RET, MET and NTRK Mutations/Fusions in NSCLC

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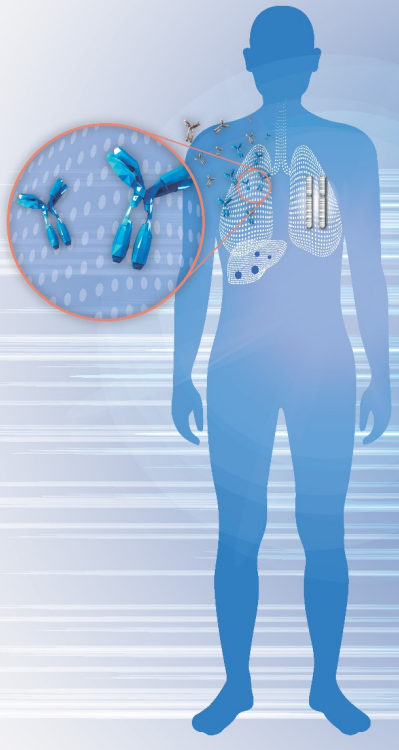
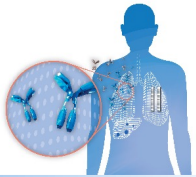
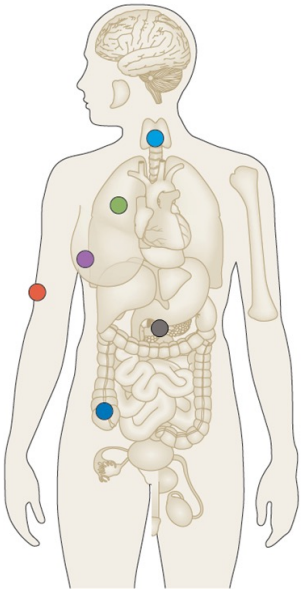


RET

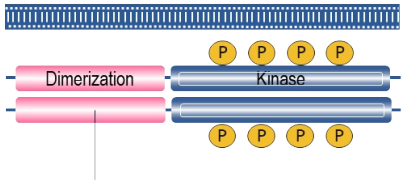


- *RET* fusions are known oncogenic drivers in NSCLC[1,2]
- Up to half of patients with advanced NSCLC will develop brain metastases[3]
- Multikinase inhibitors
  - Provide a modest clinical benefit
  - Associated with significant toxicity (non-*RET* kinase inhibition)
- Immunotherapy drugs (PD-1/PD-L1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

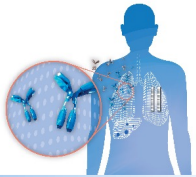


KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

Presented by Loong HH, et al. ESMO 2021.

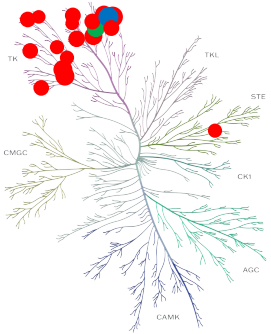
1. Drilon A, et al. *Nat Rev Clin Oncol.* 2018;15(3):151-167. 2. Wang R, et al. *J Clin Oncol.* 2012;30(35):4352-4359.
3. Drilon A, et al. *J Clin Oncol.* 2017;35(Suppl):9069-9069. 4. Sabari JK, et al. *J Clin Oncol.* 2018;36(15 Suppl):9034.
5. Mazieres J, et al. *J Clin Oncol.* 2018;36(15 Suppl):9010.

RET Multikinase Inhibitors in *RET*-Rearranged NSCLC

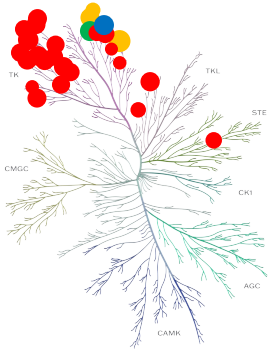


- RET
- KDR/VEGFR2
- FGFR1-3/EGFR
- MET/ALK/ROS
- Other kinases

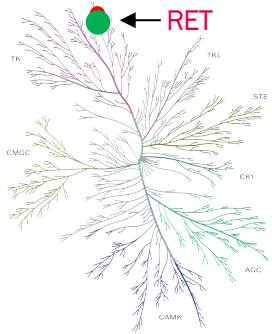
Cabozantinib



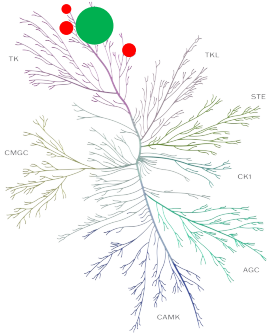
Vandetanib



Selpercatinib (LOXO-292)



Pralsetinib (BLU-667)



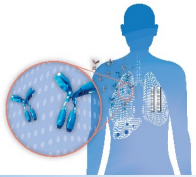
Agent	Cabozantinib	Vandetanib	Selpercatinib (LOXO-292)	Pralsetinib (BLU-667)
IC_{50} RET, nM[a]	11	4	3	0.4
ORR, %	37	18	68	58
▪ CR	5	0	2	1

[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.

LIBRETTO-001: Selpercatinib in *RET*-Altered Cancers



Phase 1 dose escalation
Selpercatinib dosed at 20 mg QD-240 mg BID

Phase 2 dose expansion
Selpercatinib dosed at 160 mg BID

Total Enrolled n=746

RET fusion–positive NSCLC n=345

RET-mutant medullary thyroid cancer

RET fusion–positive thyroid cancer

Other

RET Fusion-Positive NSCLC Efficacy Population n=266[a]

Prior platinum chemotherapy

Integrated analysis set (IAS), n=218

PAS, n=105

Treatment naive n=48

Primary Analysis Set (PAS) n=105

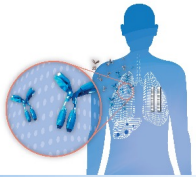
First 105 patients with *RET* fusion–positive NSCLC who received prior platinum chemotherapy

- ***RET* alteration**
  - Determined by local CLIA (or similarly accredited) laboratories
- **Primary endpoint**
  - ORR (RECIST 1.1)
- **Secondary endpoints**
  - DOR
  - PFS
  - Safety
- **Treatment beyond progression permitted with continued benefit**

Selpercatinib (LOXO-292)

[a]Efficacy population includes all patients enrolled 6 months prior to data cutoff of March 2020, to allow adequate follow up.
Besse B, et al. Presented at ASCO 2021, June 4 – June 8, 2021, Virtual Format. Abstract 9065.

LIBRETTO-001: Efficacy

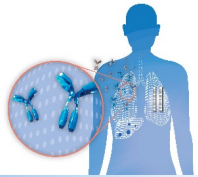


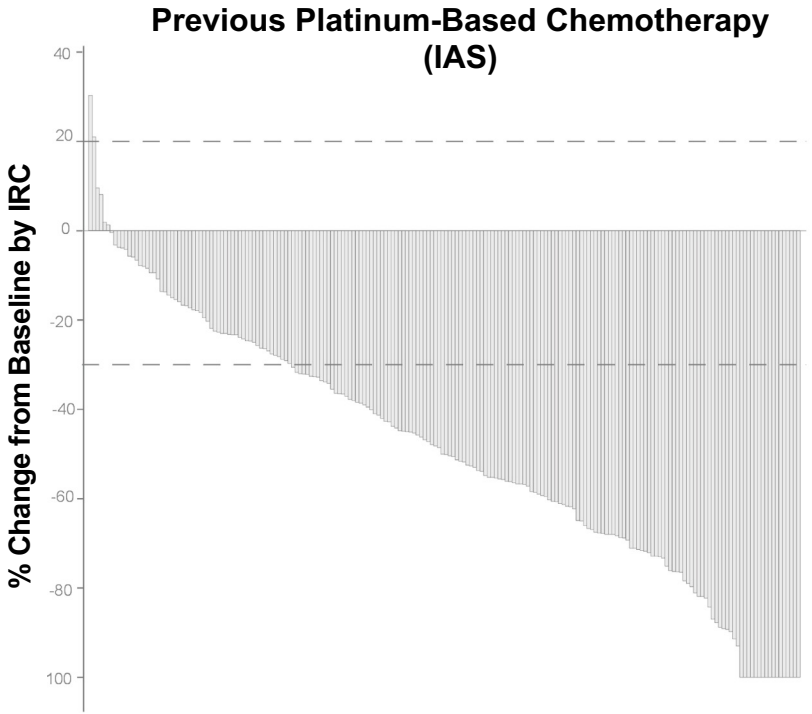
Previous Platinum-Based Chemotherapy (n=105)	
ORR (95% CI)	64% (54%, 73%)
CR, n (%)	**3 (3)**
PR, n (%)	**64 (61)**
SD, n (%)	**30 (29)**
1-year PFS rate, % (95% CI)	66 (55-74)
Median DOR	17.5 months (12.1-NE)

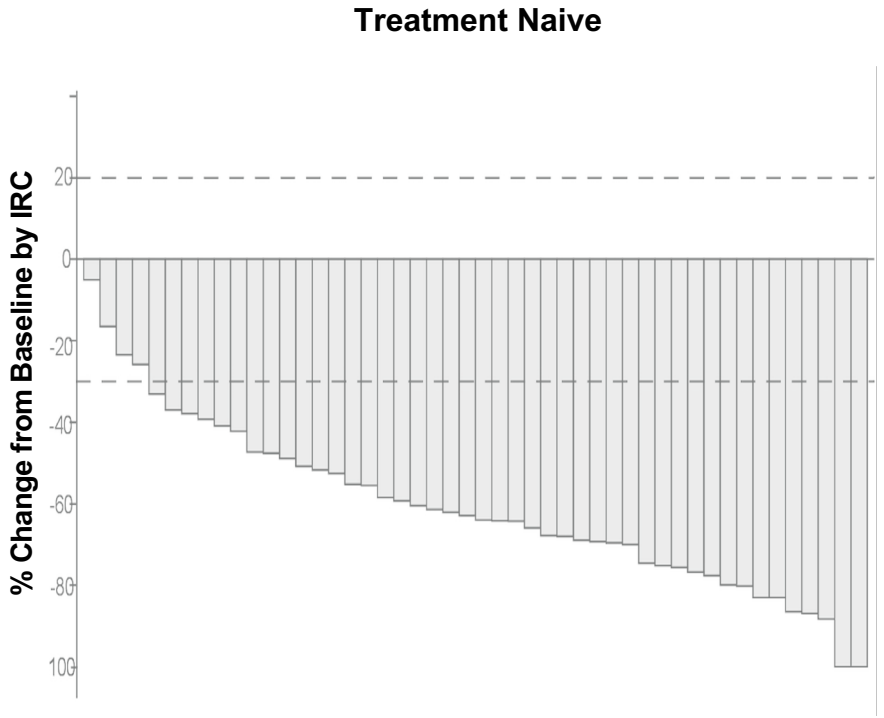
Treatment Naive (n=48)	
ORR (95% CI)	85% (72%, 94%)
CR, n (%)	**1 (2)**
PR, n (%)	**40 (83)**
SD, n (%)	**4 (8)**
1-year PFS rate, % (95% CI)	68 (50-80)
Median DOR	NE (12.0-NE)

Based on independent review, data cutoff March 2020.
Besse B, et al. Presented at ASCO 2021, June 4 – June 8, 2021, Virtual Format. Abstract 9065.

