategies

**Track 11**  **Case discussion:** A 57-year-old woman with relapsed MM whose disease progresses on pomalidomide/daratumumab experiences an excellent response to salvage therapy with carfilzomib/panobinostat/dexamethasone

**Track 12**  **Case discussion:** A 75-year-old woman with indolent MM and disease progression on maintenance lenalidomide receives ixazomib/lenalidomide/dexamethasone

**Track 13**  Strategies for promoting Bcl-2 dependence to increase venetoclax sensitivity in patients with MM

**Track 14**  Emerging research with chimeric antigen receptor T-cell (CAR-T) therapy in MM

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### Select Excerpts from the Interview

**Tracks 1, 3**

**DR LOVE:** What are some of the issues you discussed in your publication in *Blood* entitled “How I treat high risk myeloma” (Lonial 2015)?

**DR LONIAL:** There were several key unresolved issues discussed in this paper. The first is the importance of identifying which patients are at high risk at the time of diagnosis, because if you miss that opportunity, you won’t know it until they have experienced rapid disease relapse. The second is to make sure that you’re aggressive with their treatment and their maintenance because you can ultimately improve their long-term outcomes.
Another issue we explored was when patients should receive maintenance therapy and what regimen they should receive. One aspect we were trying to speak about is the idea that standard single-agent lenalidomide maintenance therapy after ASCT is not sufficient for patients with high-risk multiple myeloma (MM).

An important point I’d like to add to the messages from this paper pertains to recent data on the concept that, in general, undertreatment of MM is a bad thing. I and many others have said, “Two drugs is undertreatment,” so lenalidomide/dexamethasone as induction therapy is insufficient (Durie 2015). Every patient should get the best induction up front. If you undertreat a patient at diagnosis, when they experience relapse they do so like a patient with high-risk disease, so you’ve almost converted them to a high-risk phenotype by undertreating them.

**DR LOVE:** Would you discuss the pragmatic aspects of bortezomib/lenalidomide/dexamethasone (RVd) maintenance therapy, how long you use it and how the patients fare?

**DR LONIAL:** Delivery of long-term IV therapy is untenable. What I mean by that is that administering IV bortezomib for 3 years is not a viable option. On the other hand, administering it subcutaneously once a week is a viable option, and we’ve used that approach on clinical trials. To build on that experience we’re now beginning to experiment with replacing bortezomib with ixazomib because we are then using an all-oral combination for patients with high-risk MM that has yielded encouraging results.

**DR LOVE:** That was the first thing I thought about when I heard about oral proteasome inhibitors and I knew about this interest in maintenance. Have you had patients receive ixazomib for prolonged periods? And how do you find they fare?

**DR LONIAL:** Yes, we were involved with the original Phase I study that was published in *The Lancet Oncology* by Shaji Kumar evaluating ixazomib/lenalidomide/dexamethasone up front followed by maintenance ixazomib for patients with previously untreated MM (Kumar 2014). I believe the longest we’ve had a patient receive it was 4 1/2 years. Once you get the dose and schedule right early in the disease course, they fare well after that.

**Track 5**

**DR LOVE:** What are your thoughts on the joint IFM/DFCI 2009 trial evaluating immediate or delayed ASCT after RVd induction therapy? The French and Belgian portion of this study has been reported but the US part of the trial has not, correct?

**DR LONIAL:** Yes, that’s correct. On this trial all patients received equal amounts of RVd induction therapy, and patients in the French version received 1 year of maintenance lenalidomide. In the United States they received maintenance lenalidomide until disease progression. What has been reported thus far from the French portion of this trial is that the PFS and overall response rate clearly favored the use of high-dose therapy and transplantation. However, overall survival was similar between the 2 arms (2.1).

Another interesting aspect of these results is that if you consider the patients who achieved minimal residual disease (MRD) negativity (<10⁻⁶) by next-generation sequencing, it didn’t matter whether they underwent a transplant or not. Their PFS and
overall survival looked the same. I was struck by the fact that those patients achieved such good outcomes with only 1 year of maintenance therapy.

▶ **DR LOVE:** Do you have any idea when we’ll see the North American data, and are you expecting them to reflect less of a difference because the maintenance therapy is more effective?

