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Review

Perioperative Therapy for Non-Small Cell Lung Cancer with Immune Checkpoint Inhibitors

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Simple Summary: This review presents the development of perioperative treatment using immune checkpoint inhibitors (ICIs) in patients with resectable non-small cell lung cancers. There are several ongoing phase 3 trials for adjuvant and neoadjuvant ICI therapies. Results of adjuvant (IMpower010 trial) and neoadjuvant (Checkmate 816 trial) ICI phase 3 trials have shown prolonged disease-free survival and increased pathological complete response rate, respectively. Based on the hypothesis that 'preoperative ICI treatment, especially in combination with conventional chemotherapy, promotes a higher immune response because of preservation of the immune environment', neoadjuvant trials using a combination of ICI and conventional chemotherapy are currently being conducted more frequently than adjuvant ICI trials. Multimodality approaches using chemoradiotherapy and new ICI agents are also being examined in several phase 2 trials. To maximise ICI therapy's efficacy and minimise futile administration, methodologies for predicting and monitoring the therapeutic effects, such as detecting minimal residual disease, need to be established. (150/150 words)

Abstract: The emergence of immune checkpoint inhibitors (ICIs) has dramatically changed the treatment landscape for patients with metastatic non-small cell lung cancer (NSCLC). These achievements inspired investigators and pharmaceutical companies to conduct clinical trials in patients with early-stage NSCLC because both adjuvant and neoadjuvant platinum-based doublet chemotherapies (PT-DCs) showed only a 5% improvement in the 5-year overall survival. IMpower010, a phase 3 trial (P3), showed that adjuvant PT-DC followed by maintenance atezolitumab significantly prolonged disease-free survival than adjuvant PT-DC alone (hazard ratio, 0.79; stage II to IIIA). Since conventional therapies, including chemotherapy and radiotherapy, can promote immunogenic cell death, which releases tumour antigens from dead tumour cells, ICI combination therapies with conventional therapies are widely proposed. Checkmate 816 trial (P3) indicated a significantly higher pathological complete response rate of neoadjuvant nivolumab/PT-DC combination therapy than neoadjuvant PT-DC alone (odds ratio, 13.9, for stage IB to IIIA). Detection of circulating tumour DNA is highly anticipated for the evaluation of minimal residual disease. Multimodal approaches and new ICI agents are being attempted to improve the efficacy of ICI treatment in phase 2 trials. This review presents the development of perioperative treatment using ICIs in patients with NSCLC while discussing problems and perspectives. (198/200 words)

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Keywords: lung cancer; immune checkpoint inhibitor; perioperative therapy; neoadjuvant therapy; adjuvant therapy (5 keywords/ 3-10 keywords)

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1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide [1]. Only a small fraction of patients can be treated with curative intent. Although surgery offers the best chance for cure, the 5-year overall survival (OS) rates of patients who underwent pulmonary resection are unsatisfactory, with 68%, 60%, 53%, and 36% for pathological stages IB/IIA/IIB/IIIA, respectively [2].

Risk reduction of cancer recurrence, especially for distant recurrence, is essential for patients to achieve long-term survival after surgery. Distant recurrence occurs due to the progression of minimal residual disease (MRD), which is considered to be metastasized cancer cells that are undetectable on imaging studies prior to surgery. The current standard treatment modality for patients with pathological stage II to III non-small cell lung cancer (NSCLC) is adjuvant therapy using platinum-based doublet chemotherapy (PT-DC). However, the lung adjuvant cisplatin evaluation (LACE) meta-analysis of five randomised phase 3 trials reported that adjuvant PT-DC could improve 5-year survival by only 5.4% in patients after complete resection of NSCLC [3].

The advent of immune checkpoint inhibitors (ICIs) targeting programmed cell death-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) has led to a durable response and improved prognosis in patients with metastatic lung cancer [4-6]. In addition, the PACIFIC trial reported that concurrent chemoradiation followed by maintenance therapy of durvalumab, a PD-L1 antibody, prolonged progression-free survival (PFS), and OS. Hence, this regimen has become the standard of care for patients with unresectable stage III NSCLC [7,8]. Thus, the application of ICIs to patients with early-stage lung cancer has been actively pursued. This article summarises the perioperative treatment using ICIs in patients with NSCLC and discusses future perspectives.

2. Current status of perioperative therapy

Evidence for adjuvant chemotherapy using cytotoxic agents has been well established. In 2008, the LACE meta-analysis of five phase 3 trials [3] showed that adjuvant chemotherapy using PT-DC significantly improved OS in completely resected patients with NSCLC (hazard ratio [HR] = 0.89, 95% confidence interval [CI]: 0.82 – 0.96, p = 0.005). Furthermore, a subset analysis showed that adjuvant therapy using PT-DC improved OS in stage II (HR = 0.83; 95% CI: 0.73 – 0.95) and stage III (HR = 0.83, 95% CI: 0.72 – 0.94), but it was determined harmful in stage I NSCLC.

Evidence for the neoadjuvant chemotherapy results, although insufficient compared to adjuvant therapy, through a review and meta-analysis conducted by the NSCLC Meta-analysis Collaborate Group, showed that neoadjuvant chemotherapy followed by surgery for stage I to III NSCLC improved the 5-year OS by 5% (40% – 45%) (HR = 0.87, 95% CI: 0.78 – 0.96, p = 0.007) compared with surgery alone [9].

