Association between Tumor EGFR and KRAS Mutation Status and Clinical Outcomes in NSCLC Patients Randomized to Sorafenib plus Best Supportive Care (BSC) or BSC Alone: Subanalysis of the Phase III MISSION Trial

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Conflict of interest disclosure

Tony S. Mok

- Honoraria
  - AstraZeneca
  - Eli Lilly
  - Eisai
  - BeiGene
  - Pfizer
  - Boehringer Ingelheim
  - Hoffmann-La Roche
  - Merck Serono
  - Bristol-Myers Squibb
  - AVEO
  - Taiho
  - GlaxoSmithKline Biologicals
- Speaker
  - AstraZeneca
  - Eli Lilly
  - Boehringer Ingelheim
  - Hoffmann-La Roche
  - Merck Serono
- Research Funding
  - AstraZeneca

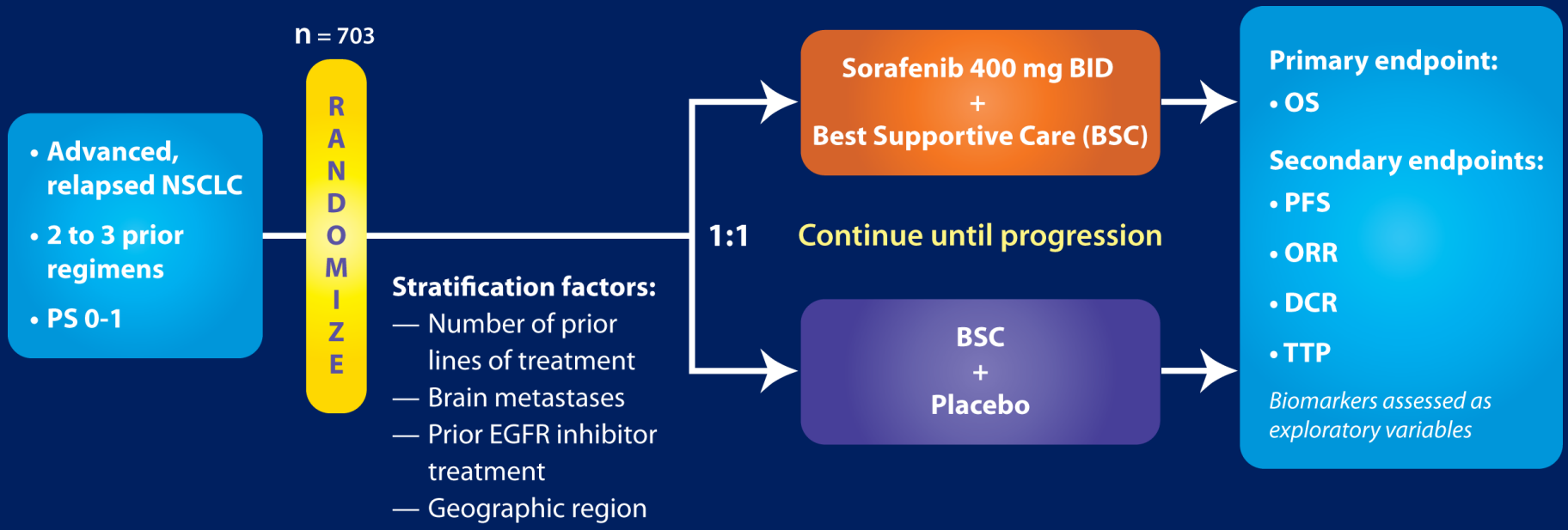
Background

- Personalized treatment with targeted agents has become standard in lung cancer patients with specific driver oncogenes[1-3]
- Sorafenib is a multi-kinase inhibitor that has been investigated in phase II and III trials as second/third-line monotherapy in patients with advanced NSCLC[4-6]
- Prior studies suggested that KRAS is a potential predictive biomarker for sorafenib efficacy in NSCLC patients[7,8]
- MISSION is a multi-nation multi-center randomized phase III study comparing sorafenib plus BSC with BSC alone as third/fourth line therapy in an unselected population with advanced NSCLC
- Current study explores the predictive value of EGFR and KRAS mutations in patients from MISSION with available tumor/plasma samples

[1]Mok TS, et al. *N Engl J Med* 2009;361:947-957.
[2]Rosell R, et al. *Lancet Oncol* 2012;13:239-246.
[3]Gandhi L, Janne PA, *Clin Cancer Res* 2012;18:3737-3742.
[4]Blumenschein GR Jr , et al. *J Clin Oncol* 2009;27:4274-4280.
[5]Schiller JH, et al. *J Clin Oncol* 2008;26 Suppl:Abstract 8014.
[6]Paz-Ares L, et al. *ESMO* 2012, Abstract LBA 33.
[7]Dingemans AM, et al. *2011 European Multidisciplinary Cancer Congress,* LBA27.
[8]Blumenschein GR Jr , et al. *Cancer Biomark* 2011;10:287-298.

