5 Minute JournalClub

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

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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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This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located on our website at ResearchToPractice.com/5MJCASCO2011/AMLMDS/CME.

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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:

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No real or apparent conflicts of interest to disclose.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Allos Therapeutics, Amgen Inc, Astellas Pharma Global Development Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Lilly USA LLC, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi and Seattle Genetics.

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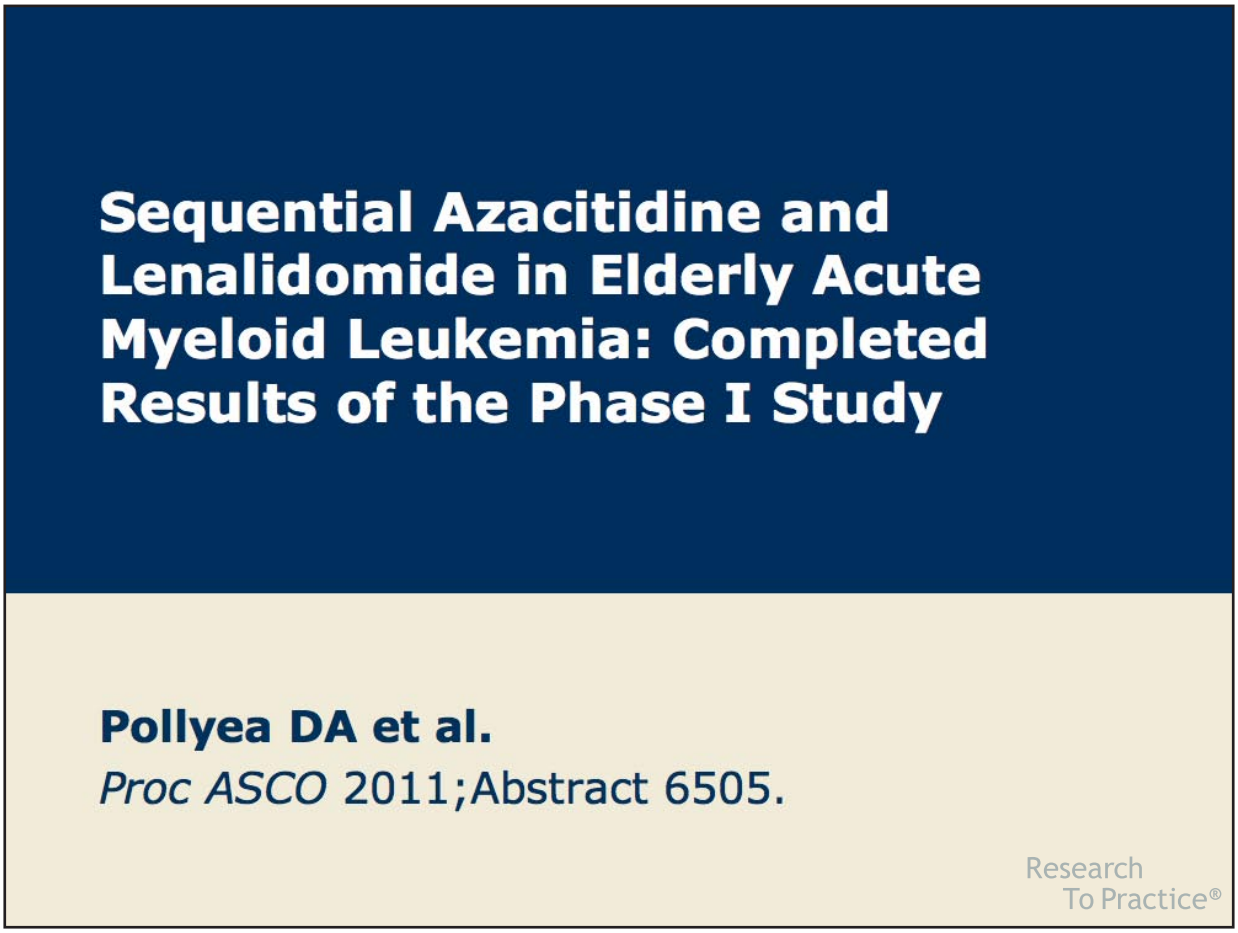
Clinical Trial Results with Novel Agents and Regimens for the Treatment of Newly Diagnosed or Relapsed/Refractory AML/MDS, Including in the Elderly

Presentation discussed in this issue

Pollyea DA et al. **Sequential azacitidine and lenalidomide in elderly acute myeloid leukemia: Completed results of the phase I study.** *Proc ASCO* 2011;**Abstract 6505**.

