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Role of surgery in a novel multimodal therapeutic approach towards complete cure of advanced lung cancer: current and future prospects

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Abstract

Non–small cell lung cancer (NSCLC), particularly locally advanced or nodal spread disease with a poor prognosis, is considered to be potentially curable by multimodal therapy in a subset of patients. Guidelines recommend perioperative chemotherapy with platinum-based regimens, with or without radiotherapy, as the standard treatment modality for high-risk resectable NSCLC. Although the classical regimens of adjuvant chemotherapy have been platinum-based doublet or oral agents such as tegafur/uracil, in recent decades, some molecular targeted therapeutic agents and immune checkpoint inhibitors have been developed with an expected favorable effect. Recent trials of perioperative therapy using these agents have shown favorable anticancer efficacy for resectable NSCLC with an acceptable adverse events profile.

The ideal timing of perioperative therapy administration, before or after surgery, is still controversial. Because some speculation and concepts have arisen from basic research, several trials are ongoing to clarify the efficacy of newly developed agents in the adjuvant or neoadjuvant setting. This review discusses the role of surgery in the new era and analyzes when and which optimal perioperative multimodal therapy including chemotherapy, radiotherapy, molecular-targeted therapy, and immunotherapy should be administered for resectable or potentially resectable NSCLC to possibly provide complete cure.

Introduction

In the field of thoracic oncology, recent clinical trials on multimodal therapy combined with newly developed agents, including molecular targeted therapy and immunotherapy, have shown a high rate of pathological response, implying the possibility of complete cure in advanced non–small cell lung cancer (NSCLC) [1-3]. Locally advanced disease is associated with the possibility of micrometastases to distant sites, which is often the cause of early disease recurrence, and the rationale for the administration of systemic therapy, typically resulting in a poor outcome. In contrast, among them, patients with so-called oligometastasis are included [4, 5]. Precision medicine in the form of optimal multimodal therapy, combining radiation and systemic therapy, with optimal timing of surgical resection may help achieve complete cure in some of these patients.

Currently, the application of surgical excision is more beneficial in early-stage NSCLC; however, when combined with multimodality therapy, complete cure can be achieved in advanced-stage NSCLC. Recent guidelines from The Japan Lung Cancer Society for NSCLC have suggested trimodality therapy for locally advanced resectable lesions [6]. Perioperative therapy has been added to surgical resection to attain complete cure; currently, neoadjuvant therapy is also accepted worldwide as a standard therapy for advanced NSCLC. In recent decades, as represented by epidermal growth factor receptor *(EGFR*) tyrosine

kinase inhibitor (TKI), newly developed drugs for NSCLC with driver oncogenes such as *EGFR, ALK* (anaplastic lymphoma kinase), *ROS-1* (reactive oxygen species-1), *BRAF* (v-raf murine sarcoma viral oncogene homolog B1), and tumor cell expression of *PD-L1* (Programmed cell death ligand 1) have provided additional therapeutic options with evidence from clinical studies; for example, EGFR TKI [7-9].

Immune checkpoint inhibitors (ICIs), which have currently gained focus, will undoubtedly be added to the new multimodality regimens of perioperative treatment [1, 2, 10]. We herein provide an overview of the current and future treatment strategies involving perioperative therapy and the role of surgical resection in advanced lung cancer.

Adjuvant therapy with platinum-based regimens

Guidelines recommend additional treatment modalities including routine chemotherapy consisting of platinum-based doublet (PT/DC) for patients with stage III disease. In Japan, the Lung Cancer Guidelines 2019 Edition recommended cisplatin (CDDP)-combined chemotherapy as an adjuvant therapy post-complete resection of stage II/IIIA NSCLC (strength of recommendation: 1, evidence of Strength: A, agreement rate: 95%) [6]. This is based on the results of a meta-analysis by the NSCLC Collaborative Group in 1995 comparing the surgery alone group with the postoperative adjuvant chemotherapy group,, and it revealed that postoperative adjuvant chemotherapy with CDDP reduced the relative mortality risk

by 13% [11]. A meta-analysis of 8,447 cases from 34 clinical trials demonstrated that postoperative adjuvant chemotherapy showed a significant survival benefit for stage II/IIIA NSCLC after complete resection [12]. In terms of combining drugs with platinum agents, a randomized phase III study (JIPANG) of PEM/CDDP vs. vinorelbine/CDDP for stage II-IIIA non-squamous NSCLC was conducted [13]. Although the JIPANG study failed to demonstrate the superiority of PEM/CDDP, this regimen showed better tolerability as adjuvant chemotherapy (Table 1). However, subgroup analysis in terms of *EGFR* mutation revealed that the disease free survival (DFS) in the VNR/CDDP group was superior to that in the PEM/CDDP group [13]. Regardless, PT/DC adjuvant therapy historically remains the recommended option with surgical resection for a certain subset of patients with stage II-III NSCLC at present, and few clinical phase III trials examining cisplatin-based perioperative therapy are being conducted after the development of new drug regimens.

