GIST research at University Campus Bio-Medico of Rome: *an update*

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On behalf of the UCBM Sarcoma and GIST Unit

Current lines of *clinical* research

1. ROLE OF DIFFERENT DOSES OF ADJUVANT IMATINIB (400 MG/DAY vs 800 MG/DAY) IN PTS WITH RESECTED KIT EXON9-MUTATED GIST

2. EFFECTS OF TREATMENT WITH ADJUVANT IMATINIB ON BONE DENSITY AND SARCOPENIA

Current lines of *translational* research

1. TRANSCRIPTOMIC DIFFERENCES BETWEEN GIST WITH DIFFERENT DRIVER MUTATIONS

2. ESTABLISHMENT OF PATIENT-DERIVED CELL LINES WITH RARE KIT MUTATIONS

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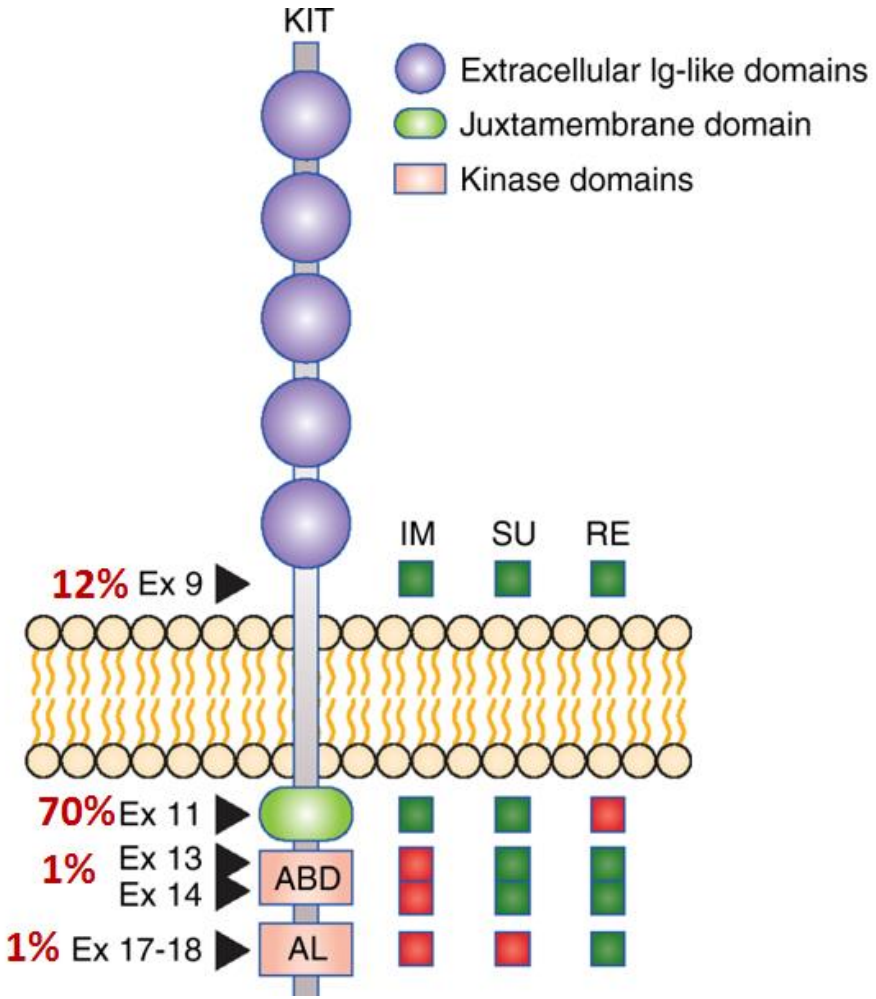
Exon 9 kit mutation



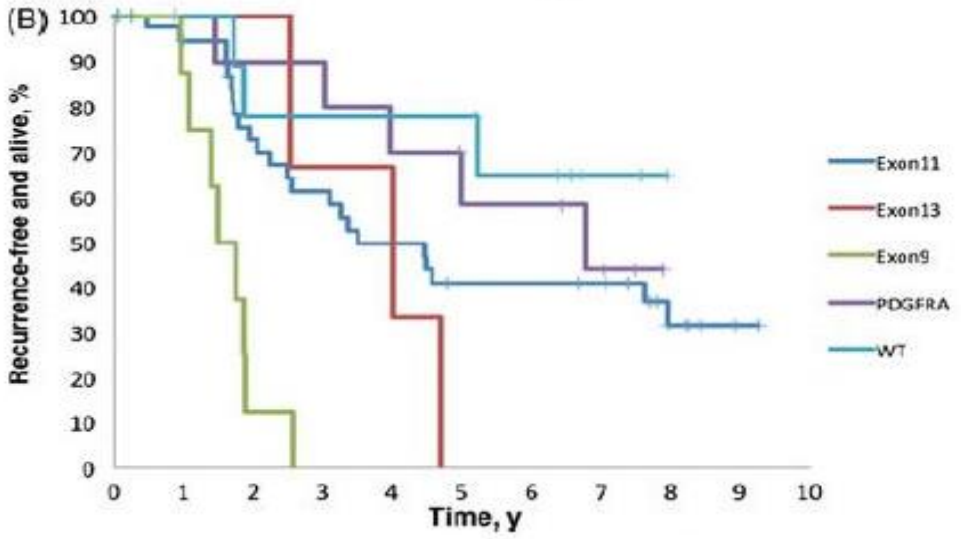
- 10–15% of newly diagnosed cases
- mostly a spindled cell morphology
- common in small intestine GIST
- relatively uncommon in stomach or large intestine GIST
- tumors with exon 9 mutations develop significantly more peritoneal than liver metastases
- no concordance in term of prognostic impact:
  better relapse free survival after curative resection vs greater malignant potential
- benefit less from imatinib in both the adjuvant and metastatic setting

