Subgroup analysis of LUX-Lung 1: A randomized phase III trial of afatinib (BIBW 2992) + best supportive care (BSC) versus placebo + BSC in patients failing 1–2 lines of chemotherapy and erlotinib or gefitinib

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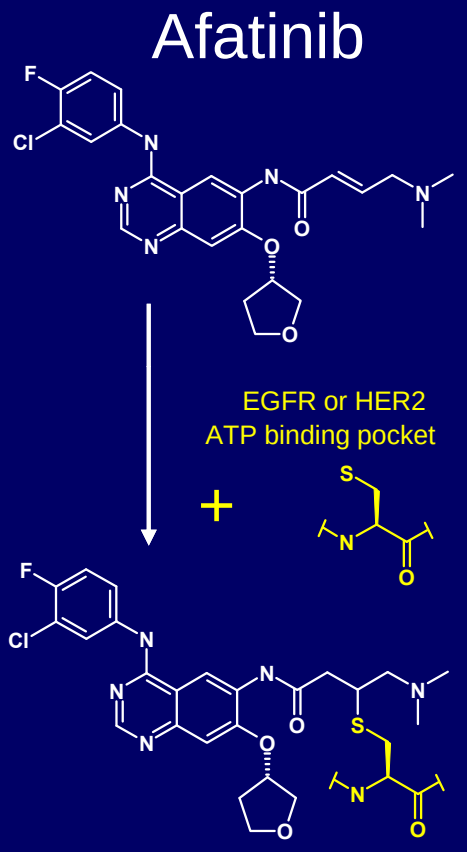
Background and rationale

Afatinib:

- **Orally bioavailable, irreversible TKI of EGFR and HER2**
- **Spectrum of preclinical activity includes EGFR T790M, main resistance mechanism in patients with EGFR mutations who initially benefit from first generation TKIs (erlotinib or gefitinib)**

Unmet need: No approved therapy for locally advanced or metastatic NSCLC in patients who have failed chemotherapy and progressed after treatment with an EGFR TKI



LUX-Lung 1: Trial design

Patients with:

- Adenocarcinoma of the lung
- Stage IIIB/IV
- Progressed after one or two lines of chemotherapy (incl. one platinum-based regimen) and ≥ 12 weeks of treatment with erlotinib or gefitinib
- ECOG 0–2

N=585

Randomization 2:1 (Double Blind)

Oral afatinib 50 mg once daily plus BSC	Oral placebo once daily plus BSC

Primary endpoint: Overall survival (OS)

Secondary: PFS, RECIST response, QoL (LC13 & C30), safety

- Radiographic assessments at 4, 8, 12 wks and every 8 wks thereafter
- Exploratory biomarkers:
  - Archival tissue testing for EGFR mutations (optional; central lab)
  - Serum EGFR mutational analysis (all patients)

