New Treatments in the Pipeline for GIST

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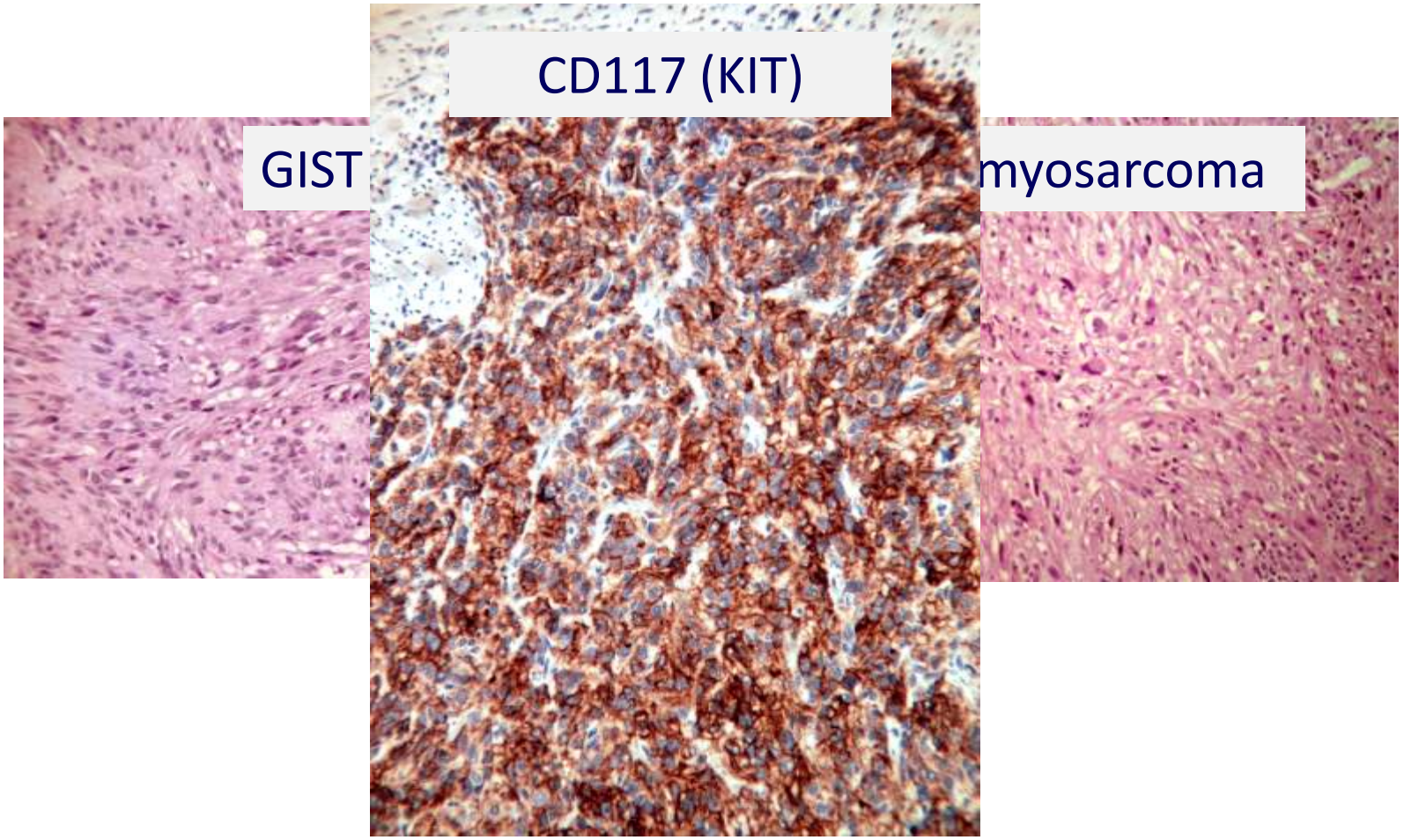
How Do We Develop New Treatments?

1. Empiricism – Give a drug to patients, and see if it works (how do you know?)
2. Scientific Approach – Identify the problem in the cancer, design/develop a drug that blocks that process, test in laboratory models (if you have them), test for safety in people, test how well it works, test if it works better than standard treatment (takes a long time!)
3. Combination of (1) and (2)

Step 1: Identify the disease



Step 2: Identify the abnormality

Gain-of-Function Mutations of c-*kit* in Human Gastrointestinal Stromal Tumors

Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiko Kitamura†

Science 279:577-580, 1998

Step 3: Test drug in laboratory models

Oncogene (2001) 20, 5054–5058

www.nature.com/onc

SHORT REPORTS

STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications

David A Tuveson*[,1,2,3,4], Nicholas A Willis[1], Tyler Jacks[1,2], James D Griffin[3,4], Samuel Singer[3,4,5], Christopher DM Fletcher[6], Jonathan A Fletcher[3,4,6] and George D Demetri[3,4]

These cell-culture-based studies support an important role for c-KIT signaling in GIST and suggest therapeutic potential for STI571 in patients afflicted by this chemoresistant tumor. *Oncogene* (2001) **20,** 5054–5058.

Steps 4 and 5: Test drug for efficacy in patients with GIST

The New England Journal of Medicine 2002

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.

Step 6: Test if it is better than standard treatment

- Duh! Nothing else worked. Imatinib did for >80% of patients
- Some things are obvious – don't need to test whether jumping out of an airplane is safer with a parachute than without one
- FDA granted approval in 2002. This was fast.

But imatinib doesn't work for all patients, or it stops working

- Steps 1 and 2: Identify the disease/abnormality
  - Additional KIT mutations causing imatinib resistance (about 80%)
  - Other mutations (about 20%):
    - PDFGRA D842V (stomach, epithelioid)
    - NF1 (small bowel, spindle cell)
    - SDH deficiency/"pediatric GIST" (stomach, epithelioid)
    - BRAF
    - Other as of yet unidentified mutations

Next steps

- Test in lab models (if you have them)
- Test for safety (if not already done)
- Test for efficacy
- Test if better than standard of care

- Let’s discuss some pathways and emerging drugs. Most will focus on KIT/PDGFR signaling; brief discussion of SDH-deficient GIST

But first…
Brief foray into clinical trials and (…gasp…) statistics

Clinical Trials

What - Research (experiments) involving people.

Types - Therapeutic, Prevention, Quality of Life

Why - Find better treatments

When - Potentially at any point

How – Safety and consent of patient is paramount. Involves oversight of Institutional Review Board (IRB) and FDA. Guided by principles of human rights, ethics, and by Federal Law. Thus, the “protocol”.

Major Types of Drug Studies

- Phase I
  - First time drug administered to patients
  - Study goal is to determine safety, side effects, and maximal safe dose
  - Drug levels (pharmacokinetics/PK) closely measured. Lots of blood draws.
  - Drug effect on body (pharmacodynamics/PD) often measured. Blood draws and biopsies.
  - Frequent safety assessments (blood tests, EKGs, etc). Lots of visits.
  - Patients enrolled in small groups at a given dose level, observed for toxicity, then next group at higher dose level, etc. Few slots.
  - Often the only access to exciting new drugs for patients with rare diseases
  - Outcomes: Maximally tolerated dose (MTD), Recommended Phase 2 Dose (RP2D), side effect profile

Major Types of Drug Studies

- Phase II
  - All patients get same dose of drug. Everyone gets the same drug.
  - Testing efficacy in patients with shared type of disease.
  - Typical Outcomes: Response rate (RR) or progression-free survival (PFS). Stay tuned.

Major Types of Drug Studies

- Phase III studies
  - Testing whether one treatment is better than another, or better than the standard of care
  - Patients are randomly assigned (by a computer) to one treatment group. Sometimes the patient and the doctor do not know what the patient is getting ("double-blind").
  - Require many patients to participate.
  - If properly done, often viewed as "gold standard" and can lead to FDA approval.
  - RR, PFS, and overall survival (OS) or hazard ratio (HR) are typical endpoints

Some Outcome definitions

How do we report outcomes in clinical studies?

1. Response Rate
2. Progression-Free Survival
3. Overall Survival

Typical Outcome Measurements

1. Response Rate (RR)
   - Proportion of patients whose tumors shrank by some standard amount
   - Response Evaluation Criteria in Solid Tumors (RECIST)
   - Other measures: Choi criteria, EORTC PET criteria, etc.
   - Usually, response = drug effect

2. Progression-Free Survival (PFS)
   - Proportion of patients who have not died and whose tumors have not grown by some standard amount
   - If the tumor didn't grow, is that an effect of the drug, or is the tumor just growing very slowly on its own?
   - Compare to "historical controls" or to a different treatment within the same study to find out

Typical Outcome Measurements

3. Overall Survival (OS)
    - Proportion of patients who are still alive
    - Compare to “historical controls” or to a different treatment within the same study to find out
    - Generally viewed to be the gold standard

How are they reported?

1. Response Rate: percentage (ok, so it's not really a rate)
   - "The response rate was 45%"

2. PFS and OS: median (different than the mean, or average – see next slide), rate, or hazard ratio
   - "The median PFS was 28 weeks"
   - "The PFS rate at 6 months was 37%"
   - "The hazard ratio was 0.5"

Very Brief Foray into Statistics

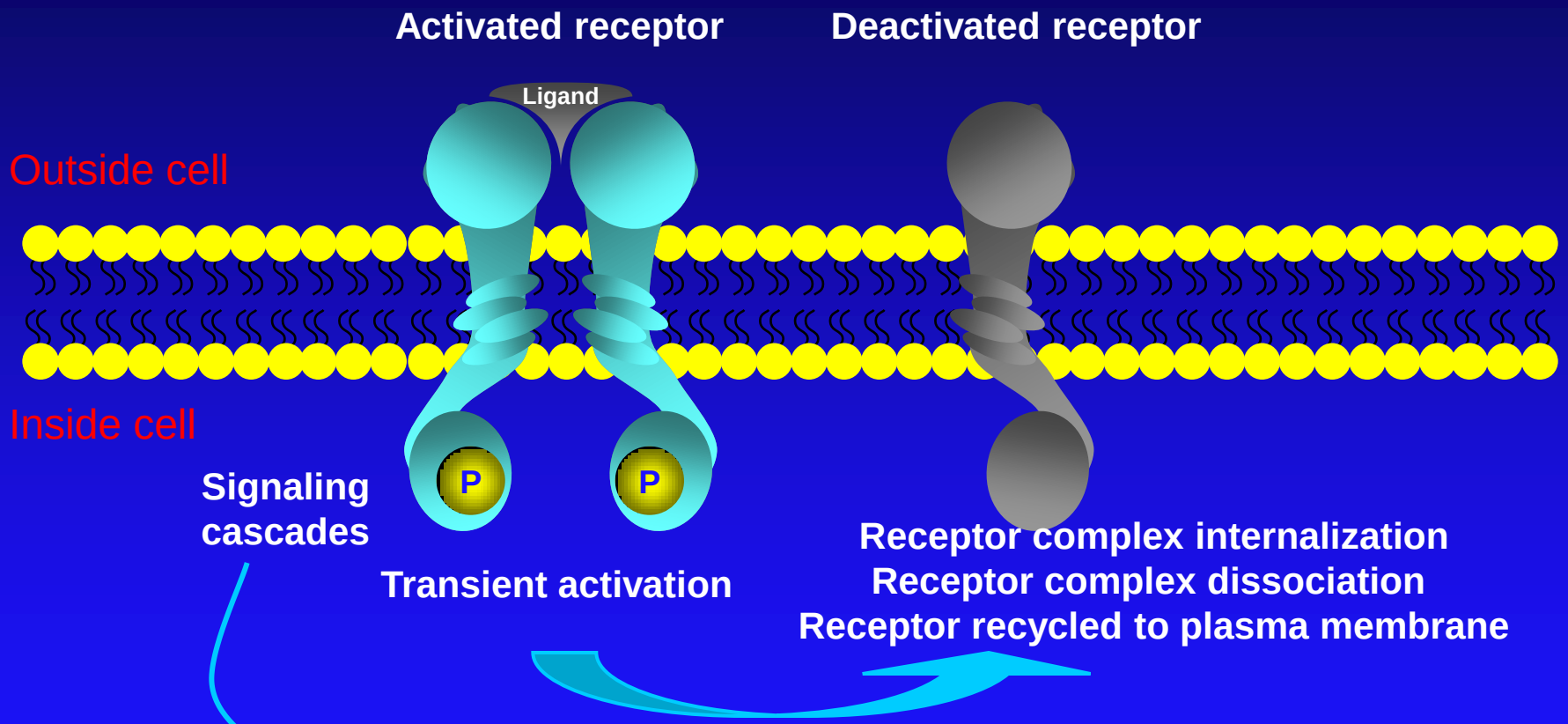
- Mean = average value
  - Mean of 1,3,5,7,9 = 25/5 = 5
  - Mean of 1,3,5,10,101 = 120/5 = 24
  - Useful for repeated measurements of related values (eg weight of one person)
- Median = middle value of a range of values
  - Median of 1,3,5,7,9 = 5
  - Median of 1,3,5,10,101 = 5
  - Useful for measurements of unrelated values so that values at either extreme don't introduce bias

