Novel Strategies to Optimize Treatment in Metastatic EGFRm NSCLC

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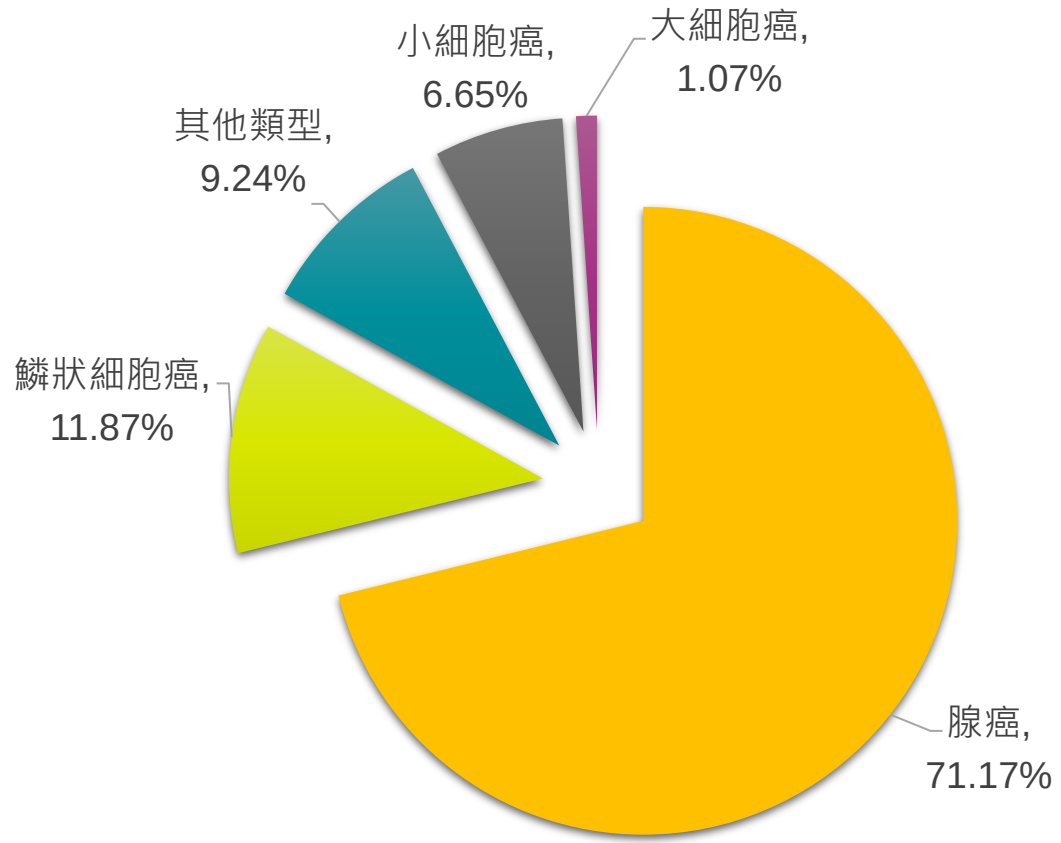
輔仁大學 醫學院

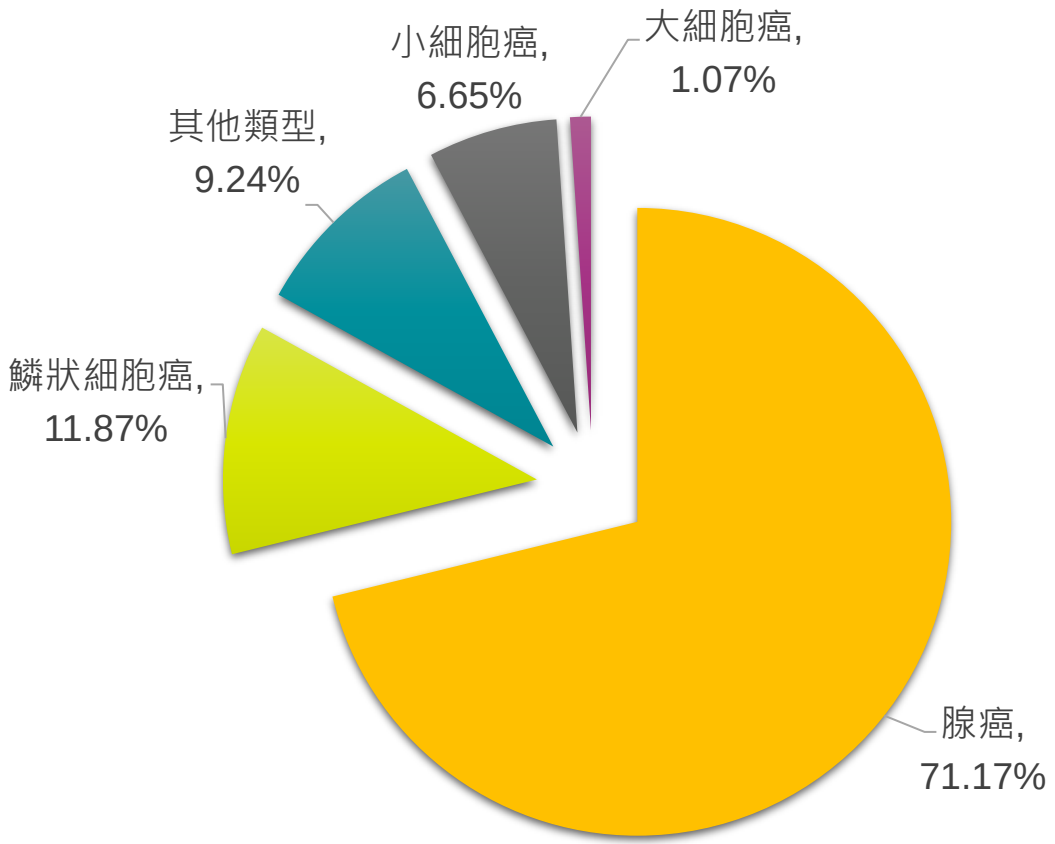
Distribution of pathological subtype in Lung Cancer

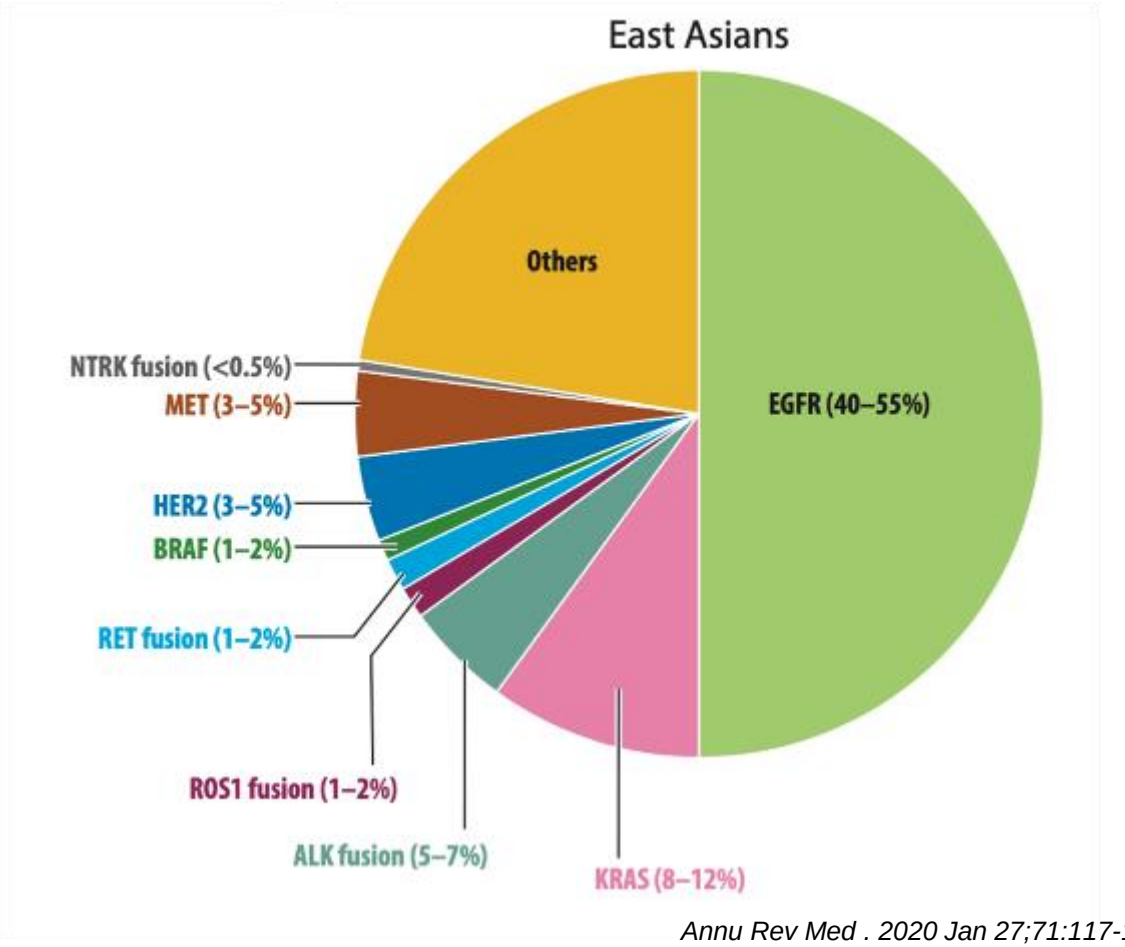
中華民國108年癌症登記報告



Distribution of pathological subtype in Lung Cancer

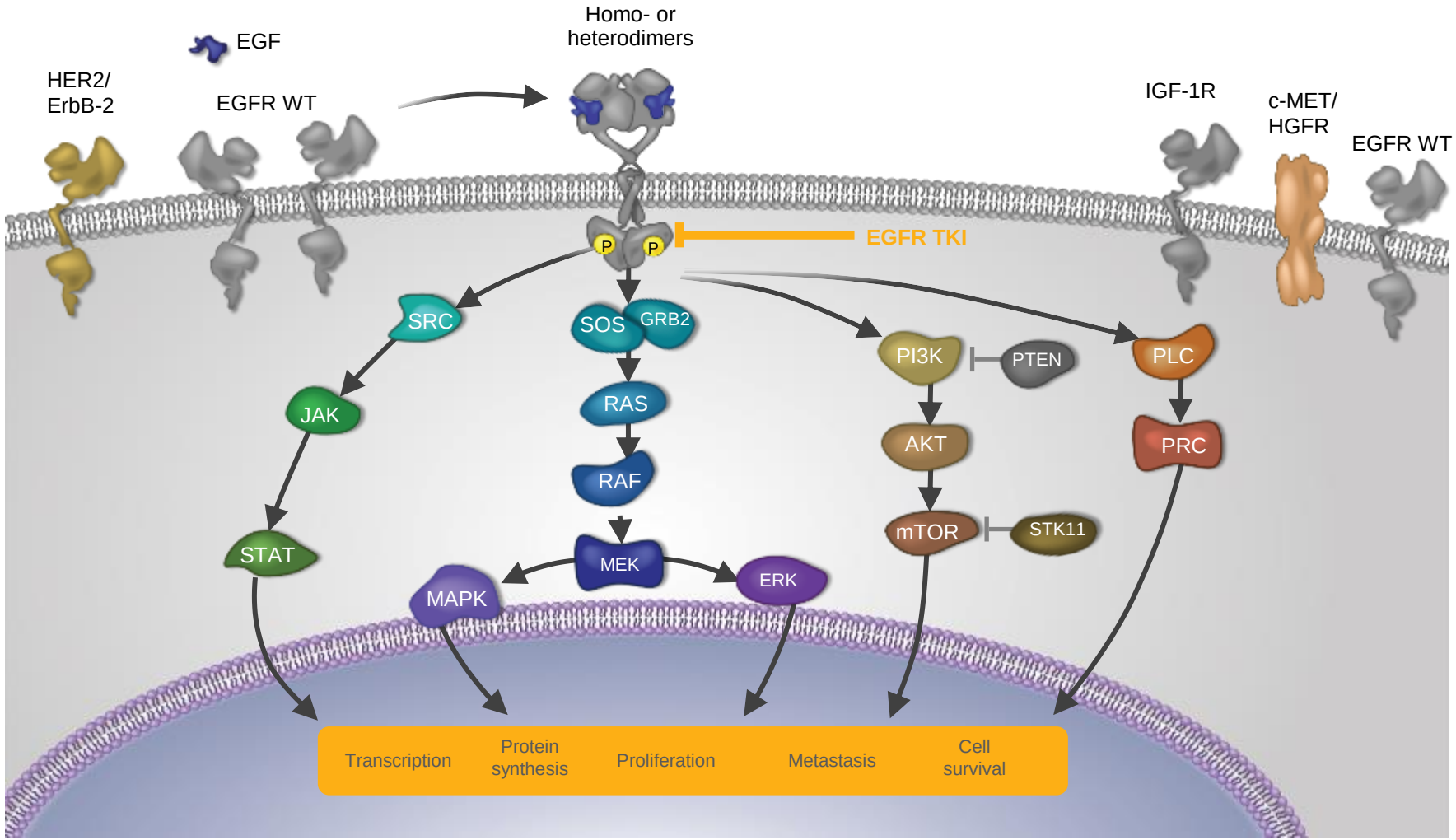
中華民國108年癌症登記報告





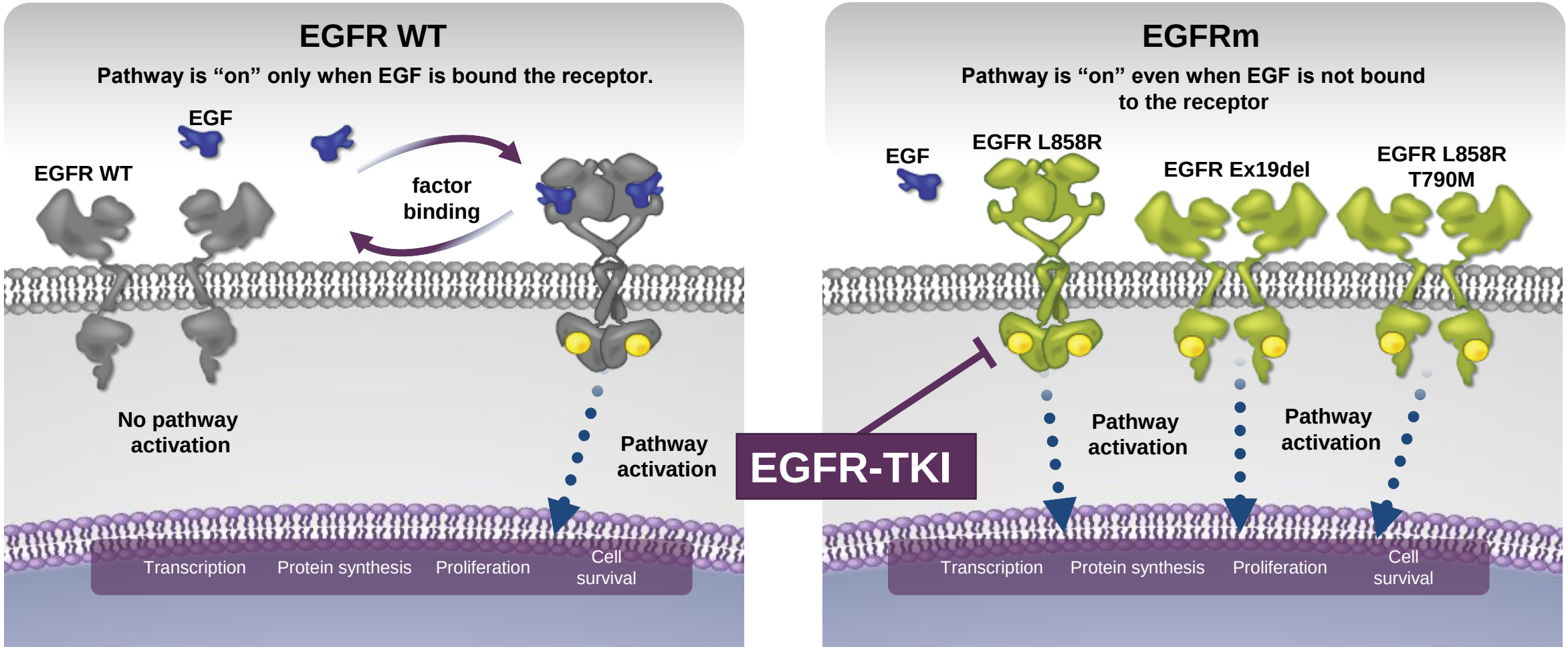
Annu Rev Med . 2020 Jan 27;71:117-136.

EGFR is an oncogenic driver of NSCLC and regulates cellular signaling through multiple pathways

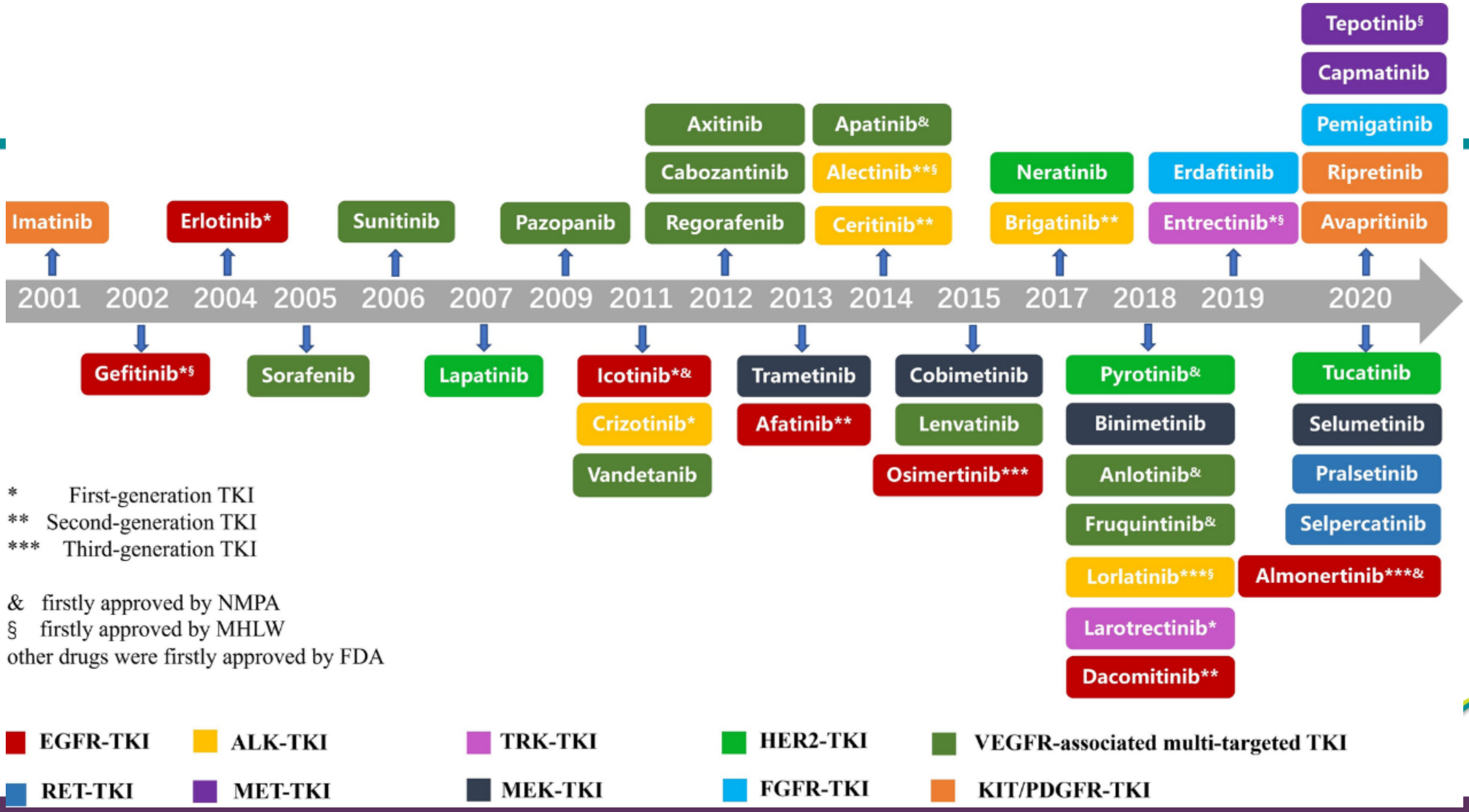


Lung Cancer. 2014;83(3):374-382;
PLoS One. 2015;10(5):e0128360

The mechanism and the target of EGFR TKI

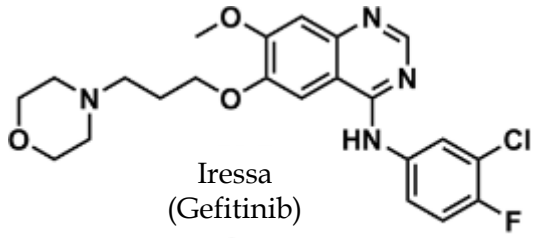


Adapted based on Cho J, et al.Cancer Res. 2013; 73(22); 6770–6779; Plönes T, et al. J Pers Med. 2016;6(1); Wang DD, et al. PLoS One. 2015;10(5):e0128360; Brambilla E, et al. Eur Respir J. 2009;33:1485-1497.