Statistical design and study conduct

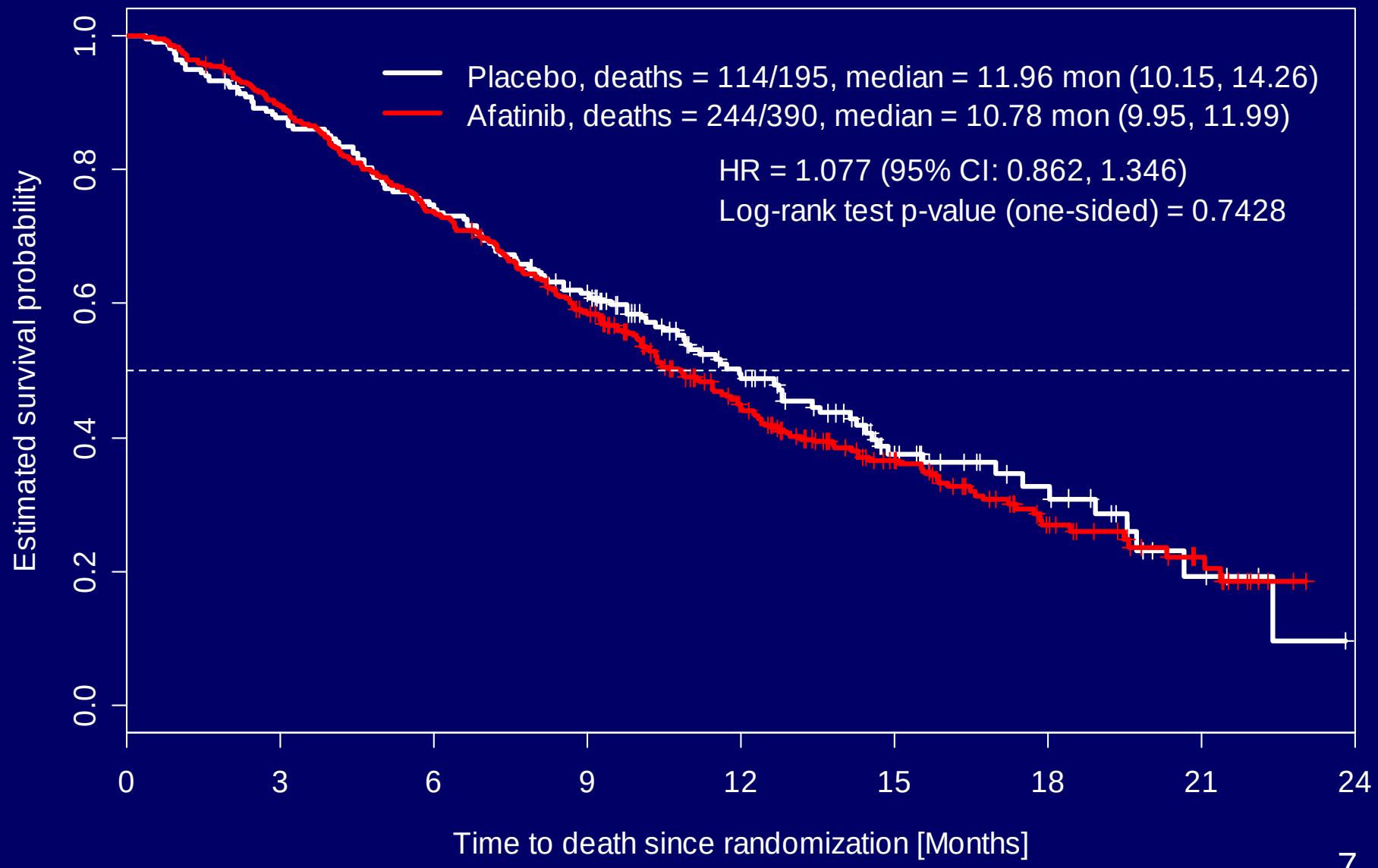
- **Statistical design and analysis**
  - **Primary analysis for overall survival**
    - **359 events needed for a 90% power to detect a HR of at least 0.70 (e.g., an increase in median survival from 4.7 to 6.7 months) at one-sided 0.025 significance level**
  - **Pre-specified subgroups included those based on the duration* of prior TKI and response to prior TKI**
- **Study conduct**
  - **585 patients randomized from May 2008 to Sept 2009**
  - **84 sites in 15 countries located in North America, Europe and Asia**
  - **358 events (61%) reached in July 2010 for primary analysis**

