# 5 Minute JournalClub

**POST-ASH** Issue 2, 2013

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# CME Information

**LEARNING OBJECTIVES**

- Appraise recent clinical research findings with lenalidomide/rituximab for patients with untreated indolent lymphoma and, where appropriate, counsel patients regarding participation in ongoing pivotal trials assessing this strategy.
- Evaluate the early efficacy and safety data with the anti-PD-1 monoclonal antibody pidilizumab (CT-011) for patients with relapsed/ refractory FL.
- Assess the benefits and risks of novel therapeutic approaches — PI3 kinase inhibitors, Btk inhibitors and chimeric antigen receptor T cells — under investigation in B-cell neoplasms and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Optimize outcomes for elderly patients with CLL through the application of emerging clinical research data.

**CREDIT DESIGNATION STATEMENT**

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# CME Information (Continued)

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**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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# CME Information (Continued)

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5 MinuteJournalClub

POST-ASH Issue 2, 2013

# ASH 2012 and the postrituximab era of new biologic treatments for B-cell neoplasms

Since the late 1990s rituximab (R) has been the major biologic agent integrated into management of B-cell cancers. However, these days some of the most cautious, evidence-based investigators are having a hard time hiding their enthusiasm for an array of emerging novel agents that are shaking up the non-Hodgkin lymphoma (NHL)/chronic lymphocytic leukemia (CLL) research database. On this second issue of our 7-part ASH highlights series, we profile several promising new strategies, including a few that MD Anderson's Dr Hagop Kantarjian believes may soon lead to CML-like long-term disease control in CLL. Here's an overview of what we learned in Atlanta:

## 1. Small-molecule B-cell receptor inhibitors: Ibrutinib (Ib) and idelalisib (GS-1101)

These oral, relatively nontoxic agents interfere with the B-cell receptor signaling pathway and have intriguing activity in CLL, follicular lymphoma (FL) and mantle-cell lymphoma (MCL). Perhaps the greatest excitement surrounds Ib,

an inhibitor of Bruton's tyrosine kinase, which is critical for proliferation and survival in most B-cell tumors. Ib was the subject of **2 spectacular CLL ASH papers**. The first was a Phase I-II monotherapy study of 116 patients that resulted in response rates Dr Bruce Cheson called "phenomenal" and exceeded 65% overall, including 12 of 24 patients with 17p and 11q deletions.

The second major related paper was a Phase II study evaluating the combination of Ib and R in 40 patients with previously treated high-risk CLL. I was struck by the title of the abstract, which states that this combination had "profound" activity. Given that description, the eye-popping waterfall plots, which pretty much all point south and included 13 patients with del 17p, were not that surprising. A highlight of this paper was the discussion of a patient who had primary resistance to FCR then hyper-CVAD and a number of other therapies but achieved a CR with Ib/R.

With regard to idelalisib, at ASH we saw findings from **a Phase I study** evaluating this PI3 kinase delta inhibitor combined with R and/or bendamustine (B) in 52 patients with relapsed/refractory (RR) CLL. PI3K delta is thought to drive proliferation and survival of malignant B cells, and as in many Phase I studies in this era of molecular-targeted treatment, most (about 80%) of the patients responded despite extensive prior treatments, including B and R. This well-tolerated combination approach is now being tested in Phase III trials.

## 2. Lenalidomide (len)

The first issue of this ASH series profiled immunomodulatory agents in multiple myeloma, including the newly approved pomalidomide, but this intriguing class of drugs clearly is also of great interest in B-cell cancers. The last several ASH meetings have included a number of presentations suggesting that len alone or with R ("R squared — $R^2$") has significant activity in CLL and NHL, and at the 2012 conference the good news continued.

Notably, Dr Nathan Fowler presented the final results of **a Phase II trial** of 110 patients with indolent lymphoma treated with the $R^2$ regimen. High rates of durable responses were observed, including CRs in 42/45 patients with FL who converted to PET negativity, and this encouraging data set and others have spawned a number of studies like the Phase III RELEVANCE trial comparing $R^2$ to chemotherapy/R, raising the possibility of a future world without chemotherapy for this disease.

**Another Phase II CLL study** evaluated a strategy now often used in myeloma, namely len maintenance, in this case for 12 months after BR induction. The encouraging median PFS of 24.3 months in 34 patients has led to interest in testing $R^2$ maintenance, an approach that is also the focus of a current ECOG MCL trial.

## 3. Other novel treatments: Chimeric antigen receptor (CAR) therapy, anti-PD-1

The spectacular science and clinical challenges of next-generation biologic therapy were on full display in a **paper profiling the use of CART19 cells** targeting the CD19 antigen, which is expressed on the surface of most B-cell

cancers. This Star Wars-like treatment involves gene transfer techniques to genetically modify T cells, which in this study was demonstrated to have rapid and potent antitumor activity in chemotherapy-refractory CD19-positive CLL and ALL. The development of a cytokine release syndrome in some cases is a signal for caution in this maybe revolutionary approach to immune-based treatment.

Similarly, while anti-PD-1 has gotten a lot of press across solid tumor oncology, this immunotherapeutic strategy is also under investigation in hematologic cancers. In this regard, an **early paper** reported encouraging results with the combination of R and the anti-PD-1 monoclonal antibody pidilizumab (CT-011) in patients with RR FL.

While ASH was a treasure trove of exciting papers on biologics, more is on the way, as witnessed by a recent press release concerning a large Phase III German CLL trial evaluating the glycoengineered, humanized type II CD20 antibody obinutuzumab (O; GA101) that reported an advantage to adding this agent to chlorambucil (CLB), but this is just an appetizer to the main dish — the comparison to R-CLB. R seems to have less activity in CLL than in many lymphomas, and the hope is that O will yield greater benefit.

Next on this ASH series — new data on myelofibrosis, a cancer that finally has effective but complex treatment options, including 2 key follow-up reports of landmark Phase III trials of ruxolitinib.

**Neil Love, MD**
**Research To Practice**
**Miami, Florida**

# A Phase 1 Study of the Selective Phosphatidylinositol 3-Kinase-Delta (PI3Kδ) Inhibitor, Idelalisib (GS-1101) in Combination with Rituximab and/or Bendamustine in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL)

**Coutre SE et al.**

*Proc ASH* 2012;Abstract 191.

# Background

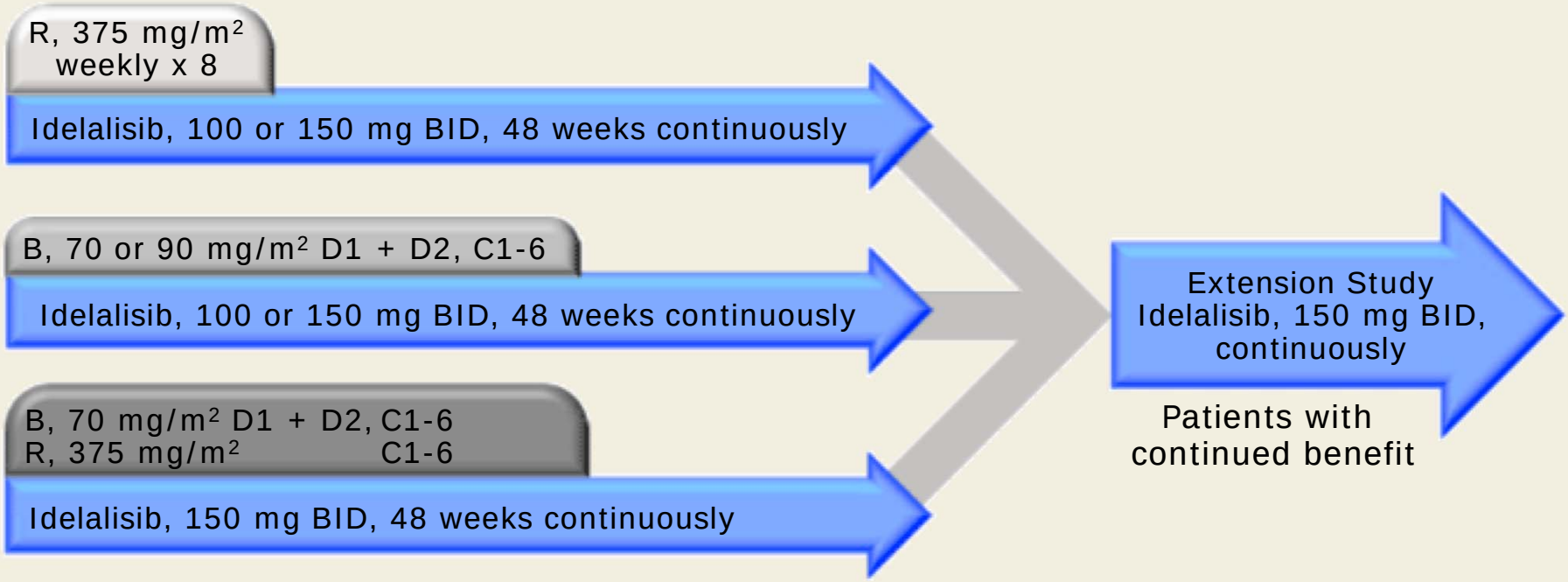
- CLL treatment regimens have substantial toxicity and are less effective with recurrent use.
- PI3Kδ drives proliferation, homing and survival of CLL cells (*Blood* 2010;116(12):2078).
- Monotherapy with idelalisib (GS-1101), an orally bioavailable small molecule inhibitor of PI3Kδ, has shown considerable activity in patients with heavily pretreated CLL (*Expert Opin Invest Drugs* 2012;21(1):15-22).
- **Study objective**: To evaluate the safety and efficacy of idelalisib in combination with rituximab (R) and/or bendamustine (B) for relapsed/refractory CLL.

Coutre SE et al. *Proc ASH* 2012;Abstract 191.

# Phase Ib Combination Study Design

**Eligibility (n = 52)**

Relapsed/refractory CLL requiring treatment by 2008 International Workshop on CLL criteria




Coutre SE et al. *Proc ASH* 2012;Abstract 191.

# Demographics and Baseline Characteristics

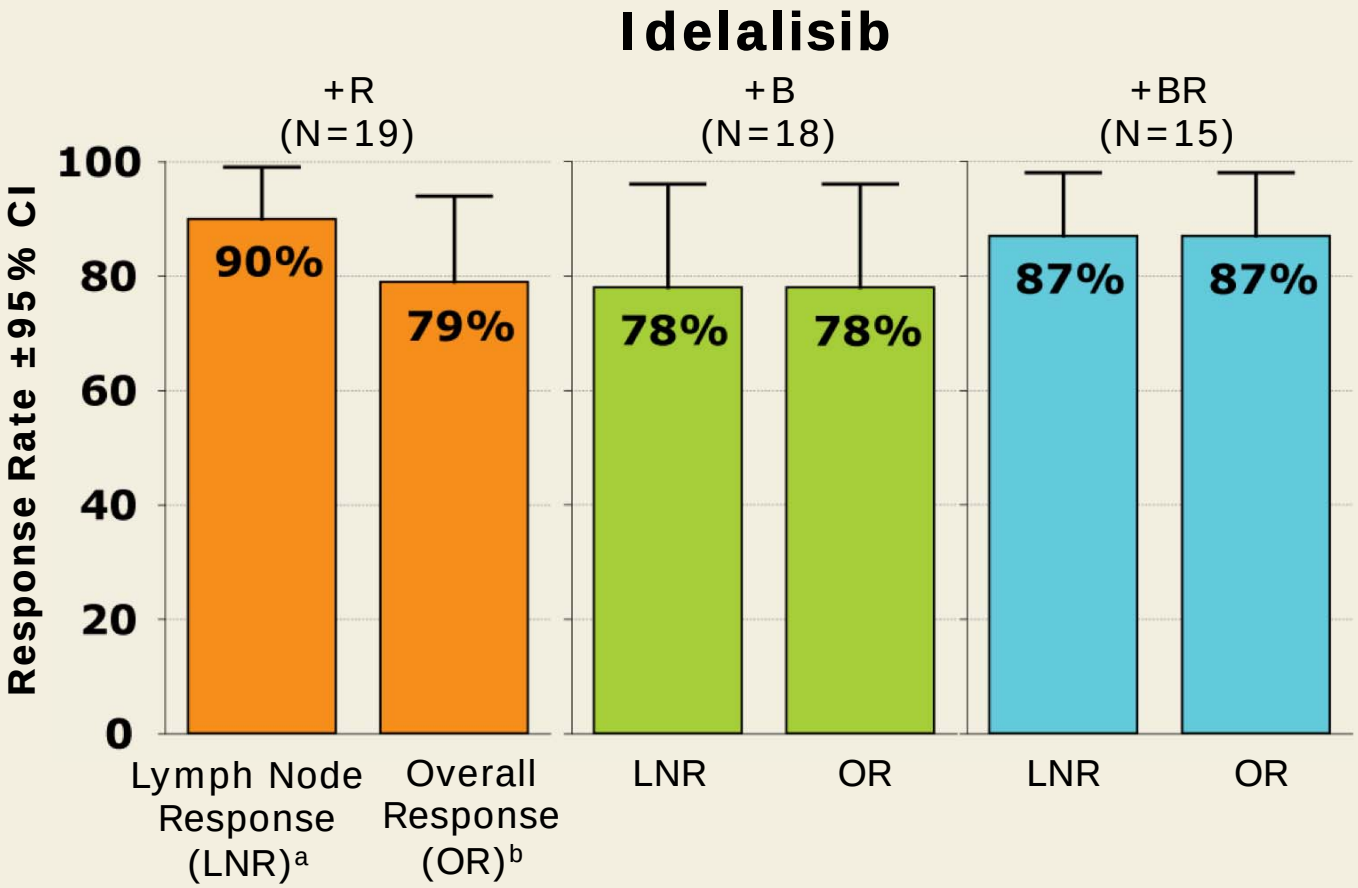
| | Combination | | | All (N = 52) |
|---|---|---|---|---|
| | Idelalisib + R (N = 19) | Idelalisib + B (N = 18) | Idelalisib + BR (N = 15) | |
| Age, median (range), years | 66 (54-87) | 64 (41-86) | 61 (45-72) | 64 (41-87) |
| Gender, males, % | 68 | 44 | 60 | 58 |
| Bulky adenopathy,[a] % | 58 | 61 | 67 | 62 |
| Refractory disease,[b] % | 37 | 72 | 47 | 52 |
| Prior therapies, median (range), n | 2 (1-8) | 3 (1-9) | 4 (1-9) | 3 (1-9) |

[a] Presence of ≥1 node with diameter ≥5 cm

[b] Progression within 6 months of last therapy

Coutre SE et al. *Proc ASH* 2012;Abstract 191.

