New developments in locally advanced nonsmall cell lung cancer

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Shareable abstract (@ERSpublications)
Locally advanced NSCLC comprises TNM stage IIIA–C. Immune-checkpoint inhibition after chemoradiotherapy is standard and part of multimodal trials with surgery. Exact staging, genetics, immunology and functional testing are important. https://bit.ly/366lNQ2

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Abstract

Locally advanced nonsmall cell lung cancer, due to its varying prognosis, is grouped according to TNM stage IIIA, IIIB and IIIC. Developments over the last 3 years have been focused on the integration of immunotherapy into the combination treatment of a locally definitive therapy (surgery or radiotherapy) and chemotherapy. For concurrent chemoradiotherapy, consolidation therapy with durvalumab was established. Adjuvant targeted therapy has again gained increasing interest. In order to adapt treatment to the specific stage subgroup and its prognosis, fluorodeoxyglucose positron emission tomography/computed tomography and pathological evaluation of the mediastinum are important. Tumours should be investigated for immunological features and driver mutations. Regarding toxicity, evaluation of pulmonary and cardiac function, as well as symptoms and quality of life, is of increasing importance. To improve the management and prognosis of this heterogeneous entity, clinical trials and registries should take these factors into account.

Introduction

Locally advanced nonsmall cell lung cancer (NSCLC) comprises a variety of different entities, which are grouped according to the TNM system (version 8) in stage IIIA, IIIB and IIIC. This classification was chosen due to the varying prognosis in these substages (table 1) [1]. For years, a locally definitive therapy was combined with systemic platinum-based doublet chemotherapy. The locally definitive therapy depends on the functional situation, comorbidities, performance status, the amount of involvement of mediastinal lymph nodes and technical issues, as well as the patient's preference and will be discussed in the interdisciplinary tumour board, as outlined recently in the *European Respiratory Review* in accordance with international guidelines [2–4]. Some aspects of these discussions are summarised in table 2. There are still many questions in the optimal management regarding the various stages and histologies, the tumour biology and the condition of the individual patients [5–9]. Also, efforts to improve the functional situation pre-therapeutically may be relevant and need further evaluation [10]. Accordingly, there is also limited standardisation of the management of these patients in the clinical practice [11, 12]. Presently, following developments in stage IV, attempts have been made to integrate targeted therapy and immunotherapy into the management of this heterogenous group of NSCLC of usually poor prognosis. Consolidation immune-checkpoint inhibition after chemoradiotherapy is already a standard of care in many parts of the world [13]. But also new techniques for imaging, functional and biological assessment have to be taken into account. In this article we provide an overview of the developments in the field over the past 3 years.

TABLE 1 5-year survival rates in stage III depending on sub-stage and specific staging methods

TNM 8	Clinical stage %	Pathological stage %
IIIA	36	41
IIIB	26	24
IIIC	13	12

Data from [1].

Evaluation by imaging, function and metabolism in locally advanced NSCLC

Endobronchial ultrasound with transbronchial tissue probes is currently well established and standardised. Apart from mediastinal lymph node staging it can also be used for centrally located lung tumours [14]. These techniques have largely replaced more invasive techniques. Even in restaging after neoadjuvant treatment, endobronchial ultrasound has its place, where mediastinoscopy and even remediastinoscopy may be challenging [15].

For surgery, the preoperative evaluation of pulmonary and cardiac function is well established [16]. Following the discussions of the Radioation Therapy Oncology Group (RTOG) 0617 [6] and other radiation dose escalation trials, cardiac toxicity and pulmonary toxicity have also received more attention in the chemoradiotherapy setting. Right ventricular function seems to be correlated with prognosis after chemoradiotherapy [17, 18]. A pre-therapeutic reduced left ventricular ejection fraction may increase the risk of radiation pneumonitis [19]. Pulmonary and cardiac toxicities can be increased by chemo- and immunotherapy [20–24]. The frequencies in clinical scenarios may be higher than in the original licensing trials [25]. Pre-existing lung diseases and other clinical risk factors increase the probability of pulmonary toxicity [26, 27].

