



2018

# SAUDI LUNG CANCER GUIDELINE

National Cancer Center  
(NCC)

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## Table of Contents

<b>Indications</b> .....	6
<b>Contraindications</b> .....	6
Absolute-Possible with high risk .....	6
Relative .....	6
<b>Imaging Modality of Guidance</b> .....	6
<b>Needles</b> .....	8
<b>Techniques</b> .....	8
<b>Biopsy Procedure</b> .....	8
<b>Planning</b> .....	8
<b>Patient Positioning</b> .....	9
<b>Sedation</b> .....	9
<b>CT Scan Parameters</b> .....	9
<b>Biopsy Process</b> .....	10
<b>Post-Biopsy Care</b> .....	10
<b>Complications</b> .....	11
<b>Pneumothorax</b> .....	11
<b>Hemorrhage</b> .....	11
<b>Air embolism</b> .....	12
<b>Suggested References</b> .....	13
<b>Title</b> .....	16
<b>EUS-FNA in Staging of NSCLC</b> .....	16
<b>Role in Primary Tumor (T) Evaluation and Mediastinal Invasion (T4)</b> .....	17
<b>Mediastinal Nodal Staging (N Stage)</b> .....	17
<b>Assessment of Distant Metastasis (M Staging)</b> .....	18
<b>Restaging</b> .....	18
<b>Combined EUS-FNA and EBUS-TBNA for Mediastinal Evaluation</b> .....	18
<b>Impact of EUS on Patient Management</b> .....	18
<b>Position of EUS/EBUS in Current Guidelines</b> .....	18
<b>Future Perspectives</b> .....	19
<b>References:</b> .....	20

<b>Title: Guiding Principles of Systemic Therapy in Metastatic Non-Small Cell Lung Cancer</b> .....	23
<b>Introduction</b> .....	27
<b>Immunotherapy in the First-line setting:</b> .....	27
<b>Pembrolizumab:</b> .....	27
<b>Nivolumab:</b> .....	27
<b>Immunotherapy in pretreated patient with advanced NSCLC (Following platinum-based chemotherapy):</b> .....	28
<b>Nivolumab:</b> .....	28
<b>Pembrolizumab:</b> .....	29
<b>Atezolizumab:</b> .....	29
<b>Role of tumor PD-L1 expression as a biomarker:</b> .....	29
<b>References:</b> .....	30
<b>General approach to management of irAEs</b> .....	32
<b>Specific immune-related adverse events and its management:</b> .....	32
<b>Immune-mediated skin rash:</b> .....	32
<b>Immune-mediated Pneumonitis:</b> .....	33
<b>Immune-mediated Colitis:</b> .....	33
<b>Immune-mediated hepatitis:</b> .....	34
<b>Immune-mediated endocrinopathies:</b> .....	34
<b>Table 1: Summary of management guidelines for irAEs</b> .....	35
<b>Conclusion:</b> .....	36
<b>References</b> .....	37
<b>Conclusion</b> .....	42
<b>Conclusions</b> .....	46
<b>References:</b> .....	47
<b>Dermatological toxicities:</b> .....	49
<b>Diarrhea:</b> .....	50
<b>Interstitial lung disease (ILD):</b> .....	50
<b>References:</b> .....	51



2018

**IMAGE-GUIDED PERCUTANEOUS TRANSTHORACIC BIOPSY  
IN LUNG CANCER**

**National Cancer Center  
(NCC)**

**Title: Image-Guided Percutaneous Transthoracic Biopsy in Lung Cancer**

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Percutaneous transthoracic core biopsy requires careful manipulation and special attention to prevent or reduce procedure related complications.

- Fine needle aspiration biopsy
- Core biopsy

**Indications**

As with any interventional procedure, the potential benefits of core biopsy must outweigh the risks; and in each case the technique should be considered likely to affect patient management. Typically, percutaneous transthoracic core biopsy is performed in patients to

- Confirm the diagnosis of indeterminate pulmonary nodule or mass
- Characterize the tumor histopathology

**Contraindications**

Absolute-Possible with high risk

- Previous pneumonectomy and other instances of a single lung
- Suspected hydatid cyst or vascular malformation

Relative

- Coagulopathy or anticoagulant therapy
- Significant pulmonary arterial hypertension
- Severe lung disease (respiratory failure--mechanical ventilation, severe obstructive lung disease, and severe emphysematous disease)
- Large bullae
- Inability of the patient to cooperate (may performed under general anesthesia).

**Imaging Modality of Guidance**

Choice of the imaging modality is determined by

- Size and location of the lesion
- Availability of imaging systems
- Local expertise and preference.

**Fluoroscopy** is used less frequently imaging

- Advantages*
- Low cost
  - Short procedure time
  - Real-time visualization of the needle advancement

- Disadvantages*
- Difficulty in accessing central lesions
  - Difficulty in avoidance of bullae and vascular structures in the needle pass

**Ultrasonography (US)** is most often used imaging modality for accessing the peripheral, pleural-based lesions producing acoustic window as ultrasound beam does not pass through air.

It should be used whenever possible and appropriate

- Advantages*
- Real-time visualization of the needle advancement with multiplanar capability allowing accurate placement of the needle

- Low cost
- Short procedure time
- No radiation - safe

- Disadvantages*
- Can't access be used for accessing central lesions
  - Difficulty in avoidance of bullae and vascular structures in the needle pass

**Computed tomography (CT)** is the preferred and most common and standard used guidance imaging modality.

- Advantages*
- Revealing the anatomic structure
  - Characterizes the lesion (shape, necrosis and solid tumor)
  - Minimizing needle passage through aerated lung, bullae, fissures or vessels
  - Accurate accessing central and small lesion

- Disadvantages*
- Radiation
  - Relative long procedure time

## Needles

An ideal core biopsy needle should obtain sufficient tissue amount free of crush injury for histologic evaluation while minimizing possible complications.

*Type:* The needles types are based on the volume of the obtained tissue.

- End-cut biopsy needle provides full cannular width of tissue as the entire lumen with the whole length of needle advancement within the lesion.
- Side-notch biopsy needle provides shorter length of tissue than the needle advancement with less tissue volume than the entire needle lumen.

## Techniques

### *Coaxial technique*

- Needle stability in the chest wall
- Obtaining multiple sampling with a single pleural puncture.

### *Single shaft (non-coaxial) technique*

- More flexible
- Guiding the needle to the correct location.

Choice between needles and techniques based on

- Operator's preference and expertise
- Needle availability
- Institutional experience

## Biopsy Procedure

### Planning

- Obtaining the patient history and indications for the biopsy
- Obtaining an informed consent including potential risks and benefits in details
- Obtaining baseline chest CT to determine the biopsy route and technique based on the size and location of the lesion, availability of imaging systems, and local expertise
- Choosing the needle path as a straight pathway from the skin to lesion with a 90-degree angle between the needle and the pleura avoiding transversal of bullae, vessels and bronchi

- Choosing the more peripheral or upper lesion or upper over a deep or lower lesion
- Avoiding necrotic portions of lesions

#### **Patient Positioning**

- Consideration of position should be made during biopsy planning as the patient should maintain the same position throughout the entire procedure.
- Prone position is ideal due to
  - Least amount of chest wall motion.
  - More comfortable "biopsy side down" supine position during recovery, which may reduce the chance of developing a pneumothorax.
  - The patient will not see the biopsy needle which may reduce both anxiety and movement.

