5 Minute JournalClub

POST-ASH Issue 2, 2013

PI3K Delta Inhibitor Idelalisib (GS-1101) with Rituximab and/or Bendamustine for Relapsed/Refractory CLL

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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

5 MinuteJournalClub

POST-ASH Issue 2, 2013

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 — R^2") 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 R^2 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 R^2 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 R^2 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.

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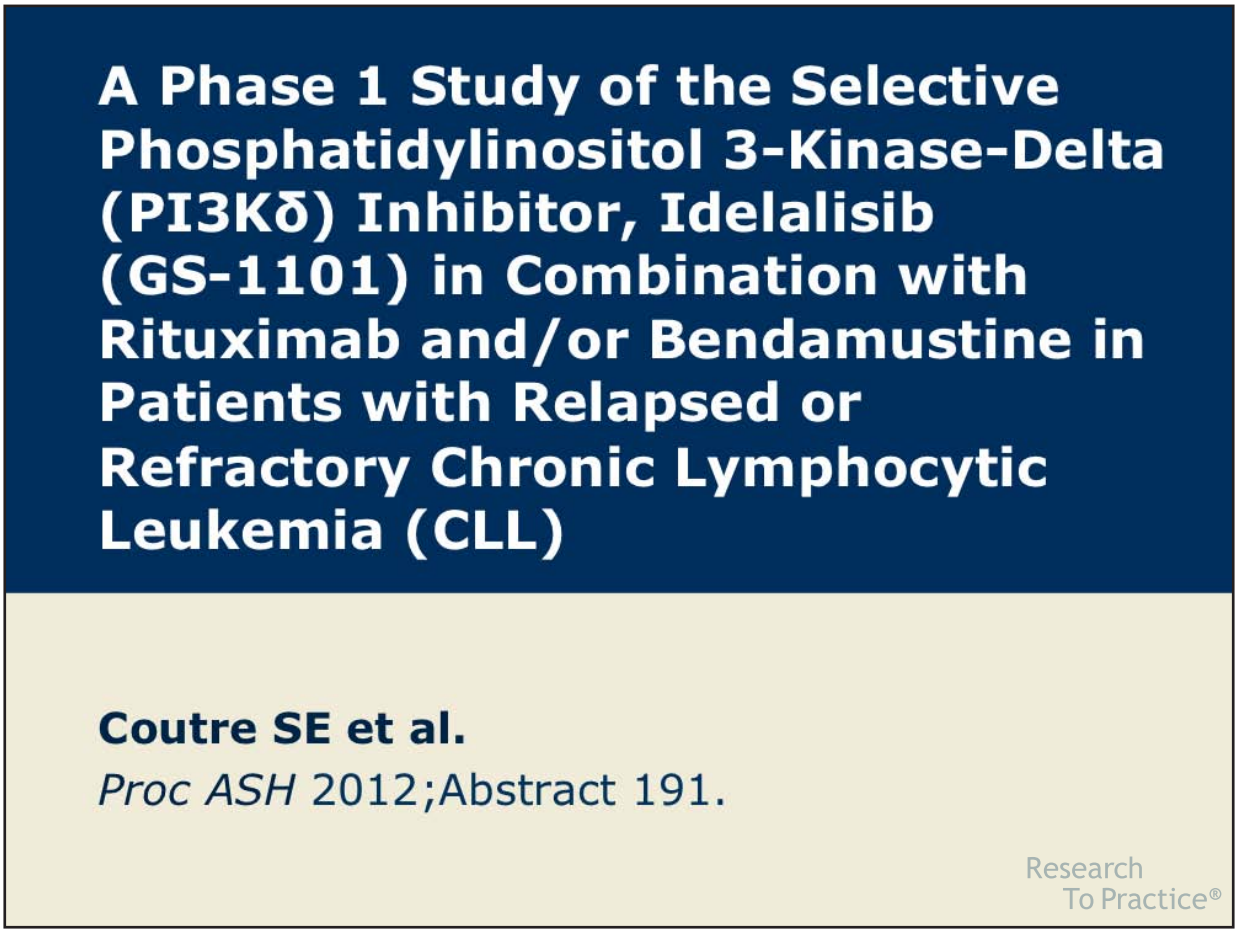
PI3K Delta Inhibitor Idelalisib (GS-1101) with Rituximab and/or Bendamustine for Relapsed/Refractory CLL

Presentation discussed in this issue

Coutre SE et al. **Combinations of the selective phosphatidylinositol 3-kinase-delta (PI3Kdelta) inhibitor GS-1101 (CAL-101) with rituximab and/or bendamustine are tolerable and highly active in patients with relapsed or refractory chronic lymphocytic leukemia (CLL): Results from a Phase I study.** *Proc ASH* 2012;**Abstract 191**.

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



Background

- CLL treatment regimens have substantial toxicity and are less effective with recurrent use.
- PI3Kδ drives proliferation, homing and survival of CLL cells (*Blood* 2010;116(12):2078).
- Monotherapy with idelalisib (GS-1101), an orally bioavailable small molecule inhibitor of PI3Kδ, has shown considerable activity in patients with heavily pretreated CLL (*Expert Opin Invest Drugs* 2012;21(1):15-22).
- **Study objective**: To evaluate the safety and efficacy of idelalisib in combination with rituximab (R) and/or bendamustine (B) for relapsed/refractory CLL.

