

Managing Advanced ALK-Positive Non-Small-Cell Lung Cancer: Considerations for Community Practitioners

- Treatment for advanced non-small-cell lung cancer (NSCLC) has evolved rapidly in recent years; more than 50% of patients with advanced nonsquamous NSCLC have a driver gene alteration that is targetable by an FDA-approved agent¹
 - Studies have shown that patients with identified actionable driver gene alterations who receive appropriate targeted therapy have improved outcomes vs those who receive conventional cytotoxic chemotherapy²
 - RNA is superior to DNA for detecting *ALK* fusions by NGS, as RNA NGS detects a mature mRNA produced by the chromosomal rearrangement

Biomarker Testing for Advanced or Metastatic NSCLC

- Broad molecular profiling should be used to identify actionable alterations in all patients with advanced nonsquamous NSCLC and considered in patients with squamous NSCLC³
 - Broad molecular profiling: molecular testing that identifies key NSCLC biomarkers in a single assay or limited number of assays; most commonly next-generation sequencing (NGS) based
- National guideline recommendations for molecular profiling:

NONSQUAMOUS

Broad molecular testing recommended

- *EGFR* mutation
- *ALK* rearrangements
- *KRAS* G12C mutation
- *ROS1* rearrangements
- *BRAF* V600E mutation
- *NTRK1-3* rearrangements
- *MET* exon 14 skipping mutations
- *RET* rearrangements
- *ERBB2/HER2* mutations
- *NRG1* rearrangements
- PD-L1 expression by IHC
- HER2 expression by IHC

SQUAMOUS

Consider broad molecular testing

- *EGFR* mutation
- *ALK* rearrangements
- *KRAS* G12C mutation
- *ROS1* rearrangements
- *BRAF* V600E mutation
- *NTRK1-3* rearrangements
- *MET* exon 14 skipping mutations
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- A limitation to molecular testing can occur when there is insufficient tumor tissue for molecular, biomarker, and histologic testing
 - It is important that bronchoscopists, interventional radiologists, and other healthcare professionals obtain sufficient tissue to allow optimal testing
 - In the event of insufficient tissue for testing, plasma ctDNA NGS testing may be considered as a complement to tumor tissue NGS; however, it is important to note that “not detectable” on ctDNA requires an additional tissue biopsy, as this is not equivalent to “negative”

Focus on ALK Testing

- In NSCLC, *ALK* may be rearranged in ~5% of cases^{4,5}
 - Most commonly in NSCLC, a fusion with *EML4* occurs
- *ALK* fusions are most commonly detected by NGS, FISH, and IHC³
 - As mentioned above, broad molecular profiling NGS panels are often preferred to detect *ALK* rearrangements; NGS testing with both DNA and RNA will maximize the number of patients captured
 - RNA is superior to DNA for detecting *ALK* fusions by NGS, as RNA NGS detects a mature mRNA produced by the chromosomal rearrangement
 - In assessing the value of NGS, FISH, and IHC to detect *EML4-ALK* fusions in NSCLC cases, a single-center study found a positive rate of 94.5% for IHC, 92.7% for NGS, and 82.4% for FISH; there was highest concordance between IHC and NGS (87.3%)⁶
- Advanced *ALK*-positive NSCLC can be treated with several approved *ALK*-targeting TKI

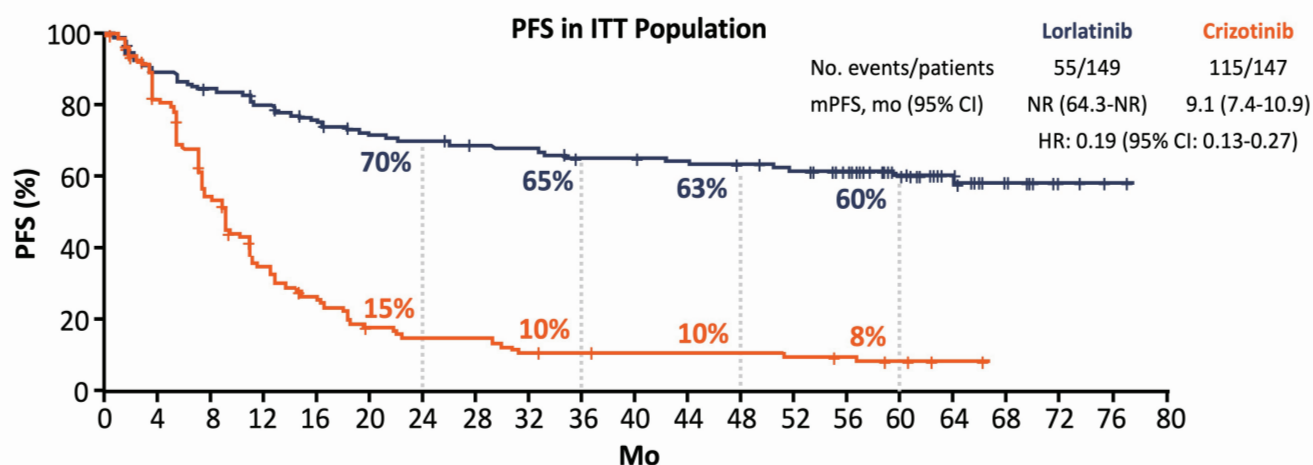
Treatment Options for Advanced ALK-Positive NSCLC