#### **Sedation**

- Sedation and intravenous analgesic medications are usually not required with the liberal use of chest wall local anesthetic.
- The pain and burning sensation are usually limited and momentary, and arises from administration of the local anesthetic via the needle into the partial pleura.
- Sedation and analgesia are primarily used for anxious and uncooperative patients, some selected elderly people with musculoskeletal diseases who cannot maintain raised arms, lesions adherent to periosteum and chest wall or when the procedure is lengthy.

#### **CT Scan Parameters**

- mA and slice thickness
- Choosing low-dose axial scan with 120 kVp with 40mA or lower per slice.
- Choosing slice thickness should be less than half the diameter of the targeted lesion as the following:
  - one centimeter or 5 mm for lesions > 3 cm in diameter,
  - 5 mm for lesion 1- 3 cm in diameter
  - 3mm cm for lesions 5mm - 1cm
  - 3mm for lesions < 5mm in diameter

**Biopsy Process**

- Positioning the patient on the CT table
- Placing a radiopaque marker or grid on the patient's skin over the area of interest
- Obtaining a short CT scan of the region of interest with suspended respiration
- Choosing the appropriate table position and needle
- Measuring the depth from the skin entry site to the lesion
- Prepping and draping the skin site using sterile technique
- Administering local anesthesia into the skin, subcutaneous tissues, and intercostal muscles
- Advancing 17- or 19- gauge introducer needle with appropriate length based on the lesion depth while the patient's respiration is suspended
- Coaxial advancing an 18- or 20-gauge automated cutting needle smaller than the introducer needle toward the periphery of or inside the lesion
- Obtaining a short segment CT to verify the needle angle and tip position based on the last scan (a sequential technique). The needle is then advanced in one motion through the pleura to the prescribed depth.
- Confirming and documenting the location of needle tip position at the periphery of or within the lesion
- Firing the needle into the lesion during suspended respiration and obtaining at least two tissue samples but more can be obtained based on the lesion characteristics.

**Post-Biopsy Care**

- Obtaining a short CT scan to evaluate for immediate complications. If the scan is normal with no significant pneumothorax and the patient is asymptomatic, the patient is transported to the designated area for clinical monitoring
- The patient should remain recumbent throughout the monitoring period
- Obtaining follow-up sitting upright expiratory chest radiographs at 1 to 2 hours after biopsy
- Discharging the patient If the chest radiograph shows no new changes
- Instructing the patient to abstain from strenuous or weight-bearing activities for 3 days.

- Anticoagulants, antiplatelets and nonsteroidal anti-inflammatory drugs are not allowed.

### Complications

- The overall accepted complication rate of percutaneous transthoracic lung biopsies of 10% with threshold success rate of 85% are acceptable
- Most complications occur immediately or within the first hour of a biopsy and they can be treated conservatively, often on an outpatient basis (35-37).
- Common complications include pneumothorax and hemorrhage.
- Rare complications include air embolism, vasovagal reaction, cardiac tamponade, and seeding of the tract with tumor.

### Pneumothorax

- The average incidence is 20%
- Requiring chest tube varies from 5 to 18 %
- Occur during or immediately after the procedure
- Risk factors include lesion contact with the pleura (23), the presence of emphysema, transgression of fissures, a small angle of the needle with the thoracic pleura, and multiple repositioning of the needle
- Small pneumothorax (<20% lung volume) is asymptomatic and stable - do not require treatment except conservative management
- Symptomatic pneumothorax, size > 30% of the lung volume, and / or its size continues to increase is requiring treatment (supplemental nasal oxygen and positioning biopsy side-down if possible, manual aspiration If the biopsy needle is still within the thorax, decompression with a chest tube if the biopsy needle has been removed)
- Serial expiratory upright chest radiographs should be obtained to observe for the recurrence of pneumothorax with appropriate clinical monitoring

### Hemorrhage

- Second most common and most dangerous potential complication
- Every biopsy is associated with some degree of hemorrhage
- Most often self-limited and resolves spontaneously without treatment
- It may occur with or without hemoptysis
- Hemorrhage and hemoptysis occur in approximately 11% and up to 7%, respectively

- More likely to occur with abnormal coagulation, pulmonary arterial hypertension, cutting needles larger than 18 gauge, lesion depth greater than 2cm, lesion size smaller than 2 cm, vascularity, cavitations, enlarged bronchial vessels in the vicinity, and central location
- The patient should be placed in decubitus position with the biopsy side down to prevent transbronchial aspiration of blood. If the patient is hemodynamically unstable, appropriate supportive management with fluid resuscitation with or without blood transfusion is required.

**Air embolism**

- Most severe complications but it is one of the least frequent (0.07%)
- Air enters the pulmonary venous system leading to systemic air embolism. Air embolism can cause myocardial infarction, arrhythmia, stroke and death.
- The patient should be placed in the left lateral decubitus position or in Trendelenberg position to prevent residual air in the left atrium from entering the cerebral circulation. Supplemental 100% oxygen should be administered and general symptomatic support should be provided

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2018

**THE ROLE OF ENDOSCOPIC  
ULTRASOUND/GASTROENTEROLOGIST IN LUNG CANCER  
DIAGNOSIS AND MANAGEMENT**

**National Cancer Center  
(NCC)**



**Title: The role of Endoscopic ultrasound/Gastroenterologist in lung cancer diagnosis  
and management**

**AbdulMonem Swied, MD**

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Accurate diagnosis and staging is of paramount importance for both prognostic and therapeutic reasons in lung cancers.

Mediastinal staging conventionally relied heavily on invasive modalities like mediastinoscopies, and thoracotomies. Endoscopic ultrasound (EUS) evaluation of mediastinum, EUS guided fine needle aspiration (EUS-FNA) and endobronchial ultrasound guided transbronchial needle aspirations (EBUS-TBNA) have evolved over last few years as novel and minimally invasive modalities for accurately staging mediastinal nodes, to guide appropriate therapy, and to avoid unnecessary surgeries especially in NSCLC patients.<sup>3</sup>

According to 7th edition of TNM (Tumor, Nodal status, Metastasis) staging for NSCLC, stage I and II patients are treated with surgical resection, whereas stage III (N2 nodal status, T4 mediastinal invasion) are offered chemo-radiation with only limited role of surgical resection.

Mediastinal nodal sampling by using EUS/EBUS has been documented to be superior to surgical staging in several published studies. This has been emphasized also in the latest 2013 guidelines for lung cancer by American College of Chest Physicians which state that EUS/EBUS are the techniques of choice for mediastinal staging.

**EUS-FNA in Staging of NSCLC**

NSCLC is staged according to the tumor-node-metastasis (TNM) system. This system takes into account the characteristics of the local tumor (T), the presence or absence of regional lymph node metastasis (N), and the presence or absence of distant metastases (M). The stage of the tumor (stage I through IV) depends upon the particular combination of T, N, and M characteristics for the given patient.

