GIST: Harnessing the Complexities of Cancer and Its Care

William D. Tap, MD
Chief, Sarcoma Medical Oncology Service
Memorial Sloan Kettering Cancer Center

The Life Raft Group
New Horizons Gist

Wayne, New Jersey
October 1, 2017

Memorial Sloan Kettering Cancer Center

Gastrointestinal Stromal Tumor – GIST

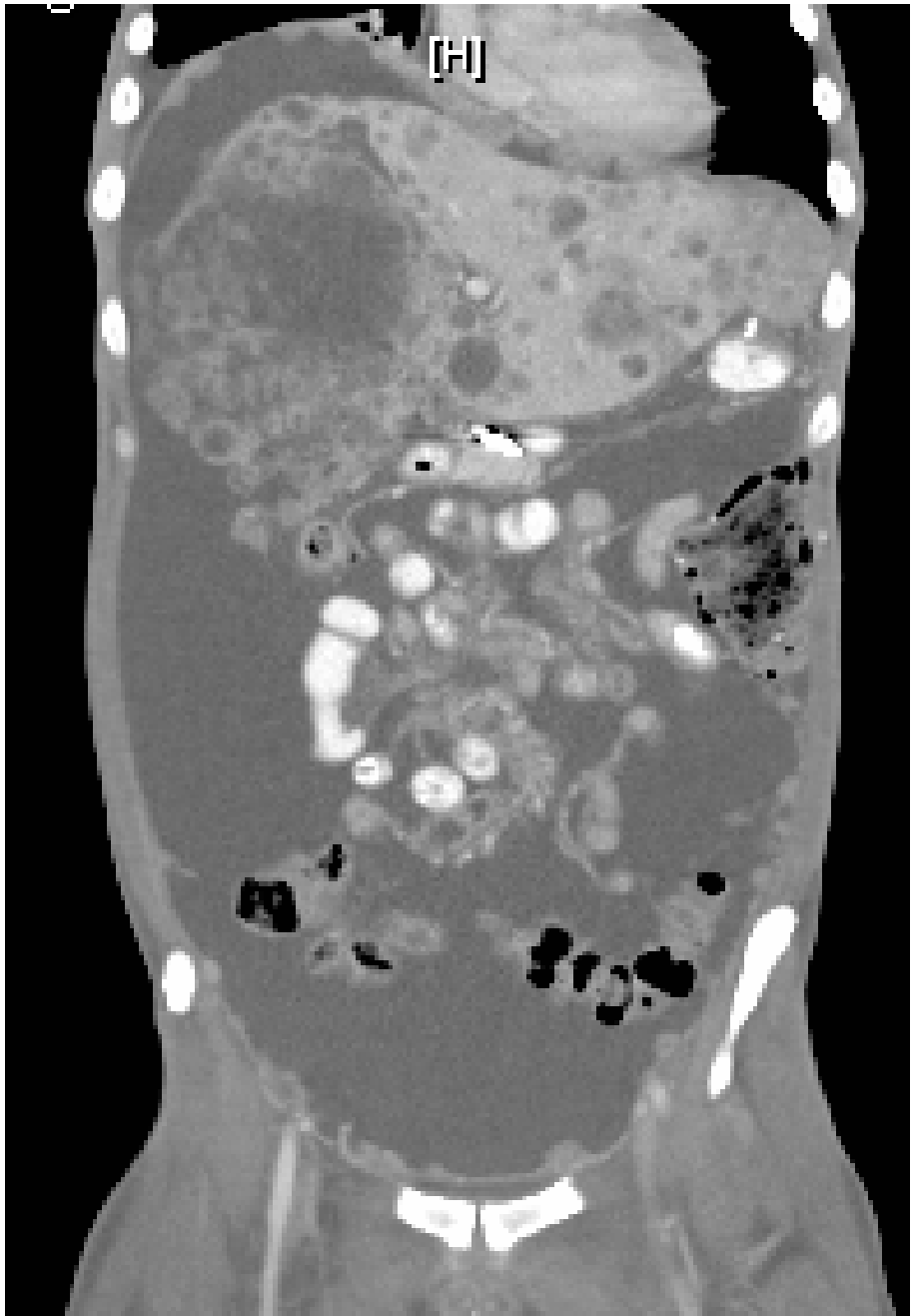

Table 2. PATIENT PRESENTATION IN 200 PATIENTS WITH GASTROINTESTINAL STROMAL TUMOR

Presentation	n	Median Survival (months)	Complete Resection n	Complete Resection % of Row Total
Primary	93	60	80	86
Metastatic	94	19	28	30
Metastasis only	51	22	16	31
Primary tumor + metastasis	26	23	8	31
Local recurrence + metastasis	17	9	4	24
Locally recurrent	13	12	6	46

ANNALS OF SURGERY
Vol. 231, No. 1, 51–58

TABLE 1. Response Rates to Chemotherapy in Patients With Metastatic GIST

Regimen	Partial Response n	Partial Response n (%)	Reference
DOX + DTIC	43	3 (7%)	56
DOX + DTIC +/− IF	60	10 (15%)	57
DOX + DTIC+ IF	11	3 (27%)	58
IF + VP-16	10	0 (0%)	59
Paclitaxel	15	1 (7%)	60
Gemcitabine	17	0 (0%)	61
Liposomal DOX	15	0 (0%)	62
DOX	12	0 (0%)	62
DOX or docetaxel	9	0 (0%)	63
High-dose IF	26	NR (0–8%)	64
EPI + IF	13	0 (0%)	61,65
Various (e.g., DOX, gemcitabine, CT2584)	40	4 (10%)	21
DTIC + MMC + DOX + CDDP + GM−CSF	21	1 (5%)	20
TOTAL	266	22 (8.3%)	

Abbreviations: DOX, doxorubin; DTIC, dacarbazine; IF, ifosfamide; CDDP, cisplatin; VP16, etoposide; EPI, epirubicin; NR, not reported.

HUMAN PATHOLOGY Volume 33, No. 5 (May 2002)

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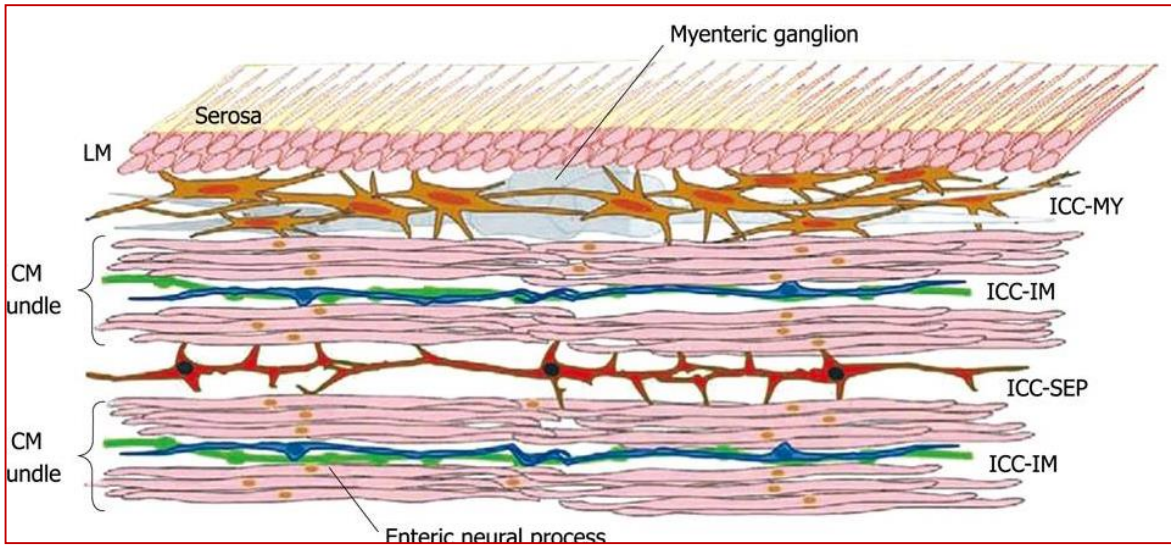
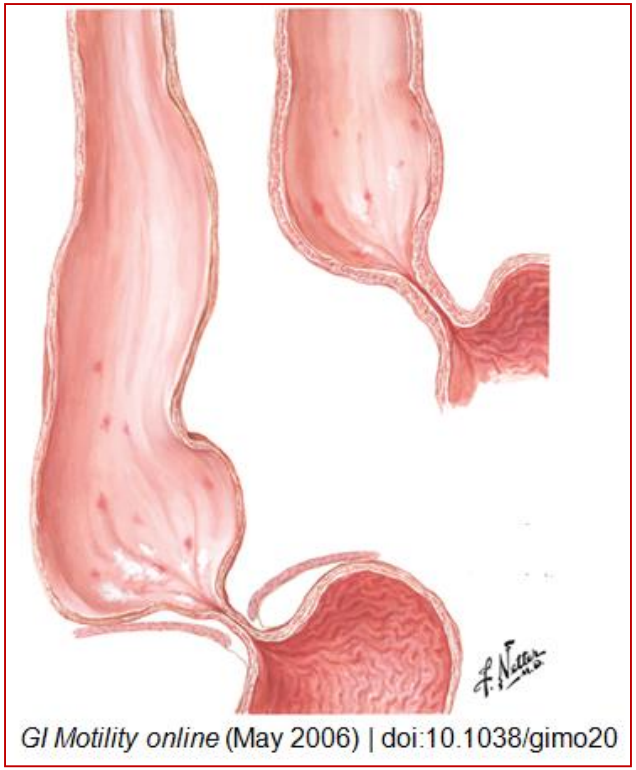
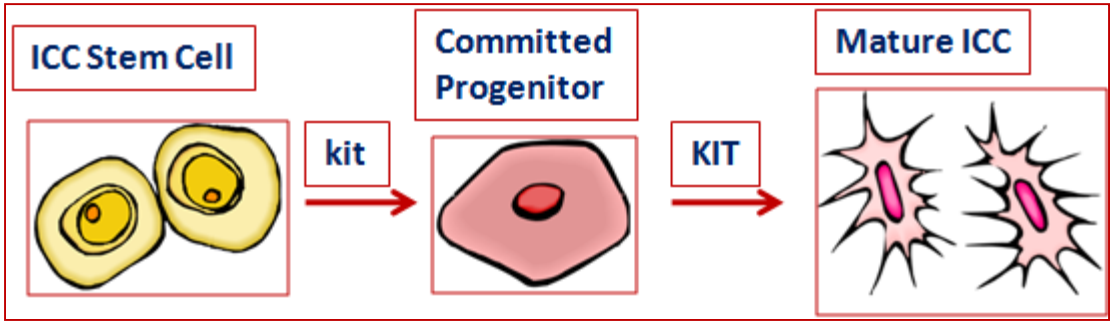


World J Gastroenterol. 2010. 16(26):3329-3248.