* Cutoff of 24 wks; other subgroups in this presentation were post-hoc

Patient characteristics

	Afatinib (n=390)	Placebo (n=195)
Median age, (range)	58 (30–85) yrs	59 (32–82) yrs
Female (%)	59	60
ECOG PS 0/1/2 (%)	24/69/8	27/65/8
Caucasian/East Asian/other (%)	31/58/11	37/56/7
Never smoker/Light ex-smoker/Other (%)	63/7/30	62/7/31
Stage IIIB/IV (%)	4/96	3/97
Prior chemo: 1 line/> 1 line (%)	59/41	61/39
Prior EGFR TKI: E/G/E+G (%)	55/39/6	55/41/4
Median duration of prior E/G	10.2 mos	9.7 mos
≥ 48 wks duration on prior E/G (%)	45	47
< 8 wks between prior E/G and randomization (%)	57	63
CR/PR on prior E/G (%)	46	44

Overall survival

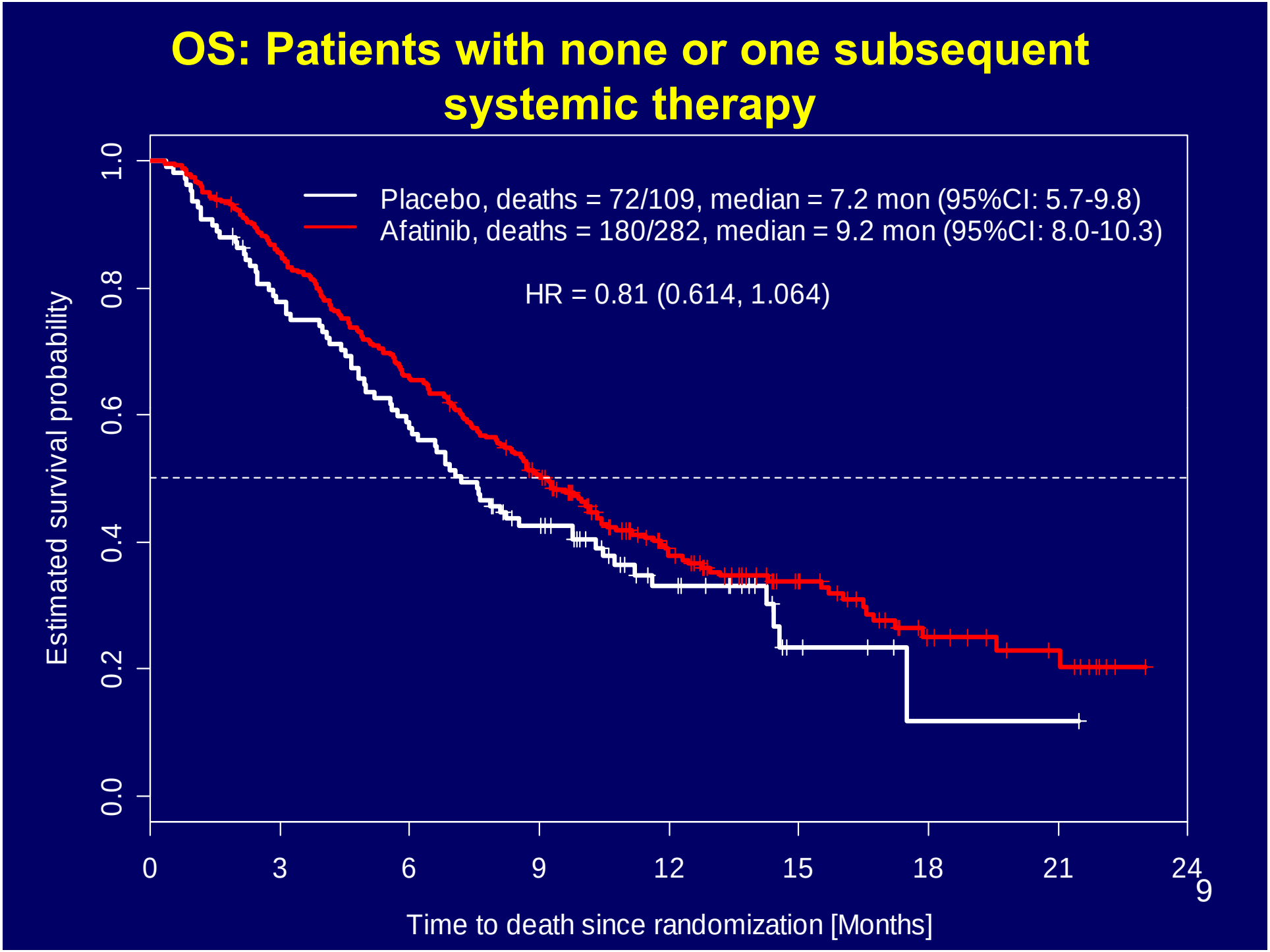


Post-discontinuation treatments

Anticancer therapy	Afatinib (%)	Placebo (%)
Any	68	79
Chemotherapy	61	70
Pemetrexed	36	47
Docetaxel	21	26
Vinorelbine	15	19
Other	26	26
EGFR TKI	12	24
Anti-angiogenesis	4	6
2 or more regimens	28	44*

* P < 0.05 compared to the afatinib arm

OS: Patients with none or one subsequent systemic therapy



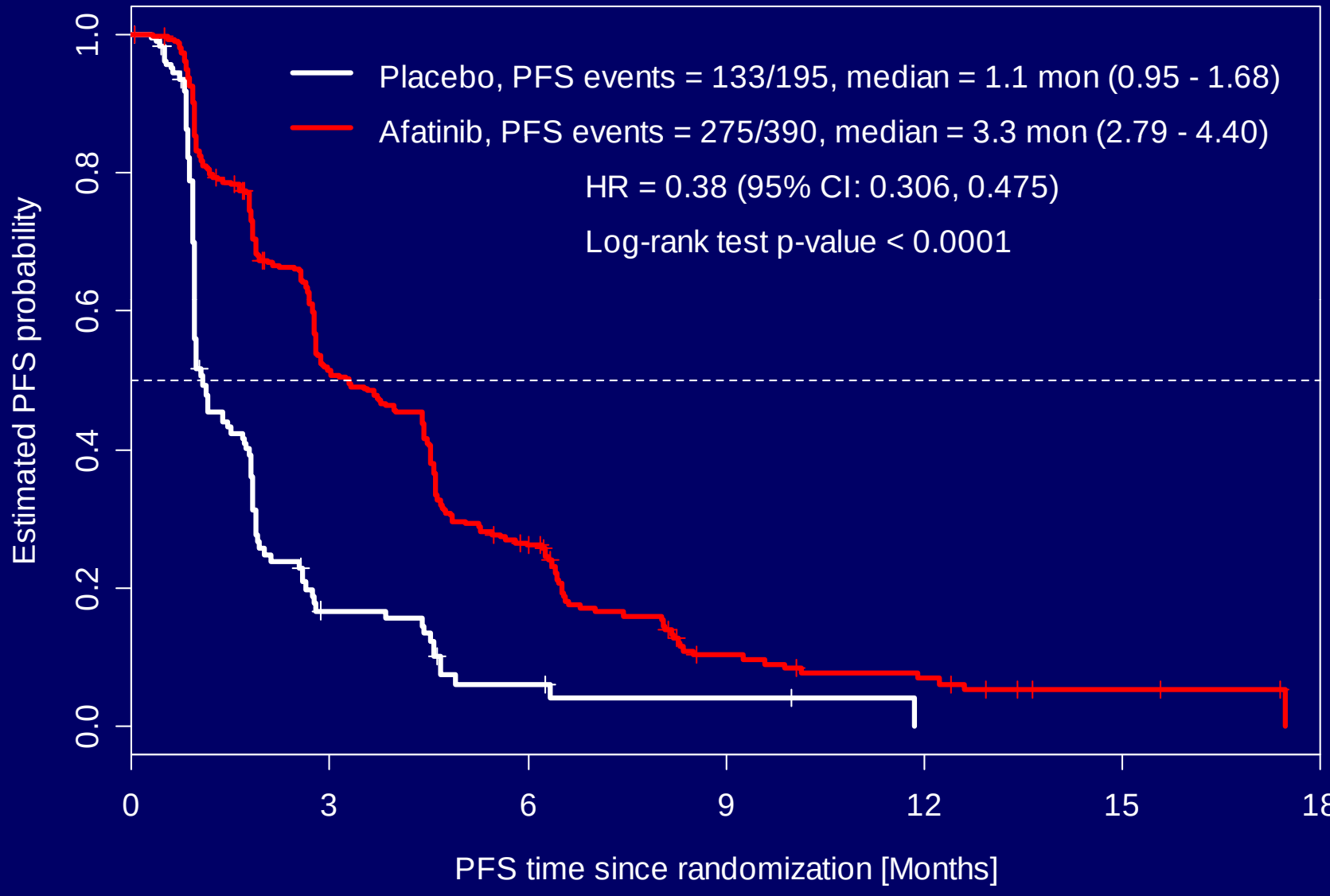
Disease control rate and objective responses

