Afatinib versus methotrexate as second-line treatment for patients with R/M HNSCC who progressed after platinum-based therapy: primary efficacy results of LUX-Head & Neck 1, a Phase III trial

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Disclosures

- Advisory board without compensation
  - Boehringer Ingelheim

Background

- Patients with R/M HNSCC who progress after first-line platinum-based therapy have a dismal prognosis and limited efficacious treatment options[1–3]
  - Median overall survival of approximately 3–6 months[1–3]
- Epidermal growth factor receptor (EGFR) is overexpressed in ~90% of HNSCC and is associated with poor prognosis[4,5]
- Afatinib, an orally available, irreversible ErbB family blocker, showed promising anti-tumour activity in a Phase II trial in patients with R/M HNSCC[6]

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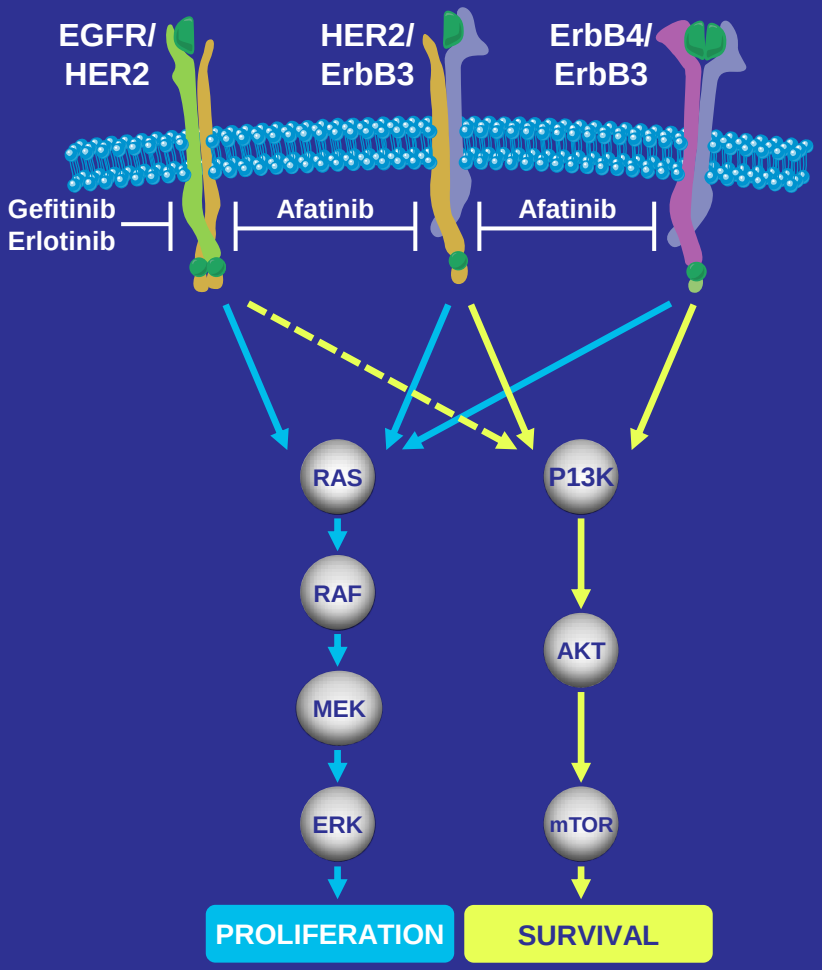
Afatinib: irreversible ErbB-family inhibition

- **Afatinib is an irreversible ErbB-family blocker[1–3]**
  - **Inhibits all kinase-active members: EGFR, HER2 and HER4**
  - **Proof of concept in squamous histology in various trials in lung, and head and neck cancer**
  - **Approved* in the major ICH regions of US,[4] EU[5] and Japan[6] for the treatment of patients with NSCLC harbouring distinct types of *EGFR*-activating mutations**



HER2, human epidermal growth factor receptor-2; HER4, human epidermal growth factor receptor-4; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
*Indications differ between countries

