

SAUDI GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF LUNG CANCER

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Saudi Lung Cancer Association
المجموعة السعودية لسرطان الرئة





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المجموعة السعودية لسرطان الرئة



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For interactive lung cancer guideline and point of care resources click below :

- Non-Small Cell Lung Cancer
- Small Cell Lung Cancer

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ABBREVIATIONS:

CBC	Complete blood count
LFT	liver function test
NOS	Not otherwise specified
PCR	Polymerase chain reaction
CK7	Cytokeratin 7
EGFR	Epidermal growth factor receptor
IHC	Immunohistochemistry
EML4-ALK	Echinoderm microtubule-associated protein-like 4 & Anaplastic lymphoma kinase
TTF-1	Thyroid transcription factor 1
MRI	Magnetic Resonance Imaging
SBRT	Stereotactic Body Radiation Therapy
TKIs	Tyrosine kinase inhibitors



EVIDENCE LEVELS:

The following evidence levels (EL) were adopted for these guidelines:

- (EL-1) High Level: well conducted phase III randomized studies or well done meta- analyses.
- (EL-2) Intermediate Level: good phase II data or phase III trials with limitations.
- (EL-3) Low Level: observational or retrospectives studies expert opinions.
General Oncology Recourses

I. ALL LUNG CANCER PATIENTS

General Lung Cancer Recourses

1.1 INITIAL PATIENT ASSESSMENT.

- 1.1.1 Perform history and physical examination, and document smoking history and performance status.
- 1.1.2 Perform the following laboratory tests: Complete blood count (CBC), differential, liver function test (LFT), renal function, electrolytes, calcium, serum albumin, magnesium and phosphorus.
- 1.1.3 Two-view chest x-ray.



1.2 DIAGNOSIS

- 1.2.1 Obtain adequate tissue specimen for diagnostic and predictive markers.
- 1.2.2 Confirm histopathological diagnosis of lung cancer and determine the histological subtypes of non-small cell lung cancer i.e. adenocarcinoma vs squamous cell vs large cell carcinoma using most recent pathological classification of lung cancer. Utilization of proper immunohistochemistry is try staining (minimal panel to include TTF1 (most important), CK7, and CK20 for adenocarcinoma and P40 (preferred) or P63 to minimize the diagnosis of “not otherwise specified” (NOS).
- 1.2.3 Obtain epidermal growth factor receptor (EGFR) mutation testing by PCR in certified laboratory for all histology except pure squamous cell.
- 1.2.4 In EGFR Wild Type (WT) tumors, obtain EML4-ALK fusion test by FISH in certified laboratory. IHC can be done to screen for positive tumors to be tested by FISH.
- 1.2.5 For patients with wild type EGFR & ALK, consider obtaining the ROS1 test.
- 1.2.6 If immune therapy is considered, PDL1 testing by IHC can be done.

1.3 STAGING

1.3.1. Non-Small Cell Lung Cancer

- 1.3.1.1 Obtain contrast enhanced CT scan of the chest and upper abdomen.



- 1.3.1.2 Obtain Magnetic Resonance Imaging (MRI) of brain for stages IB-IV (preferred over contrast enhanced CT scan).
- 1.3.1.3 Obtain total body positron emission tomography/computed tomography(PET/CT) scan when available if the patient is considered for radical therapy (such as surgery or chemoradiotherapy).
- 1.3.1.4 Obtain bone scan for stages IB-IV if PET/CT is not done.
- 1.3.1.5 Perform mediastinoscopy in selected cases; i.e. clinical stages (IB-III).Mediastinoscopy can be omitted if PET/CT scan is negative.
- 1.3.1.6 Determine precise TNM staging using 7th edition (2009).

