LUX-Lung 8

GIOTRIF® (afatinib) tablets

Background

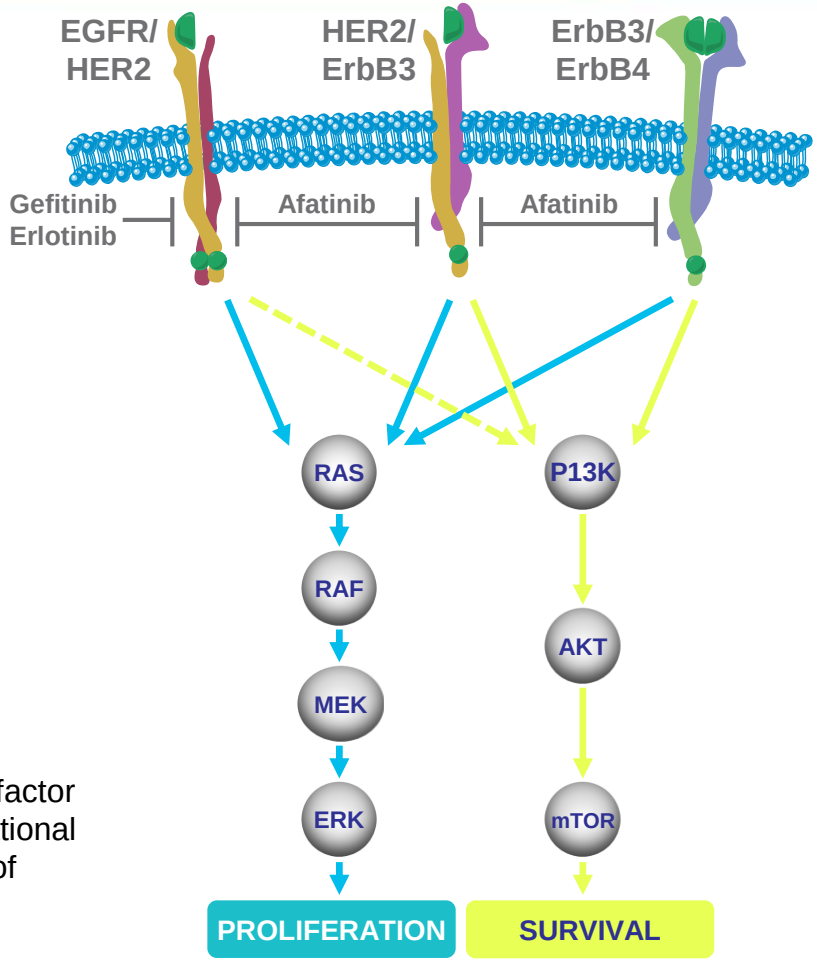
- **Squamous** histology represents approximately **30% of NSCLC**[1,2]
- **Limited** progress and **therapeutic options** for patients **in second-line** setting
  - **Targetable oncogenic** alterations are **limited** and have **not yet** translated to a **therapeutic paradigm**
  - Patients often have extensive comorbidities
  - **Erlotinib** – last drug approved (in 2005)[3]
    - Based on efficacy versus placebo in second-/third-line setting[4]
    - Survival benefit confirmed in subset analysis of male, ever-smokers with squamous cell carcinoma[5]

NSCLC, non small cell lung cancer

1. Heighway J & Betticher DC. Atlas Genet Cytogenet Oncol Haematol. 2004;8:133–6;
2. Bryant A., Cerfolio RJ. Chest 2007;132:185–92
3. Tarceva EPAR assessment EMA 2007. http://www.ema.europa.eu (Accessed 05 Sept 2014);
4. Shepherd FA, et al. New Engl J Med 2005;353:123–32
5. Clark GM, et al. Clin Lung Cancer 2006;7:389–94
6. Goss et al. ESMO 2014. Abstract 12220.

Afatinib: Irreversible ErbB Family Inhibition

- Afatinib is an irreversible ErbB-family blocker[1,2]
  - 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,[3] EU[4] and Japan[5] for the treatment of patients with NSCLC harbouring distinct types of EGFR-activating mutations



EGFR, epidermal growth factor receptor; 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

1. Li D, et al. Oncogene 2008;27:4702–11; 2. Solca F, et al. J Pharmacol Exp Ther 2012;343:342–50;
3. Gilotrif prescribing information 2013. http://www.accessdata.fda.gov (Accessed: 05 Sept 2014);
4. Giotrif EPAR assessment EMA 2013. http://www.ema.europa.eu (Accessed 05 Sept 2014);
5. PMDA Japan new drug approvals 2013. http://www.pmda.go.jp (Accessed 05 September 2014)
6. Goss et al. ESMO 2014. Abstract 12220.

