NON-SMALL CELL LUNG CANCER

Introduction

- It is clearly noticed that the incidence of lung cancer in Kuwait is increasing over the last years, particularly non-small cell lung cancer (NSCLC) of adenocarcinoma subtype.
- Our current guidelines for the management of NSCLC were implemented through the utilization of the standard of care with consideration of our daily clinical experience, institutional rules for accepting new medications, the adverse effect profiles, the published long-term safety data, cost, and the available therapeutic options.
- On a weekly basis, the thoracic oncology multidisciplinary team (MDT) should discuss every single lung cancer case to formulate the optimal treatment plan for such a patient. The medical oncology team is responsible for organizing MDT meetings.
- This team consists of members from thoracic surgery, medical oncology, radiation oncology, thoracic imaging, pathology, and any ad-hoc members invited to discuss a case from a specific point of view.

Initial Assessment and Staging Workup

- On acceptance of a new lung cancer patient, a medical oncologist should:
- Interview the patient for a detailed history and risk assessment.
- Complete physical examination.
- Basic laboratory investigations:
    - Complete blood count (CBC),
    - Renal profile,
    - Liver profile,
    - Electrolytes,
    - Coagulation profile and
    - Any other labs are requested as indicated
- Serological studies are requested according to the presentation and risk assessment, including:
    - Hepatitis B surface antigen (HBsAg), anti-HBs Ab and anti-HBc Ab
    - Hepatitis C virus (HCV) Ab
    - Human immunodeficiency virus (HIV) Ab
- Cardio-pulmonary Assessment by a highly specialized team:
    - Electrocardiogram (ECG)
    - Echocardiography (ECHO) and gated pool study.
    - Pulmonary functions test.
- Imaging:
    - **For the primary site:**
        - Chest X-ray.
        - Computed tomography (CT) scan chest and abdomen with intravenous (IV) contrast.

- Magnetic resonance imaging (MRI) chest, if intravenous (IV) contrast is medically contraindicated.
- Mediastinal staging.

- **For the metastatic sites and staging workup:**
  - Bone scan.
  - Positron emission tomography with ^{18}F-labeled fluoro-2-deoxyglucose (FDG-PET) for the whole body.
  - MRI brain would be indicated in:
    - Metastatic NSCLC
    - Almost all small cell lung cancer.
  - Although sodium fluoride scan (NAF-PET) had shown better results in the evaluation of bone metastasis, it is not approved yet to be standard of care.

International Association for the Study of Lung Cancer: 8th Edition of the TNM Classification for Lung Cancer

T – Primary Tumor	
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 3 cm or less in greatest dimension, Surrounded by lung or visceral pleura, Without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus).[1]
T1im	Minimally invasive adenocarcinoma.[2]
T1a	Tumor 1 cm or less in greatest dimension.[1]
T1b	Tumor more than 1 cm but not more than 2 cm in greatest dimension.[1]
T1c	Tumor more than 2 cm but not more than 3 cm In greatest dimension.[1]
T2	Tumor > 3 cm but ≤ 5 cm or having any of the following features:[3] Involves the main bronchus regardless of the distance to the carina, but without the involvement of the carina, Invades visceral pleura, Associated with atelectasis or obstructive pneumonitis that extend to the hilar region, either involving part of the lung or the entire lung.
T2a	Tumor > 3 cm but ≤ 4 cm in greatest dimension.

T2b	Tumor > 4 cm but ≤ 5 cm in greatest dimension.
T3	Tumor > 5 cm but ≤ 7 cm in greatest dimension or directly invading any of the following: Chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or associated separate tumor nodule(s) In the same lobe as the primary.
T4	Tumor > 7 cm or the tumor of any size invading one or more of the following: Diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe to that of the primary.

N – Regional Lymph Nodes	
NX	Regional LN cannot be assessed.
N0	No regional LN metastasis.
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar LNs and intrapulmonary nodes, including involvement by direct extension.
N2	Metastasis in ipsilateral mediastinal and/or subcarinal LNs.
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular LNs.

M – Distant Metastasis	
M0	No distance metastasis
M1	Distance metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe, tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion.[4]
M1b	Single extrathoracic metastasis in a single organ.[5]
M1c	Multiple extrathoracic metastases in a single organ or several organs.

[1]The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

[2]Solitary adenocarcinoma (≤ 3 cm), with a pre-dominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension in any one focus.

[3]T2 tumors with these features are classified T2a if 4 cm or less, or if the size cannot be determined and T2b if greater than 4 cm but not larger than 5 cm.

[4]Most pleural (pericardial) effusions with lung cancer are due to the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

[5]This preludes involvement of a single distant (non-regional) node.

