Lung Cancer UPDATES
ASCO HIGHLIGTHS
04-08 JUNIO 2021

Iniciativa científica de:
GECP
lung cancer research

CPNCP metastásico. Terapias dirigidas otras mutaciones

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Disclosure Information

Consultant or Advisory Role: BMS, MSD, ROCHE, ASTRA ZENECA, BOEHRINGER INGELHEIM, NOVARTIS, Lilly.

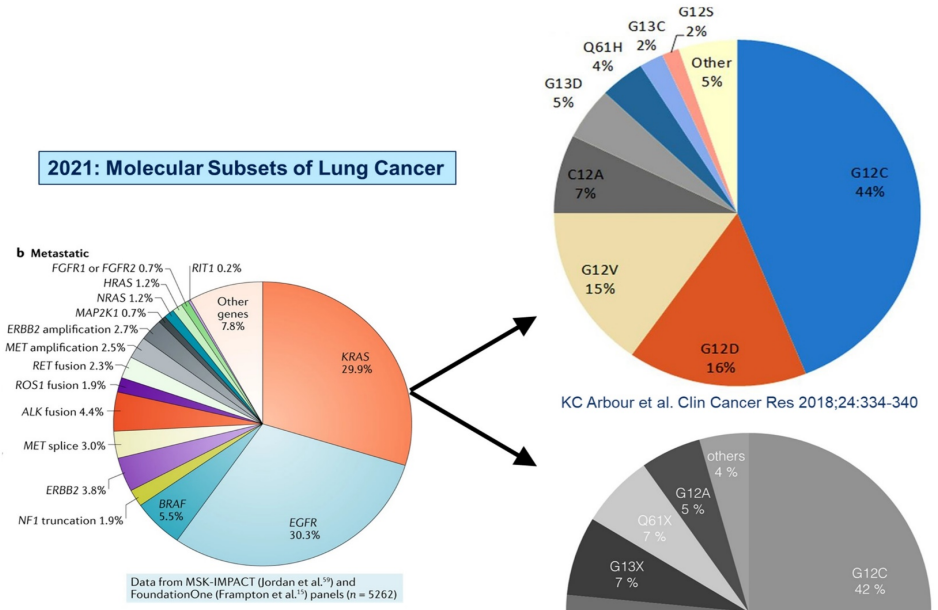
Lectures: BMS, MSD, ROCHE, ASTRA ZENECA, BOEHRINGER INGELHEIM, Lilly.

KRAS disease

- Overall survival and exploratory subgroup analyses from the phase 2 CodeBreaK 100 trial evaluating sotorasib in pretreated KRAS p.G12C mutated non-small cell lung cancer. **Ferdinandos Skoulidis, et al.** J Clin Oncol 39, 2021 (suppl 15; abstr 9003)

- Clinicogenomic real-world data analysis of patients (pts) with KRAS G12C-mutant advanced non-small cell lung cancer (aNSCLC) from the natural history cohort of the Blood First Assay Screening Trial (BFAST). **Rafal Dziadziuszko et al.** J Clin Oncol 39, 2021 (suppl 15; abstr 9023)

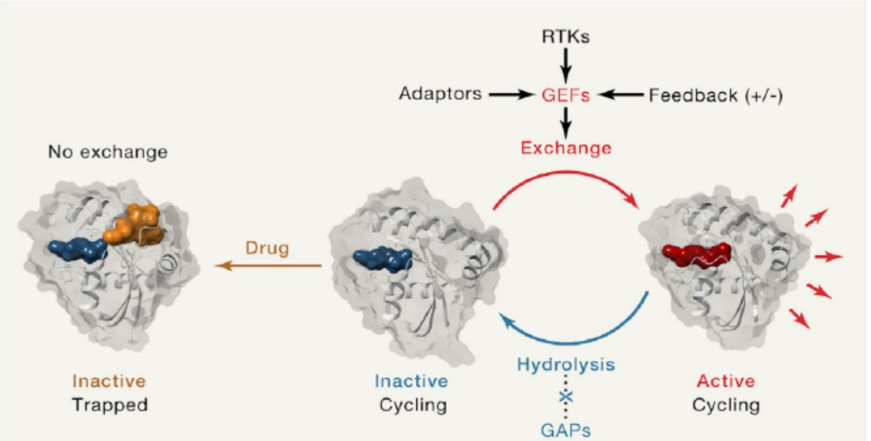
Focus on KRAS mutations in Non-Small Cell Lung Cancer



- KRAS G12C most common KRAS variant
- 13% (1 in 8) or all lung adenocarcinomas
- Multiple KRAS G12C inhibitors being developed

KRAS G12C Inhibitors - Mechanism of Action

- Novel class of drugs → these are targeted therapies but they are not TKIs
- Allele-specific inhibitors targeting the Cysteine (C) residue.
- The inhibitors bind covalently to the mutant cysteine residue and occupy a pocket in the switch II region (SIIP) when KRAS G12C is in its inactive GDP-bound state (inactive-state selective drugs).



D. Kim et al. Cell Volume 183, Issue 4, 12 November 2020, Pages 850-859

Phase 2 CodeBreaK100 trial (NCT03600883)

- Trial enrolled patients with KRAS G12C–mutated NSCLC who had progressed following treatment with immunotherapy and/or chemotherapy.
  - N= 126 patients across 11 countries, 3 continents

- New at #ASCO21:
  - updated efficacy, including mature OS data from data cut off 3/15/21 (median follow-up time of 15.3 mos)
  - updated safety
  - first sub-group analysis

Baseline Characteristics

- 93% current smokers
- 57.1% had received ≥ 2 lines of prior therapy
- 81% had received platinum-based chemotherapy *and* PD-1/PD-L1 inhibitors

Safety

- TRAEs led to dose modification in 22.2%
- TRAEs led to permanent discontinuation in 7.1%
- Most common toxicity was diarrhea (31.7% all grades, 4.0% grade 3), nausea, and LFT abnormalities

