5 Minute JournalClub

SPECIAL EDITION
Issue 2, 2011

Phase Ib/II Study of the Activity and Tolerability of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 in CLL/SLL

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for diverse forms of cancer.

LEARNING OBJECTIVE

- Recall the efficacy and tolerability of the novel Bruton's tyrosine kinase inhibitor PCI-32765 for patients with newly diagnosed or relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

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To go directly to the slides and investigator commentary for the featured abstracts, **click here**.

An oncology specialist would be hard pressed to find a better hour of television than the first half of the oral leukemia/myelodysplasia plenary session from ASCO 2011. This riveting segment of the conference, available for your viewing pleasure as part of the virtual meeting, began with 2 complementary presentations of Phase III trials evaluating the JAK1/2 inhibitor ruxolitinib **(ab 6500**, **ab LBA6501)** in patients with myelofibrosis. These were followed by a fascinating BCR-ABL mutation analysis from the ENESTnd CML study **(ab 6502)** comparing nilotinib to imatinib and then a brilliant follow-up discussion by Dr Ross Levine outlining a new paradigm in myeloproliferative disorders focused on the search for mutations and related novel blocking agents. These 3 presentations and 14 other compelling ASCO heme-onc data sets are detailed in our slide sets and profiled below in this, the second half of our super-succinct special edition *5-Minute Journal Club*.

1. Ruxolitinib in myelofibrosis

As mentioned above, this trial duet occupies a unique spot on the ASCO highlights reel, and while our understanding of the exact mechanism of action of this oral TKI may be somewhat hazy and may relate to reduction in elevated cytokine levels, what is crystal clear is that this uncommon but merciless disease has instantly entered a new era. The US-based COMFORT-I study evaluating ruxolitinib versus placebo had a number of interesting and innovative features, including the use of MRI to objectively evaluate spleen size and electronic daily diaries to record patient symptoms. The dramatic waterfall plots visibly illustrate how treatment at least temporarily reversed an otherwise downhill course in most patients.

2. CML

Dr Giuseppe Saglio presented the other previously discussed ASCO standout — the landmark substudy from the ENESTnd trial **(ab 6502)** demonstrating that prior to treatment patients had almost no BCR-ABL mutations but after therapy a fascinating panoply of alterations was observed in some individuals. Dr Levine predicted that in the near future, mutation assays will be regularly integrated into the treatment algorithm.

Additionally, 24-month follow-up from 2 key Phase III studies (ENESTnd **[ab 6511]** and DASISION **[ab 6510]**) was also unveiled in Chicago, suggesting greater efficacy and perhaps less toxicity with up-front treatment with the second-generation TKIs nilotinib and dasatinib when compared to imatinib.

3. Inotuzumab ozogamicin (our vote for name of the year)
This antibody-drug conjugate in the lineage of brentuximab vedotin in lymphoma and T-DM1 in HER2-positive breast cancer links an anti-CD22 antibody to a cytotoxic agent from the calicheamicins class (runner up). The ASCO findings **(ab 6507)** in relapsed/ refractory ALL demonstrated some type of CR in 61% of patients.

4. Myeloma
For more than a year we have witnessed the evolution of data from 2 major trials (CALGB, French IFM group) demonstrating an impressive delay in disease progression but the suggestion of an increased risk of second primary cancers (SPC) with 2 years of lenalidomide maintenance following stem cell transplant (SCT). At ASCO, 3 additional reports **(ab 8007, ab 8008, ab 8009)** have for the moment reinforced the concept that if there is an SPC signal it is relatively modest in magnitude and far outweighed by the antimyeloma benefit of maintenance len.

The other much-discussed myeloma paper was a landmark Italian study **(ab 8020)** that for the first time evaluated the role of autologous SCT in the era of novel antimyeloma agents. A progression-free survival benefit was reported with SCT, but other maturing studies are evaluating this important question.

5. CLL
Maybe the most exciting development in B-cell neoplasm research is the rapid evolution of small molecules that block B-cell receptor signaling, and at ASCO we saw more to be optimistic about with a report on the Bruton's tyrosine kinase inhibitor PCI-32765 in CLL. In this Phase Ib/II single-agent study **(ab 6508)**, response rates in excess of 50% were observed with minimal toxicity.

