5 Minute JournalClub

POST-ASH Issue 3, 2015

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CME Information

LEARNING OBJECTIVES

- Develop an understanding of emerging efficacy and side-effect data with novel agents and combination regimens — including next-generation anti-CD20 antibodies and PI3 kinase, BTK and Bcl-2 inhibitors — under evaluation for previously untreated and relapsed/refractory CLL and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Appreciate the recent FDA approvals of novel targeted agents indicated for the treatment of newly diagnosed and relapsed/refractory CLL, and discern how these treatments can be appropriately integrated into clinical practice.
- Compare and contrast the benefits and risks of chemoimmunotherapy with fludarabine/cyclophosphamide/rituximab versus bendamustine/rituximab as first-line therapy for fit patients with CLL.

CME Information (Continued)

LEARNING OBJECTIVES

- Apply recent clinical research findings with the newly FDA-approved combination of obinutuzumab and chlorambucil to the care of patients with previously untreated CLL.
- Recall the activity of salvage therapy with obinutuzumab and chlorambucil after treatment failure of chlorambucil alone in patients with CLL and comorbidities.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2015/3/CME.

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

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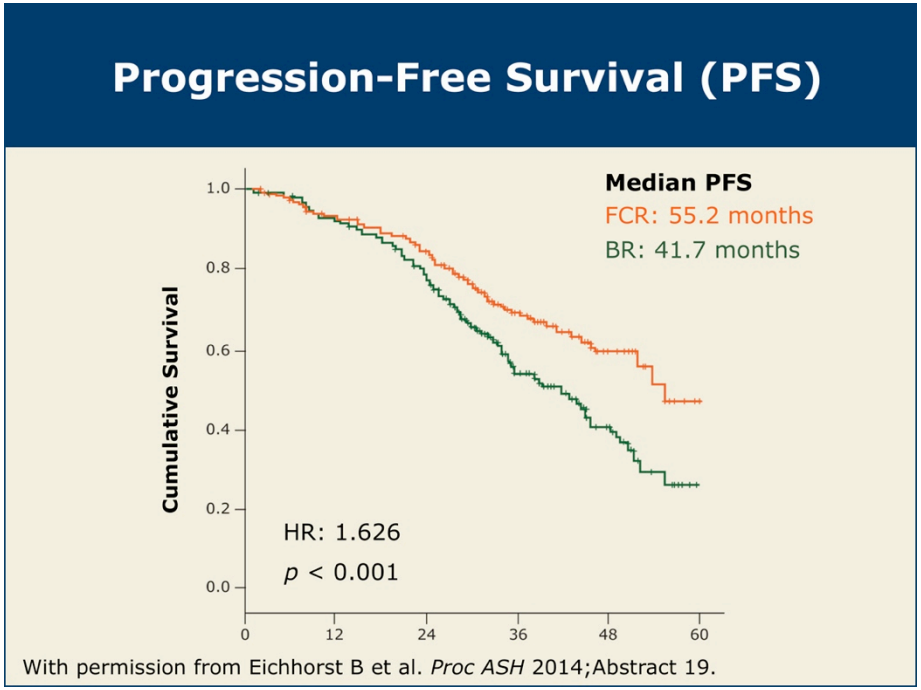
When the German CLL Study Group — one of the most prolific clinical trial organizations in the world — launched the landmark Phase III CLL10 trial in 2008, few, if any, expected that the central question the study sought to answer would in essence be outdated by the time the results became available. CLL10 focused on a classic oncology research issue — the comparative clinical benefits of 2 chemobiologic regimens (fludarabine/ cyclophosphamide/ rituximab [FCR] and bendamustine/rituximab [BR]), and although the results as summarized below have important practical clinical implications today, it is increasingly evident that the overall treatment strategy in this disease is undergoing a massive reconfiguration. For that reason, this issue of *5-Minute Journal Club* evaluates not only the seminal CLL10 trial findings but also a sample of 2014 ASH data sets on several new agents, regimens and strategies that have burst onto the scene in the past couple of years and have many investigators thinking that chronic lymphocytic leukemia (CLL) may soon fall into the basic clinical paradigm of chronic myelogenous leukemia (CML) — namely a chronic disease requiring long-term outpatient management that may be associated with prolonged survival.

Here's a summary of what happened in San Francisco related to CLL.

CLL10: FCR versus BR (patients without del[17p])



The updated data from CLL10 continue to support what clinical experience had already strongly suggested, namely that FCR yields clear-cut improvements in disease-related outcomes, including a statistically and clinically significant increase in median progression-free survival (PFS) (55.2 versus 41.7 months) and rates of bone marrow minimal residual disease (MRD) negativity at final restaging (26.6% versus 11.1%). However, with less than 3 years of follow-up, no overall survival benefit has been seen. Just as predictably, the data reveal that FCR produced considerably more toxicity, particularly in older individuals (>65 years) in whom the rate of infection was 47.7% compared to 20.6% with BR. The bottom line is that most investigators believe that both regimens have a role and the risk for toxicity must be carefully considered during patient selection.

Impact of MRD status

The intriguing concept of defining undetectable levels of disease after treatment to better understand potential prognosis has been explored in various forms across many hematologic cancers. In this regard, at ASH we saw a **report from**

the German group evaluating pooled data from the CLL8 (FC versus FCR) and CLL10 trials examining the value of peripheral blood MRD-negative status at response evaluation. What was seen was a strong correlation between MRD status and outcome that seemed at least as predictive of PFS as clinical response, and of particular interest, patients considered to have a partial response clinically had a much better prognosis if their bone marrow was MRD-negative (61.7 versus 28.1 months). Discussions are now ongoing about how to integrate MRD status into prospective trial design and potentially clinical decision-making.

Obinutuzumab (Ob)

Since the FDA approval of Ob in combination with chlorambucil — a drug that many had not been regularly using for CLL — there has been constant questioning about whether this novel Type II anti-CD20 antibody could be employed with other chemotherapeutic regimens. Not surprisingly, a number of studies are ongoing that examine this issue, including the Phase III GREEN trial, which is targeting 800 patients with both previously treated and untreated CLL and evaluates Ob alone or with one of several types of chemotherapy. This effort is also interesting in that it examines a modified dosing scheme of 25 mg on day 1 and 975 mg on day 2 in an attempt to address the high rates of infusion-related reactions that have previously been reported with Ob. At ASH we saw **early safety data** from the previously untreated cohort in the study, which showed a 13.3% rate of Grade 3 or higher infusion-related reactions with 2.5% of patients discontinuing treatment due to this side effect. As greater experience is gained with this interesting agent, it has become clear that these infusion

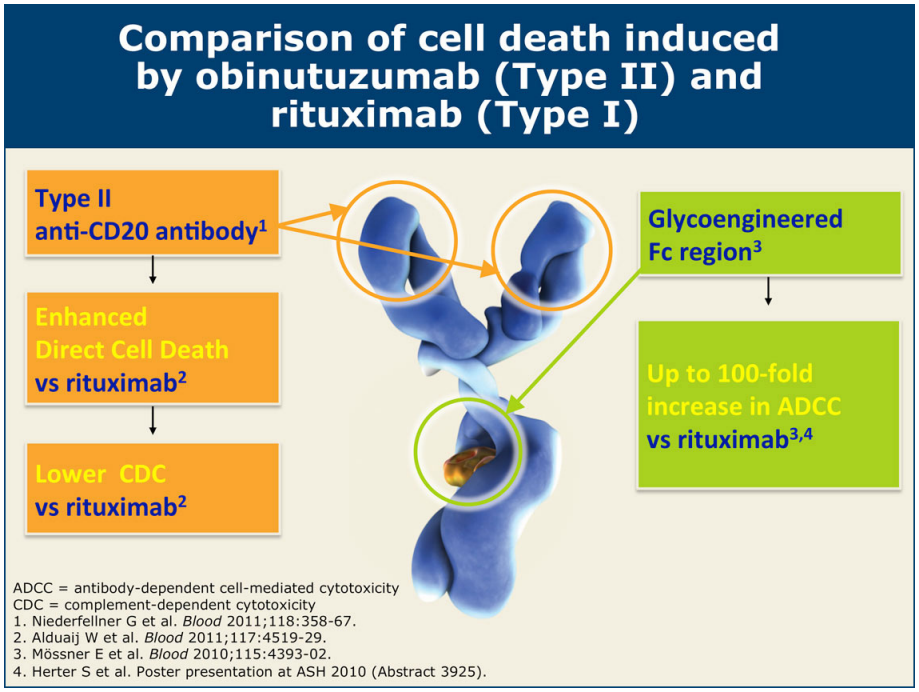
reactions occur mainly during the first cycle and may be related to cell death and/or cytokine release.

Efficacy findings from this study are not yet available, and until then, clinicians will need to consider whether they want to dust off chlorambucil and give it a go with Ob. Interestingly, during a recent interview for our audio series with investigator Dr Jeffrey Sharman, I was surprised to learn that he avoids this issue altogether and unabashedly uses Ob alone as up-front therapy in select patients.

Clearly, the German CLL group was busy at ASH as they also treated us to **more from the pivotal CLL11 trial**, which was first presented at ASCO 2013 and paved the way for the approval of Ob. From that and related presentations, we learned, among other things, that Ob/chlorambucil is superior to rituximab/chlorambucil in a number of ways, including rates of MRD negativity in blood (38% versus 3%). Additional data unveiled at ASH evaluated patients in the trial who were initially randomly assigned to chlorambucil alone but upon relapse (generally due to lack of response to chlorambucil) were crossed over to Ob/chlorambucil. Of great interest, 26 of 30 patients (87%) experienced objective responses, further suggesting that Ob itself might have significant and perhaps underappreciated intrinsic anti-CLL activity that is greater than that previously observed with rituximab monotherapy, an important and useful therapeutic tool in follicular lymphoma.

Anti-CD20 maintenance in CLL

Although maintenance rituximab has been commonly used in many patients receiving R-chemotherapy for follicular and mantle-cell lymphoma, our survey and polling data have clearly illustrated that hematologic investigators do not endorse this approach in CLL. However, provocative results from **2 interesting trials** unveiled at ASH have some beginning to reevaluate this stance.



First, the AGMT-CLL8/a trial randomly assigned 263 patients who completed first- or second-line chemotherapy/rituximab to 24 months of rituximab maintenance or observation and demonstrated an approximately 50% reduction in the rate of disease progression with maintenance. No survival benefit was seen, although crossover in the control group was allowed. The other related and cleverly named Phase III effort (the PROLONG trial) evaluated ofatumumab maintenance after second- or third-line treatment with chemotherapy/anti-CD20, and again there was an approximate 50% reduction in risk of disease progression. Although more data on this important question would be ideal, some investigators feel that these results are enough to compel clinicians to discuss and/or recommend this approach in select patients, at least until the many new options and treatments are sorted out.

Ibrutinib

You can't attend a conference these days without witnessing a new and relevant data set with this blockbuster Bruton tyrosine kinase inhibitor, and ASH was no exception, as we saw results from the Phase II RESONATE™-17 trial focused on 144 patients with del(17p) CLL who experienced disease progression while receiving between 1 and 4 prior lines of therapy. Perhaps not surprisingly, as few of these studies fail to disappoint, most patients had objective responses, and about 80% were progression free at 1 year. These relevant findings are central to the current first-line approval of the drug in this situation. However, it is important to note that although ibrutinib results in similar response rates in this population, these patients have shorter PFS and overall survival.

Interestingly, there is a belief that del(17p) may only be part of the story, and for that reason investigators at MD Anderson evaluated CKT (complex metaphase karyotype by whole genome sequencing defined as 3 or more distinct chromosomal abnormalities) in 100 consecutive cases of CLL treated with ibrutinib. What they found is that CKT is a better predictor of benefit from ibrutinib than del(17p). However, this clearly needs additional confirmation before whole genome sequencing makes its way into trials or clinical practice.

Idelalisib

One of the important features of ibrutinib in CLL is the consistency of response in patients with adverse prognostic factors like 17p deletion, but the drug is not alone in this regard. At ASH we saw a **subset analysis** from the major Phase III trial reported in the *New England Journal* demonstrating that idelalisib/rituximab

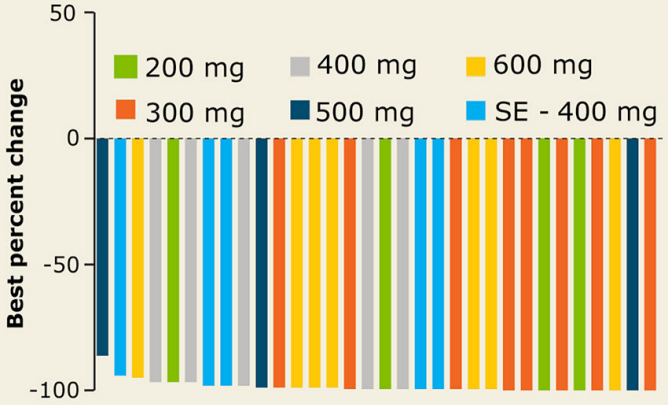
is a highly effective regimen, including in patients with del(17p), del(11q) and unmutated IGHV. These findings suggest that this regimen may have an important early role in patients with these genetic abnormalities who have previously received or are not candidates for ibrutinib.

Venetoclax (formerly ABT-199)

Despite the new moniker, more data presented at ASH reveal that things remain entirely the same and that this novel Bcl-2 inhibitor/antiapoptotic agent is a very active drug. Most notably, in a **Phase II trial** of 49 patients with relapsed or refractory CLL/small lymphocytic lymphoma, the combination of venetoclax with rituximab demonstrated an impressive 88% objective response rate with 31% complete response (CR) or CR with incomplete blood count recovery, including in 7 of 9 patients with del(17p). MRD negativity in the bone marrow was recorded in 17 patients. Significantly, 5 dose cohorts were studied, and it appears that a schedule was uncovered that seems to avoid tumor lysis syndrome — a complication reported previously with this agent.

Although it remains to be seen how these novel and encouraging therapies will be optimally mixed, matched and sequenced in CLL, it

Phase II Study of Venetoclax/Rituximab: Best Percent Change from Baseline in Lymphocyte Count



- 30/32 (94%) patients with baseline lymphocyte counts >5 x 10^9 had a reduction to <4 x 10^9 within 5 weeks of starting venetoclax

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

seems highly likely that the survival of patients will continue to be extended and perhaps soon mirror the normal life expectancies of patients under active treatment for CML. ASH 2014 will be remembered as another important step forward in this rewarding march toward a new standard.

Next on this series, we provide an ASH update on myeloproliferative neoplasms, including more data on the most recently approved treatment in these diseases, the use of ruxolitinib in polycythemia vera.

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Frontline Chemoimmunotherapy with Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) Shows Superior Efficacy in Comparison to Bendamustine (B) and Rituximab (BR) in Previously Untreated and Physically Fit Patients (pts) with Advanced Chronic Lymphocytic Leukemia (CLL): Final Analysis of an International, Randomized Study of the German CLL Study Group (GCLLSG) (CLL10-Study)

Eichhorst B et al.

