RESPIRATORNI EDUKATIVNI CENTAR

I MEDICAL NSCLC PRECEPTORSHIP
EGFR+ MUTACIJE U NSCLC

Takeda

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Klinika za pulmologiju, Univerzitetski klinički centar Srbije

Beograd, Srbija

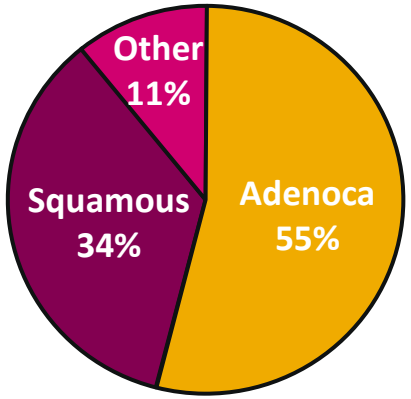
ONCOLOGY

28/04/2023

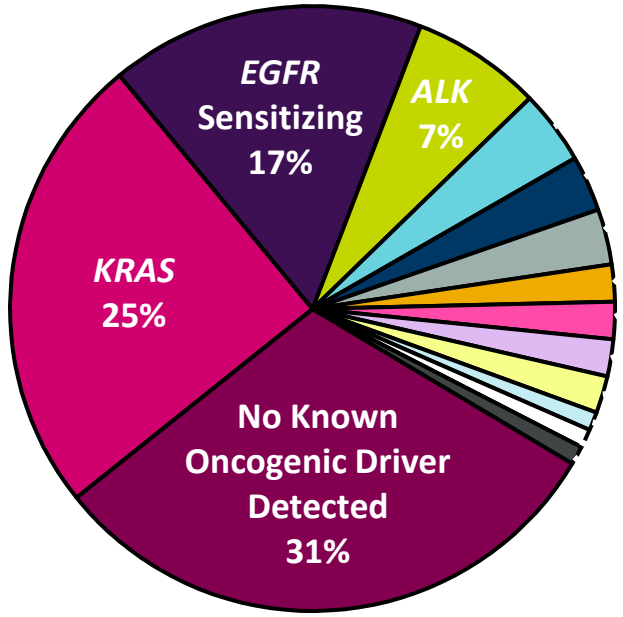
Samo za stručnu javnost

The meeting is initiated, organized and funded by Takeda

Non-Small-Cell Lung Cancer: ***Not One Disease, but Many***!



Adenocarcinoma

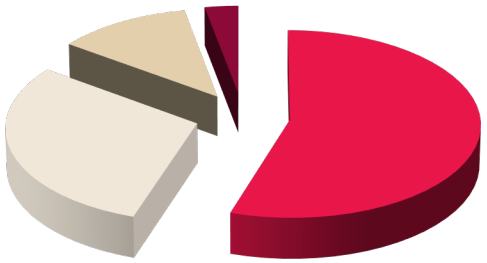


EGFR **Other 4%**
MET **3%**
> 1 Mutation 3%
HER2 **2%**
ROS1 **2%**
BRAF **2%**
RET **2%**
NTRK **< 1%**
PIK3CA **1%**
MEK1 **< 1%**

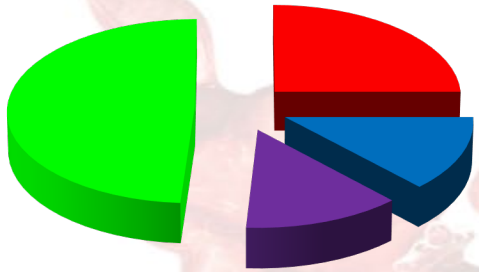
Then **Histology-Based Subtyping** **Now**

Li. JCO. 2013;31:1039. Tsao. J Thorac Oncol. 2016;11:613.

Genetska istraživanja NSCLC EGFR mutacija (2004 g.)



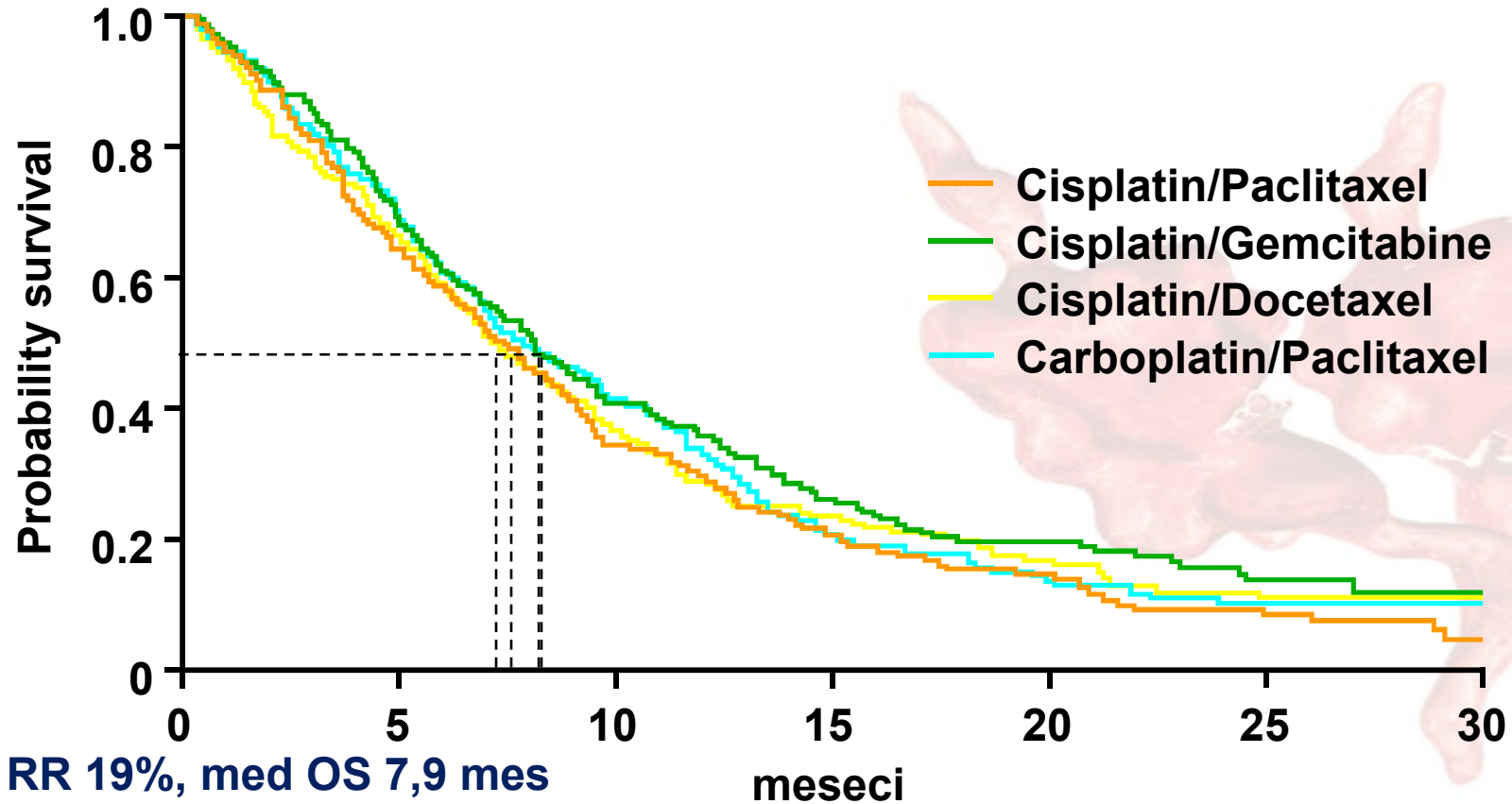
- Adeno ca
- Skvamo. Ca
- SCLC
- ostali



- KRAS 25%
- EGFR 13%
- ostale 13%
- bez mutacije

Tarceva
erlotinib

Terapijski plato postignut sa hemioterapijom kod NSCLC



RR 19%, med OS 7,9 mes
1-god 33%, 2-god 11%

Schiller, et al. NEJM 2002

Tarceva
erlotinib

Benchmark treatment: platinum-based chemotherapy

Platinum-based chemotherapy causes apoptosis of rapidly growing cells (tumor or wild type) by crosslinking with DNA bases, disrupting repair mechanisms[1]

For patients with advanced NSCLC:

- Platinum-based chemotherapy *vs* best SC[2,3]
  - Prolongs survival, improves symptom control, and quality of life
- Limitations[2–4]
  - Efficacy plateau
    - Overall RR: 25–35%
    - Time to progression: 4–6 months
    - Median survival: 8–10 months
  - Severe AEs
  - Inherent resistance

Survival: SC *vs* chemotherapy[2,*]

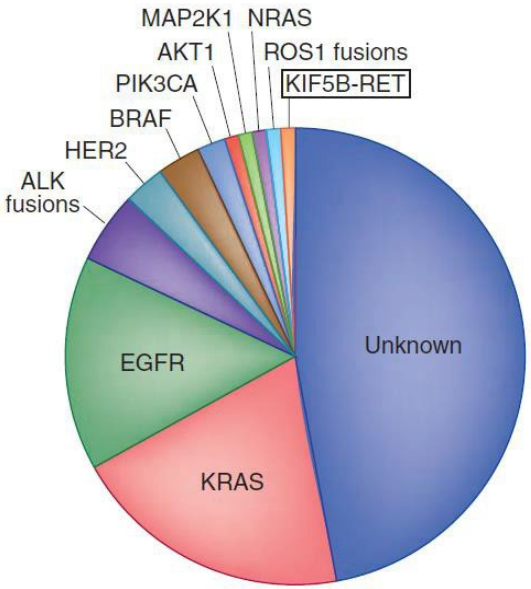
	SC+chemo-therapy (no. events/no. entered)	SC alone (no. events/no. entered)	HR (fixed)
Age			Trend *P*=0.64
<60	429/456	368/382	
60–64	275/299	267/289	
65–69	243/268	253/267	
≥70	336/365	344/367	
Sex			Interaction *P*=0.77
Male	997/1076	933/984	
Female	287/313	301/322	
Stage			Trend *P*=0.35
I & II	37/40	27/28	
IIIa	86/92	101/106	
IIIb	313/337	289/300	
IV	477/508	451/466	
Histology			Interaction *P*=0.75
Adenocarcinoma	302/320	295/300	
Squamous cell	567/605	532/554	
Other	214/224	194/204	
PS			Interaction *P*=0.54
Good	946/1034	904/969	
Poor	298/310	279/284	
Exploratory analysis PS (WHO or Karnofsky)			Trend *P*=0.76
0 or 100–90	310/347	273/299	
1 or 80–70	636/687	631/670	
2+ or ≤60	298/310	279/284	

*Meta-analysis of 2,714 patients from 16 randomized controlled trials

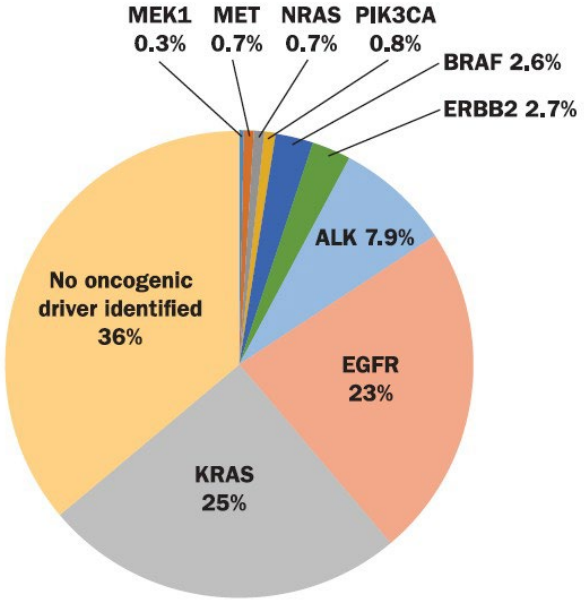
AEs, adverse events; DNA, deoxyribonucleic acid; HR, hazard ratio; NCCN, National Comprehensive Cancer Network; PS, performance status; RR, response rate; SC, supportive care; WHO, World Health Organization

1. Huang Y and Li L. *Transl Cancer Res* 2013;2:144–154; 2. Non-small Cell Lung Cancer Collaborative Group. *J Clin Oncol* 2008;26:4617–4625; 3. NCCN Guidelines: Non-small Cell Lung Cancer, v3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 4 Feb 2019; 4. Chang A. *Lung Cancer* 2011;71:3–10.

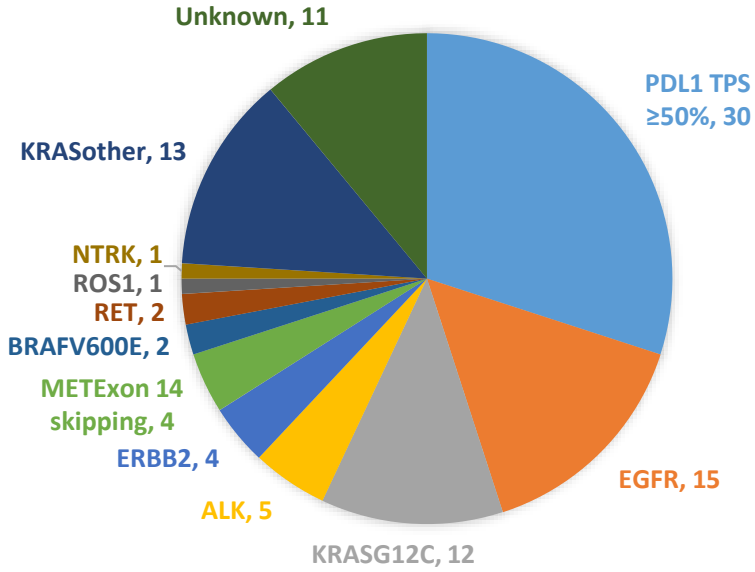
NSCLC mutacije



Pao and Hutchinson 'Chipping away at the lung cancer genome'
Nature Medicine. **March 2012**

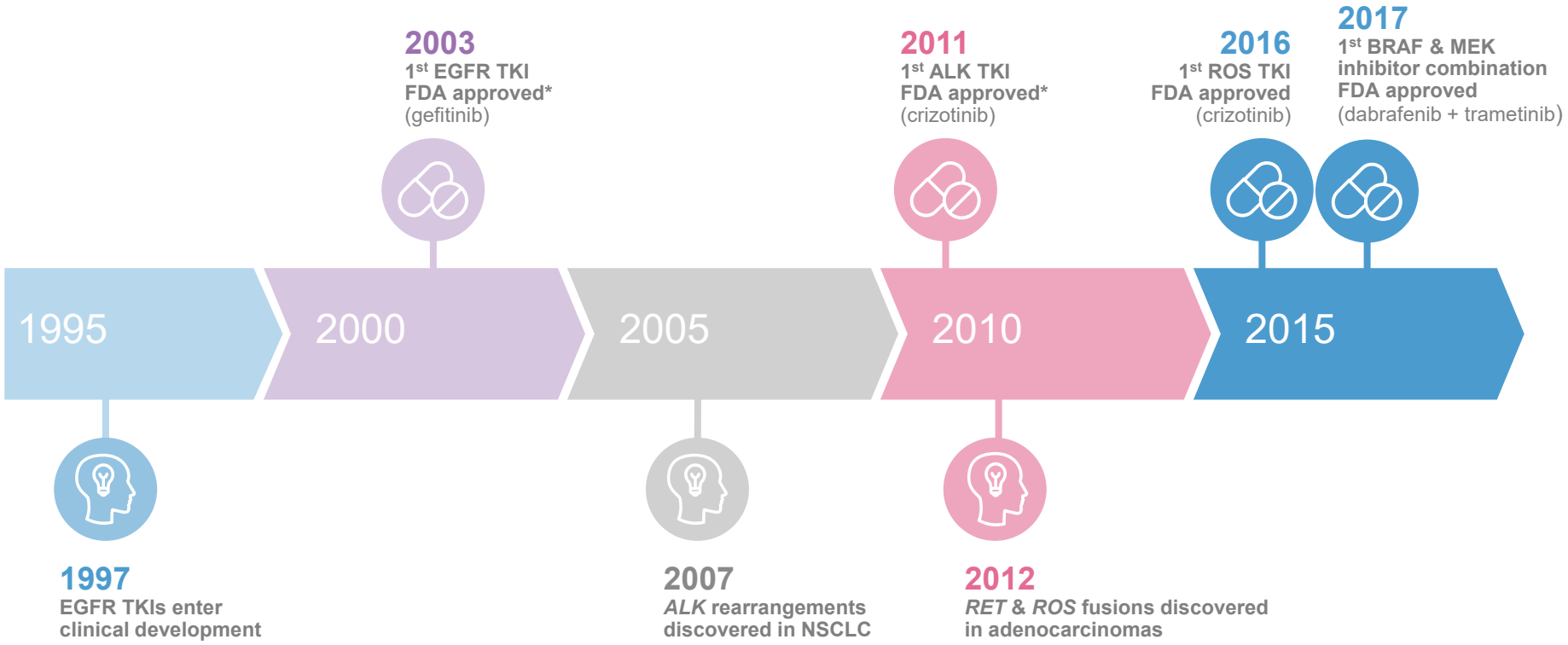


Sholl et al. Lung Cancer Mutation Consortium
J Thorac Oncol. **May 2015**



2021: biomarkers with FDA-approved drugs

Superiority of EGFR TKIs over chemotherapy transformed the management of NSCLC

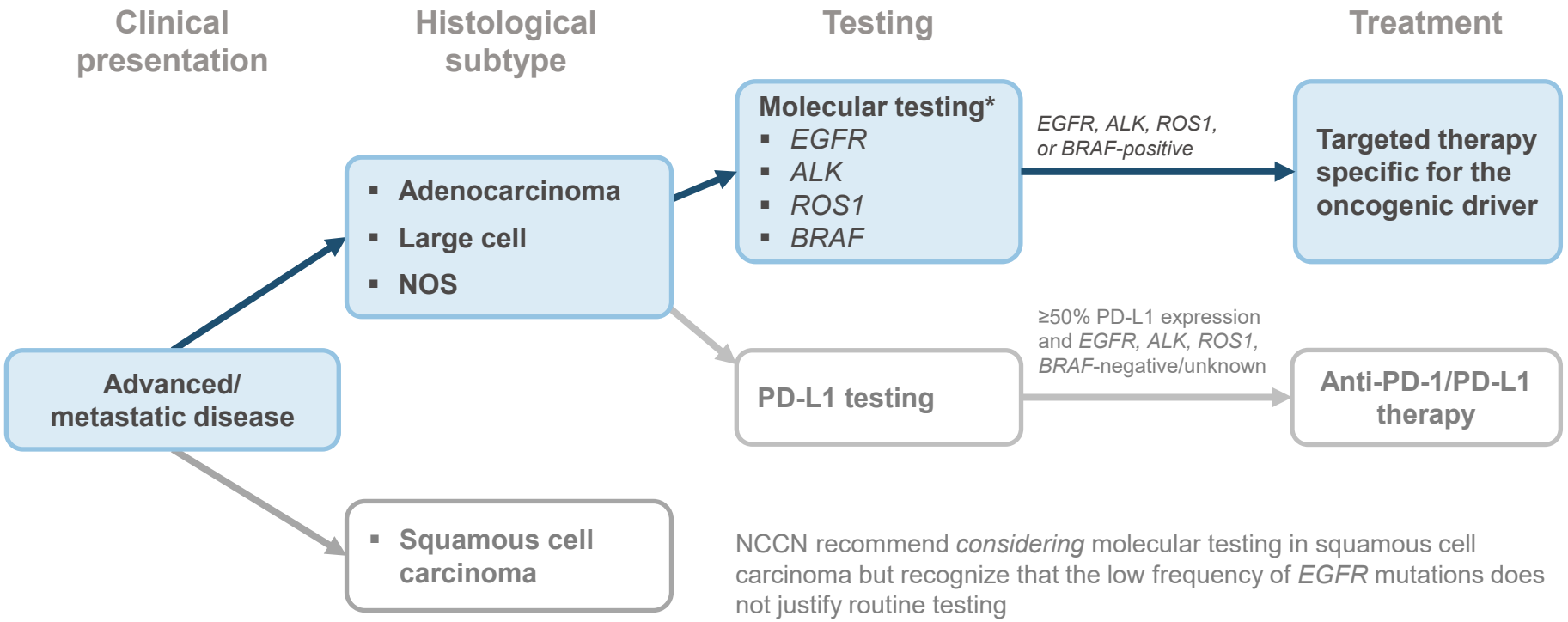


Therapies developed to target mutant EGFR shaped the treatment landscape

*Accelerated approval
BRAF, rapidly accelerated fibrosarcoma – B; FDA, US Food and Drug Administration

Herbst R et al., *Nature* 2018;553:446–454; Liu X et al., *Oncotarget* 2017;8:50209–50220; FDA. Available at: www.fda.gov/. Accessed 17 Oct 2018; Kazandjian D et al., *Oncologist* 2014;19:e5–e11.

Targeted treatment is now the standard of care for patients with non-squamous carcinoma



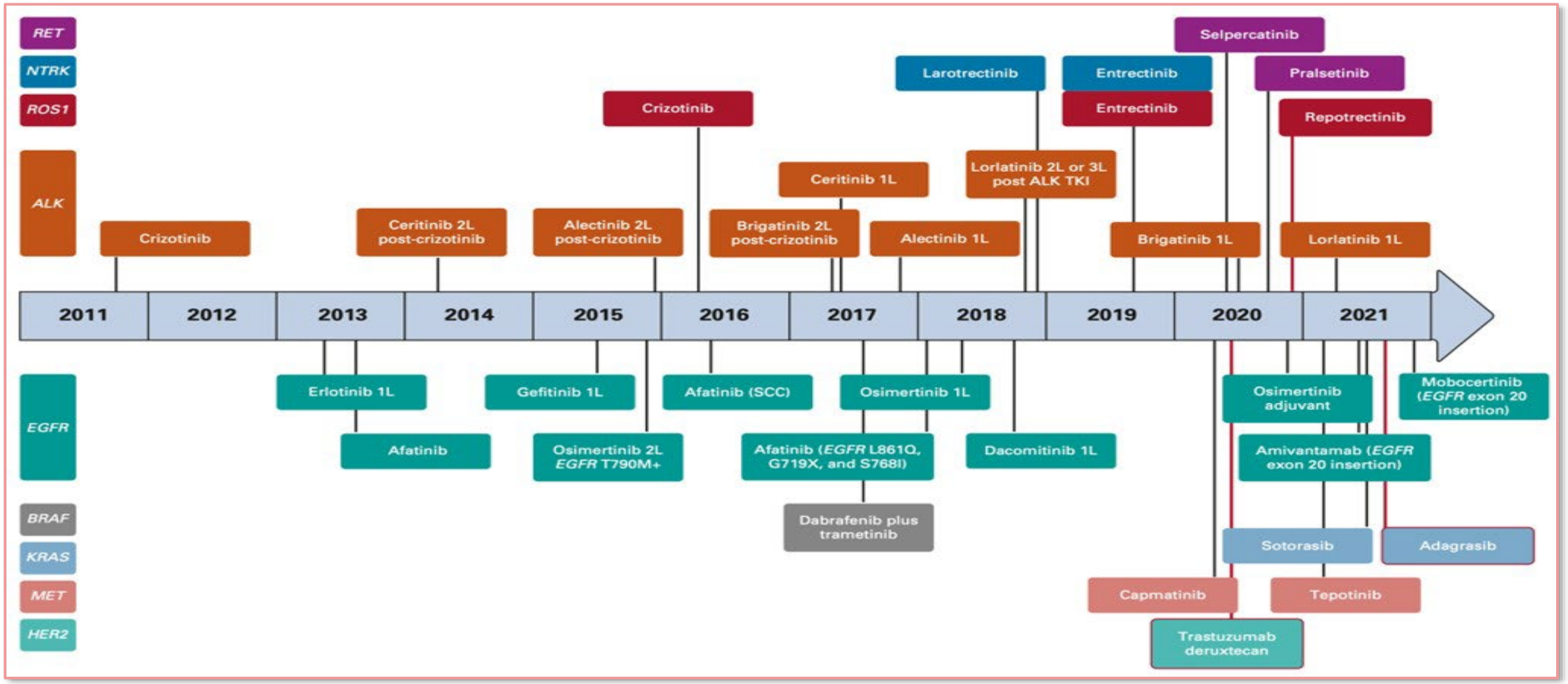
NCCN recommend *considering* molecular testing in squamous cell carcinoma but recognize that the low frequency of *EGFR* mutations does not justify routine testing

ESMO do not recommend molecular testing in squamous cell carcinoma unless never-, long-time ex-, or light-smoker

*Testing should be conducted as part of broad molecular profiling
ESMO, European Society for Medical Oncology; NOS, not otherwise specified; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1

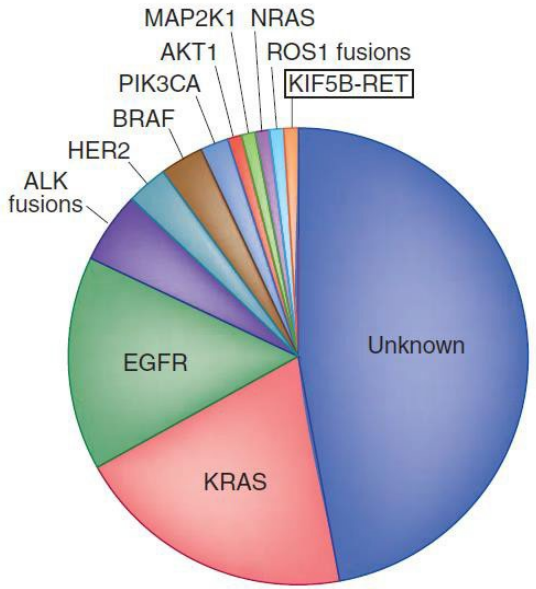
1. NCCN Guidelines: Non-small Cell Lung Cancer, v3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 4 Feb 2019;
2. Planchard D et al., *Ann Oncol* 2018;29(Suppl 4):iv192–iv237.

Brze promene terapijskih preporuka!



Tan AC, et al. *J Clin Oncol*. 2022.

NSCLC MUTACIJE



Pao and Hutchinson 'Chipping away at the lung cancer genome'
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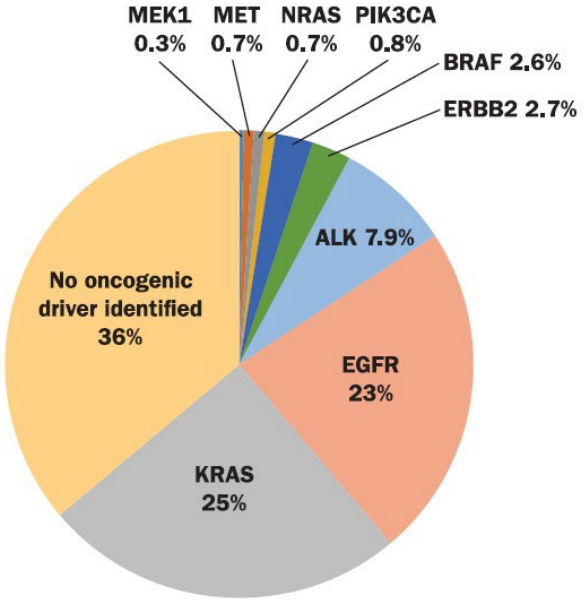
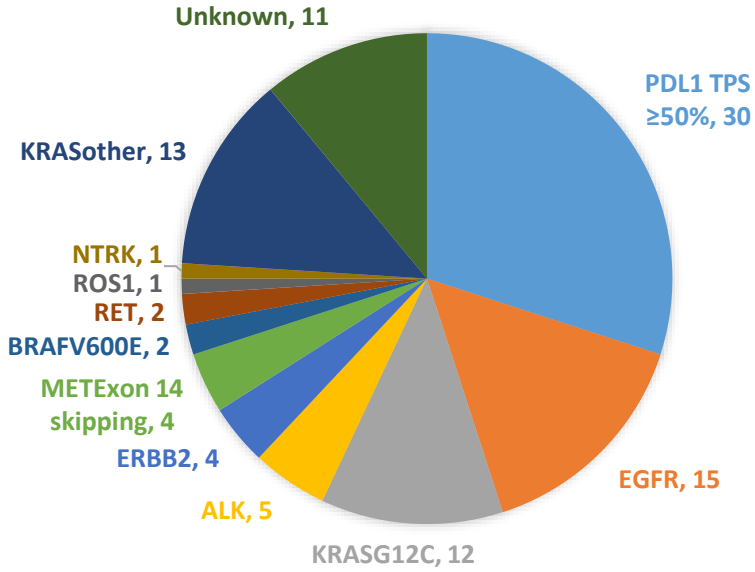
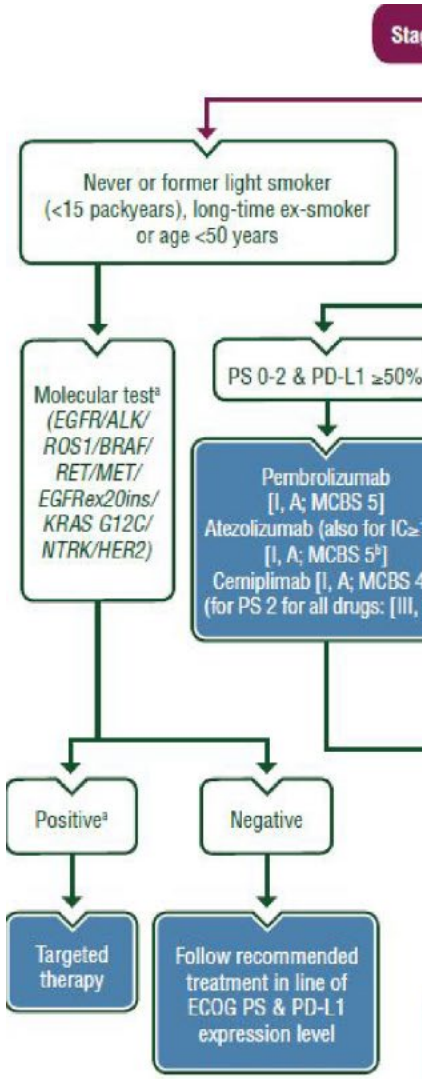


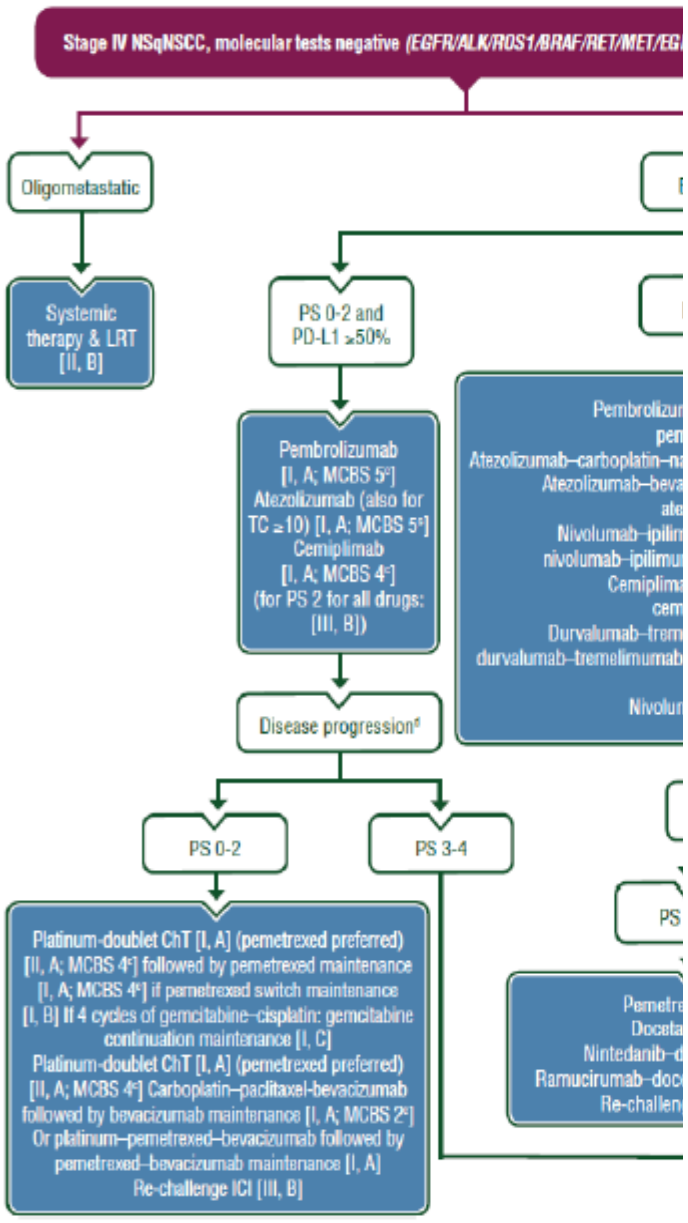
Sholl et al. Lung Cancer Mutation Consortium
J Thorac Oncol. **May 2015**



2021: biomarkers with FDA-approved drugs

The NSCLC treatment algorithm is complex & rapidly expanding





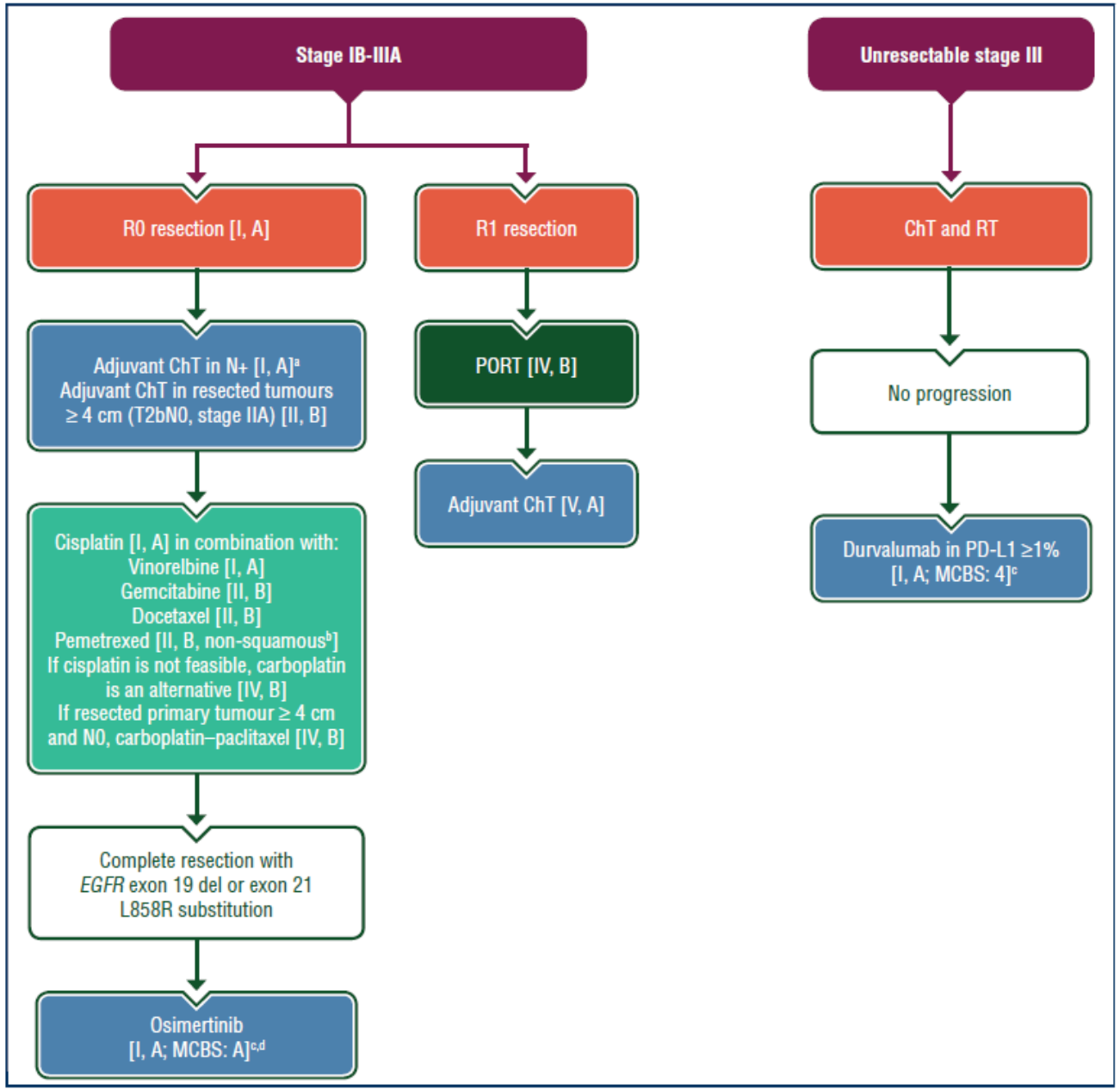
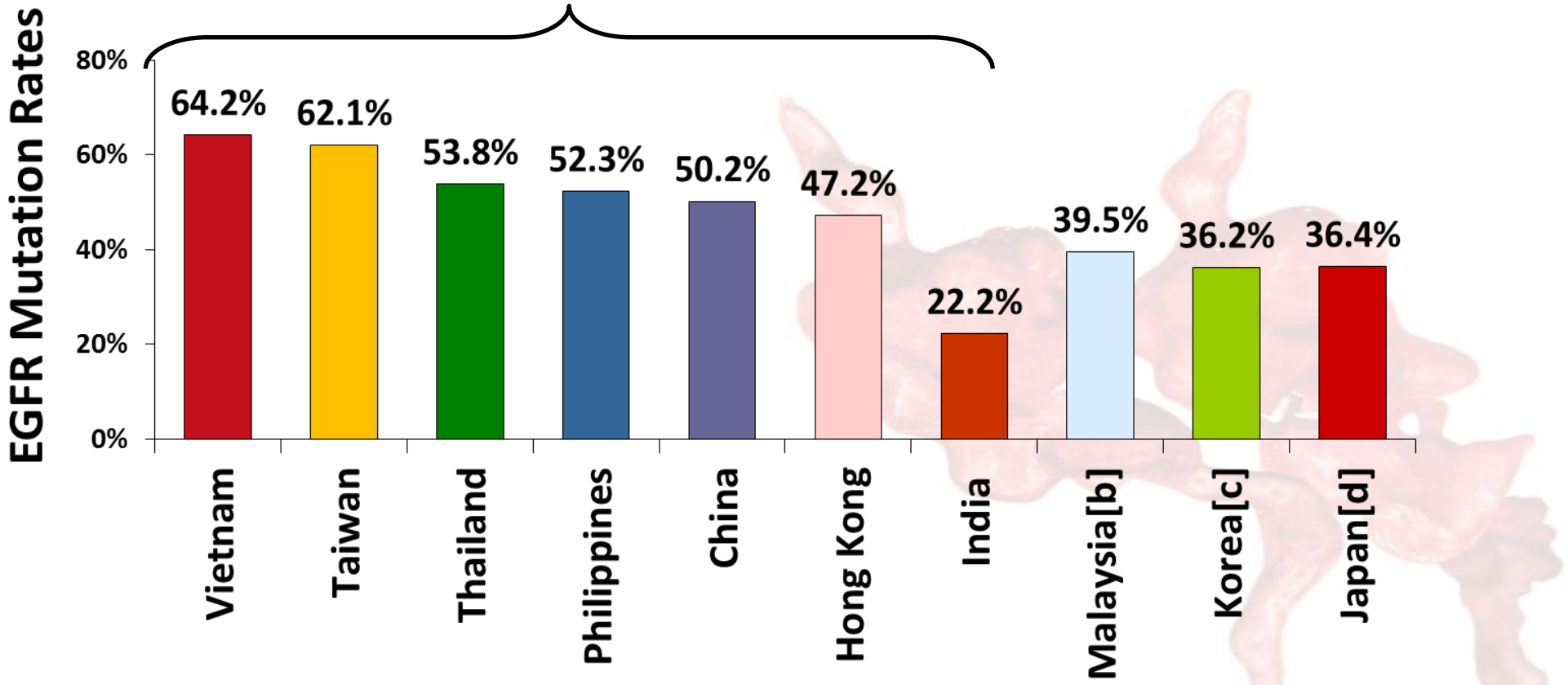


Figure 6. Systemic treatment algorithm for early-stage (stage IB-IIIA) and unresectable locally advanced (stage III) NSCLC.

