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Novel Strategies in the Management of Advanced GIST After the Failure of Standard Tyrosine Kinase Inhibitors

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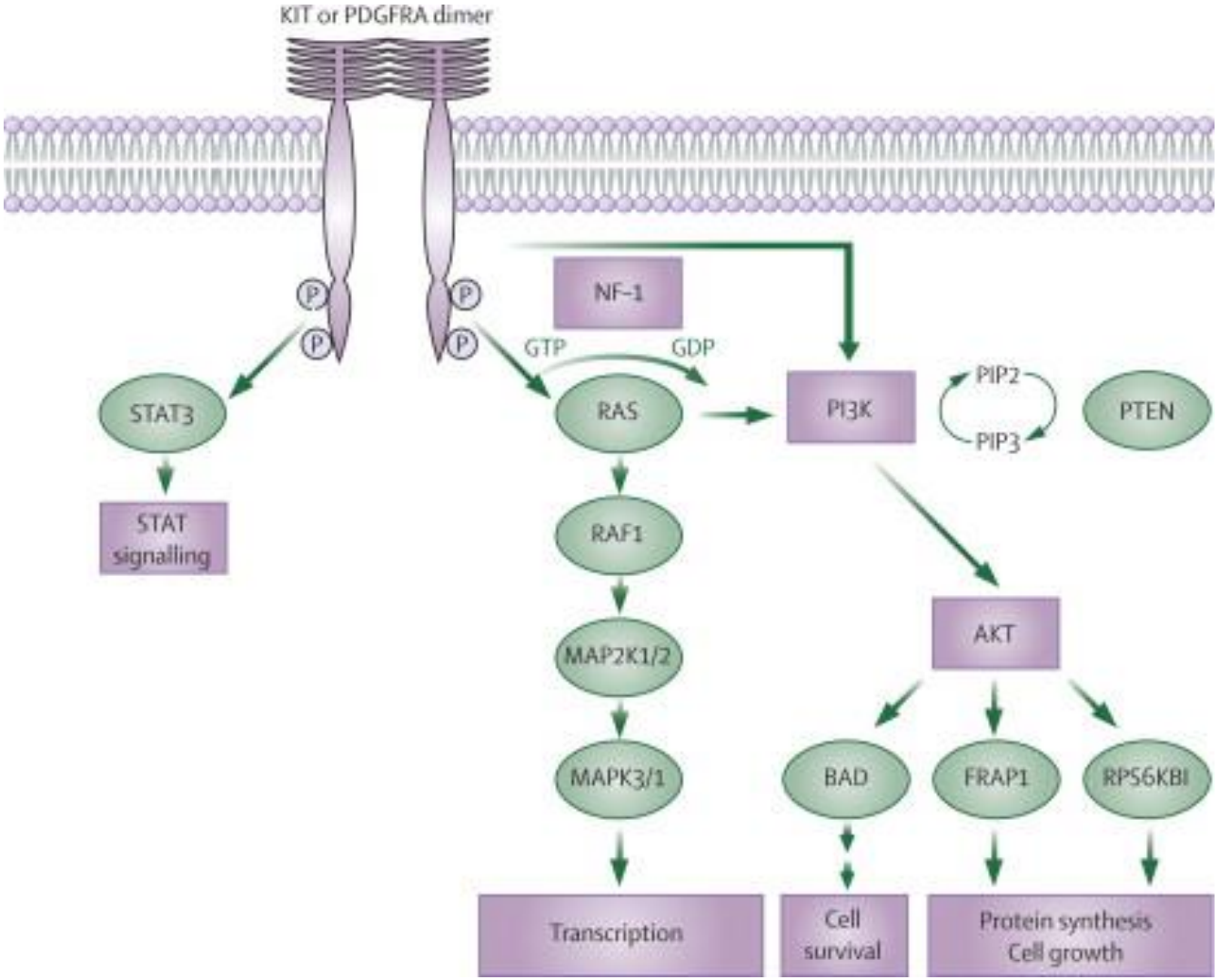
Aberrant Signaling Pathways in GISTs



Rubin et al, The Lancet Volume 369, No. 9574, p1731–1741, 2007

Molecular Heterogeneity in GIST

- **80 to 85% of GIST tumors involve gain-of-function KIT mutations.**
- **5 to 10% involve PDGFRA mutations.**
- **A small minority of GIST tumors lack kinase mutations and are referred to as wild type (WT)**

  → heterogeneous population that probably involves five or more distinct types of disease rather than a single type.

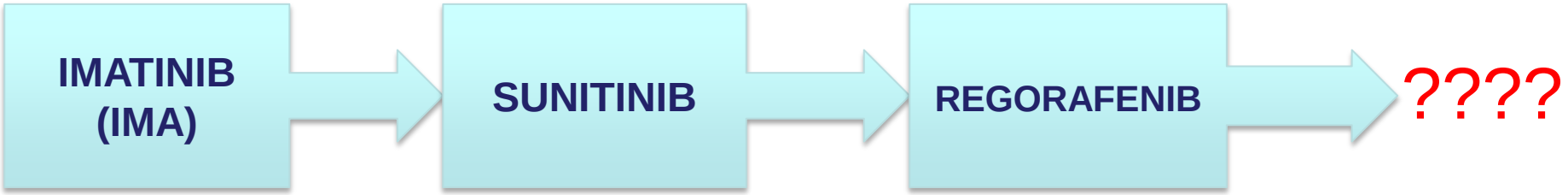
GIST heterogeneity: optimizing the systemic therapeutic approach based on GIST mutation genotype

- **KIT-mutant Exon 11 GISTs, tumor response has been shown to be similar whether the IMA dose is 400 or 800 mg.**

- **KIT-mutant Exon 9 GISTs - IMA 800 mg is recommended dose**

- **PDGFRA-mutant GIST have different dosing requirements depending on their mutational status.**
  - Exon 12 or 14, Exon 18 mutations that are D842V negative/IM sensitive → 400 mg dose is appropriate
  - Patients with the D842V mutation or other IMA-mutation associated with primary resistance to all of the TKIs, including IMA, sunitinib, nilotinib, and sorafenib → require higher IMA doses (generally 800 mg)

Current challenges in the standard of care for metastatic GIST



Adequate dosing and consistent compliance are essential for long term use to avoid pharmacokinetic failure

- Primary resistance in 10-20% i.e. progression within 6mths of therapy

ORR: 7%
PFS: 6.8 mths

ORR: 4.5%
PFS: 4.8 mths

- Secondary resistance:
  50% in 2 years
  80% in 7 years

Corless CL, et al. *Annu Rev Pathol. 2008; 3: 557–86;* Antonescu C, al. *Clin Cancer Res. 2005; 11: 4182–90;* Antonescu CR. *J Pathol. 2011; 223(2): 251–61.*

Primary resistant GIST

- **Most common PDGFRA mutation associated with GIST, D842V, is strongly resistant to inhibition by imatinib or sunitinib**
  - Crenolanib, type I mutant-specific inhibitor that preferentially binds to phosphorylated active kinases has shown efficacy in blocking the activity of D842V mutant kinases (Heinrich et a CCR 2012) → ongoing Phase II study

- **KIT-WT GIST may have any of an array of primary mutations including**
  - BRAF and/or KRAS downstream of KIT,
  - increased IGF1R expression
  - Germline mutations of succinate dehydrogenase (SDH).
  - No agent in existence can adequately address all of these mutations → multiple pathways involved

Secondary resistance to Imatinib

- **Due emergence of resistant clones through the development of new *KIT* mutations e.g. interfere with binding of imatinib to the kinase domains**

- **Tend to be single amino acid substitutions in exon 17 (most common), also occur in exons 13 and 14**

- **Resistant patients with identifiable secondary mutations have been treated with imatinib longer than resistant patients lacking secondary mutations (median, 27 versus 14.5 months) → clonal selection of existing mutations before imatinib unlikely to explain acquired resistance.**

- **GISTs harboring KIT exon 11 mutations more commonly acquire secondary resistance mutations compared with KIT Exon 9–mutated GIST**

Debiec-Rychter et al. 2005; Heinrich et al. 2006; Guo et al 2007

Use of smaller tyrosine kinases with broader spectra of activity than imatinib

- Sunitinib (SU), a tyrosine kinase inhibitor with antiangiogenic and antitumor effects (Demetri et al. 2006).

- Structural differences between IMA and SU that allow SU, a smaller molecule, to slip into the drug-binding pocket.

- Sunitinib proved superior to placebo with respect to median progression-free survival (PFS) [median 24.1 weeks vs 6 weeks: $p < 0.0001$].

Regorafenib in resistant GIST: GRID study
(Demetri et al Lancet 2013)

- **Inhibits *KIT, PDGFRA, bFGFR, VEGFR1-3, TIE2, RET, BRAF* and *BRAF V600E***

- **In phase II study patients with wild-type GIST and *KIT* exon 9 and 11 mutations experienced clinical benefit at comparable rates**

- **Phase III GRID study:**
  - metastatic or unresectable disease that had failed to respond to at least two previous lines of therapy for GIST
  - PFS for regorafenib compared with the placebo arm = 4.8 *versus* 0.9 months, HR 0.27
  - Disease control rate was 52.6% for the regorafenib arm and 9.1% for the placebo arm ($p < 0.0001$).

