KRAS AND EGFR EXON 20 INSERTION

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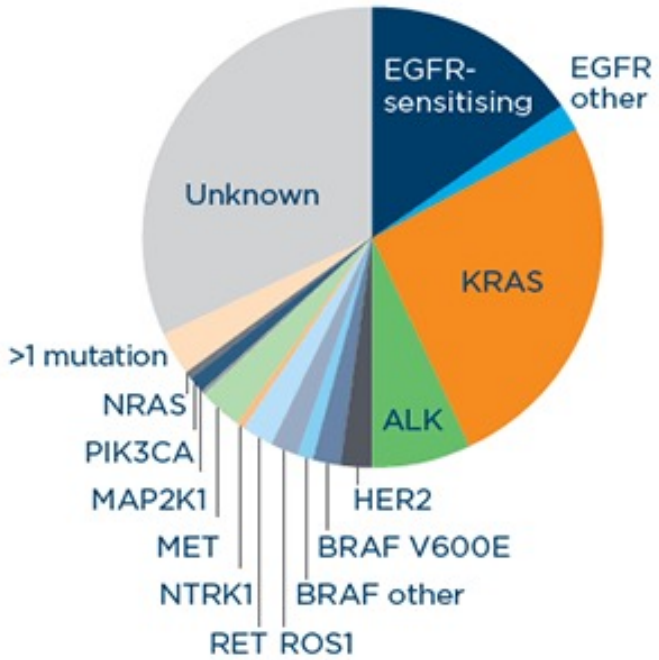
Mutations in NSCLC

DRIVER MUTATIONS IN LUNG ADENOCARCINOMA

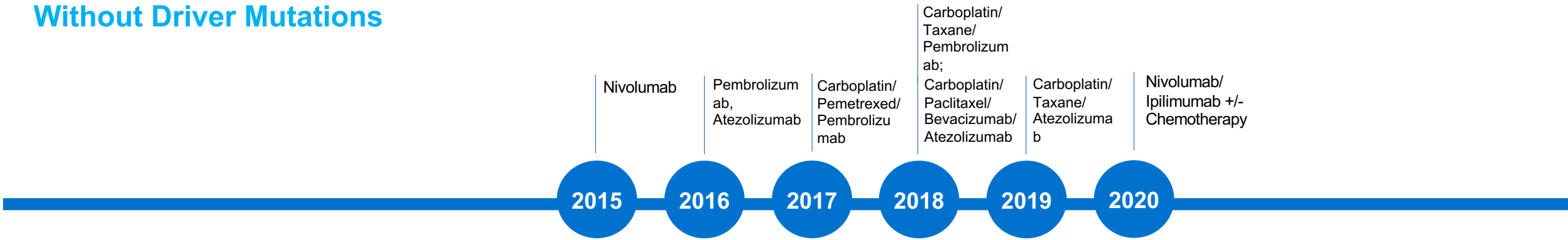


Driver mutations in lung adenocarcinoma	
EGFR-sensitizing	15%
EGFR other	2%
KRAS	25%
ALK	7%
HER2	2%
BRAF V600E	2%
BRAF other	1%
ROS1	2%
RET	2%
NTRK1	0–5%
MET	3%
MAP2K1	0–5%
PIK3CA	1%
NRAS	0–5%
>1 mutation	3%
Unknown	31%

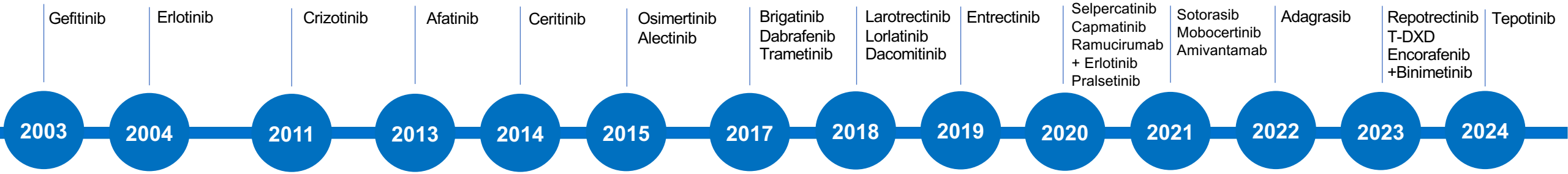
	Drug	Targets
Immunotherapy	Pembrolizumab, Nivolumab (± Ipilimumab) Atezolizumab, Durvalumab, Cemiplimab	PD-1/PD-L1/ CTLA4
EGFR	Osimertinib Erlotinib, Gefitinib, Dacomitinib Afatinib Mobocertinib Amivantamab	EGFR sensitizing mutations and resistance mutation (T790M) EGFR exon 19 deletions or exon 21 (L858R) Rare mutations (S768L, L861Q, and G719X) Exon 20 insertion mutation MET-EGFR (FDA approved for Exon 20 insertion)
ALK	Crizotinib, Alectinib, Ceritinib, Lorlatinib, Brigatinib	ALK fusion
BRAF	Dabrafenib + Trametinib Encorafenib+Binimetinib	BRAF V600E
ROS-1	Crizotinib, Entrectinib, Repotrectinib	ROS-1 fusion
NTRK	Entrectinib, Larotrectinib	NTRK mutation/fusion
MET	Capmatinib, Tepotinib	MET exon skipping mutation
RET	Selpercatinib, Pralsetinib	RET fusion
KRAS	Sotorasib, Adragasib	KRAS G12C
HER2	Trastuzumab Deruxtecan	HER2

Treatment Approvals in Metastatic NSCLC with and without Driver Mutations

Without Driver Mutations



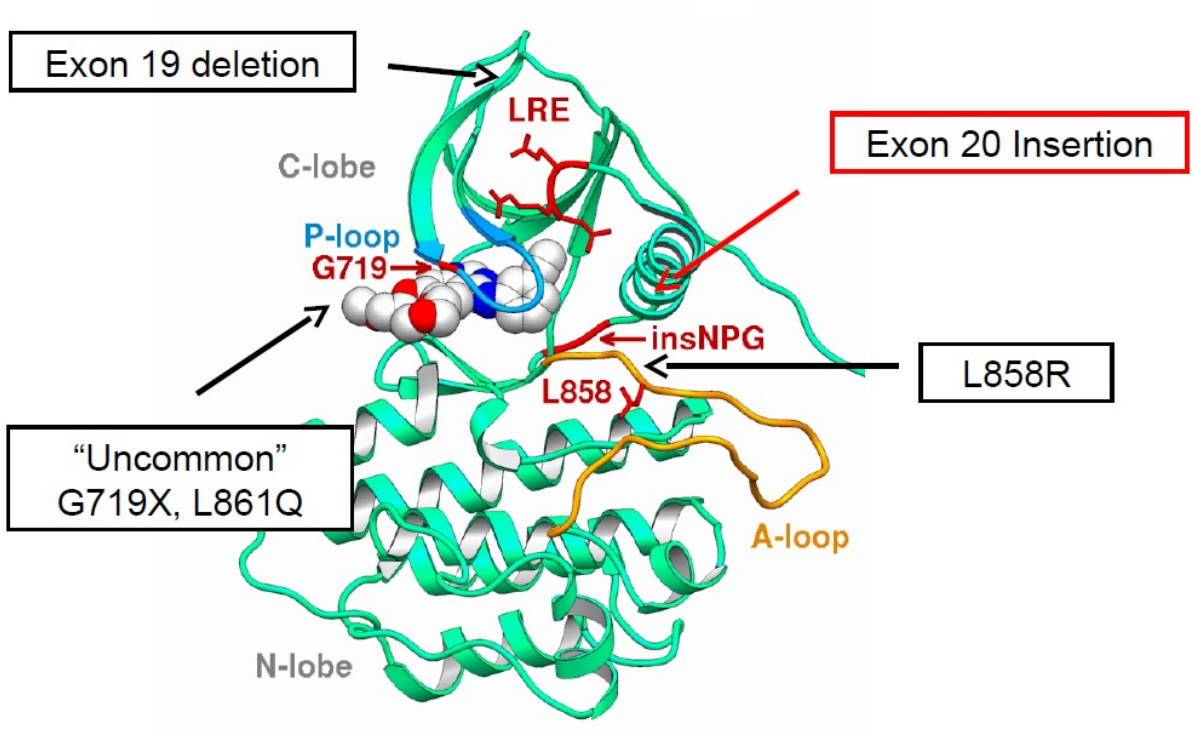
With Driver Mutations



EGFR

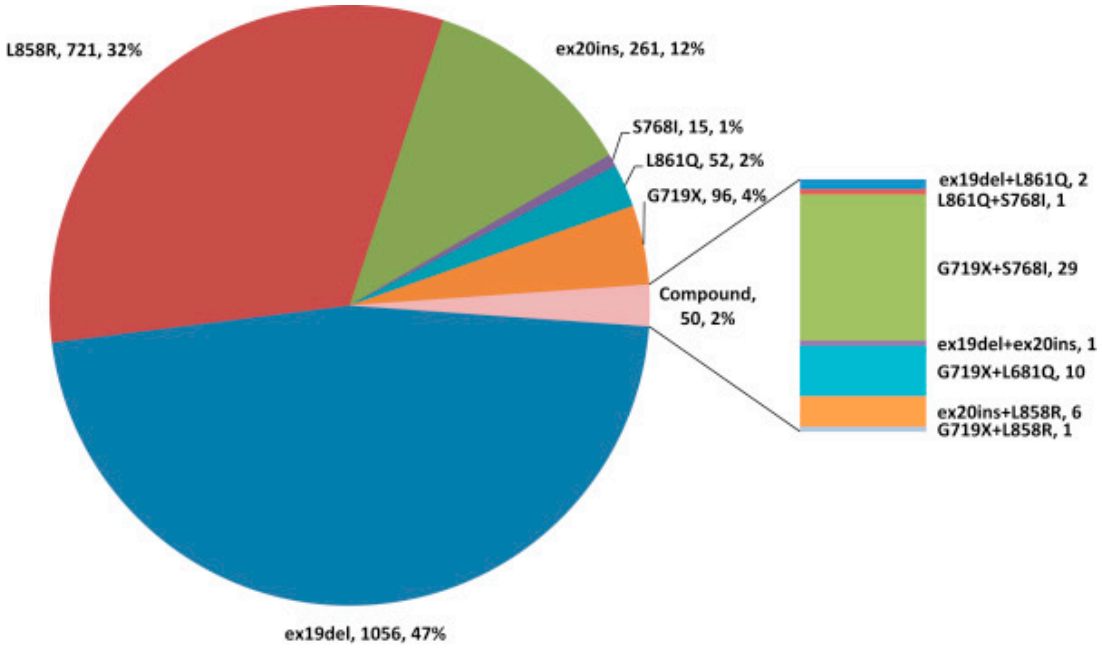
EGFR Mutations

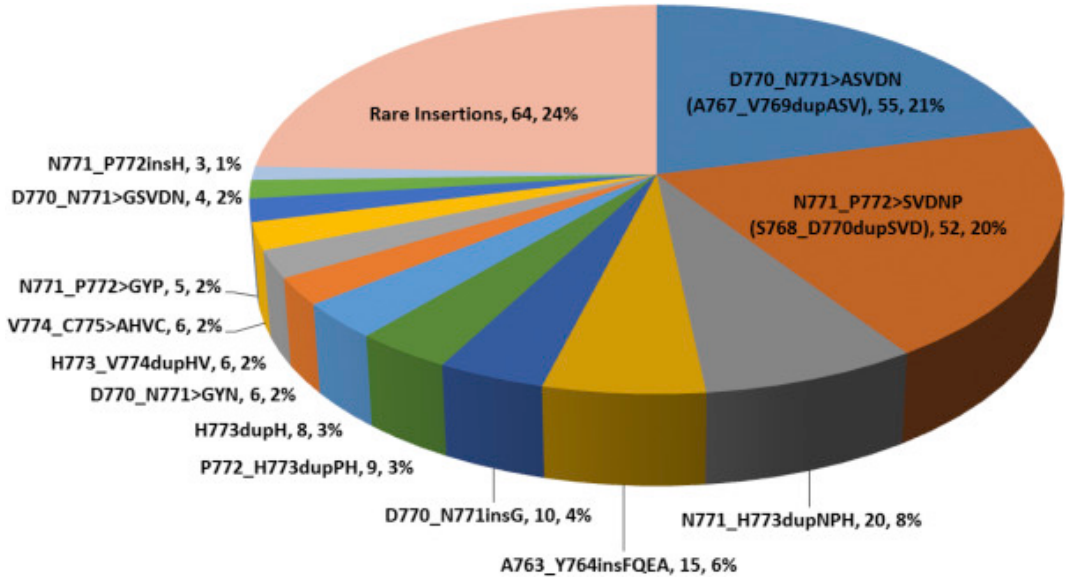
Different Subtypes of EGFR Mutations



Exon 19/L858R – 85% - erlotinib, gefitinib, afatinib, dacomitinib & osimertinib
G719X, L861Q, S768I – 8-10% - afatinib
Exon 20 - 5-7% - no approved TKI

EGFR Exon 20 Insertion Mutations are an uncommon subtype of EGFR mutant NSCLC

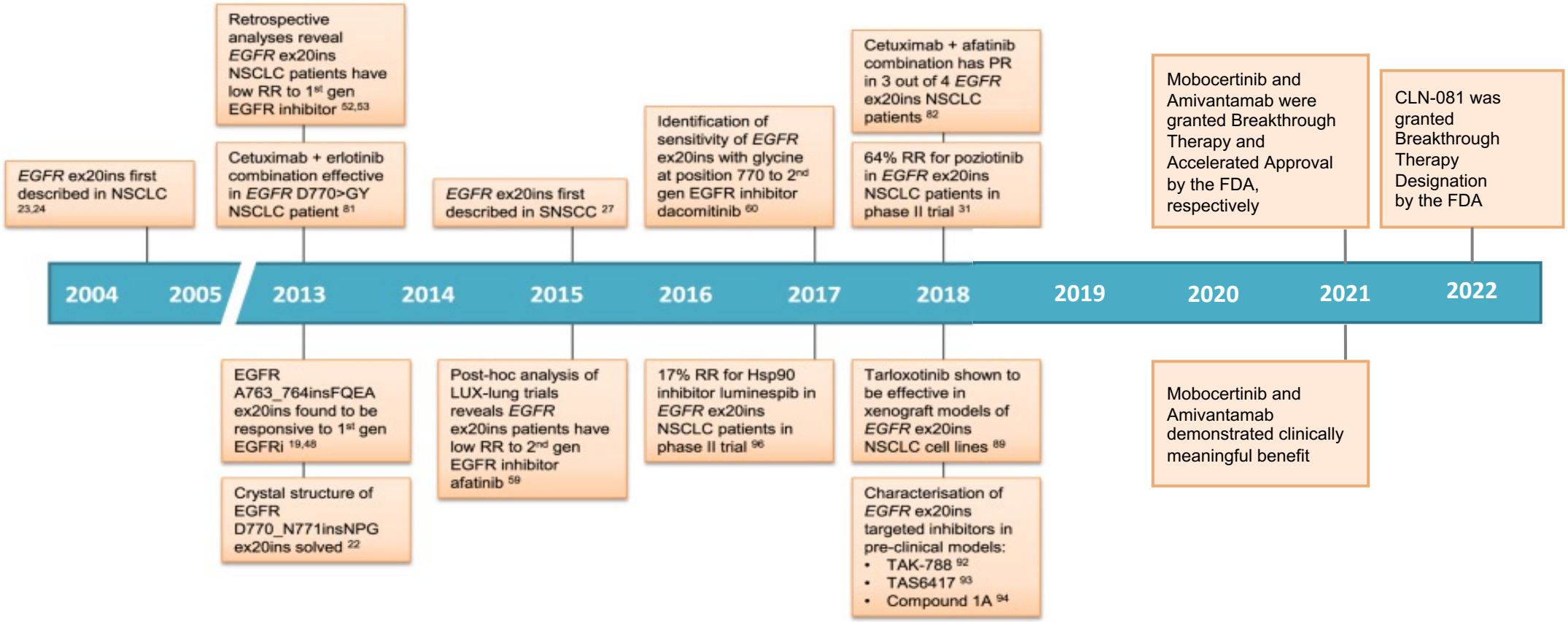




- Constitute about 1–10% of all the EGFR mutation types
- Associated with *de novo* resistance to EGFR TKIs
- Note FQEA sensitive to all EGFR TKIs

