HUMANITAS CANCER CENTER

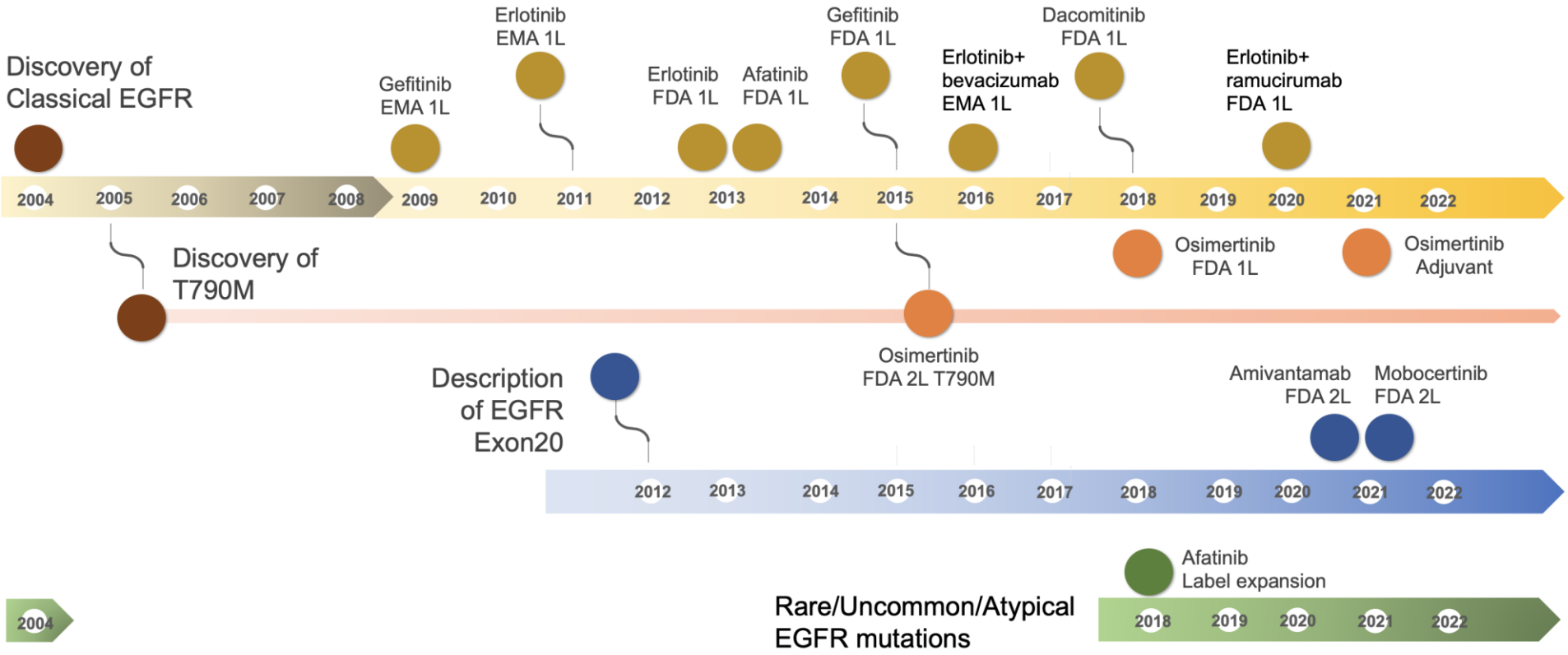
HUMANITAS UNIVERSITY

AIGOM 09 ottobre 2023

Malattia EGFR mutata e inserzioni esone 20: nuove strategie terapeutiche

Sabrina Rossi MD

History of EGFR drugs

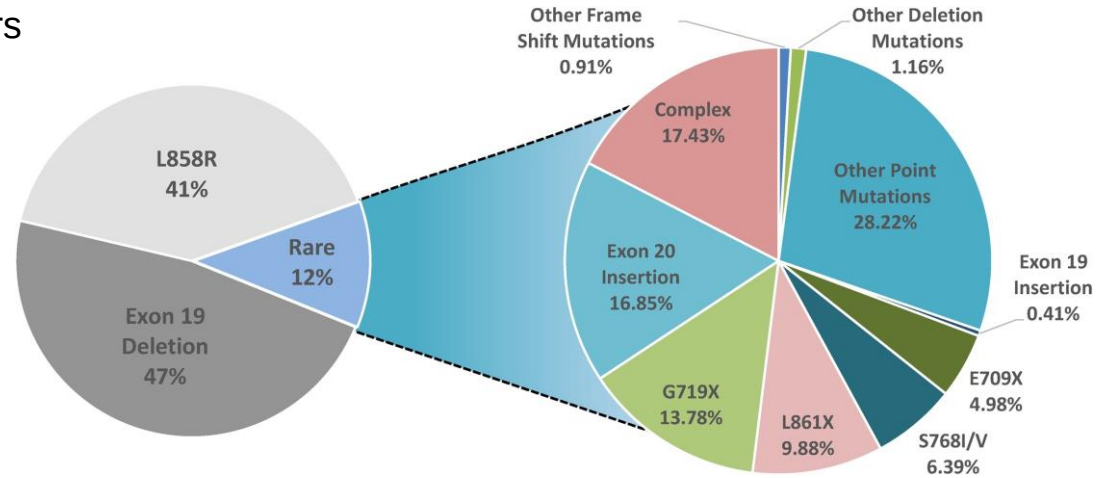


Adapted from Xiuning LE ELCC 2023

Exon 20 insertions

- ~16% of EGFR rare mutations and highly heterogeneous
- Ex20ins are the third most frequent EGFR mutation after the common mutations
- Poorer outcomes as compared with common EGFR mutations
- Usually associated with resistance to available EGFR TKIs, with few exceptions
- Controversial role of checkpoint inhibitors
- No 1L targeted therapy

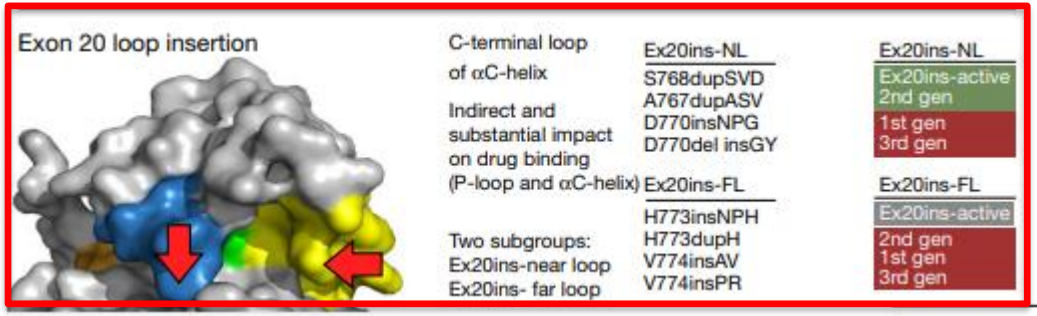
1L chemo,
regardless of PD-L1

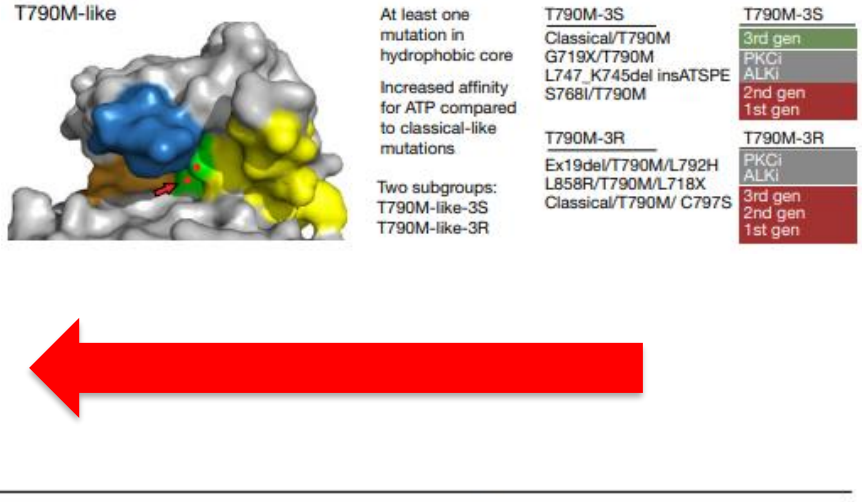


Harrison et al, Seminars in Cancer Biology 2019

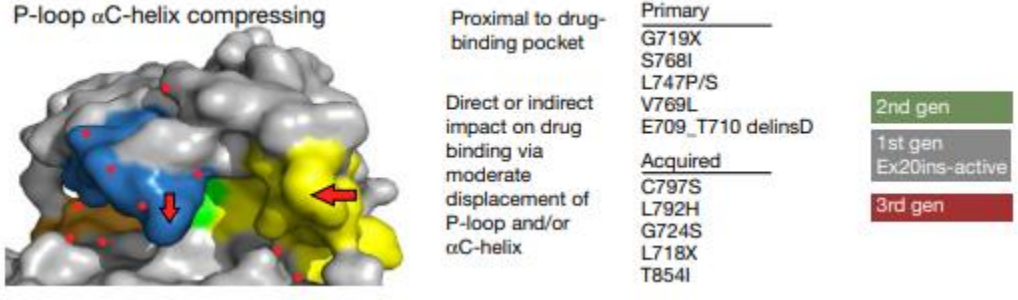
Heterogeneity of exon 20 mutations

- T790M is a recurrent missense mutation within the tyrosine kinase domain of the EGFR gene. The mutation substitutes threonine with methionine at position 790 of exon 20 of EGFR





- Mutations on the interior surface of the ATP-binding pocket or C-terminal end of the αC-helix, which were predicted to be P-loop and αC-helix compressing (PACC, es S768I point mutation).