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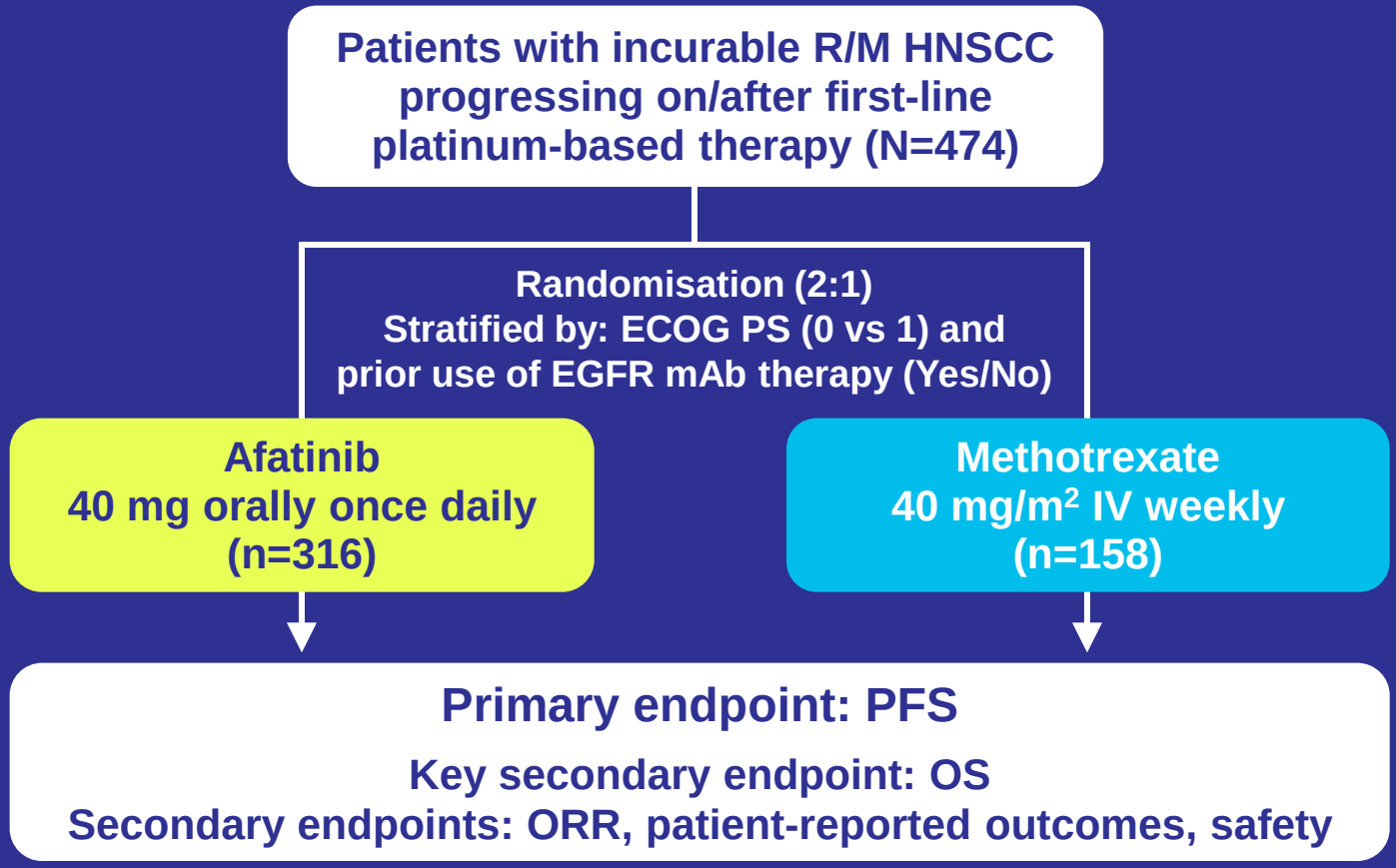
LUX-Head & Neck 1: study design



Statistical design and study conduct

- **Primary endpoint:** PFS (RECIST 1.1 primary analysis based on independent radiology review)
  - Sample size: 364 independent events to detect HR of 0.70 (increase in median PFS from 2.1 to 3.0 months) at 90% power with one-sided type-I error of α=0.025
- **Key secondary endpoint:** OS
  - Sample size: 343 deaths to detect HR of 0.73 (increase in median OS from 6.5 to 8.9 months) at 80% power with one-sided type-I error of α=0.025
- Stratified log-rank test and Cox proportional hazards model for PFS and OS comparisons (ITT for all randomised patients)