Limited evidence is available regarding the efficacy of induction CRT followed by surgery. However, the INT0139 study, a phase 3 trial, compared the standard of care radical chemoradiotherapy (CRT) with induction CRT (45 Gy) followed by surgery for pathologically proven cN2 resectable NSCLC [10]. They reported that in an exploratory subset analysis, pneumonectomy after induction CRT was associated with a 26% treatment-related mortality rate and worse OS than radical CRT. In contrast, lobectomy after induction CRT was associated with a 1% treatment-related mortality rate and significantly better OS than radical CRT (median OS, 33.6 vs. 21.7%, p = 0.002).

3. Initiation of clinical trials for perioperative therapy by ICI

ICIs extend the prognosis of patients with metastatic NSCLC [4-6,11-13]. These achievements have encouraged the introduction of immunotherapy as an adjuvant, neoadjuvant, or both for patients with earlier-stage lung cancer.

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Several large-scale phase 3 studies are under way in an adjuvant setting, investigating the efficacy of ICI after complete resection in patients with pathological stage IB to IIIA NSCLC (Table 1). There are currently at least seven phase 3 studies, including five ICI monotherapies and two combination therapies of ICI and conventional chemotherapy, estimated to accrue 5347 patients, in progress.

Recently, the main findings of the IMpower010 trial revealed that adjuvant chemotherapy followed by maintenance with atezolizumab showed significant prolongation of disease-free survival (DFS) in patients with PD-L1 TC ≥1% (per SP 263) stage II to IIIA (HR, 0.66; 95% CI, 0.50 – 0.88) NSCLC [14]. Hierarchical analysis have shown significant prolongation of DFS in patients with all-randomized stage II to IIIA (HR, 0.79; 95% CI, 0.64 – 0.96) and the intention-to-treat population with stage IB to IIIA (HR, 0.81; 95% CI, 0.67 – 0.99). The 3-year DFS rates were 55.7% in patients with all-randomized stage II to IIIA who received maintenance atezolizumab compared with 49.4% in those who did not receive maintenance atezolizumab (p = 0.02). Among patients with all-randomized stage II to IIIA, maintenance atezolizumab administration showed that patients with high PD-L1 expression of TC ≥ 50% (HR 0.43; 95% CI, 0.27 – 0.68) received the highest benefit of DFS. No survival benefit could be observed in patients with PD-L1 expression of TC < 1% (HR, 0.97; 95% CI, 0.72 – 1.31) after maintenance atezolizumab administration.

Table 1 Phase 3 clinical trials of adjuvant therapy using ICIs

Registration #	Trial	Therapy	N	Pretreatment	Experimental arm	Control Arm	Primary endpoint	Stage	Country
NCT02273375	BR.31	ICI mono	1360	Yes/No PT-DC	durvalumab 1 year	Placebo	DFS	pIB to IIIA	Global
NCT02486718	IMpower010	ICI mono	1280	Yes/No PT-DC	atezolizumab 1year	BSC	DFS	pIB to IIIA	Global
NCT02504372	PEARLS/ KEYNOTE-091	ICI mono	1177	Yes/No PT-DC t	pembrolizumab 1 year	Placebo	DFS	pIB to IIIA	Global
NCT02595944	ANVIL	ICI mono	714	Yes/No PT-DC	nivolumab 1 year	Observation	DFS/OS	pIB to IIIA	US
NCT04642469	MeRmaiD-2	ICI mono	284	Yes/No PT-DC	durvalumab	Placebo	DFS in PD-L1 TC>=1%	II to III without positive EGFR/ALK	Global
NCT04385368	MeRmaiD-1	ICI chemo	322	No	durvalumab + standard of care chemotherapy	Placebo + standard of care chemotherapy	DFS	II to III without positive EGFR/ALK	Global
NCT04564157	NADIM-ADJUVANT	ICI chemo	210	No	nivolumab + CBDCA/PTX (4 times) Maintenance: nivolumab (6 times)	Nivolumab + CBDCA/PTX (4 times) Maintenance: Observation	DFS	pIB (>=4 cm) to IIIA	Spain

ICI, immune checkpoint inhibitor; PT-DC, platinum-based doublet chemotherapy; Sq, squamous cell carcinoma, CDDP, cisplatin; PEM, pemetrexed; DTX, docetaxel; CBDCA, carboplatin; PTX, paclitaxel; BSC, best supportive care; DFS, disease-free survival; OS, overall survival; TC, tumor cells; ctDNA, circulating tumor DNA

4. Neoadjuvant vs. adjuvant

There is a possibility that neoadjuvant therapy may control micrometastases in the early phase and offer an opportunity to evaluate drug sensitivity. Thus, it could be used as a guide in determining the postoperative regimen (Figure 1). Adjuvant therapy may or may not be performed under a reduced regimen of drugs if the patients' performance

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status worsens after surgery. Neoadjuvant therapy can be performed with good compliance. However, neoadjuvant therapy may cause increased postoperative complications and treatment-related adverse events (TRAE), leading to delays in surgery or inoperability [15,16].

