SAUDI LUNG CANCER MANAGEMENT GUIDELINES 2019

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Glossary

CBC	Complete blood count
CK7	Cytokeratin 7
CR	Complete Response
CT	Computed tomography
EBUS	Endobronchial Ultrasound
EGFR	Epidermal growth factor receptor
EML4-ALK	Echinoderm microtubule-associated protein-like 4 & Anaplastic lymphoma kinase
IHC	Immunohistochemistry
IT	Immunotherapy
LFT	liver function test
MRI	Magnetic resonance imaging
NGS	Next Gen Sequencing
NSCLC	Non-small cell lung cancer
NOS	Not otherwise specified
OS	Overall Survival
PCR	polymerase chain reaction
PET scan	Positron emission tomography
PD-1	Programmed cell death-1
PD-L1	Programmed death-ligand 1
PFS	Progression Free Survival
QOL	Quality of Life
RECIST	Response evaluation criteria in solid tumors
ROS1	Repressor of Silencing 1
SBRT	Stereotactic Body Radiation Therapy
SCC	Squamous Cell Carcinoma
SCLC	Small cell lung cancer
SUV	Standardized Uptake Value
TKIs	Tyrosine kinase inhibitors
TNM	Tumor, Lymph node, Metastasis
TTF-1	Thyroid transcription factor 1

Abstract

Background
Due to the rapid change in the management of lung cancer, there was a great need to update the management guidelines to keep up with the pace of progress of our knowledge in the field especially since it has direct impact on patient care and outcome.

Methods
A multidisciplinary guidelines committee of the Saudi Lung Cancer Association reviewed the previous version of the lung cancer guidelines 2017 and modified the guidelines based on the latest available evidence. External reviewers' input was also sought. The final guidelines were reviewed by all members and final version was approved.

Results
Guidelines were developed taking into account the disease stage, patient performance status and the tumor pathological/molecular profile. The recent evidence about precision medicine and immune therapy were incorporated. The guidelines are aimed to help all disciplines approach lung cancer patient systematically during diagnosis, staging, and treatment based on patient characteristics and tumor profile.

Conclusion
The updated guidelines will help healthcare professionals access the updated knowledge in order to provide evidence-based care to patients with lung cancer.

Running title: Saudi Lung Cancer Guidelines 2019

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A. Introduction

The management of lung cancer is rapidly evolving over the last few years mandating frequent updating of the guidelines due to the emerging of practice changing evidences that have direct impact on patient outcome.

The new treatment options are heavily dependent on precision medicine and the use of immune therapy, which significantly changed over the last year.

While lung cancer is number one killer worldwide, the incidence is lower in the Kingdom than other countries especially Europe and USA. Lung cancer ranked number five (5) in male in 2015 Saudi National Cancer Registry and number fifteen (15) in female with 416 cases diagnosed that year.(1)

The guidelines should be updated to keep all disciplines involved in lung cancer diagnosis and management aware of the best option to offer their patients and understand what other disciplines are expected to do. These guidelines are directed to all thoracic oncology disciplines such as pulmonary medicine, radiology, interventional radiology, pathology, molecular oncology, thoracic surgery, radiation oncology, medical oncology and palliative care.

B. Methods

The Saudi Lung Cancer Guidelines Committee is part of the Saudi Lung Cancer Association of the Saudi Thoracic Society. It has multidisciplinary experts in all the aspects of lung cancer work-up, diagnosis and treatment.

The group reviewed the latest version of the Saudi Lung Cancer Guidelines published in 2017(2), then members suggested any required modifications; addition, deletion or editing. These modifications were made and shared again with the whole group for final approval. Once the group approved the version, the guidelines were sent to two external reviewers for their feedback. Their input was taken into consideration. Finally, endorsement of the Saudi Thoracic Society (STS) and Saudi National Cancer Center (SNCC) endorsement were obtained.

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

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

C. Emerging Evidence

Over the last two years, there were significant advances in the management of metastatic NSCLC especially in the area of precision therapy and immunetherapy. In this section, we will summarize the evidence in these areas.

Next Generation Sequencing and Liquid Biopsy

Providing precision treatment became a reality for big fraction of Non-Small Cell Lung Cancer patients. The tumor should be tested for actionable targets that has major impact on treatment efficacy and patients outcomes.(3)

The following alterations should be tested including: EGFR, ALK, ROS1, BRAF, RET fusion, MET exon 14, skipping and amplification, BRAF and ERBB2 (Her2).

The test should be done in properly accredited laboratory. Multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond EGFR, ALK and ROS1.

ALK testing can be done by IHC. ROS1 positivity by IHC requires confirmation by molecular or genetic testing.

Liquid Biopsy:

Testing cell-free/circulating tumor DNA (cfDNA) is referred to as liquid biopsy which should not be used for diagnosis but can be used to look for genetic alteration if biopsy is not feasible or no adequate tissue available cfDNA is recommended for EGFR and T790mut. However, due to reduced sensitivity, if cfDNA test is negative, NGS on tissue biopsy should be pursued to look for alteration especially when resistance to TKI is suspected.(4)

EGFR TKI as First Line Therapy For Patients with EGFR Mutant, Non-Small Cell Lung Cancer

Biomarkers are increasingly being used to monitor a patient's clinical course and response to therapy. These evolving markers are being used to predict possible benefit from a particular treatment, and tailoring it for each individual patient.

Driver gene-guided target therapy has changed the landscape of NSCLC treatment. The most well-recognized driver gene for NSCLC is epidermal growth factor receptor (EGFR).EGFR protein is expressed in most NSCLC cells and plays important roles in tumor proliferation, angiogenesis, metastases, treatment-resistance, and inhibition of apoptosis.(5)

EGFR mutation is currently the only well-established predictive and prognostic biomarker for EGFR tyrosine kinase inhibitors initiation. Agents such as gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib, are examples of (EGFR-TKIs) that can inhibit the activity of tyrosine kinase and has an anti-tumor effect.

In several classical phase III randomized controlled clinical trials EGFR-TKIs significantly improved clinical efficacy, safety and quality of life compared with chemotherapy in advanced NSCLC patients with positive EGFR mutation.(5)

Disease Response

In all studies overall response rate (ORR) to TKIs in EGFRmut patients was higher than chemotherapy.

In (IPASS) a phase III study conducted in East Asia that compared gefitinib, and carboplatin-paclitaxel among nonsmokers or former light smokers with adenocarcinoma of lung primary, previously untreated with chemotherapy. ORR was significantly higher (OR 1.88; 95% CI (1.22–2.89), (P=0.004) with gefitinib (44.6%) than with carboplatin/paclitaxel (29.8%).(6)

EURTAC is the first prospective head-to-head phase 3 study comparing efficacy and safety of erlotinib as first line, with platinum-based chemotherapy in non-Asian patients with advanced NSCLC and EGFR mutations.

