Clinical benefit with regorafenib across subgroups and post progression in patients with advanced gastrointestinal stromal tumors (GIST) after progression on imatinib (IM) and sunitinib (SU): Phase III GRID trial update

Presented at ESMO 2012 by Peter Reichardt *on behalf of Team GRID, including*

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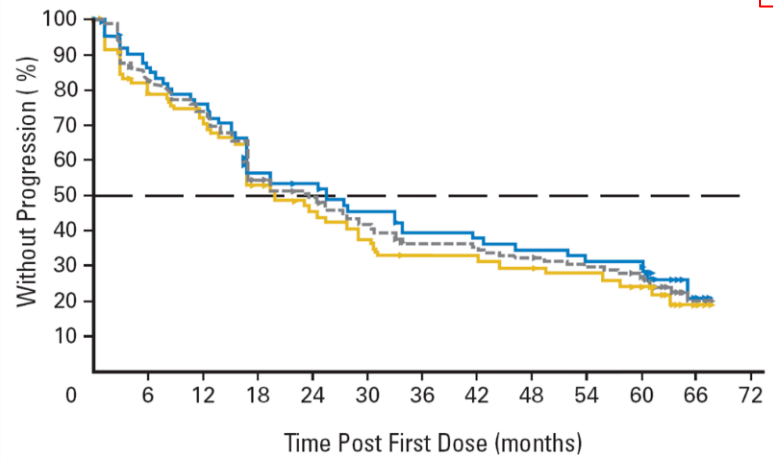
ORIGINAL REPORT

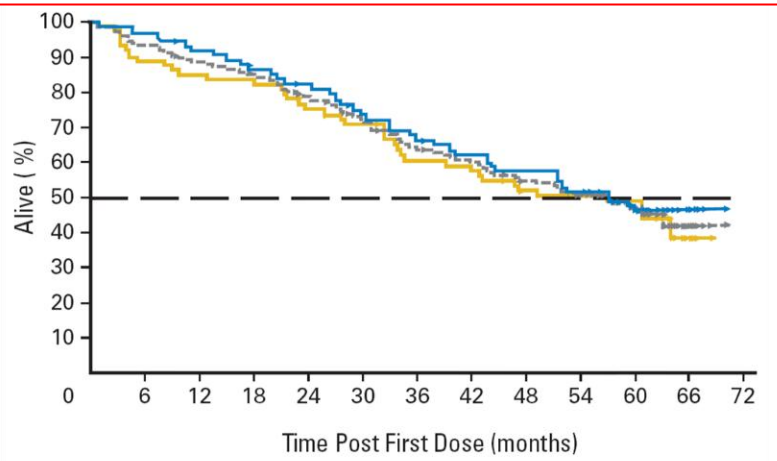
Long-Term Results From a Randomized Phase II Trial of Standard- Versus Higher-Dose Imatinib Mesylate for Patients With Unresectable or Metastatic Gastrointestinal Stromal Tumors Expressing *KIT*

Charles D. Blanke, George D. Demetri, Margaret von Mehren, Michael C. Heinrich, Burton Eisenberg, Jonathan A. Fletcher, Christopher L. Corless, Christopher D.M. Fletcher, Peter J. Roberts, Daniela Heinz, Elisabeth Wehre, Zariana Nikolova, and Heikki Joensuu

Although imatinib revolutionized the initial management of advanced GIST, TKI resistance eventually occurs in >85% of patients leading to progression of disease

Treatment	Months: 0	No. at risk 12	24	36	48	60	Median time (months)	95% CI LL	UL
400mg	73	50	29	20	18	13	20	16	29
600mg	74	54	36	25	22	19	26	16	41
Pooled	147	104	65	45	40	32	24	17	30

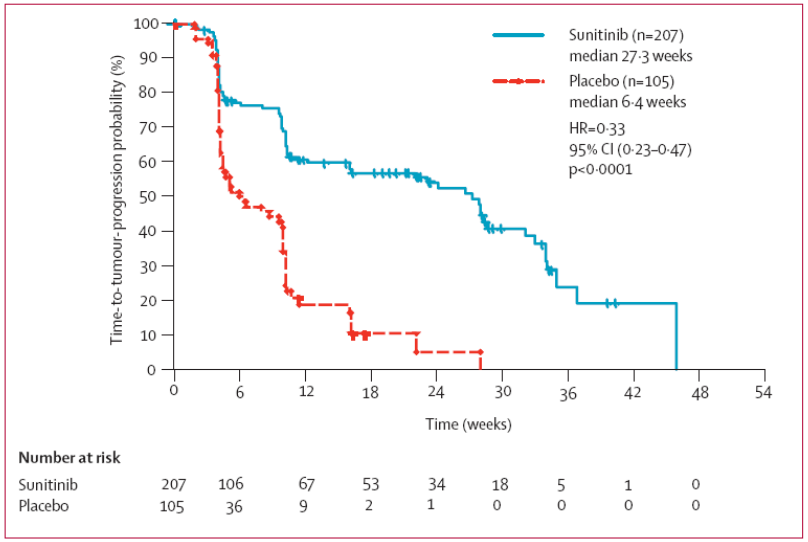


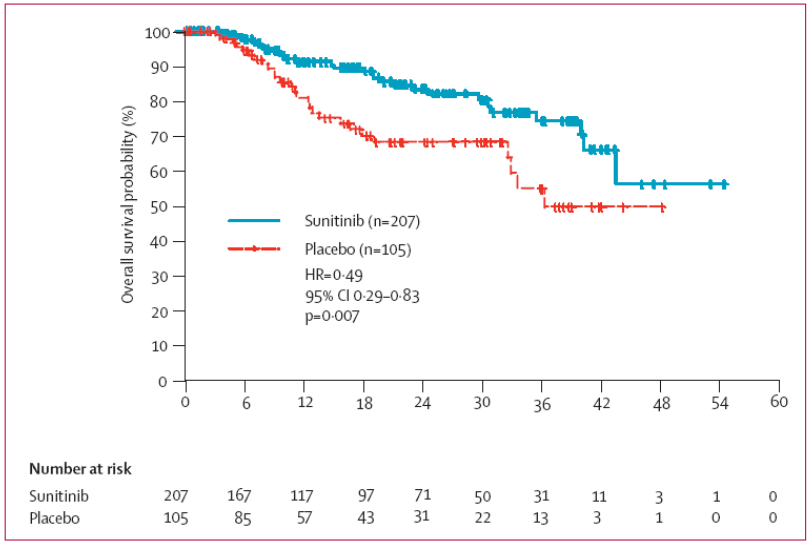


Sunitinib can benefit GIST patients after failure of imatinib – but there is no approved therapy after failure of both imatinib and sunitinib

