

# Proposte per un percorso diagnostico, terapeutico e assistenziale di Rete per i GIST

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clinical practice guidelines

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## **Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up**

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On behalf of the ESMO/CONTICANET/EUROBONET Consensus Panel of Experts\*

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# Situazione 1: Mini GIST

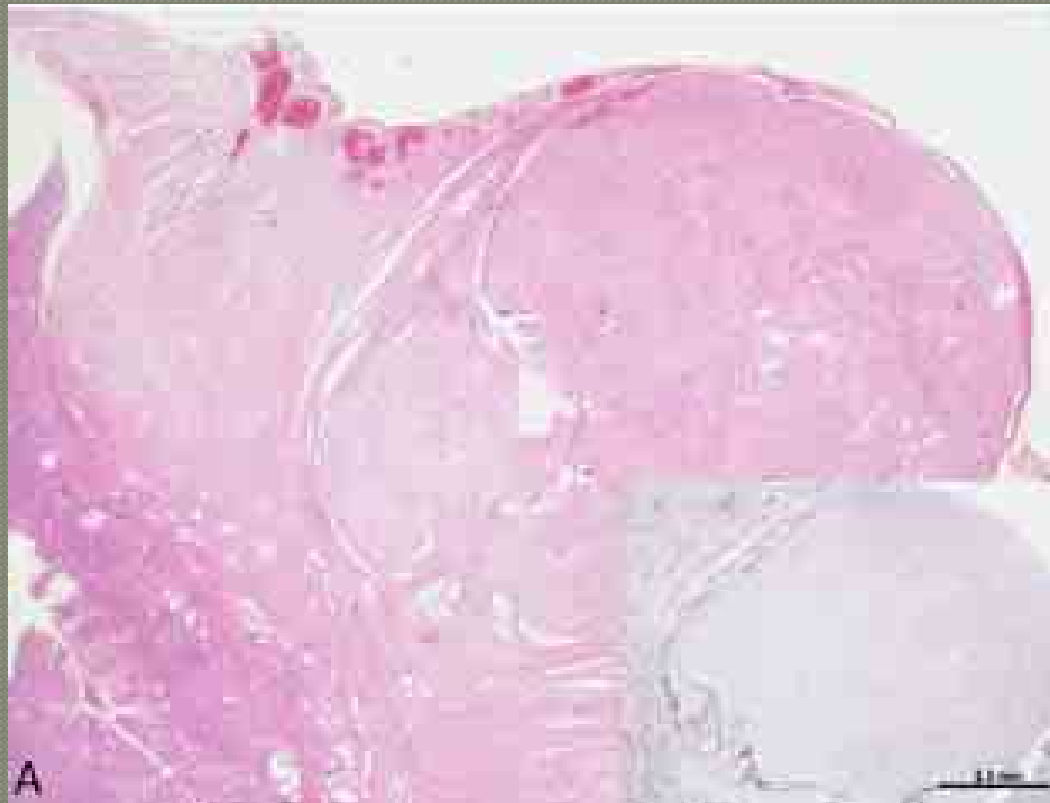


FIGURE 1. A, A case of 0.8-cm microGIST, which was incidentally found in a gastric specimen resected for a gastric adenocarcinoma. The neoplastic glands infiltrated the gastric wall, surrounding the microGIST (A), as highlighted by the

# Mini GIST

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- GIST di dimensioni da 2 mm a 2 cm
- Interessano il 15% della popolazione
- Sono visti e diagnosticati esclusivamente dai GEL
- Non si conosce esattamente la loro storia naturale. Sono benigni o maligni?
- **LG ESMO: Follow up**

# Proposta di Rete Oncologica

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- Coinvolgere le GEL per conoscere la reale incidenza
- Follow up secondo linee guida per definire l'evoluzione
- Coinvolgere Istologie e Biologie Molecolari per correlare l'eventuale evoluzione con la comparsa di nuove mutazioni.

## Situazione 2 :GIST >2 cm non metastatico . Clinica e LG

Asintomatico

Biopsia

Chirurgia

Sintomatico  
(sanguinamento)

Superare la  
situazione di  
emergenza

Biopsia  
Chirurgia

# Linee Guida ESMO

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- Biopsia della lesione
- Intervento in elezione, non in urgenza
- Interventi limitati ( non multiviscerale, non linfadenectomie)
- La rottura del GIST è evento prognosticamente molto sfavorevole
- Diagnosi istologica esatta
- Mutazioni(?)