Toxicities may be reduced by taking into account these risk factors in chemoradiotherapy and by adapting the radiation prescription accordingly [28]. Image-guided adaptive replanning [29] and image-based lung functional radiotherapy planning [30] may be of help.

In imaging positron emission tomography (PET)-computed tomography (CT) and magnetic resonance imaging of the brain are usually regarded as standard modalities for staging in these tumour entities. In addition, metabolic tumour evaluation by PET-CT for chemoradiotherapy can be of help for radiation treatment planning and dose prescription and may be of prognostic and predictive relevance. The concept of reducing the target volume to avoid toxicity and the use of PET-CT has developed over recent years [31]. In a randomised trial, this approach demonstrated that imaging based target volume reduction is feasible, and may change the standard of care [32].

There are reports that associate the pre-therapeutic metabolic activity in chemoradiotherapy with response and prognosis [33]. This seems to primarily be the case for the adenocarcinoma type of NSCLC [34]. The relevance of metabolic response to induction chemotherapy before surgery [35] and (chemo)radiotherapy [36] or the response (chemo)radiotherapy [37–40] is further evaluated. In addition, radiomic and artificial intelligence approaches are being pursued in this setting [41].

TABLE 2 Considerations in the multidisciplinary decision about locally definitive treatment

Surgery	Radiotherapy	Combined
Adequate functional status	Multilevel or bulky N2	Local tumour control is very important
Bulky, necrotic tumours with possible complications	(Small) tumours with multiple mediastinal lymph node involvement	Locally invasive tumours with slim possible resection margins (*e.g.* superior sulcus tumours)
Multiple nodules in the same lobe	Reasonable dose affections of lung and heart	
No pneumonectomy necessary	PD-L1 inhibition possible	

PD-L1: programmed death ligand 1.

Targeted therapy in locally advanced NSCLC

The application of genetic testing in stage IV NSCLC led to a substantial progress in a subgroup of these patients. There was hope early on that this would also lead to an improvement in the locally advanced disease stage. Until now, genetic testing in locally advanced NSCLC has not been the standard of care.

In resected patients, the presence of driver mutations was evaluated regarding prognosis. In 242 Japanese resected patients (stage I–III) whole-exome sequencing of the resected tumours was retrospectively performed and demonstrated prognostic relevance for recurrence-free survival [42]. In 213 resected patients in stage I–III from the Princess Margaret Cancer Center in Toronto (Canada), next-generation sequencing retrospectively demonstrated that the presence of known somatic mutations is associated with worse disease-free survival [43]; however, larger prospective trials are needed.

In the setting of chemoradiotherapy the presence of epidermal growth factor receptor (EGFR) mutations may be associated with lower locoregional recurrence and higher distant progression, especially brain metastasis [44]. Progression-free survival seems to be short, with the brain being the most common site of distant metastasis.

In early trials, targeted therapy after curative resection or chemoradiotherapy did not improve overall survival [45, 46]. In a Chinese population with stage II and III EGFR-mutated NSCLC, adjuvant gefitinib in comparison to vinorelbine and cisplatin improved progression-free survival [47]. This was also the case in a phase II trial with 100 patients in stage I–III [48]. A recent update of the Chinese trial did not demonstrate an advantage in overall survival [49]. Whether the advantage with osimertinib in progression-free survival in a similar trial setting as the Chinese trial leads to a better overall survival remains to be shown [50]. The results were presented at the congress of the American Society of Clinical Oncology 2020 and were rather good regarding progression-free survival, but the follow-up for other measures and especially overall survival was too short and not mature.

There are few reports about using targeted therapy as induction therapy [51, 52] and in combination with induction chemotherapy and resection [53], which presently allows no clear conclusion.

For the combination of EGFR inhibition with radiotherapy in EGFR-mutated patients, several small trials have been performed previously and a few are ongoing [54, 55]. There are some issues with toxicity [45] and the results to date do not allow a recommendation outside of clinical trials.

