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

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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 available clinical research reports on the formulation of therapeutic recommendations for patients with newly diagnosed and relapsed/refractory follicular and diffuse large B-cell lymphoma.
• Appreciate the FDA approvals of novel targeted agents — ibrutinib, obinutuzumab and venetoclax — for the treatment of newly diagnosed and relapsed/refractory chronic lymphocytic leukemia, and discuss how these therapies can be appropriately integrated into the clinical management of standard- and high-risk disease.
• 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 relapsed/refractory Hodgkin lymphoma.
• 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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CD 1, Tracks 1-11

Track 1  Activity of lenalidomide in primary CNS lymphoma
Track 2  Initial results of the Phase II ECOG-E2408 trial: Bendamustine/rituximab with or without bortezomib for previously untreated high-risk follicular lymphoma (FL)
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Track 8  Incorporation of the newly FDA-approved Bcl-2 inhibitor venetoclax into the treatment algorithm for patients with CLL and 17p deletions
Track 9  Evolving treatment options for younger and older patients with CLL
Track 10  Management of venetoclax-associated tumor lysis syndrome
Track 11  CD30 testing for patients with T-cell lymphomas

Select Excerpts from the Interview

CD 1, Track 1

DR LOVE: Would you comment on the activity of lenalidomide-based therapy in patients with central nervous system (CNS) lymphoma?

DR FRIEDBERG: This disease has been a struggle to treat, but recent data from a study of R² followed by lenalidomide maintenance in primary CNS lymphoma demonstrated that lenalidomide crosses the blood-brain barrier. The responses were reasonably durable, and it was tolerated well in patients with significant refractory disease (Rubenstein 2016). Primary CNS lymphoma is a disease of older patients, many of whom may not tolerate standard induction treatment with high doses of methotrexate. In that scenario the favorable tolerability and efficacy in this study make lenalidomide appealing.

DR LOVE: Do you use lenalidomide for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL)?
DR FRIEDBERG: Older, transplant-ineligible patients with disease progression on standard R-CHOP have incurable disease, and often oncologists use modifications of salvage regimens, such as modified ICE or high-dose cytarabine. I believe lenalidomide has been shown to be as active as that type of therapy, with less toxicity, and it’s my “go-to” drug for relapsed DLBCL in transplant-ineligible patients when no clinical trial is available.

CD 1, Tracks 2-3

DR LOVE: Would you discuss the results of the Phase II ECOG-E2408 trial of bendamustine/rituximab (BR) with or without bortezomib for high-risk follicular lymphoma (FL)?

DR FRIEDBERG: This was of interest to me because many years ago John Leonard, Julie Vose and I conducted a trial of bortezomib with BR. The response rate was high, particularly in FL and mantle cell lymphoma, with reasonable tolerability (Friedberg 2011).

The ECOG study was made up of 2 parts. Up front the investigators compared BR to BR with bortezomib, and the primary endpoint was complete response (CR). The second part evaluated lenalidomide as maintenance therapy. Neuropathy was more prevalent with bortezomib, but with schedule modification and subcutaneous administration it was low grade. Most patients were able to receive all the prescribed doses, which is compelling.

The CR rate was higher for the patients who received bortezomib with BR than for those who received BR alone, although the benefit was incremental (Evens 2016). We don’t generally see CR rates much higher than this, and it was higher than normal. Also, if patients experience a better response up front, it’s more likely their PET scan will be negative and they’ll maintain a longer response.

I’m not sure this constitutes a new standard, but it is important to follow because FL is a heterogeneous disease. Most patients fare well, but identifying those who do not necessitates a PET scan at the end of therapy and evaluation of the time to disease progression after first-line therapy. It will be interesting to see whether this CR rate translates to a change in the natural history of the disease. Future extensive correlative analyses should help define which patients will benefit.

DR LOVE: What do we know about obinutuzumab compared to rituximab up front for FL?

DR FRIEDBERG: Obinutuzumab is a novel CD20 antibody that’s approved for chronic lymphocytic leukemia (CLL). Combined with chlorambucil, it was shown to be better than chlorambucil/rituximab in the CLL11 trial and was recently approved for relapsed FL based on a trial for patients with rituximab-refractory disease.

In addition, the large Phase III GALLIUM trial is evaluating obinutuzumab with standard chemotherapy followed by obinutuzumab alone versus rituximab with standard chemotherapy followed by rituximab alone. A recent press release announced that the trial has been stopped because of a positive result, and I believe we’ll see the data at ASH. It will be important to understand the magnitude of benefit. Replacing rituximab with obinutuzumab would be a significant change.
CD 1, Tracks 6-9

DR LOVE: Would you discuss the available data with Bruton tyrosine kinase (BTK) inhibitors beyond ibrutinib in CLL?