Study conduct

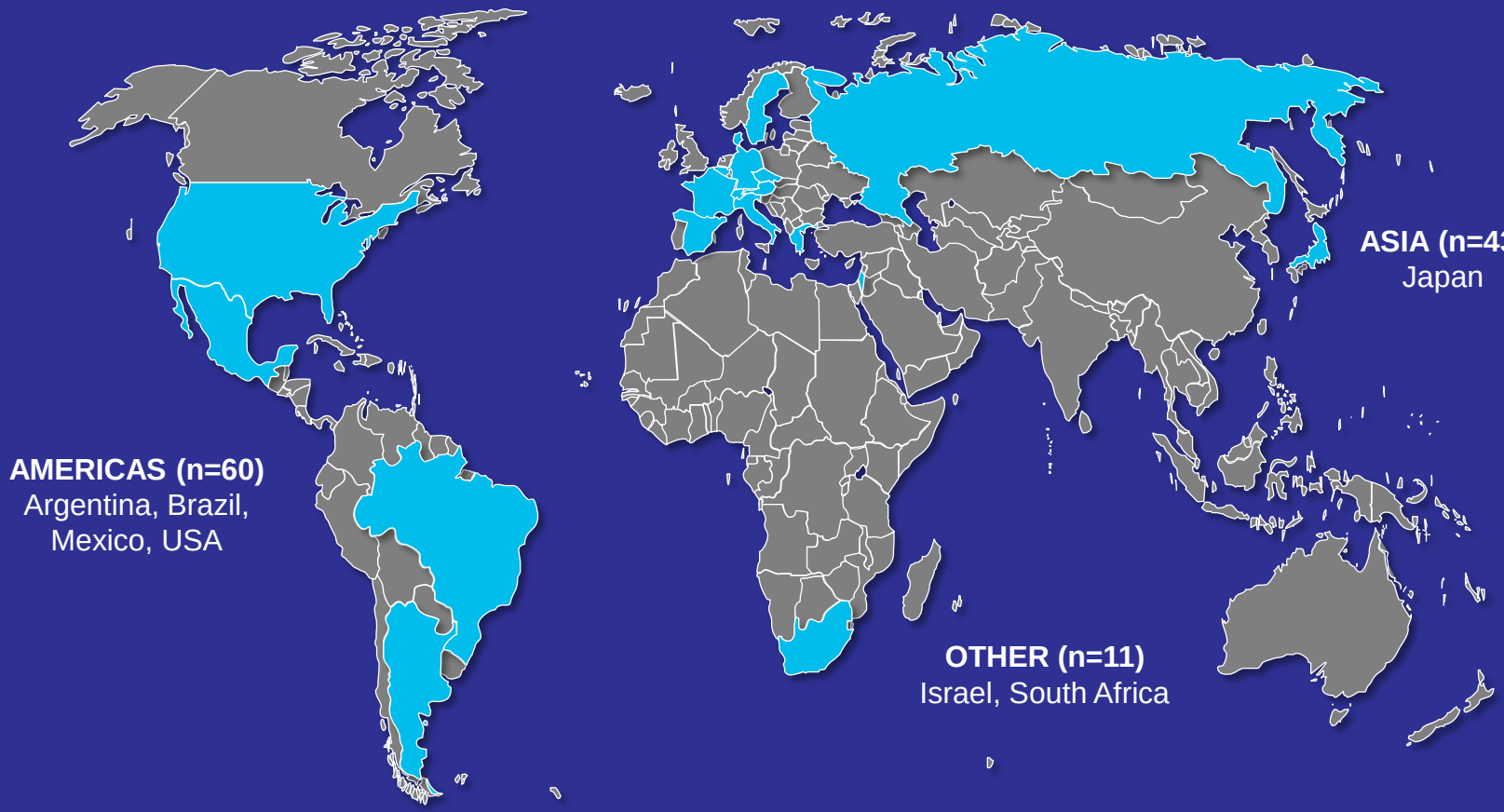
Accrual period	January 2012 – December 2013
PFS data-base lock	May 2014
OS data-base lock	June 2014
Median follow-up	6.7 months; 410 PFS events

