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Targeted therapy of metastatic GIST

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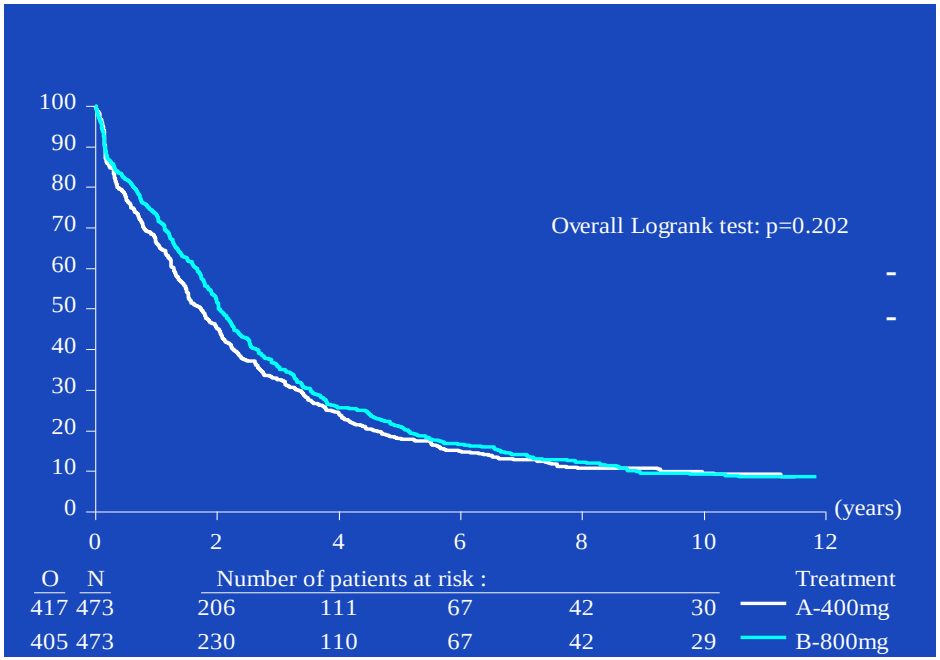
Cancer Center Berlin-Buch / Sarcoma Center Berlin-Brandenburg

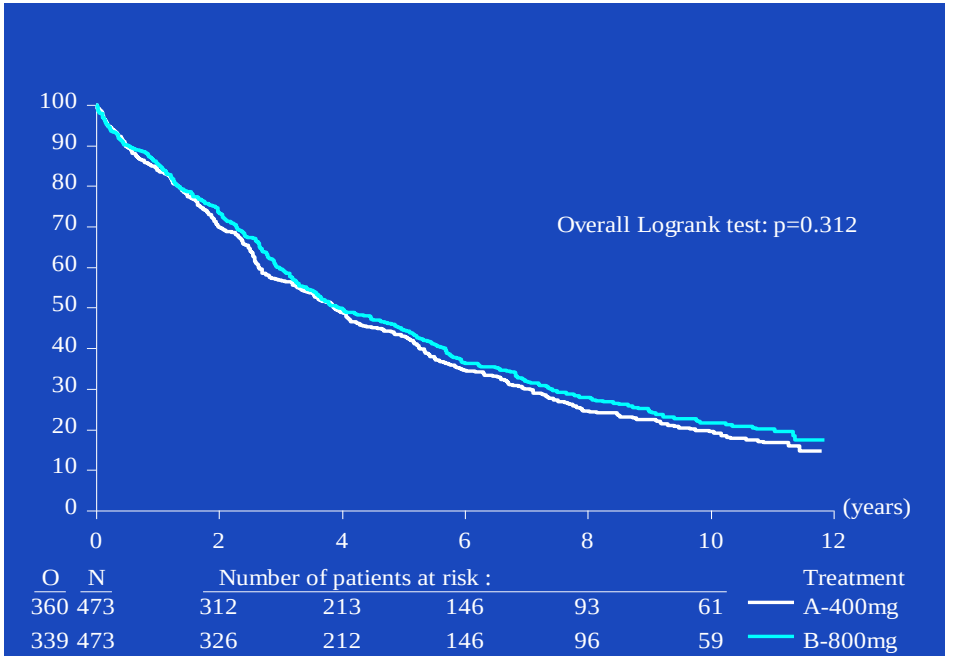
Studies of Imatinib Therapy in GIST

Pilot	Phase 1	Phase 2	Phase 3
Pilot Study Exploratory Study (N = 1)[1]	**Dose-Finding Study (N = 40)[2]**	**B2222 Open-Label Study (N = 147)[3]**	**EORTC 62005 Randomized Study (N = 946)[5]**
• 1 patient • 400 mg/d	• Efficacy and safety • 400 vs 1000 mg/d • Metastatic GIST (EORTC)	• Efficacy and safety • 400 vs 600 mg/d • Metastatic or unresectable GIST	• Efficacy and safety • 400 vs 800 mg/d • Metastatic or unresectable KIT-positive GIST
		EORTC phase 2 study (N = 51)[4]	**US Intergroup S0033 Study (N = 746)[6]**
		• Efficacy and safety • Advanced or metastatic GIST and other soft-tissue sarcomas	• Efficacy and safety • 400 vs 800mg/d • Metastatic or unresectable KIT-positive GIST

1. Joensuu H et al. N Engl J Med. 2001;344:1052-1056.
2. van Oosterom AT et al. Lancet. 2001;358:1421-1423.
3. Demetri GD et al. N Engl J Med. 2002;347:472-480.
4. Verweij J et al. Eur J Cancer. 2003;39:2006-2011.
5. Verweij J et al. The Lancet. 2004;364:1127-1134.
6. Blanke C et al. J Clin Oncol. 2008;26:620-625

EORTC 62005: PFS / OS





Casali PG et al., CTOS 2013

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%

7

Progression-Free Survival according to muational status

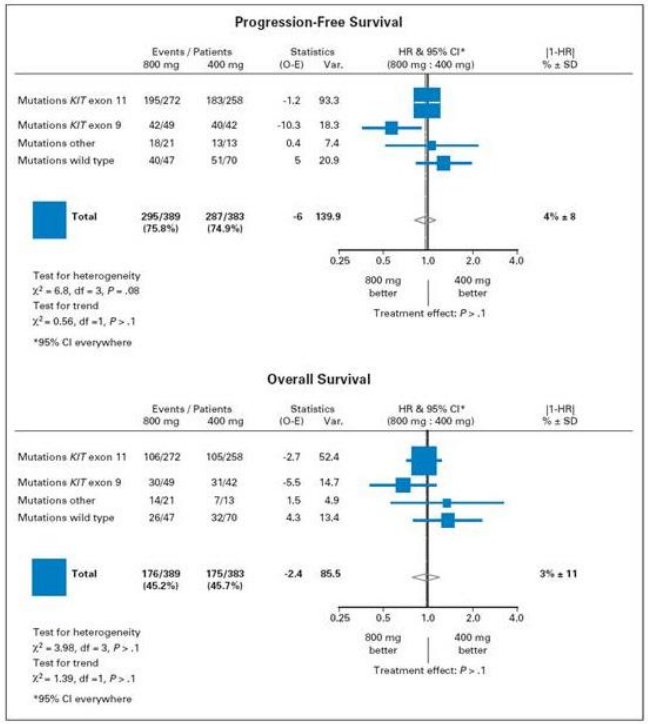
VOLUME 28 · NUMBER 7 · MARCH 1 2010

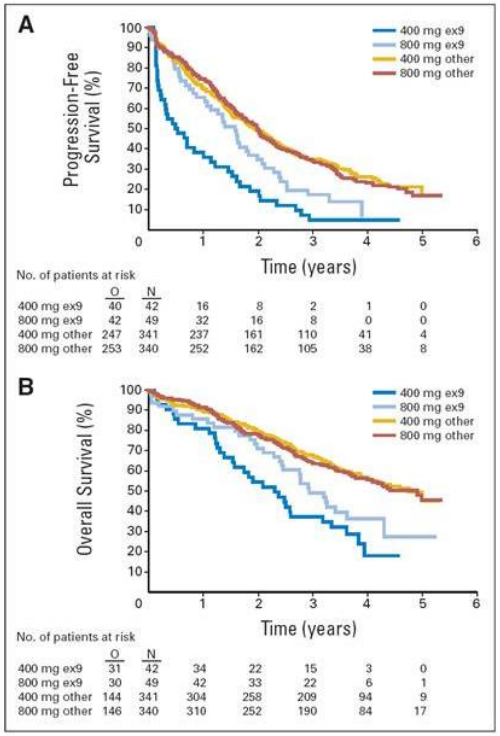
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Comparison of Two Doses of Imatinib for the Treatment of Unresectable or Metastatic Gastrointestinal Stromal Tumors: A Meta-Analysis of 1,640 Patients

Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST)





clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii21–iii26, 2014
doi:10.1093/annonc/mdu255

Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

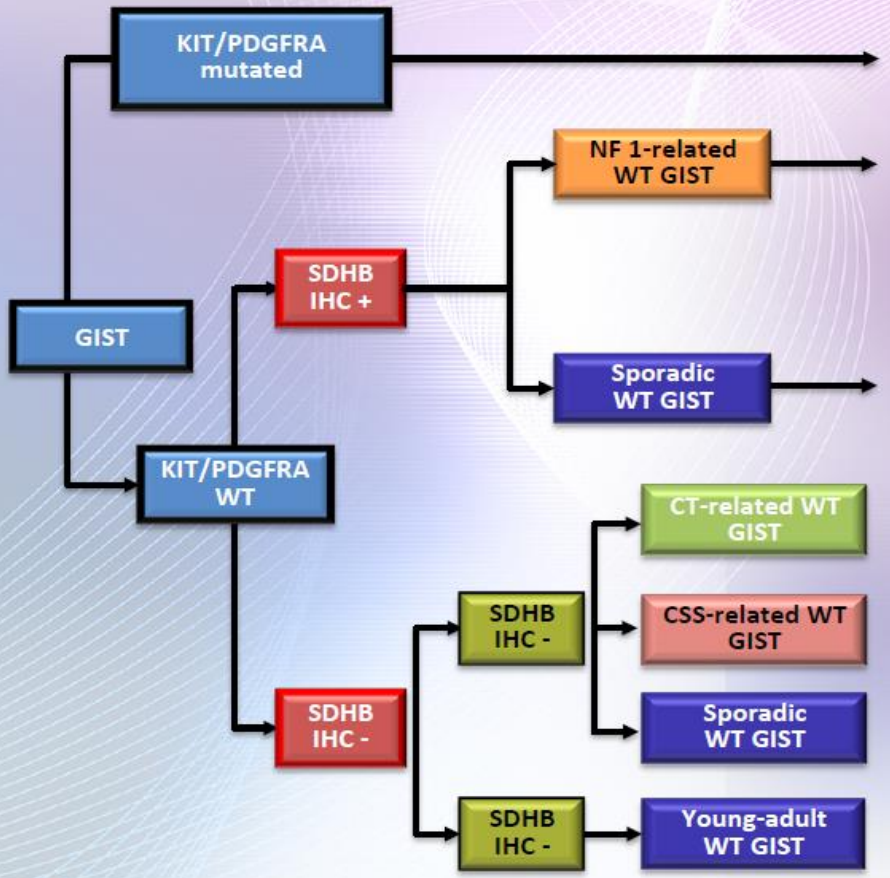
The ESMO/European Sarcoma Network Working Group*

area). Mutational analysis for known mutations involving *KIT* and PDGFRA genes can confirm the diagnosis of GIST, if doubtful (particularly in CD117/DOG1-negative suspect GIST). Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy, and prognostic value, so that its inclusion in the diagnostic work-up of all GISTs should be considered standard practice (with the possible exclusion of <2 cm non-rectal GISTs, which are very unlikely ever to be candidates for medical treatment). Centralisation of mutational analysis in a laboratory enrolled in an external quality assurance programme and with expertise in the disease may be useful. In *KIT*/PDGFRA wild type (WT) GIST, immunohistochemistry for SDHB is done. The diagnosis should be made or confirmed by an expert pathologist at a reference centre. The collection of fresh/frozen tissue is encouraged, because

Wild-Type GIST
(No KIT or PDGFRA Mutation)

WT GIST

- SDH Deficient GIST
  - Paediatric GIST
  - Carney Triad:
    - "Leiomyosarcoma"/GIST
    - Pulmonary chondroma
    - Paraganglioma
  - Carney-Stratakis Syndrome
    - GIST
    - Paraganglioma
- NF-1
- Non-Syndromic WT GIST



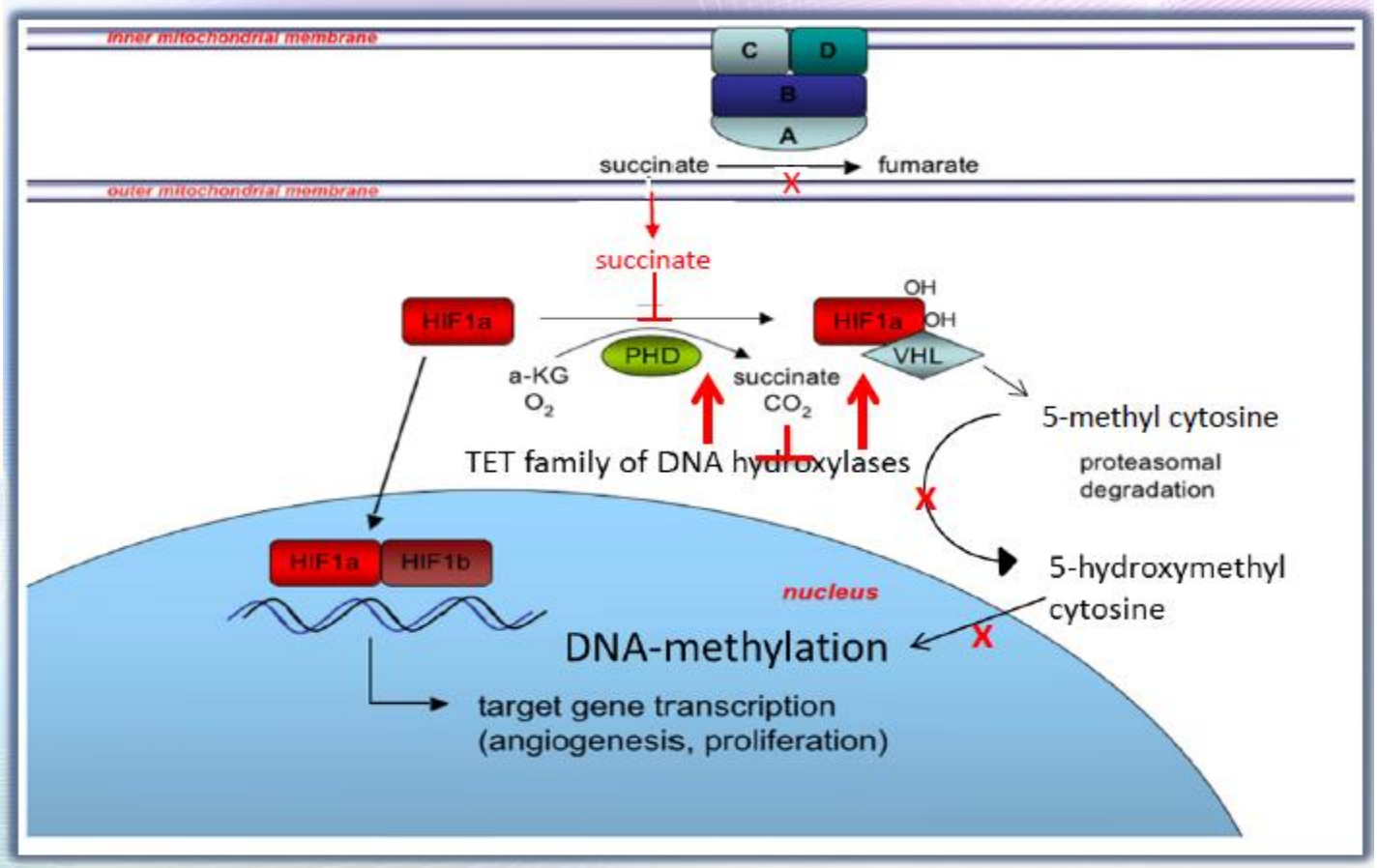
Nannini M, et al. *J Med Genet.* 2013;50(10):653-61.

Wild-Type GIST
(No KIT or PDGFRA Mutation)

Inactivation of SDH via gene mutations or other mechanisms leads to increased gene transcription, angiogenesis and cell proliferation

Inactivation of SDH may also lead to decreased DNA methylation

SDH Deficiency



Adapted from Belinsky MG, et al. *Front Oncol.* 2013;3:117.

Wild-Type GIST (No KIT or PDGFRA Mutation)

Alteration	Syndrome	Estimated Frequency	References
Germline NF1 mutation	NF type 1	Rare	Andersson et al. *Am J Surg Pathol*. 2005; 29:1170-1176
BRAF mutation		< 7%	Agaram et al. *Genes Chromosomes Cancer*. 2008;47(10):853-859 Agaimy et al. J Clin Pathol 2009;62:613–6.
KRAS or NRAS mutation		<1%	Heinrich and Corless, unpublished
Increased IGF1R expression		~50%	Tarn et al. *PNAS*. 2008;105(24):8387-8392
Germline SDHB, SDHC or SDHD mutation	Carney-Stratakis	~12%	Janeway et al. *PNAS*. 2011;108(1):314-318 Pantaleo et al. J Natl Cancer Inst. 2011;103(12):983-7
Loss of SDHB expression (probably post-transcriptional)	(Carney triad)	~30%	Janeway et al. *PNAS*. 2011;108(1):314-318

Dose escalation of imatinib

EORTC 62005*

- 133 patients cross-over to 800 mg
- response: 2% PR, 27% SD
- PFS: median 81 days

