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Management guidelines for stage III non-small cell lung cancer☆

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ABSTRACT

Management of stage III non- small cell lung cancer (NSCLC) is very challenging due to being a group of widely heterogeneous diseases that require multidisciplinary approaches with timely and coordinated care. The standards of care had significant changes over the last couple of years because of the introduction of consolidation therapy with checkpoint inhibitor following concurrent chemo-radiotherapy and the evolving new role of tyrosine kinase inhibitors in the adjuvant setting. The manuscript presents evidence-based recommendations for the workup, staging, treatment and follow up of the various subtypes of stage III NSCLC. The guidelines were developed by experts in various fields of thoracic oncology and guidelines development. The guidelines consider the sequence of interventions and the role of each discipline in the management of the disease taking into account the recent development and included required resources to help physicians provide better care.

1. Background

Lung Cancer is the leading cause of cancer-related mortality around the world and it continues to have an enormous impact on health systems of all countries. In 2018, it was estimated that there were more than 2 million new cases and more than 1.7 million deaths due to lung cancer worldwide (Bray et al., 2018). It is predicted that the lung cancer mortality will increase to 3 million by 2035, a two-fold increase from 2012 (Didkowska et al., 2016).

There are two major histological subtypes of lung cancer, the small cell lung cancer (SCLC) and the non-small cell lung cancer (NSCLC). NSCLC accounts for almost 85 % of all lung cancer cases; commonest subtypes are adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma (Travis et al., 2015). Approximately 30 % of patients affected with NSCLC are diagnosed with locally advanced disease (Stage III). This is a heterogenous group that includes a wide spectrum of clinical presentations, often with considerable tumor burden (T3-T4 and N2-N3). Beyond stages IIIA and IIIB, the latest tumor, node, metastasis (TNM) staging (8th edition) also introduces stage IIIC, which refers to a massive parenchymal localization combined with contralateral lymph node involvement (T3-T4 and N3) (Detterbeck et al., 2017; Rami-Porta et al., 2017). Despite the absence of metastases, their prognosis is poor, with 5-year overall survival (OS) rate of approximately 36 %, 26 % and 13 % for stages IIIA, IIIB, and IIIC, respectively after concomitant or sequential chemoradiation (Huber et al., 2019).

Due to the heterogeneity of stage III NSCLC, the need to involve multiple disciplines in the patients management and the recent advances in the care of these patients, our group developed the following

☆ On behalf of the Multidisciplinary Lung Cancer Consortium and Saudi Lung Cancer Association of the Saudi Thoracic Society.

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guidelines to help clinicians manage their patients in an evidence-based approach. These guidelines have methods describing the process of developing them, recommendations and discussion summarizing the evidence supporting the most recent practice changes in the last couple of years.

2. Methods

A multidisciplinary team was formed including specialized physicians from pulmonary medicine, imaging, thoracic surgery, radiation oncology, and medical oncology. The multidisciplinary team reviewed the Saudi Lung Cancer guideline recommendations and extracted the recommendations pertinent to stage III as baseline format (Jazieh et al., 2017). The team reviewed the literature including pertinent international guidelines updated the recommendations accordingly (NCCN Non Small Cell Lung Cancer Guidelines, 2020; ESMO, 2020; Eberhardt et al., 2015). A meeting of the group was held to discuss these recommendations. The manuscript has been generated and circulated among the team to reconcile the feedback. The final version of the guidelines was approved by the whole team. Previously adopted levels of evidence were used for these guidelines (Jazieh, 2020). These levels of evidence are:

- **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 retrospective studies or expert opinions.

3. Recommendations

3.1. Patient assessment

3.1.1. INITIAL PATIENT ASSESSMENT

1 Perform history and physical examination. Document smoking history, performance status, weight loss and comorbidities.
2 Perform the following laboratory tests: Complete blood count, differential, liver function test, renal function, electrolytes, calcium, serum albumin, magnesium, and phosphorus.
3 Two-view chest x-ray (EL3). Contrast enhanced CT (computed tomography) scan of the chest (EL2).

