INTERVIEW

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CD 1, Tracks 13-23 — CD 2, Tracks 1-5

CD 1

Track 13 Identifying mechanisms of resistance to imatinib and sunitinib in gastrointestinal stromal tumors (GIST)

Track 14 Similarities and differences among the multitargeted kinase inhibitors imatinib, sunitinib and regorafenib

Track 15 Activity of sorafenib in patients with imatinib- and sunitinib-resistant GIST

Track 16 **Case discussion:** A 47-year-old man with metastatic GIST refractory to imatinib and sunitinib receives regorafenib on a clinical trial

Track 17 Regorafenib dose reductions in the treatment of metastatic GIST

Track 18 Phase II efficacy and safety results with regorafenib in patients with metastatic and/or unresectable GIST after failure of imatinib and sunitinib

Track 19 GRID: Results from a Phase III trial of regorafenib in metastatic and/or unresectable GIST progressing after prior treatment with imatinib and sunitinib

Track 20 Novel agents and strategies under investigation in GIST

Track 21 **Case discussion:** A 19-year-old woman with a 13-cm mixed epithelioid and spindle cell, succinate dehydrogenase (SDH)-deficient GIST with a high mitotic index

Track 22 Clinical characteristics of a newly recognized SDH-deficient GIST subtype occurring primarily in younger patients

Track 23 Benefits of adjuvant imatinib in patients with KIT-mutant or KIT wild-type GIST

CD 2

Track 1 Threshold risk of recurrence at which to administer adjuvant imatinib therapy for resected GIST

Track 2 Perspective on optimal duration of adjuvant imatinib therapy in GIST

Track 3 **Case discussion:** A 52-year-old man with metastatic GIST experiences an excellent response to preoperative imatinib and remains on therapy 2 years after resection with NED

Track 4 Role of surgery for resectable metastatic GIST in the era of kinase inhibition

Track 5 Considerations for long-term (>3 years) adjuvant imatinib therapy in GIST

Select Excerpts from the Interview

CD 1, Tracks 18-19

DR LOVE: Would you summarize recent clinical trial results reported with regorafenib for patients with advanced gastrointestinal stromal tumors (GIST)?

DR GEORGE: Thirty-three patients received treatment on our Phase II trial evaluating regorafenib for patients with metastatic and/or unresectable GIST after disease progression on imatinib and sunitinib. The median progression-free survival (PFS) was 10 months (George 2012), which was a good hypothesis-generating PFS. The clinical benefit rate was 79%. Clinical benefit from regorafenib was noted in patients with

KIT wild-type GIST and those with mutations in exon 9 and 11 of KIT. The PFS for patients with exon 9 mutations was less than that for exon 11 mutations. With only 3 patients in the exon 9 group, it's difficult to draw any conclusions. Although dose modifications were required in approximately 80% of the patients, we did not observe any significant need to discontinue regorafenib as a result of toxicity.

Based on the data from the Phase II trial, the Phase III GRID trial evaluating regorafenib for patients with metastatic and/or unresectable GIST progressing despite prior treatment with at least imatinib and sunitinib was initiated. It was designed as a 2-to-1 randomization to regorafenib or placebo, respectively (Demetri 2012; [2.1]).

A significant improvement was reported in PFS with regorafenib, with a median PFS of approximately 5 months for regorafenib versus 0.9 months for placebo. Patients receiving the placebo were allowed to cross over to regorafenib at the time of disease progression. The PFS curves postcrossover indicated that disease control was equally as good as if the patient had initially received regorafenib. The overall survival data showed no difference between regorafenib and placebo, which was expected because of the crossover design.

We're hopeful that regorafenib will become available in this setting, and I believe its role will be in the third-line setting because that's where the current data were collected. A question that arises is whether we'll have an opportunity to test it earlier in the treatment algorithm. Some of the challenges with regorafenib, as with sunitinib,

2.1

GRID: Results from a Phase III Trial of Regorafenib for Metastatic and/or Unresectable 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
Median overall survival*	Not reached	Not reached	0.77	0.199
Disease control rate	52.6%	9.1%	—	—

	Regorafenib (n = 132)		Placebo (n = 66)	
Select adverse events (AEs)	Any grade	Grade ≥3	Any grade	Grade ≥3
Hand-foot skin reaction	56.1%	19.7%	15.2%	1.5%
Hypertension	48.5%	23.5%	16.7%	3.0%
Diarrhea	40.9%	5.3%	7.6%	0%
Fatigue	38.6%	2.3%	27.3%	3%
Oral mucositis	37.9%	1.5%	9.1%	1.5%
Alopecia	23.5%	1.5%	3.0%	0%
Hoarseness	22.0%	0%	4.5%	0%
Treatment-emergent AE leading to permanent treatment discontinuation	6.1%		7.6%	

* Lack of statistical significance between regorafenib and placebo was expected due to the crossover design.

Demetri GD et al. *Proc ASCO* 2012;**Abstract LBA10008**.

are toxicity, dose-modification management and ensuring that the disease is well controlled and that patients are able to stay on treatment that is well tolerated for extended periods.