1.3.2. Small Cell Lung Cancer

- 1.3.2.1 Obtain contrast enhanced CT scan of chest and upper abdomen.
- 1.3.2.2 Obtain Magnetic Resonance Imaging (MRI) of brain for stages IB-IV (preferred over contrast enhanced CT scan which can be if MRI is not available).
- 1.3.2.3 Obtain PET/CT scan if the disease in stages I-III.
- 1.3. 2.4 Obtain bone scan if PET/CT is not done.
- 1.3.2.5 Determine precise TNM staging using 7th edition (2009).



1.4 PRE-TREATMENT ASSESSMENT

- 1.4.1 Discuss all new cases in a multidisciplinary conference (Tumor Board).
- 1.4.2 Obtain cardiopulmonary assessment (Pulmonary Function test, 6 minute walk, ECG and echo) if surgery considered and PFT for curative radiotherapy is considered.

1.5 GENERAL

- 1.5.1 Offer available clinical research studies.
- 1.5.2 Counsel about smoking cessation and pulmonary rehabilitation.

II. NON-SMALL CELL LUNG CANCER

2.1 CLINICAL STAGE IA

- 2.1.1. Anatomical surgical resection and mediastinal lymph node sampling.
- 2.1.2. No need for adjuvant chemotherapy (EL- 1).
- 2.1.3. If optimal surgery cannot be performed, consider limited surgery(wedge resection or segmentectomy) or SBRT.
- 2.1.4. For positive surgical margins perform re-resection (EL- 1). If not possible offer curative radiotherapy (EL- 2).
- 2.1.5. If surgical resection is not possible, offer curative radiotherapy.



- 2.1.6. Follow up and surveillance per section 2.8 (follow up of non-small cell lung cancer).

2.2 CLINICAL STAGE IB

- 2.2.1 Anatomical surgical resection mediastinal lymph node sampling... (EL- 1) or dissection (EL- 3).
- 2.2.2 For lesions ≥ 4 cm or high-risk features (poorly differentiated, wedge re section, minimal margins, vascular Invasion), consider adjuvant chemo therapy. (EL- 2).
- 2.2.3 Chemotherapy of choice: 4-6 cycles of cisplatin (carboplatin only if cisplatinis contraindicated) with docetaxel, gemcitabine or venorelbine (EL- 1) or carboplatin and paclitaxel.
- 2.2.4 If optimal surgery cannot be performed, consider limited surgery (wedge resection or segmentectomy) (EL- 1).
- 2.2.5 For positive surgical margins perform re-resection (EL- 1) and if not possible, offer curative radiotherapy (EL- 2).
- 2.2.6 If surgical resection is not possible, offer curative radiotherapy.
- 2.2.7 Follow up and surveillance per section 2.8 (follow up of non-small cell lung cancer).

2.3 CLINICAL STAGE IIA

- 2.3.1 Anatomical surgical resection with lobectomy or pneumonectomy and me



diastinal lymph node sampling (EL- 1) or dissection (EL- 3).

2.3.2 Offer adjuvant chemotherapy as per 2.2.3 (EL - 1).

2.3.3 If optimal surgery cannot be performed, consider limited surgery (wedge resection or segmentectomy) or SBRT.

2.3.4 For positive surgical margins perform re-resection (EL- 1) and if not possible, offer curative radiotherapy (EL- 2).

2.3.5 If surgical resection is not possible, offer curative radiotherapy.

2.3.6 Follow up and surveillance per section 2.8 (follow up of non-small cell lung cancer).

2.4 CLINICAL STAGE IIB

2.4.1 Anatomical surgical resection and mediastinal lymph node sampling. (EL- 1) or dissection (EL- 3).

2.4.2 Offer adjuvant chemotherapy. similar to 2.2.3 (EL- 1).

2.4.3 Superior sulcus tumors patients should be induced by cisplatin/etoposide with concurrent radiation therapy followed by surgical resection (EL- 2) and 2 cycles of adjuvant chemotherapy. Assess disease extent by using MRI at baseline and pre-operative.

