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

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

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Manchester University Hospital
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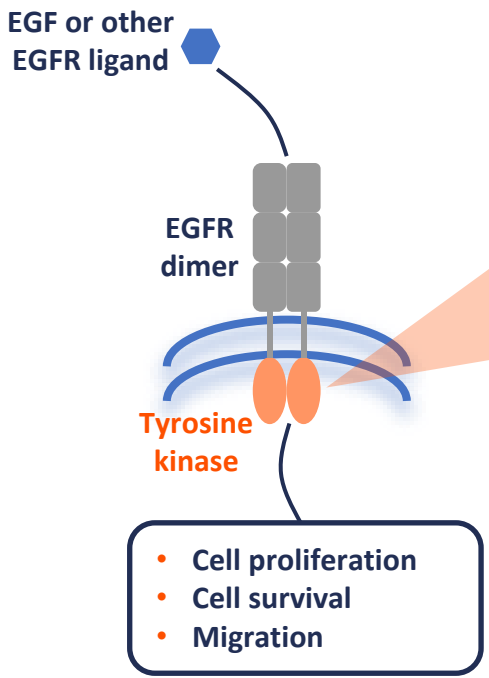
EGFR mutations in patients with NSCLC



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

EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

1. Passaro A, et al. *ESMO Open*. 2020;5:e000919; 2. O'Leary C, et al. *Pharmaceuticals.* 2020;13:273.

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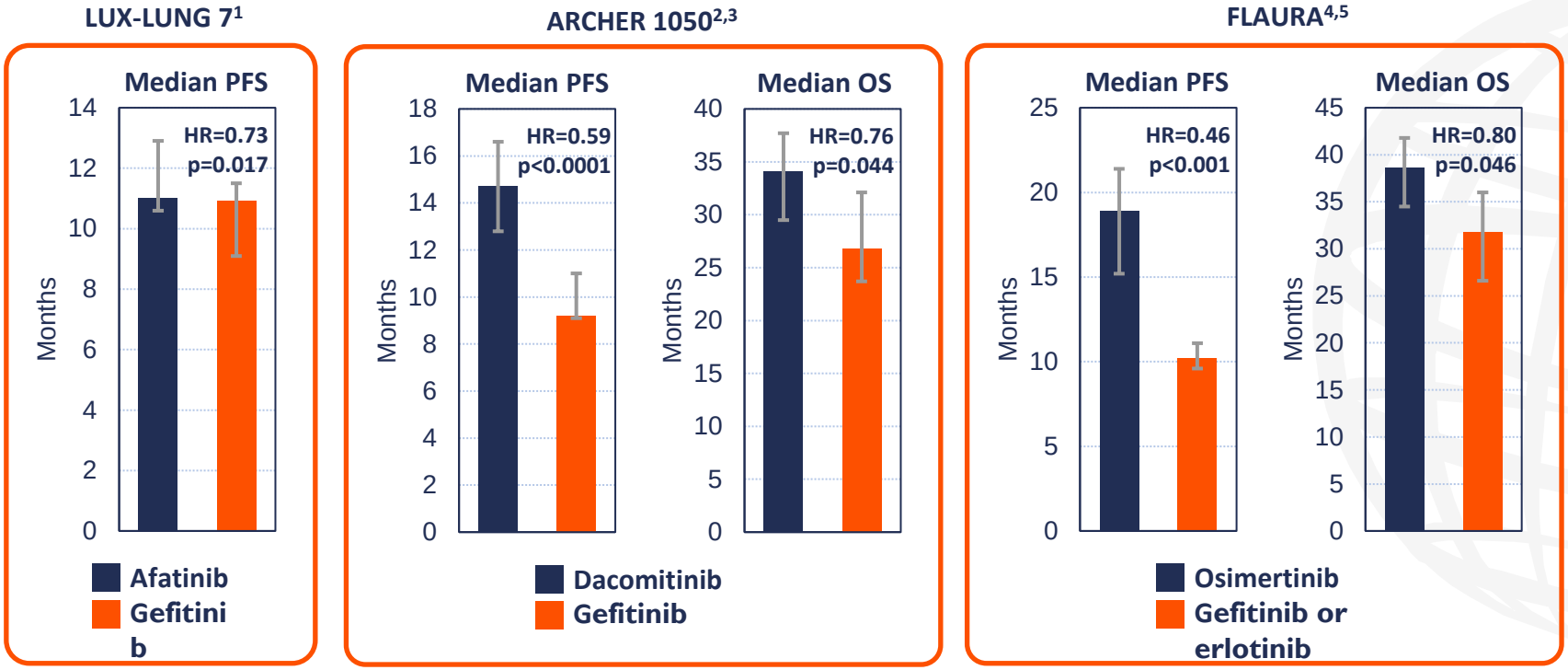
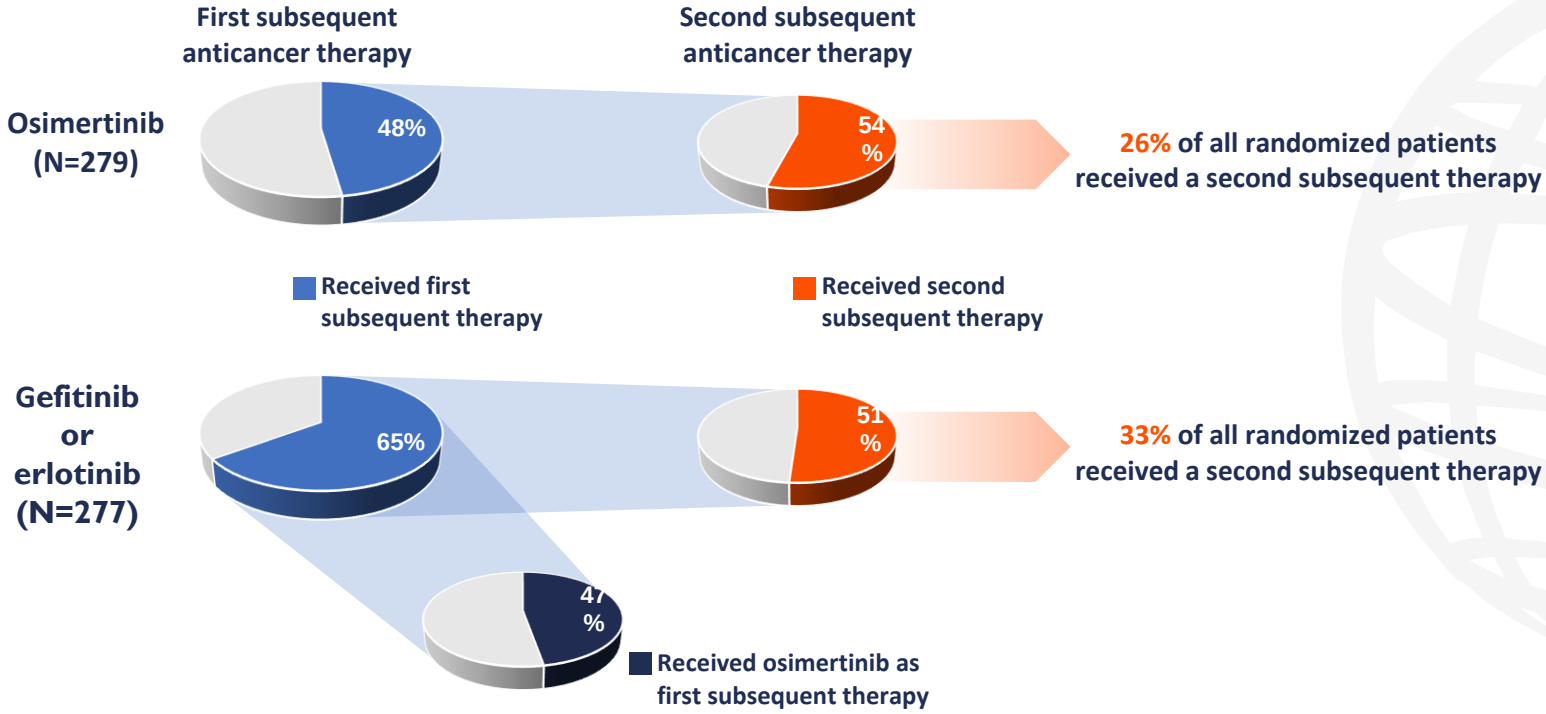
EGFR-TKI as first-line therapy for NSCLC



EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survical; 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



1. Ramalingam SS, et al. *N Engl J Med*. 2020;382:41–50.

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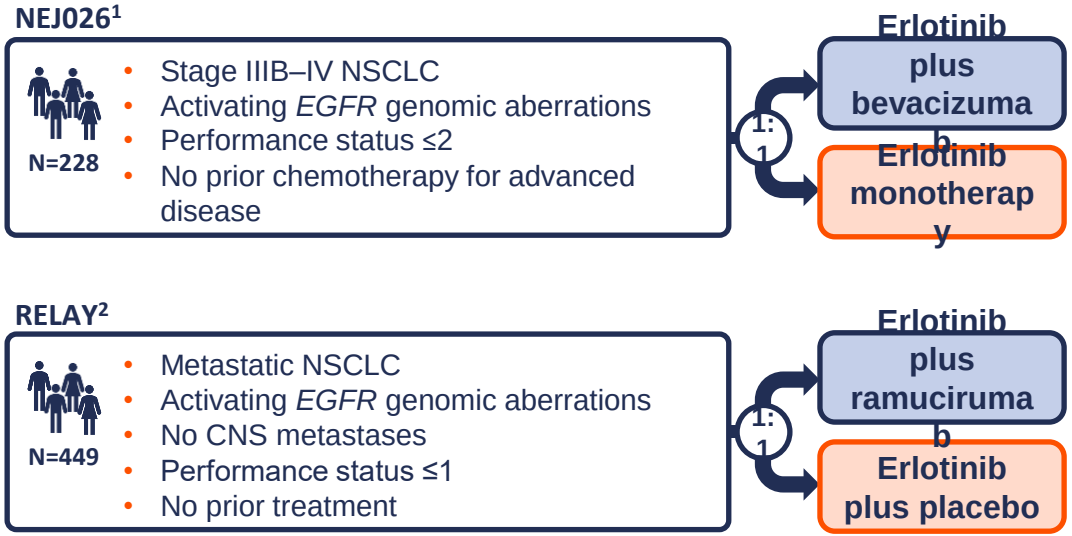
EGFR-TKI combined with anti-VEGF therapy

NEJ026 and RELAY: Study design



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.

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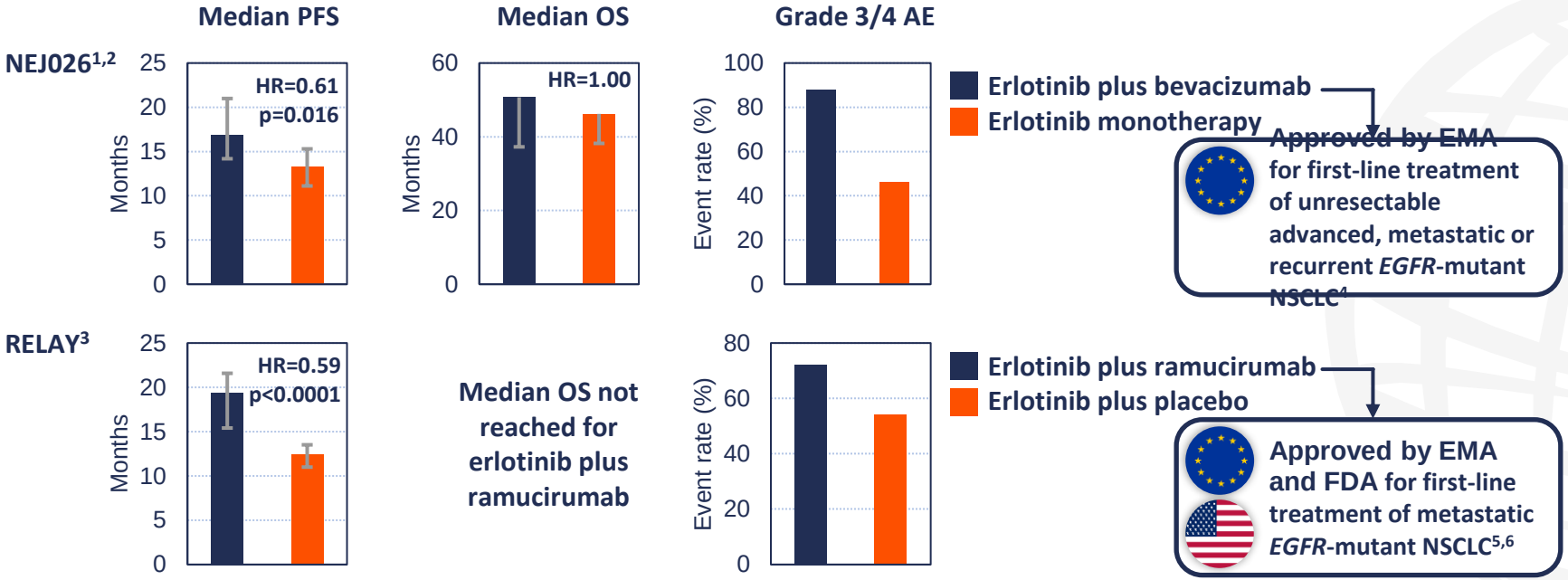
EGFR-TKI combined with anti-VEGF therapy



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.

