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UNIVERSIDAD DE LAS PALMAS
DE GRAN CANARIA

Treatment in EGFR mutated NSCLC

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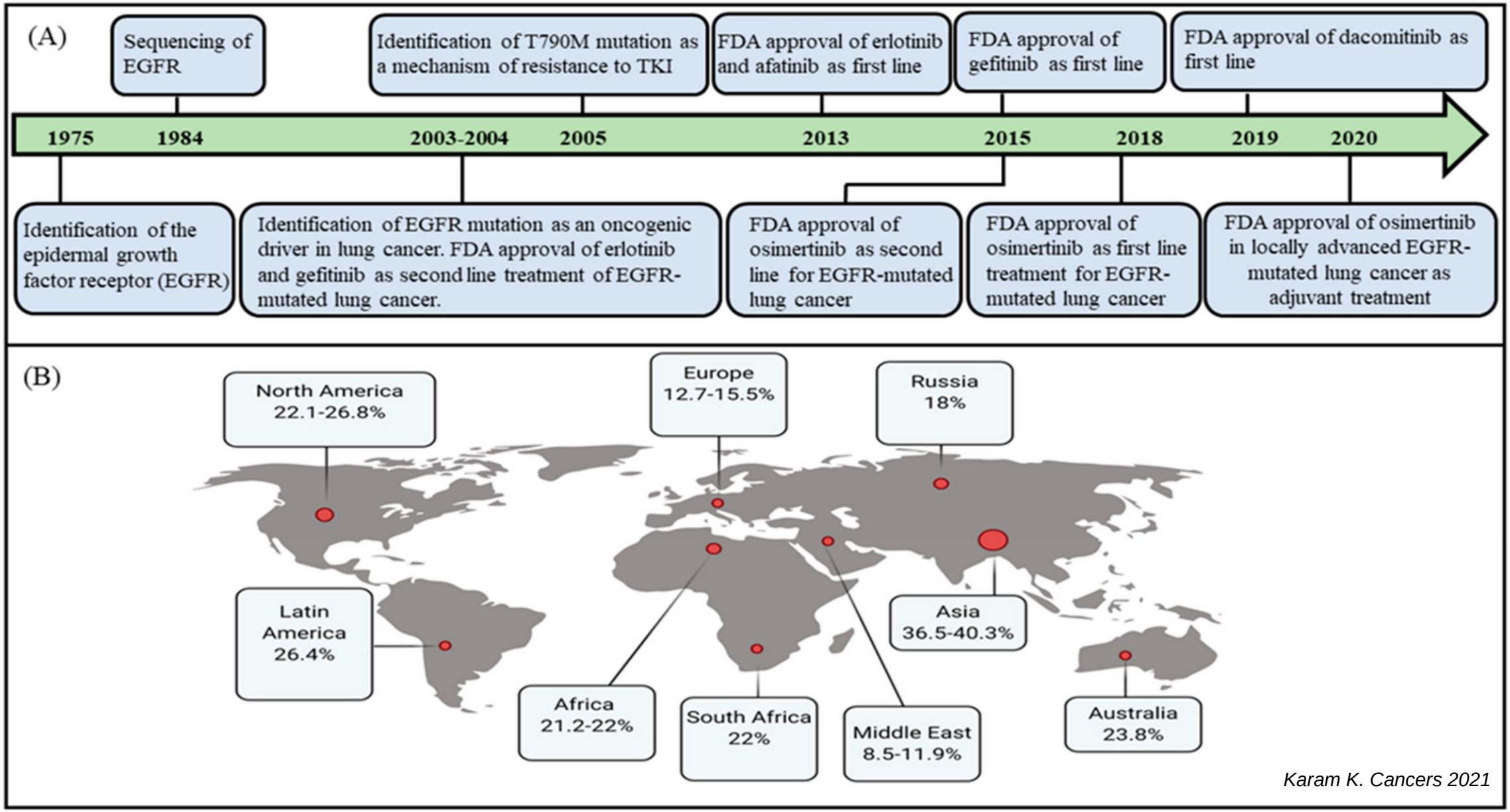
Disclosure Information

- Personal fees/honoraria for consultancy and lectures from Roche, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, MSD, Eli Lilly, Pfizer, and Novartis

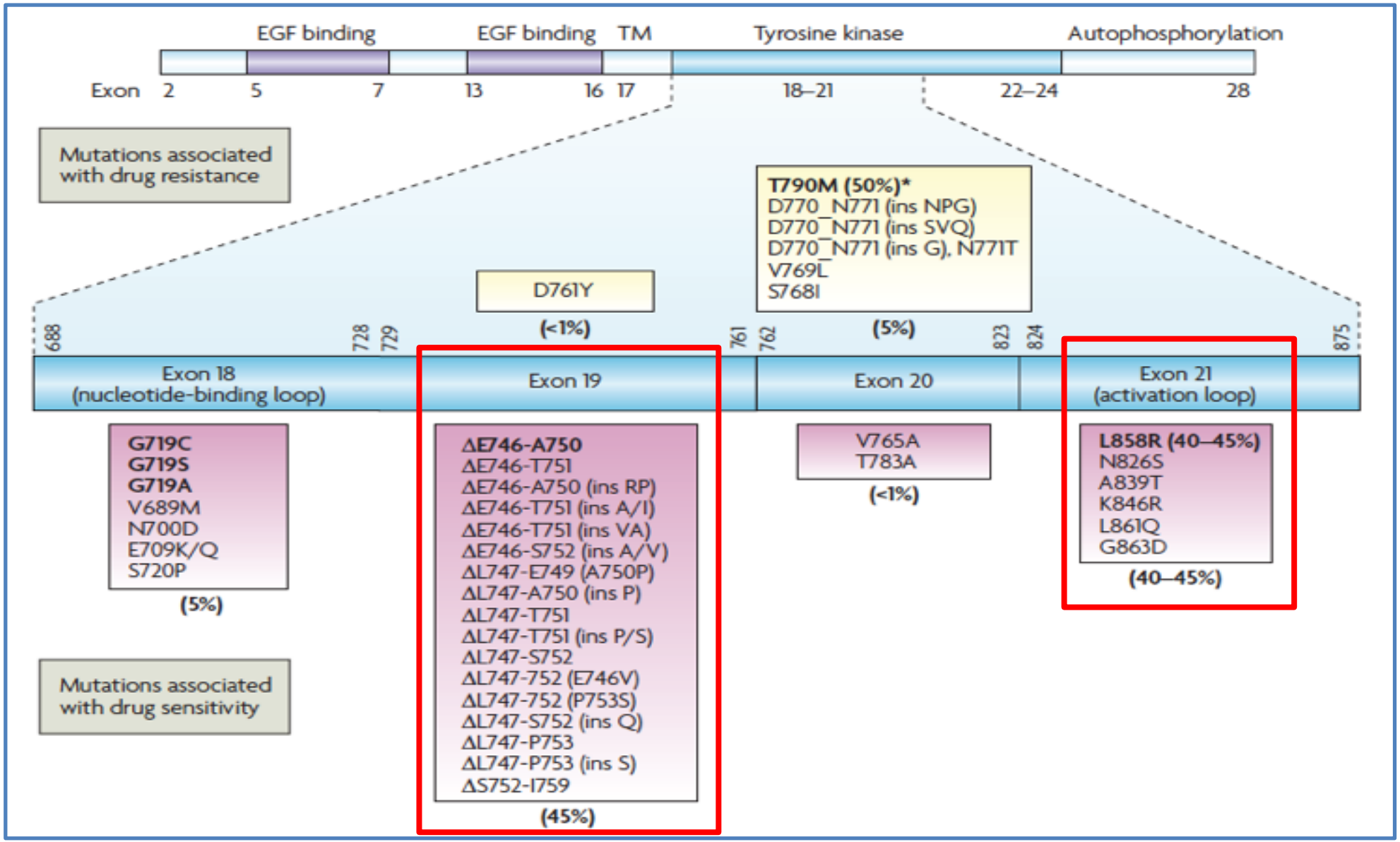
- Travel expenses from Roche, Bristol-Myers Squibb, MSD and Novartis

- Grant support for studies from BMS



Karam K. Cancers 2021

EGFR activating mutations



Sharma et al, Nat Rev Cancer 2007

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EGFR mutated NSCLC

- What do we really need?
  - Survival and Tolerability—Always!!!
  - Reduce Brain Mets and Brain relapse.

- The Best drug must be use always First.
  - Even now many patients never receive to 2nd line.

- **EGFR Mutation testing is SOC at diagnosis**

- **Five FDA approved oral TKIs:**
  - Erlotinib, Gefitinib, Afatinib
  - Osimertinib and Dacomitinib

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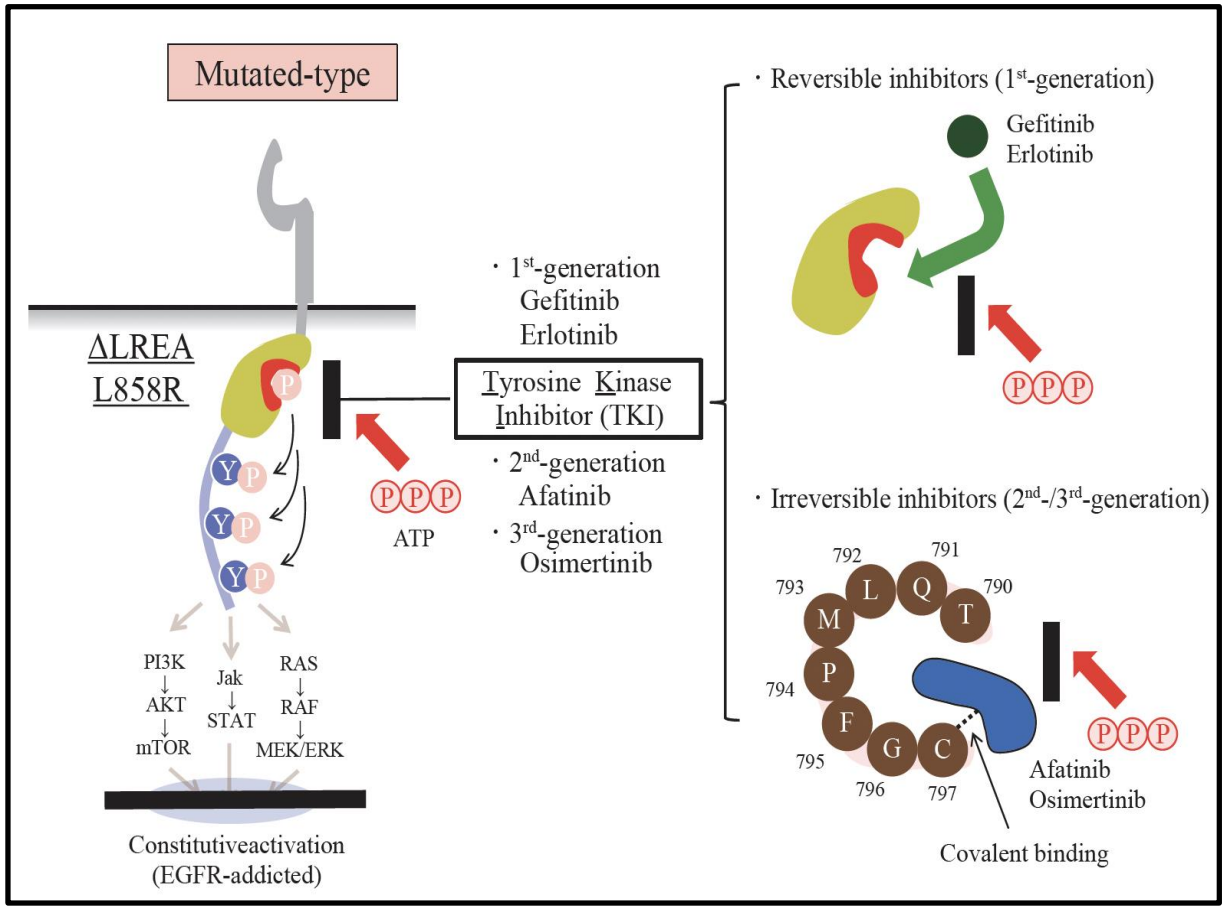
Gefitinib Afatinib Osimertinib

Not all TKI are equals

	Gefitinib	Afatinib	Osimertinib
Wild Type EGFR	+++	++++	+
EGFR exon 19/L858R	+++	++++	++++
EGFR T790M	-	+	++++

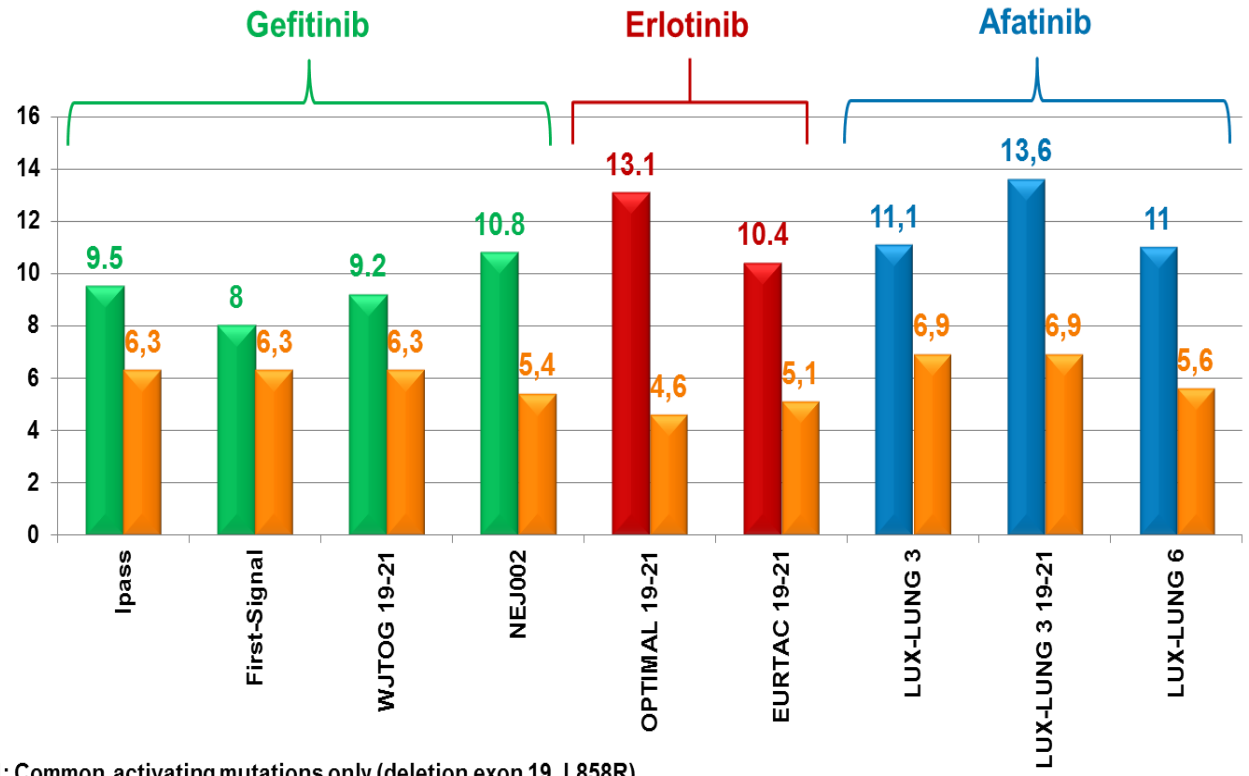
	Gefitinib	Erlotinib	Afatinib	Dacomitinib	Osimertinib
Type of EGFR TK inhibitor	Reversible	Reversible	Irreversible	Irreversible	Irreversible
T ½ (elimination)	41 hr	24-36 hr	36 hr	59-85 hr	48 hr
Tmax	3-7 hr	1-7 hr	3 hr	6-24 hr	6 hr
MTD	800 mg daily	150 mg daily	50 mg daily	45 mg daily	None
Vd/F (L)	1700	232	2870	2415	997
DLT	Diarrhea	Diarrhea, rash	Diarrhea, mucositis	stomatitis, rash, hand foot, paronychia, diarrhea	No
RP2D	250 mg daily	150 mg daily	50 mg daily	45 mg daily	80 mg
Metabolism	CYP3A4	CYP3A4	P-Glycoprotein	CYP2D6	CYP3A4, CYP3A5
Food effect	none	Increased AUC (100%)	Yes	No	Yes