Adjuvant therapy with uracil and tegafur regimens

The combination of uracil and tegafur (a prodrug of 5FU) is used as an adjuvant therapy for relatively early-stage NSCLC based on multiple positive phase III trials in Japan [14]. A meta-analysis of 2003 patients also showed a significant improvement in survival at 5 and 7 years (77.2% to 81.8% and 69.5% to 76.5%, respectively, hazard ratio [HR]: 0.74, and 95% confidence interval [CI]: 0.61 to 0.88, p=0.001) [15]. An adjuvant study was conducted in patients with stage IB–IIIA disease after complete resection of

NSCLC by a simple direct comparison between UFT and carboplatin doublets to assess whether there was a difference between the two (SLCG0401) (Table 1) [16]. Overall survival (OS) and DFS of UFT vs. carboplatin doublets were as follows: OS at 5 years: 70% versus 73% and RFS: 56% versus 57%, respectively. Carboplatin-based adjuvant therapy did not improve survival when compared with UFT; however, toxicity was milder in the UFT arm than in the carboplatin arm [16], suggesting that adjuvant UFT with the two-year oral treatment after surgery is a potential optional treatment for stage IB-IIIA NSCLC.

More recent studies in this field have explored the use of S-1, an oral agent composed of tegafur mixed with the fluorouracil metabolism inhibitors gimeracil and oteracil, which was expected to have higher effectiveness than UFT. We previously conducted a randomized feasibility study (SLCG 0701) to confirm the milder toxicity of S-1 (80–120 mg/body/day) as an adjuvant therapy (consisting of either the 4-week S-1 administration followed by a 2-week rest, or the 2-week administration and a 1-week rest) for NSCLC patients with stage IA (tumor diameter, 2-3 cm) [17]. Additionally, a randomized phase III trial (JCOG0707, UMIN000015732) evaluated the efficacy of S-1 and compared it with UFT adjuvant therapy for patients with stage I NSCLC. However, in the 963 patients enrolled in this study, S-1 adjuvant therapy was not superior to UFT therapy (5-year OS in UFT versus S-1 group; 88.8% versus 89.7%)[18]. A recent study (SLCG 1001, UMIN 000005041) for relatively advanced NSCLC (stage II-IIIA) showed the feasibility of adjuvant chemotherapy with S-1 plus carboplatin followed by 2 weeks rest and 1-year S-1

maintenance with a 2-year OS of 85.1% [19]. This regimen had modified the LETS study showing lower toxicity and higher dose intensity than the conventional paclitaxel plus carboplatin [20]. An ongoing phase III trial, LOGIK-1702, conducted by another group in Japan examined S-1 versus cisplatin plus vinorelbine for stage IB-IIIA NSCLC after complete resection in an adjuvant setting (Table 1). The primary endpoint was 2-year relapse-free survival, while the secondary endpoints were quality of adjusted life years as well as 5-year OS, 2-year OS, and rate of adverse events. Recent studies thus appear to be trying to avoid the relatively high toxicity of traditional platinum doublet regimens by evaluating new regimens containing S-1.

Adjuvant therapy with newly developed agents, TKIs and ICIs

In the past decade, a promising therapy has been developed for advanced NSCLC patients with driver mutations in the form of EGFR-targeted drugs like EGFR-TKIs [7]. However, to date, clinical trials in an adjuvant setting comprising EGFR-targeted agents have failed to show obvious benefits in NSCLC patients after surgical resection [21-23]. In Japan, a randomized phase III trial of adjuvant gefitinib vs. placebo (PBO) was conducted in patients with completely resected stage IB-IIIA NSCLC, regardless of the *EGFR* gene status [21]. This trial, which was the first to investigate the usefulness of EGFR-TKIs as an adjuvant therapy, was suspended after enrollment of only 38 patients (initially expected to recruit 670 patients) because 23 of the 38 patients were excluded from the study due to several reasons including

retraction of informed consent and onset of adverse events. Therefore, the Japanese Guideline 2019 recommends that EGFR-TKI should not be used postoperatively regardless of the *EGFR* mutation status. The randomized RADIANT trial (NCT00373425) of adjuvant erlotinib versus PBO for NSCLC with EGFR expression confirmed by immunohistochemistry or FISH (fluorescence in situ hybridization) has also been conducted (Table 1) [22]. Although adjuvant erlotinib did not significantly prolong DFS, according to the subgroup analyses of 102 *EGFR* mutation-positive patients out of a total of 973 patients, DFS favored erlotinib without significant differences (median DFS, 46.4 vs. 28.5 months; HR, 0.61; 95% CI, 0.38 to 0.98; P = 0.039) [22]. Similarly, a phase III study (BR19, NCT00049543) failed to show OS benefit from gefitinib in patients with completely resected tumor harboring *EGFR* mutation (only 15 of 359 patients, 4%), and patients with wild-type *EGFR* [23]. These results implied the importance of patient selection in maintaining a balance between adverse events due to treatment and promising benefits of targeted therapy according to the driver oncogenes.

