5 Minute JournalClub

POST-ASH Issue 3, 2015

Ibrutinib for Patients with Relapsed/ Refractory CLL and Association of Complex Karyotype with Outcomes

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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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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: April 2015
Expiration date: April 2016

5 MinuteJournalClub

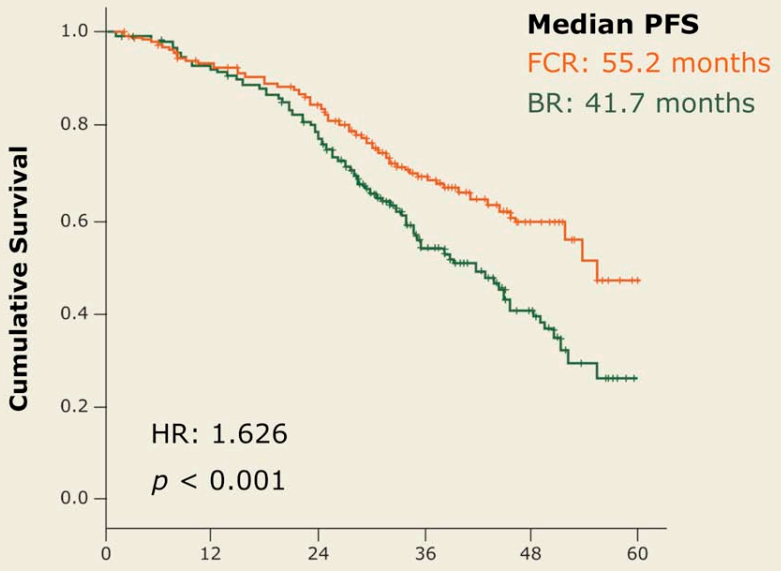
POST-ASH Issue 3, 2015

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.

Progression-Free Survival (PFS)



With permission from Eichhorst B et al. *Proc ASH* 2014;Abstract 19.

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.

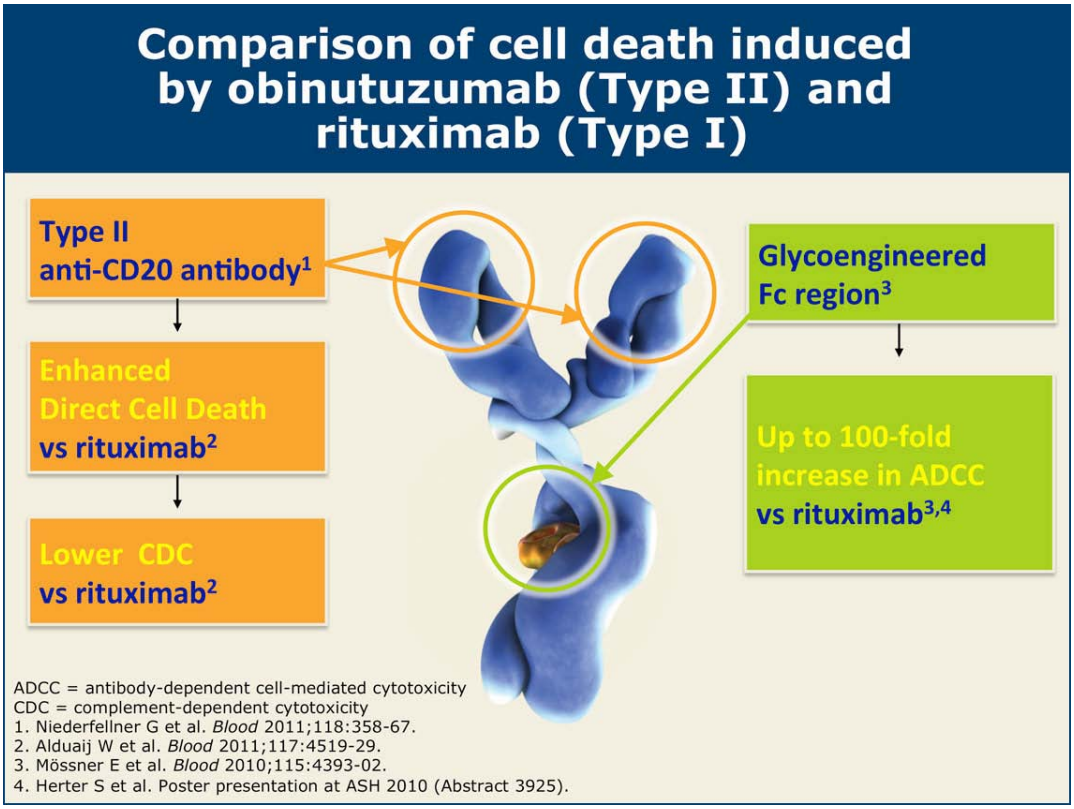
Obinutuzumab (Ob)

