

Progress in *EGFR*-mutant NSCLC: Where are we going?

Are combination strategies the way forward for *EGFR*-mutant NSCLC?

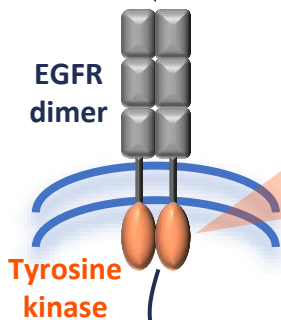
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The Christie Hospital
Manchester University Hospital
University of Manchester
Manchester, UK



EGFR mutations in patients with NSCLC

EGF or other
EGFR ligand



- Cell proliferation
- Cell survival
- Migration

Mutations in the catalytic tyrosine
kinase domain (exons 18–21)



Constitutive EGFR activation

EGFR mutations in lung cancer:

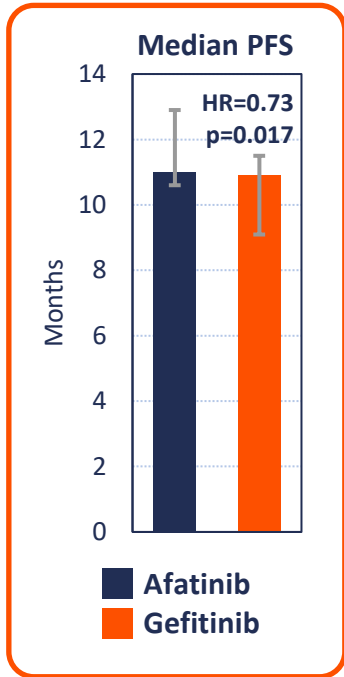
- 10–15% Caucasian patients
- Up to 50% in East-Asian patients

More frequent in:

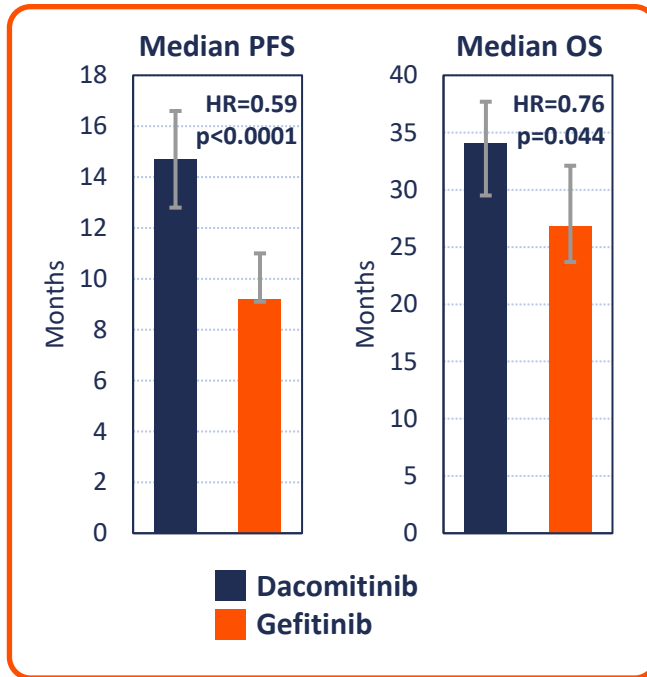
- Patients with adenocarcinoma
- Female patients
- Never/former smokers