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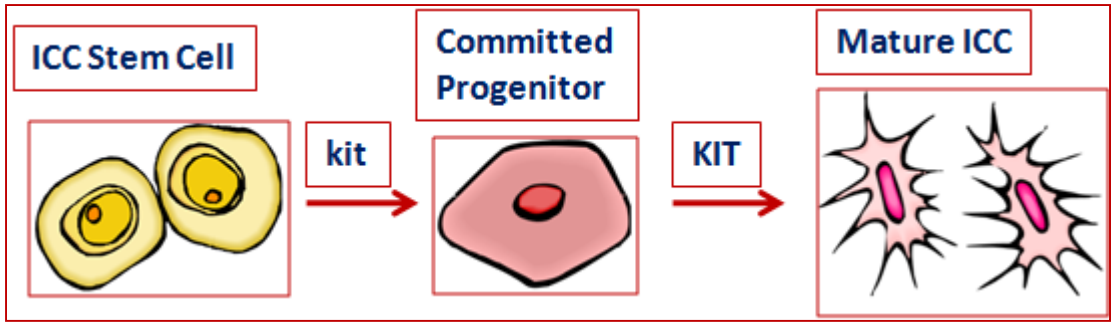
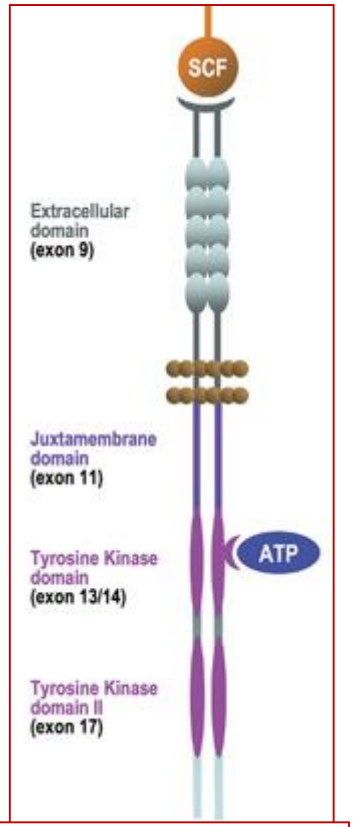
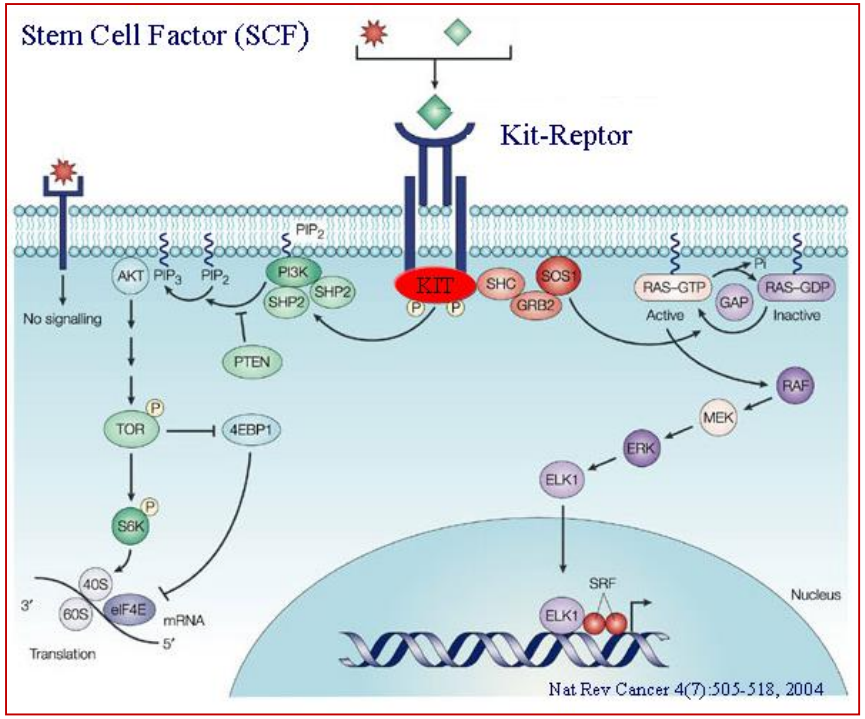


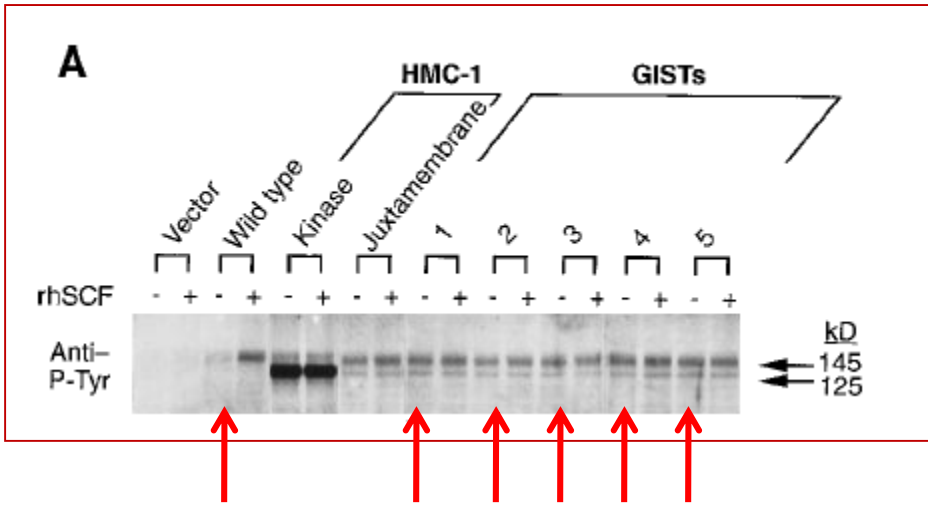


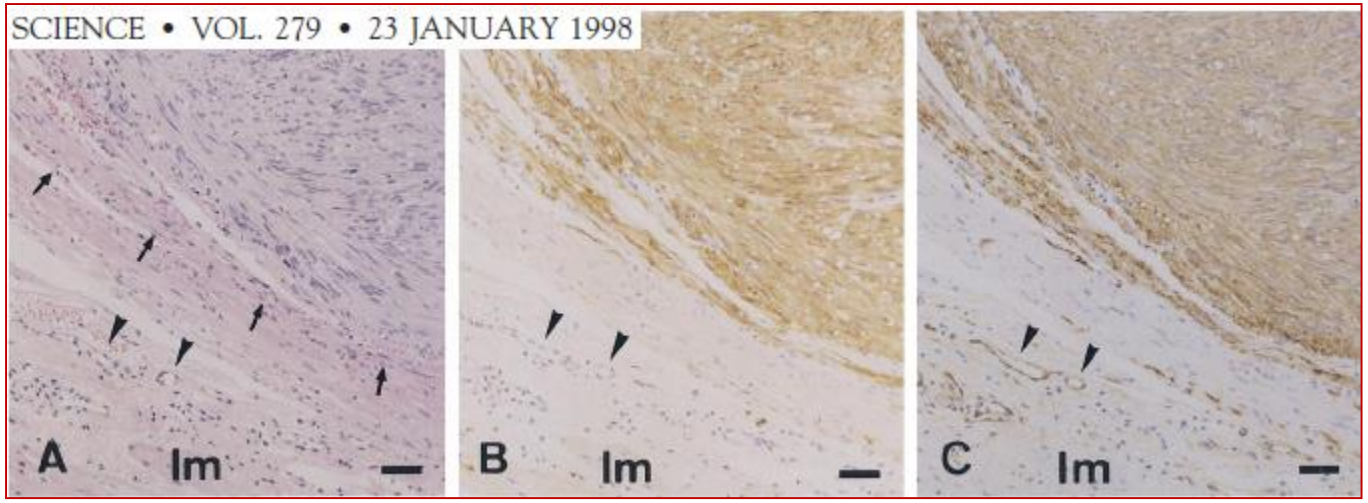
Oncogene (2011) 30, 757–769



Gastrointestinal Stromal Tumor

- 1998 Hirota et al.
  - Activating mutation in *c-kit* in GIST
  - Ligand independent activation of the KIT tyrosine kinase
- GIST defined by c-kit mutation
- Immunohistochemically CD117 +
- Product of *c-kit* proto-oncogene





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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

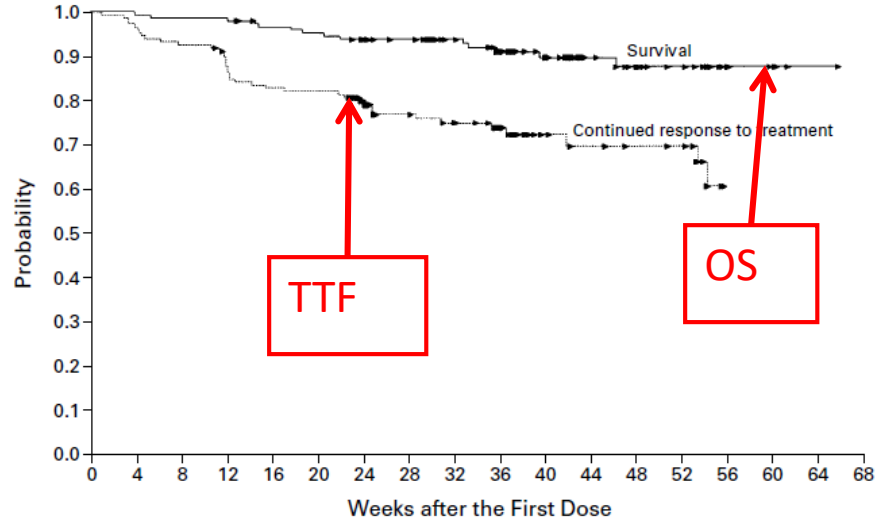
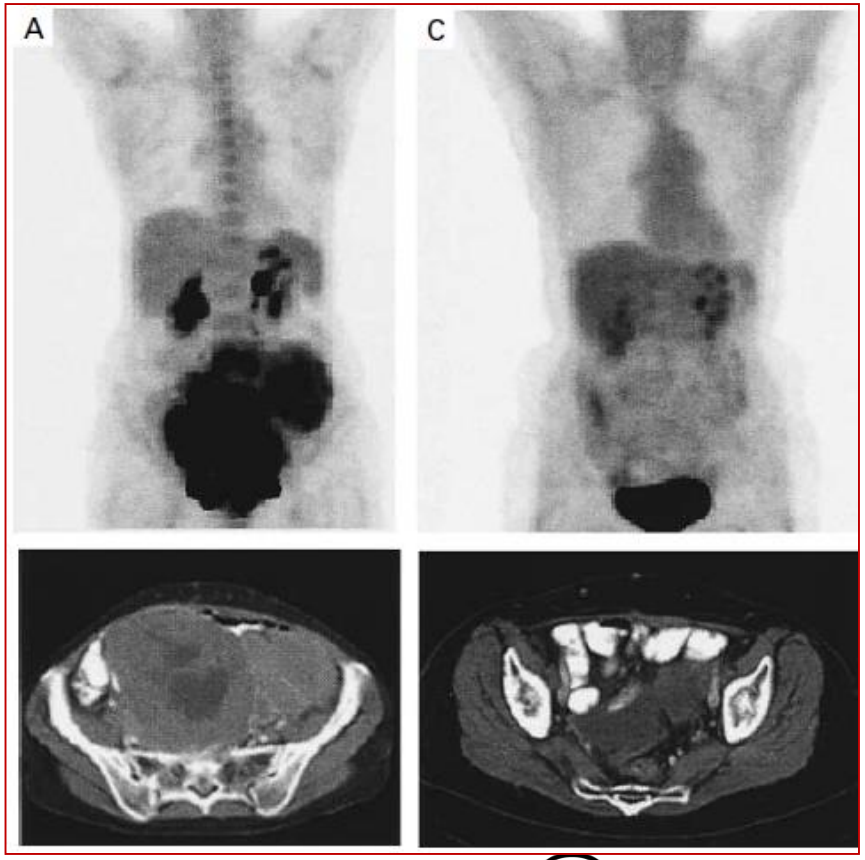


Figure 1. Kaplan–Meier Estimates of Overall Survival and Time to Treatment Failure for All Patients. Each arrowhead represents the point at which a patient's data were censored.