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

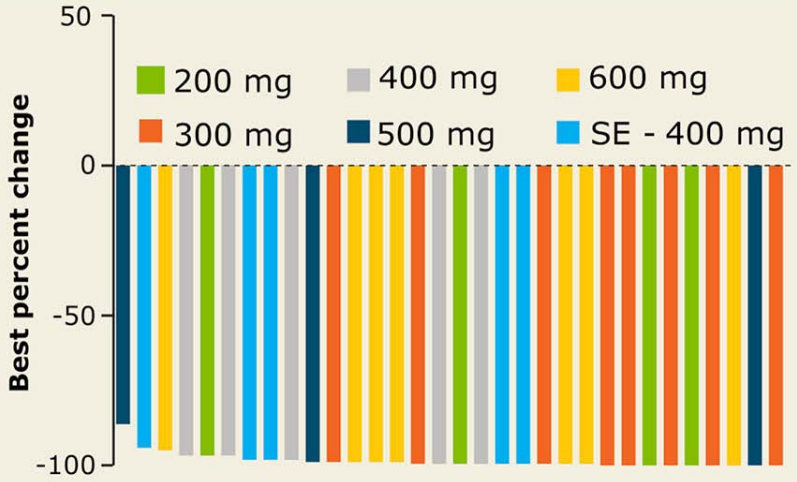
One of the important features of ibrutinib in CLL is the consistency of response in patients with adverse prognostic factors like 17p deletion, but the drug is not alone in this regard. At ASH we saw a **subset analysis** from the major Phase III trial reported in the *New England Journal* demonstrating 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.

Phase II Study of Venetoclax/Rituximab: Best Percent Change from Baseline in Lymphocyte Count



- 30/32 (94%) patients with baseline lymphocyte counts >5 x 10^9 had a reduction to <4 x 10^9 within 5 weeks of starting venetoclax

With permission from Roberts AW et al. *Proc ASH* 2014;Abstract 325.

