5 Minute JournalClub

POST-ASH Issue 7, 2015

Phase II Trial of Blinatumomab in Patients with Relapsed or Refractory DLBCL

For more visit ResearchToPractice.com/5MJCASH2015

Research To Practice®

CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel agents and salvage therapeutic options for the management of previously untreated or relapsed/refractory follicular lymphoma (FL), mantle-cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL) and T-cell lymphoma (TCL) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the efficacy and safety of rituximab and bortezomib as maintenance therapies for patients with MCL.
- Assess the results of recent Phase II studies evaluating the immunotherapeutic agents brentuximab vedotin and blinatumomab for the treatment of DLBCL.
- Appraise emerging clinical data from early-phase studies evaluating novel chemobiologic combination regimens for the treatment of TCL.
- Compare and contrast the benefits and risks of the novel up-front treatment approaches of rituximab combined with lenalidomide and obinutuzumab alone or in combination with CHOP for patients with FL.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2015/7/CME.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Stephen M Ansell, MD, PhD
Professor of Medicine
Division of Hematology
Mayo Clinic
Rochester, Minnesota

Research Funding: Bristol-Myers Squibb Company, Celldex Therapeutics.

Jonathan W Friedberg, MD, MMSc
Samuel Durand Professor of Medicine
Director, Wilmot Cancer Center
University of Rochester
Rochester, New York

Advisory Committee and Other Uncompensated Activities: Genentech BioOncology.

Craig Moskowitz, MD
Clinical Director, Division of Hematologic Oncology
Attending Physician, Lymphoma and Adult BMT Services
Member, Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University
New York, New York

Advisory Committee: Genentech BioOncology, Seattle Genetics; Contracted Research: Genentech BioOncology, GlaxoSmithKline, Merck, Seattle Genetics.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Amgen Inc, Astellas Scientific and Medical Affairs Inc, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer

HealthCare Pharmaceuticals, Biodesix Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lilly, Medivation Inc, Merck, Myriad Genetic Laboratories Inc, NanoString Technologies, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Teva Oncology, Tokai Pharmaceuticals Inc and VisionGate Inc.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This activity is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Seattle Genetics and Takeda Oncology.

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: May 2015
Expiration date: May 2016

5 MinuteJournalClub

POST-ASH Issue 7, 2015

To go directly to slides and commentary for this issue, **click here**.

Jeff Sharman, MD

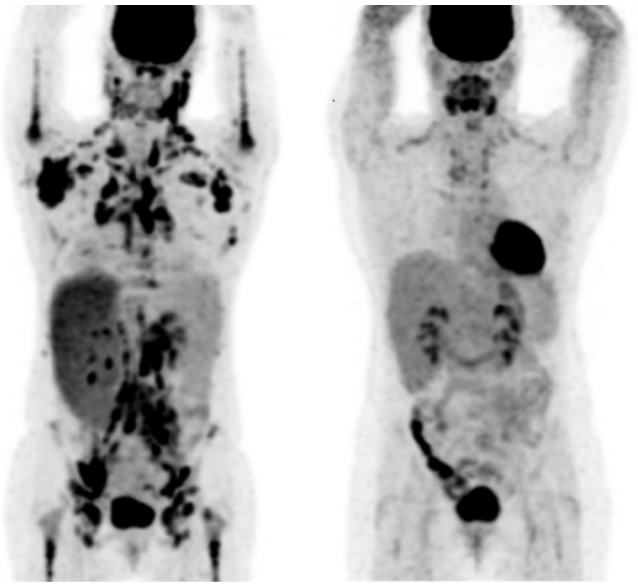
To begin a recent interview for our *Hematologic Oncology* Update audio series, Dr Jeff Sharman presented from his practice the fascinating and highly instructive case of a 57-year-old yoga instructor and motivational speaker with follicular lymphoma (FL). He started by noting that after migrating from Stanford to his current location in Eugene, Oregon, he quickly learned that a lot of people in the Pacific Northwest don't much like chemotherapy. I have heard this comment from others who practice in the area, and as a fan of the TV show Portlandia — where the characters regularly inquire about the detailed life histories of the chicken they are about to eat in a restaurant and the like — it really resonated. More importantly, however, this case relates to a critical issue in contemporary oncology: When is it acceptable to reach for an investigational therapy with encouraging Phase II data?

