



X Seminario I.T.M.O.

NEOPLASIE A BASSA INCIDENZA

***GIST: Caso clinico  
esplicativo  
sul mantenimento***



**Istituto  
di Oncologia**

Istituto di Ricovero e Cura ad Alta Specializzazione

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Monza, 7 Maggio 2012

# *Presentazione clinica*

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**M.G.** Pz 60 aa Sesso: M PS (ECOG) 0

## **Comorbidità:**

- NIDDM
- Cardiopatia ischemica in buon compenso (FE 57%)
- IA in trattamento farmacologico

05/01 Comparsa di algie addominali diffuse

**Ecografia addome:** “...in sede meso-ipogastrica si osserva lesione solida ipoecogena di 9x5 cm.”

**TC addome con mdc:** “... in regione ipogastrica si rileva formazione bilobata indovata tra le anse del tenue, senza chiari piani di clivaggio. Tale formazione presenta pareti proprie, di spessore omogeneo e a contenuto denso.”

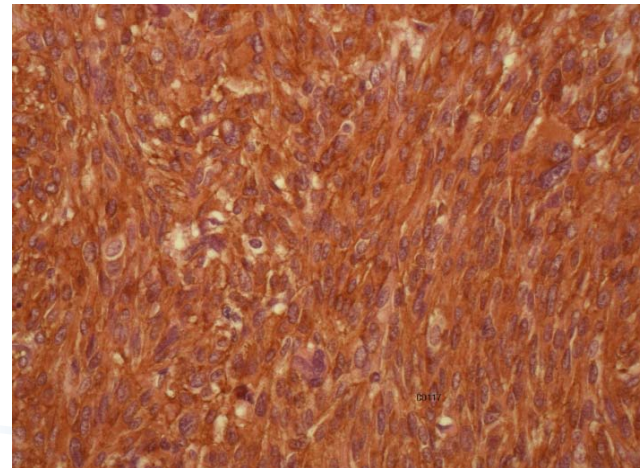
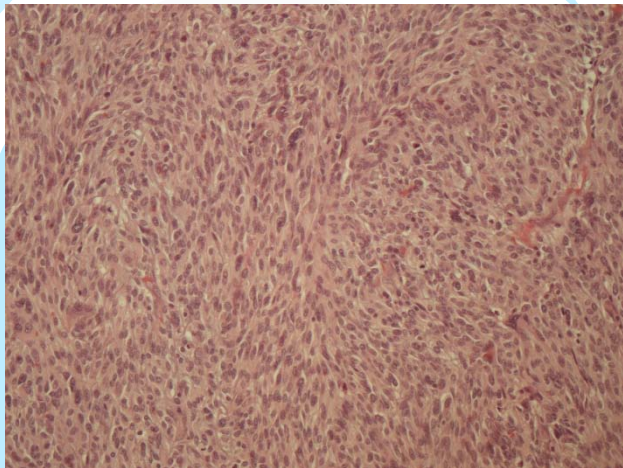
# *Diagnosi e stadiazione*

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06/01 Intervento chirurgico di resezione segmentaria ileale

**Descrizione macroscopica:** tratto di ileo di 9 cm da cui emerge a sviluppo estrinseco massa capsulata di 11x5x4 cm

**Esame istologico:** Tumore stromale gastrointestinale  
12 mitosi/50 HPF CD117+ CD34+/-



# Risk Stratification: Miettinen Table

	Size (cm)	Mitotic Index per 50 HPF	Site of Primary Tumour			
			Gastric	Jejunal/Ileal	Duodenal	Rectal
1	≤2	≤5	0 none	0 none	0 none	0 none
2	>2 ≤5	≤5	1.9% very low	4.3% low	8.3% low	8.5% low
3a	>5 ≤10	≤5	3.6% low	24% moderate		
3b	>10	≤5	12% moderate	52% high	34% high*	57% high*
4	≤2	>5	0 <sup>^</sup>	50% high <sup>^</sup>	†	54% high
5	>2 ≤5	>5	16% moderate	73% high	50% high	52% high
6a	>5 ≤10	>5	55% high	85% high		
6b	>10	>5	86% high	90% high	86% high*	71% high*

\*Groups 3a and 3b or 6a and 6b are combined in duodenal and rectal GISTs because of small number of cases

<sup>^</sup>Denotes tumour categories with very small numbers of cases

†No tumours of such category were included in the study. Note that small intestinal and other intestinal GISTs show a markedly worse prognosis in many mitosis and size categories than gastric GIST

# *Follow up*

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11/06 Politrauma da incidente stradale per cui viene sottoposto a plurimi interventi chirurgici ortopedici

