Soft Tissue Sarcoma
Chemotherapy:
Past, Present, Future

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Division of Medical Oncology
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Disclosure Statement

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  - Ariad Pharmaceuticals
  - Food and Drug Administration
    - FDA Orphan Products Development Grants Program
  - Arqule, Inc.
  - Eli Lilly Pharmaceuticals
  - Sarcoma Alliance for Research thru Collaboration
Sarcoma Introduction

- Cancer of the connective tissue
- **Soft-tissue** sarcomas: Estimated 9,530 cases in U.S. in 2006 (M 5,720 / F 3,810)
  - Deaths: 3,500 (M 1,830 / F 1,670)
- **Bone** sarcomas: Estimated 2,760 in U.S. in 2006 (M 1,500 / F 1,260)
  - Deaths: 1,260 (M 730 / F 530)

## Soft-Tissue Sarcoma Major Histologic Subtypes: >50 subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Undiff Pleomorphic (MFH)</td>
<td>(28%)</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>(15%)</td>
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<tr>
<td>Leiomyosarcoma</td>
<td>(12%)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>(11%)</td>
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<tr>
<td>Synovial sarcoma</td>
<td>(10%)</td>
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<tr>
<td>Malignant peripheral nerve sheath</td>
<td>(6%)</td>
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<tr>
<td>GIST</td>
<td>(5%)</td>
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<tr>
<td>Fibrosarcoma</td>
<td>(3%)</td>
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<tr>
<td>Angiosarcoma</td>
<td>(2%)</td>
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<tr>
<td>Epithelioid</td>
<td>(1%)</td>
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</table>

Bone Sarcoma Histologic Subtypes

• Osteosarcoma (36%)
• Chondrosarcoma (10-25%)
• Ewing sarcoma (6-8%)

Damron TA. Oncology and Basic Science. Lippincott Williams & Wilkins, Philadelphia, 2008.
**Location**

- **Upper extremity**: 538 (14%)
- **Retroperitoneal /intraabdominal**: 601 (15%)
- **Lower extremity**: 1275 (32%)
- **Trunk**: 425 (11%)
- **Visceral**: 650 (16%)
- **Other**: 479 (12%)

*Cancer: Principles & Practice of Oncology.*
Past...
Adjuvant Chemotherapy for Bone Sarcomas

• **Osteogenic sarcoma**
  – Cisplatin/Doxorubicin +/- High-Dose Methotrexate
  – Survival: <20% no Rx vs. >60% with Rx

• **Ewing sarcoma family of tumors**
  – Ifosfamide/Etoposide + Vincristine/Doxorubicin/Cyclophosphamide
  – Survival: 20% no Rx vs. >70% with Rx

• **Chondrosarcoma**
  – Adjuvant chemotherapy NOT recommended

Adjuvant Chemotherapy for Soft-Tissue Sarcomas

• Meta-analysis of 14 randomized, doxorubicin-based adjuvant chemotherapy trials
  – 6% benefit for local recurrence-free survival (p=0.016)
  – 10% benefit for distant recurrence-free survival (p=0.0003)
  – 10% benefit for overall recurrence-free survival (p=0.0001)
  – 4% benefit for overall survival (p=0.12)

Traditional Sarcoma Chemotherapy

- Results of Two Consecutive Trials of Dose-Intensive Chemotherapy with Doxorubicin (A) and Ifosfamide (I) in Patients with Sarcomas
  - AI 75/10 (Doxorubicin 75 mg/m²/72 hr + Ifosfamide 2 gm/m²/2 hr x 5 day)
    - Overall objective RR 69%
    - Febrile neutropenia 31% of cycles
  - AI 90/10 (Doxorubicin 90 mg/m²/72 hr + Ifosfamide 2 gm/m²/2 hr x 5 day)
    - Overall objective RR 59%
    - Febrile neutropenia 56% of cycles

Adjuvant Chemotherapy for Soft-Tissue Sarcomas

- Italian adjuvant trial of 5 cycles of Epirubicin/Ifosfamide for extremity STS (med. f/u 89.6 mos)
  - Only 104 patients (51 control; 53 observ.)
    - Planned 95 pts/arm (tot. 190)
    - Interim analysis after 50% enrolled.
    - Two-sided p ≤ 0.001 DFS
  - Median DFS: 47 mos vs. 16 mos (p=0.09)
  - Median OS: NR vs. 49 mos (p=0.07)
  - 5-yr OS estimate: 66.0 % vs. 46.1% (p=0.04)