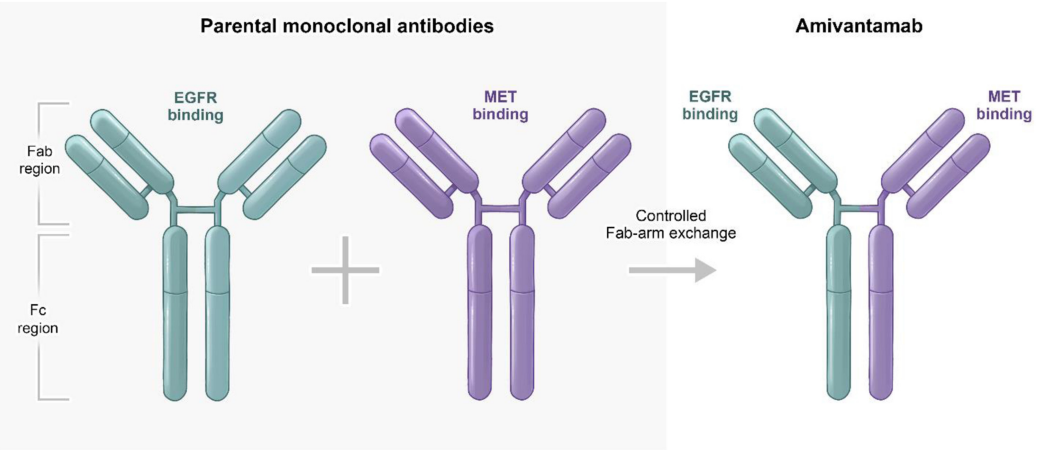
Riess JW et al, JTO 2018

EGFR Exon 20 Insertion Treatment

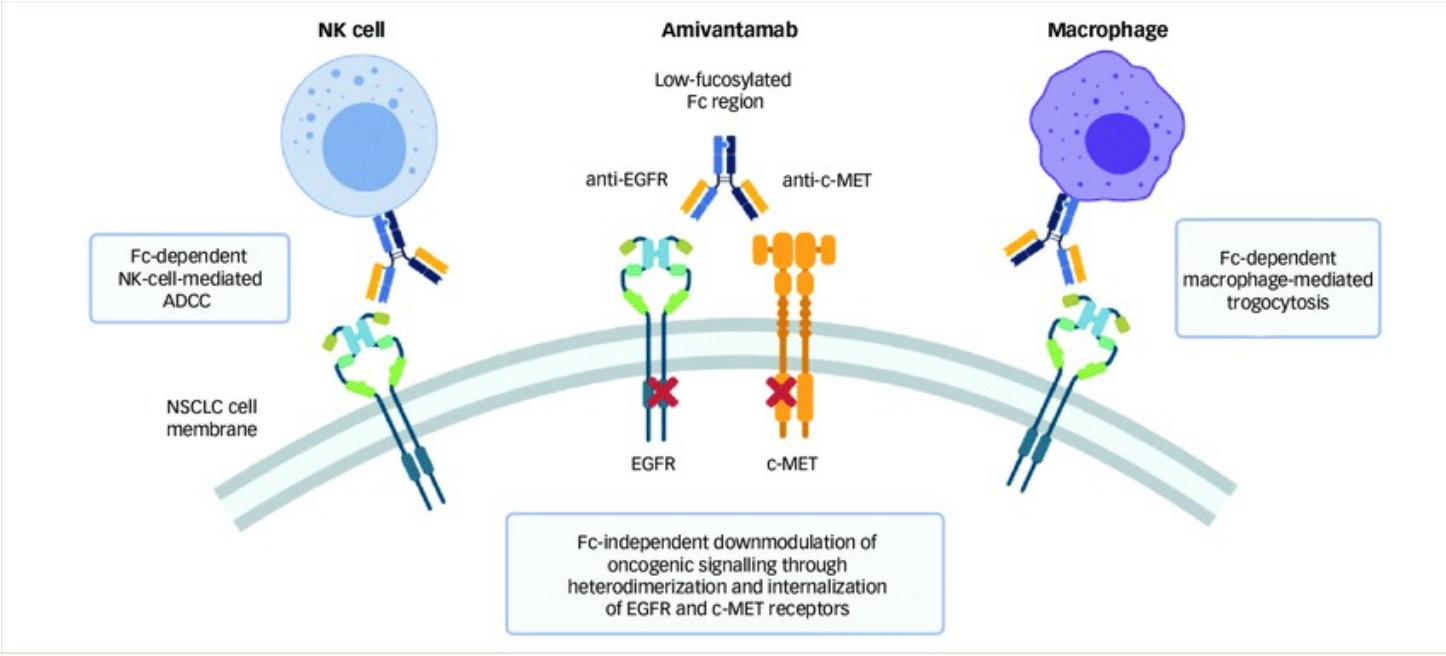


Vyse et al. Nature 2019
Presented by Lecia V. Sequist, Targeted Therapies in Lung Cancer 2020

Amivantamab

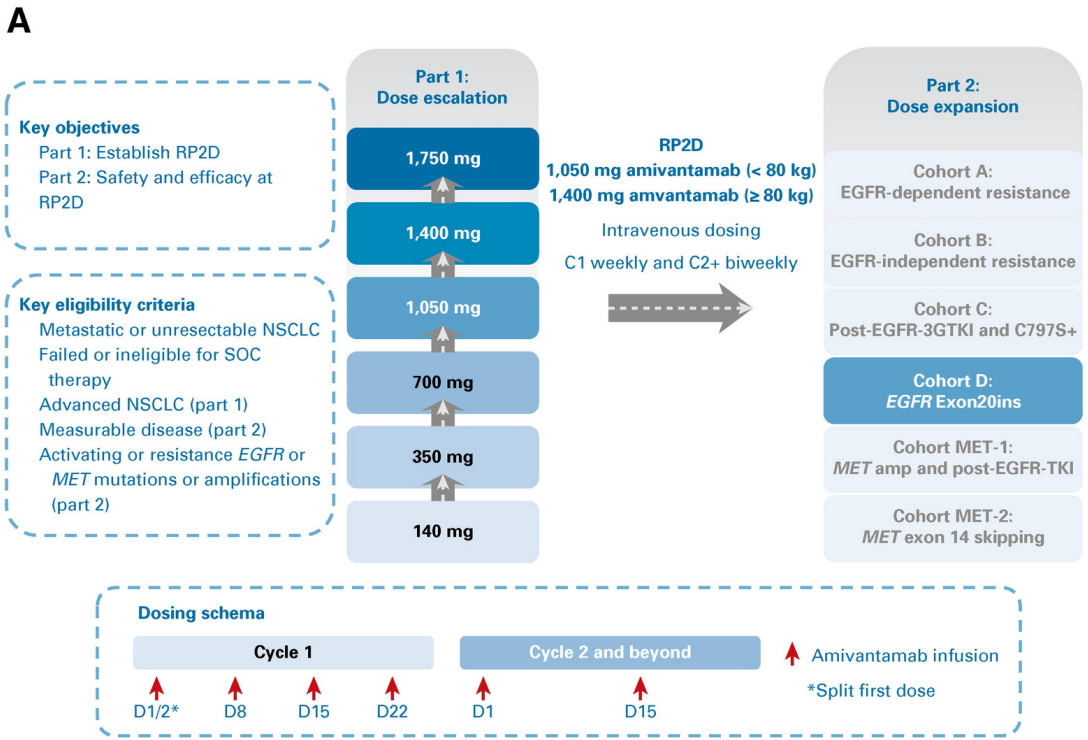


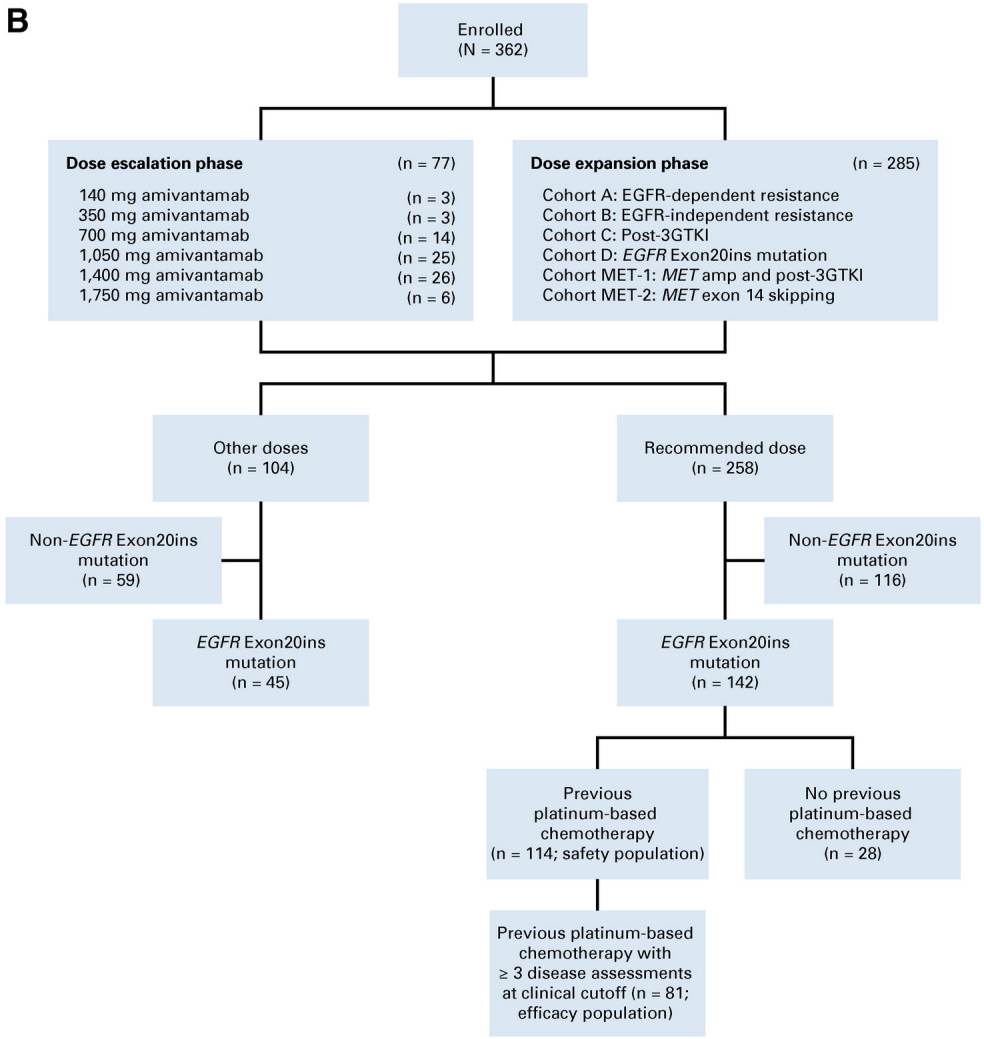
Mechanism of Action



Chul Cho B et al Clinical Lung Cancer 2023; Guo MZ et al. touchREVIEWS in Oncology & Haematology 2021

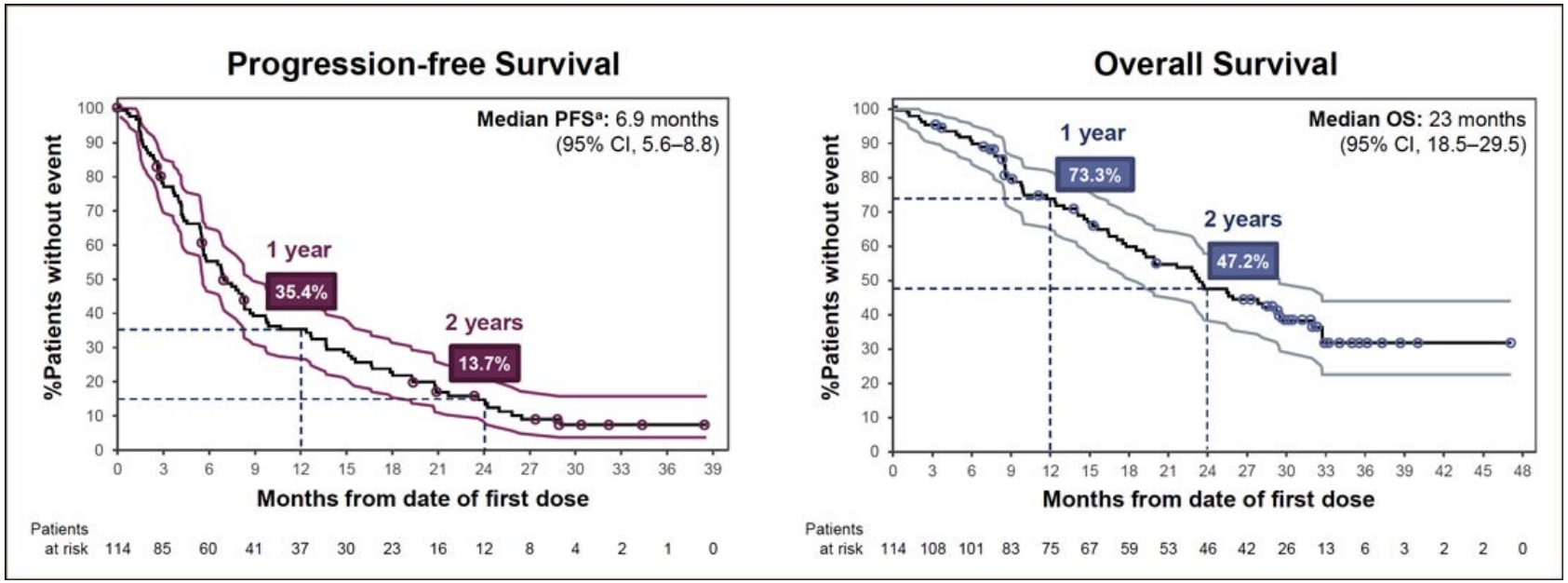
CHRYSALIS Trial: Amivantamab in EGFR Exon 20 Insertion-Mutated NSCLC Progressing on Platinum Chemotherapy

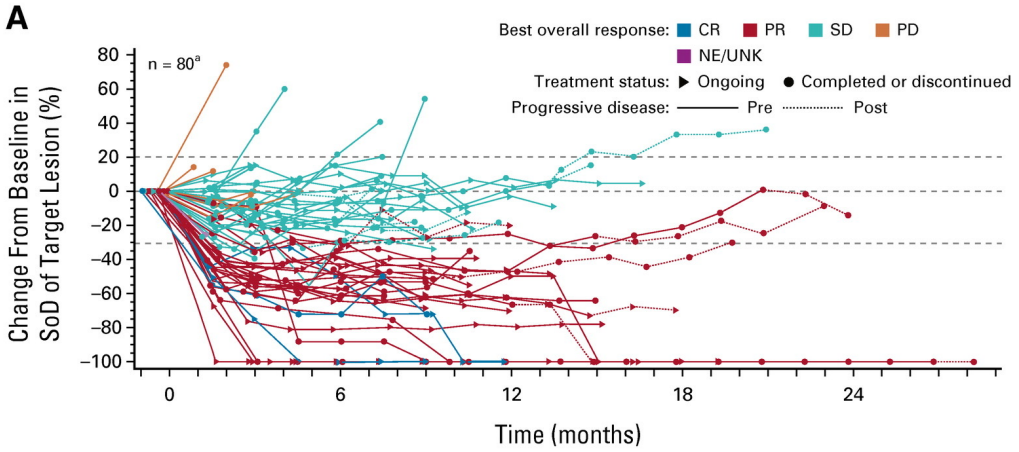




Park K et al. JCO 2021

CHRYSALIS Trial: Amivantamab Long-Term Follow-Up





- The overall response rate was 40% (95% CI, 29 to 51), including three complete responses, with a median duration of response of 11.1 months (95% CI, 6.9 to not reached).
- The median progression-free survival was 8.3 months (95% CI, 6.5 to 10.9).