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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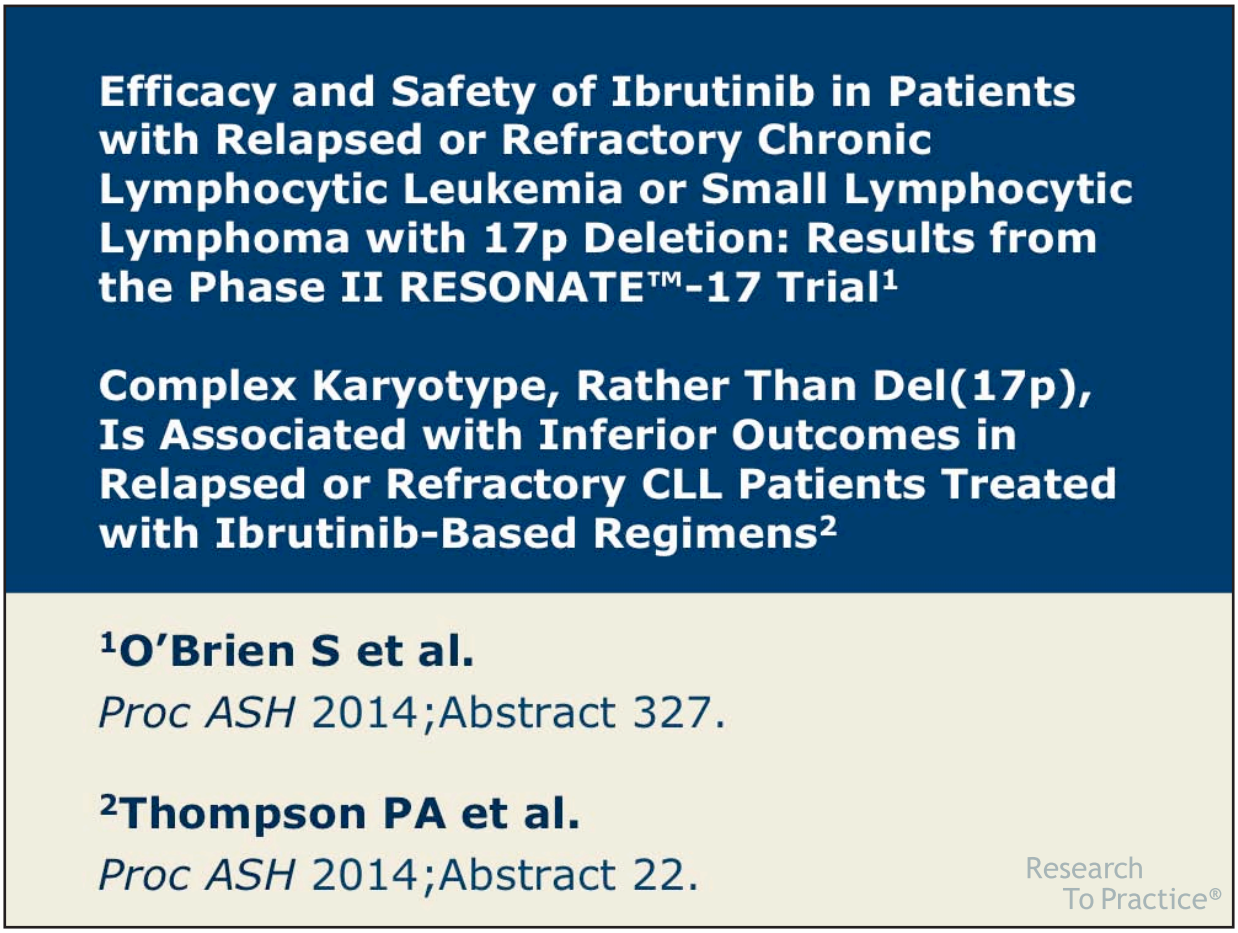
Ibrutinib for Patients with Relapsed/Refractory CLL and Association of Complex Karyotype with Outcomes

Presentations discussed in this issue

O'Brien S et al. **Efficacy and safety of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic leukemia with 17p deletion: Results from the phase II RESONATE-17 trial.** *Proc ASH* 2014;**Abstract 327**.

Thompson PA et al. **Complex karyotype, rather than del(17p), is associated with inferior outcomes in relapsed or refractory CLL patients treated with ibrutinib-based regimens.** *Proc ASH* 2014;**Abstract 22**.

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



Efficacy and Safety of Ibrutinib in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma with 17p Deletion: Results from the Phase II RESONATE™-17 Trial

O'Brien S et al.

Proc ASH 2014;Abstract 327.

Background

- Ibrutinib is a small molecule inhibitor of Bruton tyrosine kinase that is indicated for:
  - Patients with chronic lymphocytic leukemia (CLL) who have received ≥1 therapy
  - Patients with previously untreated del(17p) CLL
- The Phase III RESONATE trial demonstrated significant overall (OS) and progression-free survival (PFS) benefits with single-agent ibrutinib versus ofatumumab in relapsed/refractory (R/R) CLL (*NEJM* 2014;371(3):213).
- **Study objective:** To determine the efficacy and safety of single-agent ibrutinib for patients with R/R CLL or small lymphocytic lymphoma (SLL) harboring the del(17p) abnormality.