1. 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;
4. EMA. Avastin (bevacizumab) infusion, SPC. 2020. Available at: www.ema.europa.eu/en/documents/product-information/avastin-epar-product-information_en.pdf;
5. EMA. Cyramza (ramucirumab) infusion, SPC. 2020. Available at: www.ema.europa.eu/en/documents/product-information/cyramza-epar-product-information_en.pdf;
6. FDA. Cyramza (ramucirumab) injection, PI 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/125477s034lbl.pdf. (PI and SPC accessed 4 Nov 2020).

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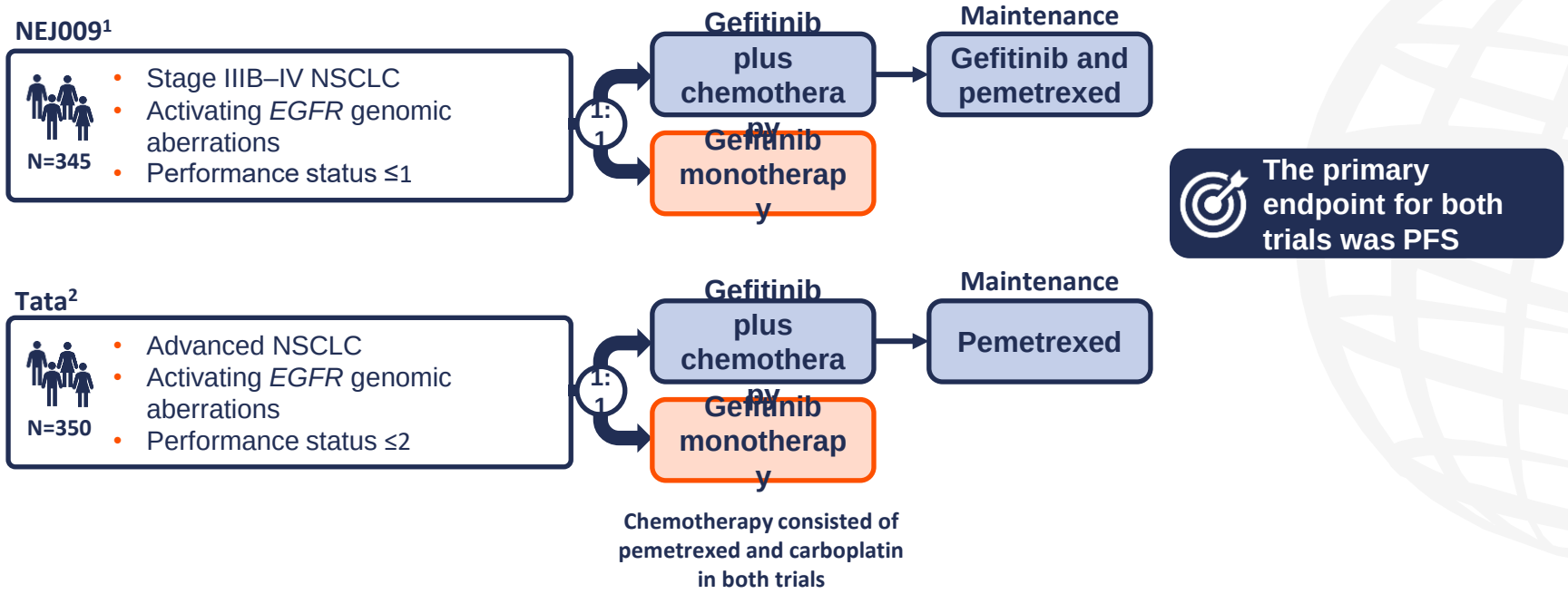
EGFR-TKI combined with chemotherapy

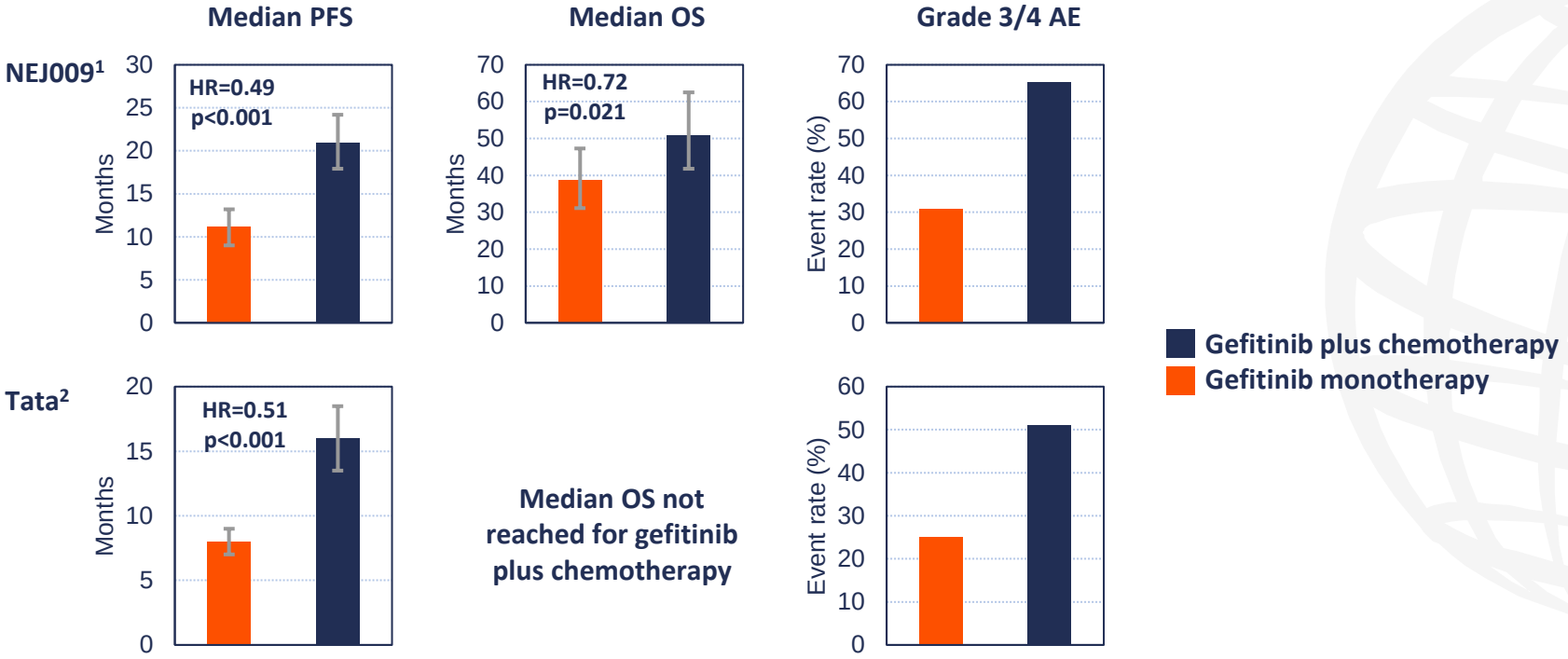
NEJ009 and Tata Memorial Centre: Study design



EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; 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.

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.

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Immunotherapy for *EGFR*-mutant NSCLC

NCT02879994[1]

Phase II trial of pembrolizumab in TKI-naive patients with *EGFR*-mutation positive, advanced NSCLC and PD-L1 positive (≥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.

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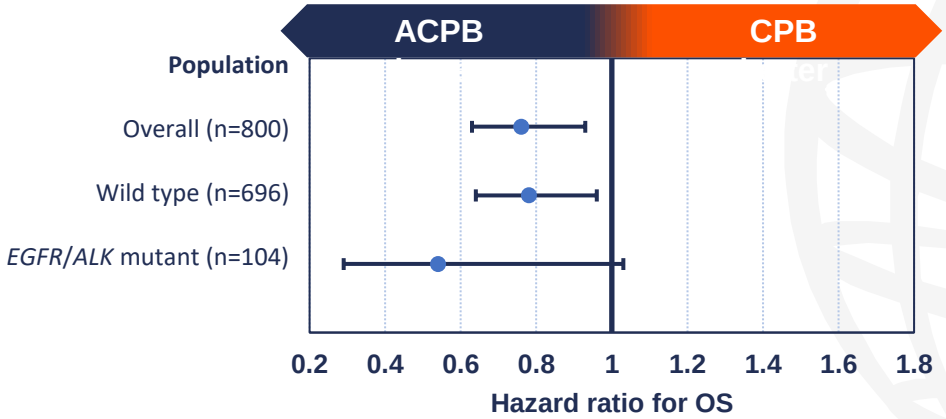
ICI, chemotherapy and anti-VEGF combination

IMpower150: Study design[1] and OS analysis[2]

- Stage IV or recurrent metastatic NSCLC
- No prior chemotherapy

N=400 → **ACPB**: Atezolizumab + carboplatin + paclitaxel + bevacizumab

N=400 → **CPB**: Carboplatin + paclitaxel + bevacizumab



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.

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

Prof. Lecia Sequist

Harvard Medical School
Massachusetts General Hospital
Boston, MA, USA

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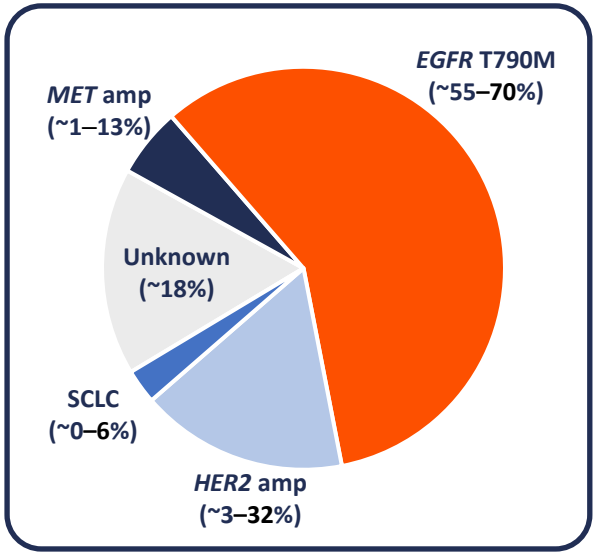
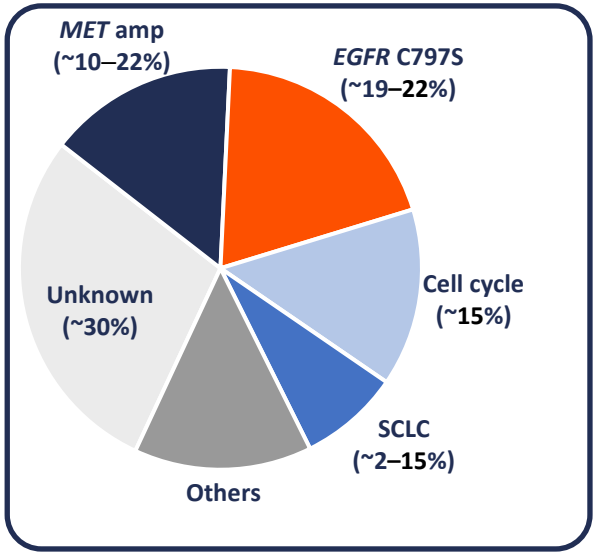
Mechanisms of resistance to EGFR-TKIs

Resistance to EGFR-TKIs is complex and setting-dependent

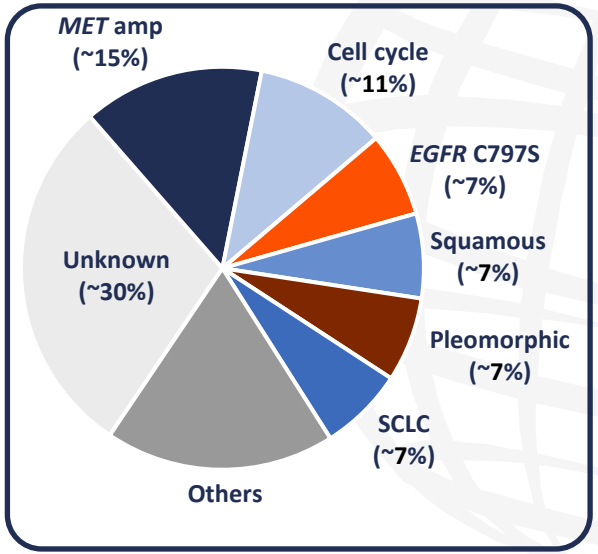
First-line first and second generation EGFR-TKIs[1]



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.

