ASCO® Guidelines

Therapy for Stage IV Non-Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
Updated Recommendations				
What is the most effective second-line therapy for patients with stage IV NSCLC with a sensitizing *EGFR* mutation and performance status of 0-2?	**2.3.** For patients with advanced NSCLC with an *EGFR* exon 20 insertion and a performance status of 0-2, who have received prior platinum-based chemotherapy, clinicians may offer amivantamab monotherapy.	EB	L	W
	Qualifying Statement: In the absence of head-to-head comparison of amivantamab with standard second-line therapies, or with evolving exon 20 insertion treatments such as mobocertinib, no recommendation for sequencing can be made. Treatment should be individualized.			
	2.4. For patients with advanced NSCLC with an *EGFR* exon 20 insertion and a performance status 0-2, who have received prior platinum-based chemotherapy, clinicians may offer mobocertinib monotherapy.	EB	L	W
	Qualifying Statement: In the absence of head-to-head comparison of mobocertinib with standard second-line therapies, or with evolving exon 20 insertion treatments, no recommendation for sequencing can be made. Treatment should be individualized.			
Unchanged Recommendations				
What is the most effective first-line therapy for patients with stage IV NSCLC with a tumor *EGFR*-sensitizing mutation and PS 0-2?	**1.1.** For patients with a sensitizing (L858R/Exon19 deletion, with or without a concomitant T790M mutation) *EGFR* mutation with stage IV NSCLC and a PS of 0-2 who have not had previous systemic therapy, clinicians should use osimertinib monotherapy	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. This statement applies to all recommendations with the word "should." In addition, use of osimertinib in patients previously treated with adjuvant or consolidation tyrosine kinase inhibitors is not part of this guideline.			

Therapy for Stage IV Non-Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
	1.2. For patients with a sensitizing (L858R/Exon19deletion) *EGFR* mutation with stage IV NSCLC and a PS of 0-2 who have not had previous systemic therapy and for whom osimertinib is not available, clinicians may use combination gefitinib with doublet chemotherapy (platinum/pemetrexed with maintenance pemetrexed).	EB	H	M
	1.3. For patients with a sensitizing (L858R/Ex19del) *EGFR* mutation with stage IV NSCLC and a PS of 0-2 previously untreated with systemic therapy and for whom osimertinib is not available, clinicians may use dacomitinib monotherapy.	EB	H	M
	1.4. For patients with a sensitizing (L858R/Ex19del) *EGFR* mutation with stage IV NSCLC and a PS of 0-2 who have not had previous systemic therapy, and do not have access to osimertinib, clinicians may use monotherapy with afatinib or erlotinib/bevacizumab or erlotinib/ramucirumab.	EB	I	M
	1.5. For patients with a sensitizing (L858R/Ex19del) *EGFR* mutation with stage IV NSCLC and a PS of 0-2 who have not had previous systemic therapy, and do not have access to other regimens, clinicians may use monotherapy with gefitinib, erlotinib, or icotinib.	EB	I	M
	1.6. For patients with a sensitizing (L858R/Ex19del) *EGFR* mutation with stage IV NSCLC and a PS of 3, who have not had previous systemic therapy, monotherapy with an EGFR tyrosine kinase inhibitor may be given, with the choice dependent on access and toxicity profile of each agent.	IC	L	W
	1.7. For patients with an activating *EGFR* mutation other than exon 20 insertion mutations, T790M, L858R or Ex19Del, (e.g., G719X, L861Q, S768I), and a PS of 0-2 who have not had previous systemic therapy, clinicians may offer afatinib monotherapy	IC	L	M
	or osimertinib	IC	L	W
	or standard treatment based on non-driver mutation guideline	IC	L	M
	1.8. For patients with any activating *EGFR* mutation, regardless of PD-L1 expression levels (including exon 20 insertion mutations), single agent immunotherapy should not be used as first-line therapy.	IC	L	M

