2018

SAUDI LUNG CANCER MANAGEMENT GUIDELINES

National Cancer Center

(NCC)

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Glossary	
CBC	Complete blood count
CK7	Cytokeratin 7
CT	Computed tomography
EGFR	Epidermal growth factor receptor
EML4-ALK	Echinoderm microtubule-associated protein-like 4 & Anaplastic lymphoma kinase
IHC	Immunohistochemistry
LFT	liver function test
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung cancer
NOS	Not otherwise specified
PCR	polymerase chain reaction
PET scan	Positron emission tomography
PD-1	Programmed cell death-1
PD-L1	Programmed death-ligand 1
SBRT	Stereotactic Body Radiation Therapy
SCC	Squamous Cell Carcinoma
SCLC	Small cell lung cancer
TKIs	Tyrosine kinase inhibitors
TNM	Tumor, Lymphnode, Metastasis
TTF-1	Thyroid transcription factor 1

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 or expert opinions.

I. ALL LUNG CANCER PATIENTS

1.1 INITIAL PATIENT ASSESSMENT

1.1.1 Perform history and physical examination. Document smoking history, performance status, weight loss and comorbidities.

1.1.2 Perform the following laboratory tests: Complete blood count, differential, liver function test, 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 using most recent pathological classification of lung cancer. Utilization of proper Immunohistochemistry (IHC) 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 (Squamous cell carcinoma with small sample or never smokers, EGFR should be done).

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, obtain the ROS1 test.

1.2.6 If tissue not adequate to do molecular testing, perform ctDNA (plasma) testing.

1.2.7 Obtain PDL1 testing by IHC 22C3 pharmDx on all NSCLC wild type

1.2.8 Next generation sequencing should be performed, if available.

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 Mediastinal LN evaluation in selected cases; i.e. clinical stages (IB-III). Especially negative with central tumor and T2 to T4.

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 or it was negative with suspected bone involvement.

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 Counsel about smoking cessation and pulmonary rehabilitation.

1.5.2 Offer available clinical research studies.

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. Adjuvant chemotherapy is not recommended (EL- 1).

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

2.1.4. Patients with positive surgical margins should be offered re-resection (EL- 1) or radical post-operative radiotherapy (EL- 2).

Definitive radical radiotherapy is an alternative for patients who are not candidates for surgery due to comorbidities, poor performance status or refusal of surgery.

2.1.5. If surgical resection is not possible, (inoperable or refusal of surgery) offer SBRT with curative intent. Poor pulmonary function test is not contra indication for SBRT. (Sec 2.3.8)

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 resection, minimal margins, vascular Invasion), consider adjuvant chemotherapy. (EL- 2).

2.2.3 Chemotherapy of choice: 4-6 cycles of platinum combination cisplatin (carboplatin only if cisplatin is contraindicated) (EL- 1)

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

2.2.5 Definitive SBRT with curative intent is an alternative option for patients who are not candidates for surgery due to comorbidities or refusal of surgery. See 2.3.8 hypo fractionated radiotherapy is second option.

2.2.6 Patients with positive surgical margins should be offered re-resection (EL- 1) radical post-operative radiotherapy (EL- 2).

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 mediastinal lymph node sampling (EL- 1) or dissection (EL- 3) is the treatment of choice.

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

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

2.3.4 Patients with positive surgical margins should be offered re-resection (EL- 1) or radical post-operative radiotherapy (EL- 2).

2.3.5 Definitive radical radiotherapy is an alternative option that should be considered for patients with T2bN0 for patients who are not candidates for surgery due to comorbidities or who refuse surgery.

2.3.6 If surgical resection is not possible, offer curative radical radiotherapy for t2b N0. See Section 2.3.8

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

2.3.8 Radiotherapy with Curative Intent in Patients with Early Stage, Medically Inoperable, Non-Small Cell Lung Cancer:

2.3.8.1 SBRT with curative intent is an option that should be considered for patients with early stage, node-negative, medically inoperable NSCLC.

