Saudi lung cancer management guidelines 2017

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Abstract:

BACKGROUND: Lung cancer management is getting more complex due to the rapid advances in all aspects of diagnostic and therapeutic options. Developing guidelines is critical to help practitioners provide standard of care.

METHODS: The Saudi Lung Cancer Guidelines Committee (SLCGC) multidisciplinary members from different specialties and from various regions and healthcare sectors of the country reviewed and updated all lung cancer guidelines with appropriate labeling of level of evidence. Supporting documents to help healthcare professionals were developed.

RESULTS: Detailed lung cancer management guidelines were finalized with appropriate resources for systemic therapy and short reviews highlighting important issues. Stage based disease management recommendation were included. A summary explanation for complex topics were included in addition to tables of approved systemic therapy.

CONCLUSION: A multidisciplinary lung cancer guidelines was developed and will be disseminated across the country.

Keywords:

Lung cancer guidelines, Saudi lung cancer, Saudi lung cancer management guidelines

Guidelines are essential tools for implementing evidence-based medicine as they help translate the knowledge gained into practice. Adherence to guidelines improves cancer patients' outcome and helps provide better quality and safer patient care with different malignancies.[1-7] The outcome of lung cancer patient in particular also improves with adherence to guidelines and standards.[8-11]

With the availability of many high-quality international guidelines, it would be necessary to develop yet another guideline. Guidelines such as the National Comprehensive Cancer Network, the American Society of Clinical Oncology, the European Society of Medical Society, and the American College of Chest Physicians (ACCP) develop guidelines relevant to their population, based on evidences and resources available in their respective region and for their own population.[12-14]

Creation of guidelines that is relevant to our patient population including patients' characteristics, disease biology, practice

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setting, and infrastructure is critical even if one used the same body of evidence of other international guidelines.[15,16]

Developing updated, easy-to-follow guidelines is more pressing nowadays for many reasons. First, the better understanding of the disease biology enabled us to define better targets and classify lung cancer bases on molecular markers such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and repressor of silencing 1 (ROS1). This coupled with the development of more effective targeted therapy, added many therapeutic options to patients with driver mutations. Our knowledge even advanced beyond the initial treatment of actionable mutation to delineate causes of secondary resistance and target that resistant gene effectively (e.g., T790 mutation).

Introducing immunotherapy was a major leap into a new era of therapeutic modality called immuno-oncology with innovative mechanism of action, superior outcome, different pattern of response, and side effects. Improving other technologies for local therapy such as stereotactic radiosurgery did enable physicians to treat oligometastatic disease more effectively. Palliative care role became more evident in management of lung cancer patients, not by improving their symptoms but also prolonging their survival.

Creating guidelines, therefore, requires involvement of multidisciplinary team who are experts in the field and develop clear methodology and framework to design the intended guidelines.

In this manuscript, we are presenting the Saudi Lung Cancer Management Guidelines 2017 developed by the Saudi Lung Cancer Association, a subsidiary of Saudi Thoracic Society.

Methodology

The Lung Cancer Guidelines Committee is a multidisciplinary team representing different disciplines involved in lung cancer management including pulmonary medicine, radiology, interventional radiology, thoracic surgery, pathology, medical oncology, radiation oncology, palliative care, and clinical pharmacy.

The format, the process, and the level of evidence were adapted from our initial guidelines that was published in 2008 Lung Cancer Guidelines and followed in subsequent guidelines.[17,18]

The team reviewed all emerging evidence in the management of lung cancer and incorporated appropriate recommendations into our previous guidelines framework according to their level of evidence.

The level of evidence we used since 2008 was adapted from the Canadian Task Force on the Periodic Health Examination Center for Evidence-Based Centers and others:[19-21] It classify the level of evidence into three categories as follows:

1. High level (evidence levels 1 [EL-1]): Well-conducted Phase III randomized studies or metaanalysis
2. Intermediate level (EL-2): Good Phase II data or Phase III trials with limitations
3. Low level (EL-3): Observational/retrospective study/expert opinion.

We had face-to-face meeting and corresponded by emails to get the approval on the update. The committee members represent various regions and health-care sections such as Ministry of Health, Military Hospitals, National Guard Health Affairs, and others.

We enlisted the recommendations based on disease stage, patient characteristics, and the tumor profiling and added chemotherapy regimen as resource in addition to brief summary about important topics related to lung cancer management.

Publishing these guidelines will be the critical step for their dissemination across the Kingdom to enable users to consider implementing them.

Lung Cancer Management Guidelines

Evidence levels

The following ELs were adopted for these guidelines:

- High level (EL-1): Well-conducted Phase III randomized studies or well done meta-analyses
- Intermediate level (EL-2): Good Phase II data or Phase III trials with limitations
- Low level (EL-3): Observational or retrospectives studies or expert opinions.

1. All lung cancer patients
   - 1.1. Initial patient assessment
     - 1.1.1. Perform history and physical examination. Document smoking history, performance status, weight loss, and comorbidities
     - 1.1.2. Perform the following laboratory tests: Complete blood count, differential, liver function test, renal function, electrolytes, calcium, serum albumin, magnesium, and phosphorus
     - 1.1.3. Two-view chest X-ray.
   - 1.2. Diagnosis
     - 1.2.1. Obtain adequate tissue specimen for diagnostic and predictive markers
     - 1.2.2. Confirm histopathological diagnosis of lung cancer and determine the histological subtypes using most recent pathological

classification of lung cancer. Utilization of proper immunohistochemistry (IHC) staining (minimal panel to include thyroid transcription factor-1 most important), cytokeratin 7 (CK7), and CK20 for adenocarcinoma and P40 (preferred) or P63 to minimize the diagnosis of "not otherwise specified"

1.2.3. Obtain EGFR mutation testing by polymerase chain reaction in certified laboratory for all histology except pure squamous cell (squamous cell carcinoma with small sample or never smokers, EGFR should be done)

