EGFRex20ins, METex14 and RET in NSCLC

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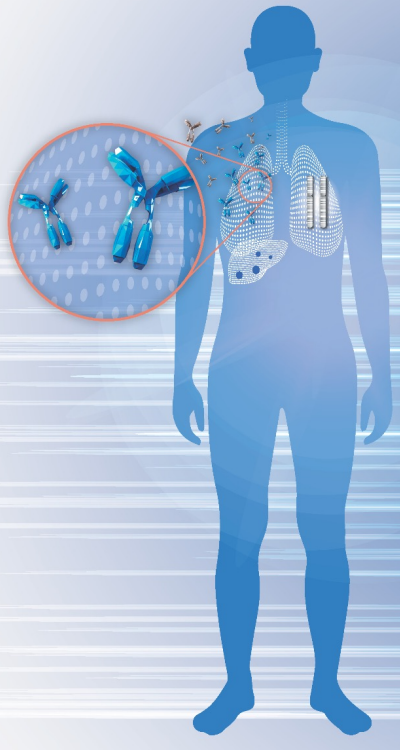
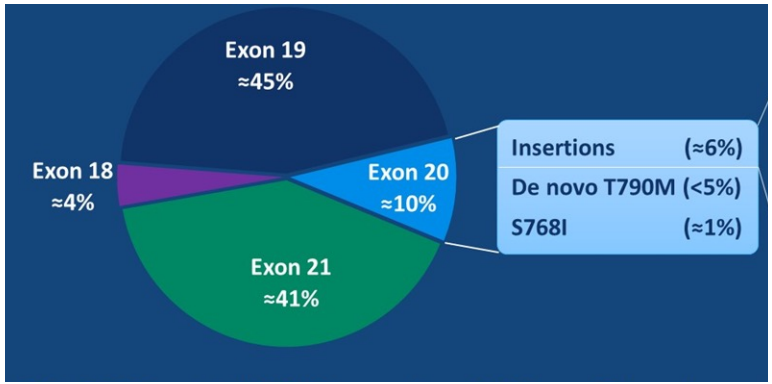
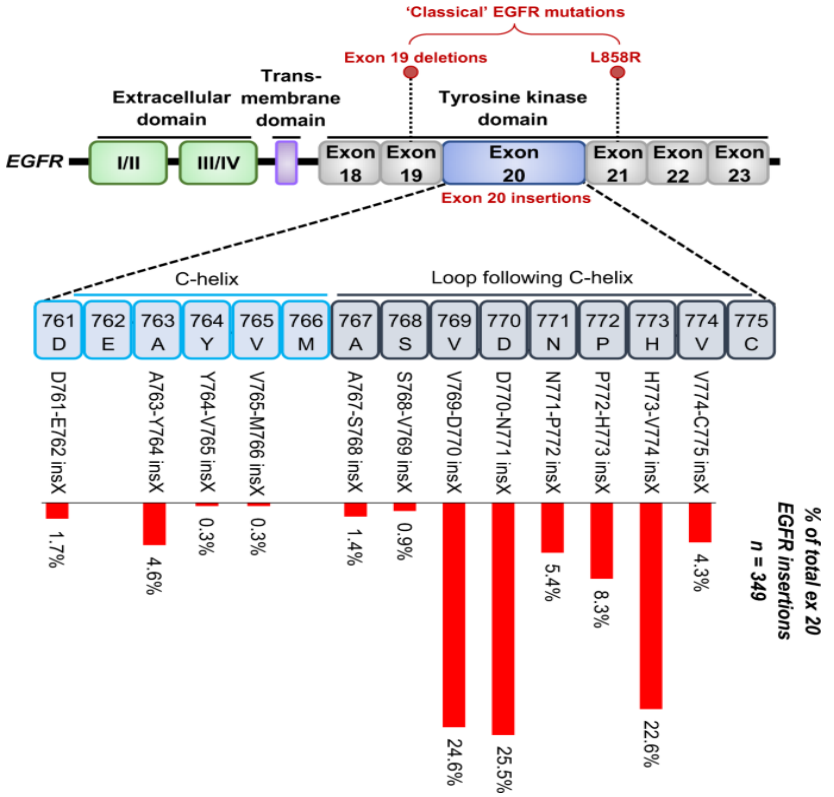


EGFR Oncogenic Driver Mutations

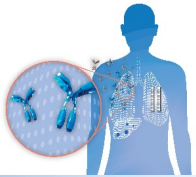
- ~6% of EGFRm NSCLC are *EGFR*ex20ins+
- EGFR TKIs used for common activating mutations are largely ineffective in EGFR ex 20 ins (poor response, mPFS 2 mo)





Meador CB et al. *Cancer Disc.* 2021;11:2145-2157.
Reily G, et al. ASCO 2019.

EGFR Exon 20 Insertions



2L: Two FDA-approved options

Amivantamab: EGFR/MET bispecific antibody infusion
(CHRYSALIS Study)

ORR 40%; PFS 8.3 months

Most significant AE: infusion reactions on first doses

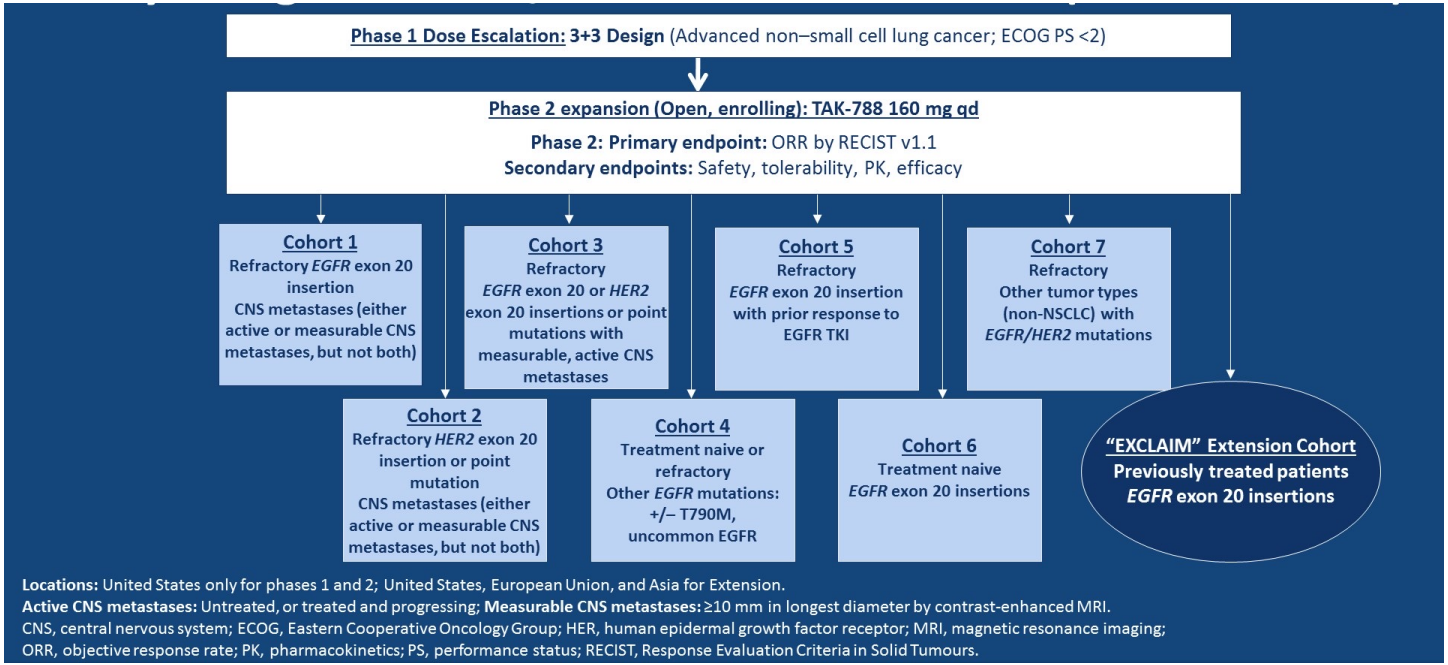
Mobocertinib: oral EGFR TKI
(EXCLAIM/PPP Cohorts)

ORR 25-28%; PFS 7.3 months

Most significant AE: Diarrhea

Zhou et al. IASLC WCLC 2020. OA04.03; Park et al. J Clin Oncol. 2021.

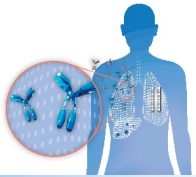
Phase 1/2 Study of Mobocertinib in Platinum-Pretreated EGFR Exon 20 Insertion-Positive mNSCLC (*EGFR*ex20ins+)



Cohort of platinum-pretreated patients (PPP): 114 pts with platinum-pretreated *EGFR* ex20 ins-positive mNSCLC who received mobocertinib 160 mg from dose-escalation (n = 6), dose-expansion (n = 22), and EXCLAIM (n = 86) cohorts. EXCLAIM cohort included 96 patients with previously treated *EGFR* ex20 ins-positive mNSCLC (10 were not platinum pretreated and thus were excluded from the PPP cohort).

Zhou C, et al. *JAMA Oncol*. 2021;7:e214761.