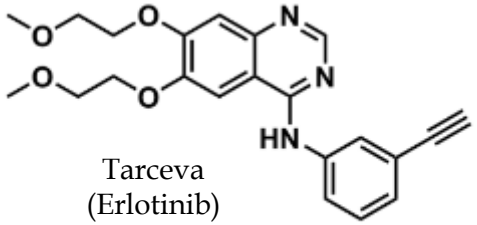

Tepotinib§
Capmatinib
Pemigatinib
Ripretinib
Avapritinib
Axitinib
Apatinib&
Cabozantinib
Alectinib**§
Regorafenib
Ceritinib**
Neratinib
Brigatinib**
Erdafitinib
Entrectinib*§
Imatinib
Erlotinib*
Sunitinib
Pazopanib
2001
2002
2004
2005
2006
2007
2009
2011
2012
2013
2014
2015
2017
2018
2019
2020
Gefitinib*§
Sorafenib
Lapatinib
Icotinib*&
Crizotinib*
Vandetanib
Trametinib
Afatinib**
Cobimetinib
Lenvatinib
Osimertinib***
Pyrotinib&
Binimetinib
Anlotinib&
Fruquintinib&
Lorlatinib***§
Larotrectinib*
Dacomitinib**
Tucatinib
Selumetinib
Pralsetinib
Selpercatinib
Almonertinib***&
* First-generation TKI
** Second-generation TKI
*** Third-generation TKI
& firstly approved by NMPA
§ firstly approved by MHLW
other drugs were firstly approved by FDA
EGFR-TKI
ALK-TKI
TRK-TKI
HER2-TKI
VEGFR-associated multi-targeted TKI
RET-TKI
MET-TKI
MEK-TKI
FGFR-TKI
KIT/PDGFR-TKI

Approved EGFR-TKIs in Locally Advanced and Metastatic NSCLC in Taiwan

First Generation (Reversible)

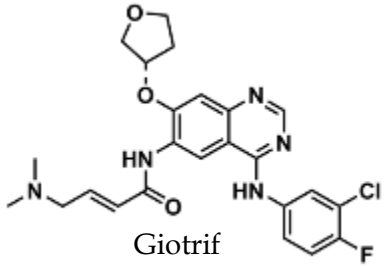


Iressa (Gefitinib)



Tarceva (Erlotinib)

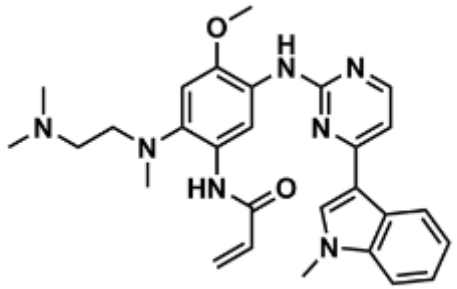
Vizimpro (Dacomitinib)



Giotrif (Afainib)

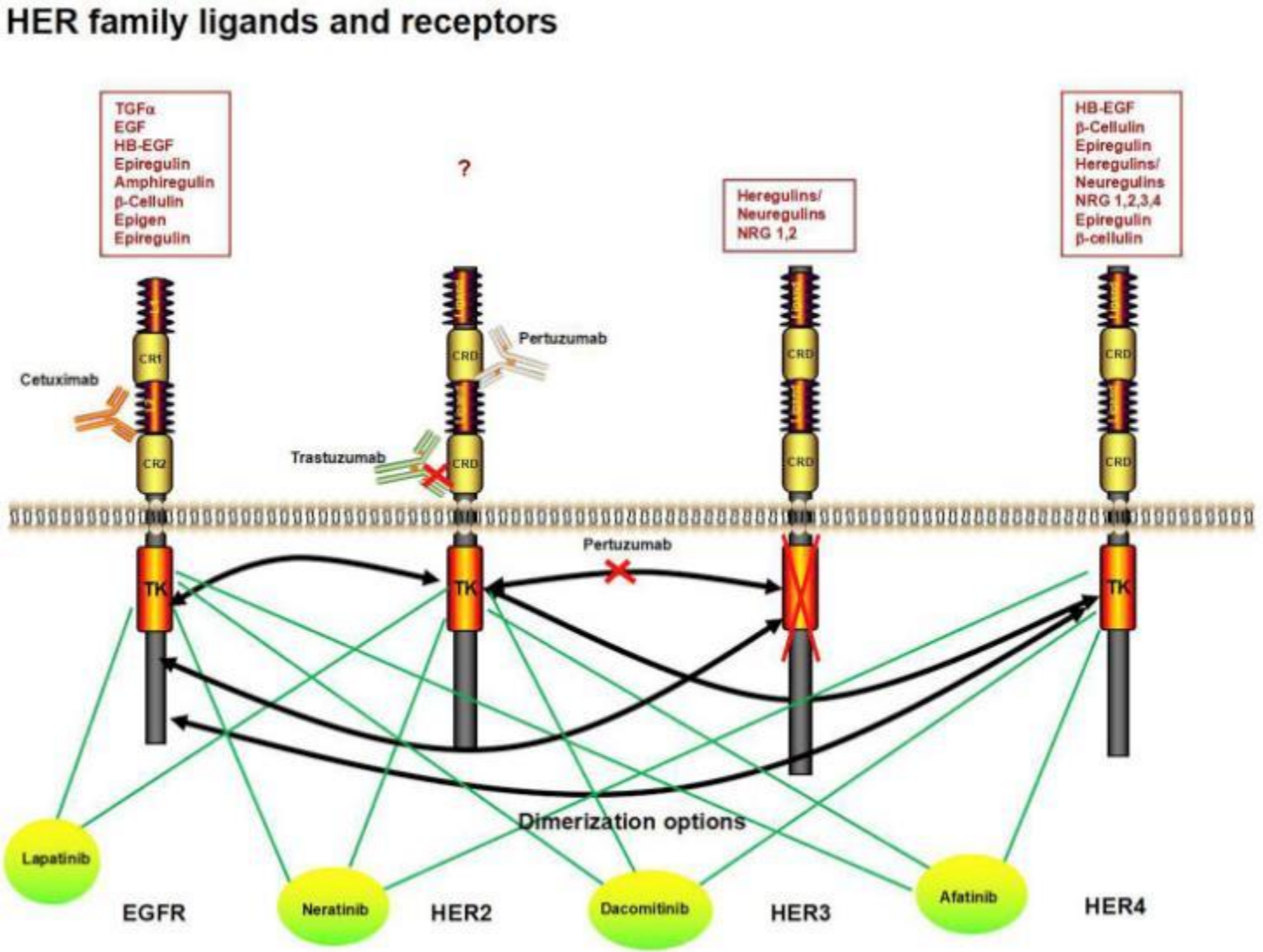
Second Generation (Irreversible)

Third Generation (Irreversible, mutant-specific)



Tagrisso (Osimertinib)

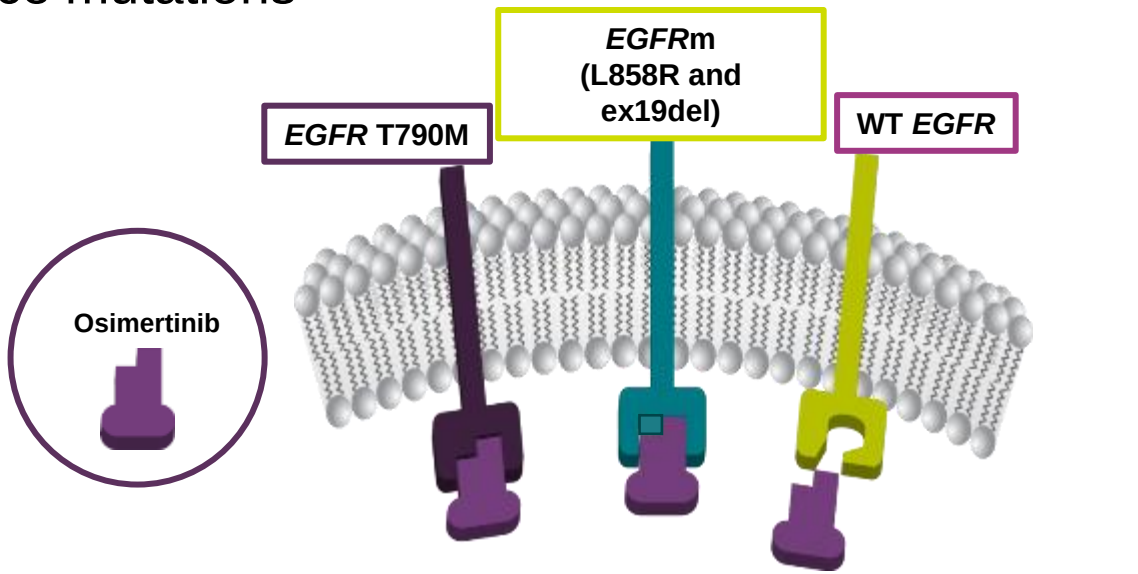
Pan-Her-targeted approach for cancer therapy



Volume 439, 28 December 2018, pages 113-130

Osimertinib: The third-generation, potent CNS active, irreversible EGFR-TKI selective for both EGFR-sensitising and EGFR T790M resistance mutations

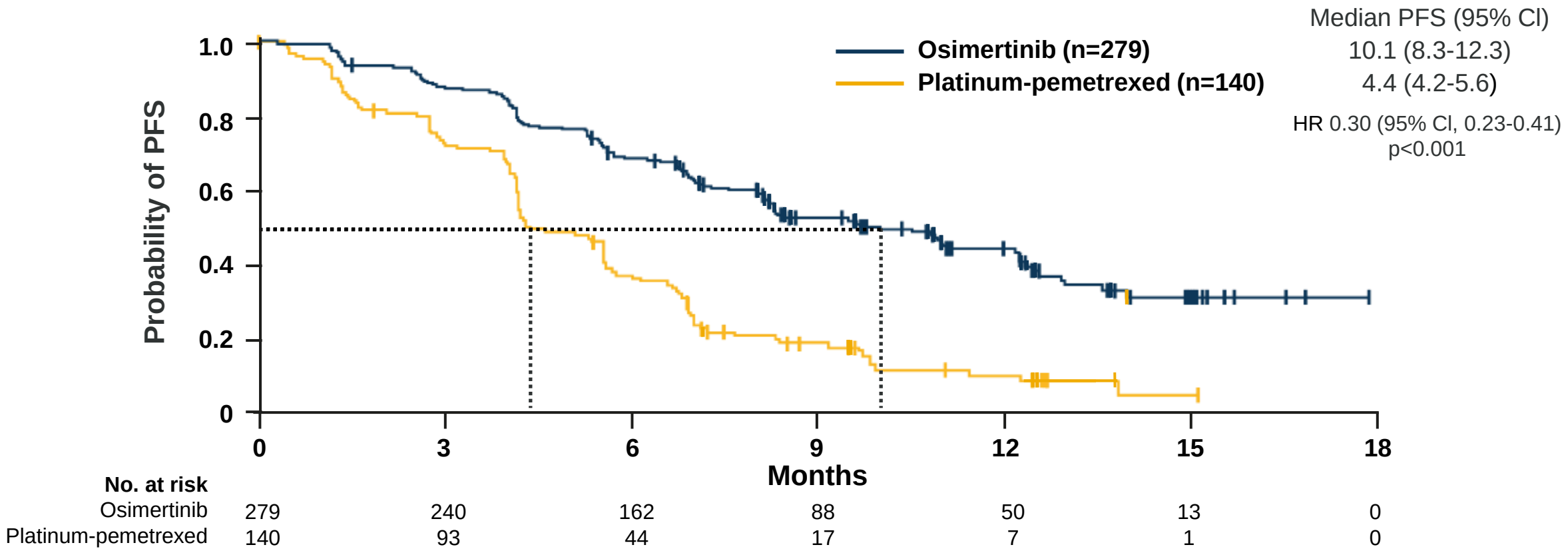
Osimertinib is selective for *EGFR*-TKI-sensitising mutations (L858R and exon 19 deletion) and T790M resistance mutations



- Inhibition of *EGFR*m (exon 19 deletion and L858R)
- Inhibition of T790M
- Lower activity against WT *EGFR*
- Crosses the intact BBB, as seen in preclinical models

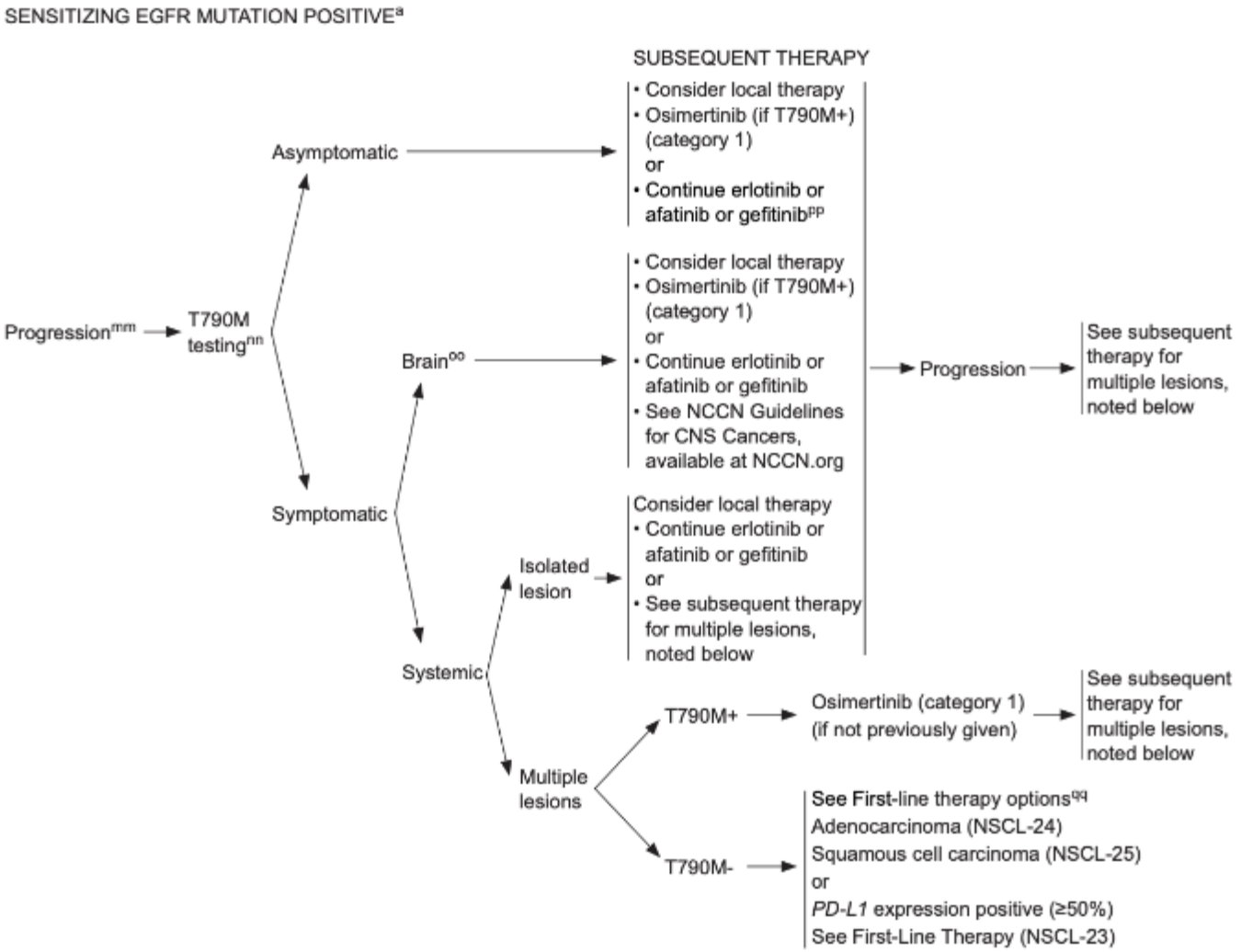
Cancer Discov. 2014;4(9):1046-1061; Clinical Cancer Res. 2016;22(20):5130-5140.

PFS in patients with EGFR T790M mutation after 1L EGFR-TKI treatment compared with platinum-pemetrexed in AURA 3

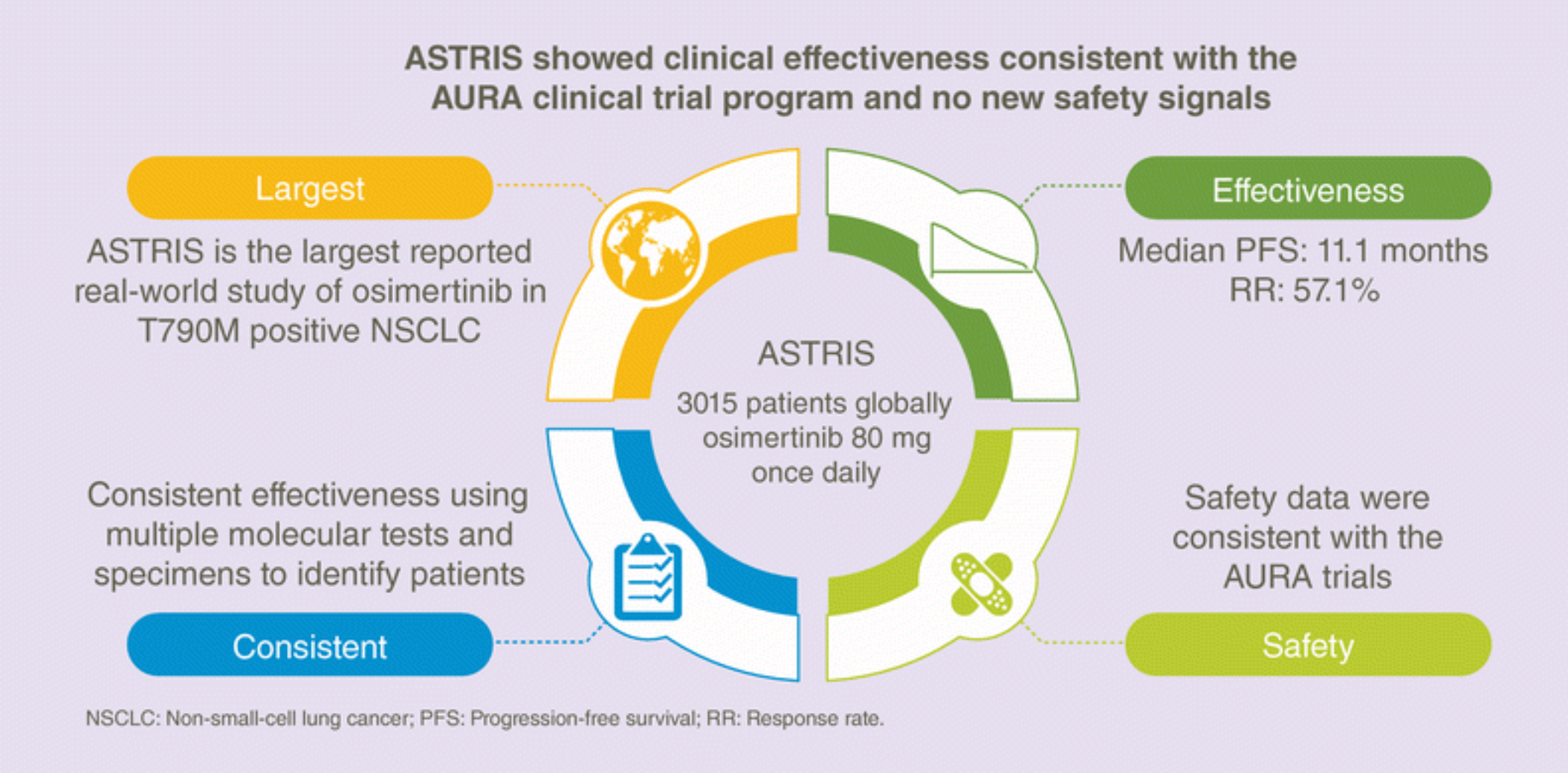


Mok TS et al. N Engl J Med. 2017;376:629-640. 2. Papadimitrakopoulou VA et al. Presented at: IASLC 17th WCLC; December 4-7, 2016; Vienna, Austria.

NCCN Guidelines Version 5. 2017
Non-Small Cell Lung Cancer



ASTRIS Study: RWE data of Tagrisso in Patient with EGFR T790M (Global, n= 3015)



Future Oncol . 2019 Sep;15(26):3003-3014.

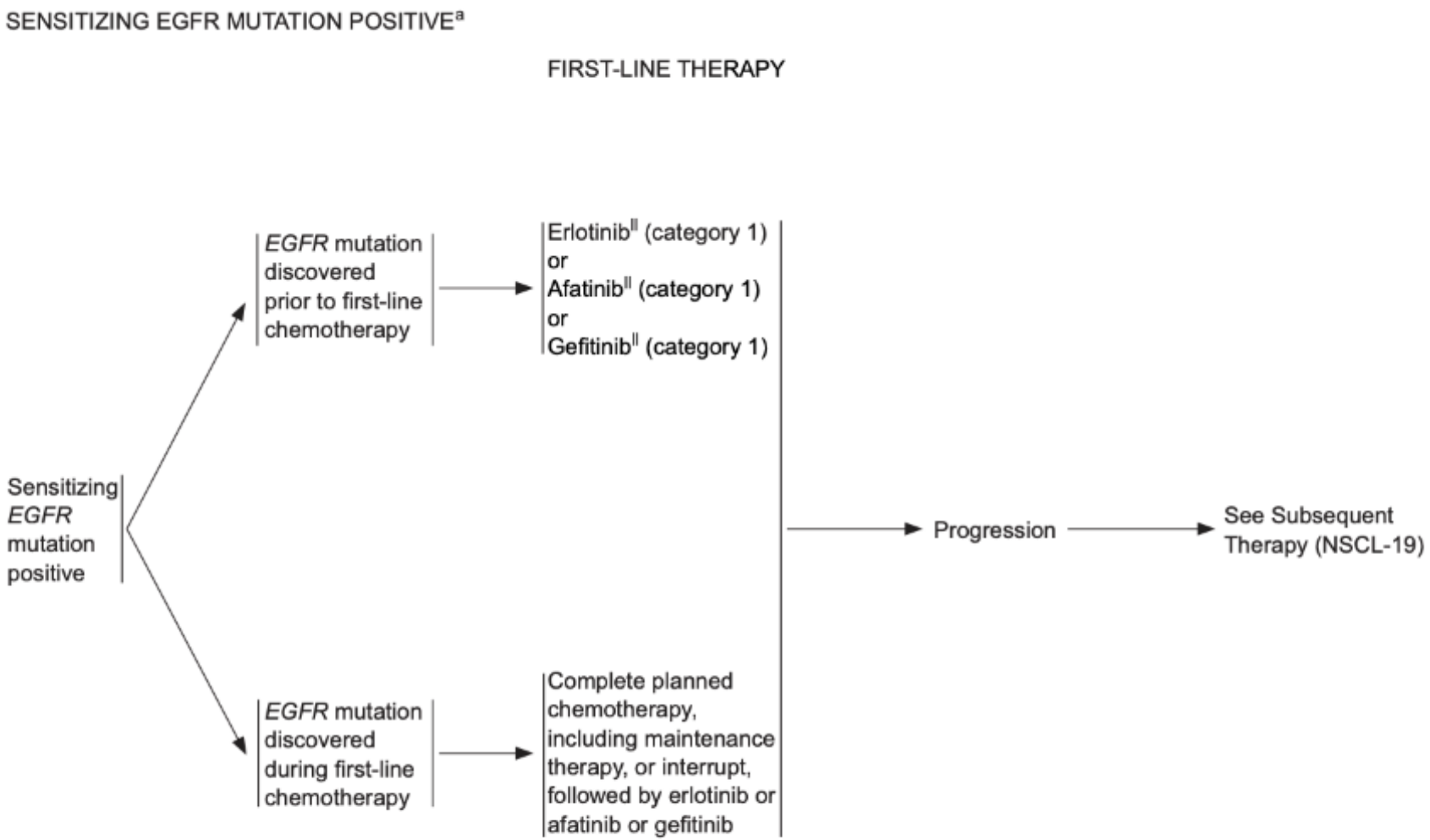
PFS in Randomized Clinical Trials of Patient harboring EGFRm in 1st line monotherapy