Cancer Stage Grouping			
Occult Carcinoma	Tx	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1im T1a	N0 N0	M0 M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a T1b T1c T2a T2b T3	N1 N1 N1 N1 N1 N0	M0 M0 M0 M0 M0 M0
Stage IIIA	T1a T1b T1c T2a T2b T3 T4 T4	N2 N2 N2 N2 N2 N1 N0 N1	M0 M0 M0 M0 M0 M0 M0 M0
Stage IIIB	T1a T1b T1c T2a T2b T3 T4	N3 N3 N3 N3 N3 N2 N2	M0 M0 M0 M0 M0 M0 M0
Stage IIIC	T3 T4	N3 N3	M0 M0
Stage IVA	Any T Any T	Any N Any N	M1a M1b
Stage IVB	Any T	Any N	M1c

1. Rami-Porta R, Bolejack V, Giroux DJ, et al. The IASLC Lung Cancer Staging Project the new database to inform the 8th edition of the TNM classification of lung cancer. J Thorac Oncol. 2014; 9:1618-1624.
2. Rami-Porta R, Bolejack V, Crowley, et al. The IASLC Lung Cancer Staging Project proposals for the revisions of the T descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. J Thorac Oncol. 2015; 10: 990- 1003.
3. Eberhardt WEE, Mitchell A, Crowley J, et al. The IASLC Lung Cancer Staging Project proposals for the revisions of the M descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. J Thorac Oncol. 2015; 10: 1515-1522.
4. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. J Thorac Oncol. 2015; 11:39-51.
5. Nicholson AG, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer. J Thorac Oncol. 2016; 11: 300-311.
6. Travis WD, Asamura H, Bankler A, et al. The IASLC Lung Cancer Staging Project proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. J Thorac Oncol. 2016; 11:1204-1223.

Histological and Pathological Assessment

- Tissue biopsy, either transthoracic or bronchoscopic, is highly preferred to:
  - Confirm diagnosis and
  - Perform molecular studies.
- Cytology may be adequate for certain cases:
  - Patients who are diagnosed based on cytology and referred from other hospitals while refusing to undergo biopsy.
  - Patients with advanced disease;
  - Patients with multiple co-morbidities in where diagnosis should be confirmed with the least invasive approach.
- Basic immunohistochemistry:
  - CK7, CK20, TTF1, Napsin, P63, and CK56.

Proceeding with a further panel of immunohistochemistry will be justified by the pathology lab.
If the initial biopsy was done outside Kuwait Cancer Control Center, slides and paraffin block would be requested for revision before initiation and/or proceeding to continue any treatment plan.

Molecular Studies

- **Tissue Sampling:**
  - Enough tissue sample will be needed for molecular testing.
  - If tissue sampling is not feasible, cytology blocks may secure as an alternative to performing mutational analysis.
- **Liquid Sampling:**
  - Liquid sampling is used for molecular testing with less sensitivity than the tissue.
  - If liquid sampling came with negative results, we would try to re-biopsy.

- **Epidermal growth factor receptor (EGFR) Mutation Testing:**
  - All cases histologically confirmed to have NSCLC of adenocarcinoma type will be tested for:
    - EGFR mutations,
    - ALK-EML rearrangements and
    - ROS1 testing before starting any Tyrosine Kinase Inhibitor.
  - In NSCLC of squamous type on histology, EGFR mutation will be considered in:
    - Never smokers,
    - Small biopsy specimens, or
    - mixed histology.
- **Testing of T790M** is considered after failure of the first anti-EGFR TKI.
- **Additional molecular testing** would be considered according to the treating physician, including:
  - HER-2,
  - RET,
  - RAF and
  - RAS.

Therapeutic Approaches [Stage Oriented]

I. Early Stages

Definition:

Early-stage NSCLC:	Stage I, II, and some cases of non-bulky IIIA (≤ 4cm).
Resectability:	Surgery is technically feasible.
Operability:	The patient is medically fit to proceed with major surgery.

Management:

For resectable and operable cases:

- Surgery is the cornerstone management for curative intent.
- The standard surgery is lobectomy with lymph node dissection.
- Segmentectomy or wedge resection may carry a higher risk of local recurrence.
- In the case of positive surgical margins, the patient should be offered re-resection or radiotherapy.

For non-operable cases:

- Radical radiotherapy is a suitable alternative treatment option for patients who:
  - Have uncontrolled major comorbidities
  - Refuse surgical therapy.
- Chemotherapy ± Radiation therapy.

Post-operative observation:

- Observation is indicated in patients with Stage IA disease who have a low-risk profile:
  - Well-differentiated tumors,
  - No vascular invasion,
  - Proper surgery, or
  - Complete lymph node (LN) sampling.
- Adjuvant therapy is considered harmful in this stage.

Adjuvant chemotherapy:

Adjuvant chemotherapy is indicated in:

- Patients with stage IA disease who have high-risk profiles:
  - Poorly differentiated tumors,
  - Vascular invasion,
  - Wedge resection, or
  - Incomplete LN sampling.
- Patients with either stage IB, stage II, or stage IIIA (non-bulky, ≤ 4cm).