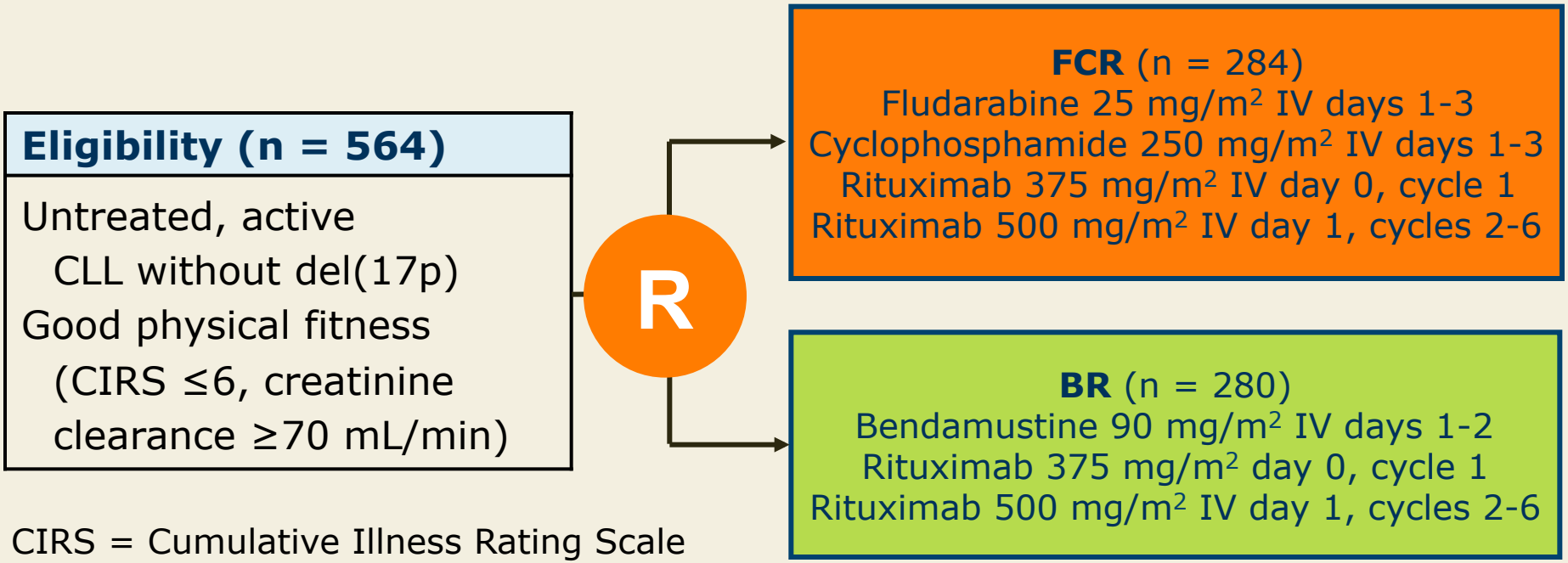
Proc ASH 2014;Abstract 19.

Background

- Fludarabine/cyclophosphamide/rituximab (FCR) is the standard front-line treatment regimen for physically fit patients with advanced chronic lymphocytic leukemia (CLL) with low comorbidity burden.
  - The addition of rituximab to fludarabine/ cyclophosphamide (FC) in the CLL8 trial led to prolongation of progression-free (PFS) and overall survival (OS) as first-line treatment for physically fit patients with CLL (*Leuk Lymphoma* 2013;54:1821).
  - However, the FCR regimen was associated with a high rate of severe infections and higher rates of secondary neoplasias compared to FC.
- **Study objective:** To evaluate the efficacy and tolerability of FCR in comparison to bendamustine/rituximab (BR) as front-line therapy for fit patients with CLL without del(17p).

Eichhorst B et al. *Proc ASH* 2014;Abstract 19.

CLL10: Final Analysis of a Phase III Trial of FCR versus BR in Advanced CLL



CIRS = Cumulative Illness Rating Scale

Primary endpoint: Noninferiority of BR vs FCR for PFS (hazard ratio BR/FCR < 1.388)

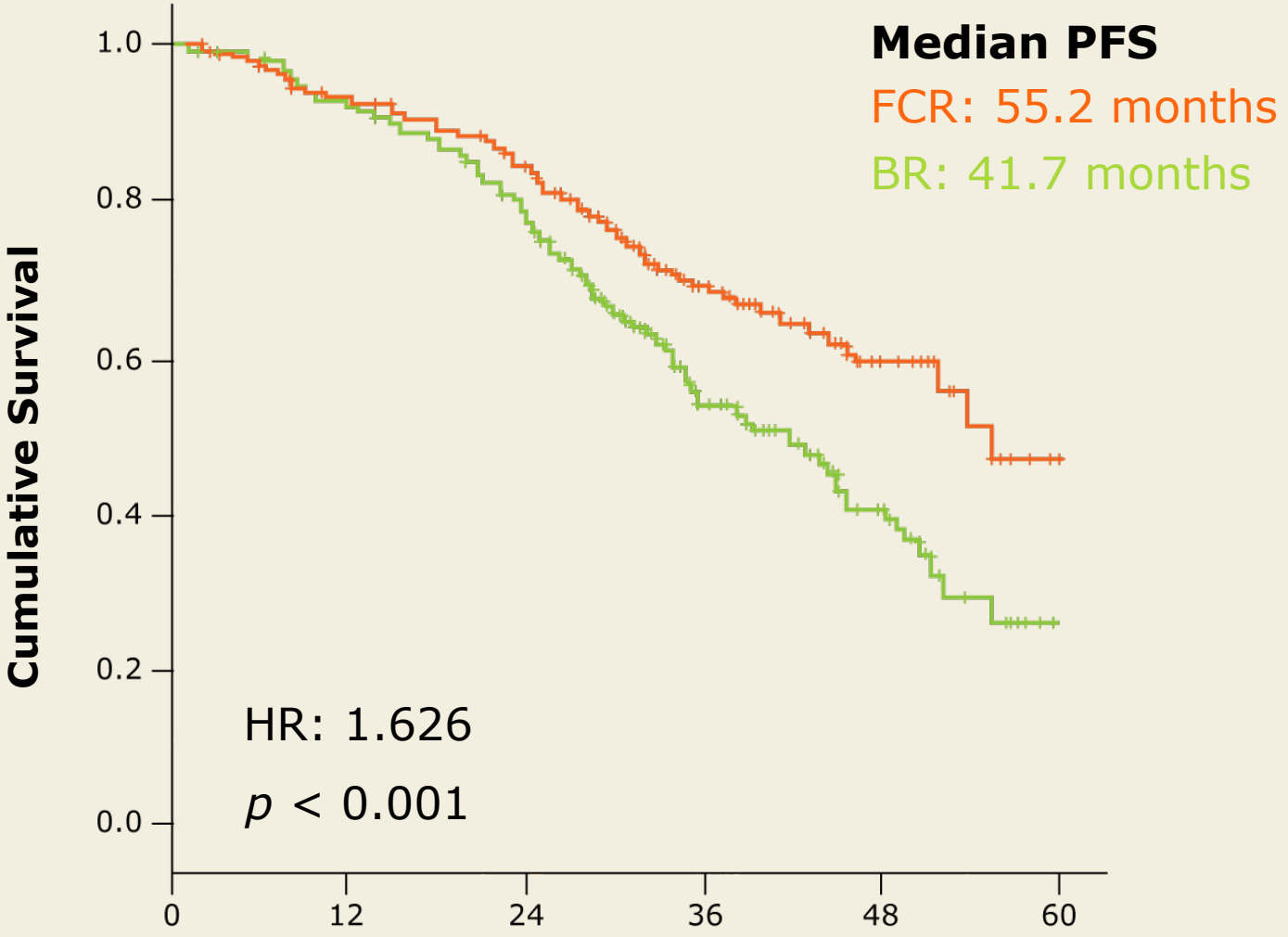
Eichhorst B et al. *Proc ASH* 2014;Abstract 19.

Patient Characteristics

Characteristics	FCR (n = 282)	BR (n = 279)
Median age	61.0 years	62.1 years
Age > 65	30.5%	38.7%
Male	71.3%	74.2%
Median time since diagnosis	21.6 months	24.6 months
ECOG PS = 0	64.1%	64.1%
CIRS	2	2
Mean number of cycles	5.27	5.41

Eichhorst B et al. *Proc ASH* 2014;Abstract 19.

Progression-Free Survival (PFS)



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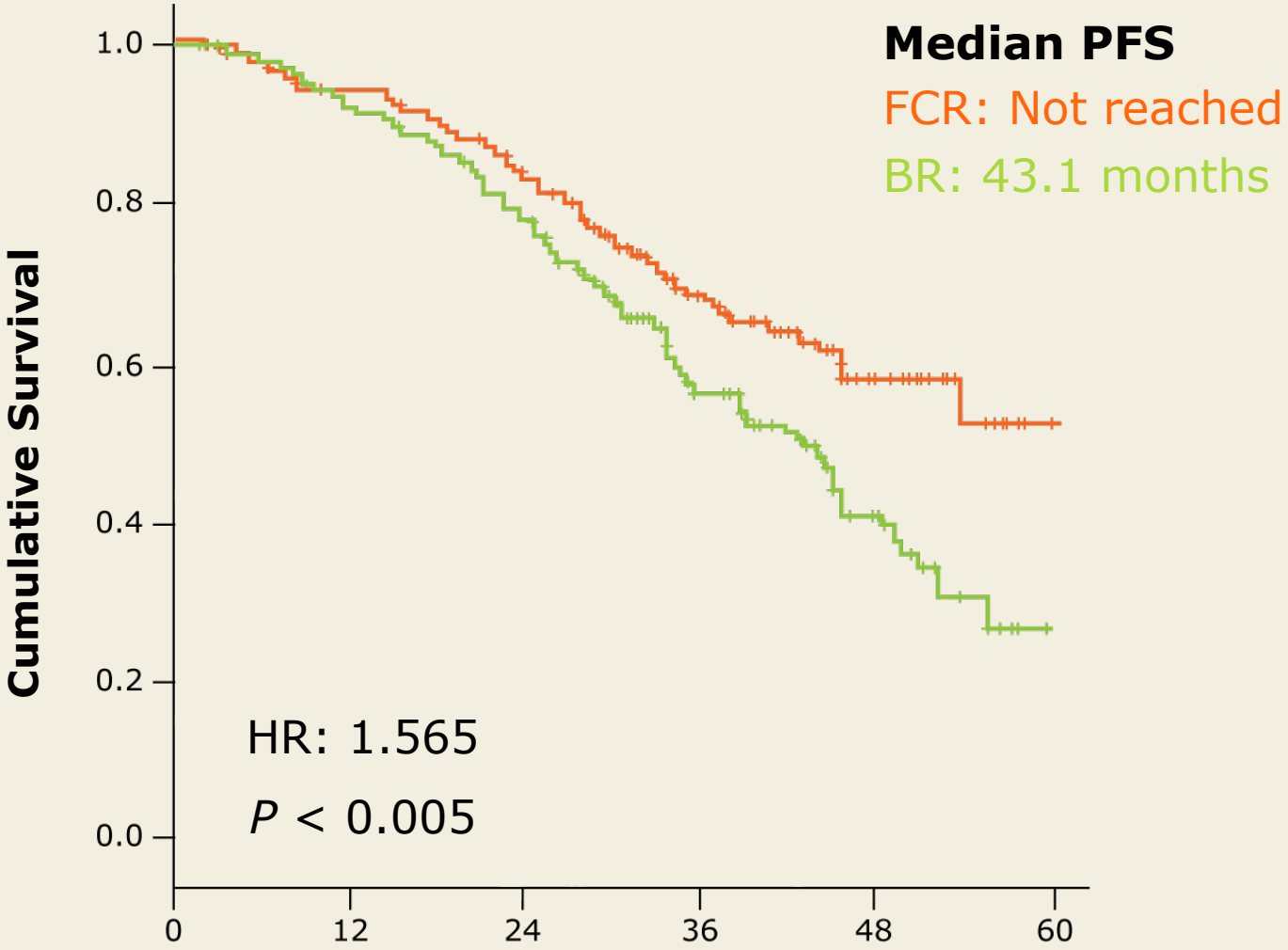
PFS in IGHV Matched Population



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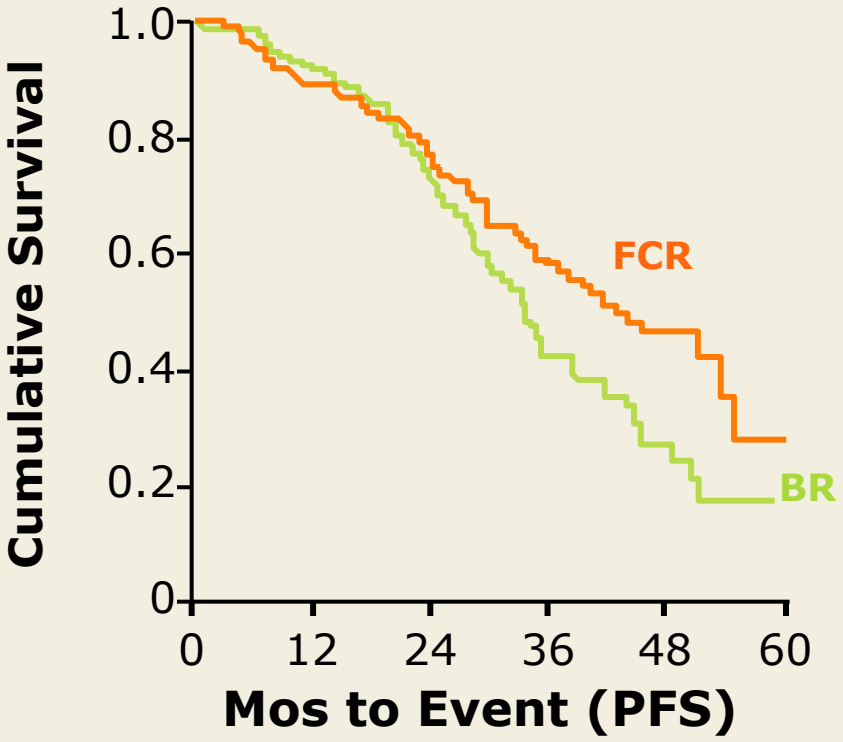
PFS by IGHV Status

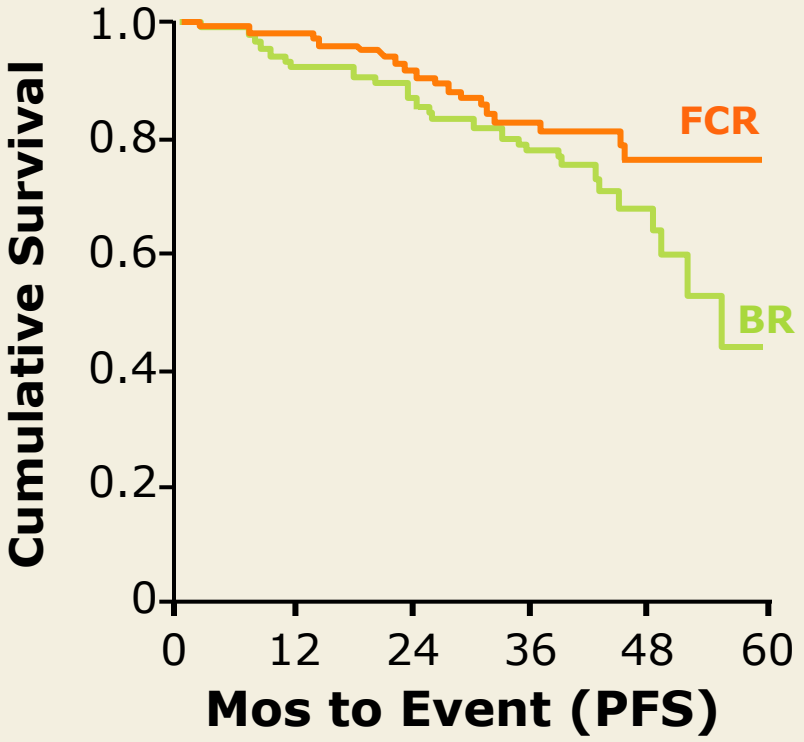
Unmutated *IGHV*: $p = 0.017$

FCR: 42.7 mo; BR: 33.6 mo



Mutated *IGHV*: $p = 0.153$

FCR: NR; BR: 52 mo



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Response

	FCR (n = 282)	BR (n = 279)	*p*-value
Overall response rate	95.4%	95.7%	1.0
Complete response (CR + CRi)	39.7%	30.8%	0.034
Complete response (CR)	35.1%	30.4%	NR
CR with incomplete marrow recovery (CRi)	4.6%	0.4%	NR
Partial response (PR)	55.7%	64.9%	NR
Stable disease/progressive disease	2.2%	2.2%	NR

NR = not reported

Eichhorst B et al. *Proc ASH* 2014;Abstract 19.