# GIST > 2 cm sintomatico

ID. No. : ■  
Sex: Age:  
D. O. Birth:

Name:

07/03/2003  
23:40:27

CVP:  
D. F:  
Ex: M

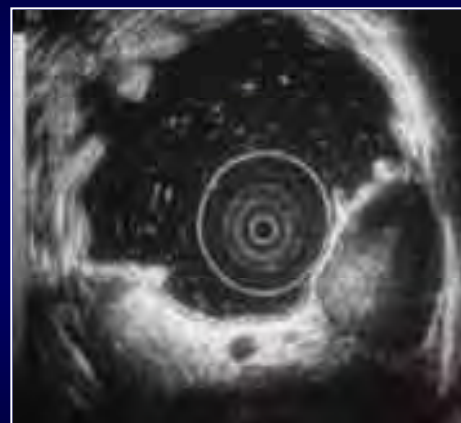
Physician  
Comment:





# GIST > 2 cm asintomatico





# Proposta di Rete Oncologica

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- Numero interventi d'urgenza /anno  
( indicatore < 10% ; nel 2005 era 18%)
- Numero di biopsie preintervento  
(indicatore : prossimo a 100%).
- Numero di interventi allargati ( ad ex  
gastrectomie radicali) .
- Rottura intraoperatoria del GIST
- Numero di diagnosi sottoposte a seconda  
valutazione. Determinazione delle  
mutazione

# Situazione 3: terapia adiuvante

## Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial



Ronald P DeMatteo, Karla V Ballman, Cristina R Antonescu, Robert G Maki, Peter W T Pisters, George D Demetri, Martin E Blackstein, Charles D Blanke, Margaret von Mehren, Murray F Brennan, Shreyaskumar Patel, Martin D McCarter, Jonathan A Pollock, Benjamin R Tur, Kouros Owzar, on behalf of the American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team

### Summary

**Background** Gastrointestinal stromal tumour is the most common sarcoma of the intestinal tract. Imatinib mesylate is a small molecule that inhibits activation of the KIT and platelet-derived growth factor receptor  $\alpha$  (PDGFR- $\alpha$ ) and is

Lancet 2009; 373: 1097-104

## SSGXVIII: Study Design

An Open-Label Phase III Study



Joensuu H, et al. J Clin Oncol. 2011;29(suppl): Abstract LBA1.