LIBRETTO-001: Changes in Tumor Sizes







Based on independent review, data cutoff March 2020.
Besse B, et al. Presented at ASCO 2021, June 4 – June 8, 2021, Virtual Format. Abstract 9065.

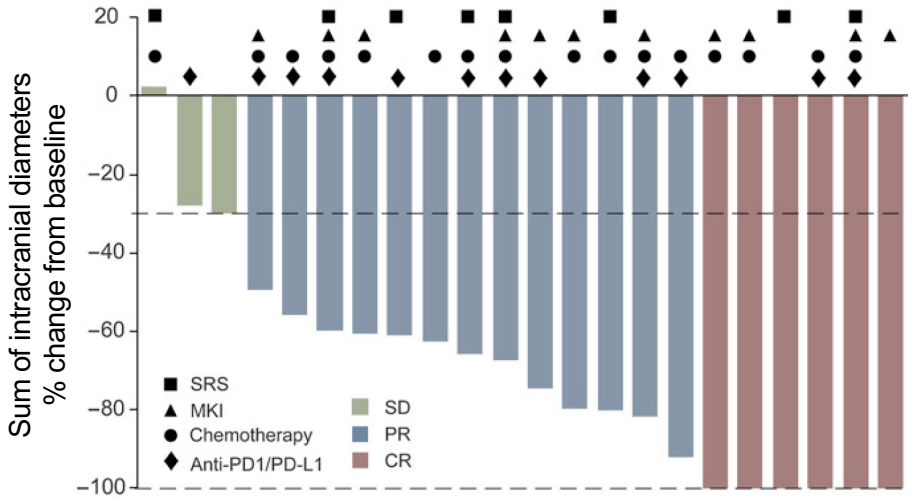
Intracranial ORR and Change in Tumor Size in *RET* Fusion–Positive NSCLC With Selpercatinib

- **Evaluable platinum-based chemotherapy – pretreated patients with measurable CNS lesions (n=22)**

Objective Response Rate

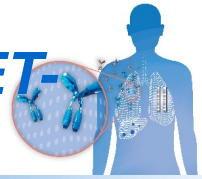
ORR, % (95% CI)	82 (60, 95)
CR, n (%)	5 (23)
PR, n (%)	13 (59)
SD, n (%)	4 (18)

Change in Tumor Size



Based on IRC assessment per RECIST 1.1.
Subbiah V, et al. *Clin Cancer Res.* 2021;27(15):4160-4167.

LIBRETTO-001: Adverse Events in 746 Patients With *RET*-Altered Cancers (≥15% Occurrence)



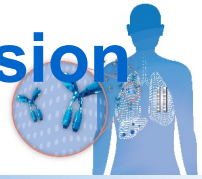
	AEs, Regardless of Attribution		Treatment-Related AEs	
	Any grade (%)	Grades 3-4 (%)	Any grade (%)	Grades 3-4 (%)
Dry mouth	40	0	36	0
Diarrhea	39	3[a]	22	2[a]
Hypertension	37	19	25	12
ALT increased	33	10	26	8
AST increased	33	9	26	7
Fatigue	31	1[a]	19	1[a]
Constipation	27	<1[a]	13	<1[a]
Peripheral edema	26	<1[a]	14	0
Headache	24	1[a]	9	<1[a]
Nausea	23	<1[a]	10	<1[a]
Blood creatinine increased	21	<1[a]	12	0
Abdominal pain	20	2[a]	6	<1[a]
Rash	19	<1[a]	12	<1[a]
Prolonged QT	18	4[a]	14	3[a]
Cough	16	0	1	0
Vomiting	16	<1[a]	4	<1[a]
Dyspnea	15	3	2	0

- 2% of patients discontinued due to treatment-related adverse events

Safety population included all patients with RET-altered cancers (includes RET-mutant MTC and RET-fusion positive NSCLC). In total, 25 of 746 patients had grade 5 TEAEs. No grade 5 TRAEs were observed. Safety among the 345 patients with NSCLC was consistent with the safety of the overall population. Data cutoff March 2020. [a]Only grade 3 AEs occurred, no grade 4 AEs.

Besse B, et al. Presented at ASCO 2021, June 4 – June 8, 2021, Virtual Format. Abstract 9065.

ARROW: Pralsetinib Dose Escalation and Expansion Study



Eligibility criteria

- Age ≥18 years
- Unresectable locally advanced or metastatic solid tumor
- Documented *RET* fusion or mutation (local testing)
- Measurable disease per RECIST v1.1
- ECOG PS 0-1

Phase 1 dose escalation (completed)
Phase 2 dose determined
400 mg once daily

Phase 2 dose expansion (ongoing)
Groups defined by disease type and prior therapy, treated at phase 2 dose

1º endpoints

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

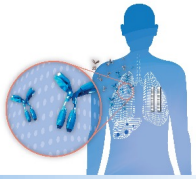
Key 2º endpoints

- DOR
- CBR[a]
- DCR
- Intracranial response rate
- PFS
- OS

	Baseline Characteristics (Efficacy Population)	
	Prior Platinum (n=92)	Treatment Naive (n=29)
Med age (range), y	60 (53-68)	65 (54-69)
Female	50%	52%
Median lines of prior therapy (range)	2 (1-3)	0
Brain metastases	41%	41%
RET Fusion Partner		
KIF5B	75%	69%
CCDC6	17%	10%
Other	2%	0%
Unknown	5%	21%

[a] Complete or partial response or stable disease of ≥16 weeks.
Gainor JF, et al. *Lancet Oncol*. 2021 Jul;22(7):959-969.

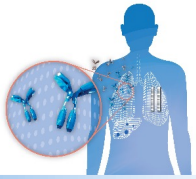
ARROW: Efficacy Summary of Pralsetinib (Blinded Independent Centralized Review)



	Patients with measurable disease	
	Prior platinum (n=87)	Treatment naive (n=27)
Overall response rate	61%[a]	70%
95% CI	50–71%	50–86%
Best overall response		
CR	6%	11%
PR	55%[a]	59%
SD	30%	15%
PD	5%	11%
NE	5%	4%
Disease control rate (95% CI)	91% (83–96)	85% (66–96)
Clinical benefit rate (95% CI)[b]	69% (58–79)	70% (50–86)
Median DOR, months	NR (15.2–NE)	9.0 (6.3–NE)

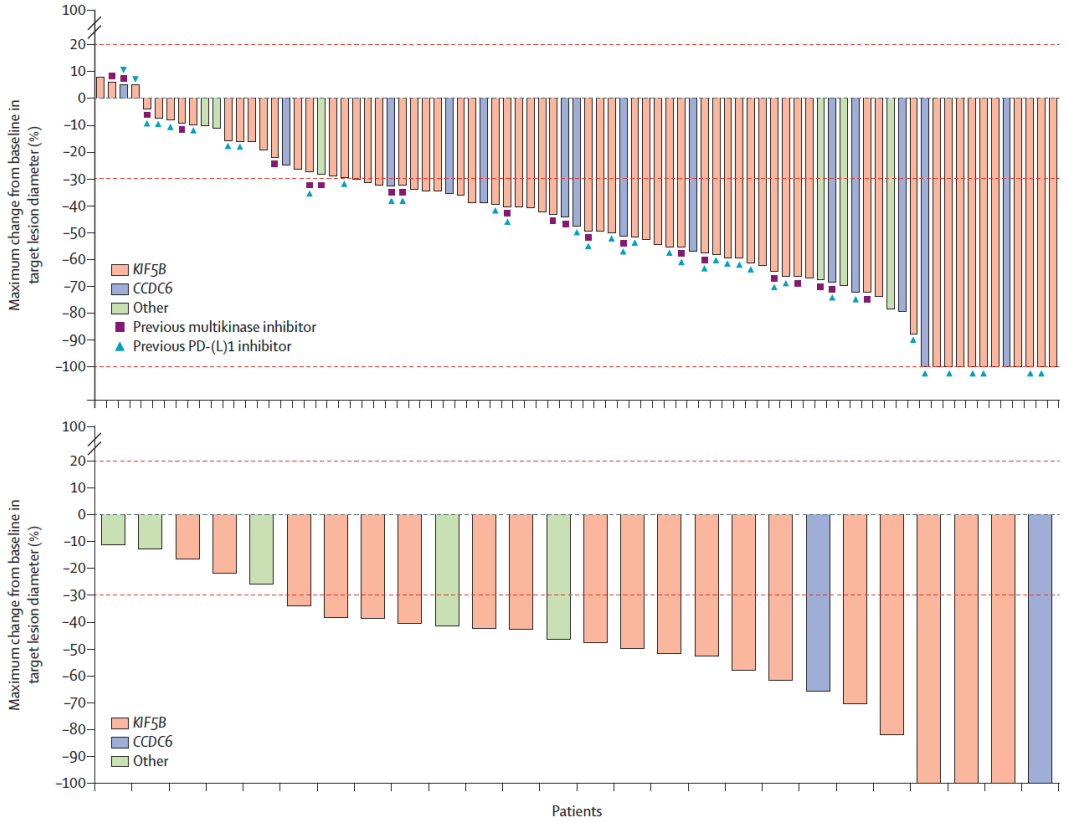
Data analysis cutoff date: May 22, 2020.
[a] Includes 2 patients still on treatment with PRs pending confirmation. [b] CR or PR or SD with duration ≥16 weeks.
Gainor JF, et al. *Lancet Oncol*. 2021 Jul;22(7):959-969.

ARROW: Tumor Shrinkage With Pralsetinib (Blinded Independent Centralized Review)



Prior platinum

Treatment naive

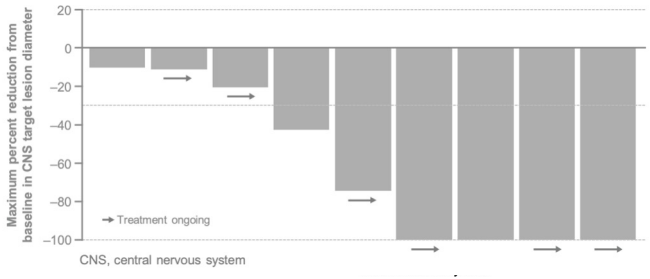


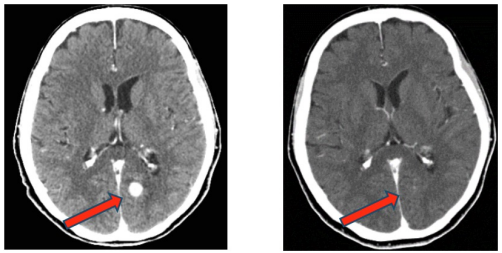
Data analysis cutoff date: May 22, 2020.

Gainor JF, et al. *Lancet Oncol*. 2021 Jul;22(7):959-969.