Minimal Residual Disease (MRD)

MRD negativity (intent to treat)	FCR (n = 282)	BR (n = 279)
BM at FR	26.6%	11.1%
PB at FR	48.6%	38.4%
PB 12 months after FR	19.7%	9.0%
PB 18 months after FR	18.0%	8.5%
MRD negativity (evaluable patients)	**FCR**	**BR**
PB at FR (n = 185, 170)	74.1%	62.9%
PB 18 months after FR (n = 65, 65)	53.8%	24.6%

BM = bone marrow; FR = final restaging; PB = peripheral blood

Eichhorst B et al. *Proc ASH* 2014;Abstract 19.

Select Adverse Events

Adverse event	FCR (n = 279)	BR (n = 278)	*p*-value
Neutropenia	84.2%	59.0%	<0.001
Anemia	13.6%	10.4%	0.20
Thrombocytopenia	21.5%	14.4%	0.03
Infection	39.1%	26.8%	<0.001
During therapy (tx) only	22.6%	17.3%	0.1
During first 5 mo after tx	11.8%	3.6%	<0.001
In patients ≤65 years	35.2%	27.5%	0.1
In patients >65 years	47.7%	20.6%	<0.001
Secondary neoplasm*	6.1%	3.6%	0.244

* sAML/MDS: FCR (n = 6); BR (n = 1)

Eichhorst B et al. *Proc ASH* 2014;Abstract 19.

Author Conclusions

- Final analysis of the Phase III CLL10 study demonstrated inferiority of BR to FCR with regard to PFS and complete response rate.
- BR is associated with lower rates of neutropenias and severe infections in elderly patients.
- FCR remains standard therapy for fit patients.
- BR may be considered for fit elderly patients as an alternative.

Eichhorst B et al. *Proc ASH* 2014;Abstract 19.

Investigator Commentary: CLL10 — Efficacy and Tolerance of FCR in Comparison with BR as Front-Line Therapy for Fit Patients with CLL without Del(17p)

The preliminary results of this large Phase III study with relatively young patients were presented at ASH last year, but these are the final data that demonstrate a higher complete response rate for patients who received FCR. Perhaps more importantly, the rate of MRD with FCR was 74% compared to 62% with BR. With 18 months of follow-up, 53% of patients who received FCR remained MRD-negative compared to only 24% with BR. Obviously, toxicity was a little higher with FCR.

What these results mean for the practicing oncologist is that we have choices. Both regimens are active. If you have a young, fit patient without a lot of contraindications to treatment, that patient's best chance at a prolonged disease-free interval using chemoimmunotherapy is with FCR. But if you have any hesitation about tolerance or the patient is older, BR is an acceptable alternative.

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

Value of Minimal Residual Disease (MRD) Negative Status at Response Evaluation in Chronic Lymphocytic Leukemia (CLL): Combined Analysis of Two Phase III Studies of the German CLL Study Group (GCLLSG)

Kovacs G et al.

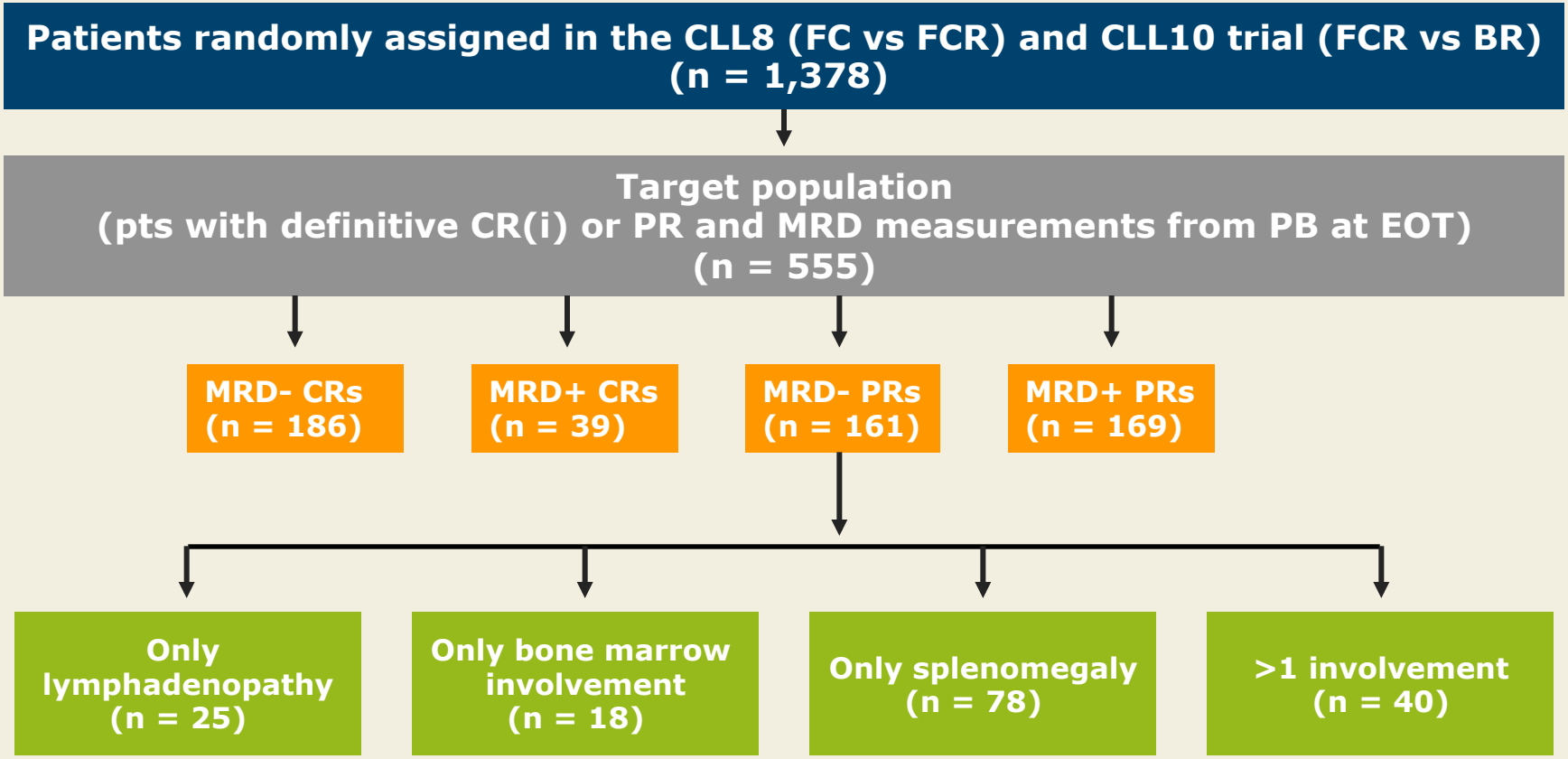
Proc ASH 2014;Abstract 23.

Background

- Detection of MRD is not formally included in the definition of response but is an important prognostic marker.
- MRD-negative status and the achievement of a complete remission (CR) together predict long progression-free survival (PFS).
- In the GCLLSG CLL8 trial, low MRD levels during and after therapy were associated with longer PFS and overall survival (OS) (*J Clin Oncol* 2012;30(9):980).
- **Study objective:** To assess the value of MRD with respect to clinical response in patients with partial and complete remission from 2 Phase III trials by the GCLLSG.

Kovacs G et al. *Proc ASH* 2014;Abstract 23.

Patient Population



CR(i) = CR with incomplete marrow recovery; PR = partial remission; PB = peripheral blood; EOT = end of treatment

Kovacs G et al. *Proc ASH* 2014;Abstract 23.

Study Methods

- Patients who received treatment in 2 Phase III trials (n = 555) from the CLL8 and the CLL10 studies who achieved a CR or a PR and had MRD measurement available were included.
- Analysis included MRD results from peripheral blood at final restaging (2 months after EOT), bone marrow and clinical and radiological assessment for organomegaly and lymphadenopathy.
- Clinical response was defined according to the IWCLL 2008 guidelines.
- Splenomegaly was determined by physical and radiological examination.
- The clinical relevance of residual splenomegaly, lymphadenopathy and bone marrow involvement in patients who were MRD-negative with PR was evaluated.

Kovacs G et al. *Proc ASH* 2014;Abstract 23.

Survival According to MRD Status and Clinical Response

MRD status and response	Median PFS	*p*-value*	Median OS	*p*-value*
MRD- CR (n = 186)	68.9 mo	—	NR	—
MRD+ CR (n = 39)	44.4 mo	0.004	NR	0.915
MRD- PR (n = 161)	61.7 mo	0.227	NR	0.59
MRD+ PR (n = 169)	28.1 mo	<0.001	79.1 mo	0.001

* Compared to MRD- CRs: NR = not reached

- PFS for MRD- PRs versus MRD+ CRs, $p = 0.047$
- OS for MRD- PRs versus MRD+ CRs, $p = 0.87$

Kovacs G et al. *Proc ASH* 2014;Abstract 23.

Multivariate Analysis Evaluating Different Prognostic Factors for PFS

COX regression PFS	Univariate comparison	Hazard ratio	*p*-value
MRD status			
Positive	vs negative	3.487	<0.001
Clinical response			
PR	vs CR	1.420	0.014
Deletion 17p			
Yes	vs no	9.082	<0.001
IgHV analysis			
Unmutated	vs mutated	2.582	<0.001

Kovacs G et al. *Proc ASH* 2014;Abstract 23.

Analysis of Patients with MRD-Negative PR Status

MRD- PR	Median PFS	*p*-value*	Median OS	*p*-value*
With splenomegaly	72.0 mo	0.331	NR	0.056
With lymphadenopathy	38.7 mo	<0.001	NR	0.077
With bone marrow involvement	56.8 mo	0.42	76.3 mo	0.395
>1 above	51.8 mo	0.202	NR	0.553

* Versus MRD- CRs

NR = not reached

Kovacs G et al. *Proc ASH* 2014;Abstract 23.

Author Conclusions

- MRD and clinical response are both strong predictors for PFS.
- MRD in combination with clinical response predicts PFS more accurately than clinical response alone.
- The persistence of splenomegaly as sole abnormality at EOT has no impact on PFS for patients with MRD-negative status who achieve a PR.

Kovacs G et al. *Proc ASH* 2014;Abstract 23.

Investigator Commentary: MRD-Negative Status in CLL — Combined Analysis of 2 Phase III Studies of the GCLLSG

I believe that the MRD data are intriguing but not practice changing. MRD is not a completely validated clinical endpoint. It is worth measuring, with the caveat that we don't know the clinical significance. It provides some signal without requiring you to wait many years for PFS or OS data. If you had to choose between 2 combinations that are relatively equal in intensity and toxicity, you would probably want the one that results in lower MRD levels. I've always been skeptical about it because responders always fare better than nonresponders and molecular responders fare better than patients who have persistent disease. We need to be aware of the pros and cons.

MRD is assuming more importance and is increasingly incorporated in clinical trials. In CLL, MRD is usually detected using 4 or more color flow cytometry, which is highly sensitive. Most major centers have this capability. CLL is unique because most of the disease is in the blood and bone marrow. MRD is a better test than a CAT scan in this disease. If a lymph node is 6 centimeters and is reduced to 3 centimeters with treatment, the patient has achieved a PR. But the disease could still be active by PET scan, which we don't use in CLL. This indicates the difficulty in determining response in CLL.

Interview with Mitchell R Smith, MD, PhD, March 24, 2015

Investigator Commentary: MRD-Negative Status in CLL — Combined Analysis of 2 Phase III Studies of the GCLLSG

This is an interesting study, but the implications for CLL are unclear at this moment because we are in this unique space where more and more oncologists are moving away from the use of chemotherapy toward the use of B-cell receptor drugs. Patients who receive agents in this class may still appear to be positive for disease although the drug is working. For this reason I believe the application of the concept of MRD is not straightforward.

I have given thought as to how I would apply this to my practice. For patients to whom I am administering chemotherapy up front, I will probably start to obtain MRD assessments using the sensitive flow cytometry techniques. If a patient is otherwise in PR or CR after chemotherapy, then examining residual disease by this sensitive flow technique can provide important prognostic information and comfort to the patient. However, I believe we will have fewer and fewer of these patients as we transition to the use of targeted drugs.

Interview with Ian W Flinn, MD, PhD, March 25, 2015

Preliminary Safety Results from the Phase IIIb GREEN Study of Obinutuzumab (GA101) Alone or in Combination with Chemotherapy for Previously Untreated or Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)

Bosch F et al.

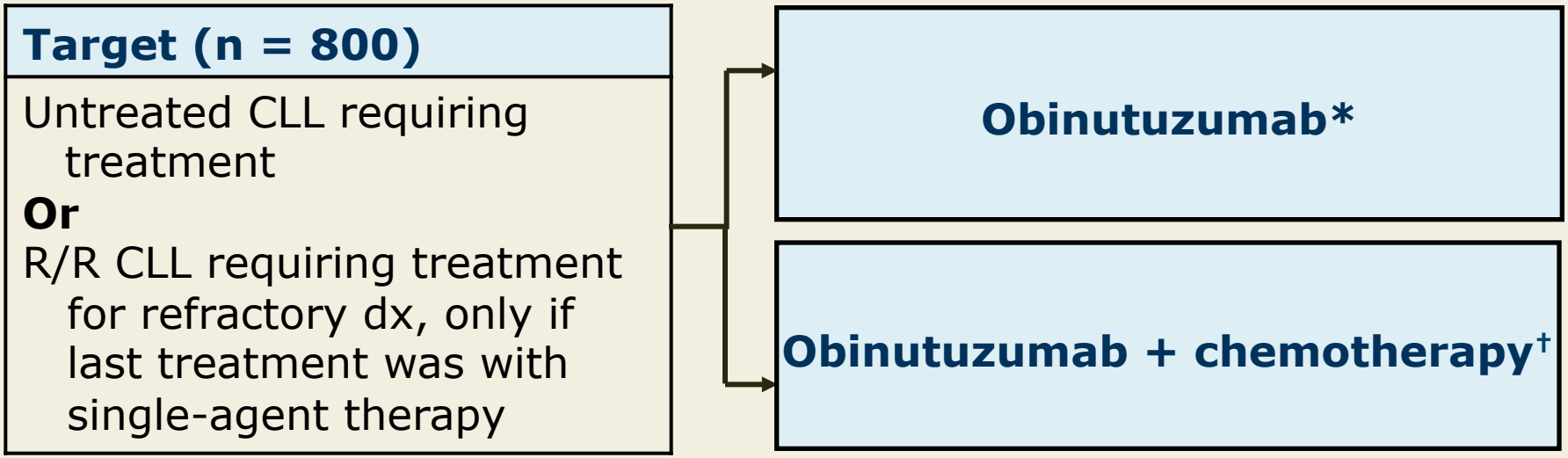
Proc ASH 2014;Abstract 3345.

