Therapy for metastatic GIST in 2012

Robert G. Maki, MD PhD
Professor of Medicine and Pediatrics
Tisch Cancer Institute
Mount Sinai School of Medicine
New York, NY

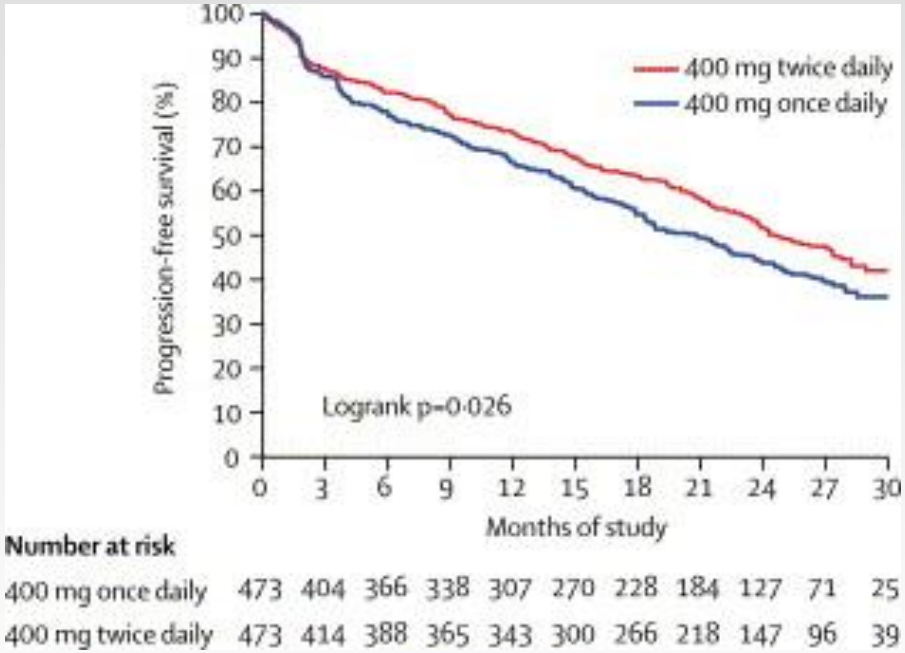
Imatinib & GIST: perfect together

- Lab data showed imatinib is active
- Single patient and Phase I activity
- Phase II study: >50% response rate
- Phase III studies:
  - Europe/Australia: n>900
  - U.S.: n>700
- FDA, EMA, and other regulators approved Rx
- Adjuvant studies
  - 0 vs 1 year
  - 1 year vs 3 years

First line metastatic disease

European data: 400 vs 800 mg

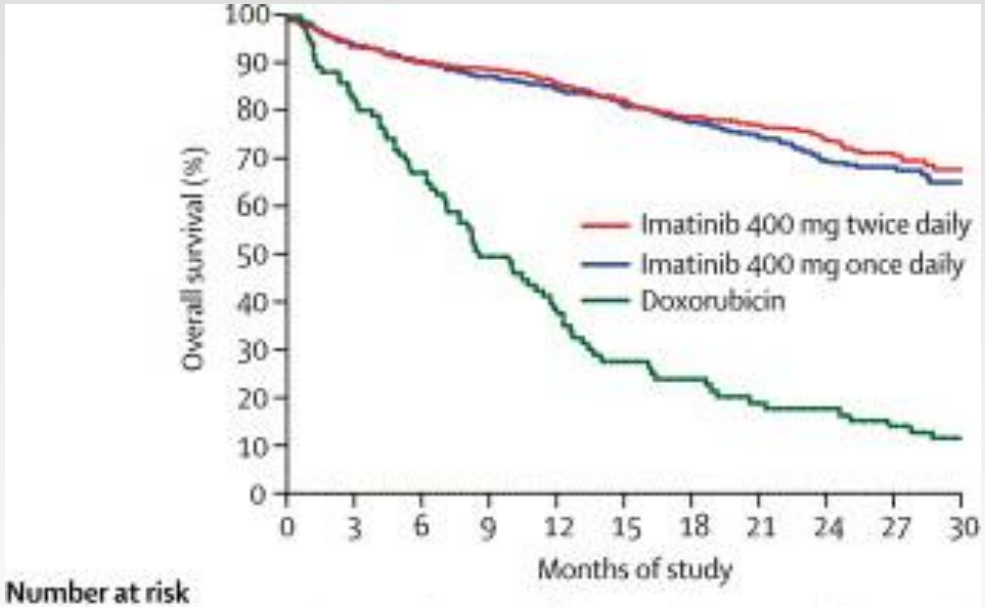
Progression-free Survival



Number at risk											
400 mg once daily	473	404	366	338	307	270	228	184	127	71	25
400 mg twice daily	473	414	388	365	343	300	266	218	147	96	39