3.1.2. Diagnosis

1 Obtain adequate tissue specimen for diagnostic and predictive markers. (EL-1)
2 A multi-disciplinary team (MDT) approach is recommended for the work-up and staging according to the availability and expertise. (EL-2)
3 Procedure risk and possible treatment options should be taken into consideration before deciding the best procedure/biopsy site to pursue.
4 The preferred initial site for tissue biopsy is the one that could simultaneously establish the histopathologic diagnosis and disease staging.
5 Minimally invasive procedures including bronchoscopy, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), endobronchial ultrasound-guided fine needle aspiration (EUS-FNA), and transthoracic needle biopsy (TTNB) carry lower risk for major complications and are preferred (Muthu et al., 2019) over more invasive procedures. (EL-2)
6 Non-surgical candidates
7 Unresectable T3−4: Imaging guided tissue biopsy from the most accessible and least invasive site is adequate procedure.
8 Scalene or supraclavicular positive N3 lymph nodes on CT/FDG-PET (F-fluorodeoxyglucose-positron emission tomography). Needle aspiration or core biopsy of these nodes (Kumaran et al., 2005) should be the first choice for sampling to identify NSCLC involvement.
9 Potential surgical candidates: require sampling of the mediastinal lymph nodes.
10 Mediastinal N2/N3 positive lymph nodes on CT/PET: Enlarged and/or increased uptake on FDG-PET of mediastinal N2/3 lymph nodes, regardless of size, should be pathologically confirmed given suboptimal imaging positive predictive value (Kumar et al., 2011).
11 Mediastinal N2/N3 negative lymph nodes on CT/PET but at increased risk for involvement: Central or primary tumor $>$ 3 cm, adenocarcinomas with high SUV (standard uptake value), or presence of cN1 (1 cm in the short axis on CT and SUV $>$ 2.5 on PET/CT) are at increased risk for N2/N3 and should be sampled (De Leyn et al., 2014).
12 Confirm histopathological diagnosis of lung cancer and determine the histopathological subtypes using most recent pathological classification of lung cancer. (EL-1) 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).
13 Testing for Epidermal Growth Factor Receptor (EGFR) mutation (EGFRmut) is required for stage 1B and higher (Herbst et al., 2020; Wu et al., 2020). (EL-1)

3.1.3. Staging

1 It is very critical to determine the accurate stage of the disease as treatment as stage dependent (Table 1).

3.1.3.1. Imaging studies.

1 CT of the chest (from thoracic inlet till the upper abdomen) with or without IV contrast is recommended for clinical tumor staging (Detterbeck et al., 2013).

2 CT chest with IV contrast is more appropriate than CT chest without IV contrast in central tumors and superior sulcus tumors (Patz Jr et al., 1999; Imai et al., 2013).

3 Respiratory dynamic (magnetic resonance) of the chest is appropriate when invasion of the chest wall and or diaphragm is equivocal on CT chest with contrast (Kajiwara et al., 2010; Akata et al., 2008).

4 MR of the superior sulcus is appropriate in the presence of neurologic symptoms/ signs referable to the brachial plexus or when invasion of the brachial plexus/ vertebrae is suspected on CT chest (Kajiwara et al., 2010; Akata et al., 2008; Bruzzi et al., 2008).

5 CINE MR of the chest/ heart is appropriate when invasion of the cardiovascular structures is equivocal on CT chest with contrast. (Seo et al., 2005).

6 All patients should have FDG-PET/CT (from skull base to mid-thigh) (Hellwig et al., 2000; Dwamena et al., 1999; Caoili et al., 2000; Tu et al., 2018). If FDG-PET/CT is not performed, the following are appropriate

Table 1
Subtypes of Stage III NSCLC.

