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Overall survival from the AURA3 Phase III study: osimertinib vs platinum-pemetrexed in patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-TKI

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Introduction

- Osimertinib is a third-generation, irreversible, EGFR-TKI that potently and selectively inhibits both EGFR-TKI sensitizing and EGFR T790M resistance mutations and has demonstrated efficacy in NSCLC CNS metastases[1–5]
- Pan-Asian adapted ESMO Clinical Practice Guidelines for metastatic NSCLC, list osimertinib as standard therapy for T790M NSCLC and also as a first-line treatment option for patients with sensitising EGFR mutations[6]
    - Recent data from FLAURA (NCT02296125) Phase III trial in patients with EGFRm advanced NSCLC showed a statistically significant improvement in OS with first-line osimertinib vs comparator EGFR-TKIs (HR 0.799 [95% CI 0.641, 0.997]; p=0.0462)[7]
- The AURA3 (NCT02151981) Phase III trial compared osimertinib with platinum-based doublet chemotherapy (platinum-pemetrexed) in patients with EGFR T790M NSCLC and disease progression on a prior EGFR-TKI therapy[2]
- The results from the primary analysis (data cut-off 15 Apr 2016) demonstrated that osimertinib PFS was statistically significant and superior to platinum-based doublet chemotherapy (platinum-pemetrexed)[2], and improved patient reported outcomes[8]
- At the time of reporting the primary analysis, OS data were not mature (15% maturity across all randomised patients)[2]
- **Here we report the results from the AURA3 final OS analysis (approximately 70% maturity)**

1. Cross et al. Cancer Discov 2014;4:1–16; 2. Mok et al. N Engl J Med 2017;376:629–640; 3. Soria et al. N Engl J Med 2018;378:113–125; 4. Wu et al. J Clin Oncol 2018;36:2702–27094: 5. Reungwetwattana et al. J Clin Oncol 2018;36:3290–3297; 6. Wu et al. Ann Oncol 2019; 30:171–210; 7. Ramalingam et al. Ann Oncol 2019;30(suppl 5, abstr LBA5_PR); 8. Lee et al. J Clin Oncol 2018;36:1853–1860.
CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor

AURA3 study design

Open-label, randomised, Phase III trial (NCT02151981)

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria

- ≥18 years (≥20 years in Japan)
- Central confirmation of tumour T790M mutation-positive status
- WHO PS 0 / 1
- Documented EGFR mutation associated with EGFR-TKI sensitivity, including Ex19del / L858R (enrolment by local[#] or central[‡] EGFR testing)
- Evidence of radiological disease progression following first-line EGFR-TKI
- Stable CNS metastases were allowed

Stratification by race (Asian / non-Asian)

Randomised 2:1

Osimertinib 80 mg orally QD (n=279)

Platinum-pemetrexed IV 500 mg / m^2 of body surface area + carboplatin AUC5 / cisplatin 75 mg / m^2, Q3W, ≤6 cycles (n=140)

