Therapies Targeting *ALK*, *ROS1*, and *NTRK* Fusions in Advanced NSCLC

Therapy	FDA approval	NCCN first line recommendation(s) in advanced NSCLC
Alectinib	*ALK*-positive	*ALK* (preferred)
Brigatinib	*ALK*-positive	*ALK* (preferred)
Ceritinib	*ALK*-positive	*ALK* (other recommended) *ROS1* (other recommended)
Crizotinib	*ALK*-positive *ROS1*-positive	*ALK* (useful in certain circumstances) *ROS1* (preferred) *MET* exon 14 (useful in certain circumstances)
Lorlatinib	*ALK*-positive	*ALK* (preferred) *ROS1* (after progression on entrectinib, crizotinib, or ceritinib)
Entrectinib	*ROS1*-positive *NTRK1/2/3*-positive (all solid tumors)	*ROS1* (preferred) *NTRK1/2/3* (preferred)
Larotrectinib	*NTRK1/2/3*-positive (all solid tumors)	*NTRK1/2/3* (preferred)

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; 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.

FDA Approved Targeted Therapies for *ROS1* Altered Advanced NSCLC

Crizotinib

PROFILE 1001

Phase 1 multicenter, single arm study

- *ROS1*-positive advanced NSCLC (n = 53)
  - *ROS1* status by break-apart FISH or RT-PCR
- 13% treatment naïve, 97% previously treated

Updated results published 2019

ORR	72% (95% CI, 58–83)
DOR	24.7 mo (95% CI, 15.2–45.3)
mPFS	19.3 mo (95% CI, 15.2–39.1)
mOS	51.4 mo (95% CI, 29.3–NR)

Entrectinib

ALKA, STARTRK-1, STARTRK-2

Pooled analysis of 3 multicenter open label trials

- *ROS1*-positive advanced NSCLC (n = 168)
  - *ROS1* status by break-apart FISH, RT-PCR, or NGS
- 20% treatment naïve, 80% previous platinum-based CT

Updated results published 2022

ORR	67.9% (95% CI, 60.2–74.8)
DOR	20.5 mo (95% CI, 14.8–34.8)
mPFS	15.7 mo (95% CI, 12.0–21.1)
mOS	47.8 mo (95% CI, 44.1–NE)

FISH, fluorescence in situ hybridization; RT-PCR, real time polymerase chain reaction; ORR, objective response rate; DOR, duration of response; mPFS, median progression-free survival; mOS, median overall survival; NGS, next-generation sequencing; CT, chemotherapy; NR, not reached; NE, not estimable.

Shaw AT et al. *Ann Oncol*. 2019;30:1121-1126; Drilon A et al. *JTO Clin Res Rep*. 2022;3:100332.

NTRK Gene Fusions in Advanced Solid Tumors

- Neurotrophic tropomyosin receptor kinase (*NTRK*) 1, 2, and 3 gene fusions are rare oncogenic drivers found in a subset of solid tumors
  - A few high prevalence tumors
- Overall prevalence of 0.30% among 45 cancers in database of >295,000 patients
  - 88 unique fusion partners, 66% previously unreported
- Occur in <1% of NSCLC tumors

Frequency	Tumor types
>90%	Mammary analogue secretory carcinoma Secretory breast carcinoma Infantile fibrosarcoma Cellular and mixed congenital mesoblastic nephroma
5% to 25%	Thyroid cancer Gastrointestinal stromal tumor (pan-negative) Spitzoid tumors
<5%	High grade glioma Head and neck, lung, breast, colorectal, and pancreatic cancers Renal cell carcinoma Melanoma Cholangiocarcinoma Sarcoma Hematological malignancies

Cocco E et al. *Nat Rev Clin Oncol.* 2018;15:731-747; Westphalen CB et al. *NPJ Precis Oncol*. 2021;5:69.

Entrectinib and Larotrectinib in *NTRK* Fusion-Positive Advanced Solid Tumors and Advanced NSCLC

Entrectinib

FDA approved Aug. 2019

ALKA, STARTRK-1, STARTRK-2

Pooled analysis of 3 multicenter open label trials

- *NTRK* fusion-positive advanced solid tumors (N = 54)
- Most common cancers = sarcoma, NSCLC, salivary gland, breast, thyroid, and colon

Full trial population (N = 54)	
ORR:	59% (95% CI, 45%–72%)
NSCLC (n = 10)	
ORR:	60% (95% CI, 26%–88%)
DOR:	Range = 3.7, 47.8+ mo

Larotrectinib

FDA approved Nov. 2018

LOXO-TRK-14001, SCOUT, and NAVIGATE

Pooled analysis of 3 multicenter open label trials

- *NTRK* fusion-positive advanced solid tumors (N = 55)
- Most common cancers = salivary gland, sarcoma, thyroid, lung, melanoma, and colon

Full trial population (N = 55)	
ORR:	75% (95% CI, 61%–85%)
NSCLC (n = 4)	
ORR:	75% (95% CI, 19%–99%)
DOR:	Range = 8.2, 36.8+ mo

FDA approved for *NTRK*-positive solid tumors without a known resistance mutation; metastatic, or where surgical resection is likely to result in severe morbidity; and that have progressed following treatment or have no satisfactory alternative therapy

NTRK, neurotrophic tropomyosin receptor kinase; ORR, objective response rate; CI, confidence interval; DOR, duration of response; mo, months. VITRAKVI. Prescribing information. Bayer; March 2021; ROZLYTREK. Prescribing information. Genentech; Nov. 2021; 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.