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

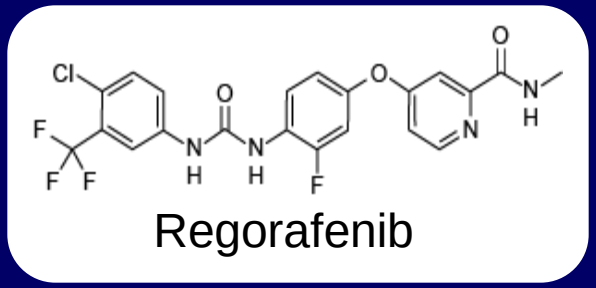
George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali



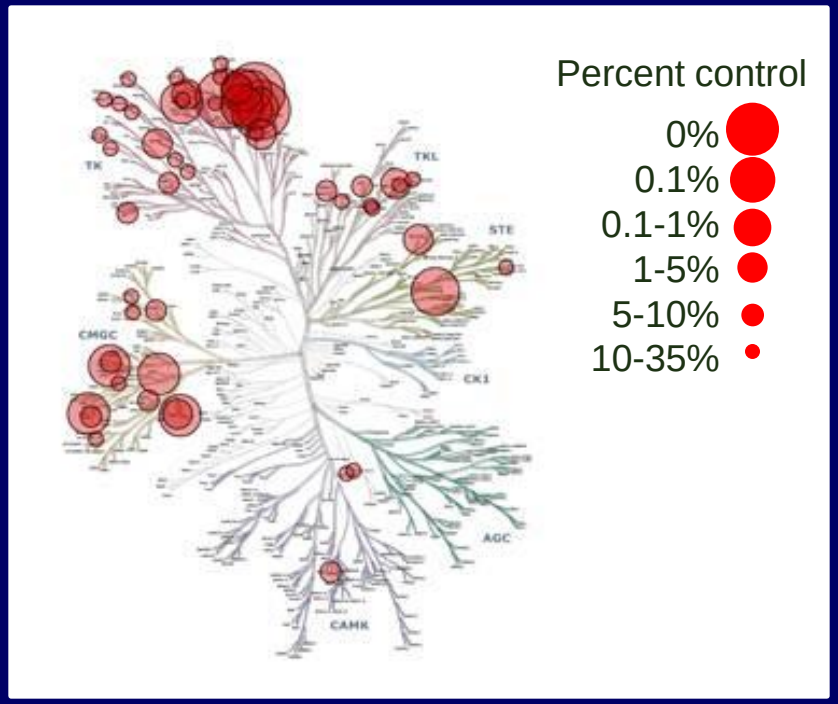


Demetri GD *et al. Lancet* 2006; **368**: 1329-1338.

Regorafenib (BAY 73-4506) is a structurally distinct oral agent with a unique profile of inhibiting multiple kinases relevant to GIST



