Targeted Therapy in Lung Cancer

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GenesisCare

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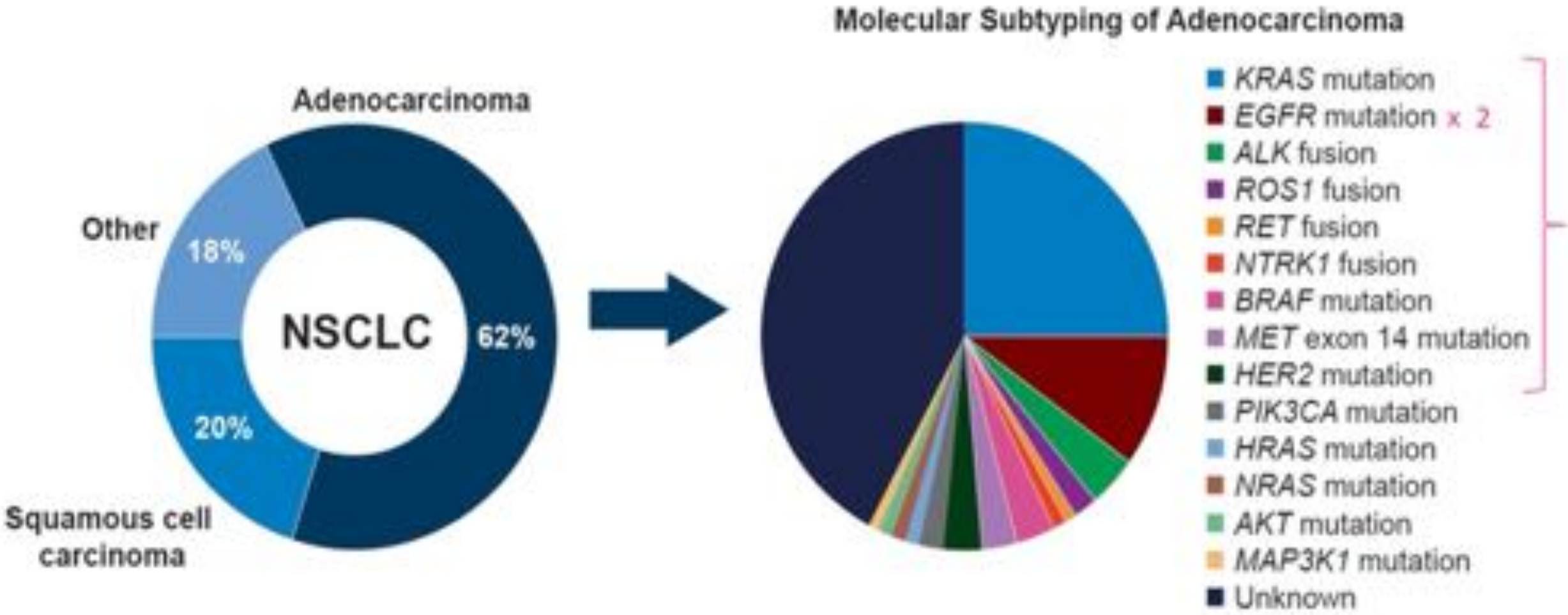
OLA

Targeted Therapy in NSCLC



Targeted Therapy for Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

EGFR Exon 19 Deletion or *L858R*
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Erlotinib + ramucirumab[7]
  - Erlotinib + bevacizumab[8] (nonsquamous)[8]
- Subsequent therapy
  - Osimertinib[9]

EGFR S768I, L861Q, and/or *G719X*
- First-line therapy
  - Afatinib[1,10]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,11]
- Subsequent therapy
  - Osimertinib[9]

EGFR Exon 20 Insertion Mutation Positive
- Subsequent therapy
  - Amivantamab-vmjw[12]
  - Mobocertinib[13]

KRAS G12C Mutation Positive
- Subsequent therapy
  - Sotorasib[14]

ALK Rearrangement Positive
- First-line therapy
  - Alectinib[15,16]
  - Brigatinib[17]
  - Ceritinib[18]
  - Crizotinib[15,19]
  - Lorlatinib[20]
- Subsequent therapy
  - Alectinib[21,22]
  - Brigatinib[23]
  - Ceritinib[24]
  - Lorlatinib[25]

ROS1 Rearrangement Positive
- First-line therapy
  - Ceritinib[24]
  - Crizotinib[27]
  - Entrectinib[28]
- Subsequent therapy
  - Lorlatinib[29]
  - Entrectinib[28]

BRAF V600E Mutation Positive
- First-line therapy
  - Dabrafenib/trametinib[30,31]
  - Dabrafenib[30]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[31,32]

NTRK1/2/3 Gene Fusion Positive
- First-line/Subsequent therapy
  - Larotrectinib[33]
  - Entrectinib[34]

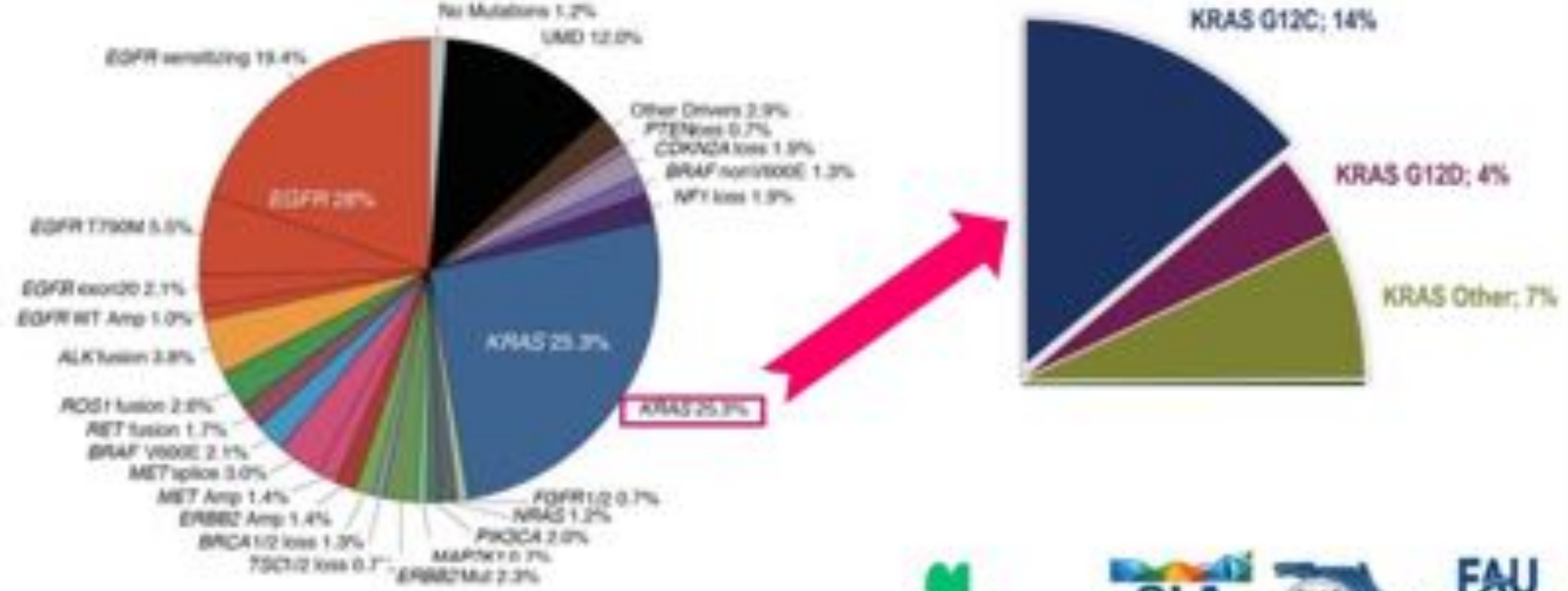
MET Exon 14 Skipping Mutation
- First-line therapy/Subsequent therapy
  - Capmatinib[35]
  - Crizotinib[36]
  - Tepotinib[37]

RET Rearrangement Positive
- First-line therapy/Subsequent therapy
  - Selpercatinib[38]
  - Pralsetinib[39]
  - Cabozantinib[40,41]

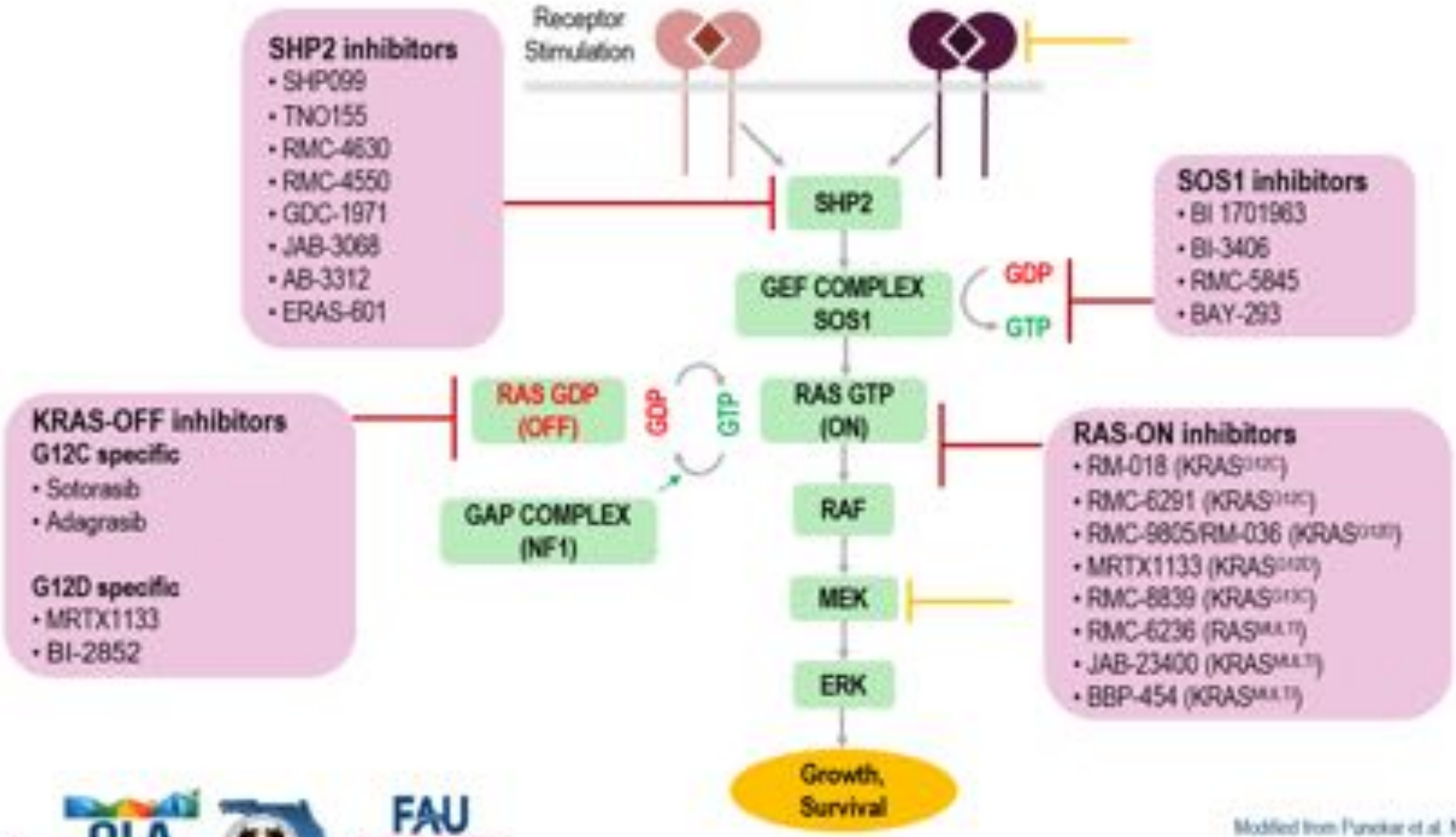
ERBB2 (HER2) Mutation Positive
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[42]
  - Ado-trastuzumab emtansine[43]

NCCN version 4.2022, 09/02/2022

K-RAS^{G12C} Pathway



Targeting KRAS: The Beating Heart Of Cancer



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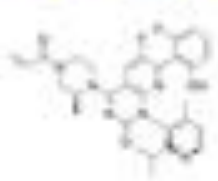
Modified from Punekar et al. Nat Rev Clin Oncol (2022) and AACR-NCI-EORTC 2019

+15 KRAS^{G12C} inhibitors under clinical development in NSCLC

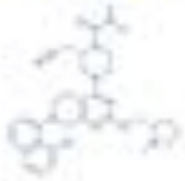
Drug	Status	ClinicalTrials.gov NCT No.
Sotorasib, AMG510	FDA & EMA approved (2L NSCLC)	NCT03600883, CodeBreaK 100
Adagrasib, MRTX849	FDA NDA submitted	NCT03785249, KRYSTAL-1
JDQ443	Phase I-II	NCT04699188
GDC-6036	Phase I-II	NCT04449874
JNJ74699157	FIH; discontinued	NCT04006301
MK-1084	Phase I	NCT05067283
BI-1823911	Phase Ia/Ib	NCT04973163
JAB-21822	Phase I-II	NCT05002270
LY3537982	Phase Ia/Ib	NCT04956640
D-1553	Phase I-II	NCT04585035
D3S-001	Phase I	NCT05410145
GFH925	Phase I-II	NCT05005234
YL15293	Phase I-II	NCT05173805
GH35	Phase I	NCT05010694
HS10370	Phase I-II	NCT05367778
BPI-421286	Phase I	NCT05315180
HBI-2438 (	Phase I	NCT05485974

KRAS G12C inhibitors in NSCLC

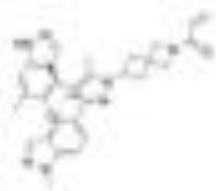
Clinical activity



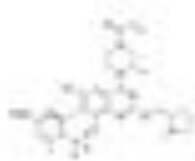
Sotorasib (AMG510)



Adagrasib (MRTX849)



JDQ443



GDC-6036

	CodeBreak 100 (n=126)	KRYSTAL-1 (n=116)	KontRASt-01 (n=20)	GDC-6036 (n=56)
Half-life (h)	5.5	23	N/A	15
Dose	960 mg QD*	600 mg BID**	200 mg BID	400 mg QD
ORR (%)	37.1	42.9	35.0	46.0
DCR (%)	80.6	79.5	-	-
mDoR (mo)	11.1	8.5	-	-
mPFS (mo)	6.8	6.5	-	-
OS	12.5 months	12.6 months	-	-
CNS activity (treated, stable)	icORR 13%	icORR 33%	N/A	N/A

*Exploratory dose of 450mg vs 960 mg ongoing
**Evaluation of alternative dosing of 400 mg bid is ongoing

Hong et al. NEJM (2020); Janne et al. NEJM (2022); Tan et al. AACR 2022; Sacher et al. WCLC 2022

KRAS G12C inhibitors in NSCLC

Safety profile

	Sotorasib (AMG510)	Adagrasib (MRTX849)	JDQ443	GDC-6036
AEs (%)	**CodeBreak 100 (n=126)**	**KRYSTAL-1 (n=116)**	**KontRASt-01 (n=20)**	**GDC-6036 (n=56)**
Dose	960 mg QD*	600 mg BID**	200 mg BID	400 mg QD
TRAEs	69.8	97.4	64	88.1
TRAES G≥2	20.6	44.8	10.3	16.9
Dose reduction	22.2	51.7	2.6	19.0
Discontinuation rate	7.1	6.9	2.6	5.0

- Most common TRAEs include nausea, diarrhea, vomiting, fatigue, decreased appetite, ALT/AST increase, dyspepsia.
- Most events Grade 1, occurred early in study treatment
- AEs were manageable with supportive medications and dose modifications

Hong et al. NEJM (2020), Janne et al. NEJM (2022)

Tan et al. AACR 2022, Sacher et al. WCLC 2022

KRAS G12C inhibitors in previously treated advanced NSCLC:

Trial design

- Prior treatment with a PD-(L)1 inhibitor and chemotherapy
- Treated brain metastases

Sotorasib	Adagrasib	JDQ443	GDC-6036
CodeBreak 200	KRYSTAL-12	KontRASt-02	BFAST (cohort G)
N=345	N=340	N=360	N=301

LBA 10: Sotorasib vs docetaxel for previously treated NSCLC with KRAS G12C mutation: CodeBreak 200 phase III study

Lead Author: M Jonhson

Date/Time: Sept 12th, 16:30 – 18:15

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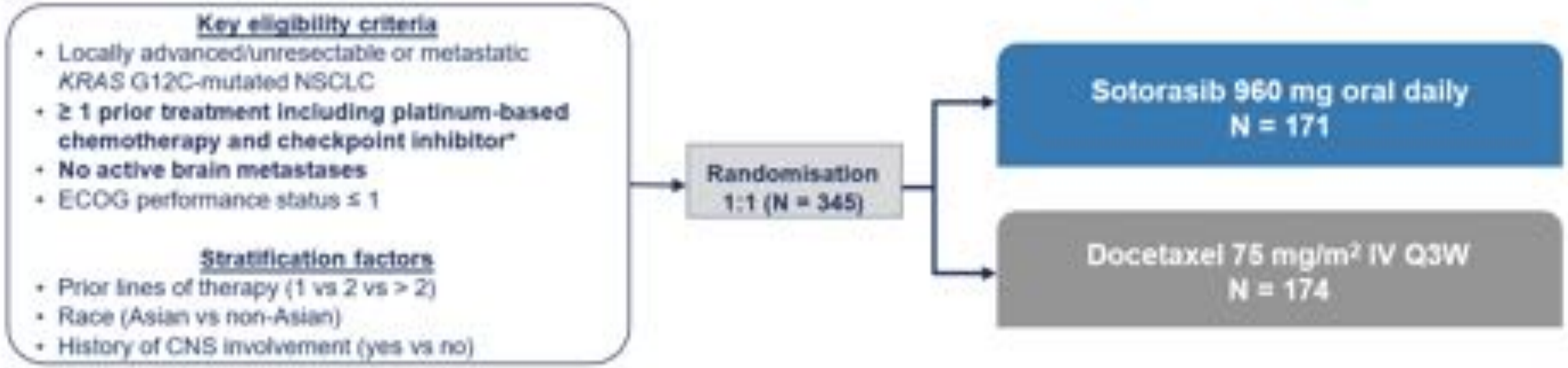
ClinicalTrials.gov accessed on August 30th, 2022: 1. NCT04303780; 2. NCT04685135; 3. NCT05132075; 4. NCT03178552

CodeBreaK 200 Phase 3 Study Design



Primary Endpoint: PFS by BICR

Secondary Endpoints: Efficacy (OS†, ORR, DOR, TTR, DCR), **safety/tolerability, PRO**

ITT population analysis included all randomised patients

Per regulatory guidance, protocol was amended to reduce planned enrolment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted.

Enrollment period: June 4, 2020 to April 26, 2021; protocol amendment: February 15, 2021; data cutoff: August 2, 2022.

NCT04303780; EudraCT: 2019-003582-18.

*Treatment with chemotherapy and checkpoint inhibitor could be concurrent or sequential; patients with medical contraindication to these therapies could be included with approval.

†Analysis of OS planned if PFS was found to be statistically significant and when at least 196 OS events have been reached.

Melissa L. Johnson, MD. 2022 ESMO Congress, September 12; Paris, France.

Baseline Characteristics

	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Age, median (range), years	64.0 (32, 88)	64.0 (35, 87)
Female, n (%)	62 (36.3)	79 (45.4)
North America/Europe/Other*, %	11.7 / 73.7 / 14.6	12.6 / 72.4 / 14.9
Race, Asian, n (%)	21 (12.3)	22 (12.6)
Smoking history (current or former), n (%)	166 (97.1)	166 (95.4)
ECOG performance status 1, n (%)	112 (65.5)	115 (66.1)
History of CNS involvement, n (%)	58 (33.9)	60 (34.5)
Liver metastasis, n (%)	30 (17.5)	35 (20.1)
Prior lines of therapy†, n (%)		
1	77 (45.0)	78 (44.8)
2	65 (38.0)	69 (39.7)
>2	29 (17.0)	27 (15.5)
PD-L1 expression, n (%)		
<1%	57 (33.3)	55 (31.6)
≥1–<50%	46 (26.9)	70 (40.2)
≥50%	60 (35.1)	40 (23.0)

*Other includes South America, Asia, and Australia. †Prior lines of therapy for advanced disease

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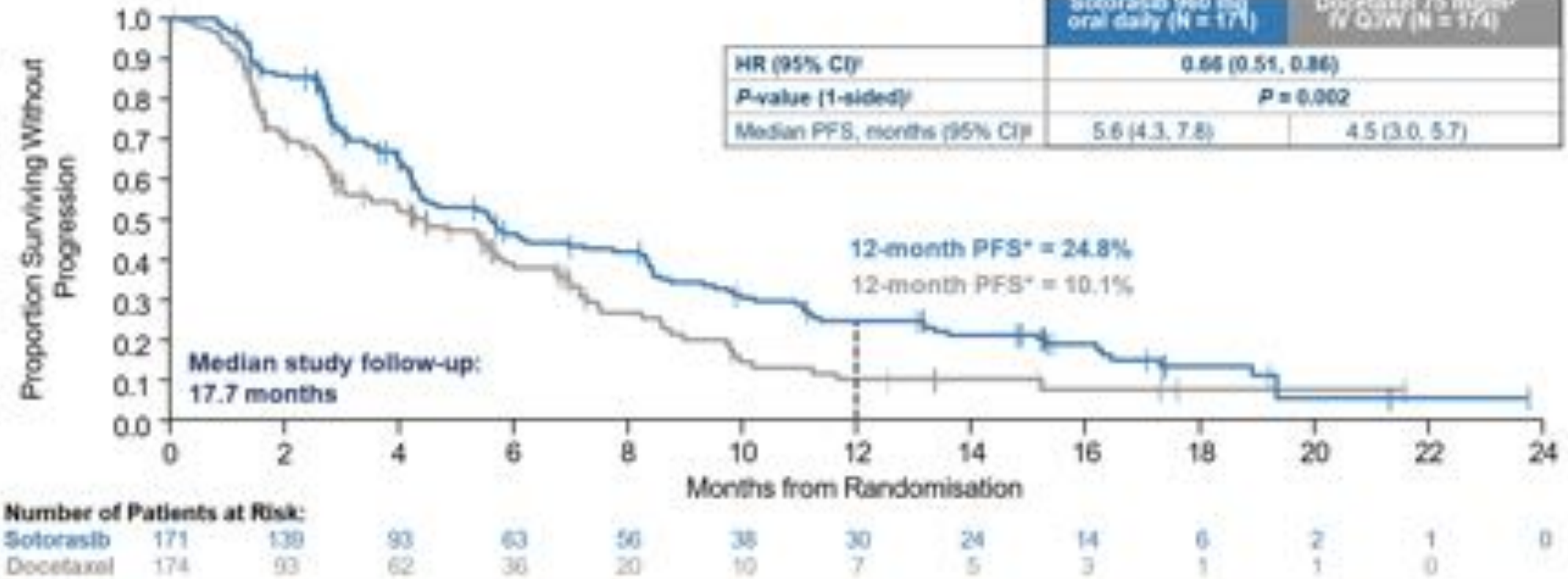
Primary Endpoint: PFS by BICR



	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)

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

*PFS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model.
‡P-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

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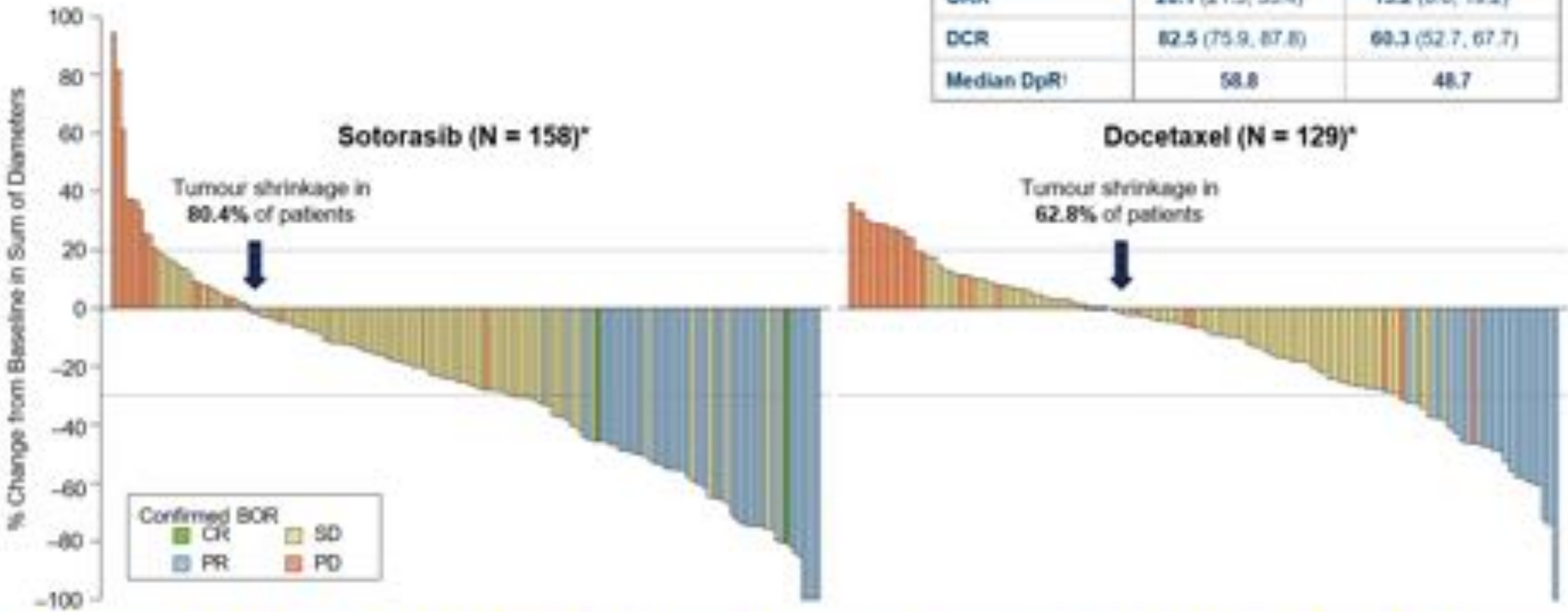
Tumour Response by BICR

% (95% CI)	Sotorasib	Docetaxel
ORR	**28.1** (21.5, 35.4)	**13.2** (8.6, 19.2)
DCR	**82.5** (75.9, 87.8)	**60.3** (52.7, 67.7)
Median DpR[†]	58.8	48.7



Response rate was significantly higher with sotorasib versus docetaxel ($P < 0.001$)

*Patients without baseline target lesions or post-baseline percent changes, or with BOR of NE are not shown.
†Median of best percent change from baseline in sum of diameters for confirmed responders.