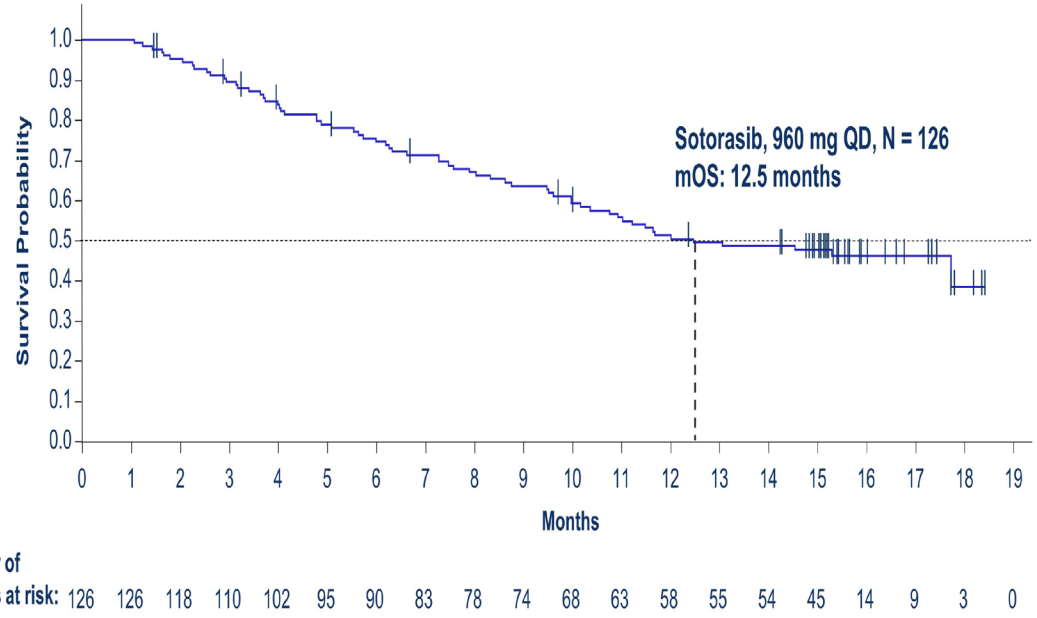
Efficacy

- ORR 37.1% (not as high as we are used to for 'targeted therapies" – but this is a different type of mutation and a different class of drugs)
- ORR did not vary much by # prior lines of therapy
- DCR 80.6%
- Median time to response 1.35 months (95% CI: 1.2,10.1)
- Median duration of response 11.1 months (95% CI 6.9, NE)
- Median PFS 6.8 months (95% CI: 5.1, 8.2)
- Median OS 12.5 months (95% CI: 10.0, NE))
- OS 17.7 months (95% CI: 7.9, NE) for patients who received 1 prior line of therapy
- OS 17.7 months (95% CI: 11.7, NE) for patients who received anti-PD1/PDL1 but no platinum-based chemo

Presented By: Christine Lovly, MD, PhD
@Christine_Lovly

CodeBreaK 100 trial

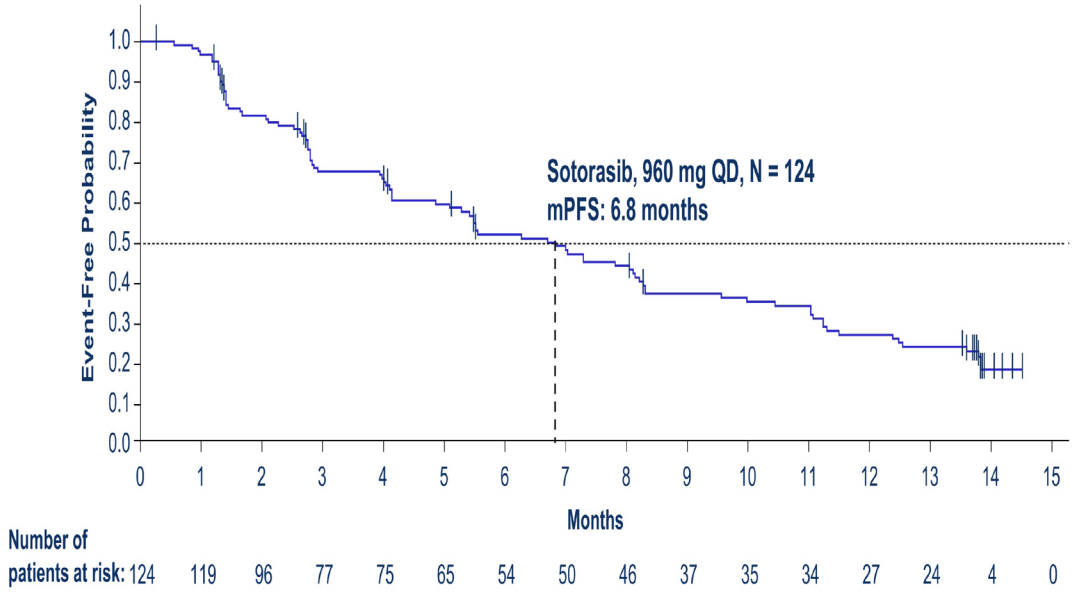
Overall Survival



QD: once a day; mOS: median overall survival; CI: confidence interval.

Median overall survival was 12.5 months (95% CI: 10.0, not evaluable)

Progression-Free Survival



QD: once a day; mPFS: median progression-free survival; CI: confidence interval.

Median progression-free survival was 6.8 months (95% CI: 5.1, 8.2)

Ferdinandos Skoulidis, et al. J Clin Oncol 39, 2021 (suppl 15; abstr 9003)

CodeBreaK100 trial: Molecular subgroup analyses

- No differences in ORR based on:
  - KRAS G12C VAF
  - TMB
  - WT vs. Mutant TP53 (80.8% of tumors were TP53 co-mutated)
  - WT vs. Mutant STK11 (33.7% of tumors were STK11 co-mutated)

- Sotorasib efficacy was lower in KEAP1 co-mutated tumor
  - 19.2% of tumors were KEAP1 mutated
  - Previous data suggests that KEAP1/NFE2L2 mutations are associated with shorter duration of initial chemotherapy and shorter overall survival from initiation of immune therapy (KC Arbour et al. Clin Cancer Res 2018;24:334-340)

- Improved PFS and OS in the STK11 mutant, KEAP1 WT group
  - small sample size but still ~20% of the entire KRAS G12C mutant group
  - Previous data sets suggest that STK11 mutations are associated with poorer response to anti-PD1 therapy (F Skoulidis et al. Cancer Discov 2015;5:860–77.)