Just one more stats slide

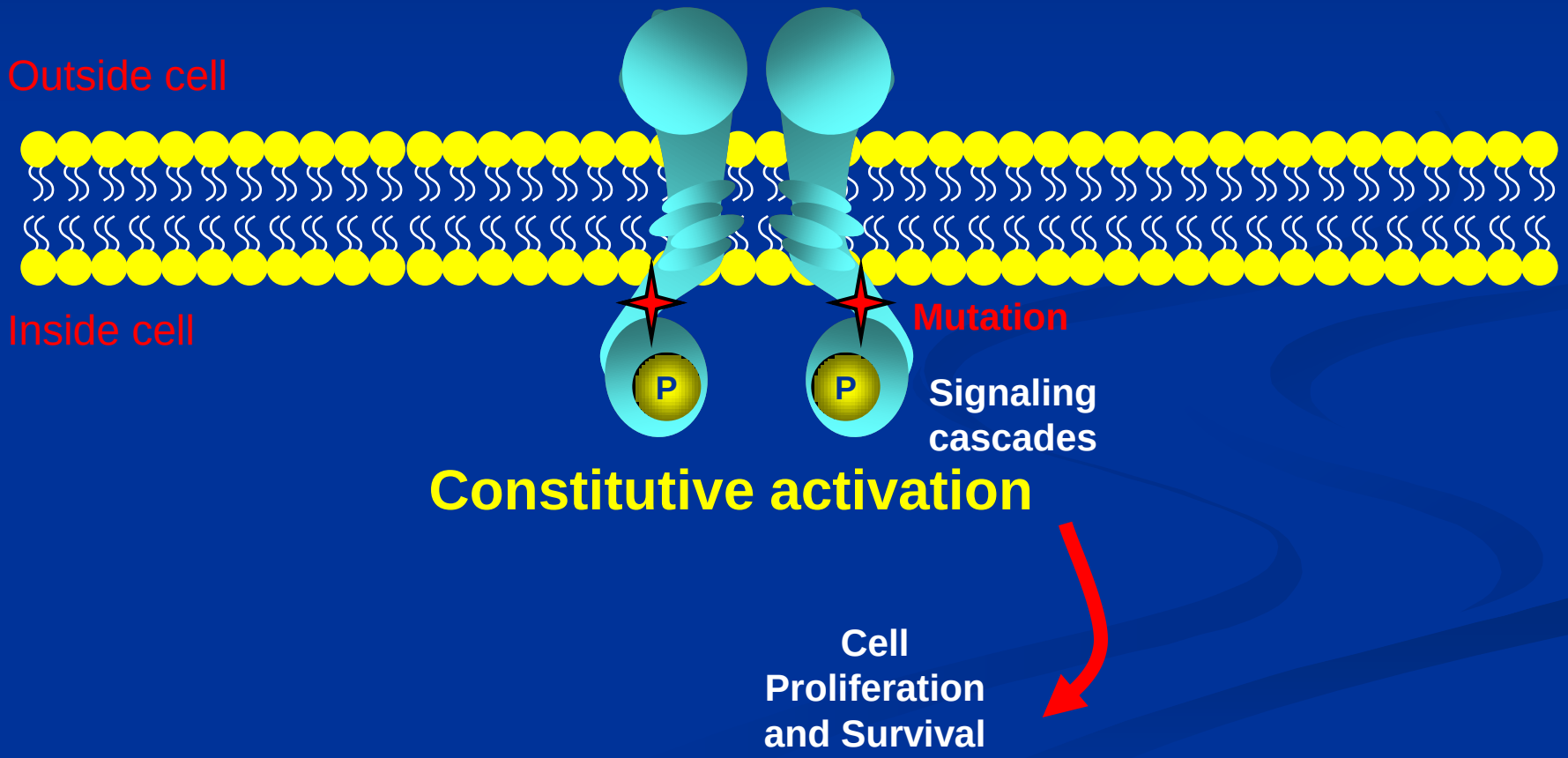
- p values
  - Represent the probability that the observation was due to chance alone
  - The higher the p value, the less likely the finding is real
  - By convention, a p value < 0.05 (connotes 5%) is typically viewed as “statistically significant”

OK – we got all that out of the way.
Now let's talk about some new drugs.

Normal Activation of KIT/PDGFRA Receptor Tyrosine Kinase Signaling



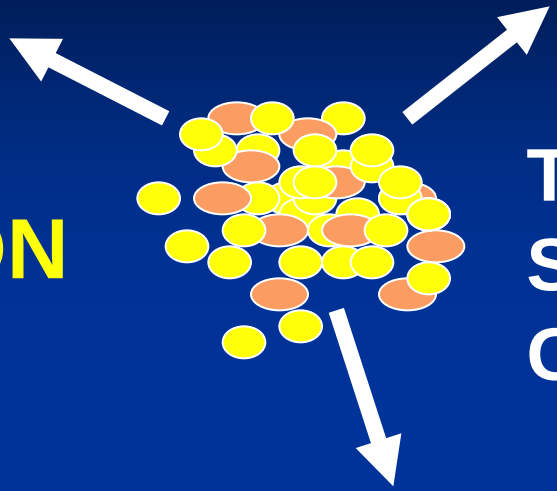
Mutations Generate Uncontrolled, Constant Activation in GIST



Imatinib turns off activated KIT

Imatinib turns off the switch in GIST

ON



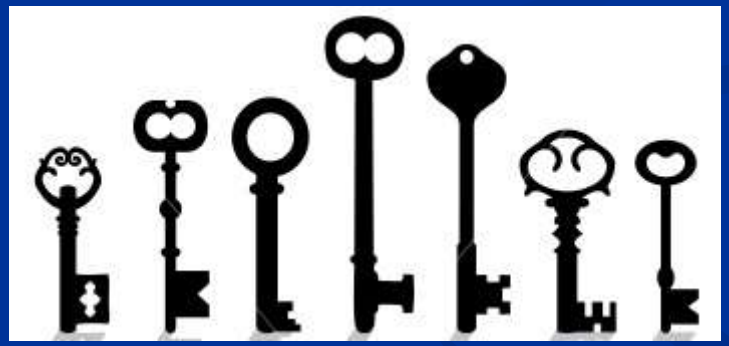
Tumor Cell Survival and Growth

OFF

Tumor Cell Growth Arrest and Cancer Regression

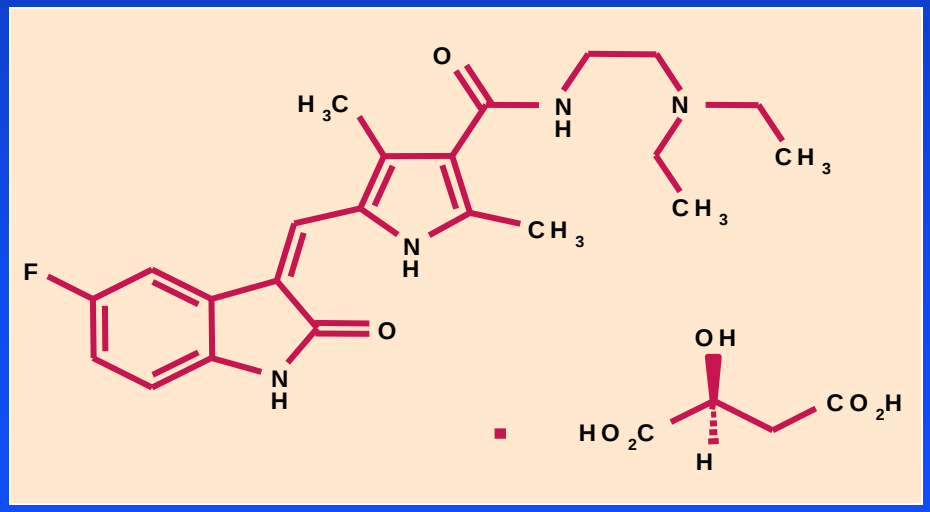
KIT

IMATINIB

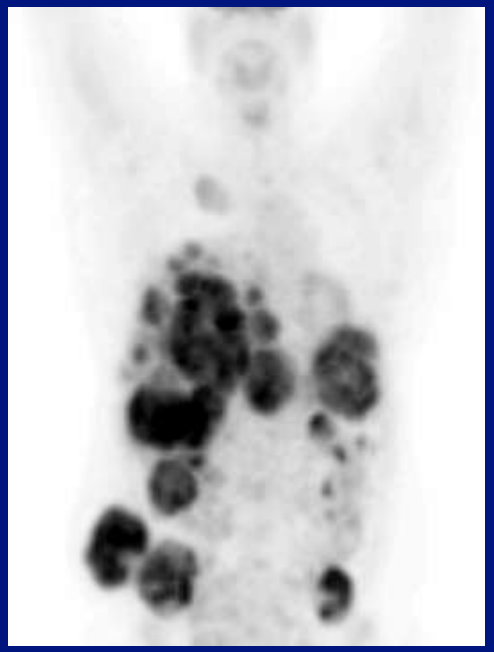


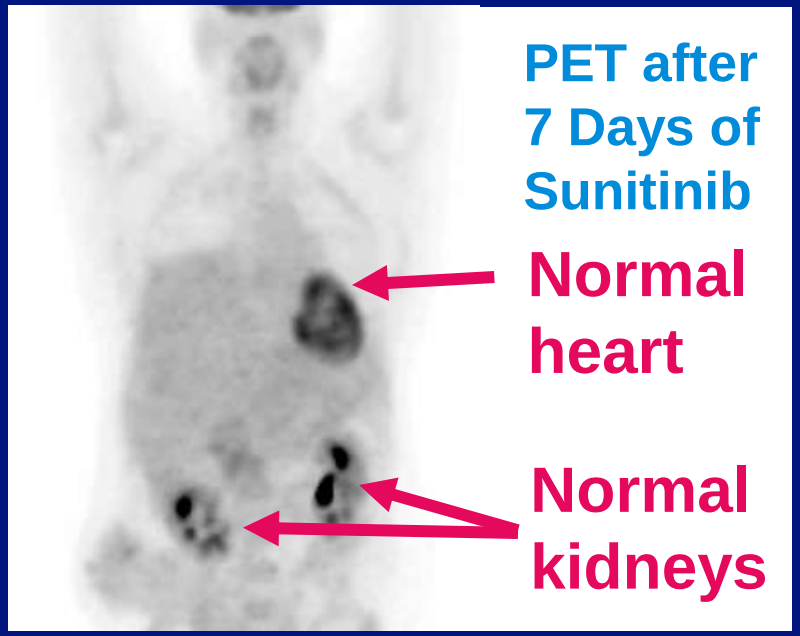
Sunitinib Malate – a Different Shaped Key

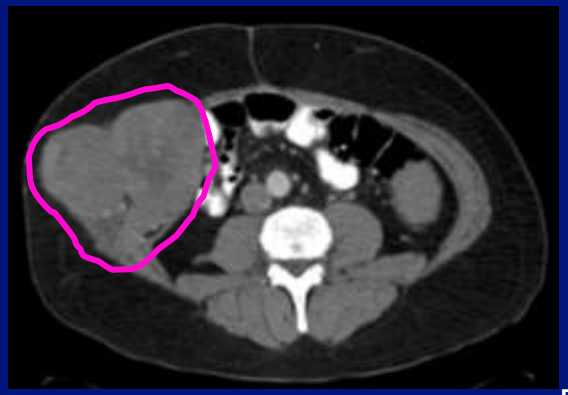
- Small-molecule receptor tyrosine kinase inhibitor
- Inhibits all VEGFRs, PDGFR-A, PDGFR-B, c-KIT, RET and FLT-3
- Oral administration
- Both antitumor and antiangiogenic activity

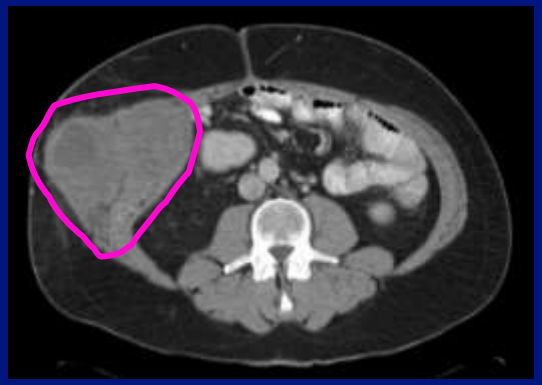


Sunitinib Control of Imatinib-Resistant GIST in a Patient with Primary Imatinib Resistance