Regorafenib

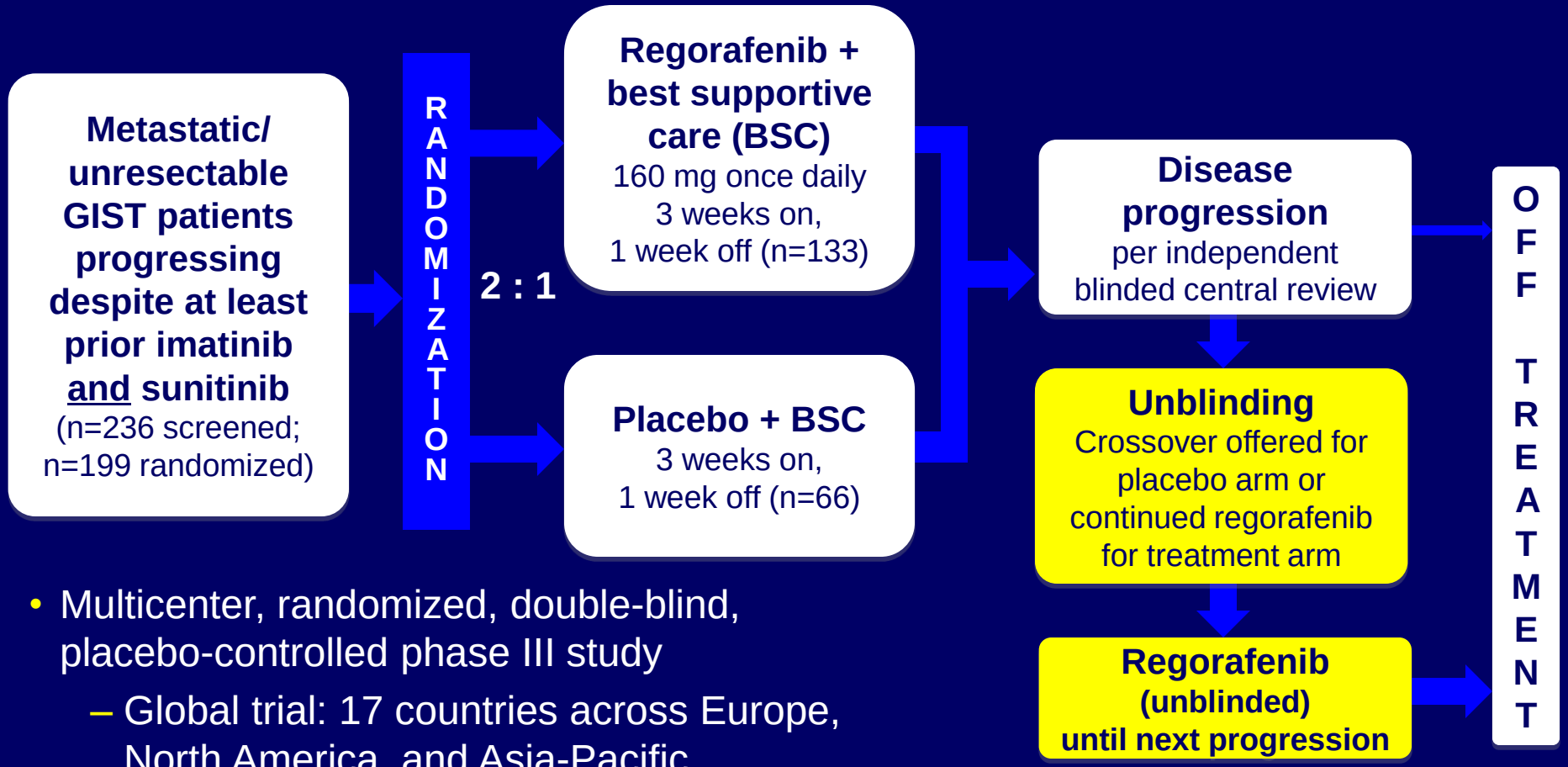


Biochemical activity

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

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

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")

Study endpoints

- **Primary endpoint:**
  - **Progression-free survival (PFS)**

    90% power to detect 100% increase in PFS, hazard ratio (HR)=0.5, with 1-sided overall α=0.01

- **Secondary endpoints:**
  - Overall survival (OS)
  - Time to progression
  - Overall response rate
  - Disease control rate
  - Duration of response

- **Exploratory endpoints:**
  - Correlative science to assess impact of GIST genotype on outcomes
  - Circulating DNA assay to screen more comprehensively for GIST kinase mutations (“liquid biopsy”)
  - Health-related quality of life

Patient eligibility

Key inclusion criteria	Key exclusion criteria
Histologically confirmed metastatic or unresectable GIST	Prior treatment with any VEGFR inhibitors other than sunitinib
Progression of GIST on imatinib (or severe intoleranceto imatinib) ***AND*** Progression of GIST on sunitinib	Other cancer (different histology) within 5 years before randomization
Age ≥18 years	Major surgical procedure, open biopsy, or significant trauma <28 days before study
ECOG performance status 0–1	Pregnancy or breastfeeding
Measurable disease according to modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1	Cardiovascular dysfunction: •Congestive heart failure •Myocardial infarction <6 months before study •Cardiac arrhythmias requiring therapy •Uncontrolled hypertension •Unstable or new-onset angina

GRID study was well balanced for baseline patient demographics

		Regorafenib (N=133)	Placebo (N=66)
Age, median years (range)		58 (18–82)	58 (25–87)
Sex, n (%)	Male	85 (63.9)	42 (63.6)
	Female	48 (36.1)	24 (36.4)
Race, n (%)	White	90 (67.7)	45 (68.2)
	Black	0 (0.0)	1 (1.5)
	Asian	34 (25.6)	16 (24.2)
Prior lines of GIST therapies, n (%)	2 (imatinib and sunitinib *only*)	74 (55.6)	39 (59.1)
	>2 (imatinib, sunitinib, and others)	59 (44.4)	27 (40.9)
ECOG, n (%)	0	73 (54.9)	37 (56.1)
	1	60 (45.1)	29 (43.9)