Adjuvant Chemotherapy Regimens Include

Cisplatin + Vinorelbine combination (ANITA study)

Cisplatin	50 mg/m^2 IV D1 & D8
Vinorelbine	25 mg/m^2 IV D1 & D8 & D15 & D22 with G-CSF support

Cycled every 28 days for four cycles

It is only prescribed for those who are young, fit, and can tolerate.

Cisplatin + Vinorelbine combination

Cisplatin	75 mg/m^2 IV D1
Vinorelbine	25 mg/m^2 IV D1 & D8

Cycled every 21 days for four cycles

Cisplatin + Pemetrexed combination (for non-squamous histology)

Cisplatin	75 mg/m^2 IV D1
Pemetrexed	500 mg/m^2 IV D1

Cycled every 21 days for four cycles

Adjunctive treatment:

Started one week before initiation of pemetrexed and stopped after two weeks of completion of pemetrexed.

Folic acid	350-1000 ug oral every day
Vitamin B12	1000 ug intramuscular (IM) every nine weeks

Cisplatin + Paclitaxel combination	
Cisplatin	75 mg/m^2 IV D1
Paclitaxel	175 mg/m2 IV D1
Cycled every 21 days for four cycles	

Carboplatin AUC-5 may substitute Cisplatin in certain cases.

II. Locally Advanced Stages

Indications: Bulky stage IIIA and stage IIIB.

Management Plan: is a combination of chemotherapy and radiotherapy:

a. Concurrent approach (preferable than sequential approach):

Patients are offered radiotherapy concurrently along with platinum-based doublet chemotherapy:

Cisplatin + Etoposide combination	
Cisplatin	50 mg/m^2 IV Days 1, 8, 29 and 36
Etoposide	50 mg/m^2 IV Days 1-5 and 29-33
May be followed by 2 additional cycles of cisplatin 50 mg/m^2 and etoposide 50 mg/m^2 with three weeks interval.	

Cisplatin + Pemetrexed combination (for non-squamous histology)	
Cisplatin	75 mg/m^2 IV D1
Pemetrexed	50 mg/m^2 IV Days 1-5 and 29-33
Cycled every three weeks for two cycles concurrently with radiation therapy.	
May be followed by two additional cycles.	

Carboplatin + Paclitaxel combination	
Paclitaxel	45-50 mg/m^2 over 1-hour weekly
Carboplatin	AUC-2 mg/ml/min over 30 min weekly
May be followed by 2 more cycles of paclitaxel 200 mg/m^2 and carboplatin AUC-5 with 3 weeks interval.	

b. Sequential Approach

Management Plan: Chemotherapy will come first followed by thoracic radiation therapy:

Cisplatin + Etoposide combination	
Cisplatin	100 mg/m^2 on days 1 and 29
Vinblastine	5 mg/m^2/weekly on days 1, 8, 15, 22, and 29

Carboplatin + Paclitaxel combination	
Paclitaxel	200 mg/m^2 over 3 hours on day 1
Carboplatin	AUC-5 over 60 minutes on day 1
To be repeated every three weeks for two cycles.	

c. Induction Chemotherapy

Indication:

- Induction chemotherapy is indicated in patients with a higher risk for toxicity from combined chemoradiotherapy. The decision may be based on the thoracic surgeon who may prefer to avoid sequelae of radiation therapy in distorting the local area, including:
  - Patients with bulky stage III in which a large radiation field will be needed.
  - Patients with compromised lung functions.

Rational:

- Induction chemotherapy is given to downstage the extent of disease to be rendered eligible for surgery or concurrent chemo-radiotherapy.

Preferred chemotherapy combination:

Paclitaxel	200 mg/m^2 over 3 hours on day 1
Carboplatin	AUC-5 over 60 minutes on day 1
To be repeated every three weeks for two cycles.	

Or

Cisplatin	75 mg/m^2 IV D1
Pemetrexed	500 mg/m^2 IV D1
To be repeated every three weeks for two cycles.	

d. Adjuvant Durvalumab:

Indications:

- Indicated in patients with stage III, unresectable NSCLC who did not have disease progression after concurrent chemoradiotherapy and received their last radiation dose within 1 to 42 days before starting treatment.

Durvalumab	IV at a dose of 10 mg/kg every two weeks

Durvalumav is given up to 12 months or until confirmed disease progression or unacceptable toxic events.

III. Recurrent and Metastatic Disease

In case of recurrence or new onset of distant metastasis, it is highly recommended to re-biopsy for proper histopathological characterization.

These patients are candidates for:

1. Systemic treatment, including:
    a. Palliative chemotherapy,
    b. Monoclonal antibodies,
    c. Tyrosine kinase inhibitors or
    d. Immunotherapy.
2. Palliative radiation therapy for symptomatic metastatic sites.
3. Participation in clinical trials, at different levels, should always be encouraged.
4. Best supportive care will be offered early in the course of the patients' disease.

a. Chemotherapy:

Chemotherapy will be offered for those having good performance status (0-2).

