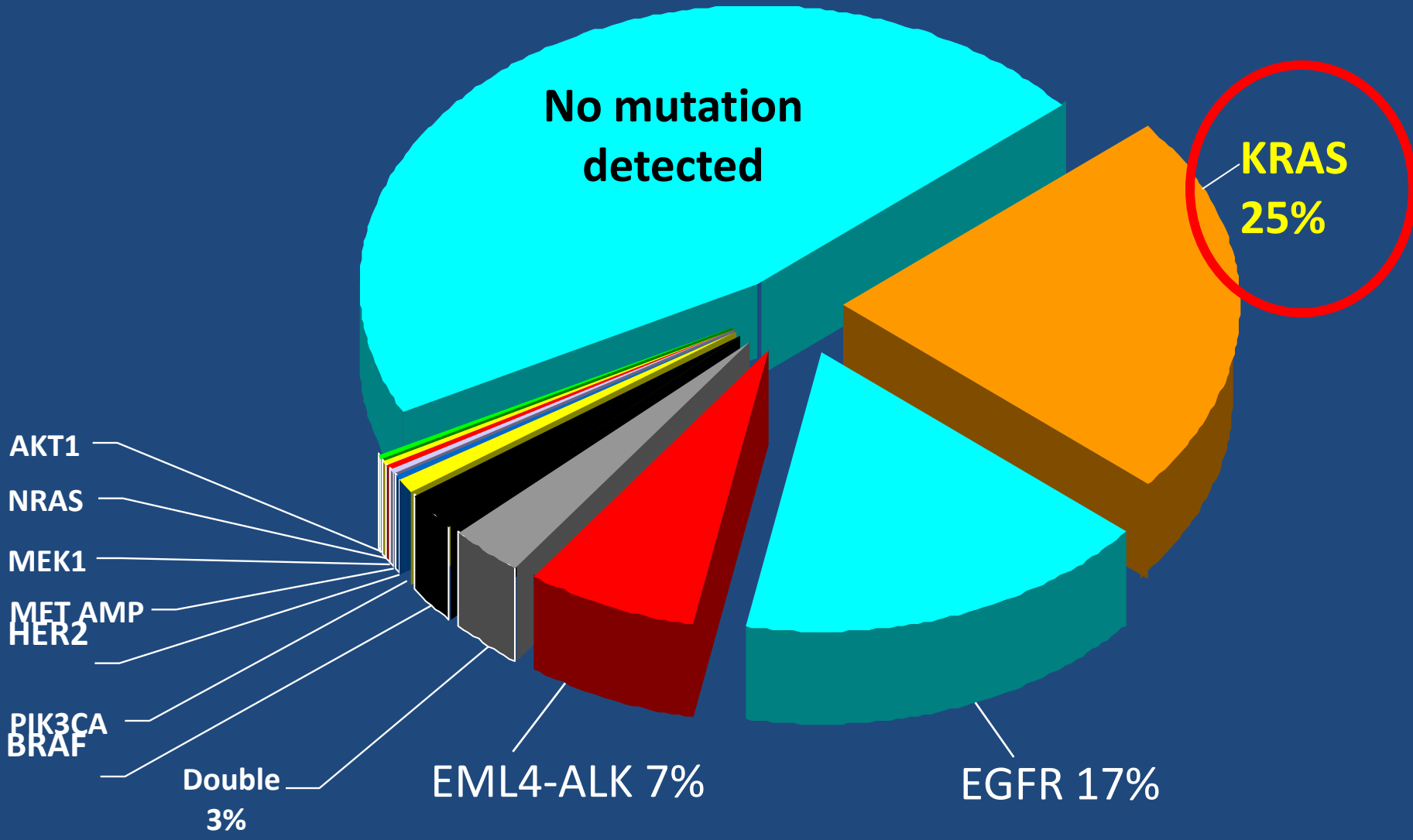
Non Small Cell Lung Cancer (*K-Ras)*

Egbert F. Smit MD PhD
Dept. Thoracic Oncology
Netherlands Cancer Institute
Amsterdam, The Netherlands

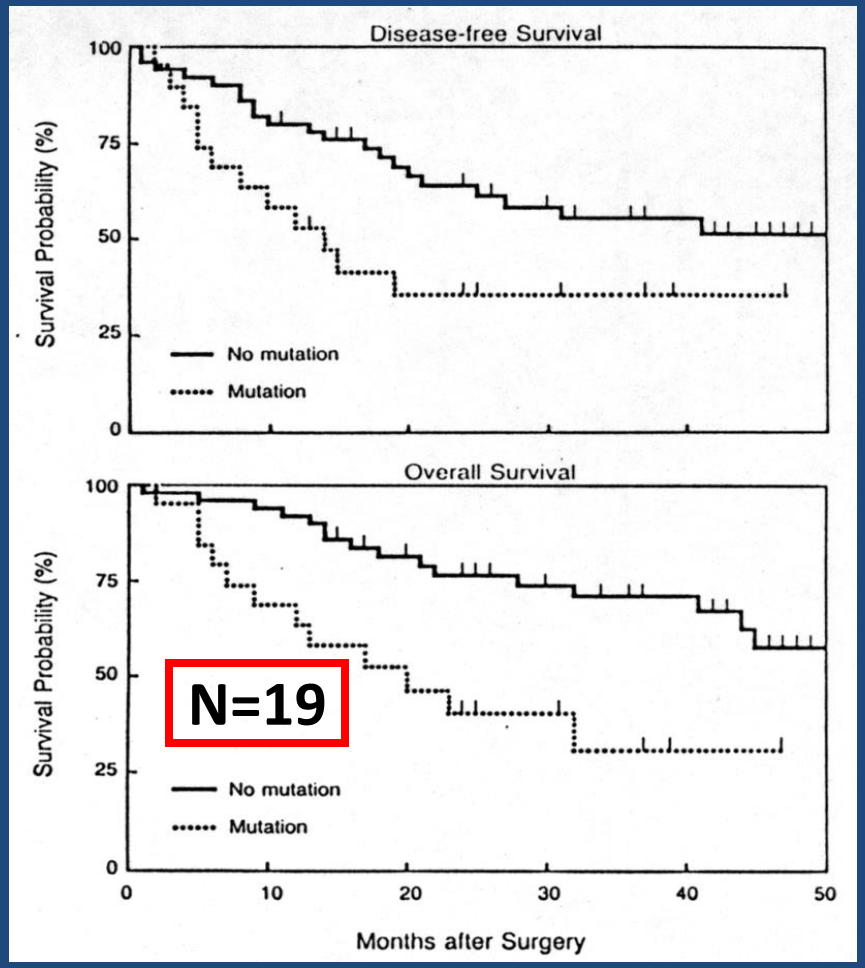
Molecular Changes Driving Lung Adenocarcinoma



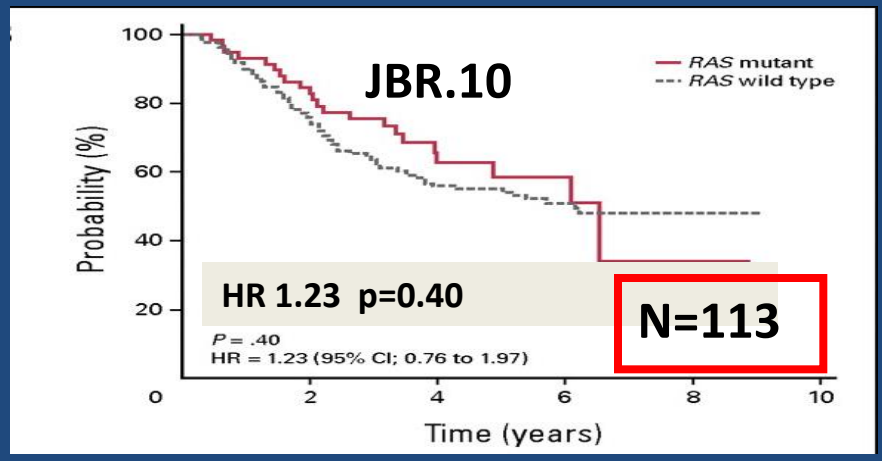
Kris, et al. *J Clin Oncol* 2011;29:Suppl(Abstr 7506).

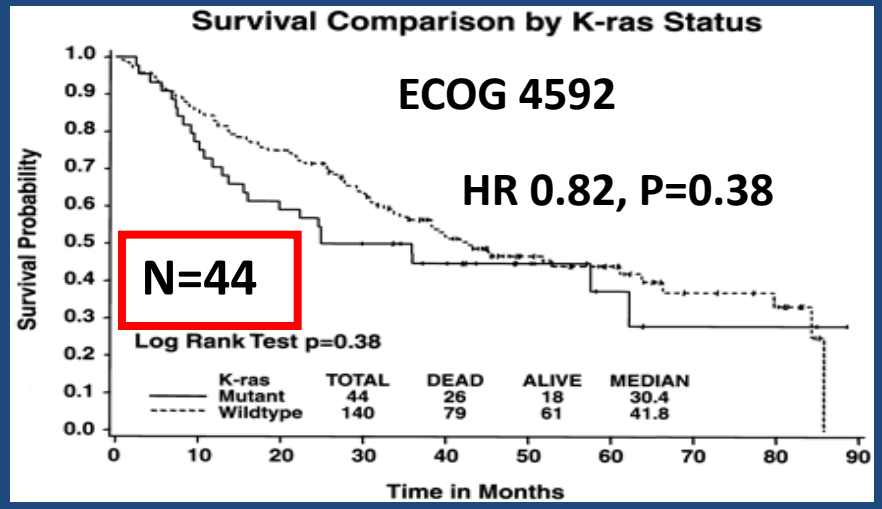
Prognostic Significance of KRAS Mutation in NSCLC

Prognostic Significance of *KRAS* in Surgical Series



Slebos NEJM 323: 561, 1990

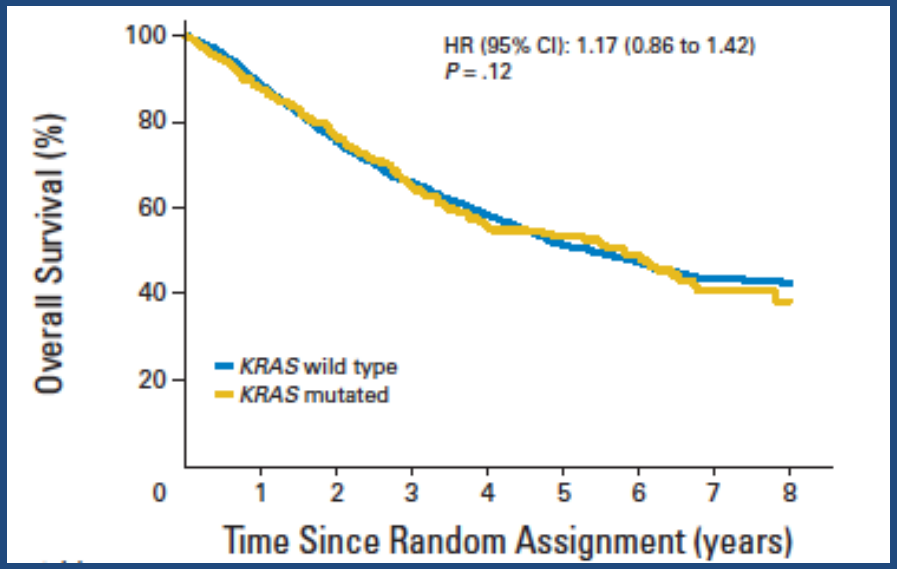




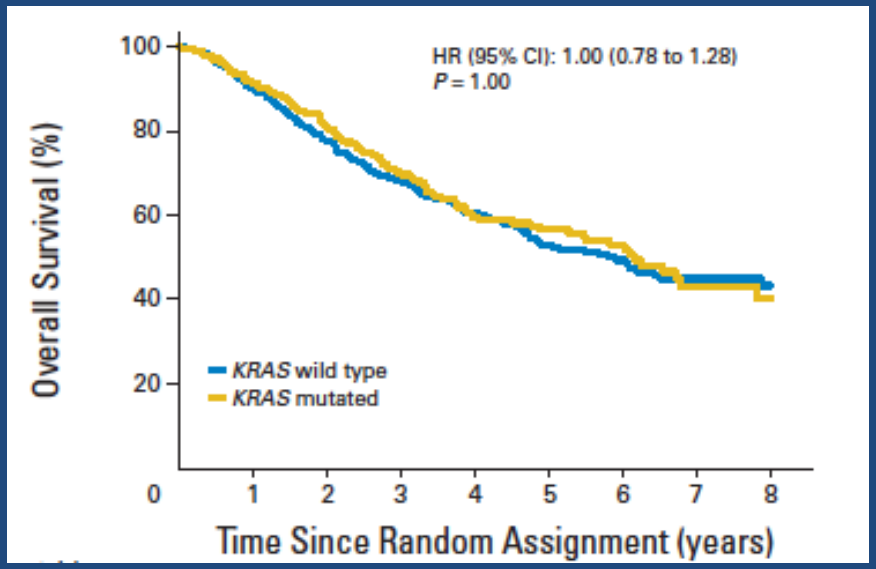
Tsao. JCO 25:5240, 2007
Schiller. J Clin Oncol 19: 448, 2001

