INTERVIEW

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Tracks 1-14

Track 1 SAL-SORAML: A Phase II study of sorafenib versus placebo in addition to standard therapy in younger patients with newly diagnosed acute myeloid leukemia (AML)

Track 2 Incidence of hand-foot syndrome and other common side effects with sorafenib in AML

Track 3 Interim report of a Phase I/II trial of quizartinib with azacitidine or low-dose cytarabine in patients with FLT3-ITD-mutated myeloid leukemias

Track 4 Role of ruxolitinib in patients with myeloproliferative neoplasms

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Track 7 Use of ruxolitinib in patients with symptomatic, earlier-stage MF

Track 8 Clinical experience with ruxolitinib in polycythemia vera

Track 9 Arsenic trioxide and ATRA in the treatment of acute promyelocytic leukemia (APL)

Track 10 Management of high-risk APL

Track 11 Choice of first-line tyrosine kinase inhibitor (TKI) therapy in chronic myeloid leukemia (CML)

Track 12 Indications to change TKI therapy in patients with CML

Track 13 Perspective on discontinuation of TKI therapy for patients with CML and prolonged major molecular responses

Track 14 Efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase CML

Select Excerpts from the Interview

Tracks 1, 3

DR LOVE: Would you discuss the results of the Phase II SORAML study of sorafenib or placebo in combination with standard therapy for younger patients with newly diagnosed acute myeloid leukemia (AML)?

DR CORTES: In this study, regardless of whether the patient's disease harbored FLT3-ITD mutations or not, they were randomly assigned to receive chemotherapy alone or with sorafenib. Sorafenib was administered during induction, consolidation and in the maintenance phase.

For the overall population, a benefit was noted in event-free survival in favor of sorafenib (Rollig 2014). This is interesting because, as far as we know, sorafenib doesn't have much of a role, certainly not as a single agent, in patients without FLT3-ITD

mutations. So this result is puzzling and cannot be explained by the benefit that was seen in the subset of patients with FLT3-ITD mutations because it's a relatively small percent of patients. More research is required to understand how sorafenib helps patients without the mutation.

DR LOVE: Would you also comment on the results of the Phase I/II trial of quizartinib and azacitidine or low-dose cytarabine for patients with FLT3-ITD mutation-positive myeloid leukemias?

DR CORTES: That is an interesting study because it is evaluating whether quizartinib can be beneficial, particularly in the older patient population. The response rate was high at about 70% (Borthakur 2014). Perhaps more impressive were event-free survival and the duration of response. Responses to FLT3-ITD inhibitors as single agents tend to be transient, but when you combine quizartinib with either one of these two agents, you see durable responses. Also, the addition of quizartinib produced little toxicity, with the main toxicity being QTc prolongation. Because the study used low-dose/low-intensity chemotherapy, the regimens ended up being well tolerated.

Tracks 4-6

DR LOVE: What is your perspective on the role of ruxolitinib in patients with myeloproliferative neoplasms outside of a trial setting?

DR CORTES: When ruxolitinib was initially approved, we had a fixed dose to use. Further studies have evaluated different doses, and we've learned that perhaps doses as low as 10 mg can be appropriate, especially when factors such as lower platelet counts come into play. So I believe this demonstrates that ruxolitinib is valuable. It can help many patients, including patients who do not meet the criteria for a clinical trial. As with all the drugs, one needs to monitor the patient.

DR LOVE: For a typical symptomatic patient with myelofibrosis (MF) and splenomegaly, what are your expectations if ruxolitinib is administered?

DR CORTES: Ruxolitinib typically improves symptoms, including splenomegaly, rapidly. Usually, within the first few weeks, you will see significant improvement. I don't discontinue treatment if I've seen no improvements within a month, as some patients have a more subtle and delayed response.

We tend to ask patients if they feel better now than before ruxolitinib therapy was initiated. We must keep improvements in context in terms of how the drug is working for that patient. If the patient feels better, eats better and can walk more, that patient is benefiting and ruxolitinib is continued indefinitely. If we see no improvement, we discontinue therapy.