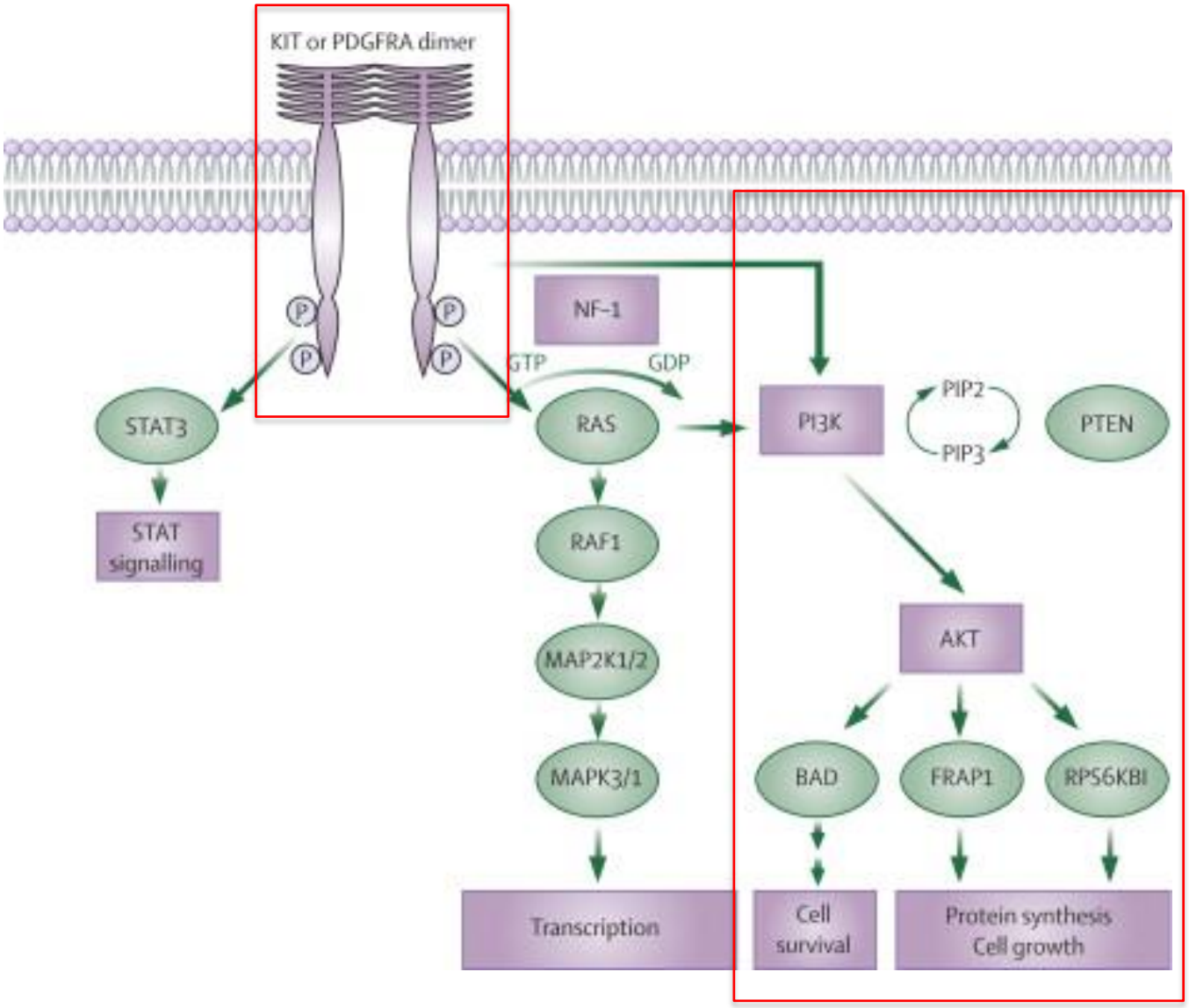
Implications of GRID study

- **GISTs may remain responsive to treatment targeted at oncogenic drivers, even with prior resistance to similar agents**

- **Broader spectrum of kinase inhibition with regorafenib**
  - Targeting of multiple recognized mechanisms of resistance
  - Targeting possibly as-yet unknown escape pathways

- **?Extend the range of effective agents in GISTs by targeting multiple pathways**
  - ?Combined therapeutic approaches for treatment resistant GIST

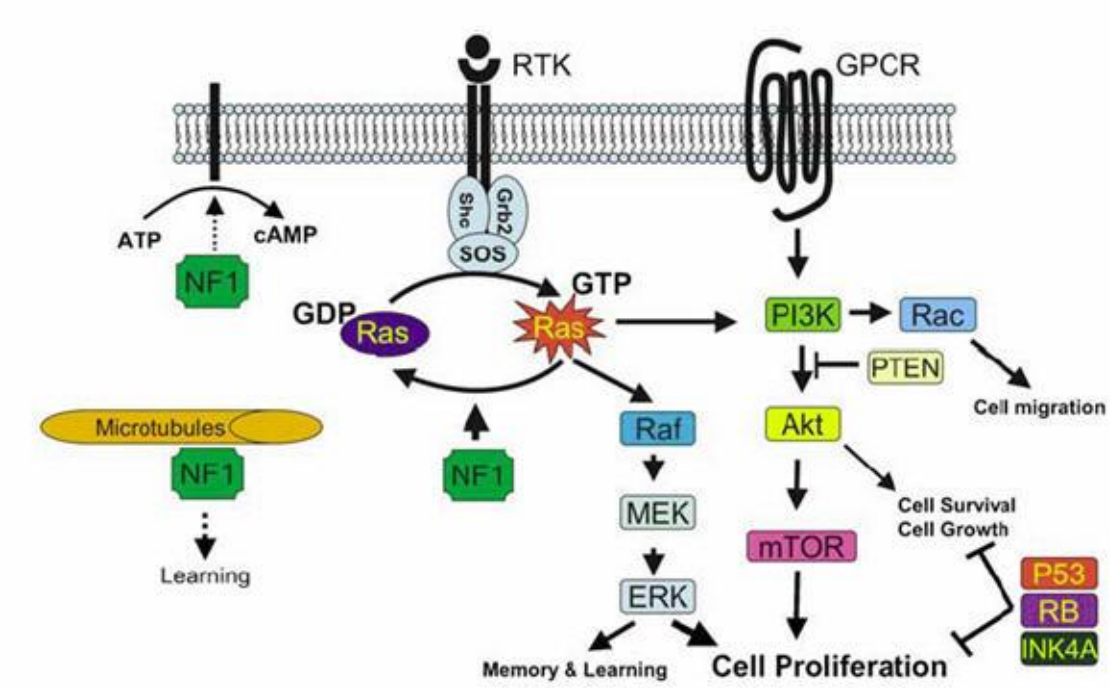
Aberrant Signaling Pathways in GISTs



Rubin et al, The Lancet Volume 369, No. 9574, p1731–1741, 2007

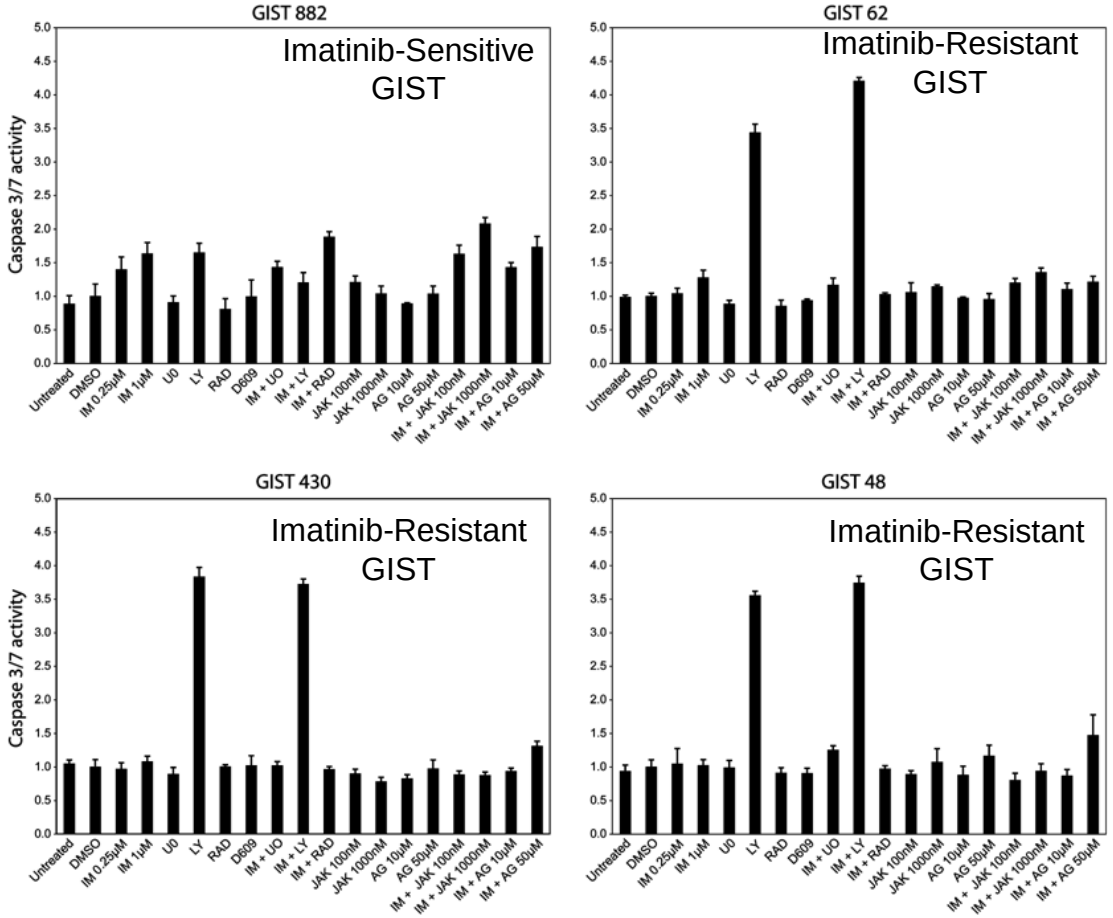
P13K-AKT Pathway Inhibitors

- **Regardless of the type of KIT/PDGFRA mutation in the receptor, the downstream P13K/AKT/mTOR signaling pathway is crucial for tumor cell survival of both imatinib-sensitive and imatinib-resistant GIST.**