Park K et al. JCO 2021; Presented by Garrido P at ESMO 2023

PAPILLON: Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions

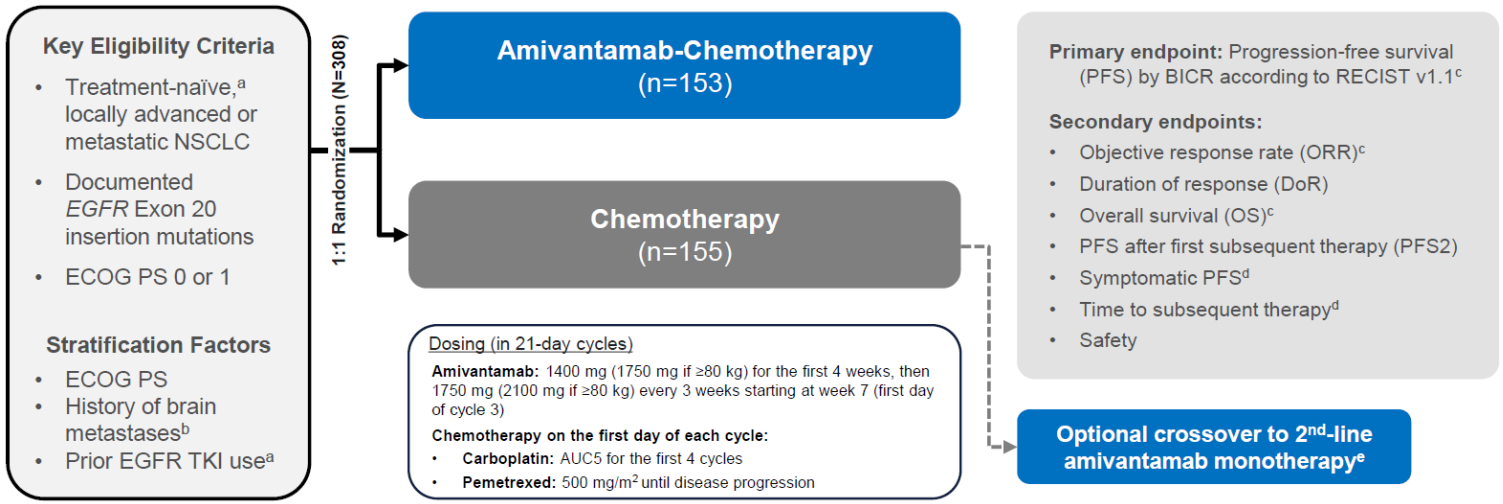
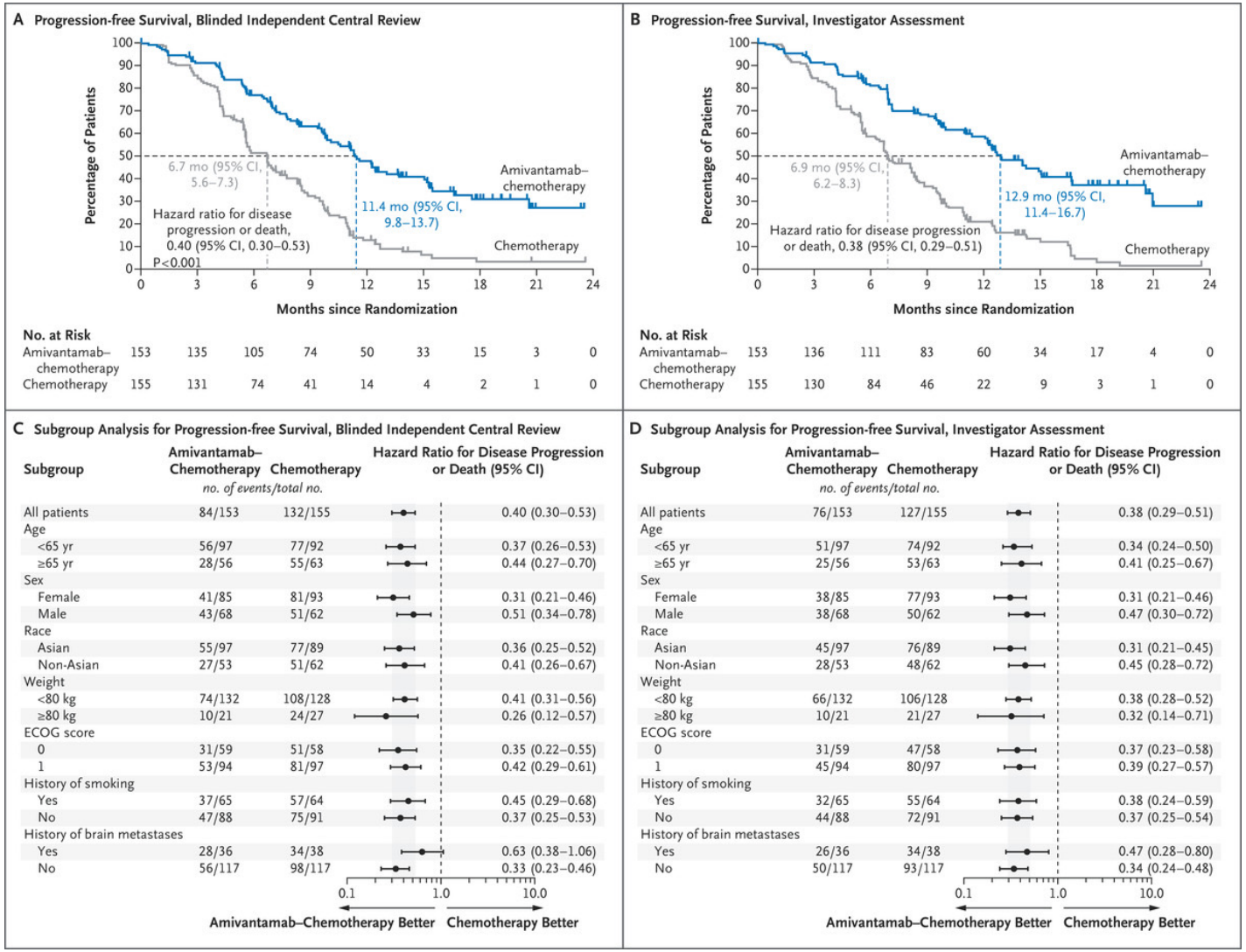


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Amivantamab–Chemotherapy (N=153)	Chemotherapy (N=155)
Age		
Median (range) — yr	61 (27–86)	62 (30–92)
Distribution — no. (%)		
<65 yr	97 (63)	92 (59)
65 to <75 yr	44 (29)	48 (31)
≥75 yr	12 (8)	15 (10)
Sex — no. (%)		
Female	85 (56)	93 (60)
Male	68 (44)	62 (40)
Race or ethnic group — no./total no. (%)†		
Asian	97/151 (64)	89/152 (59)
White	49/151 (32)	60/152 (39)
Black	2/151 (1)	0
American Indian or Alaska Native	1/151 (1)	2/152 (1)
Multiple	1/151 (1)	0
Unknown	1/151 (1)	1/152 (1)
ECOG performance-status score — no. (%)		
0	54 (35)	55 (35)
1	99 (65)	100 (65)
History of smoking — no. (%)		
No	88 (58)	91 (59)
Yes	65 (42)	64 (41)
Median time from initial diagnosis (range) — mo	1.8 (0.5–80.8)	1.8 (0.6–95.9)
Median time from metastatic diagnosis (range) — mo	1.5 (0.2–40.0)	1.6 (0.3–30.7)
Histologic type — no. (%)		
Adenocarcinoma	151 (99)	153 (99)
Large-cell carcinoma	0	1 (1)
Other§	2 (1)	1 (1)
History of brain metastases — no. (%)	35 (23)	36 (23)

