INTERVIEW

## Richard M Stone, MD

Dr Stone is Director of the Adult Leukemia Program at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

### Tracks 1-16

**Track 1** Differential management of acute myeloid leukemia (AML) and acute promyelocytic leukemia (APL)

**Track 2** Long-term prognosis with allogeneic SCT versus a chemotherapy-based treatment approach for AML

**Track 3** Care of elderly patients with AML

**Track 4** Results from the Phase III APL0406 trial of all-trans retinoic acid (ATRA) and arsenic trioxide versus ATRA and idarubicin-based chemotherapy for newly diagnosed, nonhigh-risk APL

**Track 5** **Case discussion:** A 71-year-old presents with pancytopenia and is diagnosed with myelodysplastic syndrome (MDS) with deletion 5q

**Track 6** Role of transplant in patients with MDS

**Track 7** Use of lenalidomide in patients with low- or intermediate-risk MDS

**Track 8** Indications for use of and clinical experiences with ruxolitinib for patients with myelofibrosis (MF)

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**Track 14** Monitoring responses in patients with CML receiving imatinib

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**Track 16** Perspective on results from the STIM trial: Discontinuation of imatinib after sustained complete molecular remission in patients with CML

## Select Excerpts from the Interview

### Track 4

**DR LOVE:** What are your thoughts on the Phase III study of all-trans retinoic acid (ATRA) with arsenic trioxide compared to ATRA with chemotherapy for patients with low- to intermediate-risk acute promyelocytic leukemia (APL)?

**DR STONE:** First, to clarify low- versus high-risk APL because I've been asked about this by community oncologists, all you have to remember is the white blood cell count at diagnosis. A white blood cell count higher than 10,000 equates to high-risk disease, and a count lower than 10,000 indicates either intermediate- or low-risk APL.

I believe the standard treatment has changed for patients with APL with white blood cell counts lower than 10,000 because of a seminal work published recently in *The New England Journal of Medicine* by Francisco Lo-Coco and colleagues. These authors used ATRA and arsenic trioxide without chemotherapy. The results of this trial were impressive and demonstrated an advantage with the chemotherapy-free approach (Lo-Coco 2013; [3.1]).

For patients with higher-risk disease, I'll use the CALGB-9710 regimen, which is "3 plus 7" and retinoic acid for induction therapy and then arsenic trioxide consolidation followed by more anthracycline or ATRA for late consolidation. You could also add gemtuzumab ozogamicin for patients with high-risk APL.

**3.1**

**Phase III Study of All-trans Retinoic Acid (ATRA) with Arsenic Trioxide (ATO) versus ATRA with Idarubicin (AIDA) for Patients with Low- to Intermediate-Risk Acute Promyelocytic Leukemia**

| | ATRA/ATO (n = 77) | AIDA (n = 79) | *p*-value |
|---|---|---|---|
| Two-year event-free survival | 97% | 86% | <0.001* |
| Two-year overall survival | 99% | 91% | 0.02 |

* For noninferiority; $p = 0.02$ for superiority of ATRA/ATO

Compared to AIDA, ATRA/ATO was associated with less hematologic toxicity and fewer infections but with more hepatic toxicity.

Lo-Coco F et al. *N Engl J Med* 2013;369(2):111-21.

## Tracks 8, 10-11

**DR LOVE:** What is your algorithm for managing myelofibrosis (MF), and where does ruxolitinib fit in?

**DR STONE:** A JAK2 inhibitor should be considered for patients with symptomatic splenomegaly or constitutional symptoms. For patients with anemia only, it's not clear if a JAK2 inhibitor is effective. More than 50% of patients with symptomatic splenomegaly or constitutional symptoms will experience improvement with ruxolitinib. I am concerned about worsening the anemia with treatment, but if you lower the dose, patients tend to fare well. I also watch out for cytopenias, which are usually transient. If you must stop treatment, the "rebound phenomenon" can occur.

**DR LOVE:** What is the mechanism of the rebound phenomenon?

**DR STONE:** If a patient experiences a response to ruxolitinib and then stops taking it, a cytokine storm occurs. It's difficult to understand, but my notion is that ruxolitinib reduces the circulating levels of cytokines, in turn limiting receptor binding. If treatment is stopped, the system is prepared to respond in an aggressive manner.

**DR LOVE:** Do general oncologists understand that patients without JAK mutations benefit from JAK inhibition?

**DR STONE:** Even the scientists don't understand the pathophysiologic role of JAK2 in MF. Why do some patients with JAK2 mutations develop MF and some develop polycythemia vera or essential thrombocythemia? I feel for the oncologists who treat a rare disease like MF.

**DR LOVE:** What do we know about cross resistance among JAK inhibitors?

**DR STONE:** Not much. Some of the newer trials allow patients to enroll if they have already received ruxolitinib, so we should be watching at the next ASH meeting for the data. My guess is that because each one seems to inhibit a different spectrum of the JAK2 family, we may see some noncross resistance.

The future of MF will include combination therapy. One of the prime agents to combine with a JAK2 inhibitor is an HDAC inhibitor (NCT01693601). Data indicate that HDAC inhibitors have activity in MF (DeAngelo 2013). This will be an important combination, as will combining IMiDs with JAK2 inhibitors.

## Track 13

**DR LOVE:** Where are we with the 5 tyrosine kinase inhibitors (TKIs) now approved for the treatment of CML?

**DR STONE:** Dasatinib (Hochhaus 2012) and nilotinib (Saglio 2010), when compared head to head to imatinib, seemed to be better, but that was using the endpoint of cytogenetic or molecular response. Is that a good surrogate for long-term outcome? We're not certain. The bosutinib versus imatinib trial wasn't positive, although that was probably a design issue (Cortes 2012).

Should we routinely use nilotinib or dasatinib up front? The nilotinib trial reported a reduction in transformation to accelerated phase or blast crisis, so you could argue for that. In patients with a greater risk of pleural effusion, don't use dasatinib. If the patient prefers to be able to eat immediately before and after, don't use nilotinib. In older patients, imatinib is fine. In a few years, though, if imatinib goes off patent and the cost decreases, you could make a strong case for it. The responses are great, and you can use nilotinib or dasatinib to rescue patients whose disease progresses on imatinib.

Bosutinib is probably the best-tolerated agent, aside from some initial diarrhea. Ponatinib is approved for patients with disease progression after prior TKI therapy. It is generally considered a third-line agent, and it is the only one that works for T315I mutations. It is the most potent TKI, but it's difficult to take.

Editor's note: Subsequent to this interview, the FDA suspended the marketing of ponatinib and its evaluation in clinical trials based on a recent observation of an increased risk of life-threatening blood clots and severe narrowing of blood vessels (**www.fda.gov/Drugs/DrugSafety/ucm373040.htm**). ■

## SELECT PUBLICATIONS


Cortes JE et al. **Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: Results from the BELA trial.** *J Clin Oncol* 2012;30(28):3486-92.

DeAngelo DJ et al. **Phase II trial of panobinostat, an oral pan-deacetylase inhibitor in patients with primary myelofibrosis, post-essential thrombocythaemia, and post-polycythaemia vera myelofibrosis.** *Br J Haematol* 2013;162(3):326-35.

Hochhaus A et al. **Dasatinib versus imatinib (IM) in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): DASISION 3-year follow-up.** *Proc ASCO* 2012;**Abstract 6504**.

Kantarjian H et al. **Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia.** *N Engl J Med* 2010;362(24):2260-70.

Saglio G et al. **Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia.** *N Engl J Med* 2010;362(24):2251-9.