INTERVIEW

Martin S Tallman, MD

Dr Tallman is Chief of the Leukemia Service at Memorial Sloan Kettering Cancer Center and Professor of Medicine at Weill Cornell Medical College in New York, New York.

Tracks 1-8

Select Excerpts from the Interview

Track 4

DR LOVE: Would you review what we know about the use of targeted therapy in FMS-like kinase 3 internal tandem duplication (FLT3-ITD)-positive acute myeloid leukemia (AML)?

DR TALLMAN: FLT3-ITD occurs in 20% to 25% of patients with AML and confers an unfavorable prognosis. Interestingly, it occurs at a frequency of 35% to 40% in the acute promyelocytic leukemia (APL) subtype of AML, where it appears to have less importance because patients fare so well in APL despite its presence. FLT3 inhibitors are one of the most studied and active areas for drug discovery in AML. One group of inhibitors were effective in the laboratory but not particularly effective in vitro. But then the drug quizartinib, or AC220, came along.

Quizartinib inhibits FLT3. It demonstrated single-agent activity in a Phase II trial for relapsed or refractory AML, with a composite complete remission (CR) rate of approximately 50%, which includes CR with incomplete platelet recovery and incomplete hematologic recovery (Cortes 2013; [4.1]). However, the true CR rate was low.

There's tremendous interest in moving quizartinib up front, particularly in combination with chemotherapy. We're anxious for the results of studies that have been initiated evaluating induction chemotherapy with or without quizartinib (NCT01390337).

4.1

Efficacy and Safety Results of a Phase II Trial of Quizartinib (AC220) in FLT3-ITD-Positive Relapsed or Refractory Acute Myeloid Leukemia

Best response	30 mg/d (n = 38)	60 mg/d (n = 38)
Composite complete remission (CR)	47%	47%
CR	5%	3%
CR with incomplete platelet recovery	0%	3%
CR with incomplete hematologic recovery	42%	42%
Partial response	13%	24%
Survival outcome	30 mg/d (n = 38)	60 mg/d (n = 38)
Median overall survival	20.7 weeks	25.4 weeks
Select Grade 3 or 4 adverse events	30 mg/d (n = 38)	60 mg/d (n = 36)
Anemia	39%	8%
Febrile neutropenia	26%	36%
Pyrexia	8%	8%
Diarrhea	3%	3%
Fatigue	3%	6%

Cortes JE et al. *Proc ASH* 2013;**Abstract 494**.

Track 5

DR LOVE: Volasertib recently received FDA breakthrough designation for the treatment of AML. What are your thoughts on the activity and safety of this agent?

DR TALLMAN: Volasertib is a polo-like kinase inhibitor. It's particularly involved in the regulation of the mitotic spindle function. The FDA breakthrough designation was based on the results of a randomized Phase II study of volasertib/low-dose cytarabine (LDAC) versus LDAC alone for patients with previously untreated AML who are ineligible for intensive therapy (Dohner 2014). The objective response rate was 31% with volasertib/LDAC and 13.3% with LDAC alone. Also, a trend was evident toward an improvement in overall survival (OS). Volasertib is an interesting and promising agent that has a unique mechanism of action. We need a prospective randomized Phase III trial to confirm its activity (4.2).

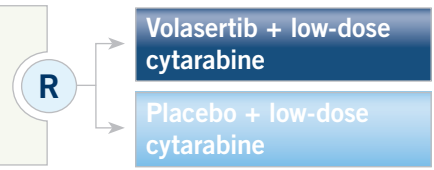
4.2

POLO-AML-2: A Phase III Trial of Volasertib and Low-Dose Cytarabine for Patients with Previously Untreated Acute Myeloid Leukemia

Protocol ID: NCT01721876 **Target Accrual:** 660

Eligibility

- Ineligible for intensive remission induction therapy
- Age ≥65 years
- ECOG PS ≤2
- No acute promyelocytic leukemia



www.clinicaltrials.gov. Accessed September 2014.

Track 6

DR LOVE: Would you discuss the results of the Phase III APL0406 trial for patients with newly diagnosed, nonhigh-risk APL?

DR TALLMAN: As remarkably effective as all-trans retinoic acid (ATRA) is, arsenic trioxide (ATO) is even more active. It's the single most active agent in this disease. The APL0406 trial compared ATRA with anthracycline-based chemotherapy, a more conventional approach, to ATRA and ATO with no provision for chemotherapy except for some hydroxyurea if the white count rises (Lo-Coco 2013; [4.3]). This study confirmed an important benefit in OS: 99% of patients appear to be cured of their disease with ATO-ATRA.

DR LOVE: Where are we today and what are the current issues requiring improvements in the management of APL?

DR TALLMAN: We have had a remarkable triumph in the treatment of APL in recent decades. The most remarkable change has been the movement away from chemotherapy. The APL0406 study included patients aged 18 to 71 years. It's an important study that established ATO in combination with ATRA as a new standard therapy for APL. It has been fascinating, as most patients with APL appear to be cured.

The major limitation to cure in most subtypes of AML is relapse and resistance. In contrast, the major limitation to cure for all patients with APL is early death, primarily due to CNS bleeding and some bleeding in the gastrointestinal tract and lungs. It's remarkable to have a subtype of AML in which resistant disease is not a major problem. In APL, there is no primary resistance. We are putting major efforts into reducing the risk of early death from APL. If we can reduce that risk and administer ATO-ATRA without chemotherapy to most patients, we will be close to curing all patients. ■

4.3

APL0406: A Phase III Trial Comparing Arsenic Trioxide (ATO) in Combination with All-Trans Retinoic Acid (ATRA) to Standard ATRA and Idarubicin-Based Chemotherapy in Newly Diagnosed, Nonhigh-Risk Acute Promyelocytic Leukemia

Response rate	ATO-ATRA	ATRA-chemotherapy	*p*-value
Hematologic complete response (n = 77, 79)	100%	95%	0.12
Two-year survival outcome	ATO-ATRA	ATRA-chemotherapy	*p*-value
Event-free survival (n = 74, 76)	97%	86%	<0.001* 0.02†
Overall survival (n = 77, 79)	99%	91%	0.02
Disease-free survival (n = 76, 73)	97%	90%	0.11

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

* Noninferiority of ATO-ATRA; † superiority of ATO-ATRA

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

SELECT PUBLICATION

Dohner H et al. **Randomized, phase 2 trial comparing low-dose cytarabine with or without volasertib in AML patients not suitable for intensive induction therapy.** *Blood* 2014;124(9):1426-33.