▶ **DR LONIAL:** The US part of the trial is only now completing enrollment, so it will be a few years before the data are presented with a reasonable median follow-up. I’m a proponent of continuous maintenance in the post-transplant setting, but these results make me wonder: Is there an endpoint at which I would say, “that’s enough” in terms of maintenance therapy?

### Tracks 13-14

▶ **DR LOVE:** Would you talk about some of your research on strategies for promoting Bcl-2 dependence in MM and how that relates to sensitivity to venetoclax?

▶ **DR LONIAL:** About 85% of myeloma tumor cells are Mcl-1 dependent, which means they will be intrinsically resistant to Bcl-2 inhibitors. That leaves about 15% of patients who have Bcl-2-dependent disease, and it turns out that many of them harbor an 11;14 translocation. Their tumors look more B-cell like than those in the average patient with MM. Thus, the tumors tend to express CD20.

One of the strategies that we employ is adding dexamethasone, not because it kills myeloma cells but because dexamethasone pushes cells toward Bcl-2 dependence (Matulis 2016). Once you make the tumor cells Bcl-2 dependent, you have an opportunity to kill them with venetoclax.

▶ **DR LOVE:** Have clinical responses been observed with venetoclax in MM?

▶ **DR LONIAL:** Yes, although in the general patient population the response rate may not be so robust. If you focus on the subset that is enriched for the 11;14 translocation, it’s quite striking — the single-agent venetoclax response rate is about 40% to 45% for those patients (Kumar 2016).

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<table>
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<th>Survival</th>
<th>RVd (n = 350)</th>
<th>RVd + ASCT (n = 350)</th>
<th>Hazard ratio</th>
<th>p-value</th>
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<td>MRD-positive by NGS (≥10^{-6})</td>
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<td>Before maintenance therapy</td>
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<td>After maintenance therapy</td>
<td>92%</td>
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RVd = bortezomib/lenalidomide/dexamethasone; MRD = minimal residual disease; NGS = next-generation sequencing.

As an example, we cared for a young woman with MM that was refractory to almost any standard agent you can imagine, and she was about to be sent for supportive care. Laboratory analysis indicated that she would be an excellent candidate for this approach, and she has received single-agent venetoclax and has been in complete remission (CR) now for 2 years.

DR LOVE: Another interesting novel approach I’d like to ask you about is CAR T-cell therapy. What is known about that approach in MM?

DR LONIAL: We know that when you use CD19 as a target you may get a few responses but they’re not long, durable responses. The real issue with CAR T cells in MM is whether we can find a better target than CD19. CD38 is one option, but to me a more interesting candidate is B−cell maturation antigen (BCMA). The NIH group has tested a CAR T cell against BCMA in MM and the response rate was impressive (Ali 2016; [2.2]). We don’t yet know about response duration, and cytokine release syndrome continues to be an issue among patients receiving the highest dose of therapy, but CAR T cells are clearly effective and they will provide a way to treat many diseases down the road.

### SELECT PUBLICATIONS


Avet-Loiseau H et al. *Evaluation of minimal residual disease (MRD) by next generation sequencing (NGS) is highly predictive of progression free survival in the IFM/DFCI 2009 trial*. *Proc ASH* 2015; **Abstract 191**.


Durie B et al. *Bortezomib, lenalidomide and dexamethasone vs lenalidomide and dexamethasone in patients (pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT): Results of the randomized phase III trial SWOG S0777*. *Proc ASH* 2015; **Abstract 25**.

Kumar SK et al. *Venetoclax monotherapy for relapsed/refractory multiple myeloma: Safety and efficacy results from a Phase I study*. *Proc ASH* 2016; **Abstract 488**.