Two (2%) of 86 patients in the erlotinib group had a complete response, whereas 48 (56%) of 86 in the erlotinib group and 13 (15%) of 87 in the standard chemotherapy group attained a partial response, Two (3%) of 77 patients in the erlotinib group had a complete response. 47 (61%)of 77patients in the erlotinib group and 13 (18%) of 73 patients in the standard chemotherapy group had partial response (odds ratio 7·5, 95% CI 3·6–15·6; p<0·0001).(7)

Survival and outcome
In EURTAC median progression free survival PFS was 9.4 months (95% CI 7.9–12.3) in the erlotinib group and 5.2 months (4.4–5.8) in the standard group.(7)

In LUX-Lung phase 3 trial Afatinib was tested against cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harboring EGFR mutations. At the time of analysis, overall survival did not differ significantly between treatment groups, which is expected for a trial of a first-line treatment with subsequent crossover between treatments arms.(8)

Indeed, neither of the previous studies in this setting showed differences in survival, despite meeting the primary endpoint of progression-free survival.
In LUX-Lung 3—in which afatinib was compared with pemetrexed and cisplatin A total of 345 were randomly assigned to treatment. Median PFS was 11.1 months for afatinib and 6.9 months for chemotherapy (hazard ratio [HR], 0.58; 95% CI, 0.43 to 0.78; P = .001.(8)

IPASS (Iressa Pan-Asia Study) An overall analysis (OS)was 18.8 months in the gefitinib group and 17.4 month in chemotherapy group (HR＝0.90), indicating no difference between the two groups. Sub group analysis respectively showed the median survival in the gefitinib and chemotherapy groups in the EGFR mutation positive subset to be 21.6 and 21.9 months, while the respective median survival in the negative cases was 11.2 and 12.7 months.(6)

These results indicate longer survival in any group among the EGFR mutation positive cases, but no difference in OS by treatment, irrespective of EGFR mutation status.

In FLAURA trial, osimertinib first-line in Asian population demonstrated a clinically meaningful improvement in PFS over an SoC (standard of care) EGFR TKI, with a safety profile consistent with that for the overall FLAURA study population.

The median PFS was 16.5 versus 11.0 months for the osimertinib and (SoC) EGFR TKI groups, respectively (hazard ratio = 0.54, 95% confidence interval: 0.41-0.72, p < 0.0001). The overall survival data were immature (24% maturity).

The objective response rates were 80% for osimertinib and 75% for and (SoC) EGFR TKI. The median central nervous system PFS was not calculable for the osimertinib group and was 13.8 months for the (SoC) EGFR TKI group (hazard ratio = 0.55, 95% confidence interval: 0.25-1.17, p = 0.118).
Fewer adverse events of grade 3 or higher (40% versus 48%) and fewer adverse events leading to treatment discontinuation (15% versus 21%) were reported with osimertinib versus with and (SoC) EGFR TKI, respectively.(9)

Safety

In First-SIGNAL, NEJ002 and WJTOG3405 trials, rash, diarrhea and liver dysfunction were the most common adverse events (AEs) reported with gefitinib. In addition, interstitial lung disease was rare but fatal.(10)

Safety In EURTAC they included all patients who had received at least one dose of a study drug in the safety analysis. The most common adverse events in the erlotinib group were rash [13%] of 84 patients at grade 3 and increased aminotransferase concentrations, two [2%] of 82 patients at grade 3. The most common adverse events in the standard chemotherapy group were anemia ,three [4%] grade 3 and neutropenia (18) [22%] grade 3–4.(7)

No increased incidence of pneumonitis was noted in the erlotinib group. Eleven (13%) patients in the erlotinib group and 19 (23%) in the standard chemotherapy group were withdrawn from the trial treatment because of adverse events. One patient in the erlotinib group and two patients in the standard chemotherapy group died from treatment-related causes.

Patients treated with erlotinib had milder side-effects than did those treated with standard chemotherapy.

Quality of Life

The OPTIMAL study was a phase III, randomised, open-label study comparing the efficacy and safety of first-line erlotinib with gemcitabine–carboplatin in Chinese patients with locally advanced or metastatic NSCLC whose tumors harbor EGFR activating mutations.(11)

The QoL and lung cancer symptoms were assessed at baseline and every 6 weeks using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire. This questionnaire includes a number of questions regarding physical well-being (including pain, nausea and fatigue), social/family well-being, emotional well-being (including depression and anxiety) and functional well-being (including sleep). It also incorporates the Lung Cancer Subscale (LCS), which assesses seven lung cancer symptoms: dyspnea, cough, thoracic pain, breathing difficulties, anorexia, weight loss and cognition, and the 21-item Trial Outcome Index (TOI), which examines the outcomes for the LCS, functional well-being and physical well-being. All patients completed questionnaires during office visits before any other study procedures.

The erlotinib group performed better than the chemotherapy group in all FACT-L subscales from baseline to cycles 2 and 4, reaching statistical significance at cycle 2 for physical well-being ($P = 0.0032$), emotional well-being ($P = 0.0357$) and LCS ($P = 0.0041$).

Convenience

Patients on oral medications (EGFR-TKIs)are having fewer hospital visits which will minimize burden on family, and caregivers. They are also having lower hospital admissions and no chemotherapy suite visits.

Cost Effectiveness

The combination use of gefitinib and EGFR testing can be considered a cost-effective first-line therapy compared to chemotherapy such as carboplatin–paclitaxel for the treatment for NSCLC in Japan.

They conducted a cost-effectiveness analysis of the combination use of EGFR mutation testing and gefitinib as first-line therapy for NSCLC patients from the point of view of the Japanese healthcare payer.

Their analysis showed that the ICER The (incremental cost-effectiveness ratio) of the EGFR-testing strategy compared with the no-testing strategy is expected to be around JP¥3.38 million (US$32,500) per QALYs(quality-adjusted life-years) gained.

This result suggests that the combination use of EGFR mutation testing and gefitinib as first-line therapy for NSCLC patients is cost-effective in Japan.(12)

Therefore, EGFR-TKIs are recommended as the standard first-line treatment for patients with advanced NSCLC harboring EGFR mutation since there were found to be effective, safe, convincing and appealing.
They need to be continued till disease progression that not amenable for local therapy, at this stage tumors need to be biopsied looking for new targetable mutation or transformation and patients should be shifted to second line accordingly. In case of oligometastatic disease patients can go for local therapy and maintained on the same first line treatment.

These medications have been approved as the standard first-line agents by FDA (US Food and Drug Administration), EMA (European Medicines Agency), and CFDA (China Food and Drug Administration) and were incorporated as first line options in NCCN, ASCO and ESMO guidelines.

Immunotherapy In Stage III Non Small Cell Lung Cancer

Management of patients with stage III NSCLC, locally advanced disease, is controversial. The potentials for resectability must be determined in all cases, especially with non-bulky stage IIIA disease. Surgery is followed by adjuvant systemic therapy to eradicates micrometastases. For unrespectable disease, bulky stage IIIA and stage IIIB, definitive chemoradiation is the treatment of choice. Despite all these multimodalities, the 5-year OS remains low,15-20%.

Not long time ago Immunotherapy is incorporated in the management of stage III NSCLC. For patients with stage III NSCLC who underwent CCRT and achieved stable disease or objective response, Durvalumab (anti-PDL-1) 10 mg/kg every two weeks for 12 months has shown to improve both PFS and OS. In patients who are not fit for surgery or radiation therapy, systemic therapy is administered as in stage IV disease.

Durvalumab

In the PACIFIC trial, a total of 709 patients with locally advanced, stage III, unresectable NSCLC were enrolled. All patients underwent concurrent chemoradiation. Then they were randomized to receive either durvalumab (n = 473), given intravenously at a dose of 10 mg/kg, or placebo (n = 236) every two weeks for 12 months duration.