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

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

RESPONSE RATE 45%

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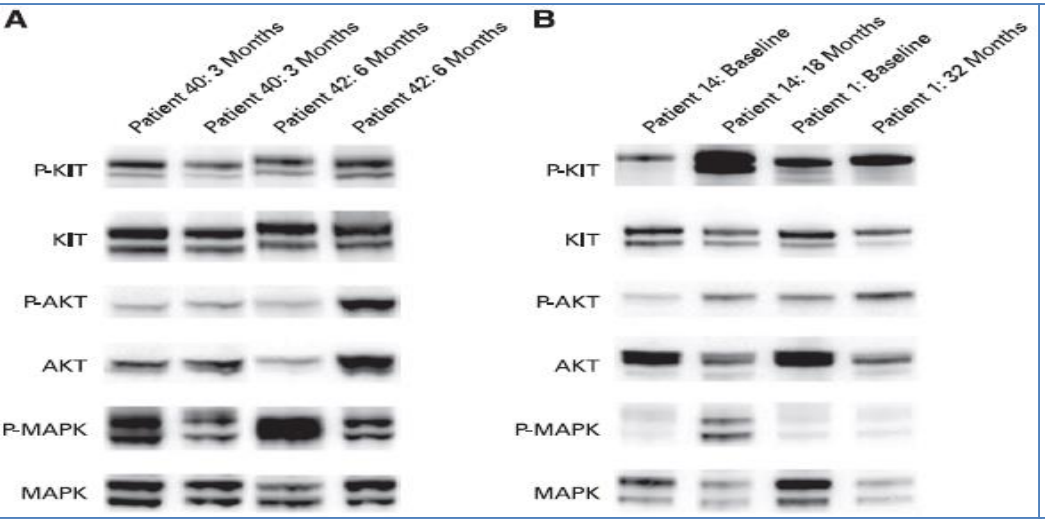
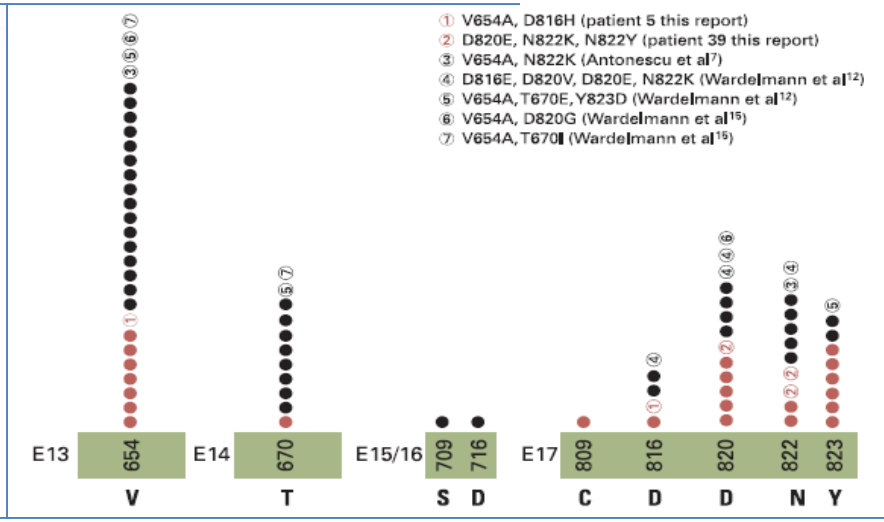
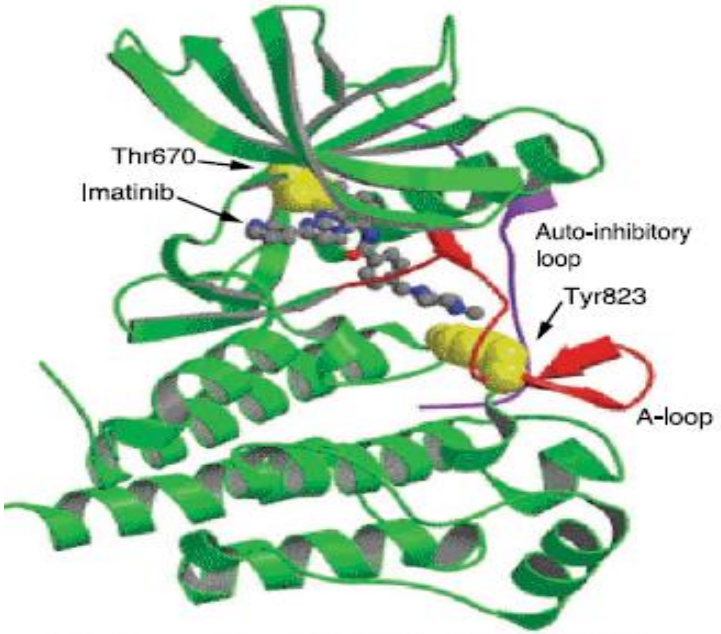
GIST – What's going on?



14% - Initially resistant



50% - Insensitive after 2 years



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

Resistance:

1. Secondary mutations
2. Genomic Amplification
   -kinase overexpression
3. Activation alternative signaling pathways
4. Activating alternate RTKs

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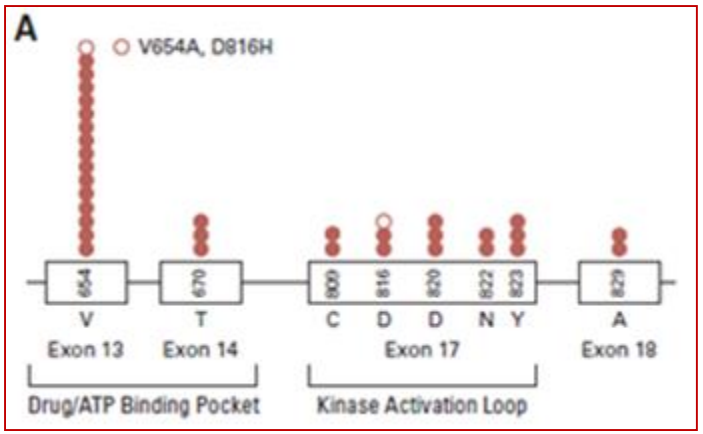
Primary and Secondary Kinase Genotypes Correlate With the Biological and Clinical Activity of Sunitinib in Imatinib-Resistant Gastrointestinal Stromal Tumor

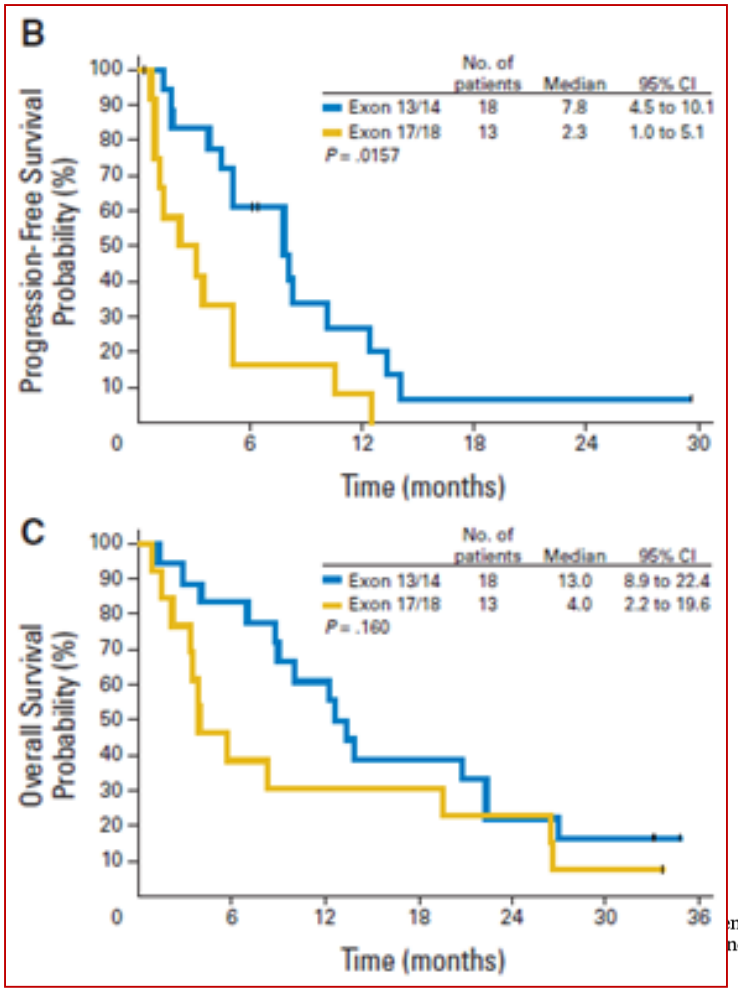
Michael C. Heinrich, Robert G. Maki, Christopher L. Corless, Cristina R. Antonescu, Amy Harlow, Diana Griffith, Ajia Town, Arin McKinley, Wen-Bin Ou, Jonathan A. Fletcher, Christopher D.M. Fletcher, Xin Huang, Darrel P. Cohen, Charles M. Baum, and George D. Demetri

J Clin Oncol 26:5352-5359. © 2008



Mutations that involve the activation loop are insensitive to sunitinib

ATP binding pocket – sensitive



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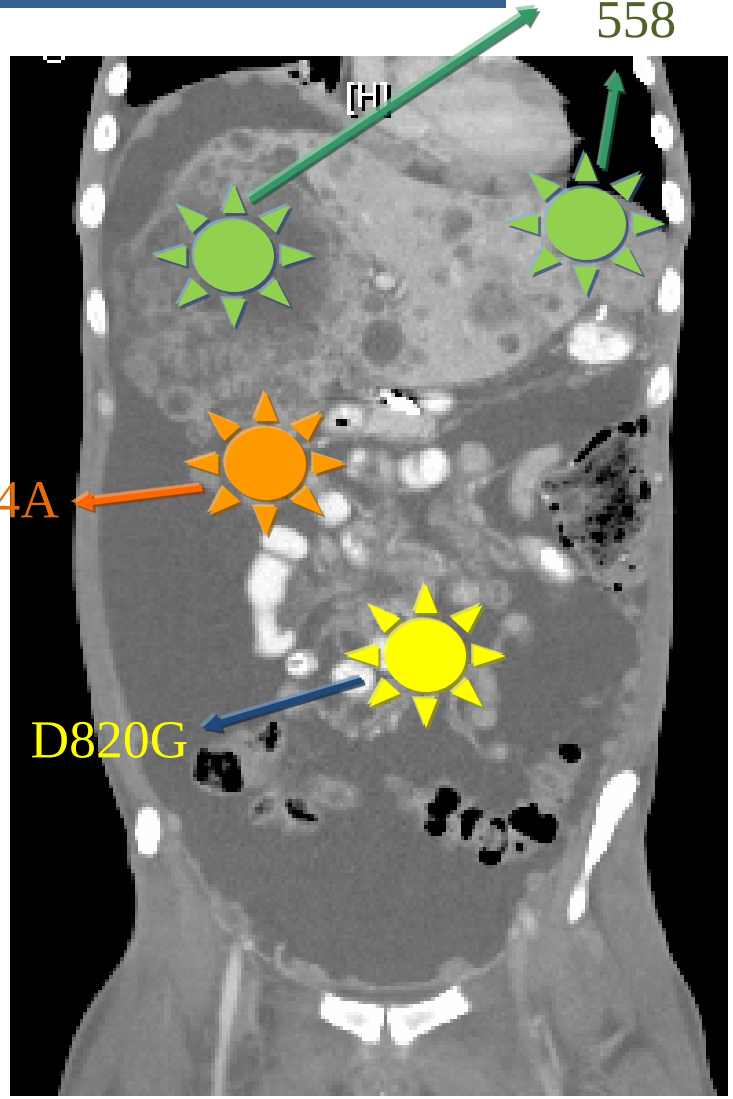
Plot thickens….