# Nodal and Overall Response Rate (ITT Population)

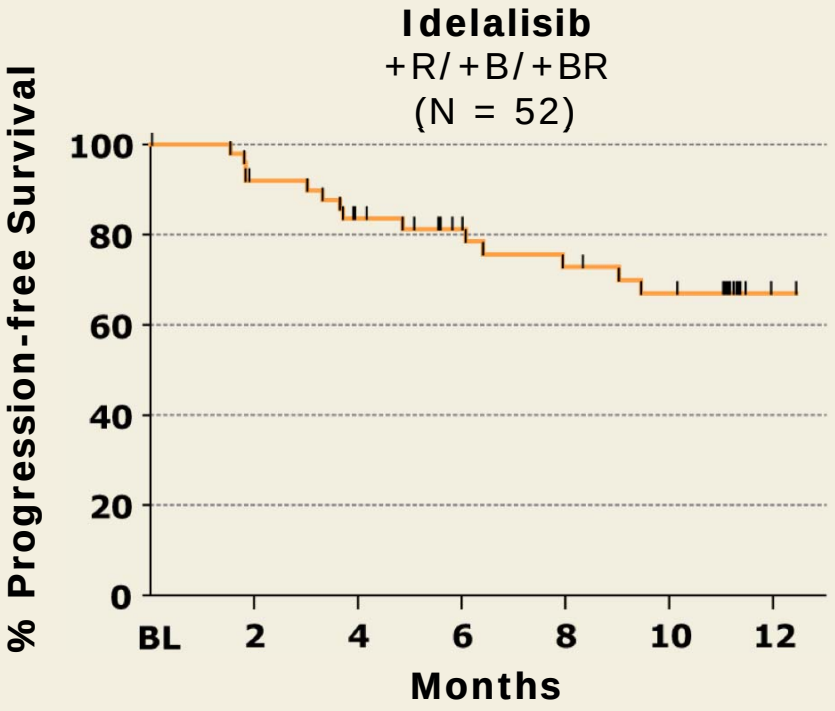



[a] Decrease by ≥50% in the nodal SPD [b] Response by 2008 IWCLL criteria

With permission from Coutre SE et al. *Proc ASH* 2012;Abstract 191.

# Progression-Free Survival (ITT Population)

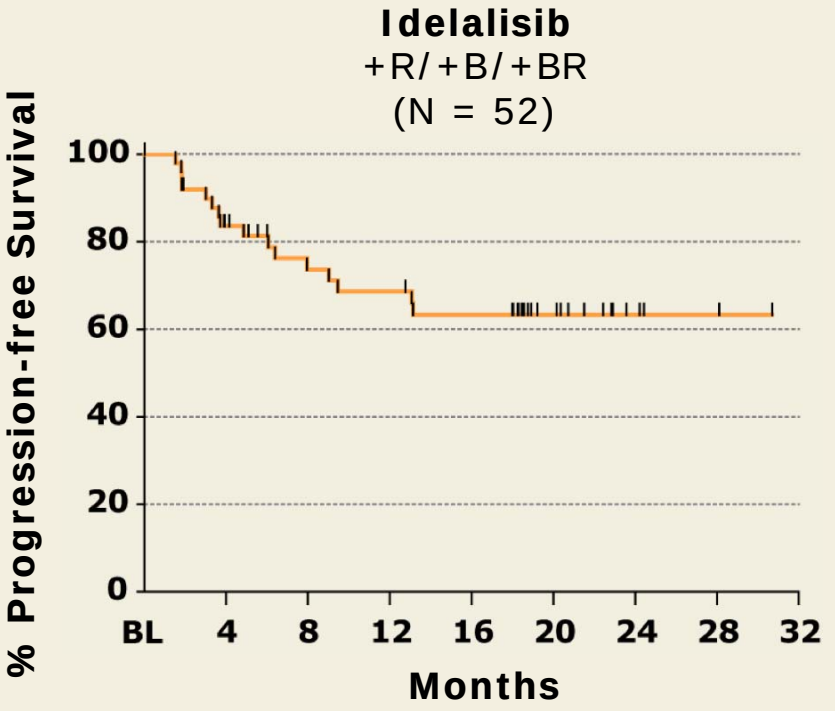
## Primary study




Median PFS: not reached

1-year PFS: 67.1%

## Primary + Extension study



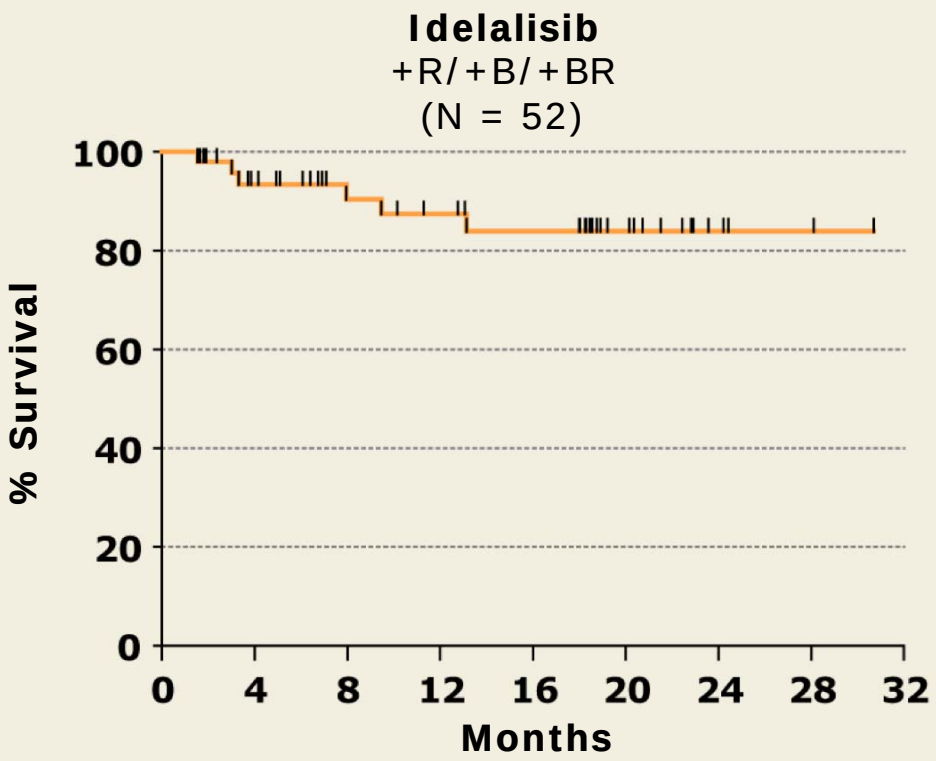

Median PFS: not reached

1-year PFS: 68.7%; 2-year PFS: 63.4%

With permission from Coutre SE et al. *Proc ASH* 2012;Abstract 191.

# Overall Survival (ITT Population)

## Primary + Extension study




Median OS: not reached

1-year OS: 87.5%; 2-year OS: 84.0%

With permission from Coutre SE et al. *Proc ASH* 2012;Abstract 191.

# Select Adverse Events (AEs)

| Grade ≥3 AEs* | (n = 52) |
|---|---|
| Febrile neutropenia | 15% |
| Pneumonia | 12% |
| Transaminase elevation | 10% |
| Diarrhea | 6% |
| Dyspnea | 4% |
| Pyrexia | 6% |

*Analysis of primary study

- AEs leading to drug discontinuation: abdominal pain (n = 1), autoimmune hemolytic anemia (n = 1), febrile neutropenia (n = 1), neutropenia (n = 1), pneumonia (n = 1), pneumonitis (n = 1), rash erythematous (n = 1), sepsis (n = 1)

Coutre SE et al. *Proc ASH* 2012;Abstract 191.

# Author Conclusions

- A lack of overlapping toxicities allowed idelalisib delivery at the full single-agent starting dose (150 mg BID) when coadministered with rituximab (R), bendamustine (B) or bendamustine/rituximab (BR).
- Idelalisib was generally well tolerated in combination therapy over periods of exposure up to 2½ years.
- Idelalisib combination therapy was highly active in patients with heavily pretreated CLL.
- Combinations of idelalisib with BR and R for the treatment of relapsed/refractory CLL are currently being evaluated in Phase III trials (GS-US-312-0115 and -0116).

Coutre SE et al. *Proc ASH* 2012;Abstract 191.

## Investigator Commentary: Idelalisib (GS-1101) in Combination with Rituximab and/or Bendamustine for Patients with Relapsed or Refractory CLL

Idelalisib is an oral, specific PI 3-kinase delta isoform inhibitor that has been quite active as a single agent in Phase I trials involving a variety of histologies, including CLL. It is well tolerated except for some transaminitis. The authors of this Phase I study took the next step of evaluating idelalisib and rituximab or bendamustine or the combination. The study enrolled about 50 patients with refractory CLL, of whom about half had bulky disease. Patients had received a median of about 3 prior regimens. All 3 combinations evaluated were active and well tolerated. Response rates and 1-year progression-free survival were much higher than one would have expected with idelalisib alone. It's difficult to ascertain from the small numbers of patients whether one of the doublets is better than another, but it would be nice if rituximab/idelalisib was as good as the others, with the goal of being able to eliminate chemotherapy. It could be another example of an exciting doublet of biological targeted agents that are as good as or at least almost as good as combining the agent with chemotherapy.

