Immunotherapy in patients with early stage resectable nonsmall cell lung cancer

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Purpose of review

'Early-stage' nonsmall cell lung cancer (NSCLC) refers to stage I and stage II disease, and selected cases of stage IIIA disease where complete tumor resection is feasible. Surgery is the standard treatment for early NSCLC, but the overall 5-year survival remains below 50%. The addition of adjuvant cisplatin-based chemotherapy to surgery improved 5-year survival rates by 5–10%, but no significant therapeutic innovation has been established thereafter. We review recent and ongoing studies looking how immunotherapy may improve the outcome of these patients.

Recent findings

Antigen-specific immunotherapy (cancer vaccination) did not fulfill its promise in a large phase III randomized trial in completely resected early-stage NSCLC. Over the past few years, immunotherapy with immune checkpoint inhibition (ICI) has led to remarkable progress in nononcogene addicted metastatic NSCLC. We review ongoing clinical investigations that want to translate these benefits to earlier stages of NSCLC. Both adjuvant and neoadjuvant large randomized controlled trials with ICI are ongoing.

Summary

Although from a mechanistic perspective the neoadjuvant administration may be preferred, it is crucial that both adjuvant and neoadjuvant trials are recruited as planned, to have a balanced view how ICI therapy may ultimately improve cure rates in these patients.

Keywords

adjuvant, early stage, immune checkpoint inhibition, neoadjuvant, nonsmall cell lung cancer

INTRODUCTION

Nonsmall cell lung cancer (NSCLC) represents 85% of all lung cancers. The prognosis and the treatment approach are highly dependent on a proper staging of the extent of the disease. Surgical resection is the cornerstone treatment for patients with stage I and II disease and selected patients with stage IIIA disease with a possibility of complete tumor resection. The expected 5-year survival of this small group of early-stage NSCLC ranges from 90 to 41%, according to the pathological stage [1]. Adjuvant chemotherapy is currently recommended for completely resected stages II and IIIA disease and can be considered in patients with resected stage IB disease and a primary tumor more than 4 cm. If single station N2 disease can be demonstrated by preoperative pathological nodal staging, both definitive chemoradiotherapy and induction therapy followed by surgery are options, with surgery preferably considered in patients in whom a complete resection by lobectomy is expected [2].

CURRENT ADJUVANT STRATEGIES

The frequency of postoperative distant recurrences – associated with significantly reduced survival – is increasing according to tumor stages, ranging from 15% in stage IA to 60% in stage IIIA [3]. The aim of adjuvant therapy is to eliminate sparse tumor cells remaining after surgery and thereby reducing the recurrence rate. The International Adjuvant Lung cancer Trial in 2004 – where adjuvant cisplatin-based chemotherapy was associated with a statistically significant 4.1% 5-year survival advantage – has brought adjuvant cisplatin-based doublet

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KEY POINTS

- Surgery is the standard treatment for early-stage NSCLC, but the overall 5-year survival remains below 50% and no significant therapeutic innovation has been established since the introduction of adjuvant chemotherapy in 2004.
- A large randomized controlled trial with MAGE-A3-directed antigen-specific immunotherapy could not confirm the hope that vaccines would be a step forward.
- The major progress with ICI targeting the programmed death 1/PD-L1 pathway in metastatic NSCLC, and the recent success of consolidation ICI in unresectable stage III NSCLC are encouraging signals to study ICI in early stage resectable NSCLC.
- There is preclinical evidence that neoadjuvant ICI could be more efficient than adjuvant immunotherapy.
- It is crucial that both adjuvant and neoadjuvant ICI trials are fully recruited as planned to have a balanced view how ICI therapy may ultimately improve cure rates in early-stage NSCLC.

chemotherapy as the standard of care for completely resected stage II and IIIA NSCLC. [4]. No further innovations in adjuvant therapy have been made since then. The role of cisplatin–pemetrexed versus cisplatin–vinorelbine was evaluated in the phase II randomized TREAT study [5]. Although the pemetrexed-based therapy was better tolerated, there were no signs of improvement of 3-year survival in a follow-up report [6]. A large phase III study on this question is fully recruited and results are awaited (JIPANG trial UMIN000006737) [7]. The addition of bevacizumab did not improve survival in the Eastern Cooperative Oncology Group 1505 study [8] nor did erlotinib in the RADIANT (A study of Erlotinib (Tarceva) after surgery with or without adjuvant chemotherapy in non-small cell lung carcinoma (NSCLC) patients who have Epidermal Growth Factor Receptor (EGFR) positive tumors) study [9].

