5 Minute JournalClub

POST-ASH Issue 4, 2014

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CME Information

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.

CME Information (Continued)

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FACULTY DISCLOSURES
The following faculty (and his spouse/partner) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

CME Information (Continued)

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5 MinuteJournalClub

POST-ASH Issue 4, 2014

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

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[1]

Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions[2]

[1] **Goede V et al.**
Proc ASH 2013;Abstract 6.

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

Background

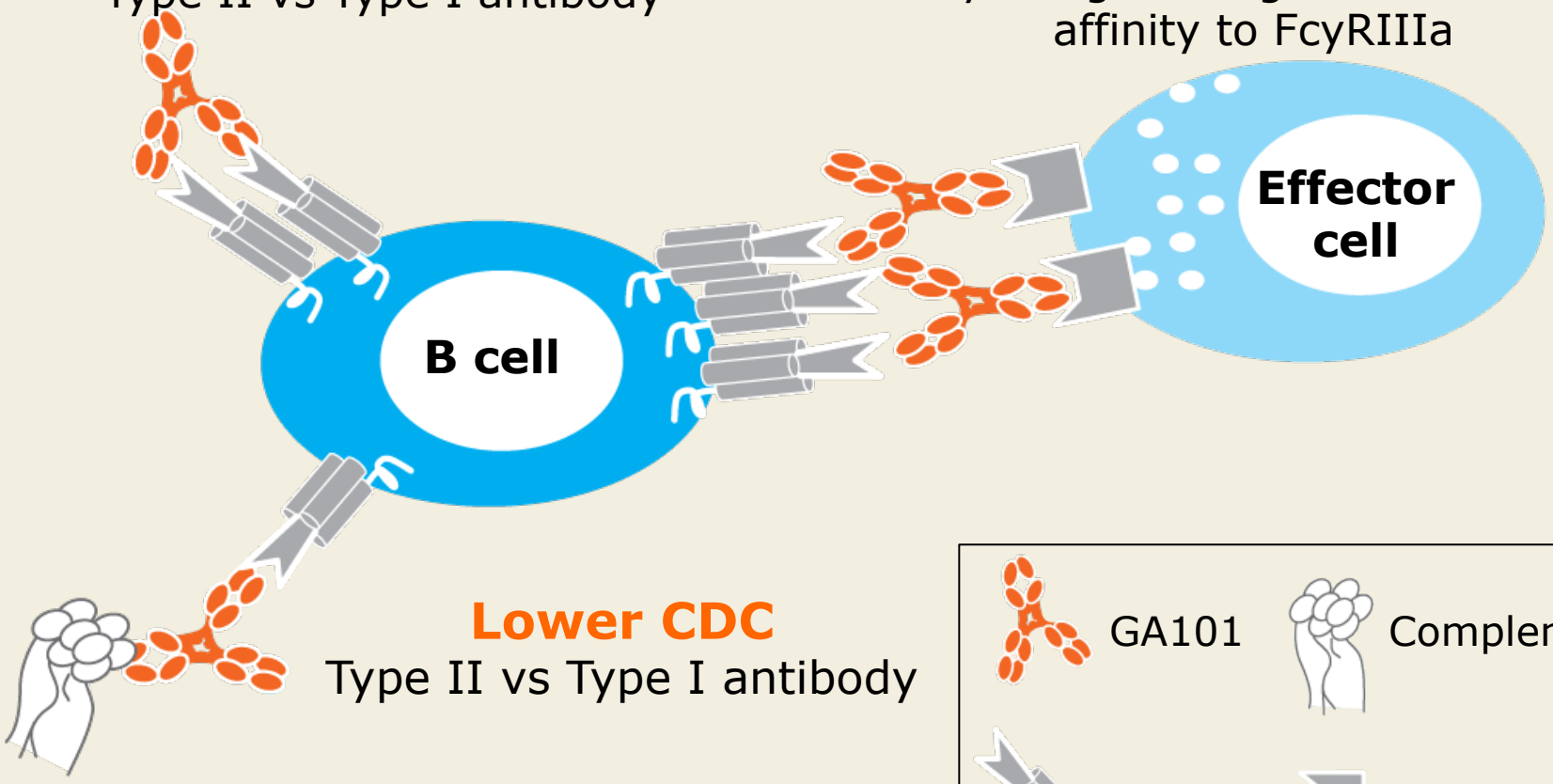
- CLL11 is a large randomized Phase III trial of first-line chemoimmunotherapy for patients with CLL and comorbidities.
- Obinutuzumab is a third-generation type II anti-CD20 antibody that selectively binds to the extracellular domain of the human CD20 antigen on malignant human B cells.
- Preliminary 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].

Mechanism of Action of Obinutuzumab

Increased Direct Cell Death
Type II vs Type I antibody

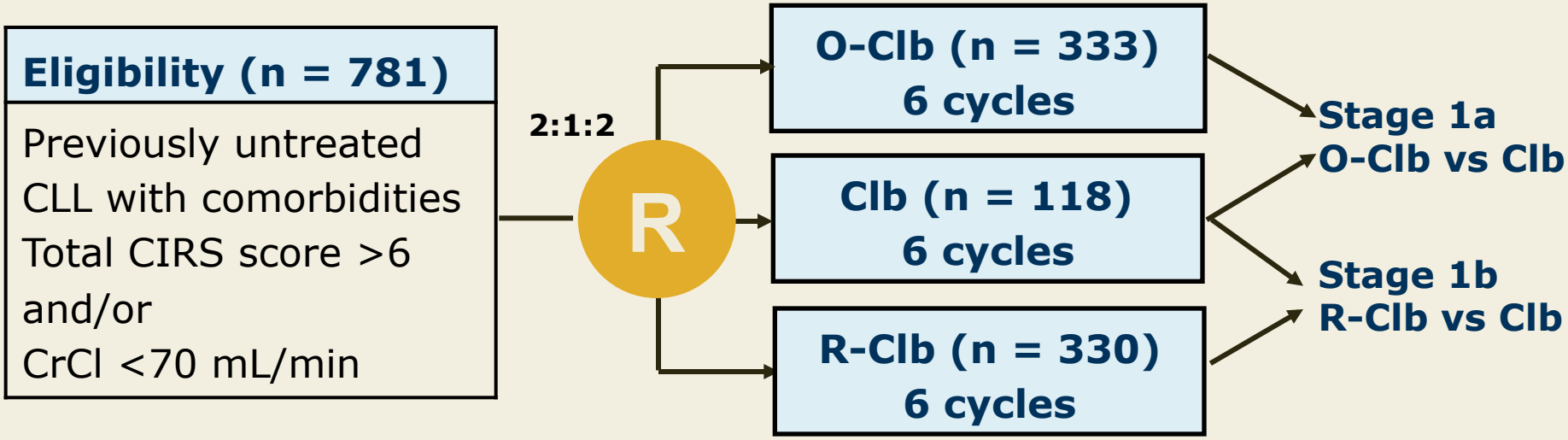
Enhanced ADCC
Glycoengineering for increased affinity to FcγRIIIa



Lower CDC
Type II vs Type I antibody

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

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].

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].

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].

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].

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].

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].

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].

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].

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

Safety and Efficacy of Obinutuzumab (GA101) with Fludarabine/Cyclophosphamide (G-FC) or Bendamustine (G-B) in the Initial Therapy of Patients with Chronic Lymphocytic Leukemia (CLL): Results from the Phase 1b GALTON Trial (GAO4779g)

Brown JR et al.

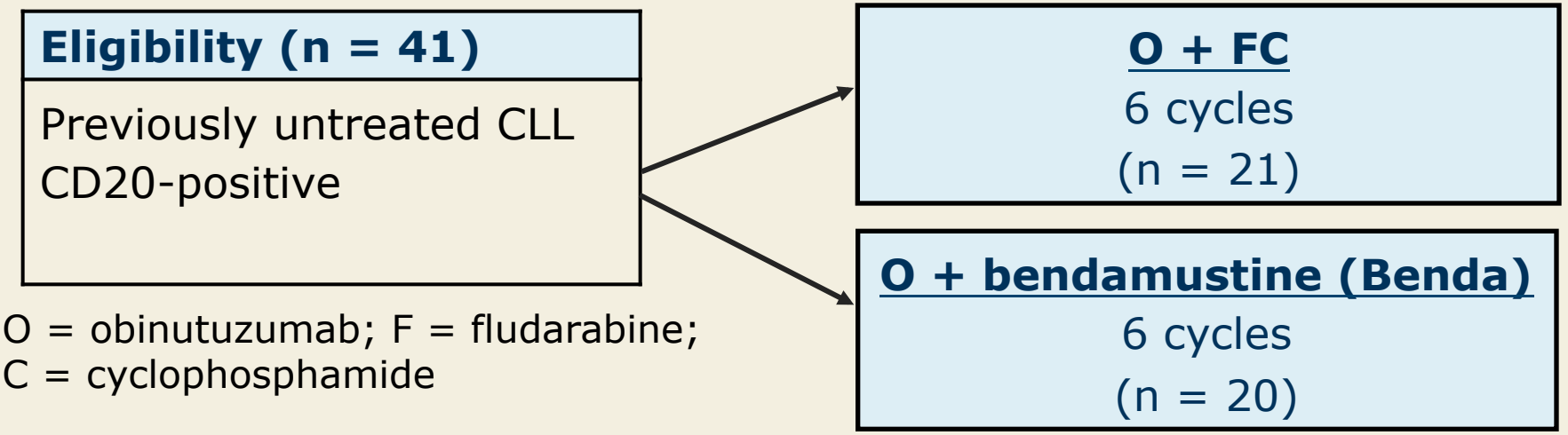
Proc ASH 2013;Abstract 523.

Background

- Chemoimmunotherapy is the standard treatment for fit patients with CLL.
- Early studies in relapsed/refractory CLL demonstrated single-agent activity of obinutuzumab, but treatment was associated with neutropenia.
- Results from the Phase III CLL11 trial of obinutuzumab/ chlorambucil (Clb) or rituximab/Clb or Clb alone for patients with untreated CLL with comorbidities demonstrated (*NEJM* 2014;[Epub ahead of print]):
  - Improved PFS and ORR with obinutuzumab/Clb compared to rituximab/Clb or Clb alone
- **Study objective:** To demonstrate the safety and preliminary efficacy of obinutuzumab in combination with common standard regimens for patients with CLL.

Brown JR et al. *Proc ASH* 2013;Abstract 523.