EUS can contribute to each component of TNM staging for lung cancer. It can help characterize the primary tumor (in centrally located tumors), assesses the mediastinal lymph nodes for evidence of metastatic disease, and evaluates some sites of distant metastasis such as the left

lobe of the liver and adrenal glands. Among these contributions, however, mediastinal lymph node evaluation is its primary role.

#### **Role in Primary Tumor (T) Evaluation and Mediastinal Invasion (T4)**

EUS aids in biopsy of intrapulmonary tumors in tumors located *centrally near or adjacent to esophagus*. Once the primary tumor has been identified, EUS can help to define mediastinal invasion, which includes involvement of mediastinal structures such as left atrium, large central vessels, esophagus, and vertebrae by the intrapulmonary tumor. This invasion if present places the patient in T4 category (stage IIIb) and generally precludes surgical resection as a treatment option.

US has a sensitivity of 87% and specificity of 98% to detect T4 mediastinal invasion in current literature. This is significantly high when compared to a preoperative computed tomography (CT) scan, which has a low sensitivity (< 75%) to detect mediastinal invasion and positron emission tomography (PET) scan which does not have a defined role in T4 staging because of poor anatomic resolution.

#### **Mediastinal Nodal Staging (N Stage)**

Mediastinal/hilar nodal involvement (N stage) by the tumor is an important determinant for staging and guiding treatment. Lymph node sampling for histopathological examination is necessary in patients with enlarged mediastinal lymph nodes on CT scan or metabolically active nodes on PET scan, as imaging modalities alone have a low accuracy in staging of mediastinal nodes.

EUS-FNA is effective at detecting and staging mediastinal metastatic disease. It can sample lymph nodes in the ***posterior mediastinum*** (level 4L, lower left paratracheal; level 6, para aortal; level 8, para esophageal; and level 9, near inferior pulmonary ligament) and subcarina (level 7), sites that are particularly susceptible to metastasis. In addition, it might be able to sample lymph nodes in the aortopulmonary window (level 5), although this is challenging in a few cases because of interposition of pulmonary artery, which makes sampling technically difficult.

***EUS visualization is limited in superior and anterior mediastinum***, especially upper paratracheal (level 2) and lower paratracheal nodes to the right (level 4R) due to interposition of air filled bronchi. This precludes sampling from these stations using EUS alone, and a combined approach using EUS + EBUS is a preferred modality in such situations. In addition to

lymph nodes, EUS can be used to sample **left adrenal gland, left liver lobe metastasis** and also centrally located intrapulmonary tumors as discussed earlier.

The role of EUS in patients with NSCLC and a negative CT finding for enlarged mediastinal nodes is still not clear, as most data for EUS-FNA is in patients with enlarged mediastinal lymph nodes. However, some emerging data have shown importance of EUS evaluation in these patients, as approximately 20% of these normal size nodes can be positive for malignancy.

#### **Assessment of Distant Metastasis (M Staging)**

Lung cancer patients can commonly (~40%) present with distant metastasis to brain, bone, adrenal glands, and liver. EUS is an effective modality to screen and sample metastasis from **celiac group of nodes, left adrenal gland and left lobe of liver**. Detection of liver, celiac and adrenal deposits on EUS defines M1 stage of the disease and excludes curative surgery. EUS thus is a unique modality wherein abdominal evaluation for such lesions can be done simultaneously during a mediastinal staging procedure.

#### **Restaging**

EUS can help in restaging of disease in patients with stage III disease after neoadjuvant therapy.

#### **Combined EUS-FNA and EBUS-TBNA for Mediastinal Evaluation**

Both EUS and EBUS are **complementary** to each other in mediastinal evaluation of lung cancer patients. Combined together both techniques can virtually reach almost all nodal stations of mediastinum. In general **EUS is an excellent modality for visualization and sampling from posterior and inferior mediastinum** whereas EBUS is a preferred modality in anterior mediastinum.

#### **Impact of EUS on Patient Management**

EUS impacts management of approximately 95% of patients with lung cancer, and has a major role in preventing unnecessary mediastinoscopies and futile thoracotomies.

#### **Position of EUS/EBUS in Current Guidelines**

- In patients with **high suspicion** of N2, N3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), EBUS-FNA, EUS-FNA or combined EBUS/EUS-FNA is recommended over surgical staging as a mostly suitable diagnostic modality (grade 1B).
- In patients with an **intermediate suspicion** of N2, N3 involvement, i.e., a radiographically normal mediastinum (by CT and PET) and a central tumor or N1 lymph

node enlargement (and no distant metastases), EBUS-TBNA, EUS-FNA or combined EBUS/EUS-FNA is suggested over surgical staging as a mostly suitable diagnostic modality (grade 2B).

**Future Perspectives**

Molecular analysis and targeted therapy for different subtypes of NSCLC are emerging areas with lot of potential for therapeutic application. Samples obtained from mediastinal lymph nodes by EUS-FNA can be used to detect lung cancer-associated genes, such as carcinoembryonic antigen, cytokeratin 19, KS1/4, lunx, muc 1, and prostate derived ETS factor.

Making combined EUS/EBUS more accessible and acceptable to both gastroenterologists and pulmonologists is a challenge, which needs to be overcome to achieve success against this deadly cancer

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2018

# GUIDING PRINCIPLES OF SYSTEMIC THERAPY IN METASTATIC NON-SMALL CELL LUNG CANCER

National Cancer Center  
(NCC)



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**Title: Guiding Principles of Systemic Therapy in Metastatic Non-Small Cell Lung Cancer**

**Abdul Rahman Jazieh, MD, MPH**

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The evolution of systemic therapy of NSCLC over the last few years has been remarkable and resulted in major shift in oncology practice. The most important recent changes include the introduction of immune therapy and treatment of TKI resistant disease. These advances changed the landscape of systemic therapy of NSCLC and presented more challenges to practicing oncologists to navigate through priority choices from multiple available options.

The following are guiding principles that will help oncologists to make treatment decision in commonly encountered clinically scenarios of NSCLC.

1. Pathology Work-up:

Tumor profiling is a must for all non-small cell lung cancer to determine:

- a. Histology subtype: especially to differentiate squamous cell from non-squamous cell for strong reasons including:
  - i. Avoiding potentially harmful treatment for squamous cell lung cancer such as bevacizumab or less beneficial treatment for this disease (i.e. pemetrexed).
  - ii. Performing molecular profiling for non-squamous non-small cell lung carcinoma.
- b. Obtaining EGFR, ALK and ROS1 testing in all non-squamous cell carcinoma; preferably using next generation sequencing.
- c. PDL1 testing in all NSCLC subtypes at diagnosis.

2. Management of EGFR sensitizing mutation tumors:

Tyrosine kinase inhibitors should be used upfront whenever possible. If systemic chemotherapy was initiated, a switch to TKI should be done as soon as possible. TKIs showed better response rate, progression free survival and quality of life compared to chemotherapy and all efforts should be made for patients to receive TKI irrespective of performance status.

3. Management of EGFR resistant tumors:

Tumors with secondary resistance should be tested for T790 mutation and if positive osimirtinib should be used.