ESMO Guideline
chest-tumours/nc

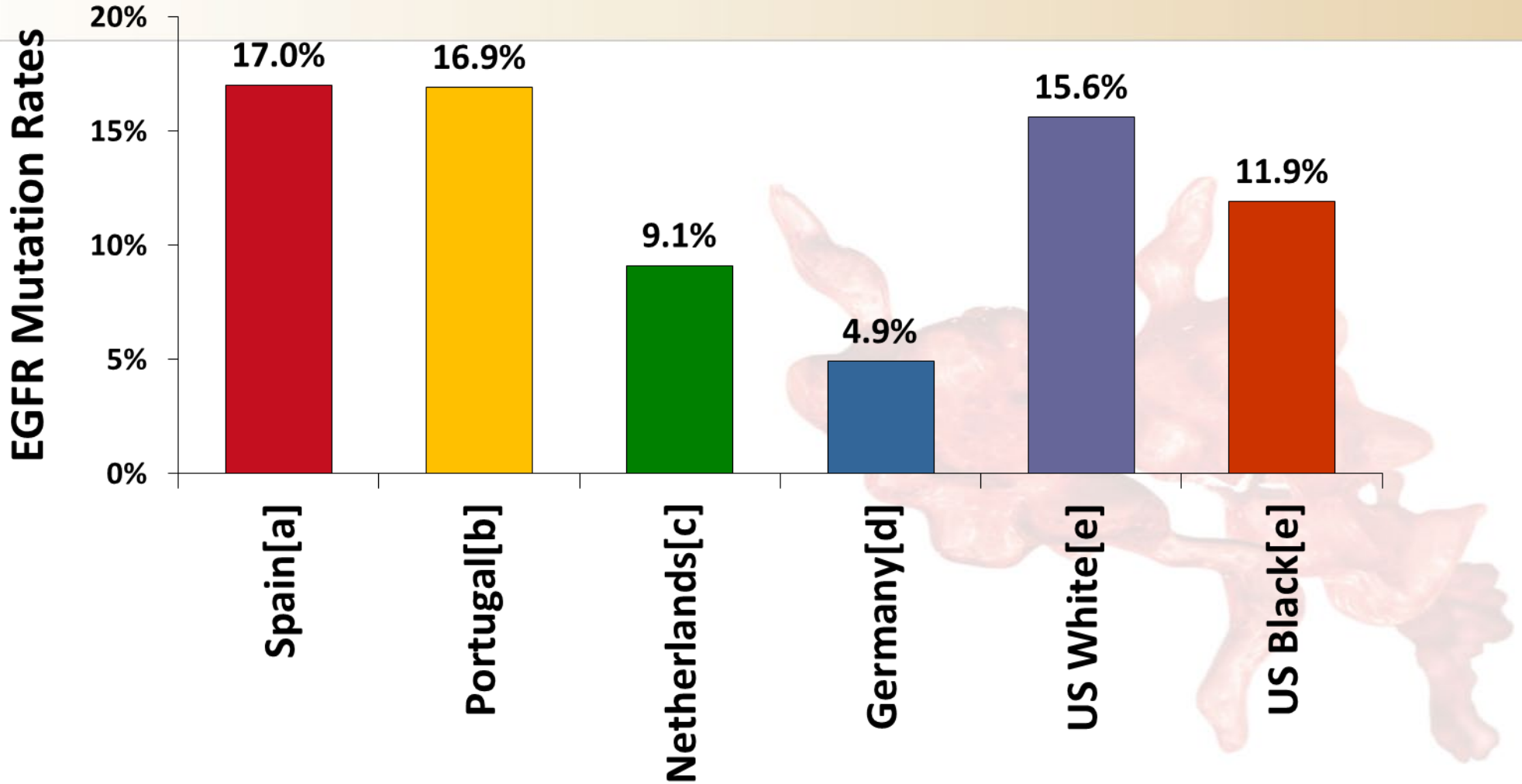
EGFR Mutacije u Aziji

PIONEER (single study)[a]



a. Yang PC, et al. ASCO 2012. Abstract 1534.
b. Liam CK, et al. *J Thorac Oncol*. 2013;8(6):766-772.
c. Choi YL, et al. *PLoS One*. 2013;8(2):e56011.
d. Tanaka T, et al. *Int J Cancer*. 2010;126(3):651-655.

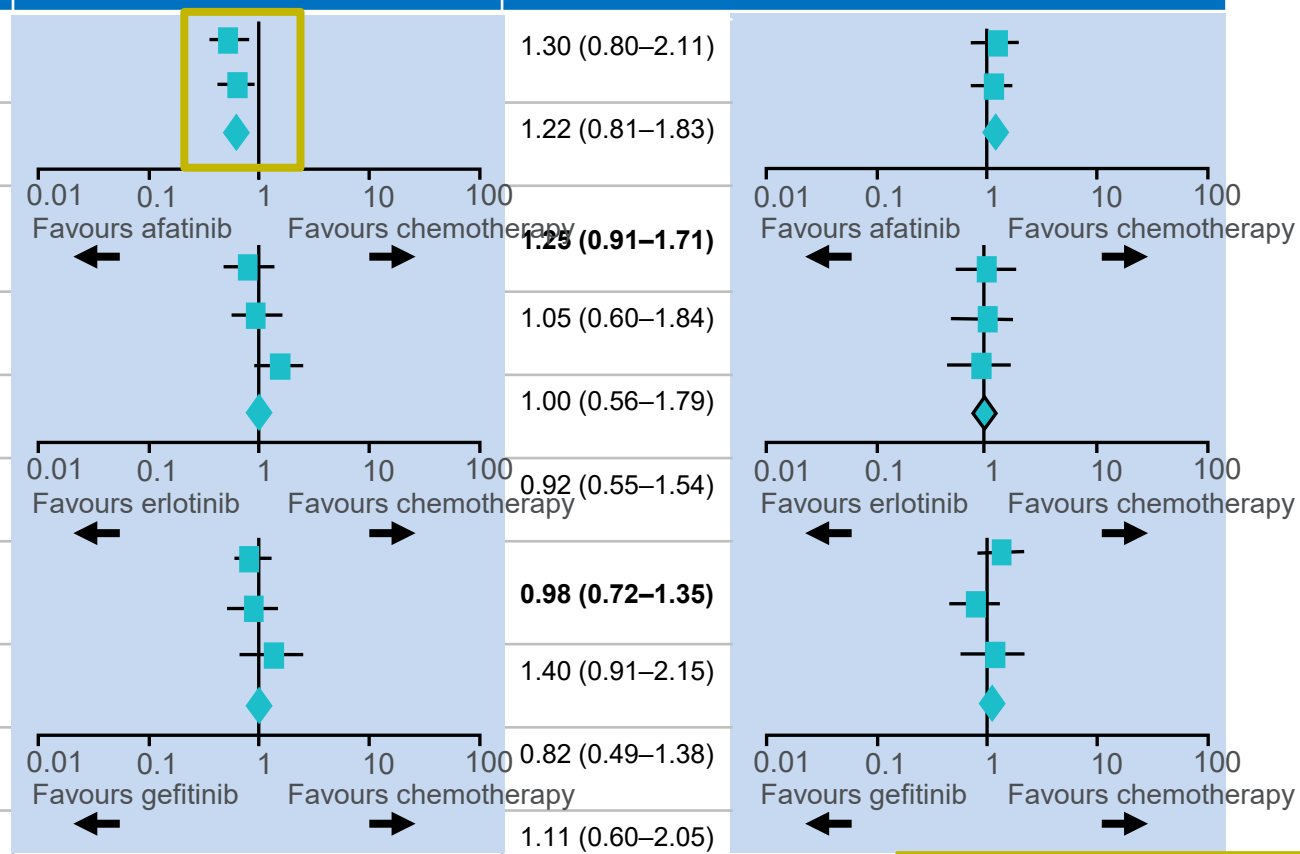
EGFR Mutacije u Evropi



a. Rosell R, et al. *N Engl J Med*. 2009;361(10):958-967; b. de Mello RA, et al. *Tumour Biol*. 2012;33(6):2061-2068; c. Smits AJ, et al. *Cell Oncol (Dordr).* 2012;35(3):189-196; d. Boch C, et al. *BMJ Open*. 2013;3(4):e002560; e. Cote ML, et al. *Thorac Oncol*. 2011;6(3):627-630.

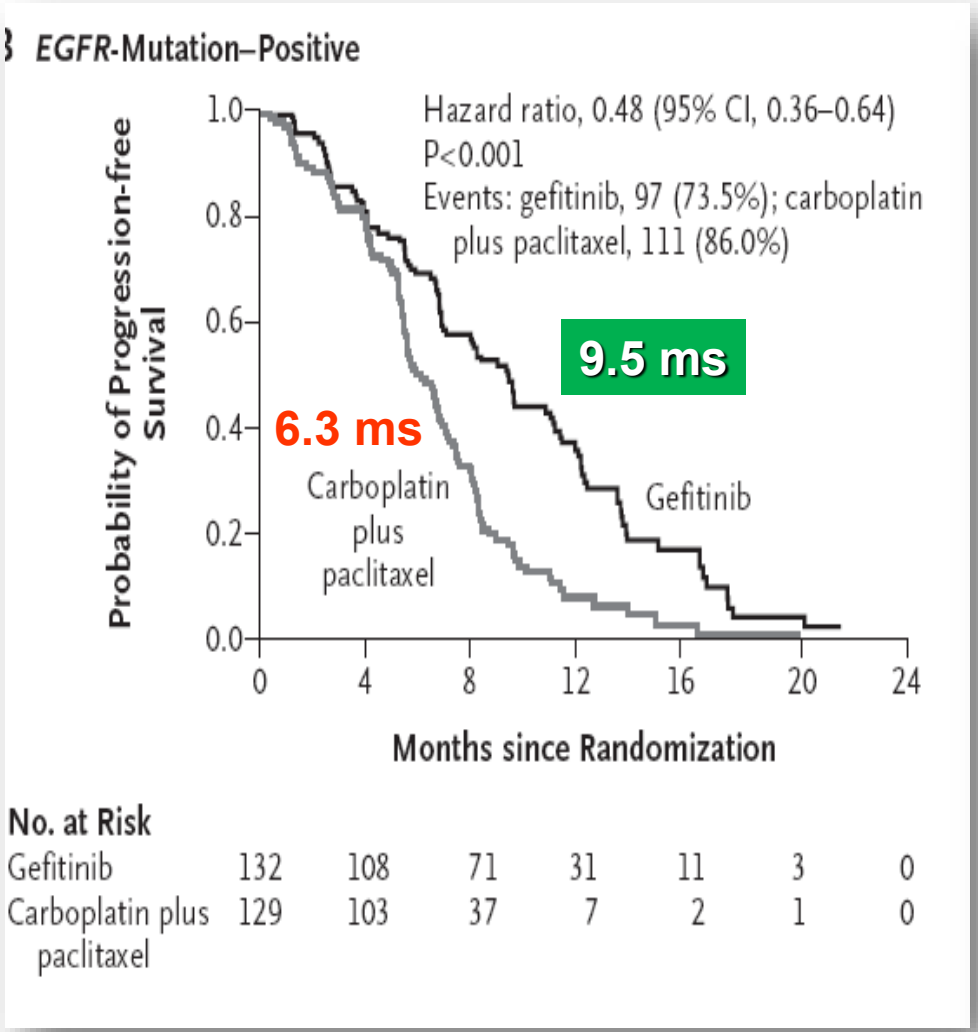
Prva linija: efikasnost (OS) postojećih TKI-a kod *EGFR* L858R/del19 mutacija nije ista

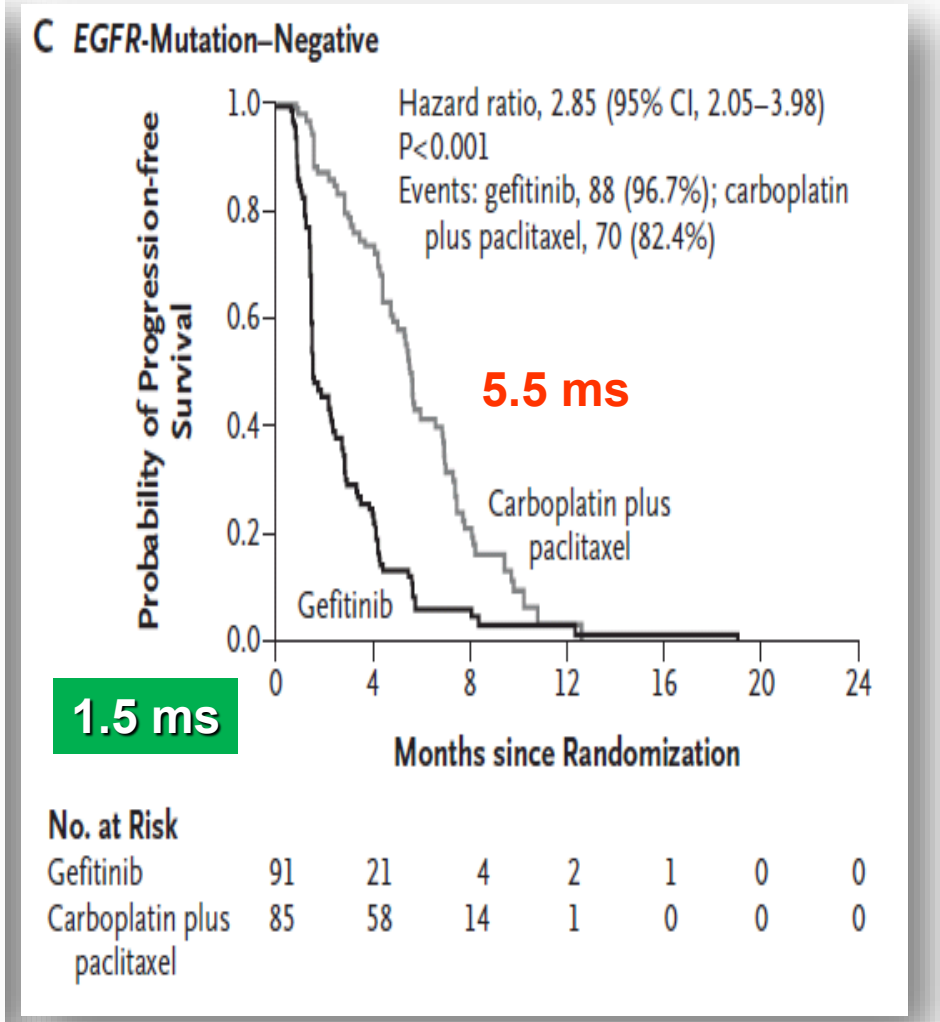
Agent	Study	Hazard Ratio (95% CI)	Del19	Hazard Ratio (95% CI)	L858R
Afatinib	LUX-Lung 3	0.53 (0.36–0.79)		1.30 (0.80–2.11)	
	LUX-Lung 6	0.64 (0.44–0.94)		1.22 (0.81–1.83)	
	Total	**0.59 (0.45–0.77)**		**1.25 (0.91–1.71)**	
Erlotinib	ENSURE	0.79 (0.48–1.30)		1.05 (0.60–1.84)	
	EURTAC	0.94 (0.57–1.54)		1.00 (0.56–1.79)	
	OPTIMAL	1.52 (0.91–2.52)		0.92 (0.55–1.54)	
	Total	**1.04 (0.71–1.51)**		**0.98 (0.72–1.35)**	
Gefitinib	IPASS	0.86 (0.61–1.22)		1.40 (0.91–2.15)	
	NEJ002	0.83 (0.52–1.34)		0.82 (0.49–1.38)	
	WJTOG3405	1.19 (0.65–2.18)		1.11 (0.60–2.05)	
	Total	**0.90 (0.70–1.17)**		**1.11 (0.81–1.54)**	



CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; TKI, tyrosine kinase inhibitor. Kato T, et al. ISPOR 2015; PCN40.

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma





T Mok et al, NEJM 2009

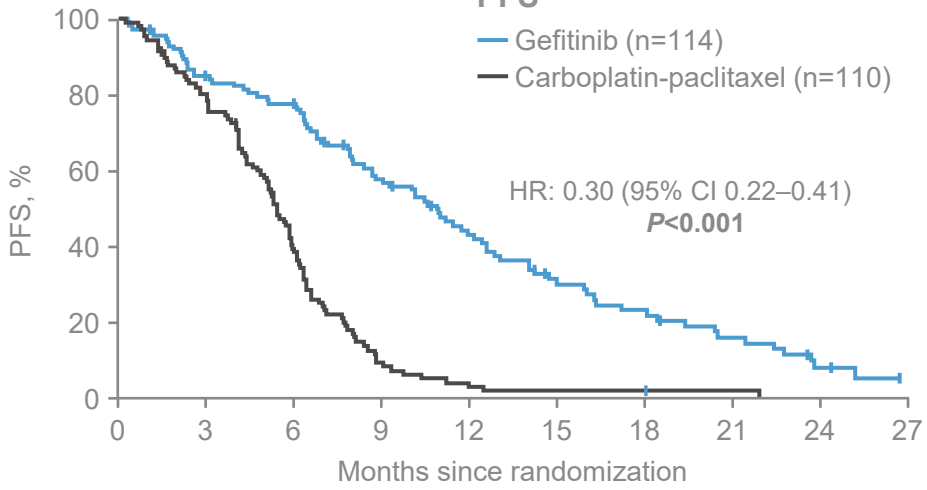
First-generation EGFR TKIs: gefitinib

- Gefitinib significantly improved *vs* SoC:[1]
  - Median PFS: 10.8 *vs* 5.4 months; *P*<0.001)
  - ORR: 73.7% *vs* 30.7%; *P*<0.001
- Median OS was not significantly different[1]
  - 30.5 months *vs* 23.6 months; *P*=0.31

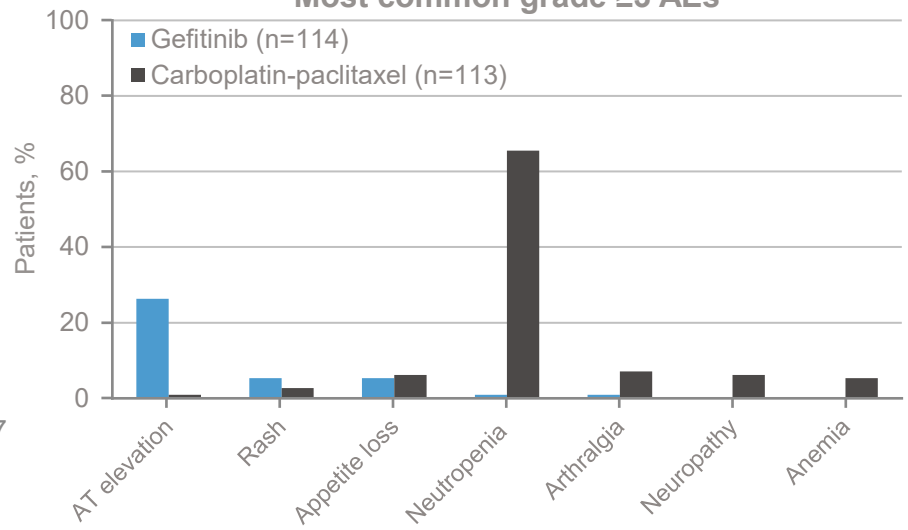
Grade ≥3 AEs were significantly less with gefitinib *vs* chemotherapy

- 41.2% *vs* 71.7%; *P*<0.001

PFS[1]



Most common grade ≥3 AEs[1]



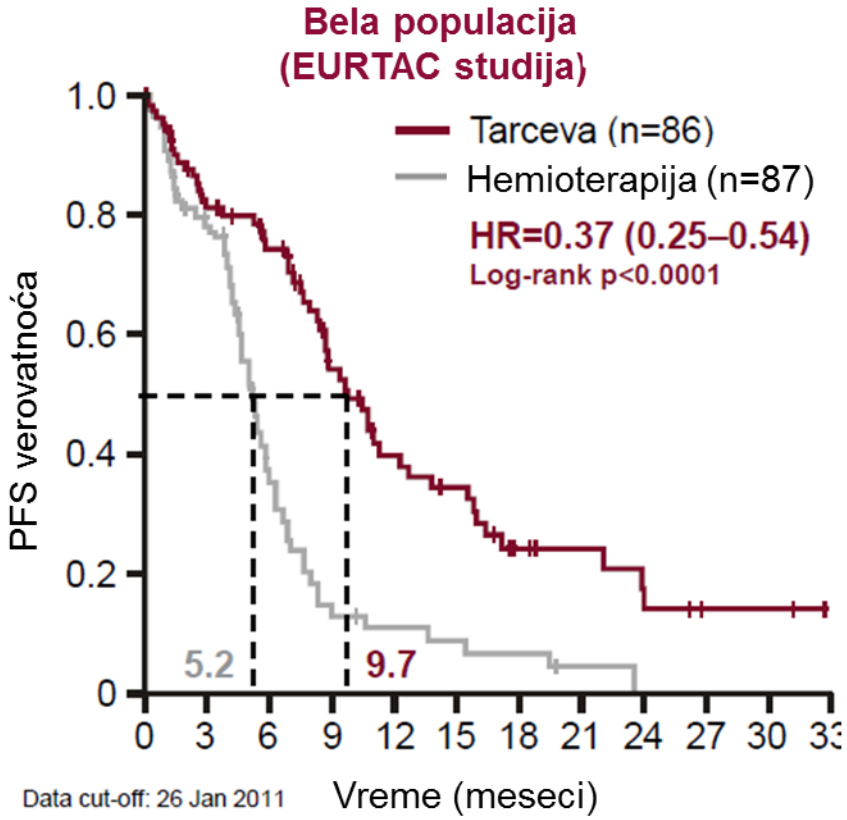
First-line gefitinib improved PFS with an acceptable safety profile *vs* platinum-based chemotherapy in previously untreated *EGFR* mutation-positive patients[1,4]

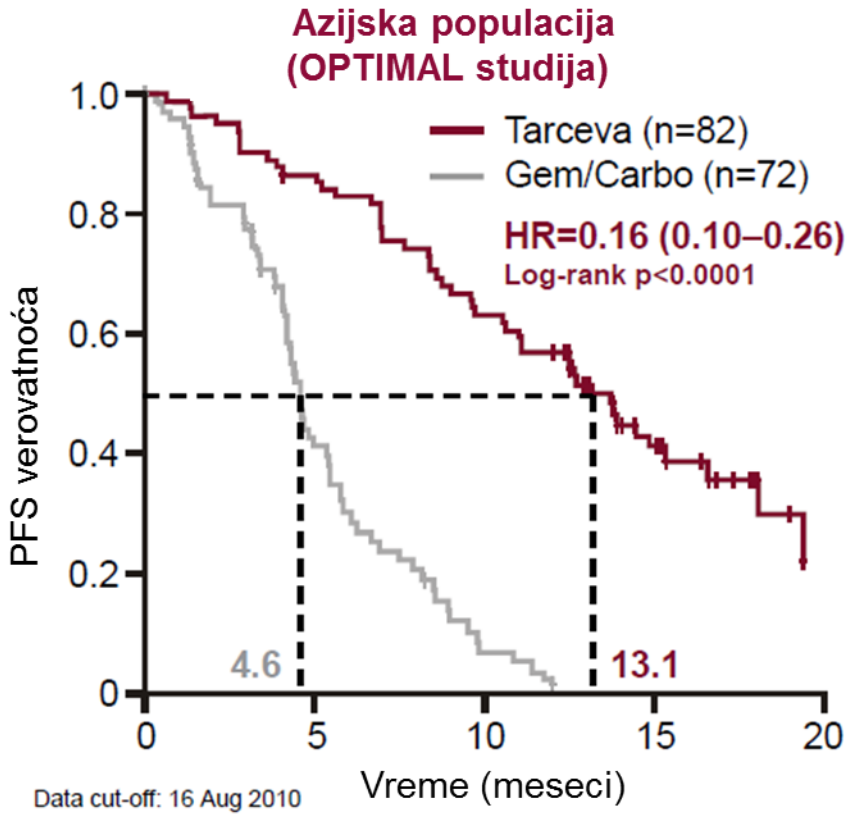
US PI, EU SmPC

AT, aminotransferase; ORR, objective RR; PI, prescribing Information; SmPC, Summary of Product Characteristics; SoC, standard of care

1. Maemondo M et al., *New Engl J Med* 2010;362:2380–2388;
2. Mok T et al., *New Engl J Med* 2009;361:947–957.

Dokazana superiornost erlotiniba u odnosu na hemioterapiju u prvoj liniji lečenja EGFR Mut+ NSCLC





Tarceva je jedini EGFR TKI sa dokazanom superiornošću u odnosu na hemioterapiju i kod bele i kod azijske populacije pacijenata sa EGFR Mut+ NSCLC

10. Zhou C. et al. Lancet Oncol 2011;12:735-742

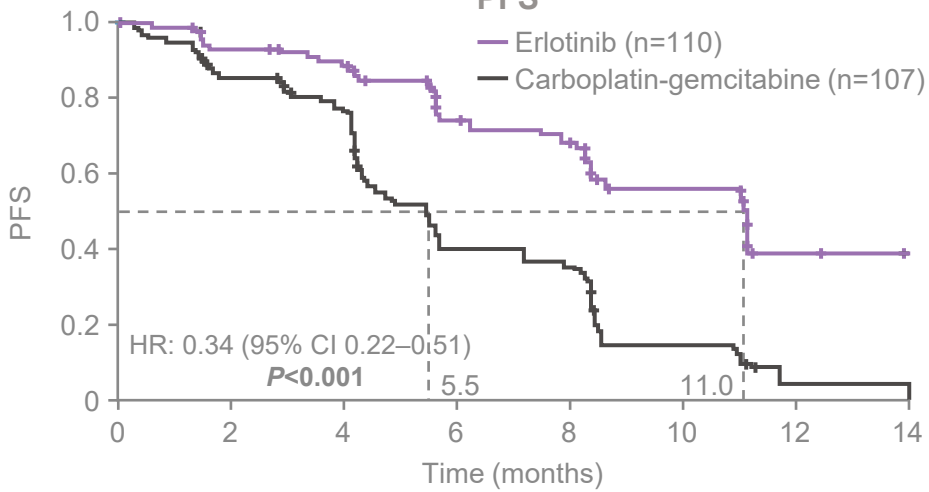
11. Rosell R. et al. Lancet Oncol 2012;13:239-246

First-generation EGFR TKIs: erlotinib

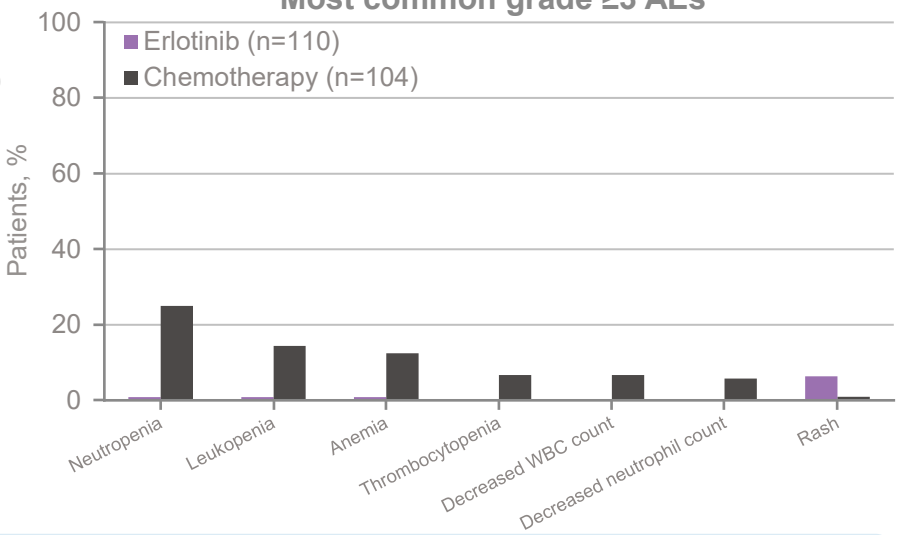
- Erlotinib significantly improved *vs* SoC:[1]
  - Median PFS: 11.0 *vs* 5.5 months; *P*>0.0001
  - ORR: 62.7% *vs* 33.6%
- Median OS was not significantly different[1]
  - 26.3 months *vs* 25.5 months; *P*=0.607[1]

Grade ≥3 AEs were experienced by 35.5% and 57.7% of patients treated with erlotinib and chemotherapy, respectively

PFS[1]



Most common grade ≥3 AEs[1]*



First-line erlotinib improved PFS with an acceptable safety profile *vs* standard chemotherapy in previously untreated *EGFR* mutation-positive patients[1,4]

US PI, EU SmPC

*≥5% of patients in either arm
WBC, white blood cell

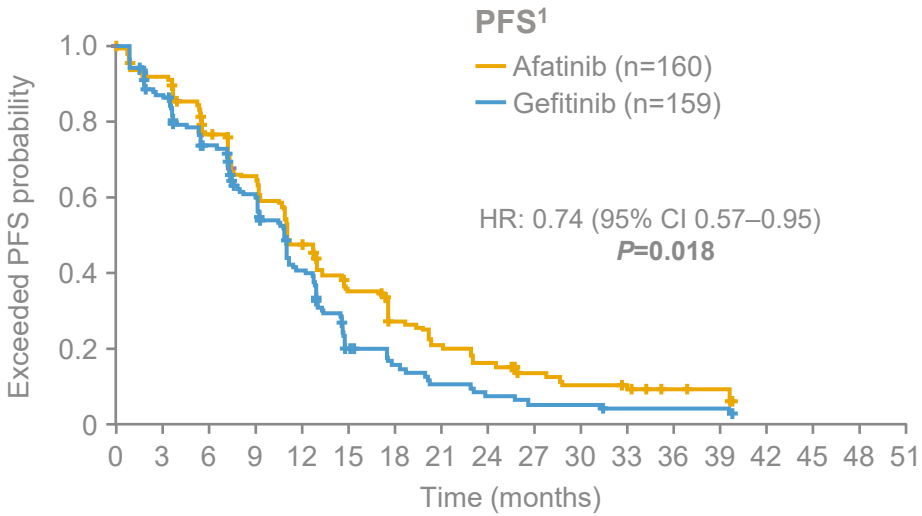
1. Wu Y et al., *Ann Oncol* 2015;26:1883–1889;
2. Rosell R et al., *Lancet Oncol* 2012;13:239–246.

