Evolving Therapeutic Scenario of Stage III Non-Small-Cell Lung Cancer

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ABSTRACT: Lung cancer remains the leading cause of cancer-related death with an incidence that continues to increase in both sexes and all ages. However, 80% to 90% of lung cancers are non-small cell lung cancer (NSCLC) and the remaining 10% to 20% are small cell lung cancer. Adenocarcinoma is the most common histologic subtype of lung cancer worldwide. More frequently, lung cancer diagnosis is made in advanced stages. Stage III NSCLC refers to locoregionally advanced disease without metastases and represents about 30% NSCLC cases. Despite the absence of metastases at diagnosis, the outcome is generally poor. Stage III comprises a heterogeneous group and optimal management requires the input of a multidisciplinary team. All modalities of oncologic treatment are involved: surgery, chemotherapy, radiotherapy, and more recently, immunotherapy and targeted therapy. We will discuss the different therapeutic options in stage III NSCLC, both in operable and inoperable scenarios, and the role of immunotherapy and targeted therapy.

KEYWORDS: non-small cell lung cancer, heterogeneity, multidisciplinary team

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Introduction

Lung cancer is the most diagnosed cancer and the main cause of cancer-related death, with an increased incidence in both sexes and all ages.[1] It is divided into non-small cell lung cancer (NSCLC), which represents about 80% to 90%, and small cell lung cancer, accounting for the remaining 10% to 20%. NSCLC is subdivided into adenocarcinoma, which is the most common histologic subgroup of lung cancer, squamous cell carcinoma, and neuroendocrine large-cell carcinoma.

The eighth edition of the American Joint Commission on Cancer (AJCC) is the reference for the TNM staging of lung cancer and is effective since January 1, 2018.[2] Proper disease staging at diagnosis provides a nomenclature to describe the spread of the tumor and is essential both for prognosis and guiding therapeutic options. Stage III NSCLC refers to locally advanced disease without distant metastasis. There is no difference in the N staging between the seventh and eighth TNM editions; but in the latest edition, a new category, stage IIIC, was defined for patients with T3/T4 and N3 disease. Furthermore, a N2 mediastinal involvement is now staged IIIA if T1/T2 and IIIB if T3/T4. Stage IIIC is defined by large tumor (T3/T4) and N3. Median overall survival (OS) of patients with stage III ranges from 9 to 34 months depending on the study evaluated.[3] While stages I to IIIA are most often treated with upfront potentially curative surgery, most patients are diagnosed at an advanced (IIIB-IIIC) or metastatic (IV) stage.

NSCLC management is well defined for stages I, II, and IV. Stages I and II, which do not involve mediastinal lymph nodes, use upfront surgery as the treatment cornerstone.[4] For stage IV, a systemic treatment based on chemotherapy, immunotherapy, or targeted therapy is the treatment of choice.

Stage III NSCLC comprises a heterogenous group of oncologic diseases. However, 2 factors come into play: proper assessment of the mediastinal lymph nodes and a discussion in a multidisciplinary team.

Assessment of Mediastinal Lymph Nodes

In the absence of distant metastases, mediastinal node involvement is the most important prognostic factor in NSCLC. Thus, the management of stage III NSCLC requires a precise assessment of the mediastinal lymph nodes. It is also important to keep in mind that in about one-third of patients, metastatic tumor cells spread directly to the mediastinal N2 station and bypass the N2 hilar lymph nodes.[5]

Radiologic evaluation by computed tomography (CT) combined with positron emission tomography (PET) is the first step of the assessment. Staging of NSCLC was one of the first approved indications for the use of PET. Then, the combination of PET and CT in the preoperative staging proved its superiority compared with CT alone or PET alone.[6] A trial published in 2009 randomized patients between conventional staging plus PET-CT and conventional staging alone.[7] Conventional staging consisted of medical history, physical examination, blood test, contrast-enhanced CT-scan of the chest and upper abdomen, bronchoscopy, and invasive procedures, such as mediastinoscopy. Patients who were considered to have operable disease underwent thoracotomy. Finally, the use of PET-CT reduced the total number of thoracotomy and the number of ineffective thoracotomies, without difference in overall mortality.[8]

A study showed that clinical staging misclassified the nodal staging in 38% of cases when compared with the final pathological staging from surgical resection.[9] Accurate staging, in particular if a surgery is feasible, requires a sampling of the mediastinal lymph nodes. There are different procedures which can be more or less invasive. An endobronchial ultrasound or an electromagnetic navigational bronchoscopy is the method of choice to biopsy mediastinal lymph nodes because they are minimally invasive and can be performed under mild sedation. Sometimes, more invasive procedures are required, such as mediastinoscopy, thoracoscopy, or anterior mediastinotomy.

After staging, a discussion in a multidisciplinary team is essential to decide management. In fit patients, if there is no mediastinal lymph node involvement, upfront surgery is generally favored. If mediastinal lymph nodes are pathologically involved, tumors may be considered secondarily resectable or unresectable.