Present...
Angiosarcoma of the Scalp or Face

- **Paclitaxel 175 mg/m² given over 1, 3, and 24 hr**
  - Memorial-Sloan Kettering Cancer Ctr
  - 8/9 patients responded:
    - 4 PR’s, 4 clinical CR’s, & 1 MR
- **Liposomal Doxorubicin**
  - Case reports of complete response in radio-resistant cutaneous angiosarcoma

84 y/o W/M w/ Scalp Angiosarcoma & CR after 4 Cycles of Paclitaxel
Radiation-induced Angiosarcoma of the Breast

- 82 y/o W/F Stage 1, ER/PR/Her-2(-) multifocal breast CA in 2001; lumpectomy, adjuvant AC & XRT.
- 2006, developed 1.9 cm angiosarcoma (AS) of breast; simple mastectomy.
- April, 2007, developed recurrence outside of vascular flap.
- May, 2007, 2 cycles of paclitaxel 80 mg/m2/week for 6 weeks every 8 weeks.
- Surgery August, 2007; path CR.
- Received 2 cycles of “consolidation” paclitaxel. Observation since Nov, 2007.
Ewing Sarcoma Family of Tumors

• AEWS0031
• COG study of chemotherapy intensification by interval compression
• Improved EFS and OS for q2 wk dose-intensive arm

AEWS0031 Regimens and Age

Gemcitabine and Docetaxel

- **MSKCC**: Combination first tested in leiomyosarcoma of uterus or other organs.
  - Gemcitabine 900 mg/m²/90 min (D1, D8) + Docetaxel 100 mg/m²/1 hr D8 + G-CSF
  - Overall RR 53% (20% SD)

- **U. Michigan**: Tested in other sarcoma histologies.
  - Gemcitabine 675 mg/m²/90 min (D1, D8) + Docetaxel 100 mg/m²/1 hr D8 + G-CSF
  - Responses observed in leiomyosarcoma, osteosarcoma, angiosarcoma, MFH, malignant peripheral nerve sheath tumor, and Ewing’s sarcoma.

Gemcitabine and Docetaxel

• SARC Cooperative Group randomized phase II study of gemcitabine +/- docetaxel
  – Gemcitabine 1200 mg/ m²/90 min (D1, D8) every 21 days.
  – Gemcitabine 900 mg/m²/90 min (D1, D8) + Docetaxel 100 mg/m²/1 hr D8 + G-CSF every 21 days.
  – RR 8% vs. 16%
  – Leiomyosarcomas and MFH/HGUPS most responsive.

Adjuvant Chemotherapy for Soft-Tissue Sarcomas

- EORTC randomized, phase III trial of 5 cycles of Doxorubicin (75 mg/m²) & Ifosfamide (5 gm/m²) q 21d vs. obs for high grade STS of any site.
- LMS (15%), lipo (13%), MFH (11%), SS (11%)
- 66% extremity; 34% trunk/pelvis; 40% > 10 cm
- 73% completed the prescribed 5 cycles of Rx
  - 63% completed without dose reduction/delay
- 5-yr RFS 53% obs arm vs. 51% CT arm
- 5-yr OS 69% obs arm vs. 64% CT arm

Targeted Therapies for Soft-Tissue Sarcomas
Gastrointestinal Stromal Tumors (GIST)

- Most common gastrointestinal sarcoma
- Highest incidence in the 40-60 year age group
- Recently identified as a distinct clinical and histopathologic entity
- GIST have an incidence of 14.5 per million annually (comparable with CML)
- U.S. Population 296,000,000 $\approx$ 4,300/year


GIST: Origin

- GIST share several characteristics with interstitial cells of Cajal (ICC)
  - Pacemaker cells of the gut
  - Mixture of neural and myogenous features by electron microscopy
  - Expression of KIT (CD117) in ~95% of cases

- ICC hyperplasia is evident in the GI tract of patients with familial GIST

- GIST and ICC may arise from a common mesenchymal stem cell of the enteric neural plexus

GIST: Clinical Presentation

- GIST may occur anywhere along the GI tract or elsewhere in the abdomen or retroperitoneum

GIST: Immunophenotype

- ~95% of reported cases of GIST are positive for KIT (CD117)
- Other markers often positive in GIST:
  - CD34 (mesenchymal/hematopoietic precursor cell marker)
    - Positive in 60%-70%
  - Smooth-muscle actin
    - Positive in 15%-60%
  - S-100
    - Positive in 10%
- GIST rarely express desmin

Courtesy of Dr. C. Corless.
GIST: Identification of KIT Gain-of-Function Mutations