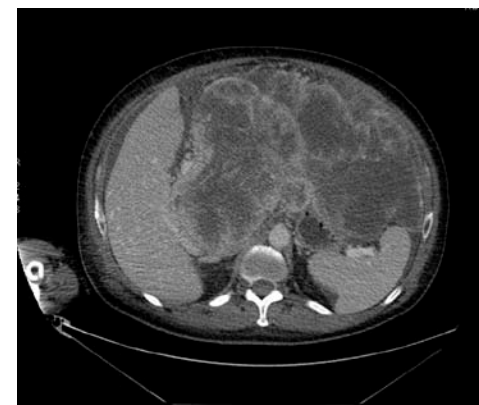
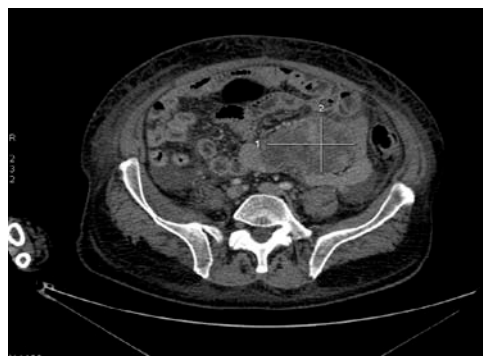
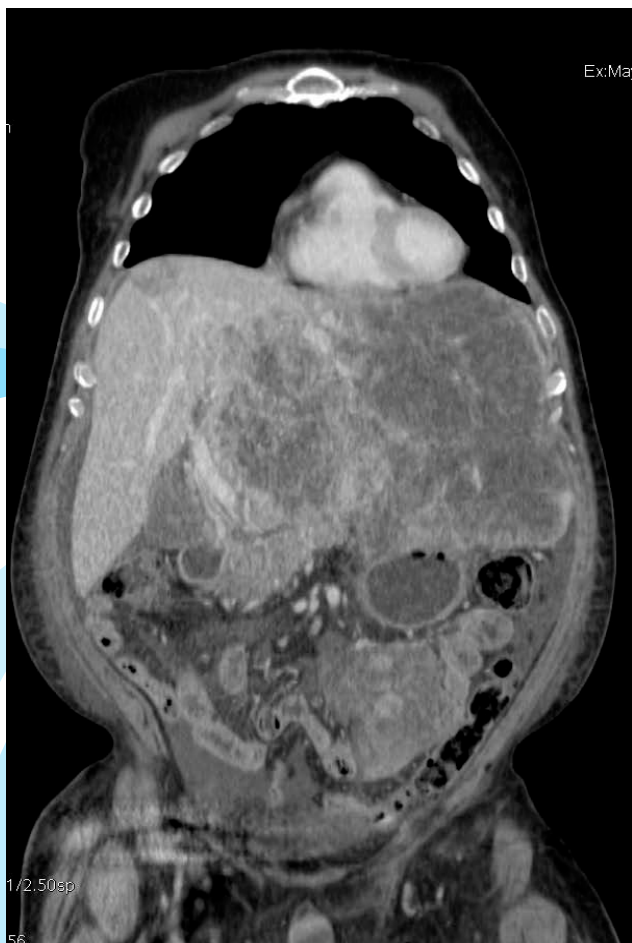
12/07 Ricovero per ultimo intervento ortopedico.

Evidenza TC :

“... voluminosa massa di oltre 25 cm a livello dei quadranti addominali superiori ... altra massa di 8 cm tra le anse in emiscavo pelvico sinistro. Nodulazione di 3 cm a livello della cupola epatica.

Versamento ascitico diffuso ai quadranti superiori, ipocondrio sinistro e scavo pelvico...”

*Dicembre 2007*



# *Decorso clinico*

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03/01/2008 Agobiopsia massa addominale

Esame istologico: recidiva da GIST.

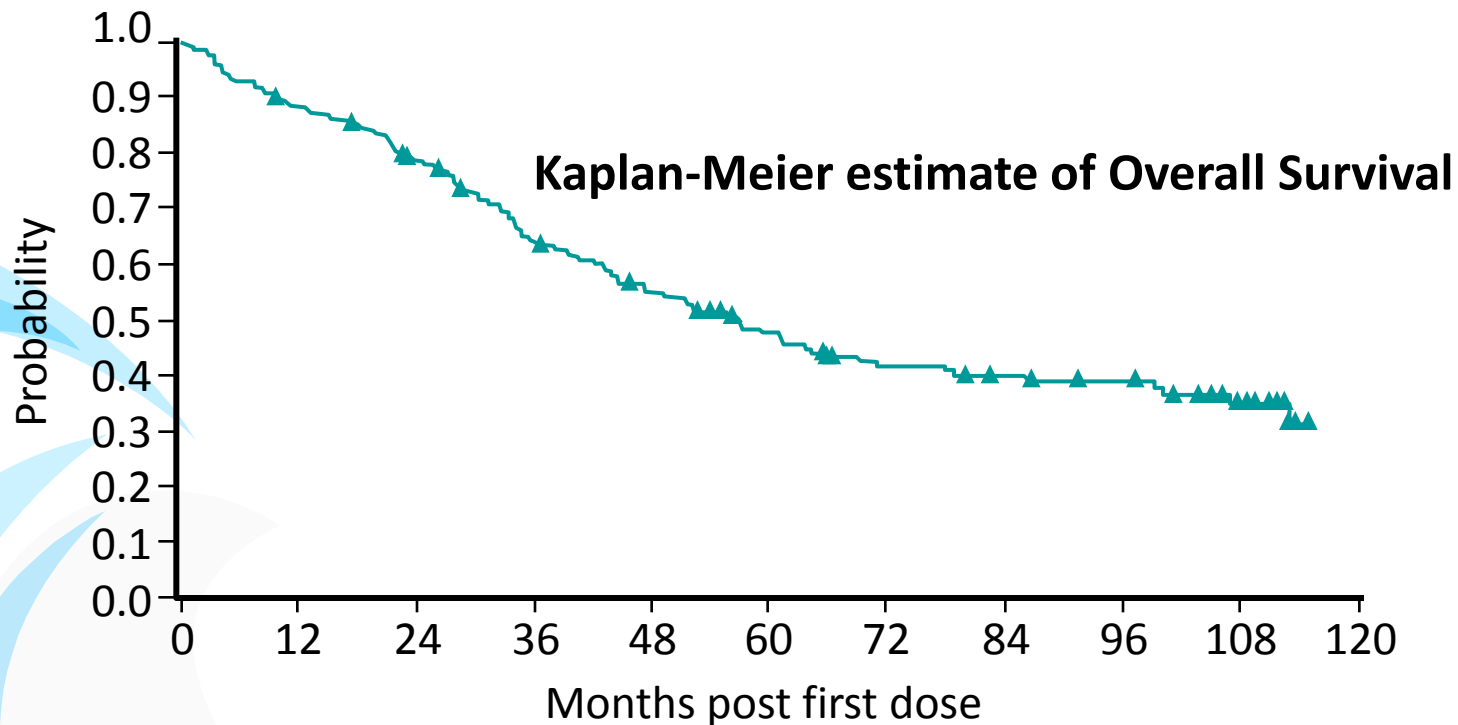
**Analisi mutazionale c-KIT e PDGFR $\alpha$ :**

