Second-line afatinib versus methotrexate in patients with recurrent and/or metastatic head and neck squamous cell carcinoma: subgroup/biomarker analysis of LUX-Head and Neck 1

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Disclosures

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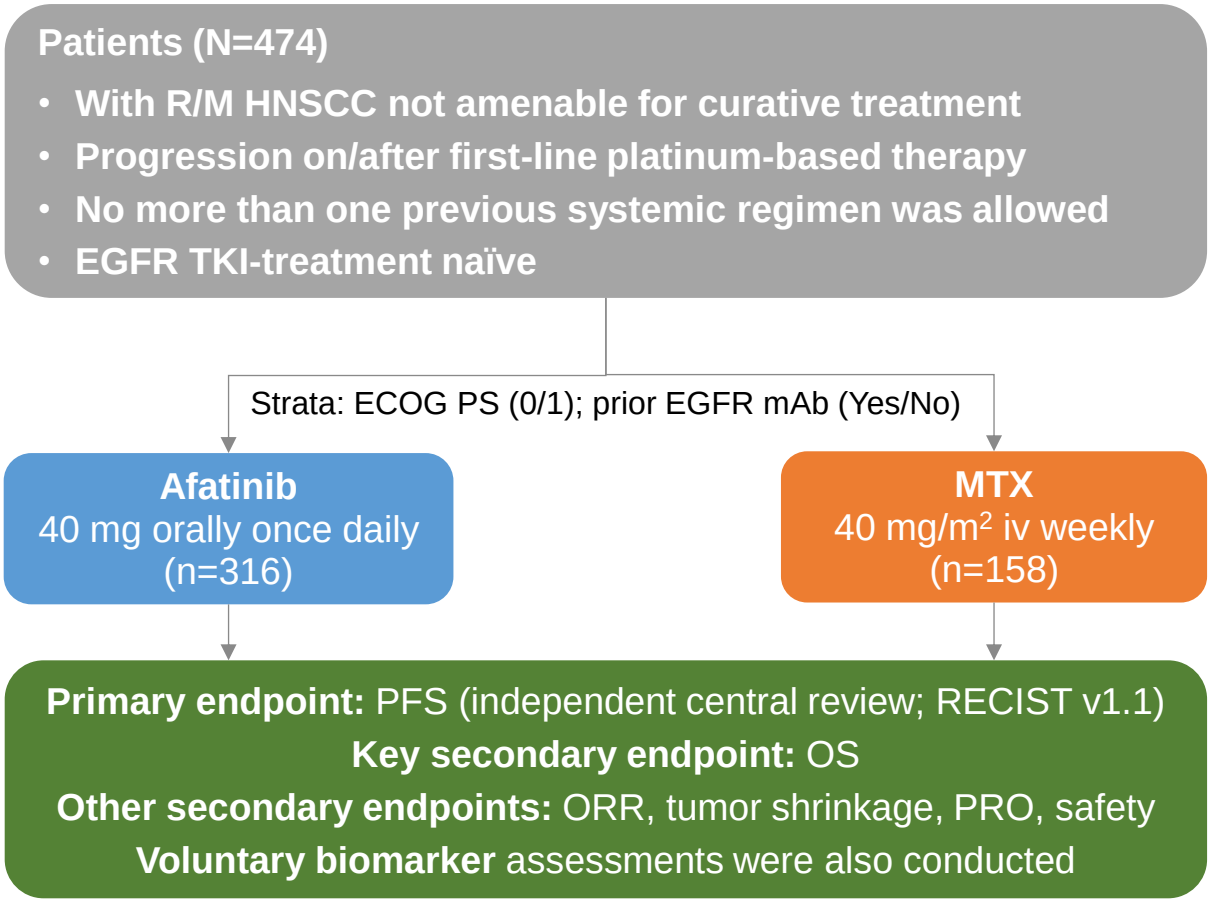
- Honoraria and consultation fees: Merck Serono, Bristol-Myers Squibb, Eisai, Otsuka and Bayer

Background

- R/M HNSCC patients progressing on/after first-line platinum therapy have poor prognosis (36 months median survival) and limited treatment options[1–3]
- While some molecular biomarkers, including p16 (surrogate for HPV infection), EGFR overexpression and PTEN loss, have been associated with prognosis in HNSCC, there are no established biomarkers predictive of treatment response[4,5]
- In the Phase III LUX-H&N1 trial, afatinib, an oral irreversible ErbB family blocker, significantly improved PFS (median 2.6 vs 1.7 months; HR=0.80; p=0.030) versus methotrexate in second-line R/M HNSCC patients[6]
  - Complete efficacy and safety findings from the overall population are published[6]
- This report focuses on efficacy outcomes in selected prespecified subgroups and biomarker-defined populations[6,7]

1. León X, et al. Clin Oncol 2005;17:418–24; 2. Vermorken JB, et al. Cancer 2008;112:2710–9; 3. Machiels JP, et al. Lancet Oncol 2011;12:333–43; 4. Kang H, et al. Nat Rev Clin Oncol 2015;12:11–26; 5. Suh Y, et al. Cell Death Dis 2014;5:e1018; 6. Machiels JP, et al. Lancet Oncol 2015;16:583–94; 7. Cohen EW, et al. J Clin Oncol 33, 2015 (Suppl.; abstract 6023)

