



POST-ASH Issue 3, 2015

**Second Interim Analysis of a Phase III
Study of Idelalisib and Rituximab for
Patients with Relapsed CLL with 17p
Deletion and Other Adverse Cytogenetics**

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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 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 the management of chronic lymphocytic leukemia (CLL) 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

- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens — including next-generation anti-CD20 antibodies and PI3 kinase, BTK and Bcl-2 inhibitors — under evaluation for previously untreated and relapsed/refractory CLL and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Appreciate the recent FDA approvals of novel targeted agents indicated for the treatment of newly diagnosed and relapsed/refractory CLL, and discern how these treatments can be appropriately integrated into clinical practice.
- Compare and contrast the benefits and risks of chemoimmunotherapy with fludarabine/cyclophosphamide/rituximab versus bendamustine/rituximab as first-line therapy for fit patients with CLL.
- Apply recent clinical research findings with the newly FDA-approved combination of obinutuzumab and chlorambucil to the care of patients with previously untreated CLL.
- Recall the activity of salvage therapy with obinutuzumab and chlorambucil after treatment failure of chlorambucil alone in patients with CLL and comorbidities.

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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

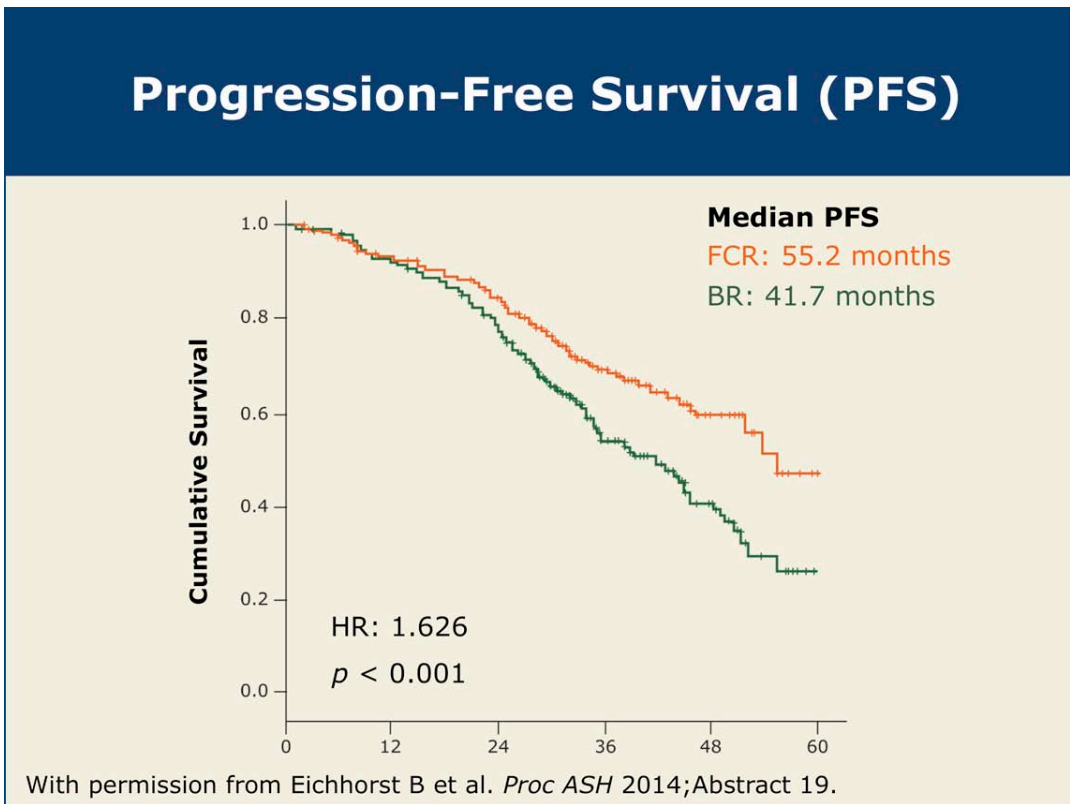
Last review date: April 2015

Expiration date: April 2016

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

When the German CLL Study Group — one of the most prolific clinical trial organizations in the world — launched the landmark Phase III CLL10 trial in 2008, few, if any, expected that the central question the study sought to answer would in essence be outdated by the time the results became available. CLL10 focused on a classic oncology research issue — the comparative clinical benefits of 2 chemobiologic regimens (fludarabine/cyclophosphamide/rituximab [FCR] and bendamustine/rituximab [BR]), and although the results as summarized below have important practical clinical implications today, it is increasingly evident that the overall treatment strategy in this disease is undergoing a massive