RECIST 1.1 assessment every 6 weeks* until objective progressive disease

Follow-up every 6 weeks for OS, increased to every 12 weeks after first OS DCO

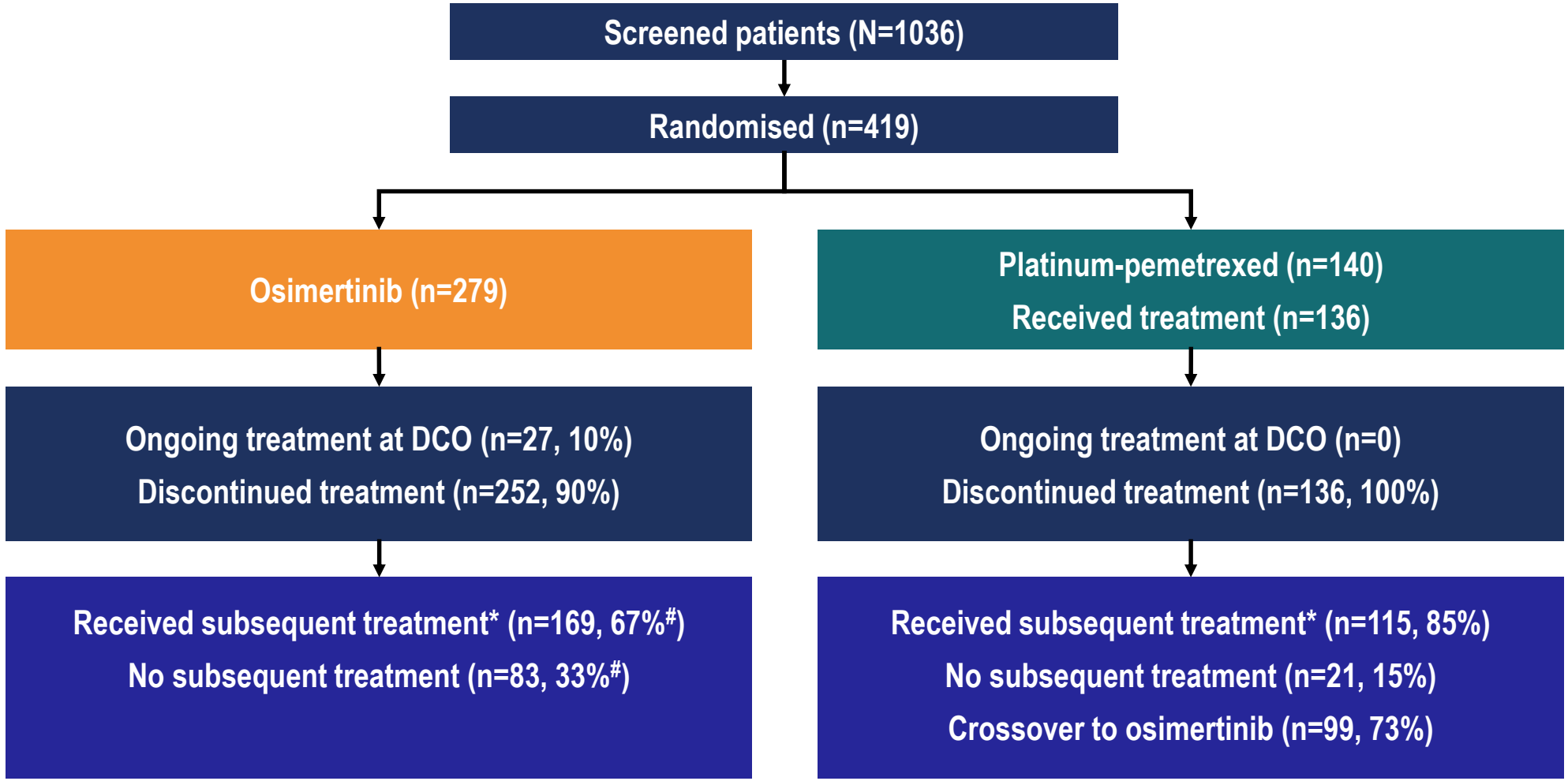
Crossover was allowed for patients in the **platinum-pemetrexed** arm, who could receive open-label osimertinib after objective disease progression (per RECIST 1.1), according to investigator assessment and confirmed by blinded independent central review

- The primary endpoint was investigator-assessed PFS
- OS and safety were secondary endpoints
- AURA3 final OS DCO: 15 March 2019 (progression events were not collected from this DCO)

Mok et al. N Engl J Med 2017;376:629–640.

*Follow-up every 12 weeks after first OS data cut-off. [#]With central laboratory assessment performed for sensitivity; [‡]cobas® EGFR Mutation Test (Roche Molecular Systems).
AUC, area under curve; DCO, data cut-off; Ex19del, exon 19 deletion; IV, intravenous; PS, performance status; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; QD, once daily; QW3. once every 3 weeks, WHO, World Health Organization

AURA3 patient disposition



Data cut-off: 15 March 2019.

*Post-treatment anti-cancer therapies at any subsequent line, including radiotherapy; #Percentage calculated as a proportion of patients who discontinued treatment (n=252).

