5 Minute JournalClub

Hematologic Oncology

Issue 2, 2013

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CME Information

LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances and potentially practice-changing clinical data in chronic lymphocytic leukemia, and consider this information in clinical practice.
- Evaluate the efficacy, safety, pharmacodynamics and pharmacokinetics of idelalisib as a single agent or in combination with rituximab for patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia.
- Determine the preliminary efficacy and safety of ABT-199, a selective BCL-2 inhibitor, for patients with relapsed or refractory chronic lymphocytic leukemia.
- Determine the benefits and risks associated with chlorambucil in combination with obinutuzumab (GA101), an anti-CD20 antibody, or rituximab versus chlorambucil alone for patients with previously untreated chronic lymphocytic leukemia and preexisting comorbidities.
- Assess the preliminary safety and response outcomes observed in studies of the orally bioavailable, small molecule inhibitor of Bruton tyrosine kinase ibrutinib as a single agent for patients with chronic lymphocytic leukemia with chromosome 17 deletion.

CME Information (Continued)

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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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Imagine…

Ten days ago your life was instantly turned upside down. After a few months of having less energy than usual, to appease a concerned spouse you visit your primary care physician who detects lymphadenopathy in your neck and a spleen tip. A blood count suggests chronic lymphocytic leukemia (CLL), and that night one of your colleagues does a bone marrow biopsy and initiates a workup that soon demonstrates you meet the criteria to initiate treatment. You consult with a noted CLL investigator who reviews with you the following options:

A. FCR
B. FR
C. BR
D. A clinical trial that includes 1 or more unapproved agents in clinical development

Which treatment would you choose to receive?

I asked this impossible question to investigator Dr Brad Kahl last week during a conversation that focused on the blindingly fast evolution of new agents in B-cell neoplasia, particularly CLL. Not surprisingly and without any hesitation Dr Kahl

replied “D, clinical trial,” and while there are many investigational agents and regimens he might consider, his first choice today would be to enter a study of the Bruton’s tyrosine kinase inhibitor ibrutinib combined with rituximab (R), although he did preface his answer by saying, “This is a moving target that could change in 6 months — especially the choice of anti-CD20 antibody, which might be different after ASH” (see below). If and when relapse occurred, at this moment Dr Kahl would elect to be enrolled on a trial of the BCL-2 inhibitor ABT-199 with obinutuzumab (O) for its added effect on cell death. He noted that his choices would be the same with del17p disease.

One of the oldest homilies in medical oncology is “The best treatment option is participation in a clinical trial,” and although in the past, study options rarely provided opportunities not available in daily practice, currently in specific corners of the field the data for one or more unapproved treatments are so compelling that oncologists who don't make patients aware of these research options are not delivering the type of care they would likely want to receive themselves.

Nowhere is this more relevant currently than in CLL, and on this issue of our short series summarizing key summer heme-onc meeting presentations we review findings with 4 classes of agents rapidly generating impressive data and speeding toward clinical practice.

1. Type II monoclonal antibodies to CD20

Perhaps the most surprising oral CLL paper at ASCO 2013 provided us with a first glimpse of data from a major Phase III, 3-arm German study in patients

with comorbidities — mostly aged 65 and older — evaluating chlorambucil alone or combined with either R or O, a third-generation glycoengineered Type II agent designed to enhance antibody-dependent cellular cytotoxicity and induce actin-dependent programmed cell death independent of BCL-2 overexpression and caspase activation.

The findings unveiled at ASCO were from the first stage of the study and revealed that both of the monoclonal antibodies added significant efficacy to chlorambucil. However, the data also hinted that O might be more effective than R. Importantly, in July a press release announced that the second stage of this historic study had reached statistical maturity and that indeed the primary endpoint of superior progression-free survival in favor of O had been met. O may have more tolerability issues, particularly infusion reactions and neutropenia, but the new data have been submitted to ASH and we shall soon have a much better idea of whether this fascinating agent could potentially replace R in treating CLL and perhaps other B-cell cancers.

2. PI3 kinase delta inhibitors: Idelalisib (idel)

The other 2 ASCO oral CLL presentations this year focused on this much-discussed oral small molecule B-cell receptor signaling inhibitor. The first was a Phase I study in relapsed disease that demonstrated a 72% response rate with a waterfall plot for nodal response that pretty much all points down. The second was a Phase II trial of R and idel in older patients with previously untreated CLL, which revealed a response rate of 97%, including all 9 patients with del17p and/or TP53 mutations. The presenter, Dr Susan O'Brien, noted that as with other

novel agents in development, treatment was often initially associated with both rapid lymph node regression and simultaneous lymphocytosis that then gradually receded. She also pointed out that with a median follow-up of 14.1 months, no patient has experienced disease progression. Both studies confirmed prior data demonstrating that the key tolerability issues are diarrhea/colitis and abnormal liver function tests, which resolve with treatment withdrawal or dose reduction.

3. Bruton's tyrosine kinase inhibitors: Ibrutinib

Perhaps the most talked about "emerging agent" in all of oncology, ibrutinib has been the subject of a plethora of recent research reports in an array of B-cell cancers. In Lugano, the database grew even larger with provocative results illustrating the impact of this agent in a CLL subset that is relatively resistant to chemotherapy-R, patients with del17p. The data reveal that nodal responses were documented in 22 of 25 patients (88%), spleen size decreased in every patient with splenomegaly and the 12-month event-free survival rate was 90%. As in prior studies, side effects and complications were minimal.

4. BCL-2 inhibitors: ABT-199 (GDC-0199)

A final exciting class of agents that has burst onto the CLL scene targets the antiapoptotic protein BCL-2, and in a Phase I study of the orally bioavailable selective BCL-2 inhibitor ABT-199 presented at ASCO and Lugano, an extraordinary 84% response rate was observed in 55 evaluable patients with relapsed/refractory disease, including 13 of 16 patients with del17p. The rapid and profound effect of this agent has led to problems with tumor lysis syndrome,

and new studies are evaluating alternate dosing strategies and enhanced measures of prophylaxis, monitoring and management. Moving forward, a key macro issue will be how to combine and sequence these and other new agents with or without chemotherapy.

Much more is happening in CLL research, including chimeric antigen receptor therapy, a promising but technologically complex approach, and as a result we are starting to hear leukemia investigators like Dr Hagop Kantarjian raise the possibility that CLL in the near future could resemble CML with indefinite disease control. In good conscience the trials seeking to achieve this lofty goal must be made available to all patients.

Next on this series, we talk about T-cell lymphoma, a corner of hematologic oncology that is witnessing exciting advances in new drug development after a long period in the doldrums.

Neil Love, MD
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Obinutuzumab (GA101) + Chlorambucil (Clb) or Rituximab (R) + Clb versus Clb Alone in Patients with Chronic Lymphocytic Leukemia (CLL) and Co-Existing Medical Conditions (Comorbidities): Final Stage I Results of the CLL11 (BO21004) Phase 3 Trial

Goede V et al.

Proc ASCO 2013;Abstract 7004.

Background

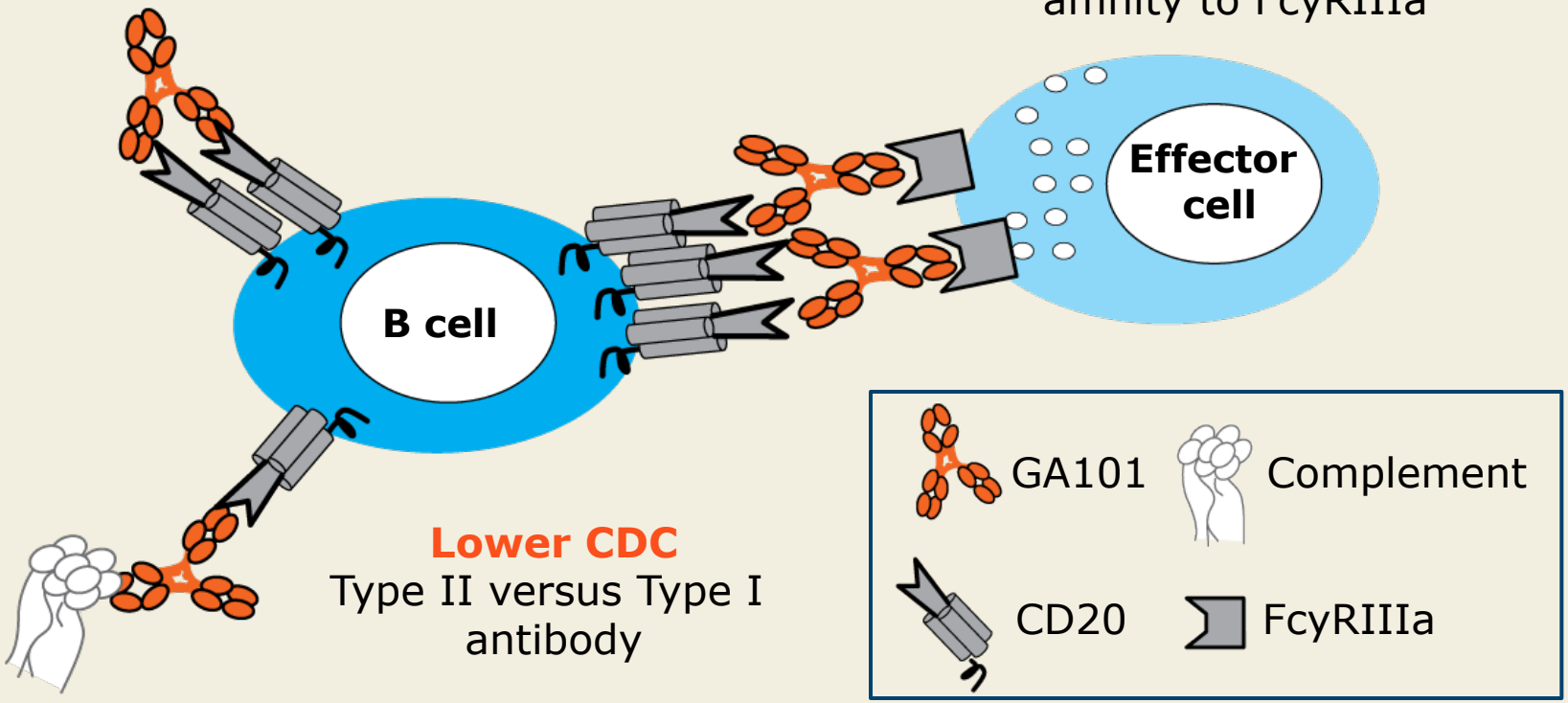
- A high number of elderly patients have CLL and coexisting medical conditions.
- In this patient population:
  - There is no conclusive evidence that currently available treatments are superior to chlorambucil (Clb) monotherapy.
  - Encouraging early data exist for the development of combinations of Clb with anti-CD20 monoclonal antibodies (mAbs) and for the evaluation of chemoimmunotherapy with the novel Type II anti-CD20 mAb obinutuzumab (*Proc ASH* 2011;Abstract 294; *Leukemia* 2013;27(5):1172).
- **Specific study aims:** To demonstrate the superiority of Clb + an anti-CD20 mAb (rituximab or obinutuzumab) to Clb alone (Stage I of study). An analysis of obinutuzumab + Clb versus rituximab + Clb is planned for Stage II of the study.

Goede V et al. *Proc ASCO* 2013;Abstract 7004.