PFS and OS by co-occurring mutations in both *STK11* and *KEAP1* (n=104)

STK11 status	*KEAP1* status	n	mPFS month (95% CI)	mOS month (95% CI)
MUT	MUT	13	2.6 (1.4, 11.1)	4.8 (2.1, 10.8)
MUT	WT	22	11.0 (2.8, NE)	15.3 (4.8, NE)
WT	MUT	7	5.5 (0, 7.0)	7.5 (0, NE)
WT	WT	62	6.8 (4.0, 11.0)	NE (NE, NE)
All evaluable	All evaluable	104	6.3 (4.1, 8.3)	13.1 (9.5, NE)

Presented By: Christine Lovly, MD, PhD
@Christine_Lovly

CodeBreaK100 trial: Molecular subgroup analyses

- No differences in ORR based on:
  - KRAS G12C VAF
  - TMB
  - WT vs. Mutant TP53 (80.8% of tumors were TP53 co-mutated)
  - WT vs. Mutant STK11 (33.7% of tumors were STK11 co-mutated)
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    mutant group
  - Previous data sets suggest that STK11 mutations are associated with poorer response to anti-PD1 therapy (F Skoulidis et al. Cancer Discov 2015;5:860–77.)

PFS and OS by co-occurring mutations

				mOS h (95% CI)
				2.1, 10.8)
				(4.8, NE)
				(0, NE)
				(NE, NE)
evaluable	evaluable	104	6.5 (4.1, 8.5)	13.1 (9.5, NE)

FDA U.S. FOOD & DRUG ADMINISTRATION

← Home / Drugs / Development & Approval Process | Drugs / Drug Approvals and Databases / FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC

FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC

May 28, 2021: The FDA has approved sotorasib as the first treatment for adult patients with non–non small cell lung cancer whose tumors harbor *KRAS* G12C mutations and who have received at least 1 prior systemic therapy.

KRAS G12C-mutant aNSCLC. Natural history cohort of BFAST trial.

In the full BFAST screening population through December 2020 (N = 5917), 23% of pts had tumors with any *KRAS* mut; 9% were *KRASG12C*.

Outcomes for patients with KRAS^{G12C} mutant NSCLC [21]

- 13 (21%) patients never received 1L treatment
- 7 died within 3 months of enrollment

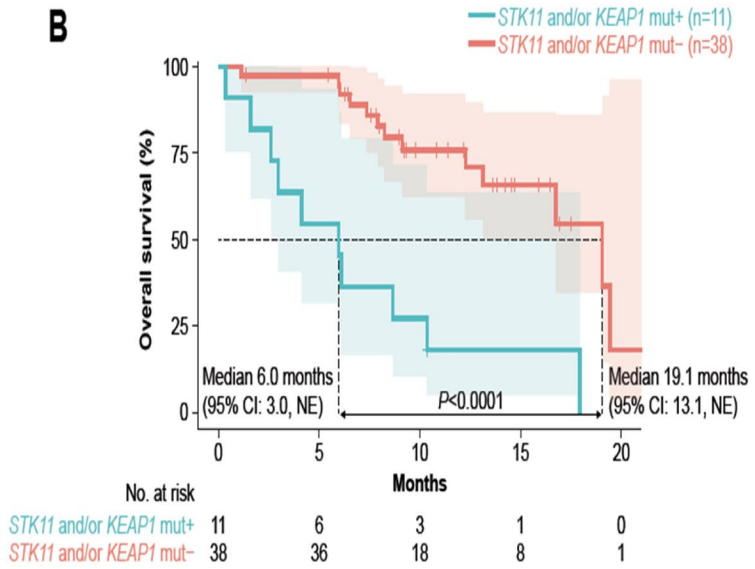
Table 2. Cancer treatment patterns

Treatment type, n (%)	*KRAS G12C* (n=63)		
	1L (n=50)	2L (n=18)	3L+ (n=3)
Chemotherapy	25 (50)	4 (22)	2 (67)
CIT	14 (28)	10 (56)	1 (33)
Chemotherapy + CIT	10 (20)	2 (11)	0
Targeted	1 (2)	2 (11)	0

1L, first line; 2L, second line; 3L+, third line and beyond; CIT, cancer immunotherapy.

Dziadziuszko R, et al, ASCO 2021 Annual Meeting.