Resectable NSCLC Stage III

NSCLC upfront resectable

There is no consensus on the definition of "potentially resectable NSCLC." Upfront surgery is considered in the absence of tumor involvement of the mediastinal lymph nodes, ie, stage III N0 or N1 NSCLC. We can extend this indication to single-station N2 without bulk (<3 cm) and T<T4. In stage I NSCLC (ie, N0), minimally invasive video-assisted thoracoscopic surgery (VATS) is associated with shorter lengths of stay than open thoracotomies.[10] There is no published trial evaluating the impact of a VATS approach to lobectomy for ⩾N1 NSCLC on short-term outcomes and survival. We have retrospective data from the National Cancer Data Base that suggests that VATS lobectomy in N1 NSCLC is associated with good outcomes and similar nodal upstaging rates when compared with open lobectomy. The standard of care of operable NSCLC remains surgery, by lobectomy or even a pneumectomy with systematic lymph node dissection.[11,12] Recently, a phase III trial conducted in Japan showed that segmentectomy is non-inferior to lobectomy regarding OS in small-peripheral NSCLC (⩽2 cm).[13] Operability depends on both surgical considerations and patient fitness, including performance status and pulmonary function (FEV1 and DLCO). In case of decreased FEV1 or DLCO, an ergospirometry (VO2max) is required.

NSCLC possibly resectable: the heterogeneous group of stage IIIA (N2)

Stages IIIA (N2) include unsuspected single N2 disease detected during surgery to multiple bulky N2 disease diagnosed on preoperative staging. Survival rates at 5 years of diagnosis of stage IIIA NSCLC are about 36%.[3] Prognosis depends on the number of stations involved and the presence or not of skip metastasis.[14]

In the case of multiple N2 disease or single bulky N2, after a multidisciplinary discussion, an induction treatment is generally proposed. This is particularly the case with high tumor volume or invasiveness of the tumor. No randomized controlled trial has specifically studied patients with single-station N2 disease vs multistation N2 disease. In cases of cN2 potentially resectable NSCLC in fit patients, trimodality treatment, as recommended by healthy authorities, with chemotherapy, radiotherapy (RT), and surgery or bimodality treatment with chemotherapy and either surgery or RT are the 2 options. In other words, in these settings, a systemic induction chemotherapy is indicated with the aim to control distant disease with better compliance than chemotherapy given after surgery and to downstage the tumor or lymph nodes.

The role of surgery in stage III NSCLC is evaluated in 4 randomized trials. Induction chemotherapy followed by a surgery with or without RT vs definitive chemoradiotherapy (CRT) was assessed in 2 phase III trials—the NTOG[15] and the EORTC-08941.[16] The first trial randomized patients with stage IIIA to N2 NSCLC between 3 cycles of induction chemotherapy with carboplatin AUC 6-paclitaxel 225 mg/m^2 followed by surgery and PORT vs induction chemotherapy followed by sequential CRT (sCRT). There was no statistically significant difference in 5-year OS and progression-free survival (PFS). The second trial, the EORTC-0894, had the same design and globally the same outcomes: surgical resection did not improve OS and PFS compared with CRT. It is important to precise that only 50% of patients who were assigned to surgical resection arm had a complete resection. Thus, conclusion about the role of surgery is not clear: do we have to improve neoadjuvant treatment to increase operability and complete resection? Concomitant CRT (cCRT) with or without surgery is evaluated in 2 phase III trials: INT0139[17] and ESPATUE.[18] The American INT0139-assessed induction CRT was followed by surgery vs further RT. In the surgical arm, there was a statistically significant gain in PFS (12.8 vs 10.5 months, hazard ratio [HR] 0.77), but not in the OS. There was a high mortality rate after pneumectomy (25%). In an ad hoc exploratory analysis which excluded patients who underwent pneumectomy, there was an improvement in the OS for patients who underwent lobectomy compared with a matched cohort of patients treated which CRT. A more recent trial, ESPATUE, compared surgery with definitive CRT in resectable stage IIIA(N2) and selected stage IIIB NSCLC. After induction chemotherapy with cisplatin and docetaxel followed by cCRT with cisplatin and vinorelbine, patients were randomized between a CRT boost and surgery. No statistical difference in OS or PFS was seen. To conclude, surgery may offer a better locoregional control but has not shown an OS advantage.

Earlier trials evaluated the role of chemotherapy alone vs cCRT before surgical resection in patients with locally advanced NSCLC (IIIA[N2]–IIIB): SAKK 00/16,[19] GLCCG trial,[20] WJTOCG9903 trial,[21] and IFCT-0101 trial.[22] In all

these trials, there was no improvement in OS with CRT vs chemotherapy alone. However, CRT demonstrated a higher tumor downstaging.

Unresectable NSCLC Stage III

When NSCLC is unresecable, which is the case for clinically N3 disease and most of patients with clinical N2 disease, the mainstay of management consists of definitive CRT.

