Building New Paradigms: Trends in Combination Therapy and Pivotal Ongoing Trials

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Talk Outline

- Background
- Tyrosine kinase inhibitors: beyond Imatinib, Sunitinib and Regorafenib
- Mechanisms of resistance
- Combination therapy: Promise and pitfalls
- Novel therapies in trial for rare subtypes:
  - PDGFR mutations (D842V)
  - BRAF mutations
  - SDH mutations
  - NTRK fusions

1983

First described by Mazur and Clark.

1995

CD34 relatively specific marker.
(Miettinen et al. Am J Surg Path)
Similarities between GIST cells and Interstitial Cells of Cajal.

1998

2 major discoveries.
(Hirota et al Science)
-KIT staining 94% of GIST
-Activating mutations in *KIT* gene (5 out of 6)

2002

Accelerated FDA approval IMATINIB

2006

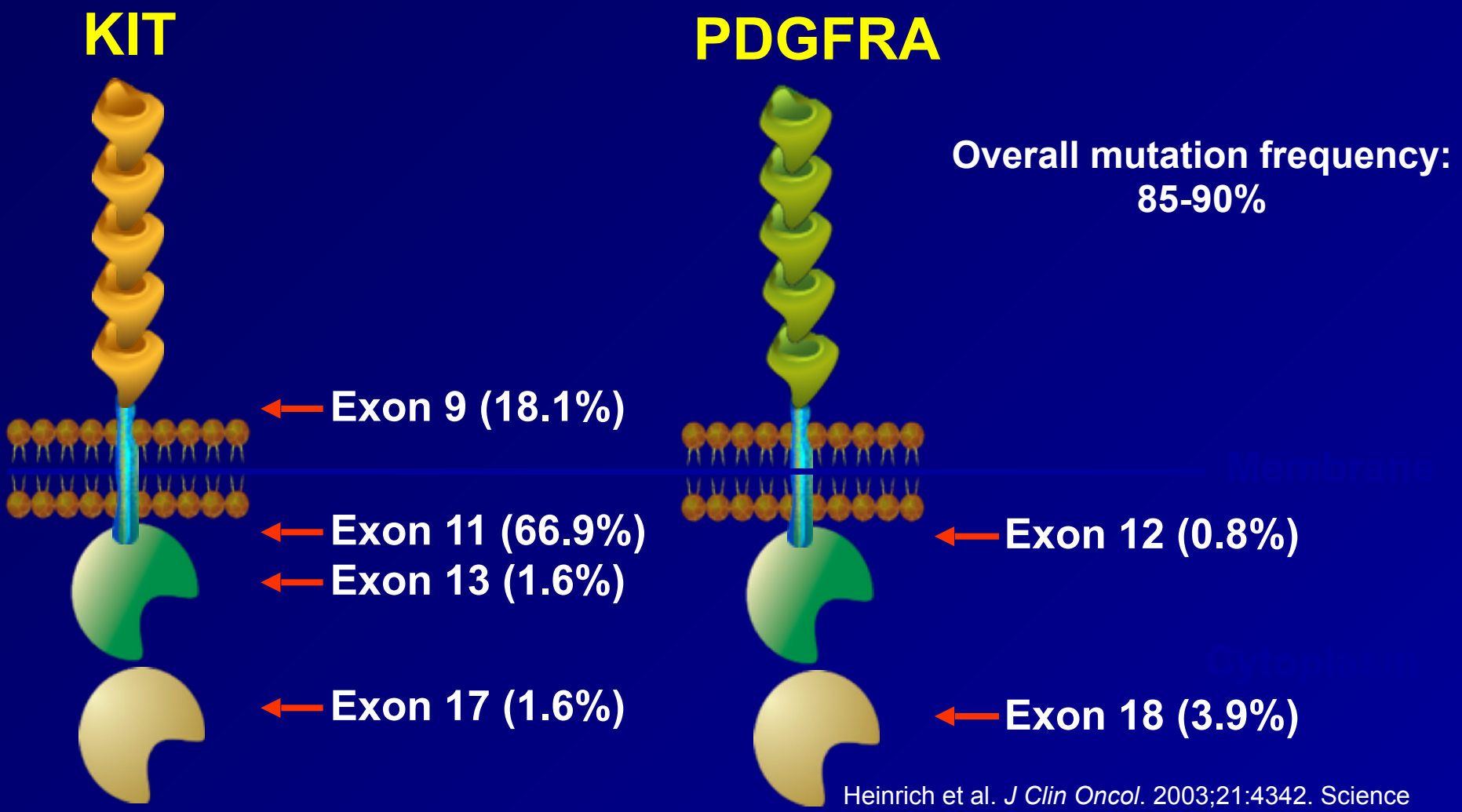
FDA Approval SUNITINIB

2013

FDA Approval REGORAFENIB

?

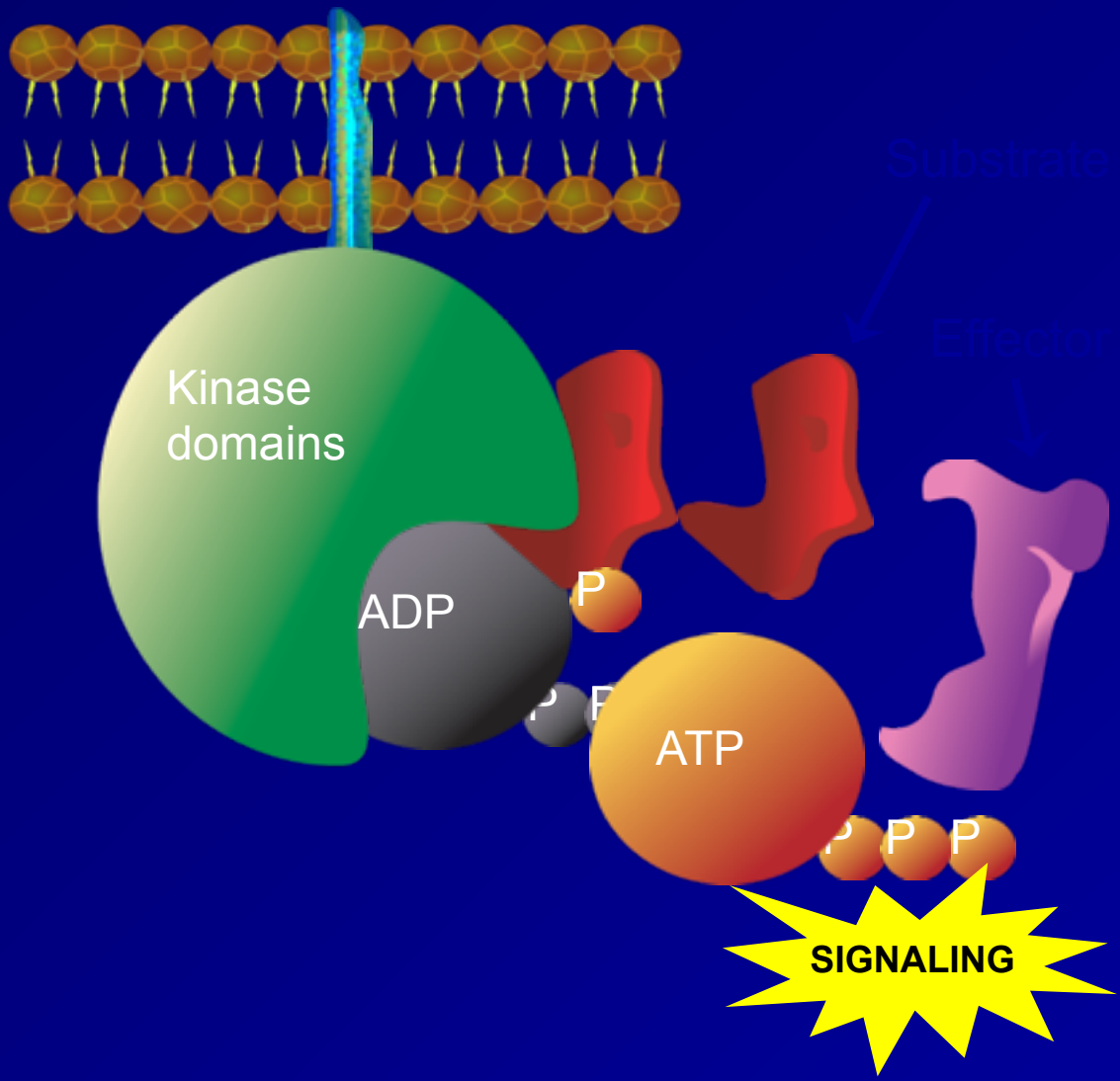
KIT and PDGFRA Mutations



Heinrich et al. *J Clin Oncol*. 2003;21:4342. Science 2003.

Normal KIT Signaling

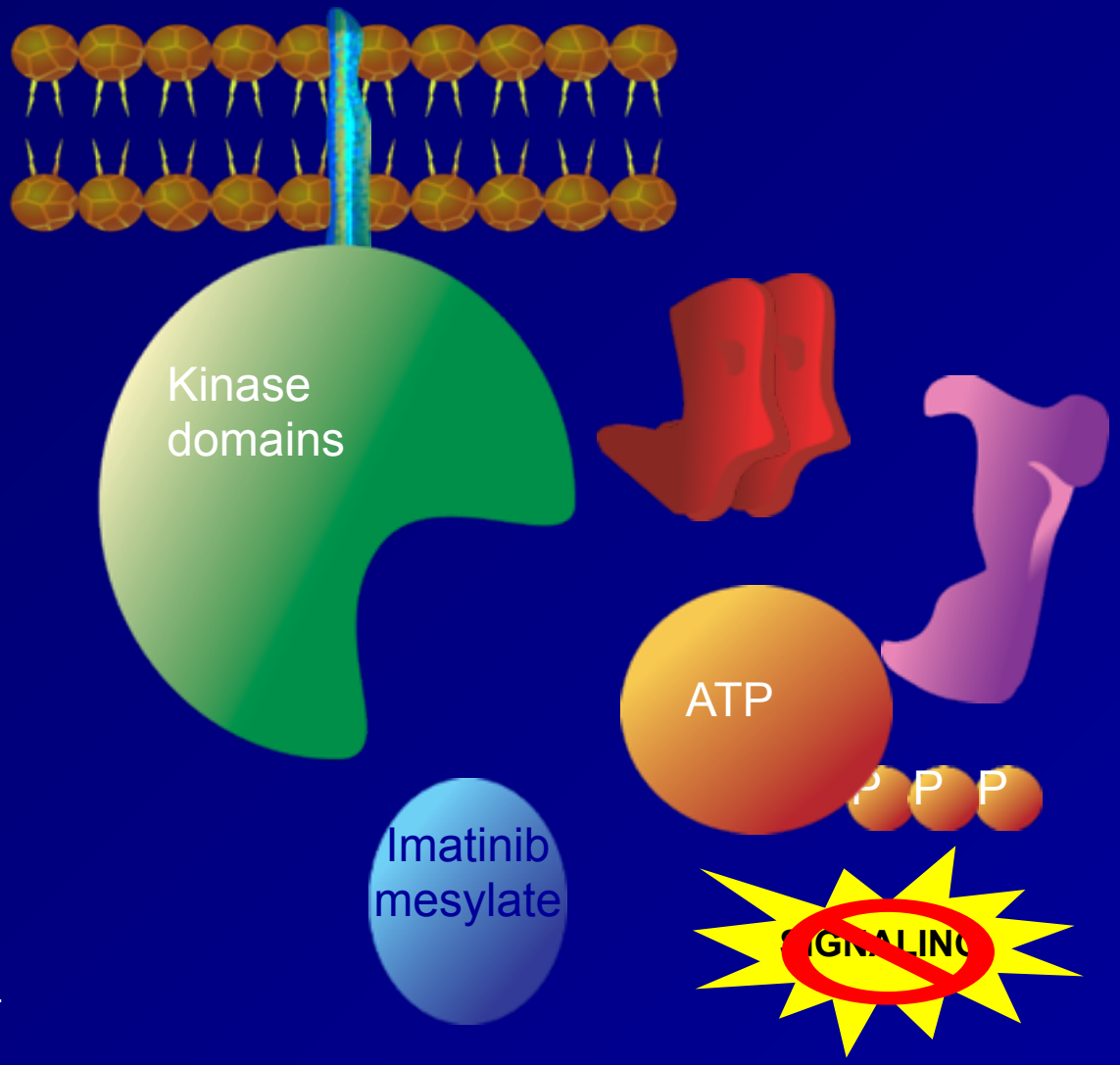
- The KIT kinase domain activates a substrate protein
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival



Savage and Antman. *N Engl J Med.* 2002;346:683.
Scheijen and Griffin. *Oncogene*. 2002;21 3314.

Imatinib Mesylate: Mechanism of Action

- Imatinib mesylate occupies the ATP binding pocket of the KIT kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival



Savage and Antman. *N Engl J Med.* 2002;346:683.
Scheijen and Griffin. *Oncogene*. 2002;21:3314.

Non-KIT/ PDGFR GIST (Wild Type) (10-15%)

- BRAF mutation (V600E exon 15)

Agaram N P et al. Genes Chromosomes and Cancer 2008

- IGF-1R

Godwin AK et al. JCO 2008, Janeway et al In J Cancer 2010

- Succinate Dehydrogenase

- Alternate mutations (AKT/PTEN/TRK)…

Janeway et al. JCO 2010,

Majority are Sporadic

Associated Syndromes

- Familial GIST syndrome — Nishida et al. Nat Genet 1998
- Neurofibromatosis-1 — Fuller CE et al. Histopathology 1991
- Carney Triad — Carney et al. NEJM 1977
- Carney Stratakis Syndrome — Carney et al. Am J Med Genet. 2002

The advent of targeted therapy has dramatically altered the prognosis

- Pre- Imatinib
  - Localized disease: 5-year survival rate **< 50%.**
  - Metastatic GIST: median survival was **5-12 months**

- Era of targeted therapy (post 2001)
  - Localized disease: 5-year survival rate **> 80 %**
  - Metastatic GIST: median survival **≥ 58 months**

Nilsson et al. Cancer. 2005;103:821-829.
Gold et al. Ann Surg Oncol. 2007;14:134-142
DeMatteo et al. JCO 2005; Joensuu et al. ASCO 2011
Verweij et al. *Lancet.* 2004;364:1127

Overall Survival Estimates for Advanced GIST patients on S0033 treated with imatinib

Survival (years)	OS Estimate	95% CI
5	46%	43% - 50%
6	39%	36% - 43%
7	35%	31% - 38%
8	31%	28% - 35%
9	26%	23% - 30%
10	22%	19% - 26%

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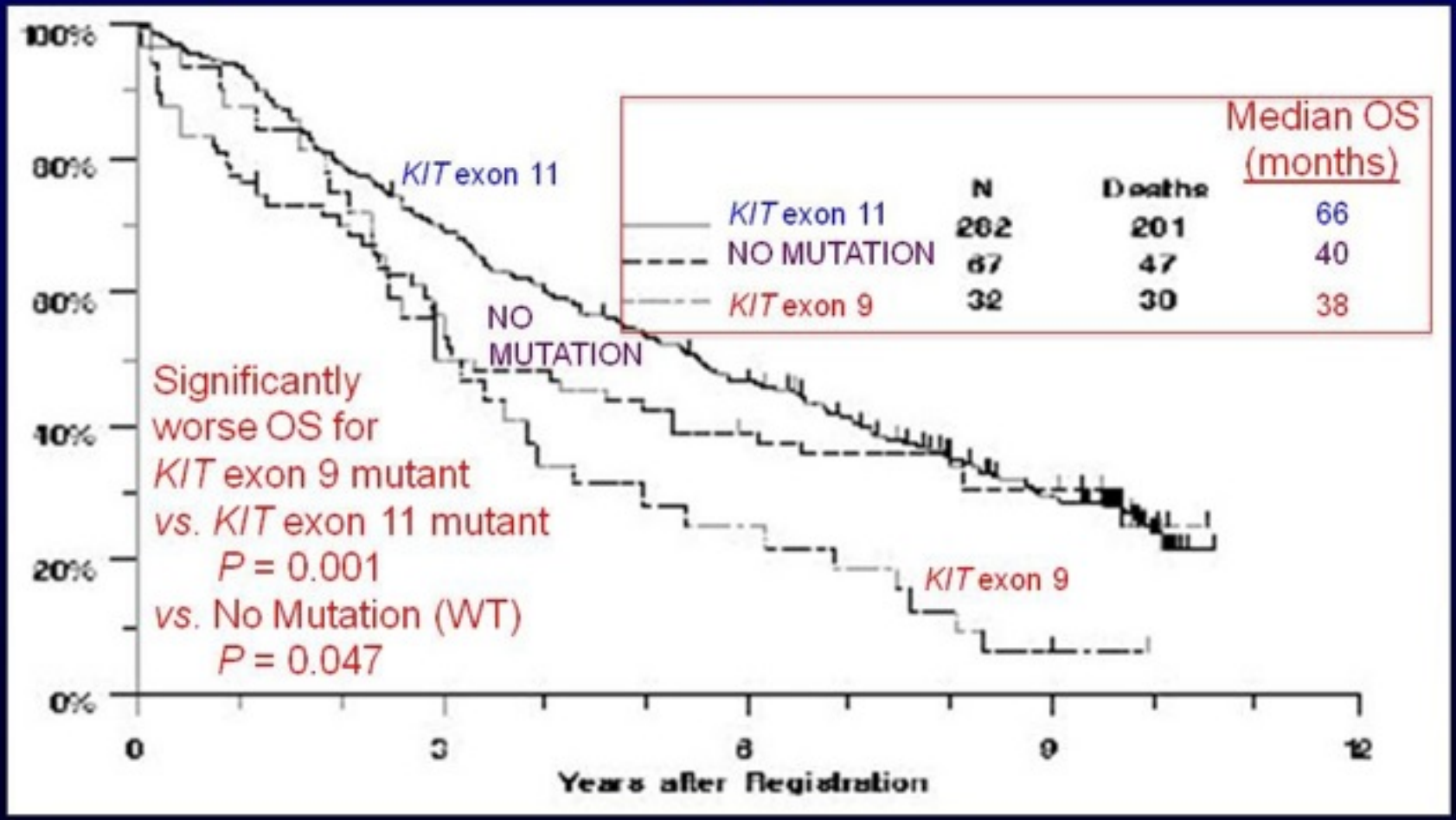
S0033 Overall Survival by GIST Genotype – 2014 data