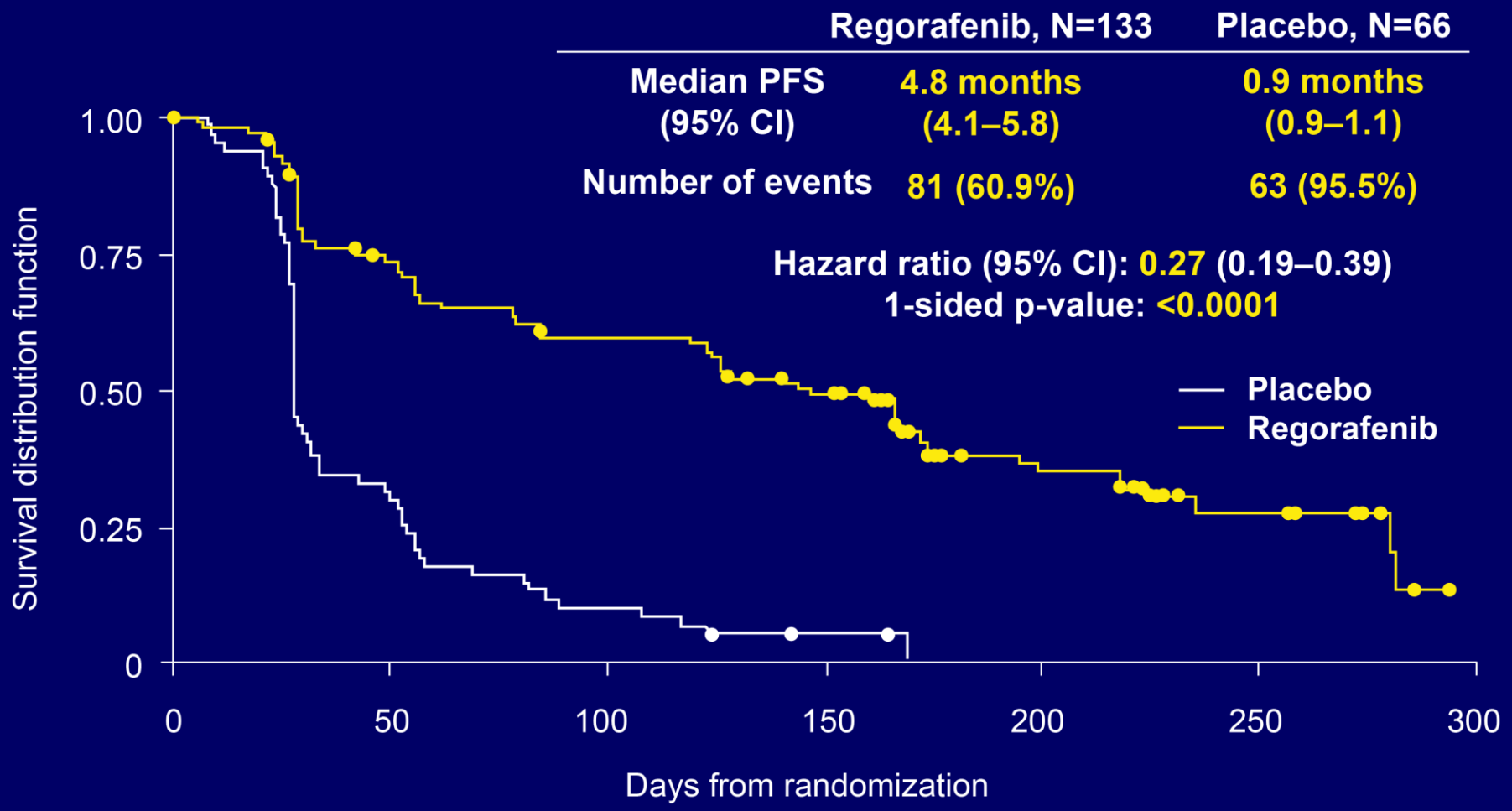
Adverse events on-study occurring in ≥20% of patients during double-blind treatment

NCI-CTCAE v4.0 term	Regorafenib (N=132), %				Placebo (N=66), %			
	All Grades	G3	G4	G5	All Grades	G3	G4	G5
Hypertension	59.1	27.3	0.8	0	27.3	4.5	0	0
HFSR	56.8	20.5	0	0	13.6	0	0	0
Fatigue	50.0	3.0	0	0	37.9	1.5	0	1.5
Diarrhea	46.2	7.6	0	0	9.1	0	0	0
Oral mucositis	40.9	1.5	0	0	9.1	1.5	0	0

On-study adverse events resulted in permanent discontinuation of study treatment, n (%)	Regorafenib	Placebo
	8 (6.1%)	5 (7.6%)

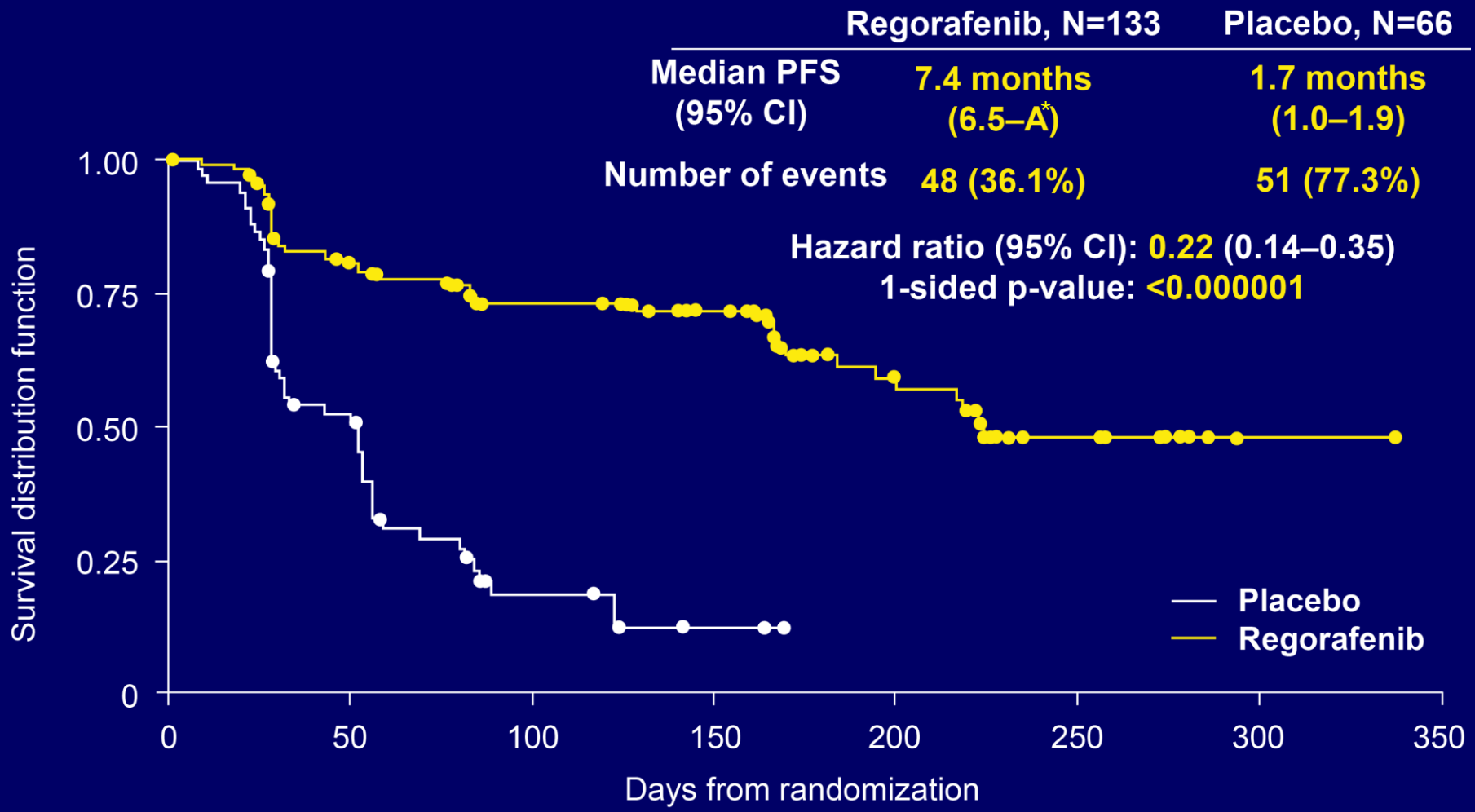
NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events
HFSR: Hand-foot skin reaction