reconfiguration. For that reason, this issue of *5-Minute Journal Club* evaluates not only the seminal CLL10 trial findings but also a sample of 2014 ASH data sets on several new agents, regimens and strategies that have burst onto the scene in the past couple of years and have many investigators thinking that chronic lymphocytic leukemia (CLL) may soon fall into the basic clinical paradigm of chronic myelogenous leukemia (CML) — namely a chronic disease requiring long-term outpatient management that may be associated with prolonged survival.

Here’s a summary of what happened in San Francisco related to CLL.



CLL10: FCR versus BR (patients without del[17p])

The updated data from CLL10 continue to support what clinical experience had already strongly suggested, namely that FCR yields clear-cut improvements in disease-related outcomes, including a statistically and clinically significant increase in median progression-free survival (PFS) (55.2 versus 41.7 months) and rates of bone marrow minimal residual disease (MRD) negativity at final restaging (26.6% versus 11.1%). However, with less than 3 years of follow-up, no overall survival benefit has been seen. Just as predictably, the data reveal that FCR produced considerably more toxicity, particularly in older individuals (>65 years) in whom the rate of infection was 47.7% compared to 20.6% with BR. The bottom line is that most investigators believe that both regimens have a role and the risk for toxicity must be carefully considered during patient selection.

Impact of MRD status

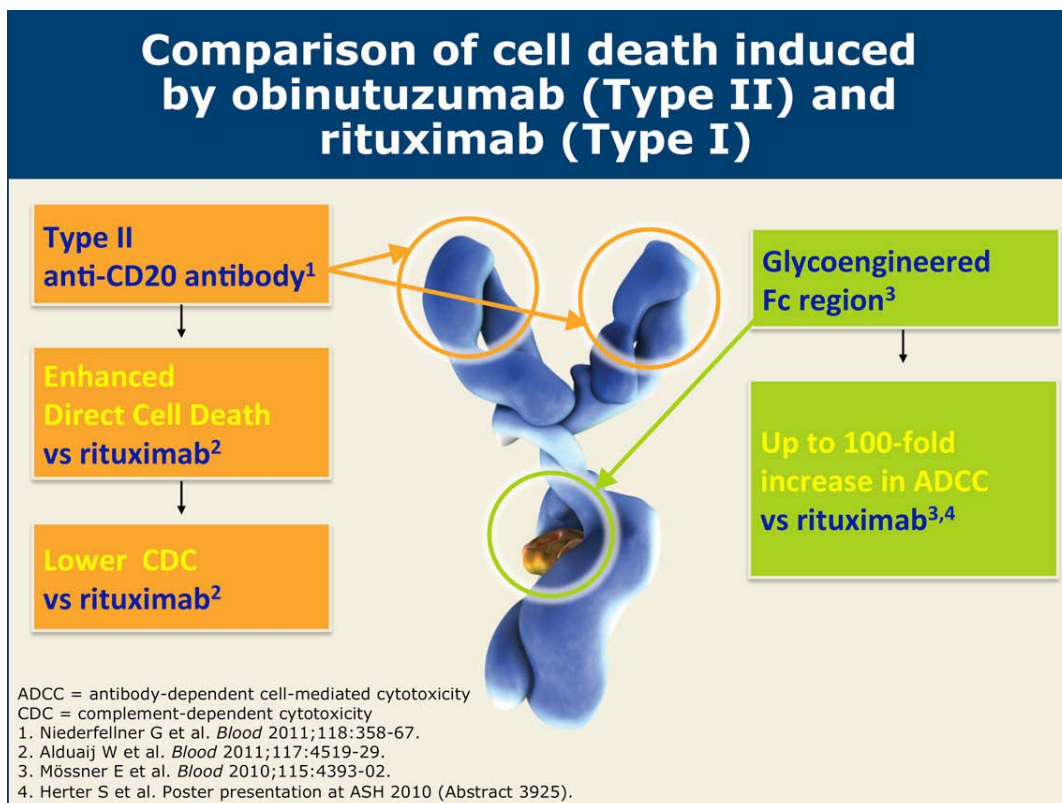
The intriguing concept of defining undetectable levels of disease after treatment to better understand potential prognosis has been explored in various forms across many hematologic cancers. In this regard, at ASH we saw a **report from the German group** evaluating pooled data from the CLL8 (FC versus FCR) and CLL10 trials examining the value of peripheral blood MRD-negative status at response evaluation. What was seen was a strong correlation between MRD status and outcome that seemed at least as predictive of PFS as clinical response, and of particular interest, patients considered to have a partial response clinically had a much better prognosis if their bone marrow was MRD-negative (61.7 versus 28.1 months). Discussions are now ongoing about how to integrate MRD status into prospective trial design and potentially clinical decision-making.