T cells get activated by recognising the presented tumour antigen. They travel through the lymphatic stream and the bloodstream to the primary and metastatic sites and exert anti-tumour effects. Hence, it has been argued that neoadjuvant ICI therapy may be more effective than adjuvant ICI therapy because lymphatic and blood flow between the tumour and regional lymph nodes are maintained in neoadjuvant, but not in adjuvant therapy [17]. These hypotheses were experimentally examined by comparing neoadjuvant and adjuvant ICI therapies using a mouse subcutaneous tumour transplantation model [18]. Mice treated with neoadjuvant ICI therapy had longer survival than those treated with adjuvant ICI therapy.

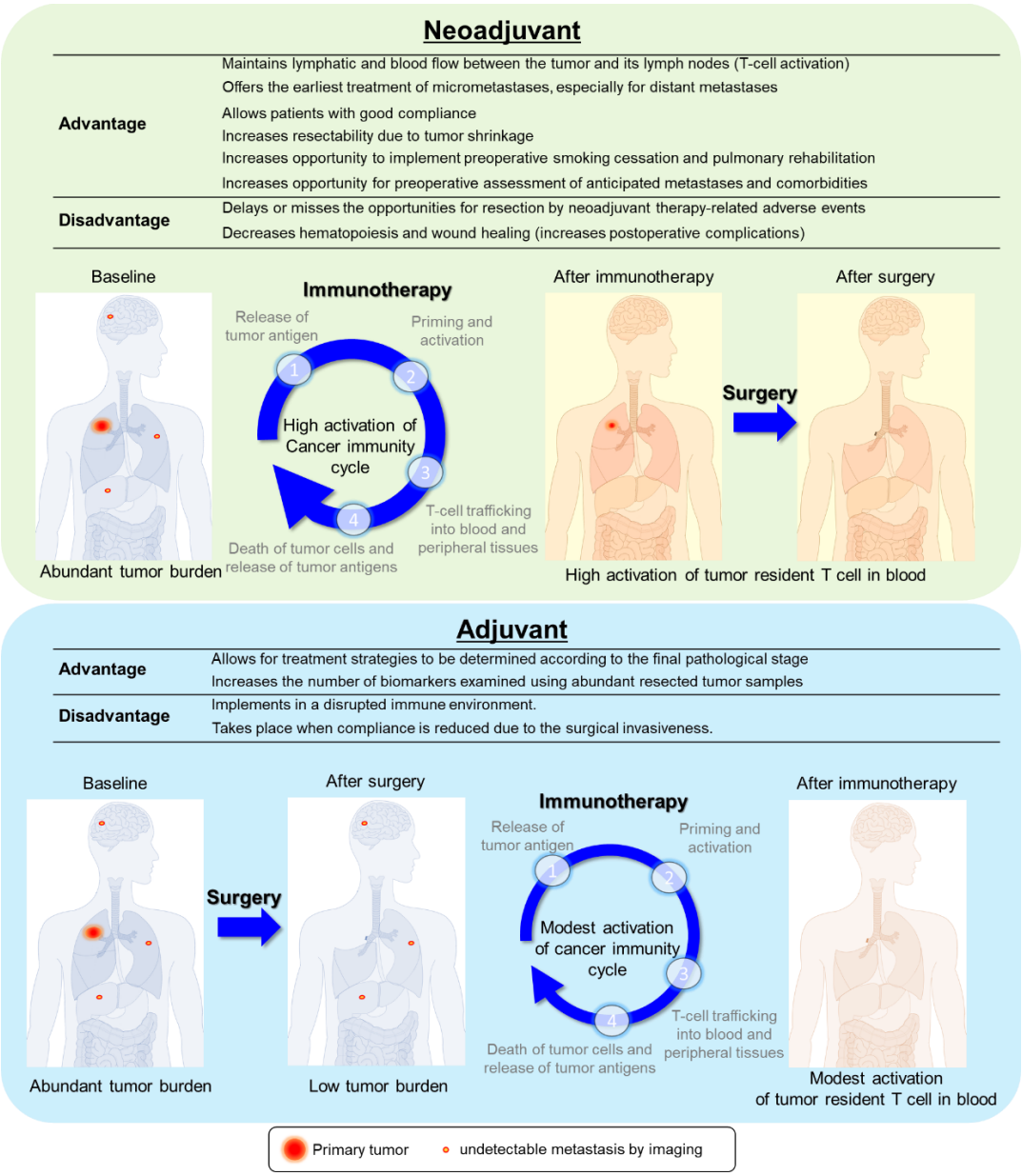

Figure 1 Comparison of neoadjuvant and adjuvant immunotherapies. Neoadjuvant immunotherapy is performed under an abundant tumor burden, which may promote the high activation of cancer immunity (upper panel). In contrast, adjuvant immunotherapy is performed under a low tumor burden, but immunotherapy may induce enough efficacy to control only minimal residual disease (lower panel).

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5. Surrogate or predictive pathological markers of therapeutic effect of ICI

In clinical trials for neoadjuvant and adjuvant therapies, the gold standard for the primary endpoint is OS. DFS and event-free survival (or OS) are generally used as the primary endpoints in clinical trials for adjuvant therapy. Since it takes a long time to obtain the final OS results, it would be challenging to provide a promising novel agent for clinical practice within a short time frame.