1.2.4. In EGFR wild-type (WT) tumors, obtain EML4-ALK fusion test by fluorescence *in situ* hybridization (FISH) in certified laboratory. IHC can be done to screen for positive tumors to be tested by FISH

1.2.5. For patients with WT EGFR and ALK, obtain the ROS1 test

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

1.2.7. Obtain programmed death-ligand 1 (PD-L1) testing by IHC 22C3 pharmDx on all nonsmall cell lung cancer (NSCLC) WT

1.2.8. Next generation sequencing should be performed, if available.

1.3. Staging

1.3.1. NSCLC

1.3.1.1 Obtain contrast-enhanced computed tomography (CT) scan of the chest and upper abdomen

1.3.1.2 Obtain magnetic resonance imaging (MRI) of brain for Stages IB-IV (preferred over contrast-enhanced CT scan)

1.3.1.3 Obtain total body positron emission tomography (PET)/CT scan when available if the patient is considered for radical therapy (such as surgery or chemoradiotherapy)

1.3.1.4 Obtain bone scan for Stages IB-IV if PET/CT is not done

1.3.1.5 Perform mediastinal lymph node (LN) evaluation in selected cases, i.e. clinical Stages (IB-III). Especially negative with central tumor and T2 to T4

1.3.1.6 Determine precise tumor, node, and metastasis (TNM) staging using 7th edition (2009).

1.3.2. Small cell lung cancer

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

1.3.2.2. Obtain MRI of brain for Stages IB-IV (preferred over contrast-enhanced CT scan which can be if MRI is not available)

1.3.2.3. Obtain PET/CT scan if the disease in Stages I-III

1.3.2.4. Obtain bone scan if PET/CT is not done or it was negative with suspected bone involvement

1.3.2.5. Determine precise TNM staging using 7th edition (2009).

1.4. Pre-treatment assessment

1.4.1. Discuss all new cases in a multidisciplinary conference (tumor board)

1.4.2. Obtain cardiopulmonary assessment (pulmonary function test [PFT], 6-min walk, electrocardiogram and echocardiogram) if surgery considered and PFT for curative radiotherapy is considered.

1.5. General

1.5.1. Counsel about smoking cessation and pulmonary rehabilitation

1.5.2. Offer available clinical research studies.

2. NSCLC

2.1. Clinical Stage IA

2.1.1. Anatomical surgical resection and mediastinal LN sampling

2.1.2. Adjuvant chemotherapy is not recommended.

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

2.1.4. Patients with positive surgical margins should be offered re-resection or radical postoperative radiotherapy.
Definitive radical radiotherapy is an alternative for patients who are not candidates for surgery due to comorbidities, poor performance status, or refusal of surgery.

2.1.5. If surgical resection is not possible, (inoperable or refusal of surgery) offer SBRT with curative intent. Poor PFT is not contraindication for SBRT (section 2.3.8)

2.1.6. Follow-up and surveillance per section 2.8. (follow-up of NSCLC).

2.2. Clinical Stage IB

2.2.1. Anatomical surgical resection mediastinal LN sampling or dissection

2.2.2. For lesions ≥4 cm or high-risk features (poorly differentiated, wedge resection, minimal margins, vascular invasion), consider adjuvant chemotherapy[22,23]

2.2.3. Chemotherapy of choice: 4–6 cycles of platinum combination cisplatin (carboplatin only if

cisplatin is contraindicated) (EL-1)[22-25]

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

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

2.2.6. Patients with positive surgical margins should be offered re-resection radical postoperative radiotherapy

2.2.7. Follow-up and surveillance per section 2.8. (follow-up of NSCLC)

2.3. Clinical Stage IIA

2.3.1. Anatomical surgical resection with lobectomy or pneumonectomy and mediastinal LN sampling (EL-1)[26,27] or dissection is the treatment of choice

2.3.2. Offer adjuvant chemotherapy as per section 2.2.3 (EL-1)[22-25]

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

2.3.4. Patients with positive surgical margins should be offered re-resection or radical postoperative radiotherapy

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

2.3.6. If surgical resection is not possible, offer curative radical radiotherapy for T2bN0 (section 2.3.8.)

2.3.7. Follow-up and surveillance as per section 2.8. (follow-up of NSCLC)

2.3.8. Radiotherapy with curative intent in patients with early stage, medically inoperable, NSCLC:

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

2.3.8.2. Most established SBRT criteria include NO patients with:

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

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

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

2.4. Clinical staage IIB

2.4.1. Anatomical surgical resection and mediastinal LN sampling. (EL-1)[26,27] or dissection is the treatment of choice

2.4.2. Offer adjuvant chemotherapy as per section 2.2.3 (EL-1)[22-25]

2.4.3. Superior sulcus tumors patients should be induced by cisplatin/etoposide with concurrent radiation therapy followed by surgical resection (EL-2)[28,29] and 2 cycles of adjuvant chemotherapy. Assess disease extent using MRI at baseline and preoperative (EL-2)[28,30-32]

2.4.4. For T3 N0 M0 perform *en bloc* resection

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

2.4.6. Patients with positive surgical margins should be re-resection or radical postoperative radiotherapy

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

2.4.8. Follow-up and surveillance per section 2.8. (follow-up of NSCLC).

2.5. Clinical Stage IIIA

2.5.1. For T3 N1 M0, perform *en bloc* resection

2.5.2. For superior sulcus tumor, offer treatment similar to section 2.4.3.[28]

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

2.5.4. If N2 disease discovered during surgery by frozen section abort surgery if pneumonectomy is required (EL-2)[33]

2.5.5. For patients with incidental pathological N2 disease, adjuvant chemotherapy is recommended (EL-1)[22-25] and in addition radiotherapy can be considered (EL-3)[34]

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

2.5.7. For T4 with (mediastinal or main airway involvement), offer surgery if potentially curative; if not possible, offer definitive concurrent chemoradiotherapy (2.5.1.)
2.5.8. For non N2 Stage IIIA, not specified above, offer surgical resection with adjuvant chemotherapy
2.5.9. Follow-up and surveillance per section 2.8 (follow-up of NSCLC).