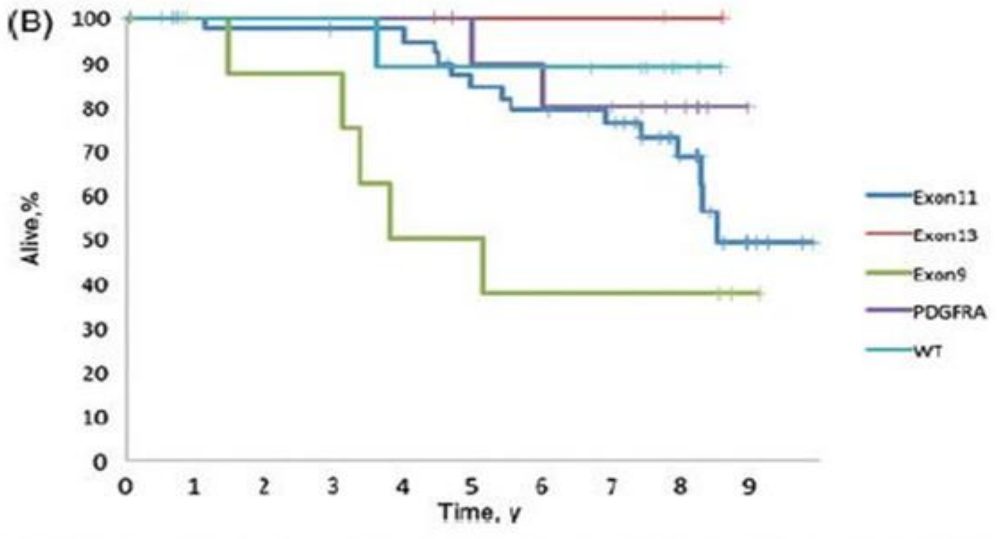
Heinrich MC, et al J Clin Oncol 2003; Lesota et al Histopathology 2008; Miettinen M. Am J Surg Pathol. 2006;
Ku¨nstlinger H Am J Surg Pathol 2013; Martin-Broto J. Clin Transl Oncol 2010; Corless CL J Clin Onco 2004

Adjuvant imatinib in exon 9 mutated GIST

Long-term Results of Adjuvant Imatinib Mesylate in Localized, High-Risk, Primary Gastrointestinal Stromal Tumor

ACOSOG Z9000 (Alliance) Intergroup Phase 2 Trial





Longer treatment may be indicated in patients with a KIT exon 9 mutation, as this group did not develop recurrence in the first year but did thereafter. It is possible that patients with a KIT exon 9 mutation would do better with higher dose imatinib (e.g., 800 mg/day), since this dose appears to delay progression in metastatic GIST.

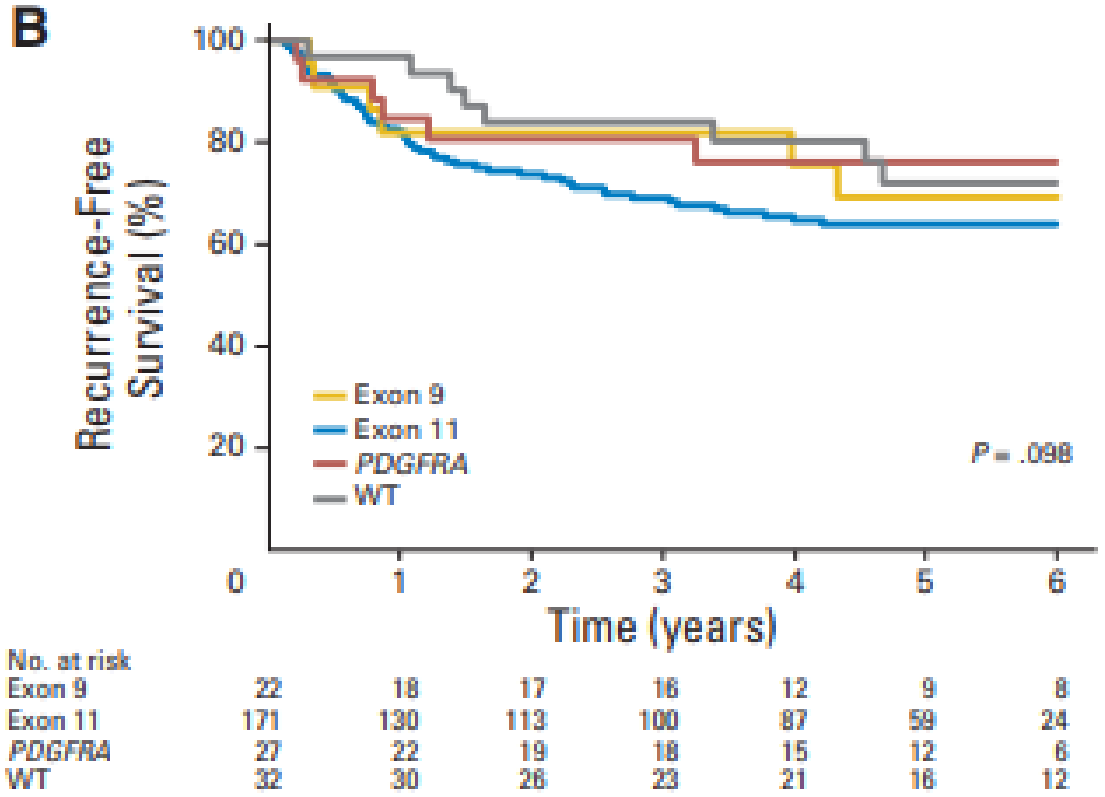
DeMatteo RP et al Ann Surg. 2013

Adjuvant imatinib in exon 9 mutated GIST

VOLUME 32 · NUMBER 15 · MAY 20 2014

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Pathologic and Molecular Features Correlate With Long-Term Outcome After Adjuvant Therapy of Resected Primary GI Stromal Tumor: The ACOSOG Z9001 Trial