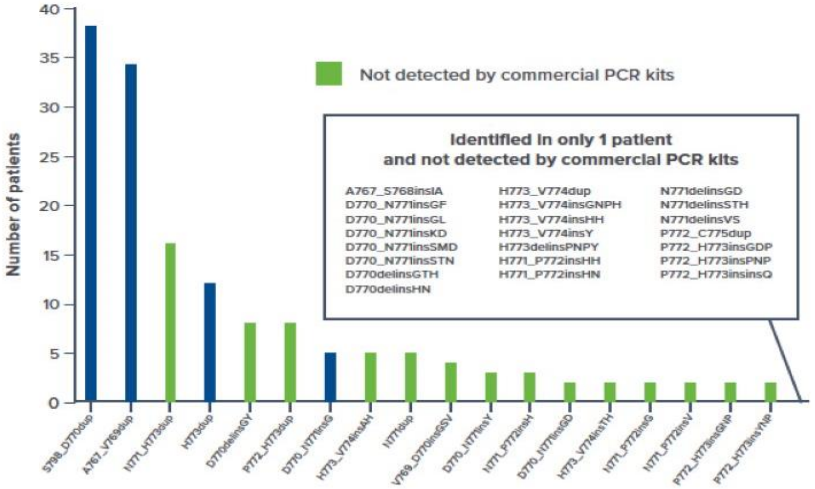


Robichaux Nature 2021

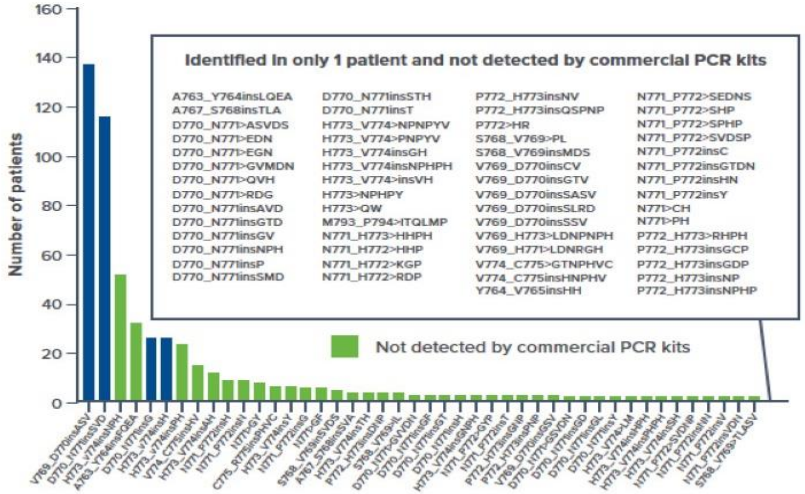
EGFR ex20ins detection: NGS is the gold standard

PCR misses ~ 50% of *EGFR* exon 20 insertions identified via NGS

Exon 20 Insertions Identified From GENIE



Exon 20 Insertions Identified From FoundationInsights

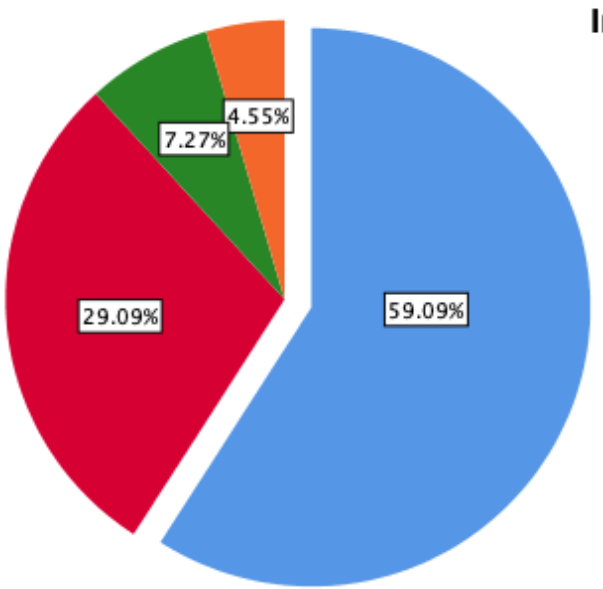


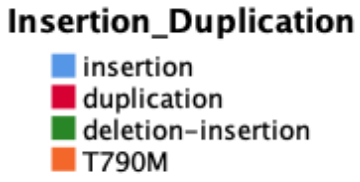
Bauml J, et al. Abstract presented at: IASLC 2020; January 28-31, 2021; Virtual. Abstract FP07.

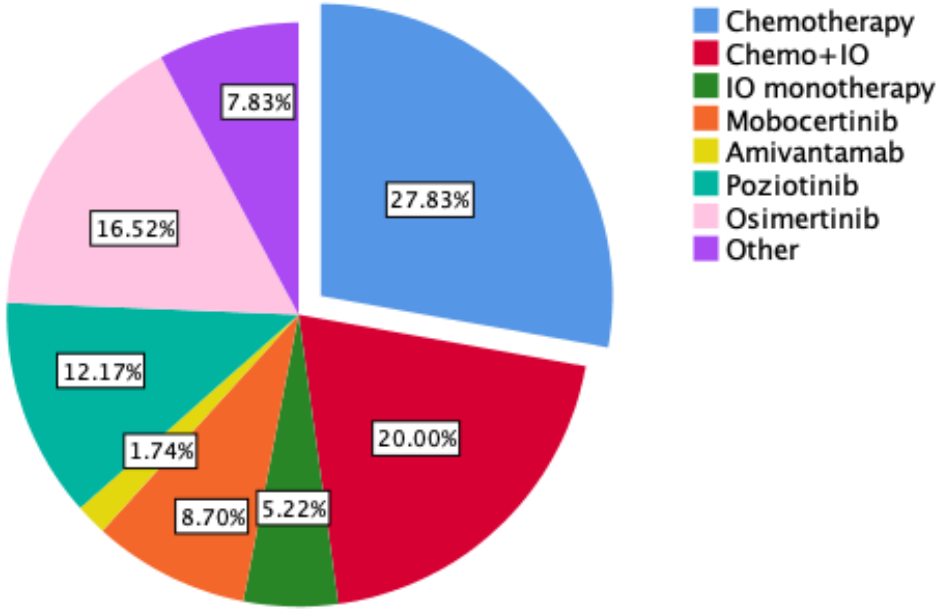
HUMANITAS CANCER CENTER

HU

Real-world management of EGFR exon 20+ NSCLC in the precision oncology era: report from the European EXOTIC registry





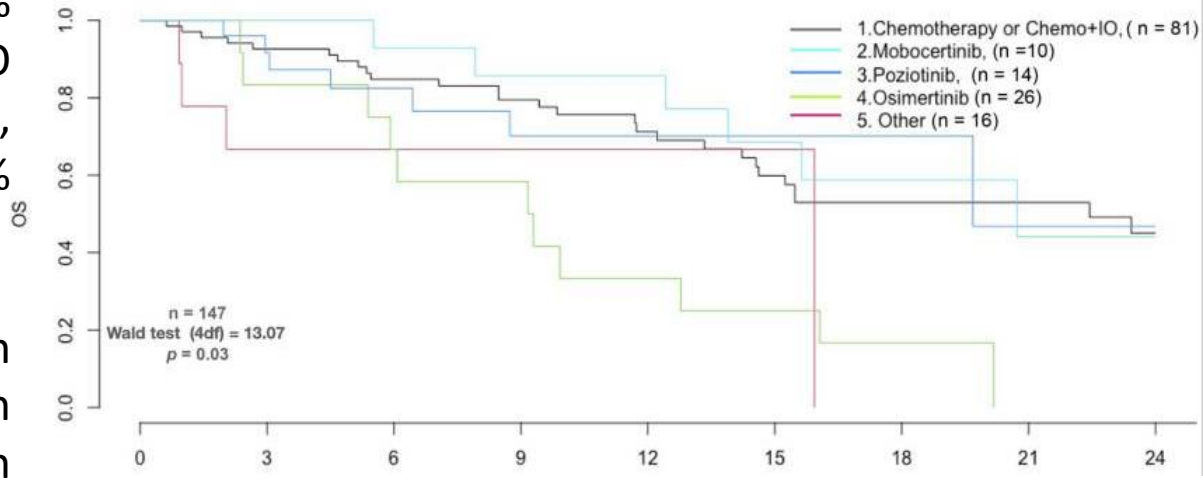


Data from 126 patients from 31 centers across 8 European countries.