Phase Ib GALTON Trial Design



O = obinutuzumab; F = fludarabine;
C = cyclophosphamide

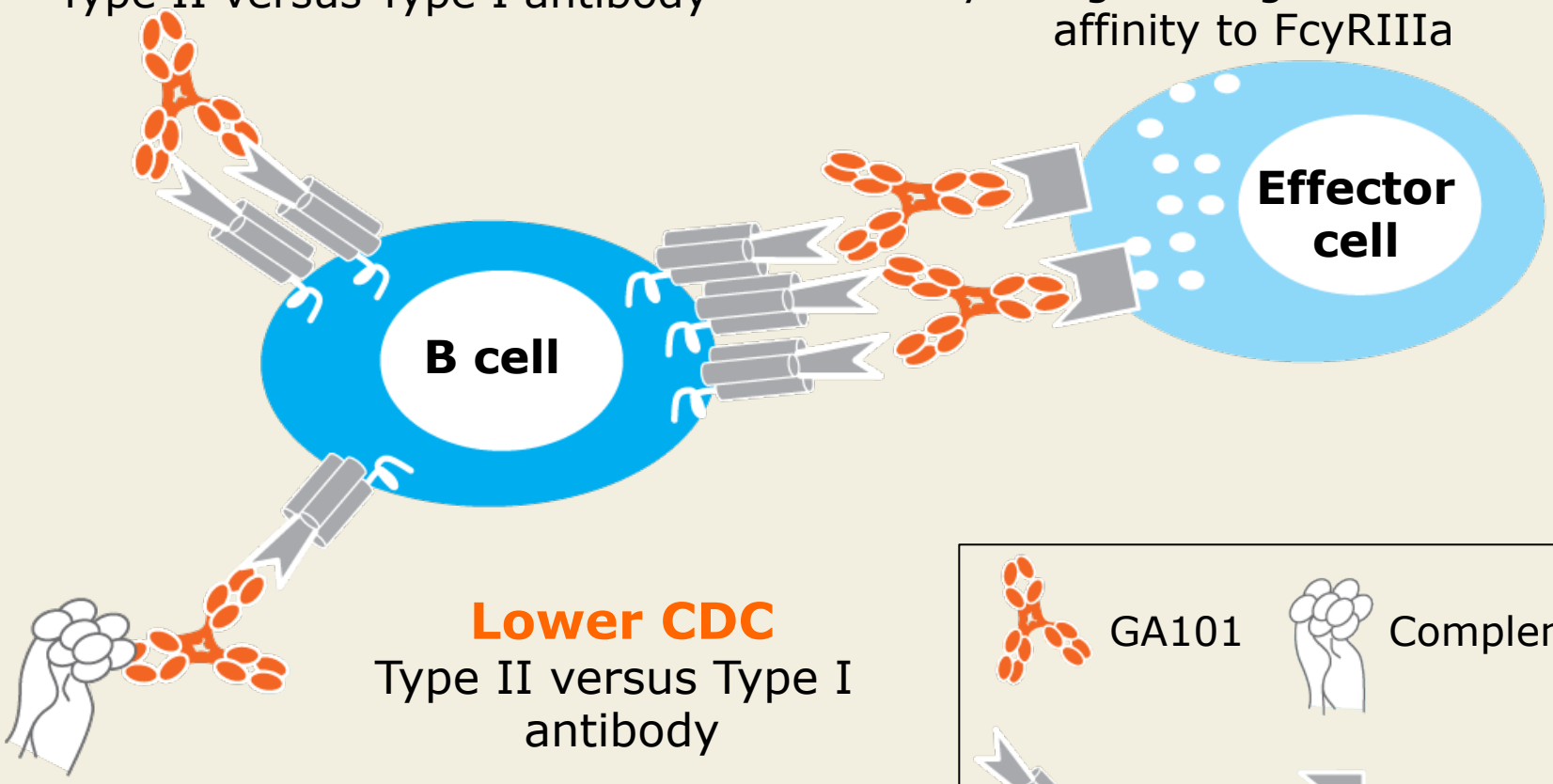
- O: IV, d1 (100 mg), d2 (900 mg), d8, 15 (1,000 mg) for cycle 1 and d1 (1,000 mg) for cycles 2-6
- F: IV, 25 mg/m^2 on d2, 3, 4 for cycle 1 and d1, 2, 3 for cycles 2-6
- C: IV, 250 mg/m^2 on d2, 3, 4 for cycle 1 and d1, 2, 3 for cycles 2-6
- Benda: IV, 90 mg/m^2 on d2, 3 for cycle 1 and d1, 2 for cycles 2-6
- **Primary endpoint: Safety and tolerability of O + FC or O + Benda**

Brown JR et al. *Proc ASH* 2013;Abstract 523.

Mechanism of Action of Obinutuzumab

Increased Direct Cell Death
Type II versus Type I antibody

Enhanced ADCC
Glycoengineering for increased affinity to FcγRIIIa



Lower CDC
Type II versus Type I antibody

With permission from Brown JR et al. *Proc ASH* 2013;Abstract 523.

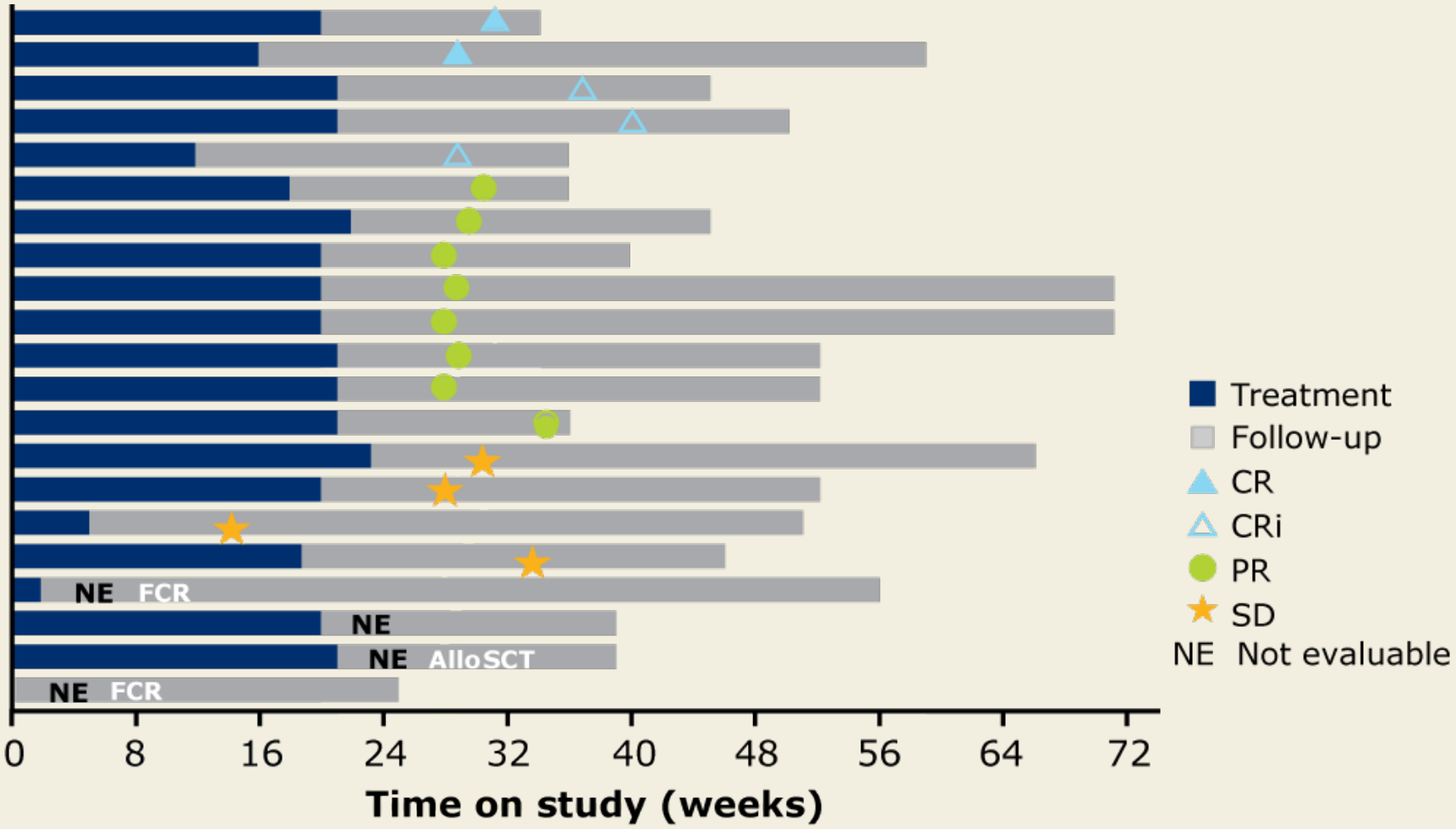
Response Rates at the End of Treatment (EOT)

Response rate	O + FC (n = 21)	O + Benda (n = 20)
ORR	62%	90%
Complete response (CR)	10%	20%
CRi	14%	25%
Partial response	38%	45%
Stable disease	19%	0%
Progressive disease (PD)	0%	0%
Not evaluable	5%	5%

CRi = CR with incomplete blood count recovery

Brown JR et al. *Proc ASH* 2013;Abstract 523.

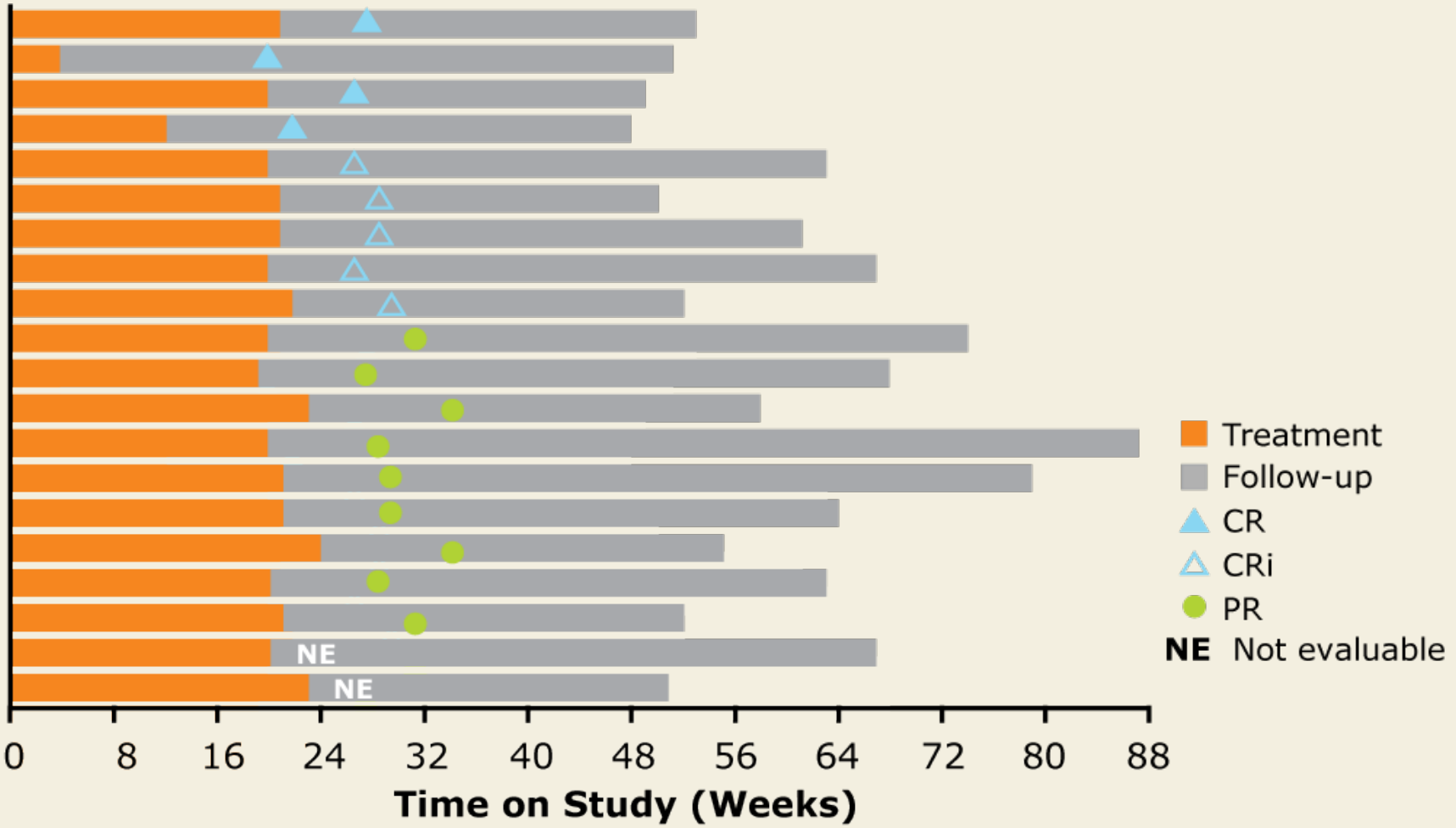
Duration of Treatment and Follow-Up: O + FC



- No patient experienced PD during the median observation time of 10.7 mo

With permission from Brown JR et al. *Proc ASH* 2013;Abstract 523.

Duration of Treatment and Follow-Up: O + Benda



- No patient experienced PD during the median observation time of 13.6 mo

With permission from Brown JR et al. *Proc ASH* 2013;Abstract 523.

Select Adverse Events (AEs)

Grade 3/4 AE	O + FC (n = 21)	O + Benda (n = 20)
Any	86%	85%
Neutropenia	29%	50%
Febrile neutropenia	19%	10%
Thrombocytopenia	5%	10%
Anemia	14%	5%
Infections	19%	5%
Increased ALT/AST	19%/10%	5%/5%
Tumor lysis syndrome (TLS)	0%	5%

Brown JR et al. *Proc ASH* 2013;Abstract 523.