The modality of choice of definitive CRT is the concurrent regimen, with a platinum-based doublet. A meta-analysis from the NSCLC Collaborative Group of 6 trials (1205 patients) evaluated cCRT vs sCRT in patients with stage III NSCLC.[23] cCRT compared, yielded, and improved the survival of patients with locally advanced NSCLC, primarily because of a better locoregional control, with an absolute benefit of 5.7% at 3 years and 4.5% at 5 years. A randomized controlled trial by the Radiation Therapy Oncology Group (RTOG 9410) demonstrated that cCRT was superior to sCRT with an increase in median OS from 14.6 to 17 months.[24] There was also a significant increase in the 5-year survival rate from 10% for sequential treatment to 16% for concomitant treatment.

However, 2 regimens of chemotherapy are usually offered: cisplatin plus etoposide[25] and weekly carboplatin–paclitaxel.[26] These 2 regimens were compared in a phase III randomized trial.[27] In this study, which randomized 191 patients between the 2 regimens, those who received cisplatin plus etoposide had an improved 3-year survival rate (41% vs 26%). There was only a trend toward improved OS (23.6 vs 20.7 months; HR 0.76; 95% CI 0.55-1.05). Toxicity is an important point to consider: in this trial, grade ⩾ 2 radiation pneumonitis was higher in the cisplatin plus etoposide arm (33.3% vs 18.9%, $P = .036$), and grade ⩾ 3 esophagitis (20% vs 6.3%, $P = .009$). Another regimen is possible in patients with adenocarcinoma: cisplatin plus pemetrexed.[28] A phase III trial randomized patients with stage III non-squamous cell histology between cisplatin–pemetrexed and cisplatin–etoposide. There was a similar survival in the 2 groups. Cisplatin–pemetrexed had a significantly lower incidence of any drug-related grade 3 to 4 adverse events, including neutropenia. A possible step forward in the setting of unresectable NSCLC is the place and the timing of immunotherapy. A non-randomized phase II trial, KEYNOTE-799, suggested a promising antitumor activity of pembrolizumab plus concurrent CRT in patients with locally advanced and unresectable stage IIIA to IIIC NSCLC, regardless of histology and PD-L1 TPS.[29] Further input is expected from ongoing phase III trial. However, the chinese phase III trial, GEMSTONE-301, showed a significant improvement in PFS with sugemalimab (anti-PD-L1) vs placebo after definitive concurrent or sCRT, in locally advanced unresectable stage III NSCLC.[30] We listed ongoing trial of chemoradioimmunotherapy in inoperable stage III NSCLC in Table 1.

Adjuvant Treatment for NSCLC Stage III Resected

After surgery

RT. Adjuvant RT is well established in cases of positive surgical margins. In a retrospective trial published in 2015, PORT was associated with improved OS in patients with incompletely resected stage II or III NSCLC (HR 0.8; 95% CI 0.7-0.92).

In case of N2 disease found during surgical resection (pN2 R0), data from the Navelbine International Trialist Association (ANITA) randomized trial suggested that there was an OS advantage in these patients.[31] However, the decision to perform postoperative radiotherapy (PORT) was not randomized and modalities were heterogeneous in different centers. However, 2 recent randomized trials showed the contrary. In the Lung Adjuvant Radiotherapy Trial (ART) trial, 501 patients with completely resected NSCLC with pathologically proven N2 disease were randomized between PORT and no PORT.[32] There was no statistically significant difference in disease-free survival (DFS) or OS at 3 years. The PORT-C trial randomized 394 patients after surgery and adjuvant chemotherapy in PORT arm or observation arm.[33] No improvement in DFS was found. RT to the mediastinum after surgery of N2 R0 disease is not a standard of care.

Chemotherapy

After surgery, there is a clear indication for adjuvant chemotherapy for pathological stages ⩾ II (ie, N+) with T > 4 cm. Even if there are no data for patients with multiple tumors in the same lobe (T3N0) or in the same lung (T4N0), the indication for adjuvant chemotherapy is extended to these patients. Cisplatin-based doublets are standard of care. Vinorelbine is the most common partner, though etoposide, gemcitabine, docetaxel, and pemetrexed can be considered.[34] The optimal total dose of cisplatin is >300 mg/m^2.[35] Patients can expect an absolute benefit in survival at 5 years about 5.4%

Based on the Surveillance, Epidemiology, and End Results (SEER) database, a trial assessed the use of chemotherapy in 35 009 cases of resected stage II to III NSCLC between 2004 and 2005.[36] Chemotherapy was used in 66.9%, 48.2%, and 25% of patients aged 20 to 69, 70 to 79, and >80 years, respectively. In the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis, efficacy of adjuvant chemotherapy was not significantly different in older patients (⩾70 years) compared with younger patients, even if lower doses and fewer cycles were given.[37] When cisplatin cannot be administrated because of hearing loss, long-term kidney disease, or significant neuropathy, carboplatin may be considered.[38]

Optimal timing to begin chemotherapy in resected NSCLC is not as well-known as in breast or colorectal cancers. In studies of adjuvant therapy in NSCLC, chemotherapy generally started within 8 weeks of surgery. In a recent retrospective trial

Table 1. Chemoradioimmunotherapy in inoperable stage III NSCLC.