The therapeutic effect of neoadjuvant therapy can be evaluated using resected pathological specimens' evaluation, but the correlation between the pathologic response and survival outcome has to be confirmed. Several clinical trials for patients with breast cancer [19 ,20-22] have used the degree of pathologic response, such as major pathologic response (MPR) and pathological complete response (pCR), as primary endpoints. Regarding lung cancers, retrospective studies have shown that significant prognostic improvement is observed in patients who showed MPR after neoadjuvant cytotoxic chemotherapy, where MPR is defined as ≤ 10% of the viable residual tumour [23,24]. Although various methods of assessing MPR have been used, they have not been defined in detail [23-26]. For example, different MPR cut-off values were proposed based on the histological subtypes [27]. In 2020, the International Association for the Study of Lung Cancer published a recommendation for the pathologic assessment of resected specimens after neoadjuvant therapy [28]. Therefore, a standardised approach is recommended to assess the percentages of (1) viable tumour, (2) necrosis, and (3) stroma (including inflammation and fibrosis) with a total adding up to 100% in an approximately 0.5 cm thick cross-section of the primary tumour bed. The definition of MPR is ≤ 10% of viable tumour in the primary tumour bed. This includes the patients harbouring the primary tumour with no viable tumour cells, but with viable metastatic carcinoma in the lymph nodes. pCR is defined as the lack of viable tumour cells after complete evaluation of a resected lung cancer specimen, including all sampled regional lymph nodes.

Since the pathologic response of resected specimens can be assessed only after completion of the surgery, it is essential to establish predictive markers before therapeutic administration in the selection of patients who are expected to benefit and not be harmed from perioperative treatment. PD-L1 expression [29-31] and tumour mutation burden [32] in tumour cells of biopsy samples have been reported as predictive biomarkers for ICI. However, they are not entirely predictive, and it is sometimes challenging to collect sufficient sample volume by a biopsy to examine several kinds of biomarkers.

6. Clinical trials of neoadjuvant mono- or dual ICI therapy

Various clinical trials of neoadjuvant ICI monotherapy or dual ICI therapy are being conducted. Among these trials, the results of five trials have been reported: four trials of ICI monotherapy and one trial of dual ICI therapy (Table 2). The proportion of patients who could not undergo surgery ranged from 0 to 12% in four trials of ICI monotherapy, but 19% in a trial of dual ICI therapy. Complete resection (R0 resection) was achieved in more than 90% of the patients. The MPR ranged from 21% to 45% in all trials in which more than two doses of ICI were scheduled. However, none of the patients showed an MPR in the PRINCEPS trial, in which only one dose of atezolizumab was administered [33].

The NEOSTAR trial is a randomised phase 2 trial of nivolumab monotherapy (the nivolumab arm) or nivolumab plus ipilimumab (the nivolumab plus ipilimumab arm) followed by surgery in patients with clinical stage I to IIIA NSCLCs [34]. The incidence of TRAEs of ≥ G3 was equivalent between the two arms (13% in the nivolumab arm vs. 10% in the nivolumab plus ipilimumab arm). However, the MPR and pCR were more prevalent in the nivolumab plus ipilimumab arm than in the nivolumab arm: 38% vs. 22% and 29% vs. 9%, respectively (not statistically significant).

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Table 2 Results of clinical trials using neoadjuvant ICI-mono or -dual therapy

Registration #	Trial & Stage	Neoadjuvant therapy	N (Plan)	N (reported)	Delay of surgery (%)	Failure to surgery (%)	R0 resection (%)	TRAE (>=G3) (%)	MPR (%)	pCR (%)	Survival	Status	Ref
NCT02259621	Johns Hopkins Univ. (p2) IB (>4cm) to IIIA	nivolumab (twice)	30	22	0	0	95	Preope: 4.5	45	15	Median RFS: NR 18mRFS: 73%	On going	[35]
NCT02927301	LCMC3 (p2) IB to IIIA, IIIB (T3N2, T4(size))	atezolizumab (twice)	180	181	12	12	92	Preope: 6 Postope: 14	21	7	1y DFS: 85% 1y OS: 95%	On going	[36]
NCT02994576	PRINCEPS (p2) IA(>=2cm) to IIIA(non-N2)	atezolizumab (once)	60	30	0	0	97	0	0	No data	No data	On going	[33]
NCT03030131	IONESCO (p2) IB to IIIA	durvalumab (3 times)	81	46	No data	0	90	ICI-related: 0 (Death:9)	No data	No data	Median OS/DFS: NR/NR 18m OS/DFS: 89%/70%	Terminated (mortality*)	[37]
NCT03158129	NEOSTAR (p2) I to IIIA	nivolumab (3 times) or nivolumab (3 times) +ipilimumab	44	44	22	Nivo: 4 N+I: 19	100	Nivo: 13 N+I: 10	Nivo: 22 N+I: 38	Nivo: 9 N+I: 29	Median OS/RFS: NR/NR	On going	[34]

p2, phase 2; Nivo, nivolumab; Ipi, ipilimumab; R0 resection, complete resection; TRAE, treatment-related adverse event; MPR, major pathologic response; pCR, pathological complete response; RFS, recurrence-free survival; OS, overall survival; DFS, disease-free survival; NR, not reached; N+I, nivolumab+ipilimumab; *, an excess in 90-day post-operative mortality (4 deaths, 9%)

7. Clinical trials for ICI combination therapy with chemotherapy or chemoradiotherapy

Tumours lacking an immune response are known as 'cold tumours'. Conventional therapies, such as chemotherapy and radiation therapy, are known to turn 'cold tumours' into 'hot tumours' with immune responses elicited by the tumour antigens released from cancer cell deaths (i.e., immunogenic cell death), thus increasing the therapeutic effects of ICI [38].

