NCCN Guidelines: Systemic Therapy for Patients with *RET* Rearrangement Positive Advanced NSCLC

First line

Targeted therapies	Other recommended systemic therapy (PS 0-1)	
Preferred • **Selpercatinib** • **Pralsetinib** **Useful in certain circumstances** • **Cabozantinib**	Preferred: pembrolizumab + chemotherapy as appropriate for histology* Other: additional combination regimens • Atezolizumab†, • Nivolumab/ipilimumab, • Cemiplimab-rwlc, or • Tremelimumab-actl/durvalumab, as appropriate for histology*	Useful in certain circumstances: Contraindications to PD-1/PD-L1 inhibitors • Chemotherapy as appropriate for histology* • Bevacizumab + chemotherapy for adenocarcinoma*

*Bevacizumab and pemetrexed not recommended for SCC
†Atezolizumab not recommended for first line treatment of SCC

Second line

Targeted therapies	Or other systemic therapy	
If not received previously: **Preferred** • **Selpercatinib** • **Pralsetinib** **Useful in certain circumstances** • **Cabozantinib**	**If not received previously (PS 0-1):** Preferred: pembrolizumab + chemotherapy as appropriate for histology* Or other systemic therapy first line regimens as shown above	Preferred (no previous IO) • Nivolumab • Pembrolizumab • Atezolizumab Other (no previous or previous IO) • Chemotherapy as appropriate for histology

See guidelines for full recommendations. PS, performance status; PD-1, programmed death protein 1; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma; IO, immunotherapy. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2023. Updated April 13, 2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450.

Selpercatinib in *RET* Fusion-Positive Advanced NSCLC

Efficacy Results

LIBRETTO-001

Phase 1/2 global multicohort open label trial

- *RET* altered advanced solid tumors
- Analysis reported here for *RET* fusion-positive advanced NSCLC
- Previously treated with platinum-based chemotherapy or no prior therapy
- Stable or asymptomatic brain metastases allowed

	Treatment-naïve (n = 69)	Previous platinum chemotherapy (n = 247)
Objective response, % (95% CI)	84 (73 to 92)	61 (55 to 67)
Median duration of response, mo (95% CI)	20.2 (13.0–NE)	28.6 (20.4–NE)
Median PFS, mo (95% CI)	22.0 (13.8–NE)	24.9 (19.3–NE)
3-year OS, % (95% CI)	57.1 (35.9–73.6)	58.5 (49.7–66.3)

IRC-assessed results shown. Data cutoff date: June 15, 2021. Median follow-up 20.3 mo for treatment naïve patients and 21.9 mo for previously treated patients.

FDA approved May 2020 for patients with locally advanced or metastatic NSCLC with a *RET* gene fusion
FDA approved Sept. 2022 for all locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options

CI, confidence interval; mo, months; PFS, progression-free survival; NE, not estimable; OS, overall survival; IRC, independent review committee. Drilon A et al. *J Clin Oncol*. 2023;41:385-394; FDA Approved Drugs: Oncology (Cancer) / Hematologic Malignancies Approval Notifications /Oncology (Cancer) Approvals & Safety Notifications. Reviewed June 20, 2023. Accessed June 20, 2023. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm.

Selpercatinib in *RET* Fusion-Positive Advanced NSCLC

Safety Results

LIBRETTO-001

Full safety population (all tumor types):
N = 796
Median treatment duration: 36.1 mo

	n (%)
Any adverse event	795 (99.9)
Grade ≥3 AEs	572 (71.9)
Grade ≥3 AEs related to treatment	307 (38.6)
Adverse event leading to discontinuation	64 (8%)

AEs in ≥30% of patients, n (%)		
	Any grade	Grade ≥3
Edema	386 (48.5)	6 (0.7)
Diarrhea	374 (47.0)	40 (5.0)
Fatigue	365 (45.9)	25 (3.1)
Dry mouth	344 (43.2)	0
Hypertension	326 (41.0)	157 (19.7)
AST increased	292 (36.7)	70 (8.8)
ALT increased	284 (35.7)	91 (11.4)
Abdominal pain	268 (33.7)	20 (2.5)
Constipation	261 (32.8)	6 (0.8)
Rash	261 (32.8)	5 (0.6)
Nausea	248 (31.2)	9 (1.1)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; mo, months.

Drilon A et al. *J Clin Oncol*. 2023;41:385-394.

Pralsetinib in *RET* Fusion-Positive Advanced NSCLC

Efficacy Results

ARROW

Phase 1/2 global single arm open label trial

- *RET* altered advanced solid tumors
- Analysis reported here for *RET* fusion-positive advanced NSCLC
- Enrollment based on circulating tumor DNA testing was allowed in NSCLC cohort
- Previously treated (with or without platinum) or no prior therapy
- Stable brain metastases allowed

	Treatment-naïve (n = 75)	Prior platinum-based chemotherapy (n = 136)	Prior non-platinum systemic therapy (n = 22)
Objective response, % (95% CI)	72 (60–82)	59 (50–67)	73 (50–89)
Median duration of response, mo (95% CI)	NR (9.0–NR)	22.3 (15.1–NR)	NR (9.2–NR)
Median PFS, mo (95% CI)	13.0 (9.1–NR)	16.5 (10.5–24.1)	12.8 (9.1–NR)
1-year OS, % (95% CI)	53 (38–68)	57 (48–66)	52 (29–76)

Data cutoff date: Nov. 6, 2020 (median follow-up 17.1 mo)

FDA approved Sept. 2020 for patients with metastatic *RET* fusion-positive NSCLC

CI, confidence interval; mo, months; ; PFS, progression-free survival; NR, not reached; OS, overall survival.

Griesinger F et al. *Ann Oncol*. 2022;33:1168-1178; FDA Approved Drugs: Oncology (Cancer) / Hematologic Malignancies Approval Notifications /Oncology (Cancer) Approvals & Safety Notifications. Reviewed June 20, 2023. Accessed June 20, 2023. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm.

Pralsetinib in *RET* Fusion-Positive Advanced NSCLC

Safety Results

ARROW

NSCLC safety population (N = 281)
Median treatment duration: 7.9 mo

	n (%)
Treatment-naïve (n = 116)	
Any TRAE	108 (93%)
Grade ≥3 TRAE	60 (52%)
Previously treated (n = 165)	
Any TRAE	156 (95%)
Grade ≥3 TRAE	93 (56%)

TRAEs in ≥20% of patients, n (%)				
	Treatment-naïve (n = 116)		Previously treated (n = 165)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	50 (43)	21 (18)	78 (47)	36 (22)
Leukopenia	45 (39)	8 (7)	51 (31)	14 (8)
Increased AST	45 (39)	2 (2)	69 (42)	6 (4)
Anemia	37 (32)	5 (4)	71 (43)	30 (18)
Increased ALT	37 (32)	1 (1)	47 (28)	5 (3)
Constipation	35 (30)	0	38 (23)	2 (1)
Fatigue	29 (25)	1 (1)	41 (25)	4 (2)
Increased blood creatine phosphokinase	27 (23)	10 (9)	22 (13)	8 (5)
Hypertension	24 (21)	12 (10)	47 (28)	22 (13)

TRAE, treatment-related adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Griesinger F et al. *Ann Oncol*. 2022;33:1168-1178.