Original article

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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

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On behalf of the GIST consensus meeting panelists†

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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

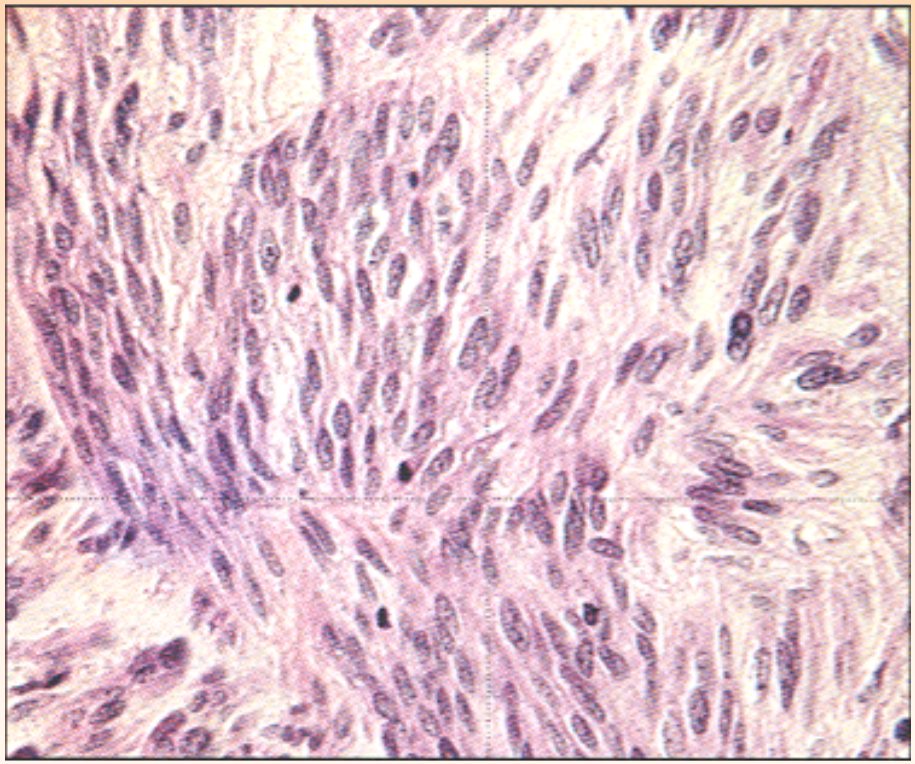
- Category 1: uniform consensus based on high-level evidence
- Category 2A: uniform consensus based on lower-level evidence
- Category 2B: non-uniform consensus (but no major disagreement) based on lower-lever evidence including clinical experience
- Category 3: major disagreement

Histological criteria

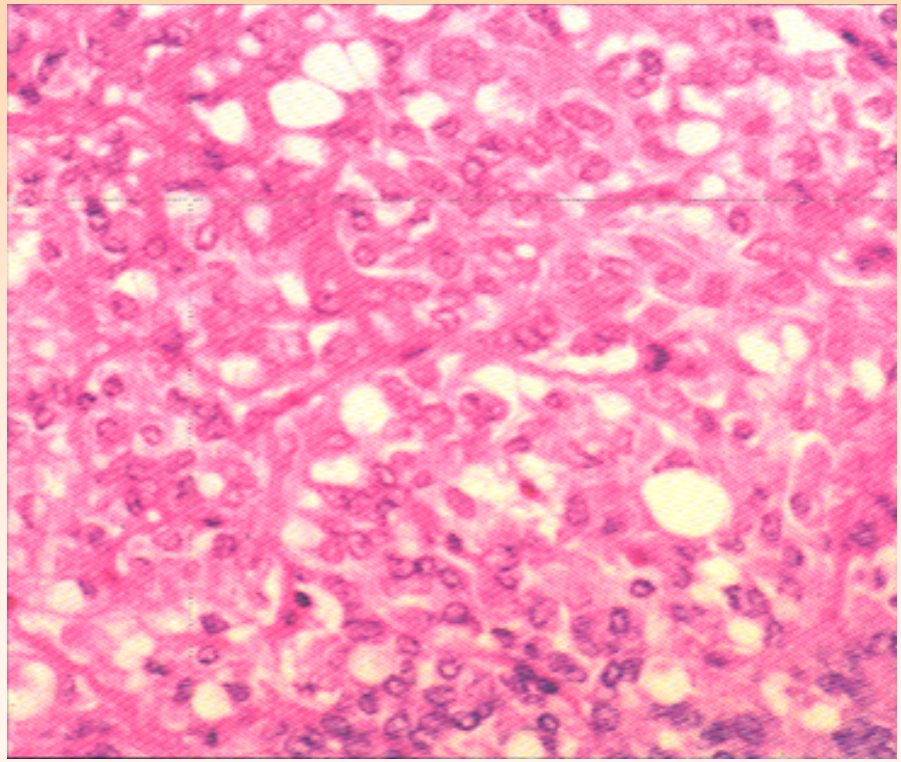
- standard histological examination with central review by an expert in sarcoma pathology (B2, 2A)
- immunohistological analysis with
  - CD117, CD34, SMA, S100, Desmin (B2, 2A)
  - no antigen retrieval
- risk assessment by size and mitotic index (B2, 2A)