LUX-Head & Neck 1: study design



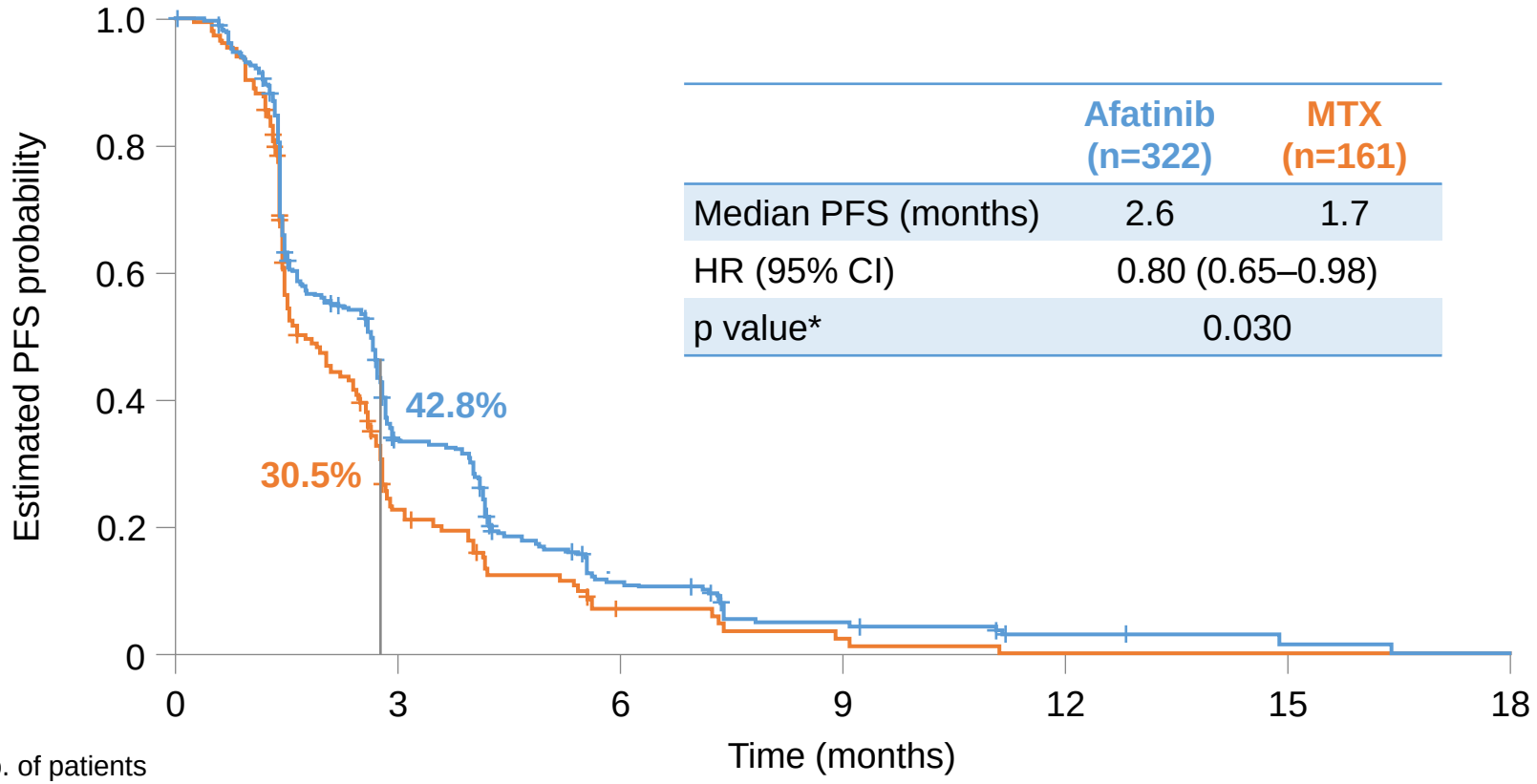
ECOG PS, Eastern Cooperative Oncology Group performance status; iv, intravenous; mAb, monoclonal antibody; MTX, methotrexate; TKI, tyrosine kinase inhibitor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1

Patient characteristics*

		Afatinib (n=322)	MTX (n=161)
Gender, %	Male/female	85/15	85/15
Median age, years (range)		60 (32–82)	59 (32–88)
Age subgroup, %	<65 years	74	72
	≥65 years	26	28
ECOG PS, %	**0/1**	**28/72**	**26/74**
Region, %†	Asia	8	11
	Europe	77	74
	North/Latin America	12	13
	Other	2	2
Smoking history, %†	<10 pack years	17	19
	≥10 pack years	79	78
	Unknown	3	3
Primary tumor site, %†	Oral cavity	29	26
	Oropharynx	31	34
	Hypopharynx	20	19
	Larynx	20	22
First-line anti-EGFR mAb, %‡		**59**	**61**
p16 status, %†,§	Positive	7	7
	Negative	42	40
	Not performed	51	53

*Biomarker analyses were conducted using tumor samples from a subset of patient volunteers, resulting in a smaller sample size (n=234) than the overall population
†Percentages may not total 100% due to rounding
‡One patient received panitumumab and all other patients received cetuximab;
§Assessed in a central laboratory

PFS in the overall population



	Afatinib (n=322)	MTX (n=161)
Median PFS (months)	2.6	1.7
HR (95% CI)	0.80 (0.65–0.98)	
p value*	0.030	