### Studio USA

**Chirurgia → R**

**(Pubblicato Lancet 2009 PFS)**

**Imatinib x 1 aa**

**Placebo**

### Studio EORTC

**Chirurgia → R**

**(Chiuso. OS- TSR )**

**Imatinib x 2 aa**

**Controllo**

### Studio SSG-G

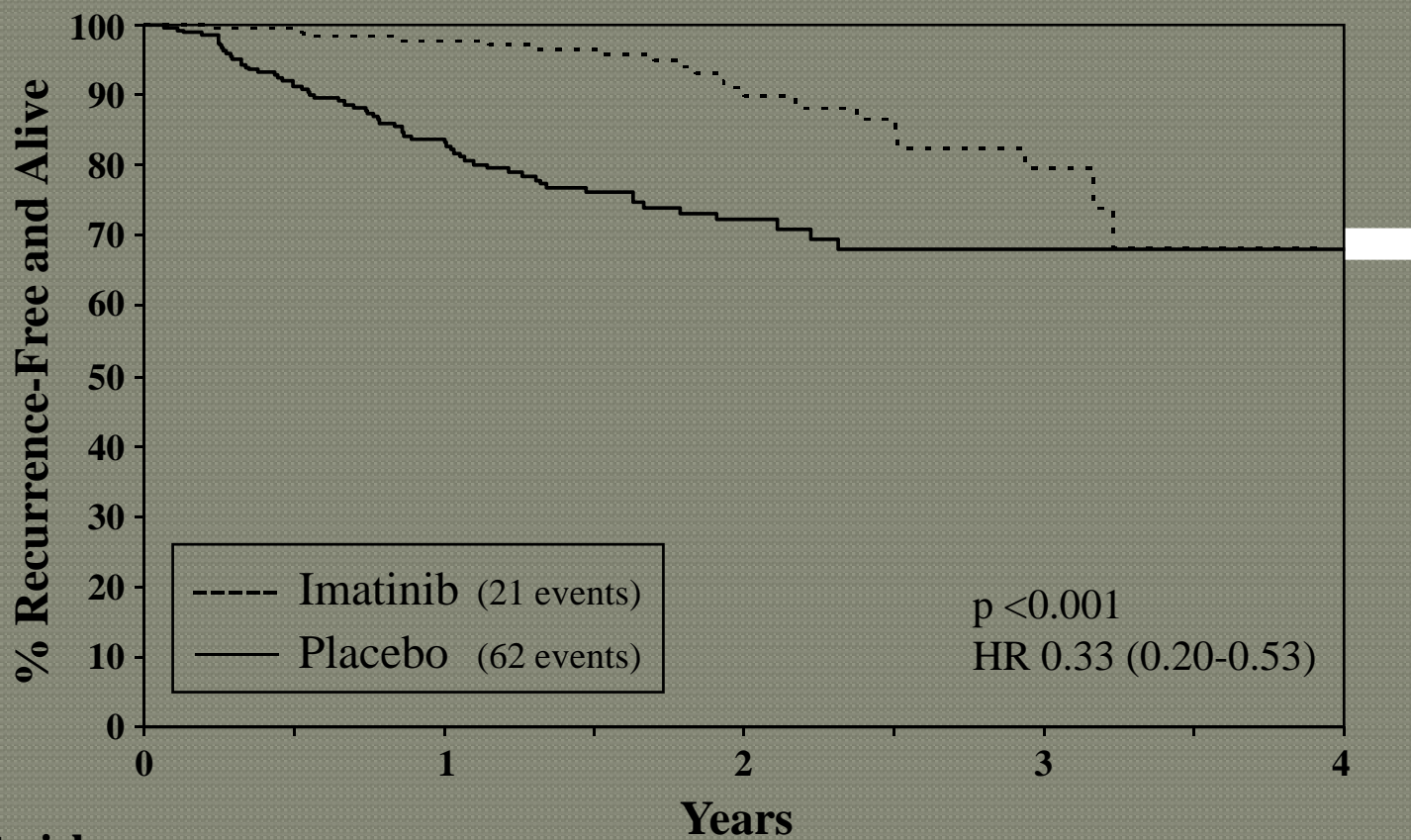
**Chirurgia → R**

**( Presentato ASCO 2011 PFS )**

**Imatinib x 3 aa**

**Imatinib x 1 aa**

# ACOSOG Z 9001 RFS

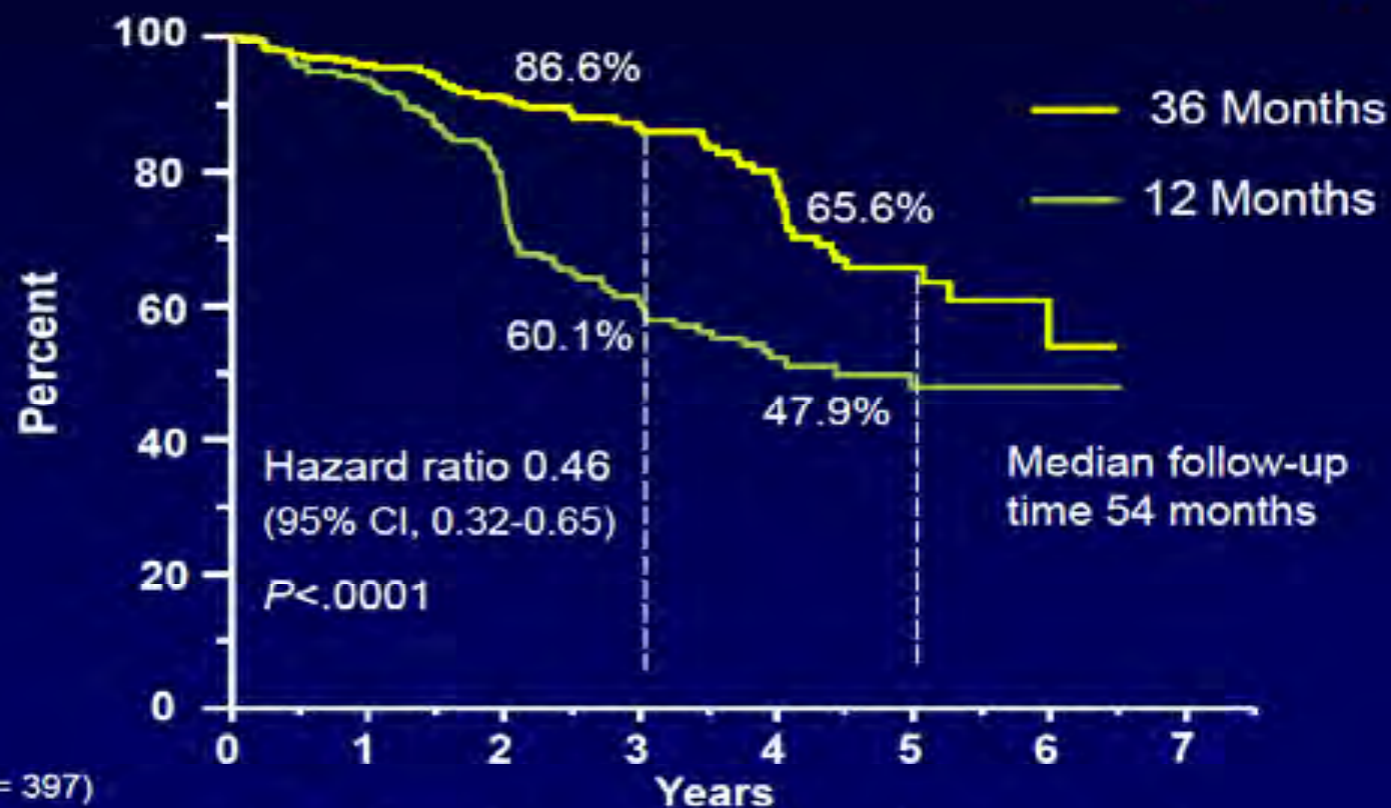


## At risk:

Imatinib	325	177	80	24
Placebo	319	170	73	23



## SSGXVIII: Recurrence-Free Survival (ITT)



No. at risk (n = 397)

36 Months of imatinib	198	184	173	133	82	39	8	0
12 Months of imatinib	199	177	137	88	49	27	10	0

Joensuu H, et al. *J Clin Oncol*. 2011;29(suppl): Abstract LBA1.



