Treatment of EGFR driver mutations in advance metastatic non small cell lung cancer

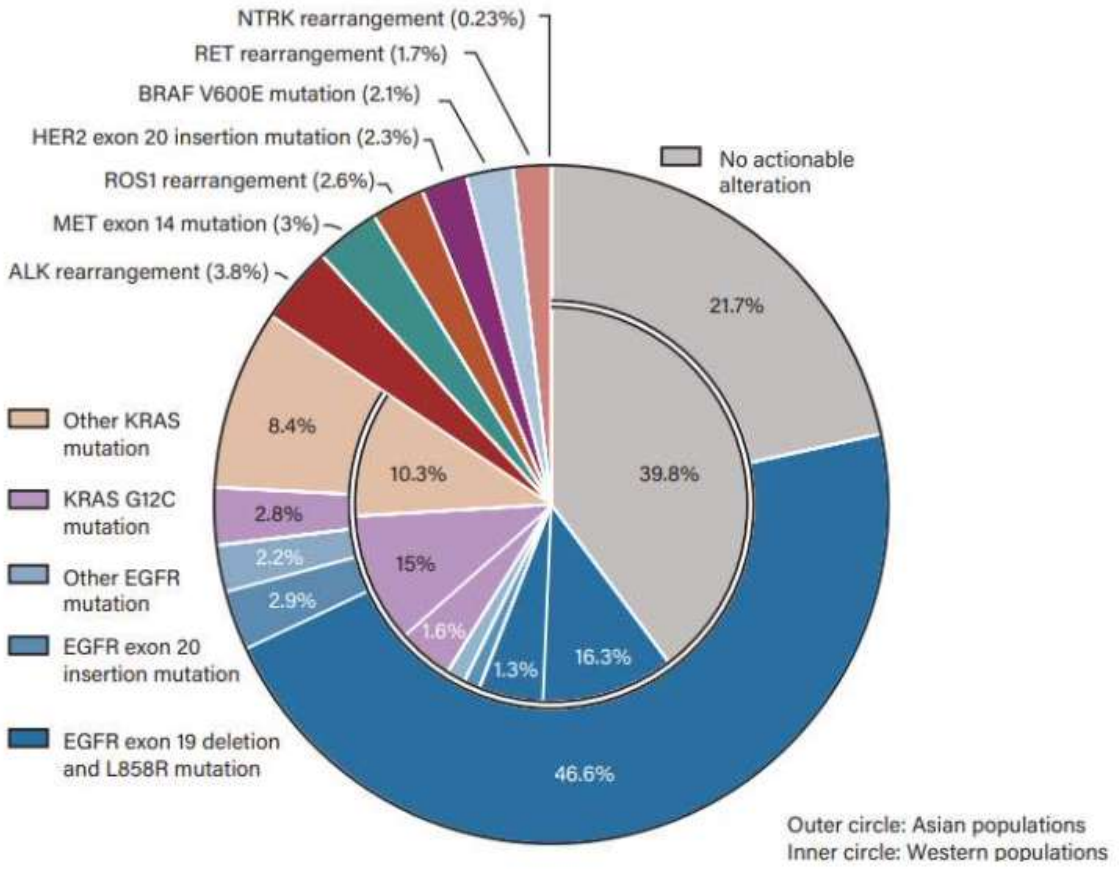
Dr. Ankit

Senior Resident

Oncogenic driver alterations

- Oncogenic driver alterations refer to mutations that are responsible for both the initiation and maintenance of the cancer
- Driver alterations lead to gain of function of oncogenes or loss of function of tumor suppressor genes
- These alterations are often found in genes that encode for signaling proteins that are critical for maintaining normal cellular proliferation and survival
- Some lung cancers harbor specific somatic alterations that are essential for malignant growth

Oncogenic driver mutations - overall

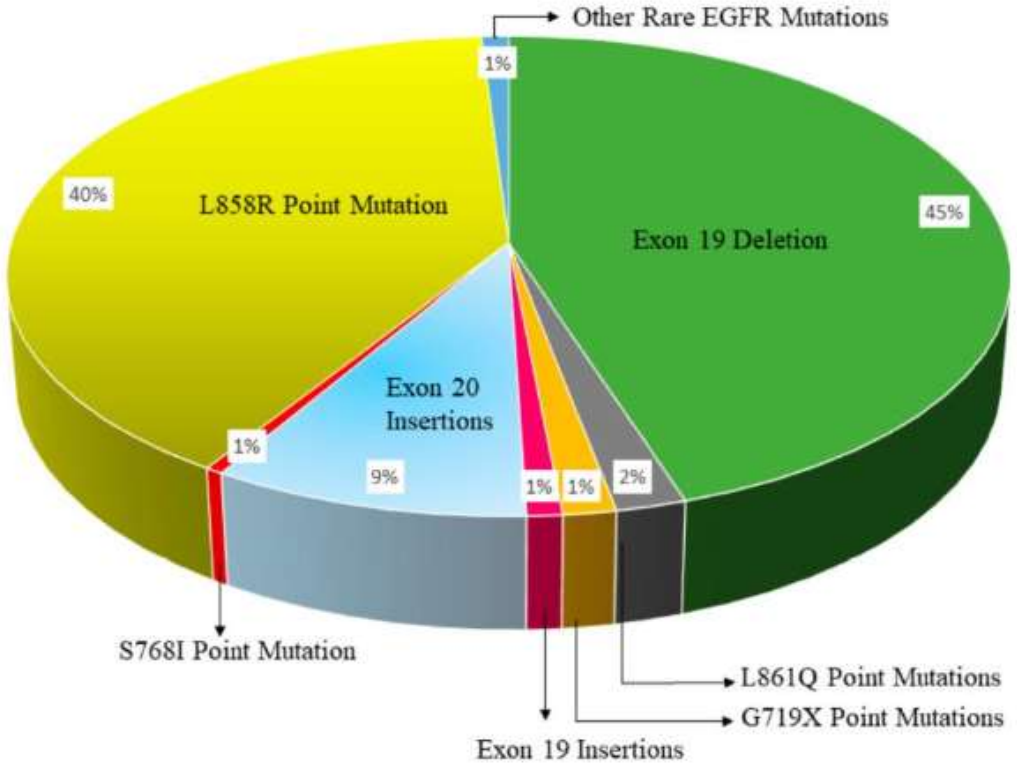


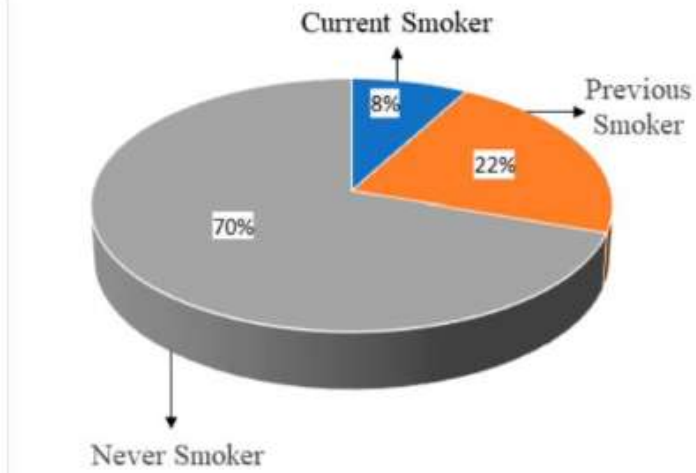
Journal of Clinical Oncology 2022 40:6, 611-625

Treatment of EGFR driver mutations

- Common EGFR mutations
- Uncommon EGFR mutations
- Exon 20 insertions

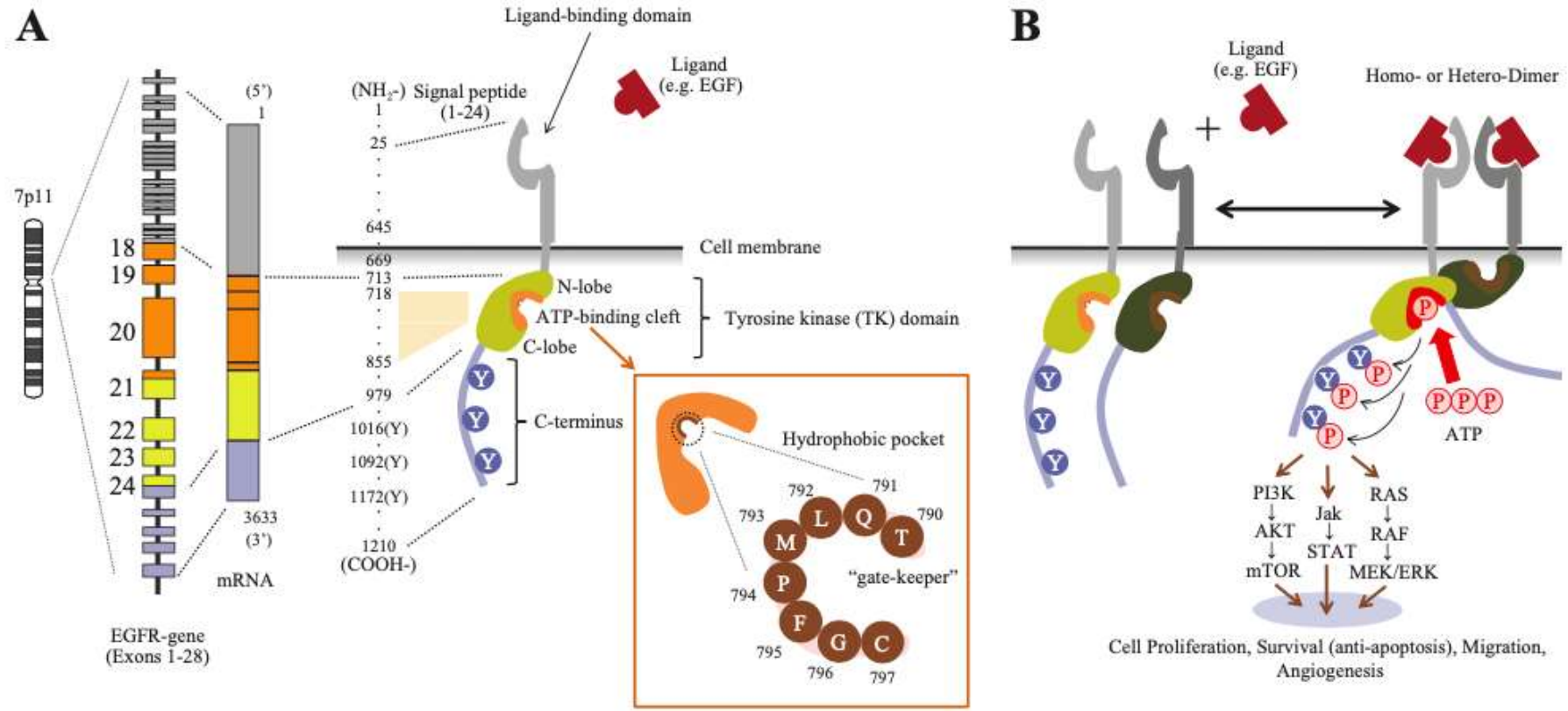
FREQUENCY OF EGFR MUTATIONS IN LUNG ADENOCARCINOMA





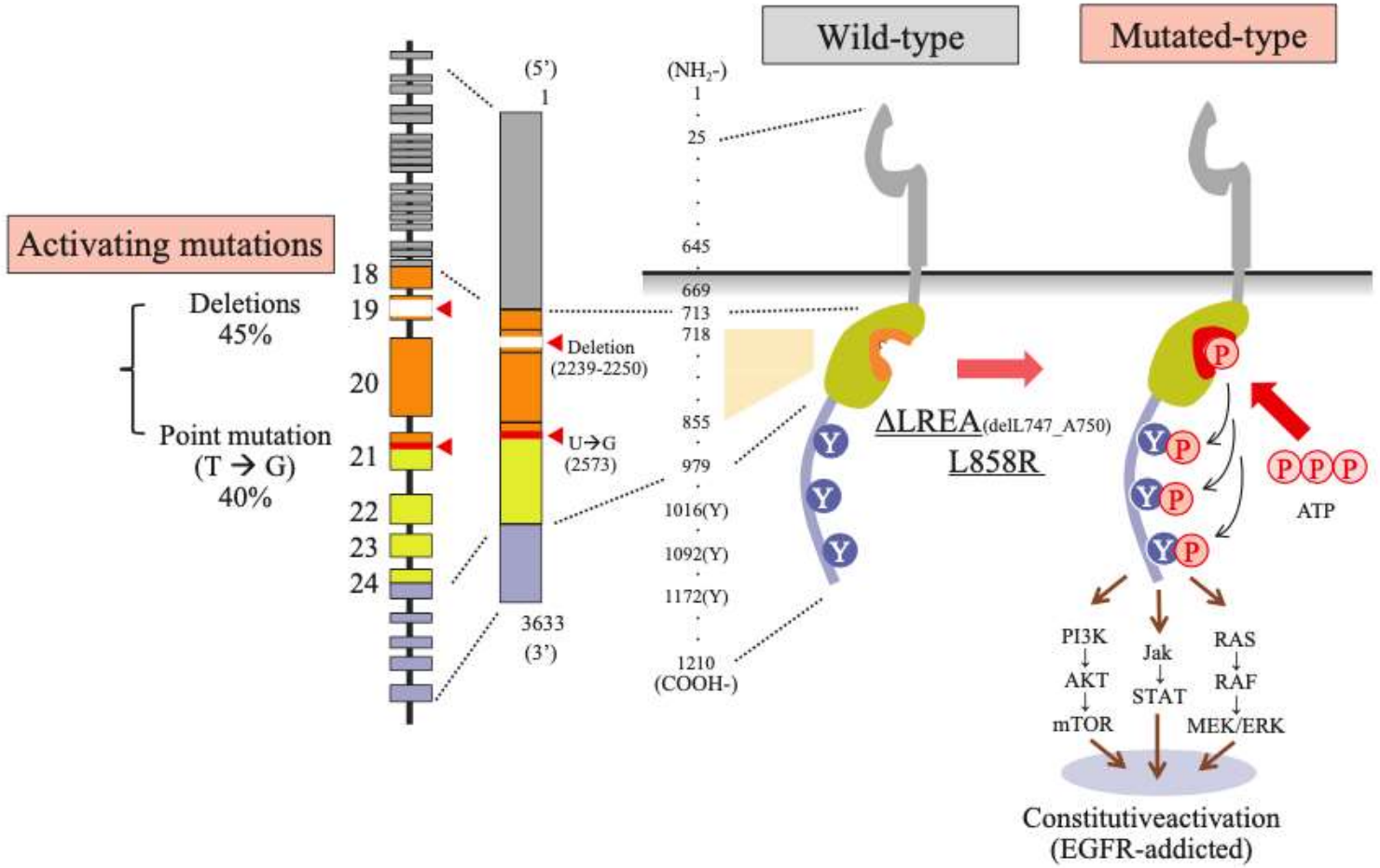
Khaddour K, *et al.* Cancers (Basel) 2021;13(13):3164