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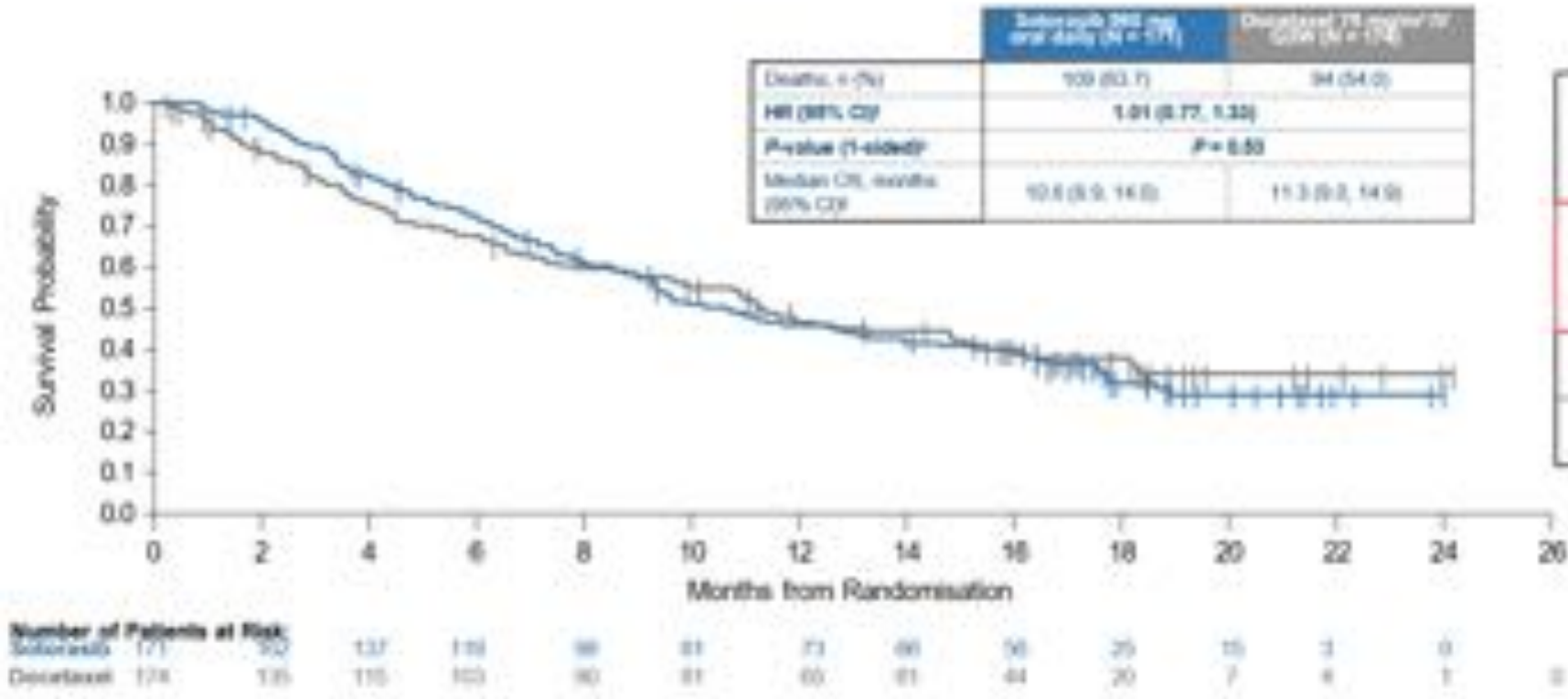
OS: Sotorasib vs Docetaxel*



	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 (9.0, 14.0)	11.3 (9.3, 14.9)

	Sotorasib	Docetaxel
Any subsequent treatment, including crossover**	36%	42%
Subsequent $KRAS^{G12C}$ inhibitor, including crossover	4%	34%
Subsequent chemo	21%	12%
Subsequent IO	9%	6%

*OS rates estimated using Kaplan-Meier method; ITT population.
‡HR and 95% CIs estimated using a stratified Cox proportional hazards model.
†*P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.
**Patients (16.4% in sotorasib arm; 5.2% in docetaxel arm) were treated beyond progression.

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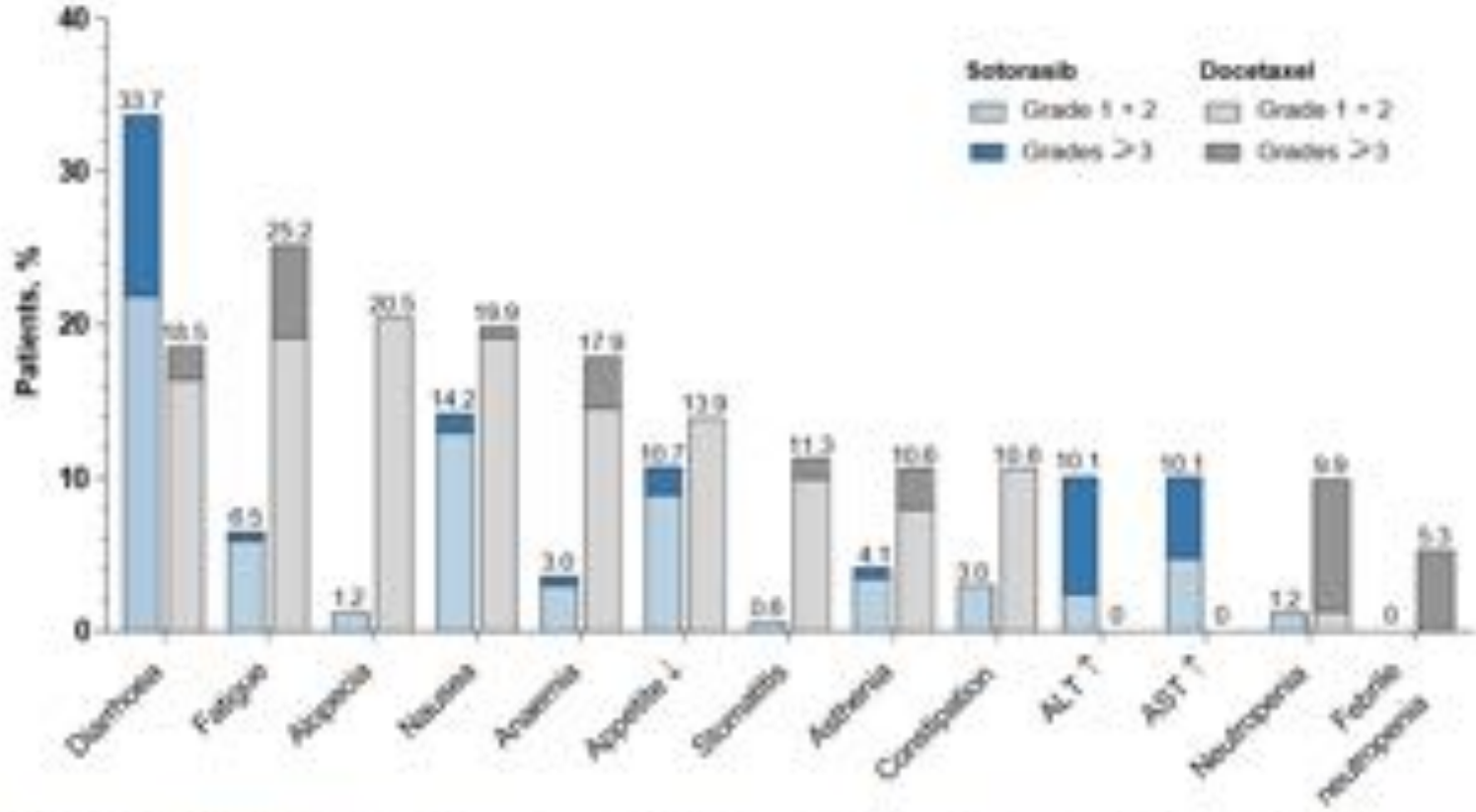
Most Common TRAEs
Any Grade TRAEs (≥ 10%) or Grade ≥ 3 (≥ 5%)



Most common Grade 3+ TRAEs with sotorasib were diarrhea and elevated liver enzymes, and with docetaxel were neutropenia, fatigue, and febrile neutropenia

*Highest-level TRAE per preferred term reported

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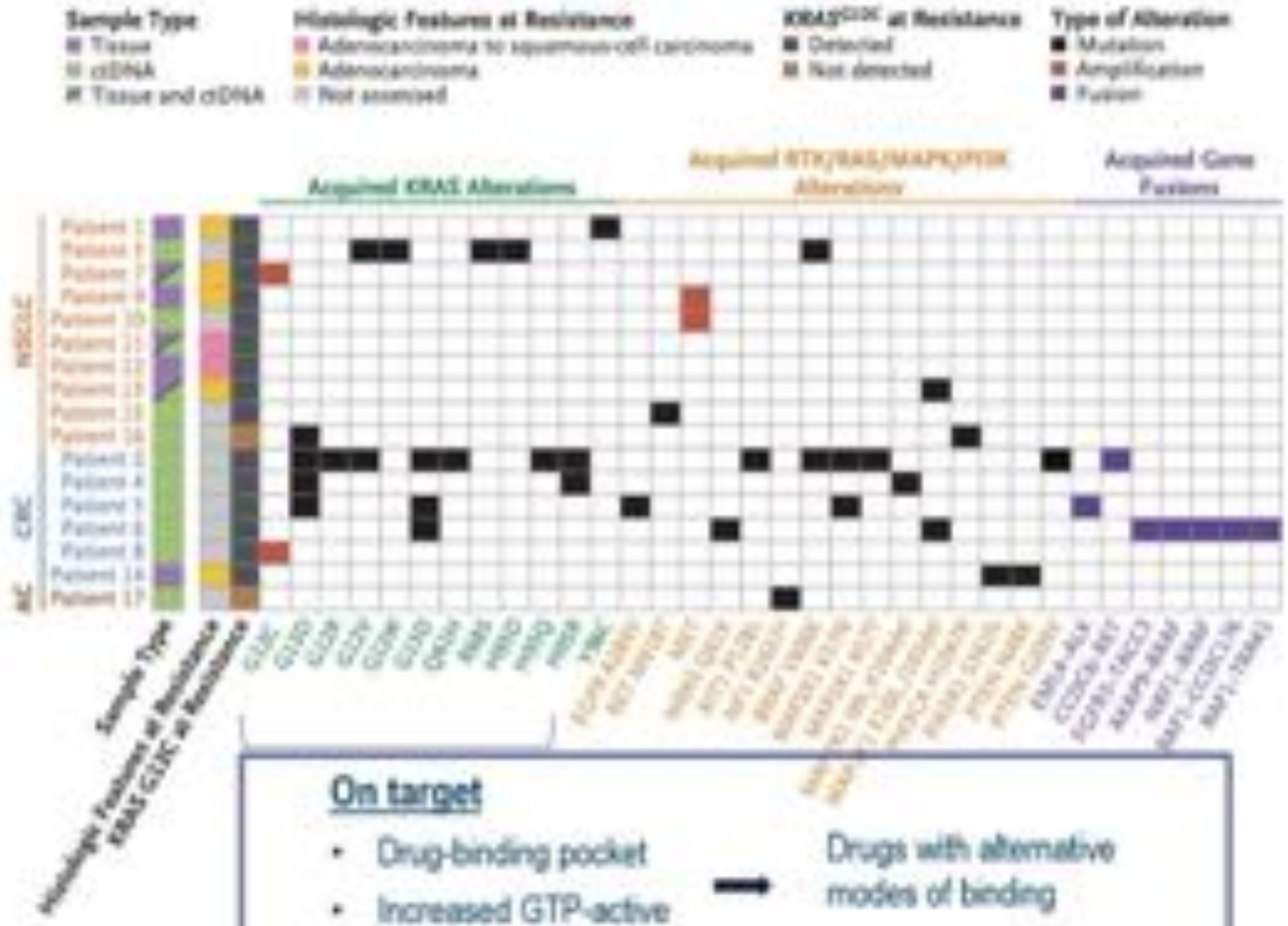
Multiple Mechanisms of Resistance to KRAS^{G12C} Inhibitors

Adagrasib

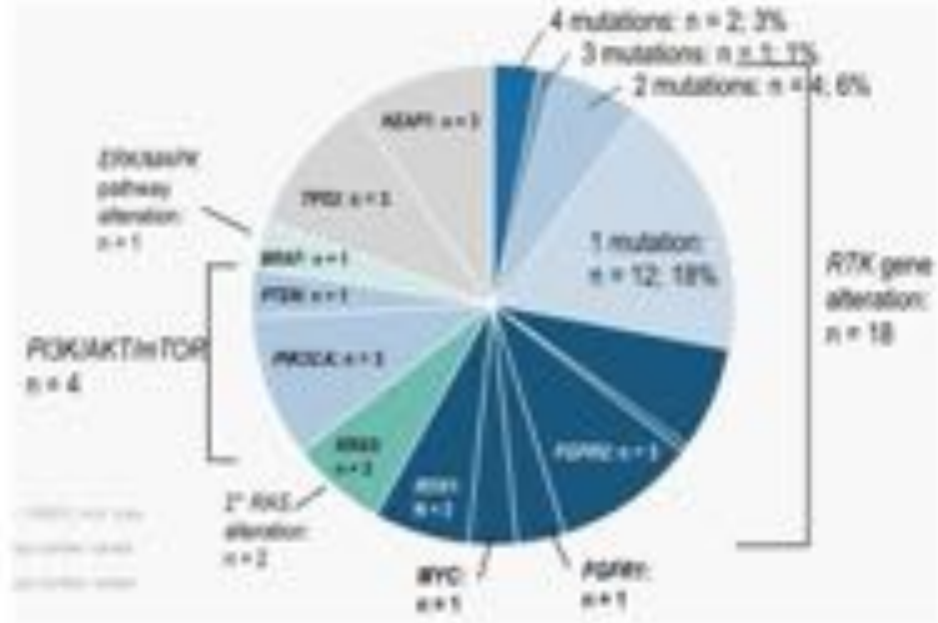


On target

- Drug-binding pocket
- Increased GTP-active

→ Drugs with alternative modes of binding

Sotorasib



Off target

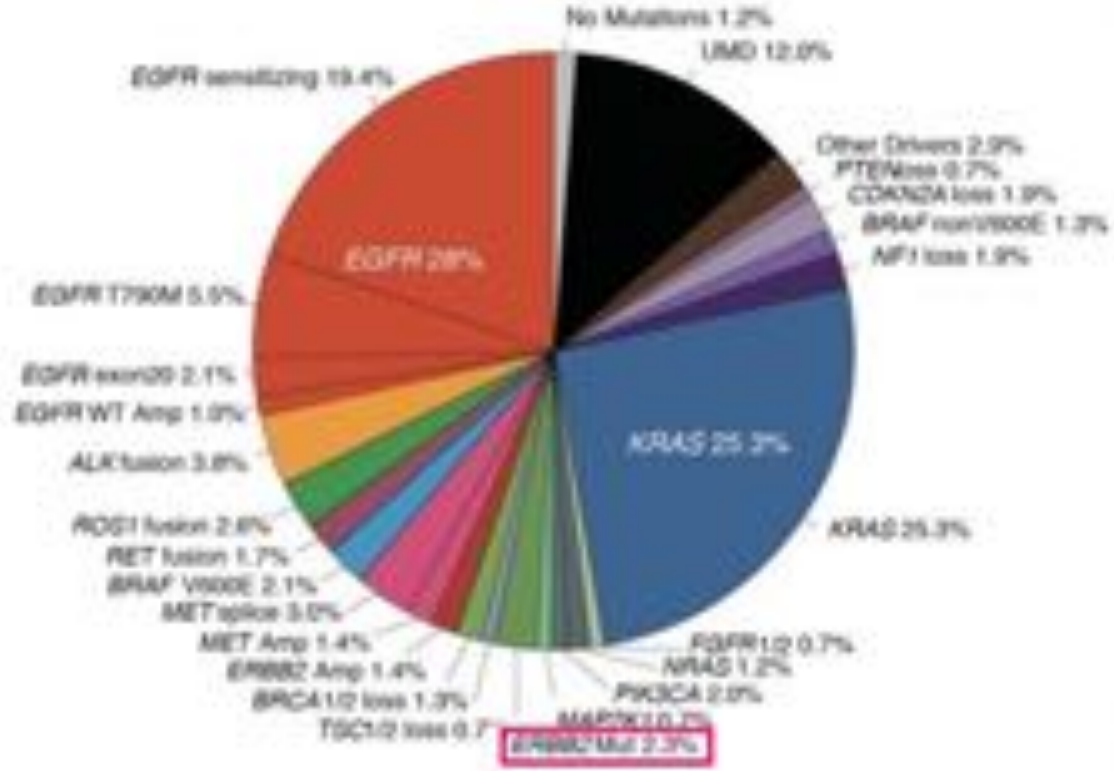
- Pathway reactivation
- By-pass signaling
- Histologic transformation

→ Biological rationale for combination therapy

Awad et al. NEJM (2021); Li et al. ASCO 2022

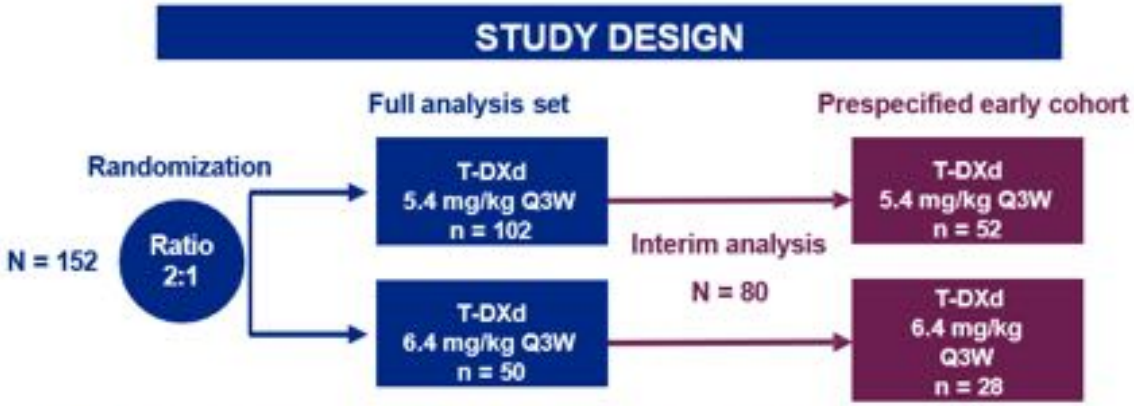
Antonio Calles, M.D. 2022 ESMO Congress, September 11; Paris, France.

HER2 Pathway



DESTINY-Lung02 Background and Study Design

Randomized, multicenter, international, 2-arm, non-comparative, phase 2 trial (NCT04644237)



- The prespecified early cohort included patients **randomized ≥ 4.5 months** before the interim analysis data cutoff to have a more robust efficacy assessment
  - *The prespecified early cohort was defined in the protocol to assess those **patients with ≥3 post-baseline assessments** at data cutoff* (assessments performed every 6 weeks)

Data cutoff: Mar 24, 2022
Median follow-up: 5.54 months (range 0.6-12.1 months)

Data cutoff: Mar 24, 2022.
2L, second-line; BICR, blinded independent central review; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; INV, investigator; OS, overall survival; PD-(L)1, programmed death (ligand)-1; PFS, progression-free survival; PK, pharmacokinetic; PRO, patient-reported outcome; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

1. Nakada T, et al. *Chem Pharm Bull* (Tokyo) 2019;67:173-185. 2. Ogitani Y, et al. *Clin Cancer Res* 2016;22:5097-5108. 3. Trail PA, et al. *Pharmacol Ther* 2018;181:126-142.
4. Li BT, et al. *N Engl J Med* 2022;386:241-251.

Response by BICR

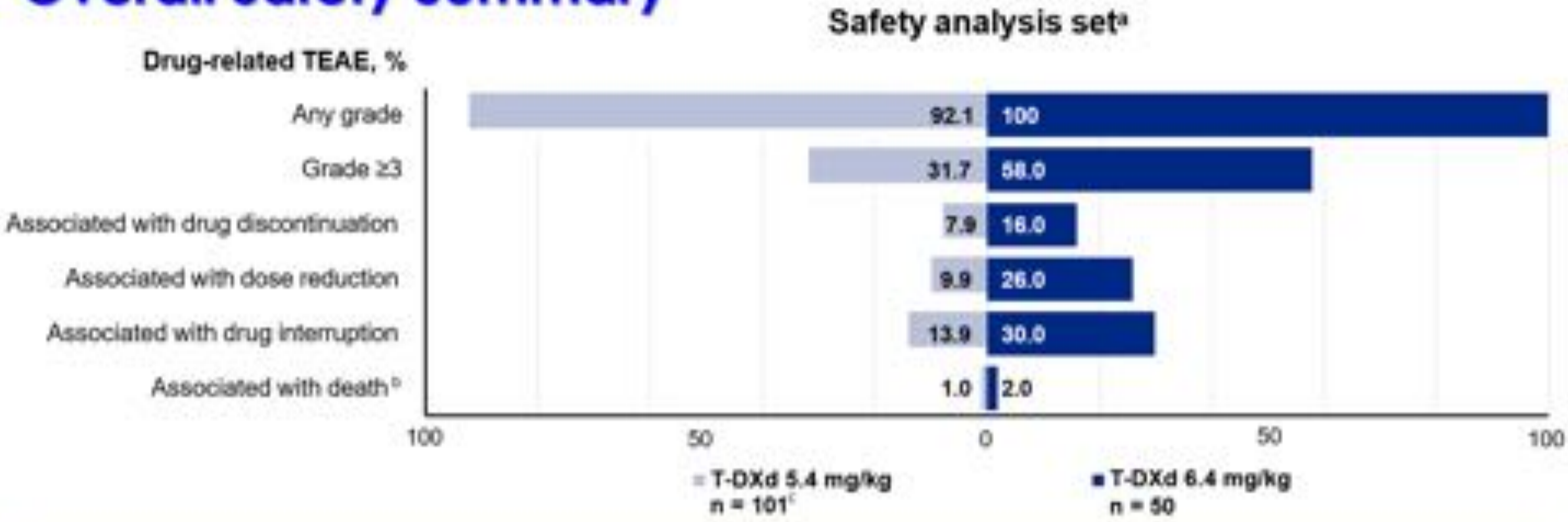
Response Assessment by BICR	Prespecified early cohort	
	T-DXd 5.4 mg/kg n = 52	T-DXd 6.4 mg/kg n = 28
Confirmed ORR,[a] n (%) [95% CI]	28 (53.8) [39.5, 67.8]	12 (42.9) [24.5, 62.8]
Best overall response, n (%)		
CR	1 (1.9)	1 (3.6)
PR	27 (51.9)	11 (39.3)
SD	19 (36.5)	14 (50.0)
PD	2 (3.8)	1 (3.6)
Not evaluable[b]	3 (5.8)	1 (3.6)
DCR,[c] n (%) [95% CI]	47 (90.4) [79.0, 96.8]	26 (92.9) [76.5, 99.1]
Median DoR, months [95% CI]	NE [4.2, NE]	5.9 [2.8, NE]
Median TTIR, months [range]	1.4 [1.2-5.8]	1.4 [1.2-3.0]
Median follow-up, months [range]	5.6 (1.1-11.7)	5.4 (0.6-12.1)

Data cutoff: Mar 24, 2022.

[a]Proportion of patients with confirmed CR or PR assessed by BICR per RECIST v1.1. [b]3 patients were not evaluable at 5.4 mg/kg (1 patient never received treatment due to Covid; 2 patients discontinued before first tumor assessment); 1 not evaluable at 6.4 mg/kg (discontinued due to adverse event before first tumor assessment). [c]Proportion of patients with confirmed CR, PR, or SD assessed by BICR.

CR, complete response; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease; TTIR, time to initial response.

Overall Safety Summary



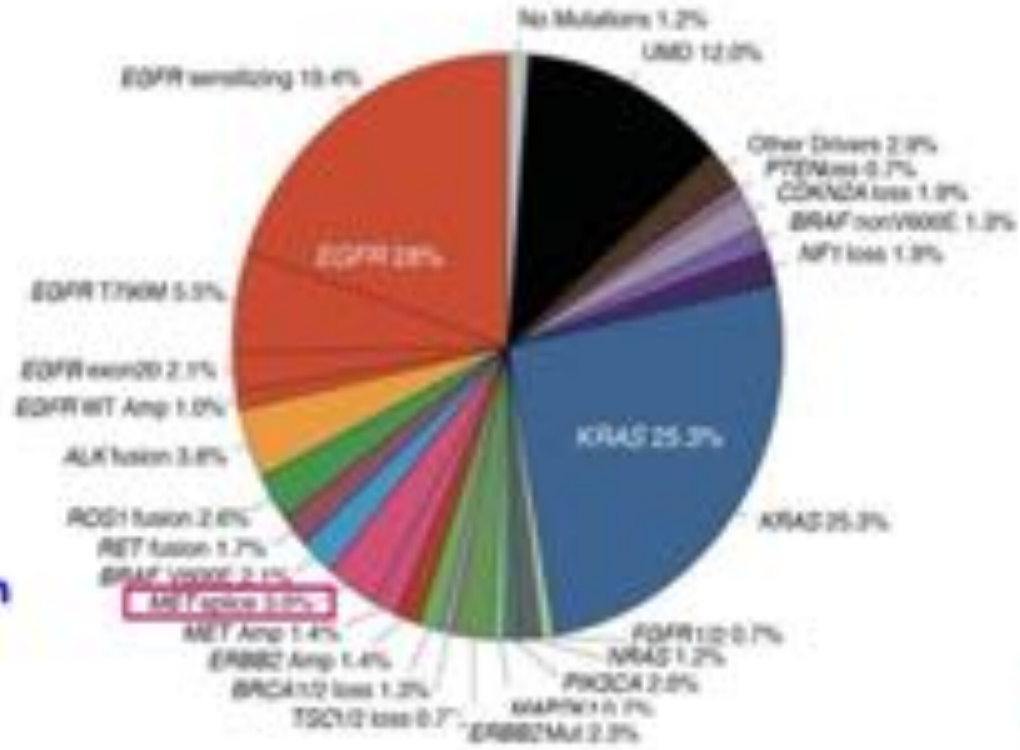
Median treatment duration, months (range)	3.7 (0.7-11.8)	3.3 (0.7-12.6)
Median follow-up, months (range)	3.8 (0-11.7)	3.9 (0.5-12.1)

Data cutoff: Mar 24, 2022.

[a]The safety analysis set included all randomized patients who received ≥1 dose of study drug. [b]In the safety analysis set, 4 patients overall had a TEAE associated with an outcome of death (2 drug-related deaths): 4 of the patients received T-DXd 5.4 mg/kg of whom 2 had malignant neoplasm progression, 1 had malignant lung neoplasm, and 1 had pneumonitis which was subsequently adjudicated by the adjudication ILD committee as not ILD; of the 2 patients who received T-DXd 6.4 mg/kg, 1 had a generally abnormal physical condition and 1 had ILD which was later confirmed by the ILD adjudication committee. [c]1 patient in the 5.4 mg/kg arm was randomized but did not receive treatment before discontinuing from the study.

TEAE, treatment-emergent adverse event.

MET Pathway



METex14 skipping mutation

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VISION and GEOMETRY Trial Designs: Single Arm Phase 2 Trials

VISION[1,2]

GEOMETRY[3,4]

1. Felip E, et al. WCLC 2021. 2. Paik PK, et al. N Engl J Med. 2020;383(10):931-943. 3. Wolf J, et al. ASCO 2021; Abstract 9020. 4. Wolf J, et al. N Engl J Med. 2020;383:944–957.

IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Tepotinib is a once daily and highly selective MET TKI approved for *MET*ex14 skipping NSCLC based mainly on Cohort A of the multi-cohort Phase II VISION study[1]

Key inclusion criteria

- Advanced NSCLC (*EGFR/ALK* wild-type, all histologies)
- Central confirmation of *MET*ex14 skipping by liquid and/or tissue biopsy
- First, second, or third line of therapy

Cohort A* *MET*ex14 skipping (primary)

Cohort C† *MET*ex14 skipping (confirmatory)

Tepotinib 500 mg‡ once daily

Selected endpoints

Primary:

Objective response by IRC (RECIST v1.1)

Secondary:

DOR, PFS, OS, Safety

Exploratory RANO-BM analysis§:

BOR per RANO-BM (patients with ≥1 evaluable post-baseline tumor assessment): disease control was defined as CR/PR/SD, or non-CR/non-PD

Here, we report the primary analysis (>9-months' follow-up) of the independent confirmatory Cohort C; data cut-off February 20, 2022[2]

*Cohort A enrollment began on September 13, 2018. †Cohort C enrollment began on August 8, 2019. ‡500 mg tepotinib hydrochloride hydrate (active ingredient) contains 456 mg tepotinib free base (active moiety). §Composite of radiographic responses, corticosteroid use, and clinical status, giving a more comprehensive overview of the patient compared with RECIST 1.1 For patients with non-measurable lesions only (enhancing and non-enhancing NTLs), non-CR/non-PD was defined as a best objective response of disease control, i.e. persistence of at least one non-progressing NTL. Brain imaging had no mandatory schedule and, as such, data for this analysis were incomplete, and confirmation of response was not required.

ALK, anaplastic lymphoma kinase; BOR, best overall response; CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; IRC, independent review committee; MET, mesenchymal-epithelial transition factor; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; NTL, non-target lesion; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; SD, stable disease; TKI, tyrosine kinase inhibitor.