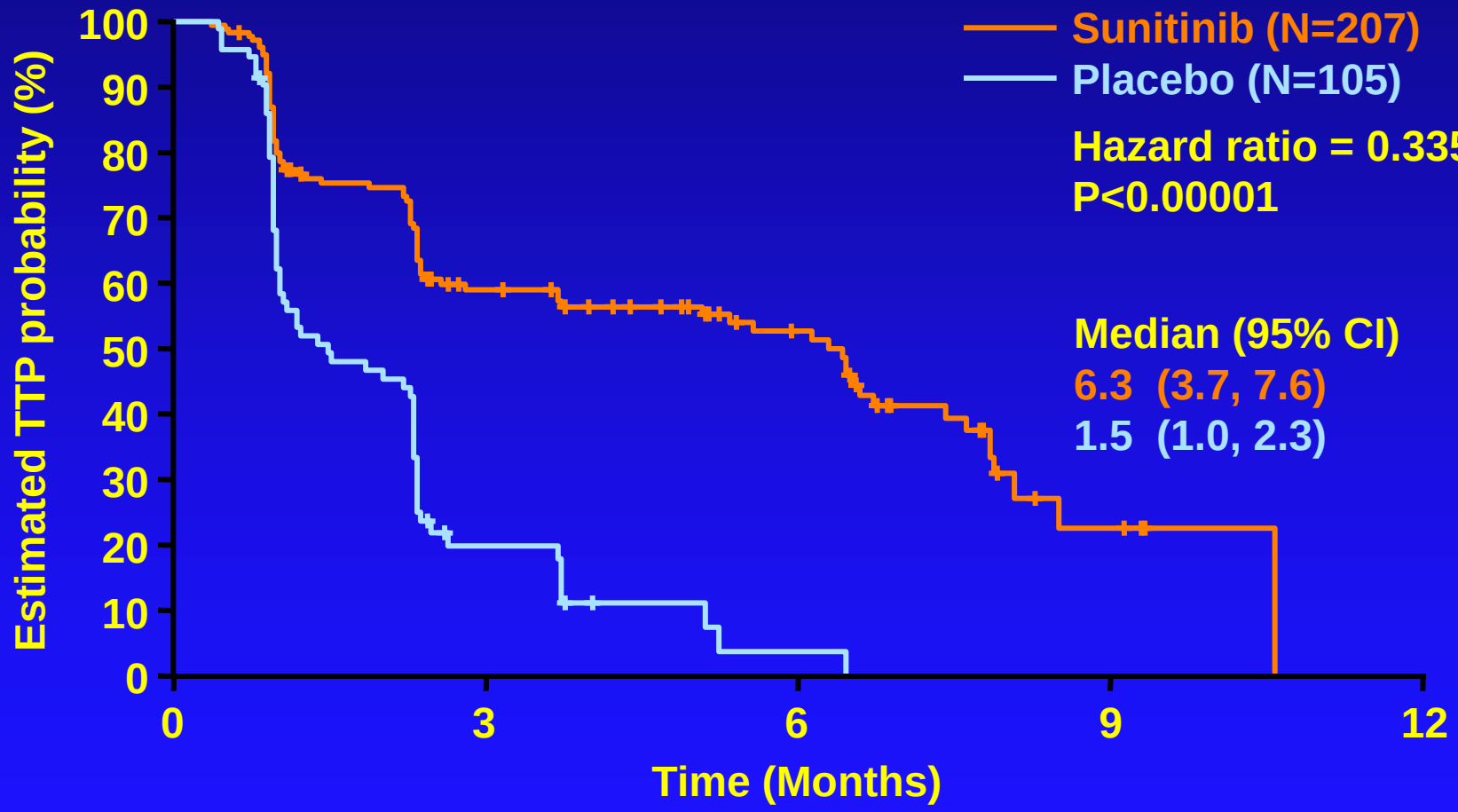




CT after 2 months of Sunitinib

Demetri GD, et al. *Proc Am Soc Clin Oncol* 2005 (Abstract 4000)

Benefit of Sunitinib on Time to Tumor Progression Following Progression on Imatinib



Demetri et al. Lancet 2006

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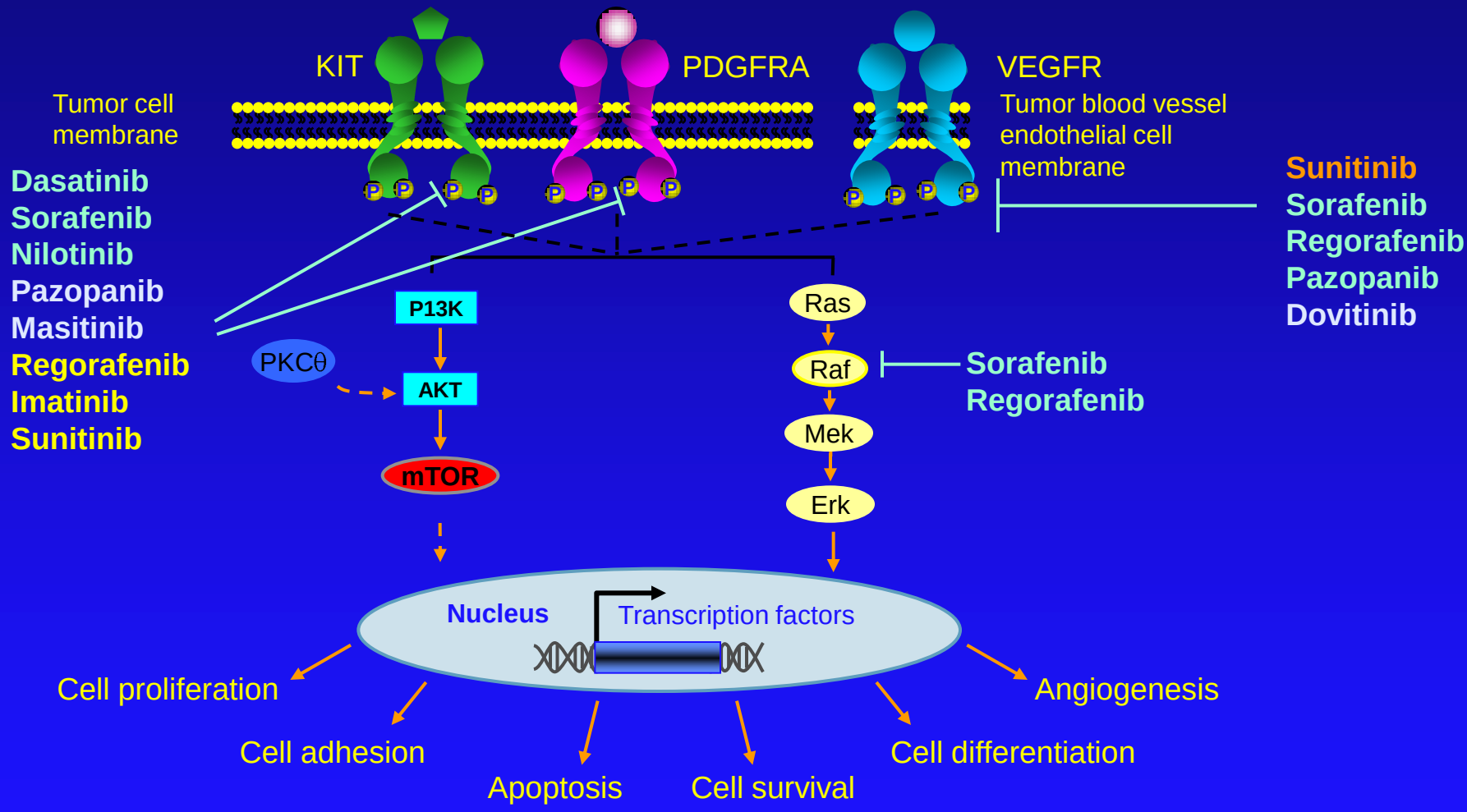
Other KIT inhibitors studied in GIST

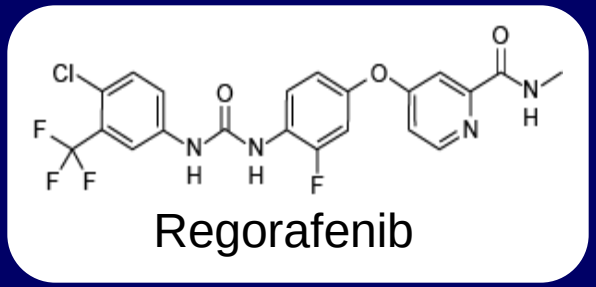


Phase II Studies of 3rd+ Line Therapy (other keys) for GIST (not intended for interstudy comparisons)

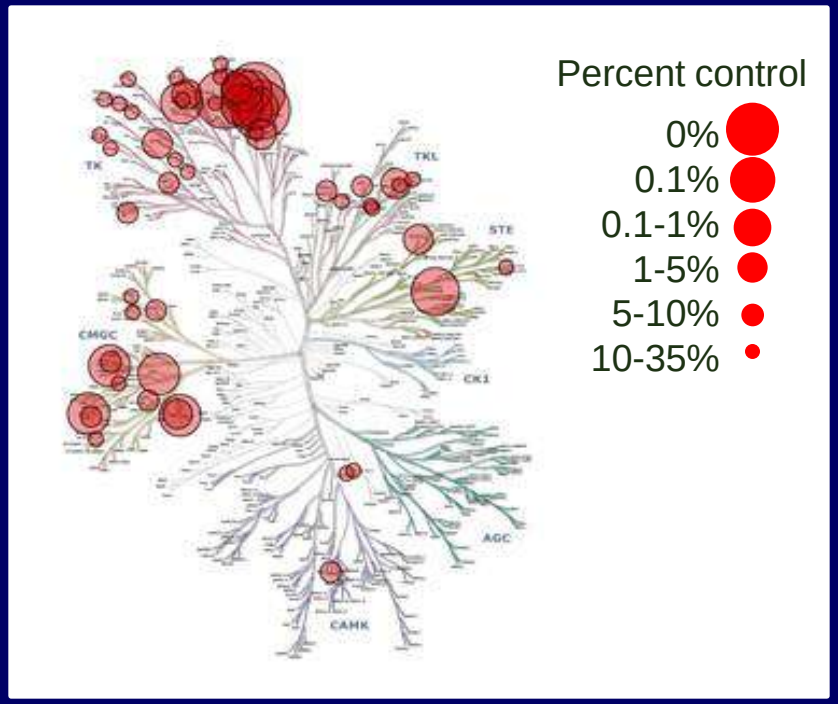
Drug	PR (%)	SD (%)	Median PFS (months)	Median OS (months)	Reference
Nilotinib	3	32	3	8	Montemurro 2009
Nilotinib	3	23	4	10	Sawaki 2011
Dasatinib (Choi criteria)	8	30	2	19	Trent ASCO 2011
Sorafenib	12	56	5	12	Kindler ASCO 2011
Sorafenib	10	54	5	10	Ruy ASCO 2011
Regorafenib	9	82	10	NR	George ASCO 2011 and JCO 2012

Adapted from Verweij ASCO 2011

Regorafenib (BAY 73-4506) is a Structurally Distinct Oral Inhibitor of Multiple Kinases Relevant to GIST and Other Cancers



Regorafenib



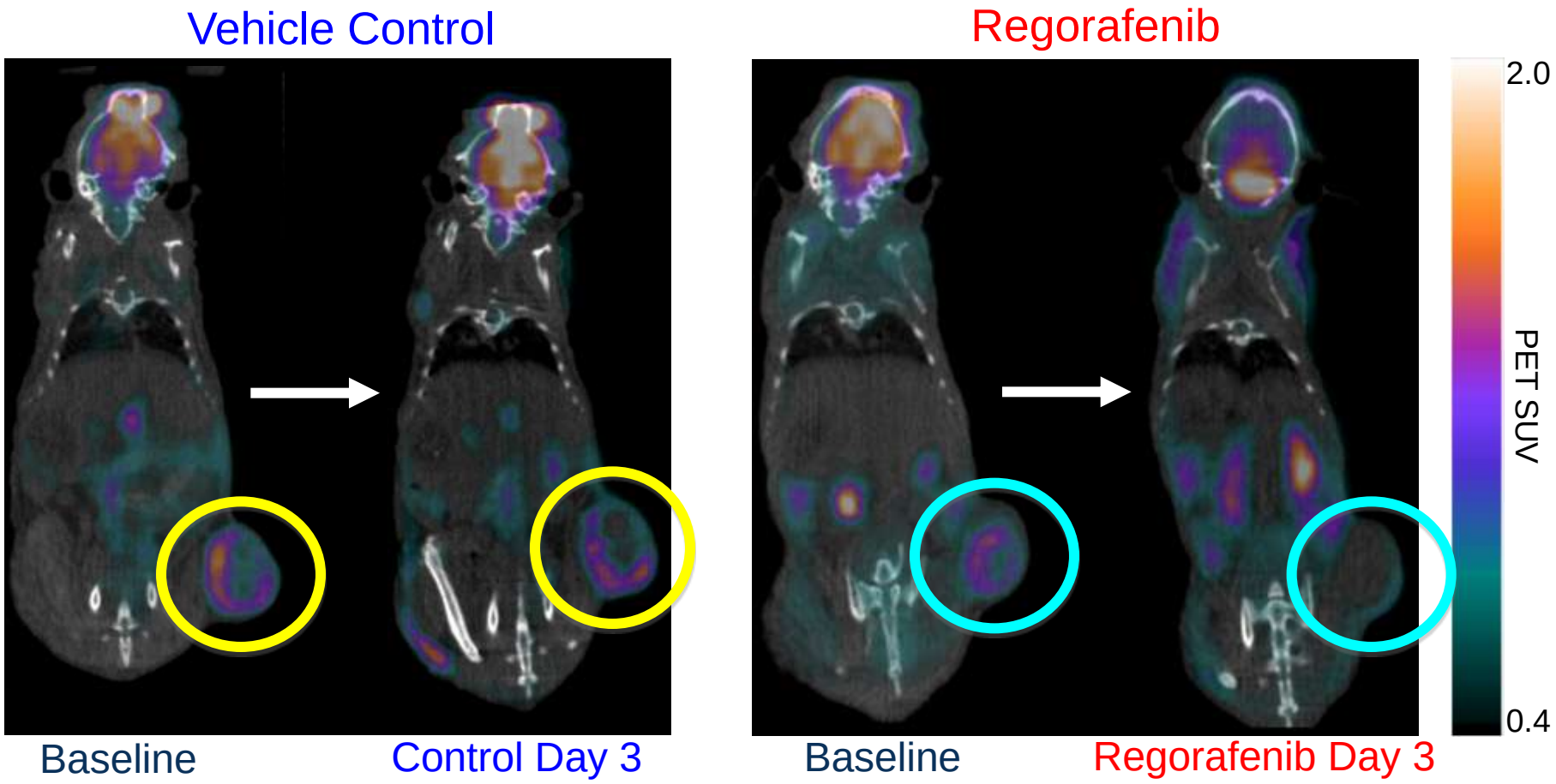
Biochemical activity

	IC_{50} (nmol/l)
KIT	7
VEGFR-1	13
Murine VEGFR-2	4
PDGFR-β	22
RET	1.5
B-RAF	28
FGFR1	202

Demetri ASCO 2012

Wilhelm SM *et al. Int J Cancer* 2011; **129**: 245-255.