The SELECT trial (NCT00567359) selected 100 patients with NSCLC harboring an *EGFR* gene mutation and showed that the 2-year DFS by stage was 96% for patients with stage I, 78% for stage II, and 91% for stage IIIA (Table 1) [24]. Although the median DFS and OS have not yet been reached, patients were evaluated for the primary endpoint of 2-year DFS, which was 88% (95% CI, 80% to 93%) and was significantly higher than the historical control of 76% (P = 0.0047). A recent randomized phase III (ADJUVANT, NCT01405079) study of gefitinib versus vinorelbine plus cisplatin as an adjuvant

treatment for stage II-IIIA (N1-N2) harboring *EGFR*-mutant NSCLC was conducted in China (Table 1) [25]. In this study, 483 patients were screened as *EGFR*-mutant and 222 were randomized. Although the results demonstrated a benefit from adjuvant gefitinib treatment because of increased DFS and reduced adverse events, immature data due to relatively short follow-up periods have not yet shown a significant difference in OS. In the ADAURA trial (NCT02511106) of adjuvant osimertinib, a third-generation TKI targeting NSCLC with *EGFR* T790M mutation, globally 682 patients with IB-IIIA NSCLC harboring *EGFR* mutations were randomized to the treatment or PBO arm (Table 1) [26]. Although OS was immature (4% maturity) with 29/682 deaths at data cutoff, two-year DFS rate was 89% with osimertinib versus 53% with PBO (HR: 0.21, 95% CI: 0.16, 0.28; p<0.0001) [26]. Mature data were reported to reach a 79% reduction in the risk of disease recurrence or death (J Clin Oncol 2020; 38(suppl):LBA5). Thus, adjuvants that are used for molecular targeted therapy, such as osimertinib, could be the first targeted agent in a global trial to be an effective new treatment strategy for patients with stage IB/II/IIIA *EGFR* mutation NSCLC after complete surgical resection.

Another clinical trial platform of NSCLC with known *EGFR* mutations or *ALK* translocations was coordinated by the United States cooperative group system under the name ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial, NCT02193282, NCT02201992, NCT02595944, and NCT04267848) (Table 1). It planned to enroll 8,300 patients and currently consists of three integrated protocols utilizing the master protocol of four different adjuvant therapies

(pembrolizumab/PT-DC, nivolumab, erlotinib, and crizotinib), according to the driver genes and PD-L status. Enrolled patients with completely resected IB-IIIA NSCLC were randomly assigned to the appropriate targeted therapy or PBO group after resection of the tumor and appropriate adjuvant chemotherapy, with the aim of identifying whether TKI treatment provides an overall survival benefit in the adjuvant setting.

Neoadjuvant therapy with platinum-based chemotherapy and radiotherapy

For potentially resectable N2 disease, a randomized study (RTOG, R9309) reported apparent favorable prognosis in patients treated with induction chemotherapy followed by surgery compared to those treated with upfront surgery [27]. Well-documented evidence exists for the enhanced cytotoxicity of platinum-based chemotherapy with the combination of radiotherapy leading to enhance radiosensitivity for NSCLC [28]. These direct and potential oncological effects of radiation on cancer cells suggest that neoadjuvant therapy including radiotherapy might be superior to chemotherapy alone before complete surgical resection in stage III NSCLC, particular in patients who acquired down staging after the induction therapy [29, 30]. Pless et al. conducted a phase III randomized trial for IIIA-N2 NSCLC patients treated with induction chemoradiotherapy, which revealed the superiority of the trimodality therapy [31]. There may be a possible advantage of induction chemoradiotherapy followed by surgical resection compared with chemotherapy followed by surgery in a select population of patients with N2

disease.

In a retrospective study of 58 patients who underwent bronchoplasty for primary lung cancer, 20 patients underwent preoperative chemoradiotherapy, and the postoperative complications were similar in both groups (with and without chemoradiotherapy) [32]. Additionally, induction chemoradiotherapy for locally advanced NSCLC might possibly contribute to securing a clear surgical margin [33]. However, the early and late postoperative complications such as radiation pneumonitis and pulmonary aspergillosis should also be considered [34]. Moreover, Soh and colleagues reported that 84% of patients who underwent induction chemoradiotherapy and subsequent surgery developed chronic lung injury in one year, after which up to 34% of patients had progressively devastated residual lung [35].