Tracks 1-9

Track 1  **Case discussion**: A 54-year-old woman with R/R FLT3 mutation-positive acute myeloid leukemia (AML)

Track 2  Comparison of the FLT3 inhibitors midostaurin, quizartinib, gilteritinib and sorafenib in AML

Track 3  Approach to FLT3 and other mutation testing for patients with AML

Track 4  **Case discussion**: A 56-year-old woman with R/R AML undergoes a repeat mutation assay that identifies both FLT3-ITD and FLT3-TKD mutations

Track 5  **Case discussion**: A 36-year-old man is newly diagnosed with chronic-phase chronic myeloid leukemia

Track 6  Activity of ruxolitinib in myeloproliferative neoplasms and therapeutic options for patients who experience a response followed by disease progression

Track 7  **Second opinion**: Dose of ruxolitinib for a 68-year-old man with symptomatic primary myelofibrosis and a platelet count of 38,000/µL

Track 8  **Second opinion**: Management of anemia and use of erythropoiesis-stimulating agents in a 59-year-old man with JAK2 mutation-positive primary myelofibrosis who responds to ruxolitinib

Track 9  **Case discussion**: A 71-year-old man with R/R myelodysplastic syndrome receives oral azacitidine with sonidegib on a clinical trial

Select Excerpts from the Interview

**Tracks 1-2**

> **DR LOVE**: Would you discuss the various FLT3 inhibitors in development and compare their efficacy for patients with acute myeloid leukemia (AML) and FLT3 mutations?

> **DR TIBES**: FLT3 is one of the most commonly mutated genes in AML, and about 30% of patients with AML harbor these mutations. Mutations in FLT3 can be divided into 2 categories: internal tandem duplications (FLT3-ITD mutations), which are more common, and mutations in the tyrosine kinase domain (FLT3-TKD mutations). It is possible for patients to have one or both mutations, so patients should be tested for both.

Several first- and second-generation FLT3 inhibitors are currently being studied in clinical trials. Patients with FLT3 mutations, particularly at relapse, should be offered an FLT3 inhibitor on a clinical trial if one is available. It is difficult to compare the efficacy of these agents across studies, but overall the responses are encouraging.

Sorafenib, a first-generation, nonspecific FLT3 inhibitor, has been studied in combination with standard chemotherapy, and high CR rates were reported (Rollig 2015). A
Phase II study evaluating sorafenib in combination with azacitidine for patients with relapsed/refractory AML and FLT3-ITD mutations demonstrated good responses (Ravandi 2013).

Midostaurin, another first-generation multikinase inhibitor, was evaluated in a global, randomized Phase III trial. The study investigated the addition of midostaurin to up-front induction chemotherapy for younger patients with newly diagnosed AML and FLT3 mutations. This was the first positive study showing that the addition of an FLT3 inhibitor to induction chemotherapy resulted in an overall survival benefit (Stone 2015; [3.1]).

I have been involved in investigating gilteritinib, a second-generation FLT3 inhibitor. About 200 patients with relapsed/refractory AML received single-agent gilteritinib in a Phase I/II study.

The composite CR rates (CR + CR with incomplete platelet recovery + CR with incomplete hematologic recovery) were approximately 40% to 50% (Levis 2015; [3.2]). Many of these patients had sustained CRs on therapy. The responses to first-generation FLT3 inhibitors were often short lived, in the range of 6 to 9 months. Gilteritinib may induce longer responses than the first-generation FLT3 inhibitors.

Quizartinib (AC220), another second-generation inhibitor, has shown activity in Phase II studies both as a single agent and in combination with chemotherapy. It has demonstrated CR rates in the range of 40% to 50% (Schiller 2014). It is currently being evaluated in Phase III studies.

### 3.1 Phase III CALGB-10603 (RATIFY) Trial of Midostaurin in Combination with Daunorubicin/Cytarabine Induction and High-Dose Cytarabine Consolidation and as Maintenance Therapy for Patients with Newly Diagnosed Acute Myeloid Leukemia with FLT3 Mutations

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<th>Hazard ratio</th>
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<td>8.2 mo</td>
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OS = overall survival; SCT = stem cell transplant; NR = not reached; EFS = event-free survival

* Censored for transplant analyses

No statistically significant differences were observed in the overall rate of Grade ≥3 hematologic or nonhematologic adverse events between midostaurin and placebo.