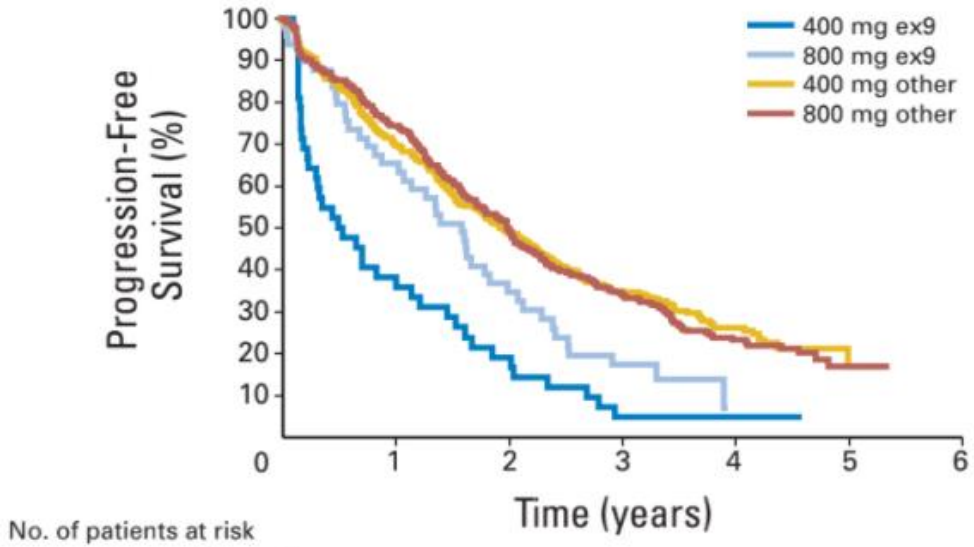
- There was no statistical difference in RFS for patients with KIT exon 9 –mutant GISTs treated with imatinib versus placebo.
- The number of patients was relatively small (35)
- Patients were not evenly distributed between the two arms (placebo, n 22 v imatinib, n 13)
- Exon 9 seem to have better outcome than ex 11

Corless C JCO 2014

Adjuvant imatinib in Exon 9 GIST

BACKGROUND

- **Standard imatinib in the adjuvant setting for high-risk patients is 400 mg/day for 3 years**
- **MetaGIST results show higher efficacy of 800 mg/day in Exon 9-mutate GIST**
- **Adjuvant imatinib at 800 mg/day is often offered to patients with resected GIST with Exon 9 mutations, *without any specific evidence***



No. of patients at risk

	O	N					
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

Adjuvant imatinib in Exon 9 GIST

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Research Article

Adjuvant imatinib in GIST patients harboring exon 9 KIT mutations: results from a multi-institutional European retrospective study.

Bruno Vincenzi, Andrea Napolitano, Marta Fiocco, Olivier Mir, Piotr Rutkowski, Jean-Yves Blay, Peter Reichardt, Heikki Joensuu, Elena Fumagalli, Spyridon Gennatas, Nadia Hindi, Margherita Nannini, Mariella Spalato Ceruso, Antoine Italiano, Giovanni Grignani, Antonella Brunello, Silvia Gasperoni, Tommaso De Pas, Giuseppe Badalamenti, Maria A Pantaleo, Winan J. van Houdt, Nikki S. IJzerman, Neeltje Steeghs, Hans Gelderblom, Ingrid M E Desar, Johanna Falkenhorst, Marianna Silletta, Marta Sbaraglia, Giuseppe Tonini, Javier Martín-Broto, Peter Hohenberger, Axel Le Cesne, Robin L. Jones, Angelo Paolo Dei Tos, Alessandro Gronchi, Sebastian Bauer, and Paolo G Casali

DOI: 10.1158/1078-0432.CCR-21-1665

Adjuvant imatinib in Exon 9 GIST

A MODEL OF COLLABORATIVE NETWORKING

- **23 specialist GIST centres in Europe**
- **8 different European countries**

Adjuvant imatinib in Exon 9 GIST

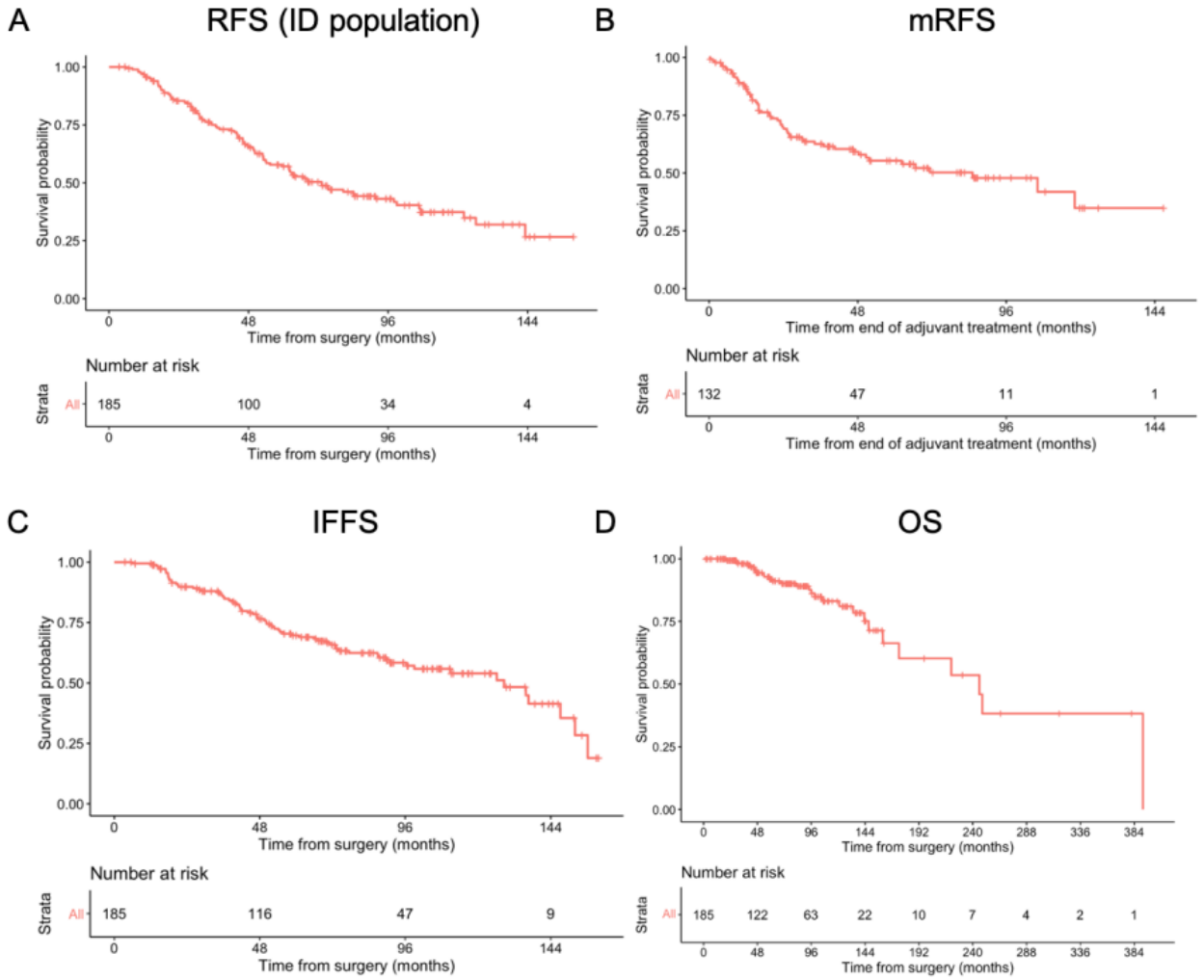
Table 1. Patients characteristics at baseline

