New Advances in Research and Clinical Insights in Gastrointestinal Stromal Tumor (GIST)

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Memorial Sloan Kettering Cancer Center

May 24, 2017

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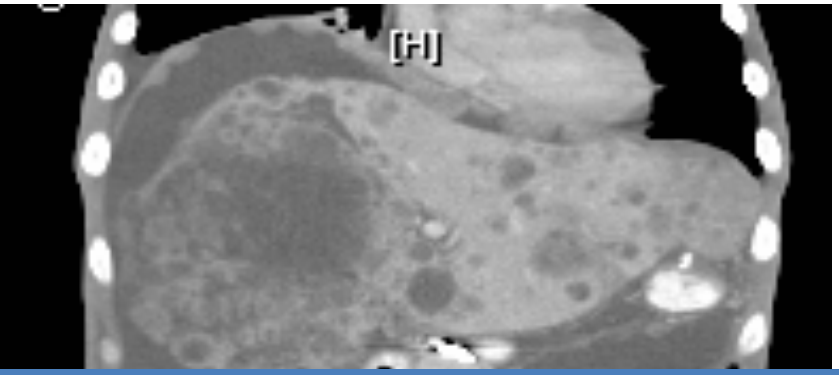
Gastrointestinal Stromal Tumor (GIST)



Management
- Surgery mainstay treatment
- Recurrence or metastatic disease - fatal
- Refractory to chemotherapy and radiation

- ~5,000 cases diagnosed per year in the US.

- One of the most common subtypes of soft tissue sarcomas, the most common mesenchymal neoplasm in the GI tract.

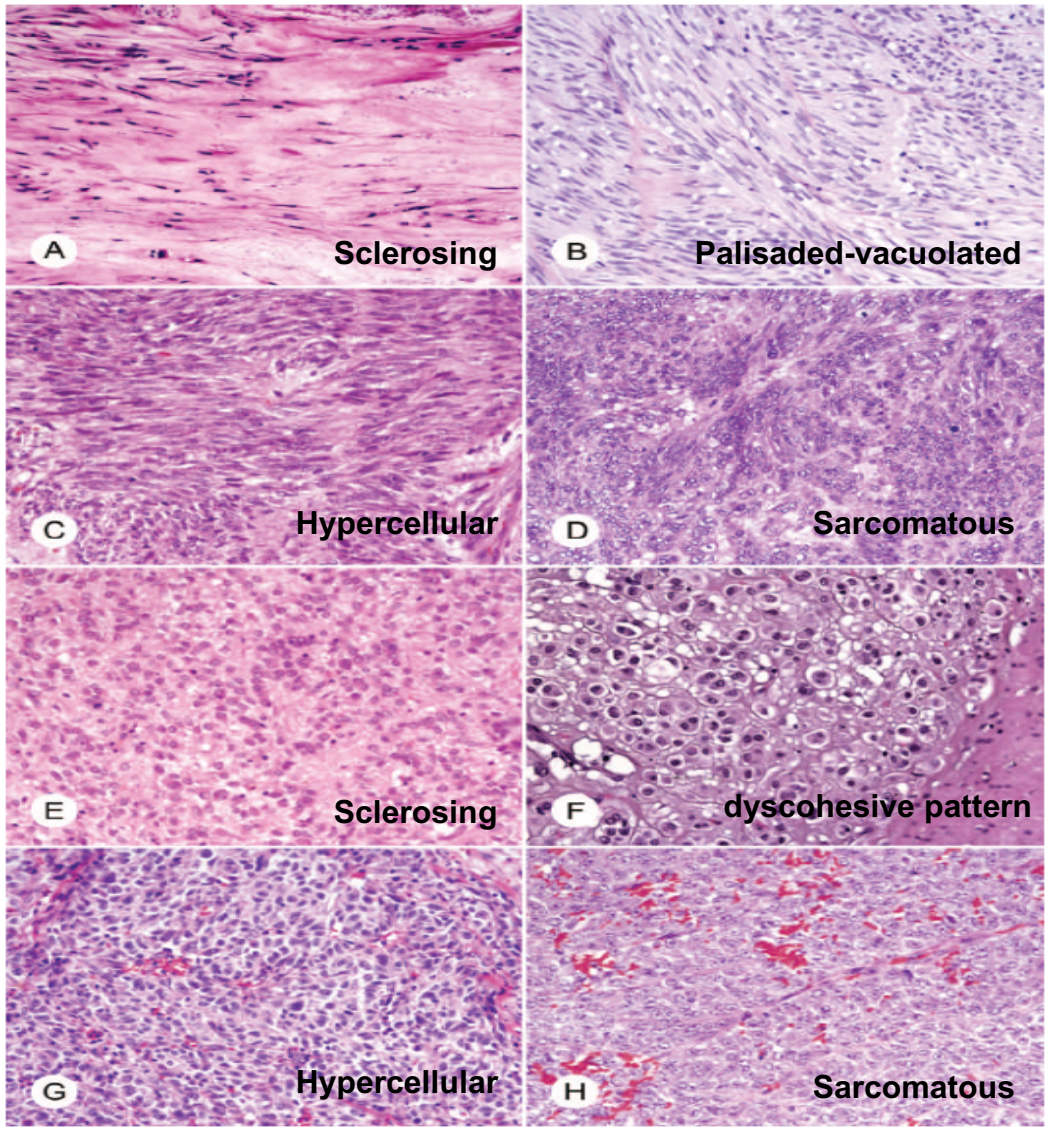
- Can arise anywhere from the entire GI tract; stomach is the most common primary site (2/3), then small bowel (1/4), esophagus/colon/rectum (the rest).

- Peak incidence 50-65 year old.

- Familial syndromes

Pre-KIT ERA: GIST- A clinicopathological challenge

GIST has broad morphological spectrum



Miettinen, M. and Lasota, Arch Pathol Lab Med 2006

- Difficult to diagnose!
- Difficult to treat!

Clinicopathologically distinct entity!

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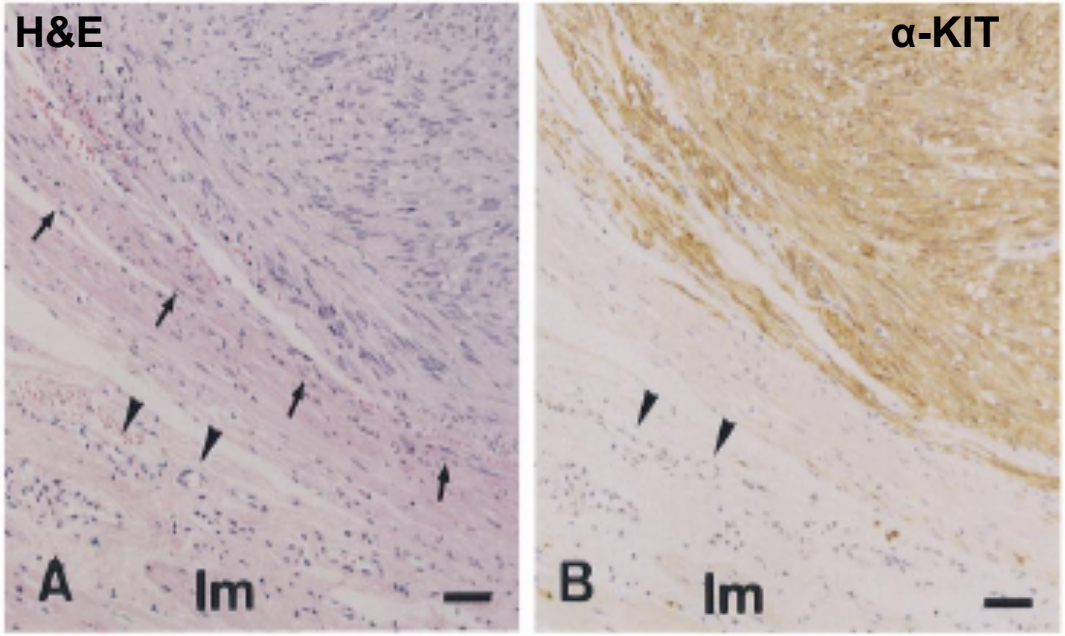
GIST originates from ICC and highly expresses KIT

- Originates from the Interstitial Cells of Cajal (ICCs) of the GI tract
- Characterized by KIT positive IHC and activating mutations in KIT or PDGFRA…

Interstitial Cell of Cajal (ICC)- Pacemaker cells of the GI tract

GIST of stomach



Hirota, S., et al., Science, 1998

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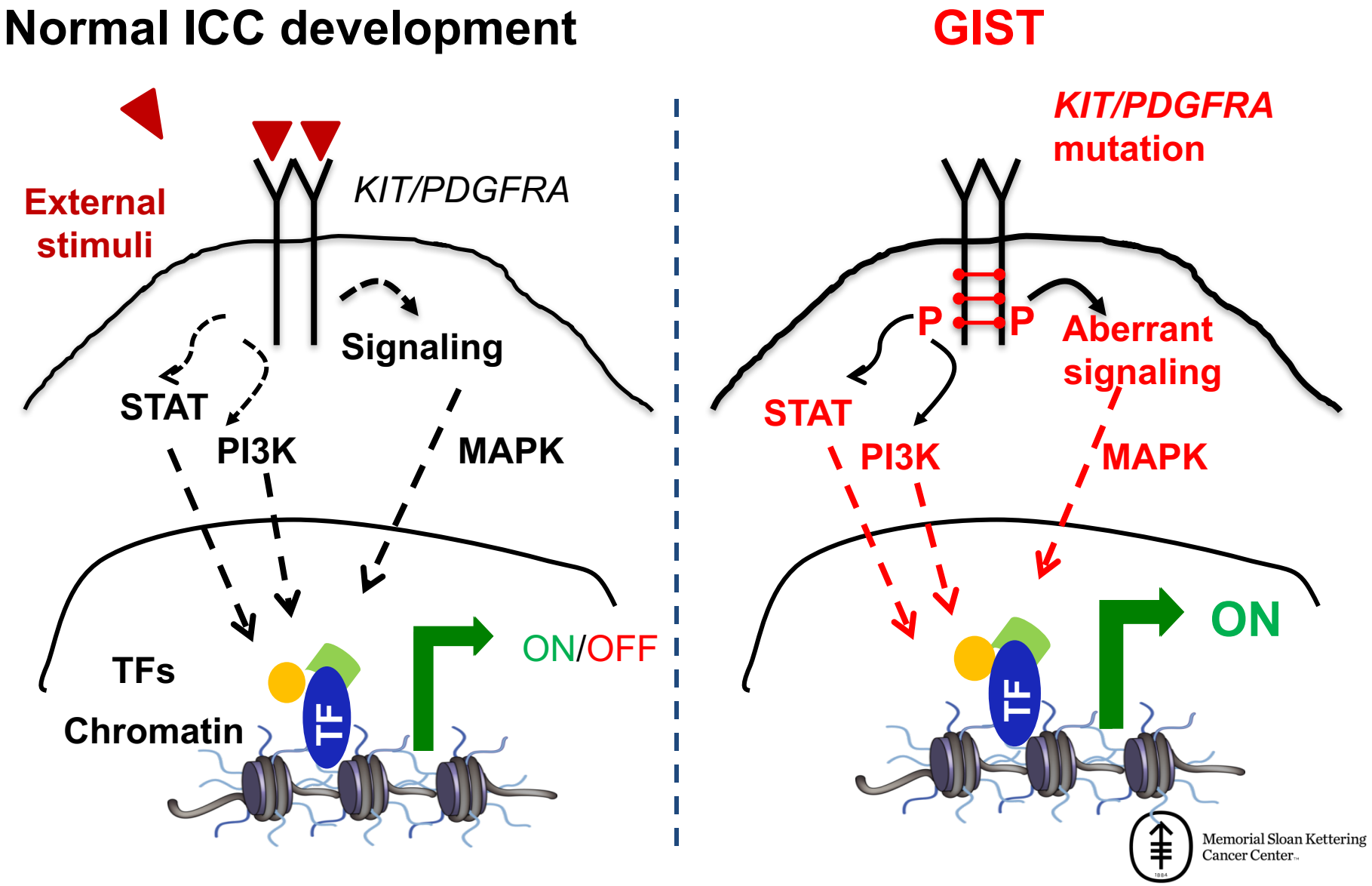
A Paradigm: Normal ICC development vs. GIST