6. Diffuse large B-cell lymphoma
The lack of progress in this common cancer since the introduction of rituximab was highlighted again this year with 1 trial failing to show an advantage with dose-dense R-CHOP **(ab 8000)** and another showing no important survival benefit to consolidation autotransplant after R-CHOP induction **(ab 8001)**.

7. AML
AML in the elderly — a true clinical conundrum — was the subject of 3 underwhelming ASCO reports. The first **(ab 6503)** showed a modest benefit that was counterbalanced by a relatively high early mortality rate when clofarabine was combined with Ara-C. The second **(ab 6504)** demonstrated a modest benefit for decitabine, but discussant Dr Gail Roboz verbalized hope that better outcomes might be observed in her ongoing trial

evaluating 10 days of decitabine combined with the proteasome inhibitor bortezomib. The third study **(ab 6505)** was a Phase I effort evaluating a sequential regimen of azacitidine and lenalidomide that resulted in CRs in 7 of 16 patients.

Finally, we saw another interesting AML study perhaps suggesting a new model for the real-time personalized treatment of the disease. In this Phase I/II trial **(ab 6506)**, the MEK1/2 inhibitor GSK1120212 was shown to have specific activity in patients with RAS mutations.

Coming soon, an online quintet of virtual presentations delving into new developments in non-small cell lung cancer.

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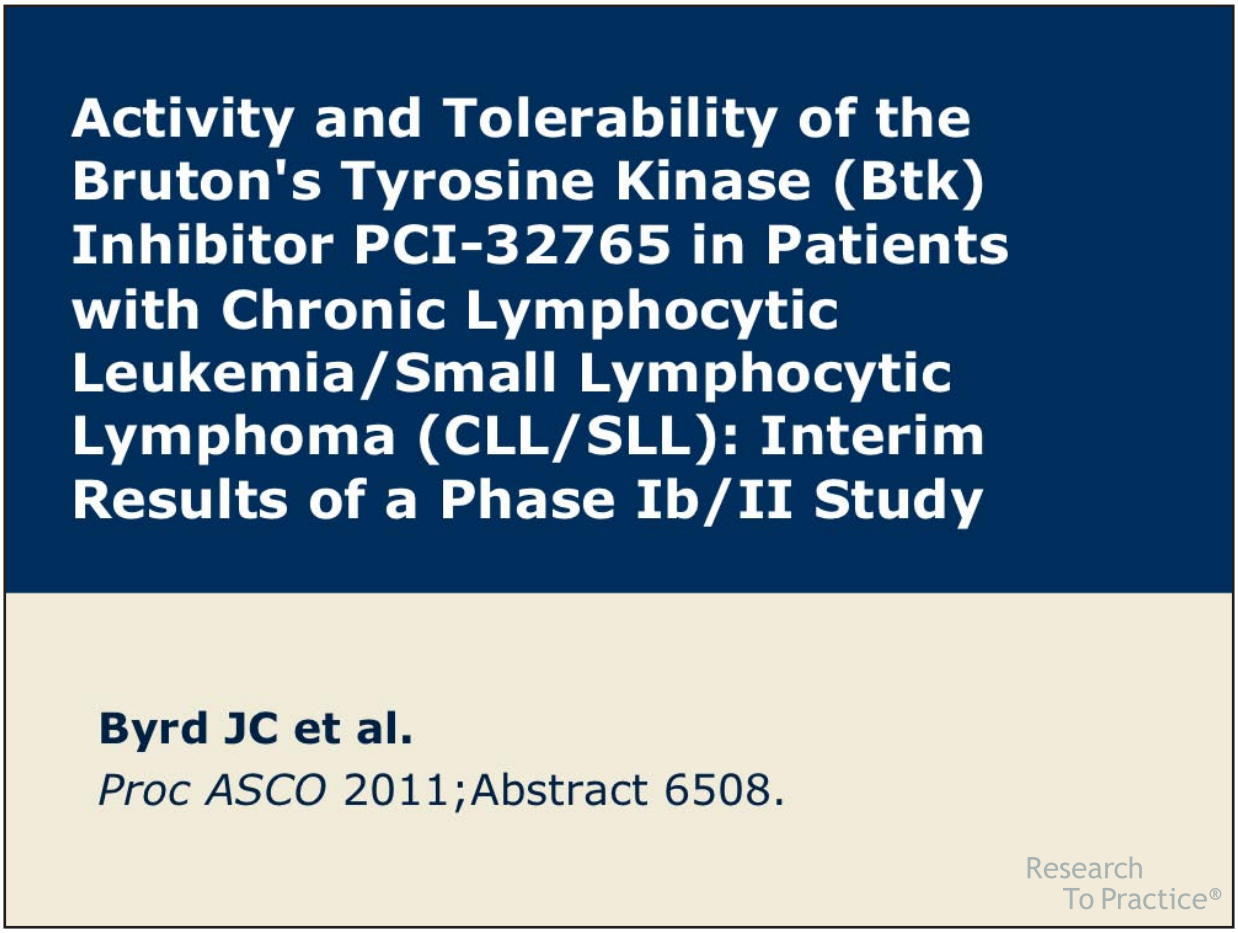
Phase Ib/II Study of the Activity and Tolerability of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 in CLL/SLL