S0033†

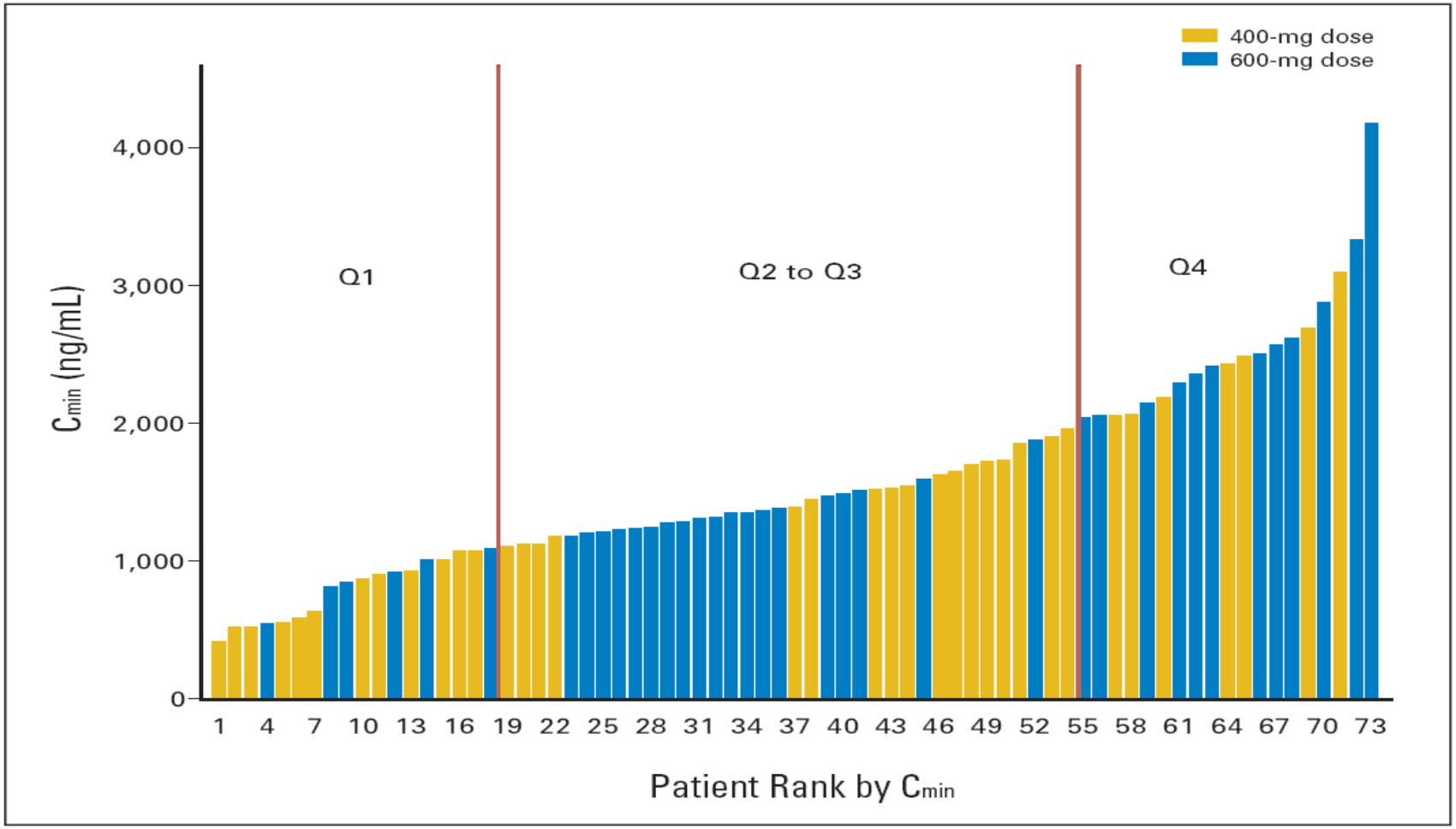
- 77 patients cross-over to 800 mg
- response: 3% PR, 28% SD
- PFS: median 5 months

Probable explanations:

- exon 9 mutation status
- insufficient imatinib blood levels

**Zalcberg et al., Eur J Cancer 2005; 41(11): 1751-1757*
†Blanke et al., J Clin Oncol 2008; 26(4): 626-632

Wide Distribution of Imatinib Exposure without Reliable Correlation with Dose



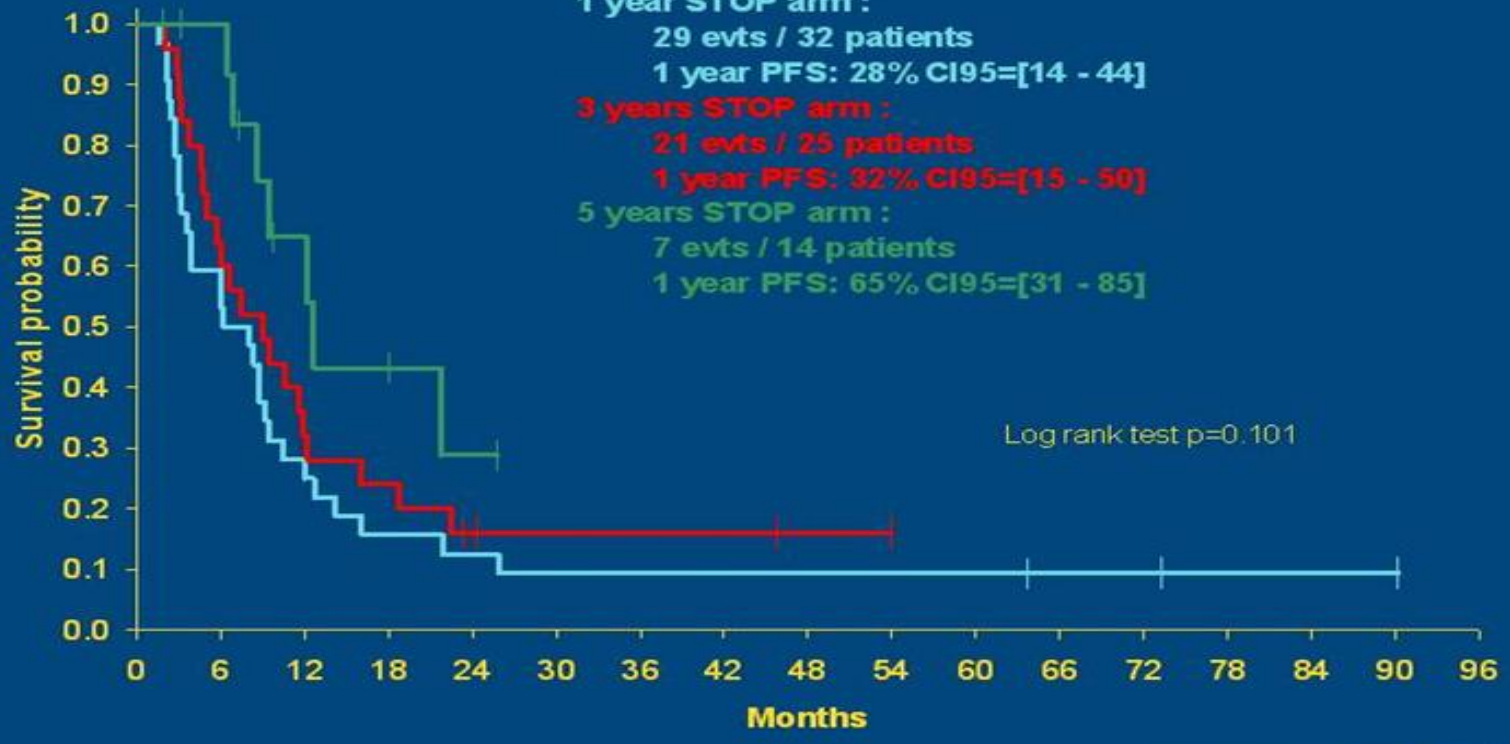
Demetri et al. J Clin Oncol. 2009 Jul 1;27(19):3141-7

Time to secondary resistance after interruption of imatinib in advanced GIST: Updated results of the prospective French Sarcoma Group randomized phase III trial on long-term survival

A. Le Cesne et al., J Clin Oncol 29: 2011 (suppl; abstr 10015)

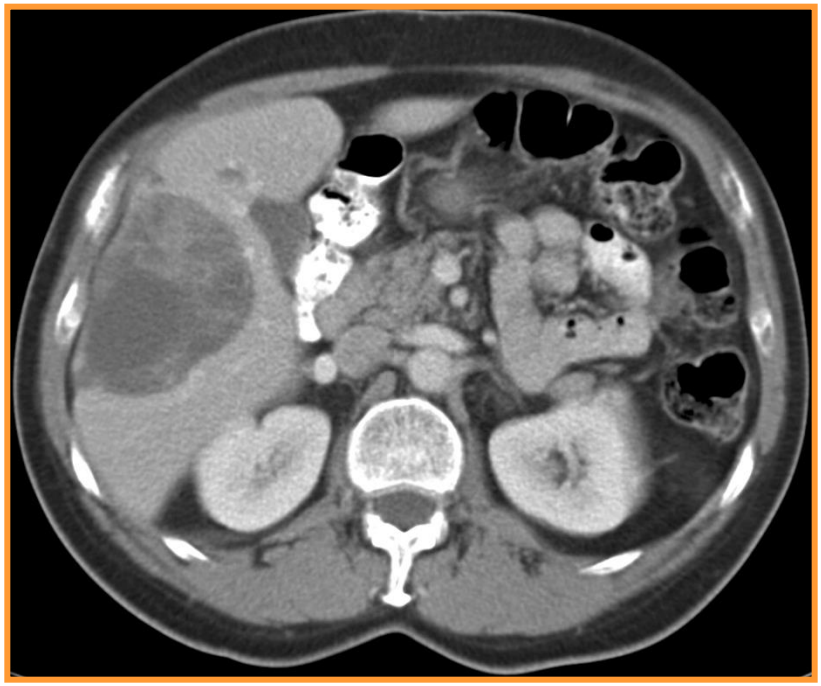
BFR14 - Interruption arms (1, 3, 5 years)

