

The logo features a white stopwatch icon with a large number '5' inside the circular face. To the right of the stopwatch, the word 'Minute' is written in a large, bold, white sans-serif font, and 'Journal Club' is written below it in a smaller, white sans-serif font.

5 Minute Journal Club

SPECIAL EDITION

Issue 2, 2011

**Clinical Trial Results with Novel Agents
and Regimens for the Treatment of Newly
Diagnosed or Relapsed/Refractory
AML/MDS, Including in the Elderly**

For more visit ResearchToPractice.com/5MJCASCOHEME2011

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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 OBJECTIVES

- Consider emerging data on the use of cytarabine in combination with clofarabine for older patients with relapsed or refractory acute myelogenous leukemia (AML).
- Consider the inclusion of decitabine in the treatment algorithm for older patients with newly diagnosed AML.
- Describe Phase I efficacy outcomes with sequential azacitidine and lenalidomide for elderly patients with AML.
- Describe Phase I/II efficacy outcomes with the MEK1/2 inhibitor GSK1120212 in patients with relapsed/refractory myeloid cancer.

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FACULTY — 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:

Susan M O'Brien, MD
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No real or apparent conflicts of interest to disclose.

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This activity is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation and Genentech BioOncology.

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Expiration date: September 2012

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.

Neil Love, MD

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Clinical Trial Results with Novel Agents and Regimens for the Treatment of Newly Diagnosed or Relapsed/Refractory AML/MDS, Including in the Elderly

Presentation discussed in this issue

Borthakur G et al. **Phase I/II trial of the MEK1/2 inhibitor GSK1120212 (GSK212) in patients (pts) with relapsed/refractory myeloid malignancies: Evidence of activity in pts with RAS mutation.** *Proc ASCO 2011*; **Abstract 6506**.

Slides from a presentation at ASCO 2011

Phase I/II Trial of the MEK1/2 Inhibitor GSK1120212 (GSK212) in Patients with Relapsed/Refractory Myeloid Malignancies: Evidence of Activity in Pts with RAS Mutation

Borthakur G et al.

Proc ASCO 2011; Abstract 6506.

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Background

- Signaling through the RAS/RAF/MEK pathway is activated in many human cancers.
- GSK212 is a potent, selective allosteric inhibitor of MEK1/2 that inhibits proliferation of myeloid cell lines in vitro.
- A Phase I/II study of a single, daily, oral dosing regimen was conducted.

- **Study Objectives:**

- Define the recommended Phase II dose (RP2D) of GSK212.
- Evaluate pharmacokinetics, toxicity and preliminary activity in patients with previously treated hematologic malignancies.

Borthakur G et al. *Proc ASCO* 2011;Abstract 6506.

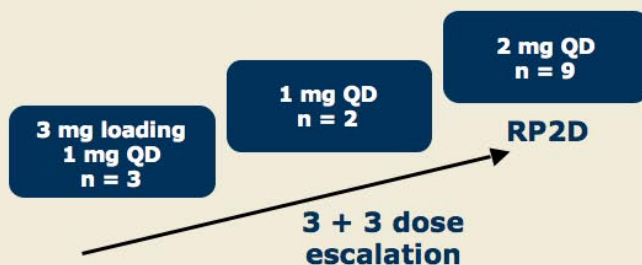
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Phase I/II Study Design

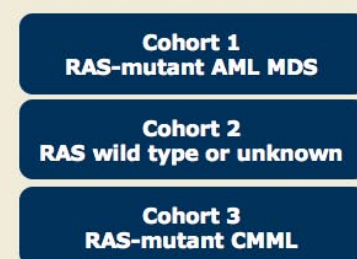
Eligibility

Relapsed/refractory AML, poor-risk MDS (>5% blasts), ALL, CMML
ECOG PS 0-2
Adequate organ function

Phase 1 – Dose escalation



Phase 2 – Expansion



Recommended Phase II dose = 2 mg QD

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome

Borthakur G et al. *Proc ASCO* 2011;Abstract 6506.

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Patient Characteristics: 2 mg/Day Dose

| Characteristic | n = 47 |
|-----------------------------------|------------|
| Median age, years (range) | 64 (21-87) |
| Number of prior therapies, median | 2 |
| ECOG PS, n (%) | |
| 0-1 | 34 (72) |
| 2 | 13 (28) |
| Diagnosis, n (%) | |
| AML | 42 (89) |
| Other | 5 (11) |
| RAS mutation, n (%) | 16 (34) |
| FLT3 mutation, n (%) | 18 (38) |
| Cytogenetics, n (%) | |
| Complex | 9 (19) |
| Core-binding factor | 2 (4) |
| Normal | 8 (17) |
| Other/unknown | 17 (37) |

Borthakur G et al. *Proc ASCO* 2011;Abstract 6506.

Clinical Activity

| Best Response, n (%) | N or KRAS Mutated (n = 16) | RAS Wild Type or Unknown (n = 31) |
|-----------------------|-------------------------------|---|
| CR/CRp | 3 (19) | 0 |
| MLFS | 1 (6) | 0 |
| Partial response | 0 | 1 (3) |
| HI/HI-N/HI-P | 1 (6) | 5 (16) |
| Stable disease | 10 (63) | 8 (26) |
| Progressive disease | 0 | 13 (42) |
| Overall response rate | 4 (25) | 1 (3) |

- MLFS = morphologic leukemic-free state
- ORR = CR/CRp/MLFS/PR

6 patients not evaluable

Borthakur G et al. *Proc ASCO* 2011;Abstract 6506.

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Select Adverse Events*

| AEs (N = 47) | All Grades | Grade 3/4 |
|---------------------|------------|-----------|
| Diarrhea | 47% | 4% |
| Pyrexia | 30% | 6% |
| Rash | 26% | 4% |
| Fatigue | 25% | 4% |
| AST increase | 24% | 11% |
| ALT increase | 23% | 11% |
| Pneumonia | 23% | 17% |
| Febrile neutropenia | 23% | 19% |

* Occurring in greater than 20% of patients

Borthakur G et al. *Proc ASCO* 2011;Abstract 6506.

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Events of Special Interest

- **Decrease in LVEF**
 - Six percent (3/47) of patients had drug-related left ventricular dysfunction (1 Grade 1 event and 2 Grade 2 events).
- **Transaminase elevations**
 - Two patients had drug held due to transaminase elevations — on rechallenge, 1 positive and 1 negative.
- **Ocular toxicity**
 - **Central Serous Retinopathy:** Fluid accumulation in the macular region between retinal pigment epithelium and out segment.
 - One patient developed a reversible retinopathy.

Borthakur G et al. *Proc ASCO* 2011;Abstract 6506.

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Author Conclusions

- **Acceptable safety profile:**
 - Monotherapy safety profile suggests potential to combine with other antileukemic therapies
- **Preliminary efficacy:**
 - Overall response rates of 25 percent (4 of 16) among patients with RAS mutation
- **Enrolling patients with RAS-mutant AML, MDS and CMML:**
 - Centralized RAS mutation analysis
 - Up to 30 sites in US and Europe open to accrual

Borthakur G et al. *Proc ASCO* 2011;Abstract 6506.

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