Bauer S, et al. *Oncogene. 2007;26:7560-7568;* Duensing A, et al. *Oncogene. 2004;23:3999-4006.*

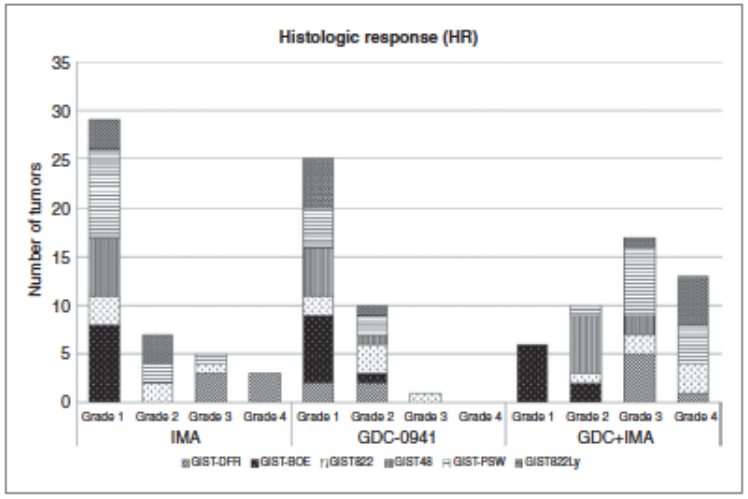
PI3K inhibition with LY294002 resulted in substantial apoptosis in the imatinib-resistant GISTs



Bauer S, et al. *Oncogene. 2007;26:7560-7568;* Duensing A, et al. *Oncogene. 2004;23:3999-4006.*

Combination of PI3K inhibition and imatinib

- **Profound tumor regression in combination of pictilisib+IMA, superior to either treatment alone in**
  - KIT exon 13 p.K642E mutation (GIST882 and GIST882Ly)
  - KIT exon11 p.V560D and KIT exon17 p.D820A (GIST48)
  - KIT exon 9 (GIST-BOE), KIT exon 11 (GISTPSW and GIST-DFR)
- **PTEN status correlated with response in GIST treated with the combination**



Floris G, et al. *Clin Can Res.* 2013;19:620-630.

A randomized phase II study of perifosine (P) plus imatinib in imatinib-resistant GIST

- **Akt and PI3K inhibitor**
- **PR rate was 4/36 (11%) by Choi (4 PR, 9 SD)**
- **CBR was 16/36 (44%) by RECIST**
- **Median PFS and OS for 40 pts were 2.2 months and 18.3 months.**

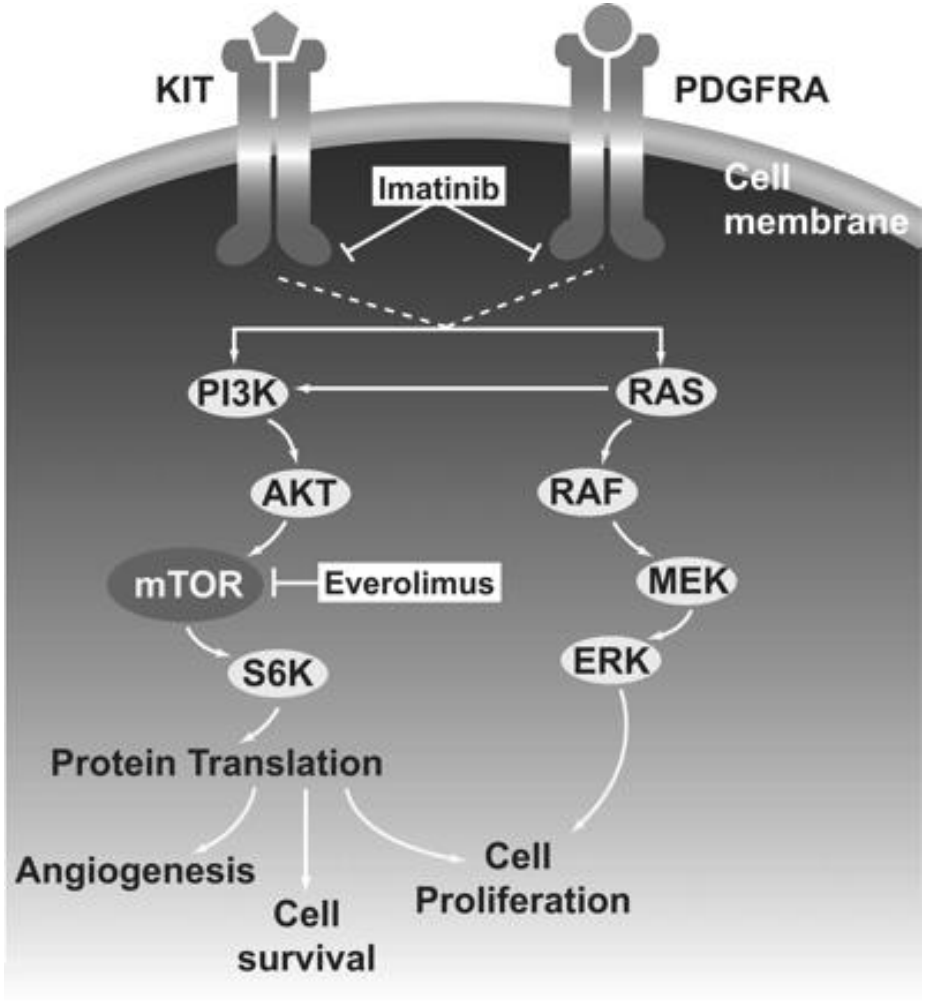
Conley A, et al. *J Clin Oncol. (ASCO Meeting Abstracts) 2009;* 27(Suppl 15):10563).

Ongoing studies focused on PI3K/AKT pathway inhibition

- **A Dose-finding Study of a Combination of Imatinib and Alpelisib (BYL-719) in the Treatment of 3rd Line GIST Patients**

- **A Dose-finding Study of a Combination of Imatinib and BKM120 in the Treatment of 3rd Line GIST Patients**

Targeting mTOR



Schoffski P, et al. *Ann Oncol. 2010;21:1990-1998*

Phase II studies of everolimus + imatinib

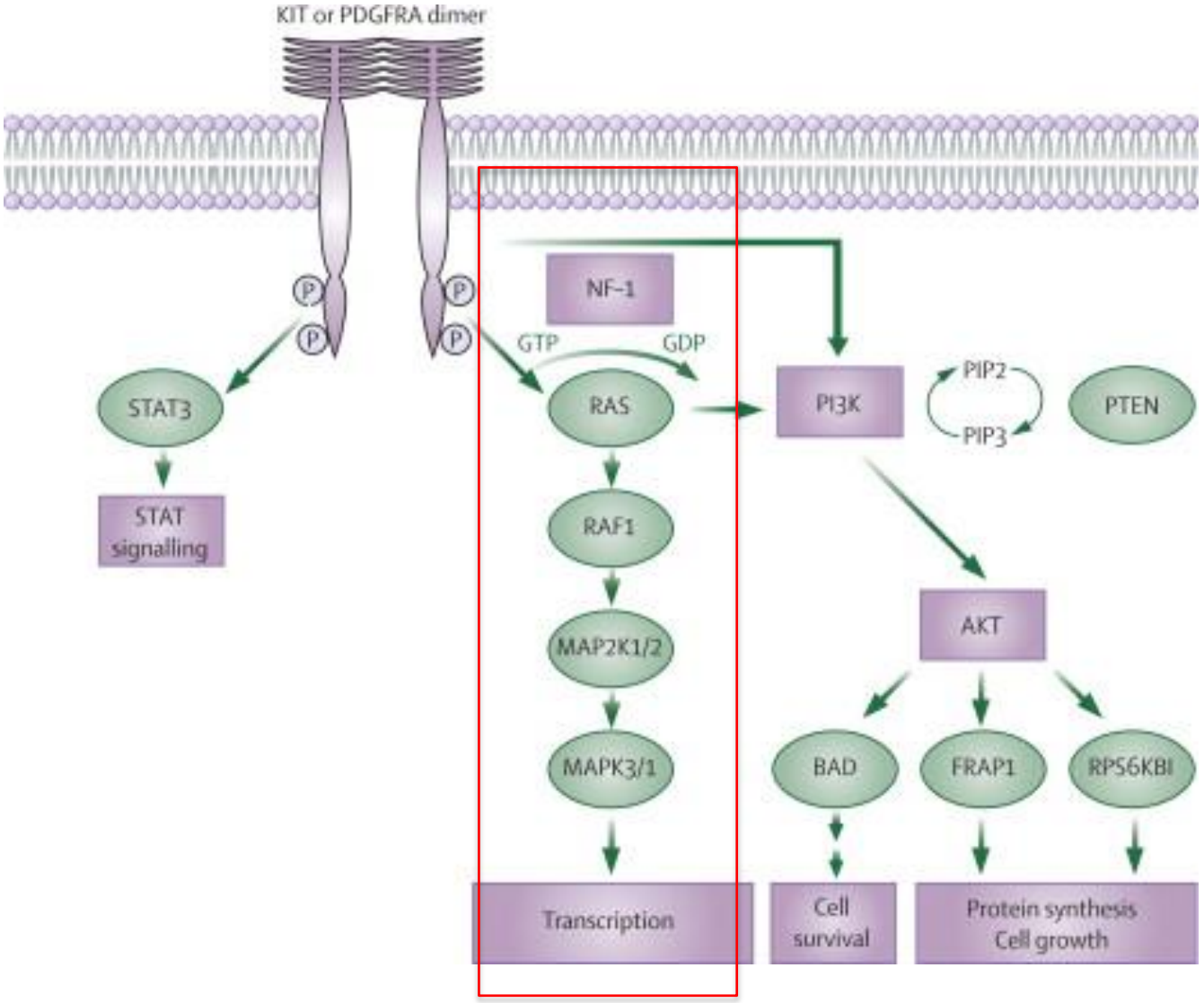
- **Phase 2 study: everolimus 2.5 mg/day with imatinib 600 mg/day achieved 2% PR and 43% SD for 4 months or greater in patients previously progressed on imatinib and sunitinib (Stratum 2).**