# Terapia Adjuvante LG ESMO

**Glivec®** EU  
**(Imatinib)**

Indicated for the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive GIST<sup>1</sup>

**Gleevec®** US  
**(Imatinib)**

Indicated for the adjuvant treatment of adult patients following resection of KIT (CD117)-positive GIST<sup>2</sup>

EU, European Union; US, United States

# Proposta di Rete Oncologica

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- ◉ Univocità sulla classificazione del rischio ( Miettinen)
- ◉ Univocità sul decision making della terapia adiuvante. ( rischio intermedio)
- ◉ Durata della terapia nell'alto rischio

## Situazione 4: malattia metastatica all' esordio

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# Malattia metastatica: LG ESMO

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- Biopsia, determinazione del genotipo
- Dose iniziale Imatinib 400 mg /die
- Esone 9 Imatinib 800 mg/die
- Il problema dei GIST wild type
- La valutazione della risposta
- La terapia neoadiuvante
- I lungo sopravvissuti (BRF 14)
- La seconda linea con Sunitinib
- La terza linea

# TAKE HOME MESSAGE: TERAPIA E GENOTIPO

## MUTAZIONE

- KIT esone 11
- KIT esone 9
- KIT eson 13 K642E
- KIT esone 17
- PDGFRA 12 e 14
- PDGFRA 18 D842V
- WT adulto
- WT pediatrico

## Prima

## Seconda linea

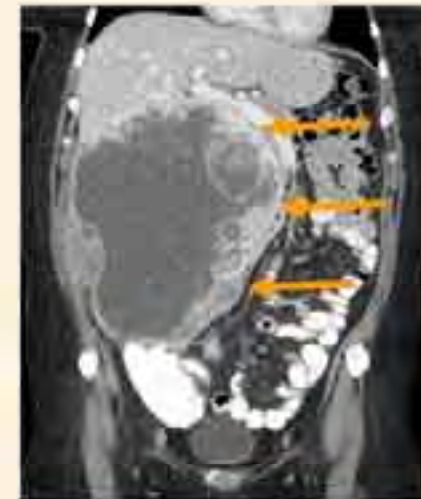
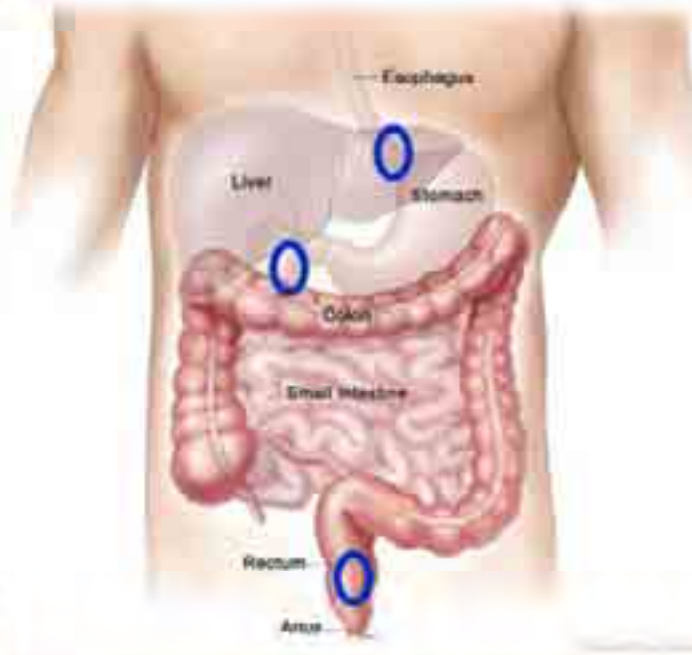
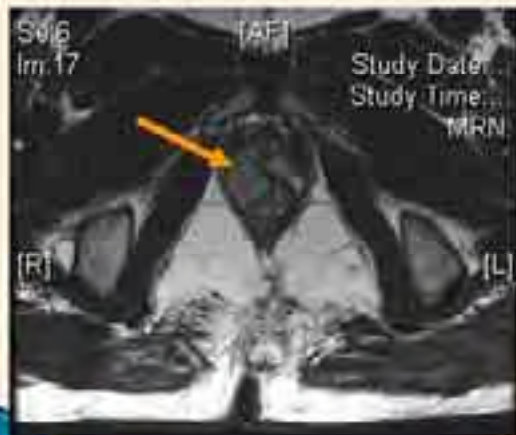
- |                       |           |
|-----------------------|-----------|
| ● IM 400 mg           | Sunitinib |
| ● <b>IM 800 mg</b>    | Sunitinib |
| ● IM 400mg            | Sunitinib |
| ● IM 400 mg           | Sunitinib |
| ● IM 400 mg           | Sunitinib |
| ● <b>Dasatinib(?)</b> | ?         |
| ● IM 400              | Sunitinib |
| ● <b>Sunitinib</b>    | ?         |