Addition of immunotherapy in the setting of surgery

Despite promising signals for vaccination in the setting of locally advanced NSCLC in phase II trials, randomised phase III trials could not demonstrate a relevant benefit. With the progress in stage IV being made by using immune-checkpoint inhibitors, there is renewed hope for immunotherapy in the operative setting [56, 57].

Adjuvant chemotherapy after curative resection improves overall survival, but only modestly. Therefore, prognostic or predictive biomarkers for tailoring systemic therapy would be helpful. The effect of driver mutations has already been discussed. Regarding immune markers, several biomarkers are being pursued. There is ongoing work for immune cells in the tumour and tumour–stroma interactions [58–62]. For tumour mutation burden (TMB) an analysis was performed in the Lung Adjuvant Cisplatin Evaluation (LACE)-Bio-II study [63]. In 908 samples, a high nonsynonymous TMB was associated with a better prognosis in patients with resected NSCLC. In addition, the benefit of adjuvant chemotherapy on lung cancer-specific survival was more pronounced in patients with low nonsynonymous TMBs. In a clinical trial with induction therapy using nivolumab, TMB was correlated with pathological response to programmed death ligand 1 (PD-L1) blockade [64].

Regarding PD-L1 expression, a meta-analysis concluded that high PD-L1 expression by immunohistochemistry was significantly associated with poor overall survival for patients with lung cancer, especially for Asian patients with surgically resected, early stage I–III tumours and using 5% as the cut-off value [65]. This negative association may primarily be present in never-smokers [66]. For adjuvant chemotherapy, PD-L1 expression is probably not predictive [67].

The correlation of PD-L1 expression with TMB is mostly absent [68]. Positive CD8 and negative PD-L1 expression together may be favourable prognostic markers in resectable NSCLC [69]. A firm conclusion regarding biomarkers cannot be drawn at the moment.

For proof of concept, immune-checkpoint inhibitors were used in clinical trials in the neoadjuvant setting with and without chemotherapy and produced promising preliminary results. In a trial with two preoperative doses of nivolumab in 21 resected patients, nine out of 20 patients had a major pathological response [64]. There was no correlation with PD-L1 expression, but pathological response correlated with the TMB. A complete response was reported by neoadjuvant treatment with chemotherapy and pembrolizumab [70]. Patients with resectable NSCLC received two cycles of atezolizumab pre-operatively in a multicentre trial and 15 out of 82 evaluable patients without driver mutations achieved a major pathological response [71]. Four of them had a complete pathological response and another four patients had progressive disease. Atezolizumab was also tested pre-operatively in combination with carboplatin and nab–paclitaxel on 30 patients with stage IB–IIIA NSCLC, who had a smoking history and had an Eastern Cooperative Oncology Group performance status of 0 or 1 [72]. Overall, 57% had a major pathological response. Pathological response does not correlate well with morphological imaging results. Therefore, for evaluation of response, a pathological analysis seems to be necessary. The relevance of a metabolic response has not yet been evaluated adequately in this setting.

Immune-checkpoint inhibition with or without chemotherapy is now being tested in the adjuvant and neoadjuvant setting and in a combination of neoadjuvant and adjuvant systemic therapies in various phase I–III trials, which are summarised in table 3. Usually they are not limited to stage III and not subclassified

TABLE 3 Current clinical trials on immunotherapy in the setting of surgery in early and locally advanced nonsmall cell lung cancer (NSCLC)

