



# Immunotherapy for locally advanced non-small cell lung cancer: current evidence and future perspectives

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**Abstract:** Non-small cell lung cancer (NSCLC) is the most common type of lung tumors, and one of the leading causes of cancer deaths worldwide. Disease stage at diagnosis significantly impacts on survival, with overall 5-year survival rates ranging from 60% for localized disease, 33% for loco-regional disease, and 5.5% for subjects with distant metastases. Locally advanced NSCLC is a disease characterized by high tumor burden, frequently not amenable of surgical intervention. Overall, only 30% of patients present with potentially resectable disease at diagnosis, and usually undergo neoadjuvant chemotherapy (CT) before surgery. The majority of patients with locally advanced NSCLC (~70%) have unresectable disease at diagnosis. In such cases, multimodal treatment approach with the association of platinum-based CT and radiotherapy (RT), has demonstrated to be superior to sequential therapy or RT alone. Maintenance with immunotherapy after combined CT/RT has further improved the progression-free survival and overall survival. Evidence have suggested that concomitant CT/RT with immunotherapy (IT) enhance disease response, mainly due to its synergized effect on the immune system. Immune checkpoint inhibitors (ICI) have gained an unprecedented success in the treatment of metastatic NSCLC, and represent a promising treatment strategy also in locally advanced disease. There is a strong biologic rationale supporting the use of ICI as a part of multimodal treatment combination of NSCLC. Several clinical trials are ongoing in locally advanced NSCLC, with the aim to explore the role of IT in earlier phases of treatment, combined with RT in place of CT, but also as a trimodal treatment. Considering non-resectable disease, ongoing efforts will help to clarify whether the association of RT with either CT and IT, alone or in combination, is feasible and effectively improve survival outcomes compared with maintenance IT alone. Results from ongoing trials will help to understand the way to improve the efficacy of IT, providing further changes in our standard of care for the treatment of locally advanced NSCLC.

**Keywords:** Locally advanced non-small cell lung cancer (NSCLC); immune checkpoint inhibitors; neoadjuvant; chemoradiotherapy

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## Introduction

Non-small cell lung cancer (NSCLC) is the most common type of lung tumors, and one of the leading causes of cancer deaths worldwide (1). Disease stage at diagnosis significantly impacts on patients' survival, with overall 5-year

survival rates ranging from 60% for localized disease, 33% for loco-regional disease, and 5.5% for subjects with distant metastases (2). According to the recently updated American Joint Committee for Cancer (AJCC) 8<sup>th</sup> edition of the NSCLC staging system, approximately one third of patients

have a “locally advanced” disease at diagnosis (3). This subgroup of patients includes NSCLC stages IIIA to IIIC, a disease characterized by high tumor burden (i.e., T3–T4, and N2–N3 tumors) (4). Though the clinical presentation of locally advanced NSCLC significantly differs according to disease substages, two third of these patients are considered not amenable for surgery due to disease extension. Multimodality treatment approach with the combination of platinum-based chemotherapy (CT) and radiotherapy (RT) has demonstrated to be superior to sequential therapy or RT alone in locally advanced unresectable NSCLC (5,6). Concurrent chemoradiation (CT/RT) using platinum doublets with etoposide, pemetrexed, vinorelbine or taxanes was accepted as the standard CT regimens. The established doses of definitive conventional fractionated RT are 60–66 Gy in 2-Gy fractions. The choice to deliver CT and RT concomitantly or subsequently depends on disease extension and patients’ clinical characteristics. However, most patients progress after CT/RT, with unsatisfactory overall survival (OS) rates, that have not significantly changed over the last years despite advances in radiotherapy techniques (7,8).

Several trials assessed the feasibility and benefits of neoadjuvant systemic treatment with platinum-based CT for patients with locally advanced NSCLC, with potentially resectable disease at diagnosis. Advantages of neoadjuvant CT consist in the possibility to reduce tumor size with nodes downstaging that correlate with better survival, and prevention of micro-metastatic spread. The NSCLC Meta-analysis Collaborative Group provided results of a pooled analysis of 15 randomized trials of neoadjuvant chemotherapy plus surgery *vs.* surgery alone, including nearly 2,500 patients (9). Results from this meta-analysis suggest that neoadjuvant treatment provides a significant survival advantage through all patients’ subgroups (regardless of age, and disease stage), with a 13% reduction in the relative risk of death. At the present time, pre-operative CT is usually considered in selected locally advanced patients who might benefit from disease downstaging.

