



POST-ASH Issue 2, 2013

**Phase II Study of the Anti-PD-1
Monoclonal Antibody Pidilizumab
(CT-011) with Rituximab
for Relapsed FL**

CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Appraise recent clinical research findings with lenalidomide/rituximab for patients with untreated indolent lymphoma and, where appropriate, counsel patients regarding participation in ongoing pivotal trials assessing this strategy.
- Evaluate the early efficacy and safety data with the anti-PD-1 monoclonal antibody pidilizumab (CT-011) for patients with relapsed/refractory FL.
- Assess the benefits and risks of novel therapeutic approaches — PI3 kinase inhibitors, Btk inhibitors and chimeric antigen receptor T cells — under investigation in B-cell neoplasms and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Optimize outcomes for elderly patients with CLL through the application of emerging clinical research data.

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Hardware/Software Requirements:

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

Last review date: February 2013

Expiration date: February 2014

ASH 2012 and the postrituximab era of new biologic treatments for B-cell neoplasms

To go directly to slides and commentary for this issue, [click here](#).

Since the late 1990s rituximab (R) has been the major biologic agent integrated into management of B-cell cancers. However, these days some of the most cautious, evidence-based investigators are having a hard time hiding their enthusiasm for an array of emerging novel agents that are shaking up the non-Hodgkin lymphoma (NHL)/chronic lymphocytic leukemia (CLL) research database. On this second issue of our 7-part ASH highlights series, we profile several promising new strategies, including a few that MD Anderson's Dr Hagop Kantarjian believes may soon lead to CML-like long-term disease control in CLL. Here's an overview of what we learned in Atlanta:

1. Small-molecule B-cell receptor inhibitors: Ibrutinib (Ib) and idelalisib (GS-1101)

These oral, relatively nontoxic agents interfere with the B-cell receptor signaling pathway and have intriguing activity in CLL, follicular lymphoma (FL) and mantle-cell lymphoma (MCL). Perhaps the greatest excitement surrounds Ib, an inhibitor of Bruton's tyrosine kinase, which is critical for proliferation and survival in most B-cell tumors. Ib was the subject of [2 spectacular CLL ASH papers](#). The first was a Phase I-II monotherapy study of 116 patients that resulted in response rates Dr Bruce Cheson called "phenomenal" and exceeded 65% overall, including 12 of 24 patients with 17p and 11q deletions.

The second major related paper was a Phase II study evaluating the combination of Ib and R in 40 patients with previously treated high-risk CLL. I was struck by the title of the abstract, which states that this combination had "profound" activity. Given that description, the eye-popping [waterfall plots](#), which pretty much all point south and included 13 patients with del 17p, were not that surprising. A highlight of this paper was the discussion of a patient who had primary resistance to FCR then hyper-CVAD and a number of other therapies but achieved a CR with Ib/R.

With regard to idelalisib, at ASH we saw findings from [a Phase I study](#) evaluating this PI3 kinase delta inhibitor combined with R and/or bendamustine (B) in 52 patients with relapsed/refractory (RR) CLL. PI3K delta is thought to drive proliferation and survival of malignant B cells, and as in many Phase I studies in this era of molecular-targeted treatment, most (about 80%) of the patients responded despite extensive prior treatments, including B and R. This well-tolerated combination approach is now being tested in Phase III trials.

2. Lenalidomide (len)

The first issue of this ASH series profiled immunomodulatory agents in multiple myeloma, including the newly approved pomalidomide, but this intriguing class of drugs clearly is also of great interest in B-cell cancers. The last several ASH meetings have included a number of presentations suggesting that len alone or with R ("R squared – R²") has significant activity in CLL and NHL, and at the 2012 conference the good news continued.

Notably, Dr Nathan Fowler presented the final results of [a Phase II trial](#) of 110 patients with indolent lymphoma treated with the R² regimen. High rates of durable responses were observed, including CRs in 42/45 patients with FL who converted to PET negativity, and this encouraging data set and others have spawned a number of studies like the Phase III RELEVANCE trial comparing R² to chemotherapy/R, raising the possibility of a future world without chemotherapy for this disease.