No. of patients							
Afatinib	322	93	26	9	3	1	0
MTX	161	28	6	2	0	0	0

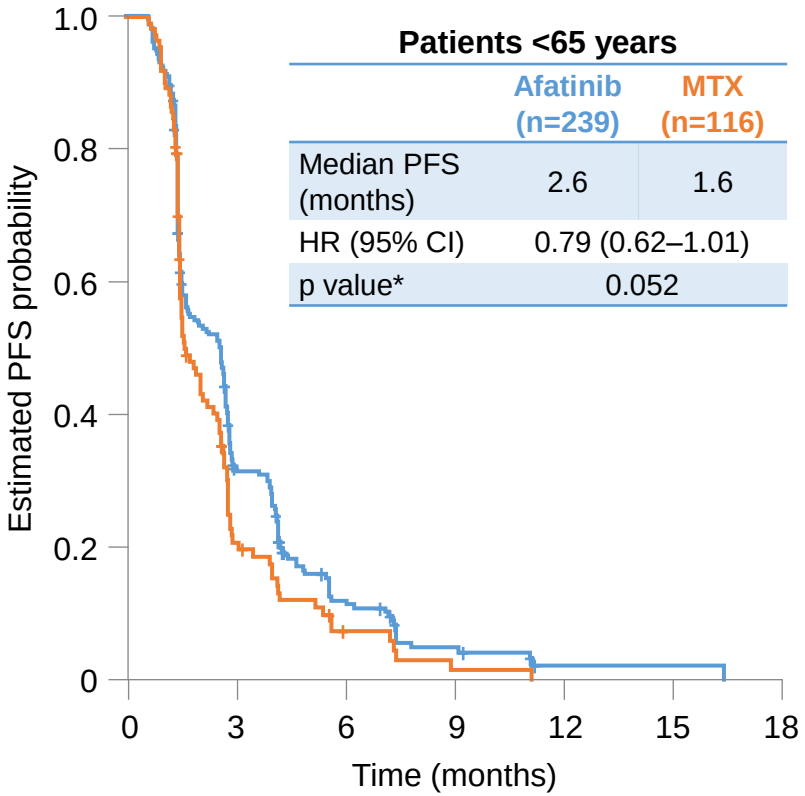
*Stratified log-rank test

PFS subgroup analysis*

Factors		No. of patients	HR (95% CI)
Total		483	0.80 (0.65–0.98)
Baseline ECOG PS	0	131	0.73 (0.49–1.10)
	1	352	0.77 (0.60–0.98)
Prior use of EGFR-targeted antibody for R/M HNSCC	No	196	0.63 (0.45–0.88)
	Yes	287	0.91 (0.70–1.19)
Gender	Male	412	0.74 (0.59–0.92)
	Female	71	0.95 (0.55–1.64)
Age	<65 years	355	0.79 (0.62–1.01)
	≥65 years	128	0.68 (0.45–1.03)
Region	Asia	43	0.62 (0.32–1.20)
	Europe	369	0.82 (0.64–1.04)
	North/Latin American	60	0.41 (0.21–0.79)
Smoking pack-years	<10 pack years	87	1.05 (0.66–1.70)
	≥10 pack years	381	0.71 (0.56–0.90)
Alcohol consumption	≤7 units/week	374	0.79 (0.62–1.00)
	>7 units/week	91	0.73 (0.46–1.14)
Primary tumor site	Oral cavity	136	0.69 (0.46–1.04)
	Oropharynx	153	0.99 (0.68–1.44)
	Hypopharynx	93	0.78 (0.48–1.25)
	Larynx	101	0.59 (0.38–0.92)
Recurrence or metastases	Recurrent	167	0.59 (0.42–0.84)
	Metastatic	64	1.18 (0.65–2.14)
	Both	241	0.81 (0.60–1.10)
Response to prior platinum therapy for R/M HNSCC	CR/PR/SD	261	0.82 (0.62–1.09)
	PD	146	0.66 (0.45–0.96)

*p16 status evaluated in the biomarker analysis (based on central laboratory assessment); CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

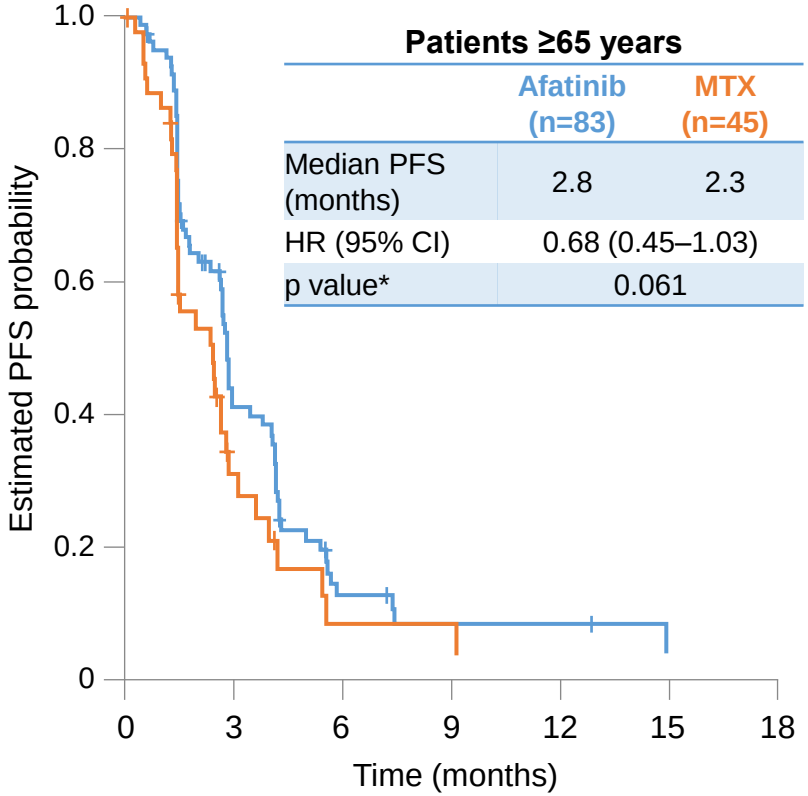
PFS by age subgroup



Patients <65 years

	Afatinib (n=239)	MTX (n=116)
Median PFS (months)	2.6	1.6
HR (95% CI)	0.79 (0.62–1.01)	
p value*	0.052	

No. of patients							
Afatinib	239	67	21	7	1	1	0
MTX	116	20	5	1	0	0	0



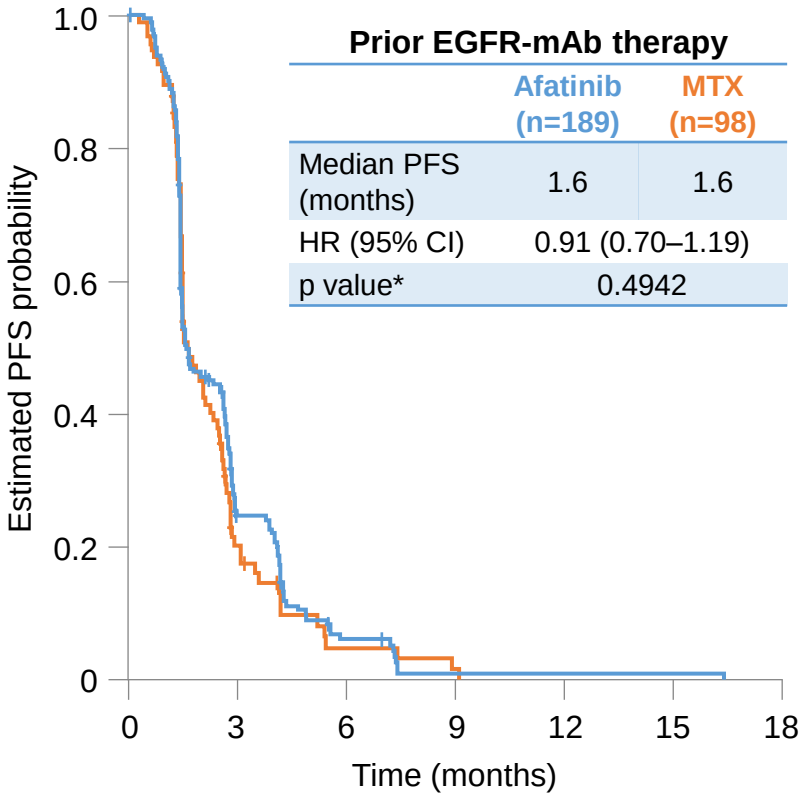
Patients ≥65 years

	Afatinib (n=83)	MTX (n=45)
Median PFS (months)	2.8	2.3
HR (95% CI)	0.68 (0.45–1.03)	
p value*	0.061	