EGFR TKI	Study	Median PFS, mo (HR [95% CI])		
		Common mutations	Del 19	L858R
Erlotinib	ENSURE[1]	11.0 (0.34 [0.22-0.51])	11.1 (0.20 [0.11-0.37])	8.3 (0.57 [0.31-1.05])
	EURTAC[2]	9.7 (0.37 [0.25-0.54])	11.0 (0.30 [0.18-0.50])	8.4 (0.55 [0.29-1.02])
	OPTIMAL[3]	13.1 (0.16 [0.10-0.26])	15.3 (0.13 [0.07-0.25])	12.5 (0.26 [0.14-0.49])
Gefitinib	IPASS[4]	NR	11.0 (0.38 [0.26-0.56])	9.2 (0.55 [0.35-0.87])
	NEJ002[5]	10.8 (0.30 [0.22-0.41])	11.5	10.8
	WJTOG3405[6]	9.2 (0.49 [0.34-0.71])	NR (0.45 [00.27-0.77])	NR (0.51 [0.29-0.90])
Afatinib	LUX-Lung 3[7]	13.6 (0.47 [0.34-0.65])	13.7 (0.28 [0.18-0.44])	10.8 (0.73 [0.46-1.17])
	LUX-Lung 6[8]	11.0 (0.25 [0.18-0.35])	13.7 (0.20 [0.13-0.33])	9.6 (0.32 [0.19-0.52])
	LUX-Lung 7[9]	11.0 (0.73 [0.57-0.95])	12.7 (0.76 [0.55-1.06])	10.9 (0.71 [0.48-1.06])
Dacomitinib	ARCHER 1050[10]	14.7 (0.59 [0.47-0.74])	16.5 (0.55 [0.41-0.75])	12.3 (0.63 [0.44-0.88])
Osimertinib	FLAURA[11]	18.9 (0.46 [0.37-0.57])	21.4 (0.43 [0.32-0.56])	14.4 (0.51 [0.36-0.71])

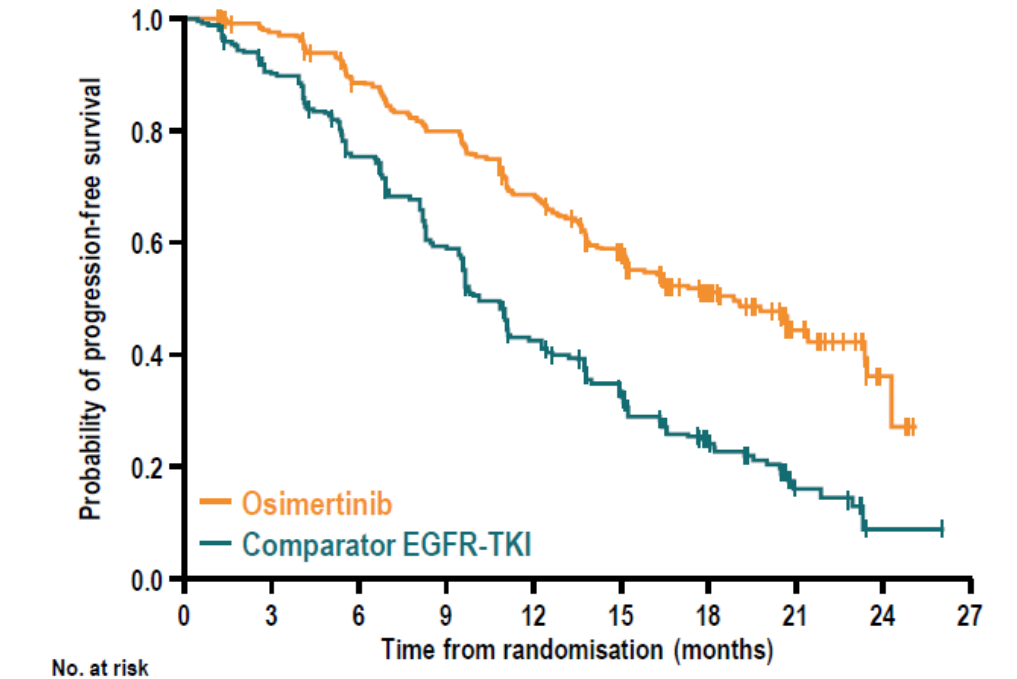
1. Ann Oncol 2015; 26:1883-9. 2. Lancet Oncol 2012; 13:239-46. 3. Lancet Oncol 2011; 12:735-42.. 4. J Clin Oncol 2011; 29: 2866-74. 5. Ann Oncol 2013; 24:54-9. 6. Lancet Oncol 2010; 11:121-8.. 7. J Clin Oncol 2013; 31:3327-34. 8. Lancet Oncol 2014; 15:213-22 9. Lancet Oncol 2016; 17:577-89. 10. Lancet Oncol 2017; 18:1454-66. 11. N Engl J Med 2018; 378:113-25.

Please note that as head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions as the study design, demographics and other criteria may be different.

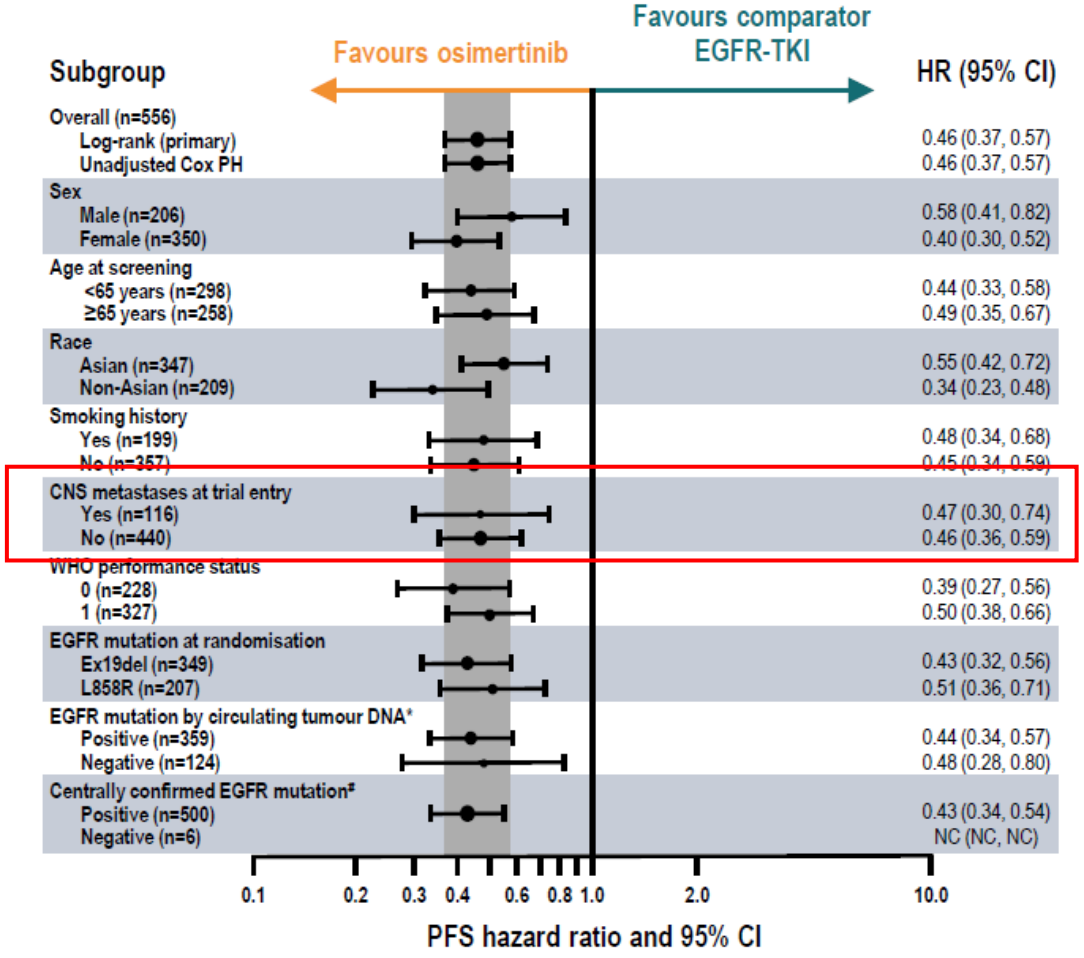
NCCN Guidelines Version 5. 2017
Non-Small Cell Lung Cancer



PFS and Subgroup Analysis in FLAURA Study



	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	18.9 (15.2, 21.4)	0.46 (0.37, 0.57); p<0.001
Comparator EGFR-TKI	10.2 (9.6, 11.1)	



Data cut-off: 12 June 2017

1. **Soria et al. N Engl J Med 2018;378:113-25**

CI, confidence interval; ctDNA, circulating tumour DNA; NC, not calculable; PH, proportional-hazards

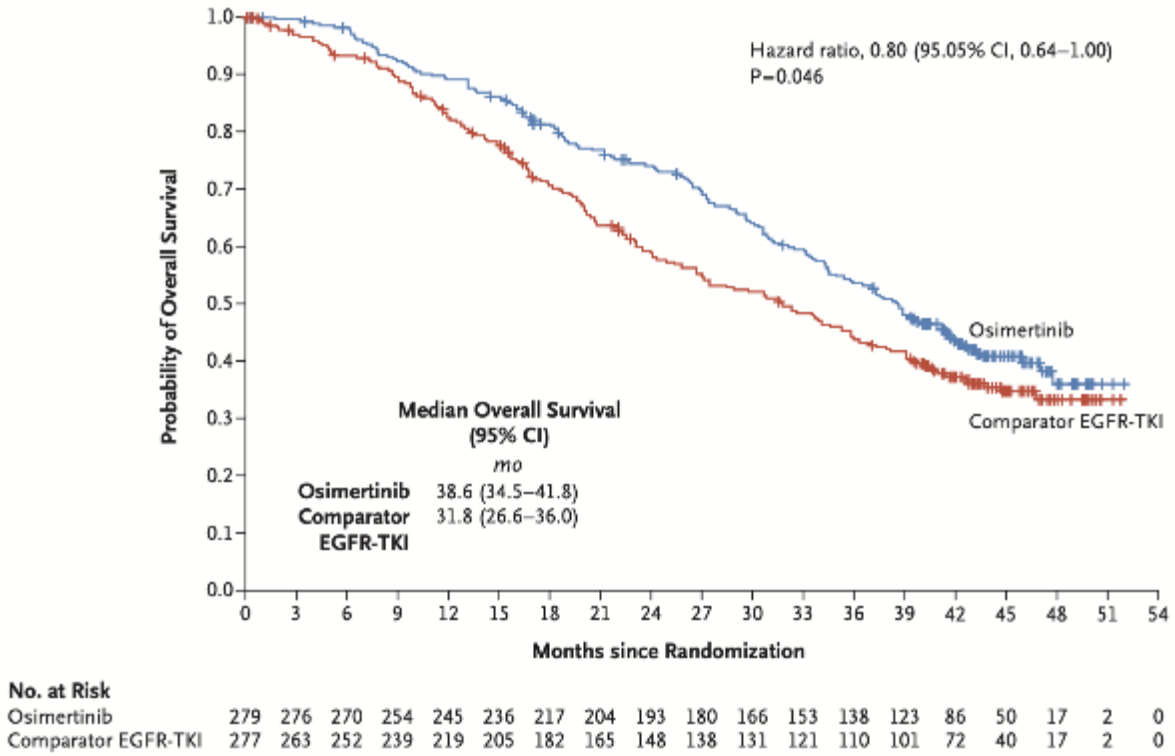
PFS in Randomized Clinical Trials of Patient harboring EGFRm in 1st line monotherapy

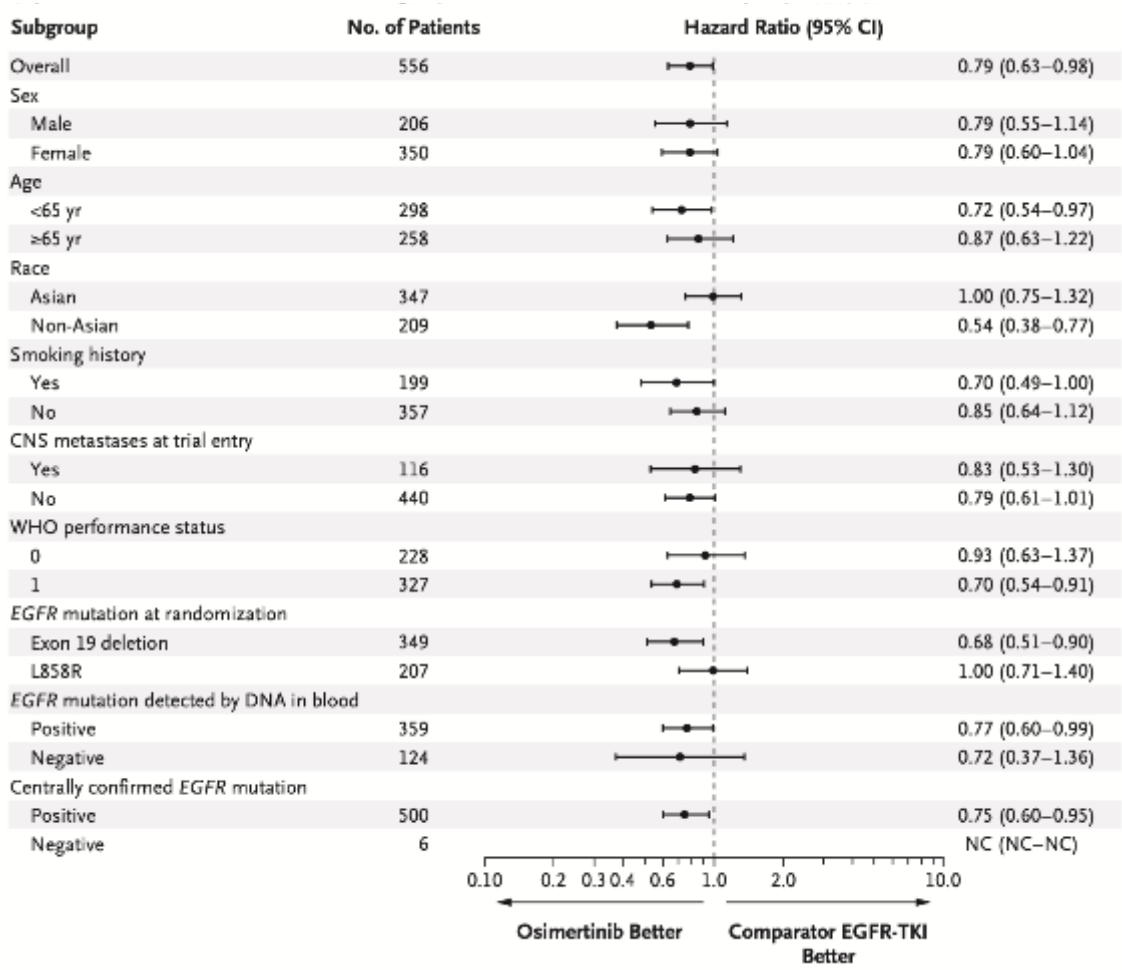
EGFR TKI	Study	Median PFS, mo (HR [95% CI])		
		Common mutations	Del 19	L858R
Erlotinib	ENSURE[1]	11.0 (0.34 [0.22-0.51])	11.1 (0.20 [0.11-0.37])	8.3 (0.57 [0.31-1.05])
	EURTAC[2]	9.7 (0.37 [0.25-0.54])	11.0 (0.30 [0.18-0.50])	8.4 (0.55 [0.29-1.02])
	OPTIMAL[3]	13.1 (0.16 [0.10-0.26])	15.3 (0.13 [0.07-0.25])	12.5 (0.26 [0.14-0.49])
Gefitinib	IPASS[4]	NR	11.0 (0.38 [0.26-0.56])	9.2 (0.55 [0.35-0.87])
	NEJ002[5]	10.8 (0.30 [0.22-0.41])	11.5	10.8
	WJTOG3405[6]	9.2 (0.49 [0.34-0.71])	NR (0.45 [00.27-0.77])	NR (0.51 [0.29-0.90])
Afatinib	LUX-Lung 3[7]	13.6 (0.47 [0.34-0.65])	13.7 (0.28 [0.18-0.44])	10.8 (0.73 [0.46-1.17])
	LUX-Lung 6[8]	11.0 (0.25 [0.18-0.35])	13.7 (0.20 [0.13-0.33])	9.6 (0.32 [0.19-0.52])
	LUX-Lung 7[9]	11.0 (0.73 [0.57-0.95])	12.7 (0.76 [0.55-1.06])	10.9 (0.71 [0.48-1.06])
Dacomitinib	ARCHER 1050[10]	14.7 (0.59 [0.47-0.74])	16.5 (0.55 [0.41-0.75])	12.3 (0.63 [0.44-0.88])
Osimertinib	FLAURA[11]	18.9 (0.46 [0.37-0.57])	21.4 (0.43 [0.32-0.56])	14.4 (0.51 [0.36-0.71])

1. Ann Oncol 2015; 26:1883-9. 2. Lancet Oncol 2012; 13:239-46. 3. Lancet Oncol 2011; 12:735-42.. 4. J Clin Oncol 2011; 29: 2866-74. 5. Ann Oncol 2013; 24:54-9. 6. Lancet Oncol 2010; 11:121-8.. 7. J Clin Oncol 2013; 31:3327-34. 8. Lancet Oncol 2014; 15:213-22 9. Lancet Oncol 2016; 17:577-89. 10. Lancet Oncol 2017; 18:1454-66. 11. N Engl J Med 2018; 378:113-25.

Please note that as head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions as the study design, demographics and other criteria may be different.

Kaplan–Meier Curve and Subgroup Analysis of Overall Survival in FLAURA





N Engl J Med . 2020 Jan 2;382(1):41-50.

OS in Randomized Clinical Trials of Patient with EGFRm in 1st line monotherapy

EGFR TKI	Study	Median OS, mo (HR [95% CI])		
		Common mutations	Del 19	L858R
Erlotinib	ENSURE[1]	26.3 (0.91 [0.63-1.31])	NR (0.79 [0.48-1.30])	NR (1.05 [0.60-1.84])
	EURTAC[2]	22.9 (0.92 [0.63-1.35])	NR (0.94 [0.57-1.54])	NR (0.99 [0.56-1.76])
	OPTIMAL[3]	22.8 (1.19 [0.83-1.71])	27.0 (1.52[0.92-2.52])	21.5 (0.92 [0.55-1.54])
Gefitinib	IPASS[4]	NR (1.00 [0.76-1.33])	27.2 (0.79 [0.54-1.15])	18.7 (1.44 [0.90-2.30])
	NEJ002[5]	27.7 (0.89 [0.63-1.24])	28.9 (0.83 [0.36-0.79])	28.0 (0.82 [0.49]1.38)
	WJTOG3405[6]	34.8 (1.25 [0.88-1.78])	35.2 (NR)	32.2 (NR)
Afatinib	LUX-Lung 3[7]	31.6 (0.78 [0.58-1.06])	33.3 (0.54 [0.36-0.79])	27.6 (1.30 [0.80-2.11])
	LUX-Lung 6[8]	23.6 (0.83 [0.62-1.09])	31.4 (0.64 [0.44-0.94])	19.6 (1.22 [0.81-1.83])
	LUX-Lung 7[9]	27.9 (0.86 [0.66-1.12])	30.7 (0.83 [0.58-0.17])	25.0 (0.91 [0.62-1.36])
Dacomitinib	ARCHER 1050[10]	34.1 (0.76 [0.58-0.99])	34.1 (0.88 [0.61-1.26])	32.5 (0.71 [0.48-1.05])
Osimertinib	FLAURA[11]	38.6 (0.8[0.64-1.00])	NR (0.68 [0.51-0.90])	NR (1.00 [0.74-1.40])

1. Ann Oncol 2015; 26:1883-9. 2. Ann Oncol 2014; 25(suppl 4):iv426- 70 (abstract 1273P). 3. Ann Oncol 2015; 26:1877-83. 4. J Clin Oncol 2011; 29: 2866-74. 5. Ann Oncol 2013; 24:54-9. 6. J Clin Oncol 2014; 32(suppl 15):abstract 8117. 7-8. Lancet Oncol 2015; 16:141-51. 9. Ann Oncol 2017; 28:270-7. 10. J Clin Oncol 2018; 36:2244-50. 11. Ann Oncol 2019; 30:v851-934.

Please note that as head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions as the study design, demographics and other criteria may be different.