Molecular characterization of GIST

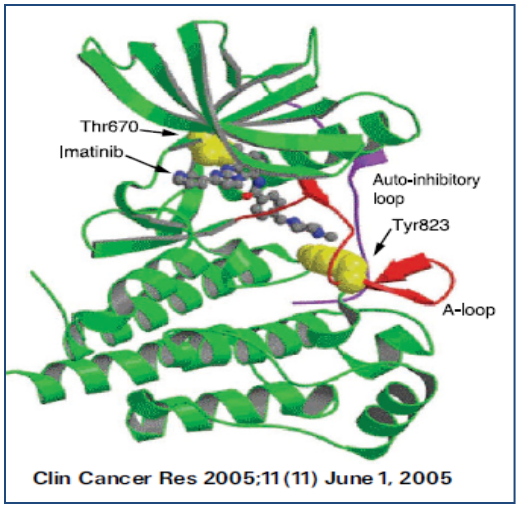
Table 1 | **Molecular classification of GISTs**

Genetic type	Relative frequency	Anatomic distribution	Germline examples
KIT mutation (relative frequency 75–80%)			
Exon 8	Rare	Small bowel	One kindred
Exon 9 insertion AY502-503	10%	Small bowel and colon	None
Exon 11 (deletions, single nucleotide substitutions and insertions)	67%	All sites	Several kindreds
Exon 13 K642E	1%	All sites	Two kindreds
Exon 17 D820Y, N822K and Y823D	1%	All sites	Five kindreds
PDGFRA mutation (relative frequency 5–8%)			
Exon 12 (such as V561D)	1%	All sites	Two kindreds
Exon 14 N659K	<1%	Stomach	None
Exon 18 D842V	5%	Stomach, mesentery and omentum	None
Exon 18 (such as deletion of amino acids IMHD 842–846)	1%	All sites	One kindred
KIT and PDGFRA wild-type (relative frequency 12–15%)			
BRAF V600E	~7–15%		
SDHA, *SDHB*, *SDHC* and *SDHD* mutations	~2%	Stomach and small bowel	Carney–Stratakis
HRAS and *NRAS* mutation	<1%		
Sporadic paediatric GISTs	~1%	Stomach	Not heritable
GISTs as part of the Carney triad	~1%	Stomach	Not heritable
NF1-related	Rare	Small bowel	Numerous

GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type I; *PDGFRA*, platelet-derived growth factor receptor-α; SDH, succinate dehydrogenase.

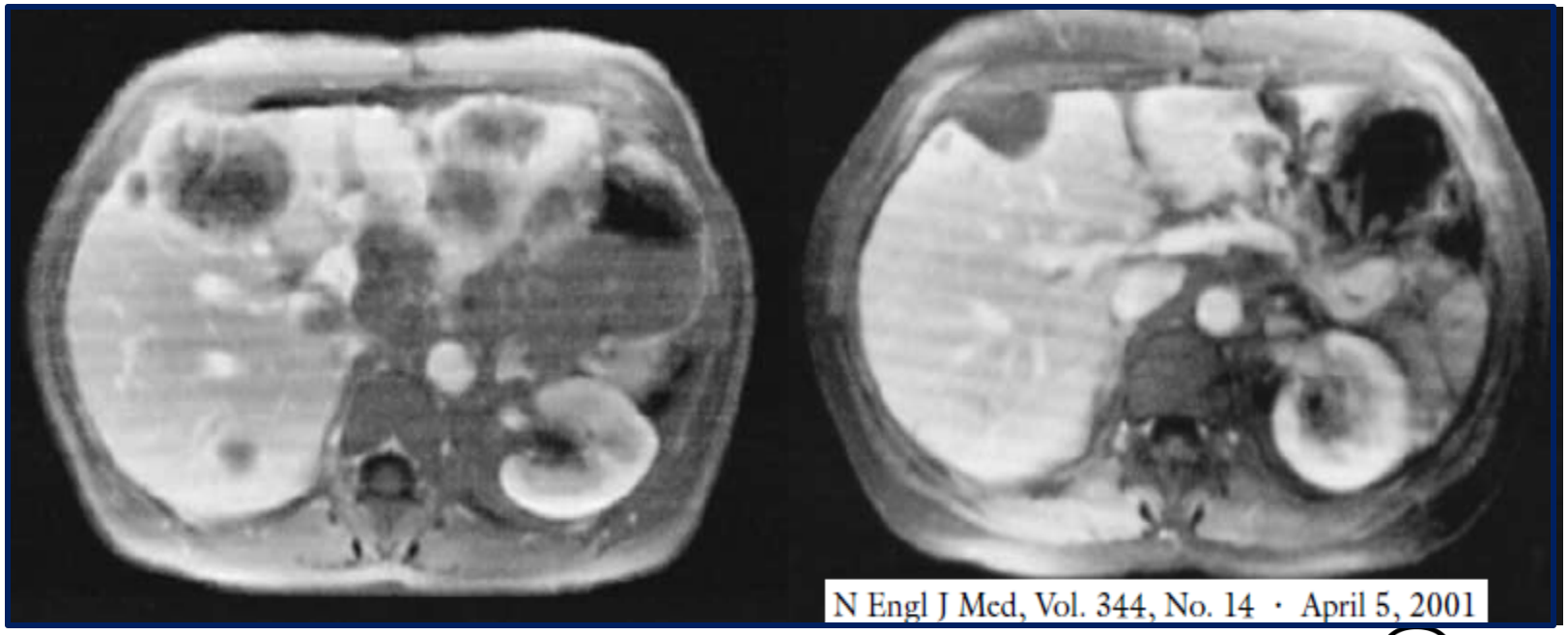
Corless et al, Nat Rev Cancer, 2011

Imatinib (Gleevec) in GIST



Clin Cancer Res 2005;11(11) June 1, 2005

- Activity – Abl kinase, *KIT, PDGFRA*



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EFFICACY AND SAFETY OF IMATINIB MESYLATE IN ADVANCED GASTROINTESTINAL STROMAL TUMORS

GEORGE D. DEMETRI, M.D., MARGARET VON MEHREN, M.D., CHARLES D. BLANKE, M.D., ANNICK D. VAN DEN ABBEELE, M.D., BURTON EISENBERG, M.D., PETER J. ROBERTS, M.D., MICHAEL C. HEINRICH, M.D., DAVID A. TUVESON, M.D., PH.D., SAMUEL SINGER, M.D., MILOS JANICEK, M.D., PH.D., JONATHAN A. FLETCHER, M.D., STUART G. SILVERMAN, M.D., SANDRA L. SILBERMAN, M.D., PH.D., RENAUD CAPDEVILLE, M.D., BEATE KIESE, M.SC., BIN PENG, M.D., PH.D., SASA DIMITRIJEVIC, PH.D., BRIAN J. DRUKER, M.D., CHRISTOPHER CORLESS, M.D., CHRISTOPHER D.M. FLETCHER, M.D., AND HEIKKI JOENSUU, M.D.