STUDY	STATUS	TRIAL NCT	STUDY PHASE	RT DETAILS (GY)	DESIGN
PACIFIC	Done	NCT02125461	IIIR	54-66	cCRT→durvalumab vs placebo
PACIFIC 2	Done	NCT03519971	IIIR	60	cCRT + durvalumab→durvalumab vs cCRT + placebo→placebo
PACIFIC 5	Ongoing	NCT03706690	IIIR	54-66	cCRT→durvalumab fixed dose vs placebo
PACIFIC 6	Ongoing	NCT03693300	II	54-66	sCRT→durvalumab
COAST	Ongoing	NCT03822351	IIR	54-66	cCRT→durvalumab vs cCRT→durvalumab + oleclumab vs cCRT→durvalumab + monalizumab
DETERRED PART I	Done	NCT02525757	II	60-66	cCRT→CH + atezolizumab→atezolizumab
DETERRED PART II	Done	NCT02525757	II	60-66	cCRT + atezoilizumab→CH + atezolizumab→atezolizumab
NICOLAS	Done	NCT02434081	II	66	3xCT→RT + nivolumab→nivolumab (sCRT arm of v2.0) OR 1xCT→cCRT + nivolumab→nivolumab
HCNR LUN 14-179	Done	NCT023434081	II	59-66.6	cCRT→pembrolizumab
RUTGERS	Done	NCT02621398	I	60	cCRT→pembrolizumab (cohort1:4 pts) and cCRT + pembrolizumab→ pembrolizumab (cohort 2-6:19 pts)
CLOVER NSCLC	Ongoing	NCT03509012	I	X	cCRT→durvalumab
KEYNOTE-799	Ongoing	NCT03631784	II	60	1xCT + pembrolizumab→cCRT + pembrolizumab→pembrolizumab
H. Lee Moffitt Cancer Center	Ongoing	NCT03663166	I/II	60	cCRT + 2x ipilimumab→nivolumab
Alliance Foundation	Done	NCT03102242	II	60	2x OR 4x atezolizumab→cCRT→2x CT→atezolizumab
EMD Serono	Ongoing	NCT03840902	IIR	60	cCRT + M7824→M7824 vs cCRT + placebo→durvalumab
CheckMate 73L	Ongoing	NCT04026412	IIIR	x	cCRT + nivolumab→nivolumab + ipilimumab or cCRT + nivolumab→nivolumab vs cCRT→durvalumab
CONSIST	Ongoing	NCT03884192	IIIR	x	cCRT→sintilimab (IB1318) vs cCRTalone
CStone Pharmaceuticals	Ongoing	NCT03728556	IIIR	x	sCRT/cCRT→CS1001 mAb vs placebo
Sun Yat-sen University	Ongoing	NCT04085250	IIR	x	CT + nivolumab→cCRT→nivolumab vs observation
NCI study	Ongoing	NCT04092283	IIR	x	cCRT + durvalumab→durvalumab vs cCRT→durvalumab
BTCRC LUNG 16-081	Ongoing	NCT03285321	IIR	x	cCRT→nivolumab vs nivolumab + ipilimumab

Abbreviations: cCRT, concomitant chemoradiotherapy; NSCLC, non-small cell lung cancer; NCT, National Clinical trial; CH, chemotherapy.

in 12 473 patients from the National Cancer Database, adjuvant chemotherapy remained efficacious when started 7 to 18 weeks after stage I to III NSCLC resection[39]

When there is an indication for adjuvant treatment by chemotherapy and RT, such as in R1 disease, a sequential administration is generally chosen. PORT is given after the completion of chemotherapy.[40]

EGFR mutation: targeted therapy after chemotherapy

Epidermal growth factor receptor (EGFR) mutations generally occur in exons 18 to 21 of the tyrosine kinase domain of the receptor and are found in 40% to 60% of South-East Asian patients and 10% to 20% of White patients with lung adenocarcinoma.[41] Most of the time, patients with EGFR mutation

are never smokers or light smokers. The use of EGFR tyrosine kinase inhibitors (TKIs) in the metastatic setting is the standard of care for NSCLC patients with exons 19 to 21 mutations of EGFR.[42]

The first phase III trials in the setting of adjuvant treatment involved first-generation EGFR TKIs, such as the RADIANT[43] or BR.19[44] study, which included patients with stage IB to IIIA NSCLC according to the AJCC sixth edition. In the RADIANT trial, 973 patients were randomized and most of them had a stage IB disease: 51% patients with stage IB, 33% patients with stage II, and 16% patients with stage III. In the BR.19 trial, 503 patients were randomized and the percentage of stages was quite similar: 52% with stage IB, 35% with stage II, and 13% with stage IIIA. The 2 trials failed to demonstrate a PFS and an OS benefit in stage IB to IIIA NSCLC.