Therapy for Stage IV Non-Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
What is the most effective second-line therapy for patients with stage IV NSCLC with a sensitizing *EGFR* mutation who received a first-line EGFR TKI and experienced disease progression?	**2.1.** For patients with a sensitizing (L858R/Ex19del) *EGFR* mutation with stage IV NSCLC and a PS of 0-2 who have had previous EGFR targeted therapy (except osimertinib) and subsequently have an *EGFR* T790M resistance mutation, clinicians should recommend osimertinib.	EB	H	S
	2.2. For patients with any *EGFR* mutation who have progressed on EGFR TKIs with no T790M mutation OR whose disease has progressed on osimertinib, clinicians may treat based on the non-driver mutation guidelines.	IC	L	M
What is the most effective third-line therapy for patients with tumor *EGFR*-sensitizing mutation positive status who have had prior platinum-based chemotherapy and EGFR TKI?	See second-line above.	-	-	-
What is the most effective first-line therapy for patients with stage IV NSCLC with *ALK* gene rearrangement and PS 0 to 1 or possibly PS 2?	**3.1.** For patients with an *ALK* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians should offer alectinib or brigatinib	EB	H	S
	or lorlatinib.	EB	L	W
	3.2. For patients with an *ALK* rearrangement, a PS of 0-2, and previously untreated NSCLC, if alectinib, brigatinib, or lorlatinib are not available, clinicians should offer ceritinib or crizotinib.	EB	H	S
What is the most effective second-line therapy for patients with stage IV NSCLC with *ALK* rearrangement with progression after first-line crizotinib?	**4.2.** For patients with an *ALK* rearrangement, a PS of 0-2, and have previously received crizotinib in the first-line setting, clinicians should offer alectinib, brigatinib, or ceritinib in the second-line setting.	EB	M	S
What is the most effective second or third-line therapy	**4.1.** For patients with an *ALK* rearrangement, a PS of 0-2, and have previously received alectinib or brigatinib, clinicians may offer lorlatinib.	IC	L	M

Therapy for Stage IV Non-Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
for patients with stage IV NSCLC with *ALK* gene rearrangement and PS 0-2?	**4.3.** For patients with an *ALK* rearrangement, a PS of 0-2 and have received prior crizotinib in the first-line setting and either alectinib, brigatinib, or ceritinib in the second-line setting, clinicians may offer lorlatinib	IC	L	M
	or clinicians may offer standard therapy following the non-driver mutation guideline in the third-line setting	IC	L	W
What is the most effective first-line therapy for patients with stage IV NSCLC with *ROS1* rearrangement?	**5.1.** For patients with *ROS1* rearrangement, a PS of 0-2, previously untreated lung cancer, clinicians may offer crizotinib or entrectinib.	IC	L	M
	5.2. For patients with *ROS1* rearrangement, a PS of 0-2, previously untreated lung cancer, clinicians may offer standard therapy based on the non-driver mutation guideline.	IC	L	M
	5.3. For patients with *ROS1* rearrangement, a PS of 0-2, previously untreated lung cancer, clinicians may offer ceritinib or lorlatinib.	IC	L	W
What is the most effective second-line therapy for patients with *ROS1* rearrangement?	**6.1.** For patients with *ROS1* rearrangement, a PS of 0-2, previously treated with ROS1 targeted therapy, clinicians should offer standard therapy following the non-driver mutation guideline.	IC	L	M
	6.2. For patients with *ROS1* rearrangement, a PS of 0-2, previously treated with non-targeted therapy first-line, clinicians may offer crizotinib or entrectinib or ceritinib.	IC	L	M
For patients with a *BRAF* V600E mutation, what is the optimal first-line therapy?	**7.1.** For patients with a *BRAF* V600E mutation, clinicians may offer dabrafenib/trametinib as first-line treatment.	IC	L	M
	7.2. For patients with a *BRAF* V600E mutation, clinicians may offer standard first-line therapy following the non-driver alterations guideline.	IC	L	M
What is appropriate second-line therapy and above for patients with a *BRAF* V600E mutation?	**8.1.** For patients with a *BRAF* V600E mutation who have had previous B-RAF/MEK targeted therapy, clinicians should offer standard first-line therapy following the non-driver alterations guideline.	IC	L	M
	8.2. For patients with a *BRAF* V600E mutation who have had previous chemotherapy or chemotherapy/immunotherapy, clinicians may offer dabrafenib/trametinib	IC	L	M
	or dabrafenib alone	IC	L	W
	or vemurafenib	IC	L	W