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

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Phase II PCYC-1117 (RESONATE-17) Trial Design

Eligibility (n = 144)

CLL or SLL
Presence of del(17p13.1) in peripheral blood by FISH analysis
R/R disease after 1-4 prior lines of therapy
Measurable nodal disease
ECOG PS 0-1

→ Single-agent ibrutinib 420 mg PO daily Until unacceptable toxicity or disease progression

- Primary analysis was performed 12 months after enrollment of last patient
- **Primary endpoint:** Overall response rate (ORR)
- **Secondary endpoints include:** Duration of response (DoR), safety and tolerability
- **Exploratory endpoints:** PFS and OS

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

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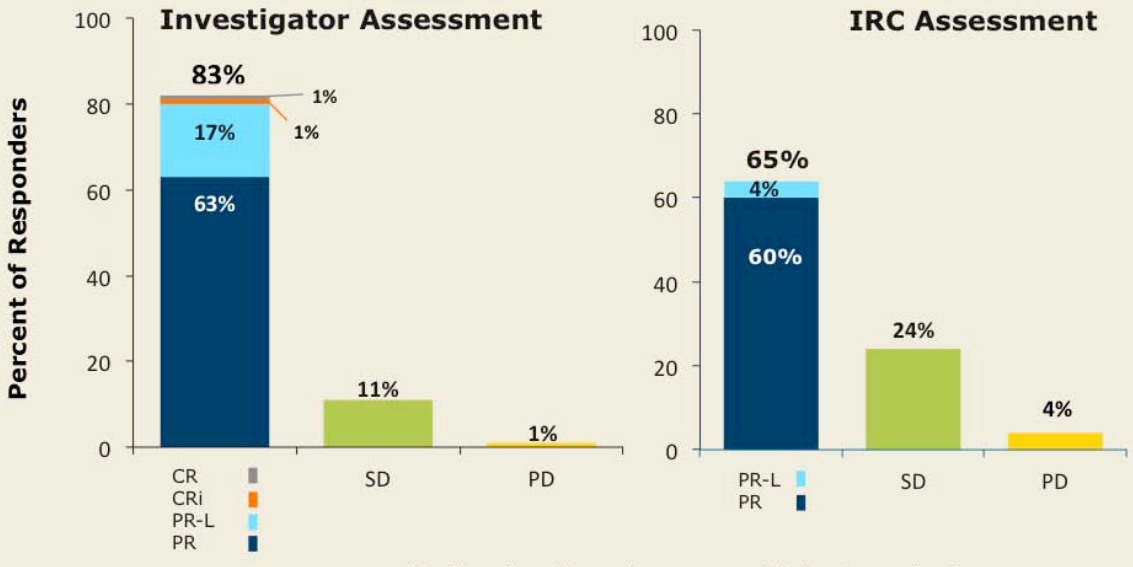
Response to Ibrutinib (N = 144)



Median duration of response: Not yet reached

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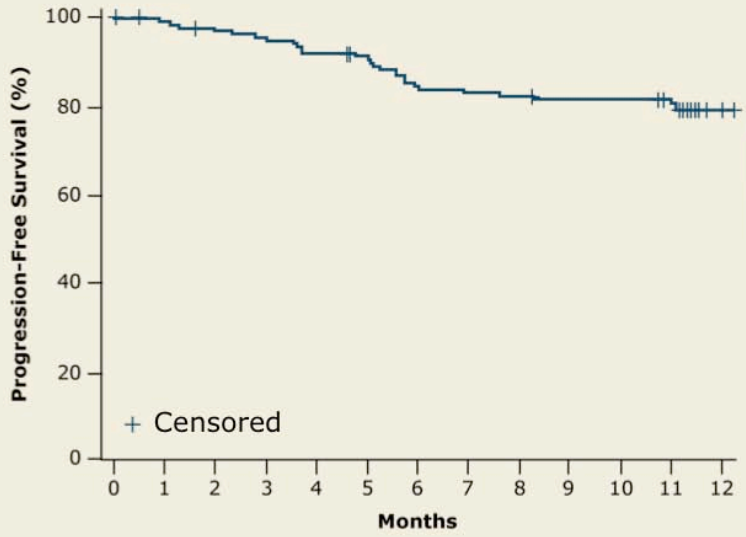
Progression-Free Survival



	N	12-month PFS rate
Overall	144	79.3%
Del17p quartiles*		
<25%	35	85%
25-50%	37	81%
50-75%	33	83%
≥75%	39	69%

* Based on % of CLL cells with del17p at baseline

- Median PFS not reached
- Median follow-up 11.5 months

With permission from O'Brien S et al. *Proc ASH* 2014;Abstract 327.