***Interview with Bruce D Cheson, MD, January 14, 2013***

**The Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Promotes High Response Rate, Durable Remissions, and is Tolerable in Treatment-Naïve (TN) and Relapsed or Refractory (RR) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Patients Including Patients with High-Risk (HR) Disease: New and Updated Results of 116 Patients in a Phase Ib/II Study[1]**

**The Btk Inhibitor Ibrutinib in Combination with Rituximab (iR) is Well Tolerated and Displays Profound Activity in High-Risk Chronic Lymphocytic Leukemia (CLL) Patients[2]**


**[1]Byrd JC et al.**
*Proc ASH* 2012;Abstract 189.

**[2]Burger JA et al.**
*Proc ASH* 2012;Abstract 187.

# The Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) Promotes High Response Rate, Durable Remissions, and is Tolerable in Treatment-Naïve (TN) and Relapsed or Refractory (RR) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Patients Including Patients with High-Risk (HR) Disease: New and Updated Results of 116 Patients in a Phase Ib/II Study

**Byrd JC et al.**

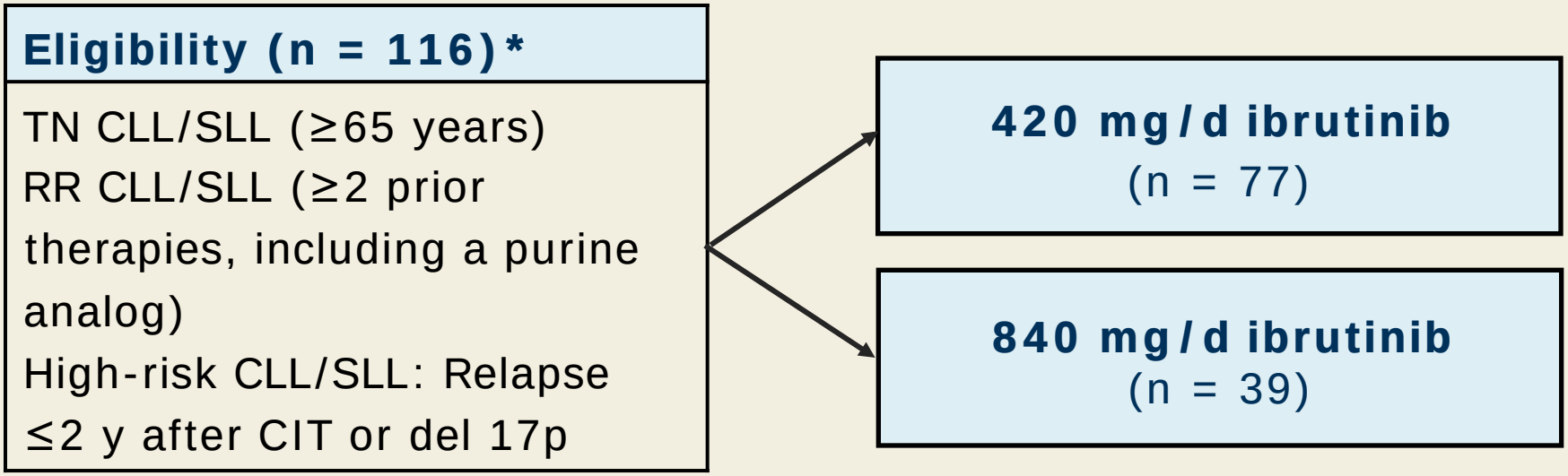
*Proc ASH* 2012;Abstract 189.

# Background

- Although fludarabine-based chemoimmunotherapy (CIT) is effective, it is not well tolerated by elderly patients (pts) and nearly all patients experience relapse after fludarabine-based CIT.
- Ibrutinib is an oral inhibitor of BTK, an essential mediator of B-cell receptor signaling, that promotes apoptosis and inhibits proliferation, migration and adhesion in CLL cells (*Blood* 2012;119:1182).
- Recent Phase I study results with ibrutinib demonstrated high response rates in pts with RR B-cell lymphoma and CLL (*J Clin Oncol* 2013;31:88).
- **Study objective:** To evaluate the efficacy and safety of ibrutinib monotherapy at 2 different doses for patients with TN and RR CLL or SLL.

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

# Phase Ib/II Trial Design




* Patients were divided into 5 cohorts between the 2 dosing regimens.

- **Primary endpoint:** Safety
- **Secondary endpoints:** Efficacy, pharmacokinetic/pharmacodynamic (PK/PD) analysis and long-term safety

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

# Patient Cohorts (Abstract Only)

| Cohort | Population with CLL/SLL | Dose | n |
|---|---|---|---|
| 1 | Relapsed or refractory | 420 mg/d | 27 |
| 2 | TN (≥65 years) | 420 mg/d | 26 |
| 3 | Relapsed or refractory | 840 mg/d | 34 |
| 4 | High-risk | 420 mg/d | 24 |
| 5 | TN (≥65 years) | 840 mg/d | 5* |

* Cohort was closed prior to full accrual after comparable activity and safety between doses was observed with patients with RR disease

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

# Best Response by Cohort (Abstract Only)

| Response rate | Cohorts 2 & 5 (n = 31) | Cohorts 1 & 3 (n = 61) | Cohort 4 (n = 24) |
|---|---|---|---|
| ORR | 71% | 67% | 50% |
| CR | 10% | 3% | 0% |
| PR | 61% | 64% | 50% |
| PR with lymphocytosis | 10% | 20% | 29% |
| Stable disease | 13% | 5% | 8% |
| Progressive disease | 0% | 2% | 4% |
| Not evaluable | 6% | 7% | 8% |

ORR = overall response rate; CR = complete response; PR = partial response

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

# Survival Rates (Abstract Only)

| **Patients with RR or high-risk disease** | **n = 85** |
|---|---|
| Estimated 22-month progression-free survival (PFS) | 76% |
| Estimated 22-month overall survival (OS) | 85% |
| **Patients with TN disease (≥65 years)** | **n = 31** |
| Estimated 22-month PFS | 96% |
| Estimated 22-month OS | 96% |

- Median PFS and OS have not been reached for any of the 5 cohorts.
- Responses were independent of poor-risk factors, including advanced disease, prior lines of therapy, beta-2 microglobulin or cytogenetics.

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

# Clinical Observations (Abstract Only)

- Serial evaluation of serum immunoglobulins (Ig) revealed:
  - A significant increase in IgA at 3, 6 and 12 months ($p < 0.005$).
  - No decline in IgG and IgM.
- 56/69 patients with relapsed disease with wild-type IgVH developed treatment-related lymphocytosis.
  - Median time to normalization: 6.2 months
- 11/11 patients with mutated IgVH developed treatment-related lymphocytosis.
  - Median time to normalization: 14.8 months
- Lymphocytosis was normalized at a higher frequency in patients with wild-type versus mutated IgVH (86% vs 55%; $p < 0.04$).

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

# Select Adverse Events (Abstract Only)

| Grade ≤2 Adverse Events (AEs) | n = 116 |
|---|---|
| Diarrhea | 54% |
| Fatigue | 29% |
| Upper respiratory tract infection | 29% |
| Rash | 28% |
| Nausea | 26% |
| Arthralgia | 25% |

- Treatment discontinuation due to AEs: 6%
- Hematologic AEs ≥Grade 3 were infrequent
- No evidence of cumulative toxicity or long-term safety concerns after a median follow-up of 16 months

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

# Author Conclusions (Abstract Only)

- Ibrutinib monotherapy is highly active, well tolerated and induces durable remissions in patients with RR and high-risk CLL and in elderly patients with treatment-naïve CLL.
- Based on these results, a Phase III study of ibrutinib in these populations of patients is warranted.

Byrd JC et al. *Proc ASH* 2012;Abstract 189.

# The Btk Inhibitor Ibrutinib in Combination with Rituximab (iR) is Well Tolerated and Displays Profound Activity in High-Risk Chronic Lymphocytic Leukemia (CLL) Patients

**Burger JA et al.**

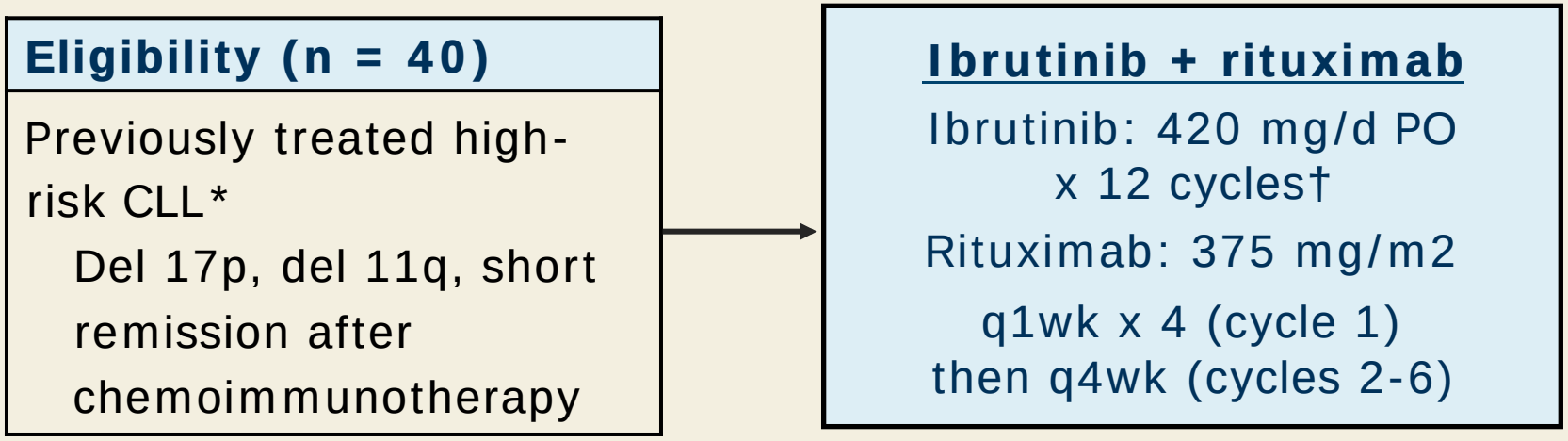
*Proc ASH* 2012;Abstract 187.

# Background

- Currently, there is no standard treatment for patients with high-risk CLL, whose disease has shorter remissions and a poor outcome with conventional CIT.
- Single-agent ibrutinib elicits a good response in patients with high-risk CLL (*Proc ASH* 2011;Abstract 983).
- However, treatment of CLL with single-agent ibrutinib often results in delayed responses or stable disease due to the development of persistent lymphocytosis.
- **Study objective:** To evaluate the activity and tolerability of ibrutinib/rituximab combination therapy for high-risk CLL.

Burger JA et al. *Proc ASH* 2012;Abstract 187.

# Phase II Trial Design

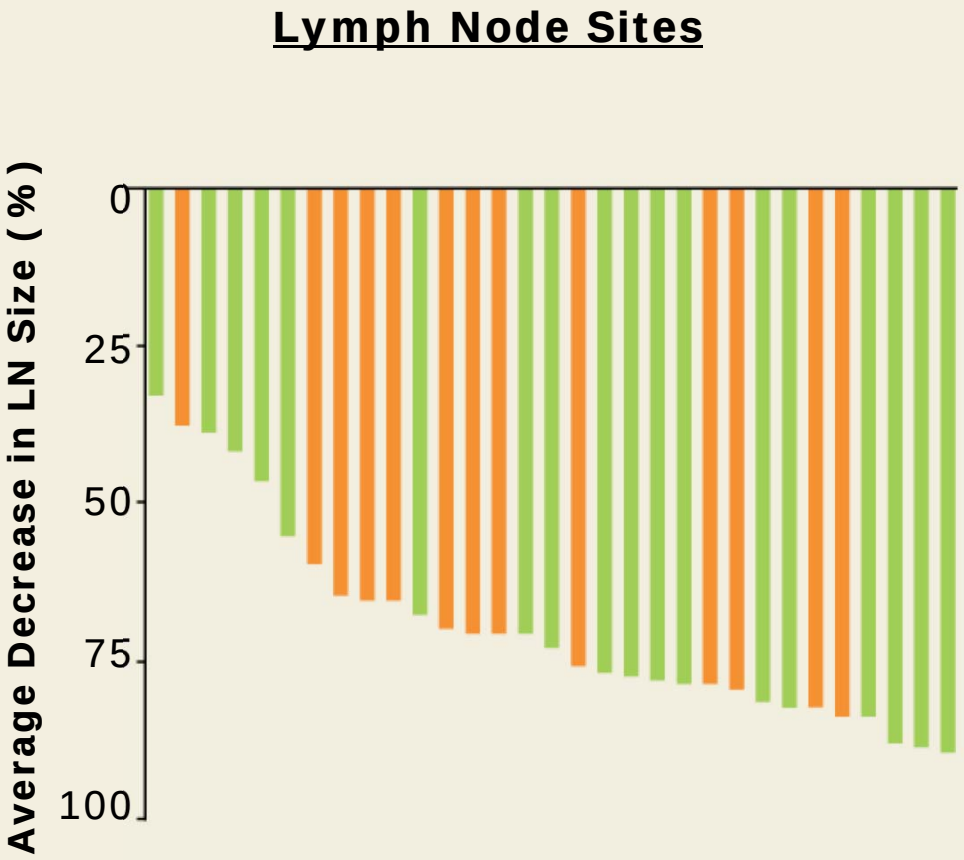


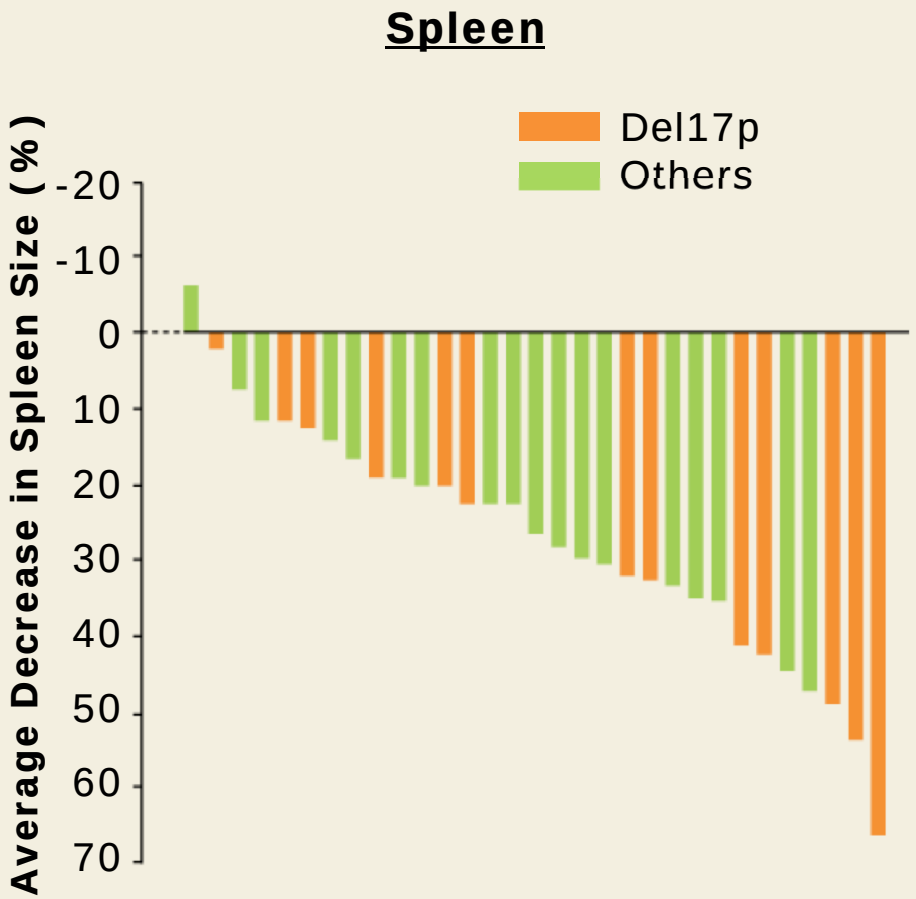

* Patients with untreated CLL with del 17p or mutant TP53 were eligible.

