

20th ANNUAL

ATLANTA

LUNG CANCER SYMPOSIUM

Beyond the Big Drivers: Targeting RET, MET and BRAF

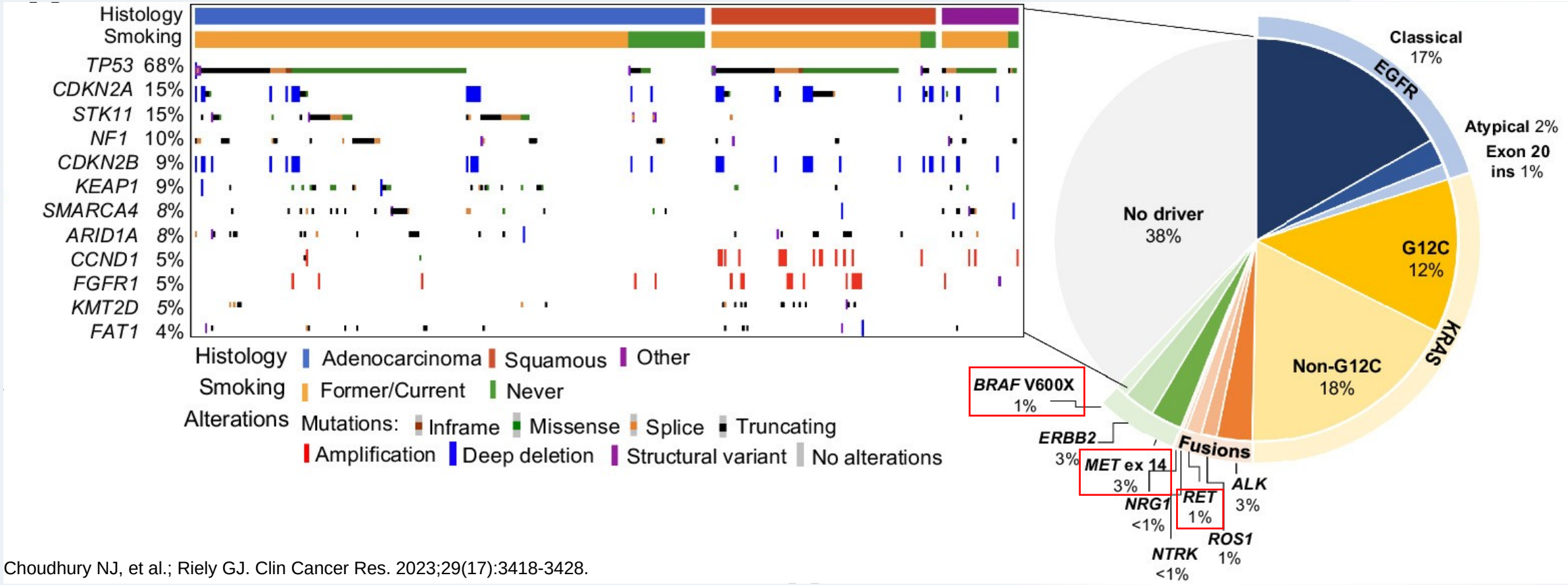
Ryan D. Gentzler, MD, MS
University of Virginia Comprehensive Cancer Center

November 7, 2026

Partners for Advancing Clinical Education
Bio Ascend™

Molecular Targets in NSCLC

RET, MET, BRAF: ~5-8%



Choudhury NJ, et al.; Riely GJ. Clin Cancer Res. 2023;29(17):3418-3428.

20th ANNUAL ATLANTA LUNG CANCER SYMPOSIUM

RET

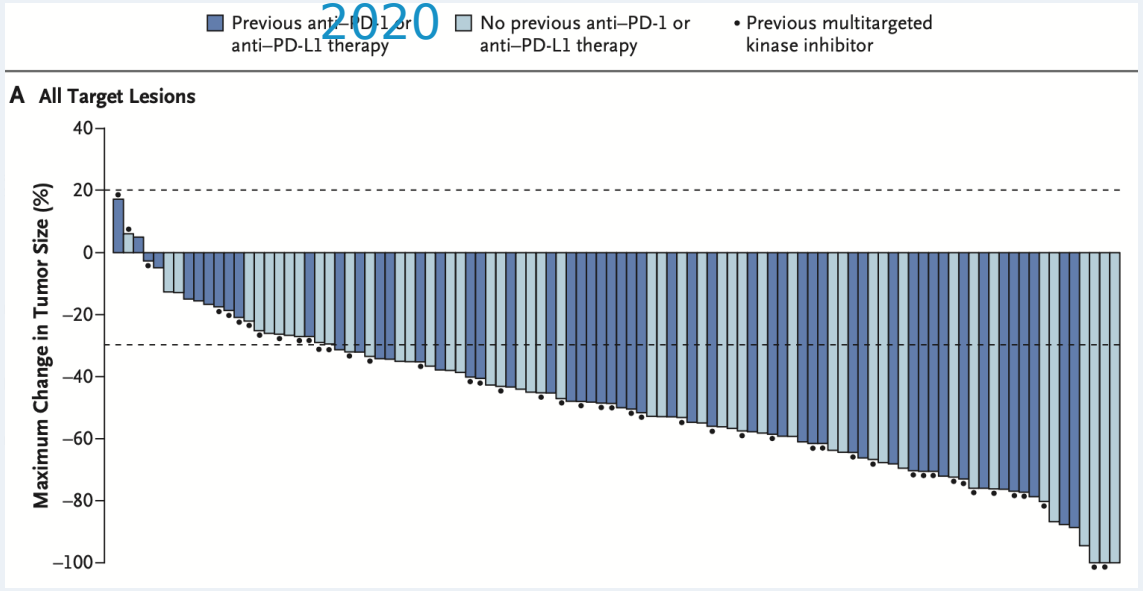
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Bio Ascend™

Selpercatinib, Pralsetinib

Libretto-001 – Selpercatinib (LOXO-292)

FDA Approved May 2020



ORR: 64%; 85% tx naïve

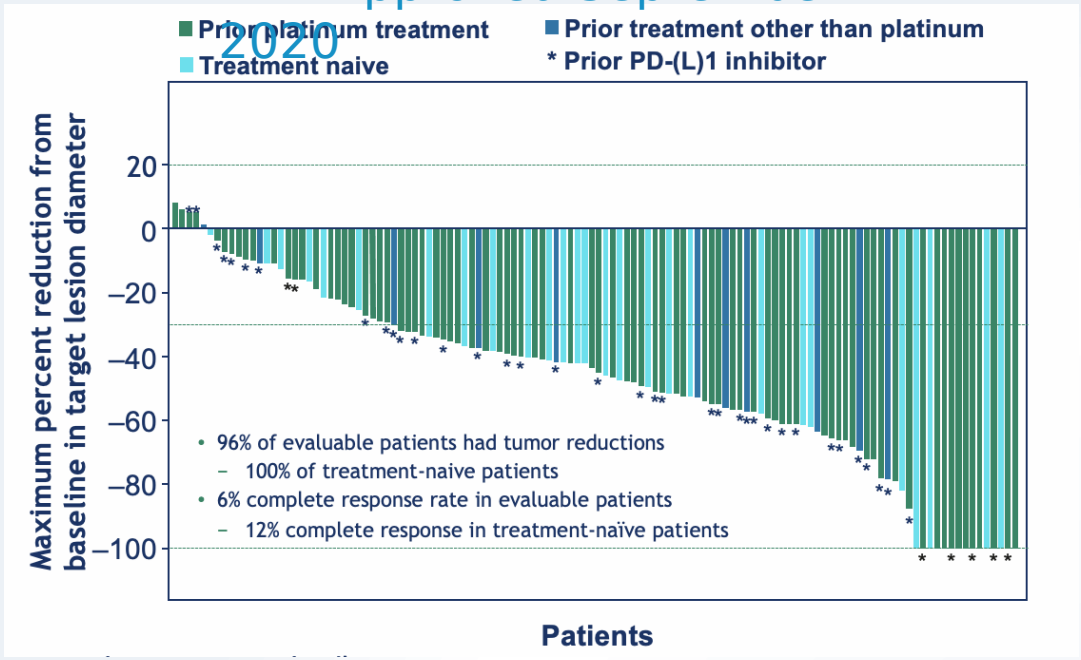
PFS 16.5 mo

Drilon A, et al. WCLC 2019; abst PL02.08

Drilon A, et al. NEJM 2020; 383(9):813-824

ARROW – Pralsetinib (BLU-667)

FDA Approved September 2020



ORR: 61%; 70% tx naïve

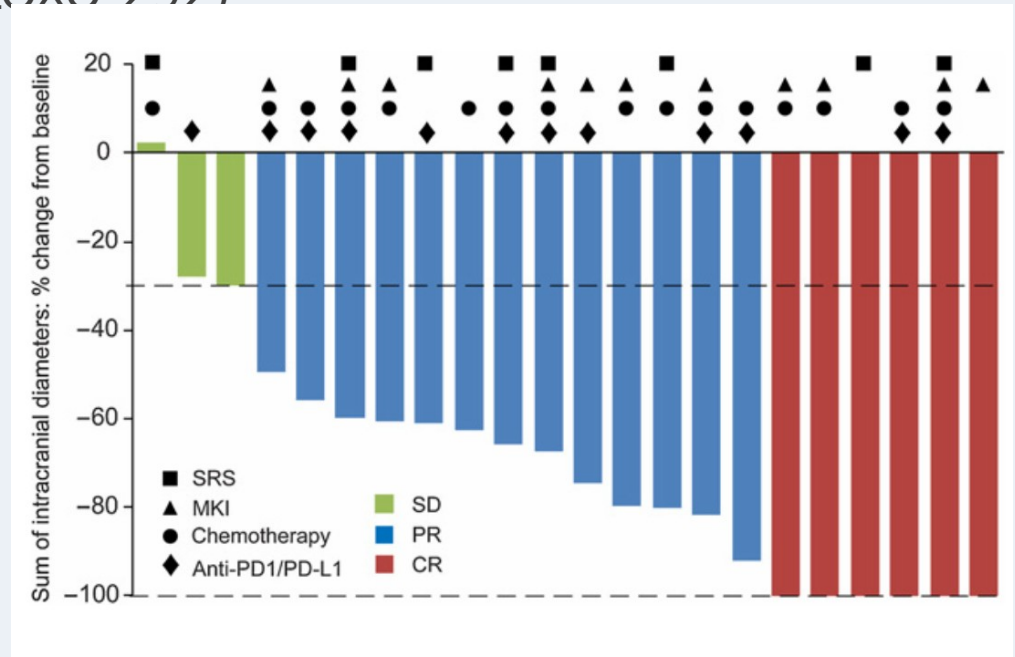
PFS: 17.1 mo

Gainor JF, et al. ASCO 2020; abst 9515

Gainor JF, et al. Lancet Onc 2021;22:959-69.

