Monotherapy Administration of Sorafenib in Patients with Non-Small Cell Lung Cancer: Phase III, Randomized, Double-Blind, Placebo-Controlled MISSION Trial

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Conflict of Interest Disclosure

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- Honoraria
  - Bayer HealthCare
  - Lilly
  - Hoffmann-La Roche
  - Pfizer

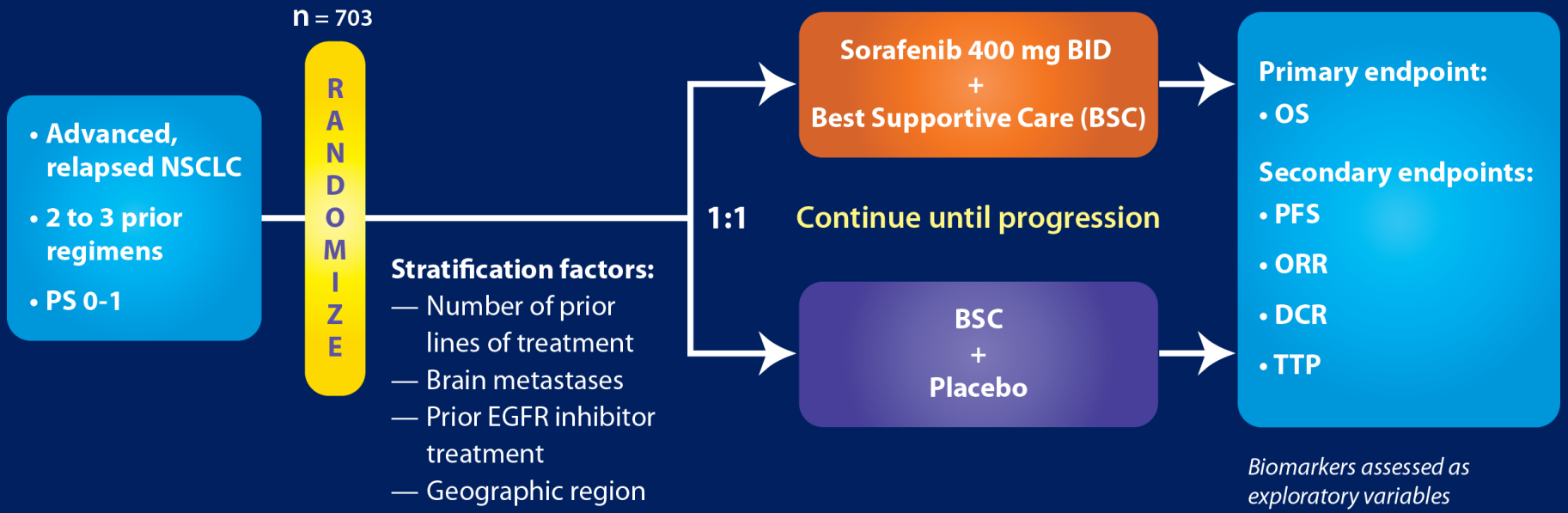
Background

- Sorafenib is a multikinase inhibitor targeting receptor tyrosine and serine/threonine kinases, including VEGF and PDGF receptors and c-Kit, and is approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma[1-3]
- The multikinase inhibitor sorafenib has been investigated and shown to have activity as monotherapy in phase II trials as second- or third-line treatment of patients with advanced NSCLC[4,5]
- Patients with prior exposure to chemotherapy and/or EGFR-TKI may benefit from further therapy
- We hypothesized that sorafenib as third-/fourth-line monotherapy in patients with relapsed or refractory, predominantly non-squamous NSCLC would improve overall survival (OS) compared with best supportive care (BSC)

[1]Wilhelm SM, et al. *Cancer Res* 2004;64:7099-7109.
[2]Escudier B, et al. *N Engl J Med* 2007;356:125-34.
[3]Llovet JM, et al. *N Engl J Med* 2008;359:378-390.
[4]Blumenschein GR Jr, et al. *J Clin Oncol* 2009;27:4274-4280.
[5]Schiller JH, et al. *J Clin Oncol* 2008;26:8014 (abst).

Study Objective and Design

- Objective
  - To compare the efficacy and safety of sorafenib plus BSC with BSC alone in patients with relapsed or refractory, advanced, predominantly non-squamous NSCLC with disease progression after two or three prior treatment regimens
- Design
  - Randomized, double-blind, placebo-controlled phase III trial conducted in 33 countries in Europe, North and South America, and Asia Pacific



Statistical Analyses

- Sample size based on OS
  - Study designed to detect a 33% increase in median OS (from 6.5 months to 8.7 months)
  - With a one-sided alpha of 0.025, a power of 92.6%, and a 1:1 randomization ratio, a total of 572 events required
- OS analyzed using log rank tests and the stratification factors used during randomization
- Secondary efficacy endpoints – PFS, DCR, best ORR, TTP – evaluated based on RECIST criteria
  - One sided significance level of 0.025