MISSION: 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



MISSION: Overall study results to be presented*

Berlin, May 22, 2012 – Bayer HealthCare and Onyx Pharmaceuticals, Inc. today announced that a Phase III trial evaluating Nexavar® (sorafenib) tablets in patients with advanced relapsed or refractory non-squamous non-small cell lung cancer (NSCLC) whose disease progressed after two or three previous treatments, did not meet its primary endpoint of improving overall survival. An improvement in the secondary endpoint of progression-free survival (PFS) was observed... (From May 22 press release)

* Full results to be presented on Monday, 1 October
Abstract: "Monotherapy Administration of Sorafenib in Patients with Non-Small Cell Lung Cancer: Phase III, Randomized, Double-Blind, Placebo-Controlled MISSION Trial" (LBA33_PR)
Session: Proffered Paper - NSCLC, metastatic II
Date/time/place: Monday, 1 October 2012, 12:00 PM, Hall A
Presenter: L. Paz-Ares

Methods: Biomarker analysis

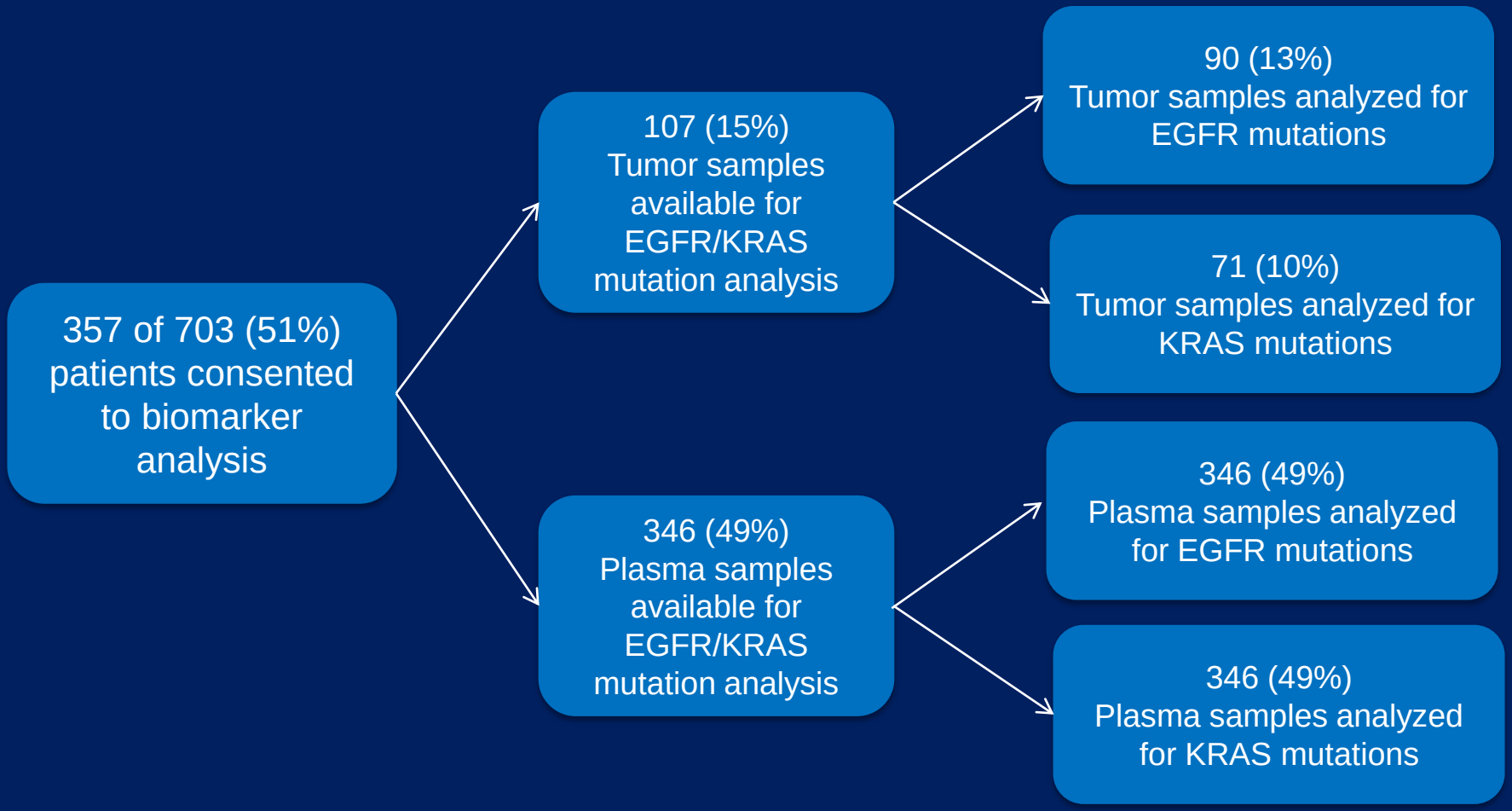
- Archival tumor samples and/or fresh blood samples (during screening) were collected from randomized patients who consented to biomarker study

