INTERVIEW

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Select Excerpts from the Interview

Tracks 2, 5

DR LOVE: Would you talk about recent developments in salvage approaches for acute myeloid leukemia (AML), including the role of new agents?

DR SMITH: Two "holy grails" persist in AML therapy. One is the treatment of AML in older patients, and the second is treatment of relapsed AML or salvage-based treatment. A few years back there was a large push toward using epigenetic-modifying agents like 5-azacitidine or decitabine as primary therapy for older patients, whose acute leukemia was likely to have arisen from myelodysplastic syndromes (MDS), for which these drugs were originally approved. The idea was that you might induce bone marrow stability

and possibly even complete remission in a proportion of patients despite the fact that those patients had AML and not simply MDS.

Some patients clearly benefit from azacitidine and decitabine in this setting. The problem is that these are not typically long-term therapies for most patients, so an effort has been made to combine other agents with azacitidine and decitabine to try to make them more effective.

One such study combined lenalidomide, an agent already approved for treatment of MDS, with 5-azacitidine as induction therapy for high-risk MDS or for AML in older patients. That combination appears to be effective (Pollyea 2013). If we can get more patients into remission and keep them there longer, that would be an exciting combination, provided it's reasonably well tolerated. And all the preliminary data suggest that it is reasonably well tolerated.

DR LOVE: Would you also discuss the study presented at ASH 2012 of volasertib in combination with low-dose cytarabine for patients with untreated AML ineligible for intensive treatment?

DR SMITH: Volasertib is an inhibitor of polo-like kinase, an enzyme that regulates cell division. Blocking this enzyme is thought to enhance cell death in the tumor. The results of the Phase II study comparing volasertib in combination with low-dose cytarabine to cytarabine alone reported that the addition of volasertib to cytarabine resulted in higher response rates but more toxicity (Maertens 2012; [4.1]). This highlights one of the challenges of developing new drugs for AML.

4.1

Randomized Phase II Study of Volasertib (V) (BI 6727) in Combination with Low-Dose Cytarabine (LDAC) versus LDAC Monotherapy for Patients with Previously Untreated Acute Myeloid Leukemia Ineligible for Intensive Treatment

	V + LDAC (n = 42)	LDAC (n = 45)	HR	*p*-value
Objective response rate	31%	13%	NR	0.0523
Median event-free survival	170 days	69 days	0.56	0.0237

"More pts who received V + LDAC experienced ≥grade 3 AEs than those who received LDAC (95.2% vs 68.9%), particularly blood and lymphatic system disorders (81.0% vs 44.4%), gastrointestinal disorders (21.4% vs 6.7%), and infections and infestations (45.2% vs 22.2%)."

HR = hazard ratio; NR = not reported

Maertens J et al. *Proc ASH* 2012;**Abstract 411**.

Tracks 4, 11

DR LOVE: What are your thoughts about the use of omacetaxine for the treatment of chronic myeloid leukemia (CML) or AML?

DR SMITH: Omacetaxine acts by blocking the translation of proteins like BCR-ABL, which is important in the development of CML. It has an important inhibitory effect in cells that are dependent on abnormal tyrosine kinase activity. One of the fascinating aspects of this agent is its ability to inhibit leukemia stem cells, which are responsible for initiation and maintenance of the disease.

Omacetaxine has been approved for the treatment of multiple tyrosine kinase inhibitor (TKI)-resistant CML but may also have potential in AML to minimize the risk of relapse or improve responses in high-risk groups. For patients with CML or AML who have minimal residual disease resistant to primary therapy, it may be possible to eradicate the disease with the addition of omacetaxine. This is particularly appealing in CML because you can get patients to a stage at which the disease is undetectable by polymerase chain reaction (PCR) with TKI therapy and potentially cure them with omacetaxine.

I have used omacetaxine to treat multiple TKI-resistant CML. It is administered twice daily for 2 weeks for induction, followed by maintenance or consolidation therapy. We have seen success with this agent, and it has enabled patients to reach a stage at which they can be evaluated for a transplant.

Track 15

DR LOVE: Would you talk about 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 SMITH: This was an interesting study comparing induction and consolidation using a nonchemotherapy regimen with ATRA and arsenic trioxide to an ATRA/idarubicin-based therapy referred to as AIDA for patients with nonhigh-risk APL (Lo-Coco 2013; [4.2]). An analysis of the primary endpoint, event-free survival at 2 years, demonstrated that the nonchemotherapy arm was not inferior to the traditional chemotherapy arm. Also, fewer deaths and less toxicity occurred in the nonchemotherapy group. It may be that with longer follow-up even more of a benefit is observed on the nonchemotherapy arm. Many academic centers and cooperative groups are now interested in incorporating a nonchemotherapy treatment arm for patients with low-risk APL. ■

4.2

Phase III Study of 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.

SELECT PUBLICATIONS

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

Larson RA et al. **Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up.** *Leukemia* 2012;26(10):2197-203.

Pollyea DA et al. **Sequential azacitidine plus lenalidomide combination for elderly patients with untreated acute myeloid leukemia.** *Haematologica* 2013;98(4):591-6.