1. Paik PK, et al. *N Engl J Med* 2020;383(10):931-943. 2. Lin MJ, et al. *Lancet Oncol* 2015;16(6):e270–e278.

Michael Thomas et al. Thoraxklinik, University Heidelberg and Translational Lung Research Center Heidelberg (TLRC-H); The German Center for Lung Research (DZL), Heidelberg, Germany

Patients in the confirmatory Cohort C had a median age of 71 years, about half were male, about half had smoking history, and most had adenocarcinoma histology.

Baseline characteristics		Cohort C (N=161)	Cohort A (N=152)
Median age, years (range)		71.0 (42–91)	73.1 (41–94)
Sex, %	Male	46.6	52.0
Race, %	White/Asian	54.0/42.2	71.1/25.0
ECOG PS, %	0/1	24.8/74.5	27.0/73.0
Smoking history, %	Yes	43.5	52.0
Histology, %	Adenocarcinoma	75.2	86.2
Brain metastases at baseline, %	Yes	21.1	15.1
Line of therapy, %	Treatment-naive/previously treated	59.0/41.0	45.4/54.6
*MET*ex14 skipping detection*	T+/L+	74.5/49.1	57.9/65.1

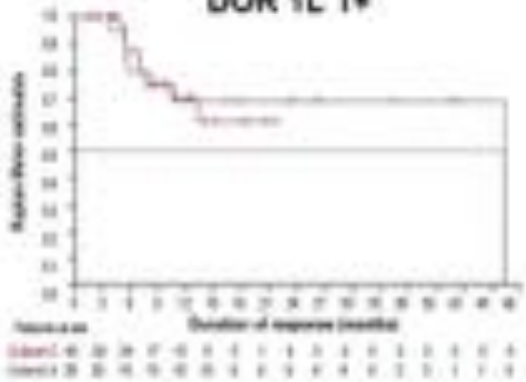
*Patients could have had METex14 skipping detected by both liquid and tissue biopsy and, as such, values do not add up to 100%; testing by both methods was not a requirement for study entry.
ECOG PS, Eastern Cooperative Oncology Group performance status; L+, METex14 skipping detected in liquid biopsy; METex14, MET exon 14; T+, METex14 skipping detected in tissue biopsy.

Efficacy was particularly meaningful in treatment-naïve patients enrolled by tissue biopsy

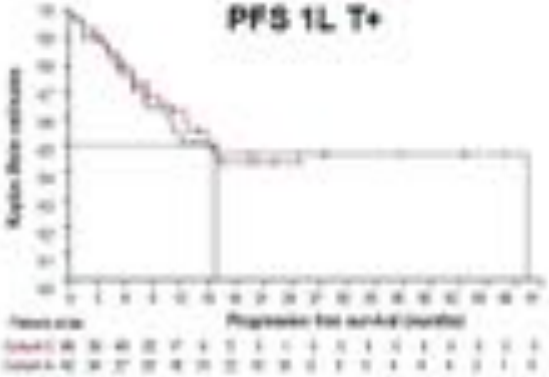
74.5% of patients were enrolled in Cohort C based on *MET*ex14 skipping detection by tissue biopsy

1L T+	Cohort C (n=69)	Cohort A (n=42)	Cohort A+C (n=111)
BOR, n (%) CR PR SD PD NE	0 43 (62.3) 17 (24.6) 7 (10.1) 2 (2.9)	1 (2.4) 19 (45.2) 13 (31.0) 3 (7.1) 6 (14.3)	1 (0.9) 62 (55.9) 30 (27.0) 10 (9.0) 8 (7.2)
ORR, % (95% CI)	62.3 (49.8, 73.7)	47.6 (32.0, 63.6)	56.8 (47.0, 66.1)
DCR, % (95% CI)	87.0 (76.7, 93.9)	78.6 (63.2, 89.7)	83.8 (75.6, 90.1)
mDOR, months (95% CI)	ne (10.4, ne)	46.4 (7.6, ne)	46.4 (13.4, ne)
mPFS, months (95% CI)	15.9 (10.8, ne)	15.3 (8.2, ne)	15.3 (11.3, ne)
mOS, months (95% CI)	22.7 (12.7, ne)	29.7 (13.5, ne)	25.9 (17.5, 36.6)

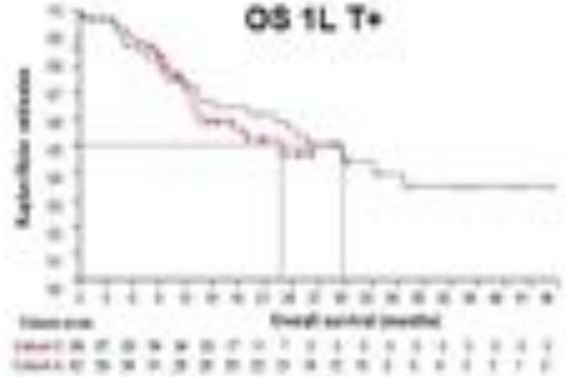
DOR 1L T+



PFS 1L T+



OS 1L T+



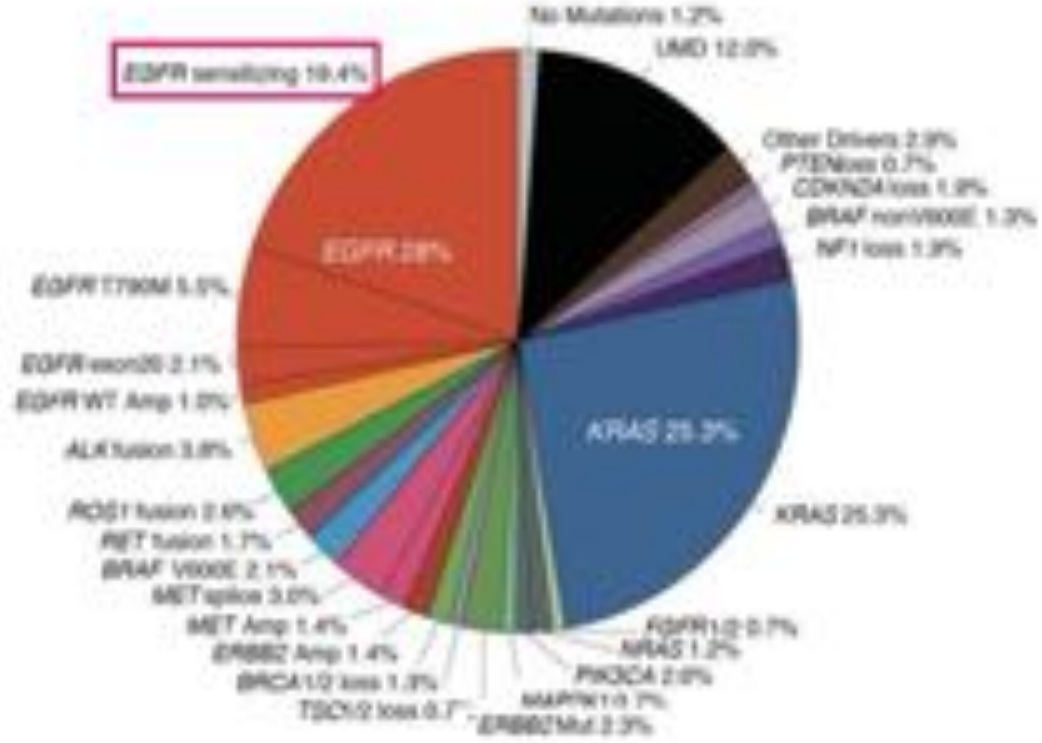
1L, first line; BOR, best objective response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; m, median; *MET*ex14, *MET* exon 14; ne, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T+, *MET*ex14 skipping detected in tissue biopsy

Safety profile: MET inhibition has a unique signature

TEAEs (Overall Rate ≥10%)	Related TEAE Crizotinib		Related TEAE Capmatinib		Related TEAE Tepotinib		Related TEAE Savolitinib	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Peripheral Edema	51%	1%	42%	8%	63%	7%	54%	7%
AST increase	17%		NR	NR	7%	2%	37%	13%
ALT increase	4%		NR	NR	7%	3%	37%	10%
Hypoalbuminemia	NR	NR	NR	NR	16%	2%	23%	0%
Creatinine increase	NR	NR	20%	0%	28%	1%	NR	NR
Fatigue	NR	NR	14%	3%	7%	1%	NR	NR
Nausea	41%	0%	33%	2%	26%	1%	44%	0%
Vision disorder	45%	1%	NR	NR	NR	NR	NR	NR

1. Drilon A, et al. Nature Med 2020. 2. Wolf et al. ASCO Annual Meeting 2019. 3. Paik et al. NEJM 2020. 4. Lu et al. ASCO Annual Meeting 2020

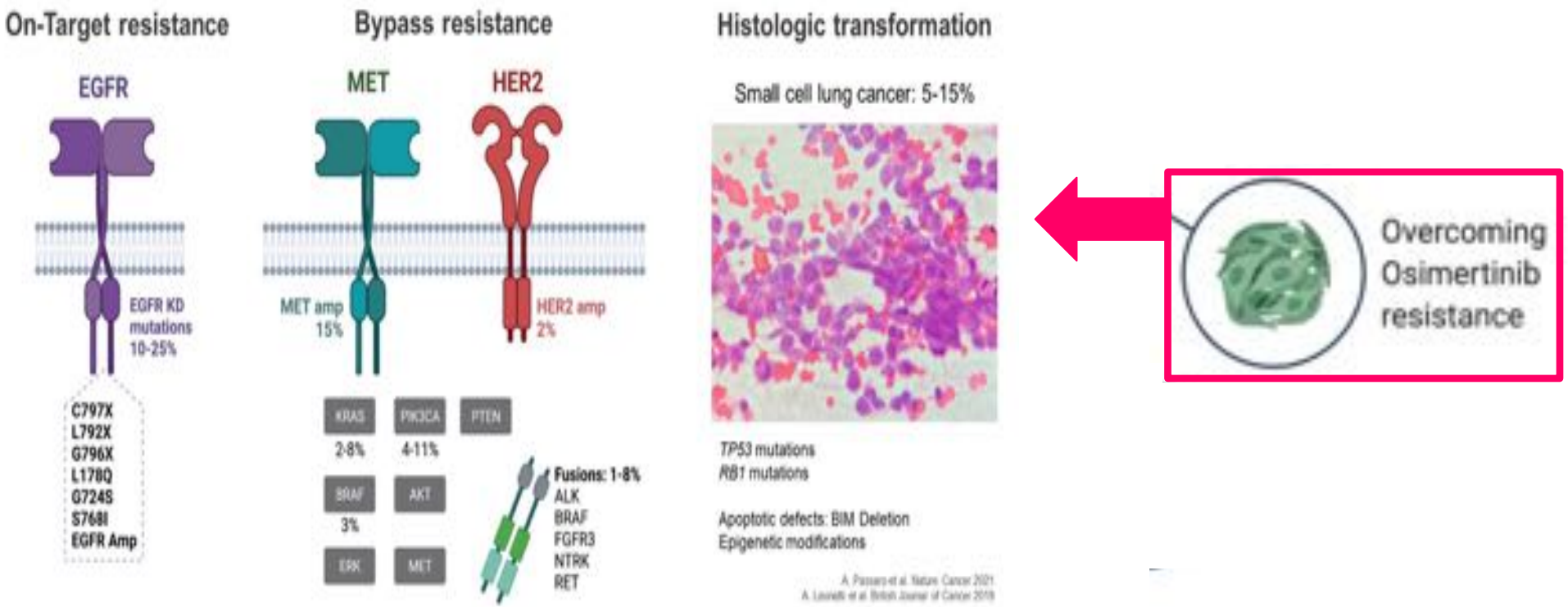
EGFR Pathway



GenesisCare
OLA
FAU MEDICINE

Research

Novel Approaches in EGFR-Mutant Lung Cancer



EGFR Pathway

Salvage Osimertinib Resistance

GenesisCare OLA FAU MEDICINE

On-Target resistance

Amivantamab and Lazertinib

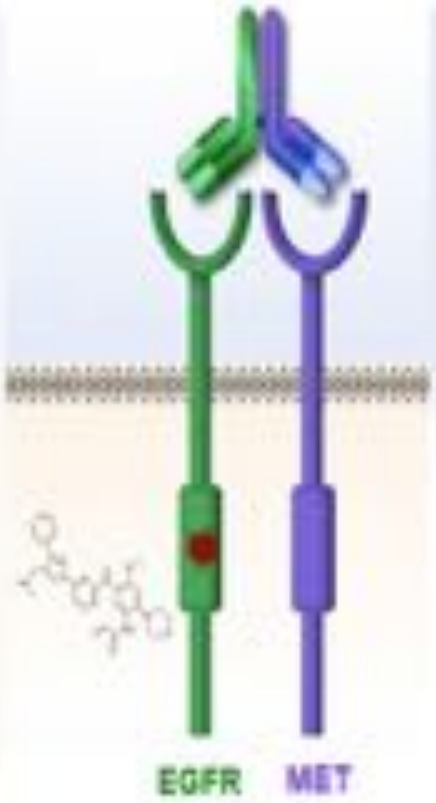
CHRYSALIS Study

Amivantamab (am-e-van-tuh-mab)

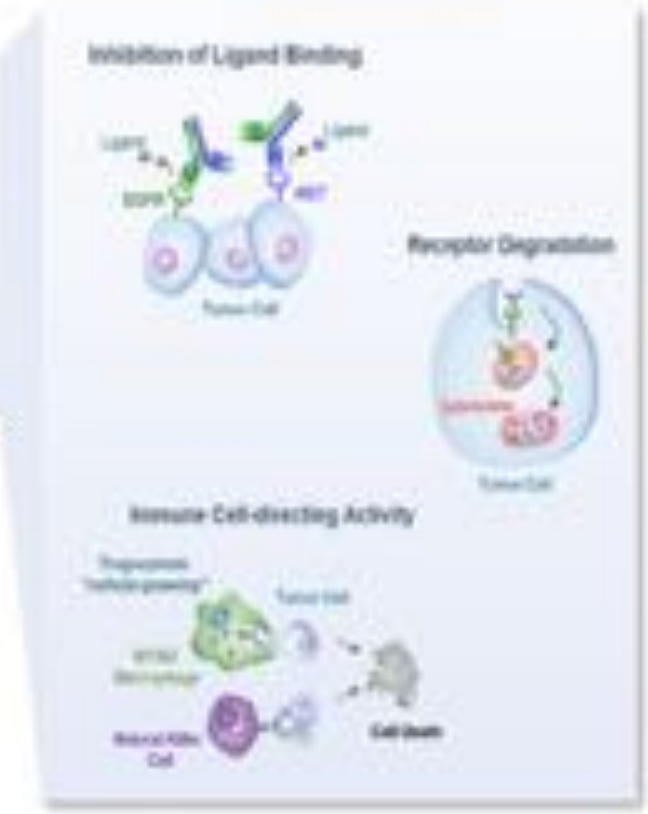
- Fully human bispecific antibody that targets EGFR and MET
- Fc portion has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[1-4]
- Granted Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy in US and China

Lazertinib (la-zer-tin-ib)

- Potent 3rd gen TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[3,4]
- Low rates of EGFR-related toxicity such as rash and diarrhea[3]
- Low cardiovascular safety risk[3]
- Safety profile that supports combination with other anti-EGFR molecules



Amivantamab MOA



BC Cho et al. 2021 ASCO. abstr 9006.

CHRYSALIS-2 (ClinicalTrails.gov Identifier: NCT04077463)
Study Design

Post-Osi Progression

Dose Expansion Cohorts

RP2CD: Lazertinib 240 mg PO +
Amivantamab 1050 mg (1400 mg for ≥80 kg) IV

Cohort A: EGFR ex19del or L858R
Post-osimertinib and platinum-based chemotherapy (n=162)

Cohort B: EGFR ex20ins
Post-standard of care and platinum-based chemotherapy

Cohort C: Uncommon EGFR mutations
Treatment naive or post-1st or 2nd generation EGFR TKI

Cohort D: EGFR ex19del or L858R
Post-osimertinib, chemotherapy naive, biomarker validation

Endpoints

- Overall response rate (primary)
- Duration of response
- Clinical benefit rate[a]
- Progression-free survival
- Overall survival
- Adverse events

Here we present updated **safety** and **efficacy** results
of the **amivantamab and lazertinib combination** from **fully enrolled Cohort A**

[a]Percentage of patients with confirmed response or durable stable disease (duration of ≥11 weeks)

EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; ex20ins, exon 20 insertion; IV, intravenous; PO, per oral; RP2CD, recommended phase 2 combination dose; TKI, tyrosine kinase inhibitor

CA Shu et al. ASCO 2022

Demographics and Baseline Characteristics

Post-Osi Progression

Characteristic, n (%)	n=162
Median age, years (range)	61.5 (31–83)
Male / female	57 (35) / 105 (65)
Race	
White	42 (26)
Asian	99 (61)
Black	1 (0.6)
Not reported	20 (12)
ECOG PS 0 /1	49 (30) / 113 (70)
Brain metastases at baseline[a]	66 (41)
Untreated	30 (19)
Treated	36 (22)

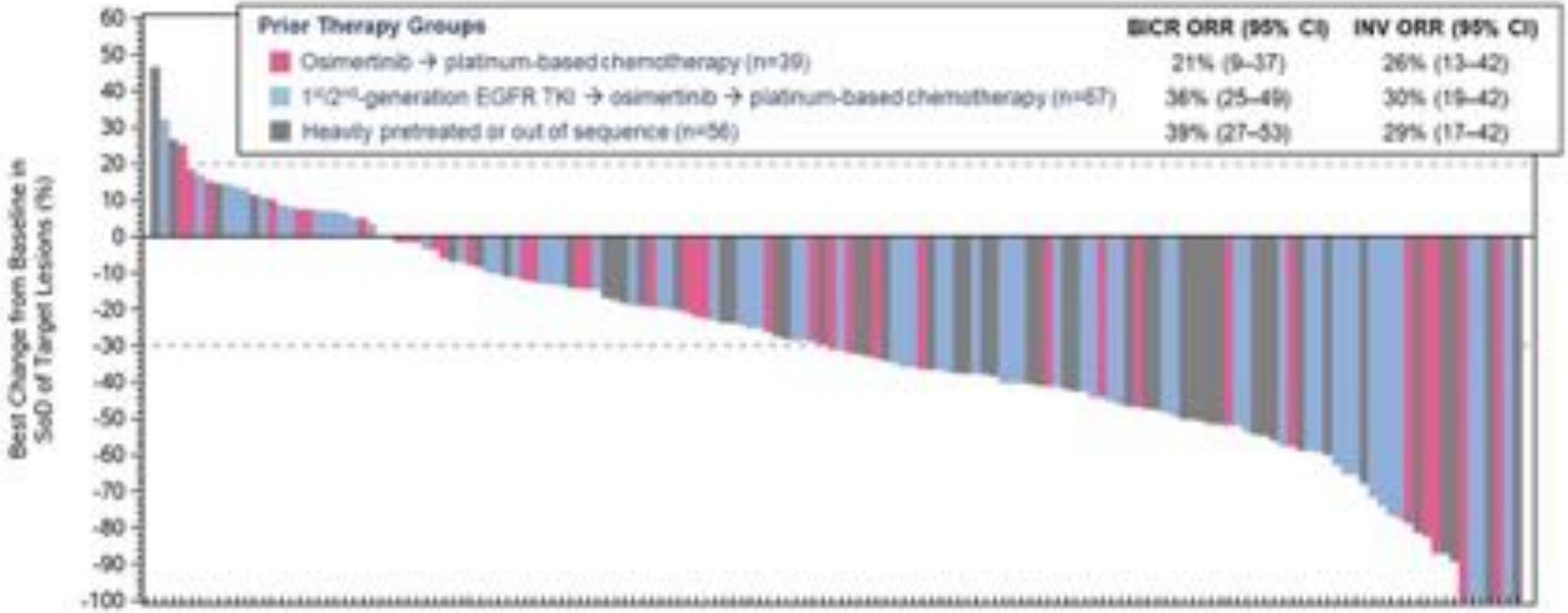
Characteristic, n (%)	n=162
Smoking history	
Non-smoker	111 (69)
Smoker	49 (30)
Unknown	2 (1)
Median number of prior therapy lines (range)	3 (2–14)
2–3	117 (72)
≥4	45 (28)
Prior therapy regimens	
Frontline osimertinib → platinum-based chemo	39 (23)
1st/2nd-gen EGFR TKI → osimertinib → platinum-based chemo	67 (42)
Heavily pretreated or out of sequence	56 (35)

[a]Study initially allowed stable asymptomatic treated or untreated brain metastases at baseline and was later amended to allow for treated brain metastases only.

Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; gen, generation; TKI, tyrosine kinase inhibitor.

CA Shu et al. ASCO 2022

Best Antitumor Response and ORR by Prior Therapy Group

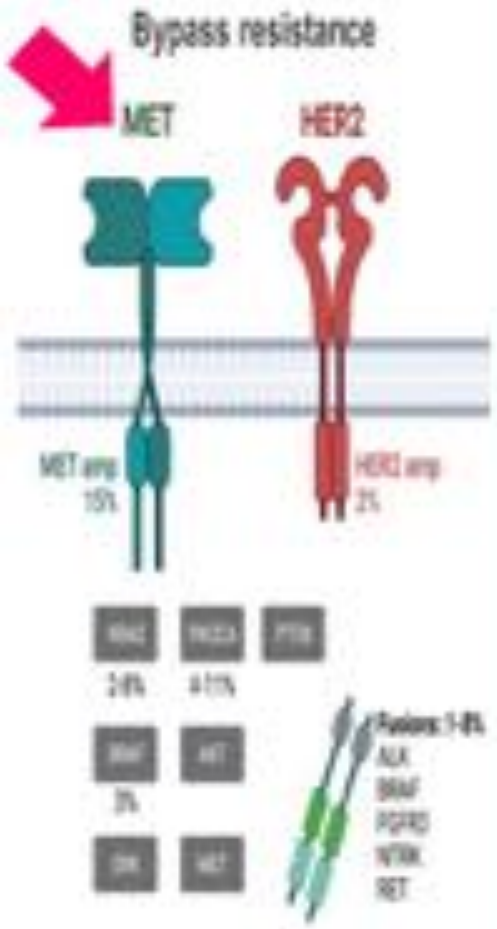


- 10 efficacy-evaluable patients did not have any evaluable post-baseline target lesion measurements

BICR, blinded independent central review; CI, confidence interval; EGFR, epidermal growth factor receptor; INV, investigator-assessed; ORR, overall response rate; SoD, sum of diameters; TKI, tyrosine kinase inhibitor.

CA Shu et al. ASCO 2022

CHRYSALIS Study



Response Among Patients with Identified EGFR/MET-based Resistance

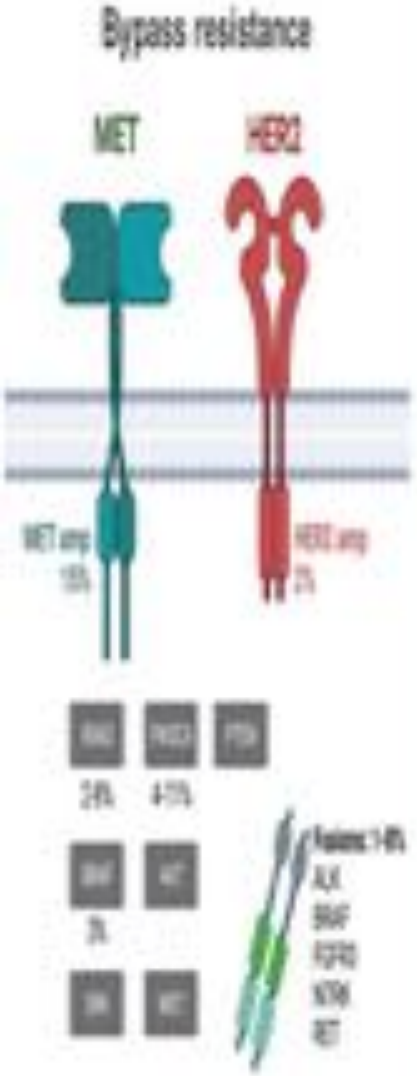
- **17 of 45** patients were **identified with either EGFR/MET-based resistance** by NGS[a] (ctDNA/tissue)
- **ORR in this subgroup was 47%,** mDOR was 10.4 months, CBR was 82%, and mPFS was 6.7 months

Resistance[a]	Alterations[a]	
EGFR-based	C797S (n=7) Amp (n=3) L718X (n=3) G724S (n=2)	L792H (n=1) G796S (n=1) E709K (n=1)
MET-based	Amp (n=5)	METex14 (n=1)
Additional	PIK3CA E542K (n=2) CCNE1 Amp (n=1) PIK3CA Amp (n=1) CCND1 Amp (n=1) CDK4 (n=1)	KRAS Amp (n=1) FGFR3-TACC3 fusion (n=1) KRAS G12D (n=1) CDKN2A G101W (n=1)

[a]Genomic analysis used QuestarDX60 for ctDNA NGS and ThermoFisher for tissue NGS; *EGFR amp (CNV ≥7) and MET amp (CNV ≥2) were based on tumor NGS; other amps were based on tumor NGS (CNV ≥7 or ctDNA NGS (CNV ≥2). Single nucleotide variants, insertions/deletions, and insertion call threshold was ≥1% allele frequency with ≥250 reads. †Eight patients had ≥1 alteration. Amp, amplification; CNV, copy number variation.

BC Cho *et al.* 2021 ASCO, abstr 9006.