Structure and function of wild-type epidermal growth factor receptor (EGFR)



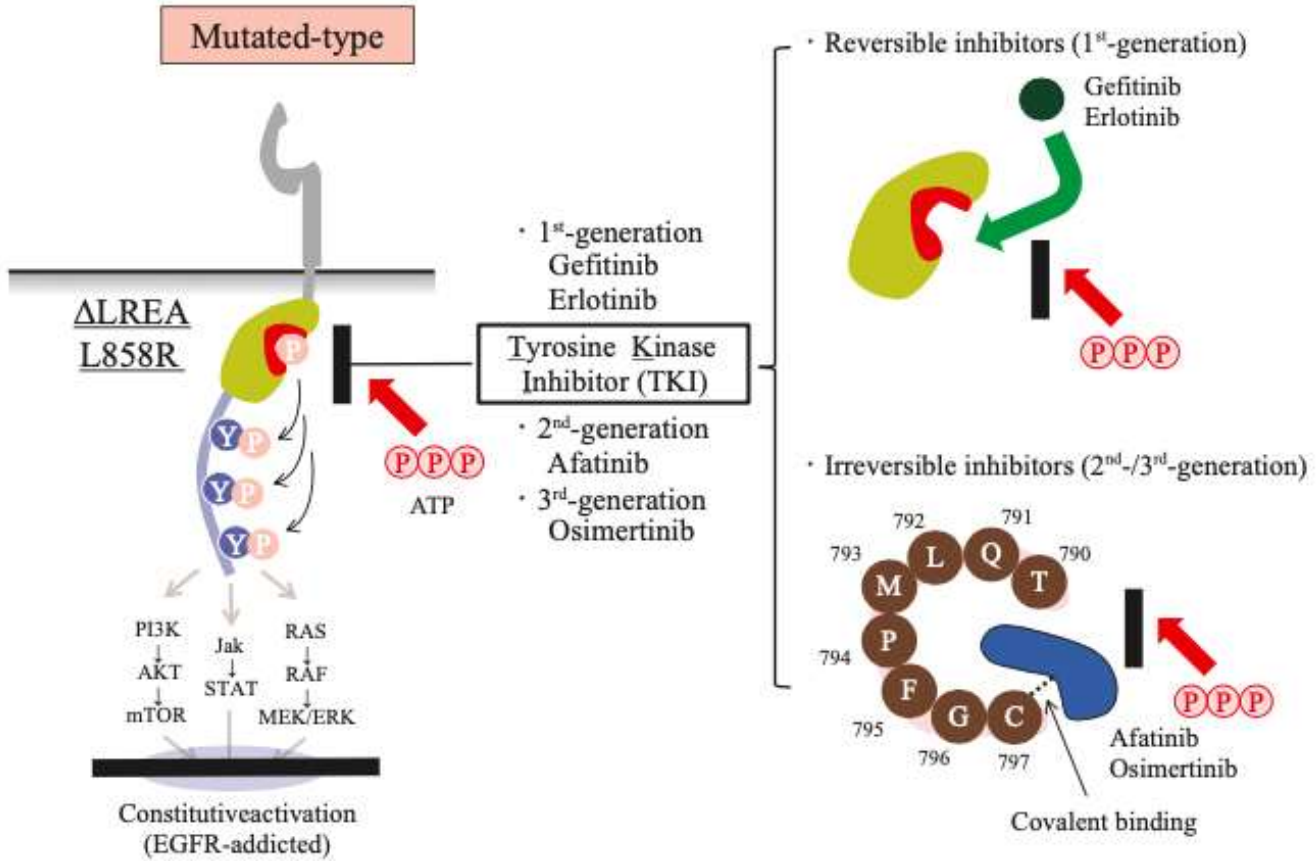
J UOEH. 2019;41(2):153-163

Oncogenic mutations in the epidermal growth factor receptor (EGFR) gene



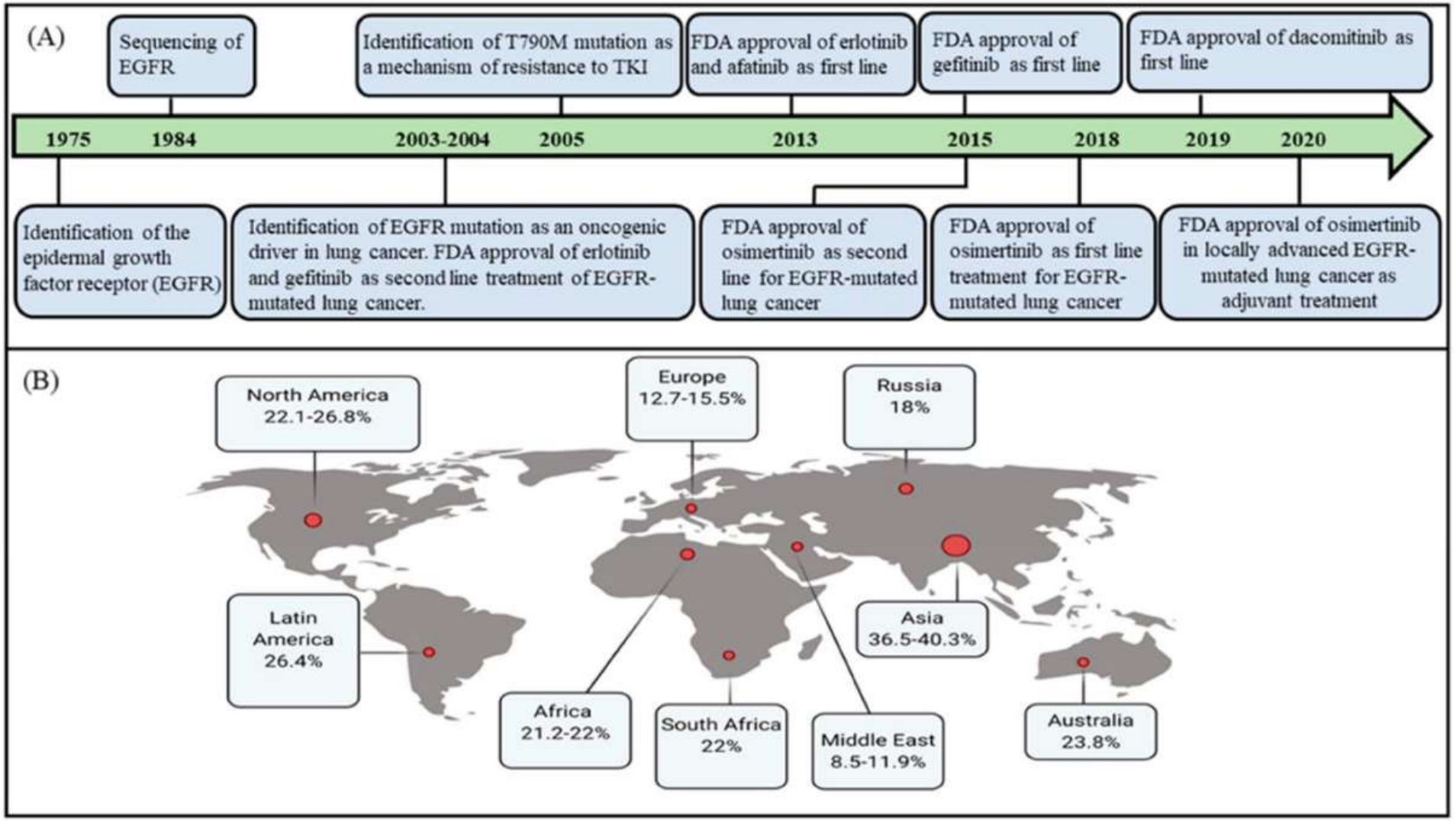
J UOEH. 2019;41(2):153-163

Tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR)



J UOEH. 2019;41(2):153-163

Timeline of EGFR TKI and development of different generations of TKI



Treatment of common EGFR mutations

Breakthrough in targeted therapy for Non small cell lung cancer

Comparison of EGFR-TKI with chemotherapy on first-line treatment

Study	EGFR-TKL	Chemotherapy	Median PFS (month)	ORR (%)	Median OS (month)
IPASS (phase III)	Gefitinib (n=132)	Carboplatin + paclitaxel (n=129)	9.8 vs 6.4 (HR 0.48; P<0.001)	71.2 vs 47.3	21.6 vs 21.9 (HR 1.00; P=0.99)
First-SIGNAL (phase III)	Gefitinib (n=26)	Cisplatin + gemcitabine (n=16)	8.0 vs 6.3 (HR 0.54; P=0.086)	84.6 vs 37.5	27.2 vs 25.6 (HR 1.04)
NEJ002 (phase III)	Gefitinib (n=114)	Carboplatin + paclitaxel (n=114)	10.8 vs 5.4 (HR 0.30; P<0.001)	73.7 vs 30.7	27.7 vs 26.6 (HR 0.89; P=0.48)
WJT0G3405 (phase III)	Gefitinib (n=86)	Cisplatin + docetaxel (n=86)	9.2 vs 6.3 (HR 0.489; P<0.0001)	62.1 vs 32.2	36.0 vs 39.0 (HR 1.25)
OPTIMAL (phase III)	Erlotinib (n=82)	Carboplatin + gemcitabine (n=72)	13.1 vs 4.6 (HR 0.16; P<0.0001	83.0 vs 36.0	22.8 vs 27.2 (HR 1.19; P=0.27)
EURTAC (phase III)	Erlotinib (n=86)	Cisplatin + docetaxel (n=87)	9.7 vs 5.2 (HR 0.37; P<0.0001)	64.0 vs 18.0	19.3 vs 19.5 (HR 1.04; P=0.87)
CONVINCE (phase III)	Icotinib (n=148)	Cisplatin + pemetrexed (n=137)	11.2 vs 7.9 (HR 0.37; P=0.0006)	NR	30.5 vs 32.1 (P=0.89)
LUX-Lung 3 (phase III)	Afatinib (n=230)	Cisplatin + pemetrexed (n=115)	11.1 vs 6.9 (HR 0.58; P=0.001)	56.1 vs 22.6	28.2 vs 28.2 (HR 0.88; P=0.39)
LUX-Lung 6 (phase III)	Afatinib (n=242)	Gemcitabine + cisplatin (n=122)	11.0 vs 5.6 (HR 0.28; P<0.0001)	66.9 vs 23.0	23.1 vs 23.5 (HR 0.93; P=0.61)

Biomed Pharmacother. 2021 Jan;133:111079

Afatinib versus Gefitinib

Afatinib versus Gefitinib

LUX – LUNG 7	PFS	OS	Tumor response	Time to treatment failure	Exploratory analysis PFS at 18 months	Exploratory analysis PFS at 24 months
Afatinib	11 months [95% CI 10·6–12·9]	27·9 months (95% CI 25·1–32·2)	112 (70%) (n = 160)	13·7 months [95% CI 11·9–15·0]	27·3% [95% CI 20·2–34·9]	17·6% [95% CI 11·7–24·6
Gefitinib	10·9 months [9·1–11·5]	25·0 months (20·6–29·3)	89 (56%) (n = 159)	11·5 months [10·1–13·1]	15·2% [95% CI 9·3–22·5]	7·6% [95% CI 3·5–13·8]
	HR - 0·73 [95% CI 0·57–0·95], p=0·017)			HR 0·73 [95% CI 0·58–0·92], p=0·0073)		

Lancet Oncol. 2016 May;17(5):577-89

Dacomitinib versus erlotinib

Dacomitinib versus erlotinib in patients with EGFR-mutated advanced nonsmall-cell lung cancer (NSCLC): pooled subset analyses from two randomized trials

ARCHER 1009 & A7471028 (n= 121)	Progression Free Survival	Overall Survival	Tumor response
Dacomitinib (n=66)	10.9 months (95% CI 7.4–17.4)	26.6 months (95% CI 21.6–41.5)	62.1% with 95% CI 49.3% to 73.8%)
Erlotinib (n=55)	9.6 months (95% CI 7.4–11.3)	23.2 months (95% CI 16.0–31.8) for erlotinib	60.0% with 95% CI 45.9% to 73.0%
	HR was 0.815 (95% CI 0.542–1.224) P=0.320	HR was 0.737 (95% CI 0.431–1.259) P=0.265	

Ann Oncol. 2016 Mar;27(3):423-9

Dacomitinib versus Gefitinib

Dacomitinib versus gefitinib as first-line treatment for patients with *EGFR*-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial

ARCHER 1050 (Phase 3 open label RCT) (N= 452)	Progression Free Survival	Overall Survival	Tumor response
Dacomitinib (n=227)	14·7 months (95% CI 11·1–16·6)	34.1 months (29.5 – 37.7)	76%; (95% CI 68–83)
Gefitinib (n=225)	9·2 months (9·1–11·0)	26.8 months (23.7 – 32.1)	70%; (95% CI 61–78)
	hazard ratio 0·59, 95% CI 0·47–0·74; p<0·0001)	0.760 (95% CI, 0.582 to 0.993; two-sided P = .044).	