HR, hazard ratio; ITT, intent-to-treat

Participating countries

- 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

ASIA (n=43)
Japan

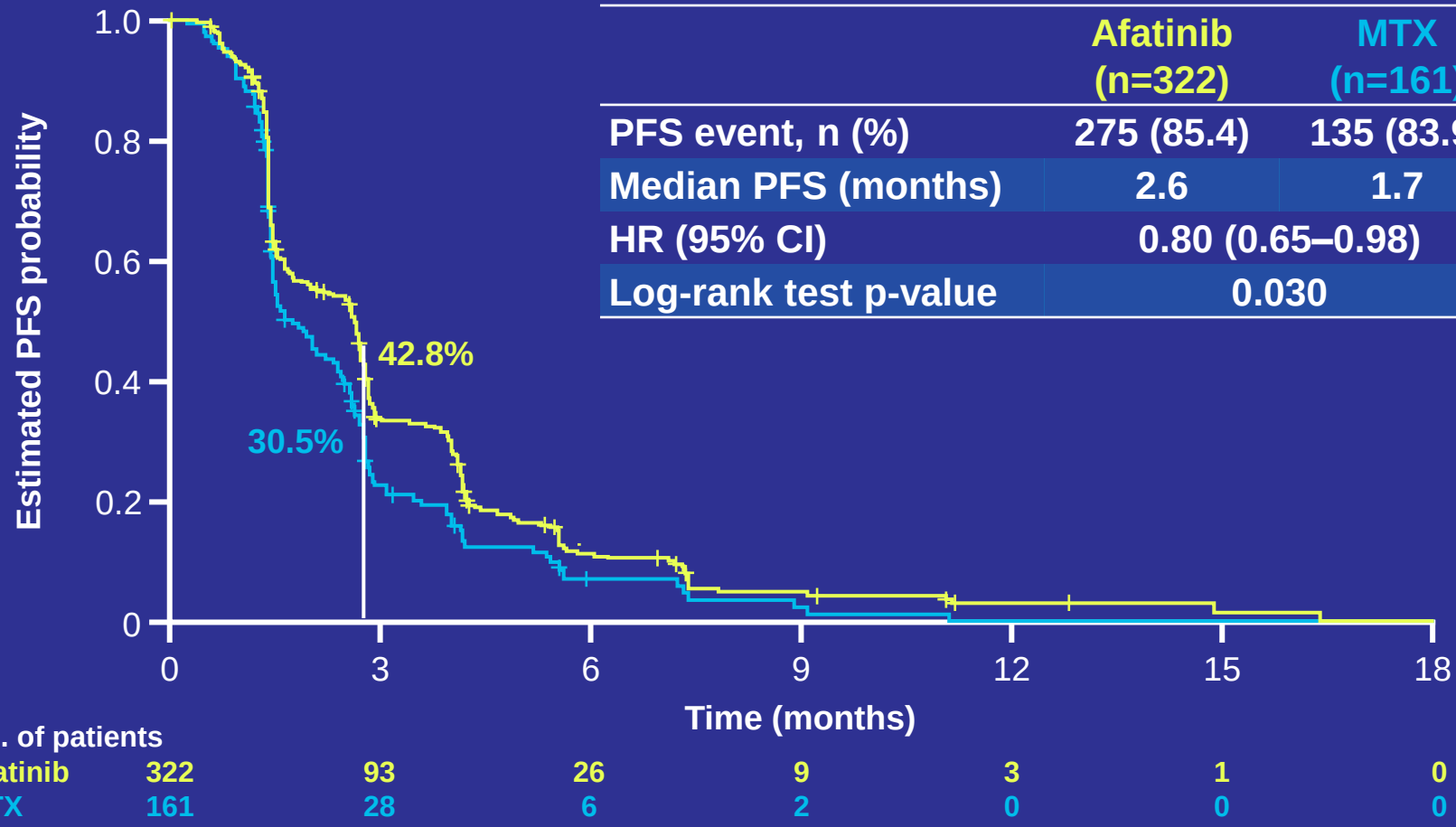
OTHER (n=11)
Israel, South Africa

Patient characteristics

Randomised patients, n		Afatinib (n=322)	Methotrexate (n=161)
Gender, %	Male/female	85/15	85/15
Median age, years (range)		60 (32–82)	59 (32–88)
ECOG PS, %	0/1	28/72	26/74
Smoking history, %*	<10 pack years	17	19
	≥10 pack years	79	78
	Unknown	3	3
Primary tumour site, %*	Oral cavity	29	26
	Oropharynx	31	34
	Hypopharynx	20	19
	Larynx	20	22
p16 status, %*	Positive	10	11
	Negative	44	42
	Not performed	47	47
First-line platinum-based therapy, %	Cisplatin	52	52
	Carboplatin	37	29
	Cisplatin and carboplatin	9	17
	Other	2	2
First-line anti-EGFR mAb†, %		59	61

*Percentages may not total 100% due to rounding
†One patient received panitumumab; all other patients received cetuximab

Primary endpoint: PFS independent review

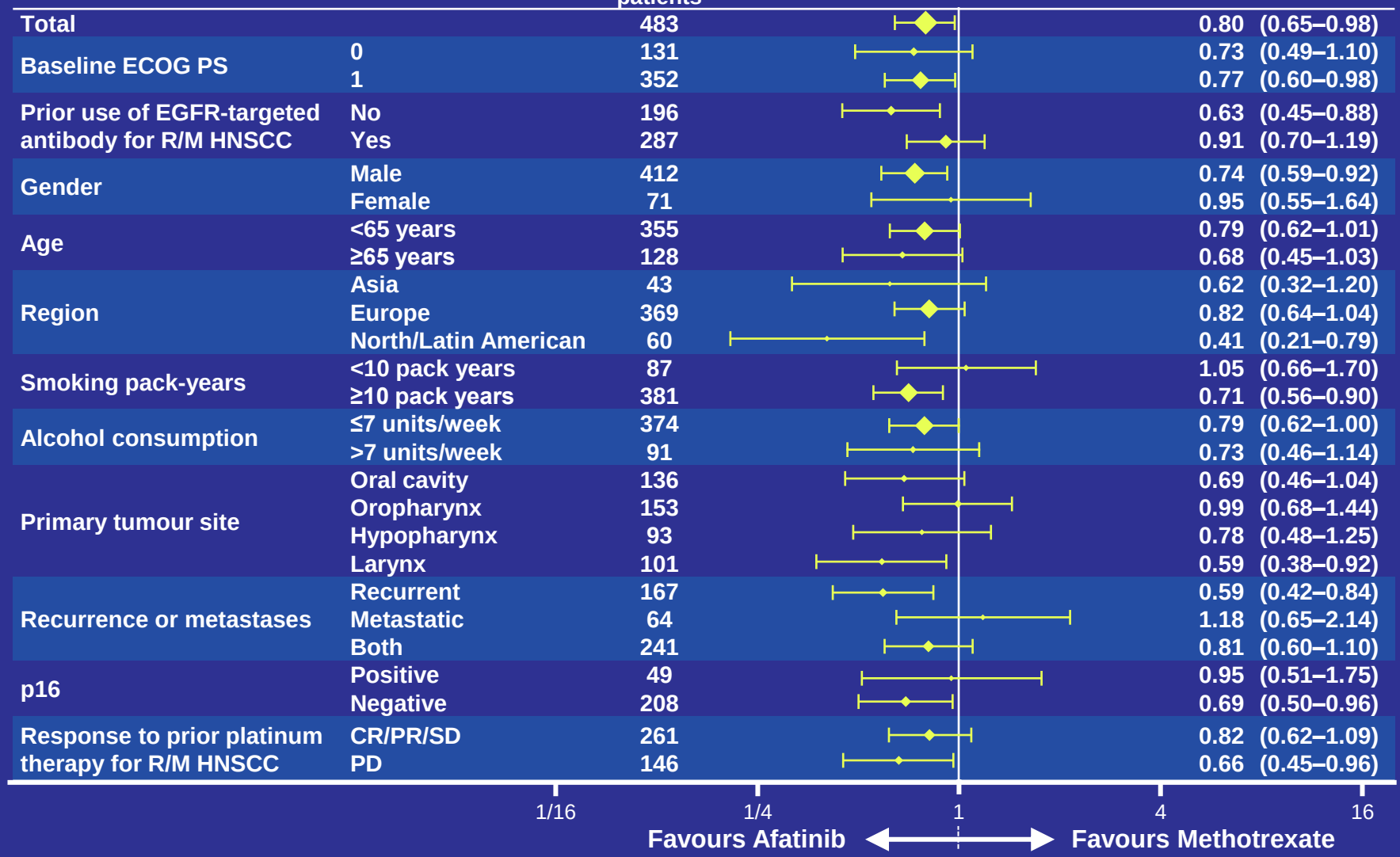


	Afatinib (n=322)	MTX (n=161)
PFS event, n (%)	275 (85.4)	135 (83.9)
Median PFS (months)	2.6	1.7
HR (95% CI)	0.80 (0.65–0.98)	
Log-rank test p-value	0.030	