ADAURA, a phase III randomized trial, evaluated the third-generation osimertinib as adjuvant therapy after surgical resection of stage IB to IIIA NSCLC, according to the seventh TNM classification.[45] Patients had classical actionable *EGFR* mutations, ie, an exon 19 or L858R exon 21 mutation. Adjuvant chemotherapy was not mandatory. Patients received daily osimertinib 80 mg for a maximum of 3 years. In the overall population of stages IB to IIIA, osimertinib improved DFS at 24 months by 80% vs placebo ($P < .0001$), with a 2-year DFS of 89% for osimertinib and 52% for placebo. Among patients with stage IIIA NSCLC, 2-year DFS was 88% in the osimertinib arm and 32% in the placebo arm (overall HR, 0.12; 95% CI 0.07-0.20). OS data, a key secondary endpoint, are still immature.

Osimertinib is approved by Food and Drugs Administration (FDA), European Medicines Agency (EMA), and Swissmedic as an adjuvant therapy, according to the indications previously cited.[46,47]

Another question that arises is whether chemotherapy could be omitted. According to the ADAURA results and prior studies demonstrating an OS benefit, the answer is clearly no. About 60% of patients received adjuvant platinum-based chemotherapy: 76% with stage II/IIIA and 26% with stage IB. It means that 33% of patients with a clear indication for adjuvant chemotherapy did not receive it. The median DFS is worse for these patients, so chemotherapy remains standard of care in the adjuvant setting.

The expanding role of EGFR inhibition for early-stage NSCLC investigates an ongoing trial. Recently, the EVIDENCE phase III trial suggested that adjuvant icotinib, a first-generation EGFR-TKI, might improve DFS compared with adjuvant chemotherapy in patients with completely resected, *EGFR*-mutant, stage II to IIIA NSCLC.[48]

Immunotherapy after chemotherapy

IMPOWER 010 is a phase III randomized trial that evaluated adjuvant atezolizumab vs best supportive care (observation and regular scans for disease recurrence) in stage IB to IIIA NSCLC (AJCC staging seventh edition), after adjuvant platinum-based chemotherapy.[49] A total of 1005 patients were randomized and most patients had stages I to II (59%). Among the 476 patients with PD-L1 $\geq$ 1%, 232 had stages IIIA (49%). Among patients with stages II to IIIA, there was a DFS benefit in the atezolizumab arm in the PD-L1 $\geq$ 1% cohort (HR 0.66; 95% CI 0.50-0.88; $P = .0039$) and in the intention-to-treat population (HR 0.79; 95% CI 0.64-0.96; $P = .02$). In the intention to treat (ITT) population, including stage IB to IIIA disease, the DFS was marginally improved (HR 0.81; 95% CI 0.67-0.99; $P = .040$). It should be noted, however, that the DFS benefit is driven by patients with high PD-L1 expression and the role in patients whose cancer expresses PD-L1 from 1% to 49% is less clear. OS survival is immature. This regimen was FDA approved on August 21.

Could it be a standard of care for all patients with resectable stages NSCLC who have an indication to adjuvant chemotherapy and PD-L1 $\geq$ 1%? We think no. IMMUNOTARGET registry is a retrospective study for patients receiving immunotherapy in advanced NSCLC harboring oncogenic driver alteration. In this study, the response rate of immune checkpoint inhibitors has been rather disappointing with the only exception of KRAS and BRAF mutations with an objective response rate of 26% and 24%, respectively.[50] Furthermore, a higher risk of toxicities has been reported with concomitant use of TKIs after checkpoint inhibitors in patient with NSCLC who harbor an oncogene mutation.[51] We listed on the Table 2 an ongoing phase III trial of adjuvant chemotherapy and immunotherapy in early-stage NSCLC.

Consolidation Treatment: Immunotherapy After CRT

PACIFIC, a randomized phase III trial has changed practice in locally advanced NSCLC. In this trial, patients received durvalumab vs placebo every 2 weeks during 1 year, as consolidation therapy after CRT in stage III (7Th TNM edition) unresectable, inoperable NSCLC. Most of the patients had stages IIIA and IIIB (respectively, 52.9% and 44.5%) disease. The PFS was significantly longer with durvalumab than with placebo (16.8 vs 5.6 months; HR 0.52; 95% CI 0.42-0.65; $P < .001$). An update data published this year demonstrated durable PFS and sustained OS benefit with durvalumab after CRT: an estimated 49.6% of patients randomized to durvalumab remain alive at 4 years (placebo, 36.3%), and 35.3% remain alive and progression-free (placebo, 19.5%).[52] Although FDA approved durvalumab in all subgroup, EMA labeled durvalumab only for PD-L1 $\geq$ 1 patients.[53]

PACIFIC-R trial is an international observational study and the first real-world study of patients who received adjuvant durvalumab as part of early access programs (EAPs), according to the indications of PACIFIC trial.[54] Median PFS with durvalumab is higher compared with that observed in the

Table 2. Ongoing phase III trials of adjuvant CT + anti-PD-(L)1 antibody therapy in early-stage NSCLC.