N Engl J Med, Vol. 347, No. 7 · August 15, 2002

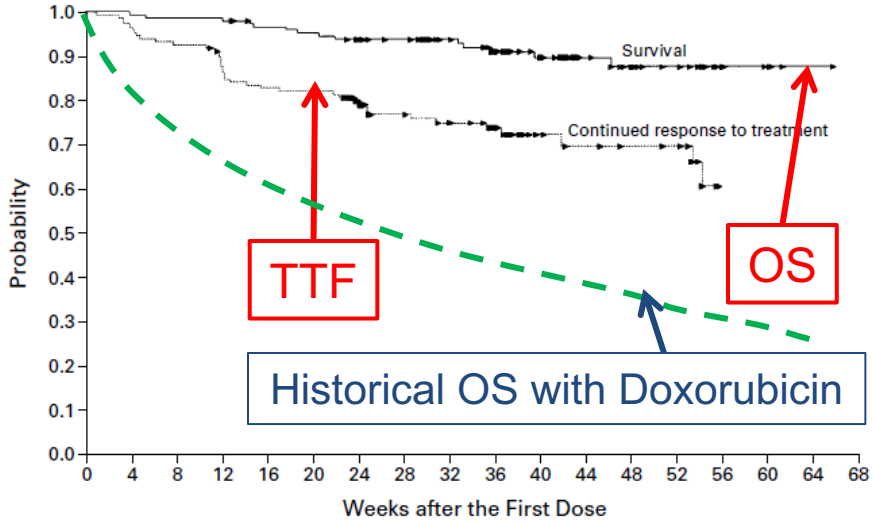
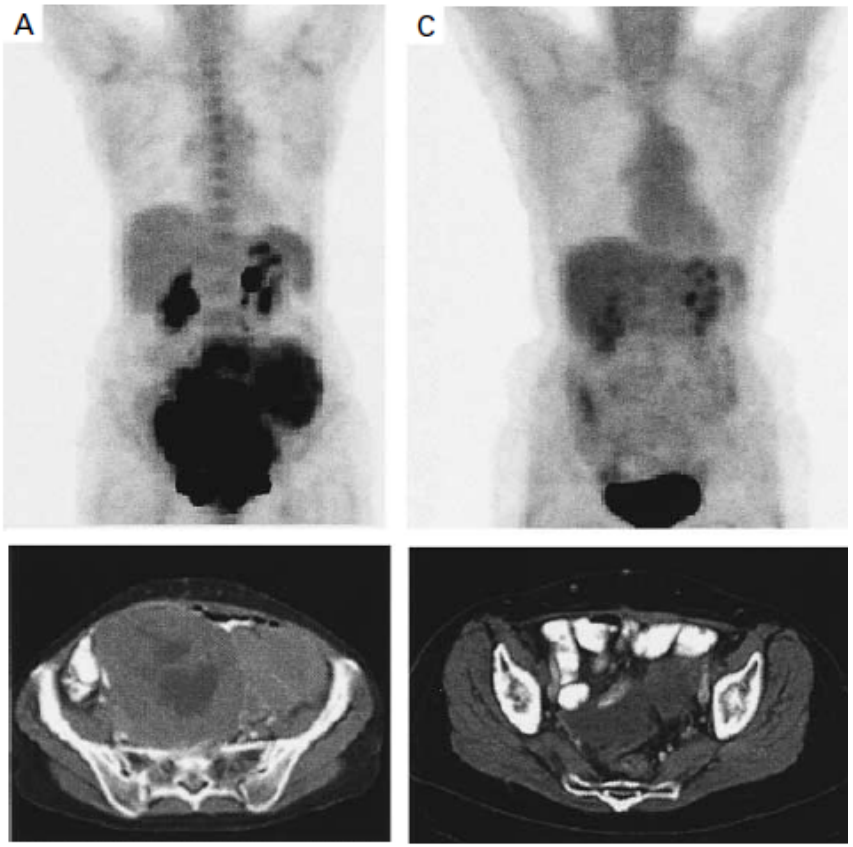


Figure 1. Kaplan–Meier Estimates of Overall Survival and Time to Treatment Failure for All Patients. Each arrowhead represents the point at which a patient's data were censored.



EORTC-62005
Phase III Trial (n = 377)[69]

SWOGS0033/CALGB150105
Phase III Trial (n = 428)[70]

Imatinib-FDA approved as 1st line therapy for GIST 2002!

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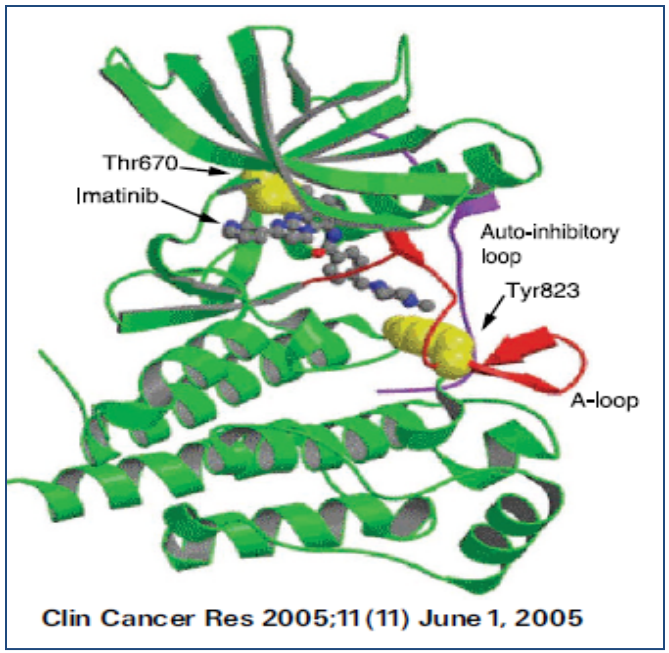
Challenges - Imatinib resistance in GIST

14% - Primary resistance; 50% - Develop imatinib resistance



Clin Cancer Res 2005;11(11) June 1, 2005

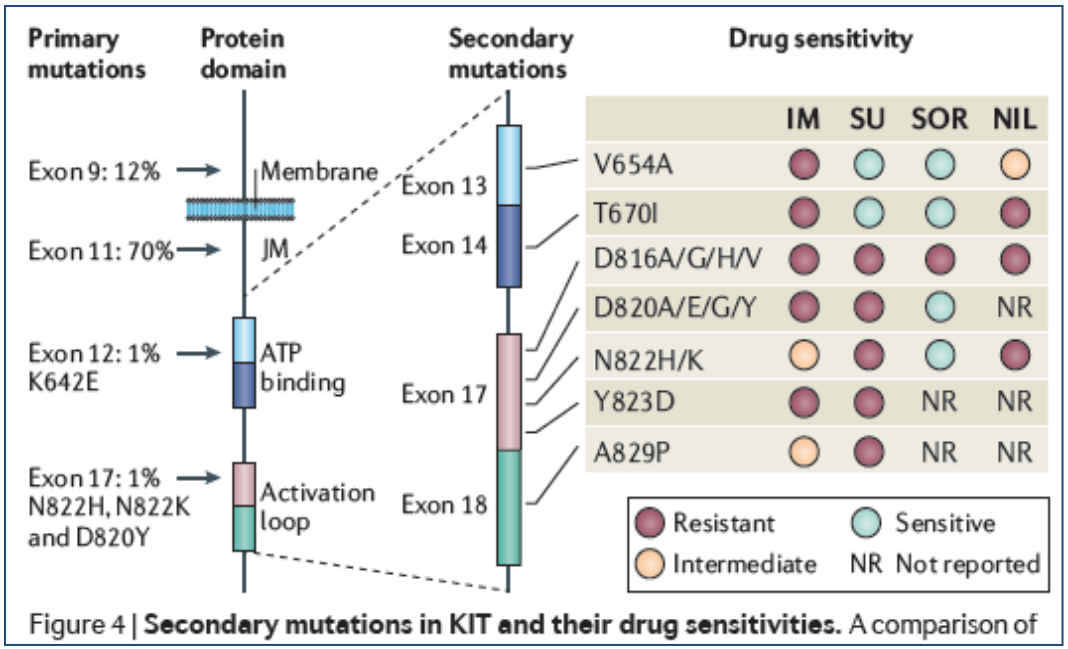


Figure 4 | **Secondary mutations in KIT and their drug sensitivities.** A comparison of

Corless et al, NRC, 2011

<u>Resistance Mechanisms:</u>

1. Secondary mutations (50-65%)
2. Genomic Amplification of RTKs
3. Activation alternative signaling pathways
4. Kit-low, imatinib-resistant GIST stem/progenitors
5. Others…

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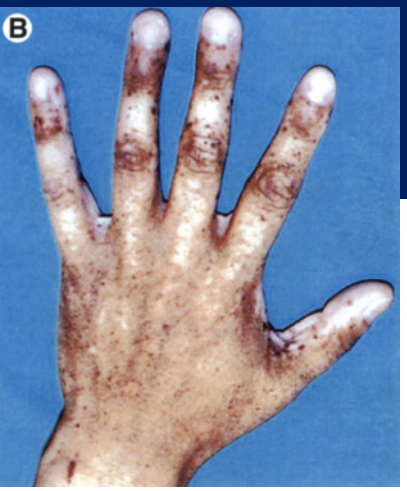
How to overcome imatinib resistance?

1) More effective first line therapy than imatinib
   - Reduce the persistence of disease
   - Reduce the adaptive responses to imatinib

2) Next generation of targeted therapy for imatinib resistant mutations, KIT exon 14 and exon 17 secondary mutations, PDGFRA D842V mutation



A Clinical Conundrum

KIT

(regulates multiple cell lineages)

ICC **Melanocyte** **Germ cell** **Mast cell**

Familial GIST

GIST

activating *KIT* mutants

What is special about the ICC lineage and GIST?

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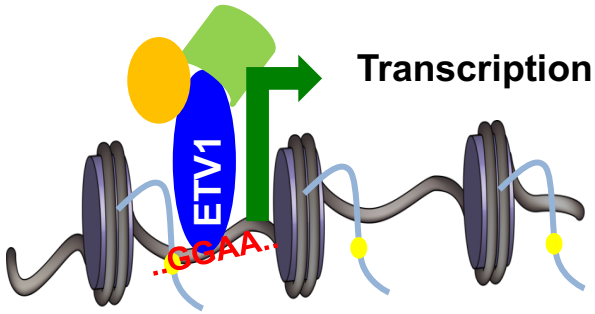
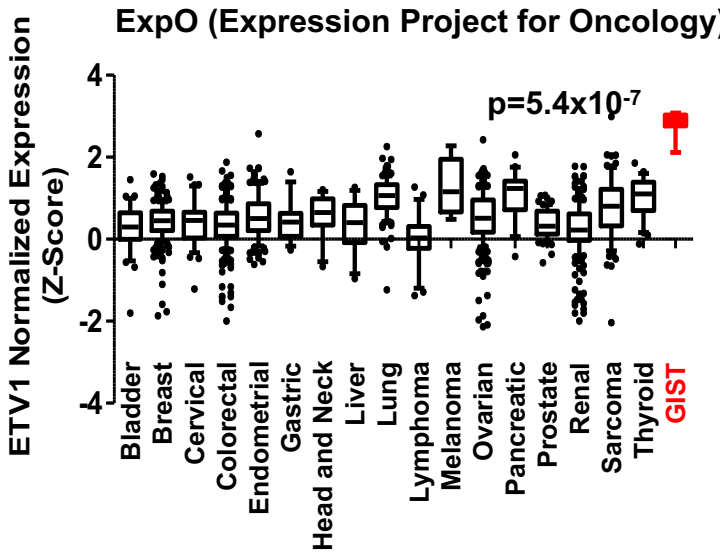
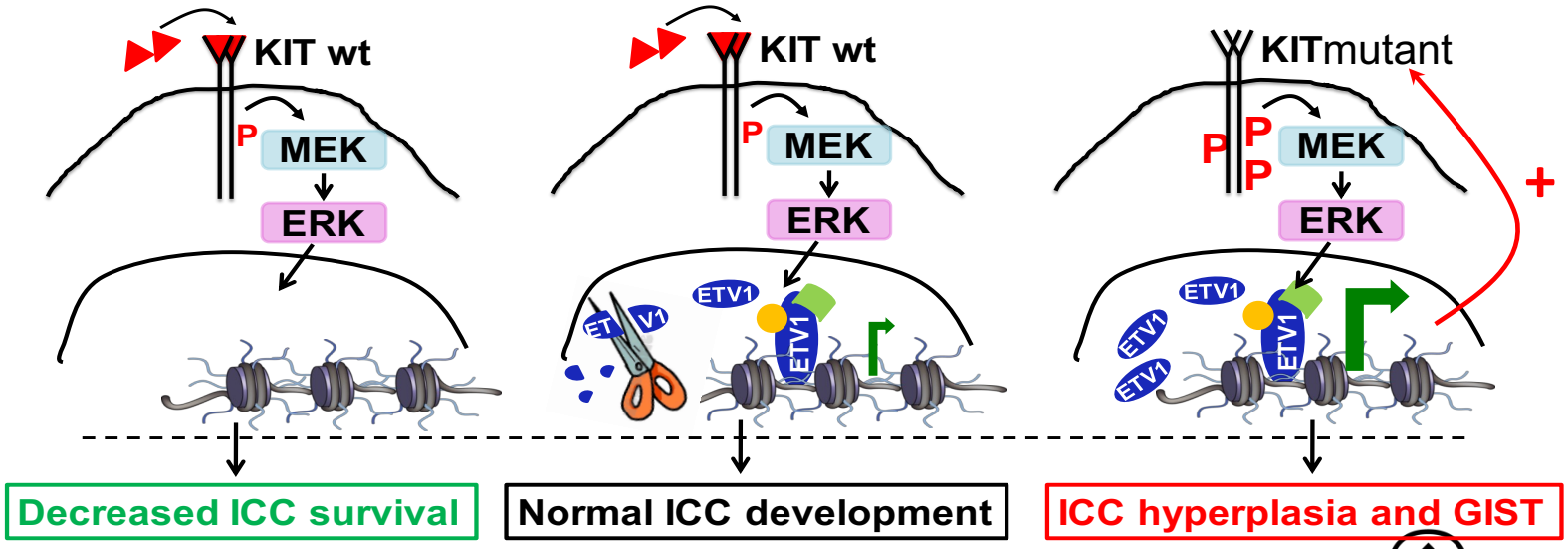
ETV1- A Lineage specific survival factor in GIST and ICC