No prognostic effect of *KRAS* mutations in the LACE-Bio pooled analysis

All Patients

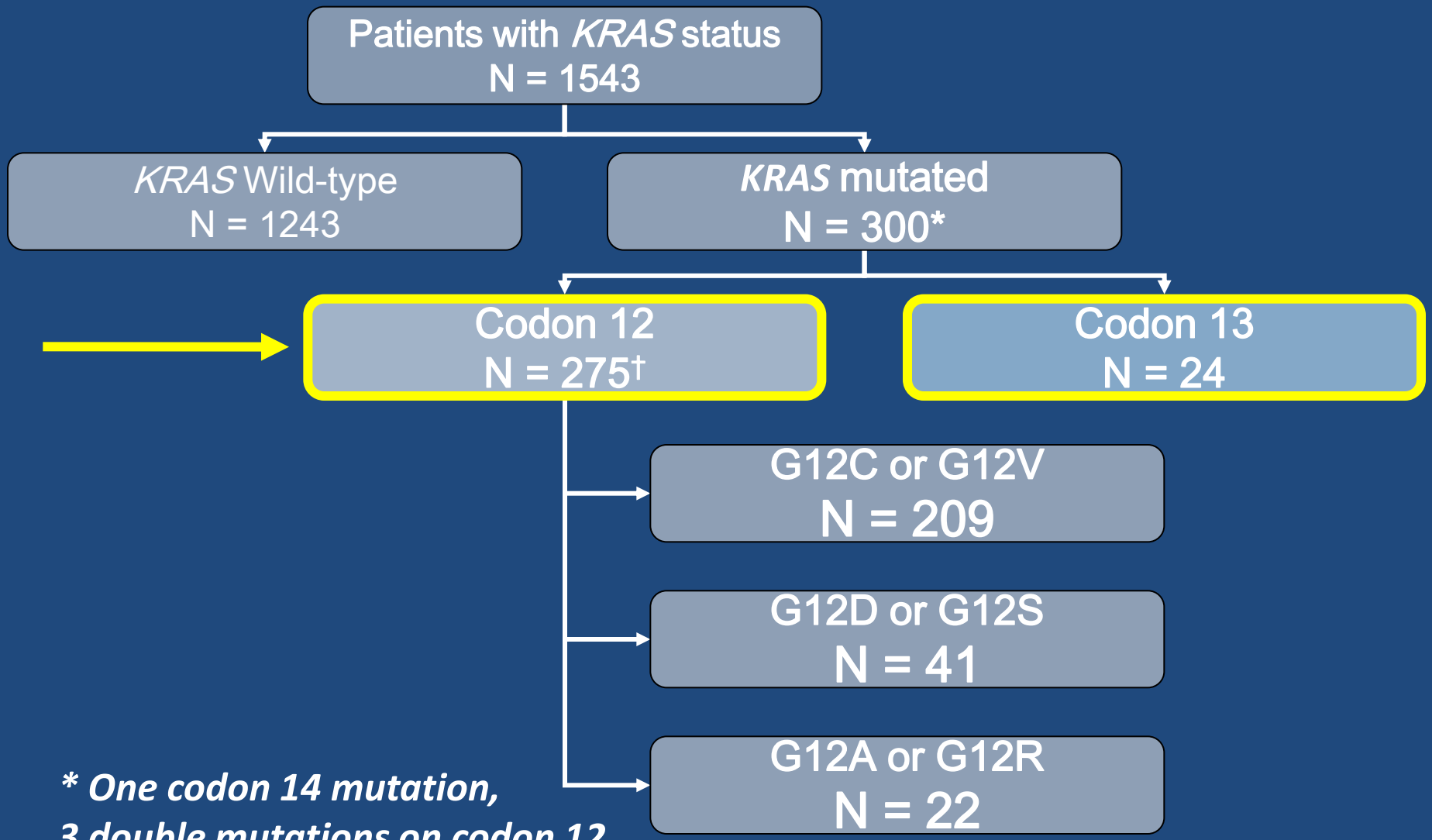


Adenocarcinoma Patients



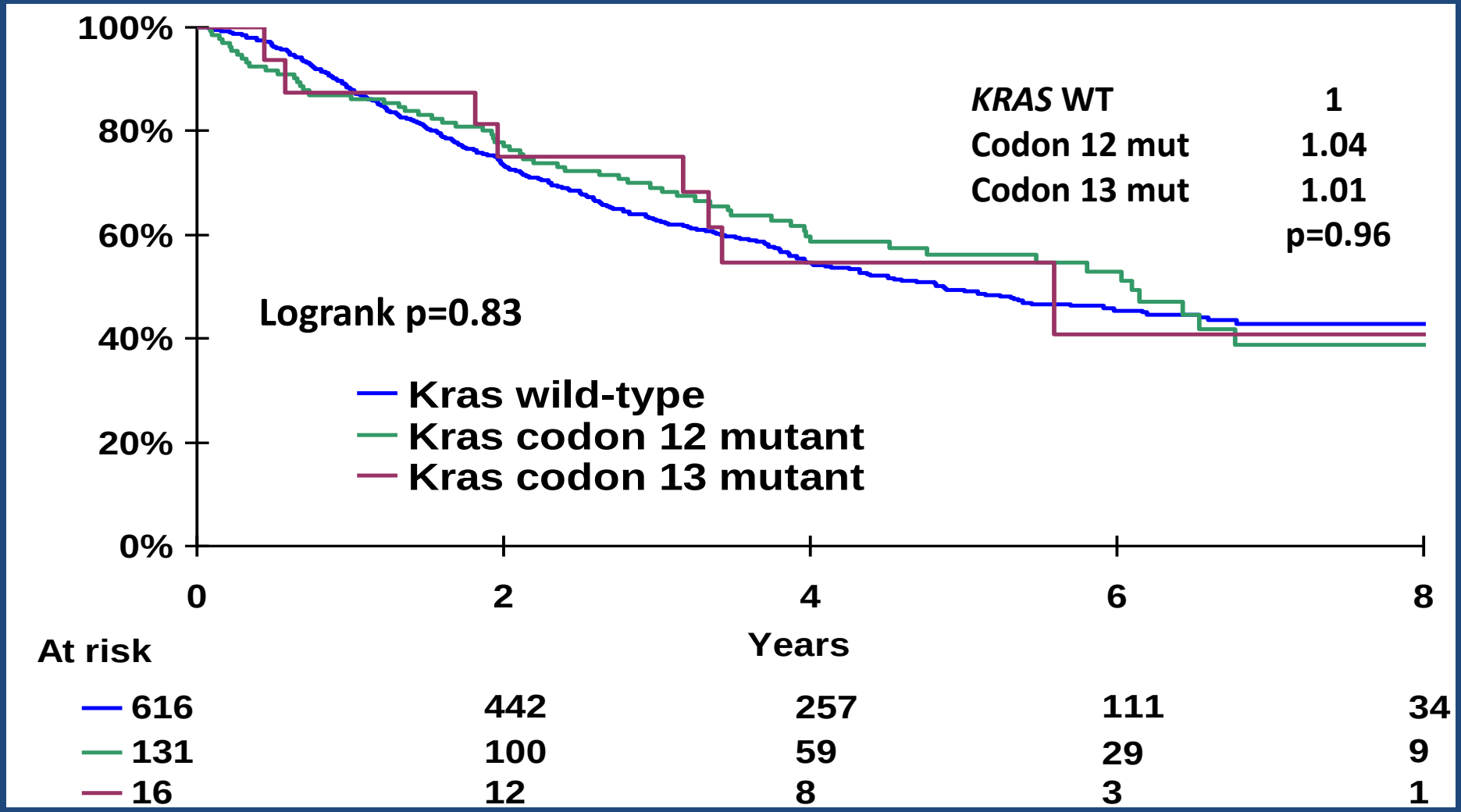
Shepherd et al. J. Clin. Oncol. 2013

LACE-Bio: *KRAS* Mutation Type



**** One codon 14 mutation,***
3 double mutations on codon 12

Prognostic Effect of *KRAS* Codon 12 &13 Mutations on OS

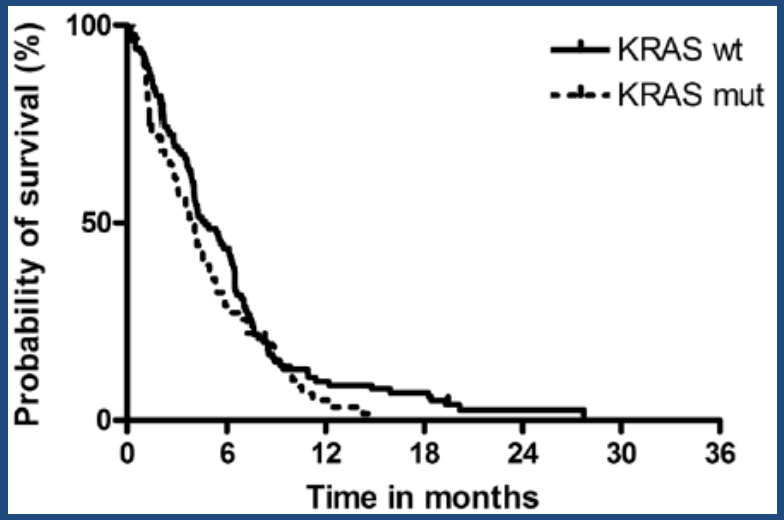


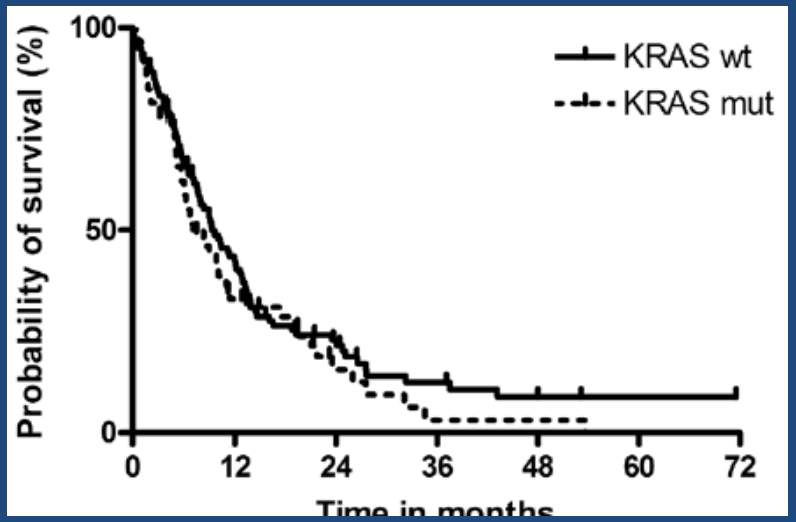
Shepherd et al. Proc ASCO, 2012

Predictive Value of *KRAS*

Chemotherapy

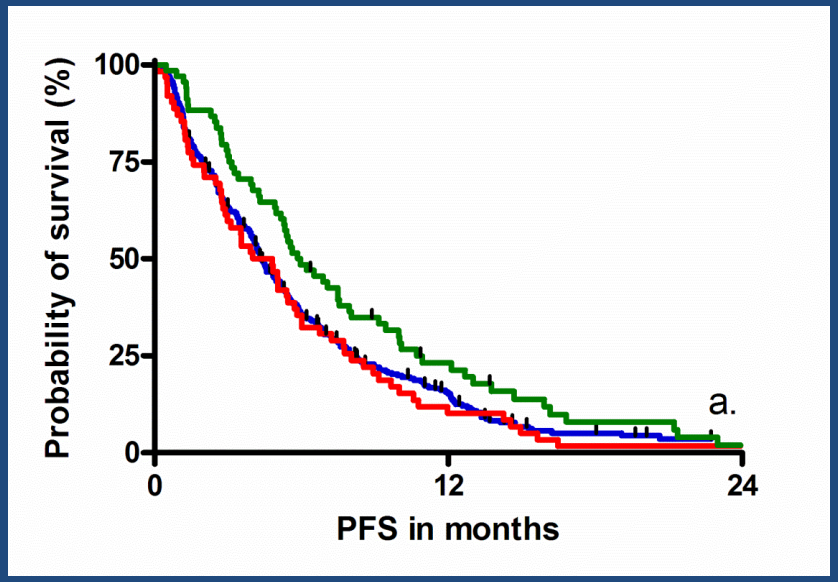