Cisplatin + Pemetrexed combination (only with non-squamous histology)	
Cisplatin	75 mg/m2 IV D1
Or Carboplatin	AUC-5 IV D1
Pemetrexed	500 mg/m2 IV D1
To be repeated every 21 days for 4-6 cycles.	
Adjunctive treatment:	
Started one week before initiation of pemetrexed and stopped after two weeks of completion of pemetrexed.	
Folic acid	350-1000 ug oral every day
Vitamin B12	1000 ug IM every nine weeks

Gemcitabine + Cisplatin combination (preferred with squamous histology)	
Gemcitabine	1200 mg/m^2 IV D1 & D8
Cisplatin	80 mg/m^2 IV D1
To be repeated every 21 days for 4-6 cycles	

Paclitaxel + Carboplatin combination	
Paclitaxel	175 mg/m^2 IV over 3 hours D1
Carboplatin	AUC-5 IV D1
To be repeated every 21 days for 4-6 cycles	

Paclitaxel + Carboplatin combination	
Paclitaxel	175 mg/m^2 IV over 3 hours D1
Carboplatin	AUC-5 IV D1
To be repeated every 21 days for 4-6 cycles	

Docetaxel + Carboplatin combination	
Docetaxel	75-100 mg/m^2 IV over 3 hours D1
Carboplatin	AUC-5 IV D1
To be repeated every 21 days for 4-6 cycles	
Or	
Docetaxel	30 mg/m^2 IV over 1-hour weekly for 3 out of 4 weeks
Carboplatin	AUC-2 IV weekly for 3 out of 4 weeks
To be repeated every 28 days for 4-6 cycles	

Nab-Paclitaxel ± Carboplatin (preferred with squamous histology)	
Nab-Paclitaxel	100 mg/m^2 weekly either alone or combined with
Carboplatin	AUC-5 every three weeks
To be repeated every 21 days for 4-6 cycles	

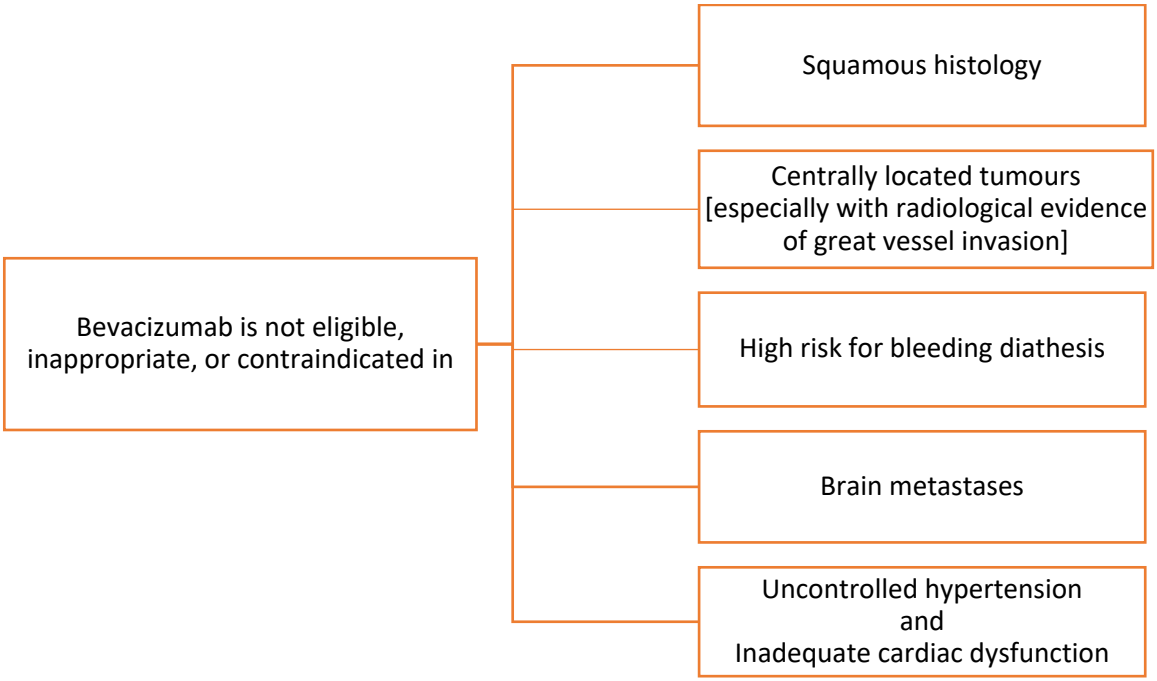
Single-agent chemotherapy:

All chemotherapies outlined in the combination protocols may be offered on a single agent basis in patients with a poor performance status or multiple comorbidities.

b. Monoclonal Antibodies:

Bevacizumab	
Bevacizumab	15 mg/kg q3w for 4 to 6 cycles, combined with any chemotherapy regimen
Bevacizumab may be added to either of the protocols mentioned above, only in eligible patients.	