ETV1: an "ETS family transcription factor"







Chi, P, Chen, Y et al, Nature 2010
Ran L et al., Cancer Discovery, 2015

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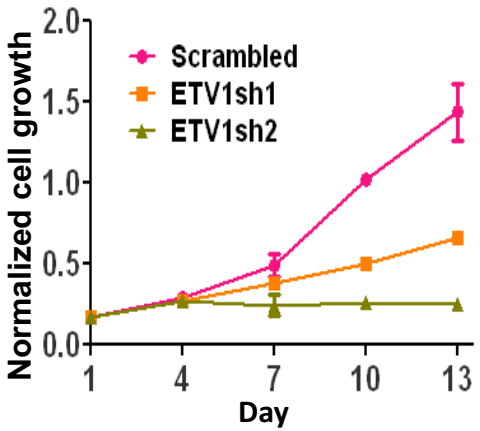
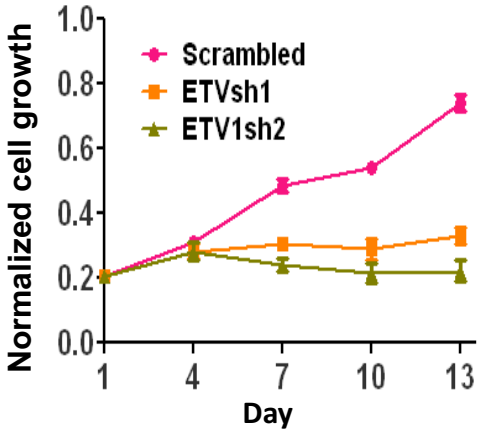
ETV1 is required for GIST growth and survival

GIST882 cell (imatinib sensitive)

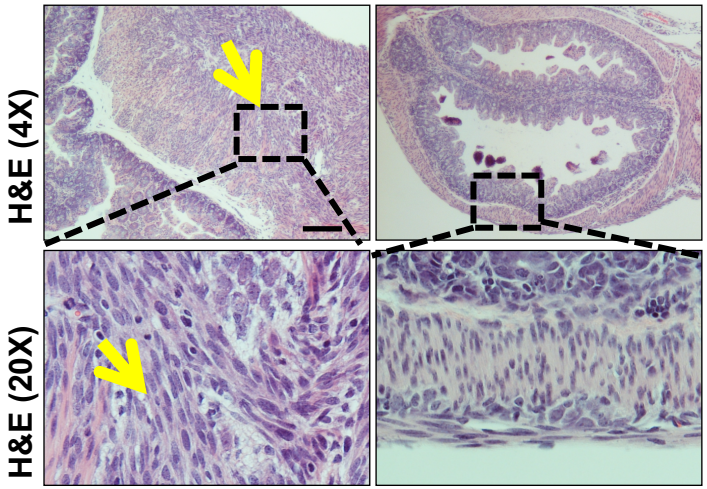


GIST48 cell (imatinib resistant)



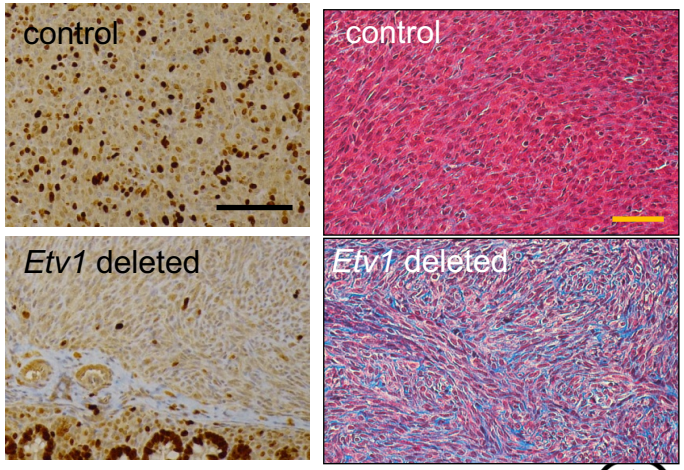
GEMM: *Kit*$^{\Delta 558/+}$

Cecum (*Etv1*$^{+/+}$;*Kit*$^{V558\Delta/+}$) **Cecum (*Etv1*$^{-/-}$;*Kit*$^{V558\Delta/+}$)**



GEMM: *Kit*$^{\Delta 558/+}$;*Etv1*$^{flox/flox}$;*Rosa26*$^{CreERT2/CreERT2}$)

Cecal tumor (Ki67 IHC) **Cecal tumor (trichrome)**



Chi, P, Chen, Y et al, Nature 2010
Ran L et al., Cancer Discovery, 2015

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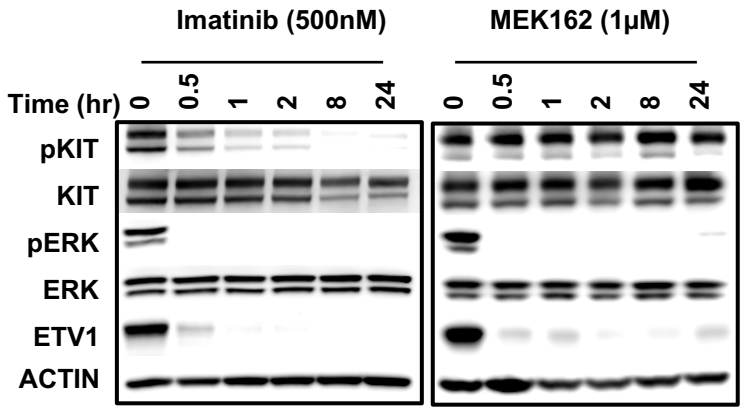
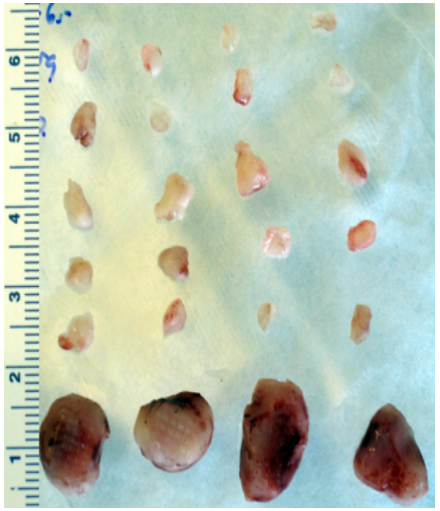
ETV1 and KIT forms a positive feedback circuit in GIST

GIST882 cells



Excised 3T3 allograft tumors



Vector

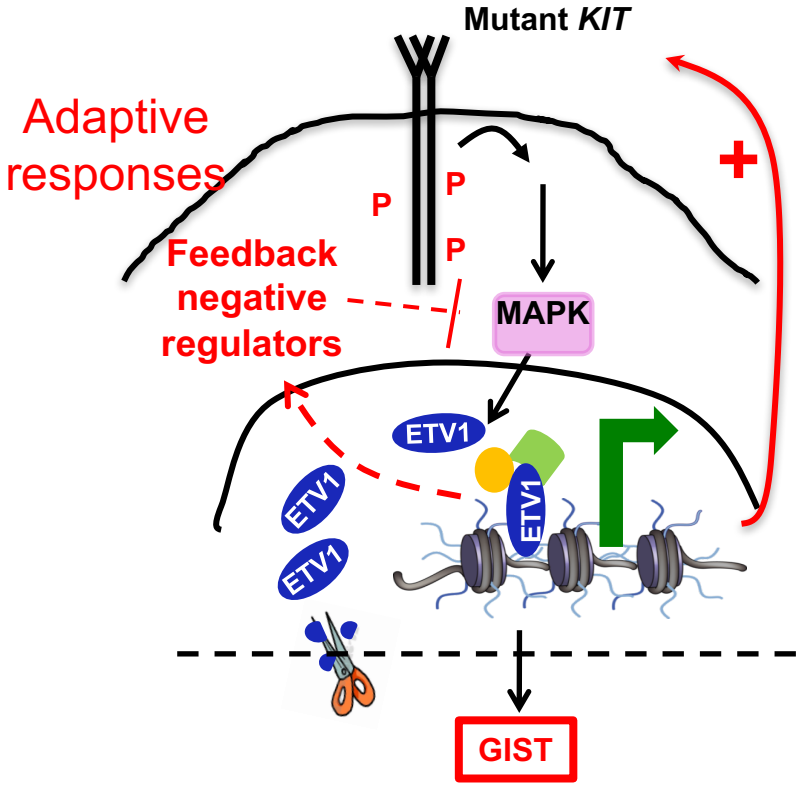
KITwt

KITΔ560

ETV1

ETV1+KITwt

ETV1+KITΔ560



ETV1 cooperates with KIT/MAPK signaling in GIST

- KIT/MAPK activation stabilizes ETV1 protein
- ETV1 directly upregulates KIT expression
- Positive feedback (ETV1 and mutant *KIT*)
- Target the adaptive responses in response to TKIs
- Targeting ETV1 protein stability – novel therapeutic approach

