GIST

Enfermedad Localizada

Dra. Nadia Hindi

Hospital Univ. Fundación Jiménez Díaz, Madrid

Universidad Europea MADRID

GEIS
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)

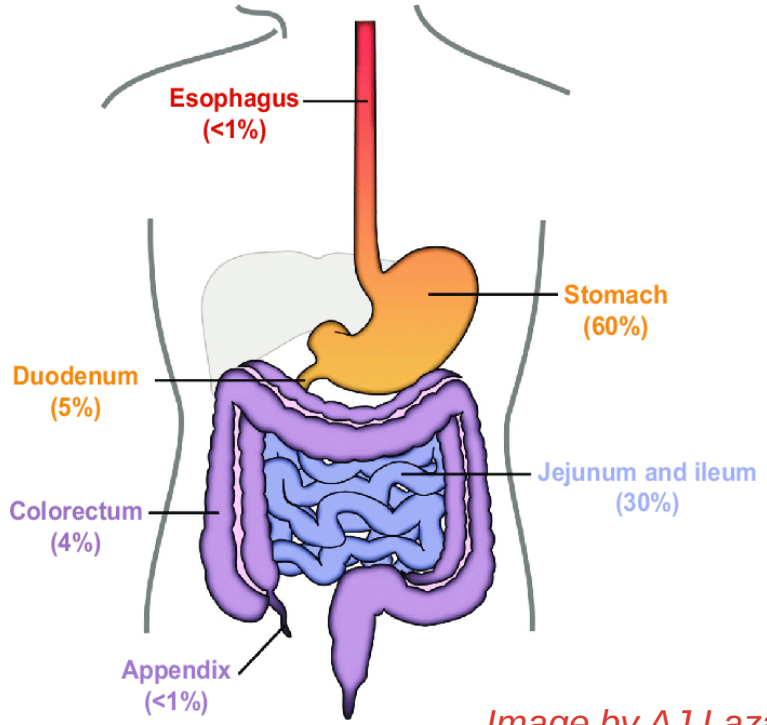
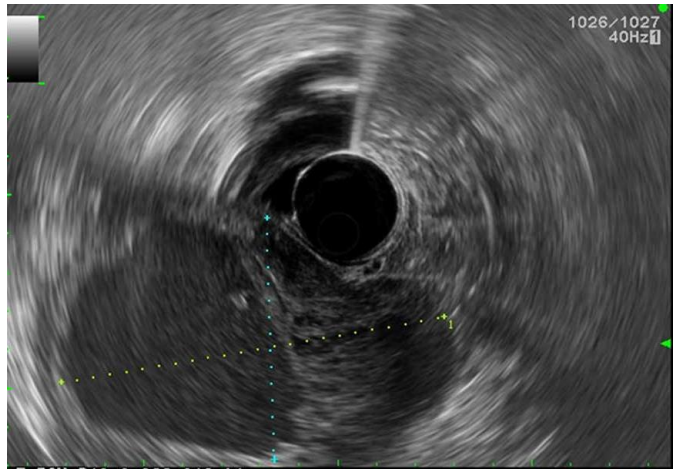


Image by AJ Lazar

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

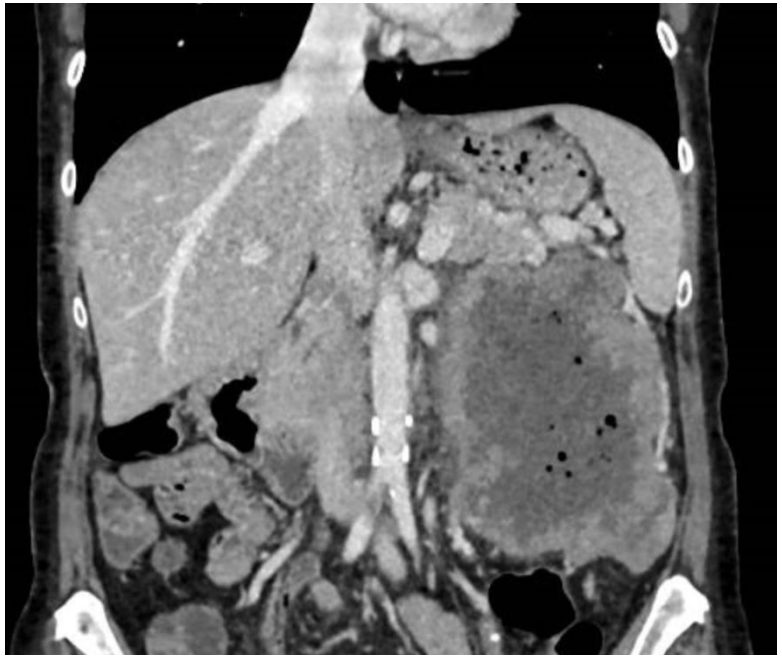
- FOLLOW-UP AND DURATION
  - An early reassessment is, in general, recommended (biphasic CT, PET)
  - Total duration 6-12 months (avoid emergence of resistance)
  - In general---> adjuvant therapy after surgery to complete 36 months

