GIST:
Enfermedad localizada

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GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS

Máster en Tumores Musculoesqueléticos

EPIDEMIOLOGY AND GENERAL PRINCIPLES IN GIST

- Gastrointestinal Stromal Tumors (GISTs) are the most frequent sarcoma subtype in the gastrointestinal tract
- Family of soft-tissue sarcoma, but with clinico-pathological and therapeutic differential characterisitcs
- Their incidence is around 0.4-2 new cases /100.000 inh /year *(Nilsson B, Cancer 2005; van der Graaf WTA, Br J Surg 2018).* Spain around 1.1 new cases / 100.000 inh/year *(Rubió J, Eur J Cancer 2007)*
- Diagnosis has improved in the last years, thus data from older registries is less consistent

EPIDEMIOLOGY AND GENERAL PRINCIPLES IN GIST

- Incidence in males slightly higher
- Peak around 6th decade of life (exceedingly rare in children)
- The most frequent primary location is stomach, followed by small intestine
- Arise in submucosal tissue (gut pacemaker cells; interstitial cells of Cajal)

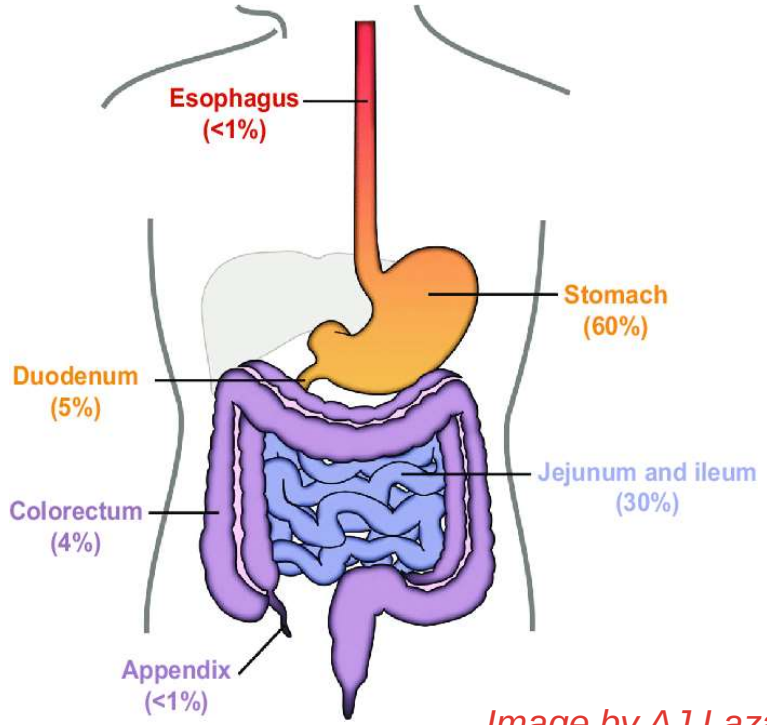
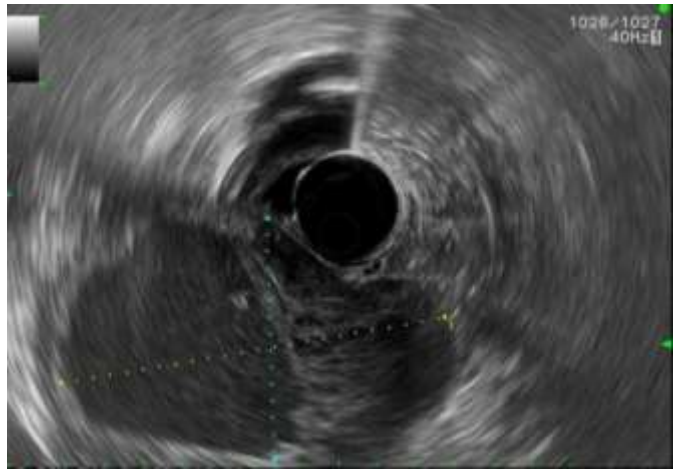


Image by AJ Lazar

DIAGNOSTIC APPROACH

- Diagnosis: endoscopic biopsy or US/CT-guided tru-cut
- In lesions very suspicious of GIST and when biopsy is not possible: excision is recommended
- In locally advanced cases (when neoadjuvant therapy is evaluated): BIOPSY is mandatory (with enough material for correct assessment of risk and molecular diagnosis)
- In advanced/metastatic debut: BIOPSY is mandatory (with enough material for molecular diagnosis)



DIAGNOSTIC APPROACH

- Based on morphology
- Immunohistochemistry (CD117, DOG1)
- Mitotic rate (in 5mm2) has to be specified, as a continuous variable (not range 0-5, > 5)

- MOLECULAR DIAGNOSIS

MANAGEMENT OF LOCALIZED DISEASE

- Discussed in MDT

- Is upfront complete surgery feasible with no comorbidities?