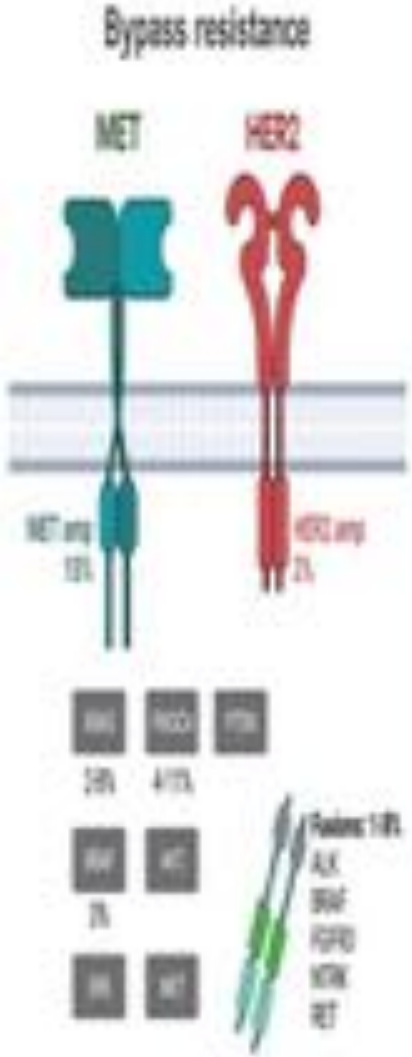
Novel Therapies Post-Osimertinib w MET as Target



Outcomes	Amivantamab + Lazertinib N = 45	Amivantamab + Lazertinib PD Chemo N = 162	Osimertinib + Savolitinib N = 69	Tella-V + Osimertinib N = 25
Trial	CHRYSALIS	CHRYSALIS-2 (A)	TATTON (B1)	NCT02099058
Target	EGFR + MET Post-Osi	EGFR + MET Post-Osi and Plat-based chemo	EGFR + MET Post 3RD Gen TKI	EGFR + MET Post-Osi
Biomarker	EGFR/MET resistance; unknown resistance; other resistance.	Without biomarker selection (underlying resistance mech. to be reported in the future)	MET Amplification	MET Expression
ORR	36%	33%	30%	58%
mDOR (months)	9.6 (95% CI: 5.3-NR)	9.6 (95% CI: 7.0-NR)	7.9 (95% CI: 6.9-11.2)	Not reported
mPFS (months)	4.9 (95% CI: 3.7-9.5)	5.1 (95% CI: 4.2-6.9)	5.4 (95% CI: 4.1-8.0)	Not reported
Grade ≥ 3 TRAE	16%	38%	57%	32%

BC Cho et al. Presented at ASCO 2021
C Shu et al. Presented at ASCO 2022
L Sequist et al. Lancet Oncology 2020
JW Goldman et al. Presented at ASCO 2022

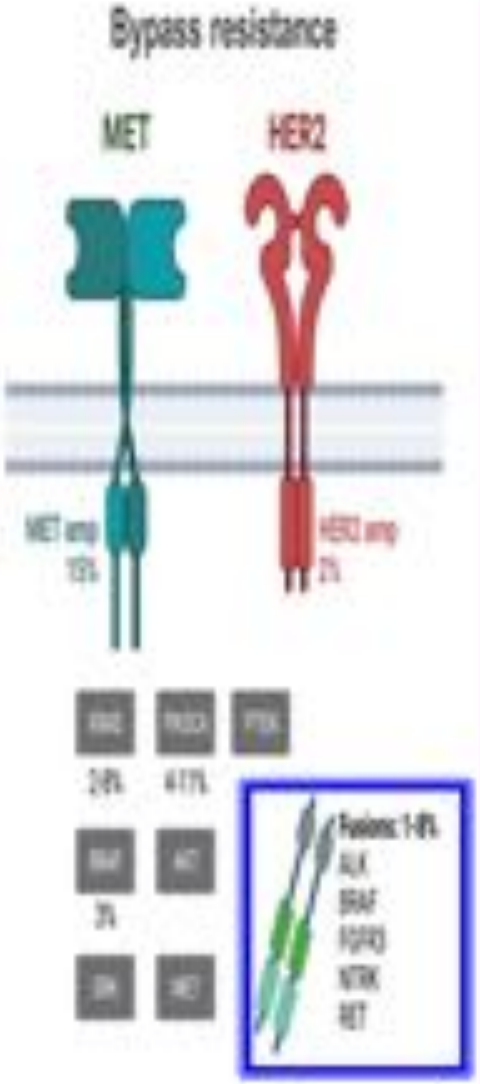
HER3/Dxd



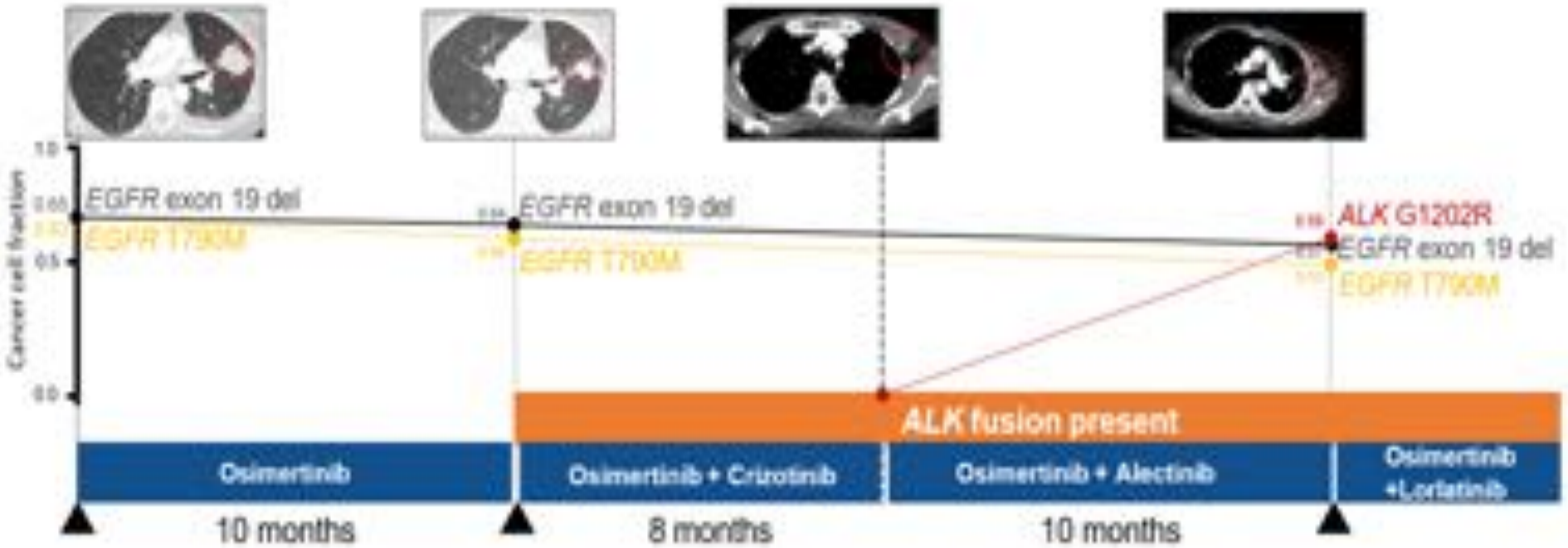
U31402-A-U102 Ph 1 Study of Patritumab Deruxtecan: Study Design

Patritumab Deruxtecan: Osimertinib-Resistant, EGFRm NSCLC

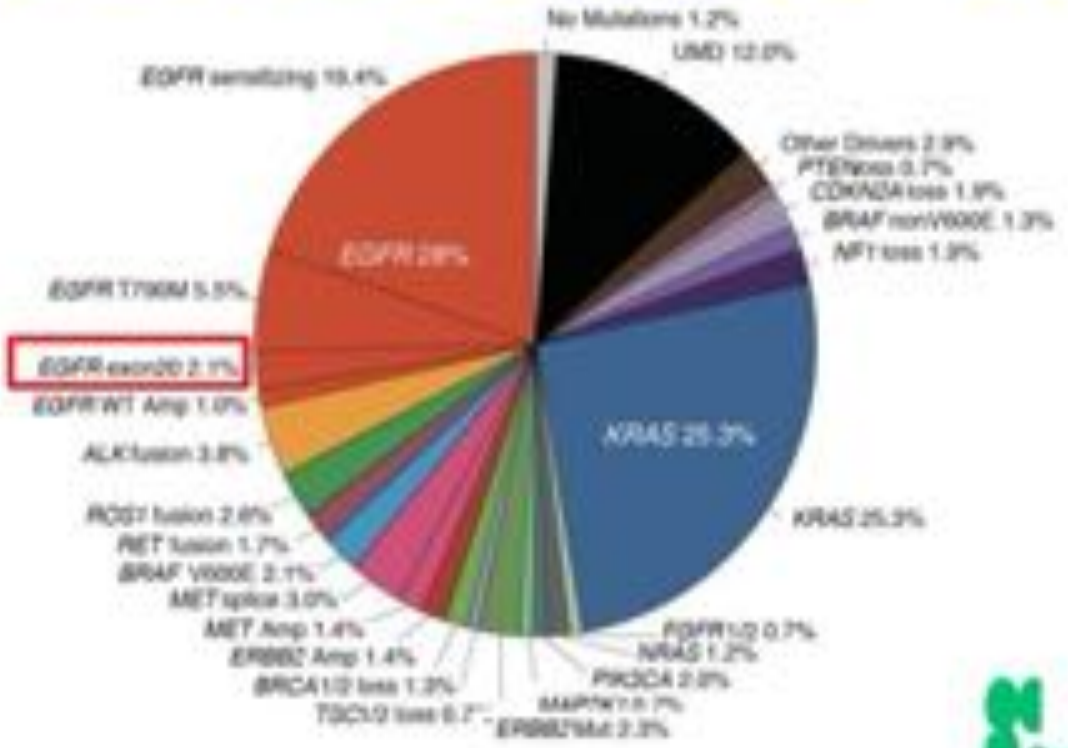
Addressing resistance to osimertinib: ALK



Combined inhibition of *ALK* and *EGFR* overcomes *ALK* mediated resistance



EGFRex20ins Pathway

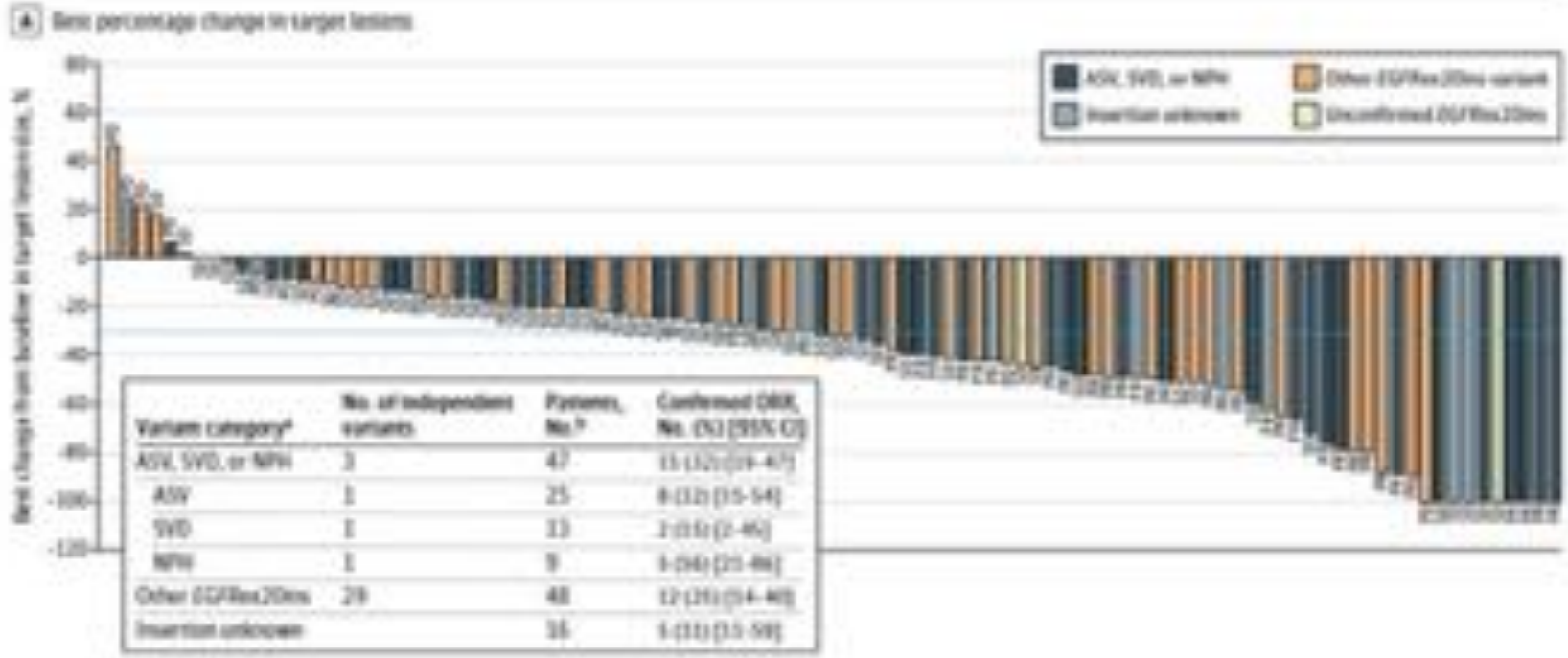


Mobocertinib

Oral, irreversible EGFR ins20 inhibitor
Approved dose: 160mg QD

	EGFR exon 20 Ph 1/2 Prior Platinum* N=114
Conf ORR (IRC)	28%
Conf ORR (Inv)	35%
mDOR (IRC)	17.5 mo (8.3-NE)
mPFS (IRC)	7.3 mos (5.5-10.2)

Figure 2. Mobocertinib Activity in Platinum-Pretreated Patients With EGFRex20ins Mutation-Positive Metastatic NSCLC (PPP Cohort)



Key Toxicities:

- GI: **Diarrhea** (91% Any Grade, 21% Grade ≥ 3), Decreased Appetite (35%), Nausea (34%)
- Derm: Rash (45% Any Grade, 0% Grade ≥ 3), Paronychia (38%)
- Cardiac: **QTc prolongation** (11% Any Grade, 3% Grade ≥ 3), one treatment-related death due to **cardiac failure**
- Dose reduction: 25% | Treatment Discontinuation: 17%

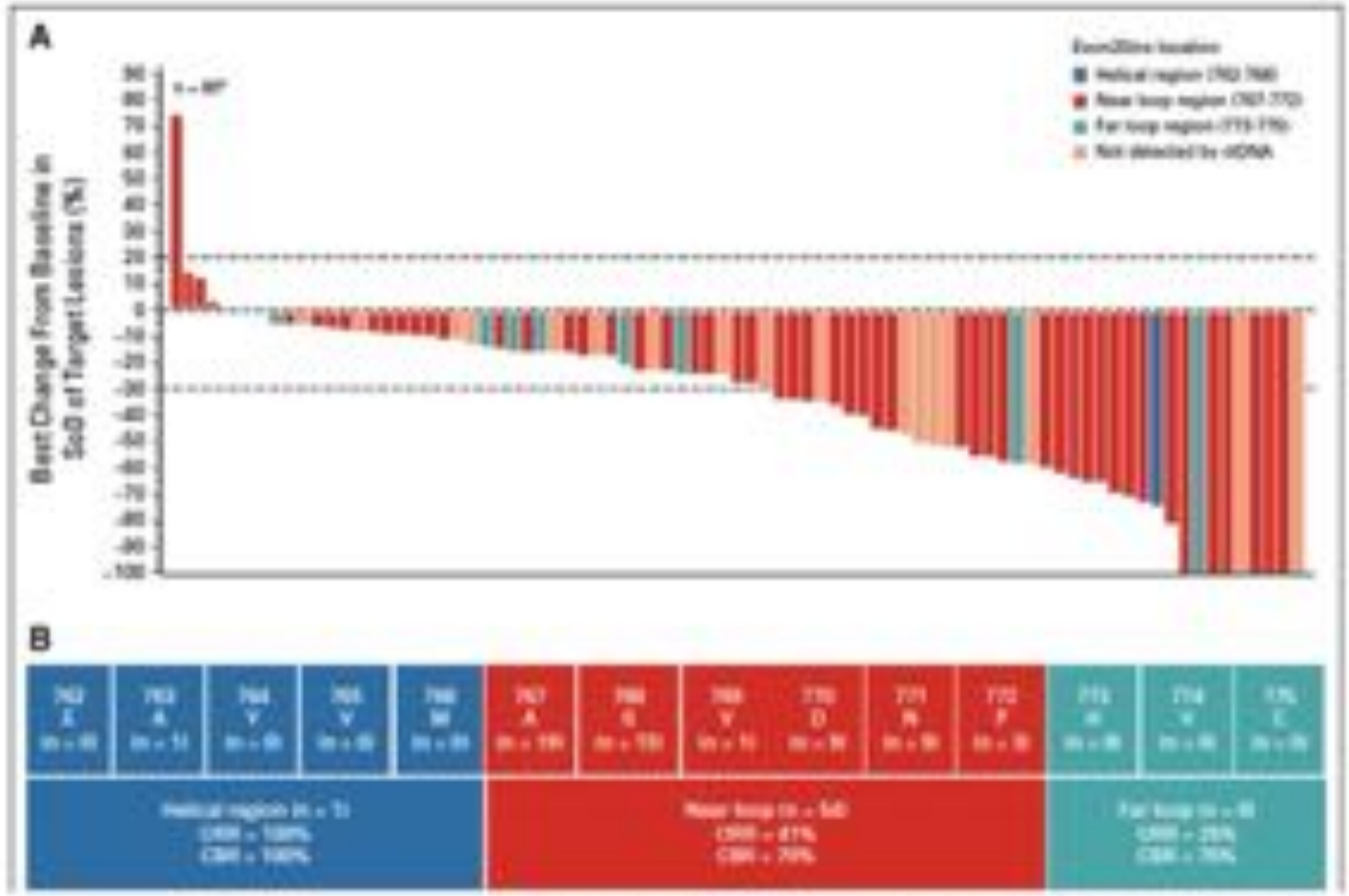
Zofia Piotrowska, MD. 2022 ESMO Congress, September 10; Paris, France.

Zhou C et al. JAMA Oncol. 2021;[Epub]:E1-E10.

Amivantamab

EGFR-MET bispecific antibody

	Post-Platinum EGFR Ins20 N=81
ORR (IRC)	40%
mDOR (IRC)	11.1 months
mPFS (IRC)	8.3 months



Park K, et al. Journal of Clinical Oncology 39, no. 30 (October 20, 2021) 3391-3402.

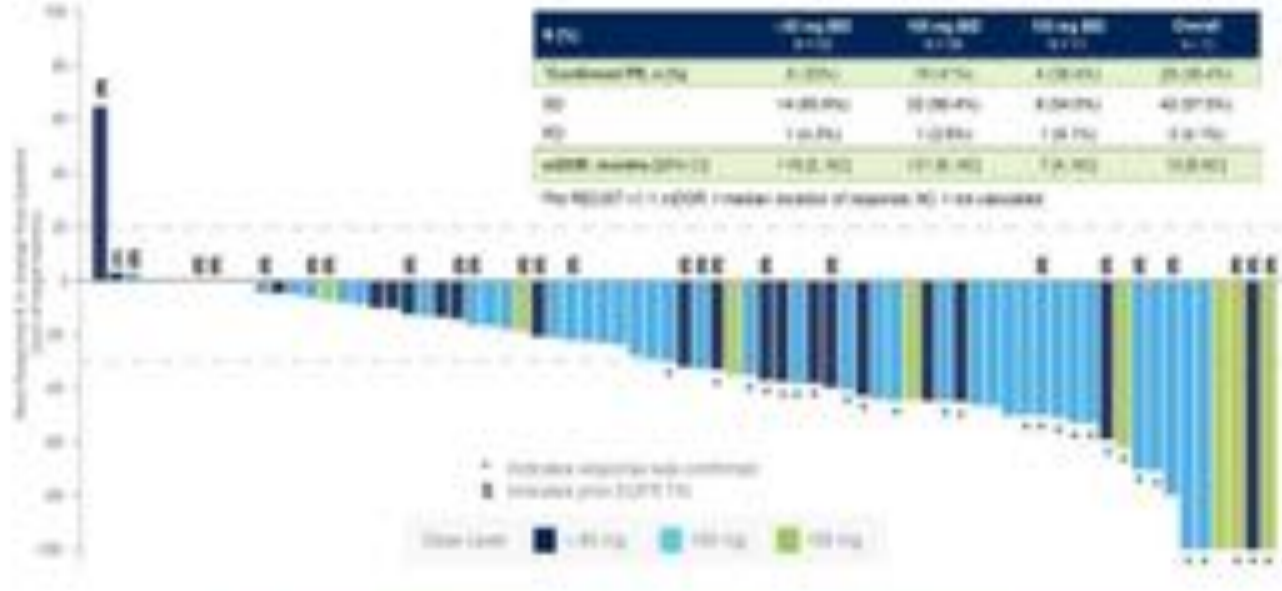
Key Toxicities:

- Infusion related reactions (66% Any Grade, 3% Grade ≥ 3) - most commonly on C1D1
- Derm: Rash (86% Any Grade, 4% Grade ≥ 3), Paronychia (45%)
- MET-related: Hypoalbuminemia (27%), Edema (18%)
- Dose Reduction: 13% | Dose discontinuation: 10%

Zofia Piotrowska, MD. 2022 ESMO Congress, September 10; Paris, France.

Emerging Agents: CLN-081 (TAS6417)

Dose BID	≤80 mg (N = 23)		100 mg (N = 39)		150 mg (N = 11)		Overall (N = 73)	
AE Term, n (%)	All grade*	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3
Rash	10 (43)	0	32 (82)	4	7 (64)	1 (9)	49 (67)	5 (7)
Paronychia	6 (26)	0	12 (31)	0	5 (45)	0	23 (32)	0
Diarrhea	4 (17)	0	14 (36)	0	4 (36)	2 (18)	22 (30)	2 (3)
Fatigue	5 (22)	0	8 (21)	0	2 (18)	0	15 (21)	0
Anemia	7 (30)	4 (17)	5 (13)	1 (3)	2 (18)	2 (18)	14 (19)	7 (10)
Dry skin	6 (26)	0	7 (18)	0	0	0	13 (18)	0
Nausea	5 (22)	0	4 (10)	0	3 (27)	0	12 (16)	0
Stomatitis	2 (9)	0	5 (13)	0	3 (27)	1 (9)	10 (14)	1 (1)
Alopecia	3 (13)	0	6 (15)	0	0	0	9 (12)	0
Dry eye	1 (4)	0	7 (18)	0	1 (9)	0	9 (12)	0
AST increased	3 (13)	1 (4)	5 (8)	1 (3)	2 (18)	1 (9)	8 (11)	3 (4)
Decreased appetite	4 (17)	0	4 (10)	0	0	0	8 (11)	0
Dose Interruptions	9 (33)		13 (33)		6 (55)		24 (33)	
Dose Reductions	3 (9)		5 (13)		3 (27)		10 (14)	
Dose Discontinuations	3 (9)		2 (5)		2 (18)		6 (8)	



Kaplan-Meier Estimates of Progression-Free Survival				
	≤80 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]	6 [1, 10]	10 [6, 12]

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

Yu HA, ASCO 2022

Zofia Piotrowska, MD. 2022 ESMO Congress, September 10; Paris, France.

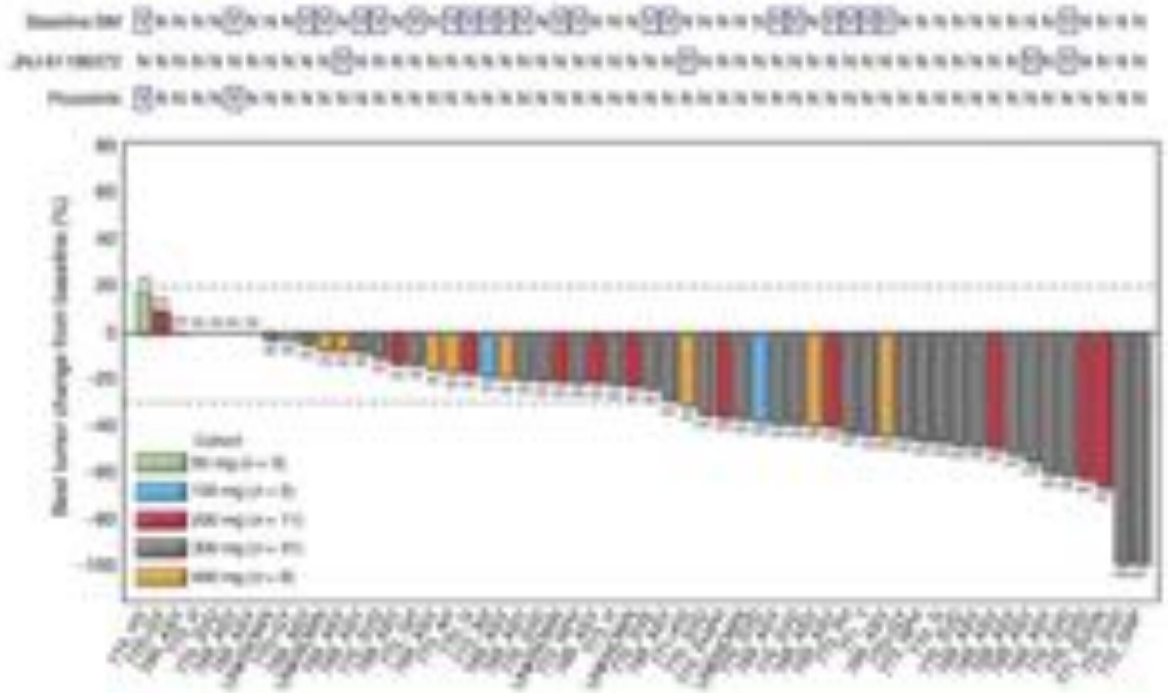
Emerging Agents: Sunvozertinib (DZD9008)

	100 mg (n=9)	200 mg (n=18)	300 mg (n=51)	400 mg (N=20)	All (N=102)
Diarrhea	1 (11)	10 (62)	29 (57)	17 (85)	58 (57)
Rash	2 (22)	3 (19)	23 (45)	14 (70)	45 (44)
Anemia	3 (33)	4 (25)	16 (31)	11 (55)	36 (35)
Nausea	3 (22)	3 (19)	19 (37)	8 (40)	34 (33)
Vomiting	2 (22)	3 (19)	13 (26)	13 (65)	32 (31)
Decr. Appetite	3 (33)	2 (13)	17 (33)	9 (45)	32 (31)
Paronychia	1 (11)	4 (25)	15 (29)	8 (40)	29 (28)
CPK incr.	2 (22)	3 (19)	9 (18)	12 (60)	26 (26)
Fatigue	1 (11)	1 (6)	11 (22)	7 (35)	22 (22)
Cr incr.	1 (11)	1 (6)	9 (18)	8 (40)	19 (19)
Mouth ulcers	1 (11)	2 (13)	11 (22)	4 (20)	18 (18)

*All AE's seen in > 15% of entire population shown (50mg DL not shown)

- TRAE Dose Reduction: 16% (All Doses), 12% (300mg)
- TRAE Dose Discontinuation: 6% (All Doses), 6% (300mg)

Zofia Piotrowska, MD. 2022 ESMO Congress, September 10; Paris, France.

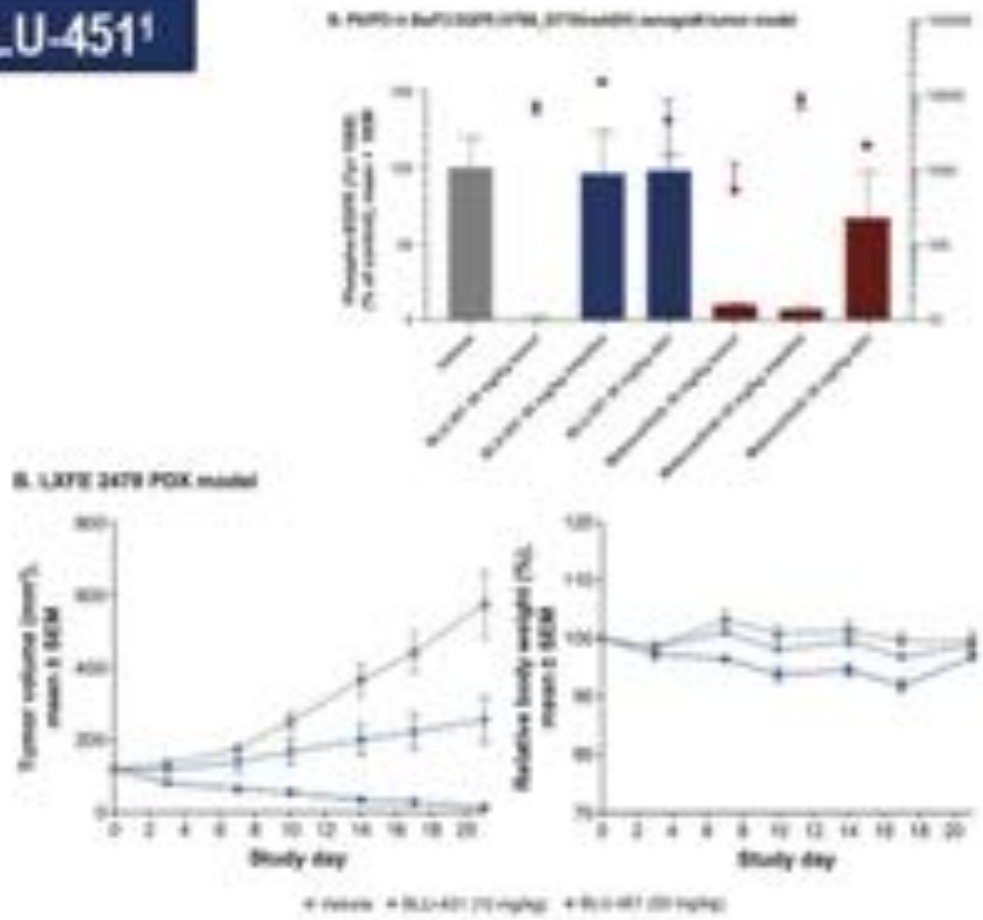


	200 mg n=11	300 mg n=31	Total n=98
Confirmed ORR	5 (45.5%)	13 (41.9 %)	21 (37.5 %)
DCR	9 (82%)	28 (90.3 %)	48 (85.7%)

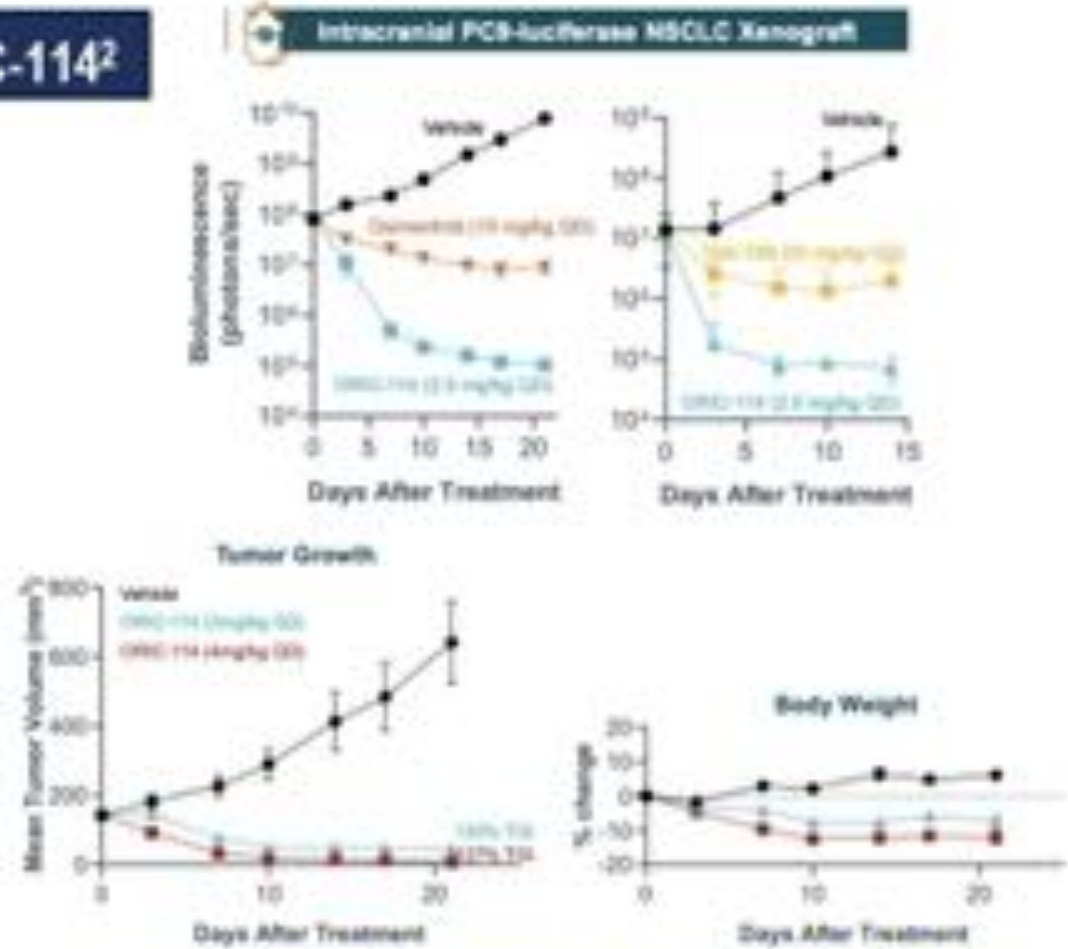
Wang M, Cancer Discov 2022.