Gain-of-Function Mutations of c-kit in Human Gastrointestinal Stromal Tumors

Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiro Kitamura†

Science 279:577-580, 1998

- KIT staining was positive in 46 of 49 GIST (94%)
- 5 of 6 GIST had mutations in KIT gene
- Mutant forms of KIT are constitutively active
- Proposed that GIST may originate from ICCs
- Studies in knock-in mice with KIT mutations
  - Demonstrated that constitutive KIT signaling is sufficient to induce GIST
  - Parallel with the pathology seen with familial KIT mutations, eg, mastocytosis

GIST: Platelet-Derived Growth Factor Receptor Alpha (PDGFRA) Mutations

- **PDGFRA mutations are present in ~5%-7% of GIST**
  - Mutually exclusive with KIT mutations
  - 35% of KIT wildtype GIST have PDGFRA mutations

- **Downstream activation targets of KIT are also activated by PDGFRA mutations in GIST**
  - AKT
  - MAP kinase
  - STATs

**KIT and PDGFRA Mutations in GIST**

**KIT**
- Exon 9 (11%)
- Exon 11 (67.5%)
- Exon 13 (0.9%)
- Exon 17 (0.5%)

**PDGFRA**
- Exon 12 (0.9%)
- Exon 14 (0.3%)
- Exon 18 (6.3%)

Overall mutation frequency: 87.4%

Heinrich et al. *Hum Pathol.* 2002;33:484.
Normal KIT Signaling

- The KIT kinase domain activates a substrate protein, e.g., PI3 kinase, by phosphorylation.
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival.

Imatinib Mesylate: Background

- A selective tyrosine kinase inhibitor of:
  - KIT
  - c-Abl/Arg
  - PDGFRA/B
- First used in Philadelphia chromosome–positive (Ph+) CML


Class: Phenylaminopyrimidines
Imatinib Mesylate: Mechanism of Action

- Imatinib mesylate occupies the ATP binding pocket of the KIT kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival

First Patient With GIST to Receive Imatinib Mesylate: Proof-of-Concept

• Exploratory study with oral imatinib mesylate at 400 mg/d

• Dramatic clinical response
  – Disappearance of excess metabolic activity at 4 weeks by \(^{18}\)FDG-PET
  – 75% reduction in tumor size at 8-month follow-up
  – Tumor biopsies showed histologic evidence of myxoid degeneration and lack of mitotic activity
  – Symptomatic relief

Multiple liver and upper abdominal $^{18}$FDG-accumulating metastases

A marked decrease in $^{18}$FDG uptake 4 weeks after starting imatinib mesylate (400 mg/d)

Effects of Imatinib Mesylate on CT

Effects of Imatinib on Histology

<table>
<thead>
<tr>
<th>Pre-Treatment</th>
<th>3 Weeks</th>
<th>Post-Treatment</th>
</tr>
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<tbody>
<tr>
<td>H&amp;E</td>
<td></td>
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<tr>
<td>Ki-67</td>
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<tr>
<td>CD117</td>
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GIST: KIT Mutation Location Predicts Imatinib Mesylate Responsiveness

- KIT mutations are predictive of response to imatinib mesylate
- Exon 11 mutants respond best

Imatinib Mesylate Therapy of GIST With Weak/Negative KIT Expression

- Approximately 5% of GIST are KIT-negative
- Weak/negative KIT staining is not predictive of a poor response to imatinib mesylate
- KIT-negative GIST may express imatinib mesylate–sensitive mutant KIT or PDGFRA
  - Documented clinical responses in KIT-negative GIST
Efficacy of Imatinib Mesylate in KIT-Negative GIST (S0033): PFS

Imatinib Mesylate in GIST: Pivotal Trial—Survival by Best Response

- Even patients who achieve only SD by SWOG will experience prolonged survival on imatinib mesylate

“We Should Desist Using RECIST, at Least in GIST”

- RECIST is insensitive in evaluating GIST response treated with imatinib.
- 172 met. GIST lesions eval. in 40 pts.
- Mean size (5.3 cm), density (72.8 HU), $SUV_{\text{max}}$ (5.8).
- 33/40 good response on FDG-PET.
- Decrease in size >10% or tumor density of >15% on CT had sensitivity 97% & specificity 100% by FDG-PET.