EGFR-TKI as first-line therapy for NSCLC

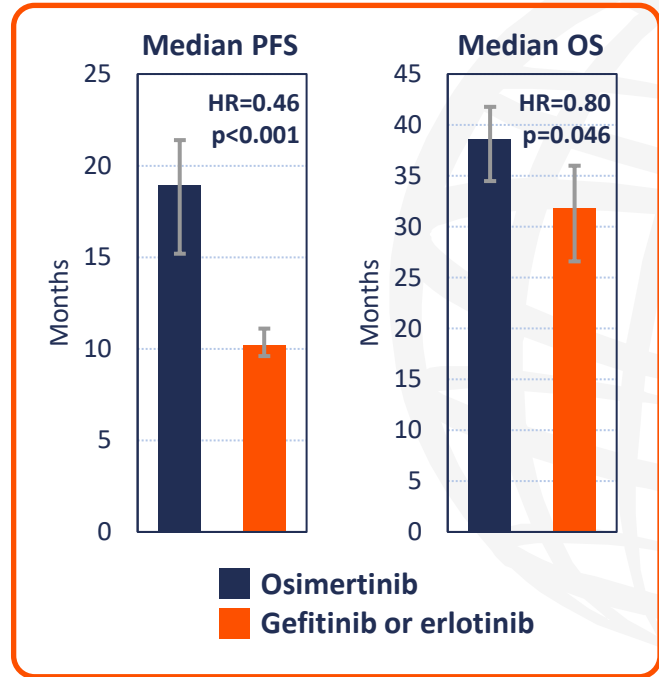
LUX-LUNG 7¹



ARCHER 1050^{2,3}



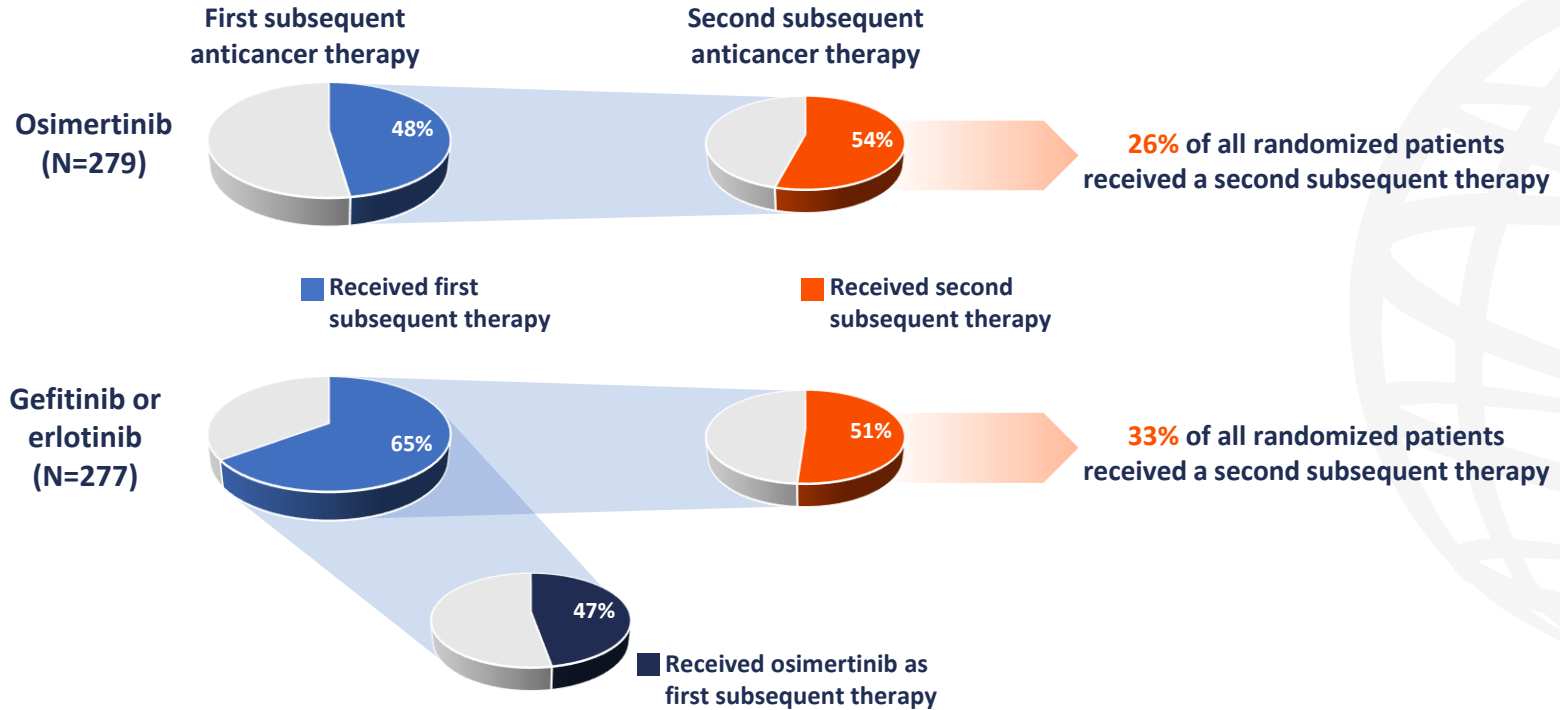
FLAURA^{4,5}



EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

1. Park K, et al. *Lancet Oncol.* 2016;17:577–89; 2. Mok TS, et al. *J Clin Oncol.* 2018;36:2244–50; 3. Wu YL, et al. *Lancet Oncol.* 2017;18:1454–66; 4. Soria J-C, et al. *N Engl J Med.* 2018;378:113–25; 5. Ramalingam SS, et al. *N Engl J Med.* 2020;382:41–50.

FLAURA trial: Subsequent therapies



EGFR-TKI combined with anti-VEGF therapy

NEJ026 and RELAY: Study design

NEJ026¹



N=228

- Stage IIIB–IV NSCLC
- Activating *EGFR* genomic aberrations
- Performance status ≤ 2
- No prior chemotherapy for advanced disease

1:1

Erlotinib plus
bevacizumab

Erlotinib
monotherapy

RELAY²



N=449

- Metastatic NSCLC
- Activating *EGFR* genomic aberrations
- No CNS metastases
- Performance status ≤ 1
- No prior treatment

1:1

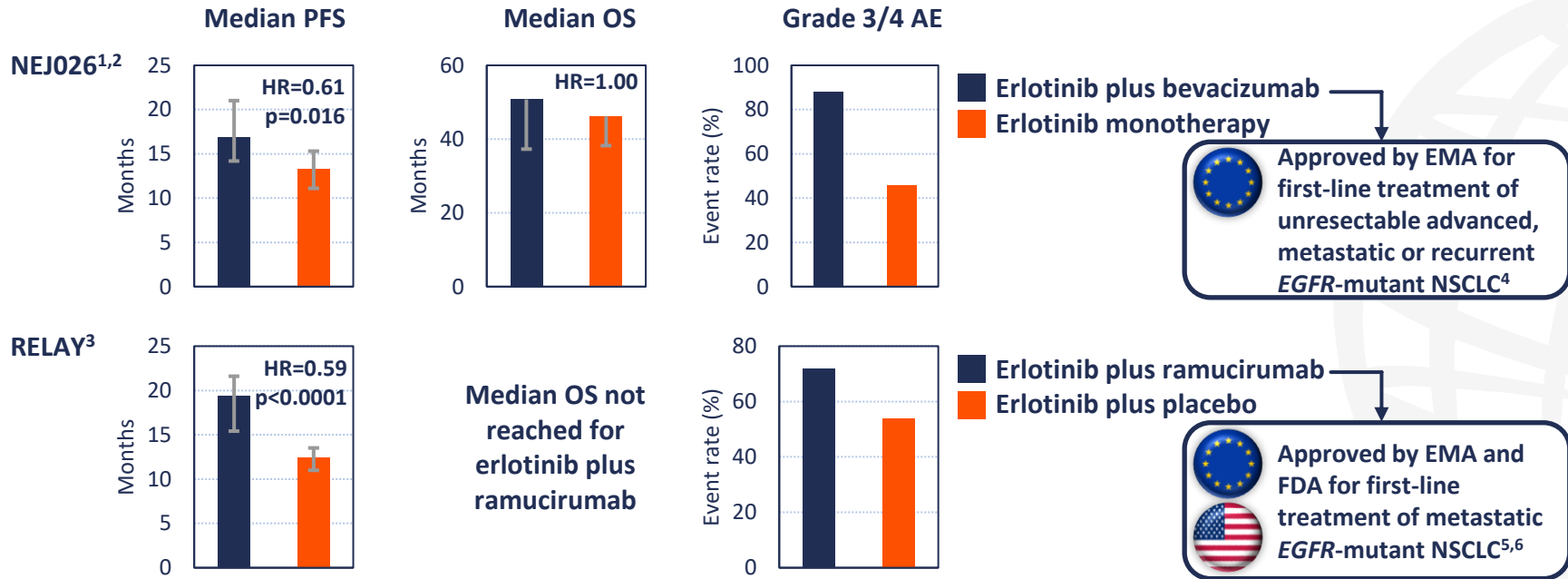
Erlotinib plus
ramucirumab

Erlotinib plus
placebo

CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

1. Saito H, et al. *Lancet Oncol.* 2019;20:625–35; 2. Nakagawa K, et al. *Lancet Oncol.* 2019;20:1655–69.

EGFR-TKI combined with anti-VEGF therapy



AE, adverse events; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, Food and Drug Administration; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PI, product information; PFS, progression-free survival; SPC, summary of product characteristics; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

- Saito H, et al. *Lancet Oncol.* 2019;20:625–35; 2. Maemondon M, et al. *J Clin Oncol.* 2020;38(15_Suppl):9506; 3. Nakagawa K, et al. *Lancet Oncol.* 2019;20:1655–69;
- EMA. Avastin (bevacizumab) infusion, SPC. 2020. Available at: www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf;
- EMA. Cytamza (ramucirumab) infusion, SPC. 2020. Available at: www.ema.europa.eu/en/documents/product-information/cytamza-epar-product-information_en.pdf;
- FDA. Cytamza (ramucirumab) injection, PI 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/125477s034lbl.pdf. (PI and SPC accessed 4 Nov 2020).