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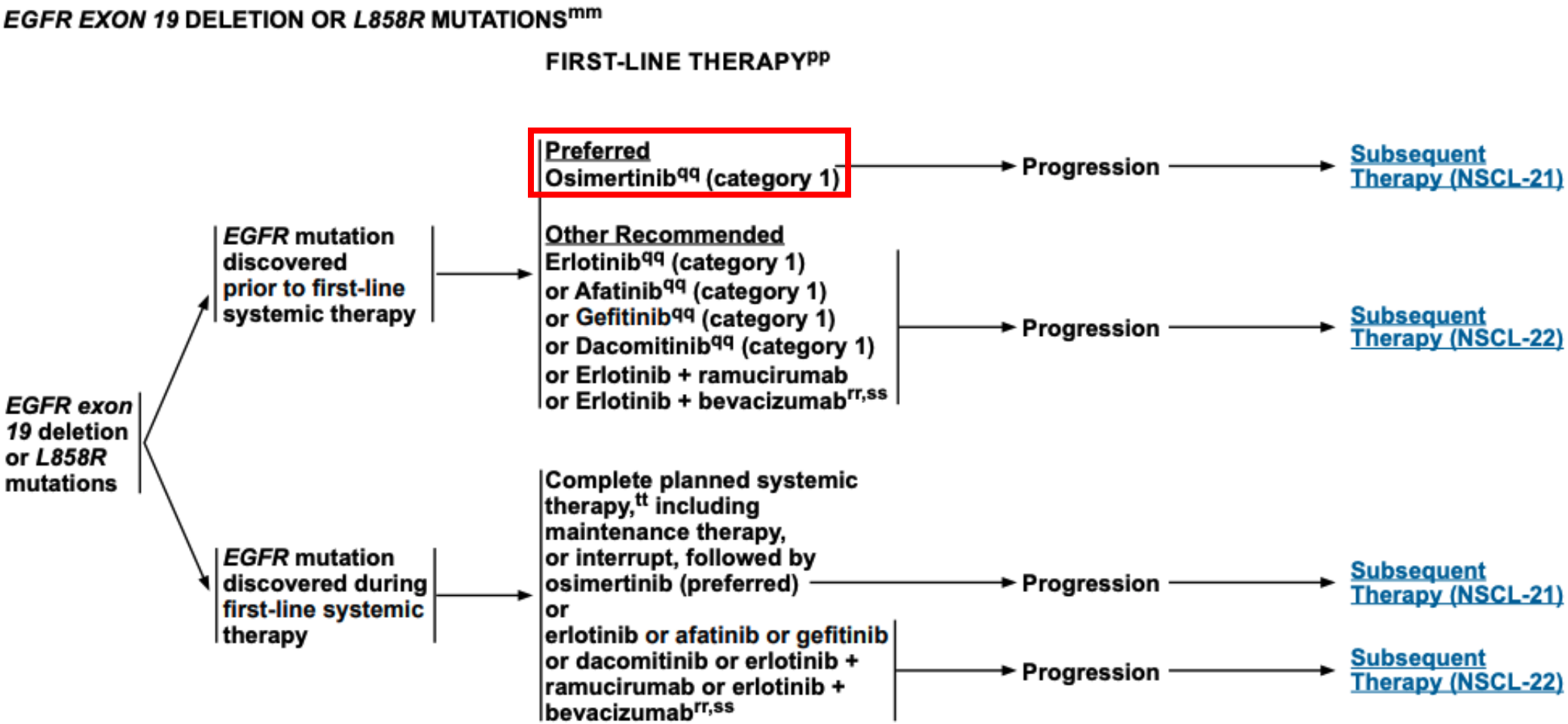
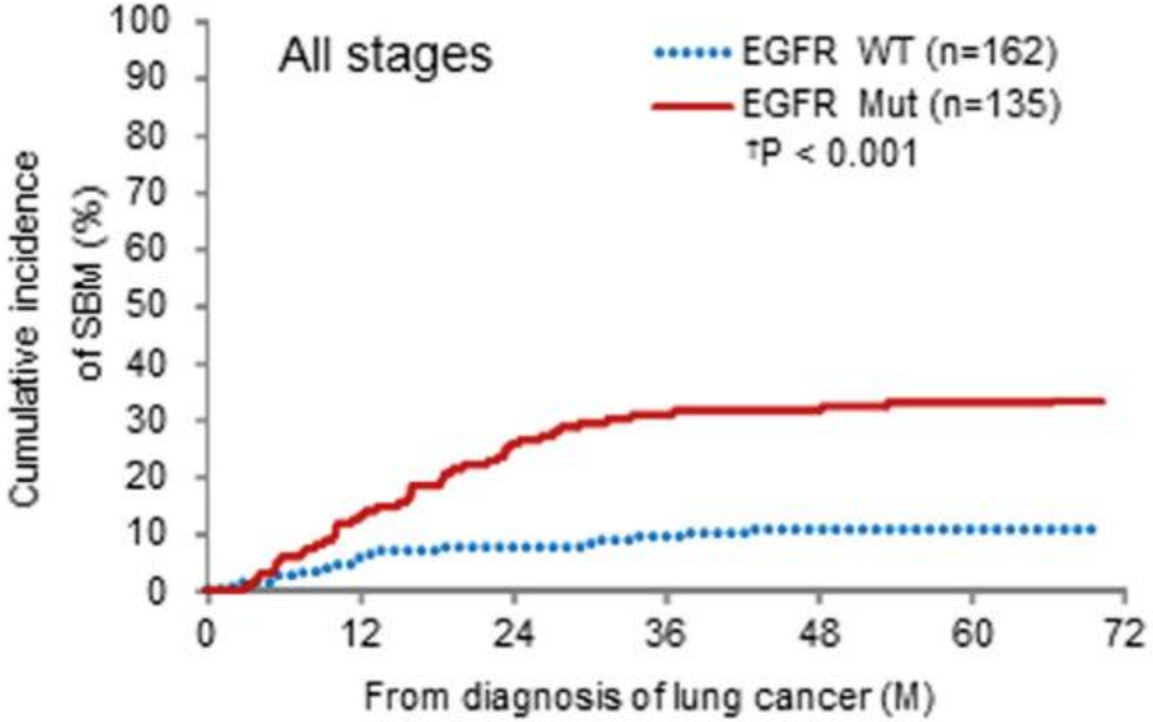
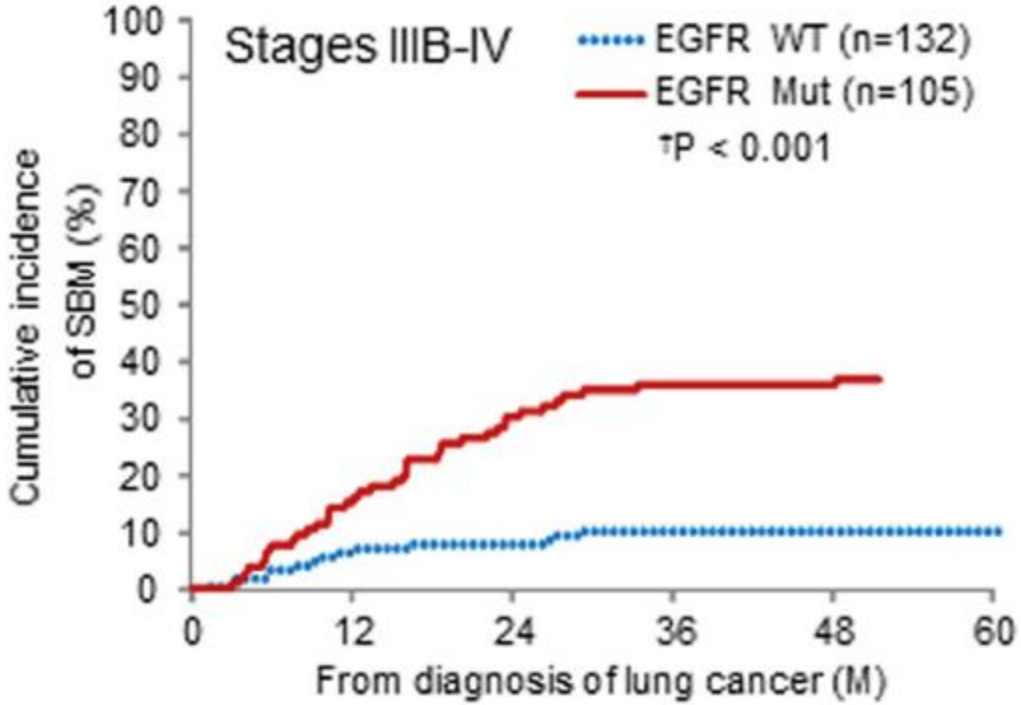
Non-Small Cell Lung Cancer



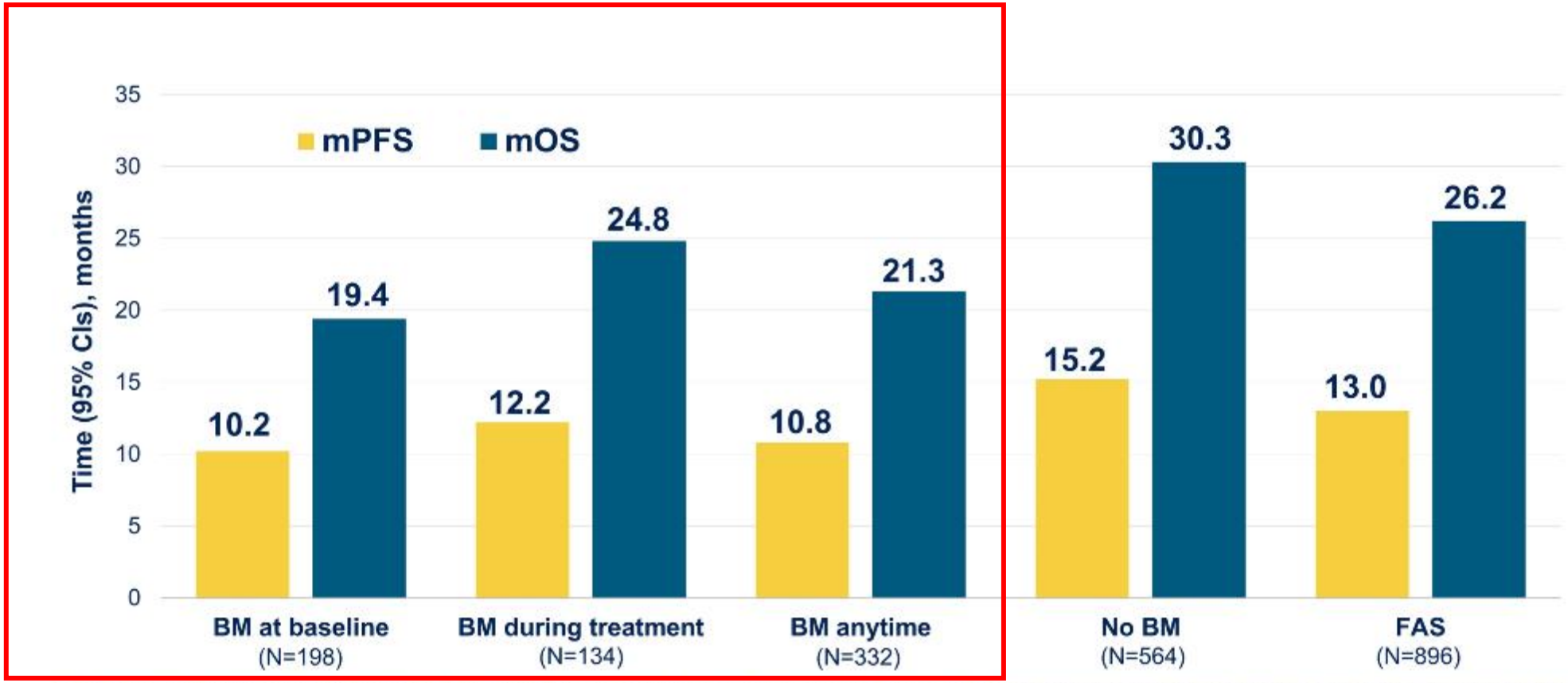
RWE of TMUH and WFH: The incidence of appearance with Brain metastases is higher in patients with EGFRm





Oncotarget. 2017 Aug 8; 8(32): 53405–53418.

REFLECT Study: Prognosis of EGFRm NSCLC patients w/ and w/o BM (n=886, Europe and Israel)

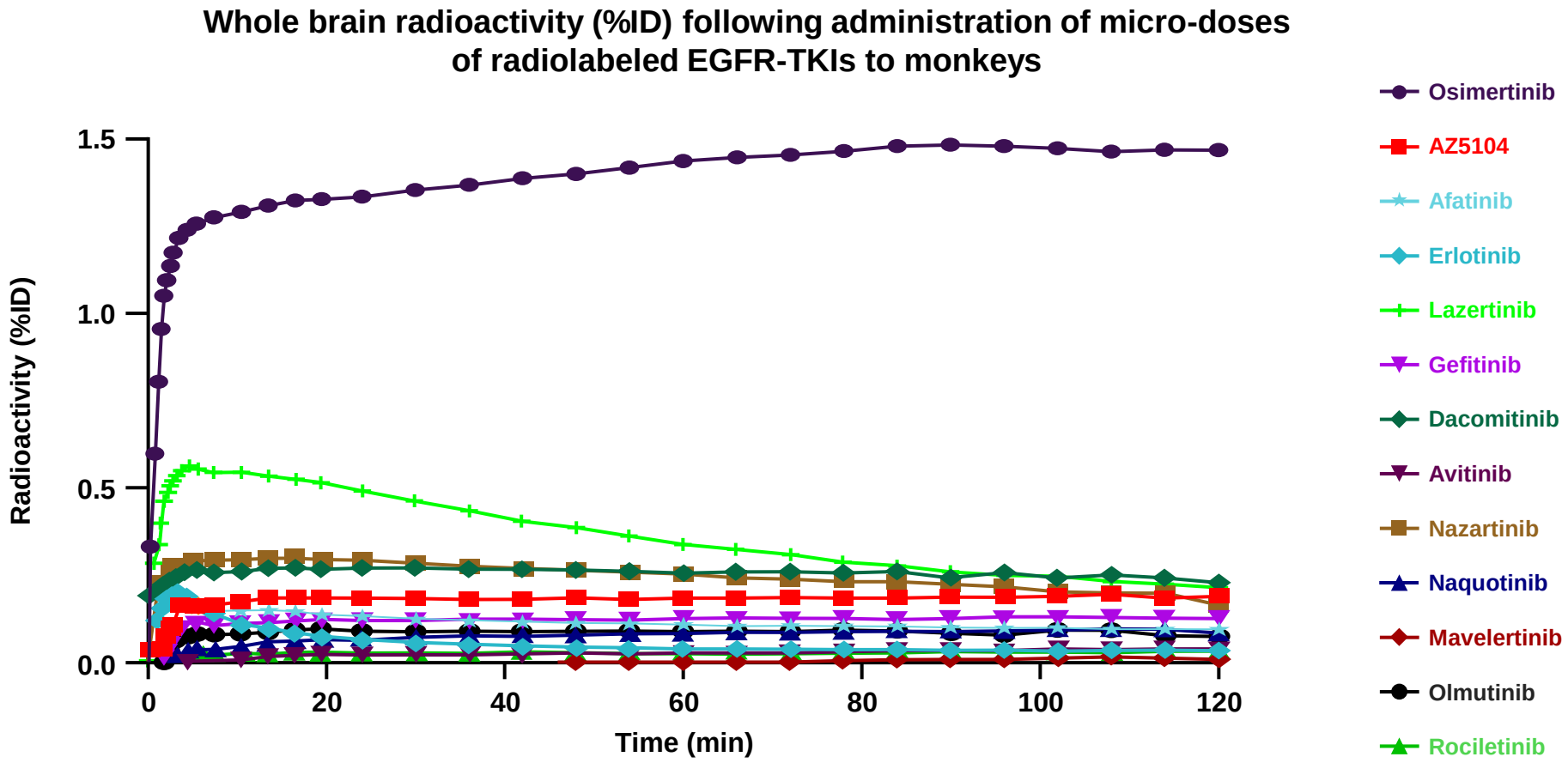


Note: In groups BM at baseline, no BM and FAS, mPFS (95% CI) was 10.2 (8.8, 11.5) months (mo), 15.2 (13.7, 16.1) mo, and 13.0 (12.3, 14.1) mo with mOS (95% CI) of 19.4 (17.1, 22.1) mo, 30.3 (27.1, 33.8) mo and 26.2 (23.6, 28.4) mo, respectively. The 95% CIs were not available for groups BM during treatment and BM anytime.

Abbreviations: BM=brain metastases, CI=confidence intervals, EGFR=epidermal growth factor receptor, FAS=full analysis set, mOS=median overall survival, mPFS=median progression free survival

Urska Janzic, 2021 ASCO #9086

Osimertinib rapidly penetrates BBB of monkeys and has the highest Cmax of 13 tested EGFR-TKIs



Cmax = maximum concentration; %ID = % injected dose

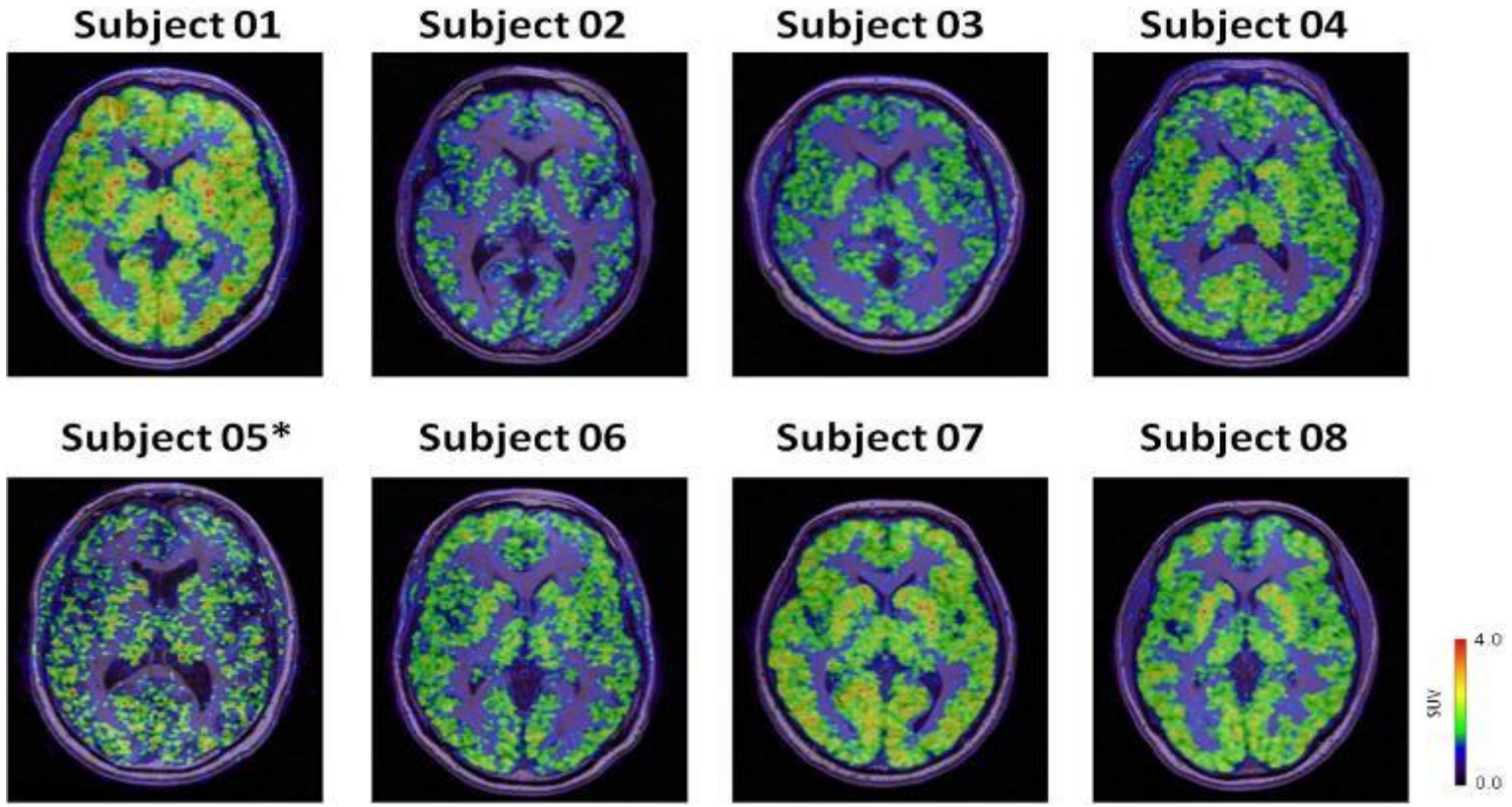
Figure adapted from Colclough N et al. Clin Cancer Res. 2020. Data corrected for radioactive decay and for radioactivity in cerebral blood.

Colclough N et al. Clin Cancer Res. 2021;27:189-201.

Osimertinib displayed high brain exposure in healthy subjects

- In all 8 healthy volunteers, Osimertinib was homogenously distributed in all regions of the brain.
- The brain distribution of osimertinib appeared to be similar to well established CNS drugs

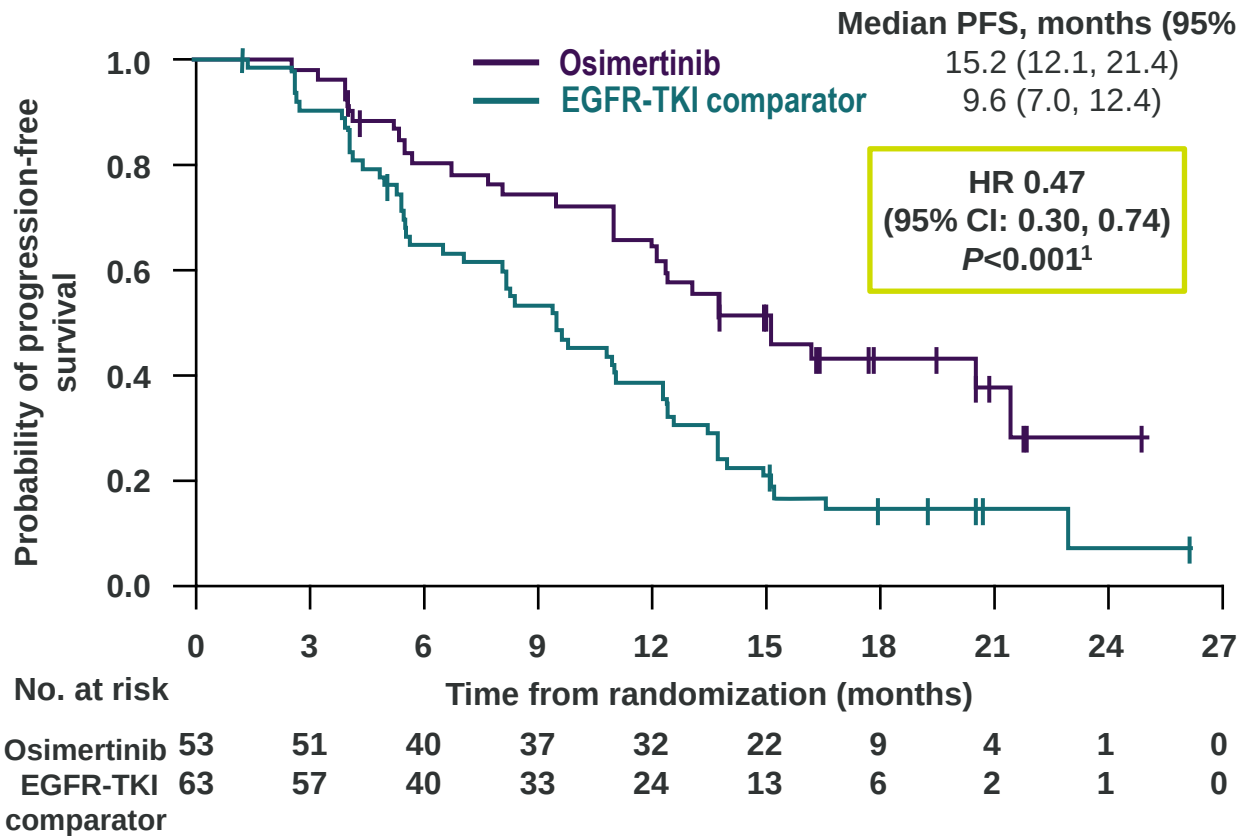
Individual regional distribution of $^{[11C]}$osimertinib



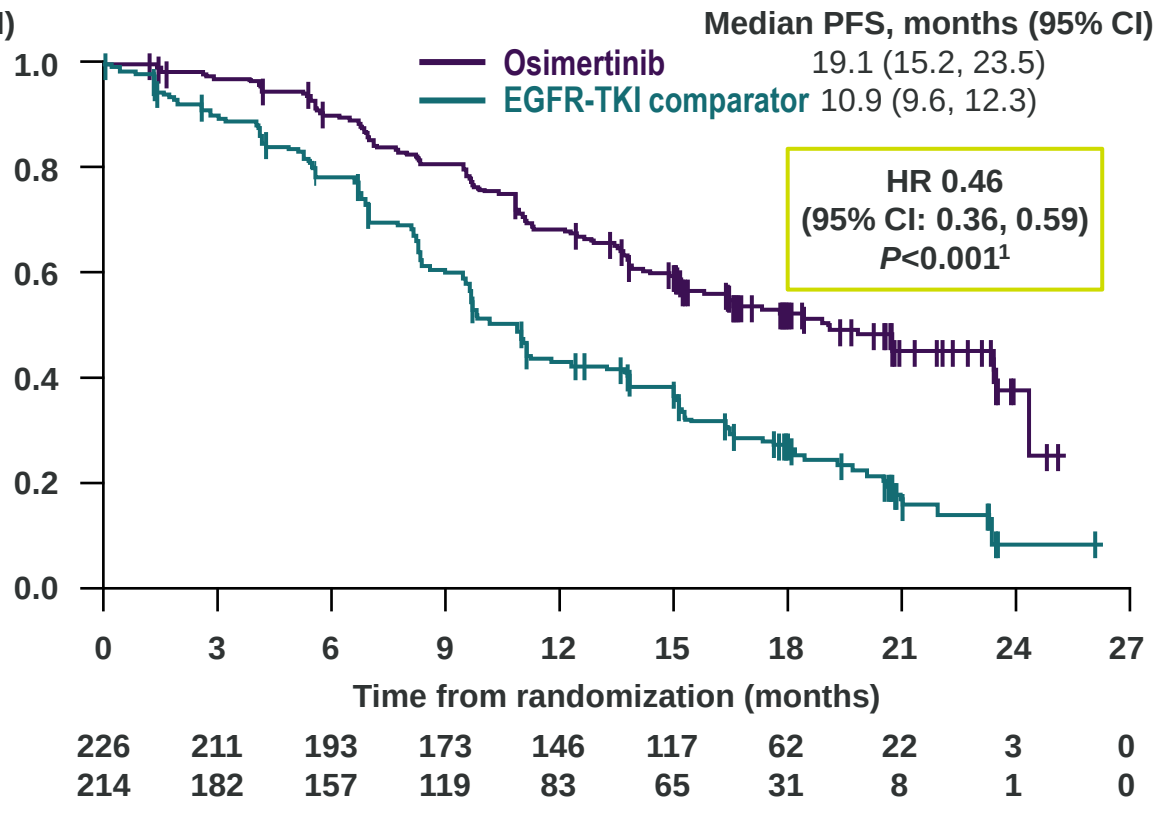
MRI = magnetic resonance imaging; PET = positron emission tomography; SUV = standardized uptake value.
Note: Radioactivity images are overlaid on MRI with horizontal sections displayed.
*Full PET data not obtained for subject 05 due to technical problems.
1. Varrone A et al. Poster presented at: AACR Annual Meeting; April 14-18, 2018; Chicago, IL. Poster CT-013. 2. Varrone A et al. J Cereb Blood Flow Metab. 2019; Apr 20 [Online ahead of print].