AURA3 patient baseline characteristics

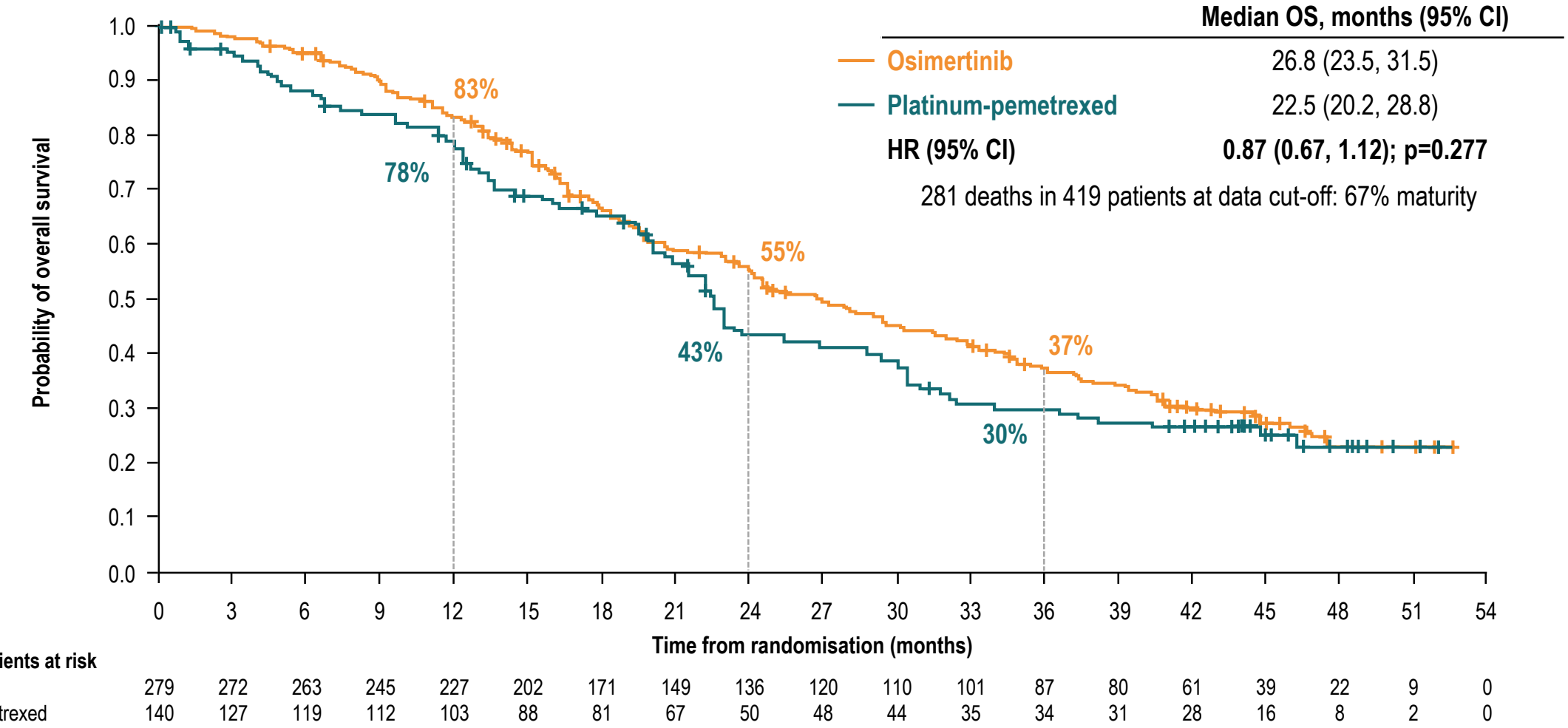
Characteristics	Osimertinib (n=279)	Platinum-pemetrexed (n=140)
Age, median (range), years	62 (25–85)	63 (20–90)
Sex: male / female, %	38 / 62	31 / 69
Race: Asian / non-Asian, %	65 / 35	66 / 34
WHO PS: 0 / 1, %	37 / 63	40 / 60
Smoking status: never / ever, %	68 / 32	67 / 33
CNS metastases*, %	33	36
Patients with M1b, %	34	38
EGFR mutations#, %		
T790M	99	99
Ex19del	68	62
L858R	30	32

Data cut-off: 15 March 2019

Mok et al. N Engl J Med 2017;376:629–640.

*CNS metastases are determined programmatically from baseline data. #EGFR mutation identified by the cobas® EGFR central test (by biopsy taken after confirmation of disease progression on the most recent treatment regimen).