Progression-free survival per blinded central review (primary endpoint)



Regorafenib significantly improved PFS *vs* placebo (p<0.0001)

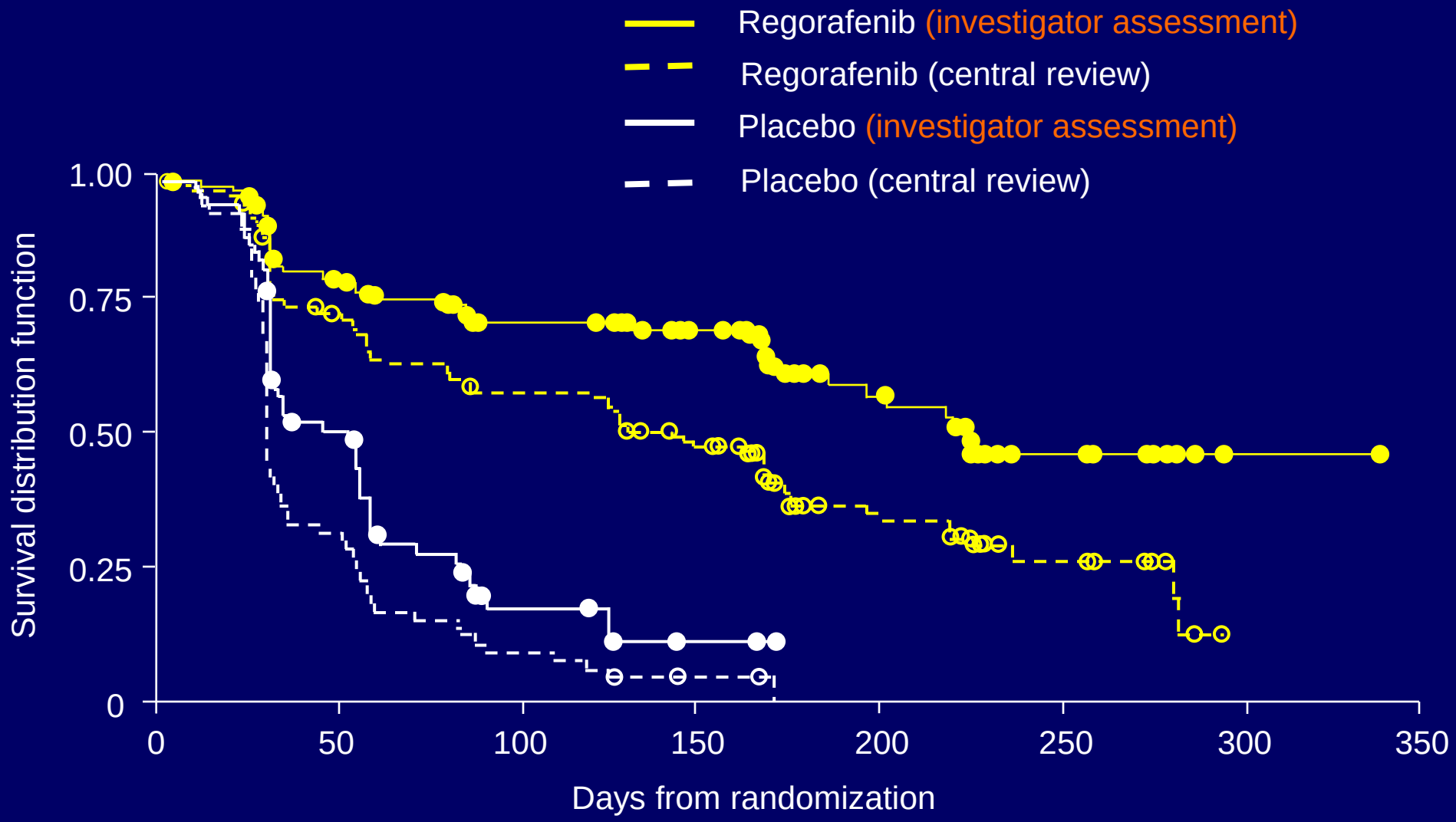
Progression-free survival per investigator assessment



Regorafenib significantly improved PFS *vs* placebo (p<0.000001)

*A: Value cannot be estimated due to censored data

Progression-free survival: Comparison of Central Review *vs* Investigator Assessments