Bevacizumab can be continued as maintenance therapy for responding cases after completion of chemotherapy until progressive disease or intolerable toxicity.



Cetuximab	
Cetuximab	A loading dose of 400 mg/m^2 IV infusion over 2 hours followed by A weekly dose of 250 mg/m2 IV infusion over 1 hour

It is indicated in metastatic NSCLC with EGFR expression, Kirsten rat sarcoma viral oncogene (KRAS) wild type.

Cetuximab is given in combination with chemotherapy, until symptomatic disease progression or unacceptable toxicity.

Necitumumab	
Necitumumab	800mg IV infusion over 1 hour on D1 and D8, prior to gemcitabine and cisplatin. It is repeated every three weeks, until symptomatic disease progression or unacceptable toxicity.

Necitumumab is indicated as a first-line treatment in people with metastatic squamous non-small cell lung cancer (NSCLC) in combination with gemcitabine and cisplatin.

Ramucirumab	
Ramucirumab	10 mg/kg IV infusion over 1 hour prior to docetaxel 75 mg/m2 IV every 12 days, until symptomatic disease progression or unacceptable toxicity.
Ramucirumab, in combination with Docetaxel, is indicated in the treatment of metastatic NSCLC after progression on platinum-based chemotherapy.	

c. Tyrosine Kinase Inhibitors

Treatment directed for EGFR mutation, ALK rearrangement, or ROS1 fusion would be the first-line therapy for adenocarcinoma histology as far as the patients having a good general condition enabling them to wait for the results of these tests that take 10-14 days. Otherwise, the patients will be started on chemotherapy as outlined earlier in this context and offered targeted therapies accordingly; interrupt or complete planned chemotherapy followed by the targeted therapy.

Gefitinib:	
Gefitinib	250 mg orally once daily without regard to food until disease progression or unacceptable toxicity. Do not administer a missed dose within 12 hours of the next dose. The dose can be increased to 500 mg orally once daily in case of leptomeningeal infiltration.
Indicated as a first or subsequent line treatment of metastatic NSCLC of adenocarcinoma subtype with positive EGFR mutation, either exon 19 deletions or exon 21 L858R substitution gene mutations. Gefitinib is approved concurrently with the therascreen EGFR rotor-gene Q (RGQ) polymerase chain reaction (PCR) kit.	

Erlotinib:	
Erlotinib	150 mg orally once daily 1 hour before or 2 hours after food until symptomatic disease progression or unacceptable toxicity.
Indicated as a first-line treatment of metastatic NSCLC of adenocarcinoma subtype with positive EGFR mutation, either exon 19 deletions or exon 21 L858R substitution gene mutations. Erlotinib is approved concurrently with the Cobas EGFR mutation test.	

Under special circumstances, Erlotinib may be prescribed in case of:

- Undetermined EGFR status with poor performance status (PS) and high probability of EGFR mutation (Asian, nonsmoker, female).
- Special cases with metastatic NSCLC of squamous histology (never smokers, small biopsy specimens, or mixed histology).
- Negative EGFR mutation in elderly patients and those with poor PS.

Afatinib:	
Afatinib	40 mg orally once daily 1 hour before or 2 hours after food until symptomatic disease progression or unacceptable toxicity.
Indicated as a first-line treatment of metastatic NSCLC of adenocarcinoma subtype with positive EGFR mutation, either exon 19 deletions or exon 21 L858R substitution gene mutations.	
Afatinib is approved concurrently with the therascreen EGFR RGQ PCR Kit.	

Osimertinib:	
Osimertinib	80 mg orally once daily until symptomatic disease progression or unacceptable toxicity.
It is indicated for the treatment of metastatic NSCLC of adenocarcinoma subtype with positive EGFR T790M mutation, after progression on or after other EGFR tyrosine kinase inhibitor therapy.	
It can be considered as a first-line treatment for EGFR mutant cases.	
Osimertinib is approved currently with the Cobas EGFR mutation test.	

Crizotinib:	
Crizotinib	250 mg orally twice daily until symptomatic disease progression or unacceptable toxicity.
Indicated in the treatment of metastatic NSCLC of adenocarcinoma subtype with anaplastic lymphoma kinase gene rearrangement (ALK-positive) which was detected in tumor tissue by fluorescence in situ hybridization	
ROS-1 re-arrangements forming fusion protein is also sensitive to Crizotinib.	

Alectinib:	
Alectinib	600 mg orally twice daily on an empty stomach until symptomatic disease progression or unacceptable toxicity.
Indicated in the treatment of metastatic NSCLC with anaplastic lymphoma kinase gene rearrangement (ALK-positive) with disease progression on or who are intolerant to crizotinib.	
It can be considered as a first-line treatment for ALK-positive cases, especially with brain metastases.	

Ceritinib:	
Ceritinib	750 mg orally once daily on an empty stomach until symptomatic disease progression or unacceptable toxicity.
Indicated in the treatment of metastatic NSCLC with anaplastic lymphoma kinase gene rearrangement (ALK-positive) with disease progression on or who are intolerant to crizotinib.	