K-RAS mutations have no predictive value for platinum based chemotherapy in NSCLC

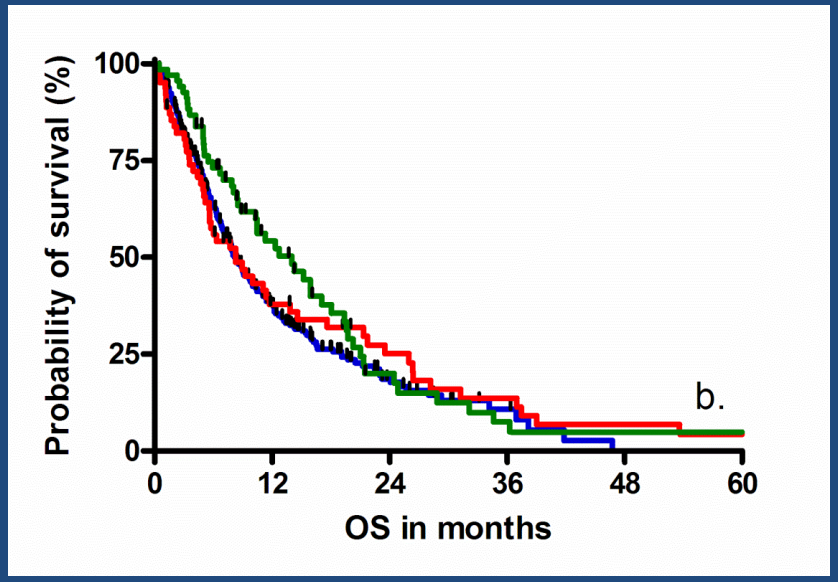




Mellema et al. J. Thor. Oncol. 2013

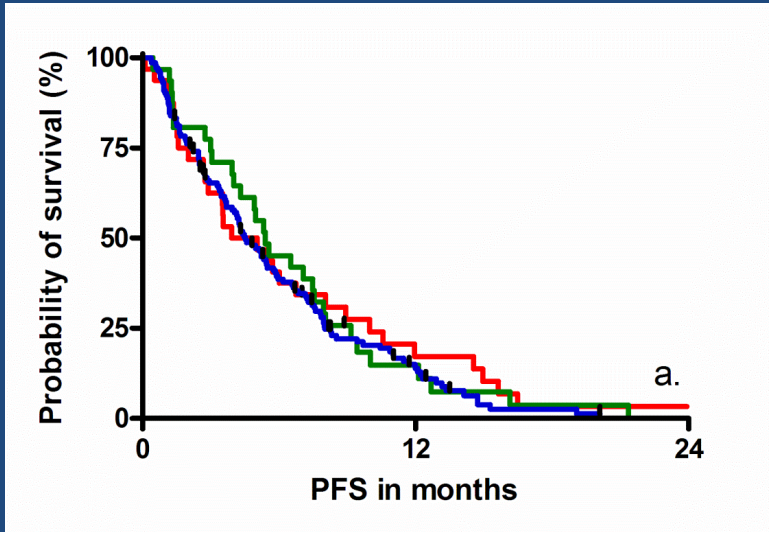
Differential sensitivity of *K-RAS* mutated NSCLC for standard chemotherapy regimen

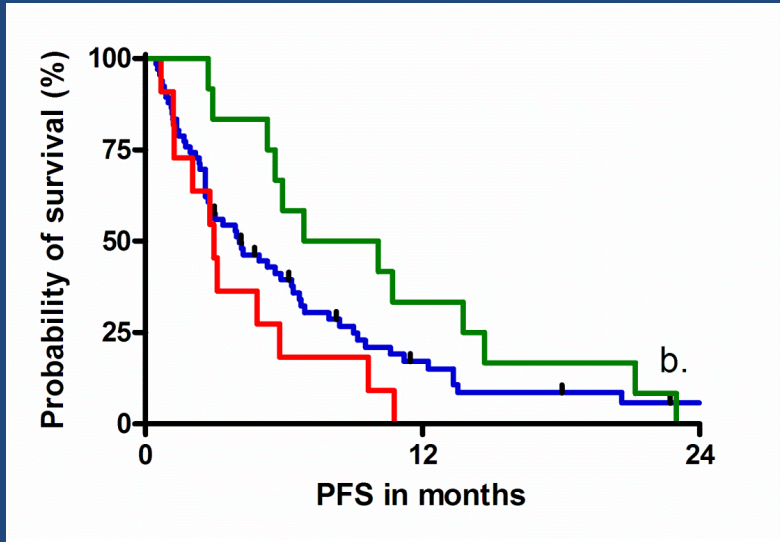


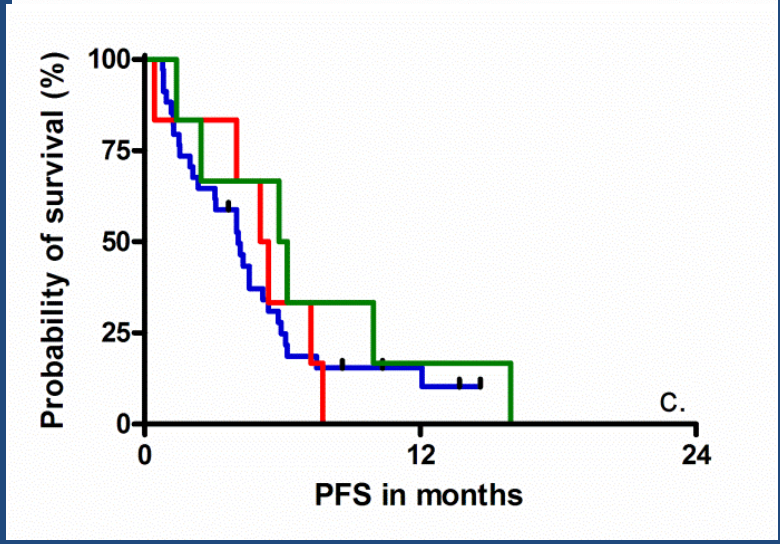


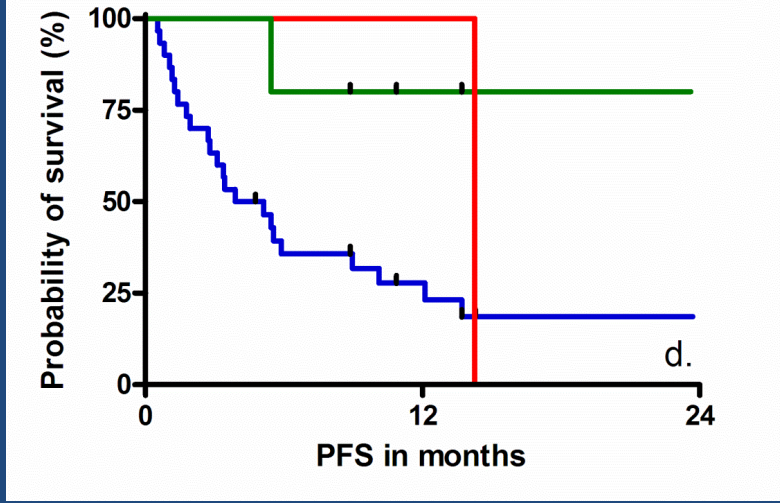
Mellema et al. In press

Which is restricted to G12V *K-RAS* mutations



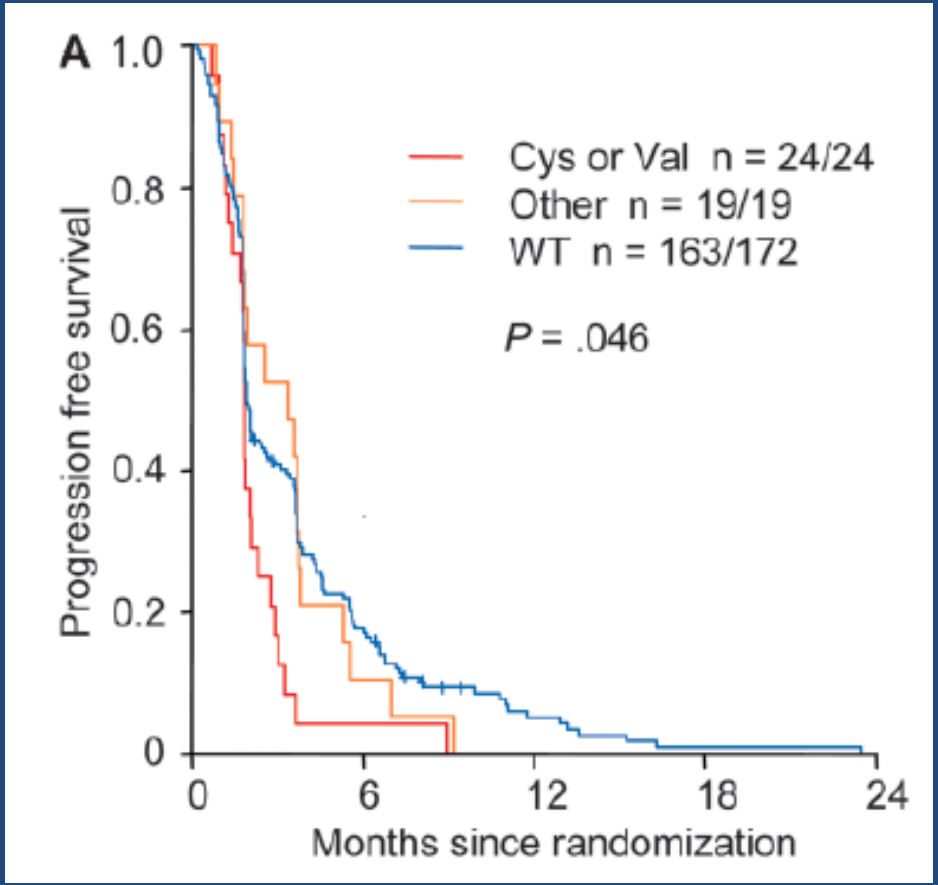






Not all *K-Ras* is created equal.