RET TKI CNS activity

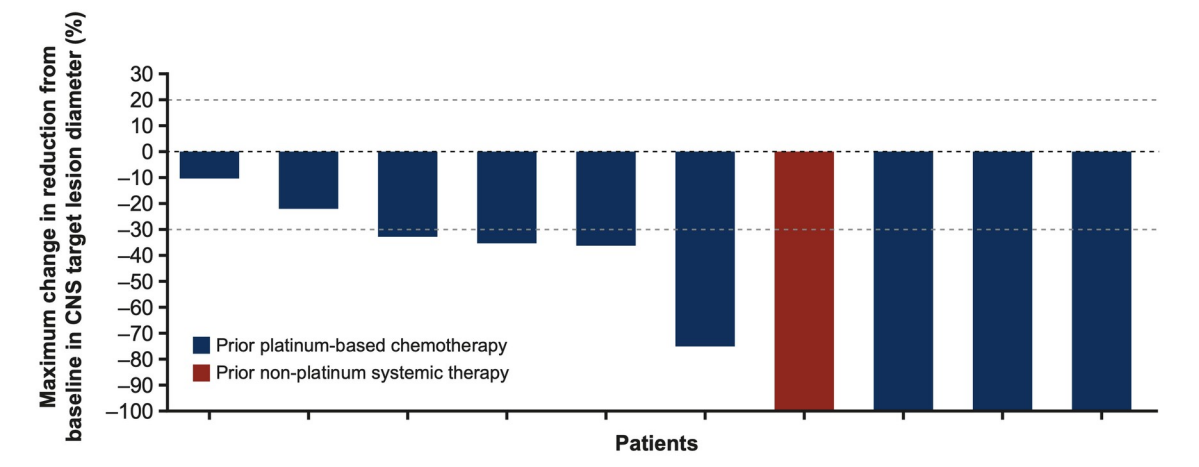
Libretto-001 – Selpercatinib (LOXO-292)



CNS ORR: 82% (n=22)

Subbiah V, et al. ASCO 2020; abst 9516
Subbiah V, et al. Clin Can Res 2021;27(15):4160-4167

ARROW – Pralsetinib (BLU-667)

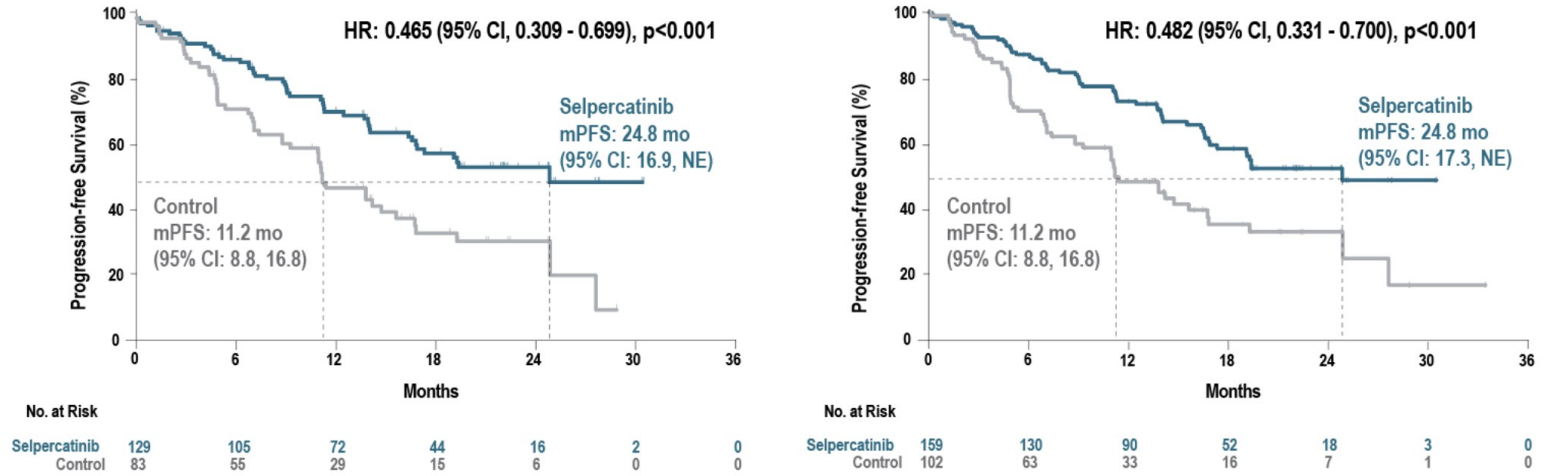


CNS ORR: 70%; (n=10)

Gainor JF, et al. ASCO 2020;abst: 9515
Griesinger F, et al. Annals Oncology 2022;33(11):1168-1178;fig S3

LIBRETTO-431 PFS

Progression-free survival (PFS) assessed by BICR



Identical results: w/wo pembrolizumab

**LIBRETTO-432 adjuvant; FDA approved 2026

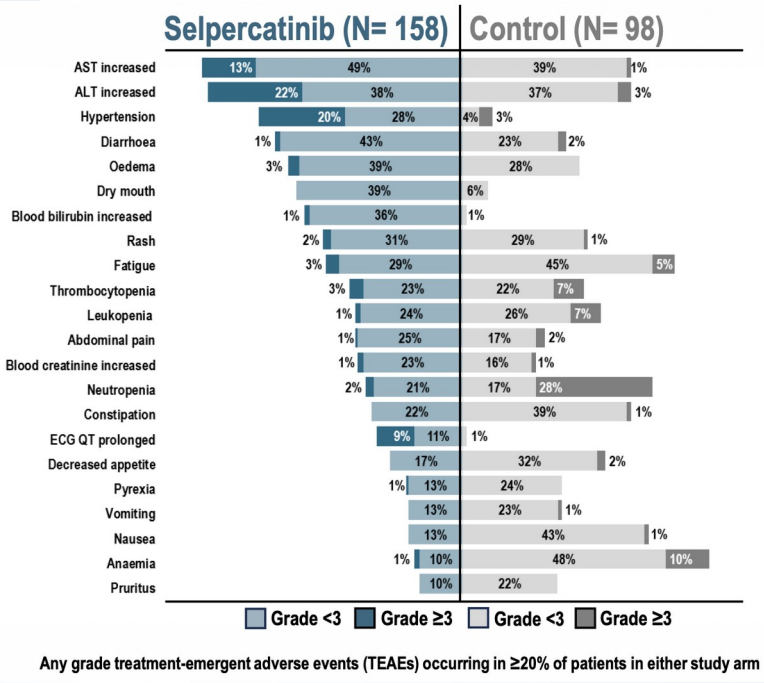
Systemic Outcomes

	Selpercatinib N= 129	Control N= 83
ORR, %	83.7	65.1
Median DOR, mo (95% CI)	24.2 (17.9, NE)	11.5 (9.7, 23.3)

Overall Survival immature (censoring rate ~80%) and confounded by crossover (75% effective rate)[1]: HR 0.961 (95% CI: 0.503, 1.835)

Intracranial Outcomes[2]

	Selpercatinib N= 17	Control N= 12
Intracranial ORR, %	82.4	58.3
Intracranial CR, %	35.3	16.7
12-mo Intracranial DOR Rate, % (95% CI)	76.0 (42.2, 91.6)	62.5 (14.2, 89.3)
Median Intracranial PFS, mo (95% CI)	16.1 (8.8, NE)	10.4 (3.8, NE)