Various neoadjuvant ICI combination therapies have been widely proposed (Table S1). Phase 2 trials and phase 3 trials are exploring combination therapies against conventional chemotherapy or ICI monotherapy. Results of the phase 3 trial of Checkmate 816 recently reported that the proportions of failure to surgery, R0 resection, and TRAE of ≥ G3 were equivalent between the combination therapy of nivolumab plus PT-DC and the PT-DC alone (16% vs. 21%, 83% vs. 78%, and 19% and 21%, respectively.) Nevertheless, the MPR and pCR rates were significantly higher in the combination therapy of nivolumab plus PT-DC than in the PT-DC therapy alone: 36.9% vs. 8.9% ($p < 0.0001$), and 24% vs. 2.2% ($p < 0.0001$), respectively [39] (Table 3). Survival data of this phase 3 trial are not currently available.

A phase 2 NCT03480230 trial exploring the combination therapy of PT-DC with avelumab was terminated because of the low response rate (Table 3). In the other phase 2 trials, the proportion of patients who could not successfully undergo surgery ranged from 3% to 27%, and R0 resection was achieved in 87%–100% of the patients. The MPR could

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be achieved in 57%–83% of the patients, and TRAE of ≥ G3 was observed in > 27% of patients. The results of the NADIM trial exploring the neoadjuvant combination therapy of carboplatin/paclitaxel plus nivolumab before surgical resection followed by adjuvant nivolumab showed favorable PFS of 95.7% and 77.1% at 1 and 2 years, respectively [40].

The 'abscopal effect', which is the effect of ionizing radiation 'at a distance from the irradiated volume. but within the same organism', was first reported in 1953 [41]. This phenomenon was revealed to be immune-mediated [42], and has been observed in combination therapy trials when ICIs are administered sequentially or concurrently with radiotherapy [43]. The PACIFIC trial examined the benefits of durvalumab maintenance therapy after concurrent CRT [8]. The results showed that durvalumab maintenance therapy significantly prolonged both PFS (median PFS, 17.2 vs. 5.6 months, HR = 0.51, with 95% CI: 0.41 – 0.63) [7] and OS (median OS, not reached vs. 29.1 months, HR = 0.69, 95% CI: 0.55 – 0.86) [44], indicating the usefulness of sequential ICI therapy after CRT.

Several multimodal approaches, in which radiotherapy is added to a combination therapy of ICI and conventional chemotherapy, have been used to improve treatment effects (Table S1) further. Interim analysis of a phase 2 trial exploring a multimodality therapy using durvalumab, PT-DC, and radiotherapy (45 Gy) (NCT03694236) indicated high MPR and pCR rates of 72.7% and 36.4%, respectively, along with a relatively low rate of TRAE of ≥ G3 (7%) [45] (Table 3). We are also conducting a multicentre, prospective, single-arm, phase 2 trial of neoadjuvant concurrent chemo-immuno-radiation therapy (carboplatin plus paclitaxel and durvalumab with radiation therapy 50 Gy) followed by surgical resection and adjuvant immunotherapy for resectable stage IIIA-B (discrete N2) NSCLC (WJOG12119L: SQUAT trial) (Japic-CTI-195069) [46] (Table S1).

Table 3 Early results of clinical trials of neoadjuvant therapy of combination regimens of ICIs

Registration #	Trial & Stage	Neoadjuvant therapy	N (Plan)	N (reported)	Delay of surgery (%)	Failure to surgery (%)	R0 resection (%)	TRAE (>=G3) (%)	MPR (%)	pCR (%)	Survival	Status	Ref
NCT02998528	Checkmate 816 (p3) IB to IIIA	Nivolumab +PT-DC vs. PT-DC	358	358	21 vs. 18	16 vs. 21	83 vs. 78	G3-4: 19 vs. 21	36.9 vs. 8.9 (p<0.0001)	24 vs. 2.2 (p<0.0001)	No data	On going	[39]
NCT02716038	Columbia Univ. (p2) IB to IIIA	atezolizumab +CBDCA /Nab-PTX	30	30	0	3	87	>=50	57	33	Median OS/DFS: NR/17.9m	On going	[47]
NCT02572843	SAKK16/14 (p2) IIIA(pN2)	durvalumab +CDDP/DTX	68	68	No data	19	No data	Any: 88.1	60	18.2	Median OS/EFS: NR/NR 1y EFS: 73.3%	On going	[48]
NCT03081689	NADIM (p2) IIIA(pN2)	nivolumab +CBDCA/PTX	46	46	0	11	100	30	83	63	Median PFS/OS: NR/NR 1y PFS:95.7% 2y PFS:77.1%	On going	[40]
NCT03480230	American Univ. of Beirut Medical Center (p2) II or IIIA	avelumab +PT-DC	60	15	No data	27	No data	27	No data	9	Median OS/RFS: NR/NR	Terminated (lower response*)	[49]
NCT03694236	Yonsei Univ. (p2)	durvalumab +CBDCA/PTX +RT 45Gy	39	14	No data	8	100	7	72.7	36.4	No data	On going	[45]