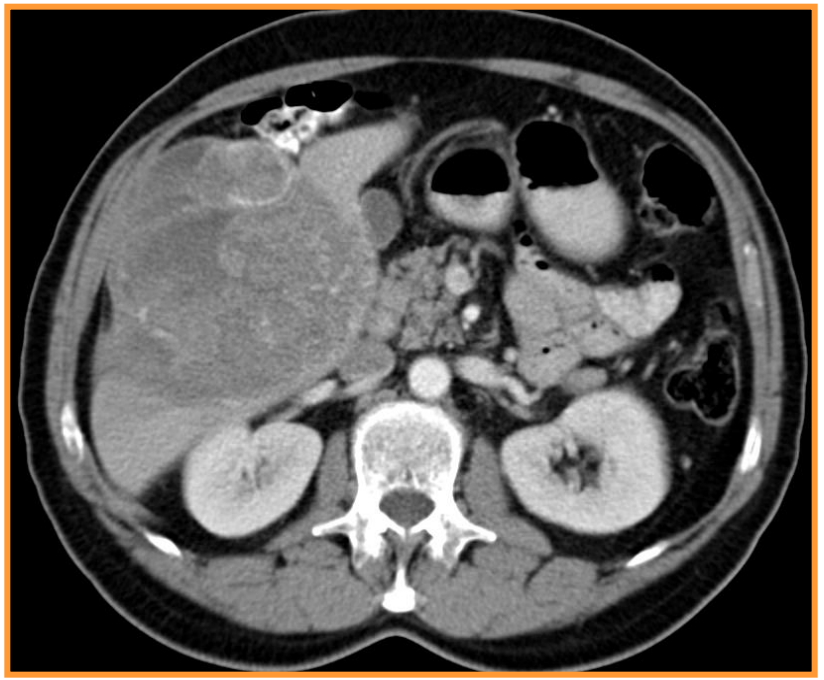
Comparison of PFS



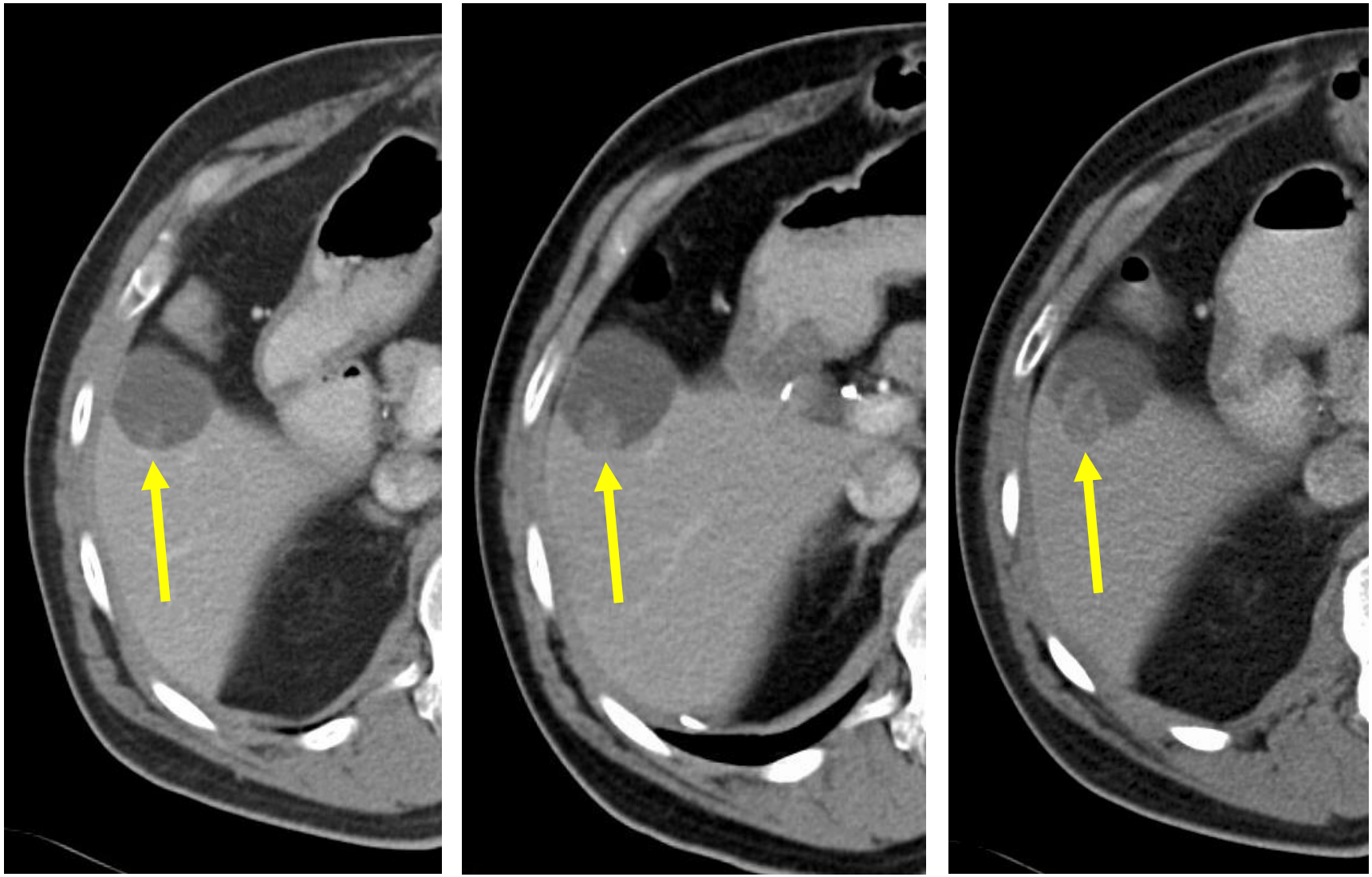
PRESENTED AT: ASCO Annual '11 Meeting

CT scan: general progression



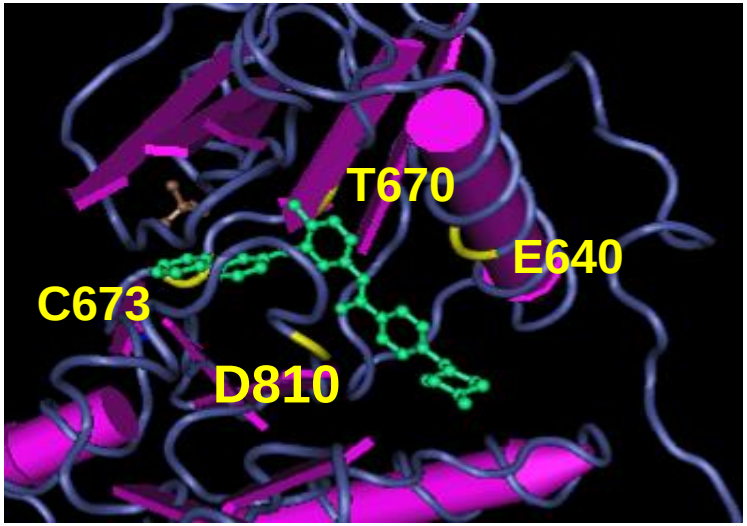


CT scan: focal progression

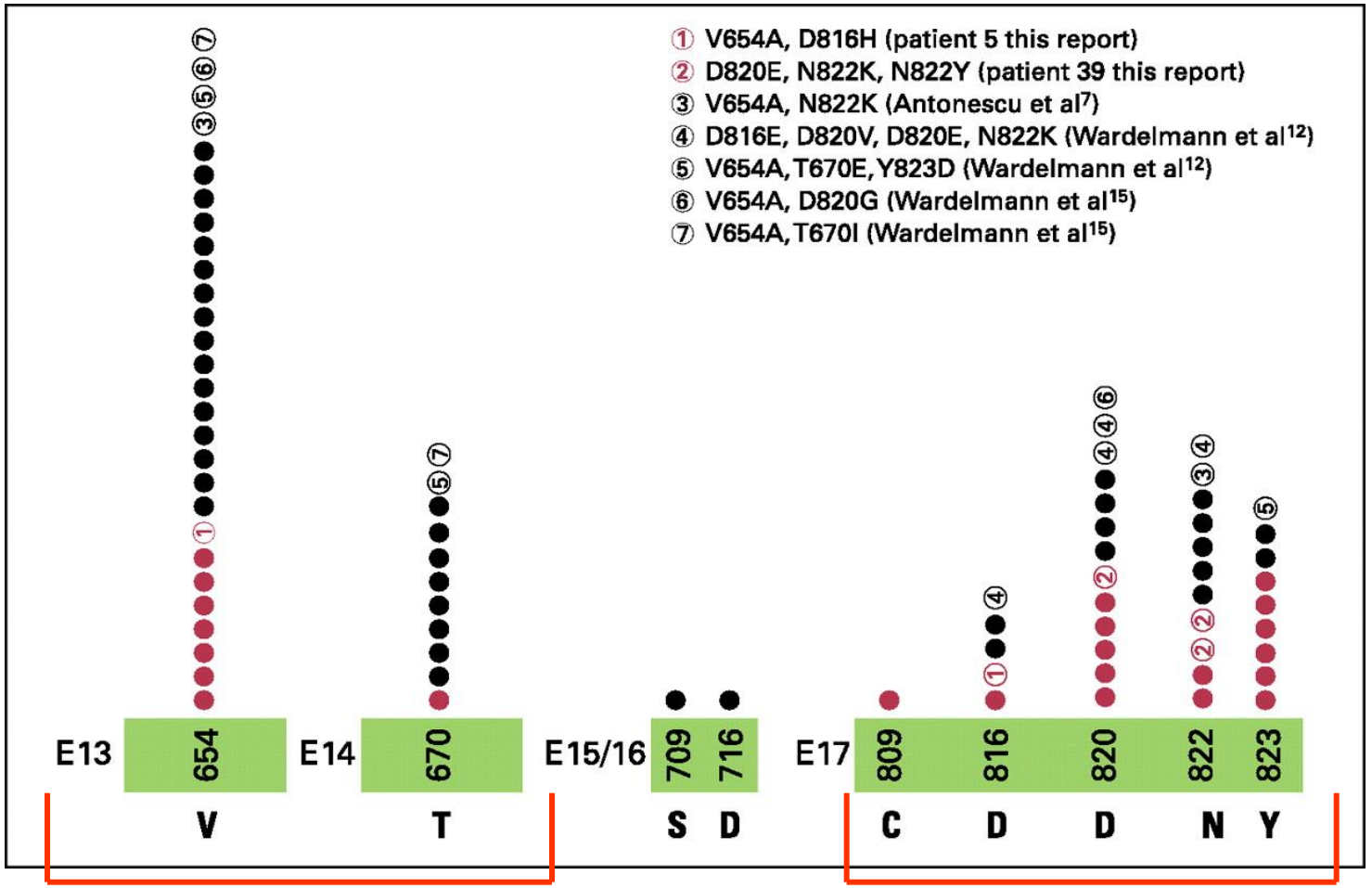


Secondary resistance in GIST

- Secondary mutations in target gene
  - Mutation of gatekeeper residue (ATP binding site)
  - Mutation in the p-loop and activation loop leading to stabilization of the activation loop in the active conformation



