



A CME On-Demand Webcast

An Interactive, Case-Based Approach to Targeted Therapies for GIST



Syllabus

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1. Be an active participant in the activity.
2. Ask questions relevant to patient-care concerns.
3. Commit yourself to the entire activity time frame, because it is only then that the total learning can be experienced, utilized, and measured.
4. Allow this activity to be only a part of your total learning experience.
5. Aid in developing future activities by being a strong participant. The evaluation form assists us in this process; please give it careful professional consideration when filling it out.
6. Return to your practice and mentor the learning experience with your colleagues. Projects In Knowledge will provide extra material for this effort.

Sincerely,

Robert S. Stern

President

Projects In Knowledge, Inc.



Faculty Biographies



Richard M. Goldberg, MD
Professor of Medicine
Chief, Division of Hematology and
Oncology
University of North Carolina School of
Medicine
Chapel Hill, North Carolina

Richard M. Goldberg, MD, is professor and chief of the Division of Hematology/Oncology and associate director for Clinical Research at the UNC Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill, North Carolina. He is also the physician-in-chief of the North Carolina Cancer Hospital.

Dr. Goldberg completed his medical training at the Upstate Medical Center in Syracuse, New York, in 1979. Following his training in internal medicine, he spent 2 years as a fellow in medical oncology at the Vincent T. Lombardi Cancer Research Center, Washington, DC. In 1984, he became an associate in medical oncology at the Geisinger Medical Center and Clinic in Danville, Pennsylvania, and was appointed vice chairman of the Departments of Medicine there in 1992. From 1994–2003, he was professor of oncology at the

Mayo Clinic in Rochester, Minnesota, and chaired the Mayo Gastrointestinal Cancer Research Program. In 2004, he was appointed the chair of the Gastrointestinal Cancer Committee for the Cancer and Acute Leukemia B Group (CALGB).

Dr. Goldberg is a member of the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), and the American Joint Commission on Cancer (AJCC) Colorectal Task Force. He has been an invited reviewer for many leading medical and oncology journals, and has served on the editorial boards of the National Cancer Institute's *Physician Data Query* program, the *Journal of Clinical Oncology*, *Clinical Colorectal Cancer*, and *Oncology*. He has coauthored more than 200 publications.



Faculty Biographies



Charles D. Blanke, MD
Professor of Medicine
UBC/British Columbia Cancer Agency
Vancouver, British Columbia

Charles D. Blanke, MD is chief of the Division of Medical Oncology in the Department of Medicine at the University of British Columbia in Vancouver and head of Medical Oncology at Vancouver General Hospital. He is also leader of the Provincial Systemic Therapy Program and head of the Provincial Medical Oncology Staff at the British Columbia Cancer Agency in Vancouver. He previously served as professor in the Division of Hematology/Medical Oncology at the Portland Veterans Administration Medical Center and as director of the Solid Tumors Program at Oregon Cancer Center.

Dr. Blanke completed his medical training with distinction in 1988 at Northwestern University in Evanston, Illinois. He was chief resident of the Internal Medicine Internship/Residency Program at Gundersen Medical Foundation, La Crosse, Wisconsin. In addition, he was chief fellow of the Hematology/Oncology Fellowship at Indiana University. He has held assistant professorships in hematology/medical oncology at Vanderbilt University, Nashville Veterans Administration, Oregon Health and Science University, and Portland Veterans Administration. He became an associate professor at both Oregon Health and Science University and Portland Veterans Administration.

Dr. Blanke is a member of the American Society of Clinical Oncology and the American College of Surgical Oncologists. He is also a fellow of the American Cancer Society. He has been a reviewer for many leading medical and oncology journals and currently serves on the editorial boards for *Current Colorectal Cancer Reports*, *Gastrointestinal Cancer Research*, and the *Journal of Clinical Oncology*. Dr. Blanke specializes in gastrointestinal oncology and is or has been an investigator on major clinical trials of targeted treatments for GIST. He is extensively published in the area of oncology, with more than 50 medical articles and abstracts to his credit, and is a frequent lecturer on GIST and other gastrointestinal tumors.