Peters, Zimmermann & Adjei, Cancer Treatment Reviews 40 (2014) 917–926. Kazue Y.2019

TKI mono versus Chemotherapy

1st and 2nd Generation EGFR TKI *vs*. chemotherapy PFS and OS



19-21: Common activating mutations only (deletion exon 19. L858R)

Trials	Common mutations (N)	Median OS EGFR TKI *vs* CT	HR OS (95% CI)
IPASS[1,2] (78% maturity)	251 (subgroup)	21.6 *vs* 21.9	1.00 (0.76-1.33)
WJTOG 3405[3] (74% maturity)	172	34.8 *vs* 37.3	1.25 (0.88-1.78)
NEJ002[4] (60% maturity)	228	27.7 *vs* 26.6	0.89 (0.63-1.24)
OPTIMAL[5] (60% maturity)	154	22.7 *vs* 28.9	1.04 (0.69-1.58)
EURTAC[6] (62% maturity)	173	22.9 *vs* 20.8	0.93 (0.64-1.35)
LUX-LUNG 3[7] (62% maturity)	307 (subgroup)	31.6 *vs* 28.2	0.78 (0.58-1.06)
LUX-LUNG 6[7] (68% maturity)	324 (subgroup)	23.6 *vs* 23.5	0.83 (0.62-1.09)

Han. *JCO* 2012. Mok et al.; *NEJM* 2009. Maemondo et al.. *NEJM*. 2010; Inoue. *Ann Oncol* 2013; Mitsudomi. ASCO 2012; Zhou. *Lancet Oncol* 2012; Mok. ESMO 2010 ; Rosell. *Lancet Oncol* 2012; Rosell. ESMO 2012; Sequist. *JCO* 2013; Wu. *Lancet Oncol* 2014

TKI versus TKI

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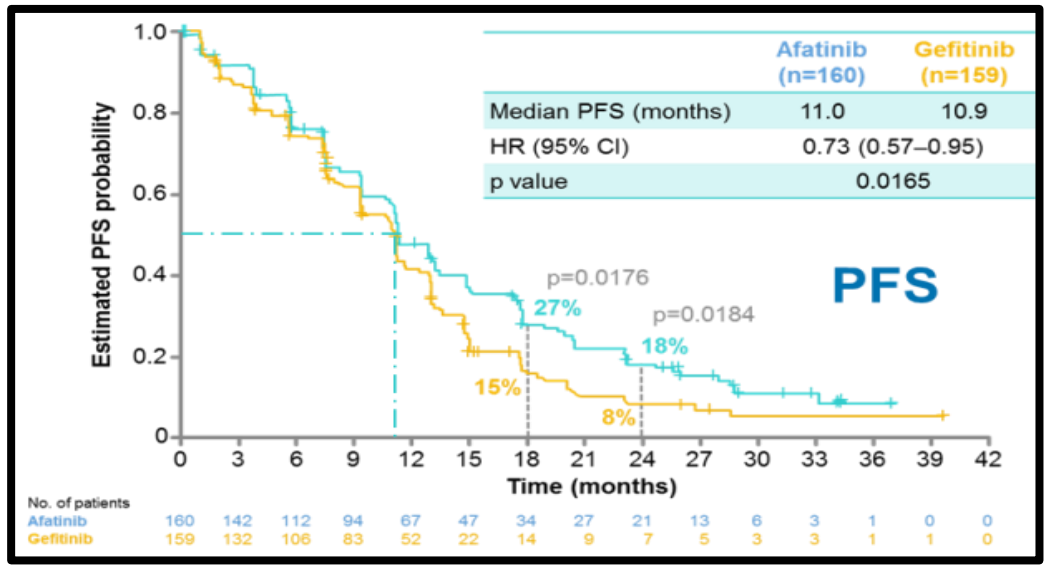
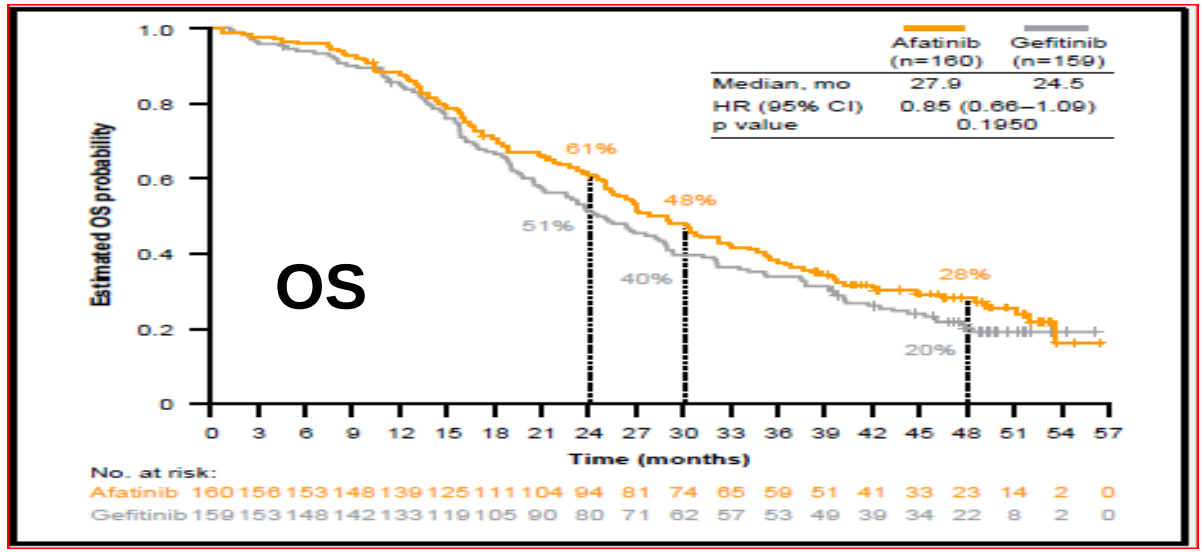
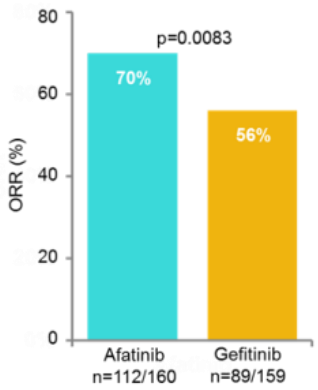
LUX-Lung 7 : Afatinib *vs*. Gefitinib



	Afatinib (n=160)	Gefitinib (n=159)
Median PFS (months)	11.0	10.9
HR (95% CI)	0.73 (0.57–0.95)	
p value	0.0165	





	Afatinib (n=112)	Gefitinib (n=89)
Median DoR (months)	10 .1	8.4
95% CI	(7.8–11.1)	(7.4–10.9)

	Afatinib (n=160)		Gefitinib (n=159)	
AE category, %	**All**	**Grade 3**	**All**	**Grade 3**
Diarrhea	90.0	11.9	61.0	1.3
Rash/acne	88.8	9.4	81.1	3.1
Stomatitis	64.4	4.4	23.9	-
Paronychia	55.6	1.9	17.0	0.6
ALT increased	9.4	-	23.9	7.5
AST increased	6.3	-	20.8	2.5

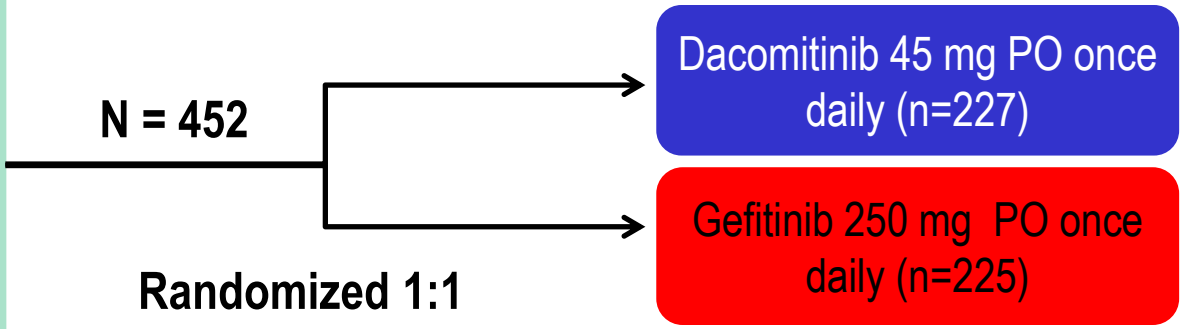
Park, Lancet Oncol 2016; Park, WCLC 2016

Study Design

ARCHER 1050 Trial

Key Eligibility Criteria

- Advanced NSCLC with *EGFR*-activating mutation(s)
- No prior systemic treatment of advanced NSCLC
- No prior EGFR TKI or other TKI
- No central nervous system metastases
- ECOG performance status of 0 or 1



Stratification factors

- Race (Japanese, Chinese, other East Asian, non-Asian)
- *EGFR* mutation type (exon 19 del, exon 21 L858R)

Primary endpoint

PFS by blinded independent review committee (IRC)

Secondary endpoints

OS, PFS (investigator-assessed), ORR, DoR, TTF, safety, PROs

Results

PFS and OS were superior with dacomitinib vs gefitinib[1, 2]

- PFS: (HR*, 0.59; 2-sided P<0.0001)
  Median of 14.7 vs 9.2 months
- OS: (HR**, 0.760; 2-sided P=0.044)
  Median of 34.1 vs 26.8 months

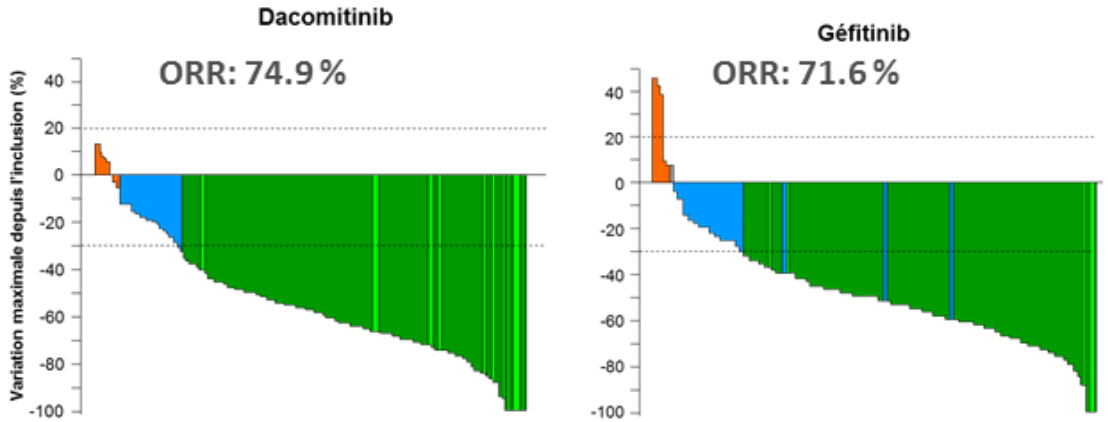
ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT01774721; 1. Wu YL et al. *Lancet Oncol*. 2017;18(11):1454–1466. 2. Mok TS et al. *J Clin Oncol.* 2018;36(22):2244–2250.
DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ORR, objective response rate; PO, orally; PROs, patient-reported outcomes; TTF, time to treatment failure.*95% confidence interval, 0.47,0.74. **95% confidence interval, 0.582, 0.993.