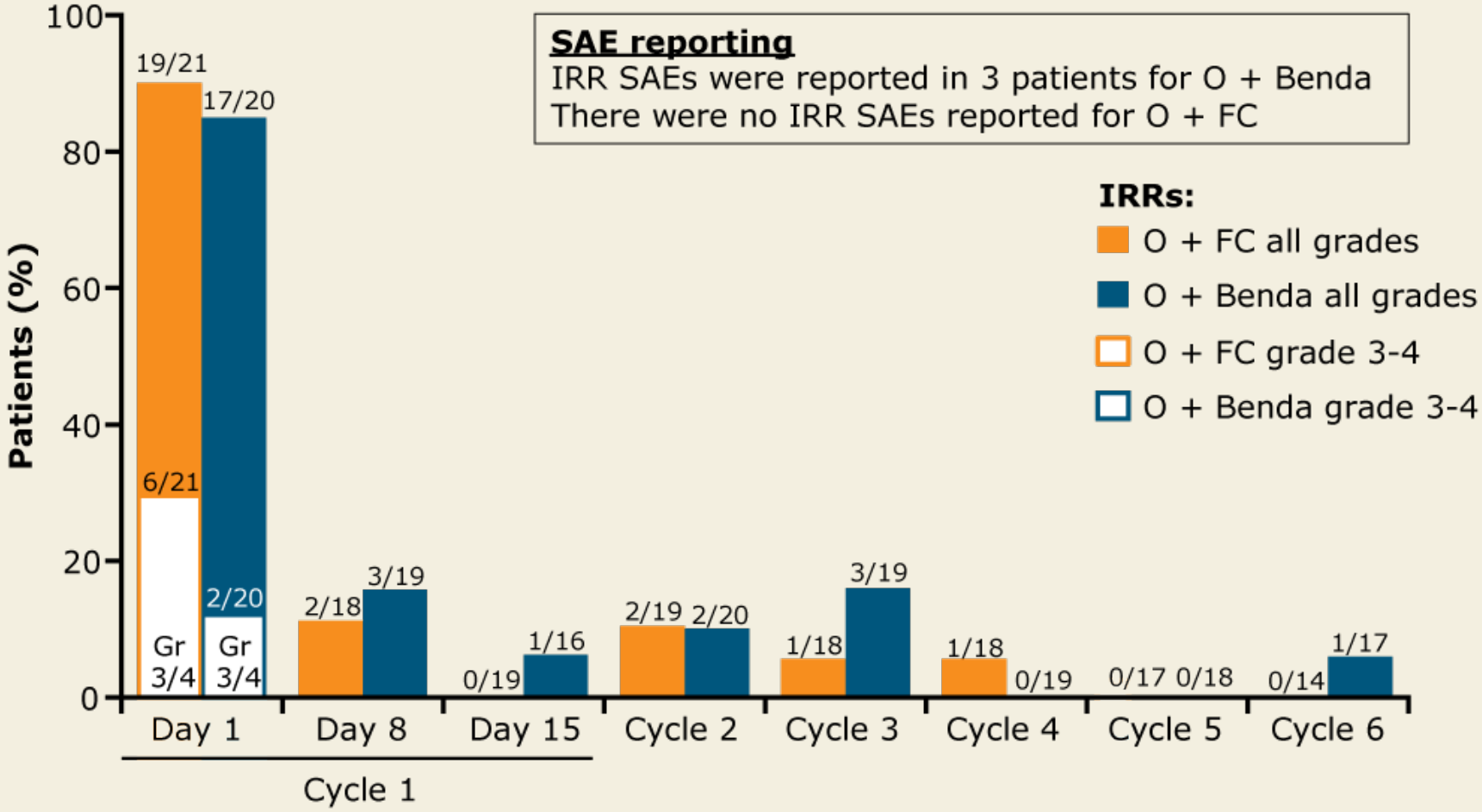
Serious AEs

	O + FC (n = 21)	O + Benda (n = 20)
Any	29%	40%
Febrile neutropenia	14%	10%
Infections	15%	5%
Pyrexia	0%	10%
Nausea	5%	5%
Vomiting	5%	5%

- Serious AEs experienced by 1 patient
  - O + FC: diarrhea, neutrophil decrease
  - O + Benda: fatigue, tachycardia, TLS, syncope, mental status change, swelling face, hypertension
- AEs leading to treatment discontinuation: O + FC (n = 7); O + Benda (n = 2)

Brown JR et al. *Proc ASH* 2013;Abstract 523.

Infusion-Related Reactions (IRR) to Obinutuzumab by Cycle



- IRR: Any AE related to O that occurred ≤24 h after the end of infusion

With permission from Brown JR et al. *Proc ASH* 2013;Abstract 523.

Pharmacokinetics, B-Cell Depletion and Minimal Residual Disease (MRD)

- Pharmacokinetic analysis (O + FC: n = 20; O + Benda: n = 18)
  - Serum concentration range with O was similar to that previously established and similar for O + FC and O + Benda
- Patients with depleted B cells:
  - EOT response: 37/41 patients
  - 6-mo follow-up after final dose: 28/28 patients
- Patients with negative bone marrow biopsies:
  - O + FC: 13/14 patients
  - O + Benda: 14/14 patients
- Patients with negative MRD in peripheral blood:
  - Multicenter at EOT — O + FC: 6/9 patients; O + Benda: 15/16 patients
  - At Dana-Farber Cancer Institute, 2-14 mo after therapy: 9/9 patients who received O + FC and underwent testing

Brown JR et al. *Proc ASH* 2013;Abstract 523.

Author Conclusions

- An acceptable safety profile was observed for obinutuzumab in combination with standard chemotherapy (FC or Benda).
- Obinutuzumab-related IRR was a common adverse event experienced by most patients.
  - IRRs typically occurred during administration of the first dose of obinutuzumab and were manageable.
  - No Grade 3/4 IRRs occurred after the first dose; no fatal IRRs occurred.
- The most common Grade ≥3 AE was neutropenia.
- Clinical activity was observed in both the obinutuzumab/FC and obinutuzumab/Benda cohorts.
- No patient has had disease progression and no deaths have occurred.

Brown JR et al. *Proc ASH* 2013;Abstract 523.

GALTON Trial: Safety and Efficacy of Obinutuzumab with FC or Benda for Previously Untreated CLL

This is a small, ongoing Phase Ib study evaluating the safety and feasibility of combining obinutuzumab with Benda or FC. In terms of safety, more infusion-related reactions (IRRs) occur with obinutuzumab — 90% of the patients had experienced IRRs. Of the 21 patients on the FC arm, 7 had to discontinue treatment early because of AEs. The most common AE on the Benda arm was profound myelosuppression, and 2 patients had to stop treatment early.

From the results, it's unclear whether the efficacy of either combination is any better than that of FC/rituximab or Benda/rituximab. However, the safely signal with obinutuzumab is striking. Personally, I would not start treating my patients with obinutuzumab and Benda or FC yet. We need more data.

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

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)

Eichhorst B et al.

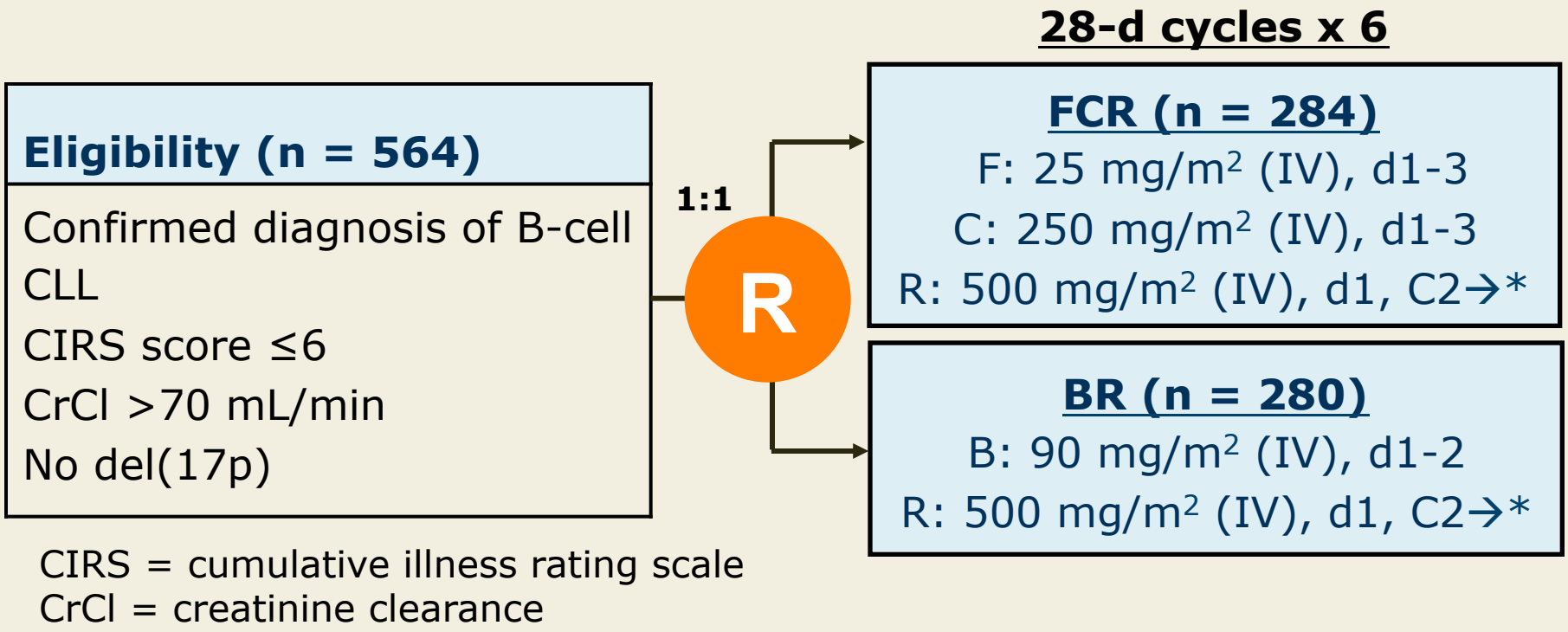
Proc ASH 2013;Abstract 526.

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.

Phase III CLL10 Trial Design



CIRS = cumulative illness rating scale
CrCl = creatinine clearance

* Starting dose for R: 375 mg/m^2 (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.

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).

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).

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).

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).

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).

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).

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).

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

Single Agent Ibrutinib (PCI-32765) Achieves Equally Good and Durable Responses in Chronic Lymphocytic Leukemia (CLL) Patients with and without Deletion 17p

Farooqui M et al.

Proc ASH 2013;Abstract 673.

Background

- Chemoimmunotherapy has markedly improved the outcomes of patients with CLL.
- However, patients harboring the del(17p) chromosome abnormality have inferior outcomes with current standard treatments, with the possible exception of allogeneic stem cell transplantation.
- In addition, elderly patients are in need of less toxic regimens.
- Ibrutinib (PCI-32765) is a covalent inhibitor of the Bruton tyrosine kinase with significant antitumor activity in CLL (*NEJM* 2013;369:32).
- **Study objective:** To determine the efficacy and safety of ibrutinib in patients with CLL who are elderly or those harboring the del(17p) chromosomal abnormality.

Farooqui M et al. *Proc ASH* 2013;Abstract 673.

Ongoing Phase II Trial Design

NCT01500733

Target accrual (n = 86)

Cohort 1:
Treated or untreated CLL or SLL
Age ≥65 years
No del(17p) abnormality

Cohort 2:
Treated or untreated CLL or SLL
Age ≥18 years
Presence of del(17p) abnormality

→ **Ibrutinib**
420 mg daily (oral)

- **Primary endpoint:** Overall response rate after 6 months
- **Secondary endpoints include:** Overall survival, progression-free survival and safety

Farooqui M et al. *Proc ASH* 2013;Abstract 673.

Baseline Characteristics

Characteristic	All patients (n = 53)*
Median age (range)	66 years (33-85)
Rai Stage III/IV	70%

* First 53 patients enrolled on the study

- Cohort 1 (n = 24)
- Cohort 2 (n = 29)

Farooqui M et al. *Proc ASH* 2013;Abstract 673 (abstract only).

Response at 6 Months

Outcome	All patients (n = 47)	Cohort 1 (n = 21)	Cohort 2 (n = 26)	*p*-value
Partial response (PR)	66%	81%	53%	0.04
PR with lymphocytosis	28%	9%	43%	0.02
Stable disease	4%	9%	0%	0.11
Progressive disease	2%	0%	4%	0.35
Nodal response (>50% reduction)	100%	100%	100%	NA

NA = not applicable

- Median follow-up: 14 months
- The apparent difference in response rates (PR vs PR with lymphocytosis) is due to a slower clearance of the treatment-induced lymphocytosis in Cohort 2
- The estimated event-free survival at 14 months was 93%

Farooqui M et al. *Proc ASH* 2013;Abstract 673 (abstract only).

Degree of Tumor Reduction at 6 Months

Site of tumor reduction	Median reduction			
	All patients (n = 47)	Cohort 1 (n = 21)	Cohort 2 (n = 26)	*p*-value
Nodes	73%	75%	70%	0.75
Spleen	44%	40%	46%	0.50
Bone marrow	80%	76%	84%	0.51
ALC	62%	71%	60%	0.42

ALC = absolute lymphocyte count

- Clinical benefit and disease control in all tissue sites were equal between cohorts.

