Osimertinib as adjuvant therapy in patients with stage IB–IIIA EGFR mutation positive NSCLC after complete tumor resection: ADAURA

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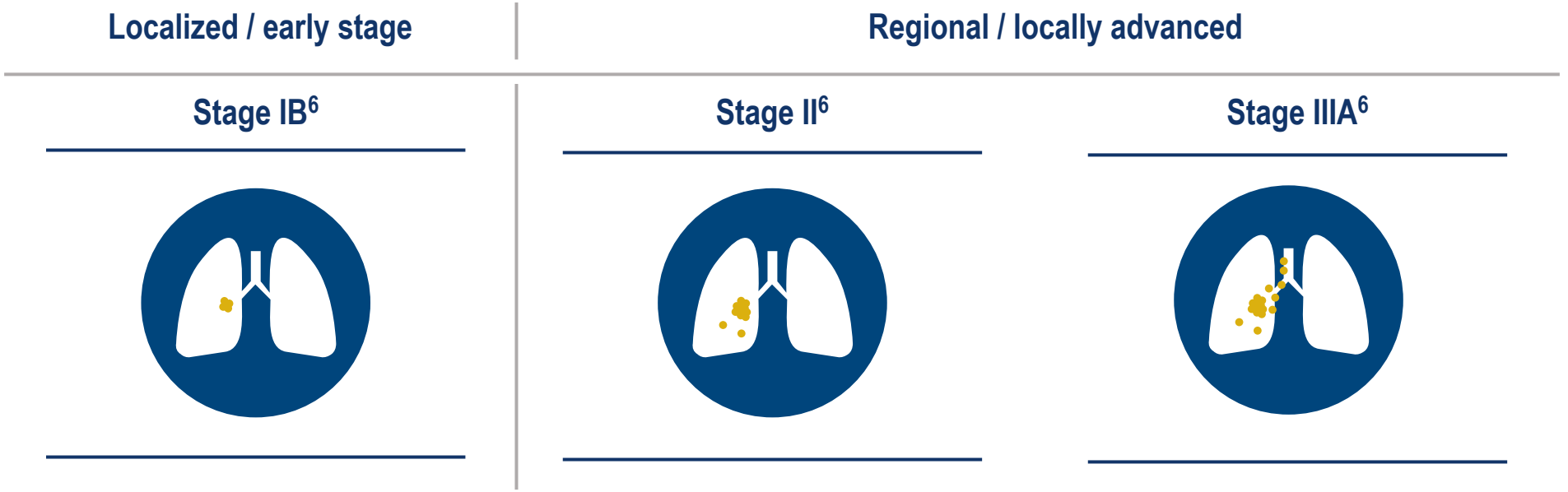
1 in 3 patients with NSCLC present with resectable disease

- Lung cancer is the leading cause of cancer death, accounting for more than 1.7 million deaths annually, and as many deaths as breast, prostate, and colorectal cancers combined[1]
- NSCLC represents 85% of all lung cancer cases,[2] with an estimated 30% of patients presenting with resectable disease at diagnosis[3–5]



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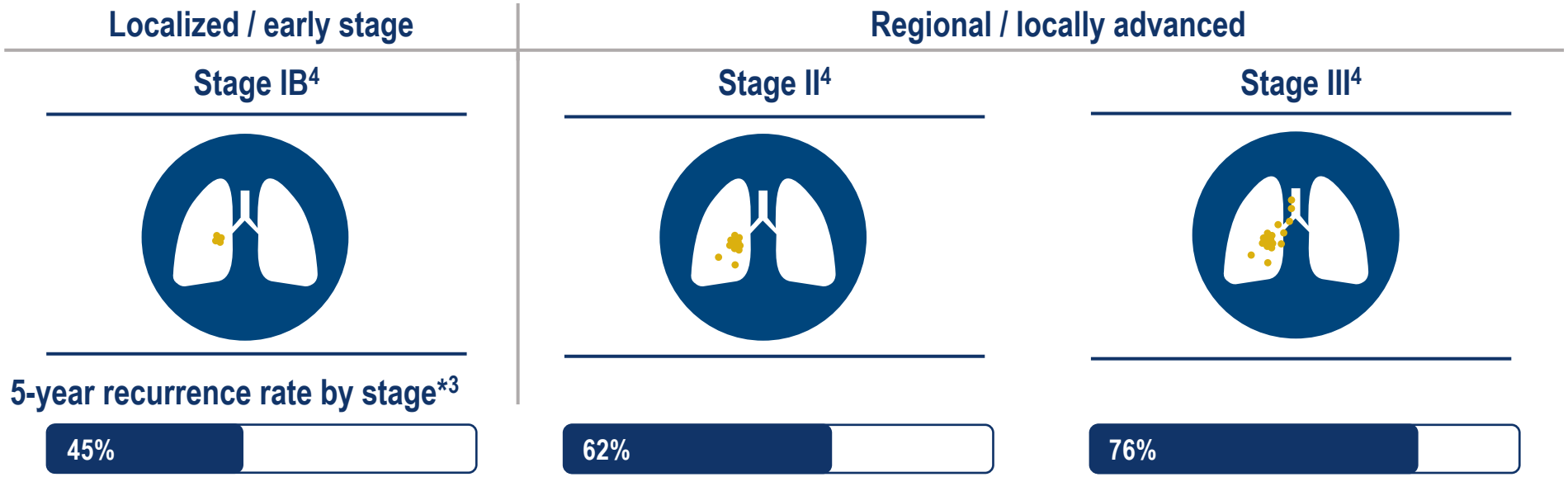
Outcomes in early stage NSCLC need to be improved