	Adjuvant 400 mg/d	Adjuvant 800 mg/d	P value
Number of patients	131	54	
Largest tumor dimension in mm (median, min-max)	75, 11-300	100, 26-230	< 0.001
Site of diagnosis (n, %)			0.055
- Stomach	8 (6.1)	8 (14.8)	
- Duodenum	19 (14.5)	4 (7.4)	
- Small bowel	89 (67.9)	40 (74.1)	
- Other	15 (11.5)	2 (3.7)	
High mitotic index (n, %)	73 (58.8)	40 (74.1)	0.065
Age in years (median, min-max)	56, 29-80	57.5, 27-79	0.52
Tumor rupture (n, %)	20 (15.3)	10 (18.5)	0.66
Female gender (n, %)	69 (52.7)	30 (55.6)	0.75
Risk by Miettinen stratification (n, %)			0.059
- Low	10 (7.6%)	4 (7.4%)	
- Intermediate	32 (24.4%)	5 (9.3%)	
- High	89 (67.9%)	45 (83.3%)	

- **Suggestion of physicians' selection bias**

- **Use of advanced statistical tools (**propensity score matching **and** inverse probability of treatment weighting**) to account for these baseline differences**

Adjuvant imatinib in Exon 9 GIST



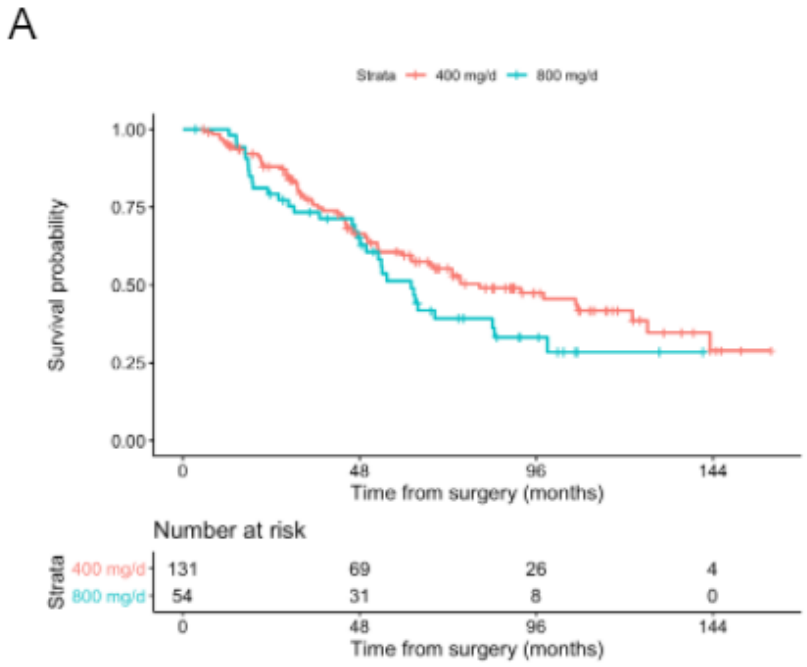
OUTCOMES

- **RFS (relapse-free survival) in the intended-dose (ID) population** (similar to intention-to-treat population): from date of surgery to relapse/death
- **mRFS (modified RFS):** from end of adjuvant treatment to relapse/death
- **IFFS (imatinib failure-free survival):** from date of surgery to imatinib failure/death
- **OS (overall survival):** from date of surgery to death