**Del 558-559 dell'esone 11 del gene c-KIT.**

**INIZIA TERAPIA CON IMATINIB DOSE STANDARD  
(400 MG/DIE)**

# B2222 Trial: 9 years of Imatinib in patients with KIT+ GIST

*An open label, randomised, multicenter phase II clinical trial (n=147)*

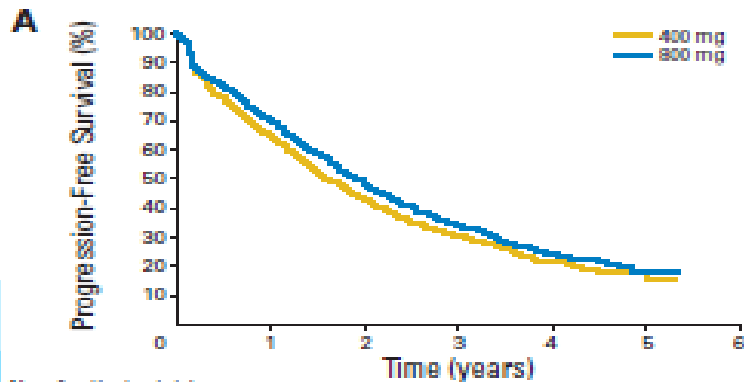


- As of May 26, 2010 a total of 89 patients (60.5%) have died
- The estimated 9-year overall survival rate was 35%



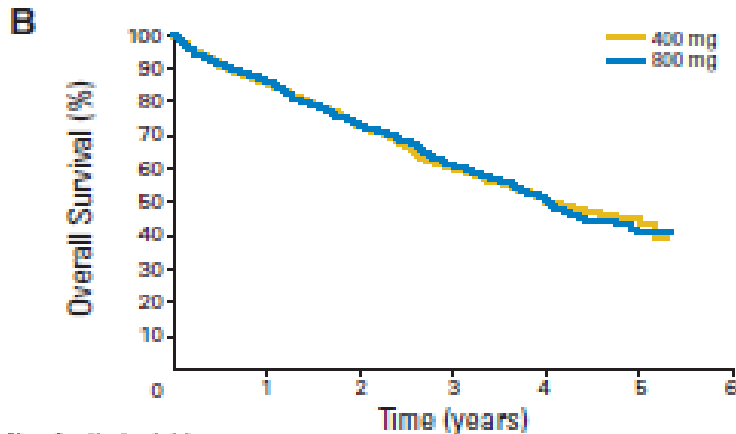
# MetaGIST: a meta-analysis of 1,640 patients

## Comparison of two doses of Imatinib



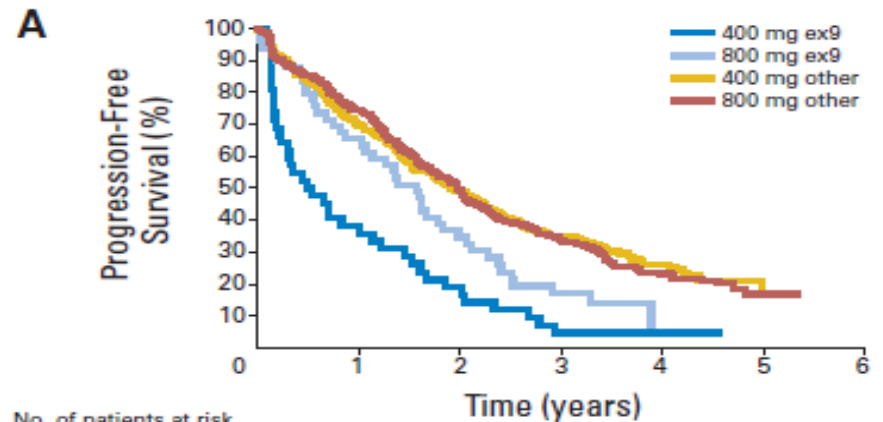
No. of patients at risk

Dose	0	N	1	2	3	4	5
400 mg	510	818	520	333	219	62	7
800 mg	591	822	572	374	247	74	11