ClinicalTrials.gov ID	Phase	NSCLC stage	IO-drug	Protocol	Primary end-point
Induction therapy					
NCT03694236	I/II	II/IIIA	Durvalumab	Chemoradiotherapy+durvalumab induction→surgery	pCR
NCT03237377	II	III	Durvalumab/ tremelimumab	Radiotherapy+durvalumab ± tremelimumab→surgery	pCR
NCT03197467	II	II/IIIA	Pembrolizumab	Pembrolizumab induction→surgery	Safety
NCT02994576	II	IB–IIIA	Atezolizumab	Atezolizumab induction→surgery	Safety
NCT03732664	I	IA–IIIA	Nivolumab	Nivolumab induction→surgery	Safety
NCT04205552	II	IB–IIIA	Nivolumab/ relatlimab	Nivolumab ± relatlimab induction→surgery	Feasibility
NCT02259621	II	IB–IIIA	Nivolumab/ ipilimumab	Nivolumab ± ipilimumab induction→surgery	Safety
NCT04348292	I	I–IIIA	Durvalumab/ sirolimus	Durvalumab+sirolimus induction→surgery	Safety
Combined induction and adjuvant therapy					
NCT03871153	II	Resectable III	Durvalumab	Chemoradiotherapy+durvalumab induction→surgery→durvalumab consolidation	pCR
NCT04062708	II	III	Durvalumab	Chemotherapy+durvalumab induction→surgery→radiotherapy→durvalumab consolidation	pCR
NCT03871153	II	Resectable III	Durvalumab	Chemotherapy+durvalumab induction→radiotherapy +durvalumab→surgery→ durvalumab consolidation	pCR
NCT04202809	II	IIIA–B	Durvalumab	Chemotherapy induction→chemoradiotherapy ± durvalumab→surgery if resectable	PFS
NCT02818920	II	IB–IIIA	Pembrolizumab	Pembrolizumab induction→surgery→pembrolizumab consolidation	Surgical feasibility rate
NCT03838159	II	IIIA	Nivolumab	Arm 1: chemotherapy+nivolumab induction→surgery→nivolumab consolidation Arm 2: chemotherapy induction→surgery	pCR
NCT02572843	II	IIIA	Durvalumab	Chemotherapy+durvalumab induction→surgery→durvalumab consolidation	DFS
NCT04025879[#]	III	II–IIIB	Nivolumab	Chemotherapy ± nivolumab→surgery→nivolumab consolidation or observation	DFS
Adjuvant therapy					
NCT02595944[#]	III	IB–IIIA	Nivolumab	Surgery→chemotherapy→nivolumab consolidation or observation	DFS, OS

Data obtained from www.clinicaltrials.gov on 7 August 2020. IO: immune-oncology; pCR: pathological complete response; PFS: progression-free survival; DFS: disease-free survival; OS: overall survival. [#]: phase III trials.

to the subtypes of stage III. The primary end-points also vary. These imprecise definitions will hinder the final interpretation of these trials.

Adjuvant radiotherapy

In stage III there is still discussion about adjuvant radiotherapy after surgery. In this context, it is of importance to understand which patients are at increased risk of relapse and the impact of local recurrence on the overall course of the disease. A further point of discussion is prophylactic cranial irradiation in locally advanced NSCLC. The technical progress in radiotherapy is rather relevant and is discussed in another article by Finazzi *et al.* (unpublished data).

Prophylactic cranial irradiation (PCI) is not routinely applied in curatively treated NSCLC, but there are still results of published clinical trials that add to the evidence base of this topic. The RTOG 0214 trial randomised PCI *versus* observation in 340 patients with stage III NSCLC [73]. PCI decreased the 5- and 10-year rate of brain metastasis and improved 5- and 10-year disease-free survival but did not improve overall survival. A multivariable analysis within the nonsurgical arm suggests that PCI also effectively prolongs overall survival. Younger patients (aged <60 years) and patients with nonsquamous disease developed more brain metastases. In the Dutch randomised phase III NVALT-11 trial, 175 patients with stage III disease were also randomised to either observation or PCI [74]. PCI significantly decreased the proportion of patients who developed symptomatic brain metastases with an increase of low-grade toxicity and without a statistically significant effect on overall survival.