Lancet Oncol. 2017 Nov;18(11):1454-1466

Gefitinib + chemotherapy versus Gefitinib

Gefitinib Versus Gefitinib Plus Pemetrexed and Carboplatin Chemotherapy in *EGFR*-Mutated Lung Cancer

- Randomised trial – Phase 3
- 350 patients randomly assigned to Gefitinib (n = 176) and Gefitinib + Chemotherapy (n = 174)
- Median PFS significantly longer with Gefitinib + Chemotherapy than Gefitinib (16 months [95% CI, 13.5 to 18.5 months] v 8 months [95% CI, 7.0 to 9.0 months], respectively; hazard ratio for disease progression or death, 0.51 [95% CI, 0.39 to 0.66]; P , .001)
- Median OS significantly longer with Gefitinib + Chemotherapy than Gefitinib (not reached v 17 months [95% CI, 13.5 to 20.5 months]; hazard ratio for death, 0.45 [95% CI, 0.31 to 0.65]; P , .001).

J Clin Oncol. 2020 Jan 10;38(2):124-136

Gefitinib Versus Gefitinib Plus Pemetrexed and Carboplatin Chemotherapy in *EGFR*-Mutated Lung Cancer

- 18-month overall survival rate is 74.3% (95% CI, 66% to 80.9%) in the combination arm compared with 48.7% (95% CI, 39.8% to 57.1%) in the Gefitinib arm

J Clin Oncol. 2020 Jan 10;38(2):124-136

A Randomized Phase 2 Study of Gefitinib With or Without Pemetrexed as First-line Treatment in Non squamous NSCLC With EGFR Mutation

- Phase 2, multicenter, randomized study
- 191 patients
- Randomised in 2:1 ratio to receive pemetrexed + gefitinib (n=126) and gefitinib (n= 65)
- Median OS - 43.4 months in combination group versus 36.8 months in gefitinib group adjusted HR 0.77 (95% CI, 0.5-1.2)
- median PFS - 16.2 months (95% CI: 12.6– 18.7) in combination arm and 11.1 months (95% CI 9.7–13.8) for gefitinib monotherapy arm with HR of 0.67 (95% CI: 0.5–0.9) and one-sided p value of 0.009

J Thorac Oncol. 2020 Jan;15(1):91-100

Gefitinib Alone Versus Gefitinib Plus Chemotherapy for Non–Small-Cell Lung Cancer With Mutated Epidermal Growth Factor Receptor: NEJ009 Study

- Randomised open label trial
- 345 Patients
- Advanced non squamous non small cell lung cancer
- Assigned to receive gefitinib combined with carboplatin plus pemetrexed or gefitinib alone
- PFS was significantly longer in combination group than in the gefitinib group (median, 20.9 v 11.2 months; HR, 0.49; 95% CI, 0.39 to 0.62; P < .001

J Clin Oncol. 2020 Jan 10;38(2):115-123

Updated Analysis of NEJ009: Gefitinib-Alone Versus Gefitinib Plus Chemotherapy for Non–Small-Cell Lung Cancer With Mutated *EGFR*

- Median OS - 38.5 months (95% CI, 31.1 to 47.1) and 49.0 months (95% CI, 41.8 to 56.7) in the gefitinib and gefitinib combination groups, respectively (hazard ratio, 0.82; 95% CI, 0.64 to 1.06; P 5 .127).

J Clin Oncol. 2022 Nov 1;40(31):3587-3592

Erlotinib +Bevacizumab versus Erlotinib

Erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-positive advanced non-squamous non-small-cell lung cancer

	Study Participants	Progression Free survival
NEJ026 PHASE 3 randomized trial	N= 114 (erlotinib + bevacizumab) & N =114(erlotinib)	16·9 months (95% CI 14·2–21·0) in combination group versus 13·3 months (11·1–15·3) in erlotinib hazard ratio 0·605, 95% CI 0·417–0·877; p=0·016
BEVERLY Multicenter Randomized Phase 3 Trial	N= 80 (erlotinib + bevacizumab) & N =80(erlotinib)	15.4 months (95% [CI]: 12.2–18.6) in combination group and 9.6 months (95% CI: 8.2–10.6) with erlotinib alone (hazard ratio = 0.66, 95% CI: 0.47–0.92)

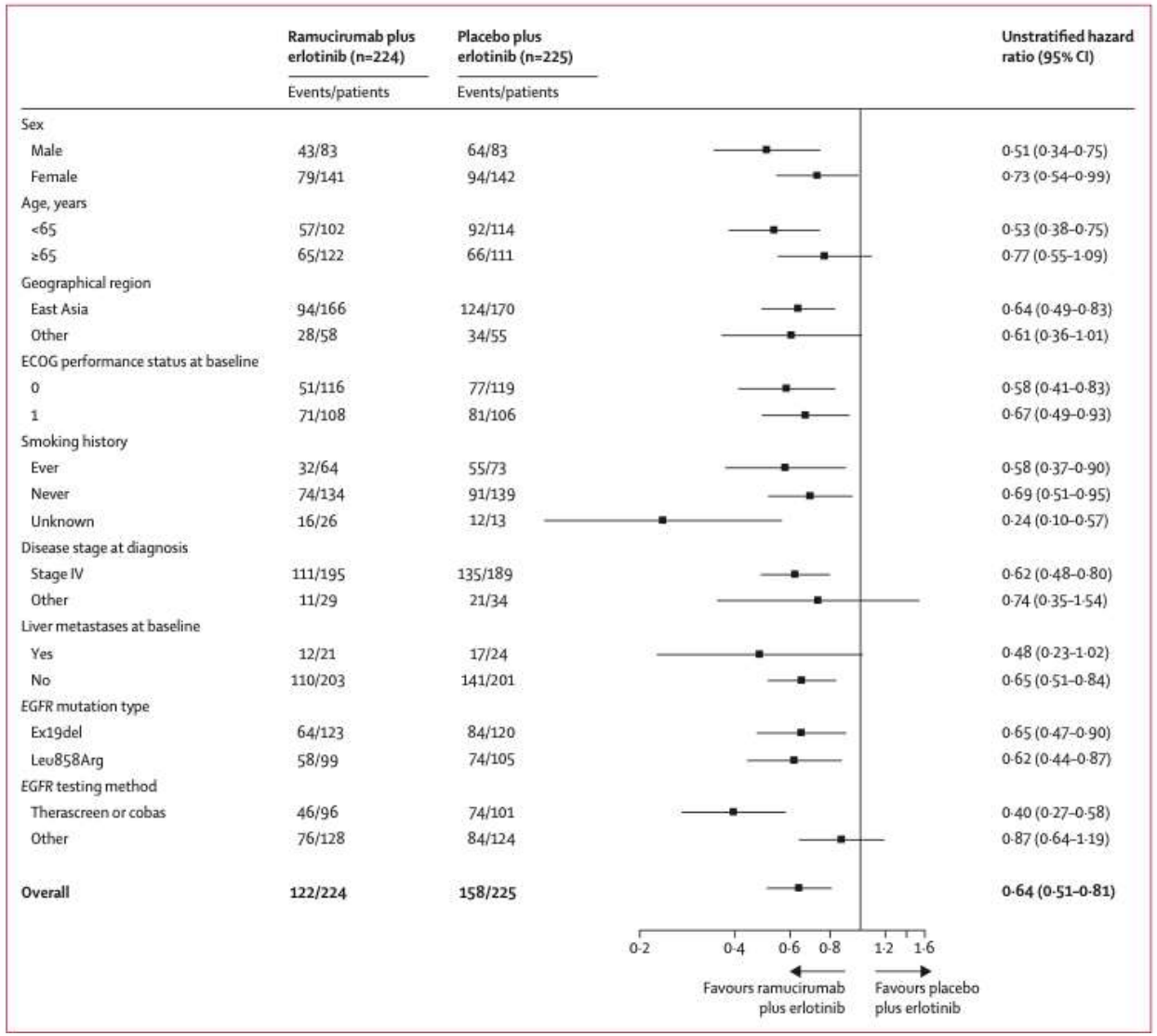
Lancet Oncol 2019; 20: 625–35
J Thorac Oncol. 2022 Sep;17(9):1086-1097

Erlotinib + Ramucirumab versus Erlotinib

Ramucirumab plus erlotinib in patients with untreated, *EGFR*-mutated, advanced non-small-cell lung cancer (RELAY)

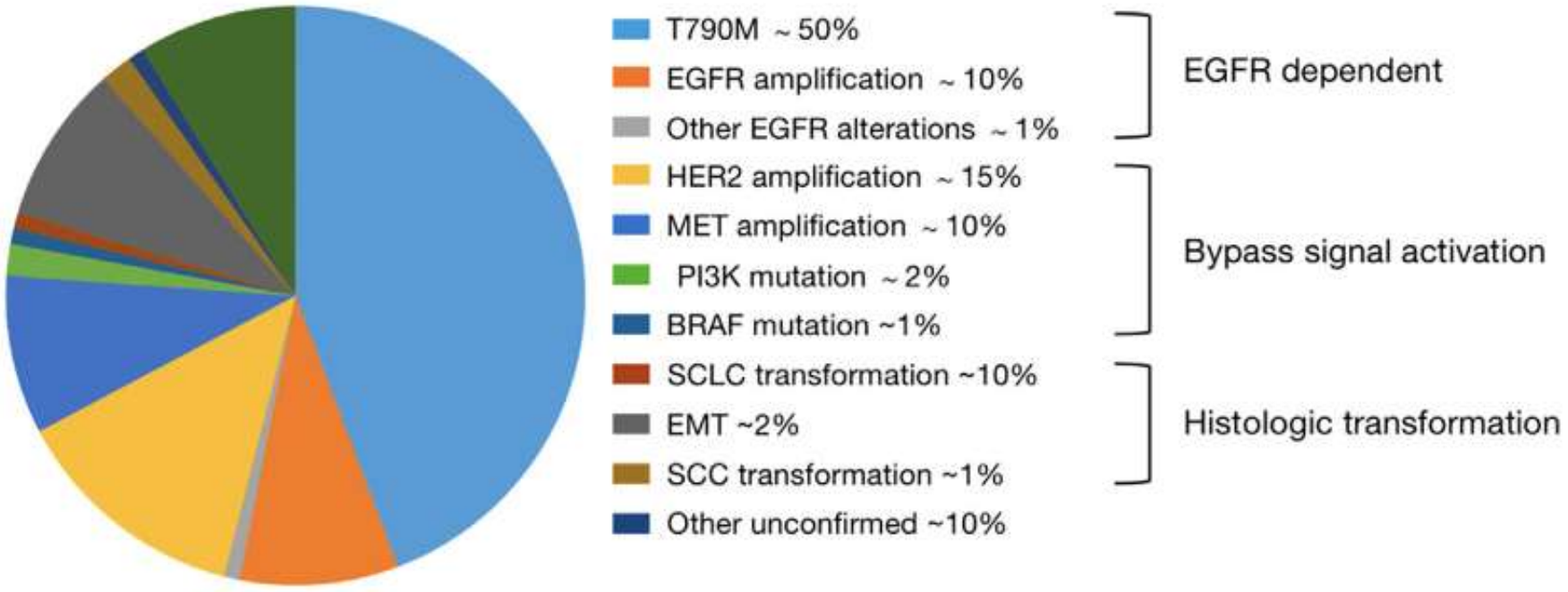
- Randomised, double-blind, placebo-controlled, phase 3 trial
- N = 449 patients
- Randomly(1:1) to receive ramucirumab plus erlotinib (n=224) or placebo plus erlotinib (n=225)
- Progression-free survival in the ramucirumab plus erlotinib group (19·4 months [95% CI 15·4–21·6]) than in the placebo plus erlotinib group (12·4 months [11·0–13·5]), with a hazard ratio of 0·59 (95% CI 0·46–0·76; p<0·0001)

Subgroup analysis of progression free survival



	Ramucirumab plus erlotinib (n=224)	Placebo plus erlotinib (n=225)	Unstratified hazard ratio (95% CI)
	Events/patients	Events/patients	
Sex			
Male	43/83	64/83	0·51 (0·34–0·75)
Female	79/141	94/142	0·73 (0·54–0·99)
Age, years			
<65	57/102	92/114	0·53 (0·38–0·75)
≥65	65/122	66/111	0·77 (0·55–1·09)
Geographical region			
East Asia	94/166	124/170	0·64 (0·49–0·83)
Other	28/58	34/55	0·61 (0·36–1·01)
ECOG performance status at baseline			
0	51/116	77/119	0·58 (0·41–0·83)
1	71/108	81/106	0·67 (0·49–0·93)
Smoking history			
Ever	32/64	55/73	0·58 (0·37–0·90)
Never	74/134	91/139	0·69 (0·51–0·95)
Unknown	16/26	12/13	0·24 (0·10–0·57)
Disease stage at diagnosis			
Stage IV	111/195	135/189	0·62 (0·48–0·80)
Other	11/29	21/34	0·74 (0·35–1·54)
Liver metastases at baseline			
Yes	12/21	17/24	0·48 (0·23–1·02)
No	110/203	141/201	0·65 (0·51–0·84)
EGFR mutation type			
Ex19del	64/123	84/120	0·65 (0·47–0·90)
Leu858Arg	58/99	74/105	0·62 (0·44–0·87)
EGFR testing method			
Therascreen or cobas	46/96	74/101	0·40 (0·27–0·58)
Other	76/128	84/124	0·87 (0·64–1·19)
Overall	**122/224**	**158/225**	**0·64 (0·51–0·81)**