2.6. Clinical Stage IIIB and unresectable IIIA
2.6.1. Offer concurrent chemoradiotherapy (EL-1)[35,36] followed by chemotherapy. Surgical resection for selected cases could be offered
2.6.2. Follow-up and surveillance per section 2.8 (follow-up of NSCLC).

2.7. Stage IV (Obtain palliative care consultation/evaluation on all patients [EL-1])[37]
2.7.1. Systemic therapy [Table 1]
2.7.1.1. Stage M1a (with pleural effusion) assess the need for thoracentesis and pleurodesis. Offer systemic therapy as below
2.7.1.2. With brain metastases [Tables 2 and 3]
2.7.1.3. Isolated adrenal metastasis; consider adrenal mass biopsy followed by surgical resection or SBRT consideration after multidisciplinary team discussion
2.7.1.4. No brain metastases/treated brain disease, no prior systemic treatment for metastatic disease [Table 4].
2.7.1.4.1. Adenocarcinoma/nonsquamous with sensitizing EGFR mutation.
Guiding principle:
Patient with driver mutation should receive tyrosine kinase inhibitor (TKI) as first line if possible. If not done, patient should receive TKI as soon as possible as switched maintenance (completing planned treatment) or any time they are available (interrupt treatment)

A. First line:
1. Performance Status 0–2:
- TKIs (erlotinib, afatinib, or gefitinib) are the preferred option (EL-1)[38-40]
- Systemic chemotherapy with a platinum doublet ± bevacizumab can be considered if the EGFR status is unknown or awaited. Platinum doublet (pemetrexed combination is preferred over a gemcitabine based combination)

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

3. Performance Status 4:
- Use TKIs (erlotinib, afatinib or gefitinib).

B. Maintenance:
1. Performance Status 0–2:
- Continuation or switch maintenance with TKIs (EL-1).[41-43] If the patient was not commenced on TKIs, then switch to TKIs as soon as possible.

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

C. Second line:
Guiding principle:
Assess for resistant mutations with either ctDNA (plasma) testing or rebiopsy of metastatic site.
For isolated or oligoprogression, consider local therapy. For multiprogression, switch to second line.
1. If T790M positive, use osimertinib.[44]
2. Performance Status 0–2:
- Use TKIs, if not used in first line
- Systemic chemotherapy (platinum doublet ± bevacizumab) (pemetrexed is preferred over gemcitabine).

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

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

D. Third line and beyond
- Obtain T790M testing if it was not done earlier, consider doing ctDNA (plasma) testing.

1. Performance Status 0–2:
- Use TKIs, if not used before
- Consider immunotherapy (nivolumab or pembrolizumab, or atezolizumab)
- Systemic chemotherapy (single-agent chemotherapy, pemetrexed if not used, docetaxel, etc.)
- Ramucirumab/docetaxel.

2. If T790M positive, use osimertinib
3. Performance Status 3 and 4:
- Use TKIs, if not used in first line
- If TKIs were used, refer to palliative care.

2.7.1.4.2. ALK-positive adenocarcinoma/non-squamous

A. First line:
1. Performance Status 0–2:
- Crizotinib is the recommended treatment option (EL-1)[45-47]
- Systemic chemotherapy with a platinum doublet (± bevacizumab) can

Table 1: Systemic therapy for metastatic non-small cell lung cancer

Diagnosis	1. Determining histology subtype 2. Egfr mutation testing 3. Eml4 alk fusion testing 4. Pdl1 5. T790 (pd in egfr mut)						
Characteristic	Performance status	Non-small cell carcinoma					Squamous cell carcinoma	
		Egfr+	Eml4- alk+	Egfr wt	Egfr unknown			
First line	0-2	Tki If tki not available: platinum doublet (pemetrexed) +/- bevacizumab	Crizotinib or If crizotinib not available, platinum doublet (pemetrexed) +/- bevacizumab	Pdl1<50% Platinum doublet (pemetrexed) +/- bevacizumab	Pdl1>50% Pembrolizumab or platinum doublet (pemetrexed) +/- bevacizumab	Pdl1<50% Platinum doublet (pemetrexed) +/- bevacizumab	Platinum doublets (no pemetrexed or bevacizumab)	Pdl1>50% Pembrolizumab or platinum doublet
	3	Tki Pemetrexed	Crizotinib Pemetrexed	Single agent chemotherapy (pemetrexed)	Erlotinib or single agent chemotherapy		Single agent chemotherapy gemcitabine	
	4	Tki Palliative care	Crizotinib* Palliative care	Palliative care	Palliative care Erlotinib		Palliative care	
Maintenance	0-2	Tki (cm or sm) Pemetrexed (cm or sm) Bevacizumab (cm)	Crizotinib (cm or sm)	Pemetrexed (cm or sm) Bevacizumab (cm) Pembrolizumab (cm)	Pemetrexed or erlotinib (cm or sm) Bevacizumab (cm) Pembrolizumab (cm)		Docetaxel	
Second line	0-2	Check for t790 (ctdna) Osimertinib in t790 mut platinum doublet with pemetrexed	Certinib or alectinib if crizotinib is used Pemetrexed/ platinum doublet	It if not used Pemetrexed (doublet) if not used Ramucirumab + docetaxel	It if not used Pemetrexed if not used (doublet) Ramucirumab + docetaxel or erlotinib or docetaxel		It if not used Afatinib Or ramucirumab, docetaxel Docetaxel or gemcitabine	
	3	Tki, if not used	Certinib/alectinib	Single agent pemetrexed	Erlotinib		Palliative care	
	4	Tki if not used	Certinib/alectinib	Palliative care	Palliative care		Palliative care	
Third line	0-2	Pemetrexed or docetaxel with or without platinum it	If two tkis used platinum/pemetrexed then it	Pemetrexed docetaxel with or without platinum	Pemetrexed doublet or single agent		It if not used, Gemcitabine if not used	
	3-4	Palliative care	Palliative care	Palliative care	Palliative care		Palliative care	