KRAS mut NSCLC with *STK11* and/or *KEAP1* mutations

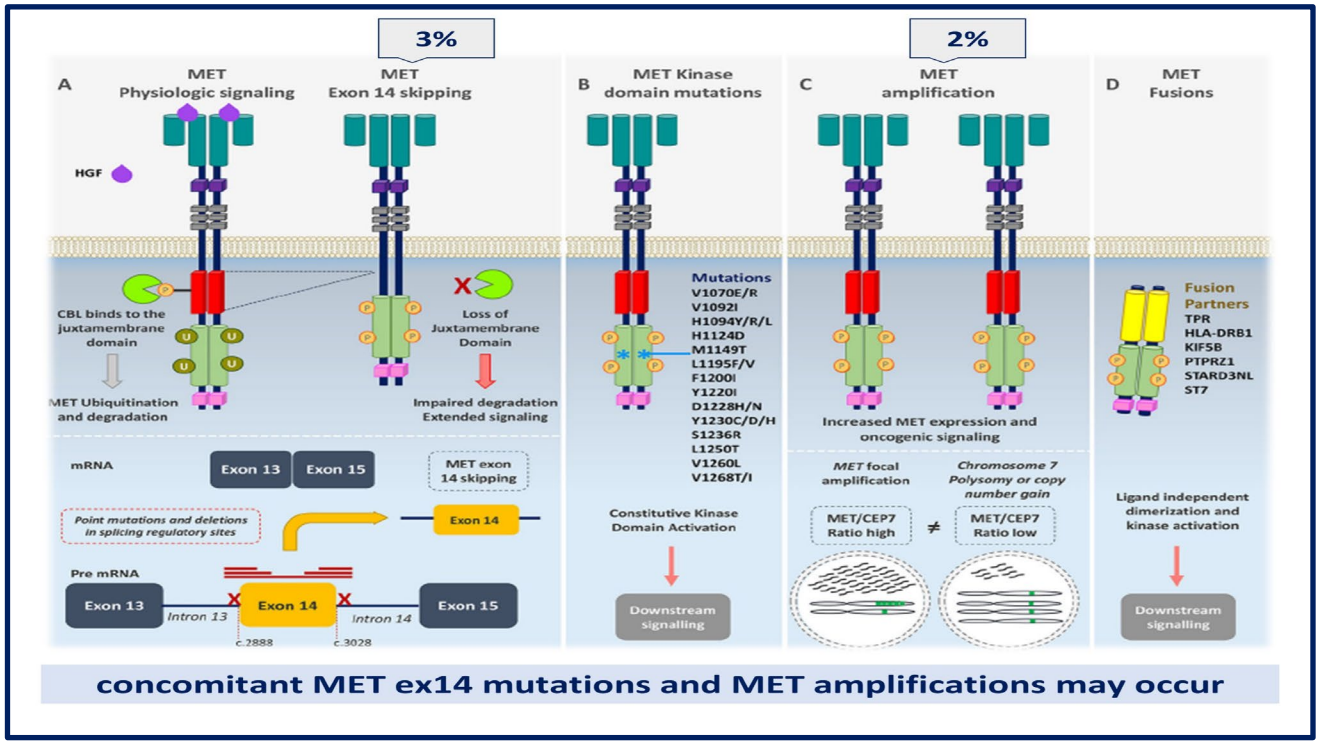


Dziadziuszko R, et al, ASCO 2021 Annual Meeting.

MET + disease

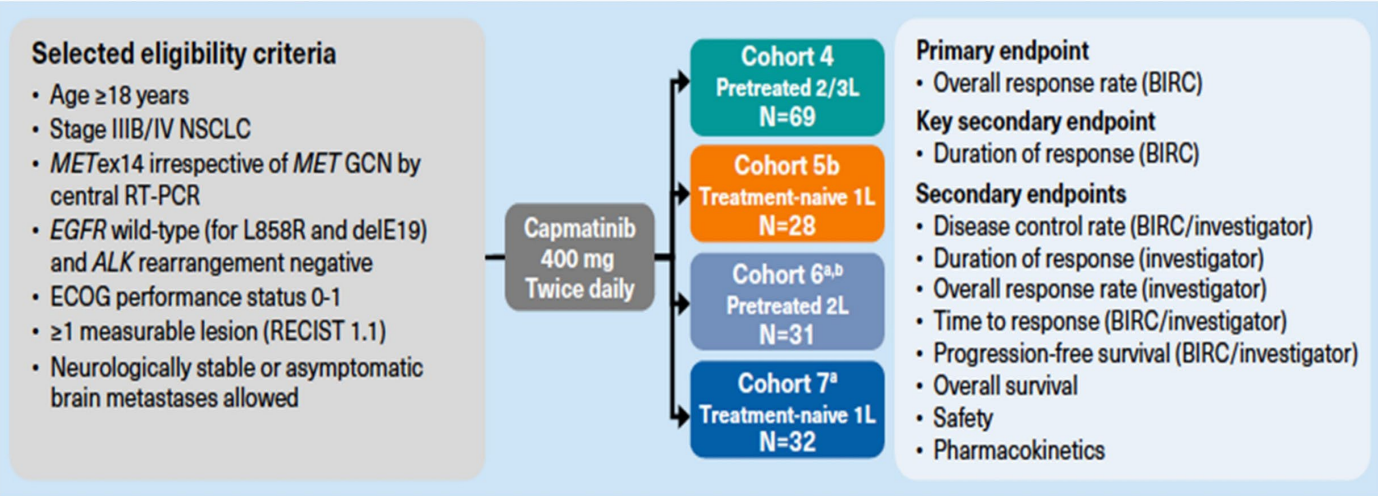
- Capmatinib in *MET* exon 14-mutated, advanced NSCLC: Updated results from the GEOMETRY mono-1 study. **Juergen Wolf, et al**. J Clin Oncol 39, 2021 (suppl 15; abstr 9020)

- Tepotinib in patients (pts) with advanced non-small cell lung cancer (NSCLC) with *MET* amplification (*MET*amp). **Xiuning Le, et al.** J Clin Oncol 39, 2021 (suppl 15; abstr 9021)



GEOMETRY mono-1 study

Abstract 9020 (342283): Capmatinib in *MET* exon 14-mutated, advanced NSCLC: Updated results from the GEOMETRY mono-1 study



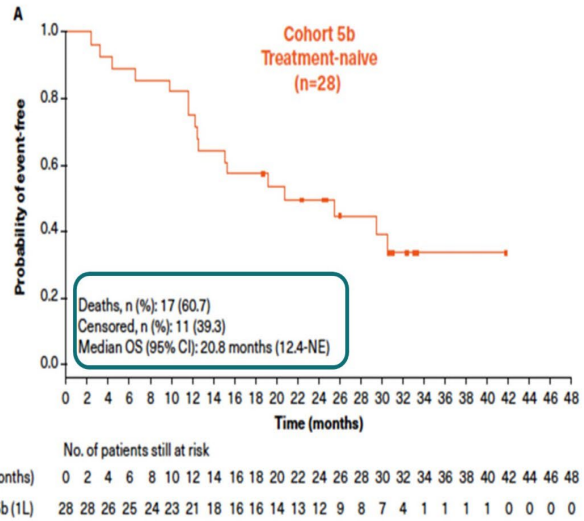
Characteristic	Treatment-naive		Pretreated		All *MET*ex14 patients
	Cohort 5b N=28	Cohort 7 N=32	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	N=160
Median age, years (range)	71 (57-86)	73 (48-86)	71 (49-90)	69 (49-81)	71 (48-90)
Female patients, n (%)	18 (64.3)	23 (71.9)	40 (58.0)	16 (51.6)	97 (60.6)
Race, n (%)					
Caucasian	24 (85.7)	26 (81.3)	49 (71.0)	24 (77.4)	123 (76.9)
Asian	4 (14.3)	3 (9.4)	19 (27.5)	5 (16.1)	31 (19.4)
Other[a]	0	3 (9.4)	1 (1.4)	2 (6.5)	6 (3.8)
ECOG PS, n (%)					
0	7 (25.0)	7 (21.9)	16 (23.2)	10 (32.3)	40 (25.0)
≥1	21 (75.0)	25 (78.1)	53 (76.8)	21 (67.7)	120 (75.0)
Smoking history, n (%)					
Never smoked	18 (64.3)	20 (62.5)	40 (58.0)	19 (61.3)	97 (60.6)
Former smoker	9 (32.1)	11 (34.4)	27 (39.1)	10 (32.3)	57 (35.6)
Current smoker	1 (3.6)	1 (3.1)	2 (2.9)	2 (6.5)	6 (3.8)
Patients with brain metastases, n (%)	3 (10.7)	6 (18.8)	10 (14.5)	7 (22.6)	26 (16.3)
Histology, n (%)					
Adenocarcinoma	25 (89.3)	29 (90.6)	53 (76.8)	25 (80.6)	132 (82.5)
Squamous cell carcinoma	2 (7.1)	1 (3.1)	6 (8.7)	4 (12.9)	13 (8.1)
Large cell carcinoma	0	1 (3.1)	1 (1.4)	1 (3.2)	3 (1.9)
Others	1 (3.6)	1 (3.1)	9 (13.0)	1 (3.2)	12 (7.5)