† Patients with benefit after cycle 12 were allowed to continue receiving single-agent ibrutinib.

Burger JA et al. *Proc ASH* 2012;Abstract 187.

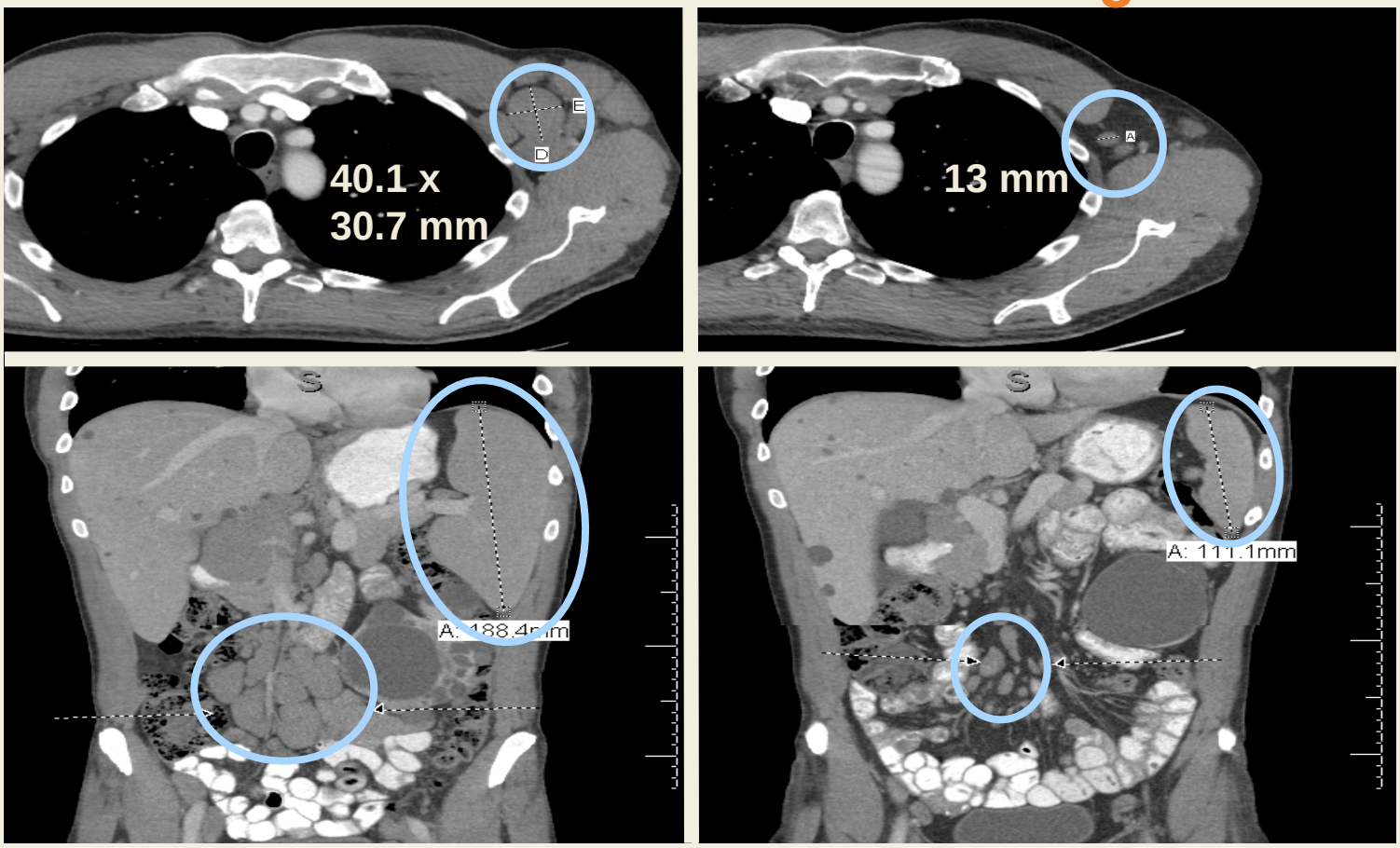
# Assessment by Computed Tomography (CT) at 3-6 Months (n = 31)




With permission from Burger JA et al. *Proc ASH* 2012;Abstract 187.

# Radiographic Response to Ibrutinib/ Rituximab Therapy




Axillary lymphadenopathy, abdominal nodes and splenomegaly all regressed during therapy.

With permission from Burger JA et al. *Proc ASH* 2012;Abstract 187.

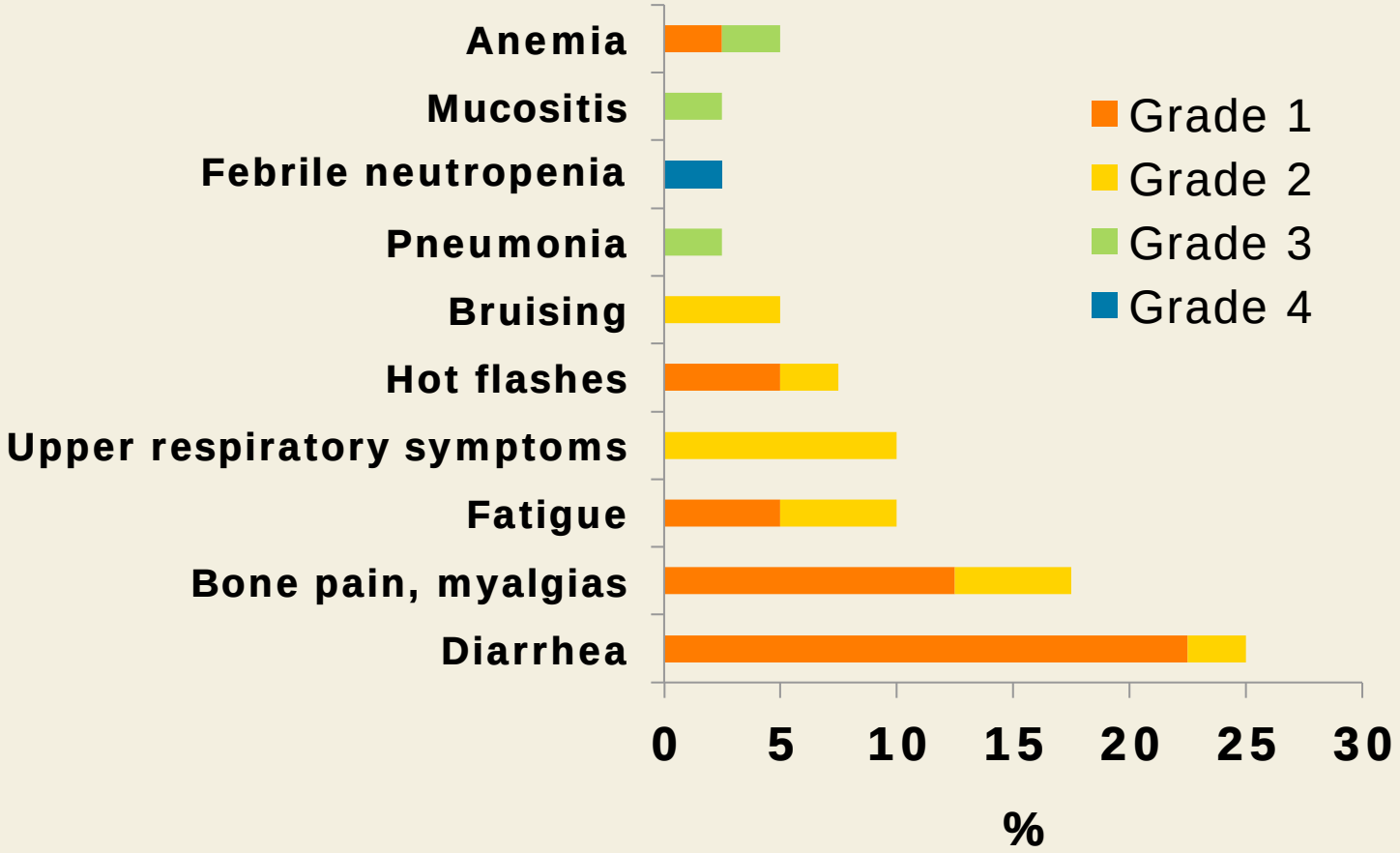
# Response Rates at 3-6 Months

| Response | n = 40 |
|---|---|
| Overall response rate | 83% |
| Complete response | 3% |
| Partial response (PR) | 80% |
| PR with persistent lymphocytosis | 8% |
| Stable disease | 5% |

It was too early for assessments for 2 patients.

Burger JA et al. *Proc ASH* 2012;Abstract 187.

# Adverse Events




Discontinuation of therapy due to aspergillosis (n = 1), oral ulcers (n = 1)

With permission from Burger JA et al. *Proc ASH* 2012;Abstract 187.

# Author Conclusions

- The combination of ibrutinib with rituximab demonstrated profound activity in patients with high-risk CLL.
  - ORR: >80%
  - Favorable toxicity profile with no hematologic toxicities observed
- The addition of rituximab to ibrutinib therapy may accelerate response in comparison to single-agent ibrutinib.
- However, the duration of remission in addition to the long-term side effects of combining ibrutinib with rituximab are unknown.
- Ibrutinib alone or in combination with rituximab should be rapidly developed for the treatment of high-risk CLL.

Burger JA et al. *Proc ASH* 2012;Abstract 187.

## Investigator Commentary: Efficacy and Tolerability of the BTK Inhibitor Ibrutinib (PCI-32765) Alone and in Combination with Rituximab for Patients with CLL

Dr Byrd presented the single-agent ibrutinib data for patients with TN, RR or high-risk CLL and the response rates were phenomenal. Overall response rate (ORR) in the untreated cohort was more than 70% and was 67% in the RR population. ORR for patients at high risk — those with 17p deletion or with an extremely short initial response to treatment — was 50%. Another striking feature of this study was the progression-free survival (PFS) numbers — for patients with TN CLL it was more than 90% and for those with RR disease it was more than 70%. Even for those patients with 17p deletion, PFS was in the 50% to 60% range. We've never seen responses like those in that patient population.

The next logical step was to combine this agent with rituximab. A presentation by Dr Burger reported an early response assessment for this combination in a small number of patients with high-risk CLL. The ORR was 83% with a relatively short follow-up, but they were astounding results nonetheless. You're combining a pill with rituximab, and more than 80% of patients respond and the combination is well tolerated.

