INTERVIEW

George D Demetri, MD

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Tracks 1, 3

DR LOVE: Would you provide an overview of recent advances in the diagnosis and treatment of gastrointestinal stromal tumors (GIST)?

DR DEMETRI: In 2000 GIST was initially characterized by the identification of the causative KIT mutation. This was the first and the most common driver mutation for GIST. Since then, patients live longer due to treatment with targeted tyrosine kinase inhibitors (TKIs). Many patients present with metastases, often in the abdomen, particularly the omentum, or the liver. The standard first-line therapy for metastatic GIST is imatinib, with objective responses achieved by two thirds of patients and an additional 20% with prolonged stable disease.

About 17% of the first set of patients diagnosed with GIST worldwide and treated with imatinib starting in 2000 have never discontinued therapy and are still being followed. Unfortunately, most patients aren't that lucky. For about 50%, the benefits from imatinib will wane with evidence of disease resistance after about 2 years. By year 5, another 40% of patients will experience disease progression. The degree of response or lack thereof from first presentation differs among patients.

DR LOVE: What is your treatment approach for patients with metastatic GIST who are experiencing systemic progression on first-line imatinib?

DR DEMETRI: It is important to emphasize that progression on imatinib does not automatically necessitate the administration of a second-line agent. So an interesting question is, what do you do if only one site of the disease is progressing? At this point we involve multidisciplinary consultation with an expert surgeon.

Our surgeons will evaluate whether only 1 lump is progressing and whether it would be easy to resect. If it is determined to be resectable without much disturbance to the vital structure of any organ and if the patient is eligible for surgery and has a good performance status, we will adopt that approach.

If the patient has progressive disease in multiple sites, the standard second-line therapy is sunitinib. Sunitinib has activity in patients with GIST progressing on imatinib. It has more side effects than imatinib and has a different spectrum of effects. Being a VEGFR TKI, it may cause high blood pressure. As such, many patients are reluctant to receive sunitinib.

Tracks 4-6

DR LOVE: Would you discuss the Phase III GRID trial, which led to the FDA approval of regorafenib for patients with advanced GIST?

DR DEMETRI: Like sunitinib, regorafenib is a VEGFR TKI and does not inhibit BCR-ABL. Regorafenib has a different binding kinetic to the mutant receptor. It is active in patients with progressive GIST after imatinib and sunitinib failure.

The Phase III GRID trial was the definitive international study of regorafenib versus placebo after progression on imatinib and sunitinib (Demetri 2013; [1.1]). The median progression-free survival for placebo was 0.9 months. Because crossover was allowed, most patients received regorafenib in 1 month or less. Regorafenib significantly controlled the disease even after 2 or more prior TKIs.

The median progression-free survival for regorafenib was 4.8 months, which seems short. The response rates for any agent after imatinib failure are low, and in this study not many patients experienced objective tumor shrinkage, which is dramatically different from durable stable disease, which was achieved by about 70% of patients. In GIST, locking the tumor into a static state controls the disease. The pain is reduced, but eventually other clones proliferate, resistance develops, symptoms occur and other therapies are needed. Based on the results of the GRID study, the FDA approved regorafenib as third-line therapy for TKI-resistant GIST.

DR LOVE: How do you sequence regorafenib for these patients?

DR DEMETRI: Our standard sequence is imatinib, sunitinib and then regorafenib. We do not know if regorafenib will be better in the second-line setting. Ongoing research suggests that patients may fare better if these agents are sequenced differently. We are currently trying to model the duration of therapy for each agent in cell lines and are excited about this hypothesis.

DR LOVE: In your experience, what are the main side effects of regorafenib?

DR DEMETRI: With GIST, we were used to multitargeted kinase inhibitors like sunitinib. The similarities between sunitinib and regorafenib are notable. Both are VEGFR and PDGFR TKIs that cause hand-foot syndrome, which is manageable and can be diagnosed before blisters occur. Symptom worsening can be prevented and

patients are able to continue treatment. In the GRID study, less than 6% of patients discontinued therapy with regorafenib due to side effects.

DR LOVE: How do you manage hand-foot syndrome?

DR DEMETRI: Our nurses utilize a number of unique emollients. The bottom line is, as long as patients are tuned in, it is a manageable side effect. Doctors need to understand the variability in the pharmacology of the 3 TKIs imatinib, sunitinib and regorafenib. Because of individual patient differences, a standard dose is not appropriate for every patient. It is important to personalize the dosing of these agents based on side effects and tolerability. ■

1.1

GRID: Results from a Phase III Trial of Regorafenib for Metastatic or Unresectable Gastrointestinal Stromal Tumor (GIST) Progressing Despite Prior Treatment with at Least Imatinib and Sunitinib

Efficacy	Regorafenib (n = 133)	Placebo (n = 66)	Hazard ratio	*p*-value
Median progression-free survival	4.8 mo	0.9 mo	0.27	<0.0001
Overall survival events	22%	26%	0.77	0.199
Disease control rate	52.6%	9.1%	—	<0.0001
	Regorafenib (n = 132)		**Placebo** (n = 66)	
Select adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Hand-foot skin reaction	56%	20%	14%	0%
Hypertension	49%	24%	17%	3%
Diarrhea	40%	5%	5%	0%
Oral mucositis	38%	2%	8%	2%
Fatigue	39%	2%	27%	0%
Alopecia	24%	2%	2%	0%
Anorexia	21%	0%	8%	0%
Maculopapular rash	18%	2%	3%	0%
Nausea	16%	1%	9%	2%
Constipation	15%	1%	6%	0%
Myalgia	14%	1%	9%	0%

Conclusion: "The results of this study show that oral regorafenib can provide a significant improvement in progression-free survival compared with placebo in patients with metastatic GIST after progression on standard treatments… This is the first clinical trial to show benefit from a kinase inhibitor in this highly refractory population of patients."

Demetri GD et al. *Lancet* 2013;381(9863):295-302.

SELECT PUBLICATIONS

Demetri GD et al. **Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): An international, multicentre, randomised, placebo-controlled, phase 3 trial.** *Lancet* 2013;381(9863):295-302.

George S et al. **Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: A multicenter phase II trial.** *J Clin Oncol* 2012;30(19):2401-7.

Pisters PW et al; reGISTry Steering Committee. **A USA registry of gastrointestinal stromal tumor patients: Changes in practice over time and differences between community and academic practices.** *Ann Oncol* 2011;22(11):2523-9.