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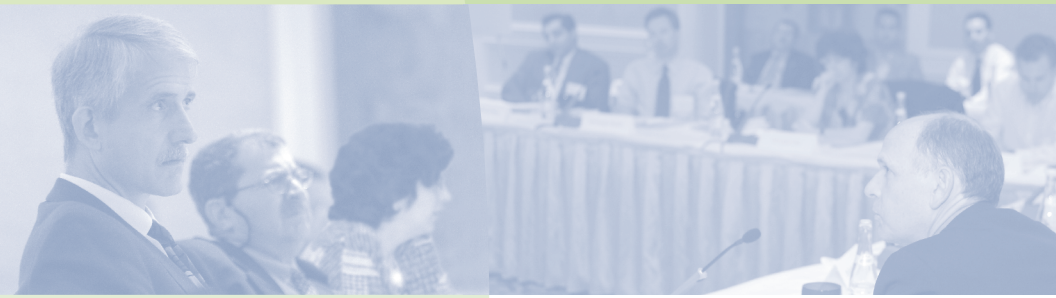
Meet The Professors

A case-based discussion on the management of gastrointestinal stromal tumors



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Meet The Professors: A case-based discussion on the management of gastrointestinal stromal tumors

STATEMENT OF NEED/TARGET AUDIENCE

Gastrointestinal stromal tumor (GIST) is one of the many histologic subsets of the soft tissue sarcomas and the most common mesenchymal neoplasm of the gastrointestinal tract. Clinical trial data in the systemic management of GIST have been sparse over the past few decades, owing to the cancer's innate resistance to conventional cytotoxic chemotherapeutics and radiation interventions. However, recent breakthroughs in the understanding of this malignancy's pathogenesis and the advent of small-molecule targeted signal transduction inhibitors and anti-angiogenesis agents have led to the approval of a number of innovative therapies that have changed the natural history of the disease.

In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. To bridge the gap between research and patient care, this *Meet The Professors* CME activity utilizes case-based discussions between clinical investigators and practicing oncologists to apply evidence-based concepts to routine clinical care. By providing access to the latest research developments and expert perspectives on the disease, this activity will assist medical oncologists in the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Demonstrate an understanding of the pathophysiology and epidemiology of GIST.
- Formulate pre- and postsurgical management strategies for patients with GIST, considering the risk of tumor rupture, postoperative histologic staining and/or mutational analyses.
- Evaluate the emerging role of adjuvant therapy for localized, resectable GIST.
- Devise therapeutic approaches to GIST in the context of the rationale for biologic agents and evidence surrounding the limited effectiveness of cytotoxic chemotherapy.
- Evaluate the established role of molecularly targeted therapy for patients with advanced GIST.
- Develop an evidence-based treatment algorithm for patients with imatinib-resistant GIST, considering the implications of mutational transformation on therapeutic choice.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.

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This program is supported by educational grants from Novartis Pharmaceuticals Corporation and Pfizer Inc.

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FACULTY — **Dr Blanke —** No real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Demetri — *Advisory Board***: Amgen Inc, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc; ***Consulting Agreements:*** Amgen Inc, Bayer Pharmaceuticals Corporation, Genentech BioOncology, GlaxoSmithKline, GPC Biotech, Novartis Pharmaceuticals Corporation, Pfizer Inc; ***Stock Ownership:*** Plexxikon Inc. **Dr Eisenberg — *Advisory Committee and Speakers Bureau:*** Novartis Pharmaceuticals Corporation. **Dr Rubin — *Advisory Committee:*** Pfizer Inc; ***Speakers Bureau:*** Novartis Pharmaceuticals Corporation. **Dr Trent — *Consulting Agreements:*** Pfizer Inc.

COMMUNITY PANEL — **Drs Glynn, Harwin and Moriarty —** No real or apparent conflicts of interest to disclose. **Dr Bhardwaj — *Advisory Committee:*** Celgene Corporation, Genentech BioOncology; ***Consulting Agreements:*** Novartis Pharmaceuticals Corporation; ***Paid Research:*** Genentech BioOncology; ***Stock Ownership:*** Celgene Corporation. **Dr Cartwright — *Advisory Committee:*** Amgen Inc, Bristol-Myers Squibb Company, Roche Laboratories Inc; ***Speakers Bureau:*** Amgen Inc, Bristol-Myers Squibb Company, Genomic Health Inc, Roche Laboratories Inc. **Dr Hart — *Speakers Bureau:*** GlaxoSmithKline. **Dr Leighton — *Paid Research:*** Amgen Inc, Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation; ***Speakers Bureau:*** Sanofi-Aventis. **Dr Pizzolato — *Advisory Committee:*** Celgene Corporation; ***Speakers Bureau:*** ImClone Systems, Sanofi-Aventis. **Dr Reeves — *Advisory Committee:*** Bayer Pharmaceuticals Corporation, Celgene Corporation, Genentech BioOncology, Millennium Pharmaceuticals Inc. **Dr Safa — *Paid Research:*** MedImmune Inc, Sanofi-Aventis; ***Speakers Bureau:*** Genentech BioOncology, Pfizer Inc.

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Cases Discussed in the Audio and Print Program

Case 1: A 65-year-old woman with a high-risk (11.5 centimeters, >20 mitoses per 50 HPF) gastrointestinal stromal tumor (GIST) in the esophagus who was treated with surgery, radiation therapy and adjuvant imatinib *(from the practice of William N Harwin, MD)*

Case 2: A 73-year-old man with a low-risk (three centimeters, ≤2 mitoses per 50 HPF) gastric GIST who was treated with surgery alone *(from the practice of Dr Harwin)*

Case 3: A 40-year-old woman with a 14-cm gastric GIST (rare mitoses and minimal Ki-67) that was resected. Five years later, the disease recurred in the liver, and she was treated with neoadjuvant and adjuvant imatinib and surgical resection *(from the practice of Malek Safa, MD)*

Case 4: A 51-year-old man with metastatic jejunal GIST with a KIT exon 9 mutation. The primary GIST was resected, and he received imatinib 800 milligrams daily. His disease eventually progressed in a liver lesion, which was resected, and he remained on imatinib. Sunitinib is now being considered because of disease progression *(from the practice of Lowell Hart, MD)*