Obinutuzumab (Ob)

Since the FDA approval of Ob in combination with chlorambucil — a drug that many had not been regularly using for CLL — there has been constant questioning about whether this novel Type II anti-CD20 antibody could be employed with other chemotherapeutic regimens. Not surprisingly, a number of studies are ongoing that examine this issue, including the Phase III GREEN trial, which is targeting 800 patients with both previously treated and untreated CLL and evaluates Ob alone or with one of several types of chemotherapy. This effort is also interesting in that it examines a modified dosing scheme of 25 mg on day 1 and 975 mg on day 2 in an attempt to address the high rates of infusion-related reactions that have previously been reported with Ob. At ASH we saw **early safety data** from the previously untreated cohort in the study, which showed a 13.3% rate of Grade 3 or higher infusion-related reactions with 2.5% of patients discontinuing treatment due to this side effect. As greater experience is gained with this interesting agent, it has become clear that these infusion reactions occur mainly during the first cycle and may be related to cell death and/or cytokine release. Efficacy findings from this study are not yet available, and until then, clinicians will need to consider whether they want to dust off chlorambucil and give it a go with Ob. Interestingly, during a recent interview for our audio series with investigator Dr Jeffrey

Sharman, I was surprised to learn that he avoids this issue altogether and unabashedly uses Ob alone as up-front therapy in select patients.

Clearly, the German CLL group was busy at ASH as they also treated us to **more from the pivotal CLL11 trial**, which was first presented at ASCO 2013 and paved the way for the approval of Ob. From that and related presentations, we learned, among other things, that Ob/chlorambucil is superior to rituximab/chlorambucil in a number of ways, including rates of MRD negativity in blood (38% versus 3%). Additional data unveiled at ASH evaluated patients in the trial who were initially randomly assigned to chlorambucil alone but upon relapse (generally due to lack of response to chlorambucil) were crossed over to Ob/chlorambucil. Of great interest, 26 of 30 patients (87%) experienced objective responses, further suggesting that Ob itself might have significant and perhaps underappreciated intrinsic anti-CLL activity that is greater than that previously observed with rituximab monotherapy, an important and useful therapeutic tool in follicular lymphoma.



Anti-CD20 maintenance in CLL

Although maintenance rituximab has been commonly used in many patients receiving R-chemotherapy for follicular and mantle-cell lymphoma, our survey and polling data have clearly illustrated that hematologic investigators do not endorse this approach in CLL. However, provocative results from **2 interesting trials** unveiled at ASH have some beginning to reevaluate this stance.

First, the AGMT-CLL8/a trial randomly assigned 263 patients who completed first- or second-line chemotherapy/rituximab to 24 months of rituximab maintenance or observation and demonstrated an approximately 50% reduction in the rate of disease

progression with maintenance. No survival benefit was seen, although crossover in the control group was allowed. The other related and cleverly named Phase III effort (the PROLONG trial) evaluated ofatumumab maintenance after second- or third-line treatment with chemotherapy/anti-CD20, and again there was an approximate 50% reduction in risk of disease progression. Although more data on this important question would be ideal, some investigators feel that these results are enough to compel clinicians to discuss and/or recommend this approach in select patients, at least until the many new options and treatments are sorted out.