946 allocated patients

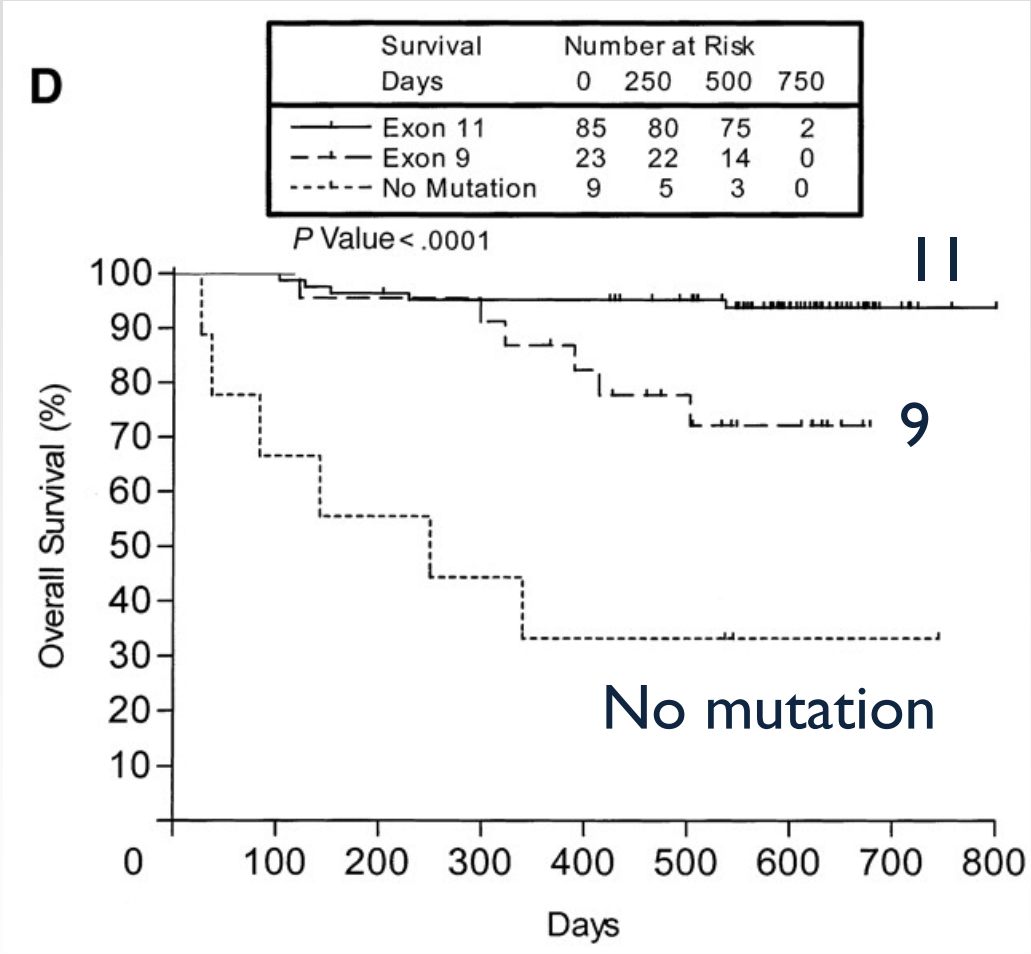
Overall Survival



Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Verweij J et al. Lancet 2004; 364:1127

KIT genotype predicts survival for patients with metastatic GIST on imatinib



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

1st line: nilotinib vs imatinib

- 1st line study, just as with CML population
- Nilotinib 800 mg qd vs imatinib 400 mg qd
- Study stopped early for inability of nilotinib to be superior to imatinib
- Leaves imatinib as 1st line therapy for GIST, in contrast to CML
- Other contenders: masatinib vs imatinib (phase III); dasatinib (phase II)

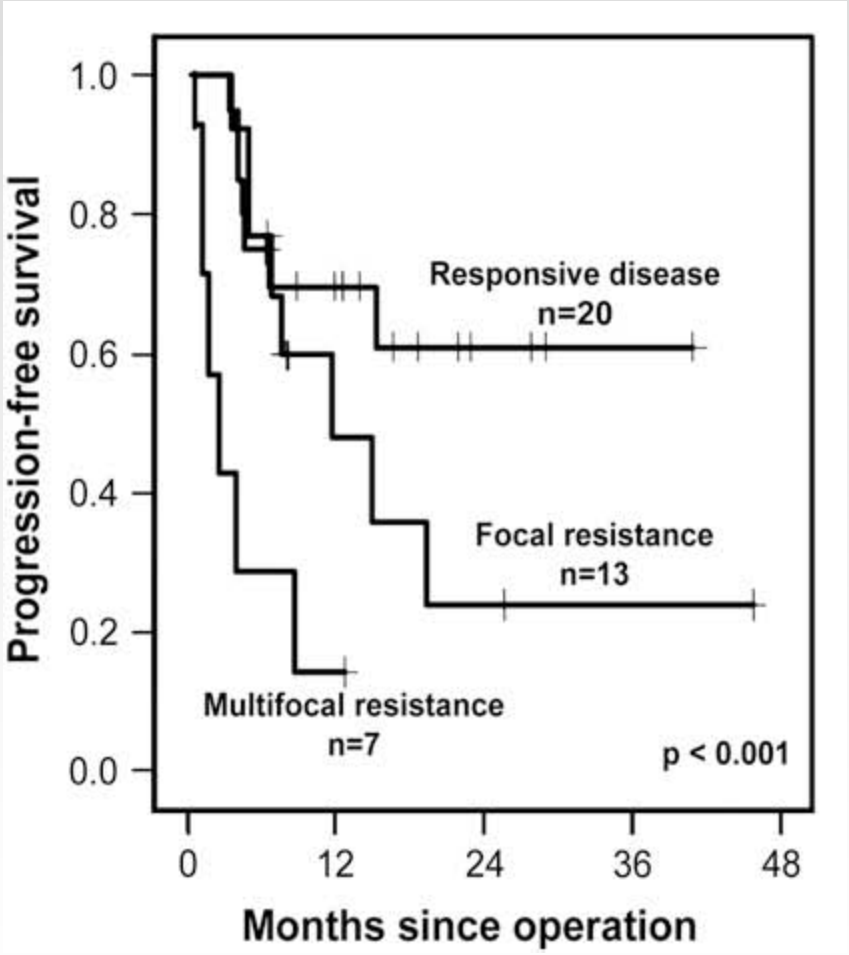
NVS news release 04/11/11

Second line metastatic disease

Imatinib resistance: what then?

- Standard of care: starting dose 400 mg PO daily
  - Some argue to use 400 mg BID if exon 9 *KIT* mutation
- Increase to (up to) 400 mg PO BID upon progression
- Surgery if "limited progression"
- Sunitinib remains 2nd line standard of care