Mechanism of resistance to 1st and 2nd generation TKI



J UOEH. 2019;41(2):153-163

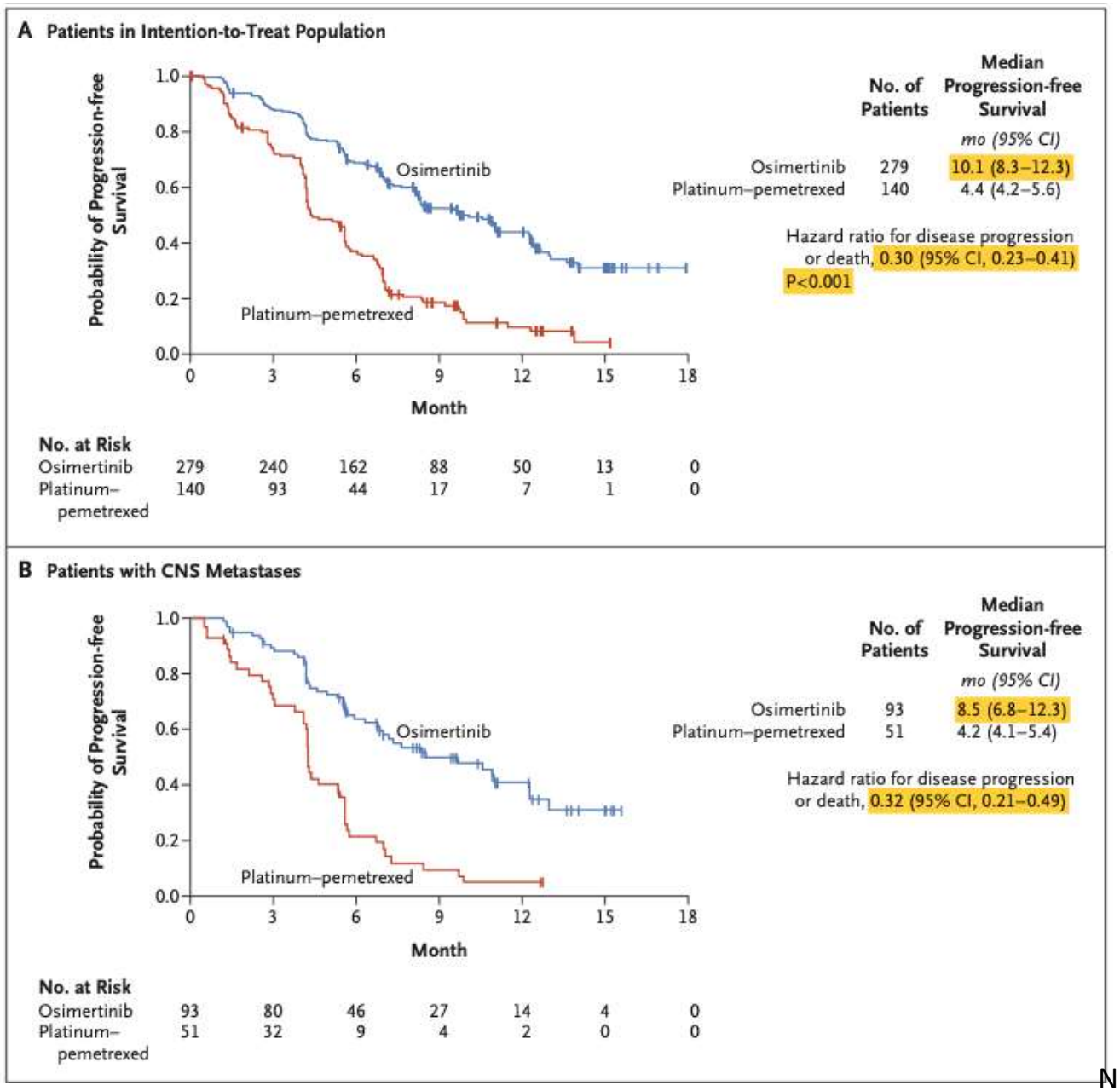
Osimertinib for EGFR TKI

Osimertinib or Platinum–Pemetrexed in *EGFR* T790M–Positive Lung Cancer

- Randomized phase 3 open label trial
- N = 419
- Patients with T790M mutations who had disease progression after first-line EGFR-TKI therapy, in a 2:1 ratio to receive either oral Osimertinib or intravenous chemotherapy
- Primary end point - progression-free survival

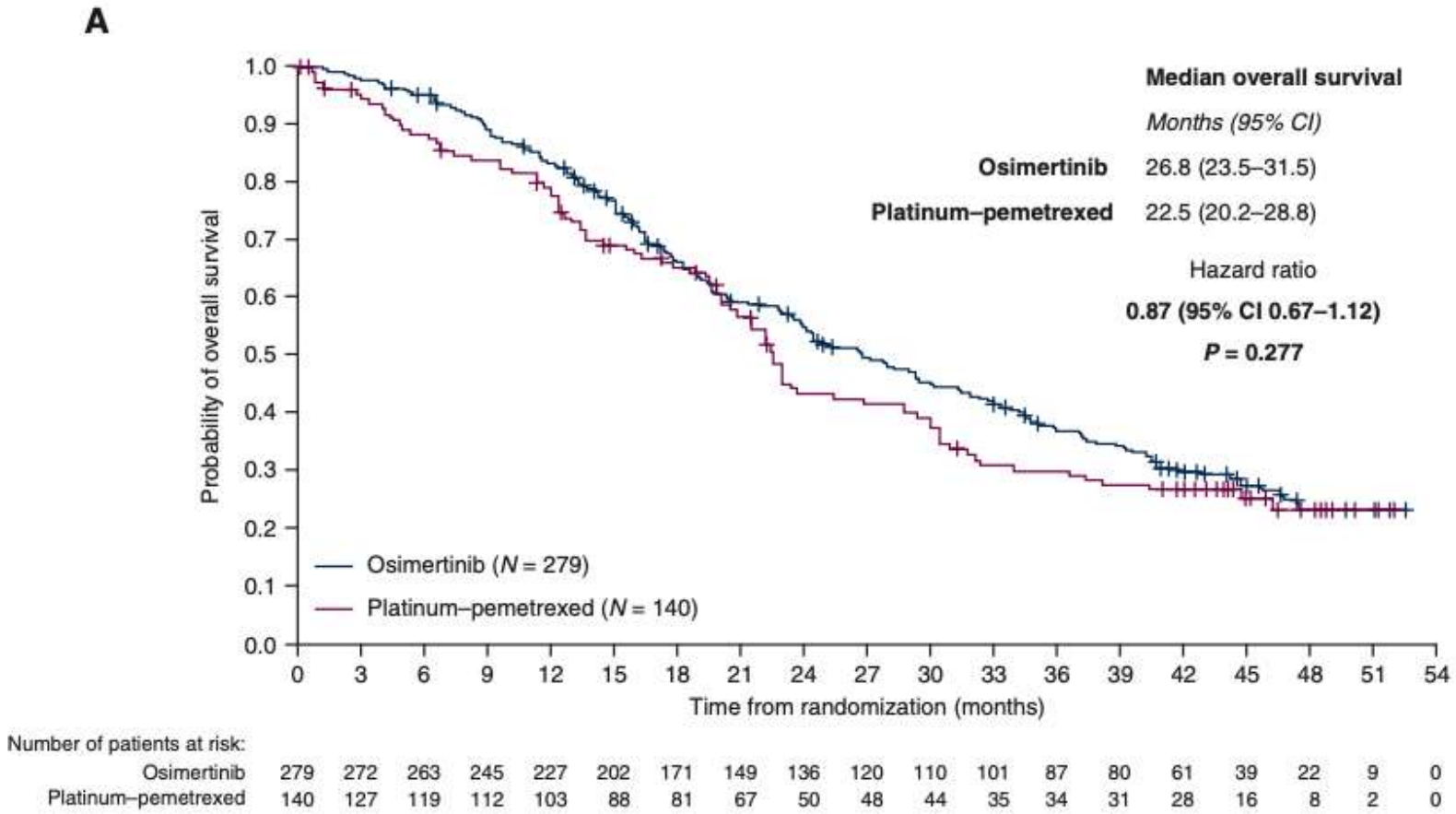
N Engl J Med 2017;376:629-40

Progression free survival in intention to treat population and CNS metastases



N Engl J Med 2017;376:629-40

AURA3 overall survival analysis



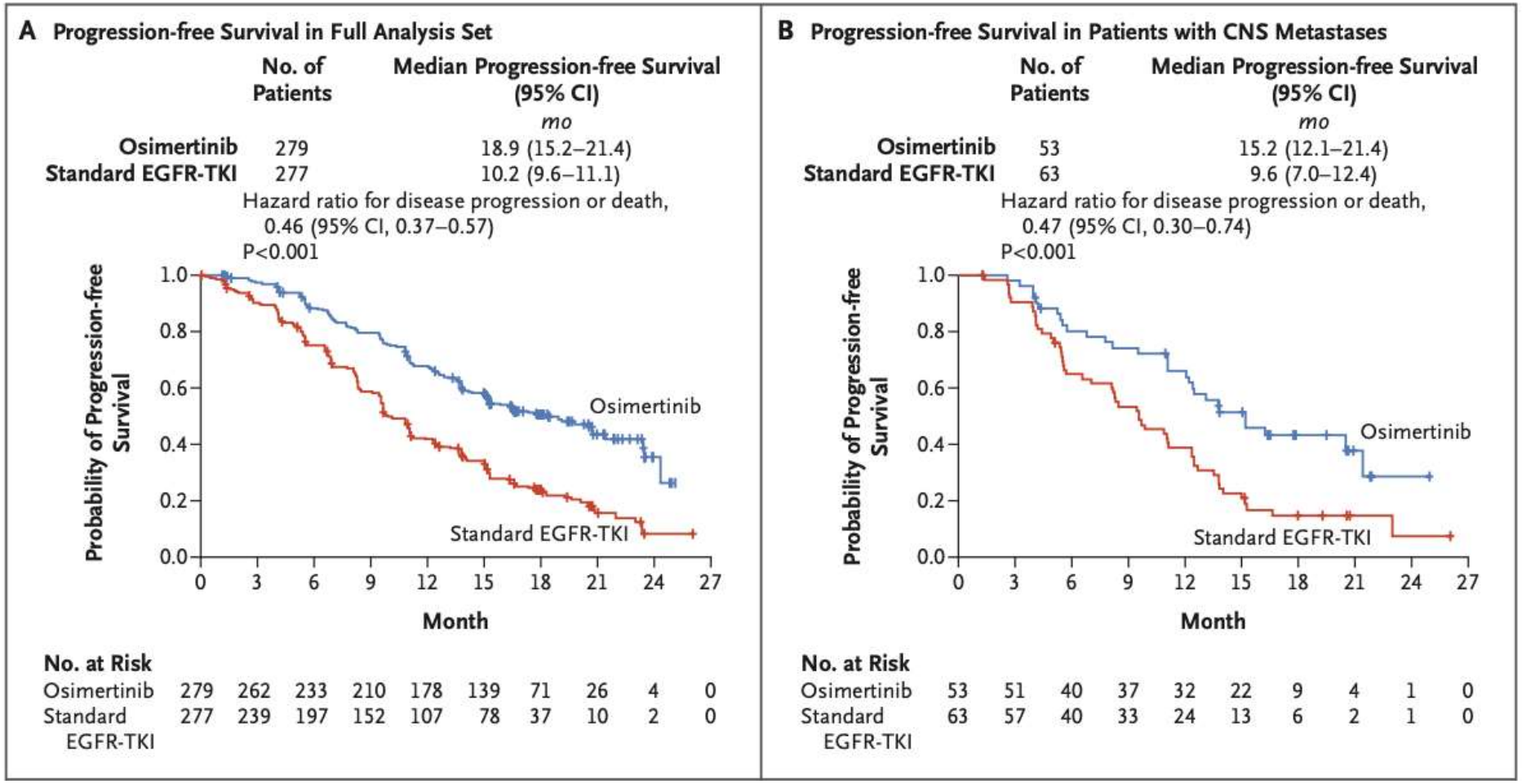
Ann Oncol. 2020 Nov;31(11):1536-1544

Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer

- Double-blind, phase 3 trial
- *EGFR* mutation–positive (exon 19 deletion or L858R) advanced NSCLC in a 1:1 ratio to receive either osimertinib (at a dose of 80 mg once daily) or a standard EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily)
- Primary end point is progression free survival