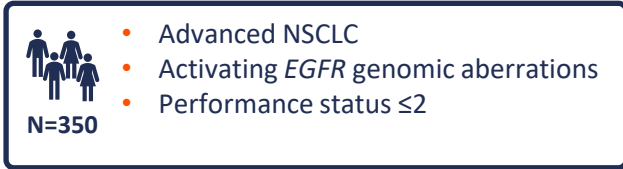
EGFR-TKI combined with chemotherapy

NEJ009 and Tata Memorial Centre: Study design

NEJ009¹



Tata²

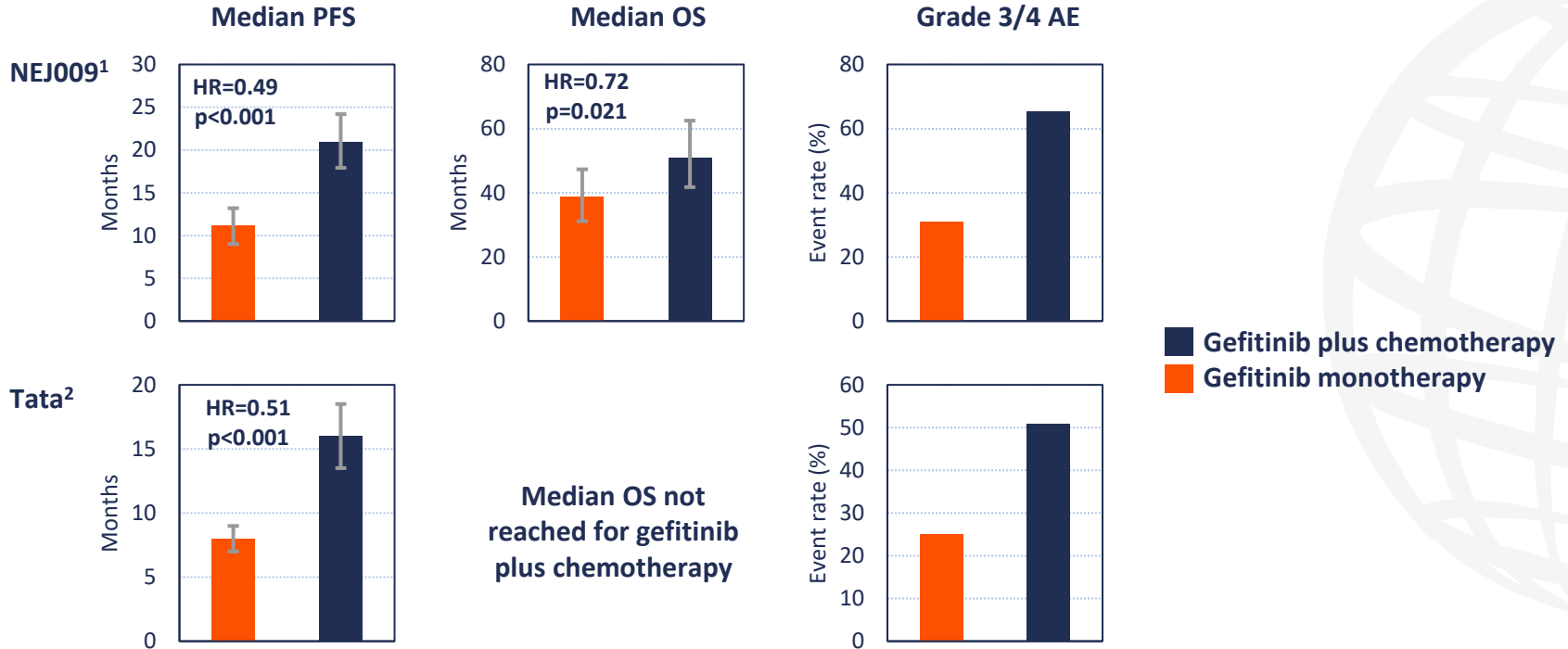


Chemotherapy consisted of pemetrexed and carboplatin in both trials



The primary endpoint for both trials was PFS

EGFR-TKI combined with chemotherapy



AE, adverse events; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

1. Hosomi Y, et al. *J Clin Oncol.* 2020;38:115–23; 2. Noronha V, et al. *J Clin Oncol.* 2020;38:124–36.

Immunotherapy for *EGFR*-mutant NSCLC

NCT02879994¹

Phase II trial of pembrolizumab in TKI-naive patients with *EGFR*-mutation positive, advanced NSCLC and PD-L1 positive ($\geq 1\%$) tumours

Enrolment was ceased due to lack of efficacy even on tumours with PD-L1 expression $>50\%$

Italian expanded access programme^{2,3}

Analysis of nivolumab therapy in patients who had relapsed after one or more prior systemic treatments for stage IIIB/IV NSCLC, with a focus on never-smokers and patients with *EGFR*-mutant tumours

Worse clinical outcomes with PD-1 inhibition in patients with *EGFR*-mutant tumours than *EGFR*-WT tumours

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor; WT, wild type.

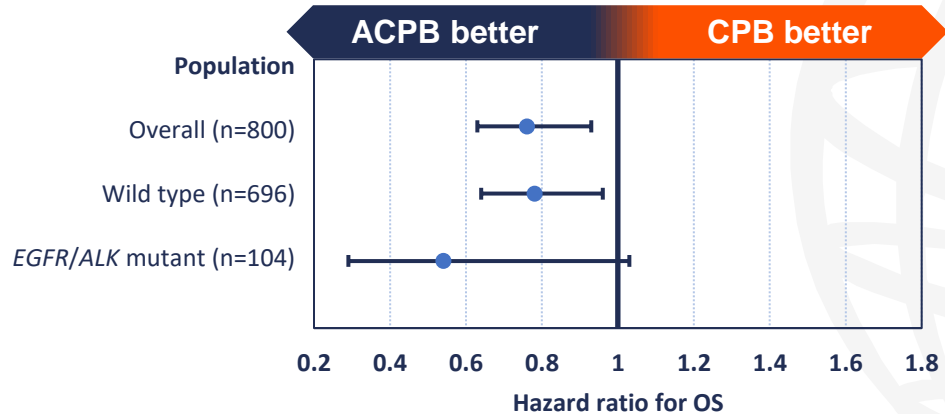
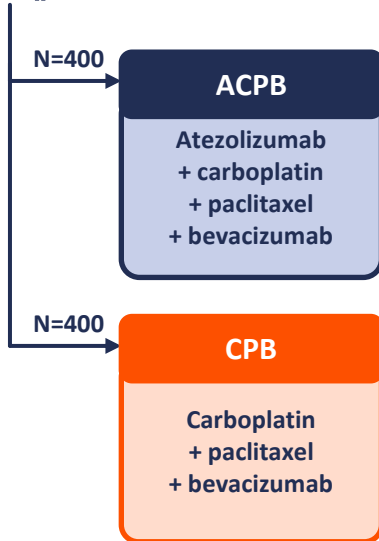
1. Lisberg A, et al. *J Clin Oncol*. 2018;13:1138–45; 2. Garassino MC, et al. *J Thorac Oncol*. 2018;13:1146–55; 3. Lisberg A, et al. *J Thorac Oncol*. 2018;13:1058–9.