This patient — described as charismatic and dynamic — presented with bulky inguinal and cervical adenopathy and increased abdominal girth. She had previously consulted her naturopath, who palpated an enlarged spleen, and this led to a "second opinion" from Jeff.

Massive splenomegaly, hepatomegaly and extensive bulky adenopathy were observed on CT, and excisional biopsy of an inguinal node revealed Grade 3a FL. Flow cytometry confirmed peripheral blood involvement with mild anemia and thrombocytopenia. Because of the high tumor burden by GELF criteria and the possibility of occult transformation, Dr Sharman recommended R-CHOP (rituximab [R]/cyclophosphamide/doxorubicin/vincristine/prednisone). However, the patient absolutely refused chemotherapy, stating, in essence, "There's no way you're going to do that to me. I would rather die of my disease than go through what you're talking about."

Taking a deep breath, Jeff brought up the possibility of treatment without chemotherapy and the patient listened with rapt attention. R monotherapy seemed suboptimal given the extent of the disease, and he reluctantly raised the possibility of a regimen that is currently being studied by many research entities, the so-called "R squared" (R2) combination of the immunomodulatory agent lenalidomide (len) with R.

The patient was more than interested, and Dr Sharman initiated 4 weekly doses of R followed by 4 more doses every 2 months as per the SAKK regimen along with len at 25 mg PO daily for 21 out of 28 days. In Jeff's words, here is what happened: "She did develop some cytopenias, had a little bit of fatigue, but the disease simply melted away. It was really a quite stunning response. Her adenopathy resolved within the first 8 weeks of therapy, and when we repeated the PET scan, she'd actually had a PET-negative complete response (CR). We even redid her marrow, which had cleared as well. Len was discontinued about the same time she completed R, and currently she's still in a CR and feeling great more than 4 years later."



Before and after treatment with lenalidomide/rituximab

As part of last week's email focused on multiple myeloma, we discussed the immune effects of len creating synergy with elotuzumab, and Dr Sharman suggests that a similar dynamic may be in play with R. He notes the suboptimal function of T cells in patients with B-cell cancers and emerging data suggesting that malignant cells are able to induce T-cell anergy/apathy.

Because the activity of R is in part through antibody-dependent cellular cytotoxicity, the effect may be blunted with a poorly functional T-cell component. For this reason, Jeff describes the R^2 combination as planning a road trip with a map (R) and a highly synergistic pot of coffee (len) — an analogy perhaps prompted by the beautiful outdoor scenes nearby. This combination is now being studied in the Intergroup Phase III RELEVANCE trial with the challenging randomization comparing R^2 to R-chemotherapy. The study is not restricted to patients with low tumor burden, and Dr Sharman hopes the result will be a new paradigm in this disease.

At a more macro level, this case illustrates the continuing dilemma that occurs every day in oncology practice — whether to recommend an intervention that involves the use of approved therapies but is the subject of ongoing investigation. In terms of Dr Sharman's yoga teacher, it could be that the same benefit would have accrued had only R been used, and it is also possible that in the long run she would have been better off embarking initially on an R-chemotherapy regimen, although that seems unlikely given what happened. It is also true that patients ideally should receive new therapies as part of clinical trials, but that is not always feasible, and in the end, the clinician evaluating the patient hopefully makes the optimal recommendation for that individual. Any way you look at it, though, Dr Sharman's case is compelling, thought provoking and may be a sign of what is to come in the near future.

With that said, on this final ASH review we profile new data with R^2 as well as a number of other intriguing papers focused on the management of FL, mantle-cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL) and T-cell lymphoma (TCL).

FL

More on R^2

Whether trials like RELEVANCE will establish equal or greater efficacy of R^2 versus R-chemotherapy, it seems clear that len adds substantially to the benefit of R monotherapy. At ASH the randomized **Phase II SAKK 35/10 study** comparing R to R^2 as up-front therapy in 154 patients with FL mirrored the results of previous trials demonstrating a substantial improvement in overall response rate (45% versus 75% at week 10), although the impact on progression-free survival (PFS) and overall survival has not been established.