ARROW: Pralsetinib CNS Activity (Blinded Independent Centralized Review)

- Intracranial overall response rate in 9 patients with measurable CNS metastases at baseline was 56%
- 3 patients (33%) with intracranial complete response

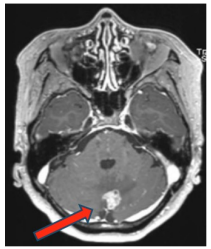




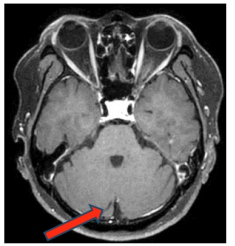
Baseline

After 8 months

71 year-old female previous smoker with *RET-CCDC6* fusion-positive metastatic NSCLC. No response and disease progression at 6 months on prior pembrolizumab monotherapy. Metastatic disease in brain, bone, adrenal gland, and lymph nodes at study entry. Complete resolution of a 12.6 mm brain target lesion observed at 1.6 months on pralsetinib. As of May 1, 2020, continues pralsetinib for 10+ months with ongoing overall partial response. (Courtesy of G. Curigliano)



Baseline

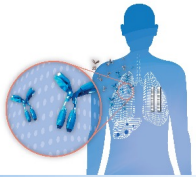


After 16 months

56 year-old female never smoker with *RET-KIF5B* fusion-positive NSCLC. Previously received adjuvant therapy with carboplatin/paclitaxel. Metastatic disease in brain, pleura, lymph nodes at study entry. 20 mm brain target lesion with rapid shrinkage and complete resolution by 7.5 months on pralsetinib As of May 1, 2020, continues pralsetinib for 16+ months with ongoing overall partial response. (Courtesy of D.W Kim)

Gainor JF, et al. ASCO 2020. Abstract 9515.
Gainor JF, et al. *Lancet Oncol*. 2021 Jul;22(7):959-969.

ARROW: Treatment-Related Adverse Events in ≥10% of Patients (N=471, All Tumor Types)

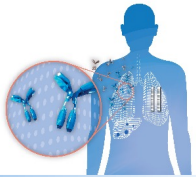


AE Preferred Term	All Patients (n=354)	
	Any grade	Grade ≥3
Neutropenia	40%	19%
AST increased	39%	3%
Anemia	35%	13%
White blood cell count decreased	32%	8%
ALT increased	28%	2%
Hypertension	26%	12%
Constipation	26%	1%
Asthenia	25%	3%
Lymphopenia	18%	11%
Hyperphosphatemia	17%	0%
Diarrhea	16%	1%
Thrombocytopenia	15%	4%
Blood creatinine increased	15%	0%
Dysgeusia	14%	0%
Blood creatine phosphokinase increased	14%	6%
Edema	14%	0%
Dry mouth	13%	0%
Pneumonitis	11%	3%

- 6% of patients discontinued due to treatment-related adverse events

Curigliano G, et al. Presented at ASCO 2021, June 4 – June 8, 2021, Virtual Format.

Conclusion on RET Inhibitors



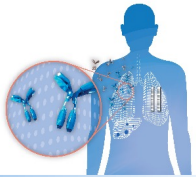
- Pralsetinib and selpercatinib both have shown durable clinical activity in patients with *RET* fusion-positive advanced NSCLC with acceptable safety profiles

	Pralsetinib (BLU-667) (N=87, 27 [471 safety[a]])	Selpercatinib (LOXO-292) (N=105, 39 [144 safety])
ORR (prior platinum)	61% (n=87)	70% (n=105)
ORR (naive)	70% (n=27)	90% (n=39)
DOR (prior platinum)	NR	20.3 months
DOR (naive)	9.0 months	NR
Active in CNS met	Yes	Yes
ORR CNS	56% (5/9)	82% (18/22)
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

[a] All tumor types.

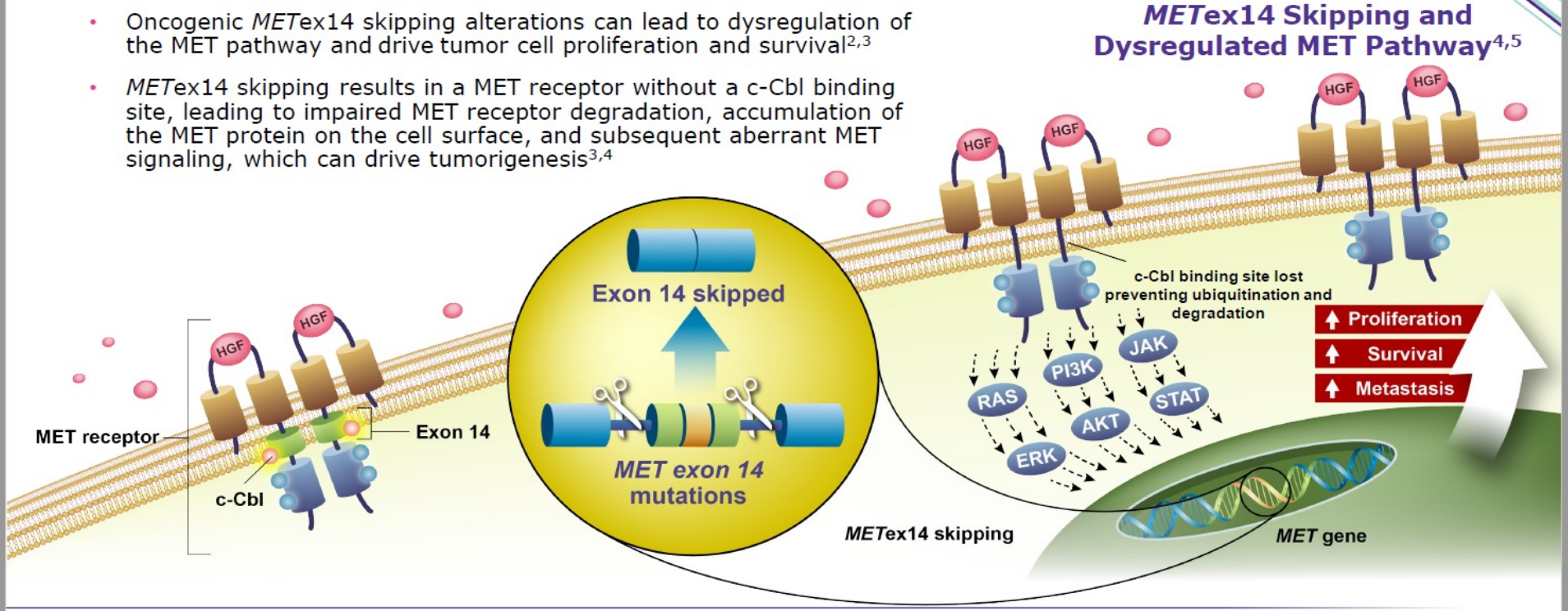
Ongoing Phase III Trials in Ret Fusion + NSCLC



Trial	NCT#	Investigational Arm	Control Arm	# Pts
Libretto-431	04194944	**Selpercatinib**	Plat + Pem ± Pembro	250
Accele-ret	04222972	**Pralsetinib**	Plat + Pem ± Pembro	250
Libretto-432	04819100	**Selpercatinib**	Adjuvant	170

MET Signaling Can Drive Tumor Growth and Progression[1]

- MET is a receptor tyrosine kinase encoded by the *MET* gene[1]
- Oncogenic *MET*ex14 skipping alterations can lead to dysregulation of the MET pathway and drive tumor cell proliferation and survival[2,3]
- *MET*ex14 skipping results in a MET receptor without a c-Cbl binding site, leading to impaired MET receptor degradation, accumulation of the MET protein on the cell surface, and subsequent aberrant MET signaling, which can drive tumorigenesis[3,4]



AKT, protein kinase B; c-Cbl, casitas B-lineage lymphoma; ERK, extracellular regulatory kinase; HGF, hepatocyte growth factor; JAK, Janus kinase; MET, mesenchymal-epithelial transition; PI3K, phosphoinositide 3-kinase; STAT, signal transducer and activator of transcription.

References: **1.** Paik PK, et al. *N Engl J Med*. 2020;383(10):1-40. **2.** Tong JH, et al. *Clin Cancer Res*. 2016;22(12):3048-3056. **3.** Liang H, Wang M. *Onco Targets Ther*. 2020;13:2491-2510. **4.** Drilon A, et al. *J Thorac Oncol*. 2017;12(1):15-26. **5.** Wu YL, et al. *Cancer Treat Rev*. 2017; 61:70-81.

*MET*ex14 Skipping Alterations Are Primary Oncogenic Drivers in NSCLC[1-6]

Patients with *MET*ex14 skipping alterations:

Have been associated with **advanced disease** and a **poor prognosis**[2]

Tend to be **considerably older** vs patients with other oncogenic drivers (average age of 54 to 65 years in *ALK, ROS1, EGFR, KRAS, and BRAF*)[1]

Are more frequently current or former smokers (60%) than never smokers (40%)[6]

_MET_ex14 skipping is the primary oncogenic driver in:

- 3% of adenocarcinomas[4,5]
- 2% of squamous cell carcinomas[5]
- 8% of sarcomatoid carcinomas[5]

Average Age at Diagnosis in Patients With *MET*ex14 Skipping Alterations[1]

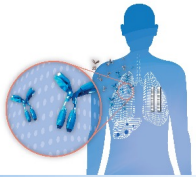
~74 years

Testing to identify patients with *MET*ex14 skipping alterations can help inform treatment decisions[2,3]

ALK, anaplastic lymphoma kinase gene; *BRAF*, proto-oncogene B-Raf; *EGFR*, epidermal growth factor receptor gene; *KRAS*, Ki-ras2 gene; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14; NSCLC, non-small cell lung cancer; *ROS1*, ROS proto-oncogene 1.

References: 1. Tong JH, et al. *Clin Cancer Res*. 2016;22(12):3048-3056. **2.** Awad MM, et al. *Lung Cancer*. 2019;133:96-102. **3.** Salgia R. *Mol Cancer Ther*. 2017;16(4): 555-565. **4.** Frampton GM, et al. *Cancer Discov*. 2015;5:850-859. **5.** Schrock AB, et al. *J Thorac Oncol*. 2016;11:1493-5102. **6.** Wolf J, et al. Presented at ENA, 2018, Poster 403.

