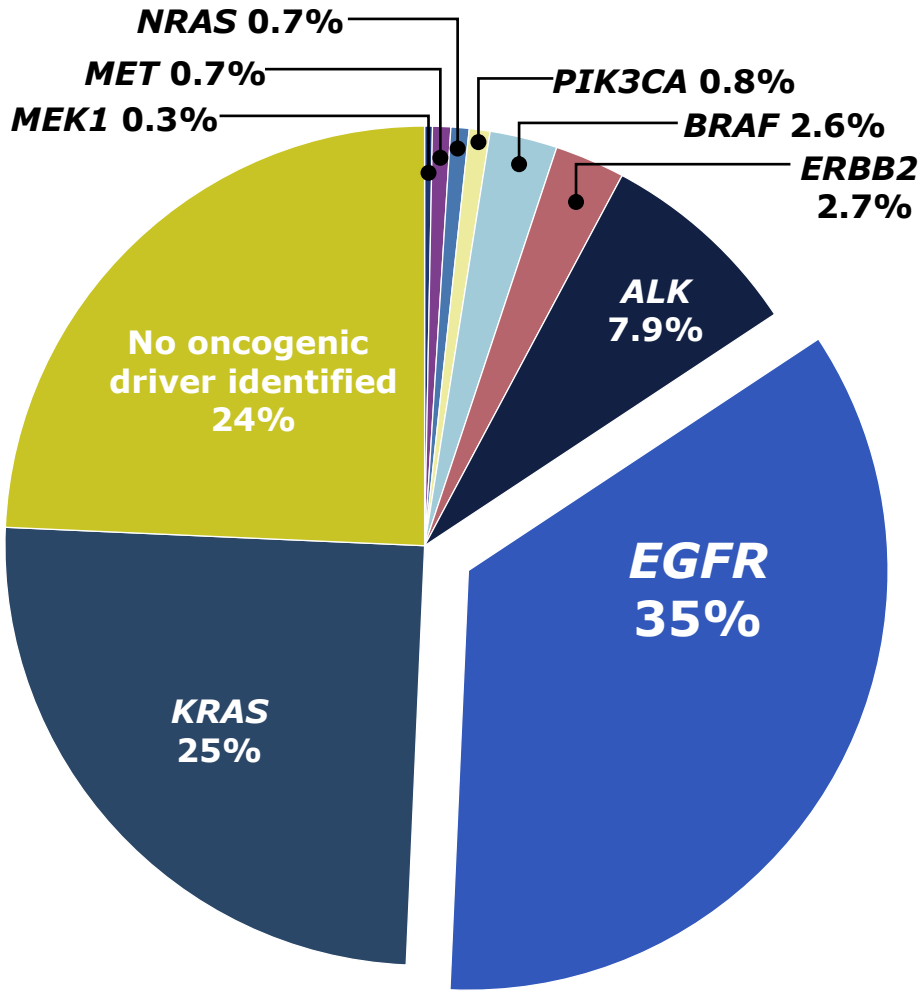
Hidden EGFR Threats and Role of Amivantamab

Exon20ins Mutations

NSCLC: Not One Disease, but Many!



- Activating mutations occur in cancer cell genes that encode proteins critical to cell growth and survival
- Malignant cells with activating mutations are uniquely susceptible to targeted therapy

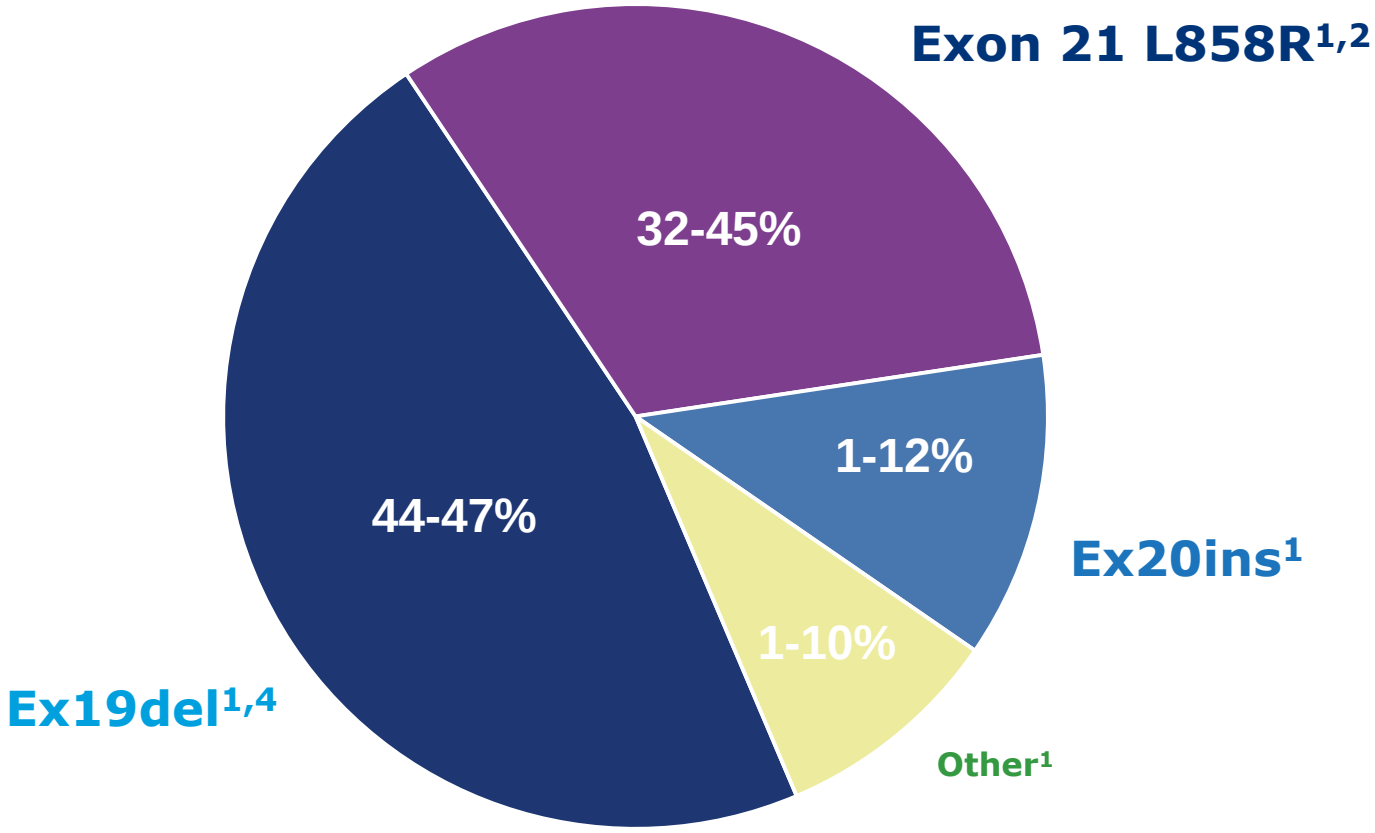
EGFR mutations are among the most prevalent actionable driver mutations in NSCLC

Figure adapted from Heydt C, et al. Oncotarget. 2018;9:15418-15434.

EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion mutation; Ex20ins, exon 20 insertion mutation; NSCLC, non–small cell lung cancer.

1. Heydt C, et al. Oncotarget. 2018;9(20):15418-15434. 2. Herbst RS, et al. *Nature*. 2018;553(7689):446-454. 3. Sequist LV, Neal JW. Personalized, genotype-directed therapy for advanced non-small cell lung cancer. 2019. https://www.uptodate.com/contents/personalized-genotype-directed-therapy-for-advanced-non-small-cell-lung-cancer. Accessed July 23, 2021.

Most Common EGFR Mutations in NSCLC[1]



- Oncogenic mutations of EGFR are found within **exons 18 to 21**
  - Encode part of the tyrosine-kinase domain around the ATP-binding pocket of the enzyme[2]
- **Exon 19 and 21** mutations are often referred to as **common** EGFR activating mutations[3]

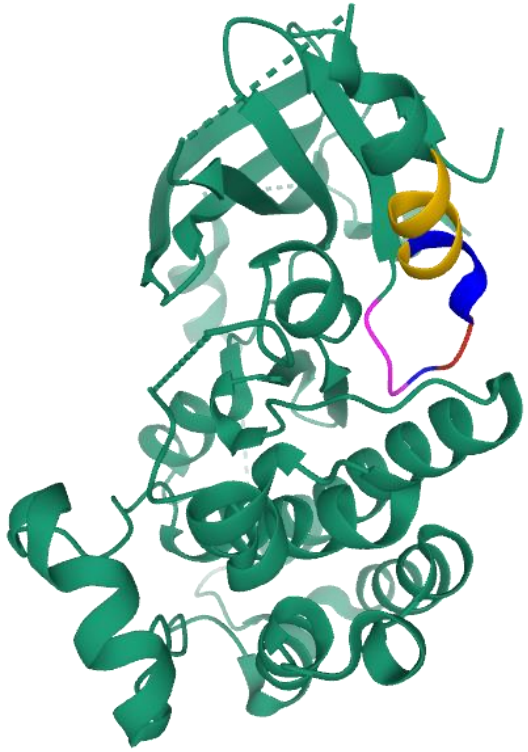
Graph modified from Reiss et al.[1]

ATP, adenosine triphosphate; EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; ex20ins, exon 20 insertion mutation; NSCLC, non–small cell lung cancer.

1. Reiss JW, et al. *J Thorac Oncol*. 2018;13(10):1560-1568. 2. Calvayrac O, et al. *Eur Respir J.* 2017;49(4):1601734. 3. Vyse S and Huang PH. *Signal Transduct Target Ther.* 2019;4:5. 4. Villabos P, et al. *Hematol Oncol Clin North Am*. 2017;31(1):13-29.

EGFR Mutation Location Determine Sensitivity to TKI Therapy

Unlike mutations in EGFR exons 18, 19, and 21, **exon 20 mutations are typically resistant to EGFR TKI therapy** (A763_Y764insFQEA is an exception)[1]



Site of NPG insertion (D770_N771insNPG)

L858R and ex19del mutations cause conformational changes that confer sensitivity to EGFR TKIs[1]

In contrast, ex20ins mutations cause conformational changes that **reduce TKI binding**[1-3]

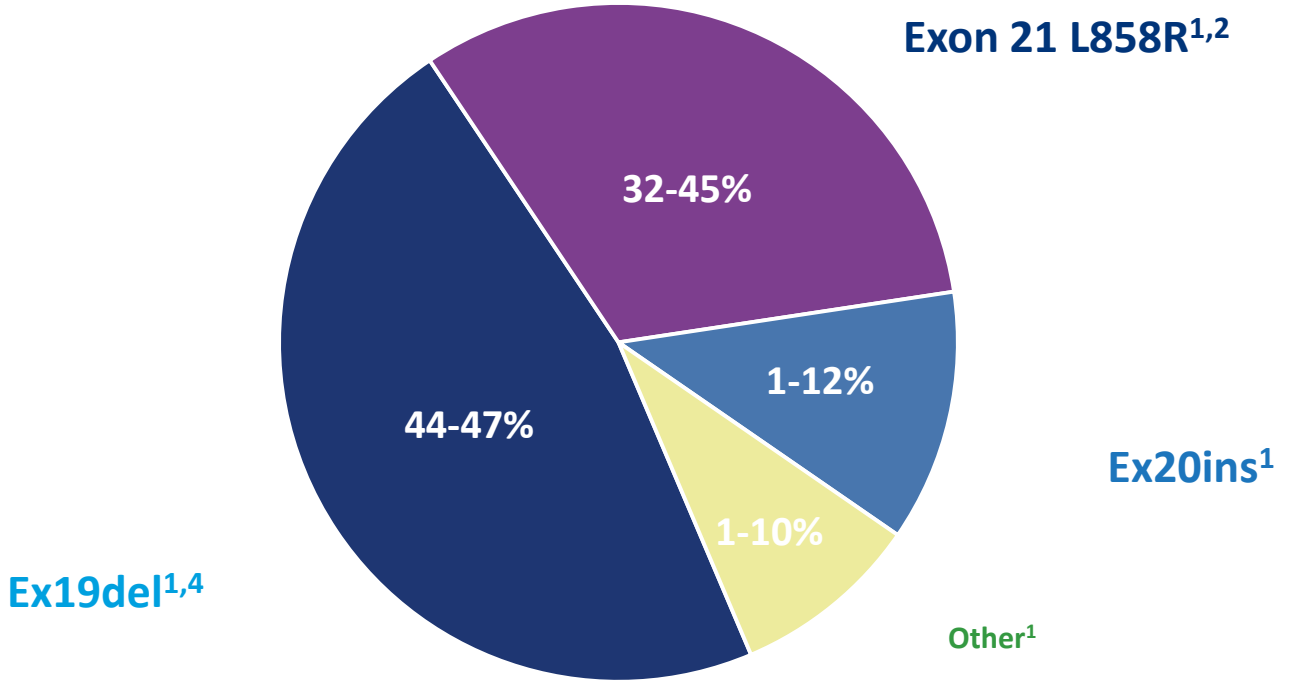
For example, insertions after site 764 (like the NPG insertion) may form a wedge at the end of the helical region that locks it in the **active state**[2,3]

Low response rates of **3-8%** have been reported in patients with EGFR ex20ins mutations treated with erlotinib, gefitinib, and afatinib[1]

EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; ex20ins, exon 20 insertion mutation; TKI, tyrosine kinase inhibitor.

1. Vyse S, et al. *Signal Transduct Target Ther*. 2019;4:5. 2. Yasuda H, et al. *Sci Transl Med*. 2013;5(216):216ra177. 3. Robichaux JP, et al. *Nat Med*. 2018;24(5):638-646.

EGFR exon20ins prevalence and biology

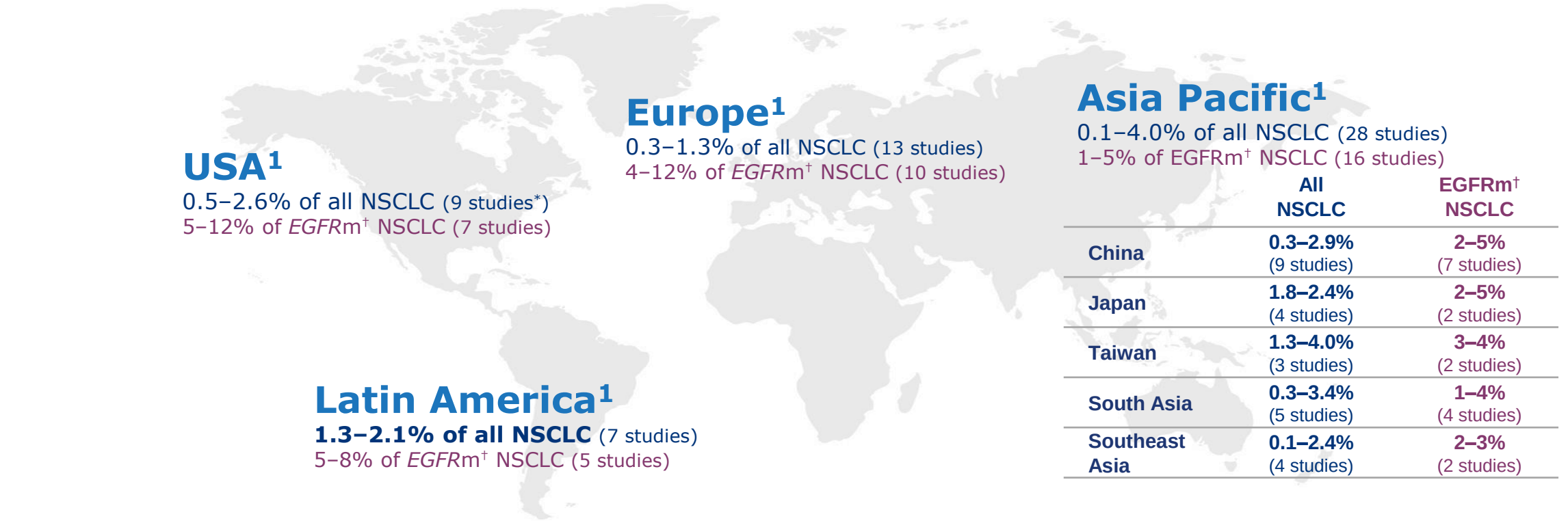


Inframe insertions in exon 20 of the EGFR gene were among the first EGFR mutations to be identified as oncogenic drivers in NSCLC and account for upto 12% of EGFR-mutated NSCLC

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

1. Vyse S, Huang PH. *Signal Transduct Target Ther*. 2019;4:5; 2. Reiss JW, et al. *J Thorac Oncol*. 2018;13:1560–1568; 3. Burnett H, et al. *PLoS One*. 2021;16:e0247620; abstract P09.61; 4. Calvayrac O, et al. *Eur Respir J*. 2017;49; 5. Villalobos P, et al. *Hematol Oncol Clin North Am*. 2017;31:13–29.