Overall Stage	TNM Subtype	Description
Stage IIIA	T1a N2 M0	≤ 1 cm met to ipsilateral Mediastinal and of Subcarinal LN
	T1b N2 M0	>1−2 cm met to ipsilateral Mediastinal and of Subcarinal LN
	T1c N2 M0	>2−3 cm met to ipsilateral Mediastinal and of Subcarinal LN
	T2a N2 M0	>3−4 cm met to ipsilateral Mediastinal and of Subcarinal LN
	T2b N2 M0	>4−5 cm met to ipsilateral Mediastinal and of Subcarinal LN
	T3 N1 M0	>5−7 cm parietal pleura or pericardium, chest wall, phrenic nerve, or separate nodule in the same lobe & ipsilateral peribronchial and/or hilar or intrapulmonary LN
	T4 N0 M0	>7 cm invading mediastinum, heart, vertebra, diaphragm, esophagus, carina and ipsilateral separate nodule in different lobe No LN
	T4 N1 M0	>7 cm, invading mediastinum, heart, vertebra, diaphragm, esophagus, carina and ipsilateral separate nodule in different lobe Ipsilateral peribronchial and/or hilar or intrapulmonary LN
Stage IIIB	T1a N3 M0	≤ 1 cm Met to contralateral hilar or mediastinal LNs, ipsilateral or contralateral scalene or supraclavicular LNs
	T1b N3 M0	>1−2 cm Met to contralateral hilar or mediastinal LNs, ipsilateral or contralateral scalene or supraclavicular LNs
	T1c N3 M0	>2−3 cm Met to contralateral hilar or mediastinal LNs, ipsilateral or contralateral scalene or supraclavicular LNs
	T2a N3 M0	>3−4 cm Met to contralateral hilar or mediastinal LNs, ipsilateral or contralateral scalene or supraclavicular LNs
	T2b N3 M0	>4−5 cm Met to contralateral hilar or mediastinal LNs, ipsilateral or contralateral scalene or supraclavicular LNs
	T3 N2 M0	>5−7 cm, parietal pleura or pericardium, chest wall, phrenic nerve, or separate nodule in the same lobe met to ipsilateral Mediastinal and of Subcarinal LN
	T4 N2 M0	>7 cm, invading mediastinum, heart, vertebra, diaphragm, esophagus, carina and ipsilateral separate nodule in different lobe met to ipsilateral Mediastinal and of Subcarinal LN
Stage IIIC	T3 N3 M0	>5−7 cm, parietal pleura or pericardium, chest wall, phrenic nerve, or separate nodule in the same lobe Met to contralateral hilar or mediastinal LNs, ipsilateral or contralateral scalene or supraclavicular LNs
	T4 N3 M0	>7 cm, invading mediastinum, heart, vertebra, diaphragm, esophagus, carina and ipsilateral separate nodule in different lobe Met to contralateral hilar or mediastinal LNs, ipsilateral or contralateral scalene or supraclavicular LNs

7 CT chest with IV contrast may be appropriate for initial clinical mediastinal staging (Cascade et al., 1998).

8 Multiphase CT abdomen with IV contrast is appropriate to detect occult abdominal metastasis (Caoili et al., 2000; Hustinx et al., 1998; Yeh and Rabinowitz, 1980).

9 Bone scan may be appropriate to detect bone metastasis.(Cheran et al., 2004)

10 Additional Imaging recommendations for extra-thoracic metastasis

11 All patients should have MR brain without and with IV contrast even in the absence of neurologic symptoms (Yokoi et al., 1999; Inoue et al., 2006; Hendriks et al., 2013).

12 CT head without and with IV contrast is appropriate to detect brain metastasis if MR brain is not performed or in the presence of neurologic symptoms/ clinical signs when MR is not performed. (Yokoi et al., 1999; Inoue et al., 2006; Hendriks et al., 2013; Matys et al., 2018).

13 Chemical shift MR of the adrenal glands is appropriate when adrenal lesion/s remain equivocal following CT and FDG/PET (if performed) (Haider et al., 2004; Yoh et al., 2008).

14 Multiphase CT of the abdomen is appropriate in the presence of clinical signs/ symptoms referable to the abdomen (Yeh and Rabinowitz, 1980; Kagohashi et al., 2003).

3.1.3.2. Mediastinal staging.

1 Endosonography FNA (fine needle aspiration) is the preferred modality for mediastinal sampling since it is minimally invasive requiring only moderate conscious sedation.

2 EBUS-TBNA is the preferred first-step procedure for sampling suspected nodal metastases in the anterior and superior mediastinum

3 Combination of EBUS/EUS, if available, increases the sensitivity and may decrease the frequency of unnecessary surgical procedures.

