5 Minute JournalClub

POST-ASH Issue 4, 2014

Final Stage II Results of the CLL11 Trial: Obinutuzumab/Chlorambucil (Clb) versus Rituximab/Clb for Patients with CLL and Coexisting Conditions

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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

- Apply recent clinical research findings with the newly FDA-approved combination of obinutuzumab and chlorambucil to the management and care of patients with previously untreated CLL.
- 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.
- Evaluate recent clinical findings with the newly FDA-approved Btk inhibitor ibrutinib, alone and in combination with chemotherapy, for patients with CLL with and without deletion 17p or those with relapsed/refractory disease.
- Compare and contrast the benefits and risks of chemoimmunotherapy with FCR versus bendamustine/rituximab (BR) as first-line therapy for fit patients with CLL.

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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: March 2014
Expiration date: March 2015

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POST-ASH Issue 4, 2014

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

Brad S Kahl, MD

Throughout a recent interview with investigator Dr Brad Kahl about the breathtaking developments in the treatment of chronic lymphocytic leukemia (CLL), my mind kept flashing back 24 hours to a similar recording session for our *Visiting Professors* audio series focused on the care of patients with a variety of advanced gastrointestinal cancers. One of the themes that regularly emerged during that discussion was the sense of desperation and hopelessness felt by patients and clinicians regarding the modest research advances that have recently taken place in that field. Coming from that concerning landscape, my conversation with Dr Kahl about CLL was a different story and hopefully the model for the future of oncology for patients, families and healthcare professionals.

Indeed, one might argue that in the short (50+ years) history of contemporary oncology the recent clinical research progress in CLL is unprecedented, as the confluence of a variety of research efforts has culminated in an abundance of new treatment options. To provide some insight into how emerging data will inform the integration of these exciting treatments into practice, here are Dr Kahl's perspectives on some of the most important CLL papers presented at the annual ASH meeting in New Orleans.

Chimeric antigen receptor (CAR) T-cell immunotherapy

A coming issue of this series will dive deeper into this extraordinary treatment that will eventually be studied in all B-cell cancers, but at ASH most of the data presented on this CAR-based T-cell therapy targeting CD19 were in CLL and acute lymphoblastic leukemia. The bottom line is that frequent, rapid and profound antitumor responses and a delayed cytokine release syndrome that requires a great deal of attention were observed. Stay tuned for full details.

Obinutuzumab

One of two recently approved agents in CLL (with more likely on the way), this type II anti-CD20 antibody was big news in the Big Easy as the plenary presentation of **the CLL11 trial** illustrated superior efficacy of obinutuzumab versus rituximab (R) in older patients and those with comorbidities receiving chlorambucil. Dr Kahl notes that clinicians must be aware of the potential for increased toxicity with this drug — particularly manageable infusion reactions mainly with the first treatment — but he believes the clear-cut benefit of obinutuzumab makes it difficult to use R in patients receiving chlorambucil.

Of course, an important related question is how this agent fits in with other chemotherapeutic regimens, and at ASH we saw data from **an ongoing Phase Ib trial** evaluating either fludarabine/cyclophosphamide (FC) or bendamustine (B) combined with obinutuzumab. The efficacy findings in this nonrandomized effort seemed similar to those historically observed with R, but this early report also described frequent infusion reactions and some myelosuppression. Dr Kahl believes that until further data become available, these combinations should not be used outside a trial setting.

FCR versus BR

Seems like eons ago when all we had to talk about was this important clinical question that was the subject of the **German CLL10 trial** in fit patients presented at ASH. Results from this much-awaited study demonstrated pretty much what most people expected and were already acting on in their practices — slightly greater efficacy in terms of complete response (CR) rates and progression-free survival (PFS) with FCR but considerably more toxicity, particularly in older patients. These data reinforce Dr Kahl's current nonprotocol approach to up-front treatment of CLL as follows:

- For younger patients, consider but do not insist on FCR, or, alternatively, administer BR.
- For older but not particularly frail patients (about age 60 to 75), usually opt for BR.
- For the difficult-to-define "very elderly," use chlorambucil/obinutuzumab.