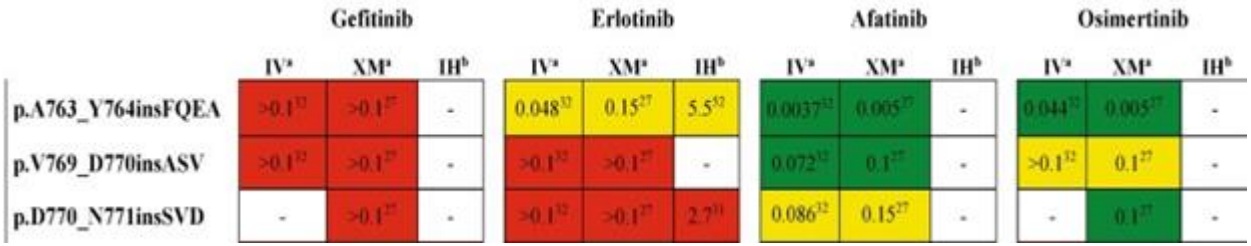
Real-world management of EGFR exon 20+ NSCLC in the precision oncology era: report from the European EXOTIC registry

Overall response rates were 39,3% **with CT+/- IO**, 16,7% with IO alone, 21,3% with **osimertinib**, 33,3% with **poziotinib** and 50% with **mobocertinib**.

Median survival (OS) was 19,7 m with **CT+/-IO**, 9,2 m with **osimertinib**, 15,9 m with **poziotinib** and 22,4 m with **mobocertinib**.



Sensitivity of exon 20 insertions to EGFR TKIs



In vitro

Outcome[1]	Group 1 (n = 38)	Group 2 (n = 14)	Group 3 (n = 23)
Objective response, n (%)	27 (71.1)	2 (14.3)	2 (8.7)
Median DoR, mo	11.1	8.2	7.1
DCR, n (%)	32 (84.2)	9 (64.3)	15 (65.2)
Median PFS, mo	10.7	2.9	2.7
Median OS, mo	19.4	14.9	9.2

Post-hoc analysis of Lux-Lung 2-3-6 trials

group 3: Exon 20 insertions (n=23)

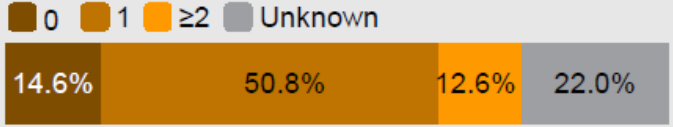
Gristina, Malapelle, Cancer Treatment Reviews 2020; Yang, Lamcet 2015

UpSwinG: real-world, non-interventional cohort study on TKI activity in patients with EGFR mutation-positive NSCLC with uncommon mutations

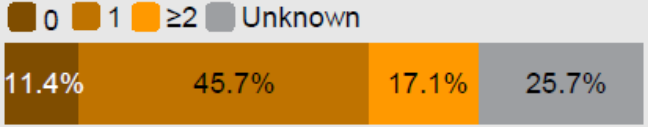
	Any TKI (n=246)				1st-gen EGFR TKIs (n=106)				Afatinib (n=132)			
	TTF, mos	OS, mos	ORR†, %	DoR†, mos	TTF, mos	OS, mos	ORR†, %	DoR†, mos	TTF, mos	OS, mos	ORR†, %	DoR†, mos
All patients	9.9	24.4	43.4	9.0	8.8	24.2	44.1	6.0	11.3	24.5	43.8	12.0
Major uncommon	11.3	25.7	49.1	10.0	9.8	28.5	47.3	6.5	14.3	24.5	50.6	12.0
Exon 20 insertion	5.5	22.5	17.4	19.3	5.2	21.0	16.7	33.0	8.3	22.5	18.8	5.5
T790M	2.8	32.7	20.0	6.0	2.1	14.2	0	-	5.7	-	33.3	6.0
Other	7.4	13.4	43.8	7.5	7.3	12.8	55.6	4.5	10.8	20.2	28.6	10.5
Compound	12.3	28.7	48.6	10.0	12.4	31.3	43.8	6.0	12.6	23.4	52.5	10.0

- In patients treated with 1st-line chemotherapy (n=20), median TTF, DoR and ORR was 6.6 months, 4.0 months and 41.2%, respectively

ECOG PS at start of 1st-line treatment (n=246)

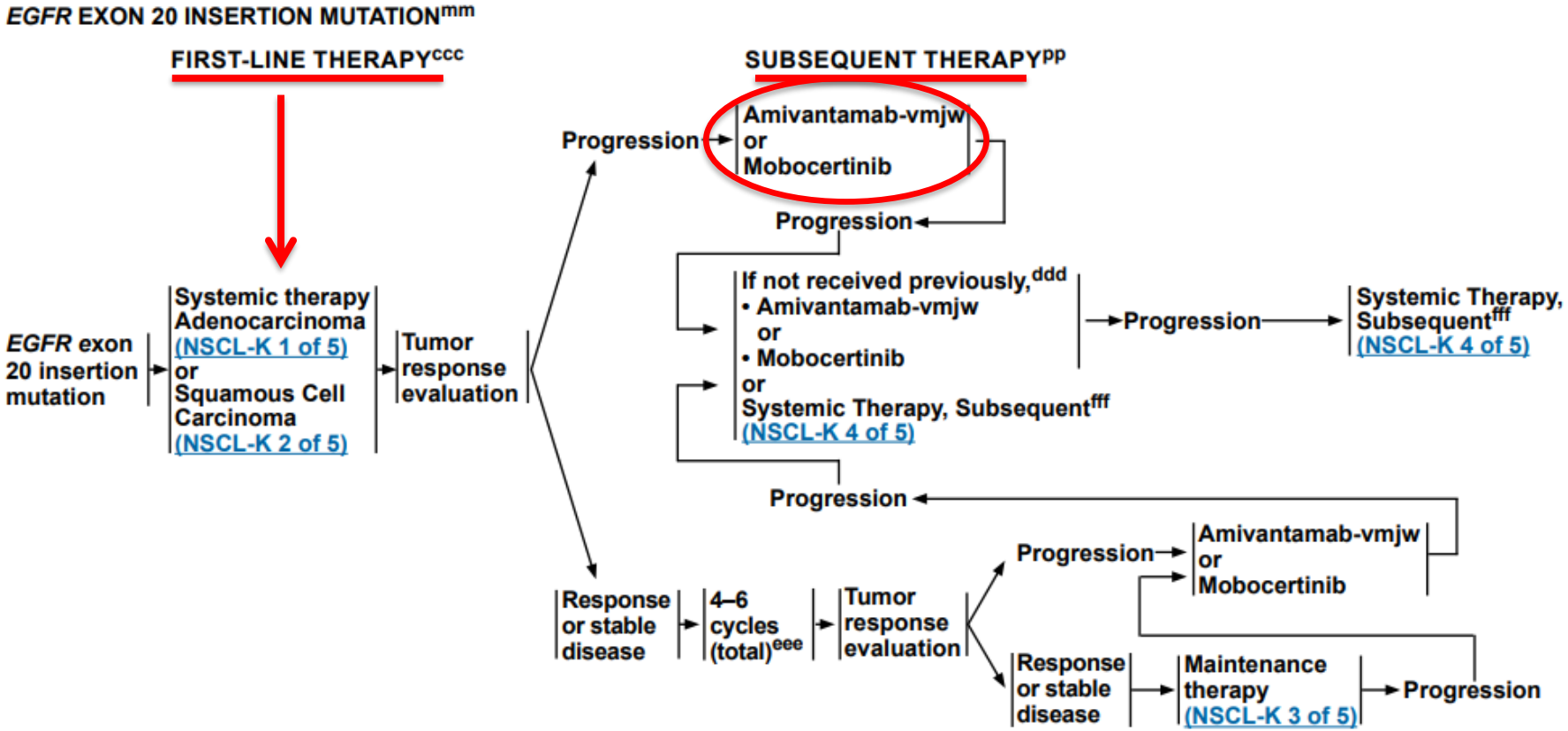


ECOG PS at start of 2nd-line treatment (n=140)



*Results from patients treated with osimertinib not shown due to small sample size; †Does not include patients with unknown best response. mos, months

Available therapies for mNSCLC wth EGFR exon 20 insertions



Role of immunotherapy

- Data about the efficacy of ICIs as monotherapy in EGFR ex20ins are scarce. In small series, a RR of about 15%, a mPFS of 2 to 4 months, and mOS up to 8 months.