Farooqui M et al. *Proc ASH* 2013;Abstract 673 (abstract only).

Effect of Ibrutinib on del(17p) Clones

- To obtain a direct measure of the relative impact of ibrutinib on tumor cells harboring the del(17p) abnormality, FISH testing was performed at 6 months (n = 20).
  - In the individual patients, del(17p) was present in 12% to 97% of the tumor cells before treatment.
  - At 6 months, del(17p) was present in 0% to 92% of tumor cells.
  - In 80% of patients, there was a decrease in the relative size of del(17p) subclones.
    - Median reduction 34%; $p < 0.02$
  - Four patients (20%) had no evidence of del(17p) after 6 months.

Farooqui M et al. *Proc ASH* 2013;Abstract 673 (abstract only).

Adverse Events (AEs)

- Most AEs were of Grade ≤2 intensity (mostly diarrhea, fatigue, arthralgia/myalgia and rash).
- Grade ≥3 infections or cytopenias were uncommon and reported in 15% of patients regardless of causality.
- Treatment-related nonhematologic AEs of Grade ≥3 intensity occurred in <5% of patients.
- Four deaths occurred on study but were not related to treatment.
- Forty-seven patients were restaged at 6 months.
- Six patients did not reach the restaging endpoint.
  - Unrelated deaths (n = 2)
  - Unrelated secondary malignancies (n = 3)
  - Progressive disease due to presumed transformation at 2 weeks in patients with del(17p) (n = 1)

Farooqui M et al. *Proc ASH* 2013;Abstract 673 (abstract only).

Author Conclusions

- Ibrutinib as a single agent appears to be equally effective against CLL in the presence or absence of the del(17p) chromosomal abnormality.
- This conclusion is based on a comparison of responses in 2 concomitantly treated cohorts of patients with CLL and supported by the absence of a treatment-related increase in the del(17p) clone in individual patients.

Farooqui M et al. *Proc ASH* 2013;Abstract 673 (abstract only).

Investigator Commentary: Single-Agent Ibrutinib Achieves Good Responses in CLL with or without del(17p)

Chemotherapy has been notoriously ineffective against CLL harboring 17p deletion. Even with bendamustine/rituximab or fludarabine/ cyclophosphamide/rituximab the results have been disappointing. However, the data to date suggest that ibrutinib and some of the other kinase inhibitors have unique activity in CLL with 17p deletion. This is exciting.

In this study of 53 patients, 24 had a normal 17p status while 29 had disease with del(17p). At 6 months the clinical results were similar in the 2 cohorts. For patients without del(17p), the overall response rate was 81% and an additional 9% of patients experienced response but also lymphocytosis. This amounts to a 90% response rate. For patients with disease harboring del(17p), the response rate was 53% using the traditional criteria. Considering this alone, one might believe that patients with del(17p) have worse outcomes. In fact, if you factor in the 43% who experienced response but with lymphocytosis, the response rate becomes 96%.

It appears that patients with CLL or SLL with del(17p) are more likely to experience prolonged lymphocytosis than those without the deletion. The question is whether this will make a difference clinically. It will be interesting to see the follow-up results with these patients over time.

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

Ibrutinib in Combination with Rituximab (iR) Is Well Tolerated and Induces a High Rate of Durable Remissions in Patients with High-Risk Chronic Lymphocytic Leukemia (CLL): New, Updated Results of a Phase II Trial in 40 Patients

Burger JA et al.

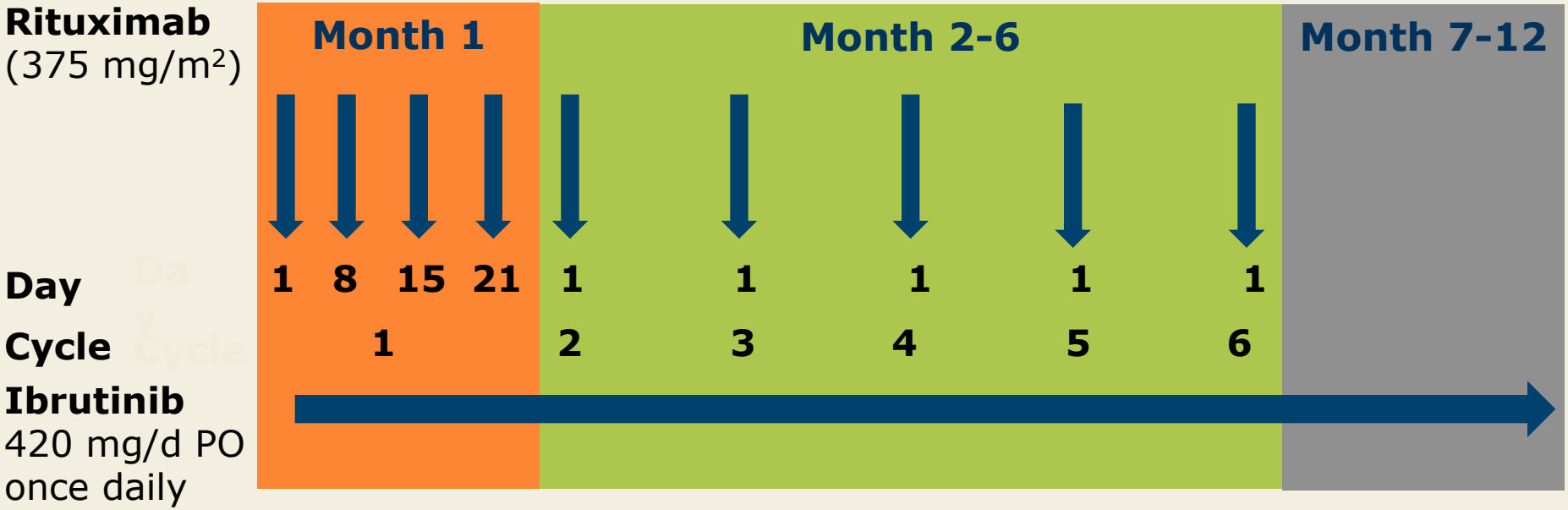
Proc ASH 2013;Abstract 675.

Background

- The Bruton tyrosine kinase inhibitor ibrutinib is a promising new targeted therapy for patients with mature B-cell hematologic cancers, especially chronic lymphocytic leukemia (CLL).
- Ibrutinib monotherapy induces high rates of durable responses in patients with previously treated CLL (*N Engl J Med* 2013;369:32):
  - Overall response rate (ORR) = 71%, with an additional 15% to 20% of patients experiencing partial response with lymphocytosis, which is generally transient (peaks after 1 to 2 months and then continuously declines)
  - Responses are independent of prognostic factors, such as del(17p)
  - At 26 months: Progression-free survival (PFS) = 75%, overall survival (OS) = 83%
- **Study objective:** To assess the activity and tolerability of ibrutinib and rituximab combination therapy (iR) in patients with high-risk CLL.

Burger JA et al. *Proc ASH* 2013;Abstract 675.

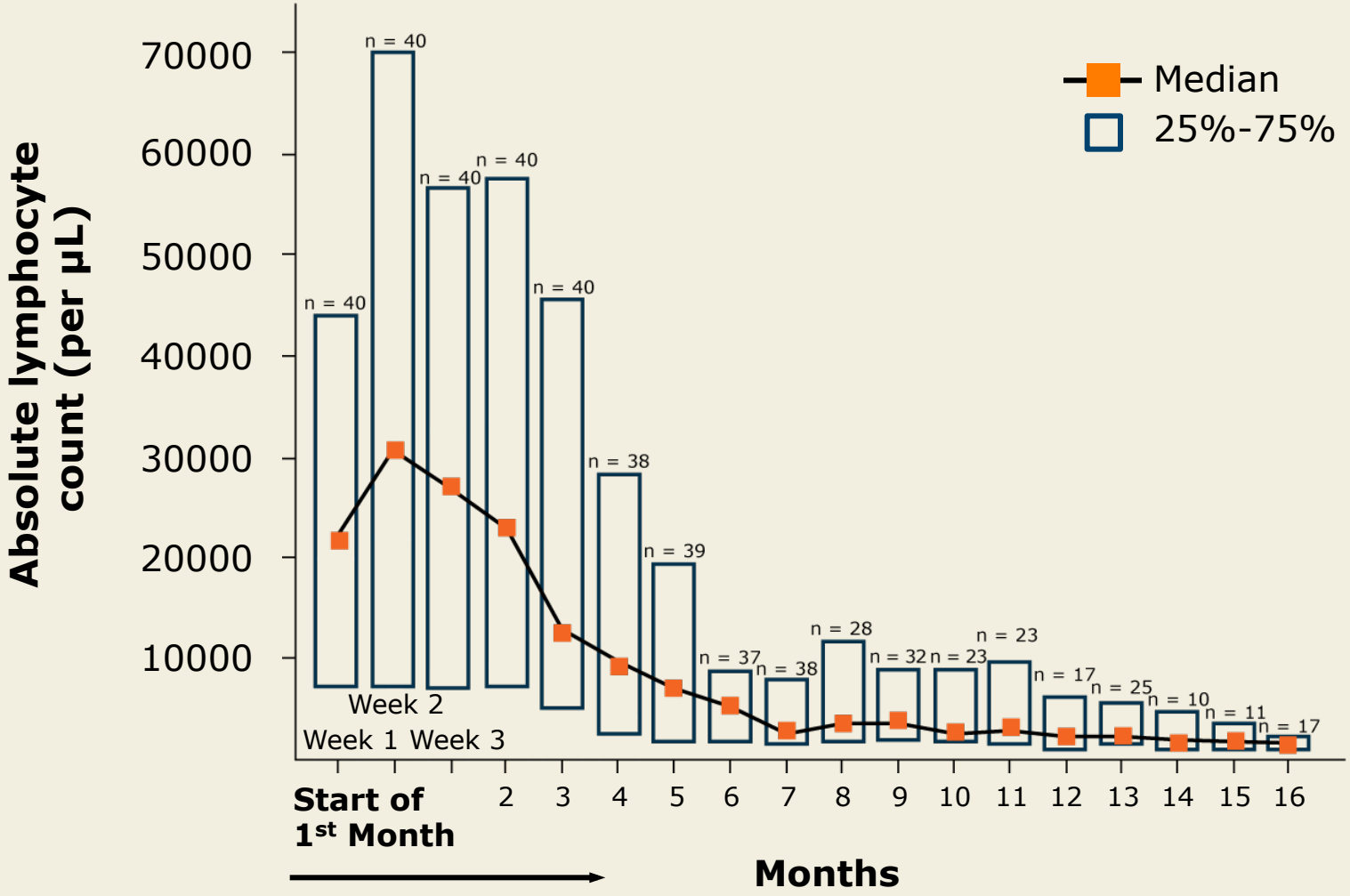
Phase II Trial Design: Dose and Schedule of iR



Patients with benefit after 12 cycles will be allowed to continue on single-agent ibrutinib.

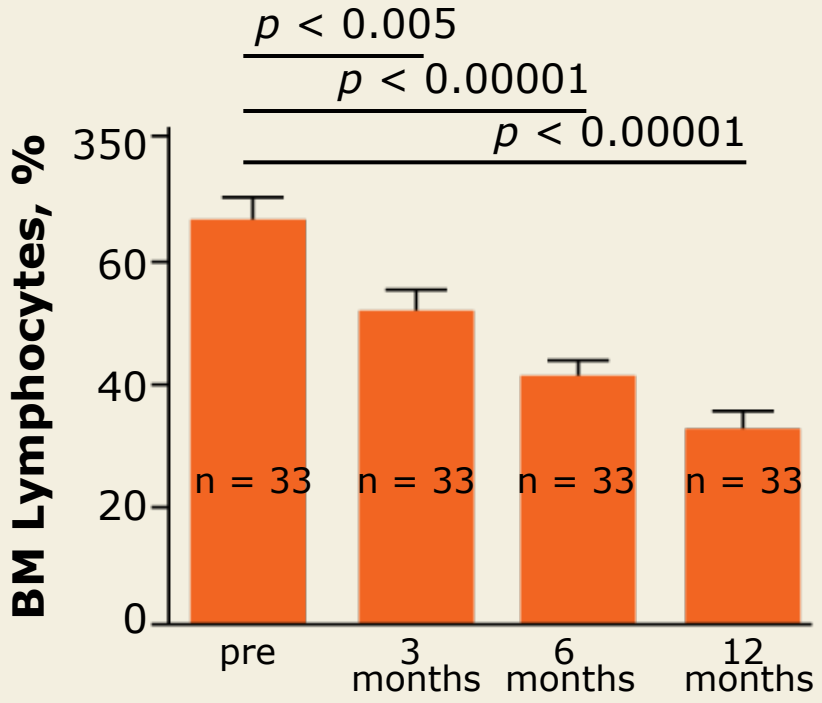
Burger JA et al. *Proc ASH* 2013;Abstract 675.