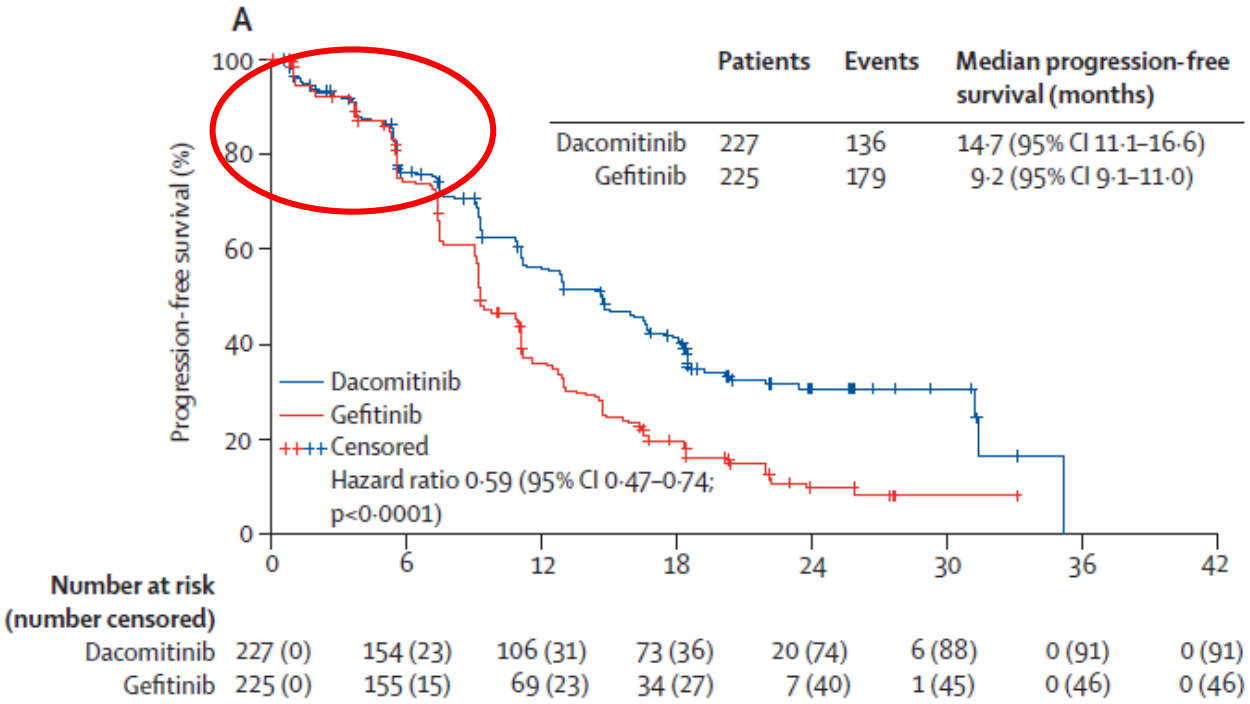
Archer 1050 Phase III Trial
Dacomitinib *vs*. Gefitinib

PFS curves separate late indicating not all daco pts perform better than gefitinib

In contrast FLAURA PFS curves separate early*

	Dacomitinib	Gefitinib
Median age (range)	62 (28-87)	61 (33-86)
M/F, %	36%/64%	44%/56%
Asian/other, %	75%/25%	78%/22%
ECOG PS 0/1, %	33%/67%	28%/72%
Smokers, %	6.6%	8.4%
Exon 19/L858R, %	59%/41%	59%/41%





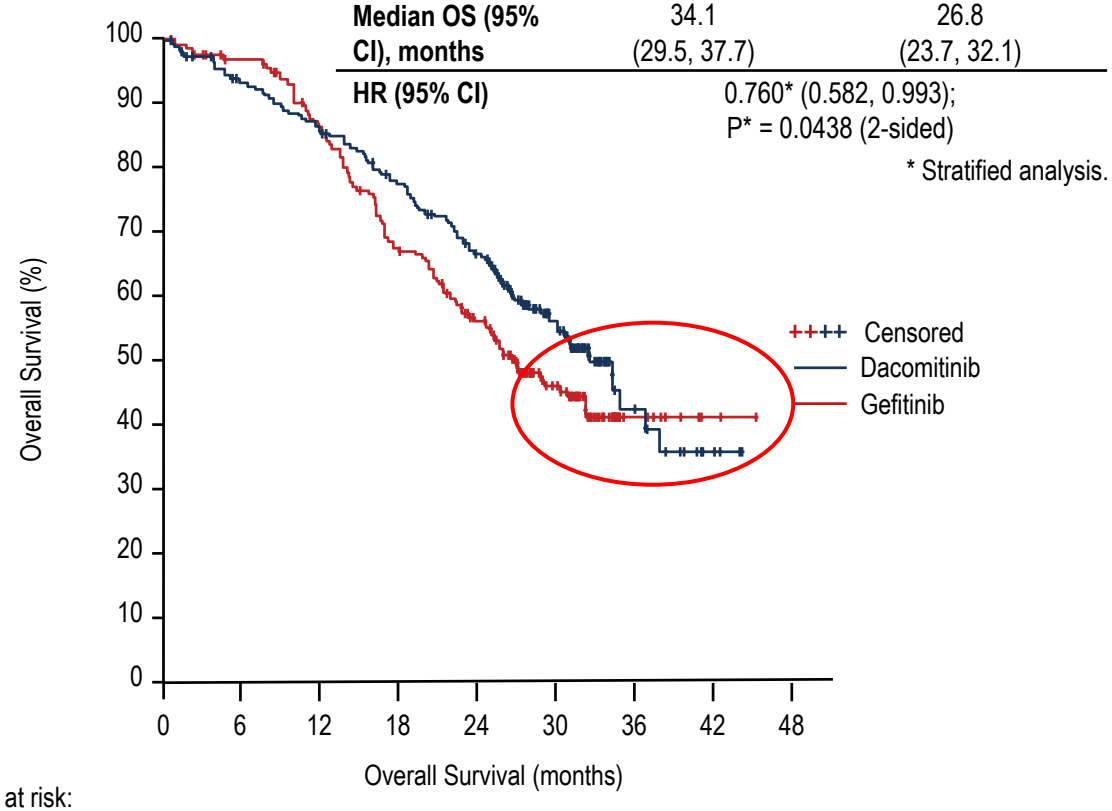
Wu, Lancet Oncol 2017

Overall Survival – Intention-to-Treat Population

Overall Survival (Feb. 17, 2017)

	Dacomitinib (n = 227)	Gefitinib (n = 225)
Events, No.	103	117
Median OS (95% CI), months	34.1 (29.5, 37.7)	26.8 (23.7, 32.1)
HR (95% CI)	0.760* (0.582, 0.993); P* = 0.0438 (2-sided)	

* Stratified analysis.



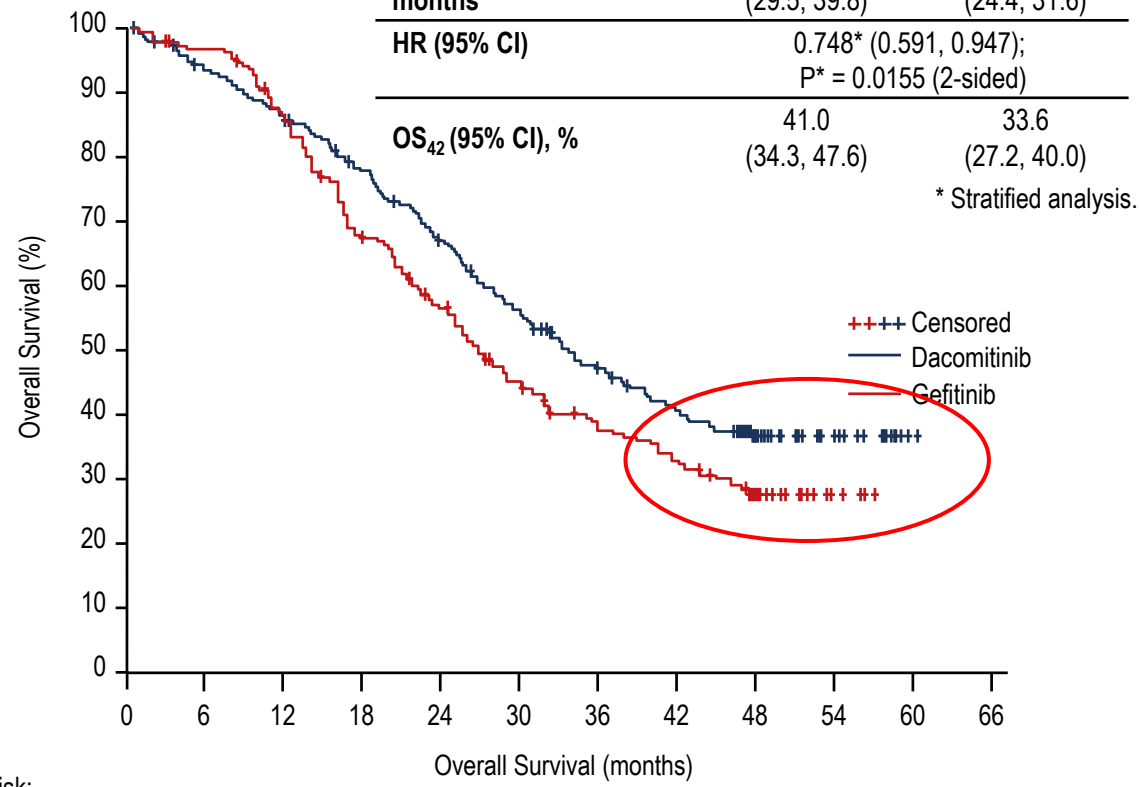
No. at risk:									
Dacomitinib	227	206	188	167	138	77	14	3	0
Gefitinib	225	213	186	144	113	63	12	3	0

Mok TS et al. *J Clin Oncol.* 2018;36(22):2244–2250.

Overall Survival (May 13, 2019)

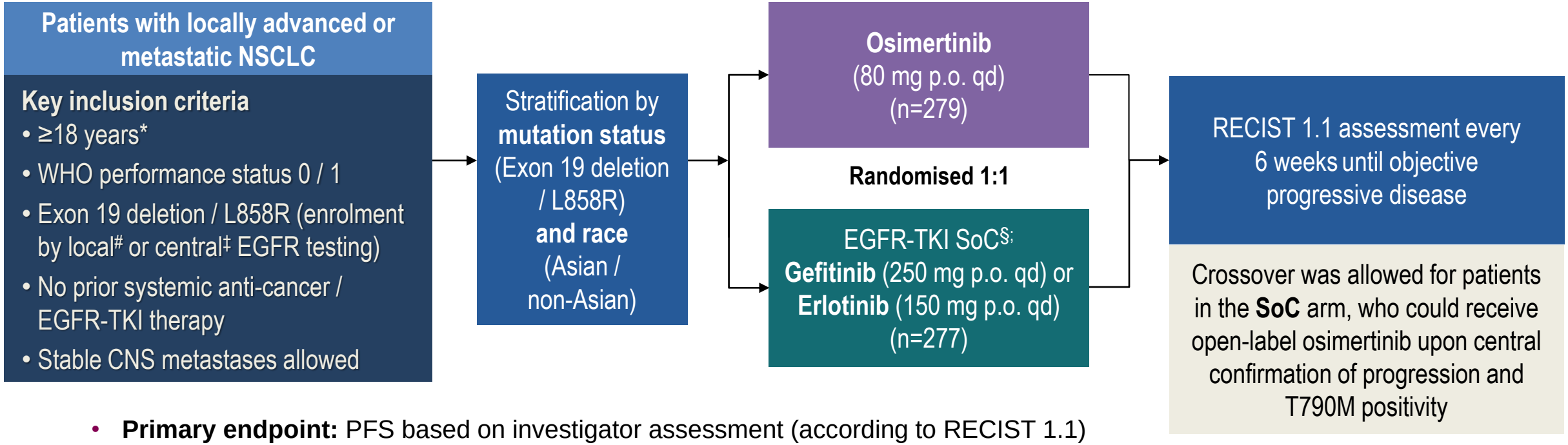
	Dacomitinib (n = 227)	Gefitinib (n = 225)
Events, No.	133	152
Median OS (95% CI), months	34.1 (29.5, 39.8)	27.0 (24.4, 31.6)
HR (95% CI)	0.748* (0.591, 0.947); P* = 0.0155 (2-sided)	
OS_{42} (95% CI), %	41.0 (34.3, 47.6)	33.6 (27.2, 40.0)

* Stratified analysis.



No. at risk:												
Dacomitinib	227	208	190	169	144	119	95	80	39	15	2	0
Gefitinib	225	216	189	147	122	95	76	65	29	4	0	0

3rd Generation EGFR TKI in Frontline FLAURA Double-Blind Study Design



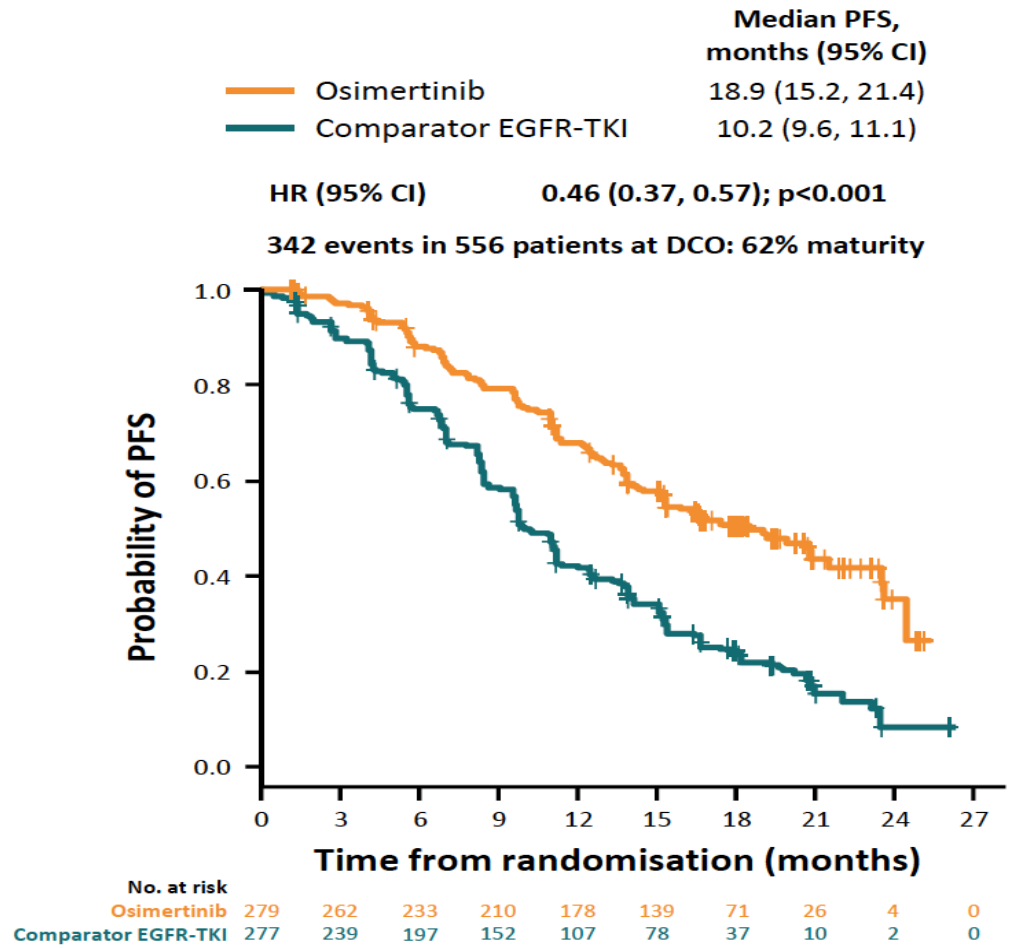
- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration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

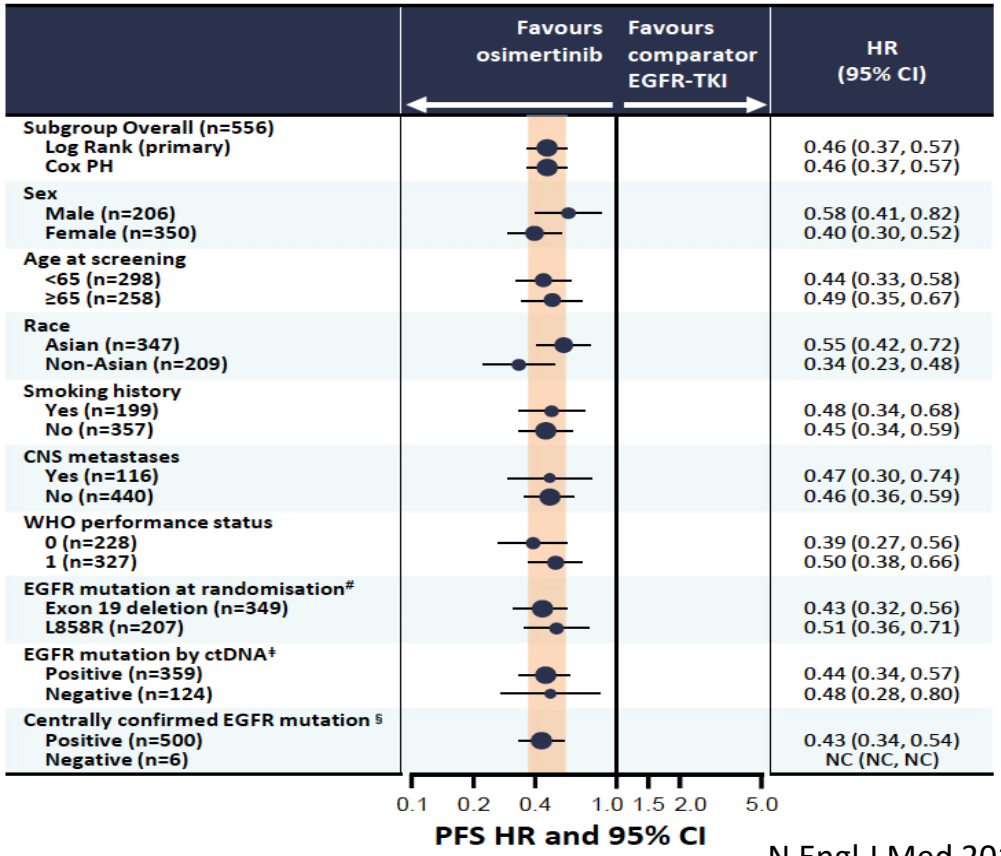
N Engl J Med 2018;378:113-25.