The co-primary endpoints of the study were progression-free survival (PFS) and overall survival (OS); secondary endpoints were safety and time to distant metastasis. Initial results, reported in 2017, showed an 11.2-month absolute improvement in PFS favoring durvalumab over placebo.(13)

Recently, with a longer median follow-up of more than 25 months, Median OS has not yet been reached for the durvalumab arm while it is 28.7 months for the placebo arm with HR of 0.68 favoring durvalumab. Moreover, the 2-year survival rate was 66.3% for durvalumab arm compared to 55.6% for placebo. The survival advantages observed with durvalumab was seen across all subgroups[2]. The Median time to distant metastases was also favoring durvalumab at 28.3 vs.16.2 months for placebo. Serious adverse events with durvalumab occurred in 29.1% compared to 23.1%

of placebo. Though the frequency of all grades pneumonitis was higher in the durvalumab group, and no deaths occurred due to this particular toxicity.(14)

Nivolumab

In a pilot study, neoadjuvant Nivolumab (3 mg/kg) was administered for two doses, every 2 weeks for patients with respectable NSCLC (stage I, II, IIIA). 21 tumors were removed, 20 were completely resected, and major pathological response was seen in 9 out of 20 resected tumors. Responses were seen regardless of PDL-1 status, but greater pathological response was seen with higher pretreatment tumor mutational burden.(15)

First line immunotherapy single agent and combination

Pembrolizumab is approved for the frontline treatment of patients with advanced epidermal growth factor receptor/anaplastic lymphoma kinase (EGFR/ALK) wild-type NSCLC whose tumors have ≥50% PD-L1 expression based on the 22C3 pharmDx test.

This is based on phase III KEYNOTE-024 trial, in which pembrolizumab monotherapy (200 mg intravenous [IV] every three weeks) was compared with standard platinum-doublet chemotherapy in 305 patients with advanced, untreated, EGFR/ALK wild-type NSCLC having at least 50% tumor cell PD-L1 staining.(16) At a median follow-up of 11.2 months, Progression-free survival (PFS) was prolonged with pembrolizumab compared with platinum-doublet chemotherapy (median PFS, 10.3 versus 6 months; hazard ratio [HR] 0.50, 95% CI 0.37-0.68). Overall survival (OS) was also prolonged with pembrolizumab compared with platinum-doublet chemotherapy (HR 0.60, 95% CI 0.41-0.89). The objective response rates (ORR) for pembrolizumab and platinum-doublet chemotherapy were 45% and 28%, respectively. Median durations of response were 12.1 and 5.7 months, respectively. Severe (grade 3 to 5) treatment-related adverse effects were seen in 27% of patients receiving pembrolizumab, compared with 53% in those treated with platinum-doublet chemotherapy. Of the 1653 screened patients with tumor tissue evaluable for PD-L1, 30 percent were found to have tumors with at least 50% PD-L1 expression.

For those without a targetable driver alteration and either less than 50% of tumor cells staining for PD-L1 or unknown PD-L1 expression, we recommend platinum-based chemotherapy combined with pembrolizumab rather than chemotherapy alone.

This is based on phase III KEYNOTE-189 trial, in which Six-hundred and sixteen patients with advanced, PD-L1-unselected, nonsquamous NSCLC were randomized in a 2:1 ratio to chemotherapy (cisplatin or carboplatin with pemetrexed) with either pembrolizumab or placebo.(17) With median follow-up of 10.5 months: OS was 69% at 12 months among those receiving pembrolizumab and chemotherapy, versus 49% for those receiving chemotherapy and placebo (HR for death 0.49, 95% CI 0.38-0.64). Median PFS was also improved with the addition of pembrolizumab (8.8 versus 4.9 months for those receiving chemotherapy and placebo; HR for disease progression or death 0.52, 95% CI 0.43-0.64). The ORR was 48% (95% CI 42.6-52.5) in the pembrolizumab-combination group and 19% (95% CI 13.8-25.0) in the placebo-combination group. The 12-month OS, with and without pembrolizumab, for those with ≥50% PD-L1 expression was 73 versus 48%; for PD-L1 expression between 1 and 50%, 72 and 51%; and for those with PD-L1 expression <1%, 62% and 52%, respectively. Severe adverse events (≥grade 3) occurred in 67% of the patients in the pembrolizumab-combination group and in 66% of those in the placebo-combination group.

KEYNOTE-407 is phase III randomized trial in which Five-hundred and fifty nine patients with PD-L1-unselected, treatment-naïve, advanced squamous NSCLC were randomized in a 1:1 ratio to chemotherapy (carboplatin with either paclitaxel or nab-paclitaxel) with either pembrolizumab or placebo.(18) With median follow-up of 87.8 months: Median OS was 15.9 months among those receiving pembrolizumab and chemotherapy, versus 11.3 months for those receiving chemotherapy and placebo (HR for death 0.64, 95% CI 0.49-0.85). Median PFS, the other primary endpoint, was also improved with the addition of pembrolizumab (6.4 versus 4.8 months for those receiving chemotherapy and placebo; HR for disease progression or death 0.56, 95% CI 0.45-0.70). The ORR was 58% (95% CI 51.9-63.8) in the pembrolizumab-combination group and 38% (95% CI 32.7-44.4) in the placebo-combination group. Severe adverse events (≥grade 3) occurred in 70% of the patients in the pembrolizumab-combination group and in 68% of those in the placebo-combination group.

The ongoing phase III KEYNOTE-042 trial is comparing pembrolizumab monotherapy with standard, histology-appropriate, platinum-doublet chemotherapy in 1274 patients with untreated, advanced, *EGFR*/*ALK* wild-type NSCLC with at least 1% tumor PD-L1 expression.(18) Patients were stratified by tumor PD-L1 expression levels (>50 versus 1 to 49%). At a median follow-up of 12.8 months, preliminary results showed that OS was prolonged among patients receiving pembrolizumab compared with those receiving chemotherapy as follows, according to PD-L1 expression: A) ≥50% (599 patients), 20 versus 12 months (HR 0.69, 95% CI 0.56-0.85). B) ≥20% (818 patients), 18 versus 13 months (HR 0.77, 95% CI 0.64-0.92). C) ≥1% (1274 patients), 17 versus 12 months (HR 0.81, 95% CI 0.71-0.93). In exploratory analysis of survival among patients with PD-L1 expression between 1 and 49%, OS was 13.4 versus 12.1 months (HR 0.92, 95% 0.77-1.11). There was no statistically significant PFS benefit among patients receiving pembrolizumab compared with those receiving chemotherapy, except for those with the highest level of PD-L1 expression (≥50%): ≥50%, 7.1 versus 6.4 months (HR 0.81, 95% CI 0.67-0.99). Therefore, for those with tumor PD-L1 1-49%, we continue to prefer the chemotherapy/immunotherapy combination, pending further data.

Although not FDA approved in the first-line setting, phase III studies have suggested benefit when atezolizumab is added to standard first-line, platinum-doublet chemotherapy for advanced NSCLC.

The IMpower 150 trial randomly assigned 1202 patients with PD-L1-unselected, advanced, non-squamous NSCLC to first-line chemotherapy (carboplatin and paclitaxel every three weeks) combined with either atezolizumab (1200 mg IV every three weeks [ACP]), atezolizumab plus bevacizumab (15 mg/kg IV every three weeks [ABCP]), or bevacizumab (BCP).(19) Among the 692 EGFR/ALK wildtype patients randomly assigned to ABCP or BCP, PFS was 8.3 versus 6.8 months, respectively (HR for disease progression or death 0.62, 95% CI 0.52-0.74). Interim analysis of median OS among the patients in the wildtype population was longer in the ABCP group than in the BCP group (19.2 versus 14.7 months; HR for death 0.78, 95% CI 0.64-0.96). Notably, the OS and PFS benefits with ABCP over BCP were also observed in the 14% of enrolled patients who had *EGFR*- or *ALK*-positive NSCLC, all of whom had received at least one line of targeted therapy. The grade 3 or 4 treatment-related adverse events were higher among those receiving ABCP than among those in the BCP.