CLINICAL CASE

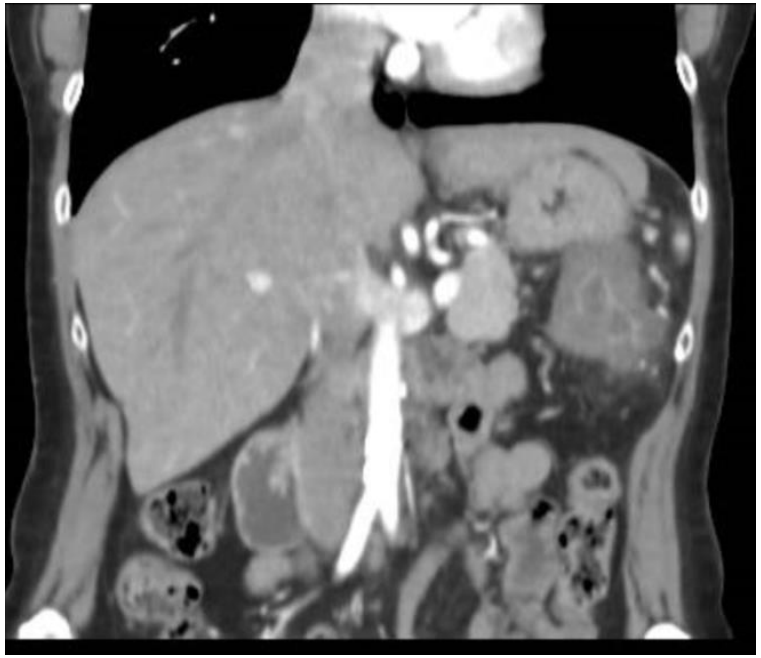
62- year-old woman, abdminal disturbances, gastric discomfort
Admission due to fever→ probable abscess of the mass→ biopsy

