CARCINOMA POLMONARE:
QUALI NOVITÀ NEL 2022?

20 Maggio 2022

IRCCS "Sacro Cuore - Don Calabria"
Negrar di Valpolicella

# Il Trattamento della malattia avanzata EGFR mutata


Diego Signorelli

*Niguarda Cancer Center*

Grande Ospedale Metropolitano Niguarda

Milano


Sistema Socio Sanitario

Ospedale Niguarda Cancer Center

Regione Lombardia

# Potential conflict of interest to declare

| Type of affiliation / financial interest | Name of commercial company |
|---|---|
| Consultant, Advisory board, Speaker fees, Travel Grants | AstraZeneca |
| Advisory Board | Boehringer Ingelheim, MSD, Sanofi |
| Speaker Fees, Travel Grants | BMS |
| Advisory Board | MSD |
| Travel Grants | Roche |

# Agenda

- First line
- Overcoming Resistance
- Exon 20 insertions and uncommon mutations

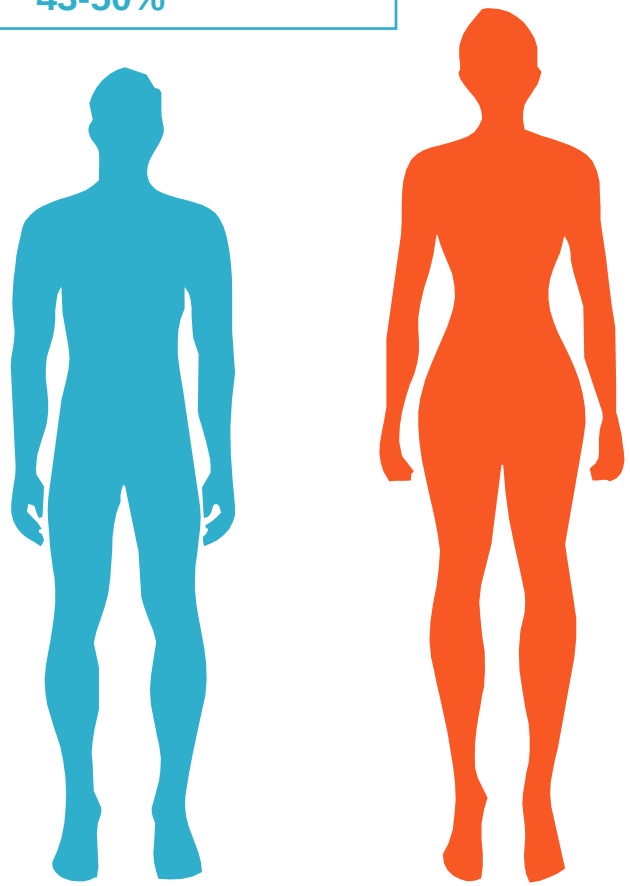
# Agenda

- First line
- Overcoming Resistance
- Exon 20 insertions and uncommon mutations

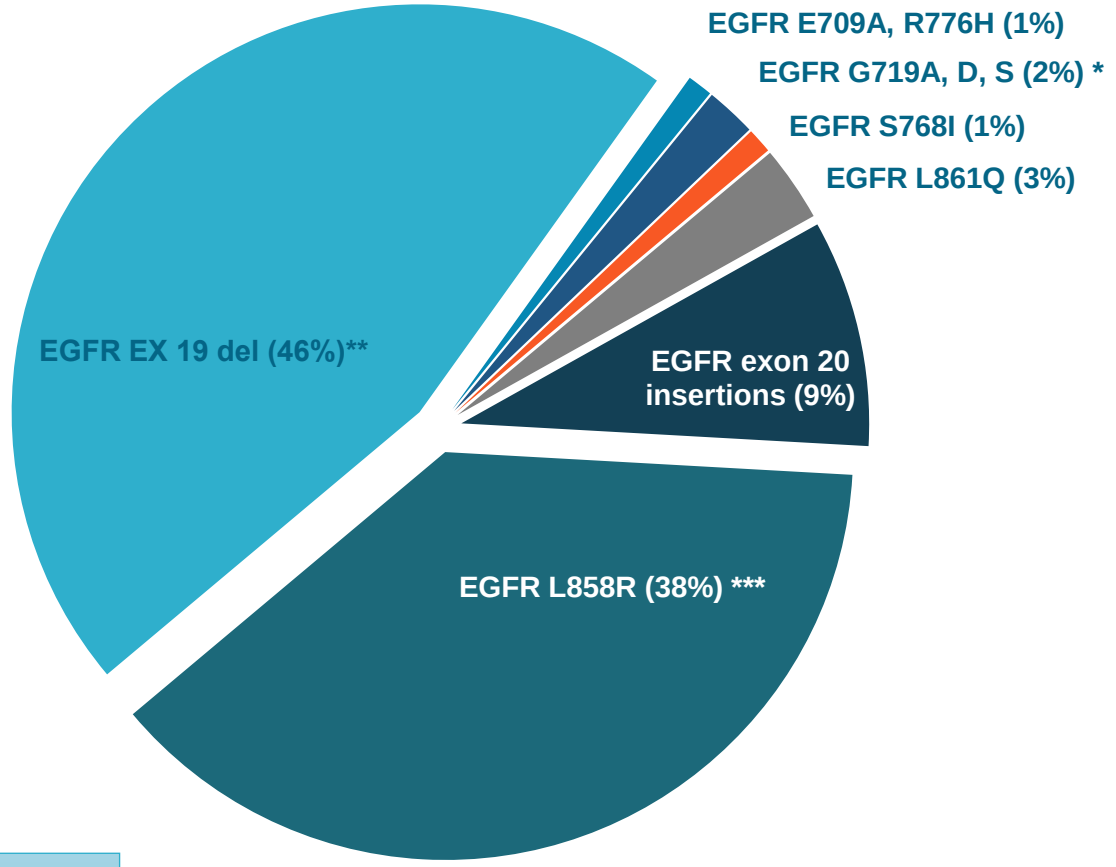
# EGFR mutations

**50% - 67%**

**43-50%**



## EGFR-mutated cases (n=367)




EGFR Young patients and no smoker

*Ramalingam NEJM 2019*

*Arcila et al. Mol Cancer Ther 2013;12:220-9*

# History of EGFRi use and approval

**2003[1]**
**2004[2]**

**GEFITINIB**

2L after CT without EGFR mut[1]
1L vs CT with EGFR mut[2]

**2011**

**ERLOTINIB**

1L For EGFR mut

**2012**

**AFATINIB**

1L in patients with EGFR mut

**2018**

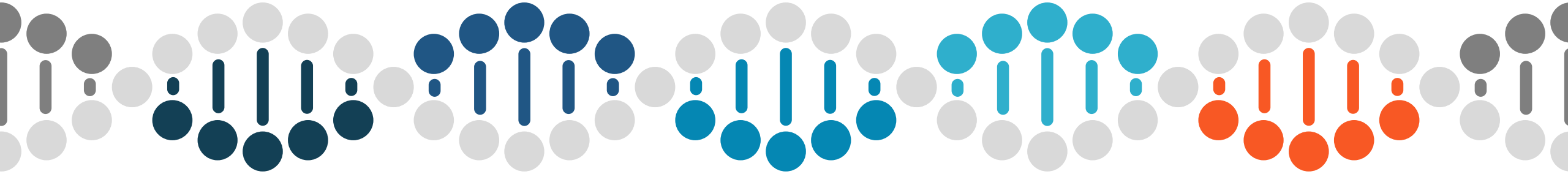
**OSIMERTINIB**

2L to overcome resistance to 1/2G TKIs

**2020**

**OSIMERTINIB**

1Line standard of CARE



1Cohen MH, et al. *Oncologist.* 2003; 2. AstraZeneca. New Drug Application For IRESSA accepted by US Food and Drug Administration. Dec 2014. 3. Karachaliou N, et al. Transl Cancer Res. 2019; 4. Kazandjian D, et al. Oncologist. 2014; US FDA. Osimertinib. July 2017. US FDA Osimertinib feb 2021;

# FLAURA Study design, Osimertinib

**Patients with locally advanced or metastatic NSCLC**

**Key inclusion criteria**

- ≥18 years*
- WHO performance status 0 / 1
- Exon 19 deletion / L858R (enrollment by local† or central‡ EGFR testing)
- No prior systemic anti-cancer / EGFR-TKI therapy
- Stable CNS metastases allowed

Stratification by **mutation status** (Exon 19 deletion / L858R) **and race** (Asian / non-Asian)

**Randomized 1:1**

**Osimertinib** (80 mg p.o. qd) (n=279)

EGFR-TKI SoC# **Gefitinib** (250 mg p.o. qd) or **Erlotinib** (150 mg p.o. qd) (n=277)

RECIST 1.1 assessment every 6 weeks¶ until objective progressive disease

Crossover was allowed for patients in the **SoC** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

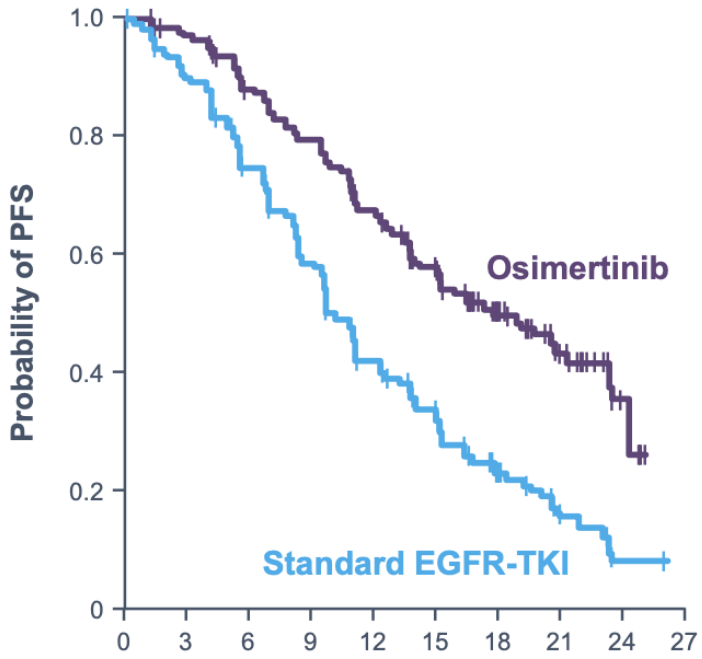
**Endpoints**

- **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 an 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

Ramalingam et al, presented at ESMO 2017, Ann Oncol (2017) 28 (suppl_5): v605-v649; Soria et al, N Engl J Med, 2018

# FLAURA PFS and OS Results

## FULL SET analysis[1]



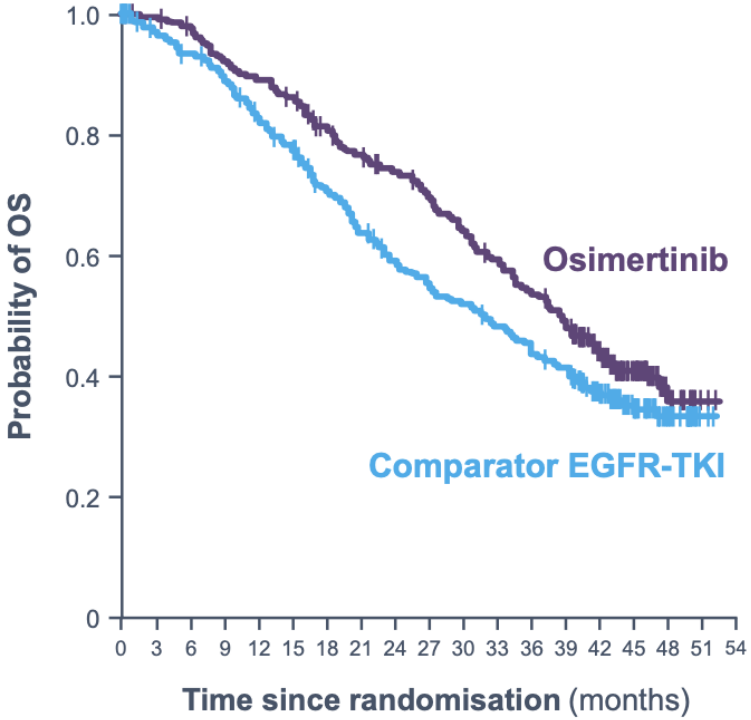

No. at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 279 | 262 | 233 | 210 | 178 | 139 | 71 | 26 | 4 | 0 |
| EGFR-TKI | 277 | 239 | 197 | 152 | 107 | 78 | 37 | 10 | 2 | 0 |

| | mPFS, months (95% CI) | HR (95% CI) | P value |
|---|---|---|---|
| Osimertinib (n=279) | **18.9** (15.2–21.4) | **0.46** (0.37–0.57) | **<0.001** |
| EGFR TKI* (n=277) | **10.2** (9.6–11.1) | | |

*Soria et al, N Engl J Med, 2018;*

## FULL SET analysis[1]



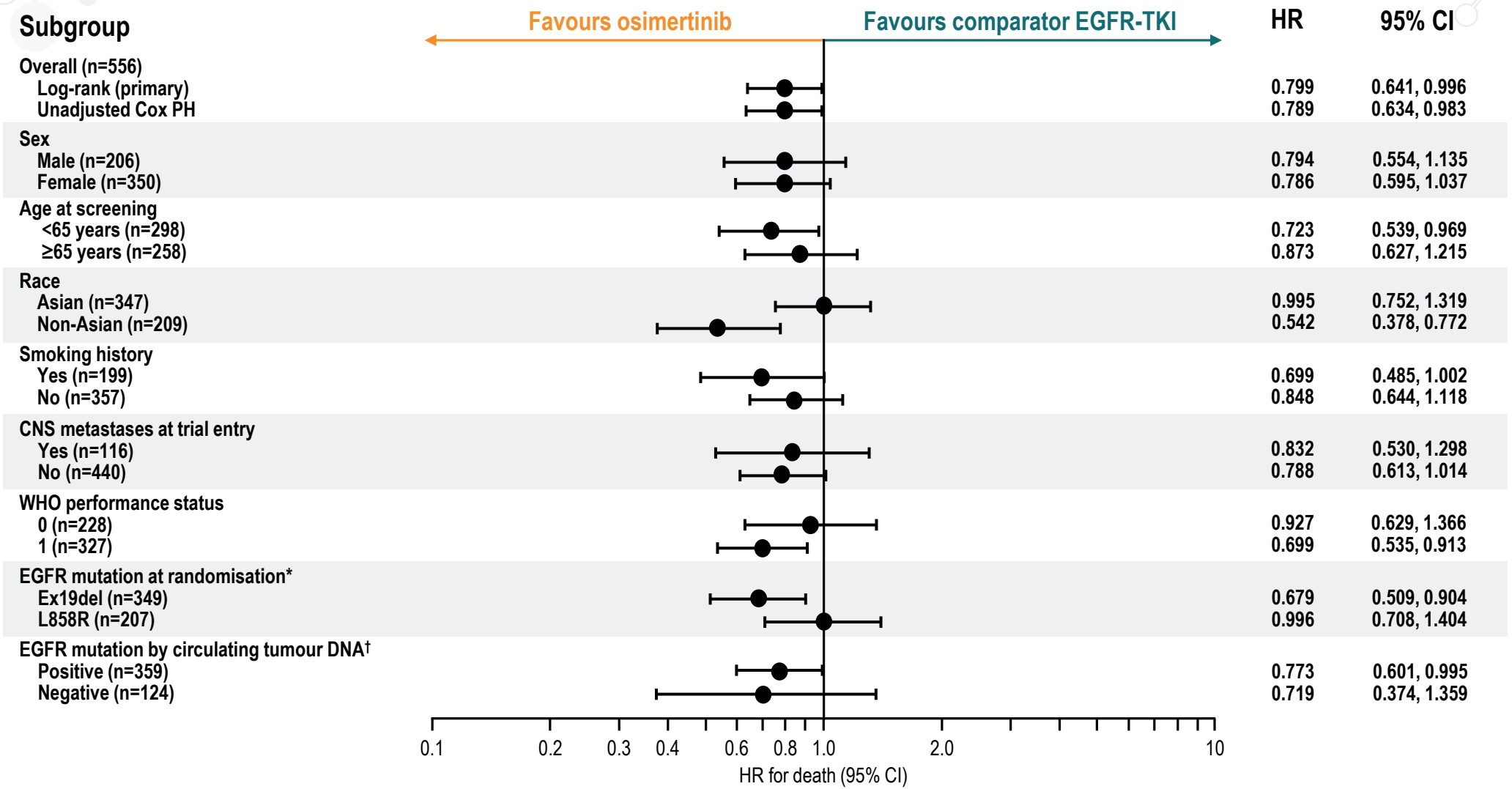

No. at risk

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 279 | 276 | 270 | 254 | 245 | 236 | 217 | 204 | 193 | 180 | 166 | 153 | 138 | 123 | 86 | 50 | 17 | 2 | 0 |
| EGFR-TKI | 277 | 263 | 252 | 239 | 219 | 205 | 182 | 165 | 148 | 138 | 131 | 121 | 110 | 101 | 72 | 40 | 17 | 2 | 0 |

| | mOS, months (95% CI) | HR (95% CI) | P value |
|---|---|---|---|
| Osimertinib (n=279) | **38.6** (34.5–41.8) | **0.80** (0.64–1.00) | **0.046** |
| EGFR TKI* (n=277) | **31.8** (26.6–36.0) | | |