Secondary KIT mutations in imatinib-resistant GIST



Heinrich et al., J Clin Oncol 24:4764-4774, 2006

In vitro-efficacy of sunitinib and imatinib in KIT-mutations

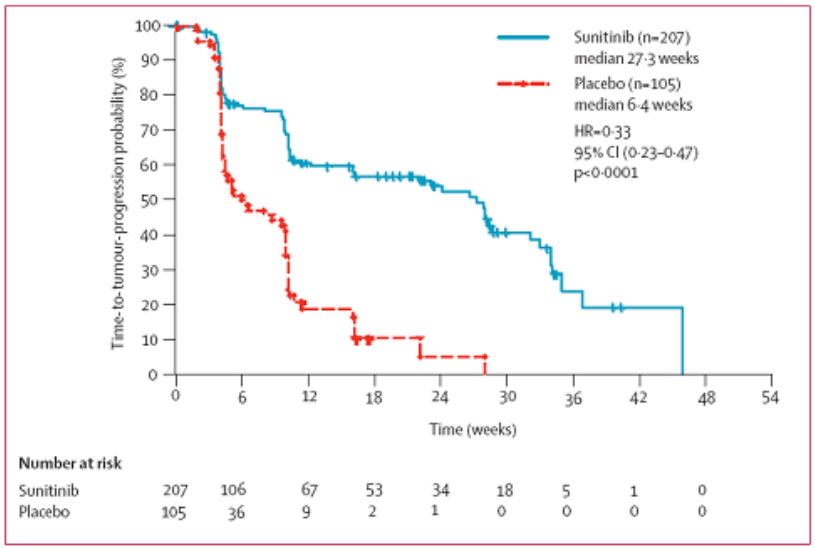
Mutation(s)	Exon(s)	Localisation of second Mutation	ca. IC_{50} (nM)	
			Sunitinib	Imatinib
V560D	11	–	< 50	~ 100
V560D + V654A	11 + 13	ATP BP	< 100	5000
V560D + T670I	11 + 14	ATP BP	< 50	10000
V560D + D816H	11 + 17	Activation Loop	1000	5000
V560D + N822K	11 + 17	Activation Loop	> 1000	~ 1000
V560D + Y823D	11 + 17	Activation Loop	> 1000	> 1000

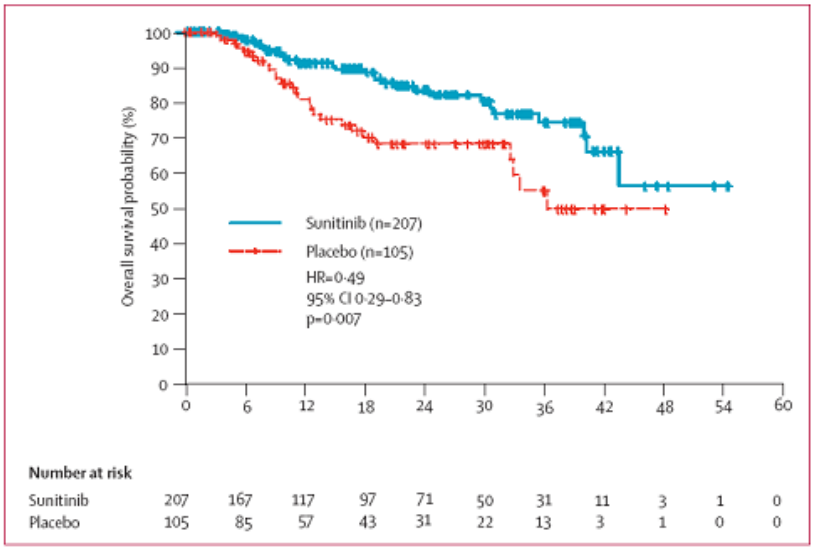
Heinrich et al., J Clin Oncol 24:4764-4774, 2006

Phase III Trial: Sunitinib in Advanced GIST After Imatinib Failure

Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial

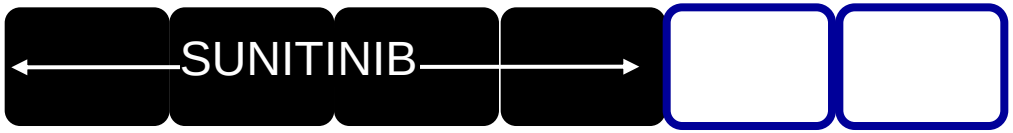
George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali



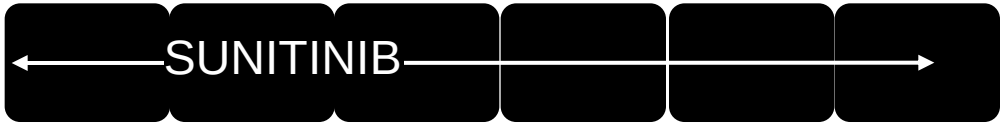


Demetri GD et al., Lancet. 2006;3681329-1338.

Sunitinib Dosing Schedules



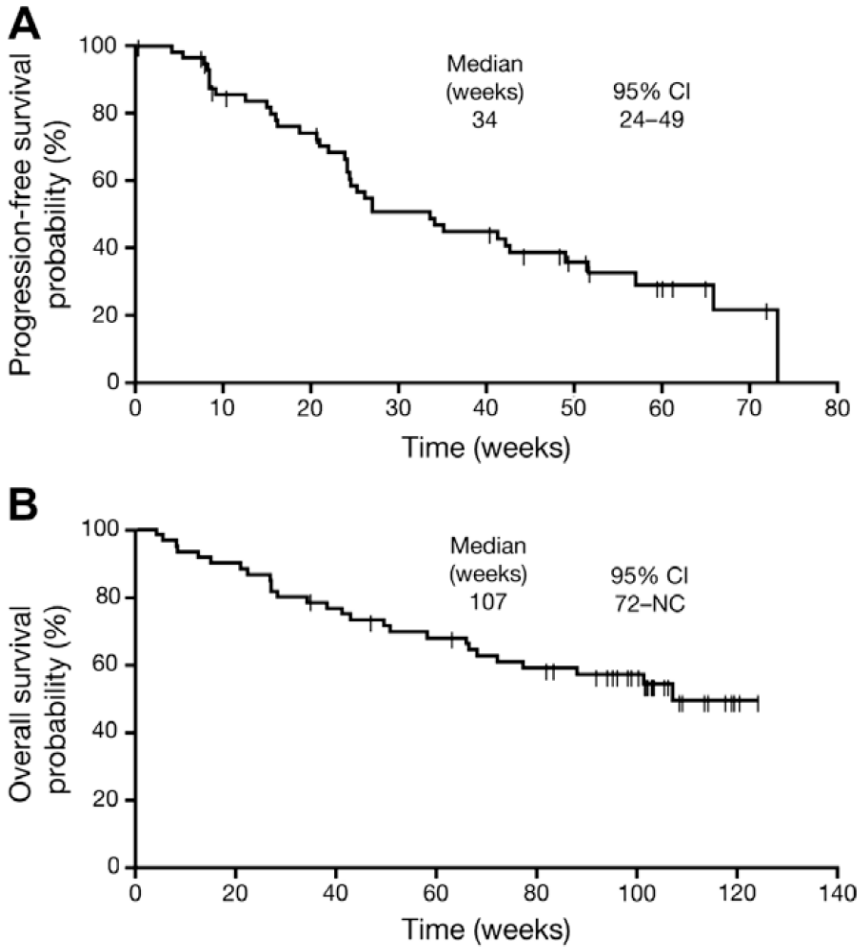
Intermittent :50 mg/day, 4 weeks on, 2 weeks off



Continuous: 37.5 mg/day

Sunitinib: PFS and OS with Continuous Dosing Schedule

n=60



George et al. Eur. J. Cancer. 2009

Original Article

Clinical Outcomes of Patients With Advanced Gastrointestinal Stromal Tumors: Safety and Efficacy in a Worldwide Treatment-Use Trial of Sunitinib

Peter Reichardt, MD, PhD[1]; Yoon-Koo Kang, MD, PhD[2]; Piotr Rutkowski, MD, PhD[3]; Jochen Schuette, MD[4]; Lee S. Rosen, MD[5]; Beatrice Seddon, PhD[6]; Suayib Yalcin, MD[7]; Hans Gelderblom, MD[8]; Charles C. Williams Jr, MD[9]; Elena Fumagalli, MD[10]; Guido Biasco, MD[11]; Herbert I. Hurwitz, MD[12]; Pamela E. Kaiser, MD[13]; Kolette Fly, PhD[14]; Ewa Matczak, MD[15]; Liang Chen, PhD[15]; Maria José Lechuga, MD[16]; and George D. Demetri, MD[17]

BACKGROUND: The objectives of this study were to provide sunitinib to patients with gastrointestinal stromal tumor (GIST) who were otherwise unable to obtain it and to collect broad safety and efficacy data from a large population of patients with advanced GIST after imatinib failure. **METHODS:** Imatinib-resistant/intolerant patients with advanced GIST received sunitinib on an initial dosing schedule of 50 mg daily in 6-week cycles (4 weeks on treatment, 2 weeks off treatment). Tumor assessment frequency was according to local practice, and response was assessed by investigators according to Response Evaluation Criteria in Solid Tumors version 1.0. Overall survival (OS) and safety were assessed regularly. Post hoc analyses evaluated different patterns of treatment management. **RESULTS:** At final data cutoff, 1124 patients comprised the intent-to-treat population, and 15% of these patients had a baseline Eastern Cooperative Oncology Group performance status ≥2. The median treatment duration was 7.0 months. The median time to tumor progression was 8.3 months (95% confidence interval [CI], 8.0-9.4 months), the median OS was 16.6 months (95% CI, 14.9-18.0 months), and 36% of patients were alive at the time of analysis. Patients for whom the initial dosing schedule was modified exhibited longer median OS (23.5 months) than those who were treated strictly according to the initial dosing schedule (11.1 months). The most common treatment-related grade 3 and 4 adverse events were hand-foot syndrome (11%), fatigue (9%), neutropenia (8%), hypertension (7%), and thrombocytopenia (6%). Treatment-related adverse events associated with cardiac function (eg, congestive heart failure and myocardial infarction) were reported at frequencies of ≤1% each. **CONCLUSIONS:** This treatment-use study confirms the long-term safety and efficacy of sunitinib in a large international population of patients with advanced GIST after imatinib failure. ***Cancer*** **2015;000:000-000.** *© 2015 American Cancer Society.*

KEYWORDS: sunitinib, gastrointestinal stromal tumor, treatment-use trial, long-term safety, efficacy, worldwide.