Efficacy	Phase I				Phase II	
	Imatinib 600 mg/day			Imatinib 800 mg/day	Imatinib 600 mg/day + everolimus 2.5 mg/day[a]	
	Everolimus 20 mg/week (*n* = 13)	Everolimus 2.5 mg/day (*n* = 13)	Everolimus 5 mg/day (*n* = 5)	Everolimus 2.5 mg/day (*n* = 11)	Stratum 1 (*n* = 28)	Stratum 2 (*n* = 47)
4-month PFS rate—PP population[a]						
n/N (%) [CI]					4/23 (17) [5.0–38.8]	13/35 (37) [21.5–55.1]
Survival (Kaplan–Meier method)—ITT population						
Median PFS, months [CI][b]	–[c]	–	–	–	1.9 [1.8–3.7]	3.5 [1.9–5.2]
4-month PFS rate, % [CI][b]	–	–	–	–	21 [4.7–37.6]	40 [24.6–55.9]
6-month PFS |rate, % [CI][b]	–	–	–	–	13 [0–26.1]	20 [7.0–33.3]
Median OS, months [CI]	9.4 [5.6–13.8]	10.9 [3.3 to NA]	18.7 [3.8 to NA]	NR [12.0 to NA]	14.9 [14.9 to NA]	10.7 [6.3–16.8]
Activity/response, *n* (%)—ITT population						
PR [CI]	0	1 (8) [0.2–36.0]	0	0	0	1 (2) [0.1–11.3]
SD	7 (54)	6 (46)	4 (80)	6 (55)	10 (36)	20 (43)
PD	4 (31)	6 (46)	0	1 (9)	15 (54)	15 (32)
Unknown	2 (15)	0	1 (20)	4 (36)	3 (11)	11 (23)

- **In another phase II study of the combination 33% achieved SD as the best response at 4 months.**

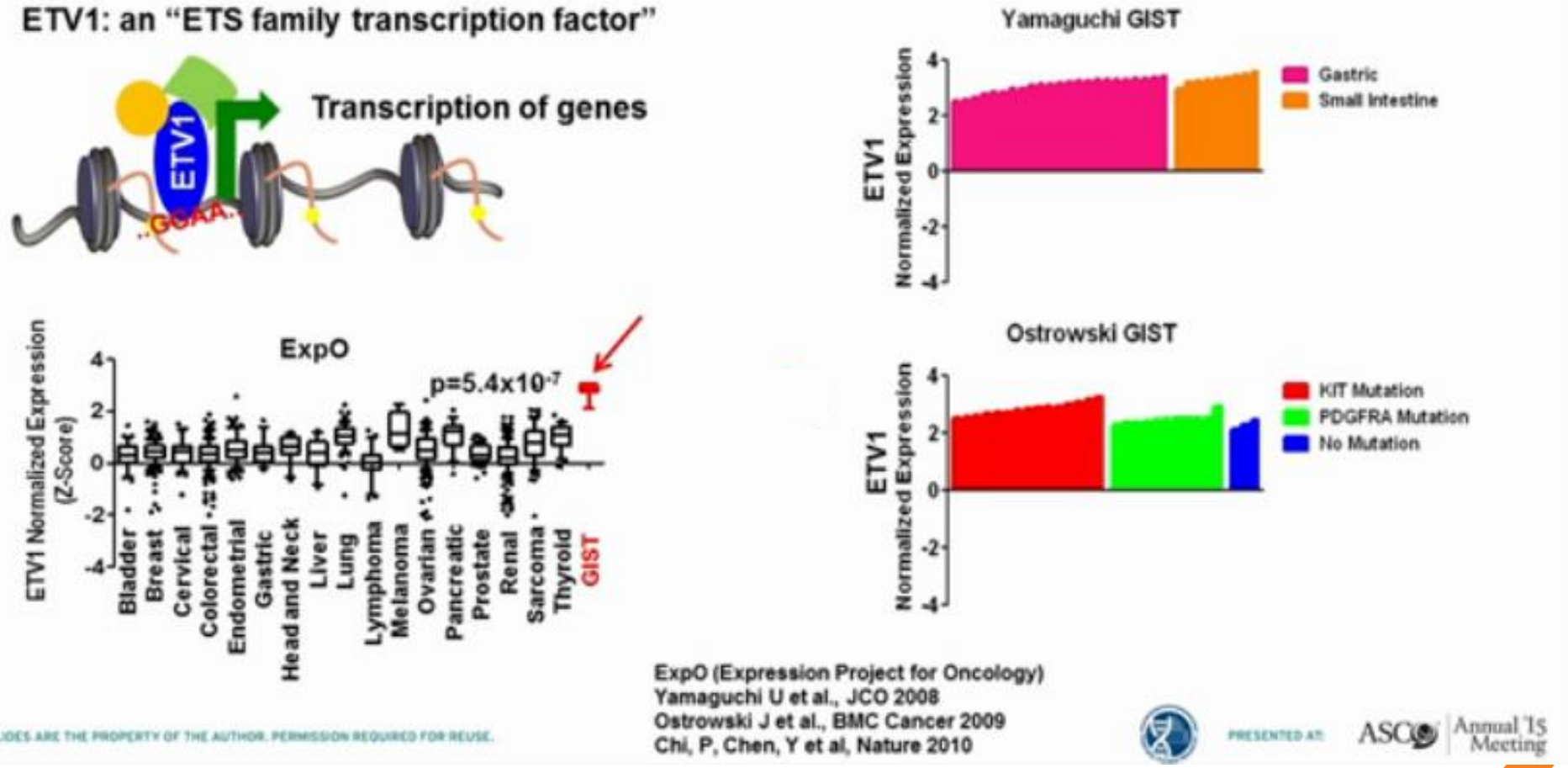
Schoffski P, et al. *Ann Oncol. 2010;21:1990-1998,* Hohenberger P, et al. ASCO Meeting Abstracts. *J Clin Oncol.28:15s, 2010 (suppl; abstr 10048).*

Aberrant Signaling Pathways in GISTs



Rubin et al, The Lancet Volume 369, No. 9574, p1731–1741, 2007

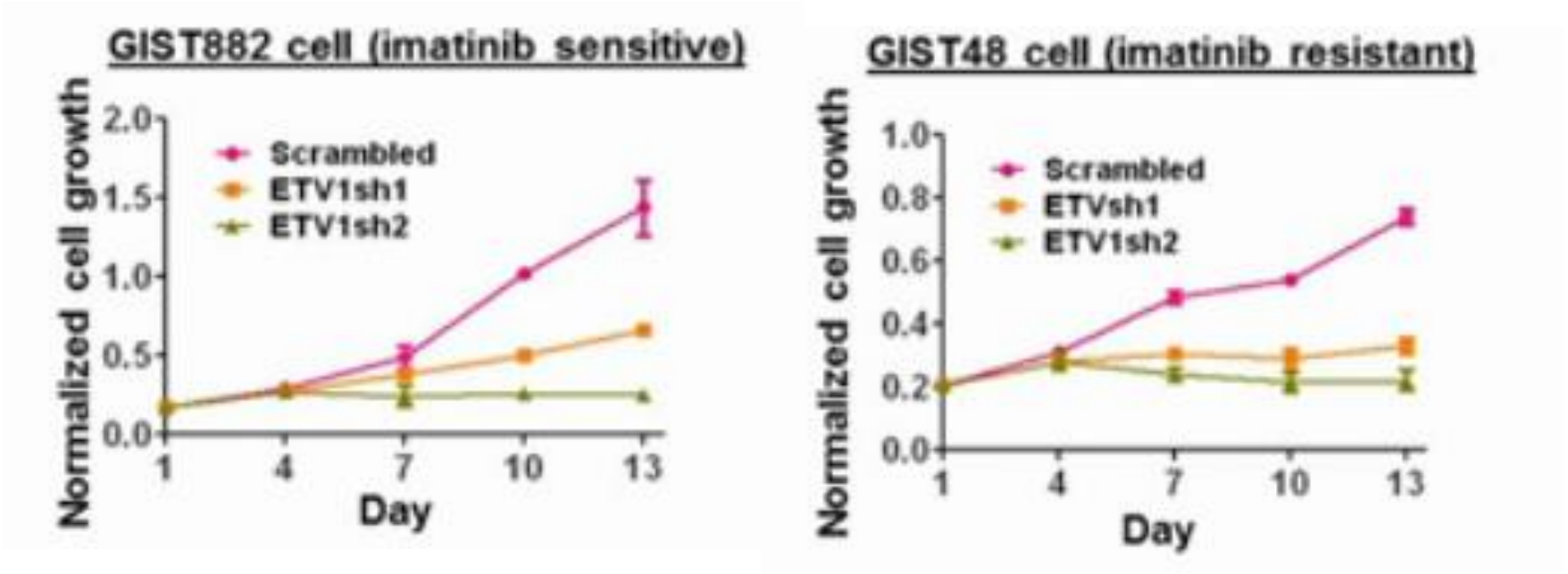
ETV1 (ETS variant 1): A Lineage specific factor in GIST