*Ramalingam SS, et al. NEJM. 2020;*

# Overall survival across subgroups




Data cut-off: 25 June 2019

Hazard ratio <1 implies a lower risk of death on osimertinib

*Local or central test; †Result missing for 36 patients in the osimertinib arm and 37 patients in the comparator EGFR-TKI arm

*1. Ramalingam SS, et al. NEJM. 2020; 2, Ramalingam SS, et al. NEJM. appendix*

# CNS Effects of III Generation EGFR TKI

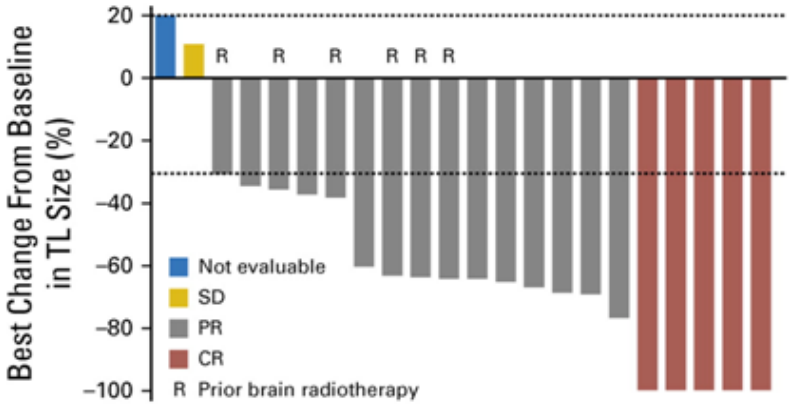
## *Practice Changing Data*

VOLUME 36 · NUMBER 33 · NOVEMBER 20, 2018

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

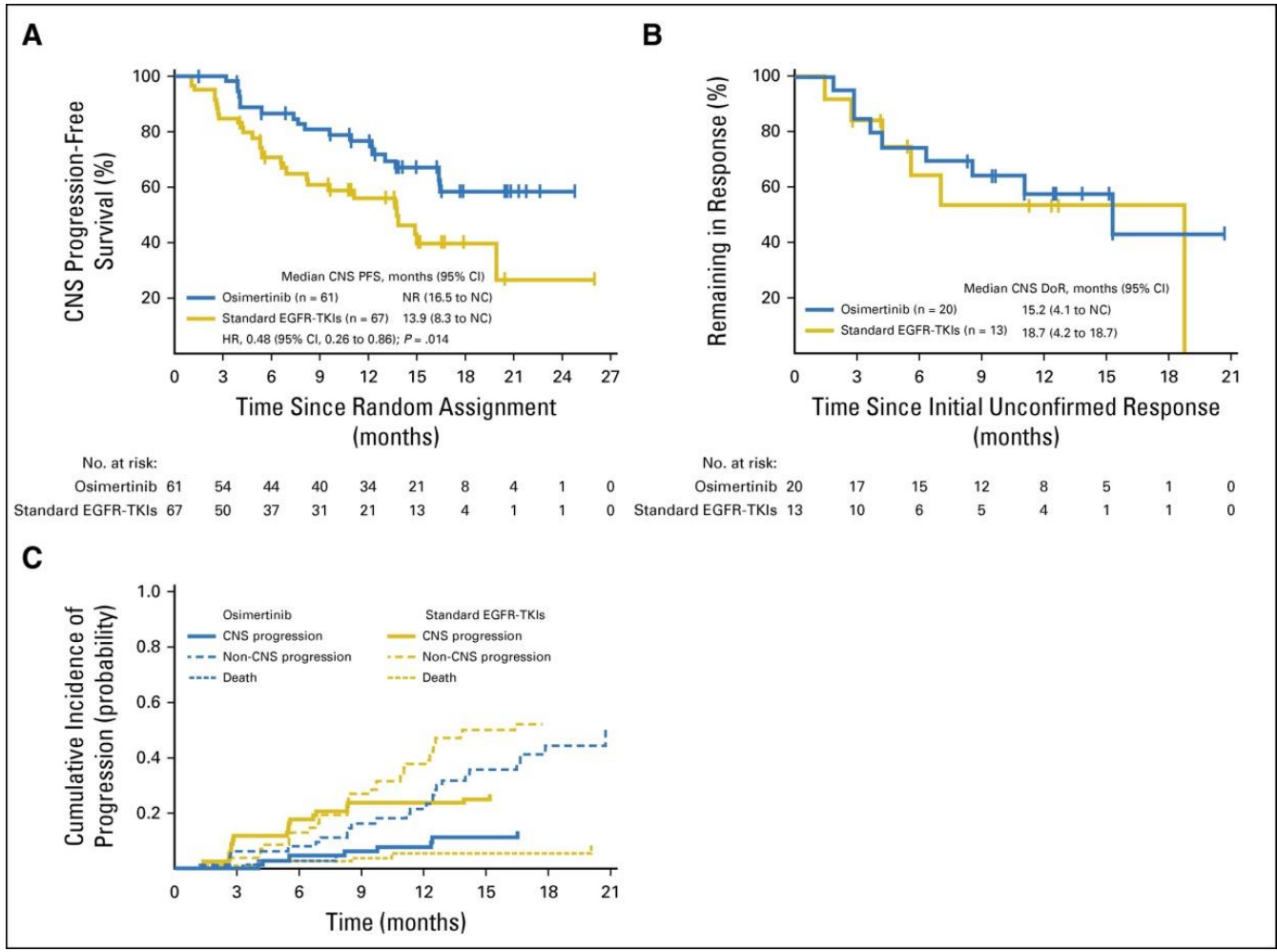
CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

*Thanyanan Reungwetwattana, Kazuhiko Nakagawa, Byoung Chul Cho, Manuel Cobo, Eun Kyung Cho, Alessandro Bertolini, Sabine Bohnet, Caicun Zhou, Ki Hyeong Lee, Naoyuki Nogami, Isamu Okamoto, Natasha Leighl, Rachel Hodge, Astrid McKeown, Andrew P. Brown, Yuri Rukazenkov, Suresh S. Ramalingam, and Johan Vansteenkiste*




| CNS evaluable for response set (n=41) | |
|---|---|
| Osimertinib (n=22) | SoC (n=19) |
| 91% (71, 99) | 68% (43, 87) |

**Odds Ratio 4.6 (95%CI 0.9-34.9, p=0.066)**




**mPFS: NR vs 13.9 months (HR 0.48, 95%CI 0.26-0.86, p=0.014)**

**1. What is the optimal first-line therapy for patients with common *EGFR* mutations?**

**STATEMENT:** First-line third-generation EGFR TKIs, such as osimertinib, is considered the preferred option for patients with a tumor with common *EGFR* mutations [I,A].

**2. What is the optimal management of patients with CNS disease and/or with leptomeningeal involvement?**

**STATEMENT:** Third-generation EGFR TKIs should be prioritized for those patients with CNS metastasis, including leptomeningeal disease, as initial therapy. The benefit of radiotherapy in addition to EGFR TKIs is not supported by prospective controlled trials data. For those with intracra-

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

# ESMO expert consensus statements on the management of *EGFR* mutant non-small-cell lung cancer

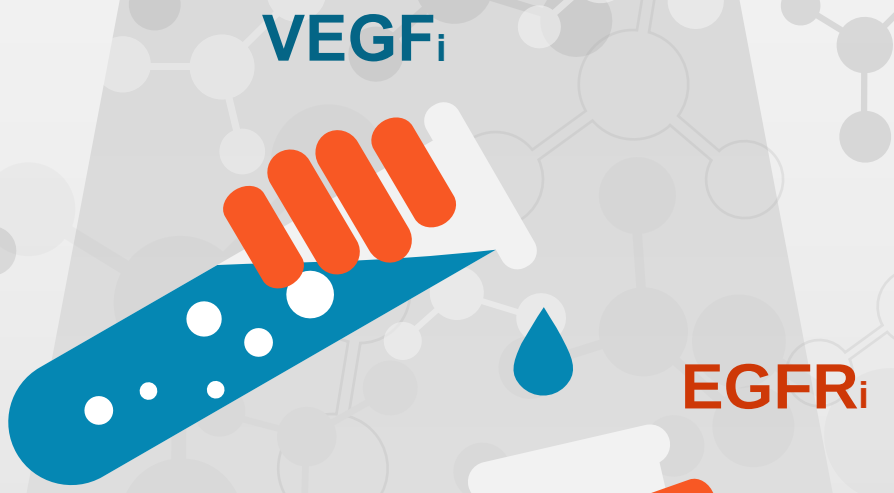
A. Passaro[1*], N. Leighl[2†], F. Blackhall[3,4†], S. Popat[5,6,7†], K. Kerr[8†], M. J. Ahn[9], M. E. Arcila[10], O. Arrieta[11], D. Planchard[12], F. de Marinis[1], A. M. Dingemans[13], R. Dziadziuszko[14], C. Faivre-Finn[15], J. Feldman[16], E. Felip[17], G. Curigliano[18], R. Herbst[19], P. A. Jänne[20], T. John[21], T. Mitsudomi[22], T. Mok[23], N. Normanno[24], L. Paz-Ares[25], S. Ramalingam[26], L. Sequist[27], J. Vansteenkiste[28], I. I. Wistuba[29], J. Wolf[30], Y. L. Wu[31], S. R. Yang[7], J. C. H. Yang[32], Y. Yatabe[33], G. Pentheroudakis[34] & S. Peters[35]

*Passaro A, et al. Ann Oncol 2022;*

# What about combination strategies in first line EGFR+?

Third generation EGFR TKIs: Standard of Care
From 2020

**BEYOND OSIMERTNIB first line?**





# EGFRi and VEGFi Combo-inhibition

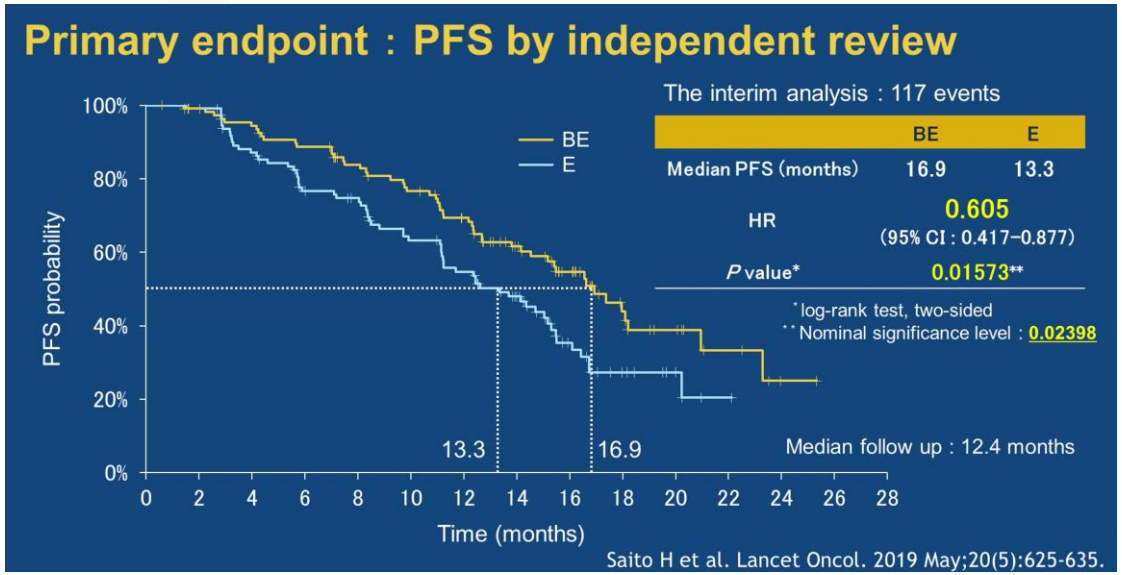
**Erlotinib + Bevacizumab**
NEJ026
BEVERLY

**Erlotinib + Ramucirumab**
RELAY

**Osimertinib + Bevacizumab**
WJOG9717L

*Saito H, Lancet Oncol 2019,* Nagakawa K, et al. *Lancet Oncol.* 2019;20:1655–69.
Presented By Maria Carmela Piccirillo at 2021 ESMO Annual Meeting

# NEJ026 PFS/OS: Bevacizumab + Erlotinib

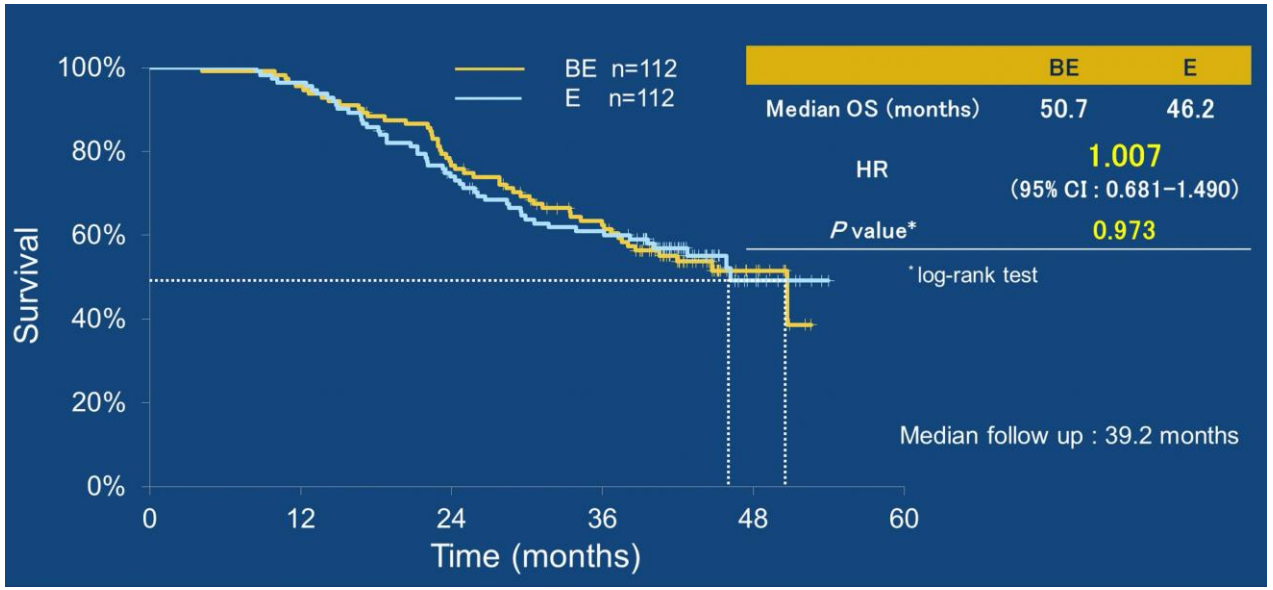



## Progression Free-Survival:

16.9 for Bev+ Erlotinib vs 13.3 for Erlotinib alone
HR 0.60 (95% CI, 0.41 – 0.87)