EGFR exon20ins prevalence and biology



USA[1]

0.5–2.6% of all NSCLC (9 studies*)
5–12% of *EGFR*m† NSCLC (7 studies)

Europe[1]

0.3–1.3% of all NSCLC (13 studies)
4–12% of *EGFR*m† NSCLC (10 studies)

Latin America[1]

1.3–2.1% of all NSCLC (7 studies)
5–8% of *EGFR*m† NSCLC (5 studies)

Asia Pacific[1]

0.1–4.0% of all NSCLC (28 studies)
1–5% of EGFRm† NSCLC (16 studies)

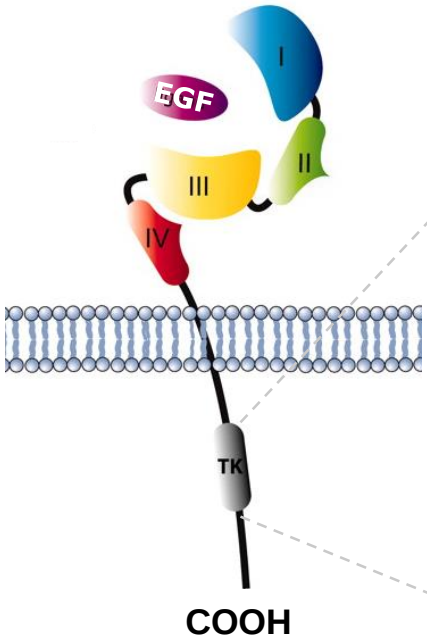
	All NSCLC	EGFRm† NSCLC
China	**0.3–2.9%** (9 studies)	**2–5%** (7 studies)
Japan	**1.8–2.4%** (4 studies)	**2–5%** (2 studies)
Taiwan	**1.3–4.0%** (3 studies)	**3–4%** (2 studies)
South Asia	**0.3–3.4%** (5 studies)	**1–4%** (4 studies)
Southeast Asia	**0.1–2.4%** (4 studies)	**2–3%** (2 studies)

The real-world frequency of exon20ins mutations varies[1] and may be underestimated due to the limitations of current testing methods used[1,2]

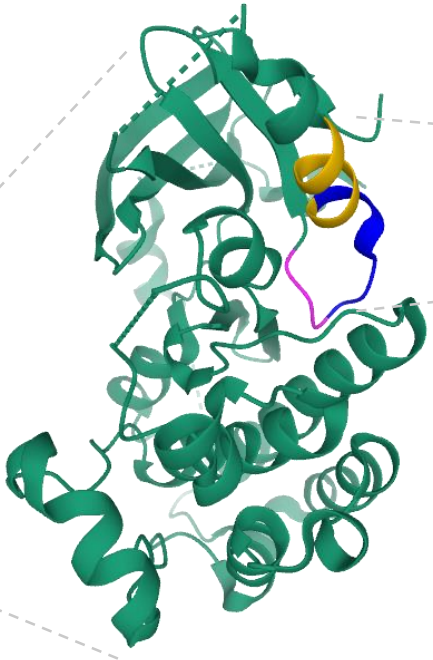
Most studies reporting frequency of mutation are based on single-centre studies, which impacts the validity of findings.
*Excludes Arcila et al. 2013 that primarily examined targeted NSCLC tumours known to be negative for major EGFR mutations (Exon 19 deletion, L858R) and KRAS and may therefore overestimate the frequency of exon20ins; †Includes all EGFR mutations.
EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer.
1. Burnett H, et al. *PLoS One*. 2021;16:e0247620; 2. Bauml JM, et al. Featured poster presentation at WCLC 2020; abstract FP07.12.

EGFR exon20ins prevalence and biology

EGFR[1]



Tyrosine kinase domain[1]



EGFR exon20ins location[1,2]

Helical region						Near loop						Far loop		
761 D	762 E	763 A	764 Y	765 V	766 M	767 A	768 S	769 V	770 D	771 N	772 P	773 H	774 V	775 C

Exon20ins are either inframe insertions or duplications[1]

Most insertions comprise 3–21 nucleotide base pairs (1–7 amino acids)[1]

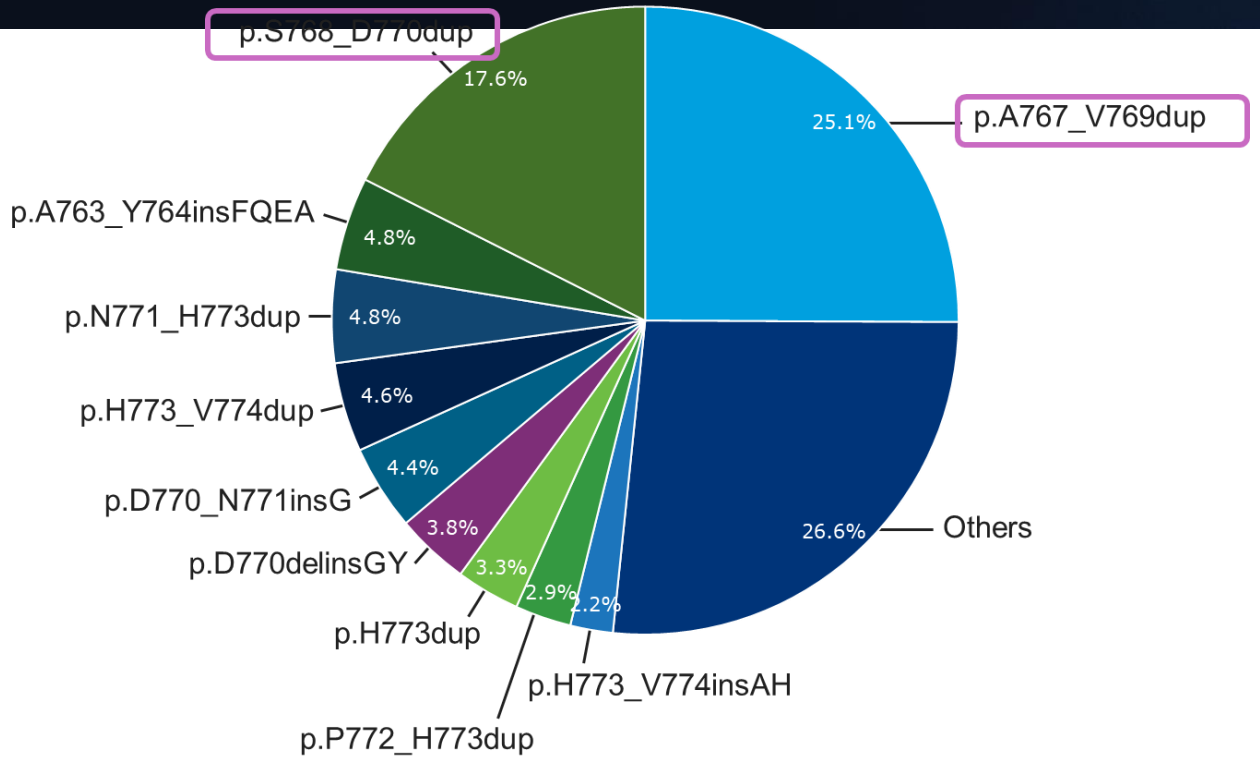
The location of these insertions can influence drug- and ATP- binding kinetics[1]

Most insertions typically occur between amino acids 761 to 775 and can be divided in according to the protein structure they form: helical, near loop, and far loop[1,2]

ATP, adenosine triphosphate; EGFR, epidermal growth factor receptor.

1. Vyse S, Huang PH. *Signal Transduct Target Ther*. 2019;4:5; 2. Choudhury NJ, et al. *Clin Cancer Res*. 2021;ePub ahead of print.

EGFR exon20ins prevalence and biology



There are a broad number of EGFR exon20ins variants;[1,2] to date, over 100 unique variants of EGFR exon20ins mutations have been identified.[1] A retrospective study suggested that p.A767_V769dup and p.S768_D770dup were the most prevalent exon20ins variants[2]

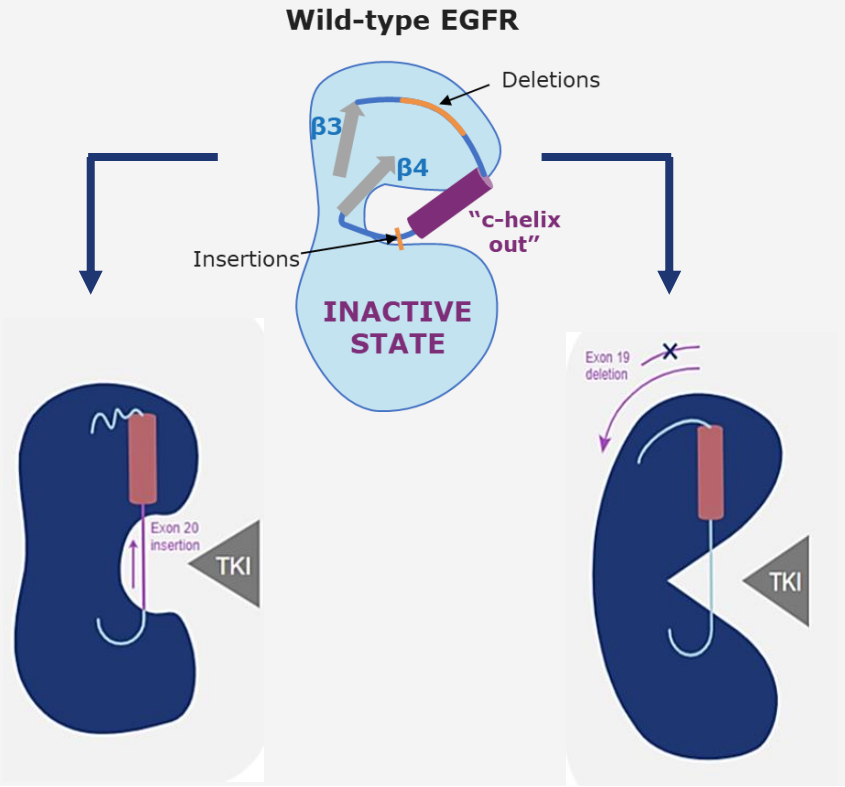
EGFR, epidermal growth factor receptor.

1. Bauml JM, et al. Oral presentation at WCLC 2020; abstract FP07.12; 2. Qin Y, et al. *Mol Oncol*. 2020;14:1695–1704.

EGFR exon20ins prevalence and biology

EGFR exon20ins result in:
- Sterically hindered drug-binding pocket[1–3]
- Activation of EGFR without markedly reduced ATP affinity or enhanced affinity for the first-generation inhibitor gefitinib[1,2]

Resistance to most EGFR TKIs with loss of therapeutic window[1,2]



Common EGFR mutations result in:
- Reduced affinity for ATP[1,2]
- Enhanced affinity for EGFR TKIs[1,2]

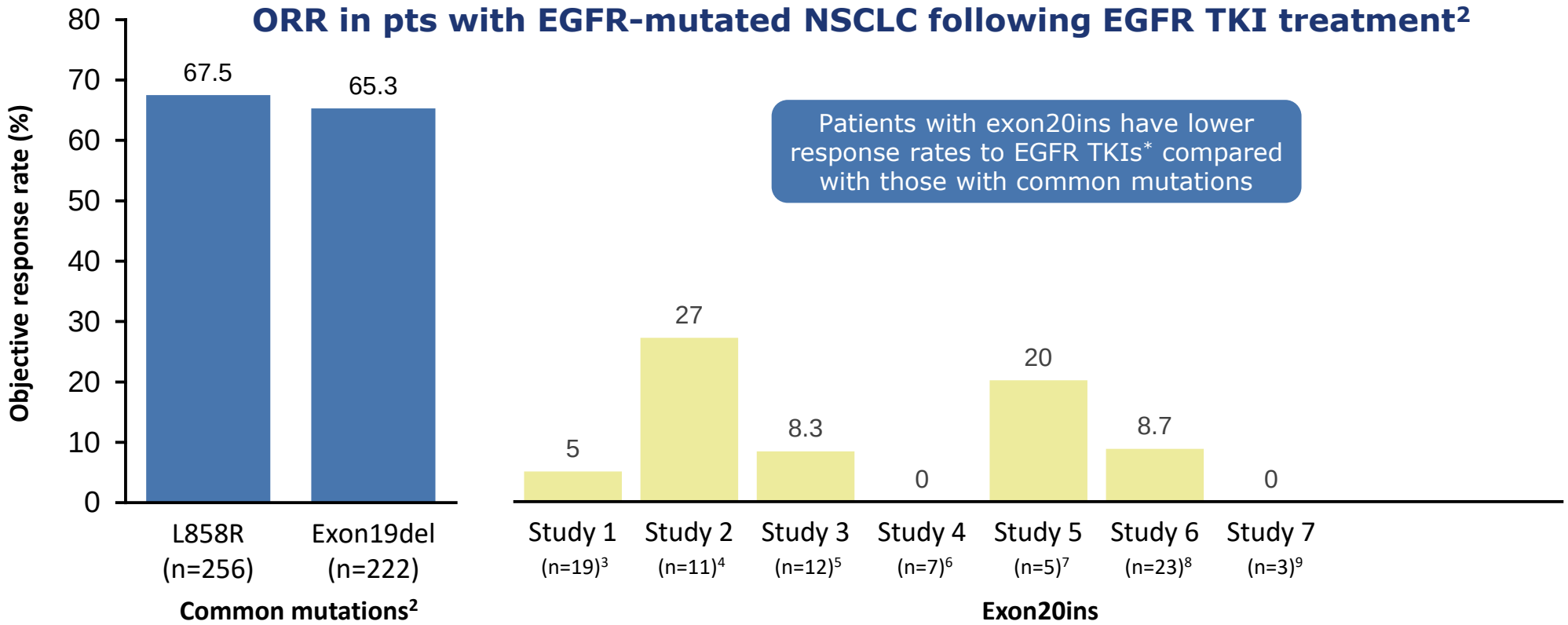
Sensitivity to EGFR TKIs with wide therapeutic window[1,2]

EGFR exon20ins are unique and distinct from common EGFR mutations. Compared with common mutations, exon20ins induce unique conformational changes in EGFR and reduce the size of the drug binding pocket and affinity for TKIs[1–3]

ATP, adenosine triphosphate; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

1. Vyse S, Huang PH. *Signal Transduct Target Ther*. 2019;4:5; 2. Yasuda H, et al. *Sci Transl Med*. 2013;5:216ra177; 3. Robichaux JP, et al. *Nat Med*. 2018;24:638–646.

Limited Treatment Options



EGFR TKIs have transformed the treatment landscape for EGFR-mutated NSCLC. However, exon20ins are generally insensitive to EGFR TKI treatment[1]

*EGFR TKIs included gefitinib, erlotinib, icotinib, afatinib, osimertinib, neratinib and dacomitinib.

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

1. Vyse S, Huang PH. *Signal Transduct Target Ther*. 2019;4:5; 2. Harrison PT, et al. *Semin Cancer Biol.* 2020;61:167–179; 3. Beau-Faller M, et al. *Ann Oncol.* 2014:25:126–131;
4. Naidoo J, et al. *Cancer*. 2015;121:3212–3220; 5. Xu J, et al. *Lung Cancer*. 2016;96:87–92; 6. Kate S, et al. *Lung Cancer.* 2019;10:1–10; 7. Janne PA, et al. *Clin Cancer Res.* 2011;17:1131–1139; 8. Yang JCH, et al. *Lancet Oncol.* 2015;16:830–838; 9. Sequist LV, et al. *J Clin Oncol.* 2010;28:3076–3083.