Case 5: A 58-year-old woman with a 4-cm gastric GIST and mixed large and small cell CD20-positive non-Hodgkin's lymphoma *(from the practice of Daniel J Moriarty, MD)*

Case 6: A 64-year-old woman with a 26-cm gastric GIST that was surgically resected and treated with adjuvant imatinib *(from the practice of John C Leighton Jr, MD)*

Case 7: An 83-year-old woman with a gastric GIST and T3N0 colon cancer. The colon cancer was resected, and imatinib caused a complete response of the GIST *(from the practice of Joseph F Pizzolato, MD)*

Case 8: A 78-year-old man with a history of cardiac disease who was treated with increasing doses of imatinib followed by sunitinib for an inoperable 18-cm gastric GIST *(from the practice of Sushil Bhardwaj, MD)*

Case 9: A 53-year-old woman with a small bowel GIST who received one year of adjuvant imatinib as part of a randomized clinical trial *(from the practice of Philip T Glynn, MD)*

Case 10: A 67-year-old man with a gastric GIST that recurred in the liver. The liver lesions were resected, and he was treated with imatinib *(from the practice of Dr Moriarty)*

Case 11: A 67-year-old woman with a small bowel GIST that recurred. She was treated with imatinib followed by resection. Upon her second recurrence, she was restarted on imatinib *(from the practice of Dr Pizzolato)*

Case 12: A 47-year-old man with metastatic GIST who was treated with imatinib *(from the practice of Dr Glynn)*

Case 13: A 42-year-old man with a high-risk (10.5 centimeters, 100 mitoses per 50 HPF) gastric GIST that was resected and recurred within one year *(from the practice of Dr Leighton)*

Cases included in this monograph

CASE 1 *from the practice of Dr Harwin:* A 65-year-old woman with a high-risk (11.5 centimeters, >20 mitoses per 50 HPF) gastrointestinal stromal tumor (GIST) in the esophagus who was treated with surgery, radiation therapy and adjuvant imatinib (presented to Drs Demetri, Eisenberg and Trent)

CASE 2 *from the practice of Dr Harwin:* A 73-year-old man with a low-risk (three centimeters, ≤2 mitoses per 50 HPF) gastric GIST who was treated with surgery alone (presented to Drs Demetri, Eisenberg and Trent)

Primary GIST: Risk stratification

DR LOVE: Dr Trent, how do these two cases fit into the spectrum of primary GIST?

DR TRENT: These are both common presentations for primary GIST. With an 11-cm GIST and a high mitotic rate, the risk of that patient developing metastases in her lifetime after surgery alone is probably more than 50 percent, which is the rationale for starting the adjuvant and neoadjuvant studies.

On the other hand, in the case of a small tumor (three centimeters) with a low mitotic rate, particularly a gastric tumor, the chance of that tumor recurring in the patient's lifetime is significantly less. I suspect it is less than 20 percent, and it may be less than 10 percent.

1.1 Risk Stratification of Primary GIST by Mitotic Rate, Size and Site*

Tumor parameters			Risk of disease progression†			
Group	Mitotic rate‡	Size	Gastric	Jejunum/ ileum	Duodenum	Rectum
1	≤5	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
2	≤5	>2 ≤ 5 cm	Very low (1.9%)	Low (4.3%)	Low (8.3%)	Low (8.5%)
3a	≤5	>5 ≤ 10 cm	Low (3.6%)	Moderate (24%)	High (34%)‖	High (57%)‖
3b	≤5	>10 cm	Moderate (12%)	High (52%)		
4	>5	≤2 cm	None§	High (50%)§	(Insuff data)	High (54%)
5	>5	>2 ≤ 5 cm	Moderate (16%)	High (73%)	High (50%)	High (52%)
6a	>5	>5 ≤ 10 cm	High (55%)	High (85%)	High (86%)‖	High (71%)‖
6b	>5	>10 cm	High (86%)	High (90%)		

* Based on previously published long-term follow-up studies on 1,055 gastric, 629 small intestinal, 144 duodenal and 111 rectal GISTs
† Defined as metastasis or tumor-related death
‡ Per 50 HPF, HPF = high power field
§ Denotes small numbers of cases
‖ Groups 3a and 3b or 6a and 6b are combined in duodenal and rectal GIST because of the small number of cases

SOURCE: Miettinen M, Lasota J. *Semin Diagn Pathol* 2006;23(2):70-83. **Abstract**

DR LOVE: Doctors are accustomed to using Adjuvant! Online in breast and colon cancer. Do we have similar algorithms for GIST?

DR TRENT: Tables are available that estimate the risk of disease progression based on tumor site, size and mitotic rate, but they have originated from different data sets, and people interpret them in different ways (Miettinen 2006; [1.1]). Therefore, no widely accepted risk model exists.

Epidemiology of GIST

DR LOVE: Dr Demetri, would you discuss the evolution of GIST as a diagnosis?

DR DEMETRI: GIST was essentially unrecognized before 1999 to 2000. It was hiding in other diagnostic "bins." Most cases were being called sarcomas, sometimes leiomyosarcomas.

At least one third of GISTs, which are epithelioid, were being incorrectly categorized as epithelioid, poorly differentiated carcinomas. We have seen patients with GISTs who initially were told they had ovarian, gastric or prostate cancer, depending on where in their body the tumor arose.

Before 2000, people thought fewer than 500 cases of GIST occurred per year. Population studies have now shown that more than 5,000 cases of GIST occur in the US alone.

Many people believe there are probably more like 15,000 cases if you include the micro-GISTs that are increasingly seen on endoscopy.

Primary GIST: Clinical trials of adjuvant imatinib

DR LOVE: Dr Eisenberg, can you review the current status of adjuvant therapy for GIST?

DR EISENBERG: Both of the ACOSOG adjuvant imatinib trials have now been completed, but they have short-term follow-up.

ACOSOG-Z9000 was a Phase II trial, which enrolled patients with the highest-risk disease (ie, tumors 10 centimeters or larger or evidence of tumor rupture during surgery).

Those patients were treated with adjuvant imatinib at 400 milligrams per day for one year (DeMatteo 2008; [1.2]).

