Emerging Multidisciplinary Approaches for the Management of

Gastrointestinal Stromal Tumors

PROGRAM SYLLABUS

A CME-certified Oncology Exchange Activity

To learn more about Oncology Exchange, go to: www.OncExchange.com
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PROGRAM CONTENT AND FORMAT

The Potomac Center for Medical Education welcomes you to “Oncology Exchange: Emerging Multidisciplinary Approaches for the Management of Gastrointestinal Stromal Tumors,” a CME-certified Visiting Professor presentation designed to give medical professionals the latest news and information on Gastrointestinal Stromal Tumors (GIST).

With the introduction of molecular targeted agents, there has been a significant transformation in the management of GIST. There is an increasing awareness among oncologists about the complex pathogenesis of GIST and the need for personalization of therapy for these patients. An increased understanding of the mechanisms of resistance in GIST, mechanisms of action of novel agents, dosing strategies, patient selection, treatment adherence, and side-effect management among the multidisciplinary cancer care team is crucial for improving patient outcomes.

This engaging activity will provide clinicians with access to new information, tools, and insights that they can integrate into their practices to improve patient outcomes.

TARGET AUDIENCE

This activity is intended for community oncologists and other health care professionals involved in the care of patients with GIST.

EDUCATIONAL OBJECTIVES

At the conclusion of this activity, participants should be able to demonstrate the ability to:

- Understand the recently updated clinical practice guidelines for GIST
- Review the treatment options for patients with very early stage disease (micro-GIST), localized disease, and metastatic disease
- Discuss surveillance strategies for patients with resected or metastatic GIST and understand the clinical spectrum of resistance
- Develop a multidisciplinary treatment approach for the management of GIST

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For information about the accreditation of this program, please email contact@potomacme.org

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Event staff will be glad to assist you with any special needs (e.g. physical, dietary, etc.).

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There is no fee for this educational activity. To receive CME/CE credit the participant must:

- Participate in this one-hour-long program in its entirety;
- Sign in / sign out on the sheet provided by the host coordinator;
- Complete and sign the registration and evaluation form;
- Return the registration and evaluation form to the host coordinator.
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The faculty reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

Steering Committee:
- Raphael E. Pollock, MD, PhD, FACS: Nothing to disclose
- Jonathan C. Trent, MD, PhD: Speaker: Novartis, Pfizer

Non-faculty Content Contributors:
Non-faculty content contributors and/or reviewers reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

- Latha Shivakumar, PhD; Bradley Pine; Blair St. Amand; Jay Katz, CCMEP; CME Peer Review: Nothing to disclose

FDA DISCLOSURE

The contents of some CME/CE activities may contain discussions of non-approved or off-label uses of some agents mentioned. Please consult the prescribing information for full disclosure of approved uses.
Raphael E. Pollock, MD, PhD, FACS was born in Chicago, IL and graduated from Oberlin College in Ohio in 1972. This was followed by medical school at the St. Louis University School of Medicine in Chicago, IL; residencies in general surgery at the University of Chicago and Rush Medical College; a fellowship in surgical oncology at the University of Texas M.D. Anderson Cancer Center, and a PhD in tumor immunology from the Graduate School of the Biological Sciences at the University of Texas-Houston Health Sciences Center. Dr. Pollock joined the Department of Surgical Oncology at the University of Texas M.D. Anderson Cancer Center as a faculty member in 1984 and has remained in this department ever since.

Dr. Pollock has a lifetime professional dedication to the care of solid tumor patients, as well as to laboratory research in this field. His clinical and research activities focus on a rare form of connective tissue cancer known as soft tissue sarcoma, and Dr. Pollock provides leadership for the Sarcoma Research Center of the M.D. Anderson Cancer Center. Dr. Pollock is the incumbent in the Senator A.M. Aiken, Jr. Distinguished Chair and holds joint appointments in the Department of Molecular and Cellular Oncology at M.D. Anderson Cancer Center and the Department of Surgery at the University of Texas Health Sciences Center/ Houston. Dr. Pollock became Chairman of the Department of Surgical Oncology in 1993 and became Head of the Division of Surgery at the M.D. Anderson Cancer Center in 1997.
STEERING COMMITTEE