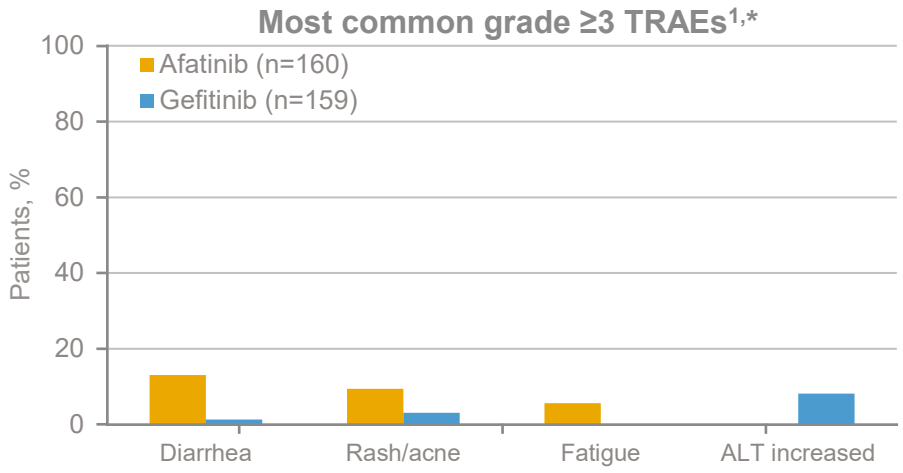
Second-generation EGFR TKIs: afatinib

- Afatinib significantly improved *vs* gefitinib:[1]
  - Median PFS: 11.0 *vs* 10.9 months; *P*=0.018
  - ORR: 72.5% *vs* 56.0%; *P* =0.002
- Median OS was not significantly different[1]
  - 27.9 *vs* 24.5 months; *P*=0.258

All-cause AEs grade ≥3 were 56.9% for afatinib and 53.5% for gefitinib[1]

TRAEs grade ≥3 occurred more frequently with afatinib (31.3%) than gefitinib (19.5%)[1]





First-line afatinib improved PFS *vs* a first-generation EGFR TKI, and had a manageable safety profile in previously untreated *EGFR* mutation-positive patients[1,4]

US PI, EU SmPC

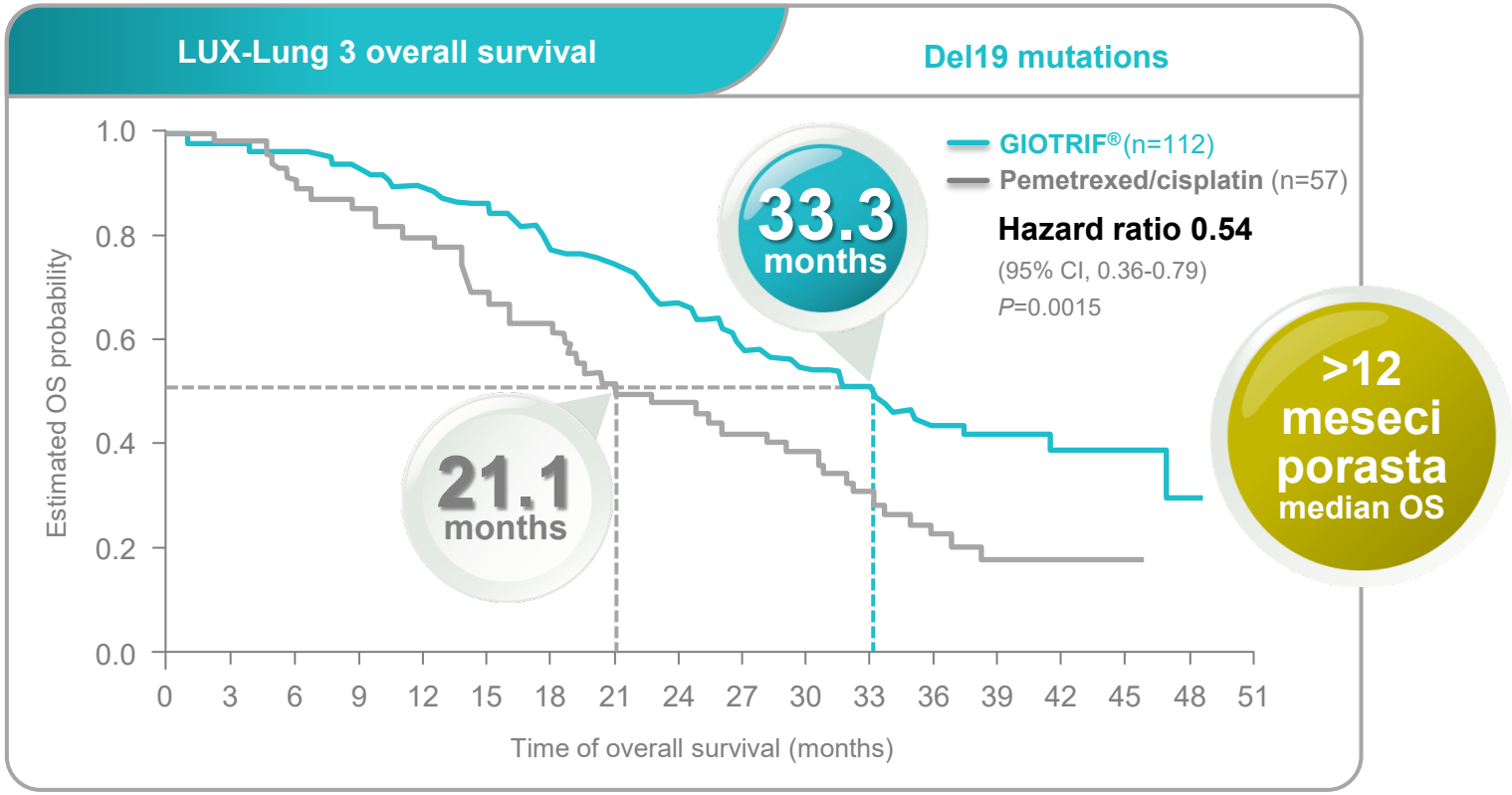
LUX-Lung 7 trial

*≥5% of patients in either arm

ALT, alanine aminotransferase; TRAE, treatment-related adverse event

1. Paz-Ares L et al., *Ann Oncol* 2017;28:270–277;
2. Park K et al., *Lancet Oncol* 2016;17:577–589.

Afatinib – značajno duže ukupno preživljavanje kod pacijenata sa delecijom na egzonu 19

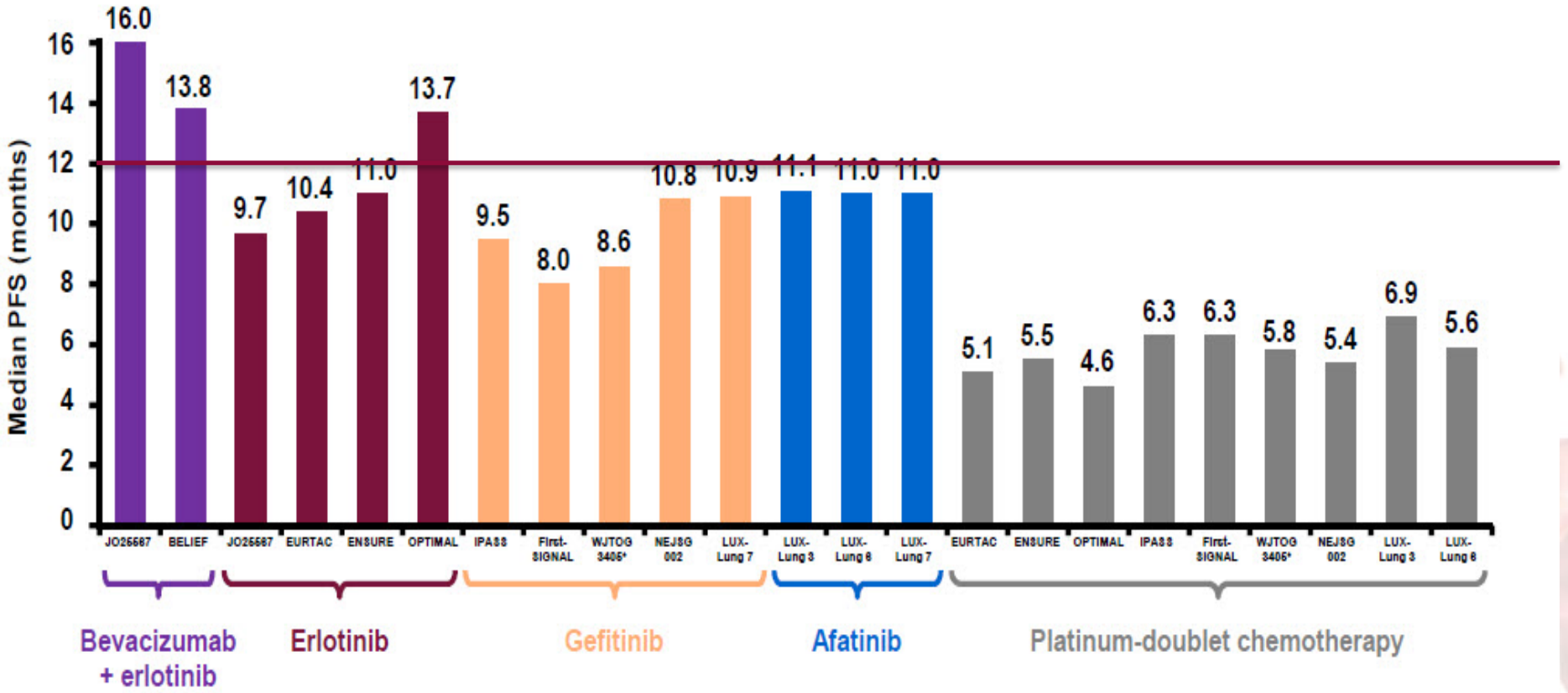


- OS duži za više od 1 godine na GIOTRIF® vs pem/cis kod pacijenata sa del19 (exon 19) (*P*=0.0015)

OS duži za više od 1 godine pokazan i u LUX-Lung 6 (31.4 vs 18.4 months)

Yang JC et al. ASCO oral presentation and abstract. J Clin Oncol 32:5s, 2014 (suppl; abstr 8004^).

TKI i **produžavanje PFS preko 1 godine** u studijama faze III kod EGFR Mut+ bolesti



Cross-trial comparison. Data should be interpreted with caution
*Data from stage IIIB/IV patients

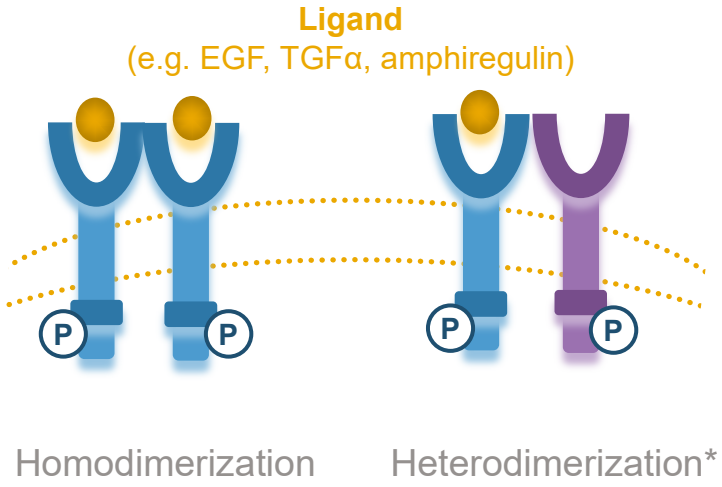
Chen, et al. Ann Oncol 2013; Costa, et al. Clin Cancer Res 2014; EMA 2017 Gefitinib SmPC 2009, last updated 2016
Han, et al. J Clin Oncol 2012; Maemondo, et al. N Engl J Med 2010; Park, et al. Lancet Oncol 2016
Sequist, et al. J Clin Oncol 2013; Seto, et al. Lancet Oncol 2014; Wu, et al. Ann Oncol 2015
Wu, et al. Lancet Oncol 2014; Yoshioka, et al. ASCO 2014

The EGFR family regulate cell proliferation, survival, migration, and metastasis

Binding of various cognate ligands to the receptor leads to receptor dimerization[1,2]

Homodimerization or heterodimerization* leads to **tyrosine kinase activity** and receptor phosphorylation[1,2]

EGFR signaling[1,2]



*HER2 is the most common partner for heterodimerization between two EGFRs; HER2 has no known ligand
EGF, epidermal growth factor; TGF, transforming growth factor

1. Siegelin M and Borczuk A. *Lab Invest* 2014;94:129–137;
2. Wee P and Wang Z. *Cancers (Basel)* 2017;9:52.

The EGFR family regulate cell proliferation, survival, migration, and metastasis

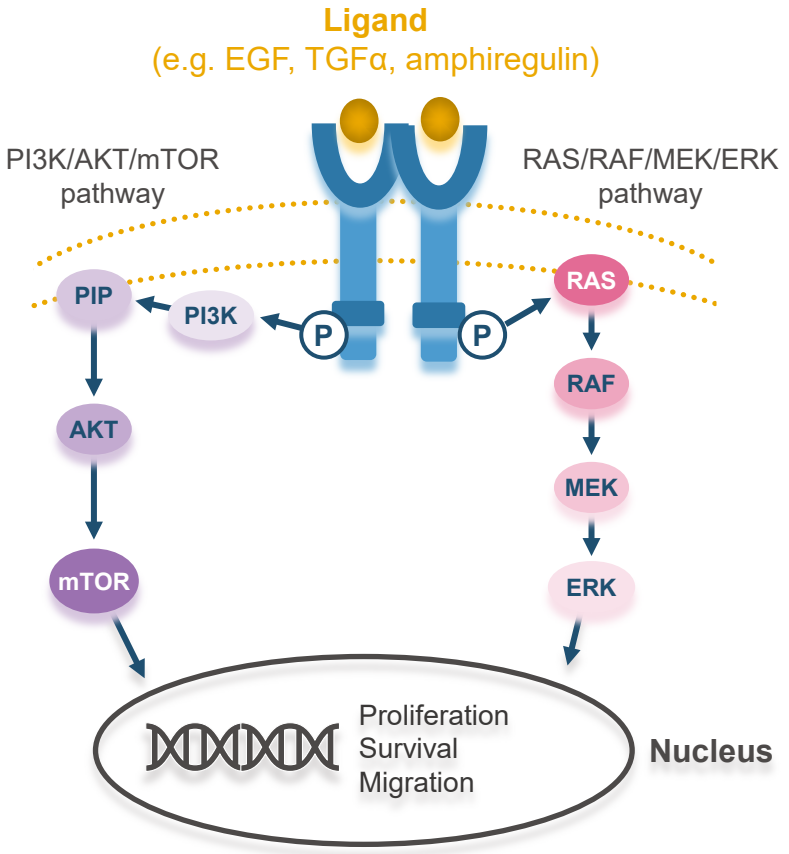
Binding of various cognate ligands to the receptor leads to receptor dimerization[1,2]

Homodimerization or heterodimerization* leads to **tyrosine kinase activity** and receptor phosphorylation[1,2]

The phosphotyrosine residues act as a docking site for various adapter molecules, resulting in the activation of the **RAS/RAF/MEK/ERK pathway** and **the PI3K/AKT/mTOR pathway**[1,2]

Transcription signaling pathways are then activated that regulate key developmental, metabolic, and physiological processes[2]

EGFR signaling[1,2]



AKT, protein kinase B; mTOR, mammalian target of rapamycin; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma

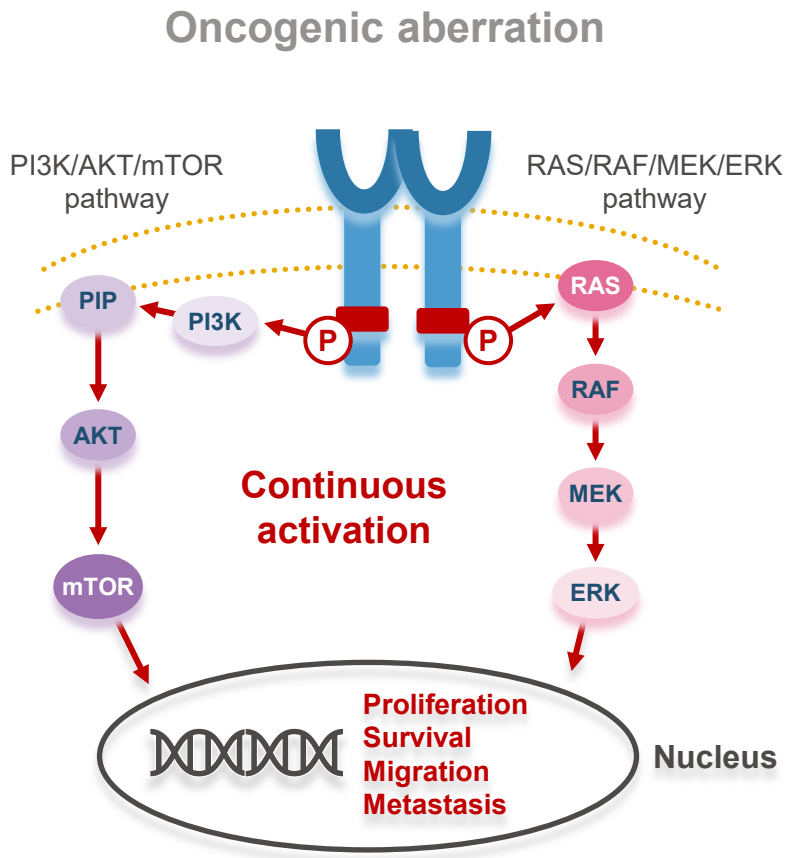
1. Siegelin M and Borczuk A. *Lab Invest* 2014;94:129–137;
2. Wee P and Wang Z. *Cancers (Basel)* 2017;9:52.

EGFR oncogenic driver mutations cause constitutive activation of the receptor

The most common *EGFR* oncogenic driver mutations are found within the genes encoding the **tyrosine kinase domain**[1]

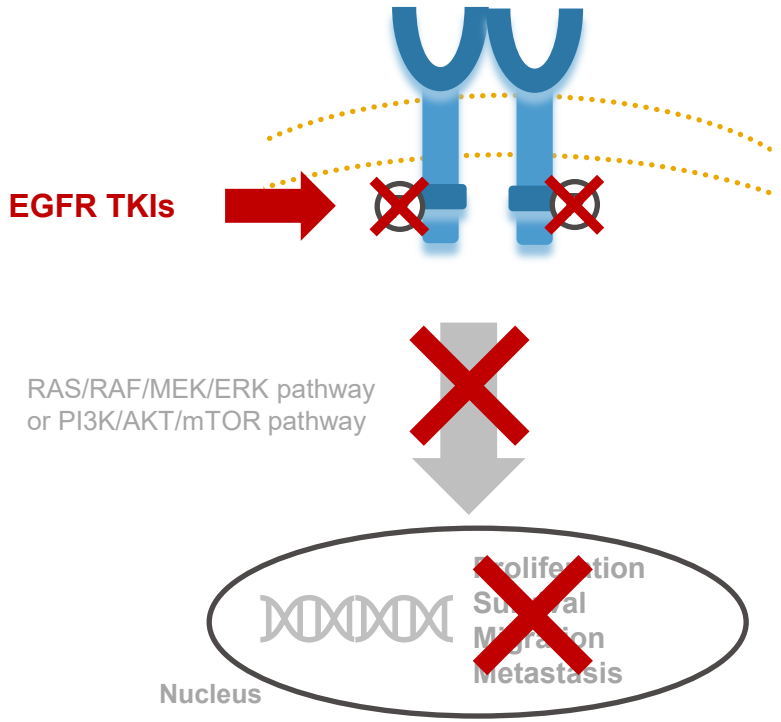
These mutations cause **increased and sustained** phosphorylation of the receptor (without ligand stimulation)[1,2]

This results in **continuous cell survival, proliferation, invasion, and metastasis**[1,2]



1. Gazdar A. *Oncogene* 2009;28(Suppl 1):S24–S31;
2. Siegelin M and Borczuk A. *Lab Invest* 2014;94:129–137.

EGFR oncogenic driver mutations are blocked by EGFR TKIs



EGFR TKIs bind to the ATP pocket of the tyrosine kinase domain

Inhibition of the intracellular signaling pathways

No cell survival, proliferation, invasion, or metastasis

EGFR TKIs bind to the ATP-binding site within the EGFR tyrosine kinase domain

ATP, adenosine triphosphate

Kobayashi Y and Mitsudomi T. *Cancer Sci* 2016;107:1179–1186;
Du Z and Lovly C. *Mol Cancer* 2018;17:58.

EGFR oncogenic driver mutations and response to EGFR TKIs

- Higher prevalence of *EGFR* oncogenic driver mutations in patients with:[1,2]

- Adenocarcinoma tumor histology *vs* other histology (40% *vs* 3%)

- Never smokers *vs* ever smokers (51% *vs* 10%)
- East Asian ethnicity *vs* other ethnicities (30% *vs* 8%)

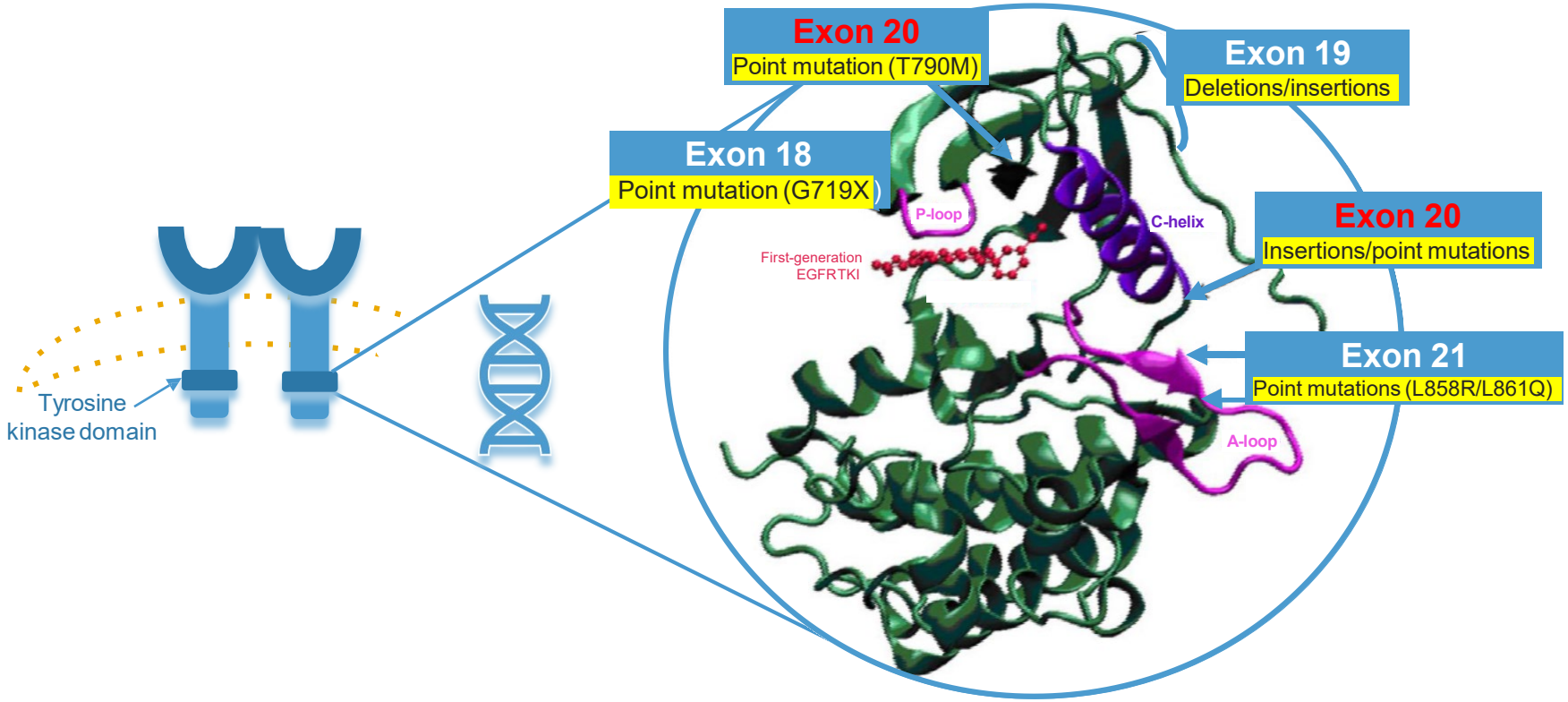
- Female sex *vs* male sex (42% *vs* 14%)

- Some of these patient characteristics have also been correlated with an improved response to EGFR TKIs and prolonged survival[3,4,*]

*Meta-analysis of randomized trials comparing EGFR TKIs with chemotherapy concluded that ethnicity and tumor histology did not significantly predict additional benefit from EGFR TKIs[4]

1. Shigematsu H. *J Natl Cancer Inst* 2005;97:339–346;
2. Reck M and Rabe K. *New Engl J Med* 2017;377:849–861;
3. Sequist L et al., *Oncologist* 2007;12:90–98;
4. Lee C et al., *J Clin Oncol* 2015;33:1958–1965.

EGFR oncogenic driver mutations

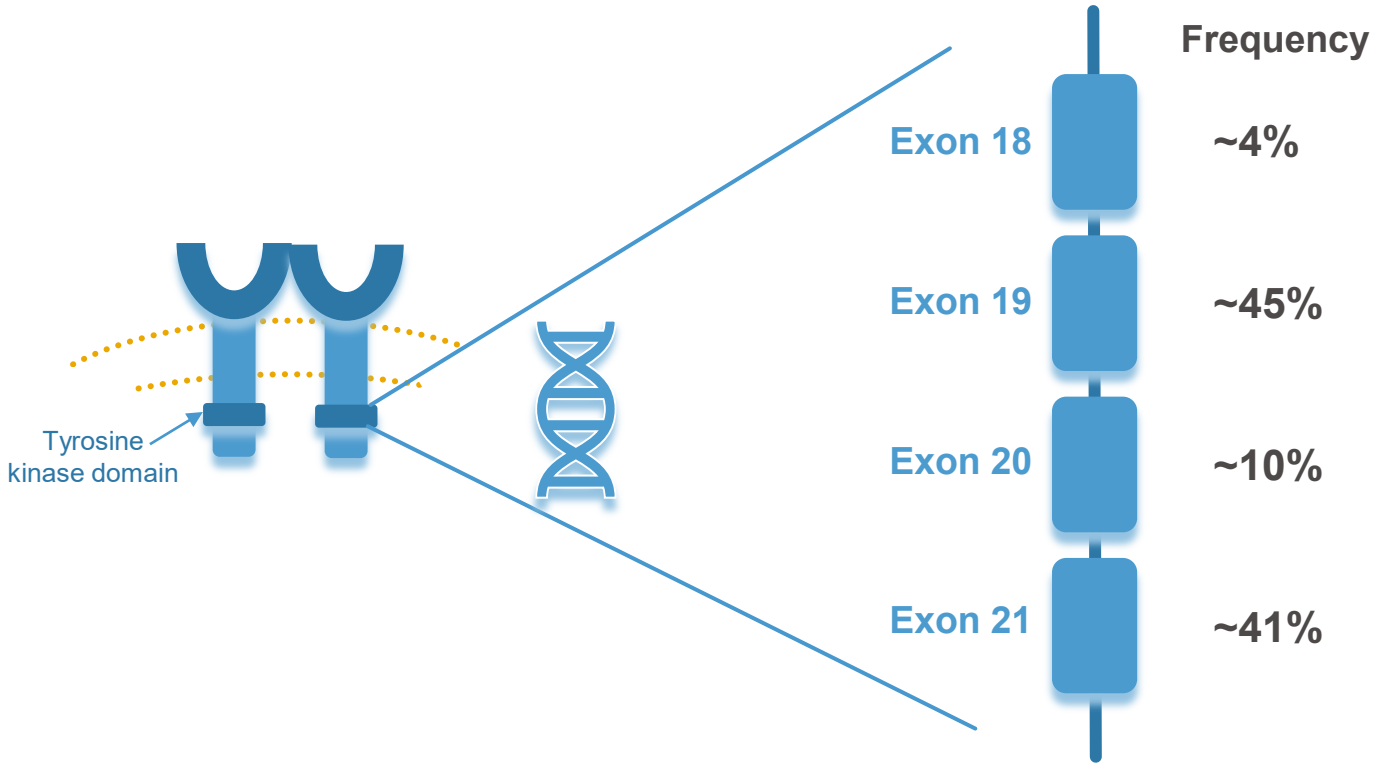


***EGFR* driver mutations are predominantly found within exons 18–21**

The incidence of mutations may vary due to the range of techniques used
L, leucine; R, arginine; Q, glutamine

Chong C and Janne P. *Nat Med* 2013;19:1389–1400; Crossland V et al., *J Thorac Oncol* 2018;13 (10 Suppl):S612–S613; Gazdar A and Minna J. *PLoS Med* 2005;2:e377; Gazdar A. *Oncogene* 2009;28(Suppl 1):S24–S31; Jorge S et al., *Braz J Med Biol Res* 2014;47:929–939; Kobayashi Y and Mitsudomi T. *Cancer Sci* 2016;107:1179–1186; Lee J et al., *Ann Oncol* 2013;24:2080–2087.

EGFR oncogenic driver mutations



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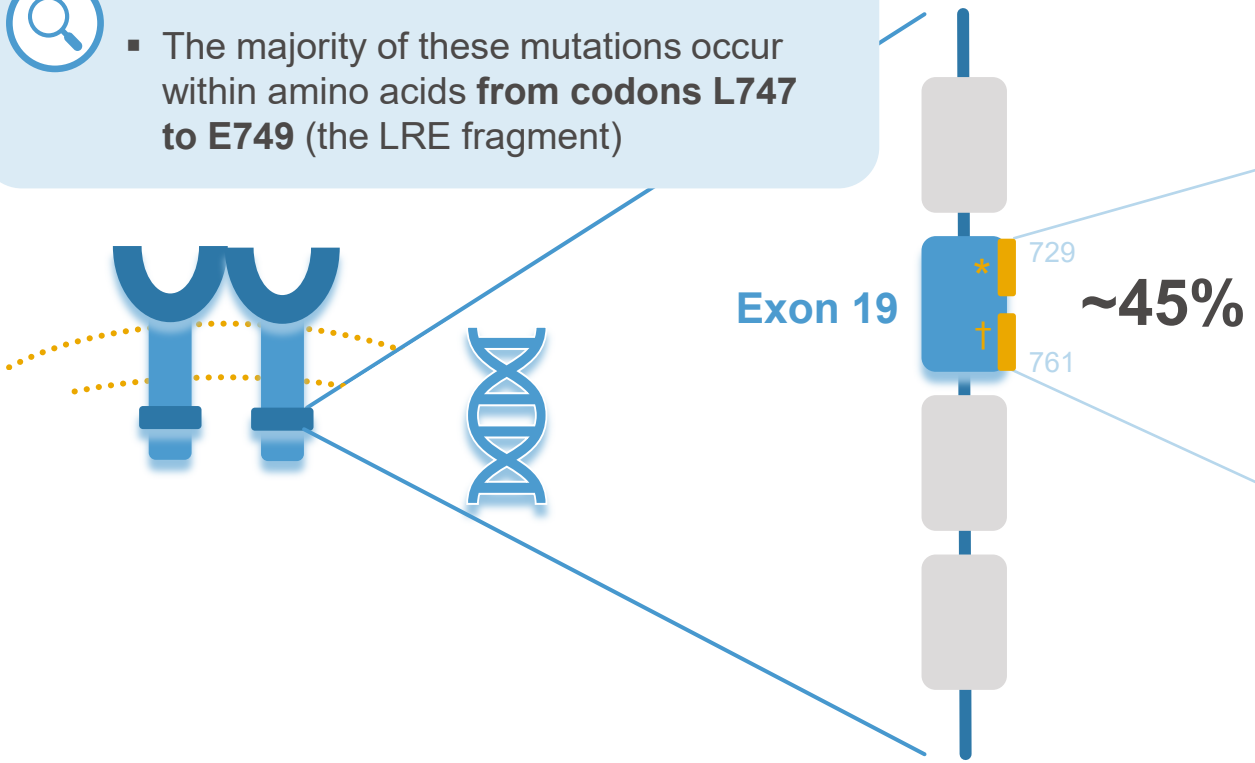
EGFR exon 19: most common mutations

- Exon 19 mutations are the most common
- The majority of these mutations occur within amino acids **from codons L747 to E749** (the LRE fragment)



Deletions (~45%)

- delE746-A750 (~67%)
- delL747-P753insS (~8%)
- delL747-T751 (~5%)
- delL747-A750insP (~3%)
- delL747_S752 (~3%)
- Others (~15%)

Insertions (<1%)

- I744_K74SinsKIPVAI (~58%)
- K745_E746inslPVAIK (~26%)
- Other (~16%)

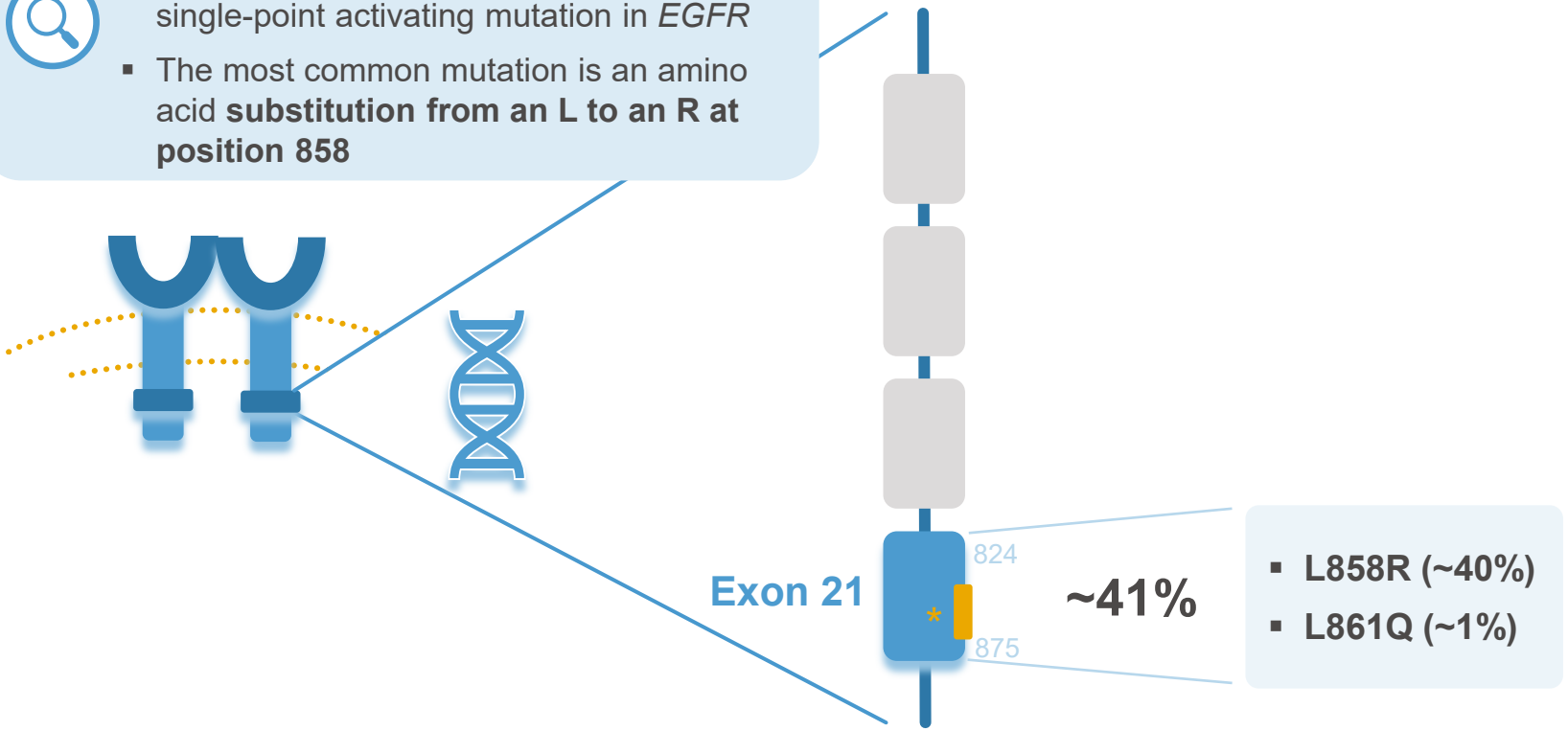
Approximately 45% of *EGFR* driver mutations are within exon 19, the most common being LRE deletions

*Codons for the phosphate binding (or P) loop; †Codons for the α-C-helix
The incidence of mutations may vary due to the range of techniques used
E, glutamate

Chong C and Janne P. *Nat Med* 2013;19:1389–1400; Gazdar A and Minna J. *PLoS Med* 2005;2:e377; Gazdar A. *Oncogene* 2009;28(Suppl 1):S24–S31; Jorge S et al., *Braz J Med Biol Res* 2014;47:929–939; Kobayashi Y and Mitsudomi T. *Cancer Sci* 2016;107:1179–1186; Su J et al., *Oncotarget* 2017;8:111246–111257.

EGFR exon 21: most common mutations

- Exon 21 has the highest prevalence of any single-point activating mutation in *EGFR*
- The most common mutation is an amino acid **substitution from an L to an R at position 858**



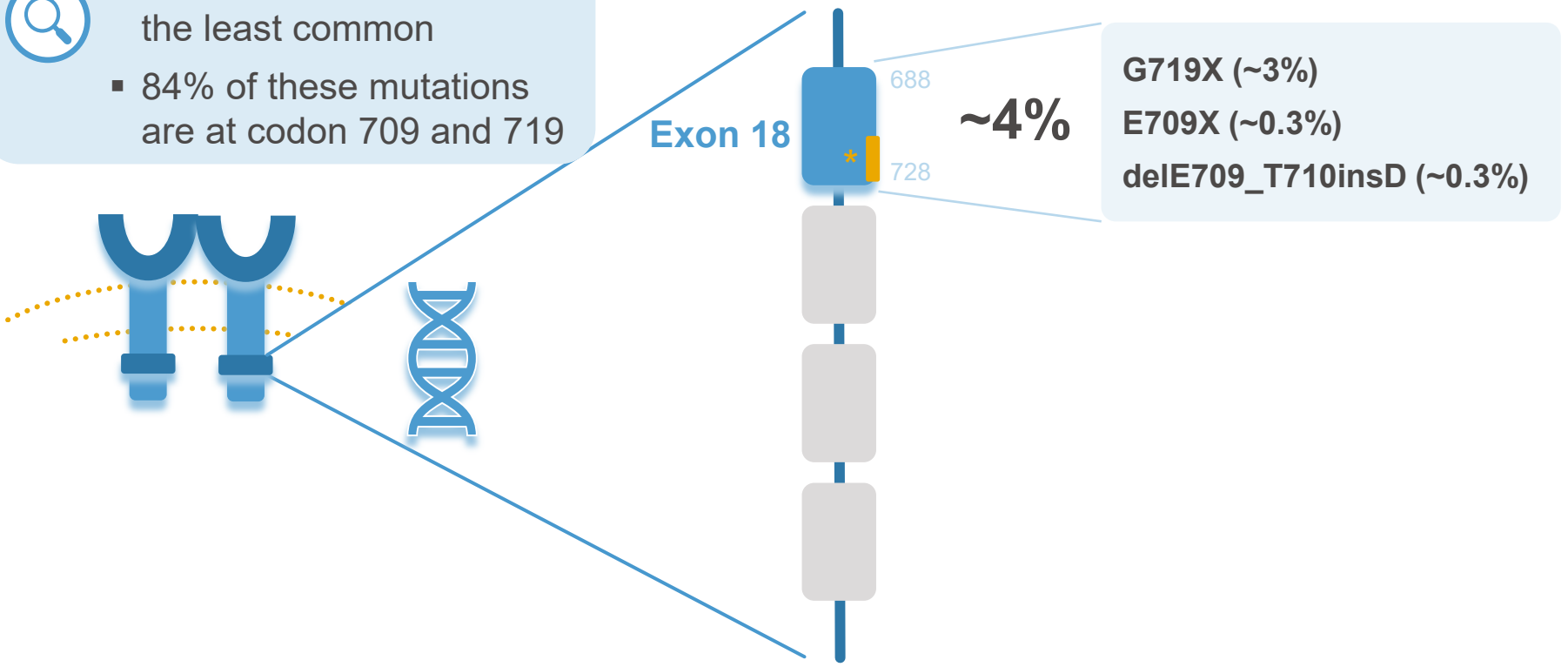
Approximately 41% of *EGFR* driver mutations are within exon 21, the most common being the L858R point mutation

*Codons for the catalytic or activation loop
The incidence of mutations may vary due to the range of techniques used

Chong C and Janne P. *Nat Med* 2013;19:1389–1400; Gazdar A and Minna J. *PLoS Med* 2005;2:e377; Gazdar A. *Oncogene* 2009;28(Suppl 1):S24–S31; Jorge S et al., *Braz J Med Biol Res* 2014;47:929–939; Kobayashi Y and Mitsudomi T. *Cancer Sci* 2016;107:1179–1186.