[Another Phase II CLL study](#) evaluated a strategy now often used in myeloma, namely len maintenance, in this case for 12 months after BR induction. The encouraging median PFS of 24.3 months in 34 patients has led to interest in testing R² maintenance, an approach that is also the focus of a current ECOG MCL trial.

3. Other novel treatments: Chimeric antigen receptor (CAR) therapy, anti-PD-1

The spectacular science and clinical challenges of next-generation biologic therapy were on full display in a [paper profiling the use of CART19 cells](#) targeting the CD19 antigen, which is expressed on the surface of most B-cell cancers. This Star Wars-like treatment involves gene transfer techniques to genetically modify T cells, which in this study was demonstrated to have rapid and potent antitumor activity in chemotherapy-refractory CD19-positive CLL and ALL. The development of a cytokine release syndrome in some cases is a signal for caution in this maybe revolutionary approach to immune-based treatment.

Similarly, while anti-PD-1 has gotten a lot of press across solid tumor oncology, this immunotherapeutic strategy is also under investigation in hematologic cancers. In this regard, an [early paper](#) reported encouraging results with the combination of R and the anti-PD-1 monoclonal antibody pidilizumab (CT-011) in patients with RR FL.

While ASH was a treasure trove of exciting papers on biologics, more is on the way, as witnessed by a recent [press release](#) concerning a large Phase III German CLL trial evaluating the glycoengineered, humanized type II CD20 antibody obinutuzumab (O; GA101) that reported an advantage to adding this agent to chlorambucil (CLB), but this is just an appetizer to the main dish — the comparison to R-CLB. R seems to have less activity in CLL than in many lymphomas, and the hope is that O will yield greater benefit.

Next on this ASH series — new data on myelofibrosis, a cancer that finally has effective but complex treatment options, including 2 key follow-up reports of landmark Phase III trials of ruxolitinib.

Neil Love, MD

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Phase II Study of the Anti-PD-1 Monoclonal Antibody Pidilizumab (CT-011) with Rituximab for Relapsed FL

Presentation discussed in this issue

Westin JR et al. **Phase II safety and efficacy study of CT-011, a humanized anti-PD-1 monoclonal antibody, in combination with rituximab in patients with relapsed follicular lymphoma.** *Proc ASH 2012*; **Abstract 793.**

**Slides from a presentation at ASH 2012 and transcribed comments
from a recent interview with Bruce D Cheson, MD (1/14/13)**

Phase II Safety and Efficacy Study of CT-011, a Humanized Anti-PD-1 Monoclonal Antibody, in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma

Westin JR et al.

Proc ASH 2012; Abstract 793.

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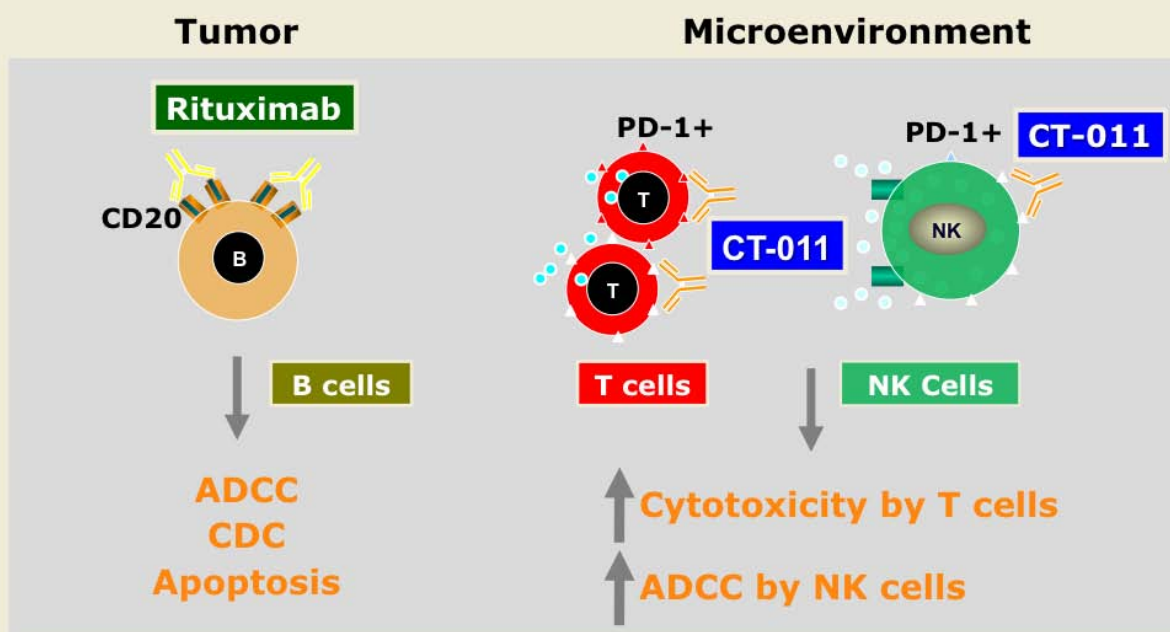
Background