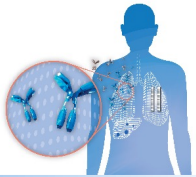
ORR in PPP and EXCLAIM cohorts



Outcome	No. (%) PPP cohort (n = 114)	EXCLAIM cohort (n = 96)
Investigator-assessed confirmed objective response[b]		
Patients, No. (%) [95% CI]	40 (35) [26-45]	31 (32) [23-43]
Complete response	1 (<1)	1 (1)
Partial response	39 (34)	30 (31)
Stable disease[c]	49 (43)	41 (43)
Not evaluable	11 (10)	9 (9)
Confirmed disease control rate, No. (%) [95% CI][d]	89 (78) [69-85]	72 (75) [65-83]
Duration of response in confirmed responders[e]		
IRC-assessed		
No.	32	24
Median (95% CI), mo	17.5 (7.4-20.3)	NR (5.6-NR)
Investigator-assessed		
No.	40	31
Median (95% CI), mo	11.2 (5.6-NR)	11.2 (7.0-NR)
Progression-free survival, median (95% CI), mo[e]		
No.	114	96
IRC-assessed	7.3 (5.5-9.2)	7.3 (5.5-9.1)
Investigator-assessed	7.3 (5.6-8.8)	7.3 (5.6-9.1)
Overall survival, median (95% CI), mo		
No.	114	96
Median (95% CI), mo	24.0 (14.6-28.8)	NR (13.1-NR)

Zhou et al., JAMA Oncol . 2021

Any-grade TRAEs in the PPP and EXCLAIM cohorts



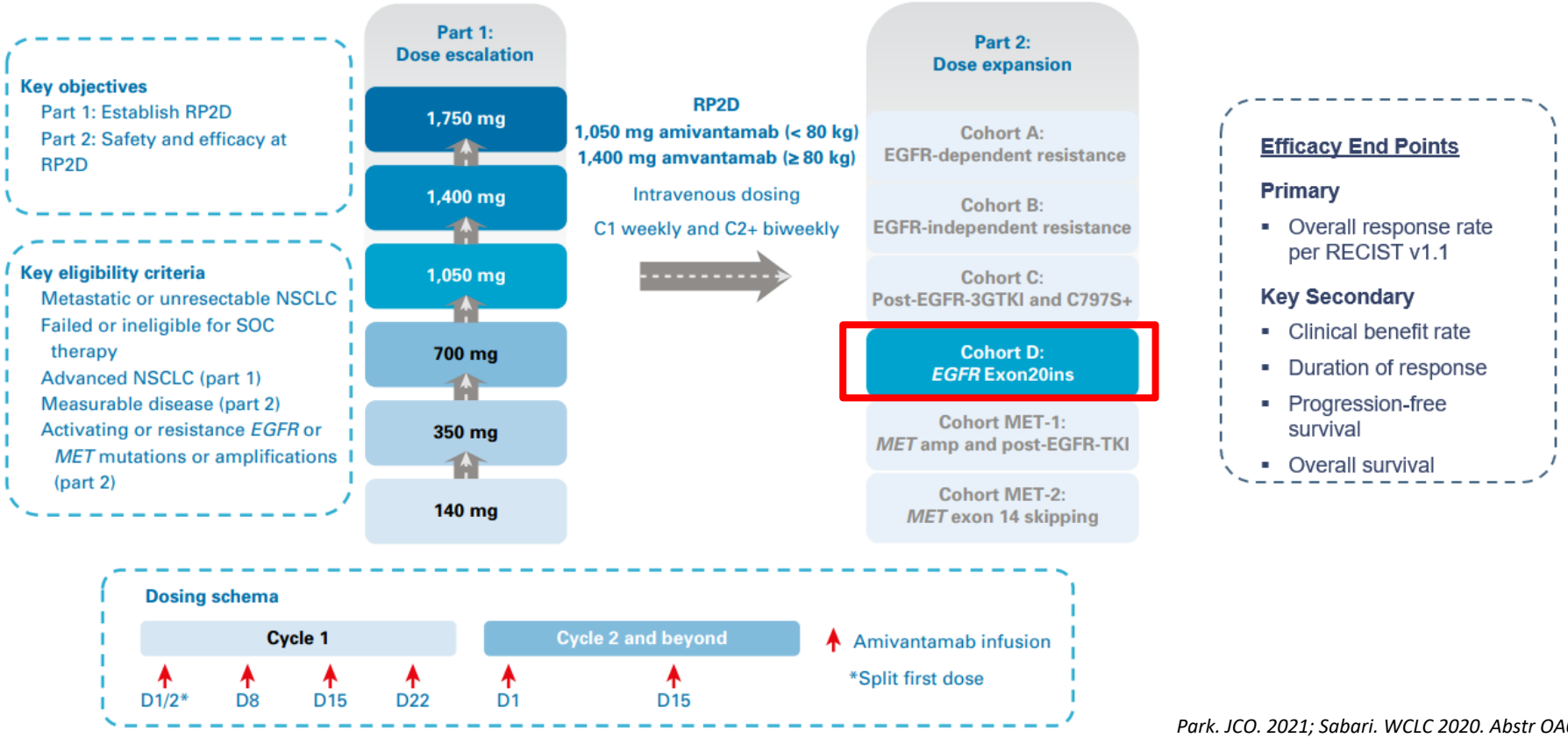
Adverse event	Patients, No (%)			
	PPP cohort (n = 114)		EXLAIM cohort (n = 96)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Treatment-related AEs of any grade reported in ≥20% of patients				
Diarrhea	104 (91)	24 (21)	89 (93)	15 (16)
Rash	51 (45)	0	43 (45)	0
Paronychia	43 (38)	1 (<1)	37 (39)	1 (1)
Decreased appetite	40 (35)	1 (<1)	31 (32)	1 (1)
Nausea	39 (34)	5 (4)	29 (30)	3 (3)
Dry skin	35 (31)	0	30 (31)	0
Vomiting	34 (30)	3 (3)	25 (26)	1 (1)
Blood creatinine increased	29 (25)	2 (2)	27 (28)	2 (2)
Stomatitis	27 (24)	5 (4)	26 (27)	3 (3)
Pruritus	24 (21)	1 (<1)	19 (20)	1 (1)
Amylase increased	21 (18)	3 (3)	19 (20)	1 (1)
Dermatitis, acneiform	21 (18)	0	20 (21)	1 (1)

Special interest: QTc prolongation 11%, Cardiomyopathy 2.7%, ILD/pneumonitis 4.3%

Zhou et al., JAMA Oncol . 2021

CHRYSALIS: Amivantamab in Advanced NSCLC With EGFR Exon 20 Insertion Mutations

- Dose-escalation and dose-expansion phase I trial of amivantamab, an EGFR-MET bispecific antibody

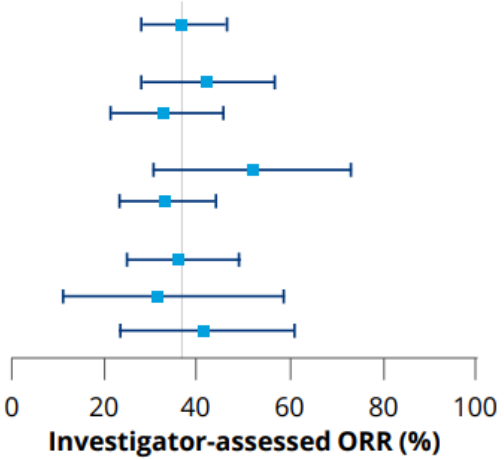


Park. JCO. 2021; Sabari. WCLC 2020. Abstr OA04.04

Amivantamab demonstrated consistent efficacy regardless of prior therapies or response to prior platinum chemo

- ORR was 37%
- Median DOR 12.5 months

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

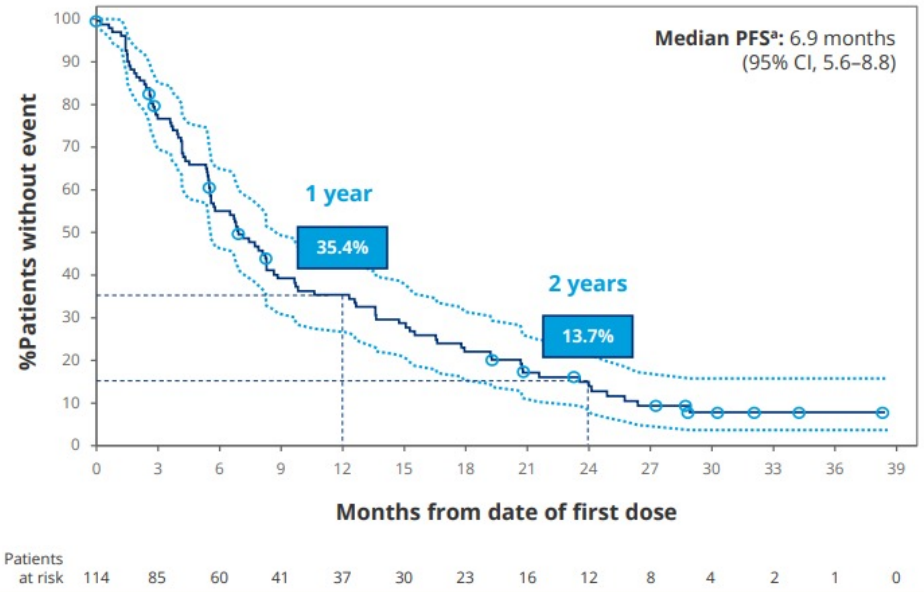


Median F/U 19.2 months

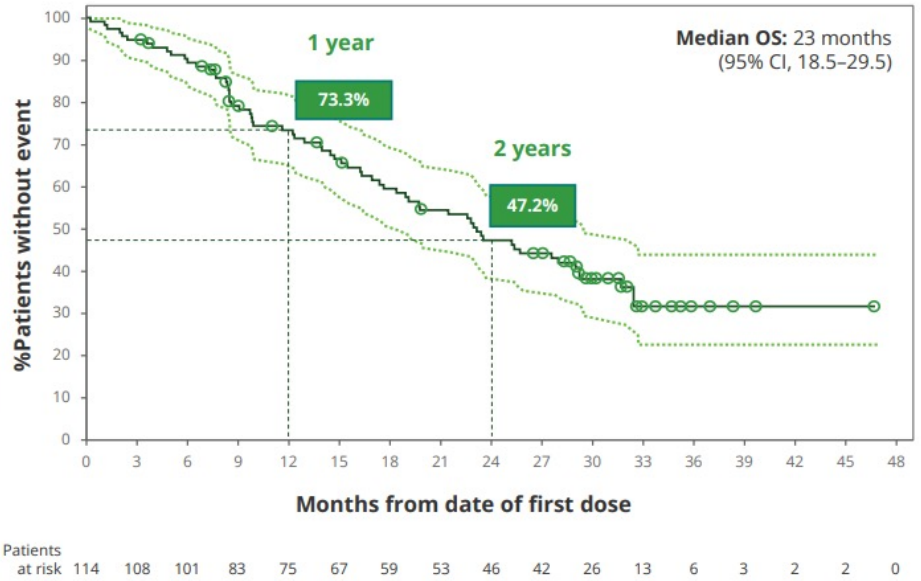
Girrado P, ELCC 2023, Abstract 3O

At median F/U of 19.2 months and median duration of treatment 7.5 months, 42% patients were alive