Obinutuzumab (GA101) Mechanisms of Action

Increased Direct Cell Death
Type II versus Type I antibody

Enhanced ADCC
Glycoengineering for increased affinity to FcγRIIIa



Lower CDC
Type II versus Type I antibody

ADCC = antibody-dependent cell-mediated cytotoxicity
CDC = complement-dependent cytotoxicity

With permission from Goede V et al. *Proc ASCO* 2013;Abstract 7004.

CLL11 (BO21004) Trial Design: Stage I

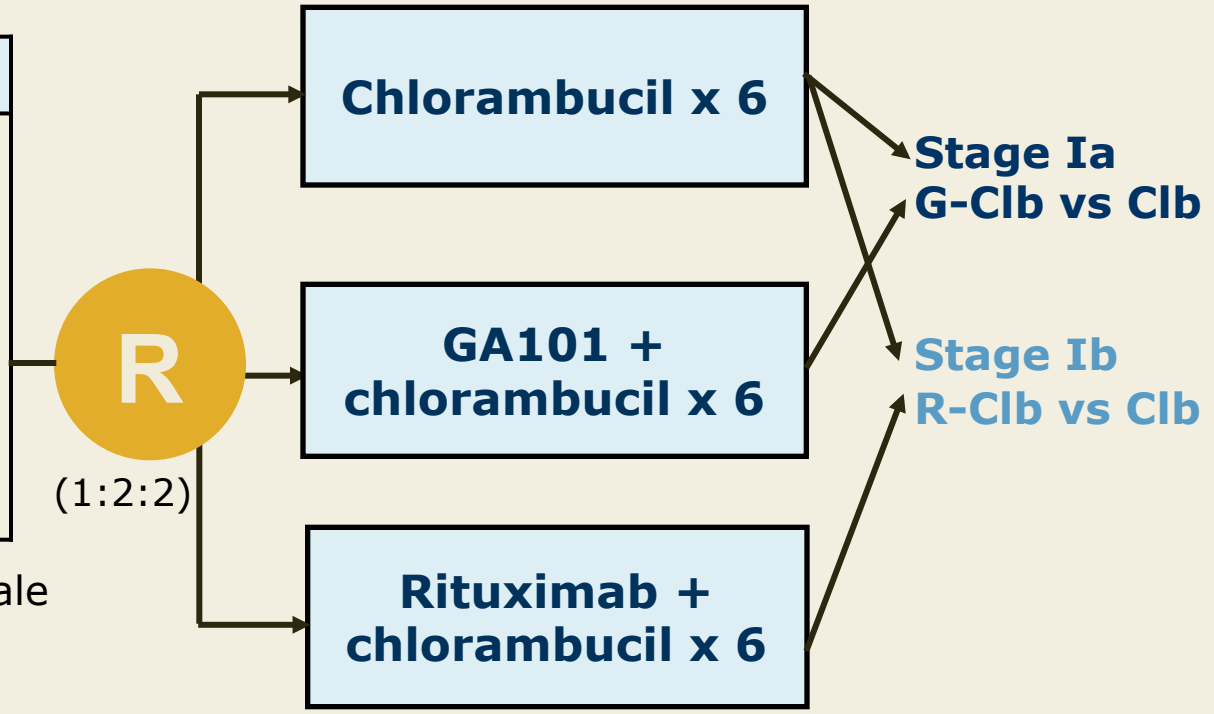
Eligibility

Previously untreated CLL with comorbidities

Total CIRS* score >6 and/or creatinine clearance <70 mL/min

(N = 590)

* Cumulative Illness Rating Scale



- GA101: 1,000 mg d 1, 8, 15 cycle 1; d 1 cycles 2-6, q28d
- Rituximab: 375 mg/m^2 d 1 cycle 1, 500 mg/m^2 d 1 cycles 2-6, q28d
- Clb: 0.5 mg/kg d 1, 15 cycles 1-6, q28d
- An additional 190 patients are enrolled in the Stage II portion of the study

Goede V et al. *Proc ASCO* 2013;Abstract 7004.

End-of-Treatment Response Rates (RR)

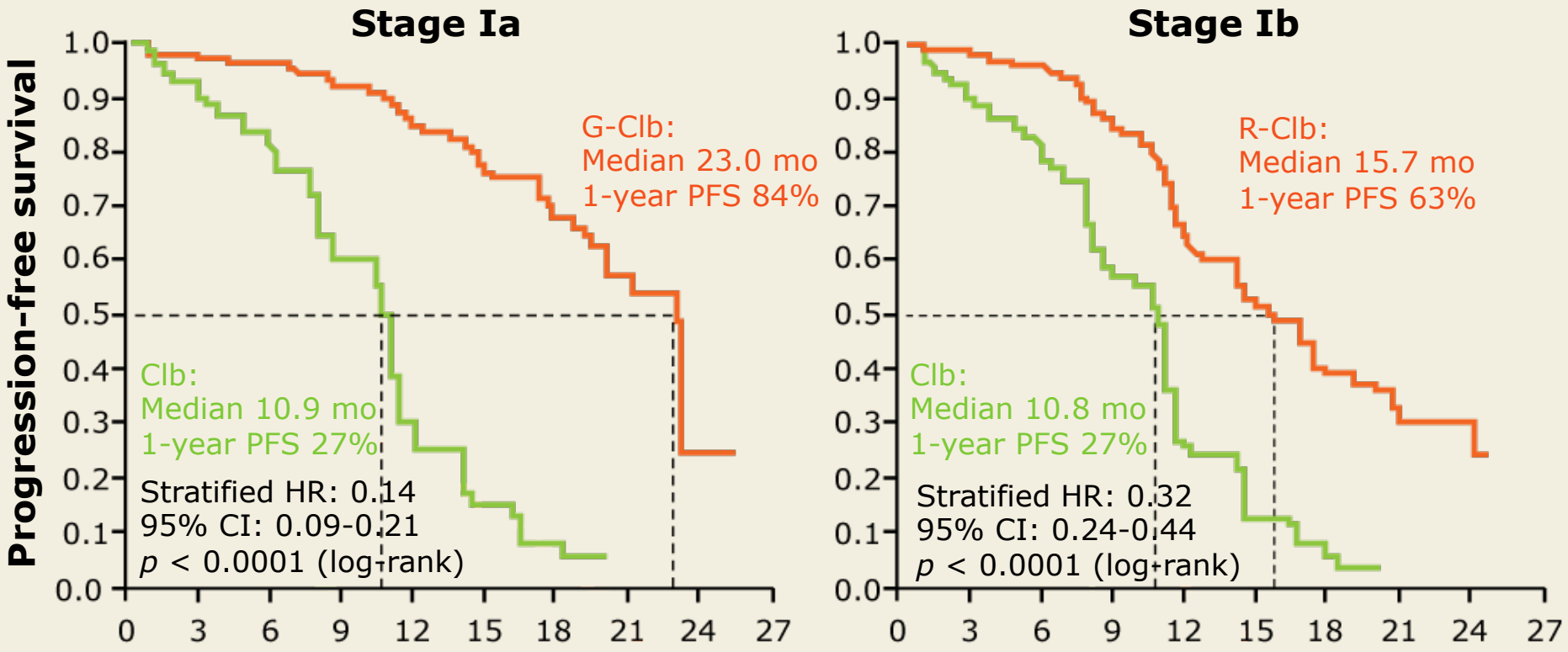
	Stage Ia		Stage Ib	
	Clb (n = 106)	G-Clb (n = 212)	Clb (n = 110)	R-Clb (n = 217)
ORR	30.2%	75.5%	30.0%	65.9%
CR*	0%	22.2%	0%	8.3%
PR†	30.2%	53.3%	30.0%	57.6%
SD	21.7%	4.7%	20.9%	13.4%
PD	25.5%	3.8%	28.2%	11.5%

ORR = overall response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

* Includes CR with incomplete hematologic recovery; † Includes nodular PR

Goede V et al. *Proc ASCO* 2013;Abstract 7004.

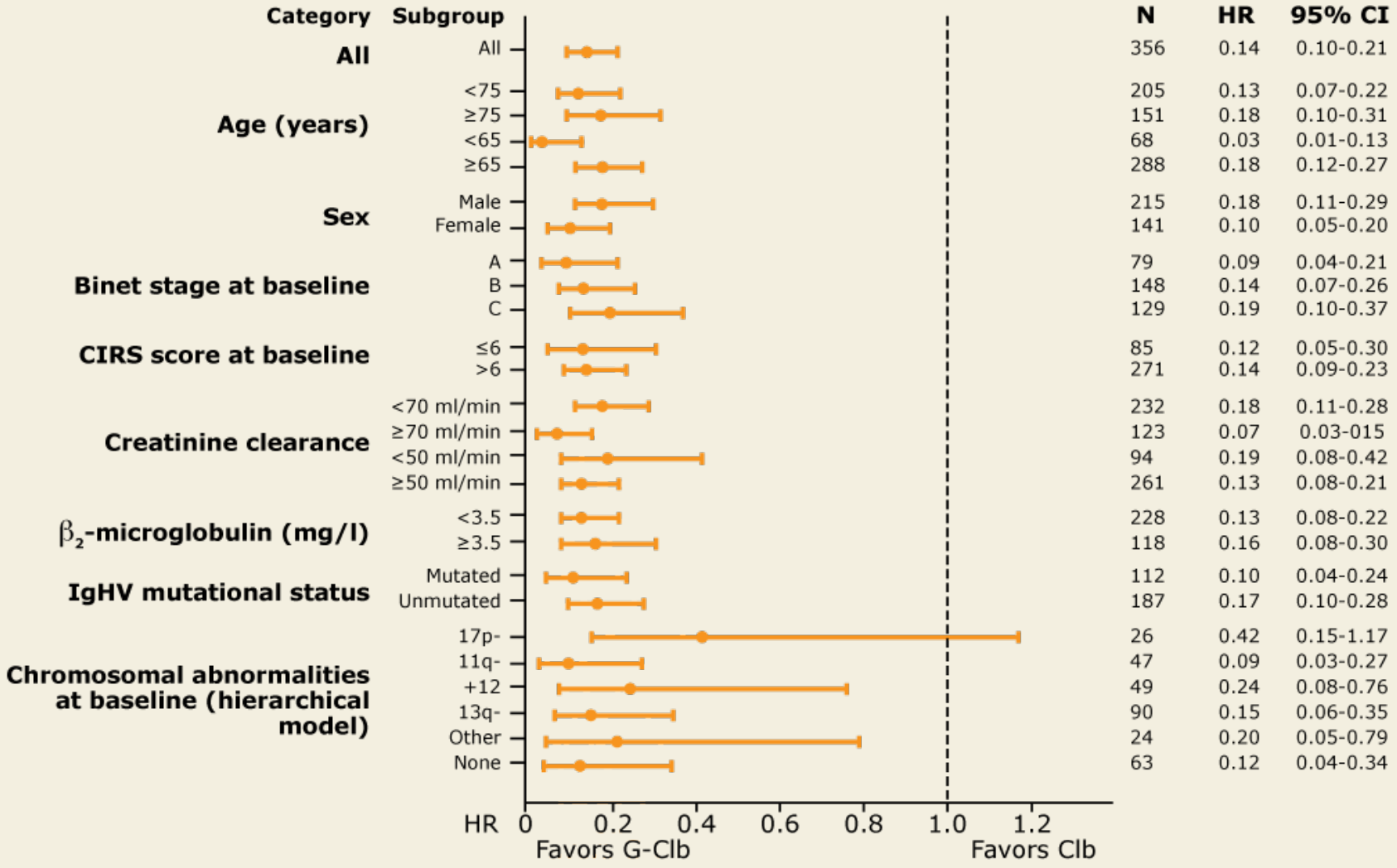
Investigator-Assessed Progression-Free Survival (PFS)



- On the G-Clb arm, <10% of patients had reached the median at cutoff. In contrast to the Clb arm, the G-Clb median PFS could not be reliably estimated due to the few patients at risk at time of median.
- Independent Review Committee-assessed PFS was consistent with investigator-assessed PFS.