(Active) tumor bulk and TTP

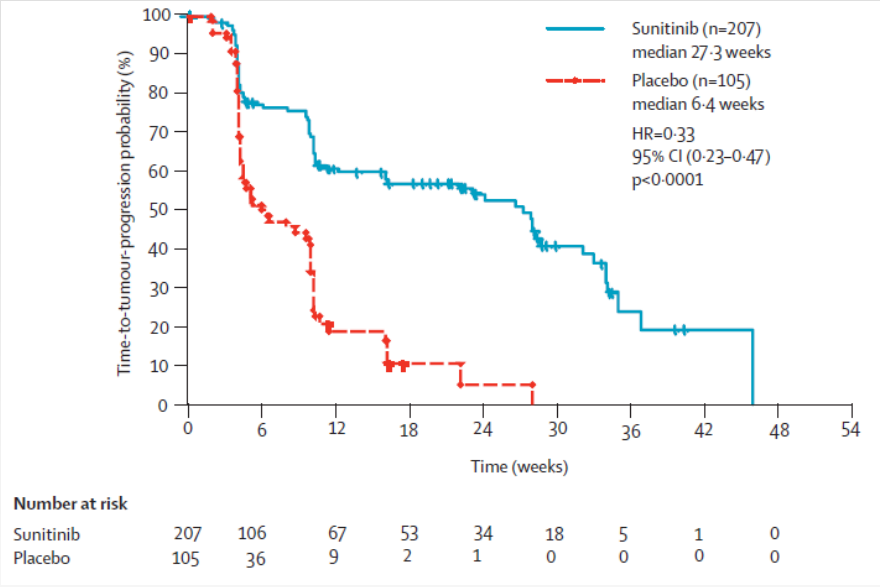


DeMatteo RP et al. Ann Surg 2007;245:347

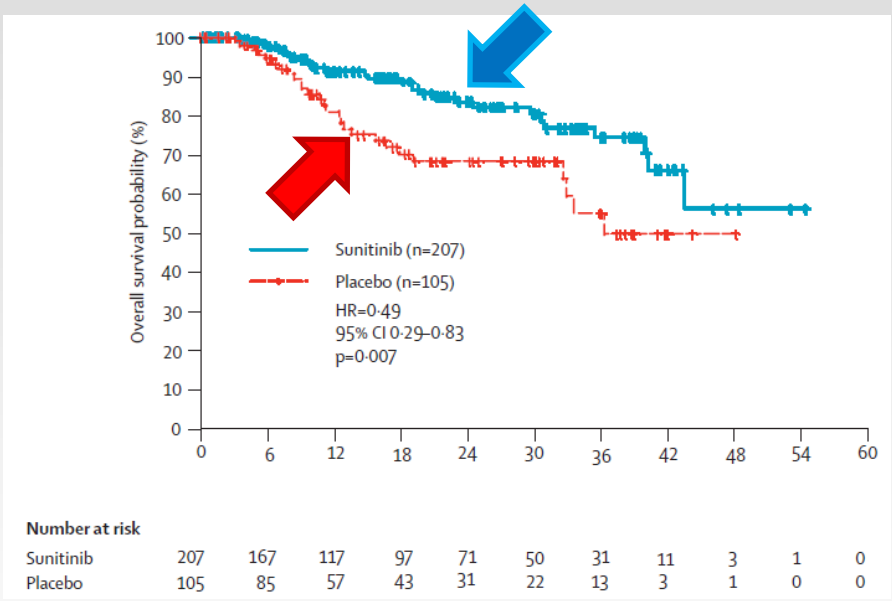
Sunitinib in GIST

- Phase III placebo vs. sunitinib study positive
- FDA approved dose/schedule:
  - 50 mg daily x 28 q 42 days
  - Investigational: 37.5 mg oral daily
- *Not tested* in the imatinib-naïve state