- EGFR and KRAS mutation status were analyzed in tumor samples and/or in circulating tumor DNA from plasma using BEAMing (Beads, Emulsions, Amplification, and Magnetics; Inostics, Hamburg, Germany).[1,2] Assay sensitivity defining mutation positivity was 0.02% for plasma and 1% for tumor tissue

- Statistical plan
  - The relationships between baseline biomarker concentrations and the effect of sorafenib treatment on OS and PFS were evaluated using Cox proportional hazards models with an interaction term
  - Due to the exploratory nature of the biomarker analyses, p-values must be interpreted with caution because they were not corrected for multiple testing, subset not balanced by randomization, sample size not powered for the analyses

[1]Dressman D, et al. *Proc Natl Acad Sci USA* 2003;100:8817-8822.
[2]Diehl F, et al. *Proc Natl Acad Sci USA* 2005;102:16368-16273.

Biomarker analysis



Results: biomarker analysis

	EGFR mutation	KRAS mutation
Tumor positive	12 / 90 (13%)	20 / 71 (28%)
Tumor negative	78 / 90 (87%)	51 / 71 (72%)
Plasma positive	85 / 346 (25%)	62 / 346 (18%)
Plasma negative	261 / 346 (75%)	284 / 346 (82%)
Either tumor or plasma positive	89 / 347 (26%)	68 / 347 (20%)

Concordance of tumor and plasma mutations

EGFR		Tumor	
		Wild-type	Mutant
Plasma	Wild-type	75	2
	Mutant	4	8
Total number		89	
Concordance (%)		93.3*	

KRAS		Tumor	
		Wild-type	Mutant
Plasma	Wild-type	45	5
	Mut	6	14
Total number		70	
Concordance (%)		84.3*	

* P<0.001 by chi-square test

Demographics based on EGFR mutation status

	EGFR mutation		EGFR wild type	
	Sorafenib n=44 (%)	**Placebo n=45 (%)**	**Sorafenib n=122 (%)**	**Placebo n=136 (%)**
Median age, yr	57.5	56	62.5	62.5
Male	17 (39)	24 (53)	71 (58)	83 (61)
Smoking status				
Non-smoker	28 (64)	23 (51)	40 (33)	32 (24)
Past or present smoker	15 (34)	22 (49)	80 (65)	104 (76)
ECOG PS				
0	12 (27)	18 (40)	45 (37)	52 (38)
1	31 (70)	27 (60)	77 (63)	84 (62)
Brain metastases present	9 (20)	13 (29)	16 (13)	20 (15)
Prior EGFR systemic therapy	37 (84)	37 (82)	68 (56)	72 (53)
Number of prior regimens				
2	21 (48)	27 (60)	66 (54)	73 (54)
3	22 (50)	18 (40)	53 (43)	63 (46)

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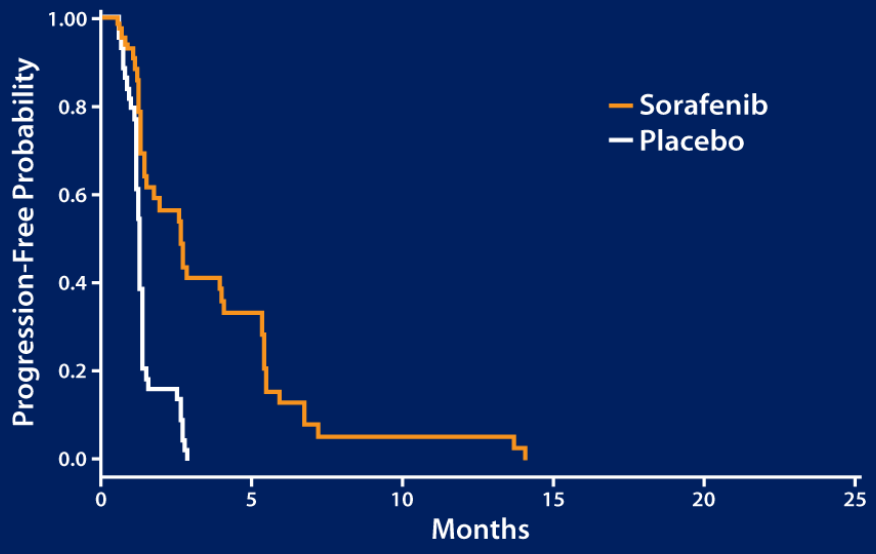
Progression-free survival based on EGFR mutation status