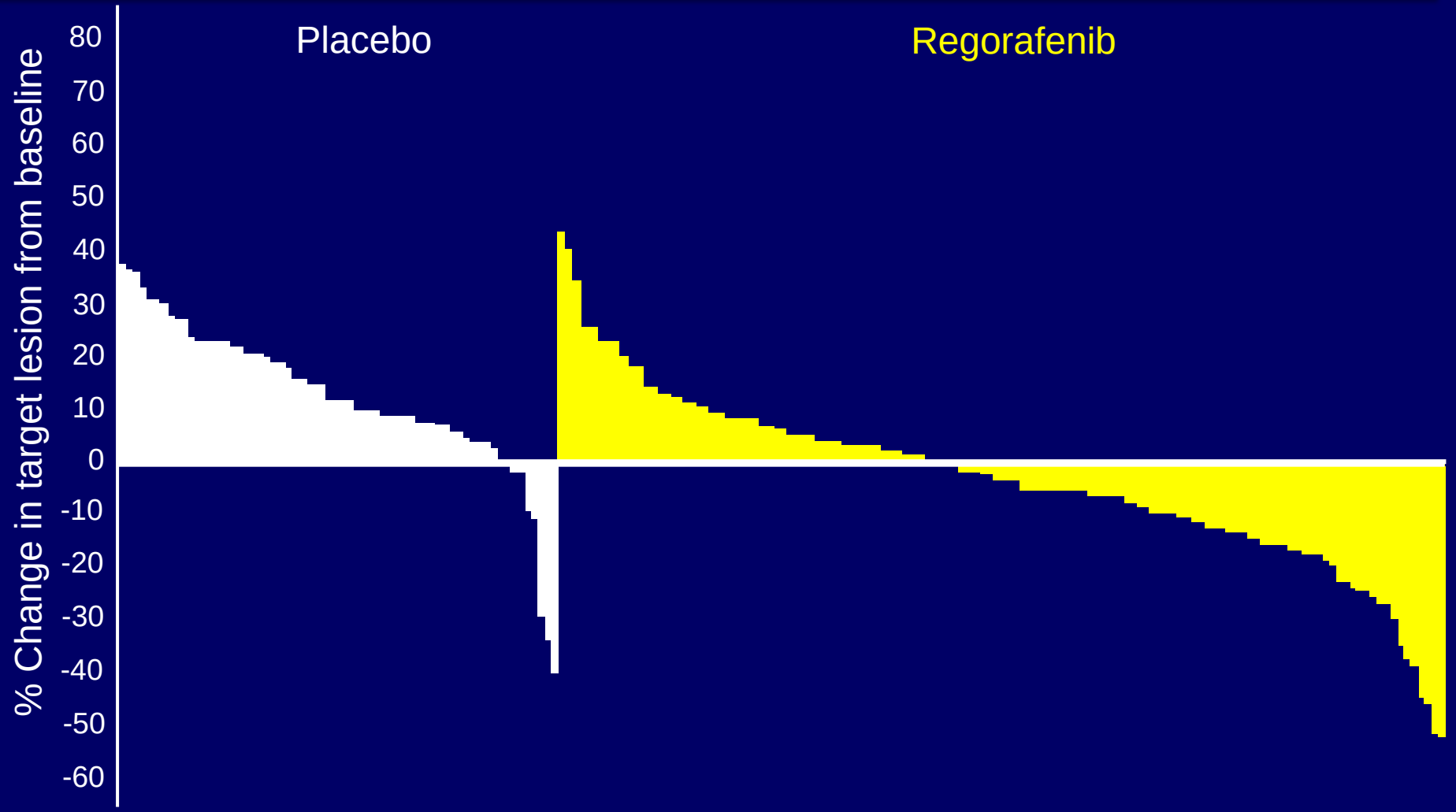


High rate of disease control despite low overall response rate with regorafenib

	Regorafenib (N=133), n (%)	Placebo (N=66), n (%)
Disease control rate Complete response + partial response + durable stable disease (≥12 weeks)	**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)