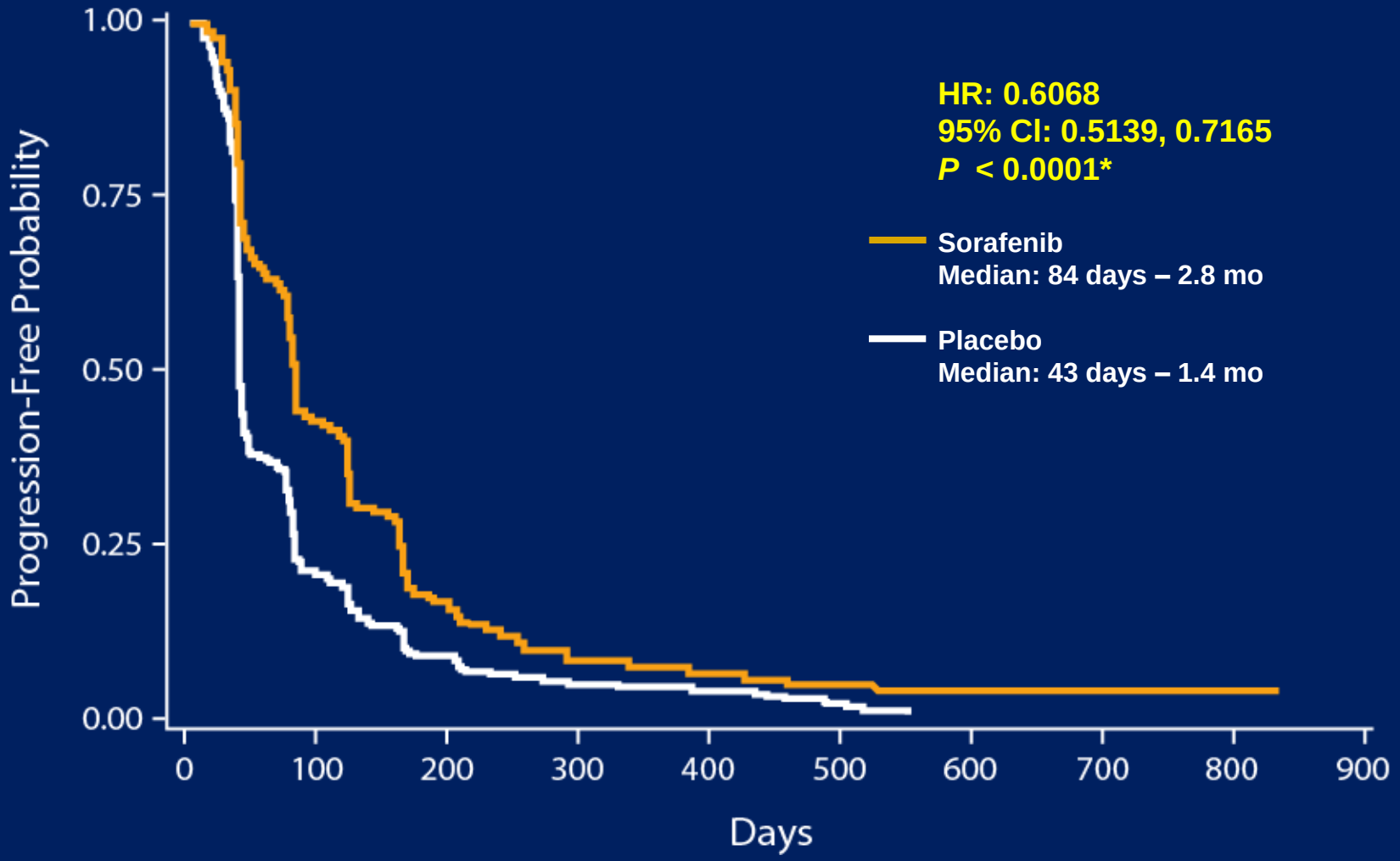
Baseline Patient Characteristics

	Sorafenib n=350 (%)	**Placebo** n=353 (%)
Median age, yr	59.0	62.0
Geographic region		
North America, Northern/ Western Europe	122 (34.9%)	119 (33.7%)
South America, Eastern Europe and Asia Pacific	228 (65.1%)	228 (65.1%)
Asia Pacific (only)	*174 (49.7%)*	*172 (48.7%)*
Male	186 (53.1%)	209 (59.2%)
Smoking status		
Non-smoker	161 (46.0%)	134 (38.0%)
Past or present smoker	181 (51.7%)	216 (61.2%)
ECOG PS		
0	110 (31.4%)	110 (31.2%)
1	233 (66.6%)	242 (68.6%)
Brain metastases present	56 (16.0%)	54 (15.3%)
Number of prior regimens		
2	188 (53.7%)	197 (55.8%)
3	158 (45.1%)	153 (43.3%)
Prior EGFR systemic therapy	209 (59.7%)	207 (58.6%)