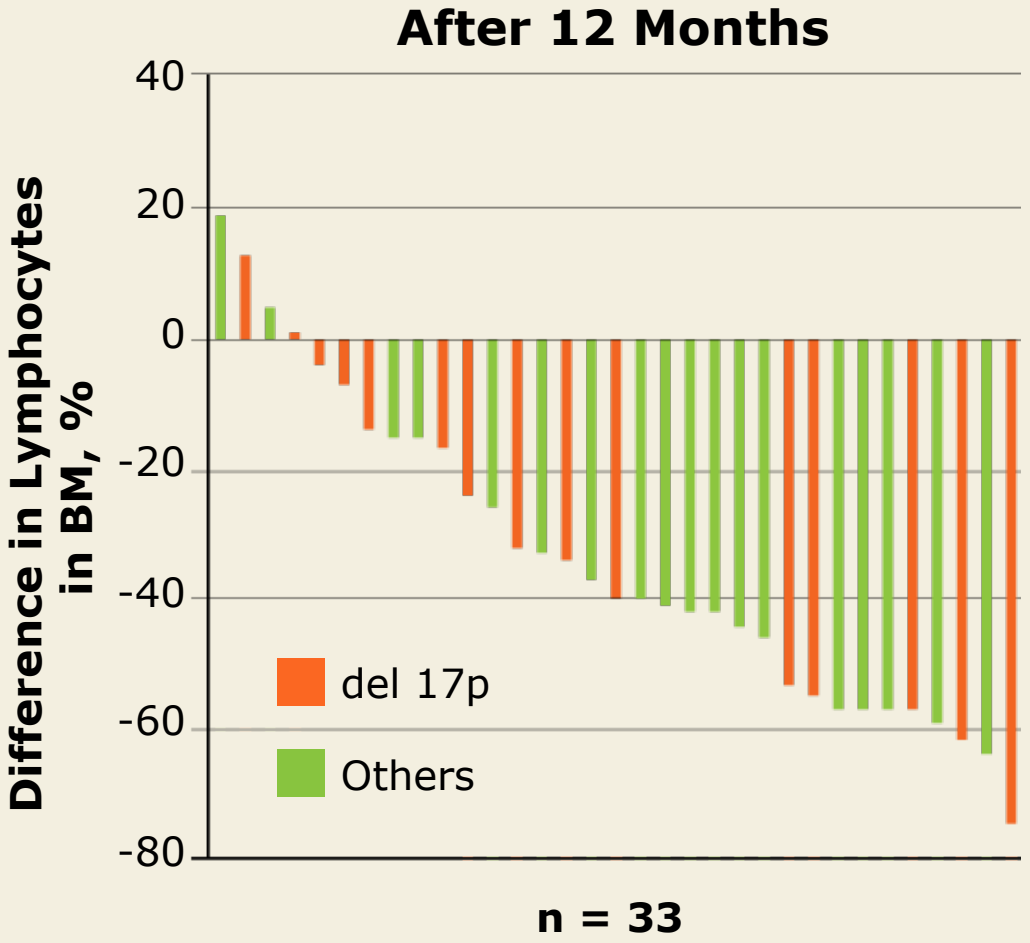
Transient Lymphocytosis on iR Therapy



With permission from Burger JA et al. *Proc ASH* 2013;Abstract 675.

Changes in Bone Marrow (BM) Infiltration During iR Therapy





With permission from Burger JA et al. *Proc ASH* 2013;Abstract 675.

Best Response*

n = 40	n (%)
ORR	38 (95%)
Complete response†	4 (10%)
Partial response	34 (85%)
No response	2 (5%)

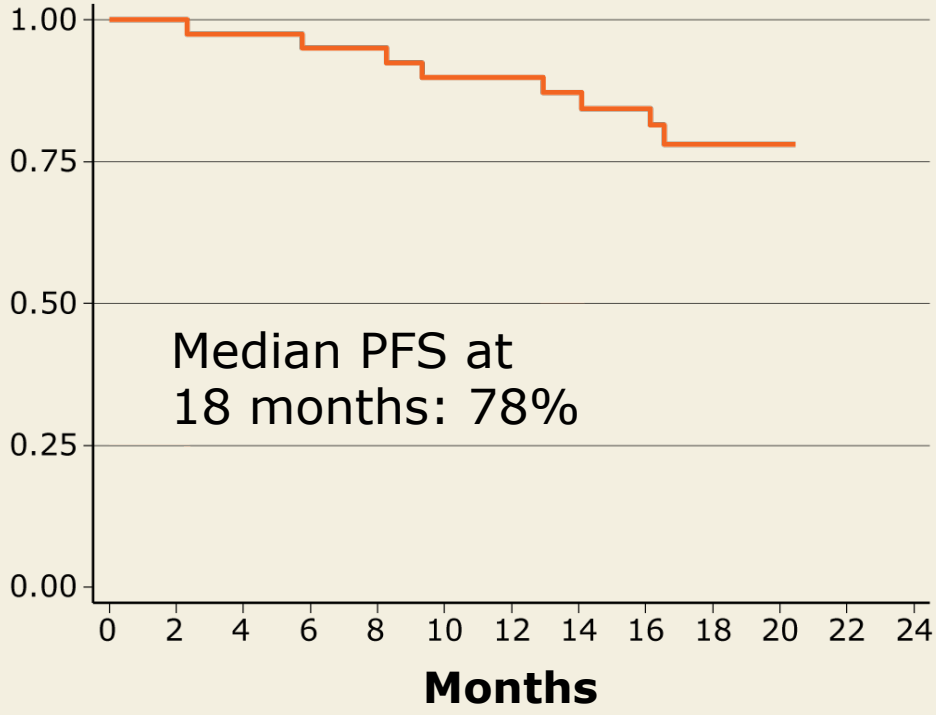
* At 12 months or best response before study discontinuation

† Minimal residual disease (MRD)-negative: 1 out of 4 patients; MRD level: 0.1%, 0.2%, 0.1%

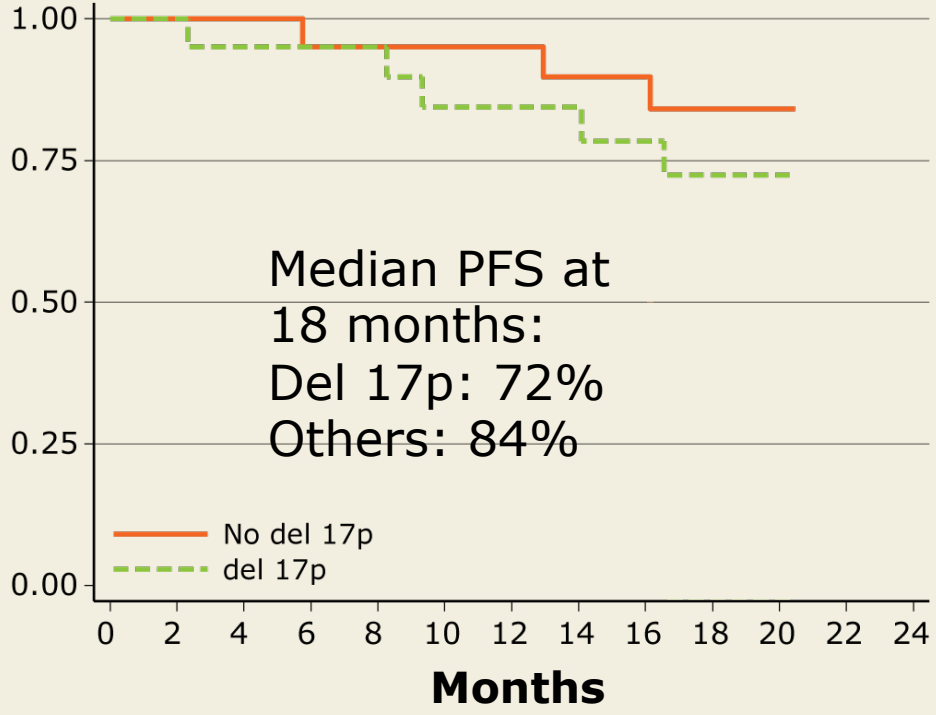
Burger JA et al. *Proc ASH* 2013;Abstract 675.

PFS

All patients



Del 17p versus others

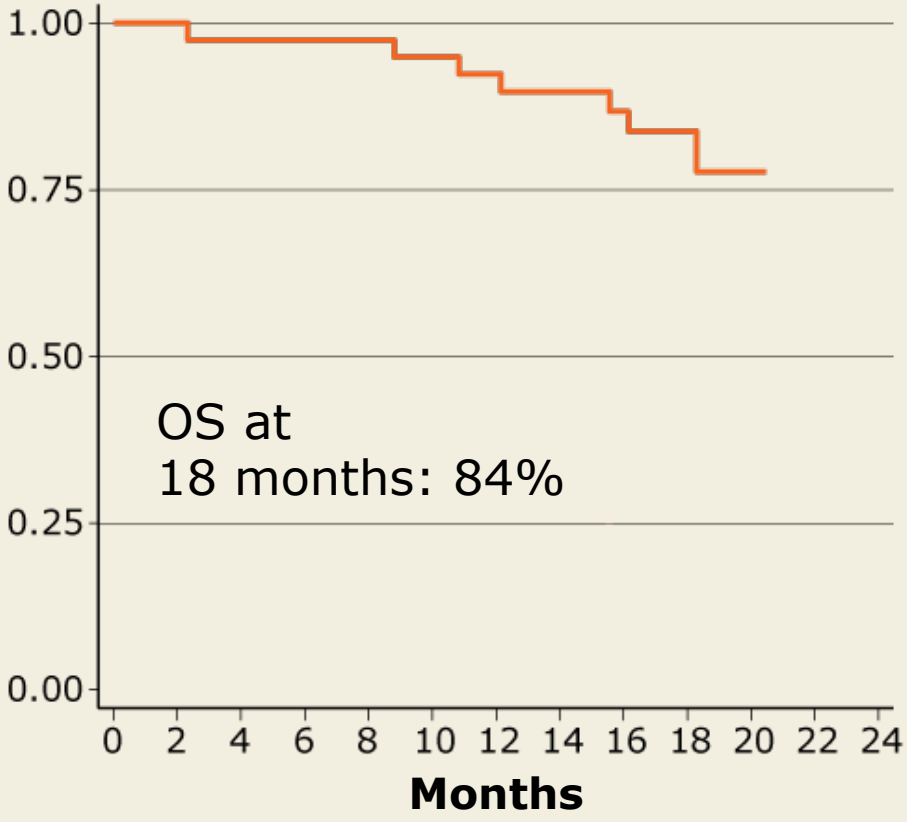


Median follow-up: 17 months

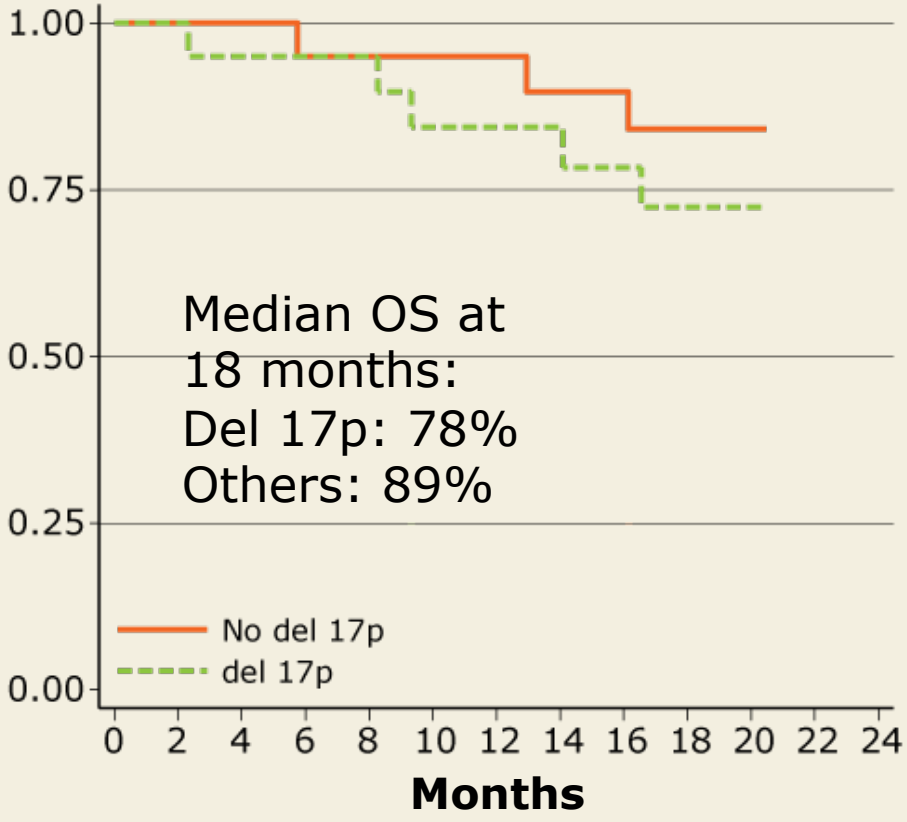
With permission from Burger JA et al. *Proc ASH* 2013;Abstract 675.