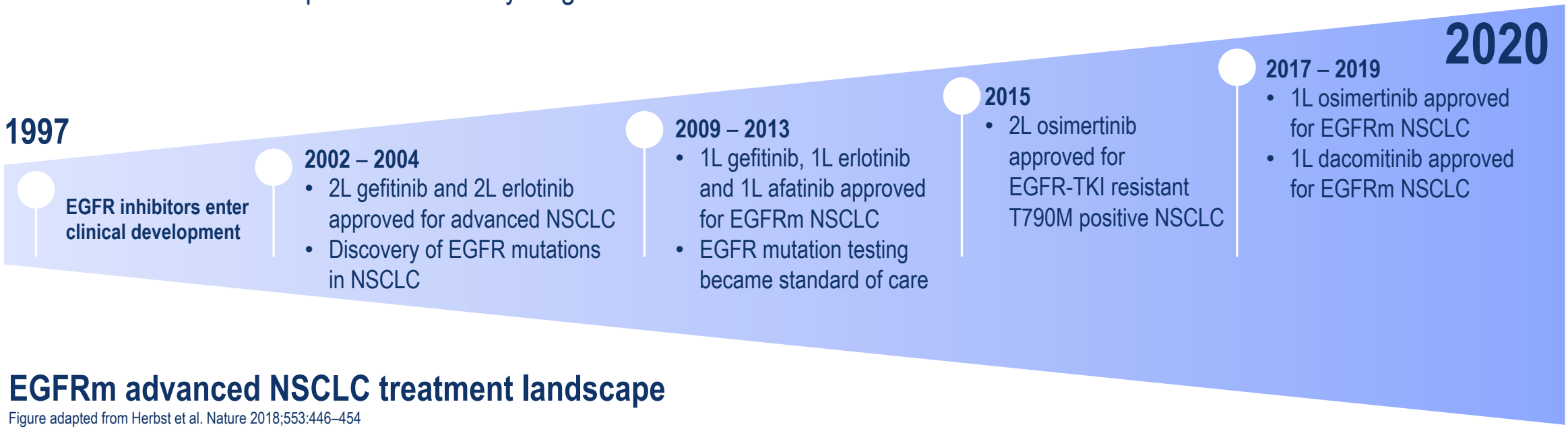
- Surgery is the primary treatment for patients with early stage NSCLC[1]
- Adjuvant cisplatin-based chemotherapy is recommended for patients with resected stage II—IIIA NSCLC and select patients with stage IB disease[2]
  - Results from large randomized trials and meta analyses showed a 5-year OS benefit with adjuvant chemotherapy in patients with early stage NSCLC, OS HR 0.89 (95% CI 0.82, 0.96); DFS also favored adjuvant chemotherapy, DFS HR 0.84 (95% CI 0.78, 0.91)[3]
- Overall, disease recurrence or death following surgery and adjuvant chemotherapy remains high across disease stages[3]



1. Chansky et al. J Thorac Oncol 2017;12:1109–1121; 2. Kris et al. J Clin Oncol 2017;35:2960–2974;
3. Pignon et al. J Clin Oncol 2008;26:3552–3559; 4. AJCC Cancer Staging Manual. 7th edn. Springer, 2010.
*Median follow up: 5.2 years, data based on AJCC Staging Manual 6th edition.
AJCC, American Joint Committee on Cancer; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

EGFR-TKIs have redefined treatment in EGFRm advanced NSCLC

- Over the course of more than 20 years, EGFR-TKIs have redefined treatment for patients with EGFRm advanced NSCLC[1–4]
- Osimertinib is a third-generation EGFR-TKI that has demonstrated a statistically significant and clinically meaningful improvement in PFS and OS vs comparator EGFR-TKIs (erlotinib / gefitinib) in EGFRm advanced NSCLC, with efficacy also demonstrated in central nervous system metastases[4–6]
- The efficacy and safety profile of osimertinib in the EGFRm advanced NSCLC setting suggests that osimertinib may be an effective treatment for patients with early stage disease[4]



EGFRm advanced NSCLC treatment landscape

Figure adapted from Herbst et al. Nature 2018;553:446–454

1. Parsons et al. JAMA Network Open. 2020;3:e202488; 2. Herbst et al. Nature 2018;553:446–454; 3. Herbst and Baselga. Nature Reviews 2004;4:956–65; 4. Soria et al. N Engl J Med 2018;378:113–125; 5. Ramalingam et al. N Engl J Med 2020;382:41–50; 6. Reungwetwattana et al. J Clin Oncol 2018;2702–9. 1L, first-line; 2L, second-line; EGFR, epidermal growth factor receptor; EGFRm, EGFR mutation positive; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

ADAURA Phase III double-blind study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO performance status 0 / 1
Confirmed primary non-squamous NSCLC Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins§
Max. interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomization 1:1 (N=682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