Outcomes of the FLAURA Study

- Improvement of PFS, primary endpoint, of **8.7 months favoring Osi (18.9 vs. 10.2, HR=0.46), benefit in all subgroups.**

Primary endpoint: PFS by investigator assessment (all pts)



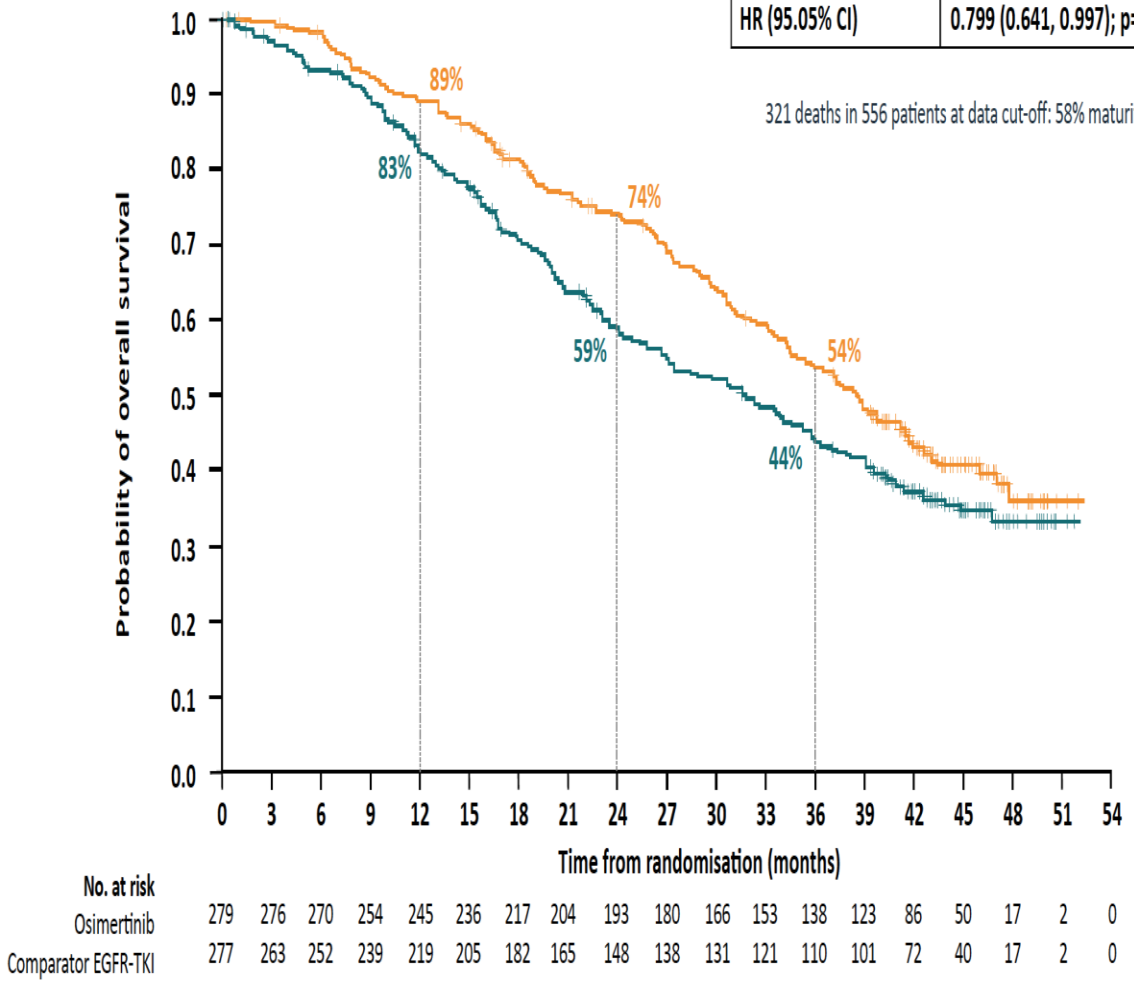


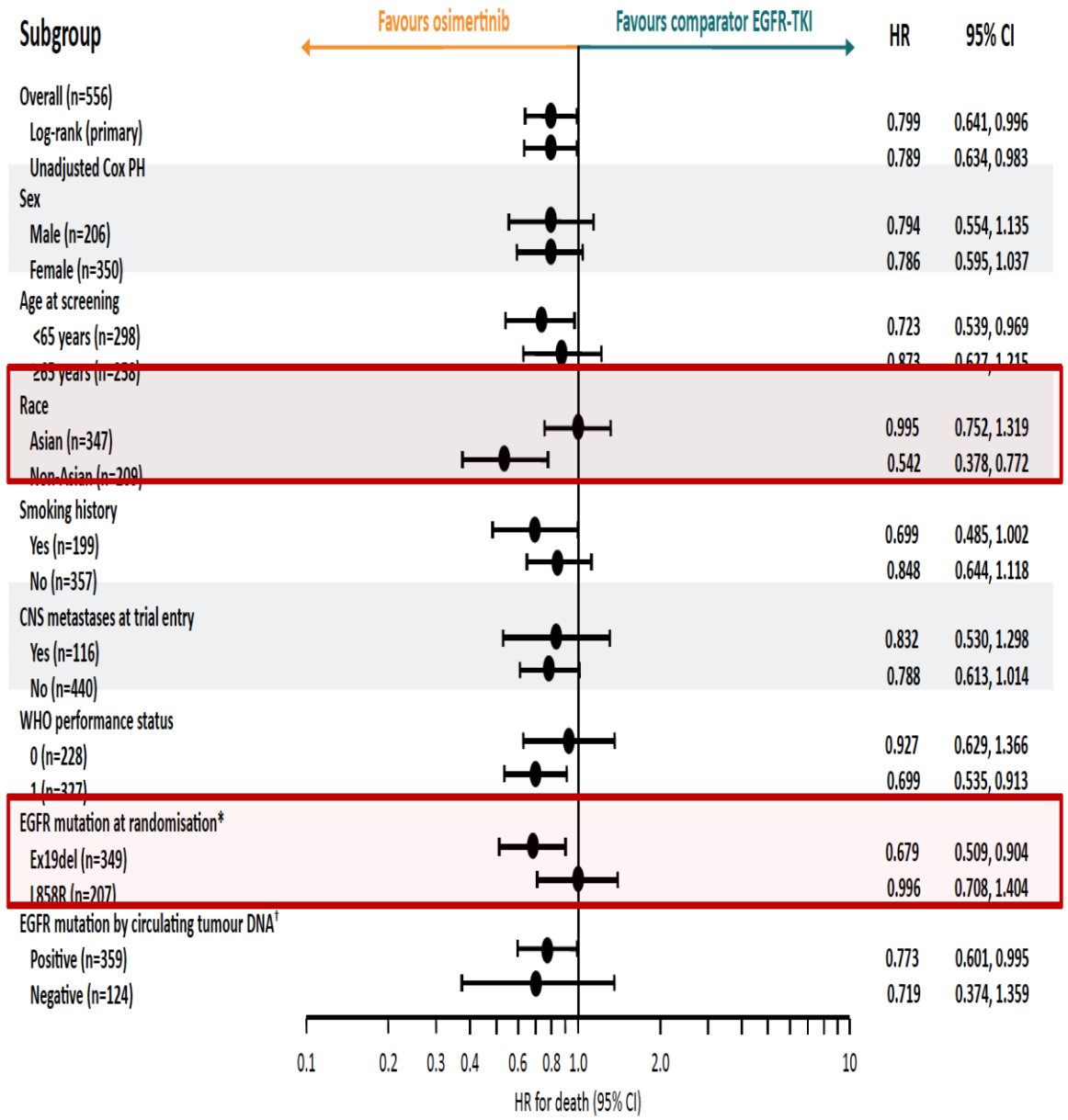
N Engl J Med 2018;378:113-25.

FLAURA: Final analysis—overall survival in subgroups

	Median OS, months (95% CI)
– Osimertinib	38.6 (34.5, 41.8)
– Comparator EGFR-TKI	31.8 (26.6, 36.0)
HR (95.05% CI)	0.799 (0.641, 0.997); p=0.0462

321 deaths in 556 patients at data cut-off: 58% maturity

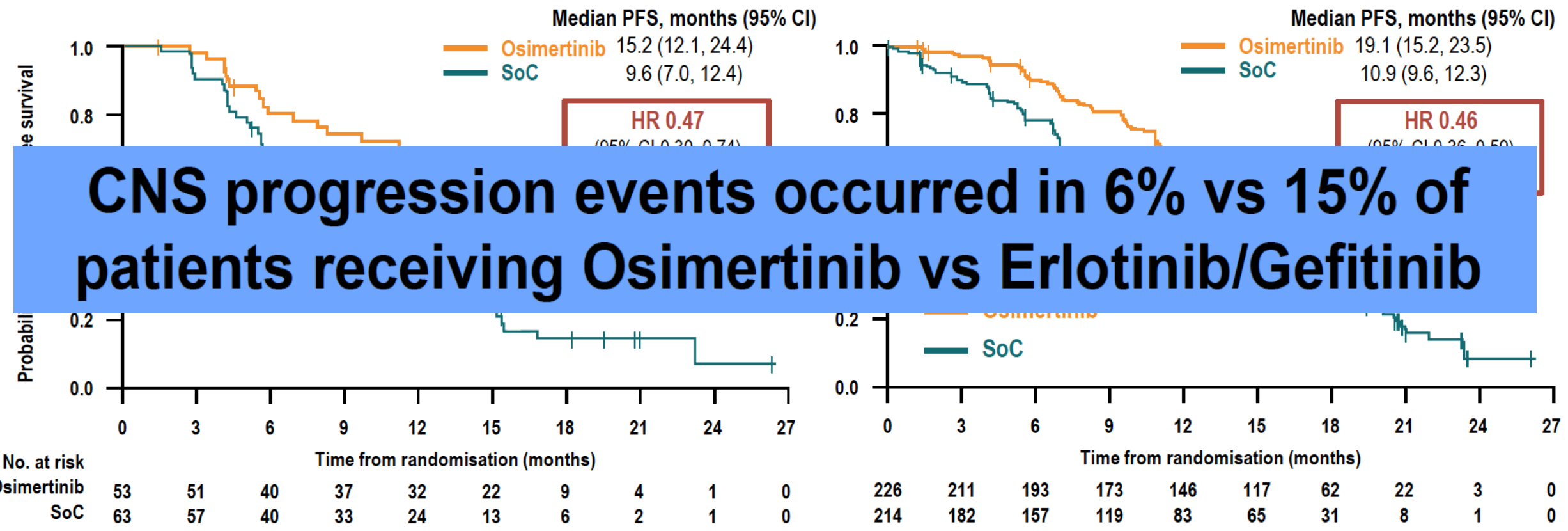




Ramalingan ESMO 19

MADRID 2017 ESMO congress

PFS* IN PATIENTS WITH AND WITHOUT CNS METASTASES AT STUDY ENTRY



CNS progression events occurred in 6% vs 15% of patients receiving Osimertinib vs Erlotinib/Gefitinib

CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)

FLAURA data cut-off: 12 June 2017
Tick marks indicate censored data; *By Investigator assessment
CI, confidence interval; CNS, central nervous system; HR, hazard ratio; PFS, progression-free survival; SoC, standard-of-care

Dacomitinib seems to have less favourable safety profile than second- and third-generation EGFR-TKIs

Most common Grade 3 and Grade 4 AEs in clinical trials*

Study: FLAURA[1]	Rash or acne[#]	Paronychia	Diarrhoea	Stomatitis	Dose reduction
Osimertinib (n = 279)	1%	<1%	2%	<1%	4%
SoC (n = 277)	7%	1%	2%	<1%	5%

Study: LUX-Lung 7[2]	Rash or acne[#]	Paronychia	Diarrhoea	Stomatitis	Dose reduction
Afatinib (n = 160)	9%	2%	13%	4%	42%
Gefitinib (n = 159)	3%	1%	1%	0%	2%

Study: ARCHER 1050[3]	Rash or acne[#]	Paronychia	Diarrhoea	Stomatitis	Dose reduction
Dacomitinib (n = 227)	14%[†]	7%	8%	4%	66%
Gefitinib (n = 224)	0%	1%	1%	<1%	8%

*These 3 drugs may not be compared directly as the data is derived from 3 different studies. No conclusions can be drawn from indirect comparisons between trials because of differences in trial designs, patients and methodologies. [#]Grouped term. [†]Dermatitis acneiform.

Presented by Solange Peters, ESMO-Asia 2017.

AE, adverse event; EGFR, epidermal growth factor receptor; SoC, standard-of-care; TKI, tyrosine kinase inhibitor.

1. Soria JC, et al. *N Engl J Med.* 2018;378:113-125. 2. Park K, et al, *Lancet Oncol.* 2016;17:577-589. 3. Wu YL, et al. *Lancet Oncol.* 2017;18:1454-1466.