Study Drug Administration
ITT Population

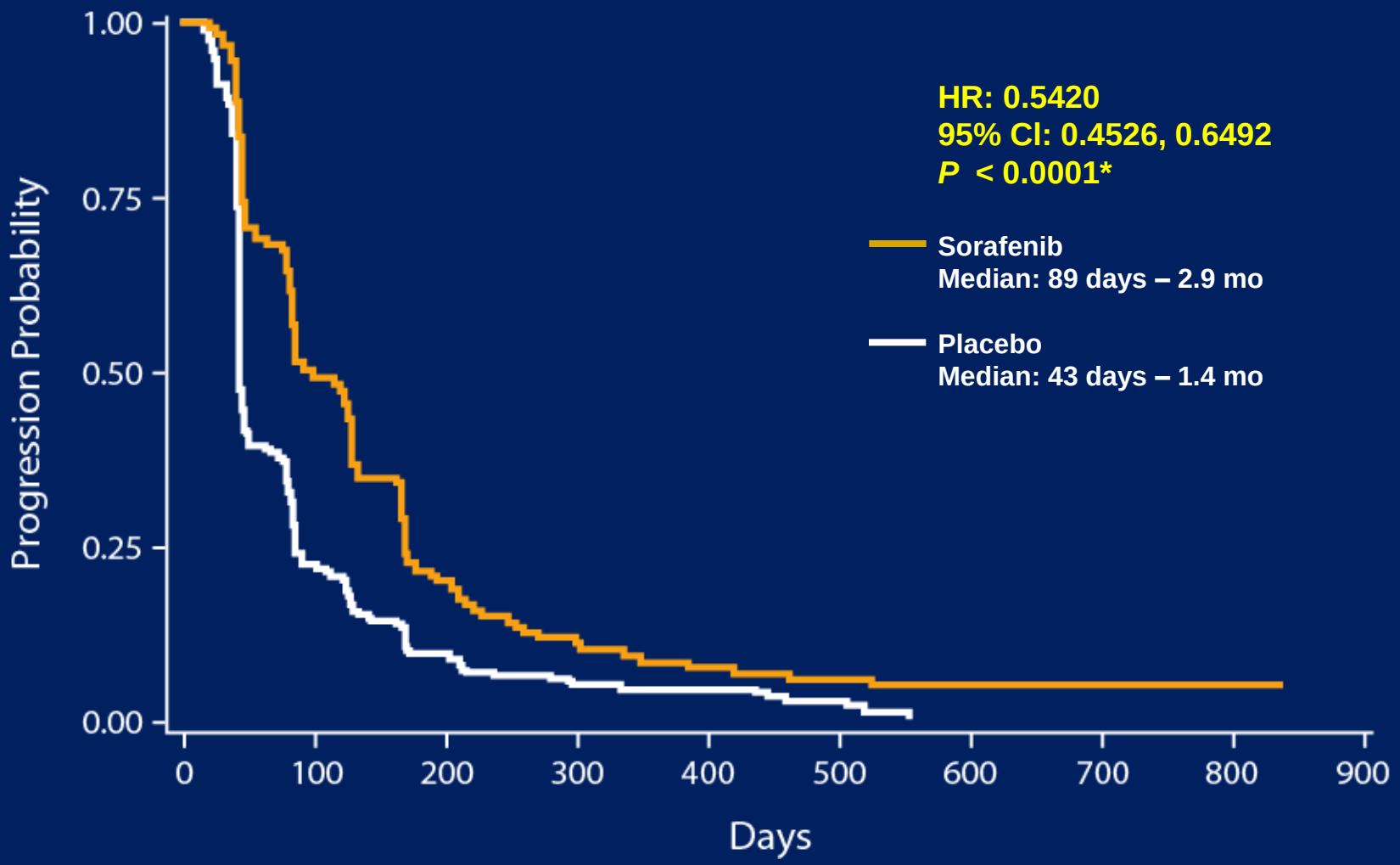
	Sorafenib (n=350)	Placebo (n=353)
Duration of treatment, weeks		
Median	12.0	6.3
Mean	18.0	11.6
Dose interruption, n (%)	181 (51.7%)	67 (19.0%)
Dose reduction, n (%)	121 (34.6%)	22 (6.2%)