JONATHAN C. TRENT, MD, PhD
Professor of Medicine
Director, Bone and Soft-tissue Sarcoma Program
Sylvester Comprehensive Cancer Center
University of Miami
Miami, FL

Jonathan C. Trent, MD, PhD has 12 years of experience focusing on patient care, research, and education related to gastrointestinal stromal tumors (GIST). Dr. Trent has published numerous abstracts and research articles in leading journals, as well as book chapters, and is a frequently requested lecturer. He is the Chief Editor of the sarcoma section of Current Opinions in Oncology and serves on the editorial board of the Chinese Journal of Clinical Oncology, Rare Tumors, and Translational Medicine. He also is a journal reviewer on a number of journals, including Nature Medicine, Lancet, Cancer, Clinical Cancer Research, and Cancer Research.

Dr. Trent’s clinical interests focus on GIST patient care, clinical trials, and translational research. The excellence of his GIST clinical team led to his recognition as the 2010 GIST Physician of the Year by the LifeRaft Group. He is the Principal Investigator, as well as a collaborator, on several ongoing clinical trials that are examining the use of kinase inhibitors alone and in combination with novel drugs in patients with primary and metastatic GIST. He is a Principal Investigator on the ongoing GIST registry and is credited with several breakthroughs in GIST that stemmed from his 5-year National Institutes of Health K-23 GIST research grant.

Dr. Trent earned his undergraduate degree in chemistry at Southeastern Oklahoma State University and his MD and PhD in cancer biology from the University of Texas Health Science Center. He completed an internship and residency in internal medicine at the University of Texas Health Science Center, and a fellowship in medical oncology at the University of Texas MD Anderson Cancer Center, while serving as Chief Fellow. Dr. Trent is board-certified in internal medicine and medical oncology.
Disclosures

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Educational Objectives

At the conclusion of this activity, participants should be able to demonstrate the ability to:

• Understand the recently updated clinical practice guidelines for GIST
• Review the treatment options for patients with very early stage disease (micro-GIST), localized disease, and metastatic disease
• Discuss surveillance strategies for patients with resected or metastatic GIST and understand the clinical spectrum of resistance
• Develop a multidisciplinary treatment approach for the management of GIST

Pre-activity Survey

• Please remove the Pre-activity Survey from your packet
• Your answers are vital to our understanding of the effectiveness of this CME program, and will help shape future educational activities and topics
• Please fill in the most appropriate answer(s) for the questions below:
  – Degree: o MD/DO o Nursing Professional o PharmD o Other: _____________________________
  – Specialty: o Oncology o Pathology o Internal Medicine o Other: _____________________________

Pre-activity Survey Question 1

Please rate your current level of knowledge on the management of GIST:

1 2 3 4 5
Not knowledgeable Expert

Pre-activity Survey Question 2

Please rate your current level of competence regarding the management of GIST:

1 2 3 4 5
Not competent Expert
Emerging Multidisciplinary Approaches for the Management of Gastrointestinal Stromal Tumors

Pre-activity Survey Question 3

According to the recently updated NCCN guidelines for soft tissue sarcoma (v.3.2012), which of the following parameters predict prognosis in GIST?

a. Tumor size
b. Gene mutational status
c. Mitotic rate
d. All of the above
e. A and C

Pre-activity Survey Question 4

For which of the following settings is there no consensus on the use of neoadjuvant therapy for patients with GIST?

a) Unresectable or borderline resectable tumors
b) Tumors that would require extensive multi-visceral resection
c) Potentially resectable metastatic disease
d) Marginally resectable tumors or whose resection would be associated with significant morbidity

Pre-activity Survey Question 5

A 58-year-old male was diagnosed with a 9 cm small intestine, KIT exon 9 mutant GIST with peritoneal sarcomatosis. He did not have any other comorbidities. What therapy would you recommend this patient?

a. Observation
b. Imatinib 400 mg/d
c. Imatinib 800 mg/d
d. Consider local therapy such as arterial embolization, radiofrequency ablation, surgical resection