Obinutuzumab (O) with CHOP or bendamustine (benda) in untreated FL

Not many people expected another anti-CD20 antibody to outperform R in any disease, but the encouraging results and FDA approval of O in chronic lymphocytic leukemia (CLL) led to the hope that similar benefits will be observed with other B-cell cancers. As such, the **Phase 1b GAUDI study** investigated O-CHOP and O-benda with 2 years of O maintenance in 81 patients with FL. Although much of the emphasis of this effort was on safety, perhaps the most interesting finding was that the CR rate increased substantially during the 2 years of O maintenance (O-benda: 37% to 61%; O-CHOP: 35% to 70%).

Phase III research is ongoing to define not only the efficacy but also the tolerability of these regimens compared to R-based approaches — particularly with the prolonged B-cell depletion during maintenance O. In a related manner, next week at ASCO we will see the results from the Phase III GADOLIN study evaluating O-benda versus benda alone in patients with R-refractory indolent non-Hodgkin lymphoma. A press release has already hinted that the data will be positive, but what that means for clinical practice remains unknown.

Over the past year there has been a great deal of understandable excitement about the rapid changes that have occurred in the management of CLL, but it seems that a similar upheaval will soon take place in FL, for which O and len may join the recently approved PI3 kinase delta inhibitor idelalisib (Id) in the clinical algorithm. Interestingly, it is Dr Sharman's impression that many clinicians mistakenly believe that ibrutinib has good activity in FL despite the documented modest benefit and fail to realize that Id — the first agent in 6 years approved in FL — on the other hand is for real and has sparked a number of combination trials up front.

In this vein, although **one ASH paper** reported durable responses with BR-Id, another data set is a **cautionary tale** of the potential dangers of empiric attempts to combine agents outside a trial setting, specifically Phase I research evaluating Id with R2 that had to be discontinued for unacceptable toxicity after 4 of the first 8 patients developed rash, fevers and hypotension suggestive of a cytokine release syndrome.

MCL

R maintenance after autologous stem cell transplant (ASCT)

Previous work had demonstrated the benefit of R maintenance in older patients receiving induction therapy. However, the role of this approach in younger individuals undergoing ASCT was poorly understood, and at ASH we saw data from the **Phase III LYMA trial** evaluating 3 years of R maintenance in 257 patients who received 4 cycles of R-DHAP followed by ASCT. At 2 years, R maintenance increased the event-free survival from 81.5% to 93.2%, but no overall survival benefit has yet been observed, although the influx of new and effective therapies for relapsed/refractory (R/R) MCL will complicate the evaluation of this important endpoint. However, from a clinical perspective these findings are likely to be practice changing as many investigators view the delay in disease progression as enough benefit to justify the use of this strategy for many/most patients with MCL.

SWOG trial of R-CHOP/bortezomib (bor) with bor maintenance

At ASH we saw the results of a **Phase II trial** in 65 evaluable patients exploring the role of the proteasome inhibitor bor (which now has a limited approval as up-front therapy in the disease) as maintenance treatment. The activity of this approach was viewed as encouraging (PFS: 2 years 62%; 5 years 28%) with acceptable tolerability, but how this will fit into the increasingly crowded MCL "space" remains to be determined.

DLBCL

Brentuximab vedotin (BV) with R-CHOP

BV has demonstrated compelling activity as a single agent in R/R DLBCL even in patients with low CD30 expression, and this has led to interest in its use up front. A Phase II trial reported at ASH evaluated the **addition of BV to R-CHOP** in 33 patients with newly diagnosed DLBCL and reported excellent activity (overall response rate: 92%; CR: 58%) with an acceptable tolerability profile. Peripheral neuropathy (PN) was about what is typically observed with BV alone and only 5 patients required dose reductions as a result. Further research will define the future role of BV up front (as is being studied in Hodgkin lymphoma), probably without the concurrent use of vincristine, and how CD30 expression relates to treatment benefit.

Blinatumomab

A recent issue of this series focusing on acute leukemias discussed the profound clinical activity with this bispecific T-cell engager antibody in acute lymphoblastic leukemia. However, the benefits of this novel agent — which engages CD3-positive cytotoxic cells leading to T-cell expansion and lysis of CD19-positive B cells — appears not to be confined solely to that disease, as objective responses have been previously reported in a number of patients with DLBCL. At ASH we saw **more evidence to substantiate** that claim as a Phase II study of 21 patients with R/R DLBCL demonstrated responses in 43%. More to come.

