EGFR-mutated Non-Small Cell Lung Cancer: Update from WCLC21 Denver

David R. Gandara, MD
University of California Davis

DISCLOSURES

Commercial Interest	Relationship(s)
Genentech	Research Grant (Institutional)
Amgen	Research Grant (Institutional)
Astex	Research Grant (Institutional)
Astra Zeneca	Consultant (Institutional)
IO Biotech	Consultant (Institutional)
Guardant Health	Consultant (Institutional)
Oncocyte	Consultant (Institutional)
Roche Genentech	Advisory Board
Merck	Advisory Board
Novartis	Advisory Board
Boehringer Ingelheim	Advisory Board
Amgen	Advisory Board
Janssen	Advisory Board
Regeneron	Advisory Board
Sanofi	Advisory Board

EGFR-mutated NSCLC: Advanced Stage Disease

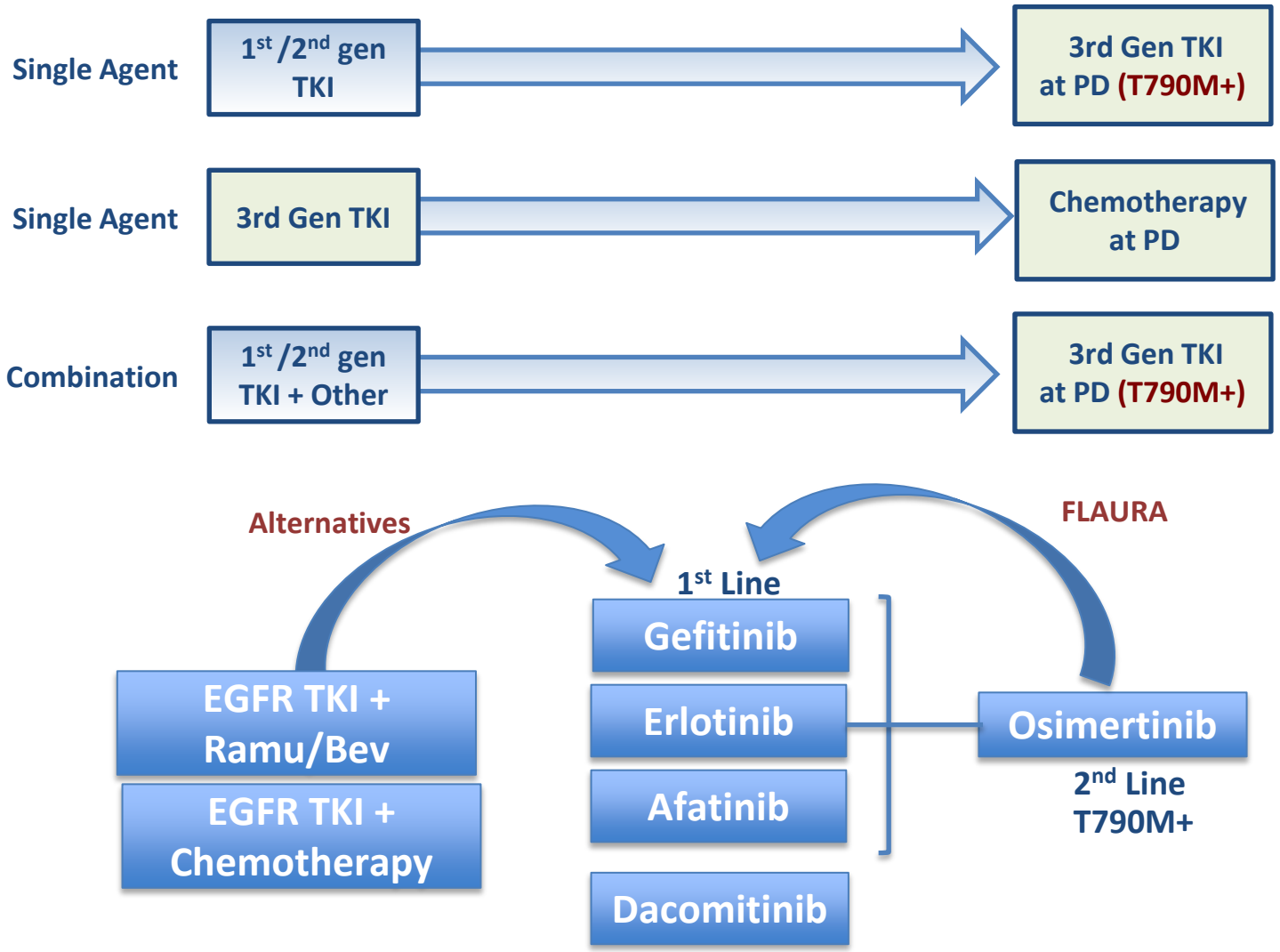
EGFR exon20 mutated NSCLC: New Therapies

- Mobocertinib in NSCLC with *EGFR* exon20ins: *(Spira)*
- Amivantamab in post-platinum *EGFR* exon20ins NSCLC: CHRYSALIS trial *(Sabari)*

EGFR mutated NSCLC: Mechanisms of Acquired Resistance to EGFR TKIs & New Approaches

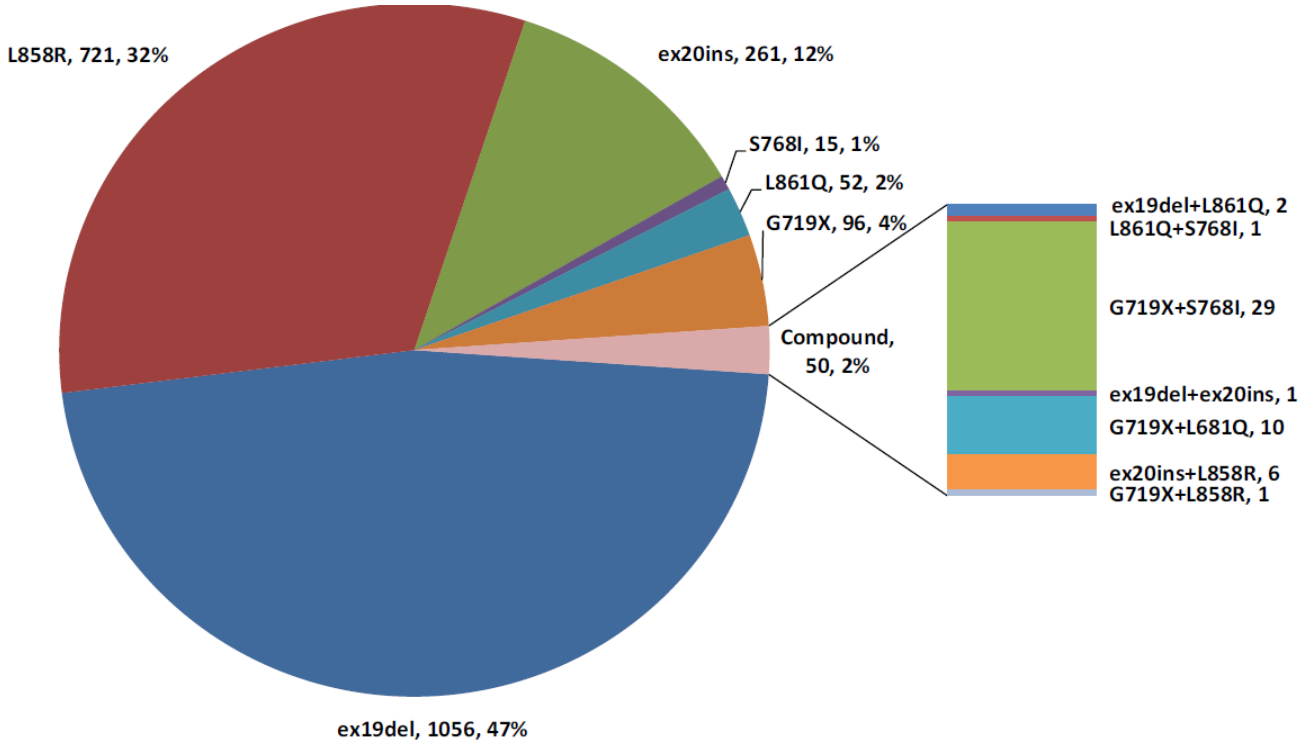
- Trastuzumab-emtansine (T-DM1 or ado-trastuxumab) plus Osimertinib to target HER2 bypass track resistance in EGFR-mutated NSCLC *(Jebbink)*
- Osimertinib + savolitinib in *EGFR*m *MET*-amplified/ overexpressed NSCLC: TATTON final analysis *(Han)*
- Efficacy and Safety of a HER3-Directed Antibody Drug Conjugate Patritumab Deruxtecan (HER3-DXd; U3-1402) in *EGFR*-Mutated NSCLC *(Yu)*

Strategies for Optimizing 1st-line Therapy for EGFR-mutated NSCLC: Options for 1st line Therapy