Preclinical GIST models demonstrate antitumor activity of regorafenib

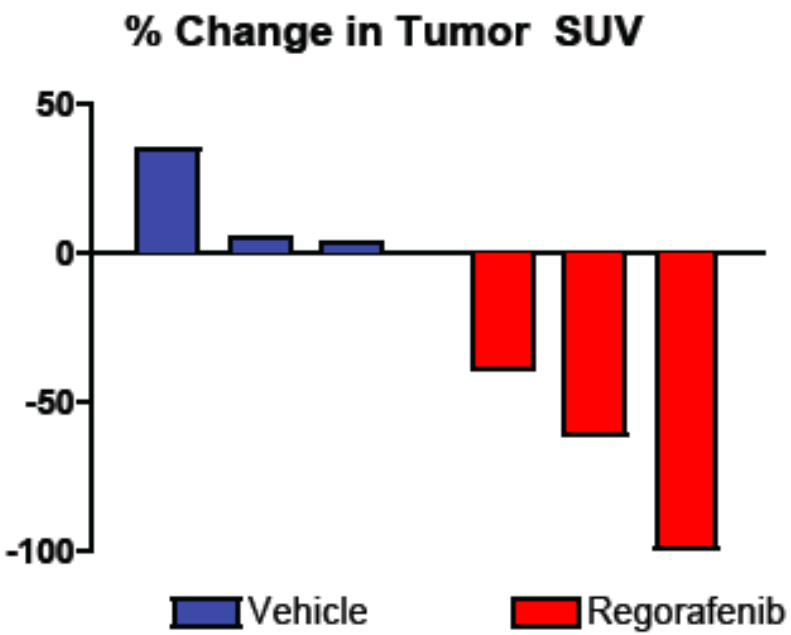


George *et al. J Clin Oncol* 2012

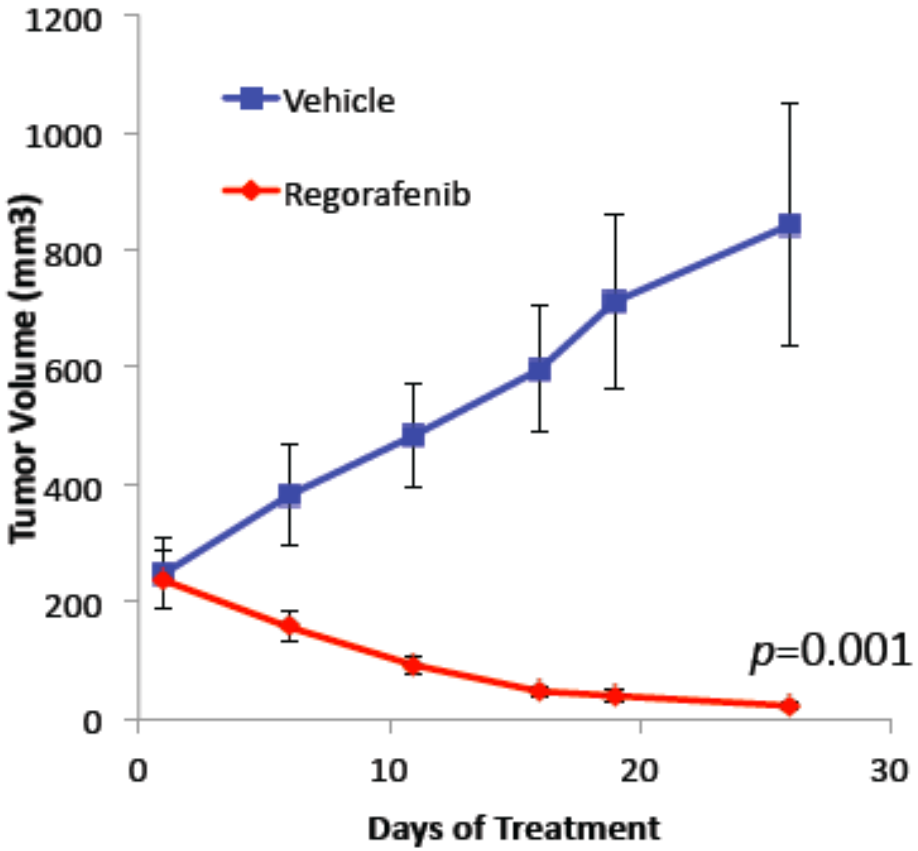
Preclinical GIST models demonstrate antitumor activity of regorafenib

- Regorafenib 50 mg/kg PO daily

Sort-term response: PET/ CT imaging after 3 doses



Anti-tumor efficacy: tumor volume



George *et al. J Clin Oncol* 2012

Regorafenib in GIST following failure of IM and SU: Best Responses To Date

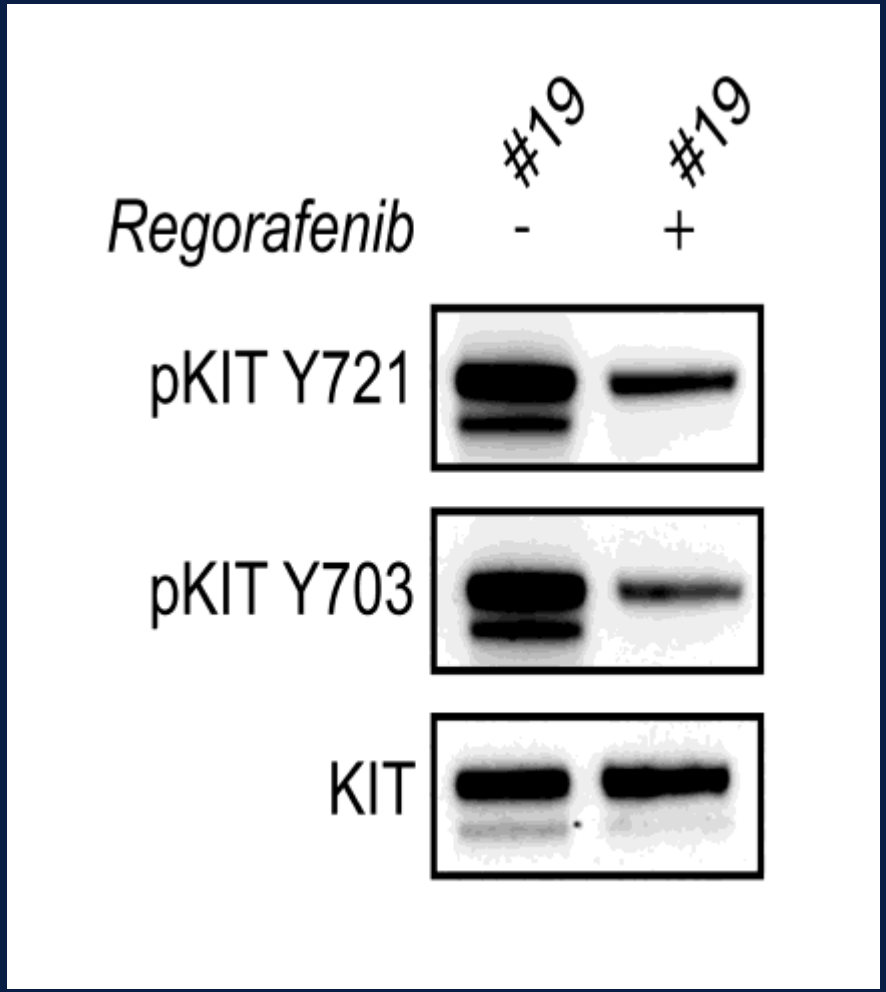
Objective response	N=33 n (%)
PR	3 (9)
SD	
≥16 weeks	21 (64)
<16 weeks	6 (18)
PD	2 (6)
Not evaluable	1 (3)

Clinical Benefit
n = 24 (73%)
95% CI: 55%-87%

George *et al. J Clin Oncol* 2012

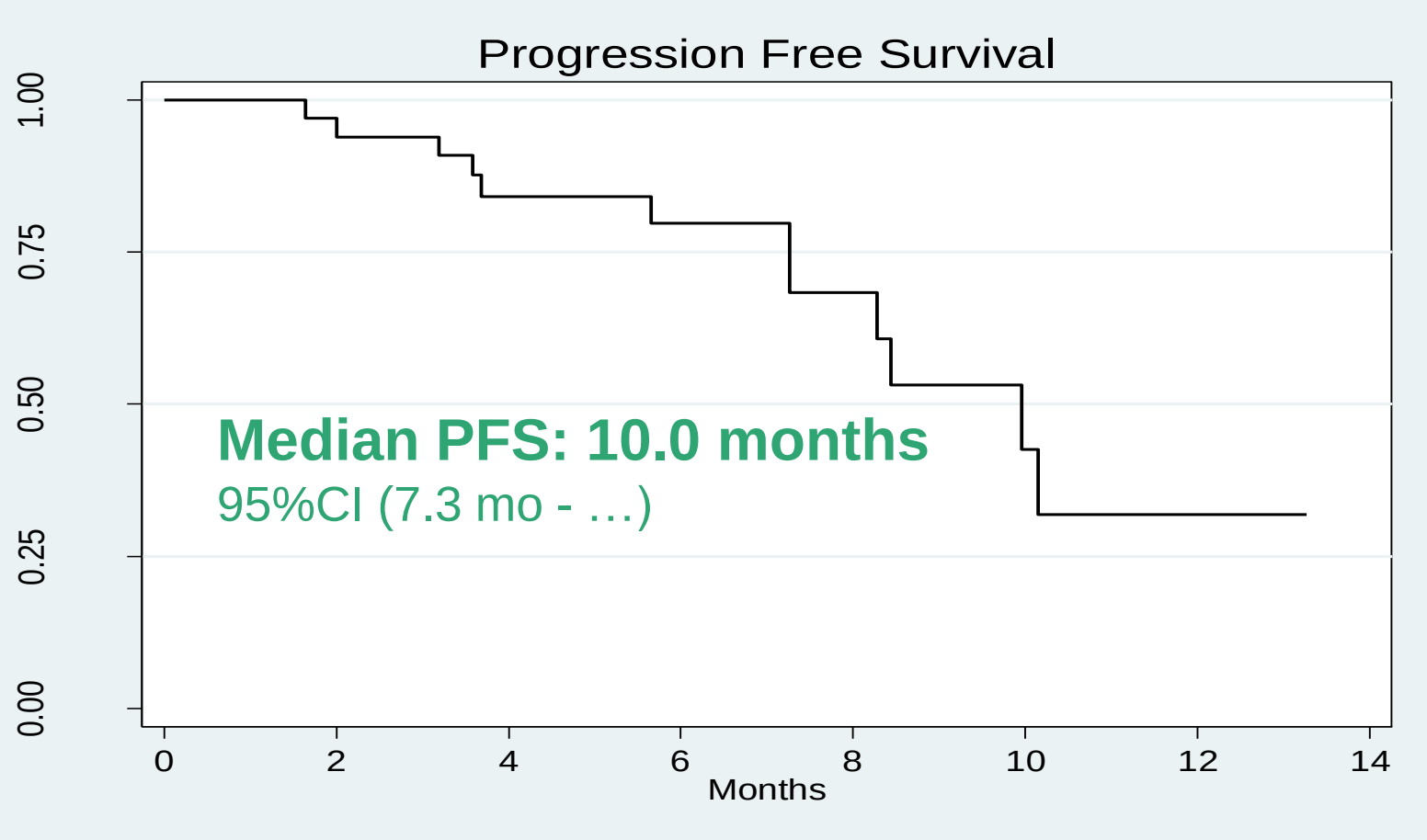
Regorafanib in GIST following failure of IM and SU: Significant target inhibition of KIT phosphorylation

- Pre- and post-treatment tumor biopsies in a patient with baseline KIT exon 11 mutation and secondary resistance mutation in KIT exon 17 (D820V)
- Significant inhibition of KIT phosphorylation
- No significant change in total KIT