ACOSOG-Z9001, which started at almost the same time, was a Phase III trial for patients with intermediate-risk disease (ie, tumors three centimeters or larger).

None of these patients were selected by mitotic rate because the general feeling was that this was rather subjective and couldn't be reproduced in a large, multi-institutional trial (DeMatteo 2007).

ACOSOG-Z9001 was subject to an independent interim analysis, which yielded a positive effect in terms of relapse-free survival for the group of patients treated with imatinib.

When you break those numbers out, you see that the group with the highest-risk tumors benefited the most. The statistical evidence that imatinib helped the patients who had 3- to 6-cm tumors was much less impressive (DeMatteo 2007; [1.3]).

Remember that these patients received imatinib for only one year. After a year, recurrences in the treated group were on a slope that was similar to the one for the untreated group (DeMatteo 2007).

It's probably reasonable to expect that (1) one year of imatinib is not enough for those patients at particularly high risk of recurrence and (2) one would obtain about a six-month progression-free survival benefit by receiving one year of imatinib.

Several ongoing trials in Europe are evaluating imatinib at different doses and intervals. EORTC-62024 is evaluating survival,

which will probably take a long time and many patients to do. So we're still trying to solve this question.

My guess is that imatinib will probably be effective in preventing recurrences in patients with high-risk disease. I believe patients will have to receive it for a long time, perhaps until their cancer recurs.

1.2 ACOSOG-Z9000: A Phase II Trial of Adjuvant Imatinib for Patients (N = 107) with High-Risk, Resected Primary GIST

Overall survival	
1 year 2 years 3 years	99% 97% 97%
Recurrence-free survival	
1 year 2 years 3 years	94% 73% 61%

SOURCE: DeMatteo R et al. Presentation. Gastrointestinal Cancers Symposium 2008;**Abstract 8**.

1.3 ACOSOG-Z9001: A Phase III Randomized Trial of Adjuvant Imatinib for Patients with Resected Primary GIST

One-year recurrence-free survival	Imatinib % (n)	Placebo % (n)	Hazard ratio	*p*-value
Overall	97% (325)	83% (319)	0.33 (0.20-0.53)	<0.001
By tumor size				
3–6 cm	100% (128)	95% (135)	0.44 (0.14-1.4)	0.15
6–10 cm	96% (112)	80% (105)	0.37 (0.17-0.81)	0.01
>10 cm	96% (82)	67% (76)	0.19 (0.09-0.41)	<0.001

SOURCE: DeMatteo R et al. *Proc ASCO* 2007;**Abstract 10079**.

Primary GIST: Clinical use of adjuvant imatinib

DR LOVE: Dr Demetri, in a clinical setting, what is a rational approach to adjuvant therapy for patients with primary GIST?

DR DEMETRI: A global argument exists about the value of a benefit in recurrence-free survival without a documented benefit in overall survival, which leads to dramatic differences even among experts.

In Europe, the consensus guidelines say, "We don't think patients should receive adjuvant therapy as a standard."

In the US, however, we are much more confident that the strength of the randomized study is sufficient to justify using adjuvant imatinib for at least one year for appropriately selected patients with high-risk disease.

What is an appropriately selected patient with high-risk disease? The curves are dramatically different for the patients whose tumors are greater than 10 centimeters.

They relapse relatively quickly if they receive no adjuvant therapy, and they relapse more slowly if they receive one year of imatinib, but they still relapse (DeMatteo 2007; [1.3]).

So the question is, are we committing these patients to potentially lifelong

therapy to keep their disease at bay?

If a young person has a 30-cm tumor, it may not be an unreasonable tradeoff. Those are unusual situations, though.

Part of the challenge for any practicing oncologist — community or academically based — is trying to help patients and families deal with the issue of the relative risk and benefit of imatinib.

Individuals make different choices. It is a matter of whether someone is saying, "I am comfortable with the concept that if my disease recurs three years from now, I will take imatinib. You have data indicating that I have a 90 percent chance of benefit."

Other people are less willing to do that, and they're much more willing to take an adjuvant approach to try to prevent recurrences.

DR LOVE: Dr Trent, what is the available evidence that earlier treatment is better?

DR TRENT: In most solid tumors, metastatic disease is not curable, so we try to avoid catching it late. I am an early adopter of the adjuvant data. These results have been presented only in abstract form, and they have not been peer reviewed or published.

However, the adjuvant data with imatinib for primary GIST are good. So I tend to maintain a low threshold for treating patients who have primary GIST with adjuvant imatinib.

On the other side of the coin are some arguments that treating with imatinib early may be selecting for resistance, so when a recurrence does develop, it is imatinib resistant and is much more difficult to treat.

Arguments exist for and against that view, but I don't let it deter me from treating a patient who I believe will benefit from adjuvant therapy.

DR EISENBERG: We have to remember also that in most of these adjuvant studies, stratification of risk will be important because, historically, some of these patients will be cured with surgery alone and won't need the drug. So that information will be extremely important.

CASE 3 *from the practice of Dr Safa:* A 40-year-old woman with a 14-cm gastric GIST (rare mitoses and minimal Ki-67) that was resected. Five years later, the disease recurred in the liver, and she was treated with neoadjuvant and adjuvant imatinib and surgical resection (presented to Drs Demetri, Eisenberg and Trent)

Metastatic GIST: Treatment for liver-only metastases

DR LOVE: Dr Eisenberg, how often do you see recurrences five years after surgery in patients with GIST?

DR EISENBERG: It depends on the individual biology of the tumor. In a patient who has a large GIST with a high mitotic rate, one would expect to see recurrences within the first year or two.

This particular patient had a large tumor, but she had minimal mitoses and her Ki-67 was barely positive, suggesting that this tumor was conflicted. It was big enough, but it did not demonstrate the other characteristics that would lead us to believe that its course would be particularly aggressive.

The recurrence was in the liver only, which is a favored site for GIST. When they develop metastatic disease, about half of these patients will have liver-only disease (DeMatteo 2000; [1.4]), which should be confirmed not only by CT but also perhaps by PET.

The workup for liver metastases is similar in the postimatinib era to the workup in the preimatinib era.