EGFR Ex20ins-mutated NSCLC

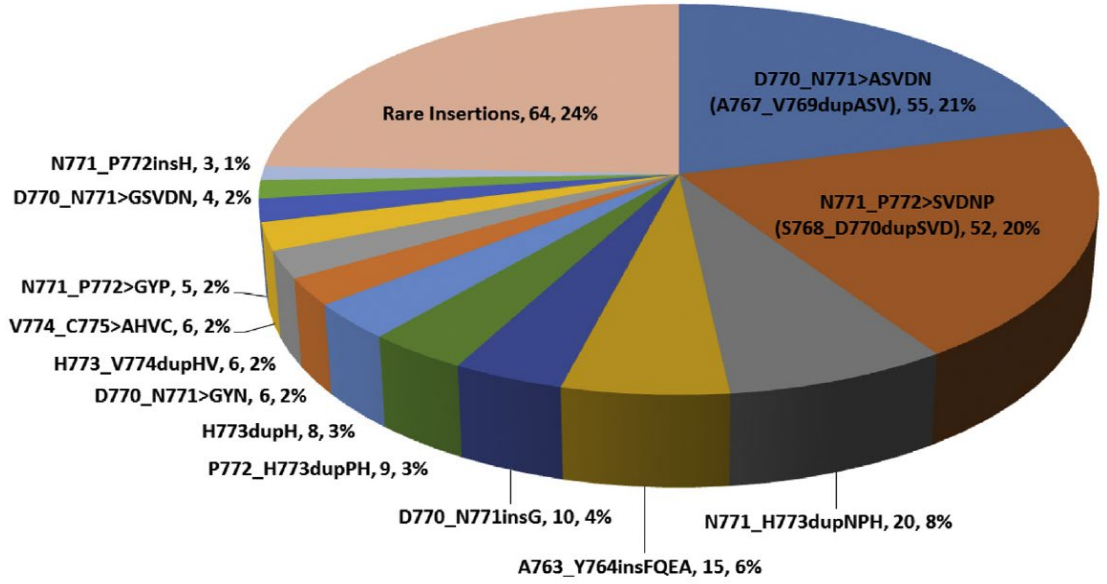
EGFR Mutation Subtypes (N=2,251)



Riess et al. JTO 2018

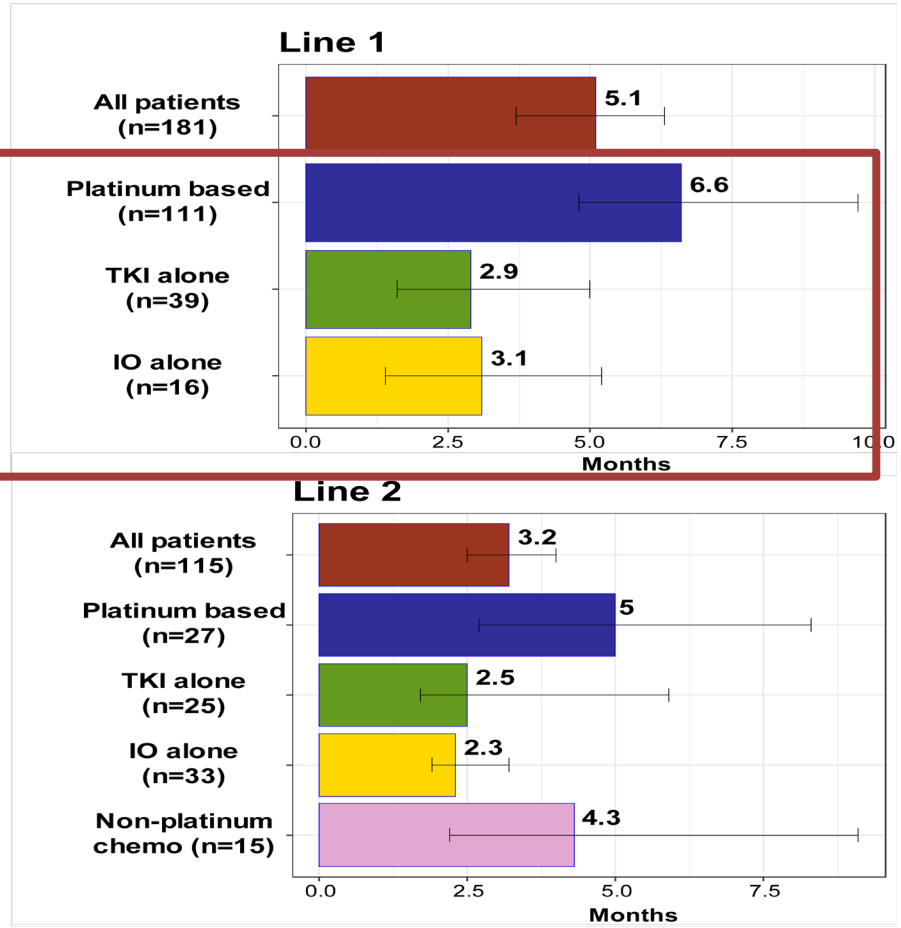
- EGFR Ex20ins mutations (~2% of NSCLC)
- ~12% of all EGFR mutations (3rd most common)
- Reliably detected by NGS platforms
- Resistant to therapy with 1st Gen EGFR TKIs
- Modest activity for 2nd and 3rd Gen EGFR TKIs

Distribution of EGFR Ex20ins mutations (N=263)

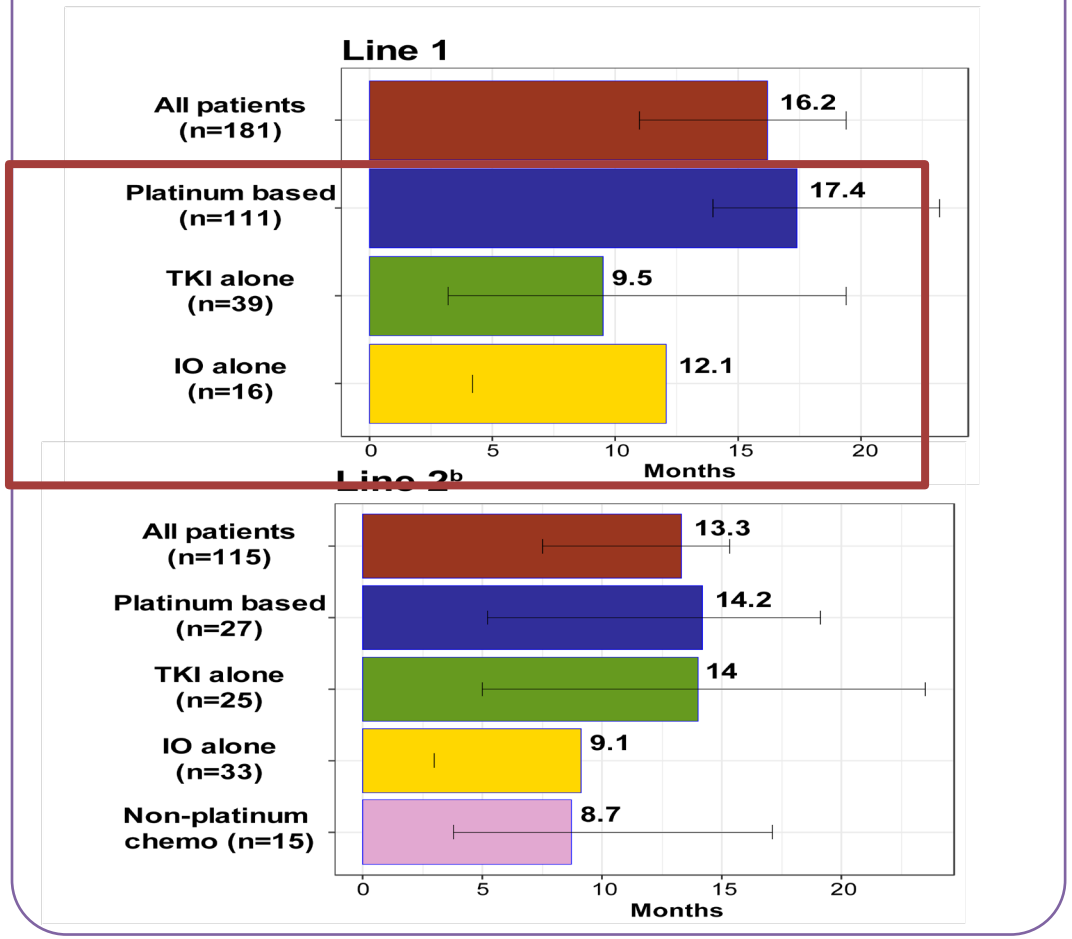


“Real World” Clinical outcomes for patients with *EGFR* exon20ins NSCLC

rwPFS by therapy type



rwOS by therapy type



- **Poor prognosis compared with patients with common *EGFRm***
- **Little benefit from current EGFR TKIs compared with patients with common *EGFR*m**
- **Platinum-based therapies were the most effective 1st-line treatment, no clear standard in 2nd- line**
- **chemotherapy should be the comparator for studies of novel agents in *EGFR* exon20ins NSCLC**

*EGFR*m, *EGFR* mutations;
rwOS, real-world overall survival;
rwPFS, real-world progression-free survival.
Girard N et al. WCLC 2020. Abstract MA04.07.