### Track 9

**CASE DISCUSSION:** A 71-year-old man with relapsed/refractory myelodysplastic syndrome (MDS) receives oral azacitidine with sonidegib on a clinical trial

**DR TIBES:** This patient presented with low-risk MDS and trisomy 8 about 5 years ago. He was red blood cell transfusion dependent and responded to erythropoietin for 14 months but became transfusion dependent again. He was enrolled on a clinical trial with
oral azacitidine for 12 months, which he tolerated well. His disease was stable, with a reduction in transfusion dependency. He went off treatment for a year and a half. His disease eventually progressed to high-risk MDS. He was evaluated for an allogeneic stem cell transplant, but he decided against it and was enrolled on a clinical trial of azacitidine in combination with a smoothened inhibitor, sonidegib (LDE225). If a patient experiences disease progression on one hypomethylating agent, he or she can be switched to another one, but the response rates are not that good. So I generally offer these patients a combination of a hypomethylating agent with a novel targeted drug. On this trial the patient achieved stabilization of his disease and improvements in his counts. After 12 cycles, unfortunately his disease progressed into AML. We discussed the option of transplant again, but he decided against it and is now receiving supportive care.

SELECT PUBLICATIONS


Schiller G et al. Final results of a randomized phase 2 study showing the clinical benefit of quizaritinib (AC220) in patients with FLT3-ITD positive relapsed or refractory acute myeloid leukemia. Proc ASCO 2014;Abstract 7100.
Case discussion: A 62-year-old man with chemotherapy-refractory diffuse large B-cell lymphoma whose disease is controlled with lenalidomide/rituximab (R²) achieves a complete response with CAR-T therapy

Clinical approach to CAR-T therapy and management of associated cytokine release syndrome

Efficacy and toxicity profile of CAR-T therapy in lymphomas

Administration of most closely HLA-matched multivirus-specific (“off-the-shelf”) T-cell therapy

Activity and tolerability of the Bruton tyrosine kinase inhibitors ibrutinib and acalabrutinib (ACP-196) in CLL

Incidence of bleeding with acalabrutinib

Case discussion: A 67-year-old man with rituximab-refractory FL receives obinutuzumab with bendamustine

Incidence and management of idelalisib-associated diarrhea

Incorporation of idelalisib into therapeutic algorithms for FL and CLL

Obinutuzumab/bendamustine-associated cytopenias

RELEVANCE: A Phase III trial evaluating R² versus rituximab-based chemotherapy followed by maintenance rituximab for previously untreated FL

Characteristics and management of rash after R² treatment for patients with previously untreated indolent NHL

Select Excerpts from the Interview

Tracks 1-4

DR LOVE: What are some of the factors that you take into account when considering a patient for CAR T-cell therapy?

DR NASTOUPIL: We generally like to have some sense of response in patients before administering CAR-T therapy. If I can initially debulk some of the tumor burden, I believe they will have a better outcome. This has not been described in prospective studies, but we do know that CAR-T therapies are generally associated with fairly high toxicity. So if we can have some idea that the patient will respond to an immune therapy approach with an agent such as lenalidomide, and if I can reduce the proliferative rate prior to proceeding with CAR-T therapy, I’m much more optimistic about the outcome.

The efficacy of CAR-T therapy appears to be quite high, but some patients do not benefit, and we’re trying to understand why. We’re observing efficacy rates of more than 60% and CR rates of more than 50%, which is quite striking. So this is an all-or-
none type of approach in which we're aiming for a CR, and we believe those CRs to be durable.

We know that the toxicity should not be discounted, and it should be managed with a multidisciplinary approach in centers with access to ICU care because these patients can become quite sick in a short time. My general opinion is that CAR-T therapy is more toxic than ASCT, but it might be applicable when a patient with chemorefractory disease is not a candidate for ASCT or an allogeneic transplant.

Some of the toxicities that have been observed are cytokine release syndrome, fever, neurotoxicity, confusion and cerebral edema. Seizure activity is not infrequent. Generally, these events have all been reversible, but the cerebral edema is what we worry about the most.

» DR LOVE: What exactly are “off-the-shelf” CAR T cells?

» DR NASTOUPIL: You identify an antigen for which a T cell is already prepared and sitting on a shelf, meaning someone else’s T cell that will bind and effectively eliminate that antigen. An ASH 2015 presentation from Dr Helen Heslop’s group evaluated these off-the-shelf CAR T cells and reported high response rates (Omer 2015). The efficacy in terms of duration of response is still an unanswered question, but this approach appears quite appealing.

» DR LOVE: Is it likely that one of these therapies will be approved soon, and in what disease?