Evaluation of whether the patient is a surgical candidate should be based on the volume of liver disease, the age of the patient, comorbidities and the anatomic location of the lesions.

In the preimatinib era, resection of GIST liver metastases was not particularly successful. Long-term survival occurred in only about five or 10 percent of those patients whose liver metastases were successfully resected.

In the postimatinib era, I am certain that has changed. Anecdotally, from several institutional reports, it has changed.

1.4 Sites of Metastatic Recurrence in Patients (N = 94) with GIST

Site	Number of patients	Percent of total
Hepatic	61	65
(Liver only)	(50)	(53)
Peritoneal	20	21
Lymph node	6	6
Bone	6	6
Lung	2	2

SOURCE: DeMatteo RP et al. *Ann Surg* 2000;231(1):51-8. **Abstract**

Metastatic GIST: Clinical use of neoadjuvant imatinib for liver-only metastases

DR LOVE: Dr Demetri, in this type of situation with liver-only metastases, do you use preoperative or postoperative systemic therapy or both?

DR DEMETRI: I believe it's a pretty standard consensus across the world that we would start with systemic therapy with the idea that surgery may play a role.

It's the opposite of what we often assume, that surgery is the primary modality. In this case, drug therapy is the primary modality.

The fact that systemic treatment, on median, will fail after a couple of years, however, has given us hope for a multimodality approach to managing this form of sarcoma. GIST is a type of sarcoma, and we're accustomed to multimodality approaches in managing other types of sarcomas.

These approaches generally involve starting with drugs to gain some control of the disease and then considering surgery later to prevent the emergence of resistant clones that are probably hiding in those bulky tumors.

DR LOVE: When the surgeon says a tumor can be resected, what is the thinking about using preoperative systemic therapy at that point, as opposed to using it afterwards as adjuvant therapy?

DR DEMETRI: The advantage is similar to the way we approach the use of chemotherapy in osteosarcoma. You start with the systemic therapy, and usually you're able to see that the tumor is not rapidly overcoming those drugs, or imatinib in this case.

If the tumor were to progress through imatinib, maybe you wouldn't benefit the patient by moving right to surgery because even after the best possible surgical resection, other cells are almost certainly left behind.

DR LOVE: What duration of preoperative therapy do you use?

DR DEMETRI: We do not know. The median time to optimal response is approximately four to six months, but there have been patients whose tumors shrink after one year.

So we negotiate with the patient. "What's good for you? Does that fall on Christmas? Is a big holiday coming up?" When we schedule these resections, we use that sort of personal factor.

DR EISENBERG: One of the advantages we have found in treating this disease systemically first is that it provides an in vivo tumor model. You can see if the agent is working, which tends to help promote post-surgical use of the same agent.

Also, the effect on the tumor is fairly dramatic in terms of degenerative change that makes it much less vascular, which makes the surgery easier.

CASE 4 *from the practice of Dr Hart:* A 51-year-old man with metastatic jejunal GIST with a KIT exon 9 mutation. The primary GIST was resected, and he received imatinib 800 milligrams daily. His disease eventually progressed in a liver lesion, which was resected, and he remained on imatinib. Sunitinib is now being considered because of disease progression (presented to Drs Demetri, Eisenberg and Trent)

Metastatic GIST: Significance of exon 9 mutations

1.5 Correlation of Dose Response with Tumor Genotype Among Patients with Advanced GIST Treated with Imatinib

	400 mg patients/events	800 mg patients/events	Hazard ratio	*p*-value
All patients	181/116	196/120	0.845 (95% CI: 0.654-1.091)	0.20
KIT exon 9 mutants	27/26	31/21	0.392 (95% CI: 0.218-0.706)	0.0013
KIT exon 11 mutants	118/67	130/68	0.821 (95% CI: 0.585-1.151)	0.25
Wild-type patients	27/15	25/22	1.823 (95% CI: 0.938-3.543)	0.07

"Patients whose tumours expressed an exon 9 mutant KIT protein show significant imatinib dose dependency for progression-free survival compared to patients whose tumours harboured mutant exon 11 or wild-type KIT isoforms.

These results suggest that imatinib should be dosed at 400 mg twice a day in patients with tumours bearing KIT exon 9 mutations. Other patients could safely start at an initial imatinib dose of 400 mg once daily, and increase to 800 mg when there is evidence of disease progression."

SOURCE: Debiec-Rychter M; EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2006;42(8):1093-103. **Abstract**

DR LOVE: Dr Trent, can you discuss the significance of the KIT exon 9 mutation?

DR TRENT: Exon 9 is in the extracellular domain. Nobody is exactly clear as to how it makes KIT active, but it clearly does.

The other peculiar characteristic of the exon 9 mutation is that a dose-response relationship is apparent in the study by Maria Debiec-Rychter comparing 800 to 400 milligrams per day of imatinib (Debiec-Rychter 2006; [1.5]).

What I've done with a few patients — and I only have two patients in whom I've tried this — is to offer them a third option of increasing the dose of imatinib up to 1,200 milligrams daily. Interestingly, in both patients, I was able to either slow the growth of their disease or actually decrease the density of and slightly shrink the tumor.

I started one patient on 400 milligrams of imatinib. When his disease progressed, I increased the dose to 600 milligrams and his disease stabilized.

When the disease again progressed, the dose of imatinib went up to 800 milligrams and again his disease stabilized. Eventually when the disease progressed, the dose went to 1,200 milligrams and his disease stabilized.

While this patient was receiving 800 milligrams of imatinib, we started testing for KIT mutations and found that he had an exon 9 mutation. He's now alternating every other day between 1,200 and 1,600 milligrams of imatinib, and he has experienced no growth of his disease.

Some of this is his choice because he doesn't want to switch drugs or go on a clinical trial. He wants to push imatinib as far as he can, and that's what we've been doing.

DR LOVE: What do we know about efficacy and side effects with this kind of dosing? Has it been reported in the literature?

DR TRENT: I don't believe so. In the couple of patients with an exon 9 mutation whom I've treated, I believe there is some efficacy.

It's not been a home run in which the patient has had a partial or a complete response, but it has had some activity. In these few patients, the side effects have been manageable.