## Overall Survival:

50.7 for Bev+ Erlotinib vs 46.2 for Erlotinib alone
HR 1 (95%CI, 0.68 – 1.49)

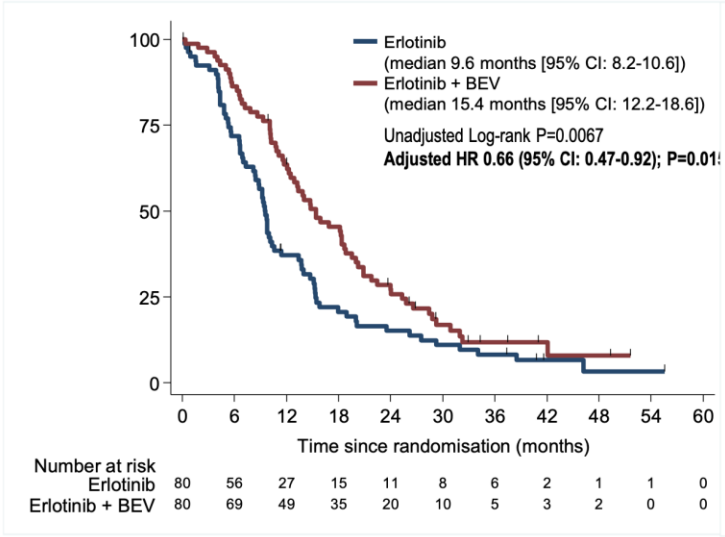



*Saito H, Lancet Oncol 2019*

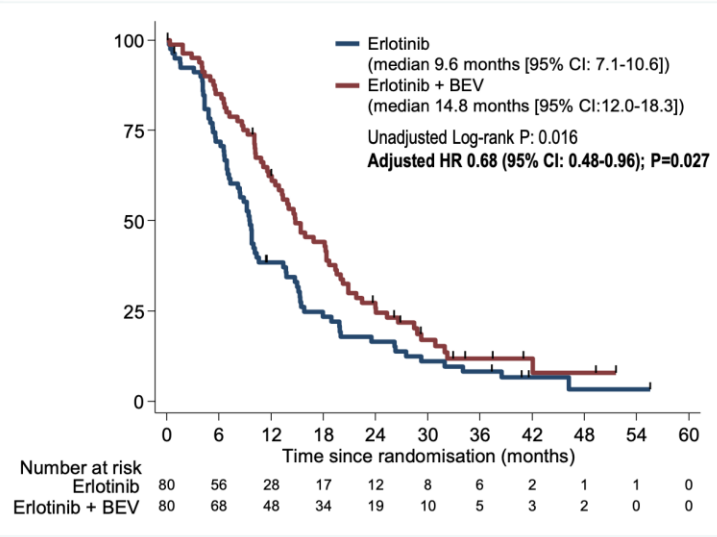
# BEVERLY OS: Bevacizumab + Erlotinib

## Progression-free survival

### Investigator-assessed



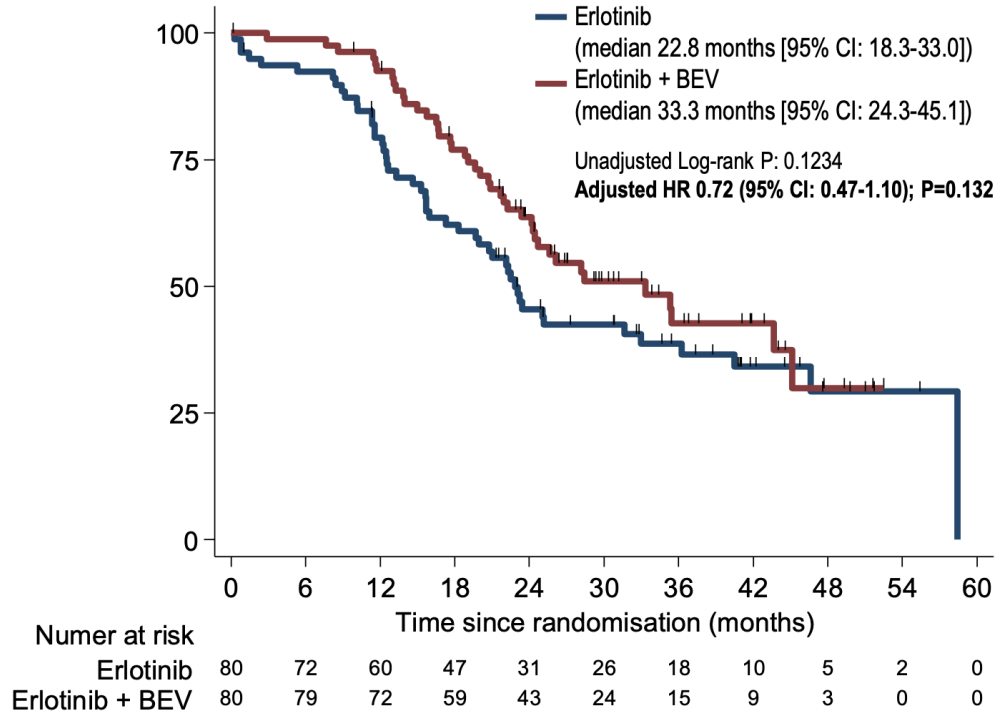

### Blinded independent centrally-reviewed




2021 ESMO congress

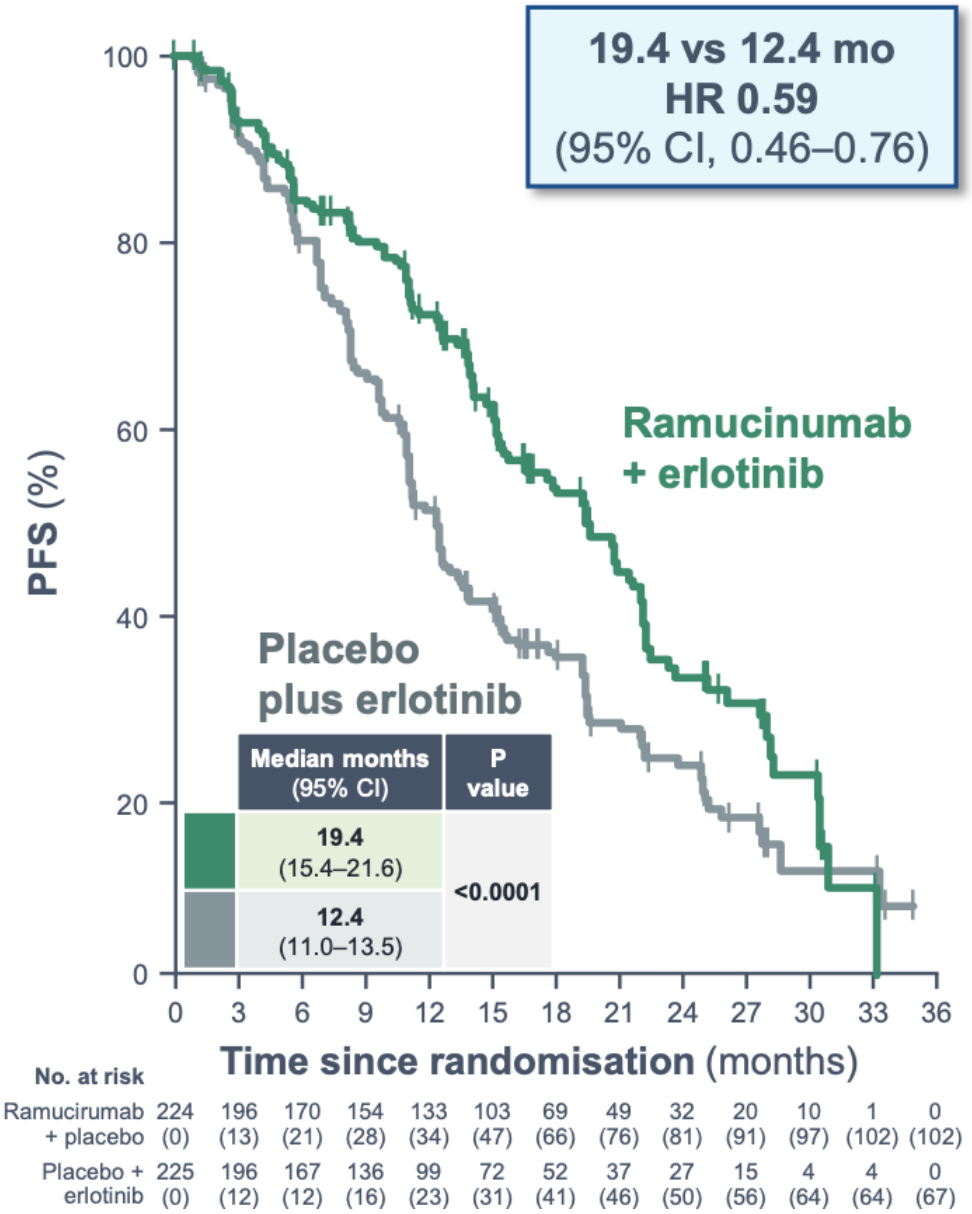


## Overall survival




**AUTHOR conclusion:** Bevacizumab + erlotinib might be considered as a first-line therapeutic option in patients who cannot receive osimertinib.

# RELAY PFS: Ramucirumab + Erlotinib

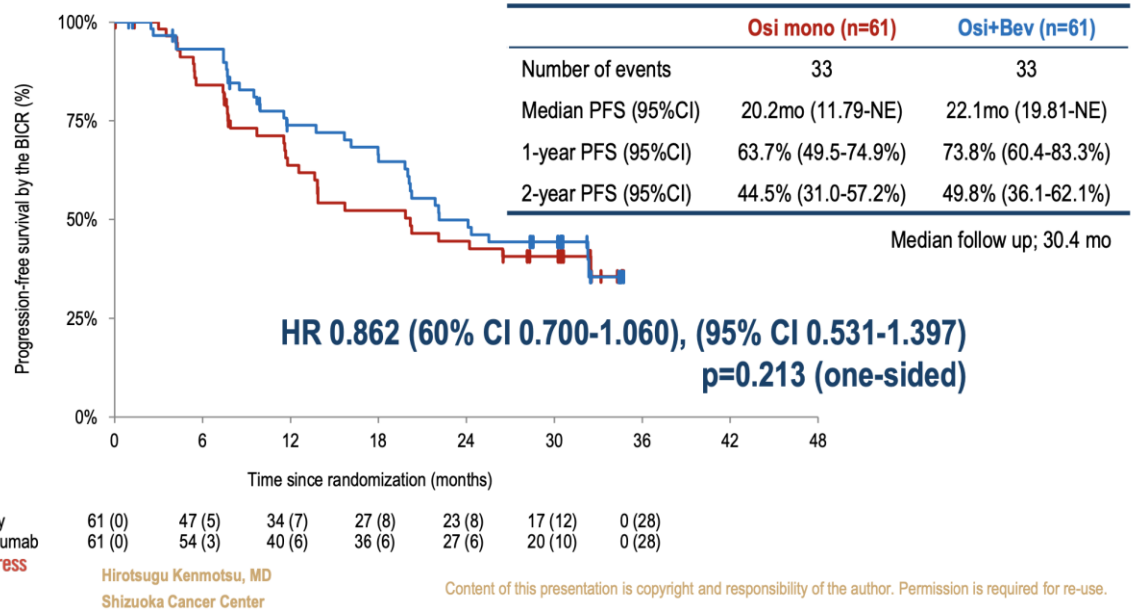



Nagakawa K, et al. *Lancet Oncol.* 2019;20:1655–69.

Adapted from B. Besse from ELCC 2022

# WJOG9717L PFS: Osimertinib + Bevacizumab

## Primary Endpoint: PFS (ITT), assessed by BICRs




| | Osi mono (n=61) | Osi+Bev (n=61) |
|---|---|---|
| Number of events | 33 | 33 |
| Median PFS (95%CI) | 20.2mo (11.79-NE) | 22.1mo (19.81-NE) |
| 1-year PFS (95%CI) | 63.7% (49.5-74.9%) | 73.8% (60.4-83.3%) |
| 2-year PFS (95%CI) | 44.5% (31.0-57.2%) | 49.8% (36.1-62.1%) |

Median follow up; 30.4 mo

**Number at risk**
(number censored)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Osimertinib monotherapy | 61 (0) | 47 (5) | 34 (7) | 27 (8) | 23 (8) | 17 (12) | 0 (28) |
| Osimertinib plus bevacizumab | 61 (0) | 54 (3) | 40 (6) | 36 (6) | 27 (6) | 20 (10) | 0 (28) |

2021 ESMO congress

Hirotsugu Kenmotsu, MD
Shizuoka Cancer Center



Primary results of a randomized phase II study of osimertinib plus bevacizumab versus osimertinib monotherapy for untreated patients with NSCLC harboring EGFR mutations; WJOG9717L study

Presented By Hirotsugu Kenmotsu at 2021 ESMO Annual Meeting

# EGFRi and Chemo Combo-inhibition

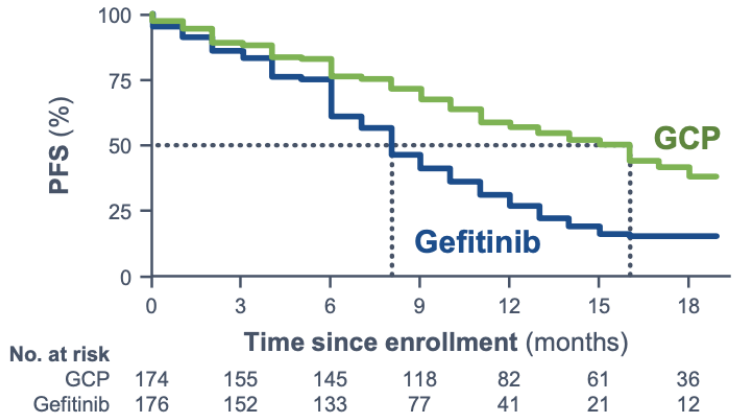

**Gefitinib + Chemotherapy**
TATA MEMORIAL
NEJ009

**Osimertinib + Chemotherapy**
FLAURA 2

Nagakawa K, et al. *Lancet Oncol.* 2019;20:1655–69; 2. Hosomi Y, et al. J Clin Oncol. 2020;38:115−23. Ramalingam et al, presented at ESMO 2017, Ann Oncol (2017) 28 (suppl_5): v605-v649; Soria et al, N Engl J Med. 2018

# PFS, OS: Chemotherapy + Gefitinib

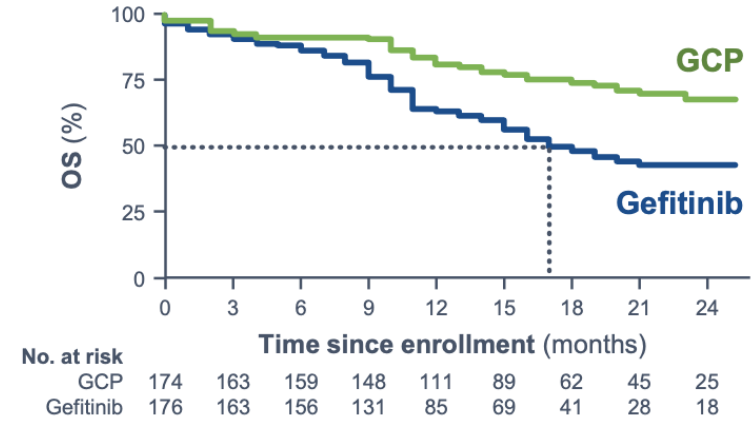
## TATA MEMORIAL[1]