Sunitinib vs placebo phase III



PFS



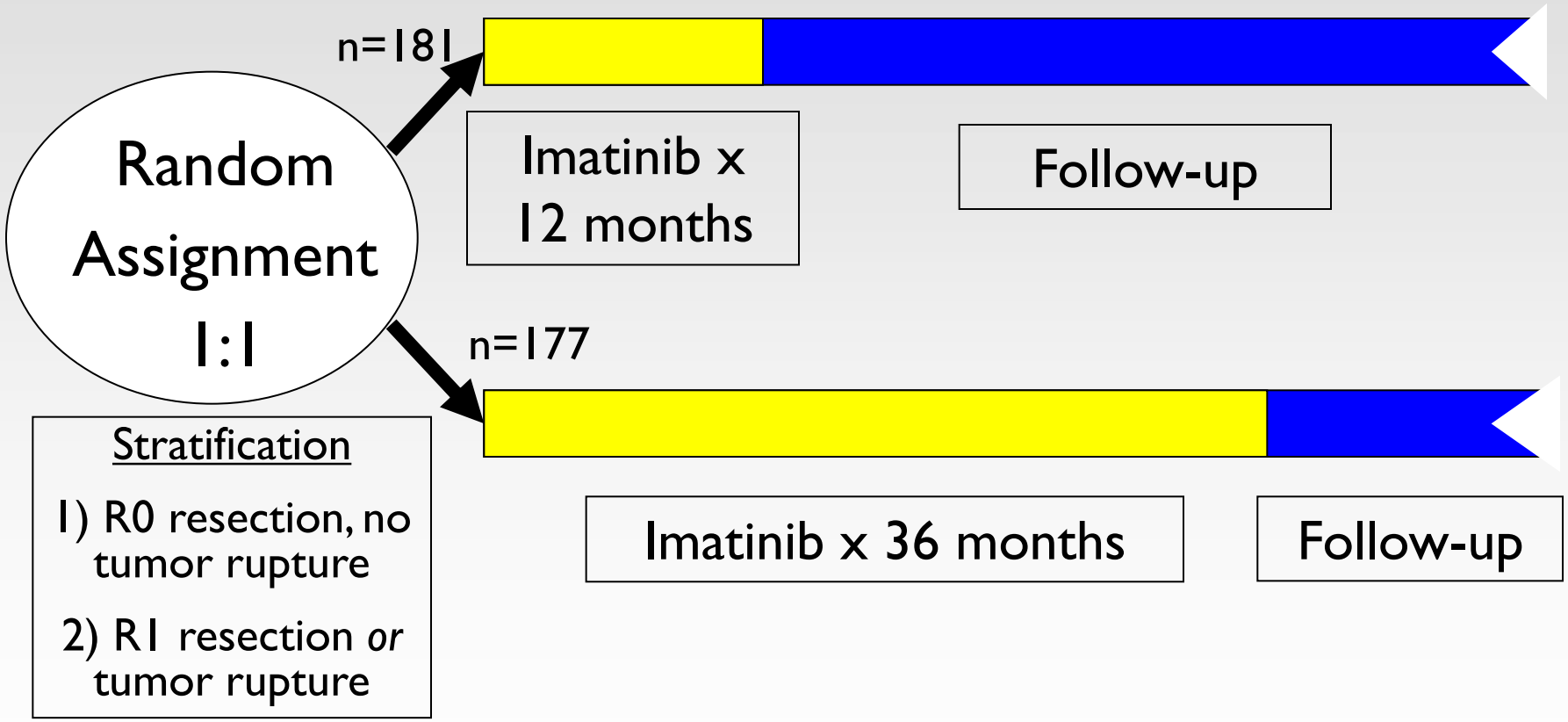
OS

Demetri GD et al. Lancet 2006; 368:1329

Adjuvant therapy

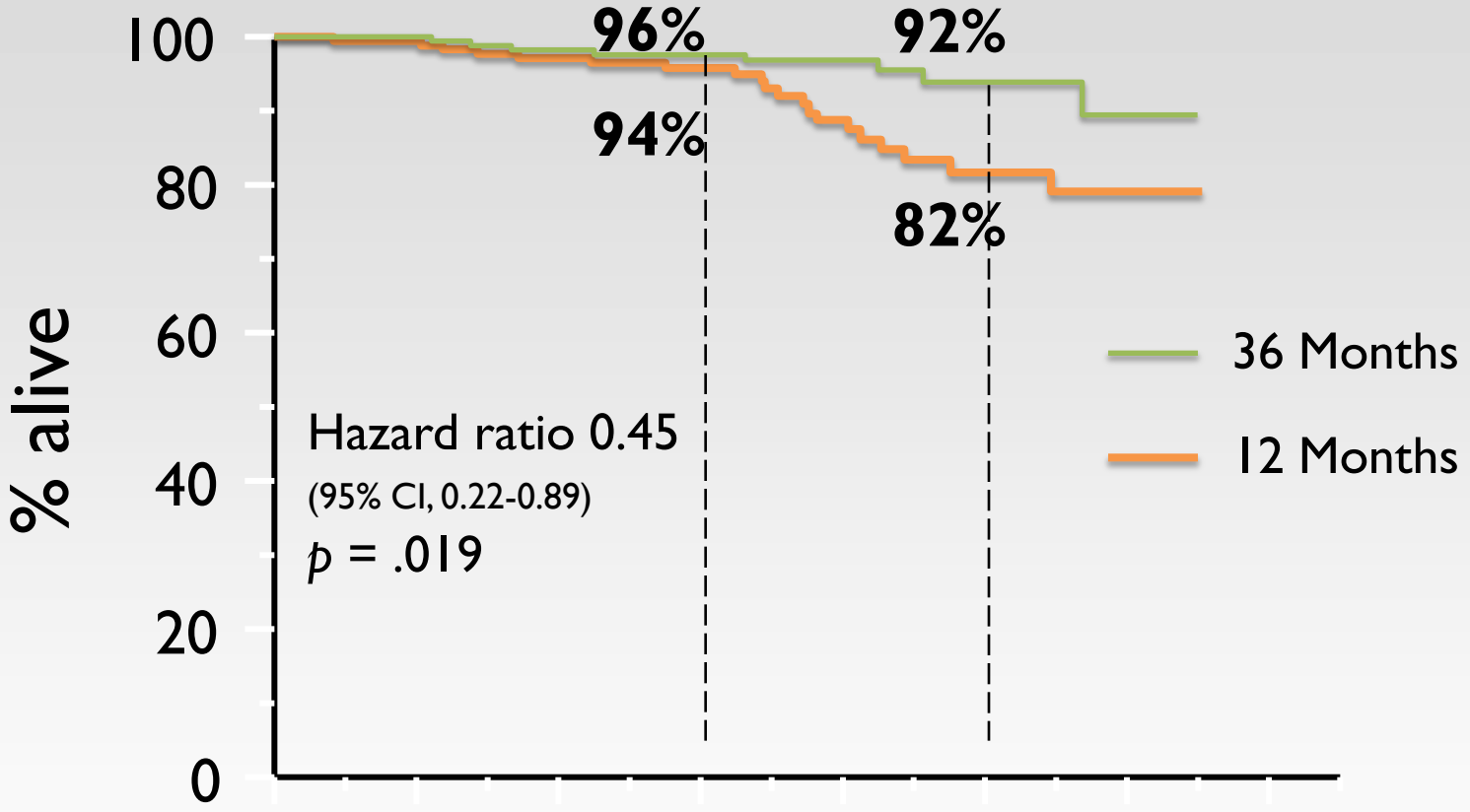
SSG XVIII: study design

An open-label phase III study



Joensuu H et al. JAMA. 2012; 307:1265

SSG XVIII: overall survival (ITT)

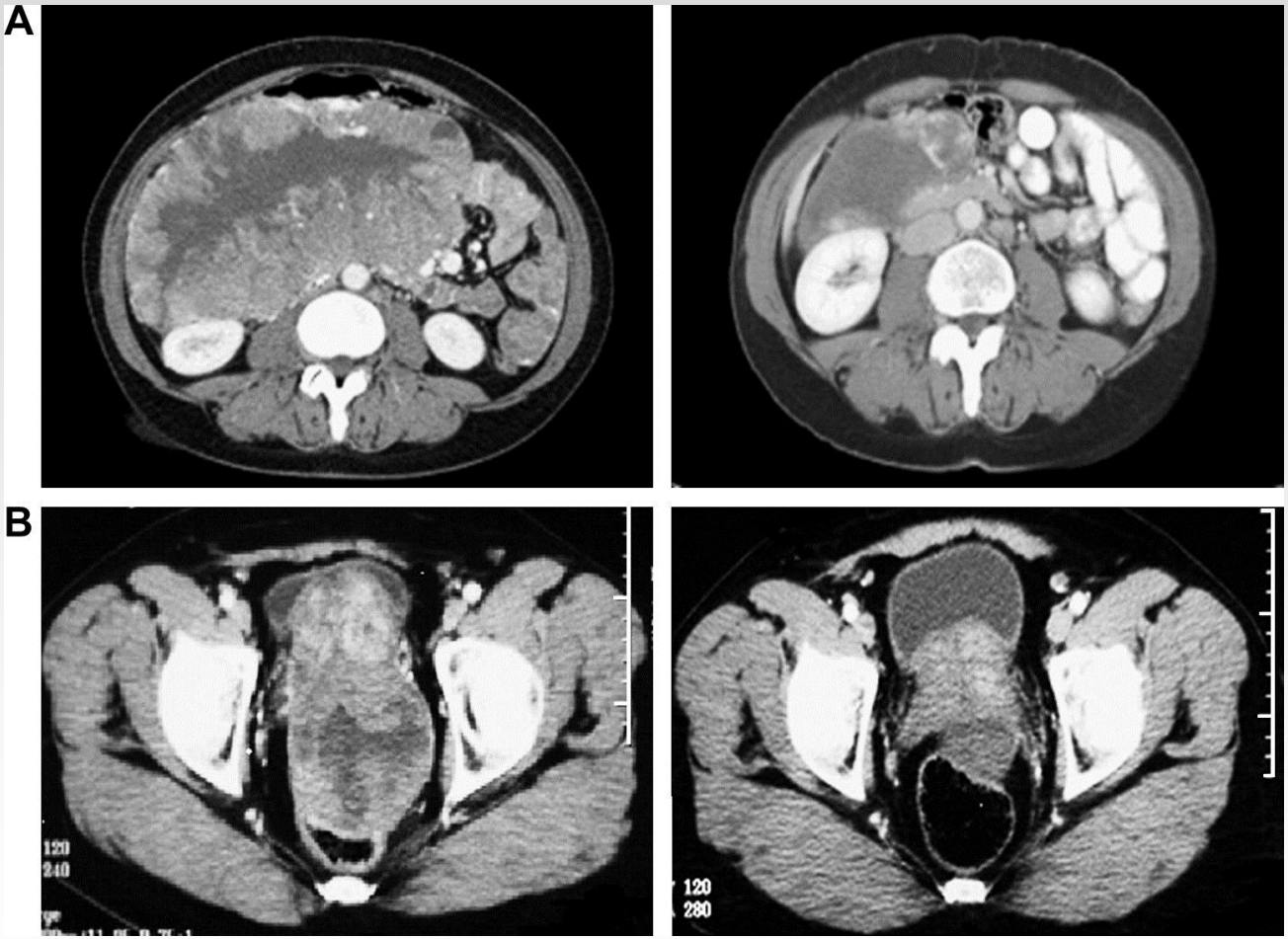


No. at risk (n=397)	0	1	2	3	4	5	6	7	Years
36 Months of imatinib	198	192	184	152	100	56	13	0	
12 Months of imatinib	199	188	176	140	87	46	20	0	

Joensuu H et al. JAMA. 2012; 307:1265

“Unresectable” disease: neoadjuvant therapy

Options for very large GIST



0 +7-15 mo

Rutkowski P et al. J Surg Oncol 2006; 93:304
Fiore M et al. Eur J Surg Oncol 2009; 35: 739

Neoadjuvant imatinib

- Most of these GIST are exon 11 *KIT* mutant
- Neoadjuvant imatinib 400 mg daily
- Resect at time of best response
  - Usually 3-9 months
- *Nearly all patients recur off imatinib*
- Continue treatment for a total of at least 3 years (adjuvant data)…or even longer?