ADJUVANT IMMUNOTHERAPY

Antigen-specific immunotherapy (cancer vaccination)

Because the standard adjuvant therapy – cisplatin-based chemotherapy – is often poorly tolerated after thoracic surgery, therapeutic vaccines with minimal toxicity have been studied for their improvement of outcome in the postresection setting with often minimal residual tumor. The melanoma-associated antigen (MAGE)-A3 is a tumor-specific antigen and is present on the surface of NSCLC cells (30–50%). The MAGE-A3 vaccine (a recombinant protein-based vaccine based on the full MAGE-A3 protein combined with a strong immunostimulant) has been studied in the large phase III double-blind, randomized, placebo-controlled MAGRIT (MAGE-A3 as adjuvant non-small cell lung cancer immunotherapy) trial. A total of 2272 patients with resected stage IB–IIIA MAGE-A3-positive NSCLC, who could receive adjuvant chemotherapy according to standard practice, were randomly assigned (2:1) to the MAGE-A3 immunotherapeutic or placebo during 27 months [10]. The primary end point, disease-free survival (DFS) was unfortunately not improved. Based on the current insights in tumor immunology, one can hypothesize that the truly-generated MAGE-A3-directed lymphocytes were probably not able to achieve their tumor cell killing properties, as they were inactivated by checkpoint interactions in the tumor microenvironment.

Adjuvant immune checkpoint inhibition

Based on the revolutionary results of immune checkpoint inhibition (ICI) in metastatic NSCLC, exploration in early-stage NSCLC was a logical next step. The interest in ICI for nonmetastatic NSCLC was recently further enhanced by the remarkable success of durvalumab ICI in stage III unresectable NSCLC [11].

Four large randomized controlled phase III trials are currently investigating the use of ICI as adjuvant treatment after surgical resection (Table 1): PEARLS

Table 1. Ongoing phase III trials of adjuvant immunotherapy in stage I–IIIA NSCLC

Study (identifier)	Sponsor	Compound	Target accrual	Primary end point
PEARLS (NCT02504372)	EORTC/ETOP and MSD	Pembrolizumab	1380	DFS
ANVIL (NCT02595944)	NCI and BMS	Nivolumab	714	DFS and OS
BR31 (NCT02273375)	NCIC and AZ	Durvalumab	1100	DFS in PD-L1 positive
IMpower-010 (NCT02486718)	Hoffman-La Roche	Atezolizumab	1127	DFS and DFS in PD-L1 positive

AZ, AstraZeneca; BMS, Bristol-Myers Squibb; DFS, disease-free survival; EORTC, European Organisation for Research and Treatment of Cancer; ETOP, European Thoracic Oncology Platform; MSD, Merck Sharp & Dohme; NCI, National Cancer Institute; OS, overall survival; PD-L1, programmed death ligand 1.

(pembrolizumab versus placebo for patients with early-stage NSCLC after resection and completion of standard adjuvant therapy, NCT02504372), Canadian cancer trial groups BR31 (NCT02273375), ANVIL (adjuvant nivolumab in resected lung cancers, NCT02595944), and IMpower-010 (NCT02486718). Although each of these trials has its merits, they also illustrate how each pharma partner is replicating the same question. All trials are in patients with completely resected stage IB more than 4 cm, II, or IIIA, and allow adjuvant chemotherapy as per standard practice. Most allow resected tumors of any programmed death ligand 1 (PD-L1) status, but the BR31 trial will enrich the trial population with PD-L1 positive tumors after enrolment of 600 patients. Two trials are placebo-controlled, whereas the ANVIL and IMpower-010 are not. DFS is the primary end point in PEARLS, for the BR31 this is DFS in PD-L1 positive tumors, IMpower-010 has both of these endpoints, and ANVIL targets DFS and overall survival.

The success of ICI therapy in advanced NSCLC is based on the interaction between tumor cells, antigen-presenting cells, and cytotoxic T lymphocytes, from which the inhibition by the programmed death 1/PD-L1 pathway is taken away anti-programmed death 1/PD-L1 monoclonal antibodies. Therefore, potential disadvantages of adjuvant ICI administration are the paucity of remaining tumor cells after complete resection, hence the lower tumor burden and presentation of tumor neoantigens, and the disturbed locoregional lymph node function after the lymph node dissection during surgical resection. Moreover, as there are no early surrogate end points in the adjuvant setting, it will take time before this question will be answered, as the read-outs of these trials are expected from 2021 onwards.

NEOADJUVANT IMMUNE CHECKPOINT INHIBITION IMMUNOTHERAPY

Although resection of the primary tumor is indispensable for tumor control in early-stage lung cancer, the surgical procedure itself has been suspected to promote the postoperative recurrence by

inducing perioperative dissemination of micrometastases, clearing tumor-derived antiangiogenic signals, and evoking the secretion of tumor growth factors and inducing postoperative cell-mediated immunosuppression [12]. Hence, neoadjuvant therapy – used to reduce tumor vitality and early action on micrometastatic disease – is an attractive strategy, even if this may give a delay in the surgical procedure. Even in early-stage NSCLC, there is an immunosuppressive tumor microenvironment with increased regulatory T cells and reduced natural killer cells in the tumor environment when compared with normal lung tissue [13], an additional reason why early repriming of the immune system may be beneficial. In the neoadjuvant setting, when the tumor mass and locoregional lymph nodes are intact, T-cell invigoration with ICI therapy seems particularly attractive.