TCL

BV in mycosis fungoides (MF) and Sézary syndrome (SS)

Although much has been previously made of the activity of BV in peripheral TCL (PTCL) — most relevantly anaplastic large cell lymphoma — it appears that this agent may also have utility in cutaneous TCL. Notably, we saw data from a **Phase II trial** of 30 evaluable patients, the majority of whom had advanced-stage MF or SS, that demonstrated a 70% response rate (mostly partial responses) with acceptable toxicity (mainly PN). While there was a suggested correlation of activity with CD30 levels and it remains to be seen whether an antitumor effect occurs without CD30 expression, these results will likely lead to the use of BV in these patients.

Romidepsin/CHOP in PTCL

For quite some time investigators have been struggling to develop more impactful long-term treatment strategies for patients with PTCL, who generally face a bleak prognosis even with postinduction ASCT. In this regard there has been significant interest in moving novel agents with activity in the R/R setting into up-front regimens. This dynamic was on full display at ASH as we saw final results from a **Phase Ib/II report** of 35 evaluable patients who received romidepsin-CHOP as up-front therapy with a CR rate of 51% and 17% partial responses. These data are far from definitive but suggest the combination is safe, providing additional support for ongoing Phase III studies.

This concludes our ASH series, and as we saddle up and head out to the Windy City we encourage you to stay tuned this summer for virtual replays of the 4 evening satellite symposia focused on **lung cancer**, **GI cancers**, **myeloma/lymphoma** and **breast cancer** we will be hosting at the annual ASCO extravaganza.

Neil Love, MD
Research To Practice
Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

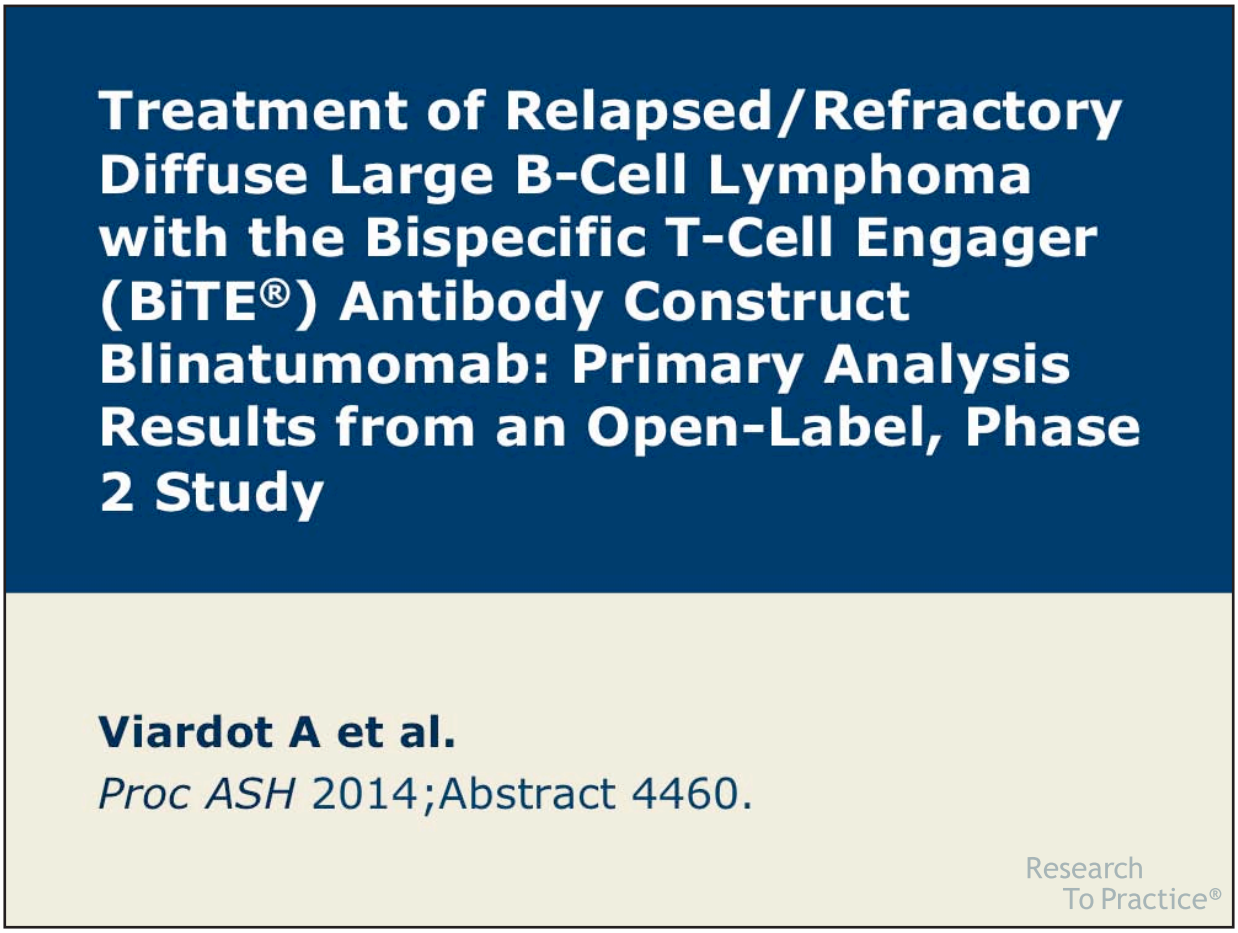
This activity is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Seattle Genetics and Takeda Oncology.