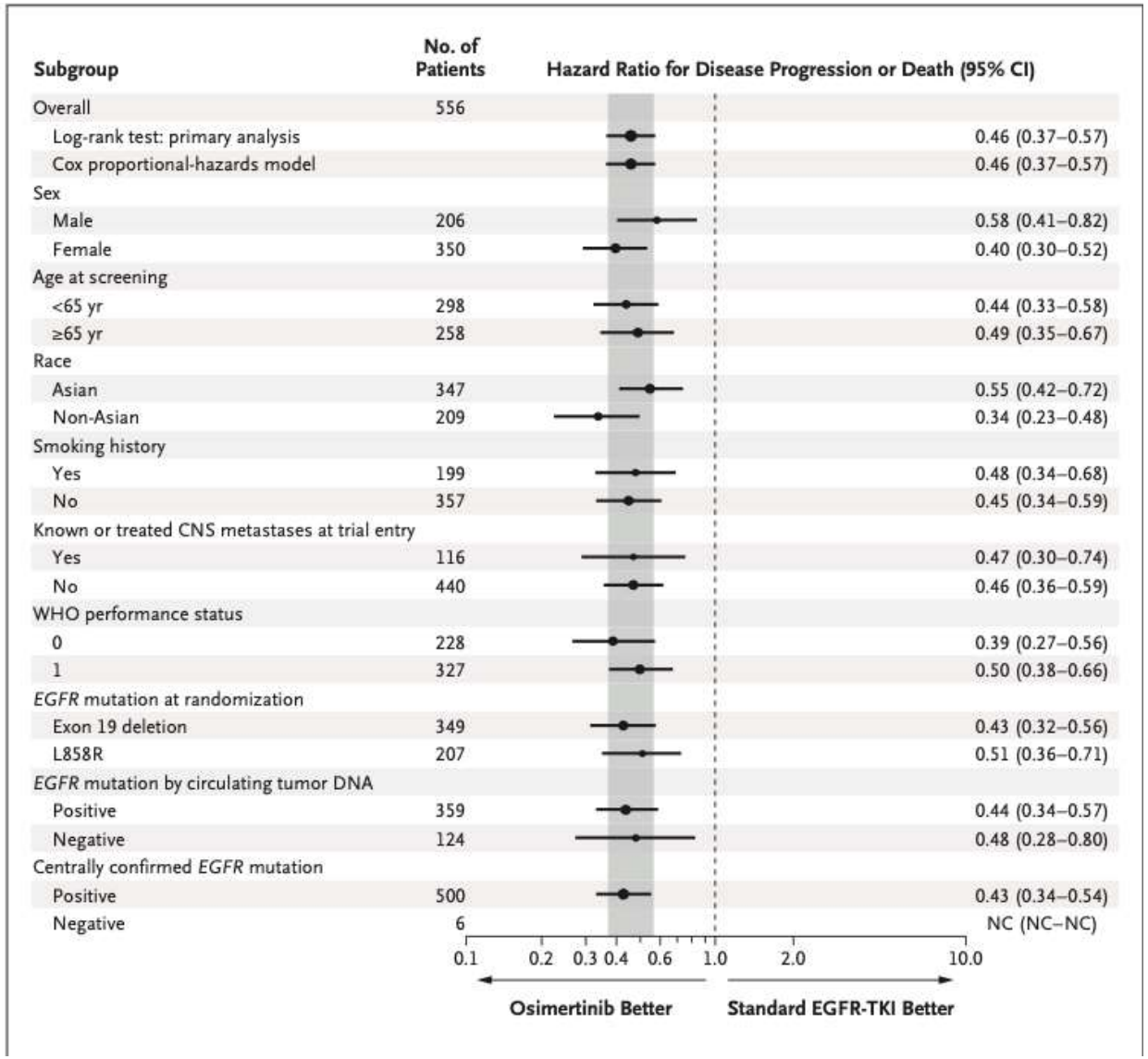
N Engl J Med 2018;378:113-25

Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer



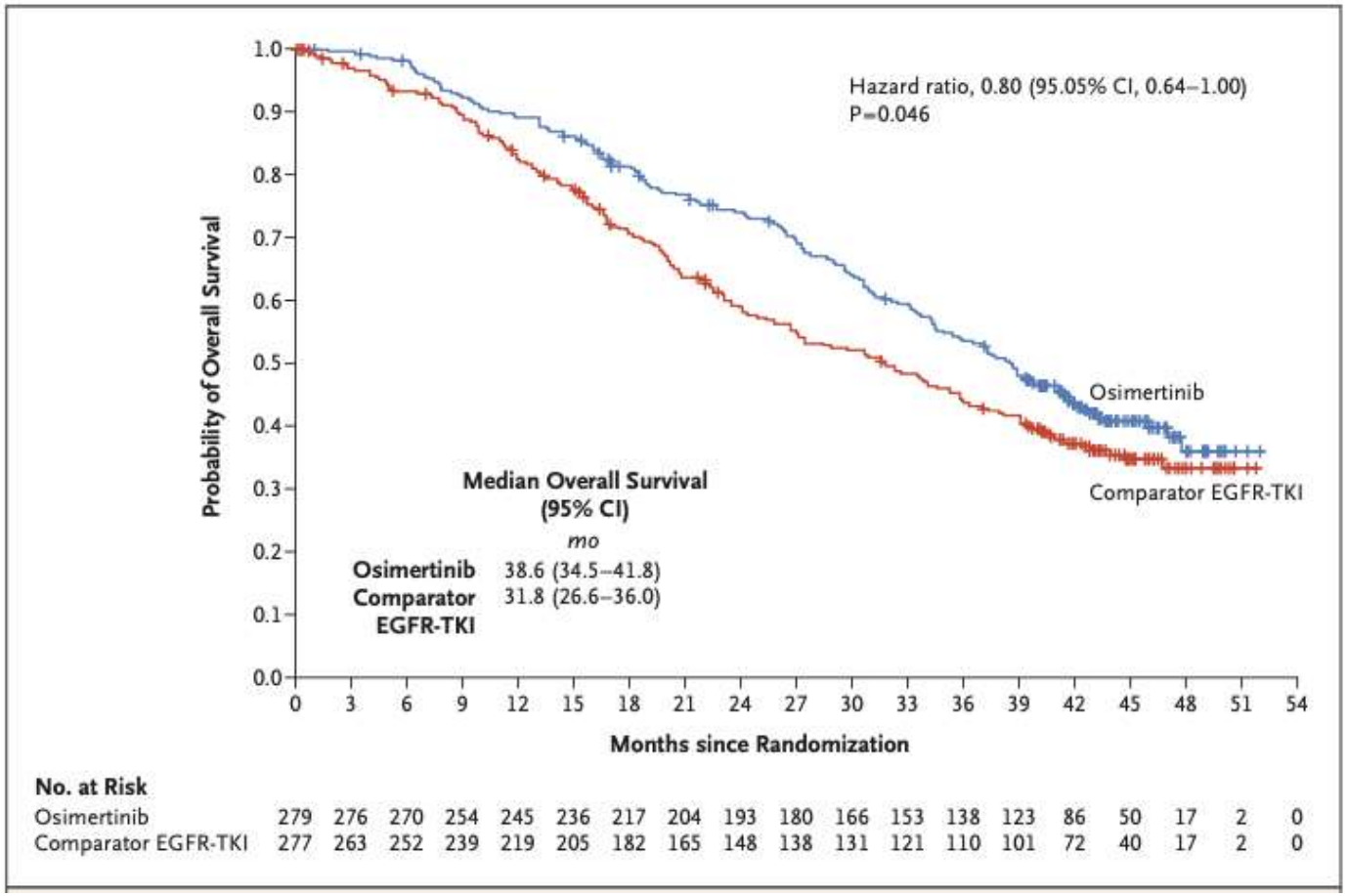
N Engl J Med 2018;378:113-25

Subgroup Analyses of Progression-free Survival



N Engl J Med 2018;378:113-25

Overall Survival:

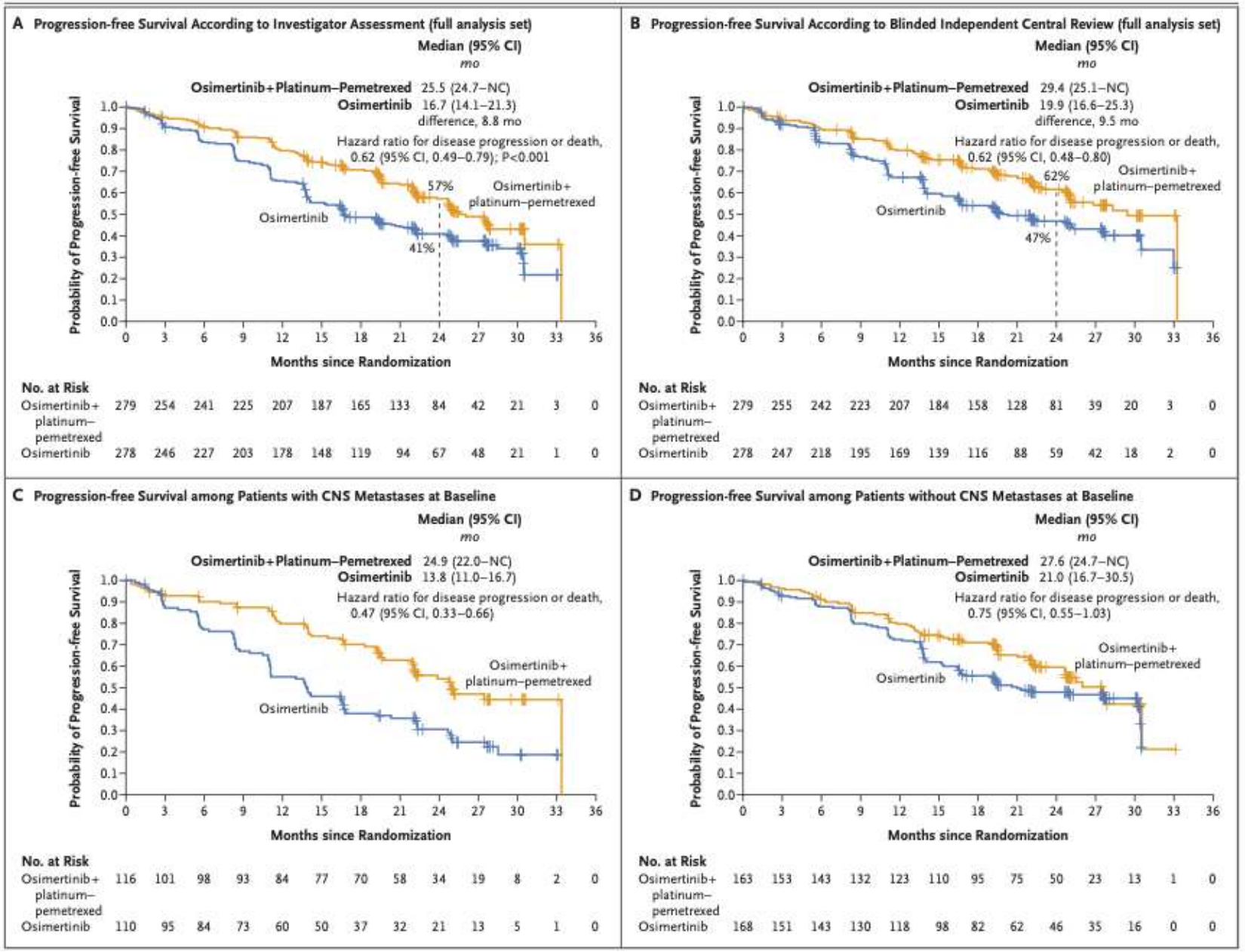


N Engl J Med 2020;382:41-50

Osimertinib with or without Chemotherapy in *EGFR*-Mutated Advanced NSCLC

- Phase 3, international, open-label trial
- Randomly assigned in a 1:1 ratio patients with *EGFR*-mutated (exon 19 deletion or L858R mutation) advanced non– small-cell lung cancer (NSCLC) – treatment naive
- Osimertinib with chemotherapy (pemetrexed plus either cisplatin or carboplatin) or osimertinib monotherapy
- Primary end point - progression-free survival