No. of patients							
Afatinib	83	26	5	2	2	0	0
MTX	45	8	1	1	0	0	0

*Log-rank test

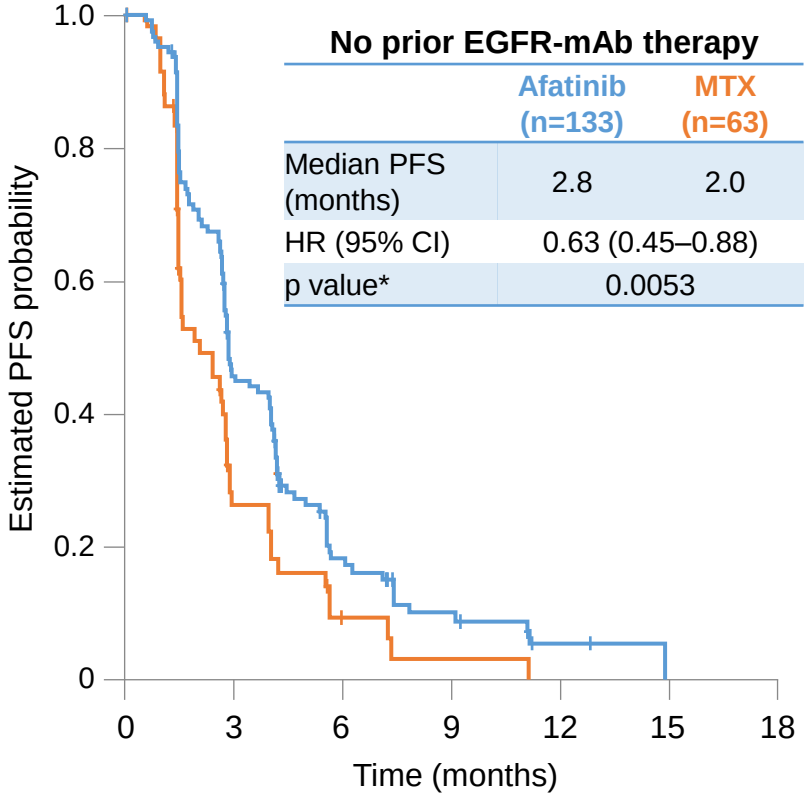
PFS by prior EGFR-mAb therapy



Prior EGFR-mAb therapy

	Afatinib (n=189)	MTX (n=98)
Median PFS (months)	1.6	1.6
HR (95% CI)	0.91 (0.70–1.19)	
p value*	0.4942	