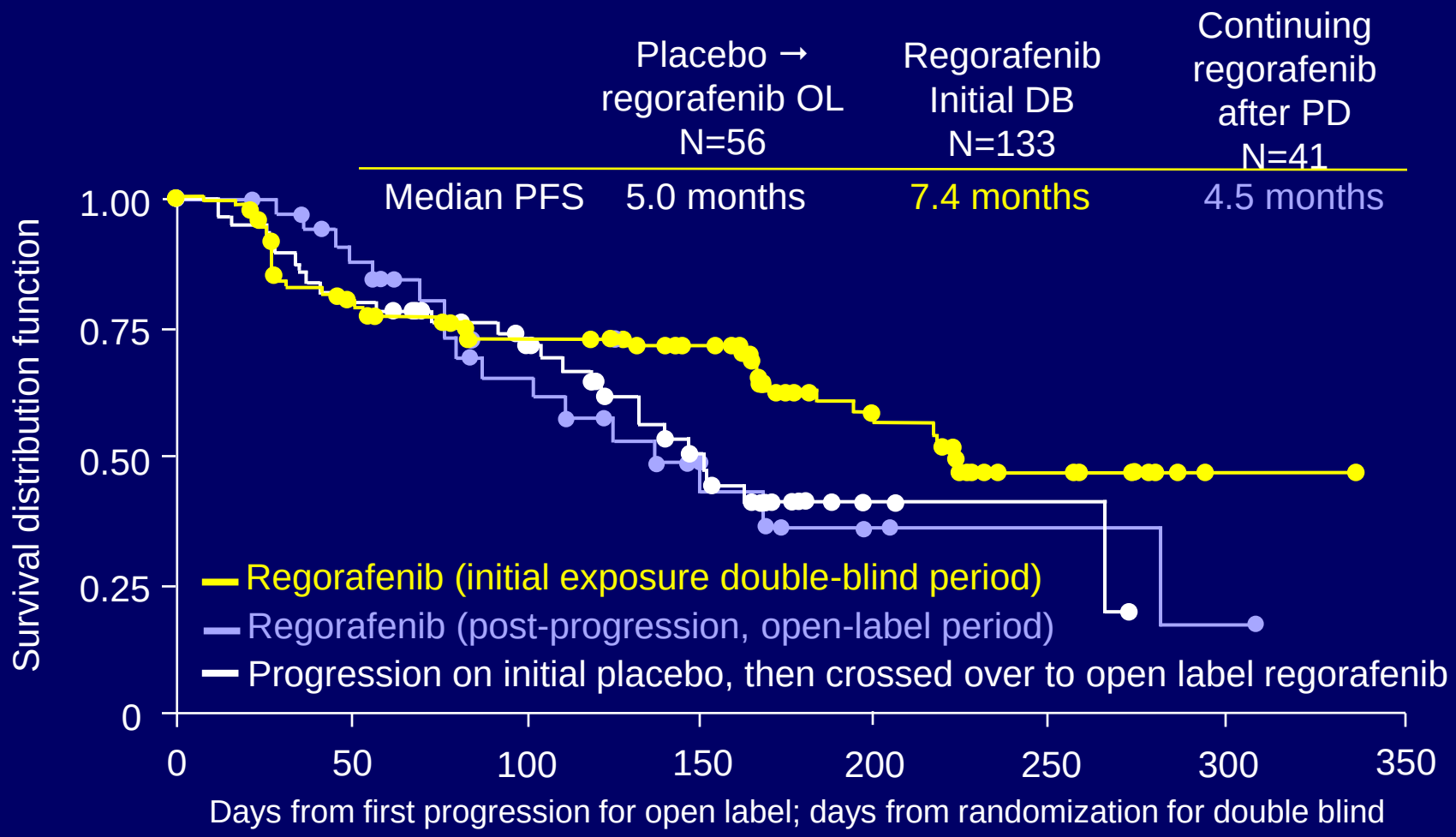
Responses based on modified RECIST v1.1

Despite low objective response rate, more frequent tumor shrinkage with regorafenib noted as best response in target lesion per central assessment

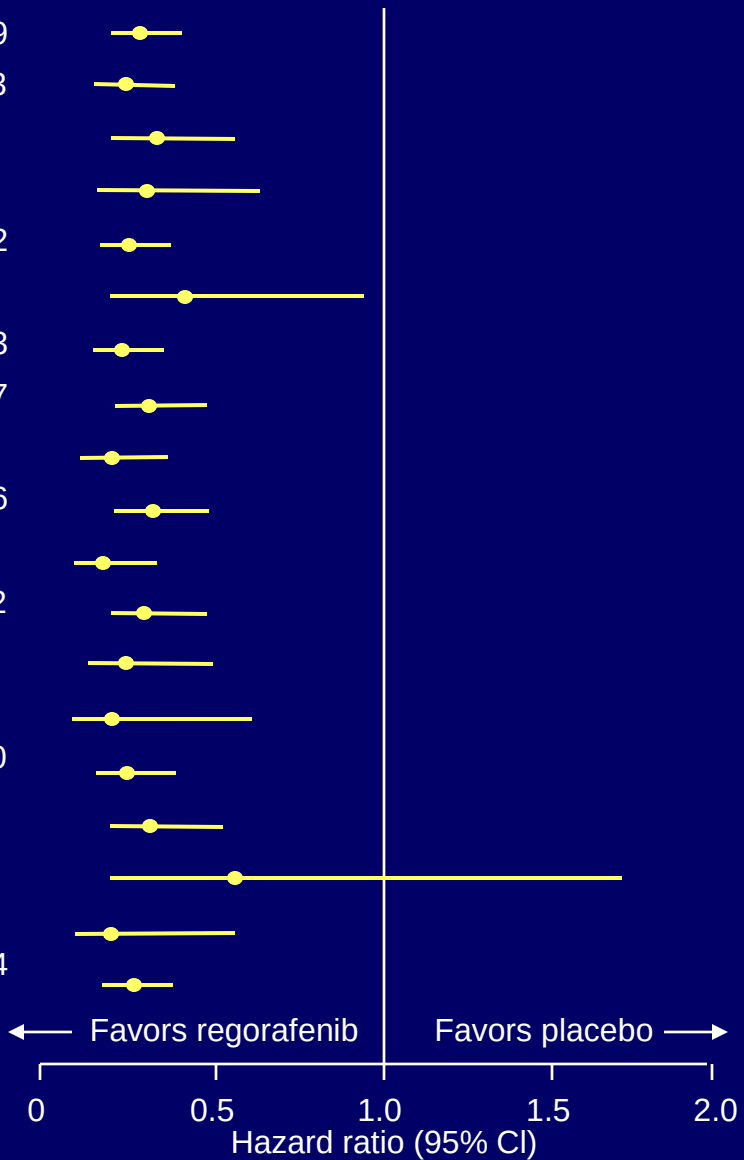


Continuing regorafenib dosing after progression: PFS with initial exposure during double-blind (DB) and following progression on DB

(all per investigator assessment)