ICI, chemotherapy and anti-VEGF combination

IMpower150: Study design¹ and OS analysis²



- Stage IV or recurrent metastatic NSCLC
- No prior chemotherapy



ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; OS, overall survival; VEGF, vascular endothelial growth factor.

1. Socinski MA, et al. *N Engl J Med*. 2018;378:2288–301; 2. Socinski MA, et al. *J Clin Oncol*. 2018;36(15_Suppl):9002.

How will acquired resistance drive treatment choices in *EGFR*-mutant NSCLC?

Prof. Lecia Sequist

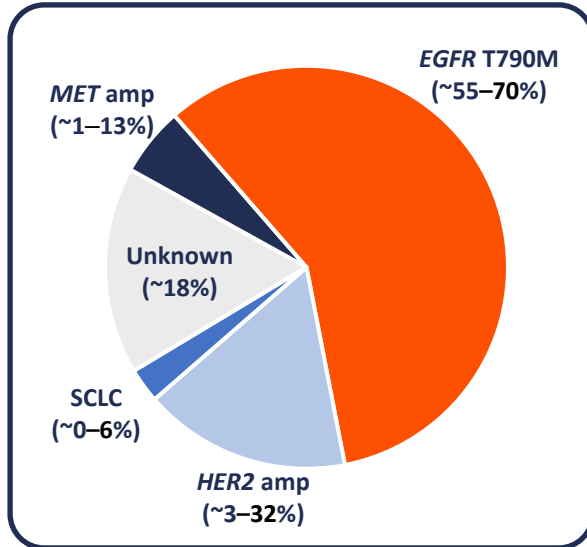
Harvard Medical School
Massachusetts General Hospital
Boston, MA, USA



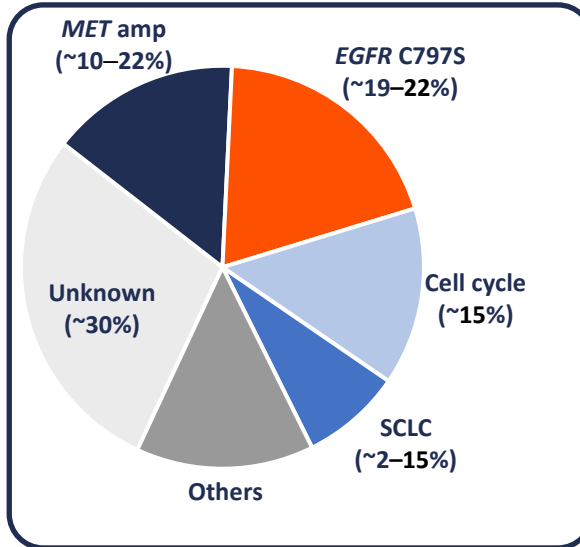
Mechanisms of resistance to EGFR-TKIs

Resistance to EGFR-TKIs is complex and setting-dependent

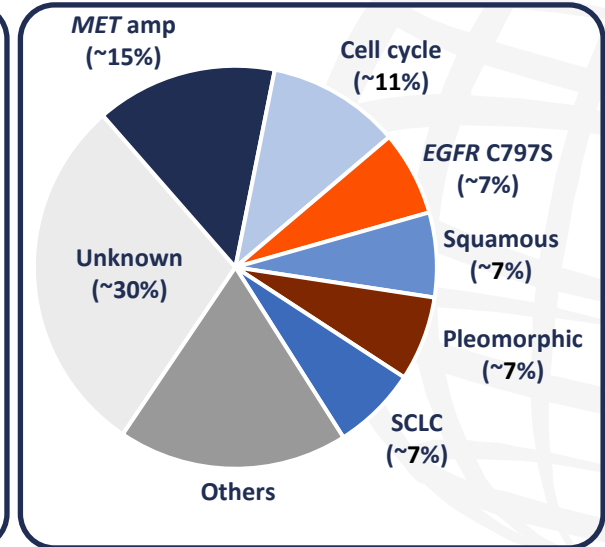
First-line first and second generation EGFR-TKIs¹



Second or further-line 3rd generation EGFR-TKI^{2–4}



First-line third generation^{5,6}



Amp, amplification; EGFR, epithelial growth factor receptor; HER2, human epidermal growth factor receptor 2; MET, mesenchymal-epithelial transition factor; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor.

1. Yu HA, et al. *Clin Cancer Res.* 2013;19:2240–7; 2. Piotrowska Z, et al. *Cancer Discov.* 2018;8:1529–39; 3. Oxnard GR, et al. *JAMA Oncol.* 2018;4:1527–34;

4. Papadimitrakopoulou VA, et al. *Ann Oncol.* 2018;29:viii741; 5. Ramalingam SS, et al. *Ann Oncol.* 2018;29:viii740; 6. Schoenfeld AJ, et al. *Clin Cancer Res.* 2020;26:2654–63.

EGFR-TKIs + MET inhibitors

TATTON (NCT02143466): Osimertinib + savolitinib in EGFR-mutant, MET-amplified NSCLC

Study design



N=46

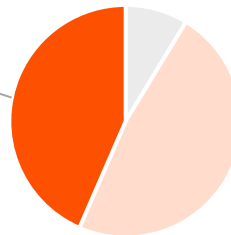
- Locally advanced or metastatic NSCLC
- EGFR-mutant T790M negative
- Progressed on one prior first/second-generation EGFR-TKI (no prior third-generation EGFR-TKI)
- Performance status ≤ 1
- MET-positive status



Osimertinib 80 mg once daily
plus
Savolitinib 600 mg once daily

Safety profile

Grade ≥ 3 TRAE
43%



Grade 1 or 2
TRAE...

Anti-tumour activity

ORR

52%

7.1 months

Median DoR

DoR, duration of response; EGFR, epithelial growth factor receptor; MET, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer; ORR, objective response rate; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse effect.

Yu H, et al. *Cancer Res* 2019;79(13 Suppl):Abstract CT032.