DR LOVE: What is known about the efficacy and safety of pacritinib in the management of myeloproliferative neoplasms?

DR CORTES: Pacritinib is a novel and selective inhibitor of JAK2 and FLT3. Compared to other JAK2 inhibitors, it may be associated with less myelosuppression. In terms of efficacy, we know that pacritinib works and yields improvements in spleen size and symptoms. In the results of the randomized Phase III PERSIST-1 trial of pacritinib versus best available therapy for patients with primary MF, postpolycythemia vera MF or postessential thrombocythemia MF, one of the key investigations was its efficacy among patients with low platelet counts (Mesa 2015; [3.1]).

PERSIST-1 demonstrated that pacritinib was significantly better than best available therapy. Pacritinib causes more GI toxicities than ruxolitinib. Although one should not compare across trials, it appears that pacritinib does not yield as great a benefit when compared to best available therapy as ruxolitinib does. ■

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PERSIST-1: A Phase III Trial of Pacritinib (Pac) versus Best Available Therapy (BAT) in Primary Myelofibrosis (MF), Postpolycythemia Vera MF or Postessential Thrombocythemia MF

	ITT population			Evaluable patients*		
	Pac (n = 220)	**BAT** (n = 107)	*p*-value	**Pac** (n = 168)	**BAT** (n = 85)	*p*-value
SVR ≥35%†	19.1%	4.7%	0.0003	25.0%	5.9%	0.0001
	n = 220	n = 107	*p*-value	n = 132	n = 71	*p*-value
TSS ≥50%†	24.5%	6.5%	<0.0001	40.9%	9.9%	<0.0001
Correlation of SVR with OS†	**Pac** (n = 220)			**BAT** (n = 106)		
SVR	Hazard ratio		*p*-value	Hazard ratio		*p*-value
≥10% and <20%	0.15		0.071	2.31		0.287
≥20%	0.26		0.014	NA		NA
Select AEs	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Diarrhea	53.2%	5.0%	0%	12.3%	0%	0%
Nausea	26.8%	0.9%	0%	6.6%	0%	0%
Anemia	22.3%	14.5%	2.3%	19.8%	12.3%	2.8%
Thrombocytopenia	16.8%	5.5%	6.4%	13.2%	6.6%	2.8%
Vomiting	15.9%	0.9%	0%	5.7%	0%	0%
Neutropenia	3.6%	0.5%	1.8%	1.9%	0.9%	0.9%

* Patients with both baseline and week 24 spleen assessment by MRI or CT

† At week 24

ITT = intent to treat; SVR = spleen volume reduction; TSS = total symptom score; OS = overall survival; NA = not applicable; AEs = adverse events

- SVR ≥35% in patients with baseline thrombocytopenia (ITT):
  - <50,000/uL: 22.9% (pac) versus 0% (BAT), $p = 0.0451$
  - <100,000/uL: 16.7% (pac) versus 0% (BAT), $p = 0.0086$
- Patients achieving transfusion independence: 25.7% (pac) versus 0% (BAT)

Mesa RA et al. *Proc ASCO* 2015;**Abstract LBA7006**.

SELECT PUBLICATIONS

Borthakur G et al. **The combination of quizartinib with azacitidine or low dose cytarabine is highly active in patients (pts) with FLT3-ITD mutated myeloid leukemias: Interim report of a Phase I/II trial.** *Proc ASH* 2014;**Abstract 388**.

Mesa RA et al. **Results of the PERSIST-1 phase III study of pacritinib (PAC) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia-myelofibrosis (PET-MF).** *Proc ASCO* 2015;**Abstract LBA7006**.

Rollig C et al. **Sorafenib versus placebo in addition to standard therapy in younger patients with newly diagnosed acute myeloid leukemia: Results from 267 patients treated in the randomized placebo-controlled SAL-Soraml trial.** *Proc ASH* 2014;**Abstract 6**.

Vannucchi A et al. **Ruxolitinib versus standard therapy for the treatment of polycythemia vera.** *N Engl J Med* 2015;372(5):426-35.