N Engl J Med2023;389:1935-48



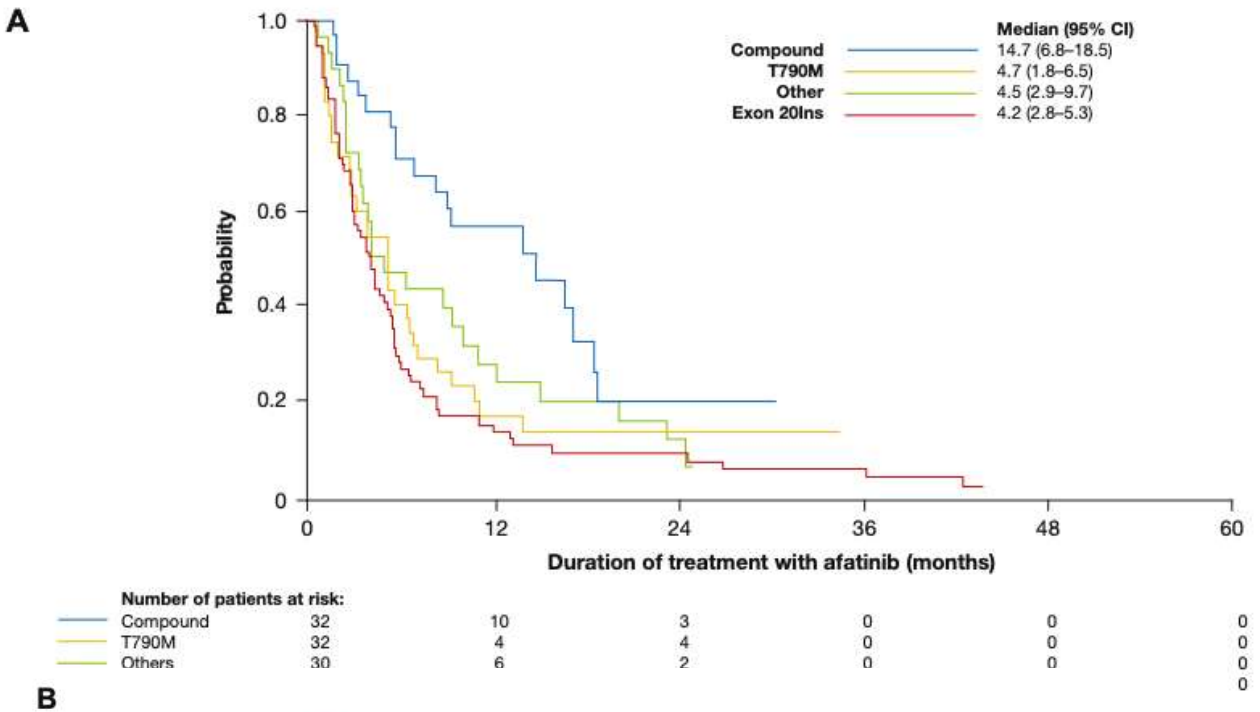
N Engl J Med2023;389:1935-48

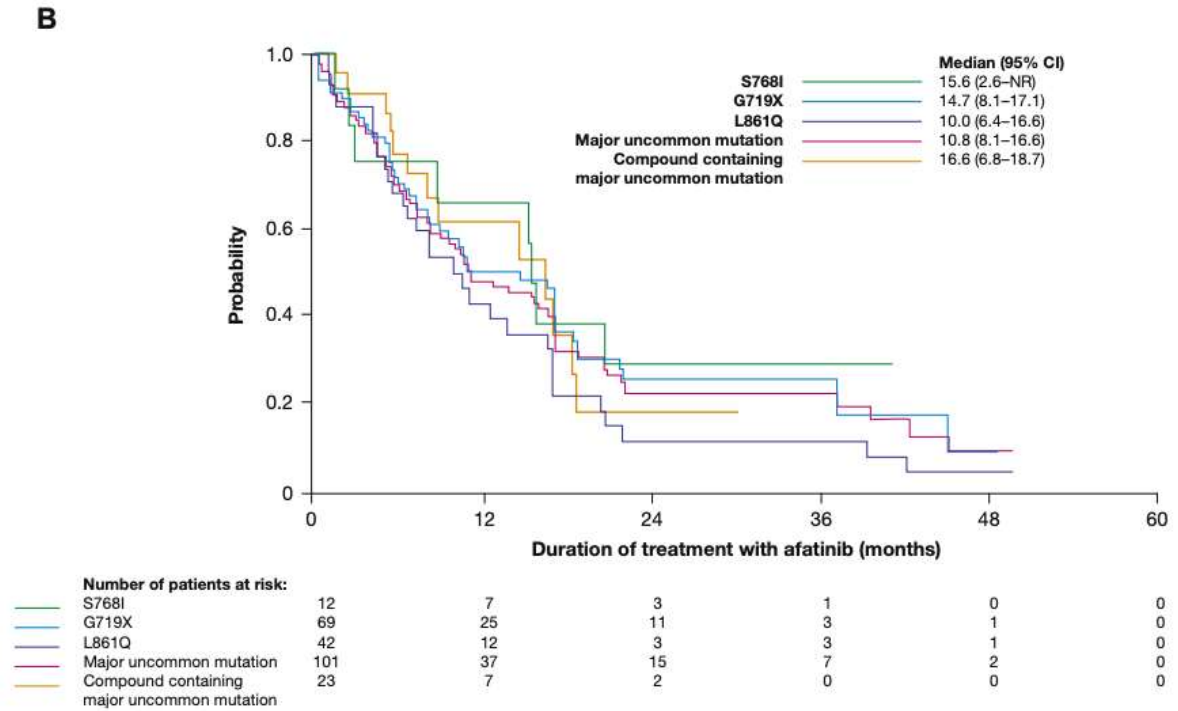
Treatment of uncommon EGFR mutations

Afatinib for the Treatment of NSCLC Harboring Uncommon *EGFR* Mutations: A Database of 693 Cases

- Activity of afatinib in 693 patients uncommon EGFR mutations treated in randomized clinical trials, compassionate-use and expanded-access programs, phase 3b trials, noninterventional trials, and case series or studies
- EGFR TKI–naive patients (n =315)
- Primary end points - overall response rate (ORR), duration of response, and time to treatment failure (TTF)

J Thorac Oncol. 2020 May;15(5):803-815

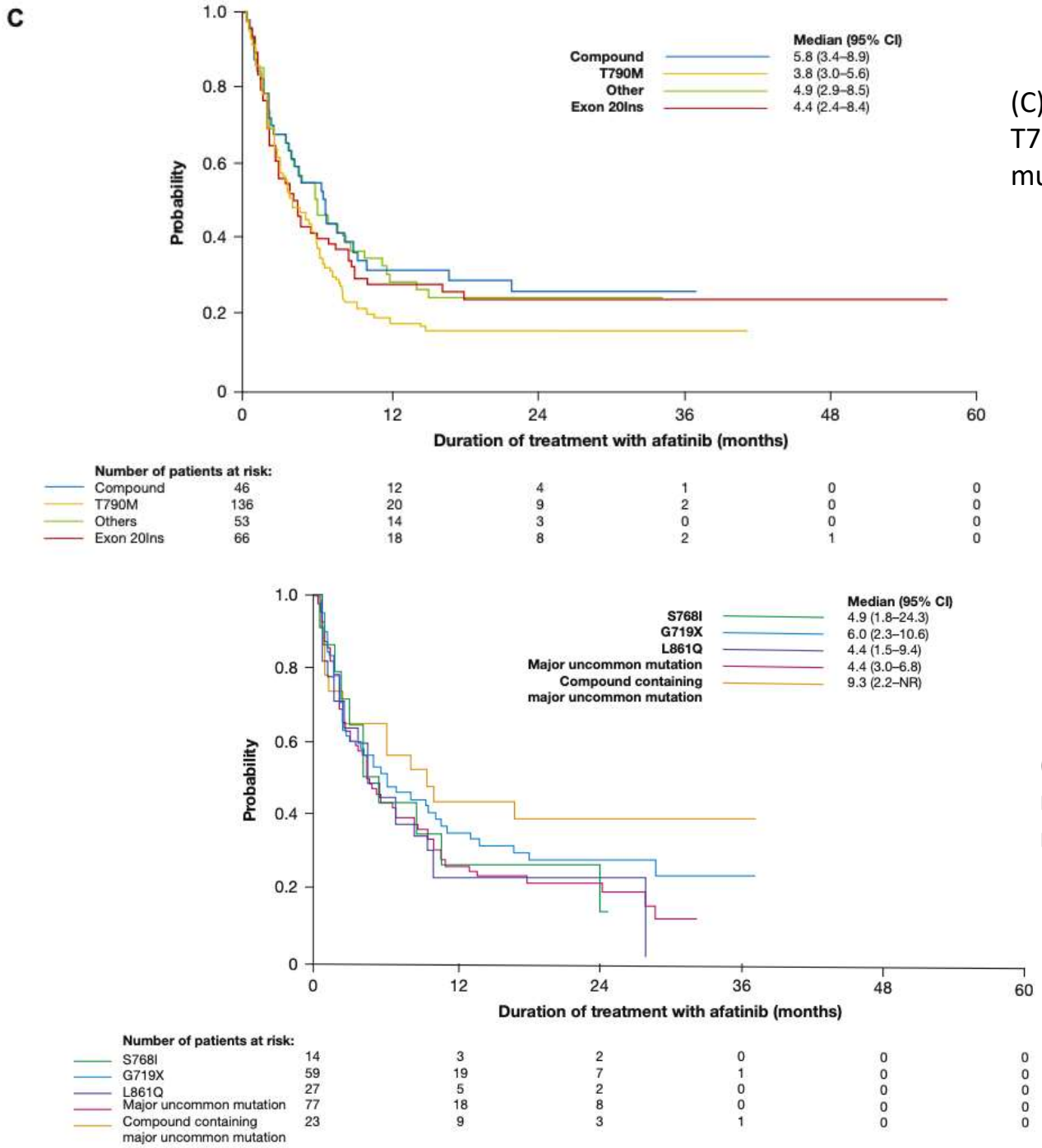




(A) Tyrosine kinase inhibitor (TKI)–naive patients with compound mutations, T790M, exon 20 insertions, and other uncommon mutations

(B) TKI- naive patients with major uncommon mutations (S768I, G719X, L861Q) and compound mutations containing a major un- common mutation

J Thorac Oncol. 2020 May;15(5):803-815



(C) TKI-pretreated patients with compound mutations, T790M, exon 20 insertions, and other uncommon mutations

(D) TKI-pretreated patients with major uncommon mutations (S768I, G719X, L861Q) and compound mutations containing a major uncommon mutation

J Thorac Oncol. 2020 May;15(5):803-815

UNcommon EGFR Mutations: International Case Series on Efficacy of Osimertinib in Real-Life Practice in First-LiNe Setting (UNICORN)

- Multicenter, retrospective study of uncommon EGFR mutations metastatic NSCLC treated with Osimertinib as first EGFR inhibitor

Table 2. Efficacy of Osimertinib in Various Subgroups

Patient Subgroups	n (% of 60)	RR[a] (95% CI)	PFS, mo (95% CI)	OS, mo (95% CI)	DOR, mo (95% CI)
All patients	60 (100)	61 (47-73)	9.5 (8.5-17.4)	24.5 (17.4-35.1)	17.4 (9.1-NA)
Group A: only uncommon	44 (73)	60 (45-74)	8.6 (7.3-13.5)	22.1 (13.5-NA)	11.0 (9.0-NA)
Group B: uncommon with L858R/del19[b]/T790M	16 (27)	61 (35-82)	30.0 (12.7-NA)	31.4 (14.7-NA)	46.2 (30.7-NA)
G719X	18 (30)	47 (26-69)	8.8 (7.9-NA)	NA (17.4-NA)	9.1 (8.6-NA)
G719X, group A	16 (27)	53 (30-75)	8.6 (6.9-NA)	18.4 (10.2-NA)	9.1 (8.6-NA)
L861Q	12 (20)	80 (49-94)	16 (11-NA)	26.3 (22.1-NA)	16 (11-NA)
L861Q, group A	11 (18)	78 (45-94)	15.7 (8.9-18.8)	25.9 (21.8-NA)	16.0 (9.0-NA)
T790M	9 (15)	44 (19-73)	12.7 (9.5-NA)	NA (12-NA)	46.2 (3.8-NA)
TP53 mutant	21 (35)	60 (36-80)	8.5 (6.8-22.1)	26.3 (13.5-NA)	9.0 (7.9-NA)

J Thorac Oncol. 2023 Feb;18(2):169-180

First-Line Osimertinib for Previously Untreated Patients With NSCLC and Uncommon *EGFR* Mutations
The UNICORN Phase 2 Nonrandomized Clinical Trial

- Multicenter, open-label, single-group, phase 2 nonrandomized clinical trial
- 40 patients with uncommon EGFR mutations

	Objective Response Rate	Progression Free Survival	Overall Survival	Duration of response
Overall (N = 40)	55.0 (40.9-68.5)	9.4 (3.7-15.2)	NR (19.3-NR)	22.7 (9.5-NR)
Solitary mutations(n =22)	45.5 (26.9-65.3)	5.4 (3.6-22.7)	5.4 (3.6-22.7)	22.7 (3.6-22.7)
Compound mutations (n=18)	66.7 (43.7-83.7)	9.8 (5.1-NR)	9.8 (5.1-NR)	NR (5.7-NR)

JAMA Oncol. 2024 Jan 1;10(1):43-51.

Treatment of EXON 20 Insertion

Real-World Response and Outcomes in Patients With NSCLC With *EGFR* Exon 20 Insertion Mutations

	Confirmed rw ORR%	Overall survival(months) Median (95%CI)	Real world Progression free survival (months) – Median (95%CI)
Any 1L therapy (N= 129)	18.6 (12.3 – 26.4)	17.0 (11.2 – 19.5)	5.2 (3.1 – 6.9)
Any >=2L therapy (N = 114)	9.6 (4.9- 16.6)	13.6 (8.2 – 15.4)	3.7 (2.7 – 5.2)
Any >= therapy in post platinum trial (N = 50)	14 (5.8 – 26.7)	11.5(7.9 – 16.6)	3.3(2.3 – 5.9)

JTO Clin Res Rep. 2023 Aug16;4(10):100558

Real-World Response and Outcomes in Patients With NSCLC With *EGFR* Exon 20 Insertion Mutations

Table 2. Treatment Patterns of Index Therapy[a]

Index Line of Therapy, n (%)[b]	1L Cohort n = 129	≥2L Cohort n = 114	≥2L Postplatinum Trial-Aligned Cohort n = 50
EGFR TKI	37 (28.7)	20 (17.5)	10 (20.0)
EGFR TKI + mAb	1 (0.8)	-	-
IO monotherapy	11 (8.5)	32 (28.1)	20 (40.0)
Nonplatinum chemo	3 (2.3)	13 (11.4)	7 (14.0)
Nonplatinum chemo + mAb	1 (0.8)	11 (9.6)	4 (8.0)
Nonplatinum chemo + IO therapy	-	1 (0.9)	-
Platinum chemo	1 (0.8)	1 (0.9)	-
Platinum chemo + nonplatinum chemo	40 (31.0)	13 (11.4)	5 (10.0)
Platinum chemo + nonplatinum chemo + mAb	16 (12.4)	6 (5.3)	1 (2.0)
Platinum chemo + nonplatinum chemo + IO therapy	16 (12.4)	7 (6.1)	3 (6.0)
Other therapy	3 (2.3)[c]	10 (8.8)[d]	-

JTO Clin Res Rep. 2023 Aug16;4(10):100558

Amivantamab plus Chemotherapy in NSCLC with *EGFR* Exon 20 Insertions

- Randomized controlled trial – phase 3
- 308 patients (treatment naïve)
- Randomization 1:1 to receive amivantamab plus chemotherapy (n = 153) or chemotherapy alone(n=155)
- Primary outcome – progression free survival