Major morphologic patterns

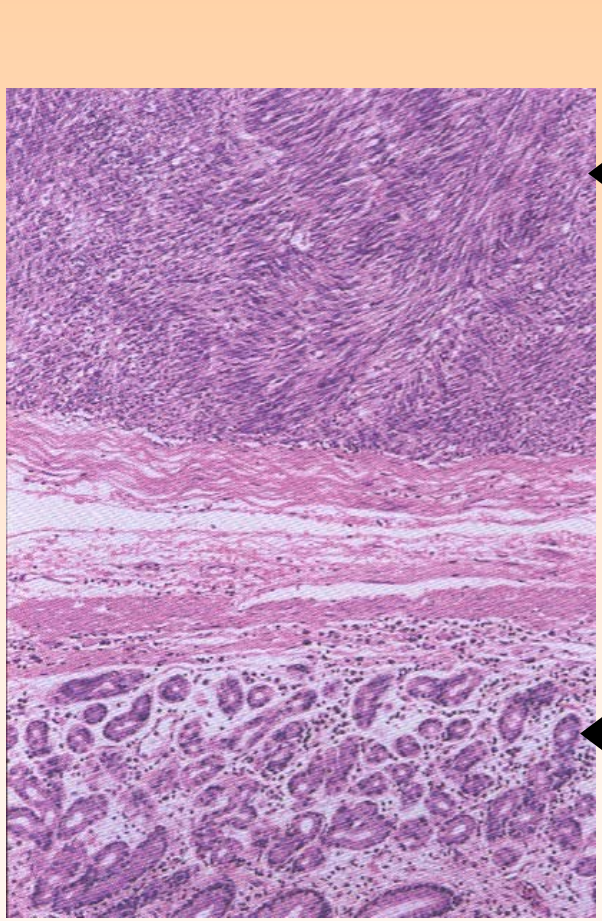
Spindle-Shaped



Epithelioid

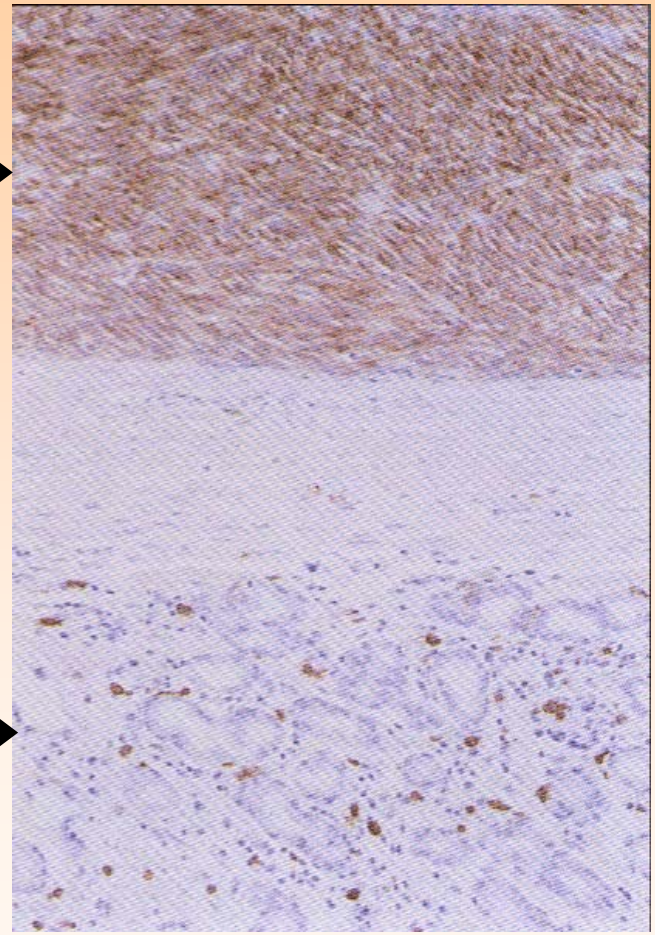


KIT staining in tissue



GIST

Normal
small intestine



H&E

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.

Heinrich et al. ASCO, 2005. Abstract 7.

*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

Mutational analysis:	Median overall survival
KIT exon 9 mutation	31 months
KIT exon 11 mutation	5 months

Demetri et al. ASCO, 2004. Abstract 3001.
Maki et al. ASCO, 2005. Abstract 9011.

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 prefered 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
  - safety data: Dematteo et al. ASCO, 2005. Abstract 9009.
- 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 surgey 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*

Le Cesne et al. ASCO, 2005. Abstract 9031.

****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

# patients	23*	25#
Op. after response to imatinib	16	19
Recurrence with cont. Imatinib	0/11	0/16
Recurrence w/o cont. Imatinib	3/5	2/3
Salvage	7	6
Progression	4/7	6/6

Continuation of imatinib is mandatory

Surgery in progressive disease not supported

*Rutkowski et al. ASCO, 2005. Abstract 9037.

#Gronchi et al. ASCO, 2005. Abstract 9038.

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

EORTC 62005*

- 133 patients crossed over to 800 mg
- Response: 2.5% PR, 30.3% SD
- PFS: median 81 days, 18% at 1 year

S0033†

- 77 patients crossed over to 800 mg
- Response: 7% PR, 32% SD
- PFS: median 4 months

Zalcberg et al. ASCO, 2004. Abstract 9004.

†Rankin et al. ASCO, 2004. Abstract 9005.

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

Reichardt et al. ASCO, 2005. Abstract 3016.

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 ≥4 months (including 1 confirmed and one contestable PR) as well as 2 additional patients with some evidence of SD*.

van Oosterom et al. ASCO, 2004. Abstract 3002.
*van Oosterom et al. ASCO, 2005. Abstract 9033.

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 planed 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, $P<0.00001$)

Demetri et al. ASCO, 2005. Abstract 4000.