Limited Treatment Options

Summary of prognostic impact of exon20ins compared with other genotypes

	Outcomes with EGFR TKIs[1]		
	Median OS (months)	Median PFS (months)	ORR (%)
Exon20ins	**4.8–19** 6 studies 177 patients (11–67)	**1.4–3.0** 8 studies 183 patients (11–67)	**0–20%** 7 studies 194 patients (11–67)
Classic EGFRm (19del or L858R)	19.6–27.7 3 studies 501 patients (37–278)	8.5–15.2 3 studies 501 patients (37–278)	27.4–84% 5 studies 1,193 patients (37–692)

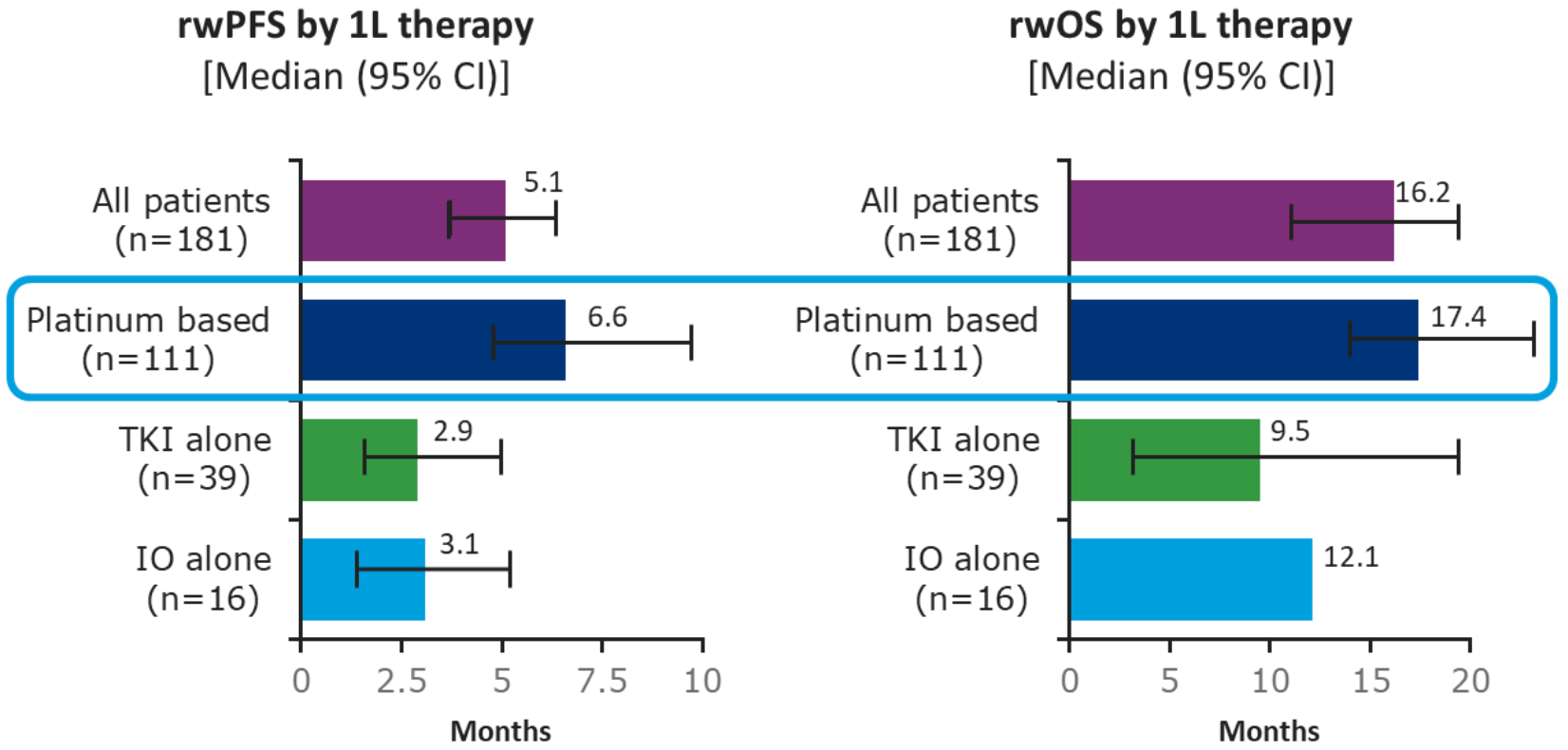
A systematic literature review of 78 studies found that currently available EGFR TKIs were generally ineffective against EGFR exon20ins (ORR of 0–20%; mPFS of 1.4–3.0 months with erlotinib/gefitinib/osimertinib treatment)

EGFR, epidermal growth factor receptor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Burnett H, et al. *PLoS One*. 2021;16:e0247620.

Limited Treatment Options

Including platinum-based chemotherapy in combination with IO agents

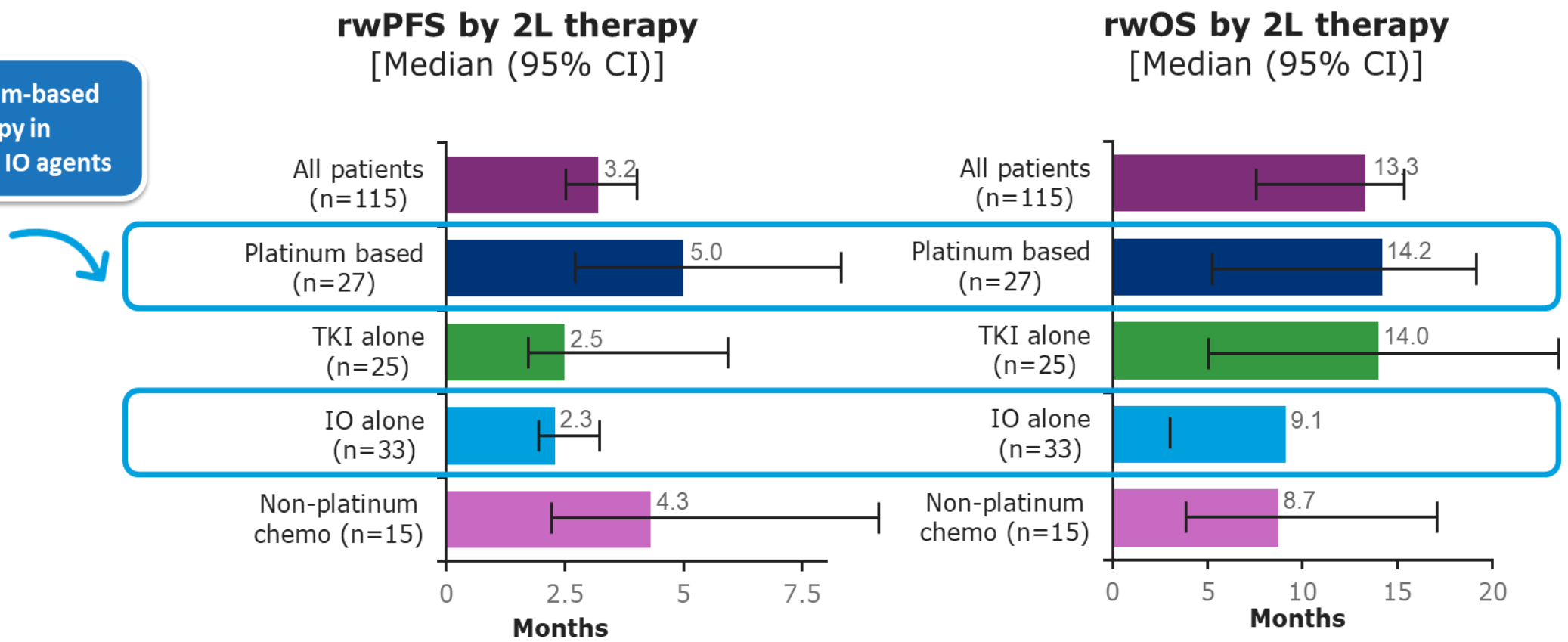


Platinum-based therapies are the most common first-line treatment for patients with EGFR exon20ins.[1,2] However, responses are still not durable (mOS: 17.4–18.2 months[1–4]; mPFS: 5.3–6.6 months)[2,4]

CI, confidence interval; IO, immuno-oncology; mOS, median overall survival; mPFS, median progression-free survival; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; TKI, tyrosine kinase inhibitor; VEGFi, vascular endothelial growth factor inhibitor. 1. Dersarkissian M, et al. Poster presentation at IASLC 2019; abstract P2.01-103; 2. Girard N, et al. Oral presentation at WCLC 2020; abstract MA04.07; 3. Choudhury NJ, et al. *Clin Cancer Res.* 2021;ePub ahead of print; 4. Burnett H, et al. *PLoS One*. 2021;16:e0247620.

Limited Treatment Options

Including platinum-based chemotherapy in combination with IO agents



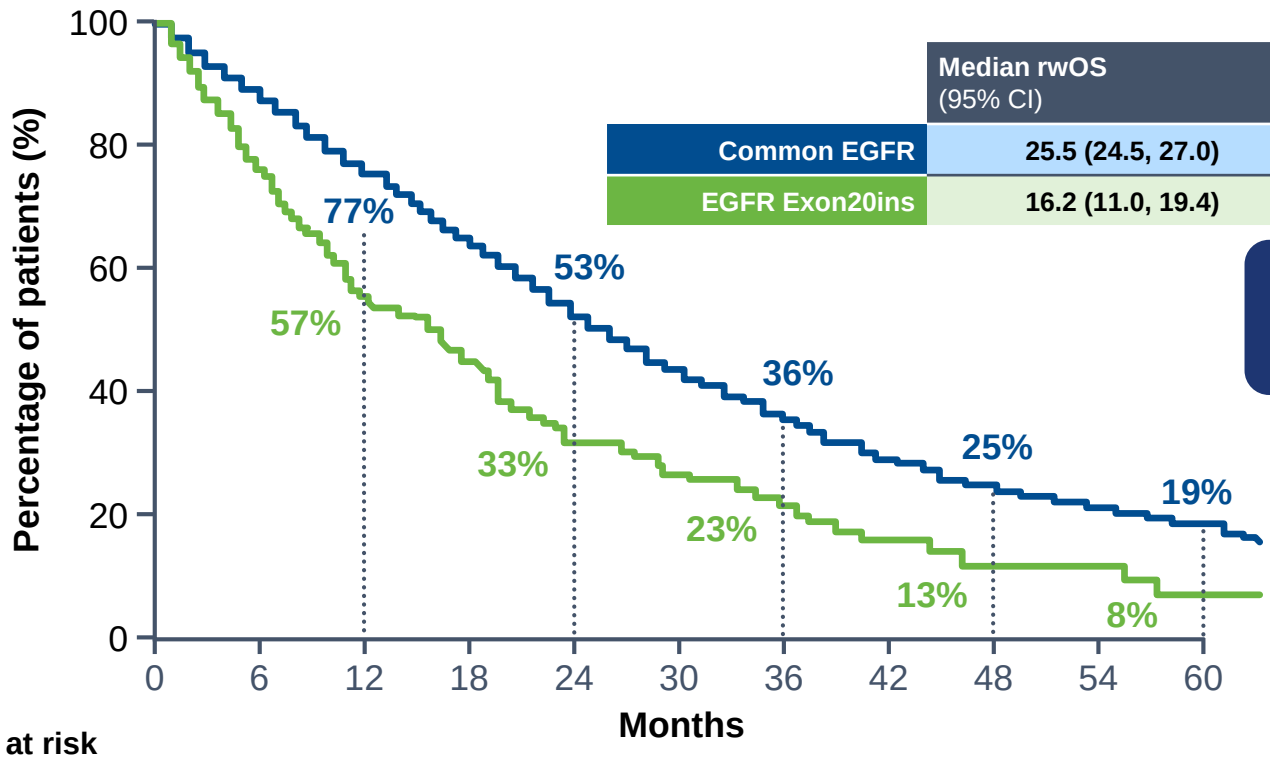
There is no standard of care for second line treatment, with IO and chemotherapy, having limited efficacy both alone, and in combination[1–3]

CI, confidence interval; IO, immuno-oncology; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; TKI, tyrosine kinase inhibitor.

1. Choudhury NJ, et al. *Clin Cancer Res*. 2021;ePub ahead of print; 2. Dersarkissian M, et al. Poster presentation at IASLC 2019; abstract P2.01-103;
3. Fang W, et al. *BMC Cancer.* 2019;19:595; 4. Girard N, et al. Oral presentation at WCLC 2020; abstract MA04.07;

RWE Analysis: Results

Real-world overall survival



	Median rwOS (95% CI)	Adjusted HR (95% CI)	P value
Common EGFR	25.5 (24.5, 27.0)	1.75 (1.5, 2.1)	<0.0001
EGFR Exon20ins	16.2 (11.0, 19.4)		

Patients with exon20ins had a poorer prognosis and 75% increased risk of death*

Patients at risk

Common *EGFR*	2833	2245	1728	1313	943	675	494	354	262	198	139
Exon20ins	181	120	77	53	30	22	16	11	6	5	3

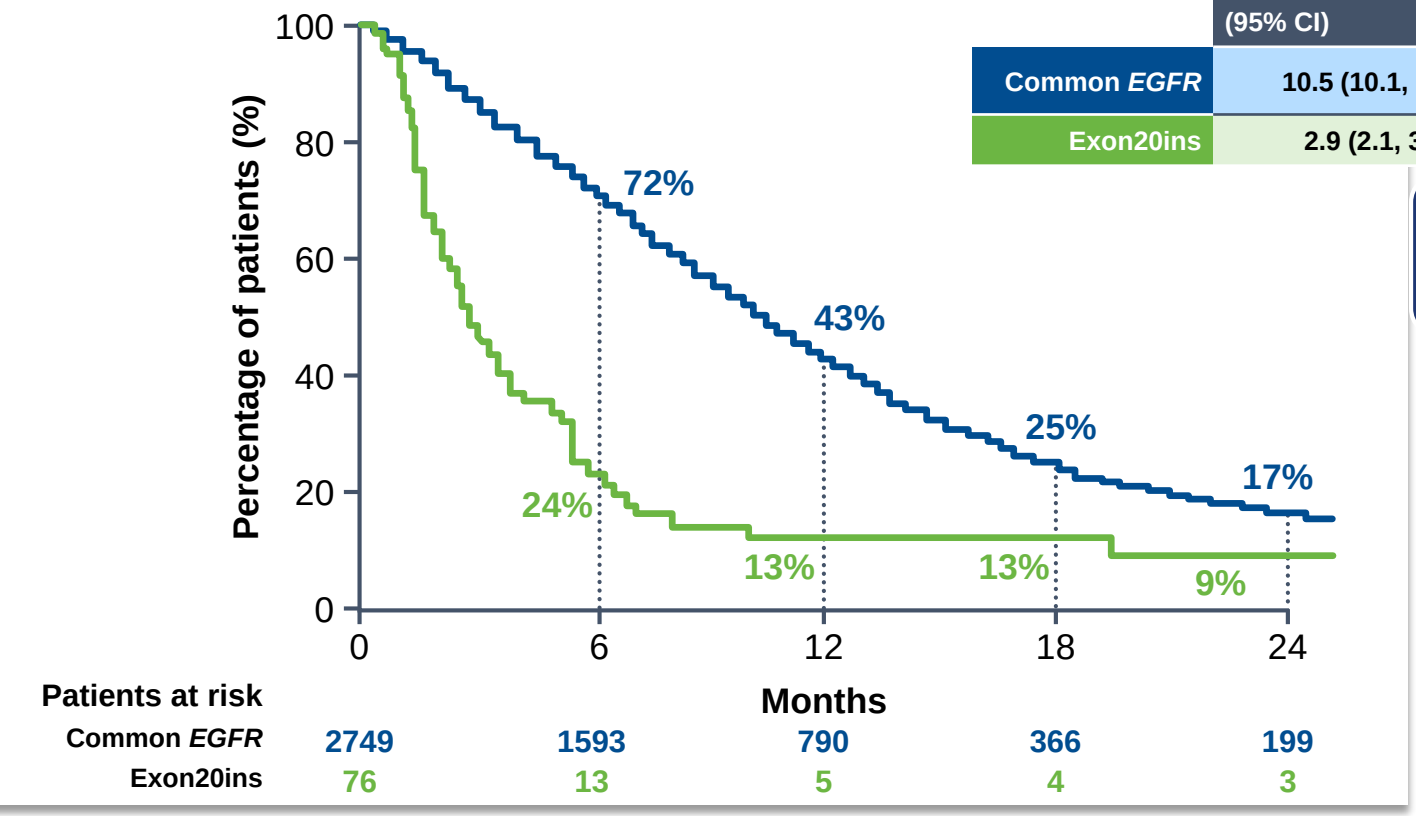
A study of 3,014 patients with advanced EGFR-mutated NSCLC investigated the prognostic value of EGFR exon20ins compared with common EGFR mutations (exon 19 deletions or L858R mutations)

*Flatiron database, 181 patients with advanced NSCLC with exon 20 insertions from 2011–2020.