Treatment Landscape for EGFR Ex20ins NSCLC

Drug	Class	*N*	ORR (%)
Chemotherapy[1]	Platinum-based	105 first line	19.2%
Gefitinib/ Erlotinib[2]	1G EGFR TKI	9 first line 16 pre-treated	8
Erlotinib[3]	1G EGFR TKI	11 pre-treated	25
Dacomitinib[4]	2G EGFR TKI	6 pre-treated	16
Afatinib[5]	2G EGFR TKI	21 TKI pre-treated 70 TKI naive	14.3 24.3
Osimertinib[6,7]	3G EGFR TKI	20 pre-treated, 80 mg OD 21 pre-treated, 160 mg OD	5 25
Poziotinib[8]	Pan-HER TKI	115 pre-treated	14.8
CLN-081[9]	EGFR TKI	22 pre-treated	35
Mobocertinib	EGFR TKI	114 pre-treated	28-35
Amivantamab	EGFR-MET bispecific Ab	81 pre-treated	40

[1]Yang G et al, Lung Cancer 2020; [2]Beau-Faller M et al, Ann Oncol 2014; [3]Naidoo J et al, Cancer 2015; [4]Janne PA et al, CCR 2011; [5]Yang JC et al, JTO 2020; [6]Veggel B et al, Ann Oncol 2018; [7]Piotrowska Z et al, ESMO 2020; [8]Le X et al, AACR 2020; [9]Piotrowska Z et al, ESMO 2020

Mobocertinib in EGFR Ex20ins-mutated NSCLC with previous Disease Control (CR/PR/Stable) on EGFR TKIs

Phase 1 Dose Escalation: 3+3 design (advanced non–small cell lung cancer; ECOG PS <2)

Phase 2 Expansion: Mobocertinib 160 mg QD

Phase 2: Primary endpoint: ORR by RECIST v1.1 per investigator
Secondary endpoints: Safety, tolerability, PK, efficacy (ORR per IRC, best overall response, best target lesion response, DCR, DoR, time to response, PFS, OS)

- Cohort 1: Refractory *EGFR* ex20ins+; no active, measurable CNS metastases[a]
- Cohort 2: Refractory *HER2* ex20ins or point mutation; no active, measurable CNS metastases[a]
- Cohort 3: Refractory *EGFR* or *HER2* ex20ins or point mutations with measurable, active CNS metastases
- Cohort 4: Treatment naive or refractory; other *EGFR* mutations: +/– T790M, uncommon *EGFR*
- **Cohort 5: Refractory *EGFR* ex20ins who progressed after objective response or stable disease for ≥6 months on any prior EGFR TKI therapy**
- Cohort 6: Treatment-naïve; *EGFR* ex20ins+
- Cohort 7: Refractory other tumor types (non-NSCLC) with *EGFR/HER2* mutations
- EXCLAIM Extension Cohort: Previously treated patients; *EGFR* ex20ins+

Locations: United States only for phases 1 and 2; United States, European Union, and Asia for phase 2 extension cohort.
Active CNS metastases: untreated or treated and progressing; measurable CNS metastases: ≥10 mm in longest diameter by contrast-enhanced MRI.
[a] Active or measurable (but not both) CNS metastases permitted.
DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ex20ins, exon 20 insertion; HER2, human epidermal growth factor receptor 2 gene; MRI, magnetic resonance imaging; ORR, objective response rate; PK, pharmacokinetics; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

Spira et al WCLC 2021

Mobocertinib Clinical Activity in EGFR Ex20ins NSCLC with PD after prior EGFR TKI

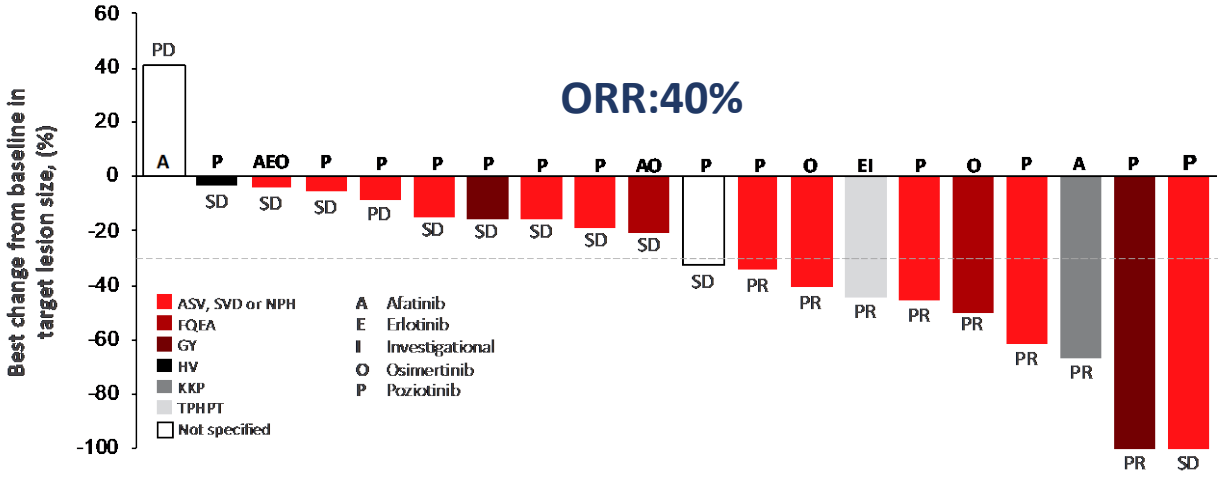
	IRC Assessment N=20
Confirmed ORR, n (%; 95% CI)	8 (40%; 19.1%−63.9%)
PR, n (%)	8 (40)
SD, n (%)	10 (50)
Confirmed ORR[a] on mobocertinib by prior TKI, n/N (%)	
Poziotinib	4/13 (31)
Osimertinib	2/4 (50)
Afatinib	1/4 (25)
Erlotinib	1/2 (50)
Investigational TKI	1/1 (100)

Data cutoff date: November 1, 2020.
IRC, independent review committee; NA, not available; ORR, objective response rate; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] Confirmed ORR defined as the proportion of the patients who are confirmed to have achieved complete or partial response after the initiation of study treatment; confirmed responses are those that persist on repeat imaging 4 weeks (allowing a minus 3-day window) or more after initial response.

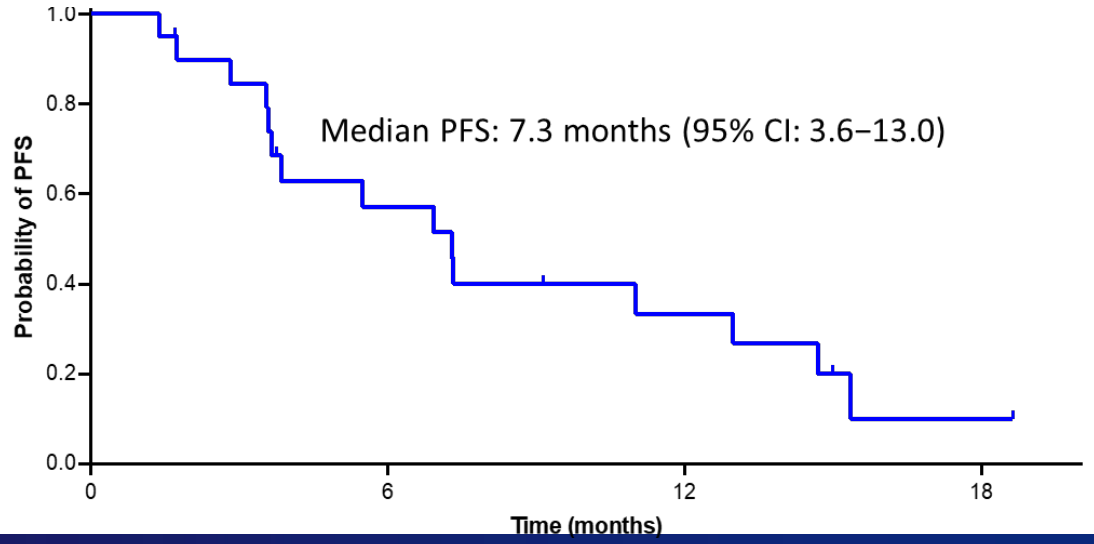
- ORR by RECIST v1.1 per investigator (primary endpoint) is 20% (95% CI, 5.7%−43.7%)