Evaluation of response to treatment will be offered after two months from initiation of treatment, then to be repeated every 4 months.

d. Maintenance Therapy

Indicated in those with the responsive or non-progressive disease after first-line therapy, and to be continued until disease progression and/or toxicity.

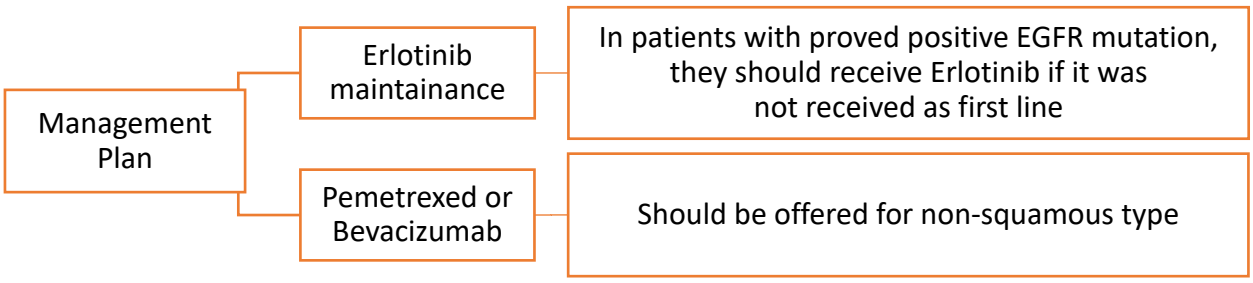
Types:

Continuation maintenance	Refers to the use of at least one of the agents given in the first line, beyond 4–6 cycles, in the absence of disease progression.
Switch maintenance	Refers to the initiation of a different agent, not included as part of the first-line regimen, after 4–6 cycles of initial therapy, in the absence of disease progression.

Agents that can be used as maintenance:

Erlotinib	Pemetrexed	Bevacizumab	Docetaxel	Gemcitabine

Planning:



e. Immunotherapy

- **Immune checkpoint inhibitors** are a subsequent therapy for patients with metastatic non-squamous NSCLC who have progressed on or after first-line chemotherapy based on data from a phase III randomized trial (CHECKMATE 057).
- These agents are preferred based on improved overall survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy.
- Human immune checkpoint inhibitor antibodies inhibit the programmed death (PD-1) receptor, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T-cells.
- Immune checkpoint inhibitors are associated with a delay in benefit when compared with targeted therapy or cytotoxic chemotherapy. Pseudoprogression has been reported; therefore, traditional RECIST criteria may not be applicable.

Nivolumab:

Nivolumab	3 mg/kg IV infusion over 1 hour every two weeks until symptomatic disease progression or unacceptable toxicity.

It is indicated as second-line treatment of metastatic NSCLC (either non-squamous or squamous) with progression on or after platinum-based chemotherapy and/or tyrosine kinase inhibitors.

Can be given as a first-line treatment for non-squamous NSCLC with high tumor mutational burden (TMB) & PDL-1 ≤1 in combination with Ipilimumab 1 mg/kg every six weeks.

Pembrolizumab:

Pembrolizumab	200mg IV infusion over 1 hour every three weeks until symptomatic disease progression or unacceptable toxicity or up to two years.

It is indicated as second-line treatment of metastatic NSCLC (either squamous or non-squamous) whose tumors express PD-L1, with progression on or after platinum-based chemotherapy and/or tyrosine kinase inhibitors.

Can be considered a first-line option for cases with non-squamous NSCLC without EGFR, ALK or ROS1 mutations as a combination with paclitaxel or nab-paclitaxel/carboplatin.

Can be considered a first-line option for cases with NSCLC without EGFR, ALK or ROS1 mutations with PDL-1 ≥50% as a monotherapy.

To determine PD-L1 expression, PD-L1 IHC 22C3 pharmDx should be used.

Atezolizumab:

Atezolizumab	**Atezolizumab**: 1200 mg **Bevacizumab**: 15 mg/kg **Paclitaxel**: 175-200 mg/m^2 **Carboplatin** AUC-6
Indication:	

First-line treatment option for non-squamous metastatic NSCLC:

Atezolizumab combined with bevacizumab/carboplatin/paclitaxel for four or six 21-day cycles then Atezolizumab every 21 days until the occurrence of unmanageable toxic effects or disease progression.

Second-line treatment of metastatic NSCLC (either squamous or non-squamous) regardless of PD-L1 status, with progression on or after platinum-based chemotherapy.

Management of Immune-related Adverse Events (irAEs):

In general, treatment of moderate or severe irAEs requires:

(1) Interruption of the checkpoint inhibitor and

(2) The use of corticosteroid immunosuppression.

- Treatment is based upon the severity of the observed toxicity:

(I) Patients with grade 2 immune-mediated toxicities [moderate]:

Treatment with checkpoint inhibitor should be withheld

Checkpoint inhibitor should not be resumed until symptoms or toxicity is grade 1 or less.