OS

All patients



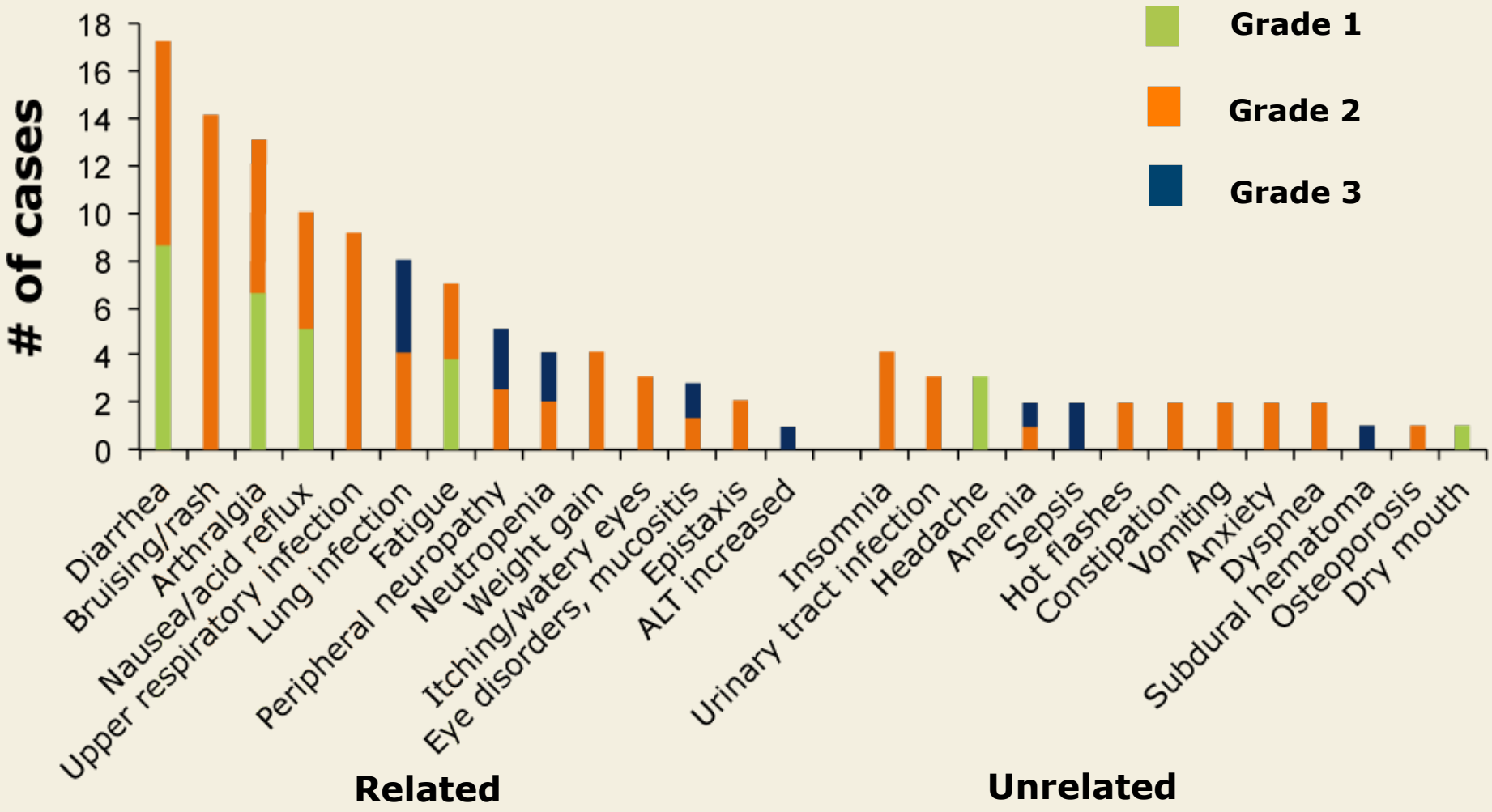
Del 17p versus others



Median follow-up: 17 months

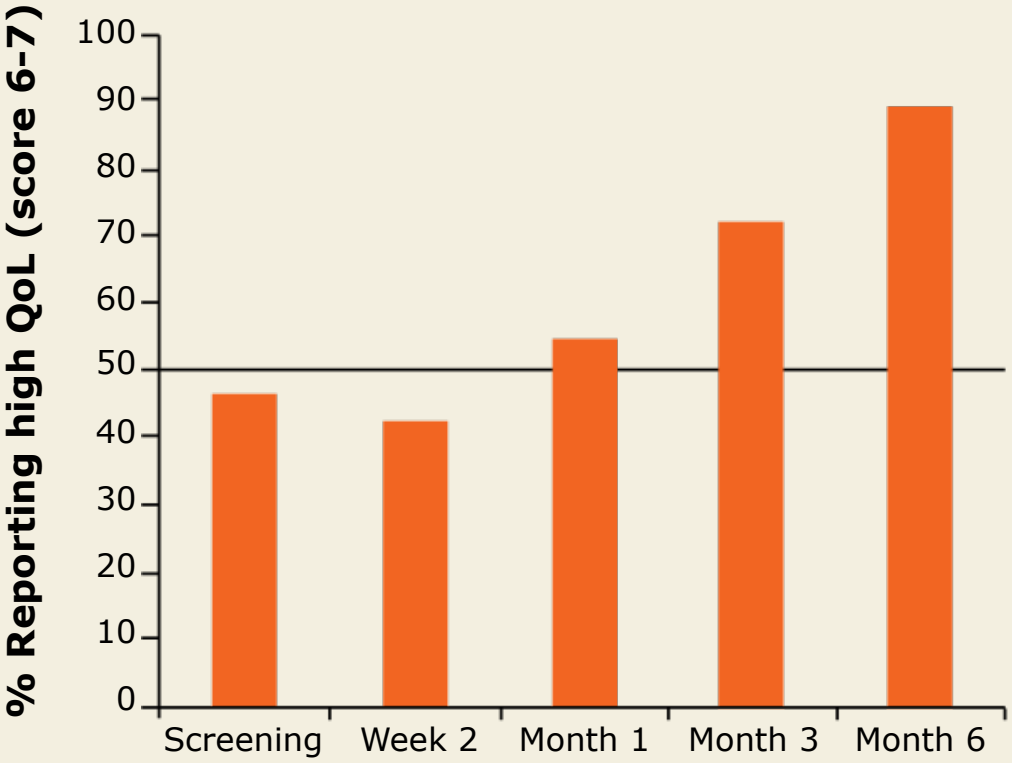
With permission from Burger JA et al. *Proc ASH* 2013;Abstract 675.

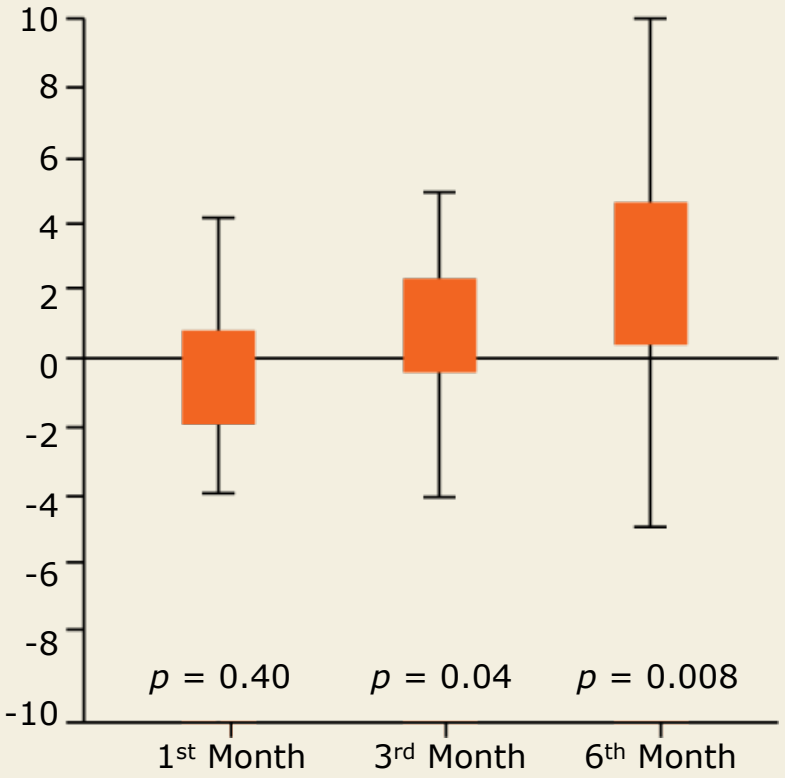
Adverse Events



With permission from Burger JA et al. *Proc ASH* 2013;Abstract 675.

Quality of Life (QoL) and Body Weight Improvement During iR Therapy





Percentage of patients who score highly in the QoL subscales (values 6-7) of the EORTC-QOLv.3 during iR therapy

Baseline Mean KG (SD)	After Cycle 1 (SD)	After Cycle 3 (SD)	After Cycle 6 (SD)
79.15 (18.88), n = 40	78.84 (19.09) n = 40	79.94 (19.01) n = 39	80.99 (18.61) n = 37
	Δ = -0.32 (2.38) *p* = 0.04	Δ = 0.09 (2.65) *p* = 0.04	Δ = 1.74 (3.8) *p* = 0.008

With permission from Burger JA et al. *Proc ASH* 2013;Abstract 675.

Author Conclusions

- The combination of ibrutinib and rituximab has profound activity in patients with high-risk CLL:
  - ORR >90%, CR = 10%
- The combination has a favorable toxicity profile and improves BM infiltration and function.
- The addition of rituximab accelerates ibrutinib response in CLL.
- iR is well tolerated and associated with improvements in QoL and body weight.
- A randomized Phase II follow-up study of ibrutinib versus iR for patients with relapsed CLL is under way (NCT02007044).

Burger JA et al. *Proc ASH* 2013;Abstract 675.

Investigator Commentary: Updated Results of a Phase II Trial of iR for Patients with High-Risk CLL

Single-agent ibrutinib is a well-tolerated agent, but its use has been associated with lymphocytosis. The rationale behind this trial was that the addition of a monoclonal antibody should help in getting rid of the lymphocytosis immediately. Forty patients with relapsed/refractory, high-risk CLL received the ibrutinib/rituximab combination. The investigators reported impressive results. The overall response rate in this patient cohort was 95%, and 18-month PFS was 78%. My conclusion from this study is that if you add rituximab to ibrutinib, lymphocytosis resolves much more quickly than if you administer ibrutinib alone.

I believe that the real question is, does that translate to a clinically meaningful advantage for the patient? In other words, is it actually beneficial to get rid of those circulating lymphocytes immediately rather than letting them die off more slowly over the next couple of months, which is what happens with single-agent ibrutinib? We don't know the answer to that yet. It will take randomized trials comparing ibrutinib to iR or ibrutinib/obinutuzumab to answer that question and ascertain whether adding the monoclonal antibody provides a meaningful benefit for patients.

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

Ibrutinib in Combination with Bendamustine and Rituximab Is Active and Tolerable in Patients with Relapsed/Refractory CLL/SLL: Final Results of a Phase 1b Study

Brown JR et al.