Analysis of Post-Progression Therapies (i.e. after progression on imatinib)

	All Long-Term Survivors (n=137)	With Known GIST Genotype		
		EXON 11 (n=70)	WILD-TYPE (n=13)	EXON 9 (n=3)
Any Additional Therapy	70 (51%)	36 (51%)	7 (54%)	3 (100%)
Systemic Therapy	54 (39%)	28 (40%)	7 (54%)	3 (100%)
Sunitinib	41 (30%)	22 (31%)	5 (38%)	2 (67%)
Sorafenib	16 (12%)	10 (14%)	1 (8%)	1 (33%)
Other Agents	42 (31%)	20 (29%)	5 (38%)	3 (100%)
Surgery	41 (30%)	20 (29%)	3 (23%)	3 (100%)
Metastasectomy	29 (21%)	15 (21%)	1(8%)	3 (100%)
Other Surgery	18 (13%)	9 (13%)	3 (23%)	0 (0%)
Radiofrequency Ablation	10 (7%)	8 (11%)	1 (8%)	1 (33%)
Radiation Therapy	6 (4%)	4 (6%)	1 (8%)	0 (0%)

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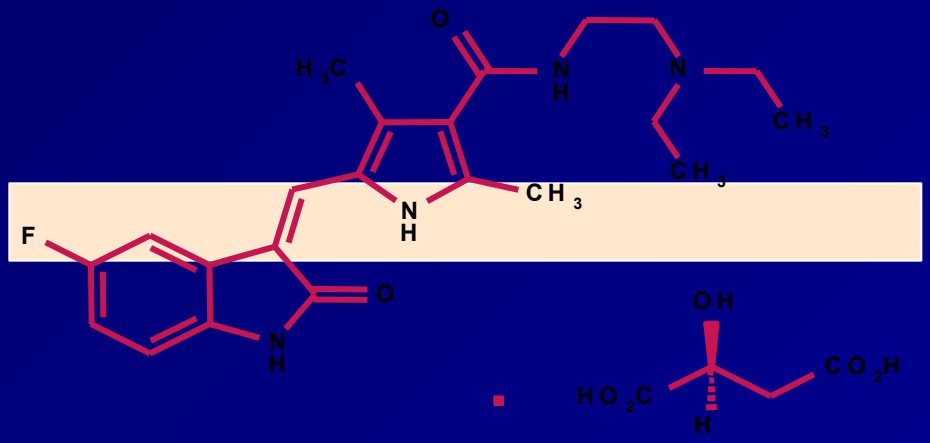
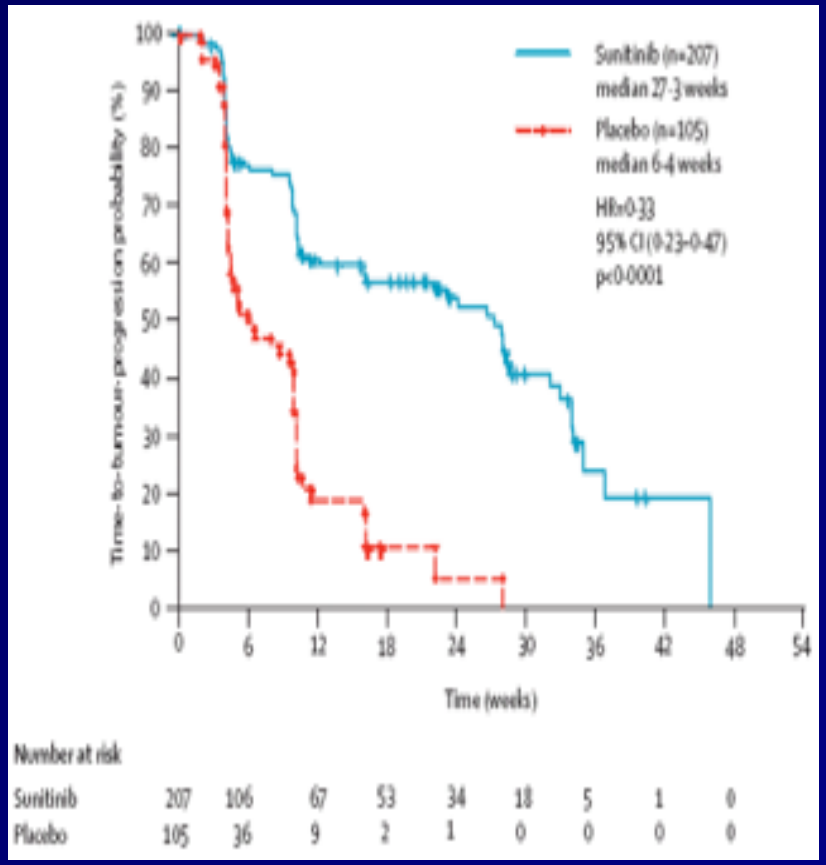
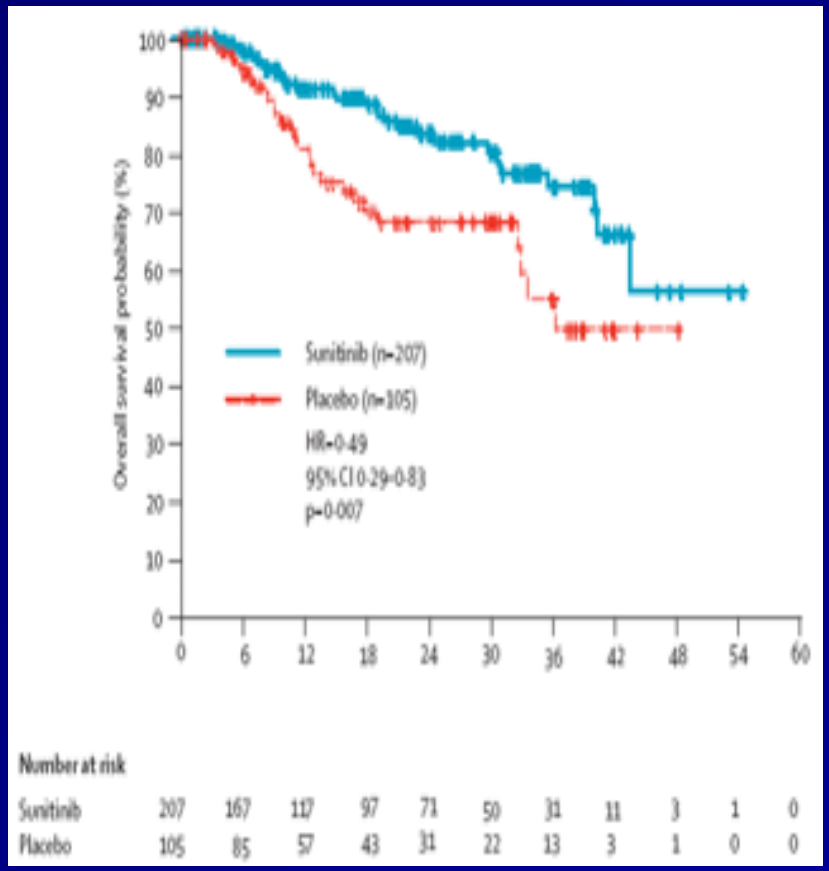
Sunitinib Malate (SU11248)

- Small-molecule receptor tyrosine kinase inhibitor
- Inhibits all VEGFRs, PDGFR-A, PDGFR-B, c-KIT, and FLT-3
- Oral administration
- Both antitumor and antiangiogenic activity
- FDA approved January 26, 2006 for treatment of advanced GIST



Sunitinib Improves PFS and OS Compared to Placebo





Demetri GD, et al. *Lancet*. 2006.14;368(9544):1329.

Potential for Disease Control with TKI Therapy based on Site of Mutation

TKI	Primary mutations				Secondary mutations	
	KIT exon9	*KIT* exon11	*KIT* exon17	*PDGFR* exon18	*KIT* exon13	*KIT* exon14
Imatinib	↓ *	↑	↓	↓	↓	↓
Sunitinib following Imatinib	↑	ND	↓	↓	↑	↑

↓: Low potential. ↑: High potential. ND: No data.

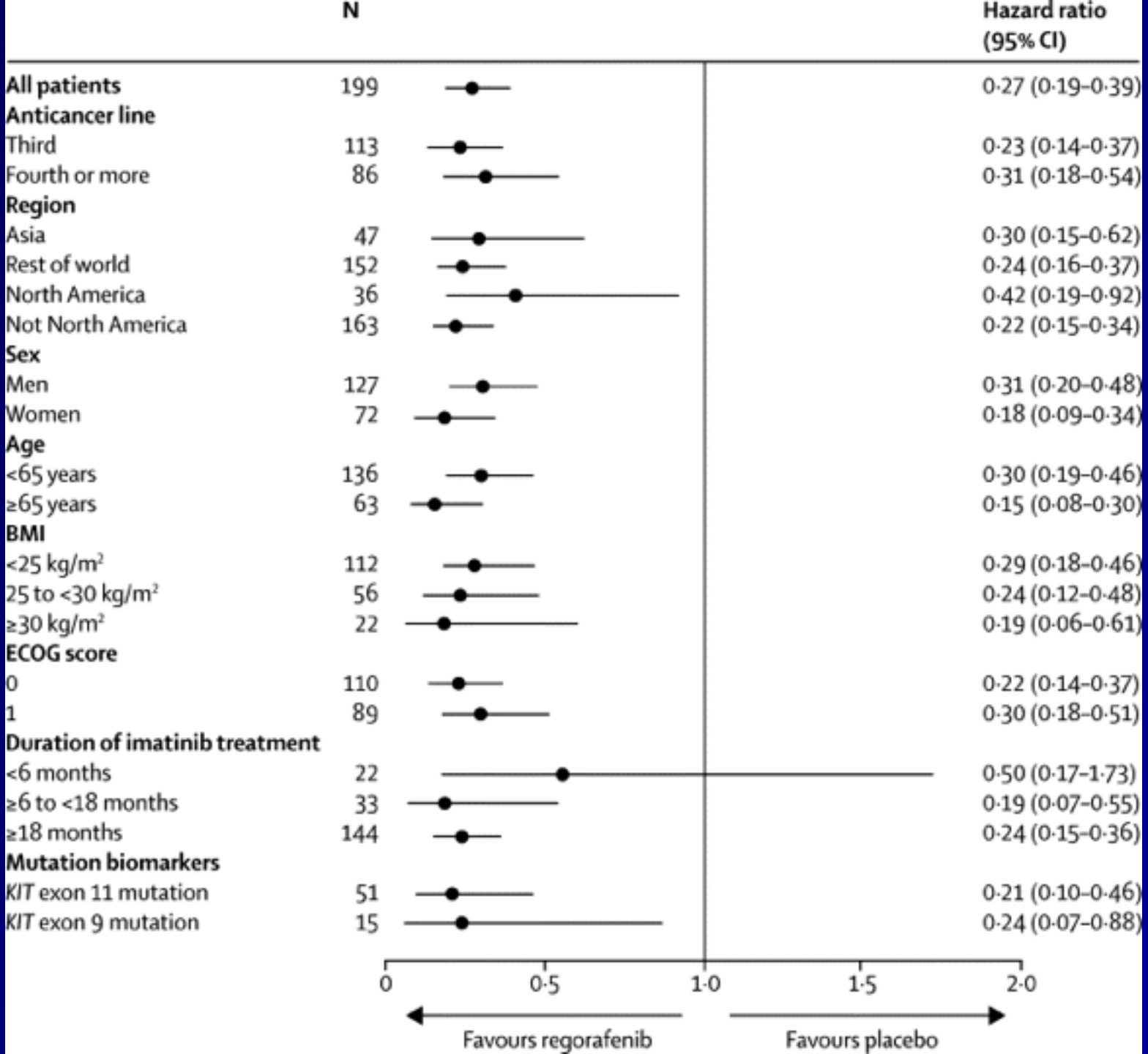
* Less likely to respond to low dose therapy

Somaiah, von Mehren. Hem Onc Clinics 2009

Randomized Phase III Trial of Regorafenib in Patients with Metastatic and/or Unresectable GIST Progressing Despite Prior Treatment with at Least Imatinib and Sunitinib: GRID Trial

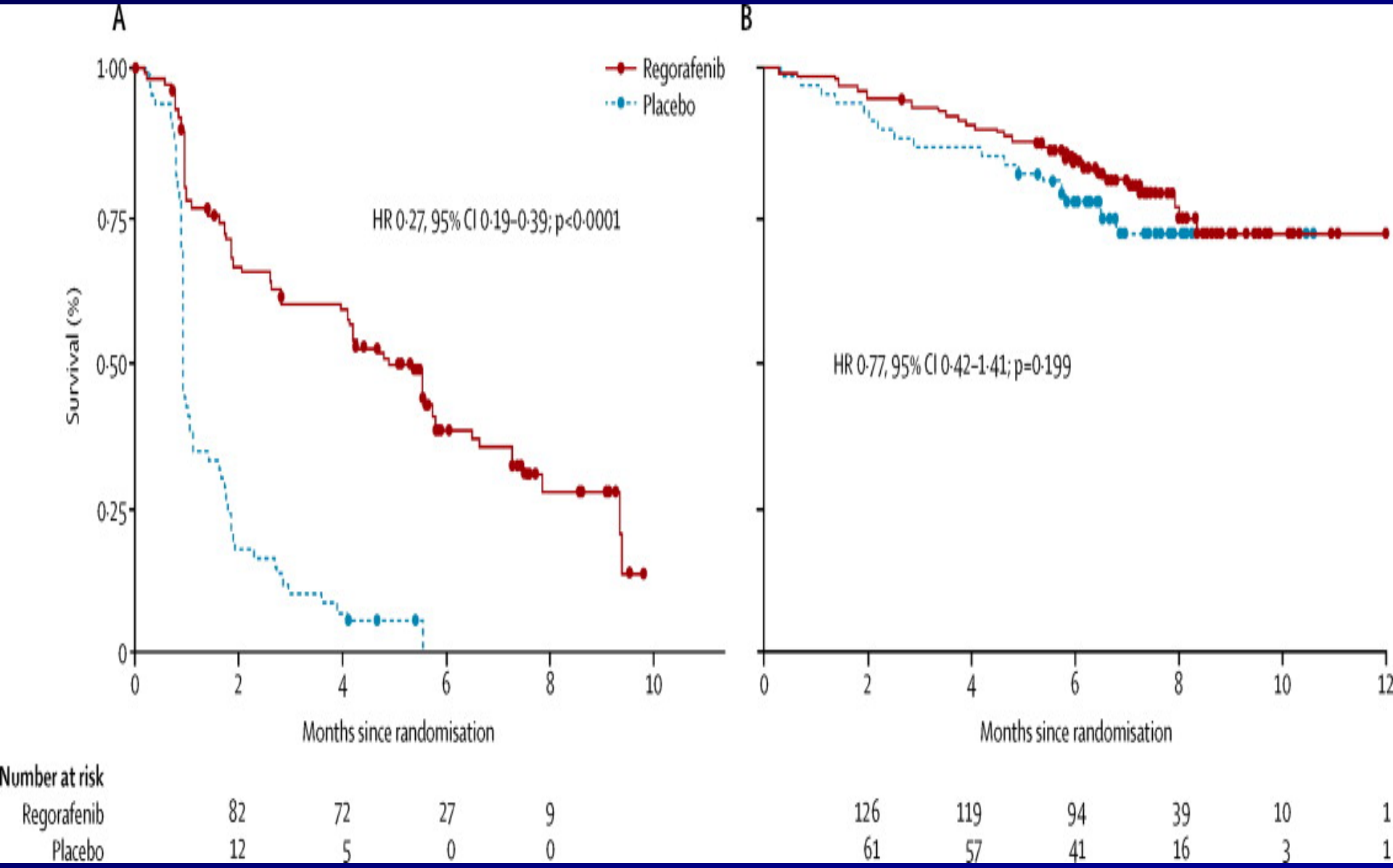
Demetri GD et al.

Proc ASCO 2012; LBA 10008.