ExpO (Expression Project for Oncology)
Yamaguchi U et al., JCO 2008
Ostrowski J et al., BMC Cancer 2009
Chi, P, Chen, Y et al, Nature 2010

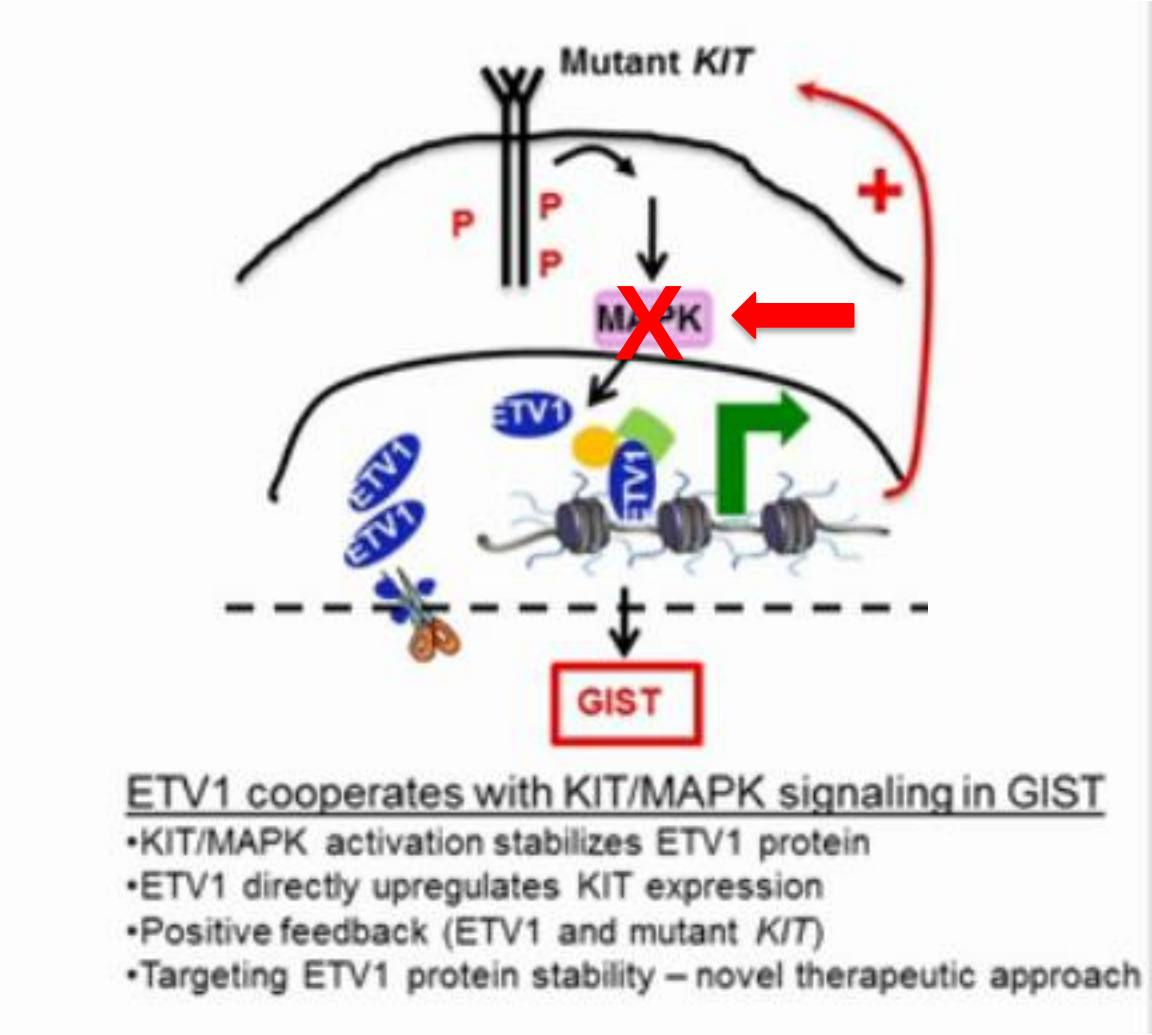
P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)

ETV1 is required for GIST survival and growth



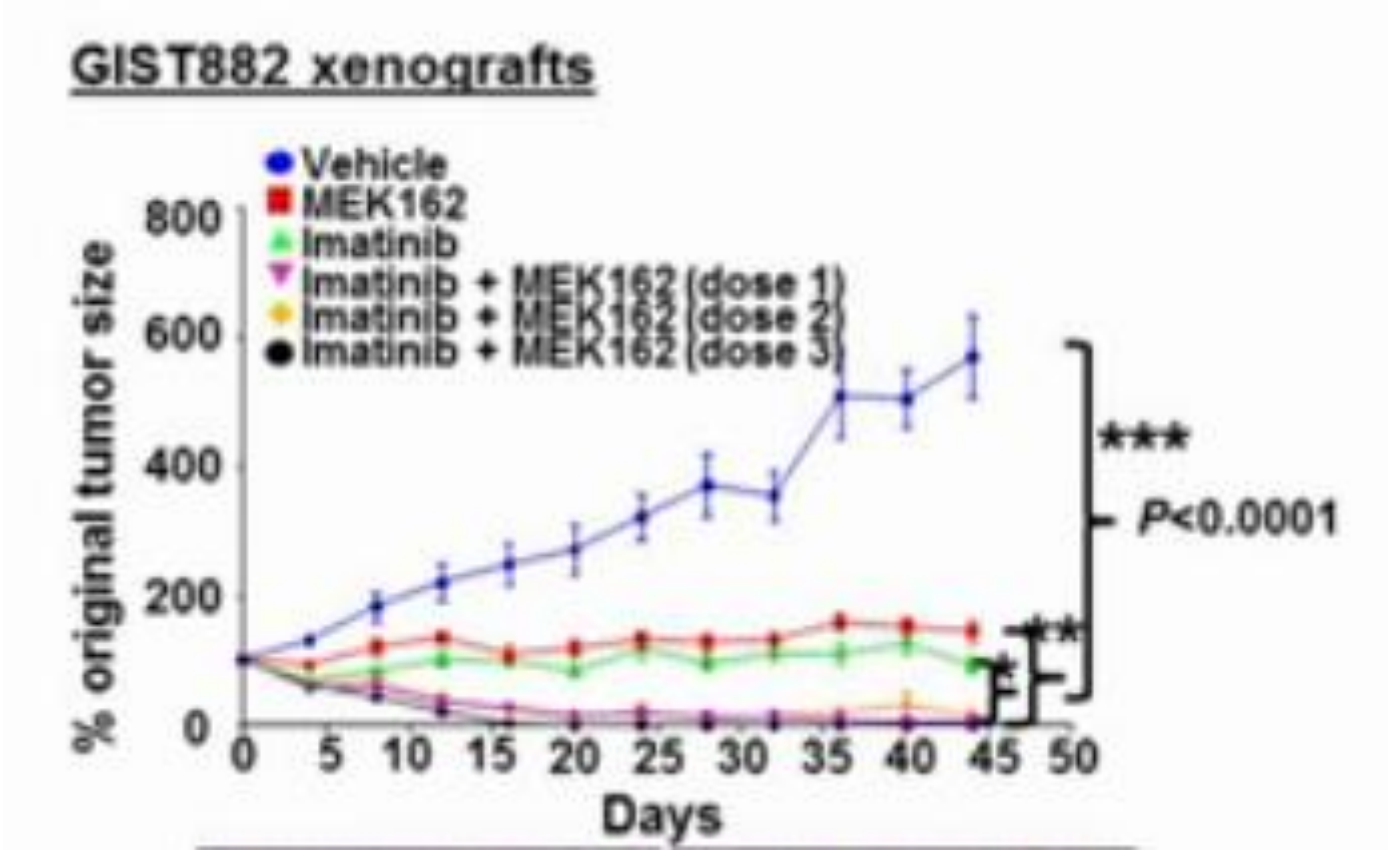
P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)