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III(N2)

R0 resection, complete resection; TRAE, treatment related adverse event; MPR, major pathologic response; pCR, pathological complete response; p3, phase 3 ; p2, phase 2; PT-DC, platinum-based doublet chemotherapy; CBDCA, carboplatin; PTX, paclitaxel; CDDP, cisplatin; DTX, docetaxel; RFS, recurrence-free survival; OS, overall survival; DFS, disease-free survival; NR, not reached; *, one radiological complete response and three partial responses were observed among the first 15 enrolled patient, but the minimum of six responses needed to continue to phase 2 of the study.

The results of the clinical trials of ICI mono- and dual therapies (Table 2) and ICI combination therapy (Table 3) suggested that the proportions of delay of surgery, failure of surgery, and complete resection were equivalent between ICI mono-/dual therapies and ICI combination therapy. In addition, although the TRAE of ≥ G3 was frequent in ICI combination therapy (19% to ≥ 50%) than in ICI mono-/dual therapies (0 – 14%), the MPR and pCR may increase in ICI combination therapy (37 to 83% and 9 to 63%, respectively) than in ICI monotherapy (0 to 45% and 7 to 15%, respectively).

8. Identification and monitoring of MRD

An attempt has been made to verify the progression and prognosis of cancer by quantifying tumour cells and tumour-derived DNA released into the blood (liquid biopsy) [50]. Quantification of circulating tumour DNA (ctDNA) is expected to be an accurate determinant of the indications for perioperative treatment [51,52]. Since blood sample collection is relatively easy, repetitive assessment is acceptable for detecting disease progression and therapeutic effects. Of note, the Checkmate 816 trial showed that ctDNA clearance was more frequent in patients who received neoadjuvant nivolumab plus PT-DC (56%) than in the neoadjuvant PT-DC alone group (34%). Additionally, patients with ctDNA clearance showed higher pCR rates than patients without ctDNA clearance in both treatment groups: 46% vs. 0% in the nivolumab plus PT-DC group, respectively, and 13% vs. 3% in PT-DC alone group, respectively [39].

The MeRmaiD-2 trial enrolled patients with stage II – III NSCLC who had completed curative-intent therapy (complete resection plus optional neoadjuvant and/or adjuvant therapy) during a 96-week surveillance period (Table 1 and Figure 2, NCT04642469) [53]. During this surveillance period, patients were monitored regularly for MRD emergence via ctDNA analysis using personalised MRD panels. Eligible patients who confirmed the presence of MRD were randomised 1:1 to receive durvalumab or placebo.

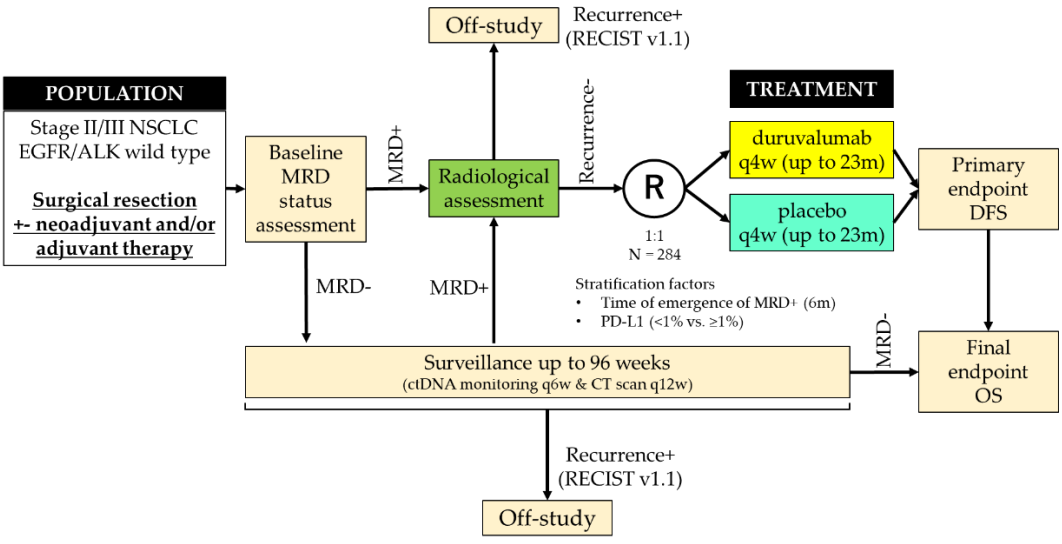

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Figure 2 Study design of MeRmaiD-2 trial (modified from the presentation of Spigel et al. [53])