Apart from the retrospective study, we reported that induction concurrent chemoradiotherapy with docetaxel and cisplatin for NSCLC with pathologically proven cN2/3 showed favorable prognosis (7-year OS rate of 63.6% after median follow-up of 8.7 years) [36]. The ESPATUE study demonstrated similar outcomes of PFS and OS between the chemotherapy plus radiation boost group and chemoradiation followed by the surgery group in resectable IIIA and IIIB NSCLC patients [37]. Although the survival curve indicated that the perioperative death rate was relatively high in the early phase after surgery and the data were not mature enough to reach statistical significance, the five-year OS was more favorable in the surgery group than in the chemoradiation group (OS rates of 44% for the surgery group and 40% for the radiation group). Long-term pooled data analysis from SAKK trials of phase II and III (16/96, 16/00,

and 16/01) was conducted for a total 368 patients with operable stage III NSCLC treated with bimodality (chemotherapy and surgery) or trimodality (bimodality plus radiotherapy) [38]. Trimodality did not improve OS, and the role of additional preoperative radiotherapy remains controversial, although the 10-year survival rate of this study reached almost 30%.

Nowadays, although the Japanese Guideline does not recommend neoadjuvant therapy for stage I-II NSCLC, they do suggest neoadjuvant chemotherapy with platinum-based regimens and radiotherapy for cIIIA NSCLC. In addition, the necessity and the regimen used for adjuvant therapy after neoadjuvant and surgery are issues of interest. Detailed analyses of biomolecules, such as by next-generation sequencing (NGS) of the resected specimen, will provide details of the effects of both optimal adjuvant therapy and induction therapy [39].

Neoadjuvant therapy with newly developed agents, TKIs and ICIs

Targeted therapeutic drugs have particularly been developed as adjuvant candidate agents for patients with resectable but high-risk NSCLC harboring driver oncogenes and have a promising effect on the reduction of cancer cells before surgery. After the confirmation of the effectiveness of osimertinib (ADAURA) as an adjuvant therapy [3], the ongoing randomized phase III NeoADUARA trial (NCT04351555) has been investigating the neoadjuvant therapeutic effects of osimertinib with or without chemotherapy over chemotherapy alone, for II-IIIB NSCLC with N2 disease harboring an *EGFR*

mutation (Table 2). Two phase II trials investigating the effects of the TKIs afatinib (NCT04201756) and icotinib (NCT02820116) as induction therapy are ongoing for stage III patients harboring *EGFR* mutation. Estimated completion dates of these studies are 2029, 2025, and 2023, respectively (Table 2). Additionally, a ongoing phase III study of CANOPY-A (NCT03447769) and a phase II study of CANOPY-B (NCT03968419) are investigating the additional effect of canakinumab, an anti-IL-1ß monoclonal antibody treatment agent used for several inflammatory diseases, as a neoadjuvant therapy added to ICI for IB-IIIA NSCLC (Table 2).

Recently, the most hopeful additional drugs for multimodal therapy in the neoadjuvant setting are the newly developed immunotherapeutic drugs, and several clinical studies on neoadjuvant immunotherapies are ongoing (Table 2) [1, 2, 40-46]. Although anti-programmed death 1 (PD-1) antibodies have revolutionized the treatment of metastatic and advanced NSCLC, their application in the neoadjuvant setting has not been well established. Results from a pilot clinical study reported the safety and feasibility of a neoadjuvant PD-1 blockade [2]. Because of these antitumor effects of immunotherapy, pseudo-progression should be considered after immunotherapy, even though radiographic evaluation does not show tumor shrinkage probably due to invasion of the tumor by immune cells such as CD8-positive T cells [46]. For this reason, iRECIST (guidelines for response criteria for use in trials testing immunotherapeutics) was released to evaluate the induction therapy including ICIs in 2017 [47]. That is, when immunotherapy is included in anticancer therapies, it is important for thoracic surgeons to know

whether or not neoadjuvant treatment is effective, especially with regard to surgical indications for resectable lesions. Shu et al reported that the neoadjuvant atezolizumab plus carboplatin and nab-paclitaxel, followed by surgery, successfully achieved 80% of major pathologic response (MPR) (NCT02716038) [2]. Furthermore, in a pilot study of the neoadjuvant nivolumab (NCT02259621), tumor mutational burden was reported to be strongly related to the effectiveness of PD-1 blockade, resulting in high MPR and complete response (CR) [46].

An early intermediate report of the CheckMate 816 trial (NCT02998528) studying PT-DC/nivolumab plus ipilimumab neoadjuvant therapy showed a 45% MPR in 21 patients in the nivolumab arm, and there is a plan to recruit a total of 350 patients [ASCO 2019, P2.16-03. DOI:https://doi.org/10.1016/j.jtho.2018.08.1478] (Table 2). Recent results from the NADIM trial (NCT 03081689) examining paclitaxel/carboplatin plus nivolumab for IIIA, N2 resectable NSCLC followed by surgery revealed that 41 out of the 46 planned recruited number of patients had been operated, and MPR and CR were 86% and 71%, respectively [DOI: 10.1200/JCO.2018.36.15_suppl.8521 Journal of Clinical Oncology 36, no. 15_suppl (May 20, 2018) 8521-8521.] (Table 2).