The IMpower 131 trial randomized 683 patients with PD-L1-unselected, advanced, squamous NSCLC to frontline chemotherapy (carboplatin and albumin-bound paclitaxel) alone or combined with atezolizumab (1200 mg IV every three weeks).(20) In preliminary results, at a median follow-up of 17 months, those assigned to atezolizumab and chemotherapy experienced an improved PFS (6.3 versus 5.6 months; HR 0.7, 95% CI 0.60-0.85) relative to those receiving chemotherapy alone. Improvements were seen in all PD-L1-positive subgroups, but not in the PD-L1-negative subgroup. In the overall population, interim OS results were not significantly different between those receiving atezolizumab and chemotherapy versus chemotherapy alone (14.0 versus 13.9 months). Treatment-related grade 3 to 4 events occurred in 68 versus 57%, with and without atezolizumab, respectively.

Nivolumab is not approved by the FDA for use in the first-line setting for NSCLC. The CheckMate 026 trial randomized 541 patients with advanced, untreated, PD-L1-positive NSCLC (at least 1 percent of tumor cells with PD-L1 staining) in a 1:1 ratio to nivolumab (3 mg/kg IV every 2 weeks) or standard first-line, histology-based, platinum-doublet chemotherapy. Neither PFS nor OS were prolonged with nivolumab (HR for disease progression or death in patients with >5% tumor PD-L1 staining 1.15, 95% CI 0.91-1.45; HR for death 1.02, 95% CI 0.80-1.30).(21)

The CheckMate 227 is a multi-part trial randomizing patients with advanced, untreated NSCLC to histology-based, platinum-doublet chemotherapy; nivolumab plus ipilimumab; or either nivolumab monotherapy (for PD-L1 ≥1%) or nivolumab plus chemotherapy (for PD-L1 <1%).(22) Patients with high TMB, defined as >10 mutations per megabase, have prolonged PFS with either nivolumab plus ipilimumab or Nivolumab and chemotherapy as compared to chemotherapy, irrespective of tumor PD-L1 expression level. OS analysis is not mature.

Second line Treatment with immunotherapy

Immunotherapy with PD-1 and PD-L1 check point inhibitors are effective strategies over conversional chemotherapy after disease progression on platinum-based chemotherapy. The blockage of PD-1 receptors and PD-L1 enhance the anti-tumor activity of the cytotoxic T-lymphocytes. Currently three agents were approved for treatment of advanced disease after progression on platinum-based chemotherapy, Pembrolizumab, Nivolumab and Atezolizumab. PD-L1 expression testing is required prior to prescribing Pembrolizumab while Nivolumab and Atezolizumab are not.

Pembrolizumab has been approved as second line treatment after progression on platinum-based chemotherapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with at least 1% of tumor cells expressing PD-L1. This approval was based on phase II/III clinical trial (KEYNOTE 010).(23) In this trial, patients with previous treatment with chemotherapy with either squamous or nonsquamous histology with PD-L1 TPS of at least 1% where randomized to receive Pembrolizumab (2 different doses of 2mg/kg or 10 mg/kg) or single agent Docetaxel chemotherapy. Overall survival was longer with immunotherapy of both doses compared to chemotherapy. The subgroup of patients with PD-L1 of 50% or more had longer survival with much lower HR compared to lower PD-L1 expressers patients. Treatment related adverse events were lower with Pembrolizumab compared to Docetaxel.

Nivolumab is another immune check point inhibitor against T-cells PD-1 receptor. It has been approved as treatment for patient with locally advanced or metastatic squamous or nonsquamous NSCLC after failure of platinum chemotherapy based on 2 phase III clinical trials (CheckMate 057 and CheckMate 017).(24–26) For patients with nonsquamous histology, Nivolumab with dose of

3mg/kg was compared to Docetaxel 75mg/m2 in phase III clinical trial (CheckMate057)(24), Nivolumab was superior to chemotherapy with regard to overall survival, overall response rate and duration of response. The subgroup of patients with higher PD-L1 expression had a longer survival compared to low expression group. In this study, current and former smokers had a higher response rate. In patients with squamous histology, Nivolumab was superior to Docetaxel as well when tested in phase III trial (CheckMate 017)(25), the benefit of Nivolumab was observed over chemotherapy across all PD-L1 levels. Response rate was almost doubled in the patient in the Nivolumab arm.

Atezolizumab is first in class anti PD-L1 check point inhibitor. It received FDA approval as a subsequent therapy in squamous and nonsquamous histological subtypes. The approval was irrespective of PD-L 1 expression status. The phase III clinical trial (OAK)(27) compared Atezolizumab in the second line setting with Docetaxel. Majority of patient were former or current smokers and very few of them had EGFR mutation or ALK rearrangements. Overall survival was significantly higher in the atezolizumab arm and benefit more pronounced in the adenocarcinoma group. The survival benefit was also seen across all subgroups with different TC and IC PD-L1 expression including those with negative expression, However; patients with higher PD-L1 expression on immune and tumor cells had better overall survival.

Immune related adverse events was higher as expected with immune check point inhibitors when compared to chemotherapy with grade 3 and higher rate of around 10%. High dose corticosteroid is recommended when immune-related adverse events is suspected. Lives threating immune related adverse events like pneumonitis are indication for permanent treatment discontinuations.

Based on the aforementioned information, subsequent treatment with immunotherapy is recommend using any of the above agents taking in consideration the following caveats: patients with EGFR or ALK rearrangements need to be treated first with chemotherapy after failure of all recommended targeted therapies. Patient treated with Pembrolizumab should have PD-L1 TPS of 1% or greater and Atezolizumab is showing some clinical activity even in TC and IC negative lung cancer patients.

Management of ALK positive NSCLC first line

Anaplastic lymphoma Kinase (ALK) rearrangement is identified in 3-7% of advanced NSCLC cases and ALK tyrosine kinase inhibitors (TKIs) have revolutionized the management of this subset of NSCLC patients and have been proven highly effective in these patients.(28) Patients with ALK rearrangements are resistant to EGFR TKIs but have similar clinical characteristics to patients with EGFR mutations (ie, adenocarcinoma histology, never smokers, or light smokers) except that they are more likely to be men and may be younger age.(29) Approximately 30% of those patients will have ALK rearrangements.(30) ALK rearrangements are not routinely found in patients with SqCC. Although rare, patients with ALK gene rearrangements can have mixed squamous cell Immunohistochemistry (IHC) can be performed to assess for ALK rearrangements; if positive, FISH analysis can confirm ALK positivity.(31) Next Generation Sequencing (NGS) can also be used to assess the presence of ALK rearrangements are present. The optimal frontline option and the sequence of TKIs are under continuous consideration in the rapidly evolving landscape of ALK inhibitors.

Crizotinib

It is a multitarget ALK, ROS1 and MET (high-level MET amplification or MET exon 14 skipping mutation) targeted tyrosine kinase inhibitor (TKI). It is FDA-approved for patients with locally advanced or metastatic NSCLC who have ALK gene rearrangements (ie, ALK-positive disease) or

ROS1 rearrangements. Randomized phase III trials have compared crizotinib with standard second-line chemotherapy (PROFILE 1007) and with standard first-line therapy (PROFILE 1014).First-line therapy with crizotinib improved PFS, response rate (74% vs 45%; P<.001), lung cancer symptoms, and quality of life compared with chemotherapy (pemetrexed with either cisplatin or carboplatin).(32) Based on this trial, crizotinib was recommended as first-line therapy in patients with ALK-positive NSCLC(6).

