Cutting Edge Treatment:
Can immunotherapy work for GIST?

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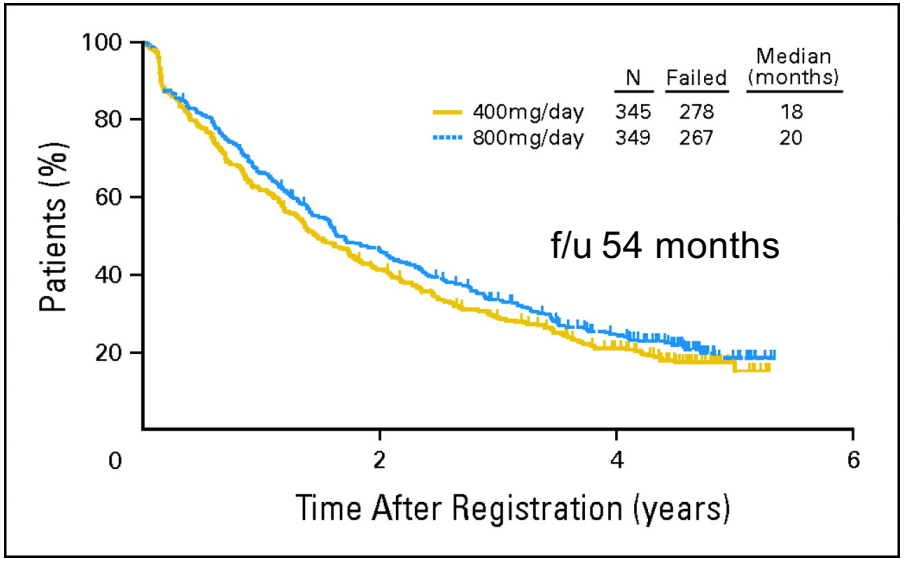
Imatinib is generally not curative in GIST

How do we improve outcome?

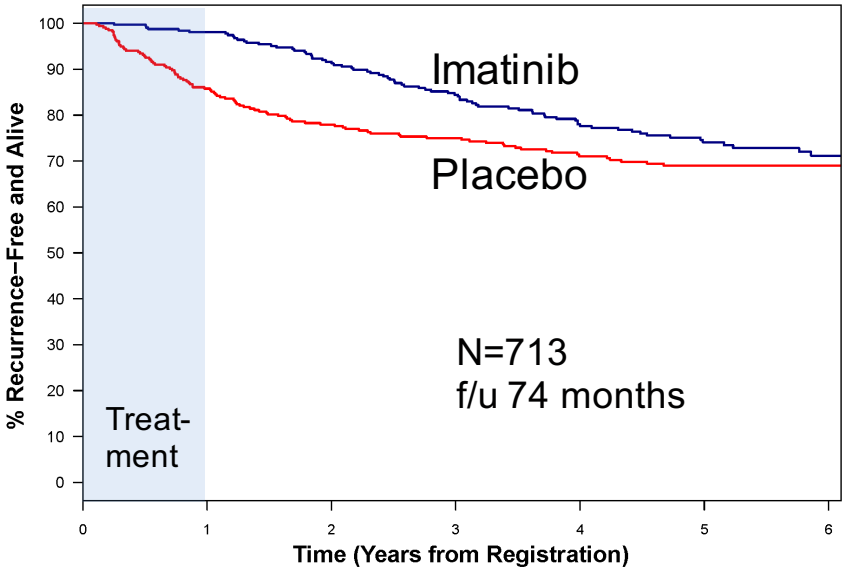
- Adjuvant imatinib
- Surgery for residual metastatic disease
- Other tyrosine kinase inhibitors
- Imatinib + immune therapy

Postoperative imatinib is not curative

Metastatic



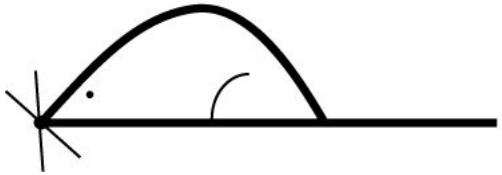
Postoperative

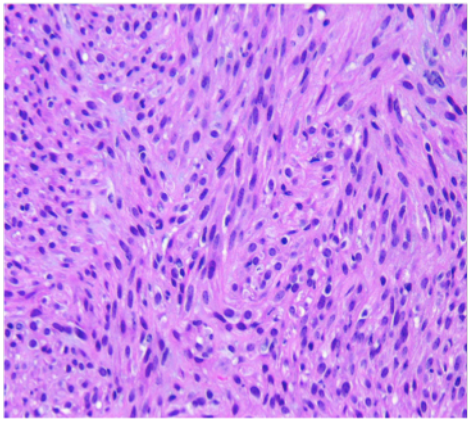


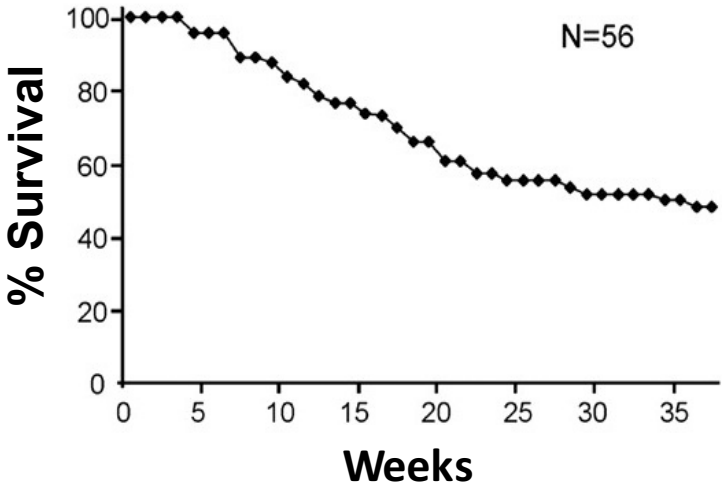
Blanke, JCO 2008;26:626
Lancet 2009; 373:1097
J Clin Oncol 2014; 32:1563