YES→ Surgery

- In general: laparotomy

- Selected cases: laparoscopy (discouraged in big tumors→ risk of rupture)

Preserving the integrity of the capsule is very relevant, as a rupture of the capsule during surgery implies potential peritoneal dissemination

Casali et al. ESMO guidelines Ann Oncol 2021

MANAGEMENT OF LOCALLY ADVANCED DISEASE

- Discussed in MDT

- Is upfront complete surgery feasible with no comorbidities?

  NO

- Has the tumor a sensitive mutation?

  NO→ surgery

  YES→ neoadjuvant imatinib

Casali et al. ESMO guidelines
Ann Oncol 2021

PRINCIPLES OF NEOADJUVANT THERAPY

- Complete prognosis information is needed BEFORE neoadjuvant start
- Neoadjuvant therapy only makes sense in sensitive genotypes

- INDICATIONS
  - Bulky tumors with risk of rupture during surgery
  - Tumors located in sites where surgery implies important comorbidity (gastroesophageal junction, oesophageal, rectum…) and a downstaging could facilitate a more conservative resection

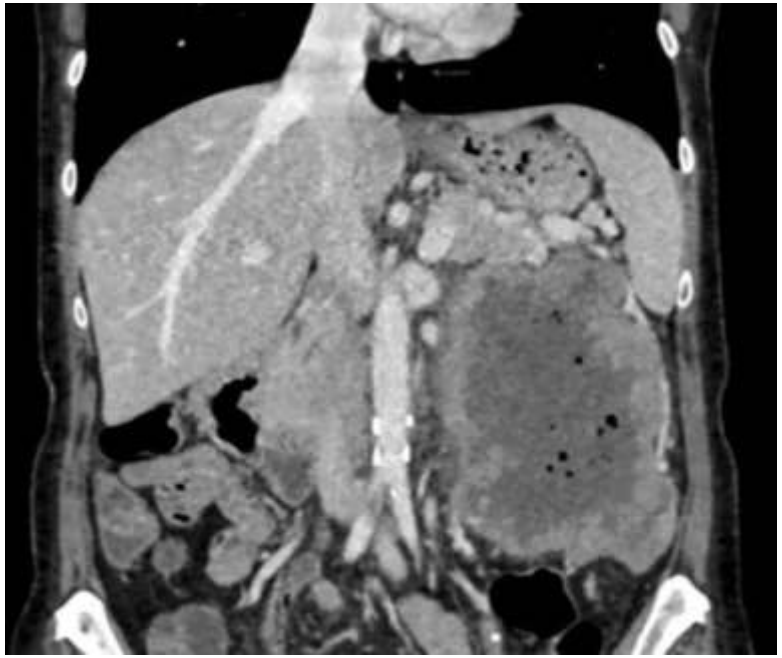
- FOLLOW-UP AND DURATION
  - An early reassessment is, in general, recommended (biphasic CT, PET)
  - Total duration 6-12 months (avoid emergence of resistance)
  - In general---> adjuvant therapy after surgery to complete 36 months

CLINICAL CASE

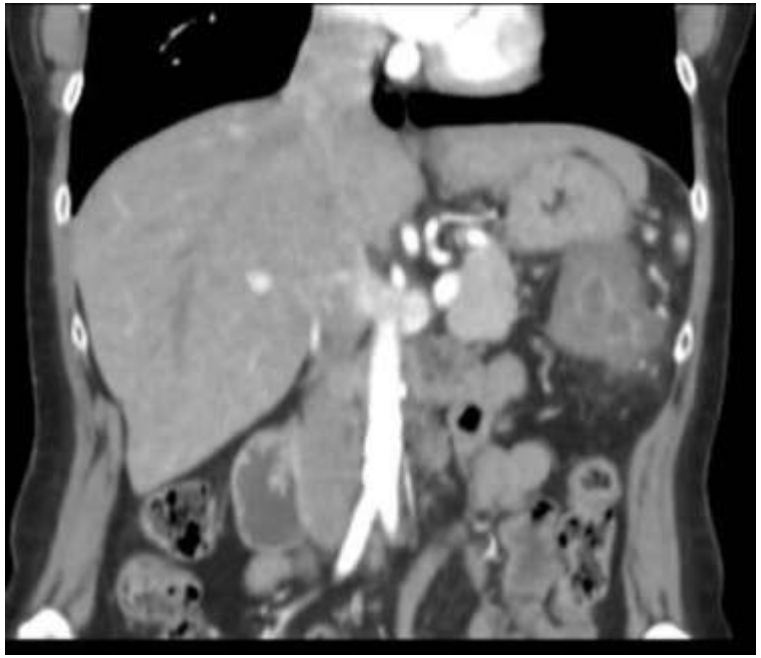
62- year-old woman, abdminal disturbances, gastric discomfort
Admission due to fever→ probable abscess of the mass→ biopsy