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; rwOS, real-world overall survival. Girard N, et al. Oral presentation at WCLC 2020; abstract MA04.07.

RWE Analysis: Results

Real-world progression-free survival



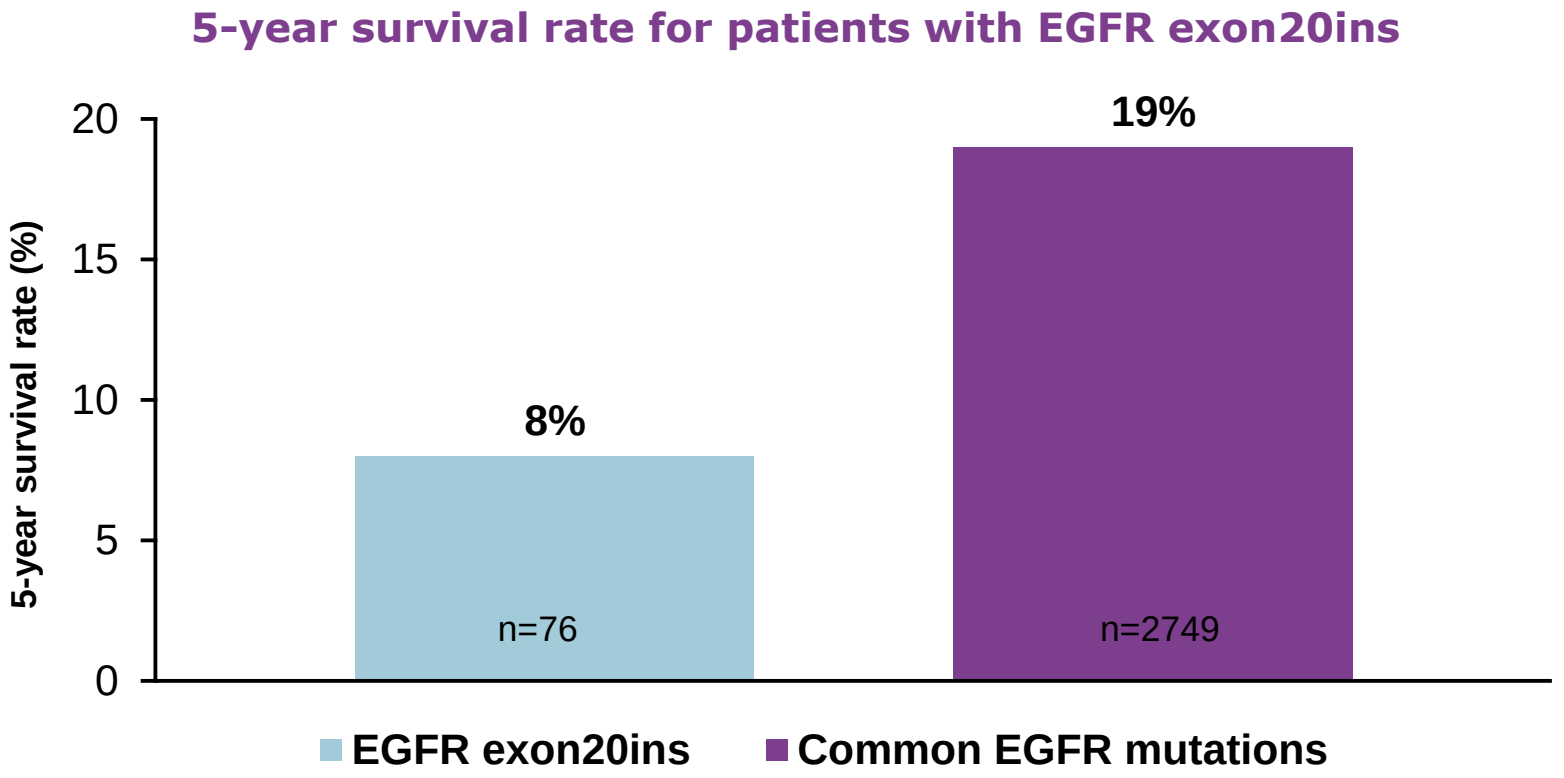
	Median rwOS (95% CI)	Adjusted HR (95% CI)	P value
Common *EGFR*	10.5 (10.1, 10.9)	2.69 (2.1, 3.6)	<0.0001
Exon20ins	2.9 (2.1, 3.9)		

Patients with exon20ins had a poorer prognosis and 169% increased risk of progression or death on EGFR TKIs

A study of 2,825 patients investigated the predictive value of exon20ins for EGFR TKI treatment. Exon20ins were associated with less benefit from EGFR TKIs compared with common EGFR mutations

*Flatiron database, 181 patients with advanced NSCLC with exon 20 insertions from 2011–2020. CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; rwOS, real-world overall survival; TKI, tyrosine kinase inhibitor. Girard N, et al. Oral presentation at WCLC 2020; abstract MA04.07.

RWE Analysis: Results



The estimated 5-year survival rate for patients with EGFR exon20ins was 8% compared with 19% for common EGFR mutations

EGFR, epidermal growth factor receptor.
Girard N, et al. Oral presentation at WCLC 2020; abstract MA04.07.

Summary

Patients with EGFR ex20ins have **poorer prognosis** compared with patients with cEGFR

- **75%** increased risk of death
- **93%** increased risk of progression or death
- 5-year overall survival of **8%**

Patients with ex20ins derived **less benefit from TKIs** compared with patients with cEGFR

- **170%** increased risk of death
- **169%** increased risk of progression or death

Platinum-based therapies were the most common first-line treatment for ex20ins NSCLC, with no clear SOC in second-line

The poor outcomes associated with ex20ins NSCLC illustrate the **need for new effective therapies**

cEGFR, common EGFR mutations; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion mutation; NSCLC, non–small cell lung cancer; SOC, standard of care; TKIs, tyrosine kinase inhibitors.

Girard N, et al. Presented at the International Association for the Study of Lung Cancer 2020 World Conference on Lung Cancer. 28-31 January 2021; Virtual. Abstract 3390.

Exon20ins: Indian Scenario

- Only 2 retrospective studies reported the efficacy of currently available treatment regimes in patients with Exon20ins mutations

- Kate S et al in their retrospective study reported that patients with Ex20ins had a mPFS of 6 months (95% CI, 2.4–9.6), and mOS of 15.8 months (95% CI, 6.2–25.3)

- In the same study mPFS with oral TKIs was 1.9 months (95% CI, 0.3–3.5)

- Noronha V et al reported dismal mOS of only 5 months (95% CI, 0.17–9.8) in patients with *EGFR* Ex20ins

The prognosis of patients with Exon20ins mutation remains poor

1. Lung Cancer. 2011 Sep;73(3):316-9.; 2. Indian J Cancer 2013;50:87-93.; 3. Onco Targets Ther. 2017 Jun 9;10:2903-2908.; 4. Lung Cancer (Auckl). 2019 Jan 29;10:1-10.; 5. Lung Cancer. 2020 Nov;149:53-60.; 6. Journal of Thoracic Oncology Vol. 16 No. 8: 1250-1266.

Exon20ins: Indian Scenario

Author Name	Year	Exon20ins % in EGFR+ domain
Sahoo R et al[1]	2011	9/220 (4.0%)
Veldore VH et al[2]	2013	17/418 (4.06%)
Chougule A et al[3]	2013	7/215 (3.25%)
Noronha V et al[4]	2017	20/227 (8.8%)
Kate S et al[5]	2019	15/227 (6.6%)
Singh S et al[6]	2020	4/391 (1.02%)
Singh N et al[7]	2021	16/298 (5.4%)

The reported prevalence of Exon20ins mutations in India is in the range of ~1 – 8%

1. Lung Cancer. 2011 Sep;73(3):316-9.; 2. Indian J Cancer 2013;50:87-93.; 3. PLoS One. 2013 Oct 4;8(10):e76164.; 4 Onco Targets Ther. 2017 Jun 9;10:2903-2908.; 5. Lung Cancer (Auckl). 2019 Jan 29;10:1-10.; 6. Lung Cancer. 2020 Nov;149:53-60.; 7. Journal of Thoracic Oncology Vol. 16 No. 8: 1250-1266.

Onco Targets Ther. 2017; 10: 2903–2908.
Published online 2017 Jun 9. doi: 10.2147/OTT.S133245
PMCID: PMC5476719
PMID: 28652772

Epidermal growth factor receptor exon 20 mutation in lung cancer: types, incidence, clinical features and impact on treatment

Vanita Noronha,[1,*] Anuradha Choughule,[2,*] Vijay M Patil,[1,*] Amit Joshi,[1] Rajiv Kumar,[3] Deepa Susan Joy Philip,[1] Shripad Banavali,[2] Amit Dutt,[4] and Kumar Prabhash[2]

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Abstract

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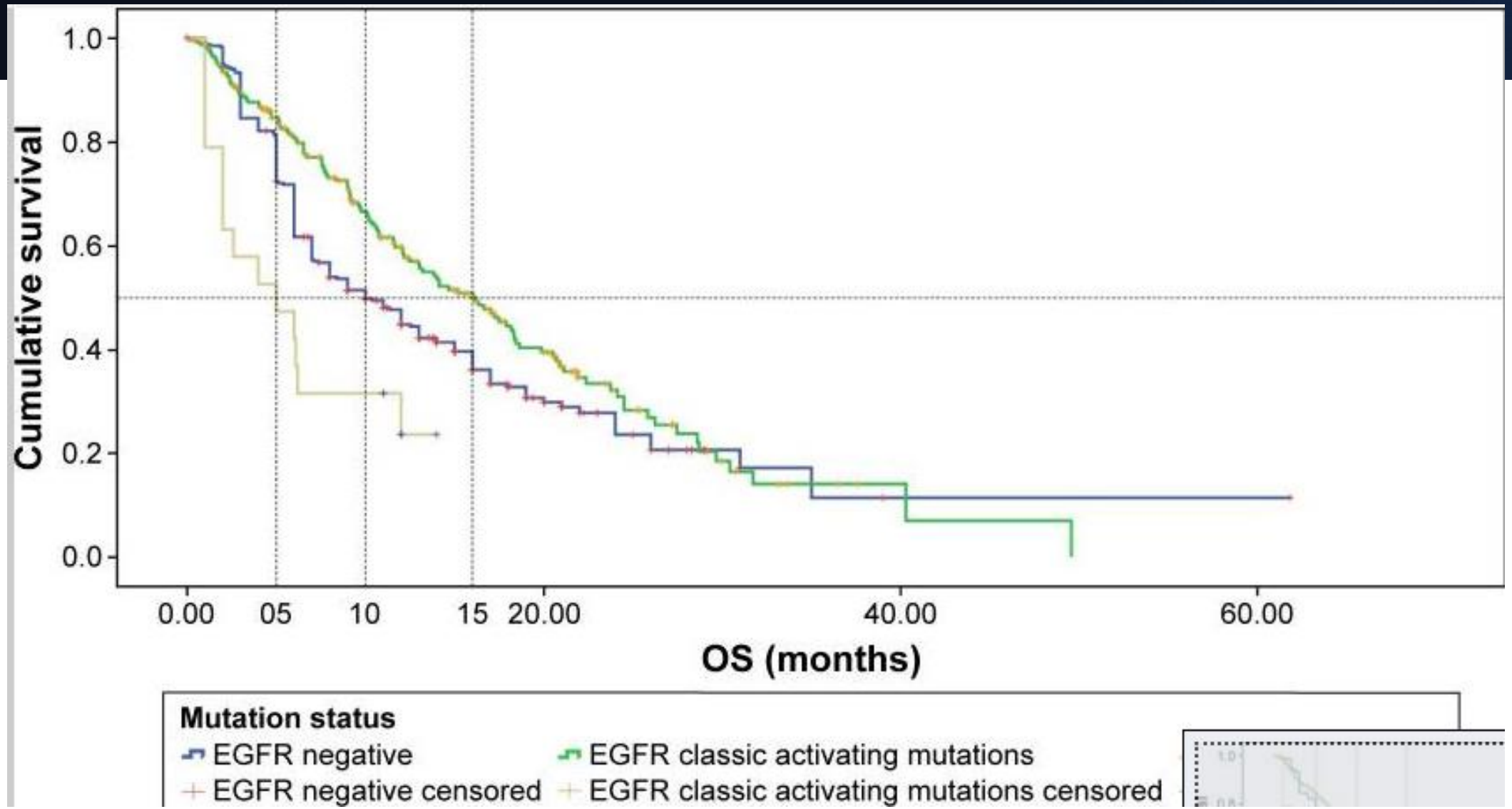
Table 1

Demographic and clinical profiles of the three patient cohorts

Variables	EGFR TKI-sensitizing activating mutations (n=227)	Exon 20 (n=20)	EGFR and ALK mutation negative (n=333)
Median age, years	56 (IQR 50–63)	59 (IQR 47.8–65)	56 (IQR 49–62)
Gender distribution, n (%)	Male: 141 (62.1)	Male: 12 (60.0)	Male: 222 (66.7)
	Female: 86 (37.9)	Female: 8 (40.0)	Female: 111 (33.3)
Nonsmokers, n (%)	168 (74.0)	13 (65.5)	168 (52.0)
PS, n (%)	0–1: 110 (48.5)	0–1: 12 (60.0)	0–1: 260 (78.5)
	2 or >2: 117 (51.5)	2 or >2: 8 (40.0)	2 or >2: 73 (21.9)
Extrathoracic metastasis, n (%)	105 (46.3)	11 (55.0)	106 (31.8)
Brain metastasis, n (%)	29 (12.8)	06 (30.0)	10 (3.0)
Bone metastasis, n (%)	59 (26.0)	05 (25.0)	84 (25.2)
Liver metastasis, n (%)	39 (17.2)	02 (10.0)	29 (08.7)
Multiple organ metastases, n (%)	19 (8.3)	02 (10.0)	17 (5.1)

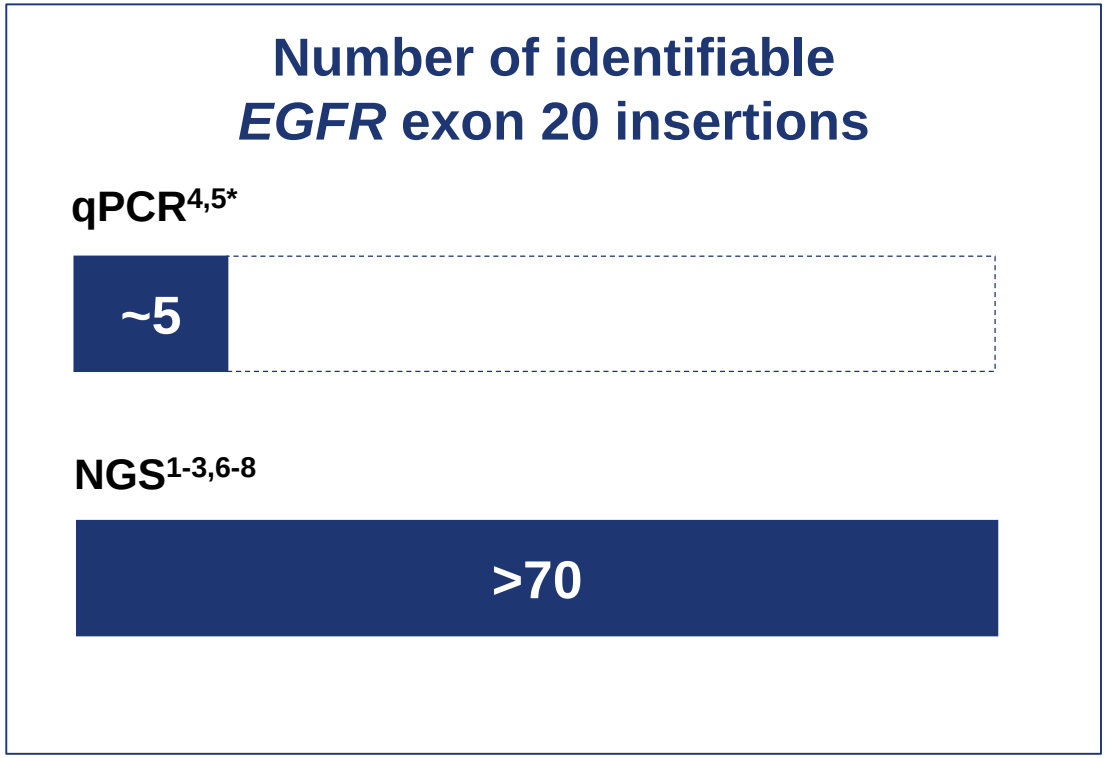
Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase; IQR, interquartile range; PS, performance status.