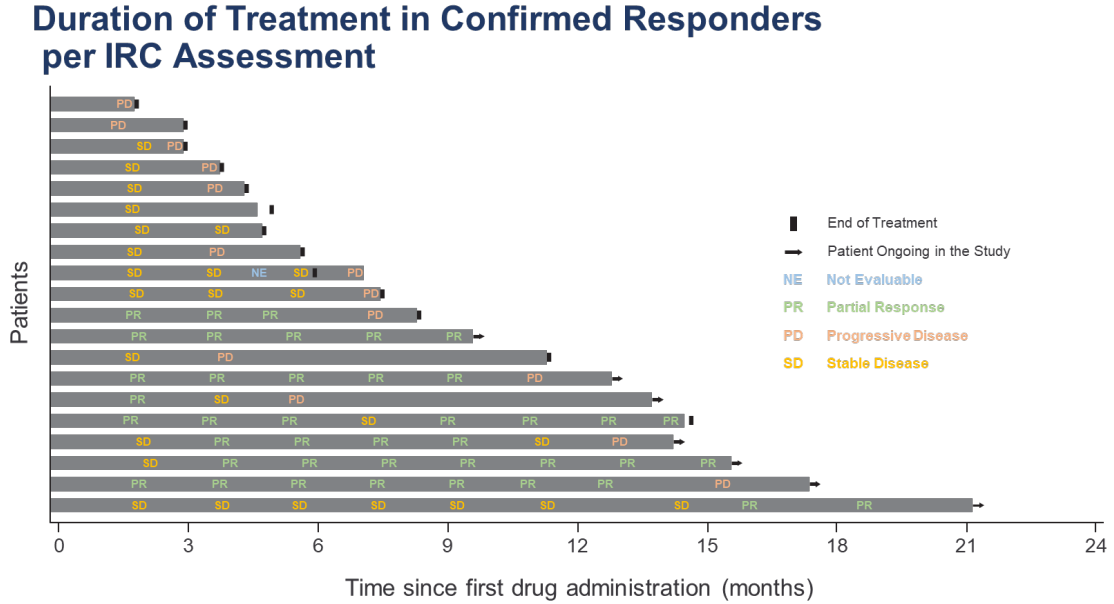
Spira et al WCLC 2021

Mobocertinib in EGFR Ex20ins-mutated NSCLC with previous Disease Control (CR/PR/Stable) on EGFR TKIs



ORR:40%



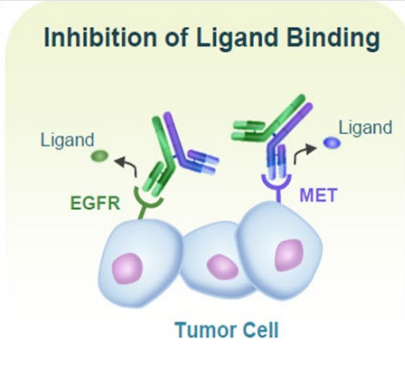


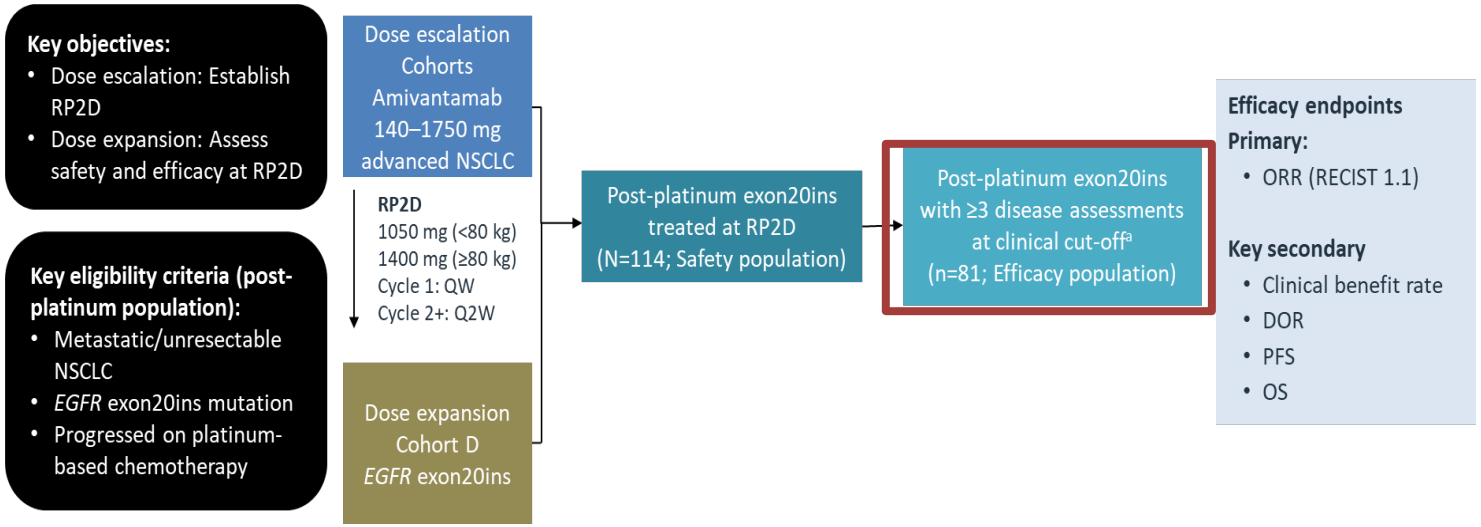
Median DoR:13.0 months

Spira et al WCLC 2021

CHRYSALIS study design: Post-platinum exon20ins population

- **Amivantamab: Fully human *EGFR-MET* bispecific antibody[2,3]**
- **Targets activating & resistance *EGFR* mutations & *MET* mutations/amplifications[4,5]**
- **Demonstrated monotherapy activity in patients with diverse *EGFRm* disease including *EGFR* exon19del, L858R, T790M, C797S, exon20ins & *MET* amplifications[4,5]**
-





NCT02609776.

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

DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QW, weekly; Q2W, twice weekly; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose.

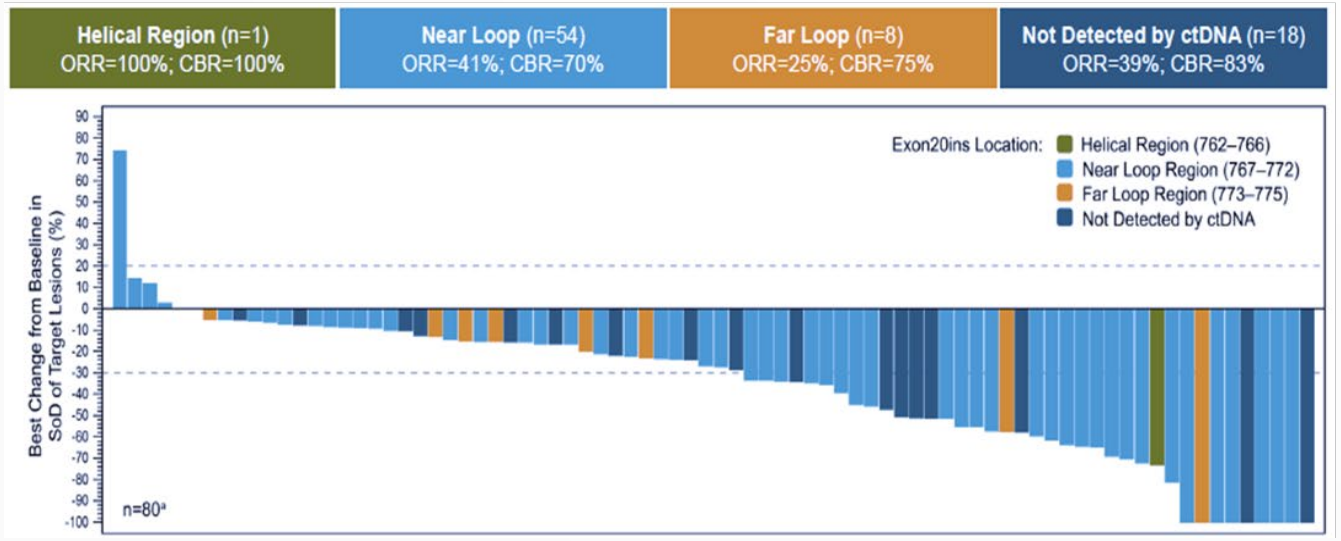
Sabari JK et al. WCLC 2020. Abstract OA04.04.