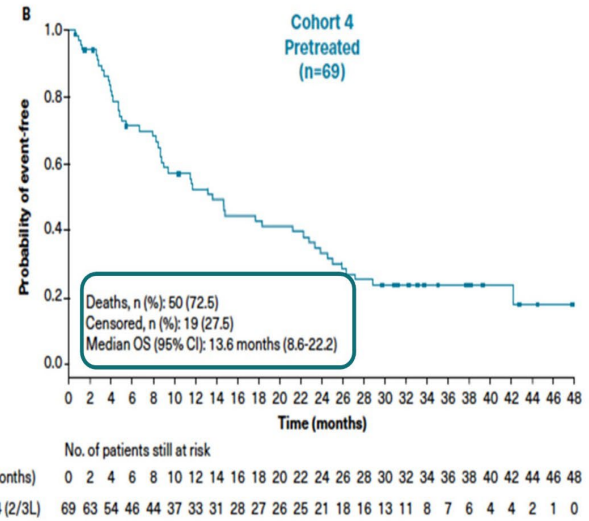
Wolf J, 2021 ASCO meeting

Abstract 9020 (342283)

	Treatment-naive			Pretreated		
	Cohort 5b N=28	Cohort 7 N=32	All patients N=60	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31	All patients N=100
Best overall response, n (%)						
Complete response	1 (3.6)	0	1 (1.7)	0	0	0
Partial response	18 (64.3)	21 (65.6)	39 (65.0)	28 (40.6)	16 (51.6)	44 (44.0)
Stable disease	7 (25.0)	11 (34.4)	18 (30.0)	25 (36.2)	11 (35.5)	36 (36.0)
Non-complete response/ non-progressive disease	1 (3.6)	0	1 (1.7)	1 (1.4)	1 (3.2)	2 (2.0)
Progressive disease	1 (3.6)	0	1 (1.7)	6 (8.7)	0	6 (6.0)
Not evaluable[a]	0	0	0	9 (13.0)	3 (9.7)	12 (12.0)
ORR,[b] % (95% CI)	67.9 (47.6-84.1)	65.6 (46.8-81.4)	66.7 (53.3-78.3)	40.6 (28.9-53.1)	51.6 (33.1-69.8)	44.0 (34.1-54.3)
DCR,[c] % (95% CI)	96.4 (81.7-99.9)	100.0 (89.1-100.0)	98.3 (91.1-100.0)	78.3 (66.7-87.3)	90.3 (74.2-98.0)	82.0 (73.1-89.0)
DOR events,[d] n (%)	12 (63.2)	5 (23.8)	17 (42.5)	23 (82.1)	11 (68.8)	34 (77.3)
Median DOR, months (95% CI)	12.6 (5.6-NE)	NE (5.5-NE)	12.6 (8.4-NE)	9.7 (5.6-13.0)	8.4 (4.2-NE)	9.7 (5.6-13.0)
PFS events, n (%)	18 (64.3)	14 (43.8)	32 (53.3)	60 (87.0)	22 (71.0)	82 (82.0)
Median PFS, months (95% CI)	12.4 (8.2-23.4)	10.8 (6.9-NE)	12.3 (8.2-21.6)	5.4 (4.2-7.00)	6.9 (4.2-13.3)	5.5 (4.2-8.1)

Figure 3. (A) Overall survival for treatment-naive patients with *MET*ex14 NSCLC in Cohort 5b. (B) Overall survival for pretreated (2/3L) patients with *MET*ex14 NSCLC in Cohort 4





	Treatment-naive				Pretreated				All patients[a]	
	Cohort 5b N=28		Cohort 7 N=32		Cohort 4 (2/3L) N=69		Cohort 6 (2L) N=31		N=373	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Any event, n (%)	28 (100)	21 (75.0)	31 (96.9)	20 (62.5)	68 (98.6)	52 (75.4)	31 (100)	18 (58.1)	367 (98.4)	256 (68.6)
Most common events, n (%)										
Peripheral edema	21 (75.0)	3 (10.7)	23 (71.9)	4 (12.5)	37 (53.6)	10 (14.5)	22 (71.0)	4 (12.9)	202 (54.2)	36 (9.7)
Nausea	13 (46.4)	0	14 (43.8)	0	32 (46.4)	0	10 (32.3)	1 (3.2)	168 (45.0)	9 (2.4)
Vomiting	7 (25.0)	0	5 (15.6)	1 (3.1)	19 (27.5)	0	8 (25.8)	0	105 (28.2)	9 (2.4)
Increased blood creatinine	10 (35.7)	0	10 (31.3)	0	23 (33.3)	0	9 (29.0)	0	99 (26.5)	0
Dyspnea	6 (21.4)	2 (7.1)	2 (6.3)	1 (3.1)	19 (27.5)	7 (10.1)	3 (9.7)	0	87 (23.3)	25 (6.7)
Fatigue	4 (14.3)	1 (3.6)	6 (18.8)	0	18 (26.1)	6 (8.7)	9 (29.0)	0	83 (22.3)	16 (4.3)
Decreased appetite	8 (28.6)	0	5 (15.6)	1 (3.1)	15 (21.7)	1 (1.4)	5 (16.1)	0	79 (21.2)	4 (1.1)

- More common TR-AEs: peripheral edema, nausea
- TR-SAE: 13%; AE discontinuation: 16.1% (unrelated)

Wolf J, 2021 ASCO meeting

VISION Cohort B evaluated tepotinib in pts with advanced NSCLC and *MET*amp, as detected by liquid biopsy assay.