Progression-free Survival



Overall Survival



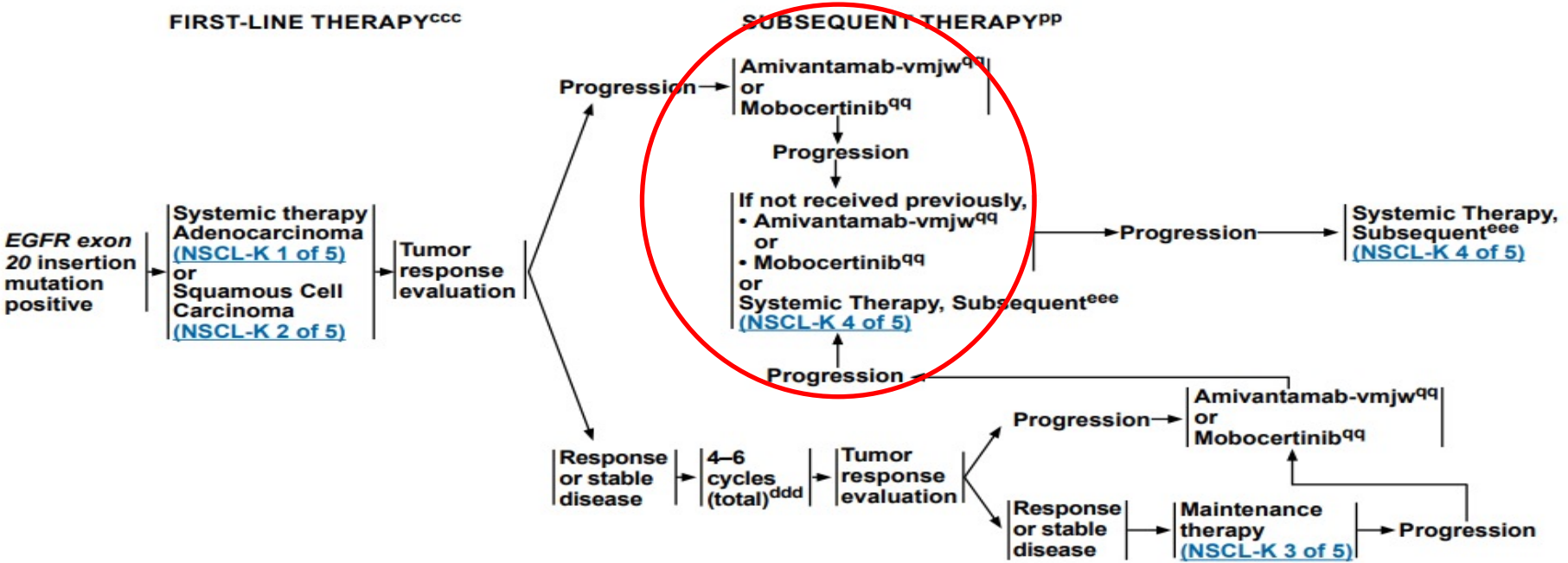
Girrado P, ELCC 2023, Abstract 3O

Long-term safety (median F/U of 19.2 months) - No new safety signals were detected, with low rates of treatment-related discontinuations

	Ex20ins Post-Platinum (n=114)		RP2D (n=474)	
AEs (≥15%) by preferred term, n (%)	**Total**	**Grade ≥3**	**Total**	**Grade ≥3**
EGFR-related				
Paronychia	66 (58)	4 (4)	204 (43)	9 (2)
Dermatitis acneiform	54 (47)	1 (1)	165 (35)	5 (1)
Rash	49 (43)	2 (2)	167 (35)	8 (2)
Stomatitis	29 (25)	1 (1)	97 (20)	2 (0.4)
Pruritus	23 (20)	0	84 (18)	0
Diarrhea	21 (18)	4 (4)	53 (11)	6 (1)
MET-related				
Hypoalbuminemia	45 (39)	5 (4)	153 (32)	11 (2)
Peripheral edema	31 (27)	1 (1)	119 (25)	5 (1)
Other				
Infusion-related reaction	76 (67)	3 (3)	319 (67)	14 (3)
Nausea	32 (28)	1 (1)	111 (23)	3 (1)
Constipation	30 (26)	0	115 (24)	1 (0.2)
Fatigue	30 (26)	4 (4)	100 (21)	9 (2)
Dyspnea	29 (25)	6 (5)	101 (21)	24 (5)
Cough	24 (21)	0	87 (18)	0
Arthralgia	24 (21)	0	53 (11)	1 (0.2)
Back pain	23 (20)	1 (1)	66 (14)	4 (1)
Decreased appetite	23 (20)	1 (1)	83 (18)	2 (0.4)
Alanine aminotransferase increased	20 (18)	4 (4)	80 (17)	10 (2)
Dry skin	19 (17)	0	59 (12)	0
Vomiting	19 (17)	1 (1)	59 (12)	2 (0.4)
AEs of special interest by grouped term, n (%)				
Rash[a]	102 (89)	5 (4)	349 (74)	17 (4)
Interstitial lung disease[b]	8 (7)	0	16 (3)	4 (1)
Venous thromboembolism[c]	13 (11)	7 (6)	50 (11)	25 (5)

Girrado P, ELCC 2023, Abstract 3O

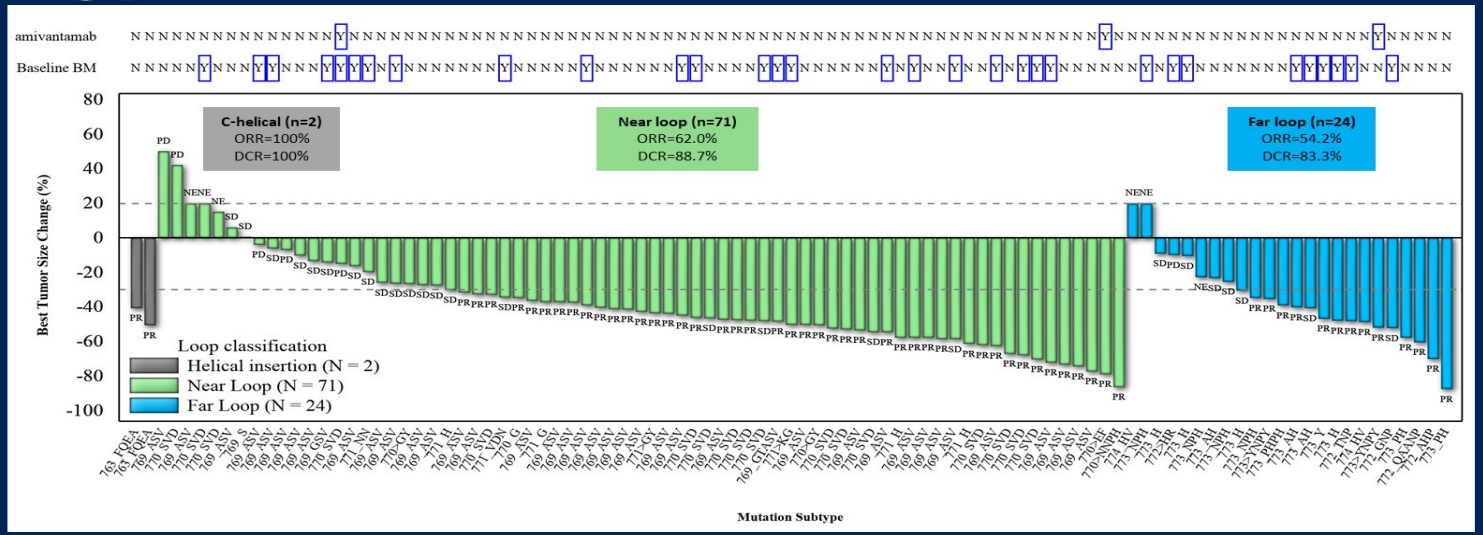
EGFR EXON 20 INSERTION MUTATION POSITIVE[mm]



[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.
[ccc] Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
[ddd] In general, 4 cycles of initial systemic therapy (ie, with carboplatin or cisplatin) are administered prior to maintenance therapy. However, if patient is tolerating therapy well, consideration can be given to continue to 6 cycles.
[eee] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

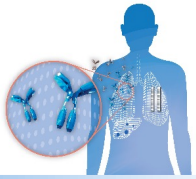
Sunvozertinib in EGFR Exon 20 Insertions

Activity by Location of EGFR Exon 20 Ins Subtypes



64.4% responding at median fup of 5.6 mo.