No. of patients at risk

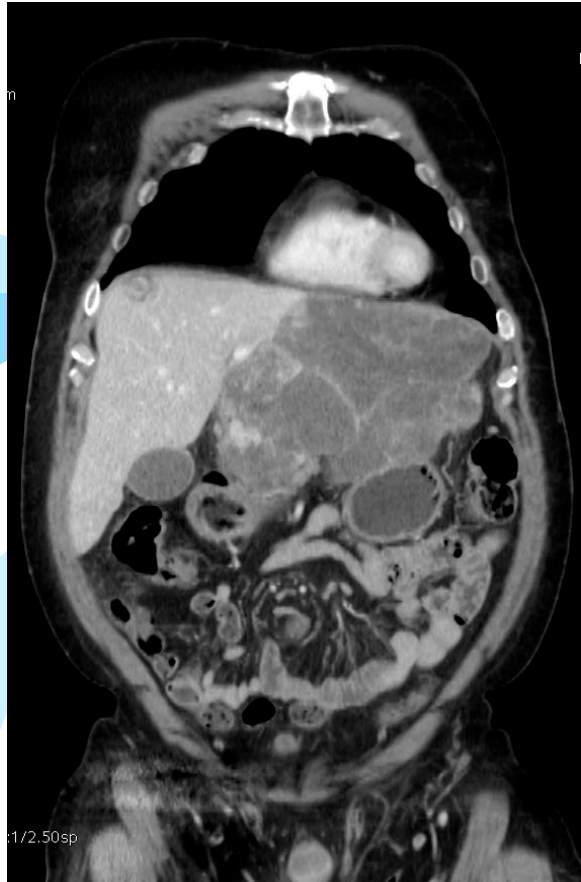
Dose	0	N	1	2	3	4	5
400 mg	376	818	602	561	436	162	20
800 mg	379	822	704	558	427	157	25



No. of patients at risk

	0	N	1	2	3	4	5
400 mg ex9	40	42	16	8	2	1	0
800 mg ex9	42	49	32	16	8	0	0
400 mg other	247	341	237	161	110	41	4
800 mg other	253	340	252	162	105	38	8

# *...dopo 6 mesi...Giugno 2008*



# Response Evaluation Criteria

Response	Definition
CR	Disappearance of all lesions No new lesions
PR	A decrease in size* of $\geq 10\%$ or a decrease in tumor density (HU) $\geq 15\%$ on CT No new lesions No obvious progression of nonmeasurable disease
SD	Does not meet the criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression
PD	An increase in tumor size of $\geq 10\%$ and does not meet criteria of PR by tumor density (HU) on CT New lesions New intratumoral nodules or increase in the size of the existing intratumoral nodules

Abbreviations: CR, complete response; PR, partial response; HU, Hounsfield unit; CT, computed tomography; SD, stable disease; PD, progression of disease; RECIST, Response Evaluation Criteria in Solid Tumors.

\*The sum of longest diameters of target lesions as defined in RECIST.<sup>10</sup>

# *Valutazione della risposta*

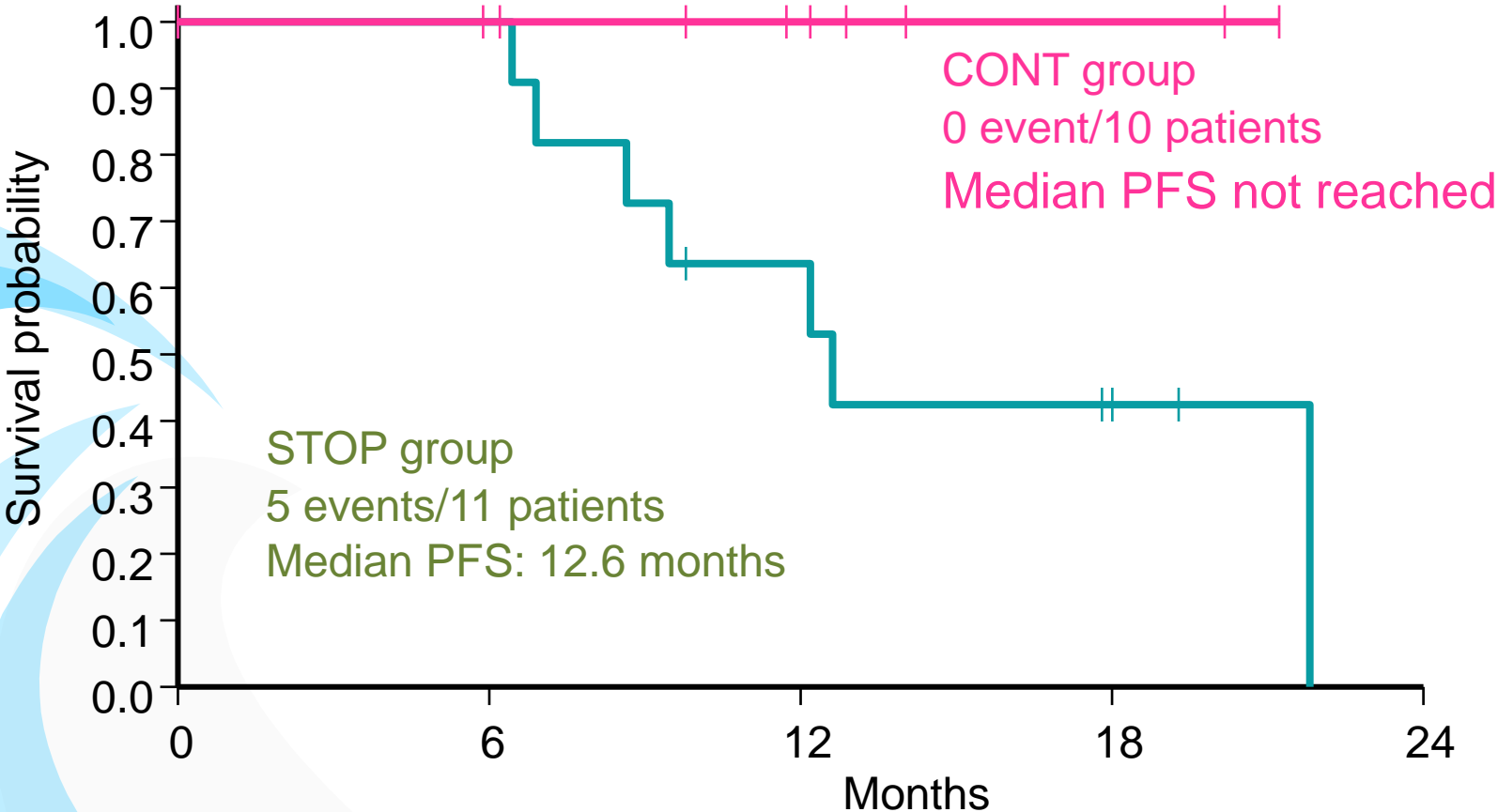
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*Prosegue terapia con Imatinib con sostanziale stabilità di malattia per circa 18 mesi.*