PFS Regardless of CNS disease status at baseline in FLAURA Study

With known or treated CNS metastases (n=116)



Without known or treated CNS metastases (n=440)



- FLAURA data cut-off: 12 June 2017. Tick marks indicate censored data.
- *By investigator assessment.

CI, confidence interval; CNS, central nervous system; EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

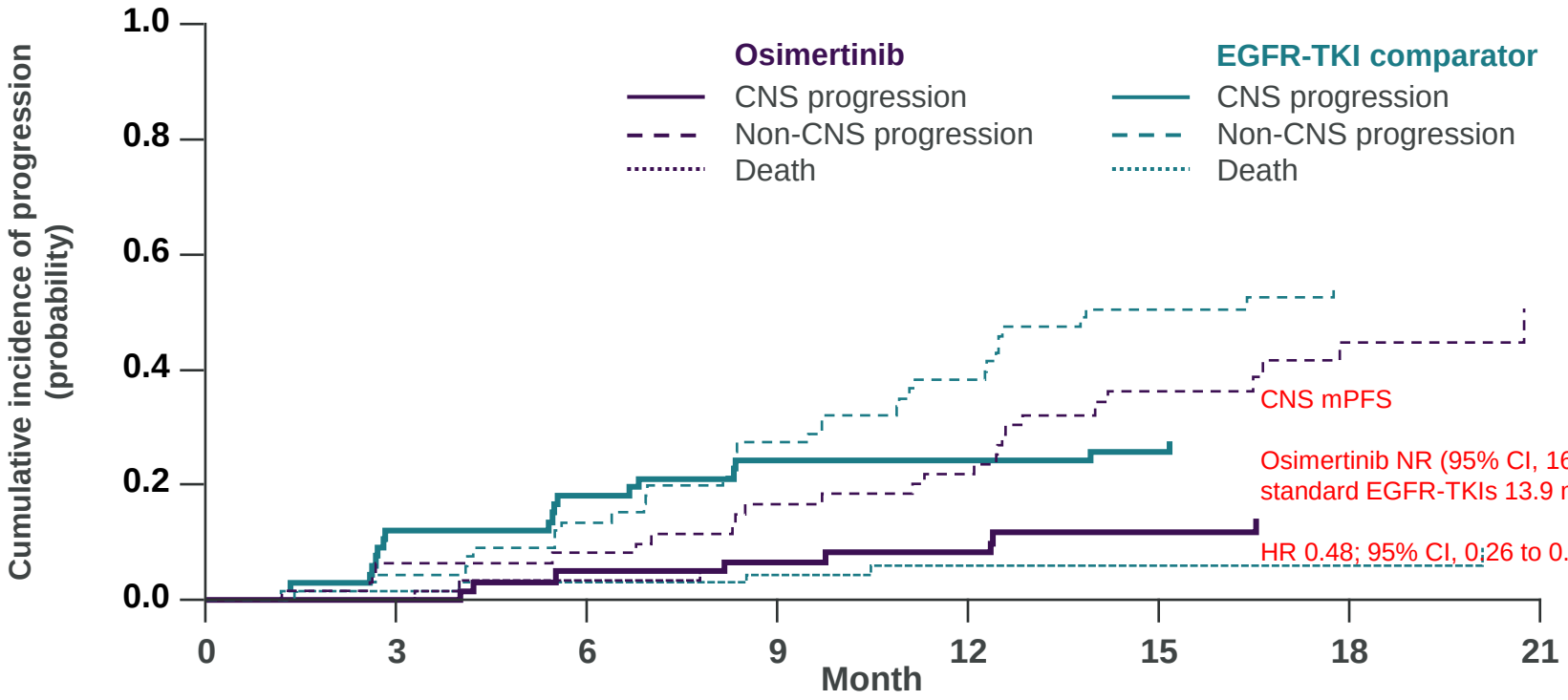
- 1. Soria JC, et al. *N Engl J Med.* 2018;378(2):113-125. 2. Ohe Y, et al. Presented at: European Society of Medical Oncology Asia Congress; 17-19 November 2017; Singapore. Abstract 413O.

The probability of patient with or without baseline BM experiencing a CNS progression in FLAURA Study

Reason for progression	Known/treated CNS metastases at trial entry		No known/treated CNS metastases at trial entry	
	Osimertinib (n=53)	Standard EGFR-TKI (n=63)	Osimertinib (n=226)	Standard EGFR-TKI (n=214)
	Number (percent)			
Total number of progression events	29 (55)	53 (84)	107 (47)	153 (71)
Number of patients with progression due to death*	4 (8)	4 (6)	7 (3)	10 (5)
Number of patients with CNS progression*	10 (19)	27 (43)	7 (3)	15 (7)
Progression in CNS only	3 (6)	10 (16)	4 (2)	12 (6)
New lesions only	3 (6)	9 (14)	4 (2)	12 (6)
Non-target lesions only	0	0	0	0
New and non-target lesions	0	1 (2)	0	0
Progression in CNS and non-CNS	7 (13)	17 (27)	3 (1)	3 (1)
New lesions only	0	0	1 (<1)	0
Non-target lesions only	4 (8)	6 (10)	0	0
New and non-target lesions	3 (6)	4 (6)	2 (1)	2 (1)
New and target lesions	0	2 (3)	0	1 (<1)
Target lesions and non-target lesions	0	1 (2)	0	0
New, target and non-target lesions	0	4 (6)	0	0
Number of patients with non-CNS progression only*	15 (28)	22 (35)	93 (41)	128 (60)

N Engl J Med . 2018 Jan 11;378(2):113-125.

The probability of patient with baseline BM experiencing a CNS progression in FLAURA Study

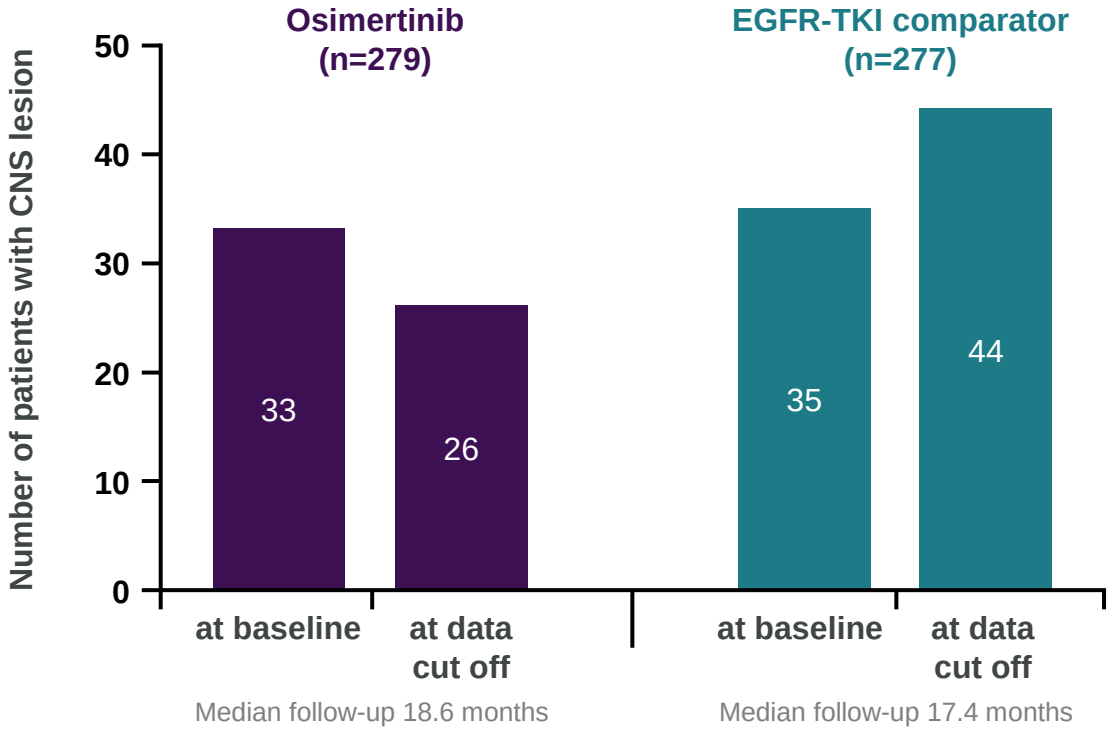


Estimated probability of CNS progression	Osimertinib (n=61)	EGFR-TKI comparator (n=67)
At 6 months	5% (95% CI 1-13)	18% (95% CI 10-28)
At 12 months	8% (95% CI 3-16)	24% (95% CI 15-35)

1. Reungwetwattana T, et al. J Clin Oncol. 2018;36:3290-3297. 2. Vansteenkiste J et al. Presented at: ESMO Asia Congress; November 17-19, 2017; Singapore.

In FLAURA, the number of patients with CNS lesions decreased with Osimertinib, but increased with 1G EGFR-TKIs

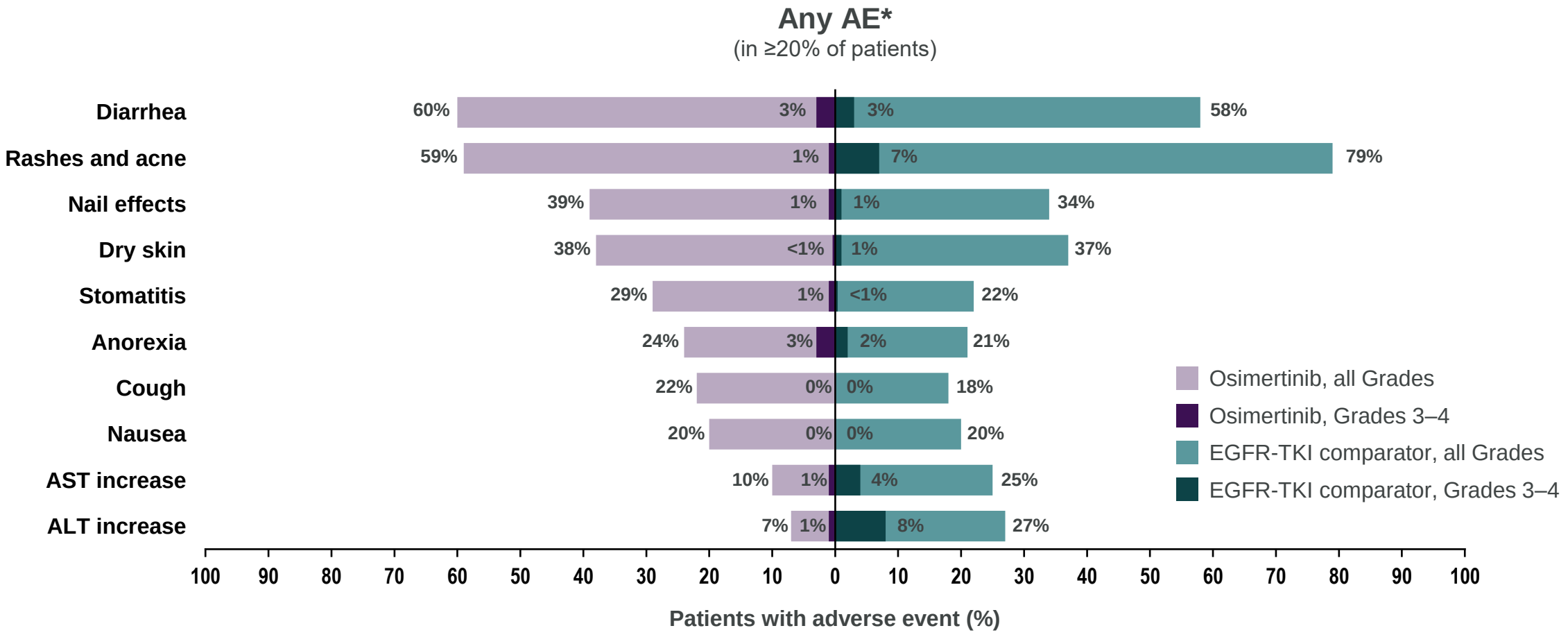
- In the osimertinib arm, 12 patients with CNS lesion at baseline had a CR; 5 patients without baseline lesion developed new CNS lesion
- In the EGFR-TKI comparator arm, 7 patients with CNS lesion at baseline had a CR; 16 patients without baseline lesion developed a new CNS lesion



Data cut-off: June 12, 2017. Figure adapted from Reungwetwattana T et al. J Clin Oncol. 2018.
CR = complete response; SD = stable disease.
Reungwetwattana T, et al. J Clin Oncol. 2018;36:3290-3297.

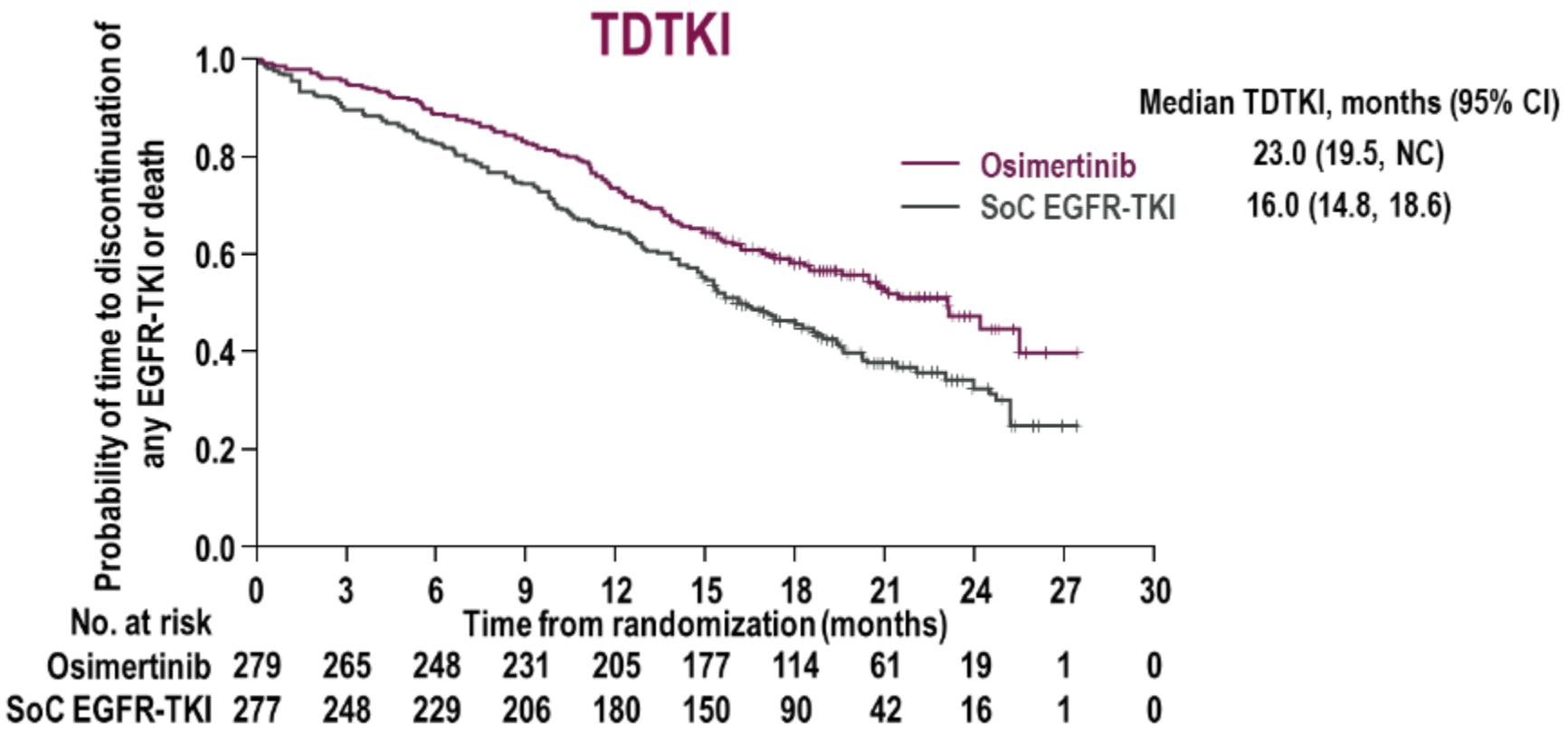
Safety Profile of FLAURA study

- Median duration of exposure: osimertinib = 20.7 months; EGFR-TKI comparator = 11.5 months
- Grade ≥3 possibly causally related AEs : Osimertinib = 18%; comparator EGFR-TKI = 29%



1. Ramalingam SS et al. Presented at: ESMO Congress; September 27-October 1, 2019; Barcelona, Spain. 2. Ramalingam SS et al. N Engl J Med. 2020;382:41-50.

Time to Discontinue TKI in FLAURA Study



1. David Planchard, et al, 2018 ESMO ASIA
2. Clin Cancer Res (2019) 25 (7): 2058–2063.

#EP08.02-108

Osimertinib long-term tolerability in patients with EGFRm NSCLC enrolled in the AURA program or FLAURA study

Marina Chiara Garassino[1], Yong He[2], Myung-Ju Ahn[3], Sergey Orlov[4], Vanessa Potter[5], Terufumi Kato[6], Janessa Laskin[7], Pei Jye Voon[8], Thanyanan Reungwetwattana[9], Suresh Ramalingam[10], Yi-Long Wu[11], Muna Albayaty[12], Sarah Cross[12], Xiangning Huang[13], Dakshayini Kulkarni[14], Byoung Chul Cho[15]

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Objective

- To report long-term safety data in patients with epidermal growth factor receptor mutant-positive (EGFRm) advanced non-small cell lung cancer (NSCLC) treated with osimertinib 80 mg once daily (QD) for ≥36 months; a post-hoc analysis of the AURA program and FLAURA trials

Conclusions

- Osimertinib was generally well tolerated in patients receiving long-term treatment of 3 years or more
- Available data are limited and should be interpreted with caution due to the constraints of post-study data collection

Plain language summary

Why did we perform this research?

- Osimertinib is a drug that blocks the activity of a protein called epidermal growth factor receptor (EGFR) on cancer cells, reducing their growth and spread
- Osimertinib is the preferred treatment for patients with non-small cell lung cancer that has a mutation in EGFR
- There is limited data available on the safety of long-term treatment with oral osimertinib. It is important to understand how well people cope with the side effects of a treatment, particularly if there is a possibility that they will be receiving it for a long time

How did we perform this research?

- We carried out an analysis to assess the long-term safety outcomes among patients who received osimertinib 80 mg once daily for at least 3 years in the:
  - FLAURA clinical trial (patients who received osimertinib as their first treatment)
  - AURA program of clinical trials (AURA, AURA2 and AURA3; patients who received osimertinib after an earlier treatment stopped working)

What were the findings of this research and what are the implications?

- The results of the analysis suggest that patients receiving osimertinib for 3 years or more are at low risk of serious side effects. However, as the data are limited, the outcomes should be interpreted with caution

Where can I access more information?