Cross Trial Comparisons



Efficacy

	Mobocertinib[1] (N=114)	Amivantamab[2] (N=81)	Sunvozertinib (DZD9008) (N=97) WUKONG6[3]
Investigator assessed			
ORR, %	35%	36%	46.4%
Disease control rate, %	78%	73%	
Duration of response, mos	11.2 mo	-	
IRC assessed (95% CI)			
ORR, % (95% CI)	28% (20-37%)	40% (29-51%)	60.8% (50.4-70.6%)
Disease control rate, %	78%	74%	87.6%
Duration of response, months	17.5 mo	11.1 mo	64.4% responding at median fup of 5.6 mo.
PFS, months	7.3 mo	8.3 mo	-
Brain Mets, ORR (N=)	-	-	44% (N=25)[4]

Safety

EGFR Exon 20 Tx	Trial	Diarrhea	Rash	Other Major Notable
Amivantamab	CHRYSALIS[2]	12% (2% G3+)	86% (4% G3+)	Infusion-related reaction 66% (8% G3+), Paronychia
Mobocertinib	EXCLAIM[1]	93% (16% G3+)	45% (0% G3+)	lipase, amylase, other GI, lipase, amylase elevation
Sunvozertinib	WUKONG6[4]	67.3% (7.7% G3+)	53.8% (1% G3+)	CPK Elevation (57.7%, 17.3% G3+)

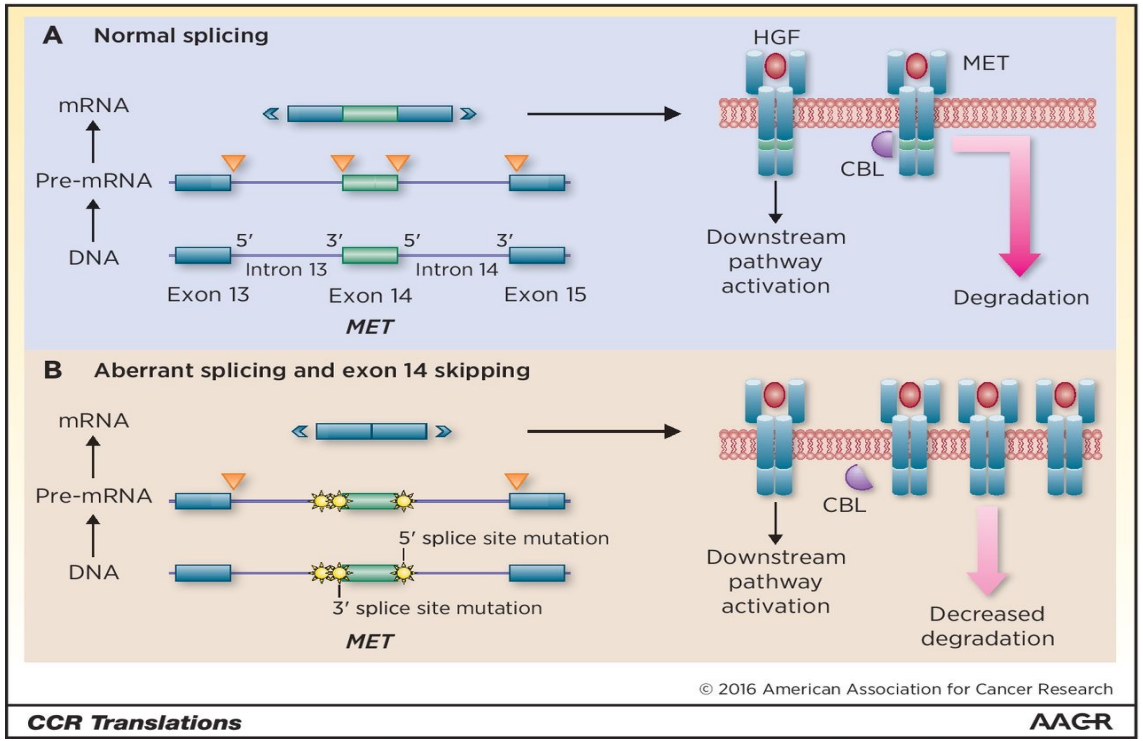
Other EGFR Exon 20 ins TKI with Putative CNS Penetration in Development

- TAS6417 (CLN-081)
- Blu-451
- Oric-114
- Furmonertinib

*WUKONG 1,2,6 pooled at 300 mg dose [5]

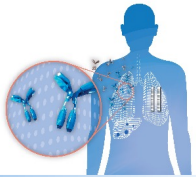
1. Zhou C. et al. *JAMA Oncol.* 2021 Oct 14;e214761. 2. Park K, et al. *J Clin Oncol.* 2021;39:3391-3404. 3. M. Wang et al ASCO 2023. ABS7 9002. 4. L. Bazhenoza et al NACLC 2022.

MET Exon 14–skipping Mutation



Drilon. *Clin Cancer Res*. 2016;22:2832-2834; Socinski. JCO Precision Oncol 2021;5:653-663

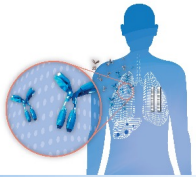
MET exon 14 skip mutation: A unique population



- Associated with advanced disease and poorer prognosis
- Older population – median age 74 years
- Current/former smokers 60%; never smokers 40%
- Seen in both histologies – squamous (2%) and non-squamous (3-4 %)
- Enriched in sarcomatoid carcinomas – 8%

1. Tong JH et al. Clin Cancer Res 2016:22;3048-56
2. Awad MM et al. Lung Cancer 2019:133;96-102
3. Salgia R et al. Mol Cancer Ther 2017:16;555-65
4. Frampton GM et al Cancer Discovery 2015:5;850-59

MOA, Selectivity and Potency of Key MET-inhibitor Competitors in NSCLC



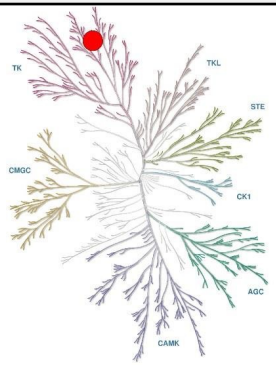
	Tepotinib	Capmatinib	Crizotinib	Savolitinib
Mode of action	Highly MET selective, potent TKI that inhibits MET phosphorylation and downstream signaling	Inhibits MET-dependent PI3K and RAS signalling	Potent MET inhibitor that is active in tumors harbouring *METex14* alterations and inhibits cell proliferation and downstream signalling	Highly selective MET inhibitor that inhibits PI3K/AKT and MAPK signaling and downregulates MYC expression
Selectivity	**1000-fold more selective** for MET	**10,000-fold more selective** for MET	**100-fold more selective** for MET	**1000-fold more selective** for MET
Potency Enzyme IC_{50}	**1.7 nM**[1]	**0.6 nM**	**8 nM** (vs ALK 24 nM, ROS 2.1 nM)	**2.1 nM**

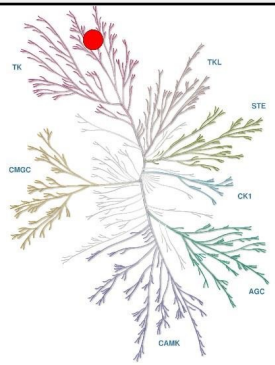
% inhibition at 1 µM

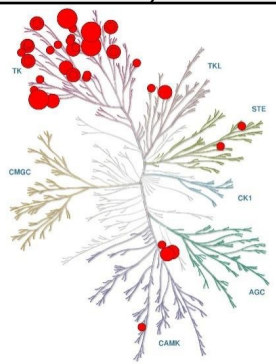
≥ 99%

> 90%

> 75%

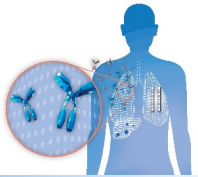


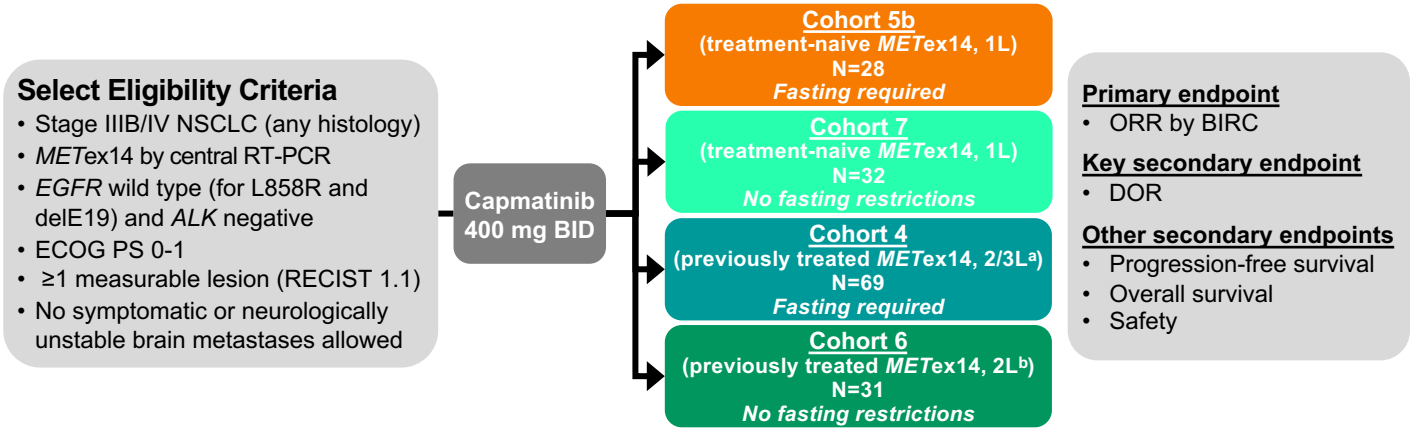




1. Paik et al., ASCO 2019, Abstract 9005

GEOMETRY mono-1: Study Design[1-5]



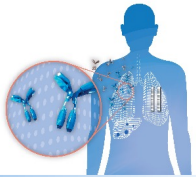


GEOMETRY mono-1 was a global, prospective, nonrandomized open-label Phase II study that enrolled 373 patients into multiple study cohorts based on their prior treatment and *MET* dysregulation (mutation and/or amplification) status

1/2/3L, first/second/third-line; *ALK*, anaplastic lymphoma kinase; BID, twice daily; BIRC, blinded independent review committee; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; *MET*, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non-small cell lung cancer; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors; RT-PCR, reverse transcription-polymerase chain reaction.
[a]Two patients in Cohort 4 received 3 prior lines of systemic therapy. [b]One patient in Cohort 6 received 3 prior lines of systemic therapy.

