Consensus meeting for the management of gastrointestinal stromal tumors
Report of the GIST Consensus Conference of 20–21 March 2004, under the auspices of ESMO

On behalf of the GIST consensus meeting panelists†
Background

• Workshop 3/04 in Lugano, Switzerland under the auspices of ESMO
• Panel experts
  – Pathology
  – Molecular biology
  – Imaging
  – Surgery
  – Medical oncology
  – Methodology for clinical practice guidelines
• 32 consensus points
• Categorization according Standard Options Recommendations (SOR) of the French Federation of Cancer Centers and the National Comprehensive Cancer Network (NCCN)
SOR Categories of Consensus

- Level A: meta-analysis or consistent RCT
- Level B: consistent RCT (B1) or prospective/retrospective studies (B2)
- Level C: studies with questionable methodology or non-consistent results
- Level D: no data or case studies; expert agreement: no data or unanimous
NCCN Categories of Consensus

- Category 1: uniform consensus based on high-level evidence
- Category 2A: uniform consensus based on lower-level evidence
- Category 2B: non-uniform consensus (but no major disagreement) based on lower-level evidence including clinical experience
- Category 3: major disagreement
Histological criteria

- standard histological examination with central review by an expert in sarcoma pathology (B2, 2A)
- immunohistological analysis with
  - CD117, CD34, SMA, S100, Desmin (B2, 2A)
  - no antigen retrieval
- risk assessment by size and mitotic index (B2, 2A)
Major morphologic patterns

Spindle-Shaped

Epithelioid
KIT staining in tissue

- H&E
- Normal small intestine
- GIST
- KIT
Mutation analysis

• CD117-neg. GIST (intra-abdominal tumors suspected to be GIST) should be considered for molecular analysis for kit and PDGFRα mutations (E.A., 2A)
• research procedure in other cases (possible clinical application in the future)
• optimal technique for mutation screening remains to be defined
KIT and PDGFRA mutations predict event-free survival: Update from S0033

332 GISTs analysed
324 KIT+
86% mutations

8 KIT-
7/8 mutations
(4 KIT, 3 PDGFRα)
PFS as KIT+ *

Exon 11 9 WT
RR % 67 40 40 sig.
TTF days 576 306 251 sig.

*Blackstein et al. ASCO, 2005. Abstract 9010
Sunitinib malate (SU011248) therapy in Imatinib mesylate–resistant GIST

- SU011248 is a multitargeted tyrosine kinase inhibitor
  - Inhibits KIT, VEGFR, and FLT3
- 97 patients have been treated
  - PR of 8%; 37% of patients with SD >6 months
- Median TTP 7.9 months
- Median OS 19.8 months
- Main toxicities: fatigue, diarrhea, nauseas

<table>
<thead>
<tr>
<th>Mutational analysis:</th>
<th>Median overall survival</th>
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<tbody>
<tr>
<td>KIT exon 9 mutation</td>
<td>31 months</td>
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<tr>
<td>KIT exon 11 mutation</td>
<td>5 months</td>
</tr>
</tbody>
</table>

**Imaging strategy**

- contrast-enhanced CT scan as imaging modality of choice for staging and surgical planning (B2, 2A)
- contrast-enhanced MRI may be used as initial evaluation
- small tumors found during endoscopy should be evaluated by endoscopic ultrasound or CT
- MRI preferred for suspected rectal GIST (E.A., 2A)
- PET is recommended when early detection of tumor response to imatinib is required (E.A., 2A)
- PET may be useful in equivocal images suspected to be metastases
- PET is not mandatory after complete resection of GIST (E.A., 2A)
Surgery (1)