Locally advanced gastric GIST, 17cm, 6 mit/1.2 mm2
Exon 11 KIT mutation (del 556-558)
Neoadjuvant IM 400mg/d was started—> rapid clinical benefit

November 2021



March 2022



ADJUVANT THERAPY IN HIGH RISK GIST: EVIDENCE

- Several clinical trials have been developed

STUDY	DESIGN	PATIENTS INCLUDED	TIME OF ADJUVANT IMATINIB	PRINCIPAL OBJECTIVE	REF
ACOSOG	Imatinib 400 vs control	Low-Intermediante-high	1 year	RFS	De Matteo et al, Lancet 2009
EORTC-ISG-GEIS-FSG	Imatinib 400 vs control	Intermediate-High	2 years	OS→ IFS	Casali et al, Ann Oncol 2021
SSG-AIO	Imatinib 400 vs Imatinib 400	High- very high	1 year vs 3 years	RFS	Joensuu et al, JAMA 2012
SSG	Imatinib 400 vs Imatinib 400	High- very high	3 years vs 5 years	RFS	Ongoing

ACOSOG Z9001 study

- Patients with diagnosis of GIST
- > 3 cm
- 1 year IM vs FU
- N= 713 randomized patients
- Recruitment stopped in interim analysis

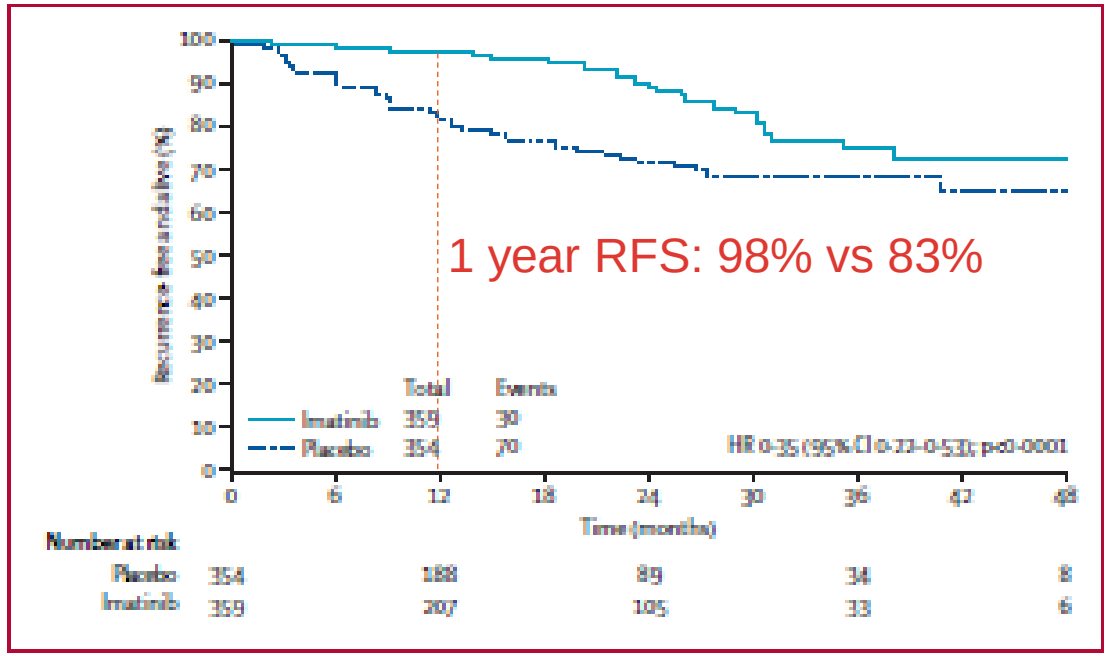


Figure 2: Recurrence-free survival

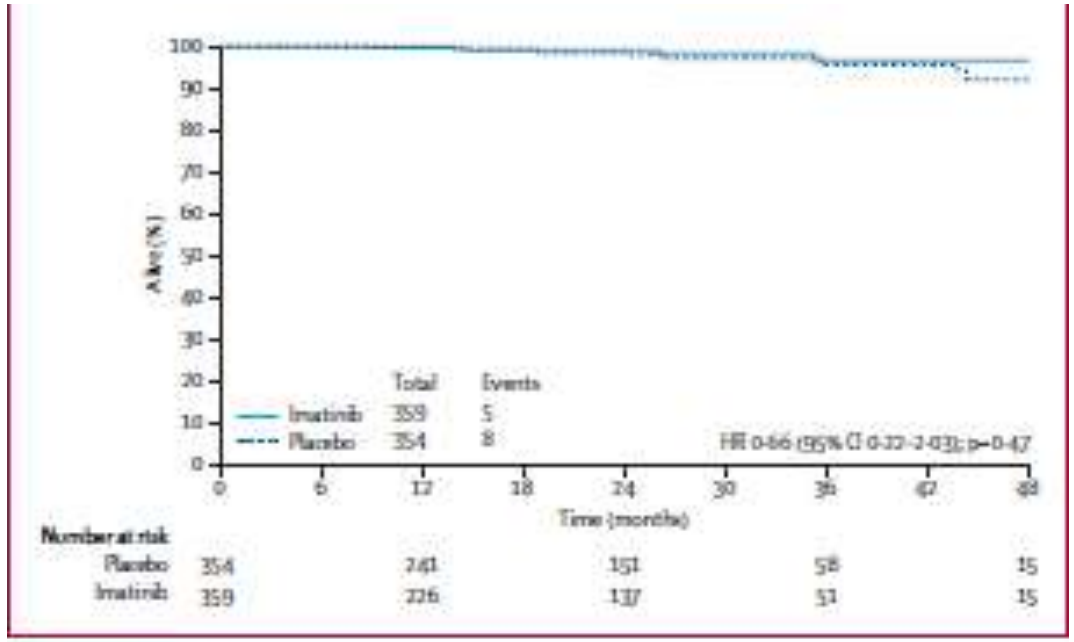


Figure 4: Overall survival

Mas DeMatteo R et al. Lancet. 2009 Mar 28;373(9669):1097-104

EORTC study

- Patients with diagnosis of GIST
- High or intermediate risk accorting to NIH classification
  - Size >10cm
  - MI> 10/50HCF
  - Size>5 and MI > 5/50HCF
  - Size< 5cm and MI 6-10/50HCF
  - Size > 5cm and MI <5/50HCF

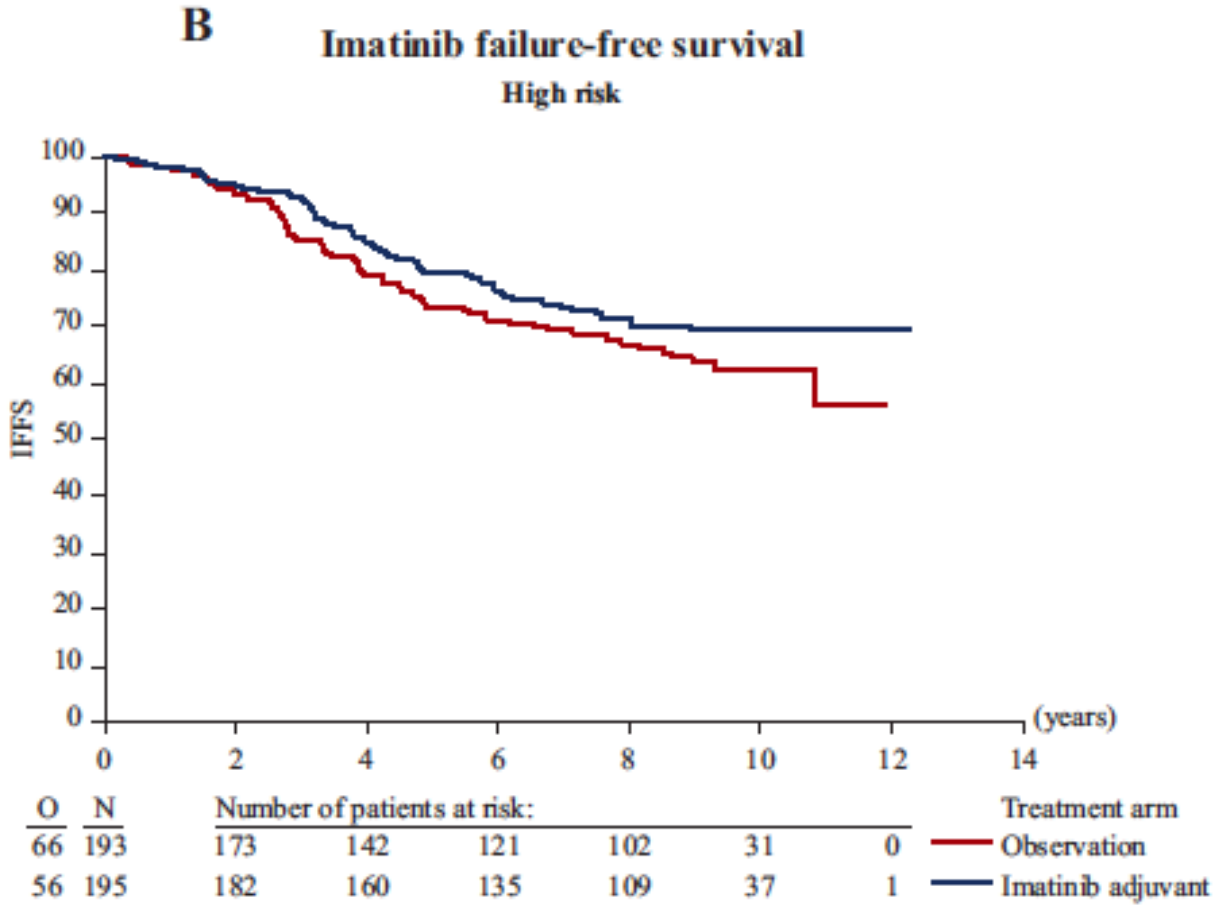
Casali et al. Ann Oncol. 2021 Apr;32(4):533-541.