Murine model of GIST

Deletion mutation in *KIT* exon 11

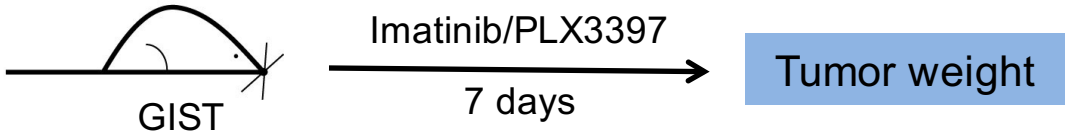


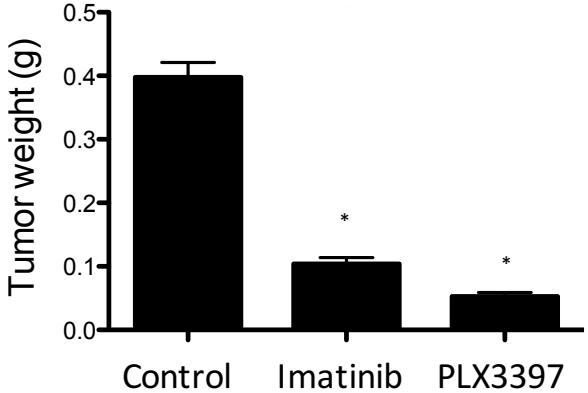


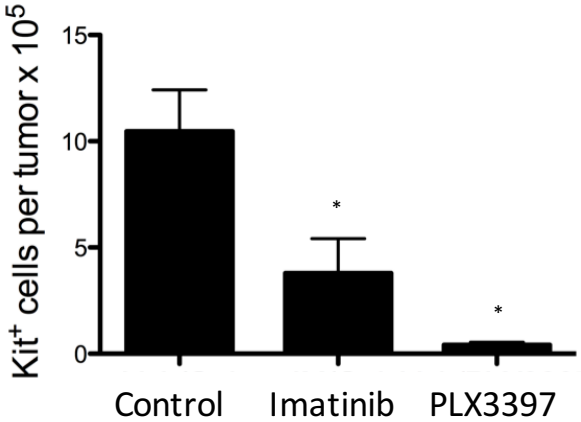


Sommer, PNAS 2003; 100:6706

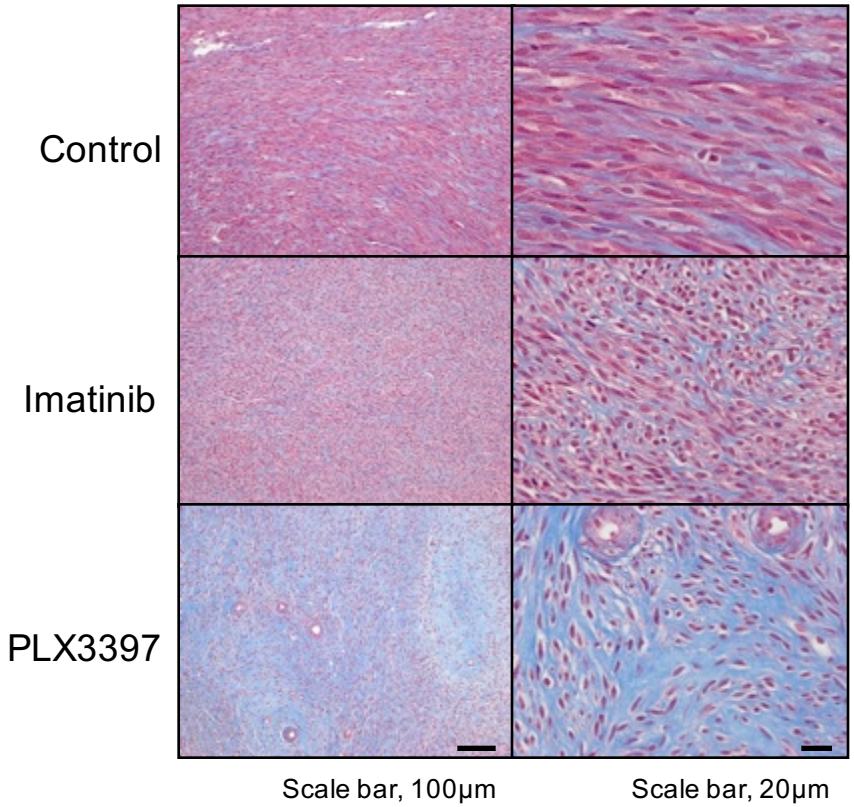
KIT/CSF1R Inhibitor > Imatinib in Mouse GIST