Crizotinib dose is 250mg twice daily, and has relatively known side effects (eg, eye disorders, edema, transient changes in renal function), However, a few patients have had life-threatening pneumonitis; crizotinib should be discontinued in these patients. Patients whose disease responds to crizotinib may have rapid improvement in symptoms (eg, cough, dyspnea, pain); median time to progression on crizotinib is approximately 7 months to 1 year.(33) Subsequent therapy with crizotinib improved PFS (7.7 vs 3.0 months; *P*<.001) and response rate (65% vs 20%; *P*<.001) compared with single-agent therapy (either docetaxel or pemetrexed) in patients with ALK-positive NSCLC whose disease had progressed after first-line chemotherapy.

Alectinib

It is as demonstrated by the ALEX trial, Alectinib is superior ALK inhibitor to crizotinib as standard first-line therapy for ALK-positive lung cancer in terms of efficacy, toxicity, and prevention of CNS metastases. Alectinib is an oral highly selective ALK TKI active both in crizotinib-naïve and in crizotinib-resistant ALK-rearranged NSCLC cases. Preclinical data revealed that it targets several ALK mutations that confer resistance to crizotinib (L1196, the gatekeeper mutation in crizotinib-resistant mutants, as well as C1156Y, F1174L, R1275Q, and G1269A), but not ROS1 and IGF-1R (34) In contrast to crizotinib, alectinib penetrates to CNS, as it is not a substrate of P-glycoprotein (P-gp), a key efflux transporter located at the blood-brain barrier.

In June 2013, alectinib was granted by the FDA for patients with ALK (+) NSCLC who progressed on crizotinib and in July 2014. Japan firstly approved alectinib in previously untreated patients with advanced ALK-rearranged NSCLC. in 2015, FDA approved alectinib in the USA, for crizotinib-resistant patients with ALK-positive NSCLC and last year 2017 alectinib receives European approval for patients with previously treated ALK-positive NSCLC. The recommended dose is 300 mg BID. Treatment with crizotinib vs. alectinib resulted in ORRs of 47.8% and 49.2%; median PFS was 6.3 and 8.9 months; duration of response continued for a median of 7.5 and 11.2 months, and intracranial response for patients with baseline CNS disease were 57% and 75%, respectively.(35) Comparing ALK inhibitors as first-line options, both randomized phase III trials, the Japan J-ALEX and the global ALEX trial, showed superiority of alectinib over crizotinib for the management of ALK-positive advanced NSCLC.(36) J-ALEX trial showed a favorable PFS for alectinib (median PFS: not reached) compared with crizotinib (median PFS: 10.2 months. Grade ≥3 AEs occurred at a greater frequency with crizotinib (52%) than alectinib (26%) while dose interruptions/discontinuations due to toxicities were also more commonly observed with crizotinib (74%/20%) than with alectinib (29%/9%). In the global ALEX trial, 41% of patients in the alectinib group versus 68% in the crizotinib group experienced a disease progression or death during follow-up.(35)

The rate of one-year PFS was significantly higher with alectinib than with crizotinib (68.4% vs. 48.7%; P<0.001) while the median PFS with alectinib was not reached. Only 12% in the alectinib group had an event of CNS progression, as compared with 45% in the crizotinib group (P<0.001). However, the ORR in the alectinib group and in the crizotinib group (82.9% and 75.5%, respectively) did not reached to significant difference (P=0.09). These results showed that alectinib has both systemic efficacy and intracranial disease control in patients with ALK-positive NSCLC and brain metastases, supporting a potential change of first-line option for ALK inhibition.

As a subsequent line option, the comparison of alectinib with pemetrexed in patients with ALK-positive NSCLC previously treated with platinum-based chemotherapy and crizotinib is under investigation by a phase III trial (NCT02604342).

Ceritinib

It is a 2nd-generation, ATP competitive, highly selective ALK inhibitor (20 times more potent than crizotinib) and a potent inhibitor of IGFR-1 but not efficient inhibitor of c-MET. Preclinical data showed that ceritinib was active against many ALK mutations that conferred resistance to crizotinib, including C1156Y, F1174C, G1202R and the gatekeeper mutation L1196M but also in crizotinib-resistant lines without known resistance mutations to crizotinib. FDA approved ceritinib for patients with advanced/metastatic ALK-positive NSCLC progressing to crizotinib. The ASCEND-4 trial showed a statistically significant and clinically meaningful improvement in outcomes of ceritinib compared to platinum-pemetrexed doublet and pemetrexed maintenance in untreated patients with advanced *ALK*-rearranged NSCLC.(37) Median PFS was 16.6 *vs.* 8.1 months (P<0.001) and overall as well as intracranial response rate were 73% *vs.* 27%, respectively in the two therapeutic arms. The ASCEND-5 trial compared ceritinib with docetaxel or pemetrexed in 231 patients with ALK-rearranged NSCLC who had previously received a platinum doublet and crizotinib and had subsequent disease progression. The primary outcome of PFS was 5.4 months with ceritinib and 1.6 months with chemotherapy (P<0.001) and ORR with ceritinib (39.1%) exceeded that of chemotherapy (6.9%).(38) The dose of ceritinib is 750mg daily and side effects were mainly gastrointestinal events included diarrhea, vomiting, dehydration, elevated aminotransferase levels, and hypophosphatemia. Because of the toxicity profile it is is not recommended as upfront therapy.

D. The Guidelines Recommendations

I. ALL LUNG CANCER PATIENTS

1.1 INITIAL PATIENT ASSESSMENT

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

1.1.2 Perform the following laboratory tests: Complete blood count, differential, liver function test, renal function, electrolytes, calcium, serum albumin, magnesium, and phosphorus.

1.1.3 Two-view chest x-ray. Contrast enhanced CT scan of the chest

1.2 DIAGNOSIS

1.2.1 Obtain adequate tissue specimen for diagnostic and predictive markers.

1.2.2 Patient with a strong suspicious of stage 1 lung cancer based on radiological and risk factors does not require biopsy (if tumor board agreed), biopsy may add time, cost, procedural risk and it may not be needed for treatment decision

1.2.3 Mediastinoscopy is needed for most of stage 1 and 2 lung cancer before surgical procedure but during the same anesthesia procedure.

- 1.2.3.1 Mediastinoscopy is needed for most of stage 1 and 2 lung cancer before surgical procedure but during the same anesthesia procedure.
- 1.2.3.2 Endobronchial Ultrasound (EBUS) for mediastinal staging for stage 1 and 2 only if tumor is central and with high Standardized Uptake Value (SUV) uptake by PET scan, If no EBUS use mediastinoscopy prior to surgical resection during the same session.

1.2.4 Patient suspected of having solitary site of metastatic disease should have tissue confirmation from that site if feasible.

1.2.5 Patient with positive pleural effusion, should have thoracentesis and cytology, negative cytology does not exclude pleural involvement another cytology/thoracoscopic evaluation of pleura with pleural biopsy should be considered before starting curative intent.

1.2.6 Confirm histopathological diagnosis of lung cancer and determine the histological subtypes using most recent pathological classification of lung cancer. Utilization of proper Immunohistochemistry (IHC) staining (minimal panel to include TTF1 (most important), CK7, and CK20 for adenocarcinoma and P40 (preferred) or P63 to minimize the diagnosis of “not otherwise specified” (NOS).

1.2.7 Obtain epidermal growth factor receptor (EGFR) mutation testing by PCR in certified laboratory for all histology except pure squamous cell (Squamous cell carcinoma with small sample or mixed histology or never smokers, EGFR should be done). Next generation sequencing (NGS) should be performed, if available.