Novel Agents Entering Clinic

BLU-451[1]



ORIC-114[2]



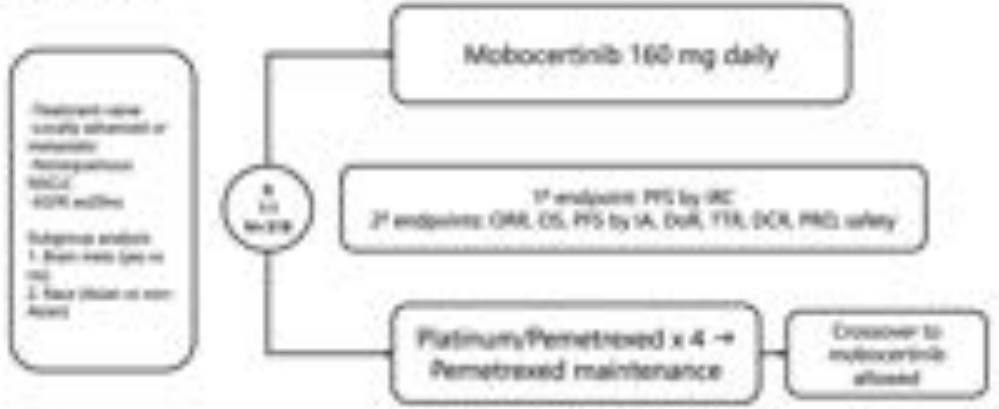
1. Murray BW, AACR 2022; 2. Junttila MR, AACR 2021

Unanswered Questions in EGFR ins20

- **Optimal First-Line Treatment Strategies**
  - PAPILLON, EXCLAIM-2 may change the standard of care
- **How should currently available therapies be sequenced?**
  - TKI -> Amivantamab | Amivantamab - > TKI | Combinations
- **Should treatment be tailored based on the location of the insertion?**
- **Management of CNS Metastases**
  - Novel agents (BLU-451, ORIC 114) may have a role
- **Overcoming acquired resistance**

Zofia Piotrowska, MD. 2022 ESMO Congress, September 10; Paris, France.

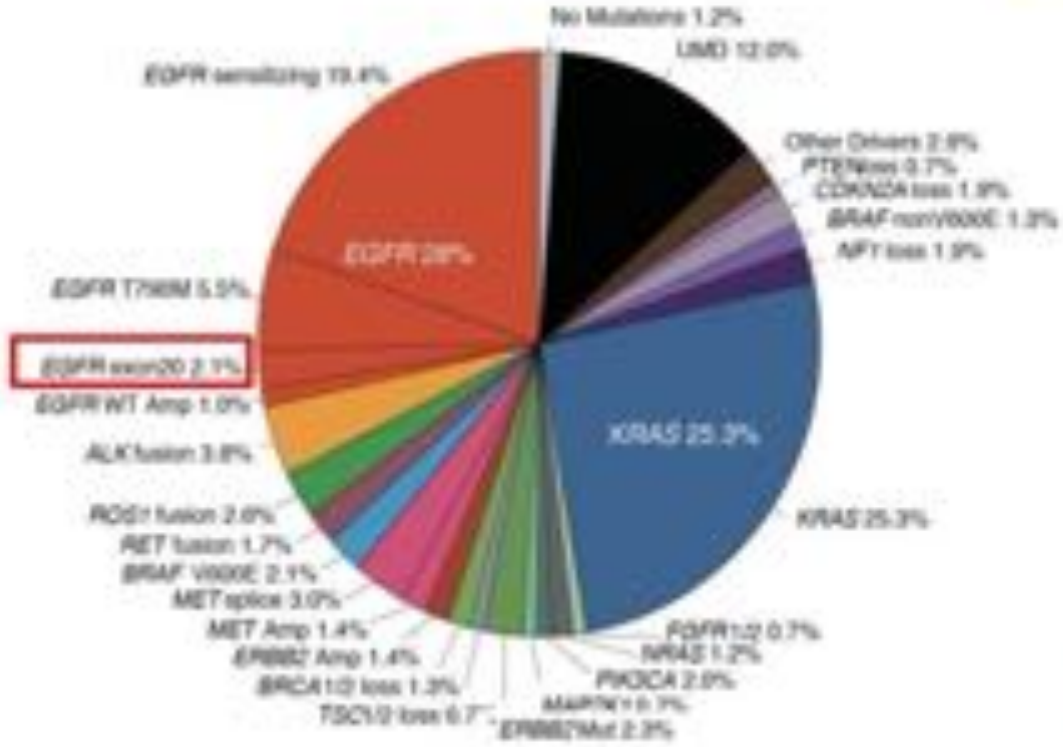
EXCLAIM-2



PAPILLON

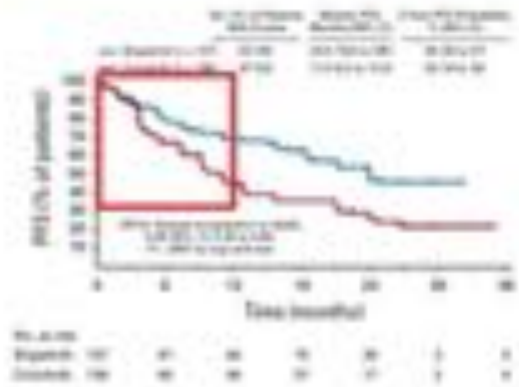
Zhang SS, Zhu VW. Lung Cancer (Auckl). 2021 Agrawal T, WCLC 2020.

ALK Pathway

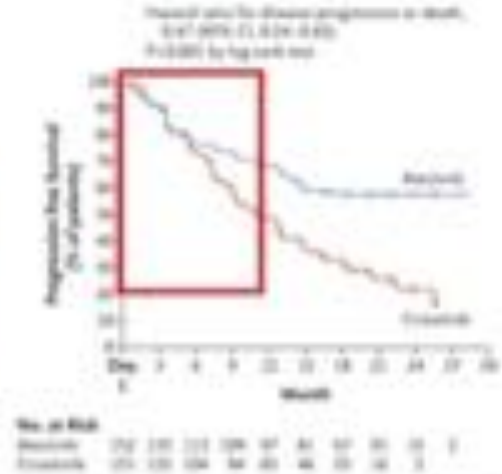

No Mutations 1.2%
UMD 12.0%
EGFR sensitizing 19.4%
Other Drivers 2.6%
PTENloss 0.7%
CDKN2A loss 1.9%
BRAF non-V600E 1.3%
NF1 loss 1.9%
EGFR 28%
EGFR T790M 5.5%
EGFR exon20 2.1%
EGFR WT Amp 1.0%
ALK fusion 3.8%
KRAS 25.3%
ROS1 fusion 2.6%
RET fusion 1.7%
BRAF V600E 2.1%
MET splice 3.0%
MET Amp 1.4%
ERBB2 Amp 1.4%
BRCA1/2 loss 1.3%
TSC1/2 loss 0.7%
KRAS 25.3%
EGFR L/Z 0.7%
NRAS 1.2%
PIK3CA 2.6%
MAP2K1 0.7%
ERBB2Mut 2.3%

Managing ALK+ NSCLC

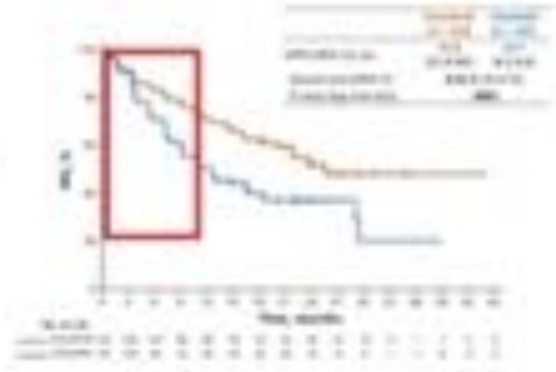
Brigatinib:
ALTA-1L
HR 0.49



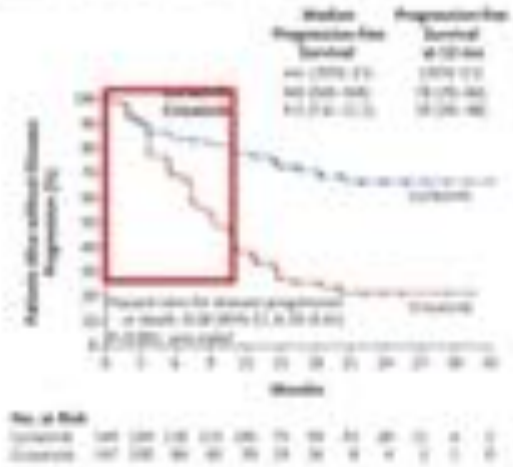
Alectinib:
ALEX
HR 0.47



Ensartinib:
eXalt3
HR 0.51



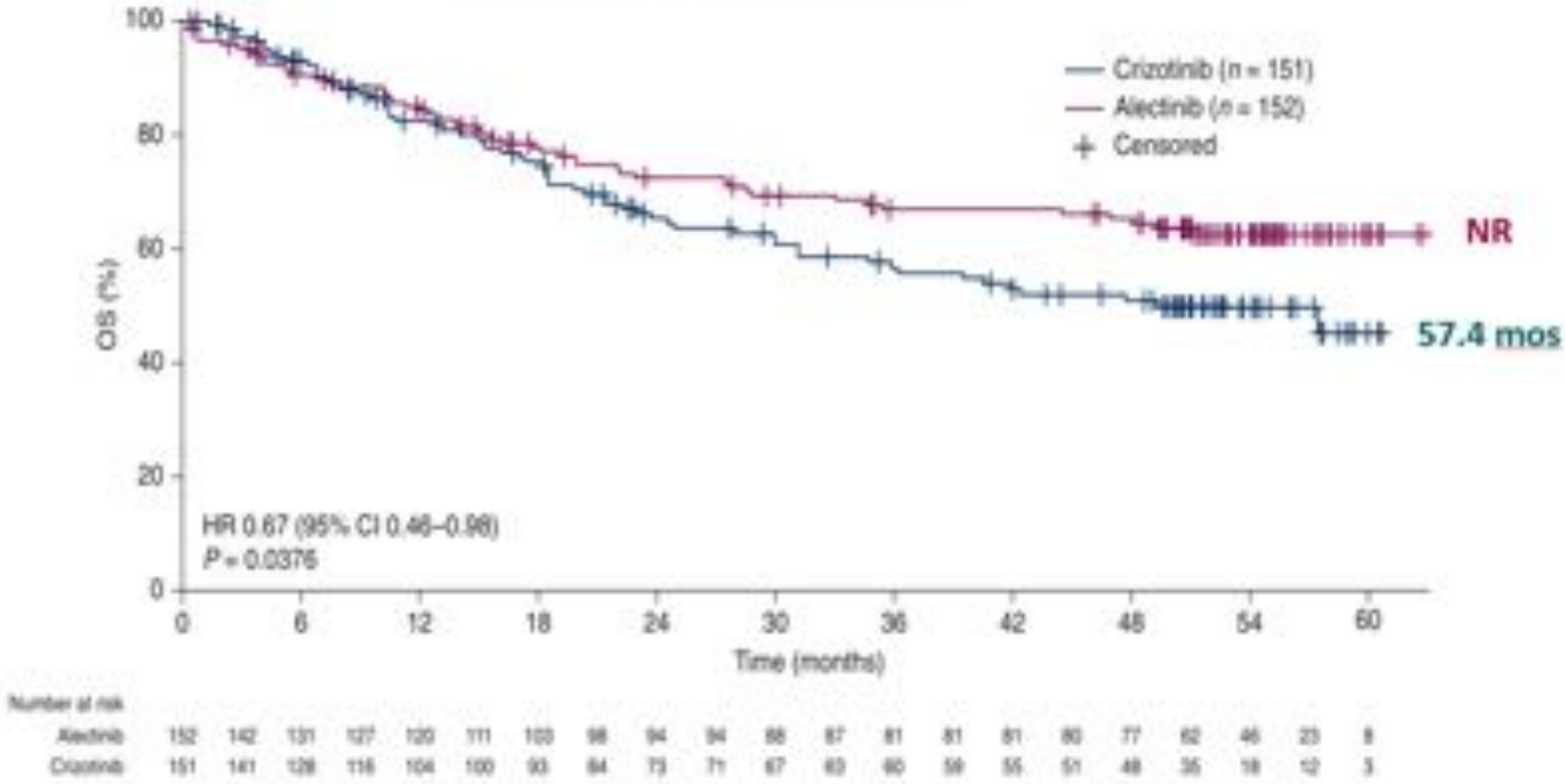
Lorlatinib:
CROWN
HR 0.28



Camidge DR, et al. J Clin Oncol. 2020 Nov 1;38(31):3592-3603. Hida T, et al. WCLC Presentation, Aug 8, 2020. Peters S, et al. N Engl J Med. 2017 Aug 31;377(9):829-838. Shaw AT, et al. N Engl J Med. 2020 Nov 19;383(21):2018-2029.

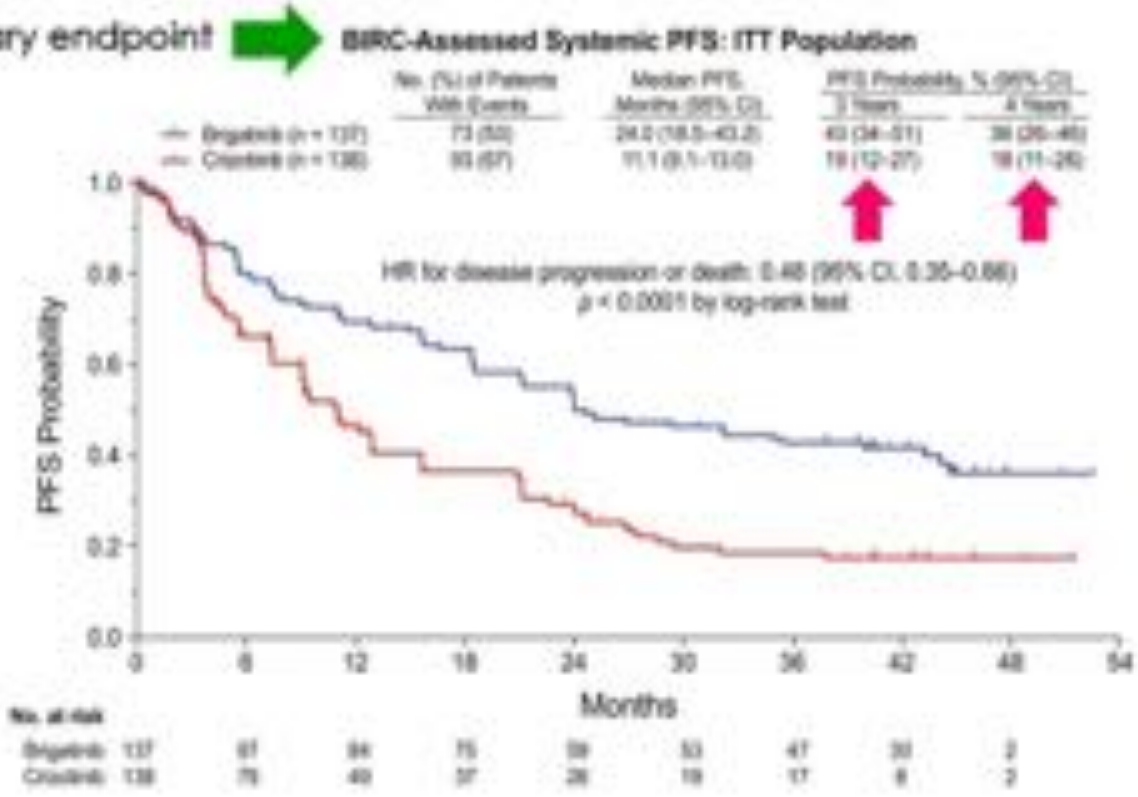
GenesisCare FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY OLA

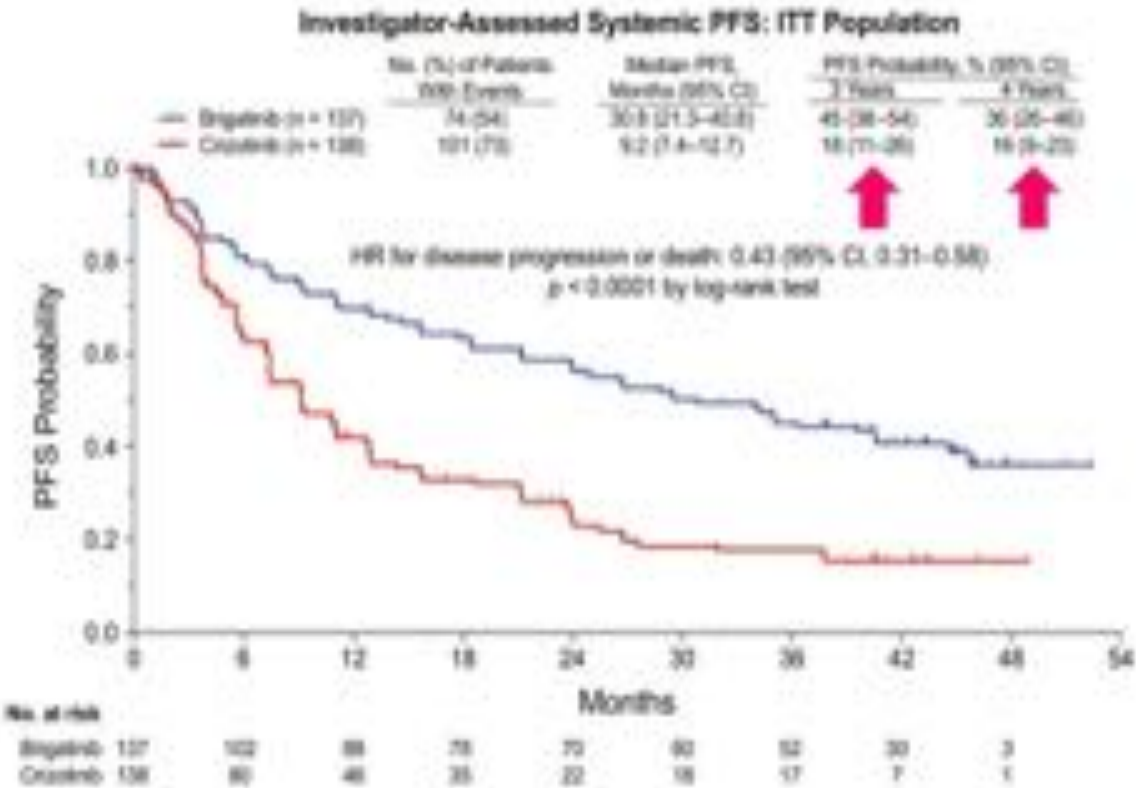
Investigator-assessed Overall Survival (OS) in the ITT Population (stratified analysis)



Phase 3 ALTA-1L Trial: Final Results

Primary endpoint



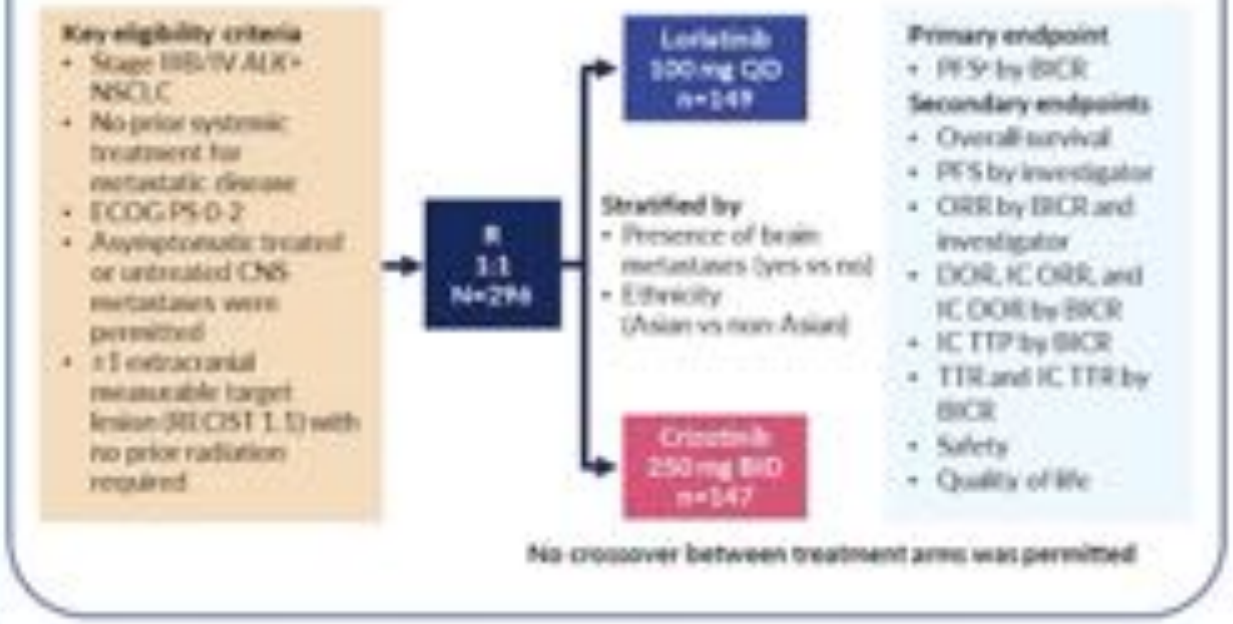


Camidge DR et al. J Thor Oncol. 2021; 16(12):2091–2108.

Lorlatinib, a potent third-generation ALK inhibitor

- In the phase 3 CROWN study (NCT03052608), lorlatinib improved progression-free survival (PFS) and demonstrated intracranial (IC) activity in patients with untreated *ALK*-positive NSCLC[1]
  - At 18.3 months of median follow-up in the lorlatinib arm, median PFS was not reached (NR; 95% CI, NR-NR) with lorlatinib and was 9.3 months (95% CI, 7.6-11.1) with crizotinib (hazard ratio [HR], 0.28; 95% CI, 0.19-0.41; P<.001)
  - In patients with measurable brain metastases at baseline, the frequency of confirmed IC response was greater with lorlatinib (82%) than crizotinib (23%)
- Based on the results of this study, lorlatinib has been approved for first-line treatment in patients with metastatic NSCLC whose tumors are *ALK*-positive[2-4]
- We report updated efficacy and safety data from the CROWN study, after approximately 3 years of follow-up

CROWN: a randomized global phase 3 study

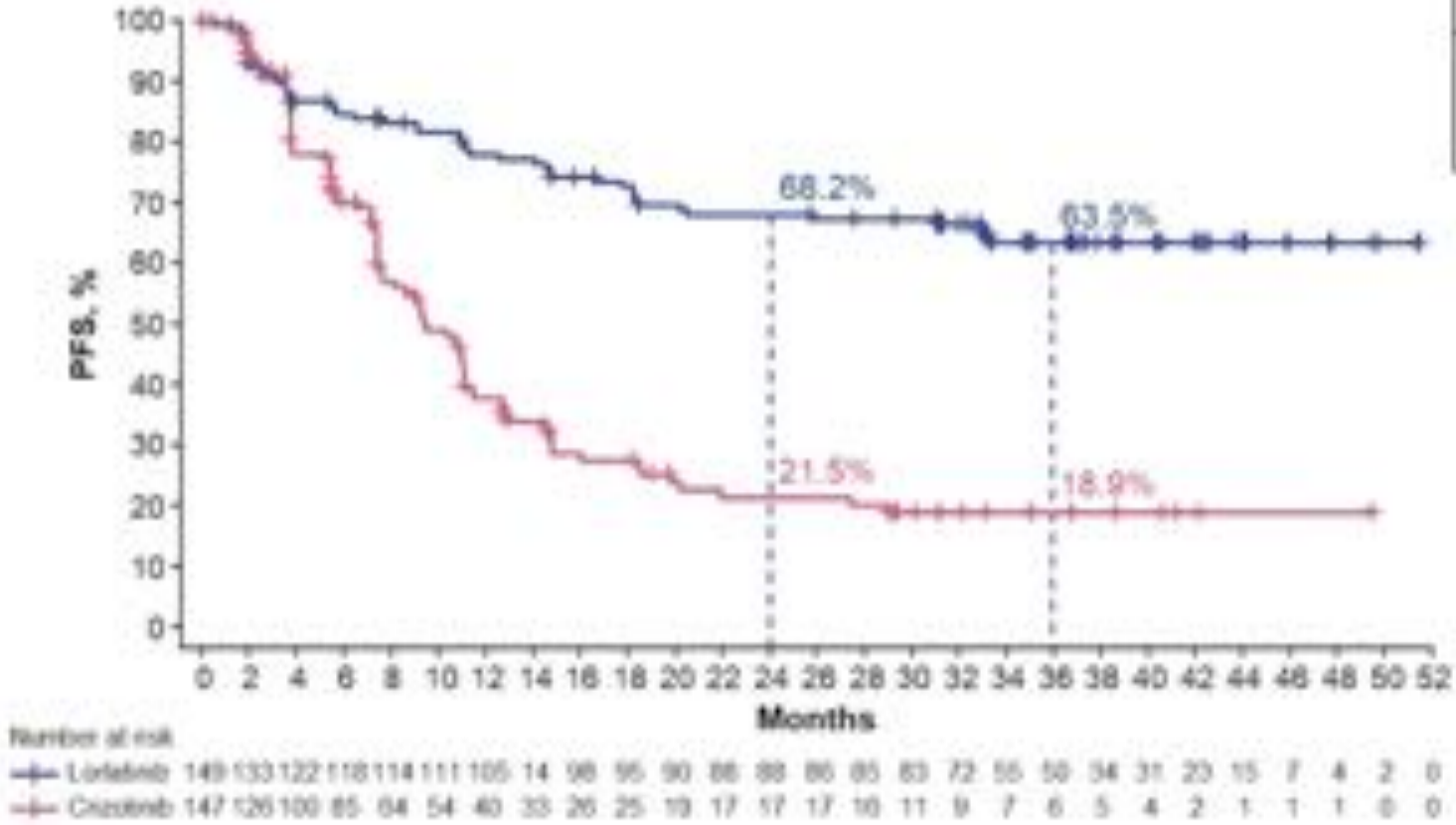


1. Shaw AT, et al. *N Engl J Med*. 2020;383:2018-2029. 2. Lorbrena (lorlatinib). Prescribing information. Pfizer Inc; 2021. Accessed March 2, 2022. https://labeling.pfizer.com/ShowLabeling.aspx?id=13182. 3. Lorbrena (lorlatinib). Japanese prescribing information. Pfizer Japan Inc; 2021. Accessed March 2, 2022. 4. European Medicines Agency. Accessed March 2, 2022. https://www.ema.europa.eu/en/documents/overview/lorviqua-epar-medicine-overview_en.pdf

BICR, blinded independent central review; BID, twice daily; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PS, performance status; QD, once daily; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression; TTR, time to tumor response.
*Defined as the time from randomization to RECIST-defined progression or death due to any cause.