If T790 mutation is not detected, switch to platinum doublet chemotherapy. Local therapy should be considered for single or oligo metastatic disease progression.

4. ALK fusion positive tumor:  
Patient should receive crizotinib as early as possible. If progressed, ceritinib should be used in 2nd line (alectinib was recently approved). Chemotherapy should be reserved for third line.
5. ROS1 positive tumor patients should be treated with crizotinib as early as possible. Chemotherapy should be used for subsequent lines.
6. Management of wild type tumors (No EGFR, ALK or ROS1 Mutation)
  - a. PDL1 TPS > 50%  
Pembrolizumab is preferred treatment option over chemotherapy.
  - b. PDL1 TPS < 50% - chemotherapy doublet is preferred option.
7. EGFR/ALK unknown NSCLC:  
All efforts should be made to get the test done including circulating tumor cell DNA (ctDNA). If not possible, it should be treated like wild type. TKI, erlotinib can be considered for 2<sup>nd</sup> or 3<sup>rd</sup> line as third of our patients may have mutations; which is much more common than Western population.
8. Immunotherapy:
  - Check point inhibitors are approved in NSCLC as follows:
    - i. Pembrolizumab first line for all NSCLC subtypes with PDL1 TPS > 50% and for second line for positive PDL1 tumors.
    - ii. Nivolumab: approved for 2<sup>nd</sup> line treatment of all NSCLC irrespective of histology or PDL1 status.
    - iii. Atezumab: approved for second line treatment of all NSCLC irrespective of histology and PDL1 status.
  - Immune therapy should be used in patients with good PS 0-1 and monitored closely for immune therapy related adverse events which are less common than chemotherapy and different pattern, but they can be serious and life threatening.
  - Role of immunotherapy in the EGFR and ALK sensitizing tumors is not known but should not be used before TKI and systemic chemotherapy combination at present time.
9. Selection of Chemotherapy Regimen
  - i. Non Squamous NSCLC
    - Chemotherapy preferred regimen is platinum doublet with or without Bevacizumab
    - Pemetrexed is very active and preferred agent due to its efficacy and toxicity profile.
  - ii. Squamous Cell Carcinoma
    - Bevacizumab should be avoided due to risk of fatal pulmonary hemorrhage.

- Pemetrexed also is not recommended due to being less efficient than Gemcitabine.
- Gemcitabine and Taxans combination are reasonable choices.

10. Managing Patients with Poor Performance Status:

- i. PS2 is the most difficult to decide about as it was not included in most studies and should be individualized. Using single agent may be reasonable.
- ii. PS 3 – 4 systemic therapy is not recommended usually except for TKI for patient with sensitizing driver mutation.

11. Patient involvement in setting the goals of care:

It is very critical to prioritize the goal of care clearly and involve the patients and their families.

12. Finally, having multidisciplinary team is more important than ever due to the complex and multiple available treatment options that can be offered to the patients and require specific work up and close monitoring.



2018

# IMMUNOTHERAPY OF NON-SMALL CELL LUNG CANCER

National Cancer Center  
(NCC)



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## **Title: Immunotherapy of Non-Small Cell Lung Cancer**

**Abdullah K. Altwaairgi, MD**

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### **Introduction**

The role of immunotherapy in non-small cell lung cancer (NSCLC) has been primarily driven by the data from prior clinical studies that have shown prolonged tumor responses and long-term survival benefit in patients with chemotherapy-refractory metastatic NSCLC utilizing different checkpoint inhibitors targeting programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1). Additional works are ongoing to demonstrate the potential biomarkers of response to such therapy.

### **Immunotherapy in the First-line setting:**

For patients with advanced NSCLC who have not received systemic therapy and had no contraindications to immunotherapy, tumor programmed death ligand 1 (PD-L1) need to be assessed on the initial biopsy. For patients in whom at least 50 % of tumor +ve for PD-L1, in the absence of an *EGFR* mutation or *ALK* translocation, we recommend first line pembrolizumab. This was based on number of recent data that have looked at two agents in this setting;

### **Pembrolizumab:**

In the KEYNOTE-024 study, phase III randomly enrolled 305 patients with advanced NSCLC having at least 50 % tumor cell PD-L1 who had not received prior systemic therapy into Pembrolizumab monotherapy vs. standard platinum-doublet chemotherapy. Patients with *EGFR* mutations or *ALK* translocations were excluded from the study. The primary endpoint of PFS, was improved with pembrolizumab compared with chemotherapy (median PFS, 10.3 versus six months; HR 0.50, 95% CI 0.37-0.68). OS was also improved (HR 0.60, 95% CI 0.41-0.89). ORRs were 45 and 28 %, for pembrolizumab and platinum-doublet chemotherapy respectively.

### **Nivolumab:**

In the CheckMate 026 trial, phase III enrolled 541 patients with advanced PD-L1-positive NSCLC ( $\geq 1$  %) who didn't receive any prior systemic therapy were randomly assigned to Nivolumab or platinum-doublet chemotherapy. The primary endpoint of PFS in patients with  $\geq 5$  % tumor PD-L1 expression, was not prolonged with Nivolumab compared with chemotherapy (median PFS, 4.2 vs. 5.9 months with one-year PFS rate 24 versus 23 %; HR 1.15, 95% CI

0.91-1.45). OS in patients with  $\geq 5\%$  tumor PD-L1 expression was not prolonged with Nivolumab compared with chemotherapy (median OS 14.2 months versus 13.2 months; HR 1.02, 95% CI 0.80-1.30).<sup>2</sup>

**Immunotherapy in pretreated patient with advanced NSCLC (Following platinum-based chemotherapy):**

For patients without a driver mutation who have progressed on prior chemotherapy for advanced NSCLC, we recommend immunotherapy. Options available are Nivolumab or Atezolizumab (regardless of PD expression status) or Pembrolizumab (If tumor PD-L1  $\geq 1\%$ ) Patient with EGFR or ALK alterations who have progressed on available targeted agents and at least one line of chemotherapy, consideration of immunotherapy or further single-agent chemotherapy are acceptable options.

**Nivolumab:**

In CheckMate 017 trial, phase III trial enrolled 272 patients with advanced squamous NSCLC who progressed on platinum-based chemotherapy were randomly enrolled to Nivolumab or docetaxel. The primary endpoint of overall survival (OS), was prolonged with Nivolumab compared with chemotherapy (median OS 9.2 vs. 6.0 months; one-year survival rate 42 vs. 24 %, HR 0.59, 95% CI 0.44-0.79). PD-L1 tumor expression did not appear to influence survival benefit with Nivolumab over docetaxel. Moreover, severe (grade 3 or higher) treatment-related adverse events were less common with Nivolumab compared with docetaxel (7 versus 54 %).<sup>3</sup>

In CheckMate 057 trial, phase III trial enrolled 582 patients with advanced non-squamous NSCLC who progressed on platinum-based chemotherapy were randomly enrolled to treatment with Nivolumab or docetaxel. The primary endpoint of overall survival (OS), was prolonged with Nivolumab compared with Docetaxel (median OS 12.2 vs. 9.4 months; HR 0.72, 95% CI 0.60-0.88). Any degree of tumor PD-L1 expression was found to be correlated with improved survival with Nivolumab. Safety data was similar to the previous trial with less severe (grade 3 to 4) treatment-related adverse effects were seen in patients receiving Nivolumab, compared to those treated with docetaxel (10 % vs. 54 %).<sup>4</sup>

