5 Minute JournalClub

POST-ASH Issue 4, 2014

Interim Analysis of the Phase III CLL10 Trial: FCR versus Bendamustine/ Rituximab for Fit Patients with 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 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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Brad S Kahl, MD
Skoronski Chair of Lymphoma Research
Associate Professor
University of Wisconsin School of Medicine and Public Health
Associate Director for Clinical Research
UW Carbone Cancer Center
Madison, Wisconsin

Advisory Committee: Celgene Corporation, Genentech BioOncology, Millennium: The Takeda Oncology Company, Roche Laboratories Inc; Contracted Research: Genentech BioOncology, Roche Laboratories Inc.

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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."

Neil Love, MD
Research To Practice
Miami, Florida

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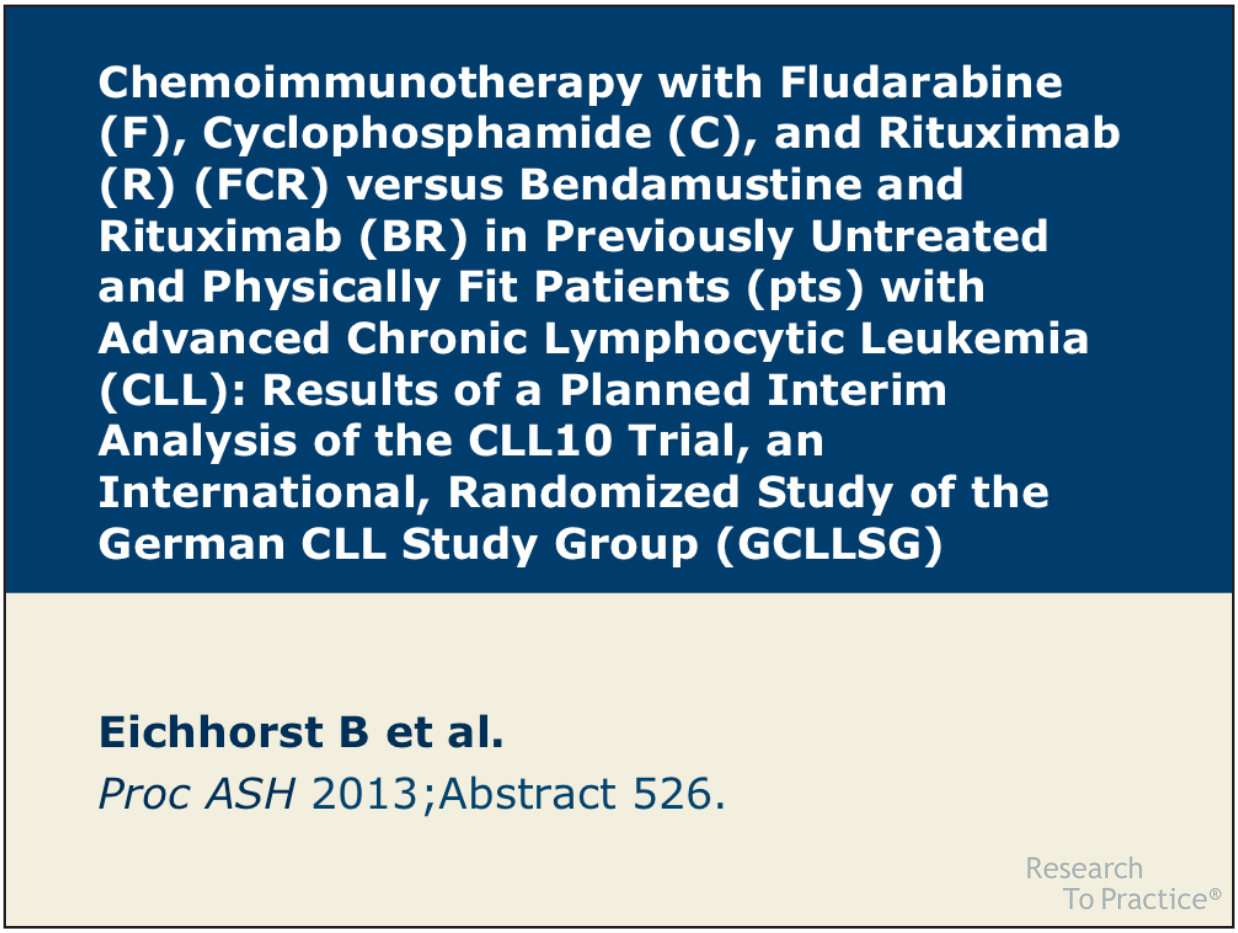
Interim Analysis of the Phase III CLL10 Trial: FCR versus Bendamustine/Rituximab for Fit Patients with Previously Untreated CLL