» DR NASTOUPIL: None of these are currently FDA approved, but studies of CAR-T therapies are much further along in the acute leukemias than in the lymphomas, although we are accumulating data with DLBCL. We’ve completed a study that we expect will be considered by the FDA in the spring of 2017.

I have a handful of patients who I know would no longer be with us if they did not have access to this therapy. I do believe that this will continue to be investigated and continue to evolve. If we can reduce the toxicity while maintaining the efficacy, this will be really exciting.

Tracks 5-6

» DR LOVE: What is your take on the activity and tolerability of the BTK inhibitors ibrutinib and acalabrutinib in CLL?

» DR NASTOUPIL: We know that ibrutinib performs well in relapsed CLL in terms of high response rates, and we know of some off-target effects with ibrutinib and that it’s not purely selective for inhibiting BTK. What is the impact of those off-target effects? We know they probably add to the toxicity, including platelet aggregation, rash and diarrhea. One of the interests in pursuing more selective agents such as acalabrutinib is the impact on efficacy. And can we reduce some of the toxicity?

The overall response rate with acalabrutinib was 95% (Byrd 2016). About 30% of patients harbored a 17p deletion, and 100% of those patients experienced a response. Most of the responses will be partial responses or partial responses with persistent leukocytosis. But for patients with relapsed CLL, is that a failure? I don’t believe so if you can gain adequate disease control for long periods.
We are learning more about acalabrutinib as time goes on. We do know from the *New England Journal* paper that no major bleeding events were reported with this agent (Byrd 2016; [4.1]). What we don’t know is, over time, will that story change? Acalabrutinib appears to be more potent, and perhaps we can intensify the dosing because we’re seeing fewer side effects.

---

**ACE-CL-001 Trial: A Novel Bruton Tyrosine Kinase Inhibitor, Acalabrutinib, for Chronic Lymphocytic Leukemia**

<table>
<thead>
<tr>
<th></th>
<th>All evaluable patients (n = 60)</th>
<th>Del(17p13.1) (n = 18)</th>
<th>Prior idelalisib (n = 4)</th>
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</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>95%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Partial response (PR) rate</td>
<td>85%</td>
<td>89%</td>
<td>75%</td>
</tr>
<tr>
<td>PR with lymphocytosis</td>
<td>10%</td>
<td>11%</td>
<td>25%</td>
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</table>

**Adverse events (n = 61)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Grades 1 and 2</th>
<th>Grades 3 and 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>43%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38%</td>
<td>2%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20%</td>
<td>3%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>23%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*No cases of major bleeding or atrial fibrillation at 14.3 months follow-up*


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**Tracks 11-12**

› **DR LOVE:** What is the design and status of the ongoing Phase III RELEVANCE study?

› **DR NASTOUPIL:** RELEVANCE is a large, international, multicenter Phase III study for which all patients must have high tumor burden to be eligible. These are patients who you typically think of as needing chemoimmunotherapy. The study is a head-to-head comparison of R-CHOP, BR or R-CVP to lenalidomide/rituximab (R²) as front-line therapy for FL (4.2).

The dosing strategy includes more intensive lenalidomide until the patient achieves a CR, which is typically assessed around 6 months. Patients can then change to maintenance lenalidomide, which is a lower dose, for 18 months duration of lenalidomide therapy. Patients also receive up to 30 months of rituximab therapy, including 24 months of maintenance, similar to the approach we use after front-line chemoimmunotherapy. The primary study endpoint is PFS. Enrollment was completed some time ago, and we’re waiting to hear the study results.

› **DR LOVE:** If the study ended up showing equivalent efficacy, would you choose R² because of tolerability?

› **DR NASTOUPIL:** I used to at least pitch to patients that this was a nonchemotherapy approach and thus would be well tolerated. But lenalidomide and rituximab have fairly high incidences of fatigue, myalgias, fever and cytopenias. It’s not infrequent to have Grade 3 or 4 neutropenia.
What’s striking about $R^2$, at least in our experience, is that the side-effect intensity seems to be higher in the first few months and then tends to stabilize or improve over time. It’s unclear whether patients become accustomed to the side-effect profile and don’t report it or don’t seem to be bothered by it or whether it becomes easier over time. But the first 2 months of $R^2$ are not a “free lunch.”