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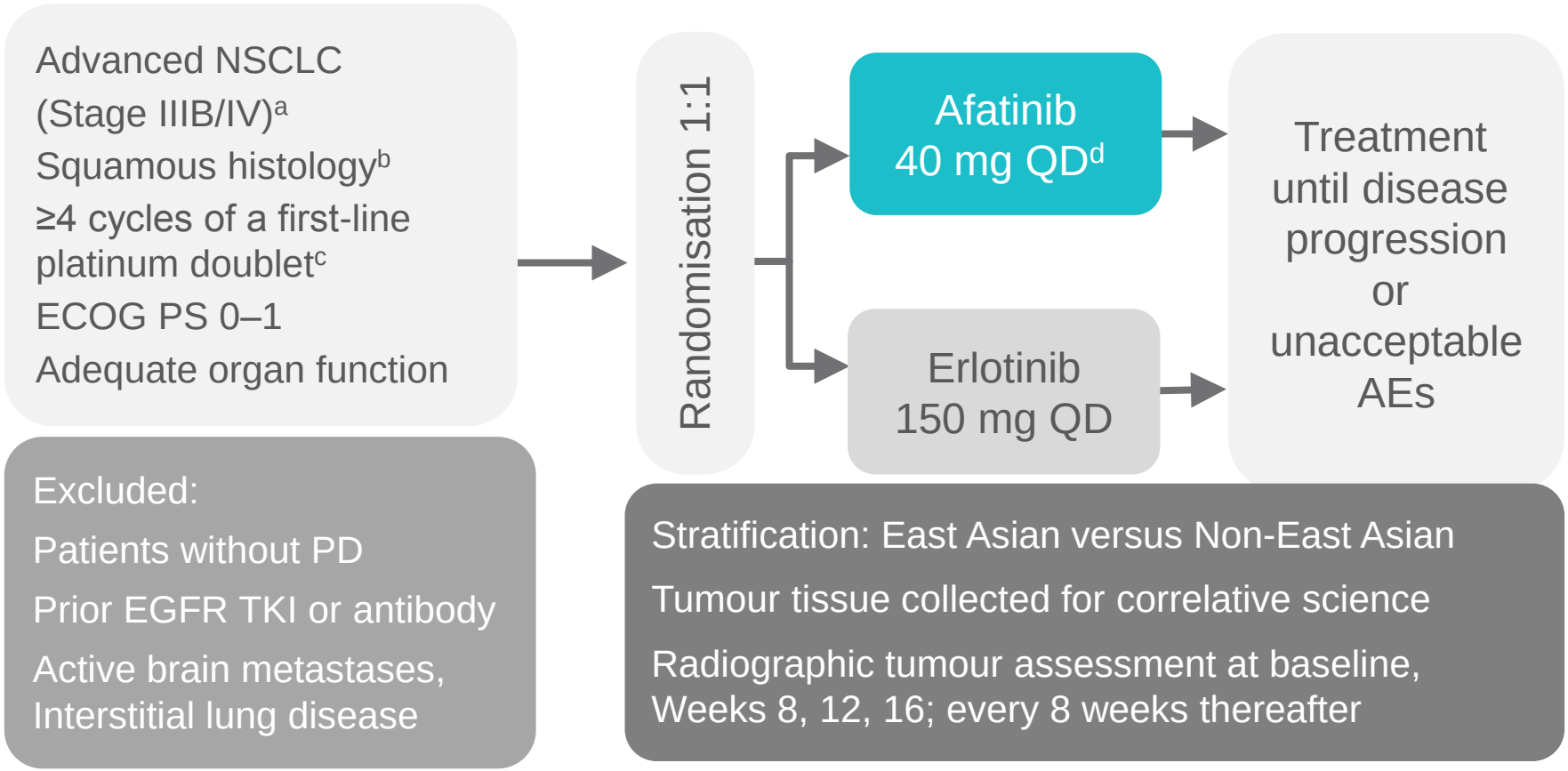
LUX-Lung 8: Study Design



[a]American Joint Committee on Cancer staging manual 7th edition

[b]As determined by the Investigator, tumours with mixed histology allowed

[c]Patients progressing within 6 months of receiving adjuvant/neoadjuvant chemo/chemoradiotherapy were allowed (as long as ≥4 cycles criterion was met)

[d]Dose escalation to 50 mg at Cycle 2 for patients meeting adverse event criteria

Goss et al. ESMO 2014. Abstract 12220.