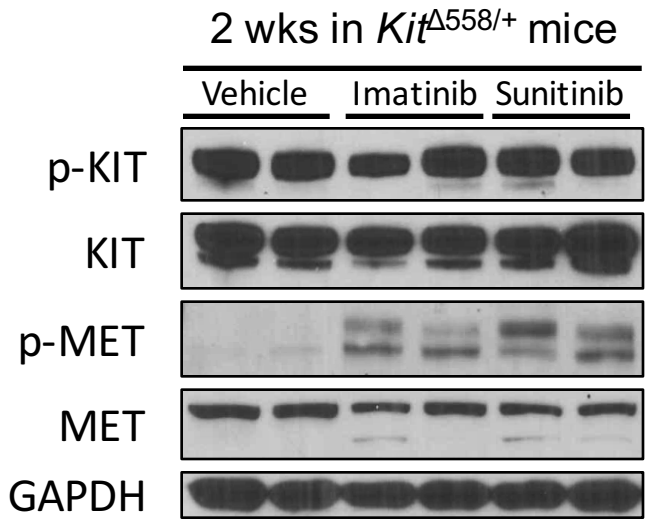


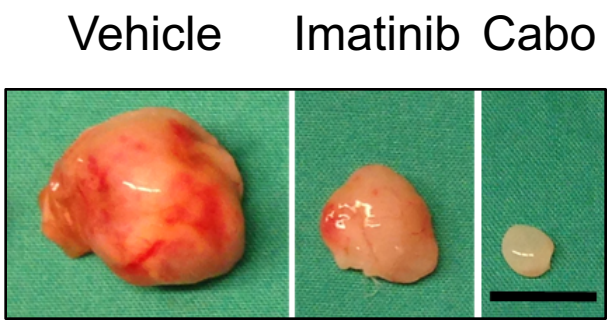
Masson's trichrome @ 4 weeks

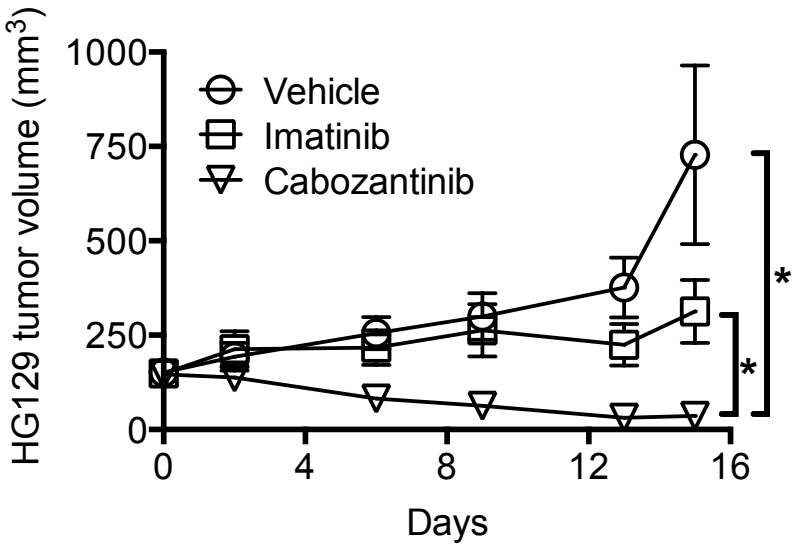


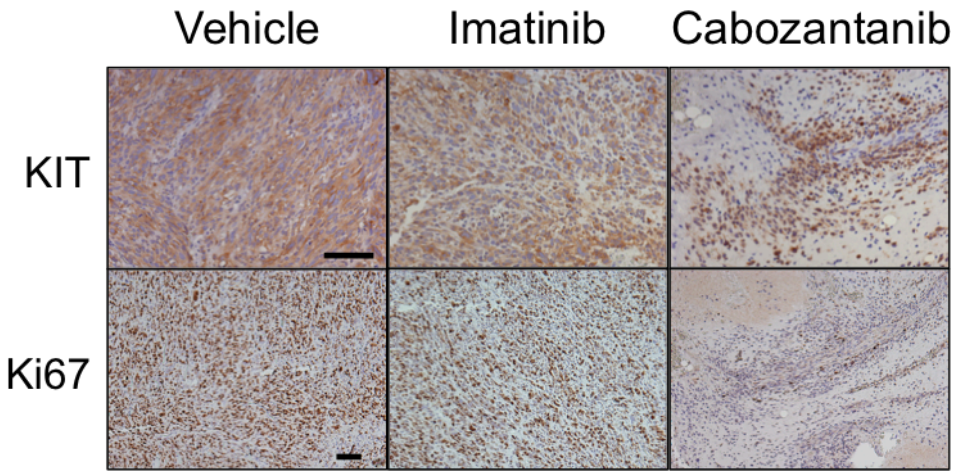
Clin Cancer Res 2014; 20:2350

MET Compensates for KIT Inhibition



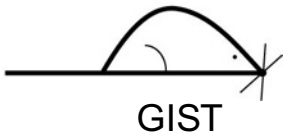






Cancer Res 2015, 75:2061

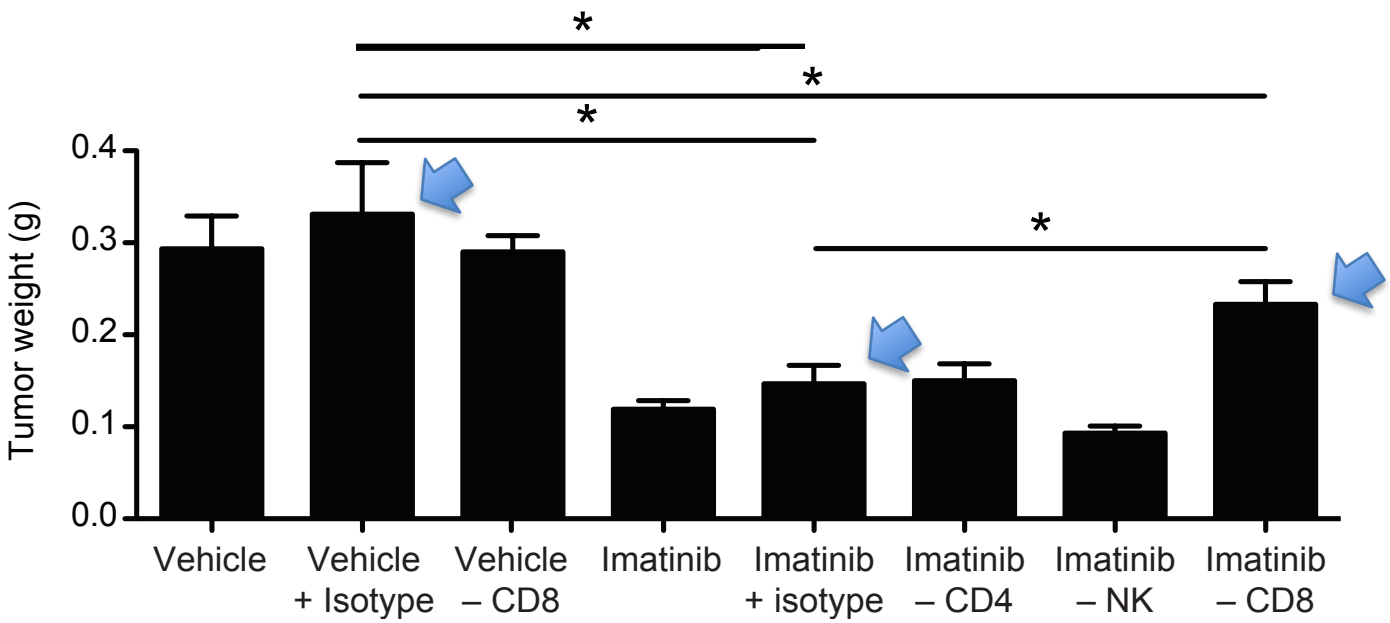
CD8$^+$ T cells contribute to imatinib's effects