EGFR-TKIs + MET inhibitors

Capmatinib¹

- NCT02414139 (phase II)
- Combination with gefitinib
- EGFR-mutant NSCLC:
 - Previous-line resistant (cohort 1a)
 - MET-amplification

• **ORR = 29%**

Tepotinib²

- NCT01982955 (phase Ib/II)
- Combination with gefitinib
- EGFR-mutant NSCLC:
 - Previous-line resistant
 - MET-amplification

• **ORR = 66.7%**

Nazartinib³

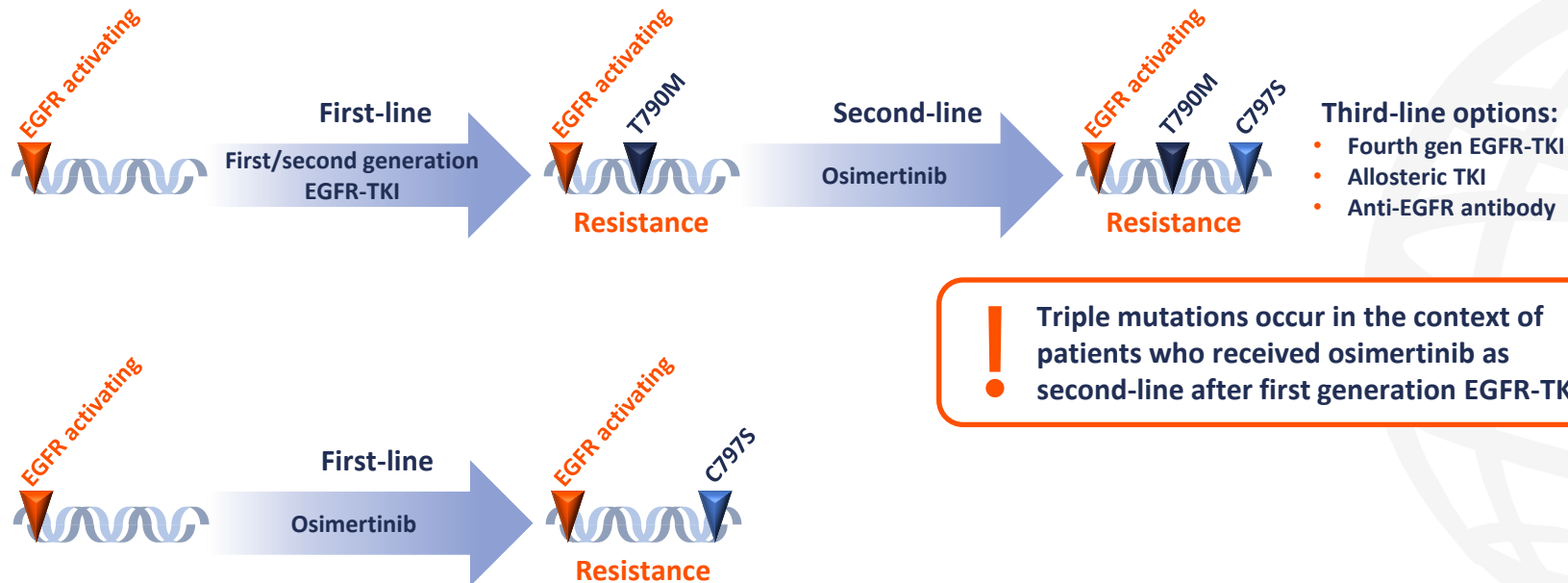
- NCT02335944 (phase Ib/II)
- Combination with capmatinib
- EGFR-mutant NSCLC:
 - Previous-line resistant
 - Any T790M/MET

• **ORR = 43.5%**

EGFR, epithelial growth factor receptor; MET, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer; ORR, overall/objective response rate; TKI, tyrosine kinase inhibitor.

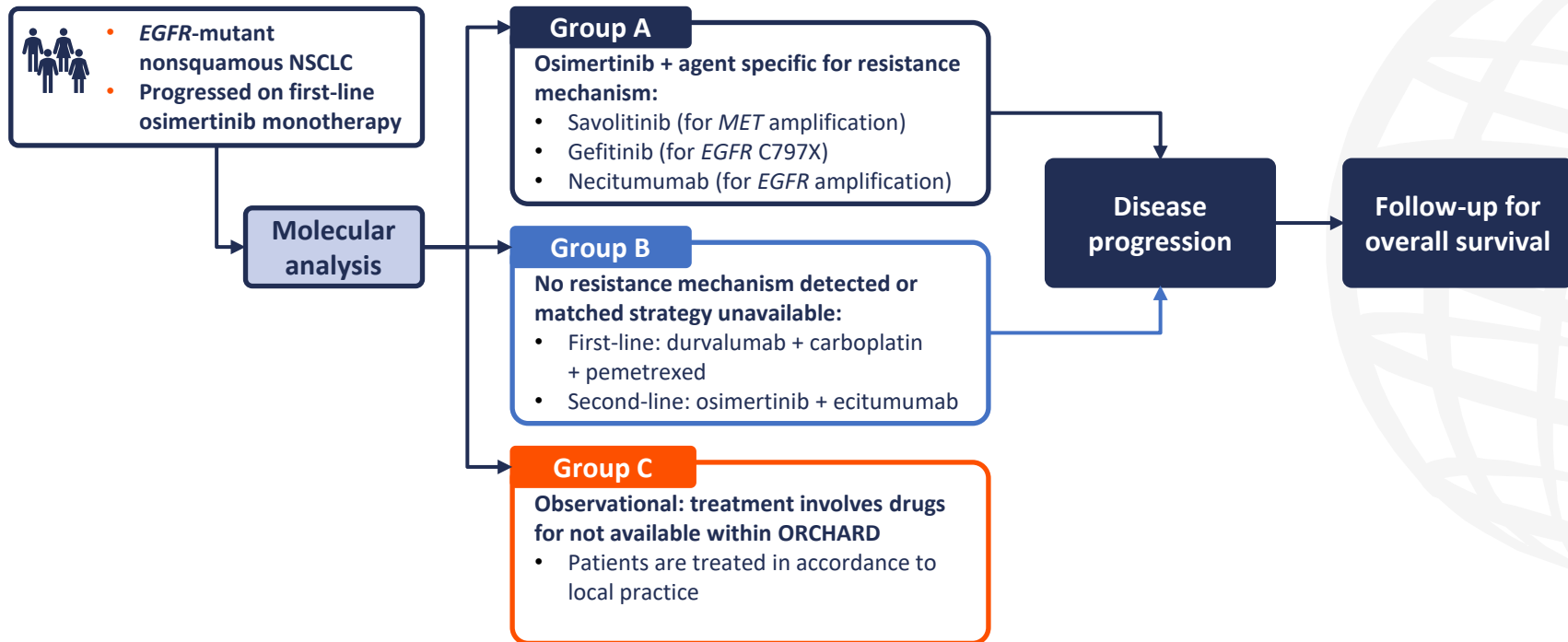
1. Wolf J, et al. *J Clin Oncol*. 2020;38(15_Suppl):9509; 2. Park K, et al. *Ann Oncol*. 2019;30(Suppl 9):ix159; 3. Felip E, et al. *Ann Oncol*. 2020;31(Suppl 4):S829.

