5 Minute JournalClub

Hematologic Oncology
Issue 2, 2013

Updated Results of a Phase I Study of ABT-199 in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia

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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 Clinical Oncology (ASCO) annual meeting and the International Conference on Malignant Lymphoma (ICML), 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 are aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because not only are they confronted almost overnight with thousands of new presentations and data sets, 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 in chronic lymphocytic leukemia from the latest ASCO and ICML meetings, including expert perspectives on how these new evidence-based concepts may 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 data on therapeutic advances and potentially practice-changing clinical data in chronic lymphocytic leukemia, and consider this information in clinical practice.
- Evaluate the efficacy, safety, pharmacodynamics and pharmacokinetics of idelalisib as a single agent or in combination with rituximab for patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia.
- Determine the preliminary efficacy and safety of ABT-199, a selective BCL-2 inhibitor, for patients with relapsed or refractory chronic lymphocytic leukemia.
- Determine the benefits and risks associated with chlorambucil in combination with obinutuzumab (GA101), an anti-CD20 antibody, or rituximab versus chlorambucil alone for patients with previously untreated chronic lymphocytic leukemia and preexisting comorbidities.
- Assess the preliminary safety and response outcomes observed in studies of the orally bioavailable, small molecule inhibitor of Bruton tyrosine kinase ibrutinib as a single agent for patients with chronic lymphocytic leukemia with chromosome 17 deletion.

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This activity is supported by educational grants from Genentech BioOncology/Biogen Idec, Onyx Pharmaceuticals Inc and Spectrum Pharmaceuticals Inc.

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: September 2013
Expiration date: September 2014

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

Imagine...

Ten days ago your life was instantly turned upside down. After a few months of having less energy than usual, to appease a concerned spouse you visit your primary care physician who detects lymphadenopathy in your neck and a spleen tip. A blood count suggests chronic lymphocytic leukemia (CLL), and that night one of your colleagues does a bone marrow biopsy and initiates a workup that soon demonstrates you meet the criteria to initiate treatment. You consult with a noted CLL investigator who reviews with you the following options:

A. FCR
B. FR
C. BR
D. A clinical trial that includes 1 or more unapproved agents in clinical development

Which treatment would you choose to receive?

I asked this impossible question to investigator Dr Brad Kahl last week during a conversation that focused on the blindingly fast evolution of new agents in B-cell neoplasia, particularly CLL. Not surprisingly and without any hesitation Dr Kahl replied "D, clinical trial," and while there are many investigational agents and regimens he might consider, his first choice today would be to enter a study of the Bruton's tyrosine kinase inhibitor ibrutinib combined with rituximab (R), although he did preface his answer by saying, "This is a moving target that could change in 6 months — especially the choice of anti-CD20 antibody, which might be different after ASH" (see below). If and when relapse occurred, at this moment Dr Kahl would elect to be enrolled on a trial of the BCL-2 inhibitor ABT-199 with obinutuzumab (O) for its added effect on cell death. He noted that his choices would be the same with del17p disease.

One of the oldest homilies in medical oncology is "The best treatment option is participation in a clinical trial," and although in the past, study options rarely provided opportunities not available in daily practice, currently in specific corners of the field the data for one or more unapproved treatments are so compelling that oncologists who don't make patients aware of these research options are not delivering the type of care they would likely want to receive themselves.

Nowhere is this more relevant currently than in CLL, and on this issue of our short series summarizing key summer heme-onc meeting presentations we review findings with 4 classes of agents rapidly generating impressive data and speeding toward clinical practice.

1. Type II monoclonal antibodies to CD20

Perhaps the most surprising oral CLL paper at ASCO 2013 provided us with a first glimpse of data from a major Phase III, 3-arm German study in patients with comorbidities — mostly aged 65 and older — evaluating chlorambucil alone or combined with either R or O, a third-generation glycoengineered Type II agent designed to enhance antibody-dependent cellular cytotoxicity and induce actin-dependent programmed cell death independent of BCL-2 overexpression and caspase activation.

The findings unveiled at ASCO were from the first stage of the study and revealed that both of the monoclonal antibodies added significant efficacy to chlorambucil. However, the data also hinted that O might be more effective than R. Importantly, in July a **press release** announced that the second stage of this historic study had reached statistical maturity and that indeed the primary endpoint of superior progression-free survival in favor of O had been met. O may have more tolerability issues, particularly infusion reactions and neutropenia, but the new data have been submitted to ASH and we shall soon have a much better idea of whether this fascinating agent could potentially replace R in treating CLL and perhaps other B-cell cancers.