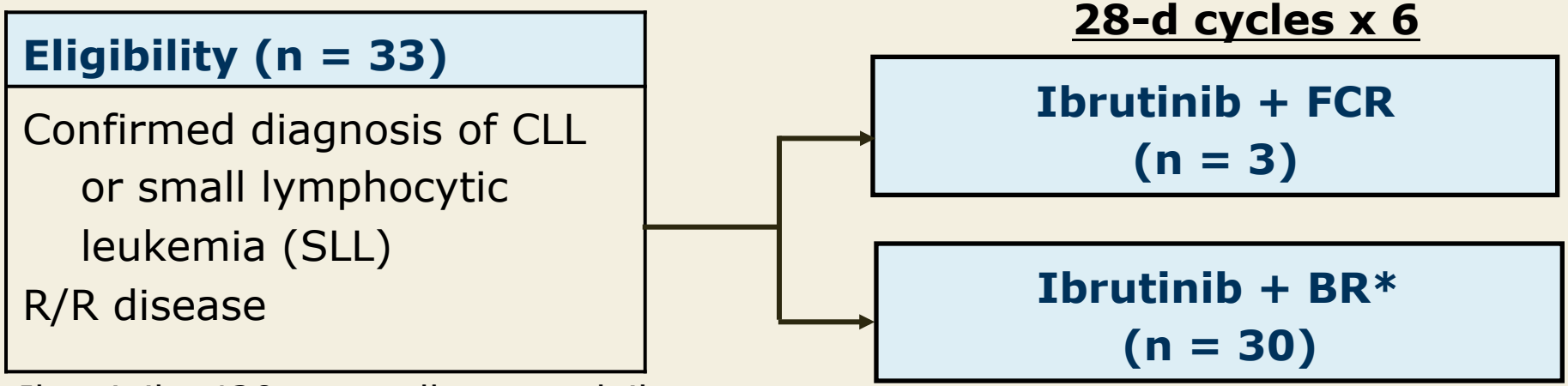
Proc ASH 2013;Abstract 525.

Background

- Ibrutinib is a potent small molecule that binds covalently to a cysteine residue (Cys-481) in the Bruton tyrosine kinase active site, resulting in inhibition of proliferation, migration and adhesion in chronic lymphocytic leukemia (CLL) cells.
- Previously, oral ibrutinib monotherapy demonstrated activity in relapsed/refractory (R/R) CLL (*NEJM* 2013;369:32).
  - Overall response rate (ORR): 71%
  - 26-month progression-free survival (PFS): 75%
- The chemoimmunotherapy regimen of bendamustine and rituximab (BR) is active and well-established in the treatment of R/R CLL.
- **Study objective:** To evaluate the efficacy and safety of ibrutinib in combination with fludarabine/cyclophosphamide/rituximab (FCR) or BR in patients with R/R CLL.

Brown JR et al. *Proc ASH* 2013;Abstract 525.

Phase Ib PCYC 1108 Trial Design



Ibrutinib: 420 mg orally, once daily

F: 25 mg/m^2 d1-3

C: 250 mg/m^2 d1-3

R: 375 mg/m^2 d1 cycle 1; 500 mg/m^2 d1 cycles 2-6

B: 70 mg/m^2 d1-2

- **Primary endpoint:** Safety
- **Secondary endpoints:** ORR, PFS

* At study completion 21 patients (70%) who were still receiving ibrutinib monotherapy after completion of BR continued ibrutinib on a long-term extension study.

Brown JR et al. *Proc ASH* 2013;Abstract 525.

Efficacy Results

Clinical variable	Ibrutinib + BR (n = 30)
ORR	93.4%
Complete response (CR)	16.7%
Partial response (PR)	66.7%
Near PR	10.0%
15-month PFS	78%

- Median duration of treatment: 16 months
- Median PFS was not reached
- One patient who achieved a PR with lymphocytosis was not included in ORR

Brown JR et al. *Proc ASH* 2013;Abstract 525.

Sustained Hematologic Improvement for Patients with Baseline Cytopenias

Ibrutinib + BR arm	
Baseline cytopenia category	**Sustained improvement rate**
ANC ≤1.5 x 10^9/L (n = 8)	63%
Hemoglobin ≤11 g/dL (n = 7)	71%
Platelets ≤100 x 10^9/L (n = 14)	57%

ANC = absolute neutrophil count

Brown JR et al. *Proc ASH* 2013;Abstract 525.

Select Adverse Events (AEs) in ≥20% of Patients

All grades	Ibrutinib + BR (n = 30)
Diarrhea*	70%
Nausea	67%
Fatigue*	47%
Neutropenia†	40%
Upper respiratory tract infection*	37%
Peripheral edema	33%
Constipation	30%
Headache	30%
Vomiting*	30%
Arthralgia	27%
Sinusitis*	27%

* Included Grade 3 AEs; † Only Grade 3 and 4 AEs observed

- AEs include: insomnia (23%), squamous cell cancer (20%), contusion (20%)

Brown JR et al. *Proc ASH* 2013;Abstract 525.

Treatment-Emergent AEs Occurring in ≥2 Patients

Grade ≥3	Ibrutinib + BR (n = 30)
Neutropenia	40%
Rash	10%
Fatigue	10%
Thrombocytopenia	7%
Cellulitis	7%
Febrile neutropenia	7%

Brown JR et al. *Proc ASH* 2013;Abstract 525.

Second-Line Ibrutinib + FCR Results

- There is limited experience with second-line ibrutinib/FCR.
- This arm was closed due to a limited number of patients with fludarabine-naïve disease in the relapsed setting.
- Safety profile of patients who received treatment (n = 3):
  - Serious gastritis (n = 1)
- All 3 patients received all 6 cycles of FCR:
  - Dose reduction (n = 1)
- Efficacy results:
  - ORR: 100%
  - Confirmed minimal residual disease (MRD)-negative CR: 67%
  - Confirmed MRD-positive CR: 33%
- All 3 patients remain progression free on ibrutinib after 22 months of follow-up.

Brown JR et al. *Proc ASH* 2013;Abstract 525.

Author Conclusions

- The combination of ibrutinib with BR had an acceptable safety profile.
  - No prolonged myelosuppression during cycle 1 was observed (data not shown).
  - Response to ibrutinib + BR was associated with improved hemoglobin and platelet counts.
  - Continuous treatment with ibrutinib after BR therapy was well tolerated.
- In this study, treatment with ibrutinib + BR resulted in:
  - ORR: 93.4%
  - Median PFS: Not yet reached
- A previous Phase II study of BR alone demonstrated an ORR of 59% and median PFS of 15.2 mo (*JCO* 2011;29:3559).
- An ongoing Phase III trial is evaluating the combination of ibrutinib with BR in R/R CLL or SLL (NCT01611090).

Brown JR et al. *Proc ASH* 2013;Abstract 525.

Investigator Commentary: PCYC 1108 — Phase Ib Trial of Ibrutinib in Combination with FCR or BR in R/R CLL or SLL

This study evaluates the combination of ibrutinib with BR or FCR for patients with R/R CLL or SLL. The big questions are, does combining ibrutinib with chemotherapy exert synergistic effects, and is the combination worthwhile in terms of safety? In this study, patients received a lower dose of bendamustine (70 mg/m^2), because it was in the relapsed setting, in combination with the standard dose of rituximab.

From the results, it's difficult to tell if the combination is measurably better than ibrutinib alone. Ibrutinib is setting a high bar. In this cohort of 30 patients, the ORR was 93%, which is an outstanding result. Compared to studies of ibrutinib alone, the results are similar. The difference is that patients don't experience lymphocytosis.

A certain proportion of patients who receive ibrutinib cannot be called "responders" by traditional criteria because their white blood cell count has increased.

However, by all other measures they've clinically improved, with smaller lymph nodes, smaller spleen size and improved cytopenias. These patients are often classified as having achieved PR with lymphocytosis. When these factors are considered, the response rate with single-agent ibrutinib becomes 80% to 90%, which is similar to what was observed with ibrutinib/BR on this study. This raises the question whether the addition of BR to ibrutinib is beneficial.

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

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib and Rituximab for Previously Treated Patients with Chronic Lymphocytic Leukemia (CLL)[1]

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia[2]

[1] **Furman RR et al.**

Proc ASH 2013;Abstract LBA-6.

[2] **Furman RR et al.**

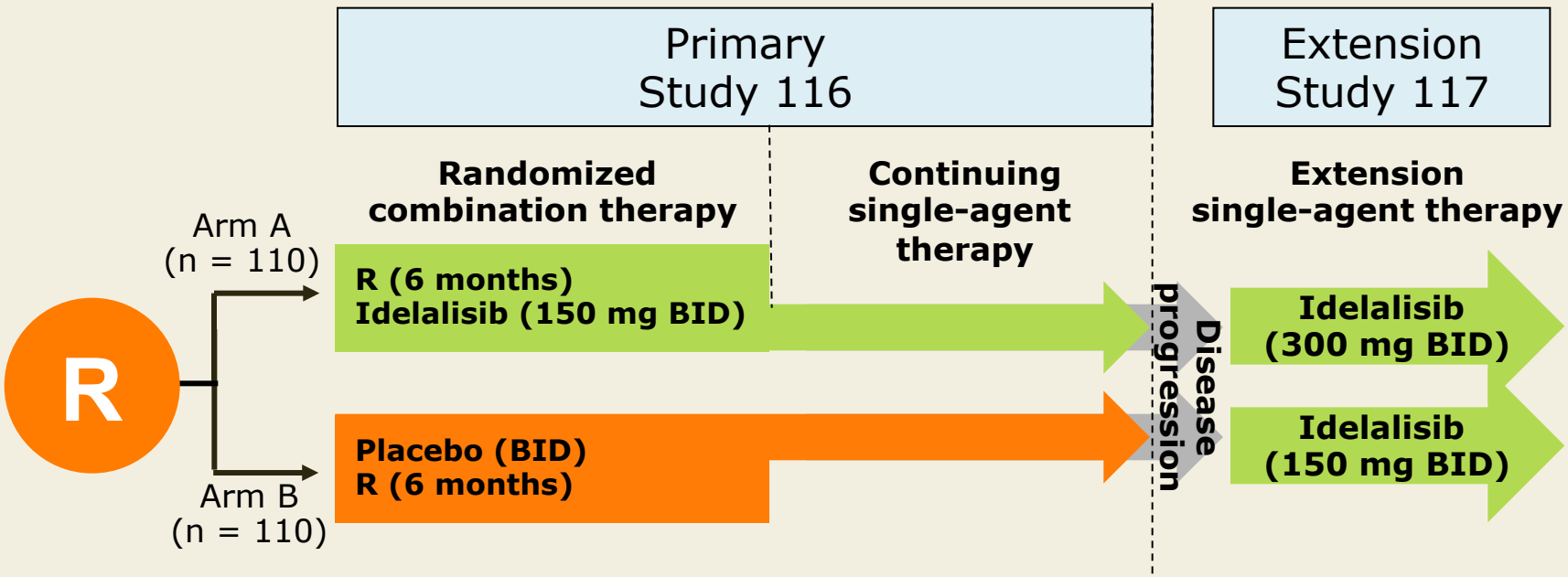
N Engl J Med 2014;[Epub ahead of print].

Background

- Elderly patients with relapsed chronic lymphocytic leukemia (CLL) who have clinically significant coexisting medical conditions are less able to undergo standard chemotherapy (*Leuk Lymphoma* 2009;50:171).
- Effective therapies with acceptable side-effect profiles are needed for this patient population.
- Idelalisib (GS-1101, CAL-101) is a potent, oral, selective small-molecule inhibitor of PI3K-delta(δ) (*Blood* 2011;117:591).
  - It has demonstrated significant clinical activity with an acceptable toxicity profile as a single agent (*Proc ASCO* 2013;Abstract 7003) and in combination with other agents, including rituximab (R) (*Proc ASCO* 2013;Abstract 7017), for patients with relapsed/refractory CLL.
- **Study objective:** To evaluate combination therapy with idelalisib and R for patients with relapsed CLL.

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

Study 116: Phase III Trial Design



R administration

- 375 mg/m^2, then 500 mg/m^2 q2wk x 4, then 500 mg/m^2 q4wk x 3

Clinical endpoints

- Primary: Independent review committee-assessed progression-free survival (PFS)
- Events: Disease progression or death
- Secondary: Overall response rate (ORR), lymph node response (LNR), overall survival (OS)

Planned interim analyses at 50% and 75% of events

Furman RR et al. *N Engl J Med* 2014;[Epub ahead of print]; *Proc ASH* 2013;Abstract LBA-6.

