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LUNG CANCER SYMPOSIUM

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18th Annual

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EGFR Exon 20 and atypical mutations

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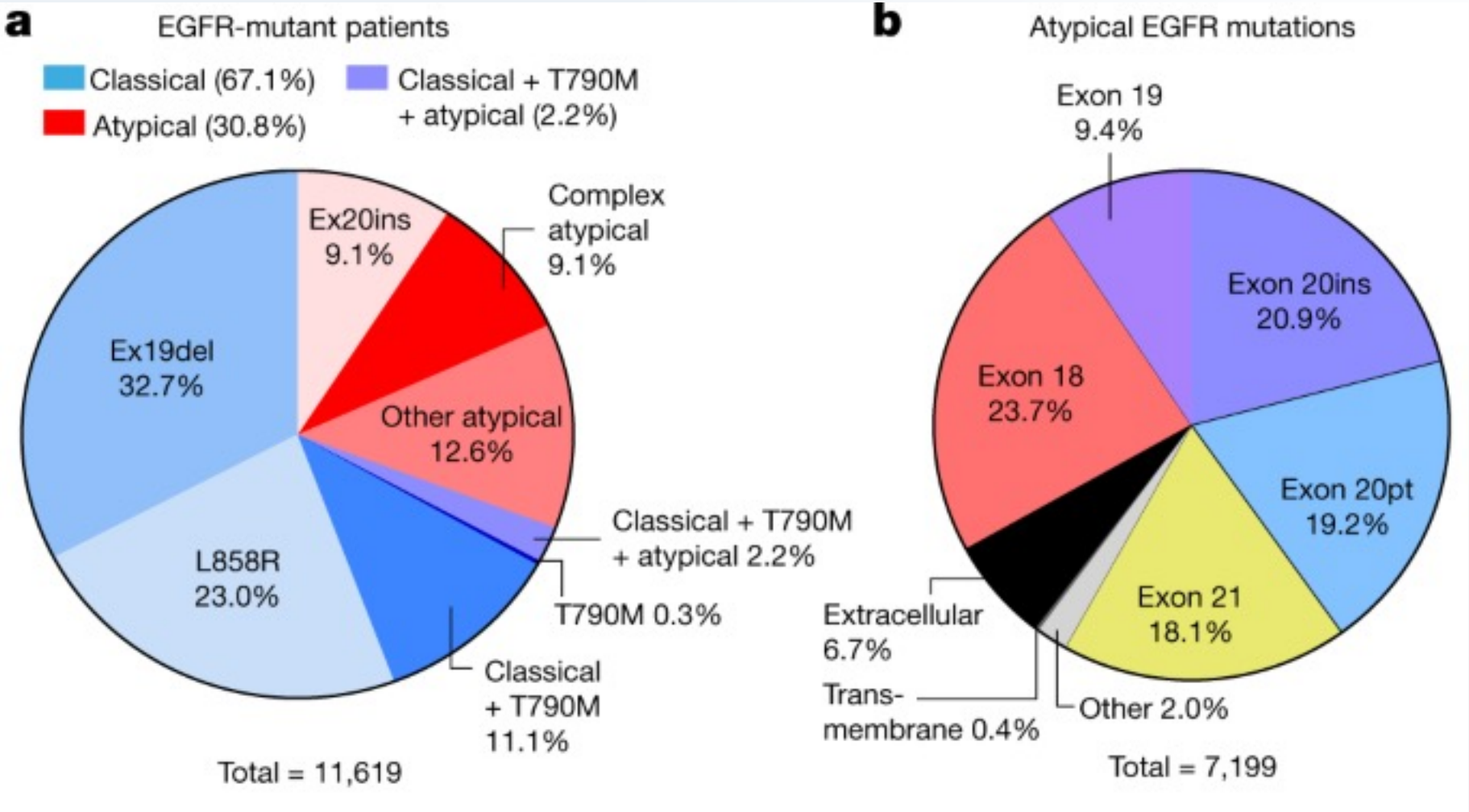
Disclosures

Research funding to institution: Amgen, AstraZeneca, Daiichi Sankyo, Parexel, Hutchmed, Chipscreen

Advisory Boards: Sanofi, Amgen, Novocure

Subtypes of EGFR mutations



Robichaux, J.P., Le, X., Vijayan, R.S.K. *et al.* Structure-based classification predicts drug response in *EGFR*-mutant NSCLC. *Nature* **597**, 732–737 (2021).

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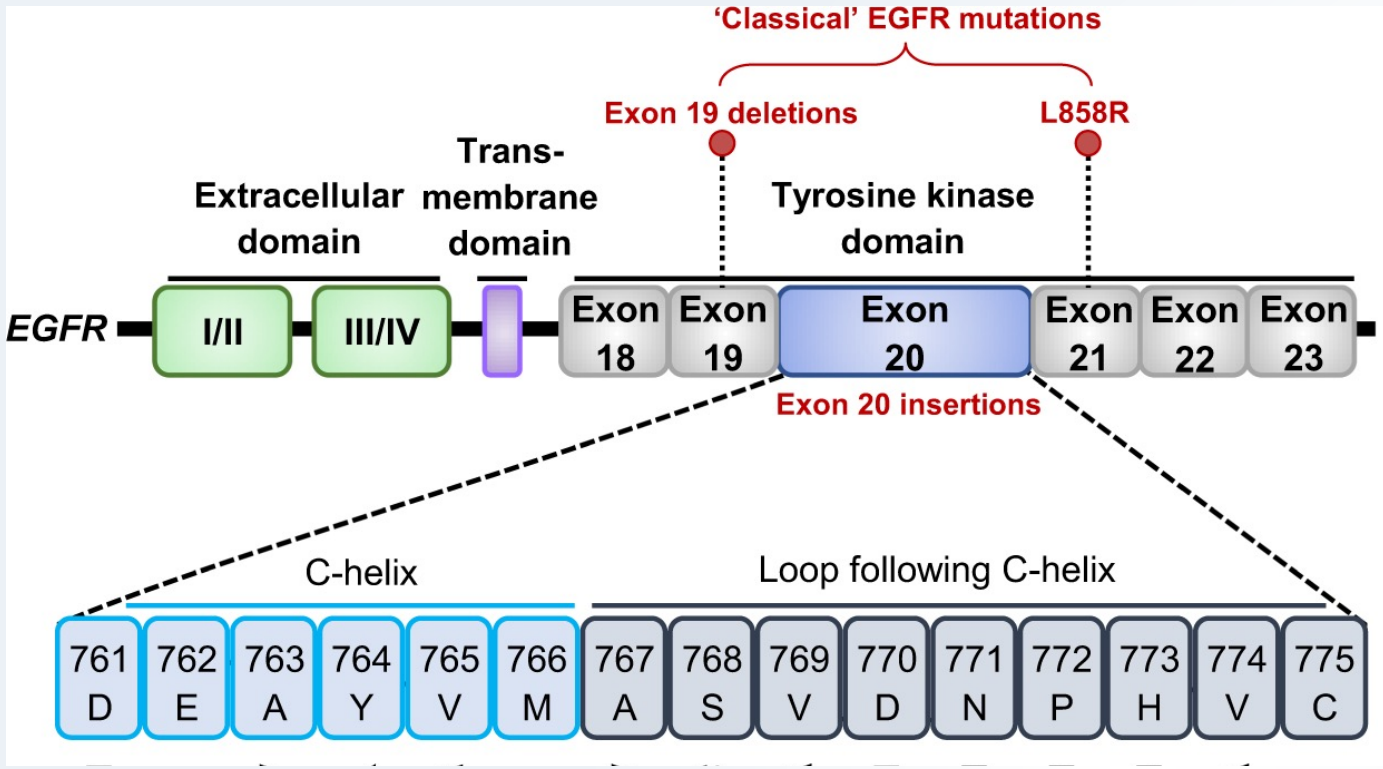
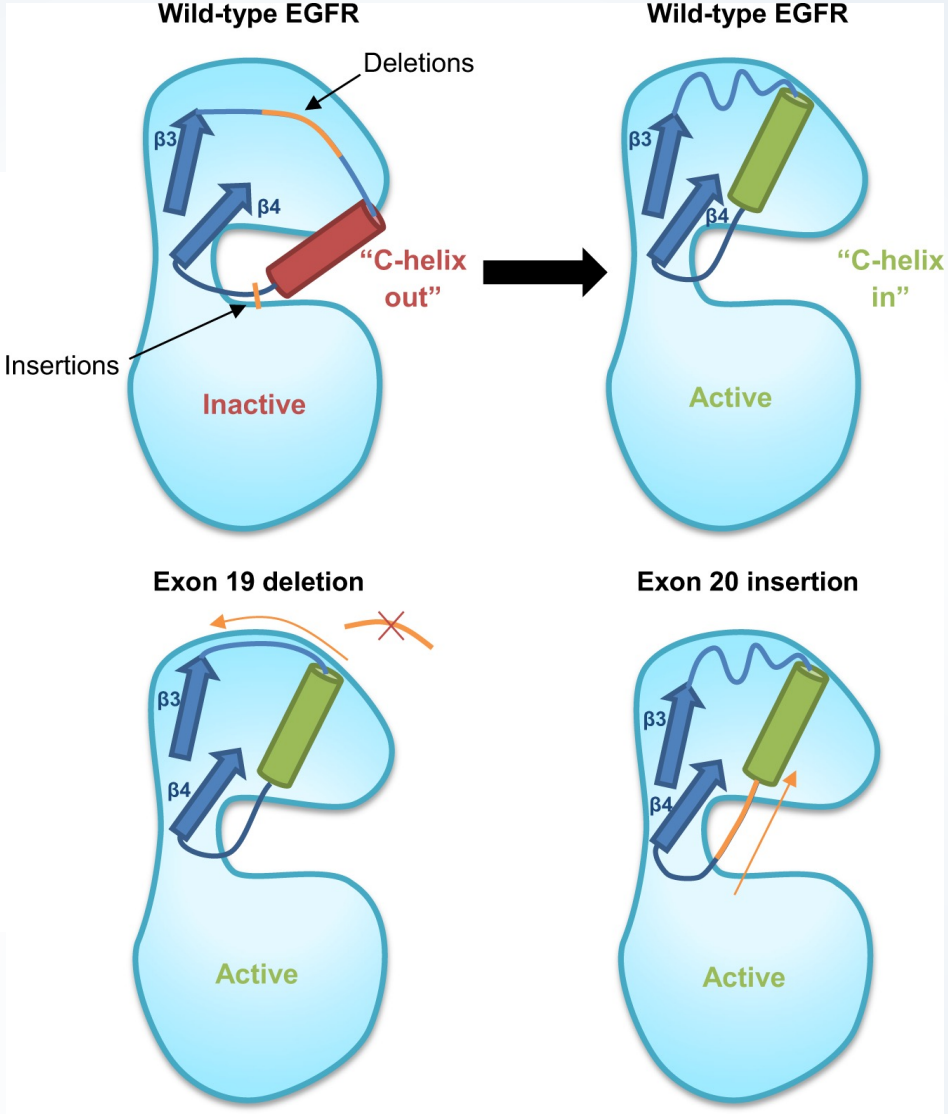
EGFR exon 20 mutations





Vyse, S., Huang, P.H. Targeting *EGFR* exon 20 insertion mutations in non-small cell lung cancer. *Sig Transduct Target Ther* **4**, 5 (2019)

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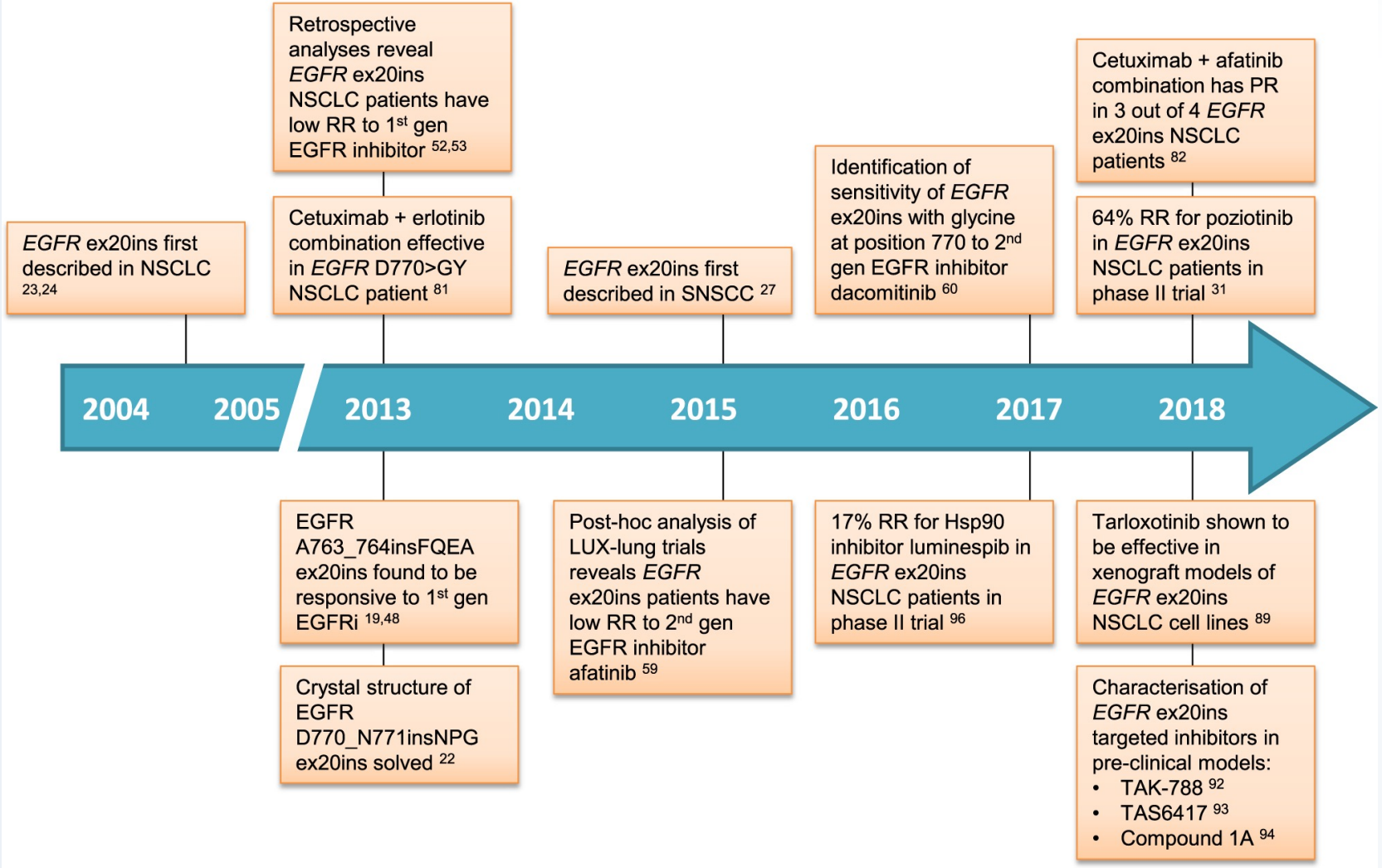
Timeline of EGFR Exon 20 therapeutics