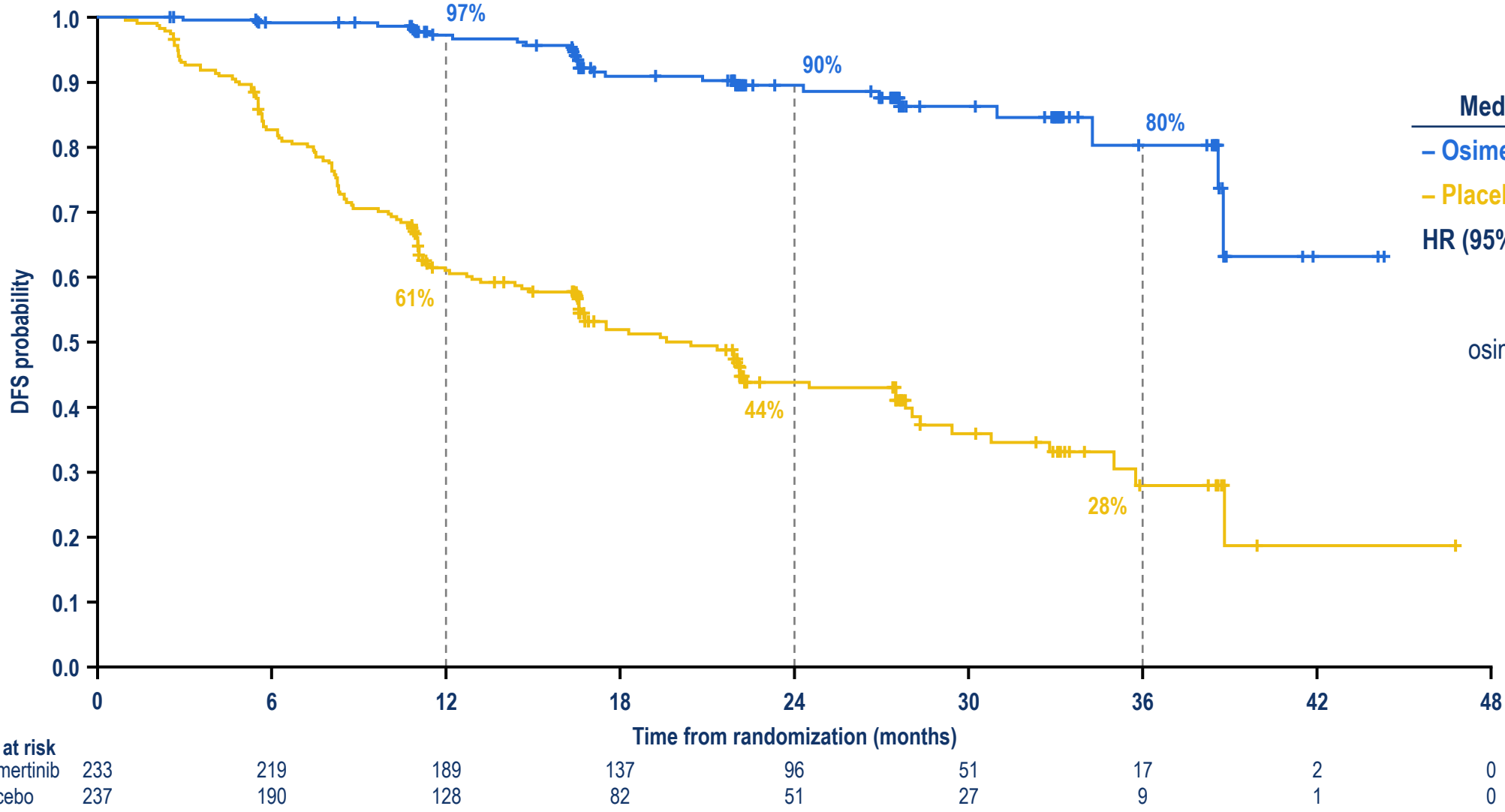
NCT02511106; ADAURA data cut-off: January 17, 2020. *AJCC 7th edition; †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue; §Patients received a CT scan after resection and within 28 days prior to treatment; ¶Stage IB / II / IIIA.
CT, computed tomography; Ex19del, exon 19 deletion;
IDMC, Independent Data Monitoring Committee; WHO, World Health Organization.

Baseline characteristics in the overall population (stage IB/II/IIIA)

Characteristic, %	Osimertinib (n=339)	Placebo (n=343)
Sex: male / female	32 / 68	28 / 72
Age, median (range), years	64 (30–86)	62 (31–82)
Smoking status: smoker* / non-smoker	32 / 68	25 / 75
Race: Asian / non-Asian	64 / 36	64 / 36
WHO performance status: 0 / 1	64 / 36	64 / 36
AJCC staging at diagnosis (7th edition): IB / II / IIIA	31 / 35 / 34	31 / 34 / 35
Histology: adenocarcinoma / other†	95 / 5	96 / 4
EGFR mutation at randomization‡: Ex19del / L858R	55 / 45	56 / 44
Adjuvant chemotherapy: yes / no	55 / 45	56 / 44

ADAURA data cut-off: January 17, 2020. *Former: osimertinib n=104, placebo n=83; current: osimertinib n=4, placebo n=3; never: osimertinib n=231, placebo n=257; †Includes bronchial gland carcinoma (NOS): osimertinib n=1; placebo n=2; malignant adenosquamous carcinoma: osimertinib n=4; placebo n=5; other: osimertinib n=11; placebo n=7; ‡Central test.