Progression-Free Survival



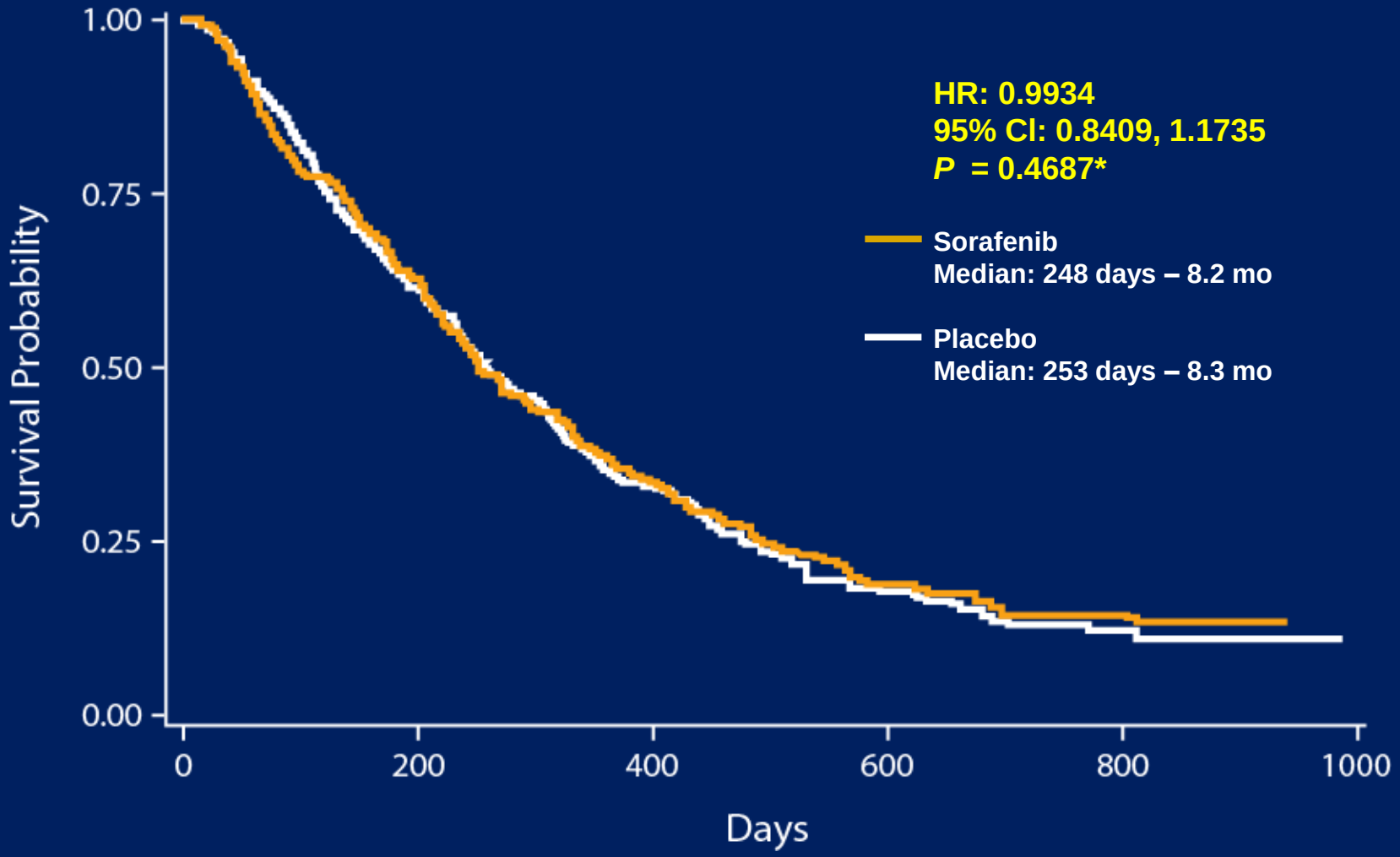
*one-sided stratified log-rank test

Time-to-Progression



*one-sided stratified log-rank test

Overall Survival (Primary endpoint)