New Approved Agents in *EGFR*^{Exon20ins}

Drug	N	ORR (%)	DoR (months)	PFS (months)	OS (months)	Reference
Amivantamab	81	40	11.1	8.3	22.8	Sabari: WCLC Jan 2021
Mobocertinib	20 (cohort 5)	40	13	7.3	NR	Spira: WCLC Sept 2021
Mobocertinib	28 (cohort 1)	43	13.9	7.3	NR	Riley: CA Disc 2021

Response by Mutation Type

Amivantamab: Possible greater efficacy in the near loop insertions



Mobocertinib: Efficacy similar in all variants

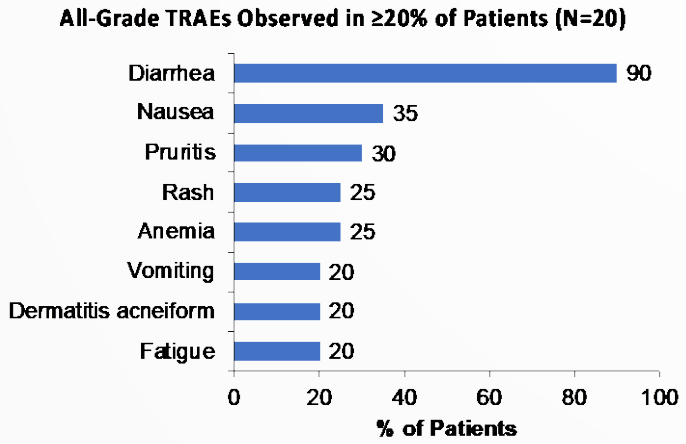
EGFR exon 20 insertion variant	No. of patients	No. of confirmed responders	Confirmed ORR
769_ASV	5	2	40%
773_NPH	4	2	50%
Other exon 20 insertion	12	6	50%
Exact variant unknown	4	2	50%

Adapted from Capuzzo: WCLC 2021

New Approved Agents in *EGFR EX20 ins: Adverse Events*

Mobocertinib-oral agent

	n (%) 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)



Diarrhea 90% (5% grade ≥3)
Dermatologic AEs very common

Amivantamab-iv 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)

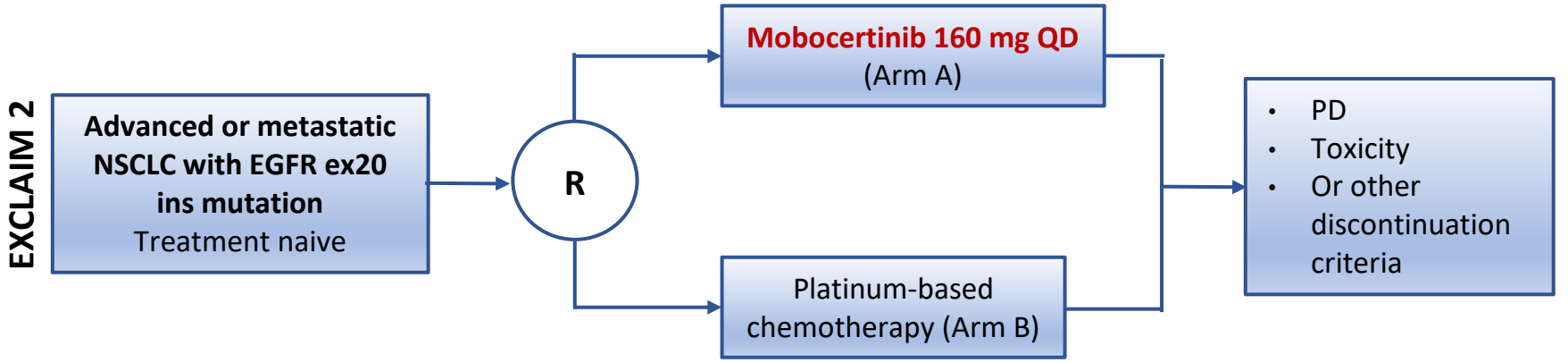
Diarrhea 12% (3.5% grade ≥3)
Infusion Reactions 68%

Adapted from Capuzzo: WCLC 2021

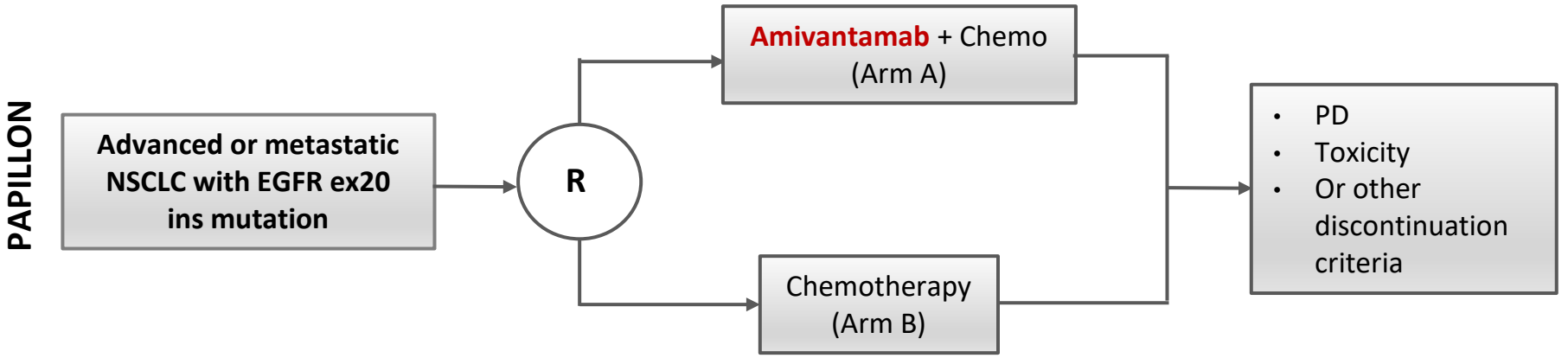
Ongoing studies in EGFR Ex20ins NSCLC

PHASE 3

NCT04129502



NCT04538664



EGFR-mutated NSCLC: Advanced Stage Disease

EGFR exon20 mutated NSCLC: New Therapies

- Mobocertinib in NSCLC with *EGFR* exon20ins: *(Spira)*
- Amivantamab in post-platinum *EGFR* exon20ins NSCLC: CHRYSALIS trial *(Sabari)*

EGFR mutated NSCLC: Mechanisms of Acquired Resistance to EGFR TKIs & New Approaches

- Trastuzumab-emtansine (T-DM1 or ado-trastuxumab) plus Osimertinib to target HER2 bypass track resistance in EGFR-mutated NSCLC *(Jebbink)*
- Osimertinib + savolitinib in *EGFR*m *MET*-amplified/ overexpressed NSCLC: TATTON final analysis *(Han)*
- Efficacy and Safety of a HER3-Directed Antibody Drug Conjugate Patritumab Deruxtecan (HER3-DXd; U3-1402) in *EGFR*-Mutated NSCLC *(Yu)*

EGFR TKIs vs Platinum Chemotherapy in *EGFR*-Mutated NSCLC

Study	Treatment	RR	Median PFS (mo)	Median OS
NEJ002[1] N=230	Gefitinib vs carboplatin/ paclitaxel	74 v 31%	10.8 vs 5.4 (*P* < .001)	30.5 vs 23.6 HR = 0.89
WJOTG[2,3] N=177	Gefitinib vs CDDP/ docetaxel	62 v 32%	9.2 vs 6.3 (*P* < .0001)	36 vs 39 HR = 1.25
OPTIMAL[4,5] N=165	Erlotinib vs carboplatin/ gemcitabine	83 v 36%	13.1 vs 4.6 (*P* < .0001)	30.4 vs 31.5 HR = 1.065
EURTAC[6] N=174	Erlotinib vs platinum-based chemotherapy	58 v 15%	9.7 vs 5.2 (*P* < .0001)	19.3 vs 19.5 HR = 0.93
LUX-Lung 3[7] N=345	Afatinib vs CDDP/Pem	61 v 22%	11.1 vs 6.9 (*P* < .0004)	28.2 vs 28.2 HR = 0.88
LUX-Lung-6 N=364	Afatinib vs CDDP/Gem	67 v 23%	11.0 vs 5.6 HR = 0.28	23.1 vs 23.5 HR = 0.93
AURA3 (2nd line)	Osimertinib vs CDDP/Pem	71 vs 31%	10.1 vs 4.4 HR = 0.30	NR

- **Gefitinib, Erlotinib, Afatinib, Decomitinib & Osimertinib all superior to Platinum chemotherapy for ORR & PFS**
- **No improvement in OS in these randomized trials due primarily to development of acquired resistance**

1. Maemondo M, et al. *N Engl J Med*. 2010;362:2380-2388. 2. Mitsudomi T, et al. *Lancet Oncol*. 2010;11:121-128. 3. Mitsudomi T, et al. ASCO 2012. Abstract 7521. 4. Zhou C, et al. *Lancet Oncol*. 2011;12:735-742. 5. Zhang C, et al. ASCO 2012. 7520. 6. Rosell R, et al. *Lancet Oncol*. 2012;13:239-246. 7. Yang J C-H, et al. ASCO 2012. Abstract LBA 7500.