CM=Continuation maintenance; SM=Switch maintenance; TKI=Tyrosine kinase inhibitors; Erlotinib=Afatinib or gefitinib; IT=Pembrolizumab, nivolumab or atezolizumab

Table 2: Radiation Therapy Oncology Group recursive partitioning analysis for brain metastases (Gasper *et al*. 1997)

Class	Characteristics
I	KPS 70-10
	Age <65
	Primary tumor controlled
	Metastases to brain only
II	All others
III	KPS <70

KPS=Karnofsky performance status

Table 3: Radiosurgery treatment indications for brain metastases

Class	Intervention
Single lesion	Surgical resection + SRS to cavity
	SRS alone
RPA class I-II	SRS alone for medically/surgically inoperable cases
KPS ≤60, extensive intracranial/extracranial disease	WBRT + dexamethasone or dexamethasone alone

SRS=Stereotactic radiosurgery, KPS=Karnofsky performance status, WBRT=Whole brain radiotherapy

be considered (platinum-pemetrexed combination is preferred over a gemcitabine-based combination)
- Crizotinib is also very effective in patients with ROS1 rearrangements.

2. Performance Status 3:
   - Use crizotinib
   - Single-agent chemotherapy can be considered.
3. Performance Status 4:
   - Use crizotinib
   - Palliative care.

B. Maintenance:
1. Performance Status 0–2:
   - Continuation or switch maintenance with crizotinib. If was not started on crizotinib, patient should be switched to crizotinib as soon as possible.
2. Performance Status 3 and 4:
   - Continuation or switch maintenance with crizotinib. If was not started on crizotinib, patient should be switched to crizotinib as soon as possible.

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

1. Performance Status 0–2:
   - Ceritinib or alectinib are the recommended treatment options for patients with disease progression or intolerance to crizotinib[48-50]
   - Use crizotinib, if not used in first line
   - Systemic chemotherapy (platinum doublet ± bevacizumab) (pemetrexed is preferred over gemcitabine).
2. Performance Status 3 and 4:
   - Use ceritinib, If crizotinib used before
   - Use crizotinib, if not used before.

D. Third line and beyond
1. Performance Status 0–2:
   - Use crizotinib or ceritinib or alectinib, if not used before
   - Systemic chemotherapy (single-agent chemotherapy, pemetrexed, if not used, docetaxel)
   - Consider immunotherapy (pembrolizumab, nivolumab or atezolizumab).
2. Performance Status 3 and 4:
   - Use crizotinib or ceritinib or alectinib, if not used in first line
   - If both agents where used, palliative care.

2.7.1.4.3. EGFR/ALK WT adenocarcinoma/non-squamous (including EGFR Exon 20 mutation or primary resistance mutation)

A. First line:
1. Performance Status 0–2:
   - If PD-L > 50%
   - Use pembrolizumab (preferred EL-1),[51-53] if it is not available use systemic chemotherapy (platinum doublet+/-bevacizumab) (pemetrexed is preferred over gemcitabine).
   - If PD-L < 50%
   - Systemic chemotherapy (platinum doublet ± bevacizumab) (pemetrexed is preferred over gemcitabine).
2. Performance Status 3:
   - Single-agent chemotherapy can be considered
   - Palliative care.
3. Performance Status 4:
   - Palliative care.

B. Maintenance:
1. Performance Status 0–2:
   - Continue pembrolizumab if commenced in first line
   - Continue or switch maintenance with pemetrexed for PD-L1 < 50%.
   - Continue bevacizumab, if started in first line.
2. Performance Status 3:
   - Continue or switch maintenance with pemetrexed.
3. Performance Status 4:
   - Palliative care.