# BFR14 Trial: Comparing Interruption vs Continuation of Imatinib Therapy at 5 years of Treatment

*A prospective, randomised phase III clinical trial*



- Median follow-up: 11.9 months

# *Decorso clinico*

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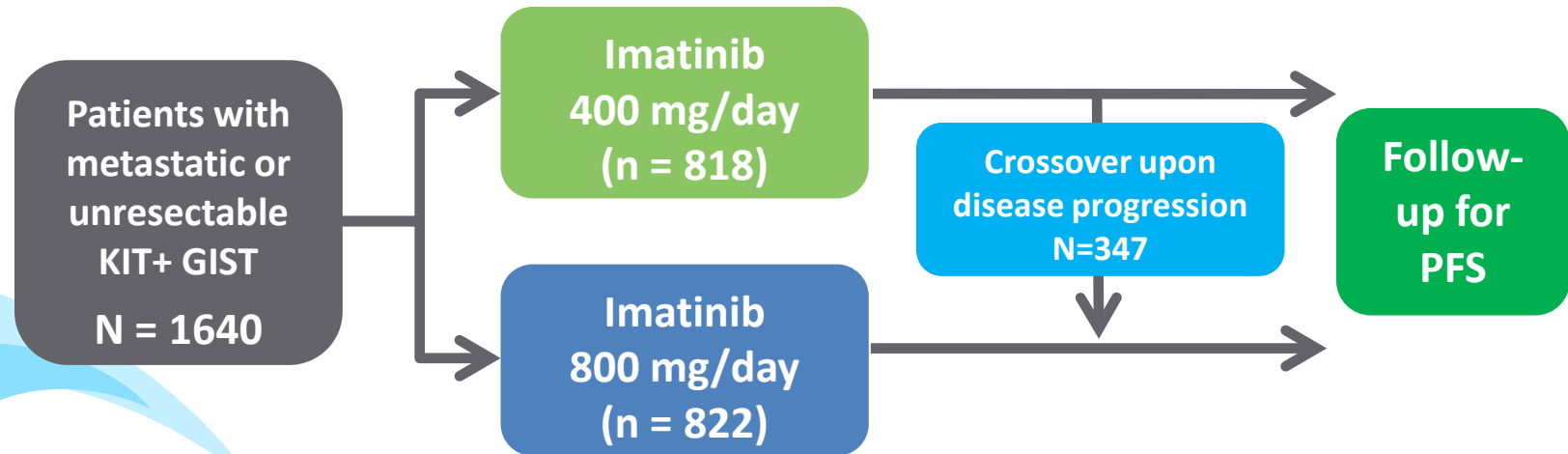
01/08-02/11 Trattamento con Imatinib 400 mg/die

02/11 TC T+A con e senza mdc:

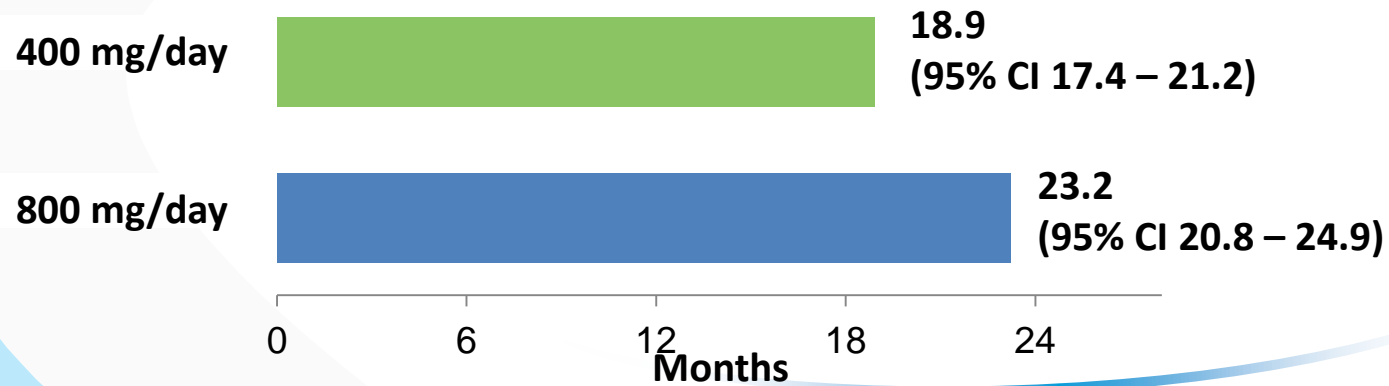
“...voluminosa massa espansiva infiltrante il lobo sinistro del fegato (IV, I segmento e ilo epatico), apparentemente non clivabile dalla vena sovraepatica media e cava intraepatica. Nodulo di 25 mm dell’VIII segmento epatico. Multiple nodulazioni peritoneali del diam. MAX di 50 mm”.