Background

- The novel, glycoengineered Type II anti-CD20 monoclonal antibody obinutuzumab has demonstrated superior efficacy compared to chlorambucil (Clb) monotherapy and to Clb in combination with rituximab (R-Clb), with an acceptable safety profile, in CLL (*NEJM* 2014;370:1101).
  - However, an increased rate of infusion-related reactions (IRRs) has been observed with the obinutuzumab-Clb combination compared to R-Clb during the first cycle of treatment.
- **Study objective:** To report the preliminary infusion-related safety results from patients with CLL in cohort 1 after receiving obinutuzumab with or without chemotherapy.
  - Cohort 1: Patients with previously untreated CLL
  - Cohort 2: Patients with relapsed/refractory (R/R) CLL

Bosch F et al. *Proc ASH* 2014;Abstract 3345.

Ongoing Phase III GREEN Trial Design (NCT01905943)



* Obinutuzumab (n = 18): 1,000 mg on d1 (25 mg), d2 (975 mg), d8, d15 (cycle 1); d1 (cycles 2-6)

† Chemotherapy includes fludarabine/cyclophosphamide (FC) for fit patients (n = 46), Clb for unfit patients (n = 8) or bendamustine for fit/unfit patients (n = 86)

- **Primary endpoint:** Safety, including infusion-related reactions (IRRs), defined as treatment-related adverse events occurring during or within 24 hours of infusion.

Bosch F et al. *Proc ASH* 2014;Abstract 3345.

GREEN Cohort 1: IRR Analysis

Event	Total* (n = 158)	O-B (n = 86)	O-FC (n = 46)	O-Clb (n = 8)	O Mono (n = 18)
IRR	51.3%	47.7%	56.5%	37.5%	61.1%
Serious IRR	8.9%	8.1%	6.5%	0%	22.2%
Grade ≥3 IRR	13.3%	10.5%	17.4%	0%	22.2%
IRR leading to O discontinuation	2.5%	0%	2.2%	0%	16.7%
Withdrawal at C1	5.7%	4.7%	2.2%	0%	22.2%
Deaths during C1	0.6%	1.2%	0%	0%	0%

O = obinutuzumab; B = bendamustine; C = cycle

* Patients eligible for IRR analysis; IRRs were most frequent during C1, day 1

Bosch F et al. *Proc ASH* 2014;Abstract 3345 (Abstract only).

GREEN Cohort 1: Incidence of IRRs

IRR event occurring in ≥10% of patients	N = 158*
Chills	14.6%
Pyrexia	15.2%
Serious IRRs occurring in ≥1% of patients	
Tumor lysis syndrome (TLS)	3.8%
Pyrexia	1.3%
Grade ≥3 IRRs occurring in ≥1% of patients	
TLS	5.7%
Hypertension	1.3%
Hypotension	1.3%

* Patients eligible for IRR analysis

- IRRs were most frequent during cycle 1, day 1

Bosch F et al. *Proc ASH* 2014;Abstract 3345 (Abstract only).

Safety in Patients with Previously Untreated CLL

- Overall safety population of patients with previously untreated CLL (n = 172)
- The most frequently reported serious adverse events of special interest included:
  - IRR (8.1%)
  - Neutropenia (11.0%)
- Adverse events of particular interest were:
  - Thrombocytopenia (16.3%)
  - Cardiac events (3.5%)
  - Hemorrhagic events (3.5%)

Bosch F et al. *Proc ASH* 2014;Abstract 3345 (Abstract only).

Author Conclusions

- Preliminary safety data for patients with untreated CLL are in line with the known safety profile of obinutuzumab in similar populations.
- Although there was limited exposure time available for patients on this study, IRRs seemed to be more manageable.
  - A lower proportion of patients with IRRs Grade ≥3 was observed compared to previous studies.
  - No new safety signals were reported.
- However, since the number of discontinuations during C1 was comparable with previous obinutuzumab studies, the decision was taken to further improve IRR rates by assessing additional dexamethasone premedication in cohort 2.

Bosch F et al. *Proc ASH* 2014;Abstract 3345 (Abstract only).

Investigator Commentary: Preliminary Safety Results of the Phase III GREEN Trial of Obinutuzumab Alone or with Chemotherapy for CLL

A major concern when administering obinutuzumab is IRRs. These can be much more severe compared to what is observed with rituximab. In my experience, we almost had to admit some patients to the hospital just to finish the infusion of obinutuzumab because it's a big dose of antibody and it takes a long time if you have to keep shutting it off to manage IRRs. In the GREEN study, a split dose was used on days 1 and 2 with a low dose of 25 mg administered on day 1 and the rest of the dose on day 2.

Obinutuzumab was combined with bendamustine, FC or Clb, and the study showed that with this strategy the risk for serious toxicity seemed to be lower. There was a risk of TLS, which I have also encountered in my practice. Although we have to appreciate that obinutuzumab is an active drug, there are risks associated with its use. Because this was a preliminary safety study of the GREEN trial, efficacy results were not included. It would be interesting to know what the efficacy results show. I believe this study will help to answer the question of whether obinutuzumab should replace rituximab in CLL.

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

continued

Investigator Commentary: Preliminary Safety Results of the Phase III GREEN trial of Obinutuzumab Alone or with Chemotherapy for CLL (continued)

It's not inherently clear why obinutuzumab is associated with such a profound rate of IRRs. Being a humanized antibody, in theory it should be even less foreign to the body than rituximab. The rate of IRRs probably reflects some of the other mechanisms involved with this antibody as far as cell kill and cytokine release are concerned. The study demonstrates that all of the IRR issues happen during the first cycle. Once you get past the first cycle, it's really not that different from rituximab.

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

Salvage Therapy with Obinutuzumab (GA101) plus Chlorambucil (Clb) After Treatment Failure of Clb Alone in Patients with Chronic Lymphocytic Leukemia (CLL) and Comorbidities: Results of the CLL11 Study

Goede V et al.

Proc ASH 2014;Abstract 3327.

Background

- Chemoimmunotherapy with the glycoengineered Type II anti-CD20 antibody obinutuzumab (O) in combination with chlorambucil (Clb), the O-Clb regimen, was investigated in the CLL11 study (*NEJM* 2014;370(12):1101).
  - O-Clb versus Clb alone demonstrated clinical benefit in patients with previously untreated chronic lymphocytic leukemia (CLL) and comorbidities.
  - Progression-free survival (PFS): 26.7 vs 11.1 months
- **Study objective:** To determine whether O-Clb is an active salvage therapy for patients with refractory CLL after front-line therapy with Clb alone in a subpopulation of patients enrolled on the CLL11 trial.

Goede V et al. *Proc ASH* 2014;Abstract 3327 (Abstract only).

Phase III CLL11: Substudy Design

Eligibility (n = 30)*

Patients with refractory CLL

Progressive disease (PD) on up-front Clb alone

≤6 mo after PD on Clb

→

O-Clb

O (IV): 100 mg (d1), 900 mg (d2), 1,000 mg (d8, 15) cycle 1 → 1,000 mg (d1) cycles 2-6

Clb (oral): 0.5 mg/kg on d1, 15 q4wk

* Subpopulation of patients enrolled on the Phase III CLL11 trial

- Patients on the study were offered O-Clb as optional salvage therapy.

Goede V et al. *Proc ASH* 2014;Abstract 3327 (Abstract only).

Patient Characteristics

Characteristic	n = 30
Median age	72 years
Median CIRS at study entry	8
Median calculated creatinine clearance	67 mL/min
Del(11q)	12%
Del(17p)	20%
Unmutated IGHV genes	64%

CIRS = cumulative illness rating scale

- All patients on the study were offered O-Clb as optional salvage therapy.
- All patients had a high comorbidity burden at study entry.
- All patients had reduced renal function.

Goede V et al. *Proc ASH* 2014;Abstract 3327 (Abstract only).

Treatment Outcomes

- At crossover to O-Clb therapy:
  - Patients who had not responded to initial treatment with Clb alone: 28 (93%)
  - Patients who initially responded to Clb alone and had achieved partial remission but relapsed early: 2 (7%)
  - The median time from Clb initiation to crossover: 9.7 months
- After crossover to O-Clb therapy:
  - Patients who completed 6 cycles of O-Clb: 29 (97%)
  - Patients who discontinued O-Clb after first infusion of O due to infusion-related reactions (IRRs): 1 (3%)

Goede V et al. *Proc ASH* 2014;Abstract 3327 (Abstract only).

Response to O-Clb

Response, n (%)	n = 30
Overall response	26 (87%)
Complete response	2 (7%)
Incomplete complete response	1 (3%)
Partial response	23 (77%)
Stable disease	2 (7%)
Progressive disease	1 (3%)
Not evaluable due to study discontinuation after IRRs	1 (3%)

- Negativity for minimal residual disease in bone marrow and/or peripheral blood after crossover treatment was achieved in 23% of patients.

Goede V et al. *Proc ASH* 2014;Abstract 3327 (Abstract only).

PFS

Outcome	n = 30
Median PFS* (95% confidence interval)	17.2 months (14.2-22.4)
Median follow-up time	23 months

* From start of crossover treatment

Goede V et al. *Proc ASH* 2014;Abstract 3327 (Abstract only).

Adverse Events (N = 30)

Event	Grade 3 or 4
Neutropenia	33%
IRRs	17%
Infections	13%
Thrombocytopenia	10%
Anemia	7%

Goede V et al. *Proc ASH* 2014;Abstract 3327 (Abstract only).

Author Conclusions

- In addition to the established role of chemoimmunotherapy with O-Clb as front-line treatment of CLL, these results suggest that:
  - The combination could be a safe and active treatment for patients with CLL refractory to prior Clb chemotherapy.

Goede V et al. *Proc ASH* 2014;Abstract 3327 (Abstract only).

Investigator Commentary: Salvage Treatment with O-Clb After Disease Progression on Clb Alone in Patients with CLL and Comorbidities

The background of this study is the randomized Phase III CLL11 trial of Clb/rituximab versus Clb alone versus Clb/O, showing that the combination of O with Clb produced much better results. The magnitude of the benefits observed with O in CLL was surprising.

The current study is like an add-on study with patients who experienced disease progression on initial therapy with Clb alone. These patients belonged to a higher-risk group. They were older, 12% of them had del(11q) and 20% had del(17p). The patients were offered Clb in combination with O. Despite the presence of high-risk disease, the study demonstrated a favorable overall response rate with a median PFS of 17.2 months. This is impressive. The results suggest that O-Clb as an option in the Clb-refractory setting should be a treatment consideration. It demonstrated that the use of O for patients with not-heavily pretreated disease has significant activity.

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

Rituximab Maintenance After Chemoimmunotherapy Induction in 1st and 2nd Line Improves Progression Free Survival: Planned Interim Analysis of the International Randomized AGMT-CLL8/a Mabtenance Trial[1]

Ofatumumab (OFA) Maintenance Prolongs PFS in Relapsed CLL: Prolong Study Interim Analysis Results[2]

[1] **Greil R et al.**

Proc ASH 2014;Abstract 20.

[2] **van Oers MHJ et al.**

Proc ASH 2014;Abstract 21.

Rituximab Maintenance After Chemoimmunotherapy Induction in 1st and 2nd Line Improves Progression Free Survival: Planned Interim Analysis of the International Randomized AGMT-CLL8/a Mabtenance Trial

Greil R et al.

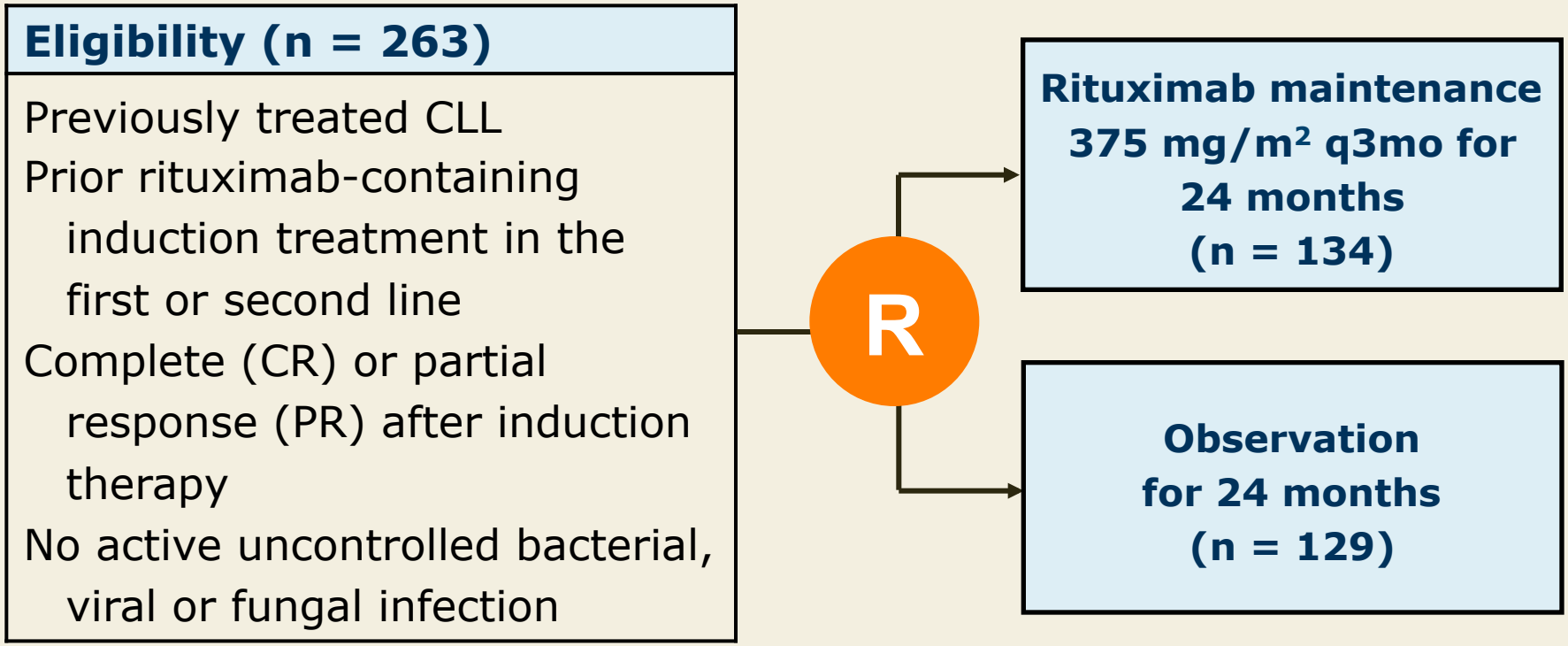
Proc ASH 2014;Abstract 20.

