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

Bruno Vincenzi

b.vincenzi@unicampus.it

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
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
➢ 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

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.
Adjuvant imatinib in exon 9 mutated GIST

➢ 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
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
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 Mil, 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, Marliana Silletta, Marta Sbaraglia, Giuseppe Tonini, Javier Martín-Broto, Peter Hohenberger, Axel Le Cesne, Robin L. Jones, Angelo Paolo Del Tos, Alessandro Gronchi, Sebastian Bauer, and Paolo G Casali

DOI: 10.1158/1078-0432.CCR-21-1665
A MODEL OF COLLABORATIVE NETWORKING

- 23 specialist GIST centres in Europe
- 8 different European countries
Adjuvant imatinib in Exon 9 GIST

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

<table>
<thead>
<tr>
<th>Table 1. Patients characteristics at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Largest tumor dimension in mm (median, min-max)</td>
</tr>
<tr>
<td>Site of diagnosis (n, %)</td>
</tr>
<tr>
<td>- Stomach</td>
</tr>
<tr>
<td>- Duodenum</td>
</tr>
<tr>
<td>- Small bowel</td>
</tr>
<tr>
<td>- Other</td>
</tr>
<tr>
<td>High mitotic index (n, %)</td>
</tr>
<tr>
<td>Age in years (median, min-max)</td>
</tr>
<tr>
<td>Tumor rupture (n, %)</td>
</tr>
<tr>
<td>Female gender (n, %)</td>
</tr>
<tr>
<td>Risk by Miettinen stratification (n, %)</td>
</tr>
<tr>
<td>- Low</td>
</tr>
<tr>
<td>- Intermediate</td>
</tr>
<tr>
<td>- High</td>
</tr>
</tbody>
</table>
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

A  B  C

Similar results for all the survival outcomes
RESULTS

• When correcting for baseline characteristics, in our retrospective study there were no differences in survival outcomes 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
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
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
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).
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.
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

Mechanisms of imatinib resistance are multiple and characterized by different secondary kit mutations, but recent evidences demonstrated that cyclin D1 overexpression is a common feature of all imatinib resistant subclones.

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

Oncogene

Article | Published: 01 August 2019

Cyclin D1 is a mediator of gastric tumor KIT-independence

Implicated in multiple cellular processes, including cell cycle progression, apoptosis, and cancer initiation.

PI3K inhibitors (taselisib, alpelisib, buparlisib, etc)

mTORC1 inhibitors (everolimus)

CDK4/6 Inhibitors
(palbociclib, ribociclib, abemaciclib)

Retinoblastoma (RB) phosphorylation

Suppressed KIT-Independent tumors Via Targeting signaling

Nacef Bahri, Boshu Sun, Yuehong Wu, and
Scientific hypothesis

IMATINIB TREATMENT

INCREASED CYCLIN D1 EXPRESSION

IMATINIB RESISTANT TUMOR CELL SPREAD

GIST CELLS

IMATINIB TREATMENT

IMATINIB + CDK INHIBITORS TREATMENT

INHIBITION OF IMATINIB RESISTANT TUMOR CELL PROGRESSION

GIST CELLS
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