**PFS**

| | HR (95% CI) | P value |
|---|---|---|
| GCP (n=174) | 0.51 (0.39–0.66) | <0.001 |
| Gefitinib (n=176) | | |

**16.0 vs 8.0 mo**
**HR 0.51**
(95% CI, 0.39–0.66)

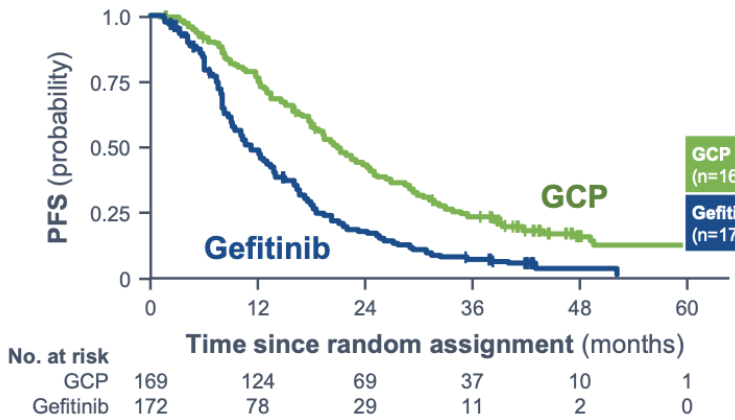



**OS**

| | HR (95% CI) | P value |
|---|---|---|
| GCP (n=174) | 0.45 (0.31–0.65) | <0.001 |
| Gefitinib (n=176) | | |

**NR vs 17.0 mo**
**HR 0.45**
(95% CI, 0.31–0.65)

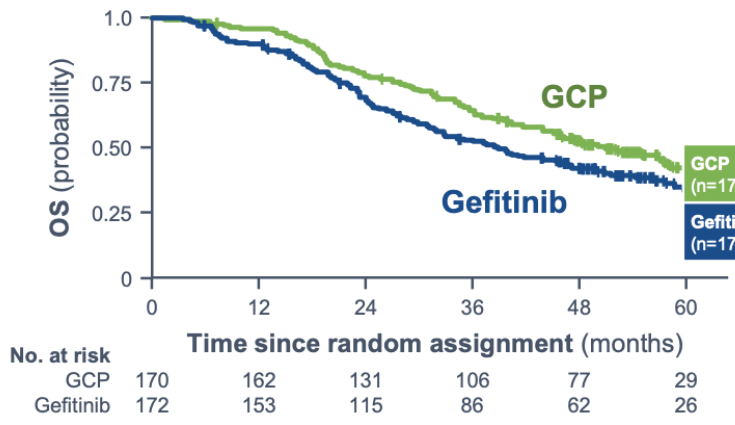
## NEJ009[2]




**PFS**

| | Median PFS (95% CI) | HR for PD or death (95% CI) | P value |
|---|---|---|---|
| GCP (n=169) | 20.93 (17.94–24.20) | 0.49 (0.39–0.62) | <0.001 |
| Gefitinib (n=172) | 11.17 (8.97–13.40) | | |

**20.93 vs 11.17 mo**
**HR 0.49**
(95% CI 0.39–0.62)




**OS**

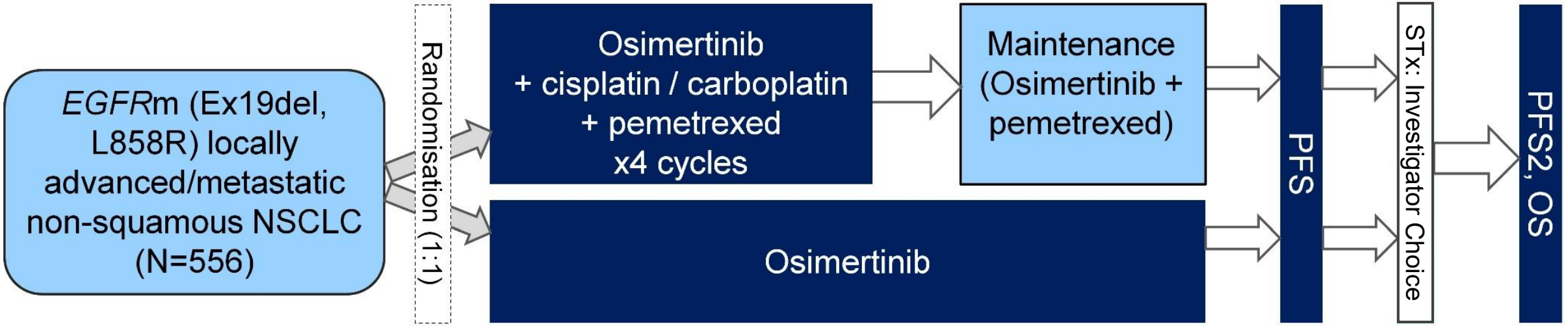
| | Median OS (95% CI) | HR for PD or death (95% CI) | P value |
|---|---|---|---|
| GCP (n=170) | 50.90 (41.77–62.50) | 0.72 (0.55–0.95) | 0.021 |
| Gefitinib (n=172) | 38.80 (31.10–47.33) | | |

**50.9 vs 38.8 mo**
**HR 0.72**
(95% CI 0.55–0.95)

Nagakawa K, et al. *Lancet Oncol.* 2019;20:1655–69; 2. Hosomi Y, et al. J Clin Oncol. 2020;38:115−23. .

Adapted from B. Besse from ELCC 2022

# FLAURA2 Design: Chemotherapy + Osimertinib




- Osimertinib given at a dose of 80 mg QD during induction and maintenance
- The osimertinib dose can be reduced to 40 mg QD for management of AEs; chemotherapy dose interruption/reduction is to be prioritised over reduction/interruption of osimertinib
- Randomisation will be stratified by race, WHO PS (0 vs 1), and tissue *EGFR* mutation test at enrolment
- Planned to involve approximately 248 sites in 27 countries

Abbreviations: AE, adverse event; EGFR, epidermal growth factor receptor; EGFRm, epidermal growth factor receptor mutation; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; PFS2, time from randomisation to second progression or death on a subsequent treatment; QD, once daily; STx, subsequent treatment; vs, versus; WHO, World Health Organization

Ramalingam et al, presented at ESMO 2017, Ann Oncol (2017) 28 (suppl_5): v605-v649; Soria et al, N Engl J Med, 2018

# Agenda

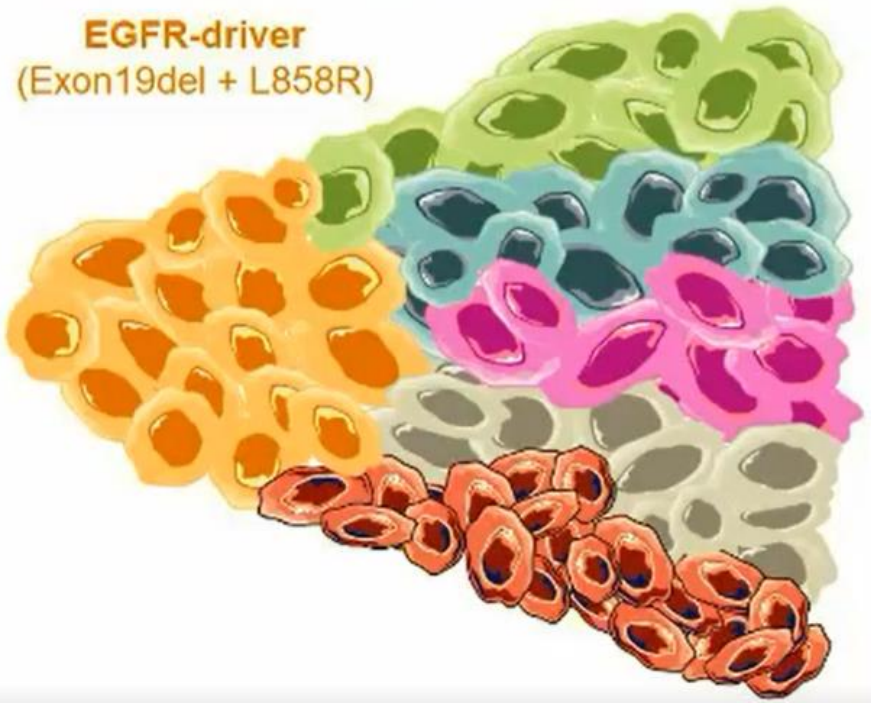
- First line
- Overcoming Resistance
- Exon 20 insertions and uncommon mutations

# Mechanisms of resistance to osimertinib

**Osimertinib** → **Platinum Chemotherapy**

**Primary Mutations** → **Resistance Mutations**

**EGFR-driver**
(Exon19del + L858R)



**EGFR-dependent**
(C797S)

**MET-dependent**
(MET amplification)

**Other Pathways**
(PIK3CA, RAS/RAF, Fusions, Cell Cycle)

**Unknown**
(~40-50%)

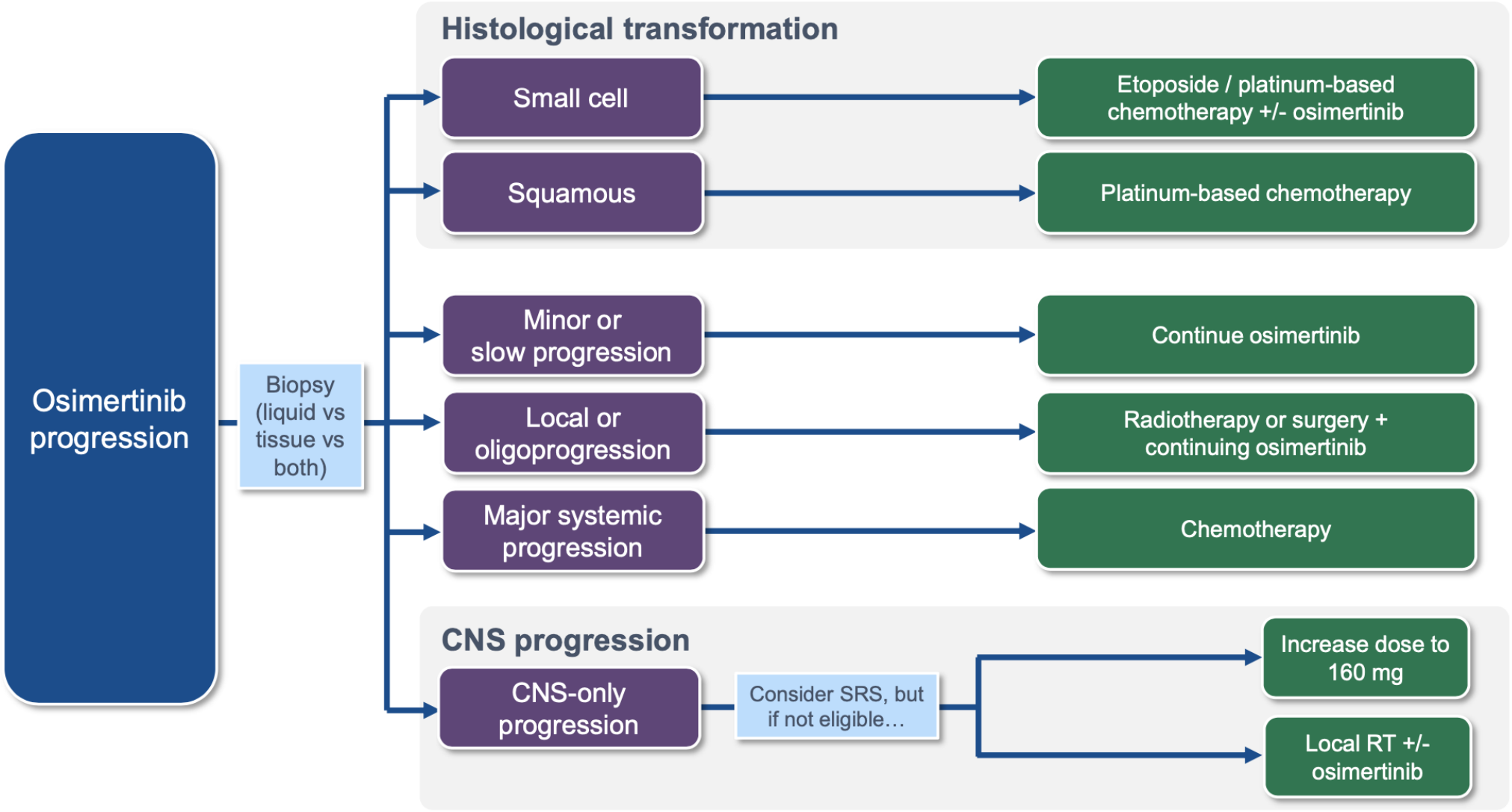
**Transformations**

**Osimertinib resistance is complex**

- Heterogenous patterns of resistance
- Co-occurrence of multiple resistance mechanisms
- NGS of ctDNA has been the most frequently used method to characterize osimertinib resistance mechanisms due to difficulties in obtaining tissue[1-2]

[1]Papadimitrakopoulou *Annals of Oncol* 29:VIII741; [2]Ramalingam *Annals of Oncol* 29:VIII740. ctDNA, circulating tumor DNA; Exon19del, exon 19 deletion; NGS, next generation sequencing

# Management of Acquired resistance

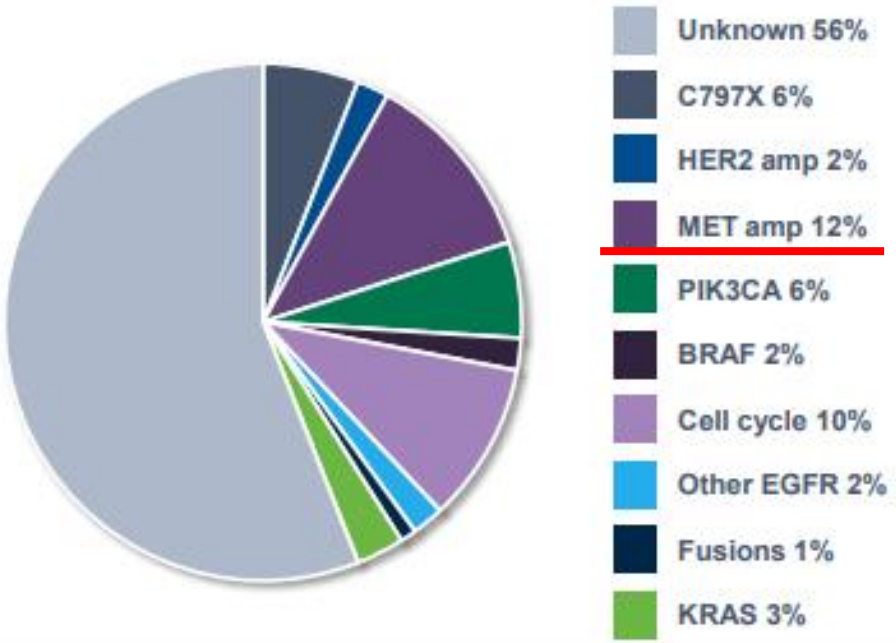



B. Besse ELCC 2022 adapted from Passaro

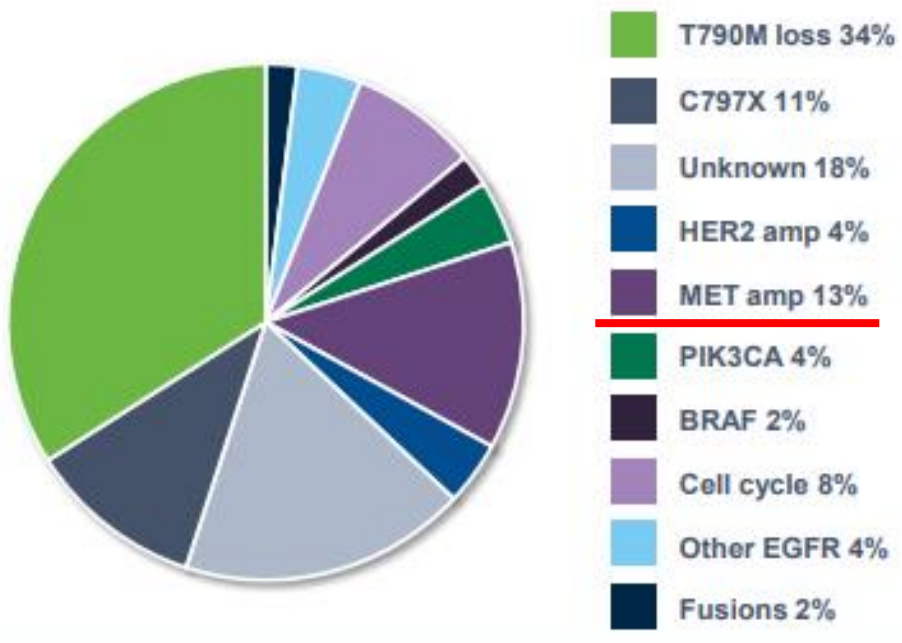
*Passaro Ann Oncol. 2022*

# What are the mechanisms of resistance to third generation EGFR TKIs?

## 1L osimertinib[1]




## 2L osimertinib[1]




**Osimertinib resistance is complex[2]**

- **Heterogeneous** patterns of resistance
- **Co-occurrence** of multiple resistance mechanisms