Pre-activity Survey Question 6

Which of the following novel targeted therapies in advanced-stage trials is a reasonable choice for a patient with GIST who has progressed following imatinib therapy?

a. Everolimus
b. Regorafenib
c. Nilotinib
d. Masitinib
e. Any of the above

GIST Overview

- Most common GI sarcoma
  - 0.2% of all GI tumors, but 80% of GI sarcomas
- Distinct clinical and histopathologic entity
  - Highest incidence in the 40-60 year age group
  - Similar male/female incidence
  - Many misclassified
- About 5,000 newly diagnosed GIST patients per year in the US
- Clinical presentation is variable
  - pain, hemorrhage, anemia, anorexia, nausea, perforation

Median Overall Survival in Metastatic GIST (Circa 1990)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of Patients</th>
<th>Partial Response n (%)</th>
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<tbody>
<tr>
<td>DOX + DTIC</td>
<td>43</td>
<td>3 (7%)</td>
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<tr>
<td>DOX + DTIC +/– IF</td>
<td>60</td>
<td>10 (15%)</td>
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<tr>
<td>IF + VP-16</td>
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<tr>
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<tr>
<td>DOX</td>
<td>12</td>
<td>0 (0%)</td>
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<tr>
<td>DOX or docetaxel</td>
<td>9</td>
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<tr>
<td>High-dose IF</td>
<td>26</td>
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<tr>
<td>EPI + IF</td>
<td>13</td>
<td>0 (0%)</td>
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<tr>
<td>Various</td>
<td>40</td>
<td>4 (10%)</td>
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<tr>
<td>DTIC/MMC/DOX/ CDDP/GM-CSF</td>
<td>21</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>19</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

TOTAL | 280 | 19 (6.8%) |

DOX = doxorubin; DTIC = dacarbazine; IF = ifosfamide; CDDP = cisplatin; VP16 = etoposide; EPI = epirubicin; NR = not reported

GIST Pathology

- GIST is believed to share several characteristics with ICC
  - Neuromuscular pacemaker cell of the GI tract
  - Found in myenteric plexus throughout GI tract
  - Expression of CD34 in ~80% of cases
  - Expression of KIT (CD117) in ~95% of cases

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Kit Receptor Structure

- Extracellular Domain ( exon 9, 10.2%)
- Juxtamembrane Domain ( exon 11, 66.1%)
- Tyrosine Kinase Domain I ( exon 13/14, 1.2%)
- Tyrosine Kinase Domain II ( exon 17, 0.6%)

= common mutation site

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Kit Receptor Phenotype

- ATP
- ADP
- Proliferation
- Survival
- Adhesion
- Invasion
- Metastasis
- Angiogenesis

\[ \text{ATP} \rightarrow \text{Proliferation} \]
\[ \text{ATP} \rightarrow \text{Survival} \]
\[ \text{ATP} \rightarrow \text{Adhesion} \]
\[ \text{ATP} \rightarrow \text{Invasion} \]
\[ \text{ATP} \rightarrow \text{Metastasis} \]
\[ \text{ATP} \rightarrow \text{Angiogenesis} \]

= imatinib contact point

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Clinical Trials of Imatinib in GIST

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>N</th>
<th>OR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>OS (2 yr)</th>
<th>TTP (median)</th>
<th>PFS</th>
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<td>36</td>
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<td>11%</td>
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<td>-</td>
<td>-</td>
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<td>740</td>
<td>71%</td>
<td>4%</td>
<td>67%</td>
<td>18%</td>
<td>11%</td>
<td>-</td>
<td>-</td>
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<td>31</td>
<td>77%</td>
<td>3%</td>
<td>74%</td>
<td>15%</td>
<td>16%</td>
<td>-</td>
<td>77% (1 yr)</td>
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<td>Verweij, 2004</td>
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<td>96</td>
<td>60%</td>
<td>5%</td>
<td>40%</td>
<td>29%</td>
<td>12%</td>
<td>70% (2 yr)</td>
<td>-</td>
<td>73% (1 yr)</td>
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<td>Verweij, 2004</td>
<td>II</td>
<td>94</td>
<td>46%</td>
<td>5%</td>
<td>40%</td>
<td>29%</td>
<td>15%</td>
<td>45% (2 yr)</td>
<td>-</td>
<td>53% (2 yr)</td>
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<tr>
<td>Rankin, 2004</td>
<td>III</td>
<td>750</td>
<td>71%</td>
<td>4%</td>
<td>67%</td>
<td>18%</td>
<td>11%</td>
<td>-</td>
<td>73% (1 yr)</td>
<td>50% (2 yr)</td>
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<tr>
<td>Verweij, 2004</td>
<td>III</td>
<td>94</td>
<td>60%</td>
<td>5%</td>
<td>40%</td>
<td>29%</td>
<td>12%</td>
<td>70% (2 yr)</td>
<td>-</td>
<td>53% (2 yr)</td>
</tr>
</tbody>
</table>