1.2.8 If NGS is not available and EGFR wild type (WT) tumors, obtain EML4-ALK fusion test by IHC or FISH in certified laboratory. (EL-1)

1.2.9 For patients with wild type EGFR & ALK, obtain the ROS1 test and BRAF, MET, RET, Her2 by Nextgen sequencing (NGS) if available. (EL-1)

1.2.10 If tissue not adequate to do molecular testing, perform ctDNA (plasma) testing.(39)

1.2.11 Obtain PDL1 testing by IHC 22C3 pharmDx on all NSCLC with wild molecular test or unknown molecular status. (EL-1)

1.3 STAGING

1.3.1. Non-Small Cell Lung Cancer

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

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

1.3.1.3 Obtain total body positron emission tomography/computed Tomography (PET/CT), concomitant staging is beneficial since it avoids additional biopsy or procedure. It is preferable to biopsy the pathology that would confer the highest stage. Therefore, PET CT is frequently best performed before biopsy is chosen in case of high clinical suspicion for aggressive advanced – stage tumors. Consider PET CT if patient is going for radical therapy (such as surgery or chemoradiotherapy).

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

1.3.1.5 Perform Mediastinal LN evaluation in selected cases; i.e. clinical stages (IB-III) even if the Pet/CT scan is positive. Especially negative nodes by imaging with central tumor and T2 to T4. (See 1.2.3)

1.3.1.6 Determine precise TNM staging using 8th edition (2017).

1.3.2. Small Cell Lung Cancer

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

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

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

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

1.3.2.5 Determine precise TNM staging using 8th edition (2017).

1.4 PRE-TREATMENT ASSESSMENT

1.4.1 Discuss all new cases in a multidisciplinary conference (Tumor Board).

1.4.2 Obtain cardiopulmonary assessment (Pulmonary Function test, 6-minute walk, ECG and echo) if surgery considered and PFT for curative radiotherapy is considered.

1.5 GENERAL

1.5.1 Counsel about smoking cessation and pulmonary rehabilitation.

1.5.2 Offer available clinical research studies.

II. <u>NON-SMALL CELL LUNG CANCER</u>

2.1 CLINICAL STAGE IA

2.1.1. Anatomical surgical resection (lobectomy) and mediastinal lymph node sampling/dissection.

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 SBRT as an option.

2.1.4. Patients with positive surgical margins should be offered re-resection or radical post-operative 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 pulmonary function test is not contra indication for SBRT. (Sec 2.3.8)

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

2.2 CLINICAL STAGE IB

2.2.1 Anatomical surgical resection mediastinal lymph node sampling or dissection.

2.2.2 For lesions ≥ 4 cm or high-risk features (poorly differentiated, wedge resection, minimal margins, vascular Invasion), consider adjuvant chemotherapy.(40,41)

2.2.3 Chemotherapy of choice: 4-6 cycles of platinum combination cisplatin (carboplatin only if cisplatin is contraindicated) (EL- 1)(40–43)

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. See 2.3.8 hypo fractionated radiotherapy is second option.

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

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

2.3 CLINICAL STAGE IIA

2.3.1 Anatomical surgical resection with lobectomy or pneumonectomy and mediastinal lymph node sampling (EL- 1)(44,45) or dissection is the treatment of choice.

2.3.2 Offer adjuvant chemotherapy as per section 2.2.3 (EL - 1).(40–43)

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

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

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

2.3.6 If surgical resection is not possible, offer curative radical radiotherapy for T2b N0. See Section 2.3.8

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

2.3.8 Radiotherapy with curative intent in patients with early stage, medically inoperable, non-small cell lung cancer:

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

2.3.8.2 Most established SBRT criteria include NO patients with:

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

2.3.8.3 Positive hilar or mediastinal LN is absolute contraindication for SBRT.

2.3.8.4 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.

2.3.8.5 Recommended fractionation schemes for SBRT should have a BED10(LQ) of $\geq$100.

2.4 CLINICAL STAGE IIB

2.4.1 Anatomical surgical resection and mediastinal lymph node sampling. (EL- 1)(44,45) or dissection is the treatment of choice.

2.4.2 Offer adjuvant chemotherapy as per section 2.2.3 (EL- 1). (40–43)

2.4.3 Superior sulcus tumors patients should be induced by cisplatin/etoposide with concurrent radiation therapy followed by surgical resection (EL- 2)(46,47) and 2 cycles of adjuvant chemotherapy. Assess disease extent by using MRI at baseline and pre-operative. (EL-2) (46,48–50)

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 post-operative radiotherapy.

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

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

2.5 CLINICAL STAGE IIIA

2.5.1 For T3 N1 M0 perform en-bloc resection.

2.5.2 For superior sulcus tumor, offer treatment similar to 2.4.3. (46)

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

2.5.4 If N_2 disease discovered during surgery by frozen section abort surgery if pneumonectomy is required (EL- 2).(51)

2.5.5 For patients with incidental pathological N_2 disease, adjuvant chemotherapy is recommended (EL-1)(40–43) and in addition radiotherapy can be considered (EL- 3). (52)

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

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

2.5.8 For non N_2 stage IIIA, not specified above, offer surgical resection with adjuvant chemotherapy.

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

2.6 CLINICAL STAGE IIIB-C AND UNRESECTABLE IIIA

2.6.1 Offer concurrent chemo- radiotherapy (EL-1)(53,54) followed by Durvalumab for 1 year. Surgical resection for selected cases could be offered after discussion by tumor board.

2.6.2 Offer Durvalumab as maintenance for 12 months post chemoradiotherapy for unresectable stage III. (EL1)

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

2.7 STAGE IV*

* Obtain palliative care consultation/evaluation on all patients, preferably as early as possible (EL-1).(55)

2.7.1 Systemic Therapy (Table 1A and Table 1B)

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

2.7.1.2. With brain metastases (Table 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/non-squamous with sensitizing EGFR mutation.**

Guiding principle:

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

A. First line:

1. Performance Status 0-2:

- TKIs Osimertinib (preferred, if not available, other TKI erlotinib, gefitinib, Afatinib or dacomitinib)(El-1). (8,56,57)

- If TKI is not available use systemic therapy like wild type.

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

3. Performance Status 4:

   - Use TKIs.

B. Maintenance:

1. Performance Status 0-2:
   - Continuation or switch maintenance with TKIs (EL-1).(58–60) 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 by NGS with either ctDNA (plasma) testing (good positive test) or re-biopsy of metastatic site if negative liquid biopsy.

For isolated or oligoprogression, consider local therapy and continue current TKI. For multiprogression, switch to second line therapy.

1. If T790M Positive, use Osimertinib, if not used in the first line setting, if it is available(EL-1). (61)

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 referral to palliative care.

D. Third Line and Beyond

* Obtain T790M testing if it was not done earlier, consider doing NGS in ctDNA (plasma) testing if tissue biopsy is not feasible.

1. Performance Status 0-2:
   - Use TKIs, if not used before.

   - Consider immunotherapy (Nivolumab or Pembrolizurab (pembrolizumab only if PD-L1 TPS is > or equal to 1%), or Atezolizumab after TKI and chemotherapy.

   - Systemic chemotherapy (single agent chemotherapy, Pemetrexed if not used, Docetaxel, etc).

   - Ramcirumab/Docetaxel

2. If T790M Positive, use Osimertinib, if not used before.

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:
    - Alectinib is the preferred first treatment option. (EL-1). (32,62,63)
    - If not available, then Crizotinib or Ceritinib or Brigatinib can be used as first line option

    - Systemic chemotherapy with a platinum doublet (+/- bevacizumab) can be considered. (Platinum-Pemetrexed combination is preferred over a gemcitabine-based combination) only if TKIs are not available.

    - Chemotherapy regimen for patients with comorbidities or not tolerating cisplatin the following regimen were added:

    - Carboplatin AUC 5 and Gemcitabine (D1.8 every 21 days)

    - Carboplatin AUC 5 and Pemetrexed 500 MG/M2 every 21 days , for nonsquamous

    - Crizotinib is also very effective in patients with ROS 1 rearrangements.