- The expression of the programmed death (PD)-1 receptor is increased on intratumoral T cells in follicular lymphoma (FL) and associated with impaired T-cell function (*Human Pathol* 2011;42(4):552).
- Pidilizumab (CT-011) is a humanized anti-PD-1 monoclonal antibody that can promote the functions of antitumor T and natural killer (NK) cells (*J Immunother* 2011;34(5):409).
- Because rituximab is a monoclonal anti-CD20 antibody that partly acts by activating NK cell-mediated cytotoxicity, its combination with CT-011 may offer additive or synergistic antitumor effects via the immune system.
- **Study objective:** Evaluate the efficacy and safety of pidilizumab and rituximab in relapsed FL.

Westin JR et al. *Proc ASH* 2012;Abstract 793.

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Rituximab + Pidilizumab (CT-011): Rationale



With permission from Westin JR et al. *Proc ASH* 2012;Abstract 793.

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Phase II Trial Design

Eligibility (n = 30)

Relapsed Grade 1/2 FL
 1-4 prior therapies
 Tumor size >1.5 cm
 No HIV, hepatitis B/C,
 autoimmune disorder or
 allogeneic SCT



Pidilizumab + rituximab (n = 30)

Pidilizumab: 3 mg/kg IV
 q4wk x 4 cycles*

Rituximab: 375 mg/m² IV
 q1wk x 4 cycles[†]

* If ≥stable disease after 4 cycles, continue with up to 8 more cycles

† Rituximab dosing started 2 weeks after the first infusion of pidilizumab

- **Primary endpoint:** Overall response rate (ORR)
- **Secondary endpoints include:** Complete response rate, time to progression and safety

Westin JR et al. *Proc ASH* 2012;Abstract 793.

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Best Response Rates

Response rate	n = 29*
ORR	66%
Complete response (CR)	52%
Partial response (PR)	14%
Tumor regression	86%

* Evaluable patients

- Median time to response: 88 days
- ORR did not correlate with FLIPI or FLIPI-2 score, amount of prior rituximab, prior chemotherapy or duration of response to prior therapy ($p > 0.05$).

Westin JR et al. *Proc ASH* 2012;Abstract 793.

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Survival Outcomes

Outcome	Pidilizumab + rituximab
Median progression-free survival*	
All patients (n = 29)	21.1 months
Responders (n = 19)	Not reached (NR)
With measurable tumor regression (n = 25)	NR
No. of deaths (n = 29)	0