N
Hazard ratio (95% CI)
All patients 199 0·27 (0·19–0·39)
Anticancer line
Third 113 0·23 (0·14–0·37)
Fourth or more 86 0·31 (0·18–0·54)
Region
Asia 47 0·30 (0·15–0·62)
Rest of world 152 0·24 (0·16–0·37)
North America 36 0·42 (0·19–0·92)
Not North America 163 0·22 (0·15–0·34)
Sex
Men 127 0·31 (0·20–0·48)
Women 72 0·18 (0·09–0·34)
Age
<65 years 136 0·30 (0·19–0·46)
≥65 years 63 0·15 (0·08–0·30)
BMI
<25 kg/m² 112 0·29 (0·18–0·46)
25 to <30 kg/m² 56 0·24 (0·12–0·48)
≥30 kg/m² 22 0·19 (0·06–0·61)
ECOG score
0 110 0·22 (0·14–0·37)
1 89 0·30 (0·18–0·51)
Duration of imatinib treatment
<6 months 22 0·50 (0·17–1·73)
≥6 to <18 months 33 0·19 (0·07–0·55)
≥18 months 144 0·24 (0·15–0·36)
Mutation biomarkers
KIT exon 11 mutation 51 0·21 (0·10–0·46)
KIT exon 9 mutation 15 0·24 (0·07–0·88)
0
0·5
1·0
1·5
2·0
Favours regorafenib
Favours placebo

Progression free survival

Overall Survival



Resection Of Progressive Or Residual GIST After Imatinib

	Surgical CR	12-mo.PFS	12-mo. OS
Stable Disease	78%	80%	95%
Limited Progression	25%	33%	86%
Generalized Progression	7%	0%	0%

P>0.001

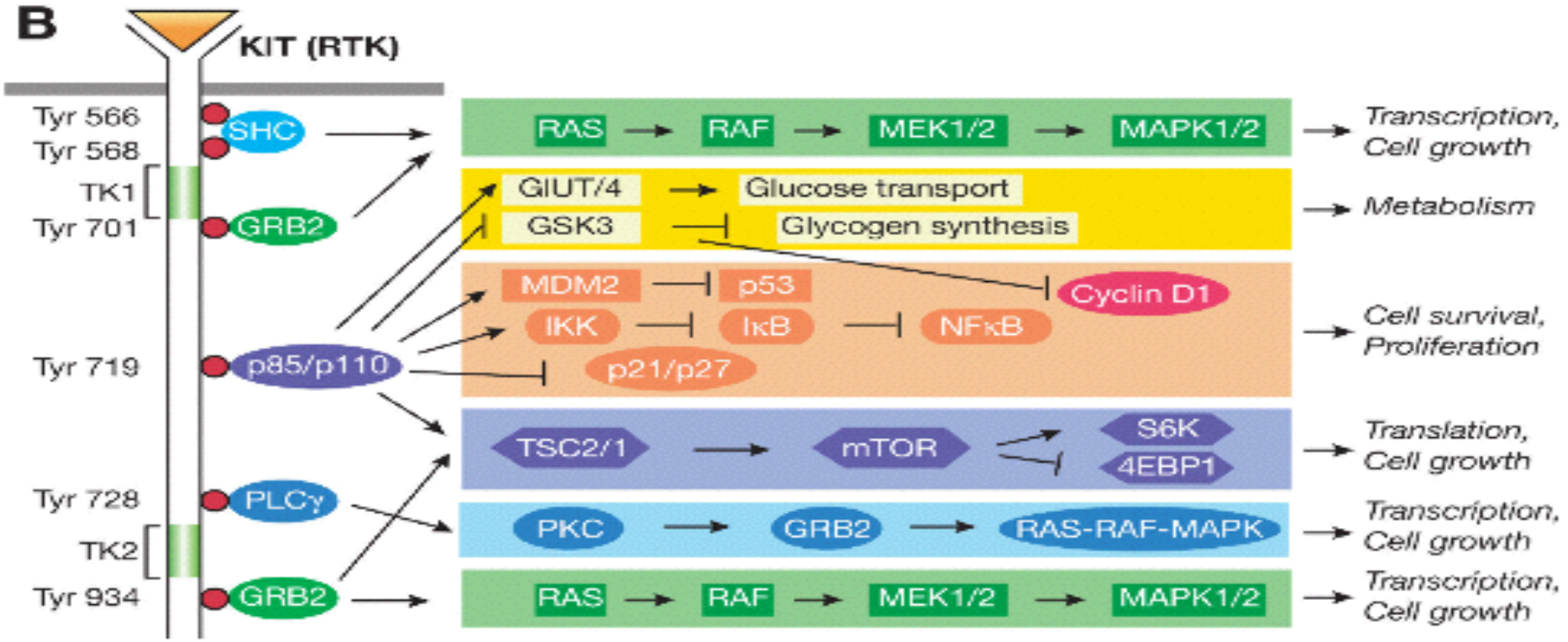
Raut et al. JCO, 2006

Mechanisms of resistance

Progression on Imatinib

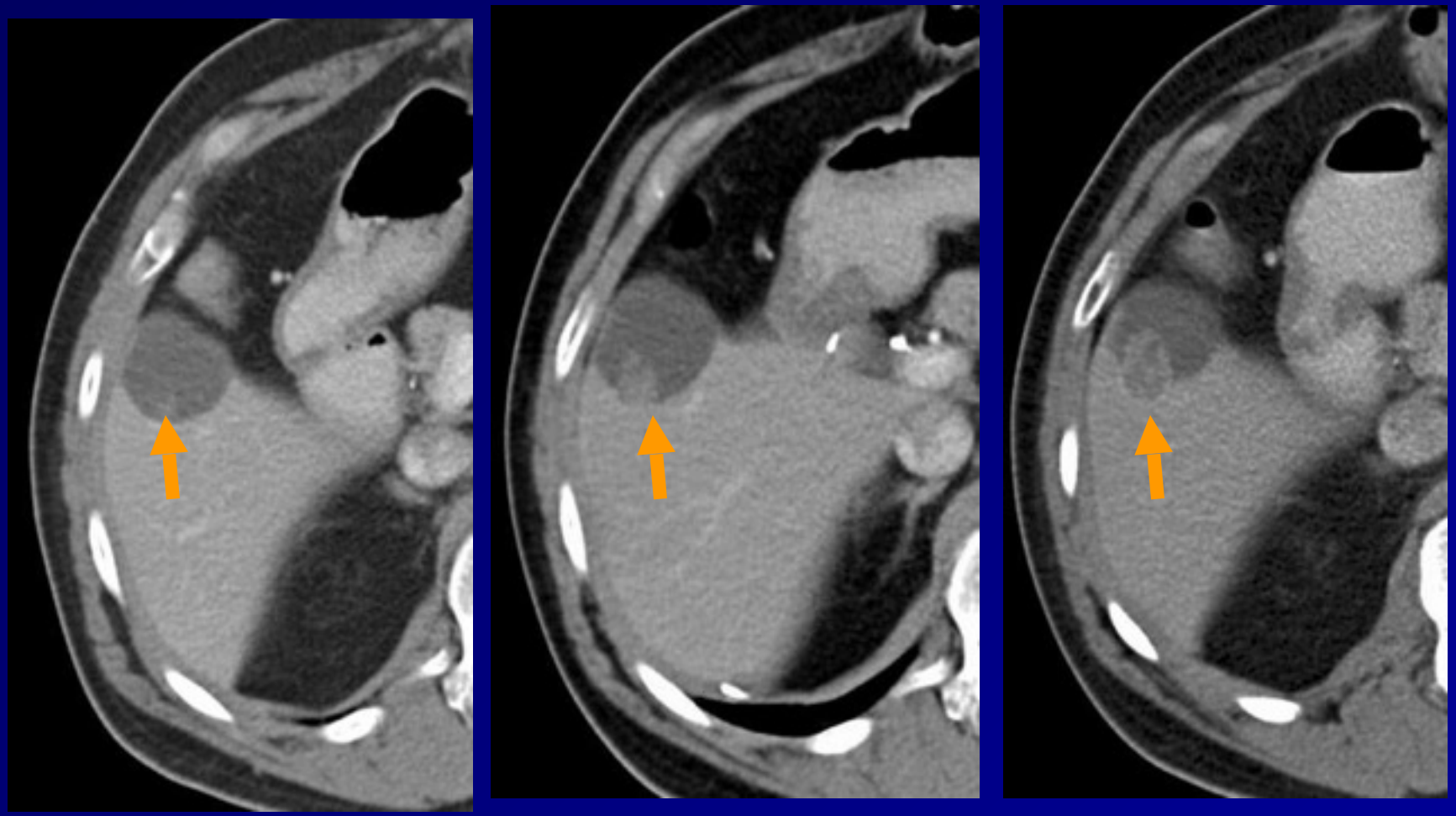
- Primary Resistance (within 6 months 10-15%):
  - KIT exon 17, PDGFR exon 18 mutations, BRAF, KRAS
  - Diffuse progression
- Secondary Resistance:
  - Acquired secondary mutations – usually in tumors with exon 11 primary mutation
  - Activation of alternate drivers/pathways: PI3K/ AKT/ mTOR, IGFR1
  - Focal progression or diffuse progression

Intracellular Signaling Pathways



Tarn and Godwin. Clin Colorectal Cancer, 2006.

Resistance :
Recognition of Clonal Evolution



Courtesy of Dr. G.D. Demetri.

Novel TyROsine kinase inhibitors

Long list….

KIT+PDGFR+VEGFR+

- Sorafenib
- Cediranib
- Cabozantinib
- Pazopanib
- Vandetinib
- Motesanib
- Dovitinib
- Famitinib

KIT+PDGFR+

- Nilotinib
- Dasatinib
- Ponatinib
- Masitinib
- XL820
- DCC2618

Sorafenib

- Targets Raf, KIT, PDGFR, VEGFR 2, 3
- Has shown benefit in phase II setting
- Although not approved often used in the third line

Wiebe et al. JCO 2008
Kindler HL et al. JCO 2011

Nilotinib

- Phase II studies showed some clinical benefit. RR<10%
- Phase III study compared to best supportive care in patients who progressed on imatinib & sunitinib showed a trend toward longer progression-free and survival but was not significant

Cauchi, Somaiah, von Mehren JCO 2010

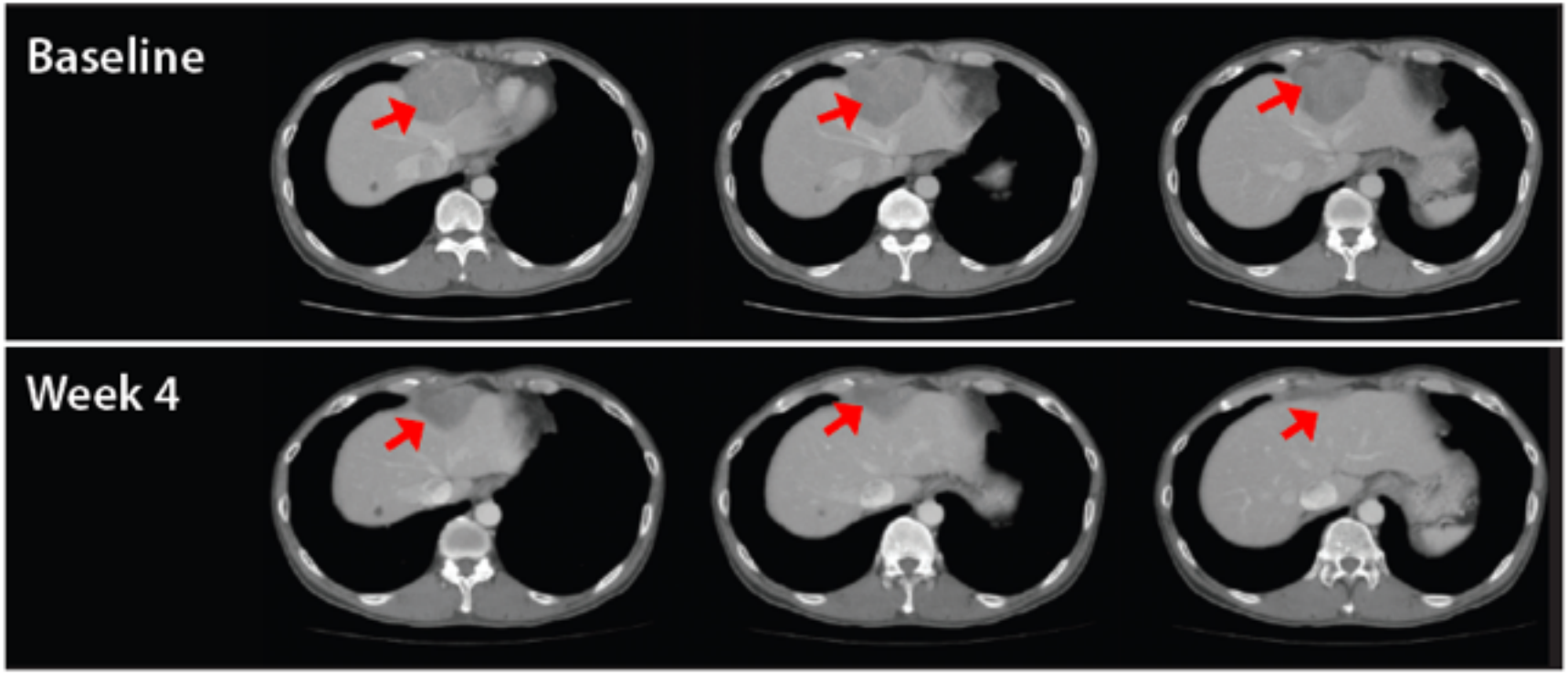
Phase I study with Cabozantinib
Yamamato et al.

- Cabozantinib is an oral, potent inhibitor of MET and VEGFR2
  - MET and its ligand HGF drive tumor cell invasion and metastasis[1,2]
  - MET and VEGFR2 promote angiogenesis[3]

Antitumor Activity

- A patient with GIST had stable disease with reductions in the sum of 5 target lesions of 16% (**Figure 4**), and continues treatment with cabozantinib

Figure 4. CT images of a patient with a primary diagnosis of GIST tumor positive for KIT over-expression (pretreated with 2 prior regimens including imatinib and sunitinib) who achieved reductions in the sum of target lesions of 16% during treatment with cabozantinib 60 mg (lesions indicated by red arrows). Grade 2 AEs included PPE, leukopenia and diarrhea. No grade 3 or greater AEs were reported.



Ph2 Trial of Ponatinib in GIST
Study Design

Key Inclusion/Exclusion Criteria

- ≥18 yrs with metastatic and/or unresectable GIST ***after failed ≥1 prior TKI****

N=45

- Presence of KIT exon 11 mutations KIT e11+ve N=30
- Absence of KIT exon 11 mutations KIT e11-ve N=15

Ponatinib 45mg QD

Primary Endpoint

- Clinical benefit rate (**CBR**): CR+PR+SD at 16 weeks KIT e11+ve pts

Secondary Endpoints

- CBR at 16 weeks KIT e11-ve pts and total
- PFS, ORR (CR+PR), OS by cohort and total
- Safety and tolerability
- PK

Exploratory Objectives

- Optional FDG-PET and tumor biopsy
- ctDNA studies

Data as of 07 April 2014: median follow-up 6 months all pts

*Protocol amended (22 Apr 2014) to include only patients with failure of all 3 TKIs approved for GIST: imatinib, sunitinib, and regorafenib

Ph2 Trial of Ponatinib in GIST
Demographics & Baseline Characteristics

	KIT e11+ve N=24	KIT e11-ve N=11	Total N=35
Median age, yrs [range]	61 [40 - 81]	53 [24 - 73]	58 [24 - 81]
Gender, male (%)	15 (63)	5 (45)	20 (57)
Median time since diagnosis, yrs [range]	6 [1 - 30]	5 [2 - 25]	6 [1 - 30]
2 prior GIST-approved TKIs, n (%)	10 (42)	6 (55)	16 (46)
3 prior GIST-approved TKIs, n (%)	12 (50)	4 (36)	16 (46)
Median number of prior cancer regimens [range]*	4 [1 - 10]	5 [2 - 7]	4 [1 - 10]