2.4.4 For T3 N0 M0 perform en-bloc resection (EL- 1).



2.4.5 If optimal surgery cannot be performed, consider limited surgery (wedge resection or segmentectomy) (EL- 1).

2.4.6 For positive surgical margins perform re-resection (EL- 1) and if not possible, offer curative radiotherapy (EL- 2).

2.4.7 If surgical resection is not possible, offer curative radiotherapy.

2.4.8 Follow up and surveillance per section 2.8 (follow up of non-small cell lung cancer).

2.5 CLINICAL STAGE IIIA

2.5.1 For T3 N1 M0 perform en-bloc resection (EL- 1).

2.5.2 For superior sulcus tumor, offer treatment similar to 2.4.3 (EL- 2).

2.5.3 For N2 disease offer neoadjuvant concurrent chemo- radiotherapy (EL- 1) assess response. If resectable, offer surgery. For non-resectable tumors, continue with the appropriate treatment based on disease status.

2.5.4 If positive N2 disease discovered during surgery by frozen section abort surgery if pneumonectomy is required (EL- 2).

2.5.5 Incidental pathological N2 disease, adjuvant chemotherapy. is indicated (EL- 1) radiotherapy can be considered (EL- 3).

2.5.6 For T4 (2 nodules in ipsilateral separate lobes), offer pneumonectomy followed by adjuvant chemotherapy.



- 2.5.7 T4 (mediastinal involvement or main airway involvement), offer surgery if potentially curative, if not possible, offer definitive concurrent chemo- radiotherapy(2.5.1.)
- 2.5.8 For non N2 stage IIIA, not specified above, offer surgical resection with Adjuvant chemotherapy (EL- 1). Adjuvant chemotherapy. for positive margins.
- 2.5.9 Follow up and surveillance per section 2.8 (follow up of non-small cell lung cancer).

2.6 CLINICAL STAGE IIIB AND UNRESECTABLE IIIA

- 2.6.1 Offer concurrent chemo- radiotherapy(EL1) followed by chemotherapy (EL2). surgical resection for selected cases could be offered.
- 2.6.2 Follow up and surveillance per section 2.8 (follow up of non-small cell lung cancer).

2.7 STAGE IV

* Obtain Palliative care. consultation / evaluation.

2.7.1 Systemic Therapy (See Table)

2.7.1.1 Stage M1a(with pleural effusion) assess the need for thoracentesis and pleurodesis. Offer systemic therapy as below.

2.7.1.2. With brain metastases



- Consider surgery for patient with single brain metastasis.
 - Refer to radiation oncology for local treatment of the CNS disease.
 - After CNS disease control, start systemic therapy as in 2.7.1.4.
- 2.7.1.3. Isolated adrenal metastasis. Consider surgical resection (confirm histologically before surgery). Discuss with multidisciplinary team.
- 2.7.1.4. No brain metastases/Treated brain disease, no prior systemic treatment for metastatic disease. (See Table 1)
- 2.7.1.4.1. Adenocarcinoma/non-squamous EGFR mutation (excluding exon 20 mutations or primary resistant mutations)

A. First line:

1. Performance Status 0-2:
 - Use TKIs (Erlotinib, Gefitinb, or Afatinib) (EL1).
 - Systemic chemotherapy (platinum doublet+/-bevacizumab) (Pemetrexed is preferred over gemcitabine).
2. Performance Status 3:
 - Use TKIs (Erlotinib, Gefitinb, or Afatinib).
 - Single agent chemotherapy (Pemetrexed is preferred over gemcitabine)
2. Performance Status 4:
 - Use TKIs (Erlotinib, Gefitinb, or Afatinib).

**B. Maintenance:**

1. Performance Status 0-2:
 - Continuation or switch maintenance with TKIs (EL1). If was not started on TKIs, patient should be switched to TKIs as soon as possible
 - Continue Bevacizumab, if started in first line.
2. Performance Status 3 and 4:
 - Continuation or switch maintenance with TKIs. If was not started on TKIs, patient should be switched to TKI as soon as possible .