Adjuvant post-operative radiotherapy (PORT), usually given in addition to adjuvant chemotherapy, is mostly given in N2 disease with increased risk of local recurrence. Recent data add to the current body of evidence. A recent study retrospectively analysed 183 Chinese patients with stage III–pN2 NSCLC regarding the status of applied post-operative radiotherapy [75]. A short local recurrence-free survival was correlated with multiple-station pN2, older age (>55 years), patients with a high positive lymph node ratio >1:3 and poor histological differentiation of the tumour. Post-operative radiotherapy reduced the risk of local recurrence and improved overall survival. In a retrospective analysis from New York (USA) of a prospectively maintained database for patients with cIII–N2 NSCLC who underwent induction chemotherapy followed by resection, 99 biopsy-proven cIII–N2 patients could be identified [76]. In this series, 95% of patients had an initial distant recurrence and on multivariable analysis PORT was not associated with locoregional recurrence or disease-free survival. An analysis of the SEER database investigated 5168 patients with stage IIIA, of whom 1711 received PORT [77]. PORT negatively influenced 3- and 5-year lung cancer-related mortality rates in N1 disease, but decreased the 3- and 5-year mortality rate by 4.67% and 10.08%, respectively, and improved overall survival in patients with N2 disease and at least six positive lymph nodes.

It seems clear that prognostic factors have to be taken into account, which influences prognosis and the relationship between local and systemic recurrence. There are some factors such as smoking, COPD or low forced expiratory volume in 1 s (FEV_1) that have already been known for some time. A recent trial analysed the quantitative emphysema severity of the whole lung using CT in 45 patients [78]. After adjusting for age, sex, smoking status and FEV_1 a more severe score was an independent predictor for recurrence and survival. For this trial, no details regarding local and systemic recurrence have been published. A Japanese study analysed the data of 1012 consecutive stage I–III NSCLC patients who underwent complete resection [79]. Local recurrence was identified in 9.4% of these patients. The most significant risk factor for local recurrence was lymph node metastasis (N1: HR=2.27, p=0.009; N2: HR=6.85, p<0.0001). For the subgroup of patients with lymph node metastasis (n=289), independent risk factors for local recurrence were N2 disease with N1 metastasis (N2 with N1: HR=3.46, p<0.0001) and no adjuvant platinum-based chemotherapy (HR=1.91, p=0.018).

Integration of immunotherapy in radiochemotherapy in locally advanced NSCLC

For years modifications of chemoradiotherapy using mostly cisplatin/etoposide or vinorelbine/cisplatin did not improve the outcome of locally advanced unresectable NSCLC [2, 80, 81]. This has now changed by integrating immunotherapy in definitive chemoradiotherapy [82, 83]. This has undoubtedly improved the prognosis of many patients with locally advanced NSCLC.

For chemoradiotherapy, consolidation with durvalumab improved progression-free and overall survival in stage III NSCLC [84]. In the PACIFIC trial, randomisation was performed after chemoradiotherapy, there were no specific staging requirements, detailed data before randomisation were missing and PETCT was not mandated.

In a retrospective subgroup analysis, patients with PD-L1 expression <1% did not have a benefit [85]. This led to some discussion and the European Medicines Agency did not approve durvalumab in this indication for tumours with a PD-L1 expression <1% [86]. However, in an analysis of long-term survival of 102 patients with inoperable locally advanced NSCLC and chemoradiotherapy without immunomodulation, overall survival was significantly shorter for patients with PD-L1 expression [87]. Of course, there is also some uncertainty about the possible heterogeneity of PD-L1 expression in small tumour samples [88] and further data are awaited.

In a Single Technology Appraisal for the UK National Institute for Health and Care Excellence (NICE) for patients with PD-L1-expressing tumours (⩾1%) more serious adverse events were reported for durvalumab (64 (30%) out of 213 *versus* 18 (20%) out of 90) [89]. The Evidence Review Group raised some concerns regarding the economic analysis and NICE recommended durvalumab as an option in the subgroup of patients with concurrent platinum-based chemoradiation therapy, with a commercially managed access agreement in place. An analysis in the context of the US healthcare system concluded cost-effectiveness with an estimated incremental cost-effectiveness ratio of US$67 421 per quality-adjusted life-year and an additional US$768 million of national cancer spending in year 1 [90].