Imatinib/Vehicle 7 days

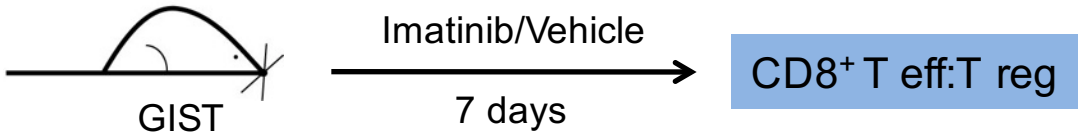
+/- CD8/CD4 depleting Ab

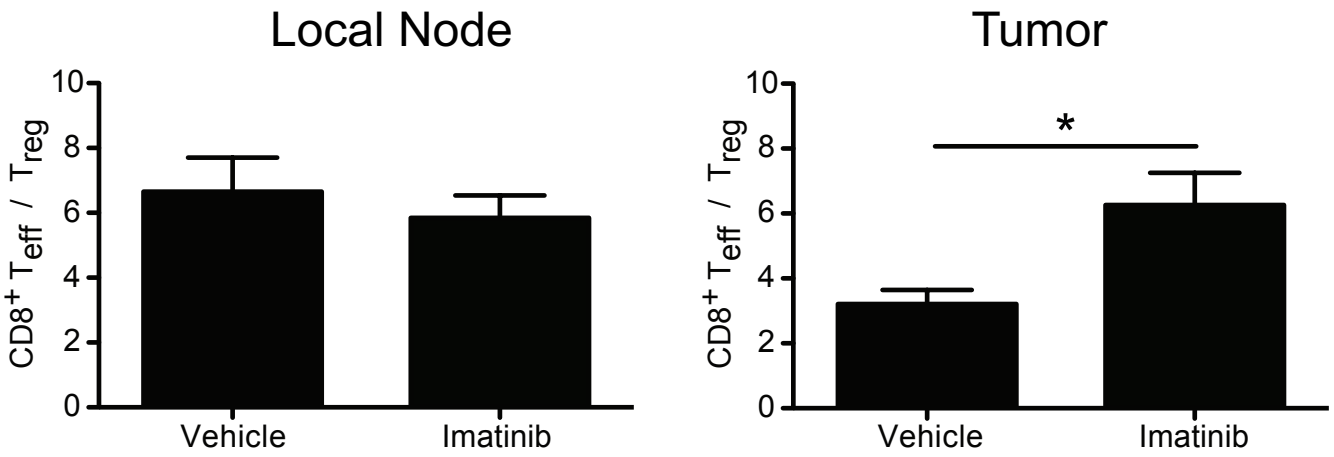
Tumor weight



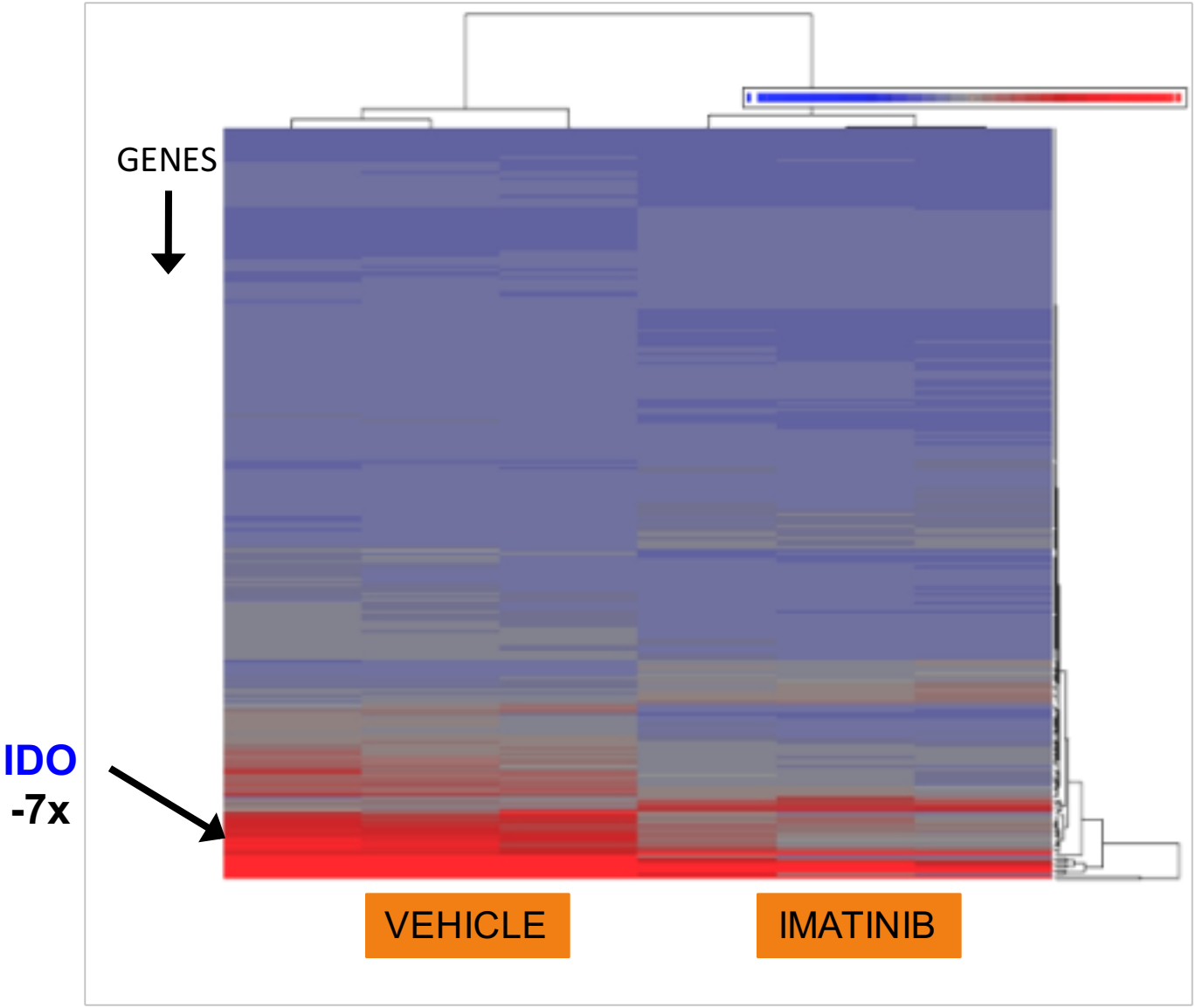
Nature Med 2011; 17:1094

Imatinib increases intratumoral T eff:T reg ratio



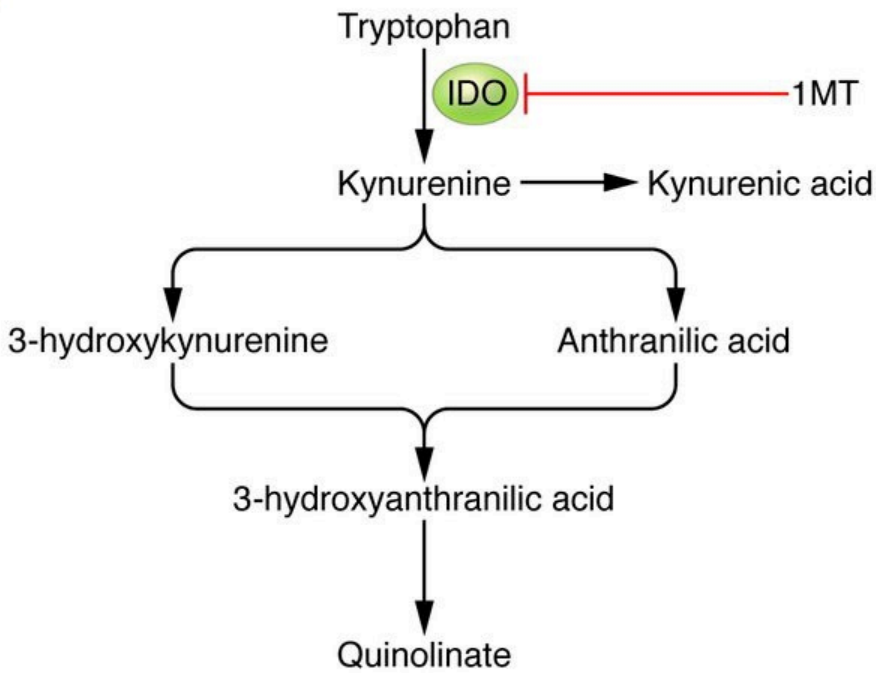


How does imatinib modulate T eff:T reg?



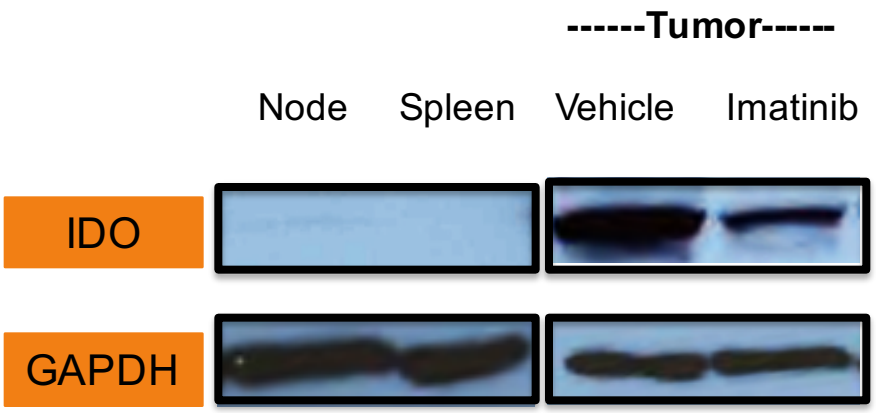
Indoleamine 2,3-dioxygenase (IDO)