With permission from Goede V et al. *Proc ASCO* 2013;Abstract 7004.

Stage Ia: Progression-Free Survival Subgroup Analysis



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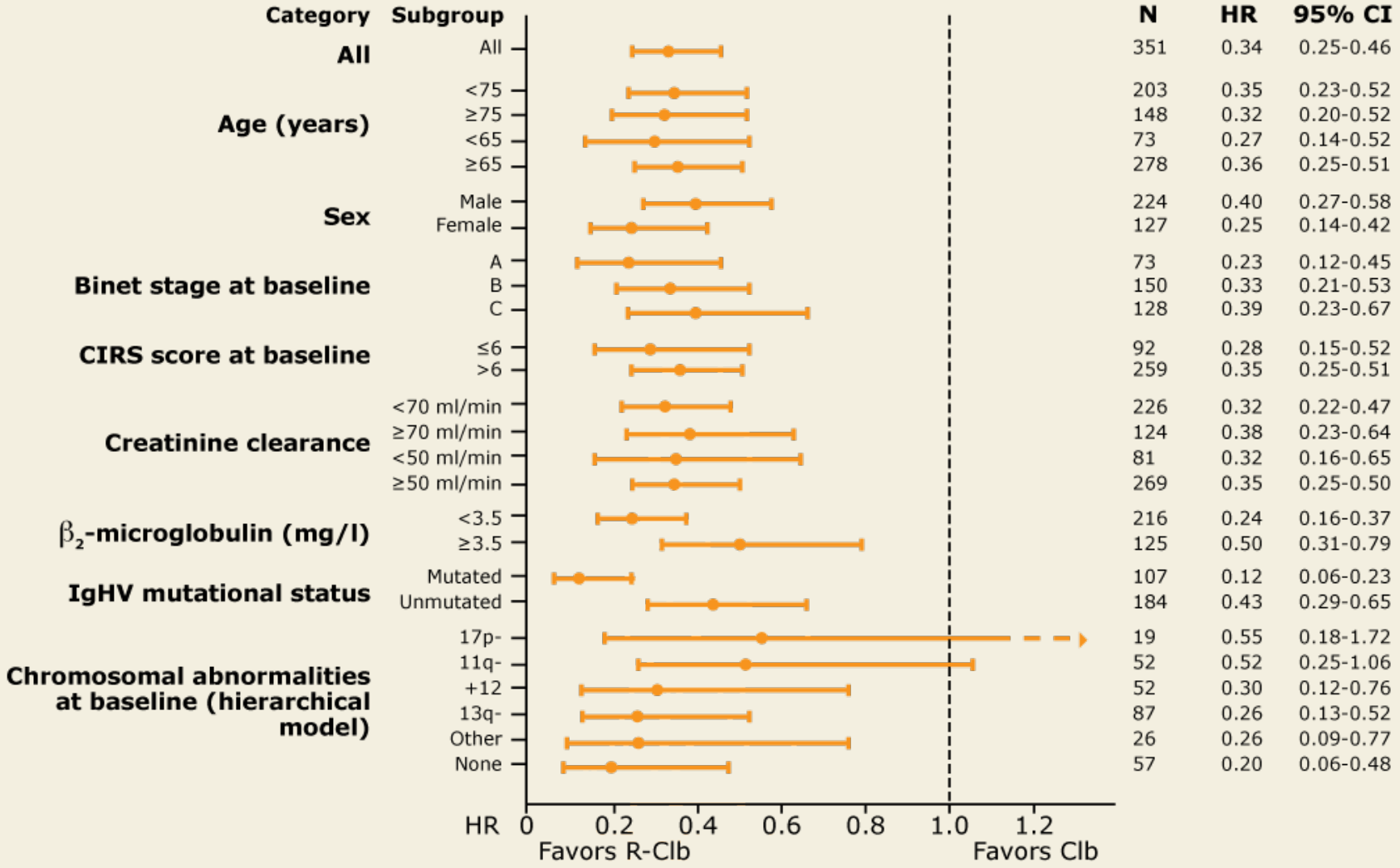
Stage Ib: Progression-Free Survival Subgroup Analysis



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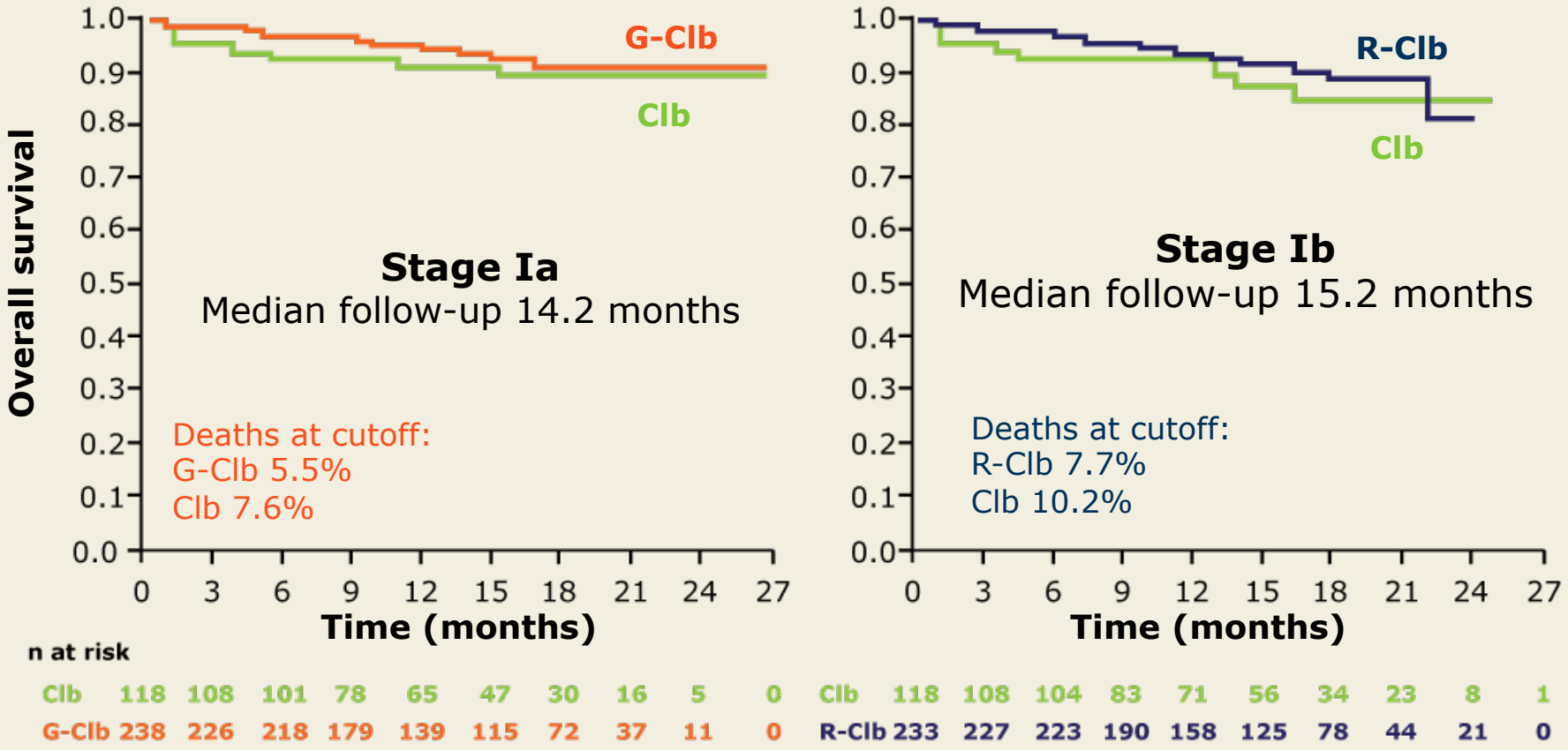
Overall Survival



- Overall survival data are immature.

With permission from Goede V et al. *Proc ASCO* 2013;Abstract 7004.

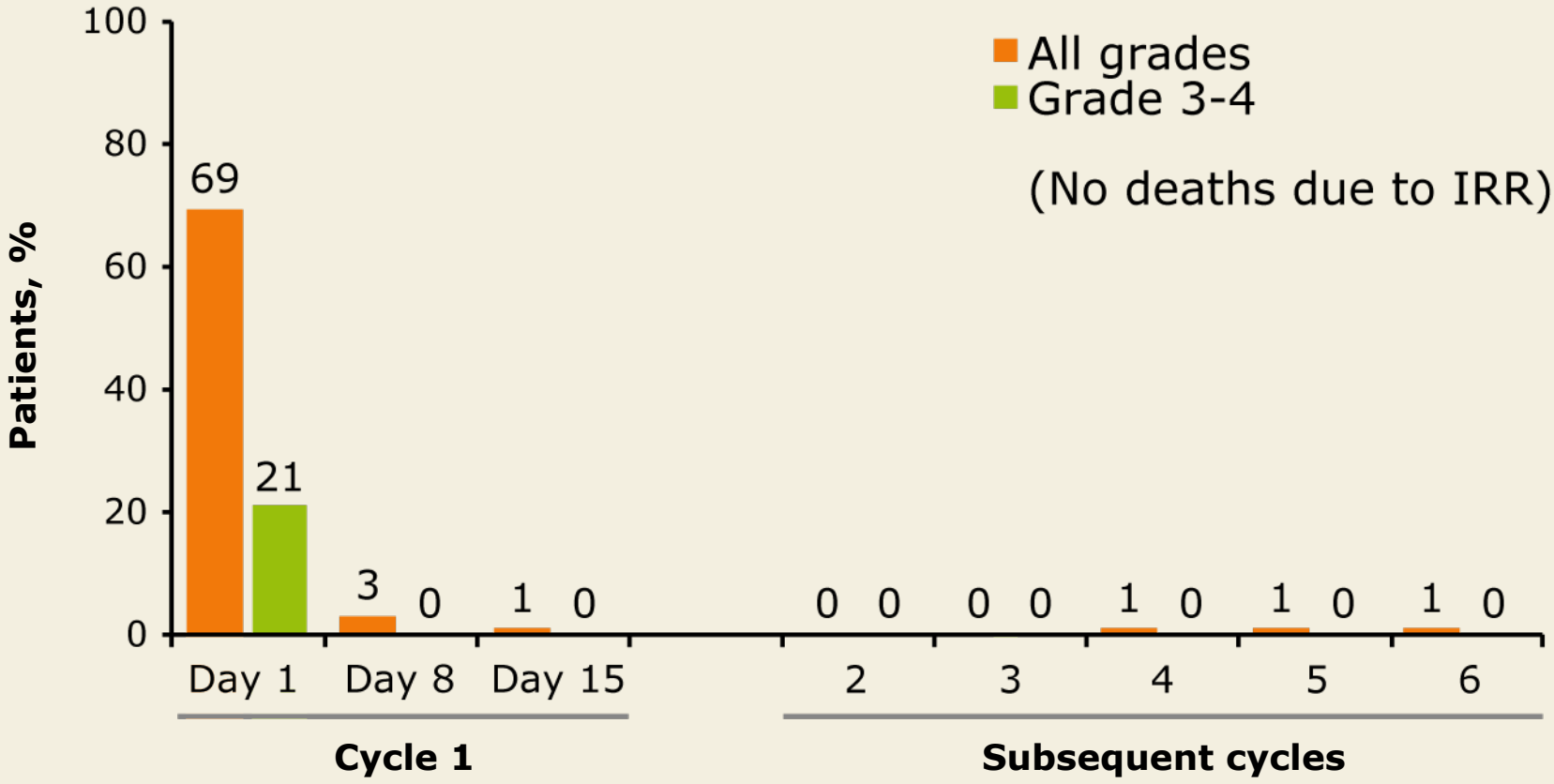
Relevant Adverse Events (AEs) During Treatment

	Stage Ia		Stage Ib	
	Clb (n = 116)	G-Clb (n = 240)*	Clb (n = 116)	R-Clb (n = 225)
Any AE Grade ≥3	41.4%	66.7%	41.4%	45.8%
Infusion-related reactions	n/a	21.3%	n/a	4.0%
Neutropenia	14.7%	34.2%	14.7%	25.3%
New malignancy	0.9%	2.5%	0.9%	2.7%

* Safety population for G-Clb includes 4 patients randomly assigned to R-Clb who received 1 infusion of GA101 in error.