***Interview with Bruce D Cheson, MD, January 14, 2013***

# Lenalidomide and Rituximab for Untreated Indolent Lymphoma: Final Results of a Phase II Study

**Fowler NH et al.**

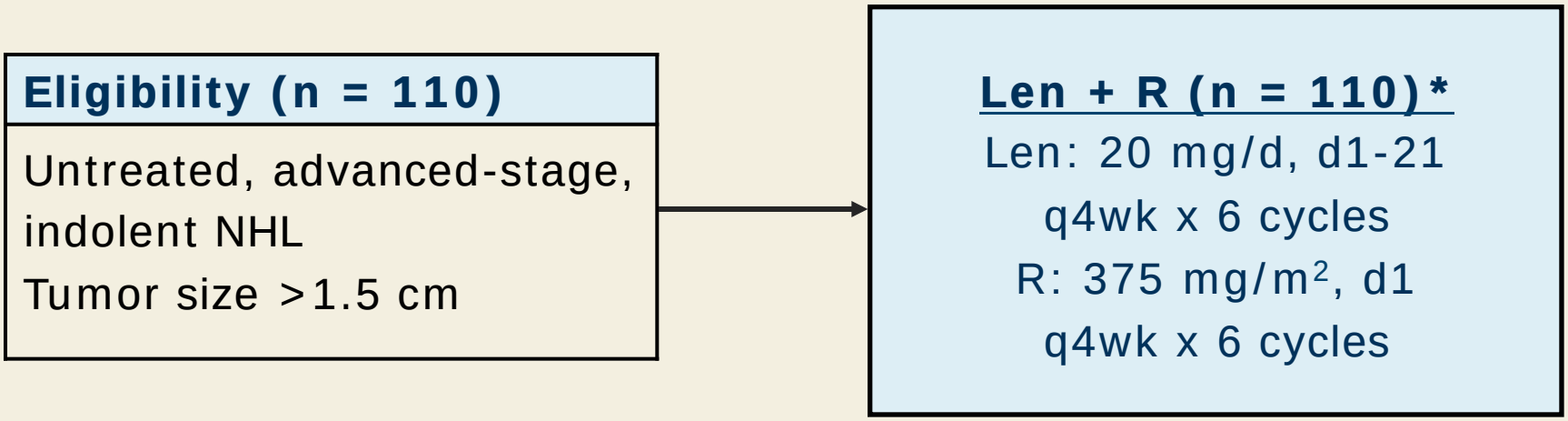
*Proc ASH* 2012;Abstract 901.

# Background

- Single-agent lenalidomide (Len) is active in relapsed, indolent non-Hodgkin lymphoma (NHL) while rituximab (R), alone or in combination with chemotherapy, is effective in untreated indolent lymphoma (*J Natl Compr Canc Netw* 2010;(8 Suppl 6):1).
- Preclinical studies using NHL cells suggested that Len may promote natural killer-cell function when R is present (*Clin Cancer Res* 2005;11:5984).
- **Study objective:** To evaluate the efficacy and safety of Len in combination with R for patients with untreated, advanced-stage indolent NHL

Fowler NH et al. *Proc ASH* 2012;Abstract 901.

# Phase II Trial Design




* Patients with evidence of tumor response could continue treatment for up to 12 cycles.

- To reduce the incidence of tumor flare, patients with small lymphocytic lymphoma (SLL) received Len (10 mg/d), with monthly dose escalation.
- Response was assessed every 3 cycles using the 1999 International Working Group Response criteria.

Fowler NH et al. *Proc ASH* 2012;Abstract 901.

# Best Response Rates (Abstract Only)

| By histology | SLL (n = 30) | MZL (n = 27) | FL (n = 46) | ALL* (n = 103) |
|---|---|---|---|---|
| Overall response rate | 80% | 89% | 98% | 90% |
| CR/CRu | 27% | 67% | 87% | 64% |
| Partial response | 53% | 22% | 11% | 26% |
| Stable disease | 13% | 11% | 2% | 8% |
| Progressive disease | 7% | 0% | 0% | 2% |

* All evaluable patients

MZL = marginal zone lymphoma; FL = follicular lymphoma; CR = complete response; CRu = CR unconfirmed

Fowler NH et al. *Proc ASH* 2012;Abstract 901.

# Clinical Outcomes (Abstract Only)

| Survival rates | % |
|---|---|
| Estimated 2-year progression-free survival* | |
| All evaluable patients (n = 103) | 83% |
| Evaluable patients with FL (n = 46) | 89% |

* Median follow-up = 22 months

- 42/45 (93%) patients with FL and a positive PET scan prior to therapy attained a complete metabolic response after treatment.
- For patients with FL, responses were high regardless of FLIPI score, tumor bulk or GELF criteria at study entry.
- At the end of therapy, almost all patients with FL demonstrated molecular response with the absence of detectable BCL-2 by PCR.

Fowler NH et al. *Proc ASH* 2012;Abstract 901.

# Select Adverse Events (Grade ≥3) (Abstract Only)

| Hematologic | % |
|---|---|
| Neutropenia | 40% |
| Thrombocytopenia | 4% |
| **Nonhematologic** | **n** |
| Rash | 8 patients |
| Muscle pain | 7 patients |
| Fatigue | 3 patients |
| Thrombosis | 3 patients |

- There were 2 episodes of neutropenic fever.
- Patients discontinuing treatment due to adverse events = 6

Fowler NH et al. *Proc ASH* 2012;Abstract 901.

# Author Conclusions

- The combination of Len with R therapy is active and tolerable in patients with untreated indolent lymphoma.
- In patients with follicular lymphoma, Len in combination with R demonstrated high complete response rates with durable remissions.
- Based on these results, randomized studies comparing this treatment schedule to traditional combination chemotherapy regimens are underway (RELEVANCE, NCT01650701).

Fowler NH et al. *Proc ASH* 2012;Abstract 901.

## Investigator Commentary: Final Results of a Phase II Trial of Lenalidomide and Rituximab for Untreated Indolent Lymphoma

This trial of lenalidomide in combination with rituximab produced an overall response rate (ORR) of 90% for all patients, including about two thirds achieving a CR. The most exciting results were observed in patients with FL on the basis of PET scans, with an ORR and CR of 98% and 87%, respectively. These appear to be somewhat durable. In fact the estimated 2-year PFS was over 80% for all patients and 90% for FL.

The so-called R-squared regimen will be compared head to head with chemotherapy/rituximab or chemoimmunotherapy in the Phase III RELEVANCE trial, in which physicians can choose from R-CHOP, R-CVP or R-bendamustine with a 1:1 randomization of patients to therapy. RELEVANCE is an international study with the potential to change how we approach patients with FL. Although we don't know if the R-squared regimen is more effective than rituximab alone for patients with untreated disease, we know that rituximab alone produces about a 50% to 75% response rate at best, lasting for a median of about 18 months. However, the R-squared regimen yields response rates into the mid- to high 90s that appear to be lasting longer. This is the rationale for the randomized RELEVANCE trial evaluating how it compares to other effective regimens.

***Interview with Bruce D Cheson, MD, January 14, 2013***

# Bendamustine + Rituximab (BR) Chemoimmunotherapy and Maintenance Lenalidomide in Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL): A Wisconsin Oncology Network (WON) Study

**Chang JE et al.**

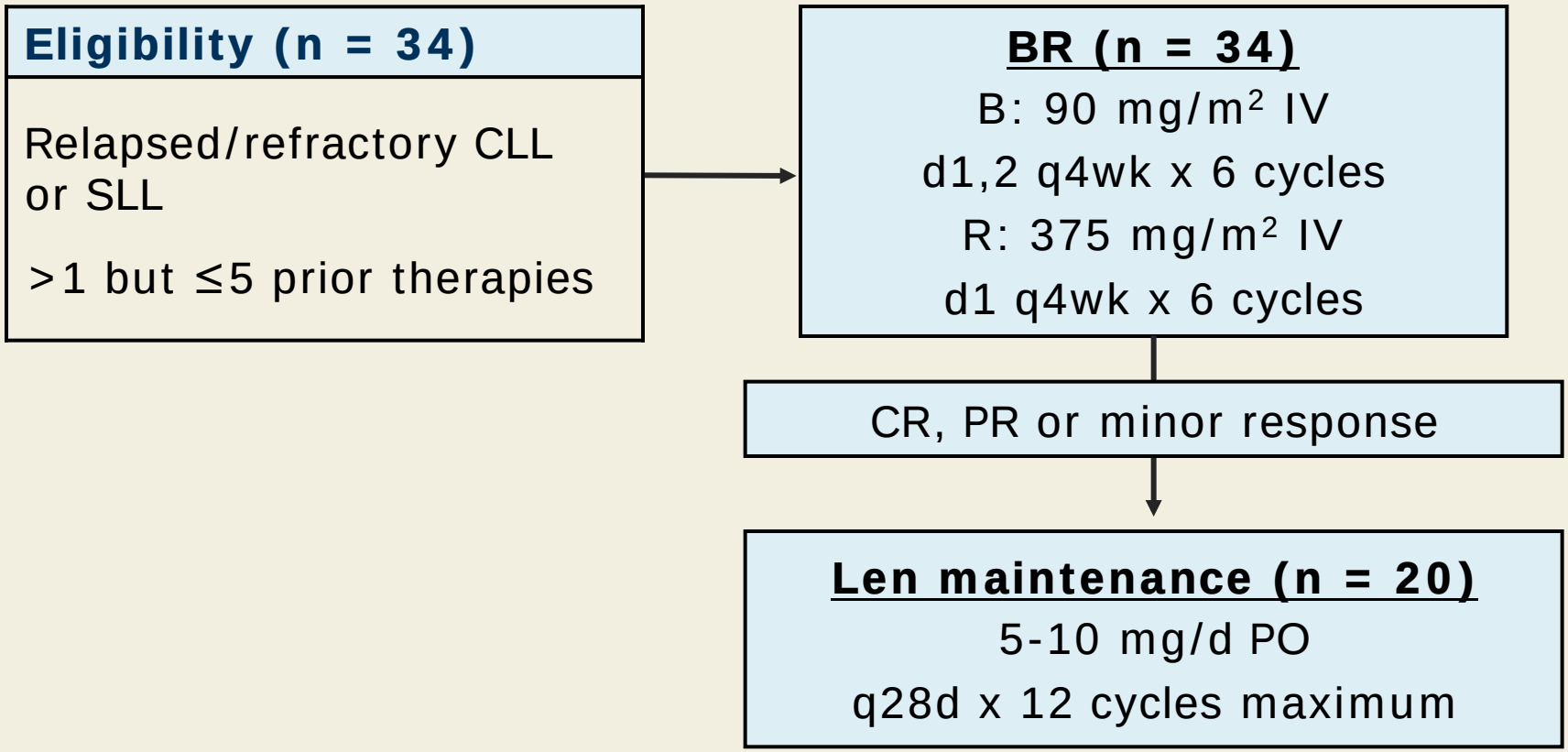
*Proc ASH* 2012;Abstract 3647.

# Background

- Previously, bendamustine/rituximab (BR) demonstrated clinical activity with an acceptable toxicity profile in R/R CLL (*J Clin Oncol* 2011;29(26):3559).
- Lenalidomide (Len) has demonstrated single-agent activity in R/R CLL (*Blood* 2008;111(11):5291).
  - Len at 10-25 mg/d resulted in an overall response rate of 31% among patients with R/R CLL with adverse prognostic indicators of 11q or 17p deletion.
- A continuous Len dosing schedule may be advantageous because rebound lymphocytosis during dosing breaks has been reported previously (*J Clin Oncol* 2011;29:1175).
- **Study Objective:** To assess whether maintenance Len after induction therapy with BR improves efficacy in R/R CLL and SLL.

Chang JE et al. *Proc ASH* 2012;Abstract 3647.

# WON Trial Design




- **Primary endpoint:** Progression-free survival (PFS)

Chang JE et al. *Proc ASH* 2012;Abstract 3647.

# Survival Outcomes (Median Follow-Up 20.1 Months)

| Outcome | n = 34 |
|---|---|
| Median PFS | 24.3 months |
| Median overall survival (OS) | 27.9 months |

- No significant difference in PFS based on patients with known cytogenetic risk profiling (n = 22)
  - Normal, trisomy 12 or 13q deletion vs 17p or 11q deletion ($p$ = 0.85)
- Comparison of outcomes in patients with 17p or 11q deletions (n = 11) vs patients without adverse cytogenetics (n = 11):
  - No difference in PFS ($p$ = 0.95) or OS ($p$ = 0.52)

Chang JE et al. *Proc ASH* 2012;Abstract 3647.

# Response Rates

| Response to induction BR therapy | n = 34* |
|---|---|
| ORR | 65% |
| CR | 18% |
| PR | 47% |
| Stable disease | 21% |
| **Subset analysis (known 11q or 17p deletion)** | **n = 11** |
| ORR | 55% |
| CR | 9% |
| PR | 45% |

* Nonevaluable patients (n = 3): 2 due to death from toxicity during cycle 1, 1 off study due to cytomegalovirus (CMV) infection during cycle 2

Chang JE et al. *Proc ASH* 2012;Abstract 3647.