EGFR exon 18: most common mutations

- Exon 18 mutations are the least common
- 84% of these mutations are at codon 709 and 719



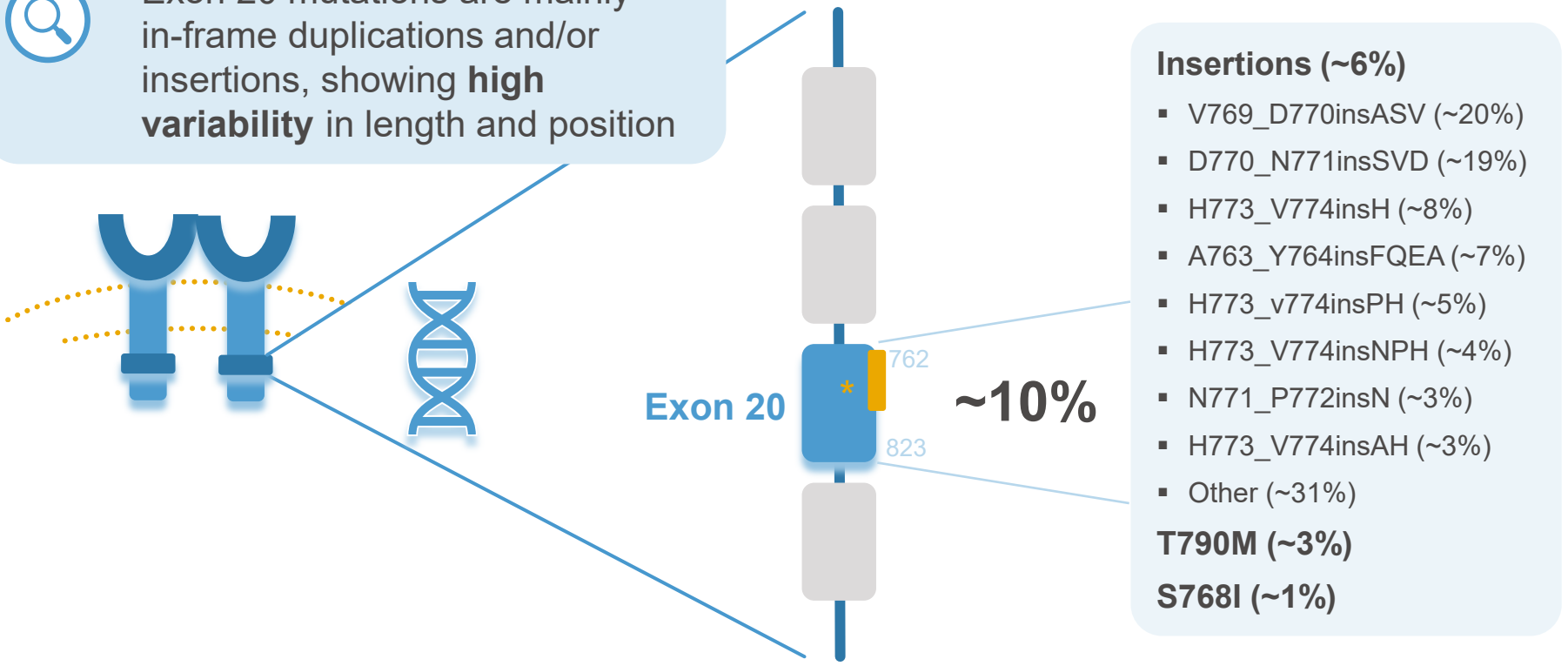
Approximately 4% of *EGFR* driver mutations are within exon 18, the most common being the G719X point mutation

*Codons for the phosphate binding loop
The incidence of mutations may vary due to the range of techniques used

Chong C and Janne P. *Nat Med* 2013;19:1389–1400; Gazdar A and Minna J. *PLoS Med* 2005;2:e377; Gazdar A. *Oncogene* 2009;28(Suppl 1):S24–S31; Jorge S et al., *Braz J Med Biol Res* 2014;47:929–939; Kobayashi Y et al., *Clin Cancer Res* 2015;21;5305–5313; Kobayashi Y and Mitsudomi T. *Cancer Sci* 2016;107:1179–1186.

EGFR exon 20: most common mutations

- Exon 20 mutations are mainly in-frame duplications and/or insertions, showing **high variability** in length and position



Insertions (~6%)

- V769_D770insASV (~20%)
- D770_N771insSVD (~19%)
- H773_V774insH (~8%)
- A763_Y764insFQEA (~7%)
- H773_v774insPH (~5%)
- H773_V774insNPH (~4%)
- N771_P772insN (~3%)
- H773_V774insAH (~3%)
- Other (~31%)

T790M (~3%)

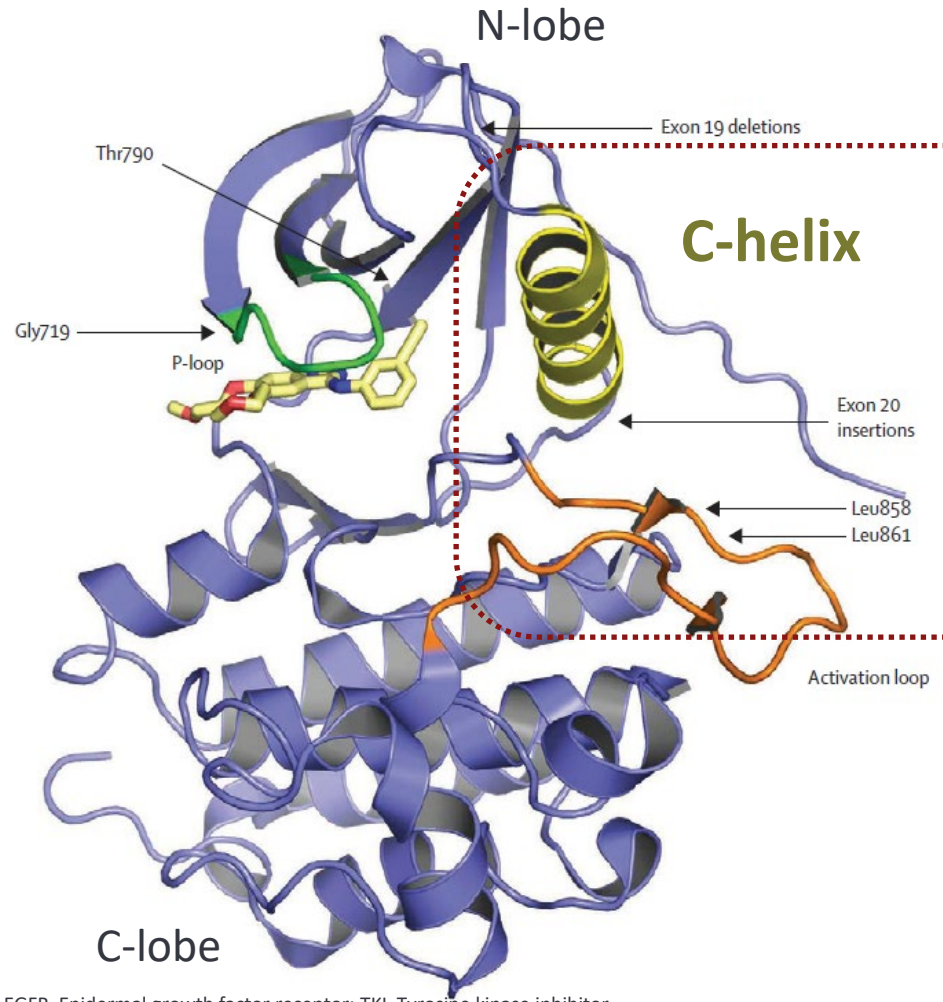
S768I (~1%)

Approximately 10% of *EGFR* driver mutations are within exon 20, the most common being V769_D770insASV

*Codons for the α-C-helix
The incidence of mutations may vary due to the range of techniques used

Arcila M et al., *Mol Cancer Ther* 2013;12:220–229; Chong C and Janne P. *Nat Med* 2013;19:1389–1400; Crossland V et al., *J Thorac Oncol* 2018;13(10 Suppl):S612–S613; Gazdar A and Minna J. *PLoS Med* 2005;2:e377; Gazdar A. *Oncogene* 2009;28(Suppl 1):S24–S31; Jorge S et al., *Braz J Med Biol Res* 2014;47:929–939; Kobayashi Y and Mitsudomi T. *Cancer Sci* 2016;107:1179–1186; Lee J et al., *Ann Oncol* 2013;24:2080–2087; Oxnard G et al., *J Thorac Oncol* 2013;8:179–184.

EGFR exon 20 codes for the C-helix and the activation loop (intracellular receptor domain)



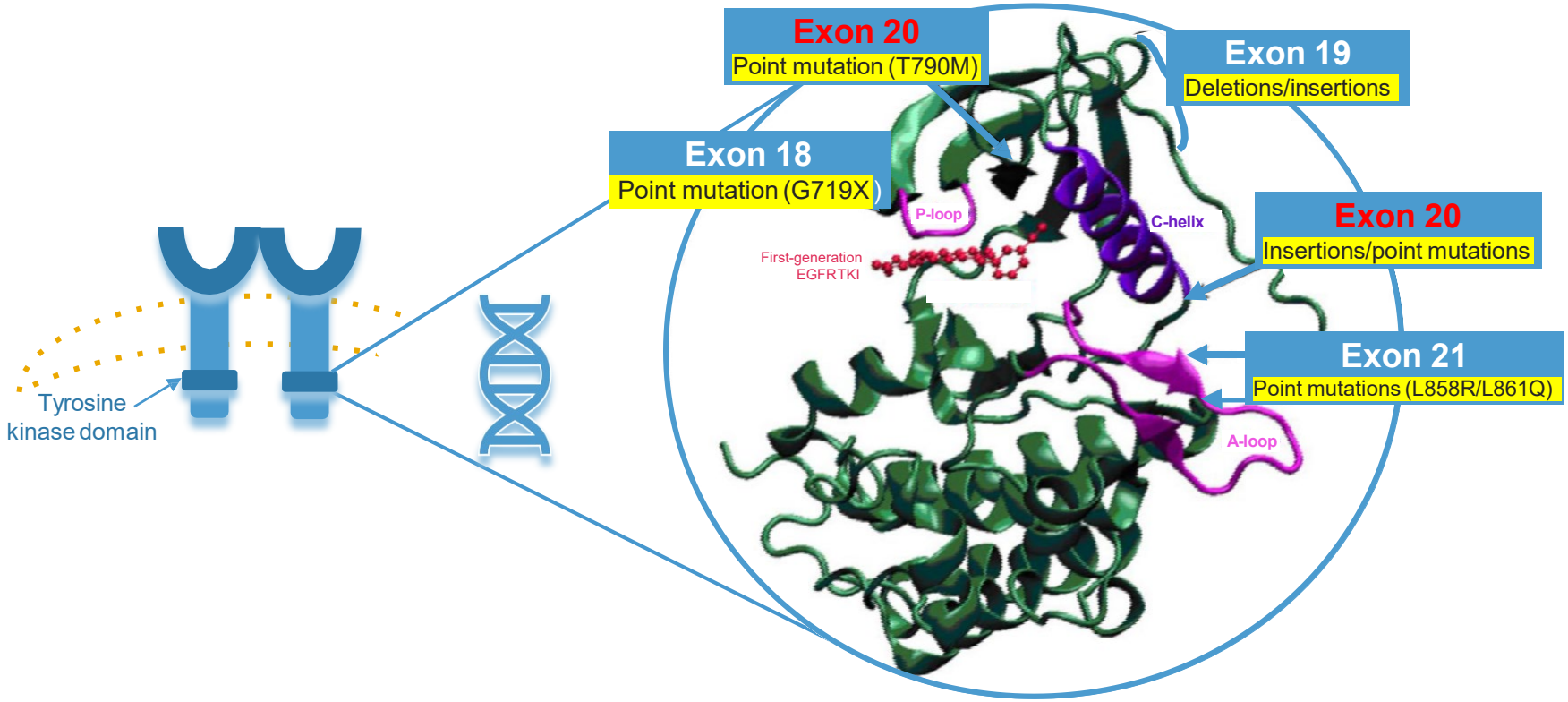
Genetic alterations in exon 20 EGFR gene

- **TKI binding site conformation may change**, resulting in **primary (de novo) resistance** to EGFR TKI.
- **Activate kinase** (independently of EGF ligand)

The epidermal growth factor receptor (EGFR) tyrosine kinase domain is made up of a larger C-terminal and a smaller N-terminal lobe (C-lobe and N-lobe). The kinase's active place is situated within the cleft between the two lobes and is depicted in the figure bound to erlotinib. The P-loop is shown in green, the activation loop (A-loop) in orange, and the C-helix in yellow. The structural location and aminoacid positions of the most crucial EGFR mutations are indicated by black arrows.

EGFR, Epidermal growth factor receptor; TKI, Tyrosine kinase inhibitor
Image and data adapted from: Kron A., et al. Ann Oncol 2018; 29: 2068–2075; Yasuda H., et al. Lancet Oncol 2012; 13: e23–31.

EGFR oncogenic driver mutations



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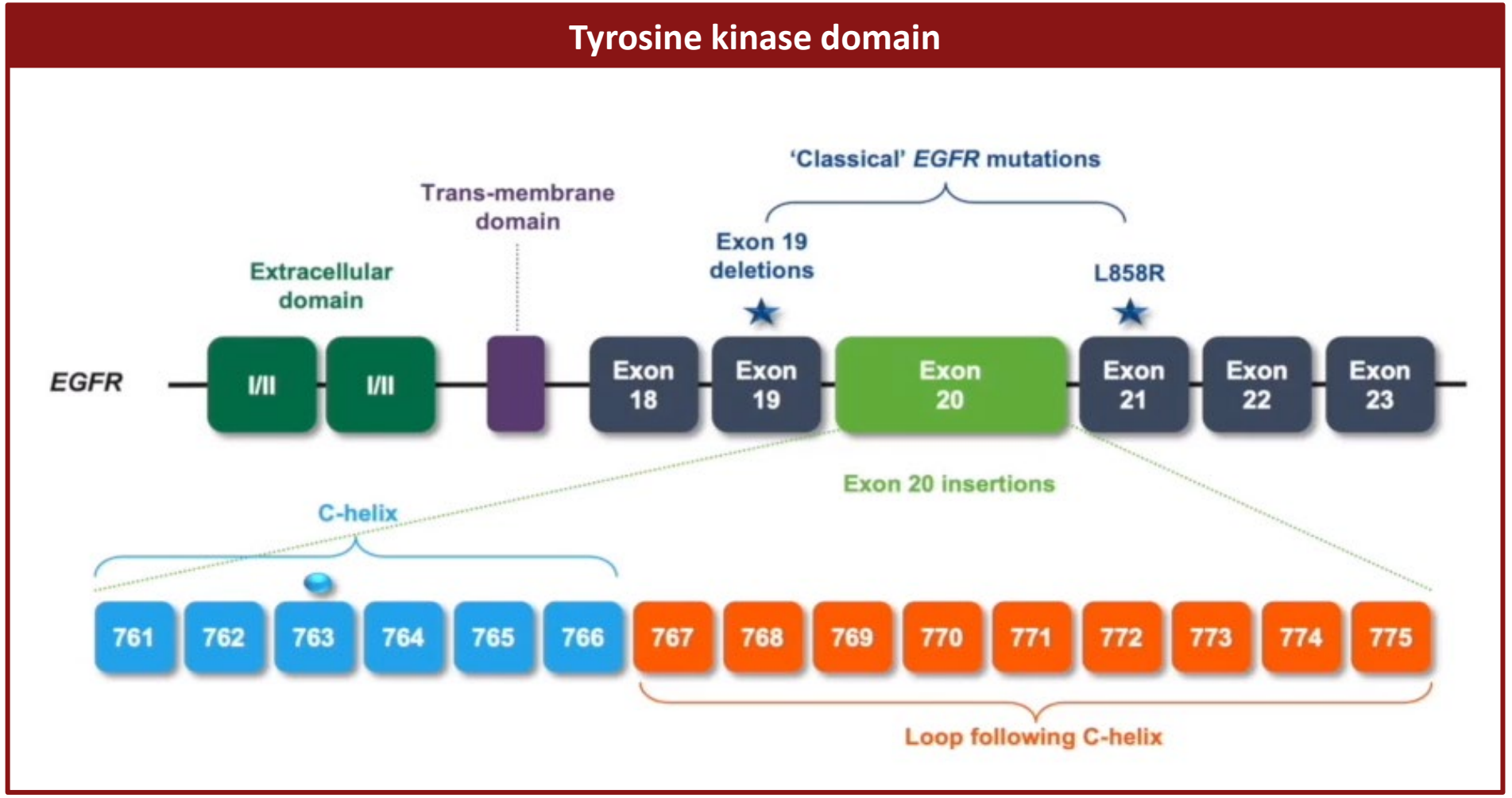
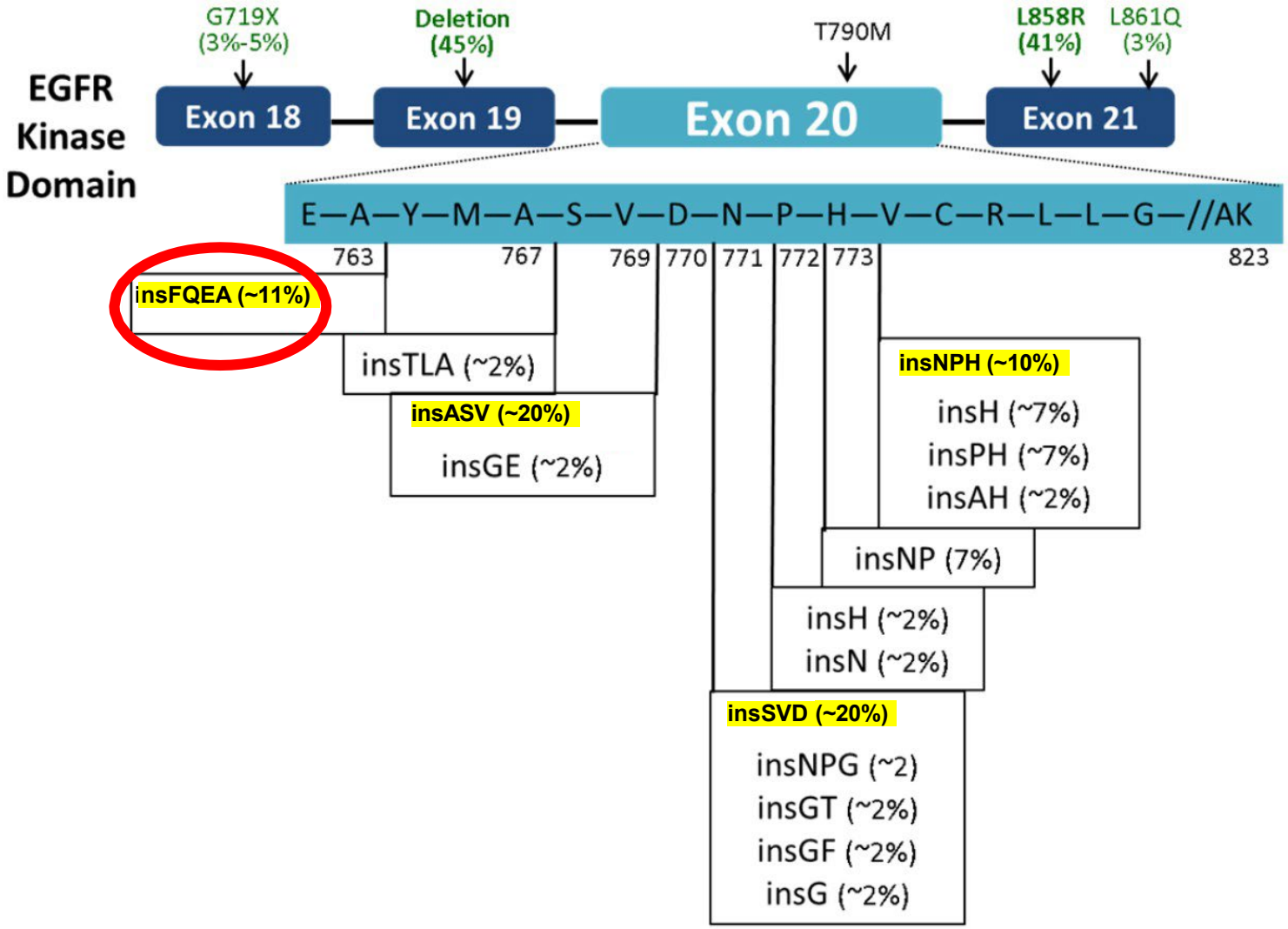
Heterogenity of *EGFR* exon 20 insertion



EGFR, Epidermal growth factor receptor
Coleman N., et al. *JTO.* 2020; 15: e162–165.

EGFR Exon 20 Insertions in NSCLC: A Diverse Array of Activating Mutations

- **Mutations have a poor response to 1st and 2nd generation therapies** (ORR ~10%) (except FQEA mutation).

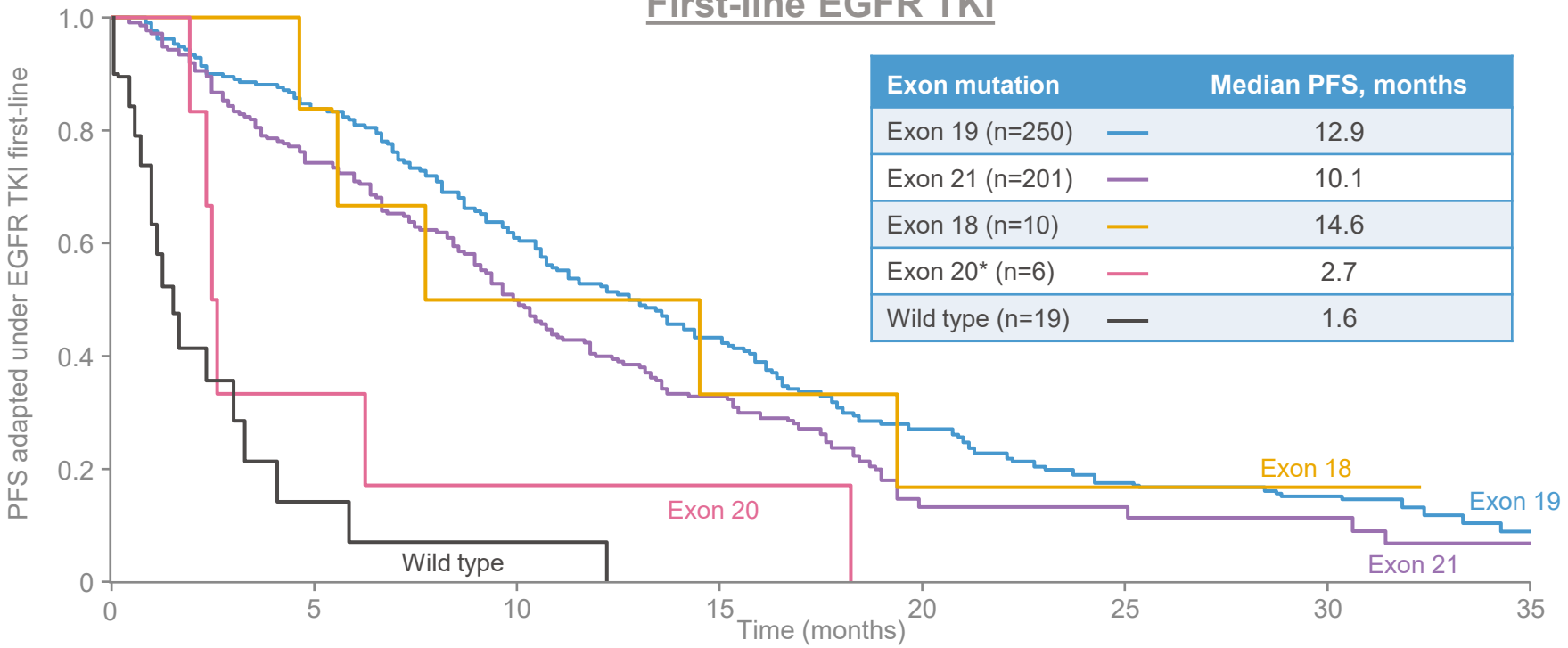


Abbreviations: EGFR = epidermal growth factor receptor; FQEA = A763_Y7
NSCLC = non-small cell lung cancer; ORR = objective response rate.

Adapted from:
Yasuda, et al. Lancet Oncol. 2012;13(1):e23-e31; Arcila, et al. Mol Cancer Ther. 2013;12(2):220-229; Oxnard, et al. J Thorac Oncol. 2013;8(2):179-184.

Exon mutation type and response to treatment: PFS

Exon mutation type *vs* wild type[1]
First-line EGFR TKI



Exon mutation	Median PFS, months
Exon 19 (n=250)	12.9
Exon 21 (n=201)	10.1
Exon 18 (n=10)	14.6
Exon 20* (n=6)	2.7
Wild type (n=19)	1.6

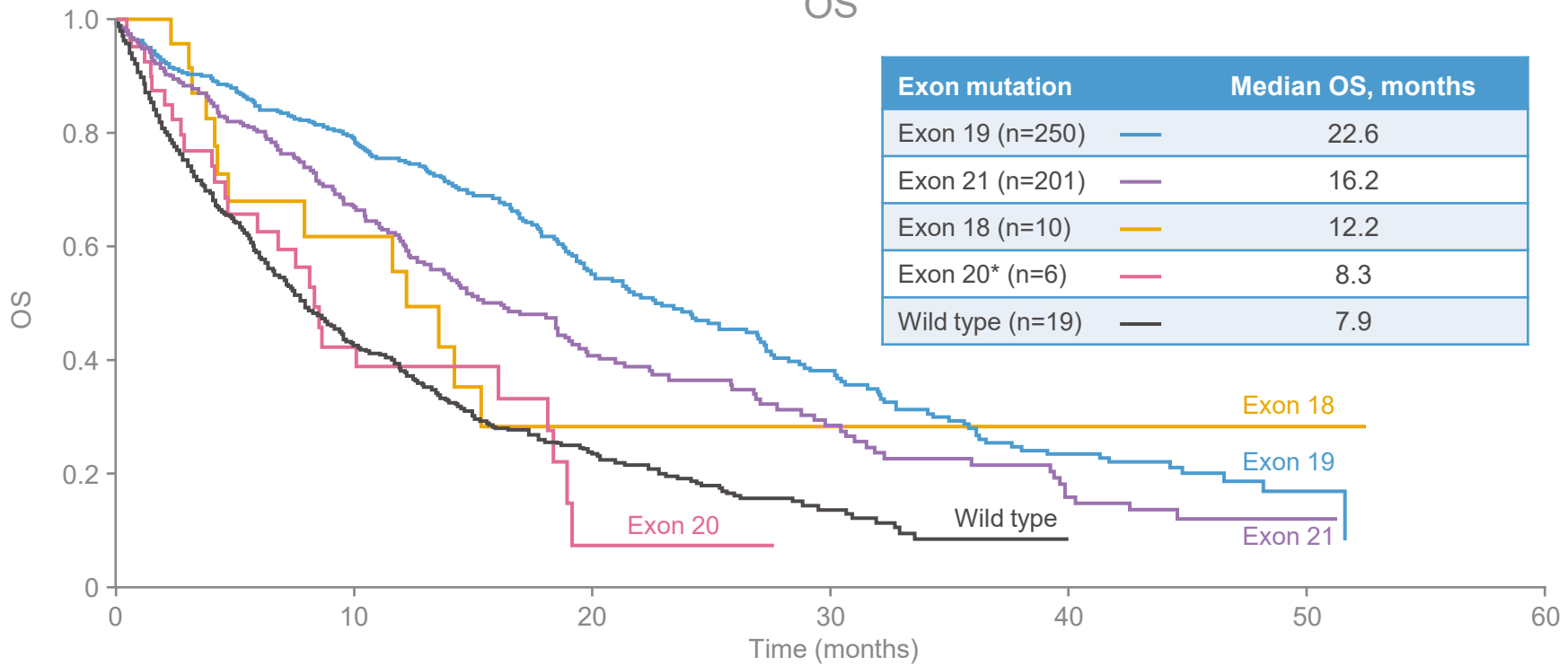
The exon mutation type determines the response to EGFR TKIs

Biomarkers France study of 17,664 patients, of which 1,837 (11%) were found to have *EGFR*-mutated NSCLC following retrospective analysis of their clinical and molecular characteristics. Results were correlated with survival and treatment response for 848 stage IV patients. These stage IV patients were non-Asian (95%), non-smokers (60%) and received an EGFR TKI (59%), platinum-based chemotherapy (27%), other treatment (6%), and best SC (8%). First-line treatment was adapted based on *EGFR* mutations in 71% of cases (n=582) Patients with exon 20 *T750M* mutations were excluded from the analysis

1. Leduc C et al., *Ann Oncol* 2017;28:2715–2724.

Exon mutation type and response to treatment: OS

Exon mutation type *vs* wild type[1]



Exon mutation	Median OS, months
Exon 19 (n=250)	22.6
Exon 21 (n=201)	16.2
Exon 18 (n=10)	12.2
Exon 20* (n=6)	8.3
Wild type (n=19)	7.9

The exon mutation type determines the response to EGFR TKIs

Biomarkers France study of 17,664 patients, of which 1,837 (11%) were found to have *EGFR*-mutated NSCLC following retrospective analysis of their clinical and molecular characteristics. Results were correlated with survival and treatment response for 848 stage IV patients. These stage IV patients were non-Asian (95%), non-smokers (60%) and received an EGFR TKI (59%), platinum-based chemotherapy (27%), other treatment (6%), and best SC (8%)
*Patients with exon 20 *T750M* mutations were excluded from the analysis
OS, overall survival

1. Leduc C et al., *Ann Oncol* 2017;28:2715–2724.

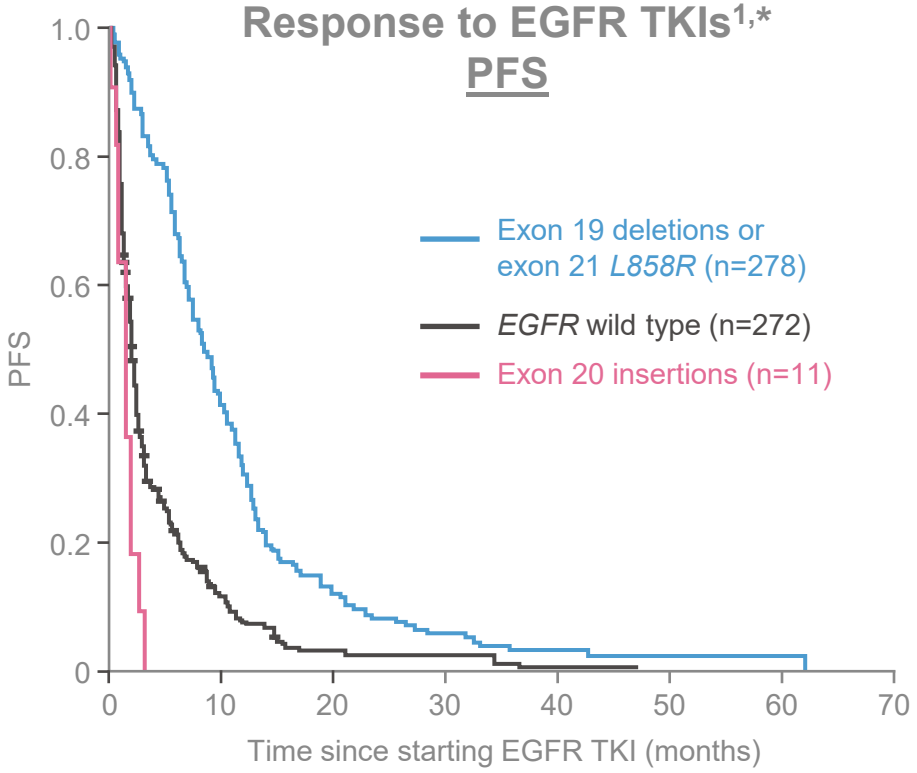
EGFR exon 20: poor outcome to EGFR TKIs

Poor RR, shorter PFS, and **shorter survival** for patients with exon 20 mutations *vs* exon 19 or 21 mutations, or wild type *EGFR*[1,2]

Response to EGFR TKIs[1]*

Exon mutation	RR, %	Median PFS, months	Median OS, months
Exon 19 deletions or exon 21 *L858R* (n=278)	74.1	8.5	19.6
EGFR wild type (n=272)	16.5	2.0	10.4
Exon 20 insertions (n=11)	0	1.4	4.8

Response to EGFR TKIs[1,*] PFS



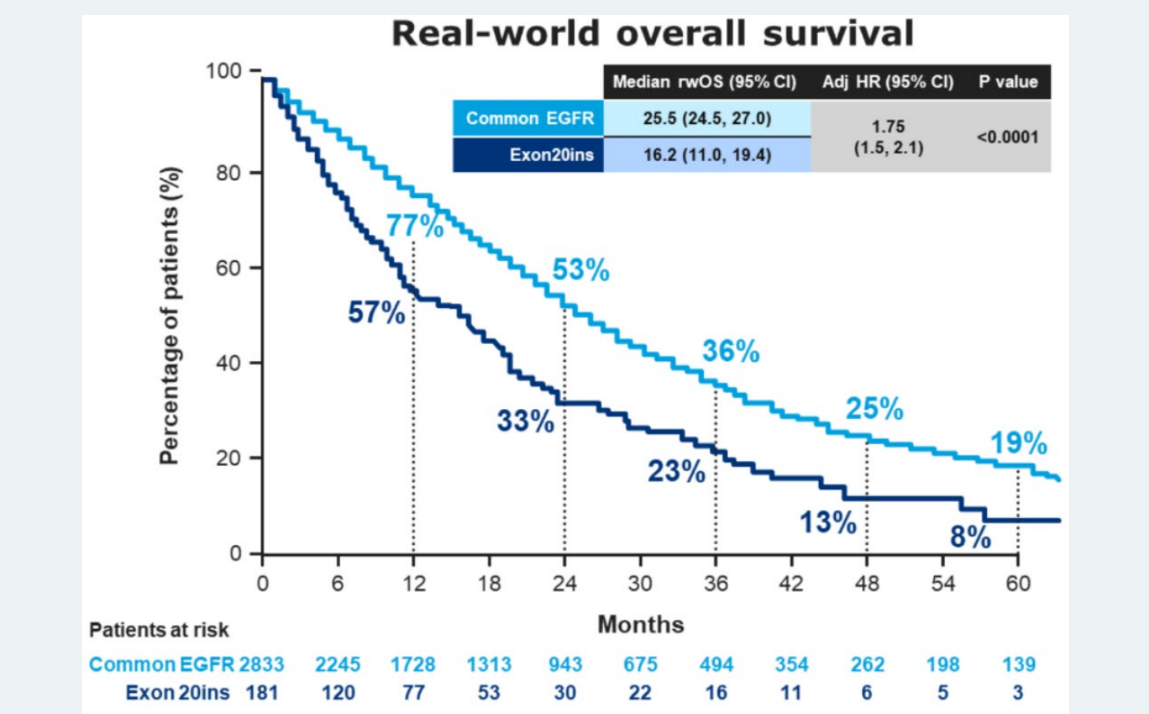
Due to a poor response to EGFR TKIs, patients with *EGFR* exon 20 insertion mutations routinely receive chemotherapy

*Analysis of 1,261 NSCLC cases, of which 627 (49.8%) had *EGFR* mutations, to evaluate the outcome to erlotinib or gefitinib treatment according to the type of mutation

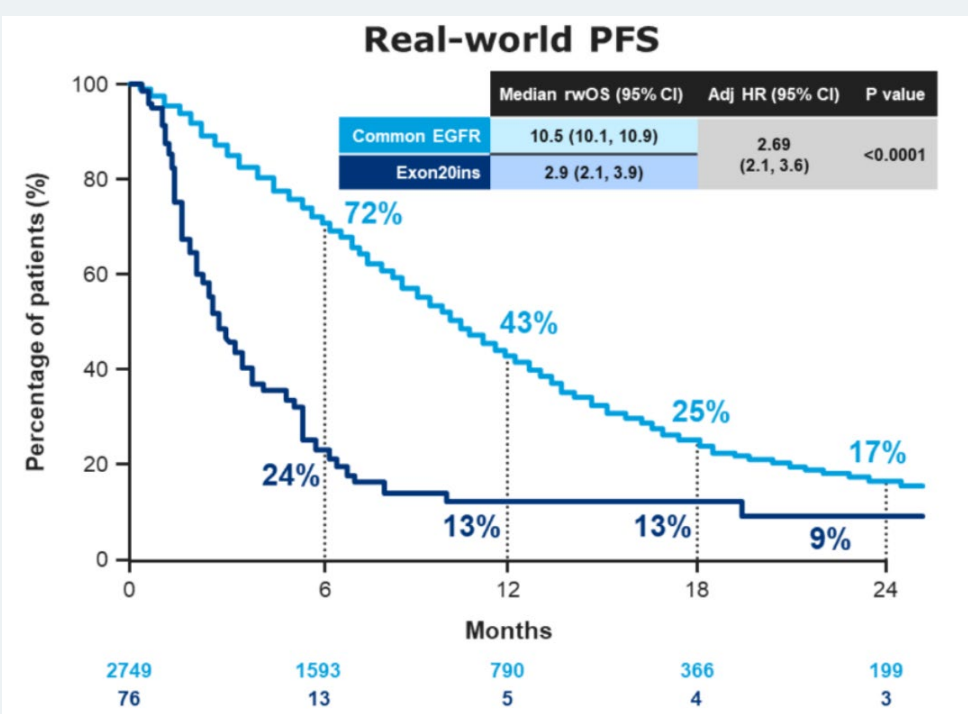
1. Wu J-Y et al., *Clin Cancer Res* 2011;17;3812–3821;
2. Noronha V et al., *Onco Targets Ther* 2017;10:2903–2908.