Therefore, there is a strong medical need to explore new treatment approaches in this subset of patients, in order to improve survival outcomes. Immune checkpoint inhibitors (ICI) have gained an unprecedented success in the treatment of metastatic NSCLC (10,11). In this review we describe the biologic rationale for immunotherapy (IT) use in locally advanced NSCLC, either alone or in combination with other treatment strategies. We also provide results of clinical trials exploring new treatment approaches for locally advanced

NSCLC, and give an overview of new IT treatments that are currently under investigation in this setting.

### **Rationale for immunotherapy use in locally advanced NSCLC**

NSCLC is an immunogenic tumor, and ICIs have demonstrated significant clinical activity, with durable responses achieved in 15–20% of patients in the metastatic setting and maintained over time (7,8). Among the ICI strategies, the most prominent in terms of clinical success are targeting the interaction between programmed cell-death 1 (PD-1) and its ligand PD-L1. Antibodies targeting the anti-PD-1 (nivolumab, and pembrolizumab) and the anti-PD-L1 (atezolizumab) are now standard treatment for metastatic NSCLC (7,8,12). Recently, ICI combined with cytotoxic CT has demonstrated to further improve survival outcomes as front-line treatment in metastatic patients (13,14).

A promising strategy to improve disease response in locally advanced NSCLC is moving IT in earlier phases of treatment. Concomitant CT/RT with IT enhance disease response, mainly due to its synergized effect on the immune system (15). Preclinical and clinical evidences have demonstrated that both RT and CT can increase antigen release, T-cells priming and tumor infiltration, and major histocompatibility complex (MHC)-1 molecules expression, thereby transforming poor immunogenic (“cold”) tumors into “hot” tumors (16–18). Thus, besides the potential role to amplify the effect of IT, combination treatment can help to overcome treatment resistance and delay disease relapse.

### **Evidence in support for immunotherapy in locally advanced unresectable NSCLC**

In the setting of locally advanced unresectable NSCLC, the combination of IT with RT might improve local control at the treated site, but also at distant sites through the so-called “abscopal” effect (19). Irradiation of a tumor results in the release of tumor-associated antigens and damage-associated molecular patterns (DAMPs), a process described as in-situ vaccination (20,21). This effect is maximized when RT and ICIs are administered concomitantly, on in close sequence; however, also ICIs maintenance therapy delivered after CT/RT has shown significant clinical activity (13).

The main study investigating the role of an anti-PD-L1 inhibitor with CT/RT was the PACIFIC trial (22). This phase III trial randomized 713 patients with stage III locally advanced unresectable NSCLC patients, who did

not progress during concurrent platinum-based CT/RT, to receive maintenance durvalumab vs placebo. Durvalumab was given for 1 year or until disease progression, intolerable treatment related adverse events (AEs), or withdrawal of informed consent, whichever came first. The co-primary endpoints were progression-free survival (PFS) and OS. Median PFS was significantly higher for patients receiving durvalumab than for patients receiving placebo (17.2 vs. 5.6 months, respectively). The 24-month OS rate was 66.3% in the durvalumab group, as compared with 55.6% in the placebo group; durvalumab significantly prolonged OS, as compared with placebo (stratified hazard ratio for death, 0.68; 99.73% CI, 0.47–0.997;  $P=0.0025$ ) (23). The median time to death or distant metastases was 28.3 months for durvalumab vs. 16.2 months for placebo, respectively; patients treated with durvalumab had a lower incidence of brain metastases (5.5% vs. 11%). The toxicity of the two treatment arms was comparable. On the basis of these results, the United States (US) Food and Drug Administration (FDA) approved the use of durvalumab as a maintenance therapy for patients with locally advanced NSCLC, whose disease has not progressed after platinum-based concomitant CT/RT. Surprisingly, the European Medicines Agency (EMA) approved the use of durvalumab only in PD-L1 positive NSCLC patients (PD-L1 expression in at least 1% of tumor cells) based on a not pre-planned analysis that observed PFS gain achieved independently of PD-L1 expression but significant better OS with durvalumab only in PD-L1 positive patients. PD-L1 testing was not mandatory for this trial, and PD-L1 status was unknown for 37% of the enrolled patients.

The potential late benefit of previous RT in patients receiving IT was assessed in a secondary analysis of patients with metastatic NSCLC treated with pembrolizumab in the KEYNOTE-001 trial (24). This phase 1 trial investigated the use of single agent pembrolizumab in patients with progressive locally advanced or metastatic NSCLC (25). This secondary analysis on a subset of patients who had received RT before receiving IT, showed that these patients had significantly longer PFS and OS, compared with patients who had not received previous RT.