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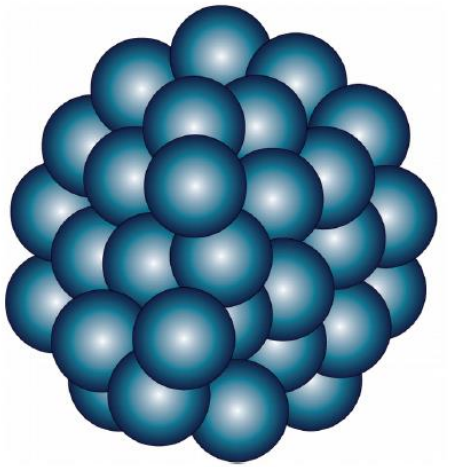
TKI COMBINATIONS

How to Further Improve on the Efficacy of Osimertinib ?

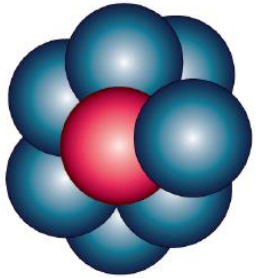
Treatment Naïve



Targeted therapy combinations:
anti-angiogenesis agents (three positive trials, mainly in Asian pts)
Chemotherapy combination

Two trials with PFS and OS benefit adding
chemotherapy to gefitinib

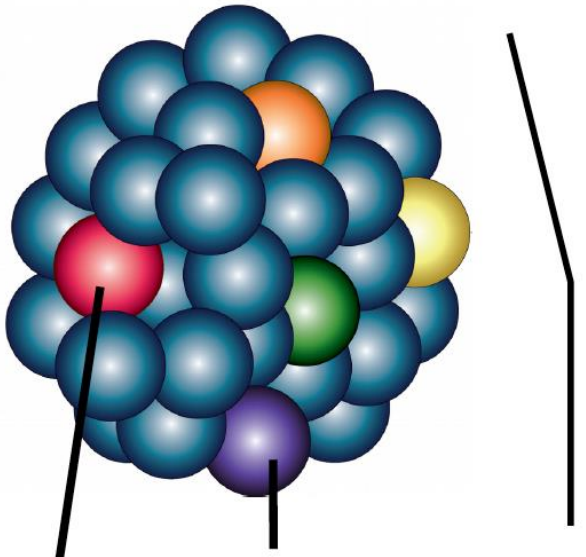
Minimal Residual Disease



Addition of a second agent?

Local therapy?

Drug Resistance

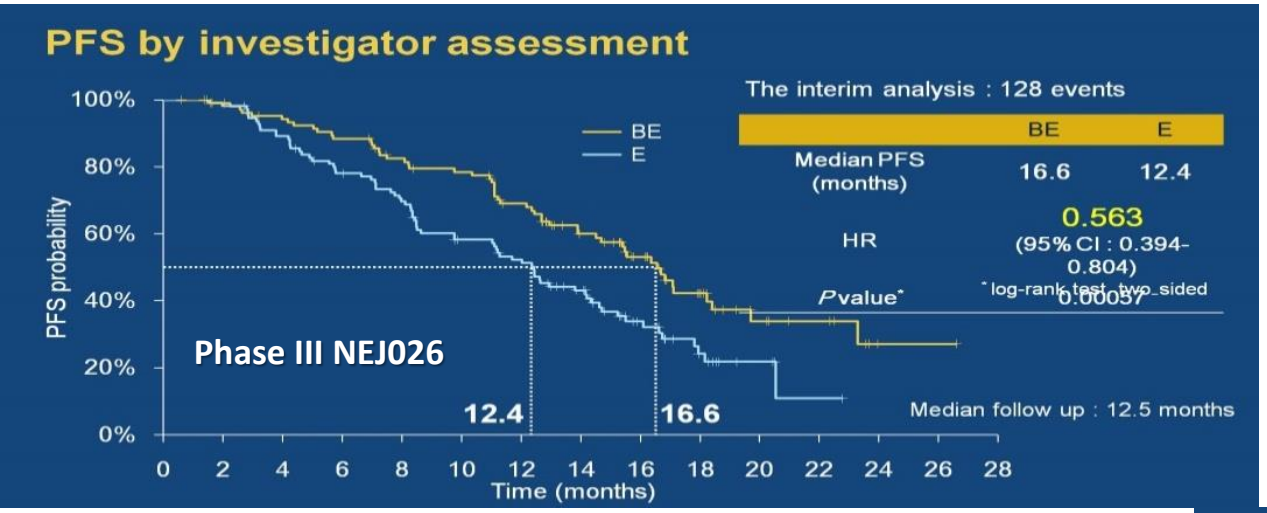


U3-1402

C797S: EGFR inhibitor

MET Amp: MET Inhibitor

JNJ-61186372



Erlotinib + - Bevacizumab

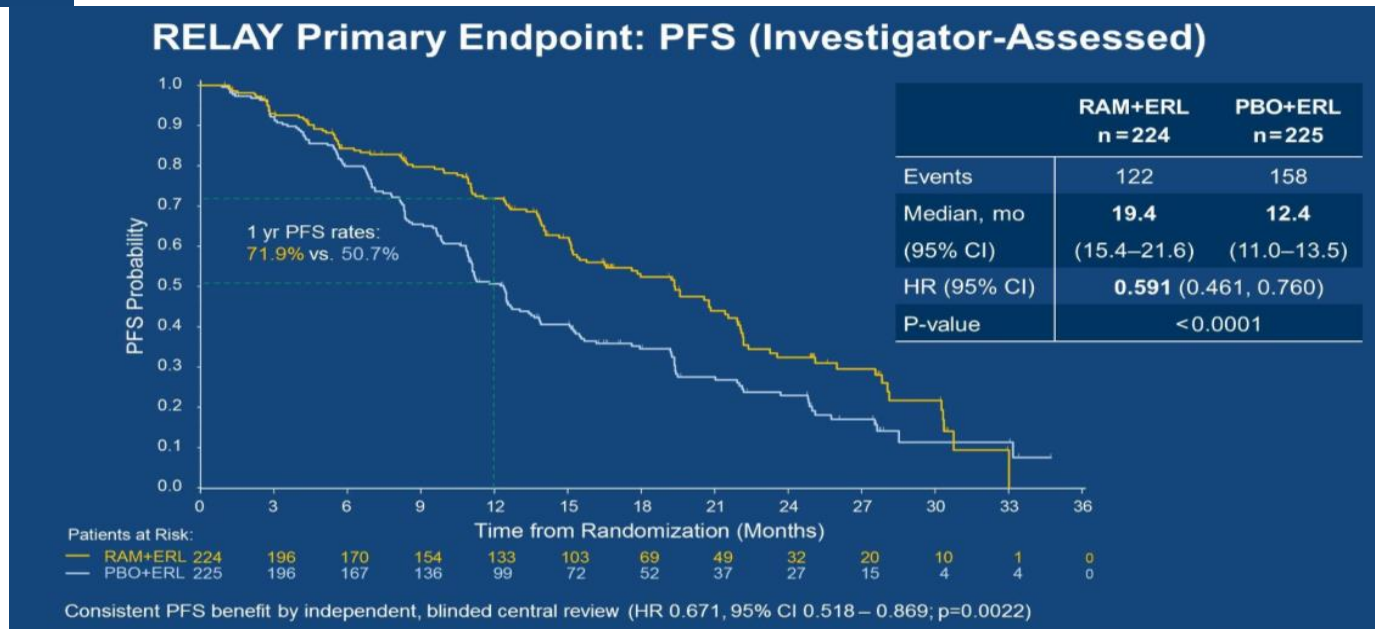
(asymptomatic brain met allowed)

mPFS 16.6 vs 12.4 (HR = 0.56)

Erlotinib + - Ramucirumab

(excluded brain met)

mPFS 19.4 vs 12.4 (HR = 0.59)



Naoki Furuya ASCO 2018. Nakagawa K. ASCO 2019

Kenmotsu H, ESMO 2021

2021 ESMO congress

WJOG

Primary results of a randomized phase II study of osimertinib plus bevacizumab versus osimertinib monotherapy for untreated patients with non-squamous non-small-cell lung cancer harboring *EGFR* mutations; WJOG9717L study

UMIN000030206

WJOG9717L: Study Design

KEY ELIGIBILITY CRITERIA

- Non-squamous NSCLC harboring *EGFR* activating mutations
- Clinical stage IIIB, IIIC, IV, or recurrence after surgical resection
- Previously untreated
- ECOG PS 0-1
- Age 20- years
- Absence of symptomatic brain metastases

N=122

RANDOMIZED

1:1

- **Osimertinib (80 mg, daily) + Bevacizumab (15 mg/kg, q3w)**
- **Osimertinib (80 mg , daily)**

ENDPOINTS

- **Primary**
  - PFS by the BICRs*
- **Secondary**
  - PFS by investigators
  - Overall response rate
  - Overall survival
  - Adverse events

Stratification factors: Sex (female vs. male), Clinical stage (IIIB-IV vs. recurrence) *EGFR* mutation (Del19 deletion vs. L858R)

*BICRs; the blinded independent central reviewers

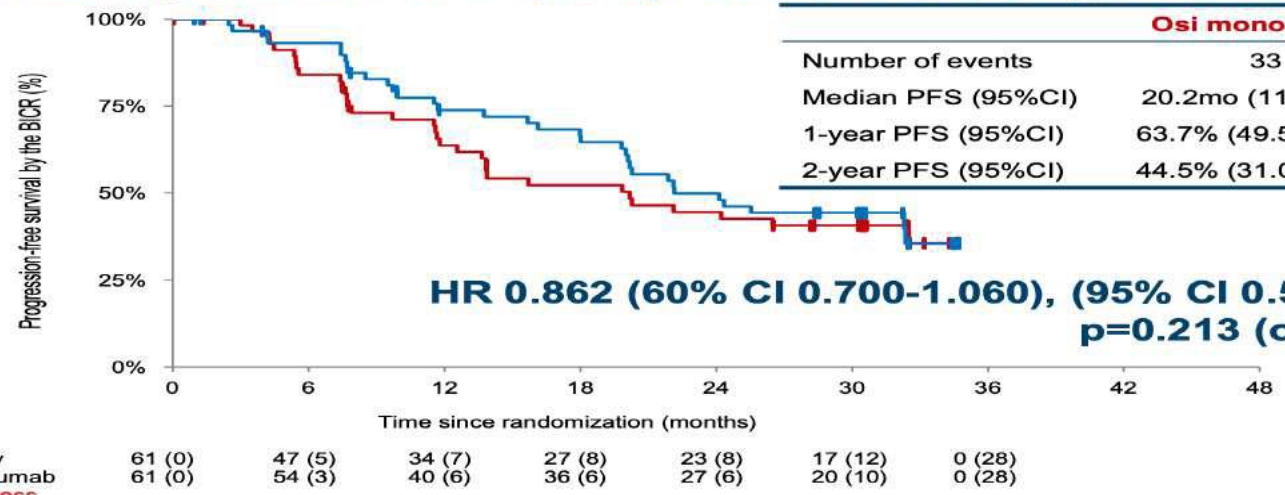
UMIN000010298; https://www.umin.ac.jp/

2021 ESMO congress

Hirotsugu Kenmotsu, MD
Shizuoka Cancer Center

NEGATIVE

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

HR 0.862 (60% CI 0.700-1.060), (95% CI 0.531-1.397)
p=0.213 (one-sided)

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Hirotsugu Kenmotsu, MD
Shizuoka Cancer Center

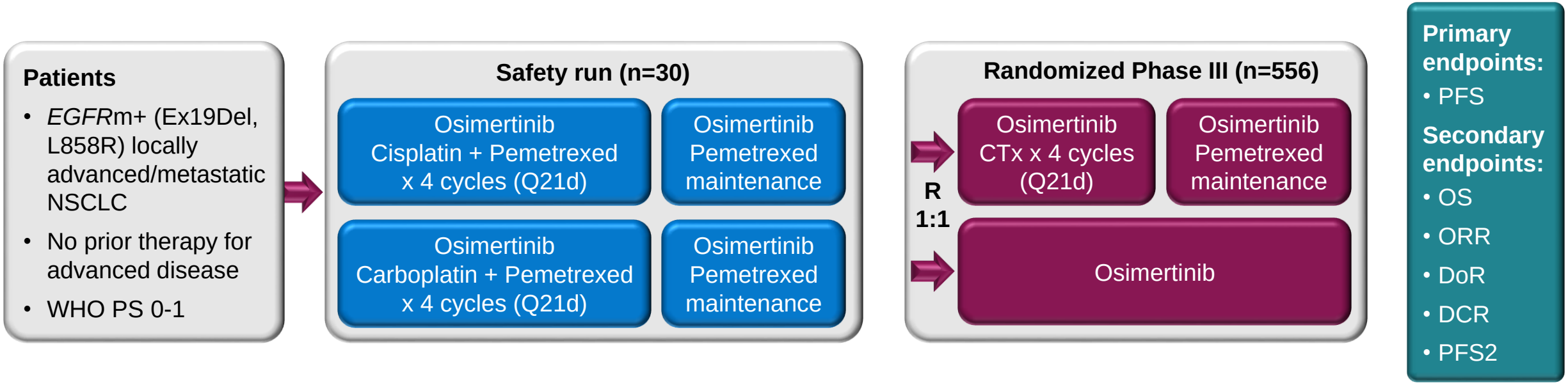
Chemo plus EGFR-TKI

Gefitinib +/-Carbo/Pemetrexed

Study	Arm	PFS (mos)	HR, p	OS (mos)	HR, p
NEJ009	Gefitinib	11.9	0.49 P<0.001	38.8	0.72 P=0.021
	Carbo/Pem + G	**20.9**		**50.9**	
Noronha, et al	Gefitinib	8	0.51 P<0.001	17	0.45 P<0.001
	Carbo/Pem + G	**16**		**NR**	

Hosomi et al, JCO 2020; Noronha V, et al, JCO 2020

FLAURA2: Phase III Trial of Osimertinib With or Without Chemotherapy in 1L NSCLC[1-2]



1L = first line; CTx = chemotherapy; DCR = disease control rate; DoR = duration of response; *EGFR*m+ = epidermal growth factor receptor mutation-positive; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = second progression-free survival on a subsequent treatment; PS = performance status; Q21d = every 3 weeks; WHO = World Health Organization.

1. Study NCT04035486. ClinicalTrials.gov website. 2. Jänne PA et al. Presented at: IASLC 20th World Conference on Lung Cancer; September 7-10, 2019; Barcelona, Spain. Abs 2383.