Comparative clinical outcomes for patients with NSCLC harboring *EGFR* exon 20 insertion mutations and common *EGFR* mutations

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



75 % increased risk of death with *EGFR* exon 20 insertion compared to cEGFR; (adjHR, 1.75 [95% CI, 1.45–2.13]; p < 0.0001)



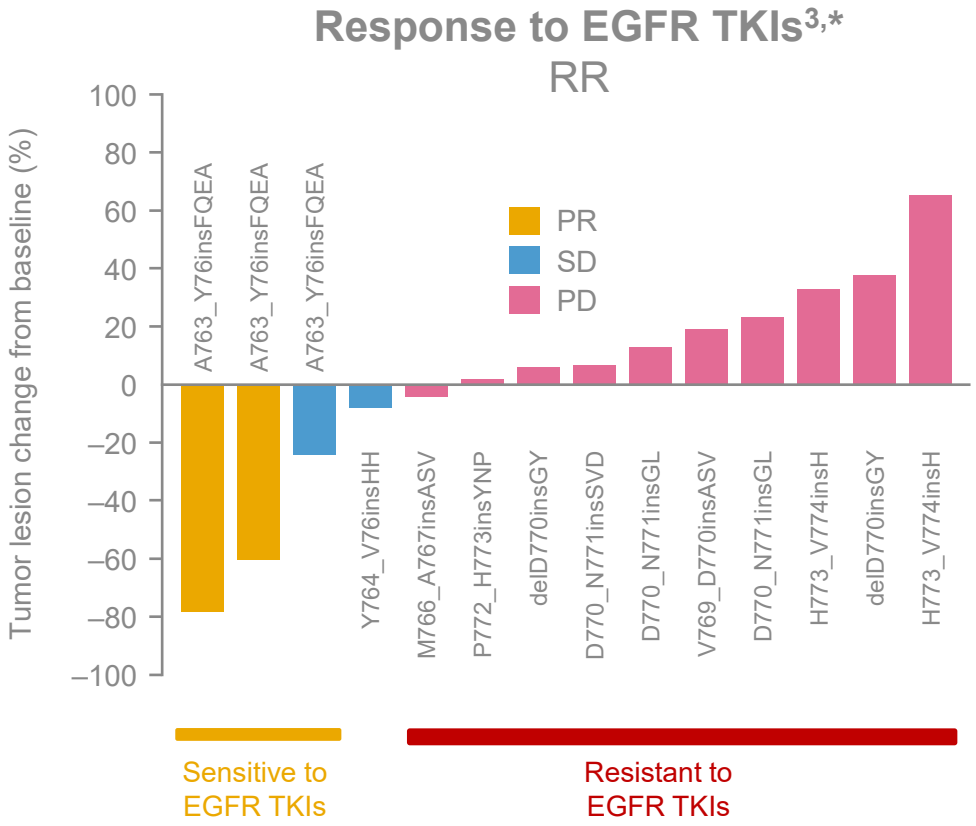
170 % increased risk of progression or death on TKI treatment with *EGFR* exon 20 insertion compared to cEGFR; (adjHR, 2.7 [95% CI, 2.06–3.55]; p < 0.0001)

Adj HR, Adjusted hazard ratio; cEGFR, Common EGFR; CI, Confidence interval; exon20ins, Exon 20 insertion; PFS, Progression-free survival; rwOS, Real-world overall survival; NSCLC, Non-small-cell lung cancer
Girard N., et al. Presented at WCLC 2020: MA04.07.

Only one specific exon 20 insertion, A763insFQEA, shows sensitivity to EGFR TKIs

Most mutations occur **within the loop following the α-C-helix** (amino acids 767–774) and are resistant to EGFR TKIs[1,2]

In contrast, a small number of patients with mutations **within the α-C-helix** (amino acid 763) have shown sensitivity to EGFR TKIs[3]



Further evidence that clinical outcome depends on the specific exon mutation type

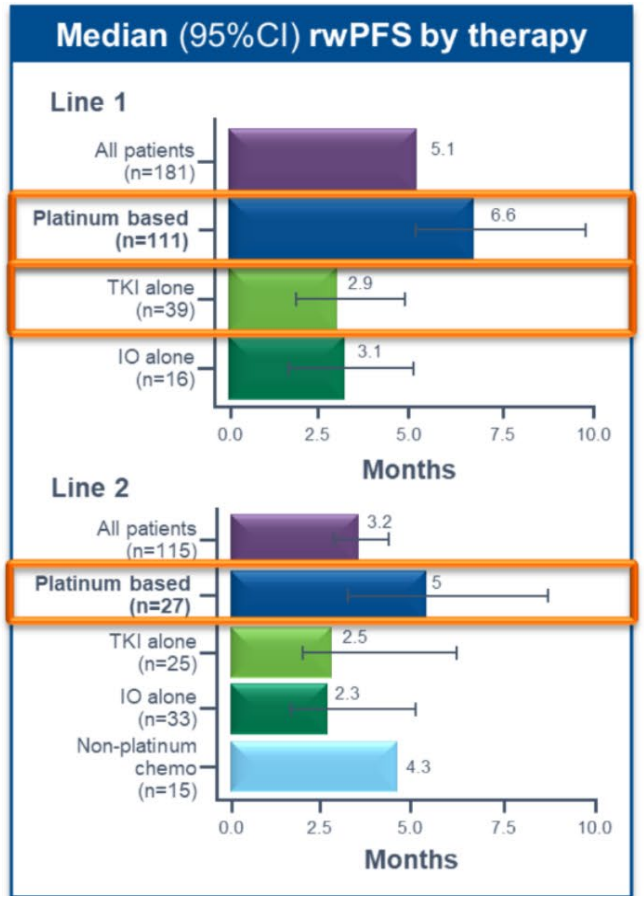
*Analysis of responses to erlotinib or gefitinib in 19 patients with NSCLC; 5 patients displayed non-measurable progressive disease
PD, progressive disease; PR, partial response; SD, stable disease

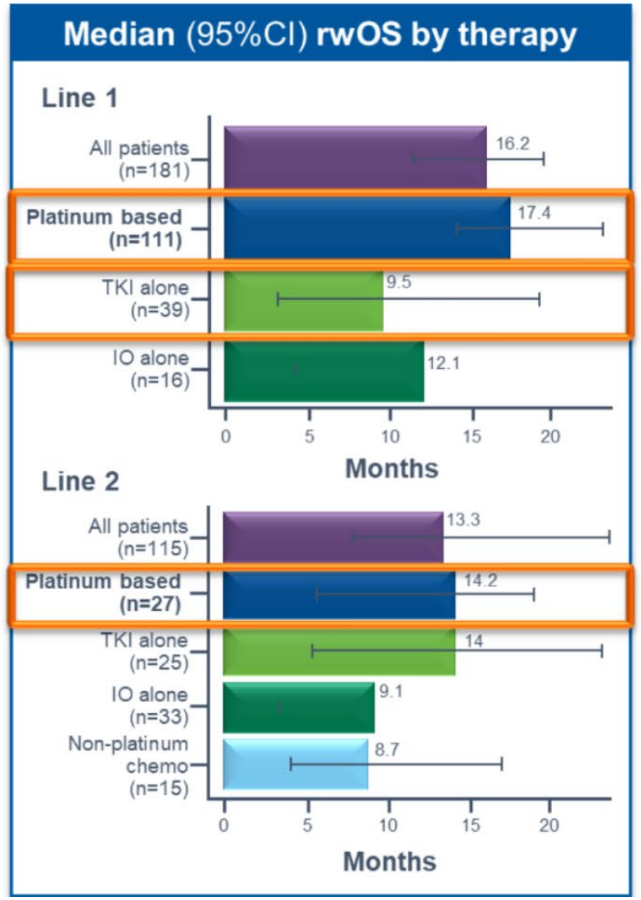
1. Stewart E et al., *Transl Lung Cancer Res* 2015;4:67–81;
2. Robichaux J et al., *Nat Med* 2018;24:638–646;
3. Yasuda H et al., *Sci Transl Med* 2013; 5:216ra177.

Historical treatments for patients with *EGFR* exon 20 insertion

Treatment patterns and outcomes in patients with *EGFR* exon 20 insertion

Treatment, n (%)	Line 1	Line 2	Line 3
Number of patients	181	115	64
Platinum-based regimen	111 (61.3)	27 (23.5)	14 (21.9)
Platinum doublet	50 (27.6)	13 (11.3)	5 (7.8)
Platinum + IO	32 (17.7)	8 (7.0)	2 (3.1)
Platinum + VEGFi	25 (13.8)	5 (4.3)	7 (10.9)
Other Platinum combinations*	4 (2.2)	0	0
Platinum alone	0	1 (0.9)	0
TKI alone	39 (21.5)	25 (21.7)	7 (10.9)
Other TKI combinations	1 (0.6)	0	0
IO alone	16 (8.8)	33 (28.7)	14 (21.9)
VEGFi alone	1 (0.6)	11 (9.6)	7 (10.9)
Non-platinum chemotherapy	5 (2.8)	15 (13.)	19 (29.7)
Others	8 (4.4)	4 (3.5)	3 (4.7)



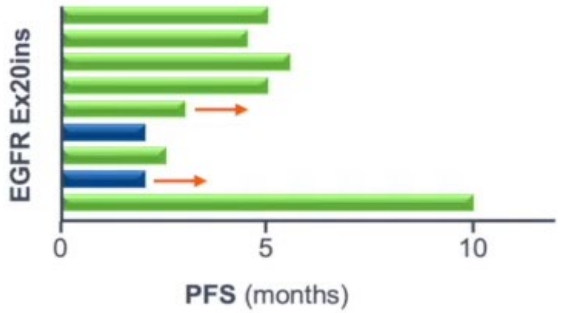


*Platinum + TKI, Platinum + TKI + VEGFi, platinum + IO + TKI, Platinum + IO + VEGFi. bOS was calculated from the start of line 2.
EGFR, Epidermal growth factor receptor; IO, Immuno-oncology; rwPFS, Real world progression free surviva, ITKI, Tyrosine kinase inhibitor; VEGFi, Vascular endothelial growth factor inhibitor
Girard N., et al. 2021. Presented at WCLC 2020; MA04.07.

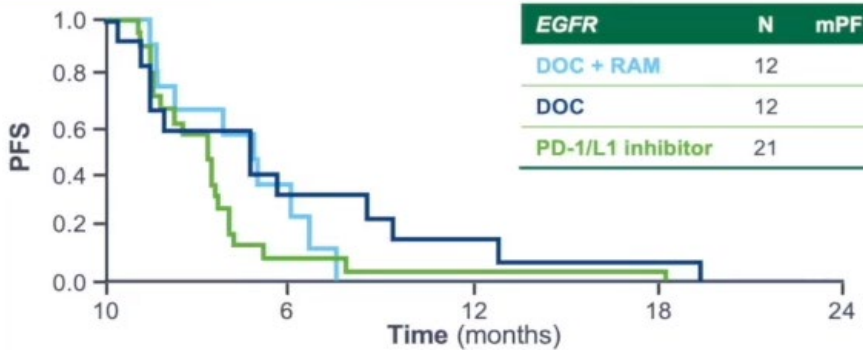
Immune checkpoint inhibitors for *EGFR* exon 20 insertion
PD-L1 expression > 1 % observed in 81,7 % patients.

Chinese cohort of 35 cases[1]

PD-L1 status	
<1%	18 (51.4%)
≥1%	17 (48.6%)
CD4 expression	
Negative	22 (62.9%)
Positive	13 (37.1%)
CD8 expression	
Negative	14 (40.0%)
Positive	21 (60.0%)

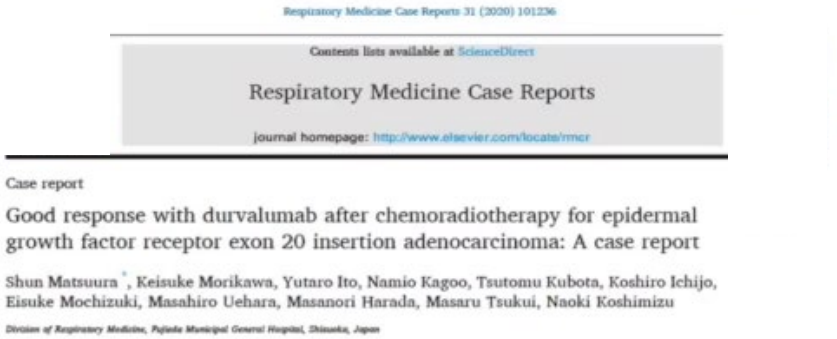


Japanese LC-SCRUM[3]



EGFR	N	mPFS (months)
DOC + RAM	12	4.8
DOC	12	4.7
PD-1/L1 inhibitor	21	3.3

Case reports[2]


Respiratory Medicine Case Reports 31 (2020) 101236

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

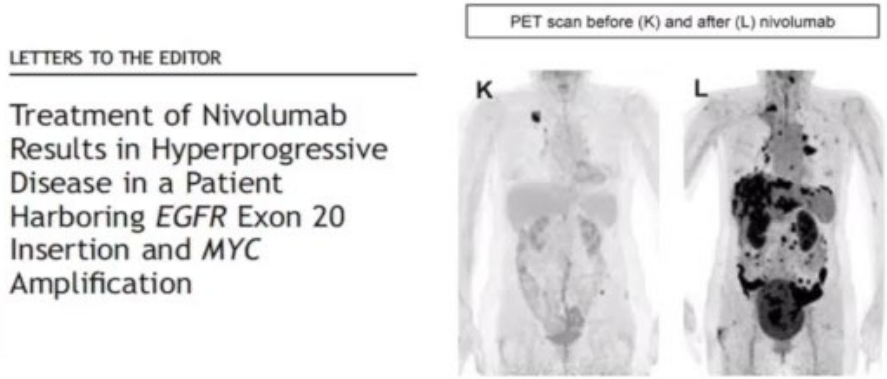
journal homepage: http://www.elsevier.com/locate/rmcr

Case report

Good response with durvalumab after chemoradiotherapy for epidermal growth factor receptor exon 20 insertion adenocarcinoma: A case report

Shun Matsuura *, Keisuke Morikawa, Yutaro Ito, Namio Kagoo, Tsutomu Kubota, Koshiro Ichijo, Eisuke Mochizuki, Masahiro Uehara, Masanori Harada, Masaru Tsukui, Naoki Koshimizu

Division of Respiratory Medicine, Fujieda Municipal General Hospital, Shizuoka, Japan


LETTERS TO THE EDITOR

Treatment of Nivolumab Results in Hyperprogressive Disease in a Patient Harboring *EGFR* Exon 20 Insertion and *MYC* Amplification

PET scan before (K) and after (L) nivolumab

K

L

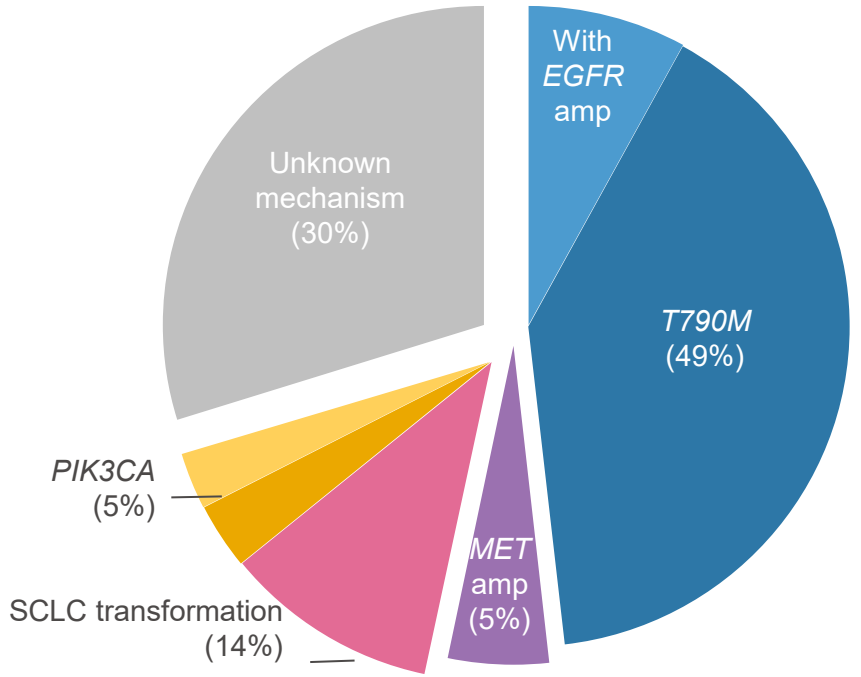
CD4/CD8, Cluster of differentiation 4/8; DOC, Docetaxel; EGFR, Epidermal growth factor receptor; RAM, Ramucirumab; PD-L1, Programmed cell death ligand 1

1. Chen et al. *Thorac Cancer*. 2021; 12: 218; 2. Huang, et al. *J Thorac Oncol* 2019; 14: e189–91; 3. Udagawa H, et al. 2019. Presented at WCLC 2019:OA07.03.

EGFR exon 20 *T790M* point mutations: the most common resistance mechanism to EGFR TKIs

Despite high RRs with EGFR TKIs in patients with exon 19 or exon 21 mutations, **resistance will develop within ~12 months**[1,2]

Resistance mechanisms to EGFR TKIs[2]

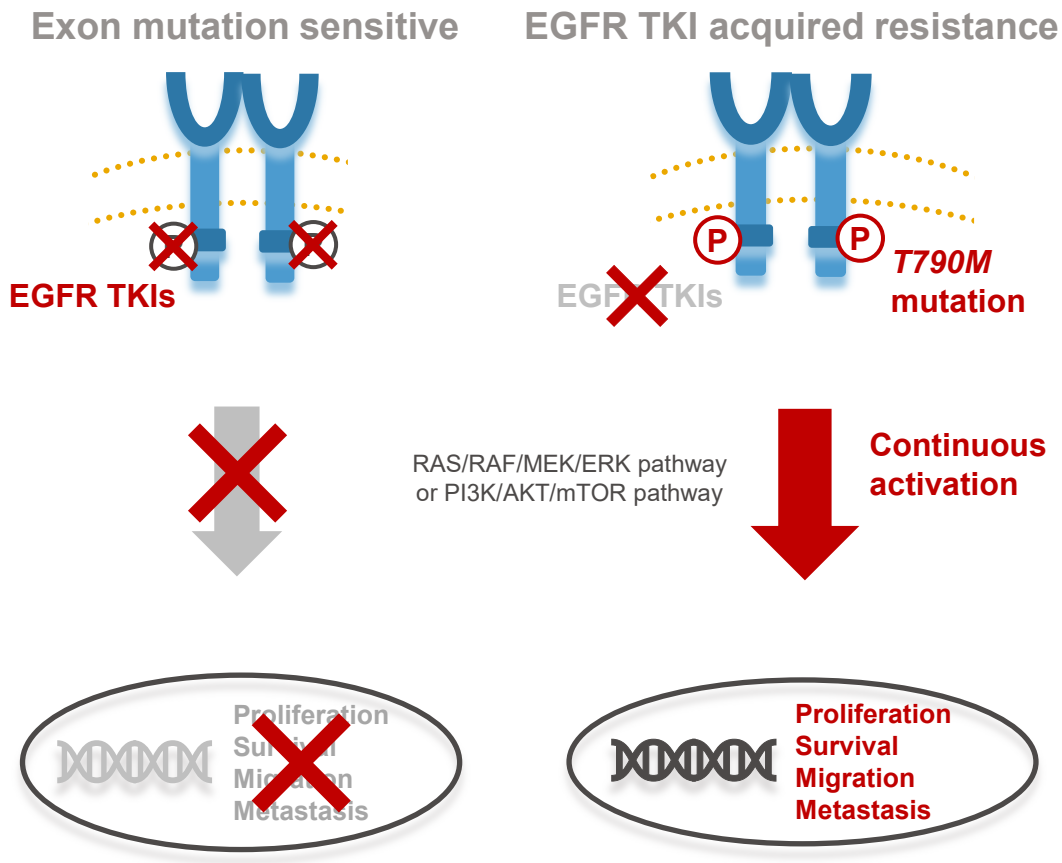


Secondary point mutations within exon 20 (*T790M*) are the most common reason for acquired resistance to EGFR TKIs

1. Stewart E et al., *Transl Lung Cancer Res* 2015;4:67–81;
2. Sequist L et al., *Sci Transl Med.* 2011;3:75ra26.

EGFR exon 20 *T790M* point mutations increase affinity for ATP

- *T790M* (the 'gate keeper') is located at a key position in the ATP-binding cleft
- Substitution of threonine 790 with methionine (*T790M*) results in increased ATP affinity and loss of EGFR TKI potency
- Second- and third-generation EGFR TKIs were developed to overcome *T790M* acquired resistance to first-generation EGFRs, but only osimertinib has shown efficacy in this setting



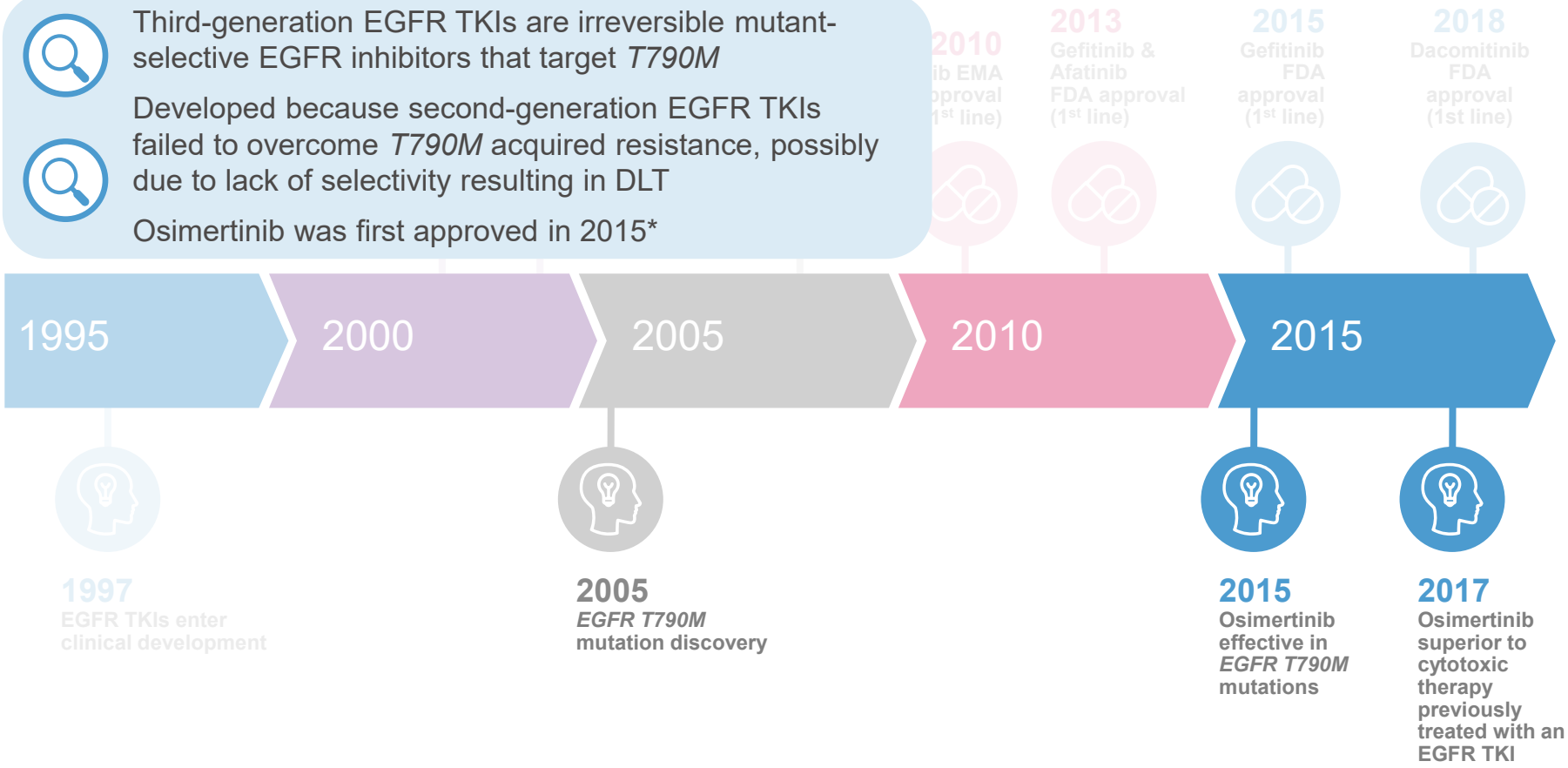
Mok T et al., *New Engl J Med* 2017;376:629–640; Soria J et al., *New Engl J Med* 2018;378:113–125; Suda K et al., *J Thorac Oncol* 2009;91–4; Zhong W et al., *Oncogene* 2017;8:71358–71370.

Approval of third-generation EGFR TKIs

Third-generation EGFR TKIs are irreversible mutant-selective EGFR inhibitors that target *T790M*

Developed because second-generation EGFR TKIs failed to overcome *T790M* acquired resistance, possibly due to lack of selectivity resulting in DLT

Osimertinib was first approved in 2015*



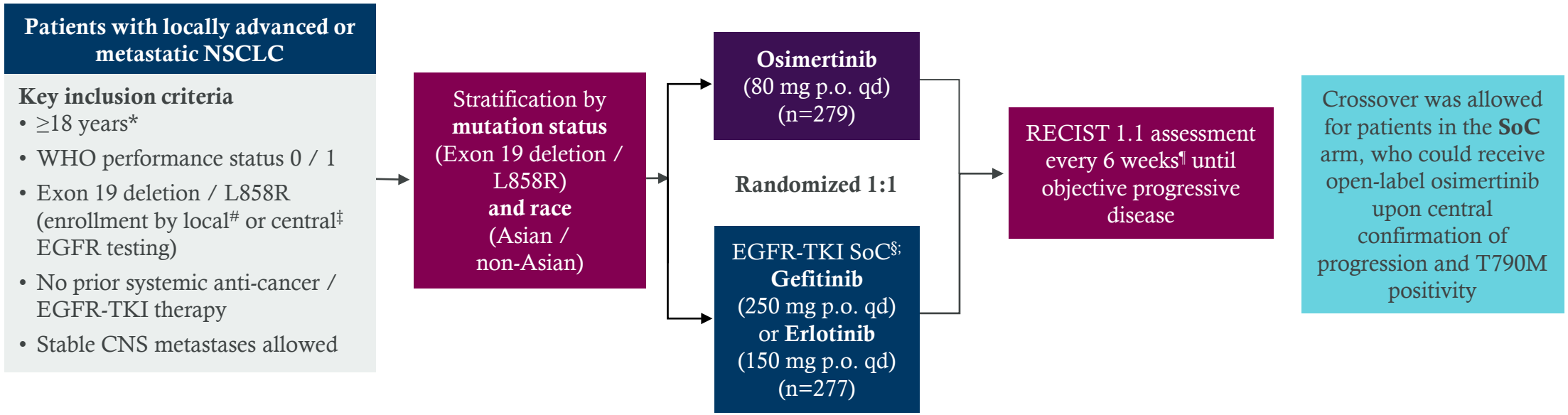
*Following the positive results from the phase III AURA trial (osimertinib *vs* pemetrexed + platinum chemotherapy), osimertinib was approved for the treatment of patients with metastatic *T790M*-positive NSCLC who have disease progression during or after EGFR-TKI therapy

DLT, dose-limiting toxicity

EMA. Available at: https://www.ema.europa.eu. Accessed 17 Oct 2018; FDA. Available at: https://www.fda.gov. Accessed 17 Oct 2018; Gao X et al., *Expert Rev Anticancer Ther* 2016;16:383–390; Mok T et al., *J Clin Oncol* 2017;35:4027–4034; Luo Y-H and Chen Y-M. *Transl Lung Cancer Res* 2014;3:368–369.

FLAURA: Study Design

Phase III, Double-Blind, Randomized Trial of Osimertinib as First-Line Therapy



- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

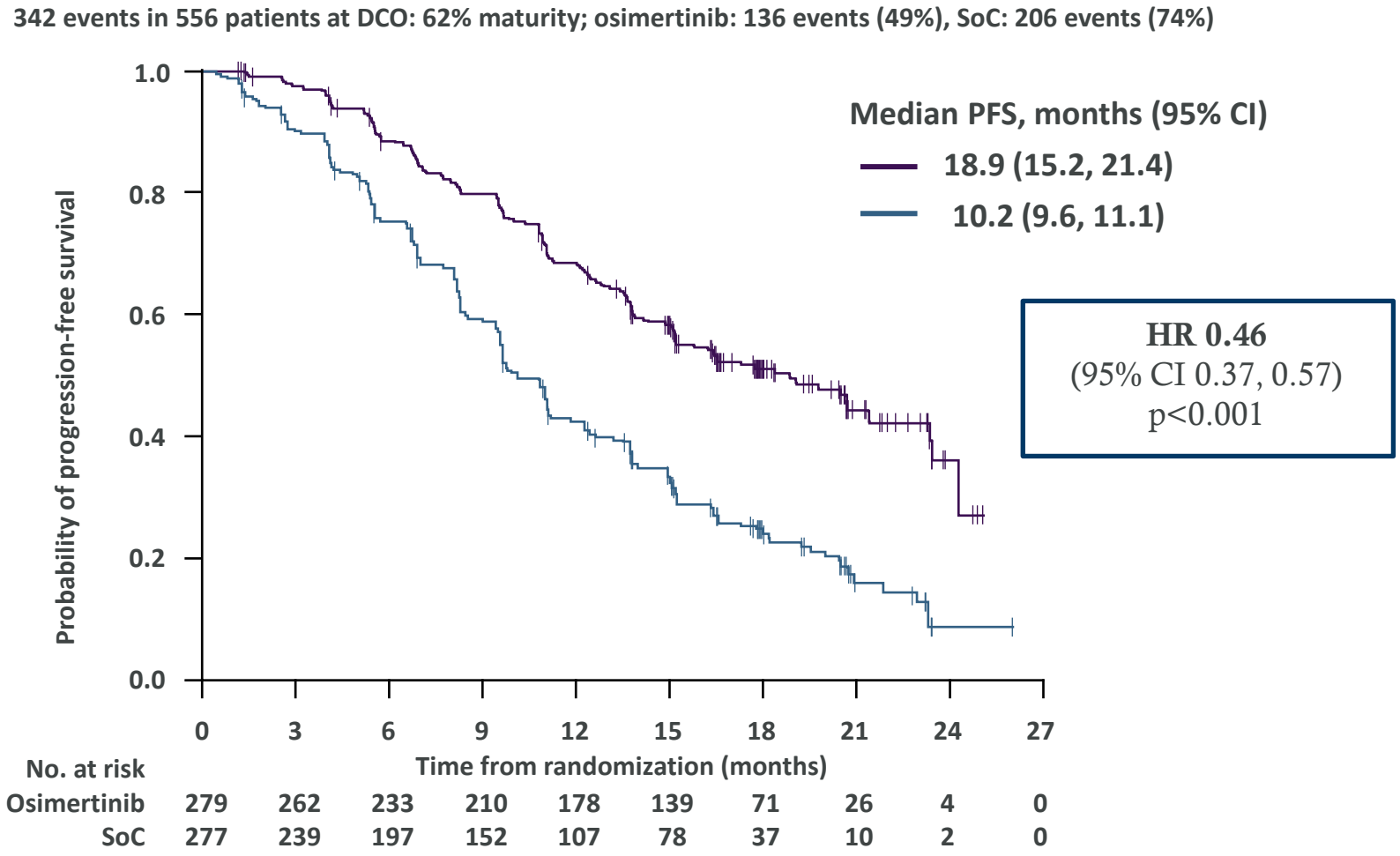
FLAURA data cut-off: 12 June 2017; NCT02296125.

*≥20 years in Japan; #With central laboratory assessment performed for sensitivity; ‡cobas EGFR Mutation Test (Roche Molecular Systems); §Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; ¶Every 12 weeks after 18 months

CNS = central nervous system; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PFS = progression-free survival; p.o. = orally; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors version 1.1; qd = once daily; SoC = standard-of-care; TKI = tyrosine kinase inhibitor; WHO = World Health Organization.

Soria J-C et al. *N Engl J Med.* 2018;378:113-125.