Goede V et al. *Proc ASCO* 2013;Abstract 7004.

Stage Ia: Infusion-Related Reactions (IRRs) by Cycle in G-Clb Study Arm



With permission from Goede V et al. *Proc ASCO* 2013;Abstract 7004.

Author Conclusions

- This is the first large, pivotal, Phase III trial reporting on an elderly patient population with CLL and coexisting medical conditions.
- It is the first direct comparison of Clb to Clb with an anti-CD20 mAb demonstrating that the addition of GA101 or rituximab is beneficial to these patients.
- Safety profile for G-Clb (and R-Clb) is acceptable; infusion-related reactions and neutropenia were the most significant adverse events.
- Final analysis of G-Clb versus R-Clb will occur in Stage II of the study as specified by the protocol.

Goede V et al. *Proc ASCO* 2013;Abstract 7004.

Investigator Commentary: Obinutuzumab/Chlorambucil (Clb) or Rituximab/Clb versus Clb Alone for Patients with CLL and Coexisting Medical Conditions

Obinutuzumab is a promising Type II anti-CD20 monoclonal antibody that has demonstrated enhanced antibody-dependent cell-mediated cytotoxicity, increased direct cell death and lower complement activation in comparison to the Type I antibody rituximab. The results of this study show that the addition of rituximab or obinutuzumab to Clb was superior to Clb alone with respect to the overall response rate, complete response rate and PFS.

The data presented at ASCO this year also hinted at the possibility that obinutuzumab is gaining an advantage over rituximab. The overall response rate was about 75% versus 66% and the complete response rate was 22% versus 8% with obinutuzumab versus rituximab. An approximate 7-month PFS advantage was reported in favor of the obinutuzumab arm. Not long after ASCO, it was announced in a press release that the second stage of the study directly comparing the obinutuzumab and rituximab arms met its final PFS endpoint. However, we will need to wait until this year's ASH meeting to see these data presented. The trial was designed so that the obinutuzumab arm would have to have a hazard ratio of 0.74 to be superior to rituximab in terms of PFS. If that can be demonstrated without a significant alteration in the toxicity profile, this would be a significant therapeutic advance for patients.

Interview with Brad S Kahl, MD, September 10, 2013

Final Results of a Phase 1 Study of Idelalisib (GS-1101), a Selective Inhibitor of Phosphatidylinositol 3-Kinase p110 Delta (PI3Kd), in Patients with Relapsed or Refractory CLL[1]

A Phase 2 Study of the Selective Phosphatidylinositol 3-Kinase Delta (PI3Kd) Inhibitor Idelalisib (GS-1101) in Combination with Rituximab in Treatment-Naïve Patients ≥65 years with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)[2]

[1]Brown JR et al.
Proc ASCO 2013;Abstract 7003.

[2]O'Brien SM et al.
Proc ASCO 2013;Abstract 7005.

Final Results of a Phase 1 Study of Idelalisib (GS-1101), a Selective Inhibitor of Phosphatidylinositol 3-Kinase p110 Delta (PI3Kd), in Patients with Relapsed or Refractory CLL

Brown JR et al.

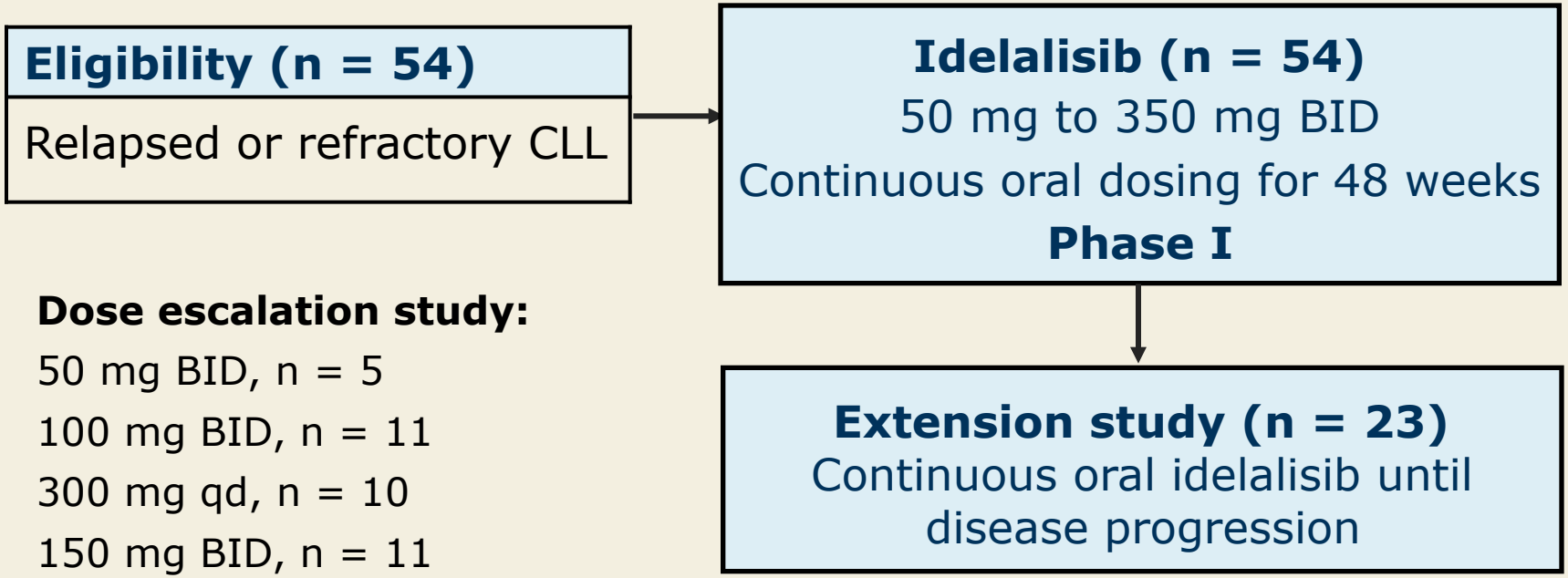
Proc ASCO 2013;Abstract 7003.

Background

- Idelalisib (GS-1101) is a first-in-class, selective, oral inhibitor of PI3Kδ.
- The inhibition of PI3Kδ has the potential to impede multiple critical pathways that promote cancer growth in chronic lymphocytic leukemia (CLL).
- Idelalisib blocks proliferation and induces apoptosis in many B-cell malignancies.
- It also inhibits homing and retention of malignant B cells in lymphoid tissues.
- **Study objective:** To determine the efficacy, safety, pharmacodynamics and pharmacokinetics of oral idelalisib as a single agent for patients with relapsed or refractory CLL.

Brown JR et al. *Proc ASCO* 2013;Abstract 7003.

Phase I Trial Design



Dose escalation study:

50 mg BID, n = 5

100 mg BID, n = 11

300 mg qd, n = 10

150 mg BID, n = 11

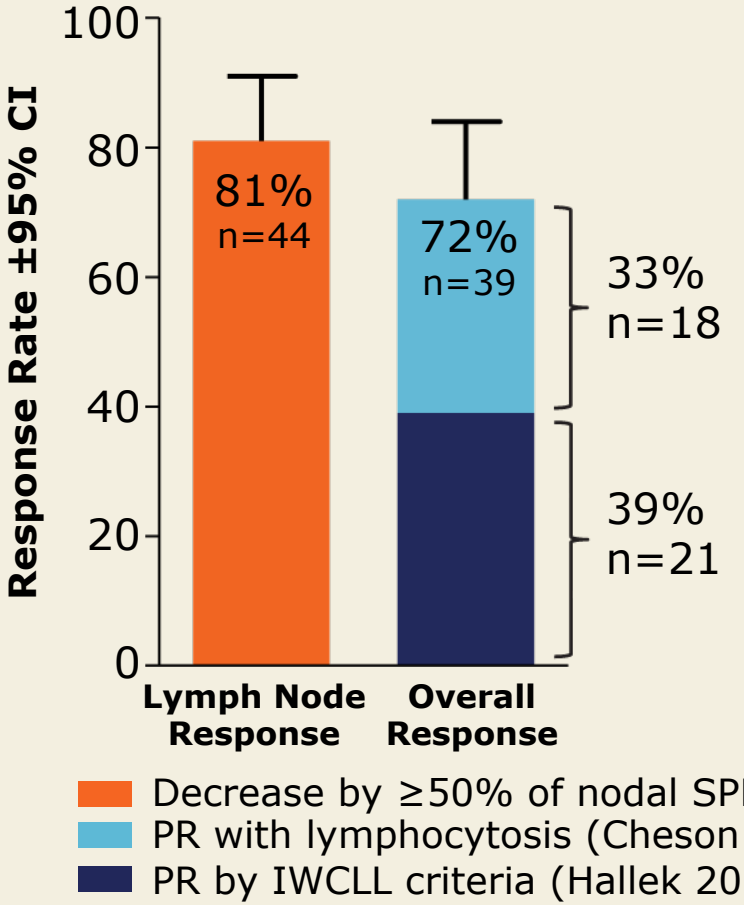
200 mg BID, n = 10

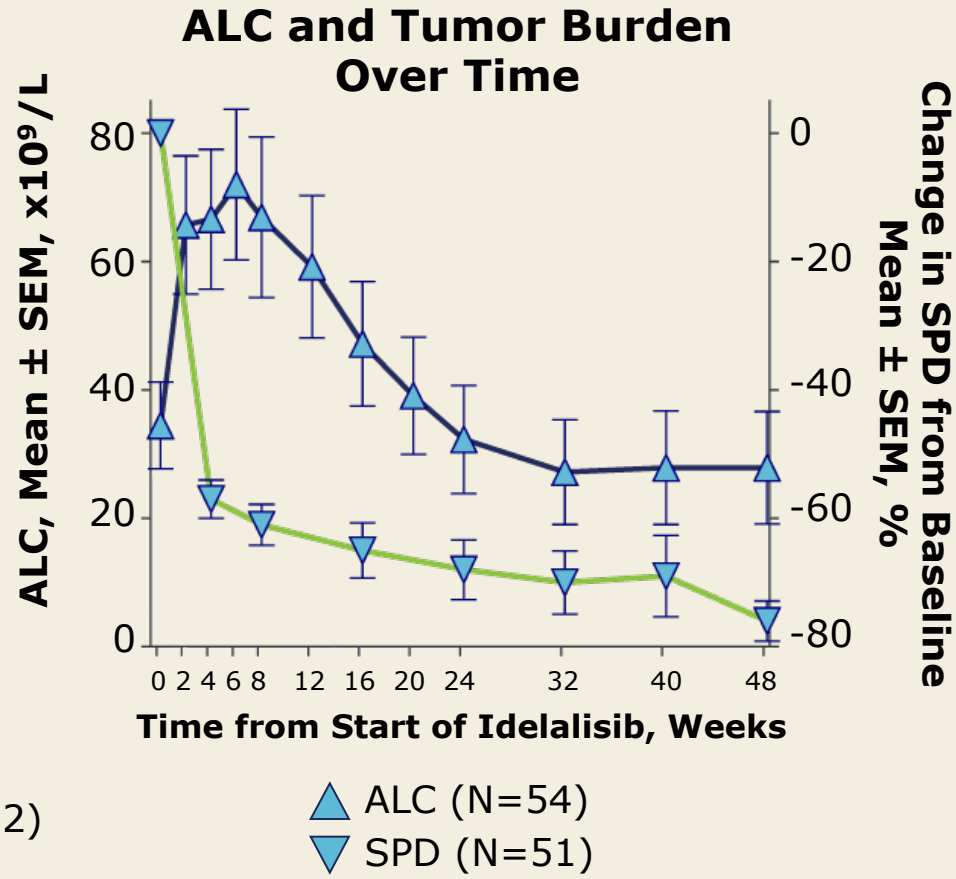
350 mg BID, n = 7

- Assessments performed at week 0, 8, 16, 24 and every 12 weeks thereafter
- **Endpoints included:** Dose selection, safety, efficacy, pharmacodynamics and pharmacokinetics

Brown JR et al. *Proc ASCO* 2013;Abstract 7003.

Nodal and Overall Response Rates

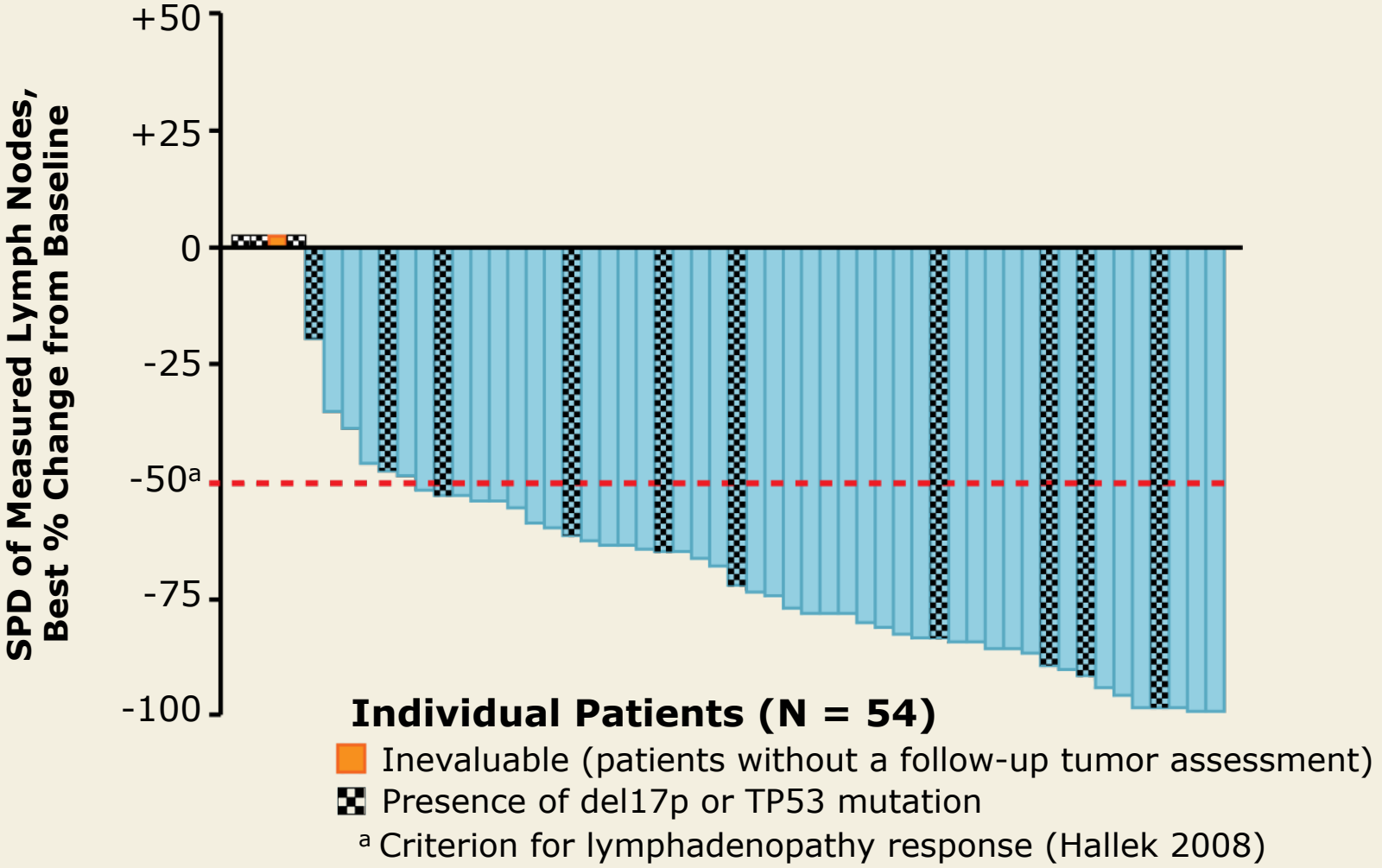




PR = partial response; ALC = absolute lymphocyte count; SPD = sum of the products of the greatest perpendicular diameters

With permission from Brown JR et al. *Proc ASCO* 2013;Abstract 7003.

Best Nodal Response



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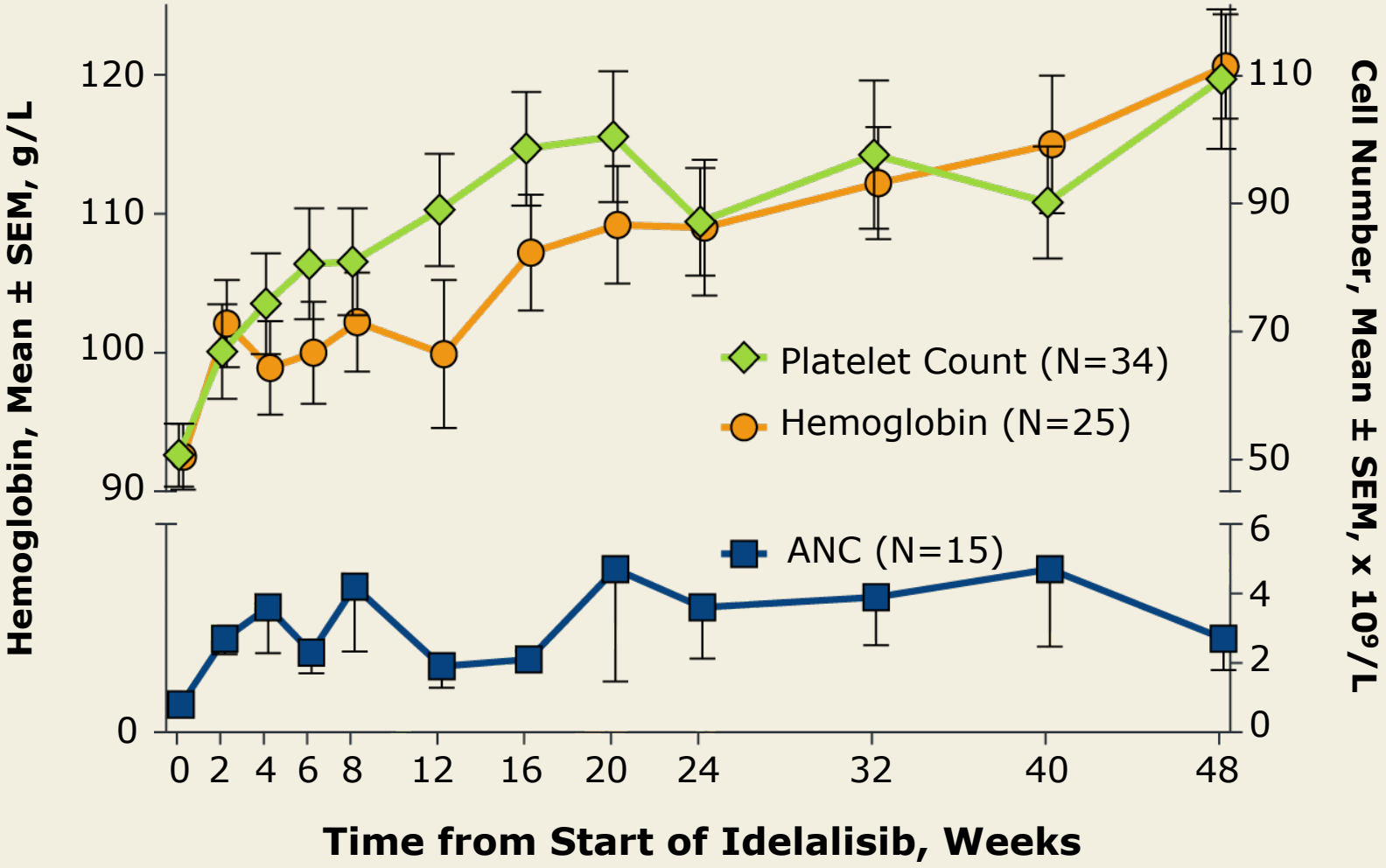
Improvement in Baseline Cytopenias



With permission from Brown JR et al. *Proc ASCO* 2013;Abstract 7003.

Survival Outcomes

Clinical parameter	Outcome
Median PFS	
Overall population (n = 54)	17.1 months
At dose ≥150 mg BID (n = 28)	29 months
At dose <150 mg BID (n = 26)	7 months
Median OS (n = 54)	Not yet reached
Median TTR (n = 39)	1.0 month
Median DoR (n = 39)	16.8 months

PFS = progression-free survival; OS = overall survival; TTR = time to response; DoR = duration of response

Brown JR et al. *Proc ASCO* 2013;Abstract 7003.

Select Adverse Events (AEs)

Event (n = 54)	Any grade	Grade ≥3
Fatigue	31.5%	1.9%
Diarrhea	29.6%	5.6%
Pyrexia	29.6%	3.7%
Pneumonia	20.4%	18.5%
Neutropenic fever	11.1%	11.1%
Vomiting	11.1%	1.9%
Increased AST*	24.1%	1.9%
Increased ALT*	18.5%	1.9%

* In total, 15 patients experienced elevated transaminases.

- Serious AEs included cellulitis (6%), colitis (6%), bronchitis (4%), infection (4%) and sepsis (4%).

Brown JR et al. *Proc ASCO* 2013;Abstract 7003.

Author Conclusions

- Idelalisib rapidly induced durable responses in patients with heavily pretreated or refractory CLL.
- Idelalisib has an acceptable safety profile.
- A dose of 150 mg BID was chosen for the Phase III trials of idelalisib.
- Several Phase III trials of idelalisib in combination with other agents are ongoing for patients with previously treated CLL:
  - Rituximab (NCT01539512)
  - Bendamustine/rituximab (NCT01569295)
  - Ofatumumab (NCT01659021)

Brown JR et al. *Proc ASCO* 2013;Abstract 7003.