AURA: https://clinicaltrials.gov/ct2/show/NCT01802632
AURA2: https://clinicaltrials.gov/ct2/show/NCT02084261
AURA3: https://clinicaltrials.gov/ct2/show/NCT02151981
FLAURA: https://clinicaltrials.gov/ct2/show/NCT02296125

Poster
Mobile-friendly poster
Plain language summary infographic

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials. Alternatively, please click on the link below.
https://bit.ly/EP08.02-108

This study was funded by AstraZeneca
Poster presented at 2020 World Conference on Lung Cancer, August 6–9, Vienna, Austria, by Marina Chiara Garassino
Corresponding author email address: mgarassino@medicine.bsd.uchicago.edu
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Introduction

- Osimertinib is a third-generation, irreversible, oral epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that potently and selectively inhibits EGFR mutant-positive (EGFRm) and EGFR T790M resistance mutations, including central nervous system metastases[1–3]
- Osimertinib is the preferred first-line treatment in EGFRm advanced non-small cell lung cancer (NSCLC), following initial approval as a second-line treatment in EGFRm NSCLC with T790M mutations. Following the ADAURA trial (NCT02511106) it is also approved as adjuvant treatment in resectable EGFRm NSCLC[4,5]
- This post-hoc analysis of the FLAURA trial and AURA program reports, for the first time, long-term safety data in EGFRm advanced NSCLC treated with first- or second-line osimertinib 80 mg once daily (QD) for ≥36 months

Methods

- In this analysis, patients from the AURA program (AURA, NCT01802632; AURA2, NCT02084261; AURA3, NCT02151981)[6–10] who had received treatment with ≥second-line osimertinib were included, and patients from FLAURA (NCT02296125)[2] who had received first-line osimertinib. All patients received osimertinib 80 mg QD. Dose reductions or interruptions due to adverse events (AEs) were allowed unless otherwise specified
- Safety data were analysed in patients who had remained on treatment for ≥36 months
- The post-study global safety database was used to capture investigator-provided serious AEs (SAEs) in patients who continued osimertinib treatment beyond the final data cut-off of the respective trials (Fig. 1). Patients enrolled in China were excluded from post-study data, due to export limitations
- Best response data was obtained from the clinical trial databases for patients who received osimertinib for at least 54 months in FLAURA and 36 months in the AURA program. This was based on 3x the median progression-free (PFS) survival, to reflect the population likely to be receiving long term benefit (median PFS in FLAURA, 18.9 months and AURA3, 10.1 months)[2,8]
- Best response data (per response evaluation criteria in solid tumors [RECIST] v1.1) was assessed by the investigator in FLAURA and AURA3 and by blinded independent central review for AURA and AURA2

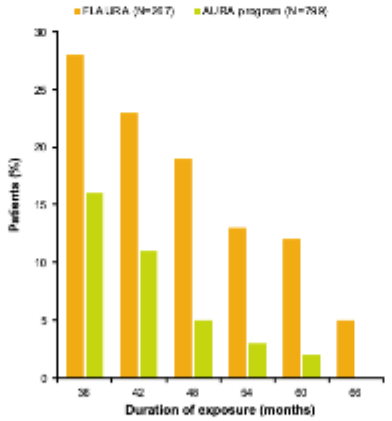
Fig 1. Osimertinib safety analysis schematic

Clinical trial cutoff for safety data was 1 April 2020. Clinical trial cutoff for response: AURA, 1 November 2016; AURA2, 1 May 2018; AURA3, 15 March 2019; FLAURA, 25 June 2019. AE, adverse event; HCP, healthcare professional; QD, once daily; SAE, serious adverse event.

Results and interpretation

- In FLAURA, 78 / 267 (28%) and 36 / 267 (13%) patients received osimertinib for ≥36 and ≥54 months, respectively (Fig. 2); median duration of exposure (range) in ≥36- and ≥54-month subgroups was 52.5 (37.4, 70.2) and 64.6 (54.5, 70.2) months, respectively
- Across AURA program, 124 / 799 (16%) patients received osimertinib for ≥36 months (AURA, n=43 / 344 [13%]; AURA2, n=35 / 210 [17%]; AURA3, n=46 / 245 [19%]) (Fig. 2); median duration of exposure (range) was 44.7 (36.0, 81.2) months
- Patient demographics and baseline disease characteristics, shown in Tables 1 & 2, were generally consistent with those in the respective overall trial populations

Fig 2. Whole population exposure duration



Safety

- In those patients who remained on osimertinib treatment for ≥36 months, any SAE was reported during the clinical trial in 17% (FLAURA) and 35% (AURA program) of patients. Treatment-related SAEs were reported in 3% (FLAURA) and 5% (AURA) of patients (Table 3)
- Data obtained from the post-trial global safety database was in line with the clinical trial data: SAEs were reported in 8 / 76 patients (11%) in FLAURA and 26 / 124 patients (21%) in the AURA program. None were deemed to be treatment related (Table 4)
- Post-trial, there were no incidences of ILD / non-infectious pneumonitis or QTc elongation

Efficacy

- The majority of patients with long-term exposure to osimertinib in the FLAURA and AURA program had a best response of partial response (Fig. 3)

Table 1. Demographics: FLAURA

Demographic characteristics	≥36 months receiving osimertinib (n=78)	≥54 months receiving osimertinib (n=36)	FLAURA overall population[2] (n=279)
Age, median (range) years	64 (39–85)	66 (42–82)	64 (26–85)
Female, n (%)	53 (65.7)	26 (72)	178 (64)
Race: White / Asian / Other, n (%)	34 (45) / 42 (55) / 0	21 (58) / 15 (42) / 0	101 (38) / 174 (63) / 4 (1)

Patients from China have been excluded from this analysis but were included in the overall population

Table 2. Demographics: AURA program

Demographic characteristics	AURA			AURA2		AURA3		AURA program
	≥36 months receiving osimertinib (n=43)	Expansion cohort[12] (n=222)	Extension cohort[13] (n=201)	≥36 months receiving osimertinib (n=35)	Overall population[11] (n=210)	≥36 months receiving osimertinib (n=46)	Overall population[9] (n=279)	≥36 months receiving osimertinib (n=124)
Age, median (range) years	63 (40–87)	60 (25–88)	62 (37–83)	68 (41–82)	64 (35–88)	65 (41–80)	62 (25–85)	65 (40–87)
Female, n (%)	29 (67)	136 (61)	133 (66)	25 (71)	145 (69)	30 (65)	172 (62)	84 (68)
Race: White / Asian / Other, n (%)	11 (26) / 32 (74) / 0	82 (37) / 134 (60) / 5 (2)*	76 (38) / 114 (57) / 9 (4)	14 (40) / 20 (57) / 1 (3)	72 (34) / 132 (63) / 6 (3)	17 (37) / 29 (63) / 0	69 (32) / 182 (65) / 8 (3)	42 (34) / 81 (65) / 1 (1)

Patients from China have been excluded from this analysis but were included in the overall population. *Missing data (n=1 (<1%))

Table 3. Safety: On-study data, AURA program (exposure duration ≥36 months) and FLAURA (exposure duration ≥36 months)

Adverse event, n (%)	FLAURA (n=76)	AURA (n=43)	AURA2 (n=35)	AURA3 (n=46)	AURA program (n=124)
Any AE	73 (96)	43 (100)	35 (100)	45 (98)	123 (99)
Any treatment-related* AE	65 (85)	41 (95)	31 (89)	41 (89)	113 (91)
Any AE ≥Grade 3	37 (38)	15 (35)	16 (46)	17 (37)	48 (39)
Any treatment-related* AE ≥Grade 3	8 (11)	6 (14)	5 (14)	5 (11)	16 (13)
Any AE resulting in death (including TRAEs)*	0	0	1 (3)	0	1 (1)
Any SAE (including outcome of death)	13 (17)	12 (28)	15 (43)	17 (37)	44 (35)
Any treatment-related* SAE (including outcome of death)	2 (3)	2 (5)	2 (6)	2 (4)	6 (5)
Any SAE leading to interruption of treatment	8 (11)	5 (12)	6 (17)	8 (17)	19 (15)
Any SAE leading to discontinuation of treatment	0	2 (5)	0	0	2 (2)

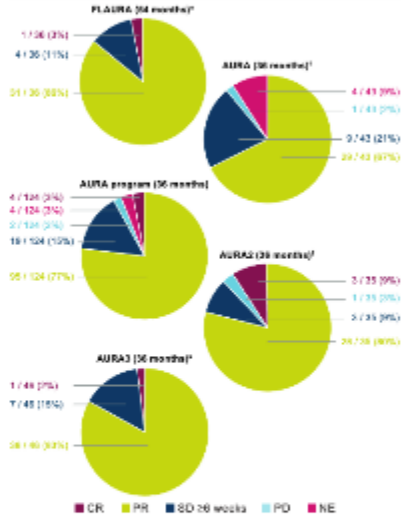
Note: Multiple SAEs may be reported for one patient. *As assessed by the investigator. AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event

Table 4. Safety: Post-study data, AURA program (exposure duration ≥36 months) and FLAURA (exposure duration ≥36 months)

Adverse event, n (%)	FLAURA (n=76)	AURA program (n=124)
Any SAEs (including outcome of death)	8 (11)	26 (21)
Any treatment-related SAEs (including outcome of death)*	0	0
Any SAEs leading to interruption of treatment	3 (4)[†]	8 (6)[‡]
Any SAEs leading to discontinuation of treatment	0	3 (2)[§]

Note: Post-clinical trial, action taken with drug and outcome are not always reported. Action taken in two SAEs is unknown. *As assessed by the investigator. [†]Duodenal ulcer perforation (n=1), sepsis (n=1) and intestinal obstruction (n=1). [‡]Pancreatitis acute / pancreatitis (n=1), impaired healing (n=1), pneumonia (n=2), arrhythmia (n=1), lower respiratory tract infection (n=1) and gastroenteritis (n=1). [§]Chronic myelomonocytic leukaemia (n=1) and cardiac arrest (n=2). SAE, serious adverse event

Fig 3. Best response on clinical trial



†Assessed by investigator; ‡Assessed by BICR
PFS, CR and SD (respectively), from the clinical trials[2,6,7,9,10]: AURA, 51%, <1%, 33%; AURA2, 57%, 3%, 31%; AURA3, 89%, 1%, 20%; FLAURA, 72%, 3%, 17%
BICR, blinded independent central review; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Limitations and considerations

- Data included in the post-study global safety database comprised reports of SAEs that were provided voluntarily by treating physicians; there may be missing data that were not reported
- Dose interruptions and discontinuations were likely due to allowing recovery of patient, as all SAEs reported were considered unrelated to osimertinib by the investigator
- Patients who remained on treatment long-term appear to have tolerated it well

Acknowledgements

Thanks to all the patients and their families.

AURA (NCT01802632), AURA2 (NCT02084261), AURA3 (NCT02151981) and FLAURA (NCT02296125) were funded by AstraZeneca, the manufacturer of osimertinib.

The authors also wish to acknowledge Emmeline Tynan, PhD, of Ashfield MedComms, an Inizio company, for medical writing support that was funded by AstraZeneca in accordance with Good Publication Practice (GPP3) guidelines (https://bit.ly/GPP3).

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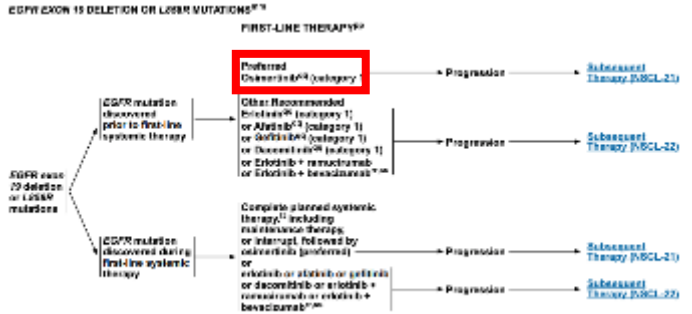
Safety Profile of Long-term exposure to Osimertinib

Table 3. Safety: On-study data, AURA program (exposure duration ≥36 months) and FLAURA (exposure duration ≥36 months)					
Adverse event, n (%)	**FLAURA (n=76)**	**AURA (n=43)**	**AURA2 (n=35)**	**AURA3 (n=46)**	**AURA program (n=124)**
Any AE	73 (96)	43 (100)	35 (100)	45 (98)	123 (99)
Any treatment-related* AE	68 (89)	41 (95)	31 (89)	41 (89)	113 (91)
Any AE ≥Grade 3	27 (36)	15 (35)	16 (46)	17 (37)	48 (39)
Any treatment-related* AE ≥Grade 3	8 (11)	6 (14)	5 (14)	5 (11)	16 (13)
Any AE resulting in death (including TRAEs)*	0	0	1 (3)	0	1 (1)
Any SAE (including outcome of death)	13 (17)	12 (28)	15 (43)	17 (37)	44 (35)
Any treatment-related* SAE (including outcome of death)	2 (3)	2 (5)	2 (6)	2 (4)	6 (5)
Any SAE leading to interruption of treatment	8 (11)	5 (12)	6 (17)	8 (17)	19 (15)
Any SAE leading to discontinuation of treatment	0	2 (5)	0	0	2 (2)

Note: Multiple SAEs may be reported for one patient. *As assessed by the investigator. AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event

Marina Chiara Garassino et al., WCLC 2022, #EP08.02-108

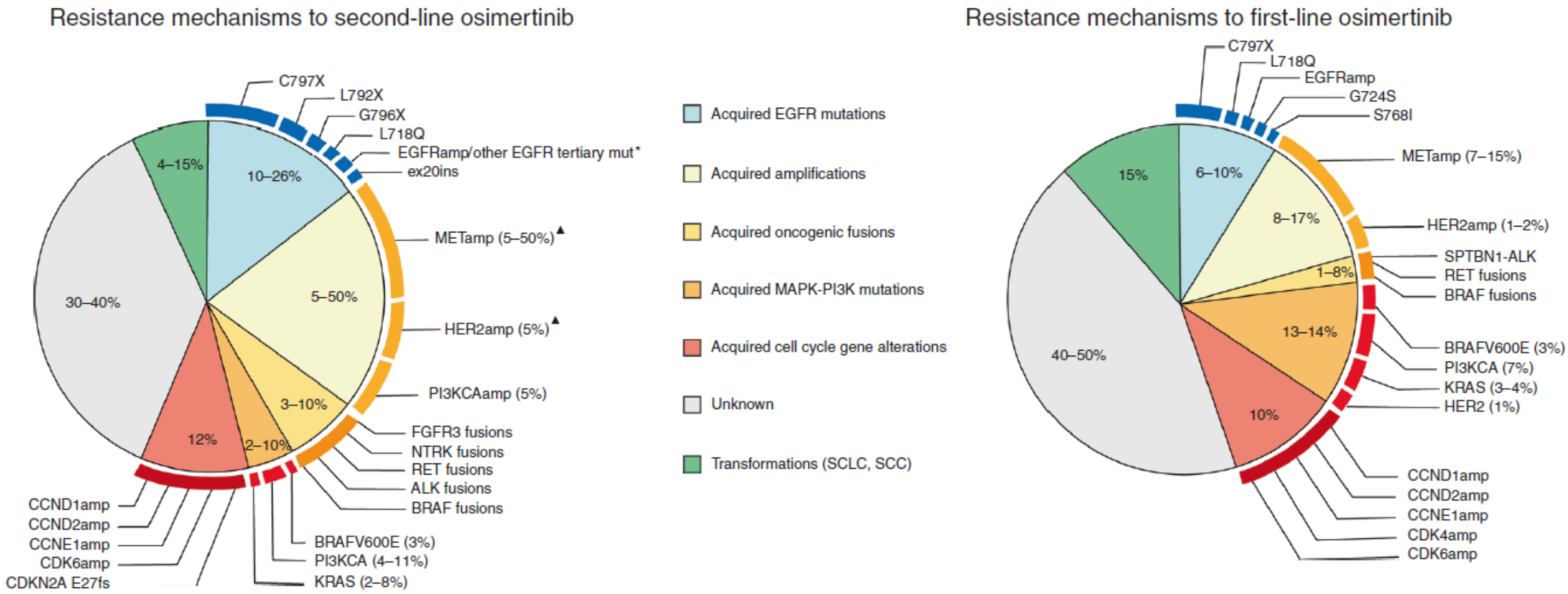
Take Home Message



- **EGFR-TKIs** are currently standard of care for metastases EGFRm patient.
- **Osimertinib** becomes a **new standard in front line** for patient with common mutation.
- Osimertinib demonstrated greater **BBB penetration** and fewer intra-cranial progressed.
- **Adverse event** with long-term exposure to Osimertinib seems **mild and manageable**. The percentage of interruption treatment due to SAE in 1st line is 11%, and the discontinuation rate is 0%. (As the latest publication in WCLC 22')

Thanks for your attention

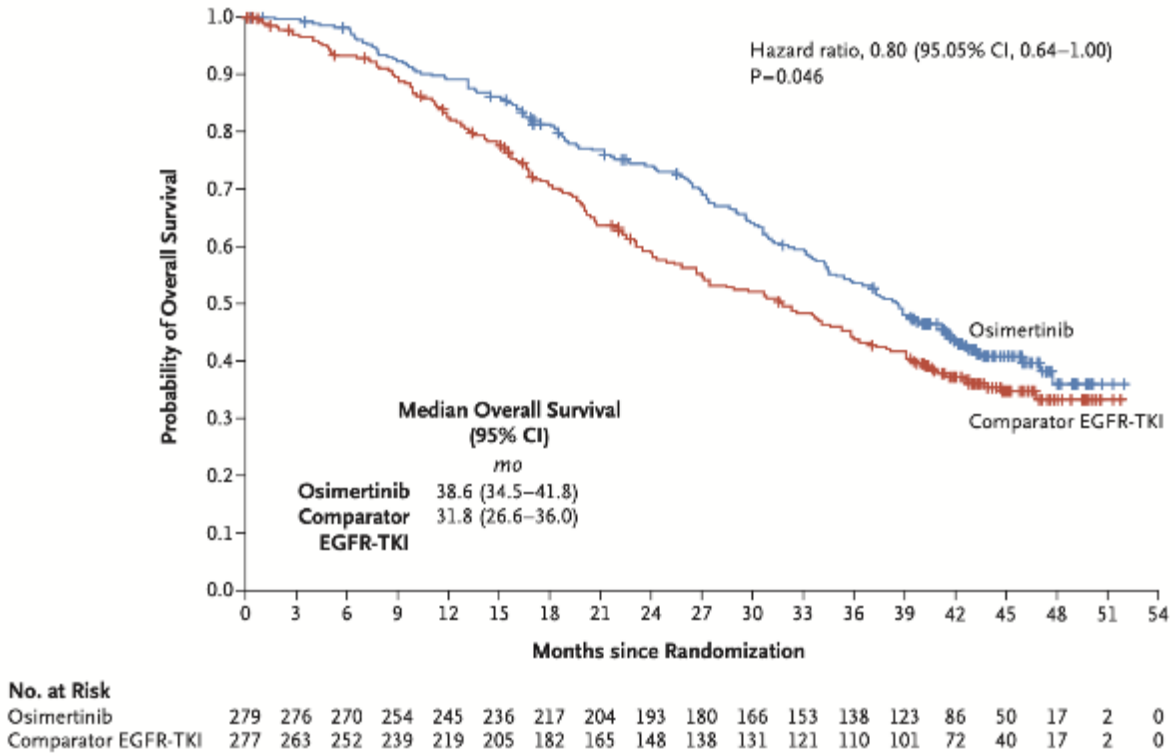
Different resistance profile in 2L and 1L osimertinib treatment

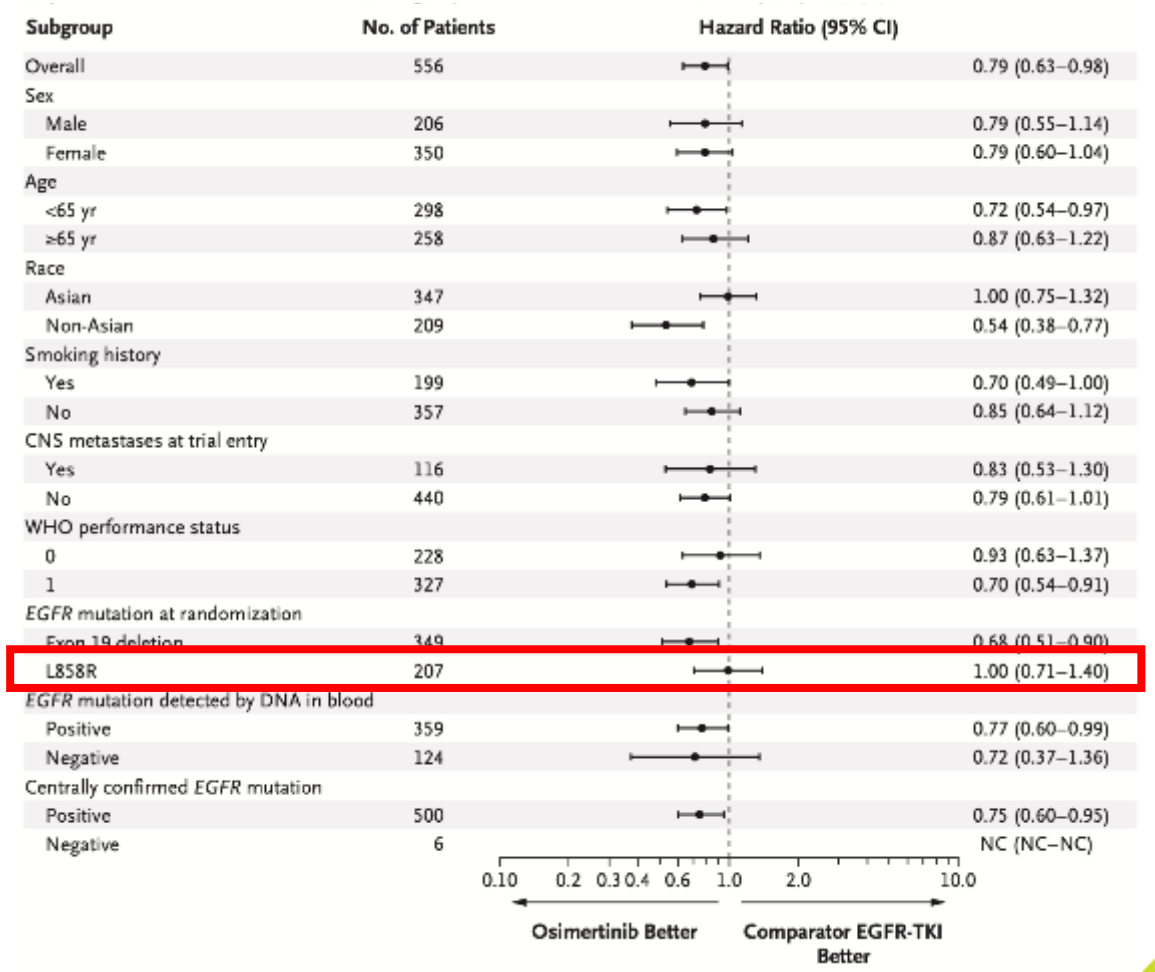


* Other EGFR tertiary mutations include G719X, G724S AND S768I
▲Mutations have also been reported

Leonetti et al. British Journal of Cancer 2019; 121: 725

Kaplan–Meier Curve and Subgroup Analysis of Overall Survival in FLAURA Study



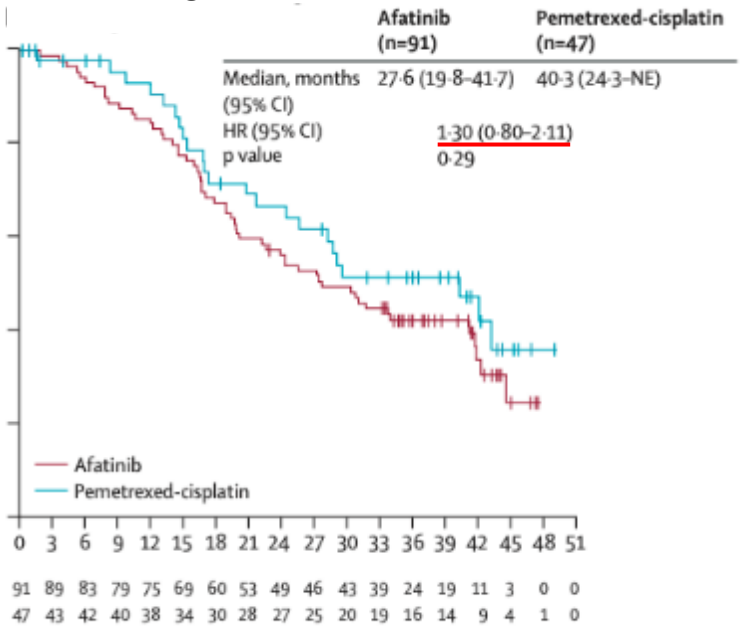


N Engl J Med . 2020 Jan 2;382(1):41-50.

