5 Minute JournalClub

Hematologic Oncology
Issue 2, 2013

Final Stage 1 Results of the Phase III CLL11 Trial of Chlorambucil with Obinutuzumab or Rituximab in Previously Untreated 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 Clinical Oncology (ASCO) annual meeting and the International Conference on Malignant Lymphoma (ICML), to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they are aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because not only are they confronted almost overnight with thousands of new presentations and data sets, but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on novel agents in chronic lymphocytic leukemia from the latest ASCO and ICML meetings, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances and potentially practice-changing clinical data in chronic lymphocytic leukemia, and consider this information in clinical practice.
- Evaluate the efficacy, safety, pharmacodynamics and pharmacokinetics of idelalisib as a single agent or in combination with rituximab for patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia.
- Determine the preliminary efficacy and safety of ABT-199, a selective BCL-2 inhibitor, for patients with relapsed or refractory chronic lymphocytic leukemia.
- Determine the benefits and risks associated with chlorambucil in combination with obinutuzumab (GA101), an anti-CD20 antibody, or rituximab versus chlorambucil alone for patients with previously untreated chronic lymphocytic leukemia and preexisting comorbidities.
- Assess the preliminary safety and response outcomes observed in studies of the orally bioavailable, small molecule inhibitor of Bruton tyrosine kinase ibrutinib as a single agent for patients with chronic lymphocytic leukemia with chromosome 17 deletion.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: September 2013
Expiration date: September 2014

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

Imagine...

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

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

Which treatment would you choose to receive?

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

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

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

1. Type II monoclonal antibodies to CD20

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

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

2. PI3 kinase delta inhibitors: Idelalisib (idel)

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

3. Bruton's tyrosine kinase inhibitors: Ibrutinib

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

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

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

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

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

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

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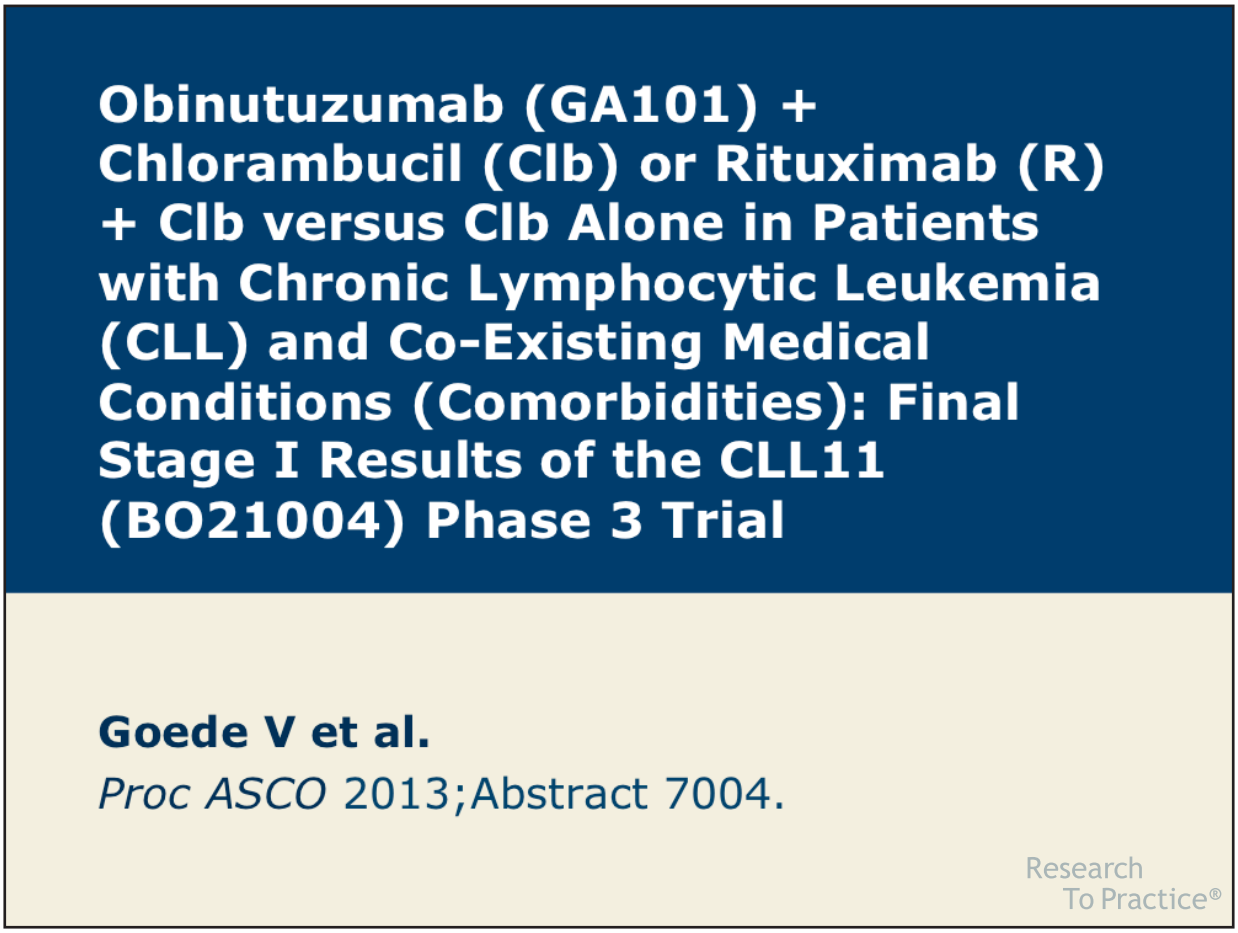
Final Stage 1 Results of the Phase III CLL11 Trial of Chlorambucil with Obinutuzumab or Rituximab in Previously Untreated CLL