	Independent Review	
	Afatinib (%)	Placebo (%)
PR, (regardless of confirmation)	13*	0.5
PR, (confirmed)	7*	0.5
SD ≥ 8 wks	51	18
DCR (PR+SD) ≥ 8 wks	58**	19

Median duration of confirmed response: 24 weeks

* P < 0.01 compared to placebo
** P < 0.0001 compard to placebo

PFS by independent review



EGFR TKI sensitivity and expected EGFR mutation frequency in subgroups

- Definition of EGFR TKI sensitivity on clinical criteria from the literature
  - CR/PR to Erlotinib (E) or Gefitinib (G)
    - > 90% EGFR mutation positive*
  - Long duration of PFS (e.g., ≥ 6 months) with E/G
    - 67% EGFR mutation positive**

      (compared with 56% positivity for ≥ 3 months PFS)

* Sholl et al., 2009 Am J Clin Pathol 133:922-34

** Jackman et al., 2010 J Clin Oncol 28:357-60

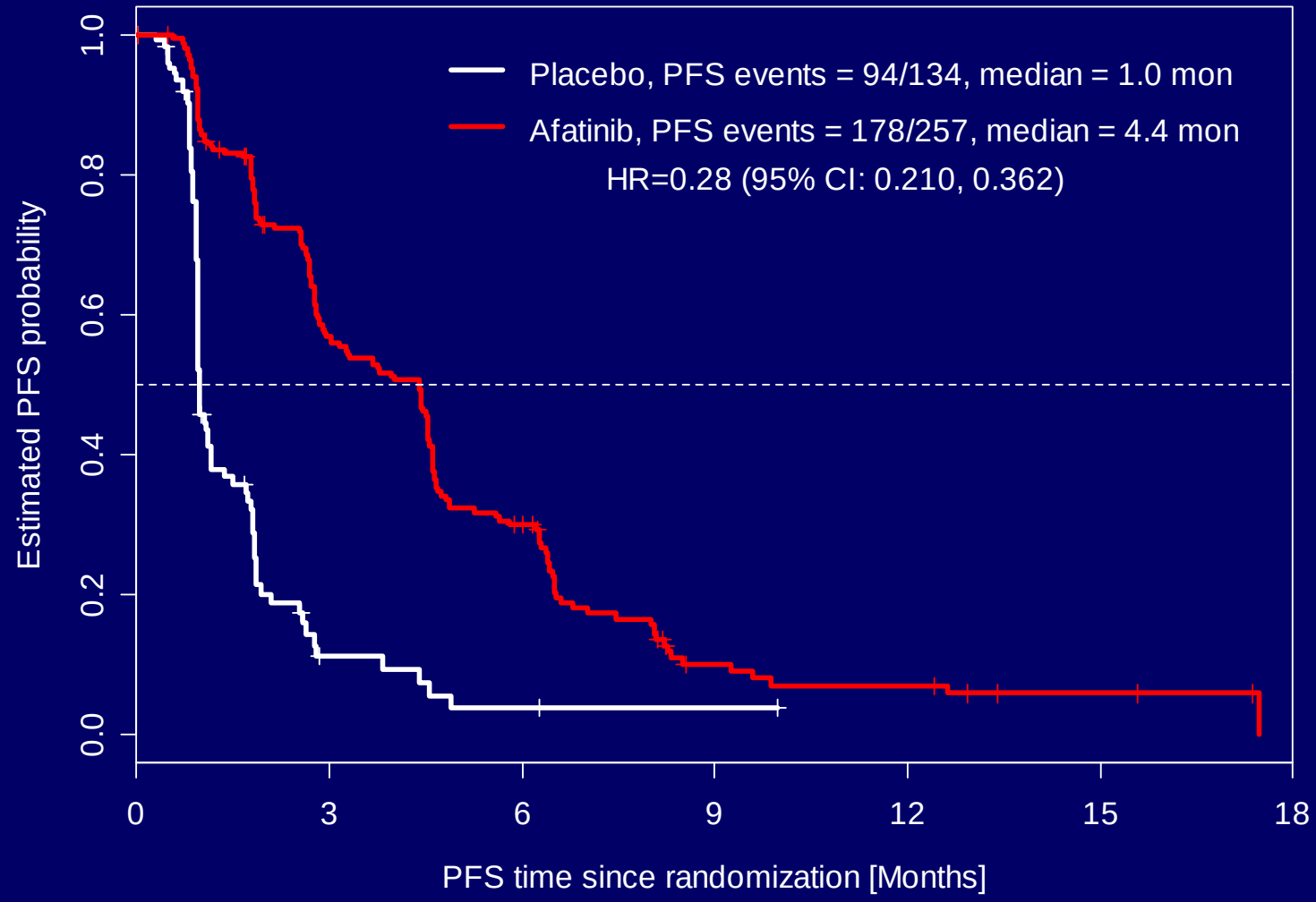
PFS and OS for subgroups with varying degrees of expected clinical enrichment for EGFR mutations

Categories	N	PFS : HR* (by independent review)	OS: HR*
Prior EGFR TKI duration			
< 24 weeks	113	0.58 (0.341, 0.990)	1.24 (0.755, 2.047)
≥ 24 weeks	472	0.35 (0.276, 0.445)	1.04 (0.807, 1.327)
≥ 48 weeks	266	0.31 (0.224, 0.441)	1.00 (0.715, 1.404)
Prior EGFR TKI : CR/PR	263	0.23 (0.167, 0.327)	0.90 (0.646, 1.249)
Prior EGFR TKI: CR/PR and/or duration ≥ 48 wks	391	0.28 (0.210, 0.363)	0.90 (0.686, 1.176)

* HR values less than 1 favor afatinib

PFS* for a subgroup with a high likelihood of EGFR mutations

CR/PR on prior E/G and/or ≥48 wks on tx with prior E/G (67% of all pts)