C. Second line
1. Performance Status 0-2:
   - Give nivolumab, atezolizumab, or

Table 4: Systematic therapy regimens in nonsmall cell lung cancer

	Chemotherapy regimen	References
Adjuvant	Carboplatin AUC 6 + paclitaxel 225 mg/m^2 on day 1	[22,23]
	21 Days cycle for 6 cycles (4-6 cycles)	
	Cisplatin 75 mg/m^2 + docetaxel 75 mg/m^2 on day 1	[22]
	21 day cycle for 6 cycles	
	Cisplatin 100 mg/m^2 + gemcitabine 1000 mg/m^2 on day 1 and 8, 15	[22]
	28 day cycle for 6 cycles	
	Usual practice is to omit day 15 and use every 21 days	
	Carboplatin AUC 5 + gemcitabine 1000 mg/m^2 on day 1 and 8	[24]
	21 days cycle for 6 cycles	
	Cisplatin 75 mg/m^2 + vinorelbine 25 mg/m^2 on day 1 and 8	[25]
	21 days cycle for 6 cycles	
Concurrent with chemoradation	Carboplatin AUC 2 + paclitaxel 45 mg/m^2	[35]
	Weekly with radiation	
	Cisplatin 50 mg/m^2 (days 1, 8, 29, 36) + etoposide 50 mg/m^2 (day 1 to 5 and 29 to 33)	[36]
	Week 1 and 5	
Metastatic	Carboplatin AUC 6 + paclitaxel 225 mg/m^2 on day 1	[22]
	21 days cycle for 6 cycles	
	Cisplatin 75 mg/m^2, pemetrexed 500 mg/m^2 every 21 day	[63]
	Cisplatin 75 mg/m^2 + docetaxel 75 mg/m^2 on day 1	[22]
	21 days cycle for 6 cycles	
	Cisplatin 100 mg/m^2 + gemcitabine 1000 mg/m^2 on day 1 and 8, 15	[22]
	28 day cycle for 6 cycles	
	Usual practice is to omit day 15 and use every 21 days	
	Carboplatin AUC 5 + gemcitabine 1000 mg/m^2 on day 1 and 8	[24]
	21 day cycle for six cycles	
	Cisplatin 75 mg/m^2 + vinorelbine 25 mg/m^2 on day 1 and 8	[25]
	21 day cycle for 6 cycles or vinorelbine 60-80 mg/m^2 (maximum 160mg) PO available as 20 and 30 mg capsules	
	Paclitaxel (200 mg/m^2) + carboplatin (AUC 6) + bevacizumab (15 mg/kg) every 21 days	[64]
	Ramucirumab 10 mg/kg IV + docetaxel 75 mg/m^2 IV	[65]
	Repeat cycle every 3 weeks	
	Nintedanib 200 mg PO twice daily days 2-21 docetaxel 60-75 mg/m^2 IV Day 1	[66]
Single agent regimens	Gemcitabine 1250 mg/m^2 (day 1 and 8)	[67]
	21 day cycle	
	Docetaxel 75 mg/m^2	[68]
	21 day cycle	
	Pemetrexed 500 mg/m^2	[69]
	21 day cycle	
	Topotecan 1.5 mg/m^2 (days 1-5)	[70]
	21 day cycle	
	Vinorelbine 60-80 mg/m^2 (maximum 160 mg) PO weekly	[71,72]
	Gefitinib 250 mg po once daily	[38]
	28 day cycle	
	Erlotinib 150 mg po once daily	[39]
	28 day cycle	
	Afatinib 40 mg p.o. once daily	[40]
	28 day cycle	
	Osimertinib	[44]
	Crizotinib 250 mg p.o. twice daily	[45-47]
	28 day cycle	
	Alectinib dose	[48]
	600 mg PO BID until disease progression	
	Ceritinib 750 mg p.o. once daily	[49,50]
	28 day cycle	
	Nivolumab IV: 240 mg once every 2 weeks infuse over 1 hour until disease progression or unacceptable toxicity	[54]

Contd...

Table 4: Contd...

	Chemotherapy regimen	References
	Pembrolizumab IV: 200 mg IV q3wk infuse over 30 min until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression	[51]
	Atezolizumab	[55]
	1200 mg administered as an intravenous infusion over 60 min every 3 weeks until disease progression or unacceptable toxicity	

IV=Intravenous, AUC=Area under curve

pembrolizumab (PD-L1 positive), if received chemotherapy as first line[51-55]
- Platinum doublet if pembrolizumab used as first line
- Single-agent systemic chemotherapy (pemetrexed if not used, docetaxel). If chemotherapy doublet is used as first line.

2. Performance Status 3:
   - Single-agent systemic chemotherapy (pemetrexed if not used, docetaxel).
3. Performance Status 4:
   - Palliative care.

D. Third line and beyond
1. Performance Status 0–1:
   - Consider ramucirumab + docetaxel or nintedanib + docetaxel
2. Performance Status 0–1
   - Single-agent systemic therapy.
3. Performance Status 3 and 4:
   - Palliative care.

2.7.1.4.4. Adenocarcinoma/nonsquamous with (EGFR and ALK unknown status)
- Consider doing ctDNA (plasma) testing of rebiopsy is not possible. All efforts should be made to test for a driver mutation.

A. First line:
1. Performance Status 0–2:
   - If PDL >50%:
   - Use pembrolizumab, if it is not available use systemic chemotherapy (platinum doublet ± bevacizumab) (pemetrexed is preferred over gemcitabine).[51-53]
   - If PD-L <50%:
   - Systemic chemotherapy (platinum doublet ± bevacizumab) (pemetrexed is preferred over gemcitabine).
2. Performance Status 3:
   - Single-agent chemotherapy (pemetrexed is preferred over gemcitabine)
   - Use TKIs (erlotinib).
3. Performance Status 4:
   - Palliative care.

B. Maintenance:
1. Performance Status 0–2:
   - Continue or switch maintenance with pemetrexed
   - Continue bevacizumab, if started in first line.
2. Performance Status 3:
   - Continue or switch maintenance with pemetrexed.
3. Performance Status 4:
   - Palliative care.

C. Second line
1. Performance Status 0–2:
   - Immune systemic chemotherapy (platinum doublet ± bevacizumab) (pemetrexed is preferred over gemcitabine).
   - If immune therapy not used, use (nivolumab or pembrolizumab or atezolizumab)[51-55]
   - Consider using ramucirumab.
2. Performance Status 3:
   - Single-agent chemotherapy (pemetrexed if not used).
3. Performance Status 4:
   - Palliative care.

D. Third line and beyond
1. Performance Status 0–2:
   - Systemic chemotherapy (single-agent chemotherapy, pemetrexed if not used or docetaxel)
   - Erlotinib, if immunotherapy and pemetrexed used.
2. Performance Status 3 and 4:
   - Palliative care.

2.7.1.4.5. Squamous cell carcinoma:

A. First line:
1. Performance Status 0–2:
   - If PD-L1 <50%[51-53]
   - Systemic chemotherapy (platinum doublet) (no bevacizumab or pemetrexed).
   - If PD-L1 >50% use pembrolizumab (EL-1).[51-53]
2. Performance Status 3:
   - Single-agent chemotherapy (no pemetrexed).
3. Performance Status 4:
   - Palliative care.

B. Maintenance:
1. Performance Status 0–2:
   - Continue pembrolizumab for 2 years
   - Continuation or switch maintenance with docetaxel.
2. Performance Status 3 and 4:
   - Palliative care.