EGFR C797S mutation occurrence



The ORCHARD trial

Study design



Emerging therapeutic agents

Amivantamab¹

EGFR-MET bispecific antibody

NCT02609776 (phase I CHRYSALIS)



Amivantamab + lazertinib

- **Part 1**
 - NSCLC, *EGFR* del19 or L858R
 - No restriction on prior therapy
 - **Part 2**
 - NSCLC, no biomarker selection
 - Progressing on osimertinib
- **Part 1: ORR = 43.5%**
(PR = 10/23)
- **Part 2: ORR = 57.1%**
(CR = 1/14, PR = 7/14)

U3-1402²

Anti-HER2 antibody-drug conjugate

NCT03260491 (phase I)



U3-1402

- Metastatic or unresectable NSCLC with *EGFR* mutation
 - T790M negative after disease progression on erlotinib, gefitinib or afatinib
 - Or disease progression on osimertinib regardless of T790M
- **12/13 evaluable patients had a decrease in SLD (median: -29%)**
- **2/13 had confirmed partial response per RECIST v1.1**

CR, complete response; EGFR, epithelial growth factor receptor; HER2, human epidermal growth factor receptor 2; MET, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer; ORR, overall response rate; PR, partial response; SLD, sum of longest diameters.

1. Cho BC, et al. *Ann Oncol.* 2020;31(Suppl_4):S754–840; 2. Janne PA, et al. *J Clin Oncol.* 2019;37(15_Suppl):9010.

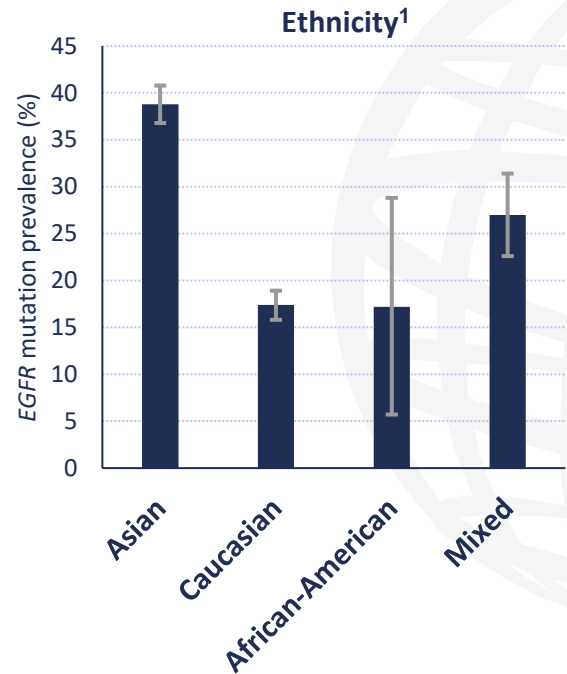
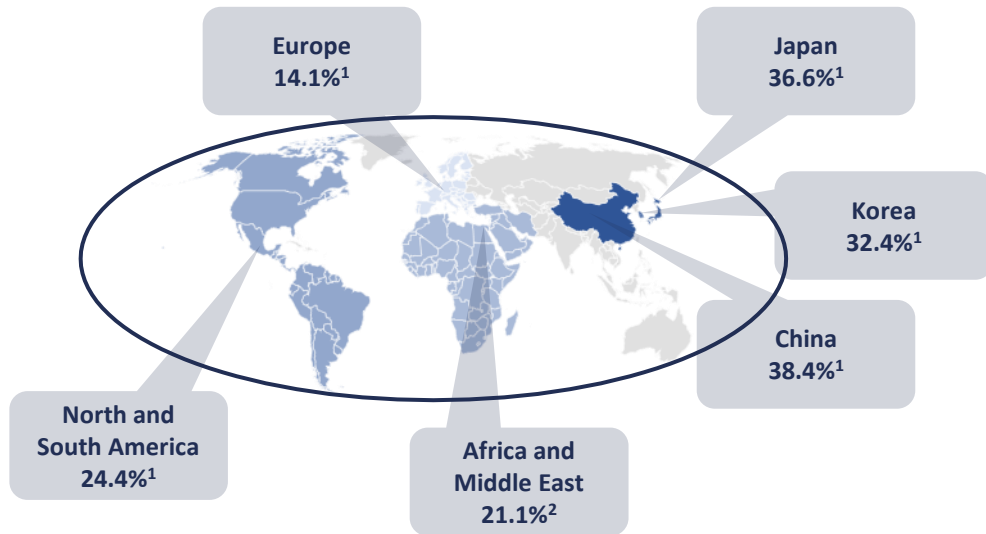
How do recent data in early-stage NSCLC impact the current treatment pathway for *EGFR*-mutant NSCLC?

Prof. Yi-Long Wu

Guangdong Lung Cancer Institute
Guangdong Provincial People's Hospital
Guangzhou, China



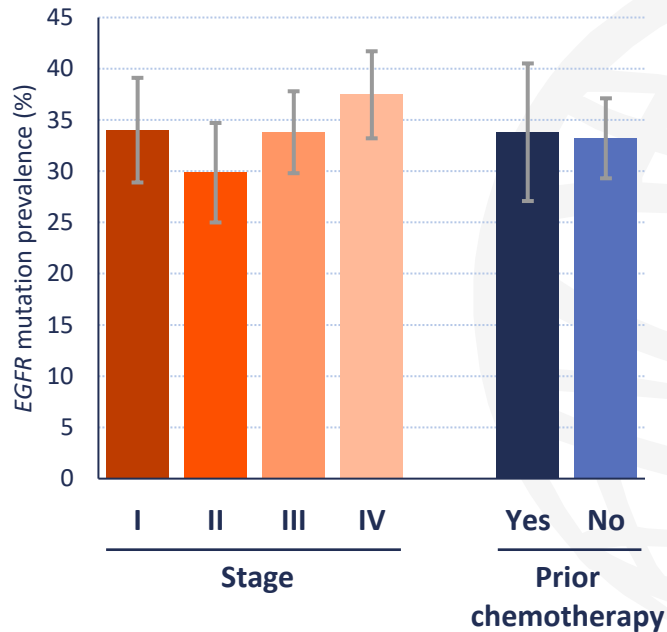
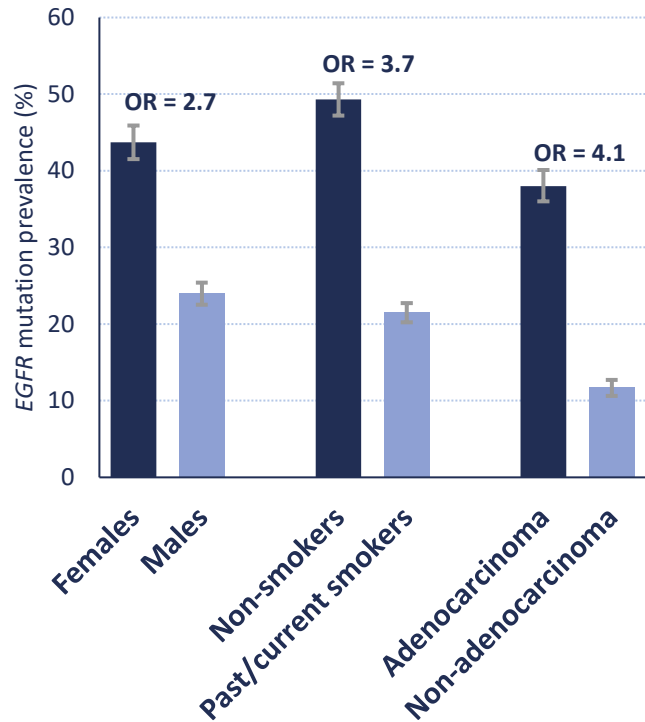
EGFR mutation prevalence



EGFR, epithelial growth factor receptor.