References: 1. Wolf J, et al. Presented at: American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2019; Chicago, IL. Oral 9004; 2. Heist RS, et al. Presented at: Sixth AACR-IASLC International Joint Conference: Lung Cancer Translational Science from the Bench to the Clinic; January 11-14, 2020; San Diego, CA. Poster B11; 4. Wolf J, et al. *N Engl J Med.* 2020;383(10):944-957; 5. Wolf J, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 4-8, 2021; Virtual. Poster 9020.

GEOMETRY mono-1: Patient Population and Efficacy Summary



GEOMETRY mono-1 evaluated capmatinib in adult patients with metastatic *MET*ex14 NSCLC[1-4]

- **Both treatment-naive and previously treated patients enrolled[1-4]**
  - Sites of metastases included bone, liver, adrenal, and brain; a total of 13 evaluable patients had brain metastasis at baseline
- **Prior to enrollment, all patients with *MET*ex14 had this mutational status confirmed in tumor tissue via RT-PCR[1-4]**
  - Retrospective analysis of cohorts 4[a] and 5b reported 99% positive percentage agreement between the RNA-based RT-PCR assay used for enrollment and the DNA-based FoundationOne®CDx NGS assay in tumor tissue[1,3]
  - Retrospective analysis of cohorts 4[a] and 5b reported 70.5% positive percentage agreement between the RNA-based RT-PCR assay used for enrollment and the FoundationOne®Liquid CDx NGS assay[5]

Primary endpoint of the GEOMETRY mono-1 trial was ORR by BIRC[1-3,6-8]

*MET*ex14 NSCLC patients treated with capmatinib (BIRC results):

	Cohort 5b treatment-naive (1L) (n=28)[b]	Cohort 7 treatment-naive (1L) (n=32)[b]	Cohort 4 previously treated (2/3L[a]) (n=69)[c]	Cohort 6 previously treated (2L[d]) (n=31)[c]
ORR, % (95% CI)	68 (48-84)	69 (50-84)	41 (29-53)	52 (33-70)
mDOR, mo (95% CI)	12.6 (5.6-NE)	16.6 (8.3-NE)	9.7 (5.6-13.0)	8.4 (4.2-NE)
mPFS, mo (95% CI)	12.4 (8.2-23.4)	12.5 (6.9-20.5)	5.4 (4.2-7.0)	6.9 (4.2-13.3)
mOS, mo (95% CI)	20.8 (12.4-NE)	NE (12.9-NE)	13.6 (8.6-22.2)	NE (13.5-NE)

Due to the nonrandomized, noncomparative nature of the GEOMETRY mono-1 trial, PFS and OS results are difficult to interpret
No statistical tests were made for PFS and OS because there was no comparator arm

Post hoc analysis: Intracranial response in 54% (7 of 13) of patients[e]

Complete resolution: 31% (4 of 13) **Partial resolution:** 23% (3 of 13)

Analysis of overall intracranial response rate included patients with measurable brain disease at baseline and at least one postbaseline assessment but omits brain imaging in patients with premature discontinuations, which may lead to bias favoring a treatment effect.

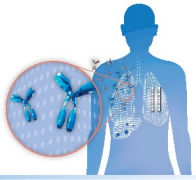
If brain lesions were documented at baseline, CT or MRI scan with intravenous contrast was mandated every 6 weeks, or otherwise, only if clinically indicated.[9]

Intracranial results are based on a noncomparative post hoc analysis and are observational in nature; as such, they should be interpreted with caution.

References: 1. Tabrecta. Prescribing information. Novartis Pharmaceuticals Corp; 2. Garon E, et al. Presented at: American Association for Cancer Research Annual Meeting; April 27-28, 2020; Virtual. Oral CT082; 3. Wolf J, et al. *N Engl J Med*. 2020;383(10):944-957; 4. Heist RS, et al. Presented at: Sixth AACR-IASLC International Joint Conference: Lung Cancer Translational Science from the Bench to the Clinic; January 11-14, 2020; San Diego, CA. Poster B11; 5. FoundationOne®Liquid CDx Technical Information. Foundation Medicine: 2021; 6. Data on file. Clinical Study Report CINC280A2201 Primary Analysis. Novartis Pharmaceuticals Corp; August 21, 2019; 7. Wolf J, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 4-8, 2021; Virtual. Poster 9020; 8. Wolf J, et al. Presented at: European Lung Cancer Conference Meeting; March 30-April 2, 2022. Poster 26P; 9. Clinical Trial Protocol CINC280A2201 Version 6 (EudraCT 2014-003850-15). Novartis Pharmaceuticals Corp; February 28, 2019.

GEOMETRY *mono-1*: Safety Summary

- The most common adverse reactions (≥20%) in patients who received capmatinib were edema[a], nausea, musculoskeletal pain, fatigue, vomiting, dyspnea, cough, and decreased appetite[1]



Edema	Edema[a] reported in 59% of patients (13% grades 3 to 4)[1,b] 2.4% discontinued capmatinib due to edema[1,a,b] 15.5% of patients had a dose adjustment and/or interruption due to peripheral edema[2,b,c]	**Peripheral edema[c]:** **Median time to first occurrence[3]** **(Grades ≥2)[d]:** 3.48 mo (range, 0.03-26.64; n=99)
Nausea and vomiting	Nausea was reported in 46% of patients (2.4% grades 3 to 4)[1,b] Vomiting was reported in 28% of patients (2.4% grades 3 to 4)[1,b] 0.8% and 0.8% discontinued capmatinib due to nausea or vomiting, respectively[2,b] 7.5% and 6.7% had a dose adjustment and/or interruption due to nausea or vomiting, respectively[2,b]	**Nausea:** **Median time to first occurrence[3]** **(Grades ≥2)[d]:** 0.44 mo (range, 0.03-21.42; n=54) **Vomiting:** **Median time to first occurrence[3]** **(Grades ≥2)[d]:** 0.56 mo (range, 0.07-21.42; n=25)
Elevated creatinine	Elevated creatinine was reported in 65% of patients (0.5% grades 3 to 4)[1,b] 0.8% discontinued capmatinib due to elevated creatinine[2,b] 9.1% had a dose adjustment and/or interruption due to elevated creatinine[2,b] Capmatinib has been shown preclinically to inhibit MATE1 and MATE2K transporters[1,4-6]	**Median time to first occurrence[3]** **(Grades ≥2)[d]:** 3.58 mo (range, 0.13-34.17; n=27)

MATE, multidrug and toxin extrusion; mo, month.
[a]Edema includes edema peripheral, generalized edema, face edema, edema, localized edema, edema genital, eyelid edema, peripheral swelling, scrotal edema, and penile edema.
[b]Data cutoff: August 30, 2021. [c]Peripheral edema includes peripheral swelling, peripheral edema and fluid overload. [d]Data cutoff: September 18, 2020.
References: 1. Tabrecta. Prescribing information. Novartis Pharmaceuticals Corp; 2. Data on file. Clinical Study Report CINC280A2201 Primary Analysis (Cohort 7). Novartis Pharmaceuticals Corp; December 21, 2021; 3. Heist RS, et al. Presented at: European Society for Medical Oncology 2021 Congress; September 16-21, 2021. Poster 1256P; 4. Lepist EI, et al. *Kidney Int.* 2014;86(2):350-357; 5. INC280 (capmatinib) Investigator's Brochure, Edition 11. Novartis Pharmaceuticals Corp; November 22, 2019; 6. Mathialagan S, et al. *J Pharm Sci.* 2017;106(9):2535-2541.

VISION: A Single-arm, Open-label, Multicenter, Nonrandomized, Multicohort Study

- Tepotinib in Adult Patients With Advanced or Metastatic NSCLC Harboring *MET*ex14 Skipping Alterations

Eligibility:

- Advanced, metastatic *MET*ex14+ NSCLC*
- *EGFR* wild-type and *ALK* negative status
- ≥1 measurable lesion by RECIST v1.1
- ECOG PS 0-1

Exclusions:

- Symptomatic CNS metastases
- Clinically significant uncontrolled cardiac disease
- Prior treatment with any MET or HGF inhibitor

Cohort A:
*MET*ex14 skipping
Detection of alterations in plasma or tissue

Cohort B:
MET amplification

Cohort C:
*MET*ex14 skipping
Detection of alterations in plasma or tissue

Confirmatory Part 2 of study

Tepotinib
500 mg† oral QD

Tepotinib was administered until disease progression or unacceptable toxicity

Major efficacy outcome

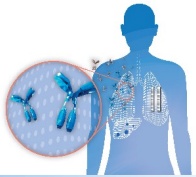
- Confirmed ORR by RECIST v1.1 as evaluated by BIRC

Additional efficacy outcome

- DOR by BIRC

*Identification of *MET*ex14 skipping was prospectively determined using central laboratories employing either a PCR-based or NGS-based clinical trial assay using tissue and/or plasma samples. An FDA-approved test for detection of *MET*exon14 skipping alterations in NSCLC for selecting patients for treatment with tepotinib is not available. †450 mg active moiety.
ALK, anaplastic lymphoma kinase; BIRC, Blinded Independent Review Committee; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; MET, mesenchymal-epithelial transition; NGS, next-generation sequencing; ORR, objective response rate; PCR, polymerase chain reaction; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.
Reference: TEPMETKO® (tepotinib) [prescribing information]. EMD Serono, Inc., Rockland, MA; 2021.