Vyse, S., Huang, P.H. Targeting *EGFR* exon 20 insertion mutations in non-small cell lung cancer. *Sig Transduct Target Ther* **4**, 5 (2019)

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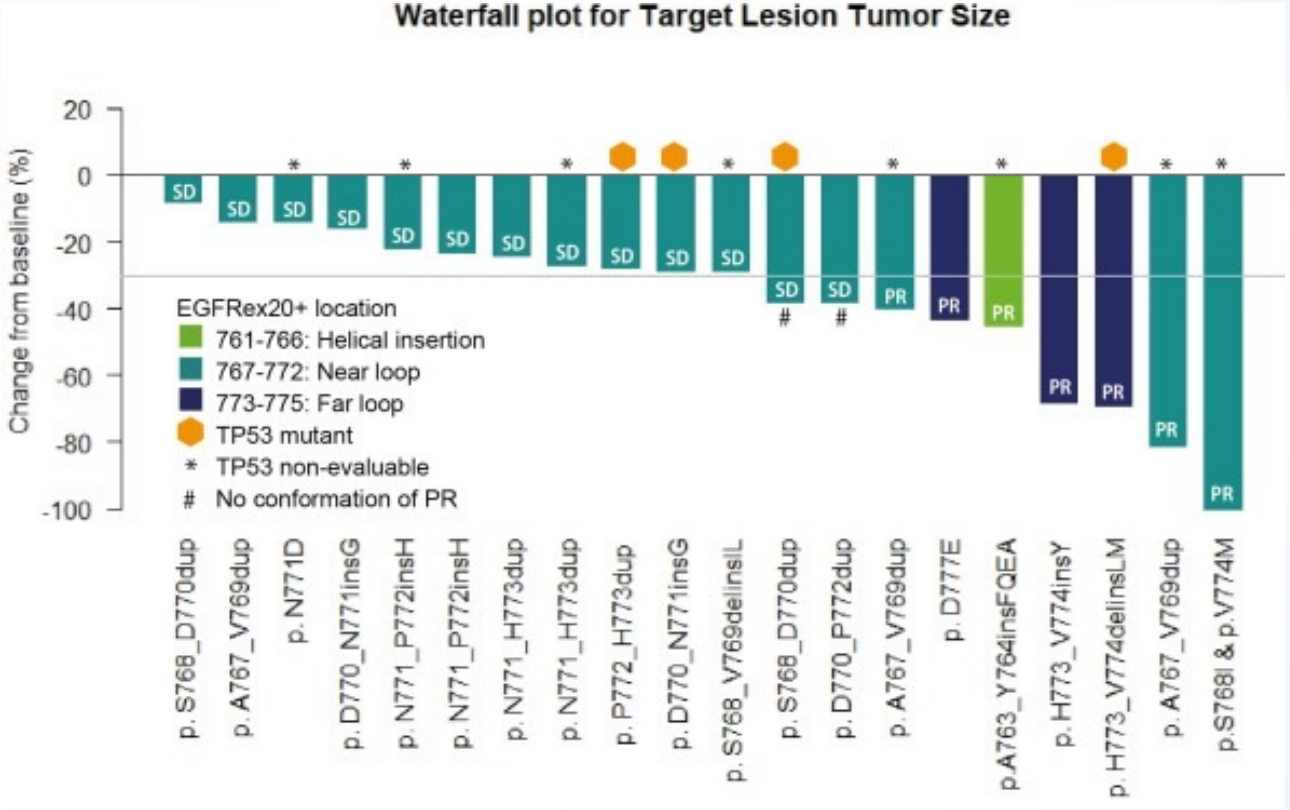
EGFR exon 20 responses to osimertinib 160

EA5162: PHASE II STUDY

Osimertinib 160mg daily is well-tolerated and showed clinical activity in EGFR ins20-mutant NSCLC
N=21 patients
response rate of 25%
disease control rate of 85%
mPFS of 9.7 months.

Phase 2 multicenter POSITION20 trial



Piotrowska, ASCO 2020

Zwierenga et al. Lung Cancer, 2022

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EA5162 Available Through ECOG-ACRIN Cancer Research Group

Phase II Study of Osimertinib (AZD9291) in Advanced NSCLC Patients with Exon 20 Insertion Mutations in EGFR

Patient Population

See Section 3 for complete eligibility criteria

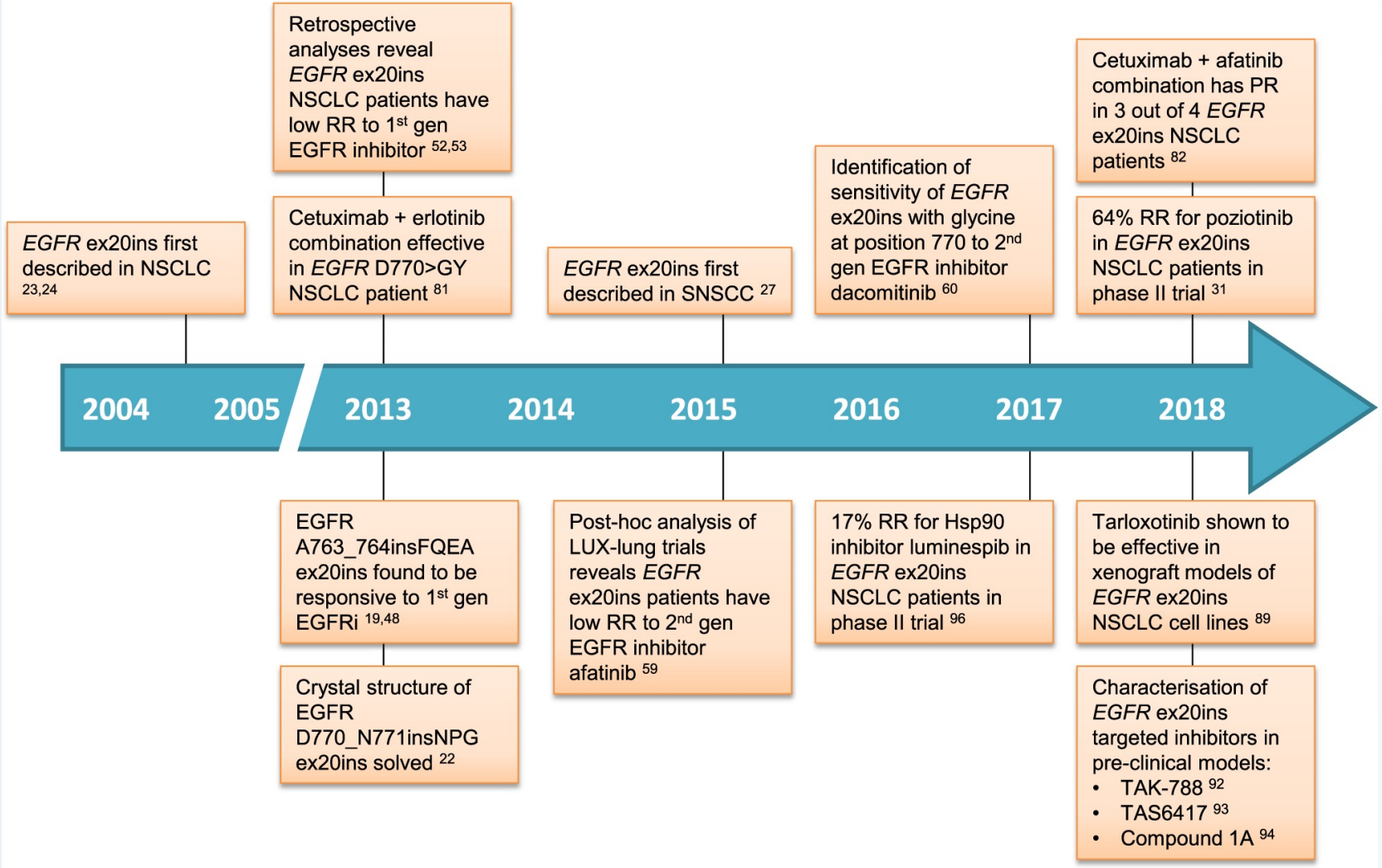
- Must have a pathologically-confirmed diagnosis of NSCLC; must have measurable disease per protocol
- Must have advanced disease– either stage IV disease, stage IIIB disease not amenable to definitive multi-modality therapy, or recurrent disease after a prior diagnosis of stage I-III disease (AJCC/IASLC 7th ed.)
- An EGFR exon 20 insertion mutation must be detected in the tumor tissue
- Must have previously received at least 1 line of therapy for advanced lung cancer (no restrictions on maximum number of prior therapies allowed)
- Must not have previously received osimertinib
- Must not have received therapies targeting PDL1, PD1, or CTLA4 within 180 days of registration
- Age ≥ 18 years, ECOG PS ≤ 1, and adequate lab values
- No clinically active or symptomatic interstitial lung disease/interstitial pneumonitis, or a history of clinically significant interstitial lung disease/radiation pneumonitis

Treatment Plan

See Section 5 for complete treatment details

- Osimertinib administered at a dose of 160 mg by mouth once daily on days 1-21 of a 21-day cycle
  - ◊ Osimertinib should be taken at the same time every day (+/- 4 hours; either in the AM or PM), with or without food
- Treatment will be given without interruption, unless interruptions are required to manage treatment-related side effects
- Missed doses will not be taken later
- Patients should continue on treatment with osimertinib until RECIST 1.1 defined progression or until treatment discontinuation criteria (per protocol) are met
- Patients may continue to receive osimertinib beyond RECIST 1.1 defined progression as long as they are continuing to show clinical benefit as judged by the investigator (i.e., there is no maximum duration of treatment)

Timeline of EGFR Exon 20 therapeutics



Amivantimab FDA accelerated approval in May 2021

Mobocertinib FDA accelerated approval in Sept 2021

Vyse, S., Huang, P.H. Targeting *EGFR* exon 20 insertion mutations in non-small cell lung cancer. *Sig Transduct Target Ther* **4**, 5 (2019)

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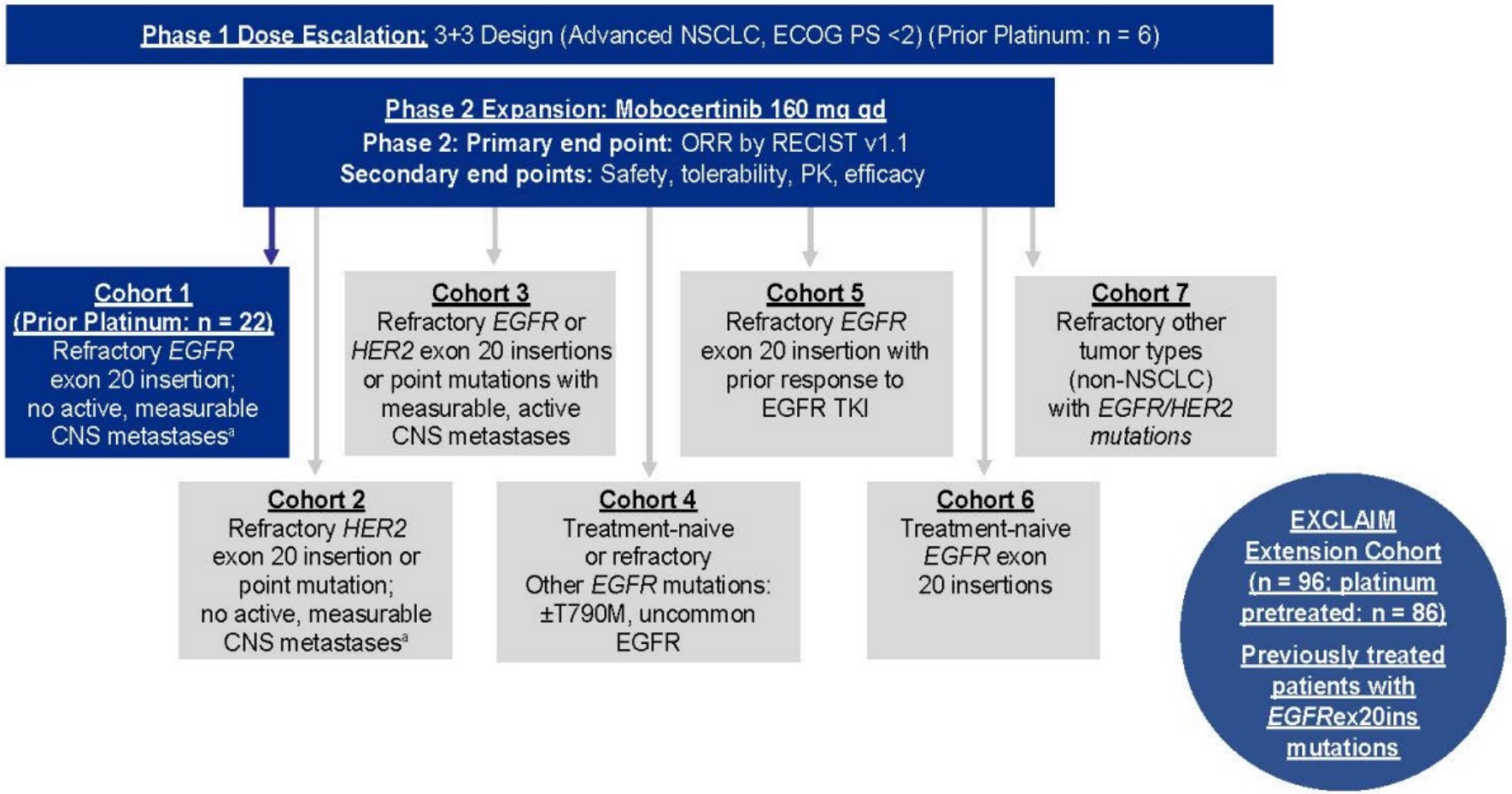
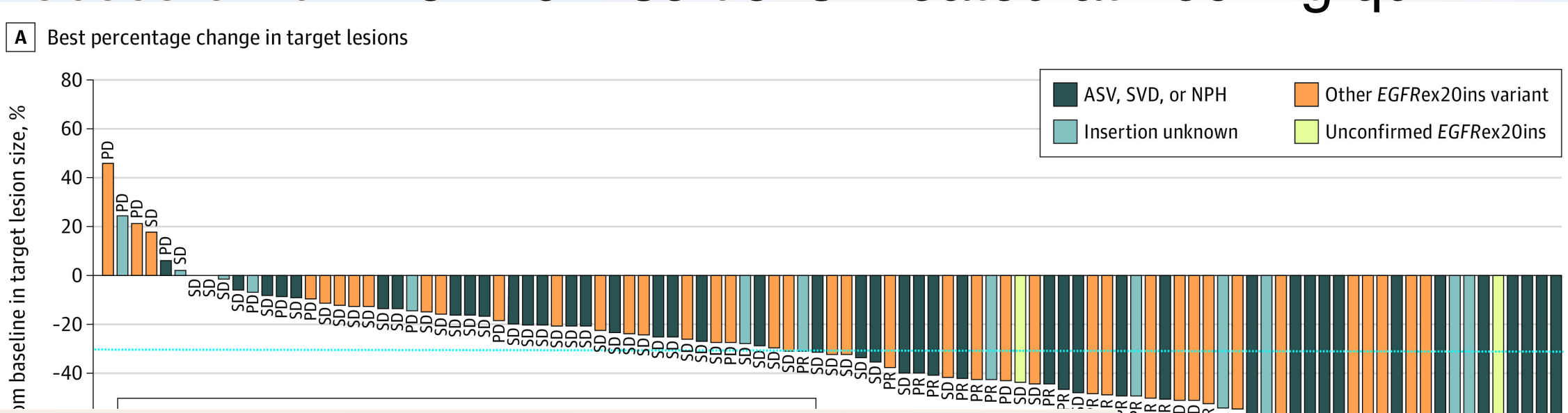
Mobocertinib: oral tyrosine kinase inhibitor