Metastatic GIST: Mechanisms of resistance to imatinib

DR LOVE: Can you discuss what we know about the mechanisms of resistance to imatinib?

DR DEMETRI: Once imatinib fails, the vast majority of patients will have a second mutation. If the first mutation is exon 11, it's not uncommon for the next mutation, unfortunately, to show up down in the kinase domain of exon 17, which essentially renders every small molecule useless.

Some secondary mutations show up in exon 13 of the same strand of DNA that encodes the KIT protein.

When this occurs, the ATP-binding site of the protein will have a mutation that excludes imatinib, but sunitinib can still bind. Wonderful structural studies are being conducted to explain this kind of resistance.

Metastatic GIST: Sunitinib as second-line therapy

DR LOVE: Dr Trent, would you talk about what we know about sunitinib in GIST (1.6)?

DR TRENT: Sunitinib is now FDA approved in the second-line setting for the treatment of patients with GIST who have experienced disease progression on or are intolerant to imatinib.

A Phase II study (George 2006) and a large Phase III study (Demetri 2006) demonstrated that sunitinib has activity in this setting.

In the Phase III study, sunitinib was compared to placebo, and patients were randomly assigned in a two-to-one fashion. The patients who were treated with sunitinib had a median progression-free survival of about six months, which was better than the median progression-free

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1.6 Sunitinib in the Treatment of Imatinib-Resistant or Imatinib-Intolerant GIST

"Imatinib, a selective tyrosine kinase inhibitor, is currently the standard of care first-line treatment for unresectable or metastatic gastrointestinal stromal tumour (GIST), improving survival time and delaying disease progression in many patients.

Nevertheless, primary and secondary (acquired) resistance to imatinib is a substantial problem in routine clinical practice. Sunitinib is an oral, multitargeted tyrosine kinase inhibitor that was approved for the treatment of imatinib-resistant or -intolerant GIST.

In the pivotal phase III study, sunitinib provided substantial clinical benefits including disease control and superior survival versus placebo as second-line treatment. Treatment with sunitinib was reasonably well tolerated.

The availability of sunitinib represents an important clinical advance in GIST management, providing physicians and patients with an effective therapy when resistance to imatinib develops."

SOURCE: Judson I, Demetri G. *Ann Oncol* 2007;18(Suppl 10):20-4. **Abstract**

1.7 Median PFS Among Patients with GISTs Treated with Sunitinib versus Placebo

	Sunitinib (n = 207)	Placebo (n = 105)	Hazard ratio	*p*-value
Median PFS	27.3 weeks	6.4 weeks	0.33 (95% CI: 0.23–0.47)	<0.0001
Median overall survival	NR	NR	0.49 (95% CI: 0.29–0.83)	0.007
Objective response rate	7%	0%	NR	0.006
Best overall objective response (ITT population)				
Partial response	7%	0%	—	—
Stable disease	58%	48%	—	—
Progressive disease	19%	37%	—	—

"Time to tumour progression, progression-free survival, overall survival, and other measures of tumour response were significantly greater in patients treated with sunitinib than in those in the placebo group in a population with advanced gastrointestinal stromal tumour in which treatment with another tyrosine kinase inhibitor had failed.

Median time to tumour progression with sunitinib was more than four times greater than with placebo, reducing the relative risk of progression or death by 67% and the relative risk of death by 51%.

Since the overall survival analysis included patients who had crossed over from placebo to sunitinib because of disease progression, and these patients were still considered part of the placebo group, the difference observed between the treatment groups might have been reduced for this measure."

PFS = progression-free survival; NR = not reported; ITT = intent to treat

SOURCE: Demetri GD et al. *Lancet* 2006;368(9544):1329-38. **Abstract**

survival in the control arm of about six weeks (Demetri 2006; [1.7]).

Additionally, many responses were observed on PET scanning. So sunitinib clearly has activity. I've used it a fair amount in my practice. Many patients don't respond, but it has reasonable efficacy in some patients.

The side-effect profile of sunitinib is a little different from that of imatinib. With imatinib, patients develop a lot of edema and periorbital edema, which can be a big problem.

Patients who are treated with sunitinib don't tend to develop that same degree of edema, electrolyte imbalances or problems with fluid shift.

Sunitinib, however, does pose a risk for hypothyroidism and hypertension due to its inhibition of the VEGF receptor. Sunitinib clearly has efficacy and is commonly used in the second-line setting.

DR LOVE: What schedules are used with sunitinib?

DR TRENT: The schedule that was approved was 50 milligrams per day, four weeks on and two weeks off. This daily dose is difficult for many patients to tolerate, and they embrace the two weeks off.

In the study, however, during the two weeks off, patients' PET scans showed flares. If you perform a PET scan after four weeks of sunitinib, you see a great response in some patients. Then they take two weeks off, and by the time they start the drug again, their PET scan shows tumor activity again and their tumor is flaring up.

So many people in the GIST community of medical oncologists are using the 37.5-mg daily dose, which is better tolerated.

The patient takes it daily, and you're able to avoid the interruption of kinase inhibitor therapy, which we've come to realize is not the best approach for this disease.

DR PIZZOLATO: Are you seeing the same kinds of responses with sunitinib that one sees with imatinib? If not, do you think that's because we're not using it as first-line therapy?

DR DEMETRI: The small subset of patients who receive sunitinib because they're imatinib intolerant are the ones, in our experience, who can derive enormous — three-year or four-year — benefit from sunitinib. I believe the sunitinib data are inevitably contaminated by the fact that we are evaluating it in patients of whom the majority started with exon 11 mutations and were imatinib and sunitinib sensitive and then developed a secondary mutation, including the exon 17 mutation. That will make the data with sunitinib or any small molecule as second-line therapy appear inferior to any up-front drug.

One might ask why we have not yet performed an up-front comparison of sunitinib and imatinib. I believe that study will be conducted. The issue will be the trade-off between toxicity and long-term disease control. I suspect that sunitinib will be as effective, if not better, than imatinib, but the toxicity profile of sunitinib will be harsher.