In a retrospective analysis of Japanese patients, 30% of patients were ineligible to receive durvalumab by using the criteria of the PACIFIC study [91]. In the group of 81 patients who received definitive chemoradiotherapy, radiation pneumonitis of any grade occurred in 73.9%. Of these, 12 (16.4%) developed radiation pneumonitis of grade 2 or more within 42 days after chemoradiotherapy, which is still in line with historical series. Another analysis in 82 Japanese patients found an ineligibility rate of 23% [92]. Old age (p=0.042), male sex (p=0.031) and radiation therapy with V20 (volume of the lung receiving ⩾20 Gy) ⩾35% (p=0.032) were associated with ineligibility after chemo-radio therapy. Moreover, ineligible patients showed shorter progression-free survival (6.6 *versus* 15.7 months, HR 2.61 (95% CI 1.16–5.89), p=0.016) and shorter overall survival (18.6 *versus* 44.3 months, HR 3.03 (95% CI 1.29–7.10), p=0.007) than eligible patients.

There are now several active clinical trials from phase I–III that use different immune-checkpoint inhibitors or different schedules, such as a concurrent application for integrating immune-checkpoint inhibitors in chemoradiotherapy schedules [72, 93–95], which are summarised in table 4. As with the trials that include surgery, various stages and conditions are included, which will impede clear interpretation of the results.

Many factors in the immunochemoradiotherapy setting have to be analysed in order to optimise the application to select the right patients for safety and efficacy. Chemoradiotherapy can have side-effects that can interfere with the effects of immune-checkpoint inhibition. There can be direct cardiac toxicity, [17–19] but radiotherapy of immune-relevant body systems may also induce immunosuppression, which can negatively influence patient outcomes [96, 97]. Concurrent chemoradiotherapy may dynamically alter PD-L1 expression and numbers of $CD8^+$ tumour infiltrating lymphocytes [98, 99]. Pre-therapeutic blood-based parameters, or their change during chemoradiotherapy, may predict prognosis [100–102].

Chemotherapy and radiotherapy, as well as immune-checkpoint inhibition, can cause damage to the lung. Risk depends on pre-conditions of the patient and its reserve, the specific chemotherapy substances [103] and the mode of radiotherapy. With adequate techniques in radiotherapy these side-effects can be reduced [104]. But also, patient-related factors such as smoking history are of relevance [105]. Patient symptoms, performance status and quality of life before and during chemoradiotherapy influence the outcome in stage III NSCLC [106–108]. This all has to be taken into account and supportive measures are recommended for patients undergoing intensified treatment [109]. Relapses, radiation and immune-related side-effects occur primarily within the first year after immunochemoradiotherapy [110, 111], which suggests that more intensive follow-up during this period may be needed.

Conclusions

Recent years have seen a major wave of developments in treating locally advanced NSCLC. We have more knowledge about driver mutations and immune aspects in patients with stage III disease. With the broader availability of fluorodeoxyglucose PET-CT we have learned about the relevance of metabolic activity for radiotherapy planning and prognosis. In addition, PET-CT may determine the necessity of additional therapy after locally applied therapies or therapies in combination. New techniques allow definitive local treatments for more patients and the addition of immune-checkpoint inhibition to chemoradiotherapy improves progression-free and overall survival. However, there are also additional side-effects, which in combination with more aggressive local approaches, demand among others, consequent evaluation and monitoring of pulmonary and cardiac function. In all clinical trials and

TABLE 4 Current clinical trials on immunotherapy and chemoradiotherapy in mostly stage II and III nonsmall stage lung cancer (NSCLC)

