ASCO GUIDELINES

SYSTEMIC THERAPY FOR STAGE IV NON-SMALL CELL LUNG CANCER: AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL PRACTICE GUIDELINE UPDATE		
Clinical Question	**Recommendation**	**Evidence Rating**
Which patients with stage IV NSCLC should be treated with chemotherapy?	For patients with performance status (PS) of 0 or 1, *receiving chemotherapy* a combination of two cytotoxic drugs is recommended. Platinum combinations are recommended over nonplatinum therapy; however, nonplatinum therapy combinations are recommended for patients who have contraindications to platinum therapy. Chemotherapy also may be used to treat selected patients with PS of 2 who desire aggressive treatment after a thorough discussion of the risks and benefits of such treatment.	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	Because there is no cure for patients with stage IV NSCLC, early concomitant assistance of palliative care has improved the survival and well-being of patients and is therefore recommended.	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
First-Line Therapy		
What is the most effective first-line therapy for patients with negative or unknown tumor *EGFR*-sensitizing mutation, *ALK* or *ROS1* gene rearrangement status, and PS 0-1 (or possibly PS 2)?		
What is the most effective first-line therapy for patients with negative or unknown tumor *EGFR*-sensitizing mutation status or *ALK* or *ROS1* gene rearrangement status and with PS of 0 or 1 (or possibly PS of 2)?	Treatment options include:	
	For patients with high PDL-1 expression (TPS ≥ 50%), single-agent pembrolizumab should be used in the absence of contraindications to immune checkpoint therapy.	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	There are insufficient data to recommend other checkpoint inhibitors or to recommend combination checkpoint inhibitors or immune checkpoint therapy with chemotherapy in the first-line setting at the time of this update	

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	For patients with low PDL-1 expression (TPS < 50%), clinicians should offer standard chemotherapy with platinum-based two drug combinations as outlined in the 2015 update	Type: Evidence-based, benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	or nonplatinum based two-drug therapy as outlined in the 2015 update for patients not deemed candidates for platinum-based therapy	Type: Evidence-based, benefits outweigh harms Evidence quality: Intermediate Strength of recommendation: Weak
	Cisplatin-based combinations • cisplatin/docetaxel • cisplatin/paclitaxel • cisplatin/pemetrexed • cisplatin/vinorelbine	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	Carboplatin-based combinations • carboplatin/nab albumin-bound paclitaxel • carboplatin/paclitaxel • carboplatin/pemetrexed • carboplatin/docetaxel	Type: Evidence-based; benefits outweigh harms Evidence quality: high Strength of recommendation: Strong
	Nonplatinum Doublets	Type: Evidence-based; benefits outweigh harms Evidence quality: Intermediate Strength of recommendation: Weak
What is the most effective first-line therapy for patients with stage IV NSCLC with negative or unknown *EGFR/ALK/ROS1* status, non-squamous cell carcinoma and no contraindications to bevacizumab?	For patients receiving carboplatin plus paclitaxel, the Update Committee recommends the addition of bevacizumab 15 mg/kg once every 3 weeks, except for patients with SCC histologic type, clinically significant hemoptysis, inadequate organ function, Eastern Cooperative Oncology Group PS > 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension; bevacizumab may be continued, as tolerated, until disease progression.	

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	There is insufficient evidence to recommend bevacizumab in combination with pemetrexed plus carboplatin for patients who do not have contraindications to bevacizumab.	
What is the most effective first-line therapy for patients with stage IV NSCLC with PS 2, non-squamous cell carcinoma, and negative or unknown tumor *EGFR*-sensitizing mutation and *ALK* or *ROS1* gene rearrangement status?	In the context of shared decision-making, combination therapy, single-agent chemotherapy, or palliative therapy alone may be used for patients in this population with PS 2.	Chemotherapy: Type: Evidence-based; benefits outweigh harms Evidence quality: Intermediate Strength of recommendation: Weak Palliative Care: Type: Evidence-based; benefits outweigh harms Evidence quality: Intermediate Strength of recommendation: Strong
What is the most effective first-line therapy for patients with stage IV NSCLC with squamous cell carcinoma, negative or unknown tumor *EGFR*-sensitizing mutation, *ALK* or *ROS1* gene rearrangement status, and PS 0-1 (or possibly PS 2)?	For patients with high PDL-1 expression (TPS ≥ 50%), single-agent pembrolizumab should be used in the absence of contraindications to immune checkpoint therapy	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	There are insufficient data to recommend other checkpoint inhibitors or to recommend combination checkpoint inhibitors or immune checkpoint inhibitors with chemotherapy in the first-line setting.	Type: Evidence-based, benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	For patients with low (TPS < 50%) or unknown PDL-1 expression, clinicians should offer standard chemotherapy with platinum-based two drug combinations as outlined in the 2015 update	
	or nonplatinum based two drug therapy as outlined in the 2015 update for patients not deemed candidates for platinum-based therapy	Type: Evidence-based, benefits outweigh harms Evidence quality: Intermediate Strength of recommendation: Weak