Presentation discussed in this issue

Byrd JC et al. **Activity and tolerability of the Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): Interim results of a phase Ib/II study.** *Proc ASCO* 2011;**Abstract 6508**.

Slides from a presentation at ASCO 2011 and comments from John P Leonard, MD



Background

- **Bruton's Tyrosine Kinase (Btk):**
  - B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation.
  - Btk is an essential element of the BCR signaling pathway.
  - Mutations in Btk prevent B-cell maturation.
  - Inhibitors of Btk block BCR signaling and induce apoptosis.
- **PCI-32765:**
  - Forms a specific and irreversible bond with cysteine-481 in Btk.
  - Orally bioavailable with daily dosing resulting in 24-hour target inhibition.
  - Inhibits BCR signaling and active in spontaneous canine B-cell lymphoma.
  - In CLL cells promotes apoptosis, inhibits ERK1/AKT phosphorylation, NF-kB DNA, binding, CpR mediated proliferation.
  - Inhibits CLL cell migration and adhesion.

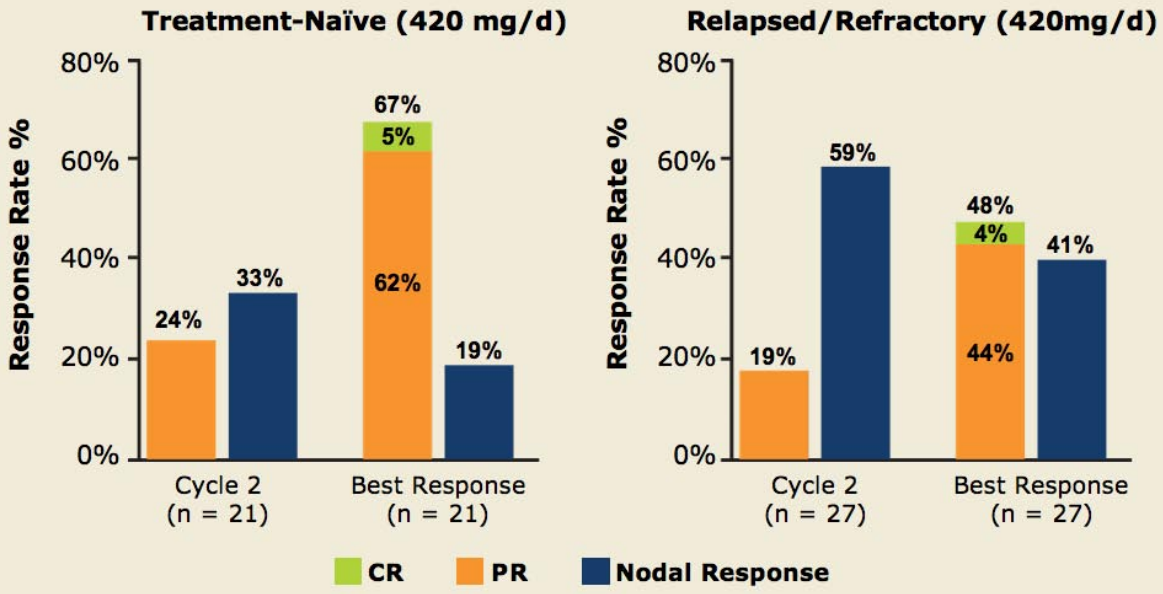
Byrd JC et al. *Proc ASCO* 2011;Abstract 6508.