Others will argue that few patients are too frail to receive bendamustine, but now that a new generation of novel agents has arrived, these issues are all being completely reconsidered anyhow.

Ibrutinib in relapsed/refractory (RR) CLL

Just approved in CLL, this Bruton tyrosine kinase inhibitor was the centerpiece of several Phase I-II ASH papers, all of which also continue to demonstrate high levels of activity, including in patients with del(17p) disease.

– **Ibrutinib alone**

A report from the NCI of the first 53 patients enrolled on **a Phase II trial** demonstrated that two thirds of these individuals responded. Most of the remaining patients responded in nodes and other sites but with increasing rather than decreasing white blood cell counts. This lymphocytosis is observed with a variety of the new small B-cell receptor inhibitors and may be part of a demargination syndrome with cells being discharged into circulation from the protected microenvironment of the marrow, spleen and the lymph nodes. With time the white counts eventually decrease — often normalizing — and this has led to a special response classification of "partial response with lymphocytosis" that occurred in 28% of 47 evaluable patients for an overall response rate of 94%. Dr Kahl views these cases as essentially CRs because the circulating cells eventually die, and it's not clear if abrogating this phenomenon with another antineoplastic agent like R or chemotherapy adds to long-term treatment benefit.

– **Ibrutinib with R**

Thirty-eight of 40 (95%) patients on **this Phase II trial** experienced objective responses, and Dr Kahl views this higher rate compared to ibrutinib monotherapy as mainly the result of counteracting the initial lymphocytosis and notes it remains to be seen if this will affect long-term outcome and survival. An ongoing randomized Phase II trial in RR CLL evaluating ibrutinib alone or with R will hopefully provide part of the answer to this important question.

– **Ibrutinib with BR**

Although 93% of 30 patients responded in **this Phase Ib trial**, as per Dr Kahl it's not clear that bendamustine is adding anything to ibrutinib or as previously stated that R provides long-term benefit. Dr Kahl, like most or all investigators, is currently using ibrutinib in relapsed CLL as per the indication, but it will be interesting to see how this evolves as more data accumulate on earlier use, particularly in cases with adverse cytogenetic factors and for the elderly.

Idelalisib

Another major story at ASH was a "late breaker" and *New England Journal* publication (along with the CLL11 obinutuzumab trial) detailing the results from **a Phase III trial** evaluating R with or without this PI3 kinase-delta inhibitor in 220 patients with relapsed disease who were not candidates for chemotherapy (median age 71). An overwhelming advantage was seen in the combination arm — 81% versus 13% overall response rate and marked improvement in PFS (HR = 0.15) and overall survival (HR = 0.28), both statistically significant. However, Dr Kahl wonders if the comparison to R, a notoriously ineffective monotherapy in CLL, will be enough to elicit FDA approval.

ABT-199

This fascinating small molecule inhibits BCL-2, which is frequently overexpressed in lymphoid cancers and a cause of dysregulation of apoptosis. While ABT-199 may still be in need of a name, it is quickly gaining a great deal of attention, and according to Dr Kahl the most significant problem may be that it "works too well," with an overall response rate of 84% among 56 evaluable patients and similar response rates irrespective of del(17p) status. Specifically, the rapid and profound antitumor activity associated with the agent frequently results in tumor lysis syndrome. As such, **an ongoing Phase I study** presented at ASH attempted to define the optimal dosing strategy to prevent this worrisome side effect. Regardless, Dr Kahl believes that ABT-199 will eventually prove to be as efficacious in CLL as ibrutinib — the agent he currently feels is the most effective available for the disease.