Chi, P, Chen, Y et al, Nature 2010
Ran L et al., Cancer Discovery, 2015
Unpublished result

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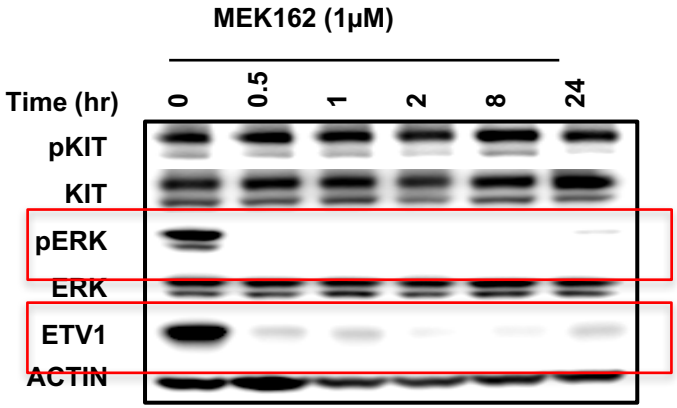
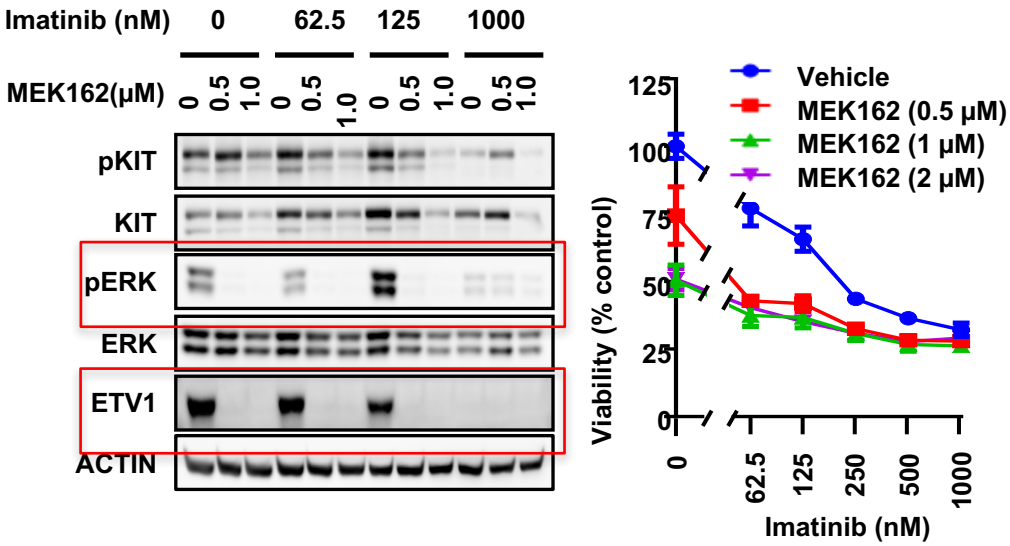
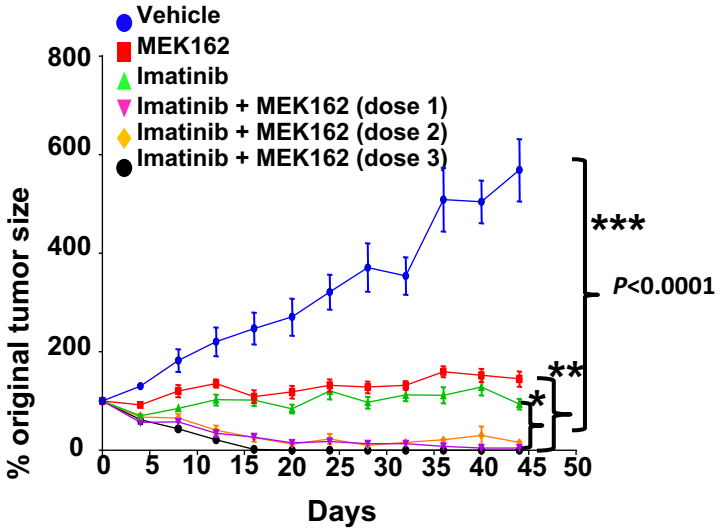
Synergy of combined MAPK and KIT pathway inhibition

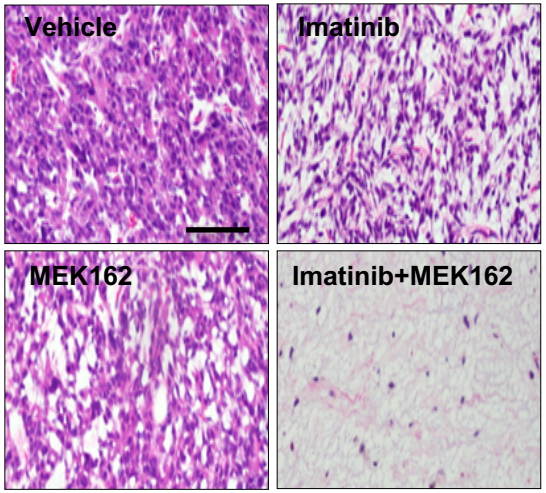
GIST882 cells





GIST882 xenografts





Chi, P, Chen, Y et al, Nature 2010
Ran L et al., Cancer Discovery, 2015

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Molecular biomarker driven novel therapies in GIST

More effective first line therapy than imatinib

-A phase Ib/II study of MEK162 (binimetinib) in combination with imatinib in patients with advanced gastrointestinal stromal tumor (GIST) (Clinicaltrials.gov#: NCT01991379)

- Phase Ib-completed and defined safety and tolerability and modest efficacy in imatinib-resistant GIST, presented in the 2015 ASCO sarcoma oral abstracts.

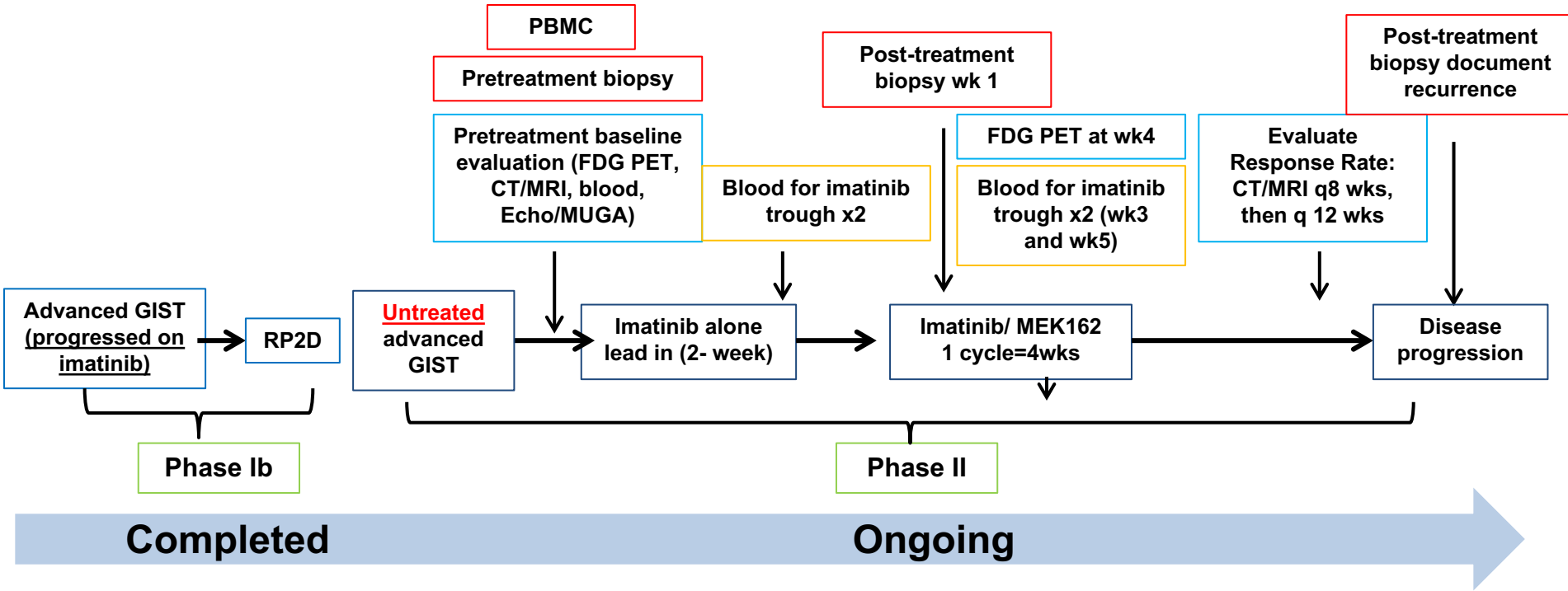
- Phase II in imatinib-naïve patient population is actively accruing.

Phase Ib/II study of MEK162 in combination with imatinib in patients with untreated locally advanced and metastatic GIST

Primary Objective:

Phase Ib: safety and tolerability of combining MEK162 (a MEK inhibitor) and imatinib, MTD and the recommended Phase II dose (RP2D) in GIST patients.