### **Neoadjuvant immunotherapy for potentially resectable locally advanced NSCLC**

In recent years, several trials have assessed the role of IT in the neoadjuvant setting for locally advanced potentially resectable NSCLC. The biologic rationale lies in the

possibility to induce immune response directed to the in-place tumor and acting through the body against micro-metastases, thus reducing the risk of disease relapse. Moreover, preoperative systemic treatment can give information regarding pathological response on resected tumor at the time of surgery. A pilot study of neoadjuvant nivolumab in patients with surgically resectable stage I–IIIA NSCLC, showed that 45% of patients reach major pathological response with only 2 courses of preoperative nivolumab, with few treatment-related AEs and without surgery delay (26). Preliminary results from an initial analysis of the ongoing LCMC3 phase II trial, evaluating neoadjuvant atezolizumab in patients with resectable early-stage (IB–IIIB) NSCLC, have shown a major pathological response rate of 24%, with 58% (11/19) of patients having less than 50% viable tumor on surgical specimen (27). Neoadjuvant IT had a manageable safety profile, with only one surgery delay because of grade 3 pneumonitis. The combination of neoadjuvant nivolumab plus CT (carboplatin-paclitaxel) in patients with resectable stage IIIA NSCLC was tested in the phase II NADIM trial (28). This trial enrolled 46 patients with stage IIIA NSCLC, who received 3 courses of preoperative IT/CT. All patients had a R0 surgical resection, with no reports of intraoperative complications. More than 80% of patients reached major pathological response, with 58% of patients experiencing complete response. Results presented at the data cutoff date of July 2019 evidenced an 18-month PFS rate of 81% and an 18-month OS rate of 91%. Neoadjuvant combination IT compared with anti-PD1 monotherapy in patients with stage I–IIIA resectable NSCLC, was tested in the NEOSTAR phase II trial. This trial randomized 44 patients to receive 3 courses of neoadjuvant nivolumab ( $n=23$ ) versus 3 courses of combined low-dose ipilimumab plus nivolumab ( $n=21$ ). The overall response rate (ORR) was 20%, with a 25% rate of major pathological response (29). Interestingly, in the NEOSTAR trial radiological disease response according to RECIST criteria was positively associated with major pathological response, suggesting that imaging can early detect patients who benefit from preoperative IT even before surgery. *Table 1* summarizes characteristics and results of the main clinical trials of neoadjuvant IT for potentially resectable NSCLC.

### **Ongoing clinical trials of immunotherapy in locally advanced NSCLC**

Several clinical trials are currently underway, exploring

**Table 1** Summary of characteristics and results of the main clinical trials of immunotherapy for locally advanced resectable NSCLC

Trial name	NCT number	Study design	Setting	Drug	Disease stage	Results
NADIM	NCT03081689	Phase II single-arm	Neoadjuvant + adjuvant (maintenance IT)	Nivolumab + CT	IIIA (N2 or T4 N0/N1)	18-month PFS 81%; 18-month OS 91%; mPR 83%
NA_00092076	NCT02259621	Phase II single-arm	Neoadjuvant	Nivolumab +/- ipilimumab	I-IIIA	mPR 45%
NEOSTAR	NCT03158129	Phase II randomized	Neoadjuvant	Nivolumab vs. nivolumab + ipilimumab	I-IIIA	ORR 20%*; mPR 25%*
LCMC3	NCT02927301	Phase II single-arm	Neoadjuvant + Adjuvant (maintenance IT)	Atezolizumab	IB-IIIB	mPR 18%*

\*only preliminary results are available. CT, chemotherapy; IT, immunotherapy; mPR, major pathological response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

IT as a part of multimodal treatment in stage III NSCLC. Given the heterogeneous nature of this disease, we can subdivide treatment strategies in at least two groups, the first including trials for unresectable NSCLC, and the other including locally advanced potentially resectable NSCLC.

In the field of unresectable stage III NSCLC, the ongoing PACIFIC 6 (NCT03693300) and IMpower010 (NCT02486718) trials of IT after concurrent CT/RT are currently recruiting patients. Other ongoing trials are exploring whether the addition of IT to concurrent CT/RT, followed by consolidation IT, could enhance immune response and anti-tumor effect. Safety of concomitant multimodal treatment was demonstrated in the phase II DETERRED trial, evaluating atezolizumab during CT/RT, followed by 1 year of atezolizumab consolidation therapy (30). Another trial is evaluating induction atezolizumab, followed by concurrent CT/RT and consolidation CT, followed by additional atezolizumab (NCT03102242). The ongoing PACIFIC 2 trial (NCT03519971) investigates the use of durvalumab concomitant with CT/RT, followed by durvalumab until disease progression. A similar phase II trial, the KEYNOTE-799 (NCT03631784), evaluates pembrolizumab with concurrent CT/RT, followed by maintenance pembrolizumab. A novel IT compound M7824, designed to simultaneously target the two immunosuppressive pathways, transforming growth factor- $\beta$  (TGF- $\beta$ ) trap and PD-L1, is being evaluated in a phase II trial (NCT03840902) with concurrent CT/RT and will be compared with the PACIFIC regimen. Another strategy under investigation for unresectable NSCLC is replacing