From the perspective of the general oncologist, the deluge of new agents and therapies in CLL is likely to result in frequently changing clinical algorithms during the next few years as trials evaluate various sequences, combinations and predictive factors. It seems inevitable that the outcomes of patients will improve significantly, and the best-case scenario is cure or a functional cure with normal life expectancy as with chronic myelogenous leukemia. It remains to be seen whether this type of exciting clinical paradigm will enter mainstream oncology in the future and include the many patients with GI cancers and other solid tumors who currently face much more limited options.

Next on this ASH review series, Dr Rafael Fonseca talks about new therapies in multiple myeloma, with more on the recently approved agents carfilzomib and pomalidomide, and a wave of promising other molecules, including several monoclonal antibodies attempting to become the "rituximab of myeloma."

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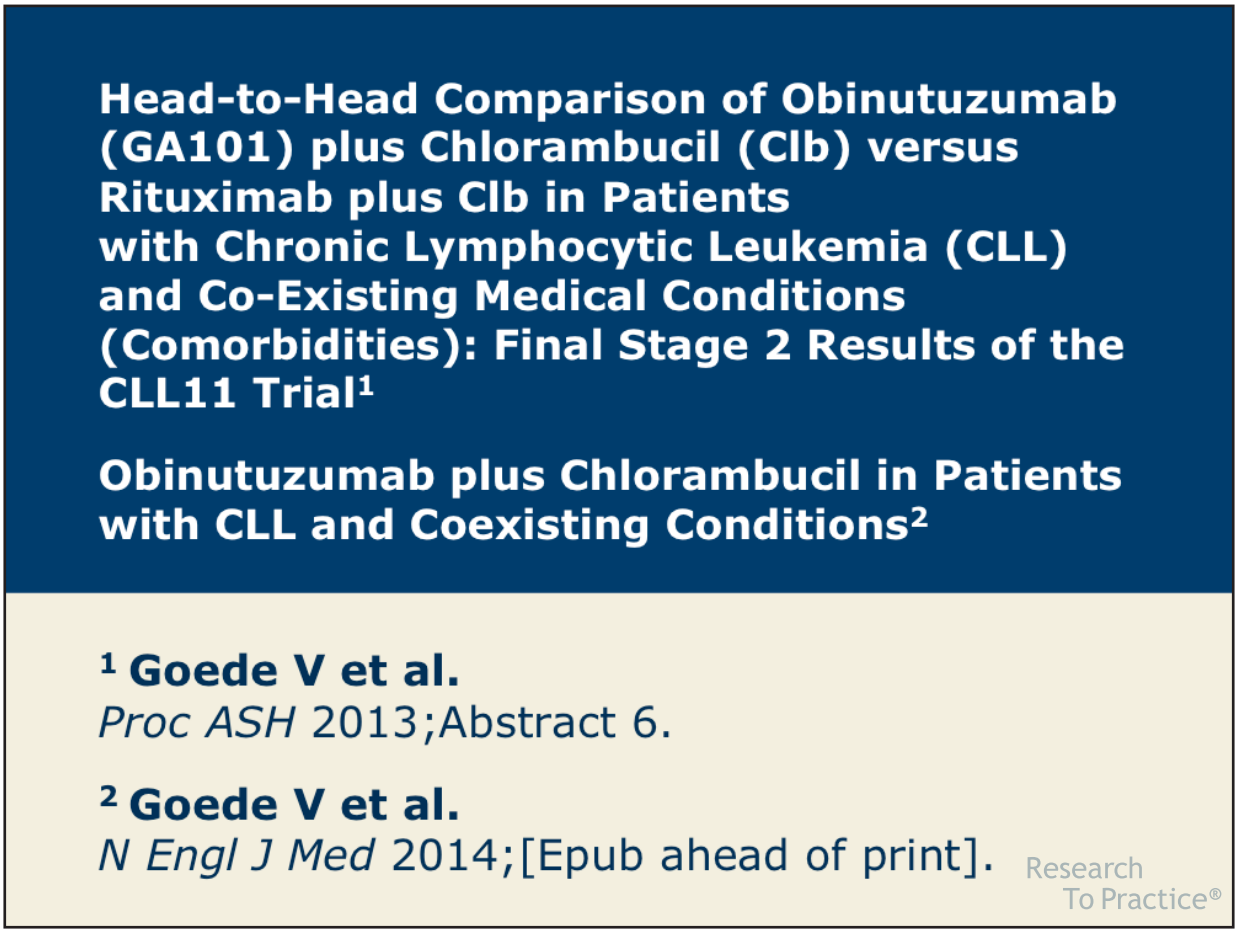
Final Stage II Results of the CLL11 Trial: Obinutuzumab/ Chlorambucil (Clb) versus Rituximab/Clb for Patients with CLL and Coexisting Conditions

