5 Minute JournalClub

POST-ASH Issue 3, 2015

Determination of Recommended Phase II Dose of Venetoclax (ABT-199) and Rituximab for Relapsed/Refractory CLL

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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

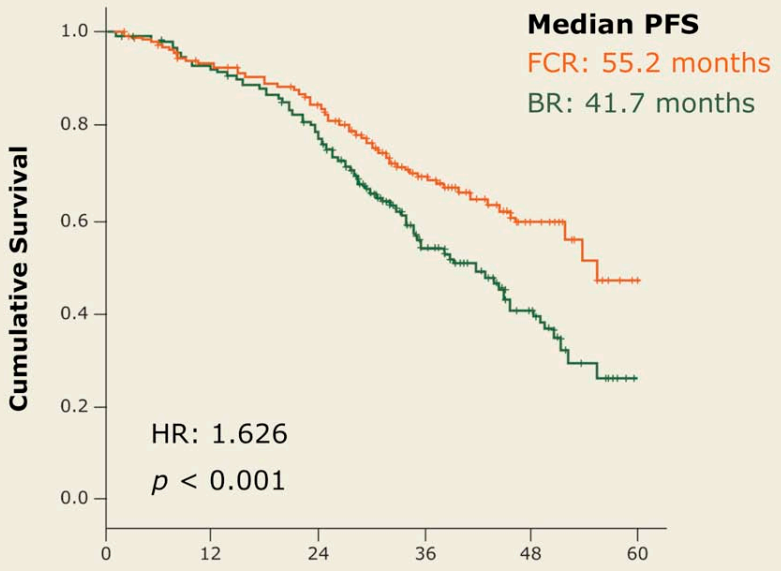
POST-ASH Issue 3, 2015

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)



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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.

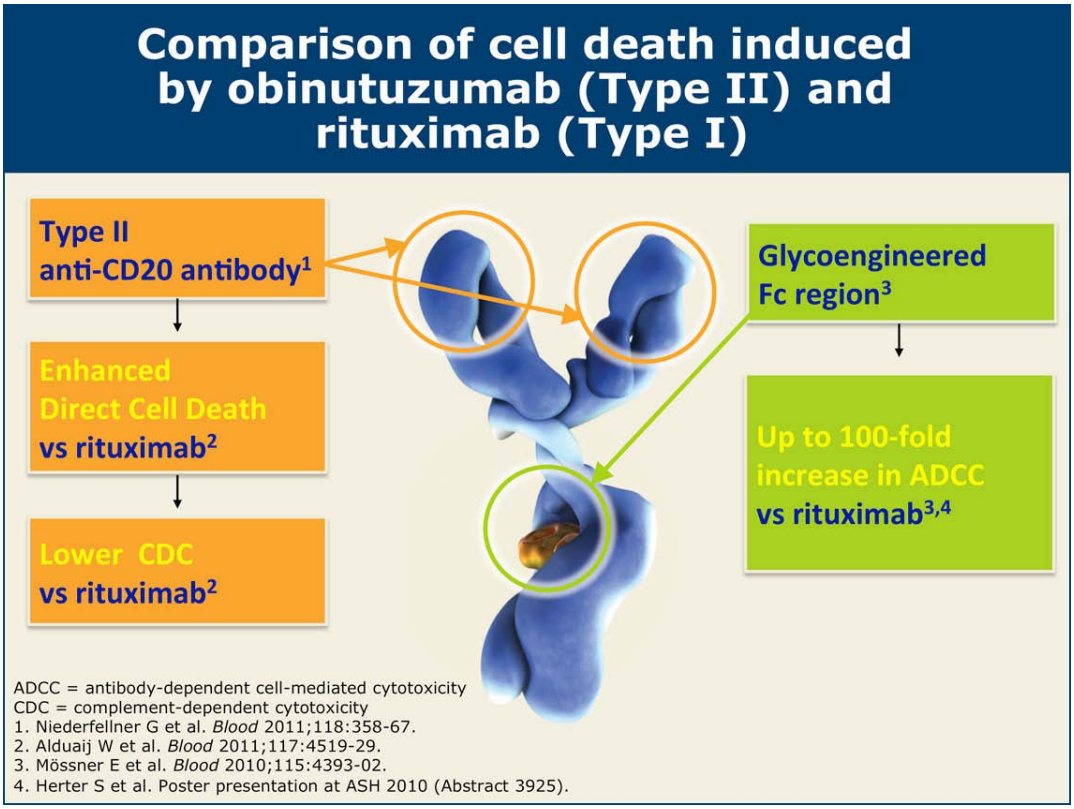
Obinutuzumab (Ob)