- Despite limited data, an ICI strategy is not uncommon in *EGFR* ex20ins tumors, as 30% to 60% of patients enrolled in mobocertinib, amivantamab, and CLN-081 trials had been previously treated with an ICI.

- Chemotherapy plus an ICI is the preferred 1st treatment option for most patients with NSCLC: data on the subgroup of *EGFR* ex20ins do not exist, as these patients were excluded from most first-line chemotherapy-ICI phase III trials.

Hasting Ann Oncol 2018; Chen Thoracic Cancer 2020; Negrao JCO 2018; Riely Ann Oncol 2020; Park, JCO 2020; Piotrowska Ann Oncol 2020

Role of immunotherapy

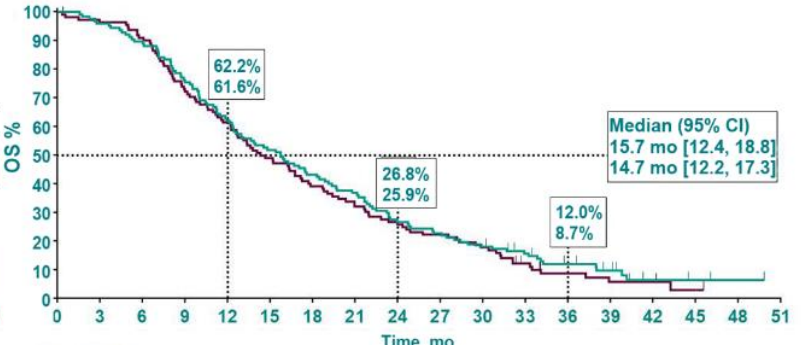
KEYNOTE-789 failed to show a significant improvement in PFS or OS with the addition of pembrolizumab to chemotherapy in patients with TKI-resistant EGFR-mutated metastatic nonsquamous NSCLC.

PD-L1 TPS ≥1%

	Events (%)	HR (95% CI)
Pembrolizumab + chemo	88 (83.0)	0.77 [0.58, 1.02]
Placebo + chemo	110 (89.4)	

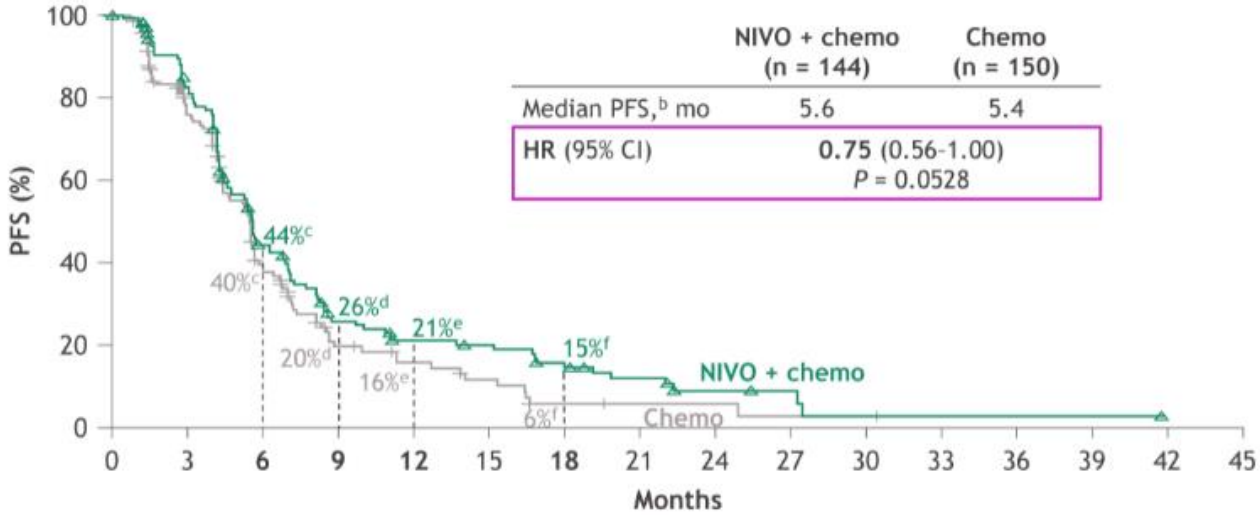
PD-L1 TPS ≤1%

	Events (%)	HR (95% CI)
Pembrolizumab + chemo	115 (90.6)	0.91 [0.70, 1.19]
Placebo + chemo	104 (92.0)	



Role of immunotherapy

Checkmate-722 failed to meet its primary endpoint in patients with cancer progressing on one or two prior lines of EGFR tyrosine-kinase inhibitors



	NIVO + chemo (n = 144)	Chemo (n = 150)
Median PFS,[b] mo	5.6	5.4
HR (95% CI)	0.75 (0.56-1.00) *P* = 0.0528	

Combination strategies to enhance ICIs efficacy in EGFR mutated NSCLC

Trial	Treatment	PFS	OS
ORIENT-31[9]	Cisplatin-Pemetrexed +/- Sintilimab (anti- PD-1)	0.72 (0.55-0.94)	0.97 (0.71-1.32)**
ORIENT-31[9]	Cisplatin-Pemetrexed+ Sintilimab + IBI305 (bevacizumab biosimilar) vs. chemo alone	0.51 (0.39-0.67)	0.98 (0.72-1.34)**
Impower 150 (EGFR-prior TKI)	carbo-paclitaxel-atezolizumab-bevacizumab (ACBP vs. CBP)	0.42 (0.22–0.80)	0.74 (0.38-1.46)

*Not statistically significant per statistical plan, ** adjusted for crossover
T790M+ allowed w/o prior osimertinib

No clear OS benefit with IO + antiangiogenesis

Potential risk of ILD-related AEs when combining osimertinib with durvalumab.

EGFR-TKI	PD-(L)1	Efficacy	Toxicity
Erlotinib	Nivolumab	ORR=15% (3/20 w/prior TKI)	24% G3 trAEs (10% diarrhea, 10%transaminitis)[1]
Osimertinib	Durvalumab	ORR=43% prior TKI	35% pneumonitis (TKI naïve)[2]; 26% (prior TKI)[3]
Afatinib	Pembrolizumab	ORR 2/11 (18%) prior EGFR TKI	36% irAEs (nephritis, adrenal insuff, colitis)[4]
Gefitinib	Durvalumab	ORR 64% - treatment naive	35% transaminitis[5]

Poziotinib

- **The <u>first oral TKI evaluated</u> for EGFR ex20 NSCLC**
- **ZENITH20 trial Cohort 1 (after platinum-based chemotherapy)**

Best Overall Response	Intent to treat (N=115) N (%)
Objective Response Rate (ORR) by independent review committee (IRC) 95% Confidence Interval	**17 (14.8%)** (8.9 - 22.6%)
Disease Control Rate (DCR=CR+PR+SD)	**79 (68.7%)** (59.4 - 77.0%)
Duration of Response, Median (months)	**7.4** (3.7, 9.7)
Progression-free Survival, Median (months)	**4.2** (3.7, 6.6)