Presentation discussed in this issue

Eichhorst B et al. **Chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus bendamustine and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): Results of a planned interim analysis of the CLL10 trial, an international, randomized study of the German CLL Study Group (GCLLSG).** *Proc ASH* 2013;**Abstract 526**.

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



Background

- FCR is the current standard first-line treatment regimen in advanced CLL, but it is associated with significant side effects (*Lancet* 2010;376:1164).
- The GCLLSG initiated an international Phase III study to test the noninferiority of BR compared to FCR in terms of efficacy and potentially better tolerability in the first-line treatment of physically fit patients with CLL without del(17p).
- **Study objective:** To report the efficacy and safety results of a planned interim analysis of first-line BR versus FCR in advanced CLL.

Eichhorst B et al. *Proc ASH* 2013;Abstract 526.

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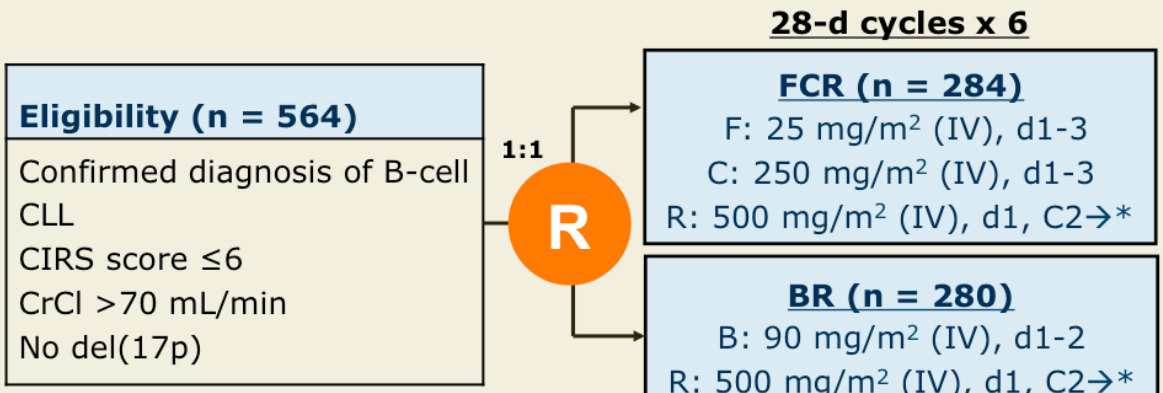
Phase III CLL10 Trial Design



CIRS = cumulative illness rating scale
CrCl = creatinine clearance

* Starting dose for R: 375 mg/m² (IV) day 0 of the first cycle

- Patients were enrolled from 158 sites in 5 countries
- **Primary endpoint:** Progression-free survival (PFS) after 24 months

Eichhorst B et al. *Proc ASH* 2013;Abstract 526.

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Patient Characteristics

Characteristic	n = 561*
Median age	62 years (range: 33-82)
Median CIRS score	2 (range: 0-6)
Binet Stage A	22%
Binet Stage B	38%
Binet Stage C	40%

* Intent-to-treat population. Three patients excluded due to deferred treatment

- There were significantly more patients with unmutated IGVH gene in the BR arm (68%) compared to the FCR arm (55%): $p = 0.003$.
- All other characteristics were well balanced.

Eichhorst B et al. *Proc ASH* 2013;Abstract 526 (abstract only).

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Study Characteristics

	FCR (n = 284)	BR (n = 280)	*p*-value
Median number of treatment cycles administered	5.27	5.41	0.022
Patients who received 6 cycles	70.6%	80.3%	0.008
Dose reduction by >10%	27.3%	31.6%	0.012

- The median observation time was 27.9 months in all patients alive.
- Intent-to-treat (ITT) patient population (n = 561)
  - Patients excluded due to deferred treatment (n = 3)

Eichhorst B et al. *Proc ASH* 2013;Abstract 526 (abstract only).