Reichardt P et al., Cancer 121:1405-1413, 2015

FD increased time to progression and OS vs SSDS

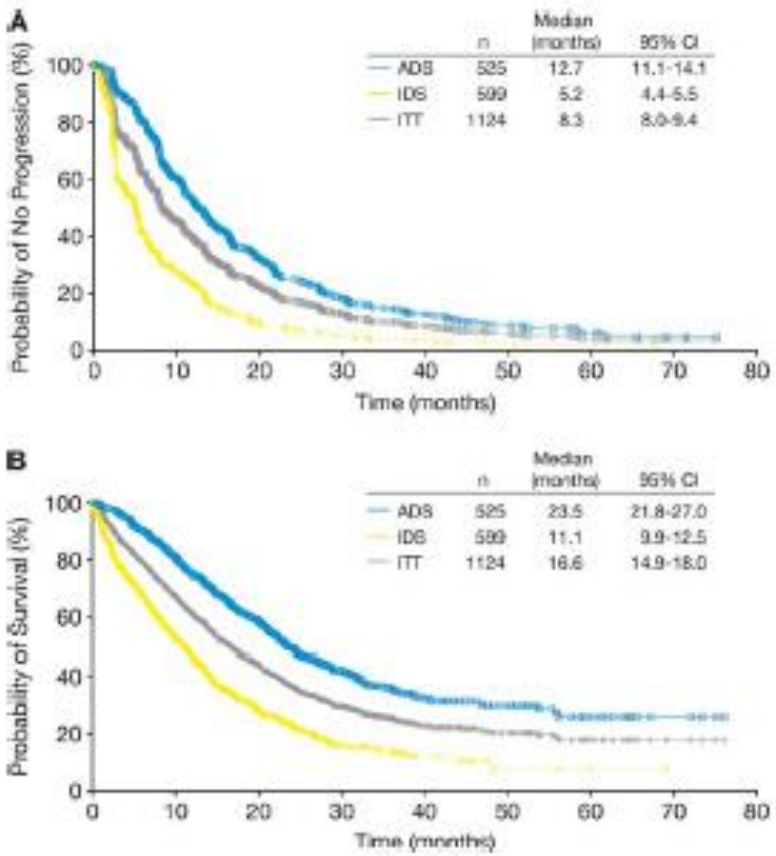


Figure 2. (A) The time to progression and (B) overall survival are illustrated in patients who received sunitinib only on the initial dosing schedule (IDS) or who ultimately received alternative dosing schedules (ADSs). Results for the intent-to-treat (ITT) population are shown for comparison.

Reichardt P et al., Cancer 2015, epub

Continuation of sunitinib treatment after PD improved overall survival vs discontinuation of treatment

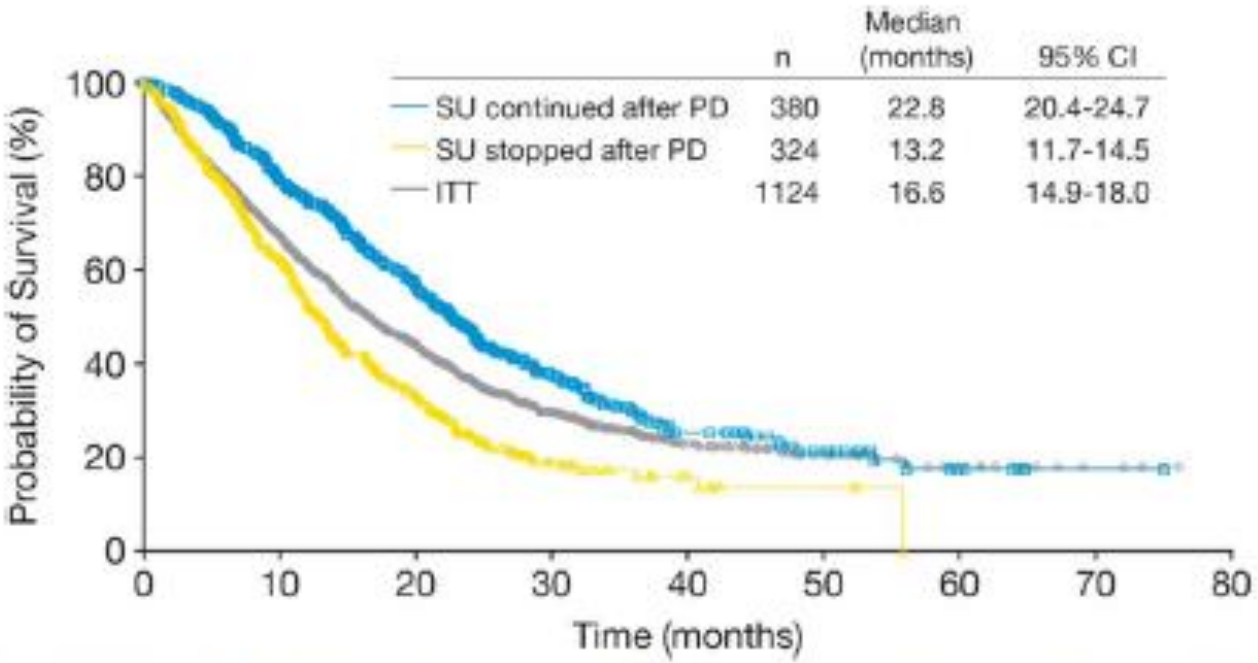


Figure 3. Overall survival is illustrated from the start of treatment in patients who continued or discontinued sunitinib (SU) treatment after progressive disease (PD). Results for the intent-to-treat (ITT) population are shown for comparison. CI indicates confidence interval.

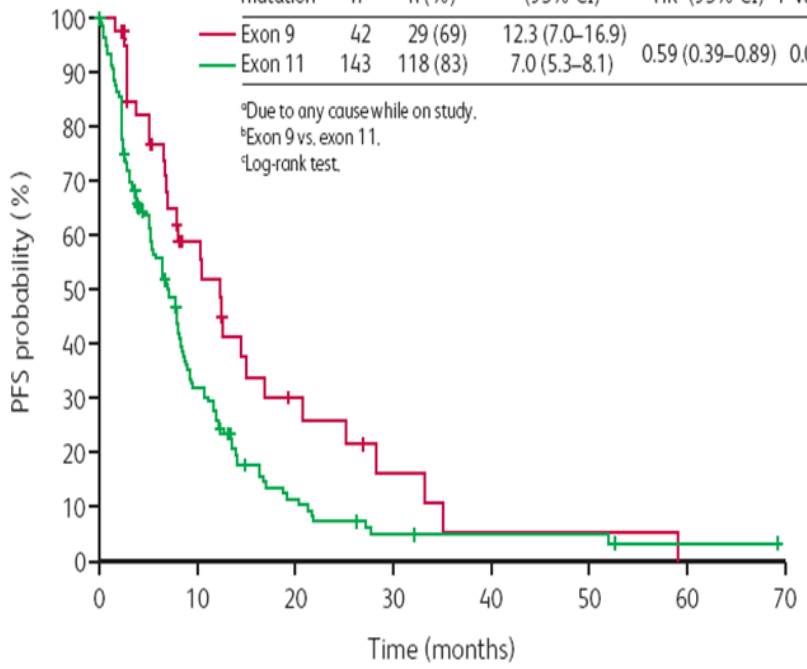
Reichardt P et al., Cancer 2015, epub

Correlation of KIT and PDGFRA mutational status with clinical benefit in patients with GIST treated with sunitinib in a worldwide treatment-use trial

PFS by primary *KIT* mutational status in study 1199*

KIT mutation	n	Progressed or died,[a] n (%)	Median, months (95% CI)	HR[b] (95% CI)	P-value[c]
Exon 9	42	29 (69)	12.3 (7.0–16.9)	0.59 (0.39–0.89)	0.011
Exon 11	143	118 (83)	7.0 (5.3–8.1)		

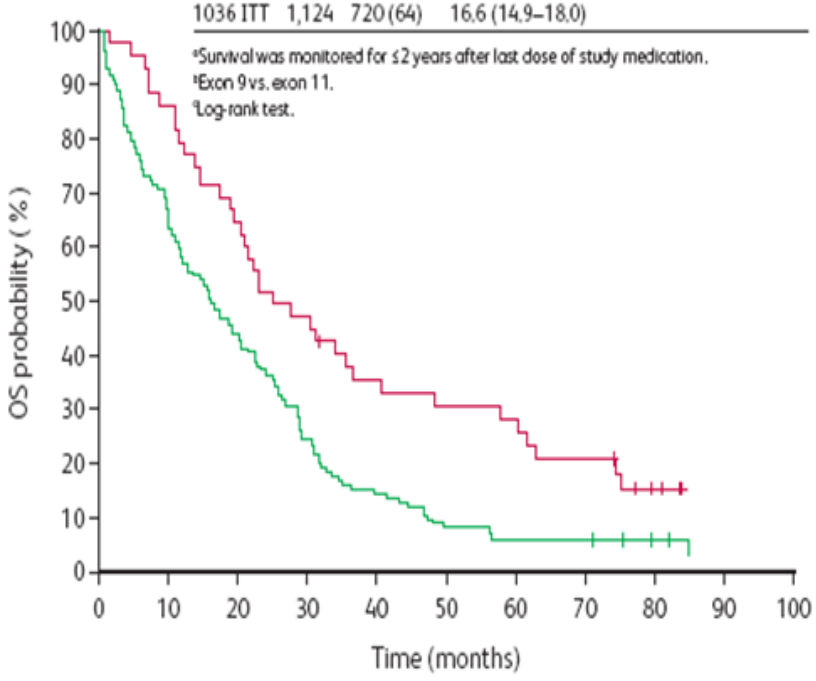
[a]Due to any cause while on study.
[b]Exon 9 vs. exon 11.
[c]Log-rank test.