At 36.7 months of median follow-up in the lorlatinib arm, BICR assessed PFS remained longer with lorlatinib than with crizotinib

Intention-to-treat population (ITT)

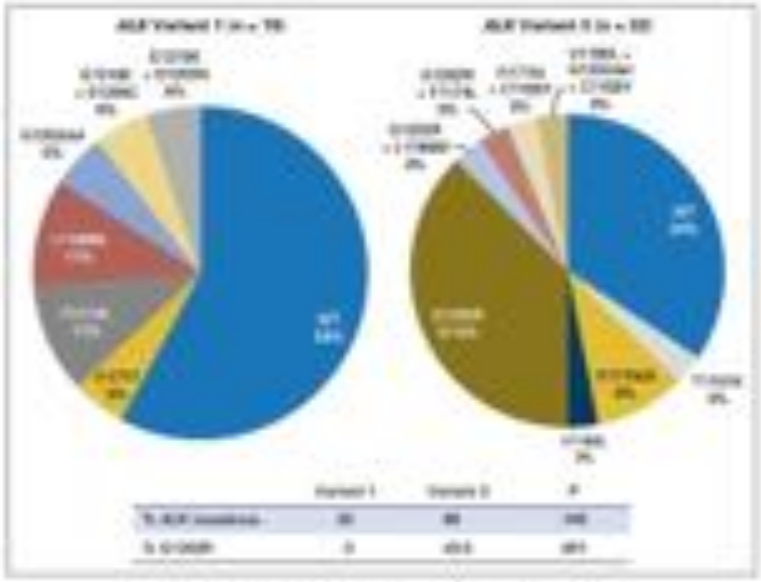


	ITT	
	Lorlatinib (n=149)	Crizotinib (n=147)
Events	49	92
PFS, median (95% CI), months	NE (NE, NE)	9.3 (7.6, 11.1)
HR (95% CI)	0.27 (0.184, 0.388)	

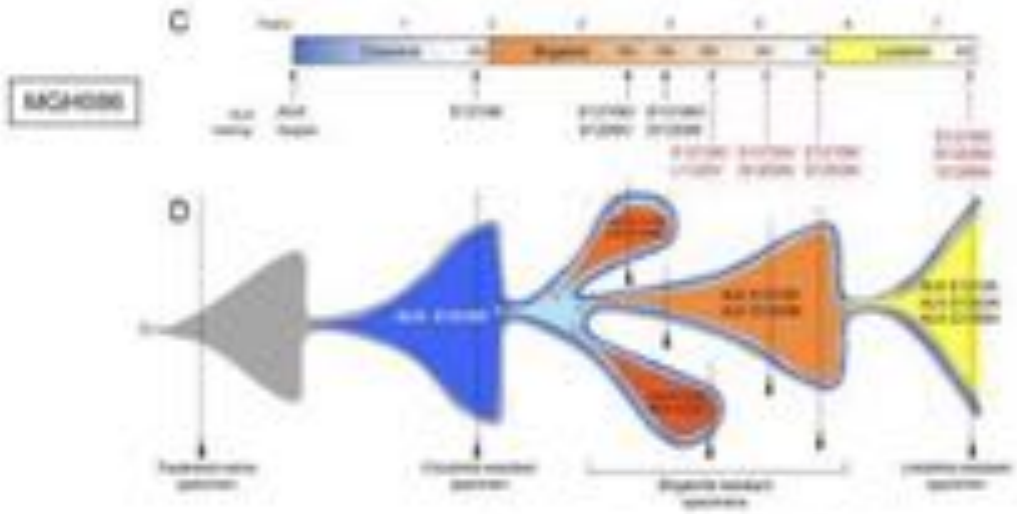
- Confirmed ORR by BICR
  - 77.2% (lorlatinib) vs 58.5% (crizotinib)
- Median DOR, months
  - NR (lorlatinib) vs 9.6 months (crizotinib)

Unanswered questions…

- 2nd vs 3rd gen TKI as 1L.
- Continuation TKI with chemotherapy after progression.
- TKI sequencing.
- Role of baseline co-mutations (TP53) or variants in making treatment decisions for 1L.
- Practical role of post progression biopsy.
- Management of compound resistance.
- How to improve testing frequency.



Lin et al. J Clin Oncol 2018; 36: 1199-1206



Yoda et al. Cancer Discov 2018; 8: 714-729

Emerging ALK Inhibitors and Combinations

- On-target resistance to 3G ALK TKI lorlatinib is mediated by compound *ALK* kinase domain mutations; novel 4G ALK TKIs with potency against double/triple ALK mutants are therefore being developed.

- **TPX-0131** is a 4G compact, macrocyclic ALK inhibitor with preclinical potency against *ALK* wild-type, G1202R, L1198F, and a broad range of *ALK* compound mutations, currently phase 1 testing (FORGE-1).

- **NVL-655** is a 4G highly selective and CNS-penetrant ALK inhibitor with preclinical potency against *ALK* wild- type, G1202R, and G1202R-based compound mutations, anticipated to enter phase 1 testing in 2022.

- Off-target resistance to next-generation ALK TKIs is common.

- Clinical trials of **combination regimens** to overcome some of the known off-target mechanisms of resistance to ALK TKIs (e.g., ALKi+METi, ALKi+MEKi, ALKi+SHP2i) are enrolling patients with goals to assess safety and preliminary efficacy.

Jessica J. Lin, MD. IASLC 2022 Targeted Therapies in Lung Cancer Meeting. Feb 22-26, 2022.

Preclinical Activity of NVL-655 in a Patient-Derived NSCLC Model with Lorlatinib-Resistant ALK G1202R/T1151M Mutation

NVL-655

Preclinical features

1. **Activity against ALK**
   ~5% of all non-small cell lung cancers (NSCLC) are ALK positive[1]
2. **Activity against ALK resistance mutations**
   such as G1202R, G1202R/L1196M, and G1202R/T1151M mutations that confer resistance to previous generation therapies[2,3]
3. **Activity in the central nervous system (CNS)**
   ~40% of patients with ALK-positive NSCLC have brain metastases at diagnosis[4]
4. **Sparing TRKB**
   TRKs, especially TRKB, are key off-target kinases whose inhibition in the CNS is associated with neurological adverse events and dose-limiting toxicities[5,6]

Feature	Crizotinib	2nd gen*	Lorlatinib	TPX-0131	NVL-655 goal
ALK activity	Yes	Yes	Yes	Yes	Yes
G1202R activity	No	No	Yes	Yes	Yes
G1202R/L1196M activity	No	No	No	Yes	Yes
CNS activity	Not on label	Yes	Yes	Likely[7]	Yes
Sparing TRKB	Limited CNS penetrance	Yes	Limited at dose developed for ALK G1202R**	No	Yes

▲ Table 1 Comparative profiles of NVL-655 versus other ALK inhibitors. *FDA/EMA-approved 2nd-generation ALK inhibitors include ceritinib, alectinib, and brigatinib. **See Figure 2.

NVL-655 is being evaluated in a Phase 1/2 clinical trial for patients with advanced NSCLC and other solid tumors harboring ALK rearrangement or activating ALK mutation (ALKOVE-1): **NCT05384626**.

Mizuta H et al. Gustave Roussy, University of Paris-Saclay, France. 2022 WCLC, Aug 6-9.

GenesisCare FAU MEDICINE OLA

Any news on ALK + in 2022 WCLC?

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Integrated Efficacy and Safety of Brigatinib Following Alectinib Treatment in the ALTA-2 and J-ALTA Studies

Background

- Alectinib is a standard-of-care anaplastic lymphoma kinase inhibitor for patients with advanced or metastatic *ALK*-positive non–small cell lung cancer; however, most patients eventually develop disease progression
- Subsequent ALK inhibitor therapy can be beneficial in these patients, but few studies have evaluated ALK inhibitors in patients with *ALK*+ NSCLC following progression on alectinib
- We conducted an integrated efficacy and safety analysis of two phase 2 studies of brigatinib treatment in patients with *ALK*+ NSCLC with disease progression on alectinib

Overview of Integrated Study Design

ALTA-2 (NCT03535740), post-alectinib cohort (n=86)[1]

Single arm, open-label study conducted in Asia, Europe, North America, and Australia

- Locally advanced or metastatic *ALK*+ NSCLC[a]
- Disease progression on alectinib
- ≤3 lines of systemic therapy for metastatic disease (included crizotinib prior to alectinib)

Brigatinib 180 mg QD (7-day lead-in at 90 mg QD)

Primary endpoint:
Confirmed BIRC-assessed ORR
Secondary endpoints:
DoR, PFS, OS, safety

J-ALTA (NCT03410108), main cohort (n=47)[2]

Single arm, open-label study conducted in Japanese patients

- Locally advanced or metastatic *ALK*+ NSCLC[a]
- Disease progression on alectinib ± prior crizotinib

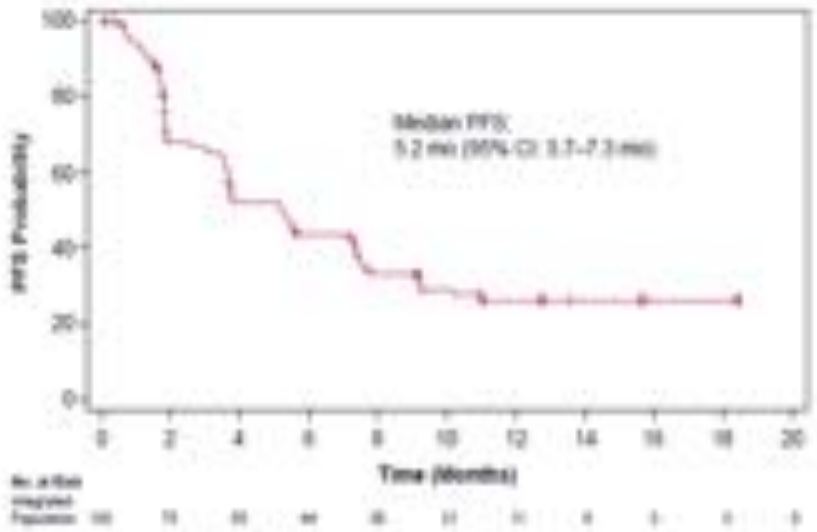
[a] Patients with asymptomatic brain metastases at screening were eligible for enrollment

ALK, anaplastic lymphoma kinase; *ALK*+, *ALK* gene rearranged; BIRC, blinded independent review committee; DoR, duration of response; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily.

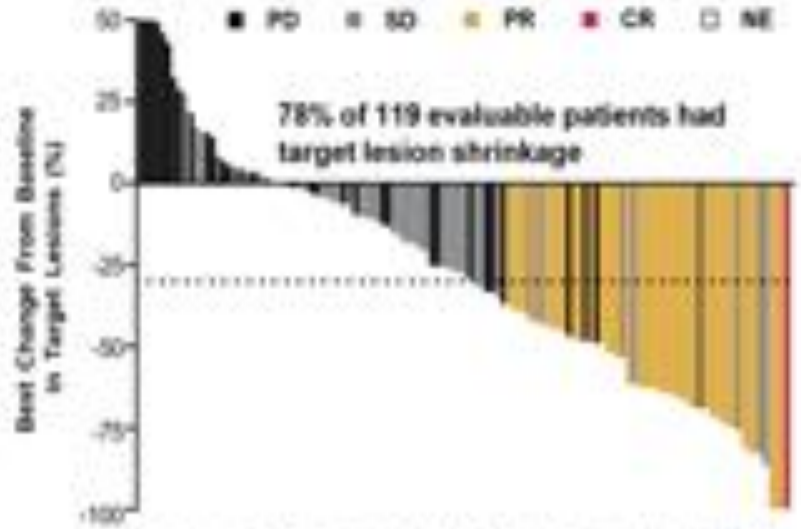
1. Ou SI, Nishio M, Ahn MJ, et al. *J Thorac Oncol*. 2021 (submitted); 2. Nishio M, Yoshida T, Kumagai T, et al. *J Thorac Oncol*. 2021;16(3):453-463.

Sai-Hong I. Ou, UCI School of Medicine, Irvine, California, USA; 2022 WCLC, Vienna, Austria, August 6-9, 2022.

BIRC-Assessed Progression-Free Survival



Best Target Lesion Response



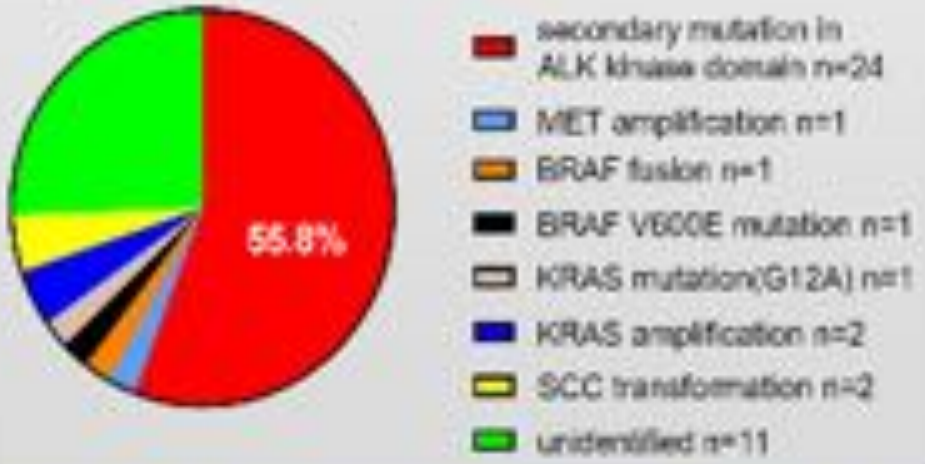
- Data cut-off: J-ALTA, January 22, 2020; ALTA-2, September 30, 2020
- Median follow-up for the integrated population: 11 months
- Thirty-four patients (26%) were still receiving brigatinib treatment at the data cut-off

- Brigatinib treatment demonstrated clinically meaningful efficacy in this integrated analysis of patients with advanced or metastatic *ALK*+ NSCLC who progressed on prior alectinib in the ALTA-2 or J-ALTA trials
- Safety results were consistent with the known profile of brigatinib, with no new safety findings observed

Pattern of Resistance- RWD

	Cohort 1 alectinib n=20	Cohort 2 crizotinib stage n=52	p value
CNS progression	15%	57.7%	0.001
symptomatic CNS progression	5%	32.7%	0.018

Figure1: Possible resistance mechanism



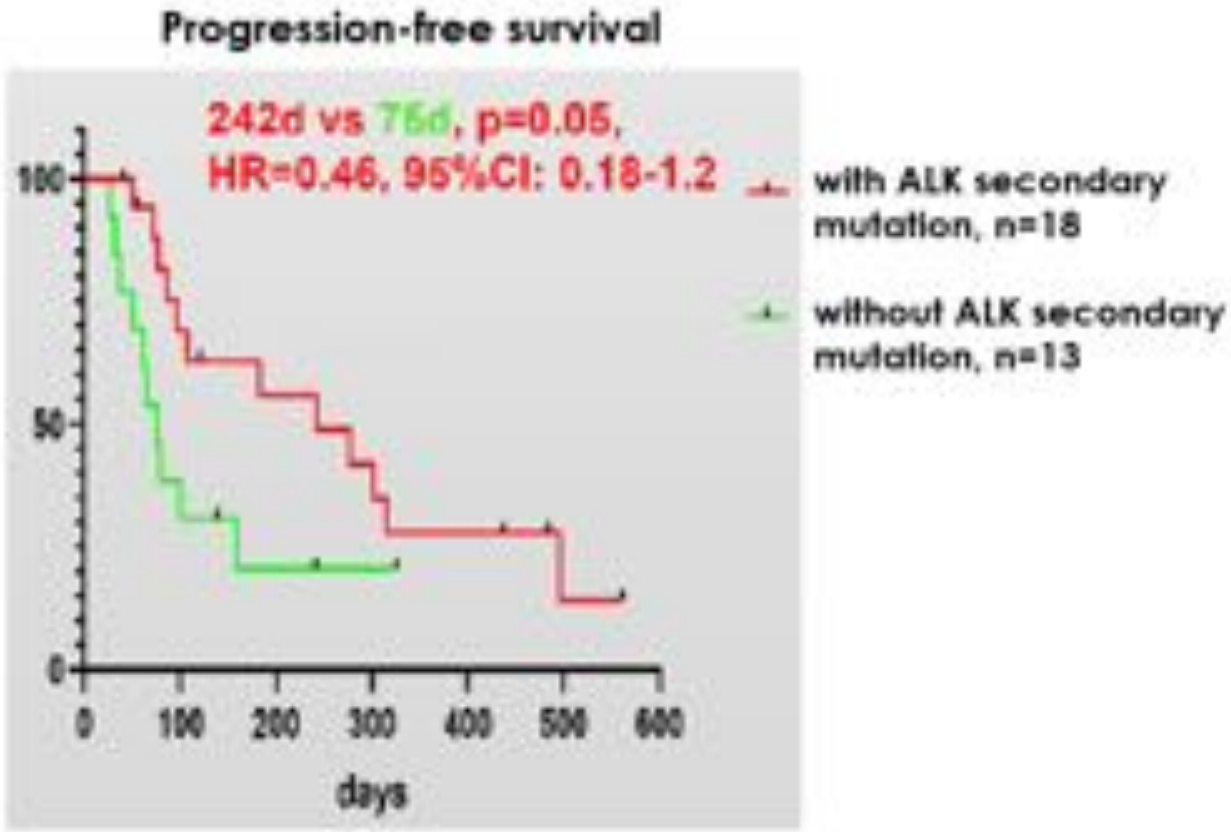
- Cohort 1: 2G alectinib as 1L, then progressed.
- Cohort 2: progressed on crizotinib followed by alectinib, then progression.

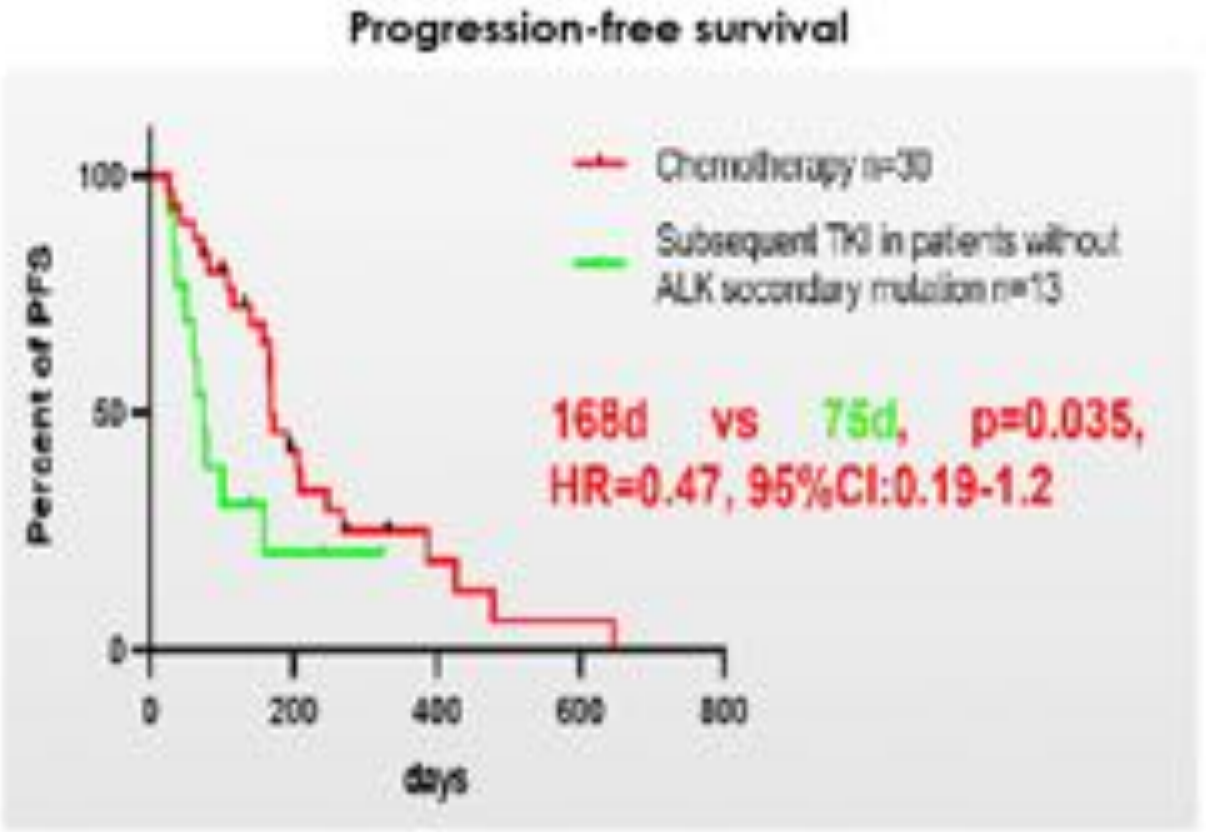
- Resistance mutation in ALK kinase domain (24/43, 55.8%) especially G1202R (15/43, 34.9%) was the dominant resistance mechanism.

- ALK compound mutation which appeared following the treatment of multiple ALK-TKIs conferred primary resistance to lorlatinib.

Zou Z et al. Progression pattern, resistance mechanism and subsequent therapy for ALK + NSCLC in the era of 2 G ALK-TKIs. National Cancer Center, Chinese Academy of Medical Sciences and Peking Union Medical College. 2022 WCLC, Vienna, Austria, Aug 6-9.

Progression pattern, resistance mechanism and subsequent therapy for ALK + NSCLC in the era of 2 G ALK-TKIs.

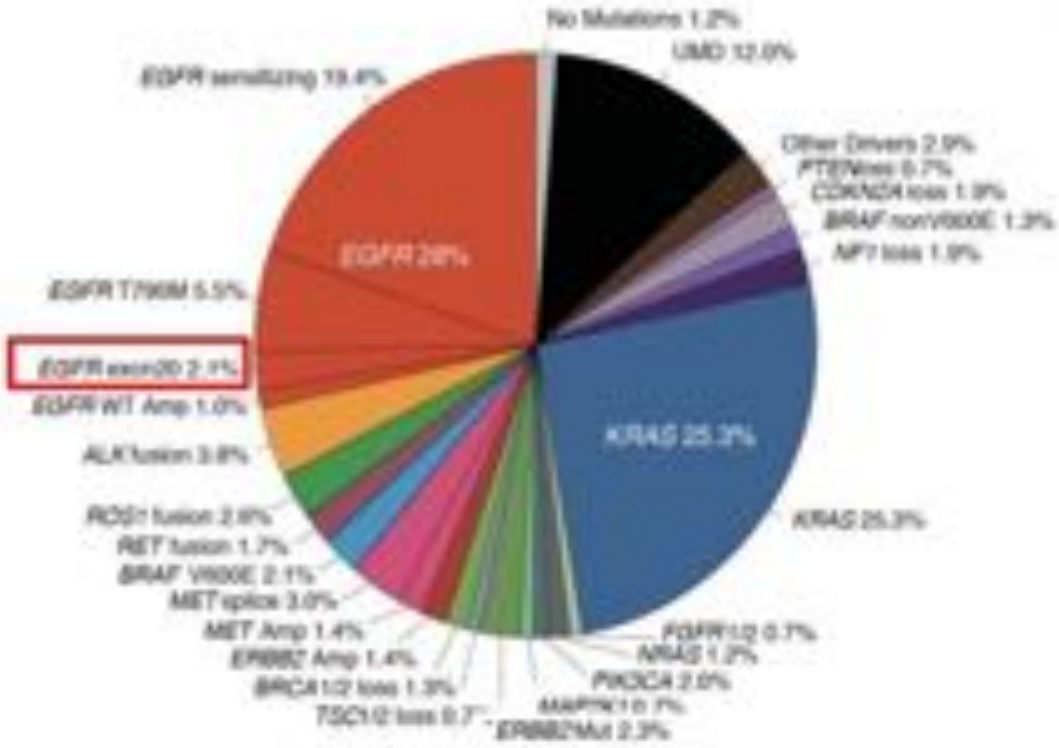




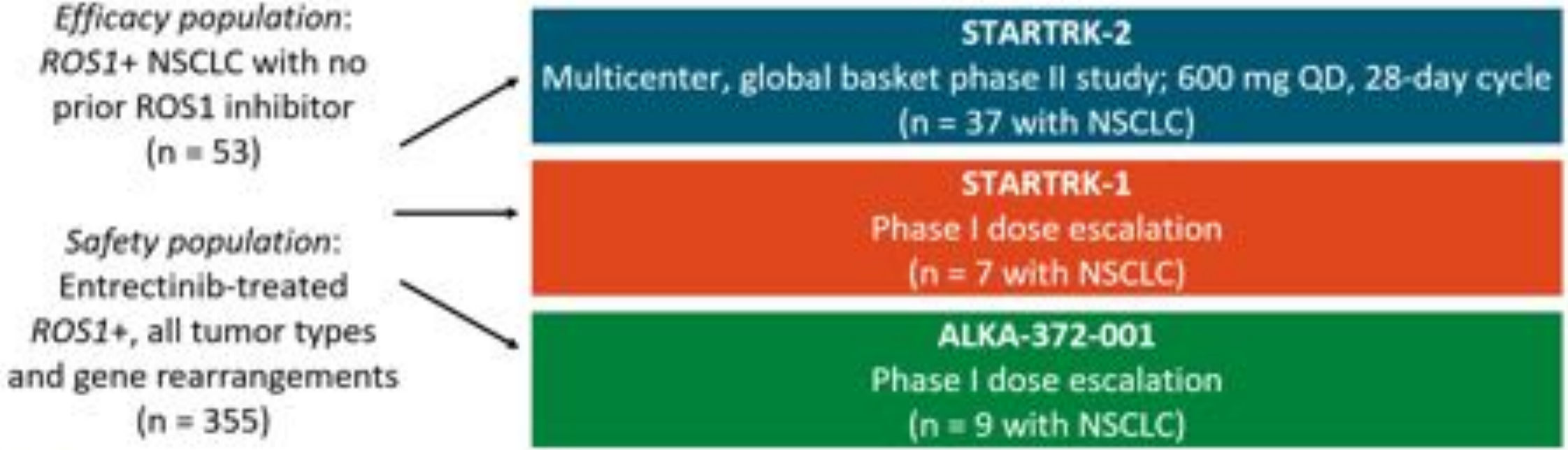
- Rebiopsy could be beneficial to establish clinical regimens and estimate effectiveness of subsequent treatments.
- Chemotherapy is still an important strategy especially in patients with insensitive to targeted therapy.

Zou Z et al. National Cancer Center, Chinese Academy of Medical Sciences and Peking Union Medical College. 2022 WCLC, Vienna, Austria, Aug 6-9.