DR FRIEDBERG: It may be a challenge for other BTK inhibitors to demonstrate superiority compared to ibrutinib in CLL. If you treat even high-risk CLL with ibrutinib, the majority of patients experience a response. It’s difficult to imagine the newer agents being better. I do see potential for patients with ibrutinib-refractory disease — can we overcome the resistance mechanism of the BTK binding site?

The other issue with ibrutinib is the risk of bleeding. Many of these patients are receiving anticoagulation medication for atrial fibrillation, and we are all nervous about administering ibrutinib in that case. If a drug clearly showed a lesser propensity for bleeding, it could become important.

Aside from ibrutinib, the BTK inhibitor furthest along in development is acalabrutinib. Data were published in The New England Journal of Medicine not long ago demonstrating its efficacy, and the early data also suggest a low risk of atrial fibrillation (Byrd 2016; [1.1]).

Many of us didn’t appreciate the atrial fibrillation risk with ibrutinib until after it was approved and used more widely. Although we must be careful comparing acalabrutinib to ibrutinib on the basis of a narrow clinical trial rather than real-world experience, the risk of atrial fibrillation with ibrutinib is in the range of 5% to 10%. It’s clearly a concern, but the majority of patients to whom I’ve administered ibrutinib have received it for a long time without that type of complication.

DR LOVE: How would you incorporate the newly FDA-approved Bcl-2 inhibitor venetoclax into the clinical treatment algorithm for patients with CLL?

DR FRIEDBERG: Venetoclax is approved for patients with 17p-deleted CLL that has already been treated with ibrutinib. The efficacy is outstanding, and some investigators believe it may be superior to ibrutinib in this subset of patients (Stilgenbauer 2015; [1.2]). Whether it becomes more widely used remains to be seen — the risk of tumor lysis syndrome makes it cumbersome because sometimes admission to the hospital is required.

DR LOVE: How do you approach choice of first-line therapy for CLL in your practice (Cramer 2016)?

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

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

- Most common Grade 1 and 2 adverse events: Headache, diarrhea, weight gain
- No cases of major bleeding or atrial fibrillation at 14.3 months follow-up

DR FRIEDBERG: For younger patients who I believe are capable of receiving it, fludarabine/cyclophosphamide/rituximab (FCR) remains a standard. But for older or frailer patients for whom I’m worried about toxicity — and that’s the majority of these patients because CLL is a disease of older people — I consider ibrutinib rather than BR as front-line therapy.

DR LOVE: People are also discussing the use of FCR as a way to launch patients into an unmaintained remission that might last for years, but isn’t that also a possibility with BR and even obinutuzumab/chlorambucil?

DR FRIEDBERG: The durability of response with obinutuzumab/chlorambucil is much shorter than that reported with FCR. A subset of patients who receive BR fare well — in a randomized trial comparing BR to FCR the progression-free survival (PFS) rates were good on both arms, although it appeared that FCR won out, albeit with more toxicity, especially among patients aged 60 to 62 years (Eichhorst 2014). For younger patients I believe the current consensus based on randomized trials is that if you want to use a chemoimmunotherapy platform to achieve a prolonged PFS, the FCR regimen does that.

### SELECT PUBLICATIONS


Eichhorst B et al. Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): Final analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 Study). *Proc ASH* 2014;Abstract 19.

Evens AM et al. Effect of bortezomib on complete remission (CR) rate when added to bendamustine-rituximab (BR) in previously untreated high-risk (HR) follicular lymphoma (FL): A randomized phase II trial of the ECOG-ACRIN Cancer Research Group (E2408). *Proc ASCO* 2016;Abstract 7507.


## 1.2 Venetoclax Monotherapy for Relapsed/Refractory Chronic Lymphocytic Leukemia with Del(17p)

<table>
<thead>
<tr>
<th>Response (assessed by independent review committee)</th>
<th>n = 107</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall response rate</strong></td>
<td>79.4%</td>
</tr>
<tr>
<td>Complete response (CR) or CR with incomplete bone marrow recovery</td>
<td>7.5%</td>
</tr>
<tr>
<td>Nodular partial remission/partial remission</td>
<td>72%</td>
</tr>
<tr>
<td><strong>Survival rate (12 months)</strong></td>
<td></td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>72%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>86.7%</td>
</tr>
</tbody>
</table>

- Risk of tumor lysis syndrome (TLS) effectively mitigated with no clinical TLS
- Incidences of neutropenia (43%) and infection Grade ≥3 (205) similar to those with front-line chemotherapy