**Pembrolizumab:**

In the KEYNOTE-010 study, phase II/III randomly enrolled over 1000 patients with previously treated advanced NSCLC and at least 1 % PD-L1 expression. Patients were enrolled to either Pembrolizumab at 2 dosages (2 mg/kg, and 10 mg/kg), or Docetaxel. Pembrolizumab was associated with improved median OS in the overall patient population (10.4 and 12.7 months vs. 8.5 months for the docetaxel treated patients. Fewer grade 3 or more treatment-related adverse events (13 and 16 %, respectively versus 35 % for the docetaxel treated patients). 5

**Atezolizumab:**

In the OAK study, a phase III trial enrolling 1225 patients with PD-L1-unselected advanced NSCLC into Atezolizumab monotherapy compared with docetaxel. The primary endpoint of OS, was prolonged with Atezolizumab compared with chemotherapy regardless of PD-L1 status (median OS, 13.8 vs. 9.6 months; HR 0.73, 95% CI 0.62-0.87) .6

**Role of tumor PD-L1 expression as a biomarker:**

Although several data of checkpoint inhibitors in NSCLC suggest that PD-L1 expression rate correlates with benefit. However, several challenges encounter adopting tumor PD-L1 as a sole criterion for the treatment of patients with prior platinum-based chemotherapy. These challenges include that the different immunohistochemistry assays that are available with variations of defining "PD-L1 positivity" and Different thresholds of PD-L1 positivity, ranging between 1 and 50 % as well as the considerable PD-L1 heterogeneity within tumors, which may not be accurately accounted for in small tumor biopsy. Moreover, the Responses to PD-1 inhibitor therapy have been seen in PD-L1-negative tumors across different trials.

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2018

# MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS (IRAES)

National Cancer Center  
(NCC)



## **Title: Management of Immune-related adverse events (irAEs)**

**Jawaher Ansari, MD**

Antibodies that target key immune check points such as programmed cell death protein-1 (PD-1; nivolumab<sup>i</sup> and pembrolizumab<sup>iii iv</sup>) on T lymphocytes and its principal ligand programmed death ligand-1 (PD-L1; atezolizumab<sup>v</sup>) on tumor cells, have recently been approved for the management of non-small cell lung cancer (NSCLC). Checkpoint inhibition is associated with a unique spectrum of side effects termed immune-related adverse events (irAEs). IrAEs can affect any organ system, but they typically involve the skin, gastrointestinal, hepatic, and endocrine systems.

### **General approach to management of irAEs**

Patients with suspected irAEs should be adequately evaluated to rule out other etiologies, as presenting symptoms can often be non-specific. In the majority of clinical trials irAEs occurring during treatment were reversible and managed with drug interruptions, administration of corticosteroids and/or supportive care. Patients should be monitored closely even after discontinuation of checkpoint inhibitors as irAEs are known to occur several months after discontinuation of therapy

Management of moderate to severe irAEs requires a temporary interruption or permanent discontinuation of checkpoint inhibitors and use of corticosteroid immunosuppression.

- For patients with grade 2 (moderate) irAEs, treatment with the checkpoint inhibitor should be withheld and should not be resumed until symptoms resolve to grade 1 or less. Corticosteroids (methylprednisolone 0.5-1 mg/kg/day or equivalent) should be commenced if symptoms do not resolve within a week.
- For patients developing grade 3-4 (severe or life-threatening) irAEs, treatment with the checkpoint inhibitor should be permanently discontinued. High dose corticosteroids (methylprednisolone 1-4 mg/kg/day or equivalent) should be administered.
- When corticosteroids are used, then this should be tapered gradually over 1 month upon improvement of symptoms as rapid tapering may lead to worsening or recurrence of the irAE.
- For patients with irAEs that do not improve with corticosteroid use, administration of other systemic immunosuppressant should be considered.

### **Specific immune-related adverse events and its management:**

#### **Immune-mediated skin rash:**

Skin rash associated with checkpoint inhibitors appears as erythematous, reticular, and maculopapular lesions commonly involving the trunk and extremities. Grade 1-2 skin rashes are usually treated with topical corticosteroid creams. Oral anti-pruritic medications can be used if

associated with troublesome pruritus. Severe rashes (grade 3 and above) should be managed with oral or intravenous corticosteroids.

**Immune-mediated Pneumonitis:**

In patients treated with checkpoint inhibitors, the incidence of grade 3-4 pneumonitis is about 1%. Patients receiving checkpoint inhibitors should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy infiltrates), cough, chest pain, dyspnoea and hypoxia. There should be a high index of suspicion for irAEs, once infectious and disease-related etiologies are ruled out.

- Grade 3 or 4 pneumonitis: checkpoint inhibitors must be permanently discontinued, and corticosteroids should be initiated at a dose of 2-4 mg/kg/day methylprednisolone equivalents.
- Grade 2 pneumonitis: checkpoint inhibitors should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, checkpoint inhibitors may be resumed after tapering of steroids. If worsening or no improvement occurs then manage as per guidelines for grade 3-4 pneumonitis.

**Immune-mediated Colitis:**

Diarrhea is relatively common in patients undergoing treatment with checkpoint inhibitors; however, the incidence of grade 3-4 diarrhea is very low (<2%). Differential diagnoses such as *Clostridium difficile* infections should be ruled out. Supportive measures such as oral hydration, diet modification, and use of anti-motility agents should be encouraged. If symptoms persist for more than 3 days, or increase, and/or no infectious causes are readily identified, the use of oral or intravenous corticosteroids is required.

- Grade 4 diarrhea or colitis: permanently discontinue checkpoint inhibitors and initiate corticosteroids at a dose of 1-2 mg/kg/day methylprednisolone equivalents.
- Grade 3 diarrhea or colitis: withhold checkpoint inhibitors and initiate corticosteroids (1-2 mg/kg/day methylprednisolone equivalents).
- Grade 2 diarrhea or colitis: withhold checkpoint inhibitors and initiate corticosteroids (0.5-1 mg/kg/day methylprednisolone equivalents).
- In severe cases where symptoms do not improve with oral corticosteroids, hospitalization for intravenous corticosteroids, hydration, and electrolyte management is required. If intravenous corticosteroids (up to 2 mg/kg methylprednisolone twice a day) do not lead to symptom resolution, infliximab at a dose of 5 mg/kg, once every 2 weeks should be considered<sup>vi</sup>.

**Immune-mediated hepatitis:**

The incidence of grade 3-4 liver function test abnormalities during treatment with checkpoint inhibitors is <2%. Monitor patients for abnormal liver tests prior to and periodically during treatment with checkpoint inhibitors. If AST and ALT increase during treatment, viral and other causes of hepatitis should be excluded. CT scan findings are non-specific, however, in severe cases findings may include mild hepatomegaly, periportal edema, or periportal lymphadenopathy<sup>vii</sup>. Administer corticosteroids for Grade 2 or greater transaminitis; withhold checkpoint inhibitors for Grade 2 and permanently discontinue for grade 3 or 4 immune-mediated hepatitis. Unlike for patients with diarrhea/colitis, infliximab should not be given to patients with hepatitis because infliximab carries a risk of hepatotoxicity.