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



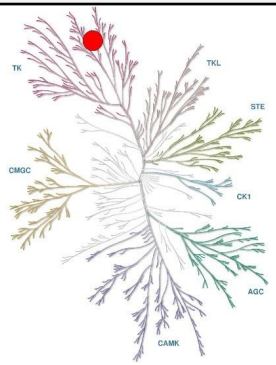
	Tepotinib	Capmatinib	Crizotinib	Savolitinib
Mode of action	Highly MET selective, potent TKI that inhibits MET phosphorylation and downstream signaling	Inhibits MET-dependent PI3K and RAS signalling	Potent MET inhibitor that is active in tumors harbouring *METex14* alterations and inhibits cell proliferation 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**

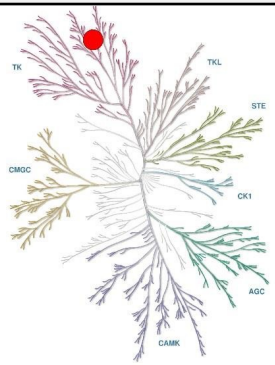
% inhibition at 1 µM

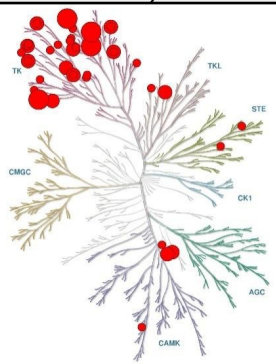
≥ 99%

> 90%

> 75%

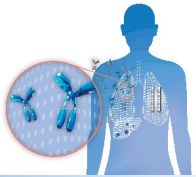






1. Paik et al., ASCO 2019, Abstract 9005

GEOMETRY mono-1: An Open-Label International Multicohort Phase II Study



- Stage IIIB/IV NSCLC
- *EGFR* WT (for L858R and delE19) and *ALK*-rearrangement negative
- ECOG PS 0-1
- ≥1 measurable lesion (RECIST 1.1)
- No symptomatic or neurologically unstable brain metastases allowed
- Centrally determined *MET* status using tissue-based samples

Capmatinib 400 mg PO BID

Cohort 5b
***MET*ex14, any *MET* GCN (treatment-naive)**
N=28

Cohort 6
***MET*ex14, any *MET* GCN (previously treated, 2L)**
N=31

Cohort 4
***MET*ex14, any *MET* GCN (previously treated, 2L/3L)**
N=69

Primary endpoint
- ORR (BIRC)

Key secondary endpoint
- DOR (BIRC)

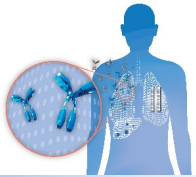
Secondary endpoints
- ORR (Inv)
- DOR (Inv)
- TTR (BIRC/Inv)
- DCR (BIRC/Inv)
- PFS (BIRC/Inv)
- Overall survival
- Safety
- PK

Key assessments by prior IO therapy
- ORR, DOR, and PFS for patients with or without prior IO, assessed by BIRC and investigators
- PFS on prior IO (prior to study entry) versus on capmatinib
- Safety

ALK, anaplastic lymphoma kinase; BID, twice daily; BIRC, blinded independent review committee; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; GCN, gene copy number; Inv, investigator review; 2L/3L, second/third line; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetics; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response; WT, wild-type.
Data cutoff: January 6, 2020.

1. Vansteenkiste J, et al. Presented at: European Society for Medical Oncology Virtual Meeting; September 19-21, 2020. Poster 1285P. 2. Wolf J, et al. *N Engl J Med.* 2020;383(10):944-957.

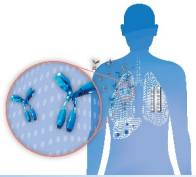
GEOMETRY mono-1: Baseline Characteristics[1-3]



Demographics		Cohorts 4 & 6 Previously treated *MET*ex14 with prior IO N=32	Cohorts 4 & 6 Previously treated *MET*ex14 without prior IO N=68	Cohort 5b Treatment-naive *MET*ex14 (without prior IO) N=28
Age, y	Median (range)	70.0 (49.0-87.0)	70.5 (49.0-90.0)	71 (57-86)
Age category, n (%)	<65 y ≥65 to <75 y ≥75 to <85 y ≥85 y	7 (21.9) 21 (65.6) 3 (9.4) 1 (3.1)	11 (16.2) 32 (47.1) 22 (32.4) 3 (4.4)	3 (10.7) 14 (50.0) 10 (35.7) 1 (3.6)
Race, n (%)	Caucasian Asian Other[a]	25 (78.1) 5 (15.6) 2 (6.3)	48 (70.6) 19 (27.9) 1 (1.5)	24 (85.7) 4 (14.3) 0
Sex, n (%)	Female Male	18 (56.3) 14 (43.8)	38 (55.9) 30 (44.1)	18 (64) 10 (36)
Smoking history, n (%)	Never smoked Former smoker Current smoker	19 (59.4) 12 (37.5) 1 (3.1)	40 (58.8) 25 (36.8) 3 (4.4)	18 (64) 9 (32) 1 (4)
ECOG status, n (%)	0 1 ≥2	8 (25.0) 23 (71.9) 1 (3.1)	18 (26.5) 50 (73.5) 0	7 (25) 21 (75) 0

1. Vansteenkiste J, et al. Presented at: European Society for Medical Oncology Virtual Meeting; September 19-21, 2020. Poster 1285P. 2. Wolf J, et al. *N Engl J Med.* 2020;383(10):944-957. 3. Data on file. Clinical Study Report CINC280A2201 Primary Analysis (Cohorts 1a, 5a, and 6). Novartis Pharmaceuticals Corp; June 16, 2020.

GEOMETRY mono-1: Key Efficacy Outcomes

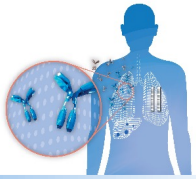


Data cutoff: January 6, 2020	Cohorts 4 & 6 Previously treated *MET*ex14 with prior IO[1] N=32		Cohorts 4 & 6 Previously treated *MET*ex14 without prior IO[1] N=68		Cohort 5b Treatment-naive *MET*ex14 (without prior IO)[2,3] N=28	
Best overall response, n (%)	**BIRC**	**Investigator**	**BIRC**	**Investigator**	**BIRC**	**Investigator**
Complete response	0	0	0	1 (1.5)	1 (4)	0
Partial response	20 (62.5)	17 (53.1)	23 (33.8)	25 (36.8)	18 (64)	17 (60.7)
Stable disease	7 (21.9)	8 (25.0)	30 (44.1)	27 (39.7)	7 (25)	10 (35.7)
Non-CR/non-PD	1 (3.1)	2 (6.3)	1 (1.5)	1 (1.5)	1 (4)	0
Progressive disease	1 (3.1)	3 (9.4)	5 (7.4)	4 (5.9)	1 (4)	1 (3.6)
Not evaluable[a]	3 (9.4)	2 (6.3)	9 (13.2)	10 (14.7)	0	0
ORR, % (95% CI)	62.5 (43.7-78.9)	53.1 (34.7-70.9)	33.8 (22.8-46.3)	38.2 (26.7-50.8)	68 (48-84)	60.7 (40.6-78.5)
DCR, % (95% CI)	87.5 (71.0-96.5)	84.4 (67.2-94.7)	79.4 (67.9-88.3)	79.4 (67.9-88.3)	96 (82-100)	96.4 (81.7-99.9)
Responders, n (%)[b]						
With event (PD or death)	14 (70.0)	12 (70.6)	17 (73.9)	20 (76.9)	11 (57.9)	12 (70.6)
Without event	6 (30.0)	5 (29.4)	6 (26.1)	5 (19.2)	8 (42.1)	5 (29.4)
DOR, median, mo (95% CI)	9.95[c] (5.55-19.52)	11.20[c] (4.34-21.65)	6.93 (4.17-11.14)	7.16 (4.17-10.87)	12.6 (5.6-NE)	13.8 (4.3-25.3)
DOR ≥6 mo, n (%)[b]	12 (60.0)	9 (52.9)	12 (52.2)	15 (57.7)	13 (68.4)	13 (76.5)
DOR ≥12 mo, n (%)[b]	5 (25.0)	5 (29.4)	5 (21.7)	5 (19.2)	9 (47.4)	9 (52.9)
PFS, median, mo (95% CI)	8.34[c] (4.17-12.58)	6.90[c] (4.70-19.81)	5.39 (4.17-6.93)	5.42 (4.17-7.39)	12.4 (8.2-NE)	12.0 (5.5-16.9)

[a]Not evaluable (unknown per RECIST 1.1): all other cases (ie, not qualifying for confirmed complete or partial response; without stable disease after >6 weeks; or progression within the first 12 weeks).
[b]Evaluated in patients with confirmed complete or partial response. [c]Results are not mature.

1. Vansteenkiste J, et al. Presented at: European Society for Medical Oncology Virtual Meeting; September 19-21, 2020. Poster 1285P. 2. Wolf J, et al. *N Engl J Med.* 2020;383(10):944-957.
3. Data on file. Clinical Study Report CINC280A2201 Primary Analysis (Cohorts 1a, 5a, and 6). Novartis Pharmaceuticals Corp; June 16, 2020.

GEOMETRY mono-1: Post Hoc Analysis of Intracranial Responses in Patients With Brain Lesions[1,2]



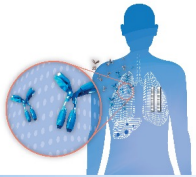
- Total of 13 evaluable patients (1L, 3 patients; 2L/3L, 10 patients) with brain metastasis at baseline by BIRC (3 brain lesions per patient [range, 1-8])
- 54% (7 of 13) of patients had intracranial response[a]
  - Complete resolution: 31% (4 of 13)
  - Partial resolution: 23% (3 of 13)
  - All 7 patients with response in the brain had intracranial response at the first evaluation (6 weeks from start of treatment)
- 3 of 7 responders had prior brain radiotherapy; 5 of 7 responders had either radiographic evidence of progression in the existing brain lesion(s) or new brain metastases at study entry
- Intracranial disease control rate[b]: 92% (12 of 13)

Intracranial disease control rate was an exploratory endpoint that accounts for CR + PR + SD,[b] which may reflect the natural history of disease in an individual patient rather than the therapeutic effect of the treatment

- This 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[3]
- Intracranial results are based on a noncomparative post hoc analysis and are observational in nature; as such, they should be interpreted with caution

1/2/3L, first/second/third-line; BIRC, blinded independent review committee; CR, complete response; CT, computed tomography; MRI, magnetic resonance imaging; PR, partial response; SD, stable disease.
[a]All responses were confirmed at next staging. [b]Intracranial disease control rate is defined as CR + PR + SD; SD is at least one SD assessment (or better) >6 weeks after randomization/start of treatment and not qualifying for CR or PR.
Data cutoff: April 15, 2019.
1. Garon E, et al. Presented at: American Association for Cancer Research Virtual Annual Meeting; April 27-28, 2020. Oral CT082. 2. Wolf J, et al. *N Engl J Med.* 2020;383(10):944-957.
3. Data on file. Clinical Trial Protocol CINC280A2201, Version 6 (EudraCT 2014-003850-15). Novartis Pharmaceuticals Corp; February 28, 2019.

GEOMETRY mono-1: Safety Summary

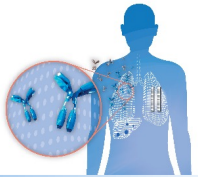


	Cohorts 4 & 6 Previously treated *MET*ex14 with prior IO N=32		Cohorts 4 & 6 Previously treated *MET*ex14 without prior IO N=68		Cohort 5b Treatment-naïve *MET*ex14 (without prior IO) N=28	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Any AE, n (%)	32 (100)	24 (75.0)	66 (97.1)	45 (66.2)	28 (100)	21 (75)
TRAEs	29 (90.6)	17 (53.1)	59 (86.8)	30 (44.1)	27 (96.4)	16 (57.1)
SAEs	16 (50.0)	13 (40.6)	29 (42.6)	25 (36.8)	14 (50)	12 (43)
Treatment-related SAEs	8 (25.0)	5 (15.6)	9 (13.2)	8 (11.8)	4 (14.3)	4 (14.3)
AEs requiring dose adjustment	13 (40.6)	5 (15.6)	19 (27.9)	6 (8.8)	NR	NR
AEs leading to drug discontinuation	8 (25.0)	5 (15.6)	9 (13.2)	6 (8.8)	6 (21)	5 (18)

- Median capmatinib treatment exposure was 32.4 weeks (range, 3.0-136.0) for *MET*ex14 mNSCLC patients who received prior IO and 25 weeks (range, 0.4-117.7) for previously treated *MET*ex14 mNSCLC patients who had not received prior IO
- Median capmatinib treatment exposure was 48.2 weeks (range, 4.0-117.4) for treatment-naive *MET*ex14 mNSCLC patients

AE, adverse event; IO, immunotherapy; *MET*ex14, *MET* exon 14 skipping mutation; mNSCLC, metastatic non-small cell lung cancer; NR, not reported; SAE, serious adverse event; TRAE, treatment-related adverse event.
Data cutoff: January 6, 2020.
1. Vansteenkiste J, et al. Presented at: European Society for Medical Oncology Virtual Meeting; September 19-21, 2020. Poster 1285P. 2. Wolf J, et al. *N Engl J Med.* 2020;383(10):944-957.