STUDY	STATUS	DISEASE STAGE	ADJUVANT INTERVENTION	ADJUVANT IO TREATMENT	PRIMARY ENDPOINT
IMpower010	Accrual completed	IB-IIIA TNM seventh	1-4 cycles platinum-based chemo mandatory	Sequential atezolizumab vs BSC	DFS
ANVIL	Accrual completed	IB-IIIA TNM seventh	Chemo and RT permitted	Sequential nivolumab vs BSC	DFS, OS
PEARLS	Accrual completed	IB-IIIA TNM seventh	Chemotherapy permitted	Sequential pembrolizumab vs BSC	DFS
BR31	Accrual completed	IB-IIIA TNM eighth	Chemotherapy permitted	Sequential durvalumab vs BSC	DFS
ALCHEMIST chemo-IO	Ongoing	IB-IIIA TNM seventh	1-4 cycles platinum-based chemo mandatory	Concurrent pembrolizumab followed by pembrolizumab vs sequential pembrolizumab vs BSC	DFS, OS

Abbreviations: CT, computed tomography; DFS, disease-free survival; NSCLC, non-small cell lung cancer; BSC, best supportive care.

durvalumab arm of PACIFIC trial. Nevertheless, this benefit could have been overestimated because of heterogeneous RECIST criteria for tumor assessment across countries, the effect of the COVID-19 pandemic (less frequent assessment of disease evaluation due to less fewer hospital visits), and that the assessment for disease progression disease is generally less frequent in the real world than in a clinical trial.[54]

PACIFIC study allowed patients with tumors harboring driver mutations. In addition, some of the most common driving mutations for NSCLC occur in EGFR. In this small subset of EGFR-mutant patients, there was a trend toward improved PFS with an HR of 0.76 (95% CI 0.35-1.64). Nevertheless, 2 points are clear: tumors harboring EGFR mutations seem to not respond to immunotherapy alone[55] and patients treated with osimertinib or other EGFR TKIs after receiving checkpoint inhibitors have increased the rates of severe immune-related adverse events, particularly pneumonitis.[56] Furthermore, the role of osimertinib in EGFR-mutant inoperable NSCLC after definitive chemoradiation is being assessed in the LAURA trial.[57]

We would recommend searching for oncogenic alterations in cases of locally advanced adenocarcinoma, to better tailor adjuvant and consolidation therapy.

Consolidation immunotherapy is now standard of care for unresectable stage III NSCLC with no progression after CRT. Nevertheless, about 50% of patients who receive this treatment gonna die within 4 years. Time is now to improve outcomes and to explore some mechanisms of resistance to RT. Two of them are CD73 and NKG2A ligand. CD73 is an ectoenzyme which catabolize extracellular adenosine monophosphate (AMP) to adenosine. Adenosine is also released from stressed or injured cells.[58] CD73 and adenosine promote neovascularization, metastasis, and immunosuppressive microenvironment. Targeting CD73 could permit to limit tumor progression and to improve antitumor immune responses. NKG2A receptor complex is expressed on the surface of natural killer (NK) cells, and its ligand is HLA-E. In contrast to classical HLA molecules which are frequently lost, HLA-E protein levels are generally increased in cancer when compared to their healthy counterparts and HLA-E expression on tumors mediates inhibition of NKG2A-expressing NK cells and $CD8^+$ T cells and leads to tumor escape.[59] COAST is a phase II study of durvalumab alone or combined with the anti-CD73 monoclonal antibody (mAb) oleclumab or anti-NKG2A mAb monalizumab as consolidation therapy.[60] First, results are encouraging with an improvement in ORR and PFS. However, 10-month PFS rates are 39.2% in the durvalumab alone arm, 64.8% in the durvalumab + oleclumab arm, and 72.7% in the durvalumab + monalizumab arm.

Neoadjuvant Treatment

Goal of surgery in early-stage NSCLC is to cure but outcomes are not so optimistic. Retrospective trial of clinical outcomes for patients with pN2 disease who underwent surgery and who received adjuvant chemotherapy found a 5-year OS rate between 39% and 58%, depending on the N2 status (single or multiple).[61] It seems that there is no difference in OS between adjuvant and neoadjuvant chemotherapy, on retrospective trial[62] or prospective trial.[63] There is also a challenge to improve outcomes, particularly OS which remains the gold-standard outcome measure in phase III trials, with better adjuvant and neoadjuvant strategy. In the adjuvant setting, immunotherapy with atezolizumab after adjuvant cisplatin-based chemotherapy could change our practice but data on OS will be available in a long time. Another challenge is to find a surrogate endpoint for OS. Trials designed with neoadjuvant chemotherapy permitted to explore the pathological response and how it can serve as a surrogate for OS. Complete resection, which is

Table 3. Ongoing phase III trials of neoadjuvant CT + anti-PD-(L)1 antibody therapy in early-stage NSCLC.