4 The lymph node of the highest stage should be biopsied first i.e. N3 followed by N2 and then N1 to prevent falsely upstaging the tumor.

5 Representative lymph node aspirate containing adequate numbers of lymphocytes does not always exclude metastases.

6 Perform staging cervical mediastinoscopy for negative EBUS/EUS if high suspicion of mediastinal node involvement i.e. N2/N3 on imaging.

7 VATS (video-assisted thoracoscopic surgery) is preferred for sampling aortopulmonary lymph nodes (Scott et al., 2007; Altorki et al., 2014).

8 Determine precise TNM staging using 8th edition. (2017) (Amin, 2020).

3.1.4. PRE-TREATMENT ASSESSMENT

1 Discuss all new cases in a multidisciplinary meeting (Tumor Board). (EL-2)
2 Obtain cardiopulmonary assessment (Pulmonary function test (PFT), 6-minute walk, ECG (electrocardiogram) and echocardiogram if surgery is considered and PFT for curative radiotherapy is considered. (EL-2)
3 Spirometry and diffusing capacity for carbon monoxide (DLCO) should be routinely done in all patients prior to lung resection to stratify the risk of surgical resection. (EL-2)
4 Patients with preserved lung function: i.e FEV1 (forced expiratory volume 1) >2 L or FEV1 and DLCO > 80 % predicted should tolerate resection well including pneumonectomy. (EL-1)
5 Patients with low lung function: stratify risk assessment based on percent predicted postoperative (%PPO) FEV1 and DLCO.

6 % PPO can be estimated with quantitative perfusion scanning or calculated based on the number of segments to be resected. (EL-3)
7 Low risk: if both PPO FEV1 or DLCO > 60 % or either <60 % percent predicted, but both >30 % and a simple stair climb >22 m or shuttle walk test>400 m.
8 Increased risk: if either PPO FEV1 or DLCO are < 30 % or stair climb < 22 m or shuttle walk test <400 m then a formal cardio-pulmonary exercise test with measurement of V02 max should be
9 Acceptable risk: VO2 max >20 mL/kg per min. (EL-2)
10 Higher risk: 10 > VO2 max < 20 mL/kg per min. Consider alternative modality. (EL-2)
11 Unacceptable risk: VO2 max < 10 mL/kg per min surgery contraindicated.

3.1.5. GENERAL RECOMMENDATIONS TO ALL PATIENTS

1 Counsel about smoking cessation and pulmonary rehabilitation. (EL-2) (Tao et al., 2013).
2 Offer available clinical research studies.

3.2. Subtypes of stage III non-small cell lung cancer

See Fig. 1.

3.2.1. CLINICAL STAGE IIIA

1 For T3 N1 M0 perform en-bloc resection. (EL-1)
2 Superior sulcus tumors patients should be induced by cisplatin/etoposide with concurrent radiation therapy followed by surgical resection (EL-2) (Rusch et al., 2007; Kunitoh et al., 2008), and 2 cycles of adjuvant chemotherapy. Assess disease extent by using MRI at baseline and pre-operative (EL-2) (Rusch et al., 2007; Takasugi et al., 1989; Heelan et al., 1989).
3 For N_2 disease the standard of care is concurrent chemo-radiotherapy, followed by one year of immunotherapy with durvalumab (EL-1) (Antonia et al., 2018). 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 (EL-2). For inoperable tumors, continue with the appropriate treatment based on disease status (Tables 2 and 3)
4 If N_2 disease discovered during surgery by frozen section abort surgery if pneumonectomy is required (EL- 2) (Martins et al., 2012; Herth et al., 2004).
5 For patients with incidental pathological N_2 disease, adjuvant chemotherapy is recommended (EL-1) (Wiener et al., 2011; Strauss et al., 2008; Zatloukal et al., 2003; Winton et al., 2005). The use of adjuvant chemotherapy demonstrated a 4–5% absolute