C. Second line

* Consider re-biopsy to assess the cause of resistance if TKI is used in first line

1. Performance Status 0-2:
 - Use TKIs, if not used in first line.
 - Systemic Chemotherapy (platinum doublet+/-bevacizumab) (Pemetrexed is preferred over gemcitabine).
 - Consider using Ramucirumab
2. Performance Status 3:
 - Use TKIs, if not used in first line.
 - If TKI used, consider single agent chemotherapy (Pemetrexed preferred over gemcitabine)
3. Performance Status 4:
 - Use TKIs, if not used in first line.
 - If TKIs were used, refer to Palliative care..

**D. Third Line and Beyond**

1. Performance Status 0-2:
 - Use TKIs, if not used before.
 - Consider immunotherapy (Nivolumab or Pembrolizurab)
 - Systemic chemotherapy (single agent chemotherapy, Pemetrexed if not used, docetaxel, etc) .
2. Performance Status 3 and 4:
 - Use TKIs, if not used in first line.
 - If TKIs were used, refer to palliative care.

2.7.1.4.2. ALK positive Adenocarcinoma/non-squamous

A. First line:

1. Performance Status 0-2:
 - Use Crizotinib. (EL1).
 - Systemic Chemotherapy (platinum doublet+/-bevacizumab) (Pemetrexed is preferred over gemcitabine).
2. Performance Status 3:
 - Use Crizotinib.
 - Single agent chemotherapy (Pemetrexed preferred over gemcitabine).
2. Performance Status 4:
 - Use Crizotinib.
 - Palliative care.

**B. Maintenance:**

1. Performance Status 0-2:
 - Continuation or switch maintenance with Crizotinib. If was not started on Crizotinib, patient should be switched to Crizotinib as soon as possible.
 - Continue Bevacizumab, if started in first line.
2. Performance Status 3 and 4:
 - Continuation or switch maintenance with Crizotinib. If was not started on Crizotinib, patient should be switched to Crizotinib as soon as possible.

C. Second line

* Consider re-biopsy to assess the cause of resistance if TKI is used in first line

1. Performance Status 0-2:
 - Use Ceritinib, if Crizotinib used before.
 - Use Crizotinib, if not used in first line.
 - Systemic Chemotherapy (platinum doublet+/- bevacizumab) (Pemetrexed is preferred over gemcitabine).
 - Consider using Ramucirumab
 - Consider using Nivolumab or pembrolizumab
2. Performance Status 3 and 4:
 - Use Ceritinib, If Crizotinib used before
 - Use Crizotinib, if not used before.

**D. Third Line and Beyond**

1. Performance Status 0-2:
 - Use Crizotinib or Ceritinib, if not used before.
 - Systemic Chemotherapy (single agent chemotherapy, Pemetrexed, if not used, docetaxel, etc)
 - Consider immunotherapy (Nivolumab and Pembrolizumab)
2. Performance Status 3 and 4:
 - Use Crizotinib, if not used in first line.
 - If both agent is used, Palliative care..

2.7.1.4.3. EGFR/ALK wild type Adenocarcinoma/non-squamous (Including EGFR Exon 20 mutation or primary resistance mutation)**A. First line:**

1. Performance Status 0-2:
 - Systemic Chemotherapy (platinum doublet+/-bevacizumab) (Pemetrexed is preferred over gemcitabine).
2. Performance Status 3:
 - Single agent chemotherapy (Pemetrexed is preferred over gemcitabine).
 - Palliative care.
3. Performance Status 4:
 - Palliative care.

**B. Maintenance:**

1. Performance Status 0-2:
 - Continue or switch maintenance with Pemetrexed
 - Continue Bevacizumab, if started in first line.
2. Performance Status 3:
 - Continue or switch maintenance with Pemetrexed.
3. Performance Status 4:
 - Palliative care.