CASE 8 *from the practice of Dr Bhardwaj:* A 78-year-old man with a history of cardiac disease who was treated with increasing doses of imatinib followed by sunitinib for an inoperable 18-cm gastric GIST (presented to Drs Blanke and Rubin)

Metastatic GIST: Salvage surgery for patients with disease progression on imatinib

DR LOVE: Should salvage surgery be attempted on patients whose disease progresses despite treatment with a tyrosine kinase inhibitor (1.8)?

DR BLANKE: Many data have emerged recently on salvage surgery in the setting

of tyrosine kinase inhibitor failure, and it doesn't work very well.

A number of series from a number of different institutions has shown that either the disease rapidly relapses systemically, or the surgery appeared easy preoperatively, but once in surgery, physicians find a lot of disease and realize they were only seeing the tip of the iceberg.

1.8 Management of Advanced GIST and Disease Progression During Imatinib Therapy

- Check for compliance with imatinib.
- These metastases may have second KIT mutations, resulting in resistance to imatinib. Consider dose escalation of imatinib from 400 to 800 milligrams per day. (Five percent of patients will respond, and 30 percent will experience stable disease.)
- Check for comedication with enzyme-inducing drugs. Higher doses of imatinib (800 to 1,000 milligrams per day) may be required.
- Consider sunitinib or participation in a clinical trial.
- Surgery may be effective for one or few metastases.

SOURCE: Adapted from Joensuu H. *Lancet* 2006;368(9544):1303-4. No abstract available

1.9 Side Effects and Tolerability of Sunitinib

"The most common clinical toxicities attributable to sunitinib include diarrhea, mucositis/stomatitis, hypertension, rash, skin discoloration, and altered taste, whereas commonly occurring laboratory abnormalities have been seen in association with gastrointestinal toxicity, renal toxicity, and hematologic toxicity.

Of grade 3/4 toxicities occurring with sunitinib (which are relatively uncommon [<10%]), those that are clinically important include hypertension, diarrhea, fatigue, and hand-foot syndrome."

SOURCE: Adams VR, Leggas M. *Clin Ther* 2007;29(7):1338-53. **Abstract**

Metastatic GIST: Tolerability and efficacy of sunitinib

DR LOVE: In your experience, how is sunitinib tolerated (1.9)?

DR BLANKE: I've used a fair bit of sunitinib and find that patients either tolerate it unbelievably well or they feel poorly and refuse to take it.

Patients may experience severe asthenia in addition to all the classic side effects. However, it is tolerated well enough to make it worth trying for patients without other options.

I have had better luck with and prefer to use the continuous daily dosing of 37.5 milligrams, which Dr Demetri and Dr George's group showed is probably as effective as the 50-mg dose daily for four weeks then off for two weeks (George 2008; [1.10]).

DR LOVE: What do we know about the antitumor effect of sunitinib?

DR BLANKE: The response rate with sunitinib is seven or eight percent in the original trial (Casali 2006). However, a progression-free survival benefit clearly occurs with this agent, and we know from the imatinib studies that achieving stable disease, in terms of how long the patient

will live, is every bit as good as achieving an actual response.

So the fact that sunitinib can stop GISTs from growing actually means something.

On the other hand, if a patient is highly symptomatic from bulky disease, sunitinib is not likely to make him or her better because of tumor shrinkage.

Metastatic GIST: Novel therapies

DR LOVE: What new combinations are being explored in the treatment of GIST?

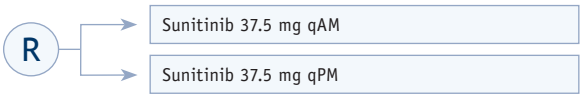
DR BLANKE: A logical combination would be sunitinib and imatinib, but investigators have been hesitant because of the potential toxicity. Jordan Berlin at Vanderbilt has finally "bitten the bullet" and is evaluating this combination in a Phase I trial (VU-VICC-GI-0621; [1.11]).

We have little information on front-line sunitinib for GIST. Probably the drug that is furthest along is nilotinib, or AMN107, which is a kind of "super imatinib." In the early trials it appeared promising as monotherapy and in combination, so now a randomized Phase III trial is evaluating this agent.

DR LOVE: Do you ever go back to imatinib after a patient fails second-line sunitinib?

DR BLANKE: That is one way in which treating GIST is different from treating colon cancer. If a patient with colon cancer

1.10 Phase II Trial of Sunitinib (SU) on a Continuous Daily Dosing (CDD) Schedule for Patients with Advanced GIST



Efficacy data from two randomized trials evaluating dose and schedule of sunitinib

Parameters	Sunitinib 37.5 mg qd continuous dosing Phase II (N = 60)*	Sunitinib 50 mg qd 4 weeks on, 2 weeks off Phase III (N = 207)†
Clinical benefit rate	53%	NR
Partial response rate	12%	7%
Median progression-free survival	35.1 weeks	27.3 weeks

"The most common non-hematologic all-causality AEs on CDD were diarrhea (43%), abdominal pain (40%), and asthenia (38%). Grade >3 hematologic laboratory abnormalities included neutropenia (12%), anemia (12%), and thrombocytopenia (3%). Dose reduction to 25 mg due to AEs occurred in 14 pts. Toxicities were comparable between AM and PM dosing, and AEs were similar to those seen in the phase III trial. SU CDD achieved constant drug exposure with no unexpected accumulation. **Conclusions:** CDD of sunitinib appears to be a safe and potentially effective dosing strategy for pts with IM-resistant/-intolerant GIST. AM and PM dosing appear to exhibit comparable safety and efficacy."

NR = not reported; AE = adverse event

SOURCES: * George S et al. Gastrointestinal Cancers Symposium 2008;**Abstract 39**; † Demetri GD et al. *Lancet* 2006;368(9544):1329-38. **Abstract**

fails FOLFOX, we do not continue to use it considering that it may be slowing the disease, even if it is not stopping it.

However, with GIST, if patients fail second-line sunitinib and for some reason can't go on a trial, there's nothing else to offer them, so we often go back to imatinib.

The analogy I've heard is that it's like putting on the parking brake while the car is moving. It won't stop it, but it will slow it down a bit.

We know that when you take these patients off the tyrosine kinase inhibitors, they die rapidly, but if they go back on imatinib, their disease continues to progress but they may live another few months to a year.