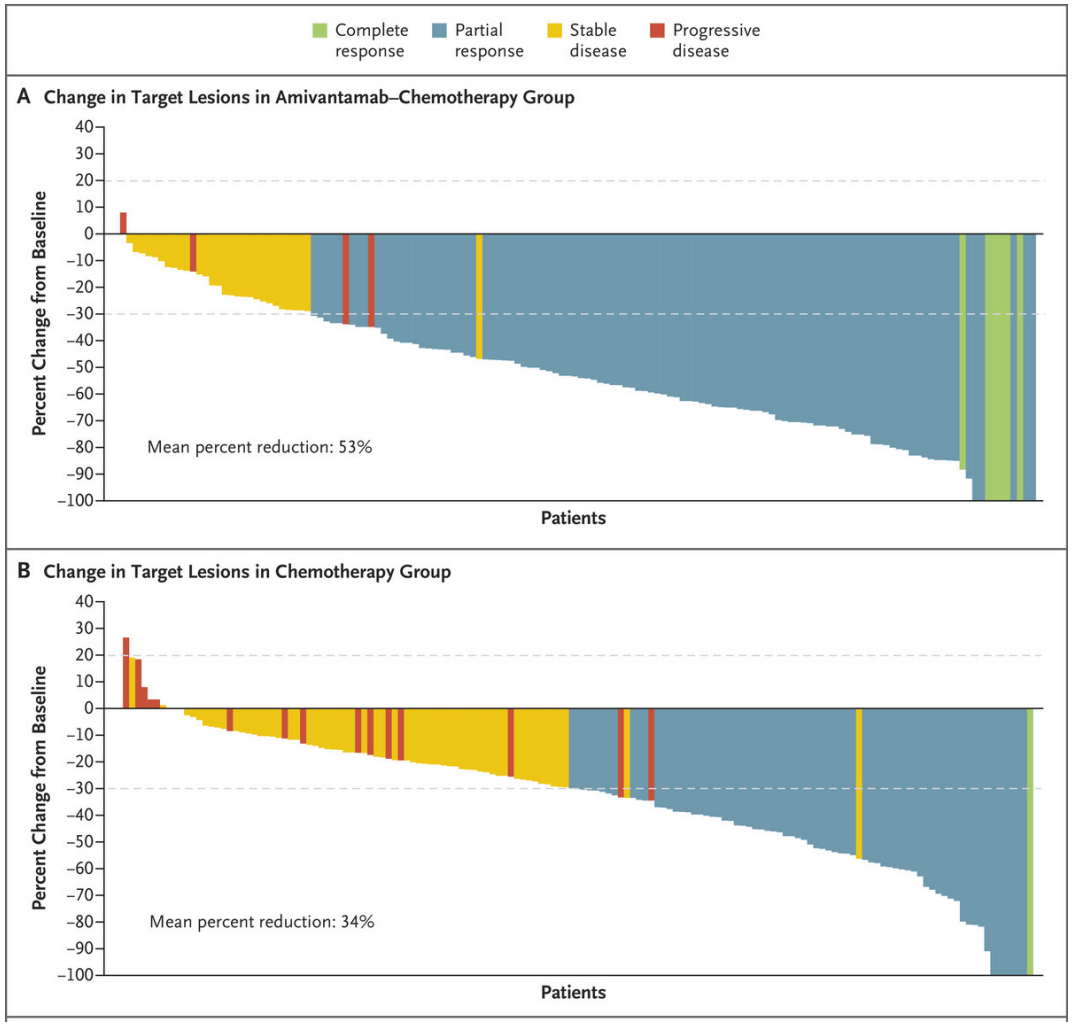
Zhou C. et al. NEJM 2023

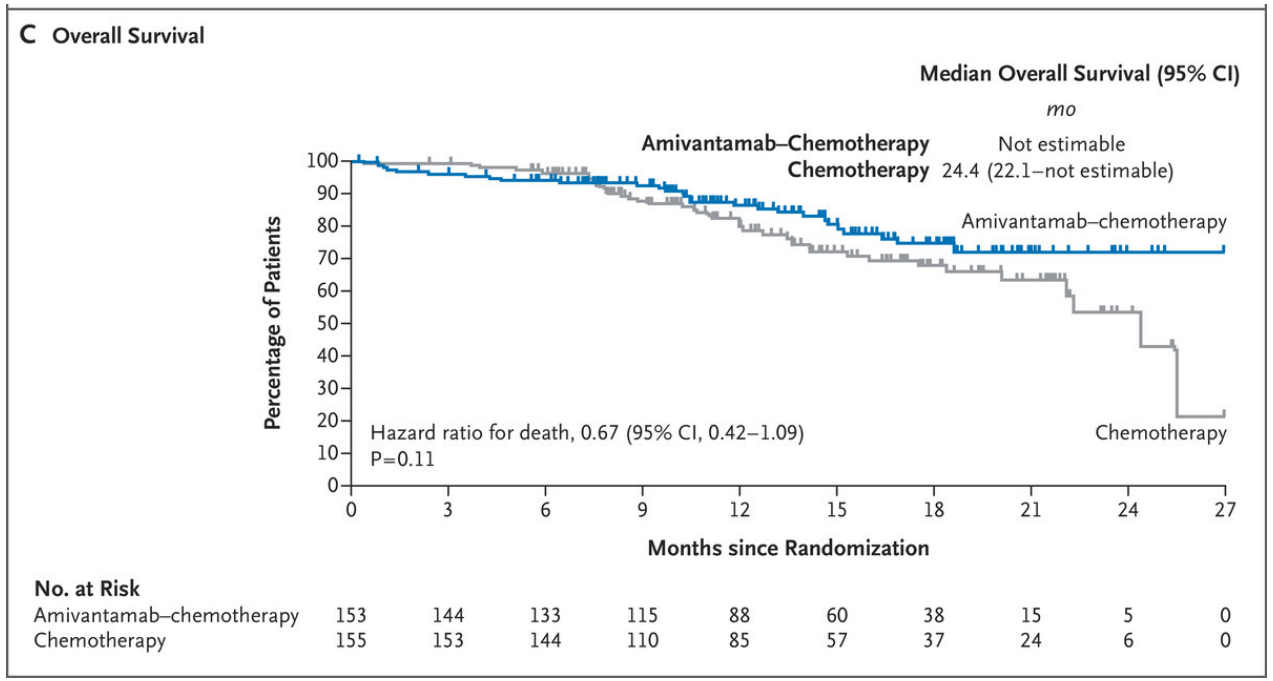
PAPILLON: Progression Free Survival



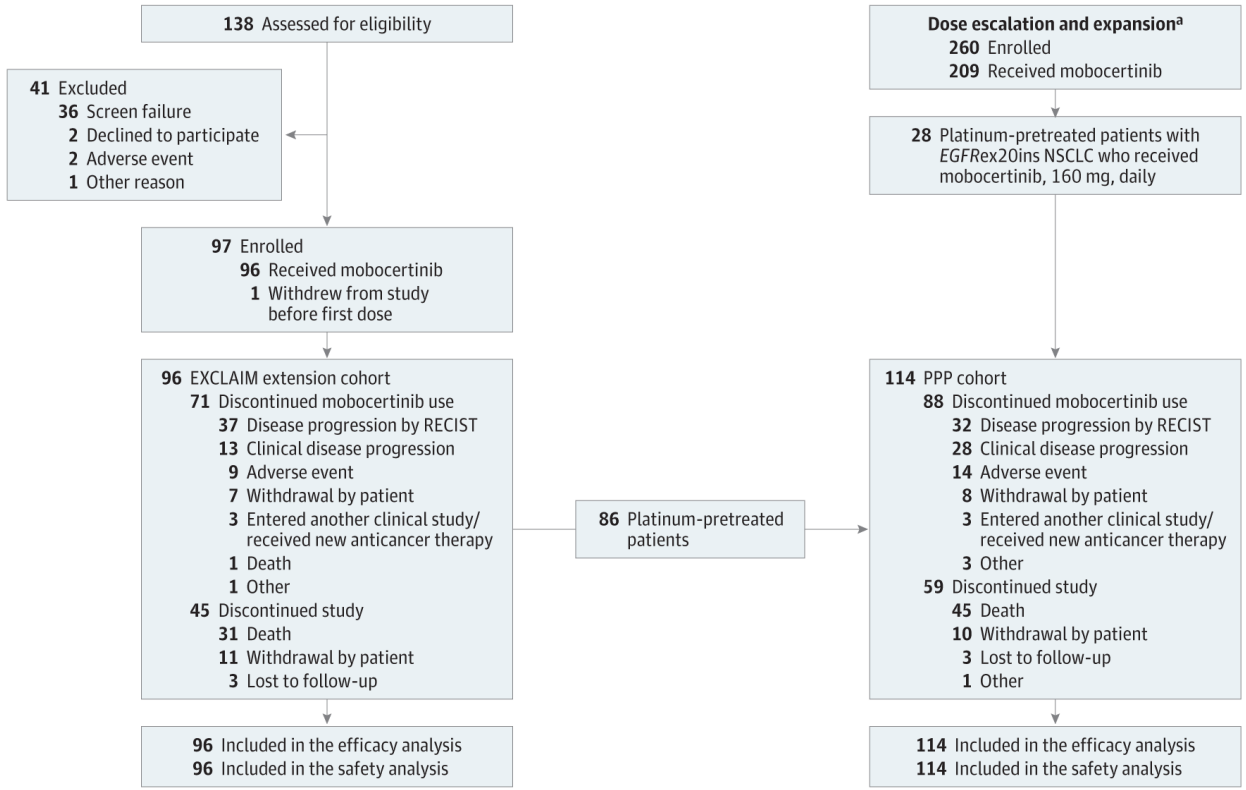
Zhou C. et al. NEJM 2023

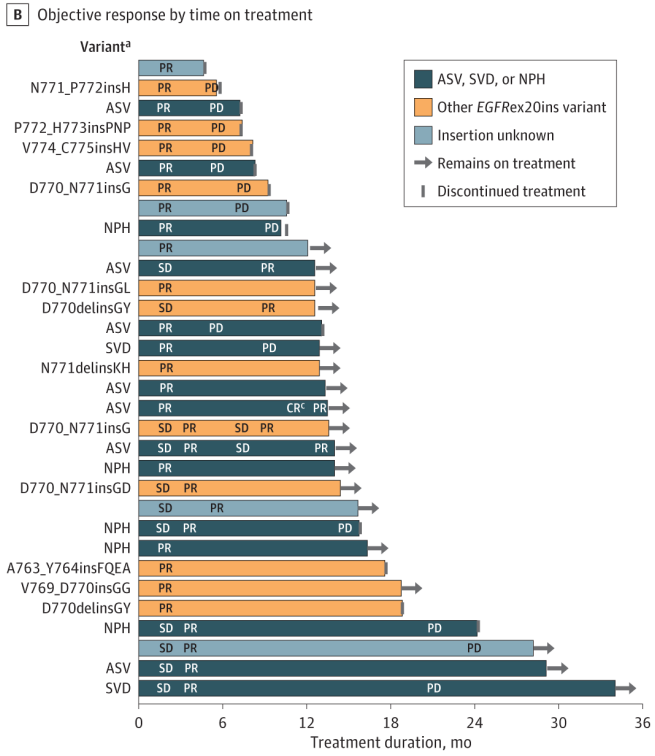
PAPILLON: Best Response and Interim Overall Survival

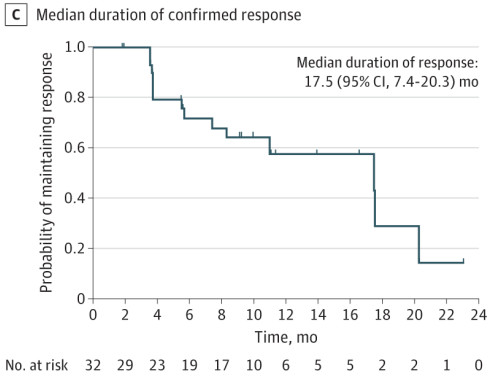


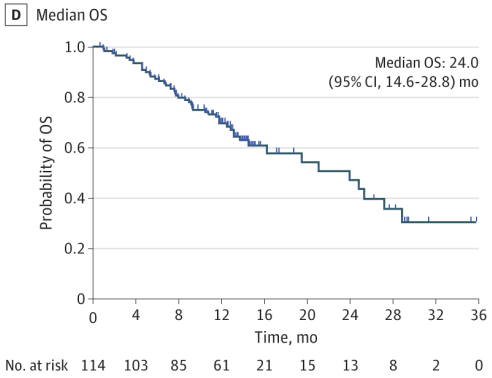


EXCLAIM Trial: Mobocertinib in Platinum-Pretreated Patients With EGFR Exon 20 Insertion-Positive Metastatic NSCLC



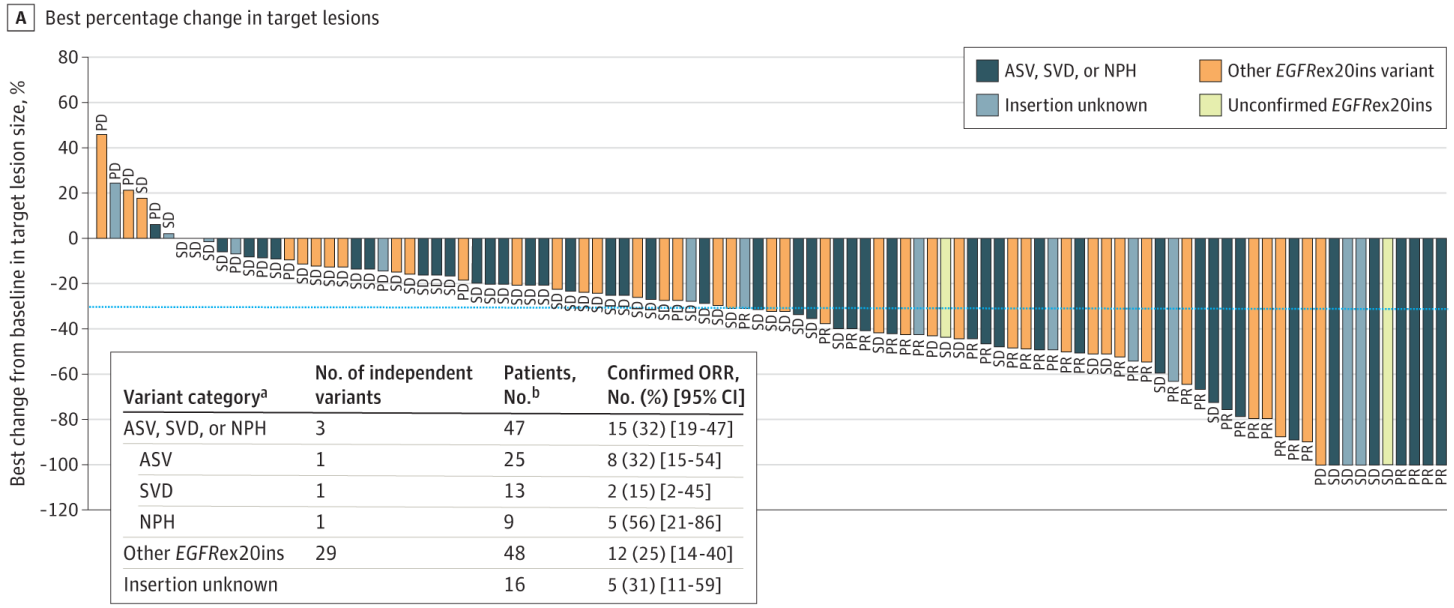






EXCLAIM Trial: Mobocertinib PFS

- The FDA has granted Breakthrough Therapy designation to mobocertinib



Variant category[a]	No. of independent variants	Patients, No.[b]	Confirmed ORR, No. (%) [95% CI]
ASV, SVD, or NPH	3	47	15 (32) [19-47]
ASV	1	25	8 (32) [15-54]
SVD	1	13	2 (15) [2-45]
NPH	1	9	5 (56) [21-86]
Other *EGFR*ex20ins	29	48	12 (25) [14-40]
Insertion unknown		16	5 (31) [11-59]

- **Overall median PFS:** 7.3 months
- In patients with and without brain metastases, the median PFS was 3.7 and 8.1 months, respectively
- Currently in phase III trial

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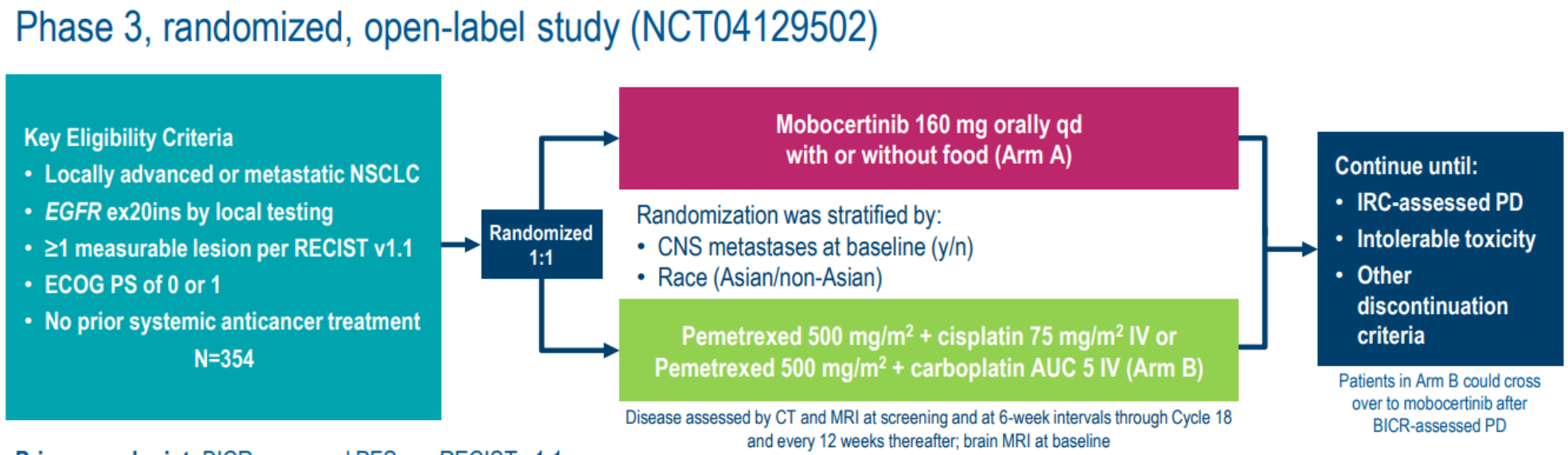
Vyse et al. Nature 2019
Presented by Lecia V. Sequist, Targeted Therapies in Lung Cancer 2020

EXCLAIM-2: First-Line Mobocertinib versus Chemotherapy in Exon 20 Positive NSCLC



Primary endpoint: BICR-assessed PFS per RECIST v1.1

Key secondary endpoints: BICR-assessed confirmed ORR and OS

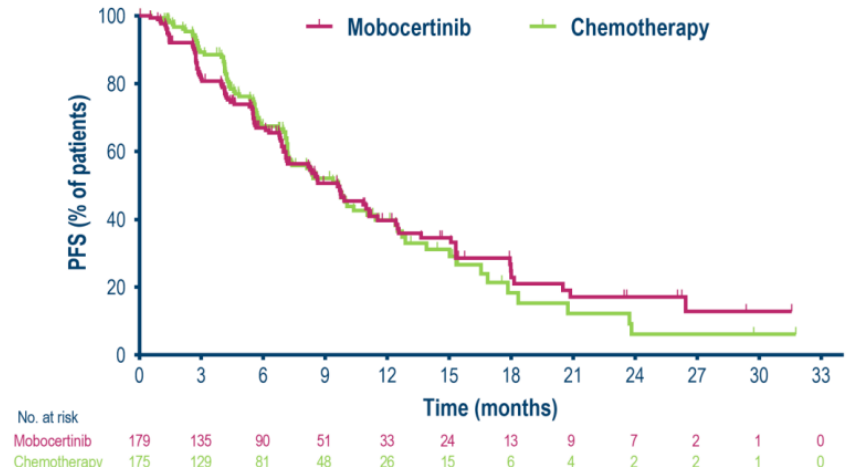
Other secondary endpoints included: DoR, time to response, DCR, and patient-reported symptoms (EORTC QLQ-C30, QLQ-LC13)

Exploratory endpoint: PFS by prespecified subgroups (age, gender, race, history of tobacco use, PS, disease stage, presence of brain metastases)

Statistical considerations: ~318 total patients (227 events) to detect a 3.5-month improvement in median PFS (HR=0.65)

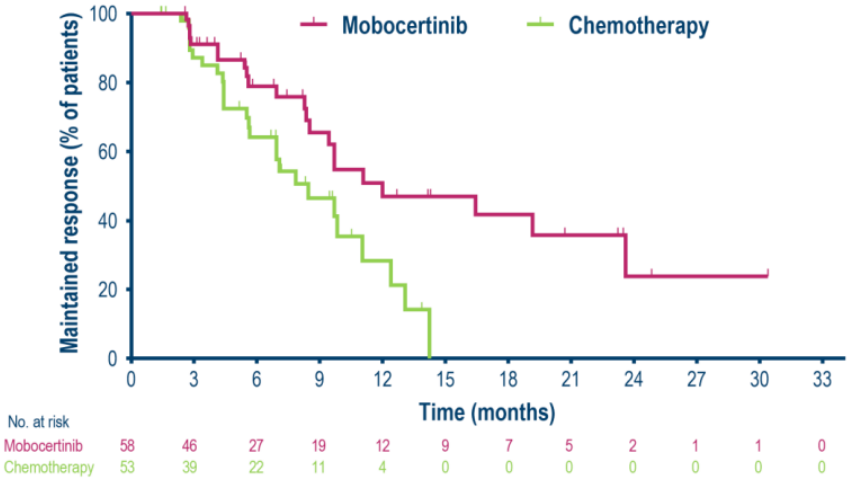
Mobocertinib is Not Superior to Chemotherapy in EGFR Exon 20 Positive NSCLC (EXCLAIM-2)

PFS



	Mobocertinib (n=179)	Chemotherapy (n=175)
PFS events, n (%)	98 (55)	86 (49)
Median PFS (95% CI), months	9.6 (7.1–11.1)	9.6 (7.2–11.4)
HR (95% CI)	1.04 (0.77–1.39) *P*=0.803	

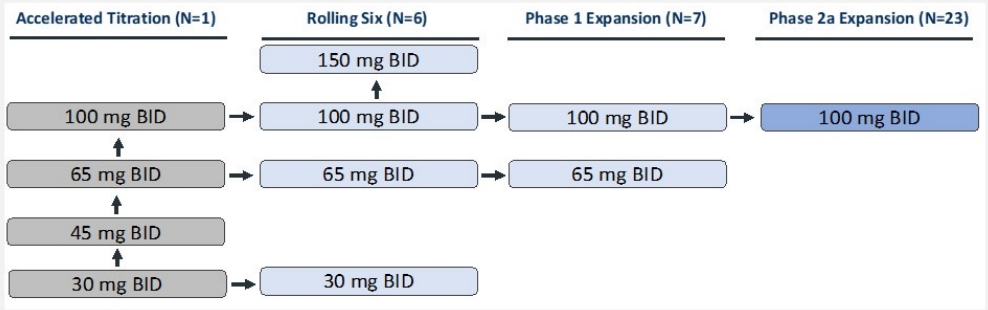
DoR



	Mobocertinib (n=58)	Chemotherapy (n=52)
Median DoR (95% CI), months	12.0 (8.5–23.6)	8.4 (5.7–11.0)
HR (95% CI)	0.48 (0.26–0.88)	