C. Second line

- .1. Performance Status 0-2:
 - Single Agent Systemic Chemotherapy (Pemetrexed if not used, docetaxel).
 - Consider using Nivolumab or pembrolizumab
 - Consider using Ramucirumab
- .2. Performance Status 3:
 - Single Agent Systemic Chemotherapy (Pemetrexed if not used, docetaxel).
 - Erlotinib (only TKI) can be used. EL3.
- .3. Performance Status 4:
 - Palliative care.

**D. Third Line and Beyond**

- .1. Performance Status 0-2:
 - Single agent systemic therapy.
 - Erlotinib (only TKI) can be used. EL3.
2. Performance Status 3 and 4:
 - Palliative care.

2.7.1.4.4. Adenocarcinoma/non-squamous with (EGFR and ALK unknown status)**A. First line:**

1. Performance Status 0-2:
 - Systemic Chemotherapy (platinum doublet+/-bevacizumab) (Pemetrexed is preferred over gemcitabine).
2. Performance Status 3:
 - Single agent chemotherapy (Pemetrexed is preferred over gemcitabine).
 - Use TKIs (Erlotinib).
3. Performance Status 4:
 - Palliative care.

B. Maintenance:

1. Performance Status 0-2:
 - Continue or switch maintenance with Pemetrexed.
 - Continue Bevacizumab, if started in first line.



2. Performance Status 3:
 - Continue or switch maintenance with Pemetrexed.
3. Performance Status 4:
 - Palliative care.

C. Second line

1. Performance Status 0-2:
 - Single Agent Systemic Chemotherapy (Pemetrexed, if not used, docetaxel).
 - Immune therapy (Nivolumab or pembrolizumab)
 - Erlotinib can be used. EL2.
 - Consider using Ramucirumab
2. Performance Status 3 and 4:
 - Palliative care.

D. Third Line and Beyond

1. Performance Status 0-2:
 - Systemic Chemotherapy (single agent chemotherapy, Pemetrexed if not used, docetaxel).
2. Performance Status 3 and 4:
 - Palliative care.

2.7.1.4.5 Squamous cell carcinoma:

A. First line:

1. Performance Status 0-2:
 - Systemic Chemotherapy (platinum doublet) (No Bevacizumab or Pemetrexed).
2. Performance Status 3:



- Single agent chemotherapy (No Pemetrexed).
3. Performance Status 4:
 - Palliative care.

B. Maintenance:

1. Performance Status 0-2:
 - Continuation or switch maintenance with docetaxel.
2. Performance Status 3 and 4:
 - Palliative care.

C. Second line

1. Performance Status 0-2:
 - Single agent systemic Chemotherapy (No Pemetrexed).
 - Immune therapy (Nivolumab or pembrolizumab)
 - Consider using Ramucirumab
2. Performance Status 3:
 - Single agent systemic therapy
3. Performance Status 4:
 - Palliative care.

D. Third Line and Beyond

1. Performance Status 0-2:
 - Single agent systemic therapy
 - Consider using Nivolumab or pembrolizumab if it's not used before
2. Performance Status 3 and 4:
 - Palliative care.



2.8 FOLLOW UP OF NON SMALL CELL LUNG CANCER

Evaluation includes: History and physical examination, laboratory and chest x-ray.

- 2.8.1 For tumor stage I-III: evaluation every 3 months for 2 years then every 6 months for 3 years then annually. CT scan of the chest every 6 months for 2 years then annually for additional 3 years. Consider annual screening CT scan after 5 years.
- 2.8.2 Stage IV: evaluation every 2-3 months as clinically indicated.

III. SMALL CELL LUNG CANCER

3.1 Stage I-III (Previously called limited stage):

- 3.1.1 Offer cisplatin/ etoposide with radiation therapy then consolidate with two cycles of cisplatin/ etoposide (EL-1). May substitute cisplatin with carboplatin in patients with neuropathy, renal dysfunction or hearing problem .
- 3.1.2 After definitive therapy with any response offer prophylactic cranial irradiation (PCI) (EL-1).
- 3.1.3 For stage (T1-2 N0 confirmed by Mediastinoscopy), offer surgical resection followed by chemotherapy and prophylactic brain radiotherapy (EL- 2).
- 3.1.4 Follow up and surveillance per section 3.3.