9. New ICI agents

Several new ICI agents are being examined in phase 2 trials as neoadjuvant ICI combination therapy (Table 4). Relatlimab is a monoclonal antibody for lymphocyte activation gene 3, which negatively regulates T lymphocytes by binding to the extracellular domain of the ligand [54]. Oleclumab is an antibody against 5'-nucleotidase ecto, also known as CD73, which binds to CD73 and inhibits the production of immunosuppressive adenosine [55]. Monalizumab is an inhibitor of CD94/NK group 2 member A, an immune checkpoint molecule expressed on tumour-infiltrating cytotoxic T cells and natural killer cells [56]. Tiragolumab is a new immune checkpoint inhibitor blocking the interaction between T-cell immunoreceptors with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) and CD155 (RVR) [57]. Canakinumab is a monoclonal antibody that neutralises IL-1β activity by blocking its interaction with the IL-1 receptor expressed on activated cytotoxic T cells and Tregs [58]. Although canakinumab is a cancer immunotherapy drug (immunomodulator), but not ICI, a phase 2 trial, Canopy-N, is under way to explore a neoadjuvant monotherapy of canakinumab and combination therapy with pembrolizumab in patients with stage IB to IIIA NSCLC (non-N2 or T4) [59].

Table 4 Clinical neoadjuvant trials using new ICI agents

Registration #	Trial	Therapy	Phase	N	Stage	New agents	Experimental arm	Primary endpoint	Country
NCT04205552	NEO-predict-Lung	ICI dual	2	60	IB to selected IIIA	relatlimab	Arm A: nivolumab(twice) Arm B: nivolumab +relatlimab (twice)	Feasibility	Belgium/ Germany/ Netherlands
NCT03794544	Neo-COAST	ICI dual	2	80	I (>2cm) to IIIA (single N2 =<3cm)	oleclumab monalizumab	Arm A: durvalumab Arm B: durvalumab +oleclumab Arm C: durvalumab +monalizumab Arm D: durvalumab +danvatirsen	MPR	Global (Western Countries)
NCT04832854	GO42501	ICI dual +Chemo	2	82	II to IIIB(T3N2)	tiragolumab	PD-L1 high: Atezolizumab +tiragolumab (4times) PD-L1 All comers: Atezolizumab +tiragolumab +PT-DC (4times)	1.Surgical delays, 2.Complications, 3.Cancellations of surgery, 4.AE, 5. MPR	US Spain Switzerland
NCT03968419	CANOPY-N	ICI + IM	2	110	IB to IIIA (non-N2 nor T4)	canakinumab	Arm A: canakinumab Arm B: canakinumab +pembrolizumab Arm C: pembrolizumab	MPR	Global

ICI, immune checkpoint inhibitor; IM, immunomodulator; MPR, major pathologic response; AE, adverse event; danvatisen, a signal transducer and activator of transcription 3 (STAT3) transcription factor inhibitor.

10. Future perspectives

Several phase 3 trials using ICI in the preoperative, postoperative, and both settings are being conducted. The primary results are promising for the efficacy of the introduction of ICI in the perioperative phase. The final results of these trials may have a significant impact on the treatment strategies for patients with resectable NSCLC. In addition, the usefulness of ctDNA-based monitoring for MRD should also be substantiated by phase 3

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trials to identify patients who genuinely need perioperative therapy with ICI. This approach may provide better clinical outcomes by intensifying the treatment for patients with a high probability of relapse and avoiding unnecessary administration of additional adjuvant chemotherapy (Figure 3).

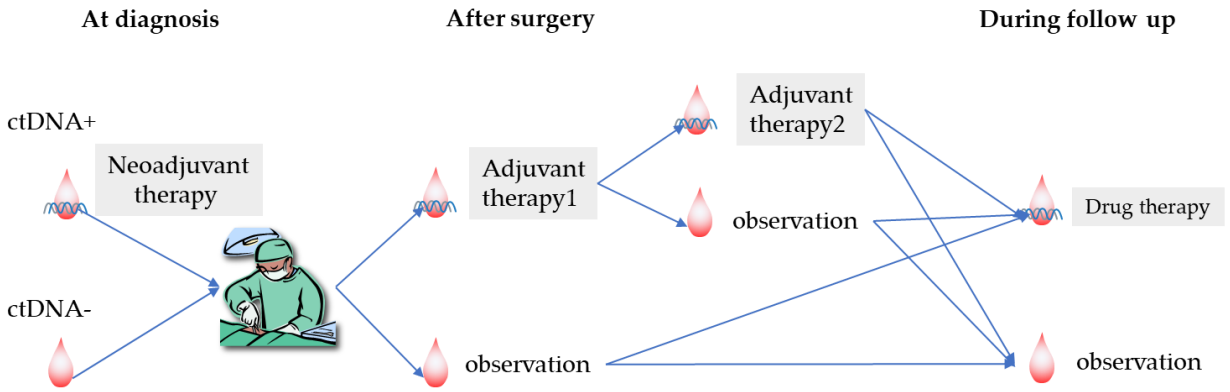

Figure 3 ctDNA guided perioperative management in the future

This figure demonstrates a future perioperative treatment strategy for patients with resectable NSCLC according to the assessment of minimal residual disease using circulating tumor DNA (ctDNA).