Phase II Trial of Blinatumomab in Patients with Relapsed or Refractory DLBCL

Presentation discussed in this issue

Viardot A et al. **Treatment of relapsed/refractory diffuse large B-cell lymphoma with the bispecific T-cell engager (BiTE®) antibody construct blinatumomab: Primary analysis results from an open-label, phase 2 study.** *Proc ASH* 2014;**Abstract 4460**.

Slides from a presentation at ASH 2014 and transcribed comments from a recent interview with Stephen M Ansell, MD, PhD (1/20/15)



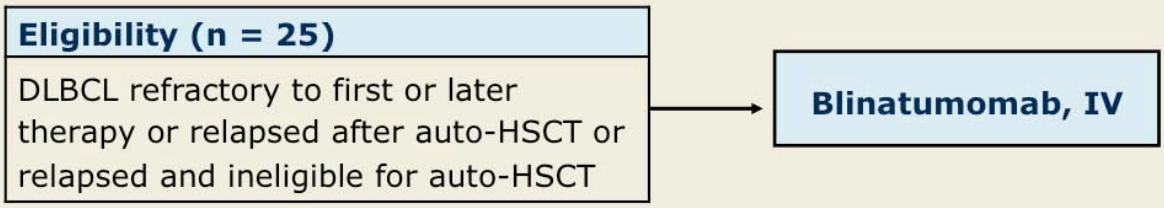
Background

- Treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) is challenging, with little progress in recent years.
- Blinatumomab, a bispecific T-cell engager (BiTE®) antibody construct, engages CD3-positive cytotoxic T cells, resulting in T-cell expansion and lysis of CD19-positive B cells.
- In a prior Phase I study, blinatumomab treatment resulted in an overall response rate (ORR) of 55% in a subset of patients with DLBCL (*Proc ASH* 2011;Abstract 1637).
- **Study objective:** To compare stepwise versus flat dosing of blinatumomab and evaluate its efficacy in patients with relapsed/refractory DLBCL.

Viardot A et al. *Proc ASH* 2014;Abstract 4460.

Research To Practice®

Ongoing Phase II Study Design (NCT01741792)



Auto-HSCT = autologous hematopoietic stem cell transplant

- Nine, 2 and 14 patients enrolled in cohorts I, II and III, respectively.
- Stage 1: Stepwise dosing (cohort I: 9, 28 and 112 µg/d) compared to constant dosing of 112 µg/d (cohort II).
- Based on the benefit/risk assessment from stage 1, stepwise dosing was chosen for cohort III in stage 2.
- Patients achieving response after 8 weeks could receive a 4-week consolidation cycle after a 4-week treatment-free period.
- All patients received prophylactic dexamethasone.
- **Primary endpoint:** ORR

Viardot A et al. *Proc ASH* 2014;Abstract 4460; www.clinicaltrials.gov.