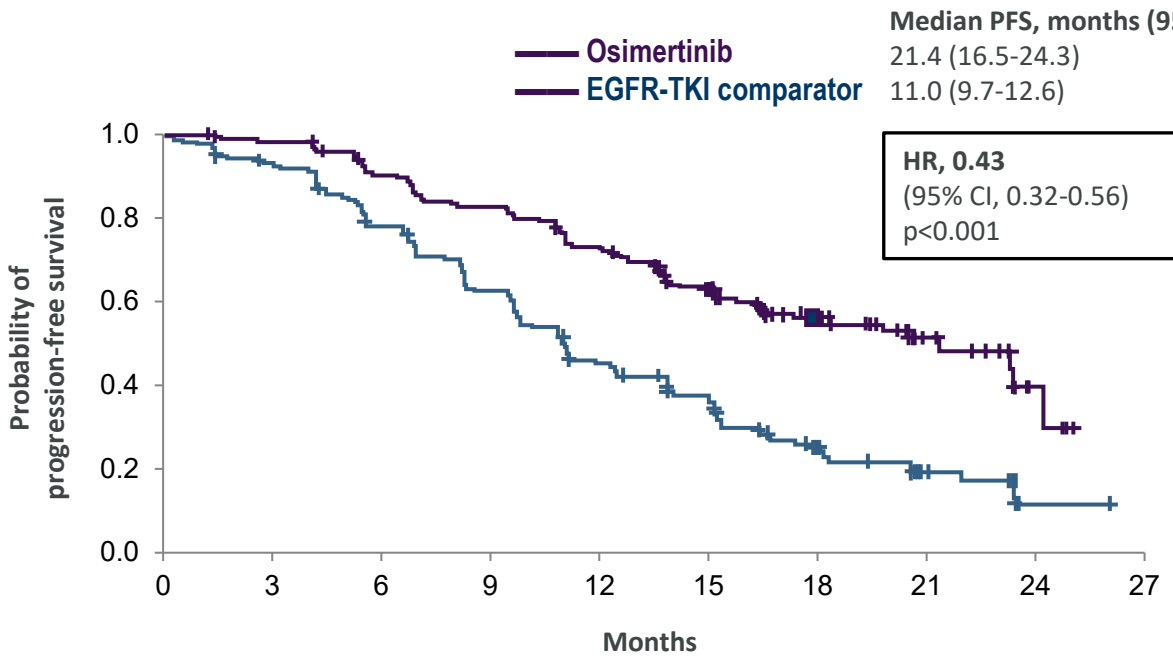
FLAURA: Primary Endpoint: PFS by Investigator Assessment



FLAURA data cut-off: 12 June 2017.
Tick marks indicate censored data;
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; SoC = standard-of-care; PFS = progression-free survival.
Soria J-C et al. *N Engl J Med.* 2018;378:113-125

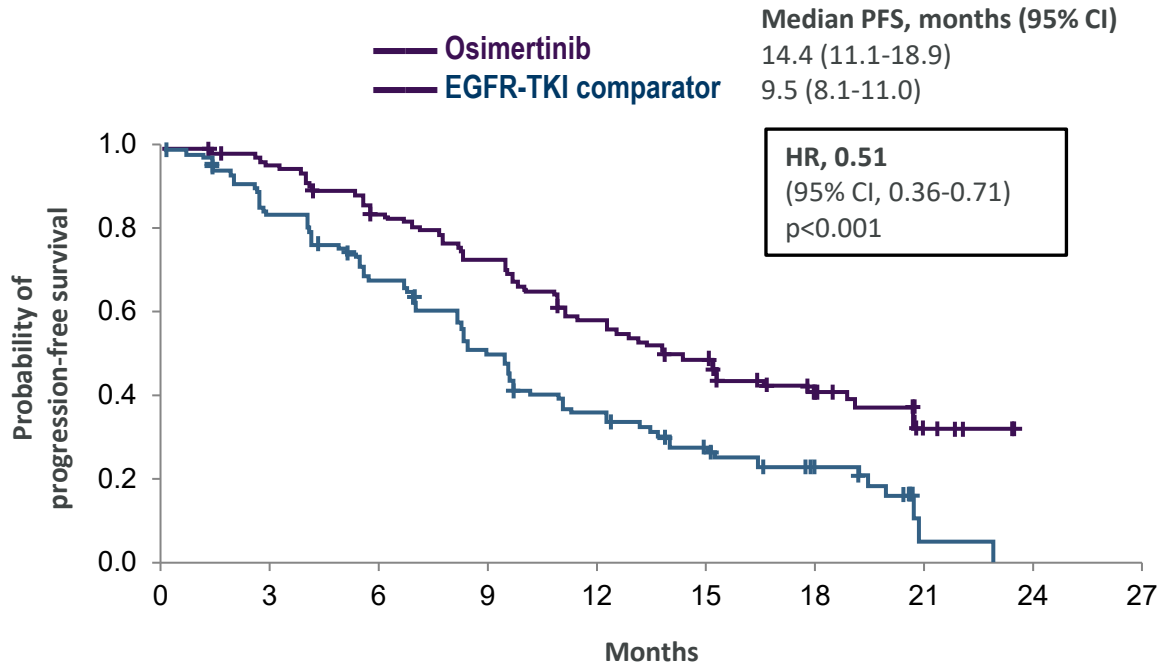
FLAURA: PFS by *EGFR* Mutation Status in the FAS

Exon 19 deletion



No. at risk										
Osimertinib	175	167	151	139	122	96	46	18	4	0
EGFR-TKI comparator	174	157	132	105	74	55	25	9	2	0

L858R



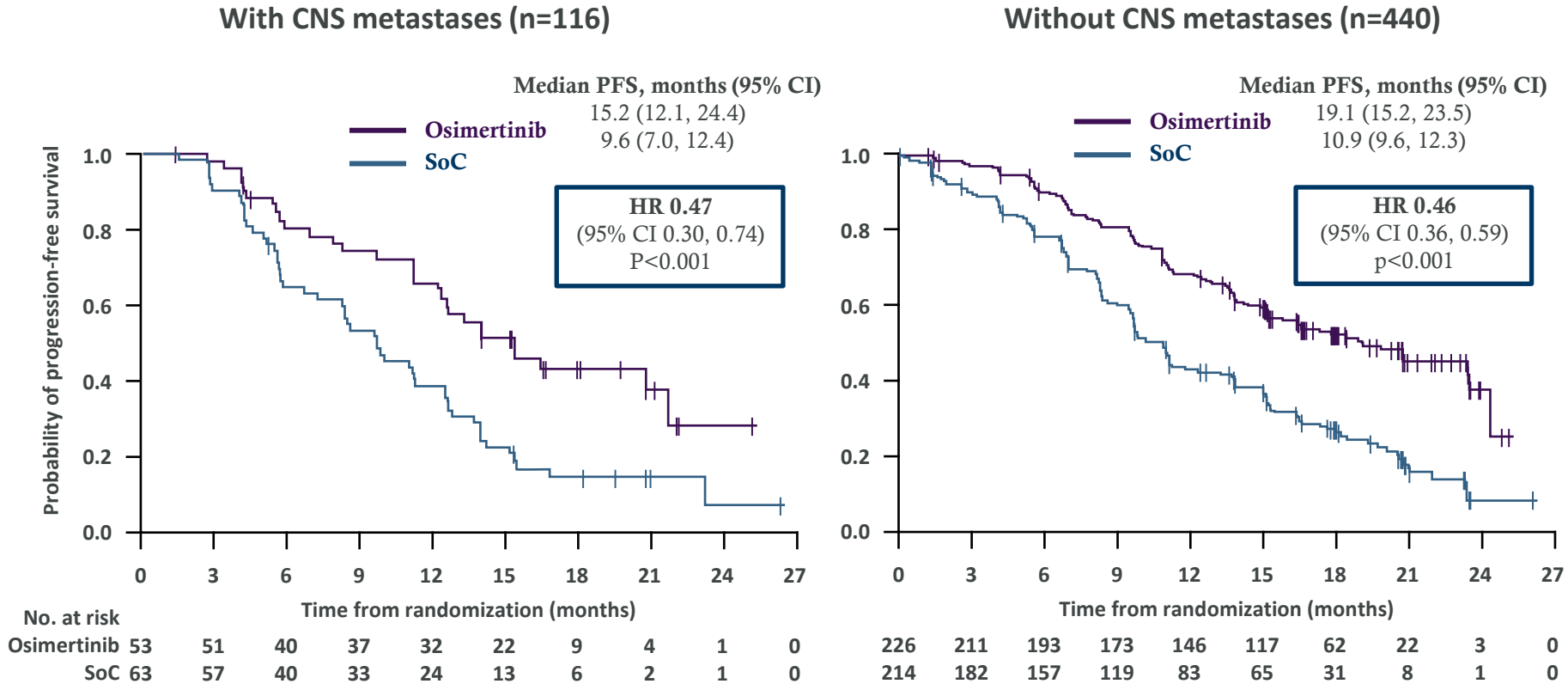
No. at risk										
Osimertinib	104	95	82	71	56	43	25	8	0	0
EGFR-TKI comparator	103	82	65	47	33	23	12	1	0	0

FLAURA data cut-off: 12 June 2017.
Tick marks indicate censored data.

EGFR = epidermal growth factor receptor; FAS = full analysis set; HR = hazard ratio; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

1. Soria J-C et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:113-125.

FLAURA: PFS[a] in Patients With And Without CNS Metastases at Study Entry



- **Across all patients, progression in the CNS occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC**

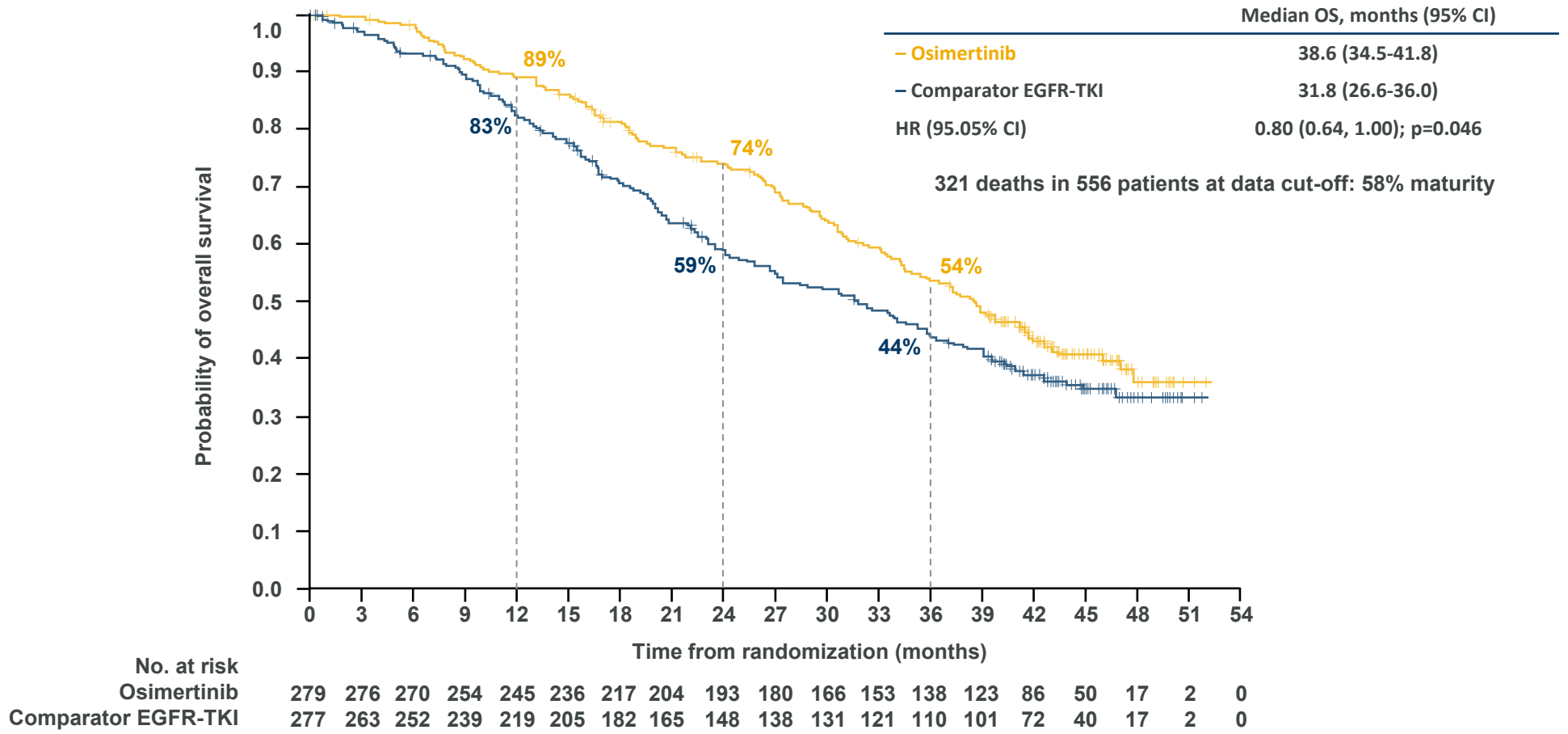
FLAURA data cut-off: 12 June 2017.

Tick marks indicate censored data; [a]By Investigator assessment.

CI = confidence interval; CNS = central nervous system; HR = hazard ratio; PFS = progression-free survival; SoC = standard-of-care.

Soria J-C et al. *N Engl J Med*. 2018;378:113-125.

FLAURA: Final Analysis: Overall Survival



FLAURA data cut-off: June 25, 2019.

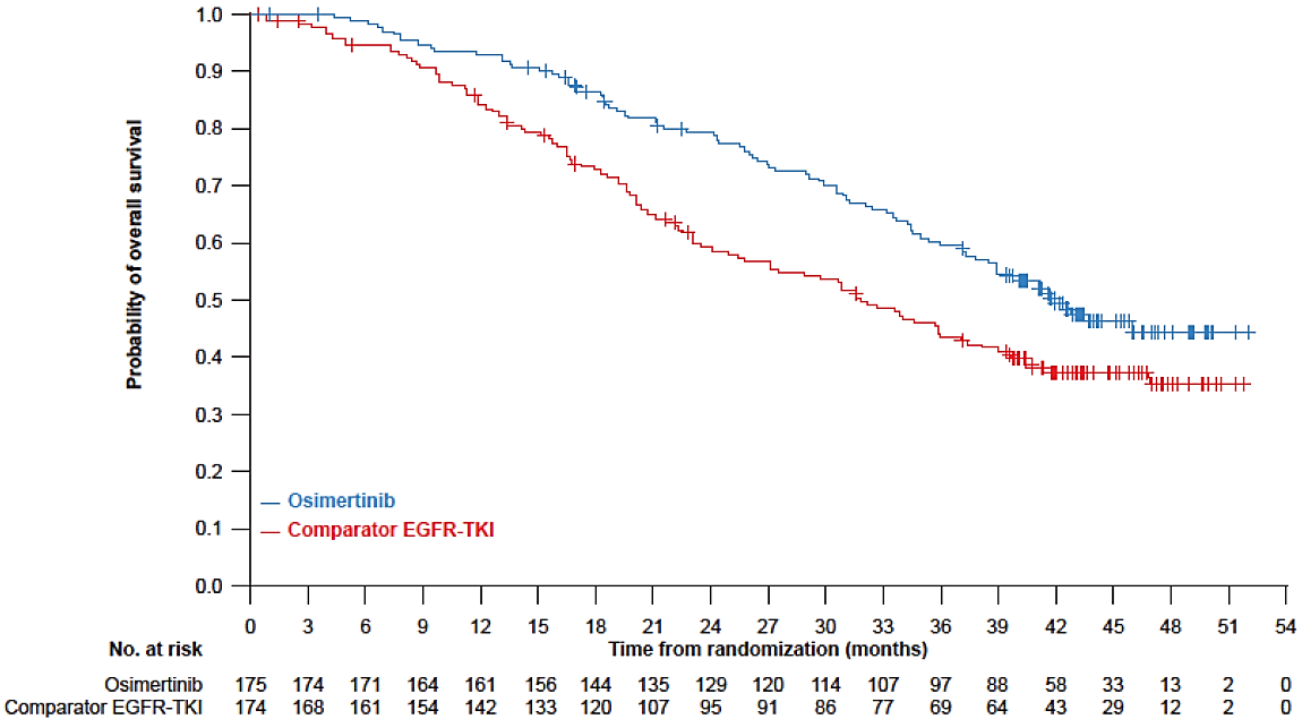
For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required.

CI = confidence interval; EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor; HR = hazard ratio; OS = overall survival.

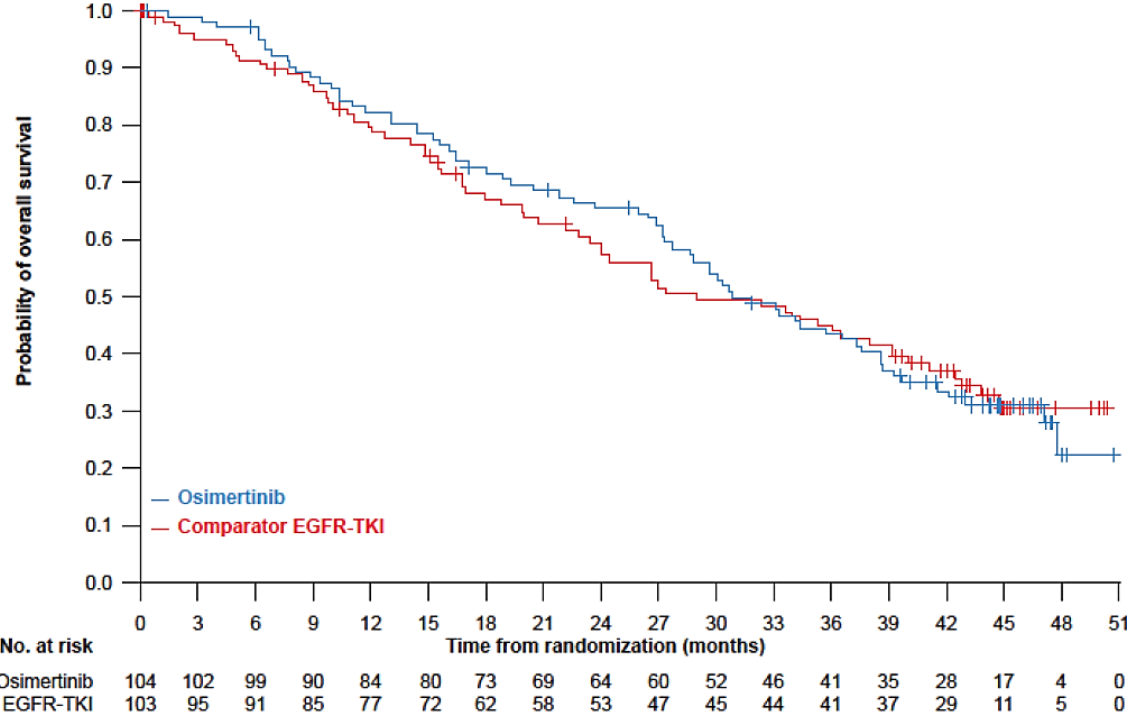
Ramalingam SS et al. *N Engl J Med*. 2020; 382:41-50.

FLAURA: OS in Patients With Ex19del and L858R mutation

Ex19del mutation



L858R mutation



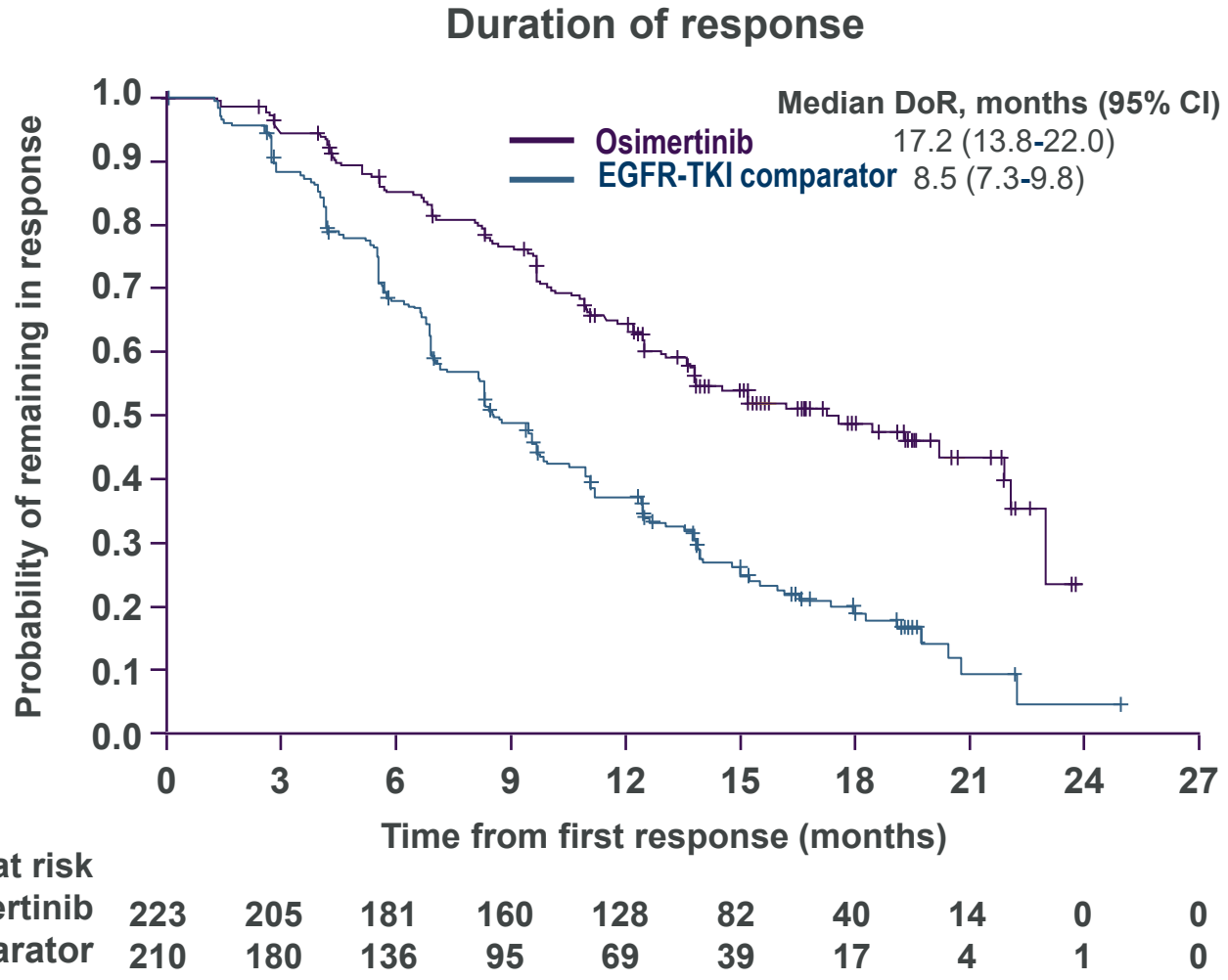
FLAURA data cut-off: June 25, 2019.

EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; OS = overall survival.

Ramalingam SS et al. Article and supplementary appendix. *N Engl J Med*. 2020; 382:41-50.

FLAURA: Objective Response Rate[1,2,a]

	Osimertinib (n=279)	EGFR-TKI comparator (n=277)
ORR (95% CI)	80% (75-85)	76% (70-81)
Odds ratio[b] (95% CI)	1.27 (0.85-1.90); p=0.24	
Complete response,[c] n (%)	7 (3)	4 (1)
Partial response,[c] n (%)	216 (77)	206 (74)
Stable disease ≥6 weeks, n (%)	47 (17)	46 (17)
Progression, n (%)	3 (1)	14 (5)
Not evaluable, n (%)	6 (2)	7 (3)
Duration of response,[d] months, median (95% CI)	17.2 (13.8-22.0)	8.5 (7.3-9.8)
Percent of patients with continued response at:[e]		
12 months, % (95% CI)	64 (58-70)	37 (31-44)
18 months, % (95% CI)	49 (41-56)	19 (13-26)



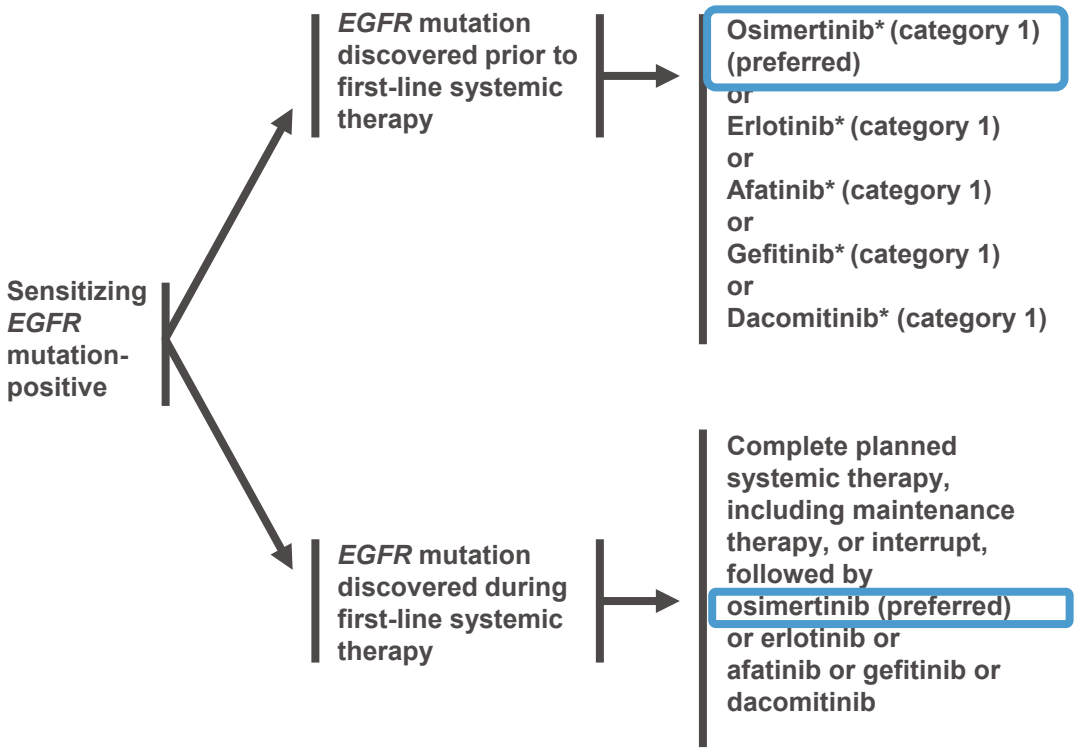
FLAURA data cut-off: 12 June 2017. Tick marks indicate censored data.

[a]By investigator assessment; [b]Analysis performed using a logistic regression stratified by race (Asian versus Non-Asian) and mutation type (Exon 19 deletion versus L858R); [c]Response did not require confirmation; [d]Calculated with the use of the Kaplan-Meier method from the date of the first documented disease progression or death in the absence of disease progression; [e]Calculated using Kaplan-Meier approach.

DoR = duration of response; EGFR = epidermal growth factor receptor; ORR = objective response rate; TKI = tyrosine kinase inhibitor.

1. Soria J-C et al. *N Engl J Med*. 2018;378:113-125. 2. Ohe Y et al. Presented at: European Society for Medical Oncology Asia Congress; 17-19 November 2017; Singapore

NCCN 2019 guidelines recommend osimertinib



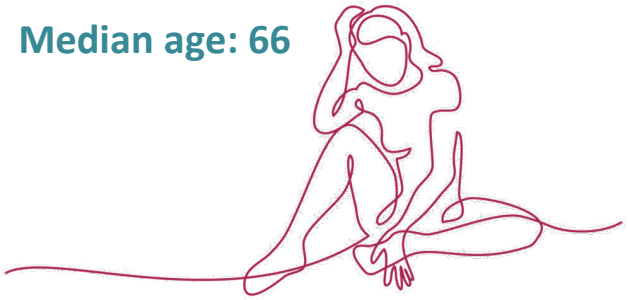
NCCN guidelines now state that osimertinib is the preferred EGFR TKI (February 2019)

Category 1: based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
*For PS 0–4

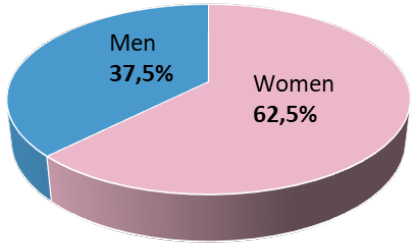
NCCN Guidelines: Non-small Cell Lung Cancer, v3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 4 Feb 2019.

EGFR exon 20 NSCLC – Patient characteristics

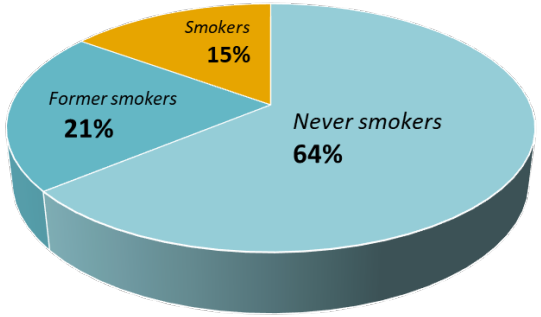
Median age: 66



Female patients predominate



Non-smokers predominate (85%)



Metastatic sites at diagnosis:

Intrathoracic
62,5%

Bone lesions
54,5%

CNS metastases
39%

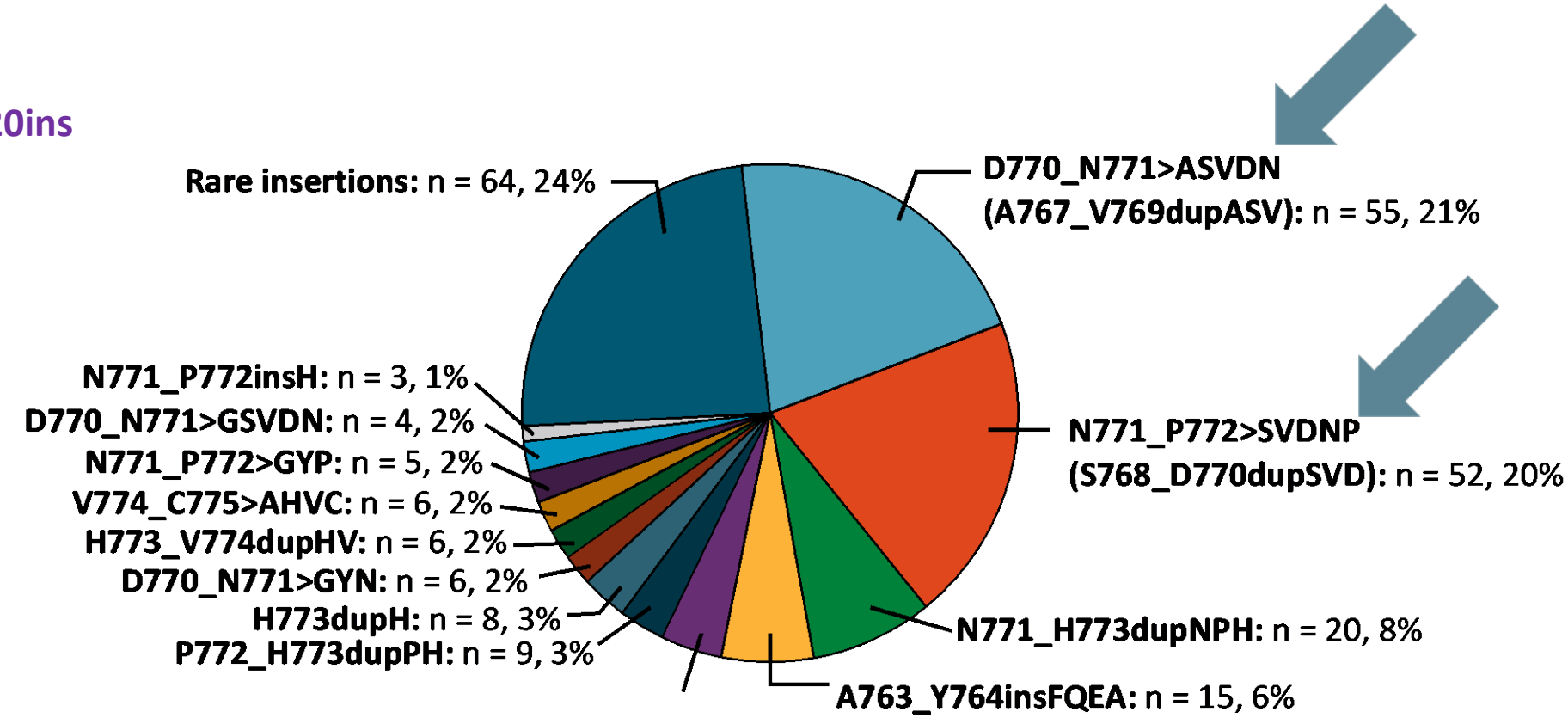
In 71,3% patients, two of these metastatic sites were observed at diagnosis

EGFR, Epidermal growth factor receptor; NSCLC, Non-small cell lung cancer; CNS, Central Nervous System
Graphics adapted and data from: Cardona AF, et al. Lung Cancer 2018; 125: 265–272.

Heterogeneity of EGFR exon 20 insertions

2,251 *EGFR* mutations

263 *EGFR* ex20ins mutations



EGFR, Epidermal growth factor receptor
Reiss JW, JTO, (2018) 13 1560–1568.

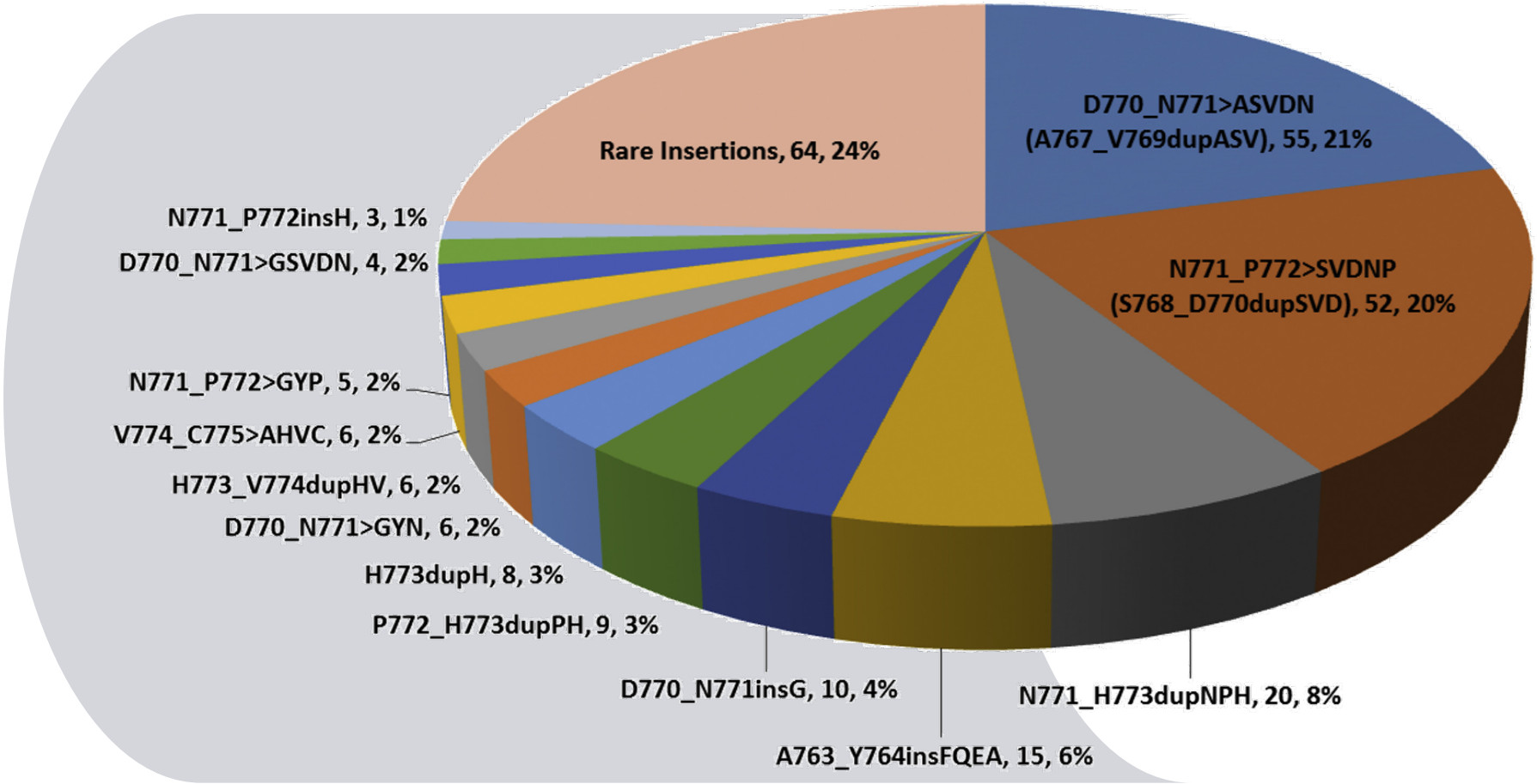
Cobas® EGFR RT-PCR diagnoses only a few common EGFR exon 20 gene alterations (50 % or less)

Exon	EGFR Mutation Group	EGFR Nucleic Acid Sequence	COSMIC ID[6]
Exon 20	S768I	2303G>T	6241
	T790M	2369C>T	6240
	Ex20Ins	2307_2308ins9GCCAGCGTG	12376
		2319_2320insCAC	12377
		2310_2311insGGT	12378
		2311_2312ins9GCGTGGACA	13428
		2309_2310AC>CCAGCGTGGAT	13558

Information on this test is available at: https://diagnostics.roche.com/global/en/products/params/cobas-egfr-mutation-test-v2.html#productInfo (February 2022). Table adapted from the specified document source.

EGFR, Epidermal growth factor receptor

Patients with heterogeneous EGFR exon 20 alterations can be diagnosed only with NGS



Schematic of genomic positions of *EGFR* exon 20 insertions detected by comprehensive genomic profiling. The positions of EGFR amino acids are indicated.