ClinicalTrials.gov ID	Phase	NSCLC stage	IO-drug	Protocol	Primary end-point
Concurrent (+consolidation) regimen					
NCT04202809	II	IIIA–B	Durvalumab	Chemotherapy induction→chemoradiotherapy ± durvalumab→surgery if resectable	PFS
NCT03694236	I/II	II/IIIA	Durvalumab	Chemoradiotherapy+durvalumab→surgery	pCR
NCT02343952	II	IIIA–B	Pembrolizumab	Chemoradiotherapy→pembrolizumab consolidation	PFS
NCT02987998	I	III	Pembrolizumab	Chemoradiotherapy+pembrolizumab	Safety
NCT03519971#	III	Unresectable	Durvalumab	Chemoradiotherapy ± durvalumab	PFS
NCT04013542	I	II–III	Nivolumab/ ipilimumab	Radiotherapy+nivolumab/ipilimumab	Safety
NCT03523702	II	II–III	Pembrolizumab	Arm 1 (PD-L1 >50%): radiotherapy+pembrolizumab Arm 2 (PD-L1 1–49%): chemoradiotherapy	PFS
NCT03631784	II	III unresectable	Pembrolizumab	Chemoradiotherapy+pembrolizumab→ pembrolizumab consolidation	Safety, ORR
NCT03644823	II	III–IV	Atezolizumab	Radiotherapy+atezolizumab	Safety
Combination regimen					
NCT04085250	II	III	Nivolumab	Chemotherapy ± nivolumab induction→ chemoradiotherapy→nivolumab consolidation or observation	PFS
NCT03589547	II	III	Durvalumab	Durvalumab→chemoradiotherapy→durvalumab	Safety, PFS
NCT04380636#	III	III	Pembrolizumab	Arm 1: chemoradiotherapy+pembrolizumab→ pembrolizumab+placebo Arm 2: chemoradiotherapy+pembrolizumab→ pembrolizumab+olaparib Arm 3: chemoradiotherapy→durvalumab	PFS, OS
NCT03871153	II	Resectable III	Durvalumab	Chemoradiotherapy+durvalumab induction→surgery→durvalumab consolidation	pCR
NCT03693300	II	III	Durvalumab	Chemoradiotherapy→durvalumab (fixed dose)	Safety
NCT03285321	II	IIIA–B	Nivolumab/ ipilimumab	Chemoradiotherapy→nivolumab ± ipilimumab consolidation	PFS
NCT04026412#	III	IIIA–C	Nivolumab/ ipilimumab	Arm 1: chemoradiotherapy+nivolumab→ nivolumab/ipilimumab consolidation Arm 2: chemoradiotherapy+nivolumab→ nivolumab consolidation Arm 3: chemoradiotherapy→durvalumab consolidation	PFS, OS
NCT04062708	II	III resectable	Durvalumab	Chemotherapy+durvalumab induction→ surgery→radiotherapy→durvalumab consolidation	pCR
NCT03237377	II	III resectable	Durvalumab/ tremelimumab	Radiotherapy+durvalumab ± tremelimumab→surgery	pCR
NCT03871153	II	III resectable	Durvalumab	Chemotherapy+durvalumab induction→radiotherapy +durvalumab→surgery→durvalumab consolidation	pCR
NCT03663166	I/II	III	Nivolumab/ ipilimumab	Chemoradiotherapy+ipilimumab→nivolumab consolidation	Safety, PFS
Induction regimen					
NCT04287894	Ib	III	Durvalumab/ tremelimumab	Durvalumab+tremelimumab induction→chemoradiotherapy	Safety
NCT03102242	II	IIIA–B	Atezolizumab	Atezolizumab induction→chemoradiotherapy	DCR

Data obtained from www.clinicaltrials.gov on 7 August 2020. IO: immune-oncology; pCR: pathological complete response; PFS: progression-free survival; OS: overall survival: PD-L1: programmed death ligand 1; ORR: overall response rate; DCR: disease control rate. #: phase III trials.

registries, quality of life of patients should be evaluated. Driver mutations seem to have an adverse effect on the overall outcome in locally advanced NSCLC. But more data and adequately specified data are needed. Whether adjuvant-targeted EGFR inhibition after surgery has to be given for tumours with classical activating EGFR mutations can be decided on the basis of more mature data. The advantage in progression-free survival with osimertinib after surgery is promising [50], but there was also a clear advantage with gefitinib in the Chinese trial, but this did not translate into an advantage for overall survival [49]. Therefore, at the moment the question remains, whether we only postpone metastasis for the time that an EGFR-tyrosine kinase inhibitor is given.