GEOMETRY mono-1: Safety[1-3]



Most common AEs, regardless of causality (≥10%, all grades in either previously treated subgroup), n (%)	Cohorts 4 & 6 Previously treated *MET*ex14 with prior IO N=32		Cohorts 4 & 6 Previously treated *MET*ex14 without prior IO N=68		Cohort 5b Treatment-naive *MET*ex14 (without prior IO) N=28	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Peripheral edema	20 (62.5)	6 (18.8)	38 (55.9)	8 (11.8)	21 (75)	3 (11)
Nausea	16 (50.0)	1 (3.1)	26 (38.2)	0	13 (46)	0
Vomiting	12 (37.5)	0	14 (20.6)	0	7 (25)	0
Fatigue	10 (31.3)	2 (6.3)	17 (25.0)	4 (5.9)	4 (14)	1 (4)
Dyspnea	8 (25.0)	2 (6.3)	13 (19.1)	5 (7.4)	6 (21)	2 (7)
Back pain	7 (21.9)	1 (3.1)	12 (17.6)	1 (1.5)	4 (14)	0
Increased blood creatinine	7 (21.9)	0	23 (33.8)	0	10 (36)	0
Cough	7 (21.9)	1 (3.1)	10 (14.7)	0	7 (25)	0
Pyrexia	6 (18.8)	1 (3.1)	5 (7.4)	1 (1.5)	2 (7)	0
Increased alanine aminotransferase	5 (15.6)	3 (9.4)	8 (11.8)	4 (5.9)	4 (14)	2 (7)
Decreased appetite	5 (15.6)	0	14 (20.6)	1 (1.5)	8 (29)	0
Diarrhea	5 (15.6)	0	9 (13.2)	0	5 (18)	0
Headache	5 (15.6)	0	5 (7.4)	0	2 (7.1)	0

Data cutoff: January 6, 2020.

1. Vansteenkiste J, et al. Presented at: European Society for Medical Oncology Virtual Meeting; September 19-21, 2020. Poster 1285P. 2. Wolf J, et al. *N Engl J Med.* 2020;383(10):944-957. 3. Data on file. Clinical Study Report CINC280A2201 Primary Analysis (Cohorts 1a, 5a, and 6). Novartis Pharmaceuticals Corp; June 16, 2020.

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.

Patient Characteristics

VISION Cohorts A + C

Feb 2021 cut-off

Disease Characteristics[1,2]

- **80%** had adenocarcinoma histology
- **19%** had CNS metastases

Smoking Status[2]

- **47%** former smokers
- **43%** never smokers

Age, ECOG PS[1,2]

- **Median age of 72 years** (range 41 to 94)
  - **80%** were ≥65 years of age
- **28%** had ECOG PS 0 and **72%** had ECOG PS 1

Race and Gender[1]

- **67%** White
- **29%** Asian
- **49%** male
- **51%** female

Line of Therapy[1]

- **50%** (n=137) treatment naive
- **50%** (n=138) previously treated*

*MET*ex14 skipping alterations were identified through PCR or NGS testing[3,†]

- **58%** of patients were enrolled by tissue (RNA-based) testing
- **63%** of patients were enrolled by plasma (ctDNA-based) testing

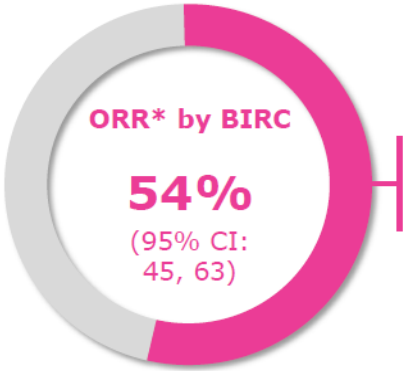
*Had progressed on up to 2 lines of prior systemic therapies.[3] †Some patients tested positive using both methodologies.[1]
ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status.
References: 1. Thomas M, et al. Presented at DGHO Annual Meeting 2021, Abstract 52. **2.** Garassino M, et al. Presented at ESMO Annual Meeting 2021, Poster 1254P. **3.** Felip E, et al. Presented at WCLC 2021, Abstract 170.

Efficacy by Previous Treatment Status

VISION Cohorts A + C

Feb 2021 cut-off

Treatment Naive (n=137)

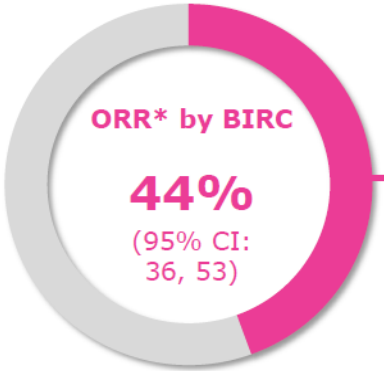


mDOR† by BIRC

32.7 mo

(95% CI: 9.0, NE)

Previously Treated (n=138)



mDOR† by BIRC

11.1 mo

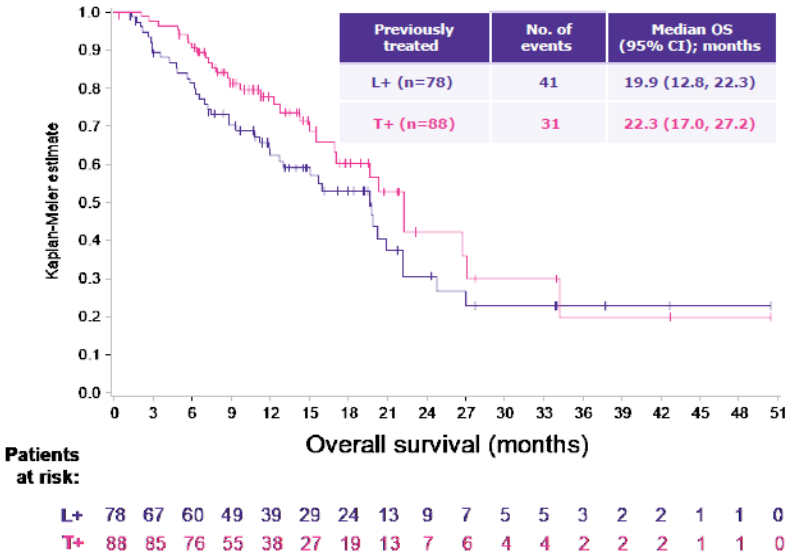
(95% CI: 8.4, 18.5)

*Confirmed responses. †Product-limit (Kaplan-Meier) estimates, 95% CI for the median using the Brookmeyer and Crowley method.
BIRC, Blinded Independent Review Committee; mo, months; mDOR, median duration of response; NE, not evaluable; ORR, objective response rate.
Reference: Thomas M, et al. Presented at DGHO Annual Meeting 2021, Abstract 52.

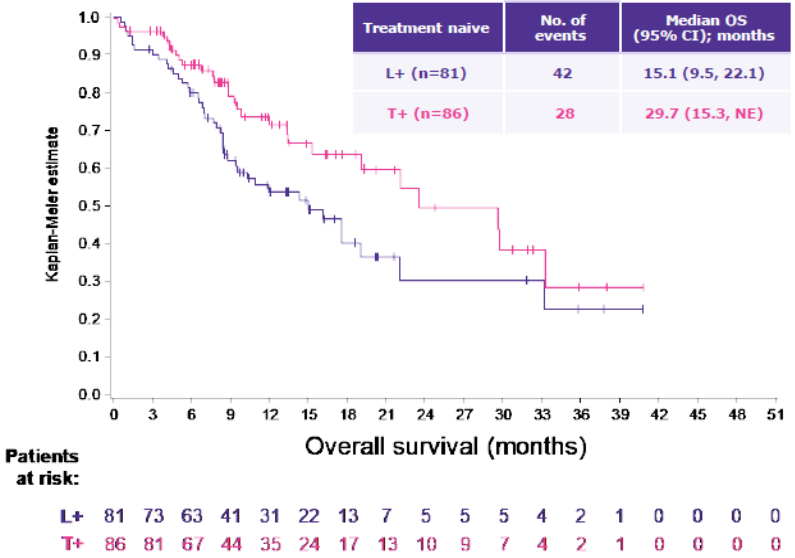
Overall Survival in Liquid vs Tissue Biopsies

VISION Cohorts A + C

Feb 2021 cut-off



Previously treated	No. of events	Median OS (95% CI); months
L+ (n=78)	41	19.9 (12.8, 22.3)
T+ (n=88)	31	22.3 (17.0, 27.2)



Treatment naive	No. of events	Median OS (95% CI); months
L+ (n=81)	42	15.1 (9.5, 22.1)
T+ (n=86)	28	29.7 (15.3, NE)

Time-dependent endpoints showed a trend for improvement in the tissue biopsy population, despite having comparable ORRs in both treatment-naive and previously treated patients

BOR, best objective response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; IRC, Independent Review Committee; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

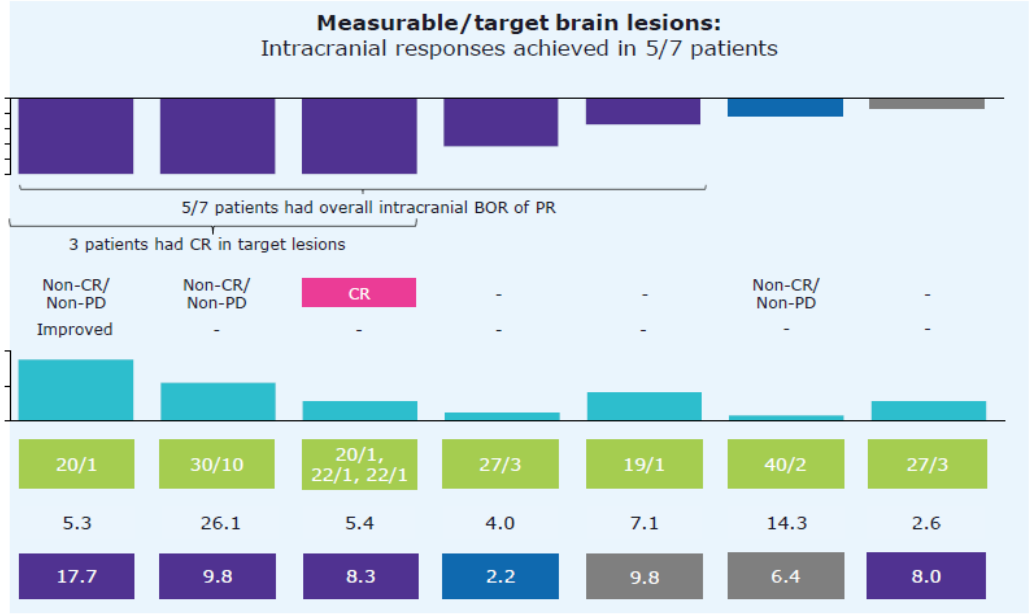
Reference: Felip E, et al. Presented at WCLC 2021, Abstract 170.