Personal Communication, Joe Trent, MD, PhD

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Ph III Trials: 400 mg/d vs 800 mg/d Imatinib in Advanced GIST

- US Intergroup SWOG S0033 Study
- EORTC 62005 Study

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MetaGIST: PFS

Case 1:

- 49 y/o female; otherwise healthy
- Presented at local health care facility in 1/2011 c/o upper abdominal pain/early satiety x past six weeks
- Underwent evaluation including abdominal CT scan and upper endoscopy
- Endoscopy revealed a 4 x 4.5 cm gastric mass with mucosal erosion. Needle biopsy demonstrated blood; not diagnostic
- Referred to tertiary care center for further evaluation by multi-disciplinary team

Case 1, Discussion point 1

What would you recommend for this patient at this time?

a) CT scan of chest, abdomen, and pelvis
b) EUS for needle biopsy
c) CT-directed core needle biopsy
d) Open operation to excise tumor
e) Laparoscopic inspection and incisional biopsy

Answer: a

CT scan 1/2011 demonstrates a > 10cm mass with areas of necrosis. Tumor extends into the gastrosplenic ligament and indents the body and tail of the pancreas. No metastatic disease.

Case 1, Discussion point 2

Mass appears to be resectable. What will the initial management strategy include?

a) CT-directed biopsy
b) EUS/FNA
c) Resect mass as excisional biopsy
d) Presentation at multi-disciplinary solid tumor management conference
e) IMRT-configured external beam radiotherapy

Answer: d

Biopsy of Suspected GIST; Initial Management

- Endoscopic ultrasound guided fine needle aspiration preferred to image-directed percutaneous core needle biopsy; less danger of rupturing fragile GIST capsule
- Biopsy needed prior to neoadjuvant non-surgical therapies to confirm malignancy

NCCN Guidelines for Pathologic Assessment of Suspected GIST

- Morphological dx is requisite standard of care
- Ancillary techniques:
  - IHC: 95% express CD117; 80% express CD34
  - Molecular genetic testing for mutations in KIT (80% incidence) or PDGFRA (10% incidence) genes; 10% w/o either mutation
- Tumor size and mitotic rate (but not gene mutational status) inform prognosis
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Initial Management Strategies

• If not a GIST but some other type of malignancy non-surgical therapies might be the optimal first steps

• For GIST, consider neoadjuvant imatinib if surgical morbidity would be improved with cytoreduction:
  – If a non-GIST malignancy non-surgical therapies might be optimal first step(s)
  – If a GIST, consider neoadjuvant imatinib if surgical morbidity would be improved with cytoreduction

Tumor Genotype and Imatinib Dose Selection


Neoadjuvant Imatinib

• Consider for:
  – Unresectable or borderline resectable tumors
  – Tumors that would require extensive multi-visceral resection
  – Potentially resectable metastatic disease

• RTOG 0132/ACRIN 6665 Trial
  – Multicenter Phase II trial

RTOG0132/ACRIN 6665: Results

Group A Group B
Response to pre-operative therapy (RECIST) 7% PR, 83% SD, 10% unknown 4.5% PR, 91% SD, PD 4.5%
Estimated 2-year PFS 62.7% 77.3%
Estimated 5-year PFS 51% 30%
Estimated 2-year OS 83.3% 95.9%
Estimated 5-year OS 77% 68%
Type of Resection R0 77% 58%
R1 4%
R2 8%
Unspecified 5%