***Quale II linea di trattamento?***

# Phase III studies with Imatinib compared Starting dose and the value of Dose Escalation



Progression-Free Survival

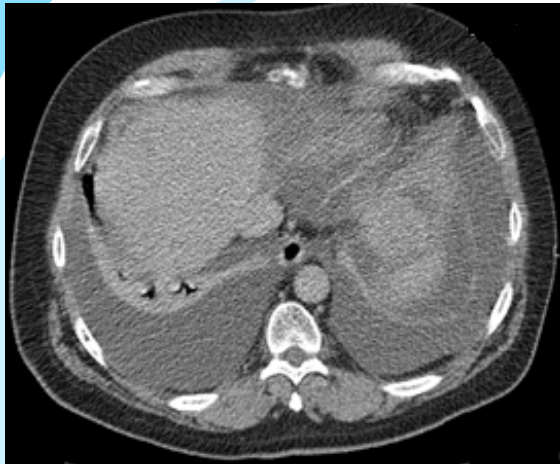


# *Decorso clinico*

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03/11-08/11 Trattamento con Imatinib 800 mg/die con sostanziale stabilità di malattia

09/11 Peggioramento clinico per comparsa di dispnea e dolori addominali diffusi





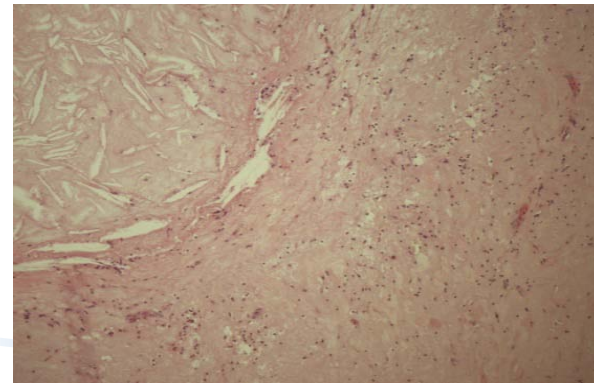
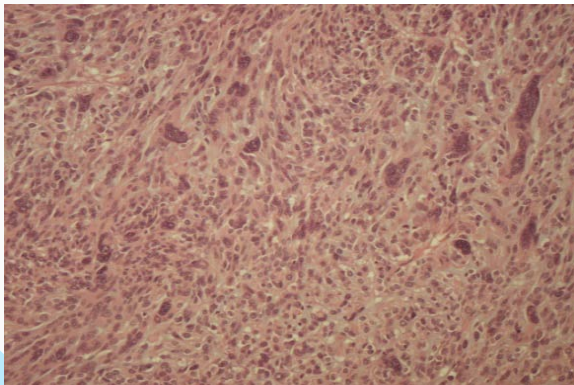
# *Settembre 2011*

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15/09/2011 Intervento chirurgico ad intento palliativo/citoriduttivo di epatectomia sinistra e omentectomia.

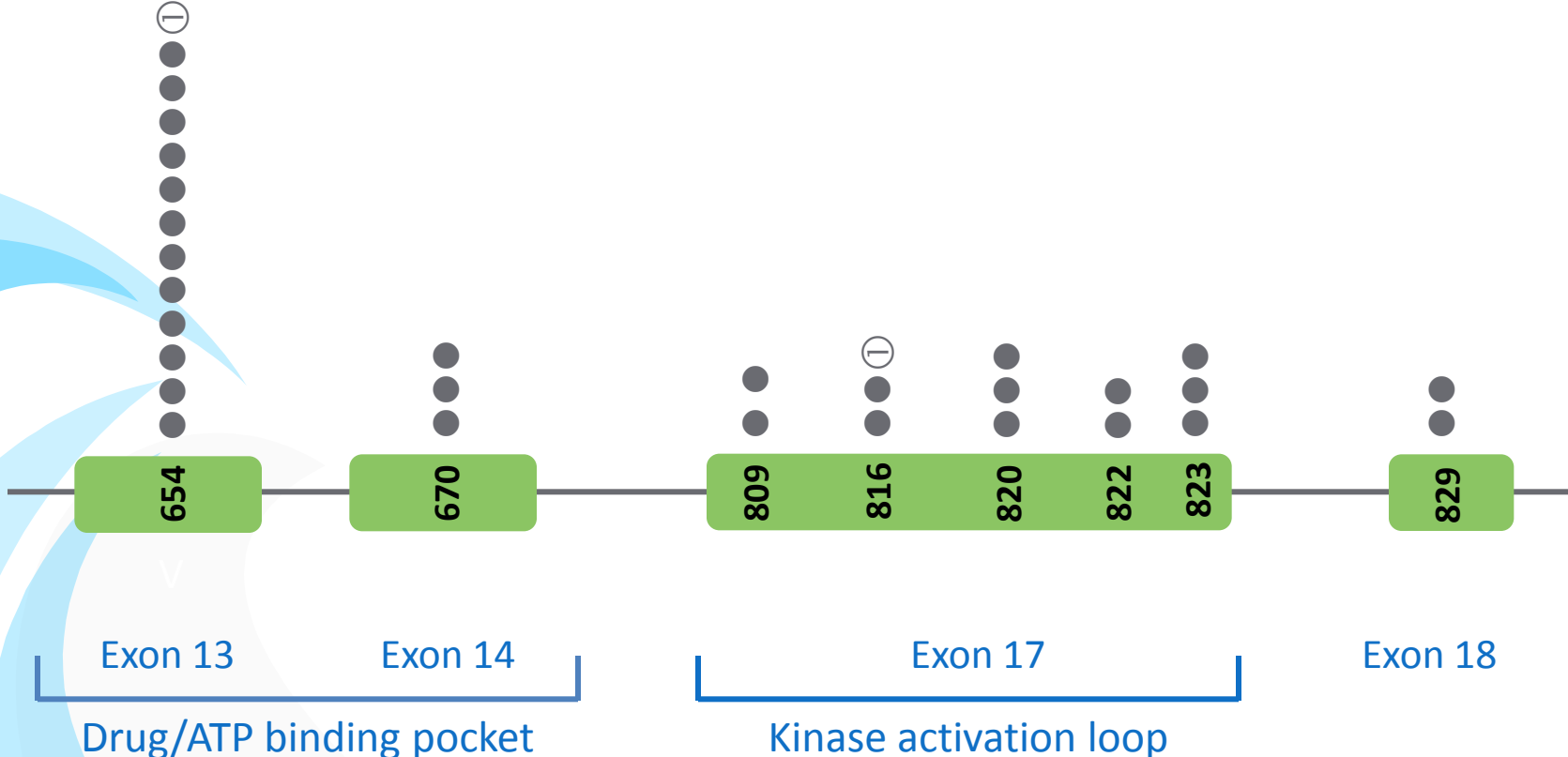
**Esame macroscopico:** tessuto epatico con estesa area necrotico-emorragica centrale con adese multiple nodularità di colorito bianco-giallastro; materiale necrotico emorragico friabilissimo, con aree mixoidi.