**Immune-mediated endocrinopathies:**

Hypophysitis, adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus can occur with checkpoint inhibitor treatment. Monitor signs, symptoms and thyroid function tests prior to and periodically during treatment.

- Hypophysitis: Administer corticosteroids for Grade 2 or higher. Withhold checkpoint inhibitors for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis.
- Adrenal insufficiency: Administer corticosteroids for Grade 3 or 4. Withhold checkpoint inhibitors for Grade 2 and permanently discontinue for Grade 3 or 4.
- Hypothyroidism: hormone-replacement therapy.
- Hyperthyroidism: medical management.
- Type I diabetes: commence on insulin. Withhold checkpoint inhibitors for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

**Table 1: Summary of management guidelines for irAEs**

	Grade 1	Grade 2	Grade 3	Grade 4
<b>Immune-mediated Pneumonitis</b>				
Checkpoint inhibitors	Withhold	Withhold	Permanently Discontinue	
Treatment	Supportive	1-2mg/kg/day methylprednisolone	2-4mg/kg/day methylprednisolone	2-4mg/kg/day methylprednisolone
Investigations	CXR	Consider bronchoscopy/ lung biopsy		
<b>Immune-mediated Colitis</b>				
Checkpoint inhibitors	Continue	Withhold	Withhold	Permanently discontinue
Treatment	Supportive	0.5-1mg/kg/day methylprednisolone	1-2mg/kg/day methylprednisolone	
Investigations	-	-	Consider colonoscopy	
<b>Immune-mediated Hepatitis</b>				
Checkpoint inhibitors	Continue	Withhold	Permanently discontinue	
Treatment	Supportive	0.5-1mg/kg/day methylprednisolone	1-2mg/kg/day methylprednisolone	
<b>Immune-mediated Nephritis</b>				
Checkpoint inhibitors	Continue	Withhold	Withhold	Permanently discontinue
Treatment		0.5-1mg/kg/day methylprednisolone		1-2mg/kg/day methylprednisolone
Investigations		Consider renal biopsy		

<b>Immune-mediated Rash</b>				
Checkpoint inhibitors	Continue	Continue	Withhold	Permanently discontinue
Treatment	Topical steroids		1-2mg/kg/day methylprednisolone	
Investigations			Skin biopsy	
<b>Immune-mediated Neurology</b>				
Checkpoint inhibitors	Continue	Withhold	permanently discontinue	
Treatment	Supportive	0.5-1mg/kg/day methylprednisolone	1-2mg/kg/day methylprednisolone	

**Conclusion:**

Checkpoint inhibitors targeting PD-1/PD-L1 have significantly improved outcomes in the first- and second-line management of patients with NSCLC. Low-grade irAEs are common and transient in the vast majority; however, occasionally severe irAEs can lead to significant morbidity or mortality. The most common irAEs are dermatitis, colitis, hepatitis and endocrinopathies, although other sites can be affected. Rapid identification of these side effects and initiation of systemic immunosuppression can improve outcomes without compromising the therapeutic efficacy. The management of irAEs has largely been formulated following clinical experience with anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) drugs in melanoma patients. No prospective trials have been conducted to assess superiority of one management option over another. Ongoing clinical trials and further clinical experience with checkpoint inhibitors is likely to refine the management guidelines for irAEs in the near future.

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2018

# INITIAL TREATMENT OF EGFR MUTATION NSCLC

National Cancer Center  
(NCC)



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**Title:** Initial Treatment of EGFR Mutation NSCLC

**Mervat Mahrous, MD**

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Over the past few years, sub-classification of NSCLC has changed from histology to molecular biomarkers after identification of pathways involved in the development of lung cancer. Aberrant Epidermal growth factor receptor (EGFR) signaling is one of most important discovered pathways that can drive the lung cancer, especially in non-smoker patient population with adenocarcinoma component. As a result, inhibition of the EGFR pathway has been demonstrated to be a strong predictor to high responsiveness to target therapy in the treatment of NSCLC, and strategy to block this pathway by small molecule tyrosine kinase inhibitors (TKIs). The most common EGFR mutations (85 – 90%) are deletions in exon 19 and L858R point mutation in exon 21 (1).

Mutations in exon 18 and 20 are considered as uncommon mutations (10%). There is a significant association between sensitivity to EGFR TKIs and the types of EGFR mutations. For instance, deletion 19, exon 21 (L858R, L861) and exon 18 (G719X) mutations are sensitizing mutations for EGFR TKIs, and had relatively longer duration of response, progression free survival (PFS) and overall survival (OS) (2).

Whereas exon 20 insertions confer resistance. Some studies reported response to all types of mutations EGFR mutations can be found in all histologic subtypes of NSCLC. It was observed in 2.7% of patients with squamous cell carcinoma (1). Its prevalence increases up to 10% in Western patient population with adenocarcinoma and up to 50% of Asian patients, with higher EGFR mutation frequency in Asian, non-smokers, women and non-mucinous cancers (3). Jazieh et al reported in a retrospective study which conducted in the gulf region, EGFR mutations were detected overall in 28.7% with a prevalence of 32.46% in adenocarcinoma which is higher than reported in western patients but still lower than the Asian population (4).

Over the last several years, multiple EGFR-targeted therapies have been developed small-molecule EGFR TKIs. Gefitinib and erlotinib are the reversible first-generation EGFR TKIs. Second-generation EGFR TKIs such as afatinib, dacomitinib, neratinib and canertinib are pan-ErbB inhibitors, which irreversibly bind to a cysteine residue at position 797 in EGFR by forming covalent

bonds. They are more potent than gefitinib and erlotinib (5). They inhibit EGFR-sensitive mutations as well as T790M in vitro, however, the dose required to overcome T790M-mediated resistance was associated with significant toxicities due to inhibition of wild-type EGFR in clinical setting (5).

FDA approved Gefitinib, erlotinib, and afatinib as first line in metastatic NSCLC EGFR mutation positive, until recently there was no comparison head to head study between one target therapy and the other one. As a matter of fact they are very similar in terms of efficacy and they are all were tested against chemotherapy (OPTIMAL, IPASS, EURTAC, LUX-Lung 3, and LUX-Lung 6) and were superior in PFS, RR, and quality of life.

The Iressa Pan-Asia Study is the first randomized Phase III study that compared gefitinib with paclitaxel/carboplatin in clinically selected chemotherapy-naïve patients with advanced NSCLC (Asian, non-/light ex-smoker population with adenocarcinoma (3). Incidence of EGFR mutation was about 60% in the trial. Gefitinib was demonstrated to be superior to chemotherapy as an initial treatment in subgroup of patients with positive EGFR mutation. It significantly prolonged progression-free survival (PFS), increased the objective response rate, reduced toxic effects and improved quality of life. Gefitinib treatment was detrimental for those without EGFR mutations. Final OS data were published in July 2011 and treatment-related differences observed for PFS in the EGFR mutation-positive subgroup were not apparent for OS, likely due to high proportion of patients' crossing over to the alternative treatment (6).