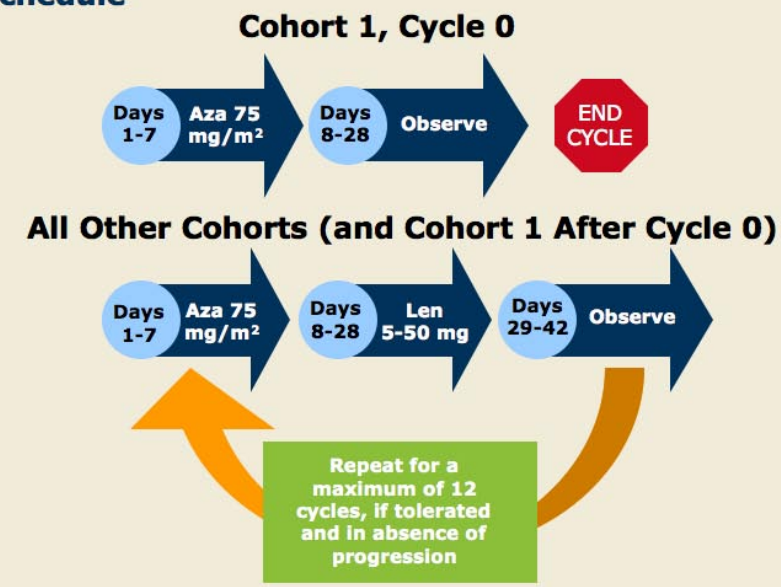
Slides from a presentation at ASCO 2011 and comments from Susan M O'Brien, MD



Phase I Study of Sequential Azacitidine and Lenalidomide

Patients ≥60 years with previously untreated nonacute promyelocytic AML (N = 18)

Dosing Schedule



Pollyea DA et al. *Proc ASCO* 2011;Abstract 6505.

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Adverse Events

Adverse Event	N = 18
Fatigue	94%
Injection reaction	72%
Constipation	61%
Nausea	61%

Pollyea DA et al. *Proc ASCO* 2011;Abstract 6505.

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Summary: Toxicity Results

- 17 serious adverse events occurred in 11 patients.
- Neutropenic fever, fatigue and cytopenias were the most common adverse events observed.
- The maximum tolerated dose of lenalidomide was not reached.
- The Phase II dose and schedule established as:
  - Azacitidine 75 mg/m^2 days 1-7, lenalidomide 50 mg days 8-28, observation on days 29-42.

Pollyea DA et al. *Proc ASCO* 2011;Abstract 6505.

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Clinical Outcomes

Clinical Variable	
Overall response rate*	63%
Complete response rate*	44%
Median number of cycles for best response	2.5
Median overall survival	8.2 mos
Median response duration	6.2 mos
Deaths due to disease progression	6

*n = 16 evaluable patients

Pollyea DA et al. *Proc ASCO* 2011;Abstract 6505.

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Response Predictors

- Clinical Response:
  - Post hoc analyses revealed that low numbers of bone marrow blasts at diagnosis statistically correlated with response (p = 0.02).
- Biological Response:
  - Hypermethylated baseline signature appeared to correlate with nonresponders.
  - Bone marrow cytokine expression profiles were altered in responders versus nonresponders.
    - M-CSF
    - MIG
    - IL-17
    - TNF-beta
    - TGF-beta

Pollyea DA et al. *Proc ASCO* 2011;Abstract 6505.

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Summary

- Sequential azacitidine and lenalidomide are generally well tolerated in elderly patients with previously untreated AML.
- Phase II dose and schedule is azacitidine 75 mg/m^2 days 1-7, lenalidomide 50 mg days 8-28 and observation days 29-42.
- In 16 evaluable patients, the overall response rate is 63% and the complete response rate is 44%.
- Low numbers of bone marrow blasts at diagnosis and methylation and cytokine signatures may predict responders.
- This less intensive treatment approach may allow equivalent response rate with less toxicity than standard remission induction chemotherapy.

Pollyea DA et al. *Proc ASCO* 2011;Abstract 6505.

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Investigator Commentary: Sequential Azacitidine and Lenalidomide Induction Therapy for Elderly Patients with AML

The nice thing about hypomethylating agents such as decitabine and azacitidine is that although myelosuppression occurs, no toxicity is present. These drugs could easily lend themselves to combinations and I believe that the combination with lenalidomide is interesting.

The issue is twofold for this study. First, this was a Phase I study with only 18 patients and therefore the high CR rate reported in these elderly patients with AML needs to be viewed with caution. Second, the incidence of fatigue was 94%, and that's also been my experience. Fatigue becomes a major issue with lenalidomide in elderly patients, particularly when administered at higher doses or for a prolonged period of time. Although I like the concept of combining azacitidine with another drug, based on the side effect profile I'm uncertain that the combination with lenalidomide will be an easy therapy to administer to elderly patients.

Susan M O'Brien, MD