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

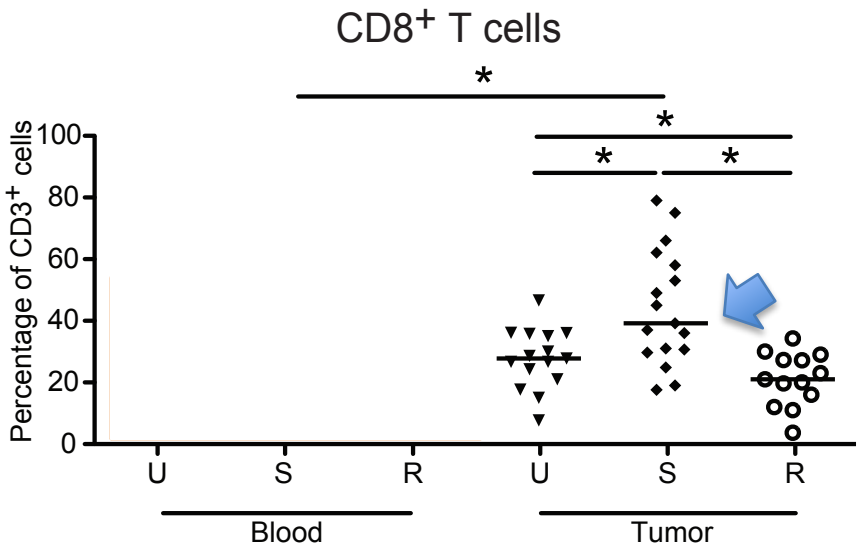


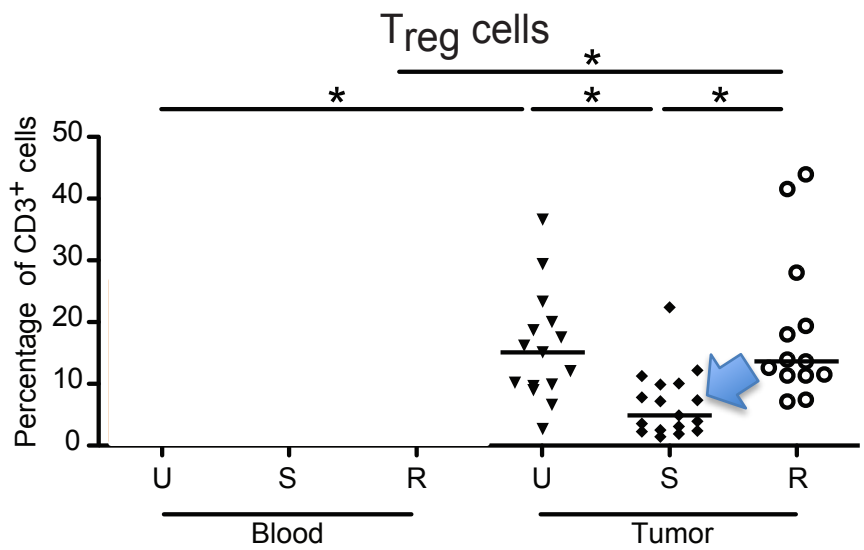
Munn, JCI 2007; 117:1147

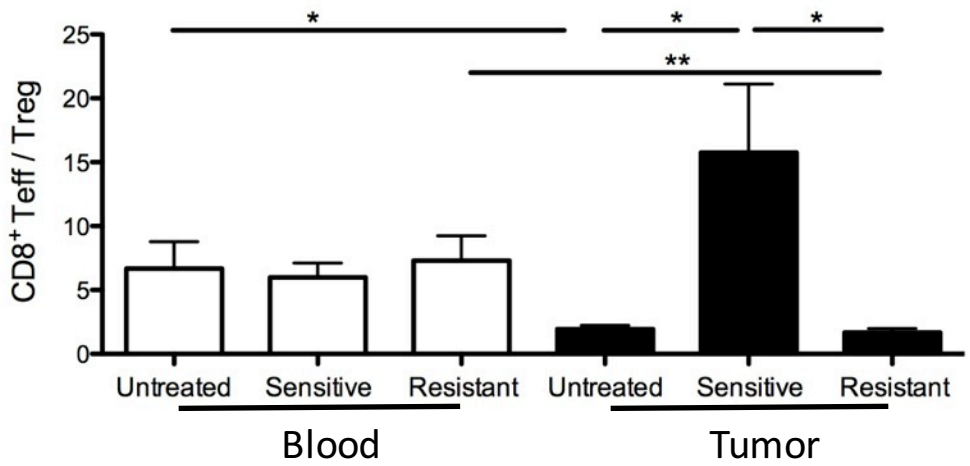
Imatinib inhibits tumor cell IDO



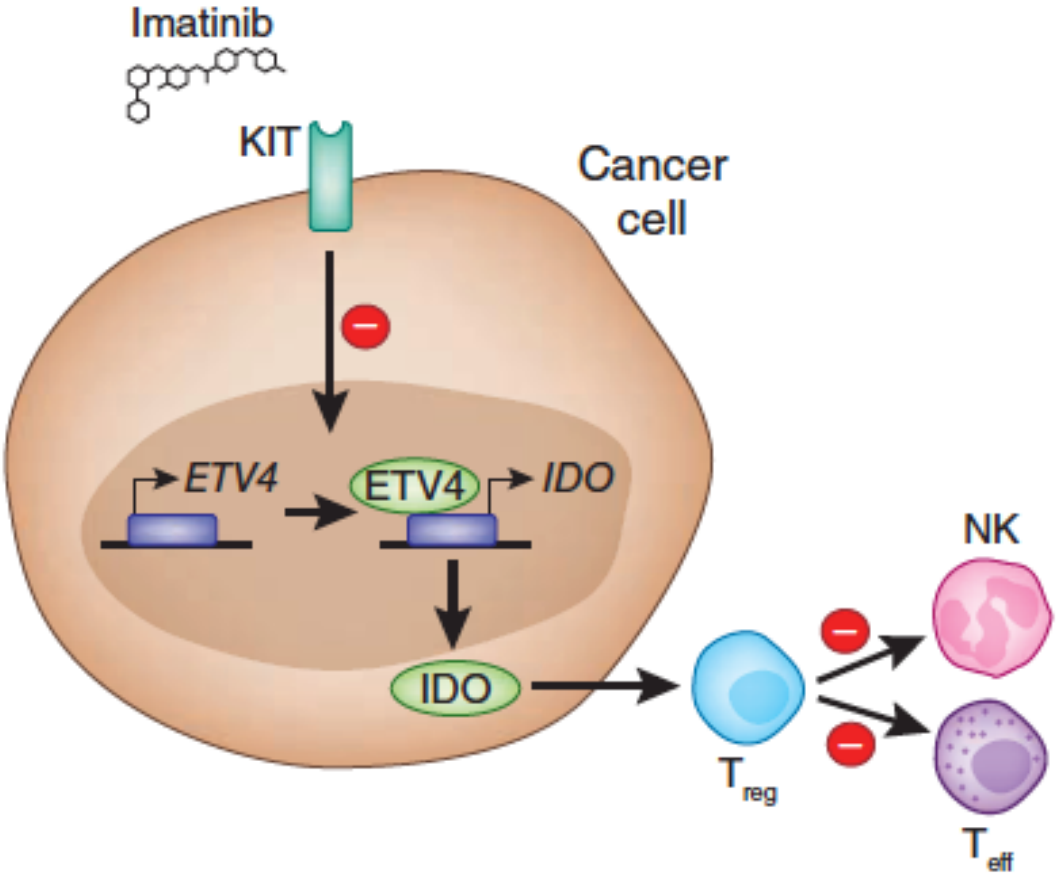
CD8:T reg correlates with imatinib sensitivity in human GIST (N=45 specimens)