However, there are several concerns associated with ICI-containing therapies, including optimisation of ICI administration methods (dosage, dose interval, dose frequency), optimisation of combination therapies (appropriate regimen and administration methods), and improved management of ICI-related side effects. These issues should be addressed in basic research and clinical trials. Aggregation of these results would significantly enhance the clinical outcomes of patients with resectable NSCLC.

(4366 words including main text and tables)

(Approximately 4000 words at a minimum of main text)

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Table S1 Clinical trials of neoadjuvant therapy using combination regimens of ICIs (phase 2/3)

Registration #	Trial	Therapy	Phase	N	Stage	Experimental arm	Control arm	Primary endpoint	Country
NCT02998528	Checkmate 816	ICI +chemo	3	358	IB to IIIA	nivolumab+PT-DC	PT-DC	EFS/pCR	Global
NCT03425643	KEYNOTE-671	ICI +chemo	3	786	II to IIIB(N2)	pembrolizumab+PT-DC +adjuvant pembrolizumab	placebo +PT-DC	EFS/OS	Global
NCT03456063	IMpower030	ICI +chemo	3	450	II to IIIB(T3N2)	atezolizumab+PT-DC	placebo +PT-DC	EFS	Global
NCT03800134	AEGEAN	ICI +chemo	3	800	II to III	durvalumab+PT-DC	placebo +PT-DC	MPR/EFS	Global
NCT04025879	Checkmate 77T	ICI +chemo	3	452	IIA(>4cm) to IIIB(T3N2)	nivolumab+PT-DC +adjuvant nivolumab	placebo +PT-DC	EFS	Global
NCT02716038	Columbia Univ.	ICI +chemo	2	30	IB to IIIA	atezolizumab +CBDCA/Nab-PTX(4times)	N/A	MPR	US
NCT02572843	SAKK16/14	ICI +chemo	2	68	IIIA(pN2)	durvalumab +CDDP/DTX (twice)	N/A	EFS	Switzerland
NCT03081689	NADIM	ICI +chemo	2	46	IIIA(pN2)	nivolumab +CBDCA/PTX (3times) +adjuvant nivolumab	N/A	PFS	Spain
NCT03366766	Thomas Jefferson Univ.	ICI +chemo	2	14	I(>=4cm) to IIIA	non-SQ: nivolumab +CDDP/PEM (3times) SQ: nivolumab +CDDP/GEM (3times)	N/A	MPR	US
NCT03480230	American Univ. of Beirut Medical Center	ICI +chemo	2	60	II or IIIA	avelumab+PT-DC (twice)	N/A	ORR	Jordan/ Lebanon
NCT03838159	NADIMII	ICI +chemo	2	90	IIIA, IIIB(T3N2)	nivolumab +CBDCA/PTX (3times) +adjuvant nivolumab	CBDCA/PTX +observation	pCR	Spain
NCT04326153	Jilin University	ICI +chemo	2	40	IIIA	sintilimab +CBDCA/albuminPTX (twice)	N/A	2-year DFS	China
NCT04061590	Univ. of California	ICI +chemo	2	84	I to IIIA	Arm A: pembrolizumab (twice) Arm B: pembrolizumab +CDDP/PEM (twice)	N/A	% of >=2-fold TIICs in post- vs. pre-treatment specimens	US
NCT03217071	Univ. of California	ICI +CRT	2	12	I to IIIA	pembrolizumab (twice) +/- SRT 12Gy	N/A	% of >=2-fold infiltrating CD3+ T cells from baseline	US
NCT03237377	Johns Hopkins Univ.	ICI +CRT	2	32	III	durvalumab+RT 45Gy durvalumab +tremelimumab +RT 45Gy	N/A	Toxixities /Feasibility	US Canada
NCT03871153	HCRN LUN17-321	ICI +CRT	2	25	T1-4N2M0	durvalumab +CBDCA/PTX (3times) +RT 45-61.2Gy	N/A	pCR	US
NCT04202809	ESPADURVA	ICI +CRT	2	90	IIIA to IIIB	durvalumab +CDDP/DTX +RT 45Gy +adjuvant durvalumab	CRT	PFS	Germany
NCT04245514	SAKK16/18	ICI +CRT	2	90	T1-3&4(>7cm)N2M0	durvalumab +CDDP/DTXl (once) +RT: 20x2Gy(4w), 5x5Gy(1w), or 3x8Gy (1w)	N/A	EFS	Switzerland

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NCT03694236	Yonsei Univ.	ICI +CRT	1/2	39	III(N2)	durvalumab +CBDCA/PTX +RT 45Gy	N/A	pCR	Korea
Japic-CTI-195069	WJOG12119L: SQUAT trial	ICI +CRT	1/2	31	IIIA(pN2)	durvalumab +CBDCA/PTX +RT 45Gy	N/A	MPR	Japan

ICI, immune checkpoint inhibitor; CRT, chemoradiotherapy; PT-DC, platinum-based doublet chemotherapy; CBDCA, carboplatin; PTX, paclitaxel; CDDP, cisplatin; DTX, docetaxel; PEM, pemetrexed; SRT, stereotactic radiotherapy; N/A, not applicable; EFS, event-free survival; OS, overall survival; MPR, major pathologic response; PFS, progression-free survival; ORR, overall response rate; pCR, pathological complete response; DFS, disease-free survival; TIIC, tumor-infiltrating immune cells