EURTAC was the first randomized trial in Europe targeting a non-Asian population of advanced NSCLC patients harboring EGFR mutations with comparison of erlotinib with standard platinum-based chemotherapy as first-line treatment. It showed superiority of erlotinib in terms of longer median PFS of 9.7 versus 5.2 months in the chemotherapy group (HR: 0.37). Higher percentage of patients achieved a partial response in the erlotinib arm (56 vs 15%). Based on data from EURTAC study, the US FDA approved erlotinib on 14 May 2013 for the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (7). Erlotinib was the first drug to be used and available in US, and worldwide, although Gefitinib was the first EGFR TKI that came to the market with accelerated 'fast track' approval by FDA in May 2003 as monotherapy for the treatment of patients with locally advanced NSCLC who had failed  $\geq 2$  courses of chemotherapies including platinum-based and docetaxel (8). However,

many oncologists had experience with Erlotinib and were comfortable using it. Later Gefitinib was available, it is very similar and more tolerable.

Afatinib is more potent due to irreversible mode of action and the only 2nd generation to be approved as 1st line in met NSCLC and has more side effects as well. LUX3 & LUX6 demonstrated better efficacy in exon 19 deletion which is the commonest type of mutation. And there were survival benefit as well over chemotherapy which were not seen in other trials. In other mutations we can consider any of the other available target therapy. LUX Lung7 compared Gefitinib and afatinib as a first line treatment and study showed PFS benefit and favoring afatinib. Pooled analysis of OS data from these two large Phase III trials (LUX-Lung 3 and LUX-Lung 6) was recently published at Lancet Oncology in February 2015. It demonstrated that median OS in patients receiving first-line afatinib versus chemotherapy was not different in whole patient population, but in preplanned analyses, afatinib significantly improved OS in patients with deletion 19 mutations in comparison with chemotherapy in both trials, but not for patients with L858R point mutations in exon 21 in either trial. This was the first time that upfront EGFR-TKI significantly improved OS compared with chemotherapy, specifically in patients harboring the EGFR deletion 19 mutation. OS benefit of afatinib could be related to its irreversible blockage of ErbB family, but further prospective studies are needed to analyze the results separately for patients with in-frame deletions in exon 19 and L858R point mutation in exon 21. These two mutations perhaps result in different biological abnormalities leading to variations in sensitivities to EGFR TKIs (9).

Erlotinib has been also combined with different combination of chemotherapy regimens for the treatment of unselected NSCLC patient population in multiple Phase III trials (carboplatin/paclitaxel in TRIBUTE trial; cisplatin/gemcitabine in TALENT trial)(10). Combinations showed no survival benefit compared with chemotherapy alone. There was no difference between treatment arms in terms of time to progression, response rate and quality of life. In EGFR-mutant patients, the 12-month OS, 6-month PFS and ORR were superior with erlotinib monotherapy compared with the intercalated treatment of chemotherapy (carboplatin/paclitaxel on day 1) plus erlotinib (days 2 – 15) (11).

About 30% of those patients with positive EGFR mutation do not respond to upfront EGFR TKI therapy. Furthermore, patients who initially responded to the therapy inevitably become

refractory to EGFR TKIs via multiple different mechanisms. Given heterogeneity of acquired resistance mechanisms, it became a major challenge for clinicians to find the appropriate management strategy for after development of resistance. Resistance to EGFR TKIs can be classified as either primary or secondary (acquired). Primary resistance can be seen in patients with exon 20 insertions or duplications (4% of EGFR mutations) and de novo T790M mutation which is associated with shorter OS and lower response rate upon treatment with upfront reversible EGFR TKI (12). A Phase I study of AZD9291 in EGFR-mutant NSCLC patients with acquired resistance, ORR was 51% (91/177) with a response rate of 64% in 89 patients with T790M mutation-positive patients and 23% in patients with T790M mutation negative patients. The overall disease control rate in T790M-positive patients was 96% (85/89), which confirms robust efficacy in patients with acquired resistance to EGFR TKIs, especially T790M-positive patients (13), unfortunately more than 50% of the patients may miss 2<sup>nd</sup> line as well.

### **Conclusion**

Targeting EGFR pathway has changed the treatment algorithm for patients with EGFR-mutant advanced NSCLC and became standard first-line therapy. EGFR TKIs provided significant benefit over systemic chemotherapy in terms of improved PFS, higher response rate and improved quality of life in this patient population. However, about one-third of patients would not respond to upfront targeted therapies and those who initially achieved a response would acquire resistance inevitably at one point. A wide variety of resistance mechanisms have been identified which led to emergence of novel therapies



2018

# TREATMENT BEYOND PROGRESSION IN DRIVER MUTANT LUNG CANCER

National Cancer Center  
(NCC)



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**Title: Treatment beyond progression in driver mutant lung cancer**

**Hamed ALHussaini, MD**

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Non-small cell lung cancer (NSCLC) represents approximately 80% of all lung cancer subtypes and it is the leading worldwide cause of cancer related death. Treatment of selected patients with advanced NSCLC was revolutionized by discovery and subsequent targeting of the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase gene (ALK) pathways.

Somatic mutations in EGFR are identified in 10–30% of patients with NSCLC. Common EGFR alterations include the L858R point mutation in exon 21 and exon 19 deletions, accounting for 90% of all EGFR activating mutations. These mutations result in enhanced EGFR signaling and confer sensitivity to the EGFR-tyrosine kinase inhibitors (TKIs). In several phase III studies, patients with EGFR mutated NSCLC achieved double overall response rates (ORR) and progression free survival (PFS) when treated with an EGFR-TKIs compared with standard chemotherapy [1, 2].

Almost all patients who initially respond to EGFR-TKIs subsequently develop disease progression. Mechanisms of acquired resistance to EGFR-TKIs are broadly divided into two categories. The first involves development of additional genetic alterations in the primary oncogene, which facilitates continued downstream signaling. This commonly arises through secondary mutations in the kinase target or through gene amplification of the kinase itself. Alternatively, resistance can develop independently of genetic changes in the target. This occurs through upregulation of bypass signaling pathways, changes in tumor histology or alterations in drug metabolism. The substitution of methionine for threonine at position 790 (T790M) are thought to account for resistance in approximately 50 percent of cases of acquired resistance to EGFR TKIs. Amplification of the MET oncogene has been associated with resistance to EGFR TKIs in 5 - 20 percent of cases [3].

Disease flare, phenomenon of rapid disease progression during a “washout period”, is observed in 23% of patients, with a median time to flare of 8 days after TKI cessation. Shorter time to progression on initial TKI therapy, and the presence of pleural or CNS disease are associated with disease flare while T790M mutation at the time of progression is not a predictive factor [4]. Local therapy for oligoprogressive disease in conjunction with continued EGFR TKI can lead to long-term survival in selected EGFR-mutant patients with acquired resistant to EGFR-TKIs [5, 6].