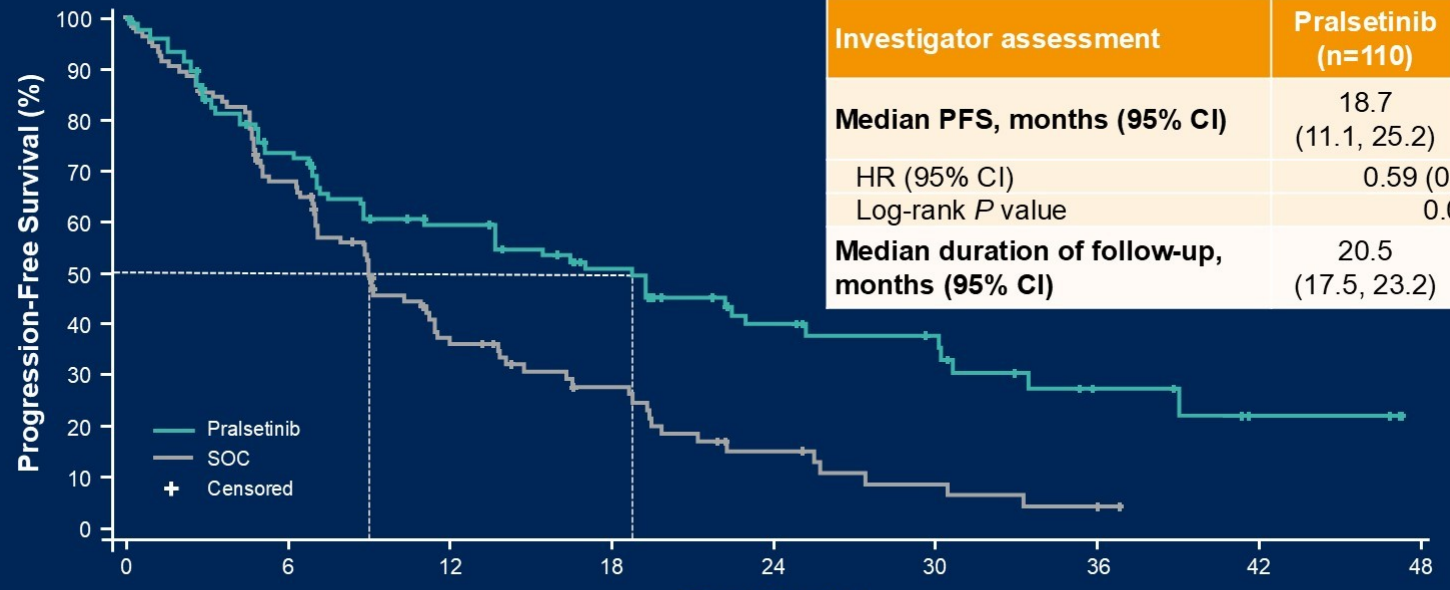


Any grade treatment-emergent adverse events (TEAEs) occurring in ≥20% of patients in either study arm

Loong HH, et al. ESMO 2023;abst:LBA4
Zhou C, et al. NEJM 2023;389(20):1839-1850

AcceleRET – Pralsetinib phase III

Pralsetinib Treatment Significantly Reduced the Risk of Progression or Death vs SOC (Primary Endpoint)



Investigator assessment	Pralsetinib (n=110)	SOC (n=113)
Median PFS, months (95% CI)	18.7 (11.1, 25.2)	9.0 (7.1, 11.5)
HR (95% CI)	0.59 (0.42, 0.84)	
Log-rank *P* value	0.0027	
Median duration of follow-up, months (95% CI)	20.5 (17.5, 23.2)	16.0 (13.7, 20.9)

Median PFS among intended use of pembrolizumab patients
Pralsetinib (n=73): 18.7 (8.6, 30.2) months SOC (n=74): 7.2 (5.1, 10.9) months (HR: 0.51)

Popat S, et al. ASCO 2026;abst: 8504

Chylous effusions – RET TKIs

MD Anderson Cohort
73 patients receiving RET TKI

N=9 (12%) with chylous effusions
Selpercatinib (7)
Pralsetinib (2)

Chylopericardium (2)
Chylous ascites (2)
Chylothorax (1)
Chylothorax and ascites (4)

Paula AG, et al. ASCO 2026;abst: e20694

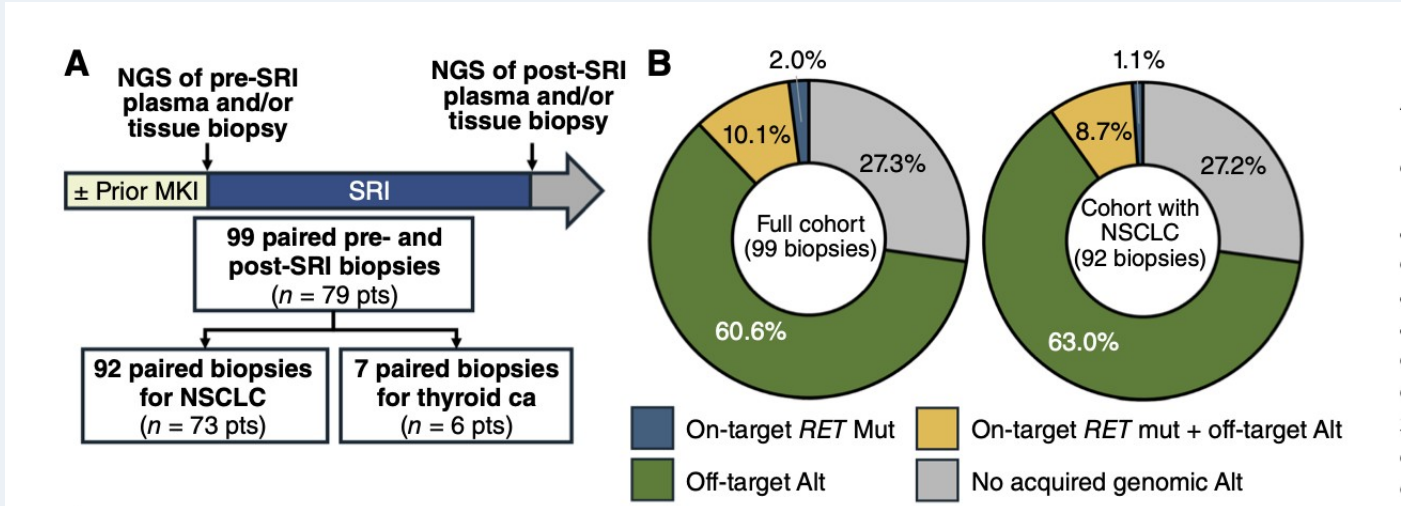
CoH Case Series (n=2)

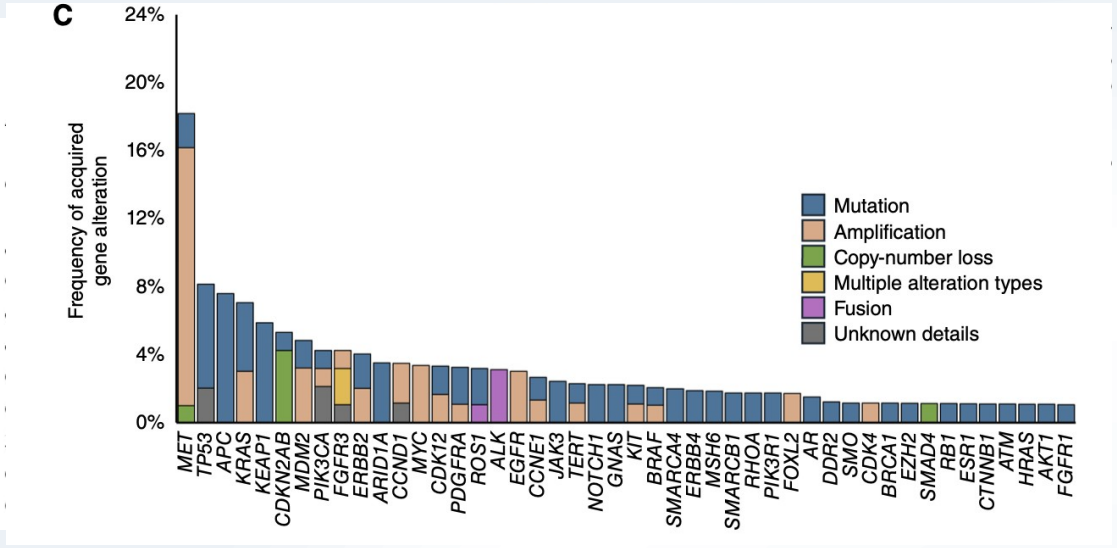


Fricke J, et al. Clinical Lung Cancer 2023;24(7):666-671

RET TKI Resistance

Complex, off-target resistance predominates





Chemotherapy remains 2nd line SOC

Waliany S, et al. Clin Can Res 2026;32(6):1157-1168

20th ANNUAL ATLANTA LUNG CANCER SYMPOSIUM

MET

Partners for Advancing Clinical Education

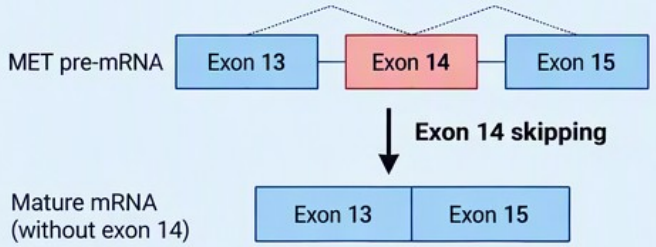
Bio Ascend™

MET Biomarker Testing in Lung Cancer

Distinct *MET* alterations can be detected using complementary testing methods and inform targeted treatment options

MET Exon 14 Skipping Mutation

Alteration at the DNA/RNA level leading to skipping of exon 14 and a more stable MET protein



Testing method(s)

- Next-generation sequencing (NGS) (DNA or RNA-based)
- RT-PCR (RNA-based)
- Other splice-site assays

FDA-approved targeted treatment(s)

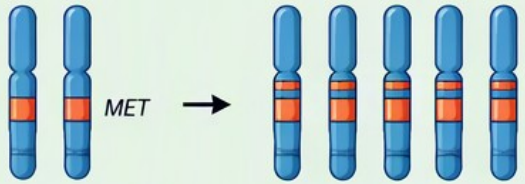
- Capmatinib
- Tepotinib

Key trial(s)

- GEOMETRY mono-1 (capmatinib)
- VISION (tepotinib)

MET Amplification

Increased copy number of the ***MET*** gene leading to overexpression and activation of MET signaling