# Select Adverse Events (AEs) During Induction Therapy*

| Hematologic AEs | Grade 3 (no.) | Grade 4 (no.) |
|---|---|---|
| Leukopenia | 5 | 5 |
| Neutropenia | 6 | 14 |
| Anemia | 1 | — |
| Thrombocytopenia | 5 | 2 |
| **Nonhematologic AEs** | | |
| Febrile neutropenia | 4 | — |
| Infections with neutropenia | 1 | — |

* Worst-grade toxicity per patient

- Dose modification was required for 14 patients due to neutropenia (12/14), thrombocytopenia (3/14) and weight loss/failure to thrive (3/14).

Chang JE et al. *Proc ASH* 2012;Abstract 3647.

# Author Conclusions

- BR induction resulted in an ORR that is comparable to that observed by the German CLL Study Group (65% vs 59%) (*J Clin Oncol* 2011;29(26):3559).
- ORR for patients with known adverse cytogenetics (11q and 17p deletions) was comparable to historical controls.
- This study demonstrated a longer PFS (24.3 vs 14.7 months), suggesting that Len maintenance may improve the duration of response.
- Based on these results, a future study of induction BR followed by Len + R maintenance therapy has been planned with B dosing at 70 mg/m$^2$. Further dose escalation of Len beyond 10 mg/d may not be possible in the maintenance setting.

Chang JE et al. *Proc ASH* 2012;Abstract 3647.

## Investigator Commentary: WON Study — Bendamustine/Rituximab (BR) Followed by Lenalidomide Maintenance in Relapsed/Refractory CLL and SLL

BR is becoming one of the more popular regimens for the front-line treatment of CLL. This group administered BR to patients with relapsed/refractory disease with the aim of prolonging the duration of response with lenalidomide maintenance. It is an interesting and reasonable concept of trying to make chemotherapy more effective. When compared to historical controls, the response rates were not much better but the durability of responses appeared to be longer. A modest amount of toxicity was associated with this regimen, including neutropenia, febrile neutropenia and thrombocytopenia. The ORR was about 65%, and about 20% of patients achieved a CR. However, the problem is that BR is increasingly being administered up front, and fewer patients will have this as an option in the relapsed setting.

The CLL10 trial of front-line FCR versus BR has been completed, and hopefully the data will be available by the next ASH meeting. This has the potential to change the "chemotherapy landscape." However, with the data on agents like ibrutinib, idelalisib and ABT-199, chemotherapy may not be of interest to anyone in the future.

***Interview with Bruce D Cheson, MD, January 14, 2013***

# Chimeric Antigen Receptor T Cells Directed Against CD19 Induce Durable Responses and Transient Cytokine Release Syndrome in Relapsed, Refractory CLL and ALL

**Porter DL et al.**

*Proc ASH* 2012;Abstract 717.

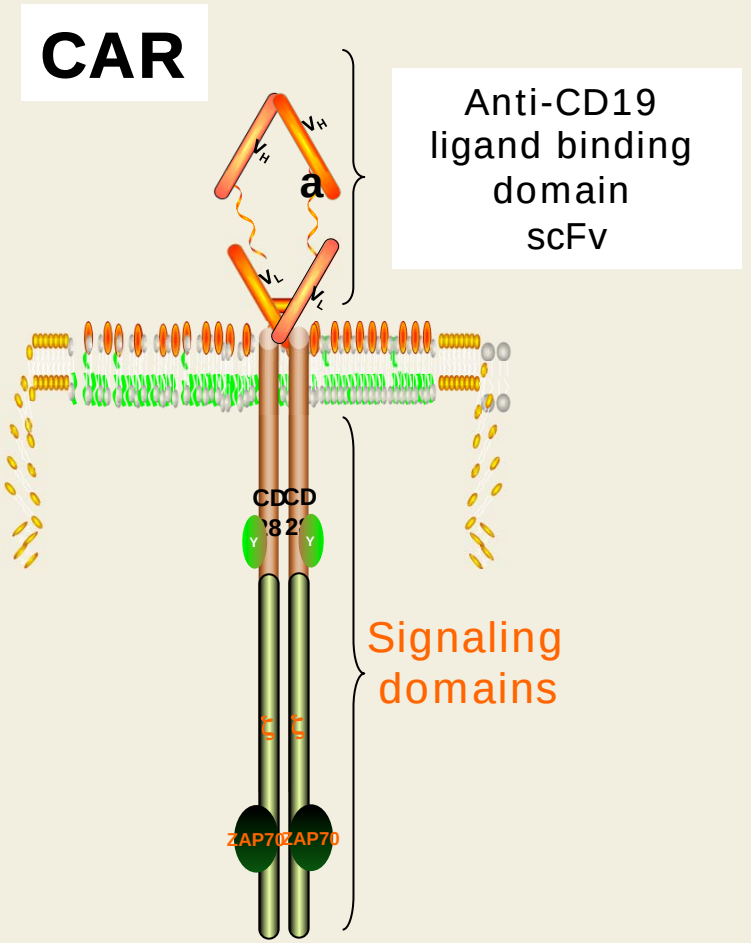
# Background

- Chimeric antigen receptors (CARs) combine the antigen recognition domain of an antibody with intracellular signaling domains into a single chimeric protein.
- CD19 is an ideal target for CARs because expression is restricted to normal and malignant B cells.
- With relatively short follow-up, initial data on antitumor activity of CAR-modified autologous T cells targeted to CD19 (CART19 cells) were reported for 3 patients with CLL (*NEJM* 2011;365:725; *Sci Transl Med* 2011;3:95ra73).
- **Study objective:** Present updated outcomes and longer follow-up analyses from 10 patients with relapsed/ refractory CLL or ALL treated with CART19 cells.

Porter DL et al. *Proc ASH* 2012;Abstract 717.

# Treatment of Patients with CART19 Cells

- Autologous T cells collected by leukapheresis were transduced with a lentivirus encoding the anti-CD19 scFv linked to the 4-1BB (CD137) and CD3-z signaling domains.
- Gene-modified T cells were expanded and activated ex vivo by exposure to anti-CD3/CD28 beads.
- Ten patients received T-cell infusions containing a proportion of CART19 cells.
- Patients with CLL received lymphodepleting chemotherapy 4 to 7 days prior to infusion.
- Patients with ALL experienced chemorefractory relapse, received 6 weeks of chemotherapy prior to infusion and did not require further lymphodepletion.




With permission from Porter DL et al. *Proc ASH* 2012;Abstract 717.

# Study Design and Eligibility

- Single-center pilot trial of CTL019 (formally CART19) cells
- **Primary objective:**
  - Safety, feasibility and immunogenicity of CTL019 in patients with CD19-positive leukemia and lymphoma
- **Eligibility:**
  - CD19-positive B-cell malignancies with no available curative options (such as autologous or allogeneic stem cell transplant)
  - Failed ≥2 prior therapies, progression within 2 years of last treatment
  - Limited prognosis (<2 years) with available therapies

Porter DL et al. *Proc ASH* 2012;Abstract 717.

# Clinical Response

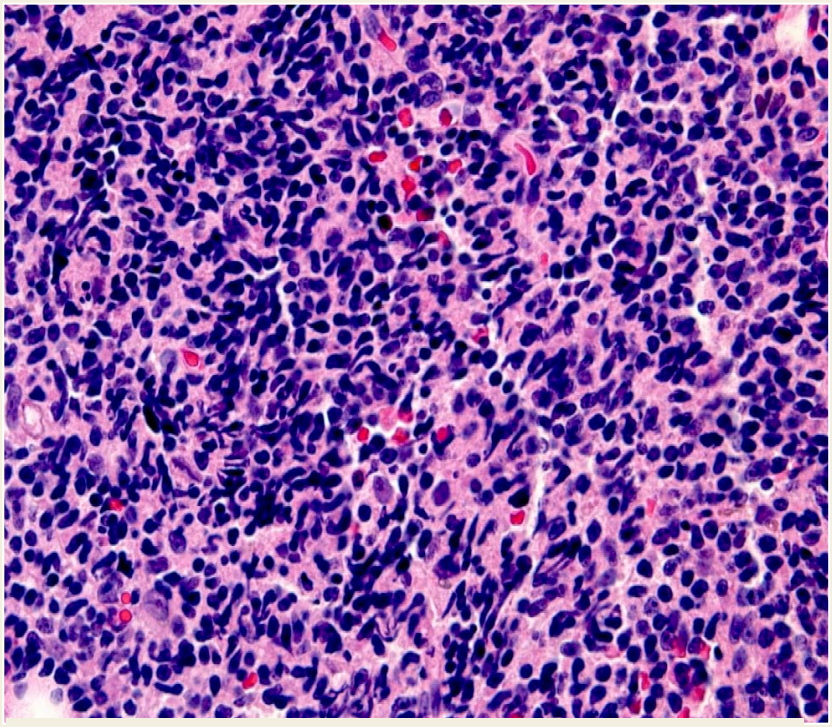
| Pt UPN# | Blood | Marrow | Nodes | Expansion | Comments | Max resp |
|---|---|---|---|---|---|---|
| 01 | NED | NED | NED | >3 log | MRD* neg | CR 28 mo+ |
| 02 | NED | NED | NED | >3 log | MRD* neg | CR 27 mo+ |
| 03 | PR | PR | PR | 2 log | | PR 4 mo |
| 04 | PR | PR | PR | 2 log | | PR 4 mo |
| 05 | NR | NR | NR | <2 log | | NR |
| 06 | NR | NR | NR | <2 log | | NR |
| 09 | NED | NED | NED | >3 log | MRD* neg | CR 7 mo+ |
| 10 | NED | NED | PR | 2 log | Bulky nodes | PR 3 mo+ |
| 12 | NED | NED | PR | 2 log | Bulky nodes | PR 2 mo+ |
| 14 | ne | ne | ne | | | ne |

NED = no evidence of disease; MRD = minimal residual disease; CR = complete response; PR = partial response; ne = not evaluated

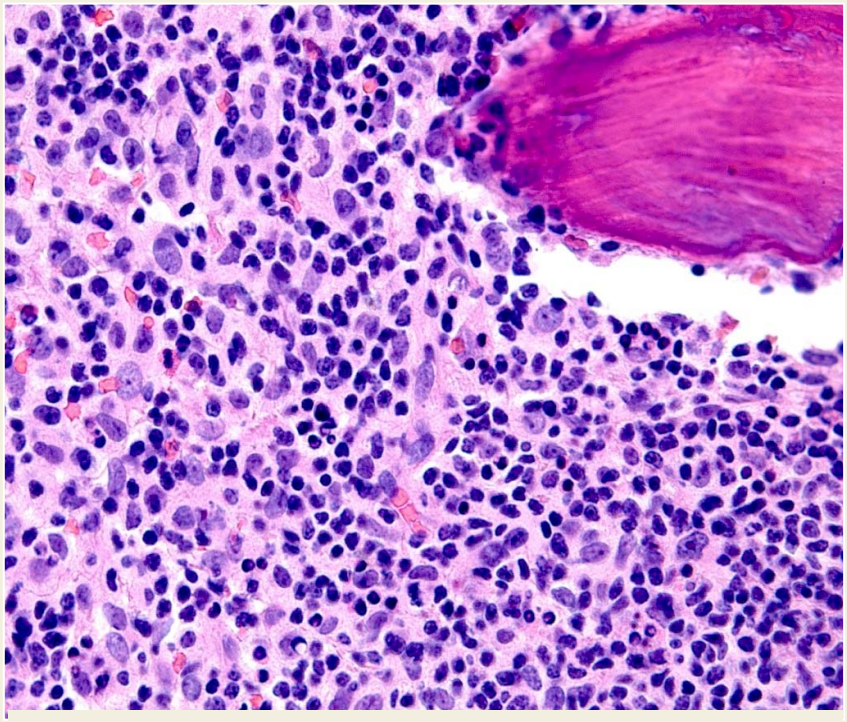
Porter DL et al. *Proc ASH* 2012;Abstract 717.