C. Second line
1. Performance Status 0–2:

- Immune therapy (nivolumab, pembrolizumab or atezolizumab), if pembrolizumab not used. (EL-1)[51-55]
  Systemic chemotherapy doublet if immune therapy used as first line (no pemetrexed)
- Consider using ramucirumab/docetaxel
- Afatinib.

2. Performance Status 3:
   - Single-agent systemic therapy.
3. Performance Status 4:
   - Palliative care.

D. Third line and beyond
1. Performance Status 0–2:
   - Single-agent systemic therapy.
2. Performance Status 3 and 4:
   - Palliative care.

2.8. Follow-up of NSCLC Evaluation includes: History and physical examination, laboratory and chest X-ray.
2.8.1. For tumor Stage I-III: Evaluation every 3 months for 2 years then every 6 months for 3 years then annually. CT scan of the chest every 6 months for 2 years then annually for additional 3 years. Consider annual screening CT scan after 5 years
2.8.2. Stage IV: Evaluation every 2–3 months as clinically indicated.

3. Small cell lung cancer
3.1. Stage I-III (Previously called limited stage):
3.1.1. Offer cisplatin/etoposide with radiation therapy then consolidate with two cycles of cisplatin/etoposide (EL-1).[56] May substitute cisplatin with carboplatin in patients with neuropathy, renal dysfunction or hearing problem
3.1.2. After definitive therapy with any response offer prophylactic cranial irradiation (PCI) (EL-1)[57-59]
3.1.3. For stage (T1-2N0 confirmed by mediastinoscopy), offer surgical resection followed by chemotherapy and prophylactic brain radiotherapy
3.1.4. Follow-up and surveillance as per section 3.3.

3.2. Stage IV (previously extensive stage)
3.2.1. Offer cisplatin/etoposide or cisplatin/irinotecan × 6 cycles (EL-1). Use of carboplatin cisplatin is not indicated[60-62]
3.2.2. After definitive chemotherapy with evidence of response and good performance status offer. Thoracic irradiation and PCI
3.2.3. For previously treated patients who relapsed in <6 months from initial treatment, offer topotecan or cyclophosphamide, adriamycin and vincristine, or irinotecan
3.2.4. For relapse after 6 months from initial treatment, may use original regimen
3.2.5. Follow-up and surveillance as per section 3.3.

3.3. Follow-up and surveillance
3.3.1. Evaluation includes: History and physical examination, laboratory data, and chest X-ray
3.3.2. Stage I-III: Evaluation every 3 months for 2 years then every 6 months for 3 years then annually. CT scan of the chest every 6 months for 2 years then annually for additional 3 years. Consider annual screening CT scan after 5 years
3.3.3. Stage IV: evaluation every 2–3 months as clinical indicated.

Image-guided Percutaneous Transthoracic Biopsy in Lung Cancer

Percutaneous transthoracic core biopsy requires careful manipulation and special attention to prevent or reduce procedure-related complications.[73]
- Fine-needle aspiration (FNA) biopsy
- Core biopsy.

Indications
As with any interventional procedure, the potential benefits of core biopsy must outweigh the risks; 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.[74-76]
- 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.[77-80]

- 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
  - Cannot access be used for accessing central lesions
  - Difficulty in avoidance of bullae and vascular structures in the needle pass.

CT is the preferred and most common and standard used guidance imaging modality.[81]

- 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.[82,83]

Type

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

- End-cut biopsy needle provides full cannula 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 (noncoaxial) 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° angle between the needle and the pleura avoiding transversal of bullae, vessels and bronchi[84]
- 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 arise from administration of the local anesthetic through 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 maintained raised arms, lesions adherent to periosteum and chest wall or when the procedure is lengthy.

Computed tomography scan parameters

- mA and slice thickness
- Choosing low-dose axial scan with 120 kVp with 40 mA or lower per slice

- Choosing slice thickness should be less than half the diameter of the targeted lesion as the following:
  - 1 cm or 5 mm for lesions >3 cm in diameter
  - 5 mm for lesion 1–3 cm in diameter
  - 3 mm cm for lesions 5 mm–1 cm
  - 3 mm for lesions <5 mm 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
- Administrating 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-guage 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 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.

Postbiopsy care

- Obtaining a short CT scan to evaluate for immediate complications.[85] 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 1–2 h 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, antiplatelet 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[86]
- Most complications occur immediately or within the first hour of a biopsy and they can be treated conservatively, often on an outpatient basis[87-89]
- Common complications include pneumothorax and hemorrhage[90]
- 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,[91] the presence of emphysema, transgression of fissures, a small angle of the needle with the thoracic pleura, and multiple repositioning of the needle[92]
- 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)[93-95]
- Serial expiratory upright chest radiographs should obtained to observe for the recurrence of pneumothorax with appropriate clinical monitoring.[96]

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[97]
- More likely to occur with abnormal coagulation, pulmonary arterial hypertension, cutting needles larger than 18 gauge, lesion depth >2 cm, lesion size smaller than 2 cm, vascularity, cavitation, enlarged bronchial vessels in the vicinity, and central location[98]
- 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[99]
- The patient should be placed in the left lateral decubitus position or in trendelenburg position to prevent residual air in the left atrium from entering the cerebral circulation. Supplemental 100% oxygen should be administer and general symptomatic support should be provided.[76]

The Role of Endoscopic Ultrasound/ Gastroenterologist in Lung Cancer Diagnosis and Management

Accurate diagnosis and staging is of paramount importance for both prognostic and therapeutic reasons in lung cancers.[100]

Mediastinal staging conventionally relied heavily on invasive modalities such as mediastinoscopies and thoracotomies. Endoscopic ultrasound (EUS) evaluation of mediastinum, EUS-guided FNA, and endobronchial ultrasound-guided transbronchial needle aspirations (EBUS-TBNA) have evolved over the past 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.[101]