CD 1, Tracks 12-23 — CD 2, Tracks 1-2

CD 1

Track 12 Novel agents under investigation for FLT3-mutated acute myeloid leukemia (AML)

Track 13 Activity and tolerability of venetoclax alone or in combination with a hypomethylating agent in patients with AML or myelodysplastic syndromes (MDS)

Track 14 Comparison of FLT3 inhibitors midostaurin, quizartinib, gilteritinib and sorafenib in AML

Track 15 Promising investigational agents and strategies in AML

Track 16 Activity of the bispecific T-cell engager blinatumomab in Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia (ALL)

Track 17 INO-VATE: Results of a Phase III trial of the anti-CD22 antibody-drug conjugate inotuzumab ozogamicin versus standard therapy for relapsed/refractory ALL

Track 18 Role of chimeric antigen receptor T-cell therapy in the treatment of relapsed/refractory ALL

Track 19 Monitoring response to TKI therapy for patients with chronic myeloid leukemia (CML) and considerations for discontinuing treatment

Track 20 Choice of first-line TKI therapy for CML and role of generic imatinib

Track 21 Efficacy and long-term outcomes of ruxolitinib in myelofibrosis and polycythemia vera

Track 22 Novel JAK inhibitors under investigation for patients with myeloproliferative neoplasms

Track 23 Activity and ongoing investigation of immune checkpoint inhibitors in acute leukemias

CD 2

Track 1 Role of first- and second-generation hypomethylating agents in MDS

Track 2 Management of MDS and outcomes for patients who experience disease progression with a first-line hypomethylating agent

Select Excerpts from the Interview

DR LOVE: Would you discuss current investigation of novel targeted agents for FLT3-mutated acute myeloid leukemia (AML)?

DR KANTARJIAN: FLT3 abnormalities occur in 20% to 30% of patients with AML. During the past 10 years we have tested several FLT3 inhibitors, and now those results are coming to fruition. The randomized Phase III RATIFY trial in front-line FLT3-positive AML was reported at ASH. Patients were randomly assigned to standard 3 + 7 chemotherapy with or without the FLT3 inhibitor midostaurin. A statistically significant improvement in median overall survival was demonstrated among the
patients who received midostaurin, which established the role of FLT3 inhibitors, and we are hoping that midostaurin will be approved soon in this setting (Stone 2015).

One question is whether patients with FLT3 wild-type disease would also benefit from FLT3 inhibitors, because on this study a benefit was evident for patients with FLT3 point mutations, who were not expected to benefit. Crenolanib has the capacity for targeting FLT3 point mutations, so it could expand the role of these agents as they are studied.

Sorafenib, one of the most potent FLT3 inhibitors, is already approved for other indications. The SORAML trial evaluated the addition of sorafenib to standard chemotherapy and demonstrated a significant improvement in event-free survival. No benefit was evident in overall survival because many more patients underwent allogeneic stem cell transplant on the standard-chemotherapy arm (Röllig 2015). However, most of the data suggest that FLT3 inhibitors will become standard therapy.

DR LOVE: What is new and promising in the treatment of myelodysplastic syndromes (MDS)?

DR KANTARJIAN: A couple of areas are promising in MDS, the first being the role of the oral hypomethylating agents, such as oral decitabine and oral azacitidine. They seem to be quite promising and at least as effective as the subcutaneous and IV formulations.

The second area of interest is the development of the second-generation hypomethylating agents. SGI-110, or guadecitabine, which is made up of guanosine and decitabine, might be a positive development in the treatment of MDS. We are proposing studies combining guadecitabine with venetoclax, checkpoint inhibitors, vosaroxin and other agents.

DR LOVE: How do you choose between the hypomethylating agents, and what schedule do you prefer?

DR KANTARJIAN: I believe the 2 hypomethylating agents are equivalent. Azacitidine is administered subcutaneously for 7 days, although one approach of interest is to administer a lower dose for only 4 days, earlier in the course of the disease. Decitabine, which is administered intravenously for 5 days, might be safe and effective when administered for only 3 days. I believe more of these lower doses of the epigenetic therapies will be used in the earlier phases of MDS.

CD 1, Tracks 16-18

DR LOVE: Any thoughts on the current treatment of acute lymphoblastic leukemia (ALL)?