Primary endpoint: DFS in patients with stage II/IIIA disease

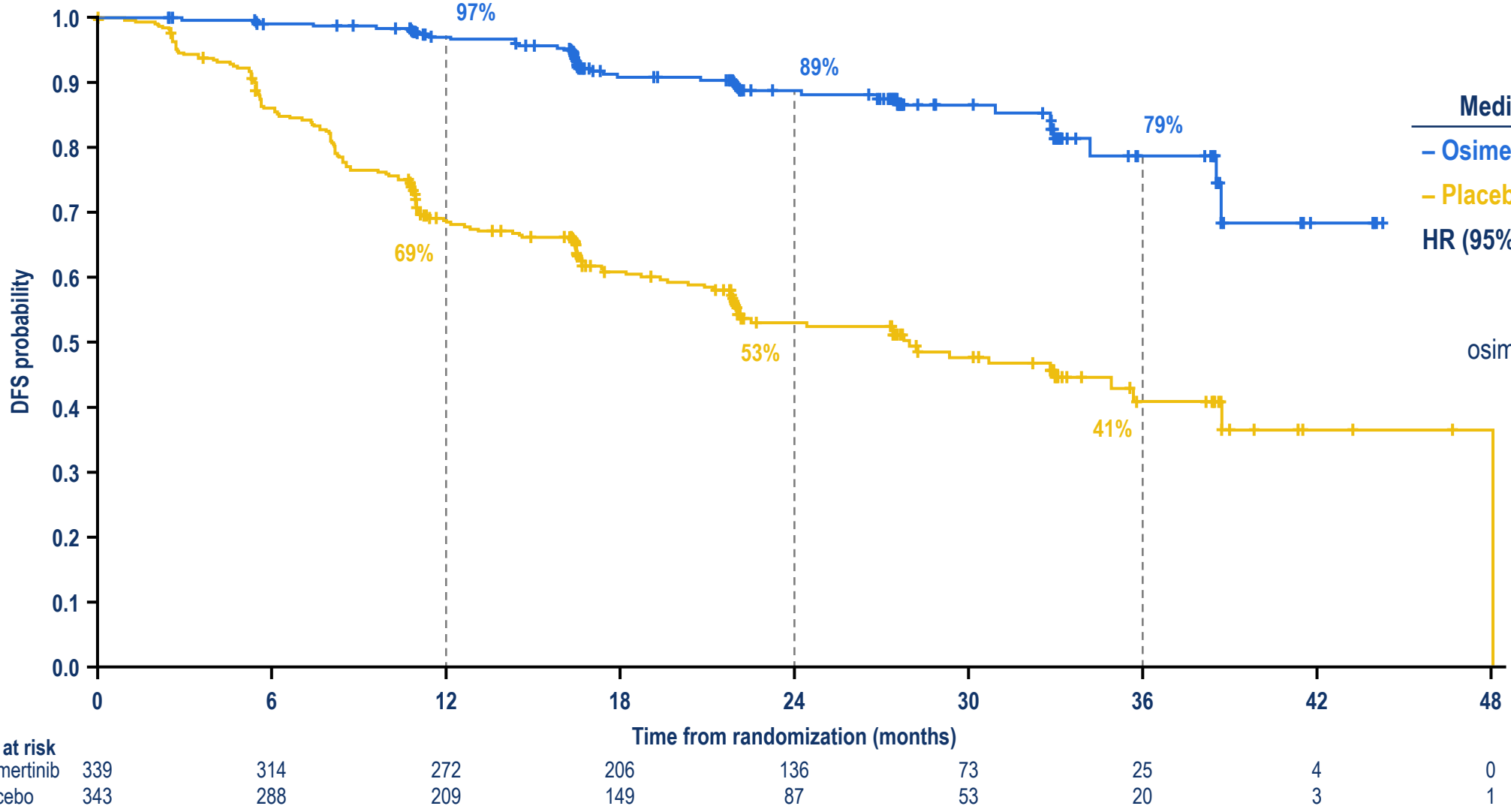


Median DFS, months (95% CI)	
– Osimertinib	NR (38.8, NC)
– Placebo	20.4 (16.6, 24.5)
HR (95% CI)	**0.17 (0.12, 0.23); p<0.0001**

Maturity 33%:
osimertinib 11%, placebo 55%

ADAURA data cut-off: January 17, 2020.
Median follow-up: osimertinib 22.1, placebo: 15.0 months;
DFS by investigator assessment; Tick marks indicate censored data.
NC, not calculable; NR, not reached.

Secondary endpoint: DFS in the overall population (stage IB/II/IIIA)