** MRD assessed with deep sequencing analysis*

# Marrow Response Observed in Patient UPN02



**Pre-infusions marrow:**
**>50% involved by CLL (40x)**



**Day 31**
**No evidence CLL and negative by flow cytometry, cytogenetics, FISH or deep sequencing**

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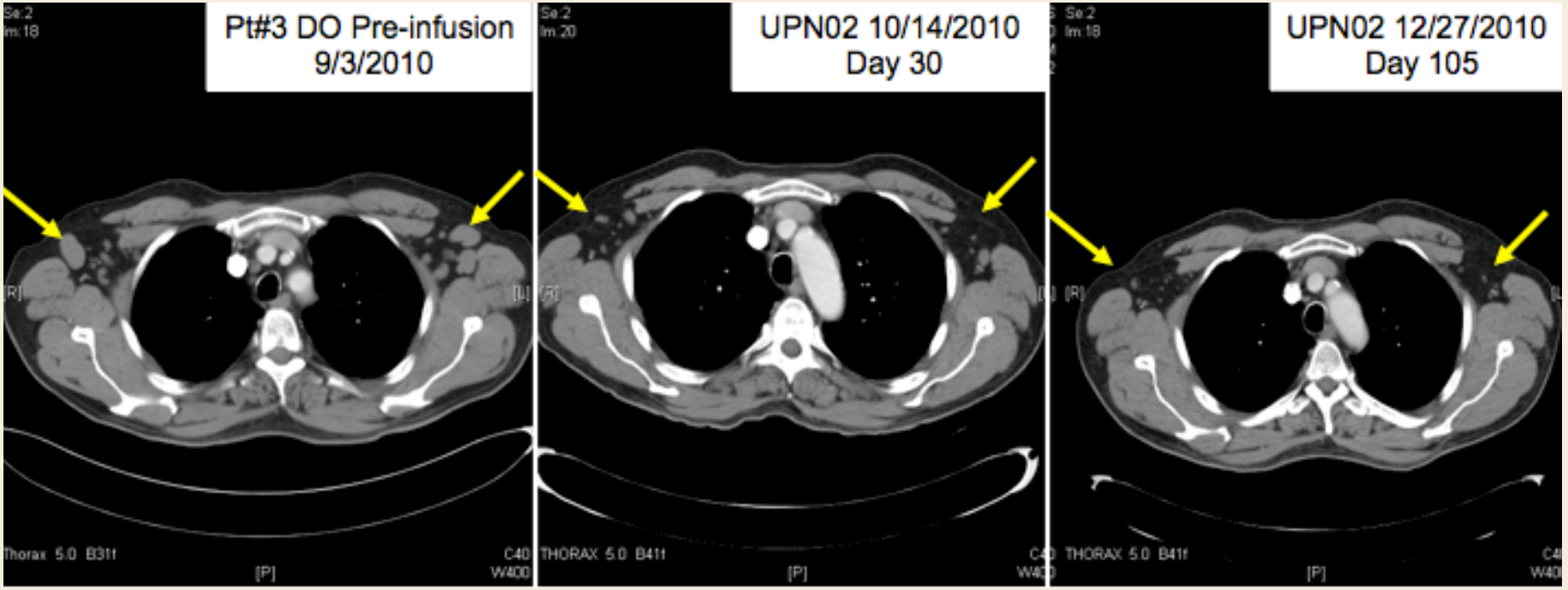
# CT Response Observed in Patient UPN02




**Response sustained >24 mo after CART-19 cell infusion**

With permission from Porter DL et al. *Proc ASH* 2012;Abstract 717.

# Toxicity Summary of CTL019 (CART19)

- No significant infusional toxicity
- Hepatotoxicity (Grade 3-4 in 5 responding patients)
- Renal toxicity (Grade 3 in 1 patient)
  - Related to tumor lysis syndrome, acute tubular necrosis from hypotension
  - Reversible
- B-cell aplasia and hypogammaglobulinemia in patients achieving complete response
  - Treated with intravenous immunoglobulin
  - No excessive or frequent infections
- Tumor lysis syndrome
- Cytokine release syndrome

Porter DL et al. *Proc ASH* 2012;Abstract 717.

# CTL019 (CART19)-Associated Cytokine Release Syndrome (CRS)

- All responding patients developed a CRS at time of T-cell expansion
  - High fevers, nausea, hypotension, hypoxia, etc
- Associated with high levels of:
  - IL-6 (6-400x)
  - IFN-gamma (89-1,000)
  - IL-2R (5-25)
  - No significant increase in TNF-alpha, IL-2
- Immediately reversed with steroids (n = 1), steroids/ etanercept/tocilizumab (n = 1), tocilizumab (n = 2)

Porter DL et al. *Proc ASH* 2012;Abstract 717.

# Author Conclusions

- Autologous T cells genetically engineered to express an anti-CD19 scFv coupled to 4-1BB/CD3-z signaling domains can undergo robust in vivo expansion and persist for more than 2 years.
- CART19 cells can induce an overall response rate of 78%.
  - 3/9 complete and 4/9 partial responses, including CR in 2/2 patients with ALL
- Responding patients develop cytokine release syndrome, which can be treated effectively with anticytokine therapy.

Porter DL et al. *Proc ASH* 2012;Abstract 717.

## Investigator Commentary — CAR T Cells Directed Against CD19 Induce Durable Responses and Transient CRS in Relapsed, Refractory CLL and ALL

CAR-targeted therapy is designed for patients with cancer that expresses CD19. Most of the patients enrolled on this study have refractory CLL. Patients' T cells are harvested and genetically modified with a vector that will express a receptor that targets CD19. The cells are then infused back into the patient. It's a time-consuming and expensive procedure, but it definitely has merit. The authors have reported about 6 objective responses to date, some of which are CRs and are durable. This is a highly attractive strategy for ALL because once a patient experiences relapse we have no effective agents against this disease. I believe this strategy deserves more development in ALL. However, the challenge for this strategy in CLL is that we have some novel, easier-to-use and active agents — ibrutinib, ABT-199 — coming down the road. A few years ago this might have been the hottest strategy out there, but the field has changed so much that I'm a little skeptical that this therapy will make it to prime time in CLL.

***Interview with Brad S Kahl, MD, January 17, 2013***

# Phase II Safety and Efficacy Study of CT-011, a Humanized Anti-PD-1 Monoclonal Antibody, in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma

**Westin JR et al.**

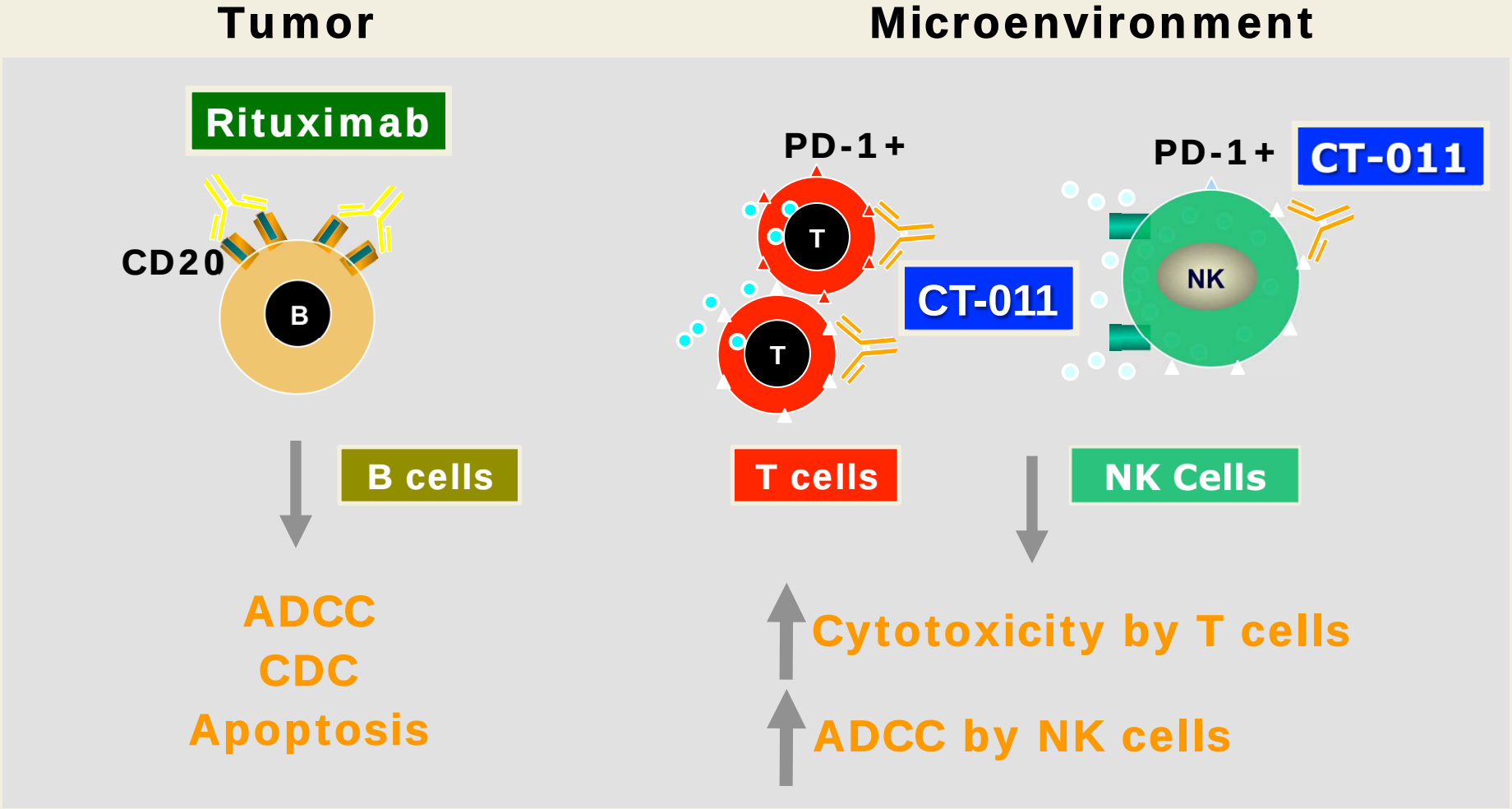
*Proc ASH* 2012;Abstract 793.

# Background

- The expression of the programmed death (PD)-1 receptor is increased on intratumoral T cells in follicular lymphoma (FL) and associated with impaired T-cell function (*Human Pathol* 2011;42(4):552).
- Pidilizumab (CT-011) is a humanized anti-PD-1 monoclonal antibody that can promote the functions of antitumor T and natural killer (NK) cells (*J Immunother* 2011;34(5):409).
- Because rituximab is a monoclonal anti-CD20 antibody that partly acts by activating NK cell-mediated cytotoxicity, its combination with CT-011 may offer additive or synergistic antitumor effects via the immune system.
- **Study objective**: Evaluate the efficacy and safety of pidilizumab and rituximab in relapsed FL.

Westin JR et al. *Proc ASH* 2012;Abstract 793.

# Rituximab + Pidilizumab (CT-011): Rationale




With permission from Westin JR et al. *Proc ASH* 2012;Abstract 793.

# Phase II Trial Design

**Eligibility (n = 30)**

Relapsed Grade 1/2 FL
1-4 prior therapies
Tumor size >1.5 cm
No HIV, hepatitis B/C, autoimmune disorder or allogeneic SCT

→

**Pidilizumab + rituximab (n = 30)**

**Pidilizumab**: 3 mg/kg IV q4wk x 4 cycles*

**Rituximab**: 375 mg/m$^2$ IV q1wk x 4 cycles†

* If ≥stable disease after 4 cycles, continue with up to 8 more cycles

† Rituximab dosing started 2 weeks after the first infusion of pidilizumab

- **Primary endpoint:** Overall response rate (ORR)
- **Secondary endpoints include:** Complete response rate, time to progression and safety

Westin JR et al. *Proc ASH* 2012;Abstract 793.

# Best Response Rates

| Response rate | n = 29* |
|---|---|
| ORR | 66% |
| Complete response (CR) | 52% |
| Partial response (PR) | 14% |
| Tumor regression | 86% |

* Evaluable patients

- Median time to response: 88 days
- ORR did not correlate with FLIPI or FLIPI-2 score, amount of prior rituximab, prior chemotherapy or duration of response to prior therapy ($p > 0.05$).

Westin JR et al. *Proc ASH* 2012;Abstract 793.

