ASCO® Guidelines

Therapy for Stage IV Non-Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2023.3				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
NOTE: • For recommendations with multiple treatment options of the same evidence quality and strength of recommendation, the decision of which agent to offer should be tailored to each patient incorporating both efficacy and toxicity. • All biomarkers should be available at the time of decision-making				
Clinical Question 1: What are the most effective first-line treatment options for patients' status based on the driver alterations:				
EGFR	***Exon 19 deletion, Exon 21 L858R substitution***			
	1.1. Clinicians should offer **osimertinib**.	EB	H	S
	Qualifying Statement: Although Recommendation 1.1 addresses many patients in the target population, the guideline manuscript presents additional options that may be reasonable, based on the evidence reviewed. In addition, use of osimertinib in patients previously treated with adjuvant tyrosine kinase inhibitors is not reflected in this guideline.			
	Others			
	1.2. For other activating *EGFR* alterations, (G719X, L861Q, S768I), clinicians may offer **afatinib.**	EB	L	S
	1.2.1. or **osimertinib.**	IC	L	W
	1.2.2. or standard treatment following the non-driver alteration guideline.	IC	L	W
	Qualifying statement: Recommendation 1.2, 1.2.1, and 1.2.2 excludes exon 20 insertion alterations, T790M.			
	1.3. For any activating *EGFR* alteration, regardless of PD-L1 expression levels (including exon 20 insertions), single-agent immune checkpoint inhibitors should not be offered as first-line therapy.	EB	M	S
	Exon 20 insertions			
	1.4. Clinicians may offer chemotherapy and **amivantamab.**	EB	M	S

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	1.5. If amivantamab is not available, clinicians should offer standard treatment following the non-driver alteration guideline.	EB	M	S
ALK	**1.6.** Clinicians should offer **alectinib** or **brigatinib** or **lorlatinib.**	EB	H	S
	1.7. If alectinib, brigatinib, or lorlatinib are not available, clinicians should offer **ceritinib** or **crizotinib**.	EB	H	S
ROS1	**1.8.** Clinicians may offer **crizotinib** or **entrectinib**.	EB	M	S
	1.9. If crizotinib or entrectinib are not available or not tolerated, clinicians may offer **ceritinib** or **lorlatinib**.	EB	L	W
***BRAF*^{V600E}**	**1.10.** Clinicians may offer **dabrafenib and trametinib,** or **encorafenib and binimetinib.**	EB	L	S
	1.11. If dabrafenib and trametinib, or encorafenib and binimetinib are not available, clinicians may offer standard first-line therapy following the non-driver alteration guideline.	IC	L	S
***MET* exon 14 skipping mutation**	**1.12.** Clinicians may offer **capmatinib** or **tepotinib**.	EB	L	S
	1.13. If **capmatinib** or **tepotinib** is not available, clinicians may offer standard first-line therapy following the non-driver alteration guidelines**.**	IC	L	S
***RET* rearrangement**	**1.14.** Clinicians should offer **selpercatinib**.	EB	H	S
	1.15. If selpercatinib is not available, clinicians may offer **pralsetinib**.	EB	M	S
	1.16. If selpercatinib or pralsetinib are not available, clinicians may offer standard therapy following the non-driver alteration guideline.	IC	L	W
***NTRK* rearrangement**	**1.17.** Clinicians may offer **entrectinib** or **larotrectinib**.	EB	L	S
	1.18. If entrectinib or larotrectinib are not available**,** clinicians may offer standard therapy following the non-driver alteration guideline.	IC	L	W
Additional first-line treatment recommendations	**1.19.** For patients with a poor PS, tyrosine kinase inhibitor may be offered based on drug access and toxicity profile.	IC	L	W
	1.20. Comprehensive genomic biomarker test results should be available and used to guide treatment.	EB	H	S
	Qualifying statement: PD-L1 IHC alone should not be used to guide treatment decisions.			