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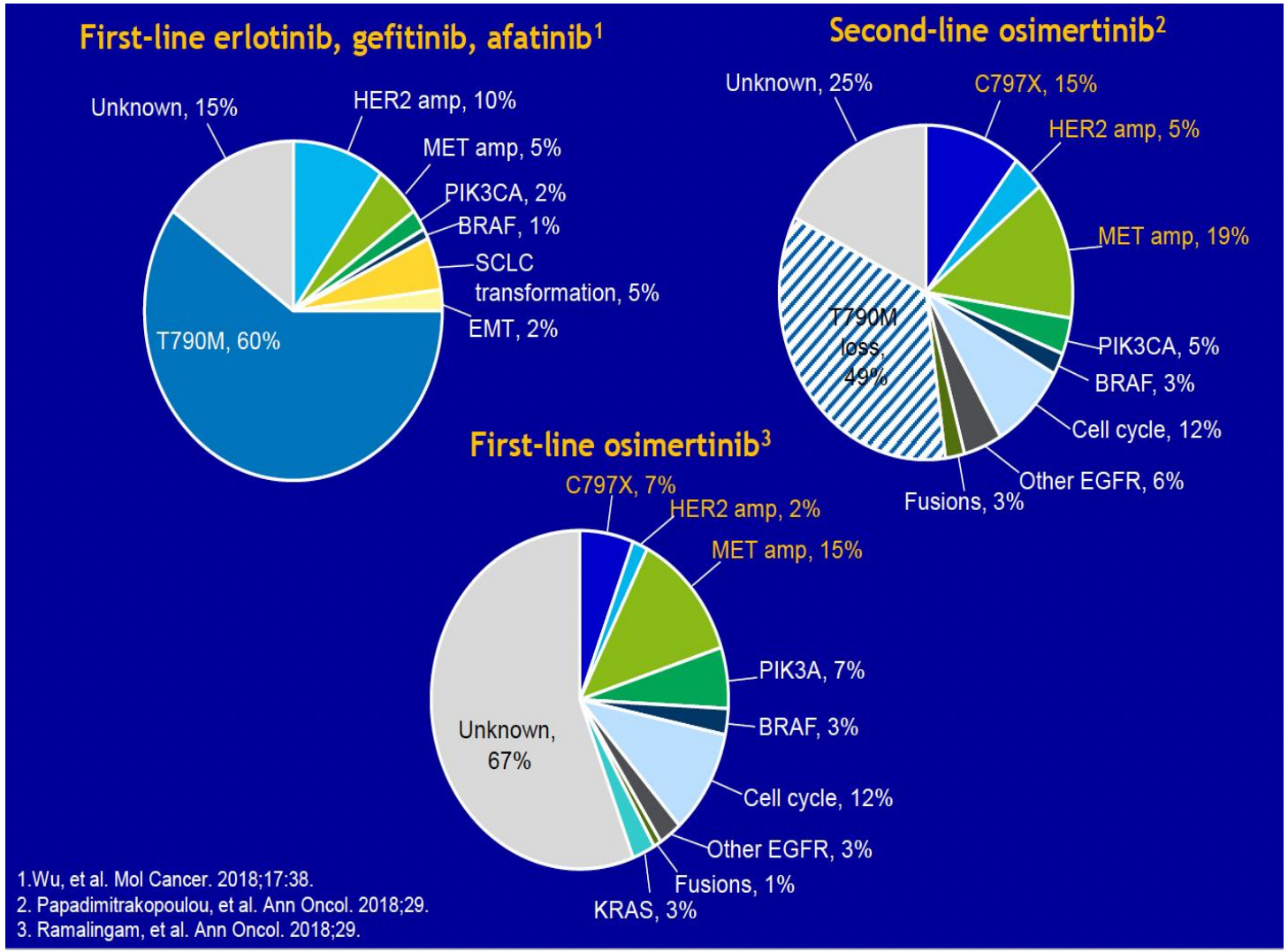
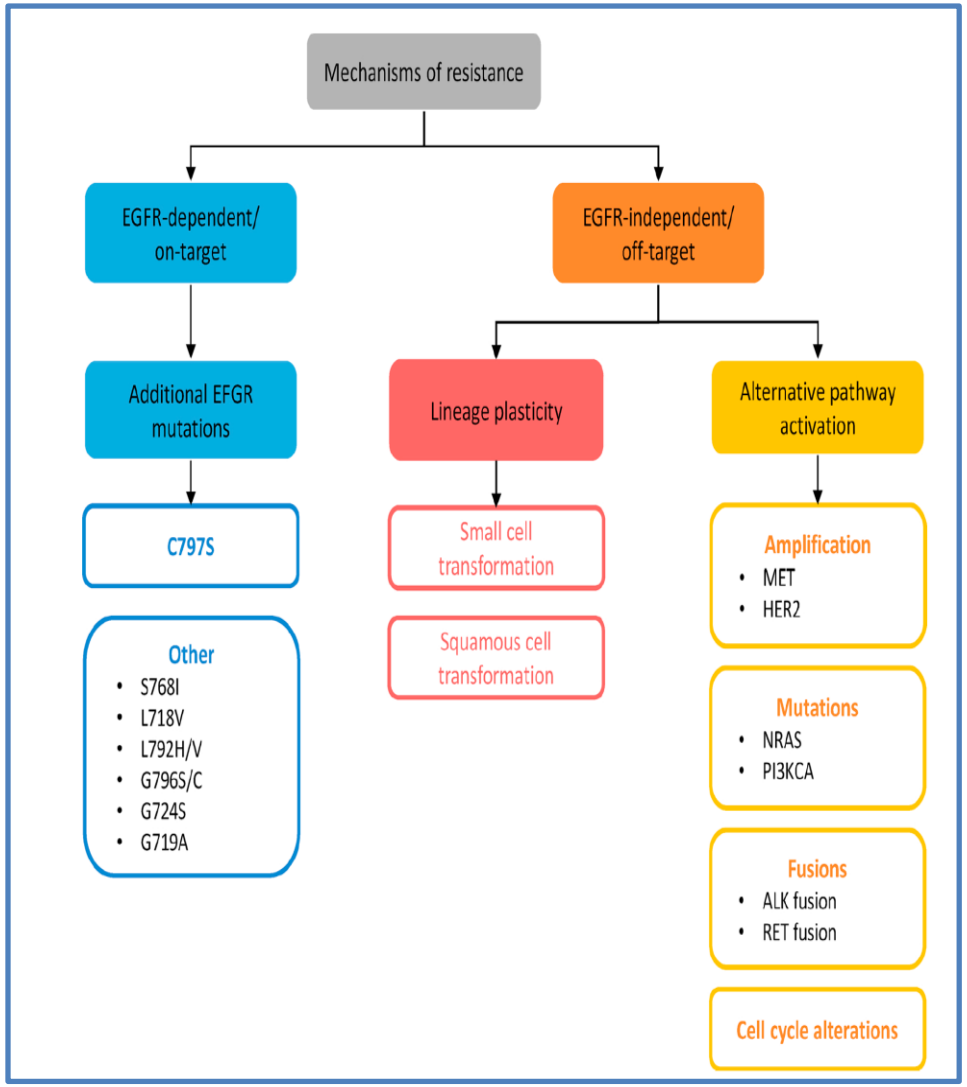
Known mechanism of resistance





Schmid et al Lung Cancer 2020

ALMORNETINIB

Producto estructuralmente optimizado de osimertinib.

Fase 1/2: pacientes previamente tratados con TKI anti-EGFR y con T790M+ :

ORR: 68'9%, mPFS: 12'3 meses
ORR Mx cerebrales: 60'9%, mPFS Mx cerebrales: 10'8 meses

LAZERTINIB

TKI anti-EGFR de 3ª generación.

Fase 1/2: pacientes previamente tratados con TKI anti-EGFR y con T790M+ :

ORR: 57%

Mejor perfil de tolerancia que osimertinib.

AFLUTINIB

TKI anti-EGFR de 3ª generación.

Fase 2B: pacientes previamente tratados con TKI anti-EGFR de 1ª o 2ª generación y con T790M+ :

ORR: 73'6%, mPFS: 7'6 meses

AVIBERTINIB

TKI anti-EGFR de 3ª generación.
Forma unión covalente entre C797 y el ATP del punto de unión.

Fase 2B: pacientes previamente tratados con TKI anti-EGFR de 1ª o 2ª generación y con T790M+ :

ORR: 57%

Dong et al. Pharmacologial Research. 2021.
Yang et al. J Thorac Oncol. 2020.

Better understanding of resistance – Novel treatment strategies

4th Generation EGFR Inhibitors can target both T790M and C797S

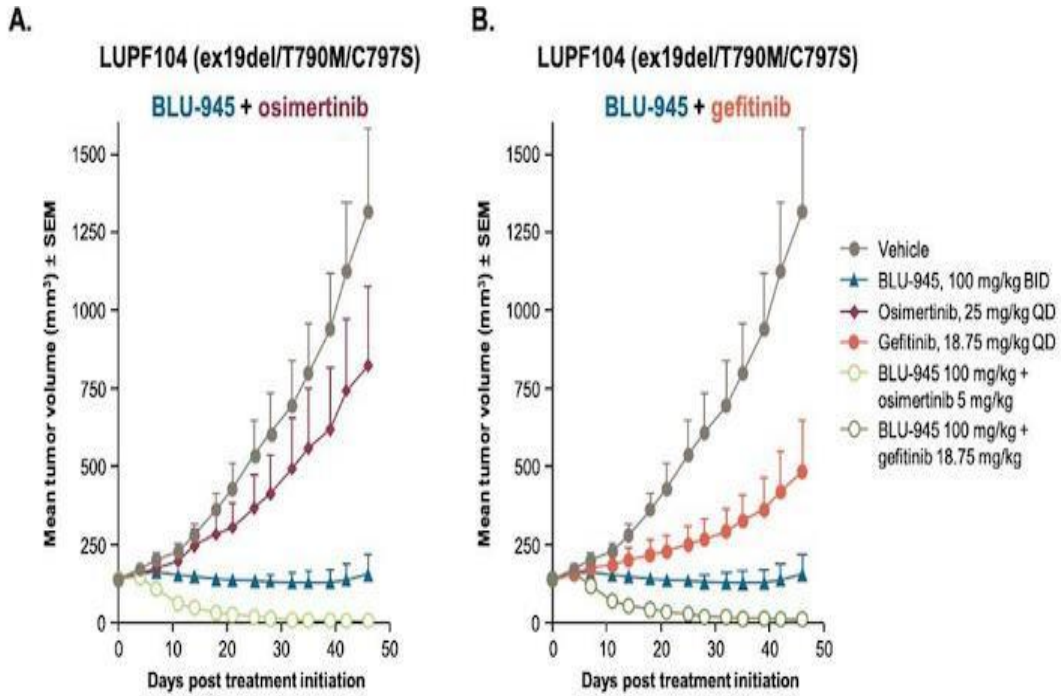
BLU-945 is a highly potent and selective EGFR+ T790M/C797S inhibitor

- Highly potent inhibitor of EGFR+/T790M/C797S and EGFR+/T790M resistant mutants
- Excellent EGFR WT and overall kinome selectivity
- BLU-945 only inhibits 1% of the kinome >90% at a concentration of 3 μM
- Selectivity profile enables combinations to cover wide spectrum of resistant mechanisms

Table 1: BLU-945 is a subnanomolar EGFR+/T790M/C797S and EGFR+/T790M inhibitor with >900-fold selectivity over EGFR WT

Compound	Enzyme activities IC_{50} (nM) at 1 mM ATP with enzyme-inhibitor pre-incubation						
	L8585R	L858R/ T790M	L858R/ T790M/C797S	ex19del (746–750)	ex19del/ T790M	ex19del/ T790M/C797S	EGFR WT
BLU-945	7.1	0.4	0.5	71.4	0.8	0.8	736.3
Erlotinib	0.3	3132.7	5654.7	0.2	1394.7	1906.6	9.8
Gefitinib	0.1	1667.2	3921.8	0.1	632.7	1219.7	3.5
Osimertinib	0.9	0.6	5461.6	0.8	0.6	649.9	1.6

ATP, adenosine triphosphate; IC_{50}, half maximal inhibitory concentration.



- Single agent BLU-945 was sufficient for tumor stasis in this model
- Co-dosing BLU-945 with either osimertinib or gefitinib led to significant tumor regression
- Single agent and combination doses were well tolerated in the animal model
- Data suggest that BLU-945 can be combined with other EGFR TKIs to address allelic EGFR heterogeneity

Schalm et al., ESMO 2020

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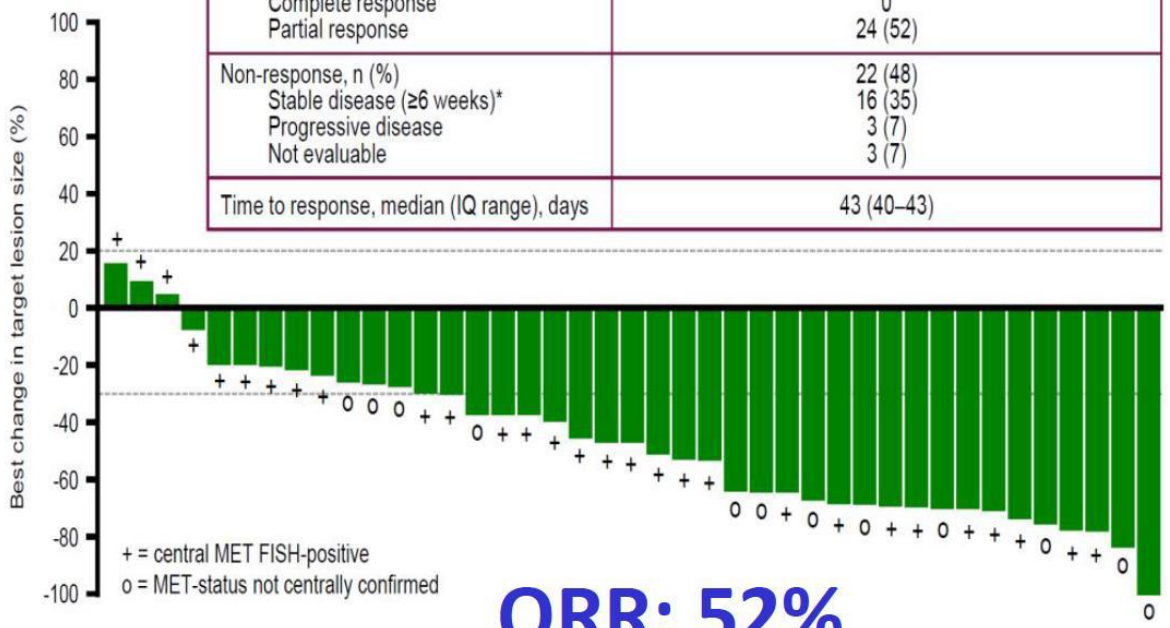
TATTON (Osimertinib+ Savolitinib)

Osimertinib + Savolitinib
Disease progression on 1st/2nd generation EGFR TKI

	OSI + SAVO: Prior 1st/2nd gen EGFR-TKI, T790M- (n=46)
Objective response, n (%) Complete response Partial response	24 (52) 0 24 (52)
Non-response, n (%) Stable disease (≥6 weeks)* Progressive disease Not evaluable	22 (48) 16 (35) 3 (7) 3 (7)
Time to response, median (IQ range), days	43 (40–43)