**Histologic transformation to SCLC in 5–15%[3]**

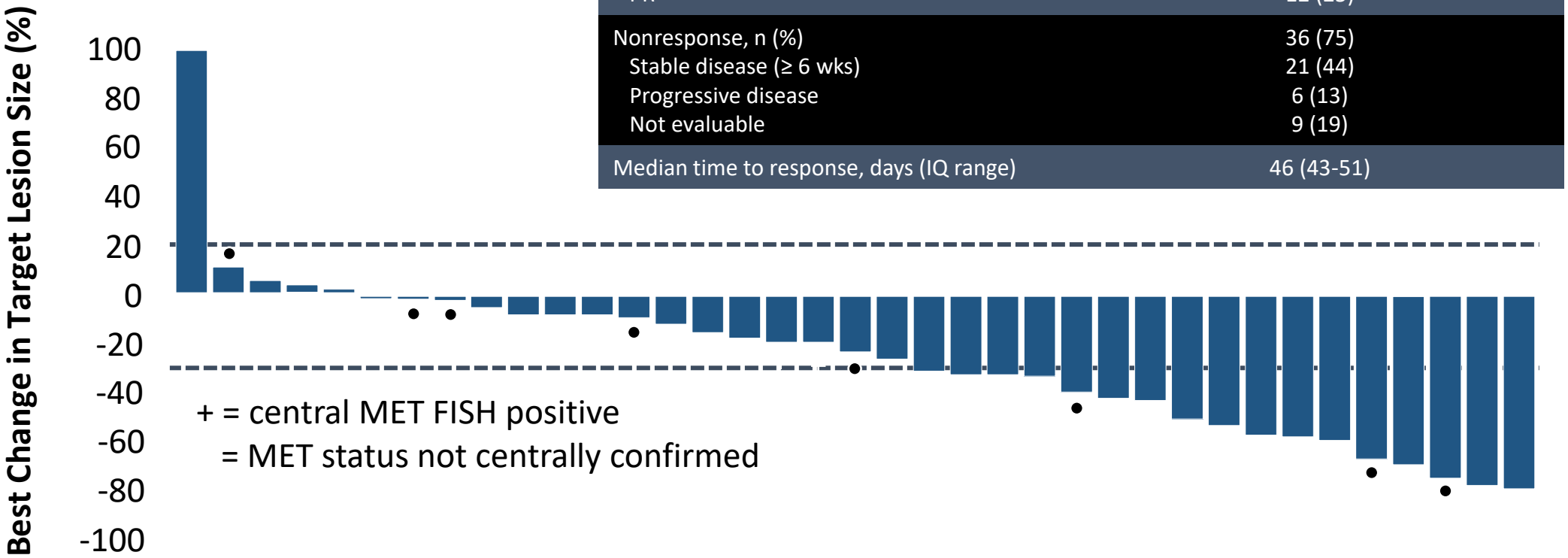
1. Jänne PA, et al. Presented at ASCO 2021:9007; 2. Baumi JM, et al. Presented at ASCO 2021 9006;
3. Pathak R, Villaflor VM. *Cancers (Basel)*. 2021;13:4641.

1L, first line; 2L second line; G, generation.

Besse B, ELCC 2022

# Targeting MET TATTON: Osimertinib + Savolitinib

| | OSI + SAVO: Prior 3rd-Gen EGFR TKI (n = 48) |
|---|---|
| Objective response, n (%) | 12 (25) |
| CR | 0 |
| PR | 12 (25) |
| Nonresponse, n (%) | 36 (75) |
| Stable disease (≥ 6 wks) | 21 (44) |
| Progressive disease | 6 (13) |
| Not evaluable | 9 (19) |
| Median time to response, days (IQ range) | 46 (43-51) |

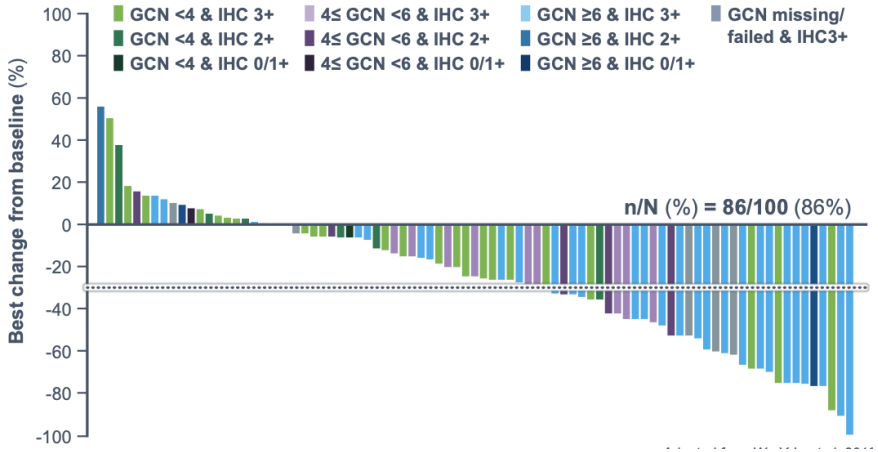



- **Median duration of response 9.7 mo**

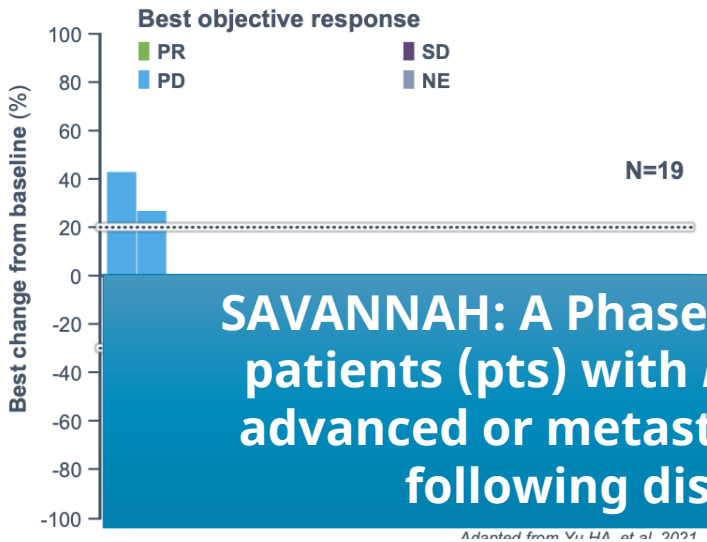
*Sequist. AACR 2019. Abstr CT033.*

# Targeting MET amplification in EGFR+

Phase II study in patients with advanced EGFR+ NSCLC and met alterations (MET amp or MET ex14 skipping mutations) progressing on 1L osimertinib[1]




**01** Osimertinib + Savolitinib **ORCHARD**[1]



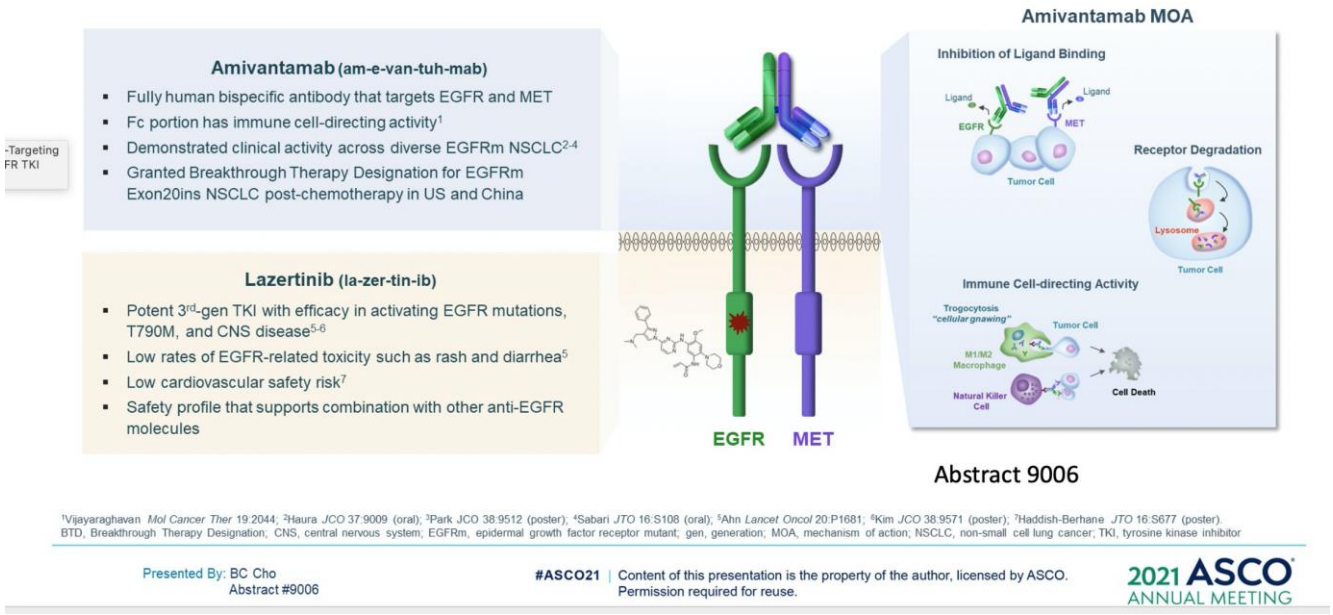

Gefitinib+ Capmatinib[2] **02**

**SAVANNAH: A Phase II trial of osimertinib plus savolitinib for patients (pts) with *EGFR*-mutant, *MET*-driven (*MET*+), locally advanced or metastatic non-small cell lung cancer (NSCLC), following disease progression on osimertinib.**

atinib in patients with
ion (METamp or MET
n EGFR TKI therapy[2]

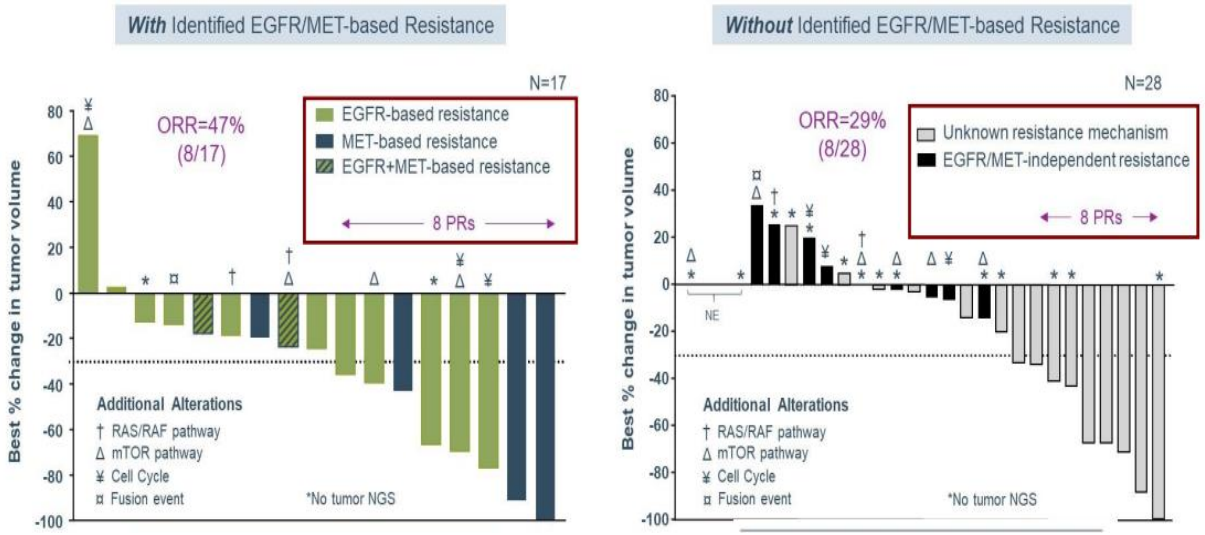
*1Yu HA Ann Oncol 2021 Supp; 2 Whu JCO 2018*

# Amivantamab + Lazertinib after Osi in patients chemo-naïve




| Outcome (N=45) | |
|---|---|
| **ORR** | **36% (95% CI, 22–51)** |
| **CBR** | 64% (95% CI, 49–78) |
| **mDoR, months** | **9.6 (95% CI, 5.3–11.0)** |
| DoR ≥6 months | 69% |
| **mPFS, months** | 4.9 (95% CI, 3.7–9.5) |
| **mF/U, months** | 11.1 (range, 1.0–15.0) |

- Safety profile consistent with previous experience with amivantamab + lazertinib[2–4]
- No new safety signals detected; toxicities consistent with inhibition of EGFR and MET[4]
- Treatment-related: grade ≥3 AE (16%), discontinuations (4%), dose reductions (18%)

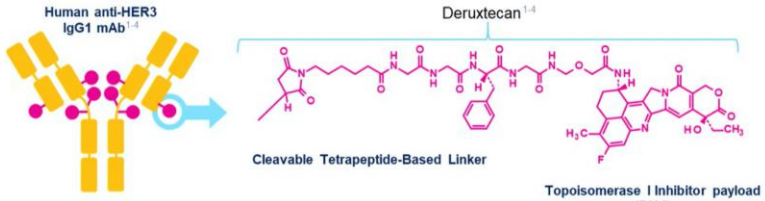




1. *Leighl NB, et al. Presented at ESMO 2021: 1192MO; 2. Park K, et al. J Clin Oncol. 2021;39:3391– 402;*
2. *3. Cho BC, et al. Ann Oncol. 2020;31(Suppl 4):S754–S840; 4. Bauml J, et al. J Clin Oncol. 2021;39 (Supply): 9006.*

# Patritumab Deruxtecan (ADC): phase I

- HER3-DXd is an ADC with 3 components:[1-6]
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to:
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker
- HER3-DXd is in clinical evaluation for NSCLC, metastatic breast cancer, and colorectal cancer




HER3 is expressed in 83% of NSCLC tumors[a]

HER3 alterations are not known to be a mechanism of resistance to EGFR TKI in *EGFR*m NSCLC

Abstract 9007

[a]HER3 overexpression is associated with metastatic progression and decreased relapse-free survival in patients with NSCLC.