Background

- Chemoimmunotherapy has become a standard approach in previously untreated and pretreated chronic lymphocytic leukemia (CLL).
- The addition of rituximab to fludarabine/cyclophosphamide (FC) for fit patients has proven superior to chemotherapy alone, and more recently an anti-CD20 agent was shown to improve outcomes in patients who received chlorambucil (*Proc ASH* 2014;Abstract 3327).
  - These results suggest that immunotherapy may be of benefit independent of the chosen chemotherapy backbone.
- In follicular and mantle-cell lymphoma, rituximab maintenance treatment has become a clinical standard.
- **Study objective:** To determine the preliminary efficacy and safety results of rituximab maintenance after induction therapy with a rituximab-containing chemoimmunotherapy regimen.

Greil R et al. *Proc ASH* 2014;Abstract 20.

Phase III AGMT-CLL8/a Mabtenance Trial Design (NCT01118234)



- Randomization was stratified by country, line of therapy, induction response and type of induction regimen
- **Primary endpoint:** Progression-free survival (PFS)
- A planned sample size of 256 patients was calculated

Greil R et al. *Proc ASH* 2014;Abstract 20.

Patient Characteristics at Interim Analysis

All patients	n = 263
Median age	63 years
Female	28.9%
Patients enrolled at 1st induction therapy	80.6%
Available FISH cytogenetic risk results	221 (84%)
Del(17p)	3.1%
Del(11q)	27.6%
Trisomy 12	10.8%
Del(13q)	36.2%
Normal FISH karyotype	21.2%
Patients with known IgVH status	161 (61%)
Patients with unmutated IgVH	67%

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).

Treatment Outcomes

Outcome	Rituximab (n = 134)	Observation (n = 129)
17.3-month PFS	85.1%	75.5%
p-value	0.007	
Disease progression	14.9%	27.9%
Deaths	7 (5.2%)	10 (7.8%)

- Median observation time: 17.3 months

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).

Induction Regimens and Response to Induction Therapy

Induction regimen	n = 263
FCR	73.5%
BR	20.2%
Response to induction treatment	
CR/CRi	58%
PR	41.8%
MRD negativity*	57%

* By an 8-color MRD flow cytometric analysis after induction

- FCR = fludarabine/cyclophosphamide/rituximab; BR = bendamustine/rituximab; CRi = incomplete CR; MRD = minimal residual disease

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).

Benefit from Treatment

- To account for toxicities and secondary neoplasms, event-free survival was calculated counting as events secondary cancer, termination of treatment due to toxicities, disease progression or death.
- In this analysis the benefit was preserved, albeit with a lower *p*-value of 0.03.
- The observed benefit seemed independent of response after induction (CR versus PR).
- However, the observed benefit was associated with a positive MRD state after induction.
- Further factors that influenced benefit from treatment in exploratory analyses of patient subgroups were sex, cytogenetics, IgVH and B symptoms at diagnosis.

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).

Adverse Events (AEs)

- Current toxicity monitoring allows an analysis on the level of serious AEs (SAEs) only.
- The causes of SAEs were well balanced between arms, with the exception of infectious SAEs:
  - Rituximab arm (n = 32) versus observation arm (n = 22)
- Treatment-related deaths (n = 3) were attributed to infections:
  - Rituximab arm (n = 1) versus observation arm (n = 2)
- Secondary cancer:
  - Rituximab arm (n = 8) versus observation arm (n = 1)
- Four of the neoplasms in the rituximab arm were localized nonmelanoma skin cancers
  - 2 deaths from malignomas occurred: 1 in each arm

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).

Author Conclusions

- Rituximab maintenance after chemoimmunotherapy induction in CLL seems feasible:
  - It shows signs of efficacy.
  - However, it is associated with an increase in infectious complications.
- This interim analysis refutes the alternative hypothesis and allows the trial to continue.
- Exploratory analyses suggest that with longer follow-up it may be possible to define subpopulations with larger benefit from extended immunotherapy.

Greil R et al. *Proc ASH* 2014;Abstract 20 (Abstract only).

Investigator Commentary: Mabtenance — Interim Analysis of Efficacy and Safety of Rituximab Maintenance in CLL

This study specifically investigated the use of rituximab maintenance versus observation for patients with CLL who had received either FCR, the standard approach, or BR. About three quarters of the patients received FCR induction.

There are few data from randomized studies on rituximab maintenance in this setting. Hence, this study is important, especially because the whole concept of prolonged therapy is at the forefront of many people's minds. Clearly, if you treat rather than observe, you are likely to get a PFS benefit. The biggest question is, does it make a significant difference overall to how long patients live? That is uncertain, and this study demonstrated no overall survival benefit. It is not clear whether it's necessary to treat on a prolonged basis or whether one can treat and then allow a treatment break and thereafter reinitiate therapy. This is still an open debate.

Interview with Stephen M Ansell, MD, PhD, January 20, 2015

continued

Investigator Commentary: Mabtenance — Interim Analysis of Efficacy and Safety of Rituximab Maintenance in CLL (continued)

Overall the treatment was well tolerated. The PFS at 17.3 months favored rituximab maintenance, with 85.1% of the patients progression free versus 75.5% on the observation arm. This suggests that rituximab maintenance may prolong benefit from initial therapy.

In conclusion, the rituximab maintenance approach was feasible. Although some treatment-related infections were observed, the regimen was efficacious and merits further evaluation. In general practice this maintenance approach is not completely standard, but I believe it is certainly going to be evaluated in the future.

Interview with Stephen M Ansell, MD, PhD, January 20, 2015

Ofatumumab (OFA) Maintenance Prolongs PFS in Relapsed CLL: Prolong Study Interim Analysis Results

van Oers MHJ et al.

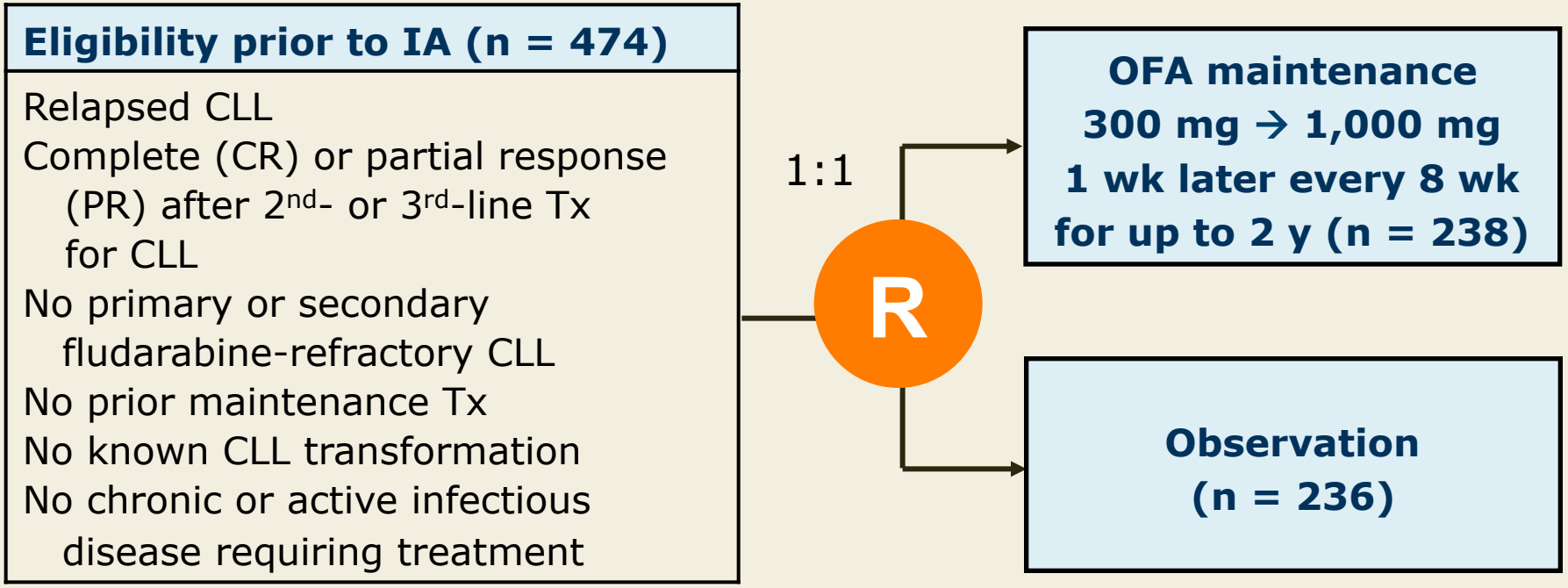
Proc ASH 2014;Abstract 21.

Background

- Despite encouraging progress in treatment results, CLL remains incurable and patients eventually experience disease relapse.
- Currently, the effects of maintenance therapy are unknown for CLL.
- Ofatumumab (OFA), a human anti-CD20 monoclonal antibody, has proven efficacy as monotherapy in refractory CLL.
- **Study objective:** To report the interim analysis of efficacy and safety of OFA maintenance for patients in remission after induction therapy for relapsed CLL.

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21.

Phase III PROLONG Trial Design (NCT01039376)



IA = interim analysis

- Premedication for patients receiving OFA included acetaminophen, antihistamines and glucocorticoids
- Stratification was by number and type of prior treatments and by CR or PR after induction
- **Primary endpoint:** Progression-free survival (PFS)

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21.

Patient Characteristics

Characteristic	OFA (n = 238)	Observation (n = 236)
Mean age	63.8 years	64.2 years
Male	68%	67%
Median time since diagnosis	5.24 years	4.59 years
Response to last CLL Tx		
CR	17%	18%
Incomplete CR	2%	2%
PR	81%	80%
Missing	0%	0.4%

- Types of prior therapies:
  - Alkylator only: OFA (3%) versus observation (2%)
  - Chemoimmunotherapy: OFA (84%) versus observation (84%)
  - Other: OFA (13%) versus Observation (14%)

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21 (Abstract only).

Efficacy Results

Outcome	OFA (n = 238)	Observation (n = 236)
Median PFS	28.6 mo	15.2 mo
Hazard ratio (*p*-value)	0.48 (<0.0001)	
Median time to start of next Tx	38.0 mo	27.4 mo
Hazard ratio (*p*-value)	0.63 (0.0076)	

- Median duration of OFA treatment: 12.5 mo
- Median follow-up: 26.1 mo (OFA) versus 24.0 mo (observation)
- At the time of interim analysis there was no difference in overall survival
  - Hazard ratio = 0.92; $p = 0.74$

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21 (Abstract only).

Adverse Events (AEs)

Event	OFA	Observation
All grades	87%	75%
All Grade 3 or 4 AEs	25%	17%
Grade 3 or 4 infections	18%	13%
Most common (>5%) Grade 3 or 4 AEs		
Neutropenia	22%	9%
Pneumonia	7%	4%
Death rate	14%	14%
AEs leading to permanent discontinuation	8%	N/A

NA = not applicable

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21 (Abstract only).

Author Conclusions

- Ofatumumab maintenance therapy provided significant clinical benefit for patients with relapsed CLL.
- Ofatumumab was well tolerated with no unexpected toxicities.
- Additional data analyses are ongoing for efficacy outcomes according to patient subgroups.

van Oers MHJ et al. *Proc ASH* 2014;Abstract 21 (Abstract only).

Investigator Commentary: Interim Analysis of the Phase III PROLONG Trial of Ofatumumab Maintenance in Relapsed CLL

In this study patients who achieved CR or PR after second- or third-line therapy for CLL were randomly assigned to receive ofatumumab maintenance or no further therapy. Patients might have received a variety of other regimens ahead of time. A highly significant benefit was recorded for patients who received ofatumumab in comparison to observation. The median PFS for the ofatumumab arm was 28.6 months versus 15.2 months for the observation arm. However, no difference in overall survival was evident between the 2 arms.

Even though one must be a little cautious comparing directly between trials, the overall outcomes of this trial seem similar to those of the Mabtenance trial. So one could probably lump the Mabtenance and the PROLONG trials into a group to state that for CD20-directed therapy, there appears to be a PFS benefit for patients who receive the antibody. I believe that if you take CLL as a part of the spectrum of indolent lymphomas, including low-grade and incurable forms of these diseases, as far as we know at this point there is certainly a trend and a theme for the maintenance strategy, and this may well be the reasonable approach to take.

Interview with Stephen M Ansell, MD, PhD, January 20, 2015

Efficacy and Safety of Ibrutinib in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma with 17p Deletion: Results from the Phase II RESONATE™-17 Trial[1]

Complex Karyotype, Rather Than Del(17p), Is Associated with Inferior Outcomes in Relapsed or Refractory CLL Patients Treated with Ibrutinib-Based Regimens[2]

[1]O'Brien S et al.

Proc ASH 2014;Abstract 327.

[2]Thompson PA et al.

Proc ASH 2014;Abstract 22.

Efficacy and Safety of Ibrutinib in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma with 17p Deletion: Results from the Phase II RESONATE™-17 Trial

O'Brien S et al.

Proc ASH 2014;Abstract 327.

Background

- Ibrutinib is a small molecule inhibitor of Bruton tyrosine kinase that is indicated for:
  - Patients with chronic lymphocytic leukemia (CLL) who have received ≥1 therapy
  - Patients with previously untreated del(17p) CLL
- The Phase III RESONATE trial demonstrated significant overall (OS) and progression-free survival (PFS) benefits with single-agent ibrutinib versus ofatumumab in relapsed/ refractory (R/R) CLL (*NEJM* 2014;371(3):213).
- **Study objective:** To determine the efficacy and safety of single-agent ibrutinib for patients with R/R CLL or small lymphocytic lymphoma (SLL) harboring the del(17p) abnormality.