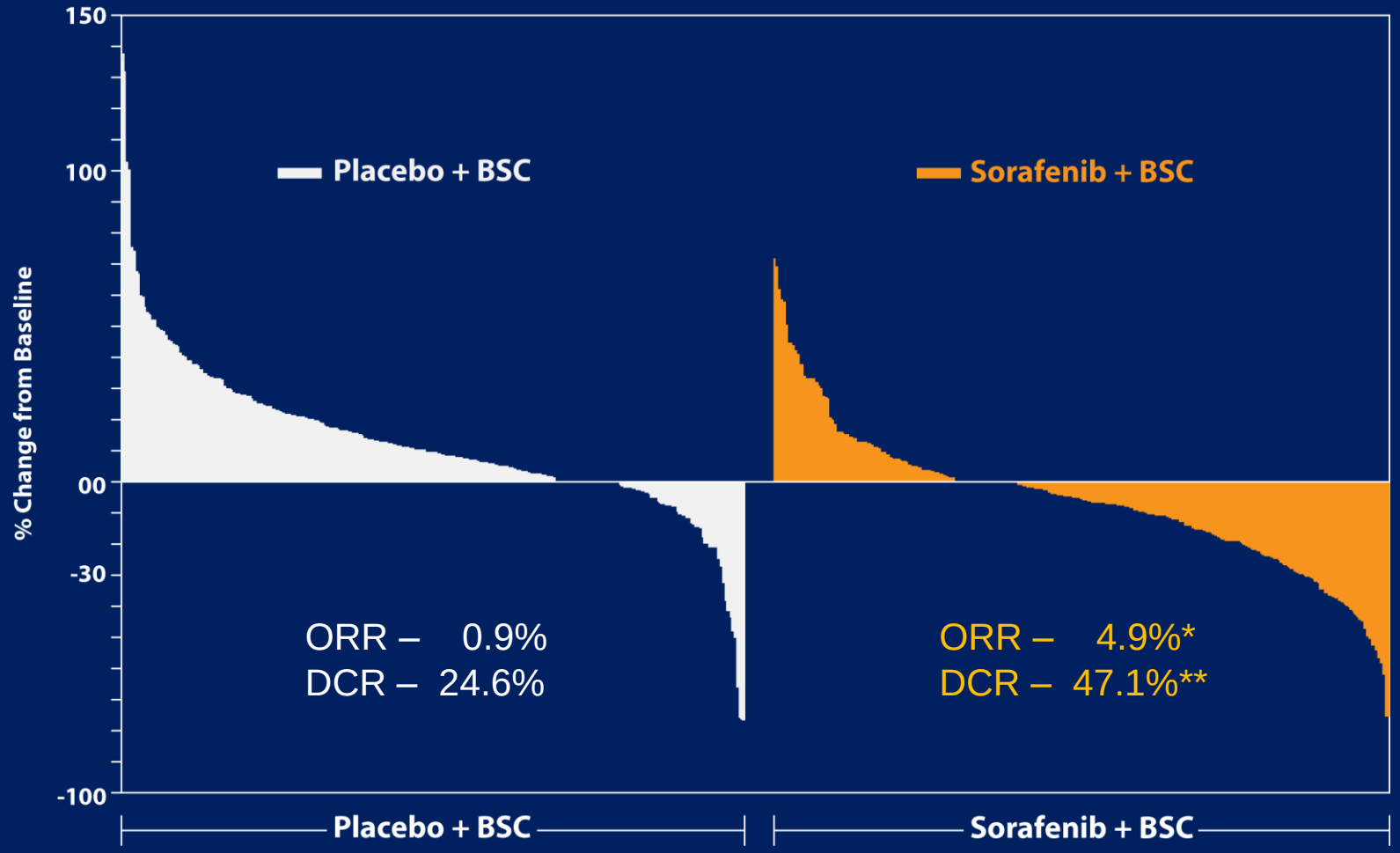


*one-sided stratified log-rank test

Post-progression Therapy

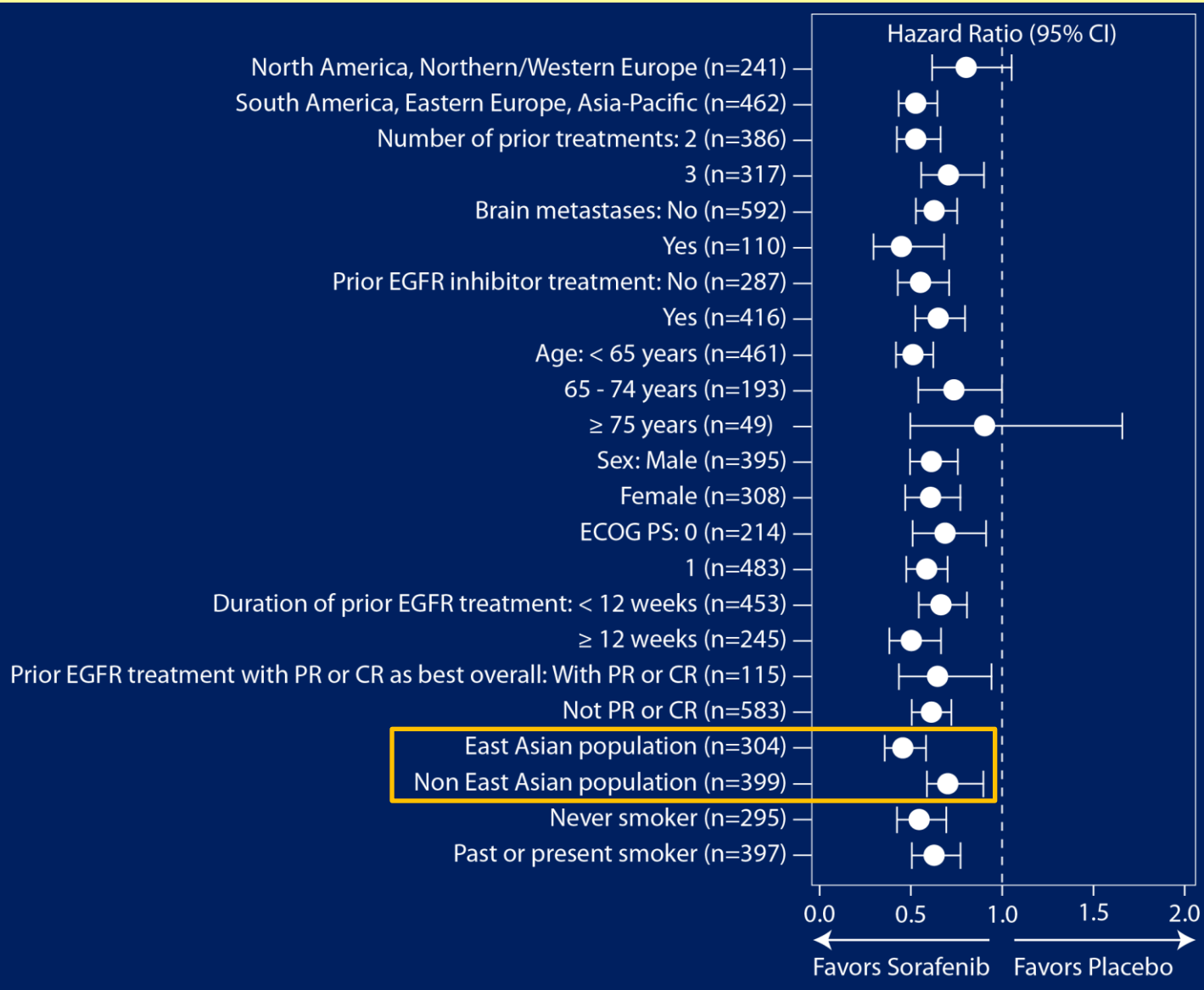
	Sorafenib n=350 (%)	Placebo n=353 (%)
Number of regimens		
1+	151 (43.1)	198 (56.1)
2+	62 (17.7)	78 (22.1)
3+	27 (7.7)	31 (8.8)
Anti-EGFR	59 (16.9)	74 (21)
Antimetabolite	67 (19.1)	94 (26.6)
Platinum	39 (11.1)	47 (13.3)
Docetaxel	28 (8.0)	34 (9.6)
Paclitaxel	5 (1.4%)	9 (2.5)
Taxane	12 (3.4)	24 (6.8)
Vinca alkaloid	34 (9.7)	35 (9.9)
Best reported outcome		
Partial response	17 (4.9)	20 (5.7)
Stable disease	49 (14)	75 (21.2)