Secondary analysis from BATTLE



Ihle et al. J. Natl. Cancer Inst. 104,1-12,2012

KRAS as Therapeutic Target

MET Inhibition

RAF Inhibition

MEK Inhibitors

Tivantinib (ARQ 197): PFS in Histologic and Molecular Subgroups

		ARQ197/erlotinib		Placebo/erlotinib		
	N	Median PFS (95% CI, months)				Unadjusted HR
Squamous Cell	26/24	3.2	1.9-4.2	2.0	1.8-4.9	HR=1.05
Non-Squamous Cell	58/59	4.4	3.5-7.3	2.3	1.9-3.7	HR=0.71
c-MET FISH >4	19/18	3.6	1.9-5.7	3.6	1.7-3.8	HR=0.71
c-MET FISH >5	8/11	5.6	3.8-NE	3.6	1.8-7.3	HR=0.45
EGFR mutant	6/11	5.6	1.9-7.5	4.9	1.9-8.4	HR=1.23
EGFR wt	51/48	3.2	1.9-4.2	1.9	1.8-2.3	HR=0.70
KRAS mutant	10/5	2.3	1.8-NE	1.0	0.3-1.9	HR=0.18
KRAS wt	49/45	3.6	1.9-4.2	2.3	1.9-3.7	HR=1.01

Sequist et al. ESMO 2010

Tivantinib (MARQUEE) Phase III study

Phase III in NSCLC
- Inoperable, locally advanced or metastatic disease
- Non-squamous histology
- 1 - 2 regimens of prior chemo (no prior EGFR TKI)
- Prior platinum-based doublet therapy required

RANDOMIZE

Arm A: Tivantinib 360 mg PO BID + **Erlotinib** 150 mg PO QD

Arm B: Placebo PO BID + **Erlotinib** 150 mg PO QD

Endpoints
1° : OS (ITT population)
2° /Exploratory:
- PFS (ITT population)
- PK and PD analysis
- OS in EGFR wt patients
- Safety and toxicity
- QOL/FACT-L
- Biologic subgroup analysis

Stratification by:
- **Gender**
- **Smoking history**
- **Number of prior systemic therapies**
- **EGFR genotype**
- **KRAS genotype**

Scagliotti et al., ECCO 2013

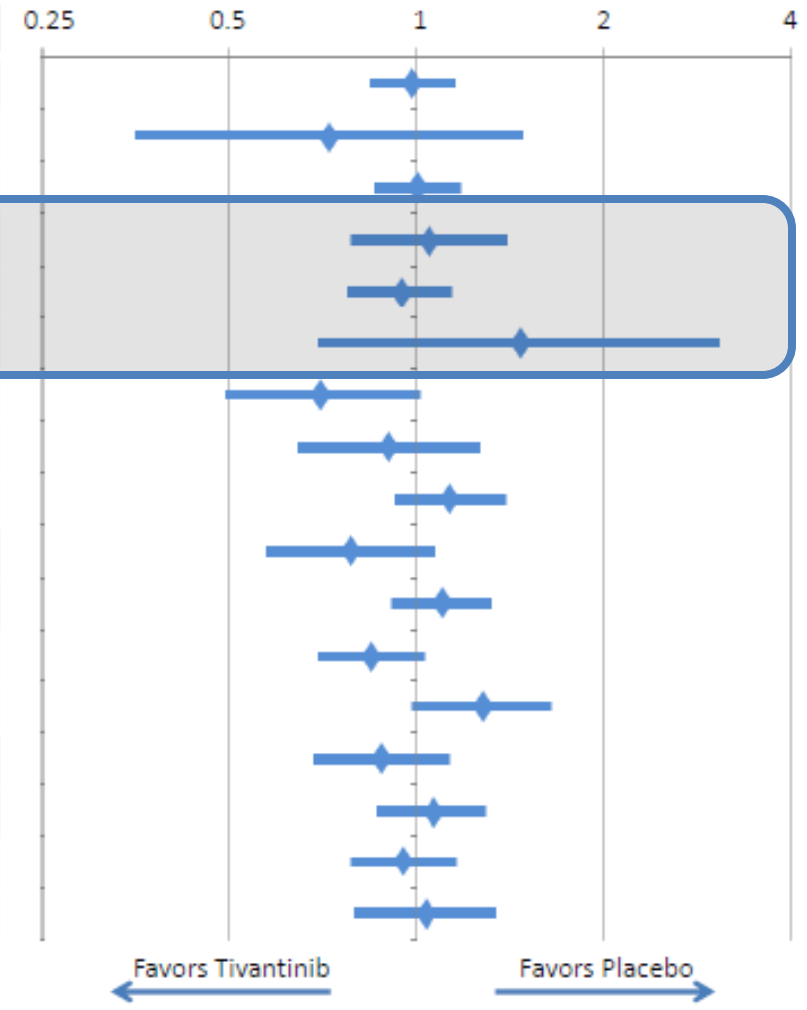
MARQUEE: Tumor Biomarker Analysis

Characteristic	Placebo (N=522)	Tivantinib (N=526)
***EGFR* Mutation Status**		
Mutant	**53 (10.2%)**	**56 (10.6%)**
Wild type	468 (89.7%)	469 (89.2%)
Unknown	1 (0.2%)	1 (0.2%)
***KRAS* Mutation Status**		
Mutant	**148 (28.4%)**	**136 (25.9%)**
Wild type	346 (66.3%)	356 (67.7%)
Unknown	28 (5.4%)	34 (6.5%)
MET Status		
High	**107 (20.5%)**	**104 (19.8%)**
Low	127 (24.3%)	107 (20.3%)
Not assessable	288 (55.2%)	315 (59.9%)

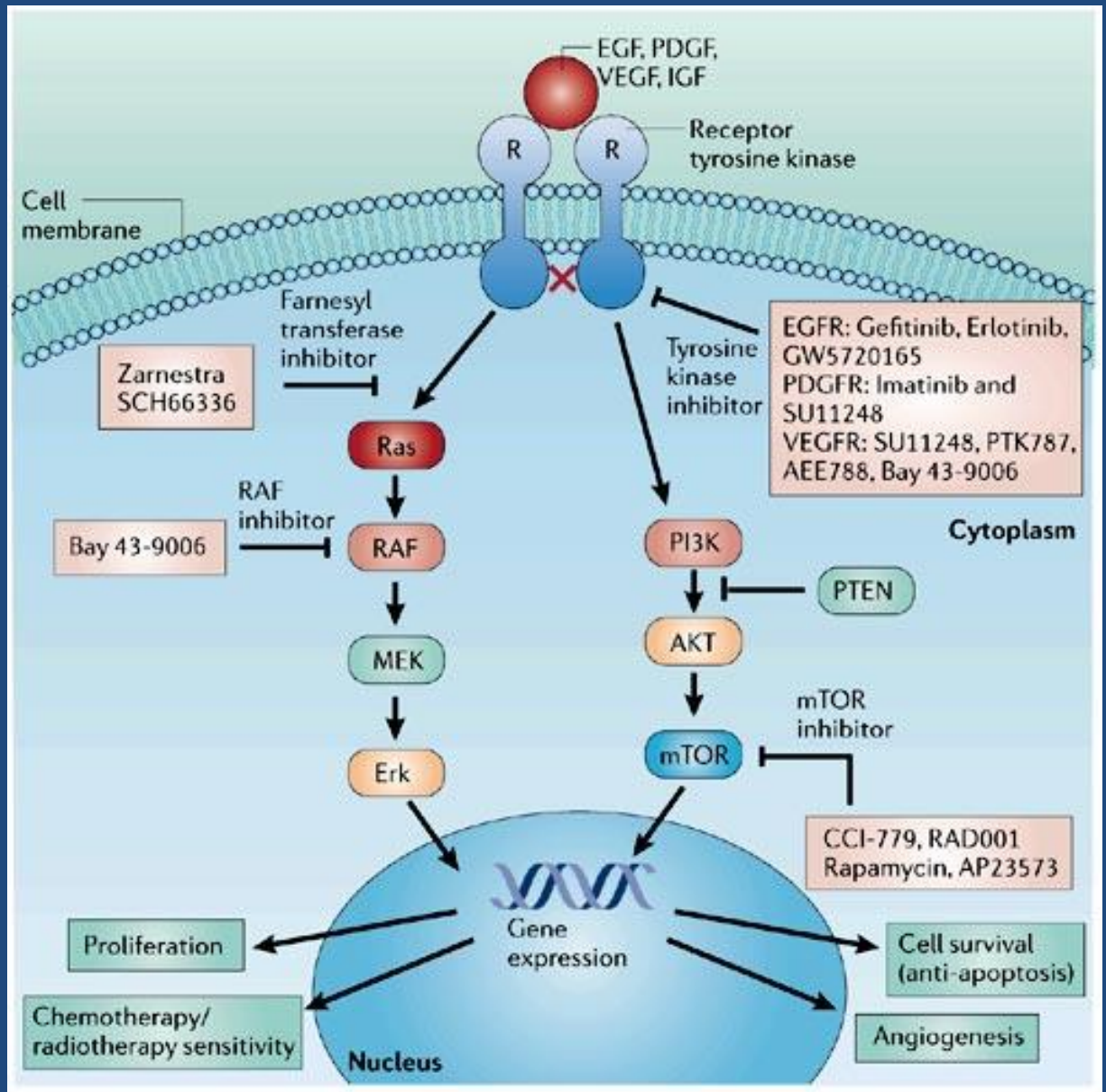
Scagliotti et al., ECCO 2013

MARQUEE: OS in Key Subgroups

Factor	Group	N	HR (95% CI)
All	All	1048	.98 (.84-1.15)
EGFR	Mutant	109	.72 (.35-1.48)
	Non-Mutant	937	1.00 (.85-1.18)
KRAS	Mutant	284	1.04 (.78-1.40)
	Non-Mutant	702	.94 (.77-1.14)
	Indeterminate	62	1.46 (.69-3.07)
MET	High	211	.70 (.49-1.01)
	Low	234	.90 (.64-1.26)
	Not Assessable	603	1.13 (.92-1.39)
ECOG PS	0	336	.78 (.57-1.07)
	1	710	1.10 (.91-1.32)
Age	<65	646	.84 (.69-1.03)
	>=65	402	1.27 (.98-1.64)
Gender	Female	429	.87 (.68-1.13)
	Male	619	1.06 (.86-1.29)
Prior Regimens	1	694	.95 (.78-1.16)
	2	354	1.03 (.79-1.34)