Therapy for Stage IV Non-Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
	8.3. For patients with a *BRAF* V600E mutation who have had previous chemotherapy, immunotherapy, and BRAF targeted therapy, clinicians should offer treatment following the non-driver mutation guideline.	IC	L	M
	8.4. For patients with *BRAF* mutations other than *BRAF* V600E mutations, clinicians should offer standard therapy following the non-driver mutation guidelines.	IC	L	M
What is the optimal first-line therapy for patients with a *MET* exon 14 skipping mutation?	**9.1.** For patients with a *MET* exon 14 skipping mutation, a PS of 0-2, previously untreated NSCLC, clinicians may offer MET-targeted therapy with capmatinib or tepotinib.	IC	L	M
	9.2. For patients with a *MET* exon 14 skipping mutation, a PS of 0-2, previously untreated NSCLC, clinicians may offer standard first-line therapy following the non-driver mutations guidelines**.**	IC	L	M
What is the optimal second-line therapy for patients with a *MET* exon 14 skipping mutation?	**10.1.** Patients with *MET* abnormalities other than exon 14 skipping mutations, a PS of 0-2, or those previously treated with MET targeted therapy, clinicians should offer standard therapy following the non-driver mutations guidelines.	IC	L	M
	10.2. For patients with a *MET* Exon 14 skipping mutation, a PS of 0-2, who have previously received or been ineligible for first-line chemotherapy with or without immunotherapy therapy, clinicians may offer MET targeted therapy with capmatinib or tepotinib.	IC	L	M
What is the most effective first-line therapy for patients with stage IV NSCLC with *RET* rearrangement and PS 0-2?	**11.1.** For patients with a *RET* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer selpercatinib or pralsetinib.	IC	L	W
	11.2. For patients with a *RET* rearrangement, a PS of 0-2, previously untreated NSCLC, clinicians may offer standard therapy following the non-driver mutation guideline.	IC	L	M
What is the most effective second-line therapy for patients with stage IV NSCLC with *RET* rearrangement with a PS 0-2?	**12.1.** For patients with *RET* rearrangement who have had previous *RET* targeted therapy, clinicians may offer treatment per the non-driver mutation guideline.	IC	L	M
	12.2. For patients with *RET* rearrangement who have not received *RET* targeted therapy, clinicians may offer selpercatinib	IC	L	M
	or pralsetinib.	IC	L	W
What is the most effective first-line therapy for	**13.1.** For patients with a *NTRK* fusion, a PS of 0-2, previously untreated lung cancer, clinicians may offer entrectinib or larotrectinib.	IC	L	M

Therapy for Stage IV Non-Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline				
Clinical Question	**Recommendation**	**Type**	**Evidence Quality**	**Strength**
patients with stage IV NSCLC with a *NTRK* rearrangement and PS 0-2?	**13.2.** For patients with *NTRK* fusion, a PS of 0-2, previously untreated lung cancer, clinicians may offer standard therapy following the non-driver mutation guideline.	IC	L	M
What is the most effective second-line therapy for patients with stage IV NSCLC with a *NTRK* rearrangement and PS 0-2?	**14.1.** For patients with *NTRK* fusion previously treated with a NTRK inhibitor, clinicians may offer standard therapy following the non-driver mutation guideline.	IC	L	M
	14.2. For patients with *NTRK* fusion previously treated lung cancer who have not received an NTRK inhibitor, clinicians may offer entrectinib or larotrectinib.	IC	L	M
What is the most effective treatment for previously treated patients with stage IV NSCLC with a *HER2* mutation?	**15.1.** For patients with advanced NSCLC and an activating human epidermal growth factor receptor 2 (*HER2, ERBB2*) mutation, as detected by an FDA-approved test, and who have received prior systemic therapy, clinicians may offer treatment (monotherapy) with trastuzumab deruxtecan.	EB	L	W
	Qualifying Statement: In the absence of head-to-head comparison of trastuzumab deruxtecan with standard first-line therapy, treatment naïve patients with advanced NSCLC and an activating human epidermal growth factor receptor 2 (HER2, ERBB2) mutation should be offered standard first-line treatment as per non-driver alteration guidelines.			
What is the most effective treatment for previously treated patients with stage IV NSCLC with a *KRAS* mutation?	**16.1.** For patients with advanced NSCLC and a *KRAS-G12C* mutation who have received prior systemic therapy, clinicians may offer treatment (monotherapy) with sotorasib.	EB	L	W
	Qualifying Statement: In the absence of head-to-head comparison of sotorasib with standard first-line therapy, treatment naïve patients with advanced NSCLC and a KRAS-G12C mutation should be offered standard first-line treatment as per non-driver alteration guidelines.			
What is the most effective therapy for patients with stage IV NSCLC with a *KRAS-G12C* mutation who have previously received treatment with chemotherapy and anti-PD(L)-1 therapy?	**16.2.** For patients with advanced NSCLC and a *KRAS-G12C* mutation who have received prior systemic therapy with chemotherapy and anti-PD(L)-1 therapy, clinicians may offer treatment (monotherapy) with adagrasib.	EB	L	W
	Qualifying Statement: Note that adagrasib is approved after failure of first-line treatment for patients with advanced KRAS-G12C *mutant NSCLC. In the first-line setting, these patients should be offered standard first-line treatment with immunotherapy and/or chemotherapy as per non-driver alteration guidelines.*			

Abbreviations. *ALK*, anaplastic lymphoma kinase; EB, evidence based; *EGFR*, epidermal growth factor receptor; FC, formal consensus; H, high; HER2, human epidermal receptor factor 2; I, intermediate; IC, informal consensus; L, low; M, moderate; N/A, not applicable; 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