Rutkowski P et al. J Surg Oncol 2006; 93:304
Fiore M et al. Eur J Surg Oncol 2009; 35: 739

Treatment beyond 2nd line metastatic disease: context for regorafenib phase III study (GRID)

Progression on imatinib, sunitininb: now what?

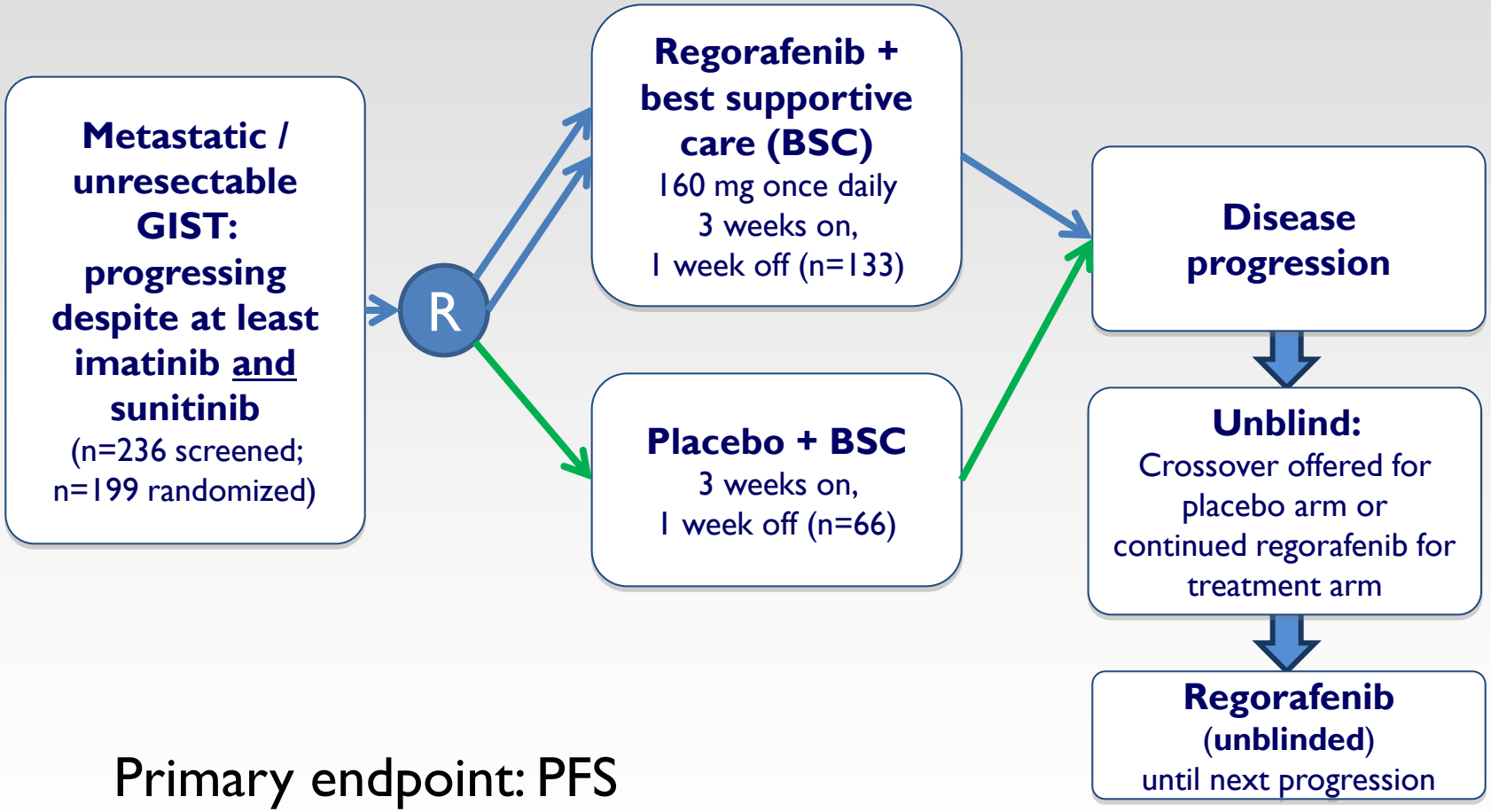
- Another TKI
  - Sorafenib
  - Regorafenib
  - Nilotinib
  - Dasatinib
  - Masatinib
- Add an mTOR inhibitor
- hsp90 or other kinase specific inhibitors
- Imatinib rechallenge

Sorafenib is active in 3rd line

- Randomized phase II discontinuation
  - 2 patients of 25 sarcomas treated (not just GIST) had PRs for ~11 mo
- Phase II U Chicago consortium (n=26)
  - PR 15% (4 PR), SD 67%, PFS 5.7 mo
- European retrospective analysis (n=24)
  - Disease refractory to imatinib, sunitinib, nilotinib
  - PR 21%, SD 42%, PFS 5.0 mo