Prior to changing therapy, tumor re-biopsy is reasonable to determine mechanism of resistance and define adequate therapeutic strategy to overcome it. The third-generation EGFR inhibitor (Osimertinib) is to be considered for use in patients with NSCLC harboring a T790M mutation, either by tissue or plasma genotyping, whose disease progressed on other EGFR-inhibiting therapy. This is based on result of a phase III trial of 419 patients with T790M-positive NSCLC who had progressed on first-line EGFR TKI, osimertinib demonstrated improved progression-free survival (10.1 versus 4.4 months) and objective response rate (71 versus 31 percent) compared with a pemetrexed- and platinum-based chemotherapy combination[7].

For those who do not have a T790M mutation, or for those who progress on osimertinib, subsequent management usually consists of platinum-doublet chemotherapy. The IMPRESS study showed no statistically significant improvement in progression-free survival with continuation of gefitinib in addition to chemotherapy beyond RECIST progression to first-line EGFR TKI for patients with EGFR mutation positive NSCLC[8].

ALK gene rearrangement occurs in approximately 5–7% of patients with NSCLC, more frequently in those with young age, adenocarcinoma histology, and never or light smokers. It is often mutually exclusive with other molecular oncogenes, including EGFR or KRAS mutation. Results of a phase III trial comparing ALK inhibition using crizotinib with chemotherapy in treatment-naïve patients have demonstrated a prolongation in progression-free survival and improved response rate and quality of life. No significant differences in overall survival were seen, potentially due to the confounding effects of crossover [9].

While crizotinib is highly active in patients with ALK-positive NSCLC, almost all patients develop resistance to the drug, typically within the first few years of treatment. Secondary ALK mutations, ALK fusion gene amplification and activation of alternative signalling pathways have been observed in a group of NSCLC patients, who repeated biopsies at the time of crizotinib failure [10]. In approximately one-third of resistant cases, tumors have acquired a secondary mutation within the ALK tyrosine kinase domain.

Local ablative therapy with the continuation of crizotinib may be a viable approach in selected patients with oligoprogressive disease. A recent retrospective analysis conducted on 414 ALK-positive NSCLC patients enrolled in PROFILE 1001 or PROFILE 1005 showed that patients derived clinical benefit from continued ALK inhibition with crizotinib after RECIST defined progression disease [11].

Second-generation ALK inhibitors ceritinib or alectinib are recommended for ALK-positive patients who develop resistance to crizotinib or who are unable to tolerate crizotinib. In preliminary results of ASCEND-5 phase III study, in which 231 patients who had received crizotinib were randomly assigned to ceritinib 750 mg/day or chemotherapy, those receiving ceritinib experienced improved progression-free survival (5.4 versus 1.6 months, HR 0.49) and objective response rate (39.1 versus 6.9 percent), differences that were both statistically significant[12]. There are two phase II studies that show response rates to alectinib of

approximately 50 percent in patients with ALK-positive locally advanced or metastatic NSCLC who had progressed on crizotinib [13, 14].

### **Conclusions**

The success of targeted agents has allowing the patients to be treated with more affective drugs, as well as to have good quality of life. Occurrence of resistance to these novel agents represents an emerging issue. RECIST alone can be inadequate to guide treatment interruption and change of therapy.

Prior to changing therapy, tumor re-biopsy is reasonable to determine mechanism of resistance and define adequate therapeutic strategy to overcome it. Local therapy and continuation of TKI should be considered for patient with oligoprogression. Patient with slow, indolent, asymptomatic progression can be continued on their original TKI. Patients with symptomatic systemic progression can be switched to new therapy with minimal time off treatment.

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2018

# MANAGEMENT OF TKIS SIDE EFFECTS

National Cancer Center  
(NCC)



**Title:** Management of TKIs side effects

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Tyrosine kinase inhibitors (TKIs) are considered as the standard of care for management of EGFR mutant non-small cell lung cancer (NSCLC). The available TKIs are erlotinib, afatinib and gefitinib. These agents are proven to delay disease progression and improve patients quality of life compared to chemotherapy. The most common side effects of TKIs are dermatological and gastrointestinal toxicities. Mostly the degree of these toxicities is mild, but if they become moderate or severe they will impact patients' quality of life negatively and might lead to dose adjustment or treatment discontinuation. Accordingly proper management of side effects and consideration of prophylactic measures are essential.

**Dermatological toxicities:**

<b>Grading</b>	<b>Description</b>	<b>Management</b>
Grade 1	Macular or papular eruption or erythema covering less than 10% of the body surface area, which may or may not be associated with symptoms.	<ul style="list-style-type: none"> <li>▪ Maintain the same dose of TKI</li> <li>▪ Might apply hydrocortisone 1% or 2.5% cream or clindamycin 1% gel</li> </ul>
Grade 2	Macular or papular eruption or erythema covering 10%-30% of the body surface area, which may or may not be associated with symptoms that are tolerable or interfere with daily life.	<ul style="list-style-type: none"> <li>▪ Maintain the same dose of TKI</li> <li>▪ Apply hydrocortisone 1% or 2.5% cream or clindamycin 1% gel</li> <li>▪ Start doxycycline 100mg twice daily or minocycline 100mg twice daily for 4 weeks</li> </ul>
Grade 3	Severe, generalized erythroderma, or macular, papular or vasicular eruption covering more than 30% of the body surface area which may or may not be associated with symptoms that limits self-care activities of daily life or associated with local superinfection that indicate starting oral antibiotics	<ul style="list-style-type: none"> <li>▪ Discontinue the TKI.</li> <li>▪ Reinstate at reduced dose when toxicity has resolved to less than grade 2.</li> <li>▪ Apply hydrocortisone 1% or 2.5% cream or clindamycin 1% gel</li> <li>▪ Start doxycycline 100mg twice daily or minocycline 100mg twice daily for 4 weeks</li> </ul>
Grade 4	Generalized exfoliative, ulcerative, or blistering skin toxicity covering any percentage of body surface area, which may or may not be associated with symptoms that are associated	

	with extensive superinfection that indicate starting intravenous antibiotics and lead to life threatening consequences	
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**Diarrhea:**

<b>Grading</b>	<b>Description</b>	<b>Management</b>
Grade 1	Less than 4 bowel movement over baseline per day	<ul style="list-style-type: none"> <li>▪ Diet modification</li> <li>▪ Standard dose of loperamide</li> </ul>
Grade 2	4-6 bowel movement over baseline per day	
Grade 3	7 or more bowel movement over baseline per day. Limits self-care activities of daily living and hospitalization indicated	<ul style="list-style-type: none"> <li>▪ Admit to hospital</li> <li>▪ IV fluid and antibiotics as needed</li> <li>▪ Consider octreotide injection</li> </ul>
Grade 4	Life threatening consequences, urgent intervention indicated	

**Interstitial lung disease (ILD):**

- It is a very rare but potentially fatal toxicity. Prompt evaluation of new or worsening pulmonary symptoms is requested to detect early radiographic signs of pulmonary toxicity.
- If toxicity confirmed, TKI should be discontinued and treat the patient appropriately.
- If toxicity confirmed, TKI should be discontinued and treat the patient appropriately.
- Start empiric treatment with corticosteroids till the toxicity ruled out as prednisolone 1mg/kg daily for 2-4 weeks. Then taper the dose to minimal

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