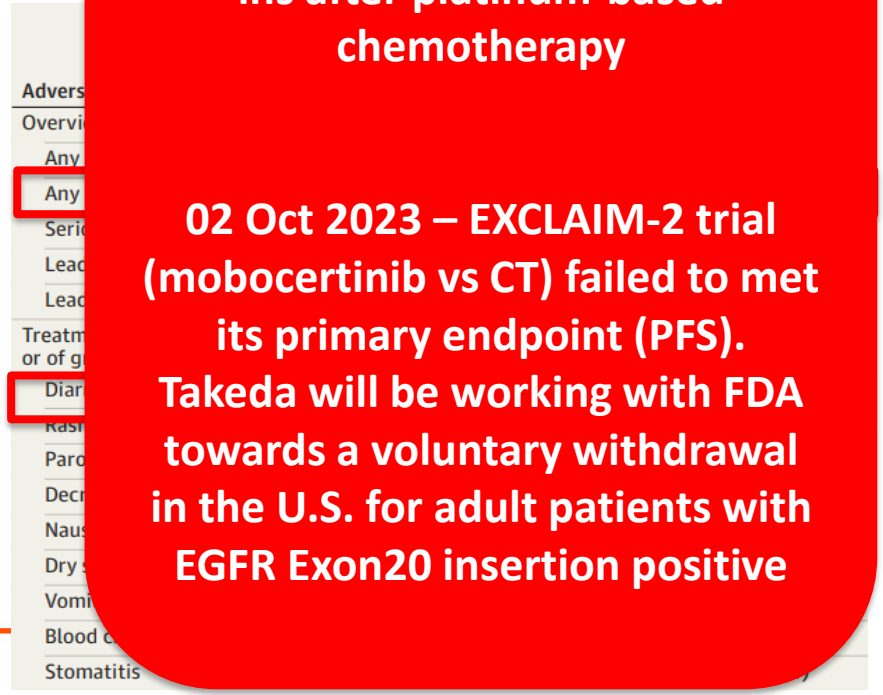
Not approved by FDA and EMA

	N = 90		
AE (preferred term)	Any Grade	Grade 3	Grade 4
Patients with at least one event, No. (%)	88 (97.8)	71 (78.9)	4 (4.4)
Rash (multiple terms)[a]	82 (91.1)	44 (48.9)	0
Diarrhea	74 (82.2)	23 (25.6)	0
Stomatitis (multiple terms)[b]	62 (68.9)	21 (23.3)	1 (1.1)
Paronychia	34 (37.8)	1 (1.1)	0
Dry skin	28 (31.1)	5 (5.6)	0
			0
			0
			0
			0
			0
Fatigue	20 (22.2)	2 (2.2)	0
Anemia	13 (14.4)	3 (3.3)	0
Weight decreased	13 (14.4)	1 (1.1)	0
Epistaxis	11 (12.2)	0	0
Hypomagnesemia	10 (11.1)	1 (1.1)	1 (1.1)
Asthenia	9 (10.0)	3 (3.3)	0
Hypokalemia	9 (10.0)	3 (3.3)	0
Dry mouth	9 (10.0)	0	0
Dyspnea	3 (3.3)	0	1 (1.1)
Hypocalcemia	3 (3.3)	1 (1.1)	1 (1.1)
Pancreatitis relapsing	1 (1.1)	0	1 (1.1)

Mobocertinib

EXCLAIM trial (after platinum-based chemotherapy)

	Mobocertinib N = 114	Poziotinib N = 115
ORR (%)	**28%**	**15%**
mDOR (months)	17.5	7.4
mPFS (months)	7.3	4.2
mOS (months)	24.0	---
Grade ≥ 3 AE	47%	---



FDA approval in 2021 for exon 20 ins after platinum-based chemotherapy

02 Oct 2023 – EXCLAIM-2 trial (mobocertinib vs CT) failed to met its primary endpoint (PFS). Takeda will be working with FDA towards a voluntary withdrawal in the U.S. for adult patients with EGFR Exon20 insertion positive

Zhou JAMA 2021

Amivantamab

EGFR and MET bispecific antibody

Chrysalys trial (after platinum-based chemotherapy)

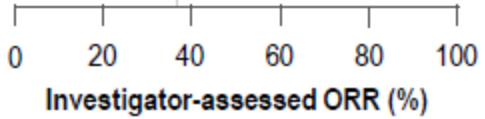
	Amivantamab n = 81	Mobocertinib N = 114	Poziotinib N = 115
ORR (%)	**40%**	**28%**	**15%**
mDOR (months)	11.1	17.5	7.4
mPFS (months)	8.3	7.3	4.2
mOS (months)	22.8	24.0	---
Grade ≥ 3 AE	35%	47%	---

AIFA approved (28/02/23) for exon 20 ins after platinum-based chemotherapy

Park JCO 2021

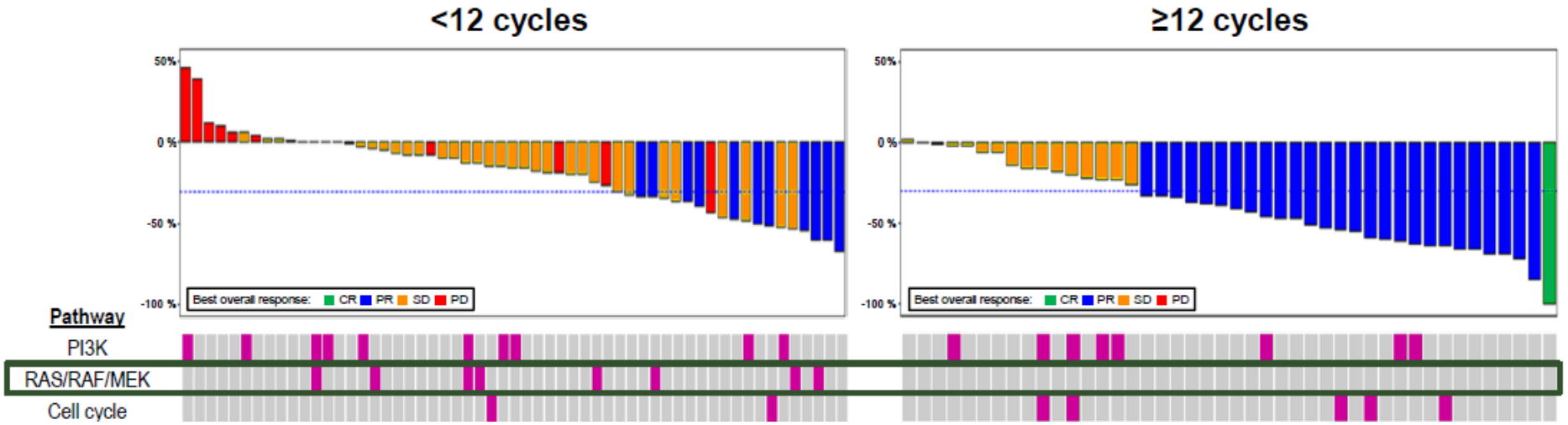
Subgroup analysis for ORR

Subgroups	n (%)	No. of responders	ORR (95% CI)
All	114 (100)	42	36.8% (28.0–46.4)
Prior immunotherapies?			
Y	50 (43.9)	21	42.0% (28.2–56.8)
N	64 (56.1)	21	32.8% (21.6–45.7)
Prior EGFR TKI(s)?			
Y	23 (20.2)	12	52.2% (30.6–73.2)
N	91 (79.8)	30	33.0% (23.5–43.6)
Response to prior platinum chemo			
CR, PR, or SD	69 (60.5)	25	36.2% (25.0–48.7)
PD	16 (14.0)	5	31.2% (11.0–58.7)
Unknown/NA	29 (25.4)	12	41.4% (23.5–61.1)



No differences for sex, age, race, basal PS ECOG, n° of prior lines, smoking history, baseline brain metastases

Sustained clinical benefit in absence of baseline RAS/RAF/MEK alterations



Sustained clinical benefit was associated with: good perfomance status, having at least a partial response to amivantamab therapy, not having baseline RAS/RAF/MEK alterations

Amivantamab safety

AE (≥15% of Treatment-emergent AEs), n (%)	Safety Population (N=114)			
	Treatment-emergent AE		Treatment-related AE	
	Total	Grade ≥3	Total	Grade ≥3
EGFR-related				
Rash[b]	98 (86)	4 (4)	98 (86)	4 (4)
Paronychia	51 (45)	1 (1)	48 (42)	1 (1)
Stomatitis	24 (21)	0	21 (18)	0
Pruritus	19 (17)	0	19 (17)	0
MET-related				
Hypoalbuminemia	31 (27)	3 (3)	17 (15)	2 (2)
Peripheral edema	21 (18)	0	11 (10)	0
Other				
Infusion related reaction	75 (66)	3 (3)	75 (66)	3 (3)
Constipation	27 (24)	0	7 (6)	0
Nausea	22 (19)	0	13 (11)	0
Dyspnea	22 (19)	2 (2)	6 (5)	0
Fatigue	21 (18)	2 (2)	14 (12)	1 (1)
Increased ALT	17 (15)	1 (1)	14 (12)	1 (1)

Park K, et al. JCO 2021; Sabari JK, et al. WCLC Annual Meeting 2021, abstract 3031