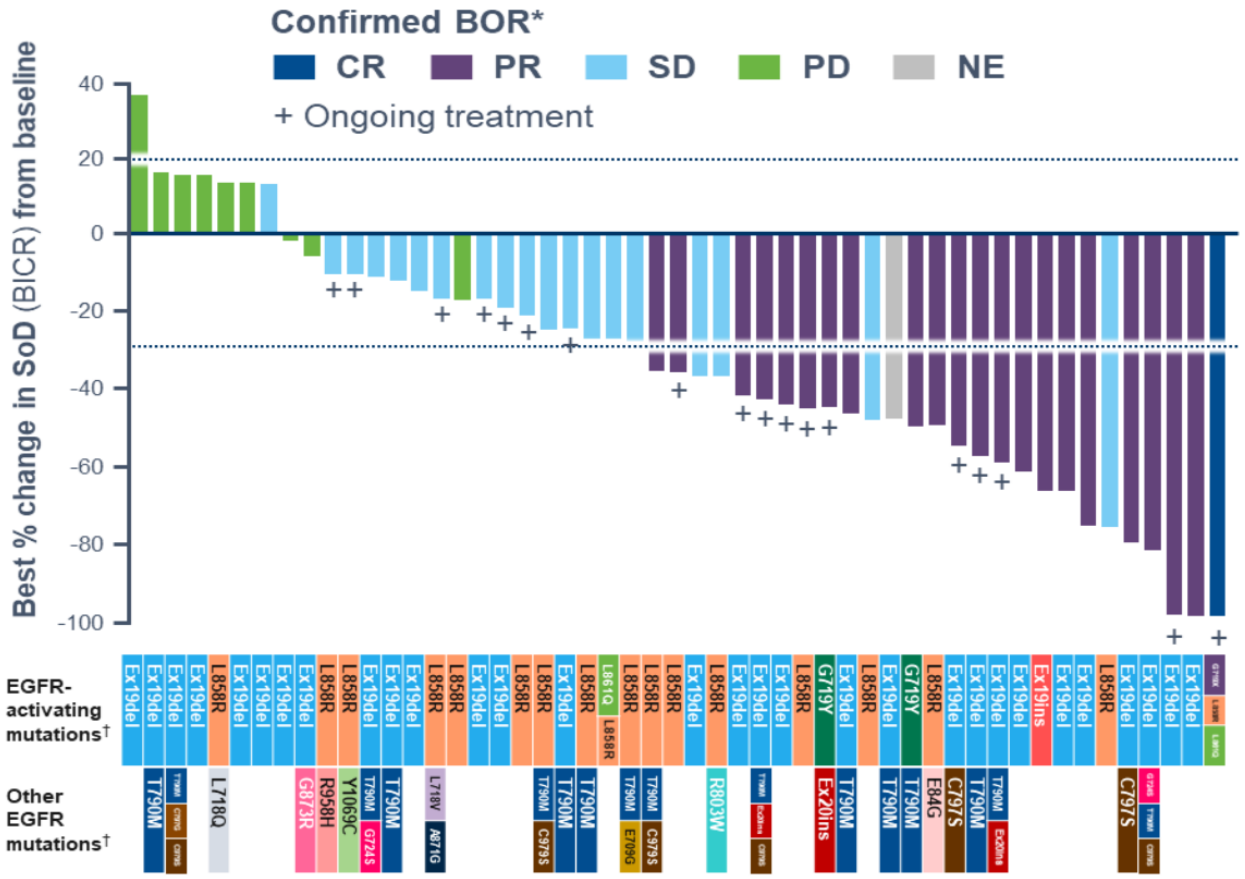
1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046. 7. Scharpenseel H et al. *Sci Rep* 2019;9(1):7406.

Presented By: Pasi A. Jänne

3



2021 ASCO ANNUAL MEETING



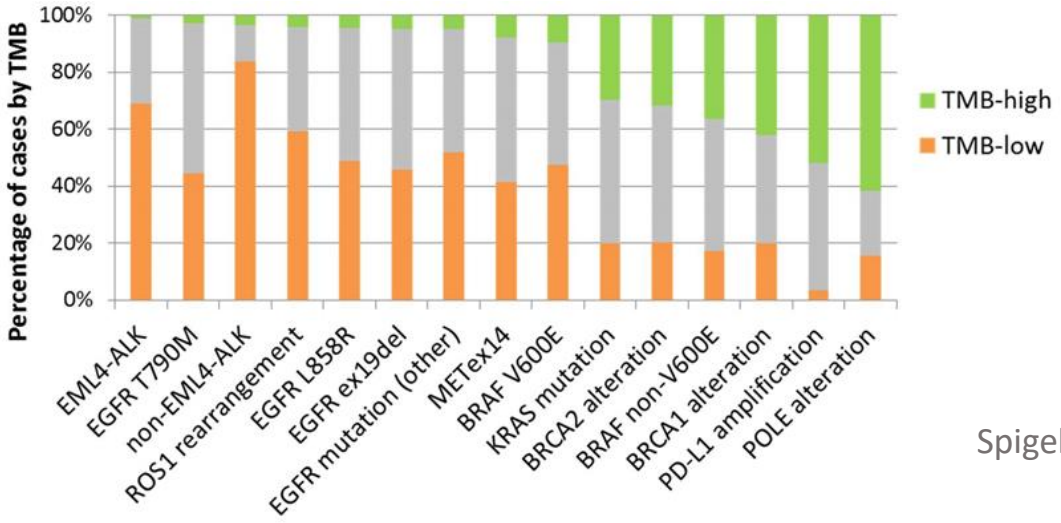

**ORR:** 39%, post PBC and osimertinib (n=44; 95% CI, 24–55)
**mDoR:** 7.0 months, post PBC and osimertinib (n=44, 95% CI, 3.1–NE)
HER3 overexpressed in 83% of primary NSCLC tumours[2]

**HER3-DXd demonstrated activity in patients with different mechanisms of resistance to EGFR TKI**

*1. Jänne PA, et al. Cancer Discov. 2022; 2. Jänne PA, et al. ASCO 2021;*

# ***Unmet clinical need:*** *è possible utilizzare l'immunoterapia nel NSCLC EGFRmut+ ?*

**Low TMB**




Spigel et al ASCO 2016

**Downregulation MHC-I**

ORIGINAL ARTICLE

WILEY Cancer Science

Mutational activation of the epidermal growth factor receptor down-regulates major histocompatibility complex class I expression via the extracellular signal-regulated kinase in non–small cell lung cancer

Satomi Watanabe[1] | Hidetoshi Hayashi[1] | Koji Haratani[1] | Shigeki Shimizu[2] | Junko Tanizaki[1] | Kazuko Sakai[3] | Hisato Kawakami[1] | Kimio Yonesaka[1] | Junji Tsurutani[1,4] | Yosuke Togashi[5] | Kazuto Nishio[3] | Akihiko Ito[2] | Kazuhiko Nakagawa[1]

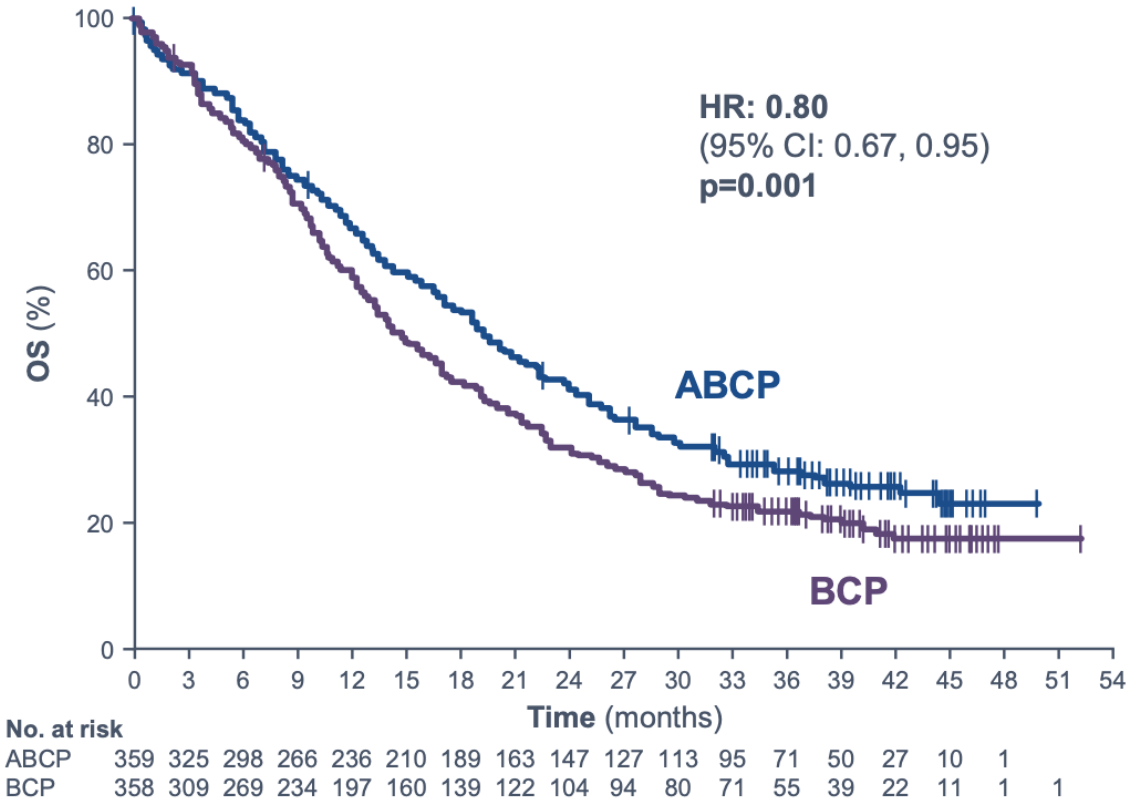
Microambiente tumorale poco immunogenico

Sovraespressione di CD73 con conseguente microambiente tumorale immunosoppressivo e ridotta IFN-γ signature

K. Streicher et al., JCO, 2017

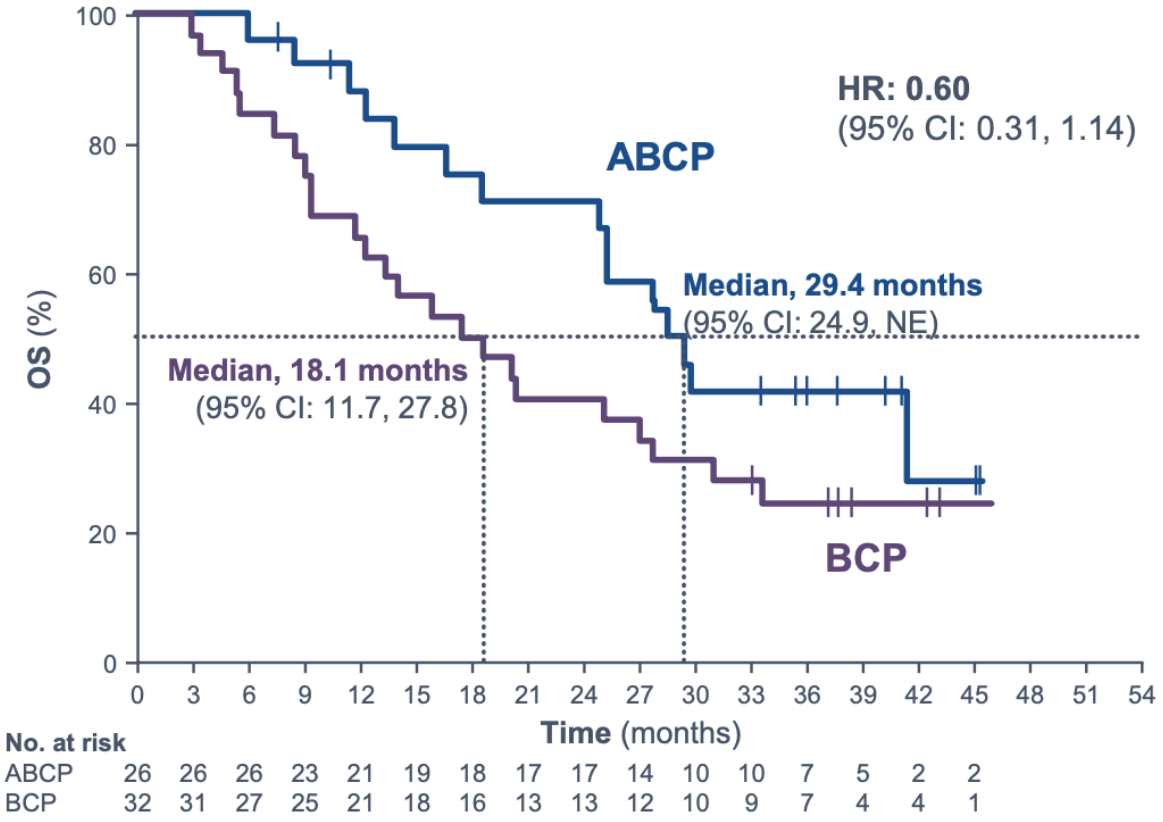
# Phase 3 IMpower150 study: chemo + bev+ atezo

## ITT-WT: ABCP vs BCP[1]




Overall survival in chemotherapy-naïve patients with WT genes (no EGFR or ALK alterations)1

## Sensitizing EGFR: ABCP vs BCP[2]




Overall survival in chemotherapy-naïve patients with sensitizing EGFR mutations[2]

1. Socinski MA, et al. *J Thoracic Oncol*. 2021;16:1909−24; 2. Nogami N, et al. *J Thorac Oncol*. 2022;17:309–23.

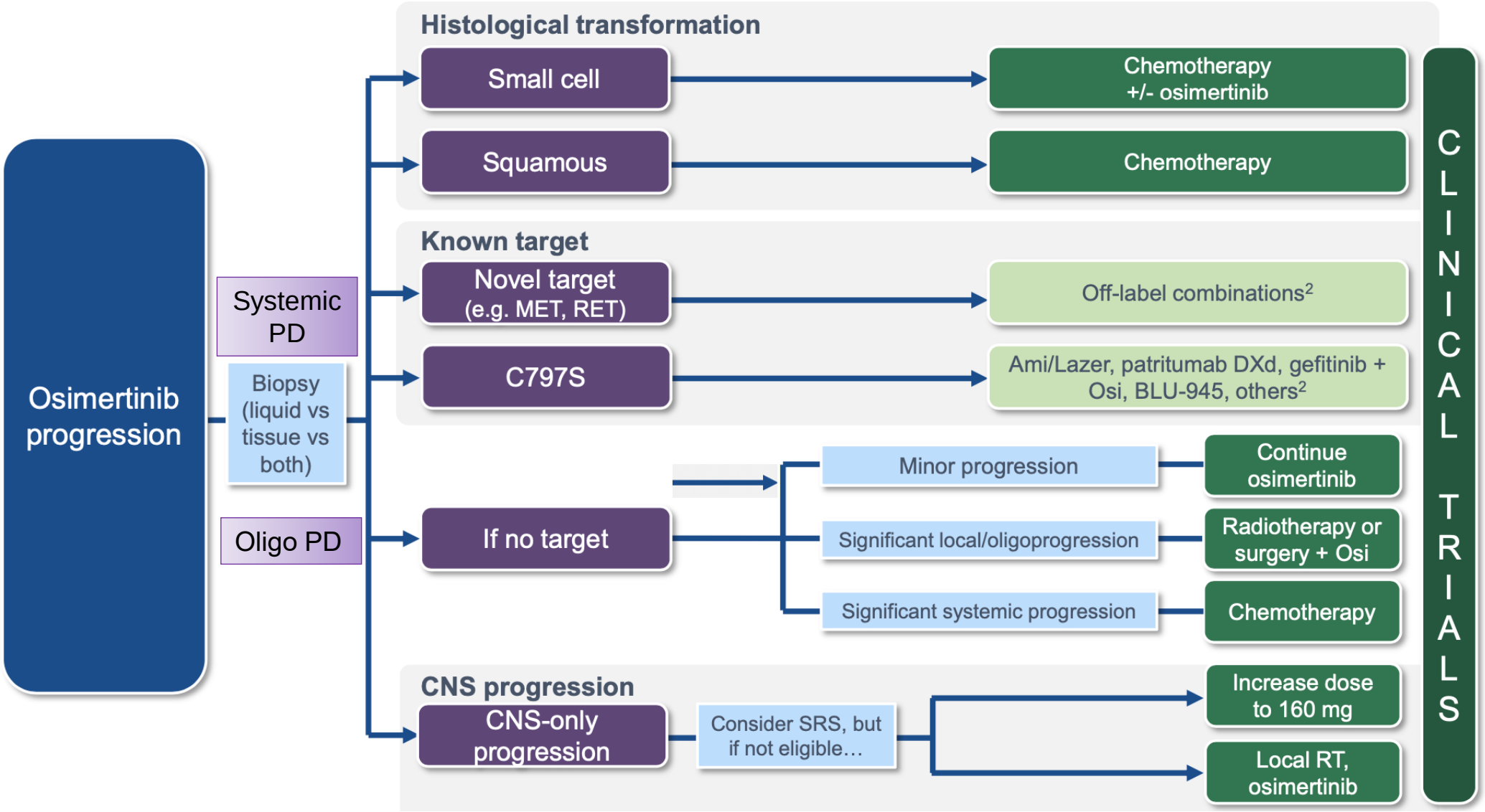
# New Target for EGFR TKI resistant in (≥2L)

