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Hematologic Oncology™ UPDATE

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 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 discern 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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FACULTY — **Dr Rajkumar** had no relevant conflicts of interest to disclose. The following faculty (and their spouses/partners) reported relevant conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Friedberg** — Consulting Agreement and Data and Safety Monitoring Board: Bayer HealthCare Pharmaceuticals. **Dr Kantarjian** — Contracted Research: Amgen Inc, Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation. **Dr Armand** — Consulting Agreements: Bristol-Myers Squibb Company, Merck.

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INTERVIEW

Jonathan W Friedberg, MD, MMSc

Dr Friedberg is Samuel E Durand Professor of Medicine and Director of the James P Wilmot Cancer Institute at the University of Rochester in Rochester, New York.

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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)

Track 3 Preliminary results of the Phase III GALLIUM trial: Progression-free survival benefit with obinutuzumab and chemotherapy compared to rituximab and chemotherapy → obinutuzumab or rituximab maintenance for previously untreated FL

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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 R^2 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 subcutanous 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

	Overall response rate	Partial response (PR) rate	PR with lymphocytosis
All evaluable patients (n = 60)	95%	85%	10%
Del(17p13.1) (n = 18)	100%	89%	11%
Prior idelalisib (n = 4)	100%	75%	25%

- 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

Byrd JC et al. *N Engl J Med* 2016;374(4):323-32.

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. ■

1.2

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

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

- 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

Stilgenbauer S et al. *Proc ASH* 2015;**Abstract LBA-6**.

SELECT PUBLICATIONS

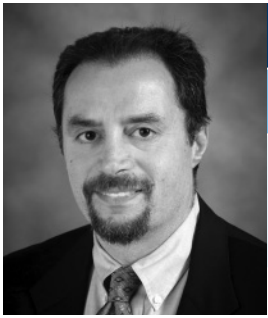
Cramer P et al. **Advances in first-line treatment of chronic lymphocytic leukemia: Current recommendations on management and first-line treatment by the German CLL Study Group (GCLLSG).** *Eur J Haematol* 2016;96(1):9-18.

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**.

Friedberg JW et al. **The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma.** *Blood* 2011;117(10):2807-12.

Rubenstein JL et al. **Phase I investigation of lenalidomide plus rituximab and outcomes of lenalidomide maintenance in recurrent CNS lymphoma.** *Proc ASCO* 2016;**Abstract 7502**.



INTERVIEW

Hagop M Kantarjian, MD

Dr Kantarjian is Chairman and Professor in the Leukemia Department at The University of Texas MD Anderson Cancer Center in Houston, Texas.

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CD 1

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

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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

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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.

2.1

TOWER: Results of a Phase III Study of Blinatumomab for Patients with Relapsed or Refractory Philadelphia Chromosome-Negative B-Cell Precursor Acute Lymphoblastic Leukemia

Efficacy	Blinatumomab (n = 271)	Chemotherapy (n = 134)	Hazard ratio	*p*-value
Median overall survival	7.7 months	4.0 months	0.71	0.011
Complete remission (CR) rate	39%	19%	—	<0.001
CR/CRh/CRi	46%	28%	—	0.001

Select adverse events (Grade ≥3)	Blinatumomab (n = 267)	Chemotherapy (n = 109)
Infection	34%	52%
Neutropenia	38%	58%
Nervous system events	9%	8%
Cytokine release syndrome	5%	0%

CRh = CR with partial hematologic recovery; CRi = CR with incomplete hematologic recovery

Topp M et al. *Proc EHA* 2016;**Abstract S149**.

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

2.2

INO-VATE ALL: Results of a Phase III Study of Inotuzumab Ozogamicin versus Standard Therapy for Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia

Survival analysis	Inotuzumab (n = 164)	Standard therapy* (n = 162)	Hazard ratio	*p*-value
Median overall survival (OS)	7.7 months	6.7 months	0.77	0.04
2-year OS rate	23%	10%		
Median progression-free survival	5.0 months	1.8 months	0.45	<0.001

Remission (primary ITT analysis)	(n = 109)	(n = 109)	*p*-value
Complete remission rate	80.7%	29.4%	<0.001
Below minimal residual disease threshold	78.4%	28.1%	<0.001
Median duration of remission	4.6 months	3.1 months	0.03

Select Grade ≥3 adverse events	Inotuzumab (n = 139)	Standard therapy (n = 120)
Febrile neutropenia	12%	18%
Veno-occlusive disease	11%	1%
Sepsis	2%	5%
Pneumonia	4%	0%
Pyrexia	1%	1%

ITT = intent to treat; * Investigator's choice of FLAG (fludarabine, cytarabine and granulocyte colony-stimulating factor), cytarabine with mitoxantrone or high-dose cytarabine

Kantarjian HM et al. *N Engl J Med* 2016;375(8):740–53.