VISION: Response and Survival



	All Pts (n=313)	1L (n=164)	2L+ (n=149)
ORR (%)	51.4	57.3	45.0
mDOR (%)	18.0	46.4	12.6
mPFS (mos)	11.2	12.6	11.0
mOS (mos)	19.6	21.3	19.3

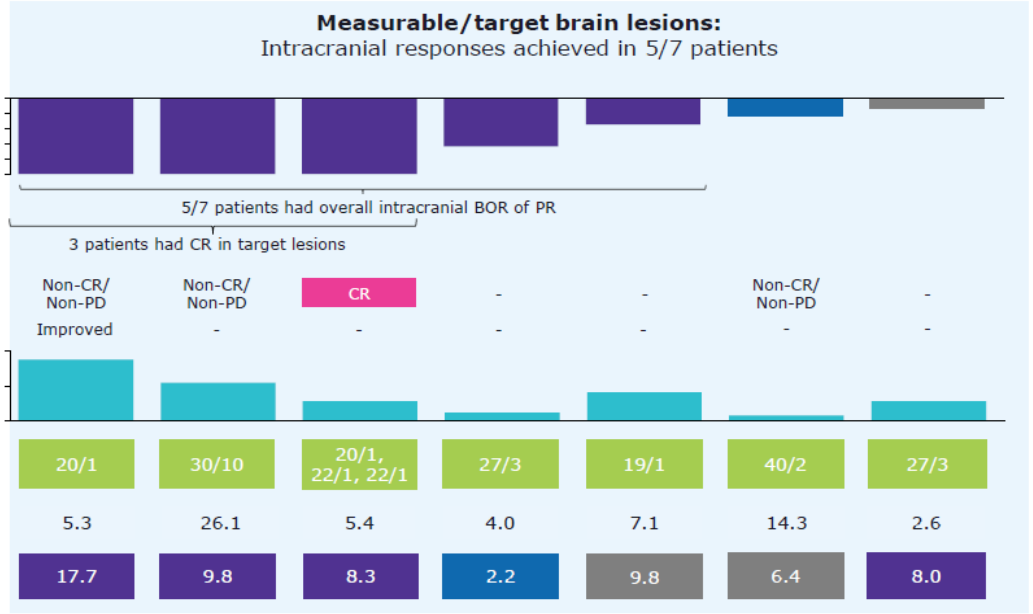
Paik P et al. ASCO 2023 (abstract 9060)
Mazieres et al. JAMA Oncol (published online June 4, 2023)

Assessment of Intracranial Response to Tepotinib by IRC

VISION Cohort A

July 2020 cut-off

- Of 7 patients with measurable/target brain lesions per RANO-BM, intracranial BOR was:
  - PR (n=5; including 3 cases of CR in target lesions
  - SD (n=1)
  - PD (n=1)



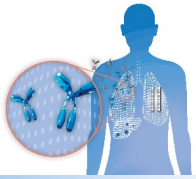
BOR

CR PR SD PD

Tepotinib demonstrated intracranial activity in evaluable patients with baseline brain metastases (per RANO-BM)
Intracranial disease control was observed in 13/15 patients

Data cutoff: July 1, 2020.
*Dashes (-) indicate NTLs were not recorded. †Radiotherapy for brain lesions.
BOR, best objective response; CR, complete response; IRC, Independent Review Committee; non-CR/non-PD, non-complete response/non-progressive disease; NTL, non-target lesion; PD, progressive disease; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
Reference: Patel JD, et al. ASCO 2021 (Poster 9084).

VISION: Safety Results



Results

Safety

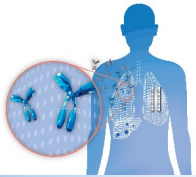
- Most treatment-related AEs were Grade 1/2; Grade ≥3 occurred in 34.8% of patients (**Table 4**)
- Peripheral edema was the most common AE and was mostly Grade 1/2; treatment-related any grade: 67.1%, Grade ≥3: 11.2% (**Table S3**)
- Patients requiring treatment interruptions or dose reductions were able to continue to benefit from tepotinib (**Figure S7**)

Table 4. Tepotinib safety profile in Cohorts A+C

AE, n (%)	Overall (N=313)	
	All cause AEs	Treatment-related AEs
Any AE	310 (99.0)	287 (91.7)
Serious AEs	159 (50.8)	49 (15.7)
Grade ≥3 AEs	203 (64.9)	109 (34.8)
Grade ≥4 AEs	57 (18.2)	12 (3.8)
AEs leading to dose reduction	113 (36.1)	105 (33.5)
AEs leading to treatment interruption	165 (52.7)	135 (43.1)
AEs leading to permanent discontinuation	78 (24.9)	46 (14.7)
AEs leading to death	41 (13.1)	3* (1.0)

*Of the three patients with treatment-related AEs leading to death, two patients were already detailed in Le X, et al. *Clin Cancer Res*. 2022;28(6):1117–1126, and the third patient had progressive disease or a lung cancer-related condition leading to multiple organ failure, which was considered treatment-related due to a missing causality report.
AEs, adverse events.
Paik P, et al. Abstract number 9060 at ASCO Annual Meeting 2023 | June 2–6, 2023 | Chicago, IL and virtual.

Conclusion on met Inhibitors for met exon 14 skip mutations



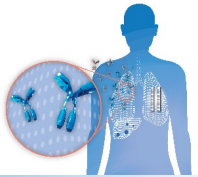
- Capmatinib and tepotinib both have shown durable clinical activity in patients with met exon 14 skip mutation-positive advanced NSCLC with acceptable safety profiles

	Capmatinib	Tepotinib
ORR (prior platinum)[A]	41%	45%
ORR (naive)	68%	57%
DOR (prior platinum)[A]	9.7 months	12.6 months
DOR (naive)	12.6 months	46.4 months
Active in CNS met	Yes	Yes
PFS, median	12.4 months 1L; 5.4 months 2L+	12.6 months 1L; 11 months 2L+
OS, median	20.8 months 1L; 13.6 months 2L+	21.3 months 1L; 19.3 months 2L+
Safety profile	Most AEs G1/2; 65% edema	Most AEs G1/2; 66% edema
Discontinuation TRAEs	16.9%	14.7%

Capmatinib and tepotinib: both FDA approved for treatment of advanced met exon 14 skip mutation-positive NSCLC

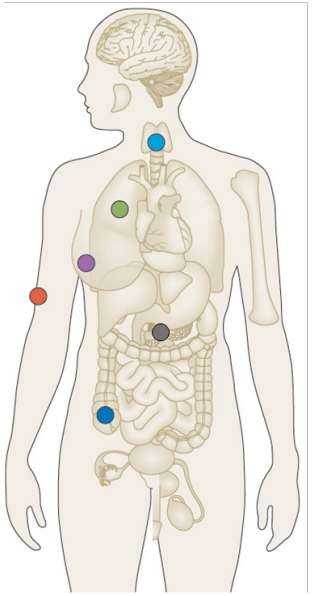
A – Cohort 4

RET

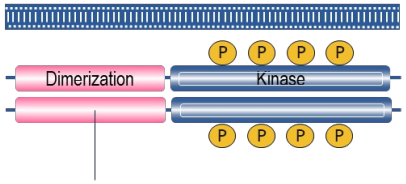


- *RET* fusions are known oncogenic drivers in NSCLC[1,2]
- Up to half of patients with advanced NSCLC will develop brain metastases[3]
- Multikinase inhibitors
  - Provide a modest clinical benefit
  - Associated with significant toxicity (non-*RET* kinase inhibition)
- Immunotherapy drugs (PD-1/PD-L1 inhibitors) may be less efficacious in patients with driver-positive NSCLC, including *RET* fusion[4,5]

RET fusions



Non-small cell lung cancer (2%)
Thyroid cancers (10–20%)
Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)

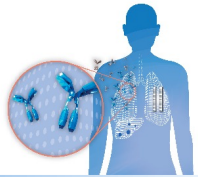


KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

Presented by Loong HH, et al. ESMO 2021.

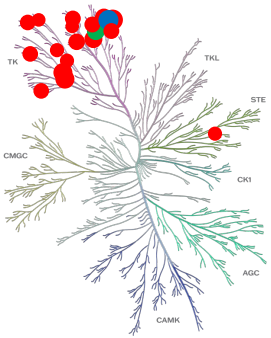
1. Drilon A, et al. *Nat Rev Clin Oncol.* 2018;15(3):151-167. 2. Wang R, et al. *J Clin Oncol.* 2012;30(35):4352-4359.
3. Drilon A, et al. *J Clin Oncol.* 2017;35(Suppl):9069-9069. 4. Sabari JK, et al. *J Clin Oncol.* 2018;36(15 Suppl):9034.
5. Mazieres J, et al. *J Clin Oncol.* 2018;36(15 Suppl):9010.