Investigator Commentary: Final Results of a Phase I Trial of Idelalisib for Relapsed or Refractory CLL

The waterfall plot of best nodal response is impressive. It resembles one that might be seen with cytotoxic agents, with rapid nodal responses observed. Idelalisib is effective in hard-to-treat patient populations with relapsed or refractory CLL harboring deletion 17p or TP53 mutations. The time to response is short at 1 month. This is not a typical observation for oral targeted agents, at least not in lymphoma, including lenalidomide and bortezomib. Idelalisib is associated with Grade ≥3 diarrhea and colitis. How it causes these toxic effects is not clear.

Interview with Andrew M Evens, DO, MSc, July 19, 2013

In this Phase I trial of idelalisib (CAL-101) the median number of prior therapies was 5, so this was not a favorable population. The clinical activity was encouraging. The ORR was 72%, and clinical benefit was prompt. The median PFS was 17.1 months and the median DoR was about 17 months. These are meaningful, durable remissions for patients with heavily pretreated, in many cases chemotherapy-refractory CLL. The drug is generally well tolerated but is associated with diarrhea. About 30% of patients experienced some degree of diarrhea. Some patients have been found to have colitis, but the mechanism of the colitis is not completely clear. Other side effects include pneumonia and elevated ALT/AST.

Interview with Brad S Kahl, MD, September 10, 2013

A Phase 2 Study of the Selective Phosphatidylinositol 3-Kinase Delta (PI3Kd) Inhibitor Idelalisib (GS-1101) in Combination with Rituximab in Treatment-Naïve Patients ≥65 years with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

O'Brien SM et al.

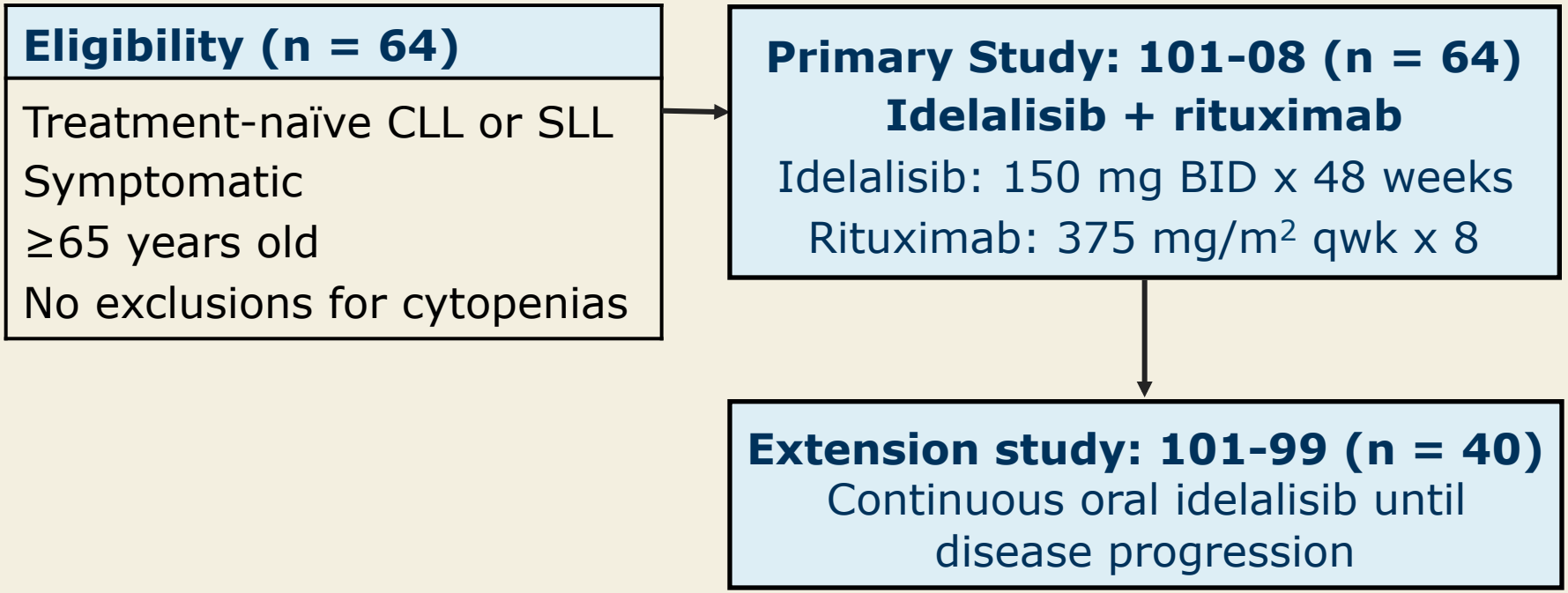
Proc ASCO 2013;Abstract 7005.

Background

- Idelalisib blocks proliferation and induces apoptosis in many B-cell malignancies.
- It was demonstrated to have an overall response rate of 79% when used in combination with rituximab for patients with relapsed/refractory CLL (*Proc ASH* 2012;Abstract 191).
- **Study objective:** To determine the efficacy and safety of oral idelalisib in combination with rituximab for elderly patients with previously untreated CLL.

O'Brien SM et al. *Proc ASCO* 2013;Abstract 7005.

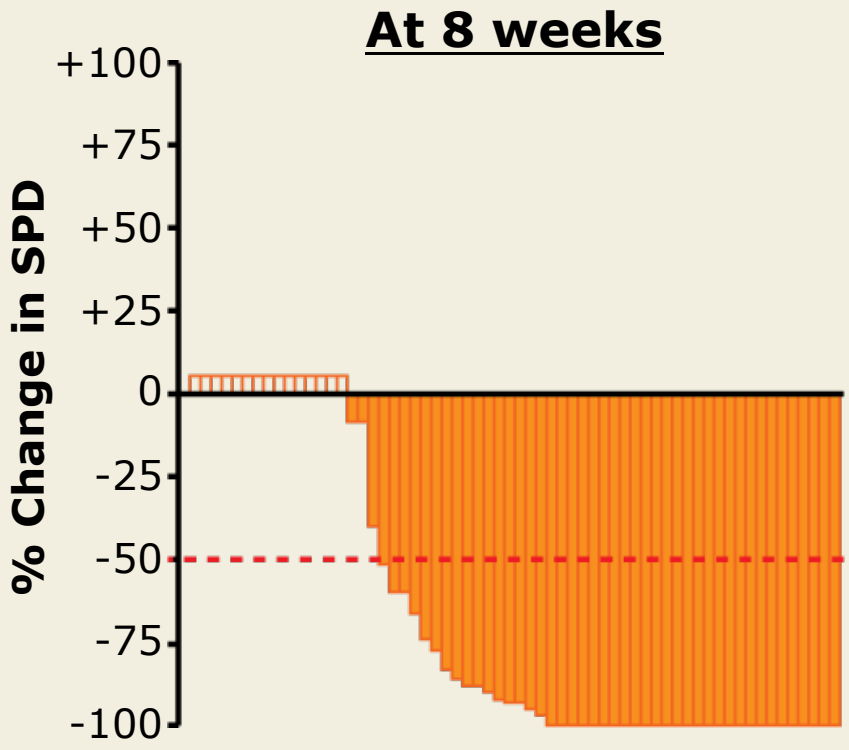
Phase II Trial Design



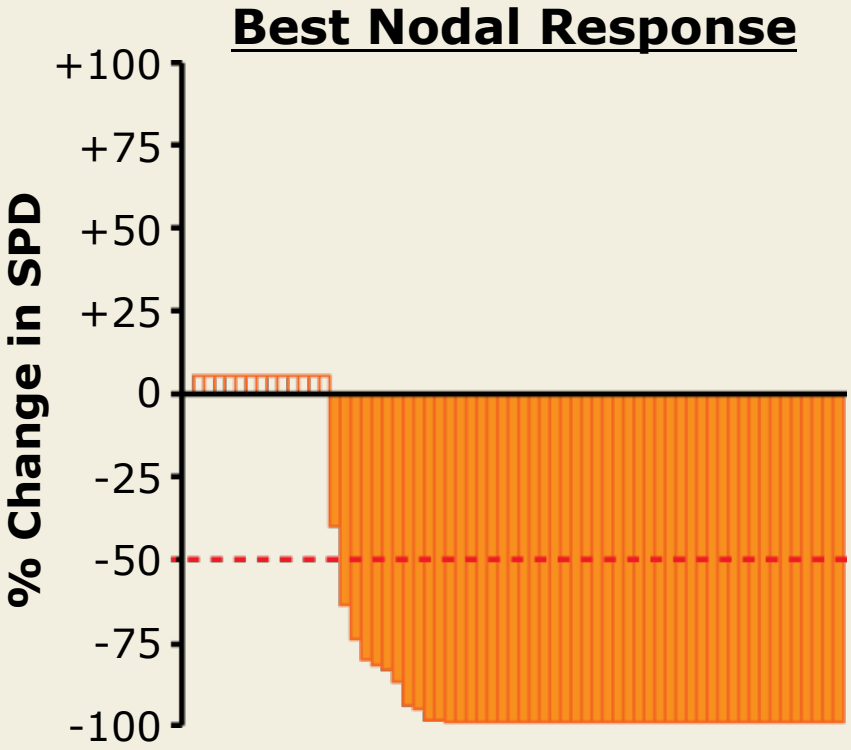
- Assessments performed at week 0, 8, 16, 24, 36, 48 and according to standard practice thereafter
- **Primary endpoint:** Overall response rate (ORR)
- **Secondary endpoints:** Duration of response, progression-free survival (PFS), safety

O'Brien SM et al. *Proc ASCO* 2013;Abstract 7005.

Nodal Response by Physical Examination or CT scan (N = 64)



- Not evaluable (n = 16)
  - No adenopathy at baseline (n = 12)
  - Early withdrawal (n = 2)
  - No assessment (n = 2)



- Not evaluable (n = 14)
  - No adenopathy at baseline (n = 12)
  - Early withdrawal (n = 2)

With permission from O'Brien SM et al. *Proc ASCO* 2013;Abstract 7005.