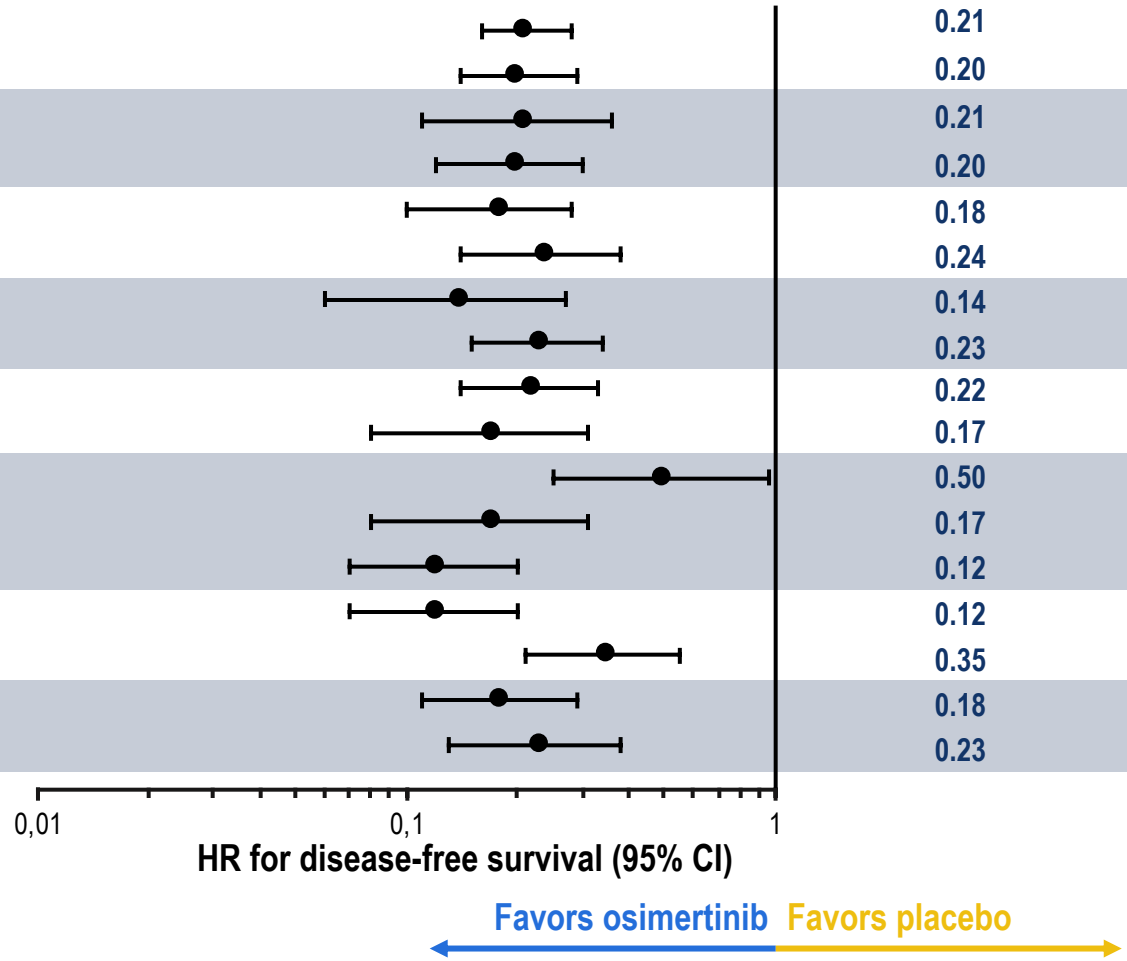
Median DFS, months (95% CI)	
– Osimertinib	NR (NC, NC)
– Placebo	28.1 (22.1, 35.8)
HR (95% CI)	**0.21 (0.16, 0.28); p<0.0001**

Maturity 29%:
osimertinib 12%, placebo 46%

ADAURA data cut-off: January 17, 2020.
Median follow-up: osimertinib 22.1, placebo: 16.6 months;
DFS by investigator assessment; Tick marks indicate censored data.

DFS across subgroups in the overall population

Subgroup		HR	95% CI
Overall (N=682)	Stratified log-rank	0.21	0.16, 0.28
	Unadjusted Cox PH	0.20	0.14, 0.29
Sex	Male (n=204)	0.21	0.11, 0.36
	Female (n=478)	0.20	0.12, 0.30
Age	<65 (n=380)	0.18	0.10, 0.28
	≥65 (n=302)	0.24	0.14, 0.38
Smoking status	Smoker (n=194)	0.14	0.06, 0.27
	Non-smoker (n=488)	0.23	0.15, 0.34
Race	Asian (n=434)	0.22	0.14, 0.33
	Non-Asian (n=248)	0.17	0.08, 0.31
Stage	Stage IB (n=212)	0.50	0.25, 0.96
	Stage II (n=236)	0.17	0.08, 0.31
	Stage IIIA (n=234)	0.12	0.07, 0.20
EGFRm	Ex19del (n=378)	0.12	0.07, 0.20
	L858R (n=304)	0.35	0.21, 0.55
Adjuvant chemotherapy	Yes (n=378)	0.18	0.11, 0.29
	No (n=304)	0.23	0.13, 0.38



ADAURA data cut-off: January 17, 2020. Overall population: stage IB / II / IIIA. DFS by investigator assessment.

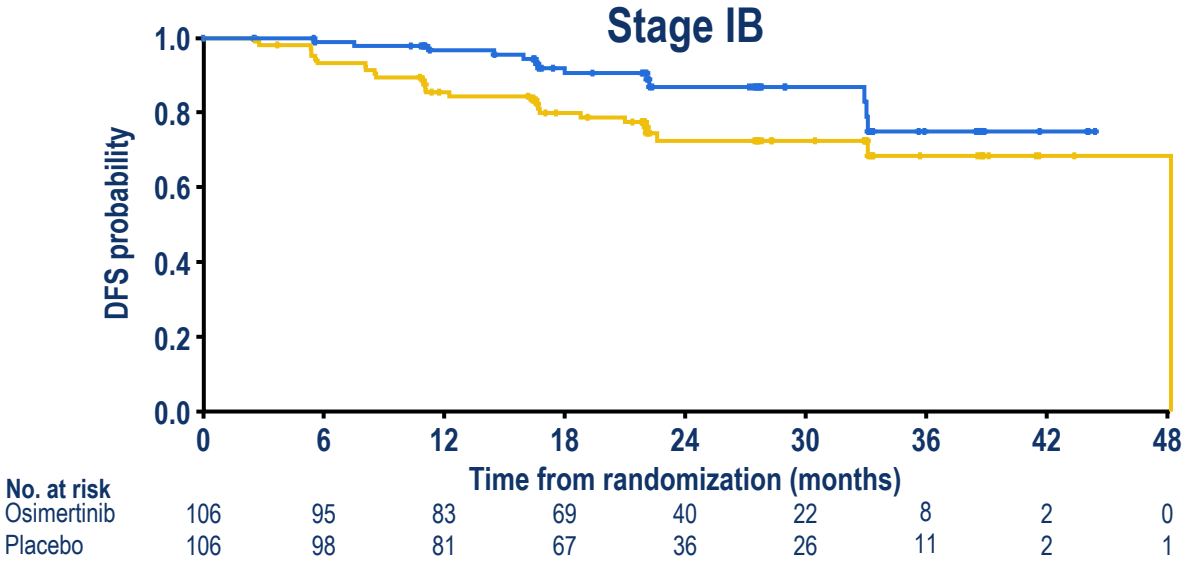
DFS by stage

	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	**0.50 (0.25, 0.96)**	**0.17 (0.08, 0.31)**	**0.12 (0.07, 0.20)**