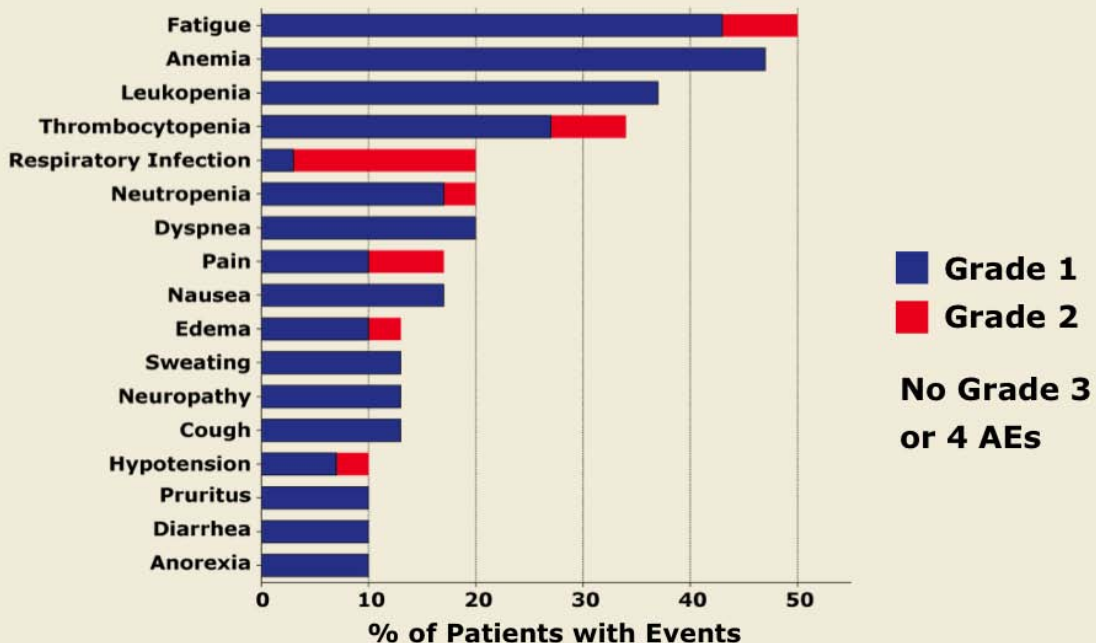
* Median follow-up = 14 months

- PFS was significantly associated with:
 - FLIPI (low/intermediate vs high): NR vs 12.65 months; $p = 0.0056$
 - FLIPI-2 (low/intermediate vs high): NR vs 13.47 months; $p = 0.0344$

Westin JR et al. *Proc ASH* 2012;Abstract 793.

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Common Adverse Events (AEs) Occurring in >10% of Patients



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Author Conclusions

- The combination of pidilizumab with rituximab was:
 - Well tolerated
 - Effective in relapsed, rituximab-sensitive FL
 - ORR: 66%; CR: 52%; PR: 14%
- The results of this single-arm Phase II trial of pidilizumab with rituximab compared favorably to previous data with rituximab re-treatment for patients with relapsed non-Hodgkin lymphoma (*JCO* 2000;18:3135).
 - ORR: 40%; CR: 11%; PR: 30%

Westin JR et al. *Proc ASH* 2012;Abstract 793.

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Investigator Commentary: A Phase II Trial of Pidilizumab and Rituximab in Relapsed Follicular Lymphoma (FL)

Certain molecules inhibit cytotoxic T-cell activity, which is enhanced in cancer. One of the mechanisms by which cancer can grow out of control is by rendering these cytotoxic cells ineffective. With the observation that molecules such as PD-1 promote the recurrence of this process, these investigators studied an anti-PD-1 monoclonal antibody in combination with rituximab in 30 patients with rituximab-relapsed but not refractory FL. The study population was not heavily pretreated, with most of the patients having some evidence of clinical activity.

About 85% of the patients experienced tumor shrinkage with an ORR of 66%, which the investigators felt was better than historical controls with rituximab alone. Also, the median PFS was >1.5 y. These results are interesting, but I would have preferred to know the effectiveness of this combination in patients with refractory FL, not only in patients with relapsed disease, because that would provide a better idea of whether there is a synergistic relationship between pidilizumab and rituximab. This combination is worth studying in patients with more resistant disease and perhaps in combination with other agents, based on scientific rationale. Pidilizumab is an example of the concept of better living through molecular genetics and biology.

Interview with Bruce D Cheson, MD, January 14, 2013