concurrent CT with IT during RT. Evidence suggest that IT can provide the same radio-sensitizing effect of CT, with less treatment-related toxicity (22,23). Evidence from clinical trials exploring IT in the neoadjuvant setting (see further) have provided enough scientific rationale to support strategies replacing CT with IT in locally advanced disease. The ongoing SPRINT trial (NCT03523702) evaluates concurrent pembrolizumab in place of CT in patients with high PD-L1 expression; while patients with PD-L1 <50% are treated with standard-of-care therapy. Two studies are evaluating IT in place of CT for patients with stage III NSCLC and poor performance status, not eligible for concurrent CT/RT (NCT03818776 and NCT03245177). *Table 2* outlines ongoing clinical trials of IT in locally advanced unresectable NSCLC.

Considering locally advanced potentially resectable NSCLC, several phase II–III trials are exploring IT approach both as monotherapy and as combination therapy. The main approach of ongoing trials is to combine different techniques in the preoperative setting. The principal strategies are combination of neoadjuvant CT/IT followed by adjuvant IT, as in the KEYNOTE-671 trial (pembrolizumab plus CT), the CheckMate 77T (nivolumab/placebo plus CT), the Impower 030 trial (atezolizumab plus CT), the NADIM II trial (nivolumab plus CT); the AEGEAN trial (durvalumab plus CT). Also neoadjuvant combo-immunotherapy trials are ongoing, evaluating different combinations of IT with different comparators in the control arms: the CANOPY-N, evaluating the combination of canakinumab and pembrolizumab; the NCT03237377 trial of durvalumab plus tremelimumab.

**Table 2** Summary of the main ongoing clinical trials of immunotherapy for unresectable locally advanced NSCLC (source: www.clinicaltrials.gov, accessed March 2020)

Trial identifier	NCT number	Study design	Setting	Drug	Disease stage	Primary endpoint(s)
PACIFIC 6	NCT03693300	Phase II	Adjuvant (after CT/RT)	Durvalumab	III (unresectable)	TRAEs
Atezolizumab for advanced NSCLC	NCT03102242	Phase II	Neoadjuvant (subsequent CT/RT)	Atezolizumab	IIIA-B (unresectable)	DCR
PACIFIC 2	NCT03519971	Phase III randomized	Concomitant with CT/RT	Durvalumab	III (unresectable)	PFS, ORR
Keynote 799	NCT03631784	Phase II	Concomitant with CT/RT	Pembrolizumab	III (unresectable)	TRAEs, ORR
M7824 with cCRT	NCT03840902	Phase III randomized	Concomitant with CT/RT	M7824	III (unresectable)	PFS
SPRINT	NCT03523702	Phase II	Concomitant with definitive RT	Pembrolizumab vs. CT	II-III (unresectable)	PFS

CT, chemotherapy; DCR, disease control rate; ORR, objective response rate; PFS, progression-free survival; RT, radiotherapy; TRAEs, treatment-related adverse events.

The CheckMate 816 has an even more intriguing study design, which aims to evaluate neoadjuvant nivolumab plus ipilimumab vs nivolumab either alone or combined with CT. Another promising approach is the combination of concurrent IT and RT delivered with different schedule (conventional and accelerated fractionation), as evaluated in the ARCHON-1 trial (NCT03801902).

Table 3 displays the main ongoing clinical trials of IT for locally advanced NSCLC in the preoperative setting.

### Open questions

Preliminary results of IT in locally advanced NSCLC deserve some major considerations. Regarding neoadjuvant IT for potentially resectable NSCLC, clinical trials mainly consist in small populations of selected patients: everyday clinical practice might not always mirror that of clinical trials, not only regarding patients' characteristics, but also the feasibility of a specific multimodal treatment. Of course, the possibility to deliver a short course of neoadjuvant IT without compromising surgical intervention and providing significant survival benefit is appealing. This is even more interesting, considering that IT use does not seem to negatively impact on pulmonary functions, and on resection rates. However, significant expertise is needed in this setting, considering the higher rate of technically difficult resection, and also the so-called nodal flare (pseudo-progression) often observed in this setting (31,32).