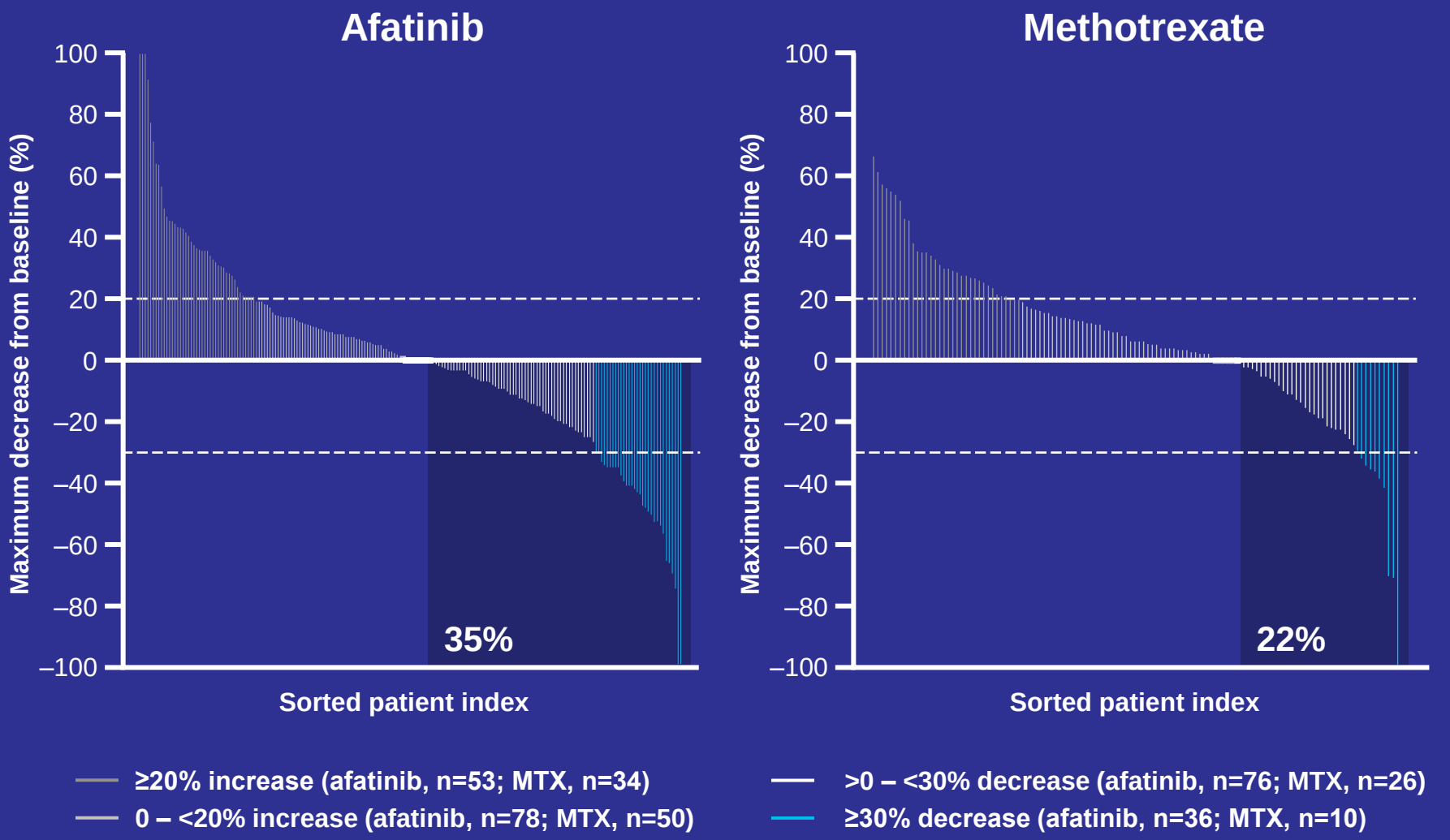
CI, confidence interval; MTX, methotrexate