We don’t know whether patients who have highly proliferative tumors or a high tumor burden need chemotherapy in that setting rather than $R^2$. We generally do see slower time to response with the immune therapy approaches than we do with chemotherapy. Hopefully, that question will be answered with this study.

**Dr Love:** What did your group report in the recent paper you published on characteristics and management of rash after treatment with $R^2$ in patients with previously untreated indolent NHL (Fowler 2015)?

**Dr Nastoupi:** We wanted to describe our experiences with this combination because we’ve seen quite a few patients for whom lenalidomide was stopped because of rash. We’ve learned that a rash is not uncommon and is frequently Grade 3, meaning a large amount of the body surface area is affected. It’s typically a red, sometimes pruritic rash. The most striking characteristic is that if you stop the lenalidomide, the rash almost always goes away.

So we wanted to reassure community doctors that an uncomfortable, full-body rash is not uncommon among patients receiving $R^2$. You can treat it with antihistamines and a short course of low-dose steroids if you want to get rid of it faster, but generally speaking, we are not altering therapy because of this rash. This phenomenon can be managed with a drug holiday if need be, and then the patient can be rechallenged, even those patients who have experienced Grade 3 rash.

**SELECT PUBLICATIONS**


1. Primary results of the Phase III GALLIUM trial evaluating obinutuzumab or rituximab in combination with chemotherapy for newly diagnosed FL demonstrated statistically significant improvement in ____________ for patients who have received obinutuzumab.
   a. Three-year PFS
   b. Three-year overall survival
   c. Three-year time to next treatment
   d. All of the above
   e. Both a and b
   f. Both a and c

2. Which of the following statements is true regarding the FLT3-ITD and FLT3-TKD mutations in AML?
   a. FLT3-ITD mutations are more common
   b. Both mutations cannot occur in the same patient
   c. The combined frequency is approximately 30%
   d. Both a and c
   e. All of the above

3. Analysis of the IFM/DFCI 2009 trial evaluating immediate or delayed ASCT after RVd induction therapy indicated both PFS and overall response rate benefits for patients who received ____________.
   a. RVd
   b. RVd and ASCT
   c. Neither a nor b — PFS and response rate were equivalent in the 2 study arms

4. An analysis of the predictive value of MRD in a subset of patients on the IFM/DFCI 2009 trial demonstrated that MRD negativity from testing by ____________ was highly predictive of PFS.
   a. Flow cytometry
   b. Next-generation sequencing
   c. Both a and b

5. Sensitivity to venetoclax for MM has primarily been observed in patients with t(11;14) disease.
   a. True
   b. False

6. The Phase III CALGB-10603 (RATIFY) trial evaluating midostaurin in combination with daunorubicin/cytarabine induction therapy and cytarabine consolidation and as maintenance therapy for patients with newly diagnosed AML with FLT3 mutations demonstrated a statistically significant improvement in ____________ on the midostaurin arm.
   a. Median overall survival
   b. Rate of Grade ≥3 hematologic adverse events
   c. Both a and b
   d. Neither a nor b

7. CAR-T therapy is currently FDA approved for the treatment of ____________.
   a. Acute leukemias
   b. DLBCL
   c. MM
   d. None of the above

8. The Phase I/II ACE-CL-001 trial evaluating acalabrutinib for relapsed CLL demonstrated ____________.
   a. A high response rate
   b. A high incidence of bleeding
   c. A favorable safety profile
   d. Both a and b
   e. Both a and c

9. A publication by Ali and colleagues in Blood demonstrated for the first time CAR T cells successfully targeting an antigen other than CD19. In this study, which of the following CAR T cells showed activity against MM that was resistant to standard therapies?
   a. Anti-BCMA CAR T cells
   b. Anti-CD38 CAR T cells
   c. Both a and b

10. Which of the following is the mechanism of action of gilteritinib (ASP2215)?
    a. Anti-CD20 monoclonal antibody
    b. CAR-T therapy
    c. FLT3 inhibitor
    d. Immunomodulatory drug
Hematologic Oncology Update — Volume 9, Issue 3

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART 1 — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