Zhou J, et al. JAMA Oncol. 2021;7(2):263-270.

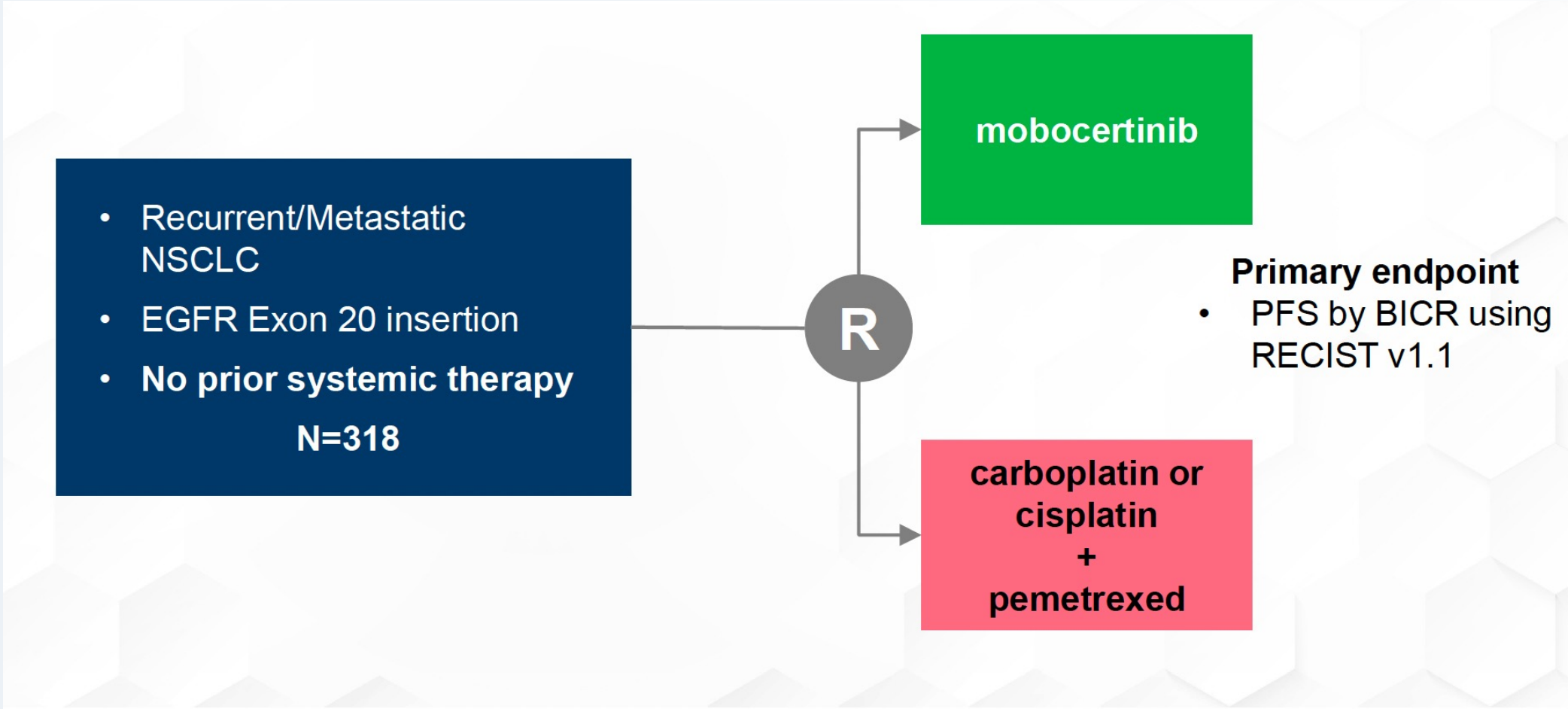
Mobocertinib: Exon 20 Insertions Treated at 160 mg qd



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]

Zhou J, et al. JAMA Oncol. 2021;7(2):263-270.

Mobocertinib: confirmatory phase III trial EXCLAIM2



NCT04538664. Accessed August 31, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT04538664.

Mobocertinib: withdrawal from market

Provides Update on (mobocertinib)

October 2, 2023

OSAKA, Japan and CAMBRIDGE, Massachusetts, October 2, 2023 · today announced that, following discussions with the U.S. Food and Drug Administration (FDA), it will be working with the FDA towards a voluntary withdrawal of (mobocertinib) in the U.S. for adult patients with epidermal growth factor receptor (EGFR) Exon20 insertion mutation-positive (insertion+) locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on or after platinum-based chemotherapy. intends to similarly initiate voluntary withdrawal globally where is approved and is working with regulators in other countries where it is currently available on next steps.

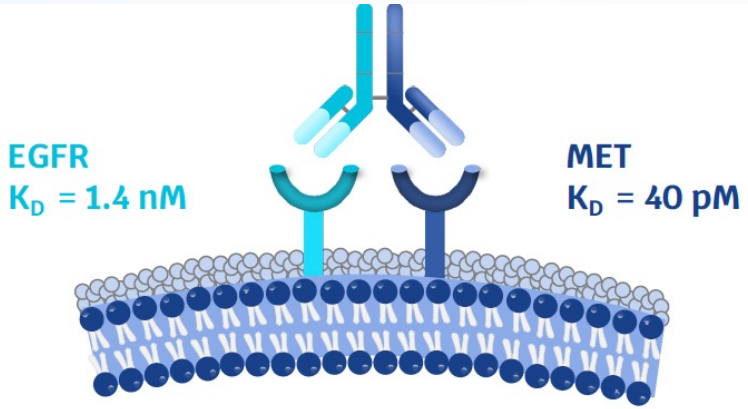
This decision was based on the outcome of the Phase 3 EXCLAIM-2 confirmatory trial, which did not meet its primary endpoint and thus did not fulfill the confirmatory data requirements of the Accelerated Approval granted by the U.S. FDA nor the conditional marketing approvals granted in other countries.

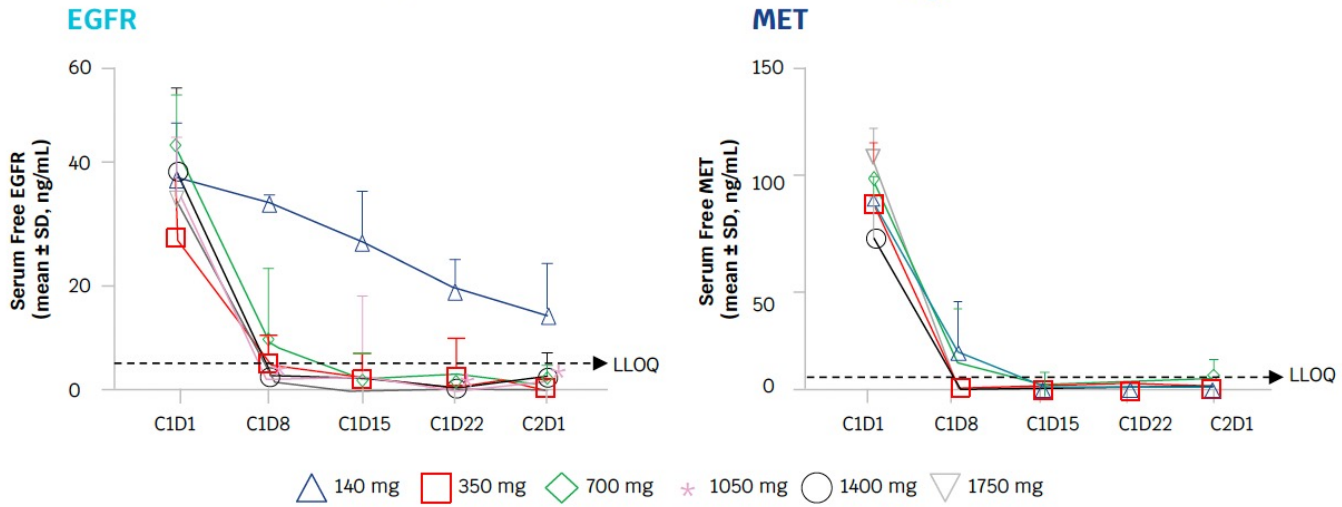
The EXCLAIM-2 trial was a Phase 3, multicenter, open-label study designed to investigate the safety and efficacy of EXKIVITY as a monotherapy versus platinum-based chemotherapy in first-line EGFR Exon20 insertion+ locally advanced or metastatic NSCLC. No new safety signals were observed in the EXCLAIM-2 trial. Full data from the trial will be presented at an upcoming medical meeting or published in a peer-reviewed journal.

Zhou J, et al. JAMA Oncol. 2021;7(2):263-270.

Amivantamab: EGFR-MET bispecific antibody

- Demonstrated monotherapy activity in EGFR ex20ins NSCLC following progression on platinum-based chemotherapy (ORR, 40%; DOR, 11.1 months)[1]
- Demonstrated activity in TKI-resistant EGFRm NSCLC with MET amplification [2,3]
- Has higher affinity for MET (40 pM) than EGFR (1.4 nM)
- Depletion of free soluble target proteins, suggesting total body target engagement, occurs at ≥140 mg for sMET and ≥350 mg for sEGFR
- Evaluation in primary MET-driven tumors is ongoing





C, cycle; D, day; DOR, duration of response; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; ex20ins, exon 20 insertion mutations; K_D, dissociation constant; LLOQ, lower limit of quantification; NSCLC, non-small cell lung cancer; ORR, overall response rate; SD, standard deviation; sEGFR, soluble EGFR; sMET, soluble MET; TKI, tyrosine kinase inhibitor.

1.Park, et al. *J Clin Oncol* 2021;39(30) : 3391-3402. 2. Haura EB, et al. Presented at : ASCO; May 31-June 4,2019 . 9009 (oral). 3. Bauml J, et al. Presented at : ASCO; June 4-8, 2021. 9006 (oral)

Amivantamab: EGFR-MET bispecific antibody

CHRYSALIS Study Design: Post-platinum Exon20ins Population

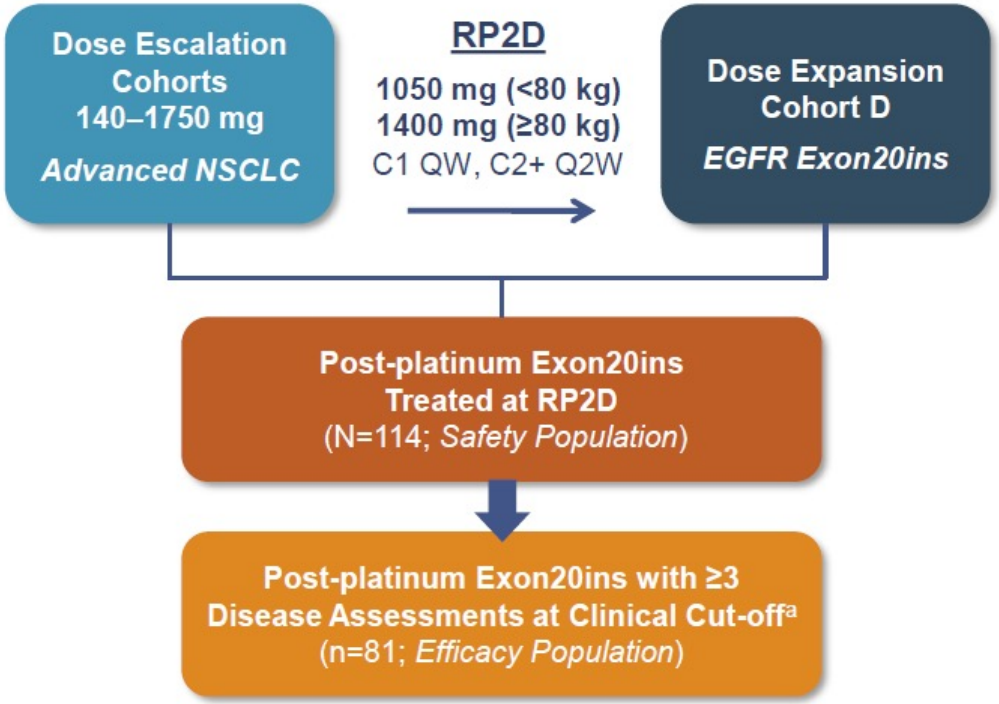
NCT02609776

Key Objectives

- Dose escalation: Establish RP2D
- Dose expansion: Assess safety and efficacy at RP2D