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Endpoints

- Primary endpoint – **Progression-free survival** by central independent radiology review (RECIST 1.1)
- Key secondary endpoint – **Overall survival**
- Secondary endpoints
  - Objective response rate
  - Disease control rate
  - Tumour shrinkage
  - Health-related quality of life
  - Safety in both treatment groups

RECIST, Response Evaluated Criteria in Solid Tumors

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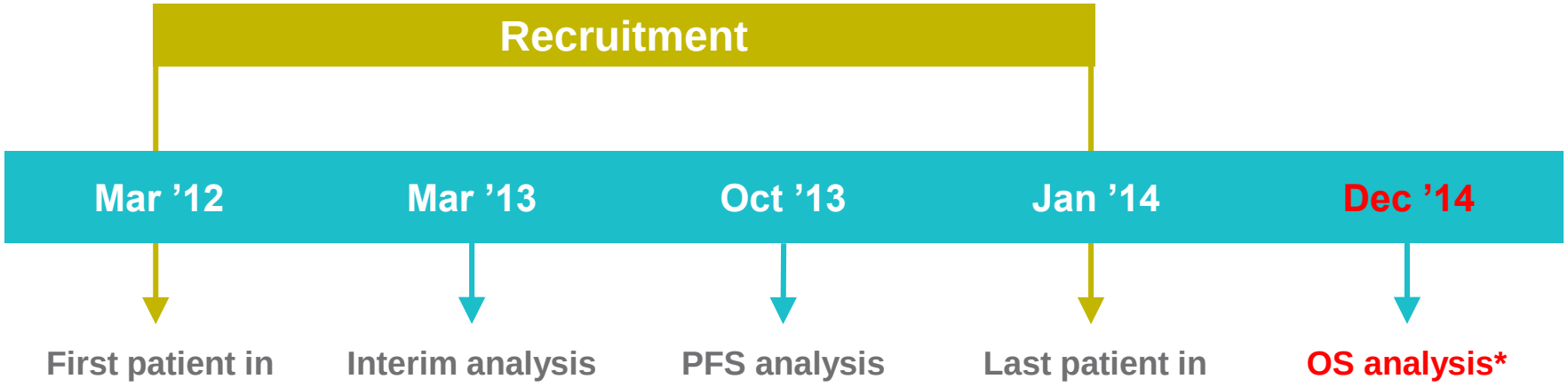
Timelines and Interim Futility Analysis



- An interim futility analysis was performed by an independent DMC and the trial was allowed to accrue to the planned 800 patients
- The PFS primary analysis was conducted when trial recruitment was ongoing

DMC, data monitoring committee; OS, overall survival; PFS, progression-free survival