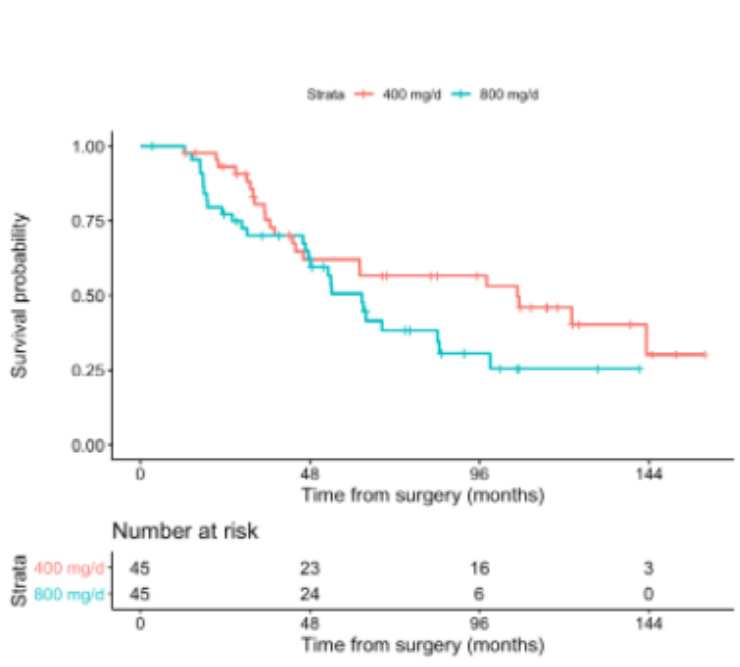
Adjuvant imatinib in Exon 9 GIST

RFS

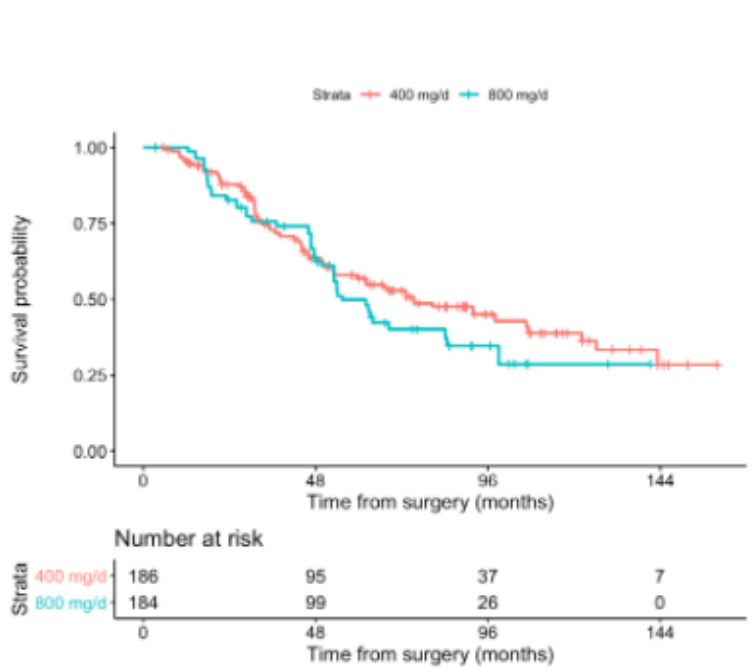
ID population



PSM



IPTW



Similar results for all the survival outcomes

Adjuvant imatinib in Exon 9 GIST

Table 2: Multivariate weighted Cox analyses

	RFS	mRFS	IFFS
	HR (95% CIs)	**HR (95% CI)**	**HR (95% CI)**
Adjuvant dose (800 mg/d)	1.24 (0.79-1.94)	1.69 (0.92-3.10)	1.35 (0.79-2.28)
High mitotic index	2.05 (1.14-3.65)	2.30 (1.05-5.05)	2.09 (1.07-4.09)
Non-gastric site	5.83 (1.72-19.74)	8.81 (2.13-36.53)	5.21 (1.13-24.05)
Age at diagnosis (per 10 years increase)	1.17 (0.99-1.39)	1.13 (0.91-1.40)	1.14 (0.95-1.38)
Male gender	1.53 (0.97-2.41)	1.48 (0.82-2.69)	1.52 (0.89-2.59)
Largest tumor dimension (per 10 cm increase)	1.41 (1.00-1.98)	1.47 (0.88-2.45)	1.29 (0.86-1.91)
Tumor rupture	1.64 (0.93-2.88)	1.25 (0.56-2.80)	2.17 (1.23-3.84)
Adjuvant duration (per 1 year increase)	N/A	1.13 (0.85-1.51)	N/A

RESULTS

- **When correcting for baseline characteristics, in our retrospective study <u>there were no differences in survival outcomes</u> between patients treated with 400 mg/day or 800 mg/day**
- **High mitotic index and non-gastric site were consistently associated to worse outcomes**
- **Validation of these findings in an external (US?) cohort as well as future perspective studies are crucial**

Adjuvant imatinib, bone density and sarcopenia

BACKGROUND

- Imatinib targets c-abl, c-KIT and PDGFR; at therapeutic concentration it can also inhibit the **macrophage-colony stimulating factor (M-CSF) receptor**
- **Imatinib can influence muscle composition,** which is closely related to **bone health**

OUR HYPOTHESES

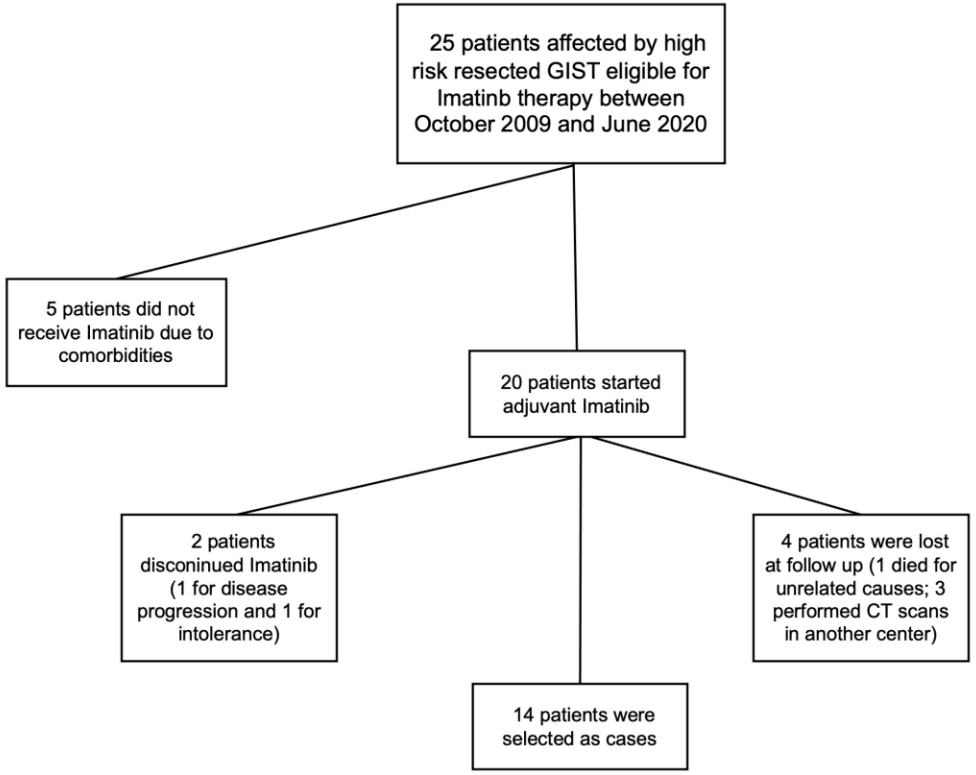
- Imatinib treatment in the adjuvant setting may have an effect on **bone mineral density (BMD)**
- Imatinib treatment in the adjuvant setting may have an effect on **muscle composition**
- These anthropometric parameters may have an impact on **imatinib-related toxicities**