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

Röllig C et al. **Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukemia (SORAML): A multicentre, phase 2, randomised controlled trial.** *Lancet Oncol* 2015;16(16):1691-9.

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**.

INTERVIEW

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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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 (POLLUX) 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

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

3.1

SWOG-S0777 Trial: Bortezomib/Lenalidomide/Dexamethasone (RVd) versus Rd for Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant

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

PFS = progression-free survival

Durie B et al. *Proc ASH* 2015;**Abstract 25**.

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?

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).

CD 2, Track 11

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.

3.2

POLLUX: Results of a Phase III Study of Daratumumab, Lenalidomide and Dexamethasone (DRd) Compared to Rd for Relapsed or Refractory Multiple Myeloma

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

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

Dimopoulos M et al. *Proc EHA* 2016;**Abstract LB2238**.

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

Efficacy	DVd (n = 251)	Vd (n = 247)	Hazard ratio	*p*-value
Median PFS	NR	7.2 mo	0.39	<0.001
Median time to progression	NR	7.3 mo	0.30	<0.001
Overall response rate	82.9%	63.2%	—	<0.001
Select Grade 3 or 4 adverse events	**DVd** (n = 243)		**Vd** (n = 237)	
Thrombocytopenia	45.3%		32.9%	
Anemia	14.4%		16.0%	
Neutropenia	12.8%		4.2%	
Pneumonia	8.2%		9.7%	
Hypertension	6.6%		0.8%	
Peripheral sensory neuropathy	4.5%		6.8%	
Fatigue	4.5%		3.4%	
Diarrhea	3.7%		1.3%	
Dyspnea	3.7%		0.8%	
Upper respiratory tract infection	1.6%		0.8%	
Asthenia	0.8%		2.1%	

PFS = progression-free survival; NR = not reached

Palumbo A et al. *N Engl J Med* 2016a;375(8):754-66.

SELECT PUBLICATIONS

Afifi S et al. **Immunotherapy: A new approach to treating multiple myeloma with daratumumab and elotuzumab.** *Ann Pharmacother* 2016;50(7):555-68.

Attal M et al. **Autologous transplantation for multiple myeloma in the era of new drugs: A phase III study of the Intergroupe Francophone du Myelome (IFM/DFCI 2009 trial).** *Proc ASH* 2015;**Abstract 391**.

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. **Daratumumab, bortezomib, and dexamethasone for multiple myeloma.** *N Engl J Med* 2016a;375(8):754-66.

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**.

INTERVIEW

Philippe Armand, MD, PhD

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.

CD 2, Tracks 18-28

Track 18 Activity of immune checkpoint inhibitors in relapsed/refractory Hodgkin lymphoma (HL)

Track 19 Evaluation of checkpoint inhibitor-based combination regimens for hematologic and solid cancers

Track 20 Predicting response to anti-PD-1 antibodies in patients with advanced HL

Track 21 Activity of nivolumab and pembrolizumab in advanced HL

Track 22 Investigating PD-L1 blockade in HL

Track 23 Consideration of immune checkpoint blockade for patients with advanced HL and prior autoimmune disease

Track 24 Integration of nivolumab into the clinical algorithm for advanced HL

Track 25 Perspective on the use of brentuximab vedotin in clinical practice

Track 26 Clinical experience with brentuximab vedotin-associated peripheral neuropathy

Track 27 Initial therapy options for elderly patients with HL

Track 28 **Case discussion:** A patient with relapsed/refractory HL receives nivolumab on a clinical trial