RTOG0132/ACRIN 6665: Surgical Complications

<table>
<thead>
<tr>
<th>Surgical Complications (n = 45)</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound infection</td>
<td>3</td>
<td>6.7</td>
</tr>
<tr>
<td>Hemorrhage requiring blood or blood product</td>
<td>2</td>
<td>4.4</td>
</tr>
<tr>
<td>Respiratory event</td>
<td>5</td>
<td>11.1</td>
</tr>
<tr>
<td>Cardiac event</td>
<td>3</td>
<td>6.7</td>
</tr>
<tr>
<td>Surgical death</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>Anastomotic disruption</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>Other surgical complication</td>
<td>15</td>
<td>33.3</td>
</tr>
<tr>
<td>Abcess (intra-abdominal)</td>
<td>2</td>
<td>4.4</td>
</tr>
</tbody>
</table>

RTOG0132/ACRIN 6665: MDACC Experience Retrospective Review (46 pts)

• 11 patients with locally advanced primary
  – Median pre-op treatment 12 mos
  – 1 CR, 8 PR
  – All 11 underwent complete surgical resection
  – Median f/u 19.5 mos
    • All 11 alive
    • 10/11 disease free
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Neoadjuvant Imatinib: MDACC Experience Retrospective Review (46pts)

- 35 patients with locally advanced or metastatic GIST
  - 11 patients able to undergo complete resection
  - Patients demonstrated to have a partial response to pre-operative therapy much more likely to undergo complete resection (91% versus 4%)
  - At median f/u 30 mos, all 11 pts completely resected were alive (6/11 with recurrence at a median of 15 mos)


Neoadjuvant Imatinib: Summary

- Neoadjuvant treatment with imatinib is feasible
- Data from retrospective series and RTOG 0132/ACRIN 6665 indicate neoadjuvant therapy may reduce tumor bulk and permit resection of initially unresectable or borderline resectable tumors
- Resection should be considered following a radiographic indication of response (before tumor progression)
- Currently no consensus on use of neoadjuvant therapy:
  - Generally for patients with marginally resectable tumors or whose resection would be associated with significant morbidity

Multi-disciplinary Assessment

Our patient is resectable with negative margins but significant risk of morbidity w/ multi-visceral resection; prior to initiating imatinib therapy:
- Obtain baseline CT or MRI
- Consider baseline PET scan; if GIST PET-avid provides additional marker to assess response to systemic therapy

Gastric GIST PET-CT (3/1/11)

Started on imatinib 400 mg/day; assess for progression vs cytoreduction. Proceed to surgery for bleeding, severe GI symptoms, GIST progression

CT Scan Re-imaging; 8/2011

CT scan 8/11 demonstrating that GIST is smaller and more necrotic, consistent with treatment effects

Gastric GIST Treatment Effects

- Patient began experiencing imatinib side effects
  - Fatigue
  - Edema
  - Nausea
- Imatinib dose decreased to 200 mg/day
- Could consider sunitinib if serious imatinib side effects
- CT scan repeated two months later

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CT Scan Re-imaging: 10/2011

CT scan 10/11 demonstrating marked additional cytoreduction (now ~ 5.5cm) with more necrosis; now probably resectable w/o multi-visceral ablation.

Principles of GIST Surgery

- Negative margins (R0) are goal; frozen section control
- GIST are friable; tumor capsule easily violated
- Usually LN (-); nodes not specifically resected
- Re-resection not performed if R1 margins on final pathology analysis.