Presentation discussed in this issue

Goede V et al. **Obinutuzumab (GA101) + chlorambucil (Clb) or rituximab (R) + Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and co-existing medical conditions (comorbidities): Final Stage I results of the CLL11 (BO21004) Phase 3 trial.** *Proc ASCO* 2013;**Abstract 7004**.

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



Background

- A high number of elderly patients have CLL and coexisting medical conditions.
- In this patient population:
  - There is no conclusive evidence that currently available treatments are superior to chlorambucil (Clb) monotherapy.
  - Encouraging early data exist for the development of combinations of Clb with anti-CD20 monoclonal antibodies (mAbs) and for the evaluation of chemoimmunotherapy with the novel Type II anti-CD20 mAb obinutuzumab (*Proc ASH* 2011;Abstract 294; *Leukemia* 2013;27(5):1172).
- **Specific study aims:** To demonstrate the superiority of Clb + an anti-CD20 mAb (rituximab or obinutuzumab) to Clb alone (Stage I of study). An analysis of obinutuzumab + Clb versus rituximab + Clb is planned for Stage II of the study.

Goede V et al. *Proc ASCO* 2013;Abstract 7004.

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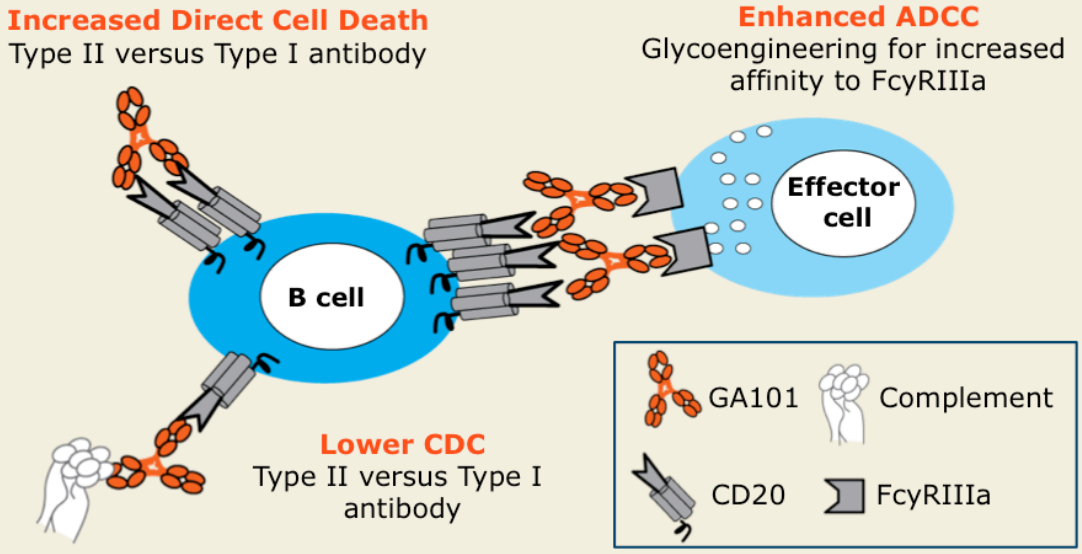
Obinutuzumab (GA101) Mechanisms of Action