| Study | Phase | Experimental arm(s) | Comparator arm |
|---|---|---|---|
| **TATTON**[1] | 1b | Osimertinib + savolitinib (MET TKI)<br>Osimertinib + selumetinib (MEK1/2 inhibitor)<br>Osimertinib + durvalumab (anti-PD-L1) | None |
| **SAVANNAH**[2] | 2 | Osimertinib + savolitinib | None |
| **ORCHARD**[3] | 2 | Osimertinib + savolitinib<br>Osimertinib + gefitinib<br>Osimertinib + necitumumab<br>Carboplatin + pemetrexed + durvalumab<br>Osimertinib + alectinib<br>Osimertinib + selpercatinib | None |
| **Capmatinib**[4] | 1b/2 | Capmatinib + gefitinib<br>Gefitinib | Gefitinib |
| **INSIGHT 2**[5] | 2 | Tepotinib + osimertinib | Tepotinib (experimental) |
| **Crizotinib**[6] | 4 | Crizotinib + EGFR TKI<br>Crizotinib<br>Chemotherapy | None |
| **U31402-A-U102**[7] | 1 | Patritumab deruxtecan | None |
| **WJOG8515L study**[8] | 2 | Nivolumab | Carboplatin pemetrexed |
| **CHRYSALIS**[9] | 1/2 | Amivantamab<br>Amivantamab + lazertinib | None |
| **CHRYSALIS-2**[10] | 1/1b | Lazertinib<br>Lazertinib + amivantamab<br>Lazertinib + amivantamab + pemetrexed + carboplatin | None |
| **MARIPOSA-2**[11] | 3 | Lazertinib + amivantamab + pemetrexed + carboplatin<br>Amivantamab + pemetrexed + carboplatin<br>Carboplatin + pemetrexed | Pemetrexed + carboplatin |

B. Besse ELCC 2022

1. ClinicalTrials.gov. NCT02143466, 2. ClinicalTrials.gov. NCT03778229, 3. ClinicalTrials.gov. NCT03944772 4. Wu Y-L, et al. Presented at ASCO 2021, 5. ClinicalTrials.gov. NCT0394070, 6. Liu L, et al. Presented at ASCO 2021. 7. Jänne PA, et al. Presented at ASCO 2021 , 8. Hayashi H, et al. Presented at ASCO 2021 , 9. ClinicalTrials.gov. NCT02609776, 10. ClinicalTrials.gov. NCT04077463. 11. ClinicalTrials.gov. NCT04988295.

# TKI management approach in the near future[1]

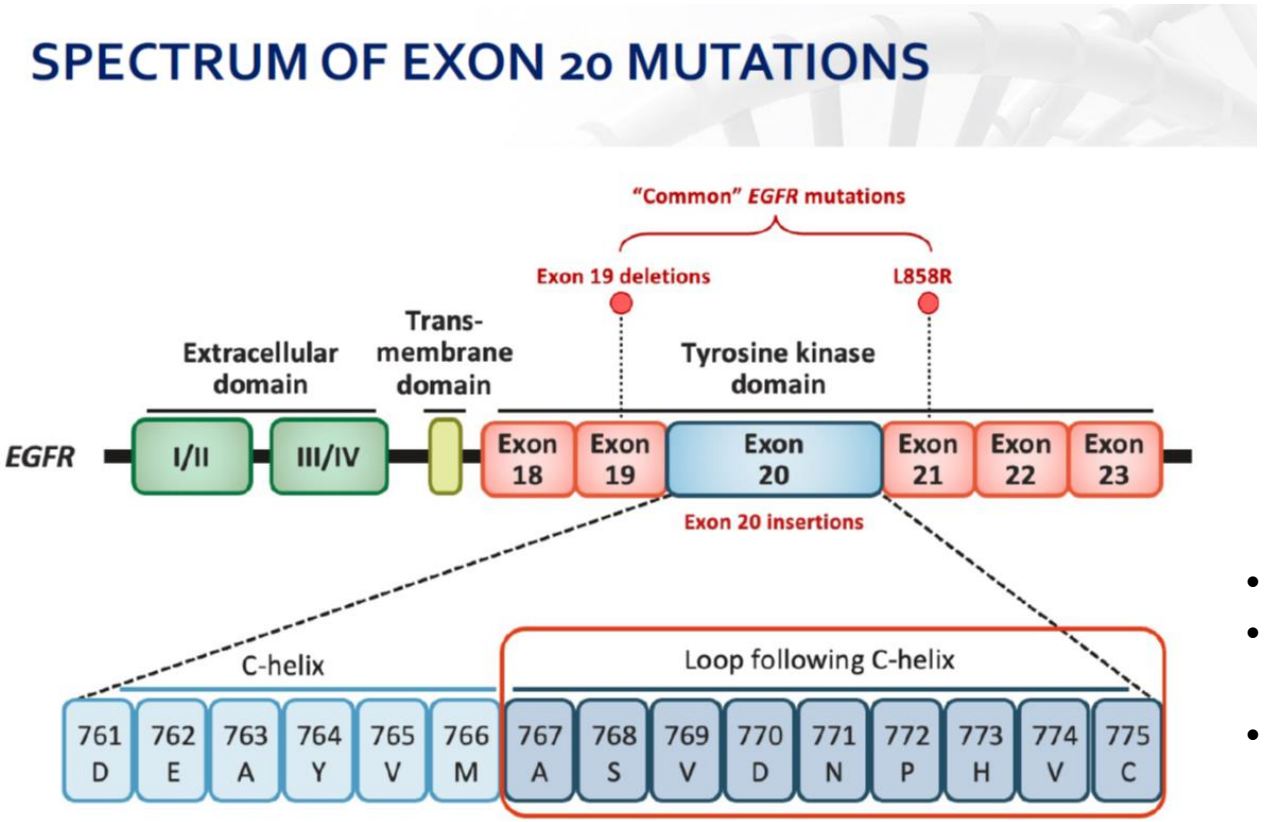


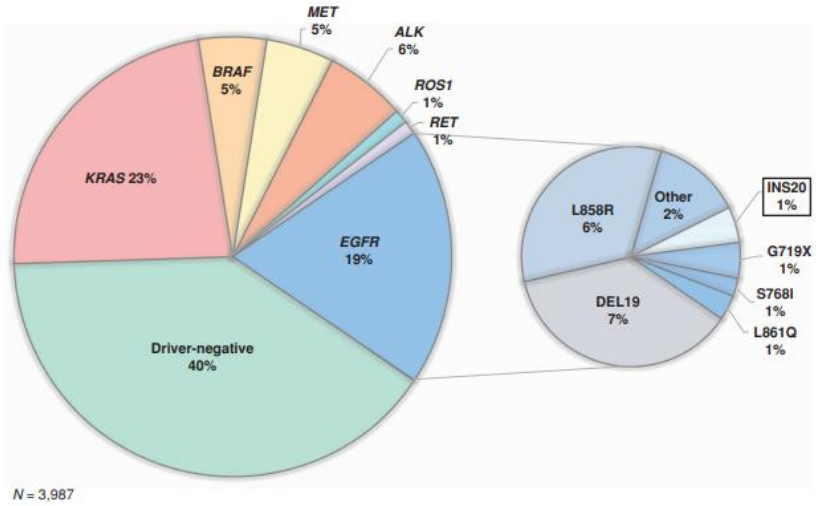

*B. Besse ELCC 2022 adapted from Passaro A, Ann Oncol 2022*

# Agenda

- First line
- Overcoming Resistance
- Exon 20 insertions and uncommon mutations

# EGFR exon 20 insertions




- 1.5 – 3% of all NSCLC cases
- Higher frequency in adc, females, necer smokers
- About 90% detected within 767 and 775 aminoacids
- Induce a wedge at the end of C-helix with constitutive activation of EGFR TK domain
- Low affinity to first generation EGFR TKIs

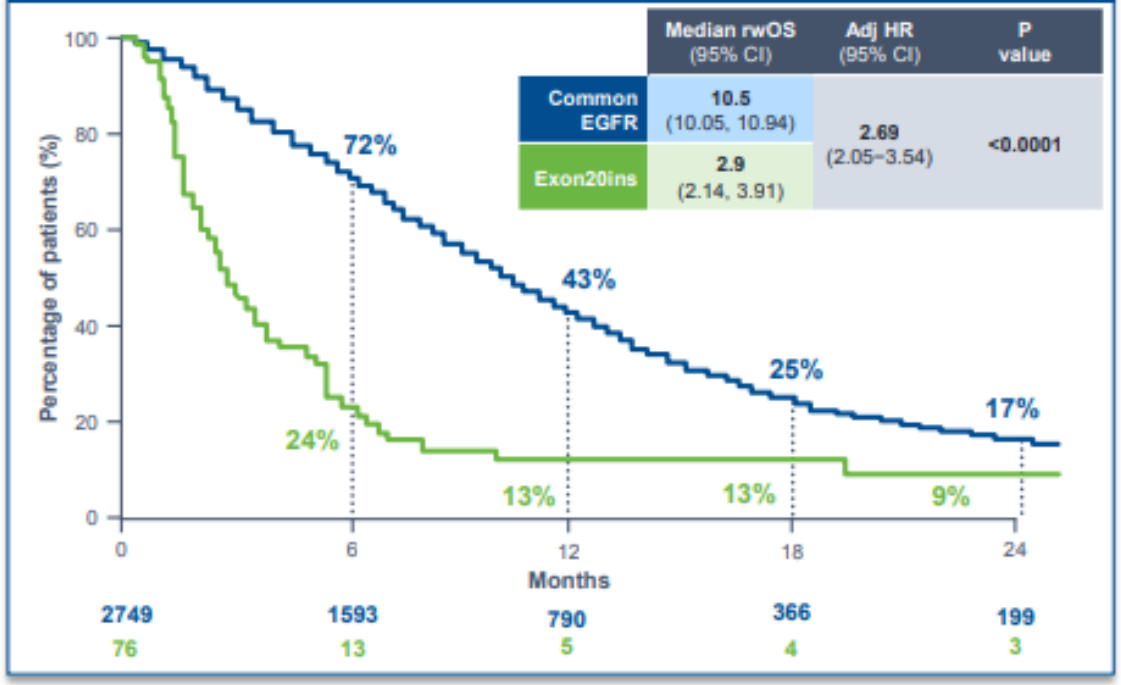
*EGFR*=epidermal growth factor receptor.
Vyse S, Huang PH. *Signal Transduct Target Ther*. 2019;4-5.

*Malapelle U, Crit Rev Oncol 2021*

# Differences in prognosis between sensitizing EGFR mutation and EGFR exon20ins

## Prognosis for EGFR exon20ins vs common mutations: Real-world OS


## Predictive value of EGFR exon20ins vs common mutations with TKI therapy: Real-world PFS*




| Risk with EGFR exon20ins vs common EGFR mutations | Increase (%) |
|---|---|
| Death† (adjHR, 1.75 [95% CI, 1.45–2.13]; p<0.0001) | +75% |
| Progression or death (adjHR, 1.93 [95% CI, 1.61–2.31]; p<0.0001) | +93% |
| Shorter time to next treatment (adjHR, 1.60 [95% CI, 1.36–1.9]; p<0.0001) | +60% |

| Risk with EGFR exon20ins vs common EGFR mutations on TKI | Increase (%) |
|---|---|
| Progression or death† (adjHR, 2.69 [95% CI, 2.05–3.54]; p<0.0001) | +169 |
| Death (adjHR, 2.70 [95% CI, 2.04–3.57]; p<0.0001) | +170 |
| Shorter time to next treatment (adjHR, 2.54 [95% CI, 1.97–3.27]; p<0.0001) | +154 |

*Adapted from Bazhenova L, et al. 2021.*

*Mok T, ELCC 2022*

# Exon 20 insertions

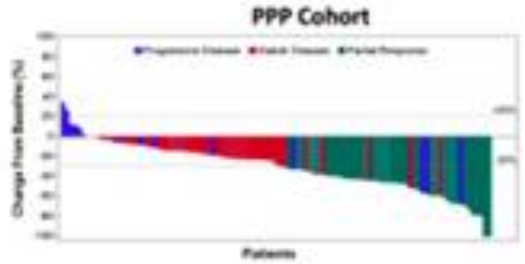
| Name of therapy | Mechanism of action | Relative mutant specificity | N | ORR | mPFS | Primary endpoint reached? (Y/N) | Level of evidence | Reference | Active clinical trials[c] |
|---|---|---|---|---|---|---|---|---|---|
| Poziotinib | EGFR TKI | + | 115 | 15% | 4.2 mo | N | Phase II clinical trial | **Le et al., 2020 (67)** | NCT03066206<br>NCT03318939 (ZENITH20) |
| Osimertinib | EGFR TKI | ++ | 17 | 24% | 9.6 mo | N | Phase II clinical trial | **Piotrowska et al., 2020 (34)** | NCT03414814<br>NCT03191149 (EA5162)[d] |
| Tarloxotinib | Hypoxia-activated EGFR TKI | + | 11 | 0% | — | N | Phase II clinical trial | **Liu et al., 2020 (60)** | NCT03805841 (RAIN-701) |
| Luminespib | HSP90 inhibitor | + | 29 | 17% | 2.8 mo | N | Phase II clinical trial | **Piotrowska et al., 2018 (54)** | – |
| Mobocertinib[a] (TAK-788) | EGFR TKI | +++ | 96 | 23% | 7.3 mo | — | Phase I/II clinical trial | Riely et al., 2021 (23)<br>**Zhou et al., 2020 (24)** | NCT02716116 (EXCLAIM)<br>NCT04129502 (EXCLAIM-2) |
| CLN-081 | EGFR TKI | +++ | 17 | 35% | — | — | Phase I/II clinical trial | **Piotrowska et al., 2020 (40)** | NCT04036682 |
| Amivantamab[b] (± lazertinib ± chemotherapy) | EGFR/cMET antibody | ++ | 81 | 40% | 8.3 mo | — | Phase I clinical trial | Park et al., 2020 (45)<br>**Sabari et al., 2020 (46)** | NCT02609776 (CHRYSALIS)<br>NCT04538664 (PAPILLON) |
| Osimertinib + necitumumab | EGFR TKI + EGFR antibody | ++ | 4 | 50% | 5.3 mo | — | Phase I clinical trial | **Riess et al., 2019 (51)** | NCT02496663 |
| Afatinib + cetuximab | EGFR TKI + EGFR antibody | + | 4 | 75% | — | — | Case series | **Van Veggel et al., 2018 (50)** | NCT03727724 (AFACET) |
| BDTX-189 | EGFR TKI | ++ | — | — | — | — | Preclinical data | — | NCT04209465 |
| JMT101 + osimertinib or afatinib | EGFR TKI + EGFR antibody | ++ | — | — | — | — | Preclinical data | — | NCT04448379 |