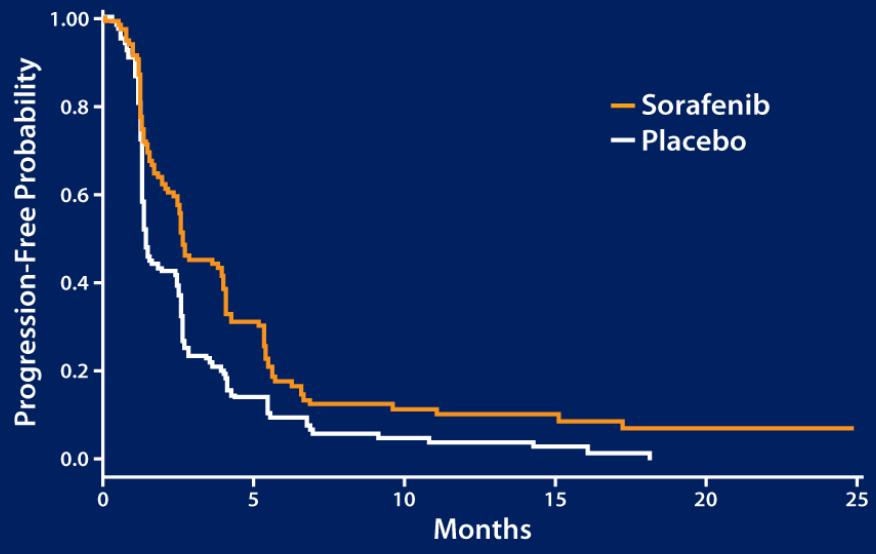
Pts with EGFR mut (in tumor or plasma)

- 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)



Pts with EGFR wt

- Sorafenib N=122; Placebo N=136
- HR=0.62 (95% CI 0.48,0.82)
- P-value<0.001
- Sorafenib median PFS= 2.7 mo (82d)
- Placebo median PFS= 1.5 mo (46d)

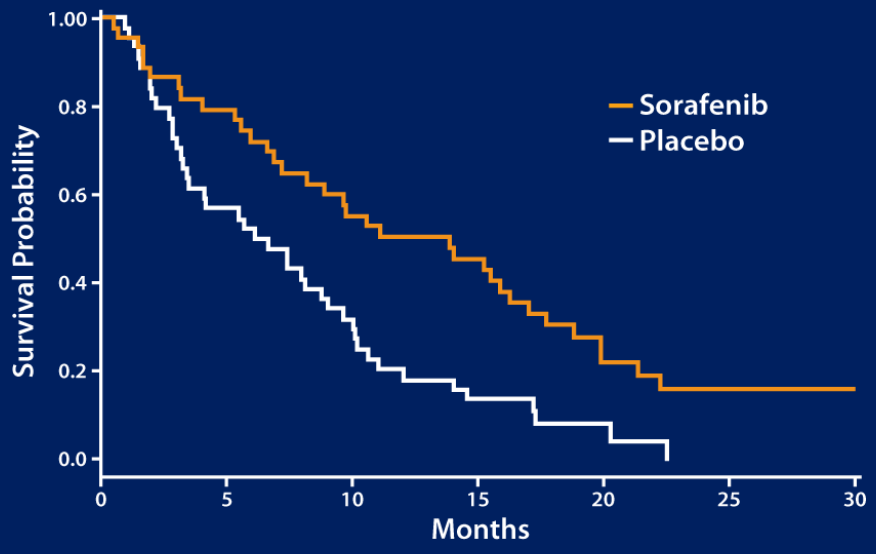


Biomarker*treatment interaction analysis: p-value=0.015

Overall survival based on EGFR mutation status

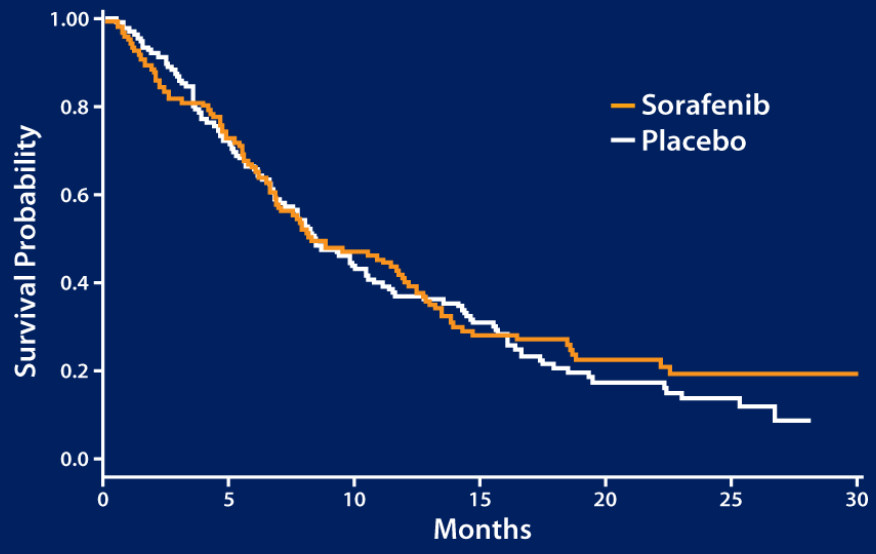
Pts with EGFR mut (in tumor or plasma)

- 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)