Ibrutinib

You can't attend a conference these days without witnessing a new and relevant data set with this blockbuster Bruton tyrosine kinase inhibitor, and ASH was no exception, as we saw results from the Phase II RESONATE™-17 trial focused on 144 patients with del(17p) CLL who experienced disease progression while receiving between 1 and 4 prior lines of therapy. Perhaps not surprisingly, as few of these studies fail to disappoint, most patients had objective responses, and about 80% were progression free at 1 year. These relevant findings are central to the current first-line approval of the drug in this situation. However, it is important to note that although ibrutinib results in similar response rates in this population, these patients have shorter PFS and overall survival.

Interestingly, there is a belief that del(17p) may only be part of the story, and for that reason investigators at MD Anderson evaluated CKT (complex metaphase karyotype by whole genome sequencing defined as 3 or more distinct chromosomal abnormalities) in 100 consecutive cases of CLL treated with ibrutinib. What they found is that CKT is a better predictor of benefit from ibrutinib than del(17p). However, this clearly needs additional confirmation before whole genome sequencing makes its way into trials or clinical practice.

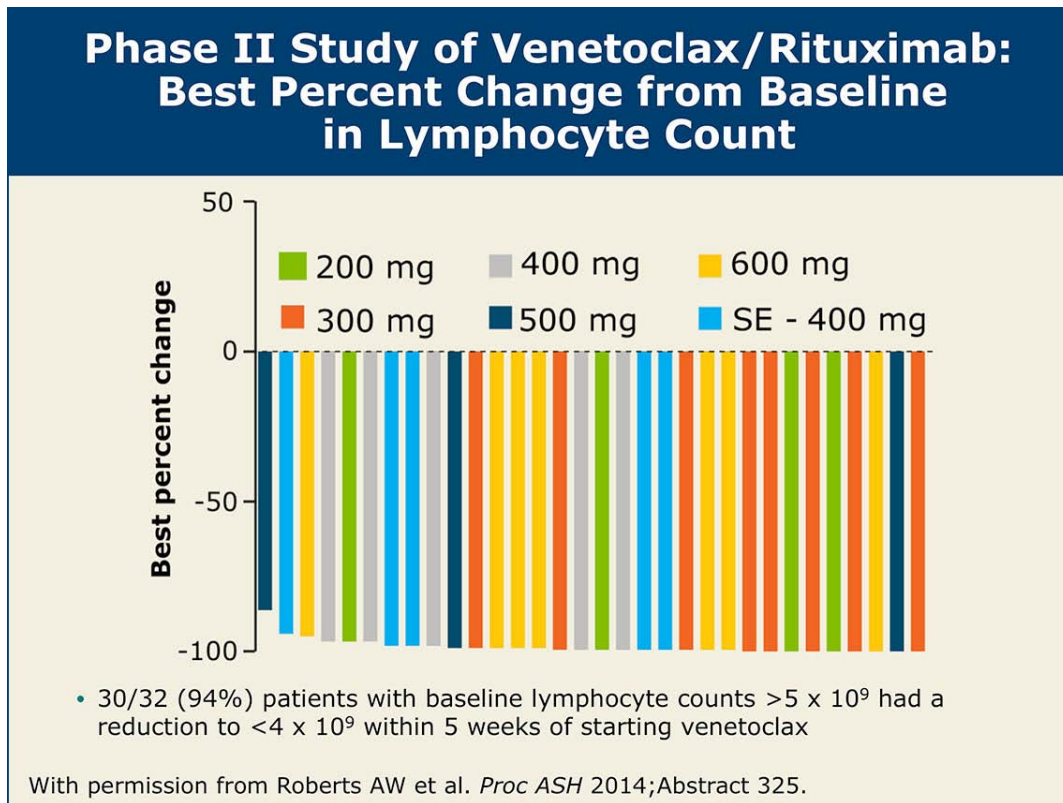
Idelalisib

One of the important features of ibrutinib in CLL is the consistency of response in patients with adverse prognostic factors like 17p deletion, but the drug is not alone in this regard. At ASH we saw a **subset analysis** from the major Phase III trial reported in the *New England Journal* demonstrating that idelalisib/rituximab is a highly effective regimen, including in patients with del(17p), del(11q) and unmutated IGHV. These findings suggest that this regimen may have an important early role in patients with these genetic abnormalities who have previously received or are not candidates for ibrutinib.