FLAURA: Osimertinib vs Gefitinib/Erlotinib in 1st line therapy of EGFR-mutated NSCLC

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria

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

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

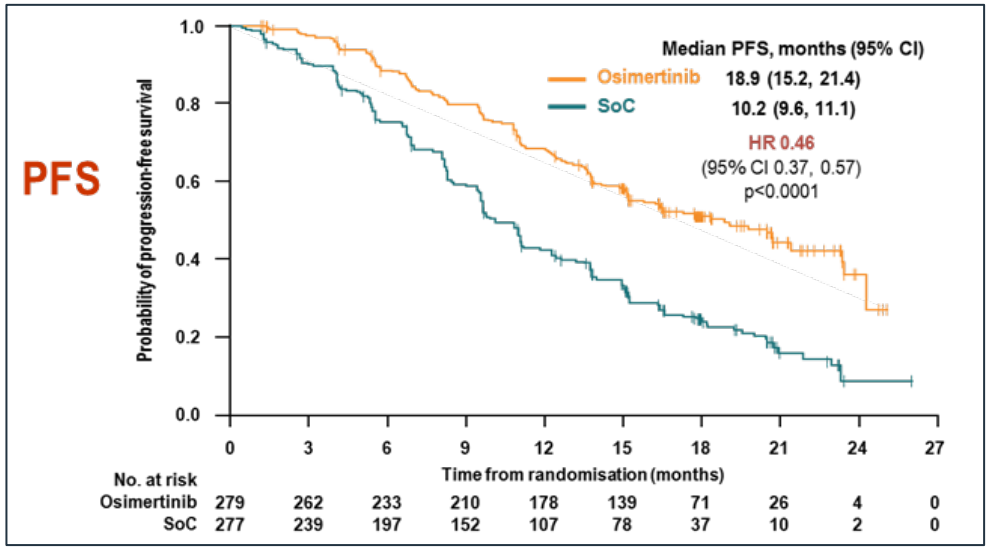
R 1:1

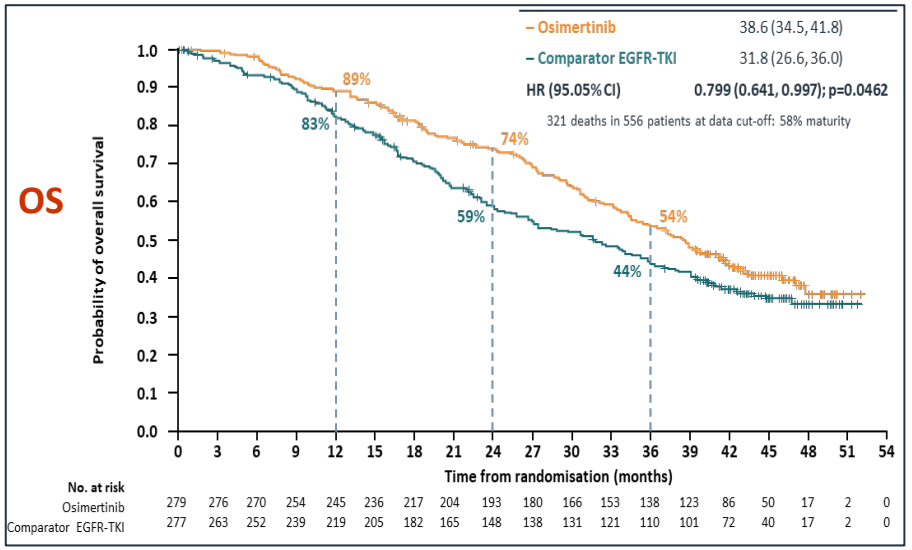
Osimertinib (80 mg po qd) (n=279)

Comparator EGFR-TKI; Gefitinib (250 mg po qd) or **Erlotinib** (150 mg po qd) (n=277)

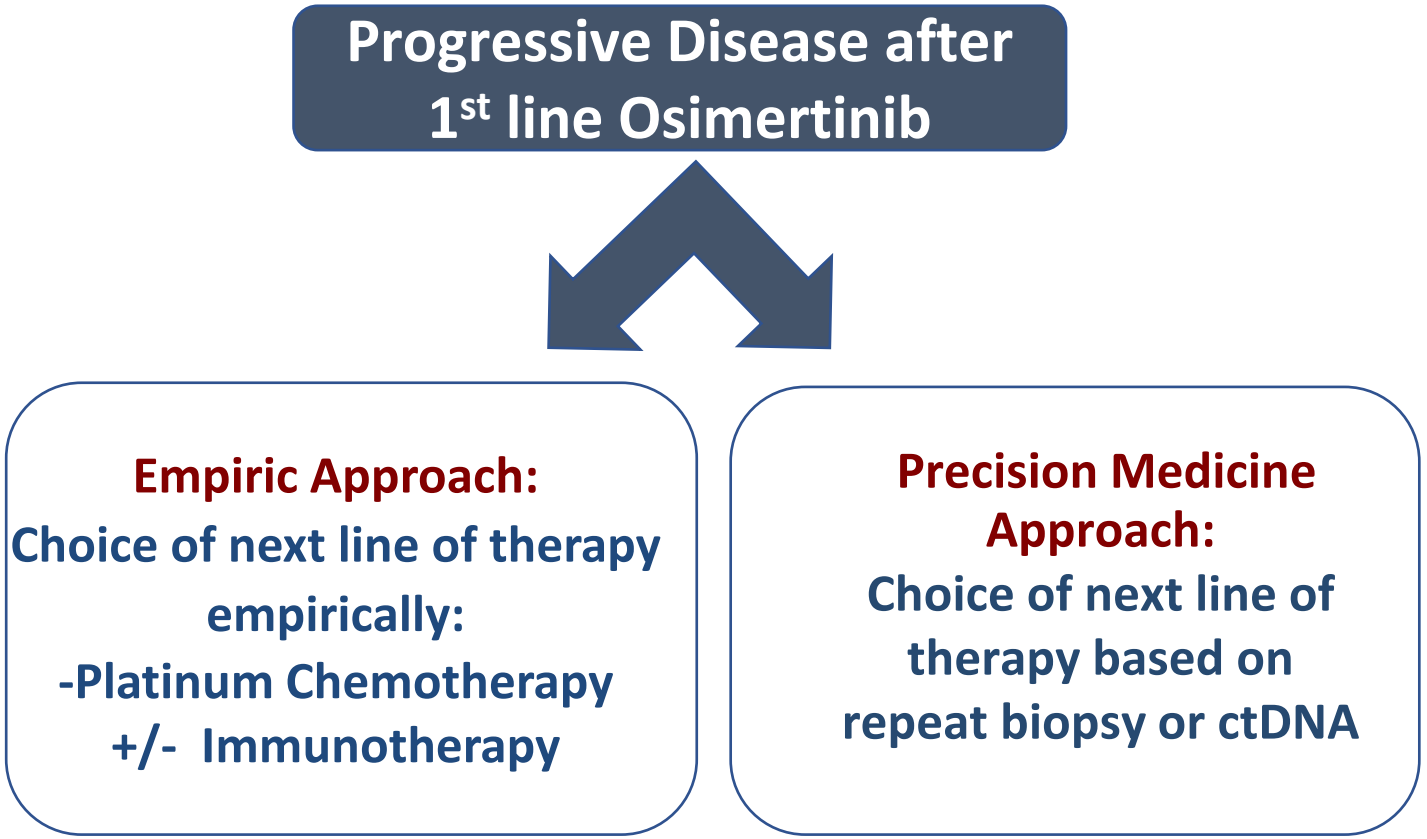
RECIST v1.1 assessment every 6 weeks until objective progressive disease
Following the primary PFS analysis, progression events per RECIST 1.1 were no longer collected centrally