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

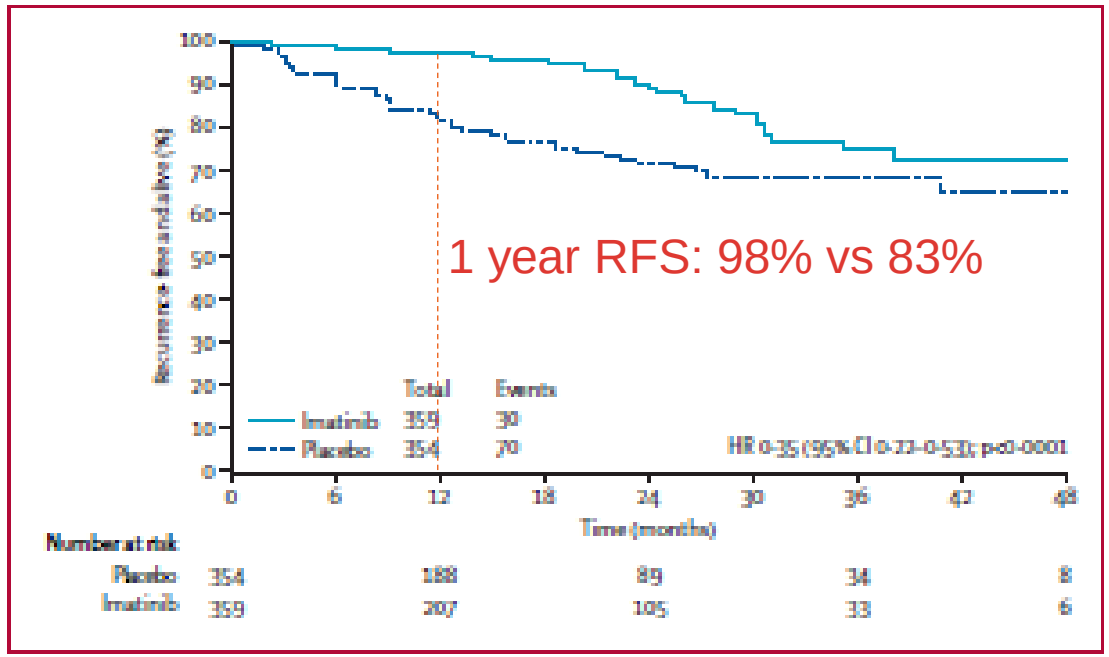


Figure 2: Recurrence-free survival

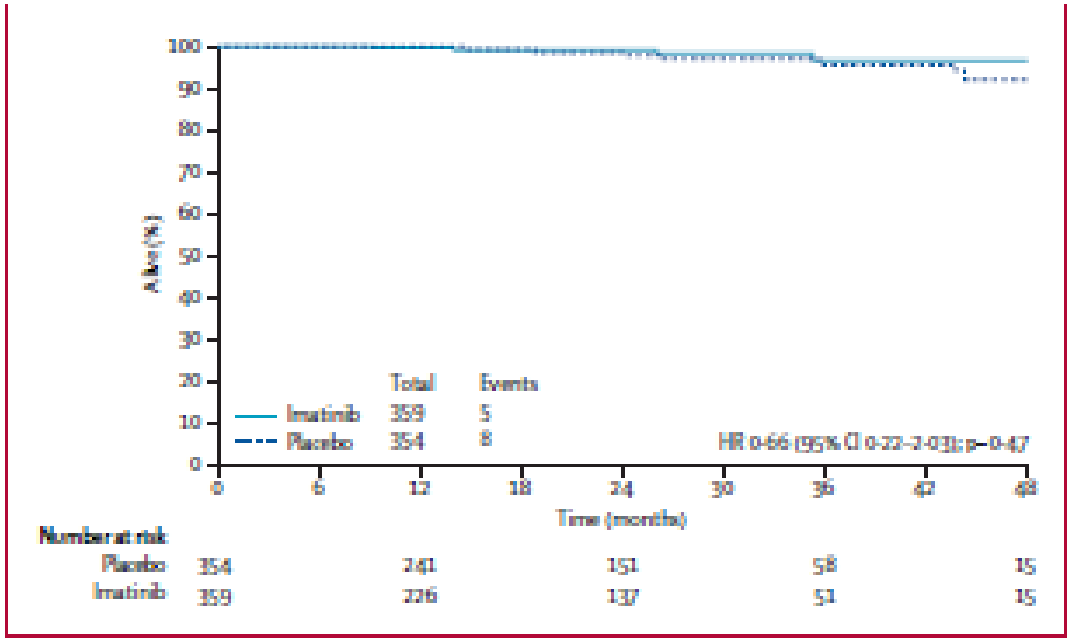


Figure 4: Overall survival