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).

TRAE Summary Across Age Subgroups and Most Common All-Cause AEs by Age

VISION Cohorts A + C

Feb 2021 cut-off

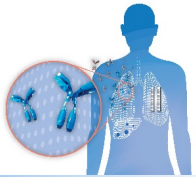
TRAE, n (%)	Overall (N=291)	Age subgroup, years			
		<65 (n=64)	≥65–<75 (n=107)	≥75–<85 (n=96)	≥85 (n=24)
Any grade Grade ≥3	264 (90.7) 86 (29.6)	52 (81.3) 9 (14.1)	105 (98.1) 28 (26.2)	84 (87.5) 39 (40.6)	23 (95.8) 10 (41.7)
Leading to dose reduction	90 (30.9)	10 (15.6)	36 (33.6)	36 (37.5)	8 (33.3)
Leading to temporary interruption	114 (39.2)	14 (21.9)	39 (36.4)	46 (47.9)	15(62.5)
Leading to permanent discontinuation	41 (14.1)	4 (6.3)	14 (13.1)	17 (17.7)	6 (25.0)

Most common all-cause AEs, n(%)	Overall (N=291)	Age subgroup, years			
		<65 (n=64)	≥65–<75 (n=107)	≥75–<85 (n=96)	≥85 (n=24)
Peripheral edema	191 (65.6)	35 (54.7)	75 (70.1)	61 (63.5)	20 (83.3)
Nausea	87 (29.9)	16 (25.0)	35 (32.7)	32 (33.3)	5 (20.8)
Diarrhea	81 (27.8)	17 (26.6)	27 (25.2)	30 (31.3)	7 (29.2)
Hypoalbuminemia	81 (27.8)	15 (23.4)	27 (25.2)	31 (32.3)	8 (33.3)
Blood creatinine increase	76 (26.1)	13 (20.3)	30 (28.0)	29 (30.2)	4 (16.7)
Dyspnea	60 (20.6)	9 (14.1)	21 (19.6)	22 (22.9)	8 (33.3)
Decreased appetite	48 (16.5)	3 (4.7)	21 (19.6)	22 (22.9)	2 (8.3)
Constipation	46 (15.8)	9 (14.1)	17 (15.9)	19 (19.8)	1 (4.2)
Fatigue	45 (15.5)	8 (12.5)	16 (15.0)	20 (20.8)	1 (4.2)

- Tepotinib was generally well tolerated with low proportion of TRAEs leading to discontinuation
- Grade ≥3 TRAEs occurred in 29.6% of patients, 30.9% of patients had TRAEs leading to dose reduction, 39.2% temporary interruption, and 14.1% permanent discontinuation
- The most common AE was peripheral edema, occurring in 66% of patients, which was considered treatment related in 60% of patients

Reference: Garassino M, et al. Presented at ESMO 2021, Poster 1254P.

Conclusion on met Inhibitors for met exon 14 skip mutations



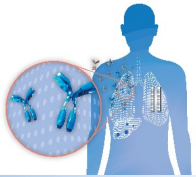
- Capmatinib and tepotinib both have shown durable clinical activity in patients with met exon 14 skip mutation-positive advanced NSCLC with acceptable safety profiles

	Capmatinib	Tepotinib
ORR (prior platinum)	62% prior IO; 34% without	44%
ORR (naive)	68%	54%
DOR (prior platinum)	7-9 months	11.1 months
DOR (naive)	11.0 months	32.7 months
Active in CNS met	Yes	Yes
Safety profile	Most AEs G1/2; 65% edema	Most AEs G1/2; 66% edema
Discontinuation TRAEs	16.9%	14.1%

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

TRK Fusions Are Found in Diverse Cancers

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



Cancers enriched for TRK fusions

Secretory breast carcinoma
Mammary analogue secretory carcinoma
Infantile fibrosarcoma

Frequency
75% to >90%

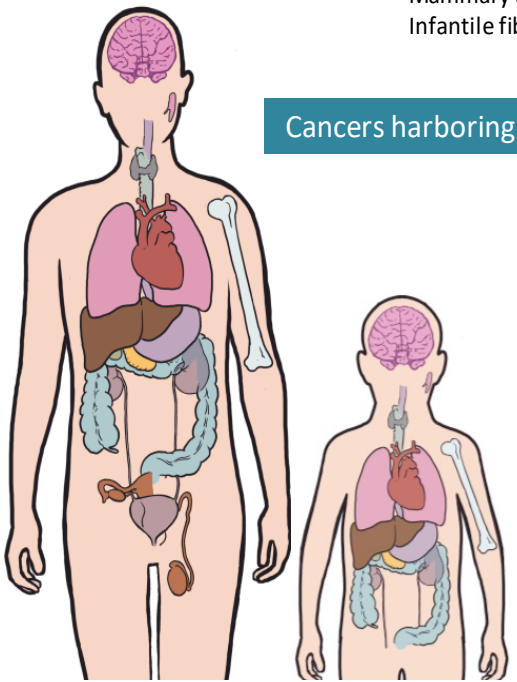
Cancers harboring TRK fusions at lower frequencies

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%

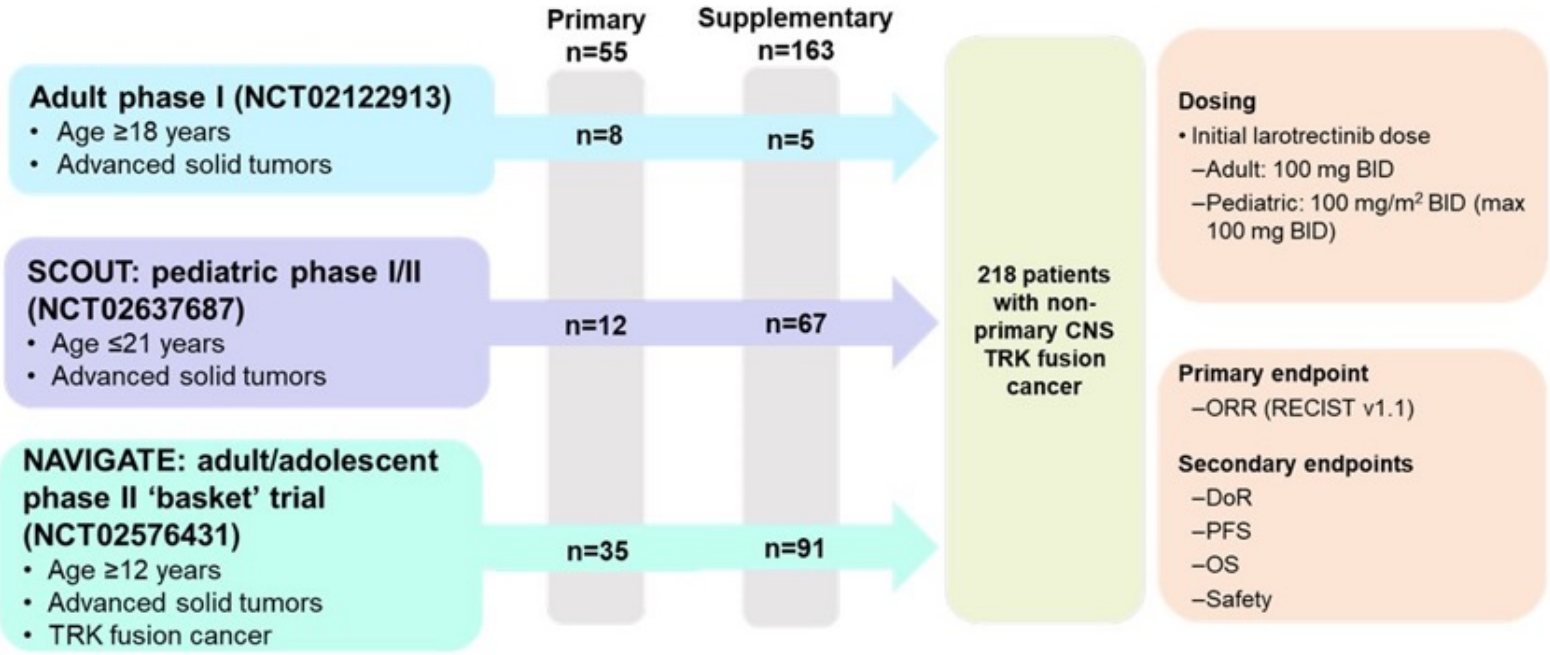


***NTRK* gene fusions detection**

NGS
FISH
RT-PCR
IHC

Cocco, Scaltriti, and Drilon, In Review

Long-term Efficacy and Safety of Larotrectinib in an Integrated Dataset of Patients With TRKf+ Cancer



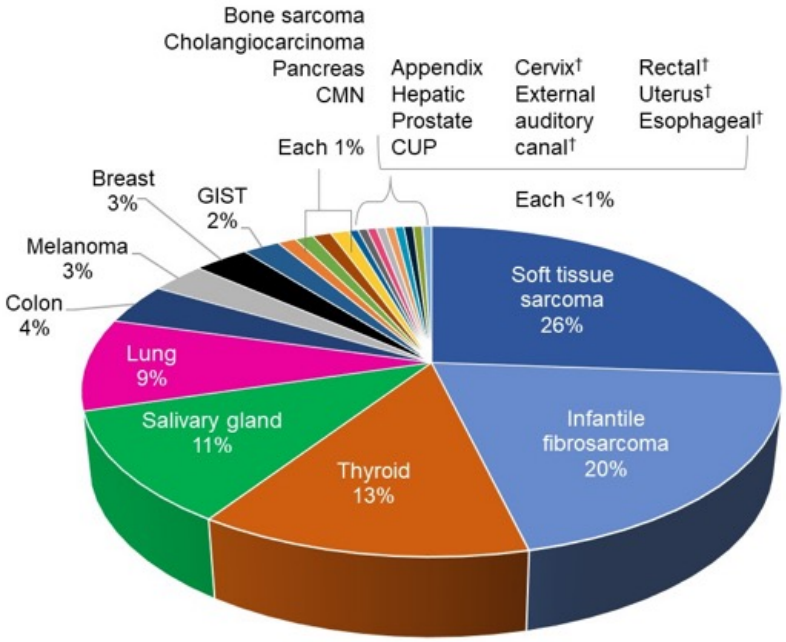
BID, twice daily; CNS, central nervous system; DoR, duration of response; *NTRK*, neurotrophic tyrosine receptor kinase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase. 1. Amatu A, et al. *Ann Oncol*. 2019;30:viii5–viii15. 2. Bazhenova L, et al. *Targ Oncol*. 2021; doi: 10.1007/s11523-021-00815-4. 3.Bayer. VITRAKVI US PI. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211710s000lbl.pdf. Accessed April 5, 2021. 4. Bayer VITRAKVI SmPC. 2018. Available at: https://www.ema.europa.eu/en/documents/productinformation/vitrakvi-epar-product-information_en.pdf. Accessed April 5, 2021. 5. Hong DS, et al. *Lancet Oncol*. 2020;21:531–540. 5.