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





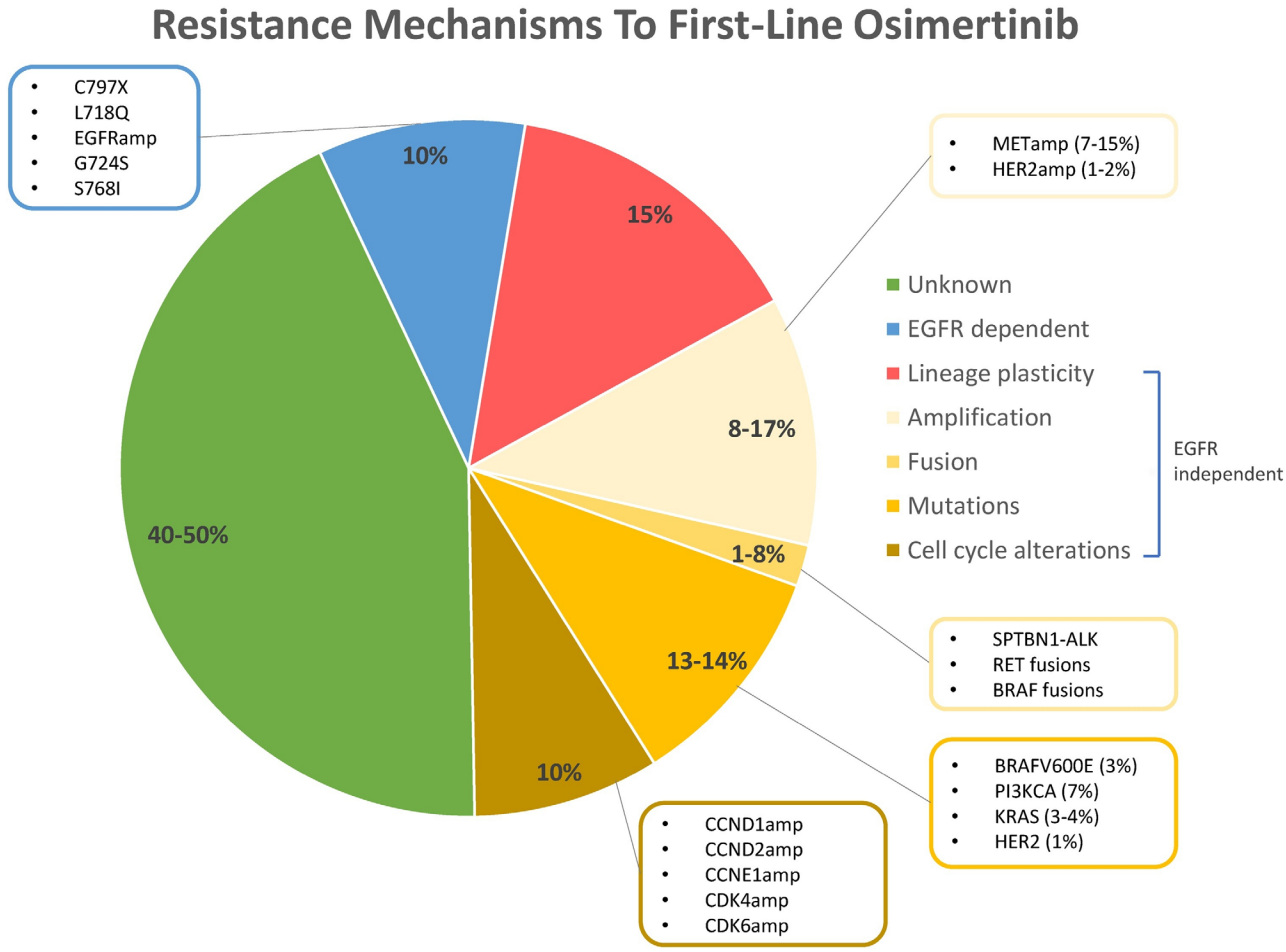
Soria et al: NEJM 2017



Adapted from Melosky, Popat, Gandara. Clin Lung Cancer. 2017

Rationale for novel approaches to acquired resistance to Osimertinib

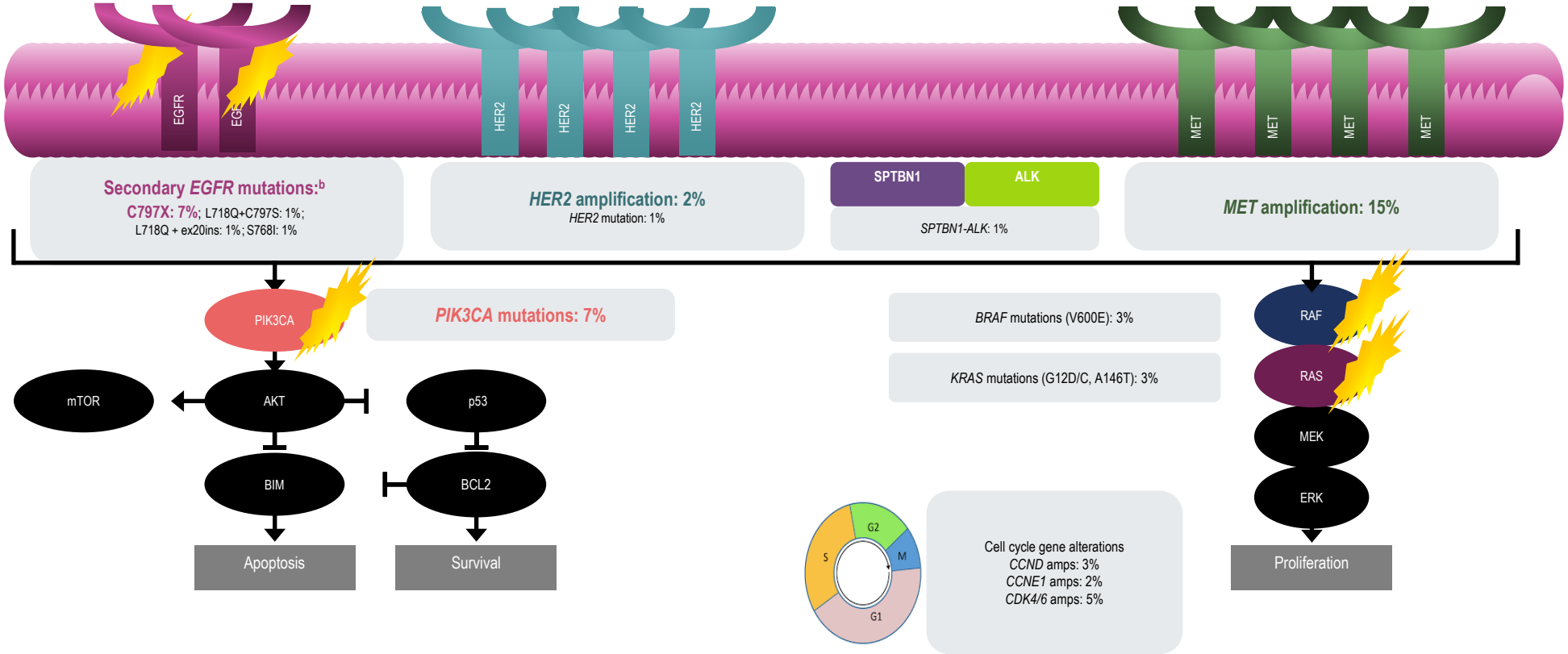
- Acquired resistance to Osimertinib is inevitable
  - Multiple mechanisms
    - **EGFR-dependent** (e.g. C797X) vs **Bypass** (e.g. MET amplification)
  - Potential to utilize combination therapy to overcome and/or prevent resistance
- Certain baseline co-mutations may predict for poor PFS (e.g. p53)
  - Potential to utilize combination therapy to extend PFS in frontline setting as well



Schmid et al., Lung Cancer. 2020

FLAURA: Acquired Resistance Mechanisms after Osimertinib 1st-line therapy (n=91)

- No cases of acquired *EGFR* T790M
- The most common resistance mechanisms were ***MET* amplification** (15%) and ***EGFR* C797X mutation** (10%)
  - Other mechanisms included HER2 amplification/mutation (3%), *PIK3CA(7%), RAS/RAF* mutations and ALK transformation



Ramalingam et al: ESMO 2019

Trastuzumab-emtansine (T-DM1 or ado-trastuxumab) plus Osimertinib to target HER2 bypass track resistance in EGFR-mutated NSCLC

Simons 2 stage minimax

Sample size determination

ORR
H0=41%
H1>55%

80% power, one-sided type I error rate of 10%

Sample size: 58 patients

Cohort A ORR 16/36 in order to proceed to cohort B

Study Phase I: classical 3+3 design

Study Phase II

Study population

EGFRm+ NSCLC, WHO PS≤2
PD on prior EGFR TKI
positive for HER2-overexpression (IHC2+ ≥10%)

Study treatment
T-DM1 3.0 and 3.6 mg/kg iv q3w
Osimertinib 80mg QD
(n=6)

Endpoints
Safety
RP2D for Phase II

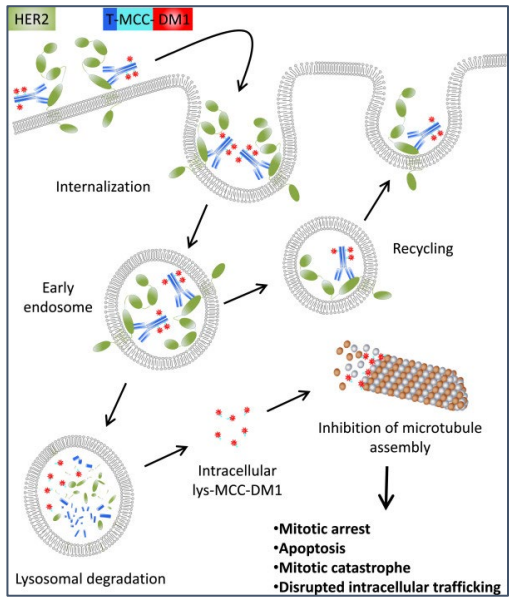
Study treatment
T-DM1 3.0 or 3.6 mg/kg iv (RP2D) q3w
Osimertinib 80mg QD
(n=58)