- Standard treatment for localized resectable GIST is surgery with negative margins.
- Biopsy:
  - No consensus on the need for preoperative diagnosis by core-needle biopsy (C, 2B).
  - Intraabdominal open biopsy is discouraged because of the risk of tumorspill.
- Margins:
  - Wedge resection of gastric GIST (B2, 2A).
  - Segmental resection of intestinal GIST (B2, 2A).
  - Wide resection of esophageal, duodenal and rectal GIST (B2, 2A).
  - Complete en bloc resection of visible disease in omental or mesenteric GIST in order to avoid rupture.
  - Re-excision in cases of intra-lesionally excised tumors (C, 2B).
Surgery (2)

- Laparoscopic surgery should be avoided (possible exception: intramural tumors ≤2cm) (E.A., 2A)
- Lymphadenectomy only for evident nodal involvement (E.A., 2A)
- All lesions suspected to be GIST should be resected (E.A., 2B)
Adjuvant treatment

- no treatment outside clinical trials
- candidates are intermediate and high-risk patients
- no treatment arm is ethically sound (E.A., 2A)
- OS as primary end point (E.A., 2A)
- patients after R1-resection are considered adjuvant
Ongoing adjuvant trials of Imatinib in GIST

- not recommended outside a clinical trial!

- **ACOSOG Z9000:**
  - phase II – trial, 400 mg/day x 1 year (T >10cm, tumor rupture, multifocal)
  - 106 patients, closed

- **ACOSOG Z9001:**
  - phase III – trial, placebo-controlled, 400 mg/day x 1 year (T ≥3cm)
  - 355/672 patients accrued as of 05/05

- **EORTC 62024:**
  - phase III – trial, 400 mg/day x 2 years vs. Control (high risk + intermediate risk)
  - 400 patients planned (start end of 2004)

- **SSG / AIO trial:**
  - randomized phase III – trial, 400 mg/day, 12 months vs. 36 months (very high risk + high risk)
  - 90/240 patients accrued as of 5/05
Neo-adjuvant treatment

- no treatment when any decrease of tumor size will not affect surgery outside clinical trials (E.A., 2A)
- in order to avoid loss of organ function
- rapid treatment response assessment by PET and CT
- duration of treatment 4 to 6 months
Follow-up after resection

- no definition of optimal time intervals available
- no proof of benefit available
- Suggestion:
  - high-risk and intermediate risk
    - CT scan every 3 months for 3 years, every 6 months until 5 years and yearly thereafter
  - low and very low risk
    - CT scan every 6 months for 5 years
Imatinib in advanced GIST (1)

- immediate treatment for unresectable and/or metastatic GIST (A, 1)
- immediate treatment even after complete resection of all visible metastasis (terminology „adjuvant“ does not apply)
Imatinib in advanced GIST(2)

• 400 mg/day is the currently recommended dose in first-line treatment (B1, 2A)
• imatinib should be given until progression, intolerance or patient refusal (A, 1)
Discontinuation of Imatinib increases the risk of progression (BFR14)

- Patients who achieved clinical benefit after 12 months were randomized to continue or to stop imatinib therapy
  - 4 / 26 (15%) vs. 21 / 32 (66%) recurred (p<0.0001)
  - 1 year survival rate 87 vs. 89%, not sig.

- Soluble KIT decreases in GIST patients treated with imatinib
- SCF levels increase significantly*

*Bono et al., Blood 2004
Response evaluation

• CT scan is the imaging modality of choice (B2, 2A)
• symptomatic improvement, CT scan HU reduction and PET scan response are predictors of tumor control by imatinib (B2, 2A)
• size reduction not mandatory
Response monitoring

- CT scan is the imaging modality of choice
- frequency every 3 to 4 months
Resection of residual disease

- resection of residual disease after response or prolonged stabilisation following imatinib is still considered experimental
- if intended, resection should be performed after maximal response, usually after 4 to 12 months
- methodology: surgical resection or destruction (e.g. radiofrequency ablation)
- no interruption (or shortest possible time) of imatinib (A, 1)
Secondary surgery in metastatic disease is still experimental