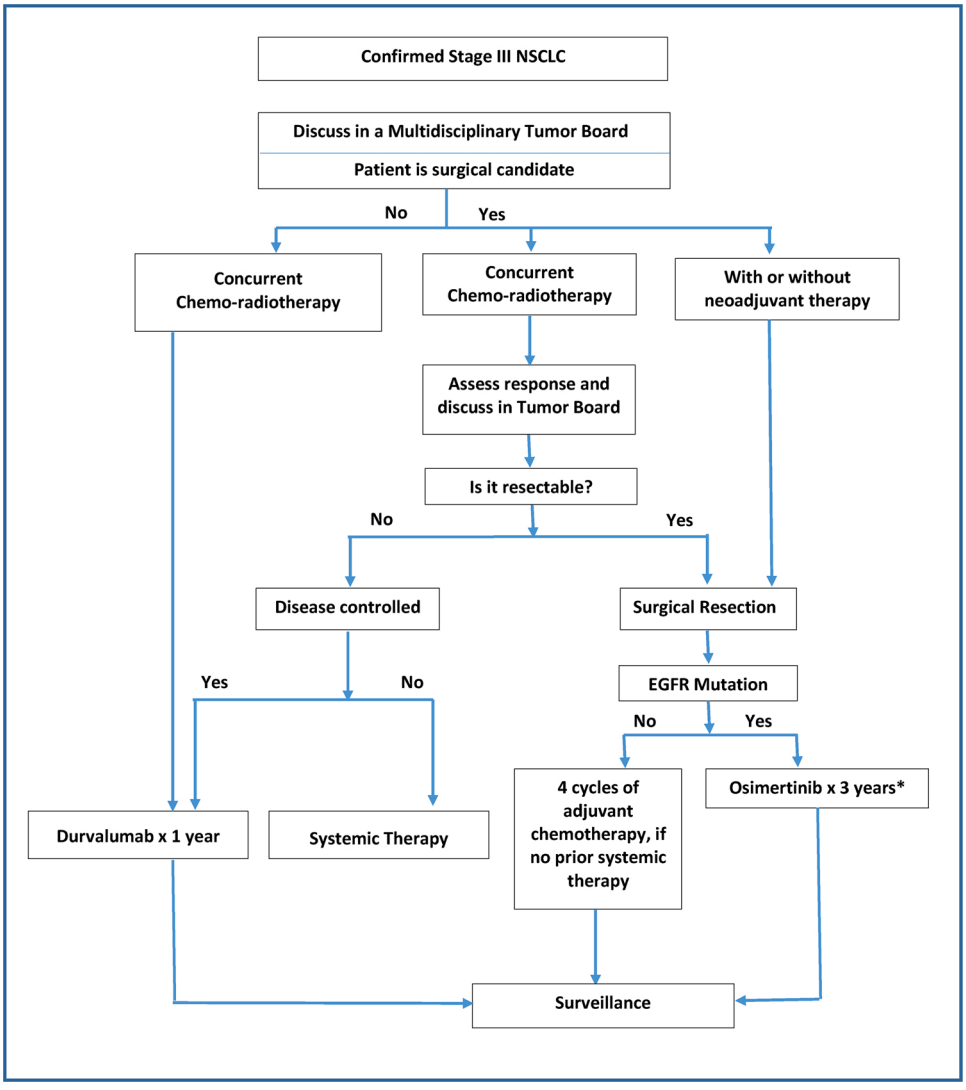

Fig. 1. Management algorithm of stage III NSCLC.
*May consider the additional of systemic therapy treatment naïve patients, recommended up to stage III only.

Table 2
Systemic Therapy Regimens in Stage 3 NSCLC.