Prespecified subgroup analysis: PFS per central review



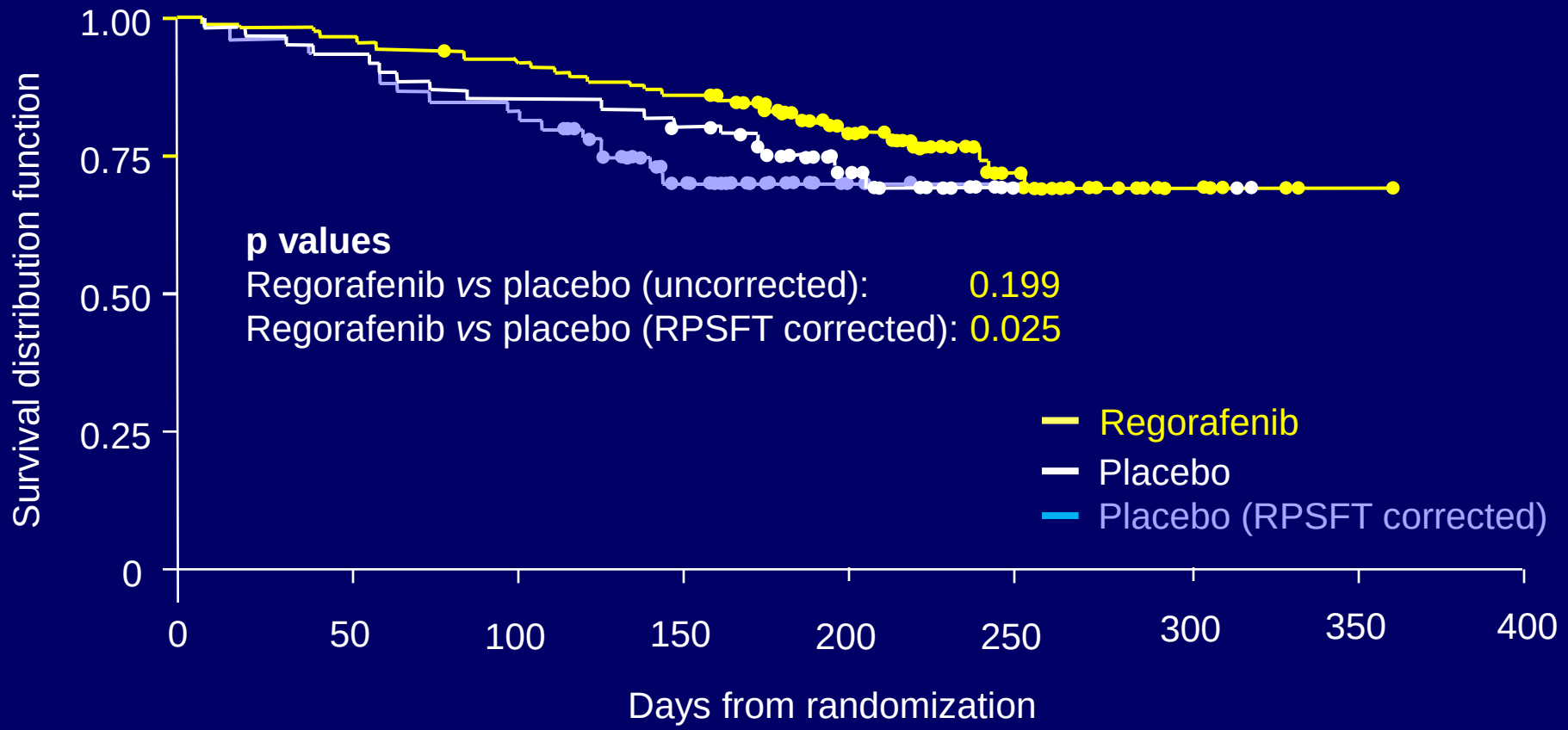
		N	Hazard ratio	95% CI
All patients		199	0.27	(0.19, 0.39)
Anticancer line	Third	113	0.23	(0.14, 0.37)
	Fourth or more	86	0.31	(0.18, 0.54)
Region	Asia	47	0.30	(0.15, 0.62)
	Rest of world	152	0.24	(0.16, 0.37)
	North America	36	0.42	(0.19, 0.92)
	Not North America	163	0.22	(0.15, 0.34)
Sex	Male	127	0.31	(0.20, 0.48)
	Female	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/m^2	112	0.29	(0.18, 0.46)
	25 to <30 kg/m^2	56	0.24	(0.12, 0.48)
	≥30 kg/m^2	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)

Baseline GIST genotype per site reports: exploratory analysis of outcomes

Tumor genotype	Regorafenib, n (%)	Placebo, n (%)	Total, n (%)
Prior GIST genotype available and reported at study entry (% total study population)	60 (45.1)	36 (54.5)	96 (48.2)
KIT exon 11 mutation	34 (56.7)	17 (47.2)	51 (53.1)
KIT exon 9 mutation	9 (15.0)	6 (16.7)	15 (15.6)
Wild-type *KIT* and *PDGFRA*	6 (10.0)	2 (5.6)	8 (8.3)
Unspecified or other exon mutant	11 (18.3)	11 (30.5)	22 (22.9)

Mutation biomarker	Progression-free survival					
	N	Events	HR	95%CI	Regorafenib, median months	Placebo, median months
KIT exon 11 mutation	51	40	0.212	0.098, 0.458	5.6	1.1
KIT exon 9 mutation	15	11	0.239	0.065, 0.876	5.4	0.9

Overall survival between GRID study arms: Estimating crossover impact via rank-preserving structural failure time (RPSFT) method*



*Crossover correction calculated using rank-preserving structural failure time (RPSFT) method

Summary

- Regorafenib significantly increased PFS compared with placebo in patients with metastatic or unresectable GIST
  - **PFS: median 4.8 *vs* 0.9 months, HR 0.27, p<0.0001**
- Regorafenib shows PFS benefit in most patient subgroups
- Interesting discrepancies between investigator assessments and central review were observed in progression assessment (and thus PFS)
- Post-progression, open-label regorafenib treatment showed sustained benefit
  - **Continuing regorafenib post-progression: median PFS, 4.5 months**
  - **Placebo crossed over to regorafenib: median PFS, 5.0 months**
- Overall survival rates were not statistically different, as expected, with crossover post-progression to regorafenib in majority of placebo-treated patients
  - RPSFT statistical correction for crossover demonstrates significant beneficial impact of regorafenib on overall survival

Thanks to patients, families, and colleagues at all of the investigating centers

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USA:	George Demetri, Mary Louise Keohan, Michael Heinrich, Margaret von Mehren, Robin Jones, Bruce Brockstein, Pamela Kaiser, Keith Skubitz, Michael Gordon

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Thank you for your attention

Back-up Slide for Question

Sensitivity analysis: investigator assessment *vs* central review

	Investigator assessment, n (%)	Central assessment, n (%)		
		Progression	No progression	All
Regorafenib (N=133)	Progression	39 (29.3)	5 (3.8)	44 (33.1)
	No Progression	37 (27.8)	52 (39.1)	89 (66.9)
	All	76 (57.1)	57 (42.9)	
Placebo (N=66)	Progression	50 (75.8)	0	50 (75.8)
	No Progression	12 (18.2)	4 (6.1)	16 (24.2)
	All	62 (93.9)	4 (6.1)	

Green shading denotes concordance; red shading denotes discordance