No. of patients							
Afatinib	189	37	8	1	1	1	0
MTX	98	15	3	1	0	0	0



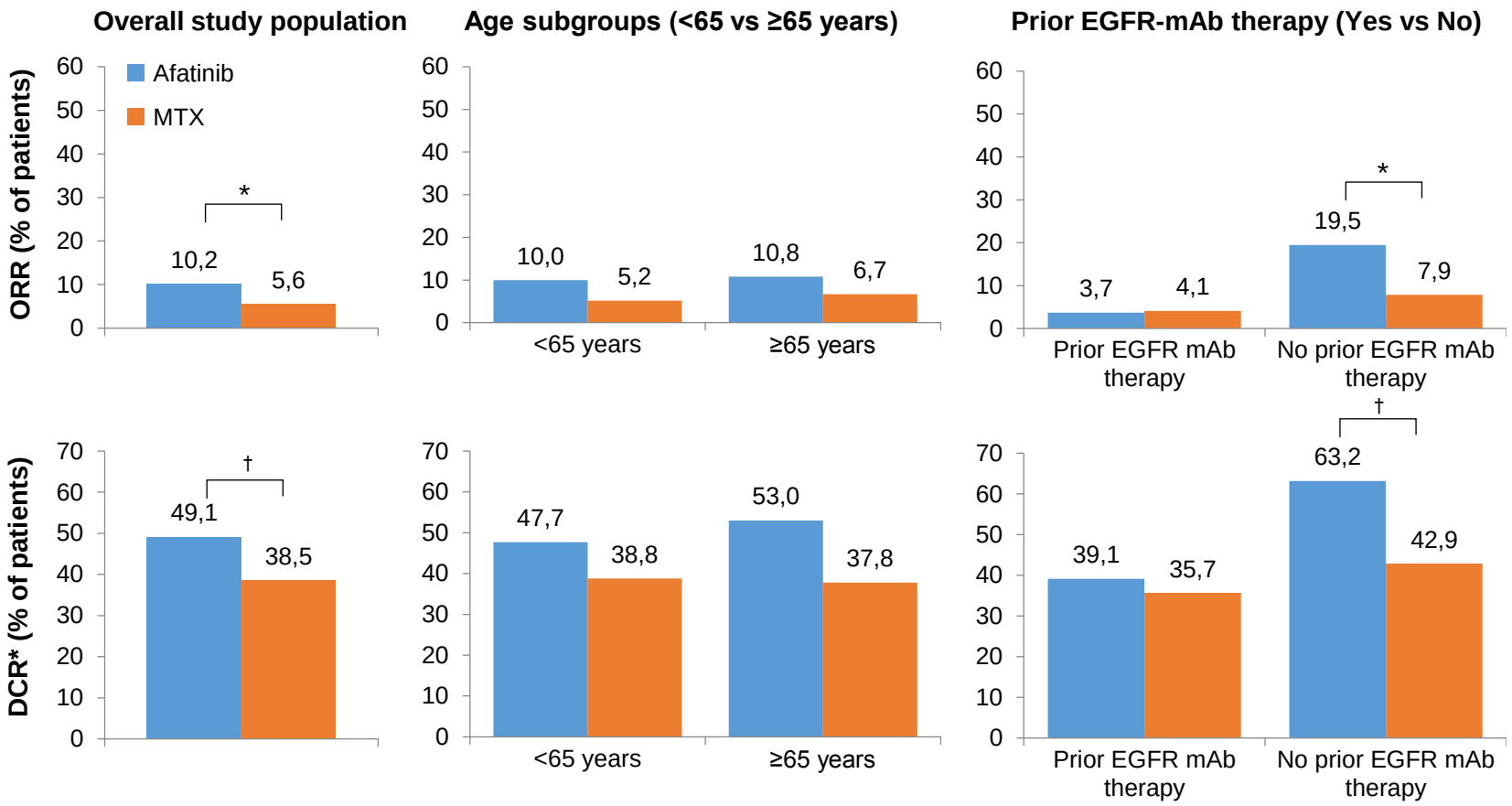
No prior EGFR-mAb therapy

	Afatinib (n=133)	MTX (n=63)
Median PFS (months)	2.8	2.0
HR (95% CI)	0.63 (0.45–0.88)	
p value*	0.0053	

No. of patients							
Afatinib	133	56	18	8	2	0	0
MTX	63	13	3	1	0	0	0

*Log-rank test

Tumor response



*OR: 1.9 (0.88–4.14); p=0.101
†OR: 1.5 (1.03–2.26); p=0.035

ORR: <65 OR: 2.0 (0.81–5.15); ≥65 OR: 1.7 (0.44–6.64)
DCR: <65 OR: 1.4 (0.92–2.26); ≥65 OR: 1.9 (0.89–3.90)

ORR: prior OR: 0.90 (0.26–3.17); *No prior OR: 2.8 (1.03–7.73)
DCR: prior OR: 1.2 (0.70–1.92); †No prior OR: 2.3 (1.24–4.21)

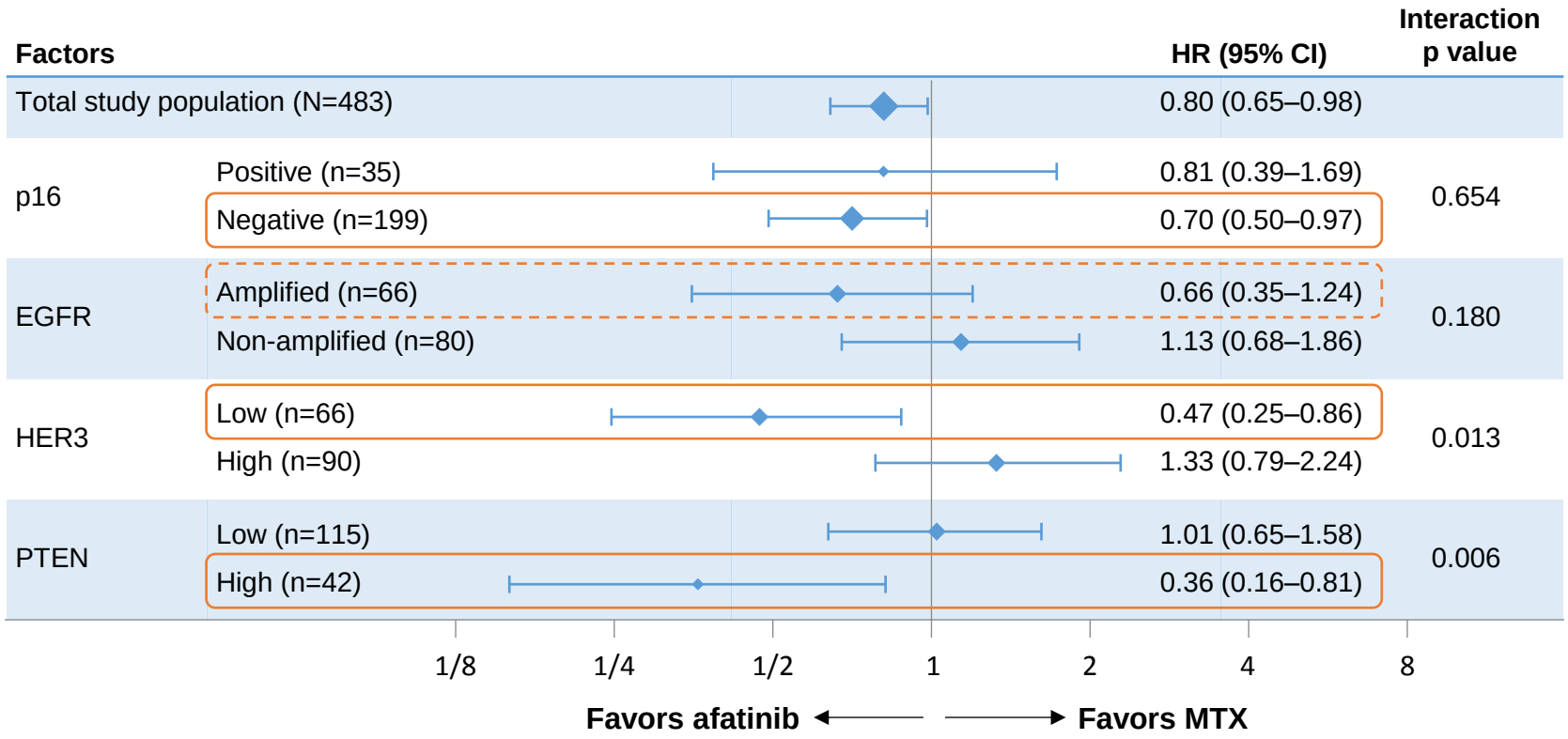
*DCR includes objective response and SD
DCR, disease control rate; OR, odds ratio; ORR, objective response rate