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



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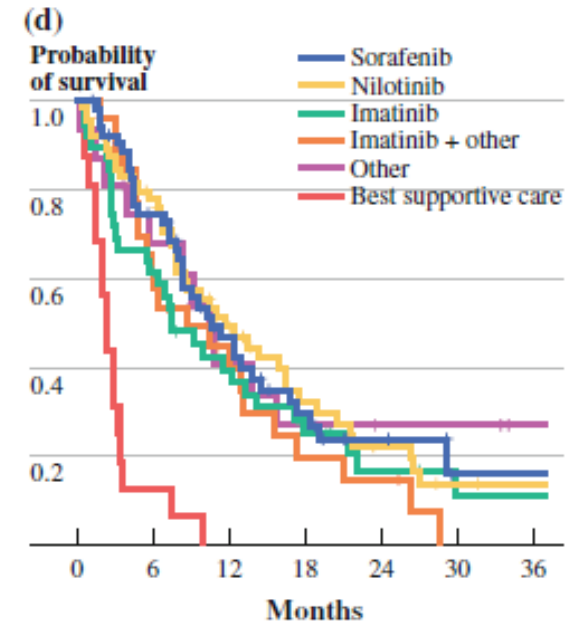
Patterns of Care, Prognosis, and Survival in Patients with Metastatic Gastrointestinal Stromal Tumors (GIST) Refractory to First-Line Imatinib and Second-Line Sunitinib

Ann Surg Oncol (2012) 19:1551–1559

TABLE 2 Patterns of treatment and related outcome

Treatment	*N* (%)	Clinical benefit rate		Progression-free survival		Overall survival	
		%	*P* value	Median (months) (95% CI)	*P* value	Median (months) 95% CI	*P* value
3rd-line setting	223		–	3.6 (3.1–4.1)	–	9.2 (7.5–10.9)	–
Imatinib (I)	40 (18)	25	0.05	2.9 (2.2–3.5)	0.001	7.5 (4–10.9)	
I + other agent (not "ib")	27 (12)	18.5		3.0 (1.7–4.3)		8.7 (2.3–15)	
Nilotinib	67 (30)	35		4.1 (2.8–5.3)		11.8 (7.2–16.3)	<0.0001
Sorafenib	55 (25)	42		4.9 (2.2–7.6)		10.7 (7.2–14.2)	
Other drugs	16 (7)	19		2.7 (1.1–4.3)		10.6 (7.5–13.7)	
Best supportive care	18 (8)	11		2.1 (1.3–2.8)		2.4 (1.8–2.9)	



Phase II Study Sorafenib
Median PFS 4.9 mos

1. **Methods to Overcome Resistance**
2. **Better Upfront Therapies**

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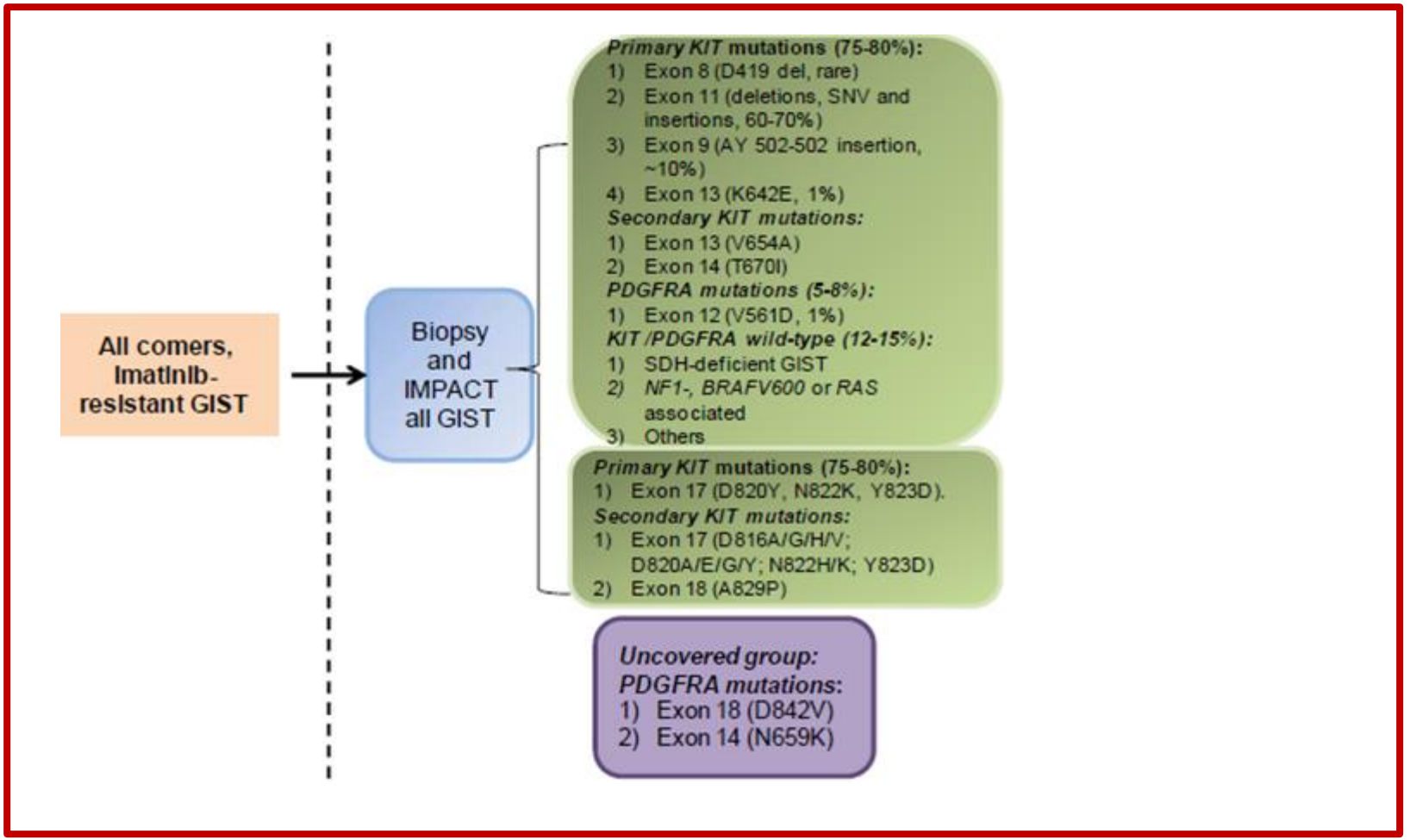
How to Apply?



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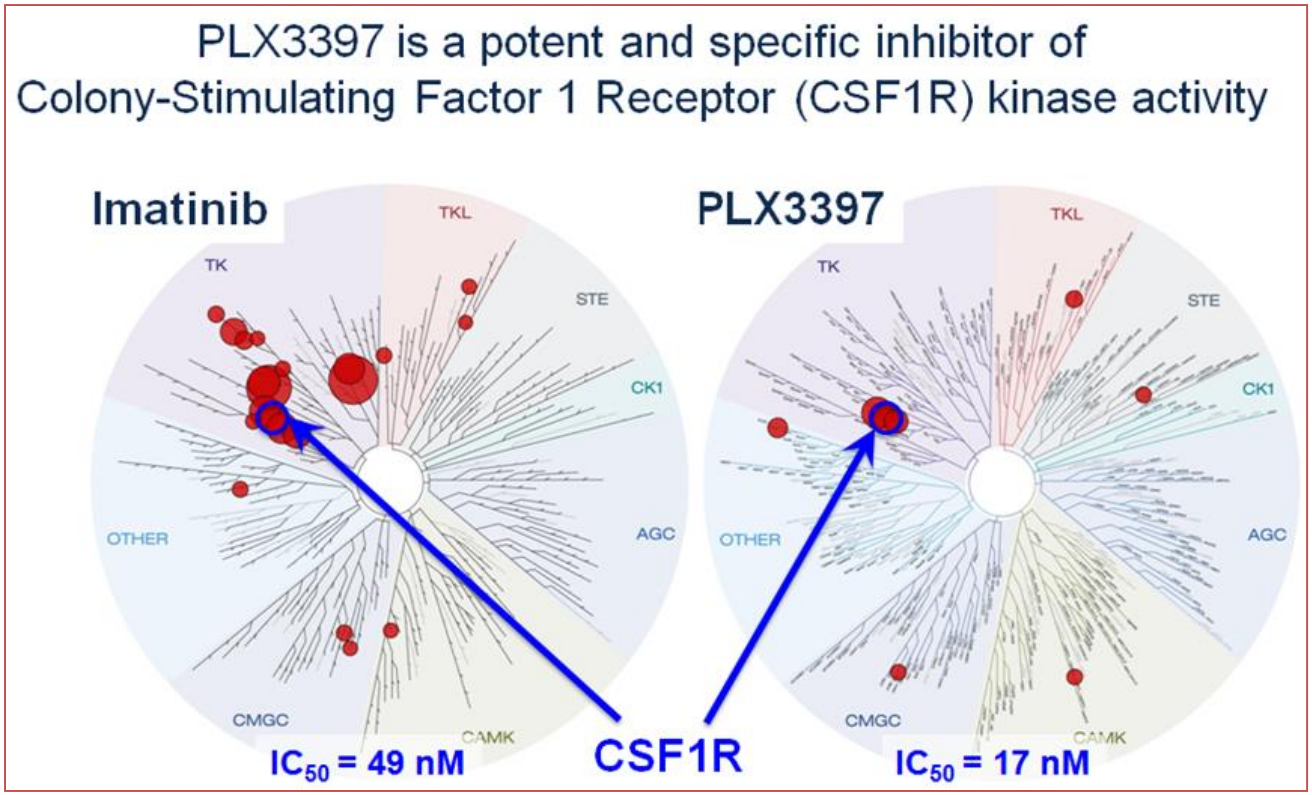
Strong and Specific KIT andCSF1R Inhibitors



Tap WD, et al. N Engl J Med. 2015; 373(5):428-437

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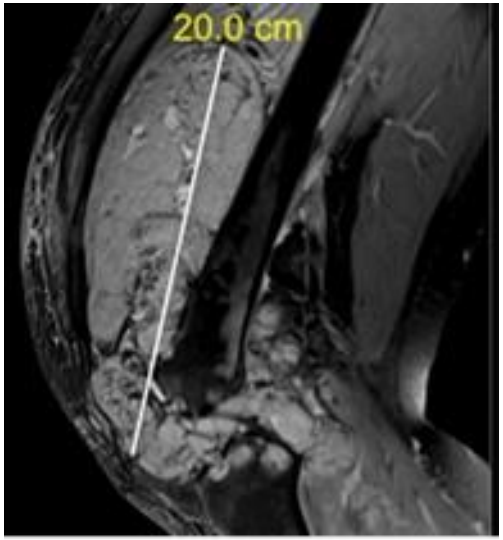
PVNS and GCT-TS

High Morbidity

- While usually not metastatic, disease is locally aggressive, and recurrence is common after surgical resection (particularly with Diffuse PVNS)
- Affects young & middle-aged adults of both sexes; no ethnic predisposition; patients are diagnosed in their 30s and 40s; and can live ~40years after diagnosis

Gross features:

- Collagen deposition
- Subchondral bone erosions
- Repeat hemarthrosis



Clinical features:

- Usually single joint:
  - Swelling
  - Pain
  - ↓ range of motion
  - Stiffness
- Functional impairment
- Narcotic use
- Disability

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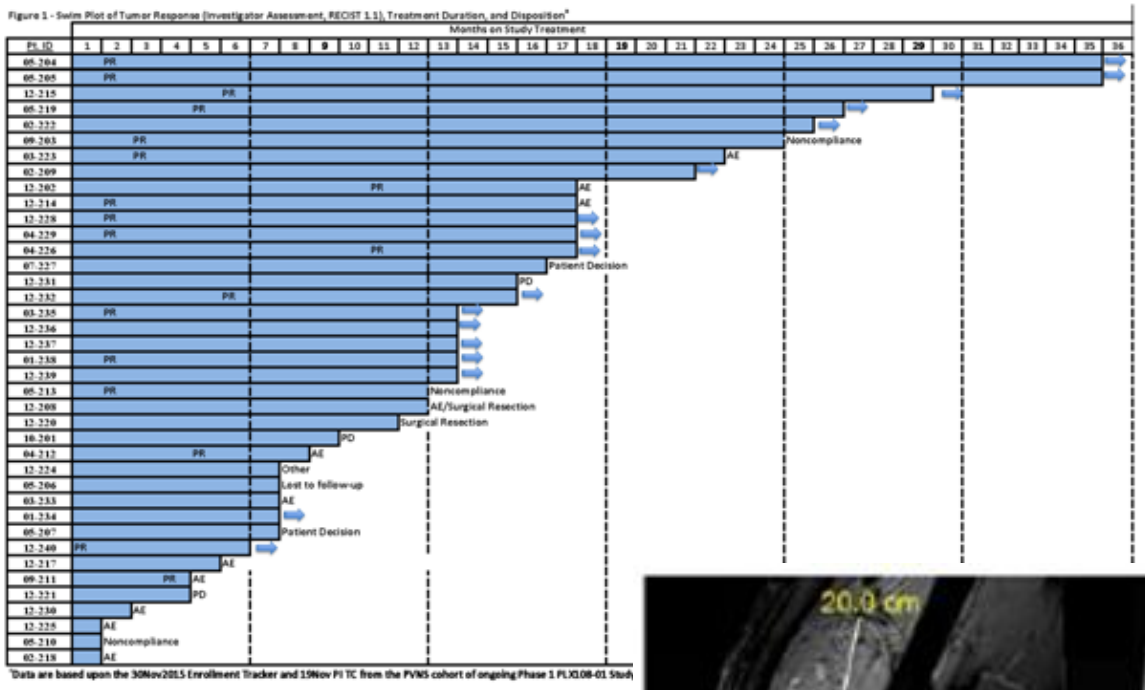