- In the osimertinib arm, 2 year DFS rates were consistent across stages IB, II, and IIIA disease
- Maturity (overall population: stage IB / II / IIIA) 29%: osimertinib events 12%, placebo events 46%

ADAURA data cut-off: January 17, 2020.

DFS by stage



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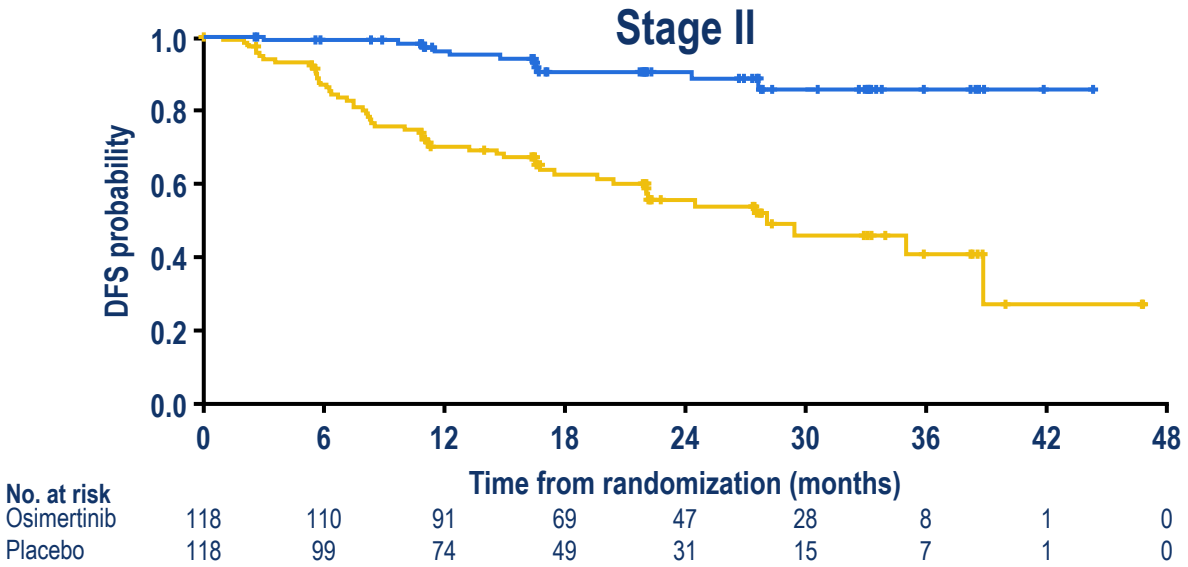
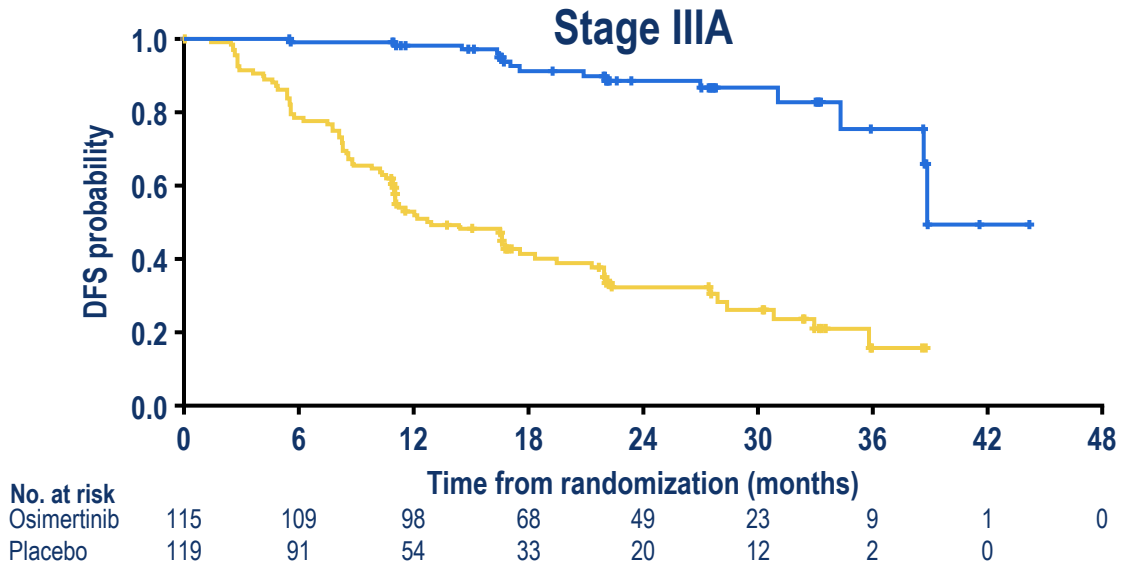
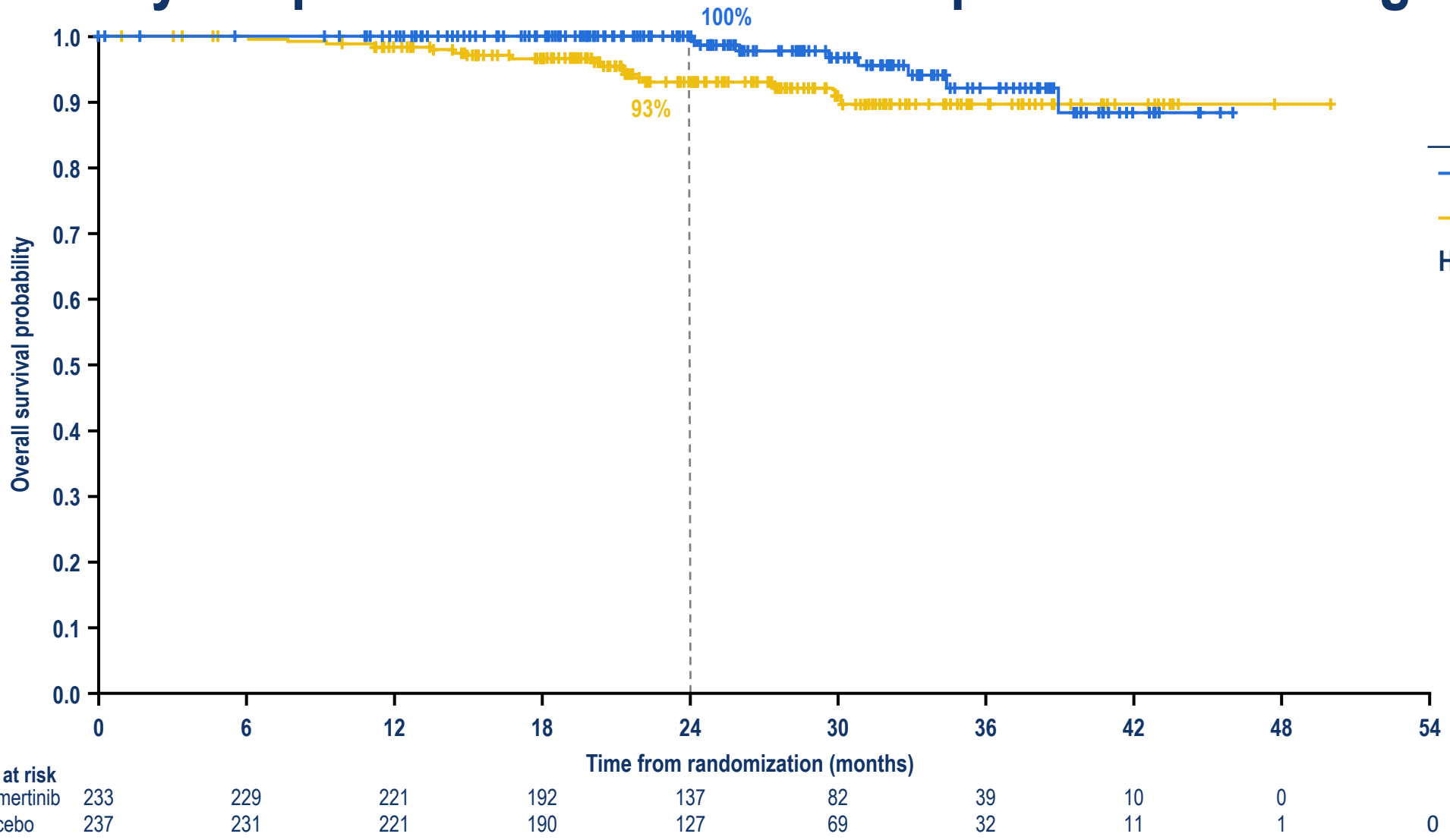