Cumulative survival
1.0
0.8
0.6
0.4
0.2
0.0
0.00
05
10
15
20.00
40.00
60.00
OS (months)
Mutation status
EGFR negative
EGFR negative censored
EGFR classic activating mutations
EGFR classic activating mutations censored

PCR-based tests only detect a limited number of *EGFR* exon 20 insertion mutations[1-3]

- While PCR-based tests are mutation-specific, NGS tests can detect a broad range of *EGFR* exon 20 insertion mutations[1-3]
  - In one study, comprehensive genomic profiling across 263 patients revealed 64 unique exon 20 insertion mutations[1]

Because targeted PCR-based approaches for detection of EGFR variants may underdetect *EGFR* exon 20 insertion mutations, the NCCN recommends NGS-based strategies[9]



*Commercially available qPCR methods, including Roche cobas® EGFR mutation test v2 and Qiagen therascreen EGFR RGQ PCR kit.[4,5]

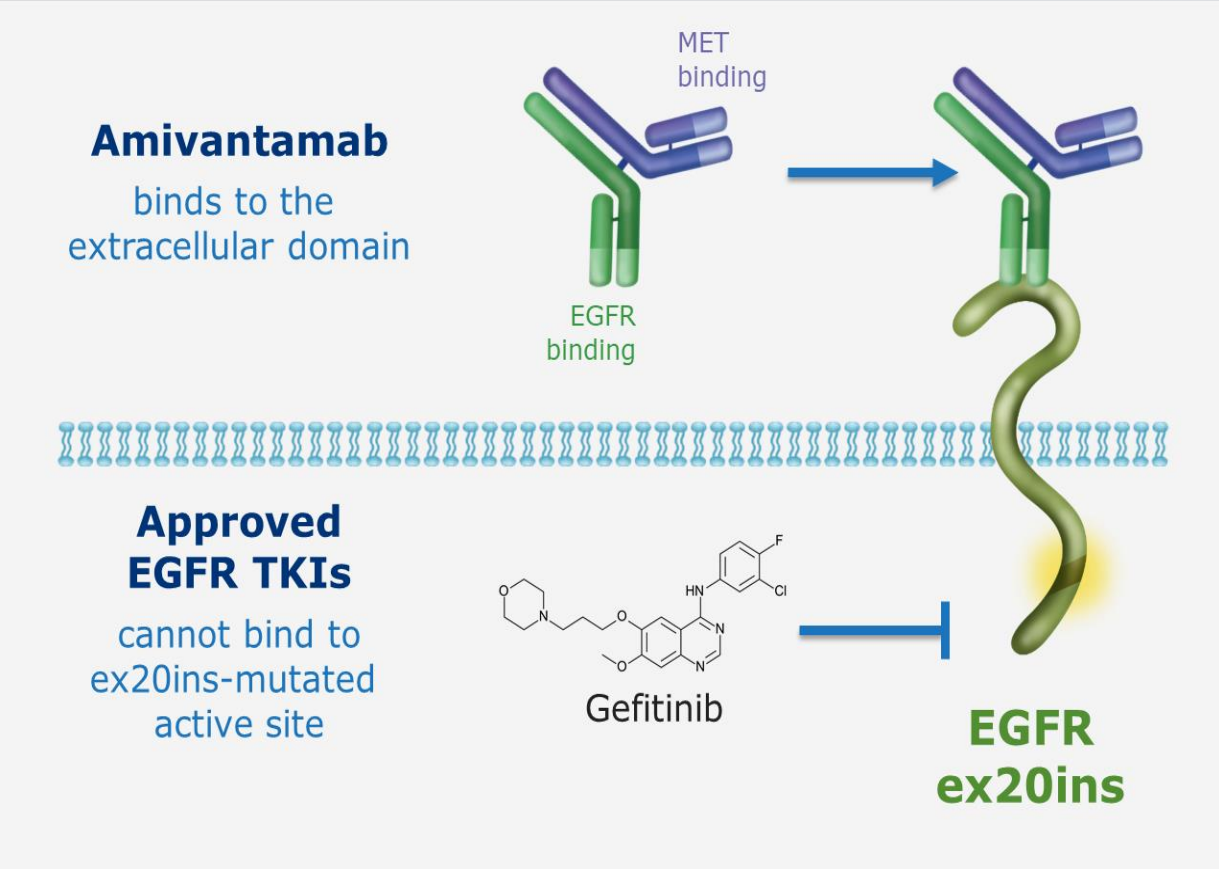
NGS, next-generation sequencing; PCR, polymerase chain reaction; qPCR, quantitative PCR; RGQ, Rotor-Gene Q.

1. Riess JW. *J Thorac Oncol*. 2018;13:1560-1568. 2. Oxnard GR. *J Thorac Oncol*. 2013;8:179-184. 3. Bauml J. Presented at: the IASLC 2020 World Conference on Lung Cancer; January 28-31, 2021; Singapore. 4. cobas® EGFR Mutation Test v2. Roche. Accessed September 27, 2021. https://pim-eservices.roche.com/LifeScience/Document/6be3ed31-f399-ea11-fc90-005056a71a5d 5. therascreen EGFR RGQ PCR Kit Handbook. QIAGEN. Accessed September 27, 2021. https://www.qiagen.com/sg/resources/download.aspx?id=db4d279d-ef20-4441-8c86-e765d23c3bba&lang=en 6. Arcila ME. *Mol Cancer Ther.* 2013;12(2):220-229. 7. Wang F. *Transl Cancer Res*. 2020;9(4):2982-2991. 8. Yasuda H. *Lancet Oncol*. 2012;13(1):e23-e31.

Role of Amivantamab

Amivantamab: A fully human, EGFR-MET bispecific antibody

- Amivantamab binds extracellularly, so it is not affected by co-mutations in the EGFR TKI binding pocket
- By targeting activating and resistance EGFR mutations and MET mutations and amplifications, amivantamab addresses 2 major mechanisms of resistance to SOC
- Amivantamab binds EGFR and MET with high affinity

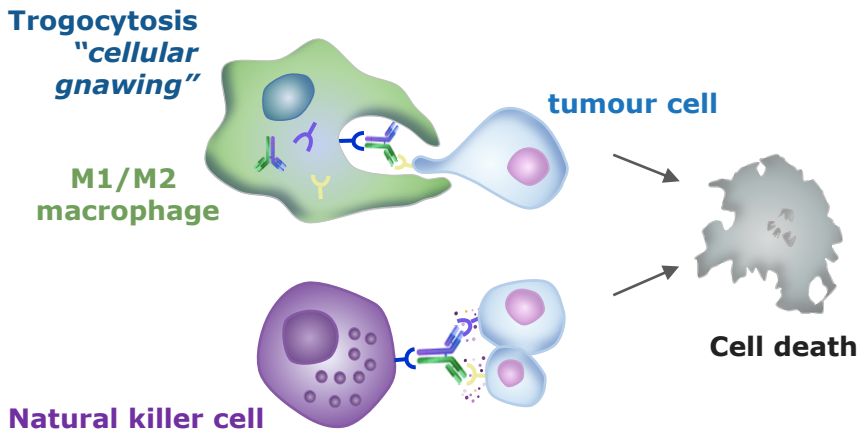


Moores SL, et al. *Cancer Res*. 2016;76(13):3942-3953.

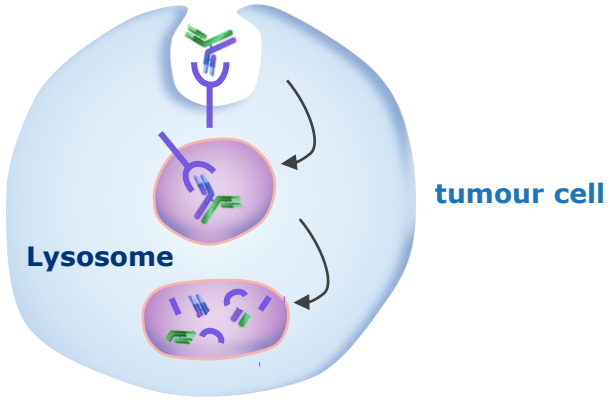
Amivantamab has demonstrated three MoAs[1–3]

MoA relevant to EGFR-mutated NSCLC

1. Immune cell–directing activity



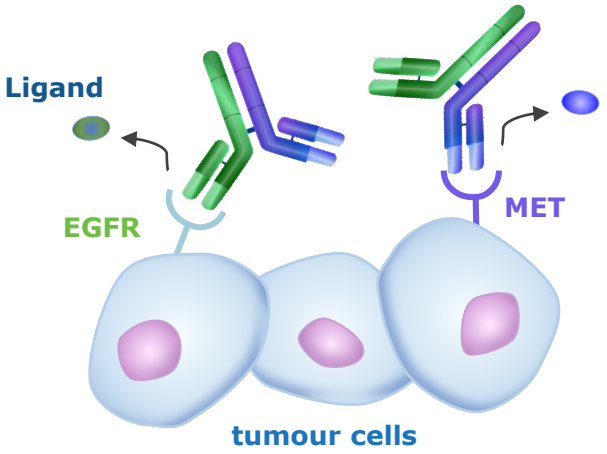
2. Receptor degradation



Trogocytosis also contributes to receptor degradation

MoA relevant to ligand-driven disease

3. Inhibition of ligand binding

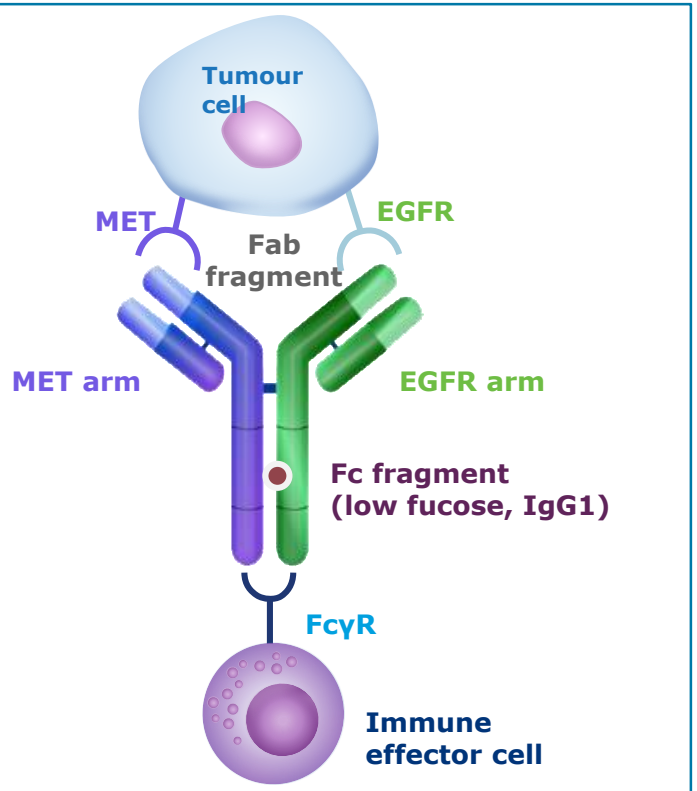


EGFR, epidermal growth factor receptor; MET, tyrosine-protein kinase MET; MoA, mechanism of action; NSCLC, non-small cell lung cancer. 1. Moores SL, et al. *Cancer Res*. 2016;76:3942–3953; 2. Haura EB, et al. Oral presentation at ASCO 2019 Congress, Chicago, USA; abstract 9009; 3. Vijayaraghavan S, et al. *Mol Cancer Ther*. 2020;19:2044–2056.

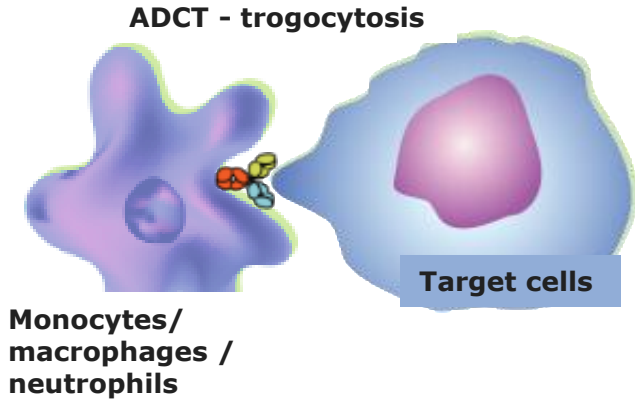
1

MoA: Immune cell-directed activity

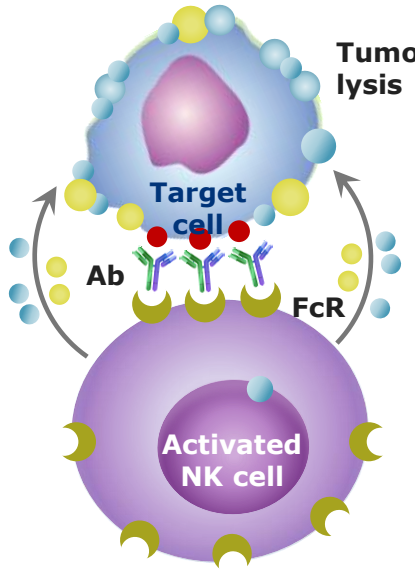
Immune cell-directing activity: ADCC[1,2,4]



The low fucose Fc region of amivantamab was engineered to bind tightly to Fc receptors on immune effector cells[3]



This binding triggers trogocytosis,[4] which leads to tumour cell apoptosis[5]



Perforin and granzymes kill the target cancer cell[6]

In NSCLC cell lines, amivantamab with a low fucose Fc region enhances NK cell-mediated lysis[3]

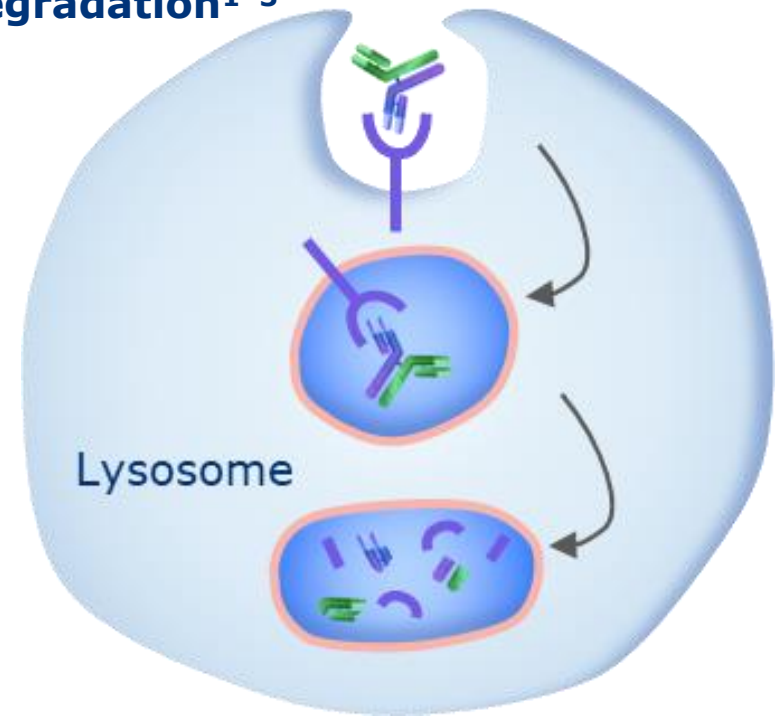
Ab, antibody; ADCC, antibody-dependent cellular cytotoxicity; ADCT, antibody-dependent cellular trogocytosis; EGFR, epidermal growth factor receptor; Fc, fragment crystallisable; IgG1, immunoglobulin G1; NK, natural killer; NSCLC, non-small cell lung cancer.