Prespecified biomarkers associated with ErbB pathway dysregulation

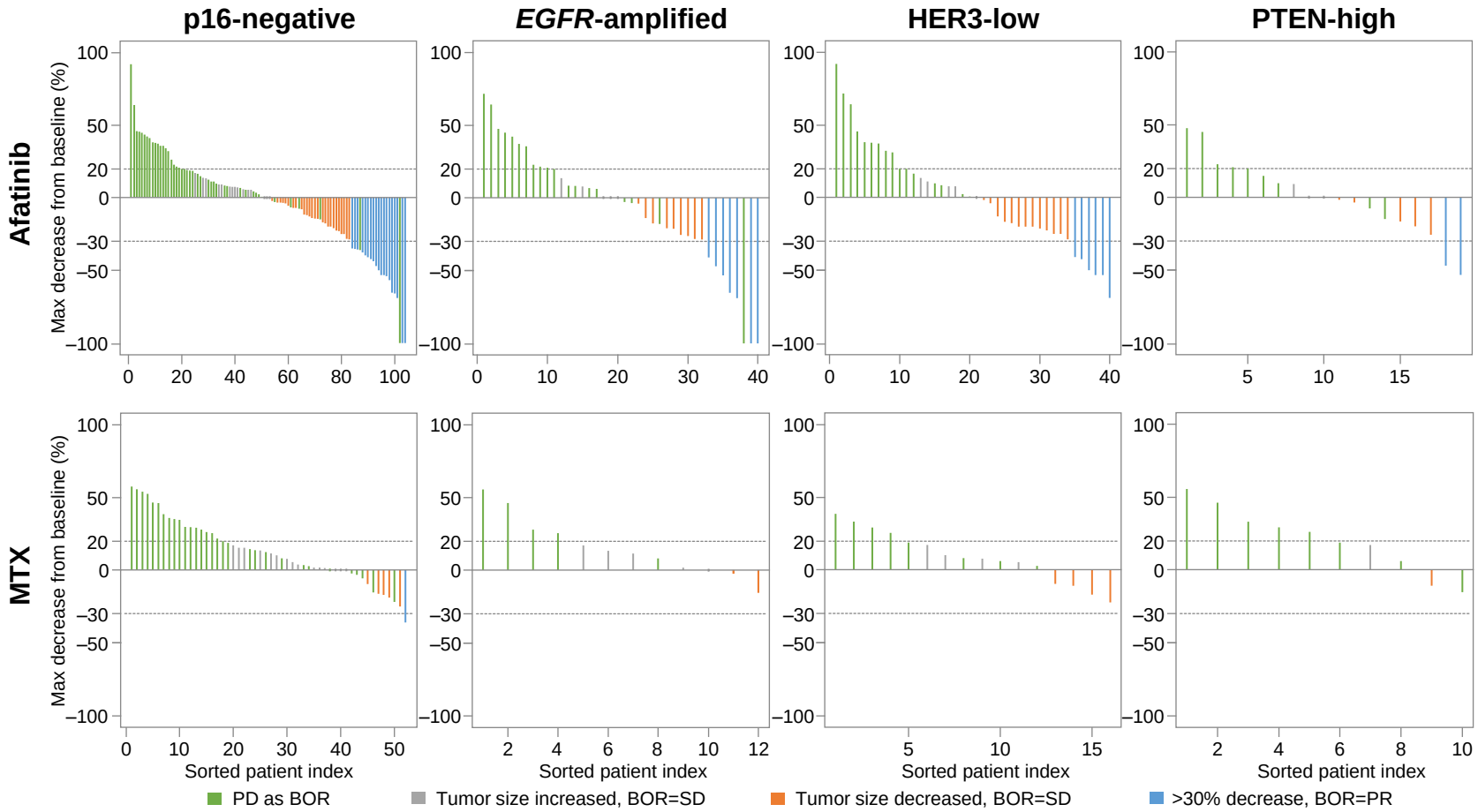
Patient disposition		
Biomarker status (cut-offs)*	**No. of patients (afatinib vs MTX)**	**Percentage of total, n/N (%)†**
p16-positive (H-score ≥210)	23 vs 12	35/234 (15%)
p16-negative (H-score <210)	135 vs 64	199/234 (85%)
EGFR-amplified‡	50 vs 16	66/146 (45%)
EGFR non-amplified	53 vs 27	80/146 (55%)
HER3-high (H-score >50)	64 vs 26	90/156 (58%)
HER3-low (H-score ≤50)	49 vs 17	66/156 (42%)
PTEN-high (H-score >150)	30 vs 12	42/157 (27%)
PTEN-low (H-score ≤150)	82 vs 33	115/157 (73%)

*Cut-offs were not prespecified in the protocol and are exploratory;
†Percentage based on total patients with specific biomarker available;
‡Amplification defined as ≥50% of cells with ≥4 copies, or ≥1 cell with ≥8 copies
H-score, histology-score