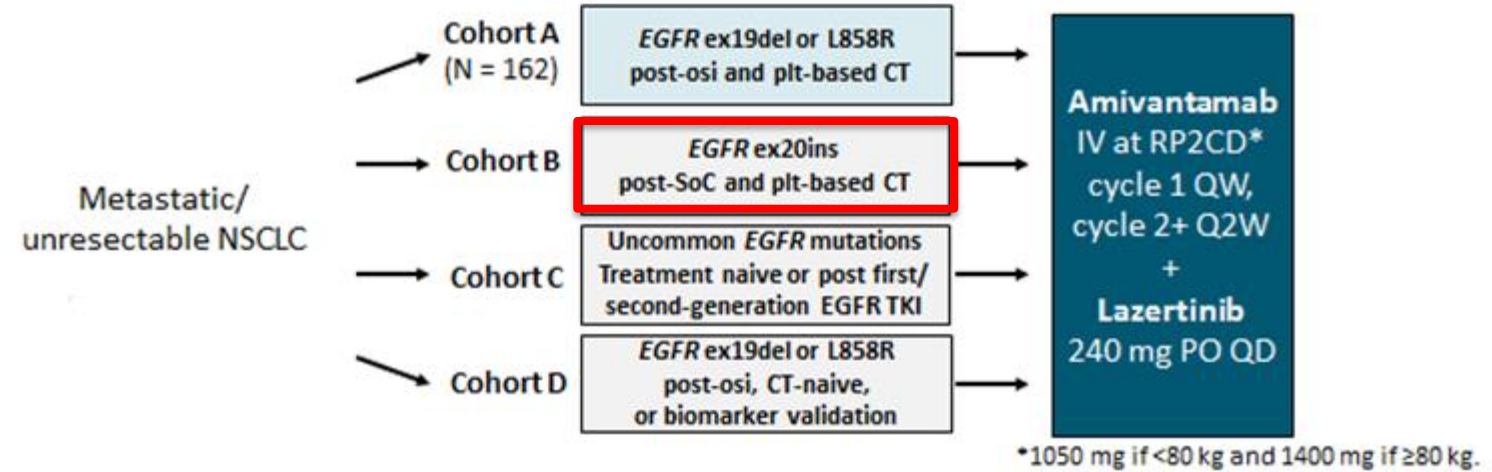
CLN-081

Novel oral TKI
phase I/IIa study

	Amivantamab n = 81	Mobocertinib N = 114	Poziotinib N = 115	CLN-081 N = 39
ORR (%)	**40%**	**28%**	**15%**	**41%**
mDOR (months)	11.1	17.5	7.4	>21
mPFS (months)	8.3	7.3	4.2	12.0
mOS (months)	22.8	24.0	---	---
Grade ≥ 3 AE	35%	47%	---	5%

FDA break-through therapy designation

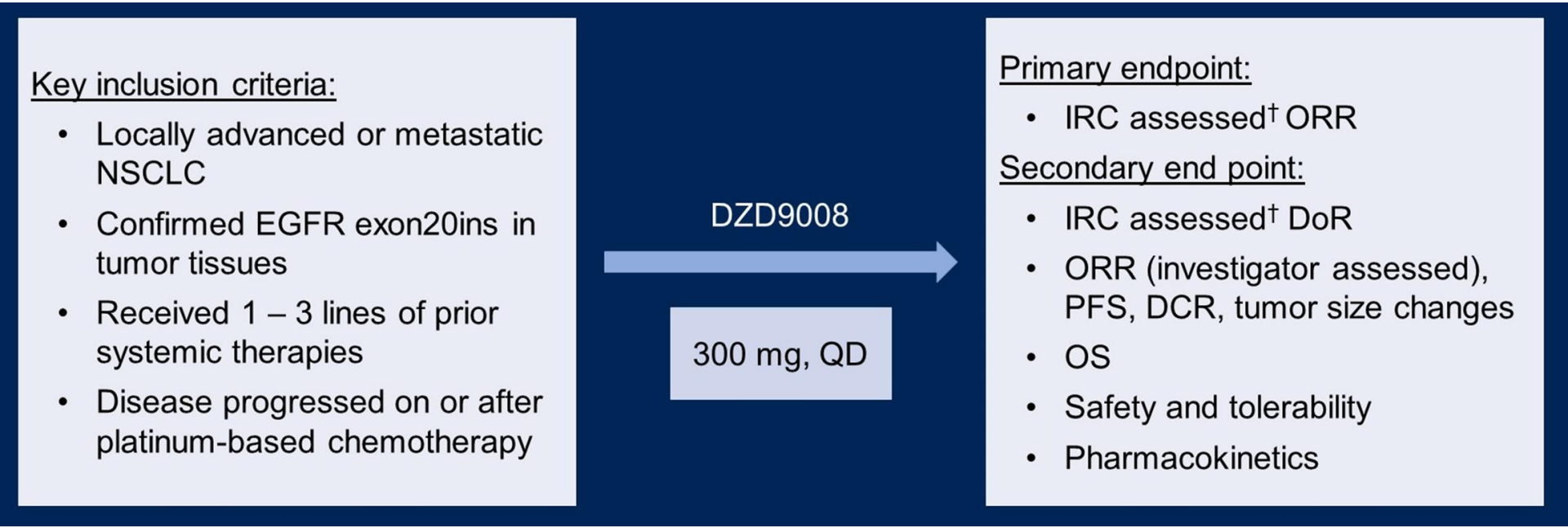
CHRYSALIS-2



Results for cohort B are still not available

WU-KONG6

Sunvozertinib was designed as an oral, potent, irreversible, and selective EGFR tyrosine kinase inhibitor, showing activity against EGFRexon20ins and other mutations.



Conducted in China

HUMANITAS CANCER CENTER HU

Adapted from Mengzhao Whan ASCO 2023

WU-KONG6 patients' characteristics

Demographics and Baseline Characteristics	N = 97
Median age, years (range)	58 (29, 79)
Male/Female, n (%)	39 (40.2)/58 (59.8)
History of smoking, Yes(%)/No(%)	32 (33)/65 (67)
Baseline brain metastasis, n (%)	31 (32.0)
Mutation subtypes, n (%)	
769_ASV	38 (39.2)
770_SVD	17 (17.5)
Others	42 (43.3)

Patient Treatment History	N = 97
Median prior anti-cancer therapy, n (range)	2 (1, 3)
Prior anti-cancer therapy type, n (%)	
Chemotherapy	97 (100)
Platinum-based chemotherapy	97 (100)
EGFR TKI	26 (26.8)
PD-1/PD-L1	34 (35.1)
Anti-VEGF	58 (59.8)
Others	16 (16.5)