Drilon A, et al. *N Engl J Med*. 2018;378:731-739.
Hong DS. ASCO Virtual Congress 2021. Poster 3108

Larotrectinib: Baseline Characteristics

	Integrated dataset (N=218)
Sex, n (%)	
Male	112 (51)
Female	106 (49)
Age, median (range), years	38 (0.1–84)
Pediatric (<18), n (%)	78 (36)
Adult (≥18), n (%)	140 (64)
ECOG or equivalent Lansky PS, n (%)	
0	114 (52)
1	78 (36)
2	23 (11)
3	3 (1)
Known CNS metastases at enrollment, n (%)	19 (9)
Number of prior systemic therapies, median (range)	1 (1–10)
Number of prior systemic regimens, n (%)	
0	59 (27)
1	60 (28)
2	42 (19)
≥3	57 (26)
***NTRK* gene fusion**, n (%)	
NTRK1	97 (44)
NTRK2	6 (3)
NTRK3	115 (53)

21 Tumor Types



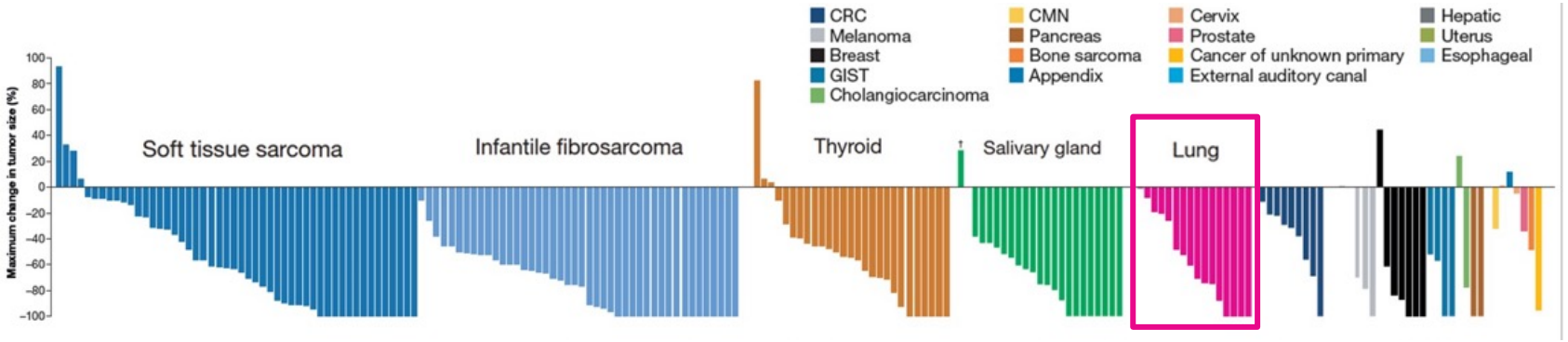
Drilon A, et al. *N Engl J Med*. 2018;378:731-739.
Hong DS. ASCO Virtual Congress 2021. Poster 3108

Larotrectinib: Tumor Response

Response	Integrated dataset (N=218)	CNS metastases at baseline (N=19)
Evaluable patients, n	206	15
ORR, % (95% CI)	**75 (68–81)**	**73 (45–92)**
Best overall response, n (%)		
Complete response	45 (22)	0
Partial response	109 (53)	11 (73)
Stable disease	33 (16)	2 (13)
Progressive disease	13 (6)	2 (13)
Not determined	6 (3)	0

Patients With TRKf+ Lung Cancer (N=20)

- ORR (INV, n=15 evaluable): 73%
  - CR: 7% (1)
  - PR: 67% (10)
  - SD: 20% (3)
  - PD: 7% (1)
- ORR baseline CNS mets (n=10): 63%

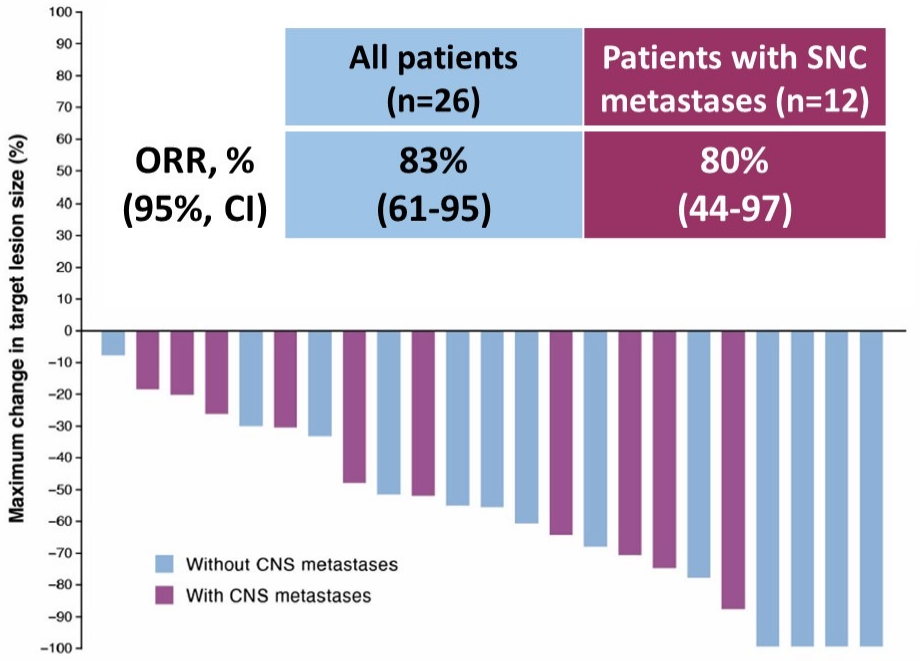


a. Data cutoff: July 20, 2020.

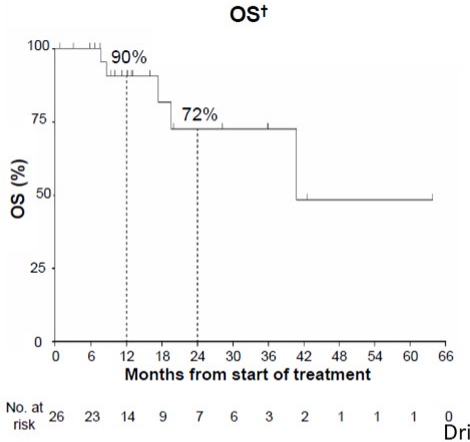
1. Hong DS. ASCO Virtual Congress 2021. Poster 3108.
2. Drilon A, et al. *JCO Precis Oncol*. 2022;6:e2100418.

Updated data on Larotrectinib in NTRK+ NSCLC

	All patients (n=26)	Patients with SNC metastases (n=12)
ORR, % (95%, CI)	83% (61-95)	80% (44-97)



Median PFS, mo (95% CI)	**14.6** (9.9–NR)
Median DoR, mo (95% CI)	**12.9** (9.5–NR)
Median OS, mo (95% CI)	**40.7** (19.4-NE)



Drilon ASCO 2022

Larotrectinib: Safety

	Treatment-emergent AEs, n (%)				Treatment-related AEs, n (%)		
Preferred term	Grade 1/2	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade
Cough	72 (33)	2 (1)	0	74 (34)	0	0	3 (1)
ALT increased	63 (29)	6 (3)	2 (1)	71 (33)	4 (2)	2 (1)	58 (27)
Diarrhea	64 (29)	6 (3)	0	70 (32)	0	0	19 (9)
Vomiting	68 (31)	1 (0)	0	69 (32)	0	0	16 (7)
Constipation	68 (31)	0	0	68 (31)	0	0	32 (15)
AST increased	60 (28)	5 (2)	1 (0)	66 (30)	3 (1)	1 (0)	55 (25)
Pyrexia	54 (25)	6 (3)	1 (0)	61 (28)	0	0	4 (2)
Fatigue	58 (27)	2 (1)	0	60 (28)	0	0	31 (14)
Nausea	59 (27)	1 (0)	0	60 (28)	1 (0)	0	31 (14)
Anemia	39 (18)	18 (8)	0	57 (26)	2 (1)	0	18 (8)
Dizziness	55 (25)	2 (1)	0	57 (26)	1 (0)	0	37 (17)
Myalgia	43 (20)	2 (1)	0	45 (21)	1 (0)	0	27 (12)
Upper respiratory tract infection	42 (19)	1 (0)	0	43 (20)	-	-	-
Arthralgia	39 (18)	2 (1)	0	41 (19)	1 (0)	0	13 (6)
Peripheral edema	38 (17)	2 (1)	0	40 (18)	0	0	13 (6)
Headache	38 (17)	1 (0)	0	39 (18)	1 (0)	0	13 (6)
Neutrophil count decreased	14 (6)	21 (10)	4 (2)	39 (18)	13 (6)	2 (1)	26 (12)
Weight increased	26 (12)	11 (5)	0	37 (17)	3 (1)	0	21 (10)
Pain in extremity	33 (15)	2 (1)	0	35 (16)	0	0	7 (3)
Dyspnea	29 (13)	5 (2)	0	34 (16)	0	0	4 (2)
Back pain	31 (14)	2 (1)	0	33 (15)	0	0	2 (1)