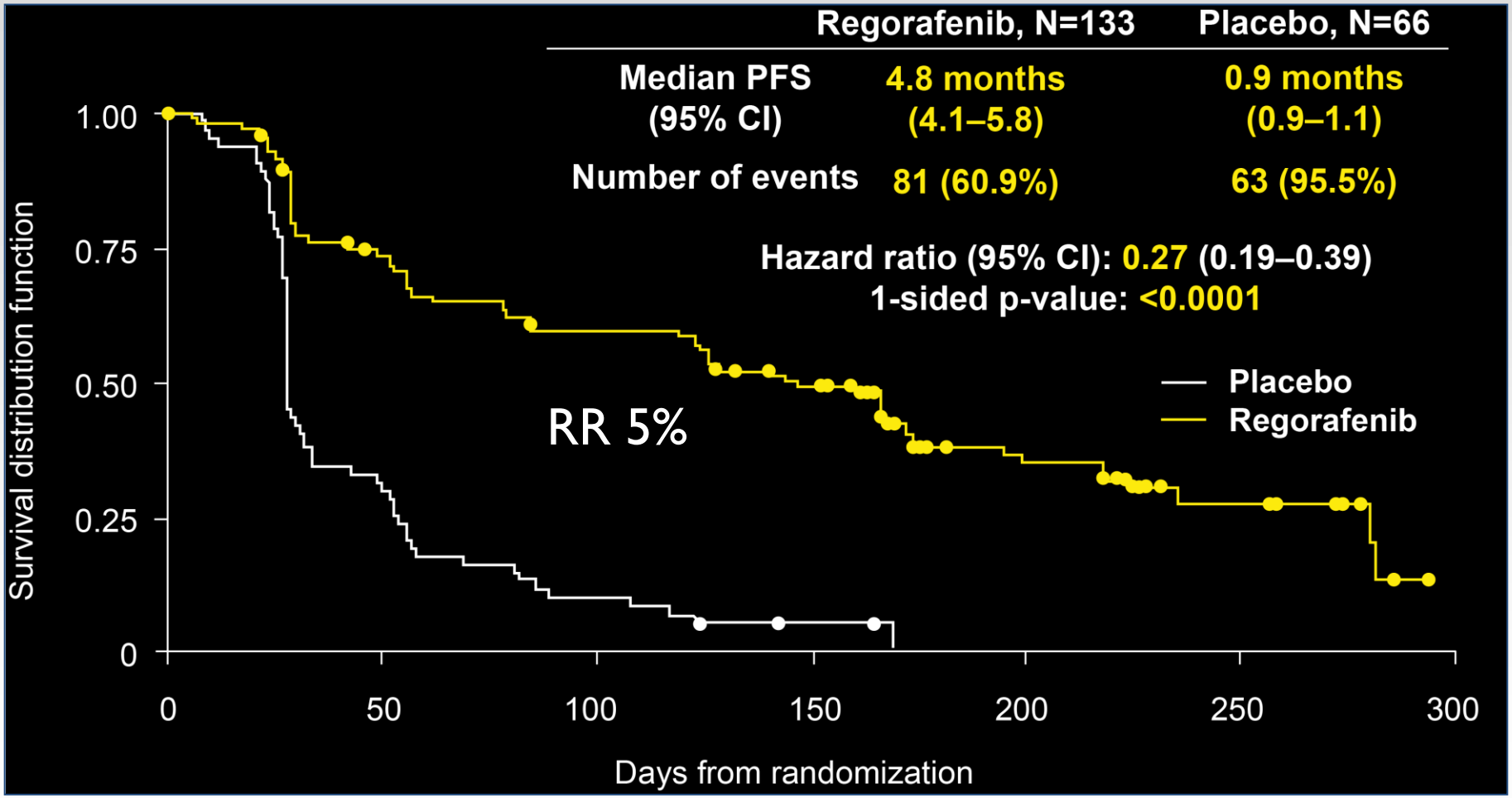
Ratain et al. ASCO 2004; 22: Abstr 4501
Wiebe et al. ASCO 2008; 26: Abstr 10502
Gelderblom GI ASCO 2009; Abstr 51

Regorafenib phase III schema



Primary endpoint: PFS

GRID results



Regorafenib vs sorafenib? Regorafenib vs imatinib rechallenge?

Most frequent drug-related adverse events

	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	**20**	.	.	15	**2**	.	.
Hypertension	49	**23**	1	.	17	**3**	.	.
Diarrhea	41	5	.	.	8	.	.	.
Fatigue	39	2	.	.	27	2	.	.
Mucositis, oral	38	1	.	.	9	2	.	.
Alopecia	23	1	.	.	3	.	.	.
Hoarseness	22	.	.	.	5	.	.	.
Anorexia	21	.	.	.	8	.	.	.
Rash, maculopapular	18	3	.	.	3	.	.	.

6% stopped regorafenib for AE vs **8%** placebo

Toxicity – "comparison across studies" – regorafenib vs sunitinib…

	Regorafenib (n=132), % Median 23 wks exposure				Sunitinib (n=202), % (Median 27 wk TTP)			
Grade	**All**	**3**	**4**	**5**	**All**	**3**	**4**	**5**
Hand-foot skin reaction	56	**20**	.	.	13	**4**	.	.
Hypertension	49	**23**	1	.	11	**3**	.	.
Diarrhea	41	5	.	.	29	3	.	.
Fatigue	39	2	.	.	34	5	.	.
Mucositis, oral	38	1	.	.	40	1	.	.
Alopecia	23	1	.	.	.	.	.	.
Hoarseness	22	.	.	.	.	.	.	.
Anorexia	21	.	.	.	19	.	.	.
Rash, maculopapular	18	3	.	.	13	1	.	.

6% stopped regorafenib for AE vs **9**% sunitinib

Wachet auf!

- **82%** of patients on GIST phase II study needed dose reduction
  - Phase III: ? -- 6% stopped for AE
  - Sorafenib sarcoma phase II: 65% needed dose reduction
- Multitargeted TKIs starting doses appear too high
  - There is a wide therapeutic index for RTK inhibitors
  - Regorafenib: start lower than 160 mg oral daily and taper up

vs.

George S et al. J Clin Oncol 2012; 30:2401

What's new?

hsp90 inhibition

- 17AAG not examined in GIST specifically
- IPI-504 (retispimycin), in phase I-II
  - Phase I: 3% RR, 67% SD rate in phase I, n=36
- Phase III randomized study of IPI-504 v. placebo stopped due to deaths on study
  - KPS worse in phase III vs phase I study?
  - "Washout" from prior to treatment
  - Short half life; low pharmacodynamic AUC?
- BIIB021 oral inhibitor in phase II not spectacular

Bauer S et al. Cancer Res 2006; 66: 9153
Dickson MA et al. Ann Oncol 2012; doi:10.1093/annonc/mds275