1. Moores SL, et al. *Cancer Res.* 2016;76:3942–3953; 2. Haura EB, et al. Oral presentation at ASCO 2019 Congress, Chicago, USA; abstract 9009;
3. Grugan KD, et al. *MAbs.* 2017;9:114–126; 4. Vijayaraghavan S, et al. *Mol Cancer Ther.* 2020;19:2044–2056;
5. Velmurugan R, et al. *Mol Cancer Ther.* 2016;15:1879–1889; 6. Hoves S, et al. *OncoImmunology*. 2012;1:219-221.

2

MoA: EGFR and MET receptor degradation

Receptor degradation[1–3]



Tumour cell

Trogocytosis also contributes to receptor degradation[3]

Amivantamab binding triggers EGFR and MET receptor degradation by the tumour cell[1]

This leads to receptor inactivation[1]

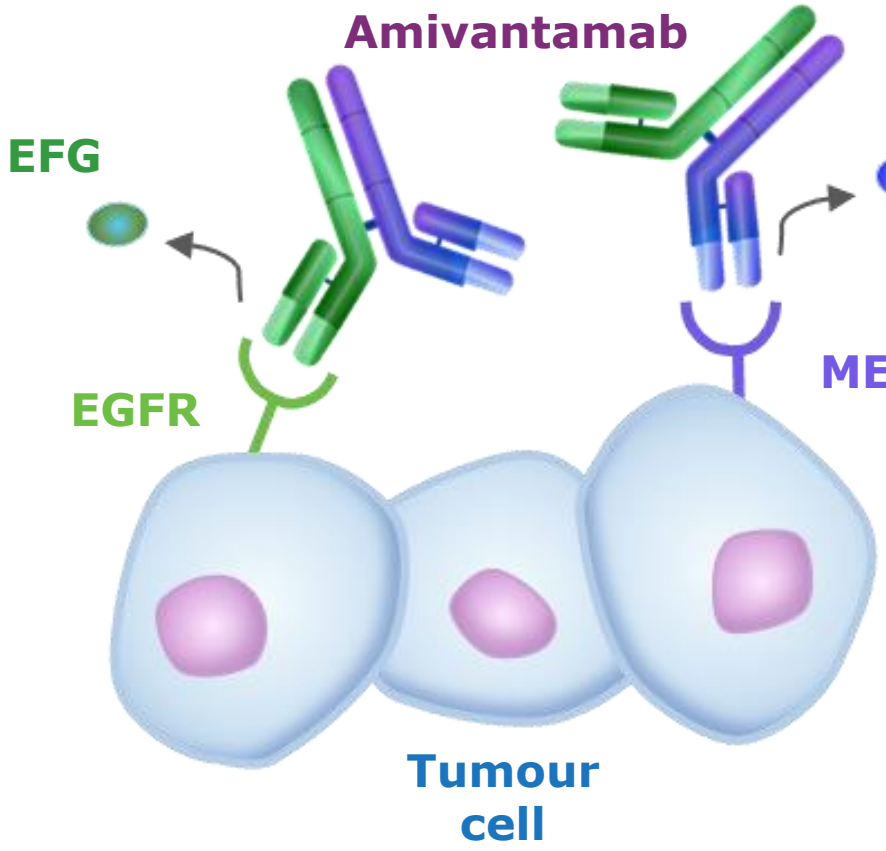
EGFR, epidermal growth factor receptor; MoA, mechanism of action.

1. Moores SL, et al. *Cancer Res.* 2016;76:3942–3953; 2. Haura EB, et al. Oral presentation at ASCO 2019 Congress, Chicago, USA; abstract 9009;
3. Vijayaraghavan S, et al. *Mol Cancer Ther.* 2020;19:2044–2056.

3

MoA: Inhibition of ligand binding

Inhibition of ligand-binding[1-3]



Amivantamab binds to the extracellular domains of EGFR and MET[1]

This inhibits ligand binding and downstream signalling from both receptors[1]

EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; MoA, mechanism of action.

1. Moores SL, et al. *Cancer Res.* 2016;76:3942–3953; 2. Haura EB, et al. Oral presentation at ASCO 2019 Congress, Chicago, USA; abstract 9009;
3. Vijayaraghavan S, et al. *Mol Cancer Ther.* 2020;19:2044–2056.

Dosing and Administration

- Amivantamab is administered intravenously once weekly for 4 weeks, then every 2 weeks thereafter
- Due to IRR frequency at first dose, infusion via a peripheral vein at week 1 through week 2 should be considered to minimize drug exposure in case of an IRR
- Infusion via central line may be administered for subsequent weeks
- First dose should be diluted as close to administration as possible to allow for maximal flexibility in IRR management

RECOMMENDED AMIVANTAMAB DOSE FOR ADULTS (≥18 YEARS)

Body Weight (at Baseline)	Recommended Dose	Number of 350 mg/ 7-mL Amivantamab Vials
<80 kg	1050 mg	3
≥80 kg	1400 mg	4

Infusion Rates for Amivantamab Administration

1050-mg Dose			
Week	**Dose (per 250-mL bag)**	**Initial infusion rate**	**Subsequent infusion rate†**
Week 1 (split dose infusion)			
Week 1 day 1	350 mg	50 mL/hr	75 mL/hr
Week 1 day 2	700 mg	50 mL/hr	75 mL/hr
Week 2	1050 mg	85 mL/hr	
Subsequent weeks*	1050 mg	125 mL/hr	
1400-mg Dose			
Week	**Dose (per 250-mL bag)**	**Initial infusion rate**	**Subsequent infusion rate†**
Week 1 (split dose infusion)			
Week 1 day 1	350 mg	50 mL/hr	75 mL/hr
Week 1 day 2	1050 mg	35 mL/hr	50 mL/hr
Week 2	1400 mg	65 mL/hr	
Week 3	1400 mg	85 mL/hr	
Subsequent weeks*	1400 mg	125 mL/hr	

*After week 4, patients are dosed every 2 weeks.
†Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of IRRs.
IRR, infusion-related reaction.
Amivantamab. Package insert. Janssen Biotech, Inc; 2021.

Amivantamab: Clinical Efficacy & Safety

CHRYSALIS: Phase 1 Study of Amivantamab in EGFRm NSCLC

Key Objectives

- Part 1: Establish RP2D
- Part 2: Safety and efficacy at RP2D

Key Eligibility Criteria

- Metastatic/unresectable NSCLC
- Failed/ineligible for SOC therapy
- Advanced NSCLC (part 1)
- Measurable disease (part 2)
- Activating/resistance EGFR or MET mutations/amplifications (part 2)

Part 1: Dose Escalation

1750 mg → 1400 mg → 1050 mg → 700 mg → 350 mg → 140 mg

RP2D

1050 mg amivantamab (<80 kg)
1400 mg amvantamab (≥80 kg)

Intravenous dosing

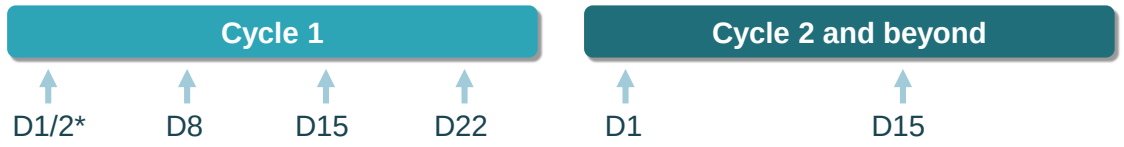
C1 weekly, C2+ biweekly

All patients in part 2 had a baseline MRI; subsequent screening was decided by the investigators

Part 2: Dose Expansion

- **Cohort A:** EGFR-dependent resistance
- **Cohort B:** EGFR-independent resistance
- **Cohort C:** Post-EGFR-3GTKI, C797S+
- **Cohort D:** EGFR ex20ins
- **Cohort E:** Amivantamab + lazertinib combination; 1L or post-EGFR-3GTKI
- **Cohort MET-1:** *MET* amplification, post-EGFR TKI
- **Cohort MET-2:** *MET* amplification, exon14 skipping
- **Amivantamab + Chemotherapy** Eligible for platinum-based chemotherapy

Dosing Schema



Monotherapy Combination

= Amivantamab infusion

*Split first dose.

1L, first-line; 3GTKI, third-generation tyrosine kinase inhibitor; amp, amplification; C, cycle; D, day; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; ex20ins, exon 20 insertion mutation; MRI, magnetic resonance imaging; NSCLC, non–small cell lung cancer; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SOC, standard of care.

1. Park K, et al. *J Clin Oncol*. 2021. doi: 10.1200/JCO.21.00662. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02609776. Accessed 18 January 2021.

Cohort D: Study Design

Patients with EGFR-mutated advanced NSCLC[2]

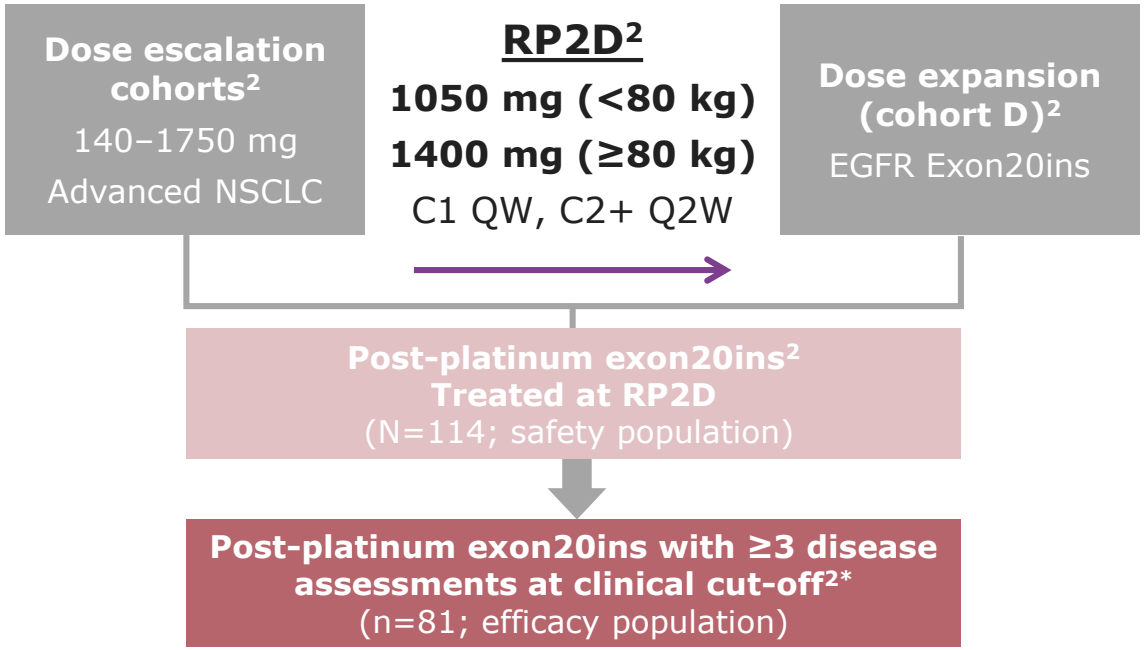
Key inclusion criteria for post-platinum population:

- Metastatic/unresectable NSCLC
- EGFR exon20ins mutation
- Progressed on platinum-based chemotherapy

Key objectives:[2]

- Dose escalation: establish RP2D
- Dose expansion: assess safety and efficacy at RP2D

Primary efficacy endpoint: ORR per RECIST v1.1[2]
Key secondary: CBR, DoR, PFS, OS[2]



C1, Cycle 1; CBR, clinical benefit rate; DoR, duration of response; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival, PFS, progression-free survival; QW, weekly; RP2D, recommended Phase 2 dose; RECIST, response evaluation criteria in solid tumours.

*Post-platinum patients treated at the RP2D and had ≥3 scheduled disease assessments or discontinued, progressed, or died prior to the third postbaseline assessment at the time of clinical cut-off (June 8, 2020). By October 8, 2020, all responders in the efficacy population had ≥6 months of follow-up from their first disease assessment.

1. Park K, et al. *J Clin Oncol*. doi:10.1200/JCO.21.00662 [published online ahead of print August 02, 2021]; 2. Sabari JK, et al. Oral presentation at WCLC 2020 Congress, Virtual meeting; abstract OA04.04.

Demographics and baseline characteristics

All patients had received prior platinum-based chemotherapy

	Efficacy population (n=81)
Age, years, median (range)	62 (42–84)
Female, n (%)	48 (59)
Race, n (%)	
Asian	40 (49)
Black	30 (37)
White	2 (2)
Not reported/multiple	9 (11)
Smoking history, n (%)	
Non-smoker	43 (53)
Smoker	38 (47)
Time from initial diagnosis, median months, (range)	17 (1–130)
History of brain metastases, n (%)	18 (22)
Number of prior therapy lines, median (range)	2 (1–7)

	Efficacy population (n=81)
Prior systemic therapies, n (%)	81 (100)
Platinum-based chemotherapy	81 (100)
Immuno-oncology therapy	37 (46)
EGFR TKI	20 (25)
First-generation TKI*	7 (9)
Second-generation TKI†	6 (7)
Third-generation TKI‡	6 (7)
Poziotinib	1 (1)

*Erlotinib and gefitinib; †Afatinib; ‡Osimertinib, ASP8273 and nintedanib.

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Sabari JK, et al. Oral presentation at WCLC 2020 Congress, Virtual meeting; abstract OA04.04; Park K, et al. *J Clin Oncol*. doi:10.1200/JCO.21.00662 [published online ahead of print August 02, 2021].