RET Multikinase Inhibitors in *RET*-Rearranged NSCLC

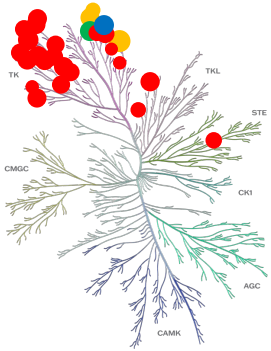


- RET
- KDR/VEGFR2
- FGFR1-3/EGFR
- MET/ALK/ROS
- Other kinases

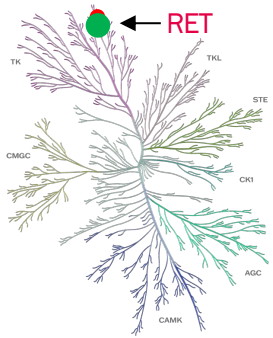
Cabozantinib



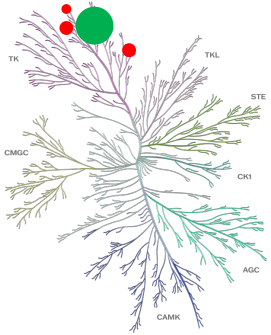
Vandetanib



Selpercatinib (LOXO-292)



Pralsetinib (BLU-667)



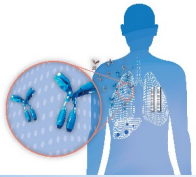
Agent	Cabozantinib	Vandetanib	Selpercatinib (LOXO-292)	Pralsetinib (BLU-667)
IC_{50} RET, nM[a]	11	4	3	0.4
ORR, %	37	18	68	58
▪ CR	5	0	2	1

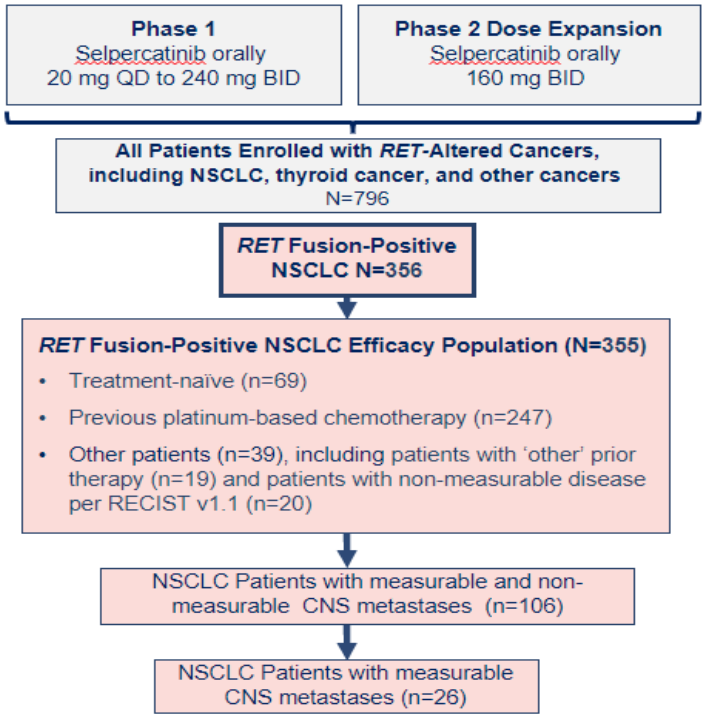
[a] Cell free.

Presented by Loong HH, et al. ESMO 2021.

1. Velcheti V, et al. WCLC 2017. Abstract OA 12.07. 2. Gautschi O, et al. *J Clin Oncol.* 2017;35(13):1403-1410. 3. Drilon A, et al. WCLC 2019. Abstract PL02.08. 4. Gainor JF, et al. ASCO 2019. Abstract 9008. 5. Rahal R, et al. AACR 2017. Abstract B151. 6. Solomon BJ, et al. *J Thorac Oncol.* 2020;15(4):541-549.

The Phase 1/2 LIBRETTO-001 Trial: Selpercatinib in Patients with *RET*-altered Cancers





Study Design
- Ongoing, global, multicenter Phase 1/2 trial (NCT03157128)
- Patients enrolled based on locally identified *RET* alterations using NGS, FISH, or PCR
- Key inclusion criteria: Diagnosis of advanced or metastatic disease, ECOG PS 0 to 2, asymptomatic CNS metastases permitted.

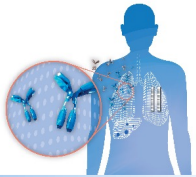
Primary Endpoint
- ORR (RECIST v 1.1) by Independent Review

Secondary Endpoints Included
- Duration of Response (DOR)
- CNS ORR/DOR by IRC
- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Safety

Safety population includes all patients who received at least one selpercatinib dose prior to June 2021 data cutoff
Efficacy population includes all patients enrolled 6 months prior to data cutoff date, to allow adequate follow-up. One patient with NSCLC who received prior treatment with another selective RET inhibitor was not included in the efficacy analysis but was included in the NSCLC safety population

Drilon et al ELCC 2022

LIBRETTO-001 - Efficacy



Response	Treatment-naïve (N=69)	Previous platinum chemotherapy (N=247)
Objective response by IRC— % (95% CI)	84.1 (73.3, 91.8)	61.1 (54.7, 67.2)
Duration of response		
Median —mo (95% CI)	20.2 (13.0, NE)	28.6 (20.4, NE)
Censoring rate (%)	55.2	60.9
1-yr DoR— % (95% CI)	66.1 (51.6, 77.3)	73.1 (64.9, 79.7)
2-yr DoR— % (95% CI)	41.6 (25.6, 56.8)	55.8 (46.4, 64.2)
Median duration of follow-up—mo	20.3	21.2
Progression-free survival		
Median —mo (95% CI)	22.0 (13.8, NE)	24.9 (19.3, NE)
Censoring rate— n (%)	37 (53.6)	138 (55.9)
1-yr PFS — % (95% CI)	70.6 (57.8, 80.2)	70.5 (64.1, 76.0)
2-yr PFS — % (95% CI)	41.6 (26.8, 55.8)	51.4 (44.3, 58.1)
Median duration of follow-up—mo	21.9	24.7
Overall survival		
Patients with censored data—n (%)	49 (71.0)	169 (68.4)
1-yr OS —% (95% CI)	92.7 (83.3, 96.9)	87.9 (83.0, 91.4)
2-yr OS —% (95% CI)	69.3 (55.2, 79.7)	68.9 (62.2, 74.7)
3-yr OS —% (95% CI)	57.1 (35.9, 73.6)	58.5 (49.7, 66.3)
Median duration of follow-up —mo	25.2	26.4

Note: ORR was consistent regardless of prior therapy or ethnicity (data not shown)

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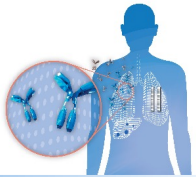
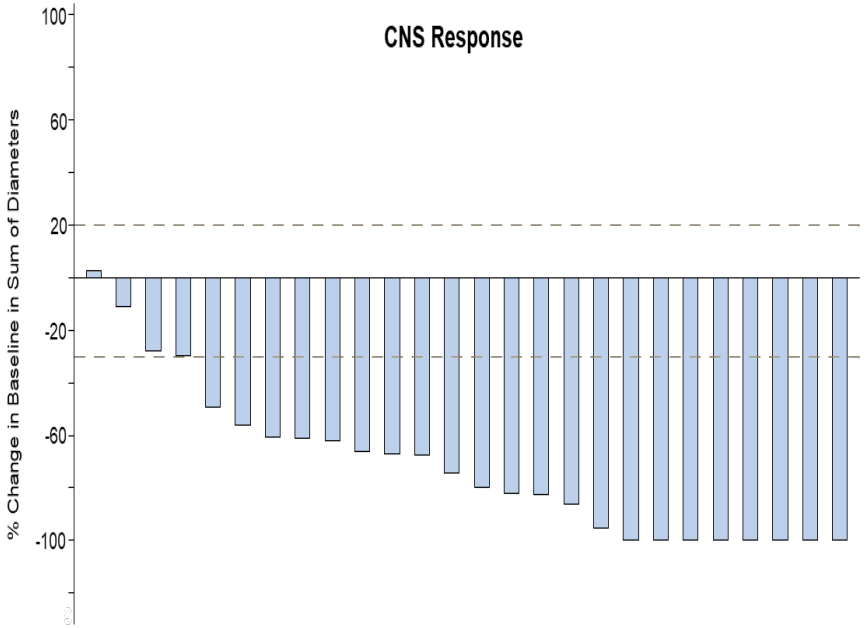
LIBRETTO-001 – CNS Efficacy



CNS response	(N=26)
Objective response by IRC– % (95% CI)	84.6 (65.1, 95.6)
Best response –n (%)	
Complete response	7 (26.9)
Partial response	15 (57.7)
Stable disease	4 (15.4)
Progressive disease	0
Could not be evaluated	0
CNS duration of response	
Median –mo (95% CI)	9.4 (7.4-15.3)
Censoring rate (%)	27.3
1-yr DoR– % (95% CI)	36.1 (16.4, 56.4)
2-yr DoR– % (95% CI)	20.6 (6.5, 40.2)
Median duration of follow-up–mo	25.8



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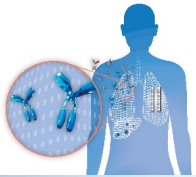
LIBRETTO-001: Adverse Events in NSCLC Safety Population



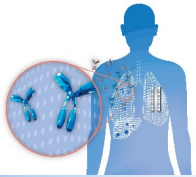
	Any Causality		Related to Treatment	
N=356, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 AE	356 (100.0)	263 (73.9)	341 (95.8)	143 (40.2)
Edema	178 (50.0)	2 (0.6)	124 (34.8)	2 (0.6)
Diarrhea	184 (51.7)	15 (4.2)	114 (32.0)	8 (2.2)
Fatigue	153 (43.0)	8 (2.2)	78 (21.9)	3 (0.8)
Dry Mouth	163 (45.8)	0	151 (42.4)	0
Hypertension (AESI)	141 (39.6)	68 (19.1)	95 (26.7)	49 (13.8)
AST increased	149 (41.9)	37 (10.4)	122 (34.3)	24 (6.7)
ALT increased	147 (41.3)	53 (14.9)	120 (33.7)	41 (11.5)
Abdominal pain	101 (28.4)	5 (1.4)	28 (7.9)	1 (0.3)
Constipation	96 (27.0)	5 (1.4)	34 (9.6)	2 (0.6)
Rash	130 (36.5)	4 (1.1)	83 (23.3)	4 (1.1)
Nausea	112 (31.5)	4 (1.1)	40 (11.2)	2 (0.6)
Blood creatinine increased	92 (25.8)	10 (2.8)	50 (14.0)	1 (0.3)
Headache	94 (26.4)	3 (0.8)	23 (6.5)	0
Cough	87 (24.4)	0	9 (2.5)	0
Dyspnea	84 (23.6)	16 (4.5)	10 (2.8)	0
Vomiting	78 (21.9)	4 (1.1)	19 (5.3)	2 (0.6)
ECG QT prolongation (AESI)	74 (20.8)	21 (5.9)	57 (16.0)	14 (3.9)
Thrombocytopenia	74 (20.8)	20 (5.9)	52 (14.6)	13 (3.7)
Decreased appetite	73 (20.5)	1 (0.3)	34 (9.6)	0
Pyrexia	79 (22.2)	1 (0.3)	21 (5.9)	1 (0.3)
Urinary tract infection	70 (19.7)	8 (2.2)	2 (0.6)	0