1.11 Phase I Study of Imatinib with Sunitinib

Protocol IDs: VU-VICC-GI-0621, VICC-GI-0621, NCT00573404 Target Accrual: 15

Eligibility
GIST
Documentation of disease progression in patients previously treated with imatinib
Untreated disease allowed
Must have one or more measurable lesions by RECIST

Outline

- Course 1 — Sunitinib qd, days 1-14
- Subsequent courses — Sunitinib qd, days 1-42 + imatinib once or twice daily, days 1-42
- Courses repeat every six weeks in the absence of unacceptable toxicity

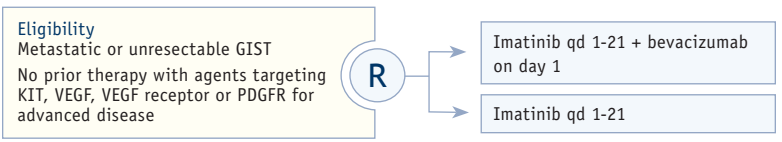
Study Contacts
Vanderbilt-Ingram Cancer Center

Jordan Berlin, MD	Tel: 615-322-4967; 800-811-8480
Charles Blanke, MD	Tel: 503-494-1556; 800-494-1234
Emily Chan, MD, PhD	Tel: 615-322-4967; 800-811-8480

SOURCE: NCI Physician Data Query, March 2008.

1.12 Phase III Study of Imatinib with or without Bevacizumab

Protocol IDs: SWOG-S0502, CALGB-S0502, CAN-NCIC-S0502, NCT00324987, 0502
Accrual: 572 (Open)



In both arms, courses repeat every 21 days in the absence of progression or unacceptable toxicity.

Study Contact
Southwest Oncology Group

Charles Blanke, MD	Tel: 503-494-1556; 800-494-1234

SOURCE: NCI Physician Data Query, February 2008.

DR LOVE: What is the role of bevacizumab in the treatment of GIST?

DR BLANKE: Recently published data suggest that VEGF is even more important in GIST than we thought five years ago. I will be conducting a Phase III trial evaluating imatinib with or without bevacizumab for patients with metastatic or unresectable GIST (SWOG-S0502; [1.12]).

However, I would not recommend using bevacizumab off study. We know that it is safe, but the concern is with bleeding — that's pretty much it.

Metastatic GIST: Testing for exon 9 mutations

DR HART: Do you believe that in clinical practice, mutation testing should be conducted for all patients prior to starting treatment?

DR BLANKE: The simple answer is yes, it probably should be (1.13). However, our registry data show that only three percent of physicians obtain mutational testing. It's difficult to do because only about three labs are performing it reliably right now.

If you have a patient in a low-risk situation — for example, a gastric primary or non-small bowel tumor — I'm not sure you need to do it at all. However, if you have a patient with a small bowel primary or metastatic disease, I would recommend it. But we don't want to blindly put those patients on the 800-mg dose. It's much more toxic and occasionally lethal, so we don't want to use that dose unless it's necessary.

DR RUBIN: I've been telling patients who are at high risk with all sites of disease to get the testing done up front because then they have the data.

DR EISENBERG: Indications have emerged that patients with exon 9 mutations respond to sunitinib. What about the idea of using up-front sunitinib versus imatinib for these patients?

DR BLANKE: It comes down to the toxicity profile of sunitinib versus imatinib at 800 milligrams. All the data we have with sunitinib are on the second line — not to say it would be any different in a primary setting, but it might be.

Therefore, I still prefer to treat those patients with higher-dose imatinib and then use sunitinib for salvage treatment. It is amazing that no one is testing sunitinib up front, but it's not happening.

DR LOVE: What do you think a trial comparing up-front sunitinib to imatinib would show?

DR BLANKE: I believe they would probably be fairly equivalent, but with different subsets benefiting a lot more from one drug or the other, and obviously with different toxicity profiles.

1.13 Mutation Analysis of GIST: Increasing Significance for Risk Assessment and Effective Targeted Therapy

"Molecular characterization of gastrointestinal stromal tumors (GISTs) plays an increasing role not only for the patient's prognosis but also for treatment options and in the context of resistance to therapy...

For metastatic disease, treatment with imatinib is still the first option, but with new upcoming substances, the molecular characterization of GISTs may become mandatory. Very recently, it has been shown that sunitinib may be especially effective in GISTs with KIT exon 9 mutation, whereas these tumors show only an intermediate response to imatinib. A European Organisation for Research and Treatment of Cancer clinical trial randomizing patients according to their mutational status is under preparation."

SOURCE: Wardelmann E et al. *Virchows Arch* 2007;451(4):743-9. **Abstract**

CASE 9 *from the practice of Dr Glynn:* A 53-year-old woman with a small bowel GIST who received one year of adjuvant imatinib as part of a randomized clinical trial (presented to Drs Blanke and Rubin)

Primary GIST: Duration of therapy with adjuvant imatinib

DR LOVE: What do we know about the optimal duration of adjuvant therapy with imatinib?

DR BLANKE: We're in a quandary because we don't know the correct duration. In the Phase III trial comparing imatinib to placebo, patients received one year of treatment, but there was a fairly high relapse rate after that year ended (DeMatteo 2007).

Two European trials are ongoing, one of which is evaluating zero versus two years of imatinib and the other is comparing one year to three years.

I believe that longer will be better. I would like to see an intermediate duration versus lifelong administration, but that's not popular in the adjuvant setting and probably will never be done. ACOSOG is trying to develop a duration question, but it is difficult because we have no data to guide us.

If we find out that three years is better than one, do we compare three to five, which doesn't seem that different, or to 10 years or even a lifetime?

We have positive trial data for one year of therapy, but we're seeing that the drug is being continued beyond that. It's hard to argue with that, but at the same time, we can't support it with any data, either.

DR LOVE: Are you worried about complications from administering imatinib for a prolonged period in an adjuvant setting, when patients may be cured and live a long time?

DR BLANKE: I'm not worried about that. We have a lot of CML data, and we're now publishing our seven-year follow-up from the metastatic GIST trial (Blanke 2008a). We don't see long-term complications in these patients, so that's not a big issue. However, it is expensive and it is associated with minor toxicities. Those are more realistic issues.