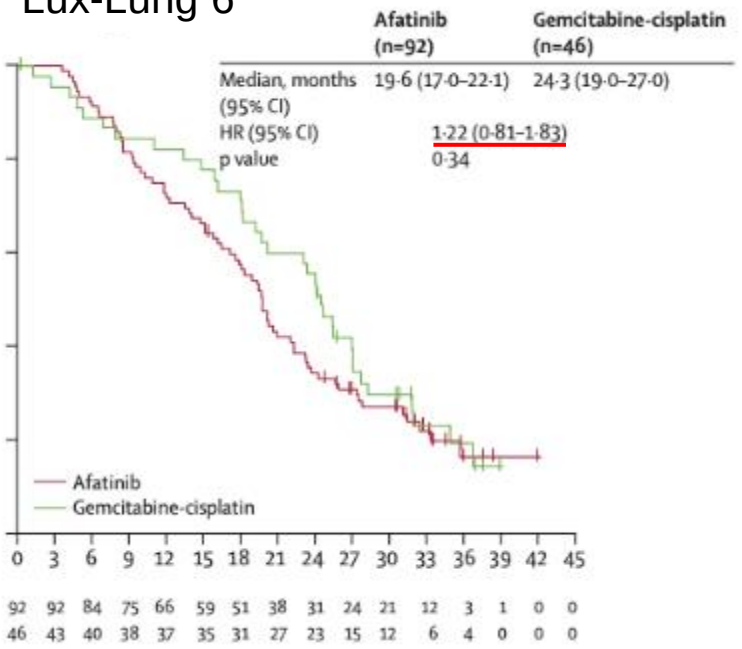
Overall Survival of Patients harboring L858R in LUX-LUNG 3 and 6 Study

Disease with L858R doesn‘t demonstrate OS benefit in Lux-Lung 3 and 6 study.

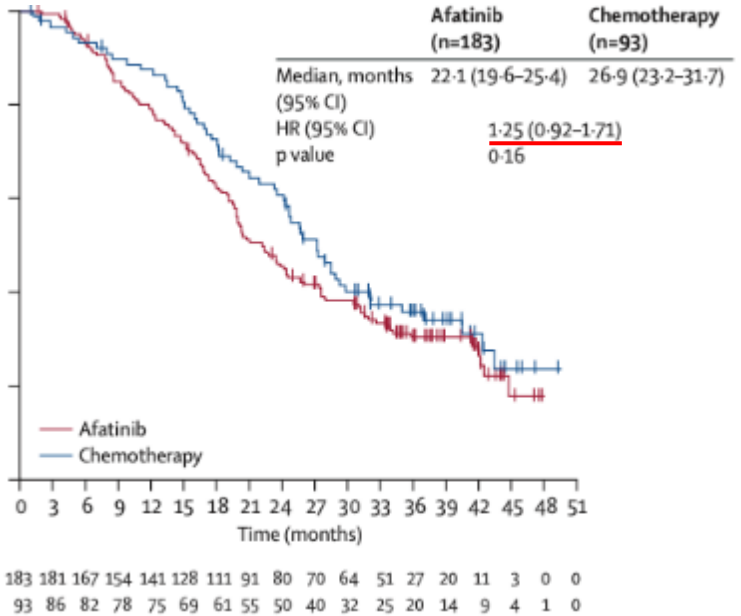
Lux-Lung 3



Lux-Lung 6



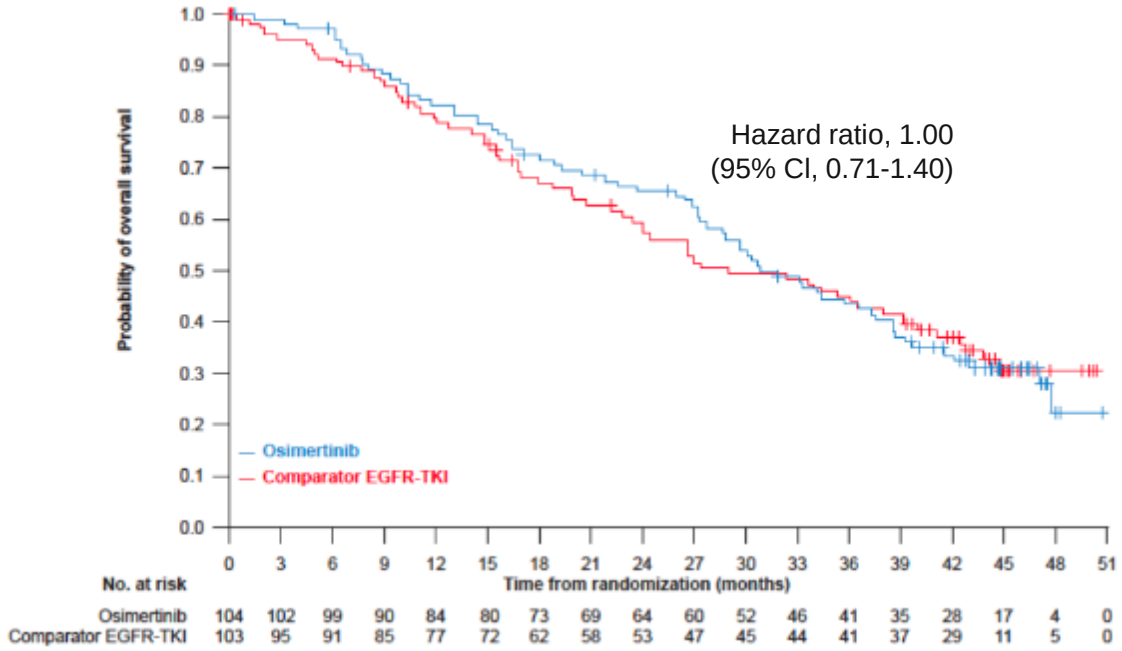
Combined Analysis



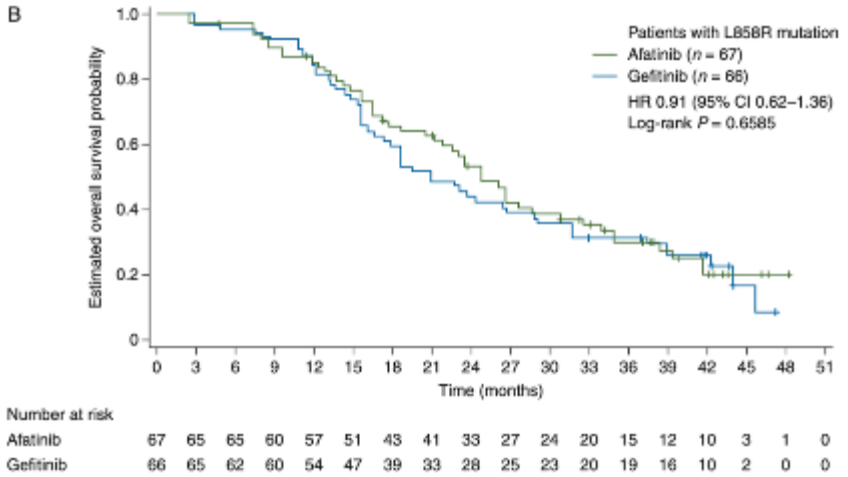
Lancet Oncol . 2015 Feb;16(2):141-51.

Overall Survival with L858R Patients in Three Different Head-to-head Study

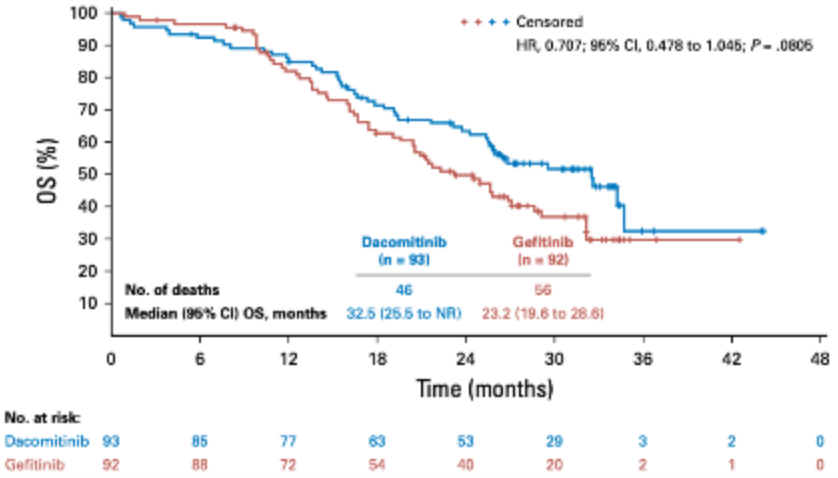
FLAURA[1]



LUX-Lung 7[2]



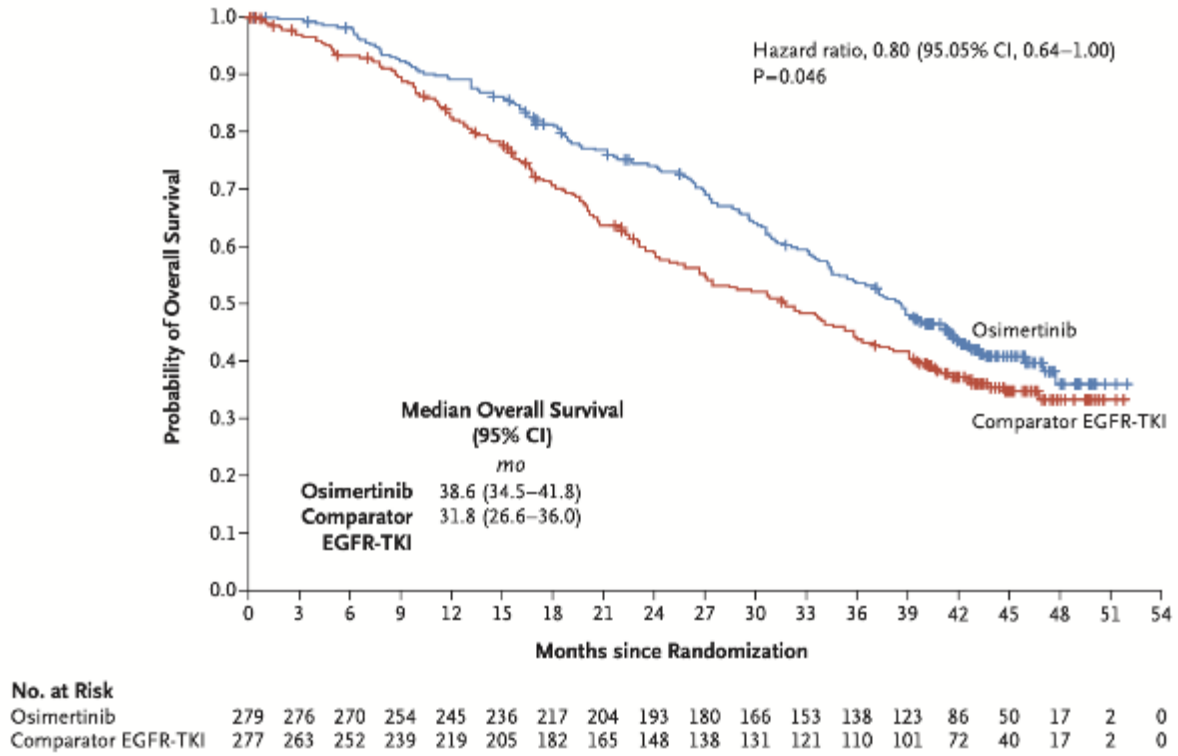
ARCHER 1050[3]

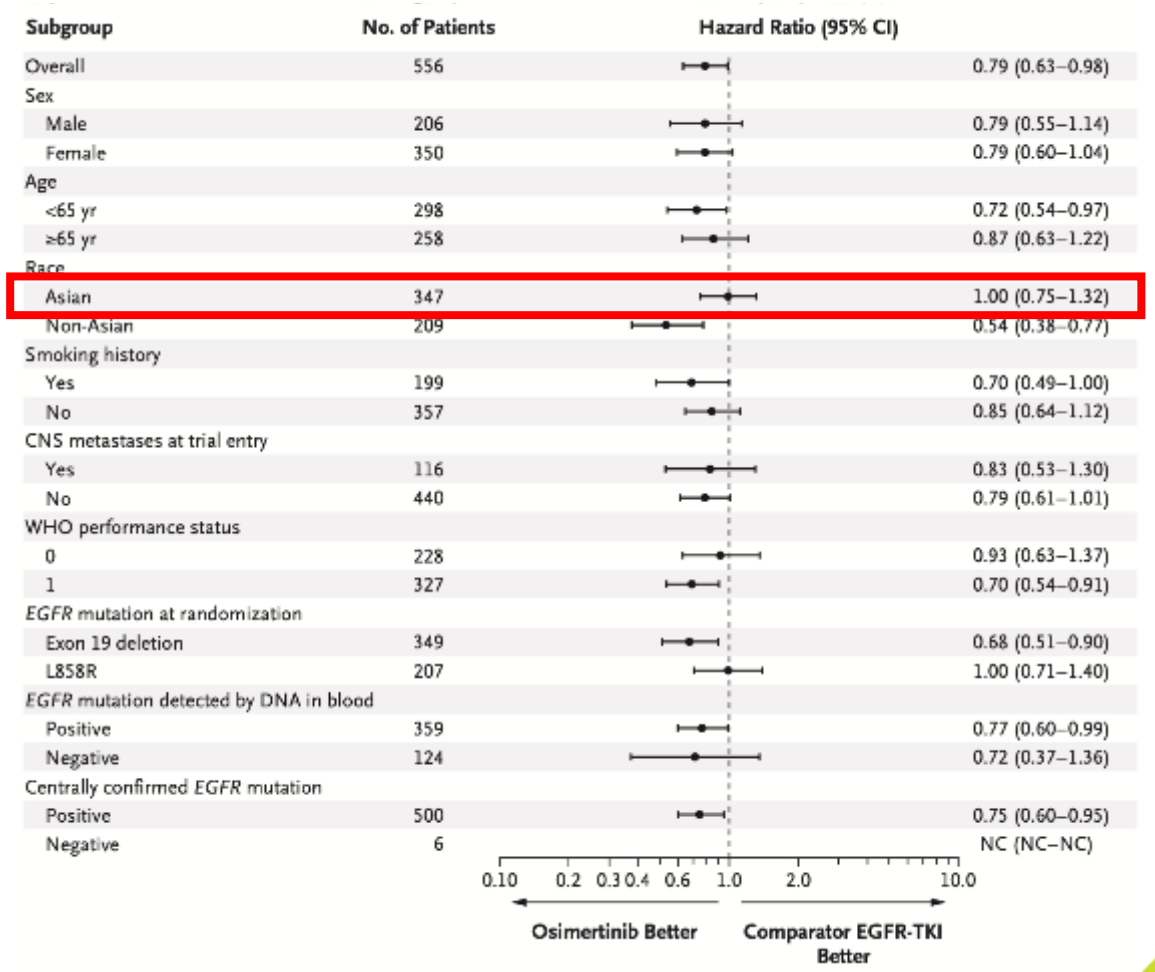


Please note that as head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions as the study design, demographics and other criteria may be different.

1. N Engl J Med . 2020 Jan 2;382(1):41-50., 2. Lancet Oncol . 2015 Feb;16(2):141-51., 3. J Clin Oncol . 2018 Aug 1;36(22):2244-2250.

Kaplan–Meier Curve and Subgroup Analysis of Overall Survival in FLAURA Study

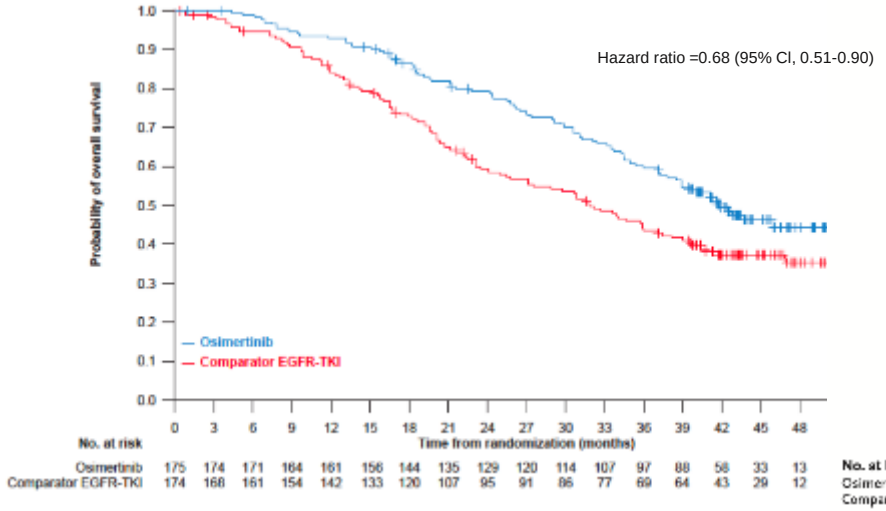




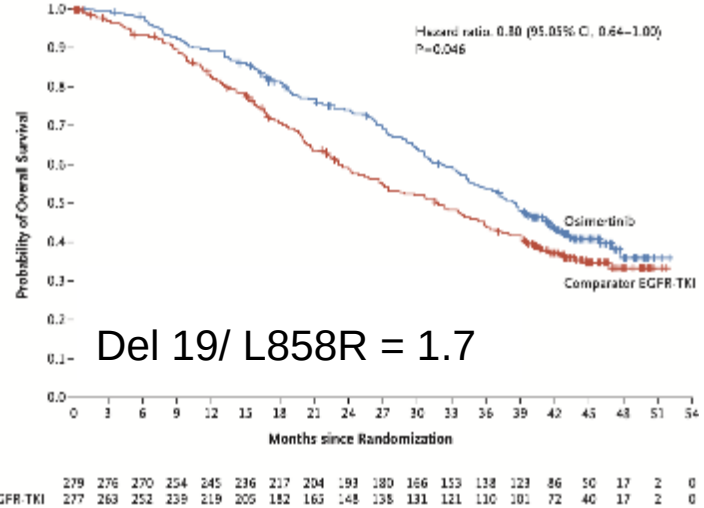
N Engl J Med . 2020 Jan 2;382(1):41-50.

Overall Survival in Different Subgroup in FLAURA Study

Exon 19 Deletion

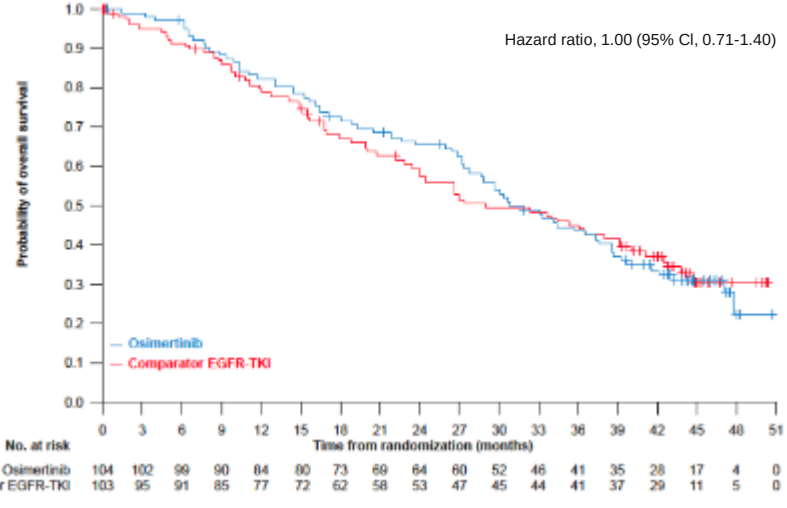


Overall



Del 19/ L858R = 1.7

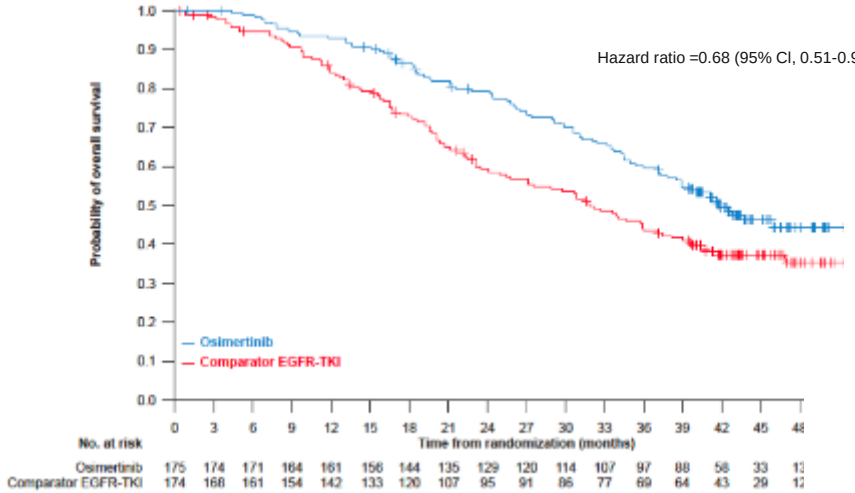
L858R



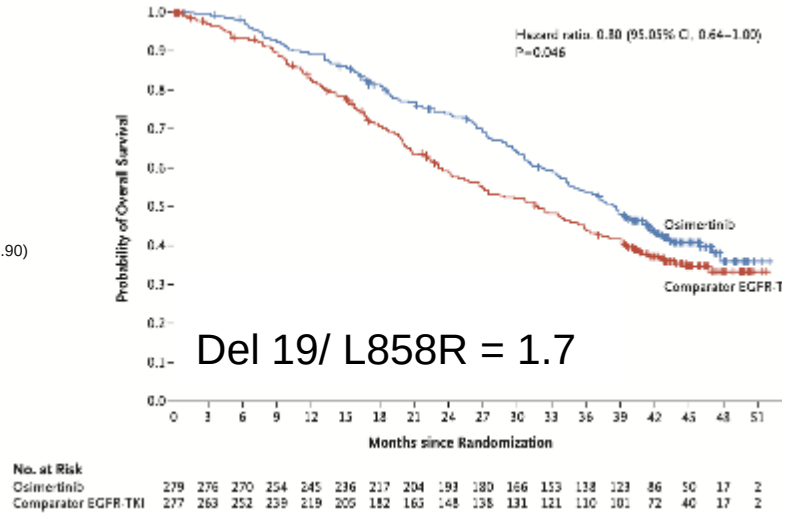
N Engl J Med . 2020 Jan 2;382(1):41-50.