	Chemotherapy Regimen	Reference
Adjuvant*	Carboplatin Area Under Curve (AUC) 6 + paclitaxel 225 mg/m^2 on day 1, every 21 days for 4 cycles (comorbidities or not able to tolerate cisplatin)	(Strauss et al., 2008; Schiller et al., 2002)
	Cisplatin 75 mg/m^2 + Docetaxel 75 mg/m^2 on day 1 every 21 days for 4 cycles	(Schiller et al., 2002)
	Cisplatin 100 mg/m^2 + gemcitabine 1000 mg/m^2 on day 1 & 8, 15 28 day cycle for 4 cycles Usual practice is to omit day 15 and use every 21 days.	(Schiller et al., 2002)
	Carboplatin AUC 5 day 1 + gemcitabine 1000 mg/m^2 on days 1 & 8 every 21 days for 4 cycles (comorbidities or not able to tolerate cisplatin)	(Zatloukal et al., 2003)
	Cisplatin 50 mg/m^2 on days 1 & 8 + vinorelbine 25 mg/m^2 on days 1, 8, 15 and 22 every 28 days for 4 cycles	(Winton et al., 2005)
	Cisplatin 75 mg/m^2 + Pemetrexed 500 mg/m^2 on day 1 every 21 days for 4 cycles for non-squamous	(Yamamoto et al., 2018)
Concurrent with Radiation	Carboplatin AUC 2 + Paclitaxel 45 mg/m^2 Weekly with radiation	(Belani et al., 2005)
	Cisplatin 50 mg/m^2 (days 1, 8, 29, 36) + etoposide 50 mg/m^2 (day 1–5 and 29–33)	(Albain et al., 2002)
	Cisplatin 75 mg/m^2 + Pemetrexed 500 mg/m^2 on day 1 21 day cycle for 3 cycles for non-squamous	(Senan et al., 2016)
Maintenance post chemo-radiotherapy	Durvalumab 10 mg/kg IV every 2 weeks for up to 12 months	(Antonia et al., 2018)

Table 3
Radiation regimens used to treat stage III NSCLC.

Indication	Dose Schedule	References
Primary definitive treatment. (Concurrent with chemotherapy)	60–66 Gy in 30–33 daily fractions.	(Curran Jr et al., 2011; Bradley et al., 2020)
Preoperative Setting Tri-modality treatment approach. (Concurrent with chemotherapy)	45 Gy in 25 daily fractions. 60 Gy in 30 daily fractions.	(Albain et al., 2009)
Adjuvant PORT setting. • (R0).	50–54 Gy (in 1.8–2.0 Gy/day).	
• (R1). • Microscopic Extracapsular extension nodal disease	54–60 Gy (in 1.8–2.0 Gy/day).	(Rodrigues et al., 2015)
• (R2). • Macroscopic nodal disease	60 Gy (in 1.8–2.0 Gy/day).	

Gy: Gray. PORT: post-resection radiation therapy, R0: completely resected, R1: microscopic residual (ie, positive margin), R2: Gross residual disease.

improvement in overall survival at 5 years in two meta-analyses (LACE and Cochrane). In addition radiotherapy can be considered for patients with positive surgical margins and those found to have incidental N2 disease at surgery (EL- 3) (Kris et al., 2017; Yasufuku et al., 2005). When both adjuvant chemotherapy and radiotherapy are planned, both modalities can be given sequentially or concurrently as currently there is no evidence to support the use of adjuvant concurrent chemotherapy as a standard guideline.

6 For T4 disease T4N0 (2 nodules in ipsilateral separate lobes), offer resection followed by adjuvant chemotherapy (EL-2). SBRT with curative intent is an option that can be considered. (EL-3)
7 For T4 with (mediastinal or main airway involvement), offer surgery if potentially curative (EL-2); if not possible, offer definitive concurrent chemo- radiotherapy (EL-1) (2.5.1.)
8 For non N_2 stage IIIA, not specified above, offer surgical resection with adjuvant chemotherapy. (EL-1) (Table 1)
9 Follow up and surveillance per section 2.8 (follow up of non-small cell lung cancer). (EL-1)

3.2.2. *Clinical stage IIIB-C and unresectable IIIA*

1 Offer concurrent chemo-radiotherapy (EL-1) (Wiener et al., 2011; Belani et al., 2005; Albain et al., 2002). followed by Durvalumab for 1 year. Surgical resection for selected cases could be offered after discussion by tumor board. (EL-3) (Table 3)
2 Offer Durvalumab as maintenance for 12 months post chemo-radiotherapy for unresectable stage III. (EL1) (Antonia et al., 2018).
3 Follow up and surveillance per section 2.8 (follow up of non-small cell lung cancer).