Case Discussion (continued)

- Decision made for surgical resection at this juncture; surgical findings:
  - 3.6 cm mass in omentum; 10% necrotic
  - 5.0 cm mass involving greater curvature of stomach; 99% necrotic
- Adjuvant imatinib initiated w/ resumption of oral intake post-operatively

Imatinib in the Adjuvant Setting

- 50% recurrence rates for GIST with surgery alone
- Cytotoxic chemotherapy ineffective for GIST
- Imatinib demonstrated to be effective
  - ACOSOG Z9000 (Phase II)
  - ACOSOG Z9001 (Phase III)
  - Scandinavian Sarcoma Group XVIII (Phase III)
- FDA approved imatinib for completely resected GIST ≥3cm in size

Adjuvant Imatinib: ACOSOG Z9001

Phase III, double-blinded, placebo controlled, multicenter trial

- Imatinib (400mg/day) vs placebo following resection of localized, primary GIST
- 1 year of adjuvant therapy
- Summary of results:
  - 1-year RFS 98% - Imatinib
  - 1-year RFS 60% - Placebo
  - Recurrence in imatinib arm increases at 18ths (times following discontinuation of therapy)
- RFS was significantly improved in imatinib arm in each tumor size category (≥3cm <6cm; ≥6cm <10cm; ≥10cm)
- Grade 3 or 4 toxicity in 30.9% of pts in Imatinib arm vs 18.3% pts in placebo arm
- Short follow up time and crossover design did not permit evaluation for differences in overall survival

Adjuvant Imatinib: SSG XVIII

Prospective, open-label, phase III trial
- 400 patients with operable primary GIST
  - >5cm, >5 mitoses/50 HPF
- Primary outcome = RFS
- Secondary outcome = OS, safety

<table>
<thead>
<tr>
<th>Imatinib (400mg/day)</th>
<th>N = 200</th>
<th>N = 200</th>
<th>P &lt; 0.001</th>
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<tr>
<td>5-year RFS</td>
<td>Imatinib 86%</td>
<td>Imatinib 48%</td>
<td>5-year OS</td>
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<tr>
<td></td>
<td>Imatinib 82%</td>
<td>Imatinib 82%</td>
<td>P = 0.019</td>
</tr>
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</table>

Therapy generally well tolerated
Adjuvant Imatinib: Summary

- At least 3 years of therapy appears effective and safe
- Which patient subsets derive the most benefit from adjuvant imatinib?
- Still need to establish cutoffs for estimated risk of disease recurrence for which adjuvant therapy is recommended

Case 1: Post-operative Follow Up

- Continue imatinib in adjuvant setting; duration uncertain
- CT scanning q 3-6 months x 5 yr, then annually for life

GIST Evaluation

- Every 2-4 months
- History and Physical Examination
- Laboratory Testing
- Abdominal/pelvic CT with contrast
  - Recommended for diagnosis and staging
  - Also useful for assessing common sites of metastasis (eg, liver, peritoneum)
  - Every 2-4 months while on therapy
- 18FDG-PET
  - Determines tumor metabolic activity
  - Useful with IV contrast allergy or renal insufficiency
  - Useful when contrast CT evaluation indeterminate

GIST Response to Therapy

Case 2: Metastatic GIST

- 58 y/o male; otherwise healthy
- Diagnosed with a 9 cm small intestine, KIT exon 9 mutant GIST with widespread peritoneal sarcomatosis
- Patient received imatinib 800 mg/d
- On CT the patient has had regression by size and contrast enhancement for 3 years.
- Patient asks whether they can discontinue imatinib at this time.
- What would you tell the patient?

Case 2, Discussion Point 1

What would you recommend for this patient?
- a) Discontinue imatinib
- b) Continue imatinib 800 mg/d
- c) Switch to sunitinib 37.5 mg/d

Answer: b
Emerging Multidisciplinary Approaches for the Management of Gastrointestinal Stromal Tumors

Continuous Target Inhibition: BFR14 3-yr Randomization

Case 3: Metastatic GIST
- 39 y/o male; otherwise healthy
- Diagnosed with a 4 x 4.5 cm gastric mass with liver metastases
- Percutaneous core needle biopsy reveals spindled cell GIST with 21 mitoses/50 hpf and KIT exon 11 mutation
- Initiated on imatinib 400 mg/d
- Initial response to imatinib but had widespread progression of disease after 18 months of therapy

Types of Disease Progression in GIST

Case 3, Discussion Point 1
What would you recommend for this patient?
- a) biopsy progressing lesion
- b) switch patient to sunitinib 37.5 mg/d
- c) Increase imatinib to 800 mg/d
- d) Consider local therapy such as arterial embolization, radiofrequency ablation, surgical resection