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Response Evaluation

	FCR (n = 274)	BR (n = 273)	*p*-value
Overall response rate	97.8%	97.8%	1.0
Complete response (CR)*	47.4%	38.1%	0.031
Partial response	50.4%	59.7%	NR
	(n = 99)	**(n = 93)**	***p*-value**
Minimal residual disease (MRD)†	71.7%	66.7%	0.448

* Confirmed by central immunohistology; † MRD levels $<10^{-4}$ in peripheral blood at final staging

NR = not reported

- Missing response evaluation (n = 14)

Eichhorst B et al. *Proc ASH* 2013;Abstract 526 (abstract only).

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PFS in ITT Population

All patients				
PFS rate	**FCR (n = 282)**	**BR (n = 279)**	**HR**	***p*-value**
2-year PFS	85.0%	78.2%	1.385	0.041
Subset analysis				
Median PFS	**FCR**	**BR**	**HR**	***p*-value**
Patients <65 years	Not reached	36.5 mo	NR	0.016
Patients ≥65 years	45.6 mo	Not reached	NR	0.757

Eichhorst B et al. *Proc ASH* 2013;Abstract 526 (abstract only).

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Event-Free Survival (EFS) and Overall Survival (OS) in ITT Population

Outcome	FCR (n = 282)	BR (n = 279)	HR	*p*-value
2-year EFS	82.6%	75.7%	1.375	0.037
2-year OS	94.2%	95.8%	0.842	0.593

- A multivariate analysis including treatment arm, Binet stage, age, sex, comorbidity, serum TK, serum beta-2 microglobulin (Beta2M), del(11q) and IGHV mutation status identified treatment arm, Beta2M, del(11q) and IGHV mutation status as independent prognostic factors for PFS and EFS.

Eichhorst B et al. *Proc ASH* 2013;Abstract 526 (abstract only).

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Adverse Events (AEs)

Grade 3-5 AEs	FCR (n = 282)	BR (n = 279)	*p*-value
All	90.8%	78.5%	<0.001
Severe hematologic AEs	90.0%	66.9%	<0.001
Severe neutropenia	81.7%	56.8%	<0.001
Severe infections	39.0%	25.4%	0.001
Elderly patients	47.4%	26.5%	0.002
Treatment-related death	3.9%	2.1%	NR

- The incidence of severe Grade 3-5 AEs was significantly greater on the FCR arm during the entire observation period.

Eichhorst B et al. *Proc ASH* 2013;Abstract 526 (abstract only).

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Author Conclusions

- The results of this planned interim analysis demonstrate that FCR seems to be more efficient than BR in the first-line treatment of fit patients with CLL.
  - CR: 47.4% (FCR) vs 38.1% (BR); $p = 0.031$
  - 2-year PFS: 85.0% (FCR) vs 78.2% (BR); $p = 0.041$
  - 2-year EFS: 82.6% (FCR) vs 75.7% (BR); $p = 0.037$
- These advantages might be balanced by a higher rate of severe AEs, in particular neutropenia and infections, associated with FCR.
- In light of these results, no firm recommendation of one regimen over the other can be made at the present time regarding first-line use for patients with good physical fitness with CLL.

Eichhorst B et al. *Proc ASH* 2013;Abstract 526 (abstract only).

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Investigator Commentary: CLL10 — Results of a Planned Interim Analysis of First-Line FCR versus BR for Fit Patients with CLL

The trial was for fit patients, and it employed a noninferiority design to test whether BR would attain results similar to those attained with FCR. The observation time was mature. The overall response rate was identical in both arms at 98%. The CR rate was better with FCR than with BR (47% vs 38%), and patients receiving FCR were more likely to have no MRD at the end of induction therapy. In terms of the 2-year PFS, 85% of patients who received FCR are still in first remission versus 78% of those receiving BR. Interestingly, for patients aged ≥65 years no difference in PFS was evident between the arms.

OS was the same in both arms. FCR was more toxic with more Grade 3 to 5 hematologic AEs and severe infections. The take-home message is that FCR produces slightly more durable remissions than does BR as front-line therapy for patients with CLL aged <65. I would counsel older patients that BR offers a better risk-benefit profile. For younger patients, I would explain the benefits and risks of FCR and BR and try to make a decision together. Because the OS is the same, some might choose BR because it is less toxic even though the remissions are not as durable. That's reasonable, provided the patients are informed about the tradeoffs.

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