ETV1 and KIT forms a positive feedback circuit in GIST



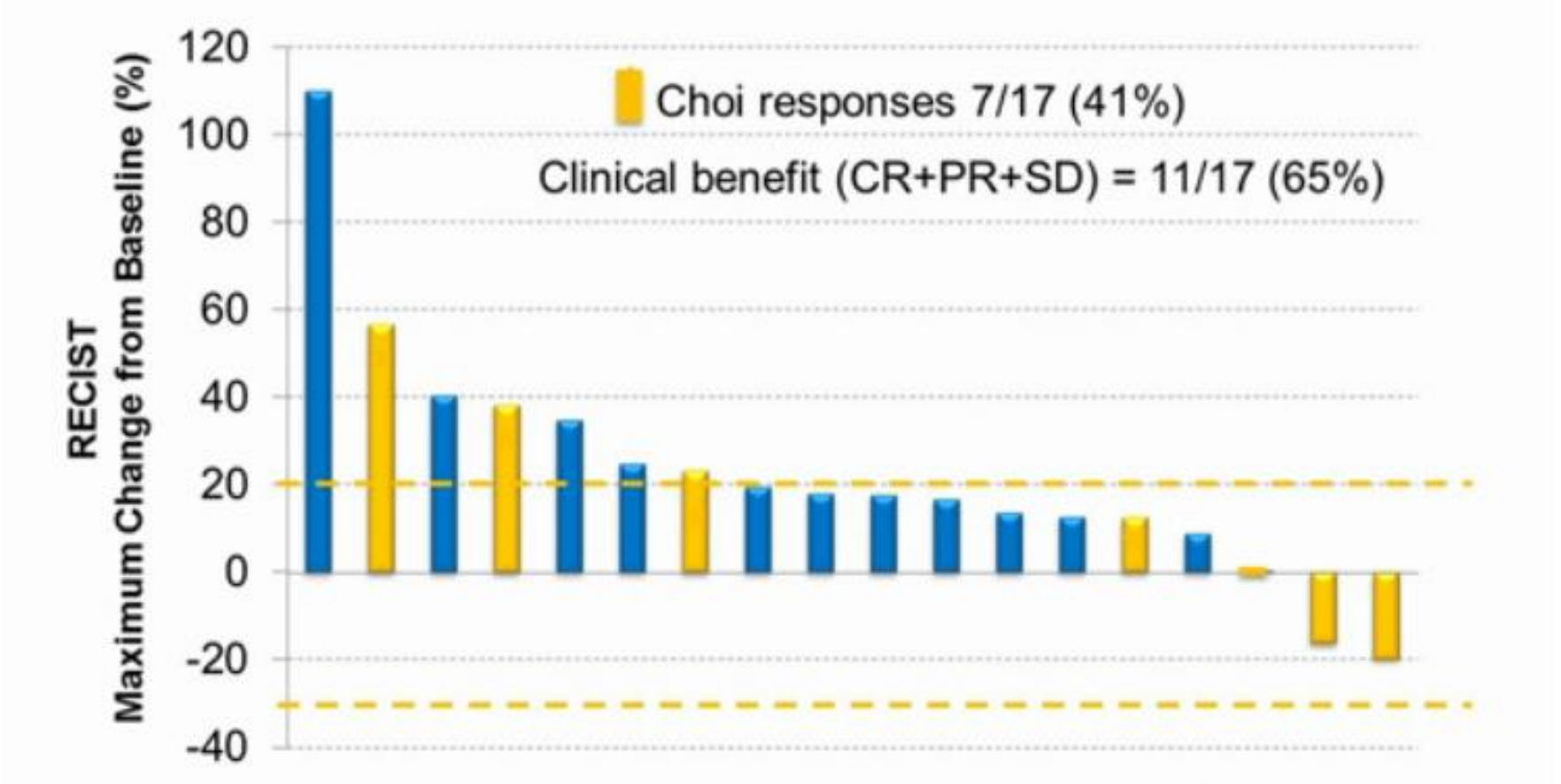
P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)

Synergy of combined MAPK and KIT inhibition



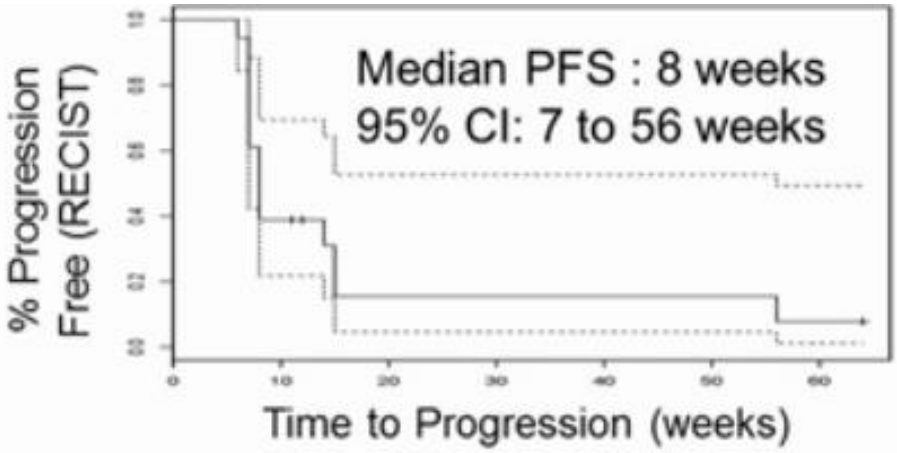
P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)

Phase Ib MEK162 (binimetinib) in combination with imatinib in patients with GIST



P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)

Mutation status of patients with prolonged disease stabilization



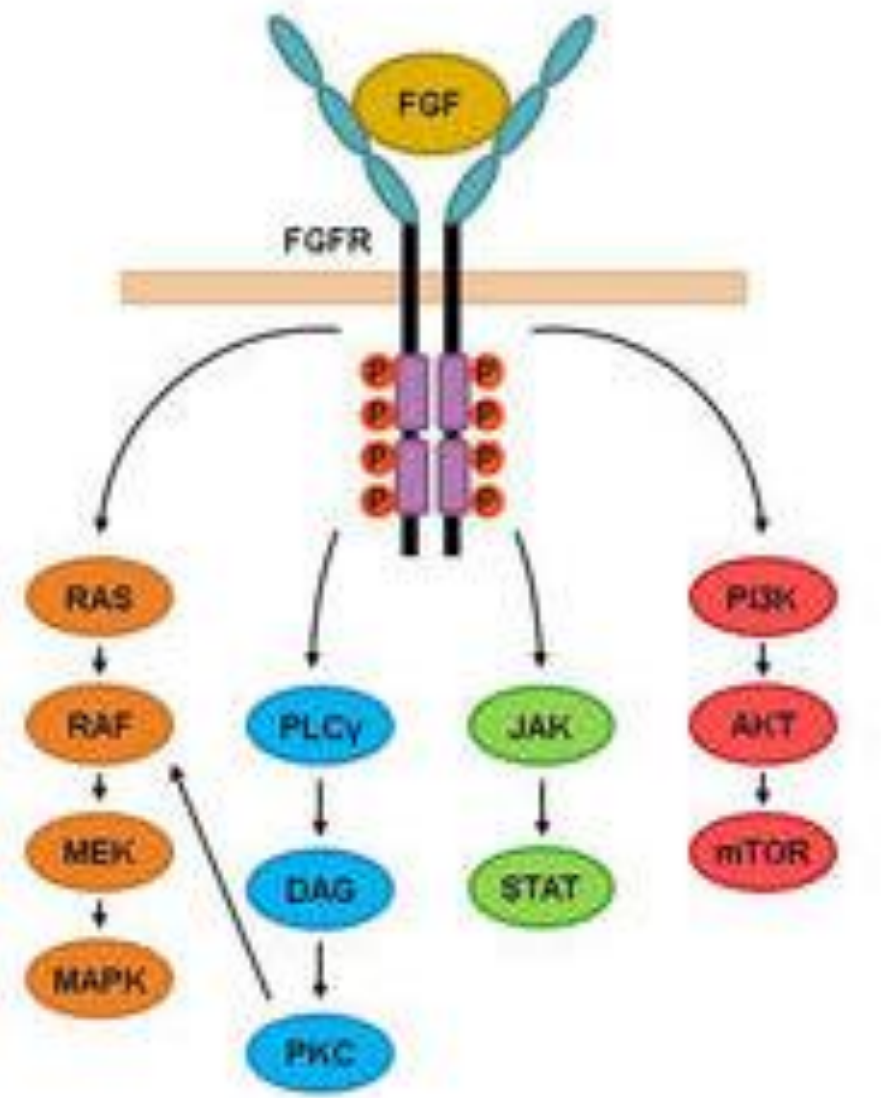
Patients who have imatinib-resistant *KIT* mutations all progressed within 16 weeks.

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, Linsitinib trial	SDHA R31X;SDHB loss by IHC	>66 (active)	SD (-20%)	PR
	8	Imatinib, Sunitinib, Sorafenib	KIT exon11, L576P	55	SD (-16%)	PR

P Ching, et al. J Clin Oncol 33, 2015 (suppl; abstr 10507)

Targeting FGFR

- **FGF/FGFR pathway**
  - **Receptors: 4 FGFRs**
  - **Ligands: 22 FGFs**
  - **Each FGFR has specificity for particular FGFs**
- **Context dependent signalling through various intracellular pathways**
- **Regulates normal biological processes**
  - **Protein synthesis**
  - **Cell growth and proliferation**
  - **Cell motility, migration, invasion**
  - **Cell differentiation**
  - **Resistance to cell death**
  - **Angiogenesis**



Turner et al Nature Reviews Cancer 2010

Targeting FGFR

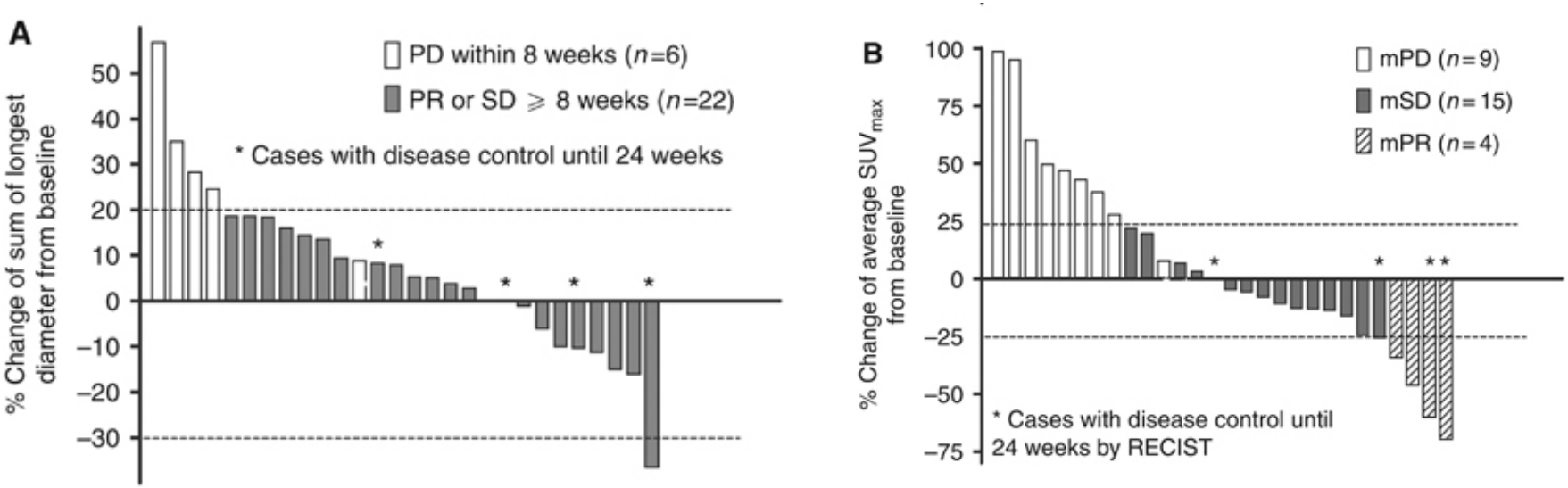
- **Gene expression data has revealed that FGF2 and FGFR1 are highly expressed in all primary GIST samples**
- **Preclinical studies combining imatinib with an FGFR inhibitor showed increased growth inhibition in imatinib-sensitive GIST cell lines**
- **Crosstalk between KIT and FGFR3 Promotes Gastrointestinal Stromal Tumor Cell Growth and Drug Resistance**