Phase II: ORR (CR + PR) by both RECIST 1.1



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Chi/Tap

Patient Characteristics (Phase Ib)

Characteristics	All Patients n=18
Age (yrs)	Median: 60; Range: 30-74
Sex	Female: 8; Male: 10
ECOG status	0-1
Number of prior therapy	Median: 3; Range: 1-6; 15/18 pts ≥ 3 prior therapies
Prior therapies: Imatinib Sunitinib Regorafenib Sorafenib Pazopanib Vemurafenib Dasatinib/Ipilimumab trial Linsitinib trial	 18 16 9 7 4 1 2 1
Molecular characteristics:	*KIT*(13, 10/13 with known imatinib-resistant *KIT* mutations); *NF1* loss (1); *BRAFV600E/NF1 loss* (1); SDH-*deficient* (1), Unknown (2)

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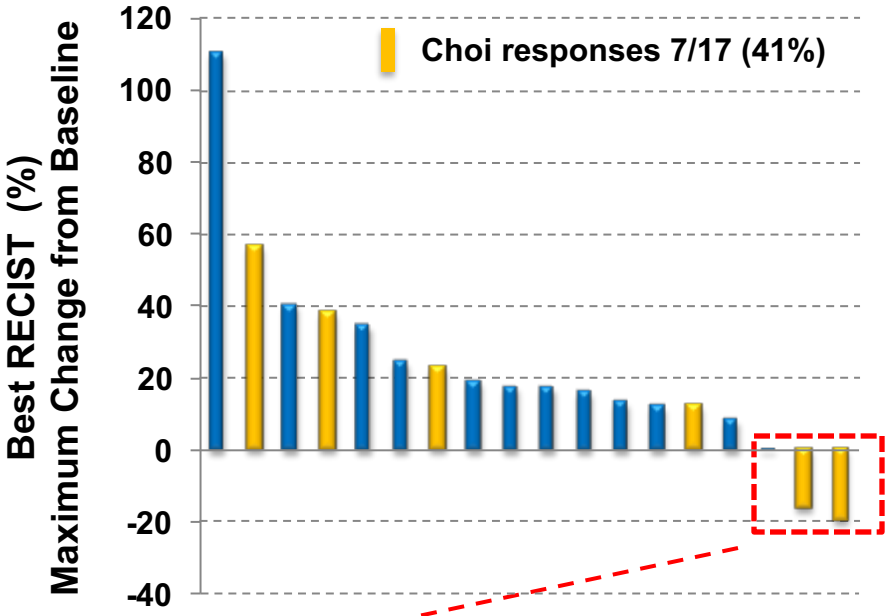
Efficacy signal from phase Ib trial of MEK162+Imatinib in GIST

a



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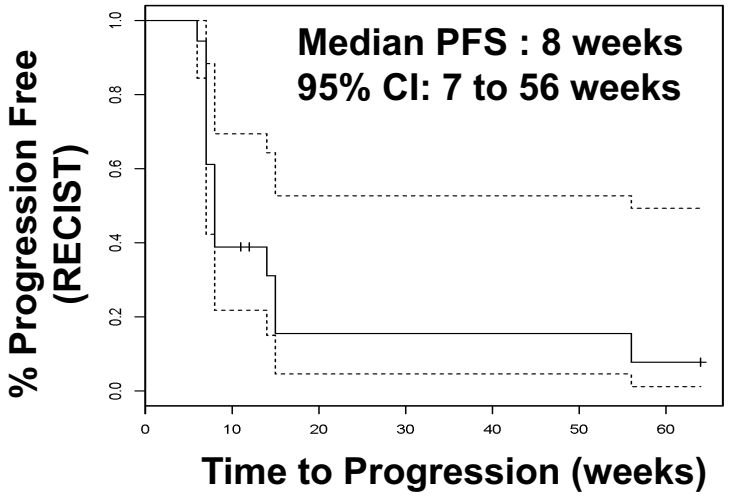

c

Dose Escalation Cohort	Pt #	Prior Therapies	Mutational Status	Duration (wks)	Best RR (RECIST)	Best RR (CHOI)
Imatinib 400mg QD + MEK162 45mg BID	4	Imatinib, Sunitinib, Linsitinib trial	SDHA R31X;SDHB loss by IHC	>135 (active)	SD (-20%)	PR
	8	Imatinib, Sunitinib, Sorafenib	KIT exon11, L576P	55	SD (-16%)	PR

Patients who have imatinib-resistant *KIT* mutations all progressed within 16 weeks.

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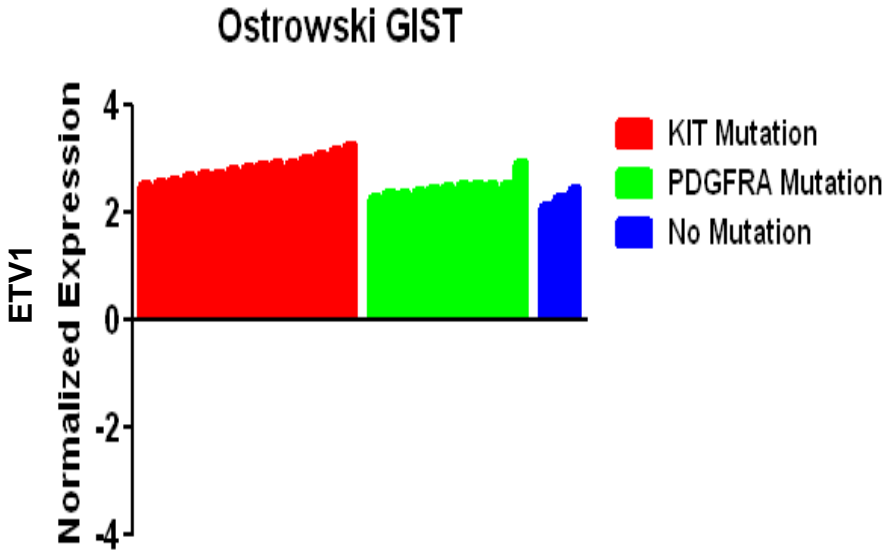
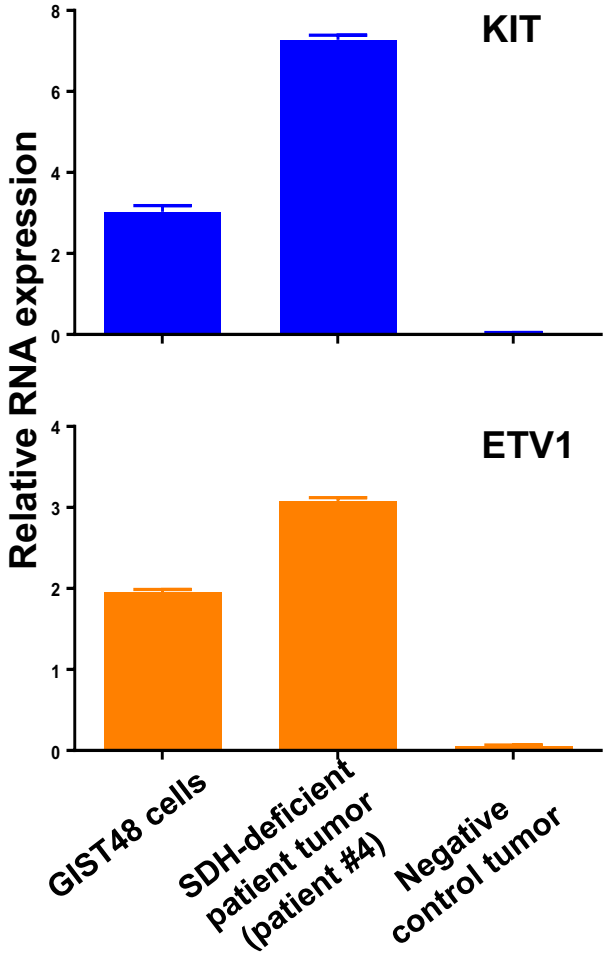
ETV1 is highly expressed in *KIT/PDGFRA* wild-type GIST



Ostrowski J et al., BMC Cancer 2009



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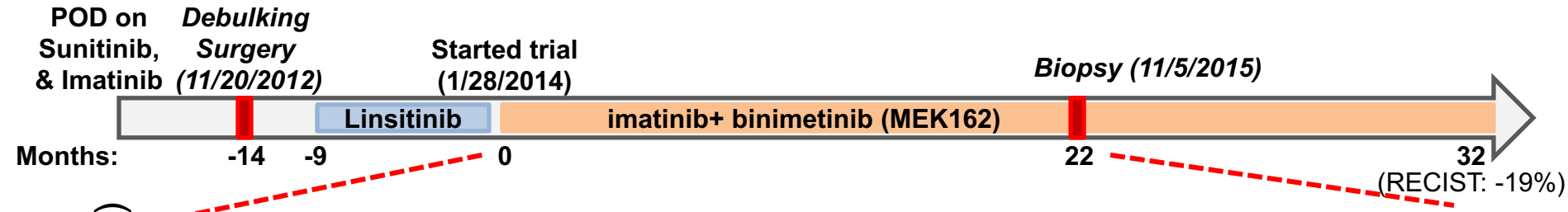
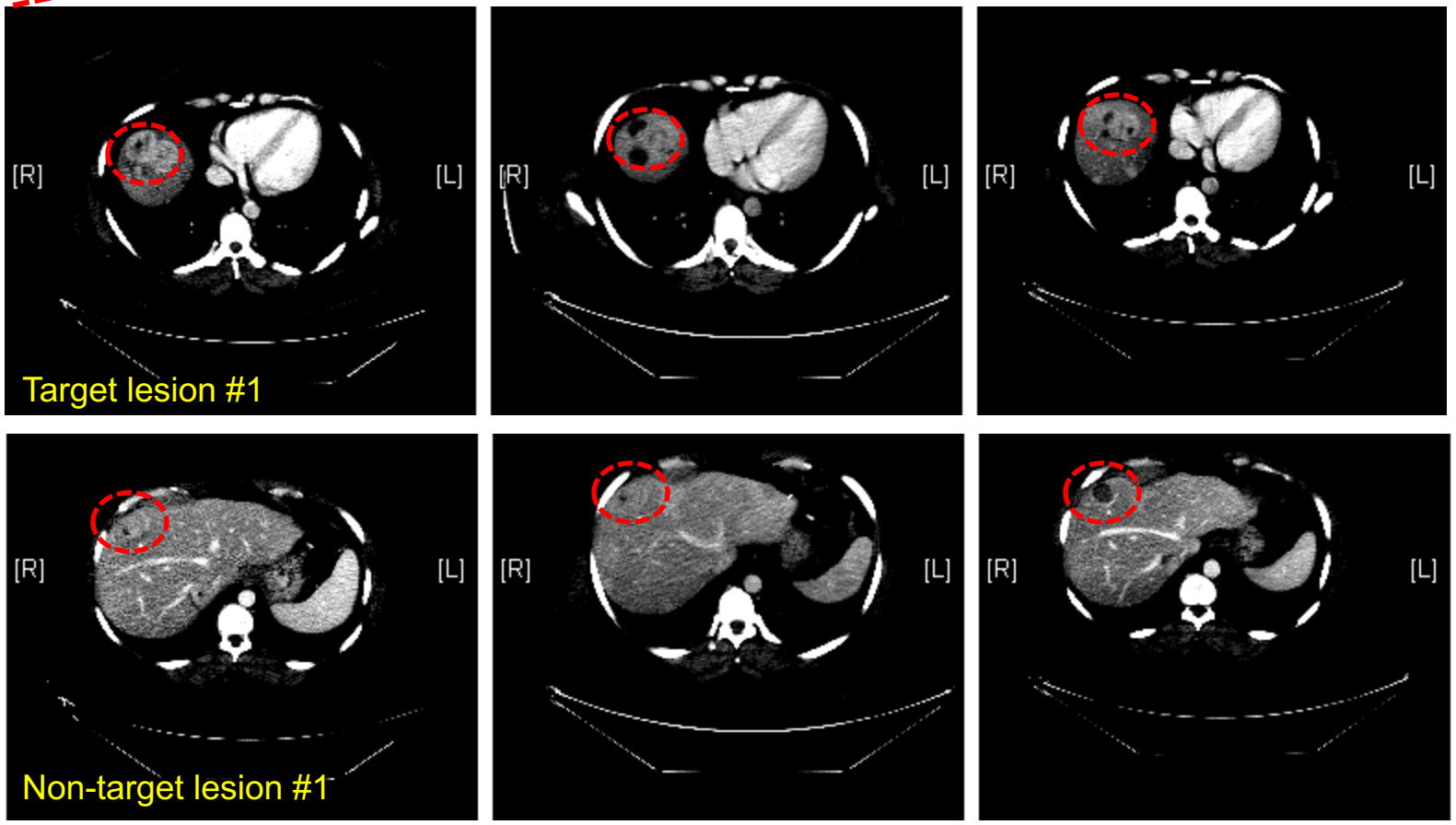
Lefli Ran/Yu Chen