STUDY	STATUS	DISEASE STAGE	NEOADJUVANT INTERVENTION	ADJUVANT TREATMENT	PRIMARY ENDPOINT
CheckMate 816	Accrual completed	IB-III TNM seventh	±Nivolumab	No	pCR, EFS
KEYNOTE-671	Ongoing	II-IIIB TNM eighth	Pembrolizumab or placebo	12 months pembrolizumab or placebo	EFS, OS
IMpower030	Ongoing	II-IIIB TNM eighth	Atezolizumab or placebo	12 months atezolizumab or placebo	EFS
AEGEAN	Ongoing	IIA-IIIB TNM eighth	Durvalumab or placebo	12 months durvalumab or placebo	pCR, EFS
CheckMate 77T	Ongoing	II-IIIB TNM eighth	Nivolumab or placebo	12 months nivolumab or placebo	EFS

Abbreviations: CT, computed tomography; DFS, disease-free survival; EFS, event-free survival; NSCLC, non-small cell lung cancer; pCR, complete pathologic response.

defined by the absence of gross and microscopic residual disease, is associated with statistically significant better survival compared with uncertain or incomplete resection.[64] Complete pathologic response (pCR), ie, the absence of residual viable tumor on histopathological examination after neoadjuvant therapy is quite rare and occurred in about 4% of the cases. Using pCR as a primary endpoint for neoadjuvant chemotherapy trials was also not possible.

Retrospective trials by Junker et al[65] and more recently by Pataer et al[66] found that major pathological response (MPR), defined as 10% or lower residual tumor cells, seems to be correlated with improved long-term outcomes. Some prospective trials have demonstrated the association between MPR and improved survival outcomes in patients with resected NSCLC.[67,68] MPR is now used to characterize the activity of neoadjuvant chemotherapy in many lung cancer trials.[69] A more precise endpoint could be the combination of the MPR in lymph nodes (LN-MPR) and the MPR in tumor (TN-MPR) which was significantly associated with OS in a retrospective study.[70]

Radiologic assessment seems not to correlate with pathologic response.[71] Also, it is even more true with immunotherapy.[72] However, percent change in standardized uptake value (SUV) is a better predictor of outcome after neoadjuvant therapy than the radiographic change in size of the same lesions.[73,74]

Neoadjuvant immunotherapy results in immune-cell infiltration into the tumor and could explain the absence of response or even progression on CT-scan. PET-CT seems more usefull and a decrease in SUVmax of primary tumor could be predictive of pathologic response for neoadjuvant PD-1 therapy in NSCLC.[75] Pathological response to neoadjuvant immunotherapy differs from neoadjuvant chemotherapy and is characterized by a regression bed which corresponds to the area of immune-mediated tumor clearance. Histopathologic features of this regression bed, ie, tumor-infiltrating lymphocytes, massive tumor cell death, tissue repair with neovascularization, and proliferative fibrosis, have been used to develop an immune-related pathologic response criteria (irPRC).[76] Prospective trial is now necessary to validate irPRC and to explore its association with long-term outcomes.

With the validity of MPR as a surrogate endpoint, many trials are ongoing and may change the treatment paradigm in operable NSCLC. In the phase III trial, CheckMate 816, neoadjuvant chemotherapy was compared with neoadjuvant chemoimmunotherapy with 3 cycles of nivolumab in patients with operable stage IB to IIIA NSCLC. Both primary endpoints of increased pathological complete response (24% vs 2.2%) and event-free survival (EFS) were met.[77] NEOSTAR is a phase II trial which is challenging the place of neoadjuvant immunotherapy in operable stage IA to IIIA NSCLC.[78] In total, 44 patients received were randomized into 2 arms, nivolumab vs ipilimumab plus nivolumab, before surgery. The primary endpoint was the MPR. A general overview of ongoing phase III trial of neoadjuvant chemotherapy and immunotherapy is found in Table 3.

Preoperative immunotherapy could induce a stronger early expansion of tumor-specific CD8+ cells than in the adjuvant setting because of the greater initial tumor burden, which may trigger a broader T cell response due to the exposure to a larger repertoire of tumor antigens.[79] A phase II trial showed encouraging results with the use of neoadjuvant durvalumab combined with stereotactic body RT in patients with potentially resectable early-stage NSCLC (clinical stages I-IIIA as per the seventh edition of the AJCC).[80] Overall, 60 patients were enrolled and a half received durvalumab alone and the other half received durvalumab plus RT. MPR was observed in 53.3% of the patients in the dual-therapy group and 6.7% patients in the monotherapy group. Furthermore, 50% of the patients with MPR in the dual therapy group had a pCR. A phase III trial is ongoing to explore the place of immunotherapy with durvalumab plus RT before surgery in stage III(N2) NSCLC (SAKK 16/18).[81]

Considering the preliminary results of the CheckMate 816 trial and the results of the phase II trial with neoadjuvant