Adapted from Mengzhao Whan ASCO 2023

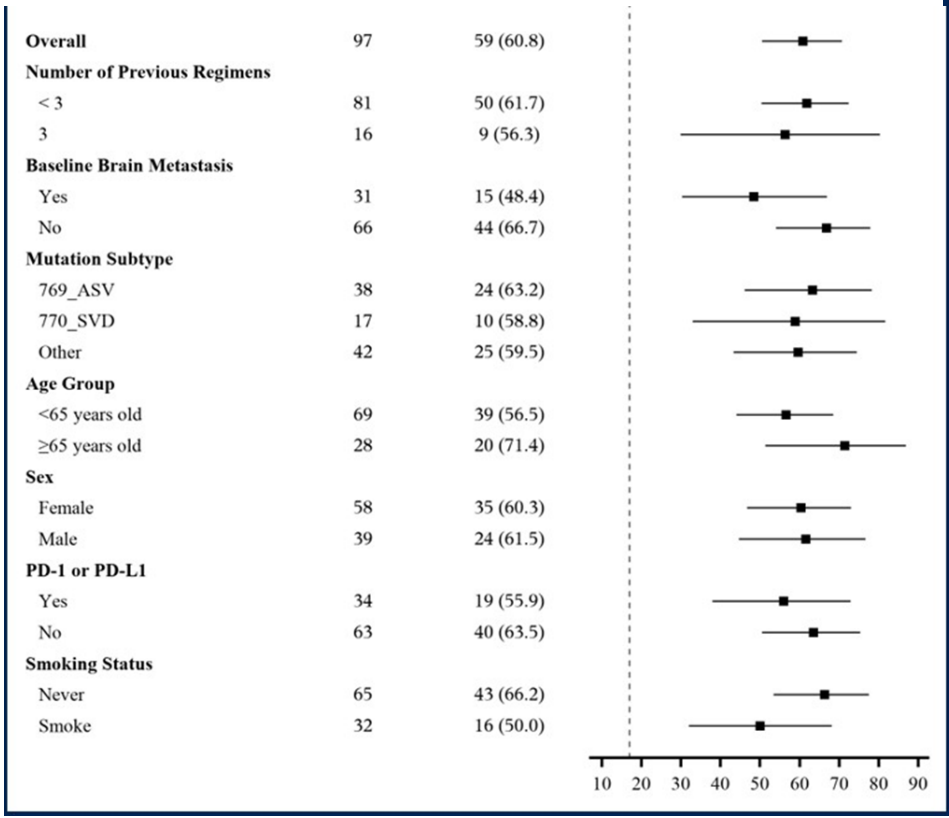
WU-KONG6 efficacy outcomes

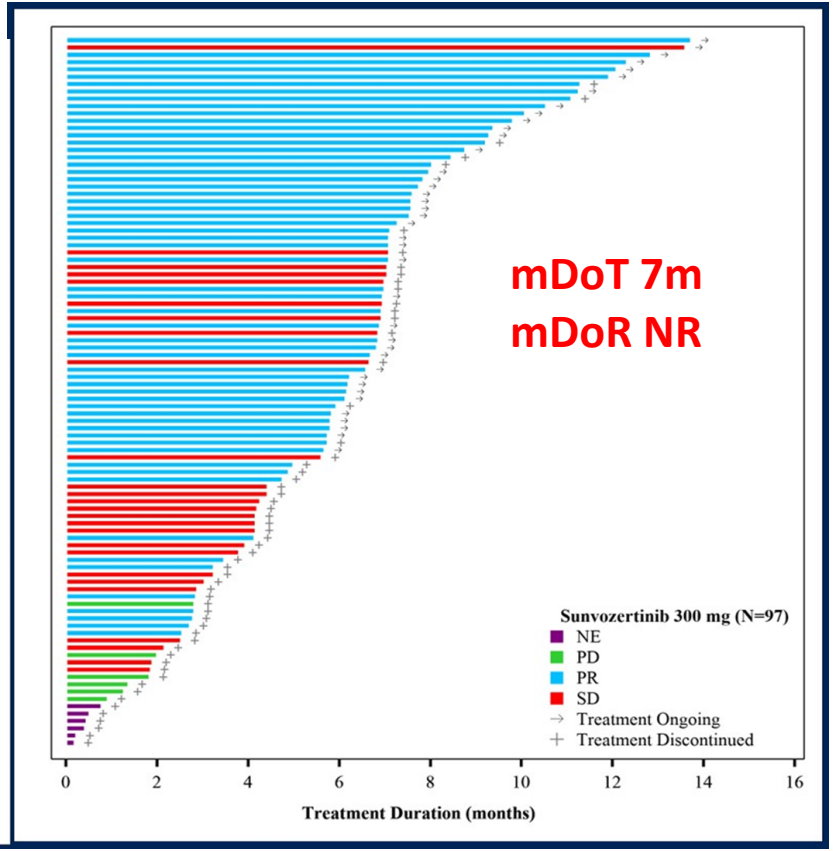
Anti-tumor Efficacy	N = 97
Tumor Response, n (%)	
Partial response (confirmed)	59 (60.8)
Stable disease	26 (26.8)
Progression disease	6 (6.2)
Not evaluable	6 (6.2)
Objective Response Rate (ORR), n (%)	59 (60.8)
(95% CI)	(50.4, 70.6)
P value	< 0.0001
Disease Control Rate (DCR), n (%)	85 (87.6)
(95% CI)	(79.4%, 93.4%)

	CLN-081 (n=39)	Amivantamab (n=81)	Sunvozertinib (n=94)
ORR %	41%	40%	60.8%
mDoR	>21 m	11.1 m	NR
mPFS	12.0 m	8.3 m	---
mOS	---	22.8 m	---
Grade≥3 AE	5%	35%	---

Adapted from Mengzhao Whan ASCO 2023

WU-KONG6 subgroup analysis



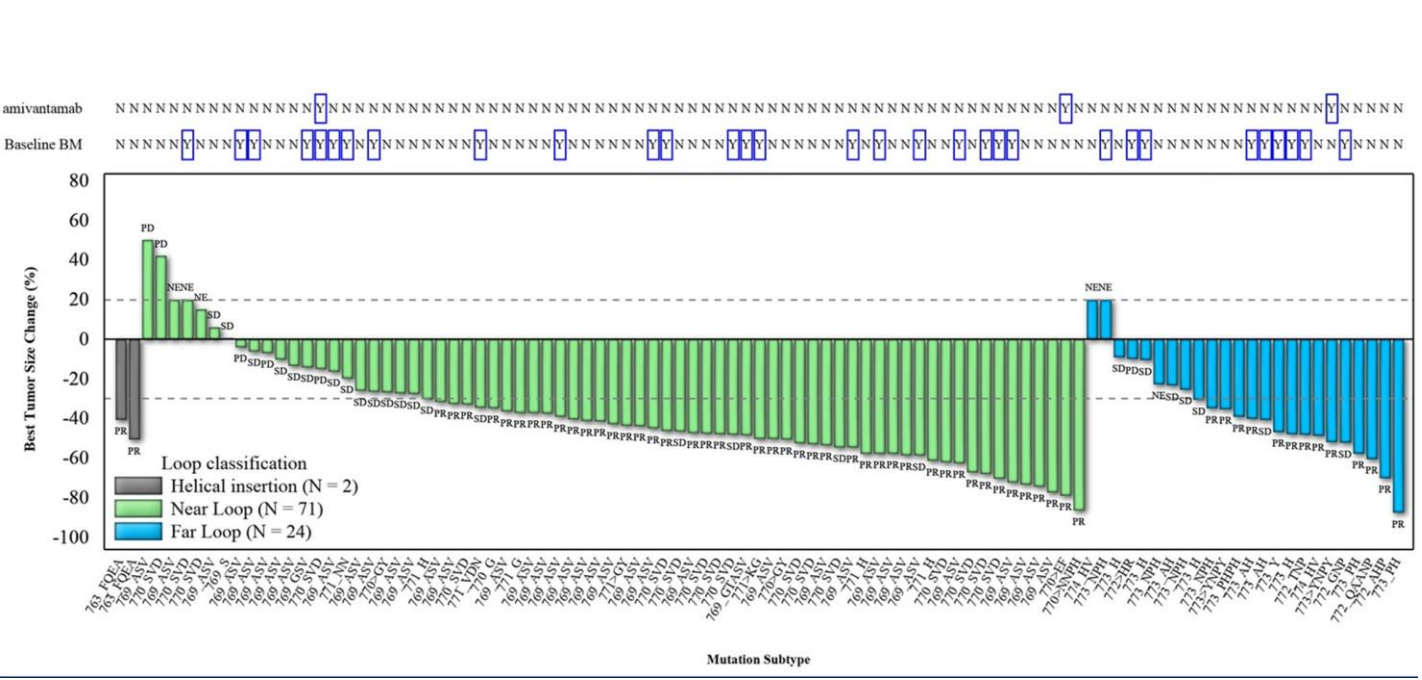


HUMANITAS CANCER CENTER

HU

Adapted from Mengzhao Whan ASCO 2023

Efficacy in different exon20ins subtypes



C-helical (n=2)
ORR=100%
DCR=100%

Near loop (n=71)
ORR=62.0%
DCR=88.7%

Far loop (n=24)
ORR=54.2%
DCR=83.3%

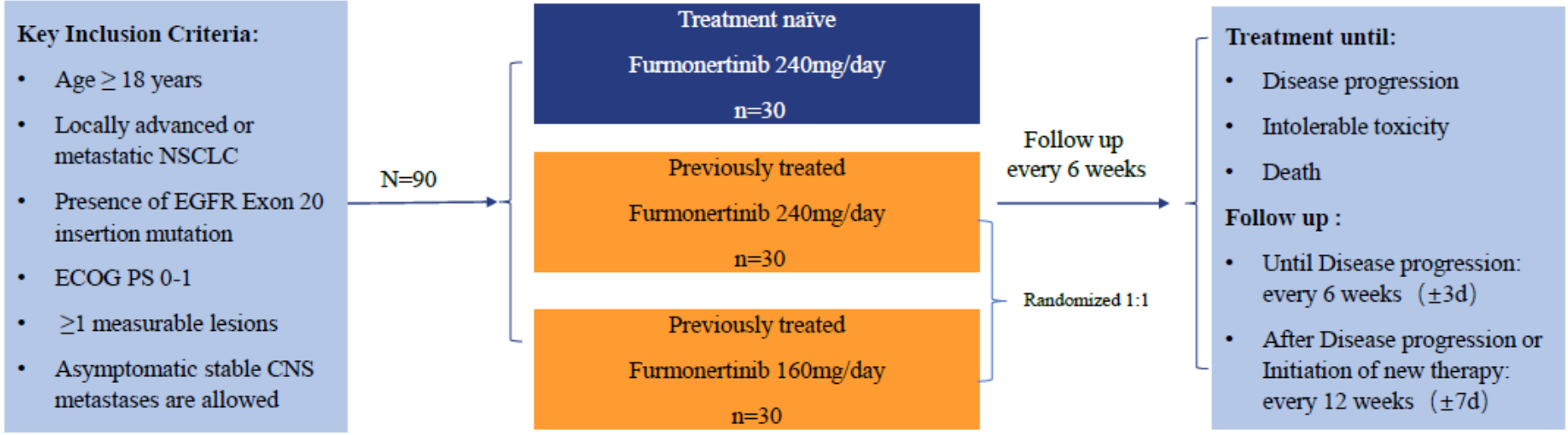
A total of 30 different subtypes of exon20ins were enrolled

Safety profile

Common TEAE by PT	N = 104 All Grade	N = 104 ≥ Grade 3
Diarrhea	70（67.3）	8（7.7）
Blood CPK increase	60（57.7）	18（17.3）
Rash	56（53.8）	1（1.0）
Anemia	51（49.0）	6（5.8）
Blood creatinine increase	39（37.5）	0（0.0）
Paronychia	34（32.7）	2（1.9）
Body weight decrease	30（28.8）	1（1.0）
White blood cell decrease	27（26.0）	0（0.0）
Lipase increase	27（26.0）	2（1.9）
Vomiting	25（24.0）	1（1.0）
Decreased appetite	25（24.0）	2（1.9）
Mouth ulceration	24（23.1）	0（0.0）

FAVOUR

Furmonertinib is a third-generation EGFR TKI, **approved since March 2021 in China** at a dose/schedule of 80 mg daily for patients with **EGFR T790M mutant NSCLC**.