Normal copy number (typically 2 copies)

Increased *MET* copies (gene amplification)

Testing method(s)



- Fluorescence in situ hybridization (FISH) (gold standard)
- Next-generation sequencing (NGS) (copy number analysis)
- Digital PCR, comparative genomic hybridization (aCGH)

FDA-approved targeted treatment(s)

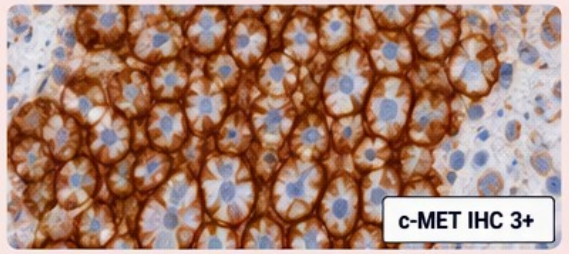
- No FDA-approved therapy specifically for *MET* amplification in NSCLC
- *MET* inhibitors (e.g., capmatinib) have shown activity in high-level amplification (e.g., GCN ≥10)
- Consider clinical trial enrollment

Key trial(s)

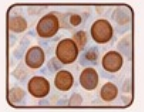
- GEOMETRY mono-1 (high-level *MET* amplification cohorts)

MET Overexpression (IHC 3+)

High c-MET protein expression on tumor cells (≥50% of tumor cells with strong (3+) IHC staining)



Testing method(s)



- Immunohistochemistry (IHC)
- FDA-approved companion diagnostic: VENTANA MET (SP44) RxDx assay

FDA-approved targeted treatment(s)

- **Telisotuzumab vedotin-tllv**
  - Approved for previously treated, locally advanced or metastatic, non-squamous NSCLC with high c-MET overexpression (≥50% tumor cells with IHC 3+ staining)
  - Accelerated approval (FDA, May 2025)

Key trial(s)

- LUMINOSITY (Phase II)
  - ORR 35% (in previously treated patients with *MET* IHC 3+ NSCLC)

Comprehensive biomarker testing for *MET* alterations helps identify appropriate patients and informs the use of approved and investigational targeted therapies.

Testing approaches may be used individually or in combination, depending on clinical context and availability.

NSCLC = non-small cell lung cancer

MET Ex14 demographics (GEOMETRY mono-1)

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	NSCLC with *MET* Exon 14 Skipping Mutation		NSCLC with *MET* Amplification				
	Cohort 4 (N=69)	Cohort 5b (N=28)	Cohort 1a (N=69)	Cohort 5a (N=15)	Cohort 1b (N=42)	Cohort 2 (N=54)	Cohort 3 (N=30)
Age							
Median (range) — yr	71 (49–90)	71 (57–86)	61 (33–76)	70 (49–86)	60 (36–76)	64 (39–84)	63 (38–78)
≥65 yr — no. (%)	55 (80)	25 (89)	28 (41)	10 (67)	13 (31)	24 (44)	14 (47)
Female sex — no. (%)	40 (58)	18 (64)	15 (22)	4 (27)	21 (50)	15 (28)	11 (37)
ECOG performance-status score — no. (%)†							
0	16 (23)	7 (25)	17 (25)	4 (27)	14 (33)	23 (43)	9 (30)
≥1	53 (77)	21 (75)	52 (75)	11 (73)	28 (67)	31 (57)	21 (70)
Smoking history — no. (%)							
Never smoked	40 (58)	18 (64)	5 (7)	2 (13)	7 (17)	11 (20)	7 (23)
Former smoking	27 (39)	9 (32)	54 (78)	8 (53)	29 (69)	34 (63)	20 (67)
Current smoking	2 (3)	1 (4)	10 (14)	5 (33)	6 (14)	9 (17)	3 (10)
Histologic findings — no. (%)							
Adenocarcinoma	53 (77)	25 (89)	57 (83)	11 (73)	35 (83)	48 (89)	22 (73)
Squamous-cell carcinoma	6 (9)	2 (7)	7 (10)	2 (13)	2 (5)	4 (7)	5 (17)
Large-cell carcinoma	1 (1)	0	2 (3)	1 (7)	1 (2)	0	1 (3)
Other	9 (13)	1 (4)	3 (4)	1 (7)	4 (10)	2 (4)	2 (7)
Brain metastases at baseline — no. (%)‡	11 (16)	3 (11)	26 (38)	7 (47)	14 (33)	18 (33)	6 (20)
No. of previous lines of antineoplastic therapy — no. (%)§							
1	51 (74)	NA	41 (59)	NA	27 (64)	28 (52)	9 (30)
2	16 (23)	NA	27 (39)	NA	15 (36)	26 (48)	21 (70)
3	2 (3)	NA	1 (1)	NA	0	0	0

Wolf J, et al. NEJM 2020;383(10):944-957

Capmatinib: GEOMETRY mono-1

Cohorts | **Expansion Cohorts**

Previous Treatment

1 or 2 Lines of therapy

- Cohort 1a: *MET* amplification, GCN ≥10 (N=69)
- Cohort 1b: *MET* amplification, GCN 6 to 9 — closed for futility (N=42)
- Cohort 2: *MET* amplification, GCN 4 or 5 — closed for futility (N=54)
- Cohort 3: *MET* amplification, GCN <4 — closed for futility (N=30)
- Cohort 4: *MET* exon 14 skipping mutation, any GCN (N=69)

1 Line of therapy

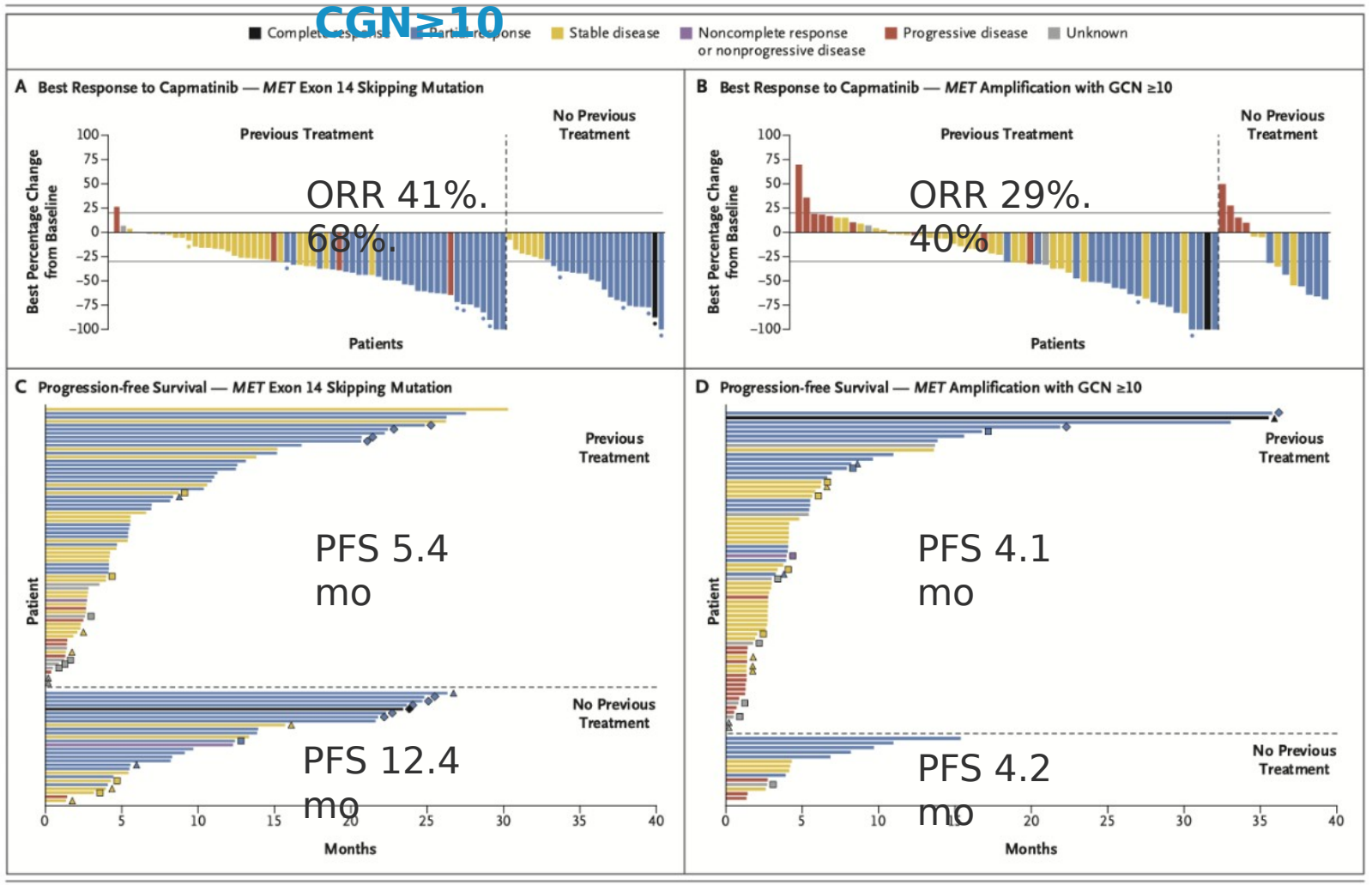
- Cohort 6: *MET* amplification, GCN ≥10; or *MET* exon 14 skipping mutation, any GCN (N=34)

No Previous Treatment

- Cohort 5a: *MET* amplification, GCN ≥10 (N=15)
- Cohort 5b: *MET* exon 14 skipping mutation, any GCN (N=28)
- Cohort 7: *MET* exon 14 skipping mutation, any GCN (N=23)