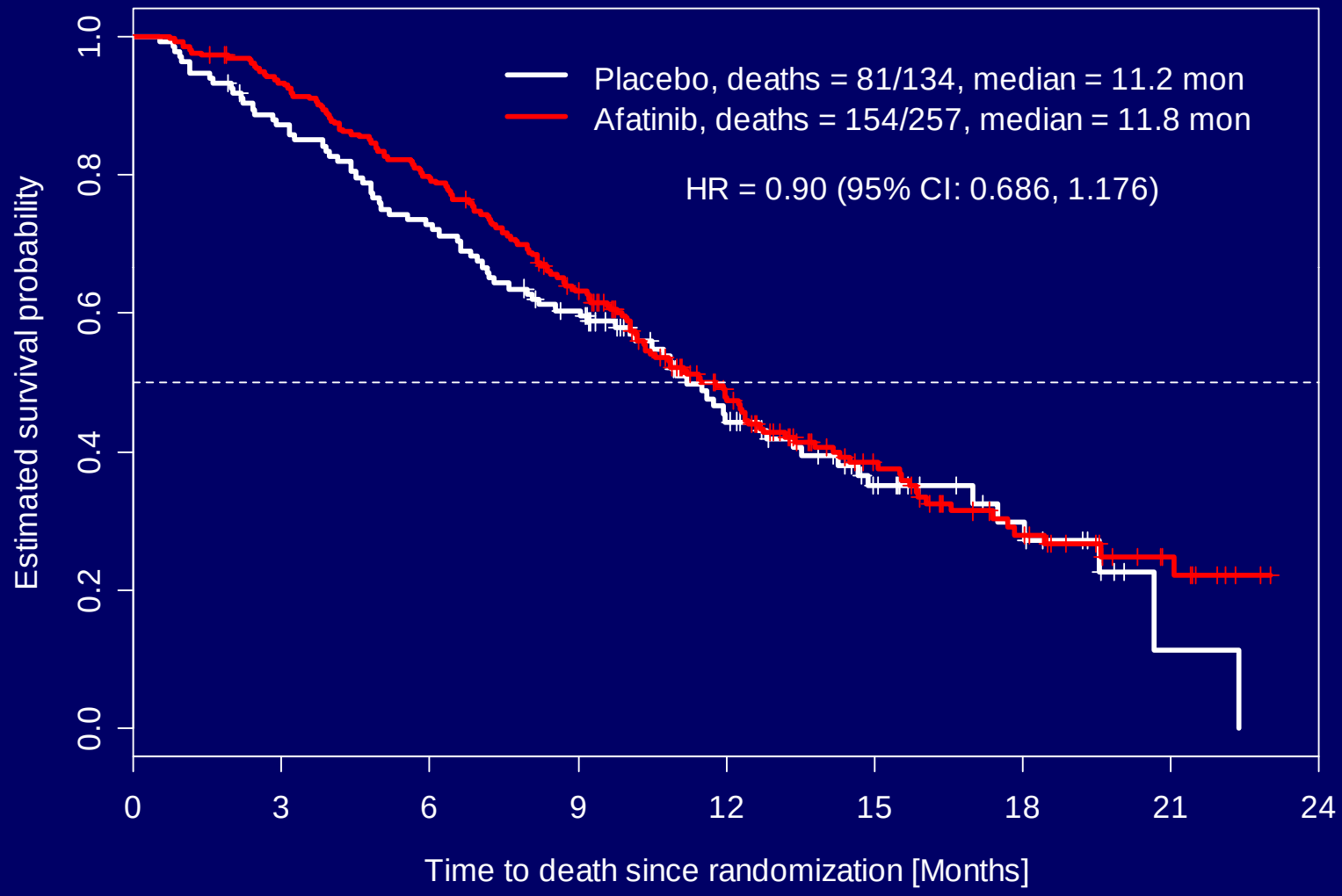


Also, Jackman criteria: Median PFS 4.5 months vs. 1.0 months

* PFS by Independent Review

OS for a subgroup with a high likelihood of EGFR mutations:

CR/PR on prior E/G and/or ≥ 48 wks on tx with prior E/G (67% of all patients)



Conclusions and future directions

- LUX-Lung 1 did not meet its primary endpoint:
  - Unprecedented long OS
  - Results likely confounded by extensive subsequent tx
- Benefit with afatinib was greater for subgroups with the highest likelihood of EGFR mutation:
  - Increase of median PFS from 1.0 to 4.4 months
  - Trend in OS in favor of afatinib (HR= 0.90; 95% CI: 0.69 to 1.18)
- EGFR mutation analysis is ongoing
- Two ongoing first line phase 3 trials of afatinib versus chemotherapy in NSCLC patients with EGFR mutations

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