INTERVIEW

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Tracks 1-9

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss the various FLT3 inhibitors in development and compare their efficacy for patients with acute myeloid leukemia (AML) and FLT3 mutations?

DR TIBES: FLT3 is one of the most commonly mutated genes in AML, and about 30% of patients with AML harbor these mutations. Mutations in FLT3 can be divided into 2 categories: internal tandem duplications (FLT3-ITD mutations), which are more common, and mutations in the tyrosine kinase domain (FLT3-TKD mutations). It is possible for patients to have one or both mutations, so patients should be tested for both.

Several first- and second-generation FLT3 inhibitors are currently being studied in clinical trials. Patients with FLT3 mutations, particularly at relapse, should be offered an FLT3 inhibitor on a clinical trial if one is available. It is difficult to compare the efficacy of these agents across studies, but overall the responses are encouraging.

Sorafenib, a first-generation, nonspecific FLT3 inhibitor, has been studied in combination with standard chemotherapy, and high CR rates were reported (Rollig 2015). A

Phase II study evaluating sorafenib in combination with azacitidine for patients with relapsed/refractory AML and FLT3-ITD mutations demonstrated good responses (Ravandi 2013).

Midostaurin, another first-generation multikinase inhibitor, was evaluated in a global, randomized Phase III trial. The study investigated the addition of midostaurin to up-front induction chemotherapy for younger patients with newly diagnosed AML and FLT3 mutations. This was the first positive study showing that the addition of an FLT3 inhibitor to induction chemotherapy resulted in an overall survival benefit (Stone 2015; [3.1]).

I have been involved in investigating gilteritinib, a second-generation FLT3 inhibitor. About 200 patients with relapsed/refractory AML received single-agent gilteritinib in a Phase I/II study.

The composite CR rates (CR + CR with incomplete platelet recovery + CR with incomplete hematologic recovery) were approximately 40% to 50% (Levis 2015; [3.2]). Many of these patients had sustained CRs on therapy. The responses to first-generation FLT3 inhibitors were often short lived, in the range of 6 to 9 months. Gilteritinib may induce longer responses than the first-generation FLT3 inhibitors.

Quizartinib (AC220), another second-generation inhibitor, has shown activity in Phase II studies both as a single agent and in combination with chemotherapy. It has demonstrated CR rates in the range of 40% to 50% (Schiller 2014). It is currently being evaluated in Phase III studies.

3.1

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 9

CASE DISCUSSION: A 71-year-old man with relapsed/refractory myelodysplastic syndrome (MDS) receives oral azacitidine with sonidegib on a clinical trial

DR TIBES: This patient presented with low-risk MDS and trisomy 8 about 5 years ago. He was red blood cell transfusion dependent and responded to erythropoietin for 14 months but became transfusion dependent again. He was enrolled on a clinical trial with

3.2

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
	Gilteritinib 20-450 mg (n = 127)	Gilteritinib ≥80 mg (n = 106)	Gilteritinib 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**.

oral azacitidine for 12 months, which he tolerated well. His disease was stable, with a reduction in transfusion dependency. He went off treatment for a year and a half.

His disease eventually progressed to high-risk MDS. He was evaluated for an allogeneic stem cell transplant, but he decided against it and was enrolled on a clinical trial of azacitidine in combination with a smoothened inhibitor, sonidegib (LDE225). If a patient experiences disease progression on one hypomethylating agent, he or she can be switched to another one, but the response rates are not that good. So I generally offer these patients a combination of a hypomethylating agent with a novel targeted drug.

On this trial the patient achieved stabilization of his disease and improvements in his counts. After 12 cycles, unfortunately his disease progressed into AML. We discussed the option of transplant again, but he decided against it and is now receiving supportive care. ■

SELECT PUBLICATIONS

Levis MJ et al. **Results of a first-in-human, phase I/II trial of ASP2215, a selective, potent inhibitor of FLT3/Axl in patients with relapsed or refractory (R/R) acute myeloid leukemia (AML).** *Proc ASCO* 2015;**Abstract 7003**.

Ravandi F et al. **Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation.** *Blood* 2013;121(23):4655-62.

Rollig C et al. **Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukaemia (SORAML): A multicentre, phase 2, randomised controlled trial.** *Lancet Oncol* 2015;16(16):1691-9.

Schiller G et al. **Final results of a randomized phase 2 study showing the clinical benefit of quizartinib (AC220) in patients with FLT3-ITD positive relapsed or refractory acute myeloid leukemia.** *Proc ASCO* 2014;**Abstract 7100**.