However, the phase II PRINCEPS (NCT02994576) trial investigating the efficacy and safety of only single injection of the neoadjuvant atezolizumab followed by surgery in patients with IA-IIIA NSCLC revealed no MPR (ESMO Virtual Congress 2020, Abstract 1215O]. The negative results of neoadjuvant immunotherapy were also early reported in the IFCT-1601 IONESCO trial of neoadjuvant durvalumab

(NCT03030131), which was stopped because of higher 90-day postoperative mortality (ESMO Virtual Congress 2020, Abstract 1214O). In this study, although the direct causes of mortality did not include adverse events of ICI itself and 41 patients received R0 resection, postoperative complication frequently occurred (resulting in 9% deaths) and 9 of 41 operated patients underwent pneumonectomies' (Table 2).

Neoadjuvant therapy with QUADRI-modality therapy

Concurrent radiotherapy with ICIs can be considered to have a positive effect on tumor cell proliferation and inflammation, which might also benefit the tumor antigens and attack the cancer cells under ICI administration [48, 49].

A phase I and II study of the Squat trial (WJOG12119L) is investigating the effect of durvalumab over neoadjuvant chemotherapy with CBDCA/PAC plus concurrent radiotherapy of 50 Gy for N2 IIIA NSCLC (Table 3). A new clinical trial of neoadjuvant chemoradiotherapy (S-1 and cisplatin with 66 Gy concurrent radiotherapy) plus durvalumab has also started for a particular tumor, so-called superior sulcus tumor (DEEP_OCEAN, NCT04465968). SAKK16/18 (NCT04245514), an ongoing phase II trial, is investigating an optimal radiotherapy regimen (2 Gy X 20 days, or 5 Gy X 5 days, or 8 Gy X 3 days) for immune-modulatory chemoradiotherapy (Table 3). This quadrimodality therapy is to evaluate the efficacy and safety of chemotherapy with CDDP/DOC plus immunotherapy with durvalumab plus chemotherapy followed by surgery, and the study is expected to complete in 2025 (Table 3). Although these ongoing

trials on quadrimodality therapy are still in phase II, the next phase is about to start and the future direction will be coming in the next decade.

Although low-dose radiation therapy (LDRT) as a neoadjuvant is the direct effect on the tumor weakened as radiation therapy, LDRT is expected to enhance immunotherapy and exert an abscopal effect; furthermore, additional adjuvant treatment can be considered in pathologically defined high-risk patients. In the future, it is expected that biological status such as genomic analysis including mutational burden will progress and genomic medicine will be further developed. Among them, surgical therapy plays a central role, and immunotherapy, conventional PT-DC, and RT may all be used as adjuvant, neoadjuvant, or both.

SALVAGE surgery and surgical treatment for oligometastatic disease or recurrence

NSCLC with an oligometastatic lesion represents a new category of patients in whom multimodal therapy may improve the prognosis. A retrospective study from Italy, investigating the role of surgery in 57 patients with oligometastatic NSCLC was reported [4]. Casiraghi et al. reported that surgical resection after adjuvant chemotherapy was conducted in 57 patients with oligometastasis stage IV NSCLC, and OS rates at two, three, and five years were 57%, 50%, and 30%, respectively [4]. In our retrospective study of 48 cases with recurrence after multimodal treatment, there were 18 cases of oligometastasis [5]. Of the 20 patients who underwent local treatment aiming at a cure, 16 patients had oligometastasis, two had

multiple brain metastases, one had supraclavicular lymph node metastasis, and one had both brain and adrenal metastases. The 2-year survival rate was 62%. Depending on the individual patient, surgical resection should be considered, with or without systemic therapy, particularly for oligometastasis [5]. For these particular situations, to aim for complete cure, the Maastricht University group is currently conducting a prospective multicenter phase II CHESS study to show the neoadjuvant effect of durvalumab, carboplatin/paclitaxel, plus radiotherapy using stereotactic body radiation therapy followed by surgical resection or chemoradiation as definitive local treatment for stage IV NSCLC (NCT03965468). This study is planned to be completed in 2021 (Table 3).

Summary and Future Direction

Although advanced NSCLC is considered to be incurable with current therapeutic options, it is clear that there has been measurable progress over the past decades. It is remarkable that, only 20 years ago, there was still discussion regarding the validity of treatment for any patient with advanced NSCLC, whereas, today, we have unequivocally established the value of treatment for essentially all fit patients with advanced disease, including second- and third-line treatments. Nowadays, adjuvant treatment can be selected on the basis of tumor characteristics such as molecular biomarkers by analyzing the resected specimen. Ethnic heterogeneity in cancer patients leads to differences in drug metabolisms and targeted therapy responses, therefore, it may be necessary to consider this while selecting suitable therapies; for

examples, *EGFR* mutation frequencies are well known to differ among the ethnic groups. [50, 51]. Multiple other biomarkers with prognostic utility are under investigation, for example, next generation sequencing is being used more commonly for analyzing many interesting gene signature profiles [52, 53], but prospective randomized data to verify their predictive capacity are still lacking. With regard to biological aspects, the neoadjuvant setting may be favored because it maintains the tumor environment, including the exposure of oncoantigens to dendritic cells to encourage antigen presentation to initiate an immune response from T cells, before the surgical disruption of immune interaction and a boost of the abscopal effect with concurrent radiotherapy.