Fang LI, et al. (Abstract B65) *Mol Cancer Ther. 2013;* 12:B65, Javidi-Sharifi N, et al. *Cancer Res*. *2015 Mar 1;75(5):880-91*

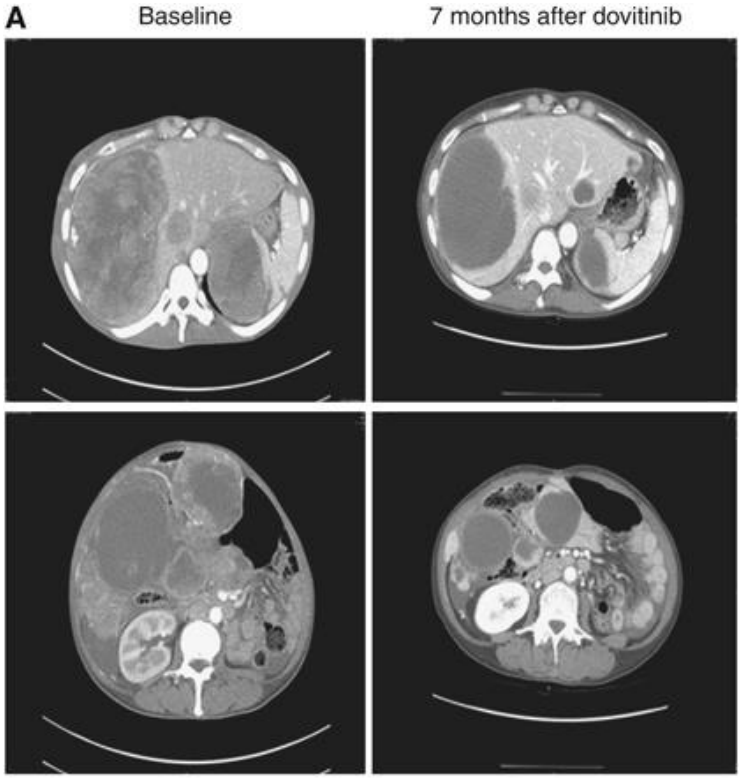
Phase II study of FGFR inhibition

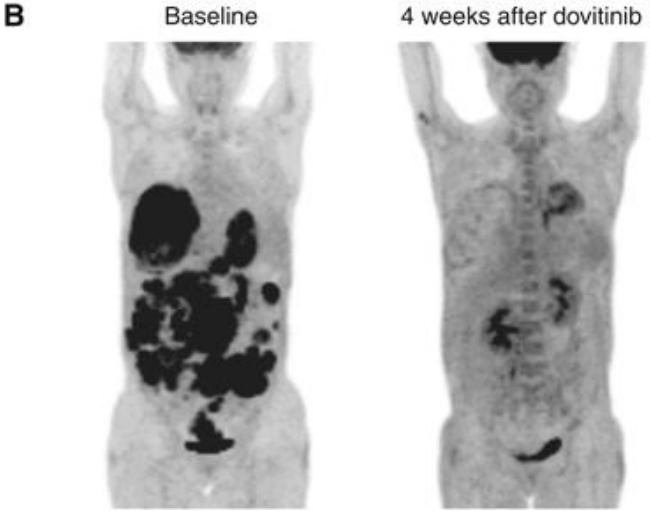
Dovitinib was administered at 500 mg orally once daily for 5 consecutive days, followed by a 2-day rest, with each cycle consisting of 28 days