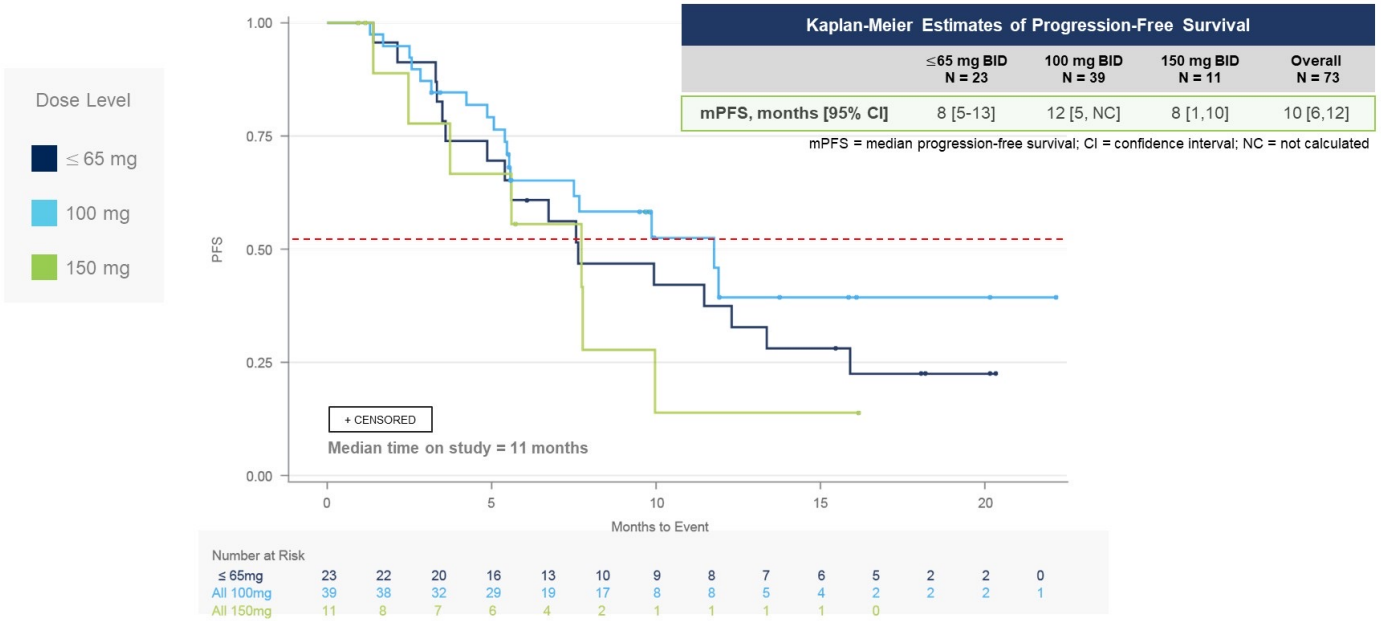
CLN-081 (Zipalertinib) in NSCLC Patients with Exon 20 Insertion Mutations

STUDY SCHEMA



- Dose escalation used both an accelerated titration and rolling-six design
- Phase 1 and Phase 2a dose expansion cohorts enrolled additional patients at dose levels meeting pre-defined thresholds for efficacy and tolerability

CLN-081-001: Progression-Free Survival (PFS) by dose level



Kaplan-Meier Estimates of Progression-Free Survival

	≤65 mg BID N = 23	100 mg BID N = 39	150 mg BID N = 11	Overall N = 73
mPFS, months [95% CI]	8 [5-13]	12 [5, NC]	8 [1,10]	10 [6,12]

mPFS = median progression-free survival; CI = confidence interval; NC = not calculated

- CLN-081 has shown an amenable safety profile and anti-tumor efficacy
- At 100 mg BID, ORR was 41%, mDOR was > 21 months, and mPFS of 12 months
- The FDA has granted Breakthrough Therapy designation for CLN-081

ECOG-ACRIN EA162: Phase II Study of High-Dose Osimertinib in NSCLC with EGFR Exon 20 Insertions

METHODS/STUDY DESIGN

KEY ELIGIBILITY
- Advanced NSCLC
- *EGFR* ins20 (local, CLIA-certified tissue assay)
- At least 1 prior line of therapy
- Stable, asymptomatic brain mets

TREATMENT REGIMEN
- **OSIMERTINIB 160mg DAILY**
- Until progression, intolerable toxicity or withdrawal

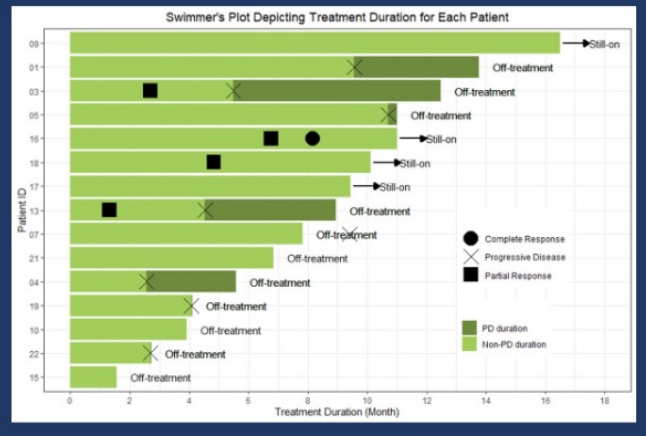
ENDPOINTS
- 1º: Objective response rate (ORR, RECIST 1.1)
- 2º: safety, progression-free survival (PFS) and overall survival.

- Osi 160 mg QS showed clinical activity with an ORR of 24%, disease control rate of 82%, and mPFS of 9.6 months

Fig 1. Waterfall Plot

OVERALL EFFICACY:
- **Confirmed ORR:** 4/17, 24%
- **DCR:** 14/17, 82%
- **mPFS:** 9.6 mo (95% CI, 4.1, 10.7)
- **mDOR:** NA (95% CI, 4.7, NA)

Fig 2. Swimmer's Plot



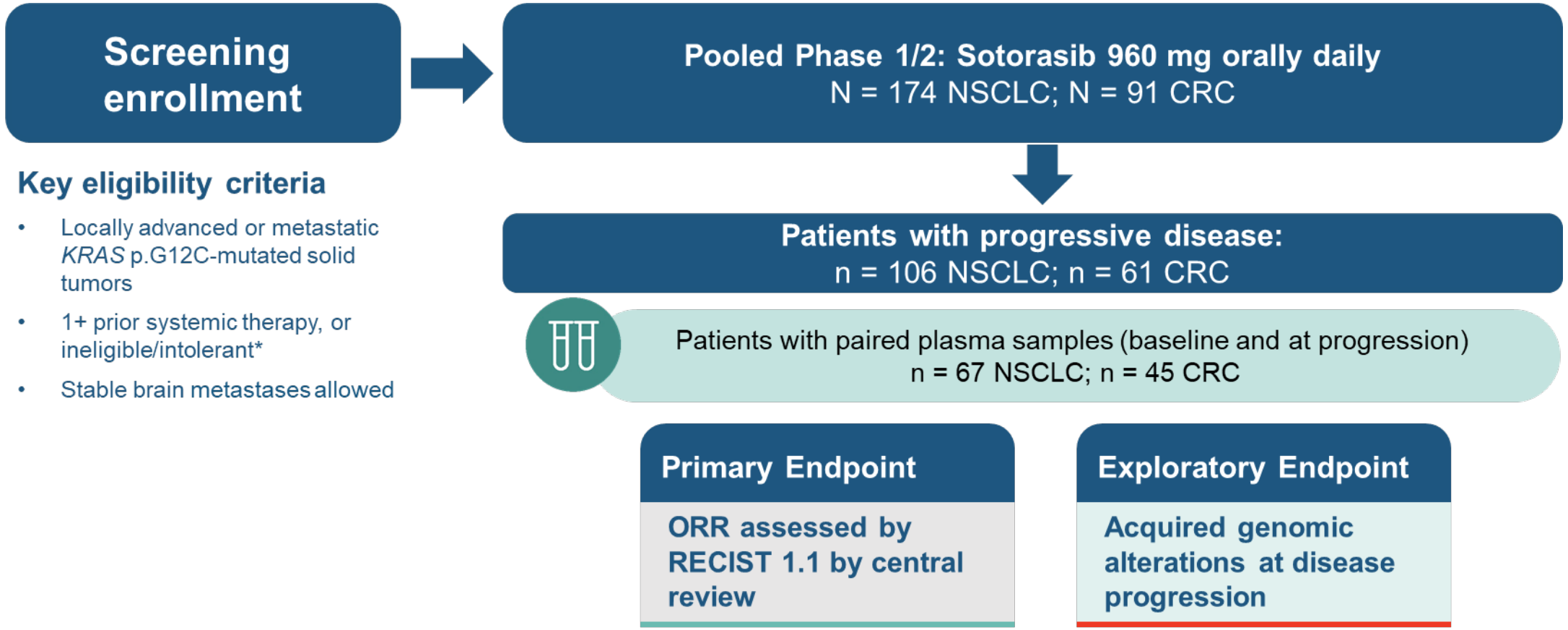
Conclusions

- Amivantamab is now FDA approved in exon 20 insertion-positive NSCLC
- Ongoing trials are investigating the TKIs as first-line or after progression on other EGFR TKIs/systemic therapy

Ongoing Trials	Agent	Phase
BAY2927088 in Participants Who Have Advanced NSCLC With EGFR/HER2 Mutations	BAY2927088	Phase 1
CLN-081 in Patients With Non-Small Cell Lung Cancer	CLN-081	Phase 1/2a
BLU-451 in Advanced Cancers With EGFR Exon 20 Insertion Mutations	BLU-451	Phase 1/2

KRASG12C

CodeBreaK100: Sotorasib Study Schema



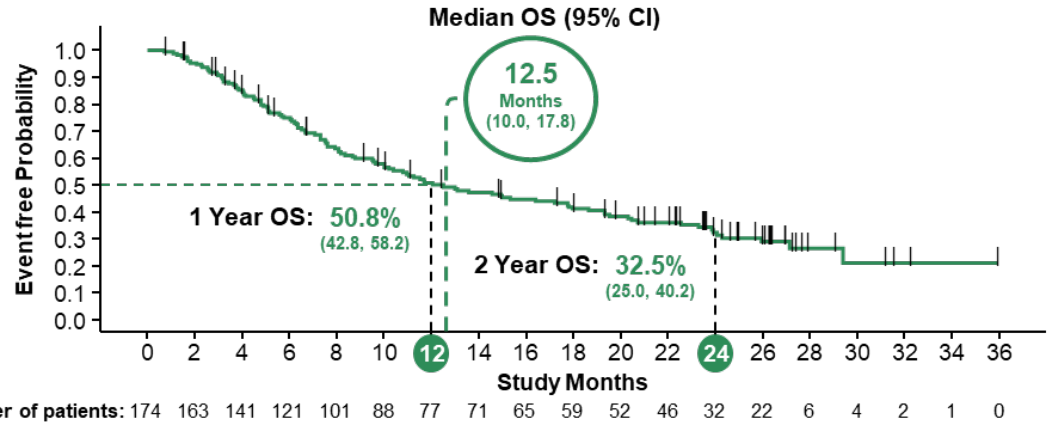
CodeBreaK100: Updated Survival of Sotorasib in KRAS+ NSCLC

Sotorasib, a selective KRAS^{G12C} inhibitor, is approved in the US and other countries in patients with previously treated *KRAS* p.G12C-mutated NSCLC[1-4]

In Phase 1/2 of the CodeBreaK 100 study,[5,6] sotorasib monotherapy demonstrated:

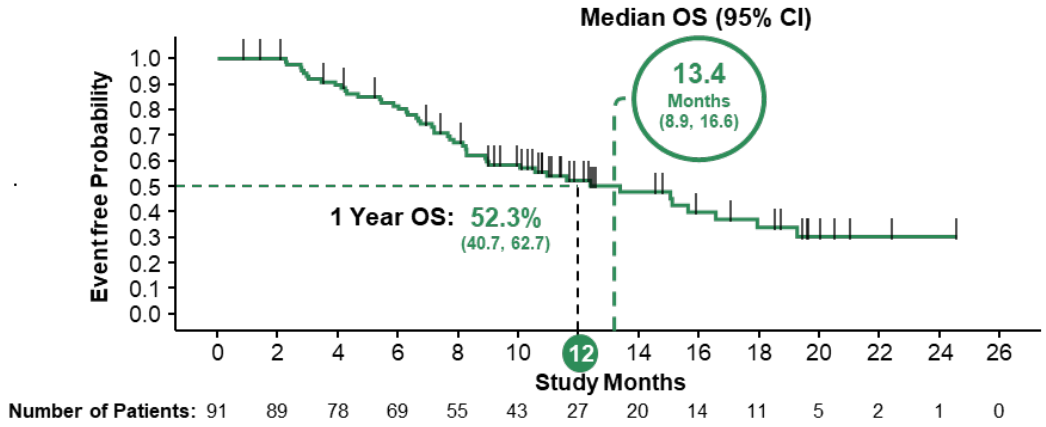
NSCLC

- **Objective response rate (ORR): 41%**
- Median progression-free survival (PFS): 6.3 months
- Disease control rate (DCR): 84%



CRC

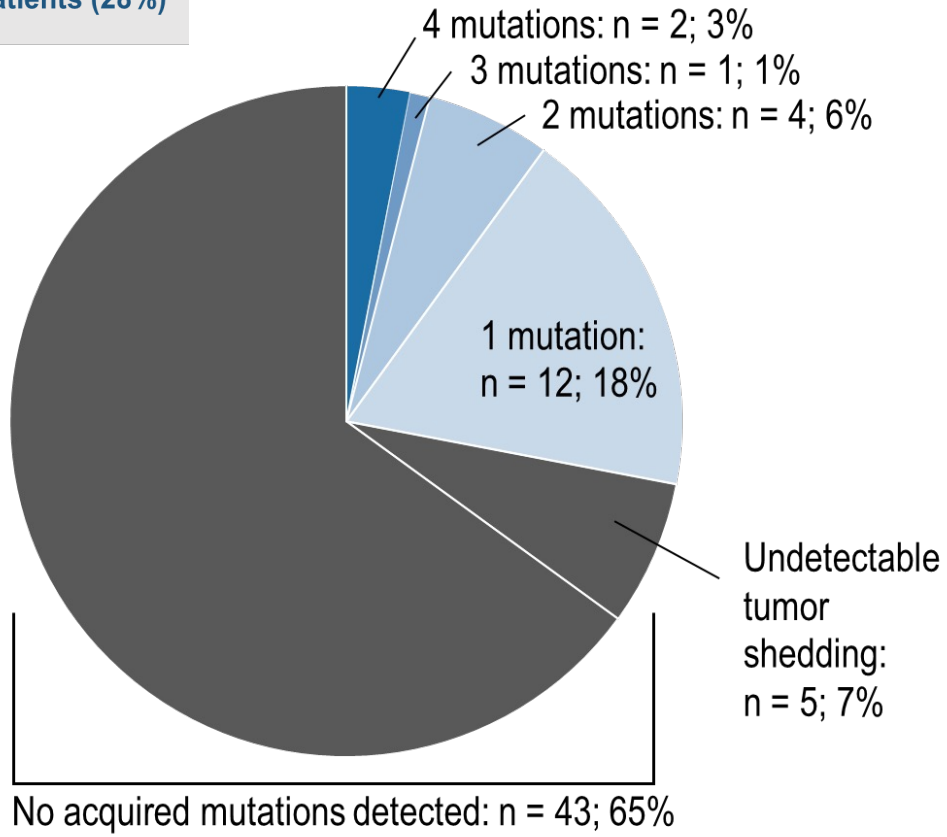
- **ORR: 12%**
- Median PFS: 4.2 months
- DCR: 82%