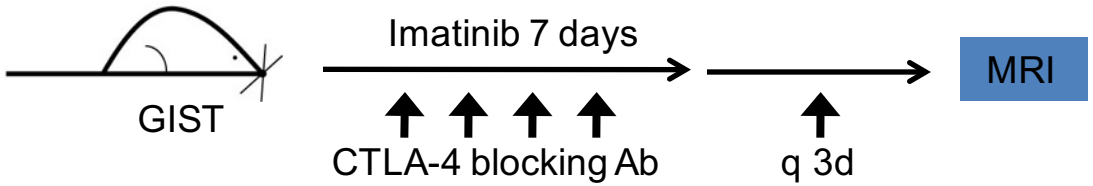


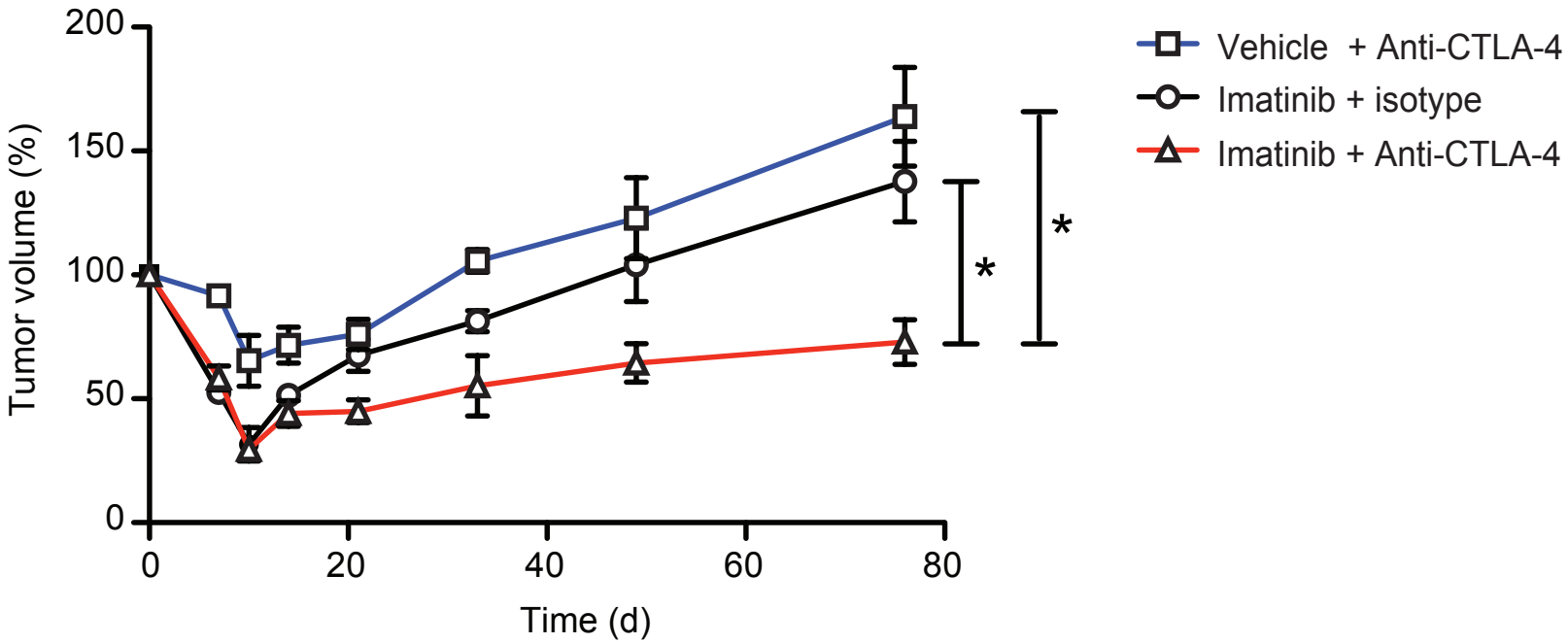
Mouse and Human T Cells in GIST



Zitvogel and Kroemer, Nat Med 2011; 17:1050

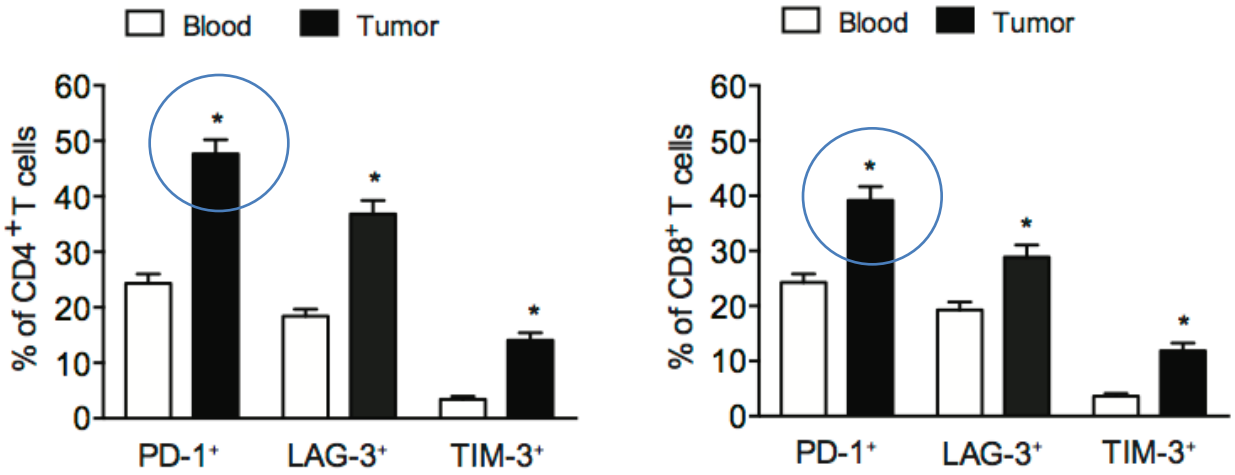
Imatinib synergizes with anti-CTLA-4 in mouse GIST





Nature Med 2011; 17:1094

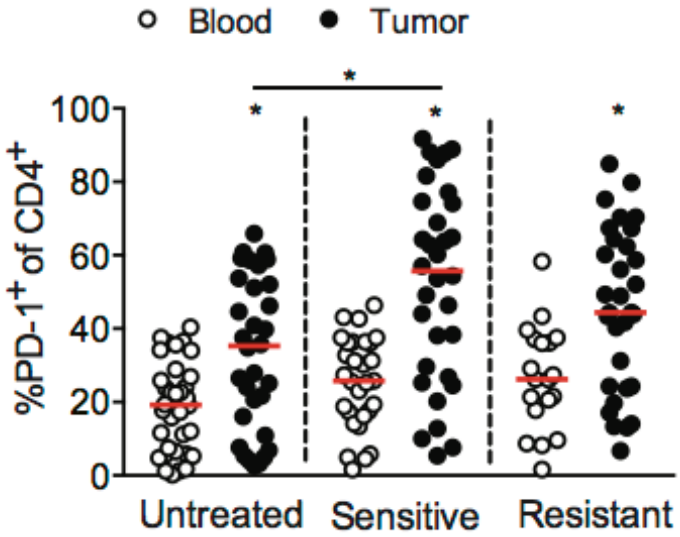
Co-inhibitory Receptors on T cells in Human GIST