PFS according to biomarker status

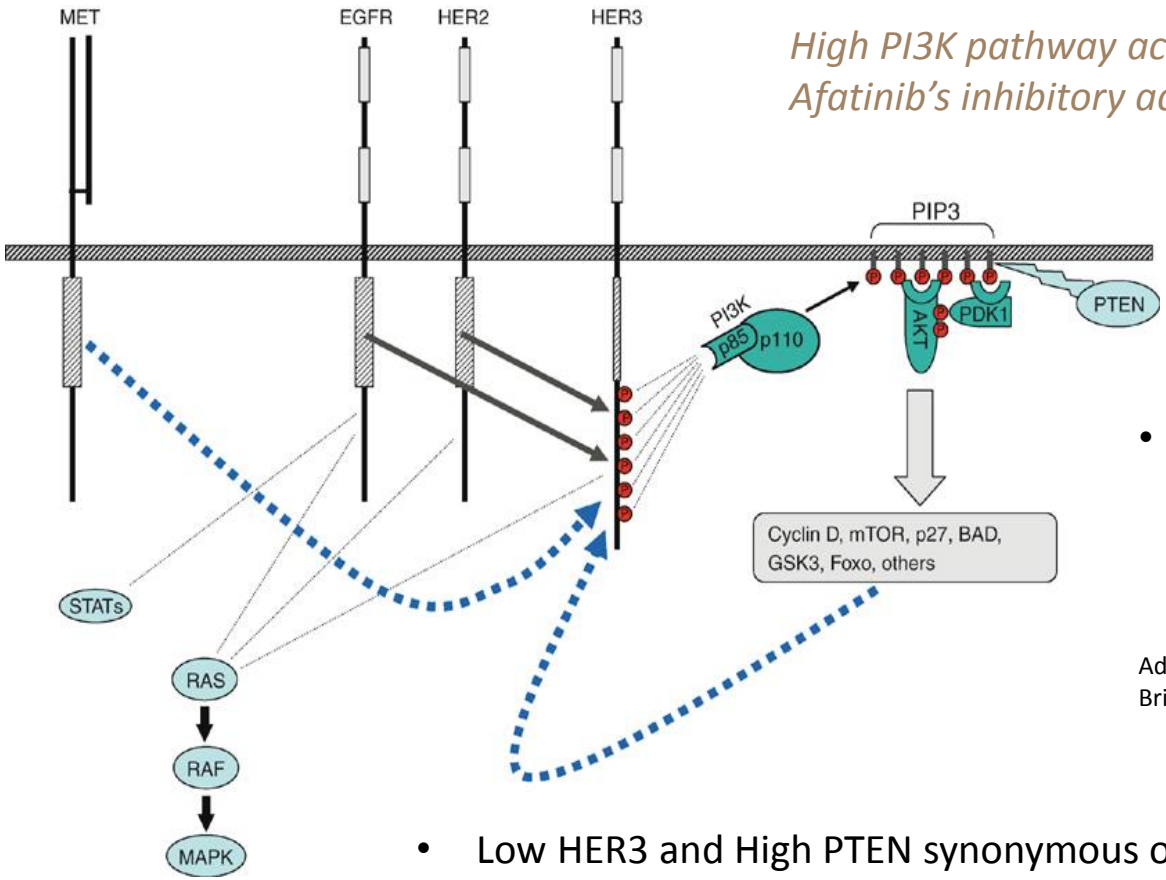


Tumor shrinkage in biomarker populations deriving more pronounced PFS benefit with afatinib



BOR, best overall response

Biological Hypothesis



High PI3K pathway activity could antagonize Afatinib's inhibitory activity

= Negative regulator of PI3K pathway

- Among the ErbB family members only HER3 can activate the PI3K/Akt pathway directly

Adapted from : AC Hsieh and MM Moasser. British Journal of Cancer (2007) 97, 453 – 457

- Low HER3 and High PTEN synonymous of Low PI3K pathway activity

Conclusions

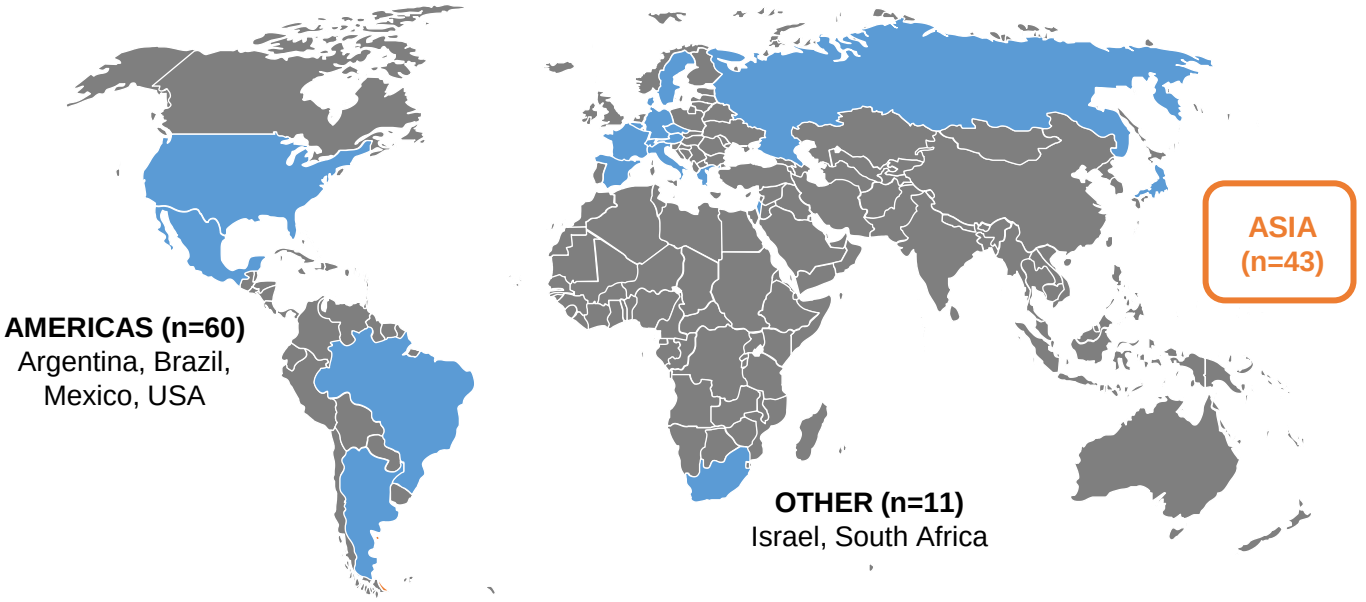
- The proportion of patients achieving clinical benefit with afatinib over methotrexate was 4 x greater in the EGFR-mAb therapy-naïve subgroup (37% reduction in risk of progression/death) compared with EGFR-mAb pretreated patients (9% reduction)
- The efficacy benefit with afatinib over methotrexate was similar between older (≥65 years) and younger (<65 years) patients
- Afatinib showed more pronounced antitumor effects in patients with p16-negative disease and dysregulation of ErbB pathway-related biomarkers (*EGFR*-amplification, HER3-low, PTEN-high expression)
- Additional samples are being evaluated to provide a more robust readout of clinical outcomes based on these biomarkers

Acknowledgments

- Thank you to all of the patients and their families, and the LUX-Head & Neck study investigators and their teams for participating in this study

101 sites in 19 countries

EUROPE (n=369)
Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, Russia, Spain, Sweden, Switzerland



AMERICAS (n=60)
Argentina, Brazil, Mexico, USA

OTHER (n=11)
Israel, South Africa

Back-up

Methodology for tumor biomarker assessments

Biomarker	Method	Manufacturer: assay	Cut-offs*
p16	IHC	Ventana: CINtec® p16	p16-positive= H-score ≥210
EGFR amplification	FISH	Abbott: Vysis™	Amplification= ≥50% of cells with ≥4 copies, or ≥1 cell with ≥8 copies
HER3	IHC	Dako: DAK-H3-IC	H-score ≤50 (low expression)
PTEN	IHC	Cell Signaling: 138G6	H-score >150 (high expression)