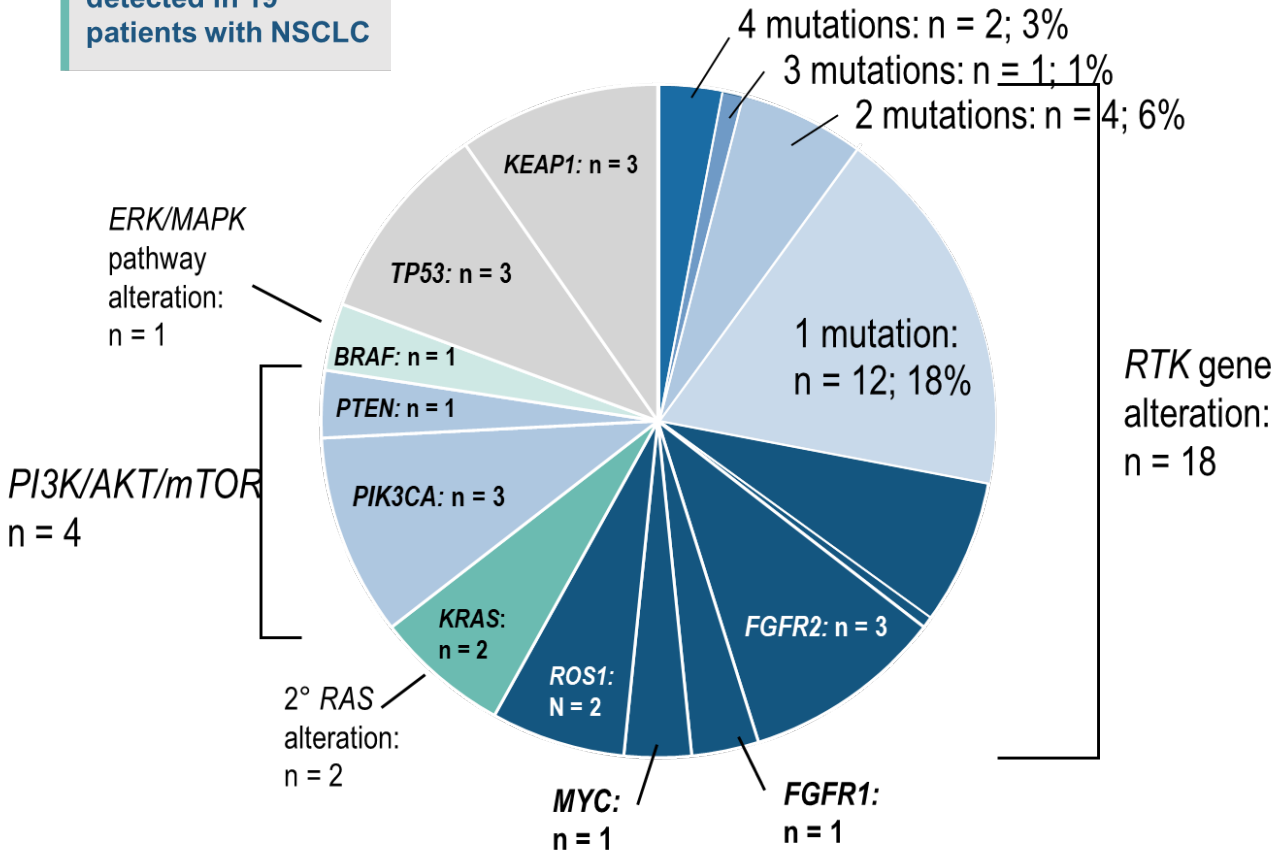
We describe putative mechanisms of acquired resistance to sotorasib from CodeBreaK 100, the largest single dataset evaluated to-date for a KRAS^{G12C} inhibitor

CodeBreaK100: NSCLC Biomarker Analysis

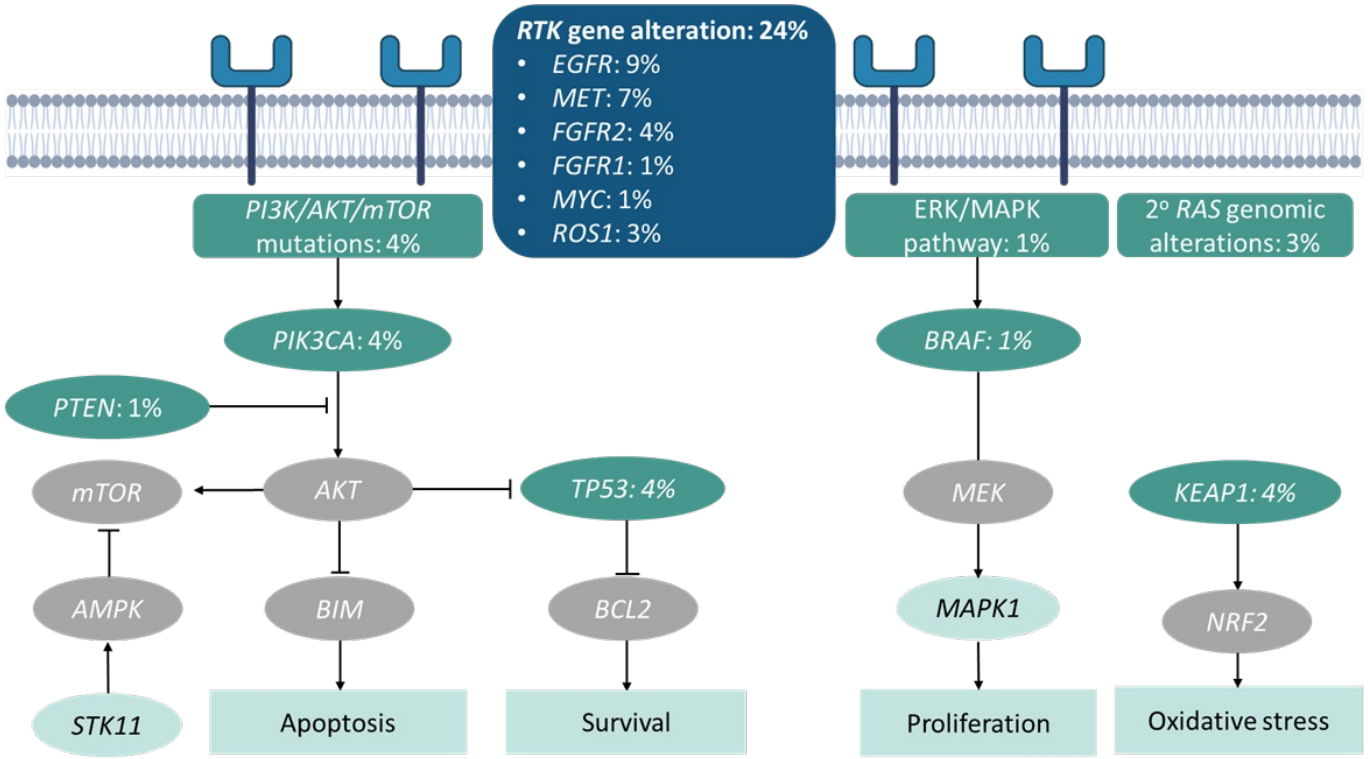
Acquired genomic alterations*:
n = 19 patients (28%)



In total, 31 acquired alterations were detected in 19 patients with NSCLC



CodeBreaK100: Putative Acquired Resistance Mechanisms to Sotorasib



OncoKB[1]

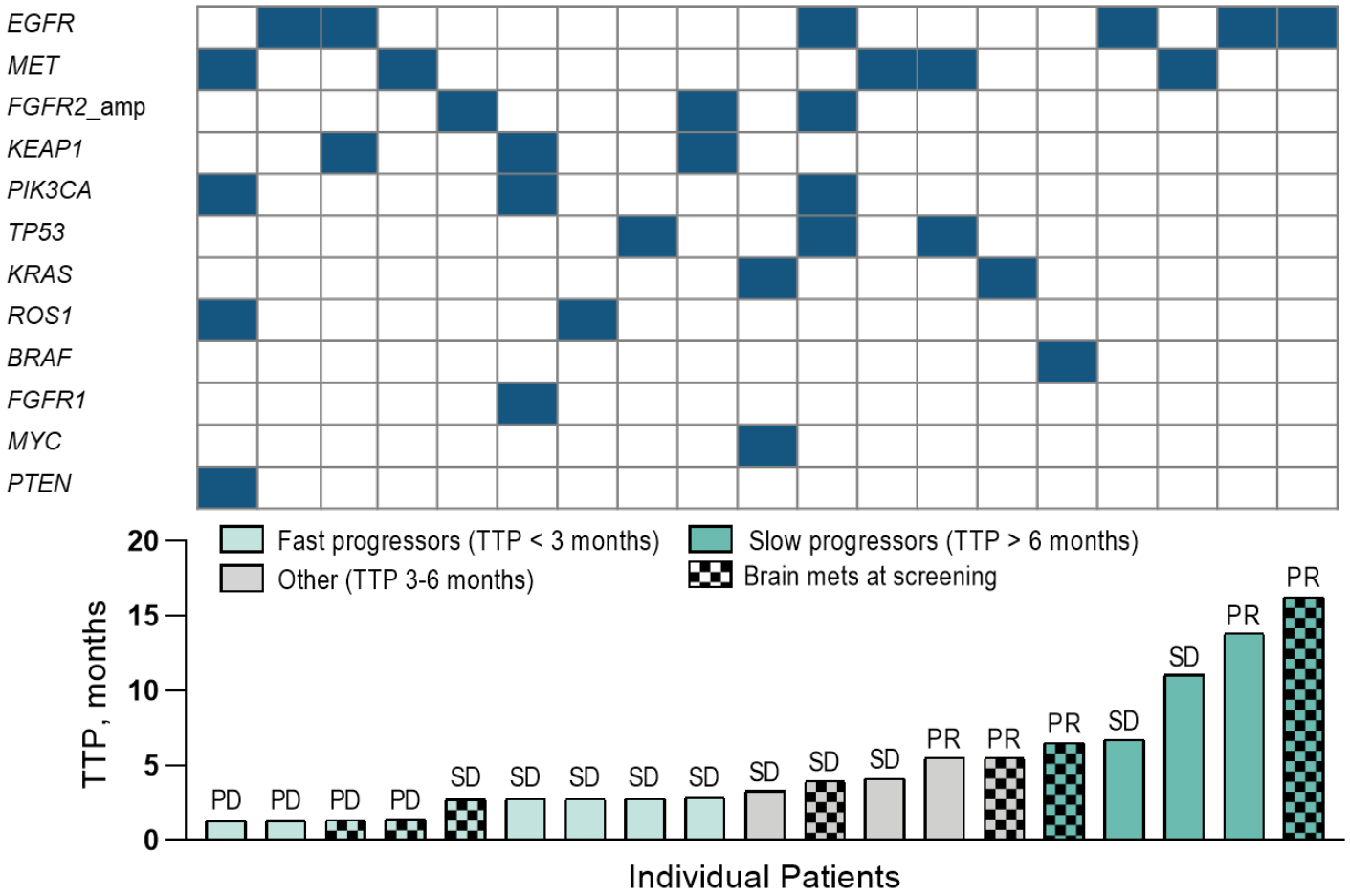
10/31 alterations were potentially targetable†

- Level 1: *PIK3CA* E542K (1)
  PIK3CA E545K (1)
- Level 2: *MET* amp. (3)‡
  BRAF K601E (1)‡
- Level 3: *FGFR1* amp. (1)
- Level 4: *EGFR* amp. (2)
  PTEN deletion (1)

***RTK* gene alterations: the most prevalent acquired genomic alteration in NSCLC patients (16/67 [24%])**

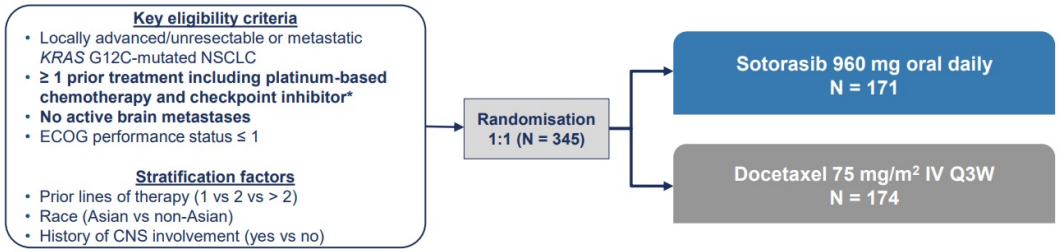
CodeBreaK100: Temporal Detection Patterns of Acquired Mutations

- **4 of 9 fast progressors versus 0 of 5 slow progressors had > 1 acquired mutation**
- 3/3 acquired *KEAP1* mutations in fast progressors
- 2/2 acquired *KRAS* mutations were not fast progressors
- 3/6 *EGFR* mutations observed in slow progressors

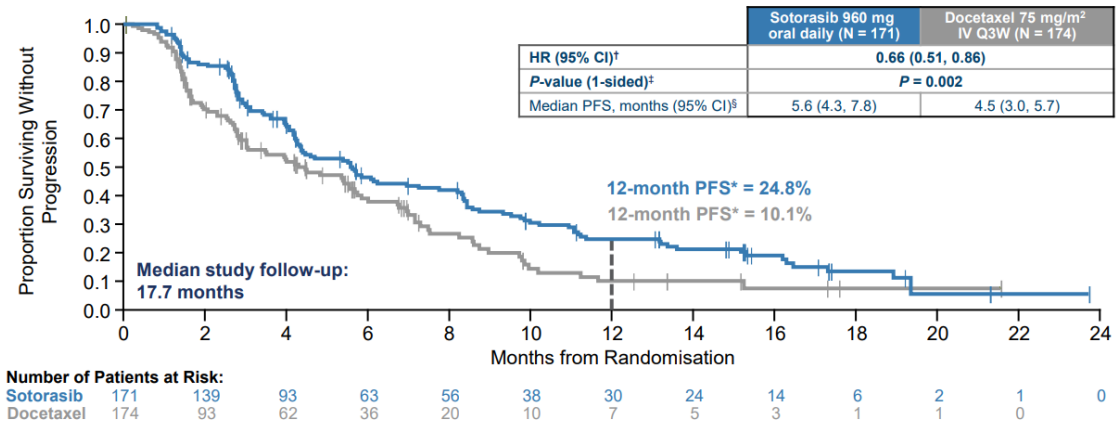


CodeBreak 200: Sotorasib versus Docetaxel

CodeBreaK 200 Phase 3 Study Design



PFS by BICR

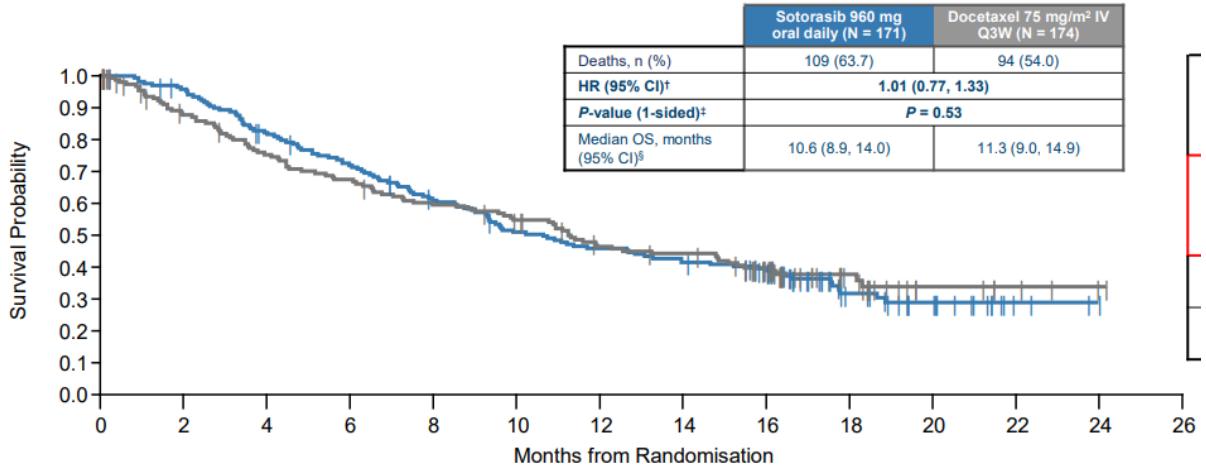


	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)