*Includes investigational TKIs

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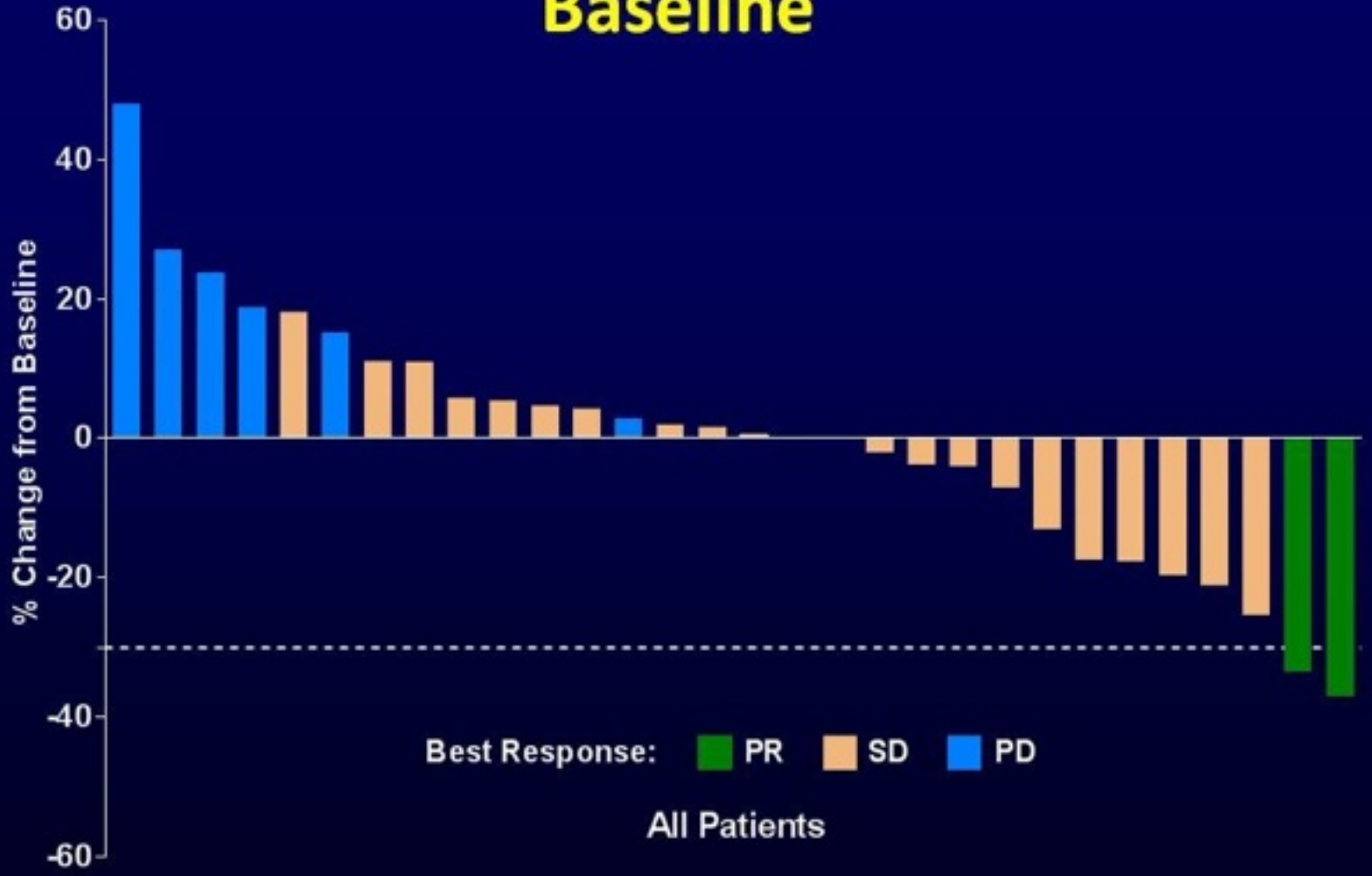
Ph2 Trial of Ponatinib in GIST
Target Tumor Lesion Best Change from Baseline



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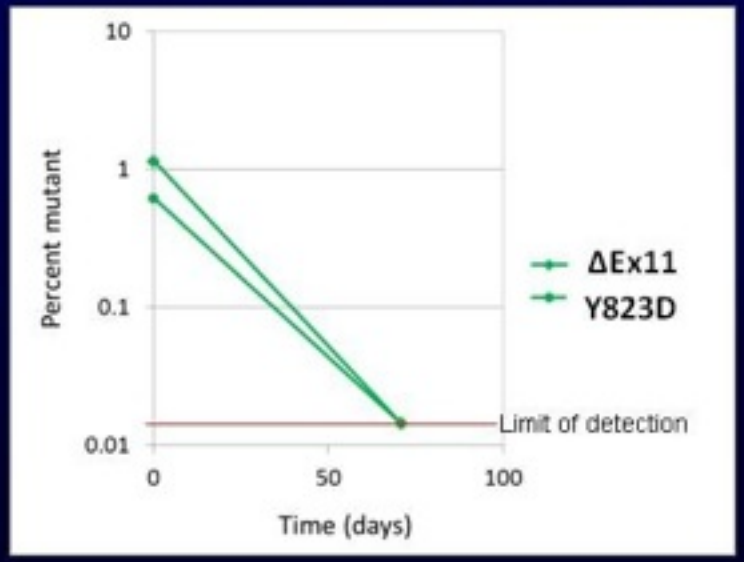
Ph2 Trial of Ponatinib in GIST
FDG-PET, Biopsy, Plasma Molecular Analysis

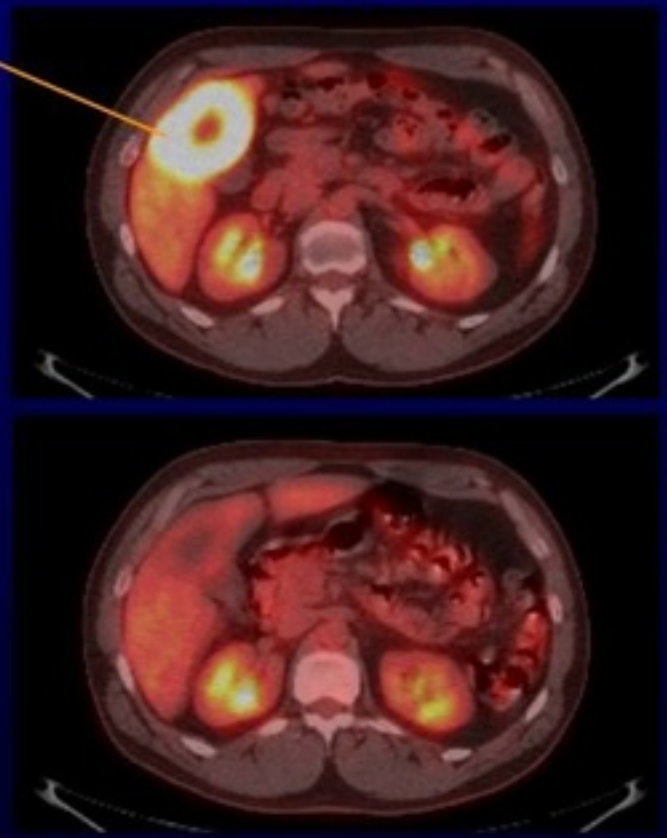
KIT mutations in biopsy (NGS, Foundation Med)

	Mutations	% reads
Primary	ΔEx11	89
Secondary	Y823D	87

KIT mutations in plasma (BEAMing)



FDG PET



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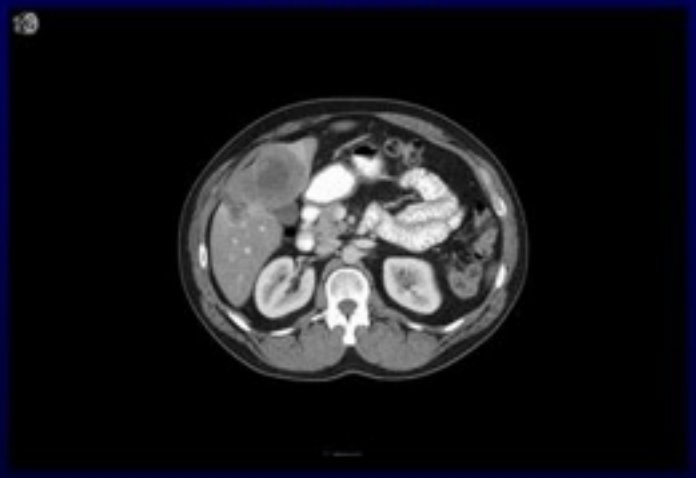
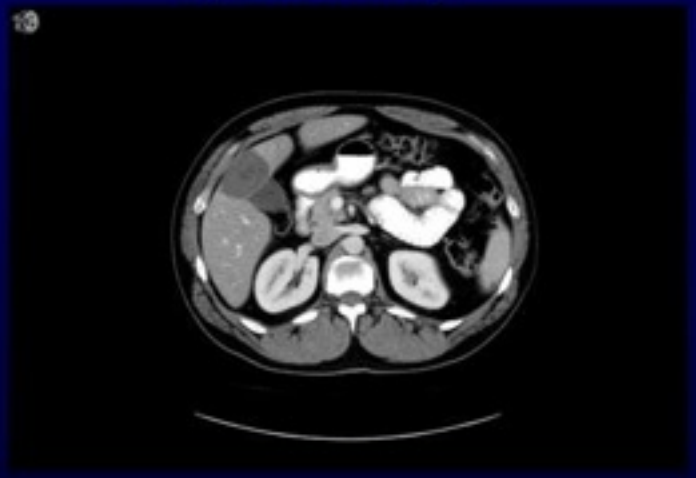
Ph2 Trial of Ponatinib in GIST
CT Scan

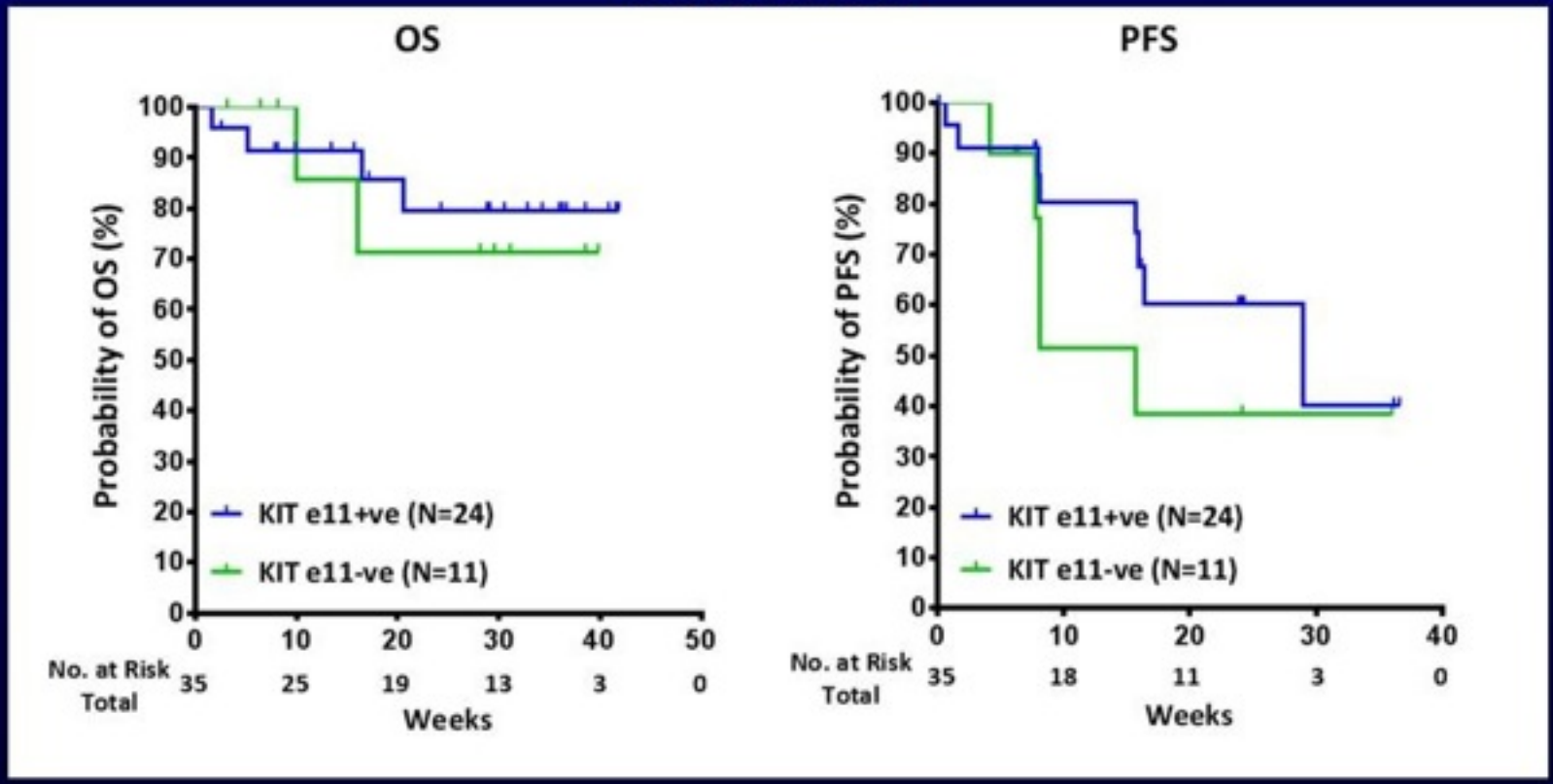
Baseline



Cycle 3 Day 1



Ph2 Trial of Ponatinib in GIST Survival



OS at 6 months (95%CI) [median]:

KIT e11+ve: 80% (54, 92) [not reached]

KIT e11-ve: 71% (26, 92) [not reached]

PFS at 6 months (95%CI) [median]:

KIT e11+ve: 60% (33, 79) [7 months]

KIT e11-ve: 39% (9, 69) [4 months]

Novel pathways / Combination therapy options

Table 1. Emerging GIST therapeutic targets and representative active agents in the preclinical,[a] phase I,[b] phase II,[c] phase III,[d] or limited clinical setting[e]

PI3K/AKT/mTOR inhibitors	HSP90 inhibitors	IGFR1 inhibitors	Immune therapy	Drug repurposing
BKM120[a]	IPI-504[a,b,d]	R1507[a,e]	Pegylated interferon alpha-2b[d]	Mithramycin A[a]
GDC-0941[a]	IPI-493[a]	Linsitinib	Ipilimumab	Mitoxantrone[a]
SF1126[b]	STA-9090[a,b]			Auranofin[a]
BEZ235[a]	BIIB021[a,b,c]			
GDC-0980[b]	AT13387[a]			
Perifosine[c]	AUY922[a,b]			
Everolimus[b,c]				
Sirolimus[d]				

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Table 2. Active GIST clinical trials with therapeutic targets beyond tyrosine kinase inhibition

PI3K/AKT/mTOR inhibitors
Phase Ib study with BKM120 and Imatinib in 3rd-line setting (NCT01468688)[a]
Phase Ib study with BYL719 and Imatinib in 3rd-line setting (NCT01735968)[a]
Phase I/II study with Perifosine and Sunitinib in advanced disease (NCT00399152)[b]
HSP90 inhibitors
Phase II study with AUY922 in 3rd-line setting (NCT01389583, NCT01404650)[a]
IGFR1 inhibitors
Phase II study with Linsitinib in adult and pediatric wild-type GIST (NCT01560260)[b]
Immune therapy
Phase I study with Ipilimumab and Dasatinib in advanced/unresectable disease (NCT01643278)[a]
Phase I study with Ipilimumab and Imatinib in advanced disease (NCT01738139)[a]

a, recruiting; b, completed and awaiting results.