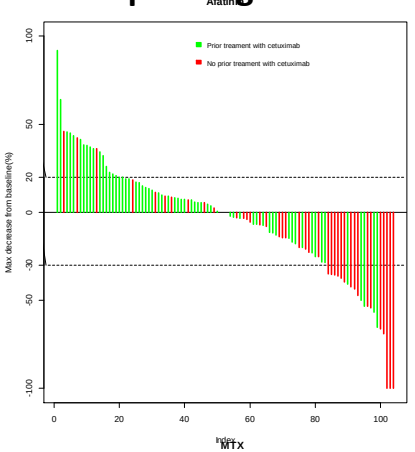
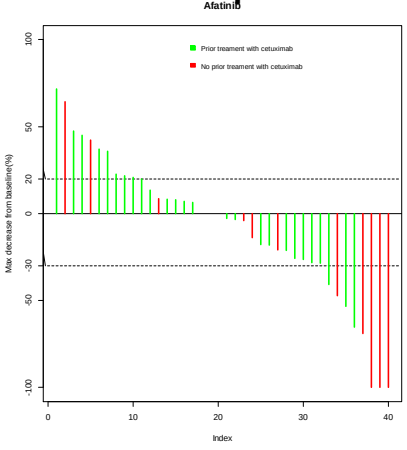
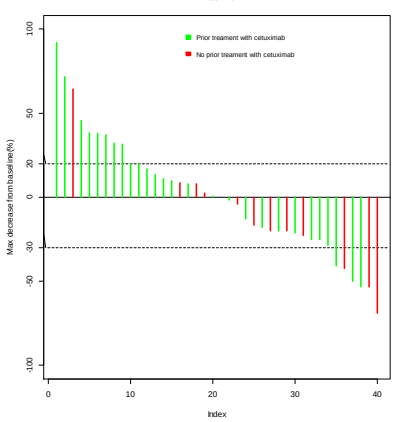
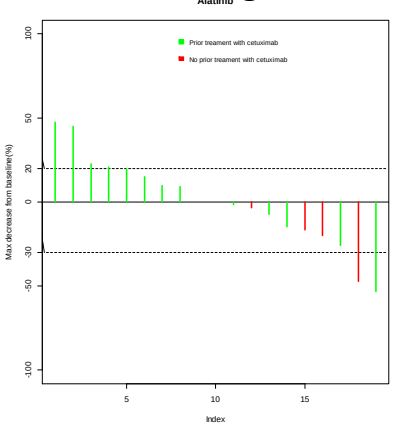
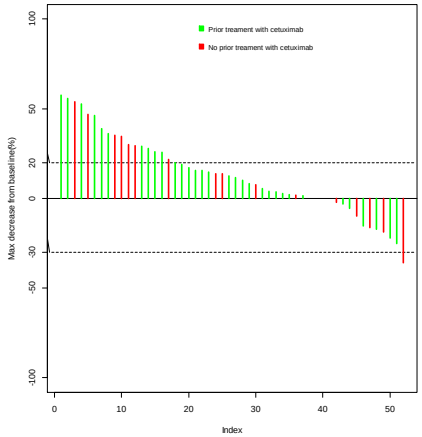
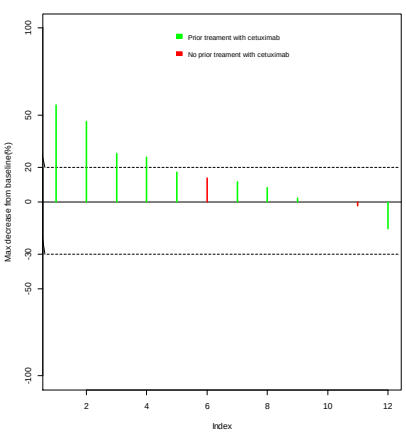
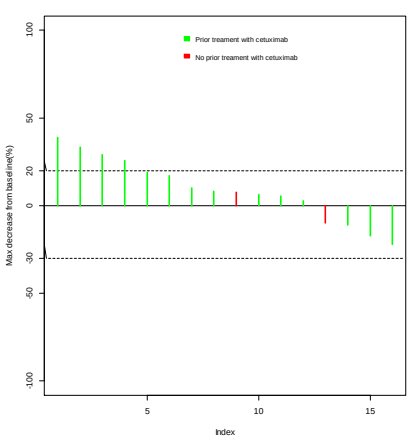
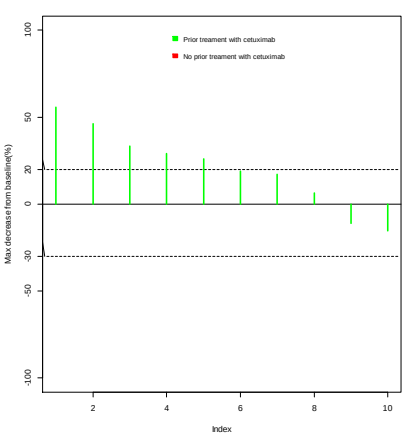
*Cut-offs were not prespecified in the protocol and are exploratory
FISH, fluorescence in situ hybridization; IHC, immunohistochemistry

Tumor response in biomarker-defined populations

	Afatinib vs MTX	
Biomarker status (cut-offs)*	**No. of patients**	**ORR, %**
p16-positive (H-score ≥210)	23 vs 12	0 vs 8.3
p16-negative (H-score <210)	135 vs 64	14.1 vs 1.6
EGFR-amplified†	50 vs 16	14.0 vs 0
EGFR non-amplified	53 vs 27	3.8 vs 0
HER3-high (H-score >50)	64 vs 26	9.4 vs 0
HER3-low (H-score ≤50)	49 vs 17	12.2 vs 0
PTEN-high (H-score >150)	30 vs 12	6.7 vs 0
PTEN-low (H-score ≤150)	82 vs 33	12.2 vs 0

*Cut-offs were not prespecified in the protocol and are exploratory;
†Amplification defined as ≥50% of cells with ≥4 copies, or ≥1 cell with ≥8 copies

Note: This slide shows tumor shrinkage in patients who received prior cetuximab (green) or did not receive prior cetuximab (red) – according to biomarker status

	p16-negative	EGFR-amplified	HER3-low	PTEN-high
Afatinib				
MTX				

Note: This slide shows tumor shrinkage in all study patients who received prior cetuximab (green) or did not receive prior cetuximab (red)

Tumor shrinkage by treatment and prior treatment with cetuximab