Key Eligibility Criteria

Criteria	Requirements
Relapsed CLL	• CLL progression <24 months since last therapy • Treatment warranted according to International Workshop on Chronic Lymphocytic Leukemia criteria
Lymphadenopathy	• Presence of ≥1 measurable nodal lesion
Prior therapies	• ≥1 anti-CD20 antibody-containing therapy or ≥2 prior cytotoxic therapies
Appropriate for noncytotoxic therapy	• Cumulative Illnes Rating Scale (CIRS) score >6 or creatinine clearance <60 mL/min (≥30 mL/min) or Grade 3/4 neutropenia or thrombocytopenia due to prior myelotoxicity
Bone marrow function	• Any grade anemia, neutropenia or thrombocytopenia allowed
Karnofsky score	• ≥40

Furman RR et al. *N Engl J Med* 2014;[Epub ahead of print]; *Proc ASH* 2013;Abstract LBA-6.

Survival

	Idelalisib + R (n = 110)	Placebo + R (n = 110)	Hazard ratio (HR)	*p*-value
Median PFS	Not reached	5.5 mo	0.15	<0.001
24-week PFS	93%	46%	—	—
Median OS	Not reached	Not reached	0.28	0.02
12-month OS	92%	80%	—	—

- Disease progression occurred in 12 patients in the idelalisib group and 53 patients in the placebo group.

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

PFS Analysis in Prespecified Subgroups

Subgroup	Idelalisib + R (n)	Placebo + R (n)	HR
All	110	110	0.15
IGHV mutated	19	17	0.25
IGHV unmutated	91	93	0.13
Del(17p) or TP53 mut	46	50	0.12
No del(17p) or TP53 mut	64	60	0.17
Del(17p)	26	31	0.14
No del(17p)	84	79	0.14
Male	76	68	0.10
Female	34	42	0.30
Age <65 years	21	27	0.24
Age ≥65 years	89	83	0.11

- HRs <1.00 indicate better results in the idelalisib group

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

Response

	Idelalisib + R	Placebo + R	Odds ratio (OR)	*p*-value
ORR* (n = 88, 88)	81%	13%	29.92	<0.001
≥50% reduction in lymphadenopathy (n = 85, 84)	93%	4%	264	<0.001

* All responses were partial responses

Furman RR et al. *N Engl J Med* 2014;[Epub ahead of print]; *Proc ASH* 2013;Abstract LBA-6.

Adverse Events (AEs) in ≥10% of Patients in Either Study Arm

	Idelalisib + R (n = 110)		Placebo + R (n = 107)	
AE, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any AE	100 (91)	62 (56)	101 (94)	51 (48)
Pyrexia	32 (29)	3 (3)	17 (16)	1 (1)
Fatigue	26 (24)	3 (3)	29 (27)	2 (2)
Nausea	26 (24)	0	23 (21)	0
Chills	24 (22)	2 (2)	17 (16)	0
Diarrhea	21 (19)	4 (4)	15 (14)	0
Infusion-related reaction	17 (15)	0	30 (28)	4 (4)
Cough	16 (15)	0	27 (25)	2 (2)
Decreased appetite	13 (12)	0	9 (8)	1 (1)
Constipation	13 (12)	0	12 (11)	0
Vomiting	13 (12)	0	8 (7)	0
Dyspnea	12 (11)	2 (2)	20 (19)	3 (3)
Rash	11 (10)	2 (2)	6 (6)	0
Night sweats	11 (10)	0	8 (7)	0

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

Serious AEs (SAEs)

SAE, n (%)	Idelalisib + R (n = 110)	Placebo + R (n = 107)
Any SAE	44 (40)	37 (35)
Pneumonia	7 (6)	9 (8)
Pyrexia	7 (6)	3 (3)
Febrile neutropenia	5 (5)	6 (6)
Sepsis	4 (4)	3 (3)
Pneumonitis	4 (4)	1 (1)
Diarrhea	3 (3)	1 (1)
Neutropenia	3 (3)	1 (1)
Pneum. jirov. pneumonia	3 (3)	1 (1)
Neutropenic sepsis	3 (3)	0
Dyspnea	1 (1)	4 (4)
Cellullitis	1 (1)	3 (3)

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

Author Conclusions

- The addition of idelalisib to R in a population of frail patients with difficult-to-treat, relapsed CLL, including those with adverse genetic features such as 17p deletion, TP53 mutations or unmutated IGHV, was superior to R monotherapy:
  - Improved PFS (HR = 0.15, $p < 0.001$)
  - Improved ORR (OR = 29.92; $p < 0.001$)
  - Improved lymphadenopathy (OR = 264; $p < 0.001$)
  - Improved OS (HR = 0.28, $p = 0.02$)
- Although the follow-up period was short, combination therapy with idelalisib had an acceptable safety profile.
- Further follow-up is needed to assess whether idelalisib is safe for long-term use.
- The combination of idelalisib and R may be a treatment option for frail patients with relapsed CLL.

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

Investigator Commentary: Idelalisib/R in Relapsed CLL

The selective PI3 kinase inhibitor idelalisib is another promising agent for CLL. Patients with relapsed/refractory CLL who were not considered suitable for chemotherapy were eligible for this study, so this was an older and certainly less fit group of patients. The median age was 71. Two hundred, twenty patients were randomly assigned to receive R with either idelalisib or placebo until disease progression. The difference in outcomes was enormous. The ORR was 81% with idelalisib/R versus 13% with R/placebo. Median PFS was not reached with idelalisib/R but was 5.5 months with R/placebo, and an OS difference was evident between the 2 arms — 92% versus 80% at 1 year.

This raises the question of whether these data will lead to FDA approval for idelalisib. Single-agent R is notoriously ineffective for this patient population, so they "beat up the weak kid on the block" to get this result. I honestly don't know how impressed the FDA will be by these data given the choice of comparator agent. However, these were infirm patients so the case could be made that they were not candidates for any other therapies. On the other hand, with the recent approval of ibrutinib presumably all the patients that went on this trial would be candidates for ibrutinib. So in the rapidly changing landscape of CLL, perhaps the bar for idelalisib to gain approval will be set higher. It's an interesting regulatory issue.

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

Bcl-2 Inhibitor ABT-199 (GDC-0199) Monotherapy Shows Anti-Tumor Activity Including Complete Remissions in High-Risk Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

Seymour JF et al.

Proc ASH 2013;Abstract 872.

Background

- The intrinsic apoptotic pathway is often dysregulated in relapsed CLL/SLL due to a deficiency in proapoptotic proteins and the overexpression of antiapoptotic proteins such as Bcl-2.
- ABT-199 is a selective, potent, orally bioavailable, small molecule Bcl-2 inhibitor that can trigger apoptosis in vitro, even in CLL cells harboring the del(17p) chromosomal abnormality.
- Rapid tumor lytic activity in a small number of patients with refractory CLL has been demonstrated with ABT-199 (*Nat Med* 2013;19:202).
- **Study objective:** To evaluate the safety, pharmacokinetics, maximum tolerated dose and preliminary efficacy of ABT-199 in relapsed/refractory CLL or SLL.

Seymour JF et al. *Proc ASH* 2013;Abstract 872.

Ongoing Phase I Study Design (NCT01328626)

Target accrual (n = 211*)

Relapsed/refractory CLL or SLL
No prior autologous or allogeneic stem cell transplant

→

Dose escalation

ABT-199
Single dose, wk1 d-3 or d-7
Continuous once-daily dosing starting wk1 d1 until PD†

* As of July 4, 2013, 56 patients were enrolled in cohorts at 150-mg to 1,200-mg doses
† Modifications were made to the dose-escalation scheme, tumor lysis syndrome (TLS) prophylaxis and monitoring schedule after TLS was observed in some patients

Primary endpoints: Safety, pharmacokinetics, maximum tolerated dose, recommended Phase II dose

Secondary endpoints include: Preliminary efficacy, biomarkers of response

Seymour JF et al. *Proc ASH* 2013;Abstract 872; www.clinicaltrials.gov, February 2014.

Baseline Characteristics

Response	All pts (n = 56)	del(17p)* (n = 17)	F-refractory* (n = 18)
Median age	67 years	69 years	66 years
Bulky disease ≥5 cm ≥10 cm	 50% 14%	 35% 0%	 56% 22%
Median lymphocyte count	4.9 x 10^9/L	5.9 x 10^9/L	4.5 x 10^9/L
Median no. of prior therapies (range)	4 (1-10)	4 (2-9)	5 (1-10)
Median time on study	10.0 mo	9.7 mo	10.4 mo

F = fludarabine

* 6 patients had both del(17p) and F-refractory disease

- 12 of 27 patients (44%) had beta-2 microglobulin levels >3 mg/L
- 20 of 24 patients (83%) had IGVH-unmutated status

Seymour JF et al. *Proc ASH* 2013;Abstract 872 (abstract only).

Response Rates

Response	All pts (n = 56)	del(17p) (n = 17)	F-refractory (n = 18)
Overall response rate	84%	82%	78%
Complete remission/ complete remission with incomplete blood count recovery (CR/CRi)	21%	12%	17%
Partial remission*	63%	71%	61%
Stable disease	7%	6%	6%
Progressive disease	2%	6%	—

* 3 patients had confirmatory CT imaging assessments at less than an 8-week interval (5, 6 and 7 weeks)

Seymour JF et al. *Proc ASH* 2013;Abstract 872 (abstract only).

Minimal Residual Disease (MRD) Assessment

- In patients achieving CR/CRi, MRD was quantified with 4-color flow cytometry (aiming to analyze >200,000 nucleated cells).
- Patients with evaluable results (n = 8):
  - No detectable MRD: n = 4 (2 with suboptimal cells analyzed)
  - Low-level MRD: n = 4
- Of the patients who had no detectable MRD, 1 had del(17p) and F-refractory disease and 2 had F-refractory disease.

Seymour JF et al. *Proc ASH* 2013;Abstract 872 (abstract only).

Adverse Events (AEs)

Grade 3/4 AE (≥4 pts)	n = 56
Neutropenia	41%
TLS	11%
Thrombocytopenia	10%
Hyperglycemia	10%
Anemia	7%
Febrile neutropenia	7%

- Most common AEs of all grades (≥25% of patients): Diarrhea (46%), neutropenia (43%), fatigue (34%), upper respiratory tract infection (29%) and cough (25%)
- 7 dose-limiting toxicities: 5 cases of TLS (1 G3 laboratory based at 50 mg; 1 G4 clinical AE at 50 mg; 1 G3 laboratory based at 100 mg and 2 at 200 mg), 1 G4 neutropenia (600 mg) and sudden death (1,200 mg) in the setting of G4 (clinical) TLS.

Seymour JF et al. *Proc ASH* 2013;Abstract 872 (abstract only).

Author Conclusions

- ABT-199 showed activity in patients with relapsed/ refractory CLL with a response rate of 84% for the study population, including a 21% rate of CR/CRi.
- Similar efficacy was seen in patients with high-risk CLL, with a response rate of 82% in patients with del(17p) and 78% in those with F-refractory disease.
- 3 of 4 patients who had no detectable MRD and achieved a CR/CRi were patients with high-risk disease.
- This study is continuing enrollment using a revised dosing schedule designed to reduce the identified risk of TLS.
- A Phase II monotherapy study in patients with relapsed/ refractory CLL with del(17p) has commenced (NCT01889186), and combination studies are ongoing with either rituximab (NCT02005471) or obinutuzumab (NCT01685892) in patients with relapsed/refractory CLL.

Seymour JF et al. *Proc ASH* 2013;Abstract 872 (abstract only).

Investigator Commentary: ABT-199 Demonstrates Antitumor Activity in High-Risk, Relapsed/Refractory CLL and SLL

Bcl-2 causes dysregulation of apoptosisis and is overexpressed in a variety of lymphoid cancers. The Bcl-2 inhibitor ABT-199 has overcome the problem of thrombocytopenia encountered with prior inhibitors in the same class. It is orally bioavailable and well absorbed.

Patients in this ongoing Phase I study received a range of doses of ABT-199 from 150 mg to 1,200 mg per day. Problems with TLS occurred, and 1 patient receiving the 1,200-mg dose died. The study had to be put on hold and redesigned with a lower dosing scheme and close monitoring.

Patients must start with a low dose of ABT-199 and undergo a carefully monitored dose escalation. It can take 4 to 6 weeks to reach the target dose, which is 400 mg per day for CLL. TLS can be an issue with this agent but is manageable. Overall the drug is well tolerated.

The efficacy of ABT-199 in CLL is amazing. It is as good as ibrutinib, which is the best drug in CLL. The overall response rate is 84% and is similar for patients with del(17p) or those with fludarabine-refractory disease. I'm very optimistic about the future of ABT-199 in CLL.

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