Corticosteroids (prednisone 0.5 mg/kg/day or equivalent) should be started if symptoms do not resolve within a week.

(II) Patients with grade 3 or 4 immune-mediated toxicities [severe or life-threatening]:

Treatment with the checkpoint inhibitor should be permanently discontinued.

High doses of corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) should be given.

When symptoms subside to grade 1 or less, steroids can be gradually tapered over at least one month.

N.B. Patients who benefit from corticosteroids do so within days.

- If symptoms do not clearly improve, particularly after approximately three days with intravenous steroids, our approach is to administer infliximab (5 mg/kg) rather than continue with a prolonged course of high-dose IV corticosteroids.
- If symptoms persist after the first infliximab dose, a second dose of infliximab (5 mg/kg) can be repeated two weeks after the initial dose.

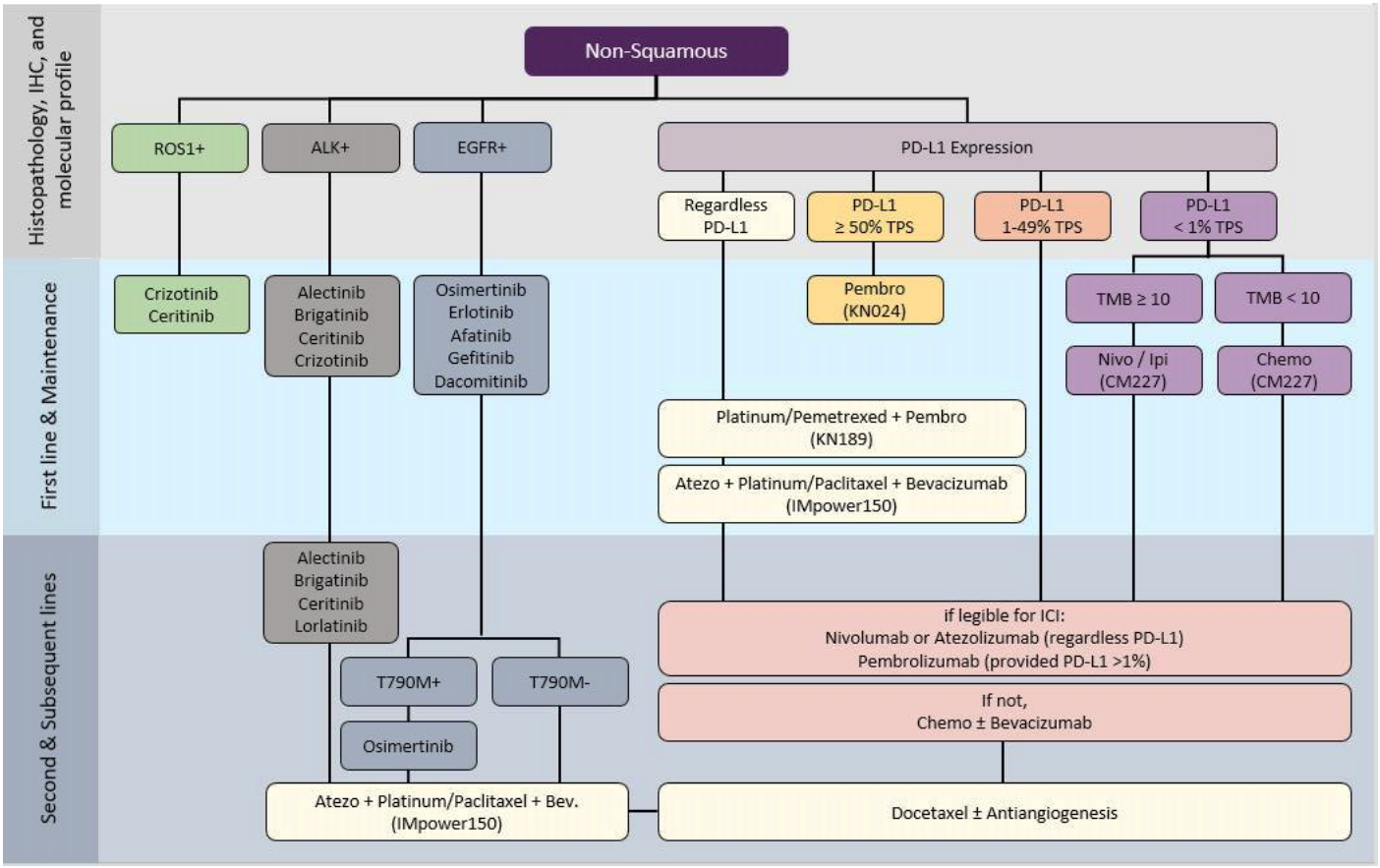
Follow Up

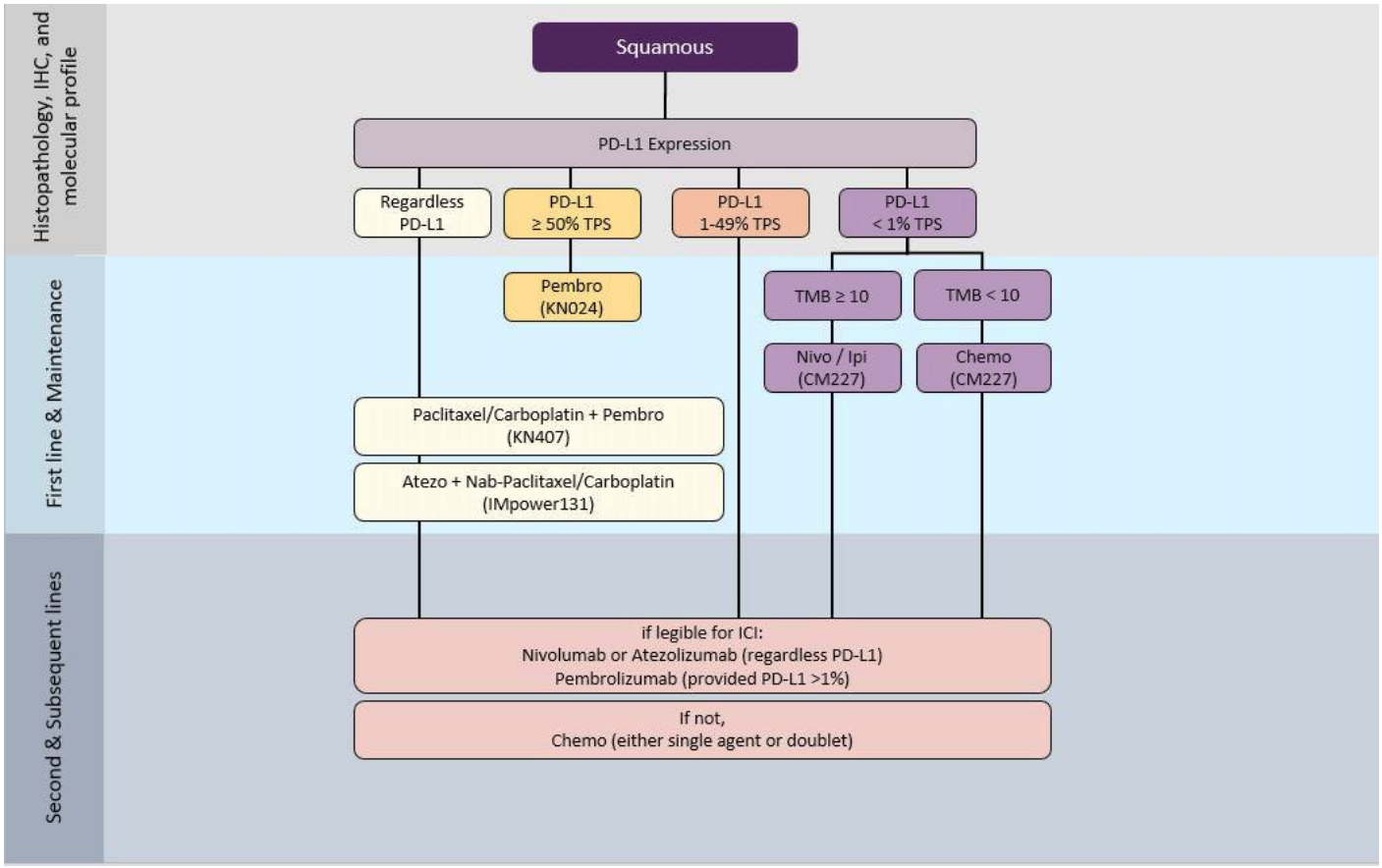
- Clinical examination, imaging, and laboratory tests performed as clinically indicated:
  - Every 3-4 months for two years.
- Tumor markers can be helpful in follow up, including:
  - Carcinoembryonic antigen (CEA),

- Ca 19.9 and
- Lactate dehydrogenase (LDH).

- Follow up then performed every:
  - Six months for three years,
  - Then annually.
- Early palliative care should be offered for all patients with NSCLC.

A proposed treatment algorithm for advanced NSCLC




Histopathology, IHC, and molecular profile
First line & Maintenance
Second & Subsequent lines
Squamous
PD-L1 Expression
Regardless PD-L1
PD-L1 ≥ 50% TPS
PD-L1 1-49% TPS
PD-L1 < 1% TPS
Pembro (KN024)
TMB ≥ 10
TMB < 10
Nivo / Ipi (CM227)
Chemo (CM227)
Paclitaxel/Carboplatin + Pembro (KN407)
Atezo + Nab-Paclitaxel/Carboplatin (IMpower131)
if legible for ICI:
Nivolumab or Atezolizumab (regardless PD-L1)
Pembrolizumab (provided PD-L1 >1%)
If not,
Chemo (either single agent or doublet)

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