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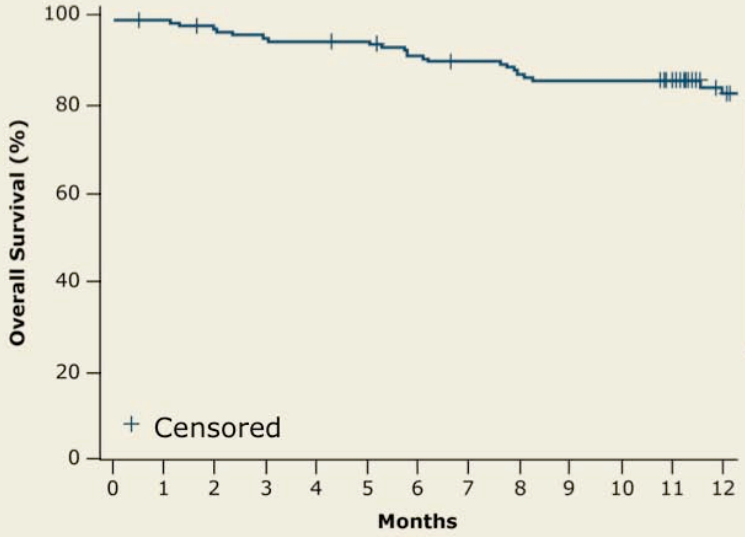
Overall Survival



	N	12-month OS rate
Overall	144	83.5 %
Del17p quartiles*		
<25%	35	85%
25-50%	37	89%
50-75%	33	86%
≥75%	39	76%

* Based on % of CLL cells with del17p at baseline

- Median OS not reached
- Median follow-up 11.5 months

With permission from O'Brien S et al. *Proc ASH* 2014;Abstract 327.

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Characteristics of Patients with Progressive Disease (PD) on Ibrutinib (n = 20)

Characteristic	Richter's transformation (n = 11)	No Richter's transformation (n = 9)	Non-PD (n = 124)
Median del(17p) cells	65%	86%	65%
Presence of del(11q)	0%	11%	18%
Median beta-2-microglobulin	7 mg/L	6 mg/L	5 mg/L
Median LDH level	471 U/L	327 U/L	249 U/L
Median no. of prior Tx (range)	2 (1-4)	2 (1-5)	2 (1-7)
Bulky disease >5 cm	64%	100%	44%
Bulky disease >10 cm	18%	22%	9%
Median time to PD	158 days	232 days	N/A

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

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Select Adverse Events

Event (n = 144)	Any grade	Grade 3-4
Diarrhea	36%	2%
Fatigue	31%	1%
Hypertension	19%	8%
Anemia	19%	8%
Neutropenia	17%	14%

- Other select adverse events:
  - Pneumonia (10%), urinary tract infection (3%)
  - Skin cancers (5%), nonskin cancers (1%)
  - Tumor lysis syndrome (<1%)

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

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Atrial Fibrillation and Bleeding-Related Events

- Atrial fibrillation of any grade occurred in 11 patients (8%):
  - Grade 3-4 events = 3.5%; no Grade 5 events
  - 5 patients had a history of atrial fibrillation
  - No treatment discontinuations occurred
- Major bleeding of Grade 2 or 3 occurred in 7 patients (5%):
  - Events included intracranial hemorrhage, spontaneous and traumatic hematomas*, hematuria, hemoptysis, gastric ulcer and intercostal artery hemorrhages
  - 3 patients were receiving concomitant medication: anticoagulants (n = 2), aspirin (n = 1)
  - 1 patient had factor XI deficiency