According to the 7th edition of TNM staging for NSCLC, Stage I and II patients are treated with surgical resection, whereas Stage III (N2 nodal status, T4 mediastinal invasion) are offered chemoradiation with only limited role of surgical resection.[101,102]

Mediastinal nodal sampling 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 ACCPs which state that EUS/EBUS are the techniques of choice for mediastinal staging.[103]

Endoscopic ultrasound-fine needle aspiration in staging of non-small cell lung cancer

NSCLC is staged according to the TNM system. This system takes into account the characteristics of the local tumor (T), the presence or absence of regional LN metastasis (N), and the presence or absence of distant metastases (M). The stage of the tumor (Stage I–IV) depends upon the particular combination of T, N, and M characteristics for the given patient.[104,105]

EUS can contribute to each component of TNM staging for lung cancer. It can help characterize the primary tumor (in centrally located tumors), assess the mediastinal LNs for evidence of metastatic disease, and evaluate some sites of distant metastasis such as the left lobe of the liver and adrenal glands. Among these contributions, however, mediastinal LN 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 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.[106,107]

EUS 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 CT scan, which has a low sensitivity (<75%) to detect mediastinal invasion and PET scan which does not have a defined role in T4 staging because of poor anatomic resolution.[108]

Mediastinal nodal staging (N stage)

Mediastinal/hilar nodal involvement (N stage) by the tumor is an important determinant for staging and guiding treatment. LN sampling for histopathological examination is necessary in patients with enlarged mediastinal LNs on CT scan or metabolically active nodes on PET scan, as imaging modalities alone have a low accuracy in staging of mediastinal nodes.[100]

EUS-FNA is effective at detecting and staging mediastinal metastatic disease. It can sample LNs 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 LNs 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 LNs, EUS can be used to sample left adrenal gland, left liver lobe

metastasis and also centrally located intrapulmonary tumors as discussed earlier.[105,109]

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 LNs. 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.[106,107,110-113]

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.[100]

Restaging

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

Combined Endoscopic Ultrasound-fine Needle Aspiration and Endobronchial Ultrasound-transbronchial Needle Aspiration 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.[100]

Impact of endoscopic ultrasound 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 endoscopic ultrasound/endobronchial ultrasound in current guidelines

- In patients with high suspicion of N2, N3 involvement, either by discrete mediastinal LN 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 LN 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).[103]

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 LNs by EUS-FNA can be used to detect lung cancer-associated genes, such as carcinoembryonic antigen, CK19, KS1/4, lunx, muc 1, and prostate derived E26 transformation specific 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.[100]

Guiding Principles of Systemic Therapy in Metastatic Non-small Cell Lung Cancer

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 [Tables 1 and 4].

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 NSCLC 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. PD-L1 testing in all NSCLC subtypes at diagnosis.
2. Management of EGFR sensitizing mutation tumors:
   - TKIs 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 (RR), progression-free survival (PFS), 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 osimertinib should be used
   - If T790 mutation is not detected, switch to platinum doublet chemotherapy. Local therapy should be considered for single or oligometastatic disease progression.
4. ALK fusion positive tumor:
   - The patient should receive crizotinib as early as possible. if progressed, ceritinib and alectinib should be used in second line. 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 WT tumors (no EGFR, ALK, or ROS1 mutation)
   a. PD-L1 tumor proportion score >50% Pembrolizumab is preferred treatment option over chemotherapy.
   b. PD-L1 TPS < 50% - chemotherapy doublet is preferred option.
7. EGFR/ALK unknown NSCLC:
   All efforts should be made to get the test done including ctDNA. If not possible, it should be treated like WT. TKI, erlotinib can be considered for second or third line as third of our patients may have mutations, which is much more common than Western population.
8. Immunotherapy:
   - Checkpoint inhibitors are approved in NSCLC as follows:
     i. Pembrolizumab first line for all NSCLC subtypes with PD-L1 TPS >50% and for second line for positive PD-L1 tumors
     ii. nivolumab: approved for 2nd line treatment of all nsclc irrespective of histology or pd-l1 status
     iii. Atezolizumab: approved for second line treatment of all NSCLC irrespective of histology and PD-L1 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
      - Preferred chemotherapy 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 texans 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. PS3–4 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 workup and close monitoring.

Immunotherapy of Non-small Cell Lung Cancer

The role of immunotherapy in 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 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 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 versus 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 vs. 6 months; hazard ratio [HR]: 0.50, 95% confidence interval [CI]: 0.37–0.68). Overall survival (OS) was also improved (HR: 0.60, 95% CI: 0.41-0.89). Overall RRs (ORRs) were 45% and 28% for pembrolizumab and platinum doublet chemotherapy, respectively.[51]

Nivolumab

In the CheckMate 026 trial, Phase III enrolled 541 patients with advanced PD-L1-positive NSCLC (≥1%) who did not receive any prior systemic therapy were randomly assigned to nivolumab or platinum doublet chemotherapy. The primary endpoint of PFS in patients with ≥5% tumor PD-L1 expression was not prolonged with nivolumab compared with chemotherapy (median PFS, 4.2 vs. 5.9 months with 1-year PFS rate 24 vs. 23%; HR: 1.15, 95% CI: 0.91–1.45). OS in patients with ≥5% tumor PD-L1 expression was not prolonged with nivolumab compared with chemotherapy (median OS 14.2 months vs. 13.2 months; HR: 1.02, 95% CI: 0.80–1.30).[114]

Immunotherapy in Pretreated Patients with Advanced Non-small Cell Lung Cancer (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 ≥1%).