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

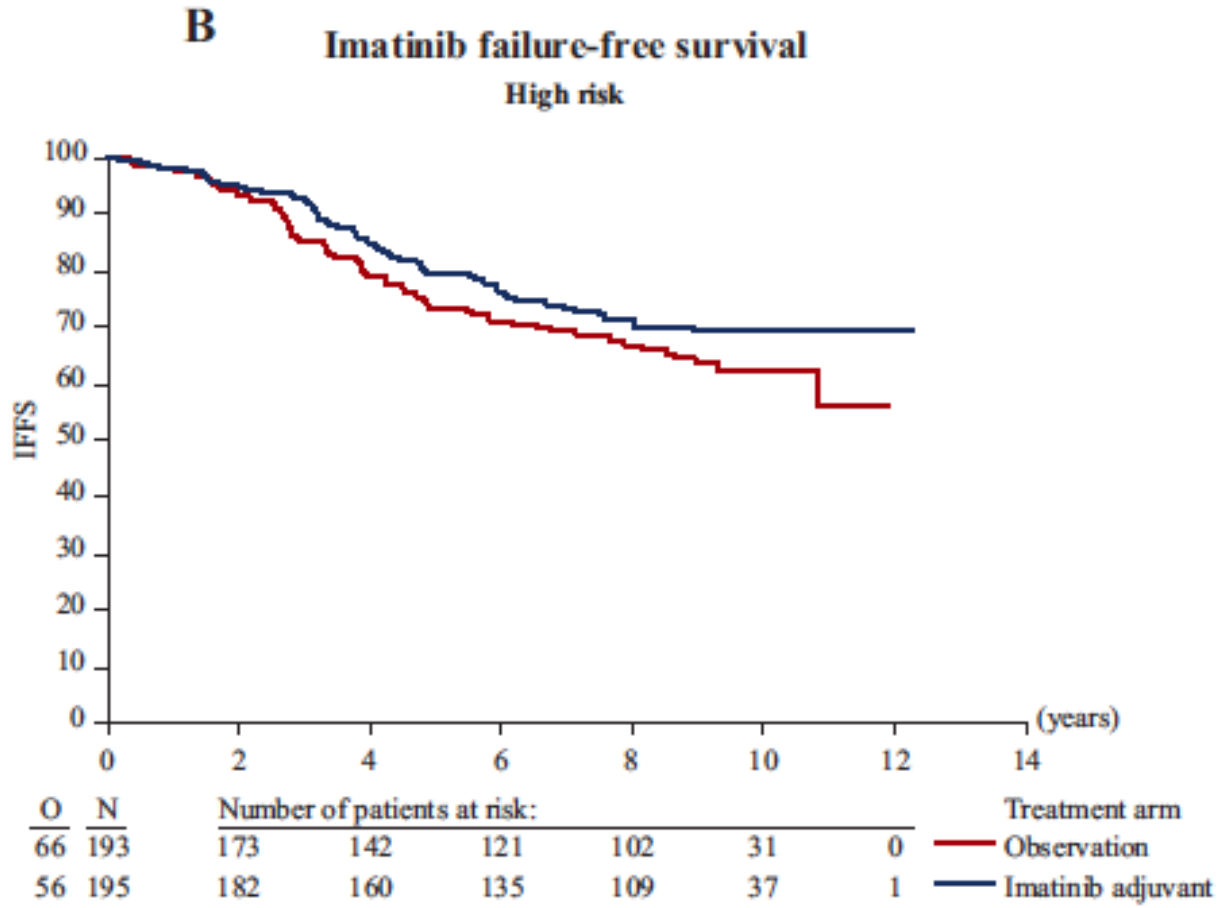
Casali et al. Ann Oncol. 2021 Apr;32(4):533-541.

- 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)