Coutre SE et al. *Proc ASH* 2012;Abstract 191.

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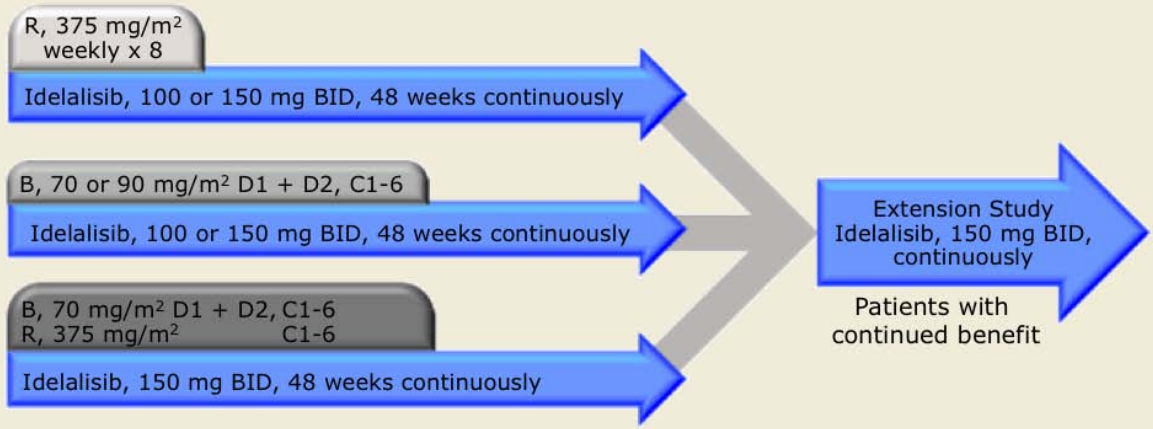
Phase Ib Combination Study Design

Eligibility (n = 52)

Relapsed/refractory CLL requiring treatment by 2008 International Workshop on CLL criteria



Coutre SE et al. *Proc ASH* 2012;Abstract 191.

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Demographics and Baseline Characteristics

	Combination			All (N = 52)
	Idelalisib + R (N = 19)	Idelalisib + B (N = 18)	Idelalisib + BR (N = 15)	
Age, median (range), years	66 (54-87)	64 (41-86)	61 (45-72)	64 (41-87)
Gender, males, %	68	44	60	58
Bulky adenopathy,[a] %	58	61	67	62
Refractory disease,[b] %	37	72	47	52
Prior therapies, median (range), n	2 (1-8)	3 (1-9)	4 (1-9)	3 (1-9)

[a] Presence of ≥1 node with diameter ≥5 cm

[b] Progression within 6 months of last therapy

Coutre SE et al. *Proc ASH* 2012;Abstract 191.

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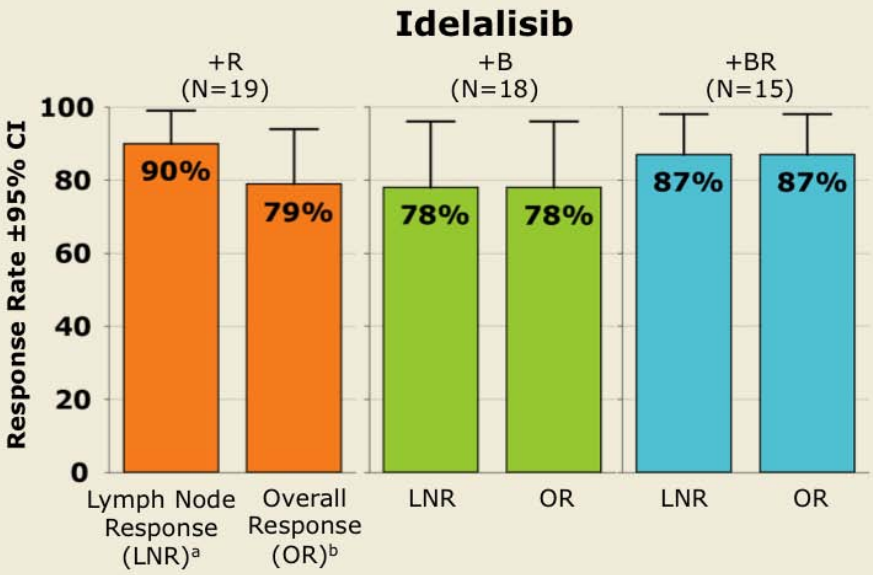
Nodal and Overall Response Rate (ITT Population)



[a] Decrease by ≥50% in the nodal SPD [b] Response by 2008 IWCLL criteria

With permission from Coutre SE et al. *Proc ASH* 2012;Abstract 191.