Endpoints

➢ **Primary**: ORR by IRC assessment; **Secondary**: DCR, DoR, PFS, OS, Depth of response, safety, quality of life

Conducted in China

Adapted from Baohui Han presented at WCLC 2023

FAVOUR patients' characteristics

	Treatment Naïve 240 mg N=30	Previously Treated 240 mg N=28	Previously Treated 160 mg N=28
Age, median (min, max) (years)	61.5 (33, 73)	55.5 (33, 73)	58.5 (22, 77)
Male/Female, %	37% / 63%	43% / 57%	39% / 61%
ECOG 0/1, %	30% / 70%	7% / 93%	11% / 89%
Disease Stage IIIB/IV, %	7% / 93%	0 / 100%	4% / 96%
Brain Metastases*, %	17%	29%	39%
Non-smoker/Smoker/Former smoker, %	77% / 3% / 20%	82% / 0 / 18%	75% / 4% /21%
Number of Prior Systemic Anti-cancer Therapy, median, (min, max)	NA	1 (1, 4)	1 (1, 3)
Prior Treatment Type, % Chemotherapy / Immunotherapy EGFR Targeted Therapy&	 13% / 0 0	 96% / 39% 7%	 86% / 32% 14%

Adapted from Baohui Han presented at WCLC 2023

FAVOUR efficacy outcomes

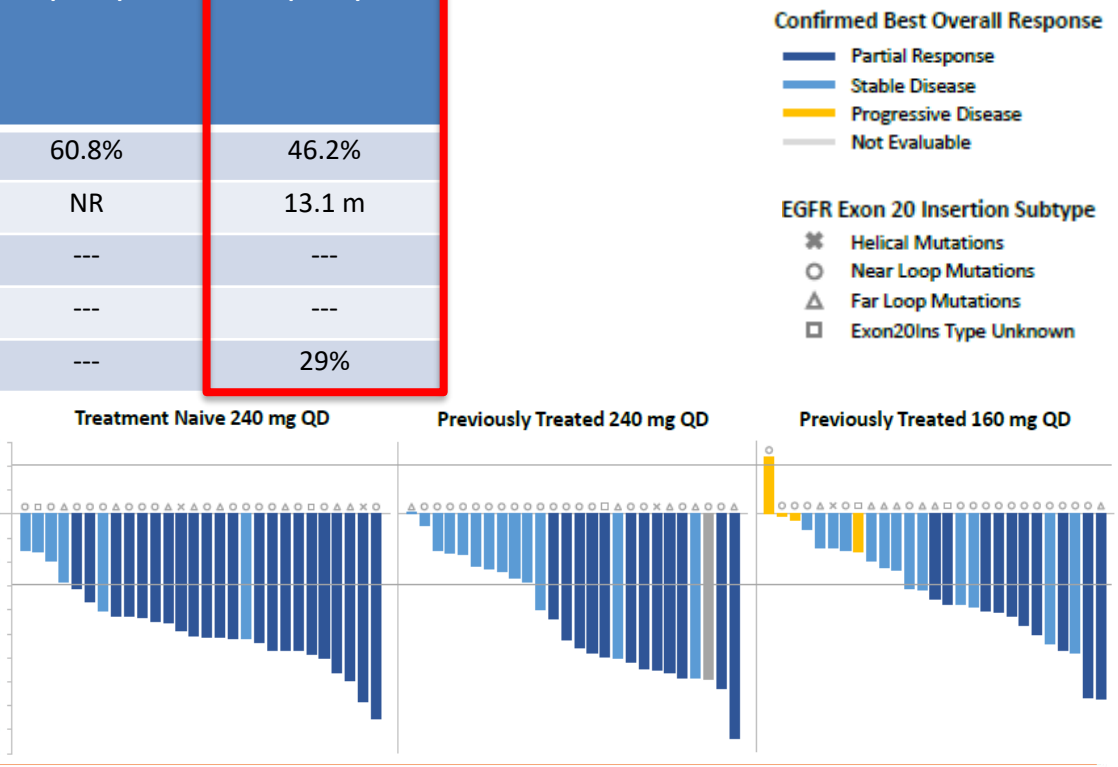
Efficacy by IRC	Treatment Naïve 240mg N=28*	Previously Treated 240mg N= 26#	Previously Treated 160mg N= 26#
Confirmed ORR, % (95% CI)	78.6% (59.05%, 91.70%)	46.2% (26.59%, 66.63%)	38.5% (20.23%, 59.43%)
Best Response, n (%)			
Partial response (PR)	22 (78.6%)	12 (46.2%)	10 (38.5%)
Stable disease (SD)	6 (21.4%)	12 (46.2%)	12 (46.2%)
Progressive disease (PD)	0	0	4 (15.4%)
Not evaluable/Not done	0 / 0	1 (3.8%) / 1 (3.8%)	0 / 0
DoR, median (months) (95% CI)	15.2 (8.74, 24.84)	13.1 (5.62, 13.80)	9.7 (5.59, NA)
DCR (CR+PR+SD), % (95% CI)	100.0% (87.66%, 100.00%)	92.3% (74.87%, 99.05%)	84.6% (65.13%, 95.64%)

- As first-line treatment, the cORR was 78,6% with a mDOR of 15.2 m
- In previosuly treated patients, cORR was 46,2% for 240 mg dose and 38,5% for 160 mg dose
- **Anti-tumor responses were observed across near-loop, far-loop and helical Exon 20ins mutations**

Adapted from Baohui Han presented at WCLC 2023

Furmonertinib efficacy outcomes

	CLN-081 (n=39)	Amivantamab (n=81)	Sunvozertinib (n=94)	Furmonertinib (n=28)
ORR %	41%	40%	60.8%	46.2%
mDoR	>21 m	11.1 m	NR	13.1 m
mPFS	12.0 m	8.3 m	---	---
mOS	---	22.8 m	---	---
Grade≥3 AE	5%	35%	---	29%



HUMANITAS CANCER CENTER

HU

Adapted from Baohui Han presented at WCLC 2023

FAVOUR safety

Preferred Term, Number of Patient(s) (%)	Treatment-naive 240 mg (N = 30)		Previously Treated 240 mg (N = 28)		Previously Treated 160 mg (N = 28)	
	Total	Grade≥3	Total	Grade≥3	Total	Grade≥3
Diarrhea	22 (73%)	0	24 (86%)	0	9 (32%)	2 (7%)
Anemia	13 (43%)	0	7 (25%)	1 (4%)	4 (14%)	1 (4%)
Aspartate aminotransferase increased	8 (27%)	0	7 (25%)	0	10 (36%)	0
Alanine aminotransferase increased	7 (23%)	0	7 (25%)	1 (4%)	8 (29%)	0
Blood creatinine increased	6 (20%)	0	8 (29%)	0	7 (25%)	0
Mouth ulceration	9 (30%)	1 (3%)	4 (14%)	0	5 (18%)	0
Rash	7 (23%)	0	6 (21%)	0	4 (14%)	0
Electrocardiogram QT prolonged	8 (27%)	1 (3%)	4 (14%)	2 (7%)	2 (7%)	0
White blood cell count decreased	6 (20%)	1 (3%)	5 (18%)	0	6 (21%)	0
Decreased appetite	3 (10%)	0	8 (29%)	0	0	0
Weight decreased	3 (10%)	0	7 (25%)	1 (4%)	3 (11%)	0
Skin fissures	6 (20%)	0	3 (11%)	0	0	0
Paronychia	6 (20%)	0	2 (7%)	0	1 (4%)	0

Adapted from Baohui Han presented at WCLC 2023

What's next

Drug	Trial	Phase	Setting
Amivantamab + CT vs CT	PAPILLON	3	1st line
Mobocertinib vs CT	EXCLAIM-2	3	1st line
Furmonertinib vs CT	FURVENT	3	1st line
Zipalertinib + CT vs CT	REZILIENT3	3	1st line
Sunvozertinib vs CT	WU-KONG28	3	1st line


THANK
YOU!