2.3.8.2 Most established SBRT criteria include NO patients with:

- <5 cm, peripherally located tumors, but tumor maybe more cautiously treated with expanded criteria of larger size (<7 cm).
- Central location.
- Multiple synchronous lesions.
- Chest wall invasion (T3N0).

2.3.8.3 Poor PFT is not contraindication to SBRT. The only practical known contraindication to SBRT that if the patient can not lie flat on the machine table during treatment delivery time.

2.3.8.4 Recommended fractionation schemes for SBRT should have a BED10 (LQ) of ≥100.

2.4 CLINICAL STAGE IIB

2.4.1 Anatomical surgical resection and mediastinal lymph node sampling. (EL-1) or dissection (EL- 3) is the treatment of choice.

2.4.2 Offer adjuvant chemotherapy as per section 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 Patients with positive surgical margins should be re-resection (EL- 1) or radical post-operative radiotherapy (EL- 2).

2.4.7 Definitive radical radiotherapy SBRT for T3N0, chest wall invasion or concurrent chemoradiotherapy for T2BN1 is an alternative for patients who are not candidates for surgery due to comorbidities or refusal of surgery.

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 N_2 disease the standard of care is concurrent chemo-radiotherapy. For selected cases of N2 that elected to be surgically resectable after discussion in tumor board neoadjuvant chemoradiotherapy can be considered followed by assessment of response. For inoperable tumors, continue with the appropriate treatment based on disease status.

2.5.4 If N_2 disease discovered during surgery by frozen section abort surgery if pneumonectomy is required (EL- 2).

2.5.5 For patients with incidental pathological N_2 disease, adjuvant chemotherapy is recommended (EL- 1) and in addition radiotherapy can be considered (EL- 3).

2.5.6 For T4 disease T4N0 (2 nodules in ipsilateral separate lobes), offer pneumonectomy followed by adjuvant chemotherapy. SBRT with curative intent is an option that can be considered.

2.5.7 For T4 with (mediastinal or main airway involvement), offer surgery if potentially curative; if not possible, offer *d*efinitive concurrent chemo-radiotherapy (2.5.1.)

2.5.8 For non N_2 stage IIIA, not specified above, offer surgical resection with adjuvant chemotherapy (EL- 1).

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 on all patients (EL1).

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

RTOG RPA for brain metastases (Gasper et al. 1997)	
Class	Characteristics
I	KPS 70-10 Age <65 Primary tumor controlled Metastases to brain only
II	All others
III	KPS <70

Radiosurgical treatment indications for brain metastases	
Single lesion	Surgical resection + SRS to cavity
RPA class I-II	SRS alone for medically/surgically inoperable cases
KPS ≤60, extensive intracranial/extracranial disease, and in combination with SRS	

2.7.1.3. Isolated adrenal metastasis; consider adrenal mass biopsy followed by surgical resection or SBRT consideration after multidisciplinary team discussion.

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 with sensitizing EGFR mutation.**

Guiding principle:

Patient with driver mutation should receive TKI as first line if possible. If not done, patient should receive TKI as soon as possible as switched maintenance (completing planned treatment) or any time they are available. (Interrupt treatment)

A. First line:

1. Performance Status 0-2:
   - TKIs (Erlotinib, Afatinib, or Gefitinb) are the preferred option (EL1).
   - Systemic chemotherapy with a platinum doublet +/- bevacizumab can be considered if the EGFR status is unknown or awaited. Platinum doublet (Pemetrexed combination is preferred over a gemcitabine based combination).

2. Performance Status 3:
   - Use TKIs (Erlotinib, Afatinib, or Gefitinb).
   - Single agent chemotherapy if TKI not available, can be considered in selected cases.

3. Performance Status 4:
   - Use TKIs (Erlotinib, Gefitinb, or Afatinib).

B. Maintenance:

1. Performance Status 0-2:
   - Continuation or switch maintenance with TKIs (EL1). If the patient was not commenced on TKIs, then switch to TKIs as soon as possible

2. Performance Status 3 and 4:
   - Continuation or switch maintenance with TKIs.

C. Second line

Guiding Principle:
Assess for resistant mutations with either ctDNA (plasma) testing or re-biopsy of metastatic site.