*Event-dependent

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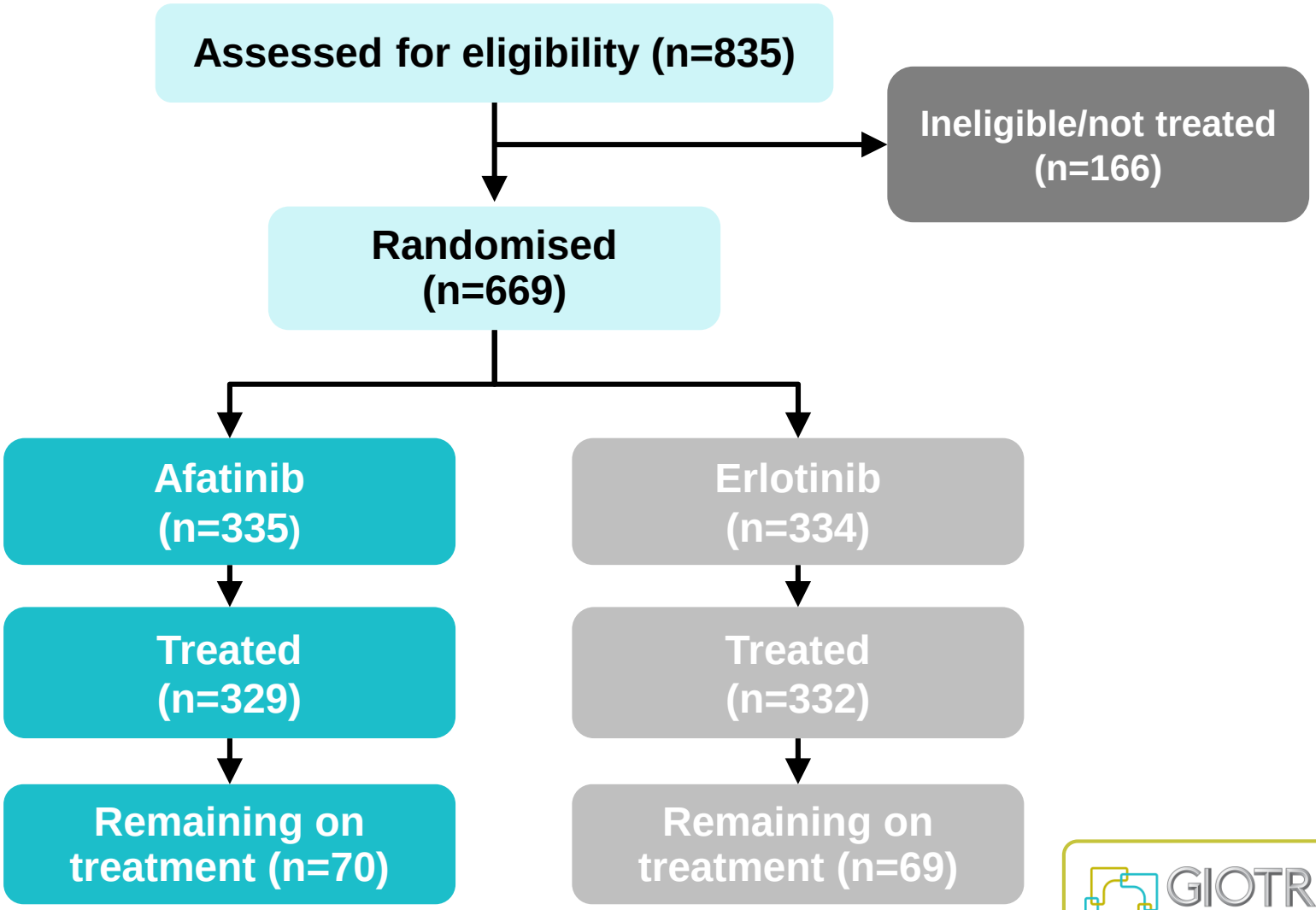
Primary PFS Analysis