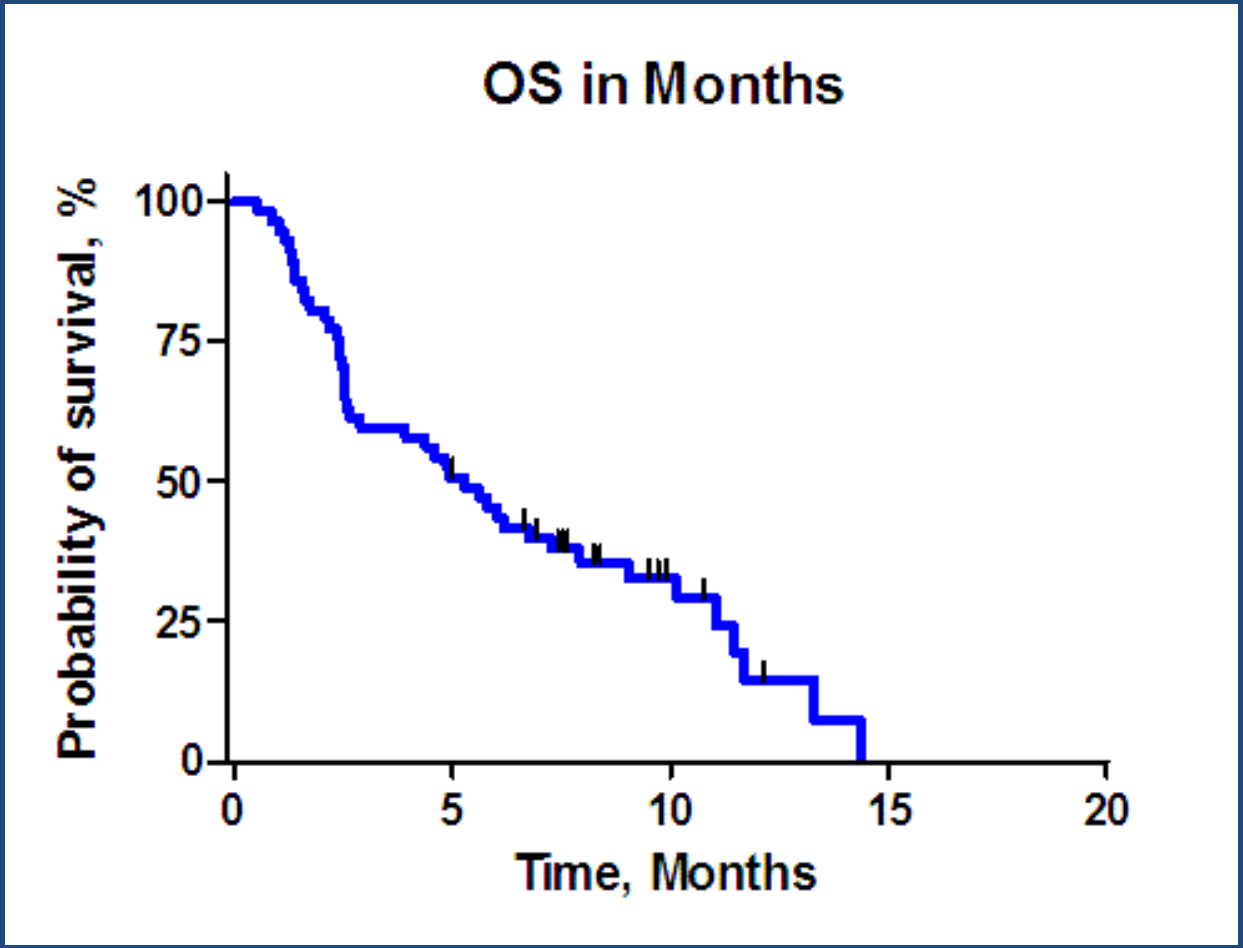


Scagliotti et al., ECCO 2013



Nature Reviews | Drug Discovery

Sorafenib in *K-RAS* mut NSCLC Overall Survival



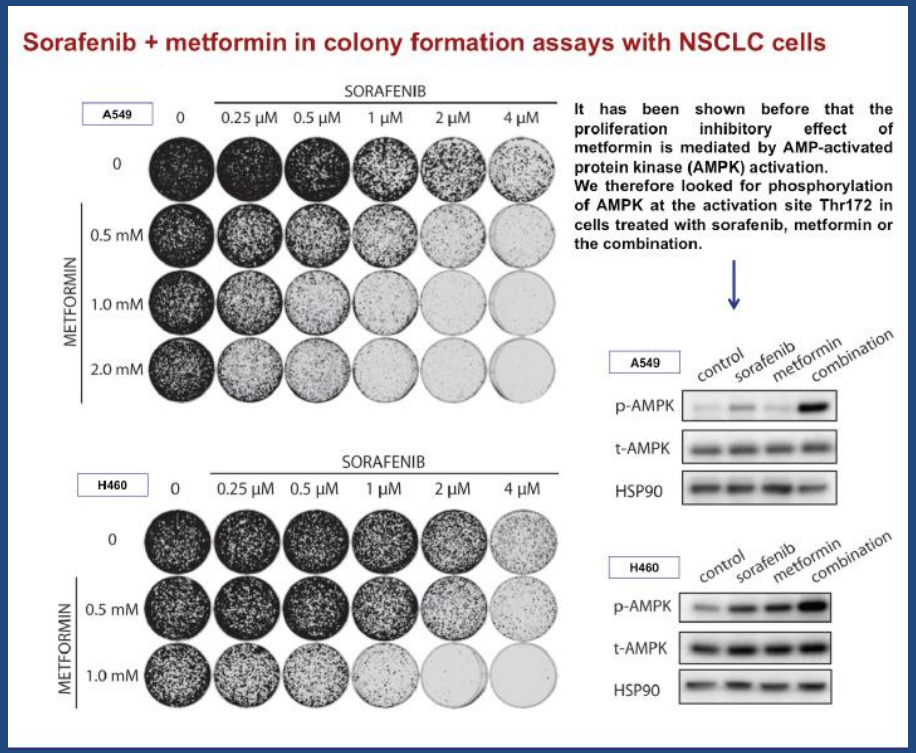
Median OS: 5.3 months (95% CI: 3.5-6.9)

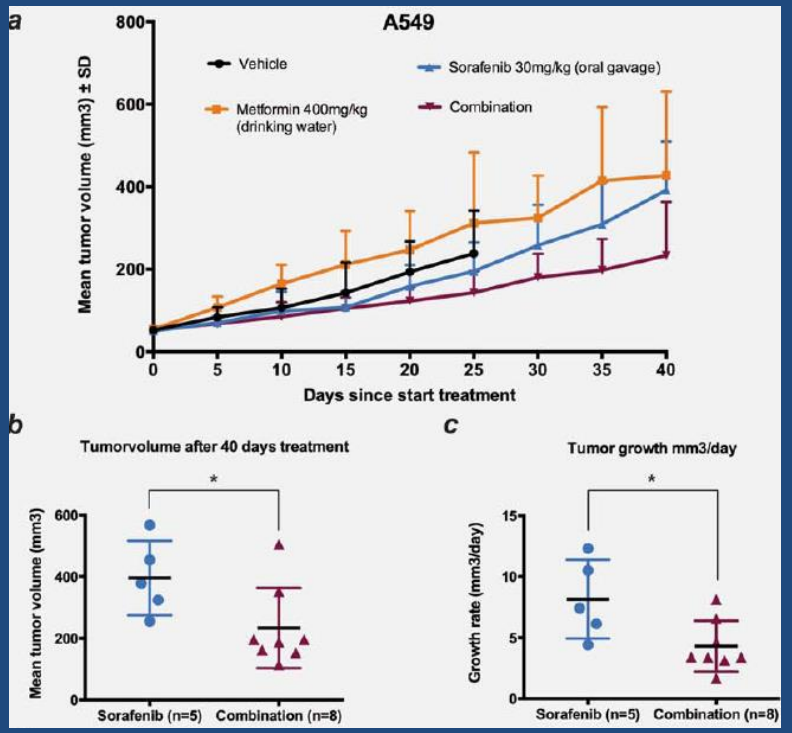
Dingemans et al. Clin. Cancer Res. 2013

Post hoc analysis

	Metformin			
	No	Yes	Total	P-value
Partial response	3	2	5	0.01
Stable disease	22	3	25	
Progressive disease	27	0	27	
Total	52	5	57	

Sorafenib synergizes with metformin through AMPK pathway activation



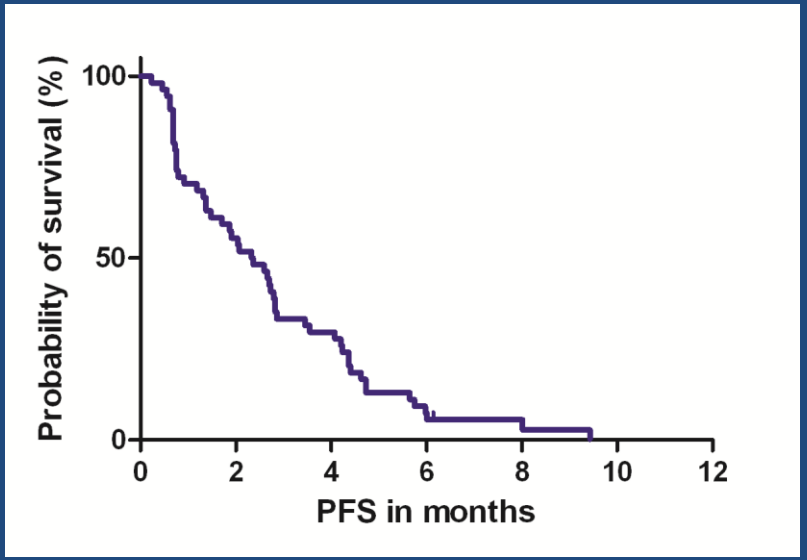


Groenendijk et al. Int. J.Cancer 2015

Phase II study Sorafenib and Metformine in *K-RAS* mutated NSCLC: Results

- July 2012 - June 2013 (4 centers): 55 patients

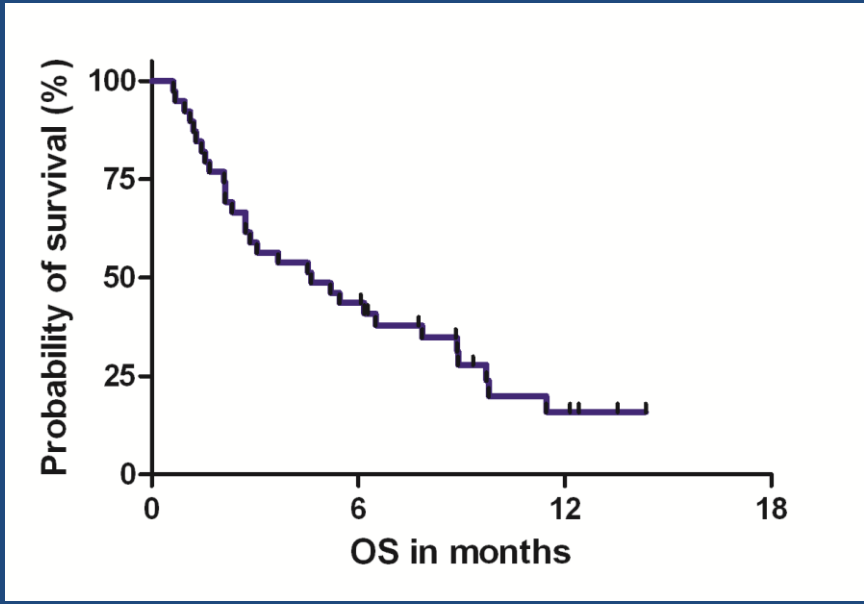
Patient Characteristics	N (%)
Median age (SD)	59(±10)
Sex	
Male/ Female	27 (49%) / 28 (51%)
ECOG PS	
0/1/2	16(29%)/ 36(65%)/1(2%)
Histology	
Adeno carcinoma	51 (93%)
Large cell carcinoma	4 (7%)
Tumor stage	
IV	55 (100%)



Mellema et al. Submitted

Results: Response and Overall Survival

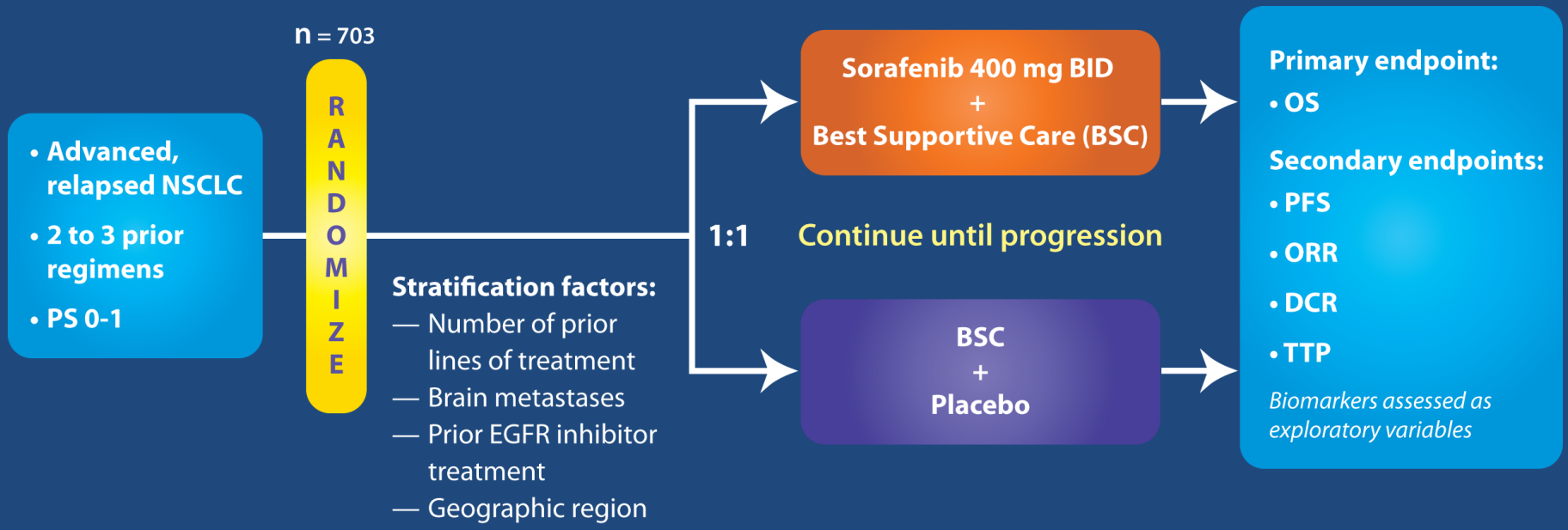
Response	N (%)
Partial response	2 (3%)
Stable disease	30 (56%)
Progressive disease	22 (41%)
Total	55 (100%)



