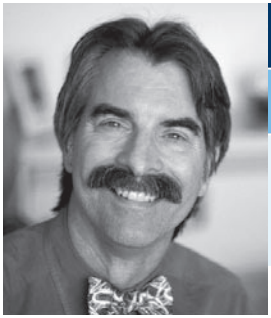

INTERVIEW

Jerald P Radich, MD

Dr Radich is a Member of the Clinical Research Division at Fred Hutchinson Cancer Research Center and Professor of Medicine at the University of Washington in Seattle, Washington.

Tracks 1-12

Select Excerpts from the Interview

Tracks 1-4, 6

DR LOVE: Would you discuss the role of second-generation tyrosine kinase inhibitors (TKIs) in the treatment of chronic myeloid leukemia (CML)?

DR RADICH: Imatinib is successful in achieving cytogenetic remissions. After a year, nearly 70% of patients will be in cytogenetic remission (Kantarjian 2010). However, 10% to 15% of patients have resistance to this agent. In patients who do experience a response it is maintained for a long time (Deininger 2009), but some patients are lost because of drug intolerance or late relapse. Follow-up of the imatinib trials reports that only about 50% of patients are still receiving the agent.

Even though imatinib is an effective agent, it has room for improvement. Enter the second-generation TKIs — nilotinib and dasatinib. These agents have now been approved for newly diagnosed chronic-phase CML and seem to be more effective than imatinib.

DR LOVE: How does the efficacy of the first- and second-generation TKIs compare clinically?

DR RADICH: A series of trials have consistently reported an advantage of dasatinib and nilotinib compared to imatinib. With imatinib about 70% of patients will go into a complete cytogenetic remission at 12 months, whereas for both nilotinib and dasatinib more than 80% of patients do so. If you evaluate major molecular response (MMR), which is a 1,000-fold reduction in the BCR-ABL mRNA, about 20% to 30% of patients achieve MMR with imatinib at 12 months. The rate of MMR is almost doubled with nilotinib or dasatinib (Saglio 2010; Kantarjian 2010).

The most important surrogate for long-term response is progression to accelerated phase or blast crisis. That is the worst outcome for patients because these agents don't work well in accelerated phase or blast crisis. In virtually all the trials to date, dasatinib and nilotinib have been associated with far less progression than imatinib.

At 1 to 2 years, approximately 1% progress to accelerated phase or blast crisis on second-generation TKIs as compared to 3% to 5% on imatinib (Kantarjian 2011, 2012; [4.1]). The follow-up on dasatinib and nilotinib isn't as long as it is with imatinib, and so far no difference in overall survival has been recorded.

DR LOVE: How would you compare the toxicity of imatinib, nilotinib and dasatinib?

DR RADICH: Long-term data exist regarding toxicity with imatinib. We don't have these data for dasatinib and nilotinib, although we've seen no signal so far that they would be any different. Imatinib causes a lot of gastrointestinal problems, such as nausea and diarrhea, and peripheral edema. Dasatinib and nilotinib don't have those issues.

These agents are remarkable because they both display cross-intolerance. If someone develops a specific toxicity with imatinib, he or she will probably not experience that with nilotinib or dasatinib. With dasatinib the main concern is pleural effusion, whereas with nilotinib the major worry is pancreatitis. Nilotinib also has a black box warning for cardiac events. However, it is not clear that cardiac events are associated with nilotinib administration.

DR LOVE: If a patient who is receiving dasatinib presents with pleural effusion, how do you manage it?

4.1

Results from the ENESTnd[1] and DASISION[2] Studies Comparing Nilotinib or Dasatinib to Imatinib for Patients with Newly Diagnosed Chronic Myeloid Leukemia

	ENESTnd study		DASISION study	
Response at 12 and 24 months	Nilotinib 400 mg BID (n = 281)	Imatinib 400 mg qd (n = 283)	Dasatinib 100 mg qd (n = 259)	Imatinib 400 mg qd (n = 260)
MMR (%)	43, 67	22, 44	46, 64	28, 46
	$p < 0.001$, $p < 0.0001$		$p < 0.0001$, $p < 0.0001$	
CCR (%)	78, 85	65, 77	77, 86	66, 82
	$p < 0.001$, $p = 0.0160$		$p = 0.007$, $p = 0.0002$	
Progression to AP/BC (%)	<1, 1.9	4, 4.8	1.9, 2.3	3.5, 5.0
	$p < 0.004$, $p = 0.0196$		—	—

MMR = major molecular response; CCR = complete cytogenetic response; AP/BC = accelerated phase/blast crisis

[1] Kantarjian HM et al. *Lancet Oncol* 2011;12(9):841-51; [2] Kantarjian HM et al. *Blood* 2012;119(5):1123-9.

DR RADICH: If the patient presents with mild pleural effusion, usually it's sufficient to interrupt the dose and ascertain whether the symptoms resolve. You can also administer diuretics, and some centers also administer steroids. Unless a compelling reason exists to keep the patient on dasatinib, I believe the most common approach now is simply to switch to nilotinib.

Track 9

DR LOVE: Would you discuss the possibility of discontinuation of imatinib therapy in CML?

DR RADICH: The thought process has been that patients with CML will have to remain on TKI therapy forever, but that doesn't seem to be the case. One trial evaluating this issue is the STIM trial (Mahon 2011). This trial studied patients who were in sustained complete molecular remission, which means undetectable PCR for BCR-ABL, for at least 2 years. Imatinib therapy was discontinued and the patients were monitored. Of the patients who discontinued imatinib therapy, 60% experienced disease relapse within 7 months.

They all responded to rechallenge with imatinib, however, and approximately 40% of the patients have remained PCR-negative for more than 2 years. This is shocking to most of us who study CML biology. Patients who were able to come off imatinib are those who present with low Sokal scores.

Although these data are encouraging, discontinuation of therapy has to be performed on a clinical trial. Even though all the patients who have discontinued therapy and experienced relapse have responded on rechallenge, they haven't all gone back to being PCR-negative. If you believe that unopposed BCR-ABL is what drives progression, you've given a person a few months of unopposed BCR-ABL. They may respond, but they may have developed clones that down the road lead to progression. I don't believe we will know the fate of those patients until 3 to 5 years from now. ■

SELECT PUBLICATIONS

Deininger M et al. **International Randomized Study of Interferon vs STI571 (IRIS) 8-year follow up: Sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib.** *Proc ASH* 2009;**Abstract 1126**.

Kantarjian HM et al. **Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION).** *Blood* 2012;119(5):1123-9.

Kantarjian HM et al. **Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial.** *Lancet Oncol* 2011;12(9):841-51.

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Takahashi N et al. **Discontinuation of imatinib in Japanese patients with chronic myeloid leukemia.** *Haematologica* 2011;[Epub ahead of print].