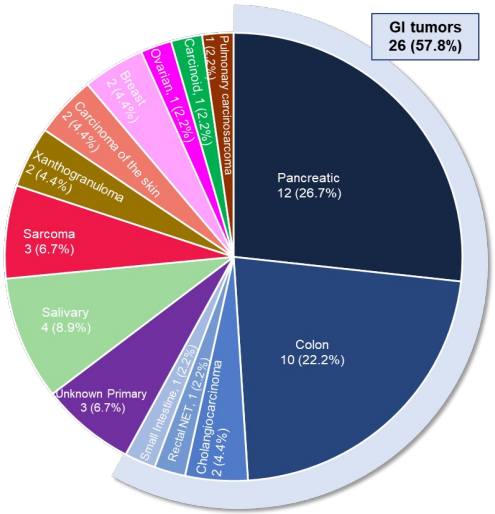
- Safety profile consistent as previously observed
- Of the 34 (9.6%) patients who discontinued due to AE, 11 (3.1%) were deemed related to study treatment per the investigator

The total percentage for any given adverse event may be different than the sum of the components for the individual grades because of rounding. The table includes adverse events which occurred in ≥20% of patients. Composite terms which are comprised of preferred terms are shown in italics. [a]In total, 24 (6.7%) patients had grade 5 TEAEs, including respiratory failure, (in 6 each), cardiac arrest (in 4 each), pneumonia, sepsis, cerebral hemorrhage (in 2 each), multiple organ dysfunction syndrome, sudden death, somnolence, dyspnea, hypoxia, corona virus infection, acute respiratory failure, and cardio-respiratory arrest (in 1 each). [b]No grade 5 TRAEs were observed.

Drilon et al, ELCC 2022

LIBRETTO-001 – Tumor Agnostic Indication



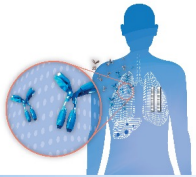


Tumor Type	Patients (n=41)	ORR by IRC		DOR Range (months)
		n (%)	95% CI	
Pancreatic	11	6 (55%)	23%, 83%	2.5, 38.3+
Colon	10	2 (20%)	2.5%, 56%	5.6, 13.3
Salivary	4	2 (50%)	7%, 93%	5.7, 28.8+
Unknown primary	3	1 (33%)	0.8%, 91%	9.2
Breast	2	PR, CR	NA	2.3+, 17.3
Sarcoma	2	PR, SD	NA	14.9+, NA
Xanthogranuloma	2	NE[a]	NA	NA
Carcinoid	1	PR	NA	24.1+
Carcinoma of the skin	1	NE	NA	NA
Cholangiocarcinoma	1	PR	NA	5.6+
Ovarian	1	PR	NA	14.5+
Pulmonary carcinosarcoma	1	NE	NA	NA
Rectal neuroendocrine	1	NE	NA	NA
Small intestine	1	CR	NA	24.5

Subbiah et al ASCO 2022

ARROW study design

A multi-cohort, open-label, phase 1/2 study



Eligibility criteria

- Age ≥18 years
- Advanced or metastatic solid tumor
- *RET* alteration per local assessment
- Measurable disease (RECIST v1.1)
- ECOG PS 0–1*

Protocol amendment (July 2019)

Eligibility criteria were expanded to allow treatment-naïve patients with NSCLC who were candidates for platinum-based therapy

Phase 1 dose escalation (Completed)

Phase 2 dose determined: 400 mg QD

Phase 2 dose expansion
Treated at 400 mg QD

- *RET* fusion–positive NSCLC
- Medullary thyroid cancer[a]
- Other *RET*-altered tumors

1º endpoints:

- ORR (BICR per RECIST v1.1)
- Safety

Key 2º endpoints:

- DOR
- CBR
- DCR
- PFS
- OS

*Limited to 0-1 after protocol amendment

[a]Patients with medullary thyroid cancer did not require documented *RET* mutations for enrollment.

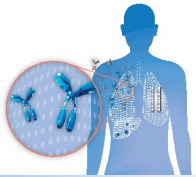
BICR, blinded independent central review; CBR, clinical benefit rate (CR or PR or SD of ≥16 weeks); CR, complete response; DCR, disease control rate (confirmed CR or PR or SD); DOR, duration of response;

ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response;

QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RET, rearranged during transfection; SD stable disease.

Slides adapted from data presented at ESMO Congress, September 9–13, 2022

ARROW Results – Summary of Efficacy



	Measurable disease population			
		Treatment naïve		
	All (n=260)	Pre-eligibility revision (n=43)	Post eligibility revision (n=64)	Prior platinum treatment (n=130)
ORR, % (95% CI)	70.0 (64.0–75.5)	74.4 (58.8–86.5)	79.7 (67.8–88.7)	63.1 (54.2–71.4)
Complete response, n (%)	15 (5.8)	4 (9.3)	3 (4.7)	8 (6.2)
Partial response, n (%)	167 (64.2)	28 (65.1)	48 (75.0)	74 (56.9)
	n=182	**n=32**	**n=51**	**n=82**
Median DOR, months (95% CI)[a]	19.1 (14.5–27.9)	14.7 (7.4–27.9)	12.6 (9.4–NR)	38.8 (14.8–40.4)
Median follow-up (95% CI)	23.9 (21.4–27.6)	27.6 (21.2–30.2)	17.4 (14.3–20.3)	29.3 (24.1–33.1)

The measurable disease population was the primary population for analysis of ORR and DOR.
[a]DOR for the measurable disease population per FDA censoring rule

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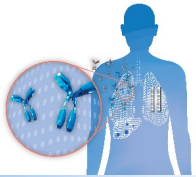
ARROW Results – Central Nervous System (CNS)



	All (n=15)
CNS ORR, % (95% CI)	53.3 (26.6–78.7)
Complete response, n (%)	3 (20.0)
Partial response, n (%)	5 (33.3)
	n=8
Median DOR, months (95% CI)[a]	11.5 (9.2–NR)
Median follow-up (95% CI)	29.7 (24.1–35.3)

Of the 15 patients, 14 had prior platinum treatment and 1 was treatment naïve. [a]Per EMA censoring rule.

Safety

- In the safety population (n=281), median treatment duration was 15.0 months with a median relative dose intensity of 86.1%
- Overall, 10% of patients discontinued pralsetinib due to treatment-related adverse events (TRAEs)

n=281, n (%)	Any causality		Treatment related	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Anaemia	151 (53.7)	65 (23.1)	119 (42.3)	55 (19.6)
AST increased	137 (48.8)	18 (6.4)	125 (44.5)	11 (3.9)
Constipation	125 (44.5)	2 (<1)	76 (27.0)	2 (<1)
Hypertension	103 (36.7)	50 (17.8)	75 (26.7)	39 (13.9)
ALT increased	101 (35.9)	13 (4.6)	92 (32.7)	9 (3.2)
Neutrophil count decreased	88 (31.3)	40 (14.2)	87 (31.0)	37 (13.2)
Diarrhoea	84 (29.9)	7 (2.5)	50 (17.8)	3 (1.1)
Cough	81 (28.8)	1 (<1)	15 (5.3)	1 (<1)
Pyrexia	81 (28.8)	2 (<1)	22 (7.8)	0
White blood cell count decreased	77 (27.4)	16 (5.7)	74 (26.3)	15 (5.3)
Fatigue	75 (26.7)	6 (2.1)	46 (16.4)	5 (1.8)
Blood creatinine increased	70 (24.9)	2 (<1)	48 (17.1)	1 (<1)
Neutropenia	64 (22.8)	30 (10.7)	60 (21.4)	26 (9.3)
Dyspnoea	62 (22.1)	8 (2.8)	5 (1.8)	1 (<1)
Pneumonia	56 (19.9)	36 (12.8)	18 (6.4)	12 (4.3)

The table includes AEs which occurred in ≥20% of patients.
AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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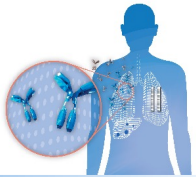
Conclusion on RET Inhibitors

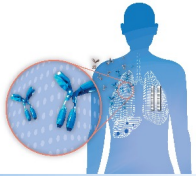


- Pralsetinib and selpercatinib both have shown durable clinical activity in patients with *RET* fusion-positive advanced NSCLC with acceptable safety profiles

	Pralsetinib (BLU-667) (N=87, 27)	Selpercatinib (LOXO-292) (n=316)
ORR (prior platinum)	63% (n=130)	61% (n=247)
ORR (naive)	77.0% (n=130)	84% (n=69)
DOR (prior platinum)	38.8	28.6 months
DOR (naive)	19.1 months	20.2 months
Active in CNS met	Yes	Yes
ORR CNS	53.3% (n=15)	84.6% (n=26)
Safety profile	Most AEs G1/2	Most AEs low grade
Discontinuation TRAEs	6%	2%

- Pralsetinib and selpercatinib: both FDA approved for treatment of advanced *RET* fusion-positive NSCLC

Some of the issues we did not have time to discuss today…….



- Mechanisms of acquired resistance
- Repeat molecular testing at PD
- Met inhibitors in met-amplified/met+ patients
- Next Generation Inhibitors

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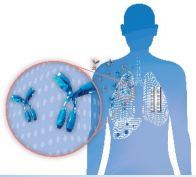

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Thank you