Number of Patients at Risk:

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

OS



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

Number of Patients at Risk:

Sotorasib	171	162	137	119	98	81	73	66	56	25	15	3	0
Docetaxel	174	135	115	103	90	81	65	61	44	20	7	4	1	0

CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

KRYSTAL-1: Adagrasib (MRTX849) in NSCLC Patients Harboring a KRAS G12C Mutation: Phase 2 Cohort A Study Design

Phase 2
NSCLC Monotherapy Treatment

Key Eligibility Criteria

- NSCLC with $KRAS^{G12C}$ mutation[a]
- Unresectable or metastatic disease
- Prior treatment with a PD-1/L1 inhibitor in combination or in sequence with chemotherapy
- Treated, stable CNS metastases were allowed

Adagrasib 600 mg BID (Capsule, Fasted)

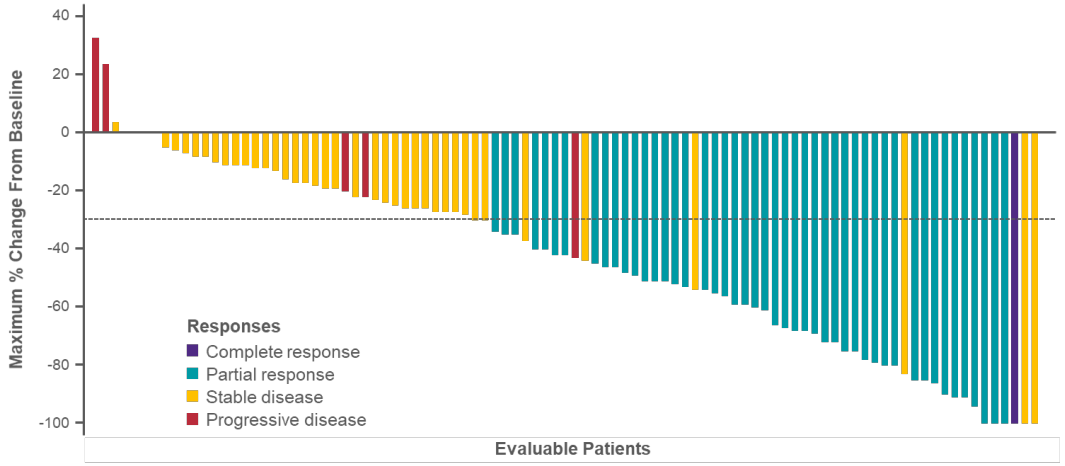
Study Objectives

- Primary endpoint: ORR (RECIST 1.1) per BICR
- Secondary endpoints: DOR, PFS, OS, safety

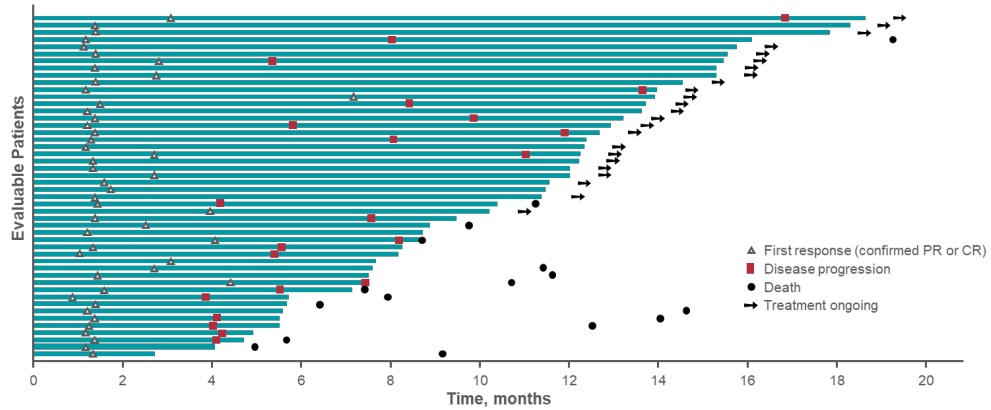
Here we report data from a registrational Phase 2 cohort evaluating adagrasib 600 mg BID in previously treated patients with NSCLC harboring a $KRAS^{G12C}$ mutation (N=116)

Enrollment period, January 2020 to December 2020

KRYSTAL-1: Best Tumor Change from Baseline and Duration of Response

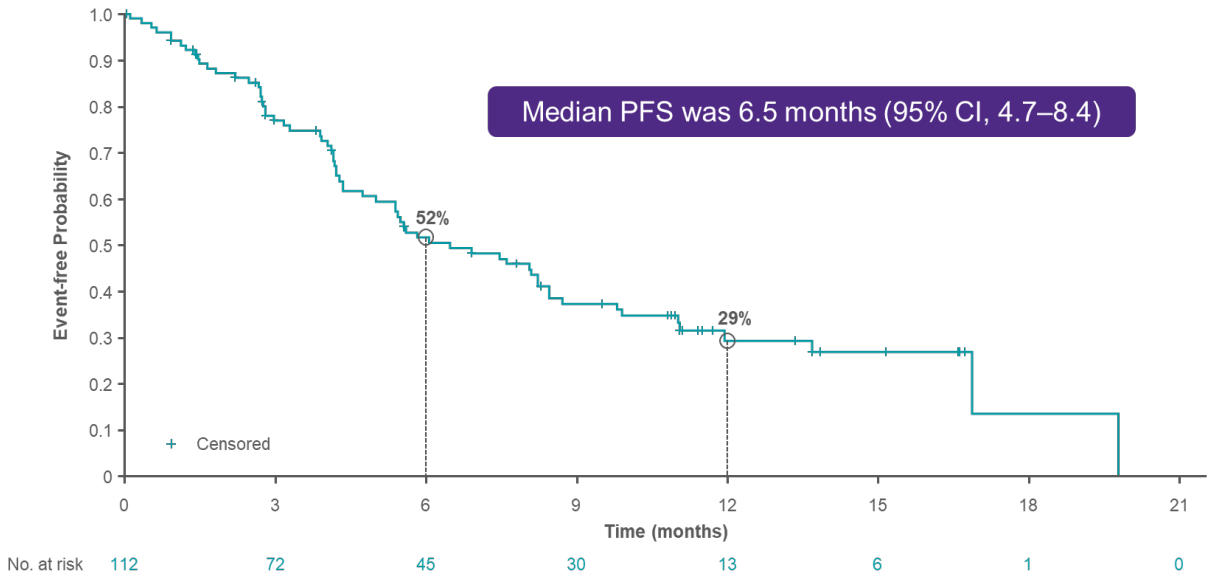


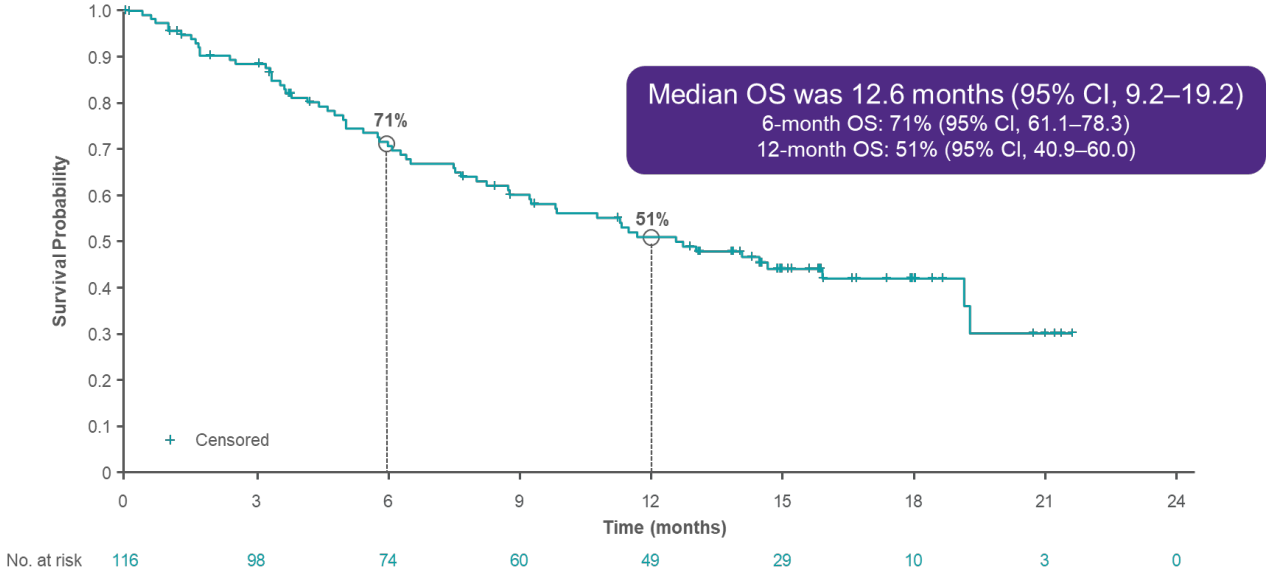
- Objective responses were observed in 43% (95% CI, 33.5–52.6); DCR was 80% (95% CI, 70.8–86.5)
- Responses were deep with 75% of responders achieving >50% tumor reduction



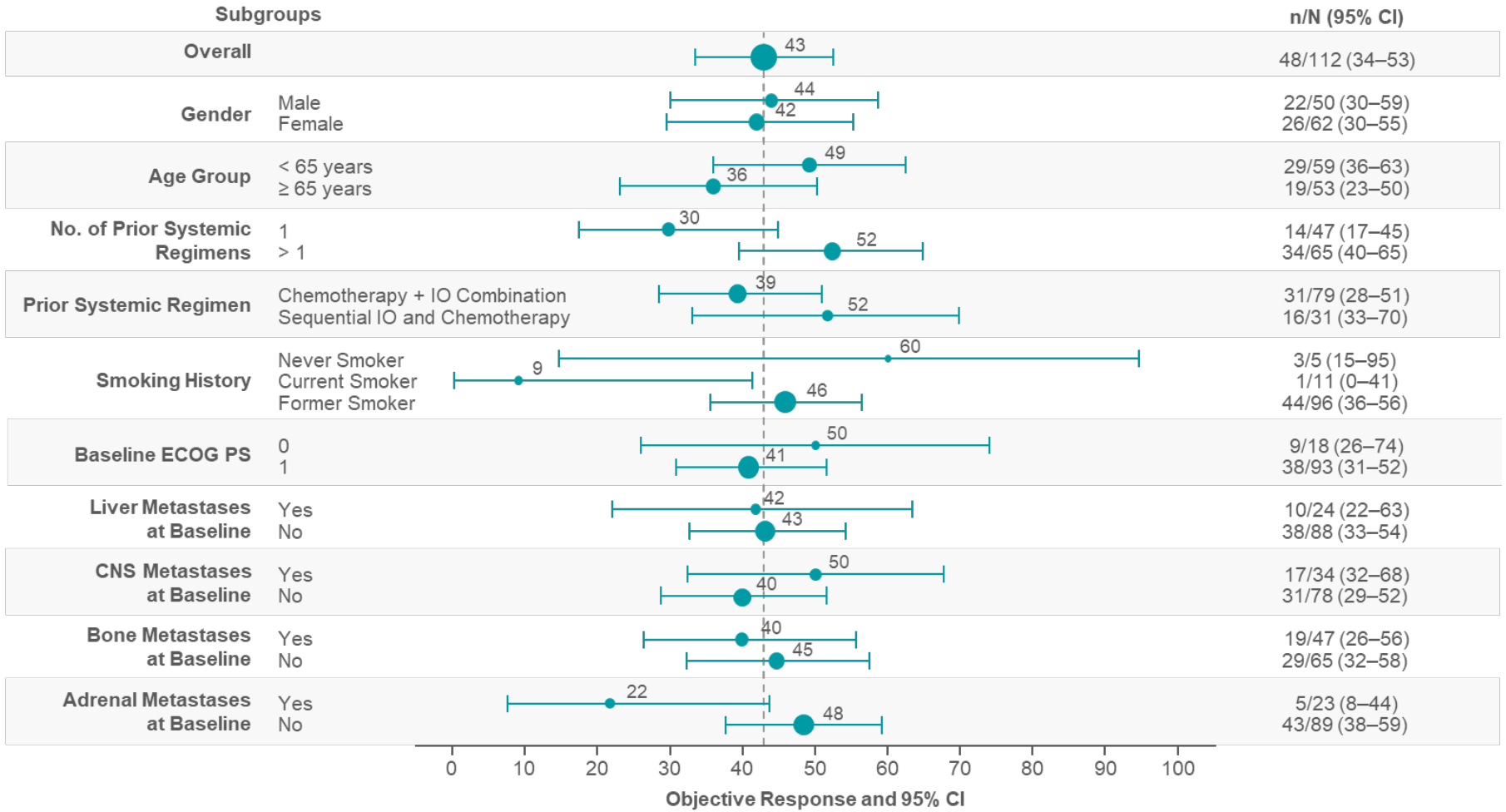
- Median TTR was 1.4 months (range, 0.9–7.2)
- Median DOR was 8.5 months (95% CI, 6.2–13.8)
- Treatment is ongoing in 50% (24/48) of patients who experienced a response, and 33% (16/48) are still in response

KRYSTAL-1: PFS and OS



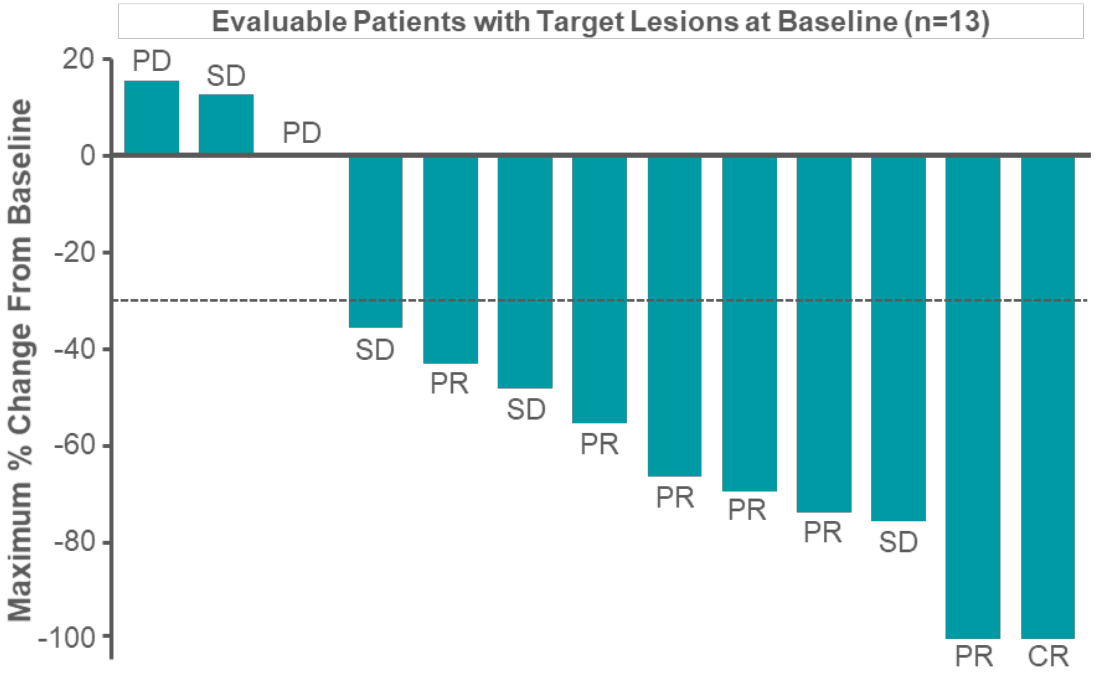


KRYSTAL-1: Exploratory Subgroup Analyses



KRYSTAL-1: Intracranial Response in Patients with Treated, Stable CNS Metastases

Best Overall Response	Overall (n=33)[b]	Patients with Non-target Lesions Only (n=19)	Patients with Target Lesions (n=13)[c]
IC ORR, n (%)	**11 (33%)**	**4 (21%)**	**7 (54%)**
Complete response	5 (15%)	4 (21%)	1 (8%)
Partial response	6 (18%)	-	6 (46%)
Stable disease	17 (52%)	13 (68%)	4 (31%)
IC DCR, n (%)	**28 (85%)**	**17 (89%)**	**11 (85%)**