ADCC = antibody-dependent cell-mediated cytotoxicity
CDC = complement-dependent cytotoxicity

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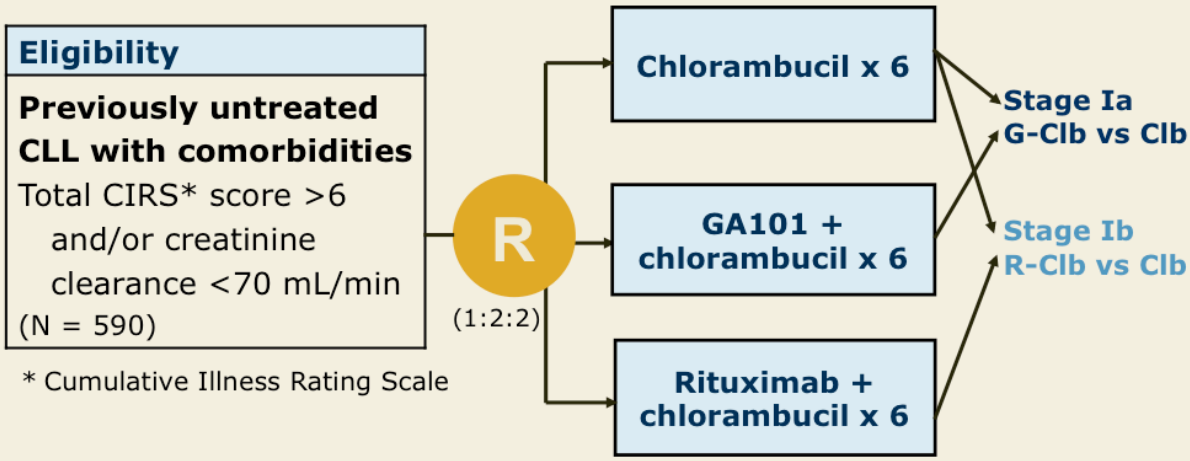
CLL11 (BO21004) Trial Design: Stage I



* Cumulative Illness Rating Scale

- GA101: 1,000 mg d 1, 8, 15 cycle 1; d 1 cycles 2-6, q28d
- Rituximab: 375 mg/m^2 d 1 cycle 1, 500 mg/m^2 d 1 cycles 2-6, q28d
- Clb: 0.5 mg/kg d 1, 15 cycles 1-6, q28d
- An additional 190 patients are enrolled in the Stage II portion of the study

Goede V et al. *Proc ASCO* 2013;Abstract 7004.

End-of-Treatment Response Rates (RR)

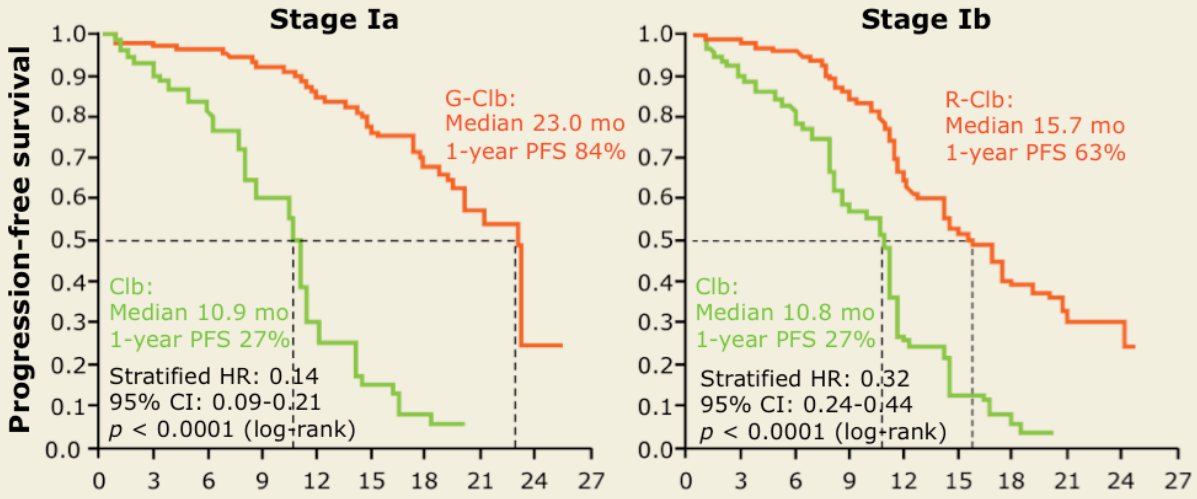
	Stage Ia		Stage Ib	
	Clb (n = 106)	G-Clb (n = 212)	Clb (n = 110)	R-Clb (n = 217)
ORR	30.2%	75.5%	30.0%	65.9%
CR*	0%	22.2%	0%	8.3%
PR†	30.2%	53.3%	30.0%	57.6%
SD	21.7%	4.7%	20.9%	13.4%
PD	25.5%	3.8%	28.2%	11.5%

ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

* Includes CR with incomplete hematologic recovery; † Includes nodular PR

Goede V et al. *Proc ASCO* 2013;Abstract 7004.

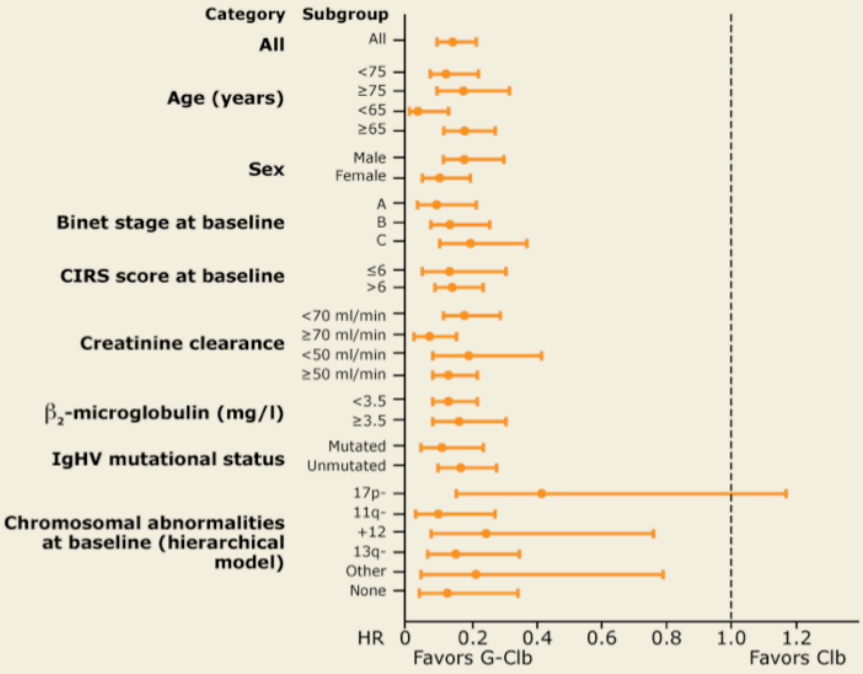
Investigator-Assessed Progression-Free Survival (PFS)



- On the G-Clb arm, <10% of patients had reached the median at cutoff. In contrast to the Clb arm, the G-Clb median PFS could not be reliably estimated due to the few patients at risk at time of median.
- Independent Review Committee-assessed PFS was consistent with investigator-assessed PFS.

With permission from Goede V et al. *Proc ASCO* 2013;Abstract 7004.