Abstract 9021 (334053): Tepotinib in patients with advanced NSCLC with MET amplification (VISION study)

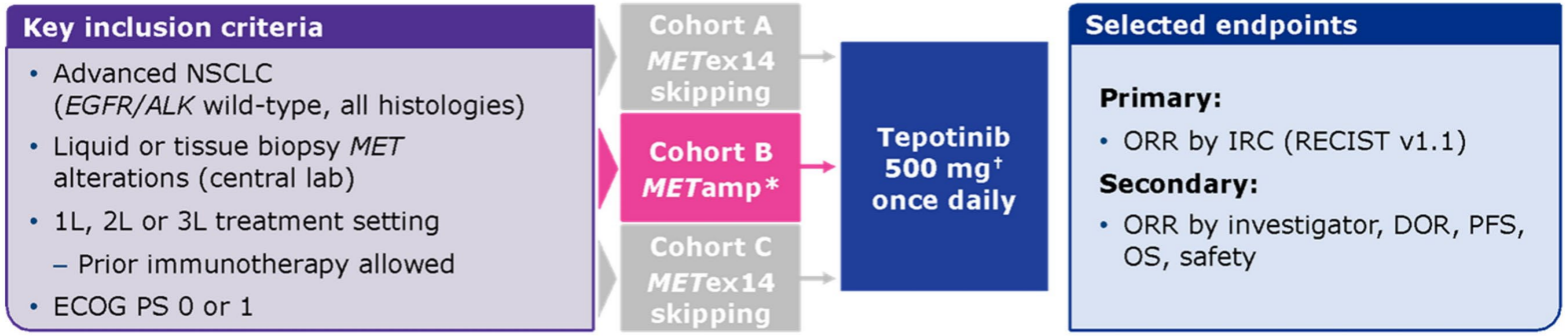


Table 1. Baseline characteristics

Characteristic		(n=24)
Male, n (%)		21 (87.5)
Median age, years (range)		63.4 (38–73)
Race, n (%)	White/Asian	17 (70.8)/7 (29.2)
Current/former smoker, n (%)		21 (87.5)
ECOG PS, n (%)	0/1	3 (12.5)/21 (87.5)
Median tumor load of target lesions (IRC), mm (range)		95.6 (26.9–231.9)
Number of prior lines of therapy, n (%)	0	7 (29.2)
	1	10 (41.7)
	2	7 (29.2)
Prior immunotherapy, n (%)		10 (41.7)
Best response to prior immunotherapy, n*	PR	1
	SD	1
	PD	5

Le X, 2021 ASCO meeting

Abstract 9021 (334053)

Table 2. Objective response by IRC, overall and by line of therapy

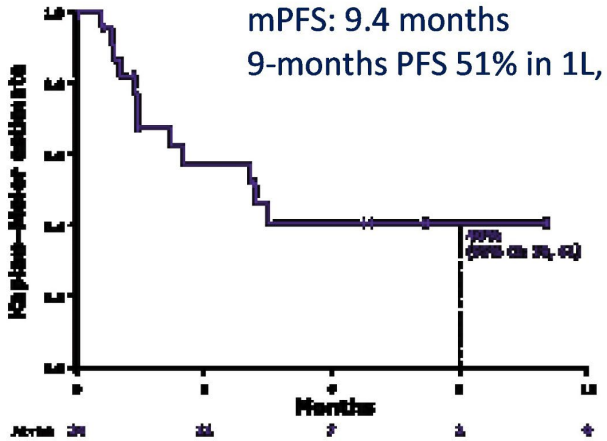
		Overall (n=24)	1L (n=7)	2L (n=10)	3L (n=7)
Best overall response, n (%)	PR	10 (41.7)	5 (71.4)	3 (30.0)	2 (28.6)
	SD	1 (4.2)	0	1 (10.0)	0
	PD	5 (20.8)	1 (14.3)	2 (20.0)	2 (28.6)
	NE	8 (33.3)	1 (14.3)	4 (40.0)	3 (42.9)
ORR, n (%) [95% CI]		10 (41.7) [22.1, 63.4]	5 (71.4) [29.0, 96.3]	3 (30.0) [6.7, 65.2]	2 (28.6) [3.7, 71.0]

Table 3. TRAEs reported in ≥5% of patients (n=24)

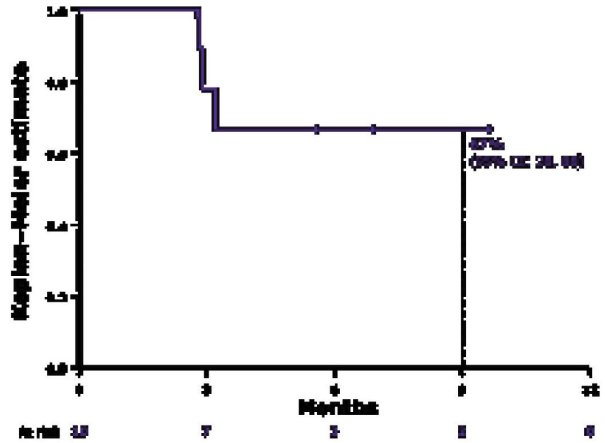
Patients, n (%)	Any grade	Grade 3	Grade 4
Peripheral edema	9 (37.5)	2 (8.3)	0
Generalized edema	4 (16.7)	2 (8.3)	0
Constipation	4 (16.7)	0	0
Diarrhea	2 (8.3)	0	0
Edema	2 (8.3)	0	0
Transaminases increased	2 (8.3)	1 (4.2)	0

- More common TR-AEs: peripheral edema, constipation
- AE-discontinuation: 20.8%, not related
- Grade 3/4 TR-AEs: 29.2%

mPFS: 9.4 months
9-months PFS 51% in 1L, 58% in 2L



mDoR: NE
9-months efr DoR 60% in 1L, 100% in 2L



Le X, 2021 ASCO meeting

Larotrectinib in TRK fusion positive NSCLC

This analysis reports updated long-term efficacy and safety data of patients with TRK fusion-positive lung cancer treated with larotrectinib

Adult phase I (NCT02122913)
- Age ≥18 years
- Advanced solid tumors

n=1

NAVIGATE: adult/adolescent phase II 'basket' trial (NCT02576431)
- Age ≥12 years
- Advanced solid tumors
- TRK fusion cancer

n=19

20 patients with metastatic lung cancer harboring an *NTRK* gene fusion

Endpoints

Primary
- ORR per investigator assessment (RECIST v1.1)

Secondary
- DoR
- PFS
- OS
- Safety

Data cut-off: July 20, 2020 **Dose:** 100 mg BID

RR, objective response rate; OS, overall survival; PFS, progression-free survival, RECIST, Response Evaluation
col. 2019;30:viii5–viii15. 2. Forsythe A, et al. Ther Adv Med Oncol. 2020;12:1–10. 3. Solomon JP, et al. Mod Pathol.
lable at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211710s000lbl.pdf. Accessed March 26, 2021.
n/vitrakvi-epar-product-information_en.pdf. Accessed March 26, 2021. 7. Hong DS, et al. Lancet Oncol.