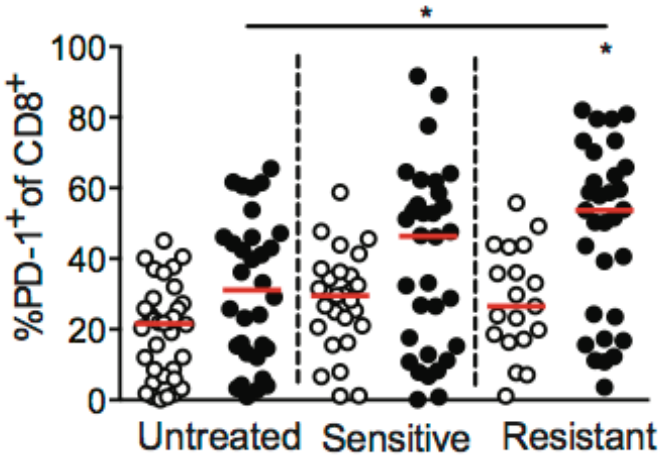


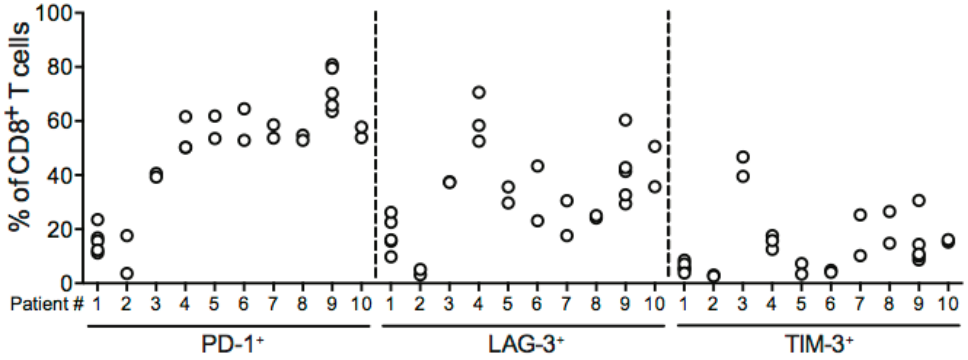
106 specimens in 85 patients

Clin Cancer Res *in press*

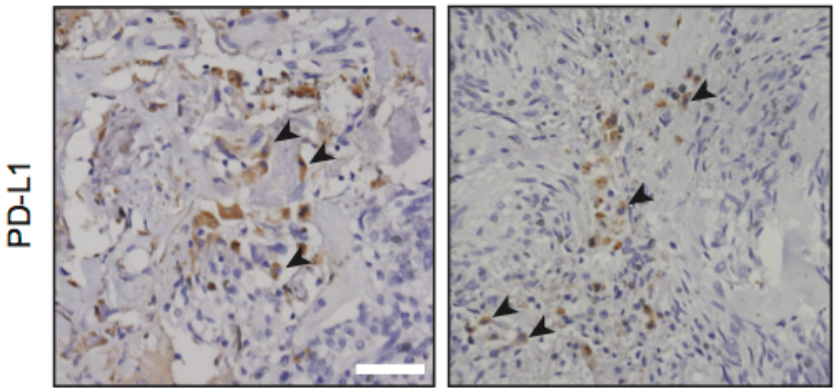
PD-1 Expression on T cells in Human GIST