For isolated or Oligoprogression, consider local therapy. For multiprogression, switch to second line.

1. If T790M Positive, use Osimertinib

2. Performance Status 0-2:
   - Use TKIs, if not used in first line.
   - Systemic Chemotherapy (platinum doublet +/- bevacizumab) (Pemetrexed is preferred over gemcitabine).

3. Performance Status 3:
   - Use TKIs, if not used in first line.
   - If TKI used, consider single agent chemotherapy (Pemetrexed preferred over gemcitabine)

4. Performance Status 4:
   - Use TKIs, if not used in first line.
   - If TKIs were used, consider single agent chemotherapy or referral to palliative care.

D. Third Line and Beyond

* Obtain T790M testing if it was not done earlier, consider doing ctDNA (plasma) testing.

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) .
   - Ramcirumab/Docetaxel

2. If T790M Positive, use Osimertinib.

3. 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:
   - Crizotinib is the recommended treatment option. (EL1).
   - Systemic chemotherapy with a platinum doublet (+/- bavacizumab) can be considered. (Platinum-Pemetrexed combination is preferred over a gemcitabine-based combination).
   - Crizotinib is also very effective in patients with ROS 1 rearrangements.

2. Performance Status 3:
   - Use Crizotinib.
   - Single agent chemotherapy can be considered.

3. Performance Status 4:
   - Use Crizotinib.
   - Palliative care.

B. Maintenance:

Performance Status 0-2:

- Continuation or switch maintenance with Crizotinib. If was not started on Crizotinib, patient should be switched to Crizotinb as soon as possible.

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

- For isolated or oligoprogression, consider local therapy
- For multiple site progression, consider re-biopsy to assess the cause of resistance if TKI is used in first line

1. Performance Status 0-2:
   - Ceritinib or alectinib are the recommended treatment options for patients with disease progression or intolerance to Crizotinib.
   - Use Crizotinib, if not used in first line.
   - Systemic chemotherapy (platinum doublet+/- bevacizumab) (Pemetrexed is preferred over gemcitabine).
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 or Alectinib, if not used before.
   - Systemic Chemotherapy (single agent chemotherapy, Pemetrexed, if not used, docetxel, etc)
   - Consider immunotherapy (Nivolumab, atezolumab, Pembrolizumab)
2. Performance Status 3 and 4:
   - Use Crizotinib or Ceritinib or Alectinib, if not used in first line.
   - If both agents where 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:

*** If PDL > 50%:**

- -Use Pembrolizumab, if it's not available use Systemic Chemotherapy (platinum doublet+/-bevacizumab) (Pemetrexed is preferred over gemcitabine).

*** If PDL <50%:**

- Systemic Chemotherapy (platinum doublet+/-bevacizumab) (Pemetrexed is preferred over gemcitabine).

2. Performance Status 3:

- Single agent chemotherapy can be considered.

- Palliative care.

3. Performance Status 4:

- Palliative care.

B. Maintenance:

1. Performance Status 0-2:
   - Continue pembrolizumab if commenced in first-line.
   - 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:

- Give Nivolumab, atezolizumab, or Pembrolizumab (PDL 1 Positive), if received chemotherapy as first line.

- Platinum doublet if pembrolizumab used as first line.

- Single agent systemic chemotherapy (Pemetrexed if not used, Docetaxel). If chemotherapy doublet is used as first line.

2. Performance Status 3:
   - Single agent systemic chemotherapy (Pemetrexed if not used, Docetaxel).

3. Performance Status 4:
   - Palliative care.

D. Third Line and Beyond

1. Performance Status 0-1:
   - Consider Ramucirumab + Docetaxel or Nintedanib + Docetaxel

2. Performance Status 0-1
   - Single agent systemic therapy.

3. Performance Status 3 and 4:
   - Palliative care.

2.7.1.4.4. Adenocarcinoma/non-squamous with (EGFR and ALK unknown status)

* consider doing ctDNA (plasma) testing of rebiopsy is not possible. All efforts should be made to test for a driver mutation.