Presentations discussed in this issue

Goede V et al. **Head-to-head comparison of obinutuzumab (GA101) plus chlorambucil (Clb) versus rituximab plus Clb in patients with chronic lymphocytic leukemia (CLL) and co-existing medical conditions (comorbidities): Final Stage 2 results of the CLL11 trial.** *Proc ASH* 2013;**Abstract 6**.

Goede V et al. **Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.** *N Engl J Med* 2014;[Epub ahead of print].

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Brad S Kahl, MD (2/13/14)



Background

- CLL11 is a large randomized Phase III trial of first-line chemoimmunotherapy for patients with CLL and comorbidities.
- Obinutuzumab is a third-generation type II anti-CD20 antibody that selectively binds to the extracellular domain of the human CD20 antigen on malignant human B cells.
- Preliminary analysis of the Stage 1 part of CLL11 demonstrated that treatment with obinutuzumab and chlorambucil (O-Clb) significantly improved progression-free survival (PFS) compared to Clb alone (*Proc ASCO* 2013;Abstract 7004).
- **Study objective:** To determine the benefit of anti-CD20 antibody-based chemoimmunotherapy (with Clb as backbone) and compare the efficacy of O-Clb to that of rituximab/Clb (R-Clb) in patients with untreated CLL and comorbidities.

Goede V et al. *N Engl J Med* 2014;[Epub ahead of print].

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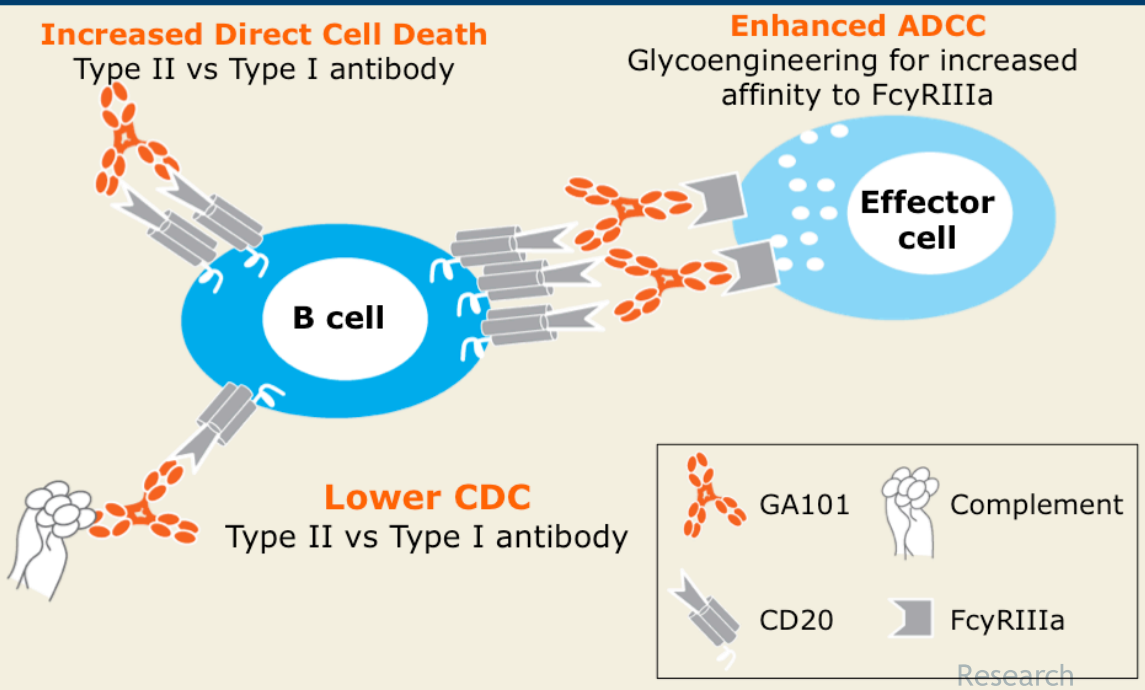
Mechanism of Action of Obinutuzumab



