INTERVIEW

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Track 2 Sorafenib in the up-front management of AML

Track 3 Novel investigational agents for FLT3-ITD-mutated AML, including gilteritinib (ASP2215)

Track 4 Perspective on the use of the multikinase inhibitor midostaurin for newly diagnosed AML

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Track 6 Activity of the immunomodulatory drugs lenalidomide and pomalidomide in patients with MDS with and without del(5q)

Track 7 **Case discussion:** A 26-year-old woman with chronic-phase chronic myeloid leukemia (CML) attains a complete cytogenetic remission with imatinib

Track 8 Choice of first-line tyrosine kinase inhibitor (TKI) therapy in CML and role of generic imatinib

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Track 11 Perspective on the discontinuation of TKI therapy for patients with CML

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Select Excerpts from the Interview

Tracks 3-4

DR LOVE: What are some of the most promising new agents and strategies under investigation for patients with FLT3-mutated acute myeloid leukemia (AML)?

DR SMITH: FLT3 is becoming a phenomenally interesting and important target in AML because, (1) we can measure it, (2) it offers prognostic implications and (3) a handful of drugs are in development to target this mutation and evaluate if we can improve outcomes.

Interestingly, one of the plenary presentations at ASH 2015 reported on an agent in this class. One of the main questions this study presented by Dr Rich Stone addressed was, what's the role of an additional agent to block FLT3 in the induction and maintenance

settings after transplant? In this trial, the addition of the FLT3 inhibitor midostaurin to induction chemotherapy and maintenance therapy for patients with newly diagnosed AML with FLT3 mutations provided a benefit (Stone 2015; [2.1]).

Everyone is quite excited about these results, and I do believe that if this drug becomes available for this indication it will be widely used and will most likely replace sorafenib. Midostaurin is not a perfect drug. It has toxicities associated with it, so we do have some work still to do to refine our FLT3 inhibitors.

Gilteritinib (ASP2215) is another agent in this class, and it has been studied in the relapsed/refractory setting, alone and in combination, in addition to in patients without an FLT3-ITD mutation. Unlike most other FLT3 inhibitors, gilteritinib has significant single-agent activity (Levis 2015; [2.2]).

We are hoping that this agent becomes available. It would be great to have it as an option for a patient with primary refractory AML whose disease progresses on induction therapy because it could bring about a remission and the patient could then undergo allogeneic transplant.

2.1

Phase III CALGB-10603 (RATIFY) Trial of Midostaurin in Combination with Daunorubicin/Cytarabine Induction and High-Dose Cytarabine Consolidation and as Maintenance Therapy for Patients with Newly Diagnosed Acute Myeloid Leukemia with FLT3 Mutations

Efficacy	Midostaurin (n = 360)	Placebo (n = 357)	Hazard ratio	*p*-value
Median OS	74.7 mo	26.0 mo	0.77	0.007
Median OS, SCT censored*	NR	NR	0.77	0.047
Median EFS	8.0 mo	3.0 mo	0.80	0.0044
Median EFS, SCT censored*	8.2 mo	3.0 mo	0.84	0.025

OS = overall survival; SCT = stem cell transplant; NR = not reached; EFS = event-free survival

* Censored for transplant analyses

No statistically significant differences were observed in the overall rate of Grade ≥3 hematologic or nonhematologic adverse events between midostaurin and placebo.

Stone RM et al. *Proc ASH* 2015;**Abstract 6**.

Track 6

DR LOVE: What is known about the efficacy and tolerability of immunomodulatory drugs (IMiDs) in patients with myelodysplastic syndromes (MDS), particularly those with non-del(5q) disease?

DR SMITH: Lenalidomide has been studied in patients with non-del(5q) MDS and is fairly effective. Obviously you have to weigh when it's appropriate to use. For instance, given a patient with low-risk disease and anemia who needed transfusions about once a month or once every 3 weeks, I'd consider lenalidomide, as about 25% or 30% of patients will have improvement of their hemoglobin and become transfusion independent on lenalidomide (Santini 2014). It's a pill the patient can take at home, and it's relatively well tolerated. You have to be careful of cytopenias, but you can easily manage patients on this agent.

2.2

Results of a Phase I/II Dose-Escalation Study of the Potent FLT3/AXL Inhibitor Gilteritinib (ASP2215) for Patients with Relapsed/Refractory Acute Myeloid Leukemia

	Clinical response by mutation status		
	FLT3 mutation-positive		FLT3 wild type
	20-450 mg (n = 127)	**≥80 mg** (n = 106)	**20-450 mg** (n = 57)
ORR (CRc + PR)	52%	57.5%	8.8%
CRc (CR + CRp + CRi)	40.9%	47.2%	5.3%
CR	6.3%	6.6%	0%
CRp	3.9%	4.7%	1.8%
CRi	30.7%	35.8%	3.5%
PR	11.0%	10.4%	3.5%

ORR = overall response rate; CR = complete remission; CRc = composite CR; PR = partial remission; CRp = CR with incomplete platelet recovery; CRi = CR with incomplete hematologic recovery

- Treatment-related adverse events included diarrhea (13.4%), fatigue (12.4%), anemia (7.2%), peripheral edema (7.2%), nausea (6.7%) and dysgeusia (5.2%).
- Serious adverse events included febrile neutropenia (27.3%), sepsis (11.9%), pneumonia (8.8%), hypotension (5.7%) and respiratory failure (5.7%).

Levis MJ et al. *Proc ASCO* 2015;**Abstract 7003**.

I do juxtapose data on lenalidomide with studies of demethylating drugs, which provide a higher likelihood of a patient with low-risk MDS becoming transfusion independent but are much more cumbersome. However, the demethylating drugs are evolving, and oral formulations of both decitabine and azacitidine have been developed (William 2014).

When we inhibit methylation continually, patients can lose their response to subcutaneous or IV drugs. If we then administer an oral formulation, we provide a different demethylating pattern by administering the agent continually for 2 or 3 weeks followed by a week or 2 off. That opens the door to gaining a better understanding of how these agents work and how we're going to use them moving forward. We do not yet have many large studies with these oral demethylating agents, but we're learning.

DR LOVE: What about other IMiDs in MDS, particularly pomalidomide?

DR SMITH: We know that pomalidomide has a lot of activity in the immunologic space, though we don't always know how these agents work. Pomalidomide hasn't been studied as formally as lenalidomide in MDS, but it does hold some promise. A number of people believe that administering pomalidomide in combination with some of the other agents we use in MDS, such as a demethylating agent or a histone deacetylase inhibitor, can provide alternative ways to target MDS and may turn out to offer some benefit for a lot of our patients. ■

SELECT PUBLICATIONS

Santini V et al. **Efficacy and safety of lenalidomide versus placebo in RBC-transfusion dependent patients with IPSS low/intermediate-risk myelodysplastic syndromes without del(5q) and unresponsive or refractory to erythropoiesis-stimulating agents: Results from a randomized phase 3 study (CC-5013-MDS-005).** *Proc ASH* 2014;**Abstract 409**.

William BM et al. **CC-486 (oral azacitidine) following allogeneic hematopoietic stem cell transplantation (AlloHSCT) in patients with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML).** *Proc ASH* 2014;**Abstract 990**.