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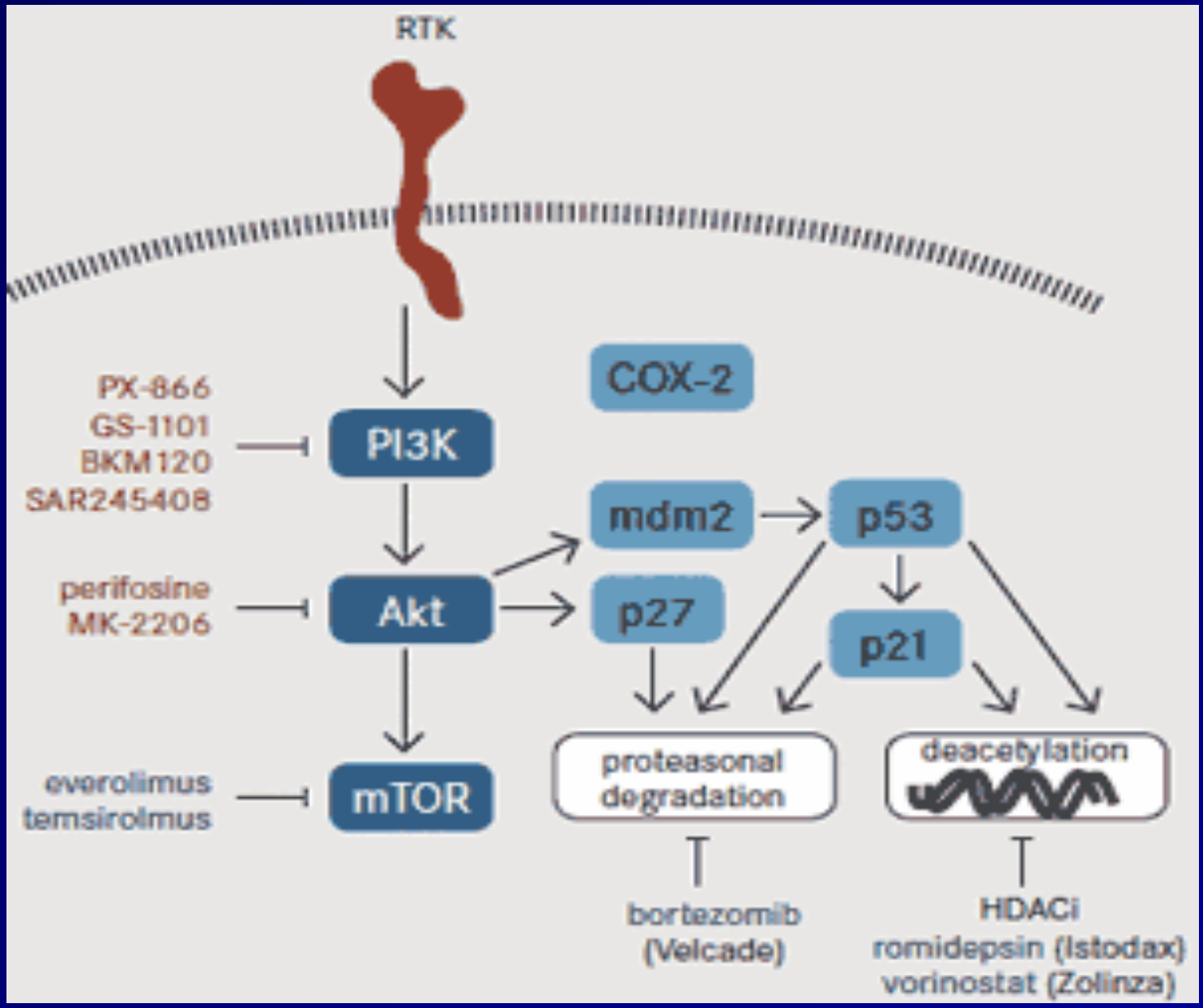
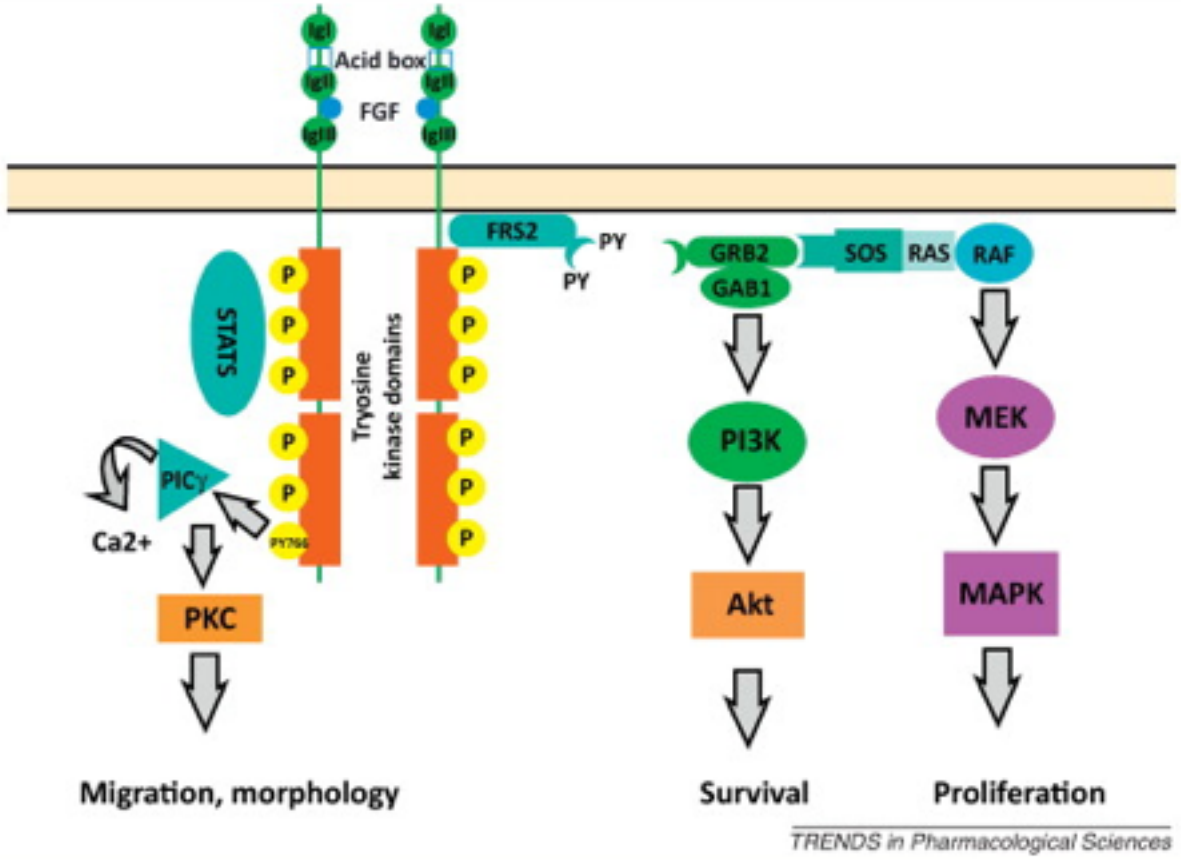
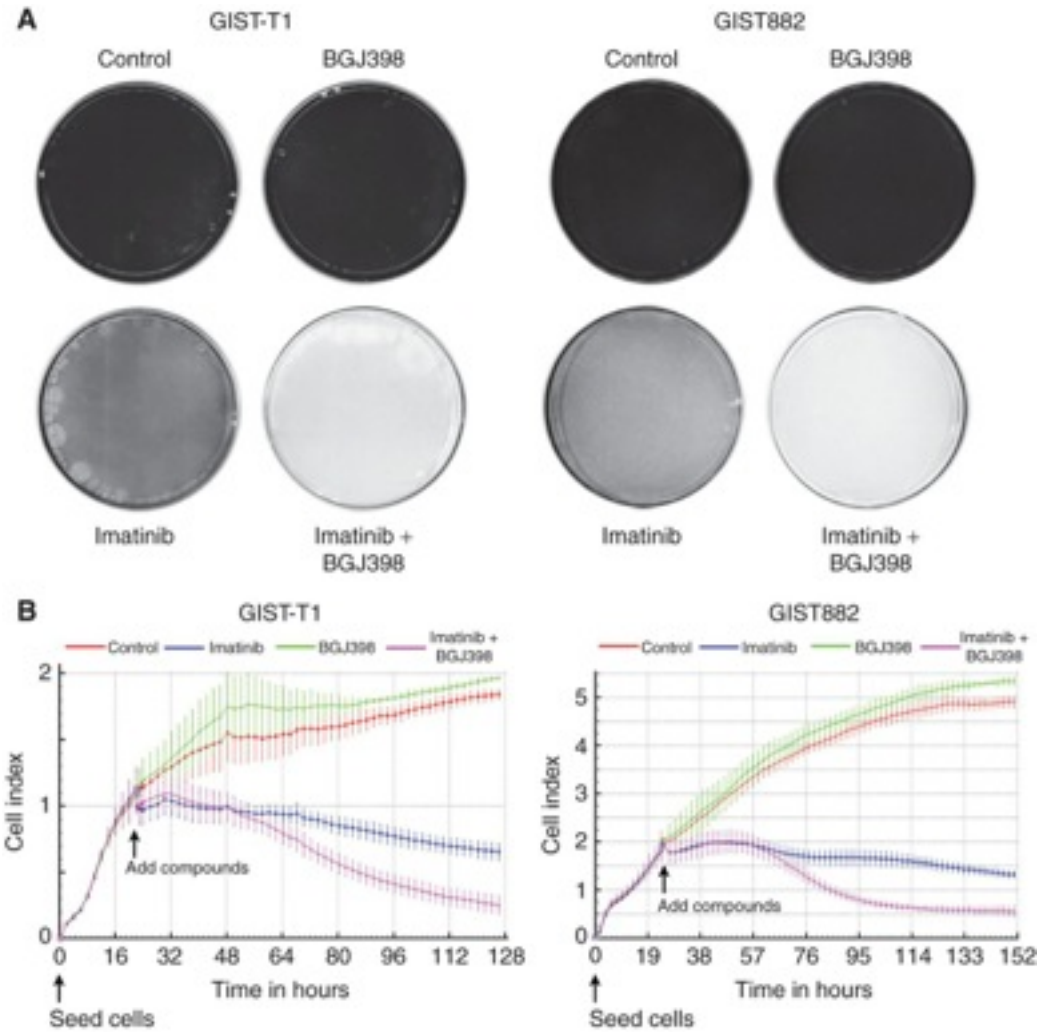

RTK
PX-866
GS-1101
BKM120
SAR245408
PI3K
COX-2
perifosine
MK-2206
Akt
mdm2
p53
p27
p21
everolimus
temsirolmus
mTOR
proteasonal degradation
deacetylation
bortezomib (Velcade)
HDACi
romidepsin (Istodax)
vorinostat (Zolinza)

FGFR- alternate pathway of activation



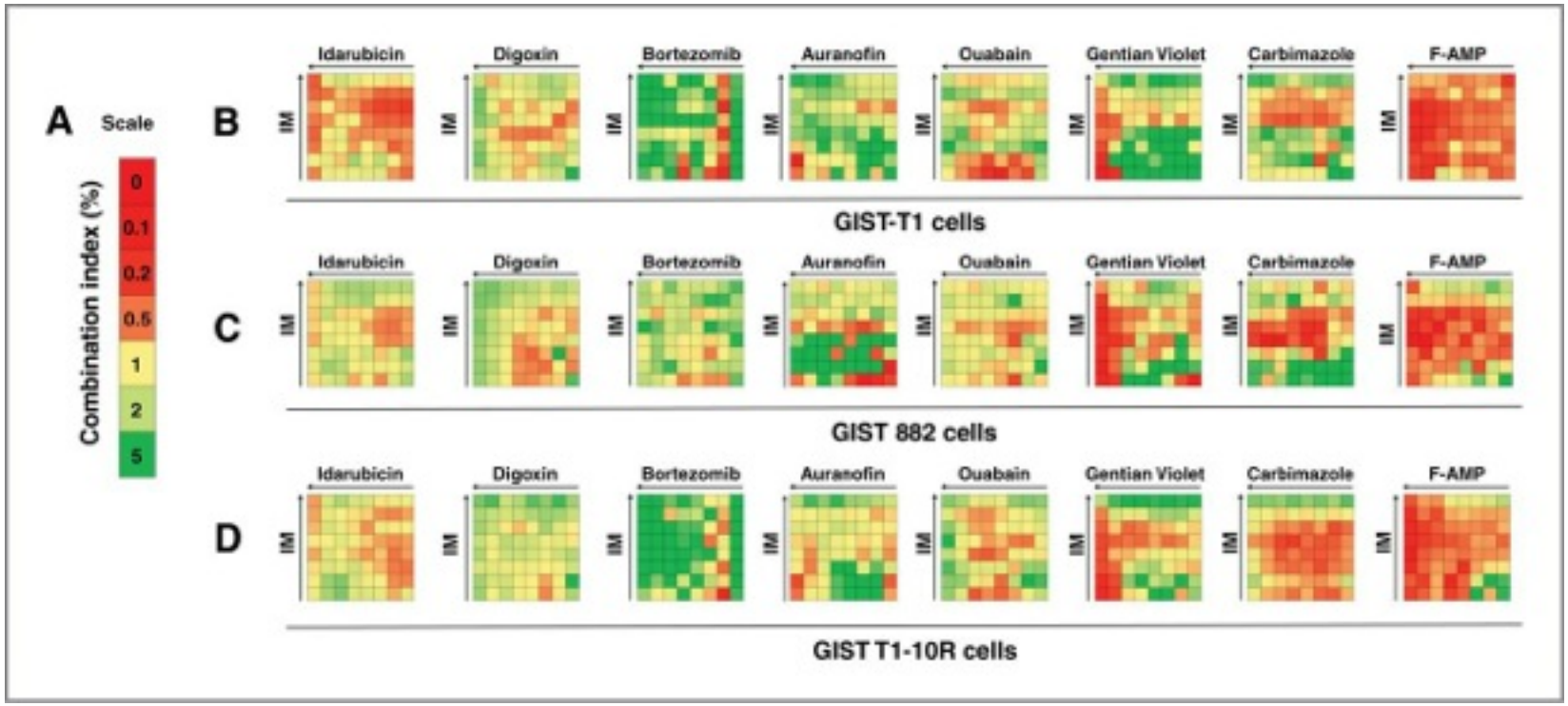
BGJ398 enhances the antiproliferation activity of imatinib in GIST cells in the absence of exogenous FGF ligands.



Fang Li et al. Cancer Discovery 2015;5:438-451

AACR
CANCER DISCOVERY

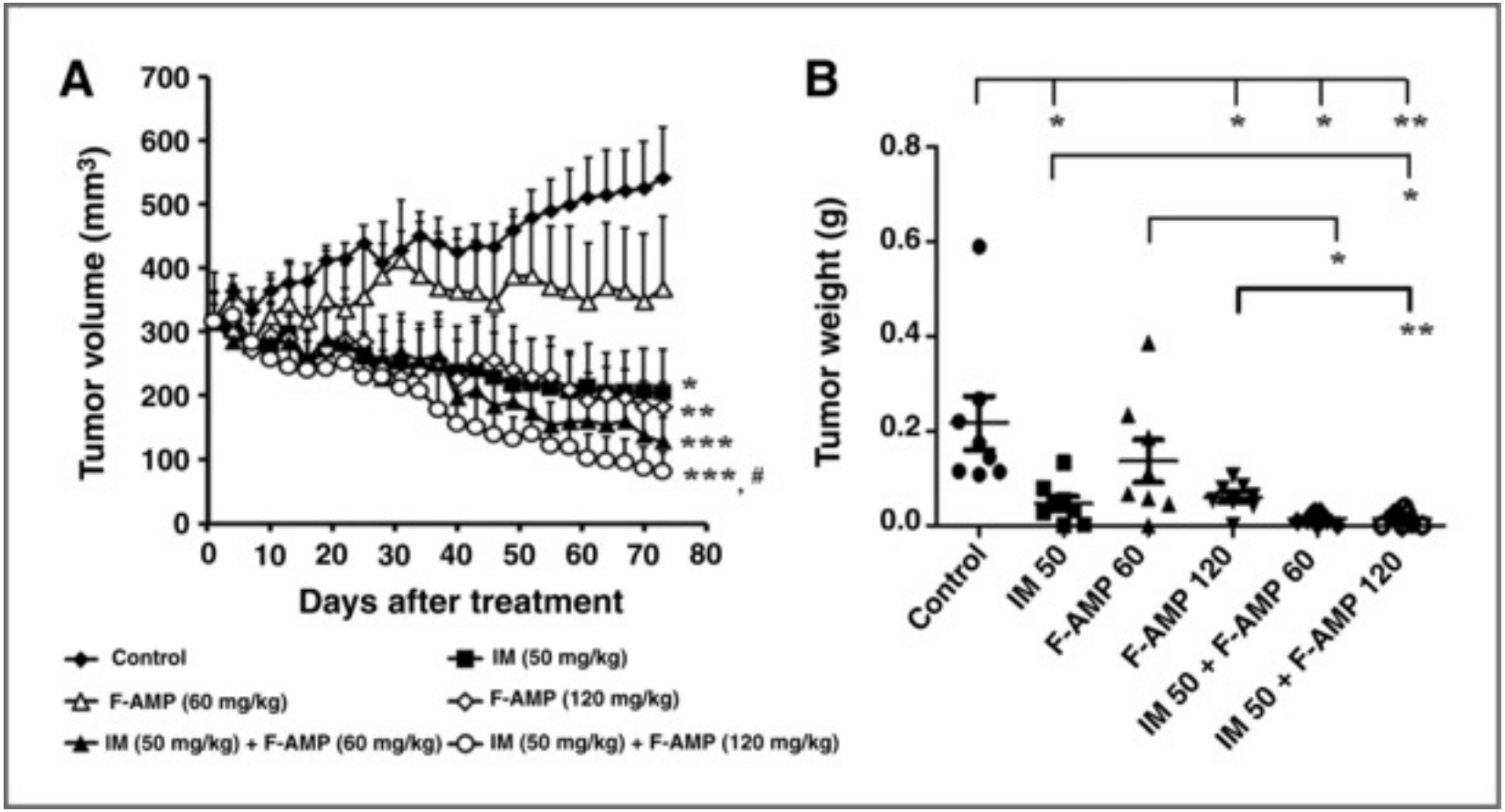
DRUG Repurposing- Identifies Fludarabine as a candidate



Ziyan Y. Pessetto et al. Mol Cancer Ther 2014;13:2276-2287

Molecular Cancer Therapeutics
AACR

Synergistic antitumor effects of imatinib mesylate (IM) in combination of F-AMP against GIST in a xenograft nude mouse model.