AURA3 overall survival

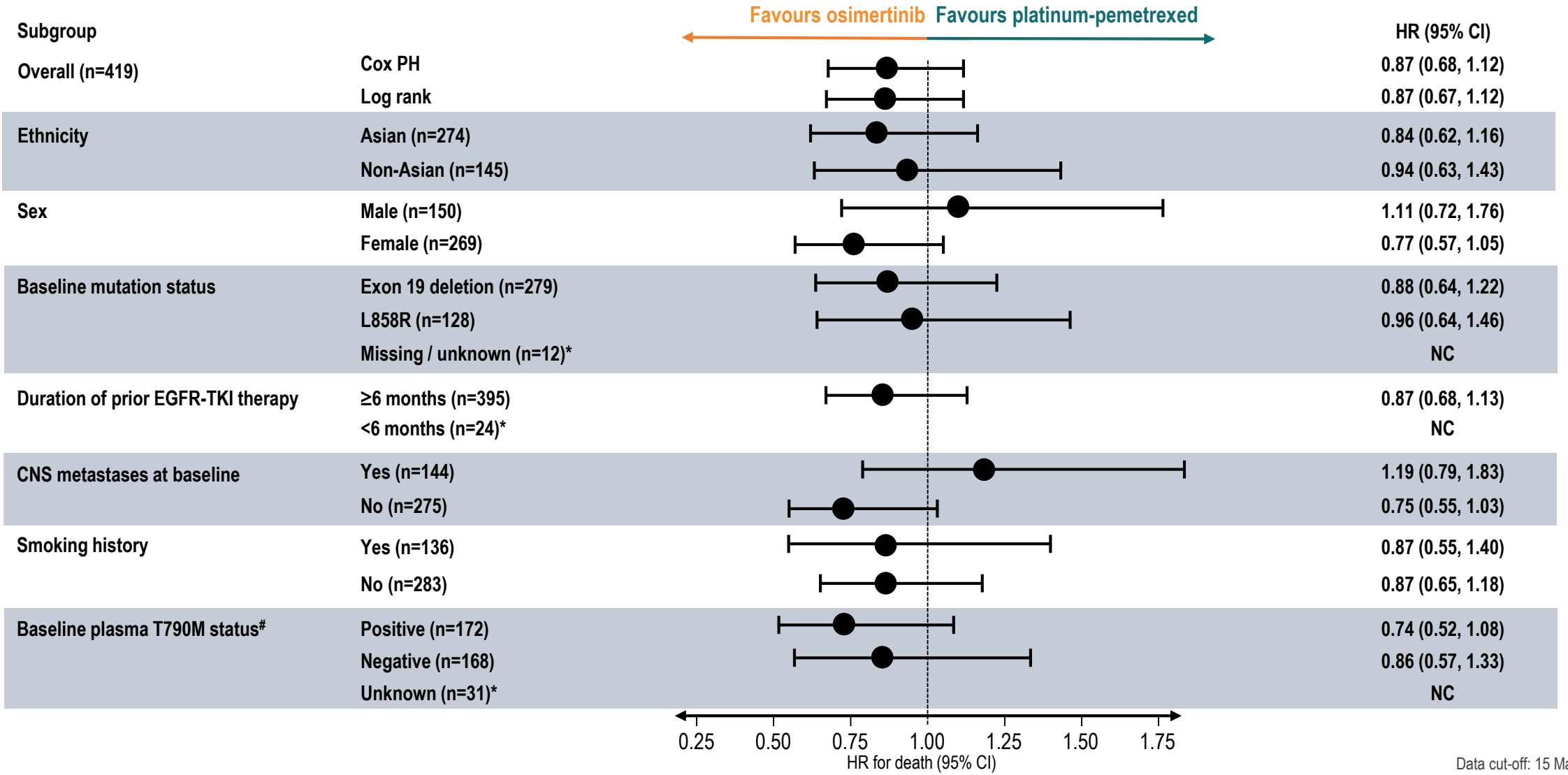


Data cut-off: 15 March 2019.

Patients not known to have died at the time of analysis are censored at the last recorded date that the patient was known to be alive. Crosses indicate censored observations.

CI, confidence interval; HR, hazard ratio.