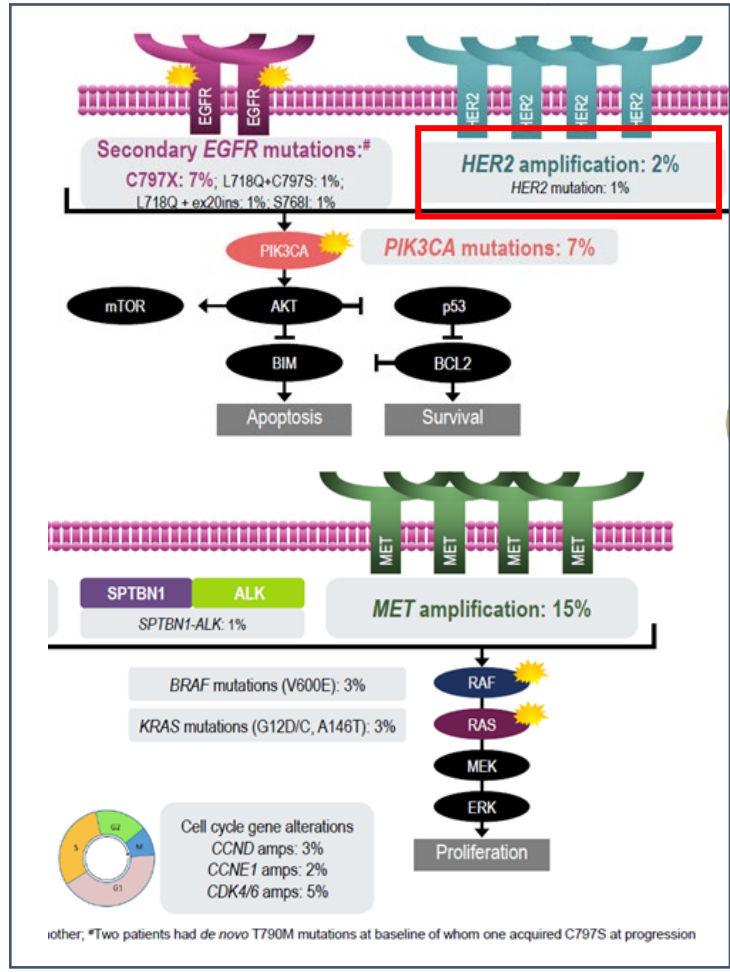
Endpoints
Objective response rate (RECIST v1.1)
Safety, DCR after 12 weeks, PFS, OS

Jebbink et al: WCLC 2021

Rationale for combination HER2/EGFR therapy in Acquired Resistance to Osimertinib

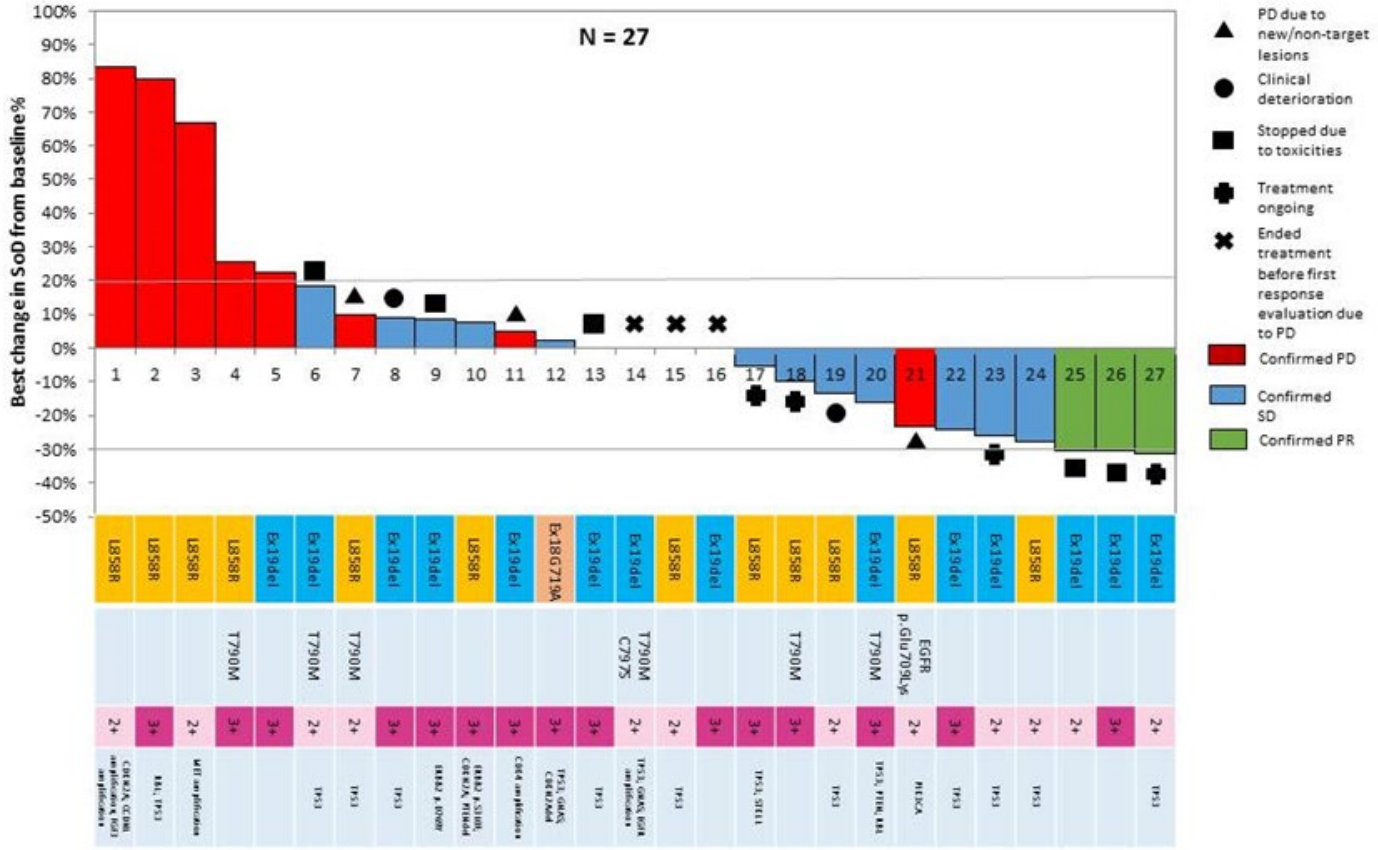
- HER2 amplification and/or mutations have been identified as mechanisms of acquired resistance to Osimertinib
- Potential to utilize HER2-targeted mABs/ADCs in combination with Osimertinib
- T-DM1 is an ADC directed against HER2 approved in HER2+ breast cancer, composed of Trastuzumb + DMI (maytansine derivative)





Jebbink et al: WCLC 2021

Trastuzumab-emtansine + Osimertinib in EGFR-mutated NSCLC with PD after Osimertinib: Efficacy & Toxicity



Median PFS: 2.7 months (95% CI, 2,1-3,5 months)

	All	HER2 IHC 2+	HER2 IHC 3+
ORR	11% (3/27)	17%	7%
DCR 12w	48% (13/27)	42%	53%

- Median # cycles T-DM1: 4 (range 1-14)
- There were no grade 4 or 5 therapy-related AEs
- Grade 2: 30%; Grade 3: 19%

- 5 patients stopped due to toxicities
  - Pneumonitis: 2
  - LVEF decrease: 1
  - Nausea and vomiting: 1
  - Stomach pain/fatigue: 1

Jebbink et al: WCLC 2021

Selected Other Novel Approaches to EGFR TKI Acquired Resistance (to Osimertinib)

Drug	N	ORR (%)	mDoR (months)	mPFS (months)	mOS (months)	Reference
HER3-DxD	49	25%	6.9	NR	NR	Yu et al: WCLC 2020
Salolitinib + Osi (MET amp/IHC++)	69	33%	NR	5.5	NR	Han et al: WCLC 2020
Necitumumab + Osi	18	17% (2/4 PR in C797S)	NR	NR	NR	Riess et al: ASCO 2019
Amivantamab	121	27%	5.9	4.2	NR	Leighl et al: ESMO 2021
Ami + Lazertinib	45	36%	9.6	4.9	NR	Leighl et al: ESMO 2021
Ami + Lazertinib	80	41%	NR	NR	NR	Shu et al: ESMO2021
T-DM1 + Osi	**27**	**11%**	**NR**	**2.7**	**NR**	**Jebbink et al: WCLC 2021**