A. First line:

1. Performance Status 0-2:

*** If PDL > 50%:**

- -Use Pembrolizumab, if it's not available use Systemic Chemotherapy (platinum doublet+/-bevacizumab) (Pemetrexed is preferred over gemcitabine).

*** If PDL <50%:**

- 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:
   - Immune systemic chemotherapy (platinum doublet+/-bevacizumab) (Pemetrexed is preferred over gemcitabine).
   - If Immune therapy not used, use (Nivolumab or Pembrolizumab or Atezolizumab).

- Consider using Ramucirumab

2. Performance Status 3:
   - Single agent chemotherapy (Pemetrexed if not used)

3. Performance Status 4:

   - Palliative care.

D. Third Line and Beyond

1. Performance Status 0-2:
   - Systemic chemotherapy (single agent chemotherapy, Pemetrexed if not used or Docetaxel).
   - Erlotinib, if Immunotherapy and Pemetrexed used

2. Performance Status 3 and 4:
   - Palliative care.

2.7.1.4.5 **Squamous cell carcinoma:**

A. First line:

1. Performance Status 0-2:
   * If PDL1 < 50%
   - Systemic Chemotherapy (platinum doublet) (No Bevacizumab or Pemetrexed).

   * If PDL1 >50% use Pembrolizumab

2. Performance Status 3:
   - Single agent chemotherapy (No Pemetrexed).

3. Performance Status 4:
   - Palliative care.

B. Maintenance:

1. Performance Status 0-2:
   - Continue on Pembrolizumab for 2 years.
   - Continuation or switch maintenance with docetaxel.

2. Performance Status 3 and 4:
   - Palliative care.

C. Second line

1. Performance Status 0-2:
   - Immune therapy (Nivolumab, Pembrolizumab or Atezolizumab), if Pembrolizumab not used.
   - Systemic chemotherapy doublet if Immune therapy used as first line (No Pemetrexed).
   - Consider using Ramucirumab / Docetaxel
   - Afatinib
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
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. Thoracic irradiation and prophylactic cranial irradiation (PCI) (EL1).

3.2.3 For previously treated patients who relapsed in less than 6 months from initial treatment, offer topotecan (EL1) or cyclophosphamide, adriamycin and vincristin (CAV), or irinotecan.

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.

IV. Tables

Appendix 1. 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	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
	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 Chemoradation	Carboplatin AUC 2 + Paclitaxel 45 mg/m^2 Weekly with radiation	Socinski 2001
	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
	Cisplatin 75mg/m^2, Pemetrexed 500mg/m^2 every 21 day.	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
	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 21 day cycle for 6 cycles	Winton 2005

	or Vinorelbine 60-80mg/m2 (Max 160mg) PO Available as 20mg & 30mg capsules	
	Paclitaxel (200 mg/m2) +carboplatin (AUC 6) + bevacizumab (15 mg/kg) every 21 days	Sandler 2006
	Ramucirumab 10mg/kg IV + docetaxel 75mg/m2 IV. Repeat cycle every 3 weeks.	Garon 2014
	Nintedanib 200mg PO Twice daily Days 2-21 Docetaxel 60-75mg/m2 IV Day 1	Reck. 2014
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 Atezolizumab 1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks until disease progression or unacceptable toxicity	Ramlau 2006
	Gefitinib 250mg po once daily 28 day cycle	Edward 2008
	Erlotinib 150mg po once daily 28 day cycle	Shepherd FA 2005
	Pemetrexed (500 mg/m^2 IV) 3 week cycle	Giorgio 2009
	Afatinib 40 mg po once daily 28 day cycle.	Sequest 2013
	Crizotinib 250 mg po twice daily 28 day cycle	Sahw 2013
	Ceritinib 750 mg p.o once daily 28 day cycle	Shaw 2014
	Nivolumab IV: 240 mg once every 2 weeks infuse over 1 hour until disease progression or unacceptable toxicity	Brahmer 2015
	Pembrolizumab IV: 200 mg IV q3wk infuse over 30 minutes until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression	Garon2015