3.2 STAGE IV (Previously Extensive Stage)

- 3.2.1 Offer cisplatin/ etoposide or cisplatin /irinotecan x 6 cycles (EL-1). Use of carboplatin cisplatin is not indicated.



- 3.2.2 After definitive chemotherapy with evidence of response and good performance status offer (EL-1). Thoracic irradiation and prophylactic cranial irradiation (PCI).
- 3.2.3 For previously treated patients who relapsed in less than 6 months from initial treatment, offer topotecan (EL-1) or cyclophosphamide, adriamycin and vincristin (CAV), or camptozar.
- 3.2.4 For relapse after six months from initial treatment, may use original regimen.
- 3.2.5 Follow up and surveillance per section 3.3

3.3 FOLLOW UP AND SURVEILLANCE

- 1.3.1 Evaluation includes: history and physical examination, laboratory data and chest x-ray.
- 1.3.2 Stage I-III: evaluation every 3 months for 2 years then every 6 months for 3 years then annually. CT scan of the chest every 6 months for 2 years then annually for additional 3 years. Consider annual screening CT scan after 5 years.
- 1.3.3 Stage IV: evaluation every 2-3 months as clinical indicated .



Appendix 2. Systematic Therapy Regimens in NSCLC

	Chemotherapy Regimen	Reference
Adjuvant	Carboplatin AUC 6 + paclitaxel 225 mg/m ² on day 1 21 DAYS cycle for 6 cycles	Schiller 2002 Strauss 2008
	Cisplatin 75mg/m ² + docetaxel 75 mg/m ² on day 1 21 day cycle for 6 cycles	Sciller 2002
	Cisplatin 100 mg/m ² + gemcitabine 1000 mg/m ² on day 1 & 8, 15 28 day cycle for 6 cycles Usual practice is to omit day 15 and use every 21 days.	Schiller 2002
	Carboplatin AUC 5 + gemcitabine 1000 mg/m ² on day 1 & 8 21 days cycle for 6 cycles	Zatloukal P 2003
	Cisplatin 75mg/m ² + vinorelbine 25 mg/m ² on day 1 & 8 21 days cycle for 6 cycles	Winton 2005
	Concurrent with Chemoradiation	Carboplatin AUC 2 + Paclitaxel 45 mg/m ² Weekly with radiation
Cisplatin 50 mg/m ² (days 1, 8, 29, 36) + etoposide 50mg/m ² (day 1 to 5 and 29 to 33) Week 1 and 5		Albain 2002
Metastatic	Carboplatin AUC 6 + paclitaxel 225 mg/m ² on day 1 21 days cycle for 6 cycles	Schiller 2002 Strauss 2008
	Cisplatin 75mg/m ² + docetaxel 75 mg/m ² on day 1 21 days cycle for 6 cycles	Schiller 2002
	Cisplatin 100 mg/m ² + gemcitabine 1000 mg/m ² on day 1 & 8, 15 28 day cycle for 6 cycles Usual practice is to omit day 15 and use every 21 days	Schiller 2002