ADAURA data cut-off: January 17, 2020.
Tick marks indicate censored data.

Early snapshot: overall survival in patients with stage II/IIIA disease



Median OS, months (95% CI)	
– Osimertinib	NR (NC, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	**0.40 (0.18, 0.90)**

Maturity 5%:
osimertinib 3%, placebo 7%

ADAURA data cut-off: January 17, 2020.
Median follow-up: osimertinib 26.1, placebo 24.7 months.
Tick marks indicate censored data.

Safety summary

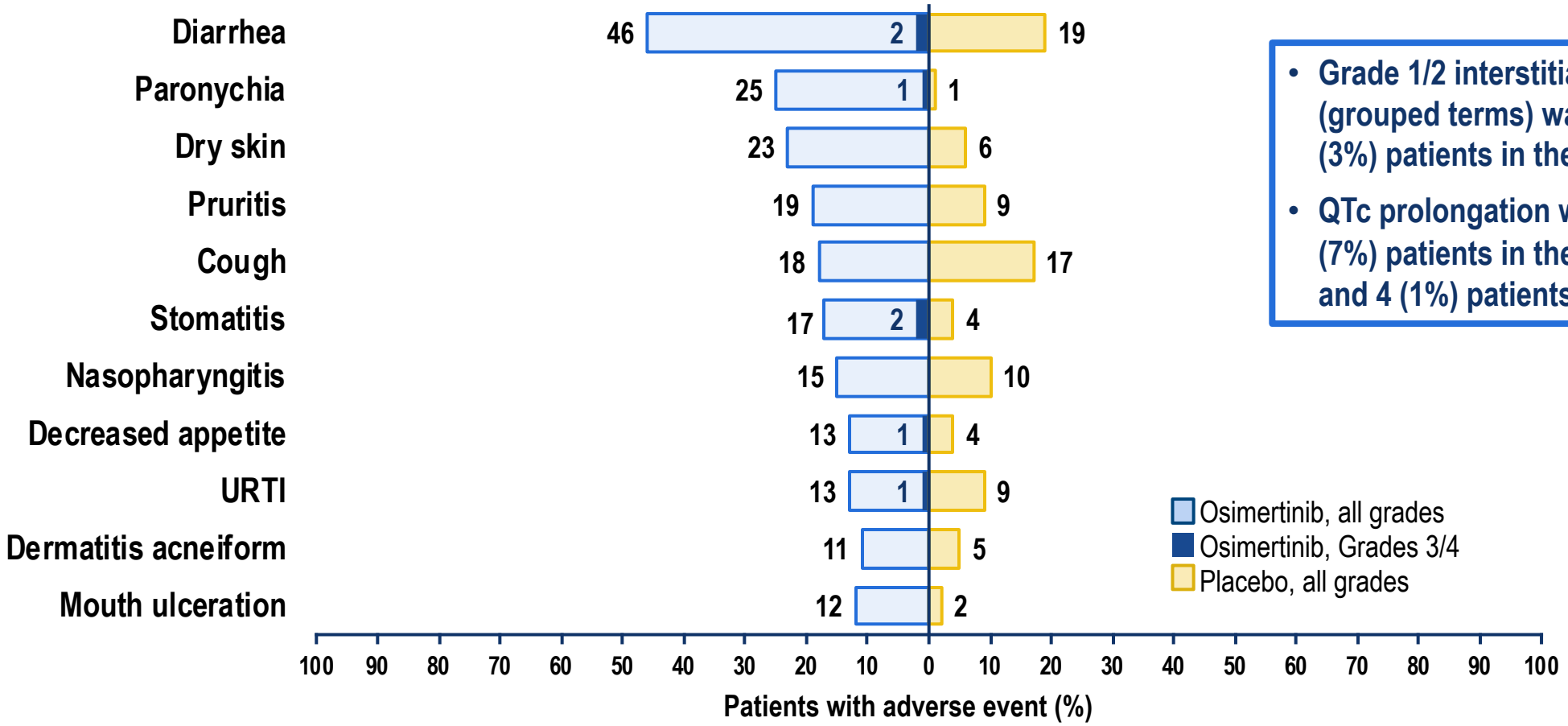
AE, any cause*, n (%)	Osimertinib (n=336)	Placebo (n=343)
Any AE	327 (97)	306 (89)
Any AE Grade ≥3	68 (20)	48 (14)
Any AE leading to death	0	1 (<1)
Any serious AE	54 (16)	44 (13)
Any AE leading to discontinuation	38 (11)	15 (4)
Any AE leading to dose reduction	25 (7)	2 (1)
AE, possibly causally related†, n (%)		
Any AE	303 (90)	190 (55)
Any AE Grade ≥3	32 (10)	9 (3)
Any AE leading to death	0	0
Any serious AE	9 (3)	2 (1)

ADAURA data cut-off: January 17, 2020.

*Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category counted once in each of those categories; †As assessed by the investigator, includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy. AE, adverse event.

All causality adverse events (≥10% of patients)

Median duration of exposure: osimertinib: 22.3 months (range 0 to 43), placebo: 18.4 months (range 0 to 48)



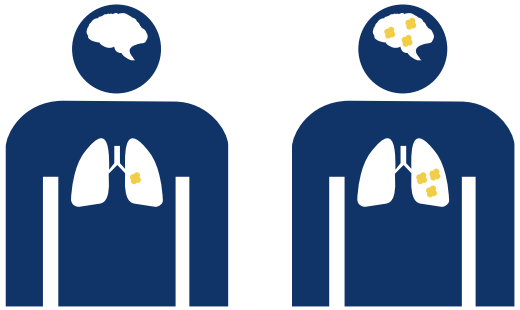
- Grade 1/2 interstitial lung disease (grouped terms) was reported in 10 (3%) patients in the osimertinib arm*
- QTc prolongation was reported in 22 (7%) patients in the osimertinib arm and 4 (1%) patients in the placebo arm†

ADAURA data cut-off: January 17, 2020.
One patient in the placebo arm reported a Grade 5 pulmonary embolism.
*Grade 1, n=6; Grade 2, n=4; †osimertinib: Grade 1, n=14; Grade 2, n=5; Grade 3, n=3; placebo: Grade 1, n=3; Grade 3, n=1.
URTI, upper respiratory tract infection.

Future considerations

1

Local versus distant recurrence



2

Sites of disease recurrence, including incidence of CNS metastases

3

Subsequent therapies

4

Quality of life

CNS, central nervous system.

Conclusions

- Adjuvant osimertinib is the first targeted agent in a global trial to show a statistically significant and clinically meaningful improvement in DFS in patients with stage IB / II / IIIA EGFRm NSCLC
  - Overall, there was a 79% reduction in the risk of disease recurrence or death with osimertinib (DFS HR 0.21 [95% CI 0.16, 0.28]; p<0.0001)
  - Osimertinib vs placebo DFS rates at 2 years were 89% vs 53%, respectively
- A consistent improvement in DFS was seen regardless of whether patients received prior adjuvant chemotherapy
- The safety profile was consistent with the established safety profile of osimertinib, with mild EGFR-TKI class effects reported; median duration of exposure to osimertinib was 22 months

Adjuvant osimertinib will provide a highly effective, practice changing treatment for patients with stage IB / II / IIIA EGFRm NSCLC after complete tumor resection

ADAURA data cut-off: January 17, 2020.

Acknowledgements

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