Margaret von Mehren, MD
Director
Sarcoma Oncology
Fox Chase Cancer Center
Philadelphia, Pennsylvania

Margaret von Mehren, MD is associate professor of medicine in the Department of Hematology and Oncology at Temple University in Philadelphia, Pennsylvania. She is also a member of the Department of Medical Oncology and director of the Sarcoma Program at Fox Chase Cancer Center, also in Philadelphia.

Dr. von Mehren received her medical degree from Albany Medical College, New York, and performed her internship and residency at New York University Medical Center. She spent the following 3 years as a fellow in medical oncology at Fox Chase Cancer Center.

Dr. von Mehren is a member of numerous professional societies, including the American Society of Clinical Oncology (ASCO), the American Association of Cancer Research (AACR), the Eastern Cooperative Oncology Group (ECOG), the Connective Tissue Oncology Society, and the Intergroup Coalition Against Sarcomas. She currently serves on the editorial board of *Expert Opinion on Biologic Therapy* and has been a reviewer for multiple publications, such as *Clinical Cancer Research* and the *Journal of Clinical Oncology*. Dr. von Mehren has published extensively in the area of oncology, including on the investigation of c-KIT signaling molecules and imatinib resistance in GIST.



Program Information

PROGRAM OVERVIEW

- Case Study of a 64-Year-Old Woman with Metastatic GIST
- Molecular Oncogenesis
- Primary Treatment with Targeted Therapy
- Tailoring Dose According to Genotype
- Use of Targeted Therapies in Adjuvant and Neoadjuvant Treatment of Earlier Disease
- Prevention and Treatment of Resistance to Targeted Therapies
- Second-Line and Investigational Therapies for GIST

Release Date: May 13, 2008

Termination Date: May 13, 2009

Estimated time for completion of this activity: .75 hours

CME INSTRUCTIONS

To obtain credit for this activity:

- View the entire webcast carefully.
- Complete/submit the posttest and evaluation.
- Instantly access and print out your certificate.

There is no fee for this activity.

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Program Information

Target Audience

This CME activity is designed for medical oncologists, gastroenterologists, and other healthcare professionals who provide care to patients with gastrointestinal stromal tumors.

Activity Goal

The goal of this CME activity is to present the molecular basis for targeted therapies and clinical strategies for their management in the treatment of gastrointestinal stromal tumors. Current therapeutic options and outcomes will be illustrated through case studies.

Learning Objectives

- Distinguish the mechanism of action, and prognostic and treatment implications of current and emerging targeted therapies in accordance with the most recent medical literature regarding the molecular basis of oncogenesis in gastrointestinal stromal tumors (GIST)
- Formulate optimal treatment strategies that maximize response and survival rates for individual patients with GIST based on the patient's molecular profile and an understanding of the mechanisms of action, efficacy, and safety of current and emerging targeted therapies
- Integrate practical approaches to the management of side effects for GIST patients taking targeted therapies in order to maintain patients with GIST on optimal therapy

CME INFORMATION: PHYSICIANS

Statement of Accreditation

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Disclosure Information

The Disclosure Policy of Projects In Knowledge requires that presenters comply with the Standards for Commercial Support. All faculty are required to disclose any personal interest or relationship they or their spouse/partner have with supporters of this activity or any commercial interest that is discussed in

their presentation. Any discussions of unlabeled/unapproved uses of drugs or devices will also be disclosed in the course materials. For complete prescribing information on the products discussed during this CME activity, please see your current *Physicians' Desk Reference (PDR)*.

Charles D. Blanke, MD, has received grants and research contracts from Novartis Pharmaceuticals Corporation.

Margaret von Mehren, MD, has received grant/research support from Novartis Pharmaceuticals Corporation and Pfizer Inc; is a consultant for MedImmune, Inc, Novartis Pharmaceuticals Corporation, and Pfizer Inc; is on the speakers bureau of Novartis Pharmaceuticals Corporation; and is on the advisory boards of MedImmune, Inc and Novartis Pharmaceuticals Corporation.

Richard M. Goldberg, MD, has received grant/research support from Pfizer Inc; and is a consultant for ALMAC Group Ltd, Amgen Inc, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc, Bristol-Myers Squibb, Genentech, Inc, Genomic Health, Inc, ImClone Systems Inc, Sanofi-Aventis, Taiho Pharmaceutical Company Ltd, and Yakult.