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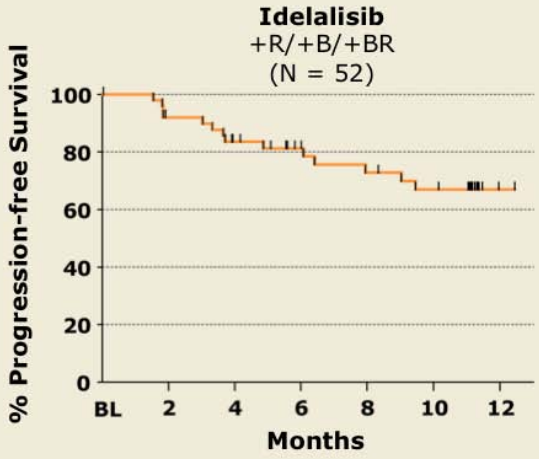
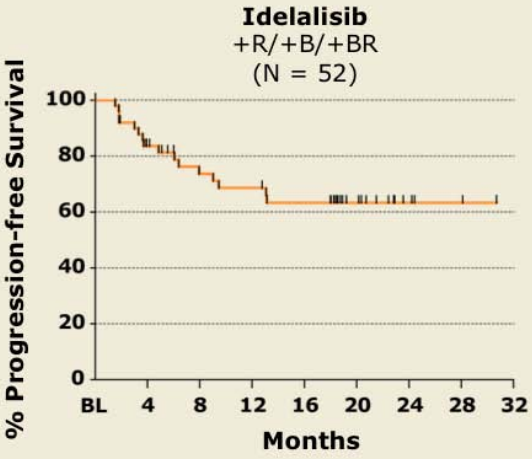
Progression-Free Survival (ITT Population)

Primary study



Median PFS: not reached
1-year PFS: 67.1%

Primary + Extension study



Median PFS: not reached
1-year PFS: 68.7%; 2-year PFS: 63.4%

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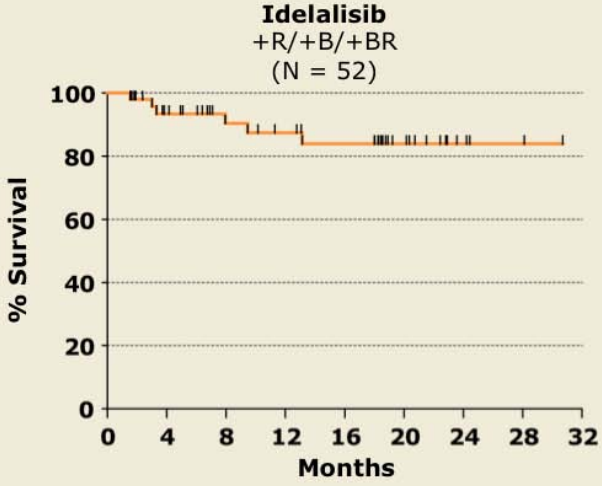
Overall Survival (ITT Population)

Primary + Extension study



Median OS: not reached
1-year OS: 87.5%; 2-year OS: 84.0%

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Select Adverse Events (AEs)

Grade ≥3 AEs*	(n = 52)
Febrile neutropenia	15%
Pneumonia	12%
Transaminase elevation	10%
Diarrhea	6%
Dyspnea	4%
Pyrexia	6%

*Analysis of primary study

- AEs leading to drug discontinuation: abdominal pain (n = 1), autoimmune hemolytic anemia (n = 1), febrile neutropenia (n = 1), neutropenia (n = 1), pneumonia (n = 1), pneumonitis (n = 1), rash erythematous (n = 1), sepsis (n = 1)

Coutre SE et al. *Proc ASH* 2012;Abstract 191.

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Author Conclusions

- A lack of overlapping toxicities allowed idelalisib delivery at the full single-agent starting dose (150 mg BID) when coadministered with rituximab (R), bendamustine (B) or bendamustine/rituximab (BR).
- Idelalisib was generally well tolerated in combination therapy over periods of exposure up to 2½ years.
- Idelalisib combination therapy was highly active in patients with heavily pretreated CLL.
- Combinations of idelalisib with BR and R for the treatment of relapsed/refractory CLL are currently being evaluated in Phase III trials (GS-US-312-0115 and -0116).

Coutre SE et al. *Proc ASH* 2012;Abstract 191.

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Investigator Commentary: Idelalisib (GS-1101) in Combination with Rituximab and/or Bendamustine for Patients with Relapsed or Refractory CLL

Idelalisib is an oral, specific PI 3-kinase delta isoform inhibitor that has been quite active as a single agent in Phase I trials involving a variety of histologies, including CLL. It is well tolerated except for some transaminitis. The authors of this Phase I study took the next step of evaluating idelalisib and rituximab or bendamustine or the combination. The study enrolled about 50 patients with refractory CLL, of whom about half had bulky disease. Patients had received a median of about 3 prior regimens. All 3 combinations evaluated were active and well tolerated. Response rates and 1-year progression-free survival were much higher than one would have expected with idelalisib alone. It's difficult to ascertain from the small numbers of patients whether one of the doublets is better than another, but it would be nice if rituximab/idelalisib was as good as the others, with the goal of being able to eliminate chemotherapy. It could be another example of an exciting doublet of biological targeted agents that are as good as or at least almost as good as combining the agent with chemotherapy.

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

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