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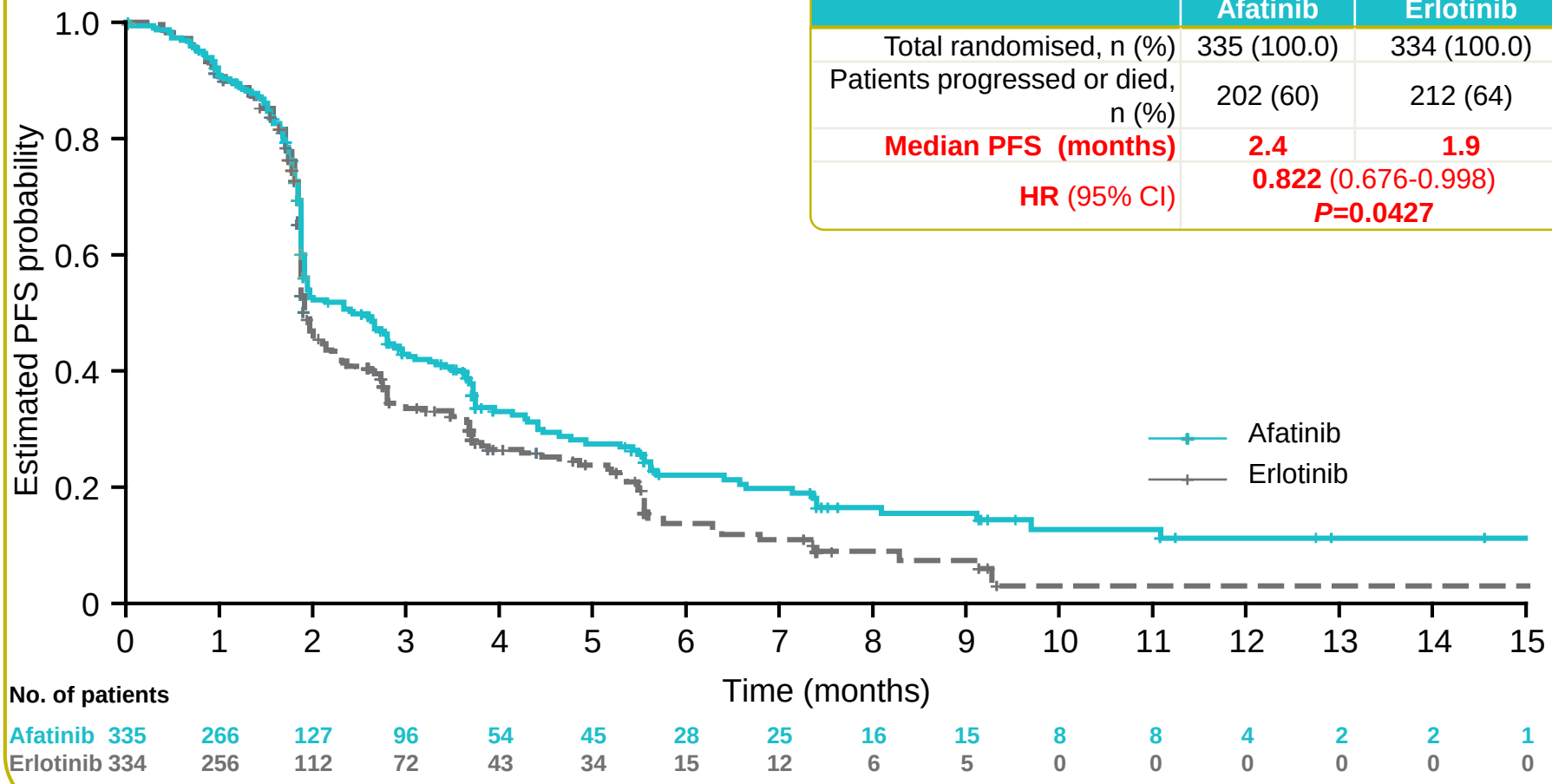
LUX-Lung 8: PFS (Independent Review)

	Afatinib	Erlotinib
Total randomised, n (%)	335 (100.0)	334 (100.0)
Patients progressed or died, n (%)	202 (60)	212 (64)
Median PFS (months)	**2.4**	**1.9**
HR (95% CI)	**0.822** (0.676-0.998) ***P*=0.0427**	