George *et al. J Clin Oncol* 2012

Regorafenib in GIST following failure of IM and SU: Progression-free survival



George *et al. J Clin Oncol* 2012

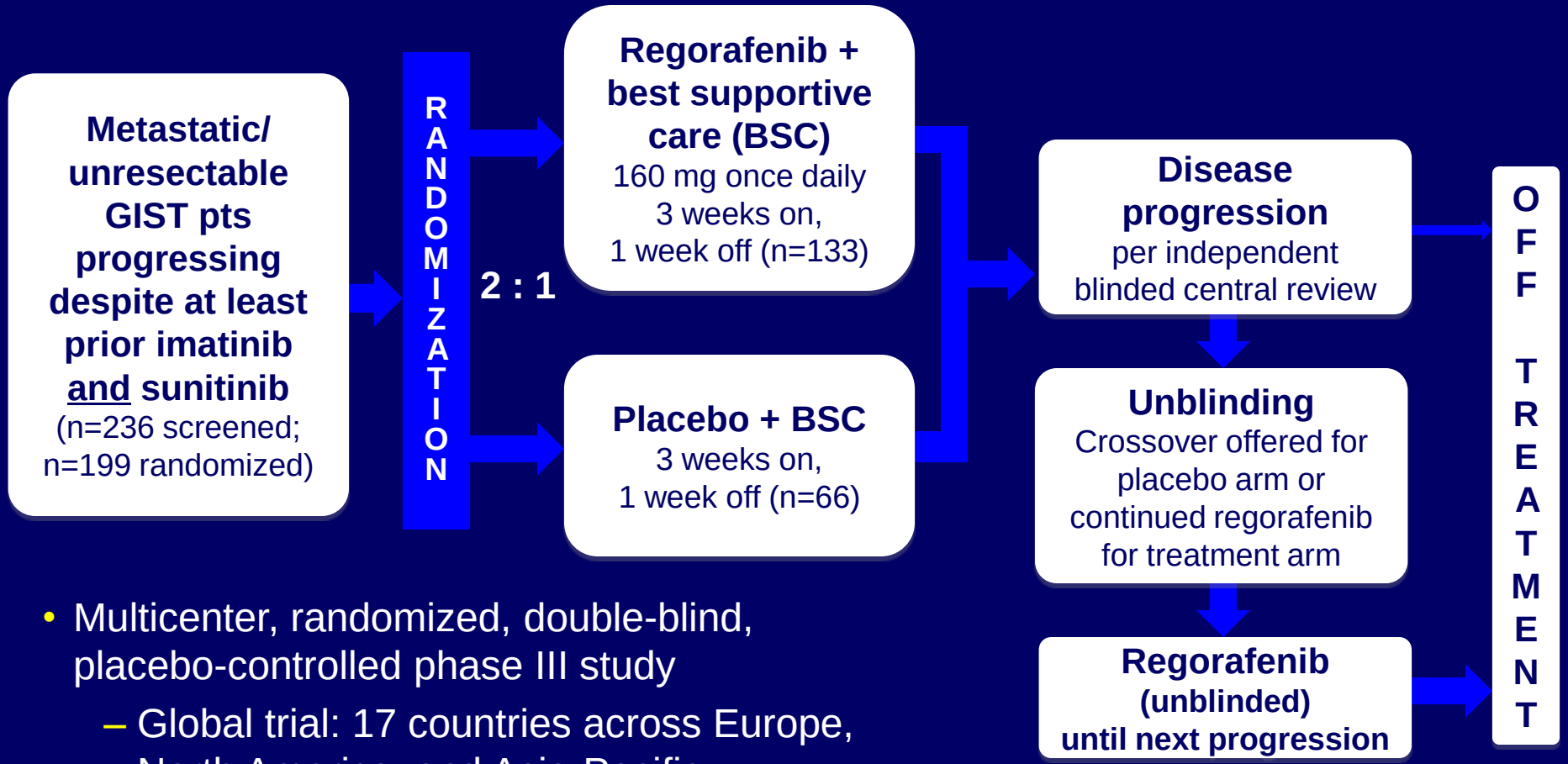
Randomized Phase III Trial of Regorafenib in Patients (pts) with Metastatic and/or Unresectable Gastrointestinal Stromal Tumor (GIST) Progressing Despite Prior Treatment with at least Imatinib (IM) and Sunitinib (SU): The GRID Trial

GD Demetri, P Reichardt, Y-K Kang, J-Y Blay, H Joensuu, RG Maki, P Rutkowski, P Hohenberger, H Gelderblom, MG Leahy, M von Mehren, P Schöffski, ME Blackstein, A Le Cesne, G Badalamenti, J-M Xu, T Nishida, D Laurent, I Kuss, and PG Casali, on behalf of GRID Investigators

Ludwig Center at Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; HELIOS Klinikum,Bad Saarow, Germany; Asan Medical Center, Seoul, South Korea; Centre Léon Bérard, Lyon, France; Helsinki University Central Hospital, Helsinki, Finland; Mount Sinai School of Medicine,New York, NY, USA; Maria Sklodowska-Curie Memorial Cancer Center, Warsaw, Poland; Mannheim University Medical Center, Mannheim, Germany; Leiden University Medical Center, Leiden, Netherlands;Christie NHS Foundation Trust, Manchester, UK; Fox Chase Cancer Center, Philadelphia,PA, USA; Universitaire Ziekenhuis Gasthuisberg, Leuven, Belgium; Mount Sinai Hospital, Toronto, Canada; Institut Gustave Roussy, Villejuif, France; University of Palermo, Italy; Affiliated Hospital of Academy Military Medical Sciences, Beijing, China; Department of Surgery, Osaka Police Hospital, Osaka, Japan; Bayer HealthCare Pharmaceuticals, Berlin, Germany; Istituto Nazionale dei Tumori, Milan, Italy

PRESENTED AT: ASCO Annual '12 Meeting

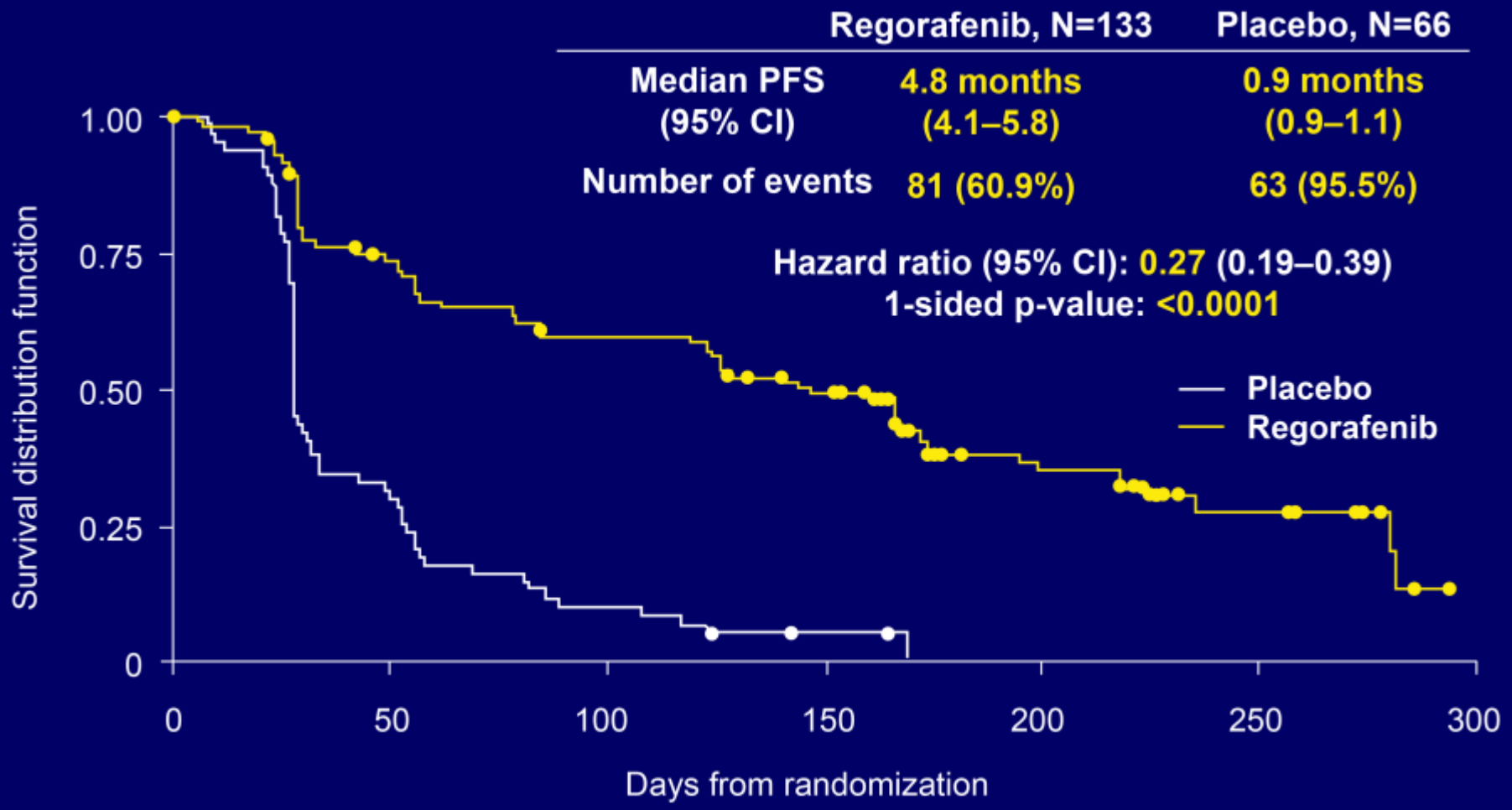
GIST – Regorafenib In Progressive Disease (GRID): Study Design



- Multicenter, randomized, double-blind, placebo-controlled phase III study
  - Global trial: 17 countries across Europe, North America, and Asia-Pacific
  - Stratification: treatment line (2 *vs* >2 prior lines), geographical location (Asia *vs* "Rest of World")

Demetri ASCO 2012

GRID Study: Progression-Free Survival (primary endpoint per blinded central review)



Regorafenib significantly improved PFS *vs* placebo (p<0.0001); primary endpoint met

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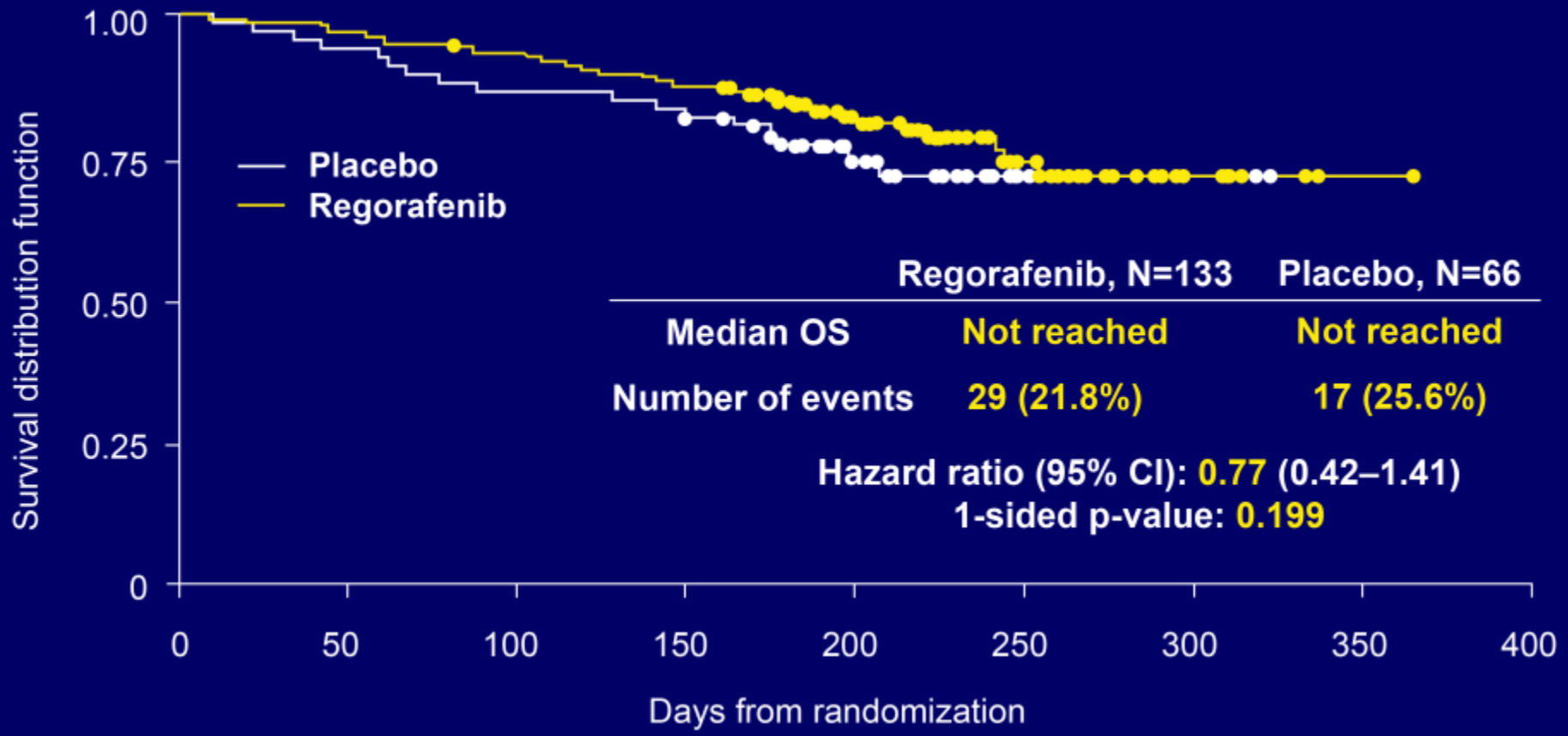
GRID Study: Overall Survival
(following 85% cross-over of patients on placebo arm)



Because of the crossover design, lack of statistical significance between regorafenib and placebo was not unexpected

Demetri ASCO 2012

Disease Control and Overall Response Rates

	Regorafenib (N=133) n (%)	Placebo (N=66) n (%)
Disease control rate CR + PR + durable SD (≥12wks)	**70 (52.6)**	**6 (9.1)**
Objective response rate	**6 (4.5)**	**1 (1.5)**
Complete response	0 (0.0)	0 (0.0)
Partial response	6 (4.5)	1 (1.5)
Stable disease (at any time)	95 (71.4)	22 (33.3)
Progressive disease	28 (21.1)	42 (63.6)

Responses based on modified RECIST v1.1

Regorafenib improved rates of disease control *vs* placebo

Demetri ASCO 2012

Drug-Related Treatment-Emergent Adverse Events in ≥10% of Patients During Double-Blind Treatment

Demetri ASCO 2012

	Regorafenib (N=132), % Median 23 wks exposure				Placebo (N=66), % Median 7 wks exposure			
Grade	All	3	4	5	All	3	4	5
Hand-foot skin reaction	56.1	**19.7**	0	0	15.2	**1.5**	0	0
Hypertension	48.5	**22.7**	0.8	0	16.7	**3.0**	0	0
Diarrhea	40.9	5.3	0	0	7.6	0	0	0
Fatigue	38.6	2.3	0	0	27.3	1.5	0	1.5
Mucositis, oral	37.9	1.5	0	0	9.1	1.5	0	0
Alopecia	23.5	1.5	0	0	3.0	0	0	0
Hoarseness	22.0	0	0	0	4.5	0	0	0

Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Study Treatment

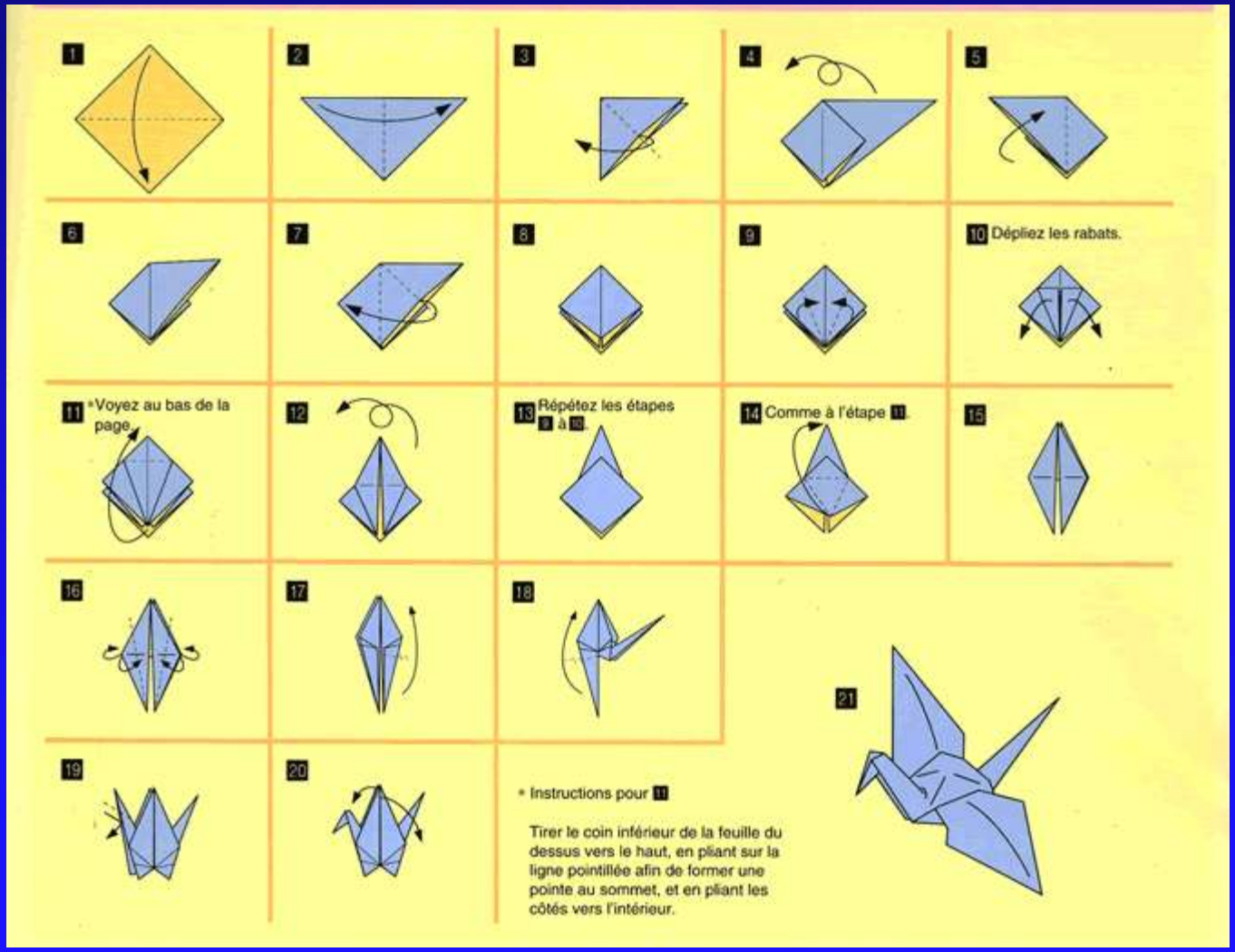
Regorafenib	Placebo
8 (6.1%)	5 (7.6%)

Demetri ASCO 2012

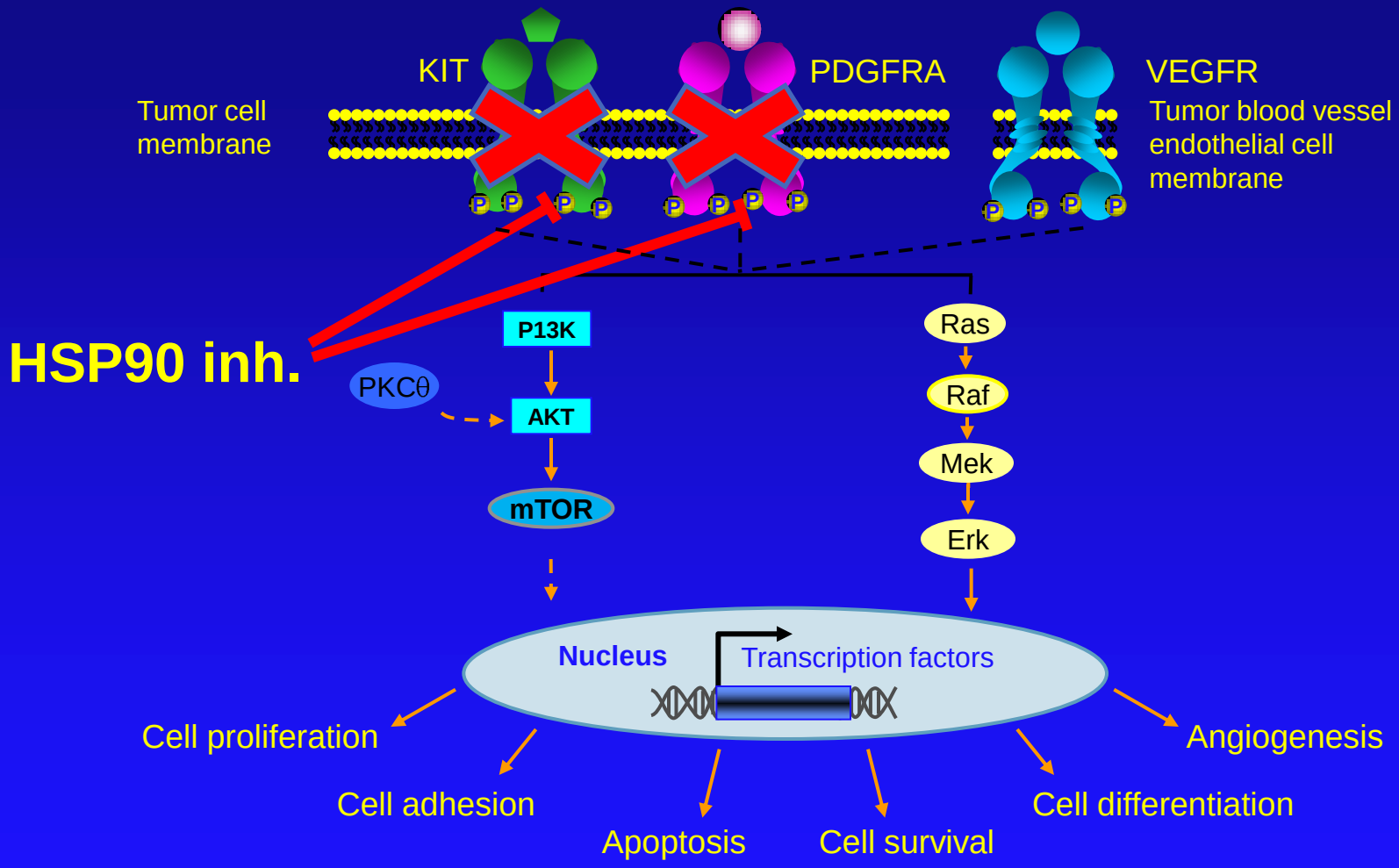
Conclusions and Questions: Regorafenib in GIST

- Novel KIT/VEGFR kinase inhibitor significantly increases PFS compared with placebo in GIST progressing despite prior therapy with at least imatinib and sunitinib
  - **PFS: median 4.8 *vs* 0.9 months, HR 0.27, p<0.0001**
- No new or unexpected safety findings with regorafenib
- Regorafenib has the potential to fulfill an unmet need for advanced GIST patients progressing after imatinib and sunitinib
- Which patients will benefit from regorafenib?
- Can other KIT kinase inhibitors be effective as 4th+ line of therapy?
  - Will other keys fit, or do we need other approaches?

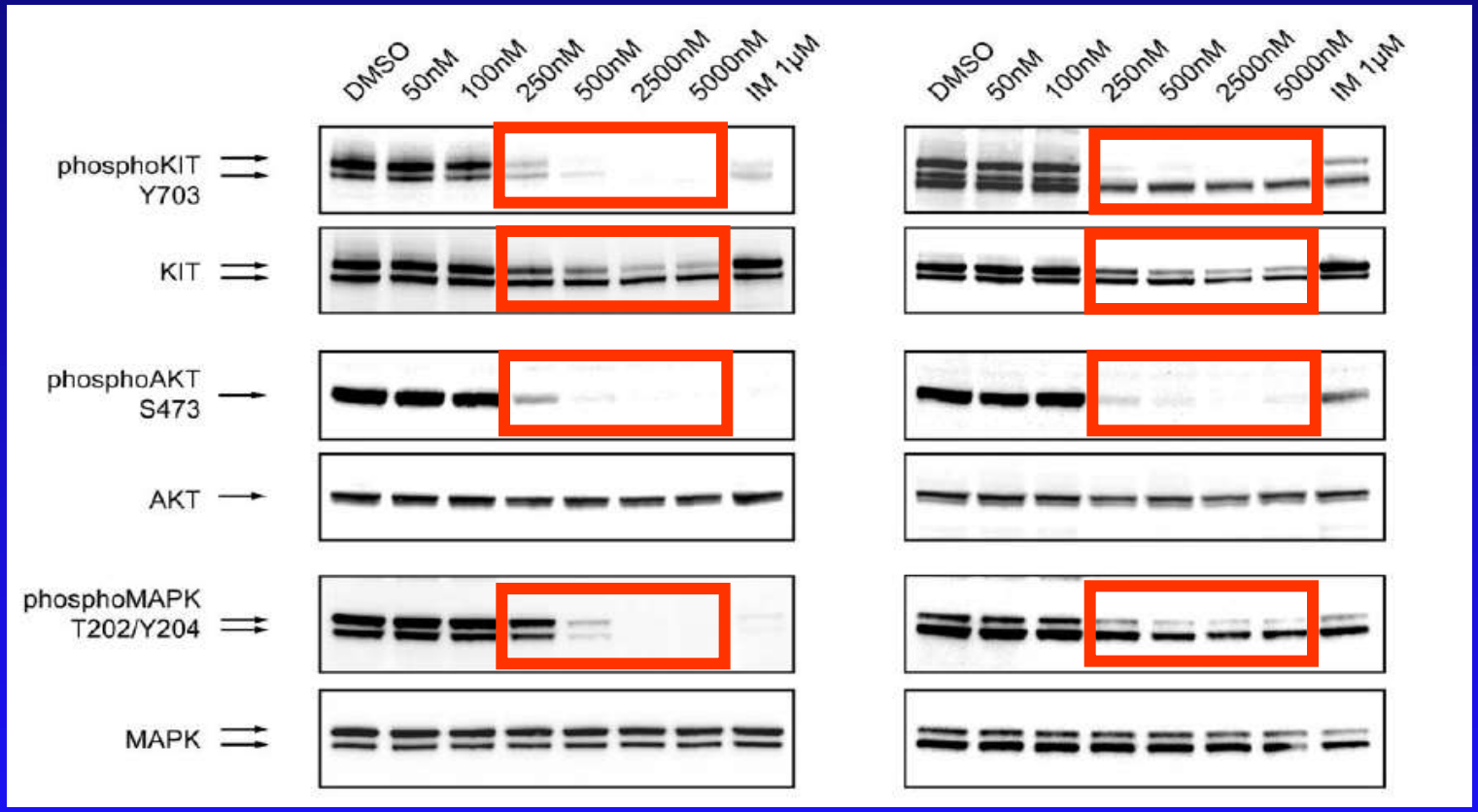
HSP90 helps proteins fold



Other Approaches to Target Specific Molecular Pathways in GIST



Without HSP90, mutated KIT is destroyed



GIST882
Imatinib Sensitive

GIST48
Imatinib Resistant
(secondary mutation)

See also S. Bauer, J. Fletcher, et al. (2006) Cancer Res. 66:9153 (17-AAG)