# REPORTED ACTIVITY

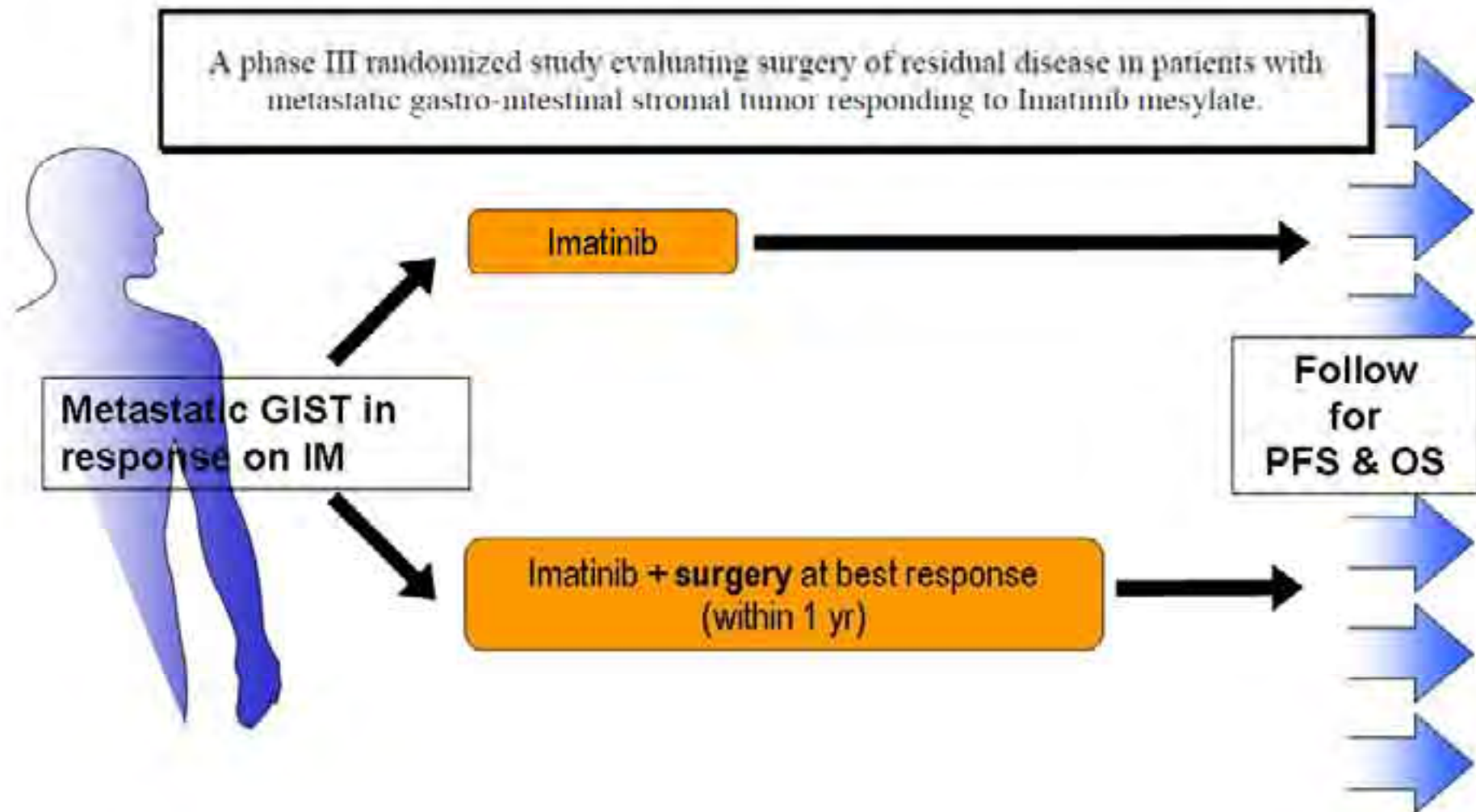
DRUG	PR	SD	PFS mo	OS mo
NILOTINIB	3%	32%	3	8
NILOTINIB	3%	23%	4	10
DASATINIB	8%	30%	2	19
REGORAFENB	9%	82%	10	NS
SORAFENIB	12%	56%	5	12
SORAFENIB	10%	54%	5	10