* In a patient with history of spontaneous hematoma, platelet count was $<100 \times 10^9$/L at time of bleeding event

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

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Author Conclusions

- Ibrutinib is efficacious with a favorable risk-benefit profile in the largest prospective study of patients with CLL/SLL harboring del(17p):
  - Best response (ORR including PR-L) by IRC: 83%
  - 12-month PFS: 79%
  - The results are consistent with previously observed efficacy (*NEJM* 2013;369:32)
- PFS outcomes were favorable compared to those of front-line FCR or alemtuzumab in CLL harboring del(17p) (*Lancet* 2010;376:1164; *JCO* 2007;10:5616).
- The safety profile is consistent with previous reports for ibrutinib (*NEJM* 2013;369:32).
- Ibrutinib is an effective therapy for patients with CLL or SLL harboring del(17p).

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

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Investigator Commentary: Efficacy and Safety Results from the Phase II RESONATE-17 Trial of Ibrutinib in R/R CLL or SLL

Patients with CLL and del(17p) have a uniquely poor outcome, and standard treatment has been inadequate. This is an important Phase II trial for 144 patients with R/R CLL or SLL with del(17p) after disease progression on ≥1 prior therapy. The efficacy of single-agent ibrutinib was marked, with about 80% of patients remaining progression free at 12 months. These results are superior to what is expected with aggressive immunochemotherapies. The PFS is favorable in comparison to FCR or alemtuzumab, at least from the Phase II experiences.

The study demonstrated that 20 patients had PD, and Richter's transformation was reported in 11. This begs the question whether these patients had underlying Richter's transformation. An important message from this study is that although ibrutinib may be effective in high-risk disease with del(17p), if there is evidence of histological transformation this agent is unlikely to be successful as a single agent. Differences in the toxicity profile between ibrutinib and regimens such as FCR will be important.

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

continued

Investigator Commentary: Efficacy and Safety Results from the Phase II RESONATE-17 Trial of Ibrutinib in R/R CLL or SLL (continued)

The question is, how durable will the responses be? What happens if the disease becomes ibrutinib resistant? I believe we're all optimistic about this and other trials investigating ibrutinib in CLL. Although the results are premature, I certainly see the appeal. I would encourage clinicians to steer their patients toward these trials because the quicker we enroll to these trials, the quicker we'll obtain the definitive answers.

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

Complex Karyotype, Rather Than Del(17p), Is Associated with Inferior Outcomes in Relapsed or Refractory CLL Patients Treated with Ibrutinib-Based Regimens

Thompson PA et al.

Proc ASH 2014;Abstract 22.

Background

- Ibrutinib is active in relapsed/refractory (R/R) CLL, including patients with del(17p)
  - Patients with del(17p) have a similar response rate to those without, but they have shorter progression-free survival and a pattern of continuous relapses (*NEJM* 2013;369:32).
- Del(17p) is frequently associated with a complex metaphase karyotype (CKT), defined as ≥3 distinct chromosomal abnormalities.
- CKT has been associated with inferior outcomes in treatment-naïve and R/R CLL, but its prognostic significance for patients receiving ibrutinib (Ib) is unknown.
- **Study objective:** To determine the prognostic value of CKT in patients with R/R CLL treated with Ib-based regimens.

Study Methods

- Patients with R/R CLL at MD Anderson Cancer Center who received Ib-based regimens from 2010-2013 (n = 100):
  - Ib monotherapy (n = 50)
  - Ib + rituximab (R) (n = 36)
  - Ib + bendamustine (B) + R (n = 14)
- Pretreatment fluorescent in situ hybridization (FISH) and CpG-stimulated metaphase cytogenetic analyses were performed on the bone marrow.
- **Endpoints include:** Overall response rate (ORR), event-free survival (EFS) and overall survival (OS).