Pts with EGFR wt

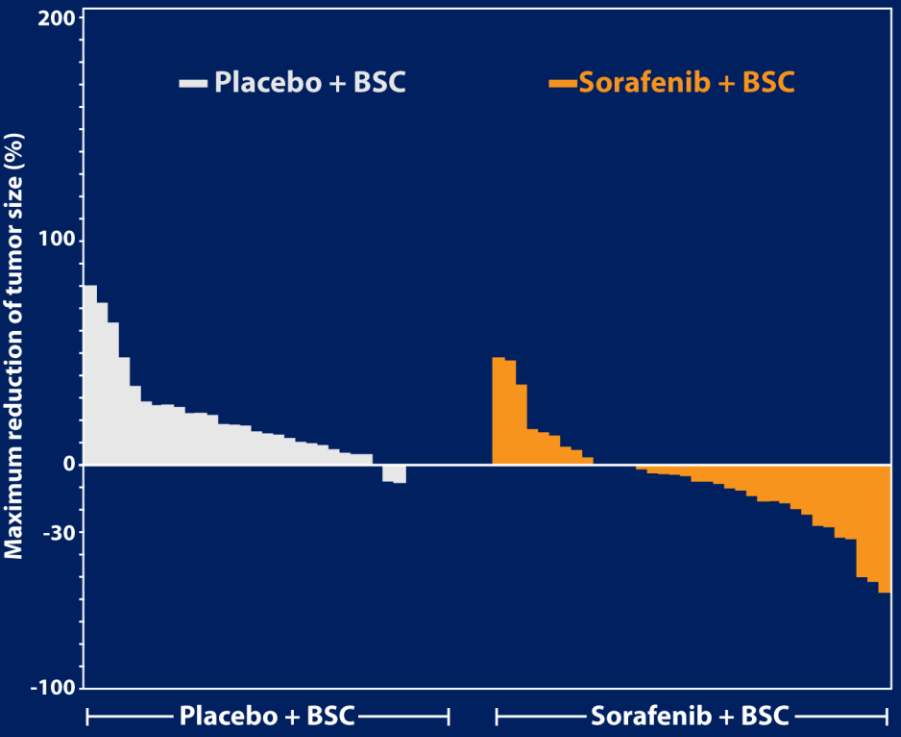
- Sorafenib N=122; Placebo N=136
- HR=0.92 (95% CI 0.7,1.21)
- P-value=0.559
- Sorafenib median OS= 8.3 mo (253d)
- Placebo median OS= 8.4 mo (256d)



Biomarker*treatment interaction analysis: p-value=0.023

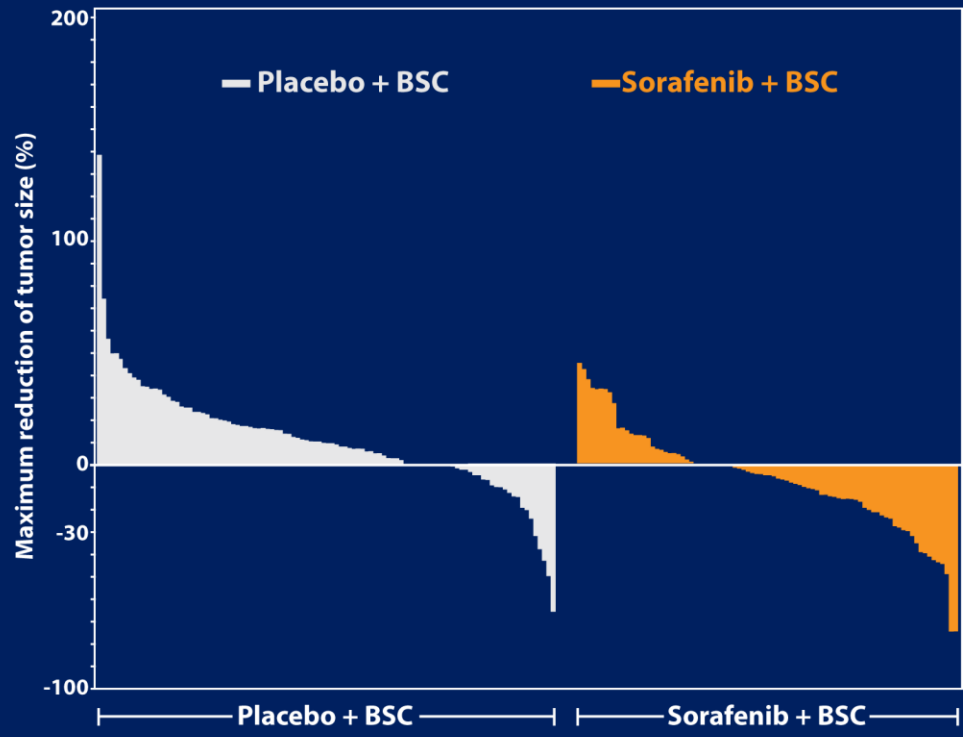
Tumor response – EGFR status (Investigator assessed)