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<thead>
<tr>
<th></th>
<th>23*</th>
<th>25#</th>
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<tbody>
<tr>
<td># patients</td>
<td></td>
<td></td>
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<tr>
<td>Op. after response to imatinib</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Recurrence with cont. Imatinib</td>
<td>0/11</td>
<td>0/16</td>
</tr>
<tr>
<td>Recurrence w/o cont. Imatinib</td>
<td>3/5</td>
<td>2/3</td>
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<tr>
<td>Salvage</td>
<td>7</td>
<td>6</td>
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<tr>
<td>Progression</td>
<td>4/7</td>
<td>6/6</td>
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Continuation of imatinib is mandatory
Surgery in progressive disease not supported

Management of progressive disease

- primary resistance defined as progression within first 6 months of imatinib
- secondary resistance beyond 6 months of imatinib
- partial resistance:
  - multidisciplinary approach with surgery/ablation and increased dose of imatinib (role of local treatment not proven)
- multifocal resistance:
  - dose increase of imatinib to 800 mg/day (B2, 2A)
  - experimental therapy in clinical trial
- chemotherapy should be avoided
Dose escalation of Imatinib in GIST with progression under 400 mg

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<tr>
<th>EORTC 62005*</th>
<th>S0033†</th>
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<tr>
<td>• 133 patients crossed over to 800 mg</td>
<td>• 77 patients crossed over to 800 mg</td>
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<tr>
<td>• Response: 2.5% PR, 30.3% SD</td>
<td>• Response: 7% PR, 32% SD</td>
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<tr>
<td>• PFS: median 81 days, 18% at 1 year</td>
<td>• PFS: median 4 months</td>
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How to manage GIST patients with systemic progression?

- systemic treatment options:
  - continue Imatinib with dose increase to 800 mg/day
  - investigational new studies
    - Imatinib + RAD001 (van Oosterom et al. ASCO, 2005. Abstract 9033.)
    - Imatinib + PKC412 (Reichardt et al. ASCO, 2005. Abstract 3016.)
    - Imatinib + AMN107
    - Sunitinib (SU11248)
    - AMG706
    - Dasatinib (BMS-354825, Evans et al. ASCO, 2005. Abstract 3034.)
    - more to come...
Imatinib mesylate and PKC-412 combination therapy in Imatinib mesylate–resistant GIST

• PKC-412 is derived from the PKC inhibitor staurosporine
  – As selective as the parent compound
  – Also inhibits VEGF, PDGF, KIT, and FLT3
  – Inhibits at least the conventional PKC isoforms (a, b, g)

• Phase I/II study: imatinib mesylate 600-1000+ mg/d + PKC-412 100-200 mg/d

• 23 patients enrolled to date

• The addition of PKC412 to IM results in a strong drug-drug interaction on both combination partners:
  – PKC412 causes a decrease in IM PK levels
  – IM causes an increase in PKC412 levels

• There is evidence of preliminary clinical activity of the combination of PKC412 and IM in IM-resistant GIST

• The trial is ongoing

Imatinib mesylate and Everolimus combination therapy in Imatinib mesylate–resistant GIST

- Phase I/II study: imatinib mesylate 600 mg/d + everolimus 20 mg/wk
- $^{18}$FDG-PET flares following interruption of imatinib mesylate
- 1 patient achieved SD for >10 months
- Study is being continued with everolimus dosed at 2.5 – 5 mg/d
- 6 of 18 patients (30%) demonstrated DFS $\geq$ 4 months (including 1 confirmed and one contestable PR) as well as 2 additional patients with some evidence of SD*.

Sunitinib malate (SU011248) therapy in Imatinib mesylate–resistant GIST: Results from the Phase III trial

• 312 patients have been accrued in 56 sites in US, Australia, Europe and Asia
  – Stratified for primary vs. secondary resistance and intolerance
  – 2:1 randomization (207:105 patients)
• Unblinded after first planned interim analysis
• PR 8% vs. 0%
• SD 58% vs. 50%
• 59 patients crossed over (10% response)
• Median TTP 6.3 vs. 1.5 months (HR 0.335, \( P<0.00001 \))