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	For patients with stage IV squamous NSCLC receiving cisplatin and gemcitabine, the panel recommends neither for nor against the addition of necitumumab to chemotherapy.	Type: Evidence-based; benefits outweigh harms Evidence quality: Intermediate Strength of recommendation: Weak
	Cisplatin-based combinations • cisplatin/docetaxel • cisplatin/gemcitabine • cisplatin/paclitaxel • cisplatin/vinorelbine	
	Carboplatin-based combinations • carboplatin/gemcitabine • carboplatin/paclitaxel • carboplatin/nab albumin-bound paclitaxel • carboplatin/docetaxel	
	Nonplatinum Doublets	
What is the most effective first therapy for patients with stage IV NSCLC with negative or unknown *EGFR/ALK* status, SCC, and PS 2?	In the context of shared decision making, combination chemotherapy, single-agent therapy, or palliative therapy alone may be used for patients with stage IV NSCLC with negative or unknown *EGFR/ALK* status, SCC, and PS 2.	Chemotherapy Type: Evidence-based, benefits outweigh harms Evidence quality: Intermediate Strength of recommendation: Weak Palliative care Type: Evidence-based, benefits outweigh harms Evidence quality: Intermediate Strength of recommendation: Strong
What is the most effective first-line therapy for patients with stage IV	If patients have stage IV NSCLC and a sensitizing *EGFR* mutation, first-line options are:	

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NSCLC with a tumor *EGFR*-sensitizing mutation and PS 0-2?	afatinib	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	erlotinib	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	gefitinib	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
Second-Line therapy		
What is the most effective first-line therapy for patients with stage IV NSCLC with a tumor *EGFR*-sensitizing mutation and PS 0-2?		
What is the most effective therapy for patients with squamous or non-squamous cell carcinoma who have received one prior chemotherapy regimen?	Squamous and non-squamous and negative/unknown *EGFR* mutation, *ALK* or *ROS1* gene rearrangement	
	For patients who received first-line chemotherapy and have not received prior immune checkpoint inhibitor therapy, clinicians should use single-agent nivolumab, pembrolizumab, or atezolizumab in patients with positive tumor PDL-1 expression (TPS ≥ 1%, 22C3 assay), in the absence of contraindications to immune checkpoint therapy	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	For patients with negative or unknown tumor PDL-1 expression (TPS < 1%) who received first line-therapy chemotherapy, clinicians should use single-agent nivolumab or atezolizumab in the absence of contraindications to imm une checkpoint therapy	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	There are insufficient data to recommend combination checkpoint inhibitors or immune checkpoint inhibitors with chemotherapy in the second-line setting	

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	For patients who received an immune checkpoint inhibitor as first-line therapy, clinicians should offer standard platinum-based chemotherapy as outlined in the 2015 update	Type: Evidence-based, benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
	or nonplatinum based two-drug therapy if platinum contraindicated as outlined in the 2015 update	Type: Informal consensus; benefits outweigh harms Evidence quality: Low Strength of recommendation: Strong
	For patients with contraindications to immune checkpoint inhibitor therapy after first-line chemotherapy, docetaxel is recommended as second-line therapy	Type: Evidence-based, benefits outweigh harms Evidence quality: Intermediate Strength of recommendation: Moderate
	Non-squamous only:	
	Patients with non-squamous cell carcinoma who have not previously received pemetrexed-based first-line or maintenance therapy should be offered pemetrexed second-line	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong
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?	For patients with stage IV NSCLC with a sensitizing *EGFR* mutation and progression following first-line therapy with an EGFR tyrosine kinase inhibitor (TKI) with the presence of the T790M resistance mutation, clinicians should recommend osimertinib	Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of Recommendation: Strong
	If the T790M mutation is not present, clinicians may offer treatment with a platinum doublet	Type: Informal consensus; benefits outweigh harms Evidence quality: Low Strength of recommendation: Strong

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ROS1 rearrangement – What is the most effective second-line therapy for patients with *ROS1* rearrangement?	Patients who have not received prior crizotinib. If patients have *ROS1* rearrangement and have not received crizotinib in the first-line, single-agent crizotinib may be offered as second-line therapy	Type: Informal consensus; benefits outweigh harms Evidence quality: Low Strength of recommendation: Moderate
	Patients who received prior crizotinib. If patients have *ROS1* rearrangement and have received crizotinib in the first-line, then they may be offered platinum-based therapy in the second-line with or without bevacizumab	Type: Informal consensus; benefits outweigh harms Evidence quality: Insufficient Strength of recommendation: Moderate
What is the most effective therapy for patients with stage IV NSCLC and *BRAF* mutations who have received prior chemotherapy?	Clinicians may offer atezolizumab, nivolumab, or pembrolizumab (if PDL-1 TPS >1%) with *BRAF* unless the patient received immune checkpoint therapy in the first-line setting	Type: Informal consensus; benefits outweigh harms Evidence quality: Insufficient Strength of recommendation: Weak
	If patients with *BRAF* mutations received immunotherapy in second-line, clinicians may offer patients dabrafenib alone or in combination with trametinib in third-line	Type: Informal consensus; benefits outweigh harms Evidence quality: Insufficient Strength of recommendation: Moderate
Third-Line Therapy		
What is the most effective third-line therapy for patients with stage IV NSCLC with non-squamous cell carcinoma, negative or unknown tumor *EGFR*-sensitizing mutation/*ALK* or *ROS1* gene rearrangement status and PS 0-1 or possibly PS 2?	For the majority of patients who received chemotherapy with or without bevacizumab and immune checkpoint therapy, clinicians should offer the options of single-agent pemetrexed or docetaxel in the third-line setting	Type: Informal consensus; benefits outweigh harms Evidence quality: Low Strength of recommendation: Strong

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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?	There are insufficient data to recommend immunotherapy in preference to chemotherapy (pemetrexed or docetaxel) for patients with *EGFR*-sensitizing mutations who have received at least one EGFR-TKI and subsequent platinum-based chemotherapy	Type: Informal consensus Evidence quality: Insufficient Strength of recommendation: Weak
Fourth-Line Therapy		
Is there a role for cytotoxic therapy for patients who have received three prior regimens and good PS?	Data are not sufficient to make a recommendation for or against using cytotoxic drugs as fourth-line therapy; patients should consider experimental treatment, clinical trials, and continued best supportive (palliative) care.	