# Survival Outcomes

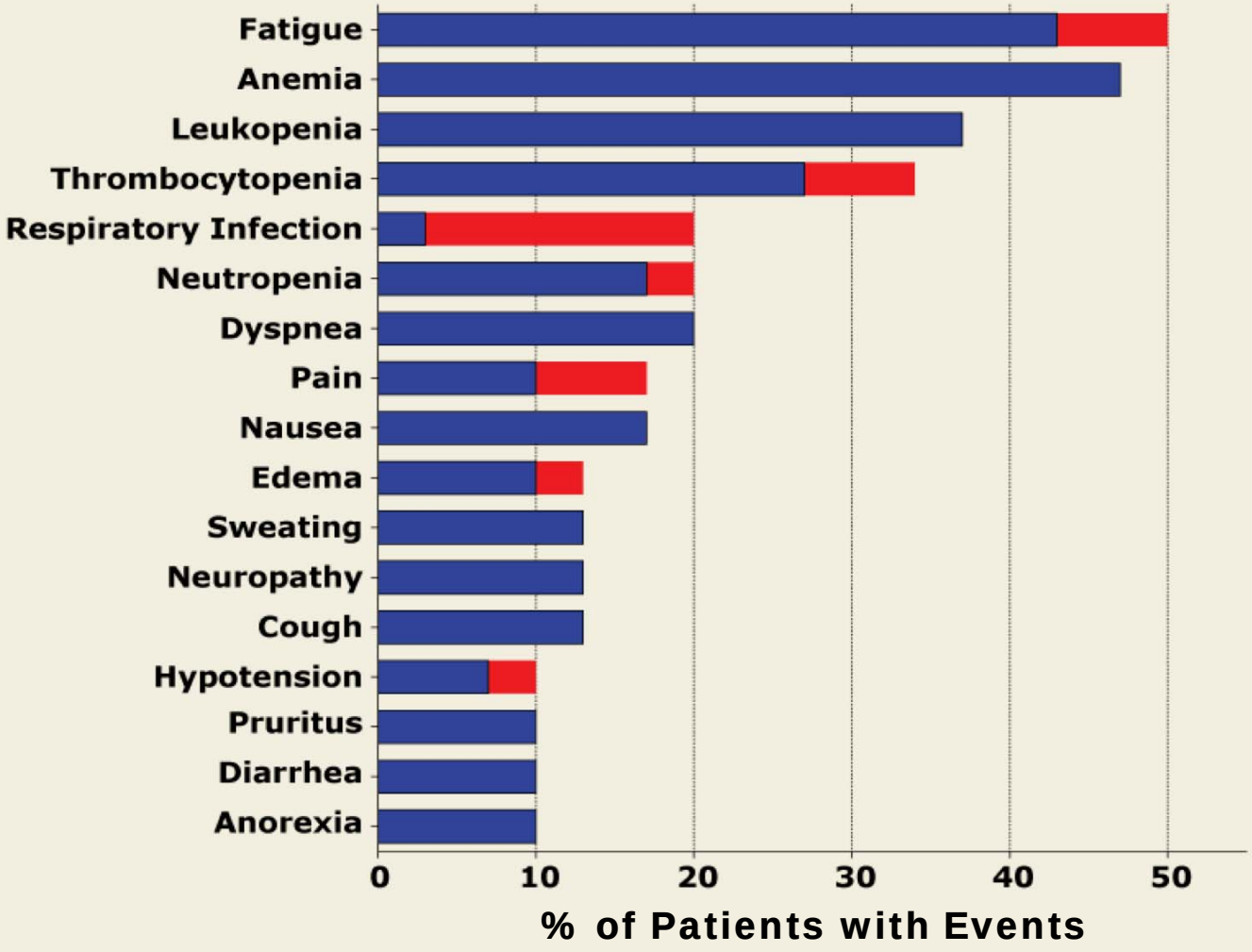
| Outcome | Pidilizumab + rituximab |
|---|---|
| Median progression-free survival* | |
| All patients (n = 29) | 21.1 months |
| Responders (n = 19) | Not reached (NR) |
| With measurable tumor regression (n = 25) | NR |
| No. of deaths (n = 29) | 0 |

* Median follow-up = 14 months

- PFS was significantly associated with:
  - FLIPI (low/intermediate vs high): NR vs 12.65 months; $p = 0.0056$
  - FLIPI-2 (low/intermediate vs high): NR vs 13.47 months; $p = 0.0344$

Westin JR et al. *Proc ASH* 2012;Abstract 793.

# Common Adverse Events (AEs) Occurring in >10% of Patients




With permission from Westin JR et al. *Proc ASH* 2012;Abstract 793.

# Author Conclusions

- The combination of pidilizumab with rituximab was:
  - Well tolerated
  - Effective in relapsed, rituximab-sensitive FL
    - ORR: 66%; CR: 52%; PR: 14%
- The results of this single-arm Phase II trial of pidilizumab with rituximab compared favorably to previous data with rituximab re-treatment for patients with relapsed non-Hodgkin lymphoma (*JCO* 2000;18:3135).
    - ORR: 40%; CR: 11%; PR: 30%

Westin JR et al. *Proc ASH* 2012;Abstract 793.

## Investigator Commentary: A Phase II Trial of Pidilizumab and Rituximab in Relapsed Follicular Lymphoma (FL)

Certain molecules inhibit cytotoxic T-cell activity, which is enhanced in cancer. One of the mechanisms by which cancer can grow out of control is by rendering these cytotoxic cells ineffective. With the observation that molecules such as PD-1 promote the recurrence of this process, these investigators studied an anti-PD-1 monoclonal antibody in combination with rituximab in 30 patients with rituximab-relapsed but not refractory FL. The study population was not heavily pretreated, with most of the patients having some evidence of clinical activity.

About 85% of the patients experienced tumor shrinkage with an ORR of 66%, which the investigators felt was better than historical controls with rituximab alone. Also, the median PFS was >1.5 y. These results are interesting, but I would have preferred to know the effectiveness of this combination in patients with refractory FL, not only in patients with relapsed disease, because that would provide a better idea of whether there is a synergistic relationship between pidilizumab and rituximab. This combination is worth studying in patients with more resistant disease and perhaps in combination with other agents, based on scientific rationale. Pidilizumab is an example of the concept of better living through molecular genetics and biology.

***Interview with Bruce D Cheson, MD, January 14, 2013***

# Safety and Efficacy of Abbreviated Induction with Oral Fludarabine (F) and Cyclophosphamide (C) Combined with Dose-Dense IV Rituximab (R) in Previously Untreated Patients with Chronic Lymphocytic Leukemia (CLL) Aged > 65 Years: Results of a Multicenter Trial (LLC 2007 SA) on Behalf of the French GOELAMS/FCGCLL-WM Intergroup

**Dartigeas C et al.**

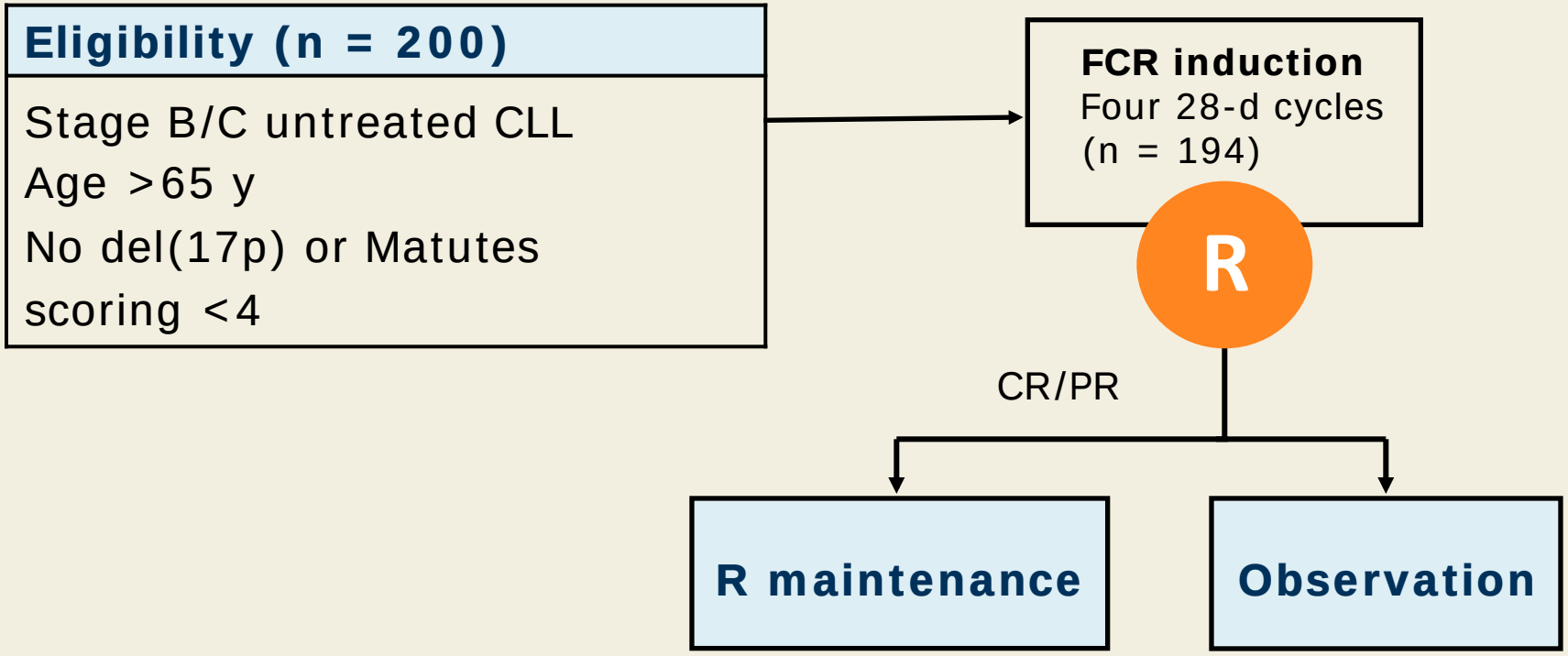
*Proc ASH* 2012;Abstract 434.

# Background

- Results of the CLL8 trial led to the recommendation of FCR as first-line therapy for fit patients with CLL (*Lancet* 2010;376:1164).
- The median age of the cohort in the CLL8 trial was 61 y, at least 10 y younger than the median age at CLL diagnosis.
- The elderly population is underrepresented in clinical trials, and it is unclear if FCR is effective for these patients.
- The LLC 2007 SA trial is evaluating abbreviated induction with FCR followed by randomization to R maintenance or observation in patients with CLL aged 65 y and older.
- **Study objective:** Assess the safety and efficacy of the abbreviated induction with FCR portion of the LLC 2007 SA trial for the first 200 patients enrolled.

Dartigeas C et al. *Proc ASH* 2012;Abstract 434.

# Study Design




FC (fludarabine 40 mg/m$^2$/d, cyclophosphamide 250 mg/m$^2$/d) PO, x 3 d
R (rituximab 375 mg/m$^2$ d1 cycle 1, 500 mg/m$^2$ d14 cycle 1, d1 and d14 cycle 2, d1 cycles 3 and 4), IV

Dartigeas C et al. *Proc ASH* 2012;Abstract 434.

# Response to FCR Induction (Abstract Only)

| Response* | (n = 188) |
|---|---|
| ORR | 96.3% |
| Complete response (CR) | 19.7% |
| CRi | 13.3% |
| Partial response | 63.3% |

* According to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 guidelines

CRi = CR with incomplete marrow recovery

Dartigeas C et al. *Proc ASH* 2012;Abstract 434.

# Select Adverse Events (AEs) During Induction Phase (Abstract Only)

| Grade ≥3 AEs | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 |
|---|---|---|---|---|
| Neutropenia* | 46% | 50% | 53% | 46% |
| Anemia | 11% | 7% | 6% | 3% |
| Infections | 6.2% | 4.8% | 7.6% | 6.2% |

* G-CSF administered to 32%, 46%, 48% and 52% of patients after cycles 1, 2, 3 and 4

- 86% of pts received all 4 cycles of FCR; 81% proceeded to randomization.
- Dose delay (by ≥1 wk) and dose reductions (by ≥25% of F and C) for cycles 2, 3 and 4 were 12% and 7%, 14% and 8%, 15% and 11%, respectively.
- Grade 4 thrombocytopenia occurred in <2% of the cycles.
- 6.3% of the 732 cycles were followed by febrile neutropenia or infection.
- Death rate from immediate toxicity during induction: 3.1% (all due to infections)

Dartigeas C et al. *Proc ASH* 2012;Abstract 434.

# Author Conclusions

- Four cycles of oral FC combined with 6 doses of R appear feasible in elderly patients with CLL; only 14% could not receive the 4 courses and only 19% could not proceed to randomization.
- Dose reduction and treatment interruption were unusual despite strict stopping criteria.
- Grade 3/4 neutropenia was frequent but rarely translated into serious infection.
- The response rate was high, and further analysis of MRD eradication is ongoing.
- This approach could enable the safe administration of first-line FCR to elderly fit patients with CLL.

Dartigeas C et al. *Proc ASH* 2012;Abstract 434.

## Investigator Commentary: Abbreviated FCR Induction in Patients Over the Age of 65 Years with Previously Untreated CLL

This report is not the first to evaluate an abbreviated FCR regimen, the initial one being FCR-lite as published by Foon and colleagues (*J Clin Oncol* 2009;27:498) with similar results. However, in the study by Dartigeas and colleagues, 14% of patients were unable to receive all 4 cycles, with an additional 19% to 26% requiring dose reductions over the 4 cycles. We need to consider what other options are available for older patients with CLL, such as R/bendamustine. Unlike fludarabine, the pharmacokinetics of bendamustine are not affected by age, so it is a preferred agent for older patients.

Nevertheless, regimens such as these will be of only historical interest in the near future. Data in untreated patients age 65 or older receiving the Bruton kinase inhibitor ibrutinib suggest comparable response rates with reasonable durability and considerably less toxicity than would be expected with chemoimmunotherapeutic regimens. The world is clearly changing rapidly and dramatically in B-cell malignancies, with kinase inhibitors and proapoptotic agents at the forefront of clinical investigation for patients of all ages with CLL as we move toward a chemotherapy-free era.

***Interview with Bruce D Cheson, MD, February 25, 2013***