MET Ex14 CGN≥10

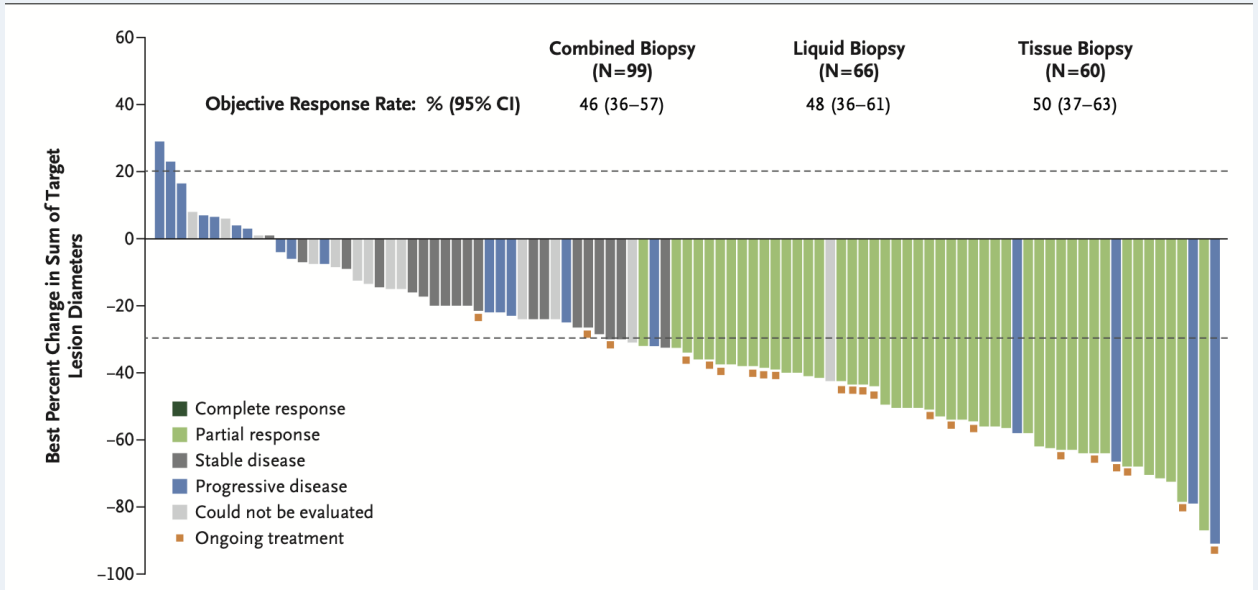
MET Amp



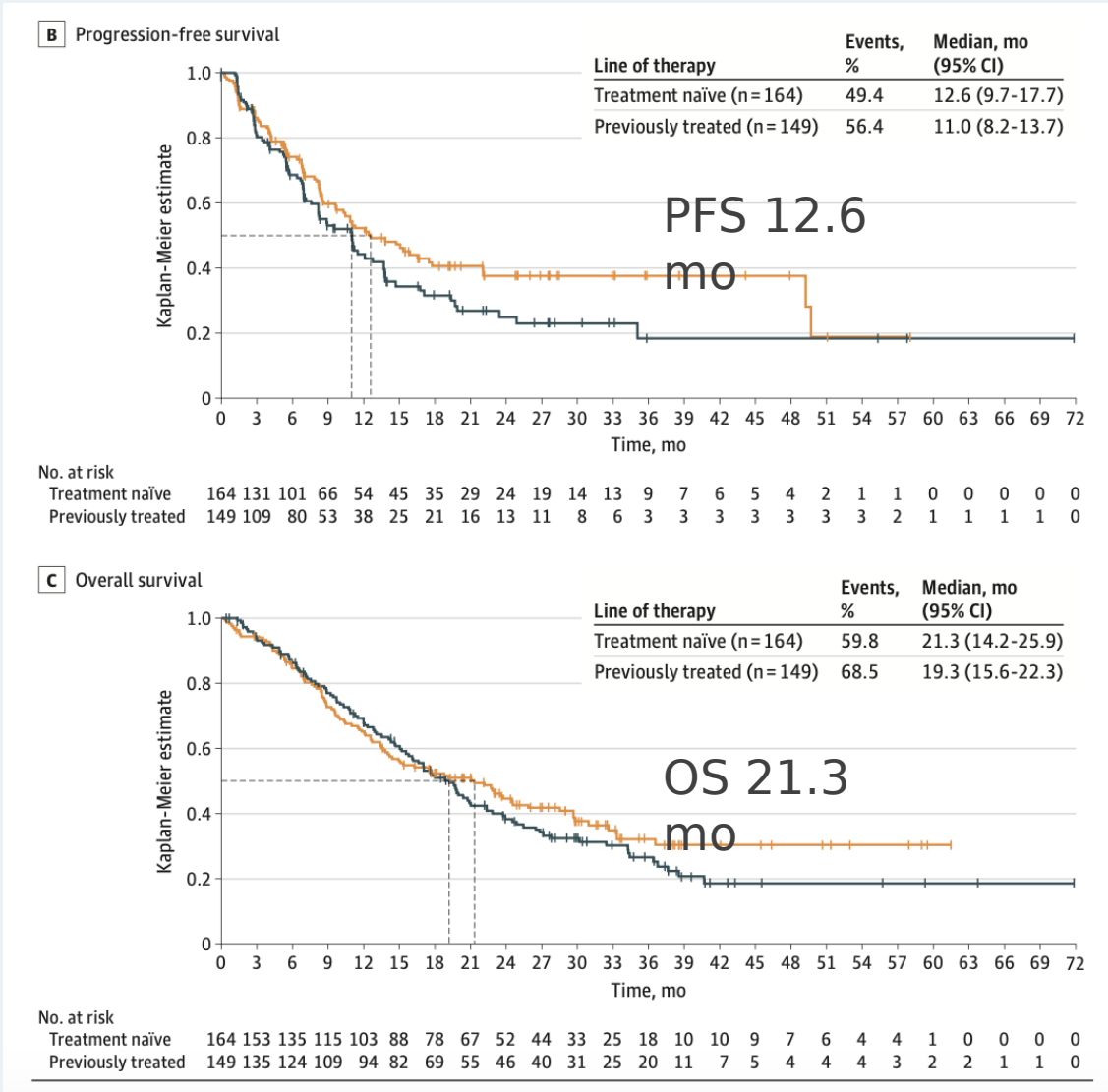
Wolf J, et al. NEJM 2020;383(10):944-957

ME
T

Tepotinib: VISION



ORR 48%
57% treatment naive



Paik PK, et al. NEJM 383;10:931-943
Mazieres J, et al. AMA Oncol. 2023;9(9):1260-1266

MET TKI AEs

Capmatinib

Variable	NSCLC with *MET* Exon 14 Skipping Mutation			
	Cohort 4 (N=69)		Cohort 5b (N=28)	
	Total	Grade 3 or 4	Total	Grade 3 or 4
Adverse events				
Any event — no. (%)	68 (99)	52 (75)	28 (100)	21 (75)
Most common events — no. (%)†				
Peripheral edema	37 (54)	10 (14)	21 (75)	3 (11)
Nausea‡	32 (46)	0	13 (46)	0
Vomiting‡	18 (26)	0	7 (25)	0
Blood creatinine increased	23 (33)	0	10 (36)	0
Dyspnea	19 (28)	7 (10)	6 (21)	2 (7)
Fatigue	18 (26)	6 (9)	4 (14)	1 (4)
Decreased appetite‡	15 (22)	1 (1)	8 (29)	0
Constipation	10 (14)	2 (3)	4 (14)	0
Diarrhea	12 (17)	0	5 (18)	0
Cough	10 (14)	1 (1)	7 (25)	0
Back pain	11 (16)	2 (3)	4 (14)	0
Pyrexia	9 (13)	1 (1)	2 (7)	0
ALT increased	8 (12)	6 (9)	4 (14)	2 (7)
Asthenia	6 (9)	3 (4)	4 (14)	2 (7)
Pneumonia	7 (10)	4 (6)	2 (7)	0
Weight loss	9 (13)	0	3 (11)	0
Noncardiac chest	5 (7)	1 (1)	1 (4)	0

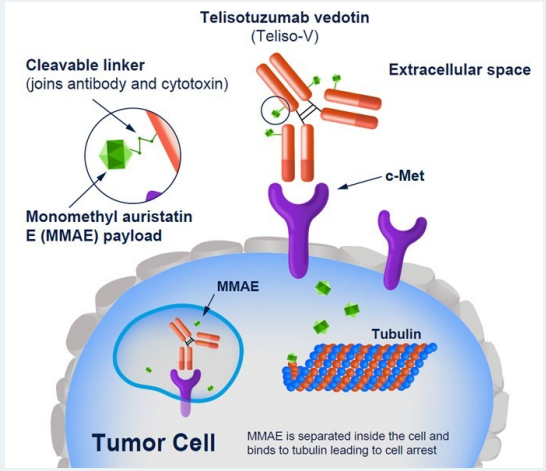
Tepotinib

Adverse Events	Safety Population (N=152)			
	All Grades	Grade 1 or 2	Grade 3	Grade 4
	number of patients (percent)			
Any adverse event†	135 (89)	93 (61)	38 (25)	3 (2)
Peripheral edema	96 (63)	85 (56)	11 (7)	0
Nausea	39 (26)	38 (25)	1 (1)	0
Diarrhea	33 (22)	32 (21)	1 (1)	0
Blood creatinine increased	27 (18)	26 (17)	1 (1)	0
Hypoalbuminemia	24 (16)	21 (14)	3 (2)	0
Amylase increased	17 (11)	13 (9)	3 (2)	1 (1)
Lipase increased	13 (9)	9 (6)	4 (3)	0
Asthenia	12 (8)	11 (7)	1 (1)	0
Decreased appetite	12 (8)	11 (7)	1 (1)	0
Pleural effusion	12 (8)	8 (5)	4 (3)	0
Alopecia	12 (8)	12 (8)	0	0
Fatigue	11 (7)	10 (7)	1 (1)	0
Alanine aminotransferase increased	11 (7)	7 (5)	3 (2)	1 (1)
Aspartate aminotransferase increased	10 (7)	7 (5)	2 (1)	1 (1)
Vomiting	9 (6)	9 (6)	0	0
General edema	9 (6)	5 (3)	4 (3)	0
Upper abdominal pain	8 (5)	8 (5)	0	0