CD 1, Track 23 — CD 2, Tracks 1-2, 5

DR LOVE: Would you comment on the use of adjuvant imatinib therapy for patients with GIST?

DR GEORGE: Two large Phase III trials have investigated adjuvant imatinib therapy in GIST. The ACOSOG-Z9001 trial reported a recurrence-free survival benefit with 1 year of adjuvant imatinib versus placebo (Dematteo 2009). This study enrolled patients with tumors larger than 3 centimeters. No difference in overall survival was observed, but the follow-up period was short. In a subset analysis of data from the Z9001 study, patients with tumors larger than 10 centimeters experienced the greatest recurrence-free survival benefit, whereas those with smaller tumors had a much smaller differential in the curves.

The Scandinavian SSGXVIII/AIO study randomly assigned patients to either 1 or 3 years of adjuvant imatinib (Joensuu 2012; [2.2]). The trial included patients stratified as having high-risk disease using the modified NIH criteria. Patients who received treatment for 3 years experienced an overall survival benefit. In fact, this was the first study to report an overall survival benefit with adjuvant therapy for GIST. I believe it's important that we understand that patients with resected GIST may fall into the category considered to be at high risk, and these patients would potentially benefit from adjuvant therapy.

DR LOVE: What about patients at lower risk of recurrence?

2.2

SSGXVIII/AIO: A Randomized Phase III Clinical Trial of 12 versus 36 Months of Adjuvant Imatinib Therapy for Patients with High-Risk Gastrointestinal Stromal Tumors

Outcome	One-year arm (n = 198)	Three-year arm (n = 199)	Hazard ratio	*p*-value
Five-year RFS	47.9%	65.6%	0.46	<0.001
Five-year OS	81.7%	92.0%	0.45	0.02
	One-year arm (n = 194)		Three-year arm (n = 198)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Periorbital edema	59.3%	0.5%	74.2%	1.0%
Nausea	44.8%	1.5%	51.0%	0.5%
Diarrhea	43.8%	0.5%	54.0%	2.0%
Muscle cramps	30.9%	0.5%	49.0%	1.0%
Discontinued imatinib for reason other than GIST recurrence	12.6%		25.8%	

RFS = recurrence-free survival; OS = overall survival

Joensuu H et al. *JAMA* 2012;307(12):1265-72.

DR GEORGE: In the SSGXVIII study, approximately 25% of patients randomly assigned to the 3-year arm stopped treatment, not because of tumor recurrence but for some other reason, raising the issue of tolerance. Although imatinib is well tolerated, the discontinuation rate was nontrivial in that study. Toxicities such as fatigue, diarrhea and muscle cramping can be an issue. In general, it's difficult to justify extended therapy for patients at a low risk of recurrence.

The consensus from the United States and European groups is that consideration of adjuvant imatinib should be for patients with intermediate- and high-risk tumors. Although the FDA label is broad, patients with low-risk tumors should not receive adjuvant imatinib.

DR LOVE: Should patients at high risk have adjuvant imatinib therapy discontinued at 3 years?

DR GEORGE: These 2 trials consistently showed that patients fare well on adjuvant imatinib. When therapy is discontinued, patients continue to fare well for about 1 to 2 years before recurrence. The risk of recurrence tends to re-emerge the longer the patient is not receiving adjuvant therapy. Because we haven't seen a "plateau of curves" after adjuvant therapy is discontinued, the question of how long to continue therapy remains an issue.

DR LOVE: Have you administered adjuvant imatinib therapy for more than 3 years?

DR GEORGE: In my practice I have seen a couple of patients who underwent marginal resections of high-risk tumors at the outset, and I administered adjuvant imatinib for more than 3 years. In those cases I believed that the risk was not only a result of the characteristics of the tumor but also may have been further compounded by the way in which the surgery was performed due to the anatomy.

When initiating adjuvant therapy now, I usually aim for a 3-year duration because that's what the data show is most effective. Three years from now I will reassess the situation and consider what data are available.

A single-arm Phase II study of 5 years of imatinib for patients at high risk of recurrence recently completed accrual (NCT00867113). It will be interesting to see the outcome of this study. ■

SELECT PUBLICATIONS

Blay JY. **Management of imatinib-associated skin rash in a patient with metastatic gastrointestinal stromal tumor: A case report.** *Clin Sarcoma Res* 2012;2(1):23.

Dematteo RP et al. **Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: A randomised, double-blind, placebo-controlled trial.** *Lancet* 2009;373(9669):1097-104.

Demetri GD et al. **Randomized Phase III trial of regorafenib in patients (pts) with metastatic and/or unresectable gastrointestinal stromal tumor (GIST) progressing despite prior treatment with at least imatinib (IM) and sunitinib (SU): GRID trial.** *Proc ASCO* 2012;**Abstract LBA10008**.

Demetri GD. **Differential properties of current tyrosine kinase inhibitors in gastrointestinal stromal tumors.** *Semin Oncol* 2011;38(Suppl 1):10-9.

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.

Joensuu H et al. **One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: A randomized trial.** *JAMA* 2012;307(12):1265-72.