CI, confidence interval; HR, hazard ratio

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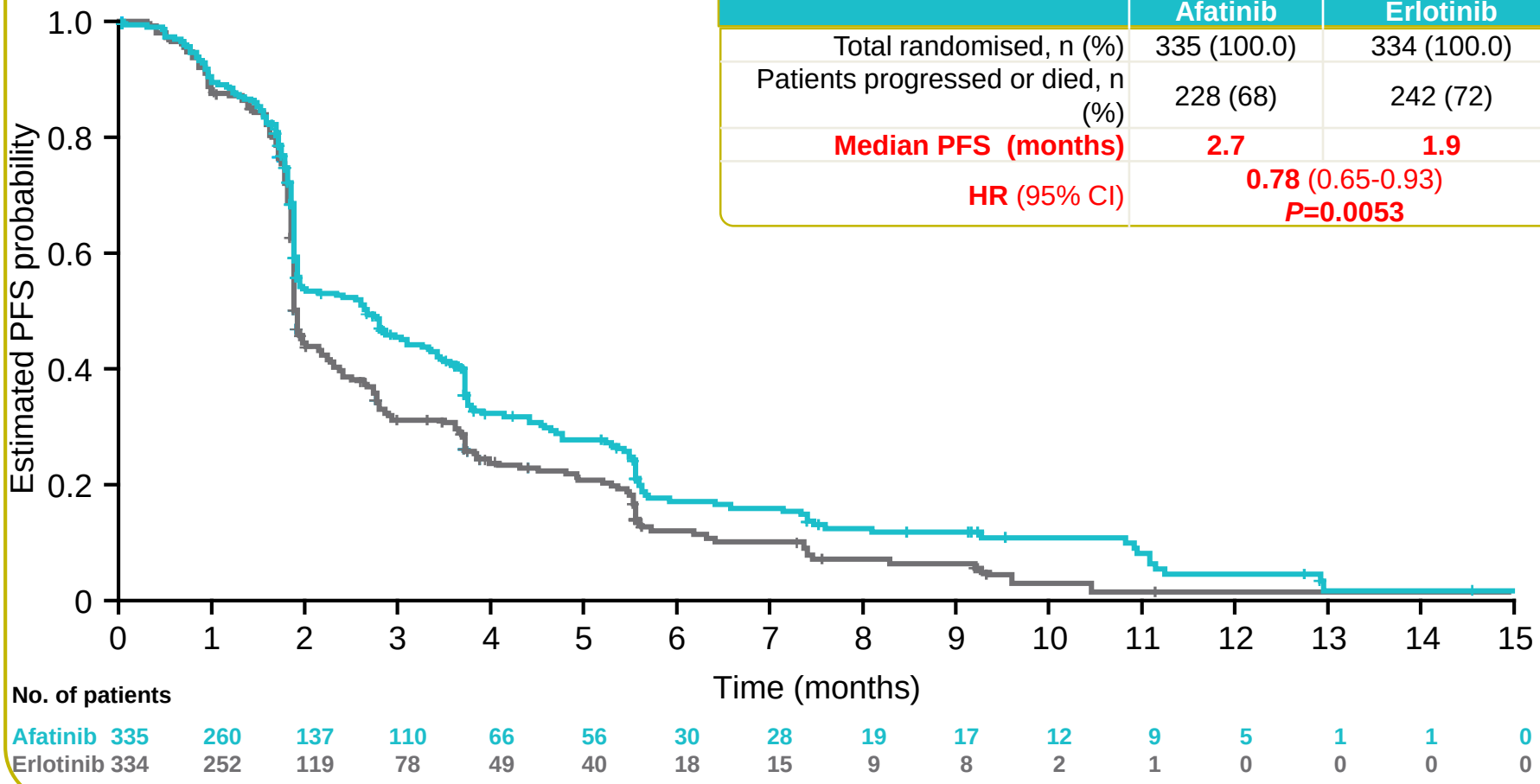
LUX-Lung 8: PFS (Investigator Review)

	Afatinib	Erlotinib
Total randomised, n (%)	335 (100.0)	334 (100.0)
Patients progressed or died, n (%)	228 (68)	242 (72)
Median PFS (months)	**2.7**	**1.9**
HR (95% CI)	**0.78** (0.65-0.93) ***P*=0.0053**	