Baseline characteristics

	N = 20
Age, median (range), years	48.5 (25.0–76.0)
Sex, n (%)	
Male	10 (50)
Female	10 (50)
CNS metastases at baseline, n (%)	
No	10 (50)
Yes	10 (50)
Previously treated with radiotherapy*	2 (10)
***NTRK* gene fusion**, n (%)	
NTRK1	16 (80)
NTRK2	0
NTRK3	4 (20)
Testing methods, n (%)	
RNA-based anchored multiplex PCR	4 (20)
RNA-based NGS	2 (10)
RNA-based whole transcriptome sequencing	1 (5)
DNA-based NGS	13 (65)
Tumor histology, n (%)	
Adenocarcinoma	19 (95)
Neuroendocrine carcinoma	1 (5)†

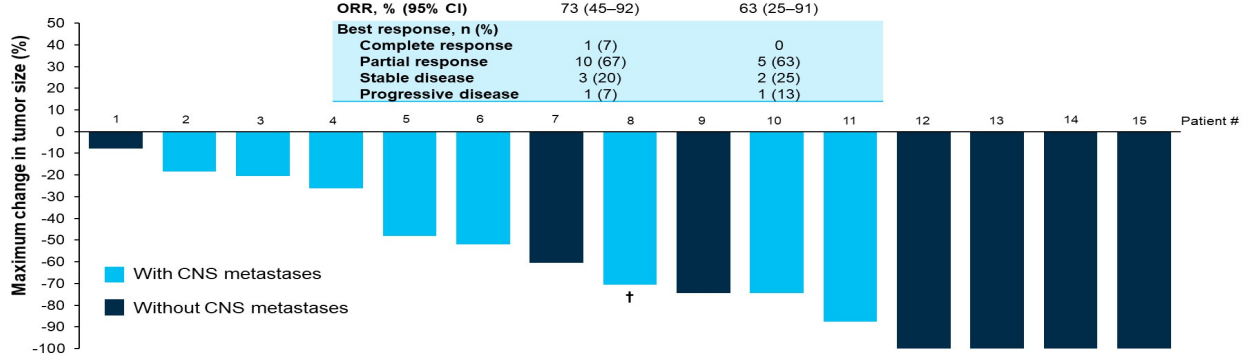
	N = 20
Prior therapies,‡ n (%)	
Surgery	10 (50)
Radiotherapy	9 (45)
Systemic therapy¶	19 (95)
Prior systemic therapies, median (range)	3 (0–6)
Prior therapies, n (%)	
0	1 (5)
1	6 (30)
2	3 (15)
≥3	10 (50)
Best response to prior therapy, n (%)	
Partial response	3 (15)
Stable disease	5 (25)
Progressive disease	5 (25)
Other§	7 (35)

*The time between radiotherapy and initiation of larotrectinib for these two patients was 1.3 and 6.5 months, respectively. †This patient was originally diagnosed with a small cell lung cancer that was subsequently reassessed as neuroendocrine carcinoma. ‡Patients may be counted in more than one category. ¶**Six patients had received prior immunotherapy.** Most recent prior systemic regimens were: cisplatin–pemetrexed; cisplatin–etoposide; docetaxel; dostarlimab; entrectinib (discontinued due to toxicity); erlotinib (in the absence of a known activating *EGFR* mutation); gemcitabine; osimertinib (in the absence of a known activating *EGFR* mutation); pemetrexed; sitravatinib; gemcitabine-lobaplatin; cisplatin-pemetrexed-bevacizumab; sindelizumab-pemetrexed; pemetrexed-nedaplatin; pemetrexed-bevacizumab; paclitaxel-gemcitabine-bevacizumab. §Including unknown, not evaluable, and not applicable.

CNS, central nervous system; *EGFR*, epidermal growth factor; NGS, next generation sequencing; *NTRK*, neurotrophic tyrosine receptor kinase; PCR, polymerase chain reaction; TRK, tyrosine receptor kinase.

Tumor response

	All patients (N = 20)	Patients with CNS metastases (N = 10)
Evaluable patients, n	15	8
ORR, % (95% CI)	73 (45–92)	63 (25–91)
Best response, n (%)		
Complete response	1 (7)	0
Partial response	10 (67)	5 (63)
Stable disease	3 (20)	2 (25)
Progressive disease	1 (7)	1 (13)



Investigator-assessed as per RECIST v1.1. †Patient with measurable intracranial disease and 100% reduction intracranial target lesions. CNS, central nervous system; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Her2 NSCLC

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2021 ASCO ANNUAL MEETING

IFCT

#9015

Combination of trastuzumab, pertuzumab and docetaxel in patients with advanced Non-Small Cell Lung Cancer (NSCLC) harboring HER2 mutation. Results from the IFCT-1703 R2D2 trial. *NCT03845270*

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June 04, 2021

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Pertuzumab/Trastuzamab/Docetaxel

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- NSCLC
- HER2 exon 20 mutation or insertion*
- Stage III (inoperable) or IV
- Previously treated
- ECOG PS 0, 1 or 2
- Age ≥ 18 ans

→ Inclusion → *From May 2019 to October 2020*

Cycle 1 :
D1 : pertuzumab 840 mg
D2 : trastuzumab 8 mg/kg + docetaxel 75 mg/m²
Subsequent cycles (every 3 weeks) :
D1 : pertuzumab 420mg + trastuzumab 6 mg/kg + docetaxel 75 mg/m²

Until disease progression or limiting toxicity

*Patients with concomitant EGFR, ALK, ROS1, MET, BRAF and/or KRAS mutation are not eligible.