ROS1 Pathway



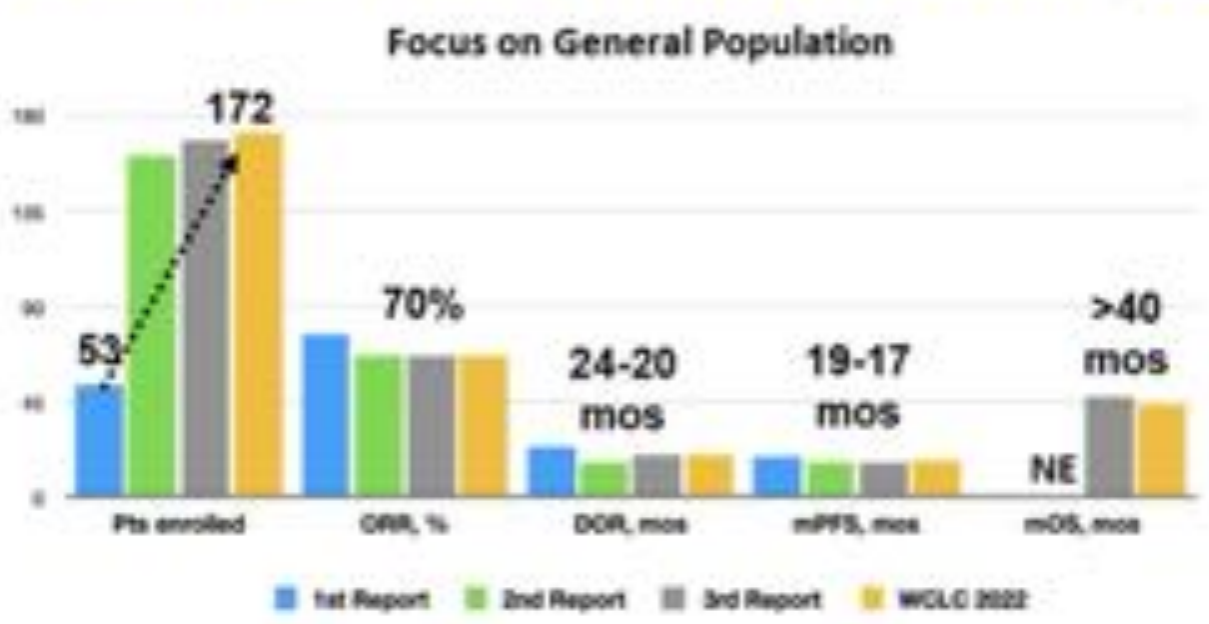
Entrectinib in *ROS1+* NSCLC: Integrated Analysis

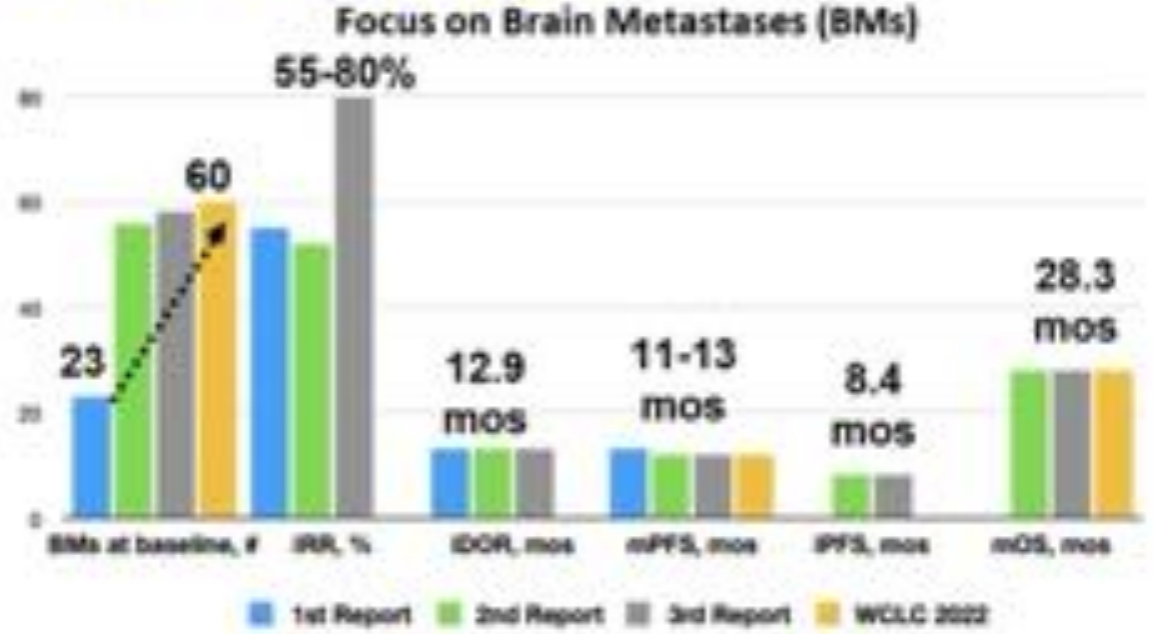


- Primary endpoints: ORR, DoR
- Secondary endpoints: PFS, OS, intracranial ORR and DoR, safety/tolerability

Doebele RC, et al. WCLC 2018. Abstract OA02.01. ClinicalTrials.gov. NCT02568267.
Drilon A, et al. Cancer Discov. 2017;7:400-409.

Entrectinib in ROS1+ NSCLC
Lessons learned from ALKA-372-001/STARTRK-1/STARTRK-2 trials



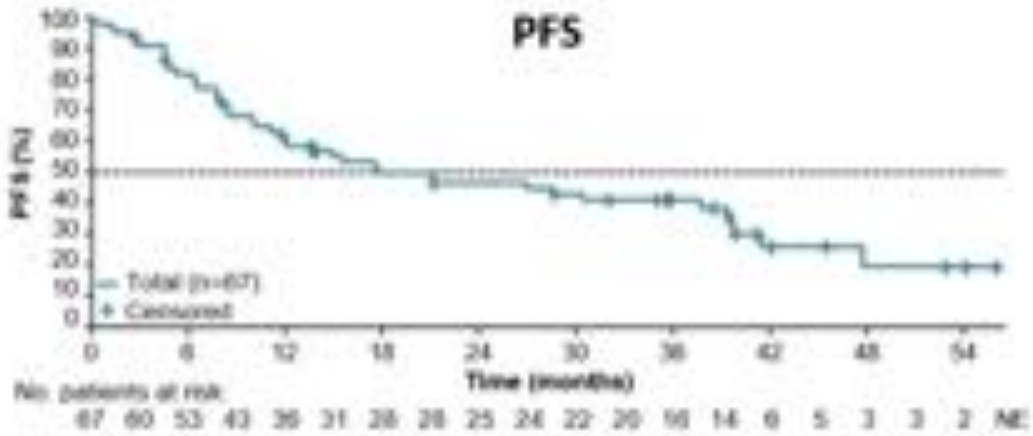


- **Entrectinib demonstrated robust overall and intracranial efficacy in ROS1 + NSCLC**
- **No new safety signals**

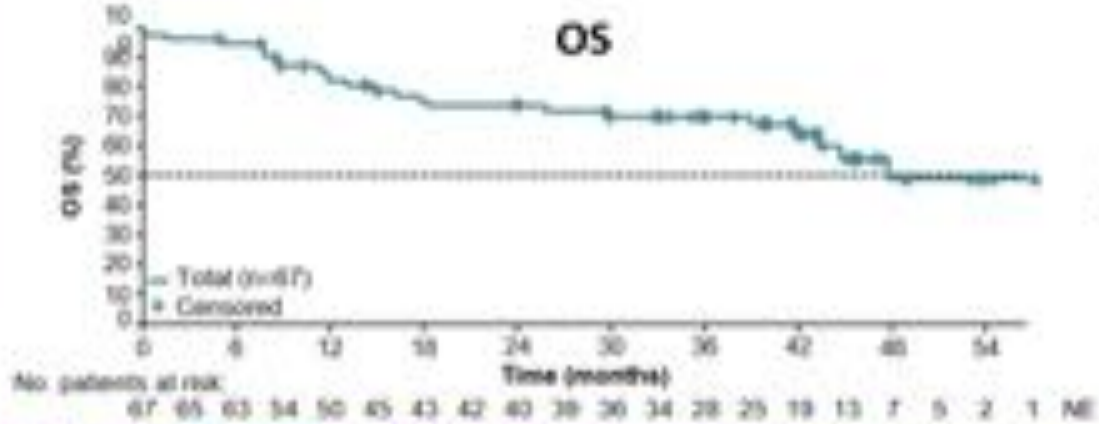
Drilon A, et al. Lancet Oncol 2019, Dziadziuszko R, et al. JCO 2021, Drilon A, et al. JTO 2022, Fan Y, et al. WCLC 2022

What's really new about Entrectinib?

	First-line population† (n=67)
ORR, n (%) [95% CI]	**46 (68.7)** [56.2–79.4]
CR	10 (14.9)
PR	36 (53.7)
SD	7 (10.4)
PD	5 (7.5)
Non-CR / PD	6 (9.0)
Missing / unevaluable	3 (4.5)
Median DoR, months [95% CI]	**35.6** [13.9–38.8]



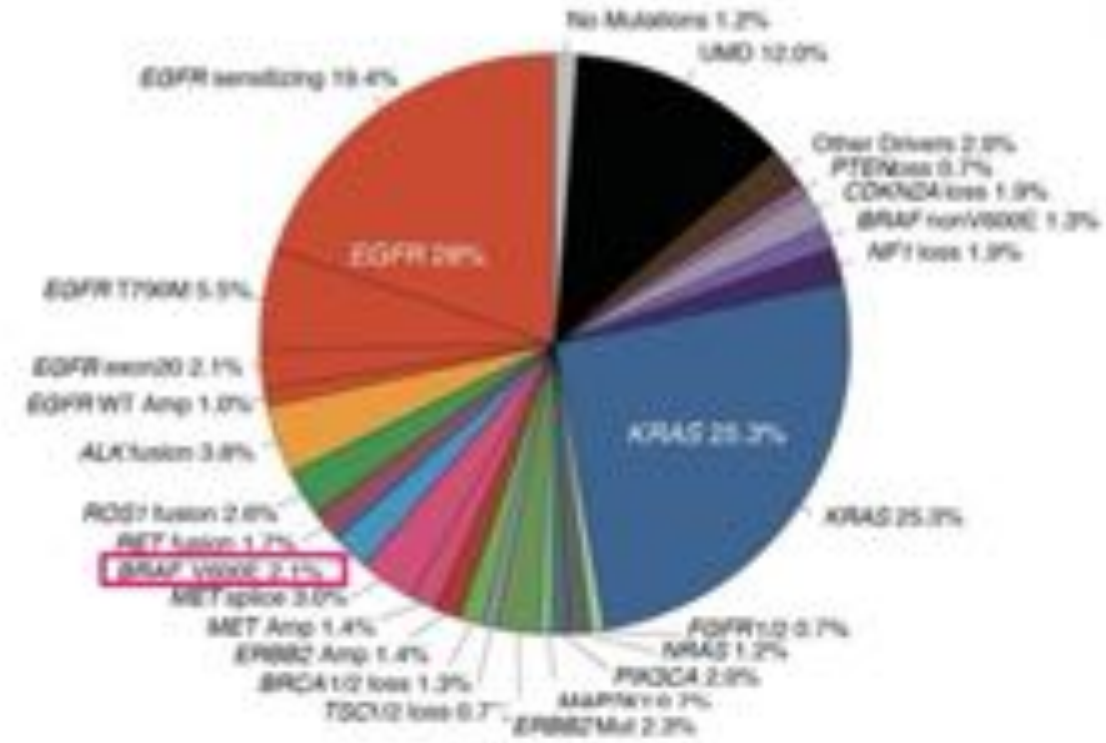
17.7 [[95% CI]11.8–39.4]



47.7 [[95% CI] 43.2–NE]

Fan Y, WCLC 2022

B-RAF Pathway



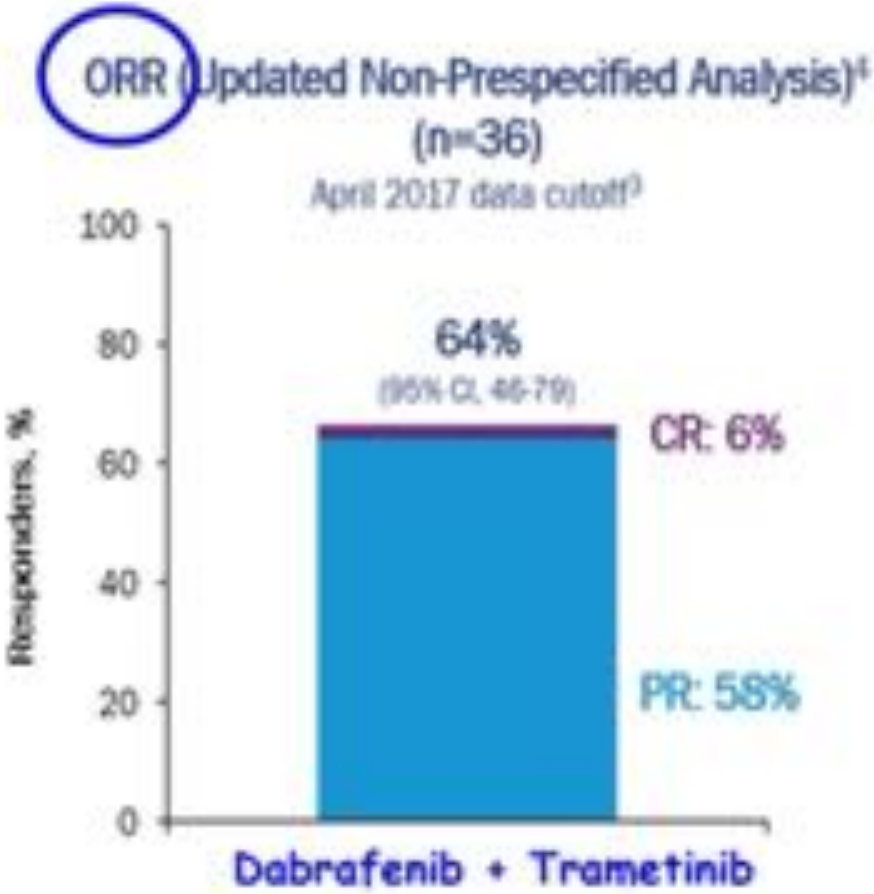
B-Raf/MEK Inhibitors

- Dabrafenib/Trametinib
  - Melanoma (metastatic and adjuvant)
  - Lung cancer (metastatic)
  - All solid tumors w $BRAF^{V600E}$

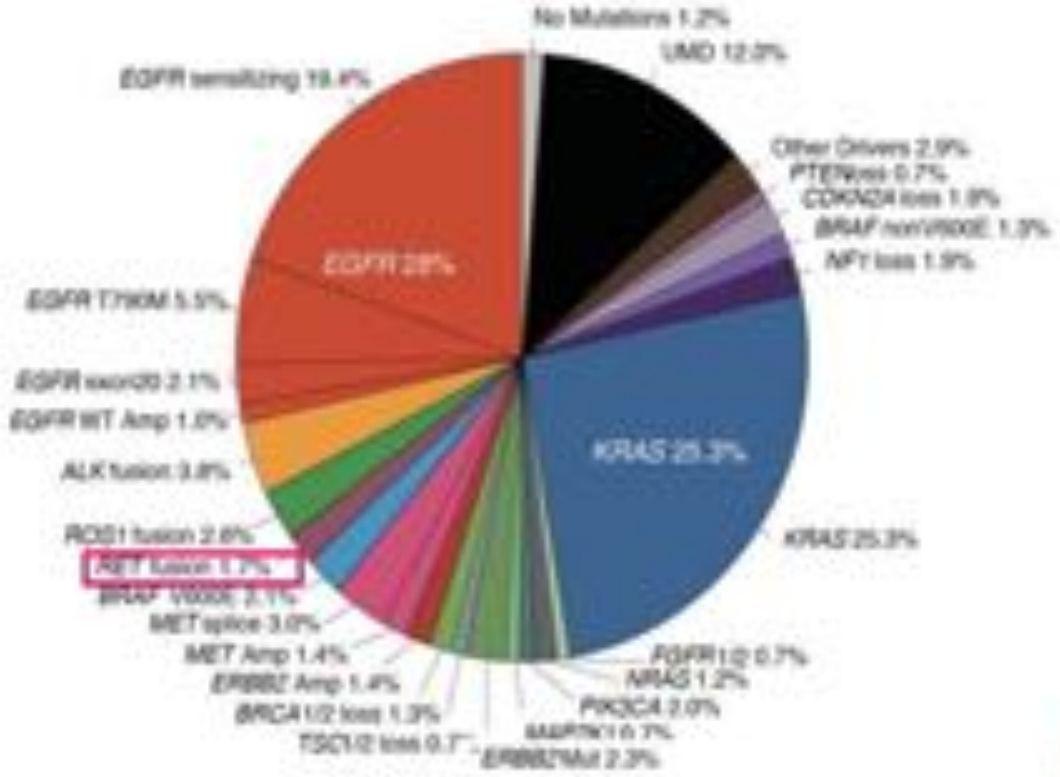
- Cobimetinib/Vemurafenib*
  - Melanoma (metastatic)
  - Erdheim-Chester Disease*

- Binimetinib/Encorafenib
  - Melanoma (metastatic)
  - Colon Cancer (metastatic)** (encorafenib plus cetuximab)

First-Line: Dabrafenib + Trametinib in Patients with B-Raf V600E Metastatic NSCLC: ORR & DOR



RET Pathway


No Mutations 1.2%
UMD 12.0%
EGFR sensitizing 19.4%
Other Drivers 2.9%
PTENloss 0.7%
CDKN2A loss 1.8%
BRAF non-V600E 1.3%
NF1 loss 1.9%
EGFR 28%
EGFR T790M 5.5%
EGFR exon20 2.1%
EGFR WT Amp 1.0%
KRAS 25.3%
ALK fusion 3.8%
ROS1 fusion 2.6%
RET fusion 1.3%
BRAF V600E 2.1%
MET splice 3.0%
MET Amp 1.4%
ERBB2 Amp 1.4%
BRCA1/2 loss 1.3%
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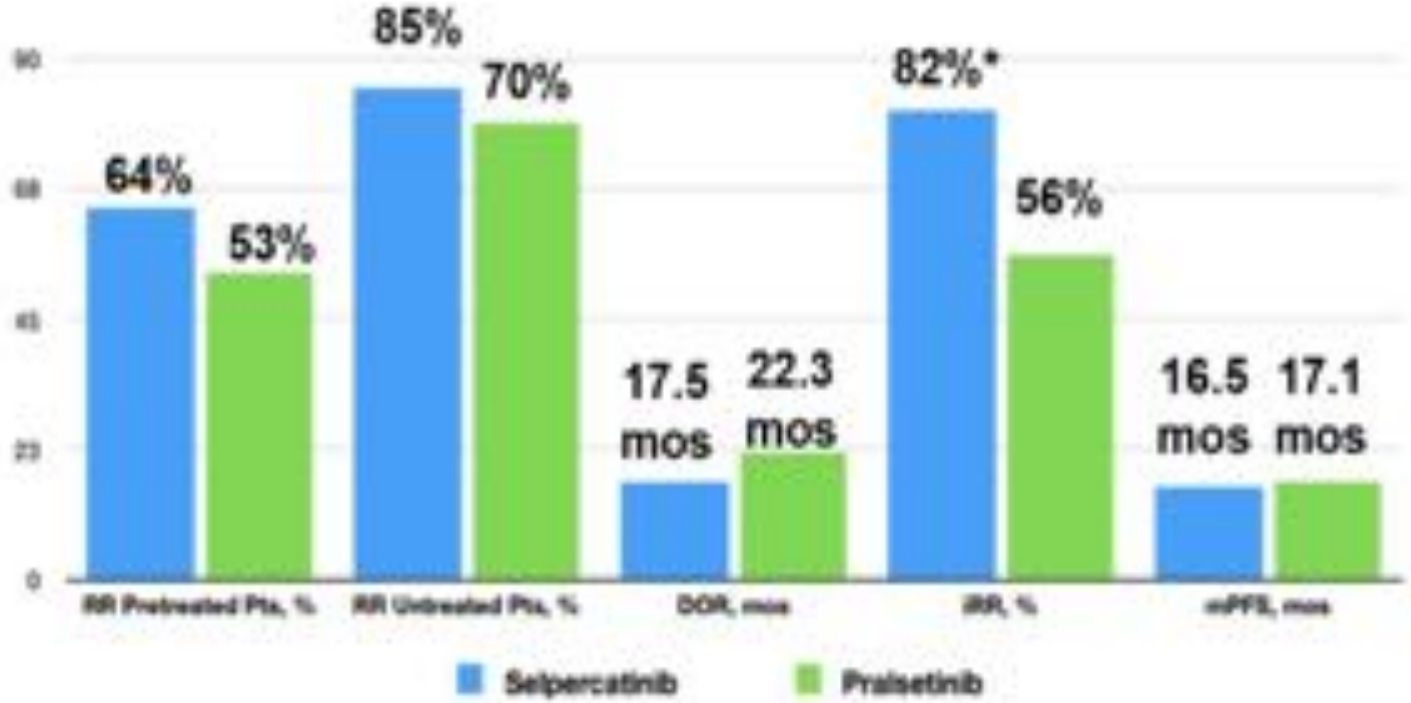
FGFR1/2 0.7%
NRAS 1.2%
PIK3CA 2.0%
MAPK1 0.7%
ERBB2Mut 2.3%

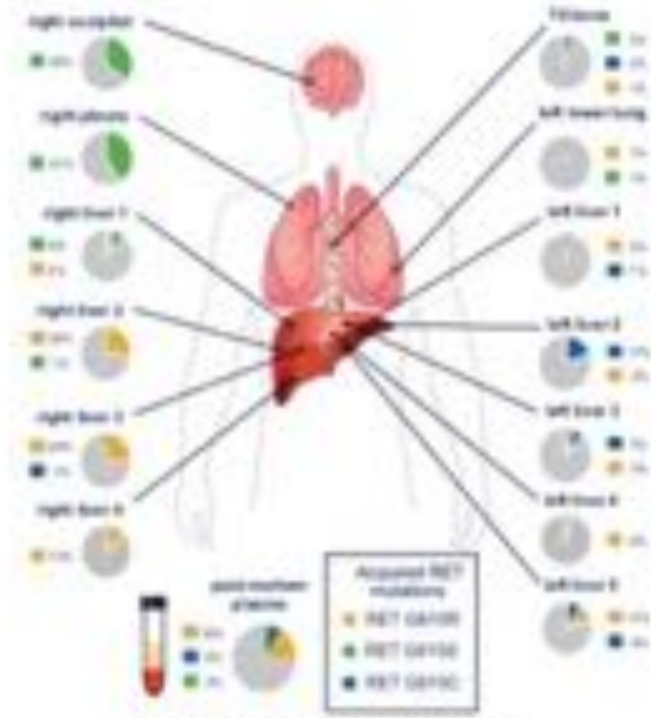
RET Inhibition in Practice

Efficacy of Selpercatinib and Pralsetinib in in *RET*+ NSCLC



Drilon A, et al. NEJM 2020; Gainor J, et al. Lancet Oncol 2021
*measurable disease

Acquired resistance to RET inhibitors

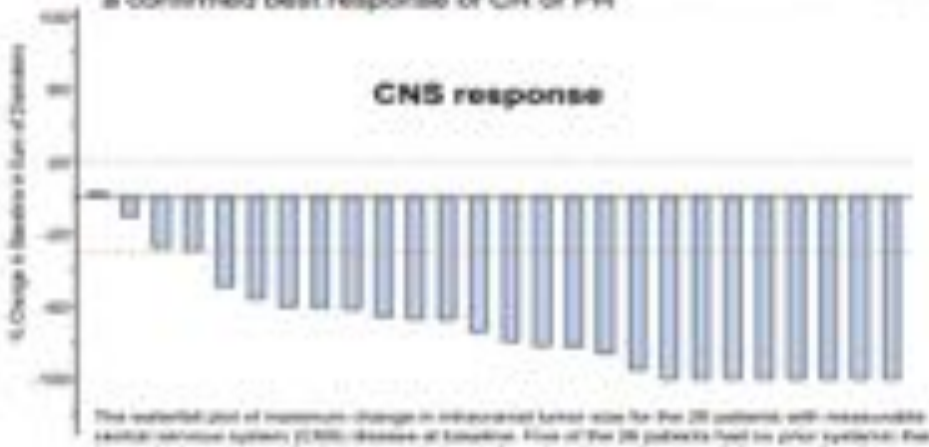


Solomon B, et al. JTO 2020

Durability of Efficacy and Safety with Selpercatinib in Patients with RET Fusion+ Non-Small-Cell Lung Cancer: LIBRETTO-001

CNS Response

- Of the 26 patients with measurable CNS disease at baseline, 22 had a confirmed best response of CR or PR



CNS ORR: 85%

Drilon A *et al.* P27. 12th European Lung Cancer Conference (ELCC): Prague, Czech Republic: 30 March – 2 April, 2022.

Ongoing Phase III & Other Trials in RET Fusion + NSCLC

Trial	NCT#	Investigational Arm	Control Arm	# Pts
LIBRETTO-431 (Phase 3)	04194944	**Selpercatinib**	Plat + Pem ± Pembro	250
AcceleRET-Lung (Phase 3)	04222972	**Pralsetinib**	Plat + Pem +/- Pembro (adeno); + gem or + pacli/nab-pacli ± Pembro (SQ)	250
LIBRETTO-432 (Ph 3; Adjuvant)	04819100	**Selpercatinib**	Placebo	170
NAUTIKA1 (Phase 2)	04302025	**Pralsetinib**	(Neo & Adj biomarker-selected; IB-IIIA	80
LUNG-MAP (Phase 2)	04280081	**Selpercatinib**	(RET fusion+ advanced NSCLC)	124
ORCHARD (Phase 2)	03944772	**Selpercatinib**	(RET+ NSCLC progressing on 1L Osi)	220

https://clinicaltrials.gov. Accessed July 2, 2022

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Unanswered Questions:

- Sequential therapy: from Selpercatinib to Pralsetinib or viceversa; (RWD; S. Dawood; 2022 ASCO, abstr 9079).

Use of RETis Among Patients with NSCLC: A Real-World Evidence Analysis.