AURA3 overall survival across subgroups



Data cut-off: 15 March 2019.

Subgroup analysis performed using a single Cox PH model containing the treatment, the subgroup covariate of interest and the treatment by subgroup. All patient analysis was performed using a log rank test stratified by ethnicity.
*The analysis was not performed for subgroups where number of events was <20. #Baseline plasma T790M mutation status subgroup analysis is performed on the full analysis set population, excluding patients enrolled in China.

AURA3 crossover: platinum-pemetrexed to osimertinib

- Of 136 patients that received platinum-pemetrexed, 99 (73%) crossed over to receive osimertinib

Characteristics	Crossover (n=99)	No crossover (n=41)
Median age, years (range)	64 (33–87)	61 (20–90)
Sex: male / female, %	32 / 68	27 / 73
Race: Asian / non-Asian, %	67 / 33	63 / 37
WHO PS: 0 / 1, %	47 / 53	22 / 78
Smoking status: never / ever, %	67 / 33	68 / 32
CNS metastases*, %	37	34
Patients with M1b, %	36	41
EGFR mutations#, %		
T790M	100	95
Exon 19 deletion	64	59
L858R	33	29

Data cut-off: 15 March 2019.

*CNS metastases are determined programmatically from baseline data. #EGFR mutation identified by the cobas® EGFR central test (by biopsy taken after confirmation of disease progression on the most recent treatment regimen).