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EGFR-TKIs + MET inhibitors

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

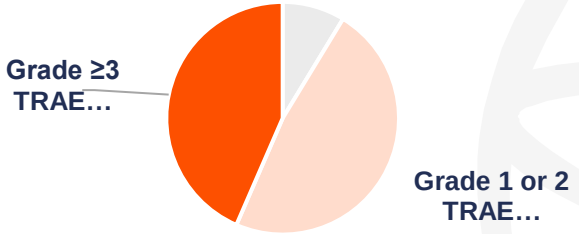
Study design

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



Anti-tumour activity

ORR

52%

Median DoR

7.1 months

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.

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EGFR-TKIs + MET inhibitors

Capmatinib[1]

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

- **ORR = 29%**

Tepotinib[2]

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

- **ORR = 66.7%**

Nazartinib[3]

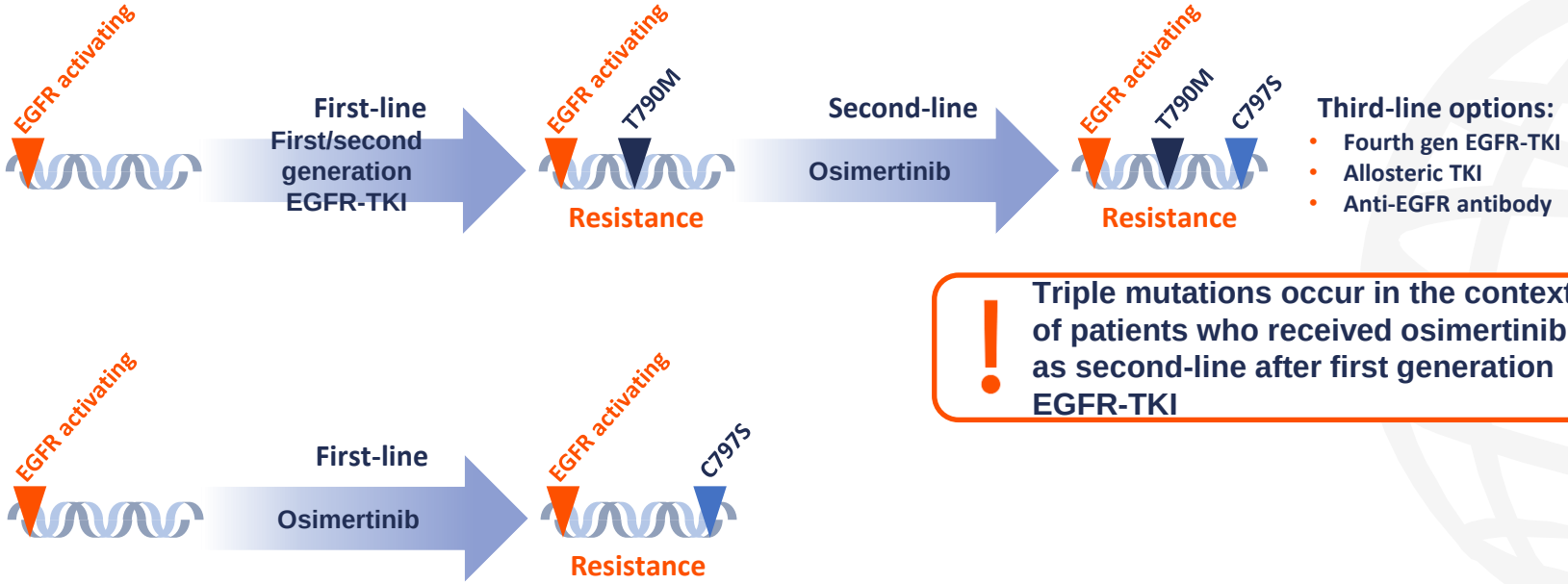
- **NCT02335944 (phase Ib/II)**
- Combination with capmatinib
- *EGFR*-mutant NSCLC:
  - Previous-line resistant
  - Any T790M/*MET*

- **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



! Triple mutations occur in the context of patients who received osimertinib as second-line after first generation EGFR-TKI

Ab, antibody; EGFR, epithelial growth factor receptor; gen, generation; TKI, tyrosine kinase inhibitor.

Leonetti A, et al. *Br J Cancer*. 2019;121:725–37.

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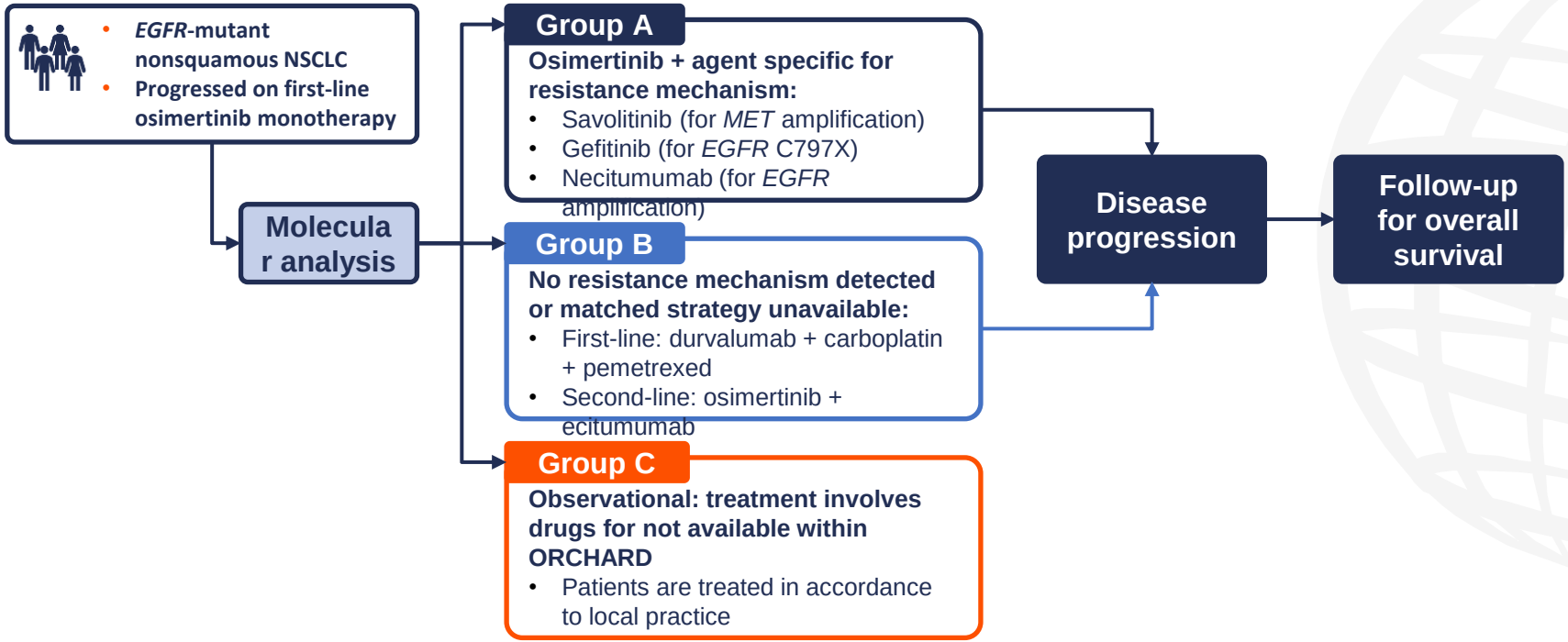
The ORCHARD trial