- 2 years IM vs FU

- N= 908 randomized patients
- Initially OS--> IFFS

- Main end point <u>imatinib failure-free survival (IFFS)</u> (randomization→ second TKI)

EORTC STUDY: primary end point (IFFS)



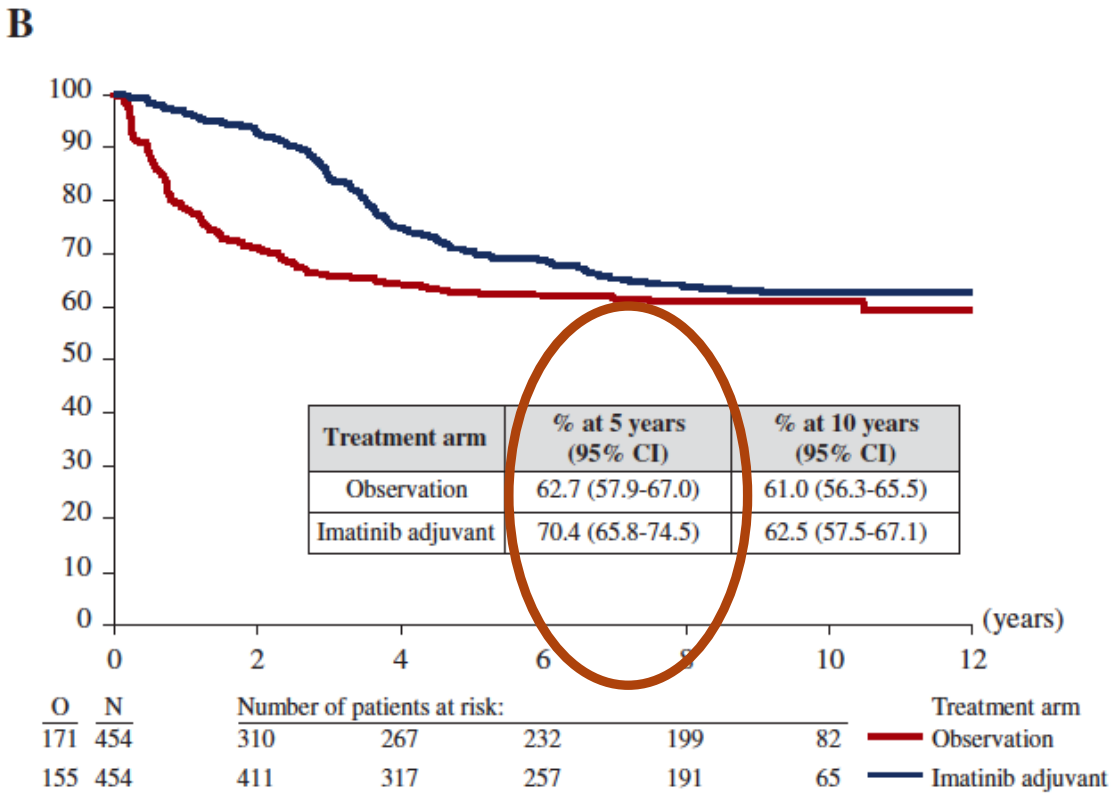
IIFS 87% vs 83% at 5 years
75% vs 74% at 10 years

HR 0.87 (95% CI 0.65-1.15, p=0.31)

Casali et al. Ann Oncol. 2021 Apr;32(4):533-541.