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

Phase II PCYC-1117 (RESONATE-17) Trial Design

Eligibility (n = 144)

CLL or SLL

Presence of del(17p13.1) in peripheral blood by FISH analysis

R/R disease after 1-4 prior lines of therapy

Measurable nodal disease

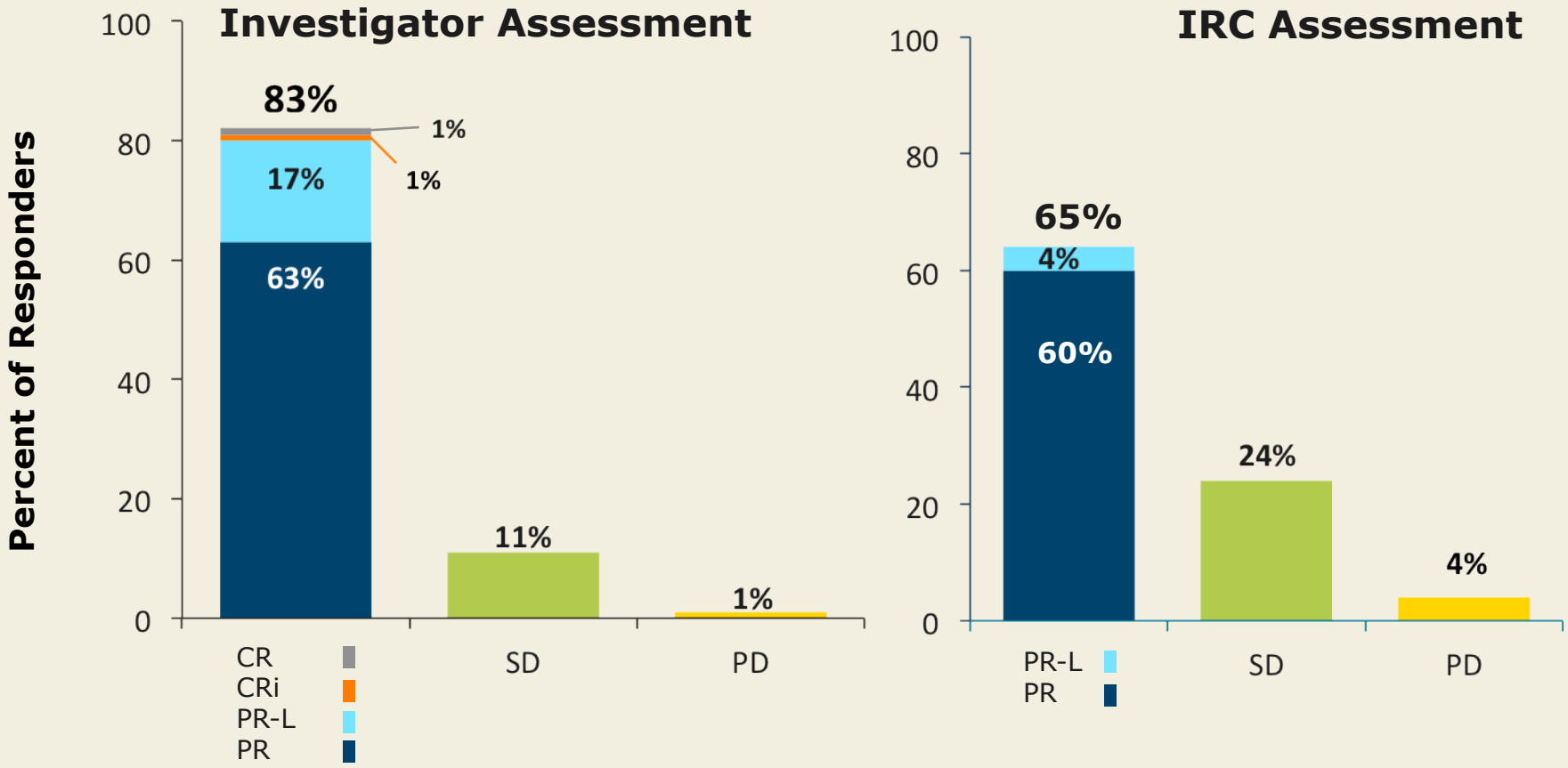
ECOG PS 0-1

→ Single-agent ibrutinib 420 mg PO daily Until unacceptable toxicity or disease progression

- Primary analysis was performed 12 months after enrollment of last patient
- **Primary endpoint:** Overall response rate (ORR)
- **Secondary endpoints include:** Duration of response (DoR), safety and tolerability
- **Exploratory endpoints:** PFS and OS

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

Response to Ibrutinib (N = 144)



Median duration of response: Not yet reached

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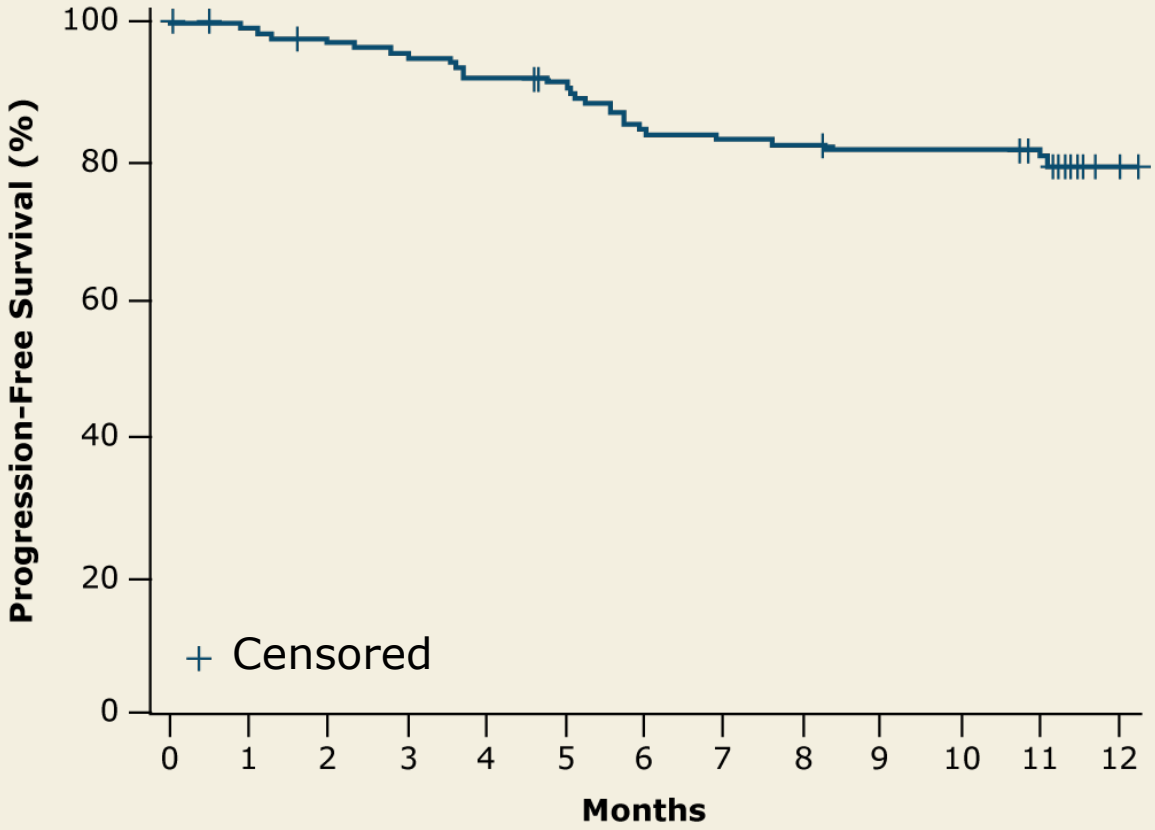
Progression-Free Survival



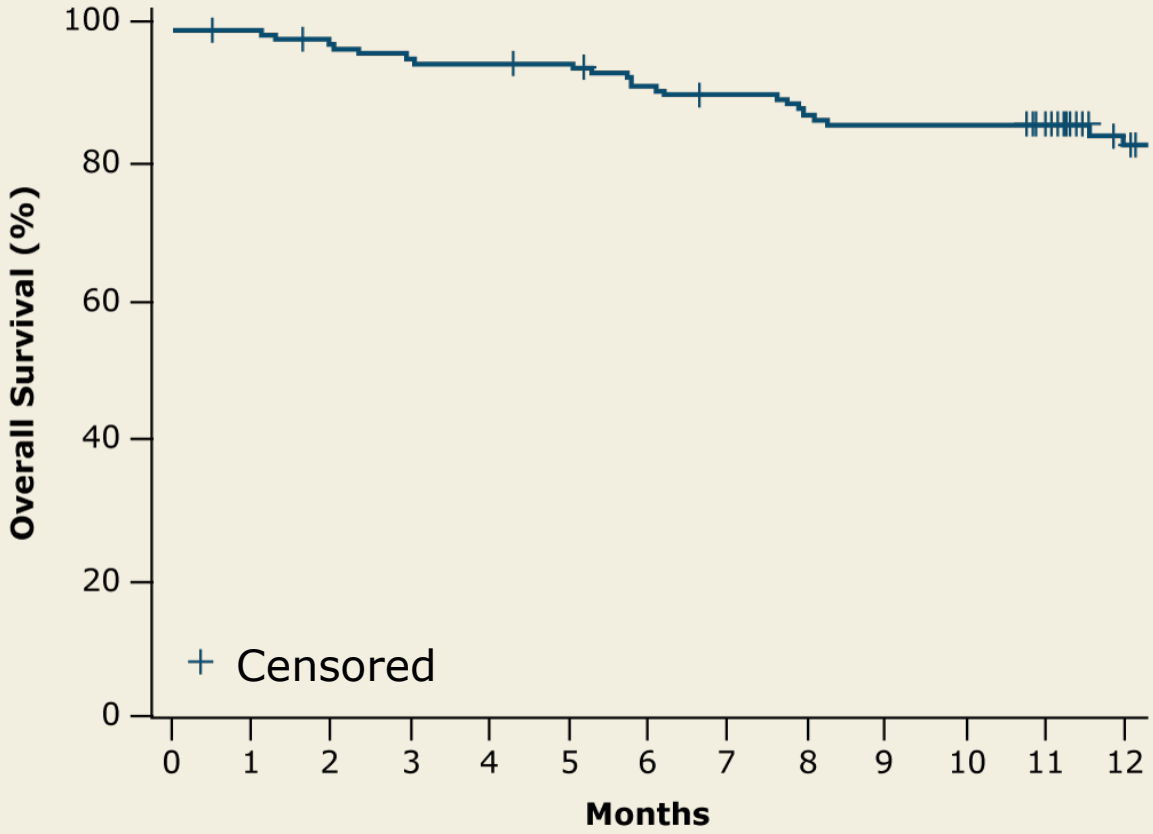
	N	12-month PFS rate
Overall	144	79.3%
Del17p quartiles*		
<25%	35	85%
25-50%	37	81%
50-75%	33	83%
≥75%	39	69%

* Based on % of CLL cells with del17p at baseline

- Median PFS not reached
- Median follow-up 11.5 months

With permission from O'Brien S et al. *Proc ASH* 2014;Abstract 327.

Overall Survival



	N	12-month OS rate
Overall	144	83.5 %
Del17p quartiles*		
<25%	35	85%
25-50%	37	89%
50-75%	33	86%
≥75%	39	76%

* Based on % of CLL cells with del17p at baseline

- Median OS not reached
- Median follow-up 11.5 months

With permission from O'Brien S et al. *Proc ASH* 2014;Abstract 327.

Characteristics of Patients with Progressive Disease (PD) on Ibrutinib (n = 20)

Characteristic	Richter's transformation (n = 11)	No Richter's transformation (n = 9)	Non-PD (n = 124)
Median del(17p) cells	65%	86%	65%
Presence of del(11q)	0%	11%	18%
Median beta-2-microglobulin	7 mg/L	6 mg/L	5 mg/L
Median LDH level	471 U/L	327 U/L	249 U/L
Median no. of prior Tx (range)	2 (1-4)	2 (1-5)	2 (1-7)
Bulky disease >5 cm	64%	100%	44%
Bulky disease >10 cm	18%	22%	9%
Median time to PD	158 days	232 days	N/A

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

Select Adverse Events

Event (n = 144)	Any grade	Grade 3-4
Diarrhea	36%	2%
Fatigue	31%	1%
Hypertension	19%	8%
Anemia	19%	8%
Neutropenia	17%	14%

- Other select adverse events:
  - Pneumonia (10%), urinary tract infection (3%)
  - Skin cancers (5%), nonskin cancers (1%)
  - Tumor lysis syndrome (<1%)

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

Atrial Fibrillation and Bleeding-Related Events

- Atrial fibrillation of any grade occurred in 11 patients (8%):
  - Grade 3-4 events = 3.5%; no Grade 5 events
  - 5 patients had a history of atrial fibrillation
  - No treatment discontinuations occurred
- Major bleeding of Grade 2 or 3 occurred in 7 patients (5%):
  - Events included intracranial hemorrhage, spontaneous and traumatic hematomas*, hematuria, hemoptysis, gastric ulcer and intercostal artery hemorrhages
  - 3 patients were receiving concomitant medication: anticoagulants (n = 2), aspirin (n = 1)
  - 1 patient had factor XI deficiency

* In a patient with history of spontaneous hematoma, platelet count was $<100 \times 10^9$/L at time of bleeding event

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

Author Conclusions

- Ibrutinib is efficacious with a favorable risk-benefit profile in the largest prospective study of patients with CLL/SLL harboring del(17p):
  - Best response (ORR including PR-L) by IRC: 83%
  - 12-month PFS: 79%
  - The results are consistent with previously observed efficacy (*NEJM* 2013;369:32)
- PFS outcomes were favorable compared to those of front-line FCR or alemtuzumab in CLL harboring del(17p) (*Lancet* 2010;376:1164; *JCO* 2007;10:5616).
- The safety profile is consistent with previous reports for ibrutinib (*NEJM* 2013;369:32).
- Ibrutinib is an effective therapy for patients with CLL or SLL harboring del(17p).

O'Brien S et al. *Proc ASH* 2014;Abstract 327.

Investigator Commentary: Efficacy and Safety Results from the Phase II RESONATE-17 Trial of Ibrutinib in R/R CLL or SLL

Patients with CLL and del(17p) have a uniquely poor outcome, and standard treatment has been inadequate. This is an important Phase II trial for 144 patients with R/R CLL or SLL with del(17p) after disease progression on ≥1 prior therapy. The efficacy of single-agent ibrutinib was marked, with about 80% of patients remaining progression free at 12 months. These results are superior to what is expected with aggressive immunochemotherapies. The PFS is favorable in comparison to FCR or alemtuzumab, at least from the Phase II experiences.

The study demonstrated that 20 patients had PD, and Richter's transformation was reported in 11. This begs the question whether these patients had underlying Richter's transformation. An important message from this study is that although ibrutinib may be effective in high-risk disease with del(17p), if there is evidence of histological transformation this agent is unlikely to be successful as a single agent. Differences in the toxicity profile between ibrutinib and regimens such as FCR will be important.

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

continued

Investigator Commentary: Efficacy and Safety Results from the Phase II RESONATE-17 Trial of Ibrutinib in R/R CLL or SLL (continued)

The question is, how durable will the responses be? What happens if the disease becomes ibrutinib resistant? I believe we're all optimistic about this and other trials investigating ibrutinib in CLL. Although the results are premature, I certainly see the appeal. I would encourage clinicians to steer their patients toward these trials because the quicker we enroll to these trials, the quicker we'll obtain the definitive answers.

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

Complex Karyotype, Rather Than Del(17p), Is Associated with Inferior Outcomes in Relapsed or Refractory CLL Patients Treated with Ibrutinib-Based Regimens

Thompson PA et al.

Proc ASH 2014;Abstract 22.

Background

- Ibrutinib is active in relapsed/refractory (R/R) CLL, including patients with del(17p)
  - Patients with del(17p) have a similar response rate to those without, but they have shorter progression-free survival and a pattern of continuous relapses (*NEJM* 2013;369:32).
- Del(17p) is frequently associated with a complex metaphase karyotype (CKT), defined as ≥3 distinct chromosomal abnormalities.
- CKT has been associated with inferior outcomes in treatment-naïve and R/R CLL, but its prognostic significance for patients receiving ibrutinib (Ib) is unknown.
- **Study objective:** To determine the prognostic value of CKT in patients with R/R CLL treated with Ib-based regimens.

Thompson PA et al. *Proc ASH* 2014;Abstract 22.

Study Methods

- Patients with R/R CLL at MD Anderson Cancer Center who received Ib-based regimens from 2010-2013 (n = 100):
  - Ib monotherapy (n = 50)
  - Ib + rituximab (R) (n = 36)
  - Ib + bendamustine (B) + R (n = 14)
- Pretreatment fluorescent in situ hybridization (FISH) and CpG-stimulated metaphase cytogenetic analyses were performed on the bone marrow.
- **Endpoints include:** Overall response rate (ORR), event-free survival (EFS) and overall survival (OS).