DR KANTARJIAN: We are witnessing a revolution in adult ALL in 2 areas — monoclonal antibodies that target CD19 and CD22, and chimeric antigen receptor (CAR) T cells. Blinatumomab, a bispecific monoclonal antibody, has yielded marrow CR rates of 40% to 50%. At the 2016 EHA meeting a randomized study was presented that evaluated blinatumomab versus chemotherapy as salvage treatment for ALL and demonstrated a median survival advantage of 7.8 months with blinatumomab versus 4 months with chemotherapy (Topp 2016, [2.1]). I believe this will be an important agent in the treatment of ALL.
Data on inotuzumab ozogamicin, another monoclonal antibody, were also presented at the EHA meeting in Europe when we reported on the Phase III INO-VATE ALL study comparing inotuzumab to standard chemotherapy for relapsed/refractory disease (Kantarjian 2016; [2.2]). These data demonstrated a 2-year survival rate of 23% with inotuzumab and 10% with chemotherapy. This is a modest improvement, but I believe...
that the monoclonal antibodies will continue to be studied in the form of combination therapies for patients with ALL.

In addition, the use of CAR T-cell therapies has generated a lot of excitement. Currently, CAR T cells are all autologous — you take the lymphocytes from the patient, expand them and administer them back to the patient. However, now some companies are evaluating off-the-shelf allogeneic CAR T cells. So in the same way you order blood transfusions and platelet transfusions, in the future we could be ordering CAR T cells, and it would be a major breakthrough if they turned out to be as active as the autologous CAR T cells. Today CAR T cells are used in the salvage setting in ALL. If we cannot cure all or most patients with chemotherapy and monoclonal antibodies, perhaps the addition of CAR T cells at the end of therapy could accomplish this. They are associated with many toxicities, but in the future they could be used in the front-line setting.

CD 1, Tracks 19-20

DR LOVE: Would you discuss the issue of discontinuing tyrosine kinase inhibitor (TKI) therapy for patients with chronic myeloid leukemia (CML)?

DR KANTARJIAN: I have no doubt that a subset of patients with CML become PCR-negative for durable periods — more than 2 to 3 years — and if you stop therapy, half of these patients will not experience disease recurrence. They are molecularly cured. The question is, do some TKIs induce a higher rate of durable complete molecular cures? And if so, should we be using them rather than generic imatinib, which is an outstanding agent that we hope will be much less expensive?

Generic imatinib is a safe and highly effective BCR-ABL inhibitor for patients with lower-risk CML and patients older than age 60, who could receive it for 10 to 20 years. I believe this agent will play a major role in front-line therapy. However, younger patients or patients with higher-risk CML might benefit from front-line second-generation TKIs in terms of both the potential rate of durable complete molecular response and the chance of discontinuing the treatment to avoid long-term side effects. Receiving treatment for the next 30 to 40 years would bring with it the potential for atherosclerosis, accelerated aging, vaso-occlusive disease and kidney problems.

In addition, my approach is driven by the issue of cost. The prices of the second-generation TKIs continue to increase. That said, these agents are producing a higher incidence of durable complete molecular response, so the second-generation TKIs do bring an advantage if the goal of therapy is durable complete molecular response that results in the discontinuation of therapy. However, you have to spend a lot of money to be able to achieve this.

SELECT PUBLICATIONS


Stone RM et al. The multi-kinase inhibitor midostaurin (M) prolongs survival compared with placebo (P) in combination with daunorubicin (D)/cytarabine (C) induction (ind), high-dose C consolidation (consol), and as maintenance (maint) therapy in newly diagnosed acute myeloid leukemia (AML) patients (pts) age 18–60 with FLT3 mutations (muts): An international prospective randomized (rand) P-controlled double-blind trial (CALGB 10603/RATIFY [Alliance]). Proc ASH 2015;Abstract 6.


**INTRODUCTION**

**S Vincent Rajkumar, MD**

Dr Rajkumar is Edward W and Betty Knight Scripps Professor of Medicine in the Division of Hematology and Chair of the Myeloma Amyloidosis Dysproteinemia Group at the Mayo Clinic in Rochester, Minnesota.

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**CD 2, Tracks 3-17**

**Track 3** Choosing the optimal induction regimen for a patient with multiple myeloma (MM)

**Track 4** Early versus delayed autologous transplant after induction therapy for MM

**Track 5** Importance of minimal residual disease assessment in MM

**Track 6** Role of proteasome inhibitors as part of post-transplant maintenance therapy

**Track 7** Treatment options for patients with disease that is refractory to agents typically used as maintenance therapy

**Track 8** Dosing of carfilzomib for patients with MM

**Track 9** Case discussion: A 72-year-old patient with previously treated MM who achieved a minimal response to pomalidomide/dexamethasone receives daratumumab

**Track 10** Selecting from the recently FDA-approved therapeutic options for relapsed/refractory MM

**Track 11** Phase III study results with daratumumab in combination with lenalidomide/dexamethasone (POLUX) or with bortezomib/dexamethasone (CASTOR) for relapsed/refractory MM