3.2.3. *Maintenance immune therapy (Durvalumab)*

1 Indication of Maintenance Durvalumab is: Stage III unresectable NSCLC (Adenocarcinoma or squamous cell carcinoma) post receiving concurrent chemotherapy and radiotherapy.
2 Contraindications: Autoimmune disease (Active or previous within the past 2 years), symptomatic interstitial lung disease (ILD), systemic immunosuppression, prior treatment with immunotherapy, history of primary immunodeficiency, ongoing infection, grade 2 or higher pneumonitis from previous chemotherapy, ongoing steroids therapy (Any Prednisone of ≥10 mg daily or its equivalent)
3 Requirements prior to initiation of durvalumab maintenance:
4 ECOG of 0–1
5 At least 2 cycles of platinum-based chemotherapy (containing etoposide, pemetrexed, taxans [docetaxel, paclitaxel], vinblastine or vinorelbine) is given concurrently with definitive radiation therapy.
6 No progression of the underlying disease after concurrent chemoradiotherapy.
7 Timing of initiation of durvalumab maintenance:
8 Within 1–42 days after last dose of radiation
9 Level of PD-L1: No cutoff level of PD-L1 is needed before the initiation of maintenance durvalumab
10 Duration of durvalumab maintenance therapy: 12 months
11 Durvalumab dose, route of administration & frequency: durvalumab 10 mg / kg IV Q 2 week
12 Monitoring of durvalumab maintenance therapy:
13 CT-scan images every 3 months to assess the response / progression of the underlying disease
14 Complete blood counts, renal functions, hepatic function / enzymes, TSH levels, urinary protein levels
15 Clinical toxicity assessment followed by appropriate investigation based on symptoms with each visit
16 Re-initiation of durvalumab after 12 months:
17 Durvalumab can be reinitiated after the 12th month, provided that the cancer was well controlled during the period of maintenance of durvalumab and progression only occurred during follow up after the 12th month mark.

3.3. Follow up of non- small cell lung cancer

Evaluation includes: History and physical examination, laboratory and chest

x-ray.

1 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.

4. Discussion

There has been significant progress in the management of stage III NSCLC over the past couple of years after couple of decades with limited progress. The previous standard treatment approach was to give concurrent chemotherapy with radiotherapy with or without consolidation with 2−3 cycles of chemotherapy. The role of surgery was limited to selected cases with good response to treatment in operable patient. Adjuvant chemotherapy role was mainly for post-operative cases who had incidental N2 positive lymph nodes with clear disadvantage in patients who requires pneumonectomy (Belani et al., 2005; Albain et al., 2009).

However, there were two major advances in the last couple of years and both are related to systemic therapy, namely maintenance immunotherapy post concurrent chemo-radiotherapy and the use of tyrosine kinase inhibitor, Osimertinib, for EGFRmut resected NSCLC.

In the PACIFIC trial, 713 patients who have disease control after concurrent chemo-radiotherapy were randomized 2 to 1 to durvalumab 10 mg/kg every 2 weeks for one year vs. placebo (Antonia et al., 2017).

The 36-month overall survival rate was 57 % in the durvalumab group vs. 43.5 % in the placebo group. Durvalumab significantly prolonged overall survival with hazard ratio for death, 0.69 (95 % CI, 0.55 to 0.86; P = 0.0025). The median OS was 29.1 months in the placebo group and had still not been reached in the durvalumab group. Median PFS was 16.8 months vs. 5.6 months in the durvalumab group vs. the placebo group, respectively (HR 0.521; 95 % CI, 0.42 to 0.65: P < 0.001). Grade 3 or 4 adverse events were noted in 29.9 % of patients in the durvalumab arm as compared to 26.1 % in the placebo arm. Treatment discontinuation was seen in 15.4 % of patients in the durvalumab arm as compared to 9.8 % in the placebo.