In patients 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 OS was prolonged with nivolumab compared to chemotherapy (median OS 9.2 vs. 6.0 months; 1-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% vs. 54%).[115]

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 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 were similar to the previous trial with less severe (Grade 3–4) treatment-related adverse effects being seen in patients receiving nivolumab, compared to those treated with docetaxel (10% vs. 54%).[54]

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 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 vs. 35% for the docetaxel treated patients).[52]

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 to chemotherapy regardless of PD-L1 status (median OS, 13.8 vs. 9.6 months; HR: 0.73, 95% CI: 0.62–0.87).[116]

Role of Tumor Programmed Death-ligand 1 Expression as a Biomarker

Although several data of checkpoint inhibitors in NSCLC suggest that PD-L1 expression rate correlates with benefit, 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 IHC 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.

Management of Immune-related Adverse Events (irAEs)

Antibodies that target key immune checkpoints such as PD-1, nivolumab, and pembrolizumab[51,52,54] on T lymphocytes and its principal ligand PD-L1, atezolizumab[116] on tumor cells, have recently been approved for the management of NSCLC. Checkpoint inhibition is associated with a unique spectrum of side effects termed irAEs. IrAEs can affect any organ system, but they typically involve the skin, gastrointestinal, hepatic, and endocrine systems.

General Approach to Management of Immune-related Adverse Events

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 filtrates), cough, chest pain, dyspnea, 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 antimotility 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.[117]

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 aspartate transaminase and alanine transaminase 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.[118] 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.

Initial Treatment of Epidermal Growth Factor Receptor Mutation Non-small Cell Lung Cancer

Over the past few years, subclassification of NSCLC has changed from histology to molecular biomarkers after identification of pathways involved in the development of lung cancer. Aberrant 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 TKIs. The most common EGFR mutations (85–90%) are deletions in exon 19 and L858R point mutation in exon 21.[119]

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, PFS, and OS.[120]

Whereas exon 20 insertions confer resistance, some studies reported that 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.[119] 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, nonsmokers, women, and non-mucinous cancers.[121] Jazieh *et al*. reported that 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.[122]

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.[38] 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.[38]

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.[121]

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 PFS, increased the objective RR, 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.[123]

EURTAC was the first randomized trial in Europe targeting a nonAsian 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.[124] 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 ≥2 courses of chemotherapies including platinum-based and docetaxel.[125] However, many oncologists had experience with erlotinib and were comfortable using it. Later, gefitinib was available, and 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. LUX3 and LUX6 demonstrated better efficacy in exon 19 deletion which is the most common type of mutation. Moreover, there were survival benefits 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 Lung 7 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 EFGR-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.[126]

Erlotinib has also been 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).[127] Combinations showed no survival benefit compared with chemotherapy alone. There was no difference between treatment arms in terms of time to progression, RR, 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).[128]

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 RR upon treatment with upfront reversible EGFR TKI.[129] A Phase I study of AZD9291 in EGFR-mutant NSCLC patients with acquired resistance, ORR was 51% (91/177) with a RR 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,[130] unfortunately more than 50% of the patients may miss 2nd line as well.

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 RR

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

Treatment beyond Progression in Driver Mutant 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 EGFR and ALK gene 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-TKIs. In several Phase III studies, patients with EGFR mutated NSCLC achieved double ORRs and PFS when treated with an EGFR-TKIs compared with standard chemotherapy.[38,131]

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 up regulation 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% of cases of acquired resistance to EGFR TKIs. Amplification of the MET oncogene has been associated with resistance to EGFR TKIs in 5%–20% of cases.[132]

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 central nervous system disease are associated with disease flare while T790M mutation at the time of progression is not a predictive factor.[133]

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.[134,135]

Prior to changing therapy, tumor rebiopsy 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 PFS (10.1 vs. 4.4 months) and objective RR (71% vs. 31%) compared with a pemetrexed- and platinum-based chemotherapy combination.[44]

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 PFS with continuation of gefitinib in addition to chemotherapy beyond response evaluation criteria in solid tumors progression to first-line EGFR TKI for patients with EGFR mutation-positive NSCLC.[136]

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 PFS and improved RR and quality of life. No significant differences in OS were seen, potentially due to the confounding effects of crossover.[45]

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 signaling pathways have been observed in a group of NSCLC patients, who repeated biopsies at the time of crizotinib failure.[137]

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.[138]

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 PFS (5.4 vs. 1.6 months, HR: 0.49) and objective RR (39.1% vs. 6.9%), differences that were both statistically significant.[139] There are two Phase II studies that show RRs to alectinib of approximately 50% in patients with ALK-positive locally advanced or metastatic NSCLC who had progressed on crizotinib.[140,141]

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 rebiopsy 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. Patients 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.

Management of Tyrosine Kinase Inhibitors Side Effects

TKIs are considered as the standard of care for management of EGFR mutant 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 [Tables 5 and 6].

Interstitial lung disease

- 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 1 mg/kg daily for 2–4 weeks. Then, tapper the dose to minimal.

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Table 5: Management of dermatological toxicities

Grading	Description	Management
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	Maintain the same dose of TKI Might apply hydrocortisone 1% or 2.5% cream or clindamycin 1% gel
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	Maintain the same dose of TKI Apply hydrocortisone 1% or 2.5% cream or clindamycin 1% gel Start doxycycline 100 mg twice daily or minocycline 100 mg twice daily for 4 weeks
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	Discontinue the TKI Reinstate at reduced dose when toxicity has resolved to less than Grade 2 Apply hydrocortisone 1% or 2.5% cream or clindamycin 1% gel Start doxycycline 100 mg twice daily or minocycline 100 mg twice daily for 4 weeks
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	

TKI=Tyrosine kinase inhibitor

Table 6: Management of diarrhea

Grading	Description	Management
Grade 1	<4 bowel movement over baseline per day	Diet modification Standard dose of loperamide
Grade 2	4-6 bowel movement over baseline per day	
Grade 3	7 or more bowel movement over baseline per day. Limits selfcare activities of daily living and hospitalization indicated	Admit to hospital IV fluid and antibiotics as needed Consider octreotide injection
Grade 4	Life-threatening consequences, urgent intervention indicated	

IV=Intravenous

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