Venetoclax (formerly ABT-199)

Despite the new moniker, more data presented at ASH reveal that things remain entirely the same and that this novel Bcl-2 inhibitor/antiapoptotic agent is a very active drug. Most notably, in a **Phase II trial** of 49 patients with relapsed or refractory CLL/small lymphocytic lymphoma, the combination of venetoclax with rituximab demonstrated an impressive 88% objective response rate with 31% complete response (CR) or CR with incomplete blood count recovery, including in 7 of 9 patients with

del(17p). MRD negativity in the bone marrow was recorded in 17 patients. Significantly, 5 dose cohorts were studied, and it appears that a schedule was uncovered that seems to avoid tumor lysis syndrome — a complication reported previously with this agent.



Although it remains to be seen how these novel and encouraging therapies will be optimally mixed, matched and sequenced in CLL, it seems highly likely that the survival of patients will continue to be extended and perhaps soon mirror the normal life expectancies of patients under active treatment for CML. ASH 2014 will be remembered as another important step forward in this rewarding march toward a new standard.

Next on this series, we provide an ASH update on myeloproliferative neoplasms, including more data on the most recently approved treatment in these diseases, the use of ruxolitinib in polycythemia vera.

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Miami, Florida

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Second Interim Analysis of a Phase III Study of Idelalisib and Rituximab for Patients with Relapsed CLL with 17p Deletion and Other Adverse Cytogenetics

Presentation discussed in this issue

Sharman J et al. **Second interim analysis of a phase 3 study of idelalisib (Zydelig) plus rituximab for relapsed chronic lymphocytic leukemia: Efficacy analysis in patient subpopulations with del(17p) and other adverse prognostic factors.** *Proc ASH 2014*; **Abstract 330**.

Slides from a presentation at ASH 2014 and transcribed comments from a recent interview with Jonathan W Friedberg, MD, MMSc (1/8/15)

Second Interim Analysis of a Phase 3 Study of Idelalisib Plus Rituximab (R) for Relapsed Chronic Lymphocytic Leukemia (CLL): Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors

Sharman JP et al.

Proc ASH 2014; Abstract 330.

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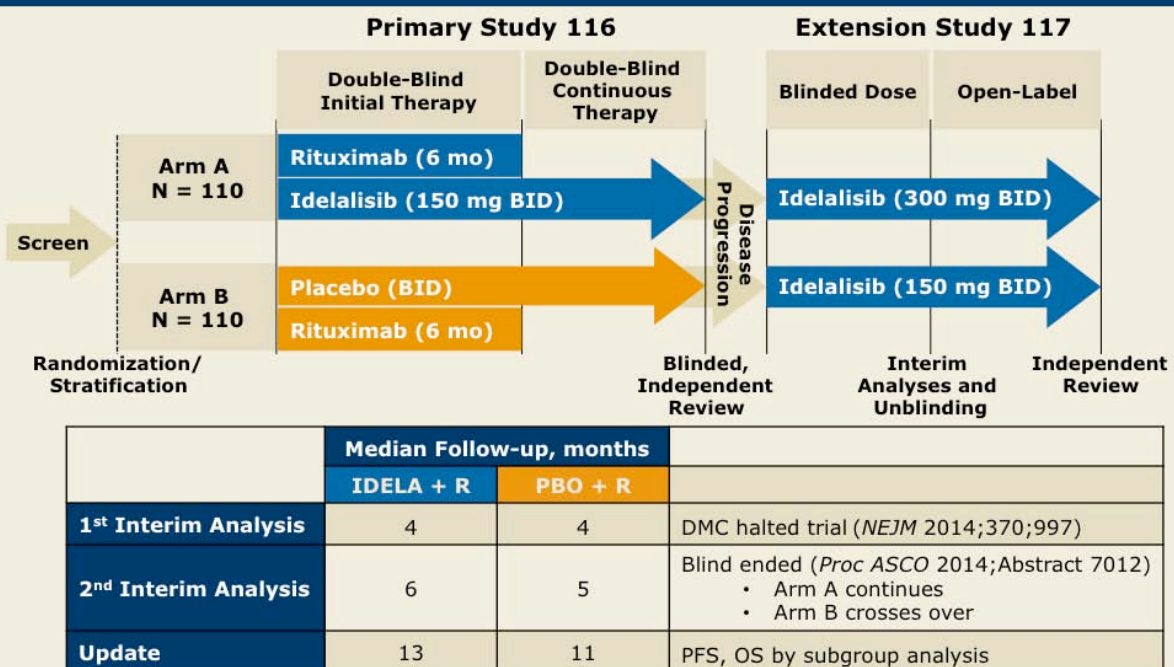
Background