Considering locally advanced unresectable NSCLC,

an important issue regards the timing of IT delivery in relation to RT. In the PACIFIC trial, durvalumab treatment started within 6 weeks from CT/RT completion, however data suggest that a shorter start-time interval may result in a better outcome. Incidence of treatment-related AEs also represents a relevant issue: pembrolizumab and other anti-PD1 therapies are generally well tolerated, however toxicity can increase when these drugs are used in combination with chemotherapy or RT. Even if uncommon, pneumonitis is a possible immune-related AE during anti-PD1 treatment, with an estimated incidence of about 4% in patients with NSCLC (all grades) (33). Thoracic RT can also cause pneumonitis, and this effect seem to be amplified in patients treated with anti-PD1, with higher incidence of any grade pulmonary toxicity, pneumonitis, and respiratory failure (23). These data again highlight the role of RT in priming immune response, thereby potentiating immune-mediated toxicity, and suggest there is a need for careful patients' selection and close toxicity monitoring during combined treatment.

Last, the subset of patients who can benefit more from adding IT to standard treatment is yet to be identified, specifically concerning disease stage and PD-L1 expression. This issue is relevant both for patients receiving neoadjuvant IT before surgery, and for those undergoing concomitant definitive CT/RT, as criteria for patients' selection through clinical trials are heterogeneous. Thus, patients' selection, both regarding disease characteristics and previous treatment, might become an important issue



**Table 3** Summary of the main ongoing clinical trials of immunotherapy for resected and potentially resectable locally advanced NSCLC (source: www.clinicaltrials.gov, accessed March 2020)

Trial identifier	NCT number	Study design	Setting	IT Drug	Disease stage	Primary endpoint(s)
KEYNOTE-671	NCT03425643	Phase III randomized	Neoadjuvant (IT + CT) + adjuvant IT	Pembrolizumab	II–IIIB	EFS, OS
CheckMate 816	NCT02998528	Phase III randomized	Neoadjuvant (IT+CT)	Nivolumab	IB–IIIA	EFS, pCR
CheckMate209-77T	NCT04025879	Phase III randomized	Neoadjuvant (IT + CT) + adjuvant IT	Nivolumab	IIA–IIIB	EFS
Impower 030	NCT03456063	Phase III randomized	Neoadjuvant (IT + CT) + adjuvant IT	Atezolizumab	II–IIIB	mPR
AEGEAN	NCT03800134	Phase III randomized	Neoadjuvant (IT + CT) + adjuvant IT	Durvalumab	II–III	mPR
NADIM II	NCT03838159	Phase II randomized	Neoadjuvant (IT + CT) + adjuvant IT	Nivolumab	IIIA–IIIB	pCR
CANOPY-N	NCT03968419	Phase II	Neoadjuvant	Canakinumab vs. Pembrolizumab vs. Canakinumab + Pembrolizumab	IB–IIIA	mPR
Neoadjuvant CT/RT + durvalumab	NCT03871153	Phase II	Neoadjuvant (IT + CT/RT) + adjuvant IT	Durvalumab	III (N2 – resectable)	pCR
ESPADURVA	NCT04202809	Phase II randomized	Neoadjuvant (IT + CT/RT) + adjuvant IT	Durvalumab	IIIA–IIIB (resectable)	PFS
ARCHON-1	NCT03801902	Phase I	Concomitant IT with definitive RT	Durvalumab	II–IIIC PD-L1 ≥50%	TRAEs

BSC, best supportive care; CT, chemotherapy; IT, immunotherapy; DCR, disease control rate; DFS, disease-free survival; EFS, event-free survival; mPR, major pathological response; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RT, radiotherapy; TRAEs, treatment-related adverse events.

to select the most appropriate treatment.

## Conclusions

Treatment strategy of locally advanced NSCLC has evolved rapidly over the last years, with the introduction of maintenance durvalumab IT after concurrent CT/RT. Numerous clinical trials are underway, in order to explore the role of IT in earlier phases of treatment, combined with RT in place of CT, but also as a trimodal treatment. Preliminary results of neoadjuvant CT/IT for potentially resectable NSCLC are impressive: if subsequent data will confirm a positive impact on survival, the combined approach in this specific setting will probably be practice-changing. Considering non-resectable disease, ongoing clinical trials will help to clarify whether the association of RT with either CT and IT, alone or in combination, is feasible and effectively

improve survival outcomes compared with maintenance IT alone. In the next future, results from ongoing trials will help to understand the way to improve the efficacy of IT, and will provide further changes in our standard of care for the treatment of locally advanced NSCLC.

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