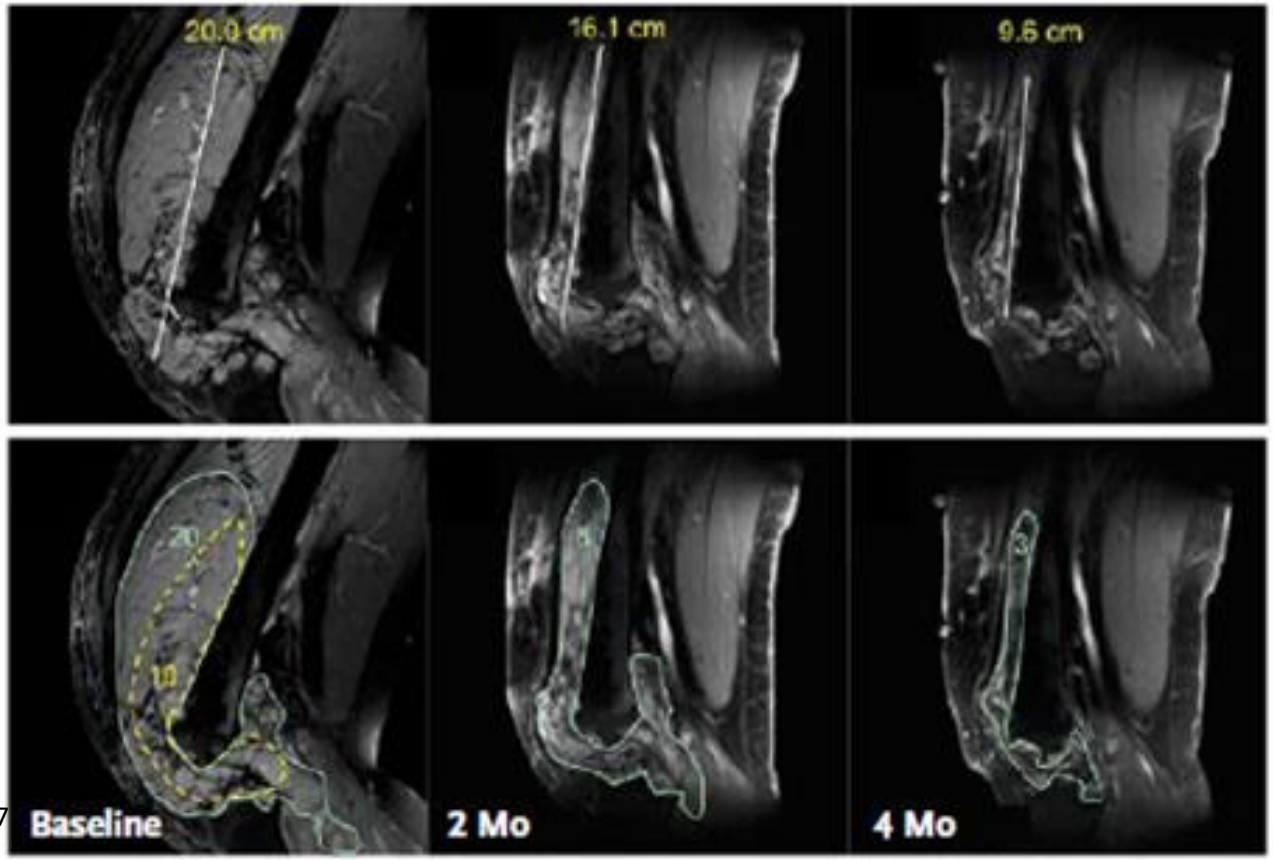

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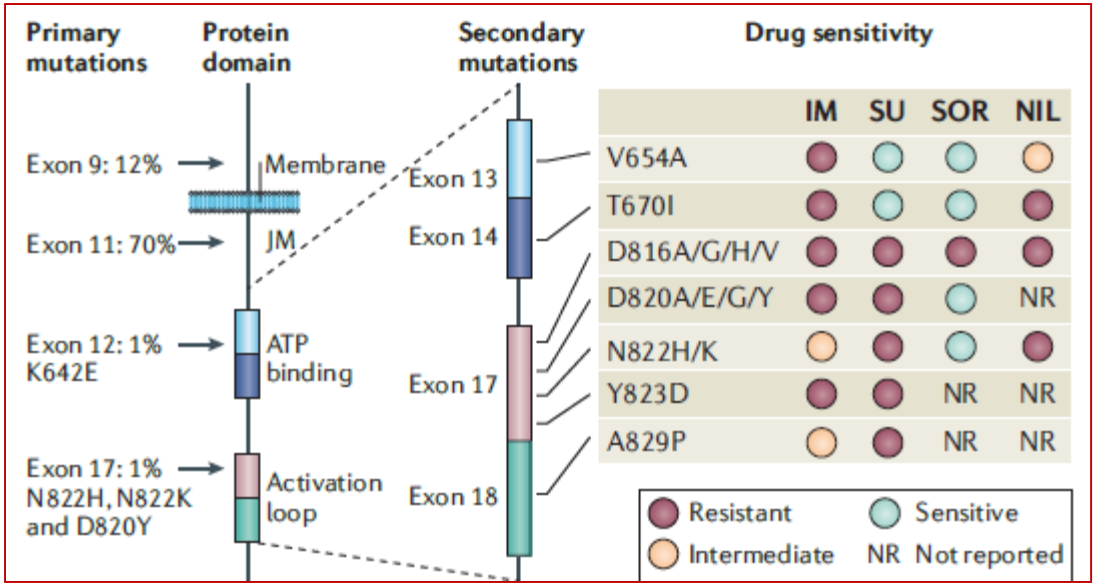

Corless et al. Nat Rev Cancer 2011

- PLX33397 – Primary 8, 9, 11
  - Resistant mutation 13 ?, 14
- PLX9486 – Primary 8, 9, 11
  - Resistant mutation 17, 18

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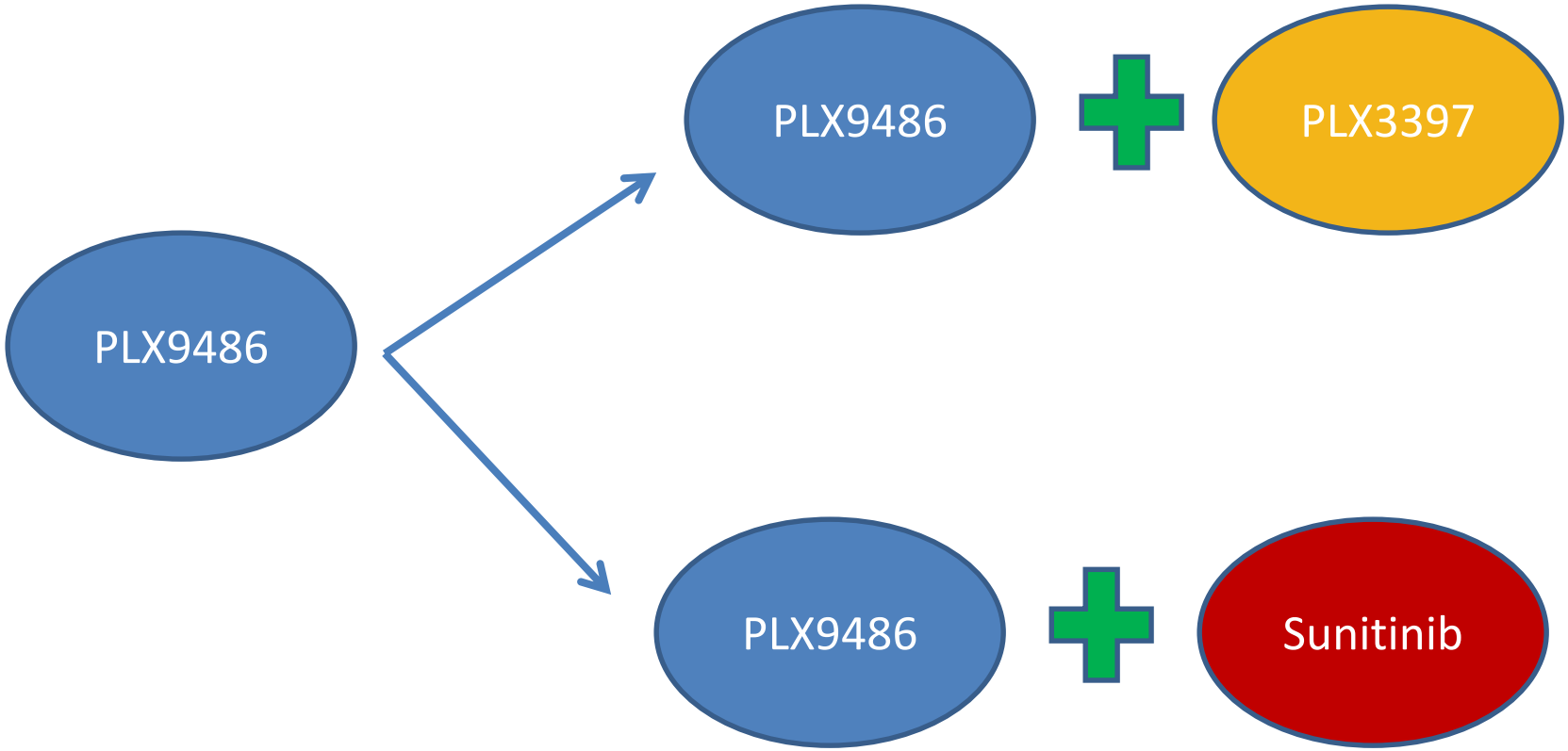
PLX9486 as a Single Agent and in Combination With PLX3397 or PLX9486 With Sunitinib in Patients With Advanced Solid Tumors



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A Phase 1b and 2a Study to Assess Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of PLX9486 as a Single Agent and in Combination With PLX3397 or Sunitinib (Sutent®) in Patients With Advanced Solid Tumors and Patients With Locally Advanced, Unresectable, or Metastatic Gastrointestinal Stromal Tumor (GIST) Who Have Been Previously Treated With Imatinib Mesylate/KIT-Directed Tyrosine Kinase Inhibitor (TKI) Therapy

Experimental: Part 1

Open-label, sequential cohort **PLX9486** single-agent Dose Escalation in patients with solid tumors.

Experimental: Part 2a

Single-agent **PLX9486** RP2D in patients with GIST who have progressed on imatinib mesylate/KIT directed TKI therapy

Experimental: Part 2c

RP2D of the **PLX9486**/PLX3397 combination in patients with GIST who have progressed on second-line or greater therapy.

Experimental: Part 2e

Open-label, sequential cohort **PLX9486** combined with Sunitinib Dose Escalation in patients with solid tumors (including GIST).