**Track 12** Daratumumab-associated infusion reactions

**Track 13** Incorporation of daratumumab into the therapeutic algorithm for MM

**Track 14** Use of panobinostat for relapsed/refractory MM

**Track 15** Case discussion: A 75-year-old patient with MM initially treated with 3 years of lenalidomide/dexamethasone (Rd) who experienced disease relapse while off active therapy now receives elotuzumab/lenalidomide

**Track 16** Case discussion: A 69-year-old patient with previously treated t(4;14) MM receives Rd with ixazomib

**Track 17** Incorporation of ibrutinib into the therapeutic algorithm for Waldenström macroglobulinemia

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**Select Excerpts from the Interview**

**CD 2, Tracks 3-4, 6-7**

▶ **DR LOVE:** What is your perspective on the optimal up-front induction treatment for patients with multiple myeloma (MM)?

▶ **DR RAJKUMAR:** Physicians in the United States have access to a wide variety of regimens to treat newly diagnosed disease, but at ASH 2015 we heard a report on the Phase III SWOG-S0777 trial, which demonstrated that bortezomib/lenalidomide/dexamethasone (RVd) yielded not only better response rates and PFS but also significantly better overall survival in comparison to lenalidomide/dexamethasone (Durie 2015; [3.1]). These are the best data we have. We have all switched to RVd as standard
front-line therapy for elderly patients and patients who are eligible for autologous stem cell transplant (ASCT).

For patients with high-risk disease I believe RVd would still be a great choice, but some of us are starting to consider carfilzomib/lenalidomide/dexamethasone (KRd) instead. Bortezomib can be difficult to administer to elderly patients who have multiple comorbidities and poor performance status, in which case lenalidomide/dexamethasone alone is a reasonable alternative. If you do use lenalidomide/dexamethasone alone, however, you must administer it until disease progression.

I am reluctant to recommend KRd for standard-risk disease, with which patients traditionally fare well, because KRd has not been compared directly to RVd in a randomized trial. Such a trial is ongoing, and in nonrandomized comparisons KRd seems to yield better CR rates and minimal residual disease negativity. However, it can cause more toxicity and raises concerns about cardiac side effects. I believe that with high-risk disease, those chances are worth taking.

The other big news at ASH was from the IFM/DFCI 2009 trial, which evaluated RVd followed by either continued RVd or early transplant (Attal 2015). That trial demonstrated a 3-year postrandomization PFS rate of 61% on the early-transplant arm versus 48% on the RVd arm.

We also discovered that whether transplant is early or delayed, the outcomes are excellent. The 3-year postrandomization overall survival rate was extremely high at 88% and similar between the 2 study groups, which is outstanding in newly diagnosed MM. The survival results may be too early to interpret, but it appears that we still need to incorporate transplantation into our treatment strategy.

DR LOVE: What are your thoughts on the use of ixazomib as opposed to bortezomib? When do you consider using it in maintenance therapy?

<table>
<thead>
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<th></th>
<th>RVd (n = 242)</th>
<th>Rd (n = 232)</th>
<th>Hazard ratio</th>
<th>p-value</th>
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<tr>
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<td>43 mo</td>
<td>30 mo</td>
<td>0.712</td>
<td>0.0018</td>
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<tr>
<td>Median overall survival</td>
<td>75 mo</td>
<td>64 mo</td>
<td>0.709</td>
<td>0.0250</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>81.5%</td>
<td>71.5%</td>
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<thead>
<tr>
<th>Select Grade ≥3 adverse events</th>
<th>RVd</th>
<th>Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory neuropathy</td>
<td>23%</td>
<td>3%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>23%</td>
<td>18%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19%</td>
<td>21%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18%</td>
<td>14%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16%</td>
<td>14%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7%</td>
<td>11%</td>
</tr>
</tbody>
</table>

PFS = progression-free survival

DR RAJKUMAR: If it’s difficult for a patient to receive bortezomib, I’m comfortable with administering ixazomib, with a couple of caveats. One is the huge cost. When generic bortezomib becomes available next year, it will be much less expensive than ixazomib, and it is more tried and tested than ixazomib. However, ixazomib is a once-weekly oral therapy, which is convenient. A Phase III randomized trial is comparing ixazomib to placebo as maintenance therapy, and the results should be available soon — I would rather wait. If exceptions exist, such as a patient who is truly not able to take bortezomib and the alternative is not receiving maintenance therapy at all, then yes, we should certainly consider ixazomib in that setting.

A meta-analysis at ASCO demonstrated a survival benefit with pooled data from 3 randomized trials of maintenance lenalidomide, so our group believes that we should offer routine maintenance (McCarthy 2016).