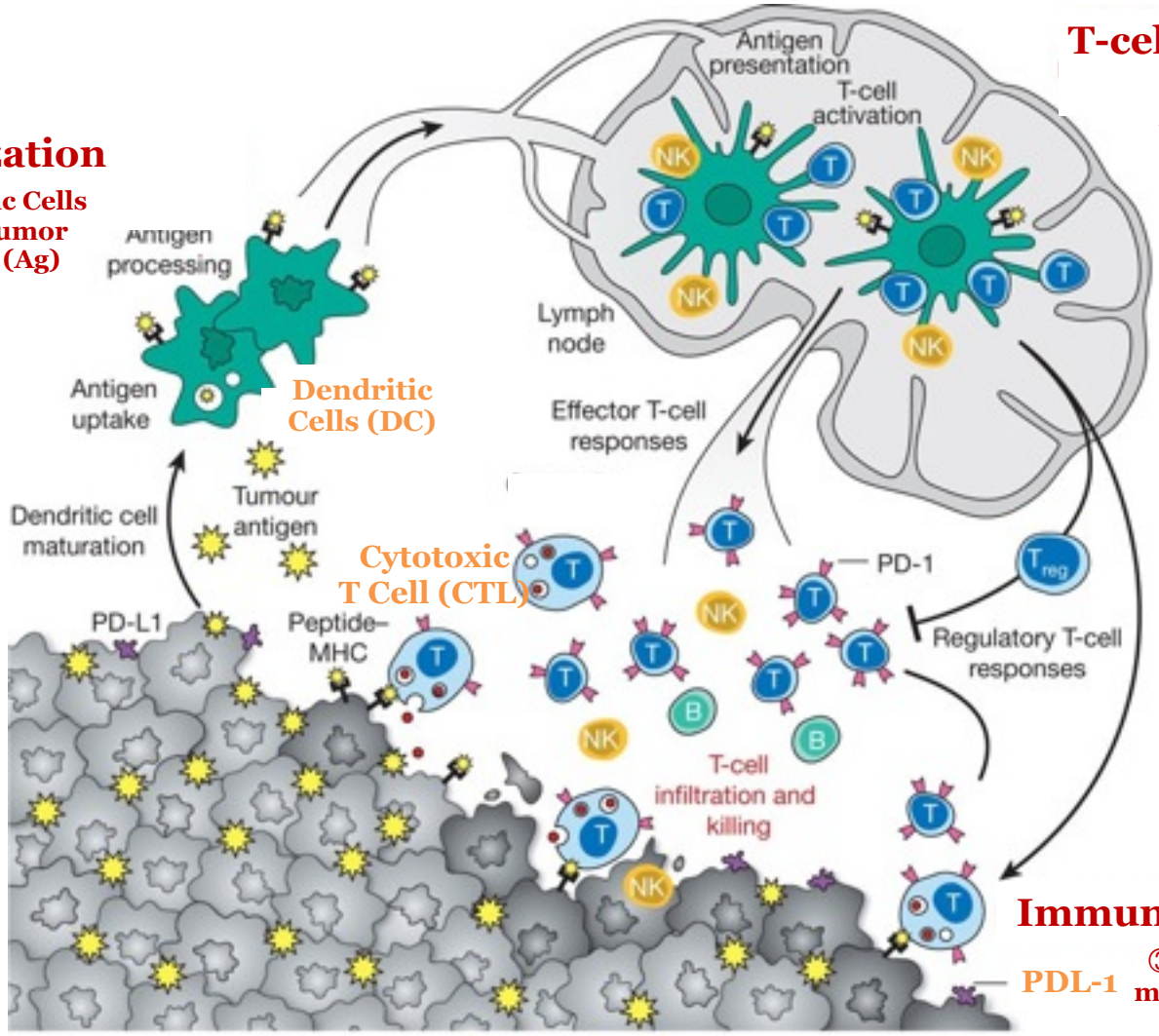
Ziyan Y. Pessetto et al. Mol Cancer Ther 2014;13:2276-2287

Molecular Cancer Therapeutics
AACR

The cancer immunotherapy premise

Immunization

① Dendritic Cells capture tumor antigens (Ag)



T-cell response

② Activated DC present tumor Ag to CD8 T cells which become anti-tumor CTLs

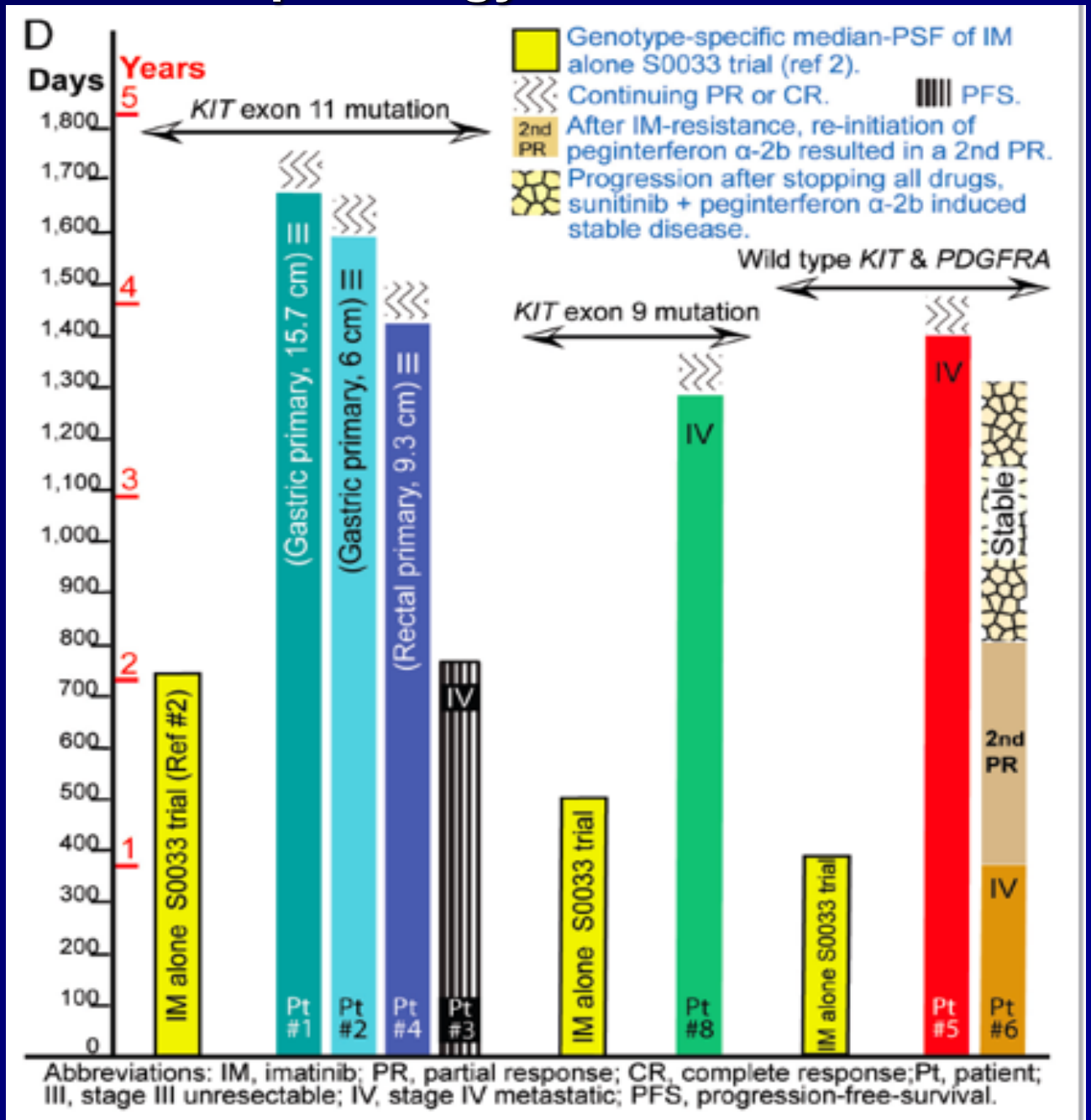
Immunosuppression

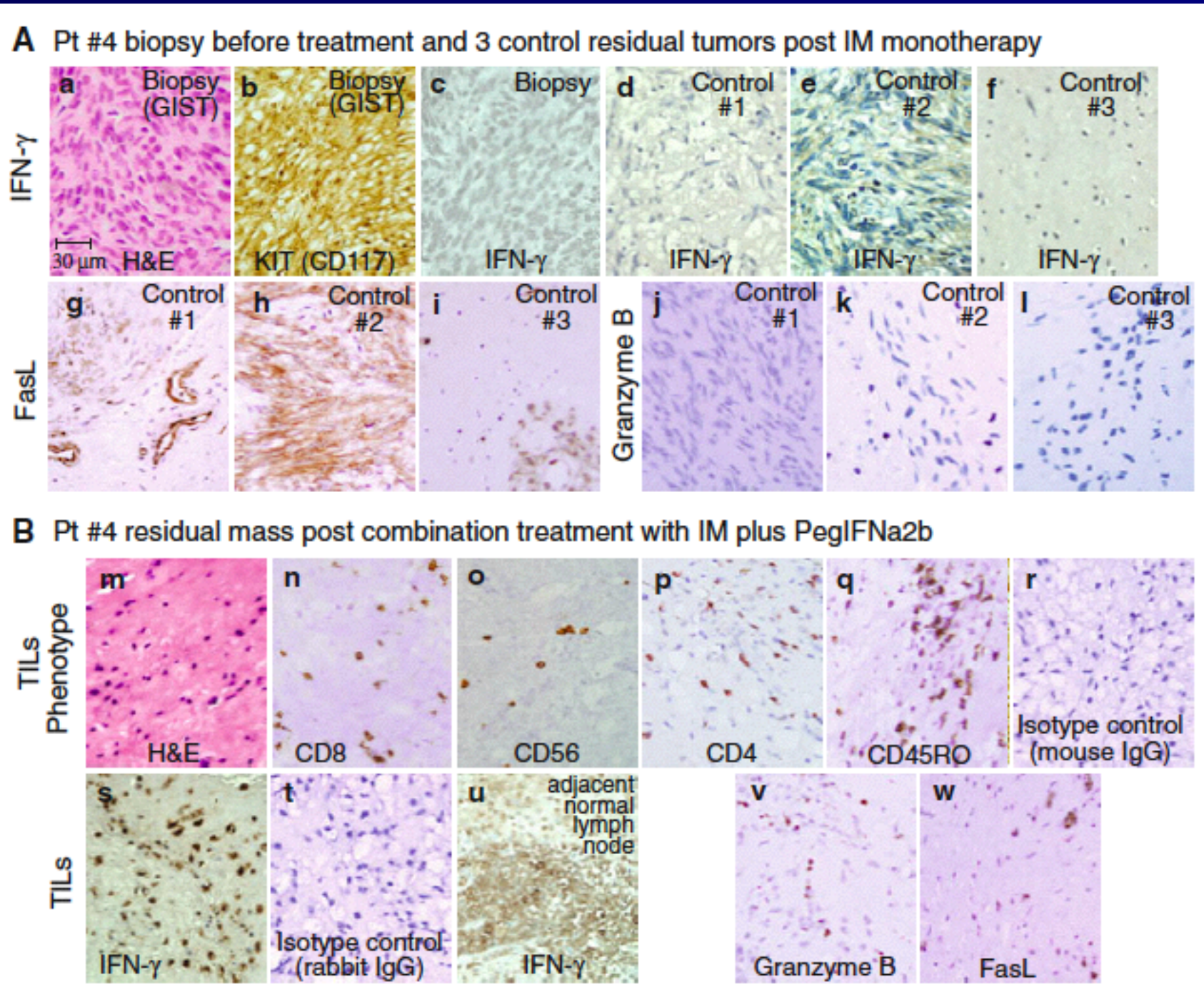
PDL-1

③ Tumor expresses molecules (e.g. PDL1) that fend off CTLs

*Mellman, Ira et al, Nature 2011

Imatinib plus Pegylated Interferon α-2b




A
Pt #4 biopsy before treatment and 3 control residual tumors post IM monotherapy
IFN-γ
FasL
Granzyme B
a Biopsy (GIST)
30 μm H&E
b Biopsy (GIST)
KIT (CD117)
c Biopsy
IFN-γ
d Control #1
IFN-γ
e Control #2
IFN-γ
f Control #3
IFN-γ
g Control #1
h Control #2
i Control #3
j Control #1
k Control #2
l Control #3
B
Pt #4 residual mass post combination treatment with IM plus PegIFNa2b
TILs Phenotype
TILs
m H&E
n CD8
o CD56
p CD4
q CD45RO
r Isotype control (mouse IgG)
s IFN-γ
t Isotype control (rabbit IgG)
u adjacent normal lymph node
IFN-γ
v Granzyme B
w FasL

Exploring the role of novel immunotherapy agents: check point inhibitors

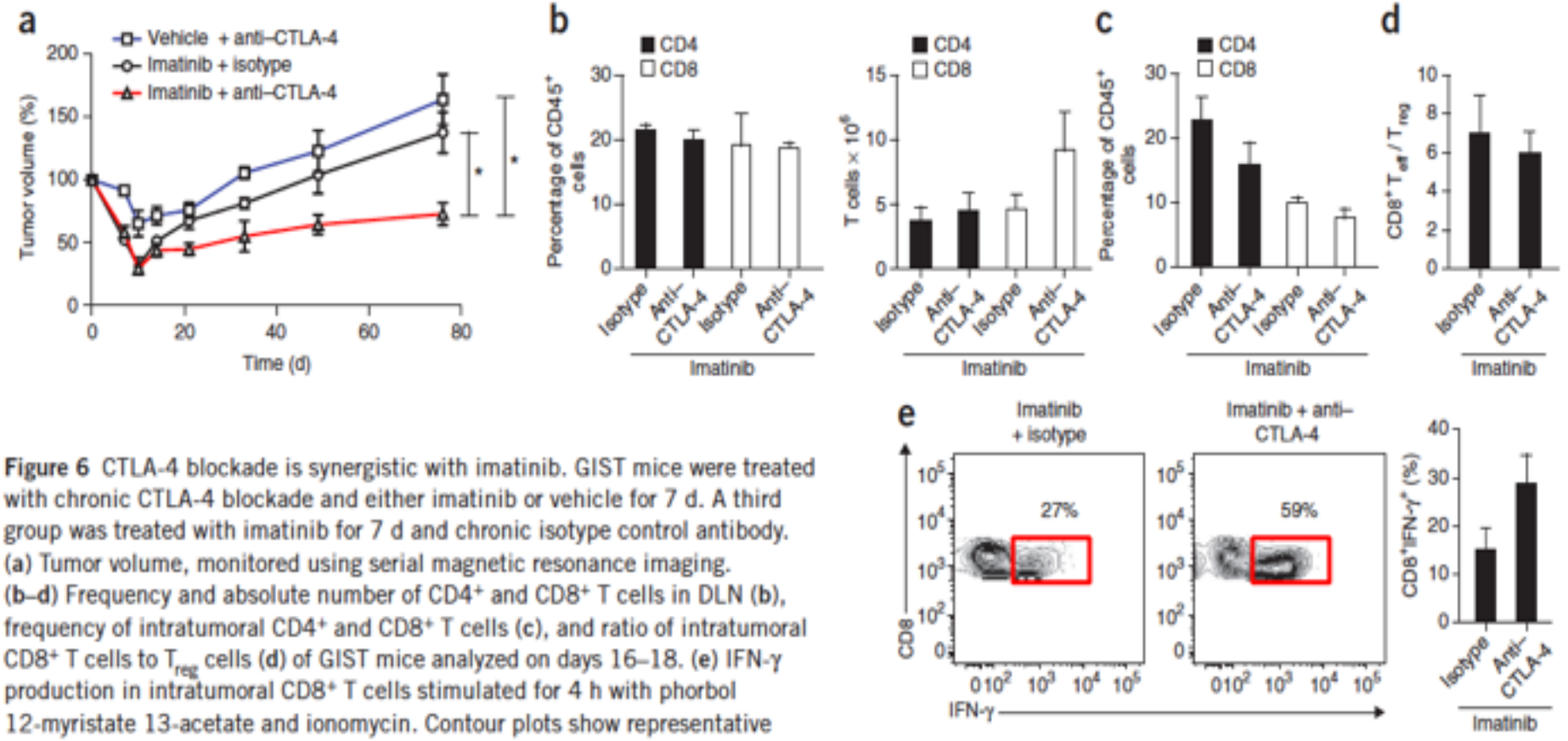


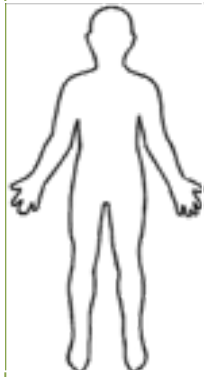
Figure 6 CTLA-4 blockade is synergistic with imatinib. GIST mice were treated with chronic CTLA-4 blockade and either imatinib or vehicle for 7 d. A third group was treated with imatinib for 7 d and chronic isotype control antibody. (**a**) Tumor volume, monitored using serial magnetic resonance imaging. (**b–d**) Frequency and absolute number of $CD4^+$ and $CD8^+$ T cells in DLN (**b**), frequency of intratumoral $CD4^+$ and $CD8^+$ T cells (**c**), and ratio of intratumoral $CD8^+$ T cells to T_{reg} cells (**d**) of GIST mice analyzed on days 16–18. (**e**) IFN-γ production in intratumoral $CD8^+$ T cells stimulated for 4 h with phorbol 12-myristate 13-acetate and ionomycin. Contour plots show representative gating of IFN-γ expression on intratumoral $CD8^+$ T cells. Bar graphs represent the intratumoral frequency of $CD8^+$ IFN-γ^+ cells; $P = 0.09$, two-tailed Student's t test. Data in **a** represent means ± s.e.m. of a composite of two independent experiments, each with 3–5 mice per group. Data in **b–e** represent means ± s.e.m. with $n = 6–8$ per group. $^*P < 0.05$.