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

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Baseline Characteristics

Characteristic	
Median age (range)	65 years (35-83)
Median no. of prior therapies (range)	2 (1-12)
Pts with del(11q), n = 95	28%
Pts with del(17p), n = 95	49%
Pts with CKT, n = 72	36%
Pts with unmutated IGHV gene, n = 98	81%
Pts with fludarabine-refractory disease, n	19
Pts with beta-2 microglobulin (ß2M) ≥4.0 mg/L, n	48

- 22/26 patients with CKT had del(17p)
- 3/26 patients with CKT had del(11q)
- 1/26 patients with CKT had no available FISH results
- No association between CKT and other baseline characteristics

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

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Response Rate

All patients	(n = 100)
ORR	95%
Complete remission (CR)	16%
Partial remission (PR)	79%
Pts who received Ib + B + R (n = 14)	
CR	50%
Pts who received Ib with or without R (n = 86)	
CR	10.7%

- ORR did not differ according to baseline characteristics
- Patients who achieved CR (Ib + B + R versus Ib with or without R):
  - Odds ratio = 40.1; $p = 0.005$
- A trend toward lower CR was observed on multivariate analysis of patients with ß2M ≥4.0 ($p = 0.055$)

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

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Event-Free Survival

- Univariate analyses demonstrated that the following were significantly associated with EFS:
  - Fludarabine-refractory CLL ($p = 0.025$)
  - Presence of del(17p) ($p = 0.008$)
  - Presence of CKT ($p < 0.0001$)
- The median follow-up for surviving patients was 27 months.
- No association was observed between del(17p) and EFS when patients with CKT were excluded from the analysis.
- Multivariate analysis demonstrated that only the presence of CKT was significantly associated with EFS:
  - Hazard ratio = 4.1; $p = 0.018$

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

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Overall Survival

- Univariate analyses demonstrated that the following were significantly associated with OS:
  - Fludarabine-refractory CLL (p = 0.009)
  - Presence of del(17p) (p = 0.024)
  - Presence of CKT (p = 0.003)
- No association was apparent between del(17p) and OS when patients with CKT were excluded.
- A trend toward inferior OS was observed among patients with baseline ß2M ≥4.0 (p = 0.07).
- Multivariate analysis demonstrated that fludarabine-refractory CLL, CKT and ß2M ≥4.0 were significantly associated with inferior OS.

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

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Author Conclusions

- The presence of CKT is independently associated with inferior EFS and OS in patients with relapsed/refractory CLL treated with Ib, while del(17p) is not.
- CKT is strongly associated with del(17p) and may be a key determinant of biological behavior in del(17p) CLL.
- These results have important implications for the treatment of del(17p) CLL.
- Patients without CKT appear to have equivalent outcomes with Ib compared to patients without del(17p).
  - These cases could potentially be managed with long-term Ib and close monitoring.

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

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Author Conclusions (continued)

- In contrast, the inferior outcomes after initial response in patients with CKT make them ideal candidates for treatment-intensification strategies after initial Ib-based treatment, either with novel drug combinations or with allogeneic stem cell transplant, ideally in the context of well-designed clinical trials.

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

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Investigator Commentary: Complex Karyotype Is Associated with Inferior Outcomes in Patients with R/R CLL Treated with Ib-Based Regimens

This is an interesting study of 100 patients with R/R CLL previously treated with Ib-containing regimens that is hypothesis generating. It suggests that CLL is a complex disease and confirms that del(17p) is not the only abnormality posing issues in the treatment of CLL. The commonly used detection method for del(17p) is FISH. In an era in which whole-genome sequencing (WGS) methods are available and one is able to fine point highly characteristic mutations, it is important to have a better understanding of subsets of patients.

In the relapsed setting in particular, numerous abnormalities evolve. To some degree of surprise, the study showed that the highest predictor of poorer outcome was CKT. When CKT was excluded, no association was apparent between del(17p) and EFS or OS. In fact it was CKT that was independently associated with inferior EFS and OS. In my mind, this opens the door to the future. As WGS becomes more routine and more sophisticated panels are developed based on individual diseases, we are likely to identify specific genes that are predictive of success or failure.

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

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