Overall Survival in Different Subgroup in FLAURA Study

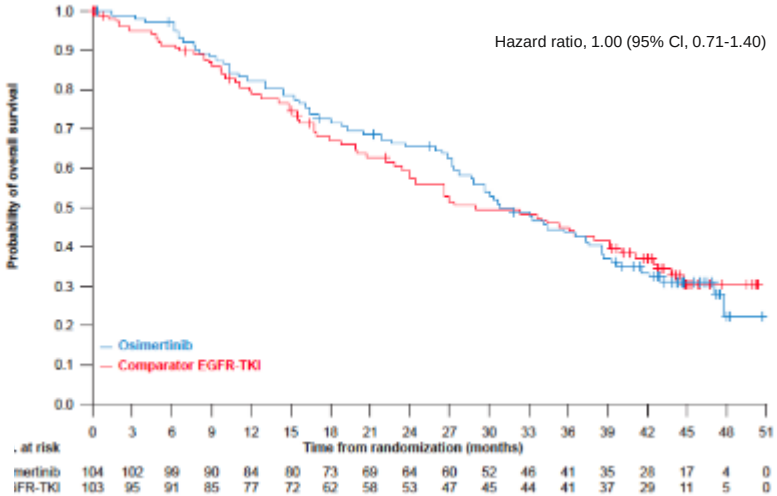
Exon 19 Deletion



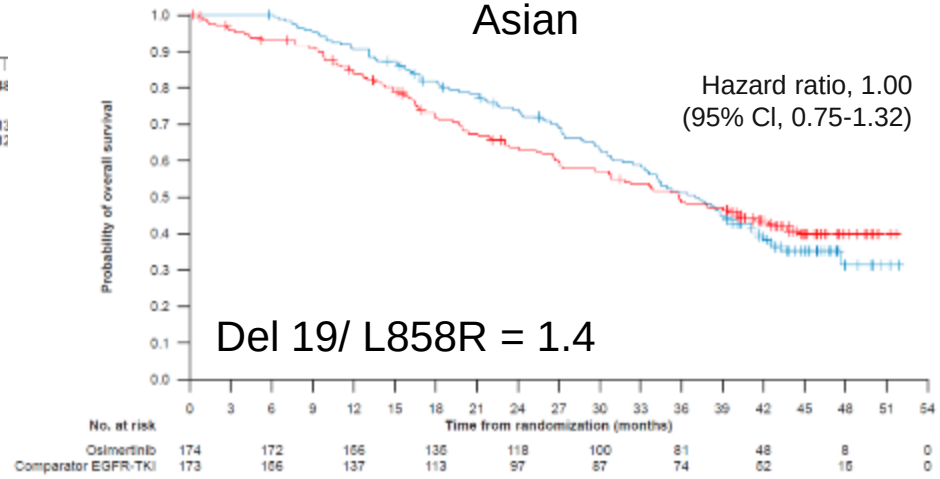
Overall



L858R



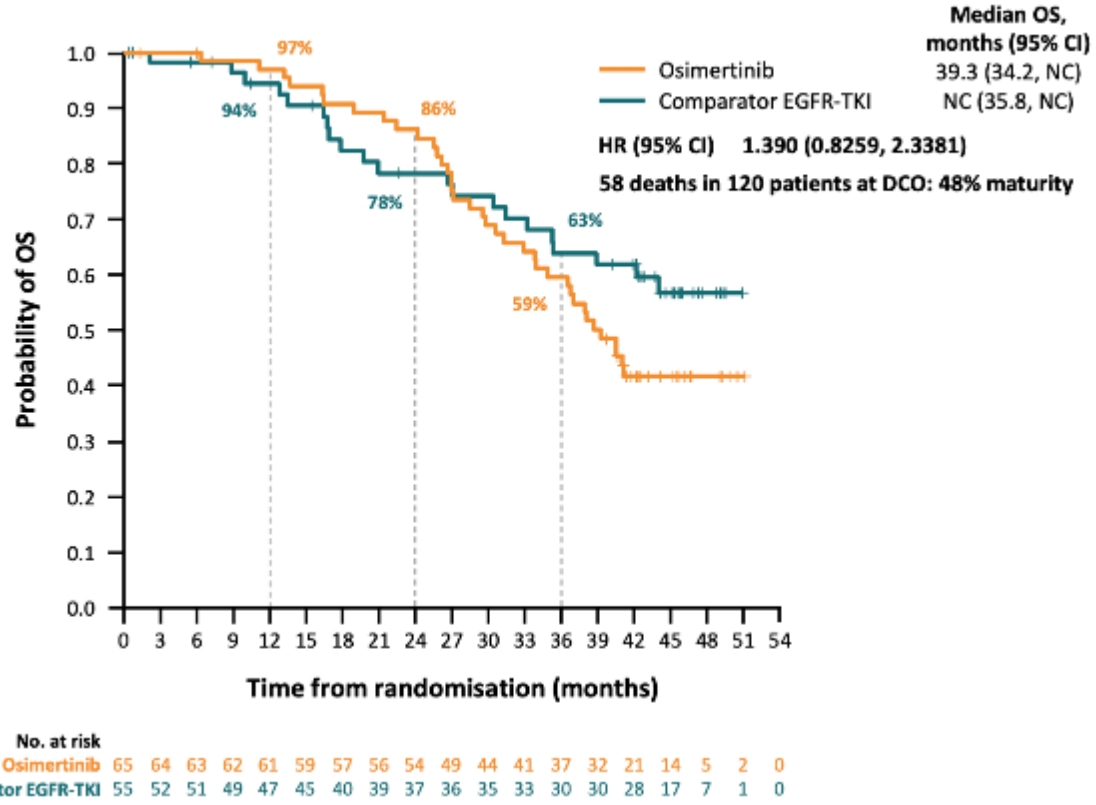
Asian



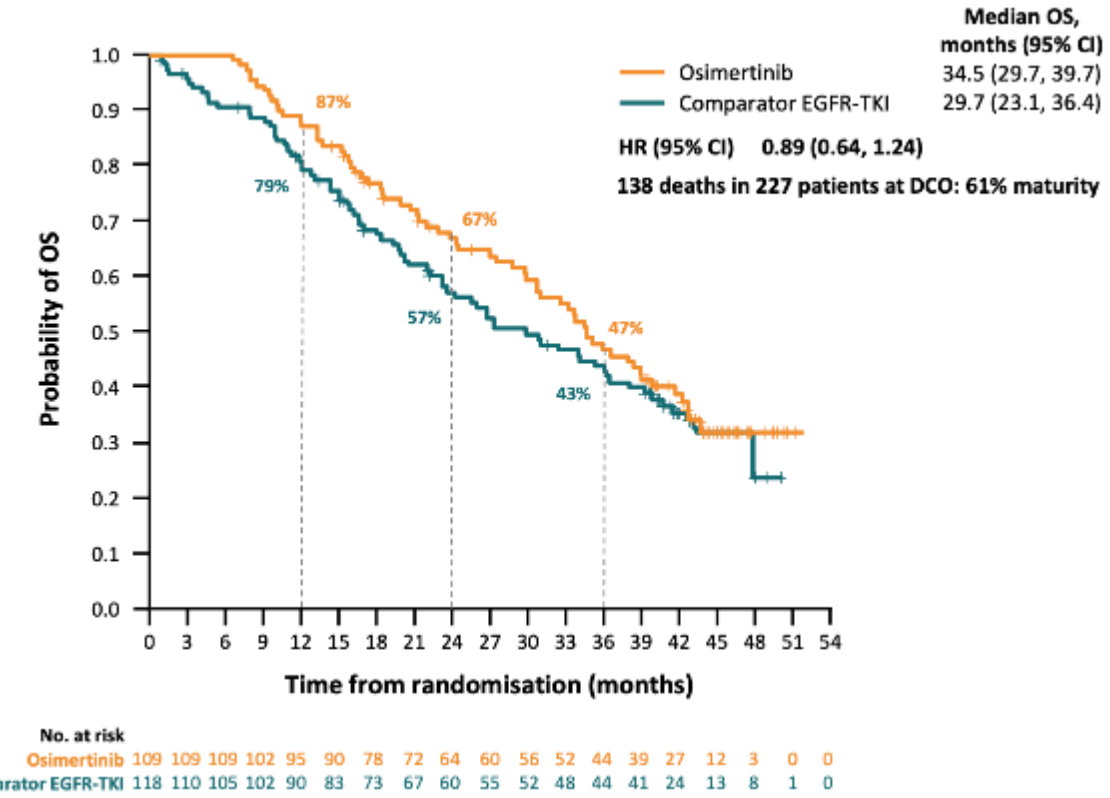
N Engl J Med . 2020 Jan 2;382(1):41-50.

Overall Survival in Japanese Subset and Asian pts excluding Japanese pts

Japanese subset in FLAURA[1]



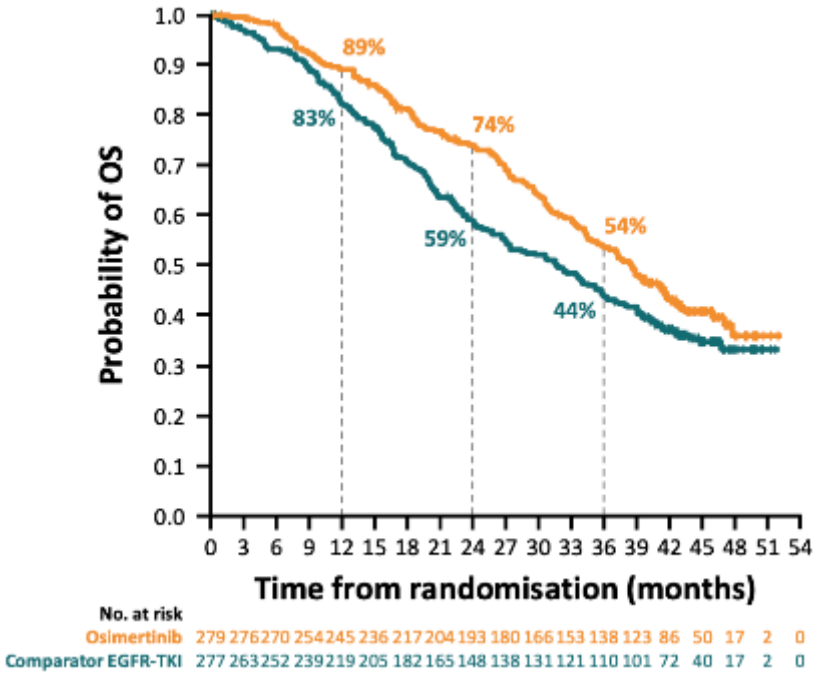
Asian pts excluding Japanese pts



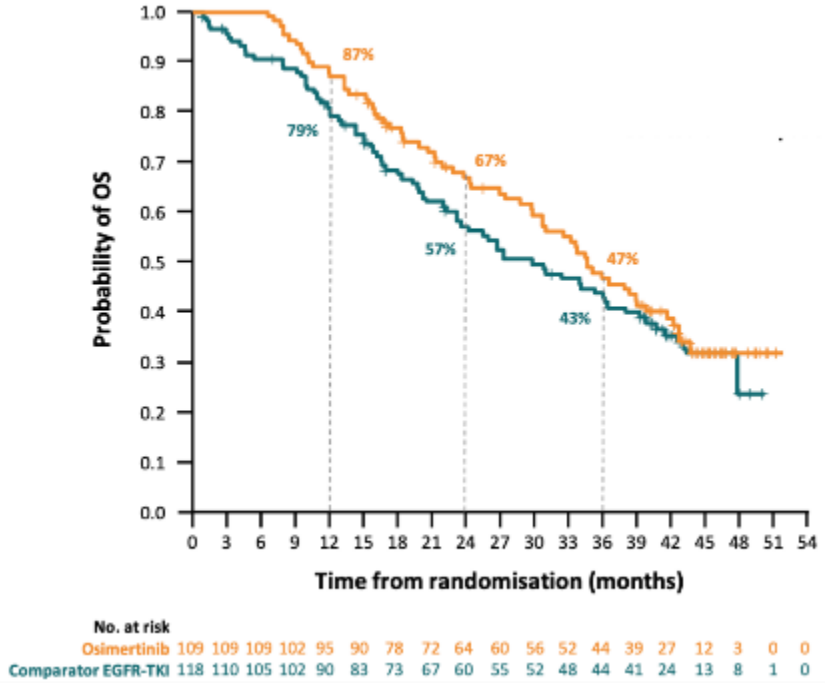
Naoyuki Nogami et al. JLCS 2019

Overall Survival in Japanese Subset and Asian pts excluding Japanese pts

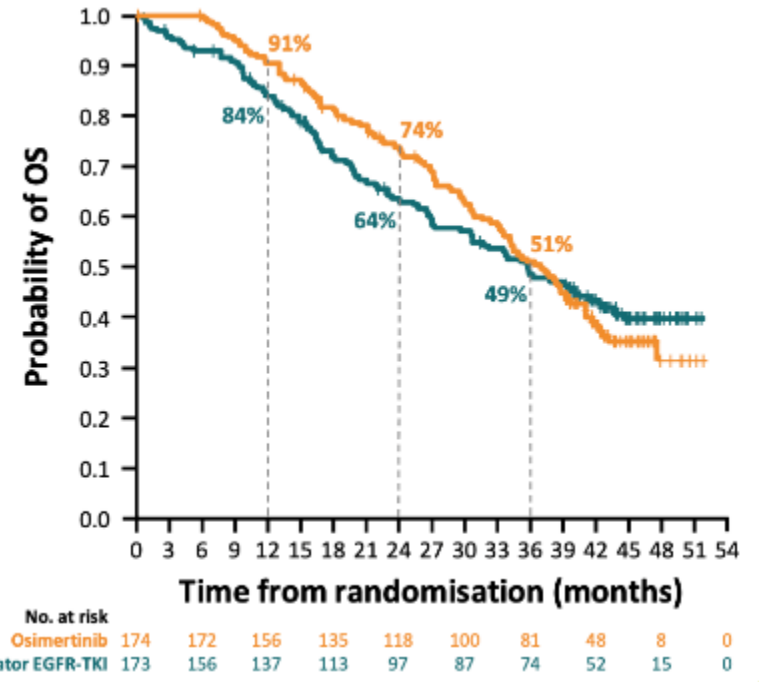
Overall



Asian pts excluding Japanese pts

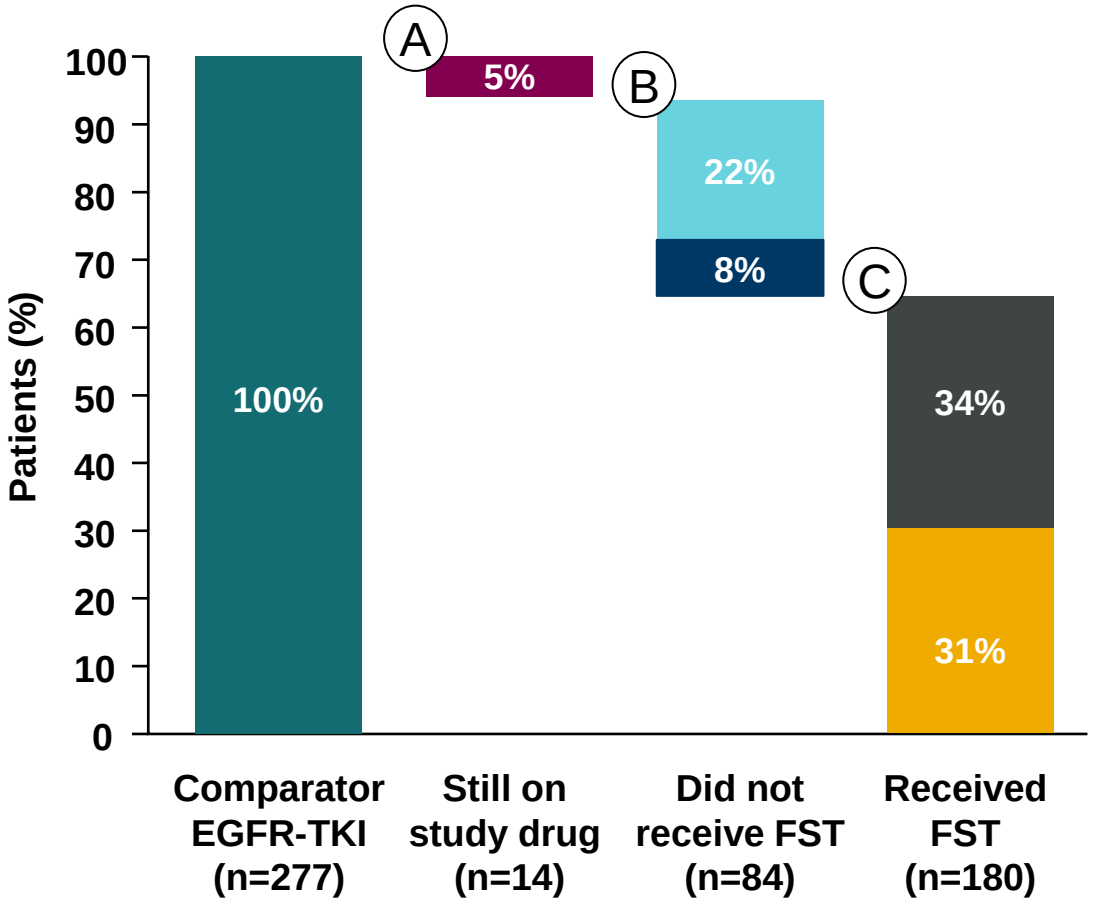


Asian



Naoyuki Nogami et al. JLCS 2019

FLAURA : 30% patients did not receive 2L treatment in comparator EGFR-TKI arm



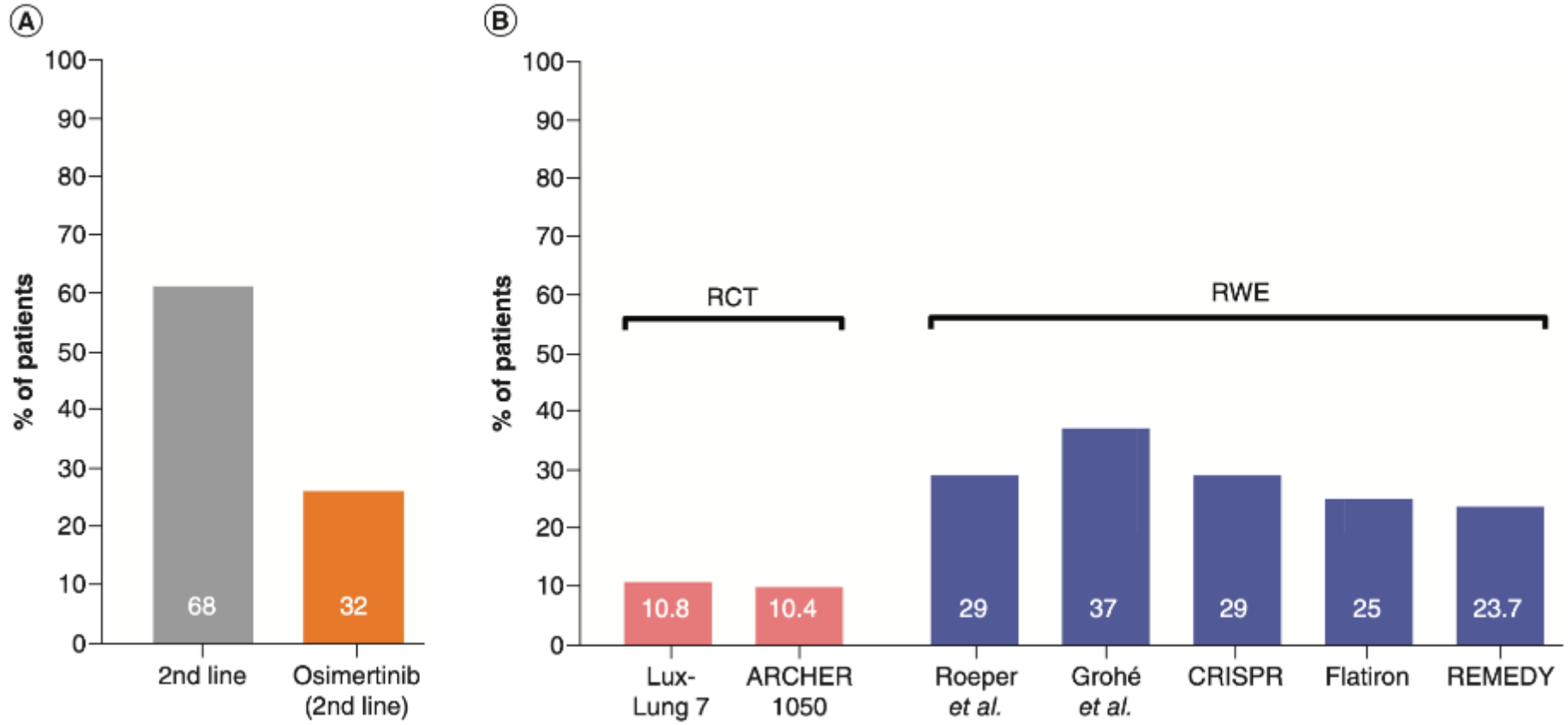
A 5% remained on study treatment (n=13)

B **30%** did not receive 2L anticancer treatment (n=84)
- 74% died (n=62)
- 26% alive (n=22)

C 65% received 2L anticancer treatment (n=180)
- 47% received osimertinib as 2L therapy (n=85)
- 53% received other 2L therapy (n=95)

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

Portion of Patient received 2nd line Tagrisso in RCT and RWE



Percentage of patient received 2nd line therapy Tagrisso
A) and all systemic therapy when progressed on 1st generation TKI in Flarua study, B) in RCT and RWE

Future Oncol . 2021 Feb;17(4):471-486.