Mellema et al. Submitted

MISSION: Study objective and design

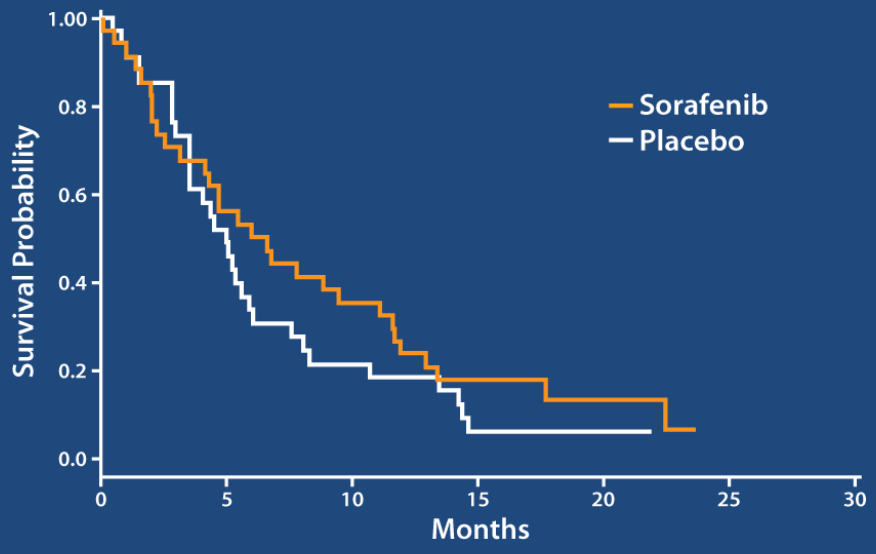
- Objective
  - To compare the efficacy and safety of sorafenib plus BSC with BSC alone in patients with relapsed or refractory, advanced, predominantly non-squamous NSCLC, with disease progression after two or three prior treatment regimens
- Design
  - Randomized, double-blind, placebo-controlled phase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



Overall survival and KRAS mutation status

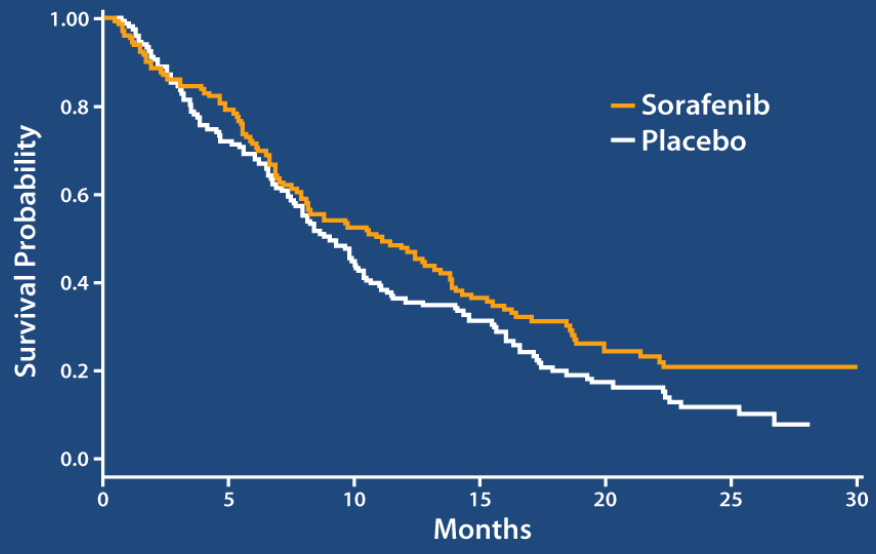
Pts with KRAS mut (in tumor or plasma)

- 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

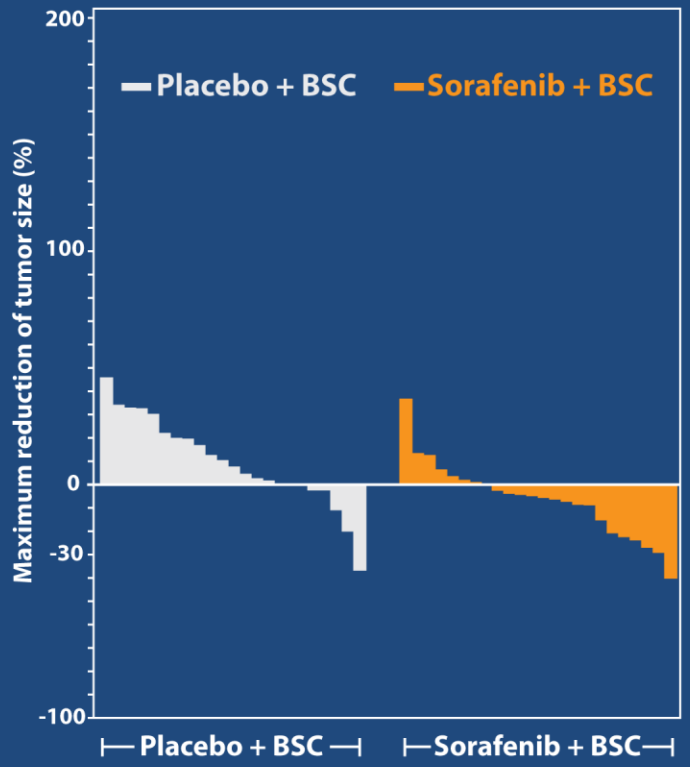
- Sorafenib N=132; Placebo N=147
- HR=0.79 (95% CI 0.6,1.03)
- P-value=0.079
- Sorafenib median OS= 11.0 mo (339d)
- Placebo median OS= 9.1 mo (278d)



Biomarker*treatment interaction analysis: p-value=0.743

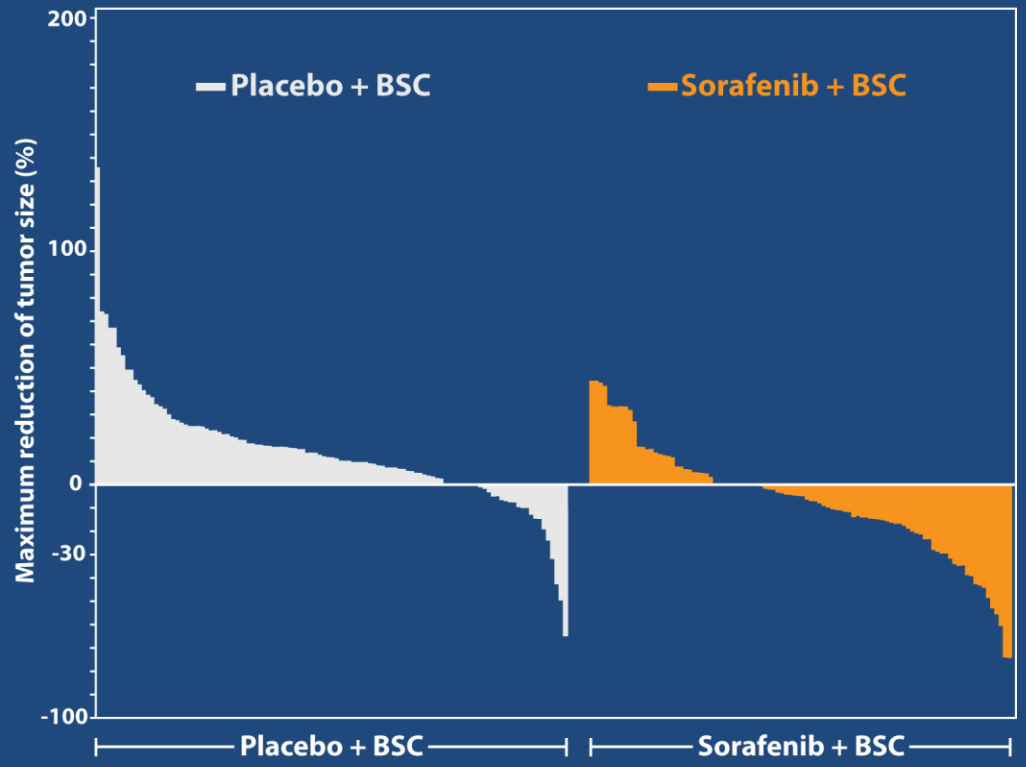
Tumor response – KRAS status (Investigator assessed)

KRAS Mutation Positive



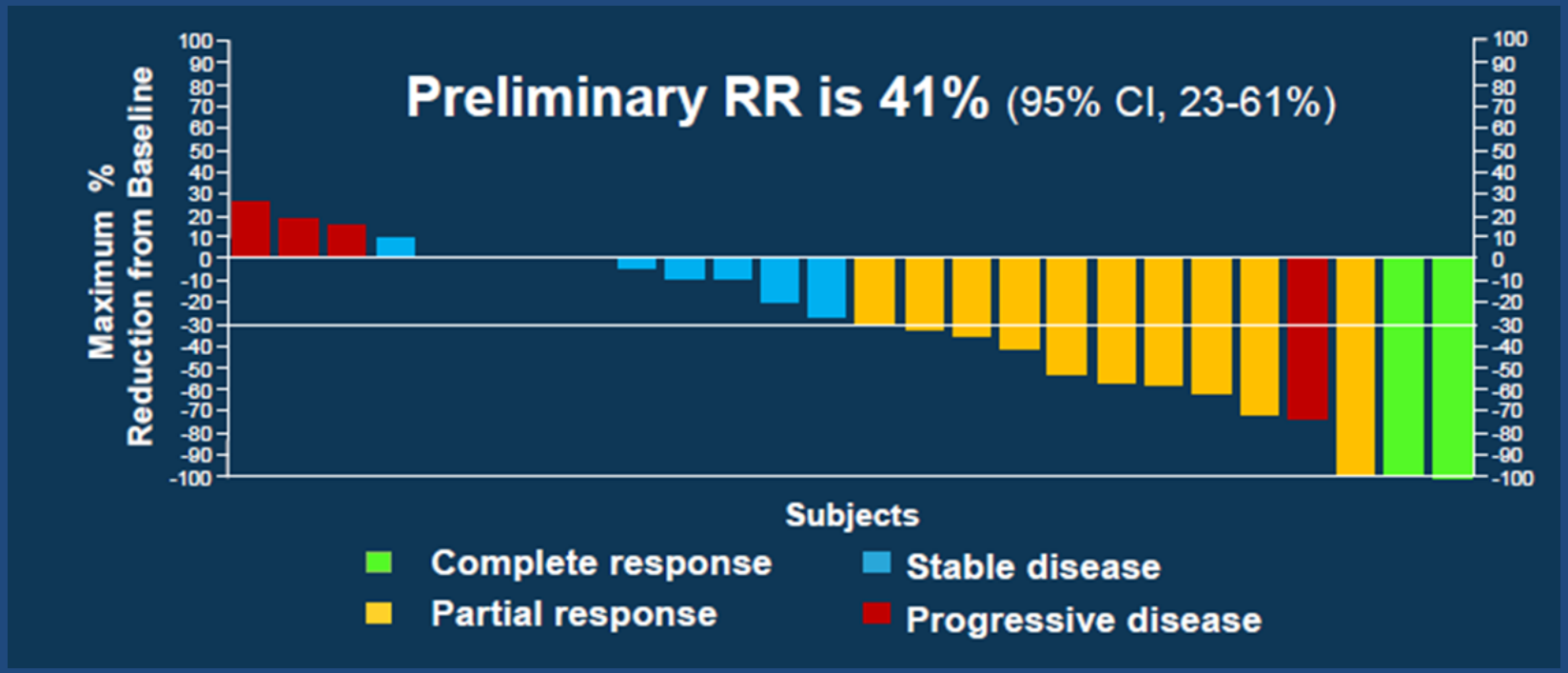
ORR – 0% vs. 2.9%
DCR – 7.6% vs. 44.1%

KRAS Wild-type



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

Efficacy of Trametinib (GSK1120212) in *BRAF*-Mutant Melanoma and *KRAS*-mutant NSCLC