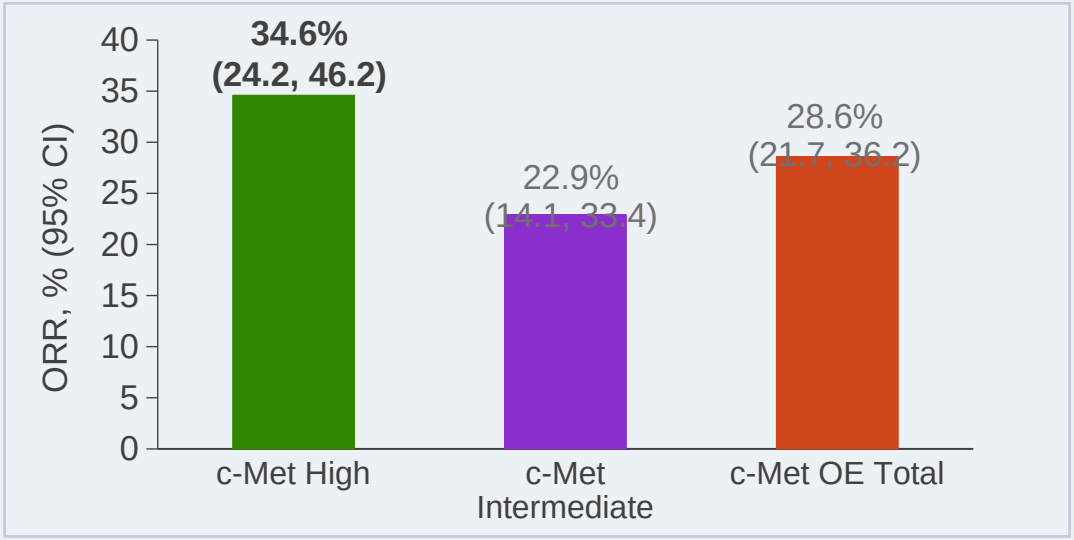
Wolf J, et al. NEJM 2020;383(10):944-957
Paik PK, et al. NEJM 383;10:931-943

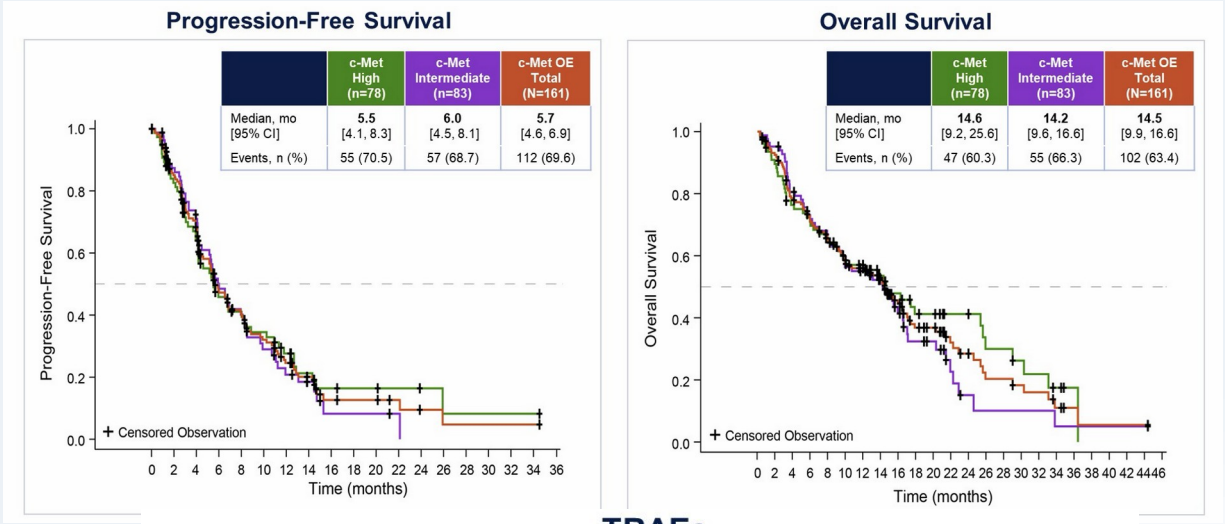
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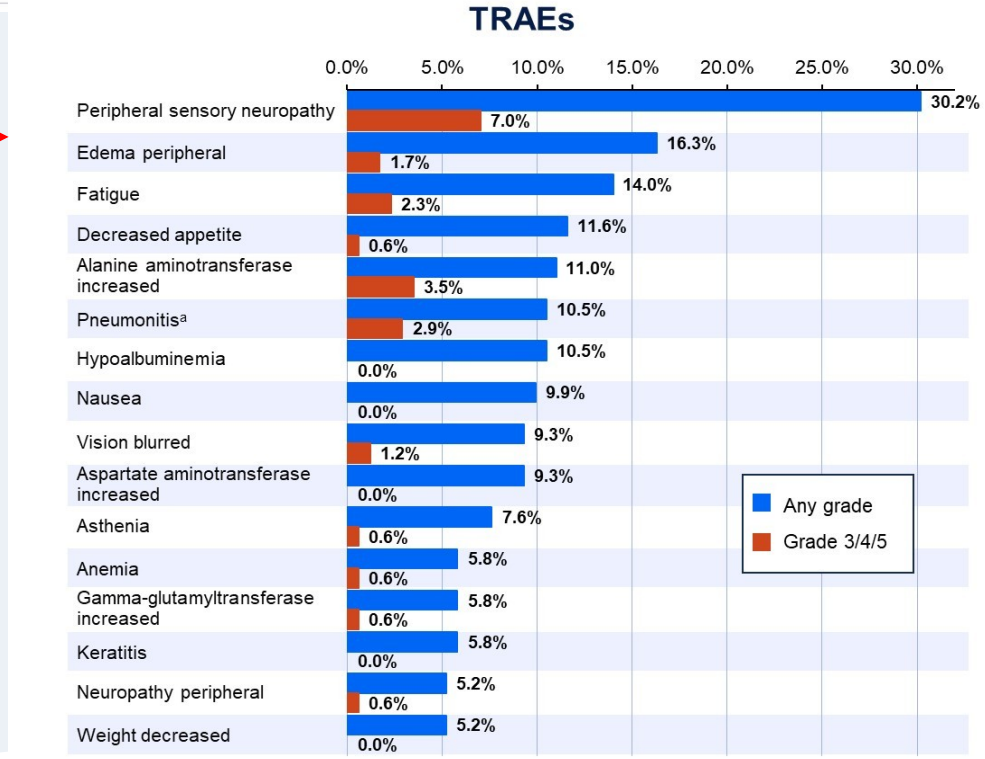
Teliso-V: Luminosity (IHC+)



ORR







Camidge DR, et al. ASCO 2024;abst 103
Camidge DR, et al. J Clin Oncol 2024;42(25):3000-3011

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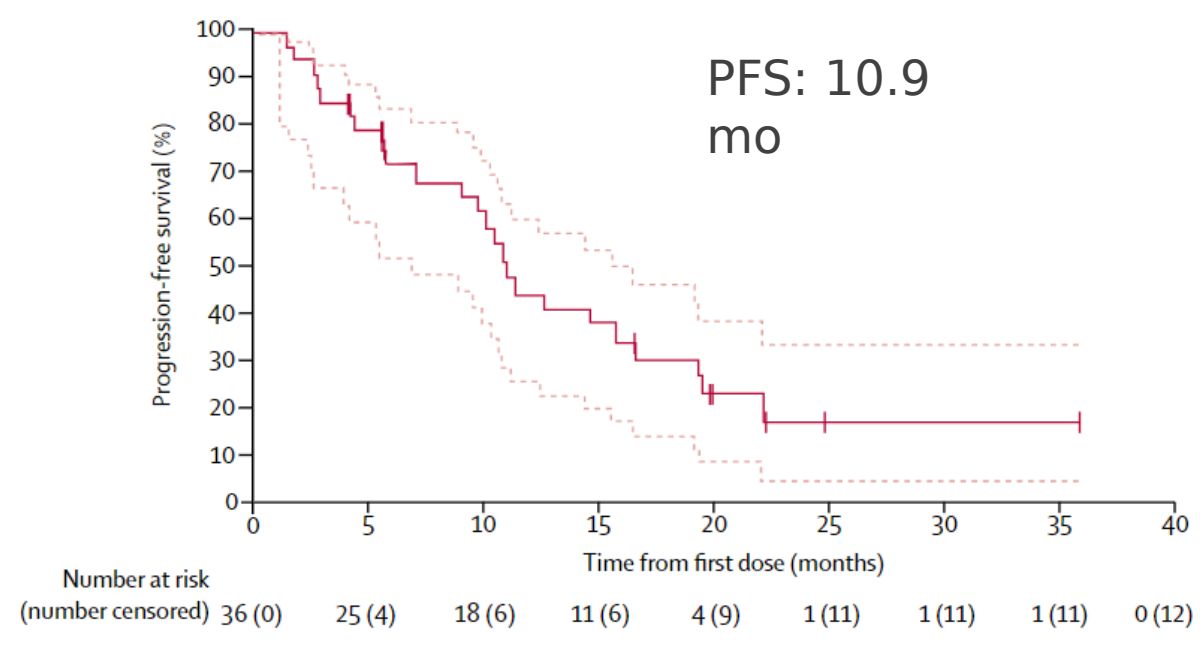
BRAF