Tumor Response in Individual Patients

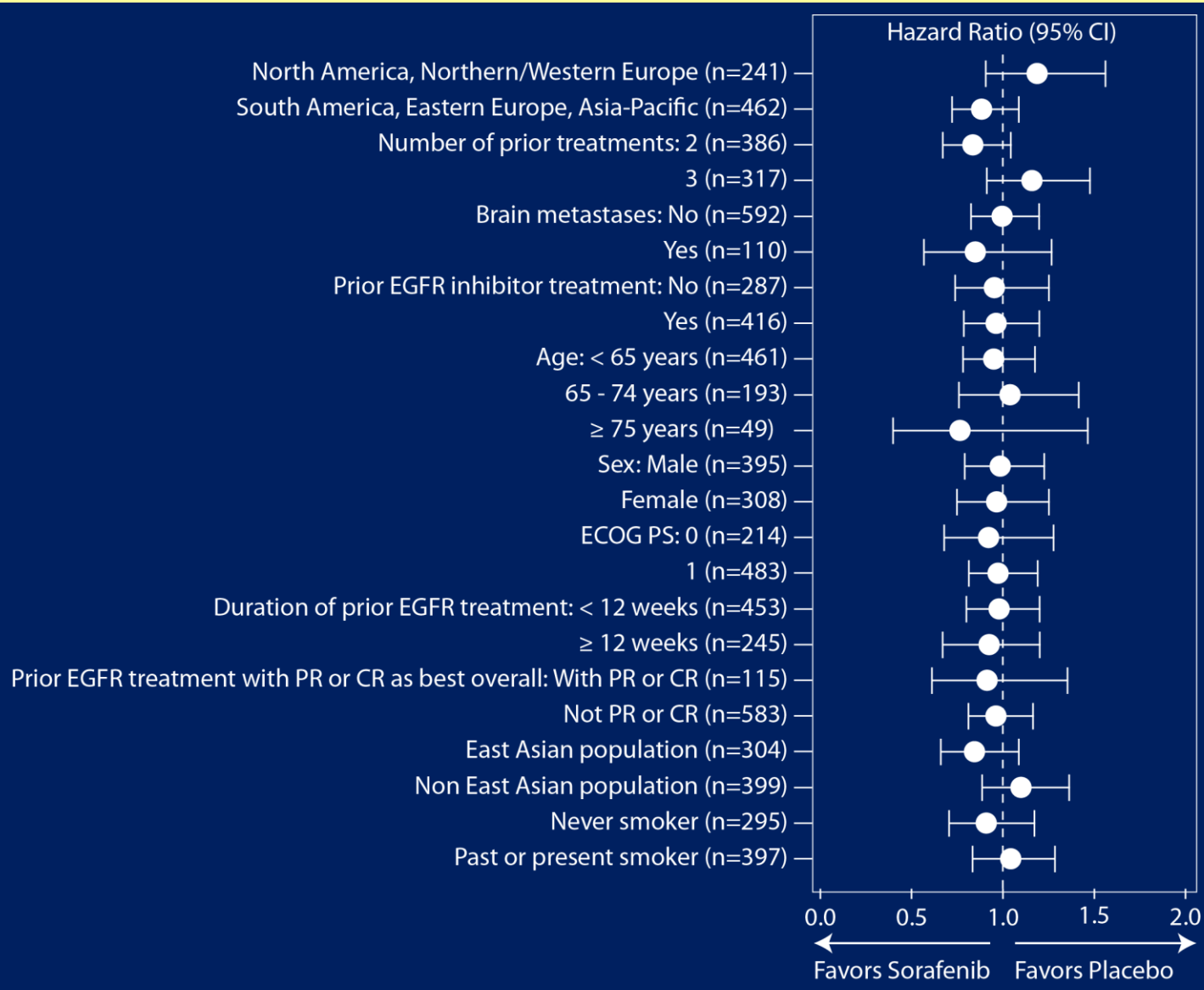


*p value <0.000001; one-sided Cochran-Mantel-Haenzel test
**p value=0.00086; one-sided Cochran-Mantel-Haenzel test

Subgroup Analyses – PFS



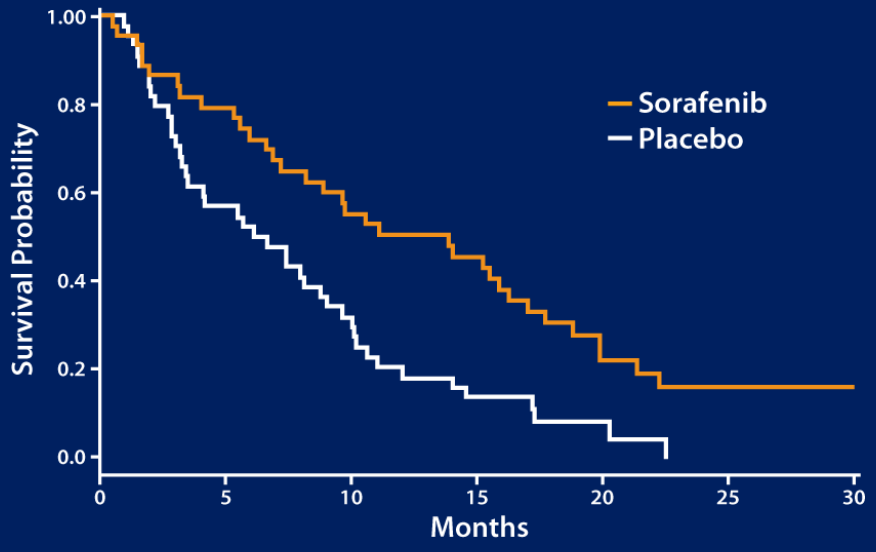
Subgroup Analyses - OS



Exploratory analysis: OS and PFS in Patients with EGFR Mutation in Tumor or Plasma

OS

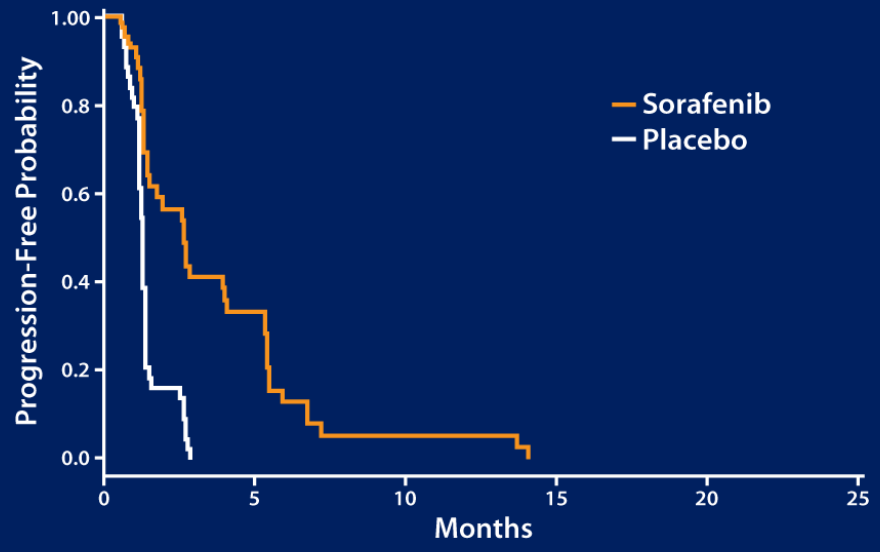
- Sorafenib N=44; Placebo N=45
- HR=0.48 (95% CI 0.3,0.76)
- P-value=0.002
- Sorafenib median OS= 13.9 mo (423d)
- Placebo median OS= 6.5 mo (197d)