With permission from Goede V et al. *Proc ASH* 2013;Abstract 6.

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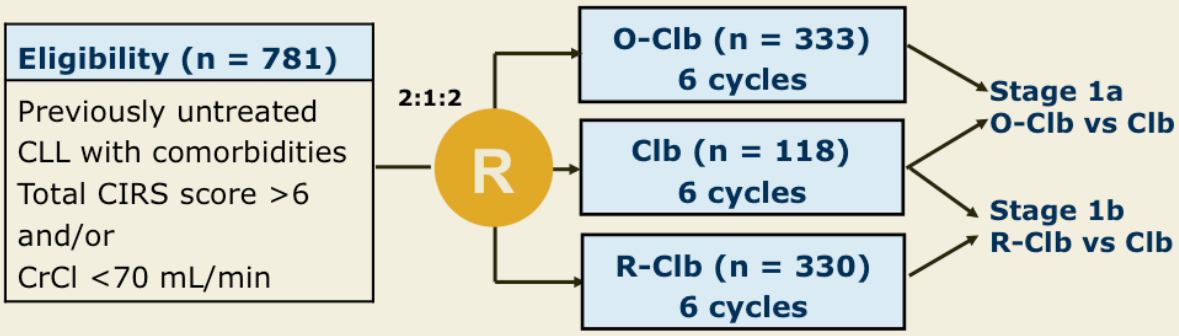
Phase III CLL11 Trial Design



CIRS = cumulative illness rating scale; CrCl = creatinine clearance

Obinutuzumab: IV, 1,000 mg on d1, 8, 15 (cycle 1); d1 (cycles 2-6), every 28 days

Rituximab: IV, 375 mg/m^2 d1 (cycle 1); 500 mg/m^2 d1 (cycles 2-6), every 28 days

Clb: PO, 0.5 mg/kg d1, 15 (cycles 1-6), every 28 days

- **Stage 2 directly compares O-Clb to R-Clb**
- Patients with progressive disease in the Clb-alone arm were allowed to cross over to O-Clb.
- **Primary endpoint:** PFS

Goede V et al. *N Engl J Med* 2014;[Epub ahead of print].

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Investigator-Assessed PFS

Stage 1

	O-Clb (n = 238)	Clb (n = 118)	R-Clb (n = 233)
Median PFS	26.7 mo	11.1 mo	16.3 mo
O-Clb vs Clb: HR = 0.18, $p < 0.001$ R-Clb vs Clb: HR = 0.44, $p < 0.001$			

Stage 2

	O-Clb (n = 333)	R-Clb (n = 330)
Median PFS	26.7 mo	15.2 mo
O-Clb vs R-Clb: HR = 0.39, $p < 0.001$		

Goede V et al. *N Engl J Med* 2014;[Epub ahead of print].

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Response Rates

Stage 1

Response	O-Clb (n = 238)	Clb (n = 118)	R-Clb (n = 233)
ORR	77.3%	31.4%	65.7%
CR	22.3%	0%	7.3%
PR	55.0%	31.4%	58.4%

Stage 2

Response	O-Clb (n = 333)	R-Clb (n = 329)
ORR	78.4%	65.1%
CR	20.7%	7.0%
PR	57.7%	58.1%

ORR: O-Clb vs Clb, $p < 0.001$; R-Clb vs Clb, $p < 0.001$; O-Clb vs R-Clb, $p < 0.001$
ORR = overall response rate; CR = complete response; PR = partial response

Goede V et al. *N Engl J Med* 2014;[Epub ahead of print].