ClinicalTrials.gov Identifier:
NCT02401815

What about the FMS Component of PLX3397 (Pexidartinib)

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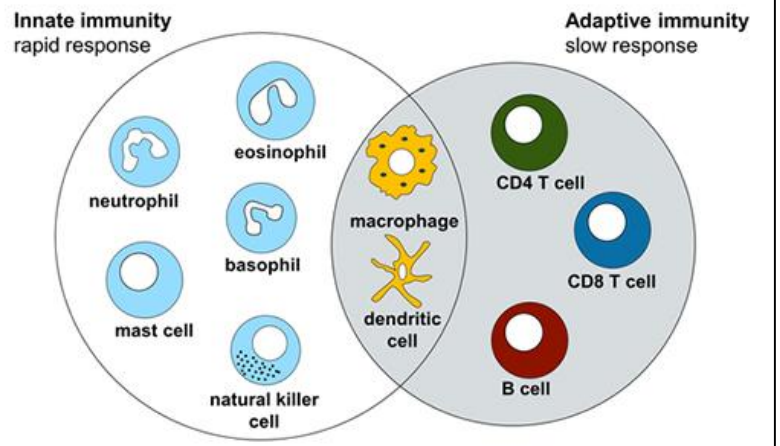
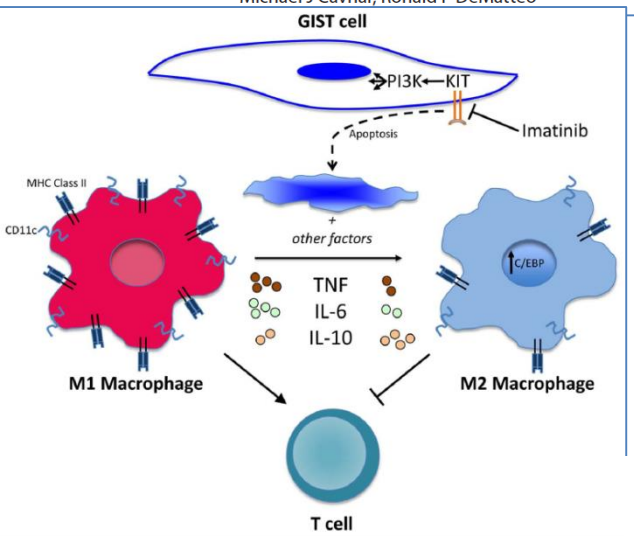
Understanding response patterns and the Sarcoma Immune Microenvironment

OncoImmunology 3, e28463; April 2014;



Sarcoma response to targeted therapy dynamically polarizes tumor-associated macrophages

Michael J Cavnar, Ronald P DeMatteo*



KIT oncogene inhibition drives intratumoral macrophage M2 polarization

J. Exp. Med. 2013 Vol. 210 No. 13 2873-2886

Michael J. Cavnar,[1] Shan Zeng,[1] Teresa S. Kim,[1] Eric C. Sorenson,[1] Lee M. Ocuin,[1] Vinod P. Balachandran,[1] Adrian M. Seifert,[1] Jonathan B. Greer,[1] Rachel Popow,[1] Megan H. Crawley,[1] Noah A. Cohen,[1] Benjamin L. Green,[1] Ferdinand Rossi,[2] Peter Besmer,[2] Cristina R. Antonescu,[3] and Ronald P. DeMatteo[1]

PD-1/PD-L1 blockade enhances T cell activity and antitumor efficacy of imatinib in gastrointestinal stromal tumors

Clin Cancer Res 2016

Adrian M. Seifert[1], Shan Zeng[1], Jennifer Q. Zhang[1], Teresa S. Kim[1], Noah A. Cohen[1], Michael J. Beckman[1], Benjamin D. Medina[1], Joanna H. Maltbaek[1], Jennifer K. Loo[1], Megan H. Crawley[1], Ferdinand Rossi[1, 2], Peter Besmer[2], Cristina R. Antonescu[3], Ronald P. DeMatteo[1]

Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of Ido

VOLUME 17 | NUMBER 9 | SEPTEMBER 2011 NATURE MEDICINE

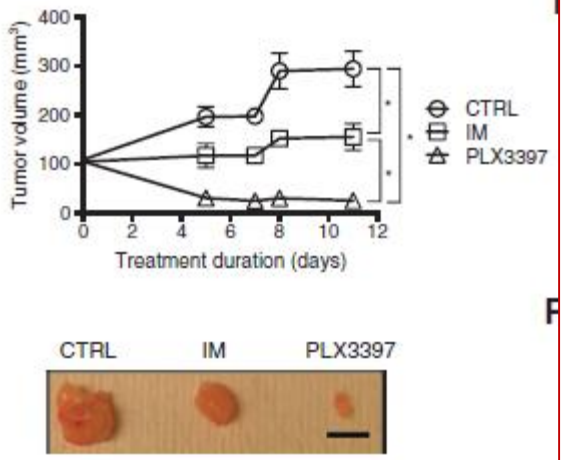
Vinod P Balachandran[1], Michael J Cavnar[1], Shan Zeng[1], Zubin M Bamboat[1], Lee M Ocuin[1], Hebroon Obaid[1], Eric C Sorenson[1], Rachel Popow[1], Charlotte Ariyan[1], Ferdinand Rossi[2], Peter Besmer[2], Tianhua Guo[3], Cristina R Antonescu[3], Takahiro Taguchi[4], Jianda Yuan[5], Jedd D Wolchok[5,6], James P Allison[5,7] & Ronald P DeMatteo[1]

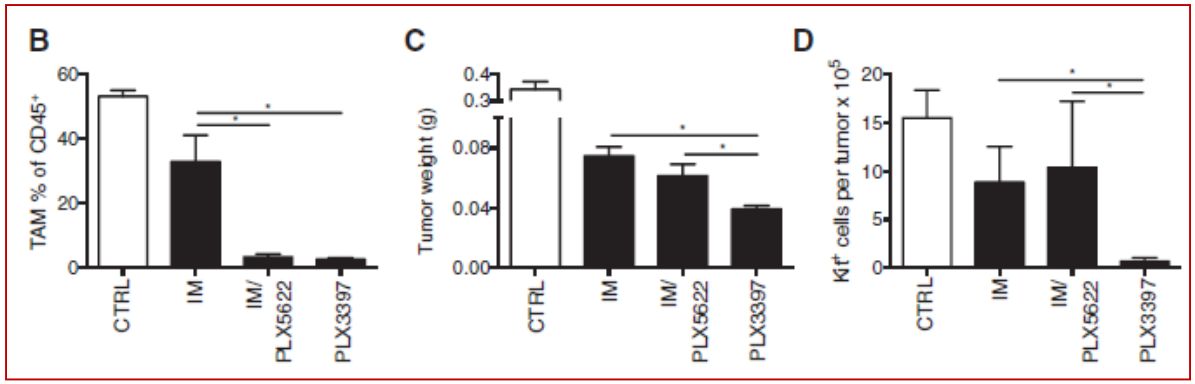
Ronald DeMatteo MD

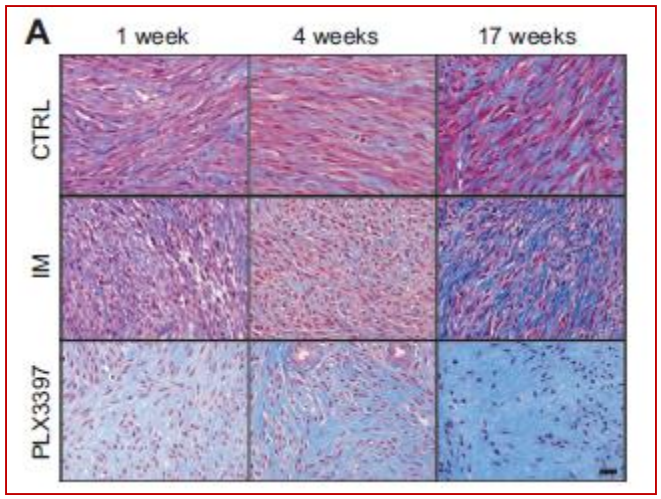
Timothy Bowler MD PhD

Increased KIT Inhibition Enhances Therapeutic Efficacy in Gastrointestinal Stromal Tumor

Teresa S. Kim[1], Michael J. Cavnar[1], Noah A. Cohen[1], Eric C. Sorenson[1], Jonathan B. Greer[1], Adrian M. Seifert[1], Megan H. Crawley[1], Benjamin L. Green[1], Rachel Popow[1], Nagavarakishore Pillarsetty[2], Darren R. Veach[2], Anson T. Ku[2], Ferdinand Rossi[1,3], Peter Besmer[3], Cristina R. Antonescu[4], Shan Zeng[1], and Ronald P. DeMatteo[1]







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GIST EXPANSION ON A091401

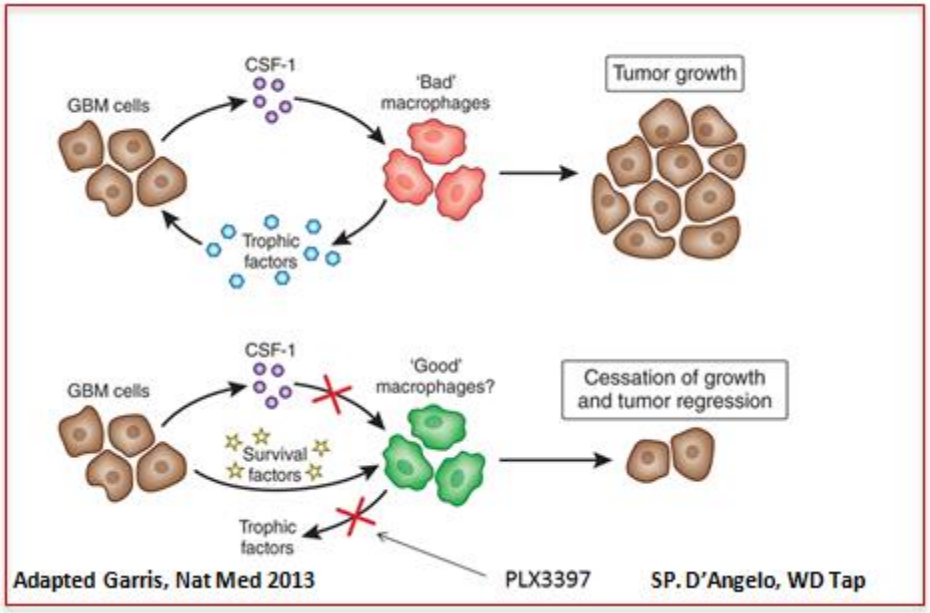
PD-1/PD-L1 blockade enhances T cell activity and antitumor efficacy of imatinib in gastrointestinal stromal tumors

Clin Cancer Res 2016

Adrian M. Seifert[1], Shan Zeng[1], Jennifer Q. Zhang[1], Teresa S. Kim[1], Noah A. Cohen[1], Michael J. Beckman[1], Benjamin D. Medina[1], Joanna H. Maltbaek[1], Jennifer K. Loo[1], Megan H. Crawley[1], Ferdinand Rossi[1,2], Peter Besmer[2], Cristina R. Antonescu[3], Ronald P. DeMatteo[1]

Metastatic GIST

Progression after imatinib



A Combination Clinical Study of PLX3397 and Pembrolizumab To Treat Advanced Melanoma and Other Solid Tumors

FMS/KIT and PD1 – LMS and GIST
MSKCC and DFCI

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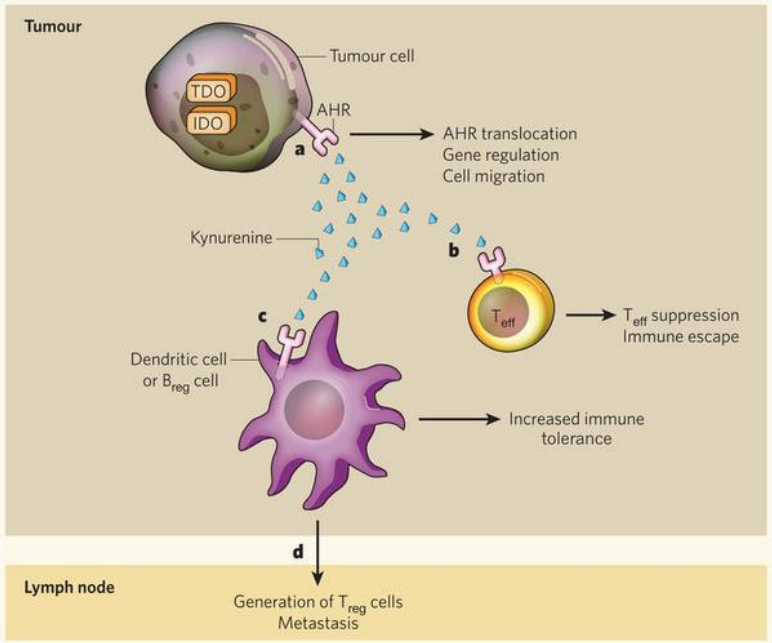
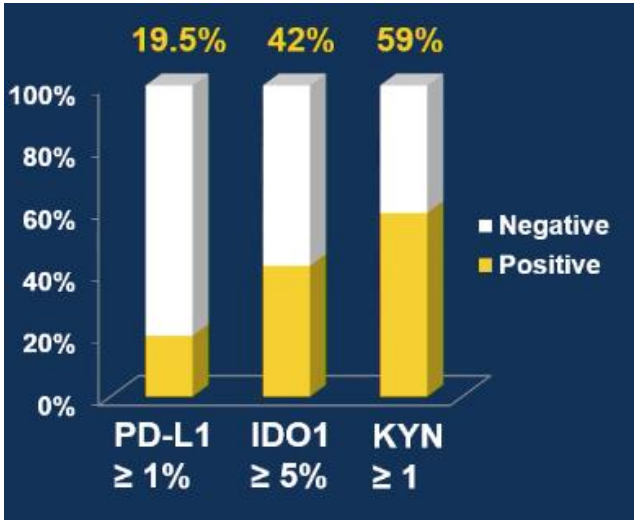
IDO contributes to immune escape and is up-regulated in sarcoma

Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of Ido

VOLUME 17 | NUMBER 9 | SEPTEMBER 2011 NATURE MEDICINE

Vinod P Balachandran[1], Michael J Cavnar[1], Shan Zeng[1], Zubin M Bamboat[1], Lee M Ocuin[1], Hebroon Obaid[1], Eric C Sorenson[1], Rachel Popow[1], Charlotte Ariyan[1], Ferdinand Rossi[2], Peter Besmer[2], Tianhua Guo[3], Cristina R Antonescu[3], Takahiro Taguchi[4], Jianda Yuan[5], Jedd D Wolchok[5,6], James P Allison[5,7] & Ronald P DeMatteo[1]





328 patients

133 UPS
111 LMS
16 DDLPS
68 MFH

Correlative Studies in collaboration

PD-L1 expression by IHC

- PBMC, Flow cytometry
- Characterization of TILs
- TCR clonality
- Mutational burden

Protocol development by Ciara Kelly

Epacadostat + pembrolizumab in "High grade" Sarcomas

Toulmonde et al. ASCO 2016
Predergast et al. Nature 2011

Memorial Sloan Kettering Cancer Center

ETV1 is a lineage survival factor that cooperates with KIT in gastrointestinal stromal tumours

14 OCTOBER 2010 | VOL 467 | NATURE | 849

Ping Chi, MD, PhD

Interesting observations….

Kit highly expressed in ICC, hematopoietic stem cells, melanocytes, mast cells, germ cells.

Families with germ-line activating Kit mutations and mice with knock-in Kit mutations almost exclusively develop ICC hyperplasia and GIST

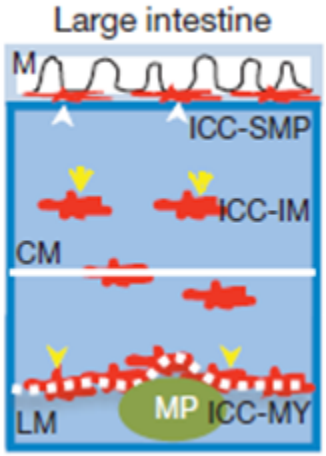
Suggest cellular context is important to for Kit to mediate oncogenesis

Mode ETV1 expression:
No obvious genomic alterations – FISH, RT-PCR, SNP array

? If ICC that give rise to GIST endogenously express ETV1

Inner circular muscle

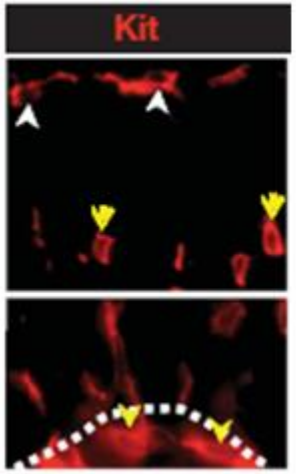
Longitudinal muscle (myenteric plexus)



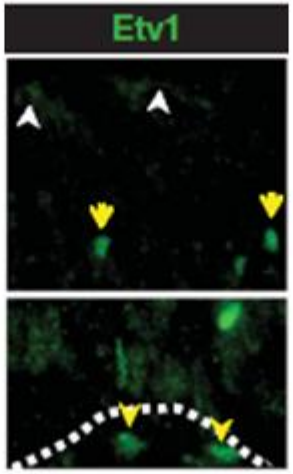
Submucosal ICC – surround submucosal plexus

Intramuscular ICC – dispersed circular muscle

Myenteric-ICC - surround myenteric plexus



All ICC subtypes express KIT



Intramuscular and myenteric ICCs express ETV1

Sloan Kettering Cancer Center

ETV1 is a lineage survival factor that cooperates with KIT in gastrointestinal stromal tumours

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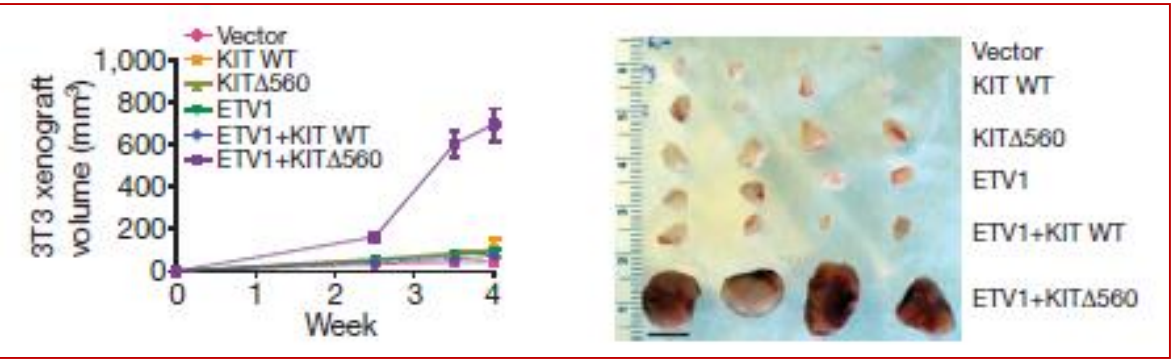
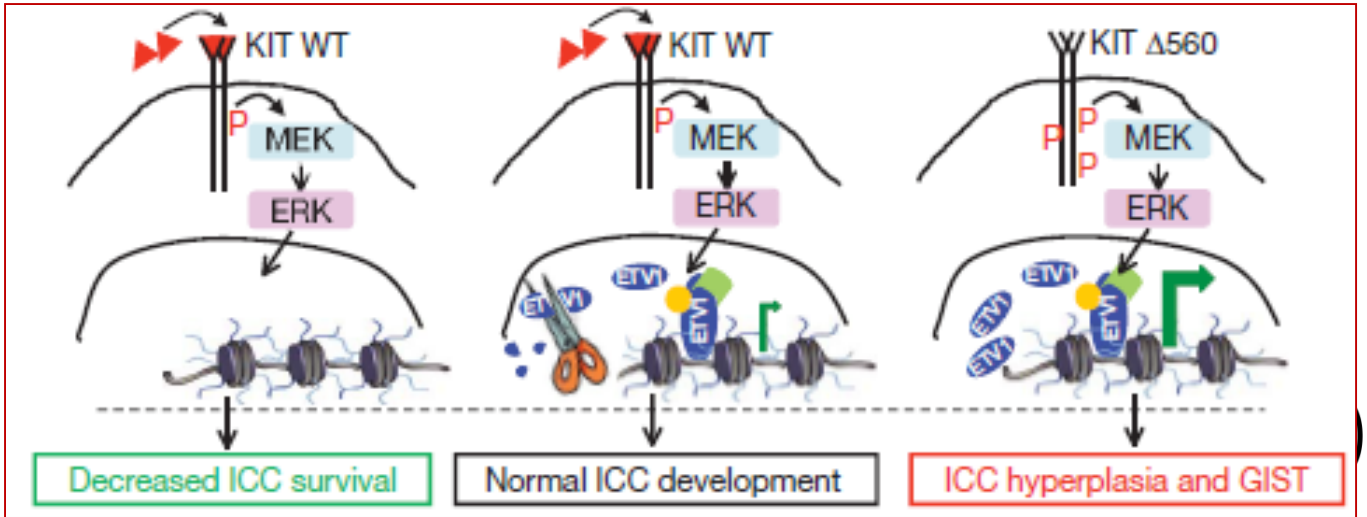
Ping Chi, MD, PhD



Mutant KIT and ETV1 strongly cooperate in conferring tumorigenic growth in SCID mice

KIT-MEK signaling stabilizes ETV1



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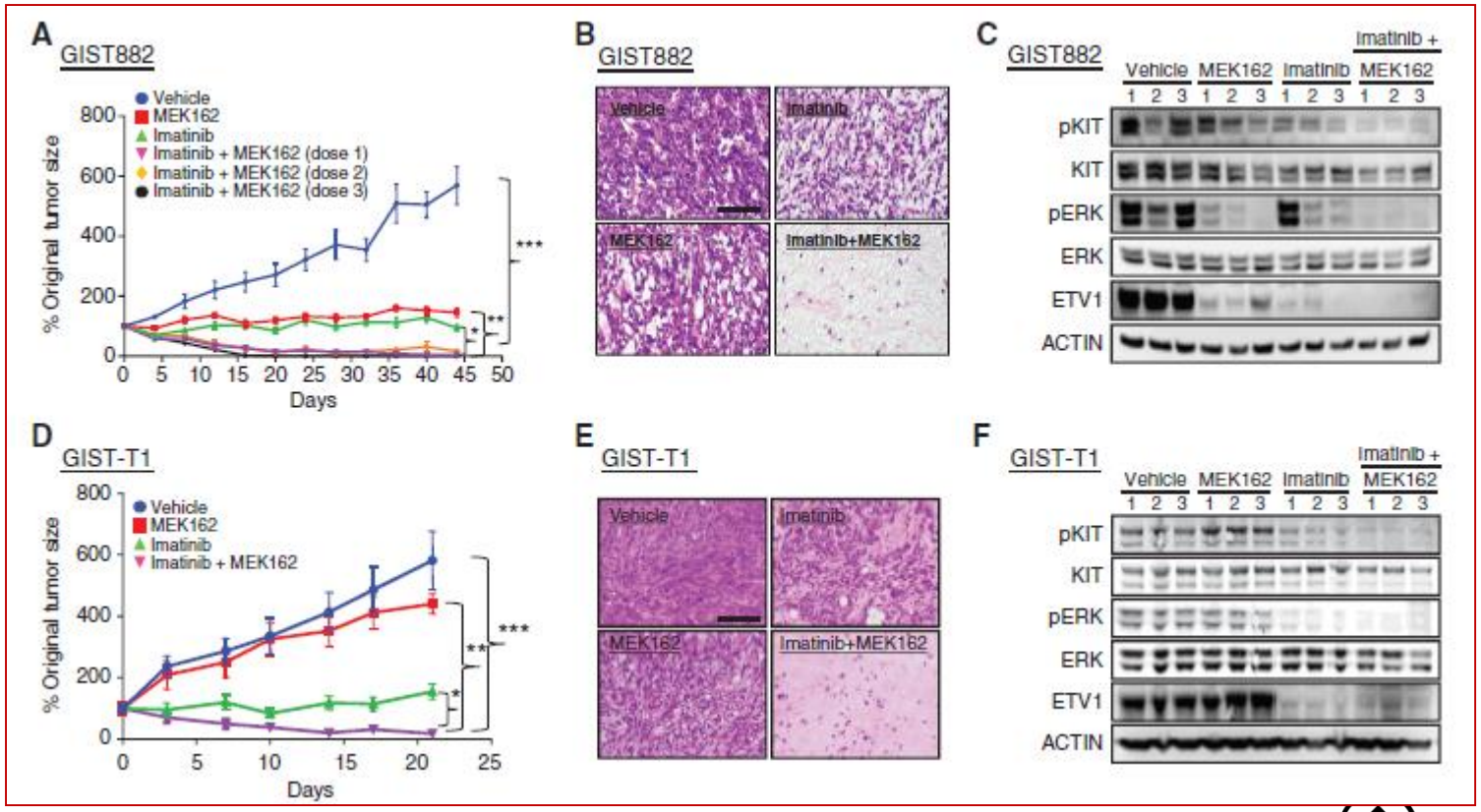
Combined Inhibition of MAP Kinase and KIT Signaling Synergistically Destabilizes ETV1 and Suppresses GIST Tumor Growth