EGFR Mutation Positive



ORR – 0% vs. 6.8%
DCR – 2.2% vs. 40.9%

EGFR Wild-type



ORR – 1.5% vs. 7.4%
DCR – 25.8% vs. 46.7%

Treatment summary

	EGFR mutation		EGFR wild type	
	Sorafenib n=44 (%)	**Placebo n=45 (%)**	**Sorafenib n=122 (%)**	**Placebo n=136 (%)**
On-study				
Duration of therapy Mean (weeks)	16.6	6.1	19.6	12.4
Dose interruption, n (%)	13 (30)	6 (13)	60 (49)	27 (20)
Dose reduction, n (%)	8 (18)	1 (2)	47 (39)	8 (6)
Post-progression Therapy				
Any	26 (59)	25 (56)	54 (44)	84 (62)
2+	16 (36)	9 (20)	22 (18)	33 (24)
Anti-EGFR	19 (43)	8 (18)	18 (15)	37 (27)

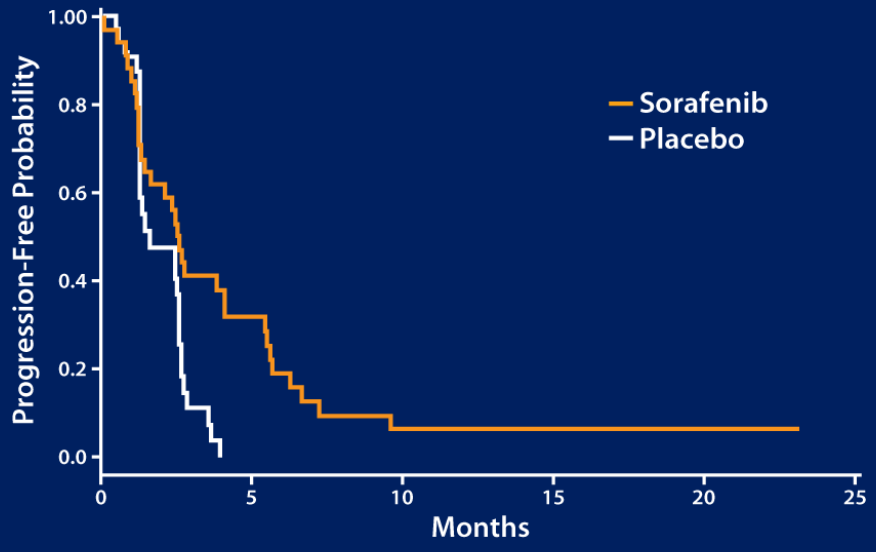
Progression-free survival based on KRAS mutation status

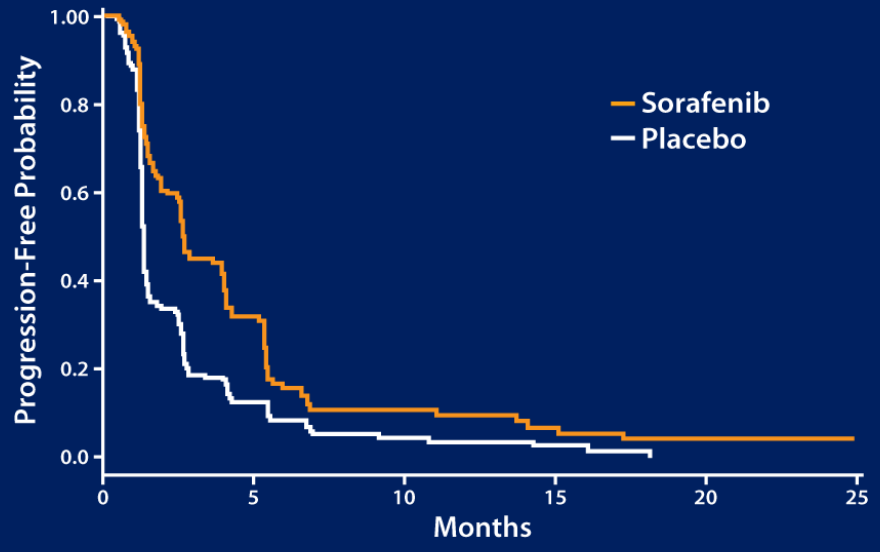
Pts with KRAS mut (in tumor or plasma)

- Sorafenib N=34; Placebo N=34
- HR=0.46 (95% CI 0.25,0.82)
- P-value=0.007
- Sorafenib median PFS= 2.6 mo (80d)
- Placebo median PFS= 1.7 mo (51d)

Pts with KRAS wt

- Sorafenib N=132; Placebo N=147
- HR=0.58 (95% CI 0.45,0.75)
- P-value<0.001
- Sorafenib median PFS= 2.7 mo (83d)
- Placebo median PFS= 1.4 mo (43d)