2. PI3 kinase delta inhibitors: Idelalisib (idel)

The other 2 ASCO oral CLL presentations this year focused on this much-discussed oral small molecule B-cell receptor signaling inhibitor. The first was a Phase I study in relapsed disease that demonstrated a 72% response rate with a waterfall plot for nodal response that pretty much all points down. The second was a Phase II trial of R and idel in older patients with previously untreated CLL, which revealed a response rate of 97%, including all 9 patients with del17p and/or TP53 mutations. The presenter, Dr Susan O'Brien, noted that as with other novel agents in development, treatment was often initially associated with both rapid lymph node regression and simultaneous lymphocytosis that then gradually receded. She also pointed out that with a median follow-up of 14.1 months, no patient has experienced disease progression. Both studies confirmed prior data demonstrating that the key tolerability issues are diarrhea/colitis and abnormal liver function tests, which resolve with treatment withdrawal or dose reduction.

3. Bruton's tyrosine kinase inhibitors: Ibrutinib

Perhaps the most talked about "emerging agent" in all of oncology, ibrutinib has been the subject of a plethora of recent research reports in an array of B-cell cancers.

In Lugano, the database grew even larger with provocative results illustrating the impact of this agent in a CLL subset that is relatively resistant to chemotherapy-R, patients with del17p. The data reveal that nodal responses were documented in 22 of 25 patients (88%), spleen size decreased in every patient with splenomegaly and the 12-month event-free survival rate was 90%. As in prior studies, side effects and complications were minimal.

4. BCL-2 inhibitors: ABT-199 (GDC-0199)

A final exciting class of agents that has burst onto the CLL scene targets the antiapoptotic protein BCL-2, and in a Phase I study of the orally bioavailable selective BCL-2 inhibitor ABT-199 presented at ASCO and Lugano, an extraordinary 84% response rate was observed in 55 evaluable patients with relapsed/refractory disease, including 13 of 16 patients with del17p. The rapid and profound effect of this agent has led to problems with tumor lysis syndrome, and new studies are evaluating alternate dosing strategies and enhanced measures of prophylaxis, monitoring and management. Moving forward, a key macro issue will be how to combine and sequence these and other new agents with or without chemotherapy.

Much more is happening in CLL research, including chimeric antigen receptor therapy, a promising but technologically complex approach, and as a result we are starting to hear leukemia investigators like Dr Hagop Kantarjian raise the possibility that CLL in the near future could resemble CML with indefinite disease control. In good conscience the trials seeking to achieve this lofty goal must be made available to all patients.

Next on this series, we talk about T-cell lymphoma, a corner of hematologic oncology that is witnessing exciting advances in new drug development after a long period in the doldrums.

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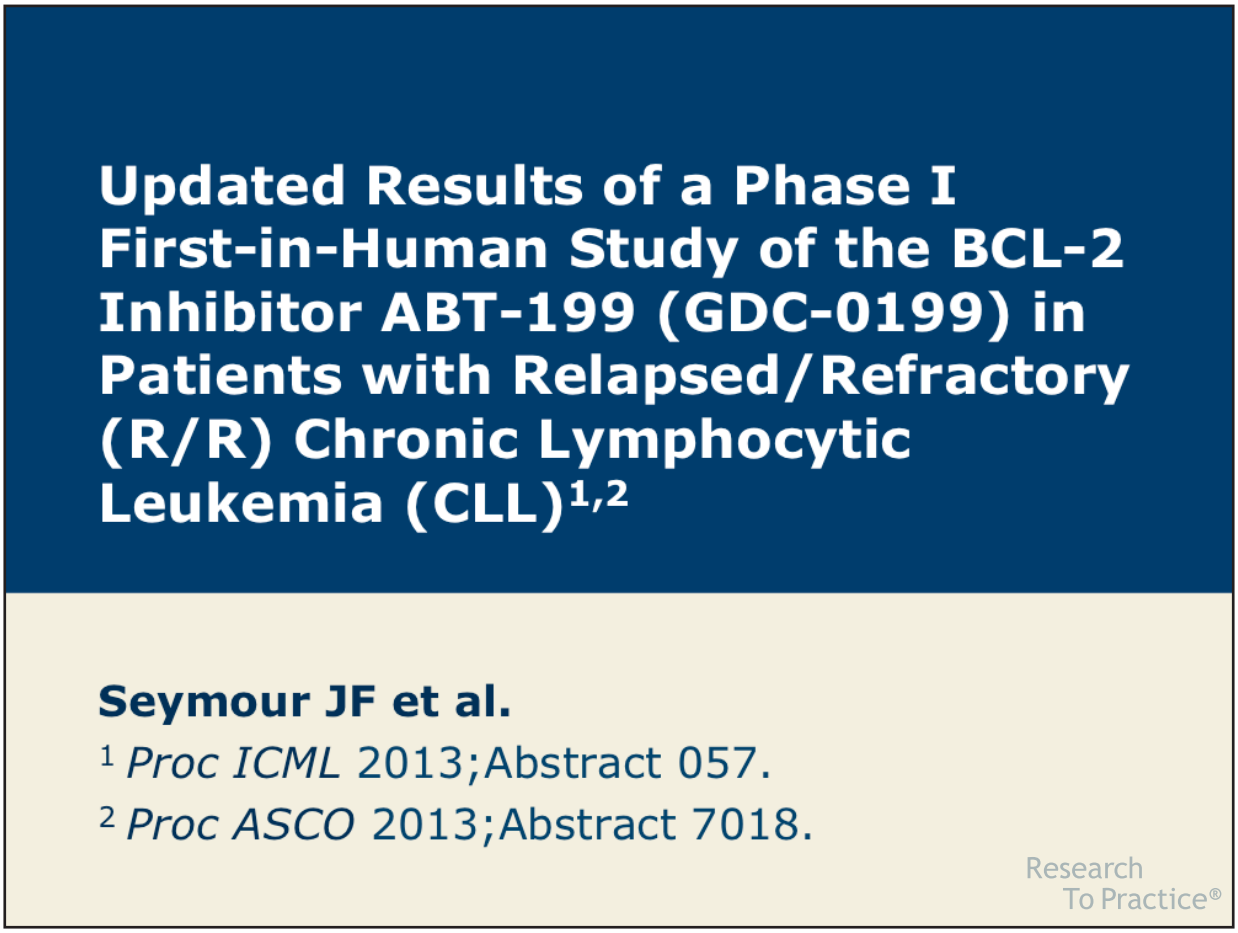
Updated Results of a Phase I Study of ABT-199 in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia

Presentations discussed in this issue

Seymour JF et al. **Updated results of a Phase I first-in-human study of the Bcl-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL).** *Proc ASCO* 2013;**Abstract 7018**.

Seymour J et al. **Updated results of a Phase I first-in-human study of the BCL-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL).** *Proc ICML* 2013;**Abstract 057**.

Slides from presentations at ASCO 2013/ICML 2013 and transcribed comments from a recent interview with Brad S Kahl, MD (9/10/13)



Background

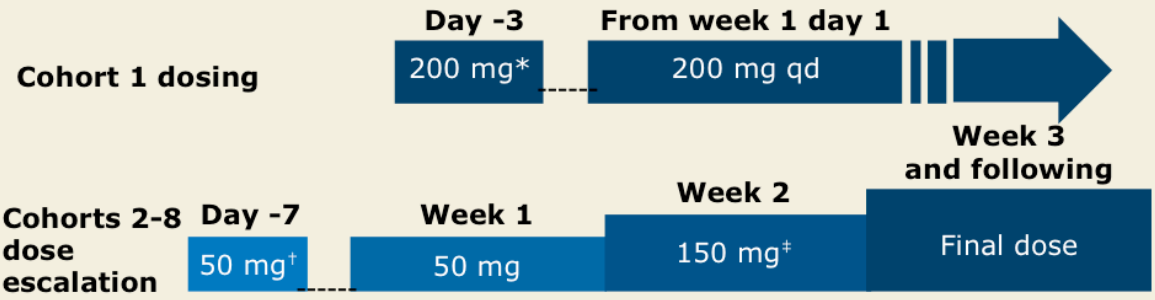
- Inhibition of the antiapoptotic protein BCL-2 shows promise for the treatment of CLL that is refractory to fludarabine (F) or CLL with 17p deletion (*Nat Med* 2013; 19(2):202-8).
- ABT-199 is an orally bioavailable, selective BCL-2 inhibitor with a greater than 500-fold higher affinity for BCL-2 than for the antiapoptotic protein BCL-2-like 1 (BCL-XL) (*Nat Med* 2013;19(2):202-8).
- **Study objective:** To determine the safety, pharmacokinetics, maximum tolerated dose, recommended Phase II dose and preliminary efficacy of ABT-199 in patients with relapsed or refractory CLL.

Seymour JF et al. *Proc ICML* 2013;Abstract 057; *Proc ASCO* 2013;Abstract 7018.

Phase I Dose-Escalation Trial Design

Eligibility (n = 56)

CLL relapsed/refractory to F or alkylator-based regimens
No prior allogeneic or autologous stem cell transplant



* An initial dose of 100 mg was administered to 1 patient; † 3 patients (1 each in cohort 2 and 3, and 1 in cohort 5) received 20 mg of ABT-199 as the initial dose; ‡ Week 2 dose in cohorts 2-5 = 100 mg

- After 3/3 patients in cohort 1 experienced dose-limiting tumor lysis syndrome, the initial dose was reduced and dosing was modified to include a stepped dose-escalation schedule.