N Engl J Med 2023;389:2039-51

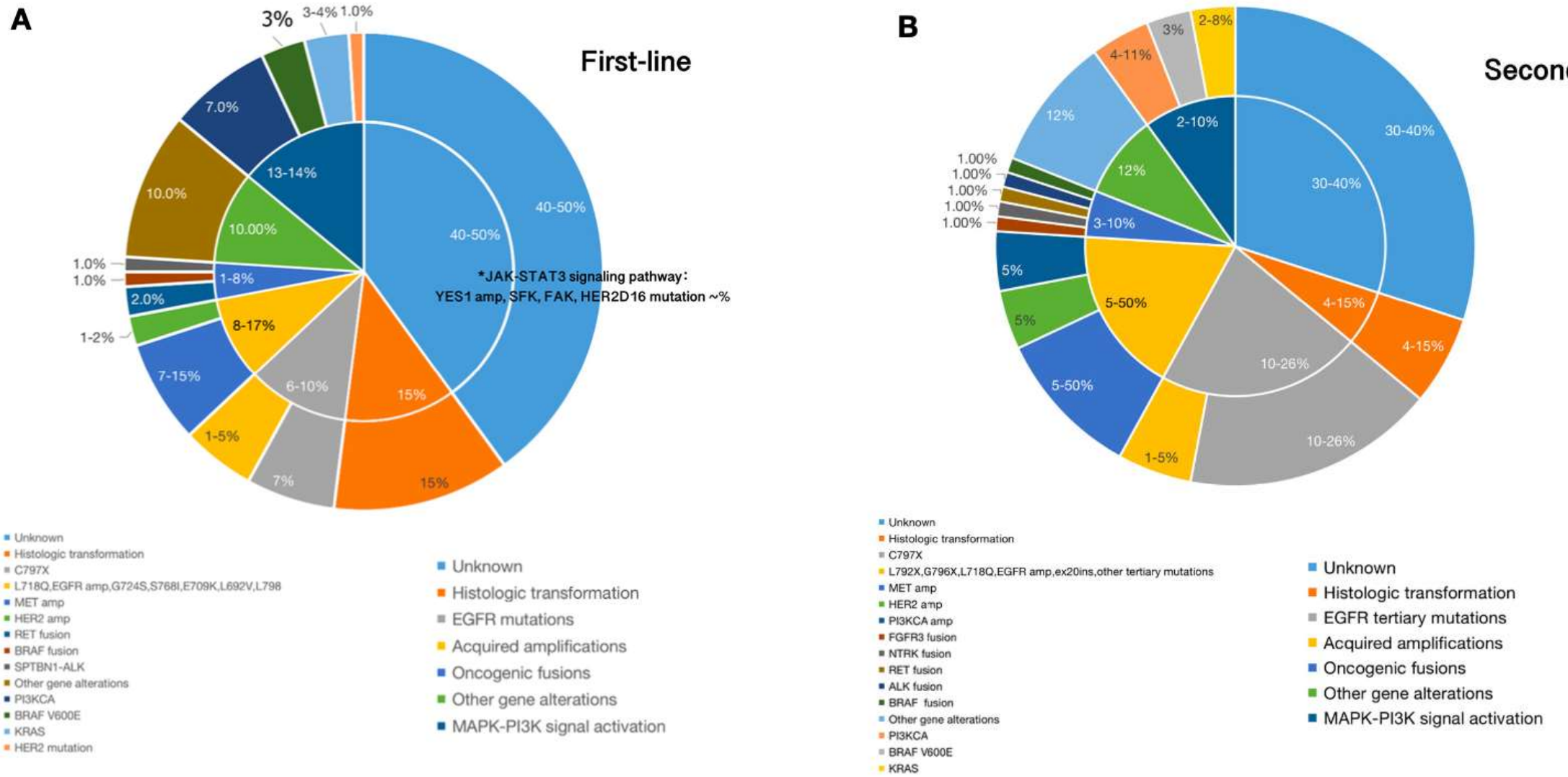
Amivantamab plus Chemotherapy in NSCLC with *EGFR* Exon 20 Insertions

Table 2. Key Efficacy Outcomes.*

Outcome	Amivantamab–Chemotherapy (N=153)	Chemotherapy (N=155)	Treatment Effect (95% CI)	P Value
Progression-free survival†				
Median (95% CI) — mo	11.4 (9.8–13.7)	6.7 (5.6–7.3)	Hazard ratio, 0.40 (0.30–0.53)	<0.001
Patients (95% CI) — %				
At 6 mo	77 (69–83)	51 (43–59)		
At 12 mo	48 (39–56)	13 (8–19)		
At 18 mo	31 (22–40)	3 (1–9)		
Objective response‡				
Patients (95% CI) — %	73 (65–80)	47 (39–56)	Rate ratio, 1.50 (1.32–1.68)	<0.001
Overall survival				
Median (95% CI) — mo	NE	24.4 (22.1–NE)	Hazard ratio, 0.67 (0.42–1.09)	0.11
Patients (95% CI) — %				
At 12 mo	86 (79–91)	82 (74–87)		
At 18 mo	74 (64–82)	68 (58–76)		
At 24 mo	72 (61–81)	54 (37–68)		

N Engl J Med 2023;389:2039-51

Resistance mechanism to osimertinib



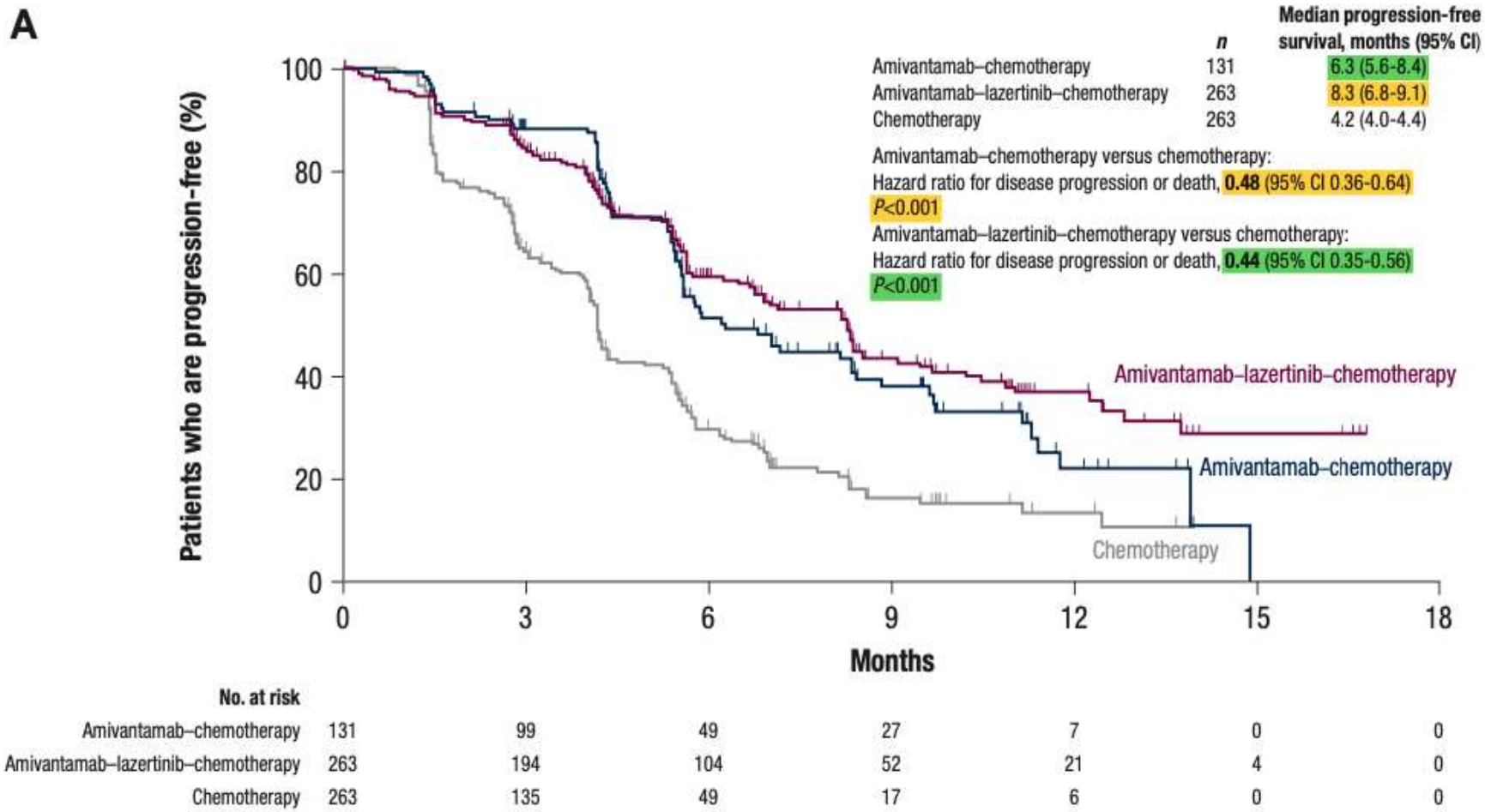
Front Oncol. 2020 Dec 18;10

Amivantamab plus chemotherapy with and without lazertinib in EGFR- mutant advanced NSCLC after disease progression on osimertinib: MARIPOSA-2 study

- Phase 3 randomized trial
- N = 657
- Randomized in 2 : 2 : 1 to receive amivantamab +Lazertinib + chemotherapy, chemotherapy, or amivantamab +chemotherapy
- Primary end points - progression free survival in amivantamab + chemotherapy versus chemotherapy and amivantamab+ Lazertinib+ chemotherapy versus chemotherapy