Peer Reviewer has received grant/research support from AstraZeneca; and has received speaker honoraria from the New York Academy of Sciences (NYAS).

Projects In Knowledge's staff members have no significant relationships to disclose.

This activity will include discussion of unlabeled/unapproved uses of chemotherapy regimens, dasatinib, adjuvant and neoadjuvant imatinib, imatinib administered at a dose of 800 mg/d for patients with exon 9 mutations, midostaurin, motasenib, nilotinib, oblimersen, rapamycin, retaspimycin, sorafenib, and continuous daily dosing of sunitinib.

Conflicts of interest are thoroughly vetted by the Executive Committee of Projects In Knowledge. All conflicts are resolved prior to the beginning of the activity by the Trust In Knowledge peer review process.

The opinions expressed in this activity are those of the faculty and do not necessarily reflect those of Projects In Knowledge.

This CME activity is provided by Projects In Knowledge solely as an educational service. Specific patient care decisions are the responsibility of the physician caring for the patient.

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Targeted Therapies for GIST

Gastrointestinal stromal tumors (GIST) are the most common nonepithelial tumors of the gut, with about 4258 new cases per year in the United States. Nearly 60% of these tumors occur in the stomach and about one third develop in the small intestine, but they may appear anywhere in the gastrointestinal system.

GIST are mesenchymal neoplasms now recognized as a distinct clinical entity. These tumors were formerly misclassified as smooth-muscle tumors (leiomyomas, leiomyoblastomas, leiomyosarcomas) or nerve-sheath tumors. These tumors likely share a common ancestor with interstitial cells of Cajal.

Molecular Oncogenesis

The KIT protein, a member of the tyrosine kinase III family, is normally expressed on hematogenic progenitor cells, mast and germ cells, and interstitial cells of Cajal. KIT ligand-dependent activation of wild-type KIT stimulates cell growth and survival through MAP kinase and PI-3 kinase signaling cascades.

KIT is also expressed in a limited range of human cancers. Nearly all GIST express KIT. The majority of GIST contain KIT gene mutations that result in constitutively active mutant forms of KIT, thereby excessively promoting cell growth and survival. Positive immunostaining for KIT is now considered diagnostic for GIST. In addition, some GIST contain activating mutations for platelet-derived growth factor receptors (PDGFR).

Treatment of Early GIST

Surgery is the only potentially curative therapy for early GIST. Imatinib mesylate, a protein tyrosine-kinase inhibitor, has shown benefit as adjuvant therapy in a phase III trial conducted by the American College of Surgeons Oncology Group. The Z9001 trial randomized treatment-naïve patients with KIT+ GIST ≥ 3 cm with complete resections within 70 days prior to registration to receive imatinib 400 mg/day or placebo for 1 year. Recurrence-free survival (RFS) at 1 year was 97% with imatinib versus 83% with placebo ($P < .001$).

The greatest benefit was seen in the subgroup of patients with tumors >10 cm, for whom RFS at 1 year was 96% versus 67%, respectively ($P < .001$). There was no significant difference in overall survival between the imatinib and control groups. Imatinib is also being evaluated as neoadjuvant therapy to determine whether cytoreduction will increase resectability and improve surgical outcomes.

Primary Treatment for Metastatic GIST

Until the advent of targeted therapy, effective treatment for metastatic GIST was notably lacking. Response rates to chemotherapy have been particularly low. Salvage surgery rarely prevents further recurrence.

Improved understanding of oncogenesis has led to development of new therapies that target underlying pathogenic mechanisms in many tumor types. Imatinib is approved as first-line treatment for KIT-positive unresectable or metastatic GIST. Imatinib inhibits KIT and PDGFR. In two large phase III studies of imatinib, about half of imatinib-treated patients showed response and another one quarter to one third had stable disease. Median progression-free survival was about 19 months with 400 mg/day, and about 30% were progression free at 3 years. Median overall survival was 49 months, and 61% were alive at 3 years. A dose of 800 mg/day was also assessed and was not found to be significantly more effective overall. It was less well tolerated. Grade 3/4 side effects of imatinib in these studies included granulocytopenia, edema, fatigue, rash, diarrhea, and bleeding.