Stage Ia: Progression-Free Survival Subgroup Analysis



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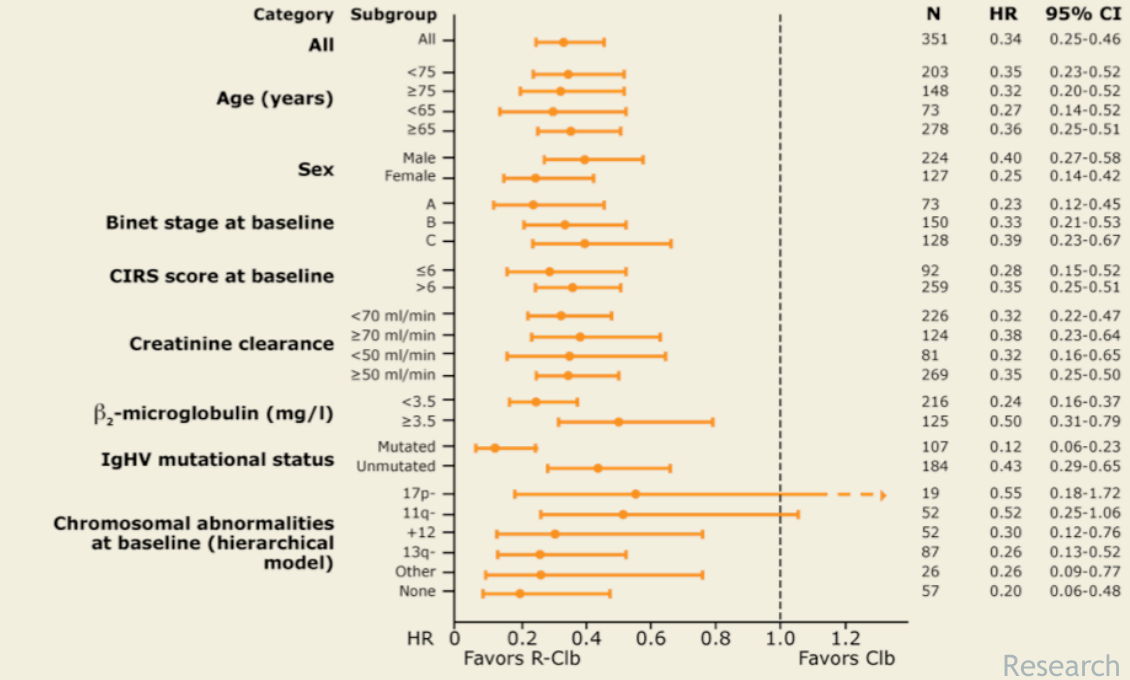
Stage Ib: Progression-Free Survival Subgroup Analysis



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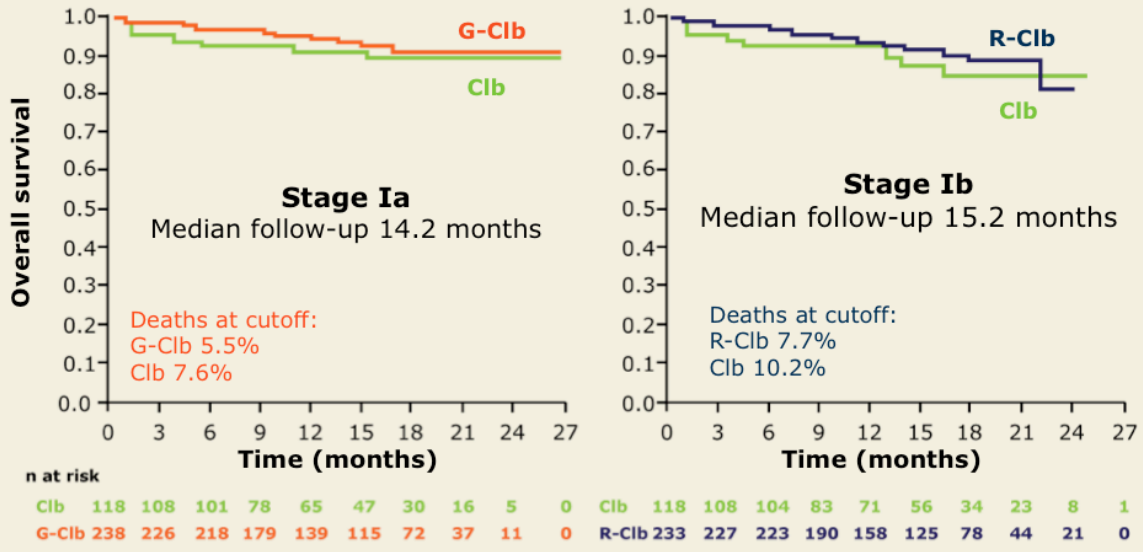
Overall Survival



- Overall survival data are immature.

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Relevant Adverse Events (AEs) During Treatment

	Stage Ia		Stage Ib	
	Clb (n = 116)	G-Clb (n = 240)*	Clb (n = 116)	R-Clb (n = 225)
Any AE Grade ≥3	41.4%	66.7%	41.4%	45.8%
Infusion-related reactions	n/a	21.3%	n/a	4.0%
Neutropenia	14.7%	34.2%	14.7%	25.3%
New malignancy	0.9%	2.5%	0.9%	2.7%

* Safety population for G-Clb includes 4 patients randomly assigned to R-Clb who received 1 infusion of GA101 in error.