PD-L1 expression

Histology	n	%	PD-L1 +	% L	PD-L1 +	% M	PD- L1 +
Angiosarcoma		3	0		100		100
GIST	14	27		100		100	
Leiomyosarcoma		4	0		0		25
Liposarcoma	5	0		20		60	
Synovial Sarcoma		3	0		33		0
Radiation associated pleomorphic sarcoma		1	100		100		100
Other	20	5		10		70	
Overall	50	12		30		58	

Sandra P. D'Angelo et al ASCO 2014

Treatment Schema



Q4W MEDI4736 20 mg/kg and Q4W tremelimumab 1 mg/kg

Follow up with restaging every 8 weeks. Confirmatory scan at 12 weeks

Treatment period 50 weeks

Follow-up

n≤25/cohort

Advanced/metastatic STS

1. Adipocytic tumors
2. Vascular tumors
3. Undifferentiated pleomorphic sarcoma
4. Synovial sarcoma
5. Osteosarcoma
6. Others

Blood draw and tumor biopsy Pre-treatment

Blood draw/ tumor biopsy at 6 weeks

Blood draw at 12 weeks

Blood draw and tumor biopsy at relapse

Primary endpoint: Progression-free survival at 12 weeks

Secondary endpoints:

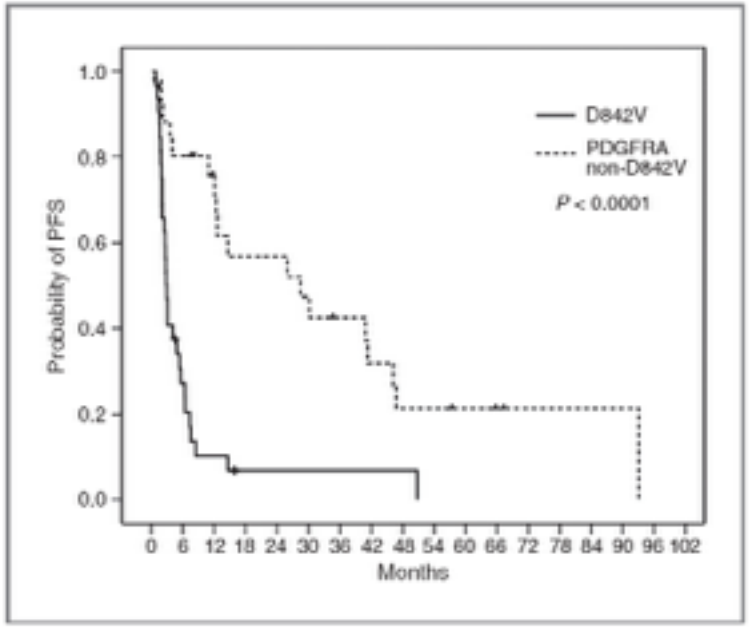
- irRC and RECIST response rate
- PFS at 24 weeks, and overall survival
- PD-1/PD-L1 expression analysis (pre & post tx samples)
- Tumor infiltrating lymphocytes (pre & post tx samples)
- Immunoscore (identification of molecular response/resistance patterns)

PDGFR mutations (D842V)

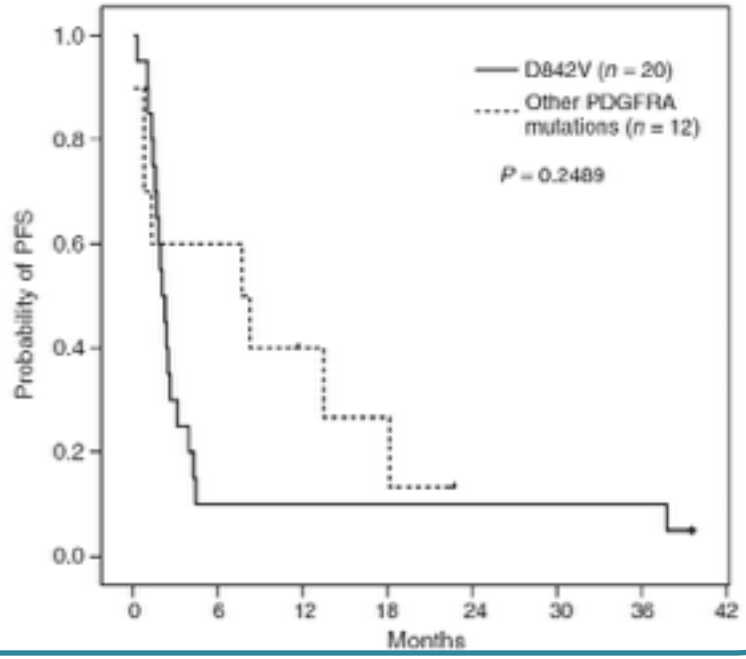
Unmet Medical Need For Patient With GIST Bearing PDGFRA D842V Mutation

- **PDGFRA D842V Mutation**
  - Identified in 2-5% of GISTs
  - Resistant to imatinib
    - Imatinib had no objective response and a median **PFS of 2.8 months and OS of 14.7 months**

First line imatinib treatment (PFS: 2.8mos)



Second line treatment (PFS: 2.1mos)



Cassier, *Clin Cancer Res*, 2012

Figure 1. PFS and OS of GISTs with or without *PDGFRA* D842V mutations

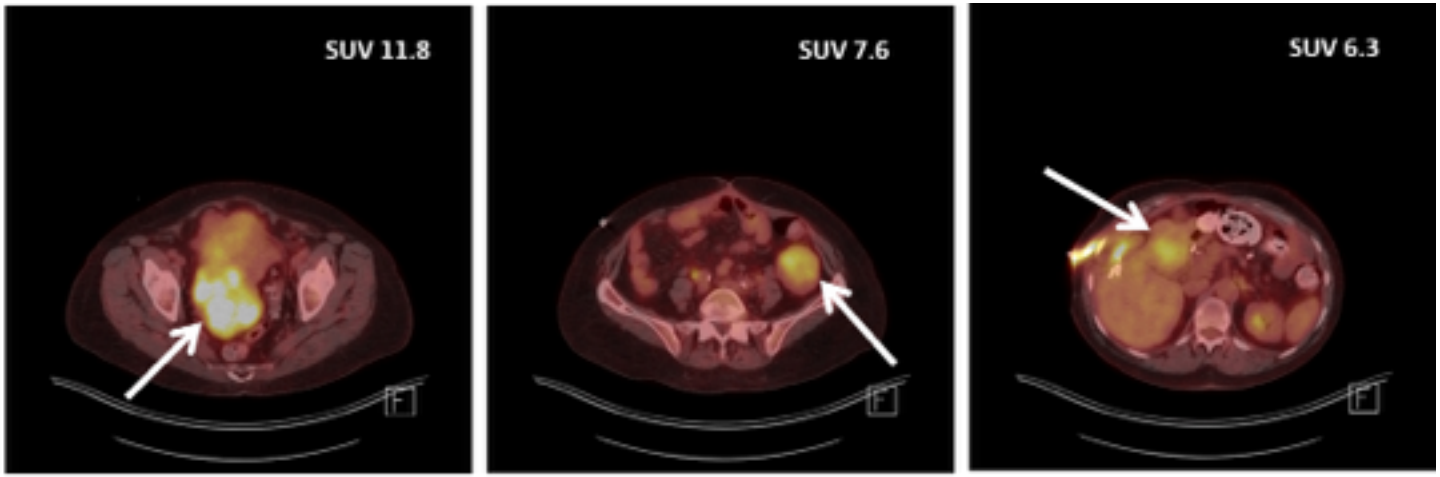
Crenolanib (CP-868,596) overview

- Crenolanib is an orally bioavailable, highly potent, specific and selective TKI
  - Targets PDGFRA, PDGFRB, and FLT3, both WT and its mutants
- Type I Inhibitor
  - Binds to the phosphorylated, constitutively active receptors
- Clinical activity in patients with select mutations
  - GIST
    - Significantly more potent than imatinib for inhibiting imatinib resistant *PDGFRA* exon 18 mutations (D842I, D842V, D842Y and DI842-843IM)

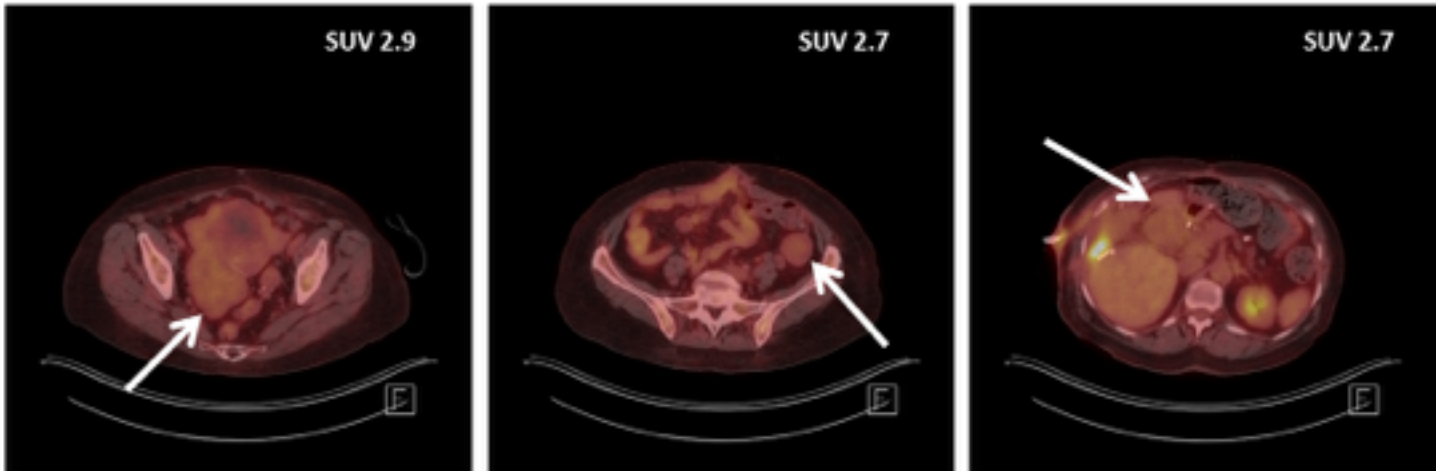
Metabolic response in poor prognosis GIST D842V mutant patient following 20 days of crenolanib therapy

ARO-002:

Baseline



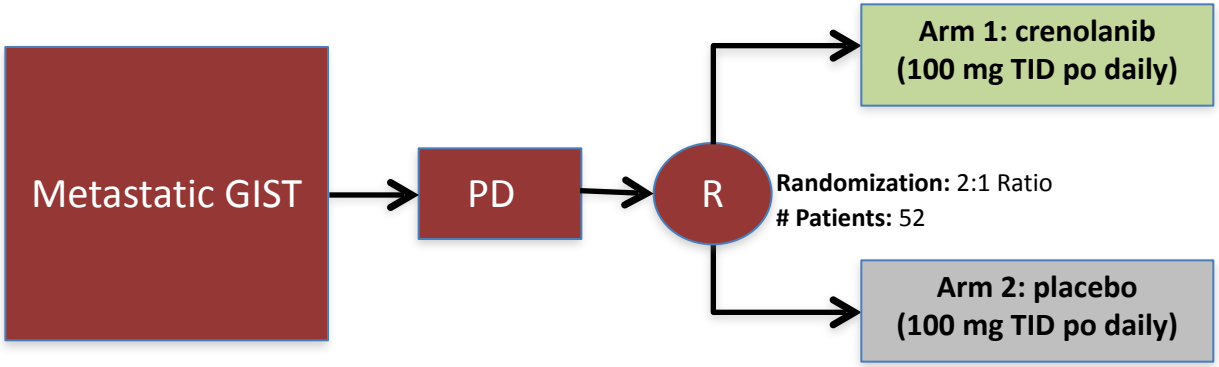
After 20 days of treatment with crenolanib, 200mg QD



von Mehren et al., CTOS 2011

Investigational Plan

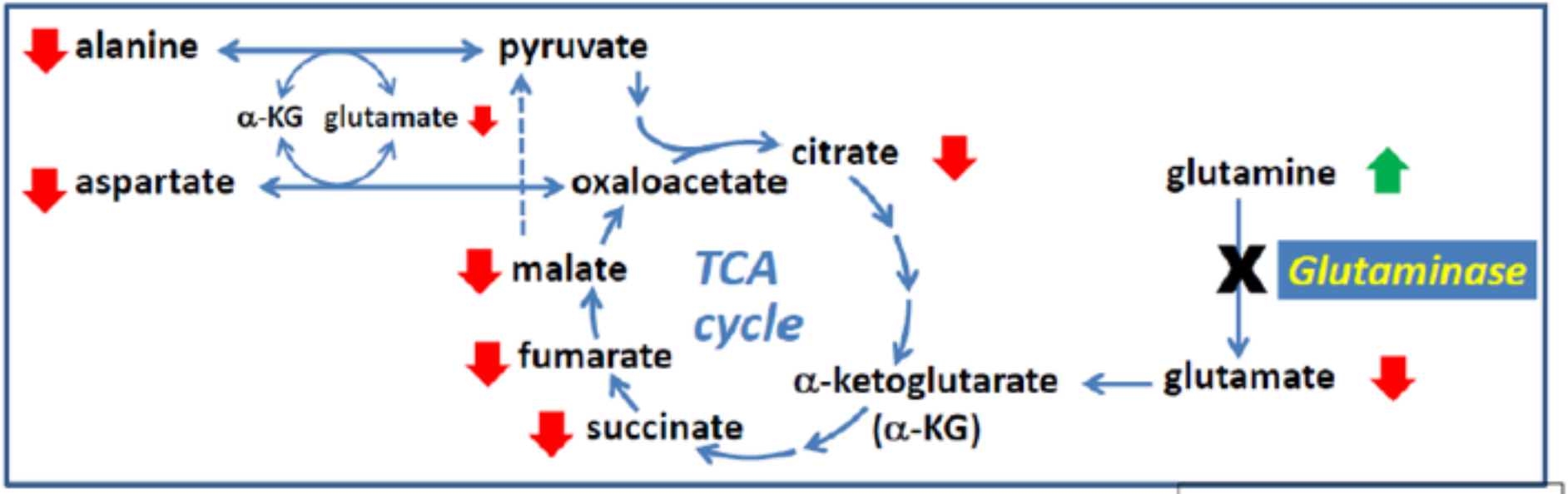
- **Overview of Study Design**
  - Patients will be randomly allocated to one of the 2 study arms (2:1) to receive
    - Arm 1: Crenolanib (300 mg/d : 100 mg TID, po, daily)
    - Arm 2: Placebo
  - Dosing will be daily, beginning on C1D1 through day 28 for a 28-day cycle. Treatment will be administered until disease progression, unacceptable toxicity or willingness to stop. Dose adaptations are planned in case of toxicity
  - Randomization will be stratified according to the number of prior lines received before randomization: 1st versus > 1 prior line of treatment at baseline