- There is a high unmet need for the treatment of frail patients with relapsed CLL, particularly those characterized by adverse prognostic factors such as the presence of del(17p) and/or TP53 mutations.
- Idelalisib, a first-in-class, targeted, highly selective, oral inhibitor of PI3K-delta, was recently approved in combination with R for the treatment of relapsed CLL on the basis of the first interim analysis results of a Phase III trial of idelalisib/R versus placebo/R (*NEJM* 2014;370;997).
 - Median progression-free survival (PFS): Not reached versus 5.0 months (HR: 0.15; $p < 0.001$).
- **Study objective:** To describe results of the second interim analysis of a Phase III trial of idelalisib and R for patients with relapsed CLL, with a focus on patients with adverse cytogenetics.

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

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Phase III Trial Design



Sharman JP et al. *Proc ASH* 2014;Abstract 330.

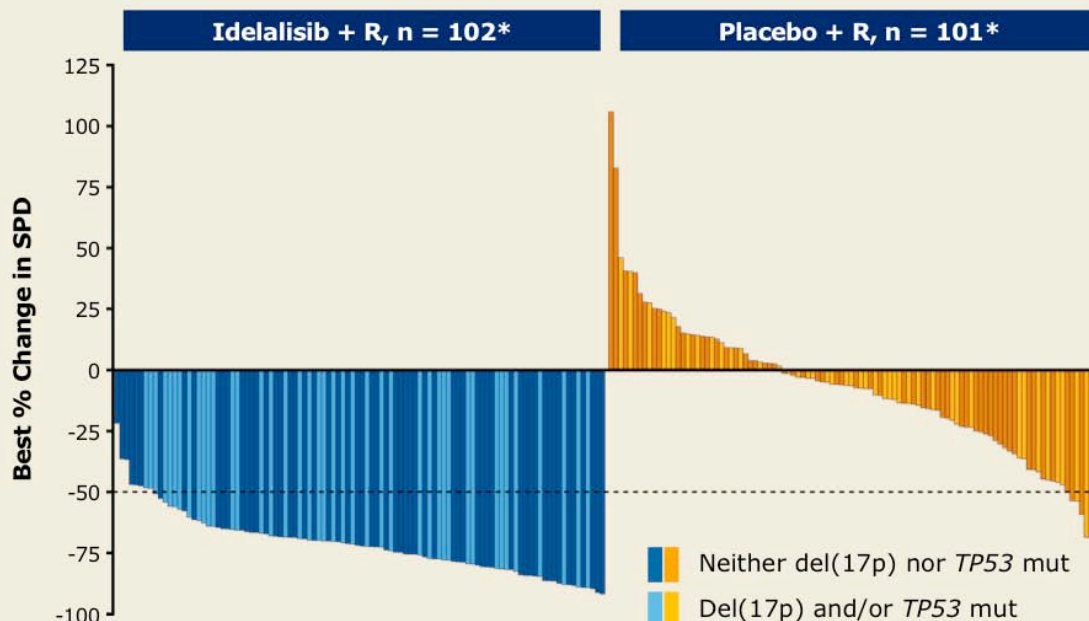
Eligibility Criteria

Criteria	Requirement
Relapsed CLL	<ul style="list-style-type: none"> • CLL progression <24 months since last therapy • Treatment warranted according to IWCLL criteria
Lymphadenopathy	Presence of ≥ 1 measurable nodal lesion
Prior therapies	≥ 1 anti-CD20 antibody-containing therapy or ≥ 2 prior cytotoxic therapies
Appropriate for non-cytotoxic therapy	CIRS score >6 or creatine clearance <60 mL/min (≥ 30 mL/min) or Grade 3 or 4 neutropenia or thrombocytopenia due to prior myelotoxicity
Bone marrow function	Any grade anemia, neutropenia or thrombocytopenia allowed
Karnofsky score	≥ 40