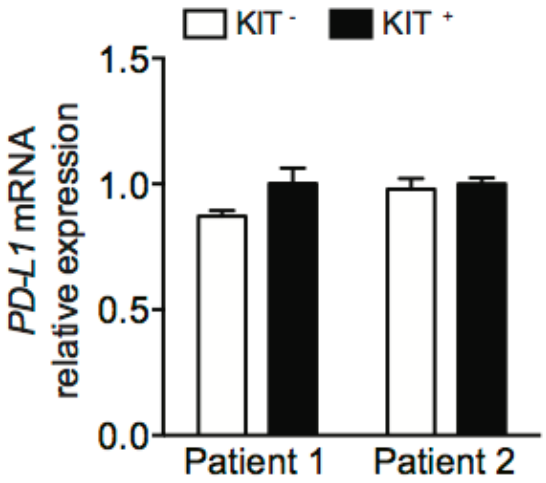


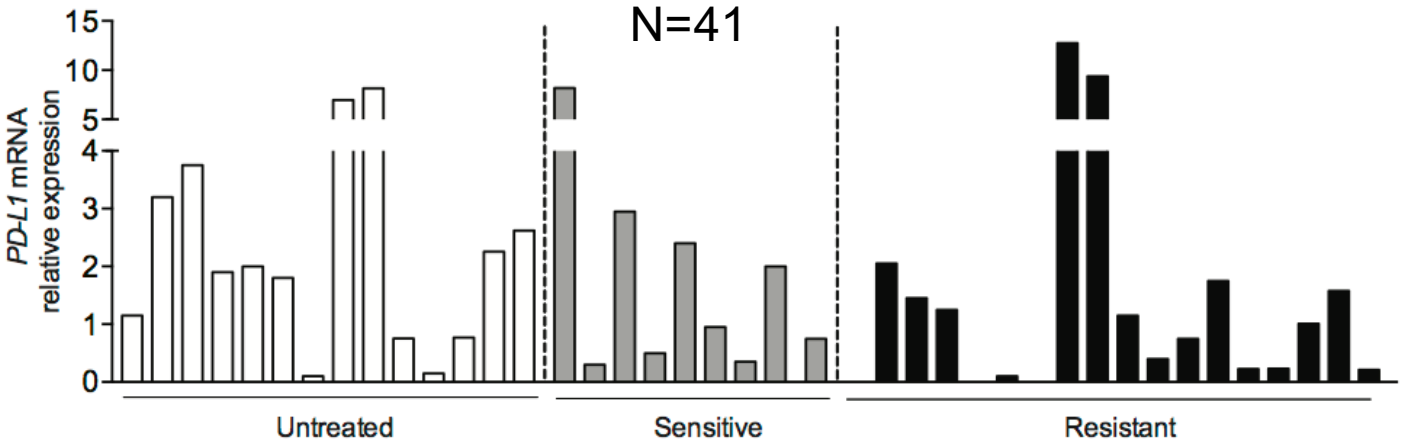




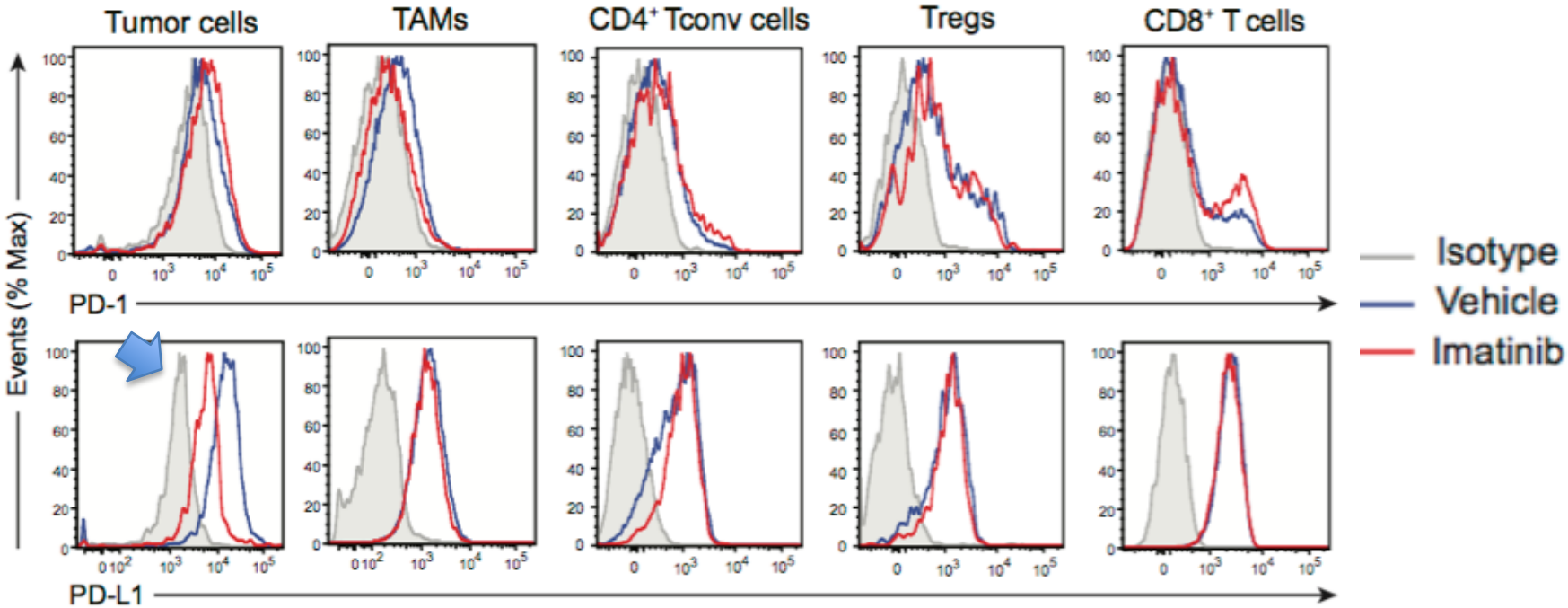
PD-L1 Expression in Human GIST

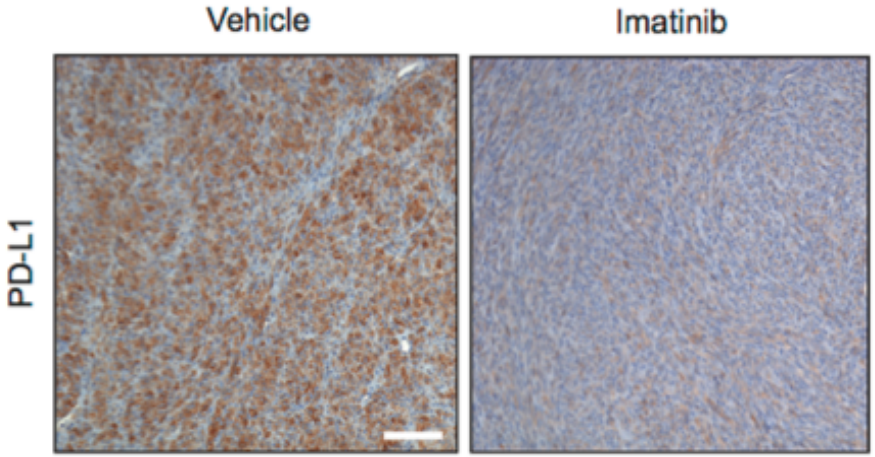




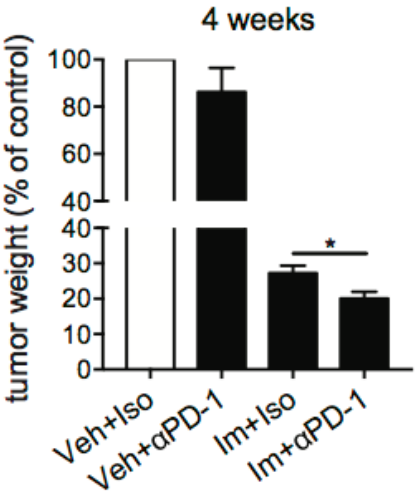


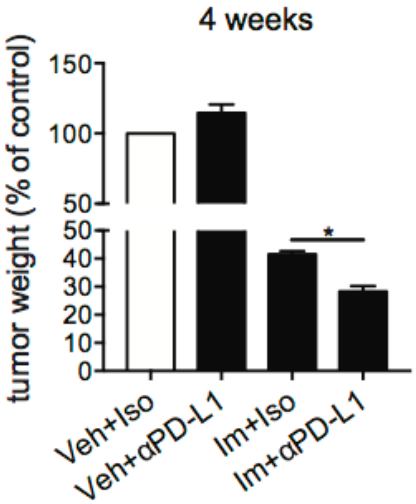
PD-1/PD-L1 in Murine GIST

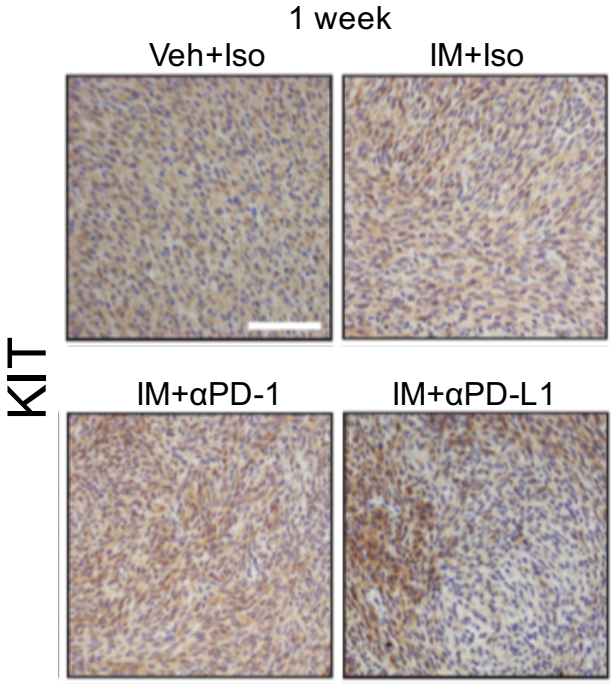


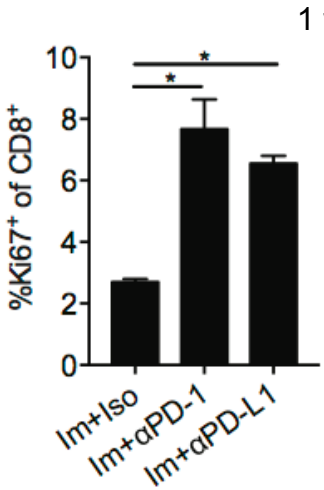


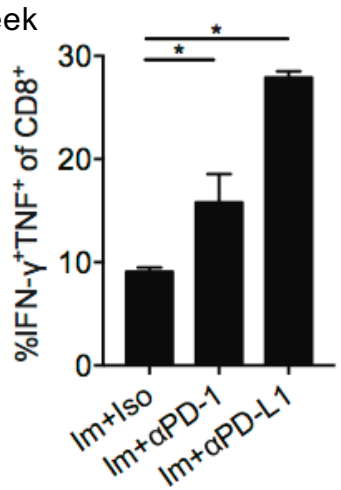
PD-1/PD-L1 Therapy in Murine GIST

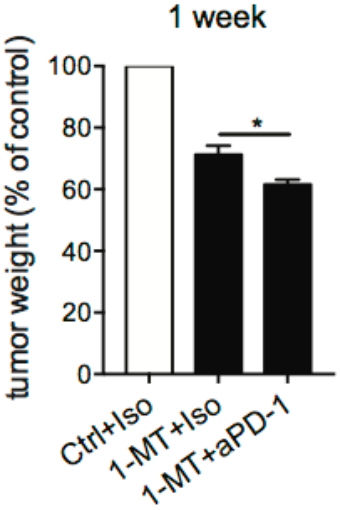












Summary

- 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

Acknowledgments

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