OS in study 1199 by primary *KIT* mutational status and in the overall ITT population of study 1036

KIT mutation	n	Patients who died,[a] n (%)	Median, months (95% CI)	HR[b] (95% CI)	P-value[c]
Exon 9	42	35 (83)	26.3 (19.3–36.5)	0.55 (0.38–0.80)	0.002
Exon 11	143	132 (92)	16.3 (11.8–20.6)		
1036 ITT	1,124	720 (64)	16.6 (14.9–18.0)		

[a]Survival was monitored for ≤2 years after last dose of study medication.
[b]Exon 9 vs. exon 11.
[c]Log-rank test.



Reichardt P et al. BMC Cancer 2016

In vitro-efficacy of sunitinib and imatinib in KIT-mutations

Mutation(s)	Exon(s)	Localisation of second Mutation	ca. IC_{50} (nM)	
			Sunitinib	Imatinib
V560D	11	–	< 50	~ 100
V560D + V654A	11 + 13	ATP BP	< 100	5000
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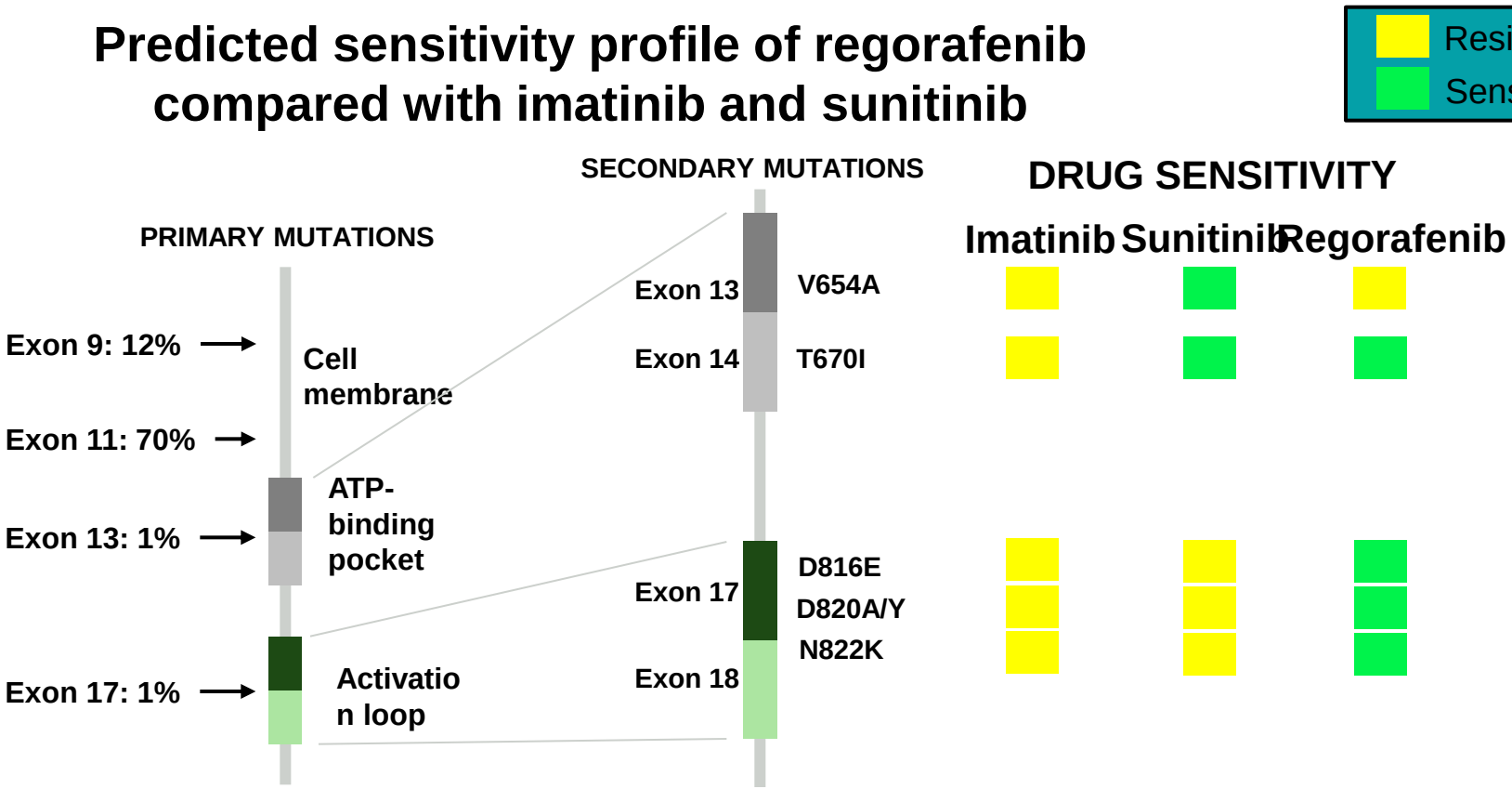
V560D + Y823D	11 + 17	Activation Loop	> 1000	> 1000

Heinrich et al., J Clin Oncol 24:4764-4774, 2006

Regorafenib Activity in Drug-Resistant GIST Cells

Predicted sensitivity profile of regorafenib compared with imatinib and sunitinib



Regorafenib has activity in GIST cells with KIT *primary* exon 11 mutations and secondary KIT exon 17 imatinib-resistant mutations,
but is less active against KIT exon 13 (V654A) mutations compared to sunitinib

Serrano-García C, et al. ASCO 2013. Abstract 10510.

Phase III Trial: Regorafenib in Advanced GIST After Imatinib and Sunitinib Failure

Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial

*George D Demetri, Peter Reichardt, Yoon-Koo Kang, Jean-Yves Blay, Piotr Rutkowski, Hans Gelderblom, Peter Hohenberger, Michael Leahy, Margaret von Mehren, Heikki Joensuu, Giuseppe Badalamenti, Martin Blackstein, Axel Le Cesne, Patrick Schöffski, Robert G Maki, Sebastian Bauer, Binh Bui Nguyen, Jianming Xu, Toshirou Nishida, John Chung, Christian Kappeler, Iris Kuss, Dirk Laurent, Paolo G Casali, on behalf of all GRID study investigators**