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

Patient Demographics

Characteristic	n = 56*
Age, median (range)	67 years (36-86)
Males	73%
Prior lines of therapy, median (range)	4 (1-10)
F-refractory CLL	32%
Del(17p) mutation	38%
Diagnosis (CLL/SLL)	49/7

* As of April 2013, 56 patients were enrolled and 40 were active in the study.

Seymour JF et al. *Proc ICML* 2013;Abstract 057; *Proc ASCO* 2013;Abstract 7018.

Best Responses

All evaluable patients	(n = 55)*
Overall response rate	**84%**
Complete response (CR)	11%
CR/incomplete marrow recovery	7%
Partial response	65%
Stable disease	7%
Disease progression	2%

* One patient had not reached week 6 for evaluation by scan; 4 patients discontinued prior to assessment at week 6.

- 30/30 patients had a >50% reduction in lymphocyte counts from baseline.
- 45/51 patients experienced a >50% reduction in nodal size from baseline by CT scan.
  - Median time to 50% reduction = 43 days
- 27 patients had a >50% reduction in bone marrow infiltrate from baseline.

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

Best Responses in Evaluable Patients with High-Risk CLL

CLL with del(17p)	n = 16*
Overall response rate	**81%**
Complete response (CR)	6%
CR/incomplete marrow recovery	6%
Partial response	69%
Stable disease	6%
Disease progression	6%
Fludarabine-refractory CLL	**n = 18†**
Overall response rate	**78%**
CR/incomplete marrow recovery	17%
Partial response	61%
Stable disease	6%

* One patient had not reached week 6 for evaluation by scan; † 3 patients discontinued prior to week 6 assessment.

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

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Select Adverse Events

Event	All grades	Grade 3 or 4
Diarrhea	41%	2%
Neutropenia	39%	38%
Upper respiratory tract infection	27%	2%
Thrombocytopenia	18%	11%
Pyrexia	14%	2%
Anemia	13%	7%
Hyperglycemia	11%	9%
Tumor lysis syndrome*	11%	11%

* Includes 3 events from cohort 1; 2 clinical events and 1 laboratory event with the new dosing schedule

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

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Tumor Lysis Syndrome (TLS)

- ABT-199 has antitumor activity in patients with relapsed/refractory CLL who have bulky disease.
- TLS occurred in all 3 patients in cohort 1.
- With the revised dosing regimen, clinical TLS occurred in 2 patients (1 with acute renal failure and 1 death) who had bulky lymphadenopathy (≥10 cm).
- Key proposed study changes:
  - Further modify the dosing scheme to use a lower starting dose and then reduce dose-escalation increments.
  - Enhance current prophylaxis measures and monitoring for all patients.

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

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Author Conclusions

- Single-agent ABT-199 demonstrated activity in patients with relapsed/refractory CLL, including those with del(17p) and fludarabine-refractory disease.
- TLS can be associated with rapid tumor reduction.
  - A titrated dosing scheme combined with more aggressive prophylaxis, monitoring and management may provide adequate protection for patients.
- ABT-199 warrants further single-agent and combination trials in CLL.
- A Phase II single-agent study and a Phase III combination study in CLL are planned to start in late 2013/early 2014.

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

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Investigator Commentary: Results of a Phase I Trial of ABT-199 in Relapsed or Refractory CLL

ABT-199 is a small-molecule oral inhibitor of BCL-2, a protein that is overexpressed in many B-cell malignancies. ABT-199 has a high affinity for BCL-2 but leaves other BCL-2 family members relatively intact, such as BCL-XL. One problem with previous BCL-2 inhibitors was thrombocytopenia. More selective agents like ABT-199 seem to have taken care of this issue. Single-agent ABT-199 appears to be remarkably active in CLL/SLL. In this Phase I study, the overall response rate was 84%. The response rate was similar in the high-risk population, such as patients with del(17p) or fludarabine-refractory CLL, to that in the overall population. ABT-199 was well tolerated. The major side effects were nausea and diarrhea. These side effects can be easily managed, sometimes with supportive care alone or by small dose reductions. One of the challenges with ABT-199 is that it's so active that some cases of tumor lysis syndrome have arisen, so the study had to use a stepped-up dose-escalation strategy, in which you start therapy with a baby dose and careful monitoring for a few days, after which a gradually higher dose can be used. This might take 2 to 3 weeks to build up to the target dose, which for CLL appears to be 400 mg daily. I believe ABT-199 will be a "home-run" drug in CLL/SLL.

Interview with Brad S Kahl, MD, September 10, 2013