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

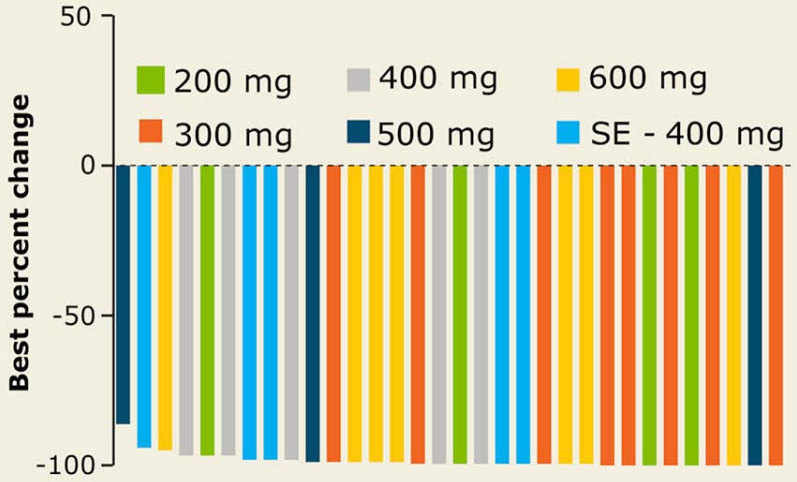
One of the important features of ibrutinib in CLL is the consistency of response in patients with adverse prognostic factors like 17p deletion, but the drug is not alone in this regard. At ASH we saw a **subset analysis** from the major Phase III trial reported in the *New England Journal* demonstrating 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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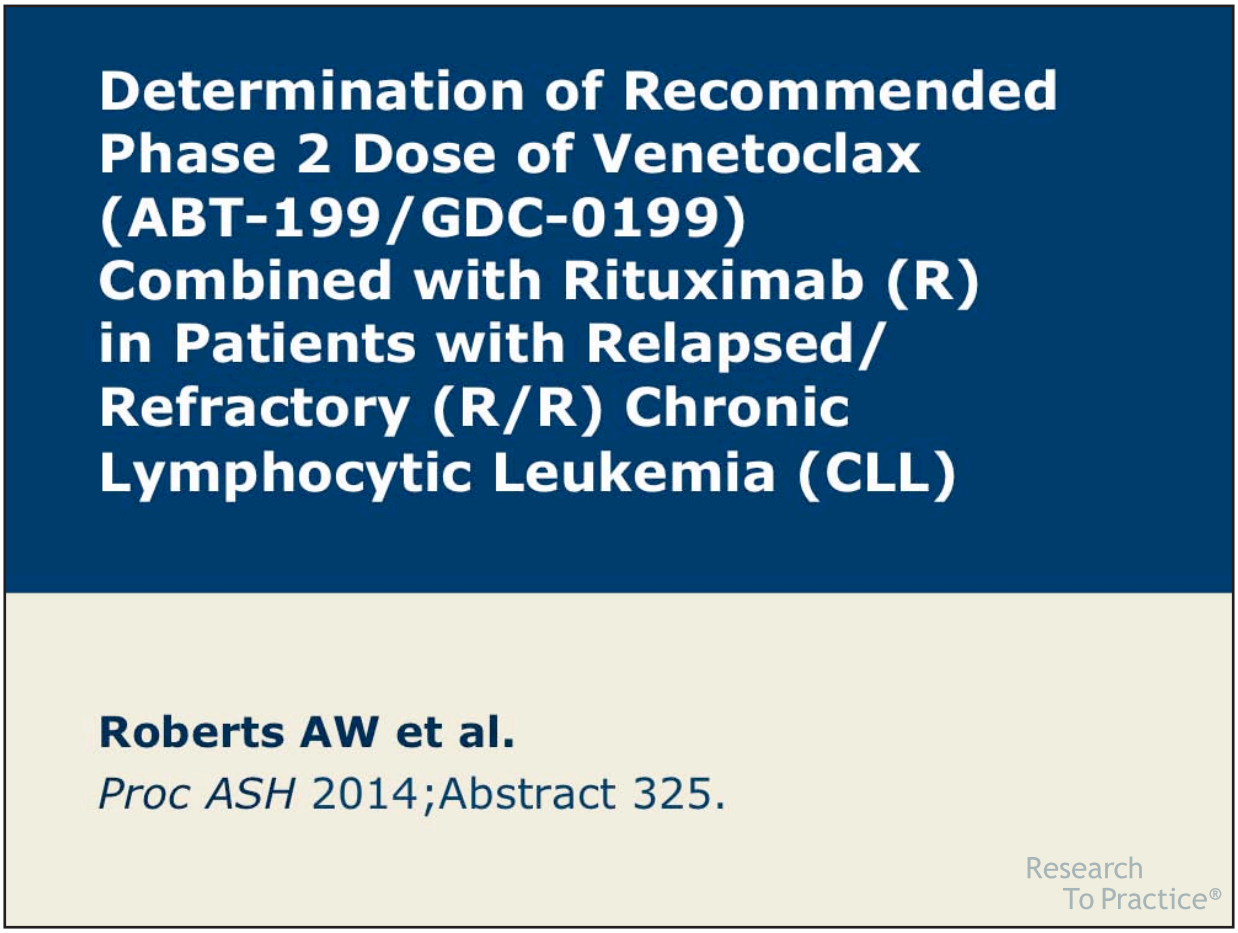
Determination of Recommended Phase II Dose of Venetoclax (ABT-199) and Rituximab for Relapsed/Refractory CLL