Answer: c

Limited Progression

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Therapy by Type of Progression

- Limited or Nodular Progression
  - Hepatic Artery Chemoembolization
  - Hepatic Radio-frequency Catheter Ablation
  - Surgical Resection
  - Radiation Therapy (esophageal or rectal)

- Widespread progression
  - Increase Imatinib to 800 mg daily
  - Sunitinib
  - Clinical Trial

Hepatic Artery Embolization

- Pre-embolization
- Post-embolization

Imatinib-Resistant Metastatic GIST

Limited Hepatic Progression

- 14 patients with imatinib-resistant GIST and progressive liver metastases
  - Treated with hepatic arterial embolization or chemoembolization
  - 13 patients evaluable for radiologic response

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>BEST RESPONSE (Choi Criteria)</th>
<th>BEST RESPONSE (RECIST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>54%</td>
<td>8%</td>
</tr>
<tr>
<td>Complete</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Partial</td>
<td>54%</td>
<td>8%</td>
</tr>
<tr>
<td>Stable</td>
<td>46%</td>
<td>92%</td>
</tr>
<tr>
<td>Progression</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Hepatic Arterial Embolization

Radiographic Response Rates

- Hepatic Resection
- Hepatic Resection + RFA

Imatinib-resistant GIST

Disease-Free Survival

- Median = 7.0 Months
Sunitinib Efficacy in Patients With Imatinib-Refractory GIST

- **Patients with advanced IM-RES GIST**
- **Sunitinib 50 mg/day, 6-wk cycles (4/2)**
  - **N=207**
- **Placebo 50 mg/day, 6-wk cycles (4/2)**
  - **N=105**

- **RA**
- **D**
- **O**
- **M**
- **I**
- **2:1**

- **Primary endpoint**
  - TTP, as defined using RECIST
- **Secondary endpoints**
  - PFS, OS, ORR, TTR, DOR, and duration of PS maintenance
- **At RECIST-defined disease progression, pts receiving placebo were eligible for crossover**


**IM=imatinib; ORR=overall response rate; RES=resistant; TTP=time to progression; TTR=time to tumor response.**

Efficacy and Safety of Sunitinib In Patients with Advanced GIST after Failure with Imatinib

**A Randomized Controlled Trial**

**TIME TO TUMOR PROGRESSION**

**TREATMENT**
- Placebo
- Sunitinib

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>Placebo</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARTIAL RESPONSE</strong></td>
<td>0%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>STABLE DISEASE</strong></td>
<td>38%</td>
<td>58%</td>
</tr>
<tr>
<td><strong>PROGRESSIVE DISEASE</strong></td>
<td>48%</td>
<td>19%</td>
</tr>
</tbody>
</table>

**RECIST Criteria**


Case 3, Discussion point 2

Patient develops widespread metastases in the liver and peritoneum. the patients metastatic tumor progressed at multiple sites on imatinib 800 and then on sunitinib 37.5 mg daily. What would you recommend?

- a) Regorafenib 160 mg/d
- b) Participation in a clinical trial
- c) Increase imatinib to 800 mg/d
- d) Consider local therapy such as arterial embolization, radiofrequency ablation, surgical resection

**Answer:** a.

Regorafenib is the most reasonable treatment choice for this patient at this point, if it receives FDA approval for use in this setting. The decision on this approval is expected by March 2 013.

Rationale for Novel Agents to Treat Imatinib-Resistant GIST

- Although imatinib revolutionized the initial management of advanced GIST, TKI resistance eventually occurs in ~85% of patients leading to progression of disease
- Sunitinib can benefit GIST patients after failure of imatinib – but there is no approved therapy after failure of both imatinib and sunitinib

GIST – Regorafenib In Progressive Disease (GRID): Study Design

**Progression-free Survival**

**Comparison of Central Review vs. Investigator Assessments**

- Regorafenib (investigator assessment)
- Regorafenib (central review)
- Placebo (investigator assessment)
- Placebo (central review)
Continuing Regorafenib Dosing After Progression

PFS with initial exposure during double-blind (DB) and following after progression on DB (all per investigator assessment)

<table>
<thead>
<tr>
<th></th>
<th>Placebo → regorafenib OL N=56</th>
<th>Regorafenib Initial DB N=153</th>
<th>Continuing Regorafenib after PD N=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>5.0 months</td>
<td>7.4 months</td>
<td>4.5 months</td>
</tr>
</tbody>
</table>

Survival distribution function

- Days from first progression for open label; days from randomization for double blind

Reichardt, ESMO 2012.