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

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Second Interim Analysis: Lymph Node Response



*Evaluable patients

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Second Interim Analysis: Overall Response Rate

Patient category (n)*	Idelalisib + R	Placebo + R
All patients (n = 106, 107)	77%	15%
Rai Stage III/IV (n = 67, 70)	70%	13%
Unmutated IGHV (n = 87, 90)	77%	16%
Del(17p)/TP53 mutant (n = 44, 47)	82%	13%
Del(11q) (n = 25, 23)	68%	17%
ZAP70-positive (n = 94, 91)	76%	17%
CD38-positive (n = 59, 49)	78%	16%
B2M (>4 mg/L) (n = 90, 80)	77%	16%

* Evaluable patients at time of analysis

B2M = beta-2 microglobulin

For all patient categories, the odds ratio was in favor of idelalisib + R

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

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Second Interim Analysis: Median PFS

Patient category (n)*	Idelalisib + R	Placebo + R
All patients (n = 110, 110)	NR	5.5 mo
Rai Stage III/IV (n = 70, 72)	NR	13.0 mo
Unmutated IGHV (n = 91, 93)	NR	5.5 mo
Del(17p)/TP53 mutant (n = 46, 49)	NR	4.0 mo
Del(11q) (n = 25, 23)	10.7 mo	6.9 mo
ZAP70-positive (n = 98, 93)	NR	5.5 mo
CD38-positive (n = 62, 51)	NR	6.9 mo
B2M (>4 mg/L) (n = 94, 83)	NR	5.0 mo

* Evaluable patients at time of analysis

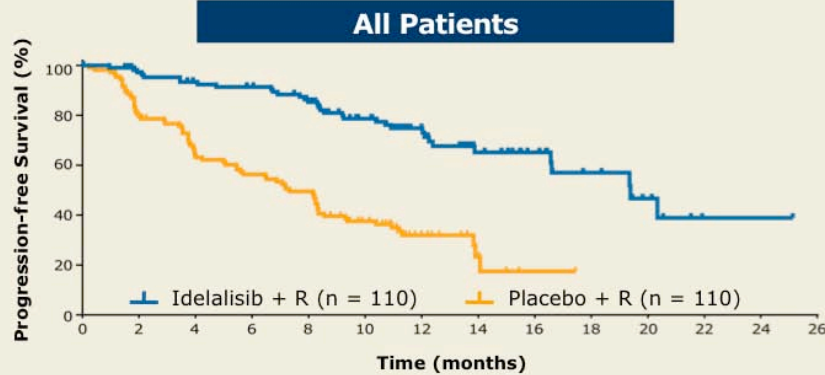
NR = not reached

For all patient categories, the hazard ratio was in favor of idelalisib + R

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

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PFS (Including Extension Study*)



	Median PFS	HR	p-value
IDELA + R	19.4 mo	0.25	<0.0001
PBO + R	7.3 mo		

* Placebo + R includes those patients who received open-label idelalisib after unblinding without prior disease progression (n = 42).