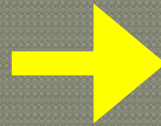
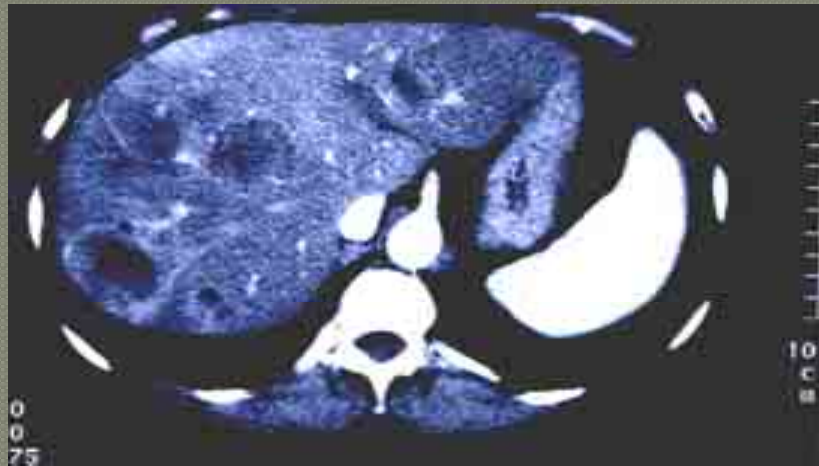
# When to Consider Neoadjuvant Therapy

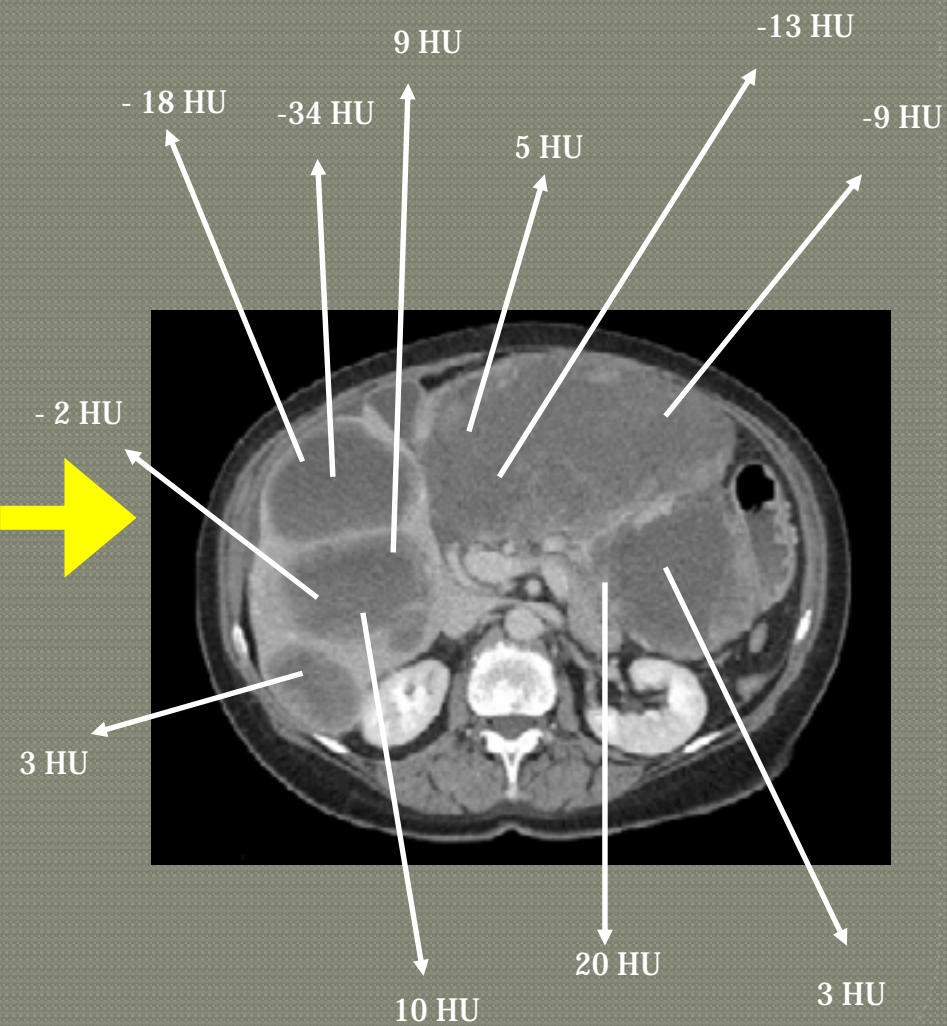
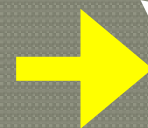
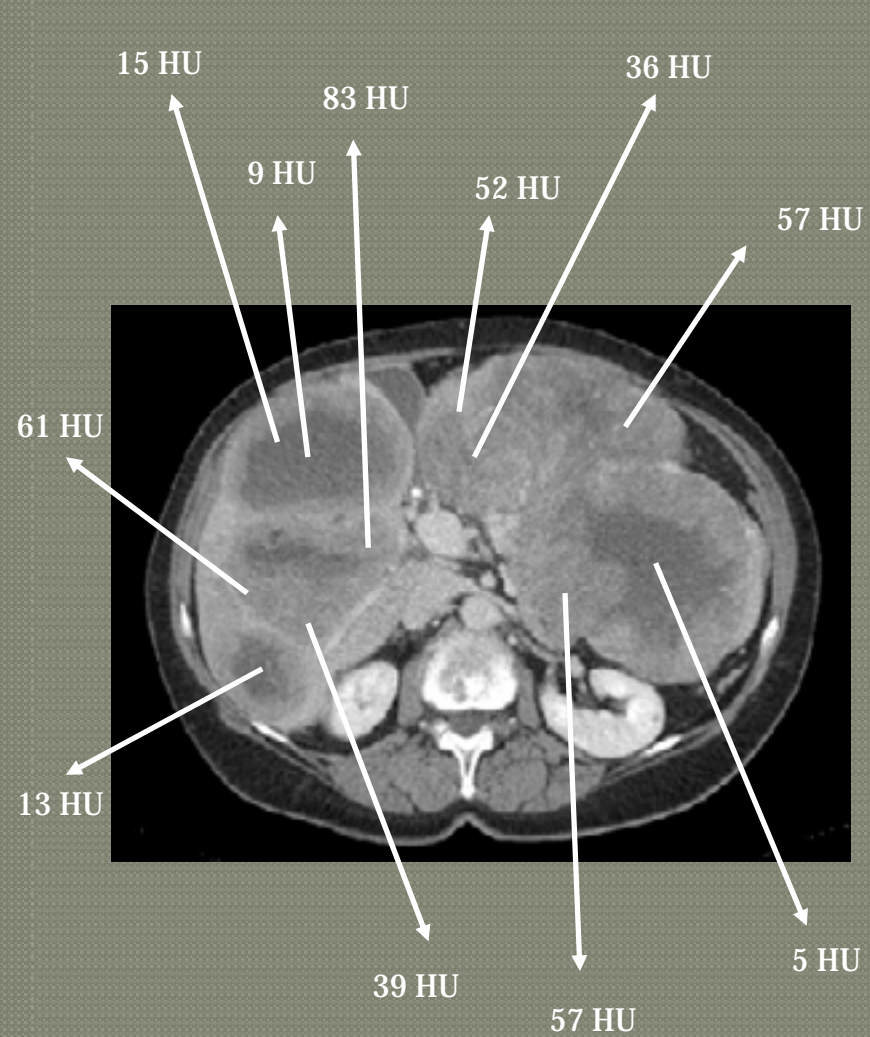