In recent years, experience in advanced surgical procedures such as complicated bronchoplasty, extended surgical resection with great vessels and vertebrae, and particularly, autologous lung transplantation has been accumulated [33], and surgical techniques and perioperative management have thus advanced. Furthermore, not only drug-related adverse events but also specific complications of multimodal therapy should be considered for short- and long-term periods after surgery, with particular attention to the high rate of chronic lung injury in the cancer survivors after chemoradiotherapy and surgical resection [34, 35]. Most ongoing studies discussed in this review will be completed in the next decade and the analyzed data might be completed and reported by 2030. With the advent of newly developed drugs, especially ICIs, the role of thoracic surgeons has become even more important in the process of deciding a strategy for complete cure in patients with advanced lung cancer. The novel mechanism of action of these drugs, with

immune and T-cell activation, is postulated to lead to unusual patterns of responses that resemble tumor flare reaction but are more pronounced and more frequent than the previously described responses. In the early melanoma trials on immune-based therapeutics, investigators described a unique response pattern called pseudo-progression.

Consequently, we will have new evidence regarding appropriate perioperative treatment approaches. ICIs are undoubtedly key agents in the neoadjuvant setting with other modalities including radiotherapy such as LDRT and surgery. Moreover, depending on the presence of oncogene drivers, TKIs will have a main role as precision medicine in addition to ICIs. Standard cancer-killing drug regimen of PD/CT may still continue to be an essential chemotherapy agent. Therefore, after reduction of tumor cells as much as possible by multimodal therapy including newly developed induction therapy and complete R0 surgical resection, sometimes even involving a complicated extended surgical procedure, advanced cancer could be completely cured. Conversely, negative results have also been reported from neoadjuvant immunotherapy studies, and thoracic surgeons should carefully analyze these study designs based on what message lies behind them. Multimodality therapies, including extended surgery or minimal invasive treatments, need to be planned such that there exists a balance between the risks and benefits of personalized therapy and molecular biomarker-based precise medicine. Thoracic oncology surgeons are in the best position to judge tumor operability including salvage surgery and resectability, not only now but also after neoadjuvant effectiveness of advanced NSCLC, in an era when systemic cancer therapies

are rapidly developing.

Conclusion

On the basis of accurate analyses of the resected specimen, the efficacy of neoadjuvant therapy could be carefully evaluated by responses such as nodal down staging, tumor viability rate, newly observed oncogenes, and estimates of the possibility of existence of microtumors. Thus, with the development of not only trimodality but also quadrimodality and multimodality therapies, and with the optimal timing of surgical complete resection, patients with advanced NSCLC have a chance to completely overcome the disease in the new era.

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Table 1. Recent and ongoing clinical trials for stage IB–III NSCLC in the adjuvant setting.

The agents used for adjuvant therapy in clinical trials are platinum-based and UFT, S-1, mainly during 2000-2010; however, recent trends are molecular targeted therapies or combination of ICIs with PT-DC. Several ongoing recent trials have been conducted on molecular targeted therapies or ICIs with or without PT-DC. In some of them, the eligibility for patient enrollment included driver oncogene status.

Abbreviations

ALK: anaplastic lymphoma kinase, BRAF: v-raf murine sarcoma viral oncogene homolog B1, CBDCA: carboplatin, CDDP: cisplatin, EGFR: epidermal growth factor receptor, PAC: paclitaxel, PT-DC: platinum-based doublet chemotherapy, RT: radiotherapy

Table 2. Recent and ongoing trials investigating the efficacy of newly developed agents for stage IB-IIIB NSCLC in the neoadjuvant setting. The recently used agents include not only ICIs but also novel therapeutic drugs such as oleclumab, monalizumab, and danvatirsen in the Neo COAST trial.

Abbreviations

ALK: anaplastic lymphoma kinase, CBDCA: carboplatin, CDDP: cisplatin, EGFR: epidermal growth factor receptor, PAC: paclitaxel, PDL: Programmed cell death ligand, PEM: Pemetrexed, PT-DC: platinum-based doublet chemotherapy, VNR: vinorelbine

Table 3. Neoadjuvant therapy with chemoimmunoradiotherapy. The latest report of induction therapy of chemoradiation without ICIs was published in 2019. Current ongoing trials investigating the efficacy of neoadjuvant therapy with radiation include ICIs without a phase III study.