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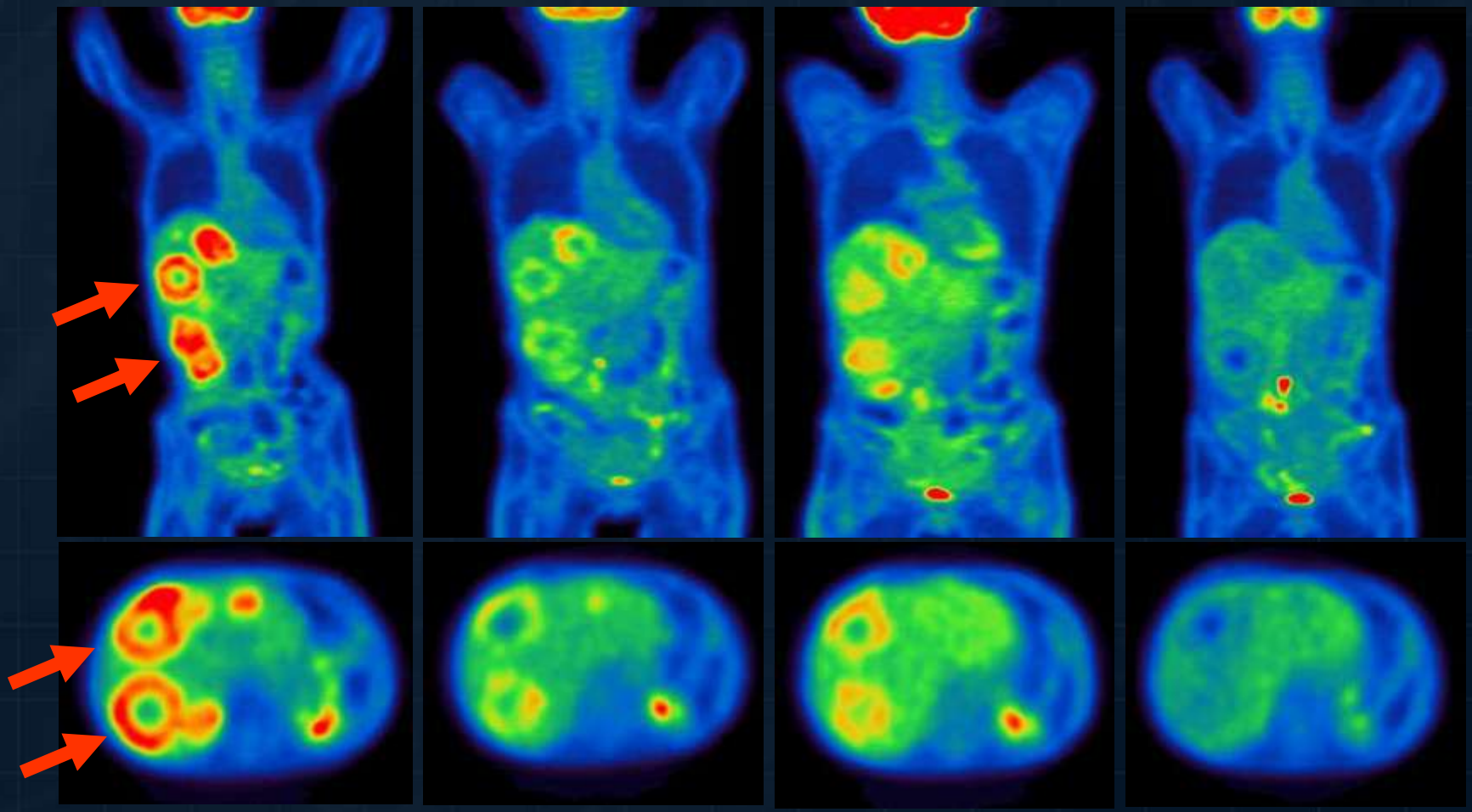
Phase 1 Trial of IPI-504 in Patients with Metastatic GIST Refractory to Tyrosine Kinase Inhibitors



Baseline

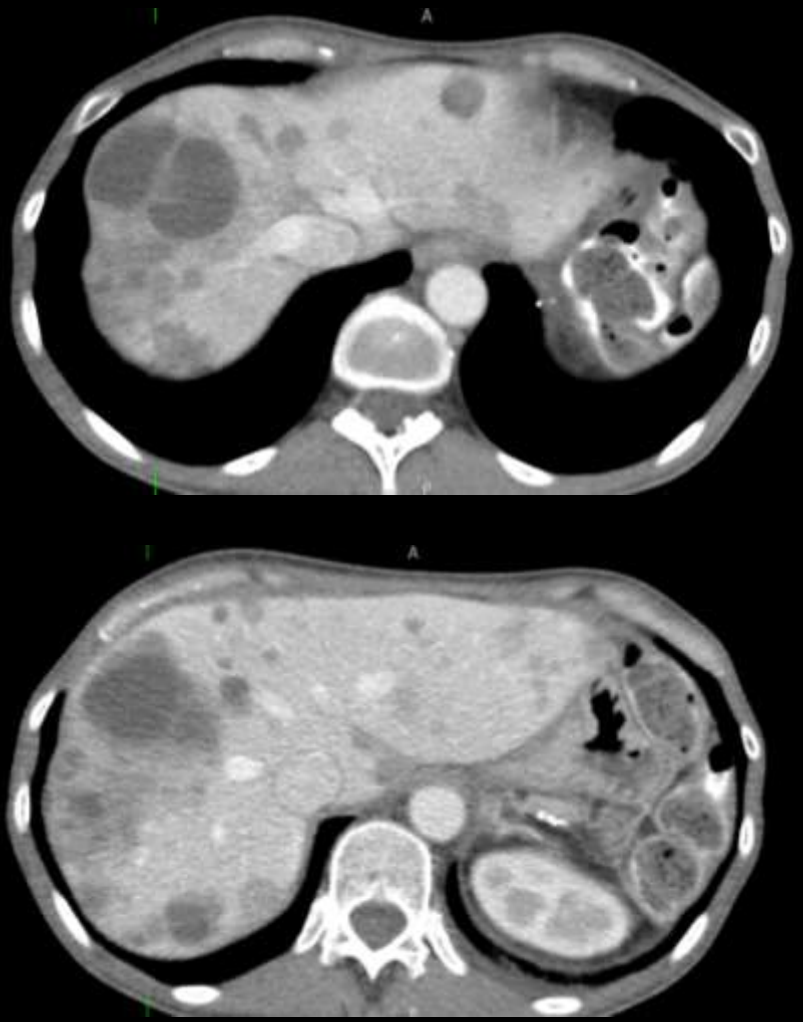
Cycle 1, Day 11
72 hours post
3rd dose of IPI-504

Cycle 1, Day 21
After 10 days
off IPI-504

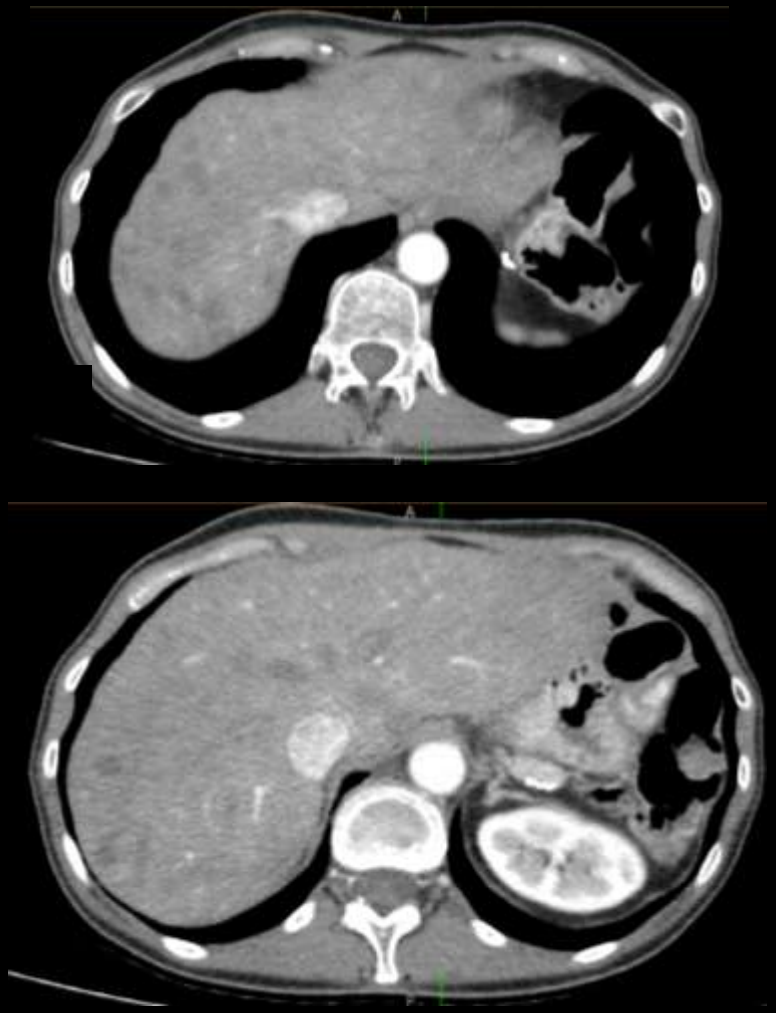
Cycle 3, Day 12
After IPI-504
dosing resumed

Metastatic GIST responding to Hsp90 Inhibitor in Phase 1 Study

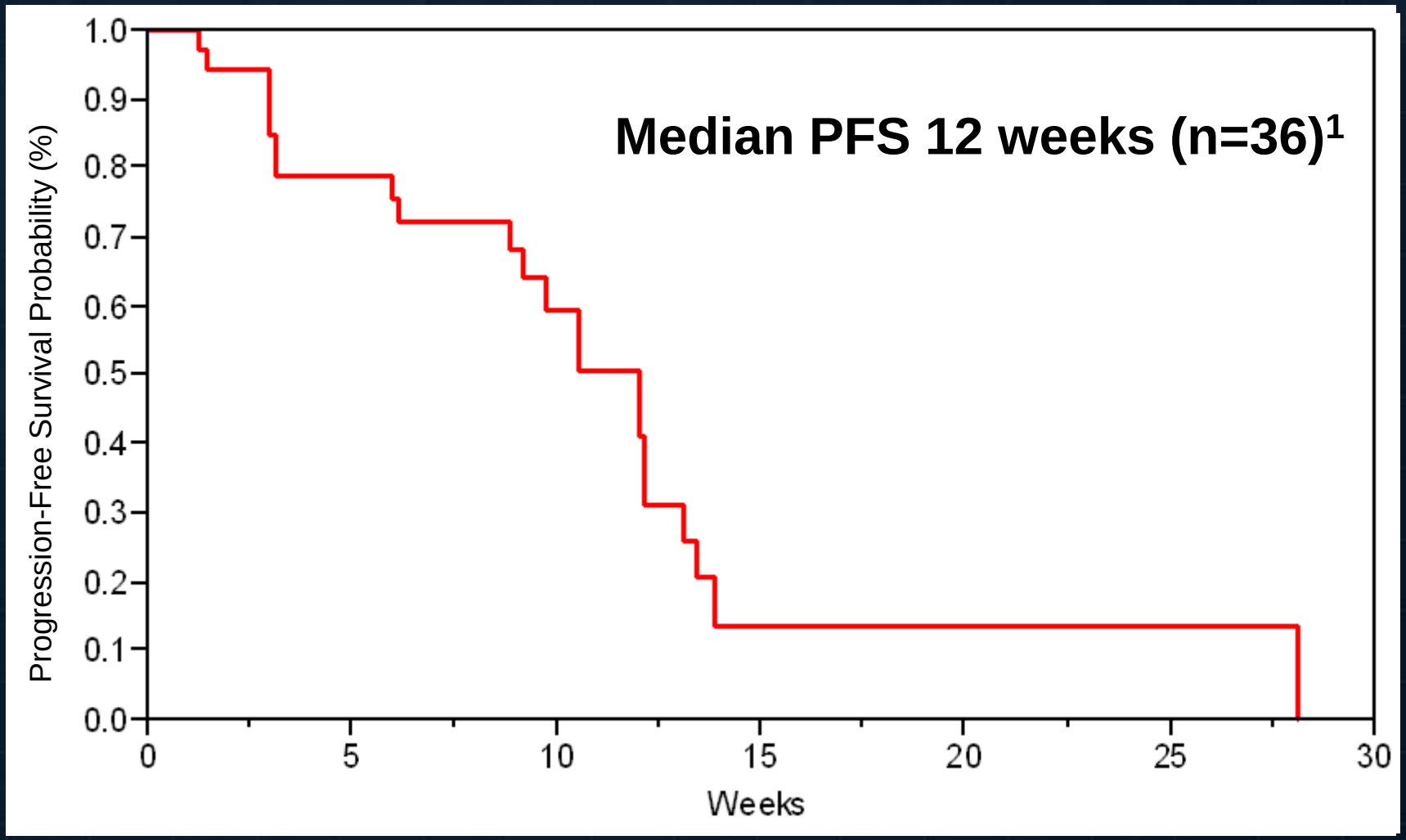
Baseline



Cycle 3



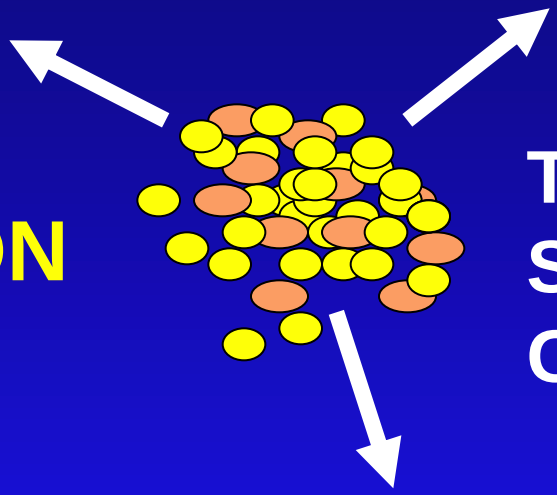
Progression Free Survival in GIST



Phase III Study of IPI-504 in GIST (RING Study)

- IPI-504 or placebo, 400 mg IV twice weekly, 2 weeks on/1 week off
- Stopped early because of 4 cases of death from liver failure in the treatment group
- Studies with other HSP90 inhibitors are ongoing
- HDAC inhibitors also likely work through HSP90