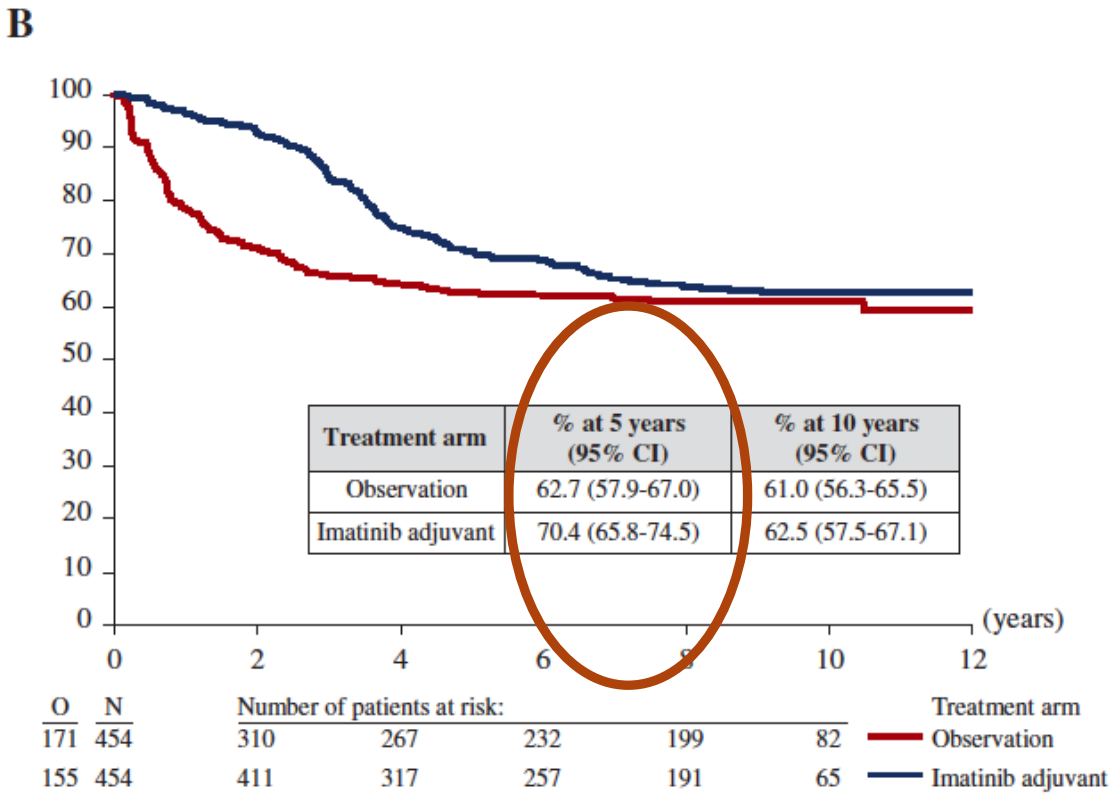
IIFS 87% vs 83% at 5 years
75% vs 74% at 10 years