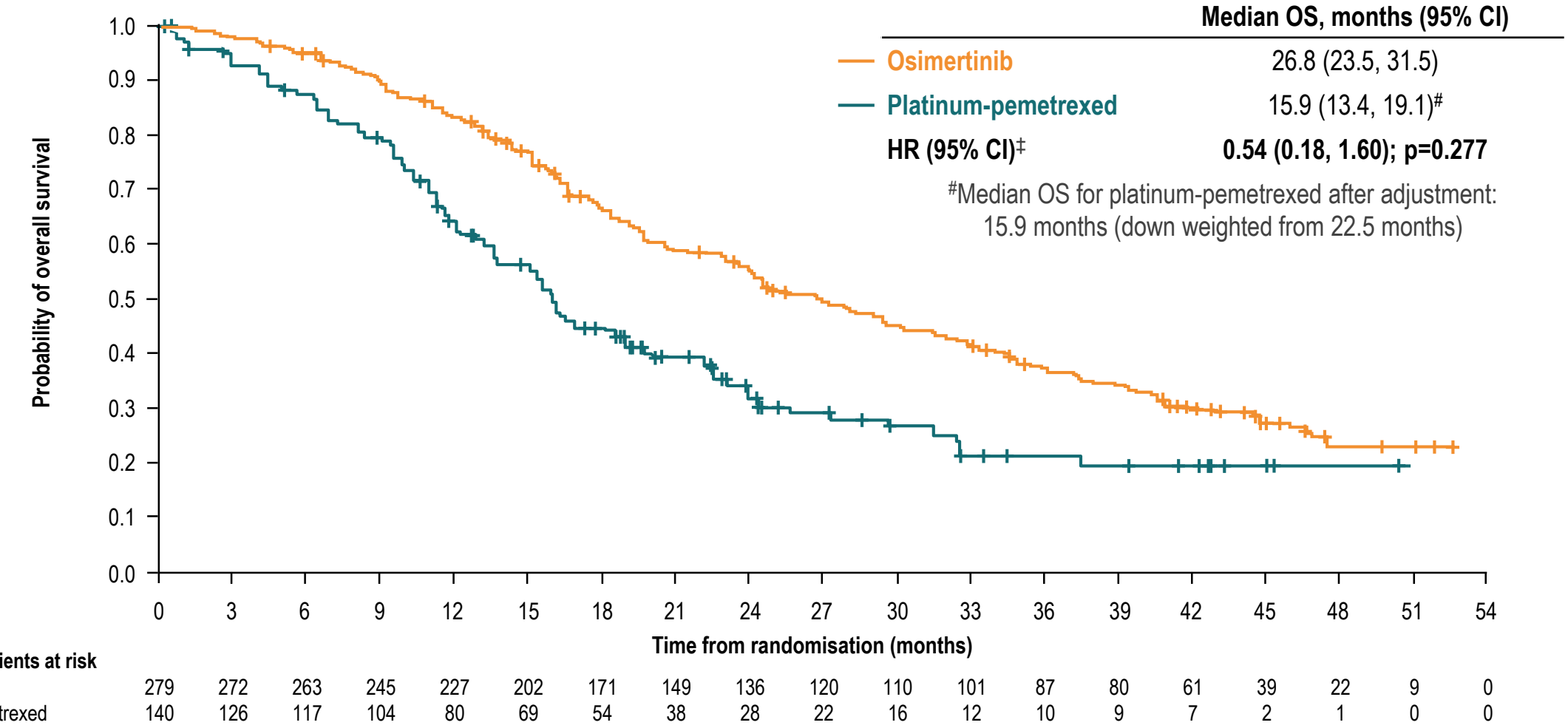
Crossover adjustment analysis

- The RPSFTM is a randomisation-based efficacy estimator with two main approaches[1]
  - **The on treatment effect,** where benefit of the crossover treatment is assumed to be restricted to the time the patient is receiving the beneficial treatment
  - **The treatment group effect**, where benefit is assumed from initiation of treatment until the end of follow-up / death
- Considering the half-life of osimertinib (~48 hours[2]), the effect of treatment is likely to wear off 2 weeks following discontinuation of treatment; therefore, for AURA3, the most clinically plausible scenario was considered to be **the on treatment effect.** This was validated through inspection of the counterfactual survival curves
- The RPSFTM was performed **to adjust for treatment switching** and to **estimate a more realistic relative OS effect of osimertinib treatment compared with platinum-pemetrexed treatment**

RPSFTM, rank preserving structural failure time model

1. White et al. Stat Med 1999;18:2617–2634; 2. Planchard et al. Cancer Chemother Pharmacol 2016;77:767–776.

AURA3 overall survival with crossover adjustment*

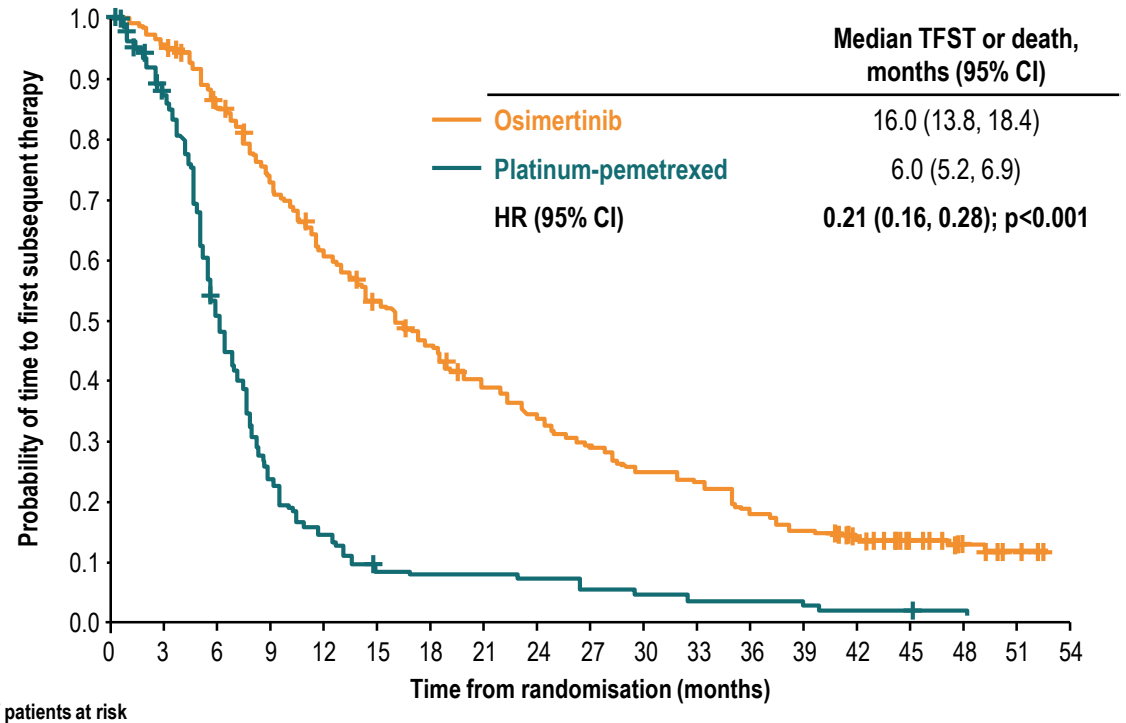


Data cut-off: 15 March 2019.