Study design



EGFR, epithelial growth factor receptor; MET, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer.

Yu H, et al. *J Thorac Oncol*. 2019;14:S647.

Emerging therapeutic agents

Amivantamab[1]
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)

U3-1402[2]
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

- **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.

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

Prof. Yi-Long Wu

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Guangzhou, China

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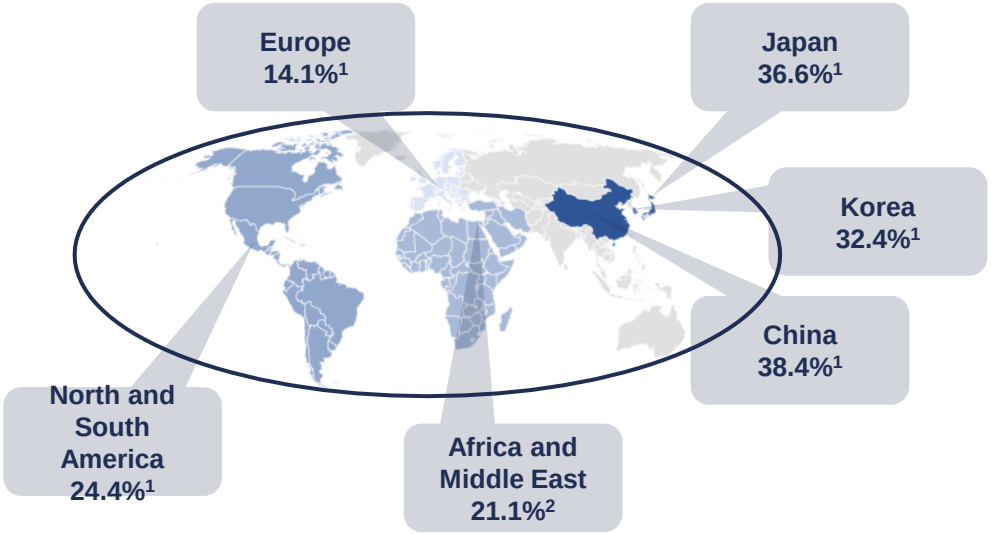
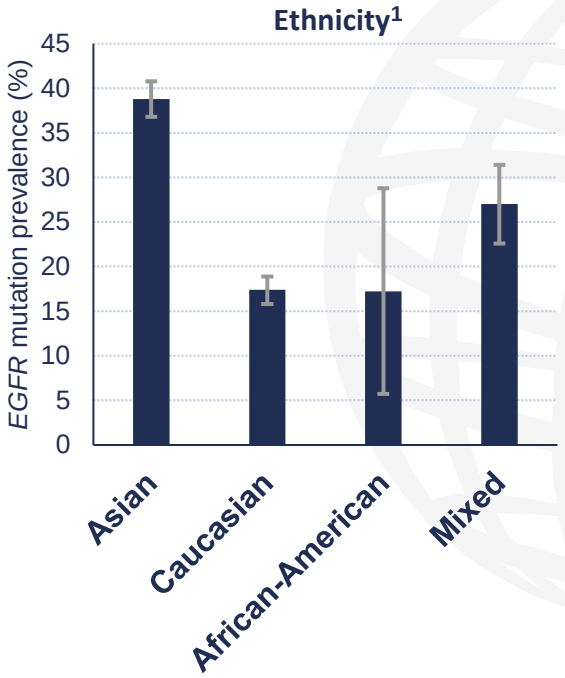
EGFR mutation prevalence





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.

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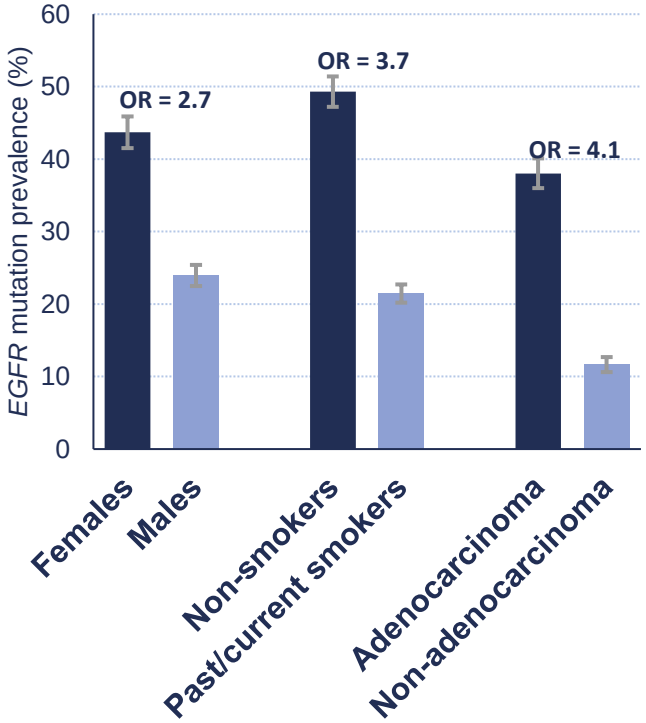
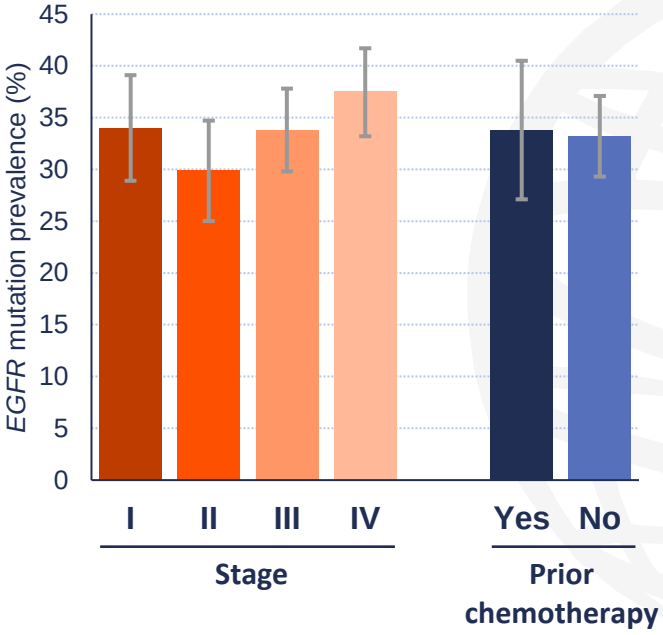
EGFR mutation prevalence