Key Eligibility Criteria for Post-platinum Population

- Metastatic/unresectable NSCLC
- EGFR Exon20ins mutation
- Progressed on platinum-based chemotherapy



Efficacy End Points

Primary

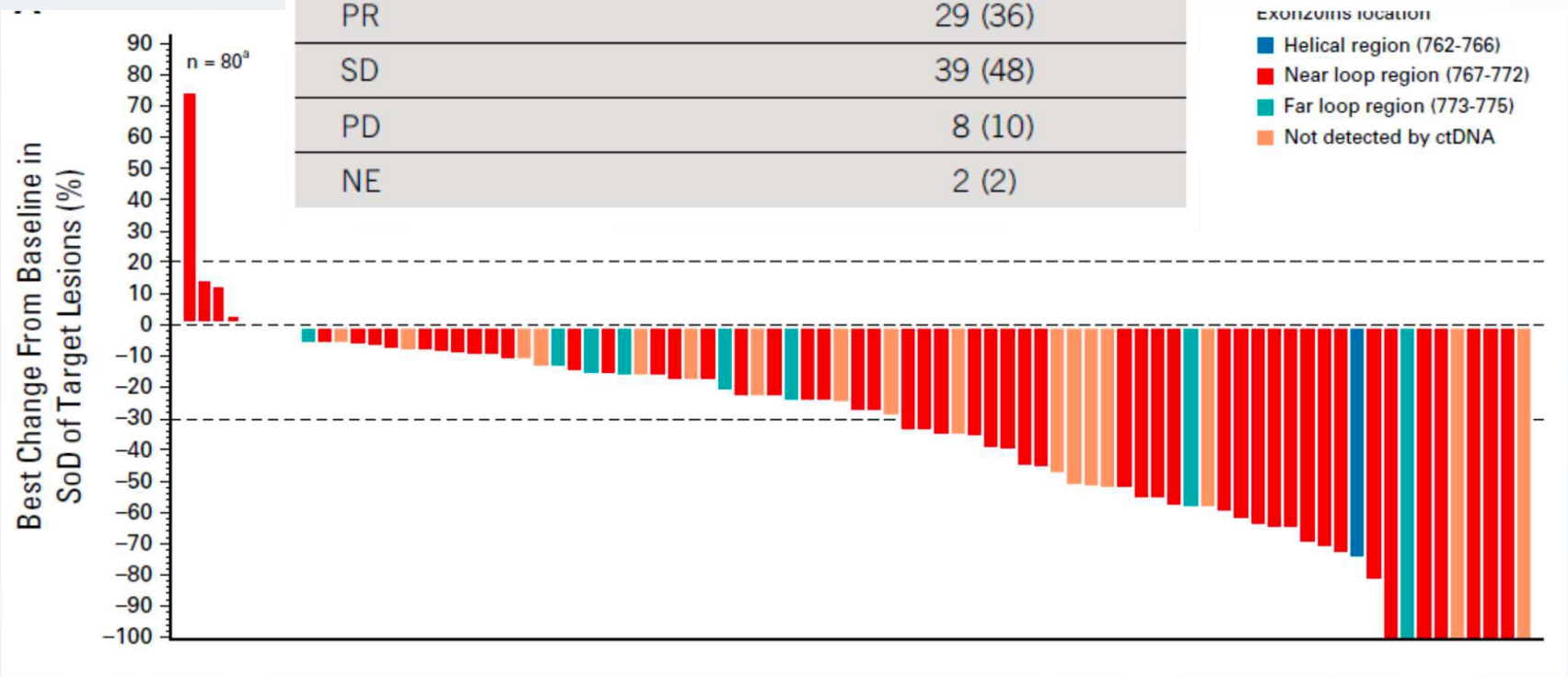
- Overall response rate per RECIST v1.1

Key Secondary

- Clinical benefit rate
- Duration of response
- Progression-free survival
- Overall survival

Amivantamab: in EGFR exon 20 post chemo

Response per RECIST	Efficacy Population (n = 81)
ORR, % (95% CI)[a]	40 (29 to 51)
CBR, % (95% CI)[b]	74 (63 to 83)
Best response, No. (%)	
CR	3 (4)
PR	29 (36)
SD	39 (48)
PD	8 (10)
NE	2 (2)



mPFS 8.3 months
mOS 22.8 months

Infusion related reaction, grade 2 occurs in 55% of patients

Park K, et al. J Clin Oncol. 2021;39(30):3391-3402.

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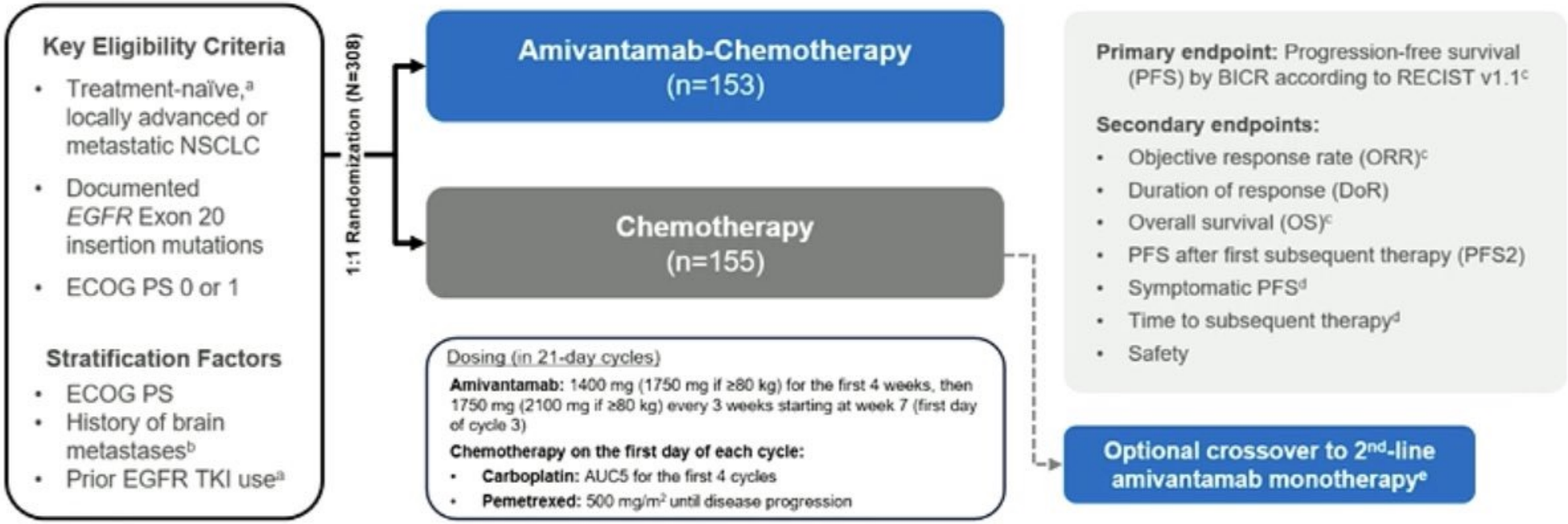
PAPILLON: Phase 3 Study Design



PAPILLON (ClinicalTrials.gov Identifier: NCT04538664) enrollment period: December 2020 to November 2022; data cut-off: 3-May-2023.

[a]Removed as stratification factor since only 4 patients had prior EGFR TKI use (brief monotherapy with common EGFR TKIs was allowed if lack of response was documented).
[b]Patients with brain metastases were eligible if they received definitive treatment and were asymptomatic, clinically stable, and off corticosteroid treatment for ≥2 weeks prior to randomization.
[c]Key statistical assumption: 300 patients with 200 events needed for 90% power to detect an HR of 0.625 (estimated PFS of 8 vs 5 months). PFS, ORR, and then OS were included in hierarchical testing.
[d]These secondary endpoints (time to subsequent therapy and symptomatic progression-free survival) will be presented at a future congress.
[e]Crossover was only allowed after BICR confirmation of disease progression; amivantamab monotherapy on Q3W dosing per main study.

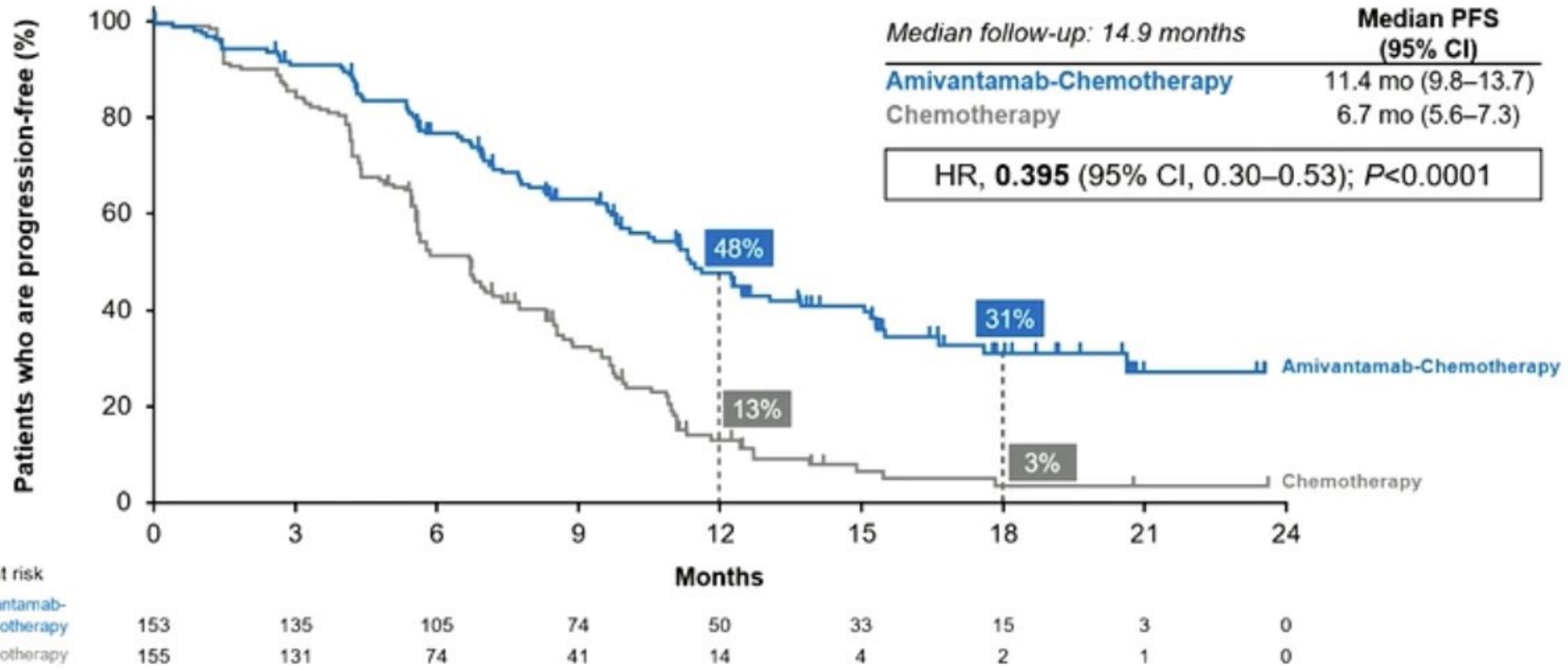
AUC, area under the curve; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

MADRID 2023 ESMO congress

Papillon:

Primary Endpoint: Progression-free Survival by BICR

Amivantamab-chemotherapy reduced risk of progression or death by 60%

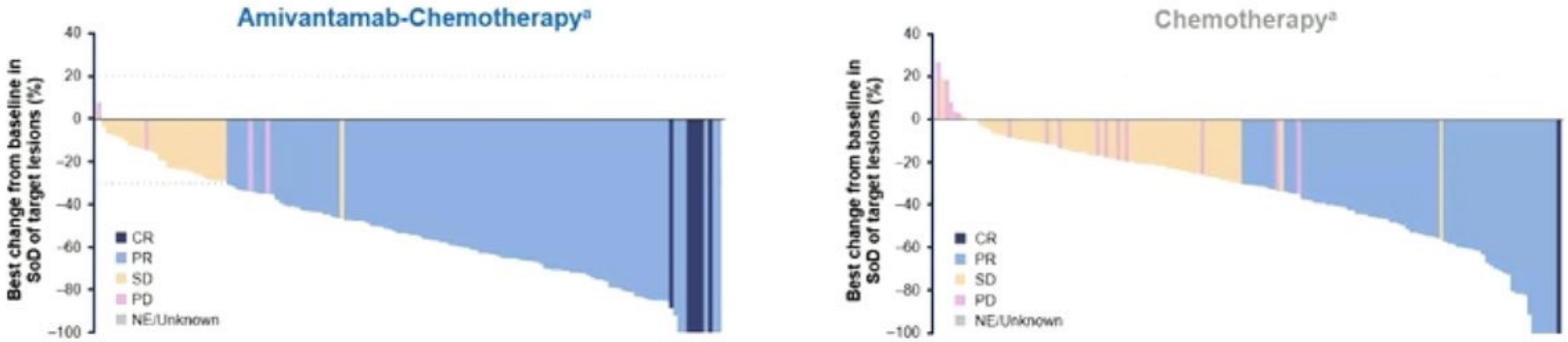


Consistent PFS benefit by investigator: 12.9 vs 6.9 mo (HR, 0.38; 95% CI, 0.29–0.51; *P*<0.0001[a])

[a]Nominal *P* value; endpoint not part of hierarchical hypothesis testing. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Papillon:

Best Response and ORR by BICR



BICR-assessed response[b]	Amivantamab-Chemotherapy (n=153)	Chemotherapy (n=155)
Mean percent change of SoD	-53%[c]	-34%
ORR	73% (95% CI, 65–80)	47% (95% CI, 39–56)
Odds ratio	3.0 (95% CI, 1.8–4.8); *P*<0.0001	
Best response, n (%)		
Complete response	6 (4)	1 (1)
Partial response	105 (69)	71 (47)
Stable disease	29 (19)	62 (41)
Progressive disease	4 (3)	16 (11)
NE/Unknown	8 (5)	2 (1)
Median time to response	6.7 wk (range, 5.1–72.5)	11.4 wk (range, 5.1–60.2)