Biomarker*treatment interaction analysis: p-value=0.023

PFS

- Sorafenib N=44; Placebo N=45
- HR=0.27 (95% CI 0.16,0.46)
- P-value<0.001
- Sorafenib median PFS= 2.7 mo (83d)
- Placebo median PFS= 1.4 mo (42d)



Biomarker*treatment interaction analysis: p-value=0.015

Mok TS, et al. *ESMO* 2012, Abstract LBA 9.

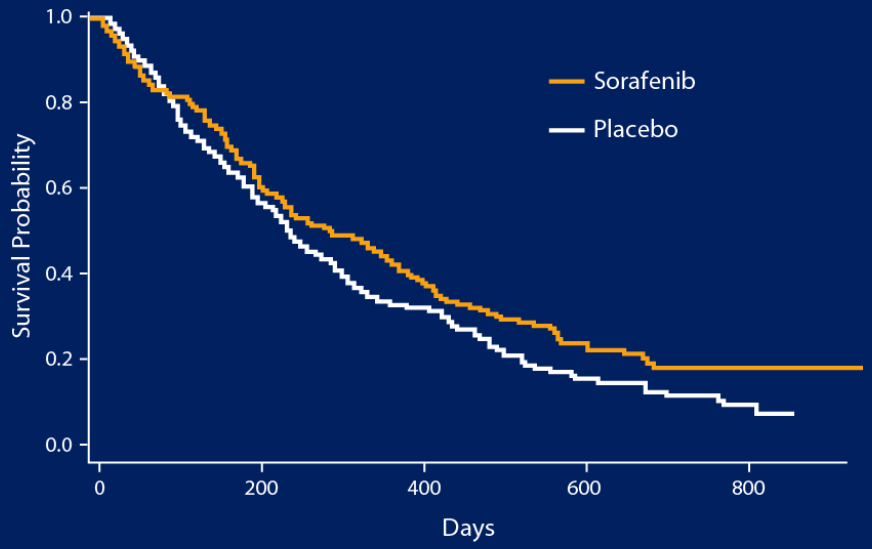
Outcomes for patients providing samples for biomarker testing (N=347)

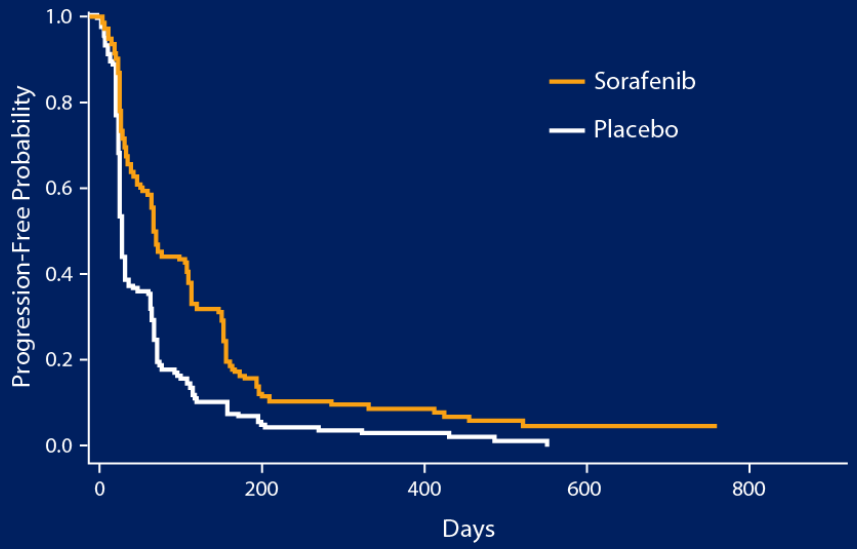
OS

- Sorafenib N=166; Placebo N=181
- HR=0.79 (95% CI 0.63,1.01)
- P-value=0.055
- Sorafenib median OS = 296d
- Placebo median OS = 249d

PFS

- Sorafenib N=166; Placebo N=181
- HR=0.56 (95% CI 0.45,0.71)
- P-value<0.001
- Sorafenib median PFS = 82d
- Placebo median PFS = 43d





Population providing biomarker samples is not representative of the overall population. Efficacy outcomes of this biomarker subgroup should be interpreted in light of the overall efficacy results.