“We Should Desist Using RECIST, at Least in GIST”
Adjuvant Imatinib for GIST

- ACOSOG Z9001 [A Phase III Randomized Double-blind Study of Adjuvant Imatinib vs. Placebo in Patients Following Resection of Primary GIST]
- Pts with GIST > 3 cm, not ruptured, nor multifocal eligible for randomization to imatinib 400 mg/day for 1 yr vs. placebo.
- Interim results reported 97% RFS for imatinib vs. 83% for placebo @ 1 yr.
- On-going adjuvant trials in Europe
  - EORTC: 2 years imatinib vs. observation
  - Scandinavian Sarcoma Group: 1 yr vs. 3 yr of imatinib
The Next Intergroup GIST Study

- SWOG S0502: A Phase III Randomized Study of Imatinib, with or without Bevacizumab, in Patients with Metastatic or Unresectable GIST.
Other Potential Imatinib-Sensitive Sarcomas

- **Dermatofibrosarcoma Protuberans**
  - Uncommon, low-gr, fibrohistiocytic tumor of interm. malignant potential of dermis and subcutis
  - Caused by autocrine/paracrine activation of platelet-derived growth factor receptor-B (PDGFR-B) via translocation (COL1A1-PDGFB fusion)
    - SARC004: Phase II Study of IM in DFSP

- **Extraabdominal Desmoid Tumors (Fibromatosis)**
  - Rare, monoclonal tumor of deep musculoaponeurotic structures
  - SWOG S0525: Phase II Study of IM in Desmoid Tumors
Other Potential Imatinib-Sensitive Sarcomas

- **Chordomas**
  - Very, rare tumor that originate from remnant of notochord.

- **Ewing’s Sarcoma/PNET?**
  - Phase 2 trial of IM for tx of pediatric solid tumors: A Children’s Oncology Group Study
    - 1/24 pts with PR.
  - Phase 2 SARC trial (Chugh D. Proc ASCO 22: 90001a, 2004).
    - 0/13 pts with PR
    - 1/7 pts with PR (Kit & PDGFR-a expression)
Imatinib Resistance in GIST
GIST: Mechanisms of Potential Resistance to Imatinib Mesylate

• Resistance can be primary or secondary (following initial response)

• Mechanisms
  – Imatinib mesylate–resistant mutations in KIT or PDGFR-A kinase domain
  – KIT or PDGFR-A gene amplification
  – Activation of alternative kinase

• Resistance may be evidenced as progression of some lesions but not others

Imatinib Mesylate in GIST: Focal Resistance Following Response

Pretreatment 6 months 10 months

Courtesy of Dr. R. DeMatteo.
GIST: Sunitinib Treatment

- An inhibitor of the receptor tyrosine kinases PDGFR, VEGFR, KIT, RET, and FLT3
  - Has antiangiogenic effects on HUVECs in vitro
- Achieved tumor control in conjunction with irradiation in murine tumor models
- Clinical activity observed in patients intolerant of or who progressed on imatinib mesylate
- DLT: fatigue, nausea, vomiting

HUVECs = human umbilical vein endothelial cells.
GIST Resistant to Imatinib Mesylate: Phase II Trial of Sunitinib

- 65% of patients in a phase I/II trial experienced clinical benefit

Imatinib Mesylate in GIST: Pivotal Trial—Survival by Best Response

- Even patients who achieve only SD by SWOG will experience prolonged survival on imatinib mesylate

GIST Resistant to Imatinib Mesylate: Phase III Trial of Sunitinib

- Median TTP 27.3 wks vs. 6.4 wks for placebo
- 7% PR (58% SD) vs. 0% for placebo
- 10% of pts exhibited PR & 7% SD after crossover
- Pts with Exon 9 mutation responded better than pts with Exon 11 (opposite of imatinib).

Future...
AP23573, an mTOR Inhibitor

- AP23573, an analog of rapamycin (Sirolimus)
- Inhibits the mammalian target of rapamycin (mTOR) protein kinase.
- mTOR is a central controller of cell proliferation
- Treatment of cells with rapamycin inhibits:
  - Cell growth
  - Cell division
mTOR Signaling

Phase 2 Study of AP23573 in Patients with Advanced Sarcomas

- 12.5 mg IV daily X 5 days every 2 weeks
- 25 previously treated pts (14M/11F):
  - Bone (5)
  - Leiomyosarcoma (5)
  - Liposarcoma (1)
  - Others (11)
- 39% demonstrated > 25% decrease in $[^{18}\text{F}]$ FDG PET uptake.
- Symptomatic improvement in 13 pts.

Phase III Trial of AP23573 Maintenance Rx in STS/Bone Sarcomas

- Randomized, placebo-controlled, double-blinded trial to compare efficacy of PO AP23573 40 mg QDx5/week vs. placebo.
- Met. sarcoma patients who have CR/PR following 4-12 cycles of cytotoxic chemotherapy.

Sorafenib

• Raf kinase, PDGFR-β, and VEGF-R inhibitor that inhibits tumor proliferation and angiogenesis.