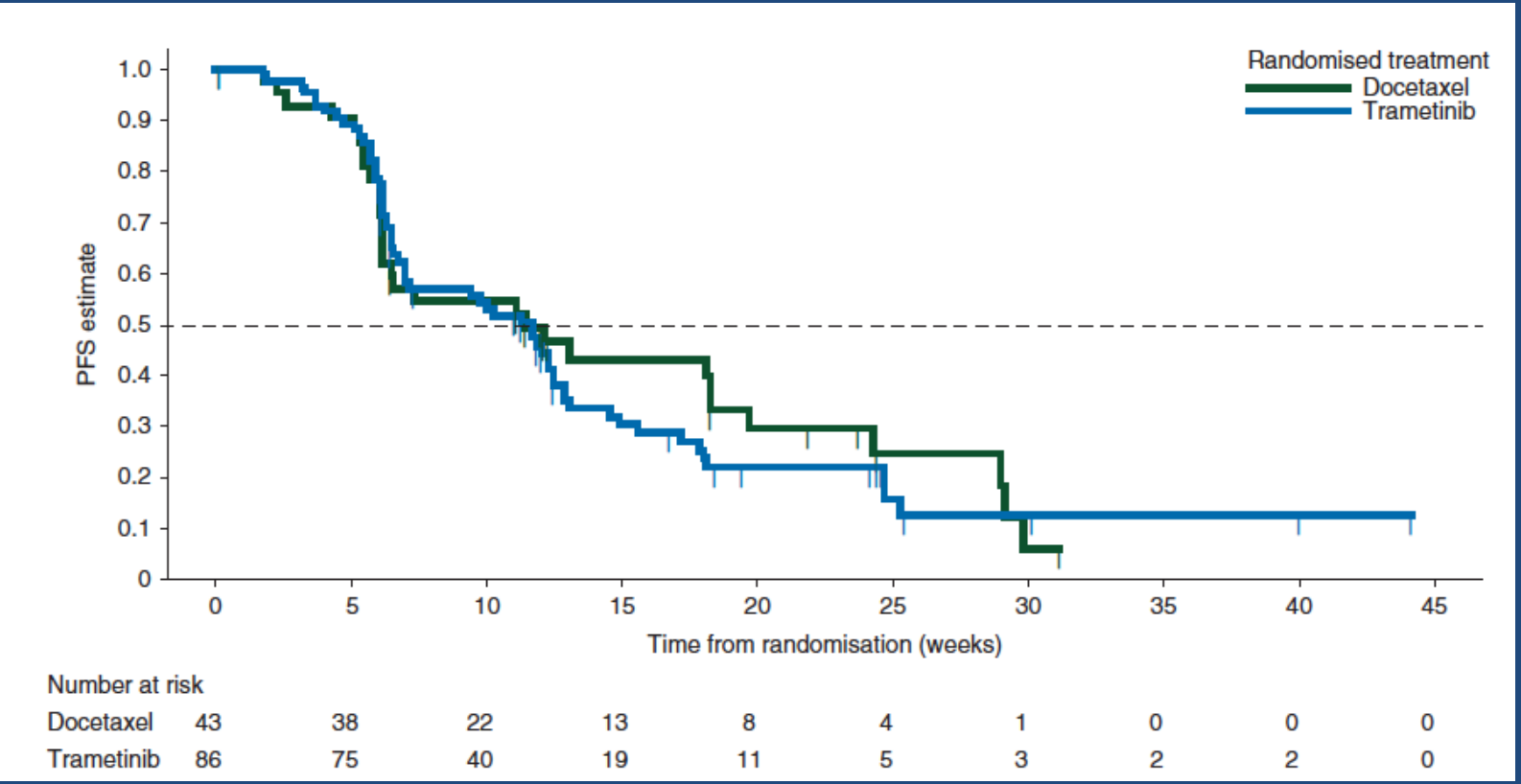
KRAS mutant NSCLC (n = 14)

2 PR (20+ and 33+ weeks)

7 SD (3 ≥16 weeks) and 5 PD

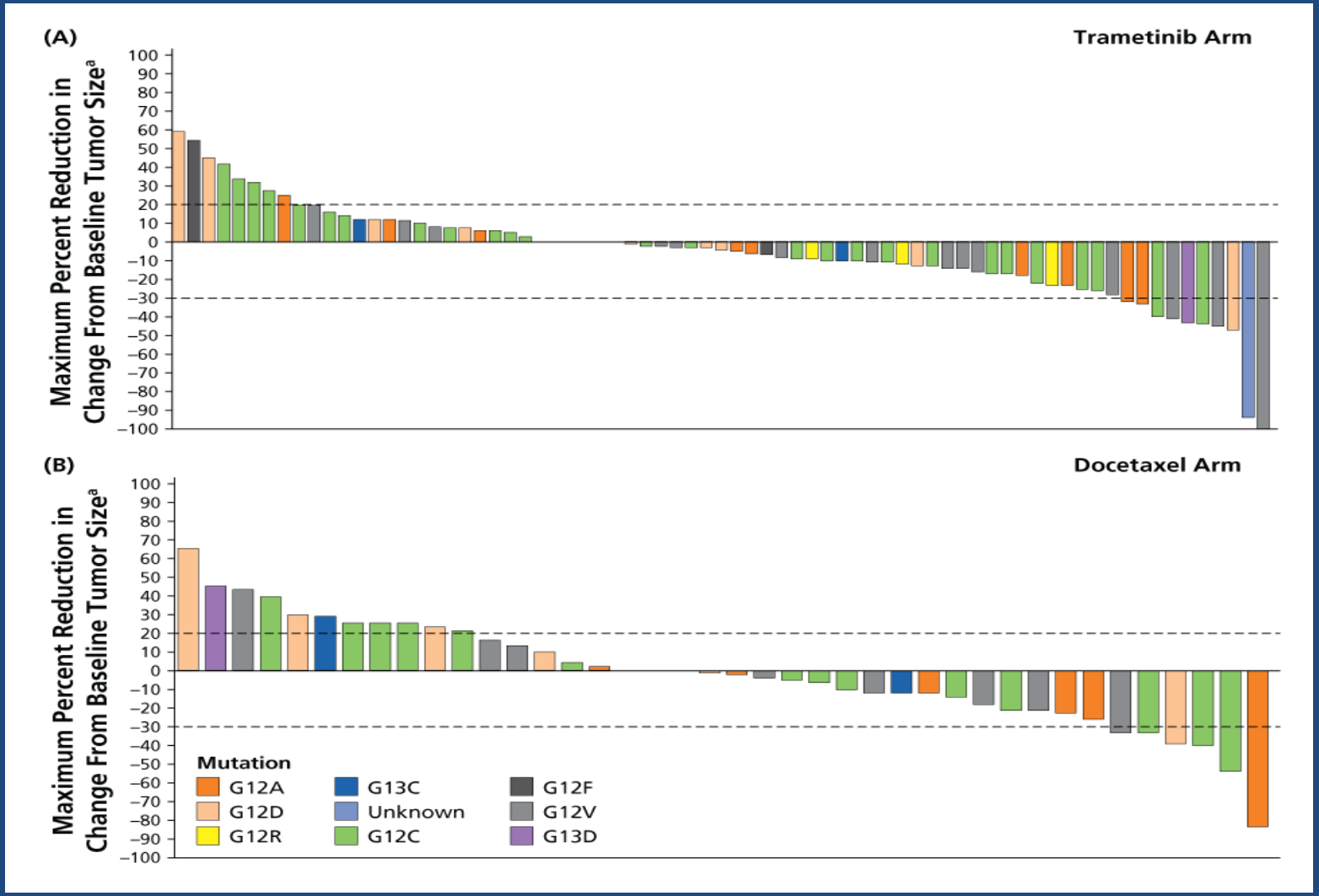
Falchook, et al. ESMO; 2010.

RPhII of Trametinib *vs* Docetaxel in *K-RAS* mut NSCLC: PFS



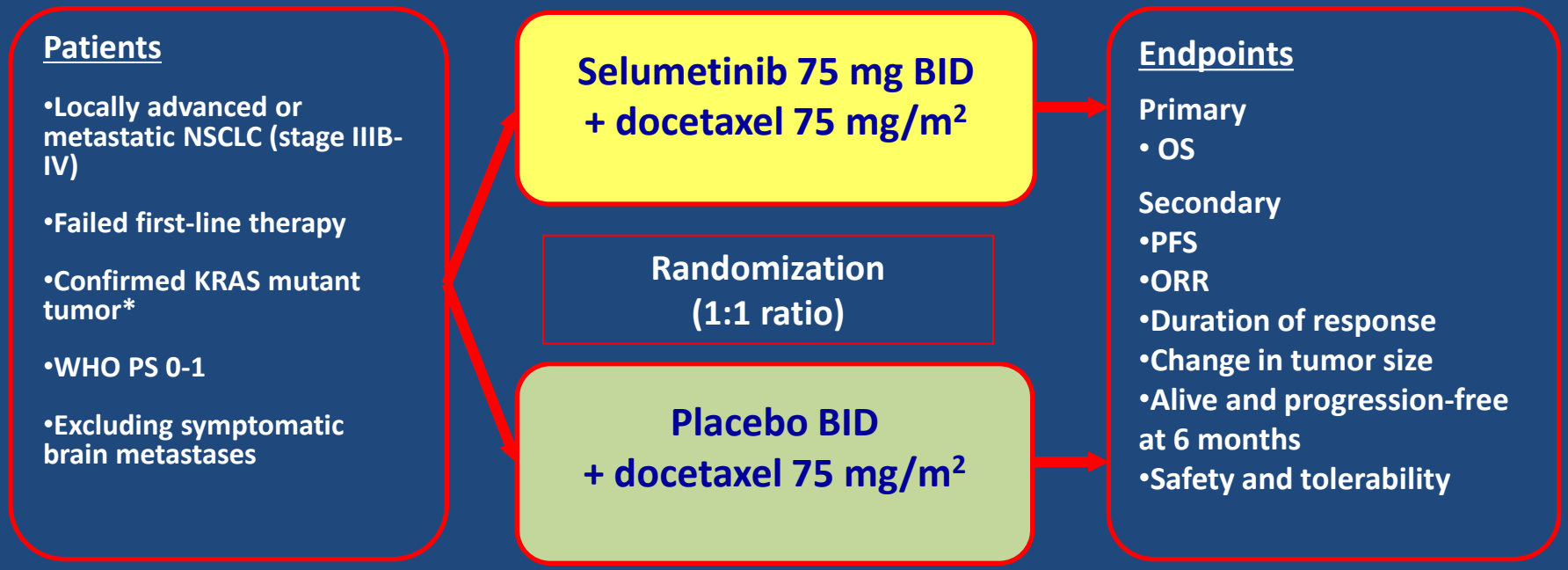
Blumenschein et al. Ann. Oncol. in press