CI, confidence interval; HR, hazard ratio

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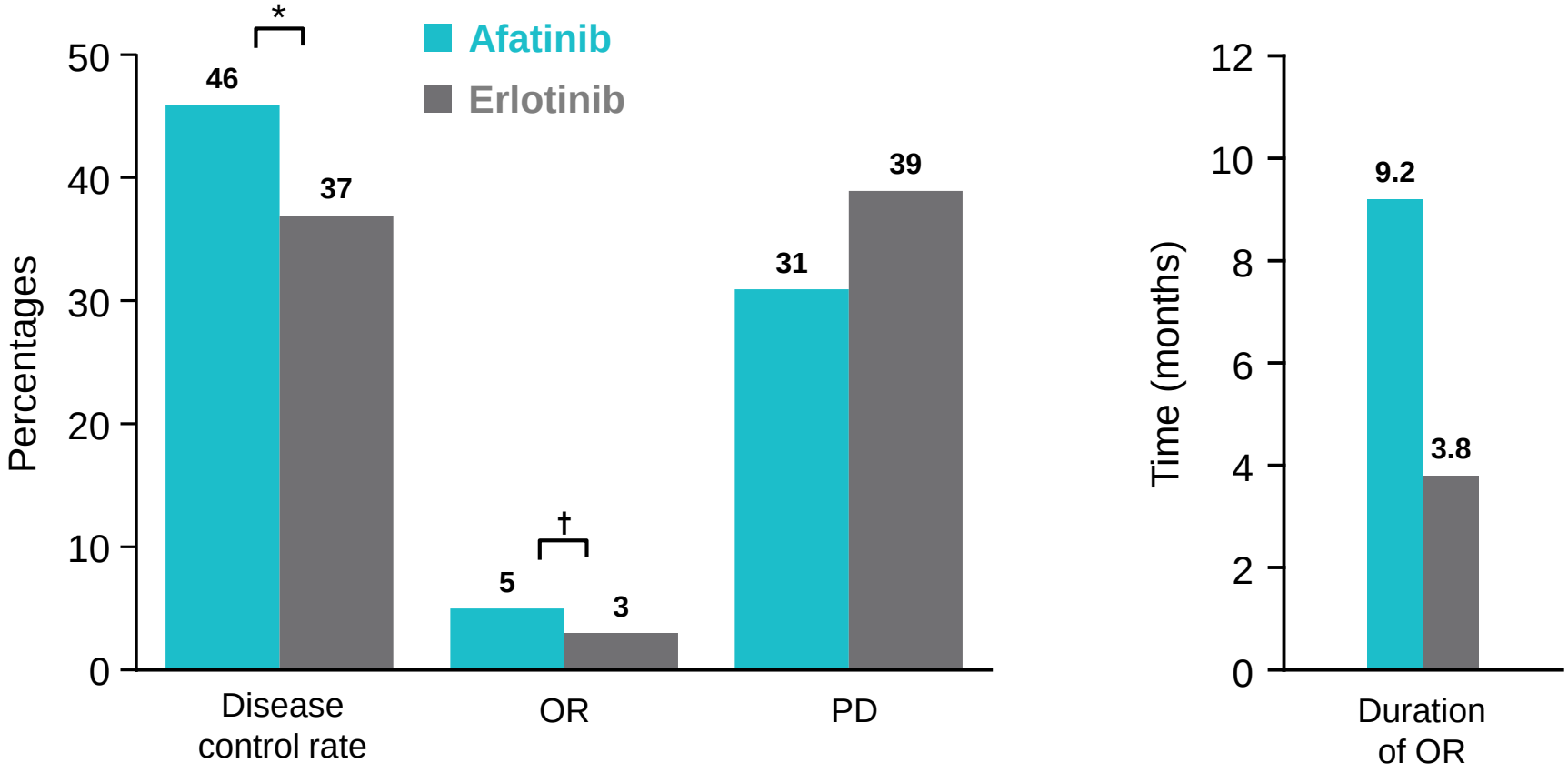
LUX-Lung 8: Objective Response (Independent Review)



*Odds ratio: 1.44 95% CI (1.06–1.96); *P*-value 0.0203

†Odds ratio: 1.63 95% CI (0.73–3.66); *P*-value 0.2332

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LUX-Lung 8: Drug-Related AEs (>5%)

Grouped categories by CTCAE grades

	Afatinib (N=329) n, (%)			Erlotinib (N=332) n, (%)		
AE category	All	Grade 3	Grade 4§	All	Grade 3	Grade 4¶
Total with related AEs	298 (91)	75 (23)	4 (1)	266 (80)	48 (15)	1 (<1)
Diarrhoea	**218 (66)**	**30 (9)**	**2 (<1)**	**103 (31)**	**7 (2)**	**1 (<1)**
Rash/acne*	208 (63)	18 (6)		221 (67)	30 (9)	
Stomatitis*	**90 (27)**	**11 (3)**		**28 (8)**		
Fatigue*	44 (13)	3 (1)		43 (13)	6 (2)	
Decreased appetite	38 (12)	3 (1)		34 (10)	2 (<1)	
Nausea	38 (12)	3 (1)		24 (7)	3 (1)	
Paronychia*	**35 (11)**	**1 (<1)**		**14 (4)**	**1 (<1)**	
Pruritus	29 (9)	1 (<1)		36 (11)		
Dry skin	27 (8)†	2 (<1)		34 (10)		
Vomiting	25 (8) ‡	2 (<1)		10 (3)	2 (<1)	

*Grouped terms; †8.2; ‡7.6; §Six patients (1.8%) in the afatinib treatment group had drug-related fatal AEs: interstitial lung disease (2 patients) and pneumonia, respiratory failure, acute renal failure, and general physical health deterioration (1 patient each); ¶Two patients (0.6%) in the erlotinib treatment group had drug-related fatal AEs: intersitial lung disease and peritonitis (1 patient each)