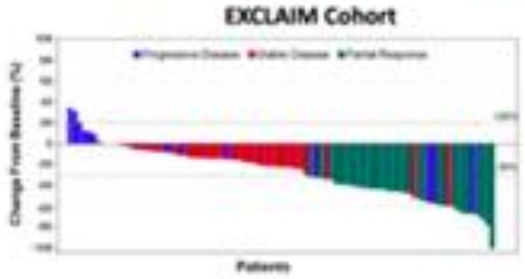
*Meador CB, Cancer Discovery 2021*

# Exon 20 insertions

## MOBOCERTINIB

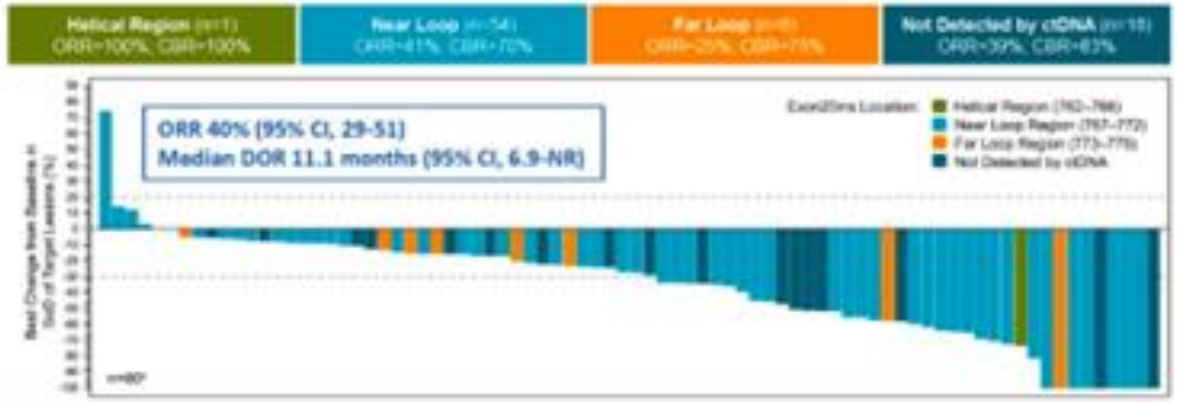
| Outcome | No. (%) | |
|---|---|---|
| | PPP cohort (n = 114) | EXCLAIM cohort (n = 96) |
| IRC-assessed confirmed objective response[b] | | |
| Patients, No. (%) [95% CI] | 32 (28) [20-37] | 24 (25) [17-35] |
| Complete response | 0 | 0 |
| Partial response | 32 (28) | 24 (25) |
| Stable disease[c] | 57 (50) | 49 (51) |
| Not evaluable | 12 (11) | 10 (10) |
| Confirmed disease control rate, No. (%) [95% CI][d] | 89 (78) [69-85] | 73 (76) [66-84] |




**EXCLAIM Trial**
(phase I/II study)


## AMIVANTAMAB




25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

**CHRYSALIS Trial**
(phase I study)

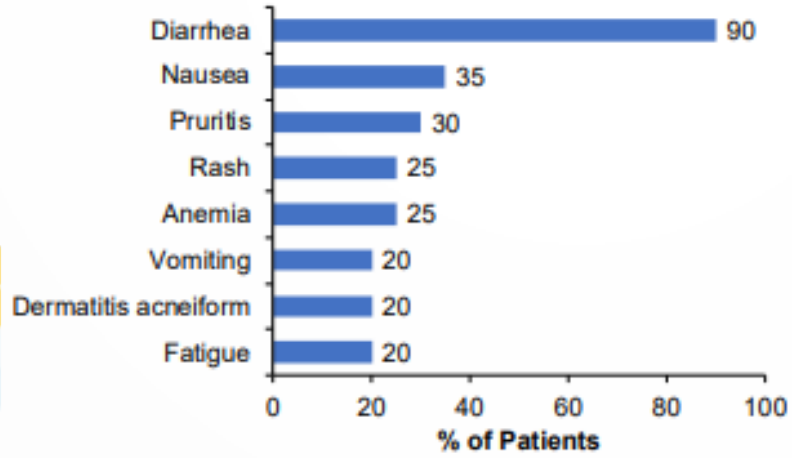

Zhou C, JAMA Oncol 2021; Park K, JCO 2021

# Exon 20 insertions

## Mobocertinib-oral agent

| | n (%)<br>N=20 |
|---|---|
| Any TEAEs | 20 (100) |
| Grade ≥3 TEAEs | 10 (50) |
| Any TRAE | 20 (100) |
| Grade ≥3 TRAE | 4 (20) |
| Serious AEs | 7 (35) |
| AEs leading to dosage reduction | 4 (20) |
| AEs leading to treatment discontinuation | 2 (10) |

**All-Grade TRAEs Observed in ≥20% of Patients (N=20)**




## Amivantamab-i.v. agent

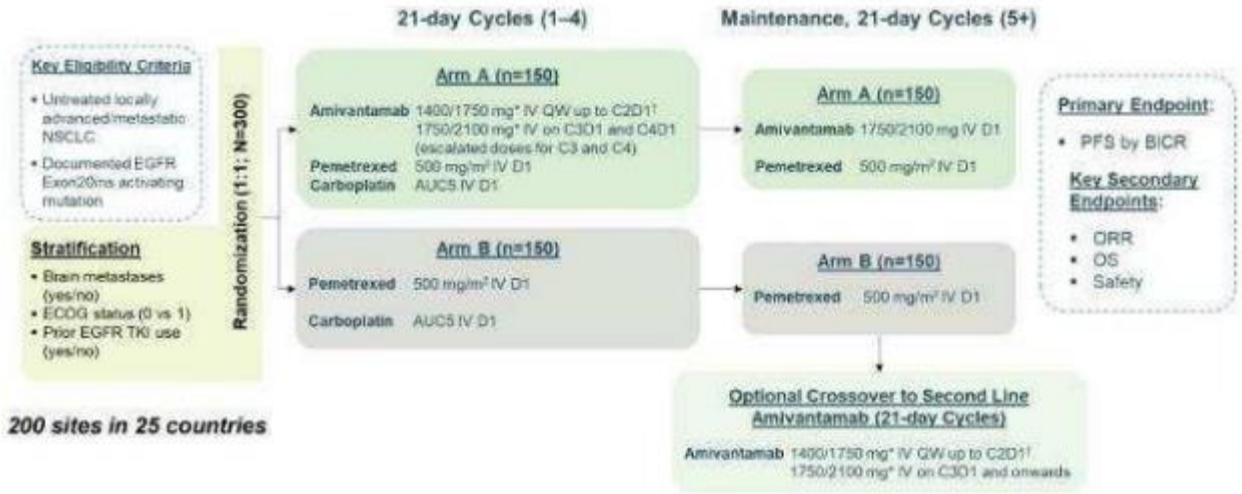
| Adverse Event, n (%) | Safety Population (N=114) | |
|---|---|---|
| | Treatment-emergent AE | Treatment-related AE |
| Any AE | 113 (99) | 112 (98) |
| Grade ≥3 AE | 40 (35) | 18 (16) |
| Serious AE | 34 (30) | 10 (9) |
| AE leading to death | 8 (7) | 0 |
| AE leading to discontinuation | 11 (10) | 5 (4) |
| AE leading to dose reduction | 15 (13) | 15 (13) |
| AE leading to dose interruption[a] | 40 (35) | 24 (21) |

Diarrhea 12% (3.5% grade 3)

Cappuzzo, WCLC 2021

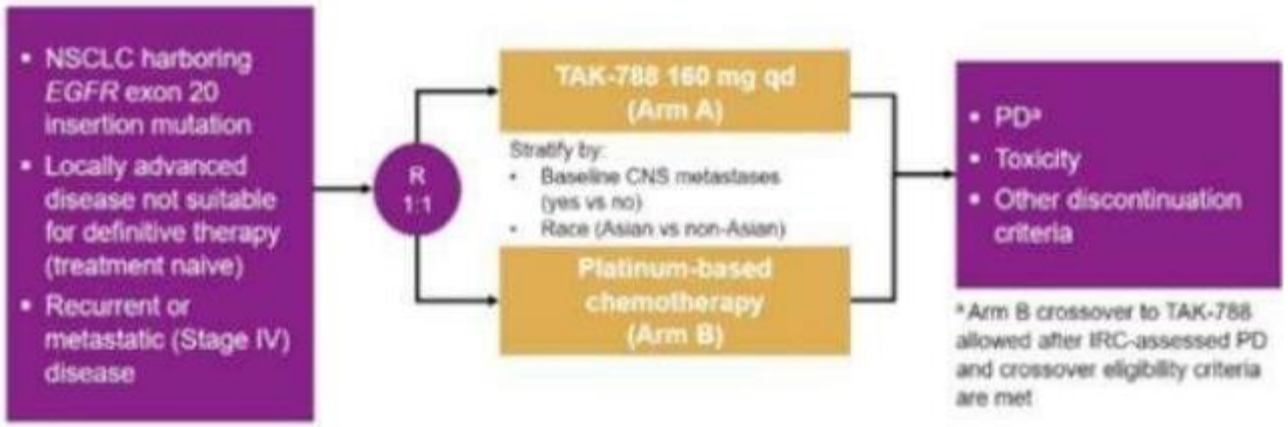
# Exon 20 insertions

## PAPILLON (NCT04538664)




Carbo/Pem + Ami vs. Carbo/Pem

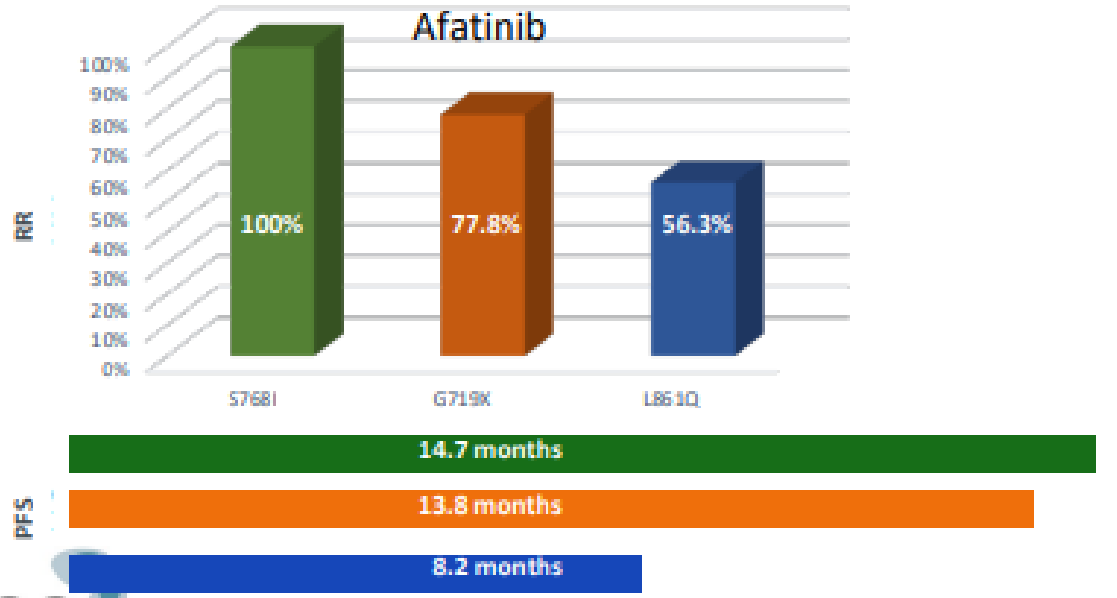
## EXCLAIM-2 (NCT04129502)

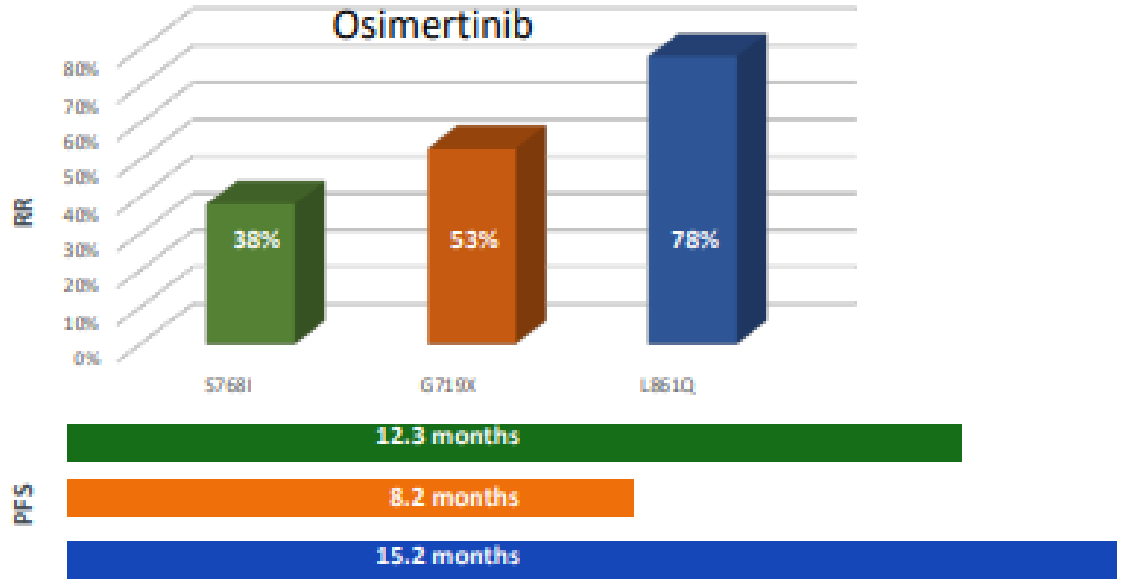



Carbo/Pem vs. Mobocertinib

# EGFR uncommon mutations

| Overall (S768I+G719X+L861Q) | First generation EGFR TKI (gefitinib) Post-hoc NEJ002 *N*=9 | Second generation EGFR TKI (afatinib) Post-hoc analysis LL 2-3-6 *N*=38 | Third generation EGFR TKI (osimertinib) Phase II *N*=36 |
|---|---|---|---|
| RR(%) | 20 | 71.1 | 50 |
| mPFS (months) | 2.2 | 10.7 | 8.2 |
| mOS (months) | 11.9 | 19.4 | NR |




elcc European Lung Cancer Congress

Giulia Pasello

*Watanabe S, JTO 2014; Yang JCH, Lancet Oncol 2015; Cho JH, JCO 2019*

# ARTICUNO

**A**ctivity of Osime**RTI**nib in Patients with NS**C**LC Harboring **UN**common EGFR Mutations: a Retrospective **O**bservational Multicenter Italian Study

Sistema Socio Sanitario

Ospedale Niguarda

Regione Lombardia

# **A**ctivity of Osime**RTI**nib in Patients with NS**C**LC Harboring **UN**common EGFR Mutations: a Retrospective **O**bservational Multicenter Italian Study (**ARTICUNO**)


ARTICUNO
Map
(14 Regions,
31 Centers)

Approvals CE up to 02-2022:
19/31 Centers

On going
Approved

# Malattia avanzata EGFR mutata
# Quali novità nel 2022?

- First line

***Osimertinib is still the gold standard***

- Overcoming Resistance

***please, refer patients to clinical trials!!!***

- Exon 20 insertions and uncommon mutations

***Amivantamab and Mobocertinib***
***new options in pretreated exon 20 insertions***


Grazie