Amivantamab: Safety Profile

AEs were consistent with EGFR and MET inhibition

AEs, n (%)	Safety population (N=114)[1]	
	TEAE	TRAE
Any AE	113 (99)	112 (98)
Grade ≥3 AE	40 (35)	18 (16)
Serious AE	34 (30)	10 (9)
AEs leading to death	8 (7)	0
AEs leading to discontinuation	11 (10)	5 (4)
AEs leading to dose reduction	15 (13)	15 (13)
AEs leading to dose interruption*	40 (35)	24 (21)

AEs ≥15%, n (%)[1]	Safety population (N=114)			
	TEAE		TRAE	
	Total	Grade ≥3	TEAE	Grade ≥3
EGFR-related				
Rash*	98 (86)	4 (4)	98 (86)	4 (4)
Paronychia	51 (45)	1 (1)	48 (42)	1 (1)
Stomatitis	24 (21)	0	21 (18)	0
Pruritus	19 (17)	0	19 (17)	0
MET-related				
Hypoalbuminemia	31 (27)	3 (3)	17 (15)	2 (2)
Peripheral oedema	21 (18)	0	11 (10)	0
Other				
Infusion related reaction	75 (66)	3 (3)	75 (66)	3 (3)
Constipation	27 (24)	0	7 (6)	0
Nausea	22 (19)	0	13 (11)	0
Dyspnoea	22 (19)	2 (2)	6 (5)	0
Fatigue	21 (18)	2 (2)	14 (12)	1 (1)
Increased ALT	17 (15)	1 (1)	14 (12)	1 (1)

*Excludes infusion-related reactions[2]. AE, adverse event; EGFR, epidermal growth factor receptor; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

1. Sabari JK, et al. Oral presentation at WCLC 2020 Congress, Virtual meeting; abstract OA04.04; 2. Park K, et al. *J Clin Oncol*. doi:10.1200/JCO.21.00662 [published online ahead of print August 02, 2021]

Safety summary

There were few treatment-related dose reductions and discontinuations

- **Treatment-related grade ≥3 AEs** were reported in 18 patients (16%)
  - Most common: rash in four patients (4%) and IRR and neutropenia in three patients (3%) each
- **Treatment-related serious AEs** were reported in ten patients (9%)
  - IRR and diarrhoea (2 patients each; 2%) and single reports each of cellulitis, infected dermal cyst, interstitial lung disease, pneumonitis, atrial flutter, rash, and toxic epidermal necrolysis
- **Treatment-related dose reductions** occurred in 15 patients (13%)
  - Rash (11 patients [10%]) was most frequently reported
- **Treatment-related discontinuation** occurred in five patients (4%)
  - Rash and IRR in two patients (1.8%) each and paronychia in one patient (1%)

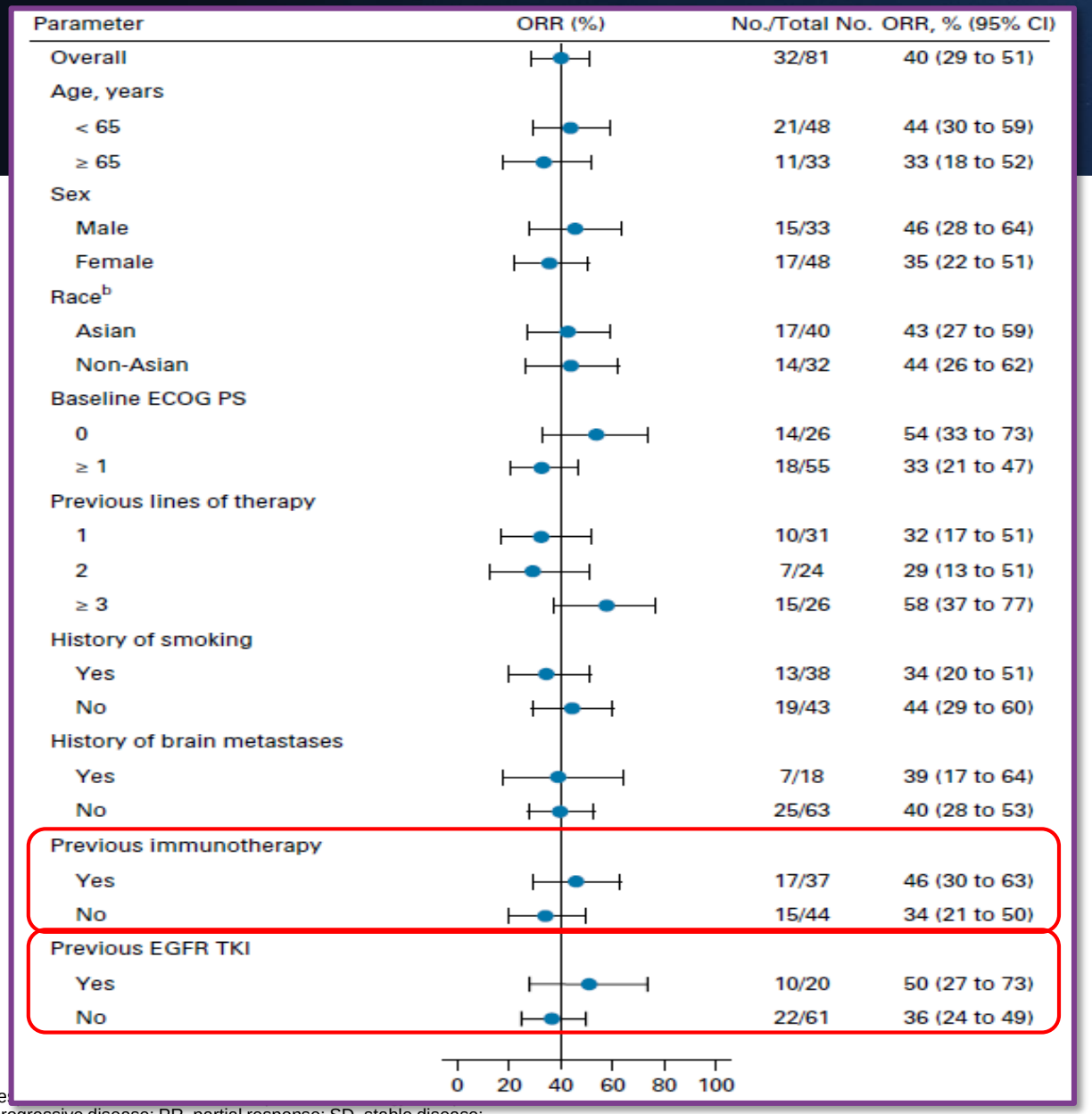
AE, adverse event; IRR, infusion-related reaction.

Park K, et al. J Clin Oncol. doi:10.1200/JCO.21.00662 [published online ahead of print August 02, 2021].

Efficacy by BICR

Median follow-up: 9.7 months (range: 1.1–29.3)

BICR-assessed response	Efficacy population (n=81)
ORR, % (95% CI)	40 (29–51)
DoR, median months (95% CI)	11.1 (6.9–NR)
Best response, n (%)	
CR	3 (4)
PR	29 (36)
SD	39 (48)
PD	8 (10)
NE	2 (2)
CBR*, % (95% CI)	74 (63–83)

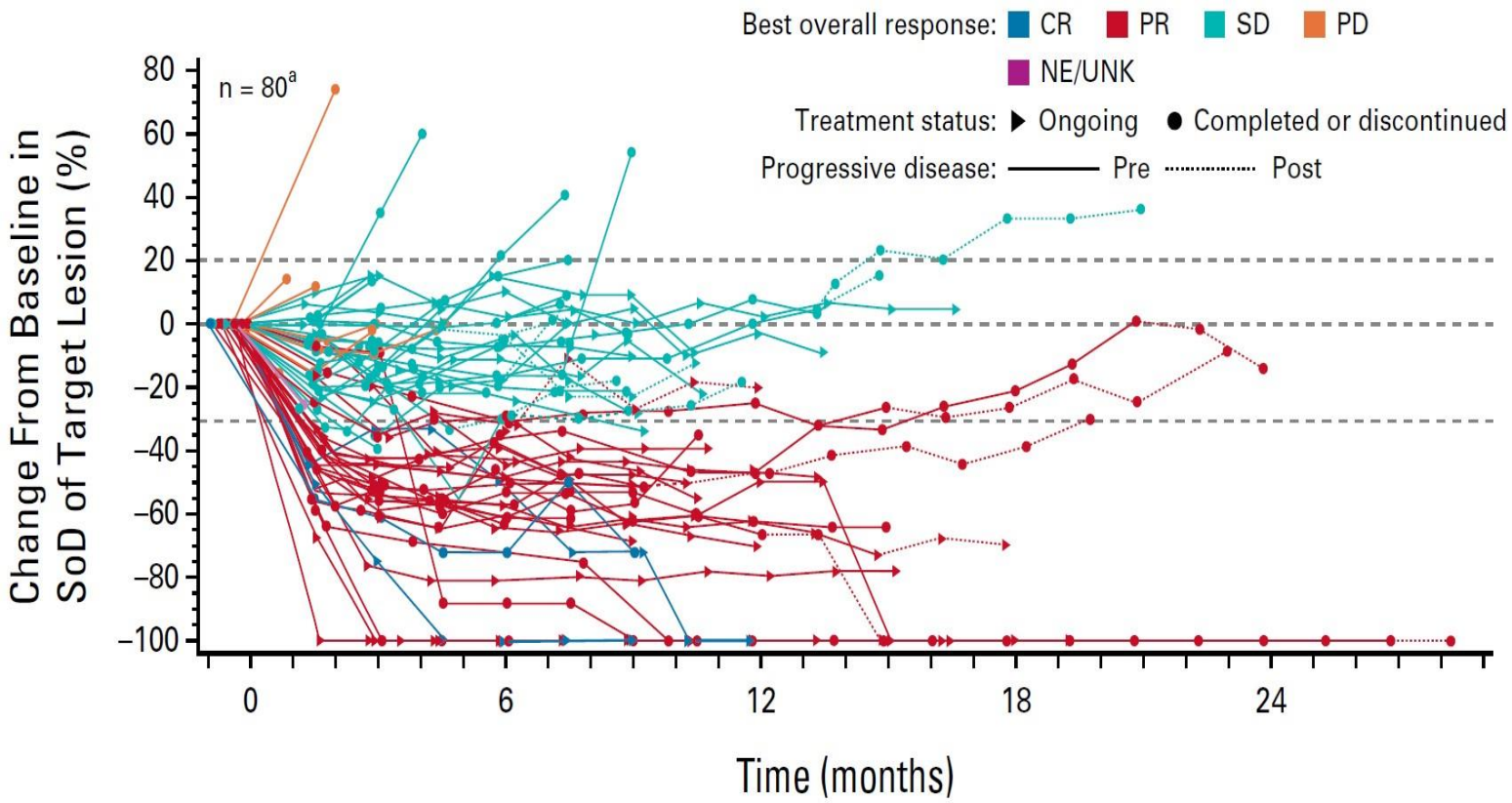


*CBR: CR, PR, SD for at least two disease assessments; [b]Does not include nine patients with race not reported and multiple race.

BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DoR, duration of re
Performance Score; EGFR, epidermal growth factor receptor; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

Park K, et al. *J Clin Oncol*. doi:10.1200/JCO.21.00662 [published online ahead of print August 02, 2021].

Amivantamab: Responses over time



- 15 of 32 (47%) patients remain on treatment at time of data cutoff[2]
- 20 of 32 (63%) patients had responses of ≥6 months[2]
- **mPFS:** 8.3 mo (95% CI, 6.5-10.9)[1]
- **mOS:** 22.8 mo (95% CI, 14.6-NR)[1]

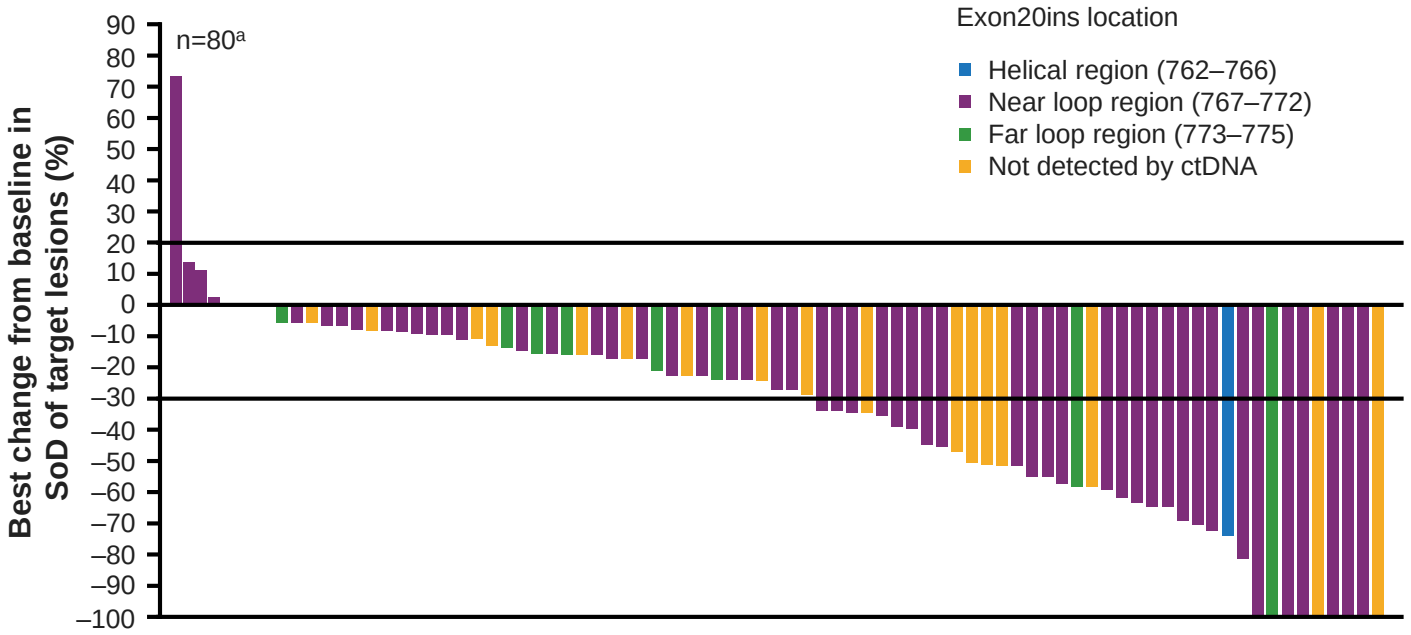
CR, complete response; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters; UNK, unknown.

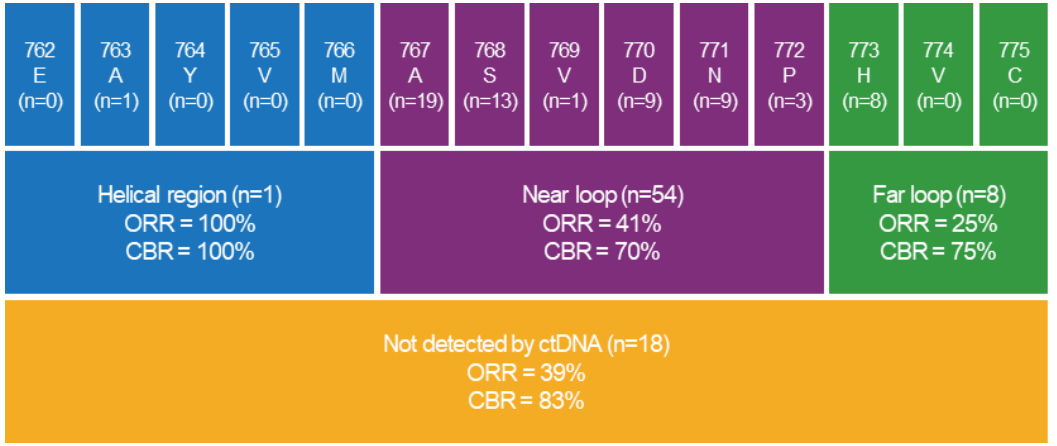
1. Park K, et al. *J Clin Oncol*. doi:10.1200/JCO.21.00662 [published online ahead of print August 02, 2021]; 2. Sabari JK, et al. Oral presentation at WCLC 2020 Congress, Virtual meeting; abstract OA04.04.

Efficacy across the EGFR exon20ins

Antitumor responses were observed across the EGFR exon20ins, in patients who harboured insertions within the helical, near-loop, and far-loop regions of exon 20[1]

Tumour reduction and responses in the efficacy population (n=80)[1]





1. Park K, et al. *J Clin Oncol.* 2021;39(30):3391–3402; 2. RYBREVANT® (amivantamab). Summary of Product Characteristics. 2022.