Primary endpoint: confirmed **objective response rate** (ORR)
Secondary endpoints :
- Confirmed ORR at 6 weeks
- Progression-free Survival (PFS)
- Overall Survival (OS)
- Duration of response (DoR)
- Tolerance (NCI-CTC 5.0)

	N = 46
Gender, N(%)	
Female	33 (**71.7**)
Male	13 (28.3)
Age (median, range)	**64.5 (31-83.7)**
Smoker, N(%)	
Current and past	16 (34.8)
Never	30 (**65.2**)
Histological type, N(%)	
Adenocarcinoma	46 (100)
Number of prior lines, N(%)	
1	34 (**73.9**)
2	10 (21.7)
3 or more	2 (4.4)
Stage TNM 8th Edition, N(%)	
IIIB	4 (8.7)
IV	42 (**91.3**)
PS, N(%)	
0	19 (**41.3**)
1	20 (**43.5**)
2	7 (15.2)
Brain metastases, N(%)	
Yes	14 (**30.4**)
No	32 (69.6)
PDL-1, N(%)	
Negative	26 (57.8)
≥1% and <50%	16 (35.5)
≥50%	3 (6.7)
Unknown	1

Abstract 9015

Pertuzumab/Trastuzamab/Docetaxel

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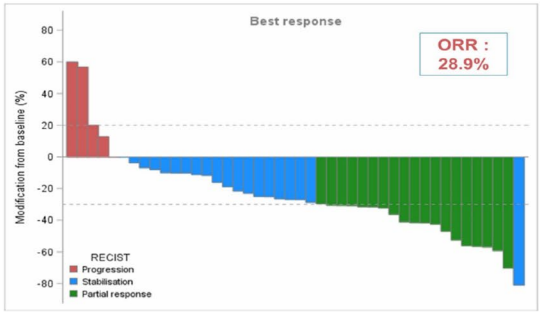

mPFS = 6.8 mo

mOS = 17.6 mo

	Any Grade	Grade 3-4
Any TRAE	44 (97.8%)	29 (64.4%)
Serious TRAE	7 (15.6%)	4 (8.9%)
Led to discontinuation	0 (0.0%)	0 (0.0%)
Led to death	1* (2.2%)	0 (0.0%)
- Diarrhea	31 (68.9%)	6 (13.3%)
- Nausea	18 (40.0%)	
- Stomatitis	13 (28.9%)	1 (2.2%)
- Vomiting	10 (22.2%)	
- Constipation	6 (13.3%)	
- Fatigue	27 (60.0%)	3 (6.7%)
- Alopecia	22 (48.9%)	
- Pruritus	8 (17.8%)	1 (2.2%)
- Dry skin	5 (11.1%)	1 (2.2%)
- Peripheral sensory neuropathy	12 (26.7%)	2 (4.4%)
- Paraesthesia	10 (22.2%)	1 (2.2%)
- Dysgeusia	7 (15.6%)	
- Anemia	23 (51.1%)	4 (8.9%)
- Neutrophil count decreased	17 (37.8%)	15 (33.3%)
- Alanine aminotransferase increasec	8 (17.8%)	1 (2.2%)
- Aspartate aminotransferase increas	5 (11.1%)	
- Weight decreased	5 (11.1%)	
- Epistaxis	9 (20.0%)	
- Conjunctivitis	6 (13.3%)	
* Sudden death at home		

Summary

IFCT-1703 R2D2 - NCT03845270 IFCT

The safety and efficacy data should be compared with other regimen currently tested in HER2 mutated NSCLC patients to define the best therapeutic strategy.

Study Design

- **This study is a prospective, single-center, single-arm phase II clinical study (ChiCTR1900021684).**

Key inclusion criteria

- Stage IV NSCLC
- HER2 insertion mutations, primary HER2 missense mutations or primary HER2 amplification
- Progressed on prior chemotherapies or anti-HER2 TKIs
- ECOG PS 0-1
- No prior treatment with pyrotinib or apatinib
- No active brain metastasis or meningeal metastasis

→ **Treatment**

- Pyrotinib: 400 mg, po, qd
- Apatinib: 250 mg, po, qd

→ **Simon's Stage I**

Enrollment of 10 evaluable subjects

→ CR/PR in ≥1 subject →

Simon's Stage II

Enrollment up to 33 subjects

- **Primary endpoint:** objective response rate (ORR)
- **Secondary endpoints:** progression-free survival (PFS), duration of response (DoR), disease control rate (DCR), overall survival (OS) and safety.

Simon's optimal two-stage design with a one-sided α error of 5% and a power of 80% was used to evaluate the objective response rate in metastatic NSCLC patients with primary HER2 mutations administered pyrotinib combined with apatinib. advanced

Pyrotinib plus Apatinib in Her2 NSCLC

Patient characteristics

- Between March 5, 2019 and December 1, 2020, 33 patients were enrolled. Baseline characteristics are shown in the Table.

Baseline characteristics	*n* = 33
Age, Median (range), years	54 (35-70)
Gender, *n* (%)	
Male	17 (51.5)
Female	16 (48.5)
Smoking history, *n* (%)	
Ever	12 (36.4)
Never	21 (63.6)
ECOG performance status, *n* (%)	
0	24 (72.7)
1	9 (27.3)
Clinical stage, *n* (%)	
IV	33 (100)
No. of metastatic organs, *n* (%)	
≤ 2	13 (39.4)
> 2	20 (60.6)

Baseline characteristics	*n* = 33
Brain metastases, *n* (%)	
Presence	13 (39.4)
Absence	20 (60.6)
Lines of study treatment, *n* (%)	
2	17 (51.5)
≥3	16 (48.5)
HER2 variant type, *n* (%)	
A775_G776insYVMA	20 (60.6)
P780_Y781insGSP	6 (18.2)
R811L with Q820K	1 (3.0)
G776V	1 (3.0)
G776delinsVC	1 (3.0)
G776_V777delinsCVC	1 (3.0)
G727A	1 (3.0)
HER2 amplification	2 (6.1)

Tumor Response

Response*	Investigator Assessment, *n* (%)
Best overall response	
Complete response	0
Partial response	15 (45.5)
Stable disease	16 (48.5)
Progressive disease	2 (6.1)
Objective response rate (ORR), 95%CI	45.5 (28.11, 63.65)
Disease control rate (DCR), 95%CI	93.9 (79.77, 99.26)
Median duration of response (DoR), months, 95%CI	6.1 (3.53, NR)

*The time of data cutoff was on April 25, 2021.

- Pyrotinib combined with apatinib therapy showed similar ORRs in patients with presence (46.2%, 6/13) or absence (45.0%, 9/20) of brain metastases, and those in second-line (47.1%, 8/17) or above-line settings (43.8%, 7/16).