Abbreviations

ALK: anaplastic lymphoma kinase, BSC, best supportive care, CBDCA: carboplatin, CDDP: cisplatin, EGFR: epidermal growth factor receptor, PAC: paclitaxel, PDL: Programmed cell death ligand, PEM: Pemetrexed, PT-DC: platinum-based doublet chemotherapy, VNR: vinorelbine

No.	Author, study group or Investigator	study phase	Trial Study ID	Drug	Control	Stage	o. of Patien	biological status	Study Completion year
1	S Toyooka	phase III	SLCG0401 UMIN000000810	UFT	CBDCA/PAC	IB-IIIA	402	-	2018
2	T Okamoto	phase II	KLSS	S-1	S-1+CDDP	II-IIIA	141	-	2018
3	T Nagayasu	phase II	LOGIK1702 UMIN000027435	S-1	CDDP+VNR	II-IIIA	190	-	2027
4	H Kenmotsu	phase III	JIPANG UMIN000006737	CDDP/PEM	CDDP+VNR	II-IIIA	804	-	2020
5	M Tsuboi	phase III	-	Gefitinib	placebo	IB-IIIA	38	-	2005
6	GD Goss	phase III	BR.19 NCT00049543	Gefitinib	placebo	IB-IIIA	503	-	2011
7	Kelly	phase III	RADIANT NCT00373425	Gefitinib	placebo	IB-IIIA	973	EGFR protein amplification	2015
8	Pennnel	phase II	SELECT NCT00567359	Erlotinib	-	IA-IIIA	100	EGFRm-positive	2018
9	W Zhong	phase III	ADJUVANT NCT01405079	Gefitinib	PT+VNR	II-IIIA (N1-2)	222	EGFRm-positive	2018
10	M Tsuboi	phase III	ADAURA NCT02511106	Osimertinib	Placebo	IB-IIIA	682	EGFRm-positive	2023
11	R Govindan	phase III	ALCHEMIST Treatment Trial NCT02193282	Erlotinib	placebo or observ	IB-IIIA	450	EGFRm-positive	2020
12	D Gerber	phase III	ALCHEMIST Treatment Trial NCT02201992	Crizotinib	observation	IB-IIIA	168	ALK Fusion Mutations	2022
13	JE Chaft	Phase III	ALCHEMIST (ANVIL) NCT02595944	Nivolumab	observation	IB-IIIA	903	stratified by PD-L1 status	2024
14	JM Sands	Phase III	ALCHEMIST Chemo-IO NCT04267848	Pembrolizumab	PT-DC	IB-IIIA	1263	stratified by PD-L1 status	2024
15	Novartis Pharm.	phase III	CANOPY-A NCT03447769	Canakinumab	Placebo	II-IIIA IIIB (N2)	1500	-	2027
16	Novartis Pharm.	phase III	CANOPY-N NCT03968419	akinumab/pembrolizu	Canakinumab or pembrolizumab	IB-IIIA	110	-	2022
17	Hoffmann-La Roche	phase III	IM power 010 NCT02486718	Atezolizumab	BSC/PT-DC	IB-IIIA	1280	-	2027
18	GD Goss	phase III	BR31 NCT02273375	Durvalumab	Placebo	IB-IIIA	1360	stratified by PD-L1 status	2024
19	Merck Sharp & Dohme Corp.	phase III	KEYNOTE-091 PEARLS NCT02504372	Pembrolizumab	Placebo	IB-IIIA	1380	-	2024