Summary of CHRYSALIS study

- Amivantamab had a tolerable safety profile consistent with EGFR and MET inhibition[1,2]
  - TRAEs were primarily grade 1–2 (16% were grade ≥3)
  - Treatment-related discontinuations were low (4%)

- Amivantamab showed robust efficacy with an ORR of 40%[1,2] and mDoR of 11.1 months[1]
  - CBR: 74%; mPFS: 8.3 months; mOS: 22.8 months[1]
  - Antitumour activity was observed in all patient subgroups and across exon 20 insertion regions[1,2]

- Amivantamab is the first bispecific antibody to demonstrate clinically meaningful efficacy in patients with EGFR exon20ins NSCLC[1]

- Amivantamab could target other EGFR and/or MET-driven tumours, as monotherapy or in combination, given its favourable safety profile[3–5]

CBR, clinical benefit rate; EGFR, epidermal growth factor receptor; mDoR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate; TRAE, treatment-related adverse event. 1. Park K, et al. *J Clin Oncol*. doi:10.1200/JCO.21.00662 [published online ahead of print August 02, 2021]; 2. Sabari JK, et al. Oral presentation at WCLC 2020 Congress, Virtual meeting; abstract OA04.04; 3. Haura EB, et al. *J Clin Oncol*. 37(15_suppl):9009; 4. Park K, et al. *J Thorac Oncol*. 2018;13(10S):S344 –S345; 5. Cho BC, et al. *Ann Oncol*. 2020;31:S813; 6. ClinicalTrials.gov. NCT04487080. Available at: https://clinicaltrials.gov/ct2/show/NCT04487080. Accessed August 2021

CHRYSALIS vs Real World Datasets Analysis

- A protocol-driven, external treatment comparison was conducted comparing CHRYSALIS to three real-world US datasets (ConcertAI, COTA, and Flatiron)

- Primary objective: to evaluate the effectiveness of amivantamab vs physician's choice of anticancer treatment in patients with:[1]
  - Confirmed advanced NSCLC
  - Tumours with EGFR exon20ins
  - Prior platinum-doublet chemotherapy

Real-world databases[1]	Inclusion criteria[2]	Endpoints[1]
ConcertAI COTA flatiron	• Advanced metastatic/unresectable NSCLC • ≥18 years • ECOG ≤1 or missing • No malignancy in the past three years • Platinum chemotherapy after metastatic diagnosis or in the 12 months before metastatic diagnosis	• OS • PFS • ORR • TTNT

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR,

Demographics and baseline characteristics

	CHRYSALIS (n=81) 81 LOT	Pooled RWD* (n=125) 227 LOT
Age, years, median (range)	62 (42–84)	62 (31–84)
Female, n (%)	48 (59)	137 (60)
Race, n (%)		
Asian	40 (56)	27 (13)
Black or African American	2 (3)	11 (5.3)
White	30 (42)	140 (67)
Other	0 (0)	30 (14)
Smoking history, n (%)		
Non-smoker	43 (53)	133 (59)
Smoker	38 (47)	93 (41)
ECOG PS, n (%)		
0	26 (32)	69 (30)
1	54 (67)	158 (70)
2	1 (1)	0 (0)
Brain metastasis at baseline, n (%)		
No	63 (78)	137 (60)
Yes	18 (22)	90 (40)
Prior lines in metastatic setting,† n (%)		
0 or 1	29 (36)	100 (44)
2	23 (28)	63 (28)
3+	29 (36)	64 (28)
Time from advanced diagnosis to line of therapy, median months (range)	14 (1–116)	15 (0–86)

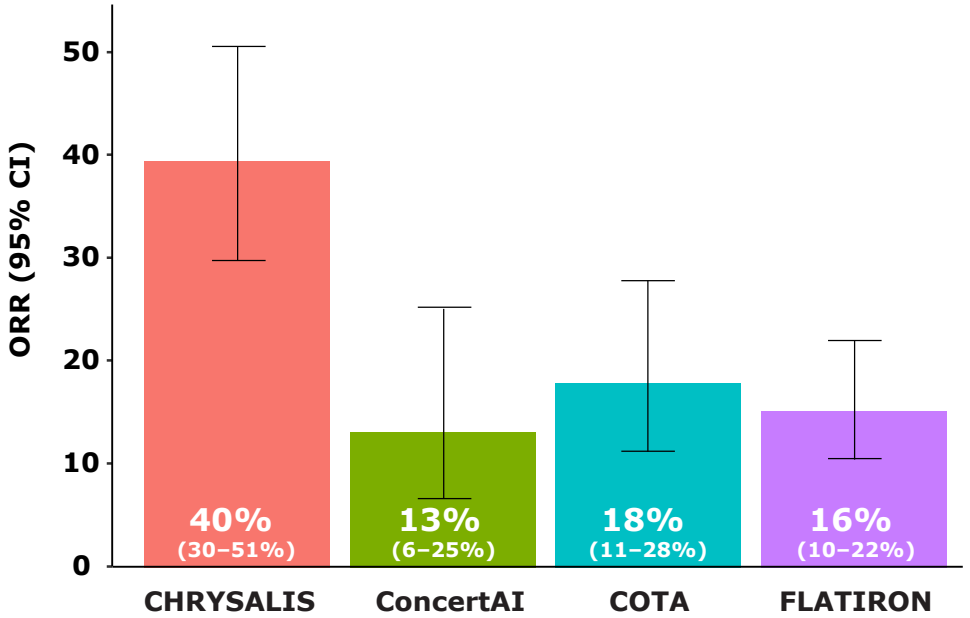
	Pooled
Unique patients, n*	125
Lines of therapy	227
Median number of therapy lines per patient	1
Real-world treatments, n (%)	
Non-platinum chemo†	57 (25)
IO‡	55 (24)
Platinum-containing regimen§	37 (16)
TKI¶	37 (16)
Others#	21 (9)
VEGFi alone	20 (9)

*De-duplication applied only for pooled data, which excludes patient lines with missing ECOG PS; †Prior LOT in metastatic setting does not include neo-adjuvant/adjuvant

Efficacy: ORR and PFS

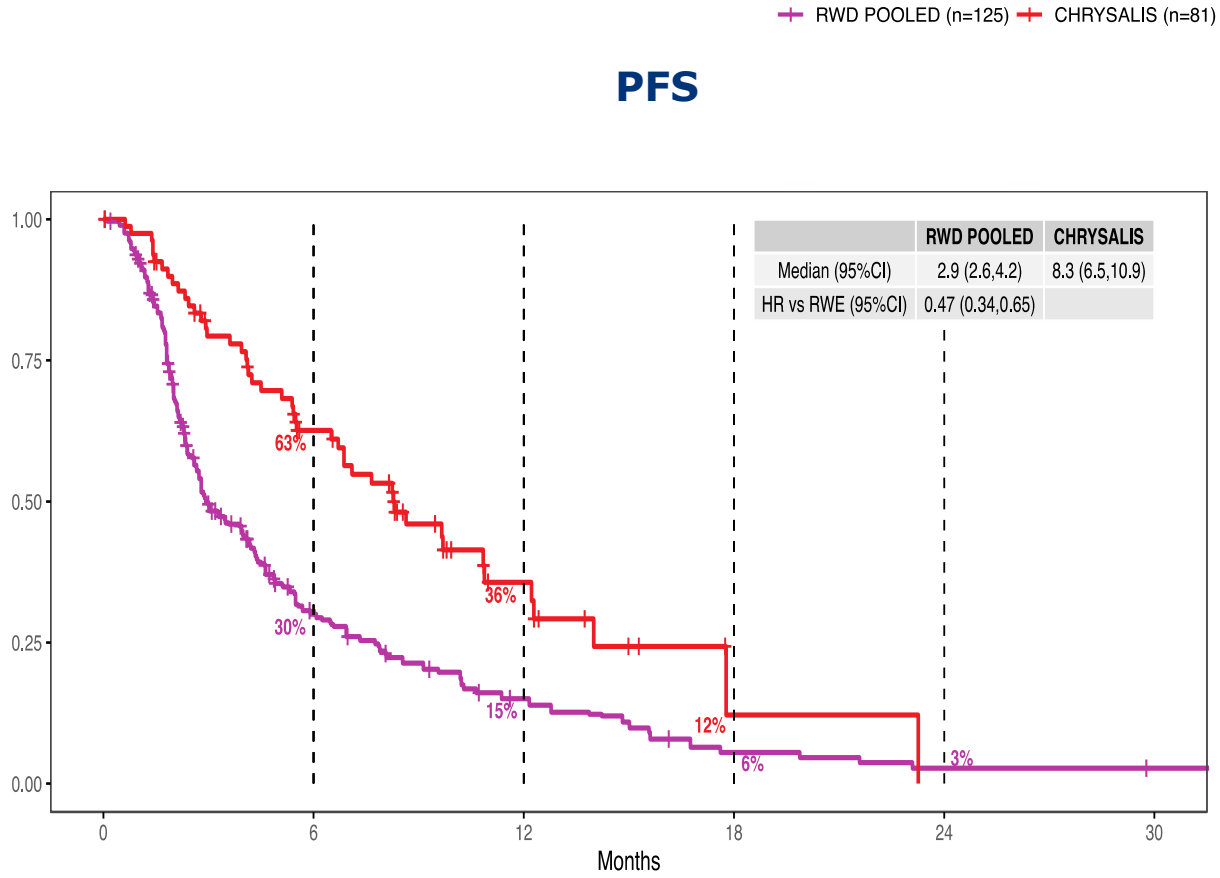
Higher ORR and lower risk of progression in CHRYSALIS vs RWD

Confirmed ORR



	CHRYSALIS	ConcertAI	COTA	FLATIRON
Patients	81	35	39	63
LOT	81	67	80	121
ORR (95% CI)		4.32 (1.73–10.77)	3.00 (1.46–6.13)	3.64 (1.94–6.83)

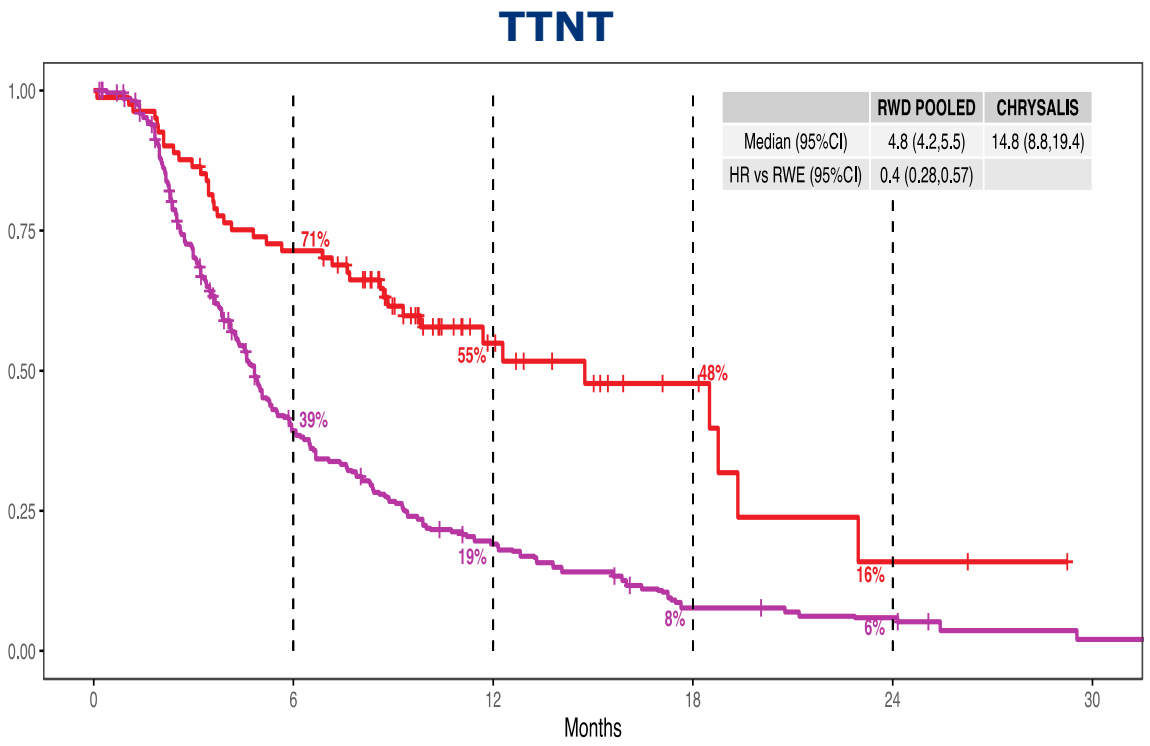
PFS

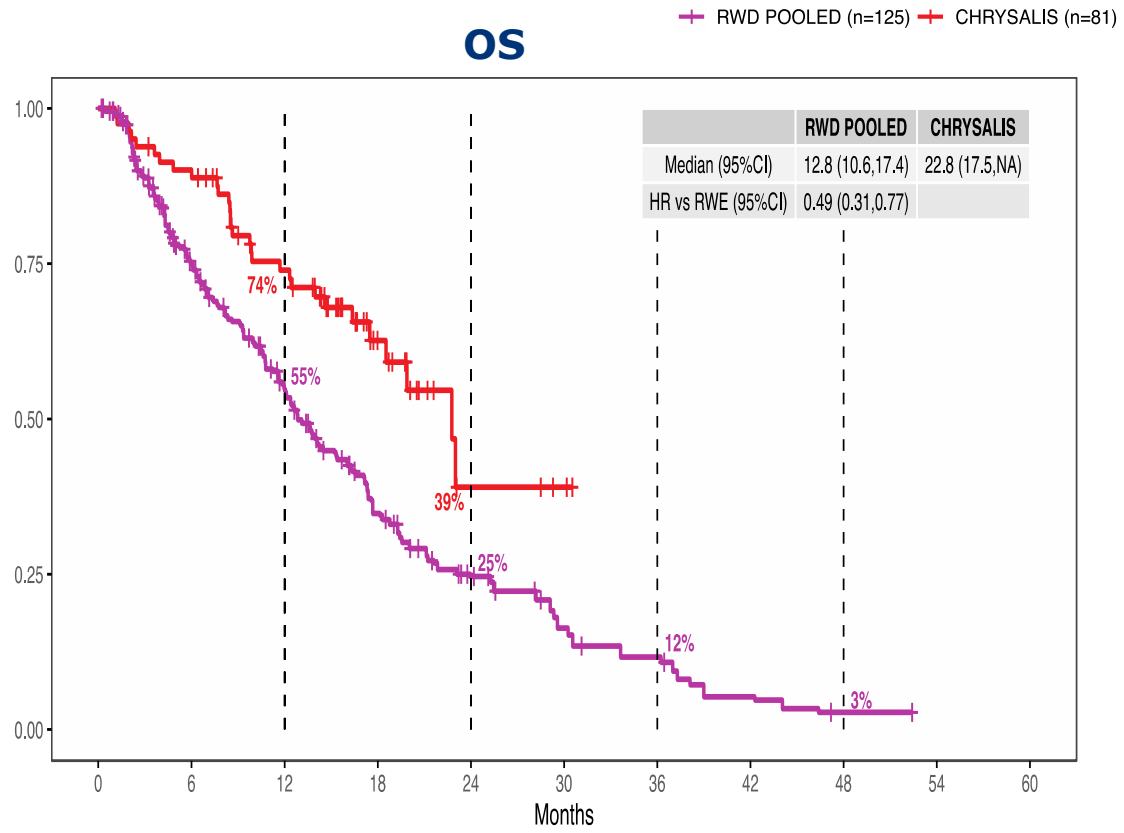


CI, confidence interval; ORR, objective response rate; PFS, progression-free survival; RWD, real-world datasets.
Minchom A, et al. Oral presentation at ASCO 2021; abstract 9052.

Efficacy: TTNT and OS

Longer time to next treatment and overall survival in CHRYSALIS vs RWD





CI, confidence interval; OS, overall survival; RWD, real-world datasets; TTNT, time to next treatment.
Minchom A, et al. Poster presented at ASCO 2021; abstract 9052.

Summary of CHRYSALIS vs RWD analysis

- Most commonly used real-world treatments for post-platinum EGFR exon20ins NSCLC included non-platinum-based chemotherapy, immuno-oncology therapies, platinum-containing therapies, and EGFR TKIs

- OS was ~10 months longer in patients treated with amivantamab vs real-world treatments, with corresponding improvements in other outcomes such as ORR, PFS and TTNT

- Poor performance of the external controls showed the relative ineffectiveness of currently available real-world treatments

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TTNT, time to next treatment.

Minchom A, et al. Poster presented at ASCO 2021; abstract 9052.

Thank You