PFS subgroup analysis

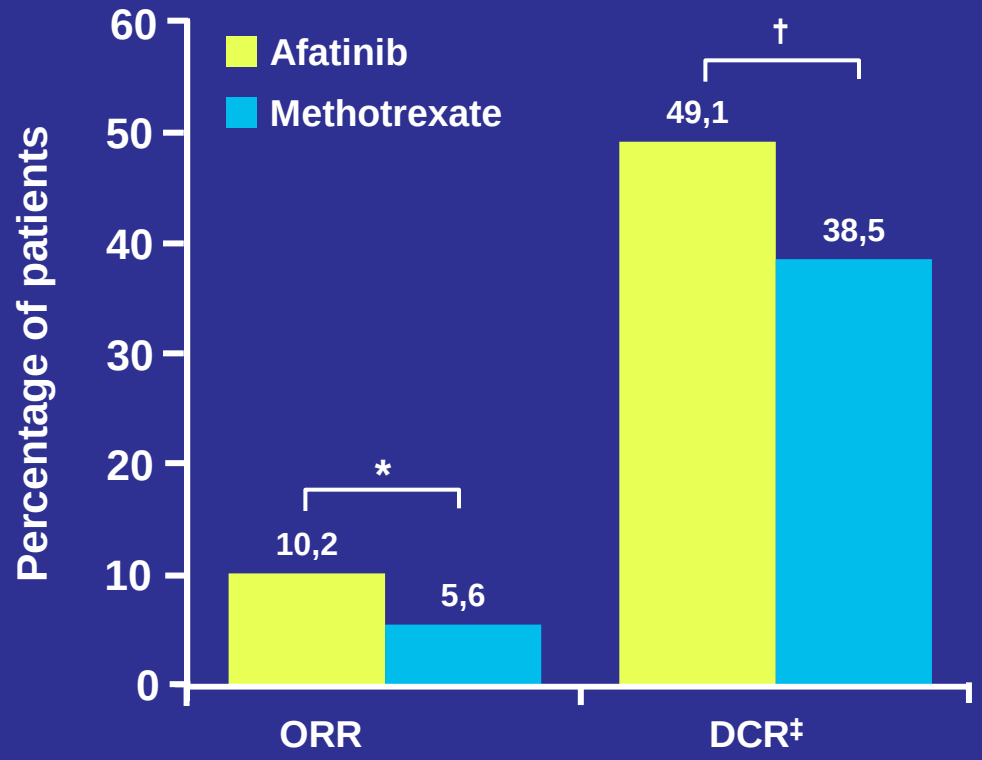
Factors		Number of patients	HR (95% CI)
Total		483	0.80 (0.65–0.98)
Baseline ECOG PS	0	131	0.73 (0.49–1.10)
	1	352	0.77 (0.60–0.98)
Prior use of EGFR-targeted antibody for R/M HNSCC	No	196	0.63 (0.45–0.88)
	Yes	287	0.91 (0.70–1.19)
Gender	Male	412	0.74 (0.59–0.92)
	Female	71	0.95 (0.55–1.64)
Age	<65 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 tumour 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)
p16	Positive	49	0.95 (0.51–1.75)
	Negative	208	0.69 (0.50–0.96)
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)