• Multi-center, phase II trial for non-GIST sarcomas reported at ASCO, 2007.
  – 2/37 RECIST PR’s in leiomyosarcoma (6% RR)
  – 3/23 PR’s in angiosarcoma (13% RR)

• U. Chicago consortium trial in imatinib and sunitinib-resistant GIST.

Dasatinib (BMS-354825)

• c-SRC is a proto-oncogene, non-receptor tyrosine kinase; induces VEGF expression thru STAT3.
• Dasatinib is a broad spectrum ATP-competitive inhibitor of SRC family kinases, BCR-ABL, c-KIT, EPhA2 receptor, and PDGFR-β.
• Dasatinib is 2-3 logs more potent than imatinib mesylate in inhibiting BCR-ABL.
• Dasatinib is capable of binding to both the open (active) and closed (inactive) conformations of c-ABL; imatinib mesylate can only bind to the inactive state.

Eli Lilly: LY573636

- Novel cytotoxic agent w/ activity across broad range of human cancer cell lines.
- Unique MOA unlike other cytotoxics.
- Promotes apoptosis via increase ROS.
- Phase II, open-label study as 2nd or 3rd line therapy for unresectable or met STS (1 must be doxorubicin-based).

Amgen: Phase Ib/2 Study of AMG 655 + Doxorubicin for 1st line Rx of STS

- Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is natural ligand for TRAIL receptor 2 (DR5).
- Activation of TR2/DR5 initiates caspase cascade and apoptosis.
- AMG 655 mimics endogenous TRAIL.
- Sarcomas express high levels of TR-1 and TR-2.
- AMG 655 AE’s: fever, fatigue, anemia, nausea, increased lipase, hypomagnesemia, lymphopenia.

Insulin-like Growth Factor-1 Signaling

Sarcoma Alliance for Research thru Collaboration (SARC) #011

- **Phase II Trial of R1507 (MoAb Insulin-Like Growth Factor-1 Receptor):**
  - Ewing’s sarcoma
  - Osteosarcoma
  - Synovial sarcoma
  - Rhabdomyosarcoma
  - Other sarcomas

- **High levels of IGF1R expressed in no. of pediatric solid tumors.**

- **R1507 inhibits downstream targets of IGF-1R (PI-3K, MAPK)**

COH: Nelfinavir and Liposarcoma

- Nelfinavir is an HIV protease inhibitor.
- HAART results in HIV lipodystrophy syndrome.
- *In vitro*, nelfinavir:
  - inhibits liposarcoma clonogenicity via upregulation of SREBP-1
  - Induces expression of Fas, Bax and p21\(^{\text{WAF1/CIP1}}\)
  - Induces liposarcoma apoptosis
  - Induces G\(_1\) cell cycle block
- “Phase I/II trial of Nelfinavir for recurrent liposarcomas”
Patient #2; 2nd Cohort (1750 mg BID)

1/17/07

4/25/07

7/23/07

1/15/08
Patient #2; 2\textsuperscript{nd} Cohort (1750 mg BID)

- 1/17/07
- 4/25/07
- 7/23/07
- 1/15/08
Patient #2; 2\textsuperscript{nd} Cohort (1750 mg BID)

1/17/07 4/25/07
7/23/07 1/15/08
Conclusions

• Benefit of adjuvant chemotherapy with Ifosfamide and an anthracycline is probably limited.

• Other chemotherapies indicated for specific histologic types of sarcomas.

• Imatinib mesylate for GISTs has produced active research in tyrosine kinase inhibition for GIST and other sarcomas.

• New targets are currently being identified in sarcomas, which may result in development of novel therapeutics.
Acknowledgements

• Chow Laboratory
  – Min Guan, Ph.D.
  – Chunling Jiang, Ph.D.
  – Song Guo (U. Wisconsin)
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<tr>
<th>Kinases Inhibited</th>
<th>Kinases Not Inhibited</th>
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<tr>
<td>Kit</td>
<td>EGFR (HER1)</td>
</tr>
<tr>
<td>Bcr-Abl</td>
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<td>PKC-α</td>
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<td>FGFR-1</td>
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GFR = growth factor receptor; EGFR = epidermal GFR; VEGFR = vascular endothelial GFR; IGFR = insulin-like GFR; PKC = protein kinase C; FGFR = fibroblast GFR.

GIST: Preclinical Efficacy of Imatinib Mesylate on GIST Cell Cultures In Vitro

- Imatinib mesylate inhibits proliferation and induces apoptosis in GIST cell culture

*GIST-882 and ST88-014 are GIST- and peripheral nerve sheath–derived cell lines, respectively. Tuveson et al. *Oncogene.* 2001;20:5054.