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

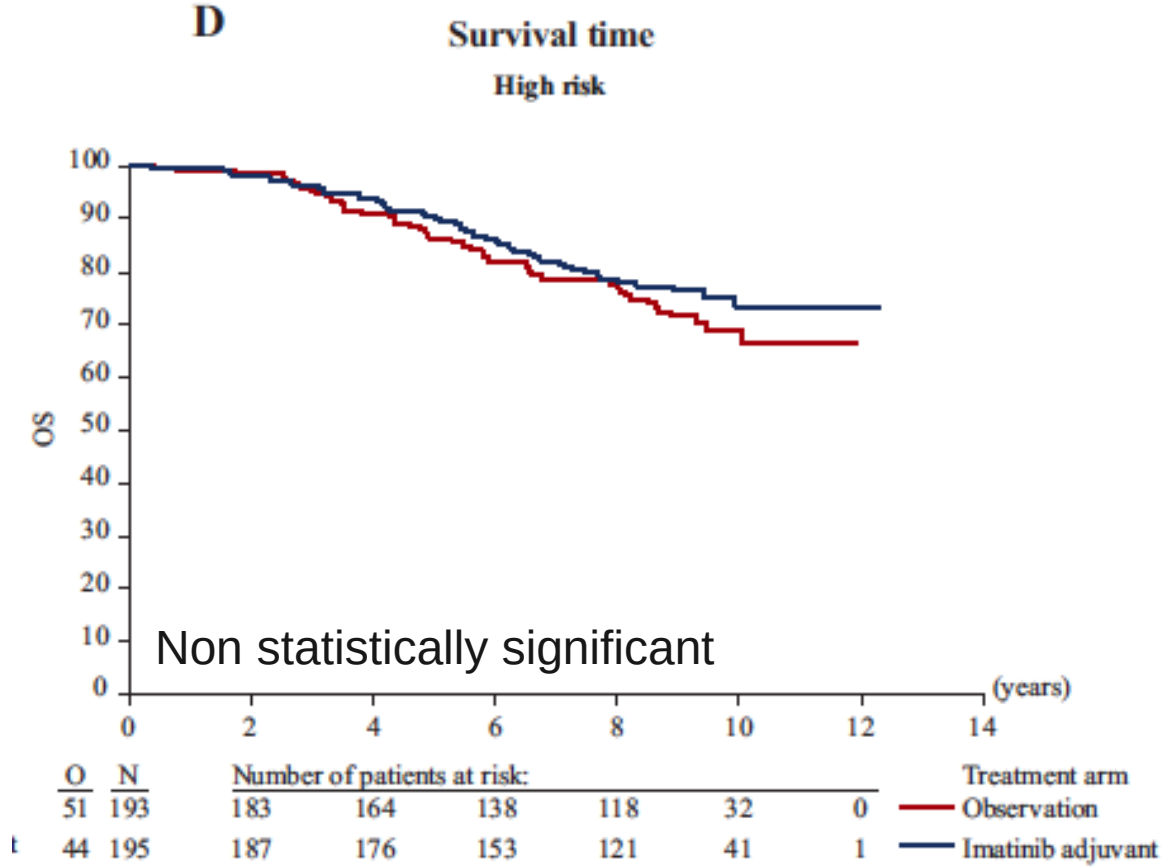
RELAPSE FREE SURVIVAL



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

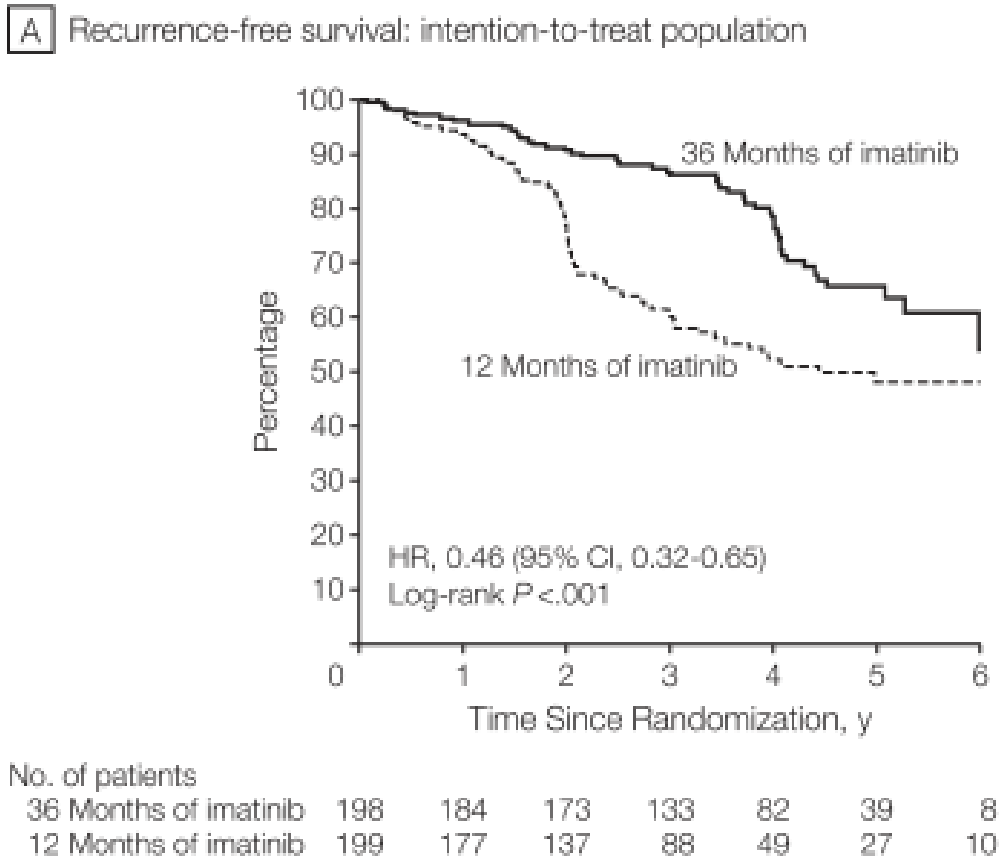
- <u>1 year vs 3 years of adjuvant IM</u>