EGFR, Epidermal growth factor receptor
NGS, Next-generation gene sequencing
Graphics and data adapted from: Riess JW, et al. J Thor Oncol 2018; 13(10): 1560–1568.

Overview of *EGFR* Mutation Testing Methods

Real-time PCR and NGS assays are the commonly used methods for *EGFR* mutation testing.[1-4]

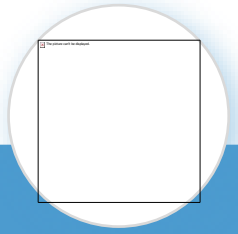
Guideline	Recommended *EGFR* Testing Methods
NCCN[1]	• Real-time PCR • NGS (DNA or RNA)[a] • Sanger sequencing[b,c] • RNA sequencing
ESMO[2]	• Any appropriate, validated method
IASLC/CAP/AMP[3,4]	• Any validated testing method that can detect *EGFR* mutations in tumors with ≥ 20% cancer cells, although IHC and FISH are not recommended for choosing TKI therapy

- Tissue samples, per NCCN guidelines, should be prioritized over cell-free/circulating tumor DNA (plasma) analysis[1]

Testing times will vary by laboratory, medical facility protocols, and additional external factors.
FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PCR, polymerase chain reaction.
[a] When feasible, general molecular testing should be performed via a broad, panel-based approach, most typically NGS. For patients who in broad panel testing don't have identifiable driver oncogenes (especially in never smokers), consider RNA-based NGS, if not already performed, to maximize detection of fusion events; [b] Not appropriate for detection in samples with < 25% to 30% tumor cells. Guidelines recommend pairing Sanger sequencing with tumor enrichment.[1] [c] Sanger, or direct, sequencing was once the standard for *EGFR* testing; however, it is no longer the method of choice due to low assay sensitivity (only detecting mutations when sufficient mutated DNA is present).

1. NCCN Clinical Practice Guidelines. Non-Small Cell Lung Cancer. v3.2020; 2. Planchard D, et al. *Ann Oncol.* 2018;29(4 suppl):iv192-iv237; 3. Lindeman NI, et al. *J Thorac Oncol.* 2018;142:321-346; 4. Lindeman NI, et al. *J Thorac Oncol.* 2013:8:823-859.

EGFR Exon 20 Insertion Testing



Patients with NSCLC adenocarcinomas should be tested at diagnosis for *EGFR* exon 20 insertions, and NGS represents the most comprehensive testing method

- NCCN guidelines recommend testing for *EGFR* exon 20 insertions at diagnosis in patients with NSCLC adenocarcinomas[1]
  - The guidelines note that identification of the specific sequence of *EGFR* exon 20 insertions is important[1]
- PCR and NGS are the commonly used testing methods for detecting *EGFR* mutations[2]
- For detection of *EGFR* exon 20 insertions, NGS-based tests are more comprehensive than PCR and can detect all *EGFR* exon 20 insertions[3]
  - PCR assays miss ≈50% of exon 20 insertions[3]

EGFR, epidermal growth factor receptor; NGS, next-generation sequencing; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction.

1. NCCN Guidelines for NSCLC.V2.2021; 2. Mok TS, et al, eds. *IASLC Atlas of EGFR Testing in Lung Cancer*. IASLC Press; 2017; 3. Bauml JM, et al. WCLC 2020. Abstract 3399.

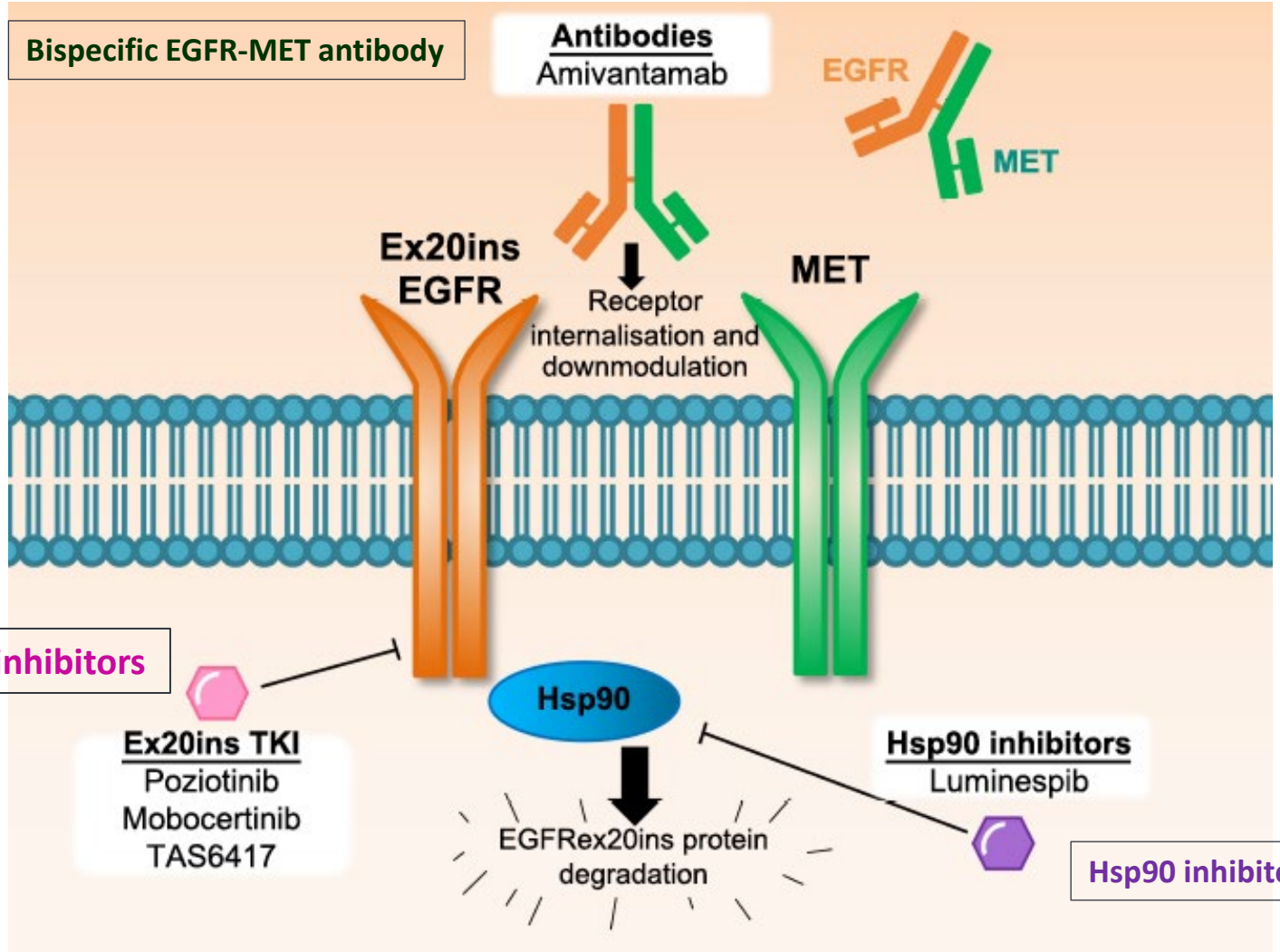
Takeda Has Partnered With Foundation Medicine and Thermo Fisher to Develop NGS-Based Companion Diagnostics for the Detection of *EGFR* Exon 20 Insertions

	STATUS	ASSAY TYPE	SAMPLE TYPE	DETECTION CAPABILITIES
Thermo Fisher Oncomine Dx target test	FDA approved[1]	NGS	Tissue	**FFPE tissue (NSCLC tumor)[2]** • RNA and DNA NGS of 23 genes (point mutations, deletions, insertions, and fusions)
FoundationOne liquid CDx	In development[3,4]	NGS	Blood	**Blood[5]** • DNA NGS of 311 genes, 4 gene rearrangements, and 3 copy number alterations

CDx, companion diagnostic; FDA, US Food and Drug Administration; FFPE, formalin fixed paraffin embedded.

1. US Food and Drug Administration. Accessed January 12, 2023. https://www.fda.gov/medical-devices/recently-approved-devices/oncominetm-dx-target-test-p160045s019; 2. Thermo Fisher Scientific. Accessed January 12, 2023. https://www.thermofisher.com/order/catalog/product/A49755; 3. Takeda Oncology. News release. Accessed January 12, 2023. https://www.takedaoncology.com/news/news-releases/foundation-medicine-and-takeda-announce-collaboration-to-develop-foundationonecdx-and-foundationoneliquid-cdx-as-companion-diagnostics-for-takedas-late-stage-lung-cancer-portfolio; 4. Takeda Pharmaceuticals. Data on file; 5. Foundation Medicine. Accessed January 12, 2023. https://www.foundationmedicine.com/test/foundationone-cdx.

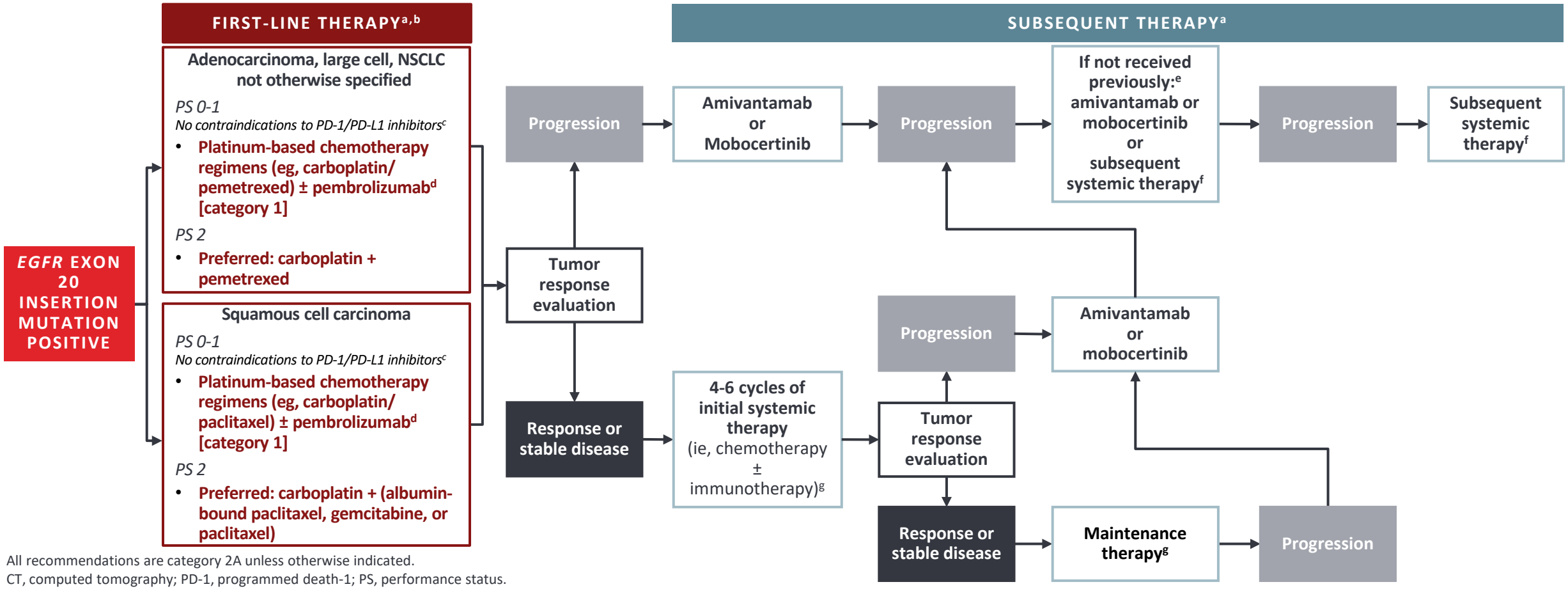
Therapeutic approaches to target EGFR ex20ins NSCLC



EGFR, Epidermal growth factor receptor, NSCLC nonsmall cell lung cancer TKIs, Tyrosine kinase inhibitor; Hsp, Heat shock protein
MET, Mesenchymal-epithelial transition factor
Pacini L et al. Pharmgenomics Pers Med. 2021 Mar 9; 14: 301−317.

Amivantamab EMA (EU) SmPC available at: https://ec.europa.eu/health/documents/community-register/2021/20211209153836/anx_153836_en.pdf last updated February 2022
Mobocertinib FDA (US) Prescribing Information available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215310s000lbl.pdf last updated September 2021
For detailed information about an individual medicinal product, please read the last approved Summary of Product Characteristics www.ema.europa.eu or at the website of your national authority. Please note that all medicinal products mentioned may not be authorized/available in all countries

Current NCCN Guidelines: Treatment of *EGFR* Exon 20 Insertion Mutation–Positive Advanced NSCLC



All recommendations are category 2A unless otherwise indicated.
CT, computed tomography; PD-1, programmed death-1; PS, performance status.
[a] During initial therapy, response assessment should be performed after 2 cycles and then every 2-4 cycles with CT of known or high-risk sites of disease with or without contrast or when clinically indicated. During subsequent therapy, response assessment should be performed with CT of known or high-risk sites of disease with or without contrast every 6-12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision; [b] See Guidelines for other recommended 1L options; [c] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents; some oncogenic drivers (ie, *EGFR* exon 19 deletion or L858R, *ALK* rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors; [d] Response rates to immunotherapy regimens vary (0%-25%), depending on the specific *EGFR* exon 20 insertion mutation; [e] Amivantamab can be used if patients have previously received mobocertinib and vice versa, because these agents have different mechanisms of action; [f] See Guidelines for details; [g] In general, 4 cycles of initial systemic therapy (ie, with carboplatin or cisplatin) are administered prior to maintenance therapy. However, if patient is tolerating therapy well, consideration can be given to continue to 6 cycles.

Amivantanab

Amivantamab EMA (EU) SmPC available at: https://ec.europa.eu/health/documents/community-register/2021/20211209153836/anx_153836_en.pdf last updated February 2022
For detailed information about an individual medicinal product, please read the last approved Summary of Product Characteristics www.ema.europa.eu or at the website of your national authority. Please note that all medicinal products mentioned may not be authorized/available in all countries

CHRYSALIS: Amivantamab + chemotherapy in NSCLC: Study design of dose-escalation cohort

Key eligibility criteria:
- Metastatic NSCLC with no particular mutation required
- Eligible for carbo/pem in accordance with SOC

Key objective:
- Determine RP2D to be given Q3W in combination with chemotherapy

Amivantamab* + carbo/pem → Amivantamab + pem

	Cycle 1, day 1	Cycle 1, day 2	Cycle 1, days 8, 15 Cycle 2, day 1	Cycle 3, day 1 Cycle 4, day 1	Cycle 5, day 1 onward
<80 kg	350 mg	1050 mg	1400 mg	1750 mg	1750 mg
≥80 kg	350 mg	1400 mg	1750 mg	2100 mg	2100 mg

*Amivantamab is dosed with standard doses of carboplatin AUC 5 (4 cycles) and pemetrexed 500 mg/m^2 in a 21-day cycle
Amivantamab dosing is weight based; dosed QW for 4 doses (first dose is split) up to cycle 2, day 1 and then Q3W until PD

AUC, area under curve; Carbo, carboplatin; DLT, dose-limiting toxicity; NSCLC, non-small cell lung cancer; PD, progressive disease; Pem, pemetrexed; QW, once per week; Q3W, once every 3 weeks; RP2D, recommended phase 2 dose; SOC, standard of care.
Nagasaka M, et al. WCLC 2021 (abstr P50.04)

CHRYSALIS: Amivantamab monotherapy in EGFR ex20ins after post-platinum chemotherapy (dose-expansion)

Characteristic, n (%)	Efficacy population (n=81)*
Median age, years (range)	62 (42–84)
Female, n (%)	48 (59)
Race	
Asian	40 (49)
Black	2 (2)
White	30 (37)
Not reported	9 (11)
Median number of previous lines of therapy	2 (1–7)
IRC-assessed response	
ORR, % (95% CI)	**40 (29–51)**
CR, n (%)	**3 (4)**
PR, n (%)	**29 (36)**
SD, n (%)	**39 (48)**
PD, n (%)	**8 (10)**
NE, n (%)	**2 (2)**
mDoR, months (95% CI)	**11.1 (6.9–NR)**
mPFS, months (95% CI)	**8.3 (6.5–10.9)**

Common AEs, n (%)	Safety population (n=114)
Rash	98 (86%)
Infusion-related reactions	75 (66%)
Paronychia	51 (45%)
Most common grade 3–4 AE, n (%)	
Hypokalaemia	6 (5)
Rash	4 (4)
Pulmonary embolism	4 (4)
Diarrhoea	4 (4)
Neutropenia	4 (4)

*Efficacy population = patients who had *EGFR* ex20ins mutation, received previous platinum-based chemotherapy and had ≥3 disease assessments at clinical cut off.
AE, adverse events; CI, confidence interval; CR, complete response; EGFR, epidermal growth factor receptor; IRC, independent review committee; mDoR, median duration of response; mPFS, median progression-free survival; NE, non-evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
Park K, et al. J Clin Oncol 2021;39:3391–3402

CHRYSALIS: Amivantamab + chemotherapy in NSCLC: Safety profile (dose-escalation)

	Total (n=20)	
TEAEs (≥30%), n (%)	**All grade**	**Grade ≥3**
Infusion-related reaction	13 (65)	0
Nausea	13 (65)	1 (5)
Acneiform dermatitis	12 (60)	0
Constipation	10 (50)	0
Fatigue	10 (50)	0
Neutropenia	9 (45)	7 (35)
Thrombocytopenia	9 (45)	3 (15)
Rash	6 (30)	0
Diarrhoea	6 (30)	1 (5)
Stomatitis	6 (30)	0
Paronychia	6 (30)	0

TRAEs, n (%)	**Total (n=20)**
Leading to treatment discontinuation	2 (10)
Leading to dose reduction	4 (20)

- Most frequent grade ≥3 TEAEs reflect cytopenias anticipated with chemotherapy
- Serious TEAEs reported in 6 patients (30%)
  - Majority of events related to chemotherapy
    - Diarrhea, nausea, upper gastrointestinal hemorrhage, cellulitis, hyponatraemia, altered mental status (n=1, each)
  - Few events were also deemed related to amivantamab
    - Diarrhea, nausea, cellulitis (n=1, each)
  - Pneumonia (n=2) not related to any study agent

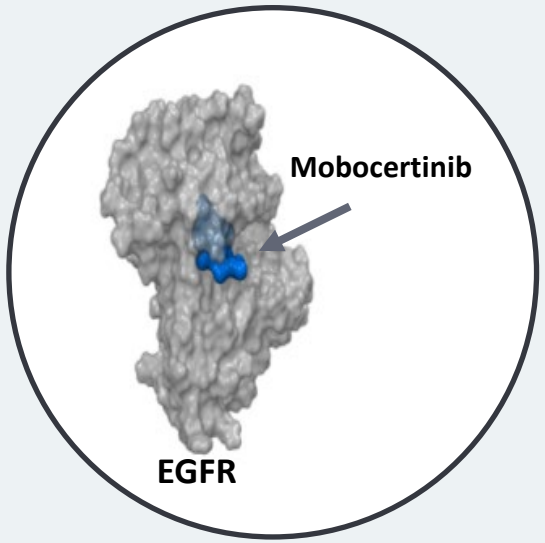
NSCLC, non-small cell lung cancer; TEAE, treatment-emergent adverse events; TRAE, treatment-related adverse events.
Nagasaka M, et al. WCLC 2021 (abstr P50.04)

Mobocertinib

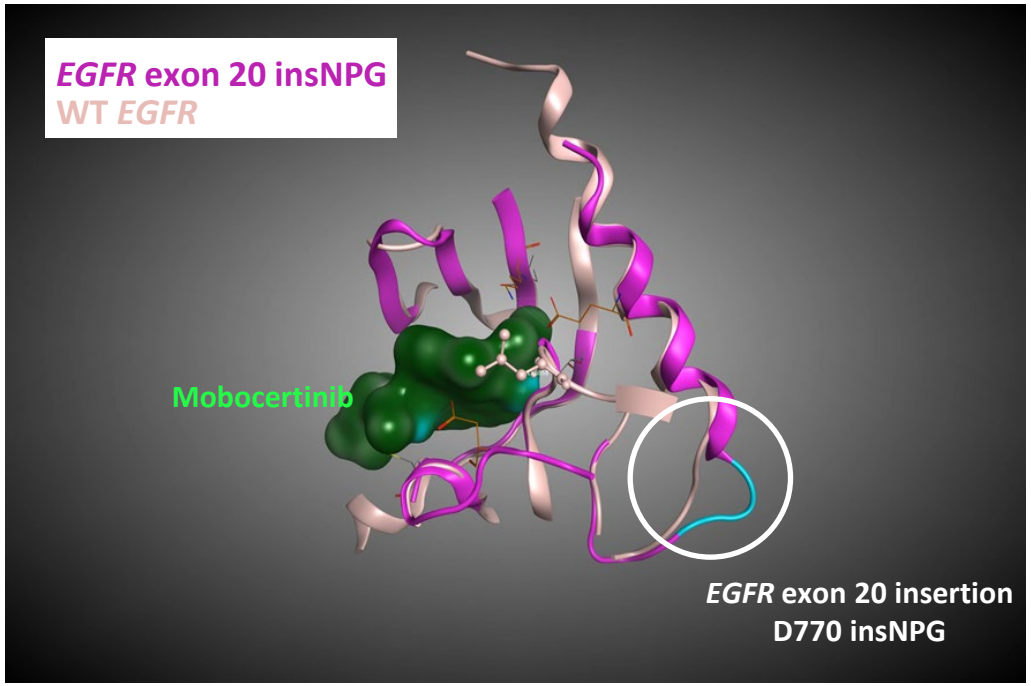
Mobocertinib FDA (US) Prescribing Information available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215310s000lbl.pdf last updated September 2021

For detailed information about an individual medicinal product, please read the last approved Summary of Product Characteristics www.ema.europa.eu or at the website of your national authority. Please note that all medicinal products mentioned may not be authorized/available in all countries

Mobocertinib Design



Mobocertinib is an orally active EGFR TKI uniquely designed to address the steric limitations of classical EGFR TKIs[1,2,a]



Mobocertinib has a unique flexible monocyclic core that may contribute to its ability to bind and inhibit *EGFR* exon 20 insertions[2]

[a] EGFR TKIs not designed to target *EGFR* exon 20 insertions.

Source of images: Takeda mobocertinib crystal structure (data on file; left image). Ramalingam SS, et al. *J Clin Oncol*. 2021;39(suppl 15). Abstract 9014 (right image).

1. Gonzalvez F, et al. *Cancer Discov*. 2021;11:1672-1687; 2. Takeda Pharmaceuticals. Data on file (BTD request).

Overview of Mobocertinib Key Clinical Trials

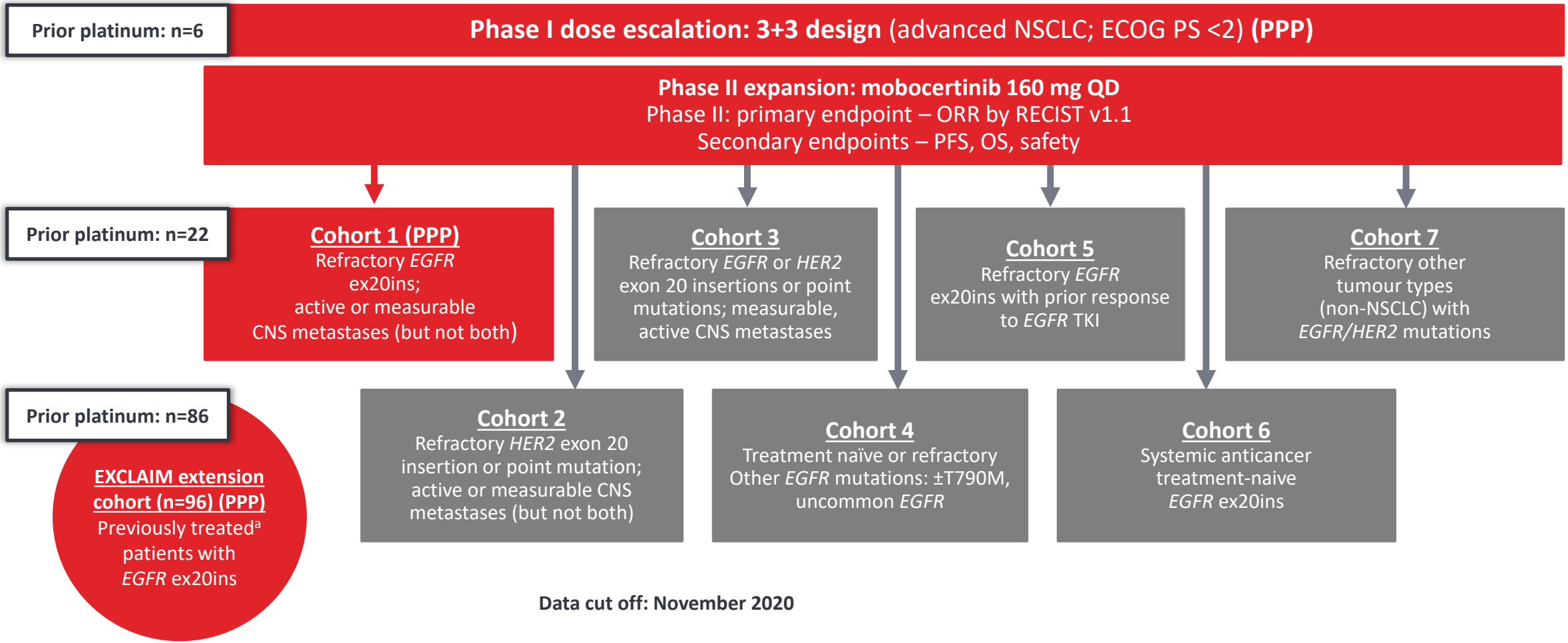
Separated into 3 parts: dose escalation, dose expansion, and extension (EXCLAIM)

TRIAL[1]	PHASE	DESCRIPTION	TRIAL DATES
NCT03807778	1/2	Study in Japanese patients with NSCLC	February 2019-March 2024
NCT02716116[2-4]	1/2	Safety, PK, and antitumor activity in NSCLC	June 2016-March 2023
NCT02716116[2,5]	2	Phase 2 extension cohort (EXCLAIM) in previously treated patients with *EGFR* exon 20 insertion–positive locally advanced or metastatic NSCLC	
NCT04129502 (EXCLAIM-2)	3	1L treatment vs platinum-based chemotherapy in patients with *EGFR* exon 20 insertion–positive locally advanced or metastatic NSCLC	January 2020-June 2026

- On September 15, 2021, the **FDA approved the use of mobocertinib** for the treatment of adult patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations, as detected by an FDA-approved test, that progressed on or after prior platinum-based chemotherapy[6]
- This indication is approved under accelerated approval based on ORR and DOR. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s)[7]
- *Please see the US prescribing information for the boxed warning and warnings and precautions*[7]

As of December 2022. Please check ClinicalTrials.gov or the Takeda website for the latest status.
DOR, duration of response; PK, pharmacokinetics.
1. ClinicalTrials.gov. Accessed January 12, 2023. https://www.clinicaltrials.gov; 2. Takeda Pharmaceuticals. Data on file (phase 1/2 protocol); 3. Riely G, et al. WCLC 2019. Abstract P1.01-127; 4. Riely GJ, et al. *Cancer Discov.* 2021;11:1688-1699; 5. Zhou C, et al. *JAMA Oncol.* 2021;7:e214761; 6. Takeda Oncology. News release. Accessed January 12, 2023. https://www.takeda.com/newsroom/newsreleases/2021/takeda-exkivity-mobocertinib-approved-by-us-fda/; 7. Exkivity (mobocertinib). Prescribing information. Takeda Pharmaceutical Company Ltd; 2021.

Mobocertinib: Design and patient cohorts in phase I/II and EXCLAIM



[a]1–2 systemic anticancer chemotherapy regimens. Prior EGFR TKI was allowed unless patient had an objective response and subsequent disease progression. Locations: United States only for phases I and II; United States, European Union, and Asia for phase II extension cohort. Active CNS metastases: untreated or treated and progressing; measurable CNS metastases: ≥10 mm in longest diameter by contrast-enhanced MRI.

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PPP, platinum-pretreated patients; QD, once a day; RECIST, response evaluation criteria in solid tumours; TKI, tyrosine kinase inhibitor.

Zhou C, et al. JAMA Oncol 2021;e214761. doi: 10.1001/jamaoncol.2021.4761. [Online ahead of print]

Mobocertinib PPP and EXCLAIM Cohorts: Baseline Characteristics

DEMOGRAPHIC AND BASELINE CHARACTERISTICS	PPP COHORT (N=114)[1,a]	EXCLAIM COHORT (N=96)[2,b]
Age, median (range), years	60 (27-84)	59 (27-80)
Female, %	66	65
Race, % Asian/White/Black or African American/not reported	60/37/3/1	69/29/2/0
ECOG PS, % 0/1	25/75	29/71
Smoking history, % Never/current/former	71/2/27	73/2/25
Baseline brain metastases, %	35	34
Prior systemic anticancer regimens 1/2/≥3, % Median, n	41/32/27 2	51/31/18 1
Prior platinum-based chemotherapy, %	100	90
Prior EGFR TKI, %	25	31
Prior IO, %	43	34

ECOG, Eastern Cooperative Oncology Group.
[a] Data cutoff: November 1, 2021; [b] Data cutoff: November 1, 2020.
1. Ramalingam SS, et al. ESMO 2022. Abstract 988P; 2. Zhou C, et al. *JAMA Oncol*. 2021;7:e214761.

Mobocertinib PPP and EXCLAIM Cohorts: Efficacy

	PPP COHORT (N=114)[1,2,a]		EXCLAIM COHORT (N=96)[3,b]	
	BY IRC	BY INVESTIGATOR	BY IRC	BY INVESTIGATOR
Median time on treatment (range), months	7.4 (0-48.0)		6.8 (0-18.8)	
Median follow-up (range), months	25.8 (24.6-26.7)		13.0 (0.7-18.8)	
Confirmed ORR (95% CI), % CR, % PR, %	28 (20-37) <1 27	35 (26-45) <1 34	25 (17-35) 0 25	32 (23-43) 1 31
Confirmed DCR (95% CI), %[c]	78 (69-85)	78 (69-85)	76 (66-84)	75 (65-83)
Median DOR (95% CI), months[d]	15.8 (7.4-19.4)	13.9 (5.6-19.4)	NR (5.6-NR)	11.2 (7.0-NR)
Median PFS (95% CI), months[d]	7.3 (5.5-9.2)	7.3 (5.6-8.8)	7.3 (5.5-9.1)	7.3 (5.6-9.1)
Median OS (95% CI), months[d]	20.2 (14.9-25.3)		NR (13.1-NR)	

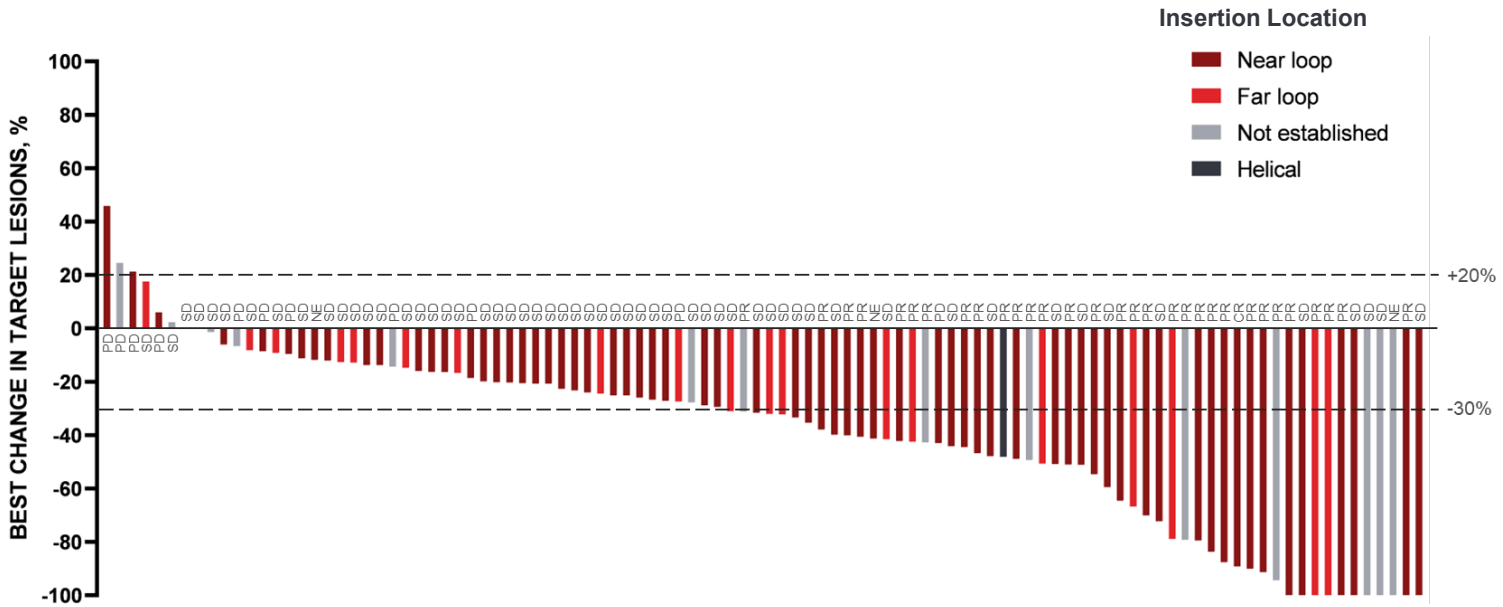
CR, complete response; PR, partial response; SD, stable disease.

[a] Data cutoff: November 1, 2021; [b] Data cutoff: November 1, 2020; [c] Defined as confirmed CR or PR or best response of SD for ≥6 weeks after initiation of study drug using RECIST v1.1; [d] DOR, PFS, and OS were estimated using Kaplan-Meier analysis.

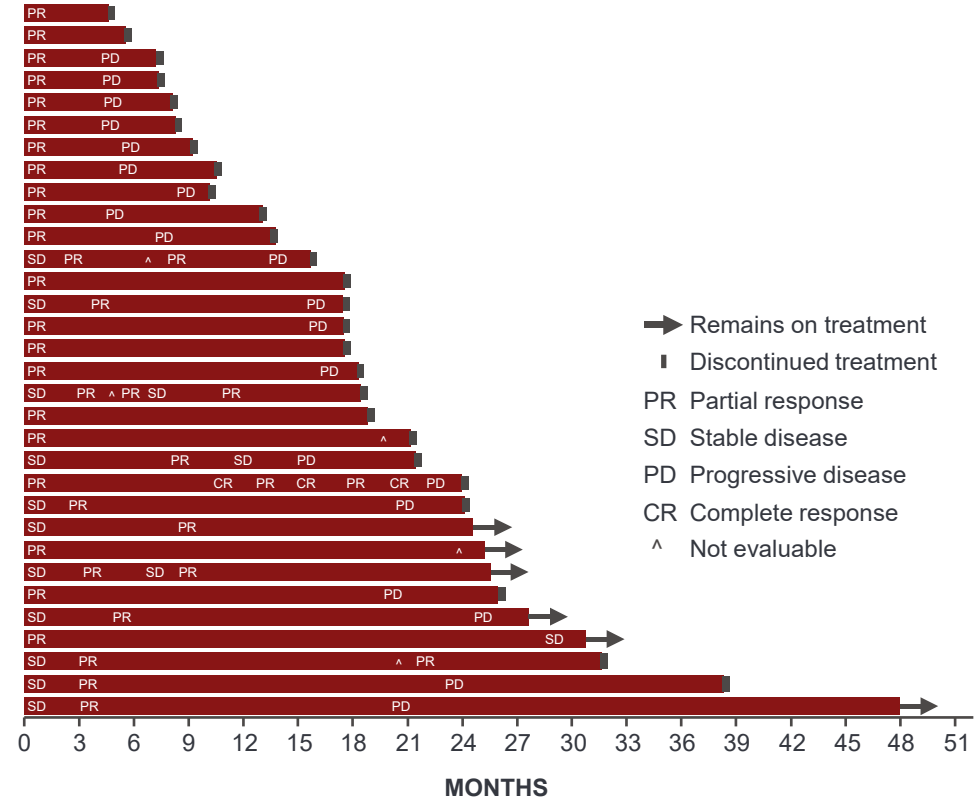
1. Ramalingam SS, et al. ESMO 2022. Abstract 988P; 2. Takeda Pharmaceuticals. Data on file; 3. Zhou C, et al. *JAMA Oncol*. 2021;7:e214761.