Adjuvant imatinib, bone density and sarcopenia

METHODS

- We retrospectively selected
  - patients with **surgically resected high-risk GIST that completed 3 years of adjuvant therapy with imatinib (starting dose 400 mg/die)**
  - an **age- and gender- matched control group** of patients with low risk surgically resected GIST

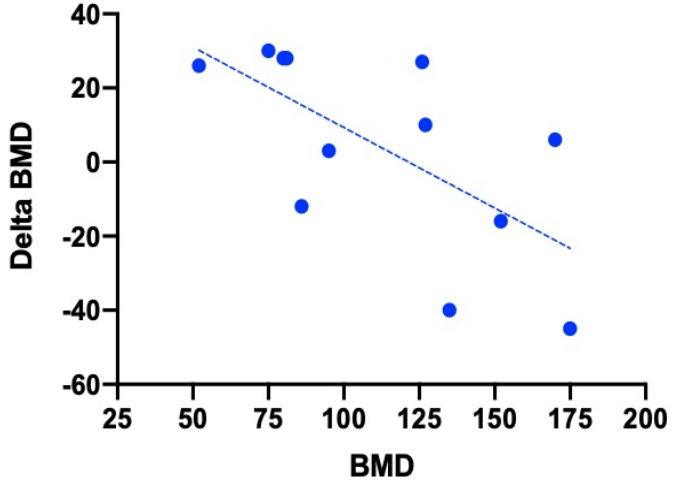
- **Muscle and bone density were evaluated on CT scan at baseline and after 6, 12 and 18 months**

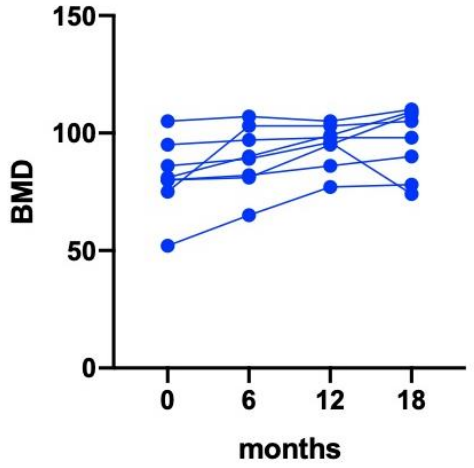


Adjuvant imatinib, bone density and sarcopenia

RESULTS

- At baseline, **men had a significantly higher bone mineral density (BMD), smooth muscle index (SMI) and lean body mass (LBM)**
- **BMD showed an overall significant increase over time (p=0.021).**
- **A significant inverse correlation between baseline BMD and its variation over time (delta BMD) was found (p=0.021, r= -0.653, r2 = 0.426).**
- **In patients with basal level <120 mg/cm3, BMD showed a significant increase over the different time points (p=0.002).**

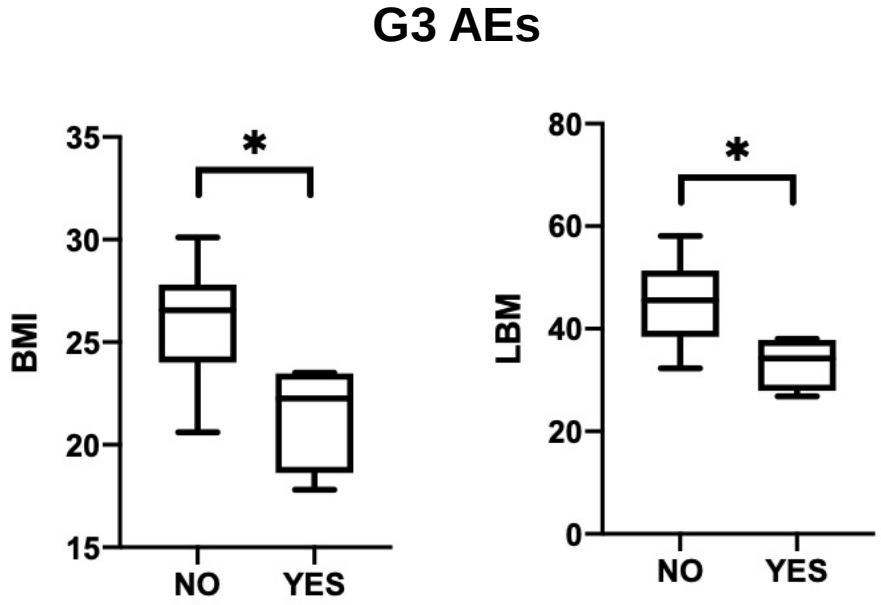




Adjuvant imatinib, bone density and sarcopenia

RESULTS

- In the control group, the BMD did not significantly change over the course of 18 months of follow-up.
- Patients who suffered from grade 3 AEs had a significantly lower baseline BMI and LBM. There also was a non-significant trend between basal BMD and grade 3 toxicities.