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Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
	1.21. Patients with advanced lung cancer should be referred to interdisciplinary palliative care teams (consultation) that provide inpatient and outpatient care early in the course of disease, alongside active treatment of their cancer.	EB	H	S
Clinical Question 2: What are the most effective second-line and subsequent treatment options for patients based on the driver alterations:				
NOTE: • Due to development of potentially targetable resistance mechanisms, every effort should be made to assess for presence of new mutation by tissue and/or blood NGS testing. • If patients have received all targeted options, or if no targeted options are available, clinicians may offer standard therapy following the non-driver alteration guideline.				
EGFR	***Exon 19 deletion, Exon 21 L858R substitution***			
	2.1. For patients that develop *EGFR* T790M resistance alterations in tumor after first- or second-generation *EGFR* TKIs, clinicians should offer **osimertinib**.	EB	H	S
	2.2. For patients who have progressed on **osimertinib** or other EGFR TKIs without emergent T790M or other targetable alterations, clinicians should offer platinum-based chemotherapy following the non-driver alteration guideline.	EB	M	S
	Qualifying statement: Anti-PD-(L)1 agents with platinum chemotherapy are not recommended although other emerging combination strategies may be considered and are discussed in manuscript.			
	Others			
	2.3. For patients with an exon 20 insertion alteration who have received prior treatment with platinum chemotherapy, clinicians may offer treatment with **amivantamab**.	EB	L	S
ALK	**2.4.** For patients who have previously received **crizotinib**, clinicians should offer **alectinib**, **brigatinib**, or **ceritinib** and may offer **lorlatinib**.	EB	M	S
	2.5. For patients who have previously received other *ALK* inhibitors including **alectinib** or **brigatinib**, clinicians may offer **lorlatinib**.	EB	L	S
ROS1	**2.6.** For patients who have previously received **crizotinib** or **entrectinib or ceritinib,** clinicians may offer **lorlatinib**.	EB	L	W
	2.7. Clinicians should offer platinum-based chemotherapy following the non-driver alteration guideline.	IC	L	S
***BRAF*^{V600E}**	**2.8.** For patients who have not received *BRAF* therapy, clinicians may offer **dabrafenib and trametinib** or **encorafenib and binimetinib.**	EB	L	S

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Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
	2.9. For patients who have previously received *BRAF* or *MEK* targeted therapy, clinicians should offer standard first-line therapy following the non-driver alteration guideline.	IC	L	S
	2.10. For *BRAF* alterations other than $BRAF^{V600E}$ alterations, clinicians should offer standard therapy following the non-driver alteration guideline.	IC	L	S
***MET* exon 14 skipping mutation**	**2.11.** For patients who have not received *MET*-targeted therapy, clinicians may offer **capmatinib** or **tepotinib**.	EB	L	S
	2.12. For patients previously treated with *MET*-targeted therapy, clinicians should offer standard therapy following the non-driver alteration guideline.	IC	L	S
***RET* rearrangement**	**2.13.** For patients who have not received a *RET* inhibitor, clinicians should offer **selpercatinib** or **pralsetinib**.	EB	M	S
	2.14. If **selpercatinib** or **pralsetinib** is not available, clinicians may offer treatment following the non-driver alteration guideline.	IC	L	S
***NTRK* rearrangement**	**2.15.** For patients who have not received an *NTRK* inhibitor, clinicians should offer **entrectinib** or **larotrectinib**.	EB	L	S
	2.16. If entrectinib or larotrectinib is not available, clinicians may offer standard therapy following the non-driver alteration guideline.	IC	L	S
HER2	**2.17.** Clinicians may offer treatment with **trastuzumab deruxtecan**.	EB	L	S
***KRAS* G12C**	**2.18.** Clinicians may offer treatment with **sotorasib**.	EB	M	S
	2.19. Clinicians may offer treatment with **adagrasib**.	EB	L	S
	Qualifying Statement: Note that adagrasib and sotorasib are approved for patients who have received prior chemotherapy and/or anti-PD-(L)1 for patients with advanced KRAS *G12C mutant NSCLC. In the first-line setting, these patients should be offered standard first-line treatment with immune checkpoint inhibitor therapy and/or chemotherapy following the non-driver alteration guideline.*			

Abbreviations. *ALK*, anaplastic lymphoma kinase; EB, evidence based; *EGFR*, epidermal growth factor receptor; H, high; HER2, human epidermal growth factor receptor 2; IC, informal consensus; L, low; M, moderate; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; PD-L1, programmed death ligand 1; PS, performance status; S, strong; TKI, tyrosine kinase inhibitor; W, weak