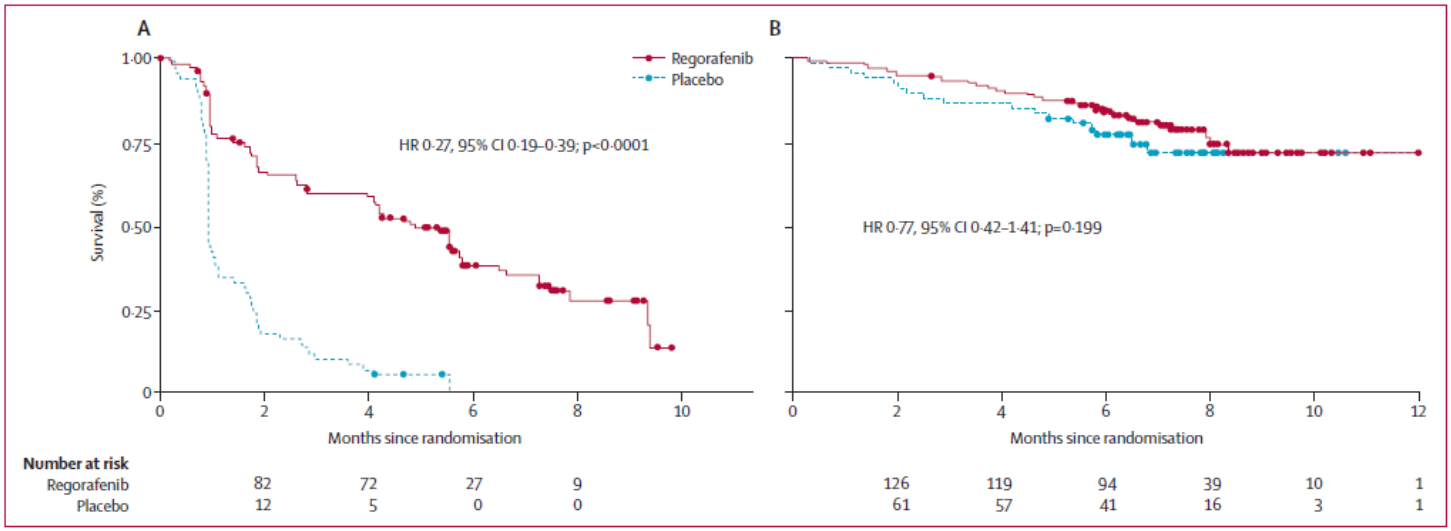


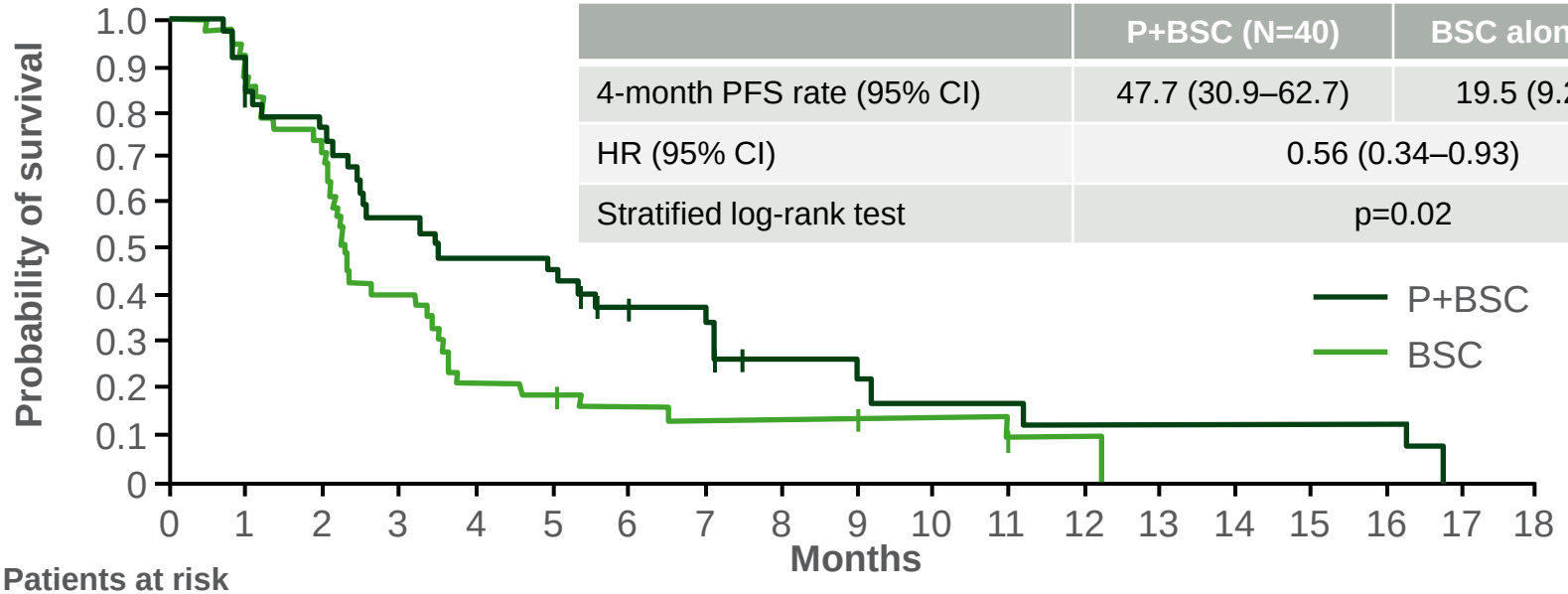
Figure 2: **Kaplan-Meier survival analysis after treatment with regorafenib or placebo**
(A) Progression-free survival, per central review (primary endpoint, final analysis). (B) Overall survival (interim analysis). HR=hazard ratio.

Demetri GD, Reichardt P, Kang YK, et al., Lancet 2013

Phase II study of pazopanib plus BSC versus BSC alone in GIST

- Overall, 81 patients with metastatic GIST resistant to imatinib and sunitinib were randomised 1:1 to receive pazopanib + BSC or BSC alone

	P+BSC (N=40)	BSC alone (N=41)
4-month PFS rate (95% CI)	47.7 (30.9–62.7)	19.5 (9.2–32.7)
HR (95% CI)	0.56 (0.34–0.93)	
Stratified log-rank test	p=0.02	



Patients at risk

P+BSC	n=38	30	27	20	17	16	11	10	5	5	3	3	2	2	2	2
BSC	n=41	35	29	16	8	7	5	4	4	4	3	1	1	0		

Blay JY et al. ESMO 2014 (abstract LBA45)

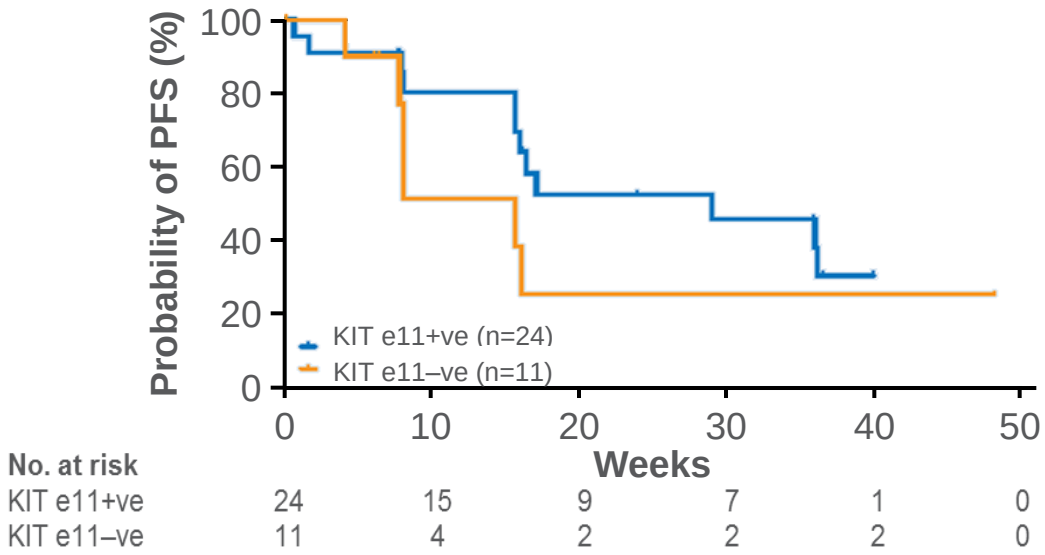
Phase II trial of ponatinib in GIST: overall tumour response

	n, %		
	KIT e11 +ve N=22*	KIT e11 –ve N=11	Total N=33*
CBR at 16 weeks	10 (46)†	2 (18)	12 (36)
ORR‡	2 (9)	0 (0)	2 (6)
Best response‡			
- CR	0 (0)	0 (0)	0 (0)
- PR	2 (9)	0 (0)	2 (6)
- SD	14 (64)	6 (55)	20 (61)
- PD	3 (14)	4 (36)	7 (21)
- NE	3 (14)	1 (9)	4 (12)

*Excludes two patients who were discontinued per FDA request
†CBR in KIT e11+ve patients with 2 or 3 prior TKIs was 44% and 50%, respectively
‡Based on patients with at least 1 scan or discontinued without a scan

Heinrich M et al. ESMO 2014 (abstract 5792)

Phase II trial of ponatinib in GIST: PFS

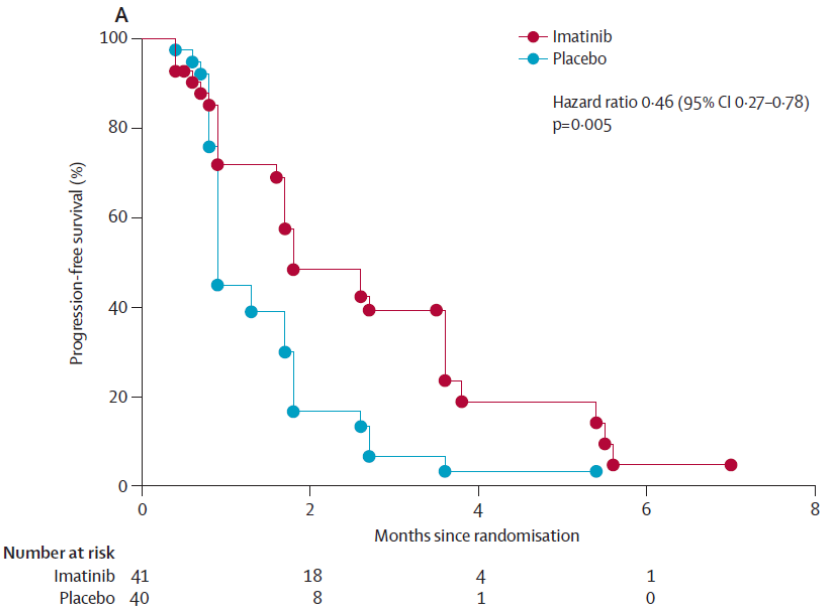


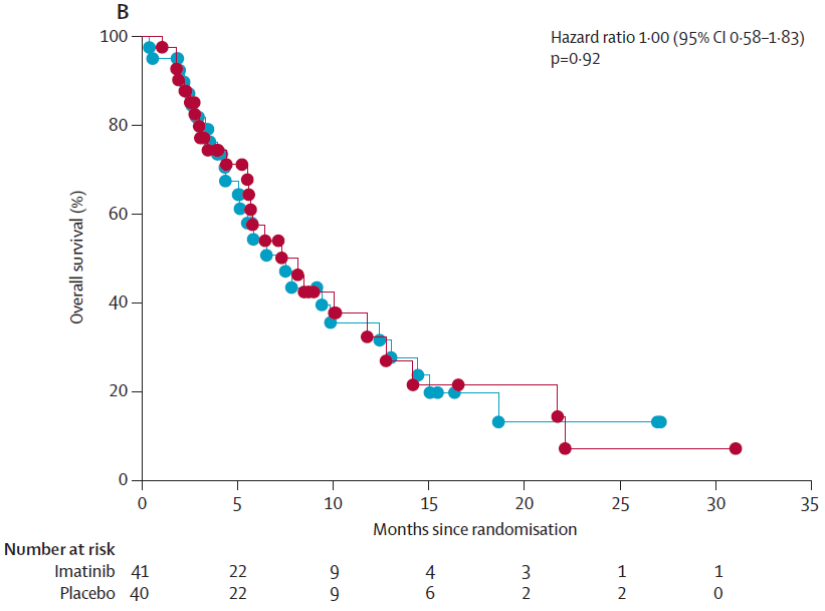
	Median PFS months (95% CI)	6-month PFS probability,% (95% CI)
KIT e11+ve (n=24)	7.3 (3.9–NA)	53 (28–72)
KIT e11–ve (n=11)	3.9 (1–NA)	26 (4–57)
Total (n=35)	4.1 (3.9–9.0)	44 (26–62)

Protocol amendments had to be made due to the risk of arterial and venous thromboembolic events.
Ponatinib has activity in advanced GIST after a median of 4 prior cancer regimens.

Heinrich M et al. ESMO 2014 (abstract 5792)

Resumption of imatinib: RIGHT phase III study





Kang Y-K et al., Lancet Oncology 2014