Mutational analysis of GIST may help determine prognosis and imatinib dosing. Patients with exon 9 mutations show increased benefit with higher-dose (800 mg/d) imatinib compared with the standard 400 mg/day.

Surgery may be considered for imatinib-stabilized disease if all gross disease can be resected.

Second-line Treatment of Metastatic GIST

Imatinib resistance may be primary or secondary (following an initial response). Resistance may theoretically be due to (a) imatinib-resistant mutations in KIT or PDGFRA kinase domain, (b) KIT or PDGFRA gene amplifi-

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cation, or (c) activation of an alternative kinase.

Another therapy that inhibits KIT and PDGFR (among other receptors), sunitinib, is currently FDA approved for treatment of metastatic GIST after disease progression or intolerance to imatinib. In a phase III placebo-controlled trial, sunitinib significantly increased time to tumor progression (median 28.9 versus 7.0 weeks). In this phase III study, sunitinib was given at a dose of 50 mg/day for 4 weeks followed by 2 weeks off therapy for 6 cycles. In a separate study, 60 patients were treated with continuous daily dosing, which appeared to extend progression-free survival but also increased hematologic toxicity.

Genotyping may be useful in predicting response to sunitinib. Mutational analysis was performed in a phase II study of sunitinib and determined that patients with exon 9 KIT mutations were most likely to benefit, whereas response rates for those with exon 11 KIT mutations were lower. Patients with wild-type KIT or PDGFR mutations showed no response. Another analysis of patients with imatinib resistance showed that whereas double mutations in the ATP binding pocket of KIT produced imatinib but not sunitinib resistance, double mutations in the KIT activation loop confers resistance to both drugs.

Looking Forward

Numerous other therapies that target KIT, PDGFR, or other receptors that may play a part in the pathogenesis of GIST are currently in development. Their roles remain to be determined in clinical trials.

A number of questions regarding the application of current and emerging therapies require further study. Is imatinib the only effective first-line targeted therapy for GIST or should other targeted therapies be tested and considered in this setting? Is there a role for combination therapy? Can mutational analysis help select not only the correct dose, but also the correct drug for an individual patient?

Until these questions are answered, imatinib remains the systemic agent of choice for metastatic GIST, and may have a role in adjuvant therapy for resected GIST, especially for patients with large tumors. The initial dose should be 400 mg/day for most patients, but those with KIT exon 9 mutations may benefit from 800 mg/day, after an initial tolerance lead-in period of 400 mg/day. Sunitinib should be considered for patients who are resistant or intolerant of imatinib.



Suggested Readings

Blanke CD, Rankin C, Demetri GD, 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.* 2008;26:626-632.

Casali PG, Garrett CR, Blackstein ME, et al. 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. *J Clin Oncol.* 2006;24(suppl):abstr 9513.

DeMatteo R, Owzar K, Maki 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 [abstract 10079]. Presented at: 43rd annual meeting of the American Society of Clinical Oncology; June 1-5, 2007.

Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomized controlled trial. *Lancet.* 2006;368:1329-1338.

George S, Blay JY, Casali PG, et al. Continuous daily dosing (CDD) of sunitinib malate (SU) compares favorably with intermittent dosing in pts with advanced GIST [abstract 10015]. Presented at: 43rd annual meeting of the American Society of Clinical Oncology; June 1-5, 2007; Chicago, Ill.

Gold JS, DeMatteo RP. Combined surgical and molecular therapy. The gastrointestinal stromal tumor model. *Ann Surg.* 2006;244:176-184.

Heinrich MC, Corless CL, Kiegl B, et al. Mechanisms of sunitinib malate (SU) resistance in gastrointestinal stromal tumors (GISTs) [abstract 10006]. Presented at: 43rd annual meeting of the American Society of Clinical Oncology; June 1-5, 2007; Chicago, Ill.

Mietten M, Lasota J. Gastrointestinal stromal tumors – definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch.* 2001;438:1-12.

Van Glabbeke M, Owzar K, Rankin C, et al. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors (GIST): a meta-analysis based on 1,640 patients (pts) [abstract 10004]. Presented at: 43rd annual meeting of the American Society of Clinical Oncology; June 1-5, 2007; Chicago, Ill.

Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomized trial. *Lancet.* 2004;364:1127-1134.