EORTC study: secondary endpoints

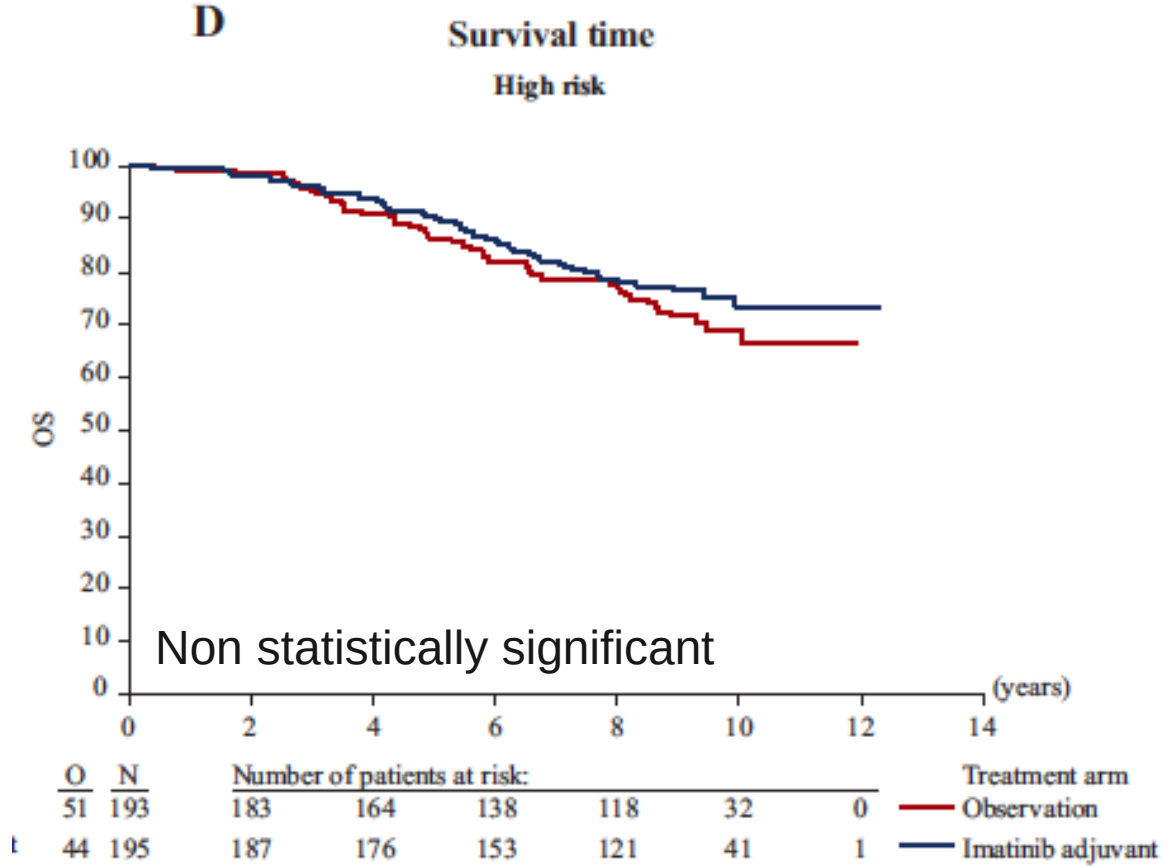
RELAPSE FREE SURVIVAL



Treatment arm	% at 5 years (95% CI)	% at 10 years (95% CI)
Observation	62.7 (57.9-67.0)	61.0 (56.3-65.5)
Imatinib adjuvant	70.4 (65.8-74.5)	62.5 (57.5-67.1)

HR: 0.71 (95% CI 0.57-0.89, p=0.002)

OS, HIGH RISK POPULATION



Casali et al. Ann Oncol. 2021 Apr;32(4):533-541.