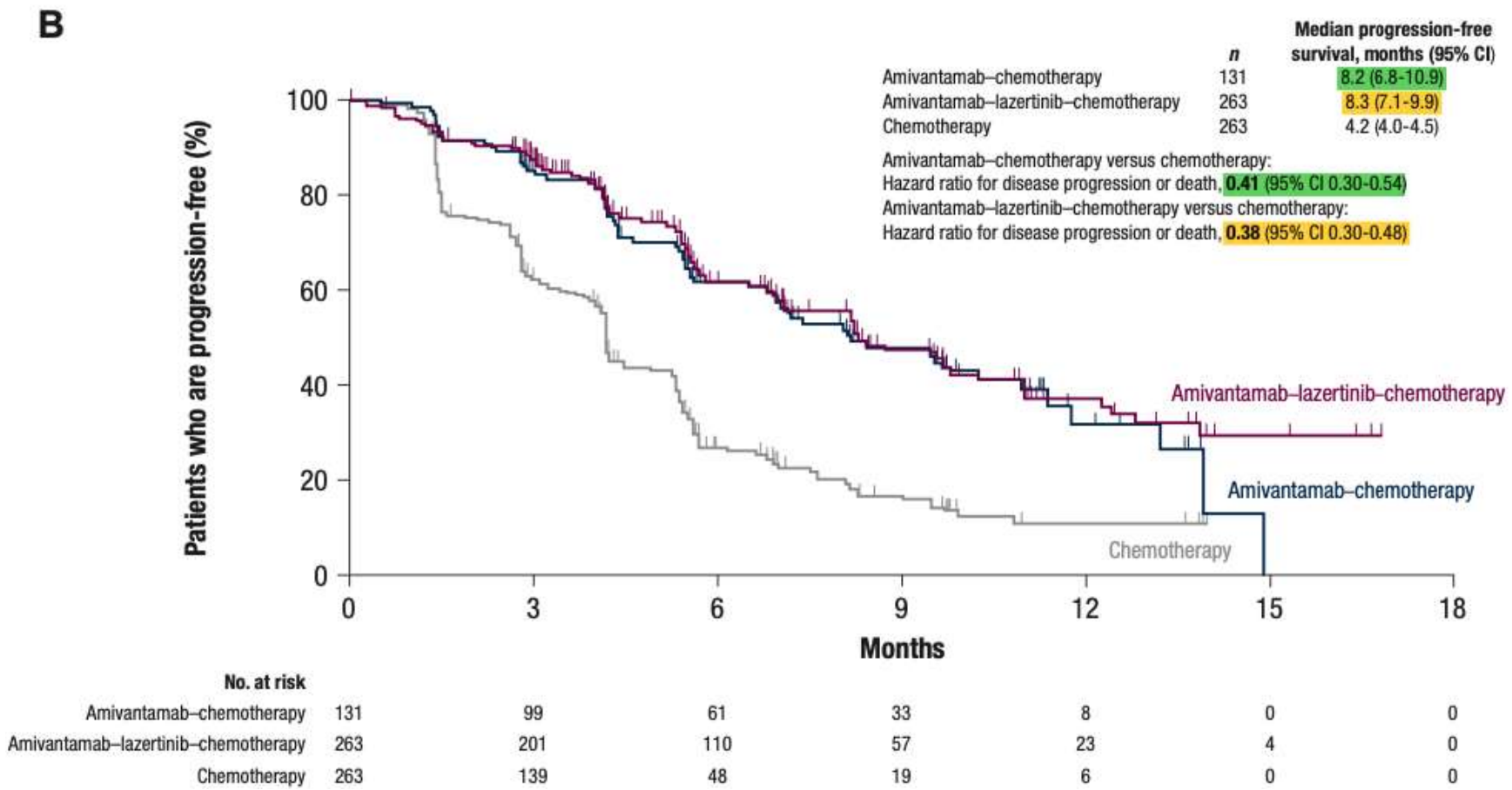
Ann Oncol. 2024 Jan;35(1):77-90

Progression free survival – Independent reviewer



Ann Oncol. 2024 Jan;35(1):77-90

Progression free survival – Investigator



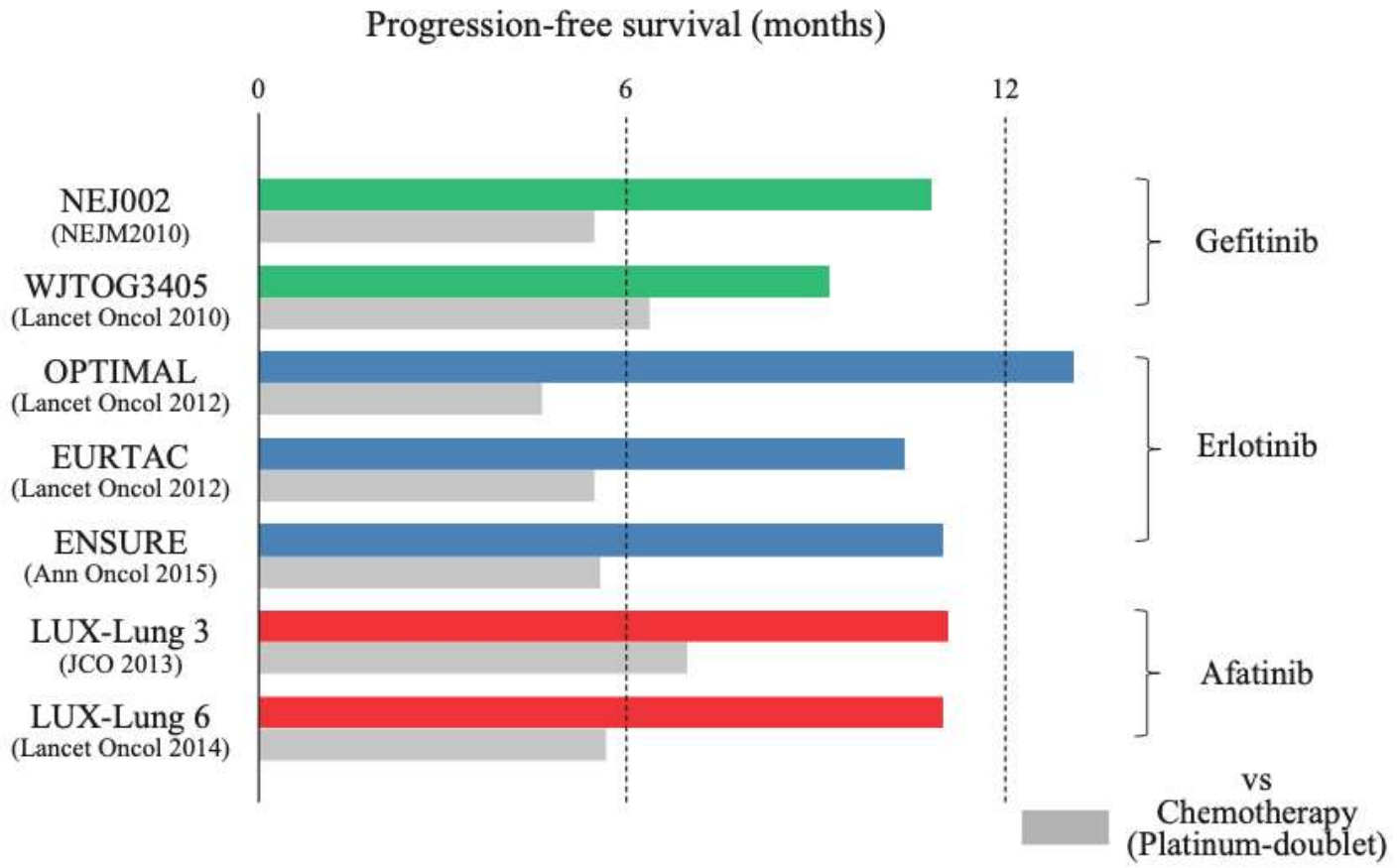
Ann Oncol. 2024 Jan;35(1):77-90

Ongoing study trials that include osimertinib-resistant patients

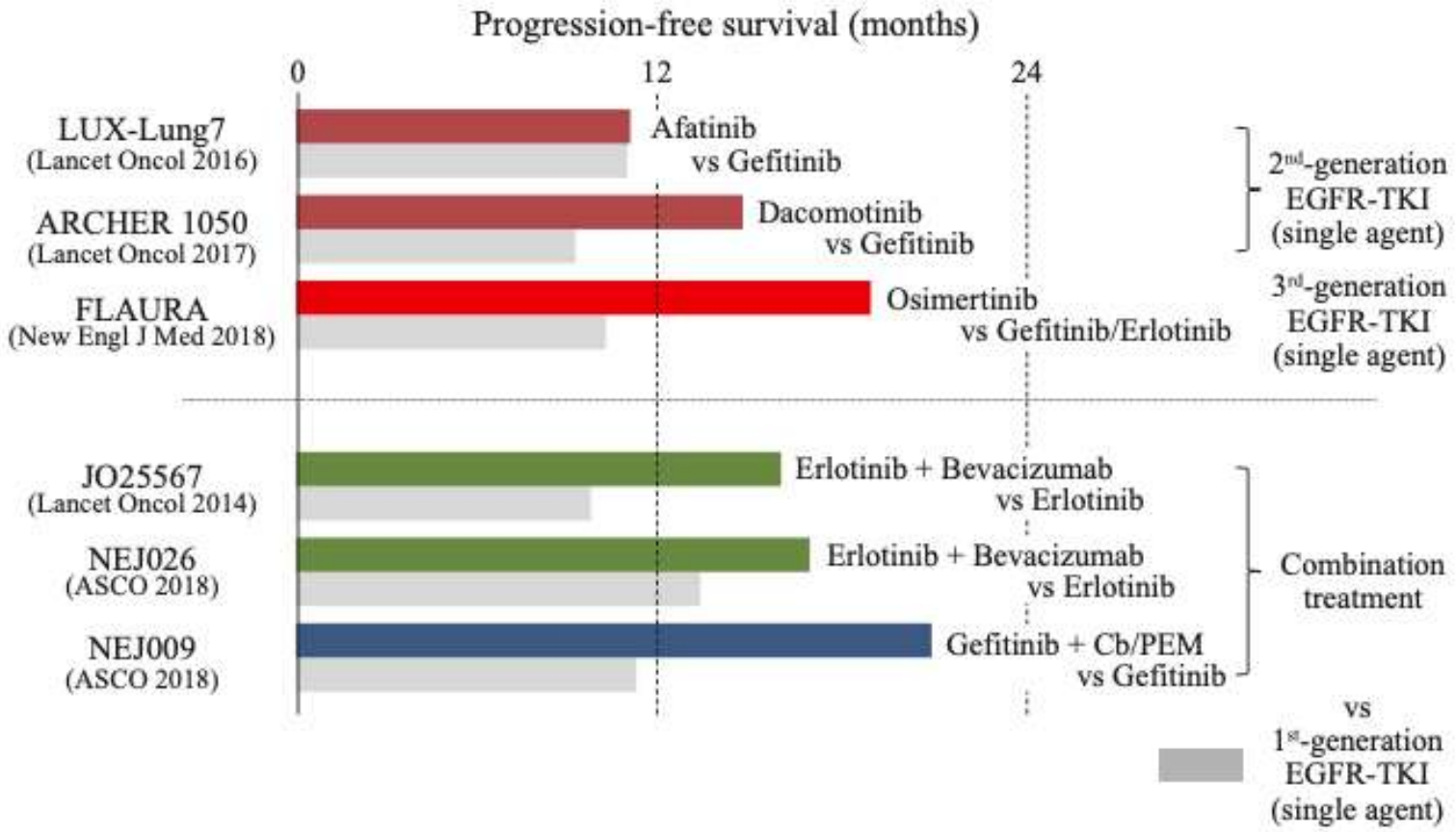
Patritumab deruxtecan	Patients with locally advanced or metastatic EGFR mutation-positive NSCLC with prior EGFR TKI therapy. About 86% of the study patients were treated with prior osimertinib	Phase I dose-escalation/ expansion study (NCT03260491)	HER3-directed antibody-drug conjugate that consists of a fully human monoclonal antibody to HER3
BLU-945	Patients with EGFR-mutated NSCLC who have previously received at least one prior EGFR-targeted TKI. Expansion groups consist of EGFR T790M and C797S mutation (group 1); EGFR T790M but not C797S (group 2); or EGFR C797S but not T790M (group 3).	Ongoing Phase I/II trial (NCT04862780) that include a dose-escalation portion	Fourth-generation EGFR TKI that potentially inhibits triple-mutant EGFR
Osimertinib in combination with other targeted therapies	Patients with EGFR-mutant NSCLC and disease progression on a prior EGFR TKI treatment	Multi-arm phase Ib TATTON study (NCT02143466)	Selumetinib (MEK1/2 inhibitor), savolitinib (MET-TKI) or durvalumab (anti-PD-L1)

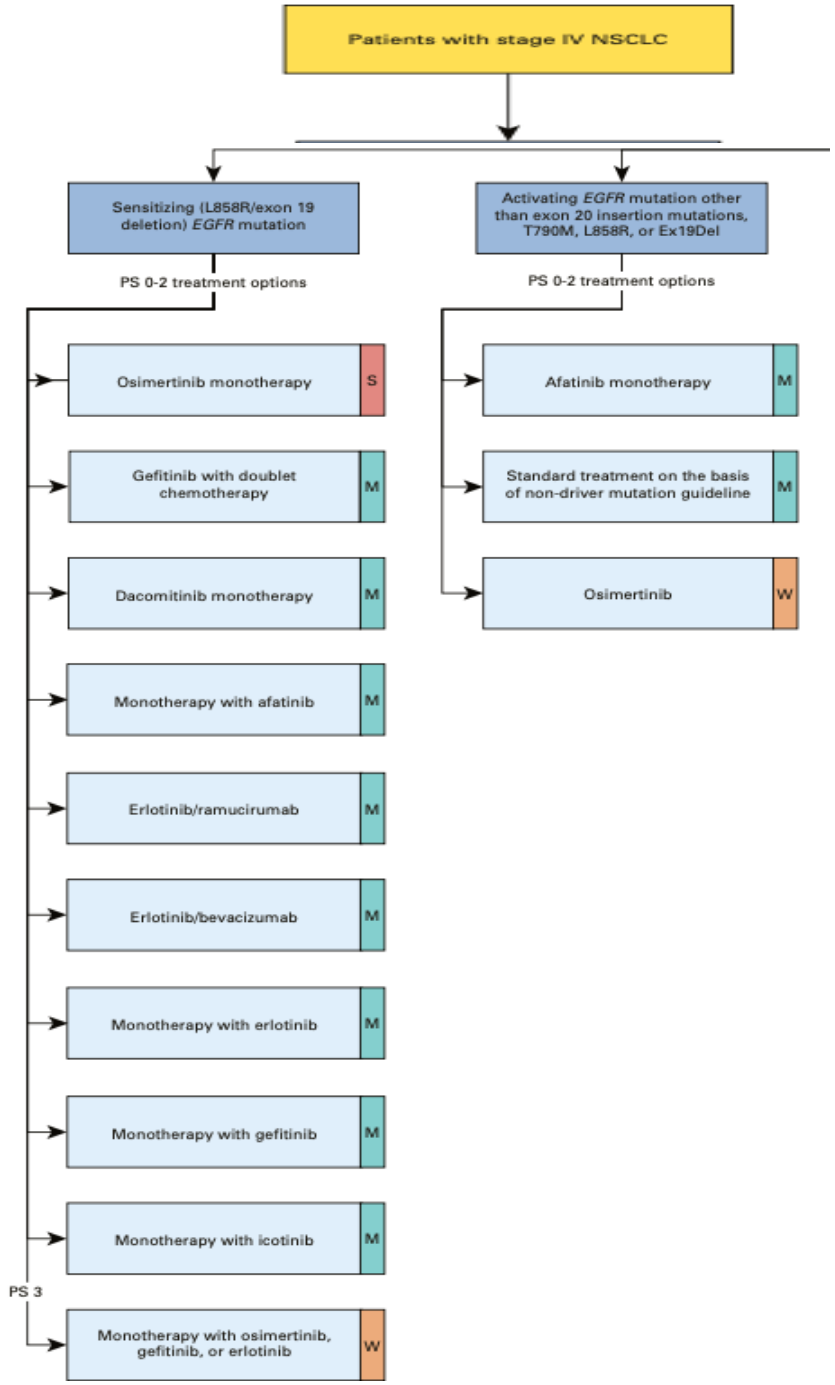
Lim JU, et al. Clinical Oncology 2021;33:619-626

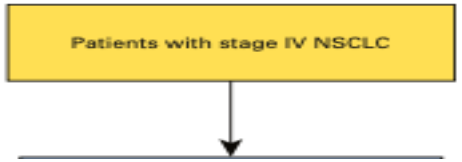
Phase 3 randomized controlled trials comparing tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR-TKIs) and platinum-based chemotherapy as first-line treatment for advanced non-small cell lung cancer (NSCLC) with activating *EGFR* mutations



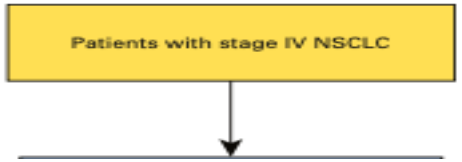
Randomized controlled trials evaluating irreversible tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR-TKIs) or combination treatments using EGFR-TKIs







EXON 20 insertion
PS 0-2 →
Amivantamab plus chemotherapy



Uncommon EGFR Mutations (S768I G719X L861Q Major uncommon mutation)
PS 0-2 → Afatinib

2nd and 3rd line treatment