Adjuvant imatinib, bone density and sarcopenia

CONCLUSIONS

- **We have analysed for the first time the impact of imatinib on anthropometric parameters expressed as BMD, SMI and LBM in GIST patients treated in the adjuvant setting**
- **The therapy with imatinib led to a significant increase in BMD in patients with low basal value**
- **The development of grade 3 toxicities was more common in patients with low BMI and low LBM.**

Overcoming imatinib resistance in GIST: Cyclin Dependent Kinase (CDK) inhibitors as potential novel combining strategy

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Article | Published: 01 August 2019

Cyclin D1 is a mediator of ga… tumor KIT-independence

Wen-Bin Ou, Nan Ni, Rui Zuo, Weihao Zhuang, Meij… Eilers, George D. Demetri, Haibo Qiu, Bin Li, Adrian Ma…

ORIGINAL RESEARCH article

Front. Pharmacol., 06 May 20… 74

…opresses KIT-Independent …umors Via Targeting …aling

…u[1], Nacef Bahri[2], Boshu Sun[1], Yuehong Wu[1] and …

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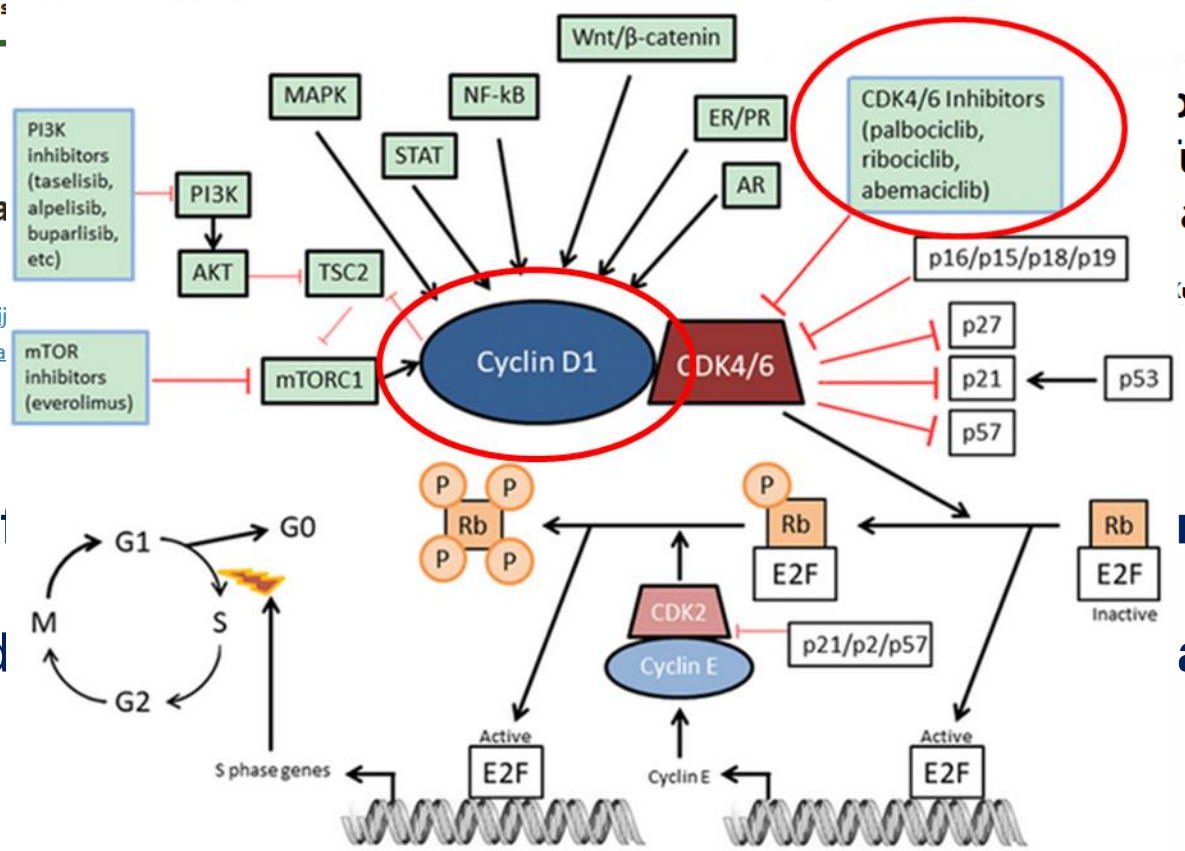
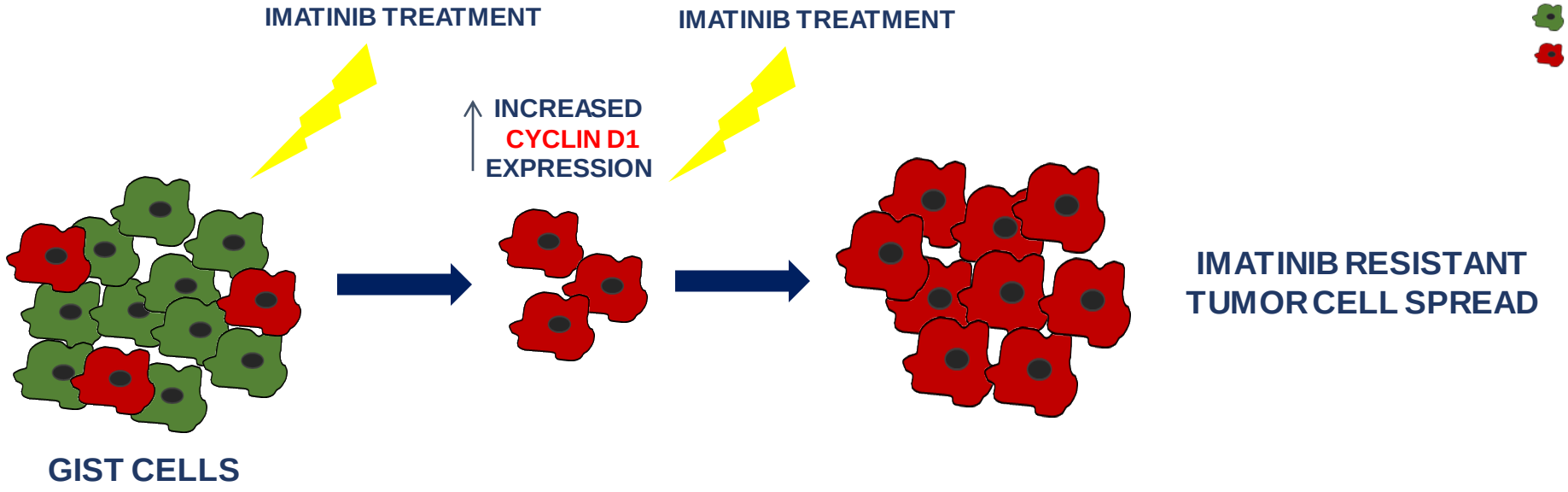
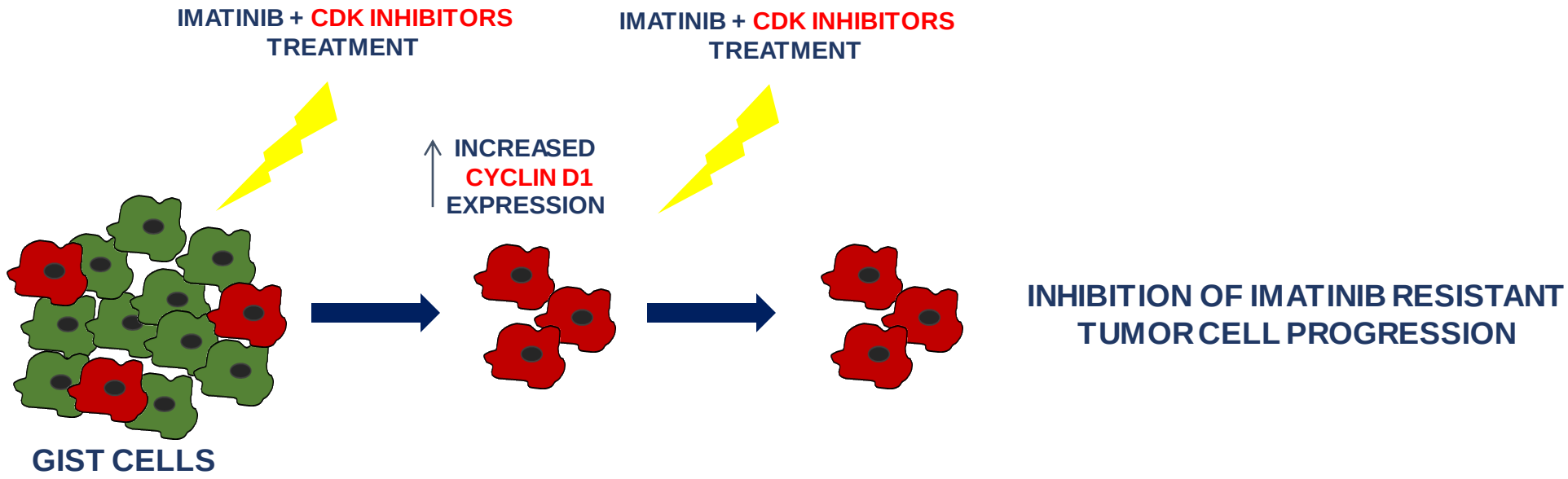