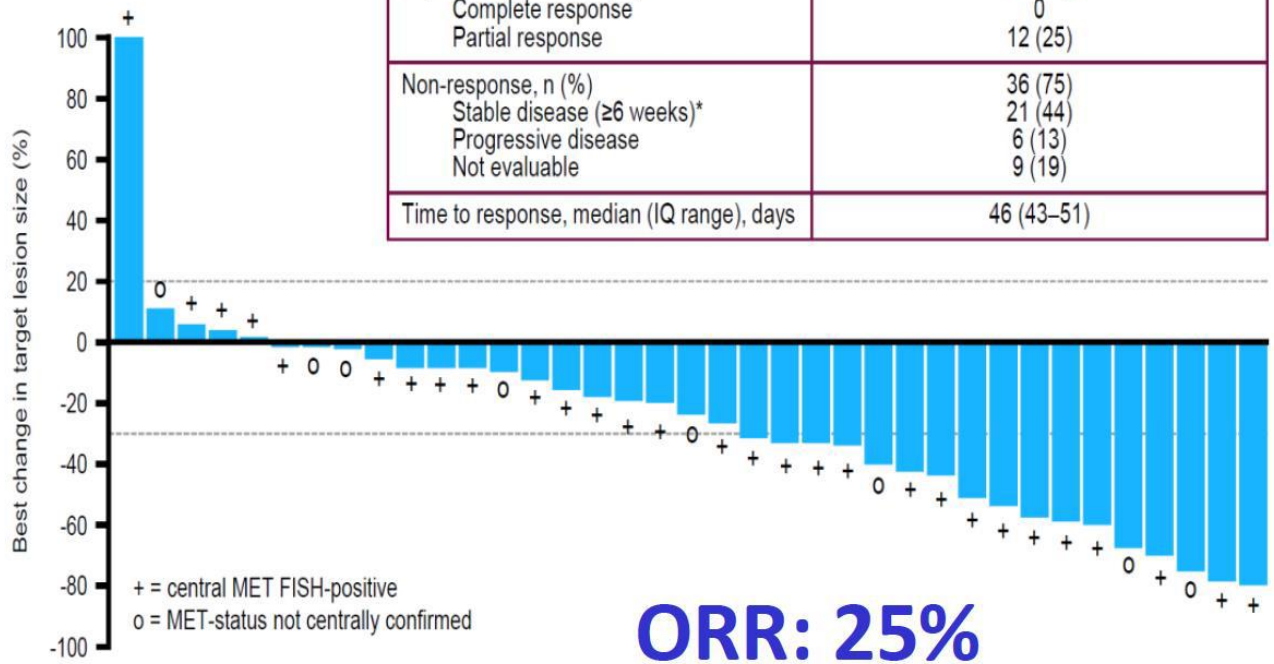


ORR: 52%

MET+, T790M-

Osimertinib + Savolitinib
Disease progression on prior 3rd generation EGFR TKI

	OSI + SAVO: Prior 3rd gen EGFR-TKI (n=48)
Objective response, n (%) Complete response Partial response	12 (25) 0 12 (25)
Non-response, n (%) Stable disease (≥6 weeks)* Progressive disease Not evaluable	36 (75) 21 (44) 6 (13) 9 (19)
Time to response, median (IQ range), days	46 (43–51)



ORR: 25%

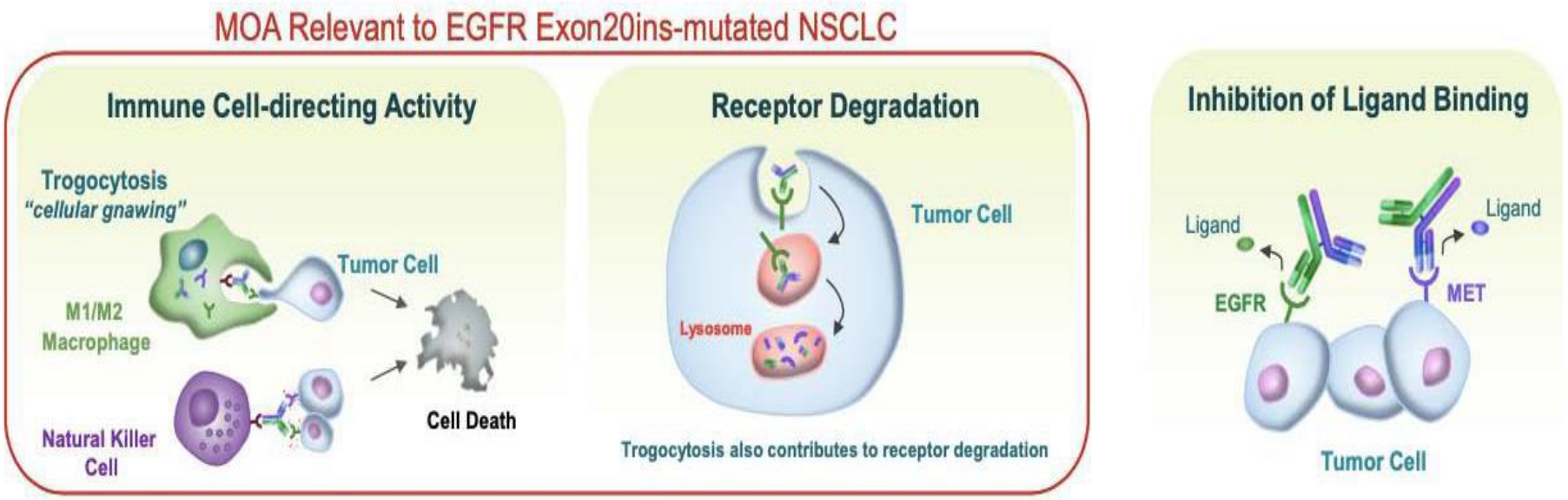
mDOR: 9.7 months

Helena Yu et al, AACR 2019

Lecia V.Sequist et al AACR 2019

Amivantamab: EGFR-MET bispecificantibody

- Fully human EGFR-MET bispecific antibody with immune cell-directing activity[1-2]
- Targets activating and resistance EGFR mutations and MET mutations and amplifications[3-4]
- Demonstrated monotherapy activity in patients with diverse EGFRm disease including EGFR Exon19del, L858R, T790M, C797S, Exon20ins, and MET amplification[3-4]

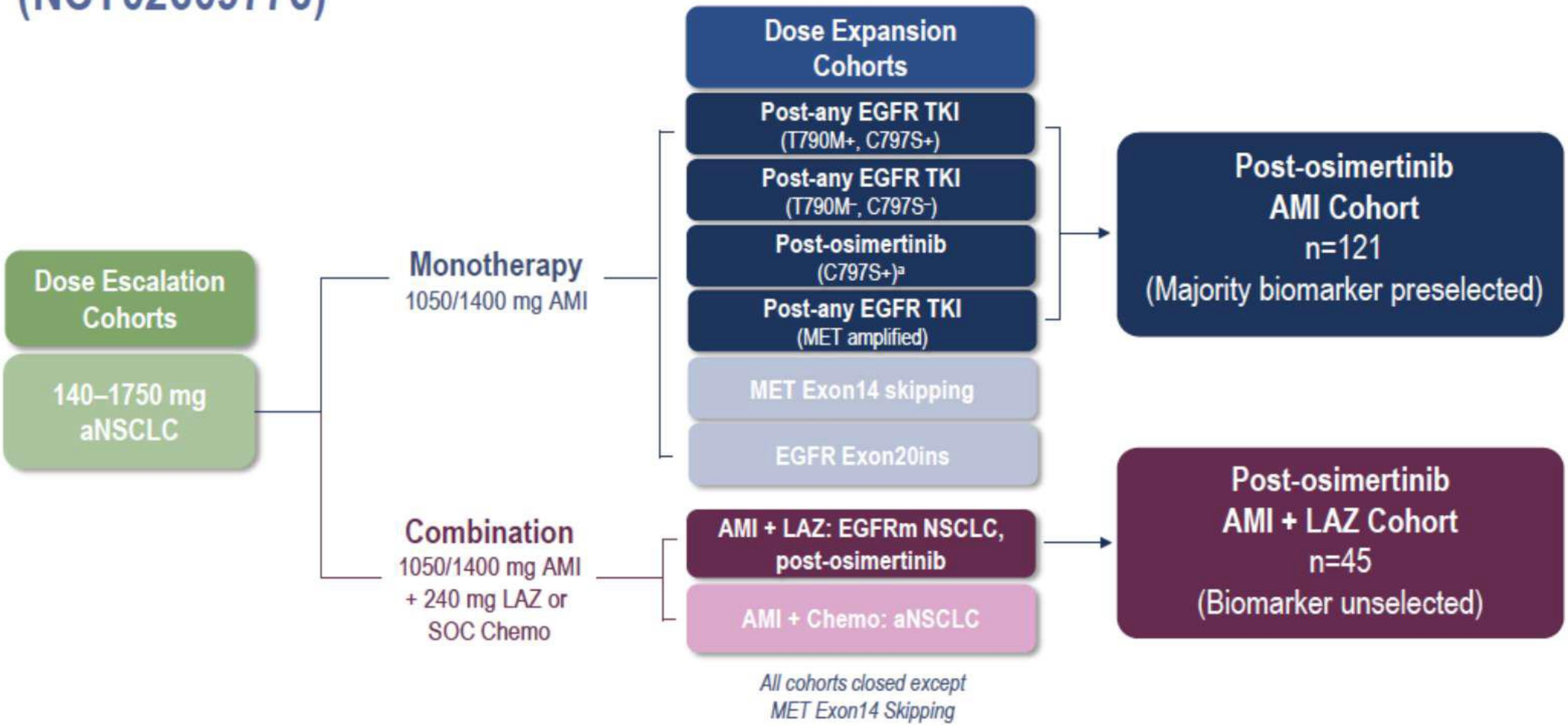


[1]Vijayaraghavan *Mol Cancer Ther* 19(10):2044. [2]Yun *Cancer Discov* 10(8):1194. [3]Haura *JCO* 37(15_suppl):9009. [4]Park *JCO* 38(15_suppl):9512
EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutant; MET, mesenchymal-epithelial transition; NSCLC, non-small cell lung cancer

SabariJK et al. Presentedat WCLC 2020. SessionOA04.04

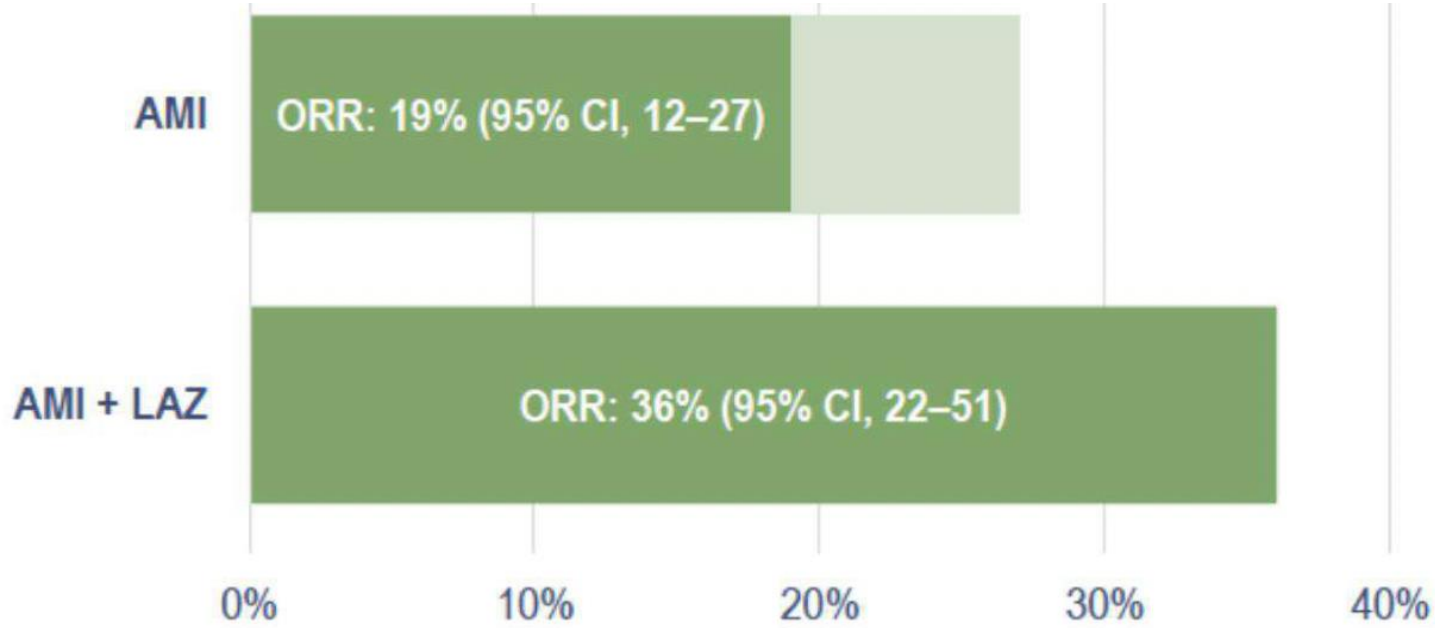
CHRYSALIS Study Design

(NCT02609776)



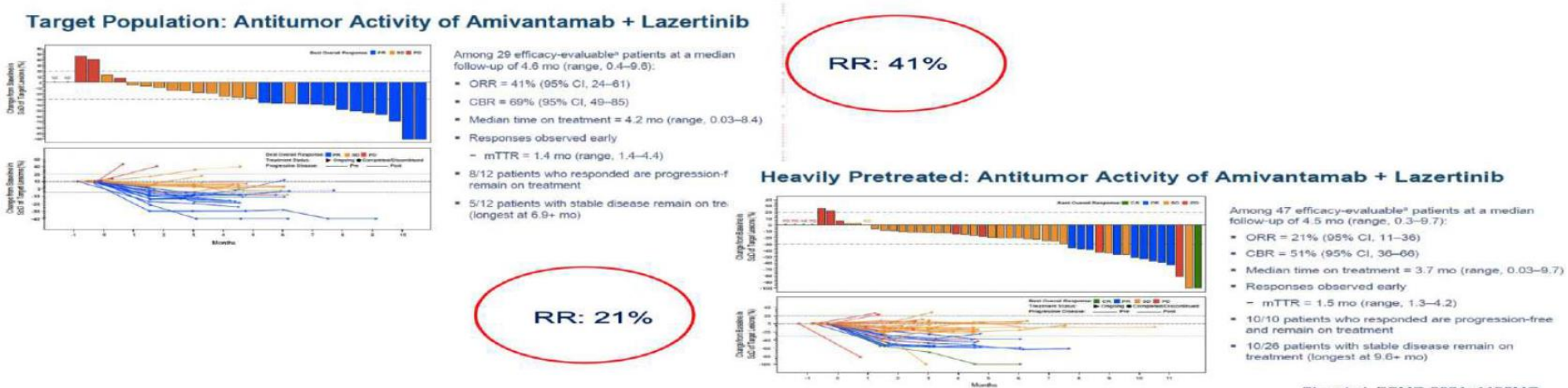
All cohorts closed except MET Exon14 Skipping