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

Baseline Characteristics

Characteristic	
Median age (range)	65 years (35-83)
Median no. of prior therapies (range)	2 (1-12)
Pts with del(11q), n = 95	28%
Pts with del(17p), n = 95	49%
Pts with CKT, n = 72	36%
Pts with unmutated IGHV gene, n = 98	81%
Pts with fludarabine-refractory disease, n	19
Pts with beta-2 microglobulin (ß2M) ≥4.0 mg/L, n	48

- 22/26 patients with CKT had del(17p)
- 3/26 patients with CKT had del(11q)
- 1/26 patients with CKT had no available FISH results
- No association between CKT and other baseline characteristics

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

Response Rate

All patients	**(n = 100)**
ORR	95%
Complete remission (CR)	16%
Partial remission (PR)	79%
Pts who received Ib + B + R (n = 14)	
CR	50%
Pts who received Ib with or without R (n = 86)	
CR	10.7%

- ORR did not differ according to baseline characteristics
- Patients who achieved CR (Ib + B + R versus Ib with or without R):
  - Odds ratio = 40.1; $p = 0.005$
- A trend toward lower CR was observed on multivariate analysis of patients with ß2M ≥4.0 ($p = 0.055$)

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

Event-Free Survival

- Univariate analyses demonstrated that the following were significantly associated with EFS:
  - Fludarabine-refractory CLL ($p = 0.025$)
  - Presence of del(17p) ($p = 0.008$)
  - Presence of CKT ($p < 0.0001$)
- The median follow-up for surviving patients was 27 months.
- No association was observed between del(17p) and EFS when patients with CKT were excluded from the analysis.
- Multivariate analysis demonstrated that only the presence of CKT was significantly associated with EFS:
  - Hazard ratio = 4.1; $p = 0.018$

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

Overall Survival

- Univariate analyses demonstrated that the following were significantly associated with OS:
  - Fludarabine-refractory CLL (p = 0.009)
  - Presence of del(17p) (p = 0.024)
  - Presence of CKT (p = 0.003)
- No association was apparent between del(17p) and OS when patients with CKT were excluded.
- A trend toward inferior OS was observed among patients with baseline ß2M ≥4.0 (p = 0.07).
- Multivariate analysis demonstrated that fludarabine-refractory CLL, CKT and ß2M ≥4.0 were significantly associated with inferior OS.

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

Author Conclusions

- The presence of CKT is independently associated with inferior EFS and OS in patients with relapsed/refractory CLL treated with Ib, while del(17p) is not.
- CKT is strongly associated with del(17p) and may be a key determinant of biological behavior in del(17p) CLL.
- These results have important implications for the treatment of del(17p) CLL.
- Patients without CKT appear to have equivalent outcomes with Ib compared to patients without del(17p).
  - These cases could potentially be managed with long-term Ib and close monitoring.

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

Author Conclusions (continued)

- In contrast, the inferior outcomes after initial response in patients with CKT make them ideal candidates for treatment-intensification strategies after initial Ib-based treatment, either with novel drug combinations or with allogeneic stem cell transplant, ideally in the context of well-designed clinical trials.

Thompson PA et al. *Proc ASH* 2014;Abstract 22 (Abstract only).

Investigator Commentary: Complex Karyotype Is Associated with Inferior Outcomes in Patients with R/R CLL Treated with Ib-Based Regimens

This is an interesting study of 100 patients with R/R CLL previously treated with Ib-containing regimens that is hypothesis generating. It suggests that CLL is a complex disease and confirms that del(17p) is not the only abnormality posing issues in the treatment of CLL. The commonly used detection method for del(17p) is FISH. In an era in which whole-genome sequencing (WGS) methods are available and one is able to fine point highly characteristic mutations, it is important to have a better understanding of subsets of patients.

In the relapsed setting in particular, numerous abnormalities evolve. To some degree of surprise, the study showed that the highest predictor of poorer outcome was CKT. When CKT was excluded, no association was apparent between del(17p) and EFS or OS. In fact it was CKT that was independently associated with inferior EFS and OS. In my mind, this opens the door to the future. As WGS becomes more routine and more sophisticated panels are developed based on individual diseases, we are likely to identify specific genes that are predictive of success or failure.

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

Second Interim Analysis of a Phase 3 Study of Idelalisib Plus Rituximab (R) for Relapsed Chronic Lymphocytic Leukemia (CLL): Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors

Sharman JP et al.

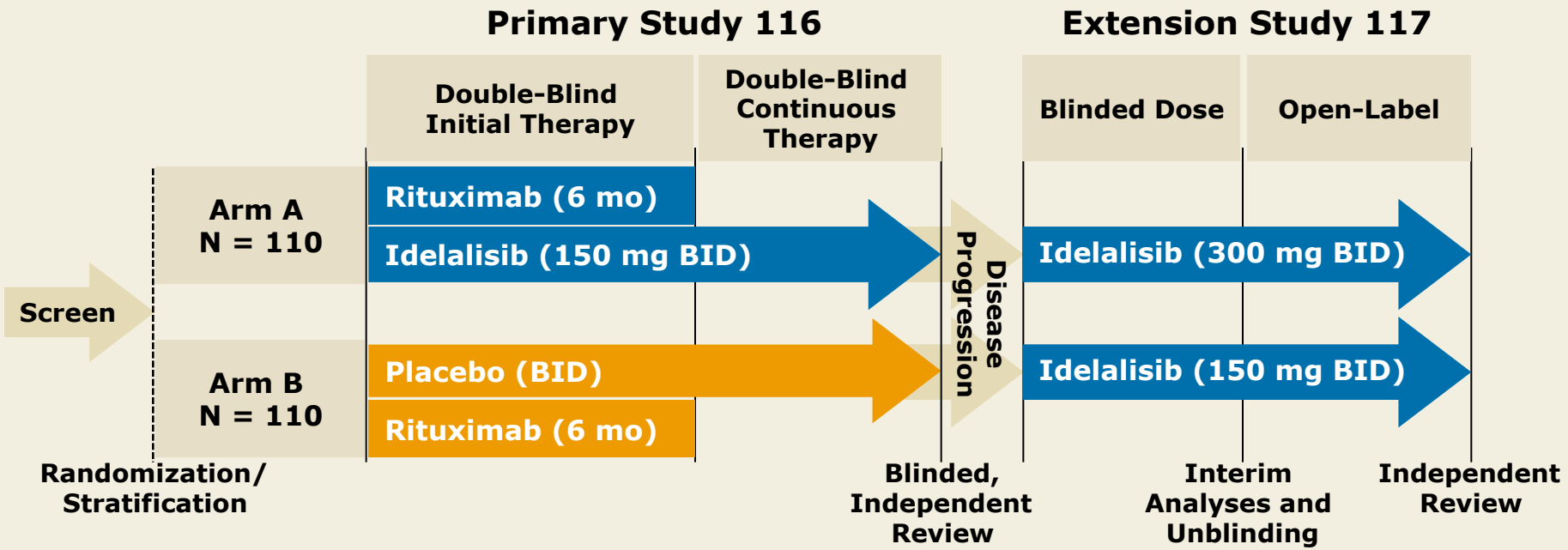
Proc ASH 2014;Abstract 330.

Background

- There is a high unmet need for the treatment of frail patients with relapsed CLL, particularly those characterized by adverse prognostic factors such as the presence of del(17p) and/or *TP53* mutations.
- Idelalisib, a first-in-class, targeted, highly selective, oral inhibitor of PI3K-delta, was recently approved in combination with R for the treatment of relapsed CLL on the basis of the first interim analysis results of a Phase III trial of idelalisib/R versus placebo/R (*NEJM* 2014;370;997).
  - Median progression-free survival (PFS): Not reached versus 5.0 months (HR: 0.15; $p < 0.001$).
- **Study objective:** To describe results of the second interim analysis of a Phase III trial of idelalisib and R for patients with relapsed CLL, with a focus on patients with adverse cytogenetics.

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

Phase III Trial Design



	Median Follow-up, months		
	IDELA + R	PBO + R	
1st Interim Analysis	4	4	DMC halted trial (*NEJM* 2014;370;997)
2nd Interim Analysis	6	5	Blind ended (*Proc ASCO* 2014;Abstract 7012) • Arm A continues • Arm B crosses over
Update	13	11	PFS, OS by subgroup analysis

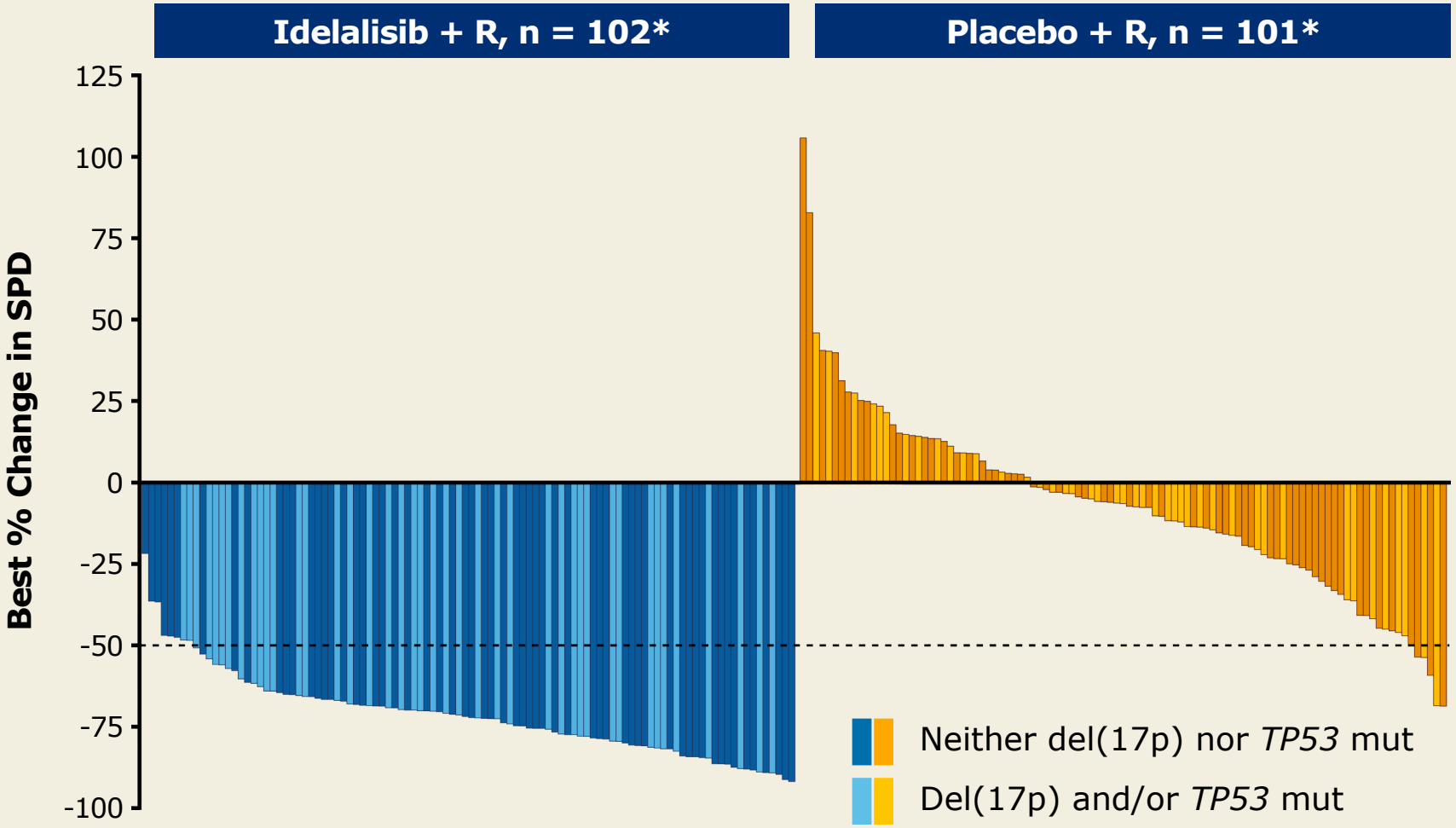
Sharman JP et al. *Proc ASH* 2014;Abstract 330.

Eligibility Criteria

Criteria	Requirement
Relapsed CLL	• CLL progression <24 months since last therapy • Treatment warranted according to IWCLL criteria
Lymphadenopathy	Presence of ≥1 measurable nodal lesion
Prior therapies	≥1 anti-CD20 antibody-containing therapy or ≥2 prior cytotoxic therapies
Appropriate for non-cytotoxic therapy	CIRS score >6 or creatine clearance <60 mL/min (≥30 mL/min) or Grade 3 or 4 neutropenia or thrombocytopenia due to prior myelotoxicity
Bone marrow function	Any grade anemia, neutropenia or thrombocytopenia allowed
Karnofsky score	≥40

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

Second Interim Analysis: Lymph Node Response



*Evaluable patients

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Second Interim Analysis: Overall Response Rate

Patient category (n)*	Idelalisib + R	Placebo + R
All patients (n = 106, 107)	77%	15%
Rai Stage III/IV (n = 67, 70)	70%	13%
Unmutated IGHV (n = 87, 90)	77%	16%
Del(17p)/TP53 mutant (n = 44, 47)	82%	13%
Del(11q) (n = 25, 23)	68%	17%
ZAP70-positive (n = 94, 91)	76%	17%
CD38-positive (n = 59, 49)	78%	16%
B2M (>4 mg/L) (n = 90, 80)	77%	16%

* Evaluable patients at time of analysis
B2M = beta-2 microglobulin
For all patient categories, the odds ratio was in favor of idelalisib + R

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

Second Interim Analysis: Median PFS

Patient category (n)*	Idelalisib + R	Placebo + R
All patients (n = 110, 110)	NR	5.5 mo
Rai Stage III/IV (n = 70, 72)	NR	13.0 mo
Unmutated IGHV (n = 91, 93)	NR	5.5 mo
Del(17p)/TP53 mutant (n = 46, 49)	NR	4.0 mo
Del(11q) (n = 25, 23)	10.7 mo	6.9 mo
ZAP70-positive (n = 98, 93)	NR	5.5 mo
CD38-positive (n = 62, 51)	NR	6.9 mo
B2M (>4 mg/L) (n = 94, 83)	NR	5.0 mo

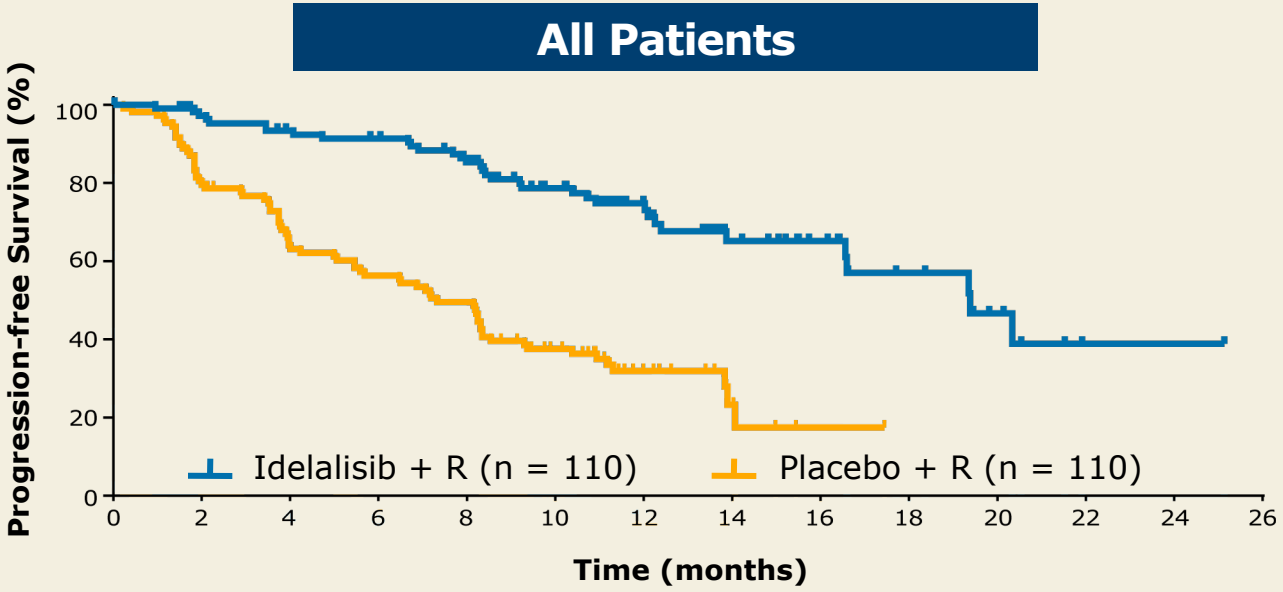
* Evaluable patients at time of analysis

NR = not reached

For all patient categories, the hazard ratio was in favor of idelalisib + R

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

PFS (Including Extension Study*)



	Median PFS	HR	*p*-value
IDELA + R	19.4 mo	0.25	<0.0001
PBO + R	7.3 mo		

* Placebo + R includes those patients who received open-label idelalisib after unblinding without prior disease progression (n = 42).