DR LOVE: Would you discuss the results recently presented on the use of daratumumab-based therapies for relapsed/refractory MM?

DR RAJKUMAR: At the EHA meeting, Dr Dimopoulos presented the results of the POLLUX trial, which compared lenalidomide/dexamethasone to daratumumab/lenalidomide/dexamethasone. The hazard ratio for PFS was 0.37, which is the best we have seen in relapsed disease (Dimopoulos 2016; [3.2]). The other triplet therapies we have available — elotuzumab/lenalidomide/dexamethasone versus lenalidomide/dexamethasone, carfilzomib/lenalidomide/dexamethasone versus lenalidomide/dexamethasone and ixazomib/lenalidomide/dexamethasone versus lenalidomide/dexamethasone — all have hazard ratios of 0.7 to 0.75.

Daratumumab was also relatively well tolerated on this study. If I had to choose, I would probably go with daratumumab/lenalidomide/dexamethasone at first relapse. I would not use daratumumab as a single agent because that results in a PFS of only 4 months.

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>DRd (n = 286)</th>
<th>Rd (n = 283)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>NR</td>
<td>18.4 mo</td>
<td>0.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>93%</td>
<td>76%</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VGPR or better</td>
<td>76%</td>
<td>44%</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Complete response or better</td>
<td>43%</td>
<td>19%</td>
<td>—</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median DoR</td>
<td>NR</td>
<td>17.4 mo</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Select Grade 3 or 4 adverse events</td>
<td>DRd</td>
<td>Rd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52%</td>
<td>37%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13%</td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>12%</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PFS = progression-free survival; NR = not reached; VGPR = very good partial response; DoR = duration of response

A plenary presentation at ASCO of the CASTOR study evaluating bortezomib/dexamethasone versus daratumumab/bortezomib/dexamethasone also demonstrated an astounding hazard ratio of 0.39 (Palumbo 2016a; [3.3]). The absolute benefit was not as striking as the benefit observed in the POLLUX trial, but I believe a synergistic effect might occur with daratumumab/lenalidomide.

### 3.3 Results of the Phase III CASTOR Study of Daratumumab, Bortezomib and Dexamethasone (DVd) Compared to Vd for Relapsed or Refractory Multiple Myeloma

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>DVd (n = 251)</th>
<th>Vd (n = 247)</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>NR</td>
<td>7.2 mo</td>
<td>0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to progression</td>
<td>NR</td>
<td>7.3 mo</td>
<td>0.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>82.9%</td>
<td>63.2%</td>
<td>—</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Select Grade 3 or 4 adverse events**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>DVd (n = 243)</th>
<th>Vd (n = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>45.3%</td>
<td>32.9%</td>
</tr>
<tr>
<td>Anemia</td>
<td>14.4%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12.8%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8.2%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.6%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>4.5%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4.5%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.7%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3.7%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1.6%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>0.8%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

PFS = progression-free survival; NR = not reached


### SELECT PUBLICATIONS


Dimopoulos M et al. *An open-label, randomised Phase 3 study of daratumumab, lenalidomide, and dexamethasone (DRd) versus lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM): POLLUX.* *Proc EHA* 2016; Abstract LB2238.

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.

McCarthy P et al. *Lenalidomide (LEN) maintenance (MNTC) after high-dose melphalan and autologous stem cell transplant (ASCT) in multiple myeloma (MM): A meta-analysis (MA) of overall survival (OS).* *Proc ASCO* 2016; Abstract 8001.


Palumbo A et al. *Phase III randomized controlled study of daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study.* *Proc ASCO* 2016b; Abstract LBA4.
Dr Armand holds the Harold and Virginia Lash Chair in Lymphoma Research in the Department of Medical Oncology at Dana-Farber Cancer Institute and is Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Select Excerpts from the Interview

**CD 2, Tracks 18, 21 and 24**

**DR LOVE:** Would you comment on the biological basis for the activity of checkpoint inhibitors in Hodgkin lymphoma (HL) and also discuss the available data with nivolumab compared to those with pembrolizumab?

**DR ARMAND:** Classical HL almost always has a genetic deregulation on the short arm of chromosome 9, and the targets of that deregulation event are the PD-1 ligands, PD-L1 and PD-L2. It’s a unique story of biology driving responses, so we have a strong reason to believe that HL might be uniquely susceptible to PD-1 blockade.