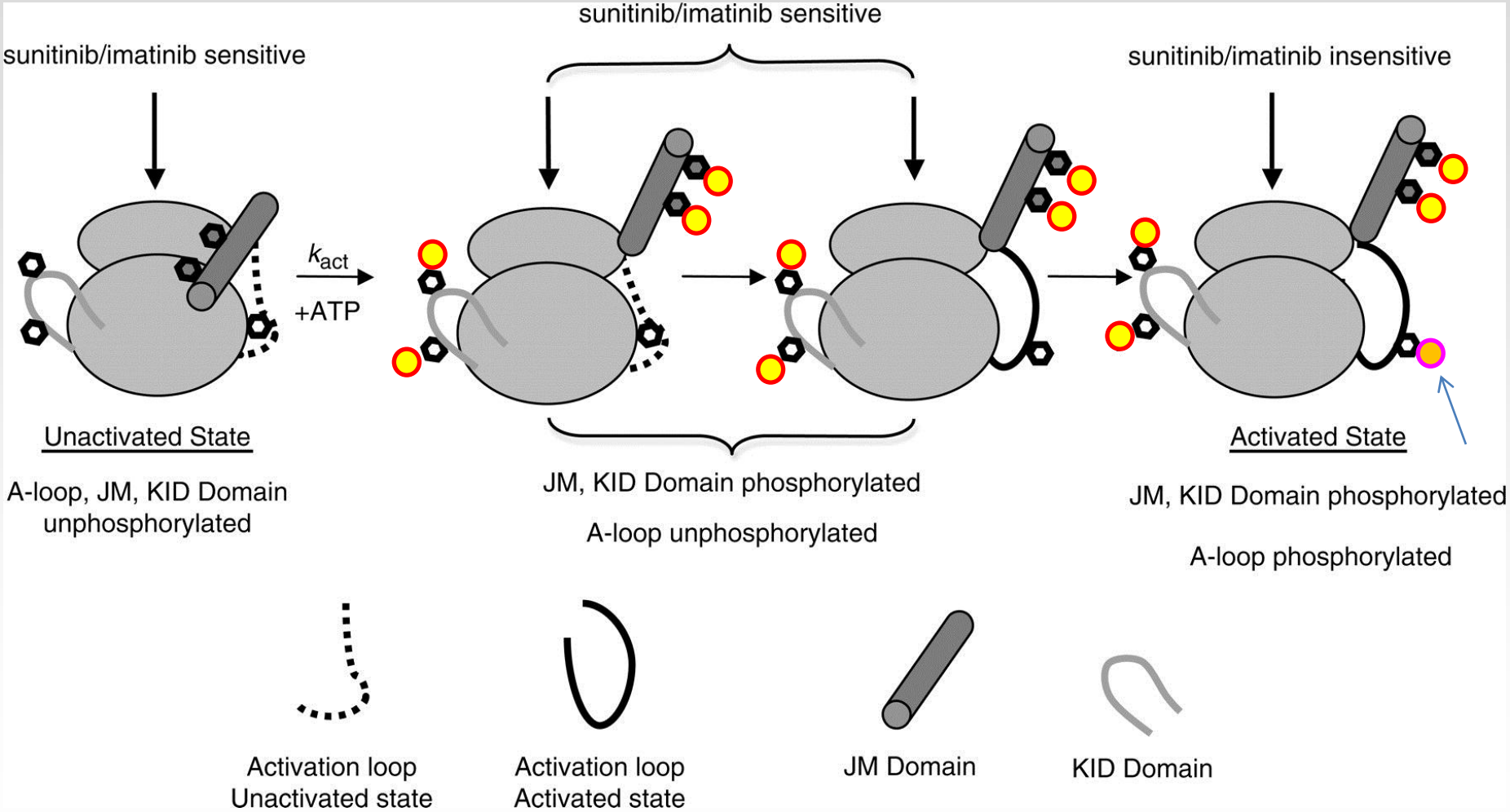
Pending data

- Adjuvant therapy
  - Europe: 0 vs 2 year imatinib adjuvant study
  - Build on prior experience
    - "PERSIST-5"
    - n=100
    - Phase II 5-year adjuvant imatinib for resected intermediate & high-risk GIST
    - Define upper limit of utility of imatinib
- Metastatic disease
  - New agents, combinations
  - PDGFRA D842V specific inhibitor
  - Switch pocket kinase inhibitor

Crenolanib for D842V mutant GIST

- Imatinib, sunitinib, sorafenib largely inactive
- Regorafenib?
- Crenolanib = specific PDGFRA, PDGFRB inhibitor
  - Akin to therapy for V600 BRAF mutant melanoma
- Phase II clinical trial underway
  - Clinicaltrials.gov ID # NCT01243346

Switch pocket kinase inhibitors



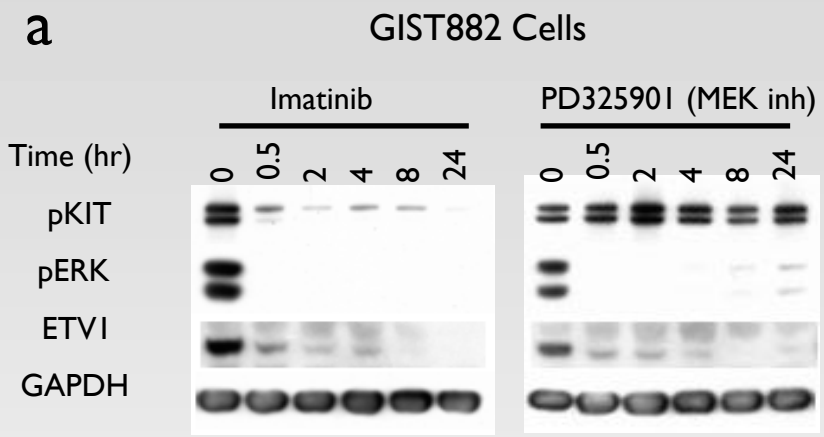
DiNitto JP et al. J Biochem 2010; 147: 601

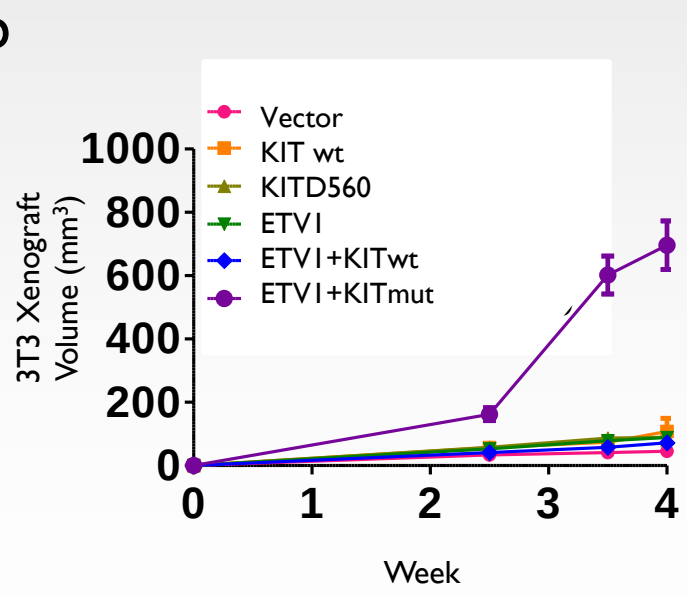
Switch pocket kinase inhibitors

- Non-competitive inhibitors of KIT kinase
  - Bind regulatory domains
- High potency, IC50 5-10 nM
  - WT KIT & PDGFRA
  - V654A, T670I, D816H, D816V mutant KIT
- PDGFRA D842V activity also, IC50 20-50 nM
- In preclinical development
- Resistance mechanism in similar drugs for ABL: P loop mutants