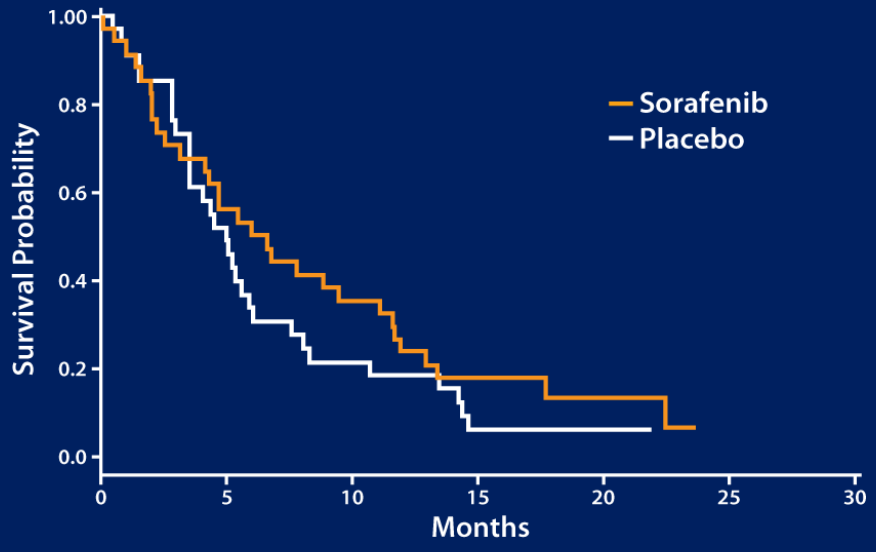


Biomarker*treatment interaction analysis: p-value=0.696

Overall survival based on KRAS mutation status

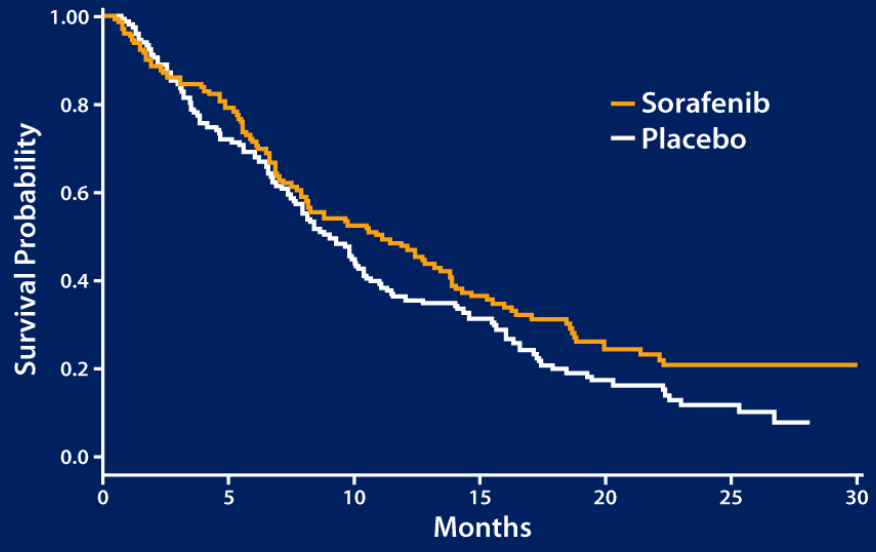
Pts with KRAS mut (in tumor or plasma)

- Sorafenib N=34; Placebo N=34
- HR=0.76 (95% CI 0.45,1.26)
- P-value=0.279
- Sorafenib median OS= 6.4 mo (195d)
- Placebo median OS= 5.1 mo (156d)



Pts with KRAS wt

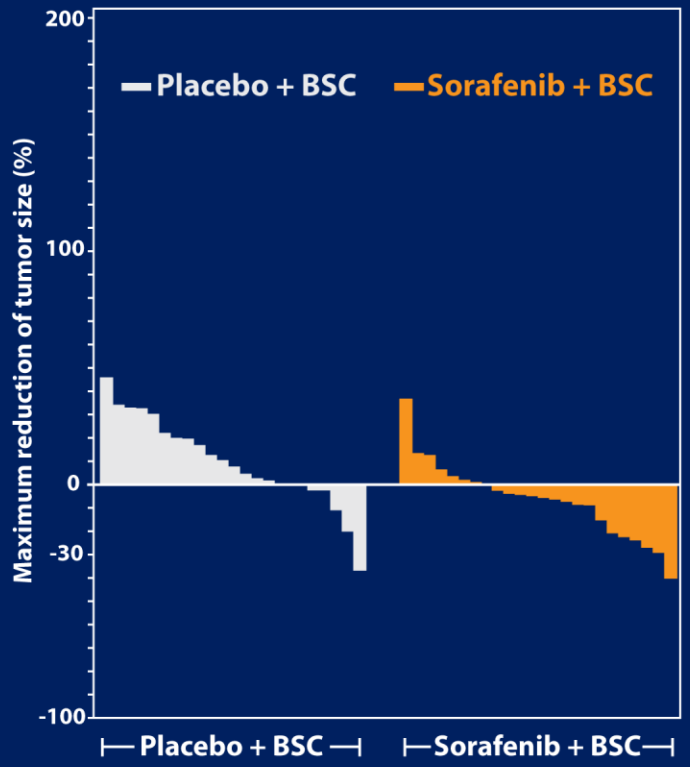
- Sorafenib N=132; Placebo N=147
- HR=0.79 (95% CI 0.6,1.03)
- P-value=0.079
- Sorafenib median OS= 11.0 mo (339d)
- Placebo median OS= 9.1 mo (278d)