Consistent results with investigator assessment: ORR of 66% vs 43% (OR, 2.6; *P*<0.0001)

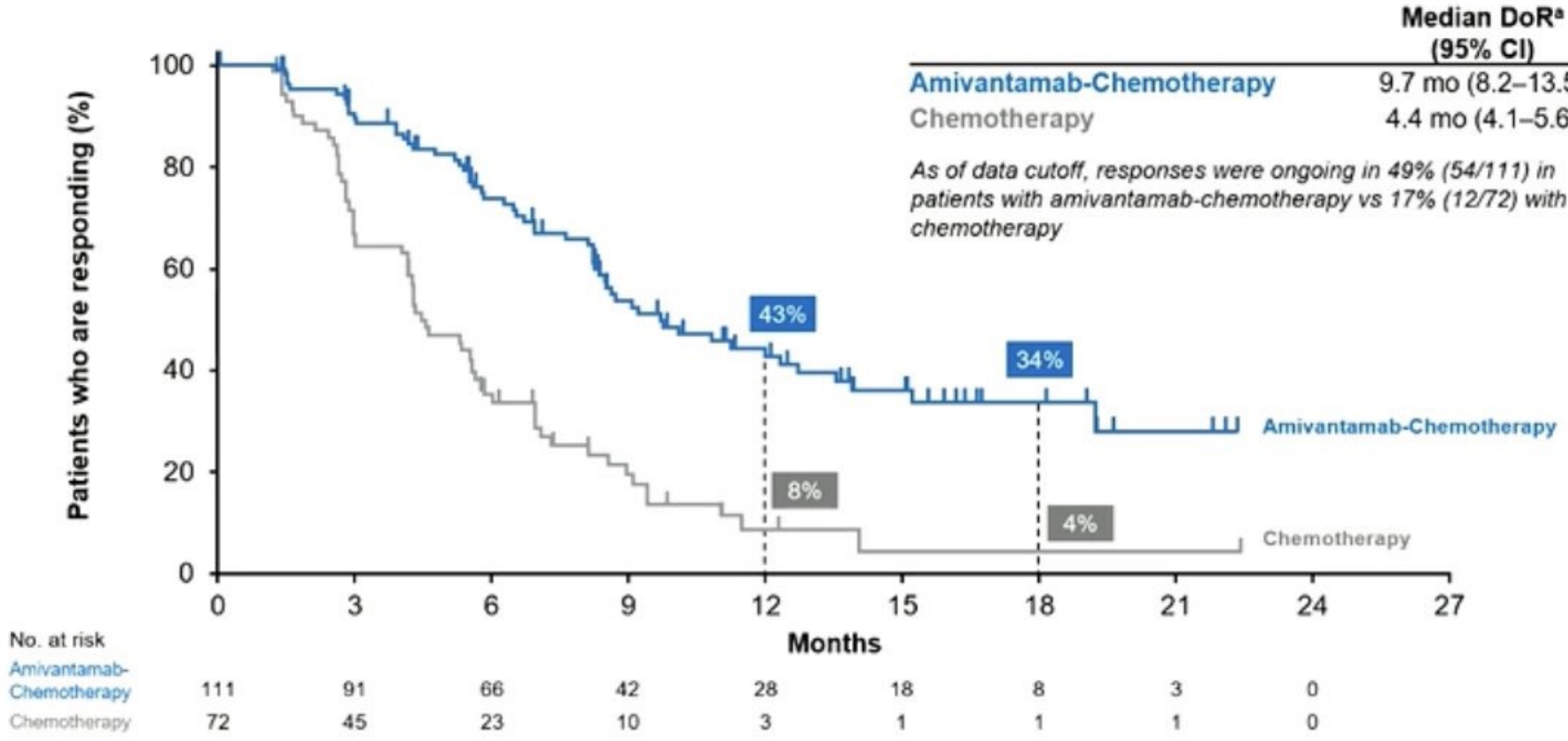
[a]Patients without postbaseline tumor assessment were not included in this plot. [b]No. of patients with measurable disease at baseline by BICR was 152 in both arms; response data presented among all responders. [c]Nominal *P*<0.001, endpoint not part of hierarchical testing.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; mo, month; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters; wk, weeks

MADRID 2023 ESMO congress

Papillon: Phase 3 Amivantamab + chemotherapy frontline

Duration of Response (DoR) by BICR

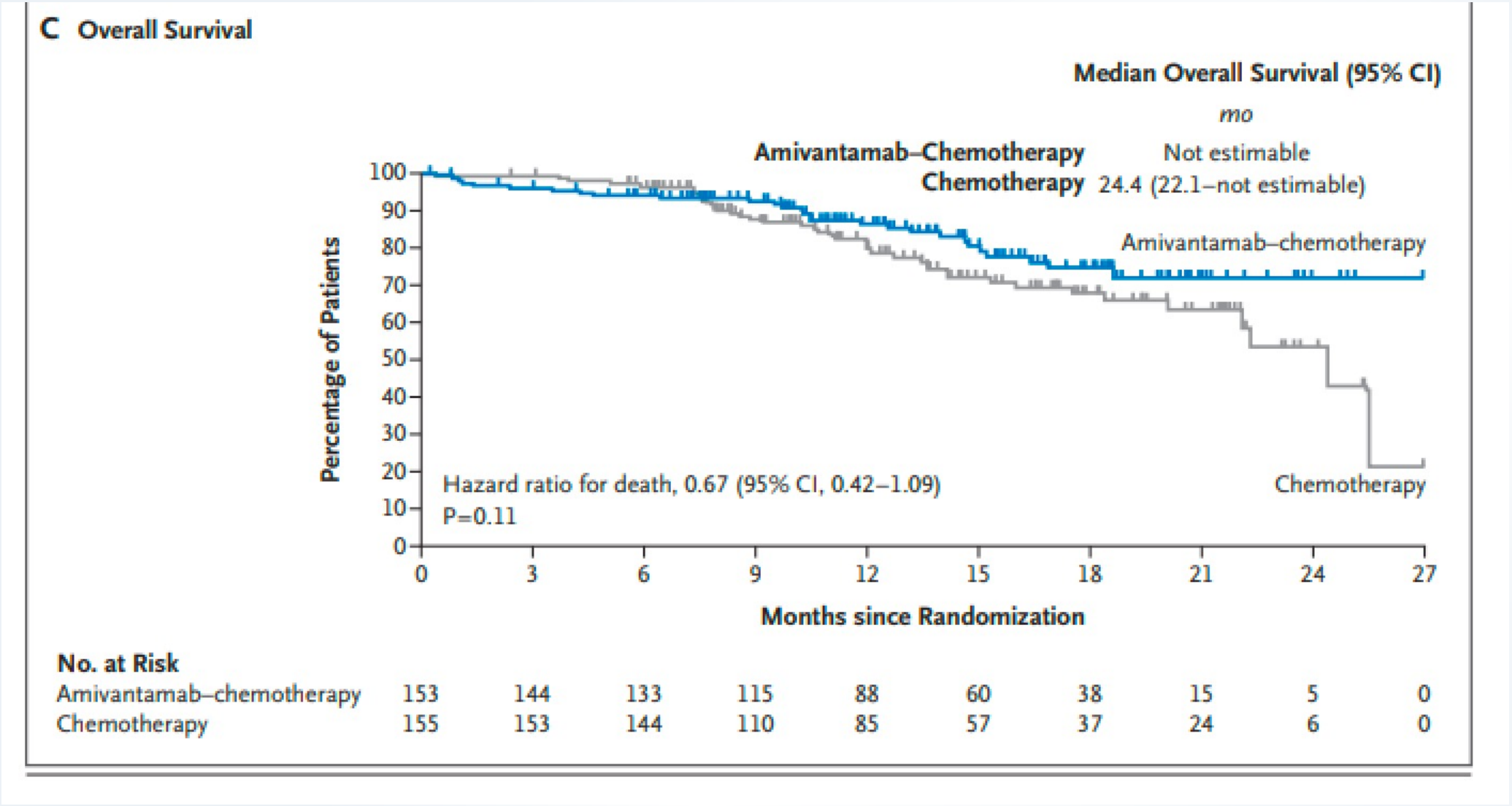


MADRID 2023 ESMO congress

Consistent DoR benefit was seen with investigator assessment: 13.5 vs 6.8 mo

[a]Among all responders. BICR, blinded independent central review; CI, confidence interval; mo, months.

Papillon: Phase 3 Amivantamab + chemotherapy frontline



Zhou J, et al. NEJM. 2023.

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Papillon: Phase 3 Amivantamab + chemotherapy frontline

Table 3. Adverse Events.*

Adverse Events	Amivantamab–Chemotherapy (N=151)		Chemotherapy (N=155)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any event	151 (100)	114 (75)	152 (98)	83 (54)
Any serious event	56 (37)		48 (31)	
Any event resulting in death	7 (5)		4 (3)	
Any event leading to interruption of any agent	104 (69)		56 (36)	
Interruption in dose of amivantamab				
Any	97 (64)			
Related to amivantamab†	63 (42)			
Any event leading to reduction of any agent	73 (48)		35 (23)	
Reduction in dose of amivantamab				
Any	54 (36)			
Related to amivantamab†	54 (36)			
Any event leading to discontinuation of any agent	36 (24)		16 (10)	
Discontinuation of amivantamab				
Any	17 (11)			
Related to amivantamab†	10 (7)			
Discontinuation of all agents because of adverse events‡	12 (8)		12 (8)	

Zhou J, et al. NEJM. 2023.

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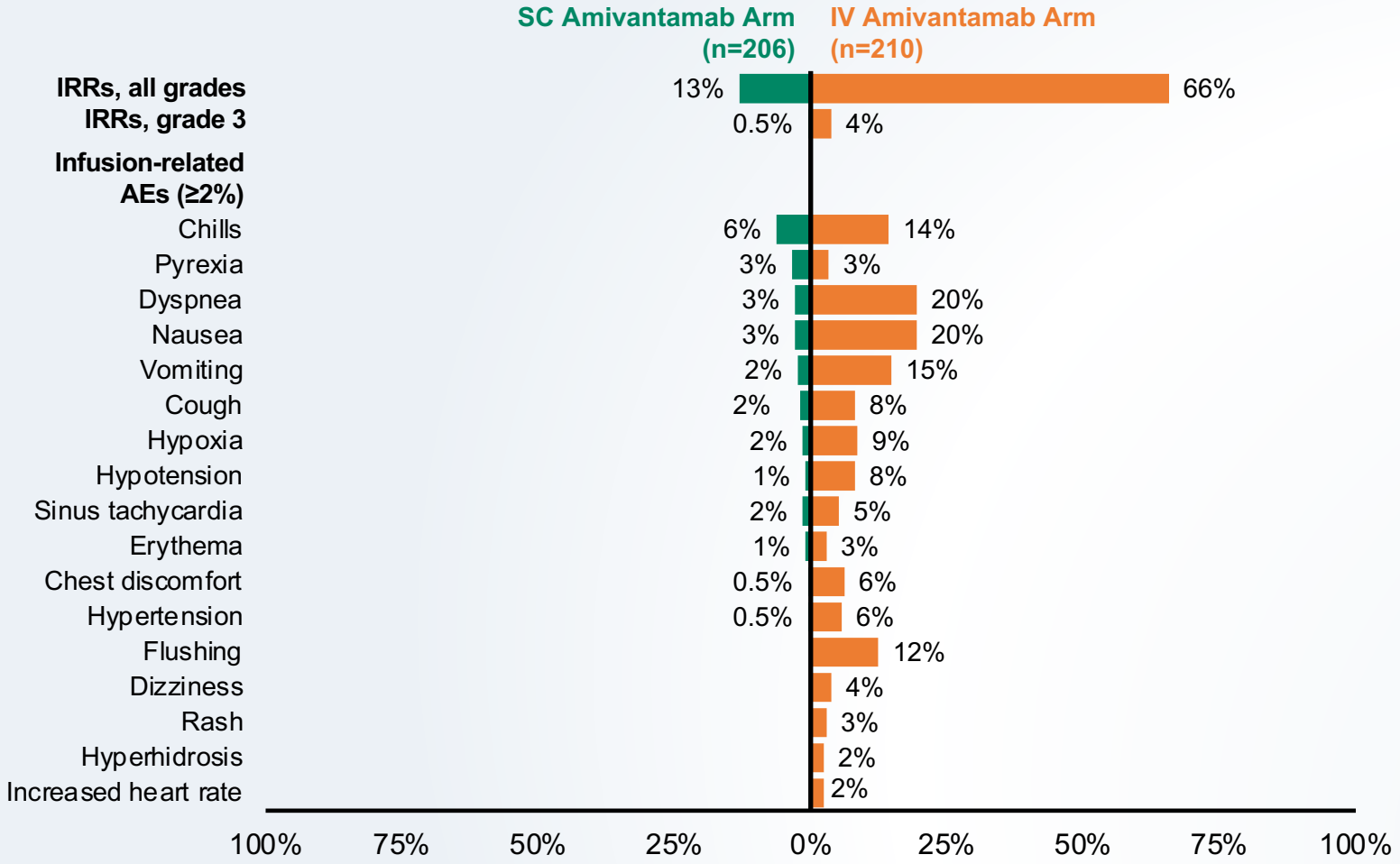
Papillon: Phase 3 Amivantamab + chemotherapy

Adverse Events	Amivantamab–Chemotherapy (N=151)		Chemotherapy (N=155)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Adverse events reported in ≥15% of patients in either group§				
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Anemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reaction	63 (42)	2 (1)	2 (1)	0
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	0
Constipation	60 (40)	0	47 (30)	1 (1)
Leukopenia	57 (38)	17 (11)	50 (32)	5 (3)
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Increased alanine aminotransferase	50 (33)	6 (4)	56 (36)	2 (1)
Increased aspartate aminotransferase	47 (31)	1 (1)	51 (33)	1 (1)
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Peripheral edema	45 (30)	2 (1)	16 (10)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0
Covid-19	36 (24)	3 (2)	21 (14)	1 (1)
Diarrhea	31 (21)	5 (3)	20 (13)	2 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)

Zhou J, et al. NEJM. 2023.