Presentation discussed in this issue

Roberts AW et al. **Determination of recommended phase 2 dose of ABT-199 (GDC-0199) combined with rituximab (R) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL).** *Proc ASH* 2014;**Abstract 325**.

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



Background

- Venetoclax (ABT-199/GDC-0199), a potent Bcl-2 inhibitor, induces rapid responses in about 80% of patients with R/R CLL or small lymphocytic lymphoma (SLL).
- Rituximab has only modest and short-lived activity as a single agent in CLL.
- Rituximab is used in combination with chemotherapy to treat CLL.
- Venetoclax and rituximab demonstrate synergy in preclinical models of CD20-positive lymphoid cancers.
- **Study objective**: To determine the maximum tolerated dose (MTD) and recommended Phase II dose (RPTD) of venetoclax and to assess its safety and efficacy in combination with rituximab in patients with R/R CLL.

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

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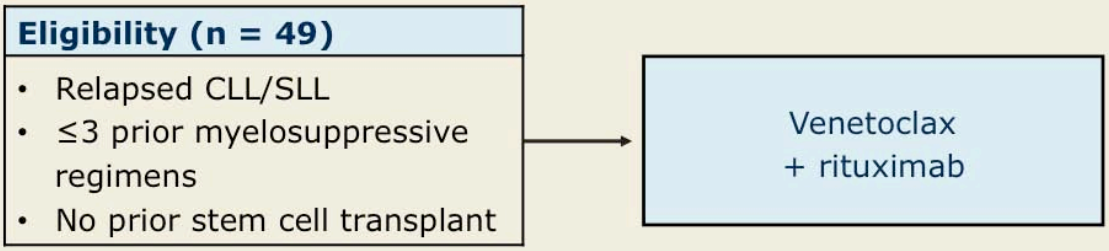
Phase Ib Study Design



Primary endpoint: Safety, MTD, RPTD and dosing schedule

Secondary endpoints: Pharmacokinetics, efficacy

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

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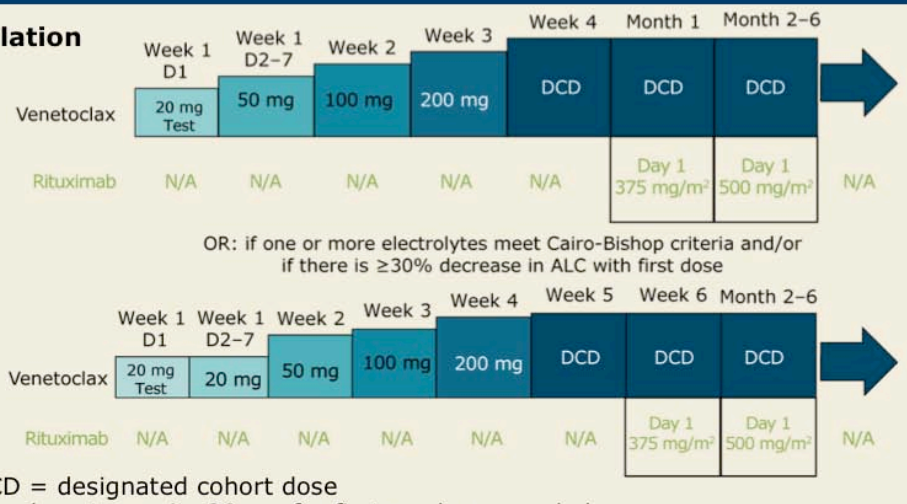
Dosing Schedule of Venetoclax and Rituximab

Final Escalation Strategy:



D = day; DCD = designated cohort dose
Protocol amendment permits 20 mg for first week, as needed

- The MTD was not identified.
- Selection of 400 mg for assessment in the safety expansion dose was based on trends of higher toxicities at doses >400 mg and informed by data from other studies.