Biomarker*treatment interaction analysis: p-value=0.743

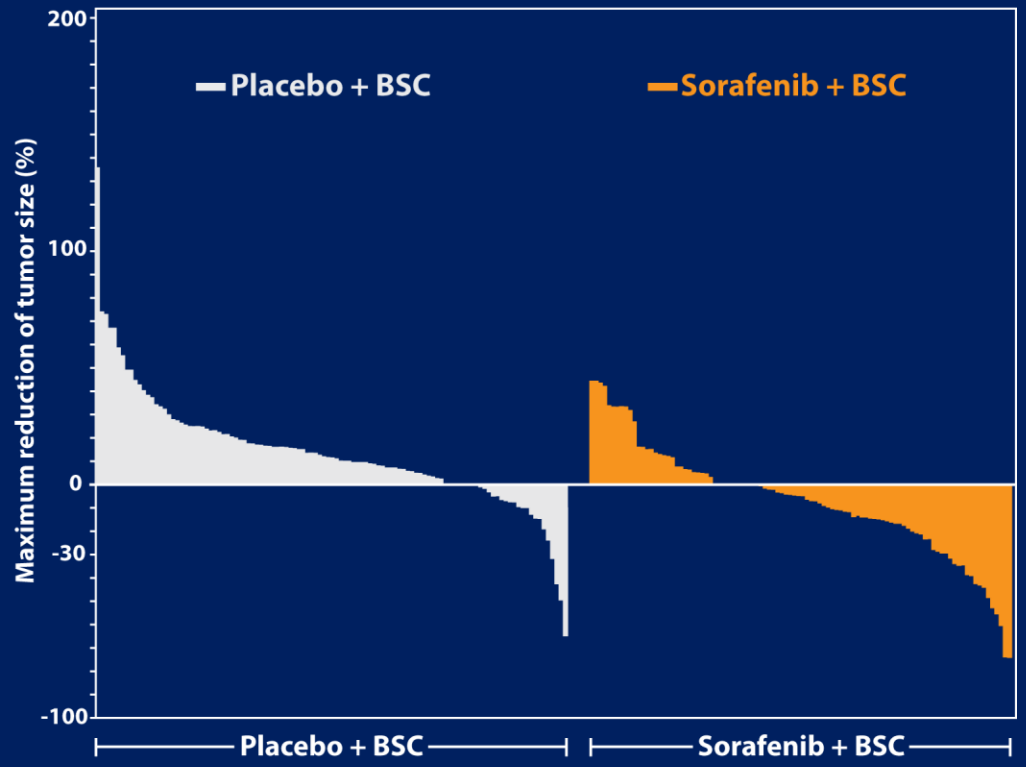
Tumor response – KRAS status (Investigator assessed)

KRAS Mutation Positive



ORR – 0% vs. 2.9%
DCR – 7.6% vs. 44.1%

KRAS Wild-type



ORR – 1.4% vs. 8.3%
DCR – 20.4% vs. 45.4%

Conclusion

- Based on current data, we hypothesize that EGFR mutation is a predictive biomarker for sorafenib in treatment of patients with advanced NSCLC
  - Positive interaction analysis for both PFS and OS
  - OS outcome may be biased by the unbalanced use of post-study EGFR TKI (sorafenib arm 43%; placebo arm 18%)
- KRAS mutation status did not appear to influence response to sorafenib
  - Negative interaction analysis for both PFS and OS
  - Sorafenib resulted in more favorable PFS outcomes than placebo in patients with both KRAS mutant and wild type tumors
- These results should be interpreted with caution
  - The patient subgroup with available samples for biomarker analysis is not representative of the overall population[1]
  - Limited sample size (47% of overall population)
  - Biomarker analyses in MISSION were retrospective

[1]Paz-Ares L, et al. *ESMO* 2012, Abstract LBA 33.

MISSION Trial Investigators

154 Centers in 33 Countries

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Austria: Horst Olschewski, Kurt Aigner, Josef Bolitschek

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United States: J. Beck, Heather Wakelee

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Backup

EGFR and KRAS mutations assayed

EGFR		
Exon	Nucleotide change	Amino acid change
19	2235_2249 del15	E746_A750del
19	2236_2250 del15	E746_A750del
19	2237_2255>T	E746_S752>V
19	2239_2248 TTAAGAGAAG>C	L747_A750>P
19	2240_2254 del15	L747_T751del
19	2240_2257 del18	L747_P753>S
20	2369 C>T	790 T>M
21	2573 T>G	858 L>R

KRAS		
Exon	Nucleotide change	Amino acid change
1	34 G>A	12 G>S
1	34 G>C	12 G>R
1	34 G>T	12 G>C
1	35 G>A	12 G>D
1	35 G>C	12 G>A
1	35 G>T	12 G>V
1	38 G>A	13 G>D