**Esame istologico:** metastasi da GIST.

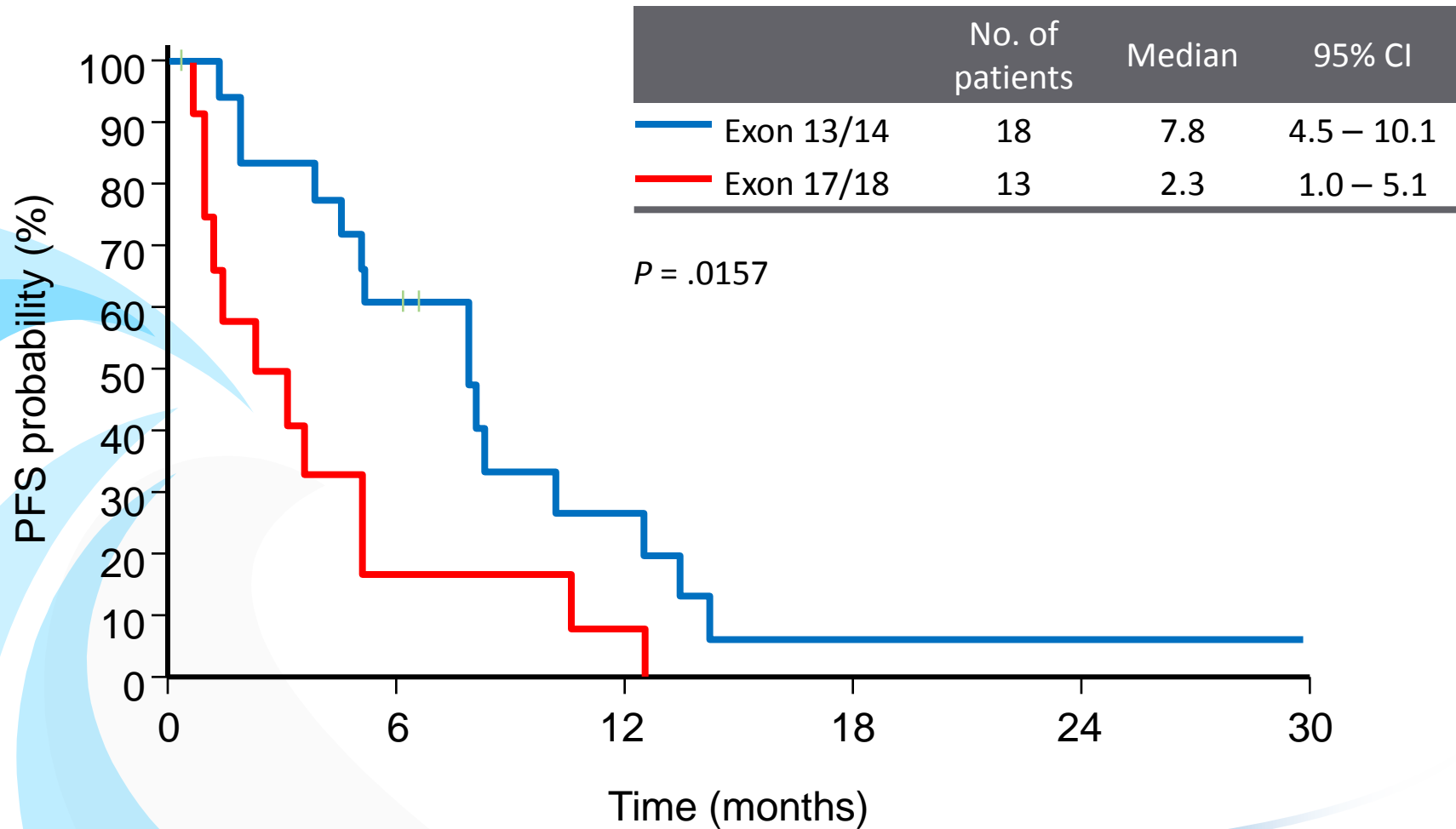


# Acquired resistance to Imatinib Therapy: Secondary KIT mutations

① V654A, D816H



# Sunitinib improves PFS in secondary KIT exon 13/14 Genotypes



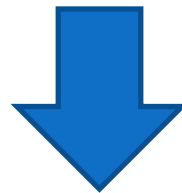
# *Novembre 2011*

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Attivazione di terapia con Sunitinib 50 mg/die per 4 sett.  
ogni 6 sett. per 1 ciclo

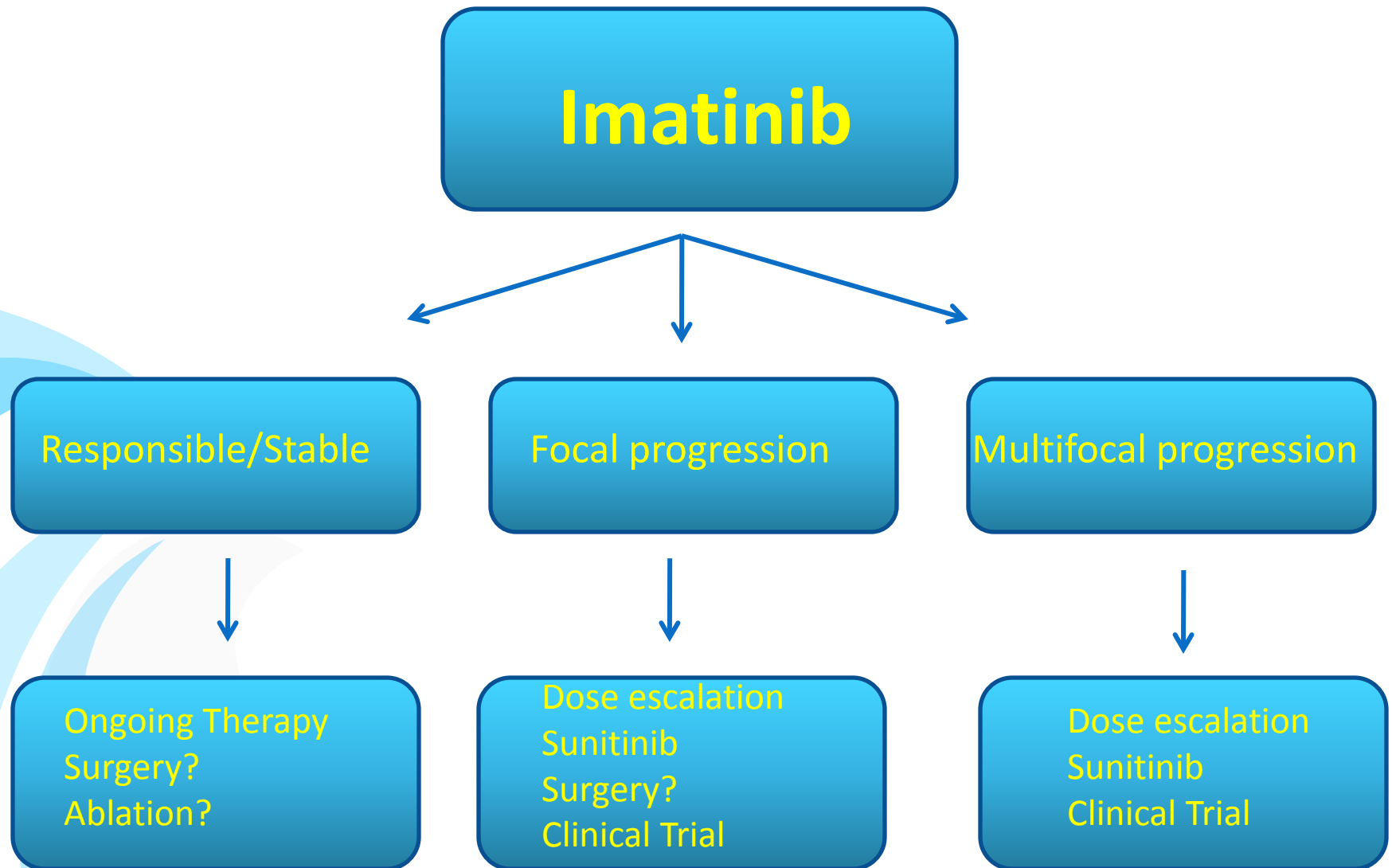


Tossicità gastrointestinale con diarrea G3  
e mucosite G2



Modifica schedula con Sunitinib 37,5 mg/die  
continuativamente tuttora in corso con SD.

# Multimodality therapy for metastatic GIST



# *“Critical points”*

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- ❖ *Primary and secondary kinase genotypes and clinical activity of TKI*
- ❖ *Intra- and interlesion heterogeneity of secondary mutations*
- ❖ *Role and timing of surgery*
- ❖ *Maintenance therapy*
  - ... to prevent a rapid tumor flare
  - ... to slow down progression
  - ... in absence of alternative treatment options





**Grazie per l'attenzione!**