Crosses indicate censored observations. *The RPSFTM was applied using the on-treatment method without recensoring, where benefit of the crossover treatment is assumed to be restricted to the time the patient is receiving the beneficial treatment. ‡ The CI for the adjusted HR is derived from the p value of the ITT analysis, which is retained.

AURA3 first subsequent therapy

Time to first subsequent therapy*



Number of patients at risk

Osimertinib	279	264	231	192	163	139	118	99	84	73	63	58	46	39	27	17	10	4	0
Platinum-pemetrexed	140	112	65	29	19	10	9	9	8	6	5	4	4	3	2	1	1	0	0

Patients who received post-treatment therapy (≥5% of patients[#])	Osimertinib, % n=165 (59%)	Platinum-pemetrexed, % n=114 (81%)
EGFR inhibitor	15	97
Osimertinib crossover	0	86[§]
EGFR protein kinase inhibitors[‡]	11	8
Cytotoxic chemotherapy platinum compounds	65	1
Cytotoxic chemotherapy folic acid analogues	66	2
Cytotoxic chemotherapy taxanes	8	1
Antibody against VEGF	8	0

Data cut-off: 15 March 2019. *Time to subsequent therapy: time from date of randomisation to first anticancer therapy (excluding radiotherapy, with exception of one patient in each treatment counted as received radiotherapy at TFST date) start date following study treatment discontinuation, or death. Crosses indicate censored observations. [#]≥5% of patients receiving subsequent treatment in either arm; patients may have received more than one subsequent anticancer therapy. [‡]Generation of EGFR-TKI was not specified; [§]98 (86%) patients as opposed to 99 (87%) patients were reported as having crossover treatment to osimertinib at the time of first subsequent treatment. One patient had a >21-day interruption between chemotherapy cycles and was therefore classified as having discontinued chemotherapy as per protocol; however, the patient received one further cycle of chemotherapy before crossing over to osimertinib after disease progression and was classified as having received first subsequent therapy post-discontinuation of platinum-based chemotherapy. TFST, time to first subsequent.t therapy; VEGF, vascular endothelial growth factor.