No.	Investigator, Auth	Study Phase	Trial, ID	Agent	Regimen	Control	Stage	biological status	No. of Patients	Study Completion Year
1	M Tsuboi	Phase III	NeoADAURA NCT04351555	Osimertinib	Osimertinib With or Without Chemotherapy	Chemotherapy Alone	II-IIIB, N2	EGFRm-positive	351	2029
2	Peng Zhang	Phase II	NCT04201756	Afatinib	Afatinib	-	III	Adenocacrinoma, EGFRm possitive	47	2025
3	Jun liu	Phase II	NCT02820116	Icotinib	Icotinib	-	IIIA-B	EGFRm-positive	67	2023
4	Mariano Provenci	Phase II	NADIM NCT03081689	Nivoumab	CBDCA/PAC/Nivolumab	-	IIIA N2	EGFRm negative ALK translocation negative	41	2022
5	Mariano Provenci	Phase II	NADIM II NCT03838159	Nivolumab	CBDCA/PAC/Nivolumab	CBDCA/PAC	IIIA-IIIB (resectable N2)	EGFRm negative ALK translocation negative	90	2027
6	Rita Axelrod	Phase II	NCT03366766	Nivoumab	PT-DC/Nivolumab	-	IB (≥4cm)-IIIA	EGFRm negative ALK translocation negative	14	2022
7	Bristol-Myers Squ	Phase III	Checkmate 77T NCT04025879	Nivolumab	PT-DC/Nivolumab	PT-DC/placebo	IIA–IIIB (T3N2	EGFRm negative ALK translocation negative	452	2024
8	Tina Cascone	Phase II	NEOSTAR NCT03158129	Nivoumab	Nivoumab +/- Ipilimumab	CDDP/DOC or PEM/Nivolumab +/- Ipilimumab	I-IIIA	none	88	2022
9	X Mignard	Phase II	IONESCO NCT03030131	Durvalumab	Durvalumab	-	IB-IIB	none	81	2019
10	John Heymach	Phase III	AEGEAN study NCT03800134	Durvalumab	PT-DC/Durvalumab	PT-DC/Placebo	II-III	tumour PD-L1 status Documented EGFR and ALK status	800	2024
11	MedImmune LLC	Phase II	NeoCOAST NCT03794544	Durvalumab	Durvalumab + (Oleclumab or Monalizumab or	Durvalumab	I-IIIA	none	160	2022
12	Sacha Rothschild	Phase II	SAKK 16/14 NCT 02572843	Durvalumab	CDDP/DOC+ durvalumab	-	IIIA(N2)	none	68	2021
13	Hoffmann-La Roc	Phase III	IM power 030 NCT03456063	Atezolizumab	PT-DC/Atezolizumab	PT-DC/Placebo	II, IIIA, IIIB (T3N2)	EGFRm negative ALK translocation negative	374	2025
14	Hoffmann-La Roc	Phase II	NCT02927301 LCMC3	Atezolizumab	Atezolizumab	-	IB-IIIA, selected IIIB	none	180	2024
15	Gustave Roussy	Phase II	PRINCEPS NCT02994576	Atezolizumab	Atezolizumab	-	IB-IIIA Non N2	none	60	2022
16	Bristol-Myers Squ	Phase III	CheckMate 816 NCT02998528	Ipilimumab	PT-DC/Nivolumab or Ipilimumab/Nivolumab	PT-DC	I-IIIA	none	350	2028
17	Chi-Fu Jeffrey Ya	Phase II	TOP1201 NCT01820754	Ipilimumab	CDDP or CBDCA/PAC/Ipilimumab	Safety and Feasibility	II-IIIA	none	13	2018
18	Merck Sharp & D	Phase III	KEYNOTE-671 NCT03425643	Pembrolizumab	PT-DC/Pembrolizumab	PT-DC/Placebo	II-IIIA, IIIB (T3-4N2)	none	786	2026
19	Florian Eichhorn	Phase II	the NEOMUN trial NCT03197467	Pembrolizumab	Pembrolizumab	-	II-IIIA	none	30	2023
20	Peng Zhang	Phase II	Neoadjuvant camrelizumab + apatinib NCT04379739	apatinib	Camrelizumab/Apatinib	PT-DC/Camrelizumab	II-IIIA	Without EGFR, ALK, ROS1 or BRAF gene mutation;	99	2026

No.	Author Investigator	Study Phase	Trial, ID	Agent	Regimen	biological status	Stage	No. Patient	Study Completion Year
1	Monica Bertagnolli	**Phase II**	CHIO3 NCT04062708	Durvalumab	PT-DC/Durvalumab RT 54Gy	-	IIIA-B, N2	55	2024
2	Matthias Guckenberger	**phase II**	CHESS NCT03965468	Durvalumab	CBDCA/PAC/Durvalumab stereotactic body radiotherapy (SBRT)	-	IV Synchronous Oligo-metastases	47	2021
3	Grg A Durm	**phase II**	NCT03871153	Durvalumab	CBDCA/PAC/Durvalumab RT 45-61.2 Gy	-	III (N2)	25	2022
4	Byoung Chul Cho	**phase I, II**	NCT03694236	Durvalumab	PT-DC/Durvalumab RT 45Gy	-	II-IIIA	39	2027
5	Sacha Rothschild	**phase II**	SAKK 16/18 NCT04245514	Durvalumab	CDDP/DOC/Durvalumab +20x2 Gy (weekdaily, 4 weeks) or 5x5 Gy (weekdaily, 1 week) or 3x8 Gy (on alternate days, 1 week)	-	III (T1-4N2)	90	2025
6	Wilfried Eberhardt	**phase II**	ESPADURVA NCT04202809	Durvalumab	PT-DC/Durvalumab RT 45Gy	-	IIIA-B	90	2024
7	Jarushka Naidoo	**phase II**	NCT03237377	Durmarmb/Trememlimumab	Durvalumab +/- Trememlimumab RT	-	IIIA	32	2021
8	Sue Yom	**phase II**	NCT03217071	Pembrolizumab	Pembrolizumab SRT 12Gy	Pembrolizumab monotherapy	I-IIIA	40	2021
9	Tetsuya Mitsudomi	**phase I, II**	SQUAT trial WJOG12119L	Durvalumab	CBDCA/PAC/Durvalmab RT 50Gy	-	IIIA-B, N2	31	2022
10	Chris Dickhoff	**phase II**	the INCREASE trial NL8435	Nivolumab/Ipilimumab	PT-DC/Nivolumab/Ipilimumab RT 50Gy	Without EGFR, ALK, ROS1 or BRAF gene mutation	T3-4N0-1	29	2022