Combination Treatment of Imatinib and Binimetinib (MEK162)

Timeline of Rx



CT scans of the liver lesions (liver window)



Before treatment

~12 months (RECIST: -20%)

~24 months (RECIST: -34%)

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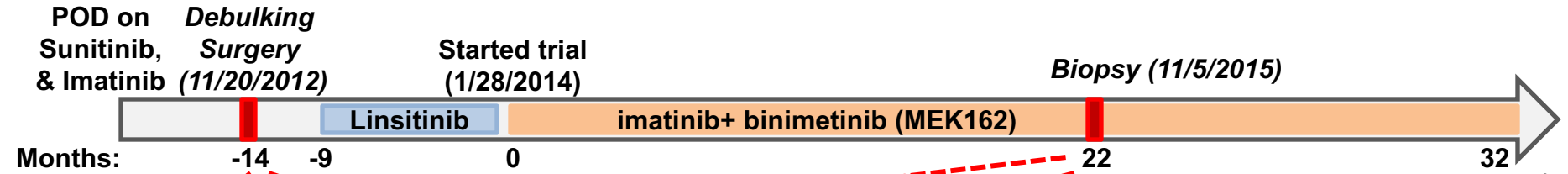
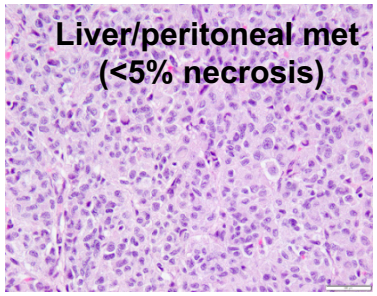
Exceptional response in a patient with SDH-deficient GIST

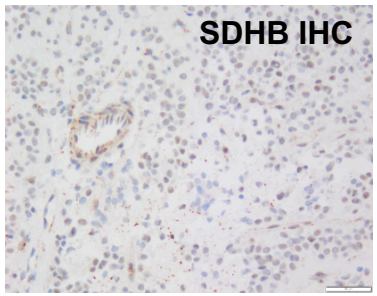
Timeline of Rx

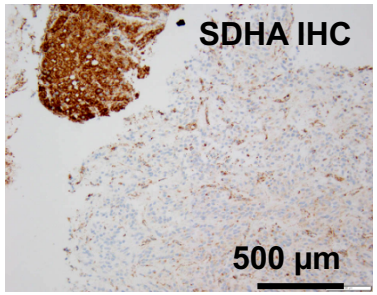


IMPACT:

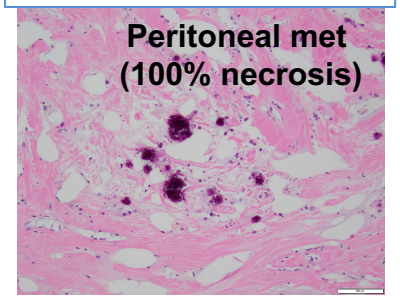
SDHA exon 2 p.R31X

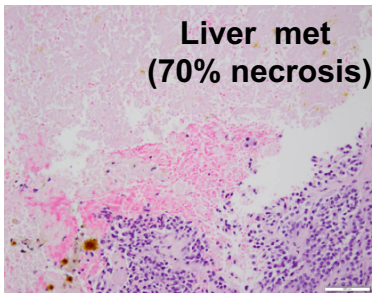


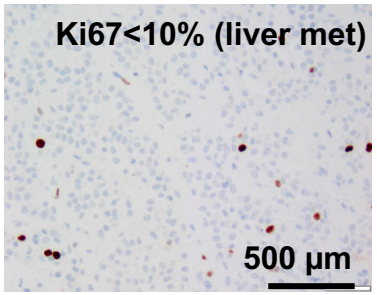


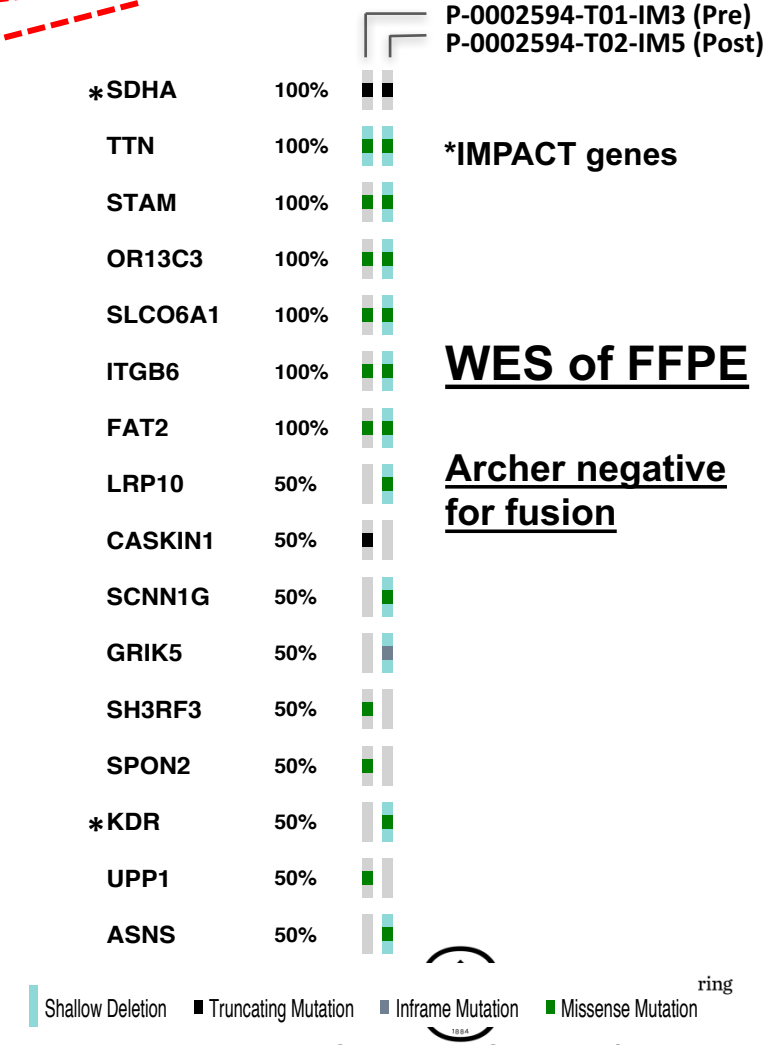


SDHA exon 2 p.R31X
KDR exon 30 p.V1334E









*IMPACT genes

WES of FFPE

Archer negative for fusion

Cristina R. Antonescu

Camacho Ordonez/Berger

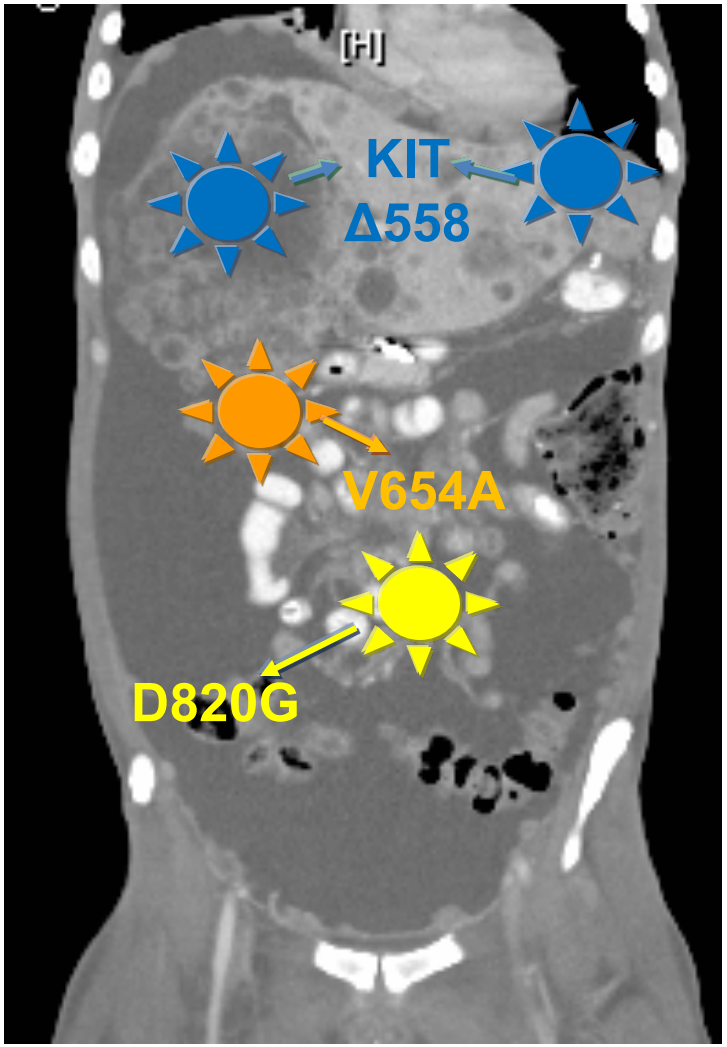
How to overcome imatinib resistance?