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

Efficacy	Phase I CA209-039 study[1] (n = 23)	Phase II CheckMate 205 study[2] (n = 80)
Objective response rate	87%	66%
Complete response	22%	9%
Partial response	65%	58%
Median PFS	Not reached	10 mo
Overall survival rate	83% (1.5 y)	99% (6 mo)
Select adverse events (any grade)	n = 23	n = 80
Fatigue	NR	25%
Skin related	22%	16%
Hepatic	12%	14%
Pulmonary	4%	2%
Diarrhea	13%	10%
Hypersensitivity/infusion reactions	9%	21%

PFS = progression-free survival; NR = not reported

[1] Ansell S et al. *Proc ASH* 2015;**Abstract 583**; [2] Younes A et al. *Lancet Oncol* 2016;17(9):1283-94.

4.2 **Best Overall Response Rates with Pembrolizumab for Relapsed/Refractory Classical Hodgkin Lymphoma: Results from the Phase II KEYNOTE-087 Study**

Efficacy	Patients with PD after ASCT and BV (n = 30)	Transplant-ineligible patients (n = 30)	Patients with PD after ASCT (n = 30)	Patients with primary refractory disease (n = 37)
Overall response rate	73%	83%	73%	78%
Complete remission	27%	30%	30%	35%
Partial remission	47%	53%	43%	43%
Stable disease	17%	7%	13%	11%
PD	10%	7%	13%	8%
Select adverse events (any grade)	n = 90			
Pyrexia	13%			
Diarrhea	10%			
Neutropenia	8%			
Fatigue	8%			

PD = progressive disease; ASCT = autologous stem cell transplant; BV = brentuximab vedotin

Chen RW et al. *Proc ASCO* 2016;**Abstract 7555**.

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**.

Armand P et al. **Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure.** *J Clin Oncol* 2016;[Epub ahead of print].

Chen RW et al. **Pembrolizumab for relapsed/refractory classical Hodgkin lymphoma (R/R cHL): Phase 2 KEYNOTE-087 study.** *Proc ASCO* 2016;**Abstract 7555**.

Younes A et al. **Checkmate 205: Nivolumab (nivo) in classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) — A phase 2 study.** *Proc ASCO* 2016;**Abstract 7535**.

QUESTIONS (PLEASE CIRCLE ANSWER):

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

Hematologic Oncology Update — Issue 2, 2016

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

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

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Initial results of the Phase II ECOG-E2408 trial: Bendamustine/rituximab with or without bortezomib for previously untreated high-risk FL	4 3 2 1	4 3 2 1
Activity of novel agents under investigation for FLT3-ITD-mutated AML (ie, sorafenib, midostaurin, quizartinib, gilteritinib)	4 3 2 1	4 3 2 1
Efficacy and tolerability of approved (blinatumomab) and promising novel (inotuzumab ozogamicin) monoclonal antibodies for the treatment of ALL	4 3 2 1	4 3 2 1
Results of Phase III studies of daratumumab in combination with lenalidomide/dexamethasone (POLLUX) or with bortezomib/dexamethasone (CASTOR) for relapsed/refractory MM	4 3 2 1	4 3 2 1
Integration of nivolumab into the clinical algorithm for advanced HL	4 3 2 1	4 3 2 1

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☐ Solo practice ☐ Government (eg, VA) ☐ Other (please specify).....

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☐ 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:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- 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..... 4 3 2 1 N/M N/A
- 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..... 4 3 2 1 N/M N/A
- Reevaluate current treatment approaches for patients with myeloproliferative disorders and acute and chronic leukemias in light of newly emerging clinical data..... 4 3 2 1 N/M N/A
- 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..... 4 3 2 1 N/M N/A
- Incorporate new therapeutic strategies into the best-practice management of newly diagnosed and relapsed/refractory Hodgkin lymphoma..... 4 3 2 1 N/M N/A
- Assess the benefits of ongoing clinical trials for patients with hematologic cancers, and inform appropriately selected patients about these options for treatment..... 4 3 2 1 N/M N/A

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.....

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If no, please explain: .....

Additional comments about this activity:

.....

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Hagop M Kantarjian, MD	4 3 2 1	4 3 2 1
S Vincent Rajkumar, MD	4 3 2 1	4 3 2 1
Philippe Armand, MD, PhD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

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