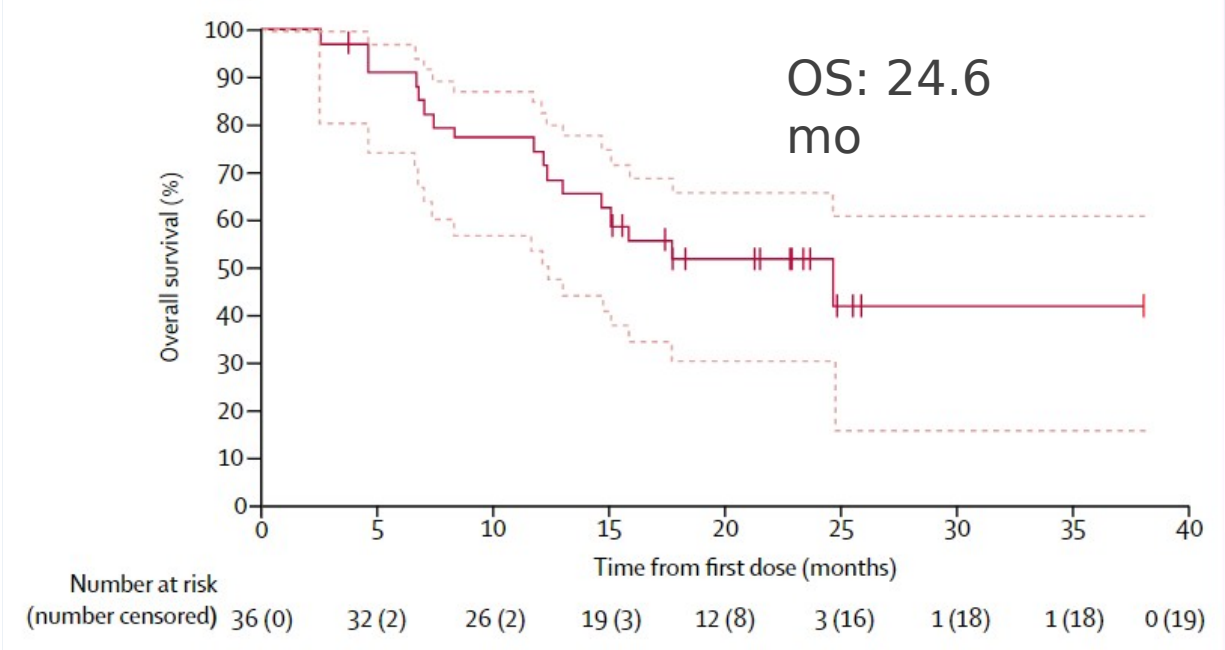
Partners for Advancing Clinical Education

Bio Ascend™

BRA
F

Dabrafenib/Trametinib 1st line



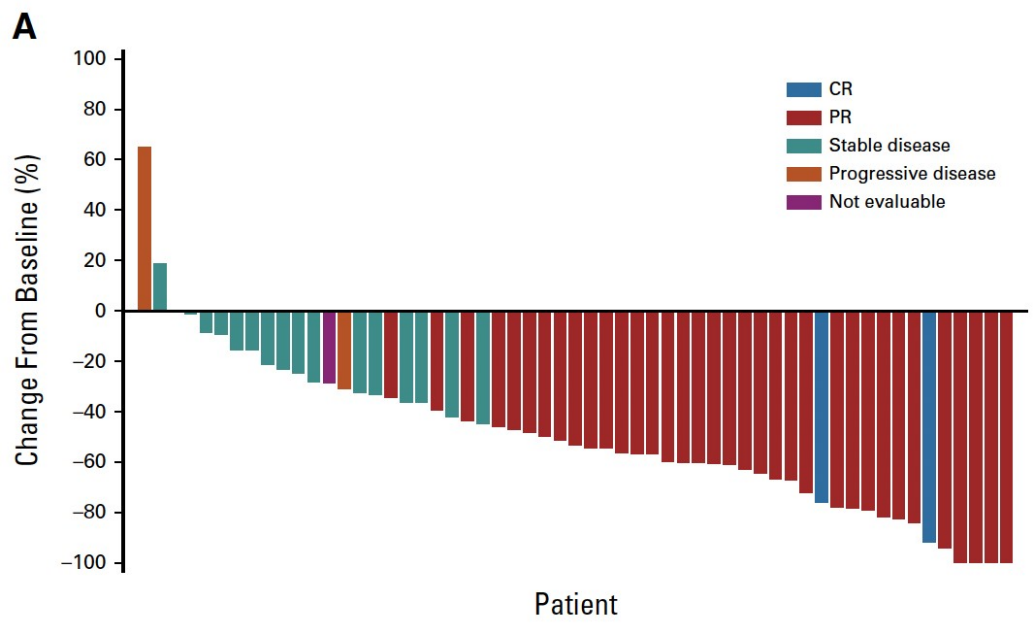


ORR: 64%

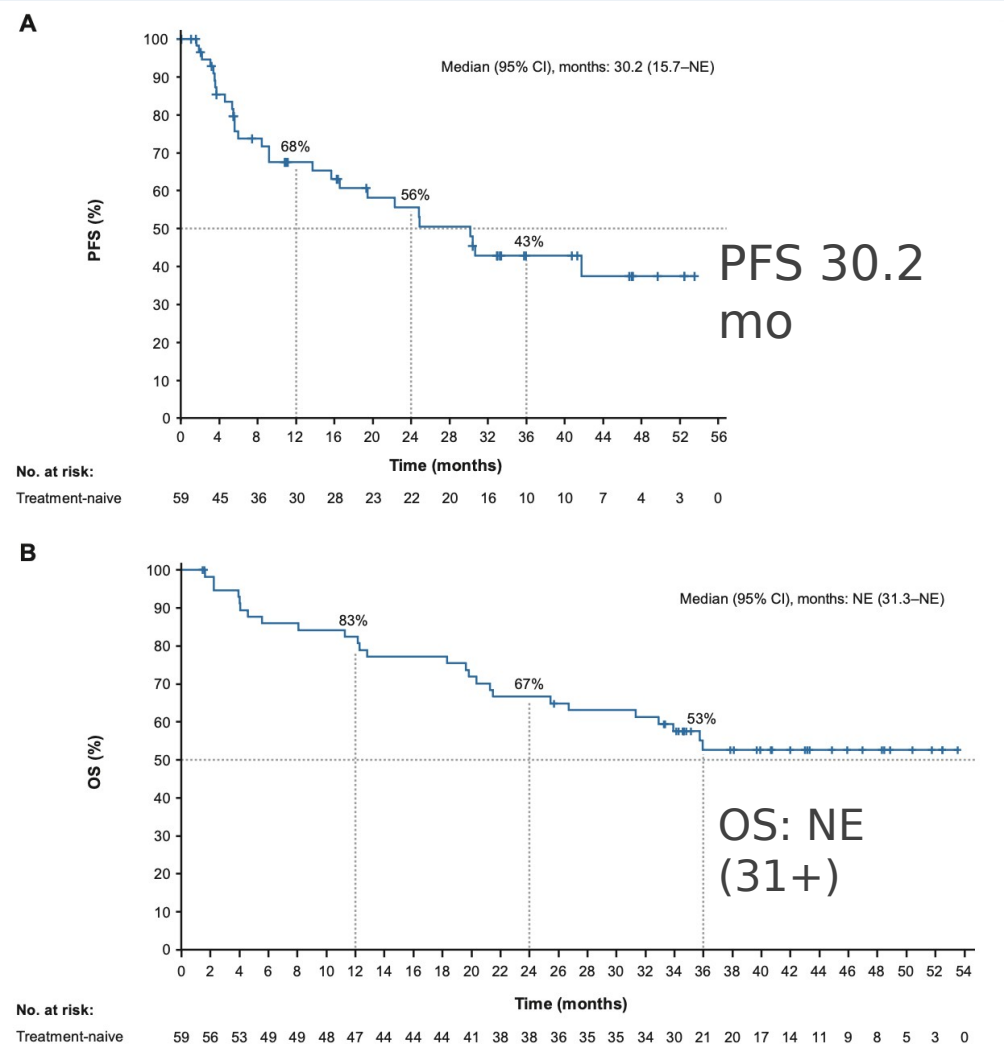
FDA Approved: June 22, 2017

Planchard et al, Lancet Oncology 2017

Encorafinib/Binemetinib (PHAROS



ORR
75%



PFS 30.2 mo

OS: NE (31+)

Riely GJ, et al. J Clin Oncol 2023;41(21):3700-3709
Riely GJ, et al. J Thorac Oncol 2025;20(10):1538-1547