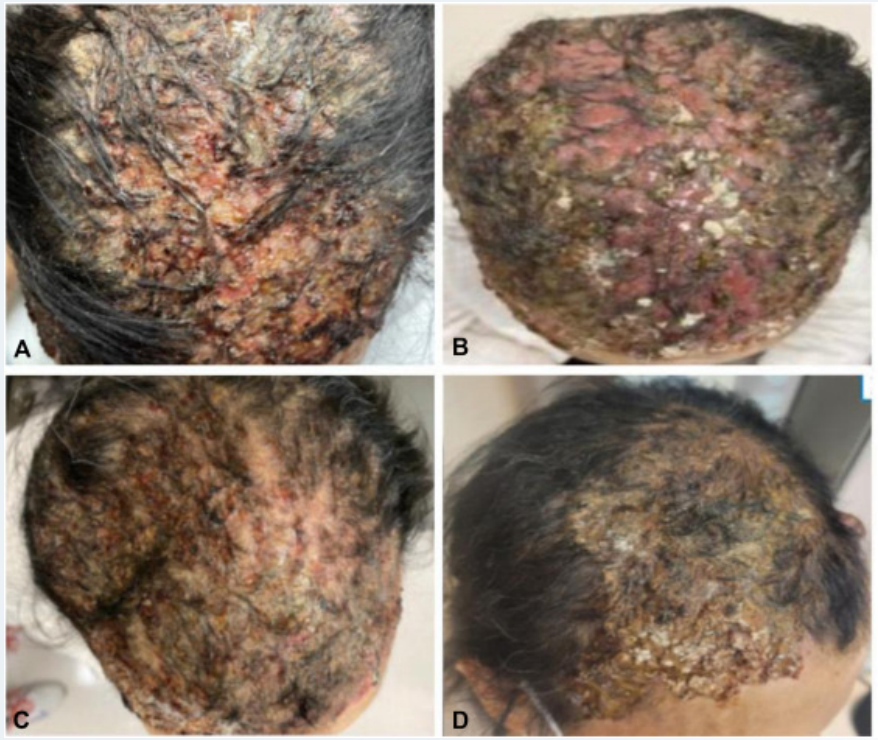
PALOMA: Subcutaneous amivantamab: Incidence of IRR-related Symptoms



- IRRs were observed in 13% of patients in the SC arm vs 66% in the IV arm, representing a 5-fold reduction
  - There were no grade 4 or 5 IRRs
  - Most IRRs occurred during Cycle 1
- IRRs leading to hospitalization were not observed in the SC arm vs 2 events in the IV arm
- No IRR-related discontinuations occurred in the SC arm vs 4 events in the IV arm

Note: The safety population included all the patients who had undergone randomization and received ≥1 dose of any trial treatment.
AE, adverse event; IRR, infusion-related reaction; IV, intravenous; SC, subcutaneous.

Amivantimab dermatologic AEs



- Erosive pustular dermatosis of the scalp:

Difficult to manage:
DERMATOLOGY consult
Oral antibioitics: Doxycycline 100mg po BID
Topical steroids: ointment/cream for body versus solution on head

Dose hold
Consider oral steroids
Consider Dakins vs antifungal shampoo
G6PD testing per dermatology

- Paronychia
- Acneiform rash
- pruritis

George, Mariya N. et al.
JAAD Case Reports, Volume 47, 72 - 79
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Papillon: frontline Amivantamab + chemotherapy

FDA approved March 1, 2024

Infusion reactions manageable with step dosing, subcutaneous formulation in development.

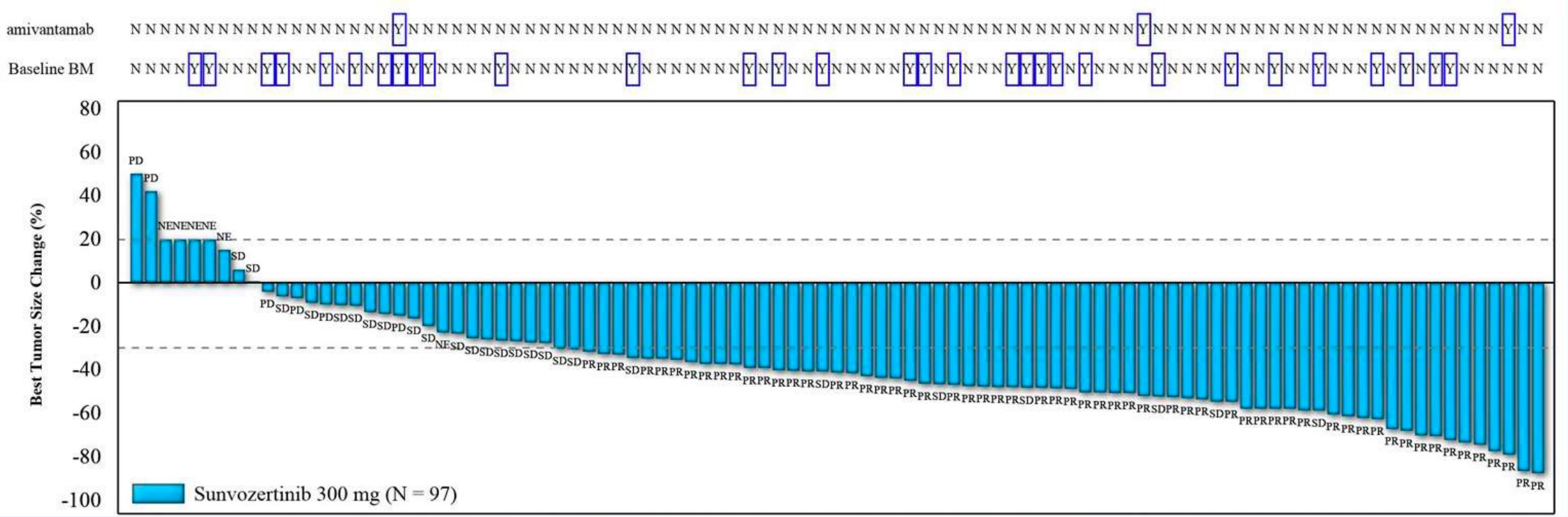
Infusion reactions seen in 42% (with use of glucocorticoid premed for chemo) compared to 67% with monotherapy.

65 patients crossed over from the chemotherapy group on trial, and 6 additional patients received amivantamab monotherapy as their first subsequent therapy off protocol, representing 66% (71 of 107) of patients in the chemotherapy group with disease progression

A hint of overall survival benefit (not yet reached maturity) despite crossover
Final OS analysis is planned at ~48 months after the first randomization

Zhou J, et al. NEJM. 2023.

Sunvozertinib: irreversible EGFR exon20 insertion (exon20ins) inhibitor



WU-KONG6 (NCT05712902 and CTR20211009) phase II, EGFR exon20ins, progressed on/after platinum-based chemotherapy. Analysis of 97 patients

confirmed ORR was 60.8% (59/97)

Wang M, et al. J Clin Oncol. 2023;41916_suppl):9002.

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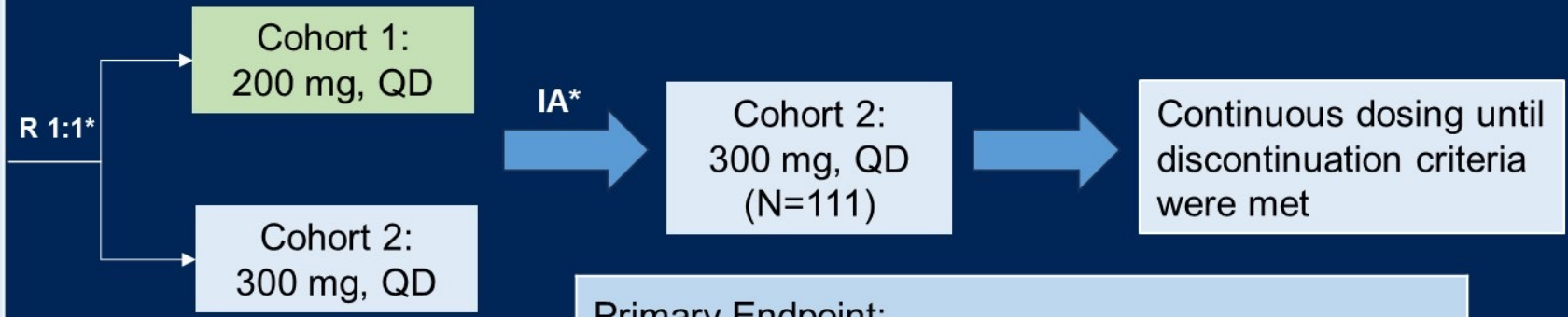
Sunvozertinib

WU-KONG1B Study Design

- Locally advanced or metastatic NSCLC
- Confirmed EGFR exon20ins in tumor tissues by local or sponsor designated laboratory testing
- ECOG PS of 0 or 1
- Prior treated with platinum-based chemotherapy



Primary Endpoint:

- ORR assessed by IRC#

Secondary Endpoints:

- DoR by IRC (key secondary endpoint), investigator assessed ORR and DoR, etc.

*Randomization ratio 1:1, and stratified by 1) brain metastasis; 2) number of prior treatment regimens.
**Interim analysis (IA) has been performed after 39 participants in each dose cohort completed at least 2 RECIST assessments.
#According to RECIST 1.1. Tumor assessment every 6 weeks from C1D1 until progression.
ORR: objective response rate; DoR: duration of response; IRC: independent review committee; INV: investigator; QD: once daily

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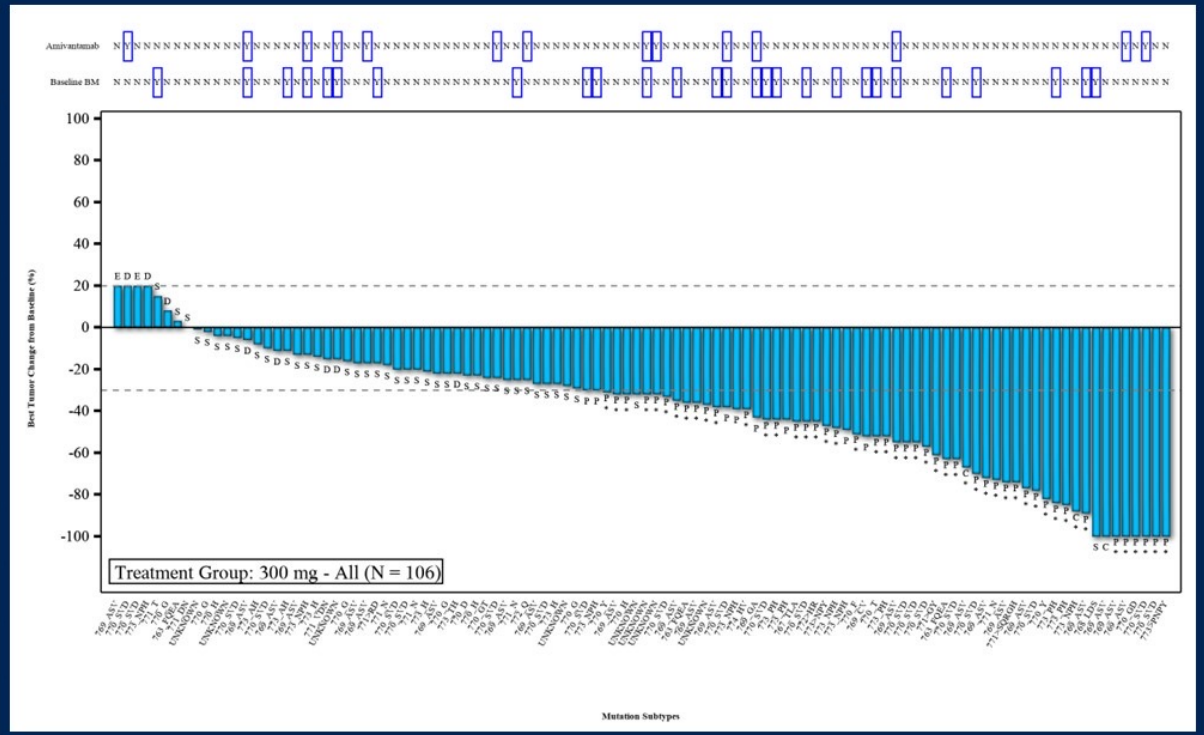
Anti-tumor Efficacy

Tumor Response Per IRC	300 mg (N = 107)
Best ORR (%) with 97.5% CI	53.3 (42.0, 64.3)
Confirmed ORR (%) with 97.5% CI	44.9 (34.0, 56.1)
Best Response, n (%)	
Complete response	3 (2.8)
Complete response (confirmed)	2 (1.9)
Partial response	54 (50.5)
Partial response (confirmed)	46 (43.0)
Partial response (pending for confirmation)	4 (3.7)
Stable disease	39 (36.4)
Progressive disease	8 (7.5)
Not evaluable	3 (2.8)



- As of March 22, 2024, per IRC assessment, the best ORR was 53.3% (44.9% confirmed, and additional 3.7% pending confirmation). Two (1.9%) patients achieved complete response (both confirmed).
- The median DoR has not been reached, and the 9-month DoR rate was 57%.
- Anti-tumor efficacy was observed regardless of amivantamab treatment. The best ORRs in patients with or without prior amivantamab treatment were 50% and 53.8%, respectively.

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Sunvozertinib

Safety

Common (≥ 2%) ≥ grade 3 TRAE, n (n%)	300 mg (N = 111)
Diarrhea	19 (17.1)
Blood creatine phosphokinase increased	12 (10.8)
Anaemia	4 (3.6)
Rash	4 (3.6)
Lipase increased	4 (3.6)
Neutrophil count decreased	3 (2.7)
Hypokalaemia	3 (2.7)
Decreased appetite	3 (2.7)
Asthenia	3 (2.7)

CTCAE: Common Terminology Criteria for Adverse Events; TRAE: Treatment-related Adverse Event.
* 1.8% ≥ grade 3 ILD, no fatal case.