Goede V et al. *Proc ASCO* 2013;Abstract 7004.

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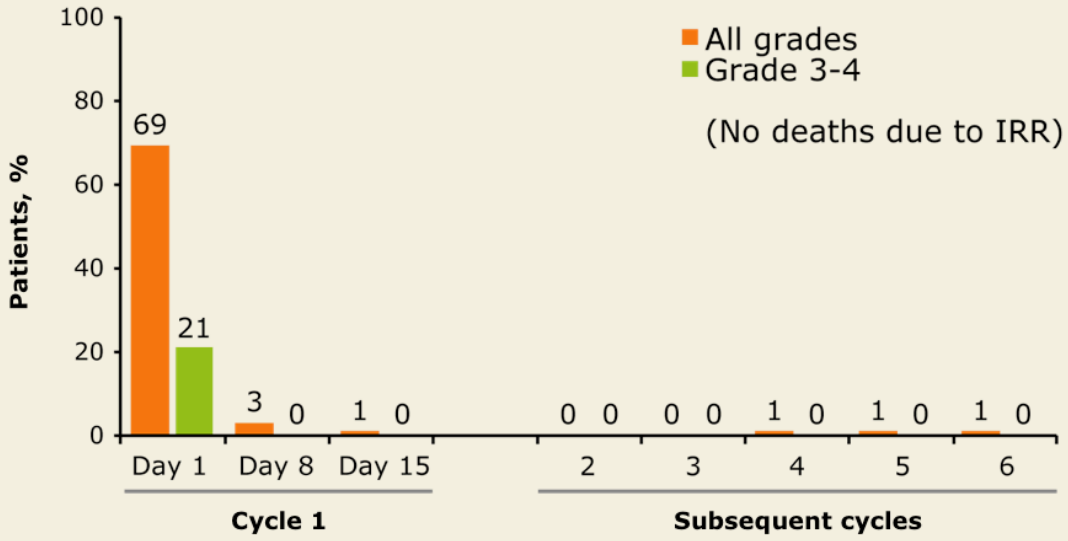
Stage Ia: Infusion-Related Reactions (IRRs) by Cycle in G-Clb Study Arm



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Author Conclusions

- This is the first large, pivotal, Phase III trial reporting on an elderly patient population with CLL and coexisting medical conditions.
- It is the first direct comparison of Clb to Clb with an anti-CD20 mAb demonstrating that the addition of GA101 or rituximab is beneficial to these patients.
- Safety profile for G-Clb (and R-Clb) is acceptable; infusion-related reactions and neutropenia were the most significant adverse events.
- Final analysis of G-Clb versus R-Clb will occur in Stage II of the study as specified by the protocol.

Goede V et al. *Proc ASCO* 2013;Abstract 7004.

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Investigator Commentary: Obinutuzumab/Chlorambucil (Clb) or Rituximab/Clb versus Clb Alone for Patients with CLL and Coexisting Medical Conditions

Obinutuzumab is a promising Type II anti-CD20 monoclonal antibody that has demonstrated enhanced antibody-dependent cell-mediated cytotoxicity, increased direct cell death and lower complement activation in comparison to the Type I antibody rituximab. The results of this study show that the addition of rituximab or obinutuzumab to Clb was superior to Clb alone with respect to the overall response rate, complete response rate and PFS.

The data presented at ASCO this year also hinted at the possibility that obinutuzumab is gaining an advantage over rituximab. The overall response rate was about 75% versus 66% and the complete response rate was 22% versus 8% with obinutuzumab versus rituximab. An approximate 7-month PFS advantage was reported in favor of the obinutuzumab arm. Not long after ASCO, it was announced in a press release that the second stage of the study directly comparing the obinutuzumab and rituximab arms met its final PFS endpoint. However, we will need to wait until this year's ASH meeting to see these data presented. The trial was designed so that the obinutuzumab arm would have to have a hazard ratio of 0.74 to be superior to rituximab in terms of PFS. If that can be demonstrated without a significant alteration in the toxicity profile, this would be a significant therapeutic advance for patients.

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