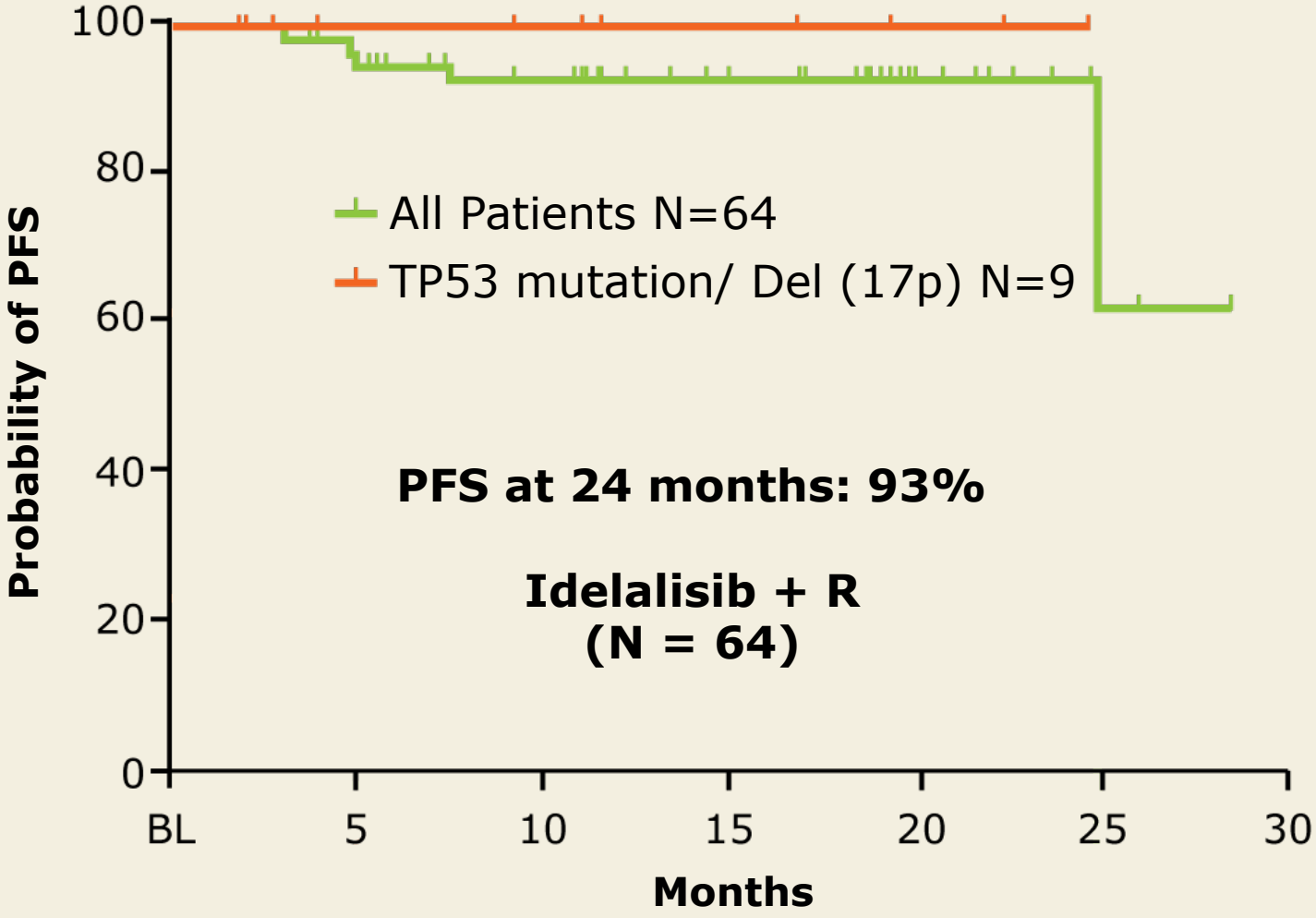
Response Rates

Response	All patients (n = 64)	With del(17p) and/or TP53 mutation (n = 9)
ORR	97%	100%
Complete response	19%	33%
Partial response	78%	67%
Stable disease	0%	0%
Progressive disease	0%	0%
Not evaluable	3%	0%

- Median time to response: 1.9 months
- 24 of 26 patients with B symptoms experienced symptom resolution by week 16

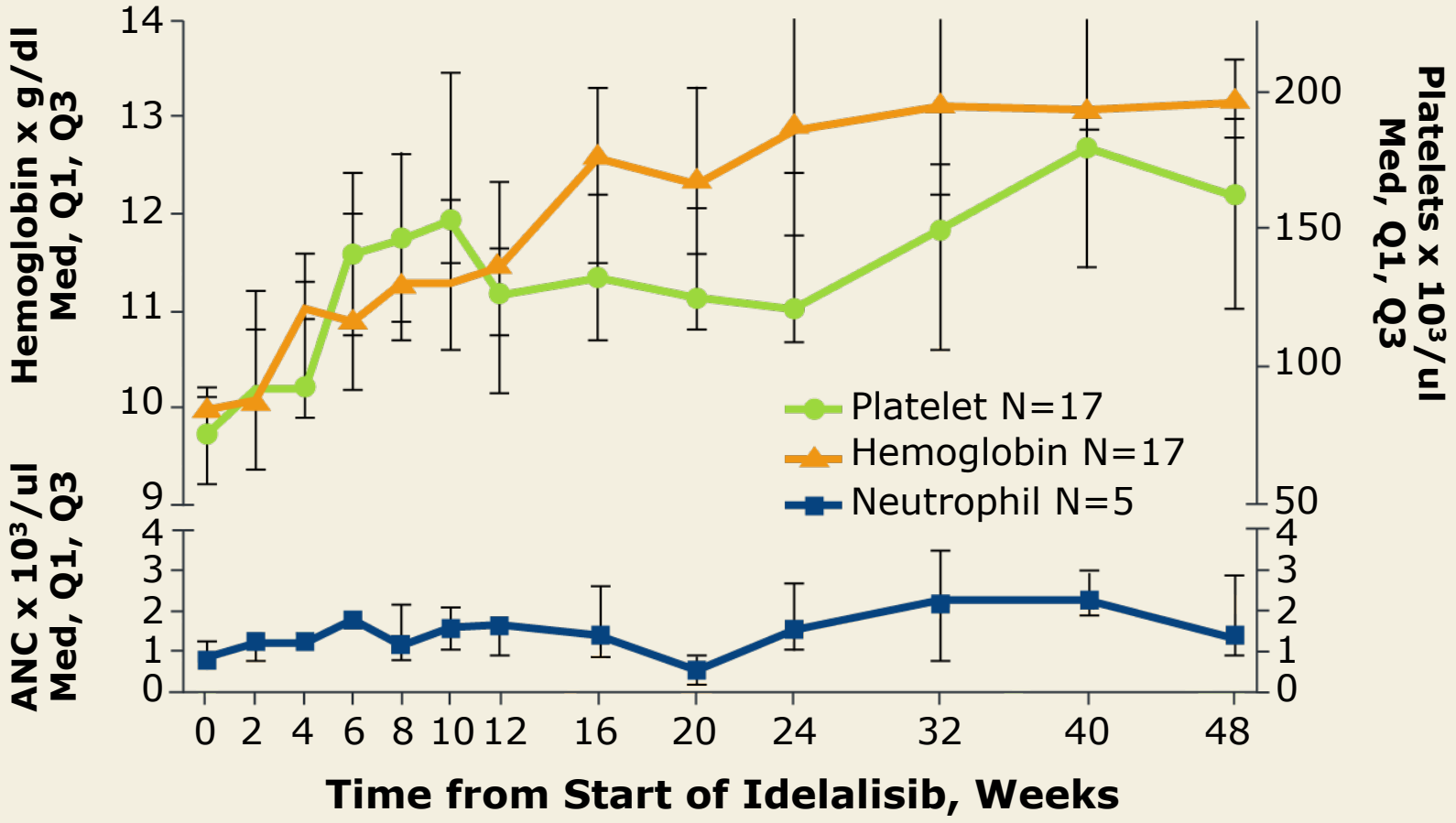
O'Brien SM et al. *Proc ASCO* 2013;Abstract 7005.

Progression-Free Survival



With permission from O'Brien SM et al. *Proc ASCO* 2013;Abstract 7005.

Improvement in Cytopenias



- Hematologic response rates:
  - Anemia (17/17), thrombocytopenia (16/17), neutropenia (5/5)

With permission from O'Brien SM et al. *Proc ASCO* 2013;Abstract 7005.

Select Adverse Events (AEs) in Primary and Extension Studies

Event	Any grade	Grade ≥3
Diarrhea	55%	23%
Pyrexia	42%	3%
Nausea	38%	2%
Rash	38%	8%
Pneumonia	27%	17%
Elevated transaminases*	NR	23%
Neutropenia*	NR	28%
Anemia; thrombocytopenia*	NR	3%; 2%

* Primary study only

- AEs leading to discontinuations included diarrhea/colitis (13%), respiratory disorders (8%), rash (5%), anemia (3%) and increased ALT/AST (2%).

O'Brien SM et al. *Proc ASCO* 2013;Abstract 7005.

Author Conclusions

- Idelalisib in combination with rituximab is highly active in older patients with treatment-naïve CLL.
  - All patients: ORR = 97% (CR, 19%; PR, 78%)
  - With del(17p)/TP53 mutation: ORR = 100% (CR, 33%; PR, 67%)
- To date, disease progression has not been reported on the study.
  - Median time on study: 14.1 months
- Idelalisib has an acceptable safety profile.
- These results support further investigation of idelalisib in front-line CLL.

O'Brien SM et al. *Proc ASCO* 2013;Abstract 7005.

Investigator Commentary: A Phase II Trial of Idelalisib and Rituximab for Patients with Treatment-Naïve CLL or SLL

In this Phase II study, idelalisib/rituximab as front-line therapy demonstrated a rapid onset of very good nodal responses. The overall response rate was 97%, with a complete response rate of 19%. For the 9 patients with 17p deletion or TP53 mutations, the overall response rate was 100%, with a complete response rate of 33%.

Interview with Andrew M Evens, DO, MSc, July 19, 2013

In the Phase II study of idelalisib for elderly patients with CLL, a dose of 150 mg BID was used in combination with rituximab. A host of other Phase II and Phase III trials are under way to find a niche for idelalisib in the marketplace. The bottom line is that PI3Kδ is a viable and meaningful therapeutic target in B-cell malignancies and in CLL. Idelalisib showed promising activity in patients with CLL with 17p deletion and TP53 mutations. It acts by targeting the PI3Kδ pathway in the cytoplasm and turning off the power inside the cell in a manner that does not involve DNA damage.

Interview with Brad S Kahl, MD, September 10, 2013

Single Agent Ibrutinib (PCI-32765) Is Highly Effective in Chronic Lymphocytic Leukaemia Patients with 17p Deletion

Wiestner A et al.

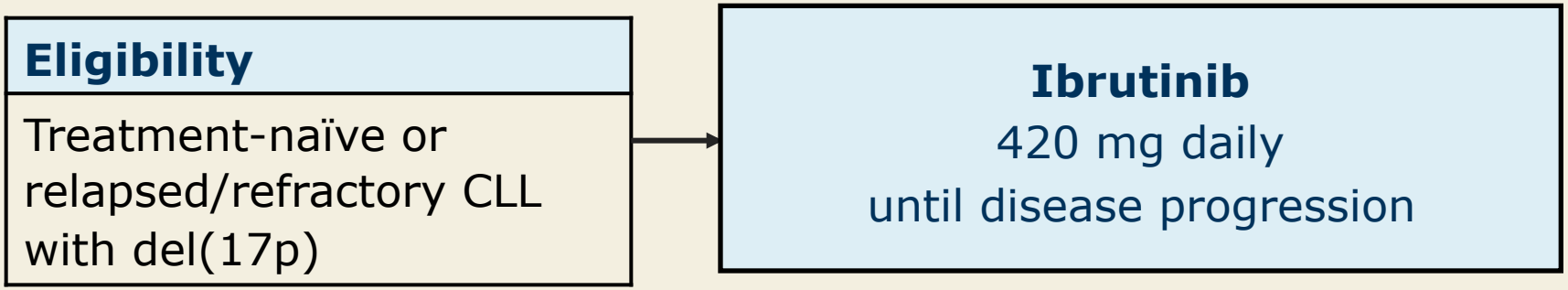
Proc ICML 2013;Abstract 008.

Background

- Patients with chronic lymphocytic leukemia (CLL) with deletion 17p experience inferior outcomes with standard chemoimmunotherapy with respect to progression-free survival and overall survival.
- Ibrutinib (PCI-32765), an inhibitor of Bruton's tyrosine kinase, has demonstrated durable antitumor activity in high-risk CLL (*NEJM* 2013;369:32).
- **Study objective:** To determine the safety and efficacy of single-agent ibrutinib in patients with CLL and del(17p).