Best Tumor Responses in KRAS-Mutant Patients in (A) Trametinib Arm and (B) Docetaxel Arm



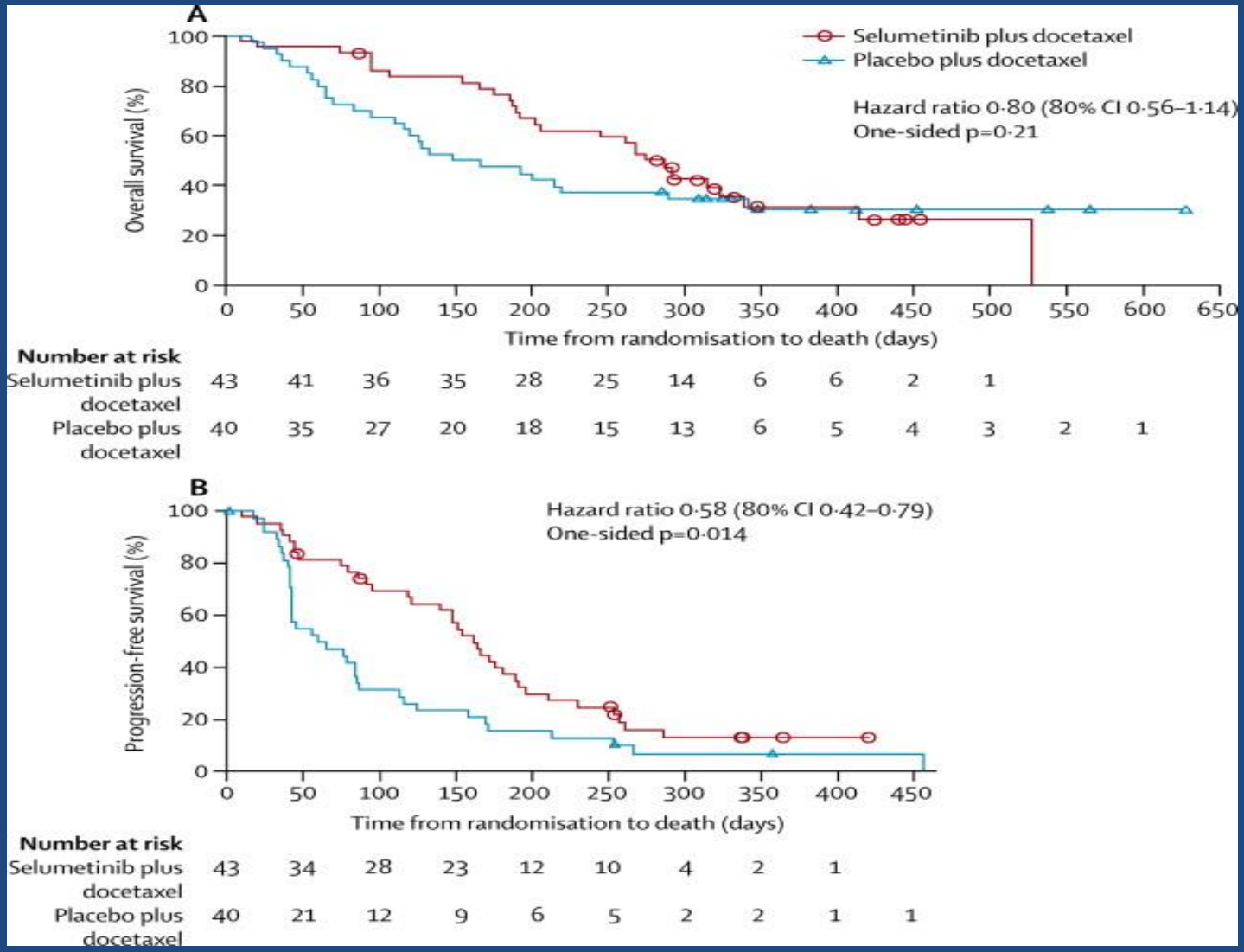
Blumenschein et al. Ann. Oncol. in press

Phase II, double-blind, randomized, placebo-controlled, multi-center trial; NCT00890825



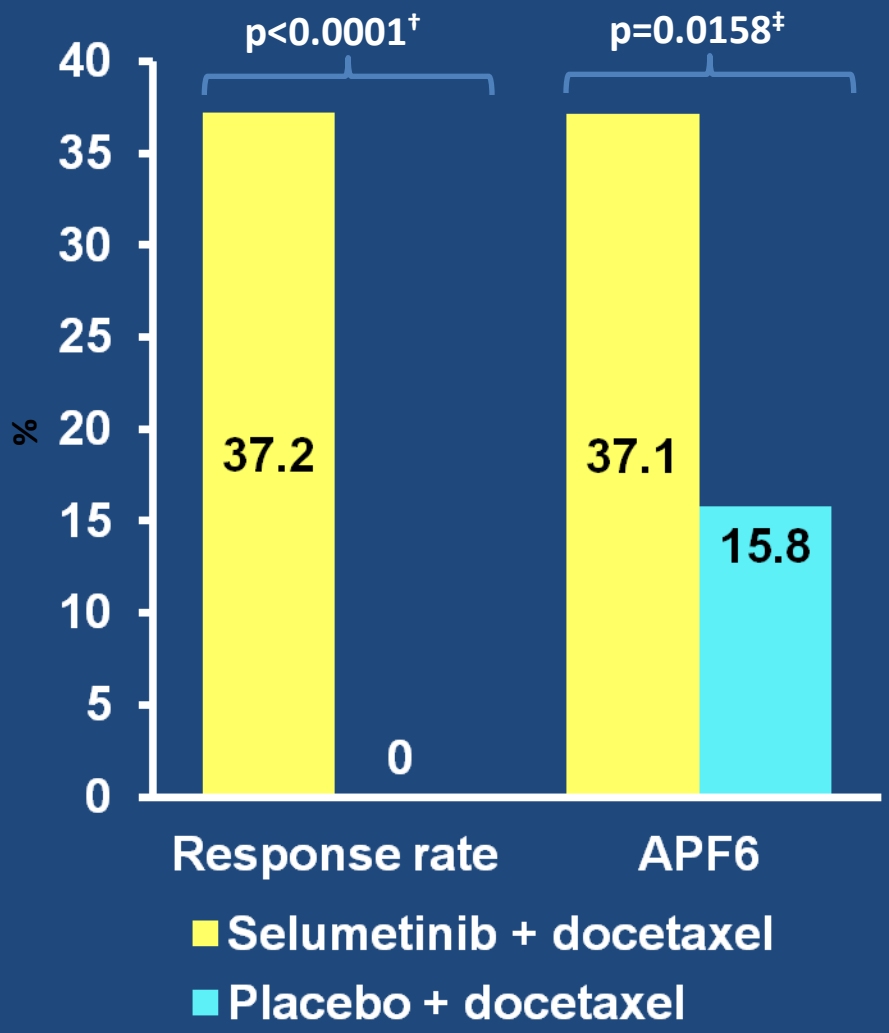
- Docetaxel was administered every 21 days; selumetinib/placebo administered daily
- Following completion of patient enrollment, the primary endpoint was changed from PFS to OS, without changing the sample size‡
  - OS analysis was planned for after approximately 58 events; HR 0.57, 80% power assuming a 1-sided 10% significance level

Docetaxel +/- Selumetinib in KRAS (+) NSCLC



Janne et al, Lancet Oncol 2012, ASCO 2012

RR and APF at 6 mos

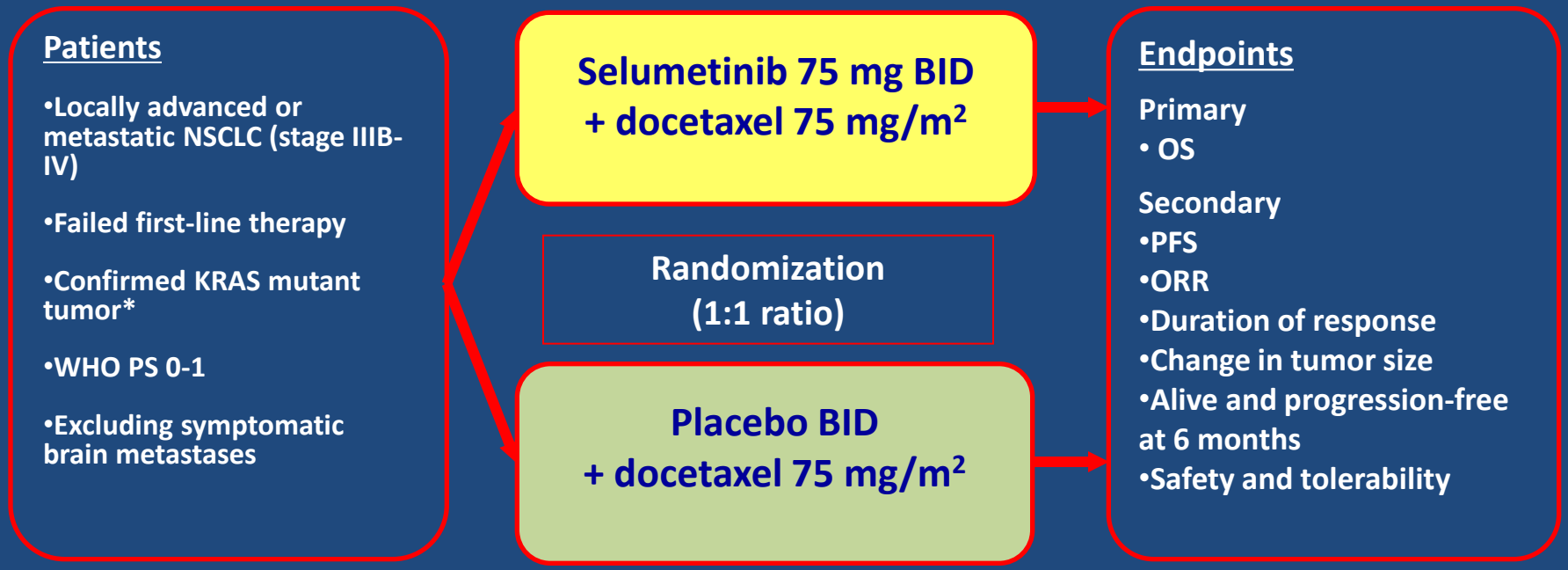


†Fisher's exact 2-sided mid p value
‡1-sided p value
APF6, alive and progression-free at 6 months

	Selumetinib + docetaxel n=44	Placebo + docetaxel n=43
Best objective response (RECIST 1.0), number (%)		
CR	0	0
PR	16 (37.2)*	0§
SD ≥6 weeks	19 (44.2)	20 (50.0)
PD	8 (18.6)	18 (45.0)
Not evaluable	0	2 (5.0)
Median DoR, days	182	-

*11 confirmed, 5 unconfirmed
§One patient was classed as non-evaluable due to non-evaluable non-target lesions and would have had a partial response according to RECIST 1.1 criteria

Phase III, double-blind, randomized, placebo-controlled, multi-center trial



- Docetaxel is administered every 21 days; selumetinib/placebo administered daily

*Mutation status determined either by central laboratory (Esoterix, ARMS) or an approved local laboratory
‡To allow decisions to be made based on OS data without breaking study blinding at the earlier endpoint of PFS
BID, twice daily; ORR, objective response rate; OS, overall survival

Conclusions
K-Ras mutations in NSCLC

- Have no prognostic value both in early and advanced stage disease
- G12V mutation may be predicitve for taxane based therapy in advanced disease
- ? predictive for currently studied *RAS-MEK-Erk* pathway inhibitors