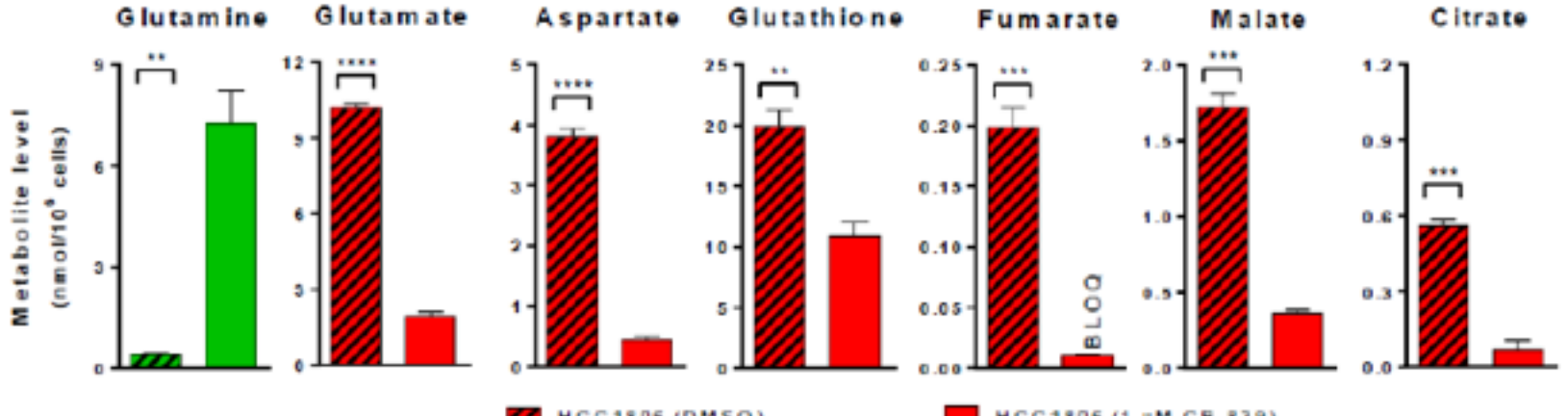
SDH mutations

Glutaminase Inhibition Suppresses Multiple Downstream Metabolic Intermediates

CALITHERA BIOSCIENCES

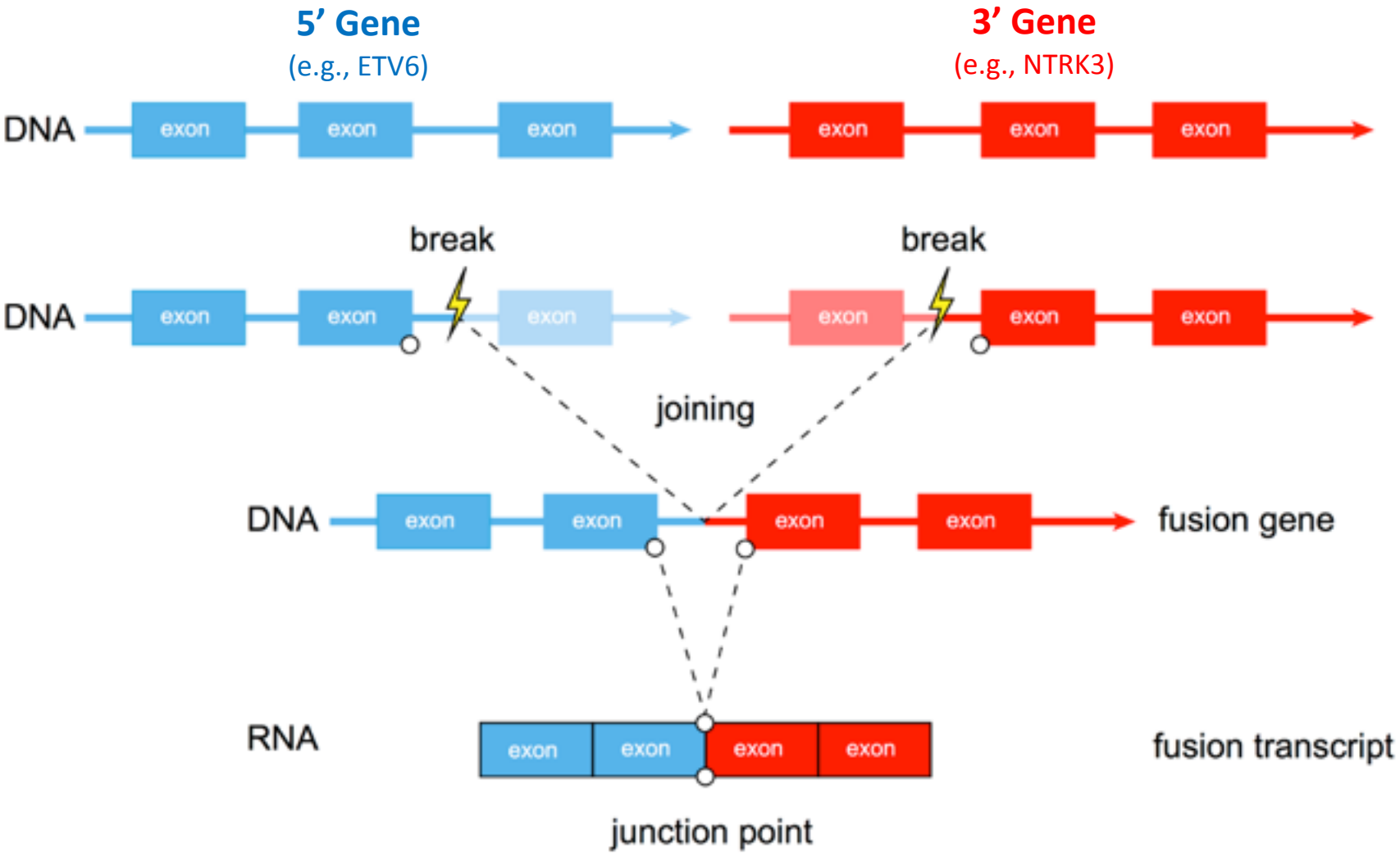


Cell line: HCC-1806 (TNBC)
Compound: CB-839 (1 μM)
Timepoint: 4 h



NTRK fusions

What is a gene fusion?



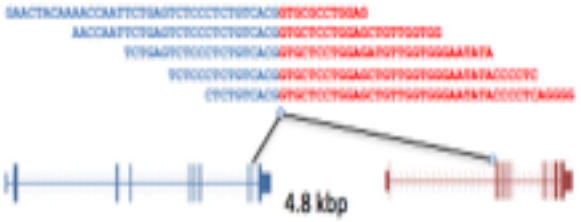
- Gene fusions can be generated by translocations, inversions & deletions.

http://54.84.12.177/PanCanFusV2/

How can we detect gene fusions?

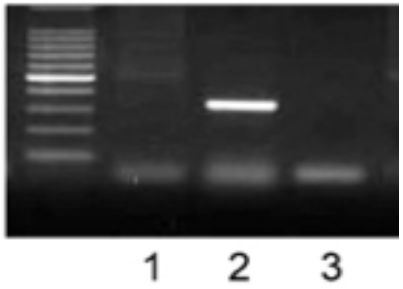
NGS, Next-Generation Sequencing

- Detects known and novel fusions with arbitrary breakpoints in DNA or RNA.
- Exact capabilities depend on enrichment strategy.



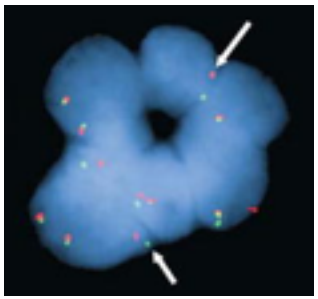
RT-PCR, Reverse Transcription Polymerase Chain Reaction

- Detects known fusion transcripts in RNA.
- Detects 5′/3′ imbalance as a fusion signature, but can not determine novel partner.



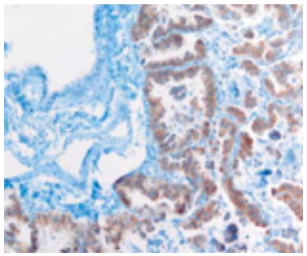
FISH, Fluorescence In Situ Hybridization

- Detects gene rearrangements in DNA that may generate a fusion transcript.



IHC, Immunohistochemistry

- Detects protein expression, which may be attributable to a fusion event.



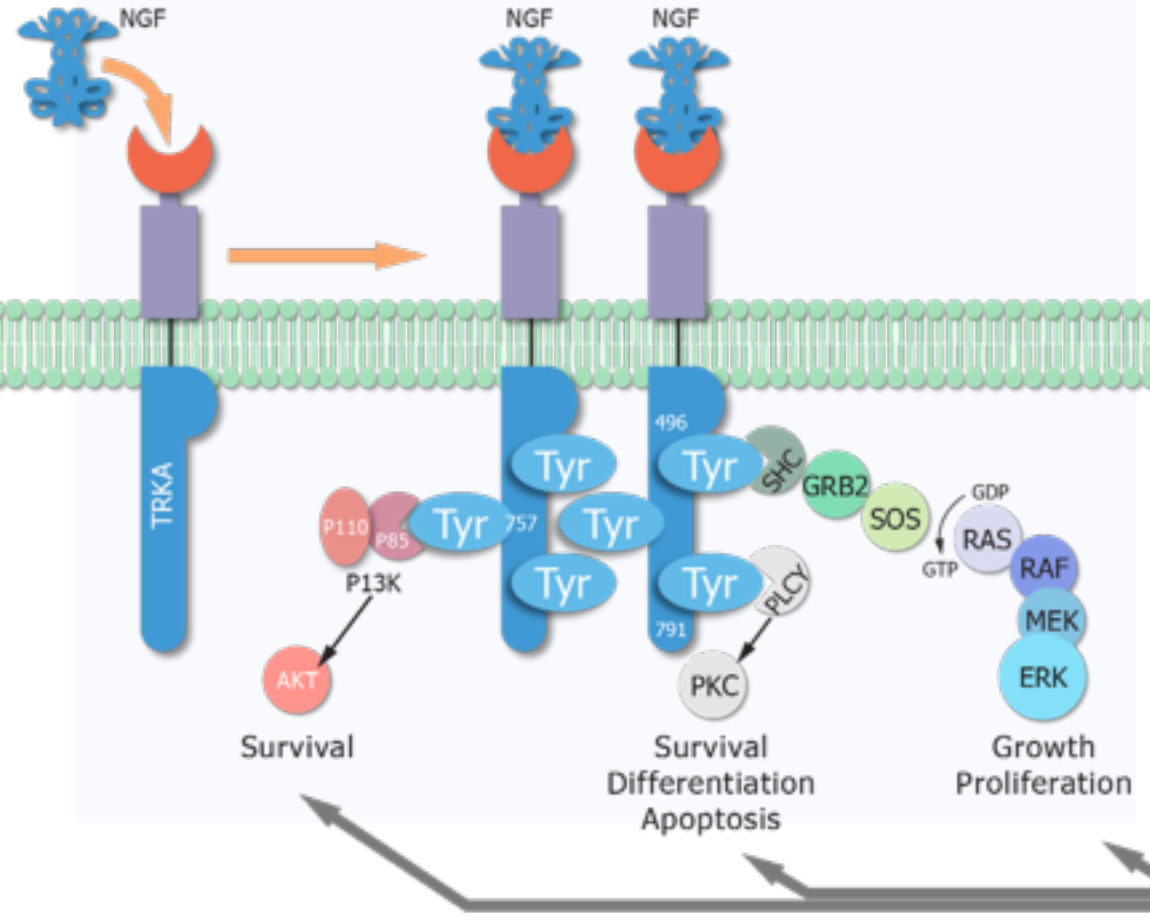
Signaling of Oncogenic TRK Fusions

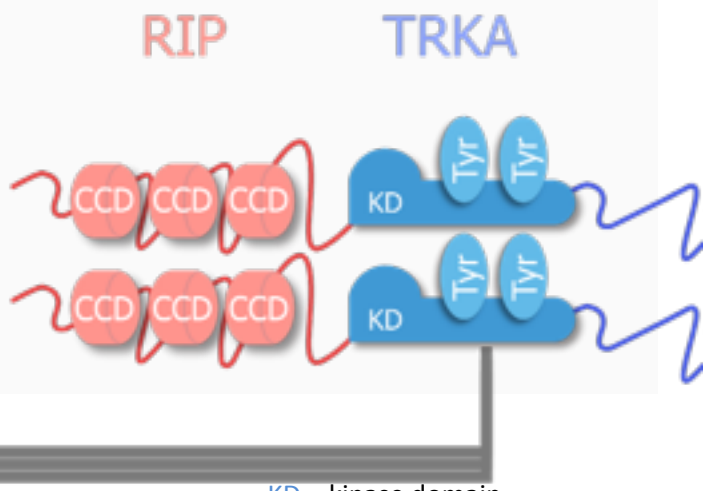
Ligand-dependent

- Expression of receptor (typically limited to nervous system)
- Availability of ligand (autocrine, paracrine)

Ligand-Independent (TRKA-fusion)

- Ligand binding domain replaced by 5' fusion gene
- Highly expressed by promoter of 5' fusion partner
- Dimerization induced by protein domains within 5' gene
- Ligand-mediated dimerization no longer a requirement for activation





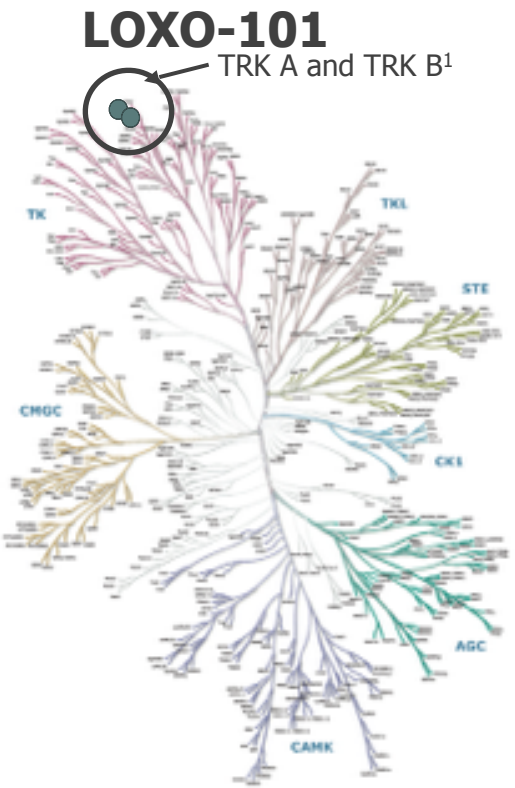
KD = kinase domain
CCD = coiled-coil domain

LOXO-101 is Highly Specific for TRK Receptors

LOXO-101 has favorable TRK inhibitor properties:

1. High potency for TRKA, TRKB, TRKC

2. Limited inhibition of other kinases



[1] Upstate kinase panel shown does not include TRK C. LOXO-101 shown to be equipotent for TRK C in other assays.

LOXO-101 Phase 1 TRK Fusion Case History

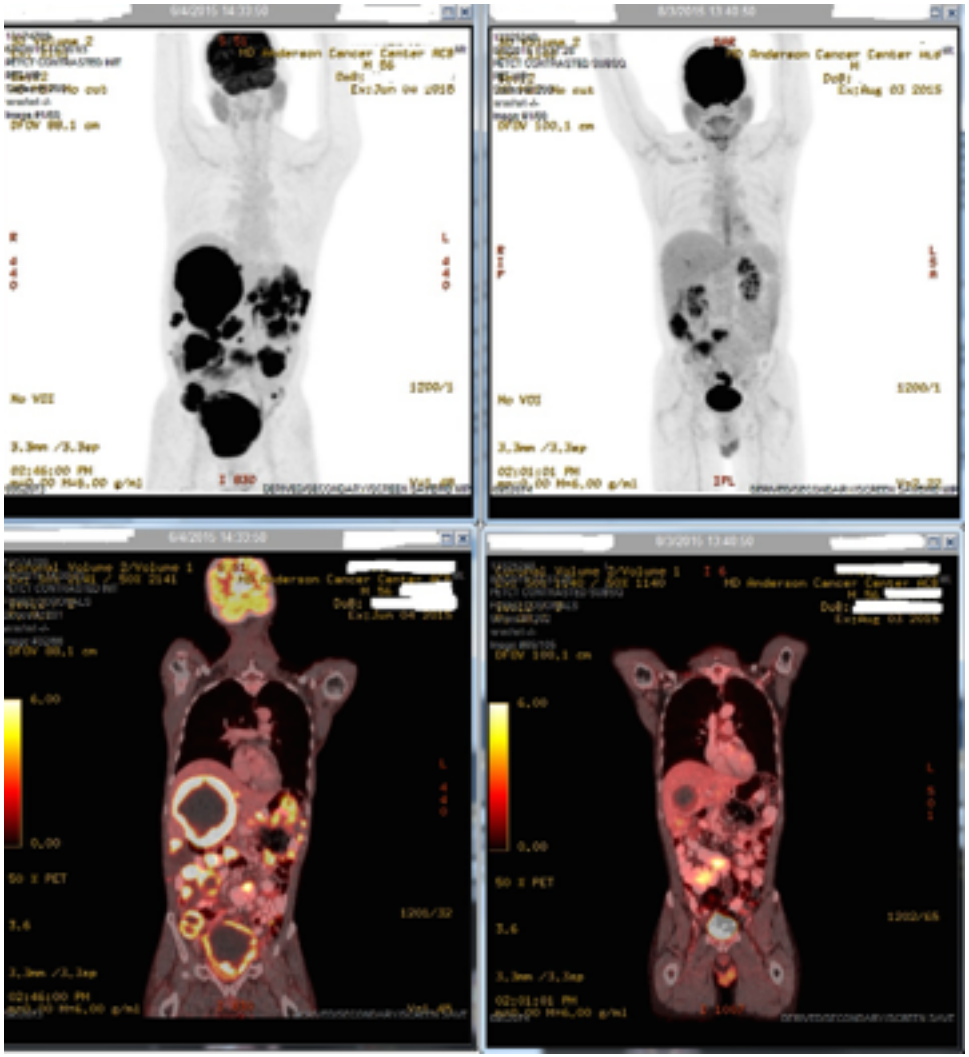
55-year-old gentleman, who initially was diagnosed with GIST in 2003. At that time, he had metastasis to liver, spleen, and GE junction of the stomach and abdomen. He underwent:

1. Subtotal gastrectomy on 05/20/03, status post 4-flap. He then went on to receive,
2. Gleevec on 06/17/03 to 12/05/03 with progression.
3. Sunitinib from 02/04/07 to 01/22/08, again with progression. He had recurrence and then underwent gastric debulking surgery on 08/08/08.
4. Sorafenib 09/25/08 to 10/07/08. He went on to receive,
5. Drug called Tasigna and with progression of disease,
6. An experimental therapy unclear as to the name.
7. They went on to also receive regorafenib, unclear as to the specific date.
8. Embolization of hepatic mass x2 in 2014 and repeat laparotomy and debulking.
9. In December 2014, he underwent a trial regorafenib in combination with Sutent and his last dose was approximately yesterday. He is here for possible enrollment in clinical trial of therapy.

- Foundation Medicine analysis showed ETV6-NTREK3 Fusion, PAX5 mutation, SETD2 mutation.
- Enrolled on LOXO 101 protocol 2014-1056

Doebele et al, Cancer Discovery. July 2015. Published OnlineFirst July 27, 2015; doi: 10.1158/2159-8290.CD-15-0443

LOXO-101 Phase 1 TRK Fusion Case History



Pre-Trial

First restaging end of cycle #2

I'll come work with you in the sarcoma when I grow up mommy!