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

Phase II Trial Design



- Responses evaluated at 6 months and every 6 months thereafter.
- Del(17p) was assessed by FISH cytogenetics.
- Spleen volumetry was determined using CT scans.
- Results reported on first 29 patients enrolled with a median follow-up of 9 months.

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

Response Rates (Abstract Only)

Response	n = 25*
Nodal response†	88%
Partial response by IWCLL criteria	48%
Partial response with lymphocytosis	40%
Progressive disease‡	4%

IWCLL = International Workshop on Chronic Lymphocytic Leukemia

* Evaluable patients

† Median reduction in lymph node size: 70%

‡ Presumed transformation

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

Nodal Response by Disease Type (Abstract Only)

Subgroup	Patients achieving response
Patients with relapsed/refractory CLL (n = 14)	93%
Patients with treatment-naïve CLL (n = 15)	82%

- All patients also experienced reduction in splenomegaly.

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

Survival and Treatment Outcomes (Abstract Only)

Outcome	
Estimated 12-month event-free survival (n = 29)	90%
Median decrease in tumor burden in bone marrow biopsies* (n = 23)	76%

* Assessed by immunohistochemistry for CD79a

- Patients with a reduction in the percentage of tumor cells with del(17p): n = 15 (median reduction = 55%)
- Patients with unchanged percentage of tumor cells with del(17p): n = 1
- Patients with increased percentage of tumor cells with del(17p): n = 3

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

Author Conclusions (Abstract Only)

- Ibrutinib as a single agent:
  - Is effective in both treatment-naïve and relapsed or refractory CLL with chromosome 17 deletion.
  - Achieves rapid control over disease in blood, nodes, spleen and bone marrow.
  - Elicits durable responses.
  - Has an acceptable safety profile:
    - Grade ≥3 nonhematologic toxicities (regardless of causality) were observed in 14% of patients.
- Ibrutinib will be further investigated as a strategy for patients with high-risk CLL.

Wiestner A et al. *Proc ICML* 2013;Abstract 008.

Investigator Commentary: Single-Agent Ibrutinib (PCI-32765) Is Highly Effective in Del(17p) CLL

This study demonstrated a high, durable response rate with ibrutinib in patients with 17p deletion, which normally predicts a poor outcome and a poor response to treatment. The study confirms that ibrutinib has similar activity in this patient population to the activity it has in patients without the deletion, and this is exciting. Almost all the patients experienced a decrease in lymph node size with ibrutinib. I believe the response rates probably underestimate the activity because at the end stage of the disease it's typically the bulky adenopathy that contributes to the illness. Even if residual circulating CLL cells are present, if patients achieve a nodal response and are feeling well, that's a victory for me.

Interview with Jonathan W Friedberg, MD, MMSc, July 18, 2013

Ibrutinib is a promising agent in the treatment of CLL, with activity in patients with del(17p) that looks just as good as it does in the rest of the population. Ibrutinib has such high activity, particularly in front-line CLL, that I believe there's a reasonable chance that it could replace cytotoxic chemotherapy in this setting.

Interview with Brad S Kahl, MD, September 10, 2013

Updated Results of a Phase I First-in-Human Study of the BCL-2 Inhibitor ABT-199 (GDC-0199) in Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)[1,2]

Seymour JF et al.

[1] *Proc ICML* 2013;Abstract 057.

[2] *Proc ASCO* 2013;Abstract 7018.

Background

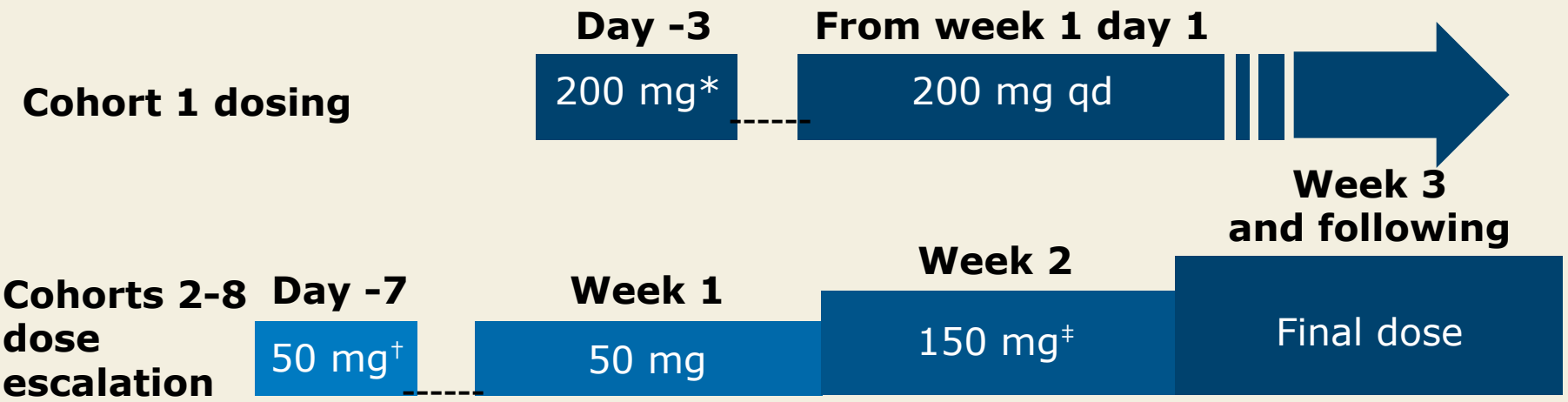
- Inhibition of the antiapoptotic protein BCL-2 shows promise for the treatment of CLL that is refractory to fludarabine (F) or CLL with 17p deletion (*Nat Med* 2013; 19(2):202-8).
- ABT-199 is an orally bioavailable, selective BCL-2 inhibitor with a greater than 500-fold higher affinity for BCL-2 than for the antiapoptotic protein BCL-2-like 1 (BCL-XL) (*Nat Med* 2013;19(2):202-8).
- **Study objective:** To determine the safety, pharmacokinetics, maximum tolerated dose, recommended Phase II dose and preliminary efficacy of ABT-199 in patients with relapsed or refractory CLL.

Seymour JF et al. *Proc ICML* 2013;Abstract 057; *Proc ASCO* 2013;Abstract 7018.

Phase I Dose-Escalation Trial Design

Eligibility (n = 56)

CLL relapsed/refractory to F or alkylator-based regimens
No prior allogeneic or autologous stem cell transplant



* An initial dose of 100 mg was administered to 1 patient; † 3 patients (1 each in cohort 2 and 3, and 1 in cohort 5) received 20 mg of ABT-199 as the initial dose; ‡ Week 2 dose in cohorts 2-5 = 100 mg

- After 3/3 patients in cohort 1 experienced dose-limiting tumor lysis syndrome, the initial dose was reduced and dosing was modified to include a stepped dose-escalation schedule.

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

Patient Demographics

Characteristic	n = 56*
Age, median (range)	67 years (36-86)
Males	73%
Prior lines of therapy, median (range)	4 (1-10)
F-refractory CLL	32%
Del(17p) mutation	38%
Diagnosis (CLL/SLL)	49/7

* As of April 2013, 56 patients were enrolled and 40 were active in the study.

Seymour JF et al. *Proc ICML* 2013;Abstract 057; *Proc ASCO* 2013;Abstract 7018.

Best Responses

All evaluable patients	(n = 55)*
Overall response rate	**84%**
Complete response (CR)	11%
CR/incomplete marrow recovery	7%
Partial response	65%
Stable disease	7%
Disease progression	2%

* One patient had not reached week 6 for evaluation by scan; 4 patients discontinued prior to assessment at week 6.

- 30/30 patients had a >50% reduction in lymphocyte counts from baseline.
- 45/51 patients experienced a >50% reduction in nodal size from baseline by CT scan.
  - Median time to 50% reduction = 43 days
- 27 patients had a >50% reduction in bone marrow infiltrate from baseline.

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

Best Responses in Evaluable Patients with High-Risk CLL

CLL with del(17p)	**n = 16***
Overall response rate	**81%**
Complete response (CR)	6%
CR/incomplete marrow recovery	6%
Partial response	69%
Stable disease	6%
Disease progression	6%
Fludarabine-refractory CLL	**n = 18†**
Overall response rate	**78%**
CR/incomplete marrow recovery	17%
Partial response	61%
Stable disease	6%

* One patient had not reached week 6 for evaluation by scan; † 3 patients discontinued prior to week 6 assessment.

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

Select Adverse Events

Event	All grades	Grade 3 or 4
Diarrhea	41%	2%
Neutropenia	39%	38%
Upper respiratory tract infection	27%	2%
Thrombocytopenia	18%	11%
Pyrexia	14%	2%
Anemia	13%	7%
Hyperglycemia	11%	9%
Tumor lysis syndrome*	11%	11%

* Includes 3 events from cohort 1; 2 clinical events and 1 laboratory event with the new dosing schedule

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

Tumor Lysis Syndrome (TLS)

- ABT-199 has antitumor activity in patients with relapsed/ refractory CLL who have bulky disease.
- TLS occurred in all 3 patients in cohort 1.
- With the revised dosing regimen, clinical TLS occurred in 2 patients (1 with acute renal failure and 1 death) who had bulky lymphadenopathy (≥10 cm).
- Key proposed study changes:
  - Further modify the dosing scheme to use a lower starting dose and then reduce dose-escalation increments.
  - Enhance current prophylaxis measures and monitoring for all patients.

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

Author Conclusions

- Single-agent ABT-199 demonstrated activity in patients with relapsed/refractory CLL, including those with del(17p) and fludarabine-refractory disease.
- TLS can be associated with rapid tumor reduction.
  - A titrated dosing scheme combined with more aggressive prophylaxis, monitoring and management may provide adequate protection for patients.
- ABT-199 warrants further single-agent and combination trials in CLL.
- A Phase II single-agent study and a Phase III combination study in CLL are planned to start in late 2013/early 2014.

Seymour JF et al. *Proc ASCO* 2013;Abstract 7018.

Investigator Commentary: Results of a Phase I Trial of ABT-199 in Relapsed or Refractory CLL

ABT-199 is a small-molecule oral inhibitor of BCL-2, a protein that is overexpressed in many B-cell malignancies. ABT-199 has a high affinity for BCL-2 but leaves other BCL-2 family members relatively intact, such as BCL-XL. One problem with previous BCL-2 inhibitors was thrombocytopenia. More selective agents like ABT-199 seem to have taken care of this issue. Single-agent ABT-199 appears to be remarkably active in CLL/SLL. In this Phase I study, the overall response rate was 84%. The response rate was similar in the high-risk population, such as patients with del(17p) or fludarabine-refractory CLL, to that in the overall population. ABT-199 was well tolerated. The major side effects were nausea and diarrhea. These side effects can be easily managed, sometimes with supportive care alone or by small dose reductions. One of the challenges with ABT-199 is that it's so active that some cases of tumor lysis syndrome have arisen, so the study had to use a stepped-up dose-escalation strategy, in which you start therapy with a baby dose and careful monitoring for a few days, after which a gradually higher dose can be used. This might take 2 to 3 weeks to build up to the target dose, which for CLL appears to be 400 mg daily. I believe ABT-199 will be a "home-run" drug in CLL/SLL.

Interview with Brad S Kahl, MD, September 10, 2013