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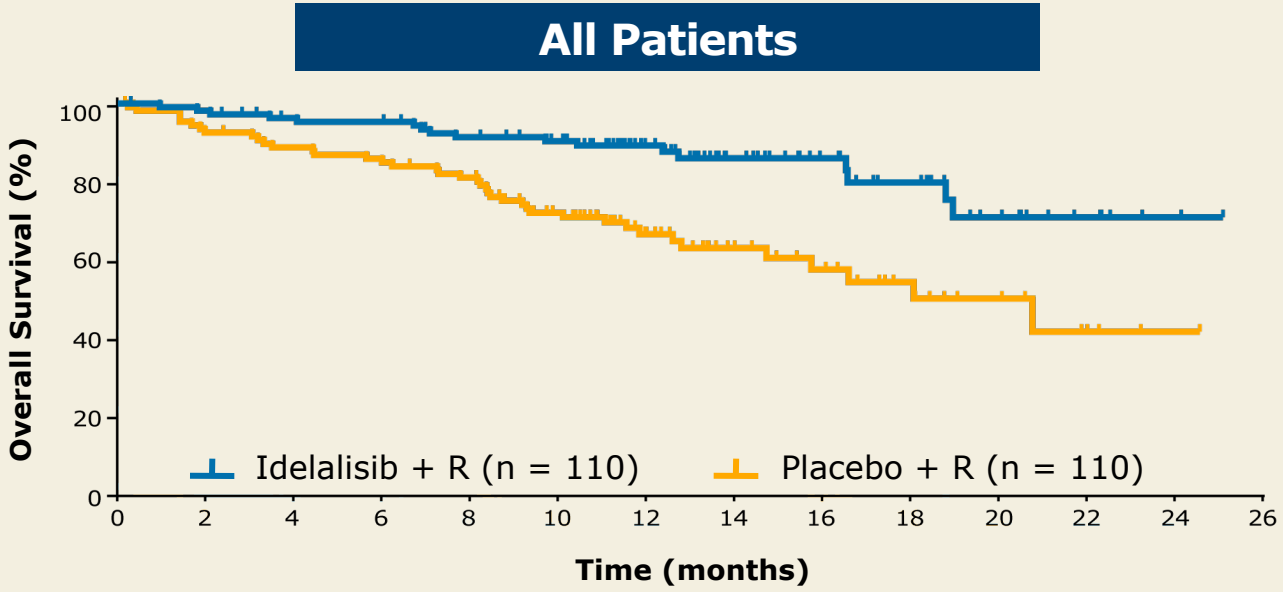
Subgroup Analysis of PFS: Idelalisib + R Arm

Median PFS*	**Mutated (n = 19)**	**Unmutated (n = 91)**	***p*-value**
IGHV	NR	19.4 mo	0.75
Median PFS*	**Present (n = 46)**	**Absent (n = 64)**	***p*-value**
Del(17p)/TP53 mut	16.6 mo	20.3 mo	0.94
Median PFS*	**Present (n = 25)**	**Absent (n = 36)**	***p*-value**
Del(11q)	20.3 mo	19.4 mo	0.84

* Including extension study

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

Overall Survival (OS) (Including Extension Study*)



	Median OS	HR	*p*-value
IDELA + R	NR	0.34	0.0001
PBO + R	20.8 mo		

* As randomized, including cross-over

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Subgroup Analysis of OS According to Treatment

Median OS*	**Idelalisib + R (n = 91)**	**Placebo + R (n = 93)**	***p*-value**
IGHV unmutated	NR	18.1 mo	0.0003
Median OS*	**Idelalisib + R (n = 46)**	**Placebo + R (n = 49)**	***p*-value**
Del(17p)/TP53 mut	NR	14.8 mo	0.001
Median OS*	**Idelalisib + R (n = 25)**	**Placebo + R (n = 23)**	***p*-value**
Del(11q)	NR	18.1 mo	0.21

* As randomized, including patients who crossed over

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

Select Grade ≥3 Adverse Events

Adverse event	Idelalisib + R (n = 110)		Placebo + R (n = 108)	
	2nd IA	Update	2nd IA	Update
Neutropenia	37%	41%	27%	43%
Thrombocytopenia	11%	14%	18%	20%
Increased ALT/AST	9%	6%	1%	6%
Pneumonia	8%	13%	9%	20%
Anemia	7%	8%	17%	24%
Diarrhea/colitis	6%	16%	0%	13%
Fatigue	5%	5%	3%	5%
Pyrexia	3%	6%	1%	3%
Dyspnea	3%	6%	3%	5%

IA = interim analysis

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

Author Conclusions

- In this Phase III trial, the subgroup analysis demonstrated comparable efficacy of idelalisib in combination with R in the presence or absence of high-risk genomic alterations such as unmutated IGHV, del(17p)/TP53 mutation and del(11q).
- Overall survival was significantly improved for patients who received idelalisib in combination with R, despite the allowance for patients to cross over in the extension study design.
- In combination with R, idelalisib has a manageable safety profile in patients with relapsed or refractory CLL.

Sharman JP et al. *Proc ASH* 2014;Abstract 330.

Investigator Commentary: Second Interim Analysis of a Phase III Trial of Idelalisib and R for Relapsed CLL

On the basis of the first interim analysis of this study, idelalisib was recently FDA approved in combination with R for patients with relapsed CLL for whom R alone would be considered an appropriate therapy because of comorbidities. This current analysis is an important contribution to the FDA approval. It suggests that idelalisib has activity in particular populations of patients expected to have poor outcomes. It is a subset analysis of a previously published Phase III study (Furman RR et al. *NEJM* 2014;370:997) that demonstrated that idelalisib/R was better than R alone for patients with CLL requiring therapy.

This analysis demonstrates that for most patients with complicated high-risk cytogenetics, the median PFS for those who received idelalisib has not been reached and is about 5 months with R alone. The authors concluded that the presence of del(17p) does not appear to significantly affect outcome for patients who received idelalisib/R. This is similar to what is seen with ibrutinib, at least with a relatively short follow-up. Overall, idelalisib is another tool in our toolbox for patients with CLL harboring the del(17p) abnormality.

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

Determination of Recommended Phase 2 Dose of Venetoclax (ABT-199/GDC-0199) Combined with Rituximab (R) in Patients with Relapsed/ Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)

Roberts AW et al.

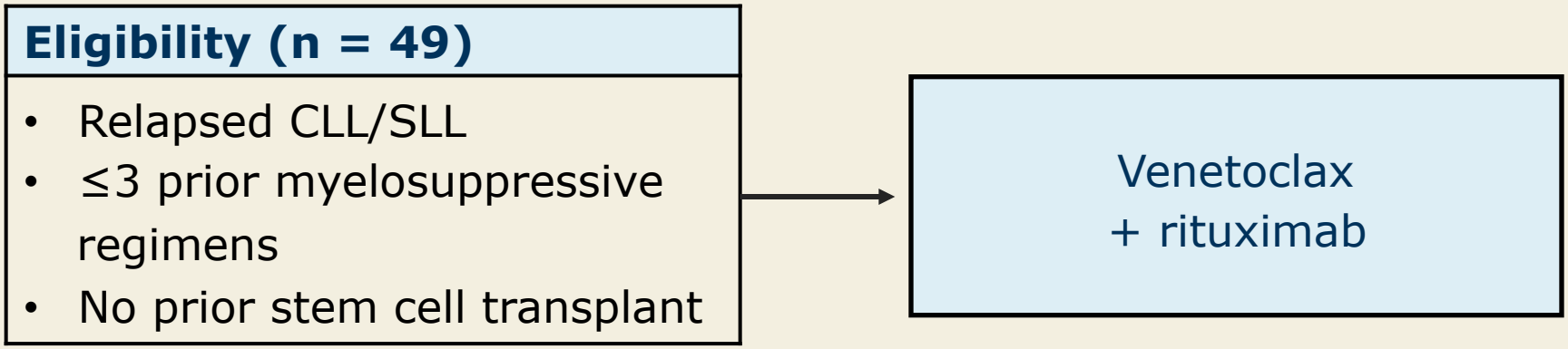
Proc ASH 2014;Abstract 325.

Background

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

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

Phase Ib Study Design



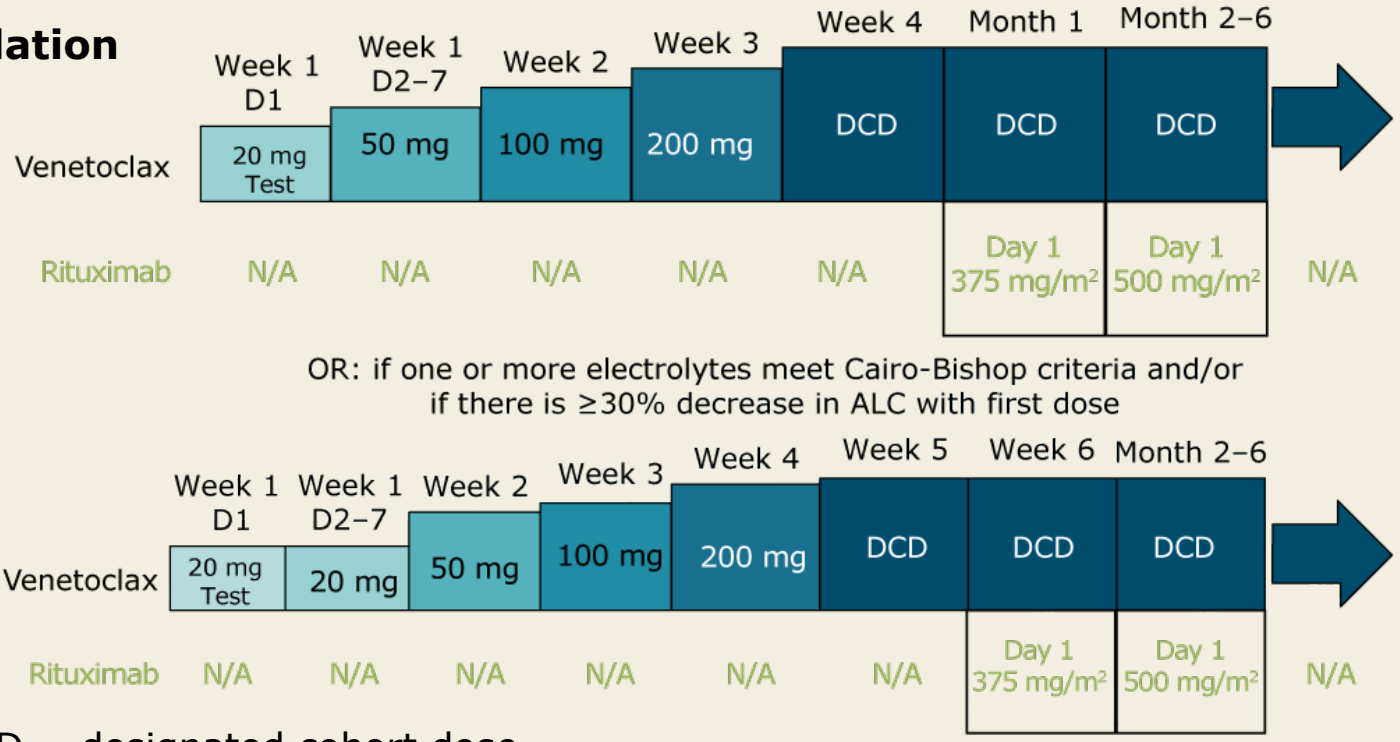
Primary endpoint: Safety, MTD, RPTD and dosing schedule

Secondary endpoints: Pharmacokinetics, efficacy

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

Dosing Schedule of Venetoclax and Rituximab

Final Escalation Strategy:



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

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

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Adverse Events (AEs)

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

* ≥20% of patients

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

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

Preliminary Efficacy Results

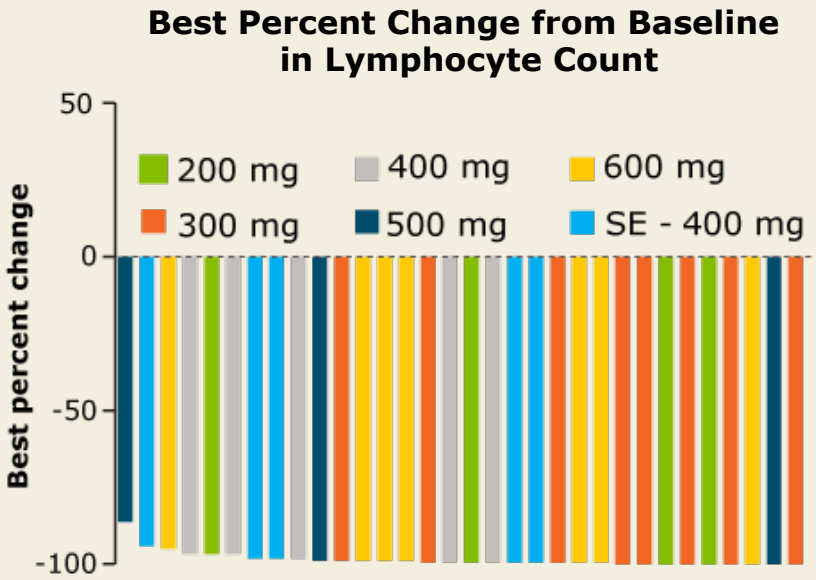
Response	All patients n = 49	Del(17p) n = 9
Overall response rate	88%	78%
Complete response (CR/CRi)	31%	22%
Partial response (PR)	45%	56%
PR unconfirmed*	12%	—
Stable disease	4%	11%

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

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

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

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



- 30/32 (94%) patients with baseline lymphocyte counts >5 x 10^9 had a reduction to <4 x 10^9 within 5 weeks of starting venetoclax

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

* As of October 7, 2014

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Bone Marrow MRD at 7 Months

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

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

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

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

Author Conclusions

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

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

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

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

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

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

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

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