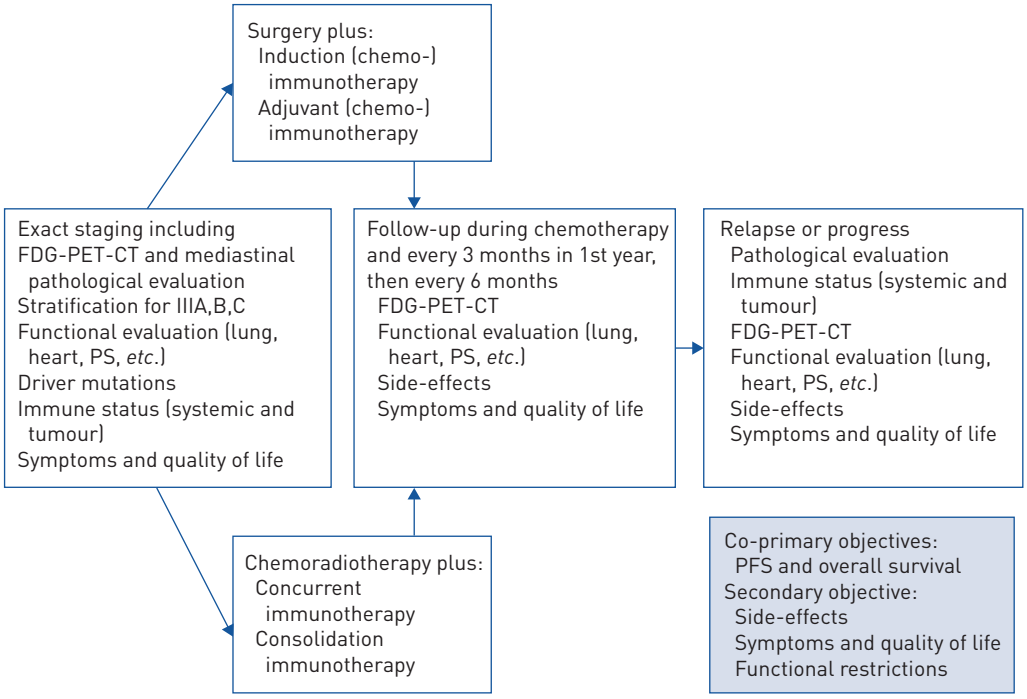

FIGURE 1 Proposal for further strategies in clinical trials and registries about the management of locally advanced nonsmall cell lung cancer (NSCLC). FDG: fluorodeoxyglucose; PET: positron emission tomography; CT: computed tomography; PS: performance status; PFS: progression-free survival.

The biological and clinical picture in locally advanced NSCLC is very heterogenous. In stage IV NSCLC it is now common sense that we have to be precise regarding staging (such as for oligometastatic disease) and histological, molecular and immunological aspects. By this we can improve the management and outcome of our patients with metastasised NSCLC. Until now these aspects have mostly not been taken into consideration for clinical trials and registries of locally advanced NSCLC. We believe that this would also be necessary in these locally advanced situations and propose a stringent functional evaluation, staging and molecular and immunological evaluation before, during and after therapeutic interventions (figure 1).

Previous articles in this series: No. 1: Eichhorn F, Winter H. How to handle oligometastatic disease in nonsmall cell lung cancer. *Eur Respir Rev* 30: 2021; 200234. No. 2: Asciak R, George V, Rahmna NM. Update on biology and management of mesothelioma. *Eur Respir Rev* 30: 2021; 200226. No. 3: Finazzi T, Schneiders FL, Senan S. Developments in radiation techniques for thoracic malignancies. *Eur Respir Rev* 30: 2021; 200224.

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