Overall Survival between GRID Study Arms

Estimating crossover impact via the rank-preserving structural failure time (RPSFT) method*

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib vs placebo (uncorrected); 0.189</th>
<th>Regorafenib vs placebo (RPSFT corrected); 0.025</th>
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</thead>
<tbody>
<tr>
<td>Survival function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p values</td>
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<tr>
<td>Placebo</td>
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<td></td>
</tr>
<tr>
<td>Placebo (RPSFT corrected)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regorafenib</td>
<td></td>
<td></td>
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</tbody>
</table>

Reichardt, ESMO 2012.

Other Agents for IM-RES GIST

<table>
<thead>
<tr>
<th>CLASS</th>
<th>AGENT</th>
<th>TRIAL PHASE</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT inhibitors</td>
<td>Sorafenib</td>
<td>II</td>
<td>PR=13%, SD=58%, PFS=5 months</td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td>II</td>
<td>PR=22%, SD=24%, PFS=2 months</td>
</tr>
<tr>
<td></td>
<td>Nilotinib</td>
<td>III/IV</td>
<td>PR=10%, SD=37%, PFS=3 months</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>II</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Avastin</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>RAF inhibitors</td>
<td>Vemurafenib</td>
<td>I</td>
<td>ND</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>Everolimus</td>
<td>III</td>
<td>PR=2%, SD=43%, PFS=3.5 months</td>
</tr>
<tr>
<td>HDAC inhibitors</td>
<td>Vorinostat</td>
<td>NA</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Various</td>
<td>III</td>
<td>PR=9%, PFS=1.5 months</td>
</tr>
</tbody>
</table>

HDAC = histone deacetylase; IGF-1R = insulin-like growth factor–1 receptor; MKI = multitargeted kinase inhibitor; mTOR = mammalian target of rapamycin.

Participant Post-program Survey

- Please remove the Participant Post-survey & CME Evaluation from your packet
- By completing both the Pre- and Post-survey forms, you will help provide benchmarks and feedback that are vital to our understanding of the effectiveness of this CME program, and will help shape future educational activities and topics

Post-program Survey Question 1

As a result of attending this educational activity, please rate your level of knowledge on the management of GIST:

1 2 3 4 5
Not knowledgeable Expert

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Post-program Survey Question 2
As a result of attending this educational activity, please rate your level of competence in managing GIST:
1 2 3 4 5
Not competent Expert

Post-program Survey Question 3
According to the recently updated NCCN guidelines for soft tissue sarcoma (v.3.2012), which of the following parameters predict prognosis in GIST?
a. Tumor size
b. Gene mutational status
c. Mitotic rate
d. All of the above
e. A and C

Post-program Survey Question 4
For which of the following settings is there no consensus on the use of neoadjuvant therapy for patients with GIST?
a) Unresectable or borderline resectable tumors
b) Tumors that would require extensive multi-visceral resection
c) Potentially resectable metastatic disease
d) Marginally resectable tumors or whose resection would be associated with significant morbidity

Post-program Survey Question 5
A 58-year-old male was diagnosed with a 9 cm small intestine, KIT exon 9 mutant GIST with peritoneal sarcomatosis. He did not have any other comorbidities. What therapy would you recommend this patient?
a. Observation
b. Imatinib 400 mg/d
c. Imatinib 800 mg/d
d. Consider local therapy such as arterial embolization, radiofrequency ablation, surgical resection

Post-program Survey Question 6
Which of the following novel targeted therapies in advanced-stage trials is a reasonable choice for a patient with GIST who has progressed following imatinib therapy?
a. Everolimus
b. Regorafenib
c. Nilotinib
d. Masitinib
e. Any of the above