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Subgroup Analysis of PFS: Idelalisib + R Arm

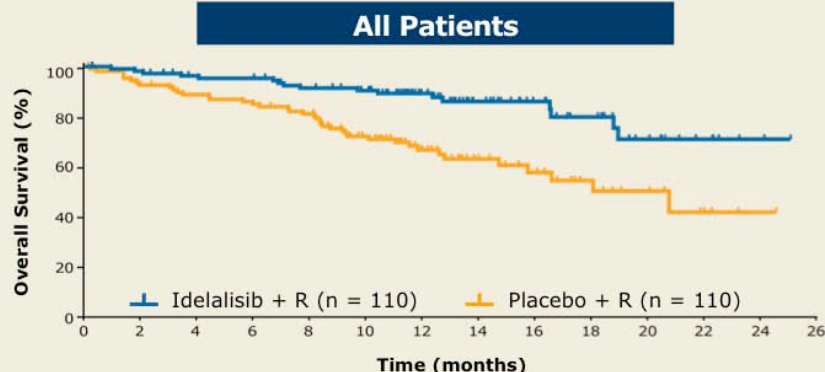
Median PFS*	Mutated (n = 19)	Unmutated (n = 91)	p-value
IGHV	NR	19.4 mo	0.75
Median PFS*	Present (n = 46)	Absent (n = 64)	p-value
Del(17p)/TP53 mut	16.6 mo	20.3 mo	0.94
Median PFS*	Present (n = 25)	Absent (n = 36)	p-value
Del(11q)	20.3 mo	19.4 mo	0.84

* Including extension study

Sharman JP et al. *Proc ASH 2014*;Abstract 330.

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Overall Survival (OS) (Including Extension Study*)



	Median OS	HR	p-value
IDELA + R	NR	0.34	0.0001
PBO + R	20.8 mo		

* As randomized, including cross-over

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Subgroup Analysis of OS According to Treatment

Median OS*	Idelalisib + R (n = 91)	Placebo + R (n = 93)	p-value
IGHV unmutated	NR	18.1 mo	0.0003
Median OS*	Idelalisib + R (n = 46)	Placebo + R (n = 49)	p-value
Del(17p)/TP53 mut	NR	14.8 mo	0.001
Median OS*	Idelalisib + R (n = 25)	Placebo + R (n = 23)	p-value
Del(11q)	NR	18.1 mo	0.21

* As randomized, including patients who crossed over

Sharman JP et al. *Proc ASH 2014*;Abstract 330.

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Select Grade ≥3 Adverse Events

Adverse event	Idelalisib + R (n = 110)		Placebo + R (n = 108)	
	2 nd IA	Update	2 nd IA	Update
Neutropenia	37%	41%	27%	43%
Thrombocytopenia	11%	14%	18%	20%
Increased ALT/AST	9%	6%	1%	6%
Pneumonia	8%	13%	9%	20%
Anemia	7%	8%	17%	24%
Diarrhea/colitis	6%	16%	0%	13%
Fatigue	5%	5%	3%	5%
Pyrexia	3%	6%	1%	3%
Dyspnea	3%	6%	3%	5%

IA = interim analysis

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

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Author Conclusions

- In this Phase III trial, the subgroup analysis demonstrated comparable efficacy of idelalisib in combination with R in the presence or absence of high-risk genomic alterations such as unmutated IGHV, del(17p)/TP53 mutation and del(11q).
- Overall survival was significantly improved for patients who received idelalisib in combination with R, despite the allowance for patients to cross over in the extension study design.
- In combination with R, idelalisib has a manageable safety profile in patients with relapsed or refractory CLL.

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

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Investigator Commentary: Second Interim Analysis of a Phase III Trial of Idelalisib and R for Relapsed CLL

On the basis of the first interim analysis of this study, idelalisib was recently FDA approved in combination with R for patients with relapsed CLL for whom R alone would be considered an appropriate therapy because of comorbidities. This current analysis is an important contribution to the FDA approval. It suggests that idelalisib has activity in particular populations of patients expected to have poor outcomes. It is a subset analysis of a previously published Phase III study (Furman RR et al. *NEJM* 2014;370:997) that demonstrated that idelalisib/R was better than R alone for patients with CLL requiring therapy.

This analysis demonstrates that for most patients with complicated high-risk cytogenetics, the median PFS for those who received idelalisib has not been reached and is about 5 months with R alone. The authors concluded that the presence of del(17p) does not appear to significantly affect outcome for patients who received idelalisib/R. This is similar to what is seen with ibrutinib, at least with a relatively short follow-up. Overall, idelalisib is another tool in our toolbox for patients with CLL harboring the del(17p) abnormality.

Interview with Jonathan W Friedberg, MD, MMSc, January 8, 2015