Tumour shrinkage

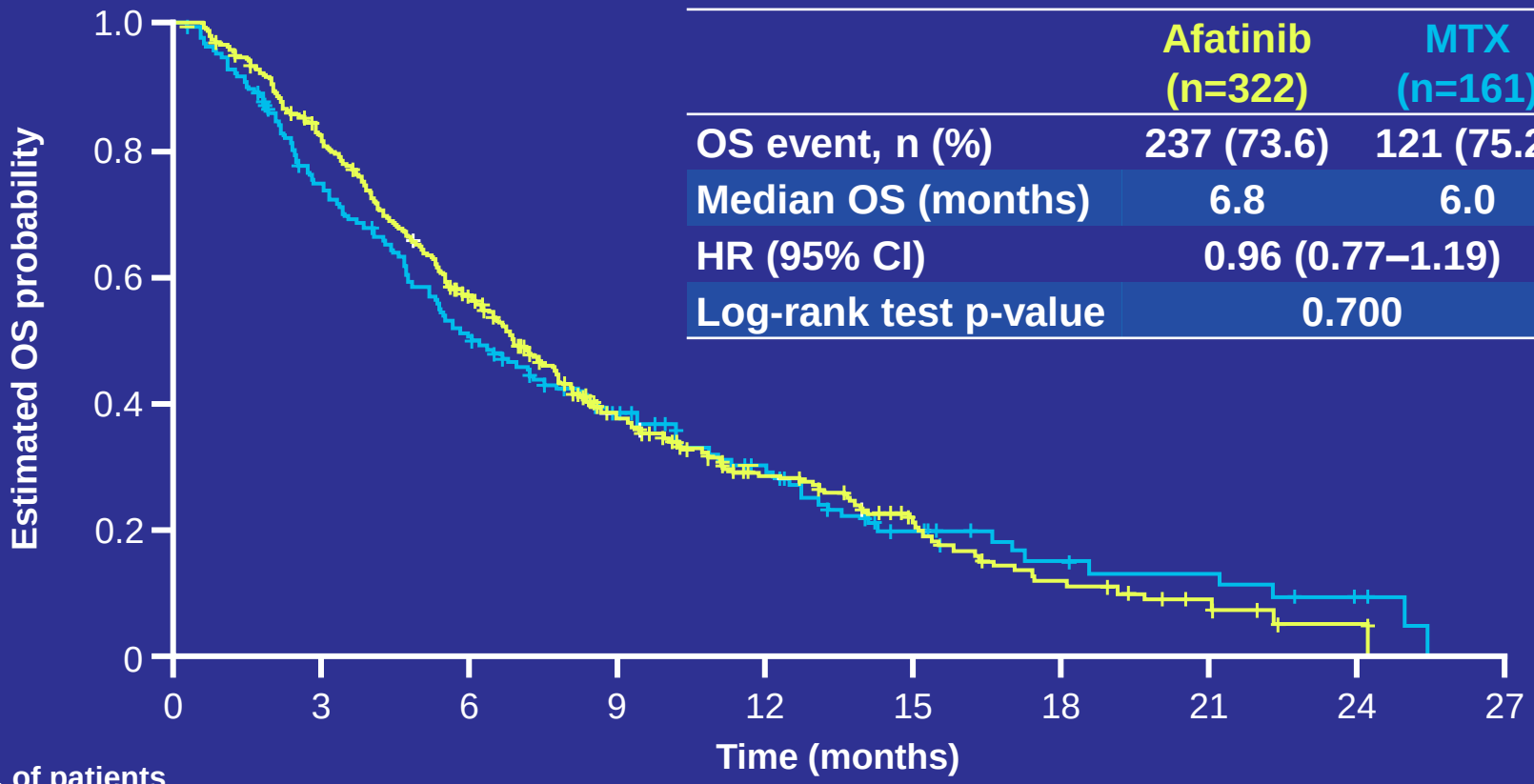


Overall tumour response



*Odds ratio: 1.9 (0.88–4.14); p-value = 0.101
†Odds ratio: 1.5 (1.03–2.26); p-value = 0.035
‡Disease control rate (DCR): includes objective response and stable disease

Overall survival



	Afatinib (n=322)	MTX (n=161)
OS event, n (%)	237 (73.6)	121 (75.2)
Median OS (months)	6.8	6.0
HR (95% CI)	0.96 (0.77–1.19)	
Log-rank test p-value	0.700	

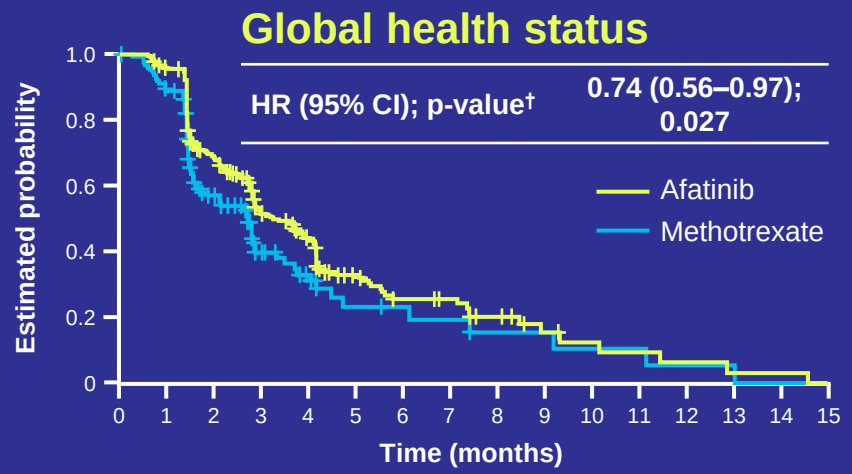
No. of patients										
Afatinib	322	255	172	89	53	28	14	6	1	0
MTX	161	115	76	48	29	16	9	7	3	0

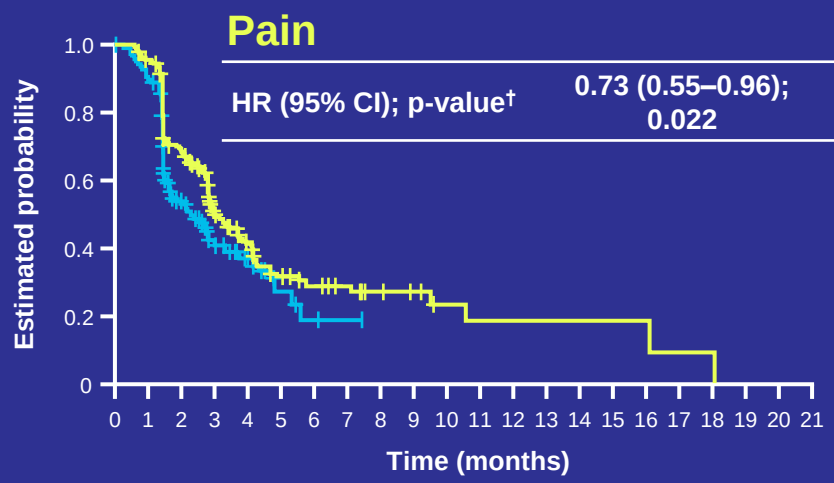
Most frequent subsequent therapies in patients who discontinued study medication