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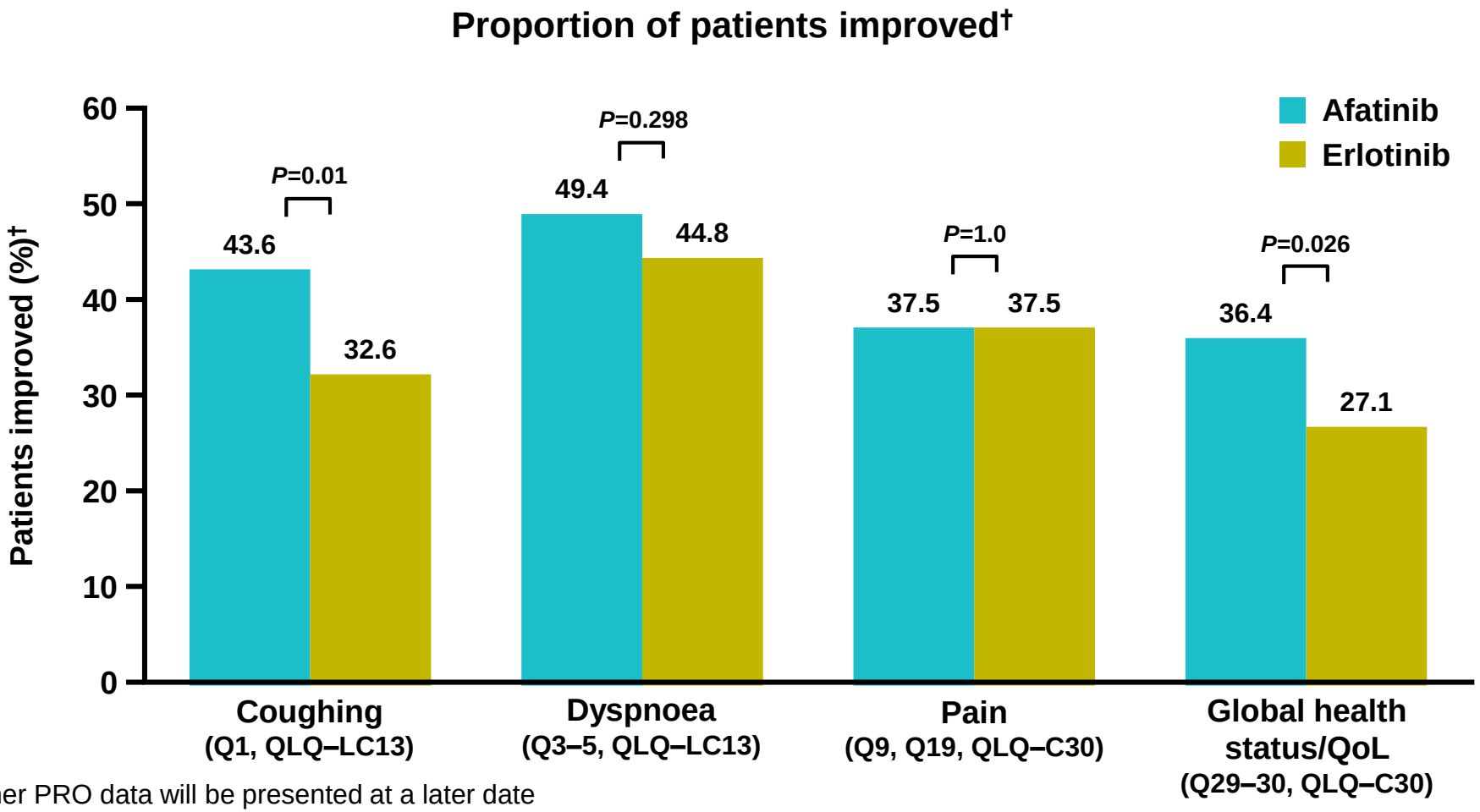
LUX-Lung 8: Patient-Reported Outcomes*



*Further PRO data will be presented at a later date

†Based on EORTC QLQ-C30 and QLQ-LC13

1. Aaronson NK, et al. J Natl Cancer Inst 1996;5:365–76.
2. Bergman B, et al. Eur J Cancer 1994;30A:635–42.
3. Goss et al. ESMO 2014. Abstract 12220.

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LUX-Lung 8: Conclusions

- **Afatinib significantly improved PFS when compared to erlotinib**
  - independent and investigator reviews were consistent
- **Tumour shrinkage was greater, response rate higher, and disease control rate significantly higher in the afatinib arm compared to the erlotinib arm**
- Overall **AE profile** was consistent with mechanistic profile and was **manageable**
  - Rate of SAEs and ≥Grade3 AEs similar for both drugs
- Patient-reported outcomes favoured afatinib versus erlotinib
- **OS data are awaited**

Goss et al. ESMO 2014. Abstract 12220.

The End

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