Adjuvant and neoadjuvant ICI therapy was studied in a very nice Australian study with murine models of triple-negative breast cancer [14[■]]. Both adjuvant and neoadjuvant checkpoint inhibition resulted in increased levels of tumor-specific CD8⁺ T lymphocytes in the tumor and in the peripheral blood, compared to controls. In the neoadjuvant administration, however, tumor-specific CD8⁺ levels were significantly higher in both the tumor and circulation. Moreover, these cells exhibited memory cell characteristics, hence, a prolonged antitumor activity, a feature of great interest in the postsurgical setting with micrometastatic disease. As a result, this led to a much longer animal survival when neoadjuvant immunotherapy was given in comparison to adjuvant administration.

At the meeting of the European Society of Medical Oncology in 2016, a first pilot study in 21 patients with resectable NSCLC was presented, and published thereafter [15[■]]. Two preoperative doses of the anti-programmed death 1 inhibitor nivolumab (3 mg/kg) were administered intravenously q2 weeks, with surgery planned about 4 weeks after start of the neoadjuvant therapy. First, neoadjuvant ICI therapy did not delay the surgical intervention. A major pathological response was seen in 9/20 complete resections. At the systemic

Table 2. Ongoing phase III trials of neoadjuvant immunotherapy in stage I–IIIA NSCLC

Study (identifier)	Sponsor	Compound	Target accrual	Primary end point
CheckMate 816 (NCT02998528)	BMS	Nivolumab ± ipilimumab	642	EFS and PCR
MK-3475-671/KEYNOTE-671 (NCT03425643)	MSD	Pembrolizumab	786	EFS and OS
IMpower-030 (NCT03456063)	Hoffmann-La Roche	Atezolizumab	302	MPR

BMS, Bristol-Myers Squibb; EFS, event-free survival; MPR, major pathological response; MSD, Merck Sharp & Dohme; OS, overall survival; PCR, pathological complete response.

level, in these patients, tumor neoantigen-specific T-cell clones were found in the peripheral blood after neoadjuvant treatment. This means that most of the interesting observations in the Australian preclinical study could be replicated in preoperative NSCLC patients.

Based on this, several dedicated academic clinical trials and large phase III trials with a neoadjuvant ICI therapy strategy have been initiated (Table 2). The safety and effectiveness of nivolumab and ipilimumab or nivolumab and chemotherapy versus chemotherapy alone in early stage (IB–IIIA) operable NSCLC is evaluated in a randomized, open label, phase III trial, with major pathologic response (MPR) rate and DFS as primary end points. The surrogate end point MPR is anticipated to be reached in September 2020 (NCT02998528). A concern with this trial is that in one arm of this trial – ipilimumab/nivolumab – the proven benefit of perioperative chemotherapy is omitted. This is not the case in the KEYNOTE-671 trial (NCT03425643). It is a randomized, placebo-controlled, double-blind phase III trial of concurrent neoadjuvant platinum doublet chemotherapy and pembrolizumab (four cycles) followed by surgery and adjuvant pembrolizumab (13 cycles) versus concomitant neoadjuvant platinum doublet chemotherapy and placebo (four cycles) followed by surgery and adjuvant placebo (13 cycles) for participants with resectable stage IIB or IIIA NSCLC. The IMpower-030 (NCT03456063) is a smaller trial that has the surrogate end point MPR as primary end point. Here as well, the proven benefit of perioperative chemotherapy is not omitted; patients with resectable stage II, IIA, and select IIIB NSCLC are randomly assigned to neoadjuvant atezolizumab and chemotherapy versus neoadjuvant placebo and chemotherapy.

CONCLUSION

The major progress with programmed death 1/PD-L1 blockade in metastatic NSCLC could not yet be translated to the resectable early NSCLC setting, but the results of large phase III trials are now being awaited.

The signal from the unresectable stage III setting in the PACIFIC trial is most encouraging. A major progress in both progression-free survival [16] and overall survival [11[■]] with durvalumab as consolidation therapy after concurrent chemoradiotherapy was documented, making ICI consolidation the new standard of care in these patients. Both adjuvant and neoadjuvant ICI therapy are now being intensively studied in different phases of clinical trials. Preclinical data based on, for example, a murine mouse model for triple-negative breast

cancer showed better efficacy of neoadjuvant immunotherapy over adjuvant immunotherapy. Moreover, neoadjuvant trials have the possibility to include surrogate end points such as MPR in their design, and will therefore have an earlier readout than the adjuvant trials. As there are no clinical trials that compare adjuvant versus neoadjuvant immunotherapy, it is vital that both ongoing adjuvant and neoadjuvant trials achieve full recruitment, so that surrogate end points will not be the only guide for future clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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