Furthermore, although the protocol allowed initiation of durvulumab up to 42 days post chemo-radiotherapy, subgroup analysis revealed that the benefit was more pronounced for patients starting treatment < 14 days (HR 0.43; 95 % CI 0.28−.026) as compared to ≥ 14–42 days (HR 0.79; 95 % CI 0.61–1.02). Therefore, timely assessment of disease response post chemo-radiotherapy is essential to rule out disease progression or decide if the patient is surgical candidate and proceed accordingly in a timely fashion. In order to avoid delay of staring Durvalumab as early as possible and avoid under treatment of certain subtypes of stage III NSCLC, it is very important to determine upfront about the surgical cases vs non-surgical cases, so the non-surgical cases (N3, extensive N2 mediastinal infiltration, non-operable) can receive definitive concurrent chemo-radiotherapy and timely consolidation immunotherapy. Undetermined cases in terms of surgical resections should be discussed in MD Tumor board in a timely fashion (Eberhardt et al., 2015).

The role of PDL-1 status has been controversial in the management of stage III NSCLC with durvalumab[53]. Based on the original PACIFIC trial, they enrolled patients regardless of PD-L1 status which is the practice that is taking place in the United States and Canada (Antonia et al., 2017).

However, in Europe a PD-L1 status of ≥ 1% (positive status) is mandatory for the initiation of durvalumab therapy which was based on a post hoc analysis study (Winton et al., 2005). This post hoc analysis led the European Medicines Agency (EMA) to mandate having a positive PD-L1 status of ≥ 1% to be given durvalumab therapy in stage III NSCLC after CCRT (Paz-Ares et al., 2020).

It is worth mentioning that, the post hoc analysis addressed a question which was not asked in the primary study especially that the PACIFIC study enrolled patients to durvalumab regardless of PD-L1 status. However, the post hoc analysis which was done to assess the magnitude of benefit of durvalumab in stage III NSCLC based on PD-L1 status which showed that all patients whom had received durvalumab had benefited from it except the ones who had negative PD-L1 status, i.e. < 1%, hence, the recommendation was made by the European Society of Medical Oncology (ESMO) to initiate durvalumab therapy in PD-L1 ≥ 1% only (Antonia et al., 2017; Paz-Ares et al., 2020).

However, we must indicate that the number of patients whom were PD-L1 negative were 148 while the total number of patients was 713 patients, which constitutes around 33 % of the overall patients treated with durvalumab. It is worth mentioning that the difference between the durvalumab group and placebo group in the PD-L1 negative population showed a HR of 1.14 in favor of placebo over durvalumab. But with a closer look at the baseline characteristic differences between durvalumab and placebo treated in that particular sub-group of PD-L1 < 1%, the placebo group had more patients whom were younger (aged <65 years), females, white, non-squamous histology and stage IIIA disease as oppose to the durvalumab group counterpart whom were more likely to be older (aged ≥ 65 years) Asians, males, squamous histology and stage IIIB disease (Antonia et al., 2017; Paz-Ares et al., 2020).

As stated above, there is significance difference in the management of stage III NSCLC when adding durvalumab as an adjuvant therapy between North America and ESMO which is mainly based on the post hoc analysis (Antonia et al., 2017; Paz-Ares et al., 2020).

In ADAURA study, 682 patients with resected IB, II, III NSCLC were randomized to osimertinib (339 patients) or placebo (342 patients). Osimertinib was prescribed as 80 mg PO daily for 3 years. In stage II–IIIA patients, disease free survival (DFS) hazard ratio (HR) was 0.17 (95 % CI 0.12, 0.23); p < 0.0001, 2-year DFS rate was 90 % with osimertinib vs. 44 % with placebo. In the overall population, DFS HR was 0.21 (0.16, 0.28); p < 0.0001, 2-year DFS rate was 89 % with osimertinib vs. 53 % with placebo. The safety profile was consistent with the known safety profile of osimertinib (Herbst et al., 2020).

This study highlights the importance of performing molecular testing on all resected non-small cell lung cancer to identify candidates for this new standard treatment.

In summary, management of stage III NSCLC remains heavily dependent on multidisciplinary team approach as each treatment modality has roles and indications requiring coordination and timely intervention. Although the two most recent practice changes are in systemic therapy, however multidisciplinary team decision making is required to identify ideal candidates for each treatment modality. If surgery is indicated then the patient would be eligible for adjuvant therapy and if not a surgical candidate, then maintenance immunotherapy would be indicated.

Declaration of Competing Interest

The authors report no declarations of interest.

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