# GIST: risposta non volumetrica

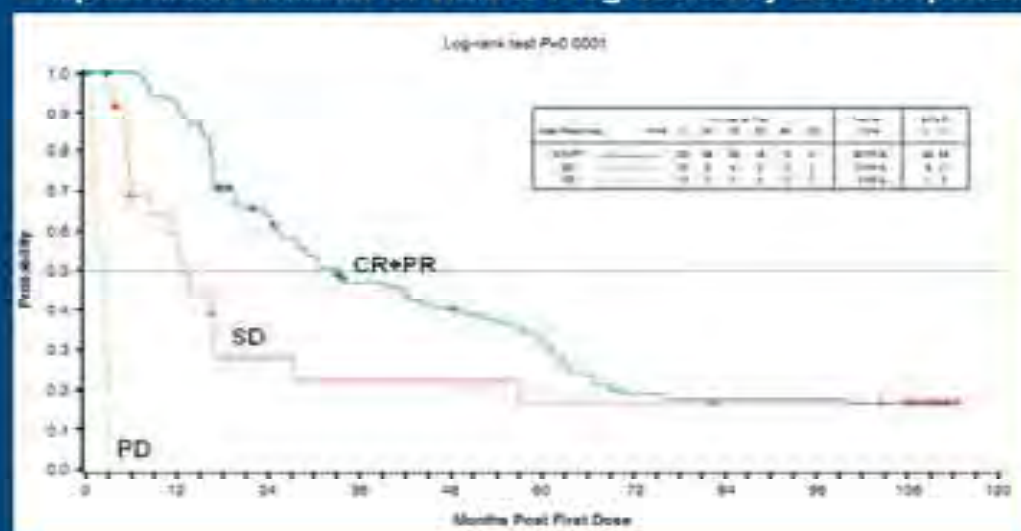




## Results

- PFS at 9 yrs was similar for patients with CR/PR (16%) or SD (17%) as best overall SWOG response

### Kaplan-Meier Estimate of Time to Progression by Best Response



YOUNG, S. M., J. A. HARRIS, and J. L. HARRIS. 1990. 100

PRESENTED AT: **ASCO** Annual '11 Meeting

# Proposta di Rete Oncologica

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- Accordo con SIAPEC per mutazioni
- Choi o RECIST ? Tavolo aperto con i Radiologi
- I lungo sopravvissuti
- I protocolli di terza linea (Portale di Rete)