BRAF TKI AEs

Dabrafenib, trametinib

	Grade 1–2	Grade 3	Grade 4	Grade 5
Total	10 (28%)	23 (64%)	2 (6%)	1 (3%)
Pyrexia	19 (53%)	4 (11%)	0	0
Nausea	20 (56%)	0	0	0
Diarrhoea	12 (33%)	1 (3%)	0	0
Fatigue	13 (36%)	0	0	0
Peripheral oedema	13 (36%)	0	0	0
Vomiting	9 (25%)	3 (8%)	0	0
Dry skin	12 (33%)	0	0	0
Decreased appetite	12 (33%)	0	0	0
Chills	9 (25%)	0	0	0
Headache	9 (25%)	0	0	0
Rash	7 (19%)	1 (3%)	0	0
Dizziness	8 (22%)	0	0	0
Cough	8 (22%)	0	0	0
Alanine aminotransferase increase	2 (6%)	4 (11%)	0	0
Dyspnoea	4 (11%)	2 (6%)	0	0
Hypotension	4 (11%)	2 (6%)	0	0
Back pain	6 (17%)	0	0	0
Weight decrease	6 (17%)	0	0	0
Abdominal pain	4 (11%)	1 (3%)	0	0
Anaemia	4 (11%)	1 (3%)	0	0
Arthralgia	4 (11%)	1 (3%)	0	0

Planchard et al, Lancet Oncology 2017
Riely GJ, et al. J Thorac Oncol 2025;20(10):1538-1547

Encorafenib, binimetinib

Table 1. TRAEs in Treatment-Naive and Previously Treated Patients (≥10% Any Grade in Either Cohort)

	Treatment-Naive (n = 59)		Previously Treated (n = 39)	
Preferred Term	Any Grade	Grade 3/4[a]	Any Grade	Grade 3/4
Any TRAE, n (%)	58 (98)	32 (54)	34 (87)	13 (33)
Nausea	35 (59)	3 (5)	16 (41)	1 (3)
Diarrhea	24 (41)	3 (5)	19 (49)	2 (5)
Fatigue	18 (31)	0	14 (36)	2 (5)
Vomiting	18 (31)	1 (2)	11 (28)	0
Vision blurred	12 (20)	1 (2)	6 (15)	0
ALT increased	11 (19)	4 (7)	2 (5)	1 (3)
AST increased	11 (19)	6 (10)	2 (5)	1 (3)
Anemia	10 (17)	2 (3)	7 (18)	1 (3)
Alopecia	9 (15)	0	3 (8)	0
Constipation	9 (15)	0	5 (13)	0
Abdominal pain	8 (14)	0	3 (8)	0
Blood alkaline phosphatase increased	8 (14)	2 (3)	0	0
Blood creatine phosphokinase increased	8 (14)	1 (2)	3 (8)	0
Dry skin	8 (14)	0	3 (8)	0
Lipase increased	8 (14)	7 (12)	1 (3)	0
Decreased appetite	7 (12)	0	2 (5)	1 (3)
Pyrexia	7 (12)	0	1 (3)	0
Rash	7 (12)	0	3 (8)	1 (3)
Rash maculopapular	7 (12)	1 (2)	4 (10)	0
Dizziness	6 (10)	0	5 (13)	1 (3)
Myalgia	6 (10)	2 (3)	5 (13)	0
Peripheral edema	6 (10)	0	5 (13)	0
Pruritus	6 (10)	0	6 (15)	0
Dysgeusia	5 (9)	0	4 (10)	0
Ejection fraction decreased	5 (9)	2 (3)	4 (10)	1 (3)
Asthenia	3 (5)	1 (2)	7 (18)	2 (5)

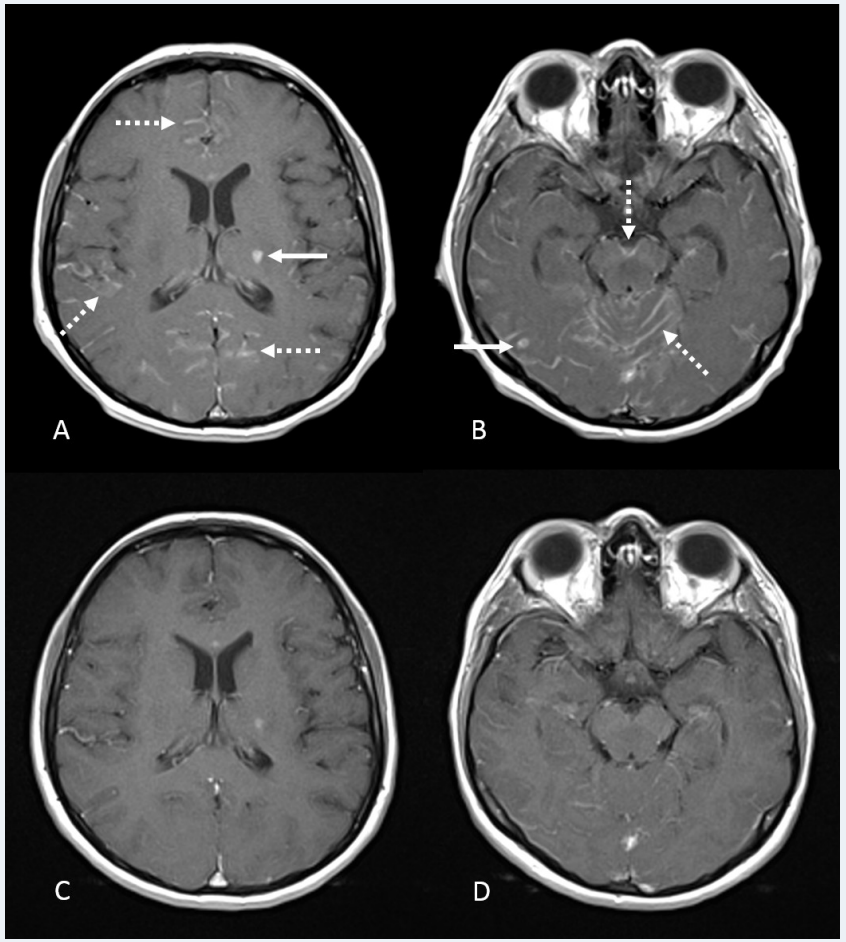
[a]There was one grade 5 AE (intracranial hemorrhage) determined by investigator to be treatment related.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

BRA
F

A tale of two BRAF V600E mutations

Case 1 (April 2017)
37 F, never smoked
32 wk pregnant p/w placenta previa
7.7 cm R lung mass, SVC syndrome
2 small brain mets
BRAF V600E, PDL1 40%
→ C-section, palliative thoracic RT, SRS

1. Dabrafenib/trametinib, 2 months
PD: new lung mets, increased LAD
2. Carbo/pem/pembro, 10 months
(pembro d/c @ 6 months: pneumonitis)
Pem maintenance, 7 mo
PR
3. Docetaxel, 3 months
PD
Peritoneal mets and CNS progression (new lepto)
4. Encorafenib/binimetinib



McLoughlin EM…Gentzler RD, et al. J Thorac Oncol 2019;14(12):e269-e271

Case 2 (June 2017)
62 M, 50 pk-yr smoking hx, current
p/w altered mental status
3.4 cm frontal lobe brain met with
edema and midline shift
6.3 cm paratracheal LN invading SVC
3.4 cm spiculated RUL mass
Numerous bilateral lung metastases
up to 2.4 cm
→Craniotomy, SRS
BRAF V600E, PDL1 100%

1. Pembrolizumab, 24 mo
PR

2. Dabrafenib/trametinib, 74 months
PR

3. Surveillance, 1+ year

Clinical and Therapeutic Characteristics of *RET*, *MET* Exon 14, and BRAF V600E NSCLC

Distinct patient populations, robust efficacy with targeted therapy, and evolving treatment paradigms

	RET Fusion	MET Exon 14 Skipping		BRAF V600E
		 Exon 14 skipping		
Typical age (at diagnosis)	Younger (55–65 years)	Older (70–75 years)		Intermediate (60–70 years)
Smoking history	Mostly never- or light smoking	40-50% former/current smoking		Highest proportion former/current smoking
Treatment-naïve objective response rate (ORR)	**84%** (LIBRETTO-431)	**68%** (Capmatinib) GEOMETRY mono-1	**57%** (Tepotinib) VISION	**75%** (PHAROS)
Median progression-free survival (PFS)	**24.8 months** (LIBRETTO-431)	**12.4 months** (Capmatinib) GEOMETRY mono-1	**11.2 months** (Tepotinib) VISION	**30.2 months** (PHAROS)
Intracranial activity (ORR)	**82%** (LIBRETTO CNS analyses)	**54%** (Capmatinib) GEOMETRY mono-1	**55%** (Tepotinib) VISION	**Limited prospective data;** meaningful intracranial responses reported
FDA approval setting	✓ **Metastatic** (2020) ✓ **Adjuvant** (2026, positive)	✓ **Metastatic** (2020/2021) ✗ **Adjuvant** (no)		✓ **Metastatic** (2023) ✗ **Adjuvant** (no)
Key clinical considerations	• Excellent CNS penetration • Manageable toxicity profile • Emerging perioperative role	• Older, more comorbid population • Edema is the major limiting toxicity • Durable responses in selected patients		• Durable outcomes with modern BRAF/MEK • Favorable tolerability (encorafenib/binimetinib) • Optimal sequencing after progression remains an area of active investigation

Take-Home Message: *RET and **BRAF**V600E NSCLC now achieve outcomes approaching those seen with established driver oncogenes, while MET exon 14 skipping remains highly effective but is often limited by patient factors and treatment-associated edema.*

Sources: Zhou C, et al. *N Engl J Med.* 2024; LIBRETTO-431. Wolf J, et al. *N Engl J Med.* 2020; GEOMETRY mono-1. Paik PK, et al. *N Engl J Med.* 2020; VISION. Riely GJ, et al. *J Thorac Oncol.* 2025; PHAROS. Johnson ML, et al. *J Clin Oncol.* 2025. Additional CNS analyses as cited.

Figure not to scale. For educational purposes only.