Nivolumab and pembrolizumab have been neck and neck, although the development of nivolumab for classical HL preceded that of pembrolizumab. The Phase I data with nivolumab came out a little earlier, and thus we know more about the durability of responses to it. In addition, the patient populations are slightly different in the Phase II trials evaluating these 2 agents. The CheckMate 205 trial of nivolumab included 3 cohorts of patients who had previously undergone ASCT, which differs from the KEYNOTE-087 trial of pembrolizumab, which contains a cohort of patients who were transplant ineligible.
The results from the CheckMate 205 and CA209-039 trials led to the recent FDA approval of nivolumab for patients with classical HL and disease progression after ASCT and brentuximab vedotin (4.1).

The Phase II KEYNOTE-087 study, which was presented at ASCO 2016, showed response rates with pembrolizumab in the range of 70% to 80% for patients with disease that progressed after ASCT and/or brentuximab vedotin (Chen 2016; [4.2]). These results, along with the results of the Phase Ib KEYNOTE-013 study (Armand 2016), led to the FDA breakthrough therapy designation for pembrolizumab in classical HL.

As I mentioned, the KEYNOTE-087 trial also included a cohort of transplant-ineligible patients, and the results indicated that pembrolizumab seems to be as effective in this population as in the post-transplant population. I imagine similar types of approval will be granted, although the labels could be slightly different because of the differences between patient populations on the trials.

» **DR LOVE:** How would you like to use nivolumab now that it is approved for relapsed/refractory HL?

» **DR ARMAND:** It would be nice to use the agent according to the label because otherwise we have little to offer patients in that setting. It is by far the best therapeutic option we have currently, the only drug that rivals nivolumab in HL being brentuximab vedotin, which these patients have already received.

However, nivolumab represents a powerful new therapeutic strategy that we want to use to cure the disease, not necessarily to administer to patients whose disease has

---

### 4.1 Efficacy and Safety of Nivolumab for Relapsed/Refractory Classical Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Phase I CA209-039 study¹ (n = 23)</th>
<th>Phase II CheckMate 205 study² (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>87%</td>
<td>66%</td>
</tr>
<tr>
<td>Complete response</td>
<td>22%</td>
<td>9%</td>
</tr>
<tr>
<td>Partial response</td>
<td>65%</td>
<td>58%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>Not reached</td>
<td>10 mo</td>
</tr>
<tr>
<td>Overall survival rate</td>
<td>83% (1.5 y)</td>
<td>99% (6 mo)</td>
</tr>
<tr>
<td>Select adverse events (any grade)</td>
<td>n = 23</td>
<td>n = 80</td>
</tr>
<tr>
<td>Fatigue</td>
<td>NR</td>
<td>25%</td>
</tr>
<tr>
<td>Skin related</td>
<td>22%</td>
<td>16%</td>
</tr>
<tr>
<td>Hepatic</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Hypersensitivity/infusion reactions</td>
<td>9%</td>
<td>21%</td>
</tr>
</tbody>
</table>

PFS = progression-free survival; NR = not reported

already progressed on everything else. So now a whole slew of studies are starting to investigate PD-1 blockade in the first-line salvage setting. We are also conducting a study of PD-1 blockade after ASCT. All the previous steps at which one could potentially position this kind of treatment are being explored.

**DR LOVE:** Have you tried to access nivolumab for a patient who has not undergone ASCT?

**DR ARMAND:** We’ve had the good fortune to participate in various clinical trials, so we haven’t run up against not being able to obtain access to nivolumab, but we have used it off label in other settings, such as mediastinal lymphoma, and we also used PD-1 blockade off label prior to its FDA approval.

Another setting of interest is after allogeneic stem cell transplant, which is certainly off label. Some of the results in that setting have been publicly reported in case series, and this is another desperate situation in which people have had success obtaining access to both nivolumab and pembrolizumab.

### SELECT PUBLICATIONS

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


1. A Phase II study by Stilgenbauer and colleagues evaluating venetoclax monotherapy for patients with relapsed/refractory del(17p) CLL demonstrated an overall response rate of approximately 80% but a high incidence of clinical tumor lysis syndrome.
   a. True
   b. False

2. 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

3. The ongoing Phase III GALLIUM trial is evaluating ___________ with chemotherapy versus rituximab/chemotherapy followed by maintenance therapy with ___________ or rituximab in patients with previously untreated FL.
   a. Bortezomib
   b. Ibritumomab tiuxetan
   c. Obinutuzumab

4. On the Phase II SORAML trial, the sequential addition of sorafenib to standard chemotherapy for younger patients with newly diagnosed AML resulted in a statistically significant improvement in ___________ versus standard chemotherapy and placebo.
   a. Event-free survival
   b. Overall survival
   c. Both a and b
   d. Neither a nor b