Heinrich MC et al. Proc ASCO 2010; abstr 10007

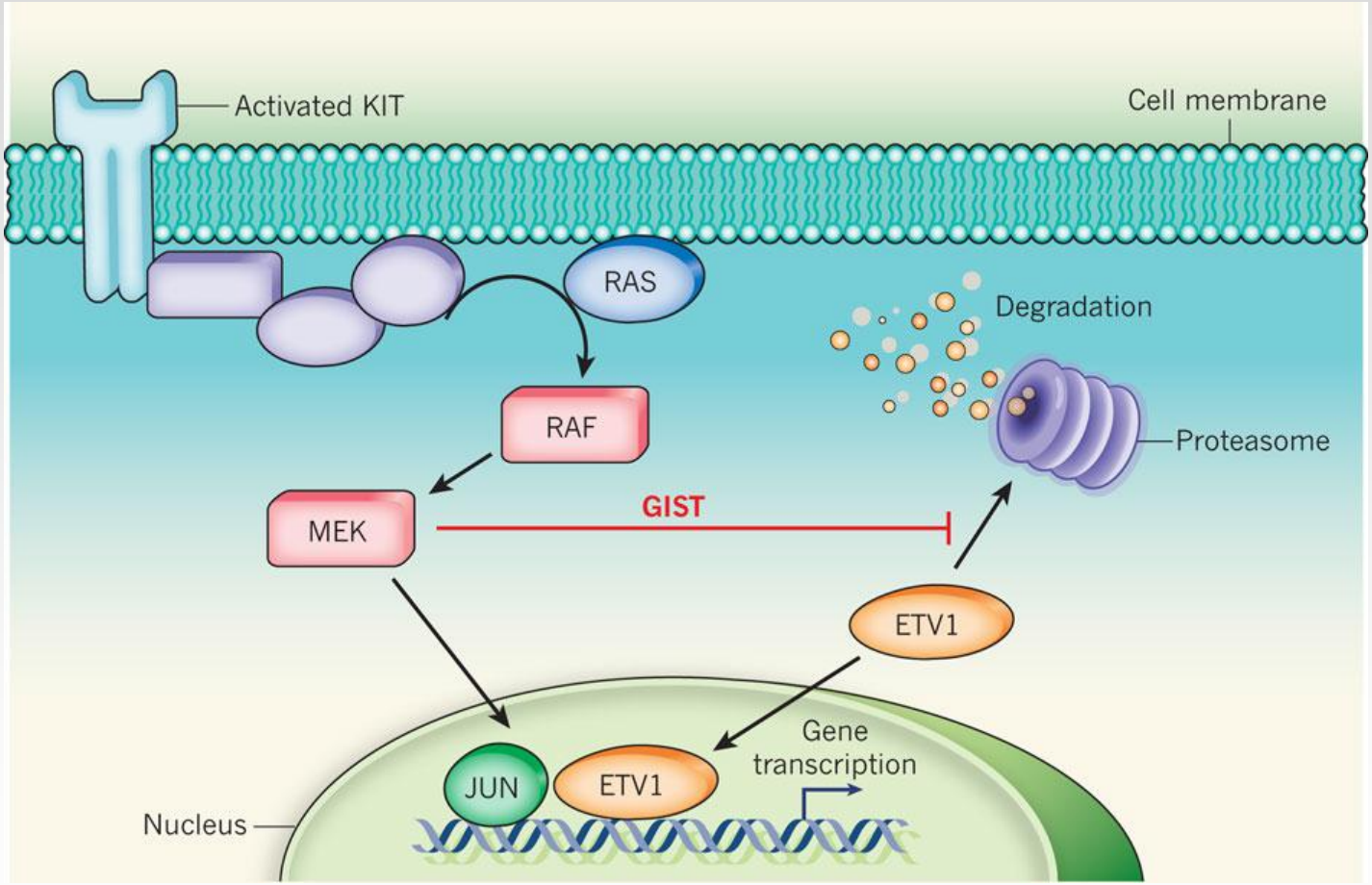
ETV1 cooperates with mutant *KIT* in oncogenesis





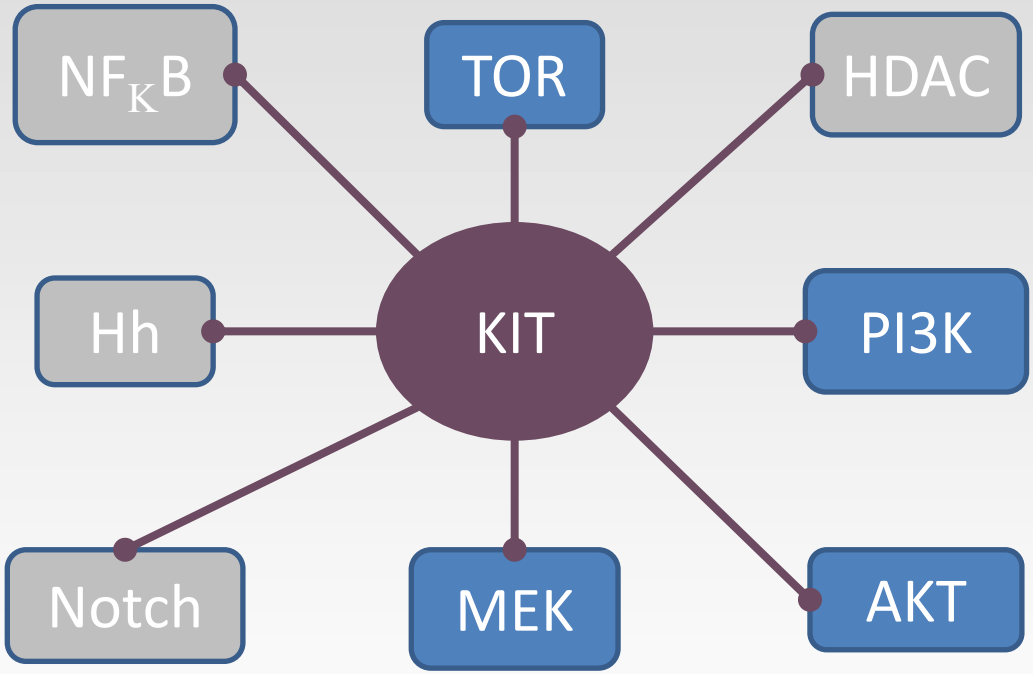
Chi P et al. Nature 2010; 467:849

Clinical implication: MEK inhibitor for GIST



Chi P et al. Nature 2010; 467:849
Corless CL and Heinrich MC. Nature 2010; 467: 796

Combinations



GIST in 2012 in one slide

- Imatinib – sunitinib – regorafenib – ?
- Adjuvant therapy: 3 yr imatinib (high risk disease)
- Surgery: consider even in metastatic disease
- New agents: inhibit ?hsp90, PI3K, MEK, TOR, …
- Greatest need: knock out that small fraction of surviving cells after imatinib therapy


Connective Tissue Oncology Society
17th Annual Meeting – November 14 - 17, 2012
Alessandro Gronchi, MD - Program Chair • Jay Wunder, MD - 2012 CTOS President
Thank you.
bobmakimd@gmail.com
Prague, Czech Republic
KARLOVY LÁZNĚ