	Vinorelbine 60-80mg/m2 (Max 160mg) PO Available as 20mg & 30mg capsules	Fossella 2000

Diagnosis	1. Determining Histology Subtype 2. EGFR Mutation Testing 3. EML4 -ALK-Fusion Testing 4. PDL1 5. T790 (PD in EGFR mut)							
Characteristics	Performance Status	Non Squamous Cell Carcinoma					Squamous Cell Carcinoma	
		EGFR+	EML4-ALK+	EGFR WT		EGFR Unknown		
First line	0-2	TKI If TKI not available: Platinum doublet (Pemetrexed) +/- Bevacizumab	Crizotinib or If Crizotinib not available, Platinum doublet (Pemetrexed) +/-Bevacizumab	PDL1<50% Platinum doublet (Pemetrexed) +/- Bevacizumab	PDL>50% Pembrolizumab or platinum doublet (Pemetrexed) +/- Bevacizumab	PDL1<50% Platinum doublet (Pemetrexed) +/- Bevacizumab	Platinum doublets (no Pemetrexed or Bevacizumab)	PDL1>50 % Pembrolizumab Or Platinum doublet
	3	TKI Pemetrexed	Crizotinib Pemetrexed	Single agent chemotherapy (pemetrexed)		erlotinib or single agent chemotherapy	single agent chemotherapy Gemcitabine	
	4	TKI Palliative Care	Crizotinib* Palliative Care	Palliative Care		Palliative Care erlotinib	Palliative Care	
Maintenance	0-2	TKI (CM or SM) Pemetrexed (CM and SM) Bevacizumab (CM)	Crizotinib (CM or SM)	Pemetrexed (CM or SM) Bevacizumab (CM) Pembrolizumab (CM)		Pemetrexed or erlotinib (CM/SM) Bevacizumab**(CM) Pembrolizumab (CM)	Docetaxel	
Second Line	0-2	Check for T790 (CTDNA) Osimertinib in T790 mut Platinum doublet with Pemetrexed	Ceritinib alectinib if Crizotinib is used. Pemetrexed /platinum doublet	IT if not used Pemetrexed (doublet) if not used. Ramucirumab+ Docetaxel		IT if not used Pemetrexed if not used (doublet) Ramucirumab+Docetaxel or erlotinib or docetaxel	IT, if not used Afatinib Or Ramucirumab+ Docetaxel, Docetaxel or gemcitabine	
	3	TKI, if not used	Ceritinib/alectinib	single agent pemetrexed		Erlotinib	Palliative care	
	4	TKI if not used	Ceritinib/alectinib	Palliative Care		Palliative Care	Palliative Care	
Third Line	0-2	pemetrexed or docetaxel with or without platinum IT	If two TKIs used platinum/pemetrexed then IT	pemetrexed or docetaxel with or without platinum		Pemetrexed doublet or single agent Erlotinib	IT if not used, Gemcitabine if not used	
	3-4	Palliative Care	Palliative Care	Palliative Care		Palliative Care	Palliative Care	

CM = Continuation Maintenance. SM: Switch maintenance TKI = Tyrosine Kinase Inhibitors: Erlotinib, Afatinib or Gefitinib. IT: Nivolumab and Pembrolizumab, atezolizumab

V. Appendices

I. Image-Guided Percutaneous Transthoracic Biopsy in Lung Cancer by Dr. Azzam Khankan
II. The role of Endoscopic ultrasound/gastroenterologist in lung cancer diagnosis and management by Dr. AbdulMonem Swied
III. Guiding principles of systemic therapy in metatastatic NSCLC by Dr. Abdul Rahman Jazieh
IV. Immunotherapy of NSCLC by Dr. Abdullah K. Altwairgi
V. Management of Immune-related adverse events by Dr. Jawaher Ansari
VI. Initial treatment of EGFR Mutation NSCLC by Dr. Mervat Mahrous
VII. Treatment beyond progression in driver mutant lung cancer by Dr. Hamed AlHussaini
VIII. Management of TKIs side effects by Dr. Nagwa Ibrahim