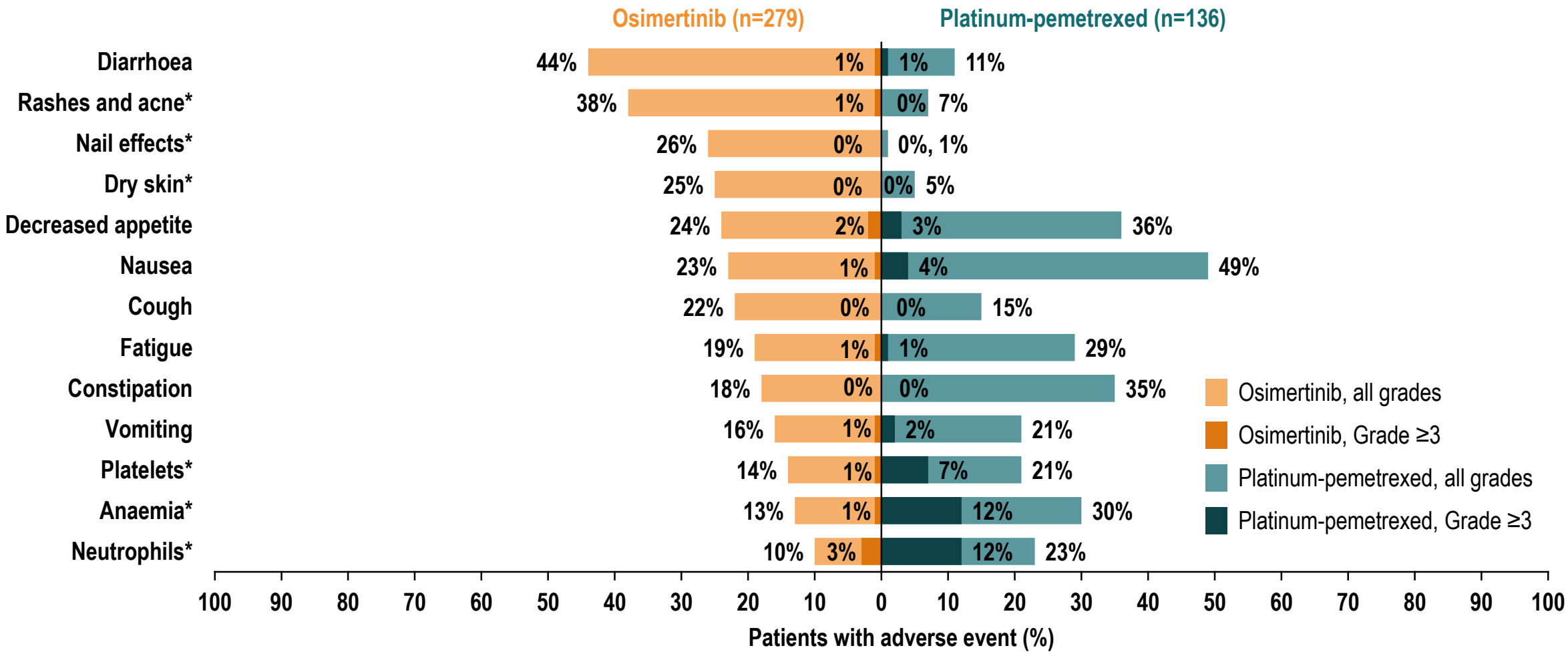
AURA3 safety summary

- At data cut-off, median duration of total treatment exposure was 13.8 months in the osimertinib arm, 4.3 months in the platinum-pemetrexed arm and 11.0 months on osimertinib in patients who crossed over

Category	Osimertinib, % n=279	Platinum-pemetrexed, % n=136	Safety with osimertinib in crossover patients#, %, n=99
Any AE	99	99	92
Any possibly related AE*	85	89	76
Any Grade ≥3 AE	37	48	36
Any possibly related Grade ≥3 AE*	9	34	9
Any AE leading to death	4	1	5
Any possibly related AE leading to death*	1	1	1
Any SAE	30	26	30
Any possibly related SAE*	4	13	5
Any AE leading to discontinuation	10	11	4
Any possibly related AE leading to discontinuation*	5	9	1

Data cut-off: 15 March 2019. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Included are adverse events with an onset date on or after the date of first dose and up to and including 28 days after the discontinuation of the trial drug or the day before the first administration of crossover treatment..
*Possibly related was assessed by the investigator, and programmatically derived from individual causality assessments. #AEs reported during osimertinib treatment in patients who crossed over from chemotherapy.
AE, adverse event; SAE, serious adverse event

AURA3 adverse events (≥20% patients)



Data cut-off: 15 March 2019.

*This category represents a grouped term for the event. If a patient had multiple preferred-term level events within a specific grouped term adverse event, then the maximum grade (according to the Common Terminology Criteria for Adverse Events) across those events was counted. Adverse events ≥20% of patients in any arm. Safety analyses included all the patients who received at least one dose of a trial drug (safety analysis set). Included are adverse events with an onset date on or after the date of first dose and up to and including 28 days after the discontinuation of the trial drug or the day before the first administration of crossover treatment. Some patients had more than one adverse event.

Conclusions

- In AURA3, the statistically and clinically significant PFS benefit with osimertinib vs platinum-pemetrexed did not result in a statistically significant improvement in OS, possibly as a result of the high crossover rates of patients from the platinum-pemetrexed arm to osimertinib

- No new safety signals were reported by patients receiving osimertinib as crossover treatment, i.e. in the third-line setting

- Based on the AURA3 and FLAURA results, using osimertinib as first-line treatment for EGFRm advanced NSCLC provides more patients with the opportunity to receive osimertinib, and the associated OS benefit vs comparator first-line EGFR-TKI[1,2]

1. Ramalingam et al. Ann Oncol 2019;30(suppl 5, abstr LBA5_PR); 2. Soria et al. N Engl J Med 2018;378:113–125.

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