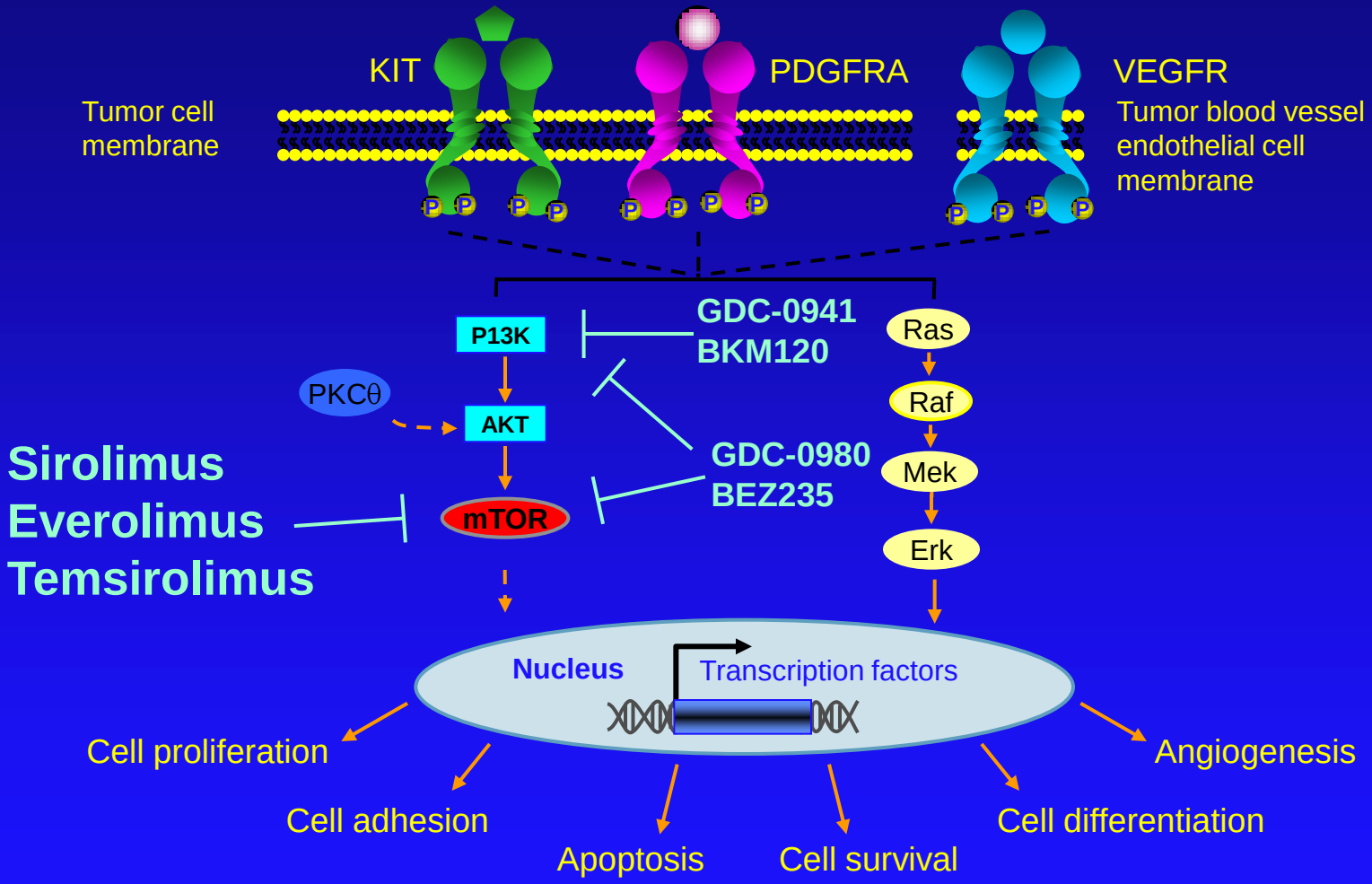
If the switch is stuck on, unscrew the lightbulb



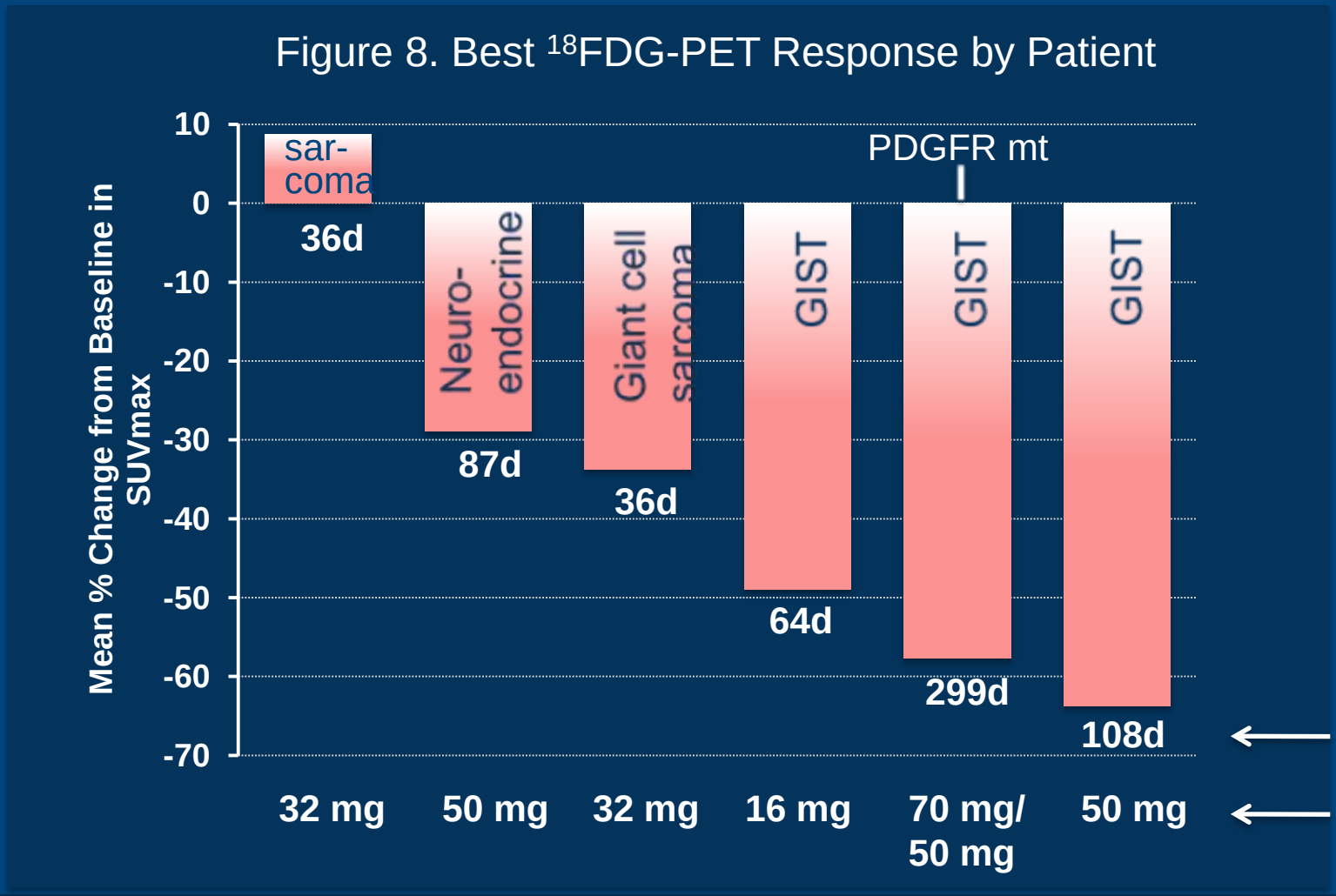
Tumor Cell Survival and Growth

DANA-FARBER CANCER INSTITUTE

Other Approaches to Target Specific Molecular Pathways in GIST



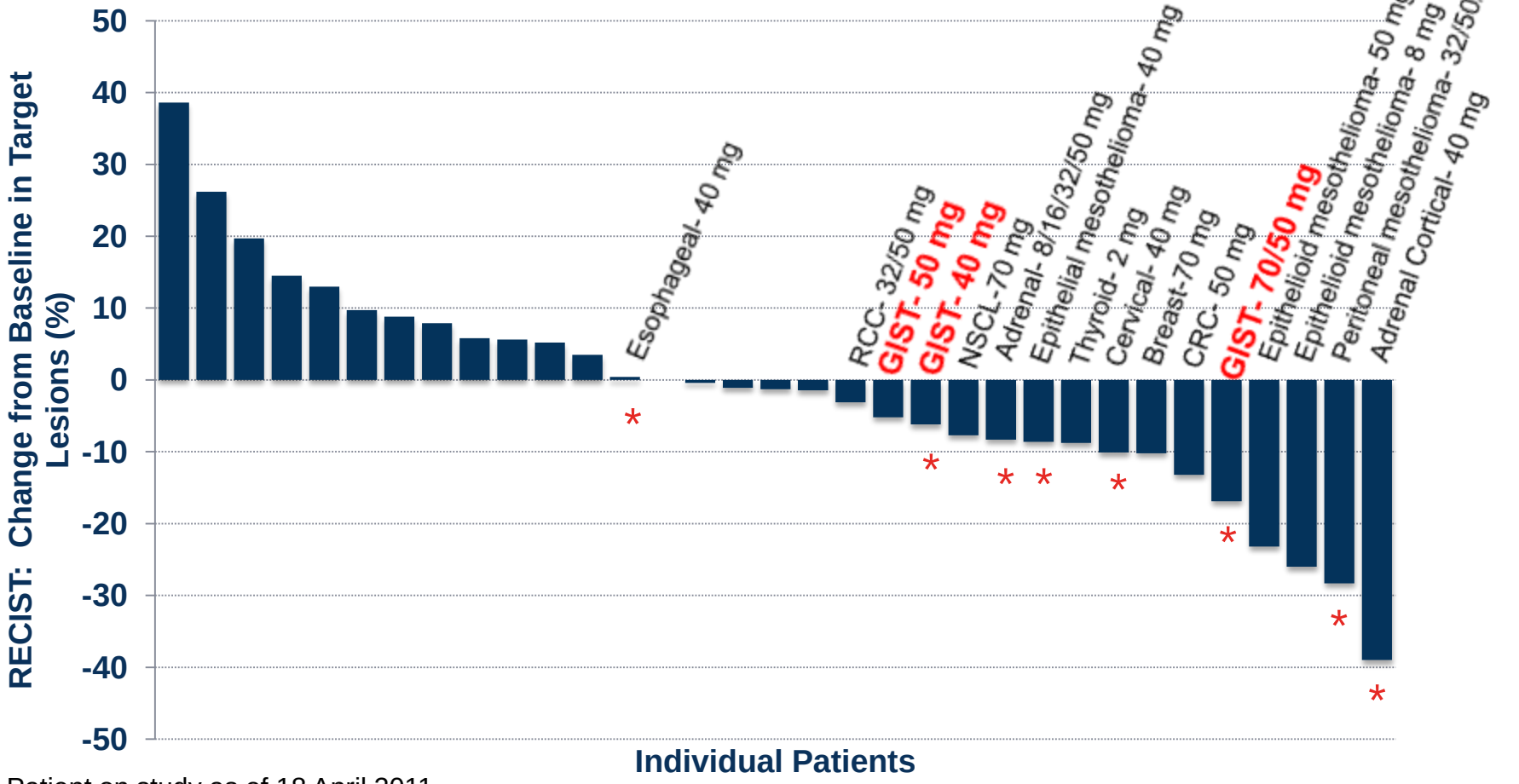
Phase I Study of PI3K/mTOR Inhibitor



Wagner et al. ASCO 2011

Phase I Study of PI3K/mTOR Inhibitor

Figure 9. Best RECIST Response by Evaluable Patient



* Patient on study as of 18 April 2011

Wagner et al. ASCO 2011

What about combining drugs? Is it safe? Does it work?

- Imatinib + mTOR inhibitor
  - Schoffski, Hohenberger
- Imatinib + HDAC inhibitor
  - Bauer – too toxic
- Imatinib + HSP90 inhibitor
  - Ongoing
- Imatinib + PI3K inhibitor
  - Ongoing

What about PDGFR mutant GIST?

- Imatinib is ineffective against D842V mutation
- Responses seen with HSP90 inhibitors
- Studies ongoing of crenolanib (PDGFR kinase inhibitor) and IMC-3G3 (anti-PDGFR antibody)
  - Results are not yet available

SDH-Deficient GIST ("pediatric-GIST") and VEGFR inhibitors

- Accumulation of succinate in cells leads to stabilization of HIF1a
- HIF1a turns on other genes such as VEGF

- Some activity reported with sunitinib and observed with regorafenib and pazopanib in patients with SDH-deficient GIST

SDH-Deficient GIST ("pediatric-GIST") and IGF1R inhibitors

- Insulin-like Growth Factor Receptor (IGF1R) is expressed in "wild-type" GIST
- Role of IGF1R signaling in GIST is not yet established
- IGF1R inhibitor study is opening for wt GIST

- Recent papers have shown that IGF1R is only expressed in SDH-deficient GIST

Pipeline Summary

- Other kinase inhibitors
  - Regorafenib now available in “expanded access”, hopefully will be approved soon
  - Pazopanib study ongoing
  - Masitinib studies ongoing
- Combination studies for safety and efficacy
  - Imatinib + HSP90 inhibitor
  - Imatinib + PI3K inhibitor
- Studies for specific subtypes
  - PDGFR inhibitors/IGF1R inhibitor

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