Cutting Edge Treatment: Can immunotherapy work for GIST?

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Imatinib is generally not curative in GIST

How do we improve outcome?

- Adjuvant imatinib
- Surgery for residual metastatic disease
- Other tyrosine kinase inhibitors
- Imatinib + immune therapy
Postoperative imatinib is not curative

**Metastatic**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Failed</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400mg/day</td>
<td>345</td>
<td>278</td>
<td>18</td>
</tr>
<tr>
<td>800mg/day</td>
<td>349</td>
<td>267</td>
<td>20</td>
</tr>
</tbody>
</table>

f/u 54 months

**Postoperative**

- Imatinib
- Placebo

N=713
f/u 74 months

Blanke, JCO 2008;26:626
Lancet 2009; 373:1097
J Clin Oncol 2014; 32:1563
Murine model of GIST

Deletion mutation in *KIT* exon 11

Sommer, PNAS 2003; 100:6706
KIT/CSF1R Inhibitor > Imatinib in Mouse GIST

Masson’s trichrome @ 4 weeks

Control

Imatinib

PLX3397

Scale bar, 100μm

Scale bar, 20μm

Clin Cancer Res 2014; 20:2350
MET Compensates for KIT Inhibition

2 wks in KitΔ558/+ mice

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Imatinib</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-KIT</td>
<td><img src="image1" alt="p-KIT" /></td>
<td><img src="image2" alt="p-KIT" /></td>
<td><img src="image3" alt="p-KIT" /></td>
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<tr>
<td>KIT</td>
<td><img src="image4" alt="KIT" /></td>
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<td><img src="image6" alt="KIT" /></td>
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<tr>
<td>p-MET</td>
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<td><img src="image11" alt="MET" /></td>
<td><img src="image12" alt="MET" /></td>
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<tr>
<td>GAPDH</td>
<td><img src="image13" alt="GAPDH" /></td>
<td><img src="image14" alt="GAPDH" /></td>
<td><img src="image15" alt="GAPDH" /></td>
</tr>
</tbody>
</table>

H129 tumor volume (mm³)

- Vehicle
- Imatinib
- Cabozantinib

Days 0 4 8 12 16

Cancer Res 2015, 75:2061
CD8+ T cells contribute to imatinib’s effects

**Diagram**

- **GIST**
- **Imatinib/Vehicle 7 days**
- **+/- CD8/CD4 depleting Ab**
- **Tumor weight**

**Graph**

- **Vehicle**
- **Vehicle + Isotype**
- **Vehicle - CD8**
- **Imatinib**
- **Imatinib + Isotype**
- **Imatinib - CD4**
- **Imatinib - NK**
- **Imatinib - CD8**

Tumor weight (g)

- 0.0
- 0.1
- 0.2
- 0.3
- 0.4

* Nature Med 2011; 17:1094
Imatinib increases intratumoral T eff:T reg ratio

Local Node

<table>
<thead>
<tr>
<th></th>
<th>CD8$^+$ T eff/T reg</th>
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<tr>
<td>Vehicle</td>
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<td>Imatinib</td>
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Tumor

<table>
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How does imatinib modulate T eff:T reg?

IDO -7x

GENES

VEHICLE

IMATINIB
Indoleamine 2,3-dioxygenase (IDO)

- Catalyzes tryptophan to immunosuppressive metabolites
- Inhibits maternal T cell immunity during gestation
- Induces T cell tolerance in tumor, infection, autoimmunity
Imatinib inhibits tumor cell IDO

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<th>Spleen</th>
<th>Vehicle</th>
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<td><img src="image1" alt="IDO" /></td>
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CD8:T reg correlates with imatinib sensitivity in human GIST (N=45 specimens)
Mouse and Human T Cells in GIST

Zitvogel and Kroemer, Nat Med 2011; 17:1050
Imatinib synergizes with anti-CTLA-4 in mouse GIST

![Graph showing the synergy between Imatinib and anti-CTLA-4 in GIST](graph.png)

Nature Med 2011; 17:1094
Co-inhibitory Receptors on T cells in Human GIST

106 specimens in 85 patients
PD-1 Expression on T cells in Human GIST
PD-L1 Expression in Human GIST

N=41
PD-1/PD-L1 Therapy in Murine GIST

Graphs showing tumor weight (% of control) over 4 weeks and 1 week for different treatment groups: Veh+Iso, Im+Iso, Veh+αPD-1, Im+αPD-1, Veh+αPD-L1, Im+αPD-L1. Significant differences are indicated by asterisks.

Images of KIT staining for Veh+Iso, IM+Iso, IM+αPD-1, IM+αPD-L1 after 1 week of treatment.

Bar graphs showing %Ki67+ and %IFN-γ+TNF+ of CD8+ over 1 week for Im+iso, Im+αPD-1, Im+αPD-L1. Significant differences are indicated by asterisks.

Bar graph showing tumor weight (% of control) for Ctr+Iso, 1-MT+Iso, 1-MT+αPD-1 after 1 week of treatment.
Summary

• GIST expresses IDO

• Imatinib works in part by decreasing IDO

• IDO inhibition alone has some anti-tumor effects

• Targeting PD-1/PD-L1 improves upon imatinib
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