POST-OSIMERTINIB

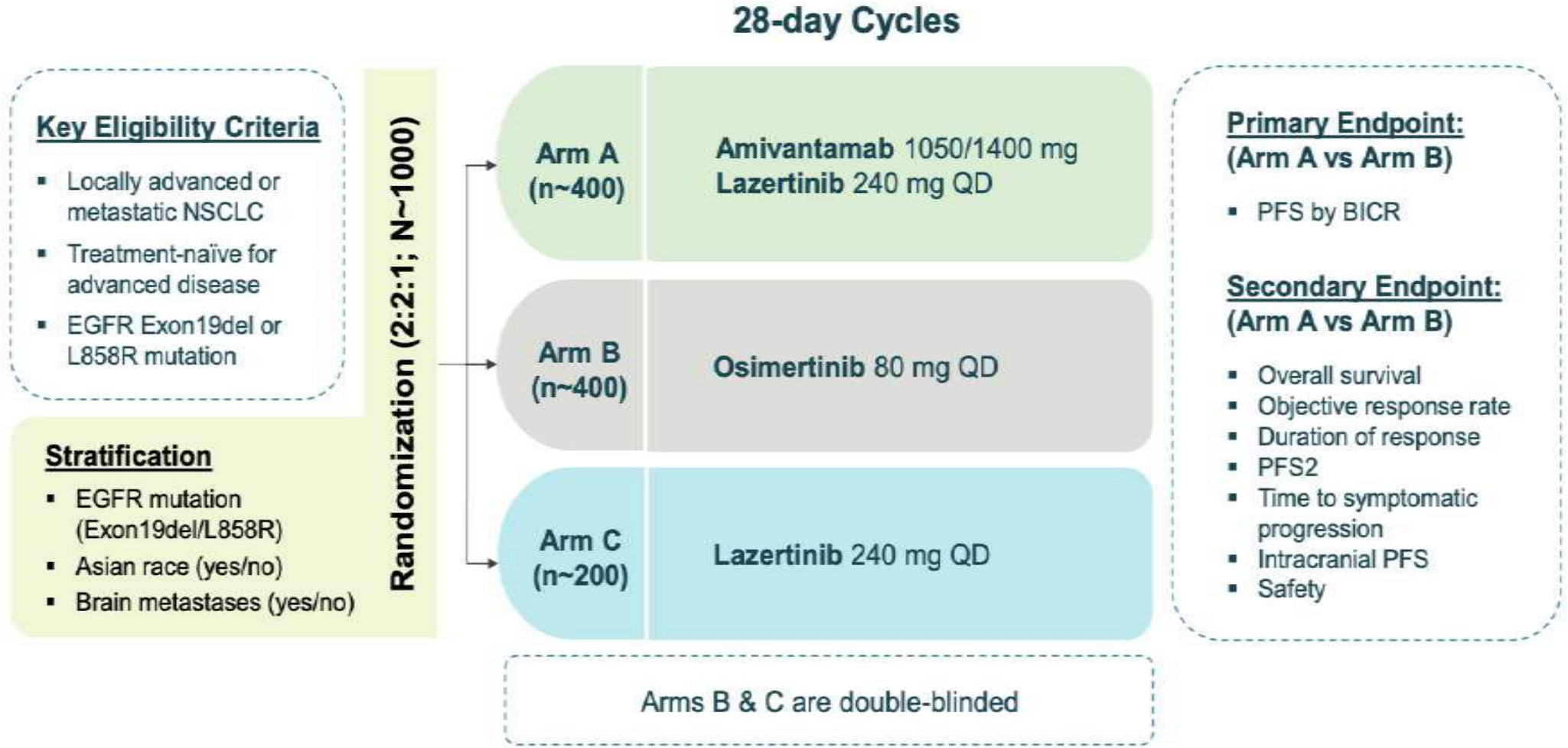


Leighl N, ESMO 2021

POST-OSIMERTINIB and CT



Phase 3 MARIPOSA Study (NCT04487080)

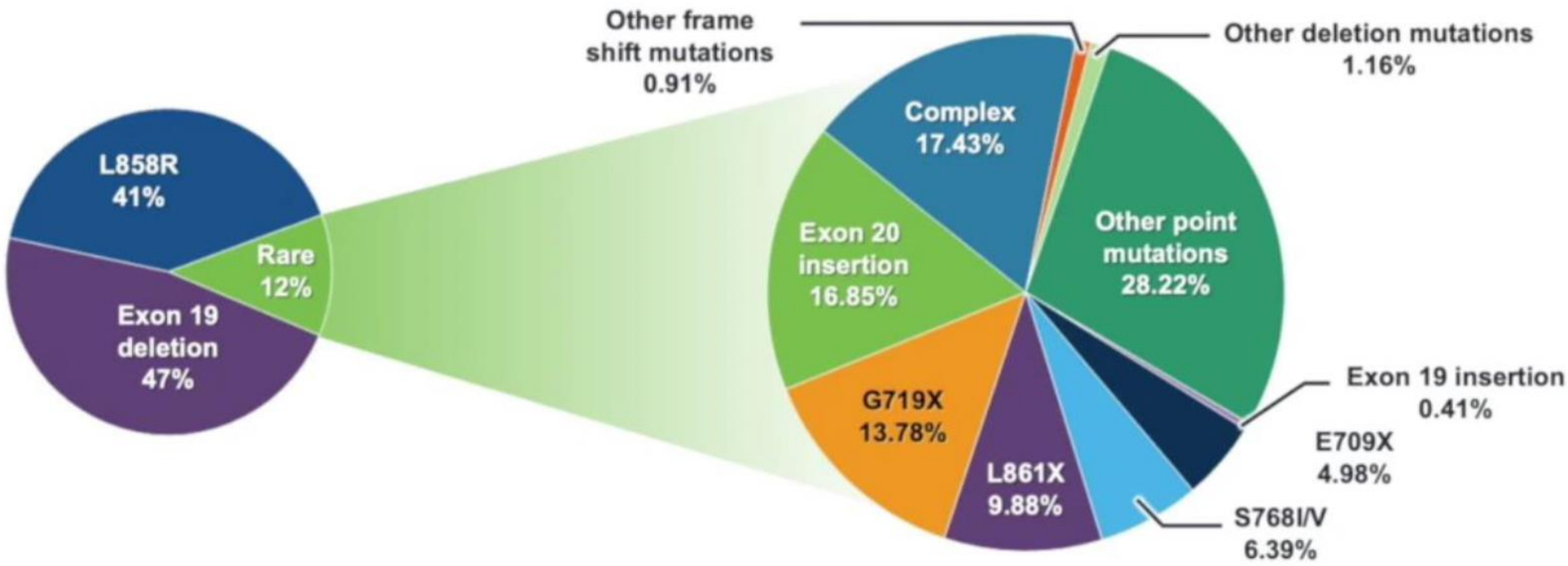


BICR, blinded independent central review; PFS, progression-free survival; PFS2, PFS after first subsequent therapy; QD, once a day

Cho et al. 45th ESMO Congress 2020. Abstract #2172

EGFR exon insertion mutations in NSCLC

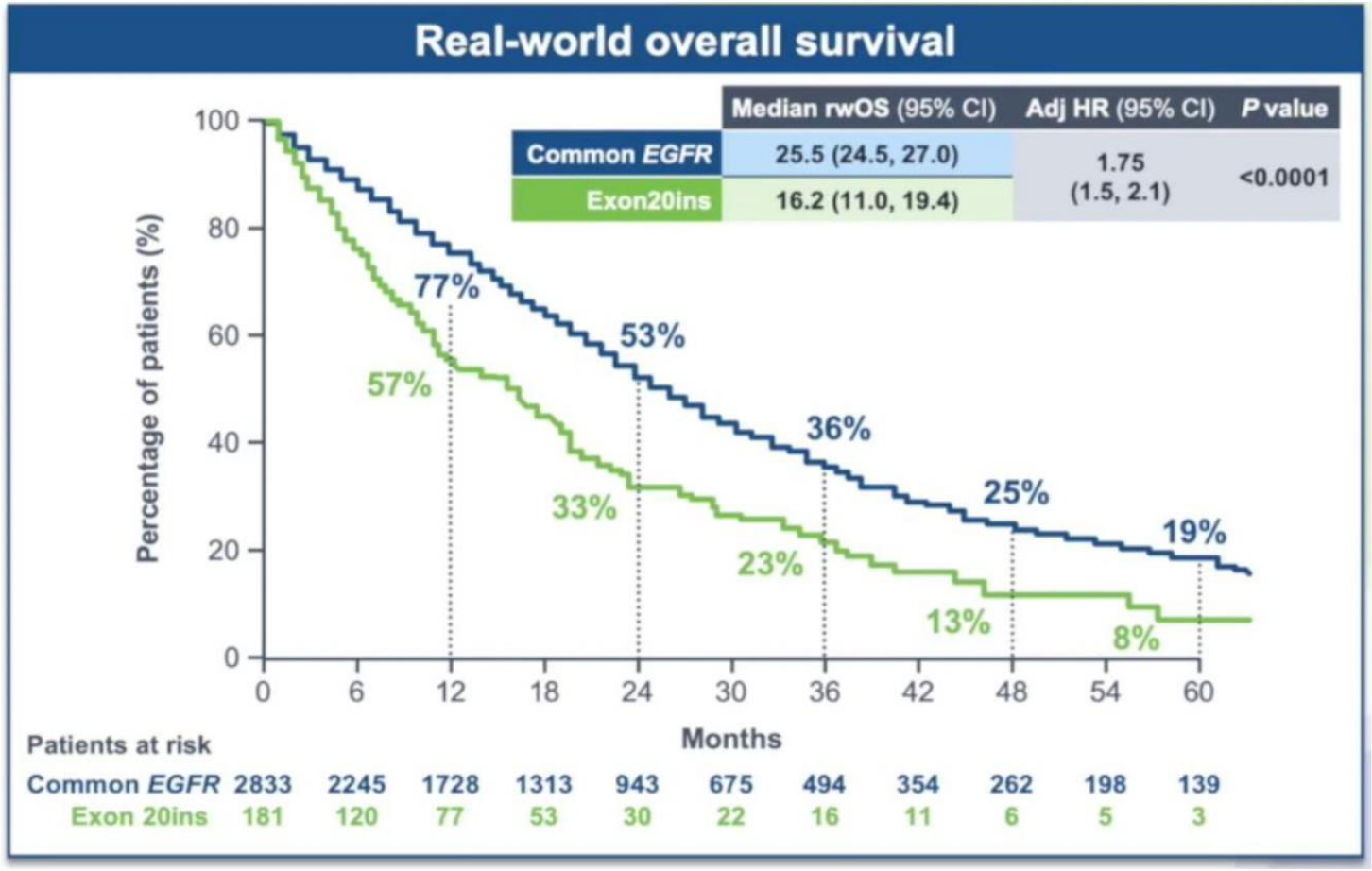
Less common mutations account for 12% of all mutations in EGFR-mutant NSCLC [1]



1. Zhang T et al. Transl Lung Cancer Res 2019;8:302-3016
2. Harrison PT. Emin Cancer Biol 2020;61:167-179

Survival of patients with EGFR exon 20 insertions

Flatiron database, 181 patients with advanced NSCLC with exon 20 insetions from 2011-2020



- 75% increased risk of death with exon20ins compared with cEGFR (primary end point)
  - 5-year survival for exon20ins is 8% vs 19% for cEGFR
- 93% increased risk of progression or death with exon20ins (secondary end point)
- 60% increased risk of shorter time to next therapy (secondary end point)

Girard N. Presented at WCLC 2020. MA04.07

Landscape of Agents Targeting EGFR Exon 20 Insertion mutations

	Mobocertinib	Amivantamab	Osimertinib	CLN-081	Poziotinib
Type of drug	EGFR TKI	EGFR/MET antibody	EGFR TKI	EGFR TKI	EGFR TKI
Clinical trial setting	After platinum chemo Active brain mets OK (35%)	After platinum chemo Brain mets (22%)	1 prior line of treatment Stable brain mets OK	After platinum chemo Stable brain mets OK	After chemo Stable brain mets OK (10%)
Number of pts	PPP N=114 EXCLAIM N=96	N=81	N=21	N=43	N=87
Prior TKI	25% (PPP) 31% (EXCLAIM)	25%	Prior TKI unknown Median prior therapy = 2	Prior 1st/2nd gen=18% Prior osi=20% Prior pozi/mobo=9%	Prior EGFR TKI=25%
Prior IO	43% (PPP) 34% (EXCLAIM)	46%	Unknown	56%	Unknown
Toxicity (Treatment-related) >30%	91-93% Diarrhea 45% Rash 39% Paronychia 32-35% Anorexia 30-34% Nausea 31% Dry skin	66% infusion reaction 86% rash 42% paronychia	76% Diarrhea 67% Fatigue 67% thrombocytopenia 43% anemia 43% leukopenia 43% anorexia 38% mucositis 38% rash	73% Rash	79% Diarrhea 60% Rash 52% Stomatitis 45% Paronychia 38% Nausea 31% Anorexia
Dose Modifications	Dose reduction 25% PPP 22% EXCLAIM Drug discontinue 17% PPP 10% EXCLAIM	Dose reduction 13% Drug discontinue 4%	Dose reduction Unknown Drug discontinue 5%	Dose reduction 11% Drug discontinue 9%	Dose reduction 68% Drug discontinue 10%
ORR	28% (PPP) 25% (EXCLAIM)	40%	24%	31% at all levels 46% at 100 BID	15%
PFS/DOR	DOR 17.5 mo (PPP) mPFS 7.3mo (PPP) OS 24 mo (PPP)	DOR 11.1 mPFS 8.3mo OS 22.8 mo	mPFS 9.6mo	Unknown	PFS 4.2mo DOR 7.4mo
CNS as Site of PD	All: CNS 38%, Not CNS (62%) Baseline brain mets: CND 68%	Not reported	Not reported	Not reported	Not reported
EGFR ex20ins Position	Efficacy across all EGFRex20ins subtypes	Efficacy across all EGFRex20ins subtypes	Not reported	Efficacy across all EGFRex20ins subtypes	Efficacy across all EGFRex20ins subtypes

Ramalingam PASCO 2021, Piotrowska PASCO 2020, Sabari WCLC 2020, Piotrowska PASCO 2021, Le AACR 2020, Yu ASCO 2021

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EGFR mutated NSCLC

- What do we really need?
  - Survival and Tolerability—Always!!!
  - Reduce Brain Mets and Brain relapse.

OSIMERTINIB meets
OS,
CNS activity &
Superior Tolerability

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THANK YOU!!

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