1. Zhang YL, et al. *Oncotarget*. 2016;7:78985–93; 2. Benbrahim Z, et al. *BMC Cancer*. 2018;18:891.

EGFR mutation prevalence



First-generation EGFR-TKIs in the adjuvant setting

RADIANT (NCT00373425, phase III)¹



N=161

- NSCLC stage IA – IIIA
- Completely resected
- EGFR-mutant tumours



- Erlotinib vs placebo

Adjuvant erlotinib did not improve DFS in EGFR-mutation positive tumours

SELECT (NCT00462995, phase II)²



N=100

- NSCLC stage IA–IIIA
- Completely resected
- Stratified by EGFR mutation



- Erlotinib

5-year DFS = 56% (95% CI, 45–66%)

5-year OS = 86% (95% CI, 77–92%)

ADJUVANT-CTONG1104 (NCT01405079, phase III)³



N=222

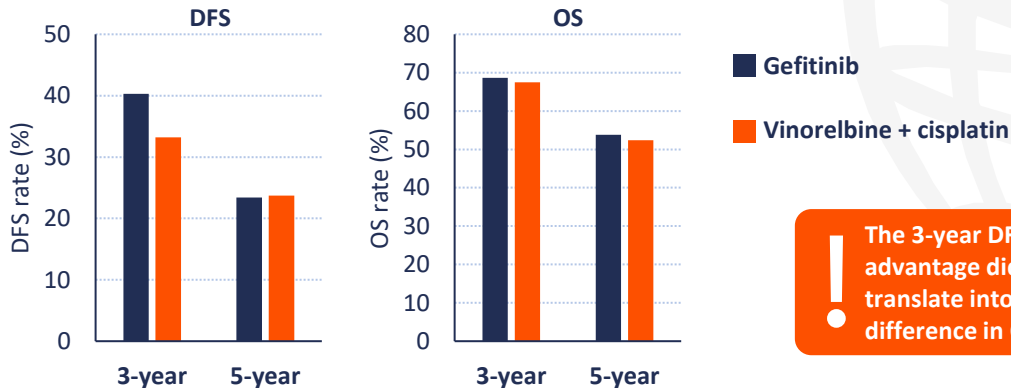
1:1

- NSCLC stage II–IIIA
- Completely resected
- EGFR-mutant tumours

Gefitinib (250 mg/day)
for 24 months

Vinorelbine (25 mg/m², day 1 and day 8)
+ cisplatin (75 mg/m², day 1)
every 3 weeks for 4 cycles

Median follow-up:
76.9 months



The 3-year DFS advantage did not translate into a difference in OS

DFS, disease-free survival; EGFR, epithelial growth factor receptor; NSCLC, non-small cell lung cancer; OS, overall survival; TKI, tyrosine kinase inhibitor.

1. Kelly K, et al. *J Clin Oncol.* 2015;33:4007–14; 2. Pennell NA, et al. *J Clin Oncol.* 2019;37:97–104; 3. Wu Y-L, et al. *J Clin Oncol.* 2020;38(15_Suppl):9005.

Osimertinib in the adjuvant setting

ADAURA (NCT02511106, phase III): Study designs and demographics

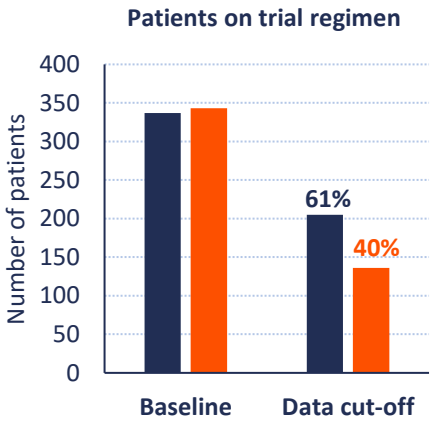
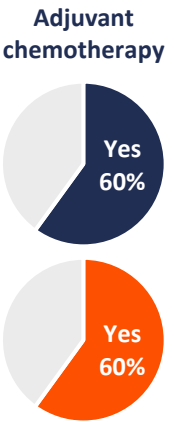
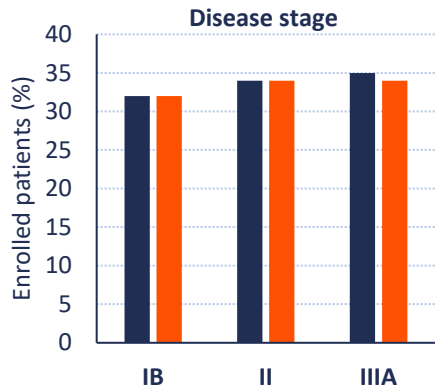


- Primary nonsquamous NSCLC
- Confirmed *EGFR* mutation (Ex19del or L858R)
- Postsurgical pathological stage IB, II or IIIA
- Postsurgical chemotherapy (if indicated)

N=682



- Primary end point:
 - DFS in patients with stage II–IIIA disease
- Secondary end points:
 - DFS in the overall population, OS, safety



■ Osimertinib

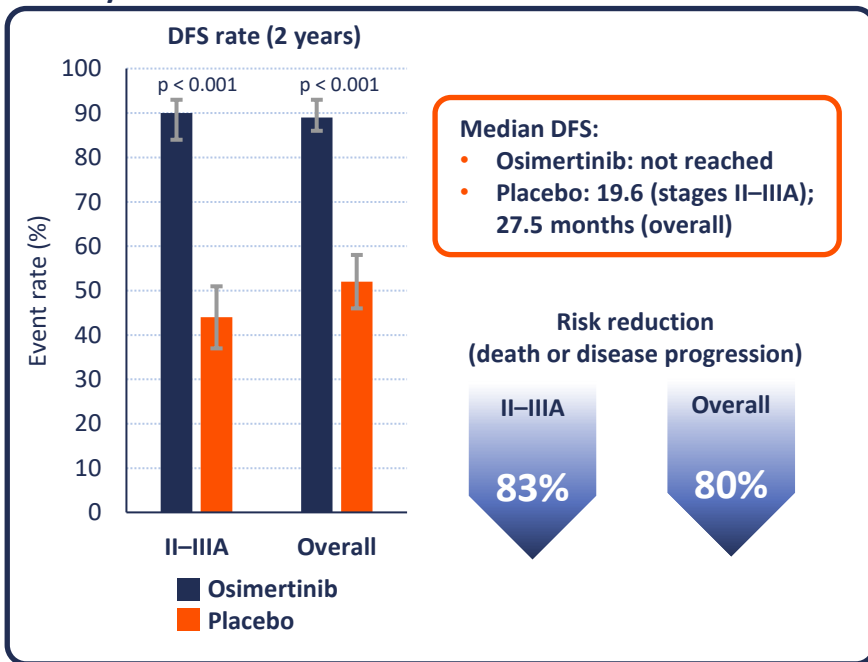
■ Placebo

DFS, disease-free survival; EGFR, epithelial growth factor receptor; NSCLC, non-small cell lung carcinoma; OS, overall survival.
Wu Y-L, et al. *N Engl J Med.* 2020;383:1711–23.