	Chemotherapy Regimen	Reference
Metastatic	Carboplatin AUC 5 + gemcitabine 1000 mg/m ² on day 1 & 8 21 day cycle for 6 cycles	Zatloukal P 2003
	Cisplatin 75mg/m ² + vinorelbine 25 mg/m ² on day 1 & 8	Winton 2005
	Paclitaxel (200 mg/m ²) +carboplatin (AUC 6) + bevacizumab (15 mg/kg) every 21 days	Sandler 2006
Single agent regimens	Gemcitabine 1250mg/m ² (day 1 and 8) 21 day cycle	Sederholm 2005
	Docetaxel 75mg/m ² 21 day cycle	Shepherd FA 2000
	Pemetrexed 500mg/m ² 21 day cycle	Hanna N 2004
	Toptecan 1.5mg/m ² (day1 to 5) 21 day cycle	Ramlau 2006
	Gefitinib 250mg daily 28 day cycle	Edward 2008
	Erlotinib 150mg po daily 28 day cycle	Shepherd FA 2005
	Pemetrexed (500 mg/m ² IV) 3 week cycle	Giorgio 2009
	Afatinib 40 mg po daily 28 day cycle.	Sequest 2013
	Crizotinib 250 mg po BID 28 day cycle	Sahw 2013
	Ceritinib 750 mg p.o daily 28 day cycle	Shaw 2014
	Nivolumab IV: 3 mg/kg once every 2 weeks until disease progression or unacceptable toxicity	Brahmer 2015
	Pembrolizumab IV: 2 mg/kg once every 3 weeks until disease progression or unacceptable toxicity	Garon2015
	Ramucirumab IV: 10 mg/kg on day 1 every 21 days in combination with docetaxel; continue until disease progression or unacceptable toxicity	Garon 2012



Diagnosis	1. Determining Histology Subtype		2. EGFR Mutation Testing	3. EML4 -ALK-Fusion Testing	4. PDL1 testing	
Characteristics	Performance Status	Non Squamous Cell Carcinoma				Squamous Cell Carcinoma
		EGFR+	EML4-ALK+	EGFR WT	EGFR Unknown	
First line	0-2	TKI or Platinum doublet (Pemetrexed) +/-Bevacizumab	Crizotinib or Platinum doublet (Pemetrexed) +/-Bevacizumab	Platinum doublet (Pemetrexed) +/-Bevacizumab	Platinum doublet (Pemetrexed) +/-Bevacizumab	Platinum doublets (no Pemetrexed or Bevacizumab)
	3	TKI single agent chemotherapy	Crizotinib, erlotinib or single agent chemotherapy	Single agent chemotherapy or erlotinib	erlotinib or single agent chemotherapy	Erlotinib or single agent chemotherapy
	4	TKI Palliative Care	Crizotinib* Palliative Care	Palliative Care	erlotinib Palliative Care	Palliative Care
Maintenance	0-2	TKI or Pemetrexed Bevacizumab (CM)	Crizotinib, Pemetrexed Bevacizumab**	Pemetrexed or erlotinib Bevacizumab (CM)	Pemetrexed or erlotinib Bevacizumab**	Docetaxel
Second Line	0-2	IT, TKI if not used. Pemetrexed or docetaxel	Crizotinib, if not used. Ceritinib if Crizotinib is used. TKI, Pemetrexed or docetaxel	IT, Pemetrexed if not used. IT, Ramucirumab+ Docetaxel Pemetrexed or Erlotinib or Docetaxel	IT, Ramucirumab+Docetaxel Pemetrexed or erlotinib or docetaxel	IT Afatinib or erlotinib Or Ramucirumab+ Docetaxel, Docetaxel or othes
	3	TKI, if not used	Crizotinib or ceritinib	Erlotinib	Erlotinib	Afatinib or erlotinib
	4	TKI if not used	Crizotinib, ceritinib or TKI if not used	Palliative Care	Palliative Care	Palliative Care
Third Line	0-3	IT, if not used TKI	IT, Crizotinib, ceritinib or erlotinib, if both ceritinib and crizotinib used	IT, if not used Erlotinib	IT, if not used erlotinib	IT if not used, Afatinib or erlotinib
	4	Palliative Care	Palliative Care	Palliative Care	Palliative Care	Palliative Care

CM = Continuation Maintenance TKI = Tyrosine Kinase Inhibitors: Erlotinib, Afatinib and Gefitinib. IT: Nivolumab and Pembrolizumab

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