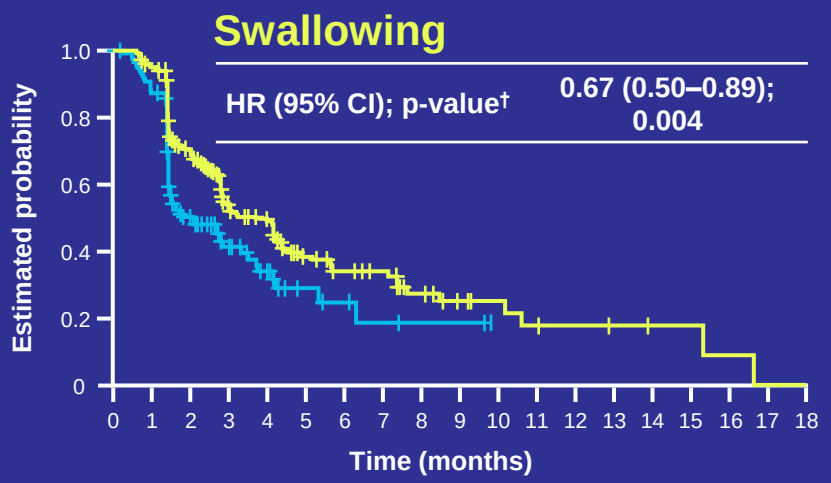
	Afatinib (n=320)	Methotrexate (n=160)
Discontinued study medication, n	304	156
Received subsequent therapy, n (%)*	156 (51)	79 (51)
Taxanes	73 (24)	50 (32)
Methotrexate	69 (23)	6 (4)
Platinum-based therapy	37 (12)	14 (9)
Cetuximab	27 (9)	25 (16)

*Percentages based on the number of patients who discontinued study medication

Time to deterioration of pre-specified patient-reported outcomes*



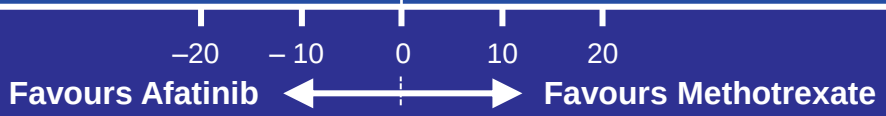




*Assessed using European Organization for Research and Treatment of Cancer (EORTC) questionnaire QLQ-C30 and Head and Neck cancer-specific module (QLQ-H&N35) for pain (composite of items 31–34) and swallowing (composite of items 35–38).
†Based on log-rank test.

Changes in patient-reported outcomes over time

Factors	Number of patients	Adjusted mean difference (95% CI)
Pain HN35 (Q1–Q4 from QLQ-HN35)	382	–4.4 (–8.3, –0.4)
Pain in mouth (Q1)	380	–3.7 (–9.2, 1.7)
Pain in jaw (Q2)	380	–7.5 (–12.5, –2.5)
Soreness in mouth (Q3)	380	–2.5 (–8.0, 2.9)
Painful throat (Q4)	382	–4.3 (–9.2, 0.6)
Swallowing scale (Q5–Q8 from QLQ-HN35)	369	–0.1 (–4.3, 4.2)
Problem swallowing liquid (Q5)	373	–2.5 (–8.3, 3.2)
Problem swallowing pureed food (Q6)	365	–1.1 (–6.6, 4.4)
Problem swallowing solid food (Q7)	364	0.0 (–5.8, 5.8)
Choked when swallowing (Q8)	361	2.5 (–2.9, 7.9)
Global health status (Q8–Q9 from QLQ-C30)	384	–0.6 (–4.4, 3.3)
Overall health rate (Q29)	384	–0.5 (–4.5, 3.5)
Quality of life rate (Q30)	378	–0.3 (–4.5, 3.9)



Adverse events overall summary

	Afatinib (n=320)	Methotrexate (n=160)
Any AEs, n (%)	318 (99)	158 (99)
Drug-related AEs, n (%)	303 (95)	137 (86)
Grade ≥3	127 (40)	57 (36)
Leading to dose reduction	103 (32)	67 (42)
Leading to discontinuation	23 (7)	26 (16)
Serious AEs	44 (14)	18 (11)
Leading to death	2 (0.6)*	5 (3)†

- Treatment duration (median)
  - Afatinib: 83 days (range, 2–546); Methotrexate: 43 days (range, 1–442)

*One septic shock and one aspiration pneumonia
†Two septicemia, one aspiration pneumonia, one general health deterioration, and one renal failure and pancytopenia

Drug-related adverse events (>10%)*

	Afatinib (n=320)			Methotrexate (n=160)		
AE, %	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
More frequent with afatinib						
Rash/acne†	74	10	0	8	0	0
Diarrhoea	72	9	1	12	2	0
Paronychia†	14	1	0	0	0	0
Decreased appetite	13	3	0	13	1	0
Vomiting	13	1	<1	9	0	0
Dry skin	11	0	0	0	0	0
More frequent with methotrexate						
Stomatitis†	39	6	<1	43	8	0
Fatigue†	25	6	0	32	3	0
Nausea	20	2	0	23	1	0
Neutropenia	<1	<1	0	19	6	1
Anaemia	7	1	0	19	5	1

*There were no Grade 5 drug-related AEs observed in >10% of patients
†Grouped term

Conclusions

- Afatinib significantly improved PFS versus methotrexate
- Tumour shrinkage was greater, response rate higher and DCR significantly higher compared to methotrexate
- Patient-reported outcomes favoured afatinib over methotrexate
- OS was not significantly different between afatinib and methotrexate
- Overall AE profiles were as expected
  - Fewer treatment-related dose reductions, discontinuations and fatal events with afatinib compared to methotrexate
- Afatinib is the first oral tyrosine kinase inhibitor to demonstrate efficacy and improved patient-reported outcomes in a Phase III trial in this setting
- Investigations with adjuvant afatinib in LA HNSCC following CRT are ongoing

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