- Safety findings were similar to what has been previously reported in other sunvozertinib clinical studies
- TRAEs leading to drug dose reduction and treatment discontinuation were 36.0% and 6.3%, respectively
- At 300 mg, the most common TRAEs included diarrhea and CPK increased, etc.
- The majority of common TRAEs were of grade 1 or 2 and clinically manageable
- No TRAEs with fatal outcome

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Summary

- WU-KONG1B study achieved its primary objective, with manageable safety profile in platinum-based chemotherapy pretreated NSCLC with EGFR exon20ins.
  - Efficacy:
    - The confirmed ORR was 44.9% with additional 3.7% pending confirmation per IRC assessment.
    - The efficacy was durable. The 9-month DoR rate was 57%.
    - Anti-tumor efficacy was observed regardless of prior amivantamab treatment.
  - Safety:
    - Similar AE profile to previously reported
- A phase III, multinational, randomized study (WU-KONG28, NCT05668988) is ongoing to assess sunvozertinib versus platinum-based chemotherapy in NSCLC patients with EGFR exon20ins NSCLC in the 1st line.

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18th Annual

ATLANTA

LUNG CANCER SYMPOSIUM

Atypical EGFR mutations

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Atypical EGFR mutations: more than just G719X, L861Q, S768I

838 patients randomly assigned or treated in LL2, LL3, and LL6

100 uncommon mutations

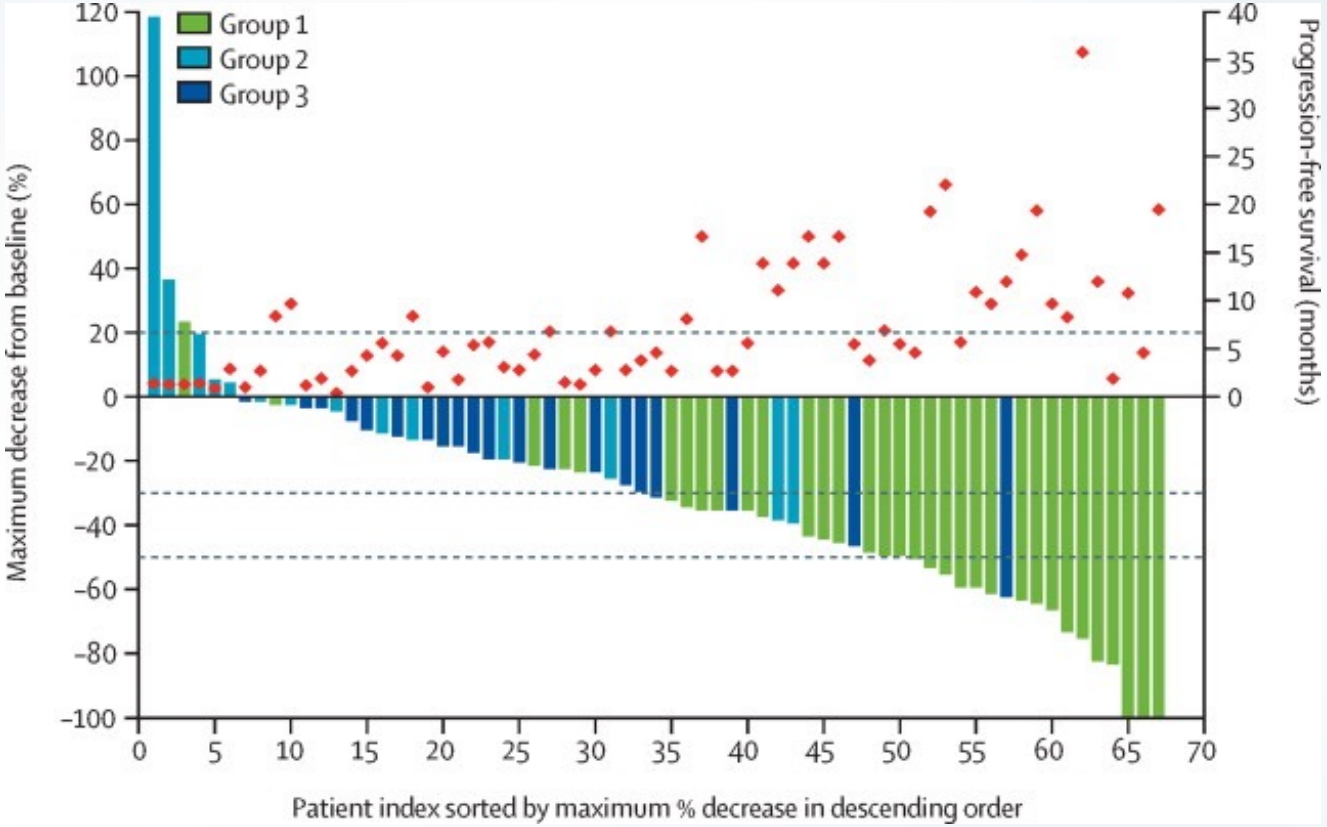
75 given afatinib

25 given chemotherapy

38 group 1: point mutations and duplications, or both, in exons 18–21
12 Leu861Gln alone
8 Gly719Xaa alone
5 Gly719Xaa + Ser768Ile
3 Gly719Xaa + Leu861Gln
2 Glu709Gly or Val + Leu858Arg
2 Ser768Ile + Leu858Arg
1 Ser768Ile alone
1 Leu861Pro alone
1 Pro848Leu alone
1 Arg776His + Leu858Arg
1 Leu861Gln + del19
1 Lys739_1744dup6

14 group 2: de-novo Thr790Met
6 Thr790Met + Leu858Arg
3 Thr790Met alone
3 Thr790Met + del19
1 Thr790Met + Gly719Xaa
1 Thr790Met + Leu858Arg + Gly719Xaa

23 group 3: exon 20 insertions



Yang, et al. Lancet Oncology, 2015.

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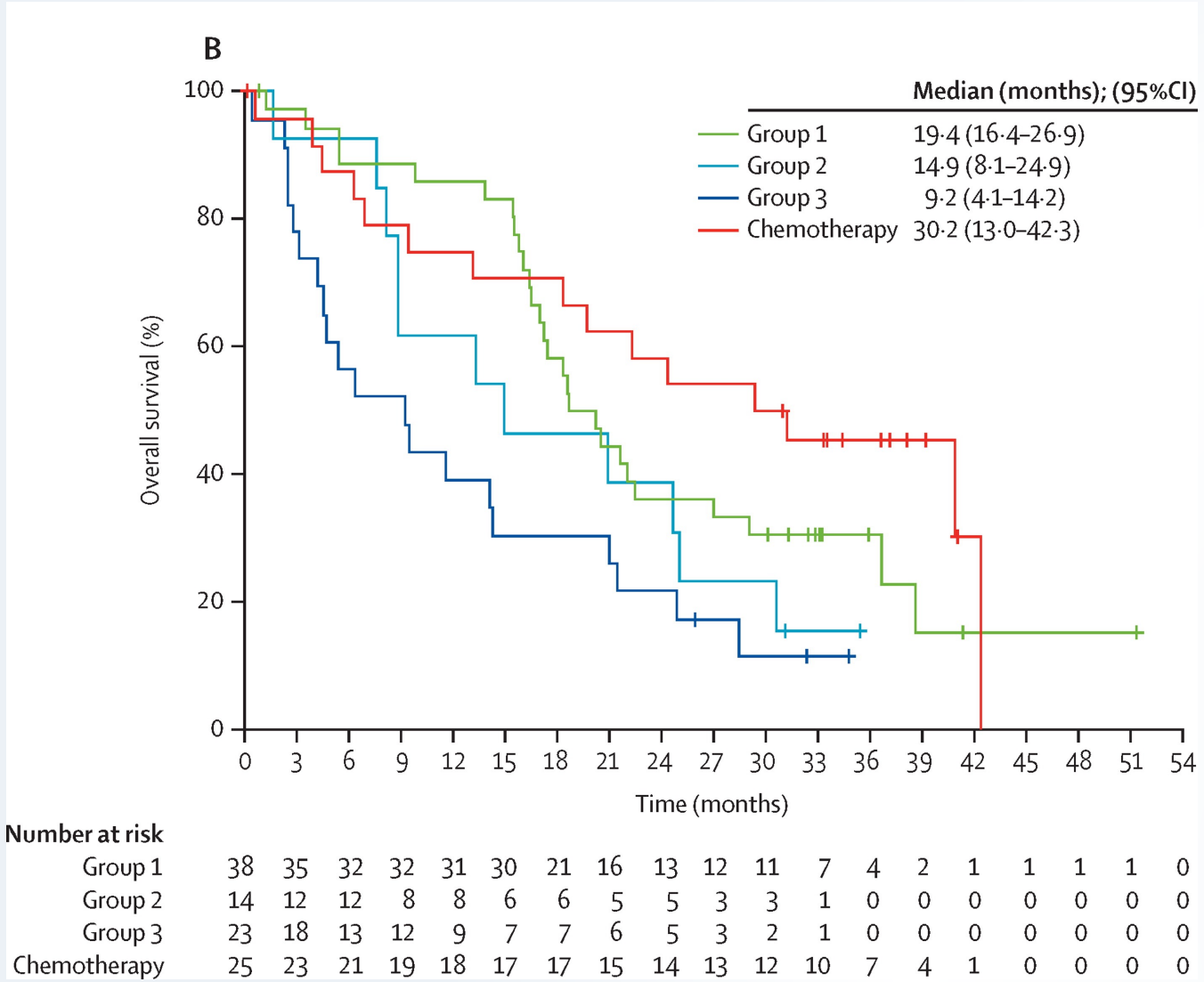
Atypical EGFR mutations: G719X, L861Q, S768I



FDA approval of afatinib for group one atypical point mutations:

Yang, et al. Lancet Oncology, 2015.

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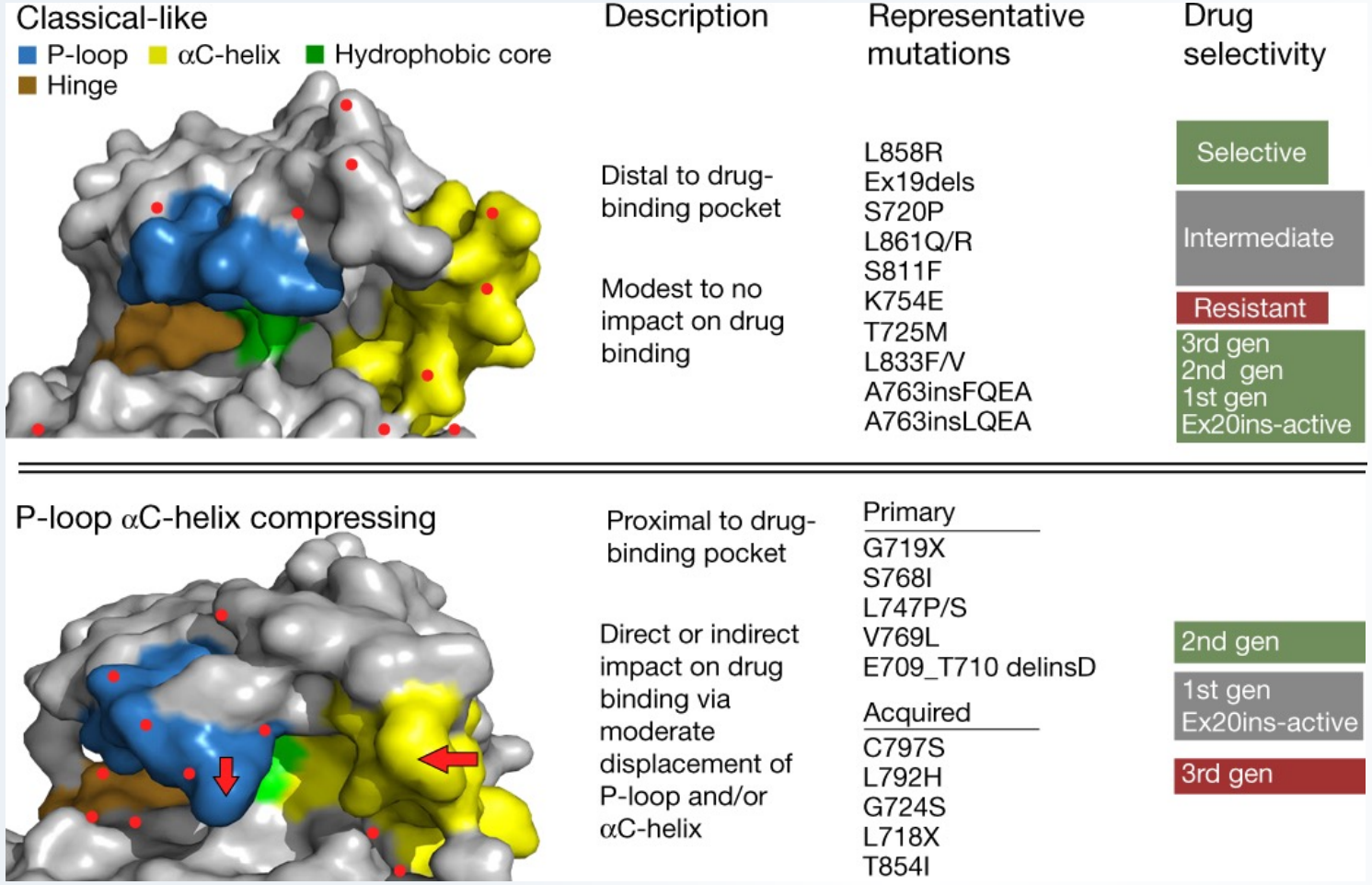
Atypical EGFR mutations: structure determines TKI response



For example, L718Q, S768I, and T854I correspond to exons 18, 20, and 21, respectively, but are all PACC mutations with similar structural effects on drug binding

Robichaux, J.P., Le, X., Vijayan, R.S.K. et al. Structure-based classification predicts drug response in EGFR-mutant NSCLC. Nature 597, 732–737 (2021).