2. Performance Status 3:

    - Use Alectinib. If not available then Crizotinib can be used as first line option.
    - Single agent chemotherapy can be considered.

3. Performance Status 4:

    - Use Alectinib. Crizotinib can be used as an alternative if Alectinib is not available.

    - Palliative care.

B. Maintenance:

Performance Status 0-2:

- Continuation or switch (if patients started on chemotherapy) maintenance with first line option. If was not started on Alectinib or Crizotinib, patient should be switched to alectinib (preferred) or Crizotinib as soon as possible.

Performance Status 3 and 4:

- Continuation or switch maintenance with Alectinib. If was not started on Alectinib, patient should be switched to Alectinib as soon as possible. Alternatively use Crizotinib if Alectinib is not available.

C. Second line

- Consider re-biopsy and retesting for mechanism of resistance.
- For isolated or oligoprogression, consider local therapy
- For multiple site progression, treat based on cause of resistance or if TKI is used in first line

1. Performance Status 0-2:
   - Alectinib (preferred) or Ceritinib are the recommended treatment options for patients with disease progression or intolerance to Crizotinib and if not used in first line setting(EL-1). (37,64,65)

   - Use TKI based on mechanism of resistance.

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

2. Performance Status 3 and 4:

   - Use Alectinib, if Crizotinib used before or no prior TKI treatment

D. Third Line and Beyond

1. Performance Status 0-2:

   - Use TKI (Alectinib preferred if not used in first line setting crizotinib or ceritinib) are alternative if not used before.

   - Systemic Chemotherapy like first line of wild type NSCLC.

- Consider immunotherapy (Pembrolizumab, Nivolumab or Atezolizumab)

2. Performance Status 3 and 4:
   - Use Alectinib, if not used in first line.
   - If both agents where used, Palliative care.

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

A. First line:

1. Performance Status 0-2:

   <u>* If PDL > 50%:</u>
   - Use Pembrolizumab alone or in combination with carboplatin/paclitaxel or cisplatin pemetrexed (Preferred EL-1),(16,23,66) if it is not available use systemic chemotherapy (platinum doublet+/-bevacizumab) (Pemetrexed is preferred over gemcitabine).

   <u>* If PDL <50%:</u>

   - Chemotherapy combination (platinum with pemetrexed or carboplatin, paclitaxel and bevacizumab) with pembrolizumab. (EL-1)
   - Atezolizumab combination with chemotherapy (Table 1B). (EL-1)
   - If pembrolizumab not available, 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 PDL1 <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 Pembrolizumab (pembrolizumab only if PDL 1 Positive at least TPS 1% or more), if received chemotherapy as first line (EL-1). (16,23,24,27,66)

   - Platinum doublet if pembrolizumab used as first line. Preferred regimen is platinum with pemetrexed.

   - 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. (Pemetrexed preferred over docetaxel) if not used previously.

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

2.7.1.4.4. Lung Carcinoma with other mutations

Patients with met amplification, RET rearrangement, HER2 mutation or BRAF mutations can be treated by targeted therapy per table 1A. (EL-2)

2.7.1.4.5 **Squamous cell carcinoma:**

A. First line:

1. Performance Status 0-2:
   * If PDL1 < 50% (16,23,66)
   - Systemic therapy, combination of immunechemotherapy combination (platinum doublet, carboplatin (nab) paclitaxel with pembrolizumab or atezolizumab) (No Bevacizumab or Pemetrexed). (EL-1)

   * If PDL1 >50% use Pembrolizumab as single agent (EL-1). (16,23,66)

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 (PD-L1 TPS 1% or greater) or Atezolizumab), if Pembrolizumab not used. (EL-1) (16,23,24,27,66,67)

- Systemic chemotherapy doublet if Immune therapy used as first line (No Pemetrexed).

- Consider using Ramucirumab / Docetaxel

- Afatinib

2. Performance Status 3:
   - Single agent systemic therapy

3. Performance Status 4:
   - Palliative care.

D. Third Line and Beyond

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

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

2.8 FOLLOW UP OF NON-SMALL CELL LUNG CANCER

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

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

2.8.2 Stage IV: evaluation every 2-3 months as clinically indicated.

III. SMALL CELL LUNG CANCER

3.1 Stage I-III (Limited stage):

3.1.1 Offer cisplatin/etoposide with radiation therapy then consolidate with two cycles of cisplatin/ etoposide (EL-1).(68) 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).(69–71)

3.1.3 For stage (T1-2 N0 confirmed by Mediastinal staging), offer surgical resection followed by chemotherapy and prophylactic brain radiotherapy.

3.1.4 Follow up and surveillance per section 3.3.

3.2 STAGE IV (Extensive Stage)

3.2.1 Offer cisplatin/ etoposide or cisplatin /irinotecan x 6 cycles (EL-1).

3.2.1.1 Use of carboplatin cisplatin is not indicated. (72–74)

3.2.1.2 Carboplatin/etoposide + atezolizumab is effective (EL-1). (75)

3.2.2 After definitive chemotherapy with evidence of response and good performance status offer consolidative thoracic irradiation and prophylactic cranial irradiation (PCI)(EL-2).

3.2.3 Nivolumab single agent or with ipilimumab for disease progression, if no prior treatment with immunotherapy. (EL-2)

3.2.3.1 If nivolumab not available, for previously treated patients who relapsed in less than 6 months from initial treatment, offer topotecan or cyclophosphamide, adriamycin and vincristine (CAV), or irinotecan.

3.2.3.2 For relapse after six months from initial treatment, may use original regimen.

3.2.4 Follow up and surveillance per section 3.3.

3.3 FOLLOW UP AND SURVEILLANCE

1.3.1 Evaluation includes: history and physical examination, laboratory data and chest x-ray.

1.3.2 Stage I-III: evaluation every 3 months for 2 years then every 6 months for 3 years then annually. CT scan of the chest every 6 months for 2 years then annually for additional 3 years. Consider annual screening CT scan after 5 years.

1.3.3 Stage IV: evaluation every 2-3 months as clinical indicated.

Table 1A. Management of Metastatic NSCLC with Driver Mutations

Mutation	EGFR	ALK	ROSI	Met amplification or Met exon 14 Skipping	RET Rearrangement	HER2 Mut	BRAF V600E Mutation
First Line	- Osimirtinib (preferred) - Other EGFR TKI - Erlotinib, Afatinib, Gefitinib - Dacominitib	- Alectinib (preferred) - Ceritinib - Crizotinib - Brigatinib - Lorlatinib	Crizotinib Ceritinib	Crizotinib	Carbozontinib or Vandetanib	Adotrastuzumab Emtasine	Dabrafenib + Trametinib
Second Line	T790 mut switch Osimertinib if not used, chemotherapy doublet if Osimertinib used (Pemetrexed preferred)	Alectinib, if not used. Lorlatinib , if not used If used, double agent chemotherapy	Chemotherapy Lorlatinib	Chemotherapy	Chemotherapy	Chemotherapy	Chemotherapy
Third Line	- Immunotherapy - Chemotherapy Doublet, if not used	Chemotherapy OR Immunotherapy, if TKI used	Immunotherapy	Chemotherapy OR IT	Chemotherapy OR IT	Chemotherapy OR IT	Chemotherapy OR IT
Fourth Line	- Single agent chemotherapy if IT and chemotherapy doublet used.	Single Agent Chemotherapy	Single Agent Chemotherapy	Chemotherapy OR IT	Chemotherapy OR IT	Chemotherapy OR IT	Chemotherapy OR IT