Research To Practice®

Patient Characteristics

Characteristic	N = 25
Median age (range)	66 years (34-85)
Men	56%
Patients who had received prior auto-HSCT	7 (28%)
Median duration of exposure for stepwise dosing*	46.8 days

* Cohorts I and III

- Blinatumomab was received as a fourth-line systemic therapy after a median (range) of 3 (1-7) prior treatments.

Viardot A et al. *Proc ASH* 2014;Abstract 4460 (Abstract only).

Research To Practice®

Response to Blinatumomab

Response	n = 21*
ORR	43%
Complete response	4 (19%)
Partial response	5 (24%)

* Evaluable patients (cohort I, n = 7; cohort II, n = 1; cohort III, n = 13)

- Four patients were not evaluable for ORR due to early treatment discontinuation (<1 week on target dose in the absence of disease progression): 1 due to investigator's decision and 3 due to adverse events.
- All patients who responded did so within the first 8-week cycle.
- Among responders (n = 9), the median duration of response was 11.6 months.

Viardot A et al. *Proc ASH* 2014;Abstract 4460 (Abstract only).

Research To Practice®

Adverse Events

- All patients (n = 25) experienced ≥1 adverse event (AE).
- The most common AEs were tremor (52%), pyrexia (44%), diarrhea (24%), fatigue (24%), edema (24%) and pneumonia (24%).
- Grade 3 and 4 AEs occurred in 96% and 20% of patients, respectively.
- Serious AEs occurred in 92% of patients.
  - Most common: pneumonia (24%), device-related infection (16%) and pyrexia (16%)
- Seven patients (cohort I, n = 3; cohort II, n = 2; cohort III, n = 2) had Grade 3 neurologic AEs.
  - Grade 3 AEs occurring in >1 patient were disorientation, encephalopathy, aphasia and epilepsy (n = 2 each).

Viardot A et al. *Proc ASH* 2014;Abstract 4460 (Abstract only).

Adverse Events (continued)

- No Grade 4 or 5 neurologic events were reported.
- Fourteen patients have died (cohort I, n = 5; cohort II, n = 1; cohort II, n = 8):
  - 11 due to disease progression, 1 due to cardiogenic shock, 1 due to organ failure after transplantation; no cause of death was reported for 1 patient

Viardot A et al. *Proc ASH* 2014;Abstract 4460 (Abstract only).

Author Conclusions

- In this Phase II study, a stepwise dosing regimen (9, 28 and 112 µg/day) was established as the preferred dosing for blinatumomab in DLBCL.
- Treatment with blinatumomab showed an acceptable safety profile and resulted in objective and durable responses in heavily pretreated relapsed/refractory DLBCL.

Viardot A et al. *Proc ASH* 2014;Abstract 4460 (Abstract only).

Research To Practice®

Investigator Commentary: Primary Analysis of a Phase II Study of Blinatumomab for Relapsed/Refractory DLBCL

Blinatumomab is a bispecific antibody that binds to CD19 on B cells and CD3 on T cells. It brings these cells into close proximity and promotes their activation. In patients with relapsed/refractory B-cell acute lymphoblastic leukemia (ALL), the results have been promising, leading to approval of blinatumomab in that setting.

In this study, the investigators assessed the efficacy of blinatumomab in patients with disease progression on standard approaches, including auto-HSCT. One of the goals was to determine the optimal dose of blinatumomab. Twenty-five patients were enrolled, with a number of cohorts and dose levels. In the 21 patients who were evaluable for responses, an ORR of 43% was reported with 4 complete responses and 5 partial responses. So in patients who haven't responded to available therapies for DLBCL, a high response rate, particularly 4 complete responses, I believe is promising and encouraging.

There are some toxicities, however. Common side effects included immune-related adverse events like fever, diarrhea, fatigue and infections. However, based on experience with other diseases like ALL, I believe this agent has real promise for relapsed/refractory DLBCL.

Interview with Stephen M Ansell, MD, PhD, January 20, 2015