CDK inhibitors suppress cell proliferation by blocking the formation of cyclin D1-Cdk4/6 complex and inhibiting retinoblastoma (RB) phosphorylation

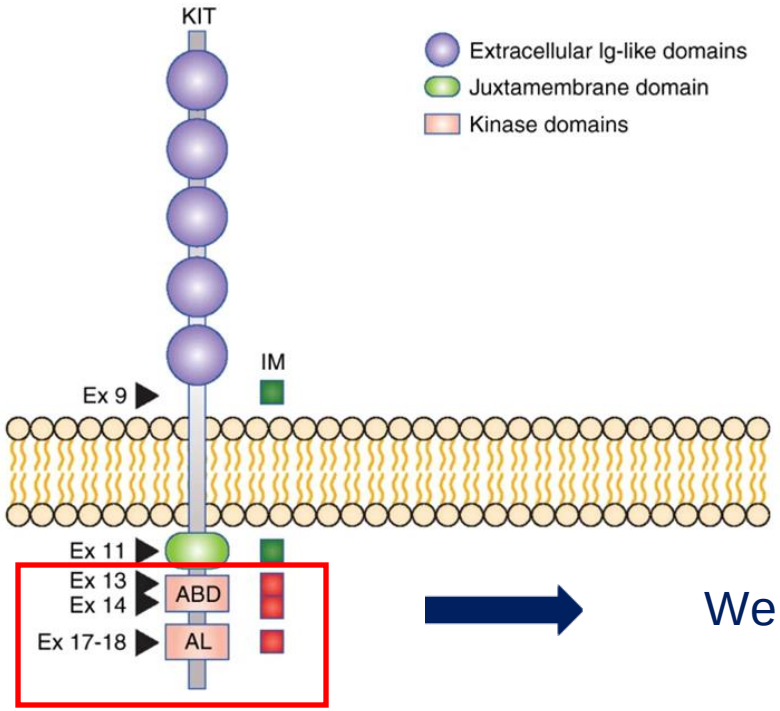
Scientific hypothesis





Project aims

To evaluate the synergistic effect of **CDK inhibitors (palbociclib, ribociclib and abemaciclib) and imatinib in GIST**



We will use different imatinib resistant GIST models harbouring secondary kit mutations

Napolitano A and Vincenzi B, BJC 2019

#uniticontroilGIST

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