1) More effective first line therapy than imatinib
   - Reduce the persistence of disease
   - Reduce the adaptive responses to imatinib

2) Next generation of targeted therapy for imatinib resistant mutations, KIT exon 14 and exon 17 secondary mutations, PDGFRA D842V mutation

Molecular biomarker driven novel therapies in GIST

Polyclonal Resistance – much like CML
Single TKI may only effect one mutation



Next generation of targeted therapy for imatinib resistant mutations

- KIT exon 17 secondary resistant mutations
  PLX9486 (open); BLU-285 (phase I open)
- KIT exon 13/14 mutations
  PLX3397+/- PLX9486 (open soon)
- PDGFRA D842V mutation
  BLU-285 (phase I open)
- PLX3397 + Pembrolizumab (open soon)
- DCC2618, an allosteric inhibitor of KIT/PDGFRA (phase I open)….

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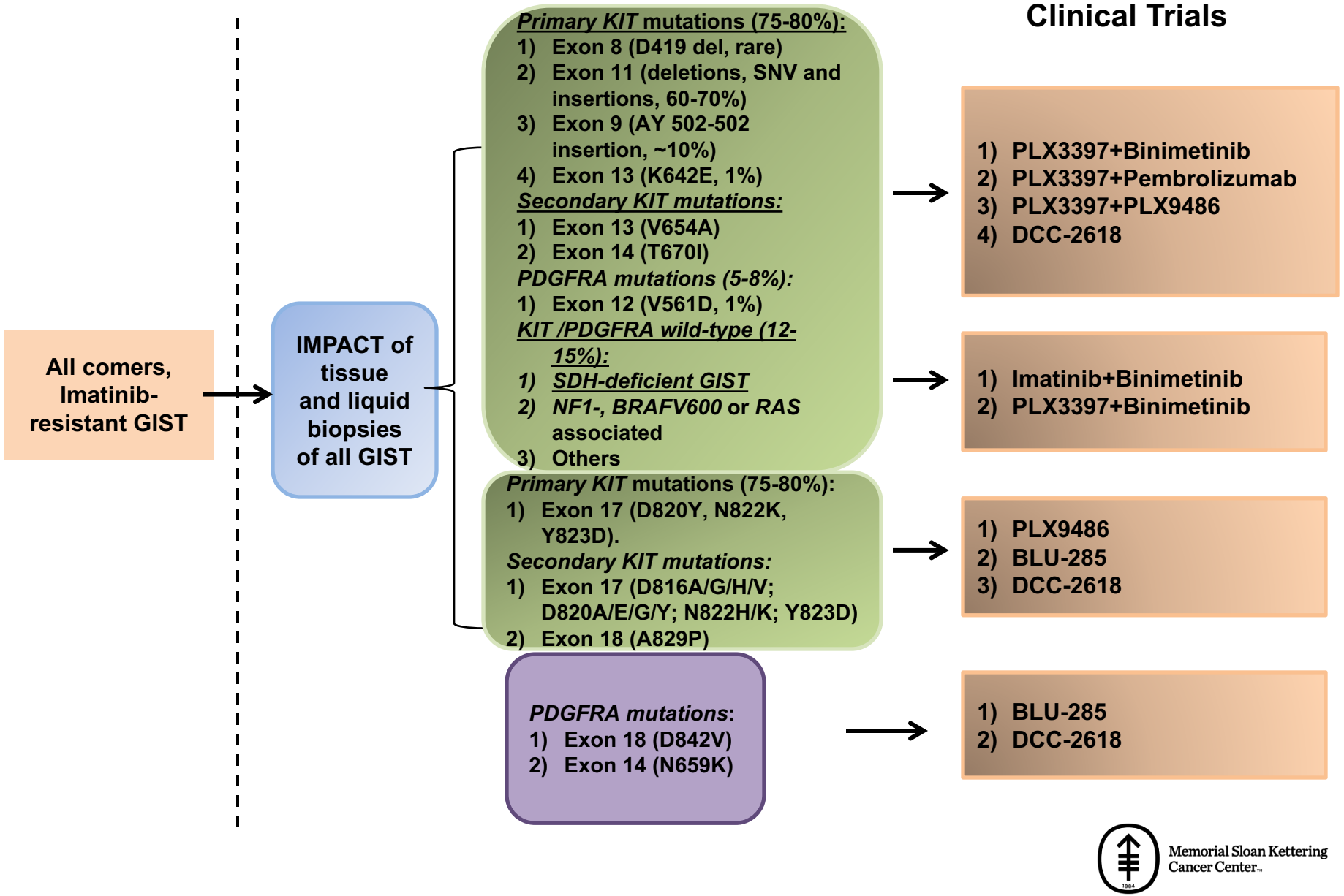
Precision therapy in imatinib-resistant setting



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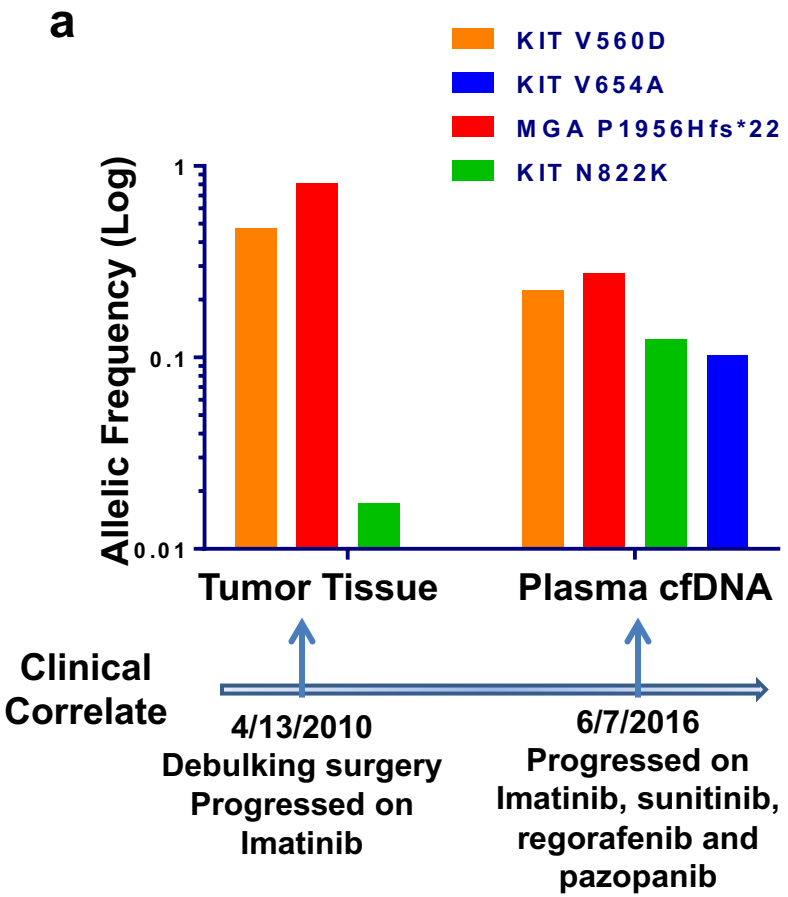
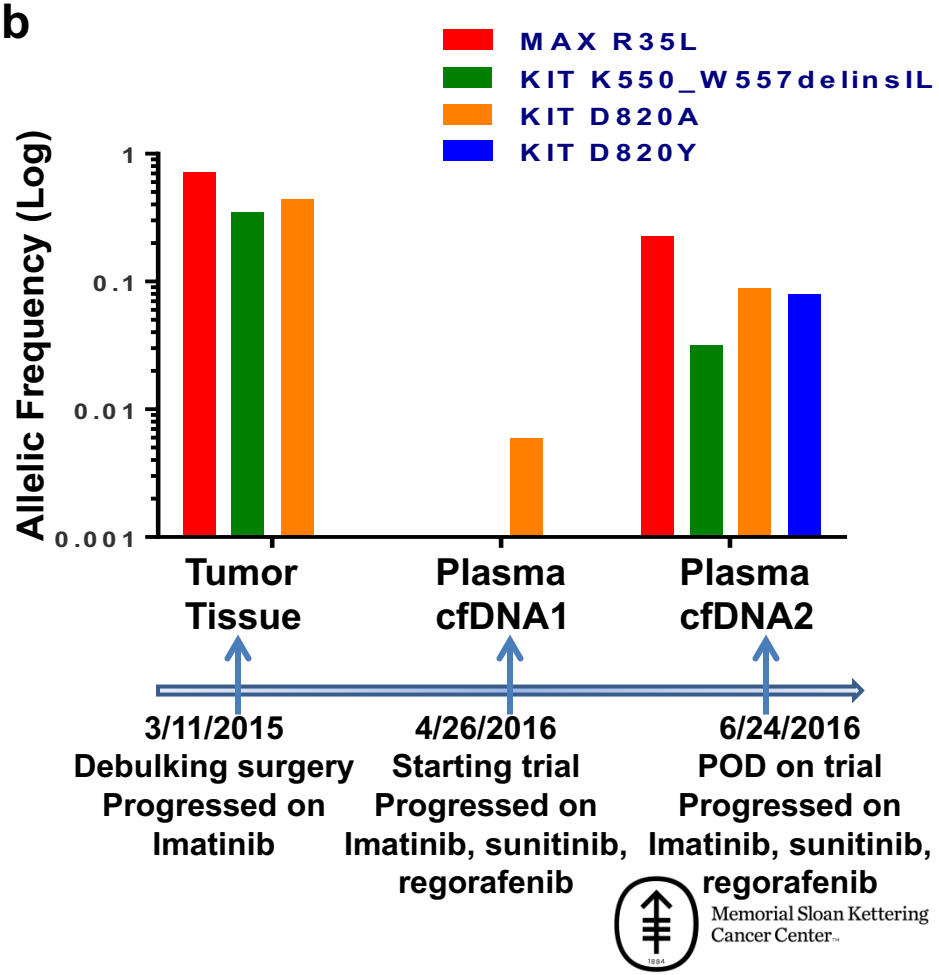
Tumor-derived cfDNA to detect tumor heterogeneity and subclonal dynamics

6/10 patients with detectable tumor-derived cfDNA consistent with IMPACT

Patient #20



Patient #3



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