IT: Immune Therapy
TKI: Tyrosine Kinase Inhibitors

Table 1B. Management of Metastatic NSCLC without Driver Mutation

	Non-Squamous Histology		Squamous
First Line	**Platinum + pemetrexed plus pembrolizumab OR Carboplatin, (paclitaxel) + atezolizumab (± Bevacizumab) OR **Platinum/Taxol, Bevacizumab + atezolizumab Use chemotherapy if IT is not available	**Pembrolizumab single agent OR **Pembrolizumab in combination with chemotherapy	**Carboplatin + (nab) paclitaxel + pembrolizumab OR carboplatin + paclitaxel + atezolizumab
Maintenance	**IT per first line - Bevacizumab if used - Pemetrexed if used	Pembrolizumab continuation	IT per First Line
Second Line	IT if not used **Nivolumab or Atezolizumab or Pembrolizumab	**IT if not used first line Nivolumab or Atezolizumab or Pembrolizumab* Chemotherapy doublet if not used	**IT if not used first line Nivolumab or Atezolizumab or Pembrolizumab* Chemotherapy doublet if not used
Third Line	Chemotherapy Single Agent, if chemotherapy doublet used.	Chemotherapy Single Agent	Chemotherapy Single Agent

IT: Immune Therapy; includes Nivolumab, Pembrolizumab and Atezolizumab
*Pembrolizumab – second line use is limited to PDL1 TPS ≥ 1%
**United State Food and Drug Administration (USFDA) approved

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

Table 3: Radiosurgery treatment indications for brain metastases

Class	Characteristics
Single lesion	• Surgical resection + SRS to cavity • SRS alone
RPA class I-II	SRS alone for medically / surgically inoperable cases
KPS $\leq$60, extensive intracranial/extracranial disease	WBRT+ Dexamethasone or Dexamethasone alone.

Table 4. Systematic Therapy Regimens in NSCLC

	Chemotherapy Regimen	Reference
Adjuvant	Carboplatin AUC 6 + paclitaxel 225 mg/m^2 on day 1 21 DAYS cycle for 6 cycles (4-6 cycles)	(40,41)
	Cisplatin 75mg/m^2 + Docetaxel 75 mg/m^2 on day 1 21 day cycle for 6 cycles	(40)
	Cisplatin 100 mg/m^2 + gemcitabine 1000 mg/m^2 on day 1 & 8, 15 28 day cycle for 6 cycles Usual practice is to omit day 15 and use every 21 days.	(40)
	Carboplatin AUC 5 + gemcitabine 1000 mg/m^2 on day 1 & 8 21 days cycle for 6 cycles	(42)
	Cisplatin 75mg/m^2+ vinorelbine 25 mg/m^2 on day 1 & 8 21 days cycle for 6 cycles	(43)
Concurrent with Chemoradation	Carboplatin AUC 2 + Paclitaxel 45 mg/m^2 Weekly with radiation	(53)

	Cisplatin 50 mg/m^2 (days 1, 8, 29, 36) + etoposide 50mg/m^2 (day 1 to 5 and 29 to 33) Week 1 and 5	(54)
Definitive chemoradiation	Durvalumab 10mg/kg IV every 2 weeks for up to 12 months	(14)
Metastatic	Carboplatin AUC 6 + paclitaxel 225 mg/m^2 on day 1 21 days cycle for 6 cycles	(40)
	Cisplatin 75mg/m^2, Pemetrexed 500mg/m^2 every 21 day.	(76)
	Cisplatin 75mg/m^2 + Docetaxel 75 mg/m^2 on day 1 21 days cycle for 6 cycles	(40)
	Cisplatin 100 mg/m^2 + gemcitabine 1000 mg/m^2 on day 1 & 8, 15 28 day cycle for 6 cycles Usual practice is to omit day 15 and use every 21 days	(40)
	Carboplatin AUC 5 + gemcitabine 1000 mg/m^2 on day 1 & 8 21 day cycle for 6 cycles	(42)
	Cisplatin 75mg/m^2+ vinorelbine 25 mg/m^2 on day 1 & 8 21 day cycle for 6 cycles or Vinorelbine 60-80mg/m2 (Max 160mg) PO Available as 20mg & 30mg capsules	(43)
	Pembrolizumab (200mg IV)+ Carboplatin AUC 6+ Paclitaxel 200mg/m^2 (or nab - paclitaxel 100mg/m^2 days 1,8,15) every 21 days	(18)
	Pembrolizumab (200 mg IV) + Cisplatin (75mg/m2) or Carboplatin AUC of 5 with Pemetrexed (500 mg/m^2) every 21 days	(17)
	Atezolizumab 1200mg IV + Carboplatin (AUC 6) + Paclitacxel 200mg/m^2 (or nab - paclitaxel 100mg/m^2 days 1,8,15) + 15mg/kg Bevacizumab every 21 days	(19,77)
	Paclitaxel (200 mg/m^2) +carboplatin (AUC 6) + bevacizumab (15 mg/kg) every 21 days	(78)
	Ramucirumab 10mg/kg IV + docetaxel 75mg/m^2 IV. Repeat cycle every 3 weeks.	(79)
	Nintedanib 200mg PO Twice daily Days 2-21 Docetaxel 60 or 75mg/m^2 IV Day 1 every 21 days	(80)
Single agent regimens	Gemcitabine 1250mg/m^2 (day 1 and 8) 21 day cycle	(81)
	Docetaxel 75mg/m^2 IV 21 day cycle	(82)
	Pemetrexed 500mg/m^2 IV 21 day cycle	(83)
	Topotecan 1.5mg/m^2 (day1 to 5) IV	(84)

	21 day cycle	
	Vinorelbine 60-80mg/m^2 (Max 160mg) PO weekly	(85,86)
	Gefitinib 250mg po once daily until disease progression or unacceptable toxicity	(56)
	Erlotinib 150mg po once daily until disease progression or unacceptable toxicity	(57)
	Afatinib 40 mg p.o. once daily until disease progression or unacceptable toxicity	(8)
	Osimeritinib 80mg p.o. once/day Until disease progression or unacceptable toxicity	(61)
	Crizotinib 250 mg p.o. twice daily until disease progression or unacceptable toxicity	(32,62,63)
	Alectinib 600 mg PO twice daily Until disease progression or unacceptable toxicity	(64)
	Ceritinib 750 mg p.o. once daily Until disease progression or unacceptable toxicity	(37,65)
	Nivolumab: 240 mg IV every 2 weeks or 480 mg every 4 weeks infuse over 1 hour until disease progression or unacceptable toxicity	(24)
	Pembrolizumab: 200 mg IV every 3 weeks over 30 minutes until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression	(16)
	Atezolizumab 1200 mg IV over 60 minutes every 3 weeks until disease progression or unacceptable toxicity	(67)
	Cabozantinib: 60mg PO once daily Until disease progression or unacceptable toxicity	(87,88)
	Vandetanib: 300mg PO once daily Until disease progression or unacceptable toxicity	(89)
	Adotrastuzumab Emtasine: 3.6mg/kg IV every 3 weeks Until disease progression or unacceptable toxicity	(90)
	Dabrafenib 150mg PO twice daily + Trametinib 2mg PO once daily for 12 months, or until disease progression or unacceptable toxicity	(91)
	Dacomitinib: 45mg PO once daily Until disease progression or unacceptable toxicity	(92)
	Brigatinib: 90mg PO once daily for the first 7 days; if tolerated, increase to 180mg PO once daily. Until disease progression or unacceptable toxicity	(93,94)
	Lorlatinib: 100mg PO once daily Until disease progression or unacceptable toxicity	(95)

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