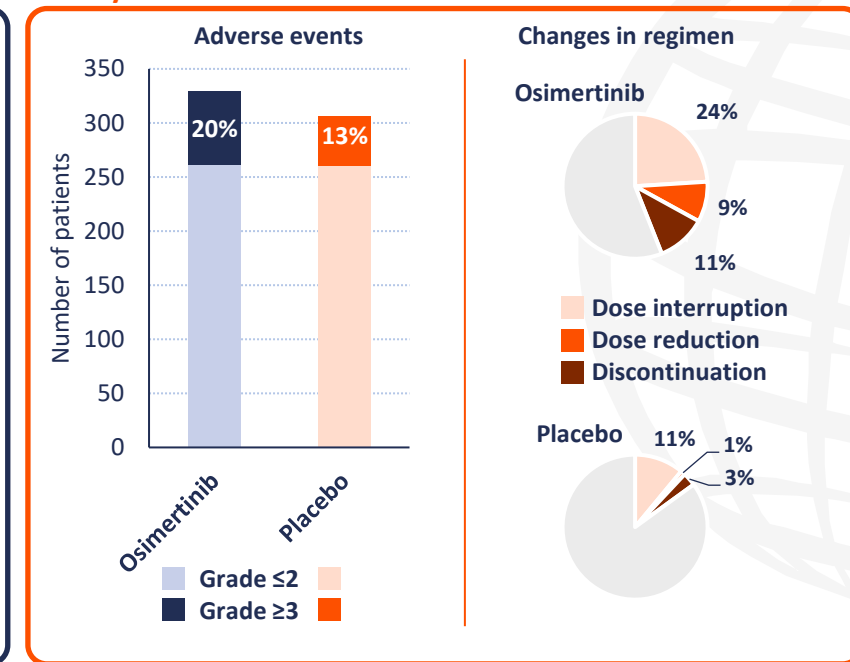
Osimertinib in the adjuvant setting

ADAURA (NCT02511106, phase III): Outcomes overview

Efficacy



Safety

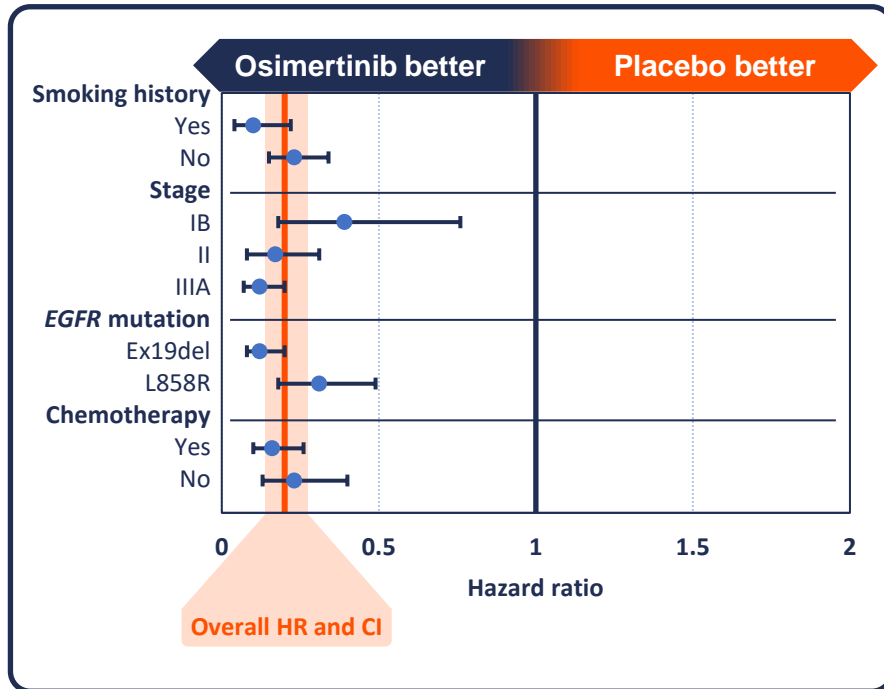


DFS, disease-free survival.

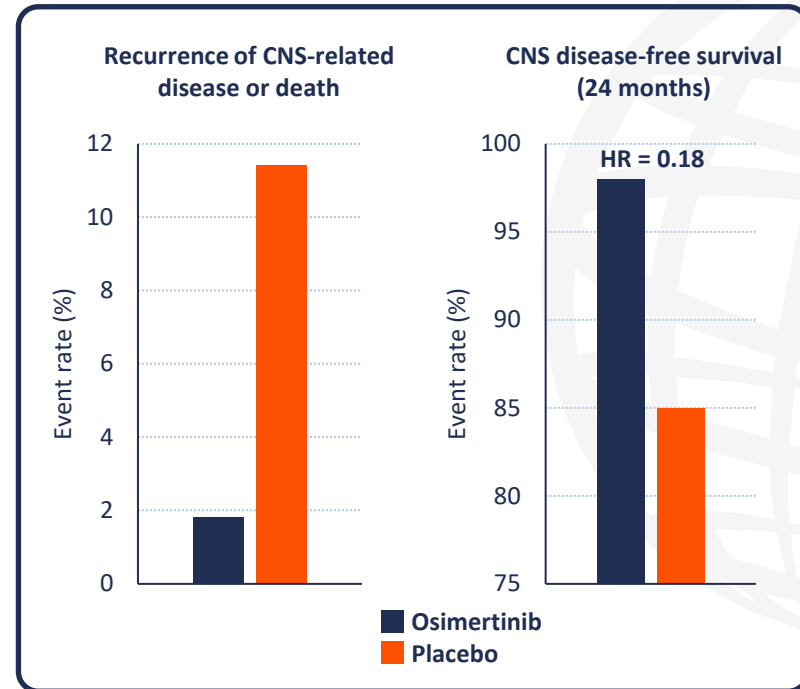
Wu Y-L, et al. *N Engl J Med.* 2020;383:1711-23.

ADAURA: Further analysis

Subgroup analysis



CNS metastasis



The evolving treatment algorithm of NSCLC