PCYC 1102 Study Design

- **Single-agent, multicohort study of PCI-32765 in two subject populations with symptomatic CLL/SLL:**
  - Treatment-naïve, aged ≥65 years
    - Dose (May 2010 – March 2011): 420 mg/day until progression
  - Relapsed/refractory
    - Dose #1 (May – September 2010): 420 mg/day until progression
    - Dose #2 (October 2010 – March 2011): 840 mg/day until progression
- **Objectives:**
  - To determine the response rate, duration of response, progression-free survival, PK/PD and toxicity of PCI-32765 in separate cohorts of CLL/SLL subjects.
  - To examine the influence of genomic features on clinical response to PCI-32765.

Byrd JC et al. *Proc ASCO* 2011;Abstract 6508.

Best Response and Initial (Cycle Two) Assessment



Byrd JC et al. *Proc ASCO* 2011;Abstract 6508.

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Best Response

	Treatment-naïve 420 mg/day (n = 21)	Relapsed/refractory 420 mg/day (n = 27)
Overall response rate	67%	48%
Complete response	5%	4%
Partial response	62%	44%
Nodal response	19%	41%
Stable disease	10%	4%
Progressive disease	0%	4%
Not estimable	5%	4%

Byrd JC et al. *Proc ASCO* 2011;Abstract 6508.

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Initial (Cycle Two) Assessment by Treatment Setting and Dose

	Treatment-naïve 420 mg/day (n = 21)	Relapsed/refractory 420 mg/day (n = 27)	Relapsed/refractory 840 mg/day (n = 33)
Complete response	0	0	0
Partial response	24%	19%	15%
Nodal response	33%	59%	64%

Byrd JC et al. *Proc ASCO* 2011;Abstract 6508.

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Select Adverse Events ≤ Grade 3

	Treatment-naïve 420 mg/day (n = 23)	Relapsed/refractory 420 mg/day (n = 27)
Diarrhea	48%	70%
Nausea	39%	33%
Vomiting	17%	22%
Dyspepsia	22%	19%
Bruising	4%	33%
Muscle spasms	17%	26%
Rash	26%	11%
Upper respiratory infection	13%	37%
Fatigue	17%	33%

Byrd JC et al. *Proc ASCO* 2011;Abstract 6508.

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Author Conclusions

- Toxicity of PCI-32765 is modest, generally allowing extended continuous dosing in patients with CLL.
  - The majority of adverse events were Grade 1 or 2 in severity.
  - Cytopenias were relatively uncommon in patients treated with PCI-32765 at 420 mg/day.
    - Grade 3/4 neutropenia was more common in the 840-mg group.
- These interim Phase II data confirm that PCI-32765 is highly active in patients with treatment-naïve and relapsed/refractory CLL/SLL.
  - 2008 CLL IWG objective responses (PR + CR) and nodal responses appear to be durable and independent of high-risk genomic features.
  - A high proportion (81%) of patients with relapsed/refractory disease are free of disease progression beyond six months (420 mg/day cohort) and continue on therapy.

Byrd JC et al. *Proc ASCO* 2011;Abstract 6508.

Investigator Commentary: The Results from a Phase Ib/II Study of the Btk Inhibitor PCI-32765 in CLL

Signaling through the B-cell receptor is an important part of B-cell physiology. It's important in B-cell tumors in keeping those cells alive and making them resistant to treatment. Btk is one of a number of compounds under investigation that inhibits kinases downstream from the B-cell receptor.

What was reported at ASCO 2011 relates to the Btk inhibitor PCI-32765. This is an oral agent that is also active in other B-cell tumors, including follicular lymphoma and mantle-cell lymphoma. Administration of PCI-32765 resulted in a significant reduction in lymph node size in the vast majority of patients with previously treated CLL.

PCI-32765 is a well-tolerated agent. The main issues regarding toxicities with this drug relate to gastrointestinal toxicity, nausea, diarrhea and stomach upset. This is of particular importance considering the fact that so many of our current CLL treatments can cause cytopenias and infections or predispose to infections. I believe PCI-32765 is a promising new agent that has a high response rate in patients with CLL, including those with adverse risk factors such as 17p deletion.

John P Leonard, MD