EGFR, epithelial growth factor receptor; OR, odds ratio.

Zhang YL, et al. *Oncotarget*. 2016;7:78985–93.

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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]

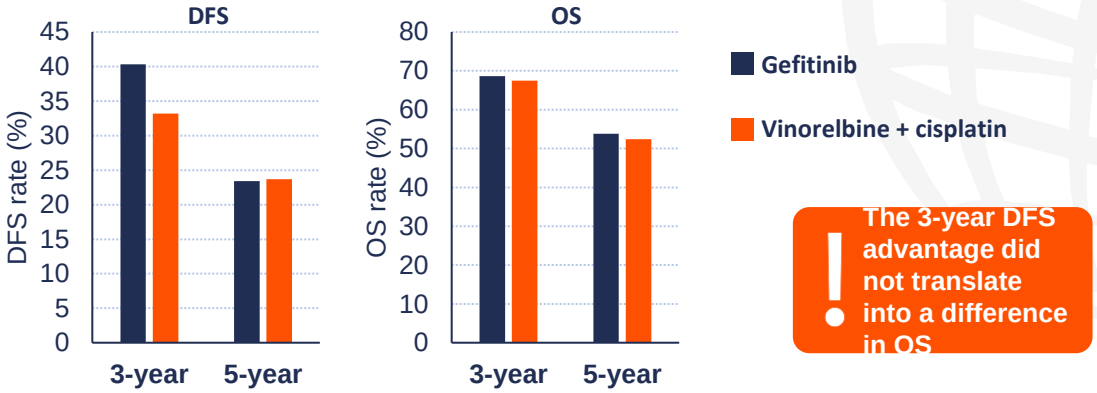
N=222

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

1:1

- Gefitinib (250 mg/day) for 24 months
- Vinorelbine (25 mg/m^2, day 1 and day 8) + cisplatin (75 mg/m^2, 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.

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Osimertinib in the adjuvant setting

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

N=682

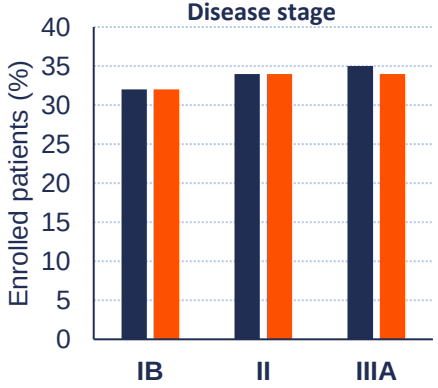
- Primary nonsquamous NSCLC
- Confirmed *EGFR* mutation (Ex19del or L858R)
- Postsurgical pathological stage IB, II or IIIA
- Postsurgical chemotherapy (if indicated)

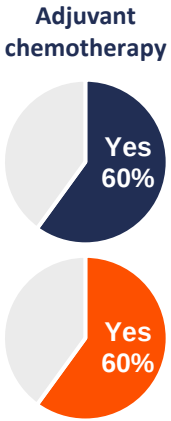
1:1

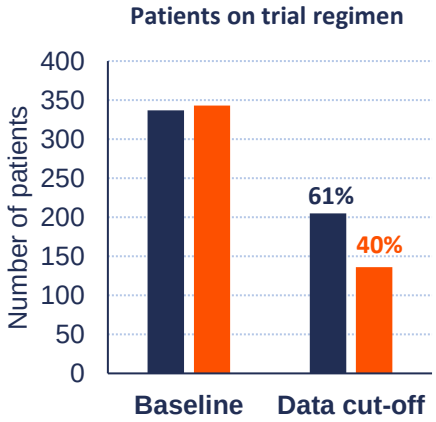
- Osimertinib (80 mg once daily)
- Placebo

Treatment duration: 3 years

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







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.

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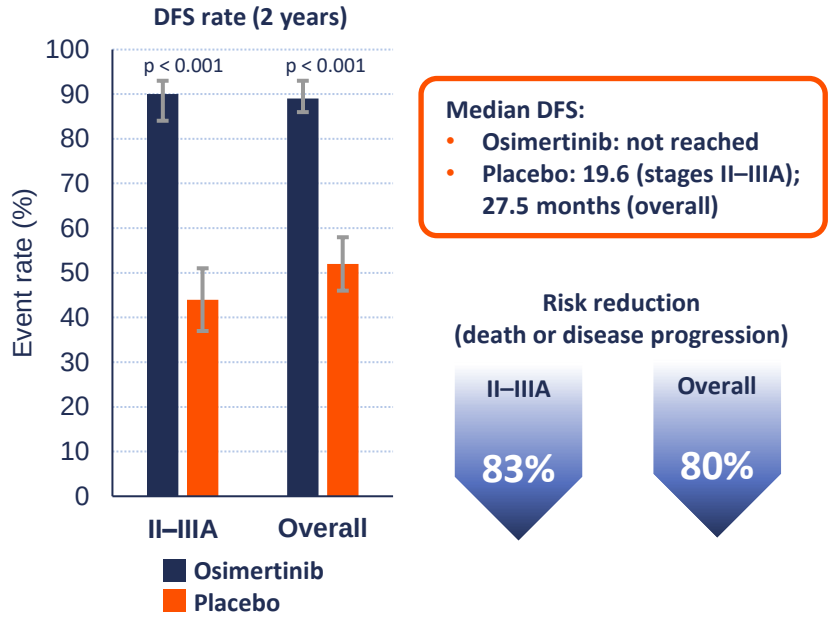
Osimertinib in the adjuvant setting