Safety Overview

	CTC Grade	Sorafenib n=346, (%)	Placebo n=351, (%)
Treatment emergent adverse events (AEs)	All	342 (98.8%)	318 (90.6%)
	3	139 (40.2%)	66 (18.8%)
	4	14 (4.0%)	24 (6.8%)
	5	80 (23.1%)	46 (13.1%)
Drug-related treatment emergent AEs	All	304 (87.9%)	173 (49.3%)
	3	127 (36.7%)	18 (5.1%)
	4	6 (1.7%)	6 (1.7%)
	5	5 (1.4%)	0
Serious treatment emergent AEs	All	135 (39.0%)	111 (31.6%)
	3	36 (10.3%)	36 (10.3%)
	4	10 (2.9%)	18 (5.1%)
	5	80 (23.1%)	46 (13.1%)
Serious drug-related AEs	All	28 (8.1%)	11 (3.1%)
	3	16 (4.6%)	2 (0.6%)
	4	6 (1.7%)	5 (1.4%)
	5*	5 (1.4%)	0

*Including 2 patients with CNS ischemia and 1 each with cardiac ischemia/infarction, constitutional symptoms (other), and infection (other).

Treatment-emergent Adverse Events Occurring in >10% of Patients in Either Group

	Sorafenib, n=346 (%)			Placebo, n=351 (%)		
	All grade	G3	G4	All grade	G3	G4
Hand-foot skin reaction	55	16	0	6	1	0
Rash/desquamation	40	4	0	12	0	0
Fatigue	36	8	<1	28	4	0
Diarrhea	36	3	0	12	<1	0
Anorexia	30	3	0	18	2	0
Dyspnea	28	5	2	30	5	2
Cough	23	2	0	19	0	0
Hypertension	20	5	<1	5	1	0
Alopecia	19	0	0	1	0	0
Nausea	17	2	0	16	1	0
Mucositis (functional/symptomatic), oral	17	1	0	4	0	0
Hemorrhage/bleeding (all)	16	1	0	11	1	0
Vomiting	15	1	0	13	1	0
Constipation	14	1	0	14	1	0
Pain, chest/thorax, NOS	13	3	0	9	1	0
Weight loss	12	1	0	5	0	0
Fever	12	0	0	5	0	0
Headache	11	1	0	7	1	0
Pain, back	10	2	0	11	1	0

Conclusions

- Sorafenib monotherapy did not improve OS (HR 0.99) as third- or fourth-line treatment in patients with advanced NSCLC
- Secondary efficacy endpoints were successfully met, including PFS (HR 0.61) and TTP (HR 0.54). Statistically significant improvements in ORR and DCR were also observed
- Safety and tolerability data were as expected
- Treatment options for third-/fourth-line NSCLC patients remain an unmet medical need. The role of targeted therapy in defined NSCLC populations (e.g. genetic and/or plasma biomarker subsets) warrants further investigation

MISSION Trial Investigators

154 Centers in 33 Countries

We thank the patients for their contribution to this study

Austria: Horst Olschewski, Kurt Aigner, Josef Bolitschek

Belgium: Philippe Collard, Michiel Thomeer, Benoit Colinet

Brazil: José Rodrigues Pereira, Aline Lima, Aline Andrade, Carlos Barrios, Oren Smaletz, Rodrigo Pereira, Henrique Fernandes

Bulgaria: Assen Dudov, Danail Damyanov, Vladimir Kanarev, Petar Petrov, Violina Taskova, Dimitar Kalev

Canada: Vera Hirsh

Chile: Osvaldo Aren, Mónica Ahumada

China: Yan Sun, Yilong Wu, Li Zhang, Meilin Liao, Caicun Zhou, Shukui Qin, Jie Wang, Hong Zhao, Xiaoqing Liu, Hongming Pan, Yiping Zhang, You Lu

France: Bruno Coudert, Jaafar Bennouna, Jean-Claude Guerin, Maurice Perol, Eric Pichon, Eric Dansin, Denis Moro-Sibilot, Radj Gervais, Thierry Chatellier

Germany: Martin Reck, Joachim von Pawel, Michael Thomas, Jörg Mezger, Jochen Greiner, Walburga Engel-Riedel, Claus-Peter Schneider

Greece: Vassilis Georgoulias, Constantinos Syrigos, Constantinos Zarogoulidis

Hong Kong: Tony Mok, James C.M. Ho

Hungary: Marton Gyulai, Edina Tolnay, Sandor Tehenes, Erzsebet Juhasz, Balazs Medgyasszay, Agnes Bartos, Gyorgy Losonczy

India: Rajanish Nagarkar, Gangadharan Vadavattan, Minish Jain

Indonesia: Noorwati Sutandyo

Israel: Maya Gottfried, Henri Hayat, Arnold Cyjon, Salomon Stemmer, Thomas Tichler, Nili Ramu

Italy: Armando Santoro, Filippo De Marinis, Lucio Crinó, Marcello Tiseo, Federico Cappuzzo, Alfredo Falcone, Silvia Novello, Paolo Bidoli, Cesare Gridelli, Francesco Grossi

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Turkey: Tuncay Goksel, Perran Yumuk, Mustafa, Ozguroglu, Haluk Onat, Gungor Utkan

United Kingdom: Mary O'Brien, Sanjay Popat, Marianne Nicolson, Clive Mulatero, Tim G. Eisen, Fiona Blackhall, Jeremy Braybrooke, David Chao

United States: J. Beck, Heather Wakelee

Supported by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals

Backup

Summary of Best Response by RECIST Criteria

n (%)	Sorafenib n=350	Placebo n=353
Overall Response Rate *(CR + PR)*	17 (4.9)*	3 (0.9)
CR	0 (0)	0 (0)
PR	17 (4.9)	3 (0.9)
SD	148 (42.3)	84 (24.3)
PD	10 (2.9)	12 (3.4)
Disease Control Rate *(CR + PR + SD)*	165 (47.1)**	87 (24.7)

*p value <0.000001; one-sided Cochran-Mantel-Haenzel test
**p value=0.00086; one-sided Cochran-Mantel-Haenzel test