- National guidelines currently list the following as preferred treatment options for **first-line therapy** for advanced *ALK*-positive NSCLC: alectinib, brigatinib, ensartinib, and lorlatinib; ceritinib and crizotinib may also be useful in specific circumstances with limited access to preferred agents³
 - Guidelines recommend interrupting therapy and starting an *ALK* inhibitor if testing identifies *ALK*-positive disease during first-line, non-*ALK* inhibitor systemic therapy such as carboplatin/pemetrexed

Efficacy of ALK TKIs as First-line Therapy for Advanced ALK-Positive NSCLC⁷⁻¹²

Agent	Median First-line PFS: First Line (Comparator)	Trial (N)	FDA Indication(s) in Advanced Disease	Recommended Dosing
Alectinib	25.9 mo vs 10.4 mo (crizotinib) HR: 0.53; $P < .0001$	ALEX (303)	ALK-positive mNSCLC	600 mg PO BID
Brigatinib	24.0 mo vs 11.1 mo (crizotinib) HR: 0.49; $P < .0001$	ALTA 1L (275)	ALK-positive mNSCLC	90 mg PO QD for first 7 days, then increase to 180 mg PO QD
Ensartinib	25.8 mo vs 12.7 mo (crizotinib) HR: 0.56; $P = .0007$	eXALT3 (290)	ALK-positive locally advanced or mNSCLC; no previous ALKi	225 mg PO QD
Lorlatinib	Not estimable vs 9.3 mo (crizotinib) HR: 0.28; $P < .0001$	CROWN (296)	ALK-positive mNSCLC	100 mg PO QD
Ceritinib	16.6 mo vs 8.1 mo (chemotherapy) HR: 0.55; $P < .0001$	ASCEND-4 (376)	ALK-positive mNSCLC	450 mg PO QD with food
Crizotinib	10.9 mo vs 7.0 mo (chemotherapy) HR: 0.45; $P < .001$	PROFILE 1014 (343)	ALK- or ROS1-positive mNSCLC	250 mg PO BID

CROWN: 5-Year Update of First-line Lorlatinib vs Crizotinib for Advanced ALK-Positive NSCLC¹³



Median PFS follow-up: 60.2 mo for lorlatinib vs 55.1 mo for crizotinib. Results per investigator assessment.

- National guidelines currently list the following treatment options as **subsequent therapy** for advanced ALK-positive NSCLC³
 - If progression on alectinib, brigatinib, ceritinib, ensartinib, or lorlatinib
 - If asymptomatic, continue ALK TKI therapy or switch to lorlatinib or consider definitive local therapy
 - If symptomatic with brain metastases, see choices for asymptomatic disease
 - If symptomatic with systemic metastases with limited progression, see choices for asymptomatic disease or treat as for multiple lesions (next)
 - If symptomatic with systemic metastases with multiple lesions, switch to lorlatinib or systemic therapy (eg, PD-1/PD-L1 inhibitor + chemotherapy)
 - If progression on crizotinib
 - If asymptomatic, continue crizotinib therapy or switch to alectinib, brigatinib, ceritinib, ensartinib, or lorlatinib or consider definitive local therapy
 - If symptomatic with brain metastases, switch to alectinib, brigatinib, ceritinib, ensartinib, or lorlatinib or consider definitive local therapy
 - If symptomatic with systemic metastases with limited progression, continue crizotinib therapy or consider definitive local therapy or treat as for multiple lesions (next)
 - If symptomatic with systemic metastases with multiple lesions, switch to alectinib, brigatinib, ceritinib, ensartinib, or lorlatinib or systemic therapy (eg, PD-1/PD-L1 inhibitor + chemotherapy)
- Lorlatinib can be considered in the presence of resistant mutations, including ALK G1202R and L1196M (excepting compound L1196M/G1202R)
- Clinical trials should be considered for any patient with advanced NSCLC, where possible

ALKi, ALK inhibitor; ctDNA, circulating tumor DNA; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; ITT, intention-to-treat; mNSCLC, metastatic non-small-cell lung cancer; NR, not reached; PFS, progression-free survival.

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