SSG XVIII study

- Patients with diagnosis of GIST
- High risk accorting to NIH classification
  - Size >10cm
  - MI> 10/50HCF
  - Size>5 and MI > 5/50HCF
  - Tumor ruptura

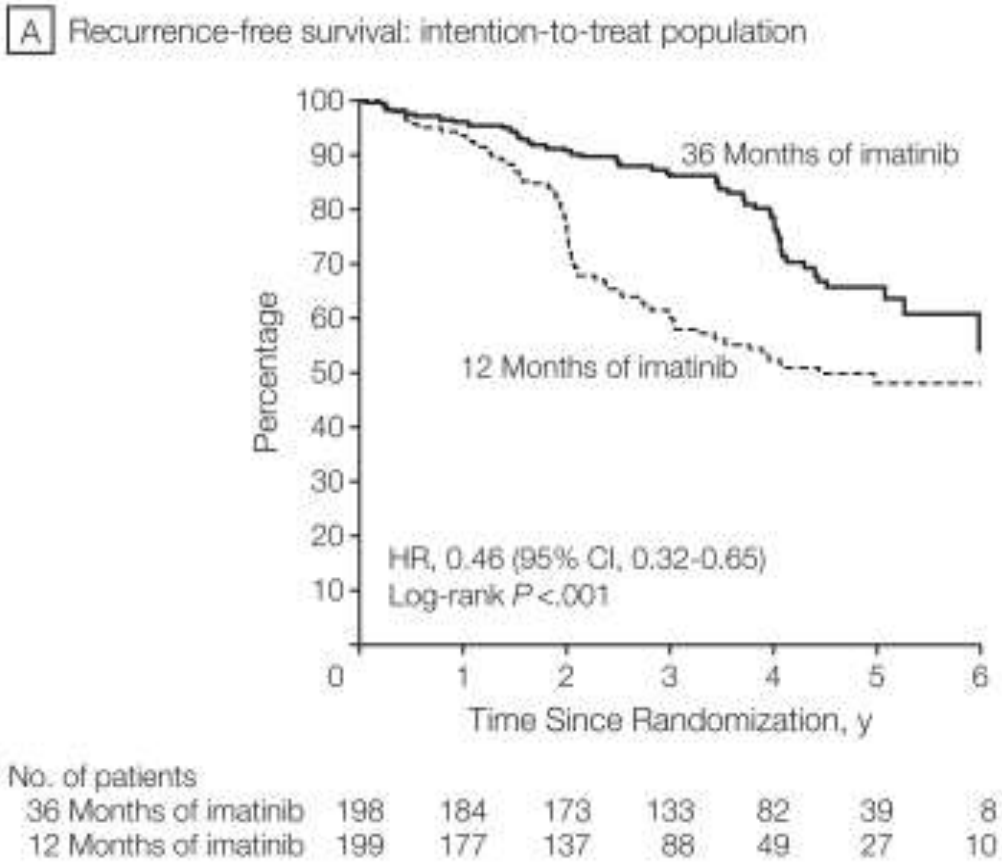
- <u>1 year vs 3 years of adjuvant IM</u>