5. The Phase III RATIFY (CALGB-10603) trial for patients with newly diagnosed FLT3-mutated AML _________ a statistically significant improvement in median overall survival with midostaurin in combination with standard induction and consolidation chemotherapy compared to standard induction and consolidation chemotherapy alone.
   a. Demonstrated
   b. Did not demonstrate

6. The Phase III randomized INO-VATE study comparing inotuzumab ozogamicin to standard chemotherapy for relapsed/refractory ALL demonstrated a 2-year survival rate of _________ with inotuzumab and 10% with chemotherapy.
   a. 5%
   b. 23%
   c. 50%

7. The SWOG-S0777 trial evaluating RVd versus Rd for patients with previously untreated MM without an intent for immediate ASCT demonstrated _________ with RVd.
   a. A significant improvement in PFS
   b. No improvement in PFS

8. The Phase III randomized CASTOR study evaluating daratumumab/bortezomib/dexamethasone versus bortezomib/dexamethasone did not demonstrate a significant improvement in PFS with the addition of daratumumab for patients with relapsed or refractory MM.
   a. True
   b. False

9. The Phase II CheckMate 205 study evaluating the efficacy of nivolumab for relapsed/refractory classical HL demonstrated a 6-month overall survival rate of approximately _________.
   a. 50%
   b. 75%
   c. 100%

10. Which of the following is the FDA-approved indication for nivolumab in classical HL?
    a. Previously untreated classical HL
    b. Classical HL after failure of at least 2 prior multiagent chemotherapy regimens in patients who are not candidates for autologous hematopoietic stem cell transplantation
    c. Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplant and post-transplant brentuximab vedotin
    d. Nivolumab is not FDA approved for the treatment of classical HL
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 Description</th>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial results of the Phase II ECOG-E2408 trial: Bendamustine/rituximab with or without bortezomib for previously untreated high-risk FL</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Activity of novel agents under investigation for FLT3-ITD-mutated AML (ie, sorafenib, midostaurin, quizartinib, gilteritinib)</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Efficacy and tolerability of approved (blinatumomab) and promising novel (inotuzumab ozogamicin) monoclonal antibodies for the treatment of ALL</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Results of Phase III studies of daratumumab in combination with lenalidomide/dexamethasone (POLLUX) or with bortezomib/dexamethasone (CASTOR) for relapsed/refractory MM</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Integration of nivolumab into the clinical algorithm for advanced HL</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

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 Description</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>
</tr>
</thead>
<tbody>
<tr>
<td>Consider available clinical research reports on the formulation of therapeutic recommendations for patients with newly diagnosed and relapsed/refractory follicular and diffuse large B-cell lymphoma.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appreciate the FDA approvals of novel targeted agents — ibrutinib, obinutuzumab and venetoclax — for the treatment of newly diagnosed and relapsed/refractory chronic lymphocytic leukemia, and discern how these therapies can be appropriately integrated into the clinical management of standard- and high-risk disease.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reevaluate current treatment approaches for patients with myeloproliferative disorders and acute and chronic leukemias in light of newly emerging clinical data.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<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.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incorporate new therapeutic strategies into the best-practice management of newly diagnosed and relapsed/refractory Hodgkin lymphoma.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess the benefits of ongoing clinical trials for patients with hematologic cancers, and inform appropriately selected patients about these options for treatment.</td>
<td>4 3 2 1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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: .........................................................................................................................

Additional comments about this activity:

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>Jonathan W Friedberg, MD, MMSc</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Hagop M Kantarjian, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>S Vincent Rajkumar, MD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
<tr>
<td>Philippe Armand, MD, PhD</td>
<td>4 3 2 1</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

Editor

<table>
<thead>
<tr>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neil Love, MD</td>
<td>4 3 2 1</td>
</tr>
</tbody>
</table>

Please recommend additional faculty for future activities:

Other comments about the faculty and editor for this activity:

REQUEST FOR CREDIT — Please print clearly

Name: ................................................................................. Specialty: ............................................................

Professional Designation:  ☐ MD  ☐ DO  ☐ PharmD  ☐ NP  ☐ RN  ☐ PA  ☐ Other............................................................

Street Address: ................................................................................................................................. Box/Suite: .................................................................................................................................

City, State, Zip: ........................................................................................................................................

Telephone: ................................................................................................................................. Fax: ........................................................................................................................................

Email: ........................................................................................................................................................

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Signature: ................................................................................................................................. Date: .................................................................................................................................

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Additional information for MOC credit (required):

Date of Birth (Month and Day Only): ___ / ___  ABIM 6-Digit ID Number: ........................................

If you are not sure of your ABIM ID, please visit http://www.abim.org/online/findcand.aspx.

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