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Overall Survival

Stage 1

	O-Clb (n = 238)	Clb (n = 118)	R-Clb (n = 233)
Death rates	9%	20%	15%
O-Clb vs Clb: HR = 0.41, $p = 0.002$ R-Clb vs Clb: HR = 0.66, $p = 0.11$			

Stage 2

	O-Clb (n = 333)	R-Clb (n = 330)
Death rates	8%	12%
O-Clb vs R-Clb: HR = 0.66, $p = 0.08$		

Goede V et al. *N Engl J Med* 2014;[Epub ahead of print].

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Minimal Residual Disease — Stage 2

	O-Clb	R-Clb	*p*-value
Bone marrow	26/133 (19.5%)	3/114 (2.6%)	<0.001
Blood	87/231 (37.7%)	8/243 (3.3%)	<0.001

Negative test results for minimal residual disease in blood after O-Clb treatment were associated with favorable disease course during follow-up.

Goede V et al. *N Engl J Med* 2014;[Epub ahead of print].

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Select Adverse Events — Stage 1 (≥3% Incidence)

Grade ≥3	O-Clb (n = 241)	Clb (n = 116)	R-Clb (n = 225)
Any	73%	50%	56%
Infusion-related reaction	21%	—	4%
Neutropenia	35%	16%	27%
Anemia	5%	4%	4%
Thrombocytopenia	11%	4%	4%
Infection	11%	14%	13%
Pneumonia	3%	3%	5%

Goede V et al. *N Engl J Med* 2014;[Epub ahead of print].

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Select Adverse Events — Stage 2 (≥3% Incidence)

Grade ≥3	O-Clb (n = 336)	R-Clb (n = 321)
Any	70%	55%
Infusion-related reaction	20%	4%
Neutropenia	33%	28%
Anemia	4%	4%
Thrombocytopenia	10%	3%
Infection	12%	14%
Pneumonia	4%	5%

Goede V et al. *N Engl J Med* 2014;[Epub ahead of print].

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Author Conclusions

- The combination of an anti-CD20 antibody (obinutuzumab or rituximab) with Clb improves outcomes for patients with previously untreated CLL and coexisting conditions.
- O-Clb provided an overall survival advantage over Clb alone and induced deeper and longer remissions than did R-Clb.

Goede V et al. *N Engl J Med* 2014;[Epub ahead of print].

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Investigator Commentary: CLL11 Trial — O-Clb in Patients with CLL and Coexisting Conditions

CLL11 was a 3-arm study comparing O-Clb to R-Clb or Clb alone for the front-line treatment of CLL. The patients in this study had to have a CIRS score of >6 and/or creatinine clearance of <70 mL/min and were not ideal candidates for treatment with fludarabine/cyclophosphamide/rituximab or bendamustine/rituximab. The median age of the patients was 73. They represent typical CLL patients, so this is an important, clinically relevant trial.

The study demonstrated superiority of O-Clb over R-Clb in terms of ORR and PFS. This is the first time we've seen rituximab beaten by another anti-CD20 antibody in a head-to-head comparison. Overall survival was also significantly better on the O-Clb arm than on the Clb arm. To my knowledge, this has never been observed in a CLL trial in this population. It is difficult to demonstrate an overall survival advantage in front-line CLL, and this gives us some sense of the magnitude of the efficacy of obinutuzumab.

More infusion reactions and myelosuppression occurred on the O-Clb arm. This did not translate into any difference in infection rates, so the safety was completely acceptable. I believe that when Clb is chosen for an older patient with CLL, obinutuzumab, which was recently approved, should be added to the regimen.

Interview with Brad S Kahl, MD, February 13, 2014