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Adverse Events (AEs)

Select AEs* (any grade)	(n = 49)
Neutropenia	49%
Pyrexia	37%
Thrombocytopenia	22%
Anemia	22%

* ≥20% of patients

- Grade 3/4 AEs in ≥3 patients: neutropenia (47%), thrombocytopenia (16%), anemia (14%), leukopenia (10%), febrile neutropenia (6%)
- Serious AEs in ≥2 patients: pyrexia (8%), febrile neutropenia (4%), infusion-related reaction (4%), tumor-lysis syndrome (4%)

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

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Preliminary Efficacy Results

Response	All patients n = 49	Del(17p) n = 9
Overall response rate	88%	78%
Complete response (CR/CRi)	31%	22%
Partial response (PR)	45%	56%
PR unconfirmed*	12%	—
Stable disease	4%	11%

* Follow-up assessment not available at time of analysis (4 pending, 2 withdrew)
CR = complete response; CRi = CR with incomplete blood count recovery

- Early data indicated substantial efficacy at all doses in evaluated patients.
- Five patients with CR/CRi have discontinued venetoclax and are being followed on study.
- Minimal residual disease (MRD) negativity in the bone marrow at 7 mo: 9/15 patients with CR and 8/22 with PR.

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

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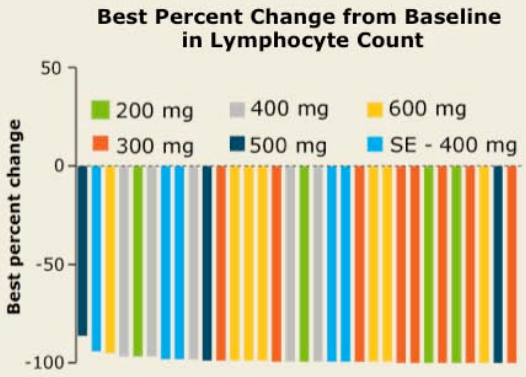
Change from Baseline in Lymphocyte Count, Nodal Mass and Bone Marrow Infiltrate*



- 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

- 43/43 (100%) patients who had post-baseline CT scan achieved at least 50% reduction in nodal mass by CT scan
- 23/35 (66%) patients who had bone marrow assessment achieved complete marrow clearance by morphology

* As of October 7, 2014

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Bone Marrow MRD at 7 Months

Response	MRD-negative	MRD-positive	Comments
CR (n = 15)	9	6	1/6 became MRD-negative at 14 months
PR (n = 22)	8*	14	4/8 MRD-negative patients have 1 remaining lymph node of >1.5 cm as the only evidence of disease

* Remaining lymph node sizes for the 8 patients with MRD-negative PR:

- 4 patients with single lymph node (cm): 1.7, 2.2, 2.3 and 2.7
- 4 patients with 2-4 lymph nodes, largest node size (cm): 2.2, 2.3, 2.3 and 2.4

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

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Author Conclusions

- The combination of rituximab and venetoclax at a dose of 400 mg is well tolerated, with no new toxicities identified in comparison to monotherapy.
- Preliminary pharmacokinetics suggest no apparent effect of rituximab on venetoclax exposure (data not shown).
- The combination is highly active in patients with R/R CLL.
  - The overall response rate is 88% to date, including 31% CR/CRi.
  - MRD negativity in the bone marrow was recorded in 17 patients:
    - 9/15 patients in CR/CRi, 8/22 patients in PR
- A Phase III trial comparing venetoclax and rituximab to bendamustine and rituximab (BR) for patients with previously treated CLL is under way (NCT02005471).

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

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Investigator Commentary: Phase Ib Study of Venetoclax in Combination with Rituximab in R/R CLL

This is an important Phase Ib study designed to select a dose of venetoclax for subsequent Phase II studies in combination with rituximab. Forty-nine patients were enrolled in 5 cohorts and were administered different doses of venetoclax. Patients had relatively poor prognoses, with 12% of cases refractory to fludarabine, 37% refractory to rituximab and 20% harboring deletion of 17p.

The overall response rate with this combination was high at 88% — single-agent rituximab elicits a much lower response rate in CLL. Thirty-one percent of the patients achieved CR, and efficacy was observed across all cohorts. Some cases of tumor lysis syndrome were observed before schedule modifications.

The plan is to move forward with the 400-mg daily dose of venetoclax. A head-to-head study of the venetoclax/rituximab combination versus BR for previously treated CLL is under way to determine whether a biologic combination like this might be better than chemoimmunotherapy.

In the relapsed setting treatment can be complicated because the patient population is heterogeneous, with some having high-risk features such as deletion of 17p. In this setting biologic agents seem to have better activity.

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