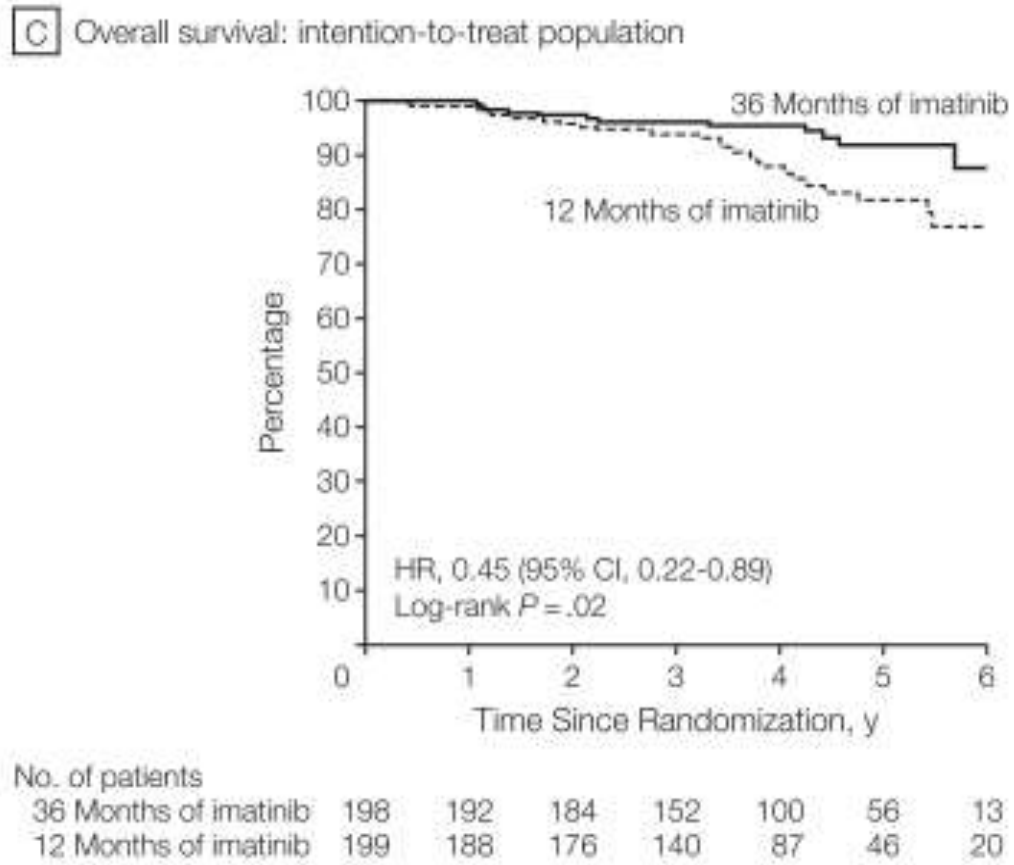
- N= 400 randomized patients

- Main end point: Relapse-free survival

Joensuu et al. JAMA. 2012;307(12):1265-1272

SSG XVIII study



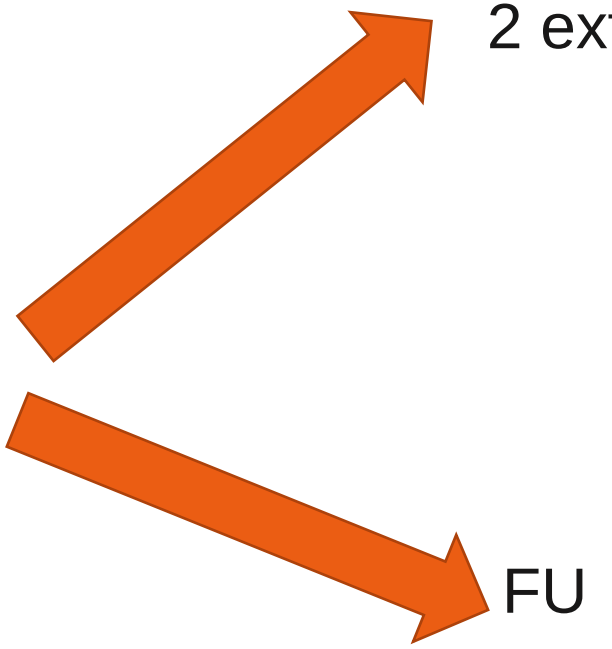


3y RFS: 86% vs 60%
5y RFS: 65 % vs 48%

Joensuu et al. JAMA. 2012;307(12):1265-1272

NOW ONGOING…

- Gastric GIST MI> 10/50HCF
- Non gastric GIST > 5/50HCF
- Tumor rupture



2 extra years

High Risk GIST patients
After 3 years of adjuvant IM

FU

GEIS maximum recruiter
Recruitment expected to be completed in September 2022

ADJUVANT IMATINIB: REMARKS

- 3 years of adjuvant imatinib is the current standard in high-risk resected localized GIST
  - >50-60% risk of relapse according to Joensuu
  - Discuss with patients with Risk> 40%
  - Consider the high-risk genotype (exon 11 KIT 557-558)
  - Sensible genotype (adjuvant with IM NOT indicated in PDGFR Exon 18 D842V; SHD deficient, BRAF, NTRK)
  - Consider 800mg/d in Exon 9 KIT GIST (non consensus)
- In patients with tumor rupture during surgery→ consider to prolong Imatinib (indefinitely)
- Patients undergoing neoadjuvant IM will complete up to 3 years (NA + A)

GIST LOCALIZED DISEASE: CONCLUSIONS

- Surgery (avoiding tumor rupture) is the standard therapy in localized resectable GIST
- Neoadjuvant Imatinib (6-12 months) can be considered in patients with sensitive genotypes and locally advanced tumors
- Complete prognostic information (including genotype) before starting therapy is needed
- 3 years of adjuvant imatinib is the current standard of therapy in high risk GIST, with sensitive genotype
- Tumor rupture→ indefinite imatinib

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