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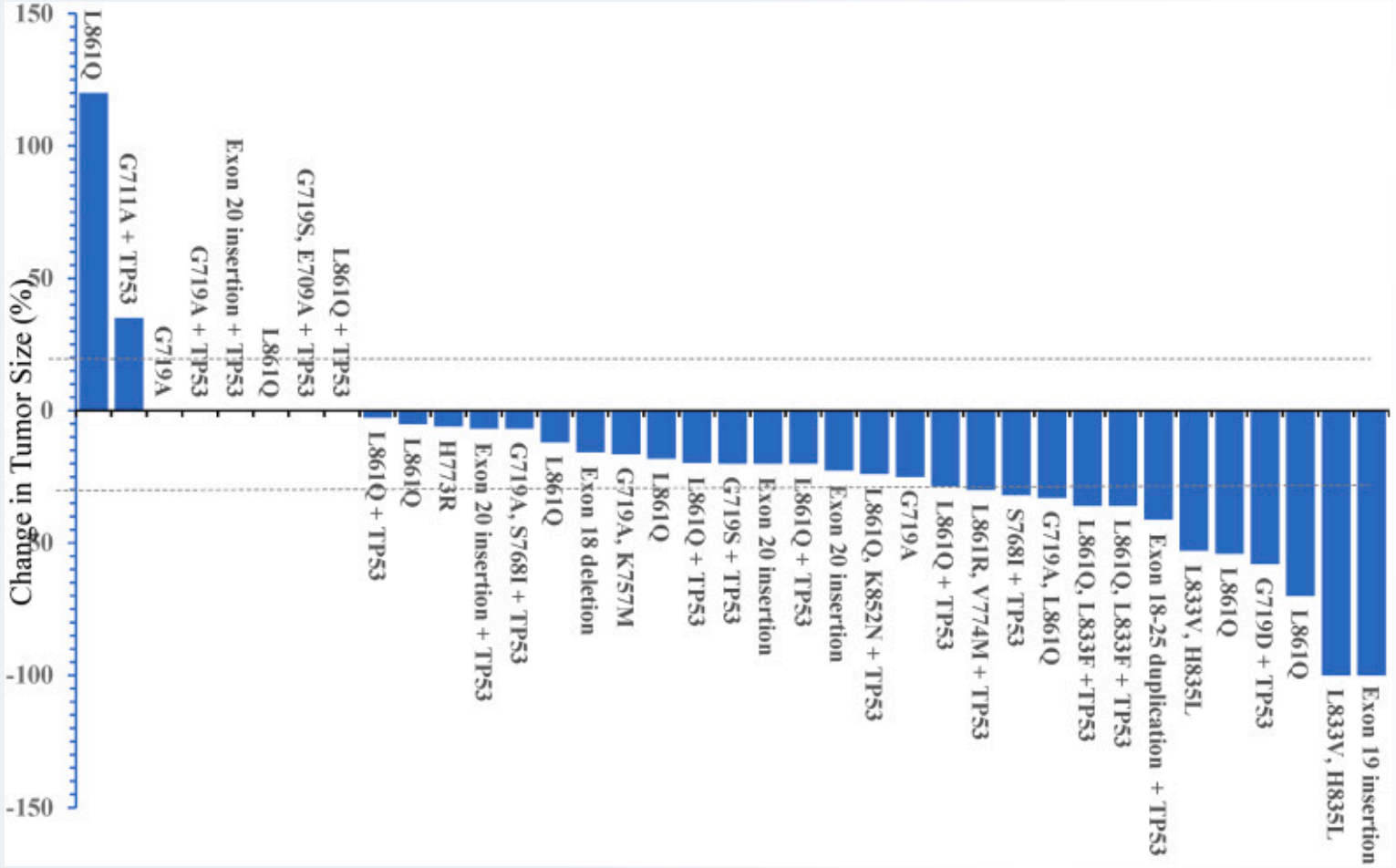
Response to osimertinib : EGFR atypicals + exon 20



50 patients at 6 US institutions
Excluded common EGFR

Median Time to treatment discontinuation varied among patients with L861Q (17.2 mo),
G719X (7.8 mo),
exon 20 insertion (1.5 mo) mutations.

Because of tolerance osimertinib also used for certain atypical EGFR mutations

Ji et al. JTO Clin Res Rep. 2023 Mar

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BDTX-1535 Preliminary Phase 2 Data in Recurrent Setting

2nd/3rd Line

Cohort 1 (up to 40 pts)

Patients with non-classical driver mutations after ≤2 prior lines of therapy with osimertinib as the preferred prior EGFR TKI

Cohort 2 (up to 40 pts)

Patients with acquired resistance C797S after ≤2 prior lines of therapy with osimertinib as the only prior EGFR TKI

1st Line

Cohort 3 (up to 40 pts)

Patients with non-classical driver mutations and no prior treatment

BDTX-1535 Phase 2 Trial Reveals a Broad Spectrum of EGFR Mutations Found in Patients Who had Received Prior EGFR TKI Therapy

Pt ID	Classical#	PACC NCMs	other NCMs*	C797S
2195	Exon 19del			C797S
2184	Exon 19del			C797S
2097	Exon 19del			C797S
2110	L858R		L833V	C797S
2160	L858R		R108K	C797S
2179	L858R		Y1016C	C797S
2158			L747_A750delinsP^	C797S
2169			L747_P753delinsS ^	C797S
2207			L747_A755delinsSKD^	C797S
2118			L747_T751del^; V834L	C797S
2115	L858R	L718V		
2199	L858R	E709A		
2152		G719S; S768I		
2172		G719A; S768I		
2181		G719A; S768I		
2124		E709_T710delinsD		
2197		K745_E746insIPVAIK	K745N	
2208		V774M; S768I		
2198		L718V	L747_P753delinsS^; G930R	
2203			L747P_P753delinS^	
2101			L861Q^	
2188			L861R^; L62R	

10 patients with C797S

9 patients with PACC-NCM

3 patients other NCM

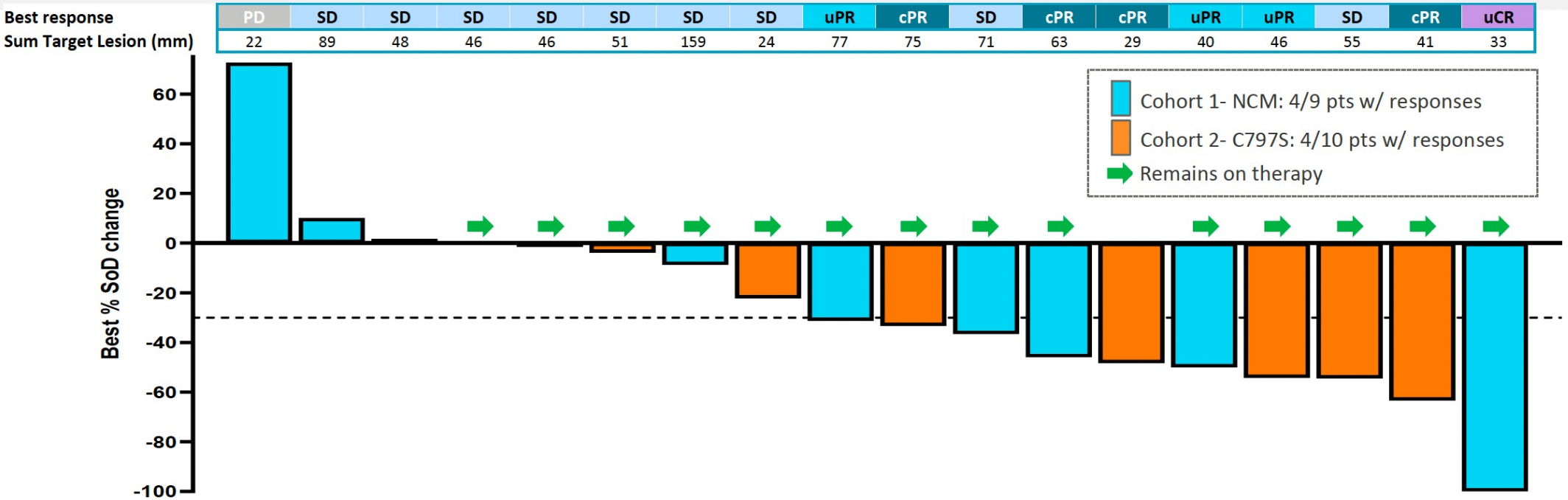
19 of 22 patients with PACC-NCM or C797S mutations

All mutations identified with standard tumor biomarker testing (via NGS) currently done in oncology clinics

*# includes Ex19del (E746_A750) and L858R; *Includes atypical Ex19dels with variable sensitivity to osimertinib (Heymach et al ESMO 2024)*
^osimertinib-sensitive mutations (Robichaux et al Nature 2021, Heymach et al ESMO 2024)

BDTX-1535 Phase 2 Preliminary Waterfall Plot

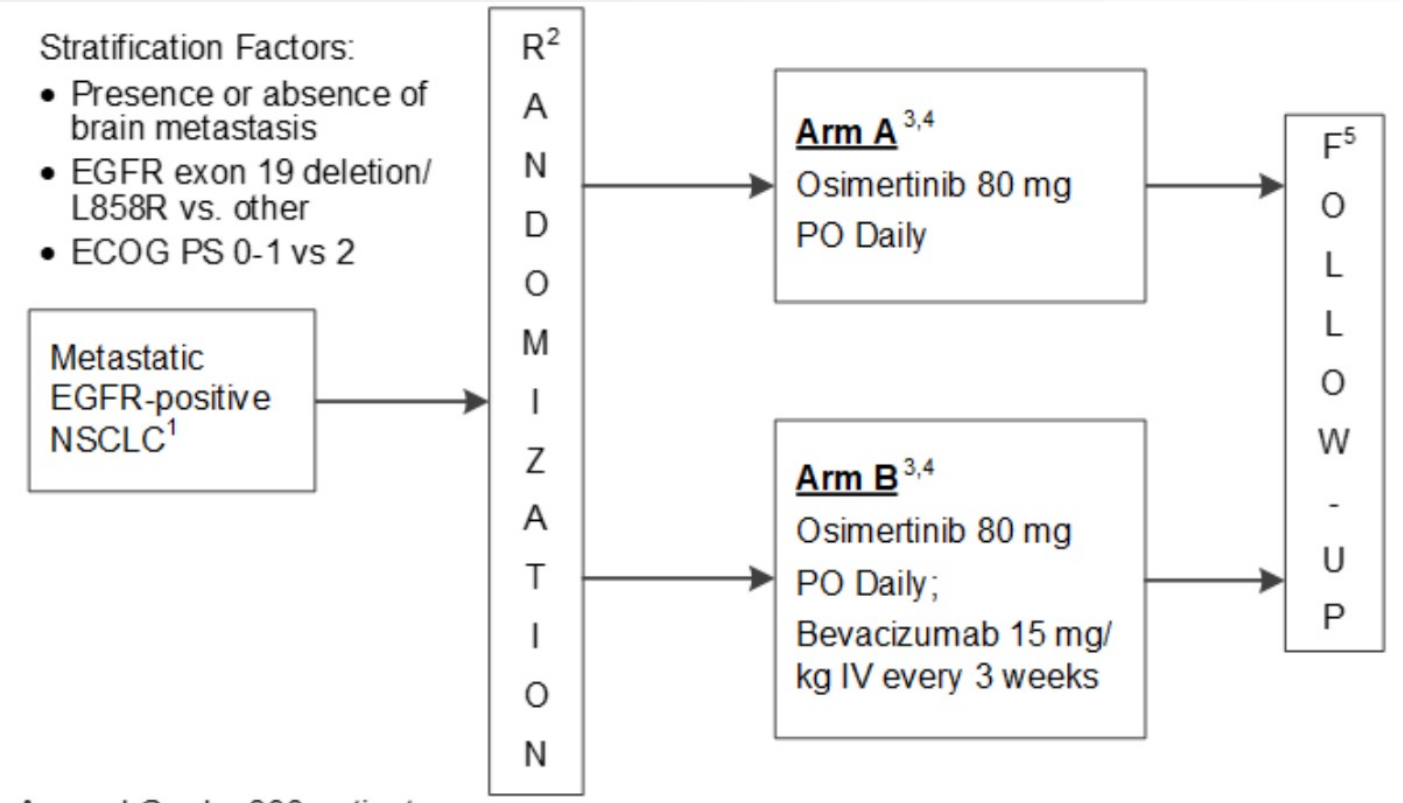
Preliminary ORR 42% in patients with PACC-NCM and/or C797S



	Patient ID	2199	2124	2160	2197	2169	2158	2181	2184	2198	2179	2172	2115	2097	2208	2207	2195	2110	2152
mEGFR*	Classical	L858R		L858R					E19del		L858R		L858R	Ex19del			Ex19del	L858R	
	NCM	E709A	E19delinsD	R108K	K745N Ex19Ins-IPVAIK K745N	L747_P753 delinsS	L747_A750 delinsP	G719A S768I		L747_P753 delinsS L718V G930R	Y1016C	G719A S768I	L718V		V774M S768I	L747_A755 delinsSKD		L833V	G719S S768I
	C797S			C797S		C797S	C797S		C797S		C797S			C797S		C797S	C797S	C797S	
	Prior 1L Duration, months	O 19.6	O 1.5	O 25.8	O 20.8	O 22.8	O 23.5	O+Cis+Pem 1.4	Osi 19.0	O+B 67.5	C+pac 1.3	O 5.1	O 24.9	O 38.3	A 13.9	O 14.1	O 15.8	O 50.0	O 8.5
	Prior 2L Duration, months				O+C+Pem 6.4			O+C+Pac 6.9		O+C+Pem 4.0	Osi 16.8	O+C+Pem 3.0	HER3-Dxd 0.8					O+C+Pem+B 26.6	C+Pac 1.8
	Off-Pathway Detected	RTK		MAPK	PI3K	RTK		TK/MAPK											

EA5182 Available Through ECOG-ACRIN Cancer Research Group

Randomized Phase III Study of Combination Osimertinib (AZD9291) and Bevacizumab versus Osimertinib (AZD9291) Alone as First-Line Treatment for Patients with Metastatic EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC)



1. Patients are eligible to enroll if they are within their first 3 weeks of osimertinib and are registered prior to 3 weeks on treatment.
2. Randomization is 1:1 for Arms A and B.
3. Imaging will be obtained every 3 cycles (9 weeks).
4. Patients will continue on study treatment until progressive disease or unacceptable toxicity.
5. All patients, including those who discontinue protocol therapy early, will be followed until progression, even if non-protocol therapy is initiated, and for survival for 10 years from date of registration.

Includes: E709X, G719X, exon 19 insertions, L861Q, S768I

Conclusions in Oct 2024:

EGFR exon 20:

Frontline: Platinum doublet plus amivantamab per PAPILLON trial

Subsequent: clinical trial; EA5162 Osimertinib 160mg, docetaxel +/- ramicurimab

Atypical EGFR mutations:

Afatinib for G719X, L861Q, S768I. Consider starting at lower dose 30mg
Consider osimertinib or EA5182 osimertinib +/- bevacizumab

Consider structure/functional subgroup for predicted TKI response

BDTX-1535 trial soon to open at Emory with frontline slots