Figure 4. **Overall Survival from date of diagnosis of stage IV disease among pts without brain metastases stratified by whether they received sRETi or MKIs**

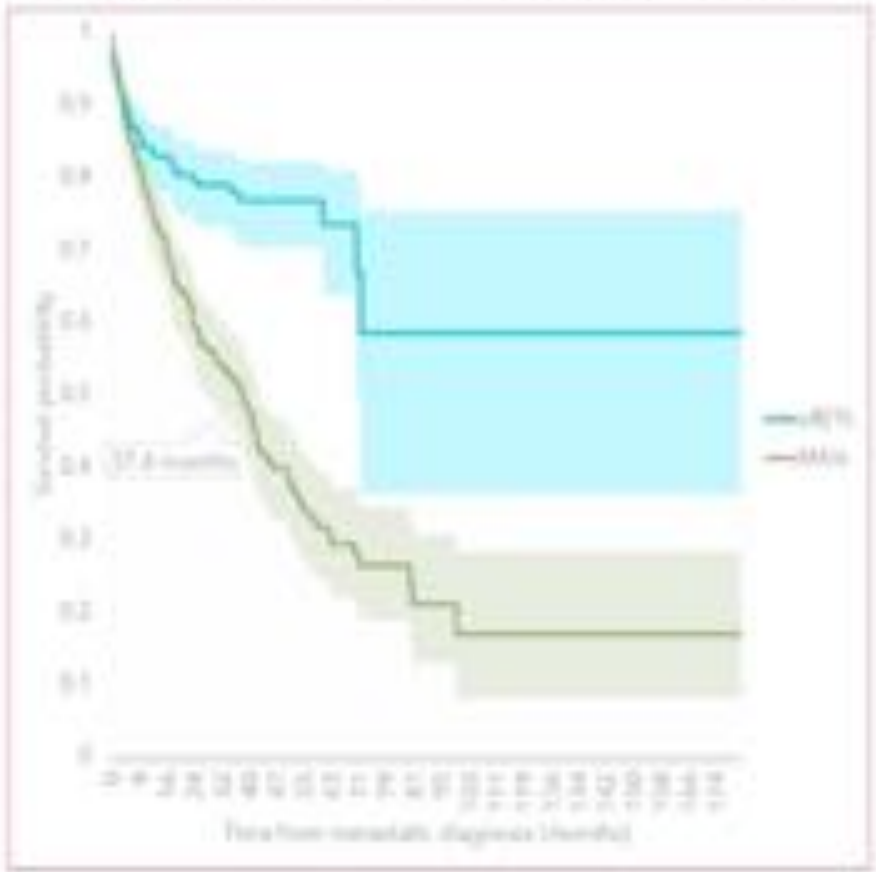
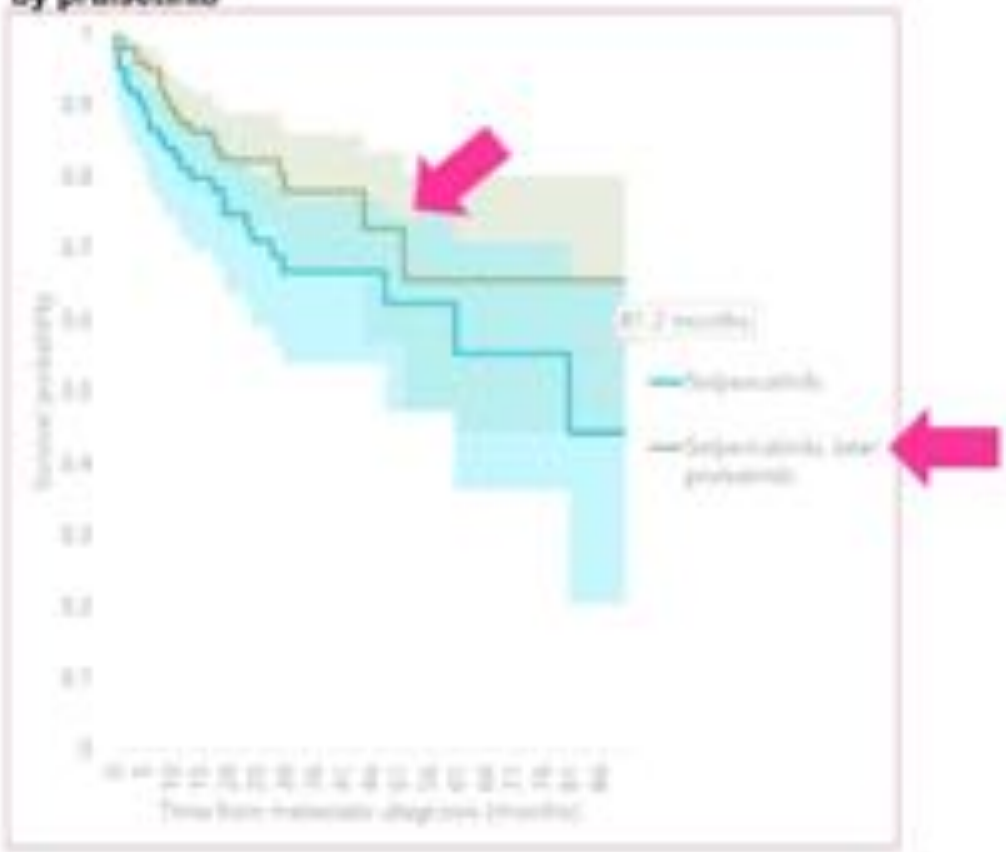


Figure 5. **Overall Survival from the date of diagnosis of stage IV disease among pts stratified by whether they received selpercatinib alone or selpercantinib followed by pralsetinib**

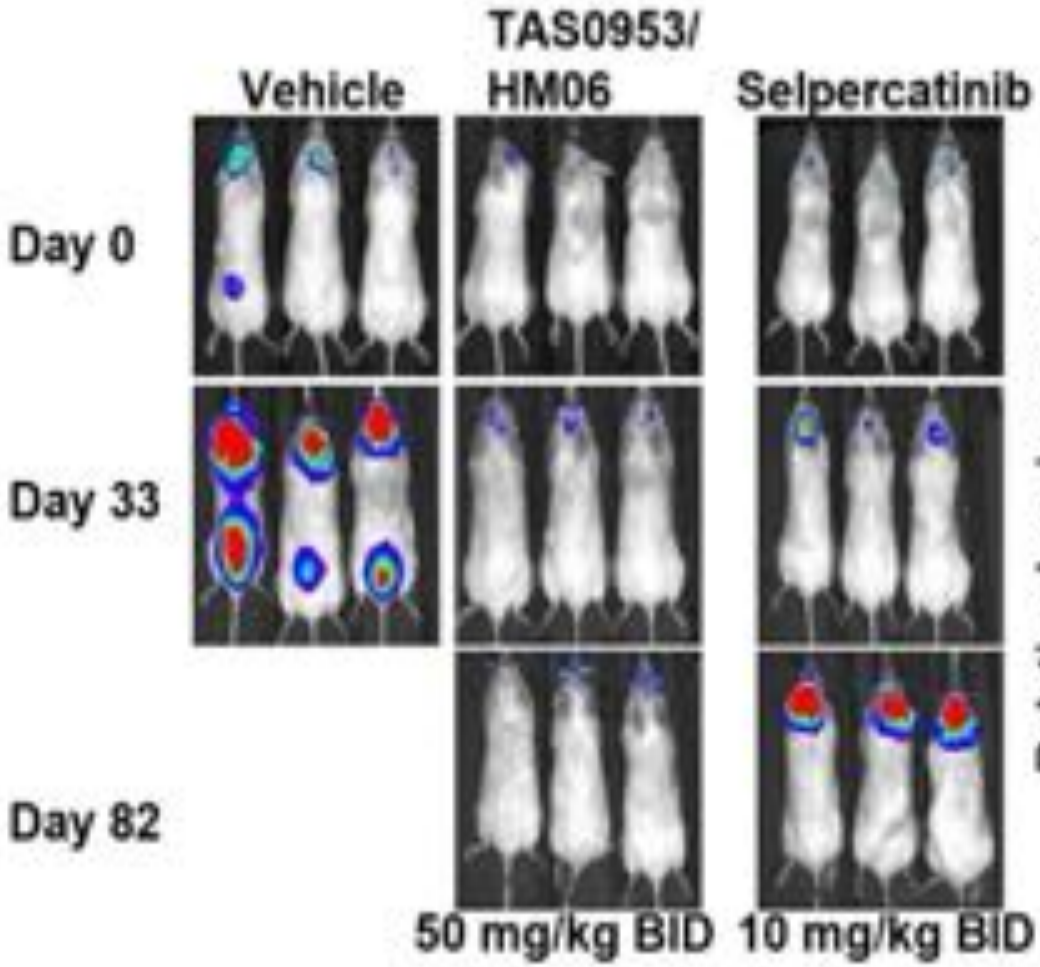


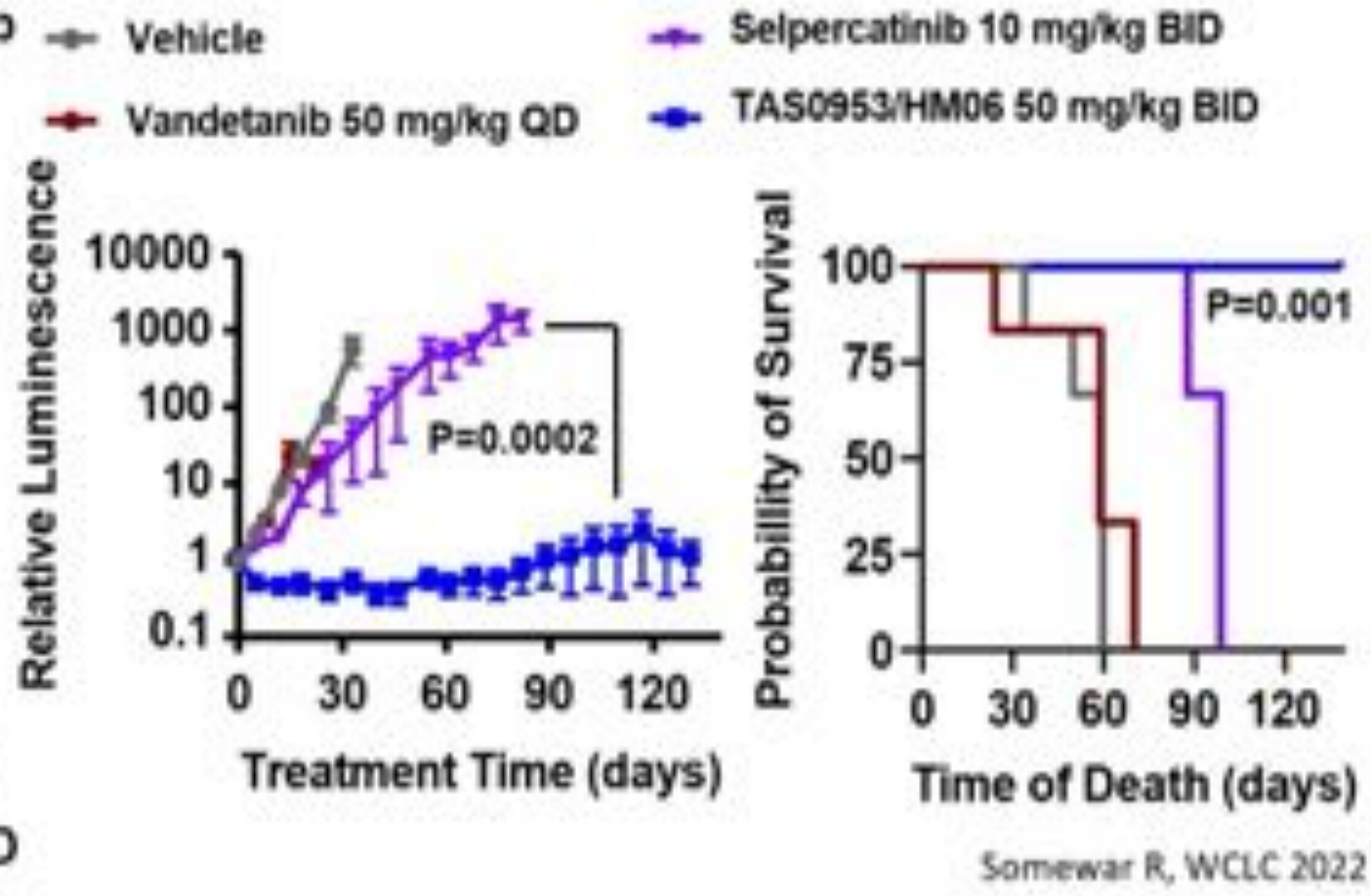
- First RWD set to show use of pralsetinib following progression on selpercatinib.
- **Real world evidence of a trend toward improved prognostic outcomes with sequential use of both agents.**
- Statistics: 48.7% received sRETi; 52.3% received MKIs; 56.6% of pts receiving pralsetinib received prior selpercatinib; 28.9% of pts receive sRETi/MKIs as first line therapy.

Let's discover novel RET inhibitors

Drug	CNS Penetration	Activity against V804 mutations	Activity against G810 mutations	Phase of development
BOS172738/DS-5010 Zeteletinib	✓	+	-	Ph. I – NCT03780517 Treatment naïve Dose escalation data reported
TPX-0046 Enbenzotinib	✓	+	+	Preclinical data available Ph. I/II ongoing NCT04161391 TKI-naïve and pretreated
LOXO- 260	✓	+	+	Preclinical data available Ph. I/II ongoing NCT05241834 TKI-pretreated
TAS0953/HM06 Vepafestinib	See next slides			

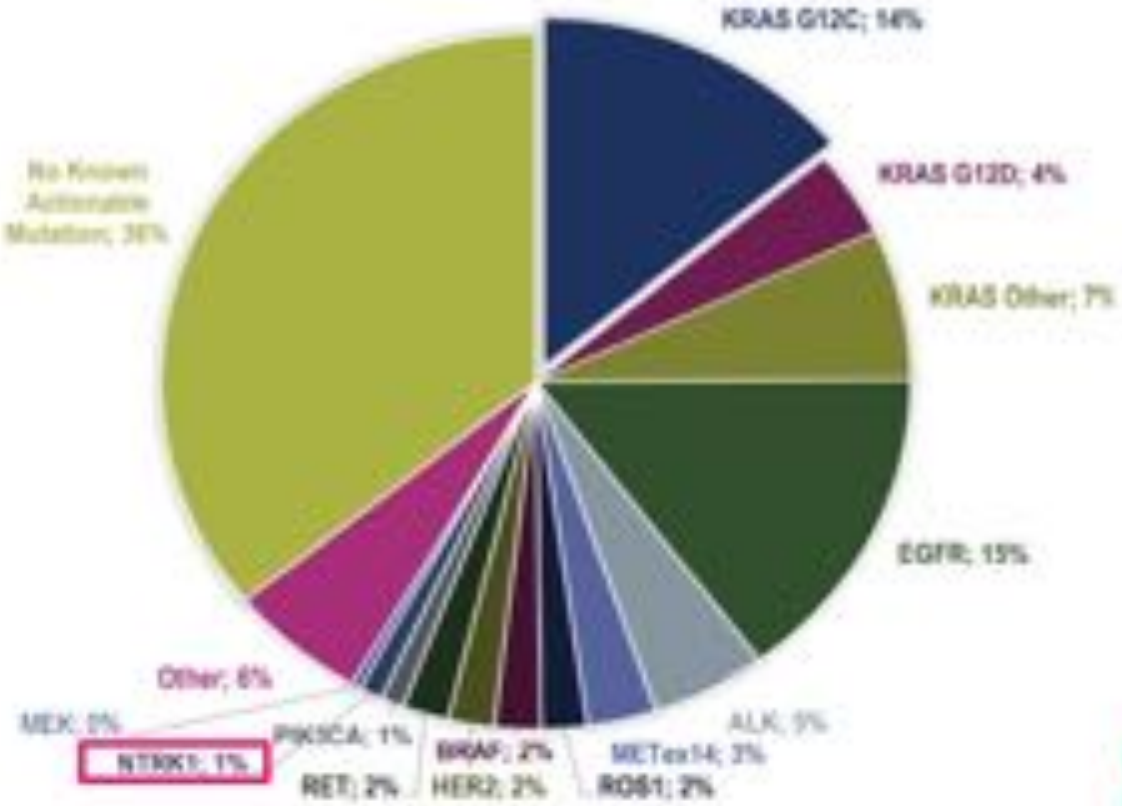
TAS0953/HM06 is more Effective than Selpercatinib in the CNS





Somewar R, WCLC 2022

NTRK Pathway



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NTRK fusions are found in diverse cancers including lung cancers

Cancers enriched for TRK fusions

Secretory breast carcinoma
Mammary analogue secretory carcinoma
Infantile fibrosarcoma

Frequency
75% to >90%

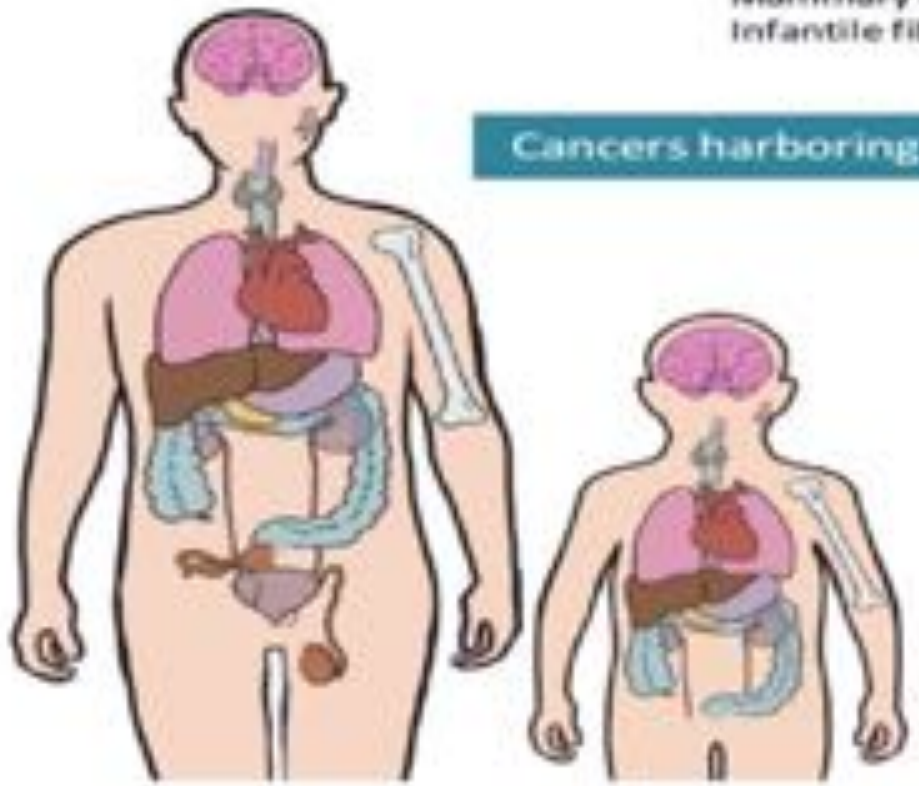
Cancers harboring TRK fusions at lower frequencies

Congenital mesoblastic nephroma
Pontine glioma
Spitzoid melanoma
Thyroid Cancer
GIST ("pan-negative")

Frequency
5% to 25%

Lung cancer
Other sarcomas
Astrocytoma/Glioblastoma
Colorectal cancer
Cholangiocarcinoma
Pancreatic cancer
Head and neck squamous cancer
Breast cancer
Melanoma

Frequency
<1% to <5%



Estimated 1,500–5,000 patients harbor TRK fusion-positive cancers in the United States annually

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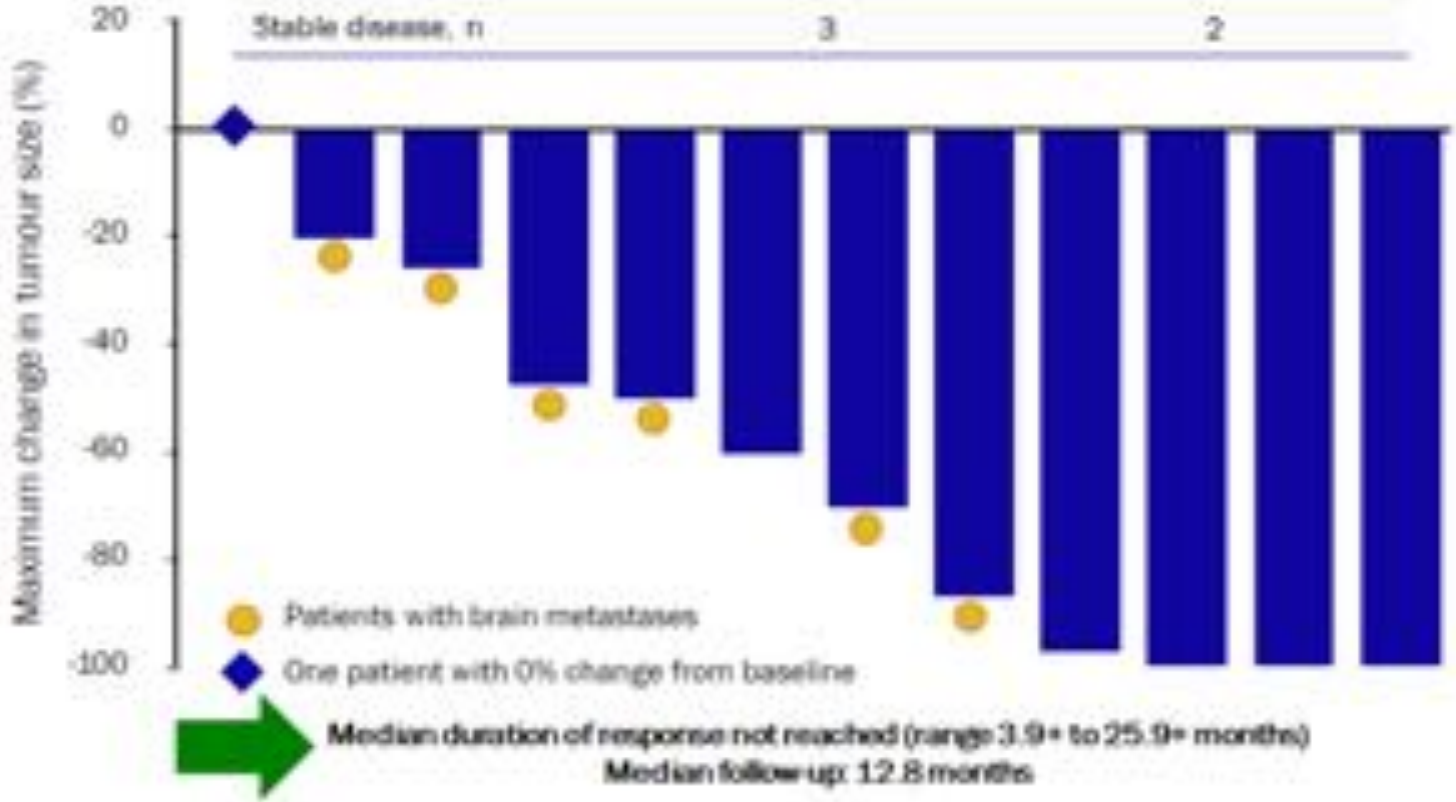
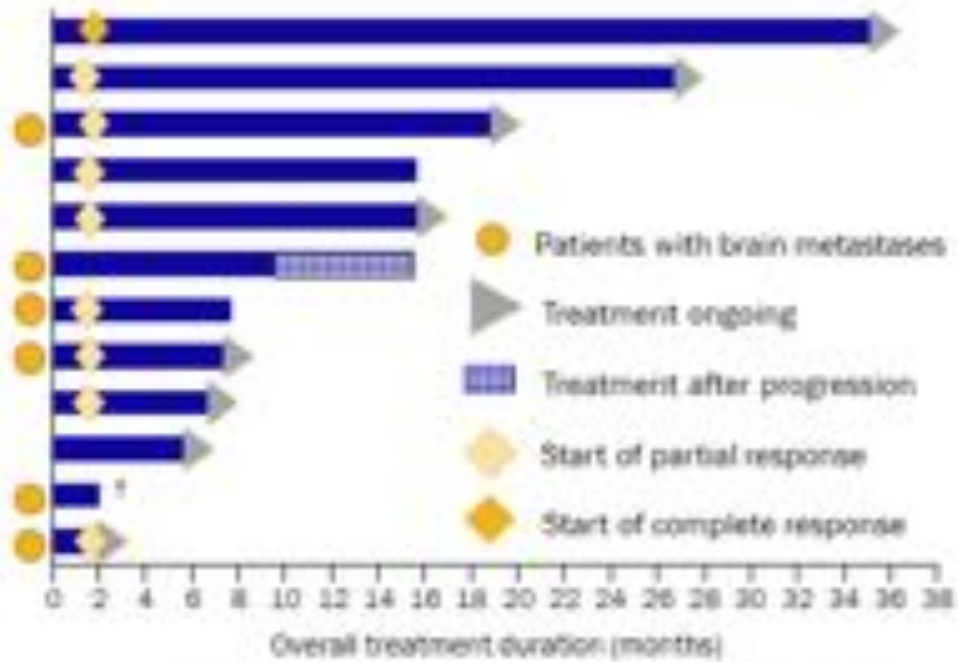
Larotrectinib is active in TRK fusion lung cancer

	All lung cancer patients (n=12)	Patients with brain metastases (n=6)
Objective response rate (%)	**75%**	**67%**
Complete response, n	1	0
Partial response, n	8*	4*
Stable disease, n	3	2



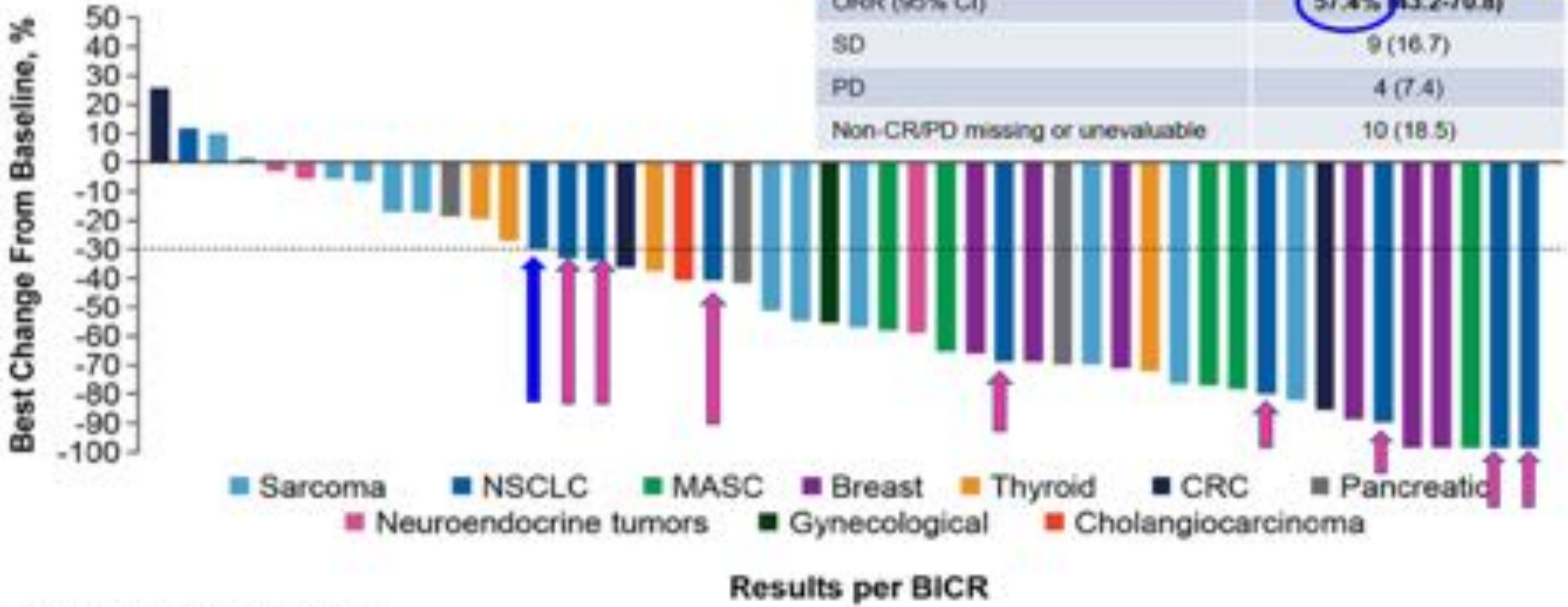


Duration of response: 1.8+ to 35.2+ months

Data cut-off: 19 February 2019 *Partial response pending confirmation in one patient. †Nontarget progressive disease in asymptomatic leptomeningeal focus. Investigator assessments as of data cut-off date. TRK, tropomyosin receptor kinase. Farago AF, et al. Presented at the World Conference on Lung Cancer. September 2019. Barcelona, Spain. Abstract MA09.07.2

Entrectinib Activity in *NTRK* Fusion-Positive Solid Tumors: Individual Patient Responses by Tumor Type[1]

	NTRK+ Patients (n = 54)
ORR (95% CI)	57.4% (43.2-70.8)
SD	9 (16.7)
PD	4 (7.4)
Non-CR/PD missing or unevaluable	10 (18.5)



1. Demetri GD et al. ESMO 2018. Abstract LBA17.

Conclusions

- Broad molecular testing at the time of diagnosis is essential to select the optimal treatment (NGS DNA & RNA to be seriously considered; new standard?).
- The number of targetable alterations is rapidly growing; recent approvals of drugs for EGFR exon 20 insertions, KRAS G12C and HER2 mutations in NSCLC.
- Repeat tissue and liquid biopsies will be required to advance our understanding of therapeutic resistance to new targeted therapies, and to develop the next generation of drugs to overcome resistance.
- Immunotherapy should be used with caution in oncogene-addicted NSCLC, given limited efficacy for most alterations and concerns about sequencing of some TKIs (most notably EGFR and ALK) following immunotherapy. Novel, more effective immunotherapy approaches are urgently needed.
- In the future, mutation subtypes and/or co-mutations may be used to further tailor therapy (including the selection of targeted therapy, use of immunotherapy, etc.).

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