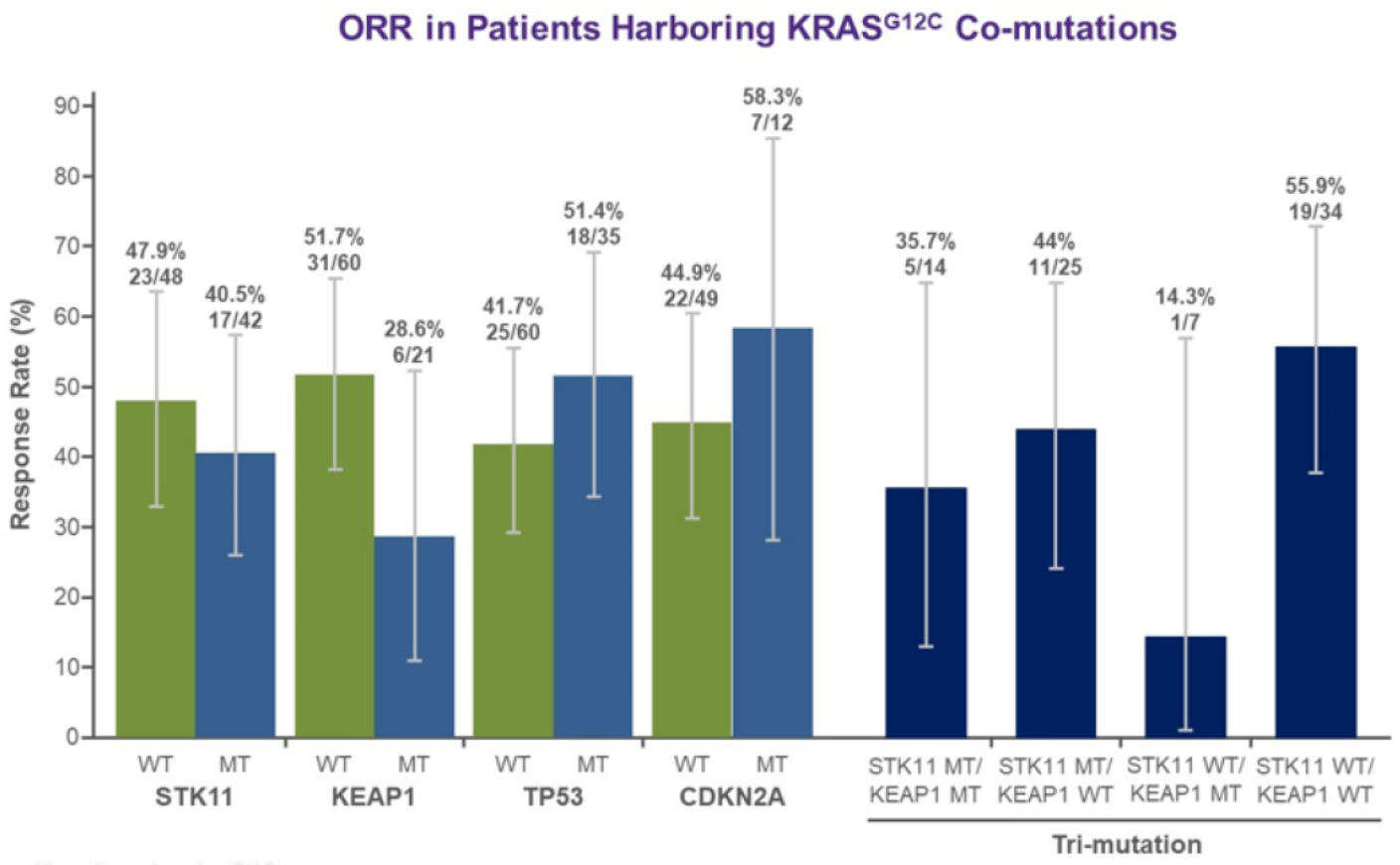
- IC ORR by modified RANO-BM was 33% (95% CI, 18–52); median IC DOR was 11.2 months (95% CI, 3.0–NE)
- IC DCR was 85% (95% CI, 68–95); median IC PFS was 5.4 months (95% CI, 3.3–11.6)

KRYSTAL-1: Treatment-Related Adverse Events

	Adagrasib Monotherapy (N=116) Capsule, Fasted	
TRAEs, n (%)	**Any Grade**	**Grades 3–4**
Any TRAEs	113 (97%)	50 (43%)
Most frequent TRAEs[a], n (%)		
Diarrhea	73 (63%)	1 (<1%)
Nausea	72 (62%)	5 (4%)
Vomiting	55 (47%)	1 (<1%)
Fatigue	47 (41%)	5 (4%)
ALT increase	32 (28%)	5 (4%)
Blood creatinine increase	30 (26%)	1 (<1%)
AST increase	29 (25%)	4 (3%)
Decreased appetite	28 (24%)	4 (3%)

- Grade 1–2 TRAEs occurred in 53% of patients
- There were 2 grade 5 TRAEs (cardiac failure [n=1] and pulmonary hemorrhage [n=1])
- TRAEs led to dose reduction in 60/116 (52%) patients[b] and to dose interruption in 71/116 (61%) patients
- TRAEs led to discontinuation of study drug in 8/116 (7%) patients

Preliminary Exploratory Correlative Analysis of Co-Mutations with KRASG12C & Response Rate in NSCLC Patients Treated with Adagrasib



GO42144: Divarasib (GDC-6036) in Solid Tumors with a KRAS G12C

ORIGINAL ARTICLE

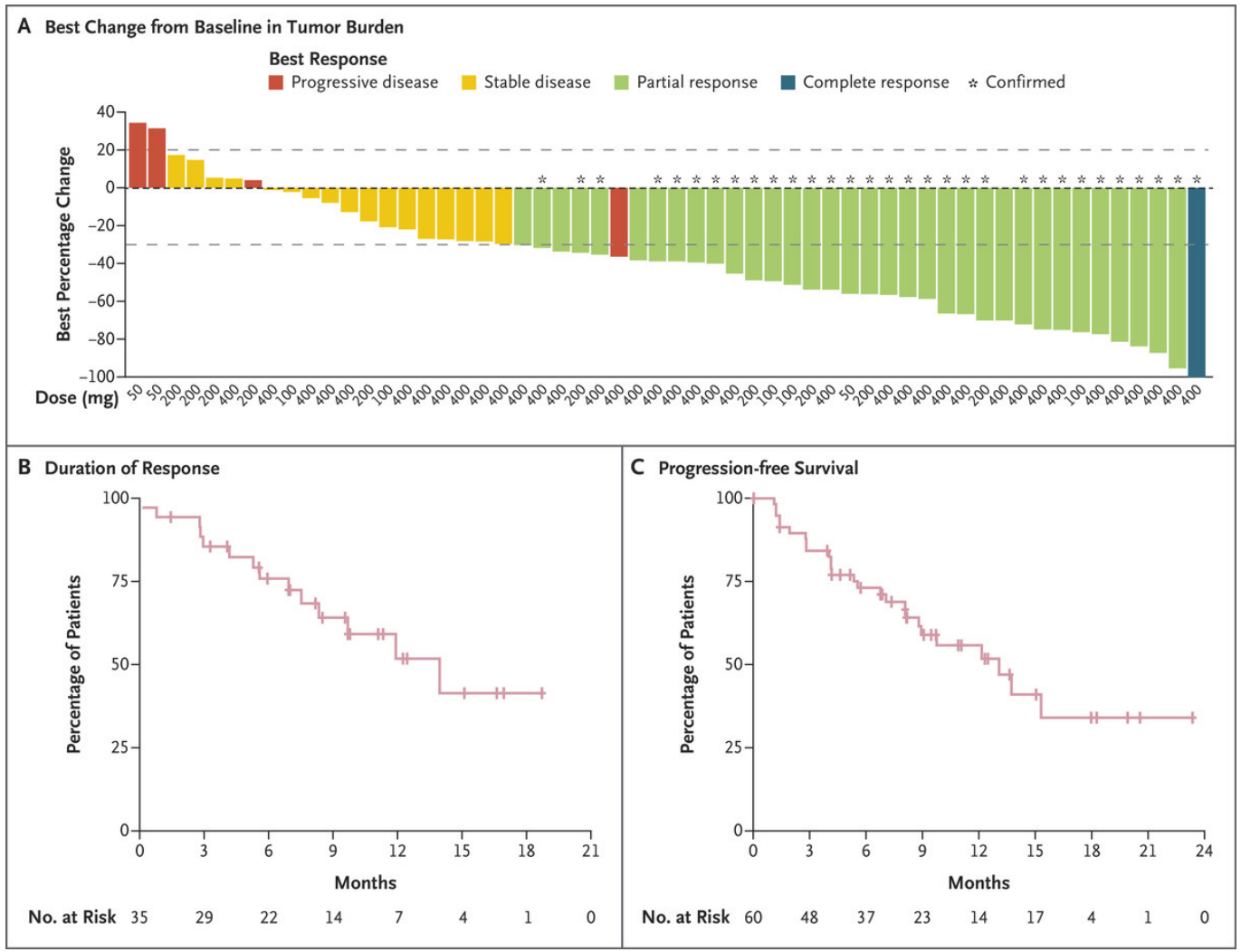
Single-Agent Divarasib (GDC-6036) in Solid Tumors with a *KRAS* G12C Mutation

Adrian Sacher, M.D., Patricia LoRusso, D.O., Manish R. Patel, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Elena Garralda, M.D., Martin D. Forster, M.D., Ph.D., Armando Santoro, M.D., Alejandro Falcon, M.D., Tae Won Kim, M.D., Ph.D., Luis Paz-Ares, M.D., Samantha Bowyer, M.B., B.Ch., M.P.H., Maria de Miguel, M.D., et al., for the GO42144 Investigator and Study Group*

Table 1. Patient Demographics and Disease Characteristics.*

Characteristic	NSCLC (N=60)	Colorectal Cancer (N=55)	Other Solid Tumors† (N=22)	All Patients (N=137)
Median age (range) — yr	67 (43–82)	62 (34–81)	64 (30–85)	65 (30–85)
Female sex — no. (%)	34 (57)	33 (60)	10 (45.5)	77 (56)
Race — no. (%)‡				
White	52 (87)	40 (73)	17 (77)	109 (80)
Asian	4 (7)	10 (18)	5 (23)	19 (14)
Black	1 (2)	0	0	1 (1)
Unknown	3 (5)	5 (9)	0	8 (6)
ECOG performance-status score — no. (%)§				
0	21 (35)	23 (43)	13 (59)	57 (42)
1	39 (65)	30 (57)	9 (41)	78 (58)
Previous systemic therapies — no. (%)				
0	1 (2)	0	0	1 (1)
1	23 (38)	6 (11)	4 (18)	33 (24)
2	17 (28)	14 (25)	7 (32)	38 (28)
3	11 (18)	15 (27)	2 (9)	28 (20)
≥4	8 (13)	20 (36)	9 (41)	37 (27)

Divarasib: Anti-Tumor Activity

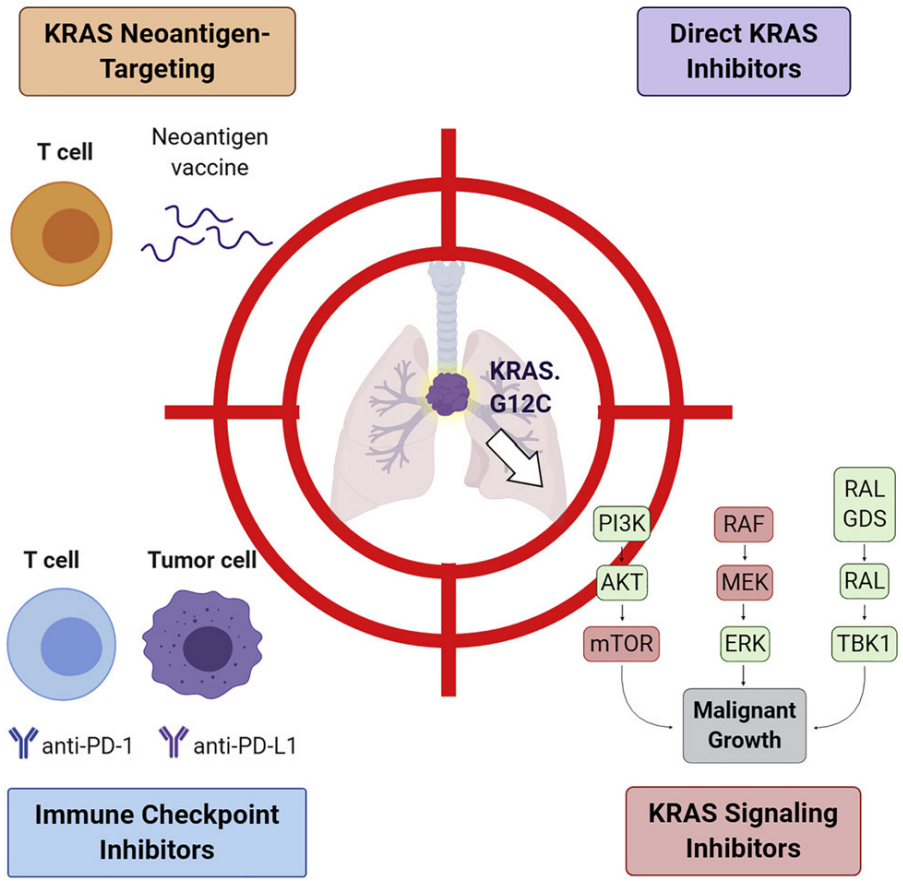


- Among patients with NSCLC, a confirmed response was observed in 53.4% of patients and the median progression-free survival was 13.1 months
- Treatment with divarasib resulted in durable clinical responses across KRAS G12C–positive tumors

Sacher A et al, NEJM 2023

Conclusions

- Sotorasib and adagrasib are approved in metastatic NSCLC patients who have received at least one prior systemic therapy
- Divarasib has shown promising activity with highest ORR and longest PFS
- Subgroup analysis of frontline trials show that chemo-immunotherapy is an effective approach for most KRAS G12C-mutated patients. Patient with co-mutations (eg. KEAP1/STK11) may benefit from a different approach
- CodeBreak 201 and KRYSTAL-7 will inform frontline use of KRAS G12C
- There are at least twelve KRAS G12C inhibitors being tested in clinical trials, either as a single agent or in combination



Salgia R et al, Cell Reports Medicine 2021

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