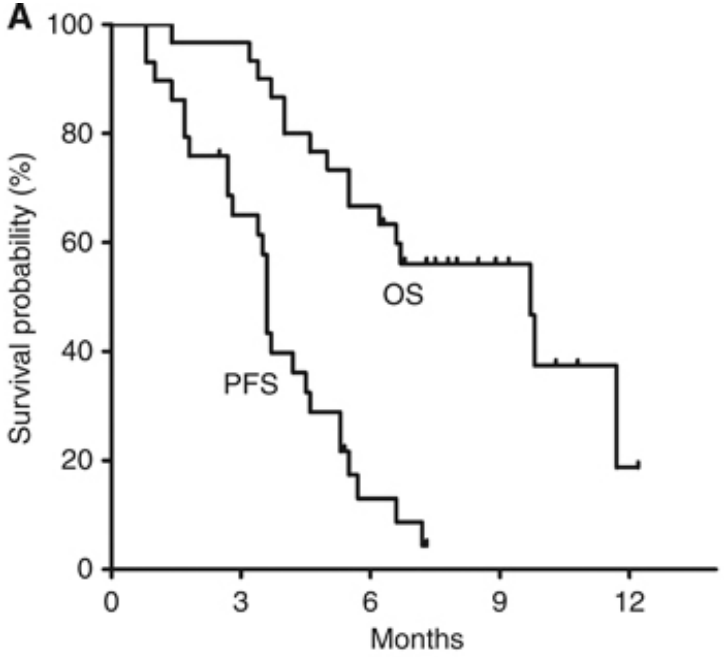
SUVmax response

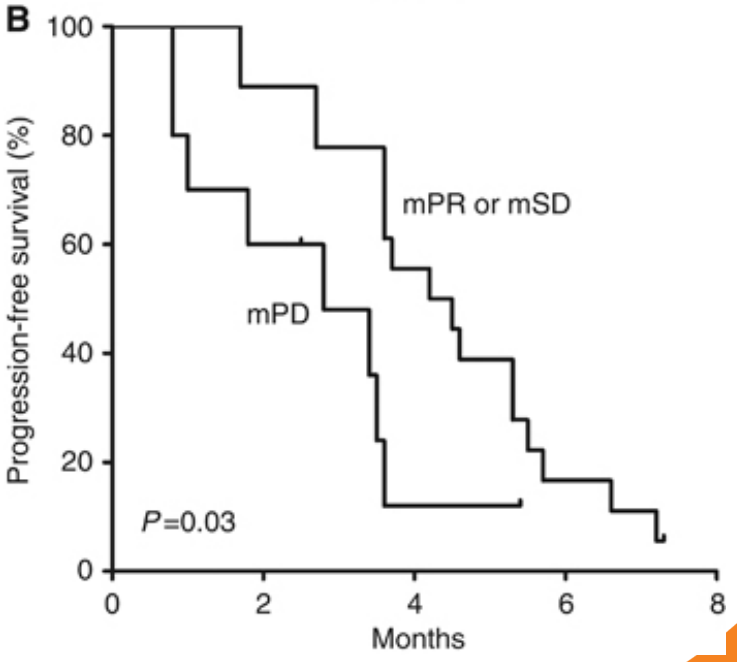


Kang Y, et al. *Br J Cancer. 2013 Oct 29;109(9):2309-15.*









Kang Y, et al. *Br J Cancer. 2013 Oct 29;109(9):2309-15.*

DOVIGIST: PII Dovitinib trial

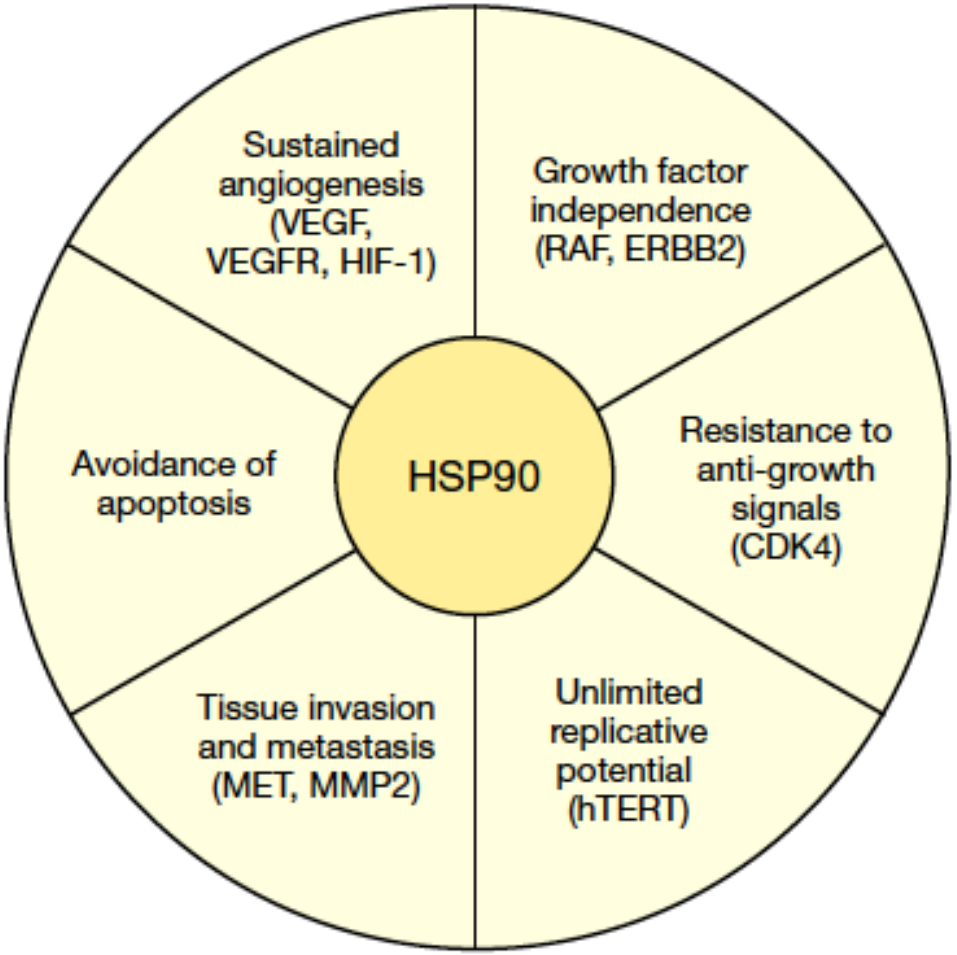
- **Efficacy of dovitinib demonstrated in a 2nd study**
- **The DCR of 52.6% compares favorably with that of other second-line treatments**

Best Response at 12 Wk, n = 38	n	%	90% CI
Partial response (PR)	1	2.6	
Stable disease (SD)	19	50.0	
PD	5	13.2	
Unknowna	13	34.2	
ORR (≥ PR)	1	2.6	0.1-11.9
DCR (≥ SD)	20	52.6	38.2-66.7

Joensuu H, et al. *Annals of Oncology (2014) 25 (5): 1-41. 10.1093*

Heat Shock Protein 90 (HSP90) Inhibition

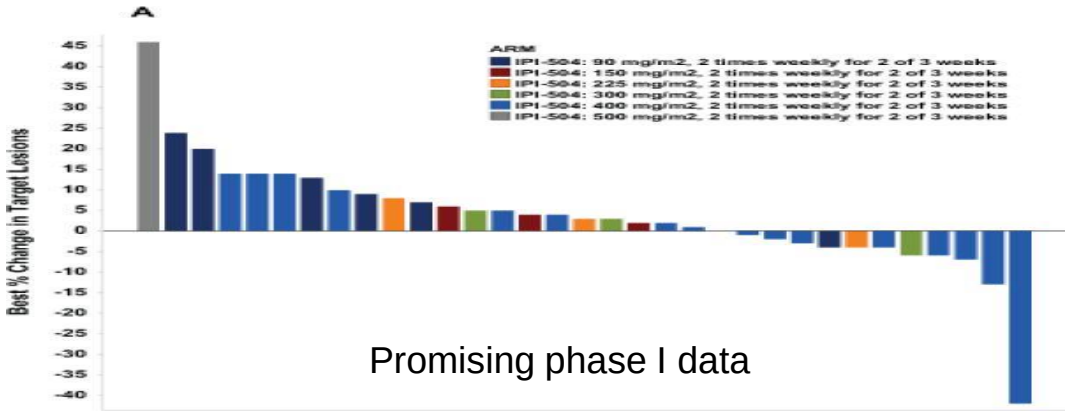
- **Chaperone protein that assists other proteins to fold properly, stabilizes proteins against heat stress, and aids in protein degradation.**
- **Stabilizes proteins required for tumor growth**
- **Inhibition of HSP90 may interfere with all of the six hallmark traits of cancer**



Powers M, et al. *Endocr Relat Cancer. 2006;13:S125-S135*

Retaspimycin hydrochloride (IPI-504)

- **HSP90 inhibition causes degradation of wild-type KIT and an imatinib-resistant KIT D816V mutant.**



Promising phase I data

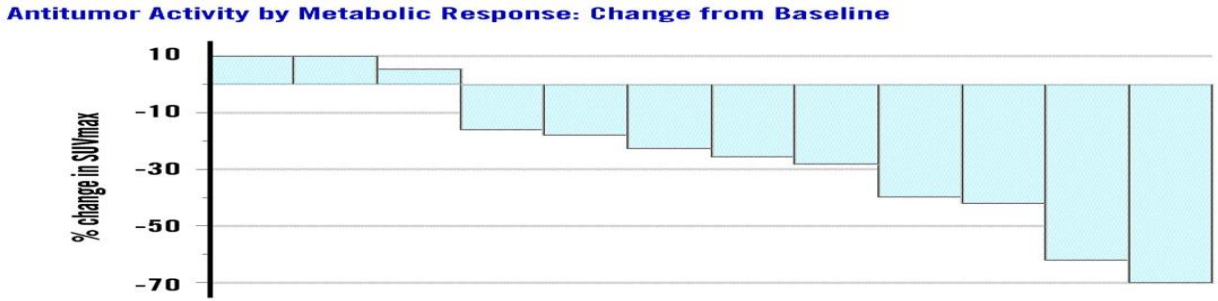
- **Phase III study of IPI-504 (retaspimycin hydrochloride) versus placebo was terminated early due to excessive treatment related death**
- **These deaths were considered drug-related and included renal failure, liver failure, metabolic acidosis, and cardiopulmonary arrest.**

Wagner AJ, et al. Clin Cancer Res. 2013 Nov 1;19(21):6020-9. Demetri GD, et al. ASCO Gastrointestinal Cancers Symposium. Orlando, FL; January 22–24, 2010. [abstract 64].

Other HSP90 inhibitors

- **BIIB021 – PII, stable disease for 10 of 23 subjects (43%)**

- **Ganetespib – PII, stable disease for 5 of 23 subjects (22%)**



- **AUY922 – PII on-going**

Dickson MA et al. *Ann Oncol. 2013 Jan;24(1):252-7*, Demetri G, et al. *ASCO Meeting Abstracts 2011;10011*.

Is there a role for immunotherapy in GIST?

- **Can we combine targeted therapy and immunotherapy in GIST?**

- **Peginterferon a-2b with imatinib for treatment of stage III/IV GIST to induce dendritic cell and cytotoxic T-lymphocyte differentiation toward Th1 response.**
  - Interim analysis of 8 patients demonstrated significant induction of IFN-γ-producing-CD8(+), -CD4(+), -NK cell, and IFN-γ-producing-tumor-infiltrating-lymphocytes,
  - Median follow-up of 3.6 years,
  - ORR = 100%, overall survival = 100%,
  - one patient died of unrelated illness while in remission

(Chen LL, et al. Oncoimmunology. 2012; 1: 773–776)

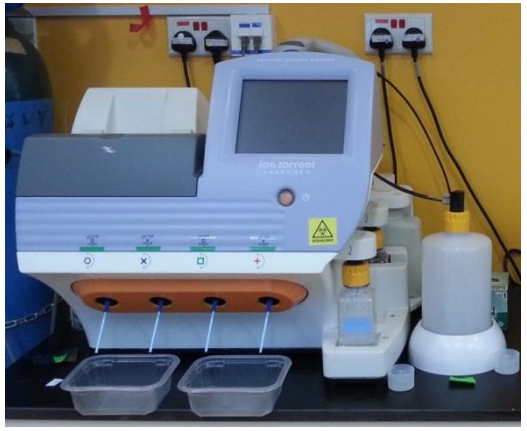
NCIS Developmental Therapeutics Unit Phase I trials 2015

Ongoing

- Pan-FGFR inhibitor - FGFR1/2/3 expression levels
- AKT inhibitor (AZD5363, Astra Zeneca)
- P-TEFb inhibitor (BAY 1143572, Bayer)
- Trastuzumab + NK-cell therapy for HER2 amplified/ overexpressed tumours
- Balanced PI3Kα/β inhibitor
- Exportin 1 (XPO1) inhibitor - selective inhibitor of nuclear export (Selinexor, Karyopharm)
- PDL-1 + MEK inhibitor (Roche)
- ASLAN001: HER1/2/4 inhibitor + carboplatin and paclitaxel
- PLK1 inhibitor: Tekmira
- Wnt/Porc inhibitor: ETC/ D3

Integrated Molecular Analysis of Cancer (IMAC) at NCIS

- Screening for actionable targets using NGS/ IHC and copy number analysis in tumour tissue
- All cancer types
- Establish prevalence of mutations in local patients
- Evaluate clinical impact of molecular profiling (RR/PFS/OS)



Next generation sequencing using Ion Torrent PGM Sequencer with minimum requirement of 10-40ng DNA

FISH and CISH/ Gene expression profiling/ immunohistochemistry

Final Profiling Report

Results reviewed by IMAC tumour board

Interpretation and recommendation

Medical Oncologist

Patient with progressive disease

?Matched Therapy

FFPE or fresh tissue

Consent, screening, tissue collection

Conclusions

- **Dual inhibition of PK13K/AKT, mTOR, MEK/ETV1, FGFR and HSP90 with KIT/PDGFR pathways +/- immunotherapeutic approaches may become a new paradigm in treatment.**

- **Challenges of combined targeted approaches include significant risk of overlapping/ unknown toxicity which could prevent clinical application**

- **The challenges, opportunities, and limitations of these approaches mean that randomized trials are needed for further evaluation.**