Objective Response by *EGFR* Exon 20 Insertion Mutation Location in the PPP Cohort (by IRC Assessment)

IRC-Assessed Best Percentage Change in Sum of Target Lesion Diameters (N=114)[1,2,a]



Time on Treatment in Confirmed Responders (n=32)[1]



96 patients (84%) had a reduction from baseline in the sum of target lesion diameters per IRC assessment.[1]

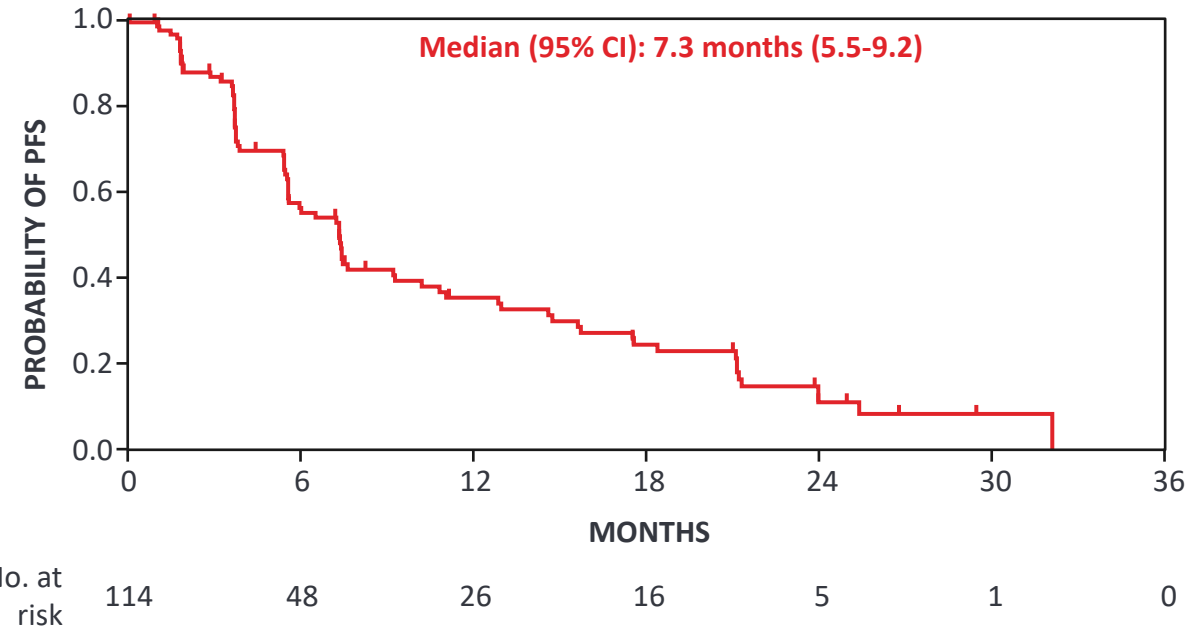
Data cutoff: November 1, 2021.

[a] Includes patients with measurable disease who have ≥1 postbaseline assessment.

1. Ramalingam SS, et al. ESMO 2022. Abstract 988P; 2. Takeda Pharmaceuticals. Data on file (PPP cohort_waterfall).

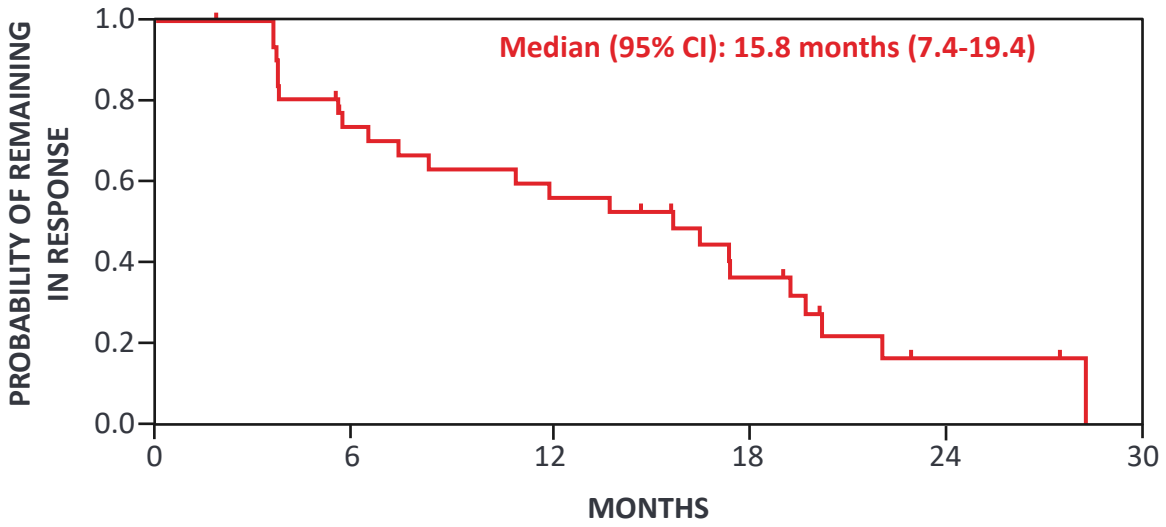
Mobocertinib PPP Cohort: PFS and DOR (by IRC Assessment)

PFS (N=114)



No. at risk						
114	48	26	16	5	1	0

DOR (n=32)

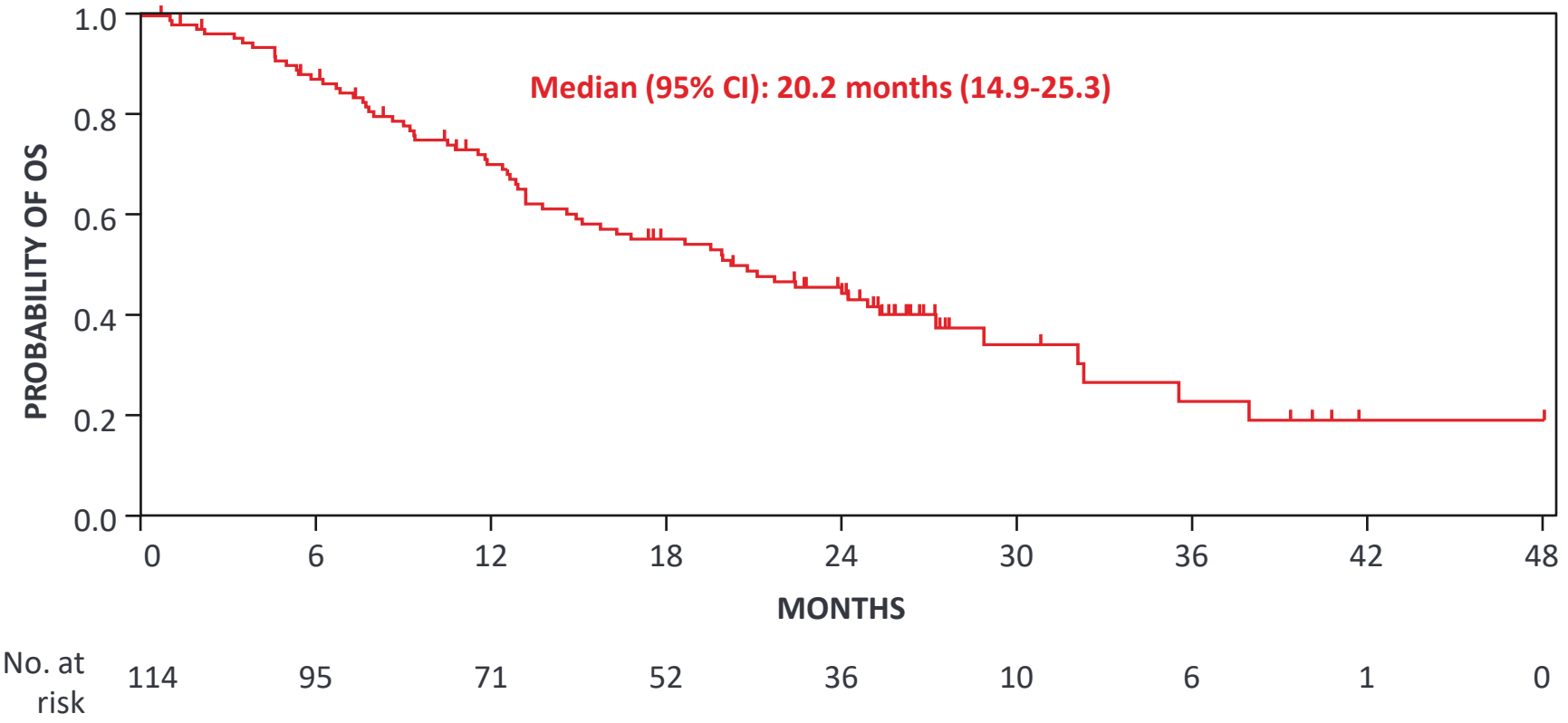


No. at risk						
32	21	16	9	2	0	

Data cutoff: November 1, 2021.
Ramalingam SS, et al. ESMO 2022. Abstract 988P.

Mobocertinib PPP Cohort: OS

OS (N=114)[1,a]



- In an indirect comparison, OS was significantly prolonged with mobocertinib (PPP cohort) vs other standard-of-care therapies (RW data): median OS, 24.0 vs 12.4 months (HR, 0.53; *P*=.0089)[2,b,c]
- Indirect comparisons have limitations that may impact estimations of outcomes[2,d]

HR, hazard ratio.

[a] Data cutoff: November 1, 2021; [b] Data cutoff: November 1, 2020; [c] Indirect comparison of outcomes in patients treated with mobocertinib in the PPP cohort vs patients with NSCLC with *EGFR* exon 20 insertions treated with standard-of-care therapies in the RW setting (data obtained from the Flatiron Health Database [February 29, 2020, data cutoff]). An inverse probability of treatment weighting based on a propensity score method was used to balance the distributions of prognostic factors for NSCLC between patient groups. Data shown here are for weighted outcomes. Indirect comparison does not imply clinical significance and is potentially confounded by differences in trial design and study population; [d] Response assessments may not be consistent in the RW setting, potentially leading to an overestimation or underestimation of confirmed ORR. Additionally, data for ECOG PS, which is a predictor of OS in patients with cancer, was not available for all patients in the RW group; therefore, ECOG PS was not adjusted in this study, potentially leading to an overestimation or underestimation of OS.

1. Ramalingam SS, et al. ESMO 2022. Abstract 988P; 2. Ou S, et al. ESMO 2021. Abstract 1211P.

Mobocertinib PPP and EXCLAIM Cohorts: Safety Profile

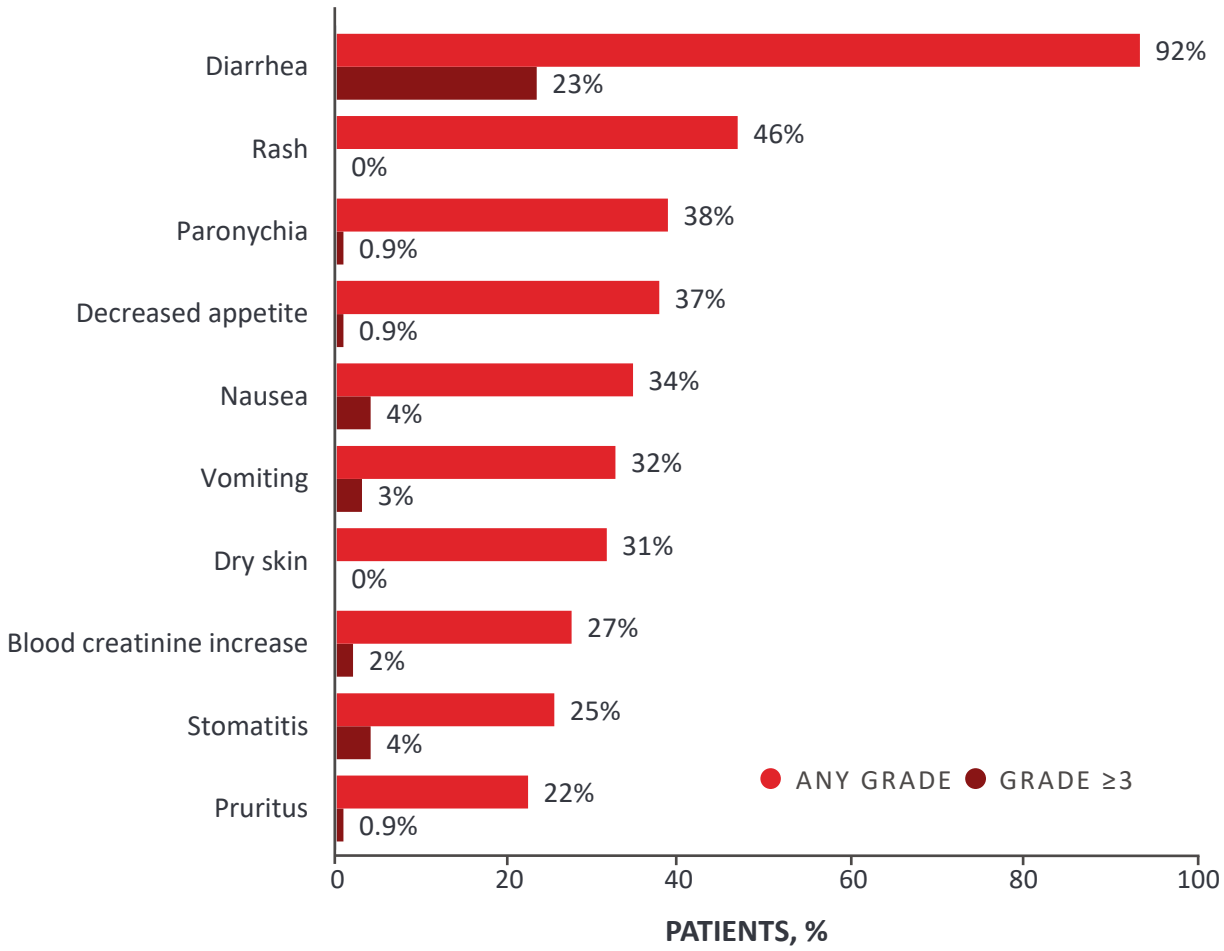
n (%)	PPP COHORT (N=114)[1,a]		EXCLAIM COHORT (N=96)[2,b]	
	ANY GRADE	GRADE ≥3	ANY GRADE	GRADE ≥3
Any TRAE	113 (99)	59 (52)	95 (99)	40 (42)
SAE	60 (53)	55 (48)	45 (47)	42 (44)
AE leading to dose reduction	31 (27)	NA[c]	21 (22)	NA[c]
AE leading to treatment discontinuation	21 (18)	NA[c]	10 (10)	NA[c]

- In the PPP cohort, AEs leading to treatment discontinuation in ≥2 patients were diarrhea (4%), nausea (2%), vomiting (2%), decreased appetite (2%), stomatitis (2%), and cardiac failure (2%)[1,a]
- In the EXCLAIM cohort, AEs leading to treatment discontinuation in ≥2 patients were nausea (2%) and diarrhea (2%)[2,b]
- 1 treatment-related death occurred due to cardiac failure in a PPP in the EXCLAIM cohort[1,2]

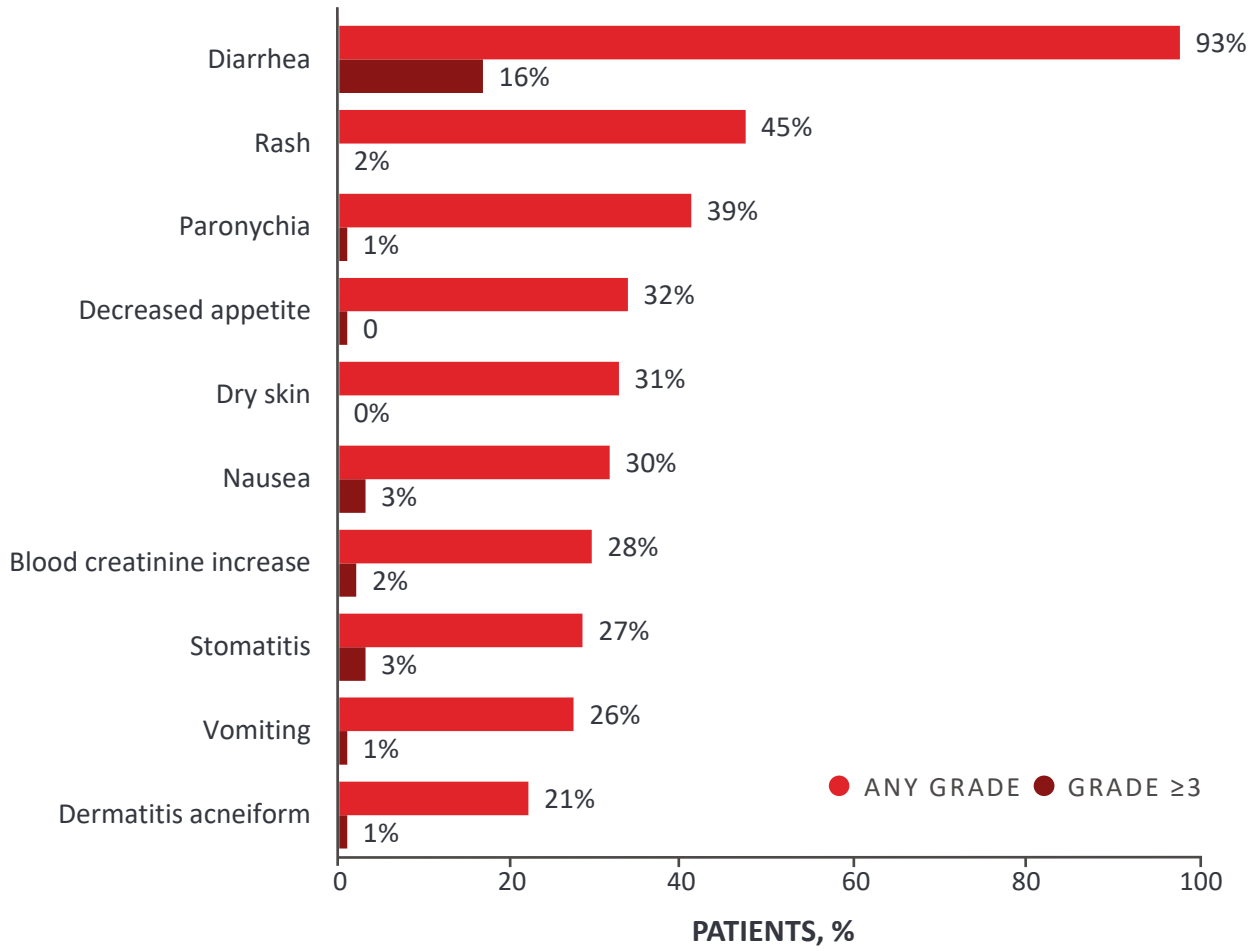
NA, not applicable; SAE, serious adverse event; TRAE, treatment-related adverse event.
[a] Data cutoff: November 1, 2021; [b] Data cutoff: November 1, 2020; [c] AEs leading to dose reduction or discontinuation were not evaluated by AE grade.
1. Ramalingam SS, et al. ESMO 2022. Abstract 988P; 2. Zhou C, et al. *JAMA Oncol*. 2021;7:e214761.

Mobocertinib PPP and EXCLAIM Cohorts: TRAEs Observed in >20% of Patients

PPP Cohort (N=114)[1,a,b]



EXCLAIM Cohort (N=96)[2,c]



[a] Data cutoff: November 1, 2021; [b] Note that AEs reported here are treatment related and differ from the adverse reactions reported in the US prescribing information.[3] Please see the US prescribing information for details; [c] Data cutoff: November 1, 2020.

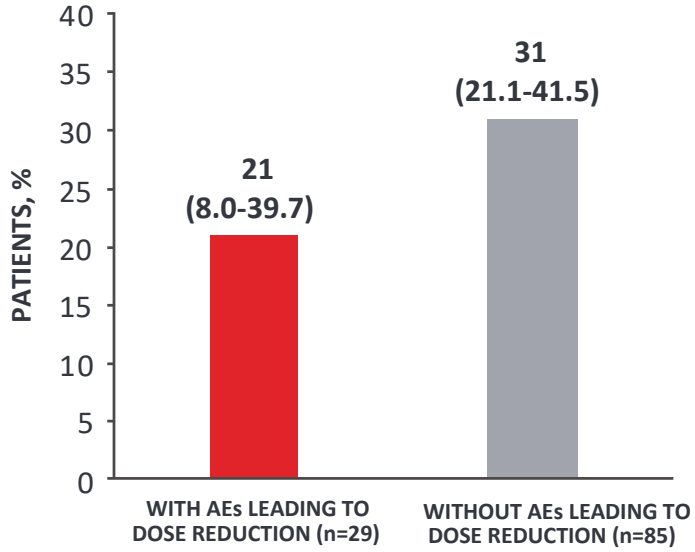
1. Ramalingam SS, et al. ESMO 2022. Abstract 988P; 2. Zhou C, et al. *JAMA Oncol*. 2021;7:e214761; 3. Exkivity (mobocertinib). Prescribing information. Takeda Pharmaceutical Company Ltd; 2021.

Mobocertinib PPP Cohort: Effect of Dose Reductions Due to AEs on Efficacy Outcomes

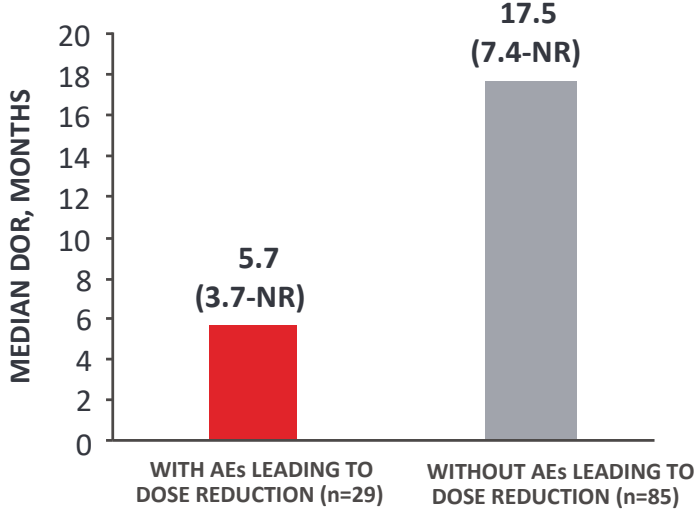
- ORR, median DOR, and median PFS were lower in patients with AEs leading to dose reductions (n=29) compared with patients without (n=85)
- The majority of dose reductions were due to AEs attributed to GI toxicity

CLINICAL OUTCOMES IN PATIENTS WITH AND WITHOUT AEs LEADING TO MOBOCERTINIB DOSE REDUCTIONS IN PPP COHORT (N=114)

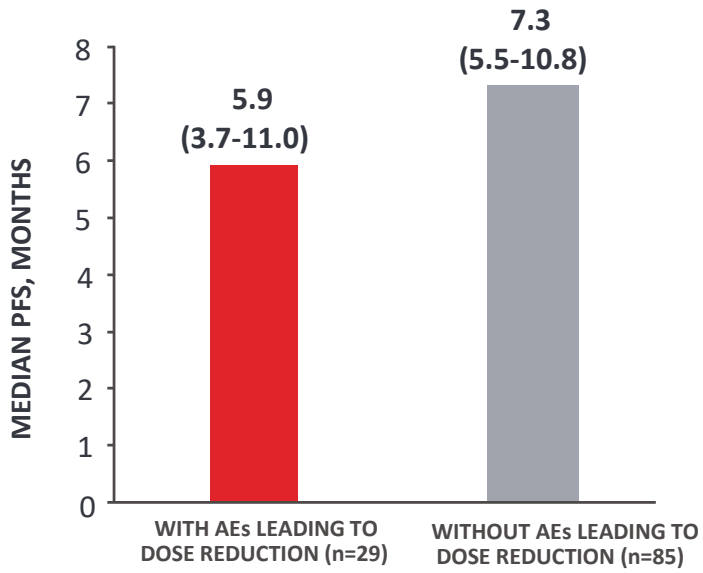
ORR (95% CI)



Median DOR (95% CI)



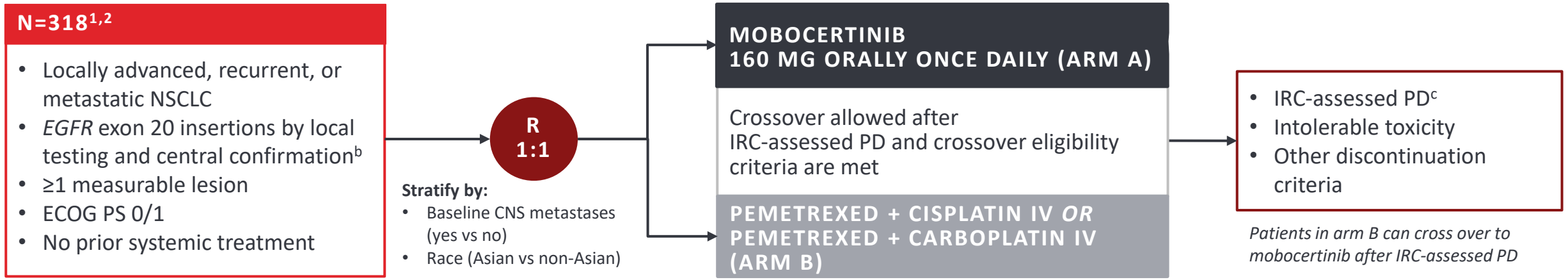
Median PFS (95% CI)



Data cutoff: November 1, 2020.
AE, adverse event; GI, gastrointestinal.
Nguyen D, et al. ESMO 2021. Abstract 1218P.

Phase 3 EXCLAIM-2: First-Line Mobocertinib vs Chemotherapy in Patients With *EGFR* Exon 20 Insertion–Positive NSCLC

Treatment-naive patients: a multicenter, randomized, open-label, phase 3 study of mobocertinib as 1L treatment vs chemotherapy for patients with *EGFR* exon 20 insertion–positive NSCLC (EXCLAIM-2; NCT04129502)[1,a]



PRIMARY ENDPOINT[1]	SECONDARY ENDPOINTS[1]		GLOBAL STUDY[2]
• IRC-assessed PFS per RECIST v1.1 (up to ≈40 months after the first patient randomization)	• IRC- and investigator-assessed confirmed ORR • DOR, time to response	• DCR • Investigator-assessed PFS • OS • HRQOL assessed by EORTC QLQ-C30 and QLQ-LC13	Including: • North America • Europe • Middle East • Asia Pacific

IV, intravenous.

[a] First patient was enrolled in January 2020; [b] *EGFR* exon 20 insertions were assessed by a clinical laboratory improvements amendment–certified (US sites) or an accredited (outside of the US) local laboratory and confirmed by central laboratory; [c] Randomized treatment with mobocertinib or platinum-based chemotherapy may be continued after PD, at the discretion of the investigator, and with the sponsor's approval if there is still evidence of clinical benefit.

1. ClinicalTrials.gov. Accessed January 12, 2023. https://clinicaltrials.gov/ct2/show/NCT04129502; 2. Gonzalvez F, et al. AACR 2020. Abstract DDT02-03.

CLN-081
Furmonertinib
Sunvozertinib
Osimertinib

Osimertinib EMA (EU) SmPC available at: https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf last updated July, 2021

For detailed information about an individual medicinal product, please read the last approved Summary of Product Characteristics www.ema.europa.eu or at the website of your national authority. Please note that all medicinal products mentioned may not be authorized/available in all countries

POSITION20: High-dose osimertinib in *EGFR* ex20ins-positive mNSCLC: Study design and baseline patient characteristics

Key eligibility criteria

- Advanced NSCLC
- *EGFR* exon20 mutation-positive (mutation, deletion, and/or insertion)
- T790M-negative
- Pre-treatment chemotherapy allowed
- Asymptomatic brain metastases
- WHO PS 0–2

Treatment regimen

- Patients treated with osimertinib **160 mg daily** until progression or unacceptable toxicity

Endpoints

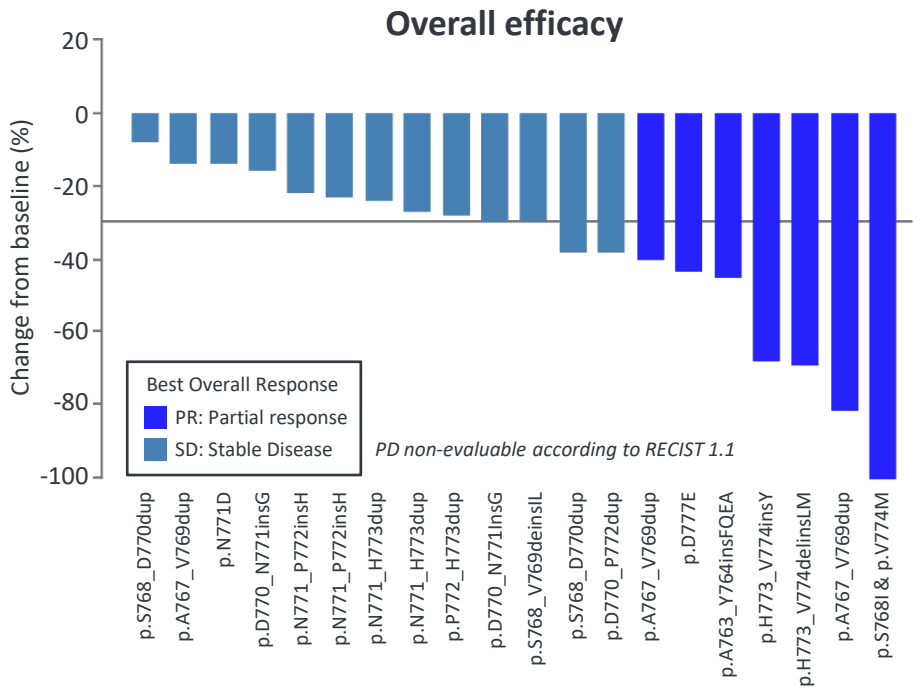
- Primary: ORR
- Secondary: Safety, DoR, PFS, OS

Characteristic	n=25
Age, years (range)	68 (46–87)
Female n (%)	18 (72)
ECOG PS, n (%) 0 1 2	 9 (36) 15 (60) 1 (4)
Baseline brain metastases (asymptomatic), n (%)	4 (16)
Prior therapies, median (range)	1 (1–3)
EGFR exon20 mutation subtype (most common >1 listed), (%)	p. A767_V769dup (12) p. N771_H773dup (12) p. S768_D770dup (8) p. D770_N771insG (8) p. N771_P772insH (8) p. P772_H773dup (8)

DoR, duration of response; ECOG, Eastern cooperative oncology group; EGFR, epidermal growth factor receptor, ; mNSCLC, metastatic non–small cell lung cancer.; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; WHO PS, World Health Organisation performance status.

Zwierenga F, et al. ESMO 2021. 1214P
Osimertinib EMA (EU) SmPC available at: https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf last updated July, 2021

POSITION20: High-dose osimertinib in *EGFR* ex20ins-positive mNSCLC: Efficacy data[1]



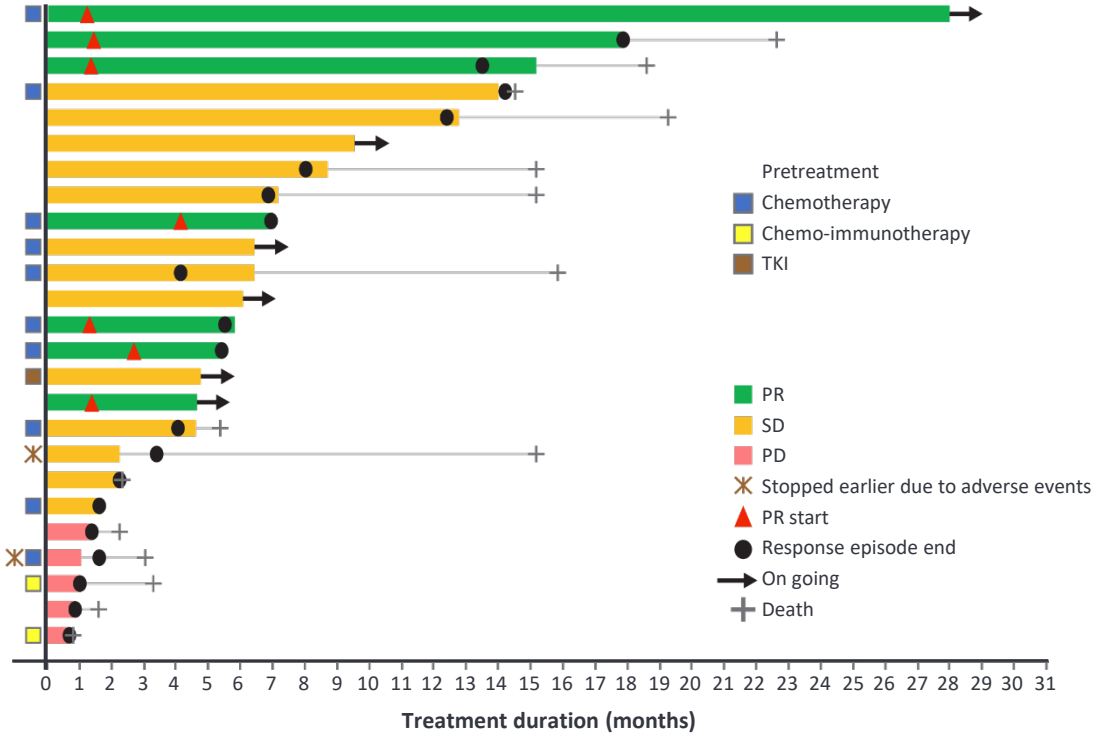
Confirmed ORR: 7/25, 28%

PR (n=7) 28%
SD (n=13) 52%
PD (n=5) 20%

DoR=4.2 months

mPFS=6.8 months

mOS=15.2 months



ECOG-ACRIN EA5162 efficacy results[2]	(n=17)
ORR, %	24
DCR, %	82
DoR, median, months (range)	NE (4.7–NE)
PFS, median, months (95% CI)	9.6 (4.1–10.7)

CI, confidence interval; DCR, disease control rate; DoR, duration of response; ECOG, Eastern cooperative oncology group; EGFR, epidermal growth factor receptor; NE, non-evaluable; mNSCLC, metastatic non–small cell lung cancer.; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

1. **Zwierenga F, et al. Poster. ESMO 2021 (abstr 1214P); 2. Piotrowska Z, et al. Poster, ASCO 2020 (abstr 9513)**

POSITION20: High-dose osimertinib in *EGFR* ex20ins-positive mNSCLC: Safety data

TRAEs in >10% of patients (n=25)	All grades[b], n (%)	Grade 3[b], n (%)
Diarrhoea	18 (72)	1 (4)
Dry skin[a]	11 (44)	0
Fatigue	11 (44)	0
Rash or acne[a]	10 (40)	0
Dyspnoea	9 (36)	0
Paronychia	9 (36)	0
Anaemia	8 (32)	1 (4)
Cough	7 (28)	0
Myalgia	7 (28)	1 (4)
Anorexia	6 (24)	0

TRAEs in >10% of patients (n=25)	All grades[b], n (%)	Grade 3[b], n (%)
CPK increased	6 (24)	2 (8)
Back pain	5 (20)	0
Dry eyes	5 (20)	0
Mucositis oral	5 (20)	0
Nausea	5 (20)	0
Platelets decreased	5 (20)	0
Constipation	3 (12)	0
Dry mouth	3 (12)	0
Pruritus	3 (12)	0
Fissures	3 (12)	0

[a]Group term; [b]No Grade 4 toxicities reported.
EGFR, epidermal growth factor receptor; mNSCLC, metastatic non–small cell lung cancer.; TRAE, treatment-related adverse events.
Zwierenga F, et al. ESMO 2021 (abstr 1214P)

ZAKLJUČAK

- EGFR insercija u egzonu 20 je veoma retka i sa veoma lošom prognozom u odnosu na ostale EGFR mutacije (5god OS 8% vs 19%)
- EGFR TKI imaju malu efikasnost u lečenju.
- NGS (Next-generation sequencing) je preporučen za testiranje i odabir najbolje strategije u lečenju[1].
- Novi lekovi su odobreni od strane FDA i EMA za lečenje pacijenata sa NSCLC EGFR insercijama u egzonu 20.
- Ispituju se novi lekovi i u prvoj liniji lečenja

EGFR, Epidermal growth factor receptor.

Reference: Author's conclusions.
Based on: 1. National Comprehensive Cancer Network (NCCN) Guidelines for Non-Small Cell Lung Cancer Version 1.2022. Available at www.nccn.org, accessed in February 2022.