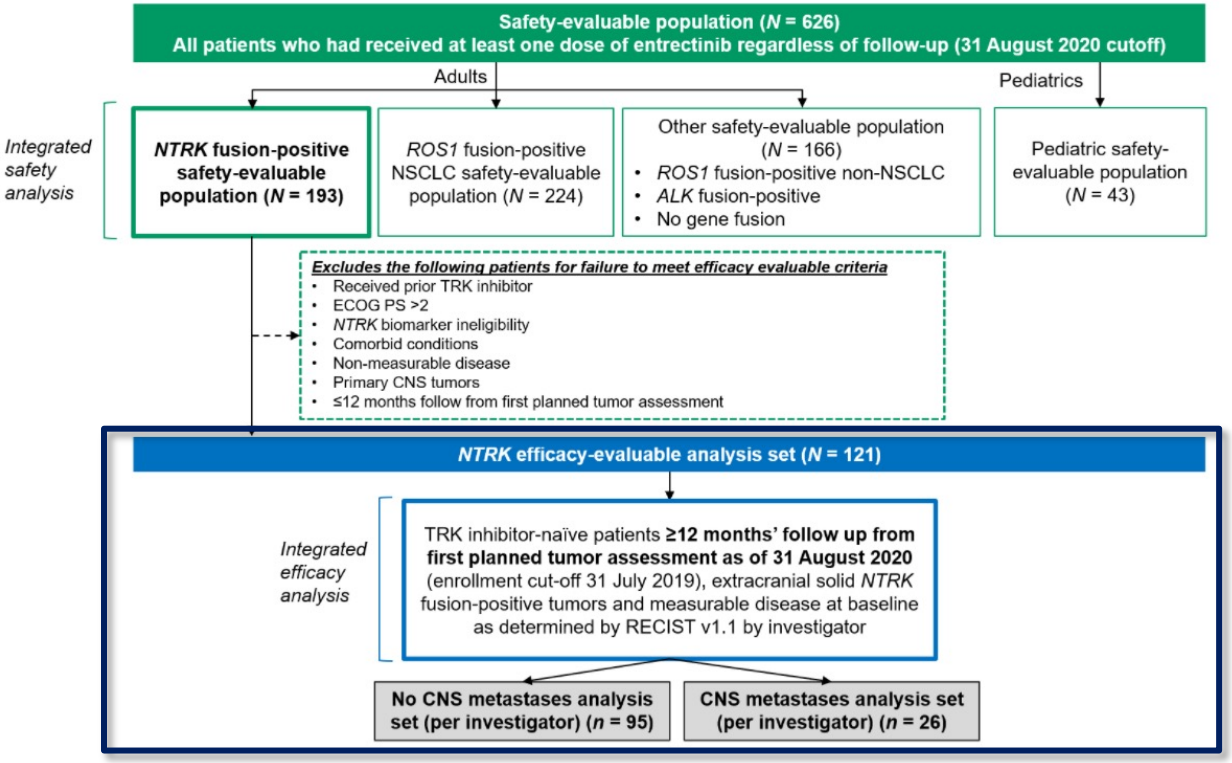
- In the safety analysis set, including 53 patients who were on treatment for over 24 months, no new safety signals were identified
- TRAEs were predominantly Grade 1–2; 2% of patients discontinued treatment due to TRAES
- Grade 3 and 4 TRAEs were reported in 18% of patients

Lung Cancer Subset[2]: No new or unexpected safety signals were observed compared with the larger data set of all larotrectinib-treated TRK fusion–positive cancers[2]

1. Hong DS. ASCO Virtual Congress 2021. Poster 3108.
2. Drilon A, et al. *JCO Precis Oncol*. 2022;6:e2100418.

Design of Integrated Analysis Across Phase 1/2 Trials of Entrectinib

This analysis included patients aged ≥18 years in one of two phase I studies (ALKA-372-001 or STARTRK-1) or a phase II global basket study (STARTRK-2), across more than 150 sites in 16 countries.



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

Data cutoff: August 31, 2020.

Demetri GD, et al. *Clin Cancer Res*. 2022;28:1302-1312.

Entrectinib: Baseline Characteristics in Adult Patients With TRKf+ Solid Tumors—Efficacy Evaluable Population

Characteristic		*NTRK* efficacy-evaluable population ($n = 121$)
Age, y	Median (range)	57.0 (21–88)
Sex, *n* (%)	Female/male	62 (51.2)/59 (48.8)
Race, *n* (%)	White/Asian/Black or African American/ other or not reported	73 (60.3)/29 (24.0)/3 (2.5)/16 (13.2)
History of smoking ($n = 118$), *n* (%)	No/yes	72 (61.0)/46 (39.0)
ECOG PS, *n* (%)	0/1/2	53 (43.8)/57 (47.1)/11 (9.1)
Prior lines of systemic therapy[a], *n* (%)	0/1/2/3/≥4	37 (30.6)/35 (28.9)/26 (21.5)/12 (9.9)/11 (9.1)
Any previous therapy[b], *n* (%)	Chemotherapy/targeted therapy/ hormonal therapy/immunotherapy	88 (72.7)/24 (19.8)/10 (8.3)/13 (10.7)
CNS metastases at baseline[c], *n* (%)	Present/measurable/absent	20 (16.5)/6 (5.0)/95 (78.5)
Prior radiotherapy of the brain[d] ($n = 26$), *n* (%)	Yes/no	17 (65.4)/9 (34.6)
Time from end of prior radiotherapy of the brain to first dose[e], *n* (%)	<2 mo/2 to <6 mo/≥6 mo	7 (41.2)/5 (29.4)/5 (29.4)
NTRK fusion, *n* (%)	*NTRK1*/*NTRK2*/*NTRK3*	48 (39.7)/6 (5.0)/67 (55.4)
Tumor category[f], *n* (%)	Sarcoma	26 (21.5)
	Salivary (MASC)	24 (19.8)
	NSCLC	22 (18.2)
	Thyroid	13 (10.7)
	Colorectal	10 (8.3)
	Breast	7 (5.8)
	Neuroendocrine	5 (4.1)
	Pancreatic	4 (3.3)
	Cancer of unknown primary	3 (2.5)
	Gynecologic	2 (1.7)
	Head and neck (other)	2 (1.7)
	Cholangiocarcinoma	1 (0.8)
	Adenocarcinoma of upper GI tract	1 (0.8)
	Neuroblastoma	1 (0.8)

Data cutoff: August 31, 2020.

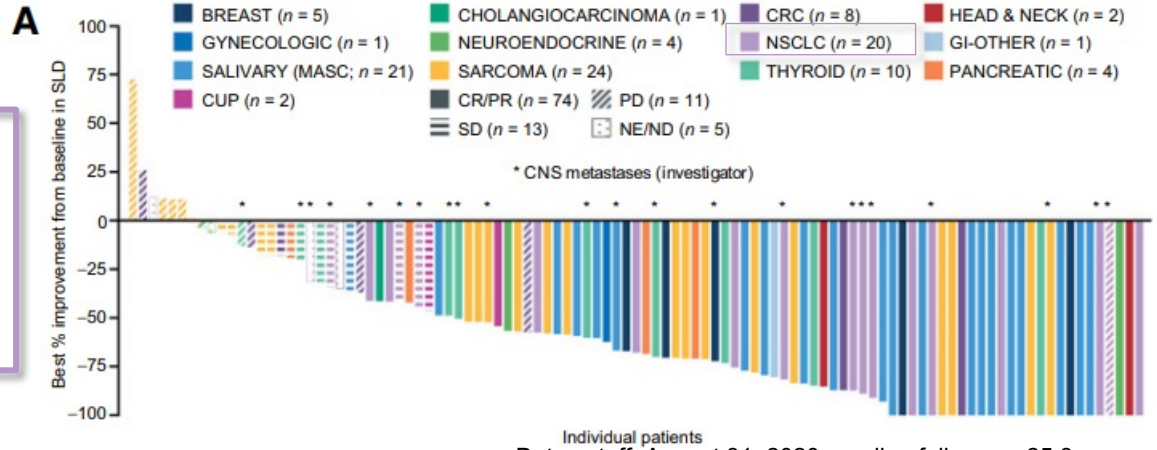
Demetri GD, et al. *Clin Cancer Res*. 2022;28:1302-1312.

Entrectinib: Response—Efficacy Evaluable Population

Efficacy parameter	Efficacy-evaluable population ($n = 121$)	Baseline CNS metastases[a] ($n = 26$)	No baseline CNS metastases[a] ($n = 95$)
ORR, *n* (%)	74 (61.2)	15 (57.7)	59 (62.1)
(95% CI)	(51.9–69.9)	(36.9–76.7)	(51.6–71.9)
CR	19 (15.7)	2 (7.7)	17 (17.9)
PR	55 (45.5)	13 (50.0)	42 (44.2)
Stable disease	13 (10.7)	4 (15.4)	9 (9.5)
Progressive disease	13 (10.7)	2 (7.7)	11 (11.6)
Non-CR/non-PD[b]	6 (5.0)	0	6 (6.3)
Missing or unevaluable[c]	15 (12.4)	5 (19.2)	10 (10.5)

Patients With TRKf+ Lung Cancer (N=22)

- ORR (BICR): 64% (40.7-82.8)
- Med DoR: 19.9 mos (10.4-29.9)
- Med PFS: 14.9 mos (6.5-30.4)
- Med OS: NE



Data cutoff: August 31, 2020; median follow up: 25.8 mo.
Demetri GD, et al. *Clin Cancer Res*. 2022;28:1302-1312.

Entrectinib: Updated Safety Analysis

TRAEs reported in ≥10% of patients Patients, %	*NTRK* fusion-positive safety population (n=193)	Overall safety population (N=626)
Dysgeusia	35.2	35.9
Diarrhoea	31.1	25.9
Fatigue	27.5	28.8
Weight increase	27.5	27.3
Constipation	25.9	25.1
Blood creatinine increase	25.9	21.2
Dizziness	24.9	26.8
Oedema peripheral	18.1	16.1
Anaemia	17.1	15.7
Nausea	16.6	20.3
AST increase	16.6	13.1
ALT increase	15.5	12.5
Paraesthesia	11.9	15.8
Myalgia	10.9	14.4
Vomiting	10.9	13.6
Arthralgia	5.2	10.2

NTRK-fp, *NTRK* fusion-positive; TRAEs, treatment-related adverse events.

Safety

- Entrectinib had a safety profile in line with that previously reported, with most treatment-related adverse events (TRAEs; Table 5) reversible and resolved via dose reductions or modifications.
- The median dose intensity was 91.3% (interquartile range [IQR] 65.9–99.6) in the *NTRK* fusion-positive safety population and 94.2% (IQR 67.8–100.0) in the overall safety population.

Data cutoff: 31 AUG 2020; median follow up: 25.8 mo.

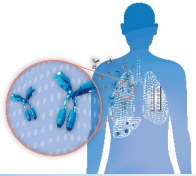
Bazhenova L, et al. ESMO 2021. Abstract 533P. Demetri GD, et al. *Clin Cancer Res*. 2022;28:1302-1312.

Summary: Efficacy Data From Studies of NTRK Inhibitors for TRKf+ Solid Tumors in Adult Patients

	Larotrectinib (N=140)	Entrectinib (N=121)
Median age, y	54.5	57.0
ECOG PS	51 (36) / 69 (49) / 17 (12) / 3 (2)	53 (43.8) / 57 (47.1) / 11 (9.1) / -
Prior lines of therapy, n (%), 0 / 1/ 2 / 3+	34 (24) / 32 (23) / 28 (20) / 44 (31)[a]	37 (30.6) / 35 (28.9) / 26 (21.5) / 23 (19.0)[b]
CNS mets at baseline, n (%)	19 (14)	26 (21.5)
Efficacy (all patients)		
Median follow up, mo[c]	24	25.8 mo
ORR, %	67% (CR, 12; PR, 55; PD, 9)	61.2% (CR, 16, PR, 46; PD, 11)
mDoR, (95% CI) mo	49.3 (26.3-NE)	20.0 (13.0-38.2)
Median TTR, mo	1.8	1.0
mPFS (95% CI), mo	25.8 (12.7-51.1)	13.8 mo (10.1-19.9)
mOS (95% CI), mo	NR (38.7-NE)	33.8 mo (23.4-46.4)
ORR in pts w/ baseline CNS mets, % (95% CI)	73 (45-92)	57.7 (36.9-76.7)

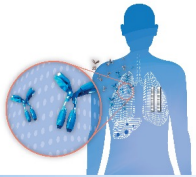
Brose M, et al. ESMO 2021. 535P. Bazhenova L, et al. ESMO 2021. Abstract 533P.
Demetri GD, et al. *Clin Cancer Res*. 2022;28:1302-1312.

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

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

Thank you