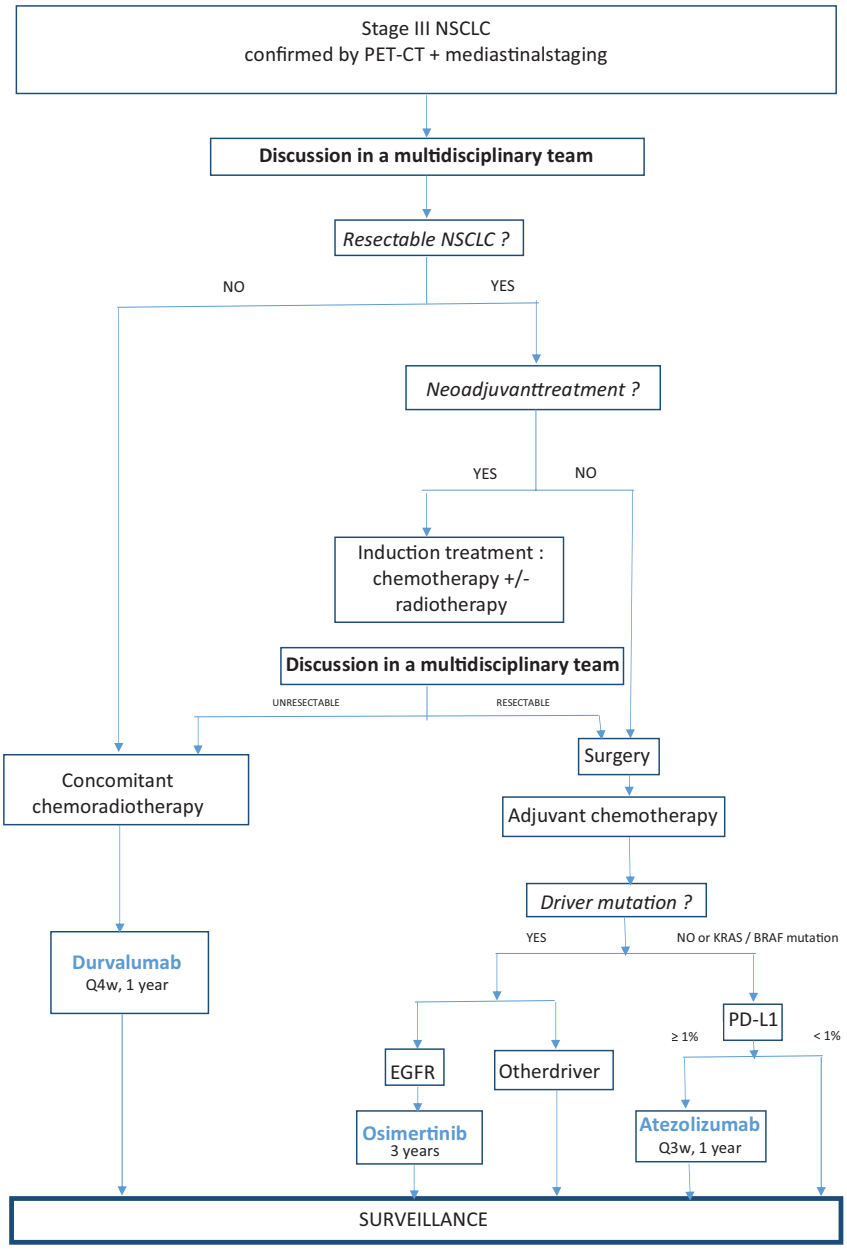

Figure 1. Algorithm for management of stage III NSCL.
CT indicates computed tomography; EGFR, Epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PET, positron emission tomography.

durvalumab combined with stereotactic body RT in patients with potentially resectable early-stage NSCLC, there will be potentially a place for RT in operable NSCLC.

Finally, the ongoing NeoADAURA trial is assessing osimertinib as a single agent or in combination with platinum-based chemotherapy, in the neoadjuvant setting of patients with resectable stage II to IIIB NSCLC harboring classical EGFR mutations.

Conclusions

Stage III NSCLC is a very heterogenous disease, and management is not as well established as in stages I, II, and IV. We classify stage III NSCLC in 3 categories—operable, possibly operable, and inoperable, Figure 1. The basis of therapy is surgery, chemotherapy, and RT. Despite advances in surgery and RT, the prognosis remains poor and the challenge is now to improve neoadjuvant and adjuvant treatment. For patients who undergo CRT, adjuvant immunotherapy is approved. With the development of targeted therapy in metastatic NSCLC, the question arises as to their role in locally advanced stages. Osimertinib is now a standard of care in adjuvant setting of resected stage IB to IIIA NSCLC with EGFR mutation. The phase III ALINA trial is ongoing, comparing alectinib to chemotherapy as adjuvant treatment for patients with stage IB to IIIA *ALK*+ NSCLC. Finally, the role of neoadjuvant chemoimmunotherapy is also evolving thanks to the recent results of CheckMate 816, showing an EFS. One key point in stage III NSCLC is clear: a multidisciplinary team

approach is essential to decide the best treatment strategy with the best sequence.

Author Contributions

NB made a substantial contribution to the concept and design of the work and approved the final version to be published. AF revised it critically for important intellectual content and approved the final version to be published. AA contributed to the concept and design of the work and approved the final version to be published.

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