ADAURA (NCT02511106, phase III): Outcomes overview

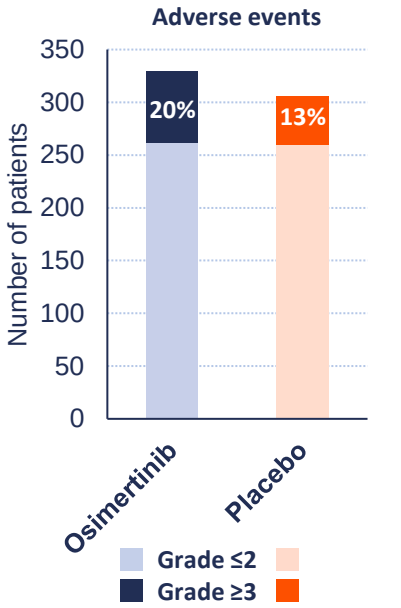
Efficacy

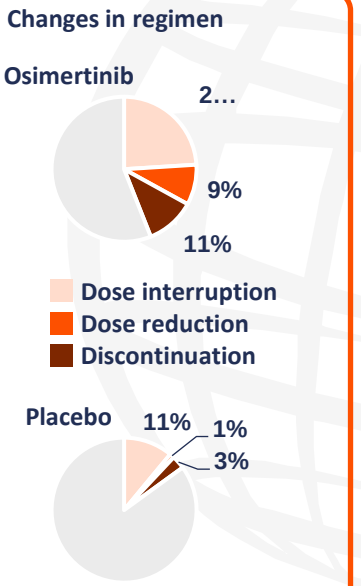


Median DFS:
- **Osimertinib: not reached**
- **Placebo: 19.6 (stages II–IIIA); 27.5 months (overall)**

Risk reduction (death or disease progression)

Safety





DFS, disease-free survival.

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

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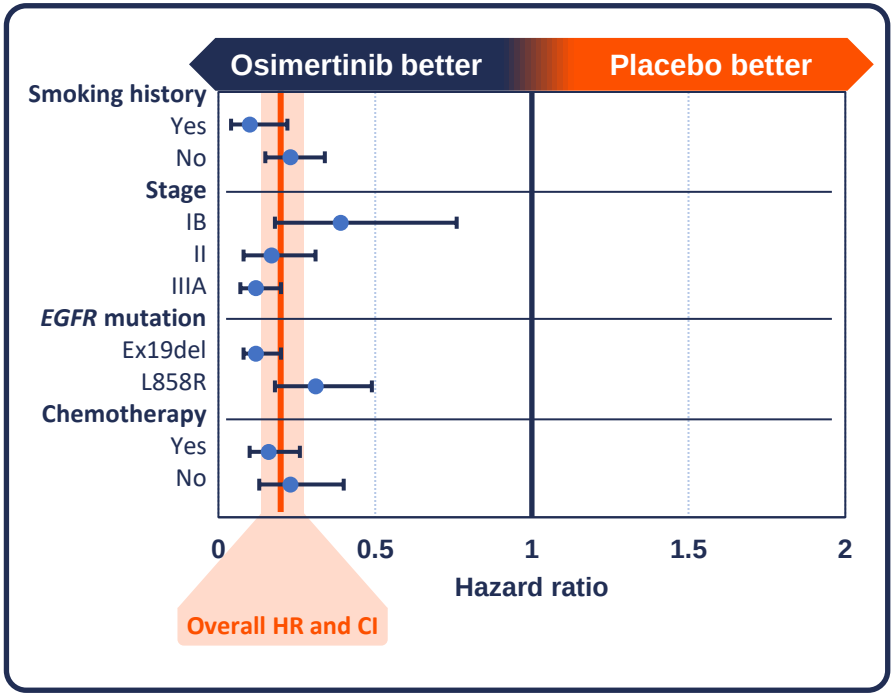
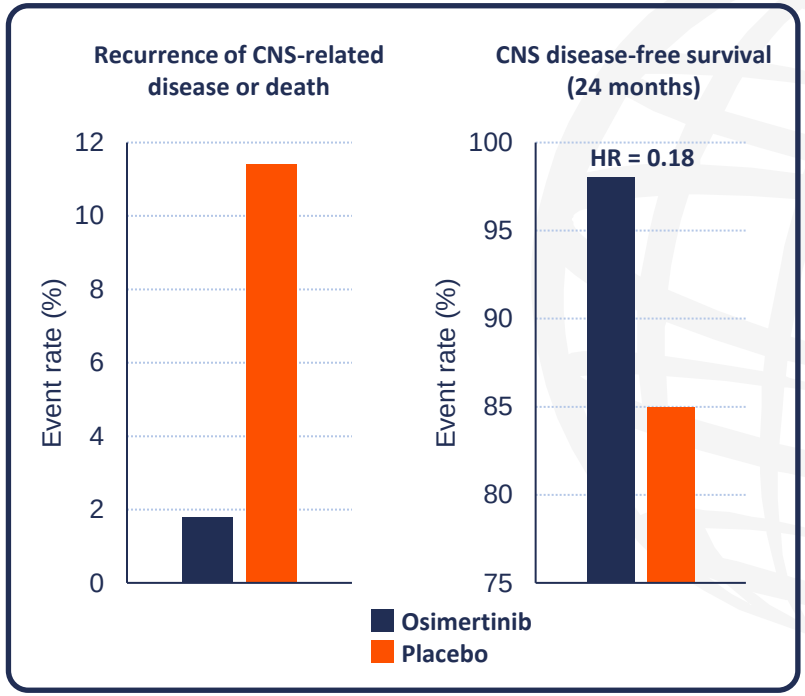
ADAURA: Further analysis

Subgroup analysis



CNS metastasis



CI, confidence interval; CNS, central nervous system; EGFR, epithelial growth factor receptor; HR, hazard ratio.

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

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The evolving treatment algorithm of NSCLC

Diagnosis → Staging → Surgery → Therapy → Follow-up

Genetic testing

- EGFR
- ALK
- MET
- PD-L1

- Early targeted therapy
- Acquired resistance
- Adjuvant therapy
- Immunotherapy
- Treatment of metastatic disease

ALK, anaplastic lymphoma kinase; EGFR, epithelial growth factor receptor; MET, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand-1.

National Institute for Health and Care Excellence (UK). Guideline, No. 122. Available at: www.ncbi.nlm.nih.gov/books/NBK558777 (accessed 11 Nov 2020).

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