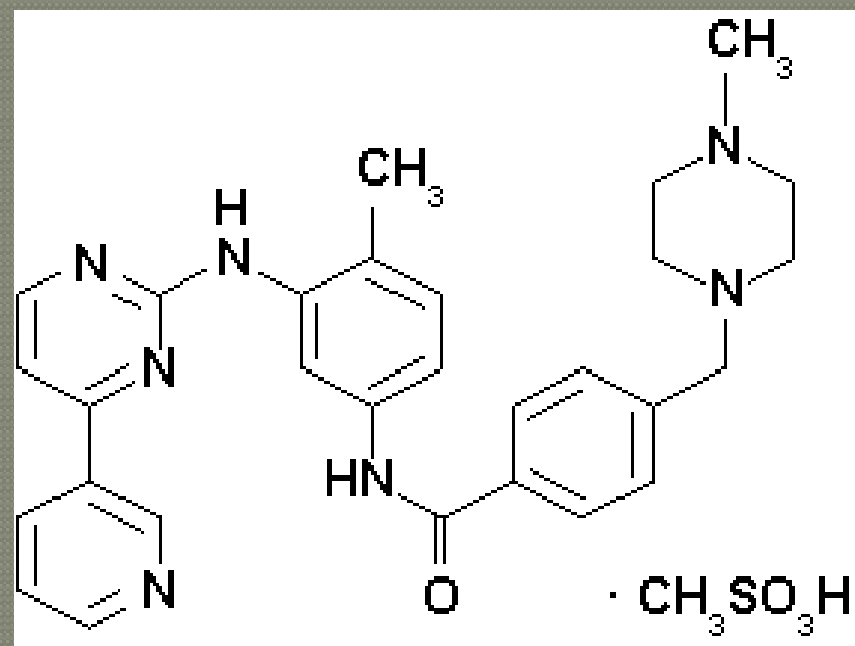


# Protocollo DOVIGIST

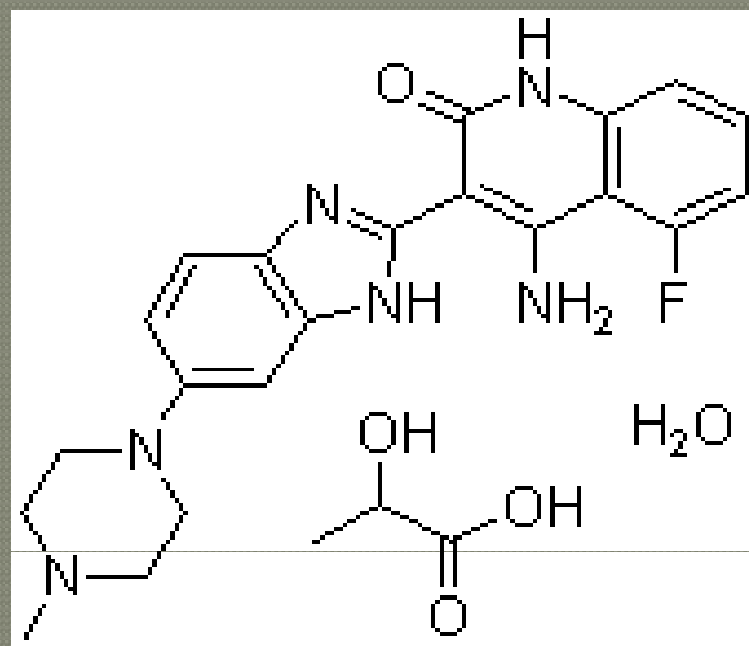
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- Protocollo sperimentale di Fase 2 non randomizzato
- Pazienti con GIST metastatico in progressione dopo Imatinib 800
- Pazienti con GIST metastatico con intolleranza a Imatinib
- Pazienti con GIST in ricaduta dopo Imatinib adiuvante < 12 mesi prima

# Imatinib



# Dovitinib





# DoviGIST : Study Design

Pilot exploratory **open-label, non-randomized phase II**  
international study (15 sites in Europe)

## Pts Population

Pts with advanced  
and/or metastatic GIST  
Intolerant to imatinib

Pts with advanced  
and/or metastatic GIST  
Refractory to imatinib

Surgically removed  
localized GIST recurrent  
on adjuvant imatinib or  
recurrent within the first  
3 months after  
discontinuation

## Treatment Phase

Dovitinib 500 mg/ 5days on-2days off

Treatment continues  
until:

- Disease progression
- Unacceptable toxicity
- Death
- Discontinuation from any other reason

Dose of Imatinib: maximum tolerated dose (800mg/d)

## Disegno dello studio ed end points

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- Paziente con GIST metastatico resistente a Imatinib
- Non pretrattato con Sunitinib
- DOVITINIB 500 mg dal lunedì al venerdì fino a PD o tossicità
- End points: PFS, OS, RR ( Choi)  
Tossicità

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Grazie

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