The Europeans feel that since we can administer salvage treatment when patients relapse, why commit them to lifelong imatinib? Rather, we can treat them for a short duration, delay the time to recurrence, and then administer it to them again later, in cyclical bursts.

It's hard to argue with that, except that it's not a particularly effective argument with patients. They don't like to hear that we're certain their disease will recur if we don't administer imatinib continuously but we'll only restart it when that happens.

I decide by examining the patient's risk. Patients with small bowel tumors with 50 mitoses I tend to allow to stay on the drug. Patients with 26-cm tumors I tend to keep on the drug.

However, I usually tell them that they will stay on it for three years, because that is the longest safety data we have in the adjuvant setting and I am not comfortable continuing it for much longer than that.

I am now approaching that three-year point with patients, and they are asking to stay on it longer. I do not believe many clinicians are administering it for the longer duration, although Ron DeMatteo does.

Although he conducted the study with a one-year duration, off study he keeps patients on it longer because, I assume, he also believes it is a relatively systemic disease.

Select publications

Blanke CD et al. **Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT.** *J Clin Oncol* 2008a;26(4):620-5. **Abstract**

Blanke CD et al. **Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033.** *J Clin Oncol* 2008b;26(4):626-32. **Abstract**

Blay JY et al. **Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: The French Sarcoma Group.** *J Clin Oncol* 2007;25(9):1107-13. **Abstract**

Casali PG. **Updated results from a phase III trial of sunitinib in GIST patients (pts) for whom imatinib (IM) therapy has failed due to resistance or intolerance.** *Proc ASCO* 2006;**Abstract 9513**.

Debiec-Rychter M; EORTC Soft Tissue and Bone Sarcoma Group. **KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours.** *Eur J Cancer* 2006;42(8):1093-103. **Abstract**

DeMatteo R et al. **Efficacy of adjuvant imatinib mesylate following complete resection of localized, primary gastrointestinal stromal tumor (GIST) at high risk of recurrence: The US Intergroup phase II trial ACOSOG Z9000.** Presentation. Gastrointestinal Cancers Symposium 2008;**Abstract 8**.

DeMatteo R et al. **Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumor (GIST): North American Intergroup Phase III trial ACOSOG Z9001.** *Proc ASCO* 2007;**Abstract 10079**.

DeMatteo RP et al. **Two hundred gastrointestinal stromal tumors: Recurrence patterns and prognostic factors for survival.** *Ann Surg* 2000;231(1):51-8. **Abstract**

Demetri GD et al. **Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: A randomised controlled trial.** *Lancet* 2006;368(9544):1329-38. **Abstract**

Demetri GD et al. **Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors.** *N Engl J Med* 2002;347(7):472-80. **Abstract**

George S et al. **Sunitinib (SU) on a continuous daily dosing (CDD) schedule in pts with advanced GIST.** Gastrointestinal Cancers Symposium 2008;**Abstract 39**.

George S et al. **Continuous daily dosing (CDD) of sunitinib malate (SU) compares favorably with intermittent dosing in pts with advanced GIST.** *Proc ASCO* 2007;**Abstract 10015**.

George S et al. **Phase II study of sunitinib administered in a continuous daily dosing regimen in patients (pts) with advanced GIST.** *Proc ASCO* 2006;**Abstract 9532**.

Heinrich MC et al. **Molecular correlates of imatinib resistance in gastrointestinal stromal tumors.** *J Clin Oncol* 2006;24(29):4764-74. **Abstract**

Miettinen M, Lasota J. **Gastrointestinal stromal tumors: Pathology and prognosis at different sites.** *Semin Diagn Pathol* 2006;23(2):70-83. **Abstract**

Morgan JA et al. **Sunitinib (SU) in a worldwide treatment-use trial of patients with GIST: Safety and efficacy.** Gastrointestinal Cancers Symposium 2008;**Abstract 31**.

Educational Assessment and Credit Form: *Meet The Professors* GIST, Issue 1, 2008

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Risk stratification for patients with primary GIST 4 3 2 1
Clinical trial results of adjuvant imatinib for GIST 4 3 2 1
Clinical use of imatinib for metastatic GIST 4 3 2 1
Sunitinib as second-line therapy for patients progressing on imatinib 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Risk stratification for patients with primary GIST 4 3 2 1
Clinical trial results of adjuvant imatinib for GIST 4 3 2 1
Clinical use of imatinib for metastatic GIST 4 3 2 1
Sunitinib as second-line therapy for patients progressing on imatinib 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: . . . . . .

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: . . . . . .

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: . . . . . .

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will:

- Demonstrate an understanding of the pathophysiology and epidemiology of GIST. . . . . 4 3 2 1 N/M N/A
- Formulate pre- and postsurgical management strategies for patients with GIST, considering the risk of tumor rupture, postoperative histologic staining and/or mutational analyses. . . . . 4 3 2 1 N/M N/A
- Evaluate the emerging role of adjuvant therapy for localized, resectable GIST. . . . 4 3 2 1 N/M N/A
- Devise therapeutic approaches to GIST in the context of the rationale for biologic agents and evidence surrounding the limited effectiveness of cytotoxic chemotherapy. . . . . 4 3 2 1 N/M N/A
- Evaluate the established role of molecularly targeted therapy for patients with advanced GIST. . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based treatment algorithm for patients with imatinib-resistant GIST, considering the implications of mutational transformation on therapeutic choice. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

. . . . . .

What additional information or training do you need on the activity topics or other oncology-related topics?

. . . . . .

Additional comments about this activity:

.....

.....

May we include you in future assessments to evaluate the effectiveness of this activity?

☐ Yes ☐ No

PART TWO — Please tell us about the faculty for this educational activity

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Faculty	Knowledge of subject matter				Effectiveness as an educator			
Charles D Blanke, MD	4	3	2	1	4	3	2	1
George D Demetri, MD	4	3	2	1	4	3	2	1
Burton L Eisenberg, MD	4	3	2	1	4	3	2	1
Brian Rubin, MD, PhD	4	3	2	1	4	3	2	1
Jonathan C Trent, MD, PhD	4	3	2	1	4	3	2	1

Please recommend additional faculty for future activities:

.....

.....

Other comments about the faculty for this activity:

.....

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