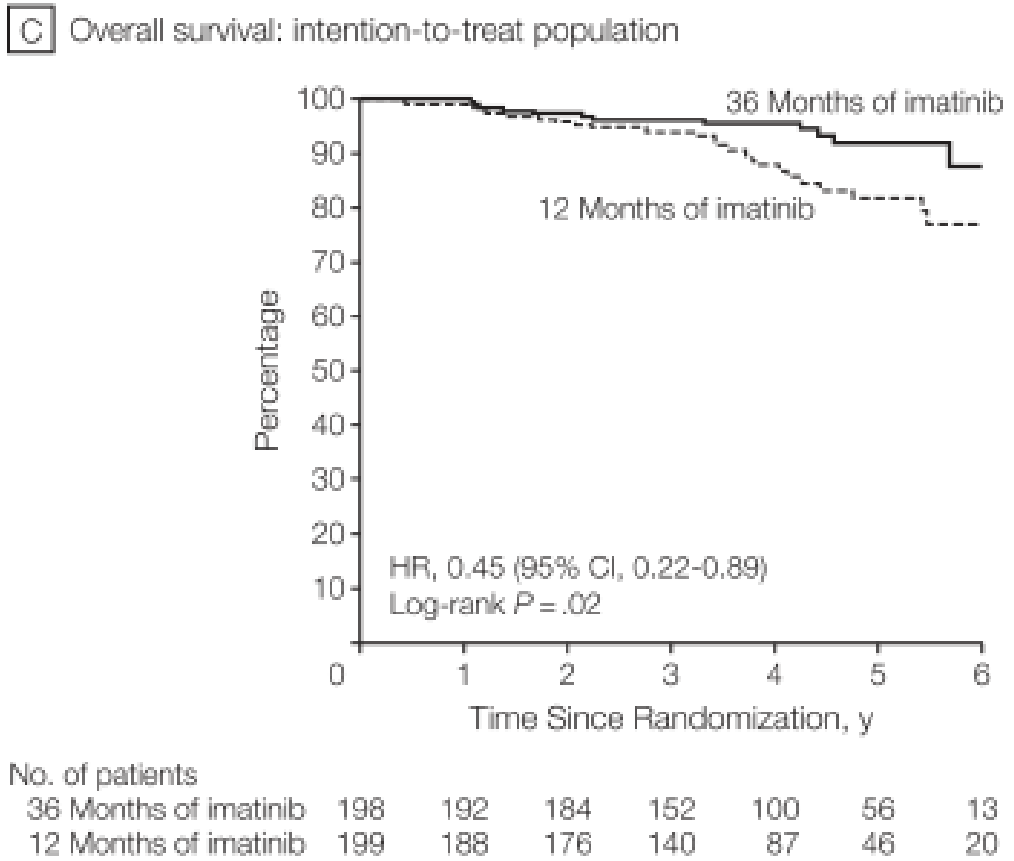
- N= 400 randomized patients

- Main end point: Relapse-free survival

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

SSG XVIII study



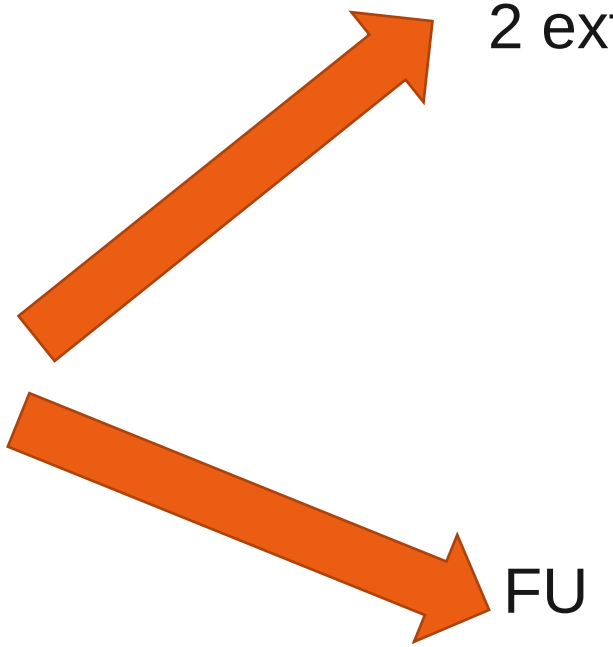


3y RFS: 86% vs 60%
5y RFS: 65 % vs 48%

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 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