Leili Ran[1], Inna Sirota[1], Zhen Cao[1], Devan Murphy[1], Yuedan Chen[1], Shipra Shukla[1], Yuanyuan Xie[1], Michael C. Kaufmann[1,2], Dong Gao[1], Sinan Zhu[1], Ferdinando Rossi[3], John Wongvipat[1], Takahiro Taguchi[4], William D. Tap[5,6], Ingo K. Mellinghoff[1,2,7], Peter Besmer[3], Cristina R. Antonescu[8], Yu Chen[1,5,6,9], and Ping Chi[1,5,6,9]

CANCER DISCOVERY MARCH 2015



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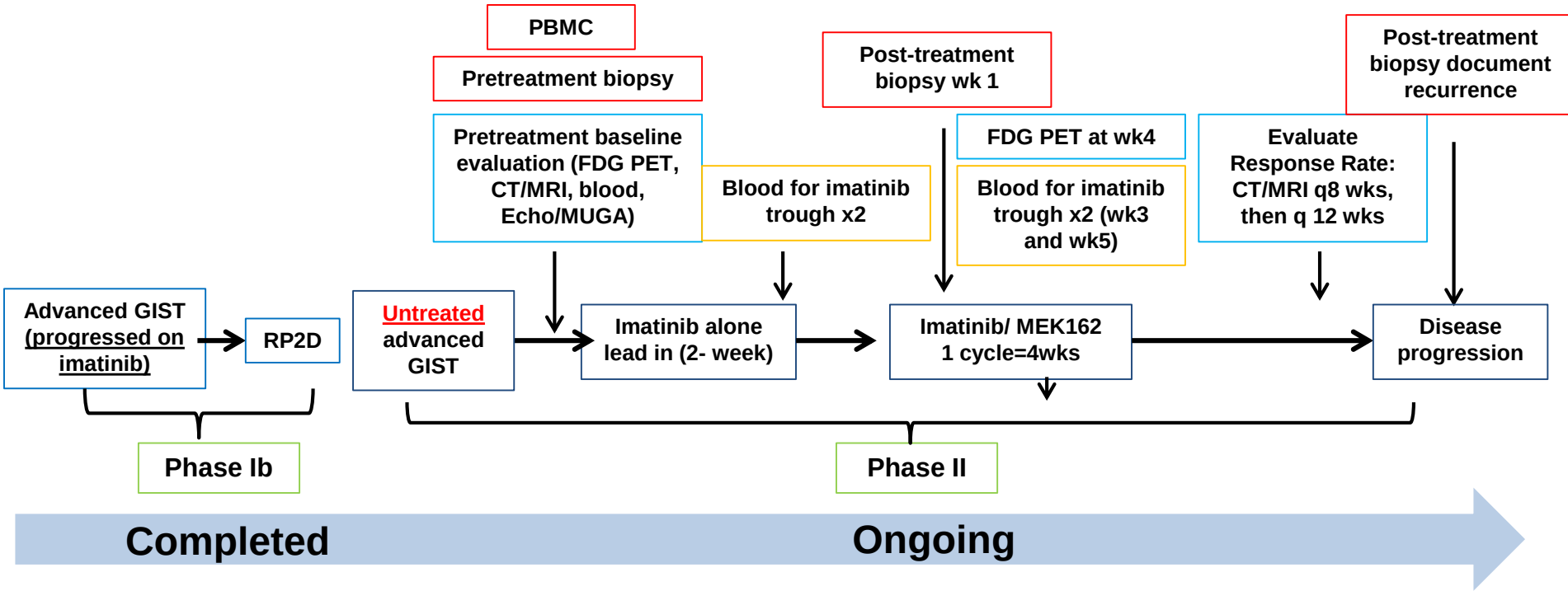
Phase Ib/II study of MEK162 in combination with imatinib in patients with untreated locally advanced and metastatic GIST

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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Patient Characteristics

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 (2); *BRAFV600E* (1); SDH-deficient (1), Unknown (2)

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Safety and Tolerability

Phase Ib Dose Escalation Cohort

Adverse Effect	Grade 3 (n=9)	Grade 4 (n=9)
CPK elevation	3	1 (DLT)
Lymphopenia	1	0
AST elevation	1	0
Hypocalcemia	1	0

Phase Ib Dose Escalation and Expansion Cohort

Adverse Effect	Grade 3 (n=18)	Grade 4 (n=18)
CPK elevation	12	4
Anemia	1	0
Lymphopenia	2	0
AST elevation	1	0
Hypocalcemia	1	0

Federally Funded Research

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Common Adverse Effects

Adverse Effect	≥Grade 2 n=18 (%)
Edema/Fluid Retention	**5(28)**
Peripheral (Limbs)	4 (22)
Facial	1 (6)
Periorbital	1 (6)
Trunk	1 (6)
Skin-related	**4 (22)**
Rash (Maculopapular, pustular)	3 (17)
Palmar-plantar erythrodysesthesia	1 (6)
Gastrointestinal-related	**3 (17)**
Diarrhea	3 (17)
Nausea	1 (6)
Vomiting	1 (6)
Mucositis, Oral	1 (6)
CPK elevation	**14 (78)**
Fatigue	**3 (17)**
Hematological AEs	**9 (50)**
Anemia	8 (44)
Leukopenia	2 (11)
Neutrophil count decrease	2 (11)
Thrombocytopenia	1 (6)
Renal/Electrolytes AEs	**7 (39)**
Hypophosphatemia	6 (33)
Hypomagnesemia	1 (6)
Creatinine increased	1 (6)
Abnormal LFTs	**3 (17)**
ALT	1 (6)
AST	1 (6)
Alk Phos	1 (6)
Dropped Head Syndrome	**1 (6)**
Pleural effusion	**1 (6)**

Asymptomatic →

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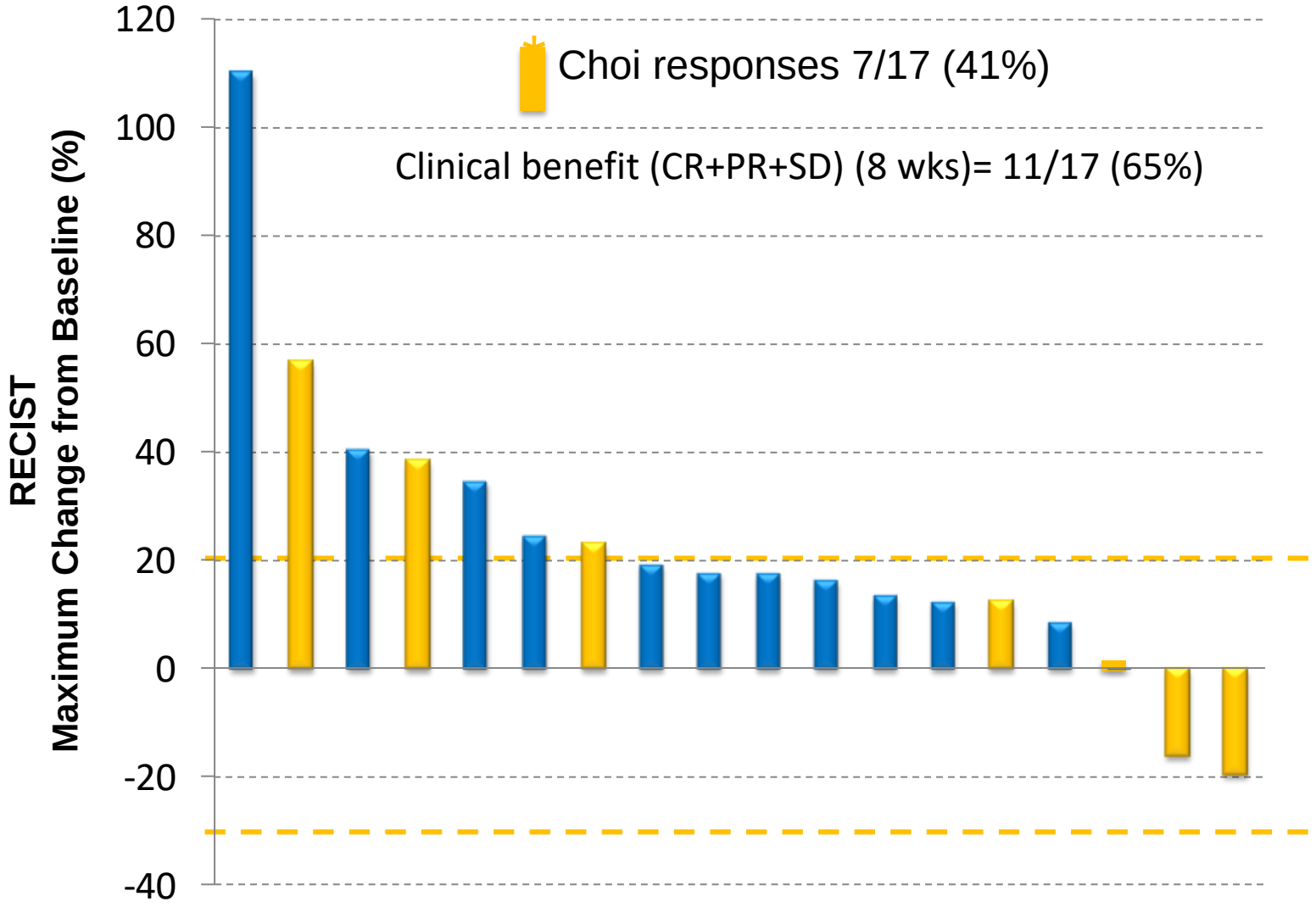
Responses



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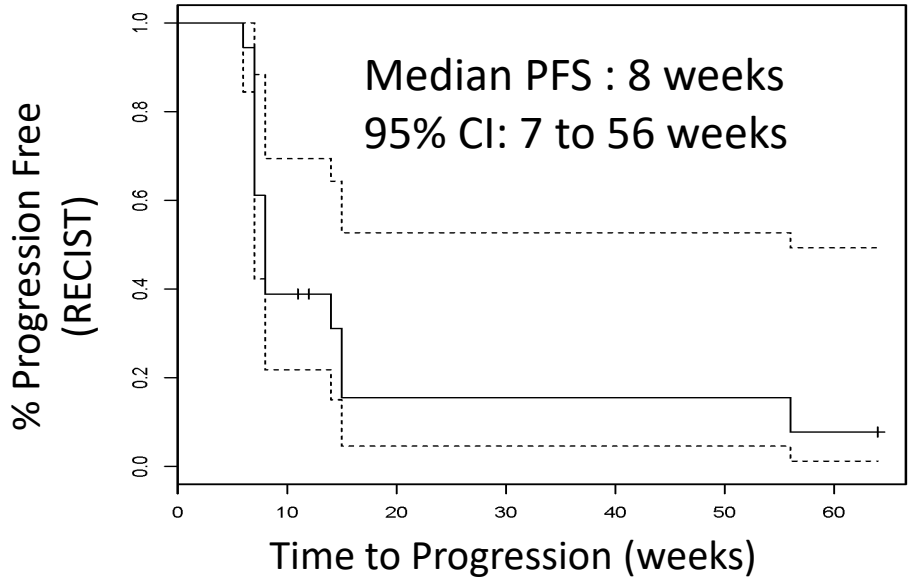
Progression Free Survival



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

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, Lisitinib trial	SDHA R31XSDHB loss by IHC	>66 (active)	(-20%)	PR
	8	Imatinib, Sunitinib, Sorafenib	KIT exon11, L576P	55	SD (-16%)	PR

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Thank You

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