<table>
<thead>
<tr>
<th>Topic</th>
<th>4 = Excellent</th>
<th>3 = Good</th>
<th>2 = Adequate</th>
<th>1 = Suboptimal</th>
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<tbody>
<tr>
<td>Results of the Phase III studies GADOLIN, evaluating the addition of obinutuzumab to bendamustine ↔ maintenance obinutuzumab for rituximab-refractory indolent NHL, and GALLIUM, comparing obinutuzumab and chemotherapy to rituximab and chemotherapy ↔ maintenance obinutuzumab or rituximab for previously untreated FL</td>
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<td>IFM/DFCI 2009: Results of a Phase III trial comparing RVd to high-dose treatment with ASCT in the initial management of MM in patients up to 65 years of age</td>
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<td>Survival advantage with the addition of midostaurin to induction chemotherapy for patients with FLT3-mutant AML; activity of other FLT3 inhibitors: sorafenib, quizartinib and gilteritinib</td>
<td>4 3 2 1</td>
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<td>Activity of recently FDA-approved (idelalisib) and investigational (copanlisib) PI3K inhibitors in indolent NHL</td>
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<td>Administration and activity of “off-the-shelf” CAR-T therapy in MM and various lymphomas</td>
<td>4 3 2 1</td>
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Practice Setting:
☐ Academic center/medical school ☐ Community cancer center/hospital ☐ Group practice
☐ Solo practice ☐ Government (eg, VA) ☐ Other (please specify) ..................................

Was the activity evidence based, fair, balanced and free from commercial bias?
☐ Yes ☐ No
If no, please explain: ................................................................................................................

Please identify how you will change your practice as a result of completing this activity (select all that apply).
☐ This activity validated my current practice
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): ..............................................................................................................

If you intend to implement any changes in your practice, please provide 1 or more examples:
..................................................................................................................................................

The content of this activity matched my current (or potential) scope of practice.
☐ Yes ☐ No
If no, please explain: ................................................................................................................

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

<table>
<thead>
<tr>
<th>LO</th>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = LO not met</th>
<th>N/A = Not applicable</th>
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<tr>
<td>As a result of this activity, I will be able to:</td>
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<td>• Consider current and emerging clinical research data in the formulation of therapeutic recommendations for patients with newly diagnosed and relapsed/refractory (R/R) follicular, mantle cell and diffuse large B-cell lymphomas. ..................................</td>
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<td>• Appreciate the recent FDA approvals of several novel therapies for the treatment of newly diagnosed and R/R chronic lymphocytic leukemia, and discern how these therapies can be appropriately and safely integrated into routine clinical practice. ..........</td>
<td>4 3 2 1 N/M N/A</td>
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<td>• Reevaluate current treatment approaches for patients with myeloproliferative disorders and acute and chronic leukemias in light of newly emerging clinical data........</td>
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<tr>
<td>• Recognize the recent FDA approvals of daratumumab, elotuzumab, ixazomib and panobinostat, and effectively identify where and how these agents should be integrated into the clinical management of relapsed or refractory multiple myeloma (MM)). ..........</td>
<td>4 3 2 1 N/M N/A</td>
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<td>• Incorporate new therapeutic strategies into the best-practice management of newly diagnosed and R/R Hodgkin lymphoma........................................</td>
<td>4 3 2 1 N/M N/A</td>
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</table>
As a result of this activity, I will be able to:

- Develop an understanding of the biologic rationale for and early efficacy and toxicity data with immunotherapeutic approaches for patients with MM or various lymphoma subtypes.
- Assess the benefits of ongoing clinical trials for patients with hematologic cancers, and inform appropriately selected patients about these options for treatment.

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

Would you recommend this activity to a colleague?

- Yes  
- No

If no, please explain:

PART 2 — Please tell us about the faculty and editor for this educational activity

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laurie H Sehn, MD, MPH</td>
<td>4 3 2 1</td>
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<tr>
<td>Sagar Lonial, MD</td>
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<tr>
<td>Raoul Tibes, MD, PhD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
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<tr>
<td>Loretta J Nastoupil, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
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Editor

<table>
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<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
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<td>4 3 2 1</td>
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Name: .............................................................  
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Date: .....................................................

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Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS
Laurie H Sehn, MD, MPH
Sagar Lonial, MD
Raoul Tibes, MD, PhD
Loretta J Nastoupil, MD

EDITOR
Neil Love, MD

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