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REVIEW

CANCER INNOVATION

Adjuvant and neo-adjuvant immunotherapy in resectable non-small cell lung cancer (NSCLC): Current status and perspectives

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Abstract

Surgery followed by adjuvant chemotherapy is the standard of care for selected patients with early-stage or locally advanced non-small cell lung cancer (NSCLC). However, many of these patients still experience postoperative recurrence at 5 years. At present, peri-operative treatment methods are emerging to prevent early relapse, such as targeted therapy and immunotherapy. Investigation on predictive biomarkers of responses to adjuvant and neoadjuvant therapies is also continuously ongoing. Immunotherapy represented by immune checkpoint inhibitors (ICIs), either by monotherapy or in combination with chemotherapy, has shown benefit in promoting pathological responses and prolonging survival for patients with NSCLC without oncogenic mutations. Exploratory studies have also provided evidence regarding the selection of patients who benefit from ICI-based perioperative treatment. This review focuses on the existing data of current clinical trials of adjuvant and neoadjuvant strategies with ICIs in resectable NSCLC, the exploration of predictive biomarkers, and the perspectives and urgent challenges in the future.

KEYWORDS
biomarker, peri-operative immunotherapy, resectable NSCLC

Abbreviations: 18F-FDG PET-CT, Fluorine-18-fluorodeoxyglucose positron emission tomography-computed tomography; BSC, best supportive care; CI, confidence interval; CR, complete response; ctDNA, circulating tumor DNA; DFS, disease-free survival; EFS, event-free survival; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; ICIs, immune checkpoint inhibitors; LCMC, Lung Cancer Mutation Consortium; MPR, major pathological response; MRD, molecular residual disease; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; pCR, complete pathological response; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PR, partial response; RFS, recurrence-free survival; SAKK, Swiss cooperative group for Cancer Research; TC, tumor cell; TCR, T-cell receptor; TMB, tumor mutation burden; TME, tumor microenvironment; TPS, tumor proportion score.

1 | BACKGROUND

Lung cancer is the leading cause of cancer-related death worldwide [1], and non-small cell lung cancer (NSCLC) is the most common type, which accounts for around 85% of lung cancer diagnosis [2]. A large amount of patients are diagnosed with advanced or metastatic NSCLC at the time of diagnosis, and only approximately 25% of these patients have localized disease [3]. The standard strategy for patients with resectable NSCLC is surgery followed by adjuvant platinum-based chemotherapy, which yields an overall survival (OS) advantage of 5% at 5 years [4, 5]. Nevertheless, approximately 50% of patients with Stage II and more than 60% of patients with Stage IIIA disease die within 5 years, despite the standard postoperative chemotherapy [6]. Therefore, exploring novel therapies and treatment strategies is urgently required to reduce the risk of recurrence and to improve the survival of resectable NSCLC. An example of required therapy is that, in patients with epidermal growth factor receptor (*EGFR*)-mutant NSCLC, adjuvant-targeted therapy would prolong disease-free survival (DFS) after complete resection, which could provide a promising strategy for this subset of the population [7]. However, in those without oncogene mutations, feasible perioperative strategies still require further exploration.

Neoadjuvant treatment is also considered as a potential approach to improve survival in patients with resectable NSCLC, with down-staging of the tumor and early control of micrometastases. However, the benefit of preoperative chemotherapy is limited. A meta-analysis showed an absolute 5% survival benefit at 5 years in patients with Stage IB–IIIA NSCLC compared with surgery alone [8], with no significant difference in the survival rate between preoperative and postoperative chemotherapy [9]. The application of blocking antibodies against programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1), named immune checkpoint inhibitor (ICI) therapy, has revolutionized the treatment of advanced NSCLC without driver gene mutations. Research has shown that ICI monotherapy or ICI in combination with chemotherapy prolongs survival in a subset of patients with advanced NSCLC [10, 11]. This finding has led to a growing interest in evaluating the efficacy and safety of ICIs as a setting of adjuvant and neoadjuvant therapy for resectable NSCLC without driver gene mutations. Preclinical model analysis has indicated an improved therapeutic efficacy of neoadjuvant compared with adjuvant immunotherapy to eradicate distant metastases, with increased tumor-specific CD8 + T cells in peripheral blood and organs, predicting long-term survival following surgery [12]. Despite the potential feasibility of neoadjuvant or adjuvant immunotherapy in resectable NSCLC shown in multiple trials [13, 14], the efficacy varies in subpopulations. This has resulted in a major pathological response (MPR) rate of 33%–85%, and a complete pathological response (pCR) rate of 10%–71%. Defining patients who could benefit from neoadjuvant immunotherapy by exploring the predictive factors of the treatment strategy is urgently required.

Current studies searching for biomarkers to predict the efficacy of neoadjuvant and adjuvant immunotherapy, and long-term survival are still on-going. Investigations of changes in biomarkers in tissue or in peripheral blood before and after neoadjuvant treatment help to comprehensively determine the course of disease and the efficacy of agents. Predictive factors include the expression levels of PD-L1, tumor mutation burden (TMB), circulating tumor DNA (ctDNA), specific mutant gene pathways, and tumor microenvironment (TME)-related biomarkers. Because liquid biopsy is noninvasive and widely used, the detection of biomarkers in peripheral blood has been the focus of attention. In this study, we reviewed (1) existing clinical data from emerging immunotherapy trials in neoadjuvant and adjuvant settings, and (2) biomarkers that could affect the efficacy and survival in patients with resectable NSCLC who receive neoadjuvant and adjuvant immunotherapy.

2 | MATERIALS AND METHODS

Multiple searches were performed in PubMed only in the English language from inception to September 2022 for clinical trials that included neoadjuvant or adjuvant immunotherapy in resectable NSCLC. Search terms included “early-stage NSCLC”, “neoadjuvant immunotherapy”, “adjuvant immunotherapy”, and “biomarker”. Moreover, ClinicalTrials. gov was searched by inserting the words “neoadjuvant immunotherapy in NSCLC” and “adjuvant immunotherapy in NSCLC”. In this review, we decided to cite the most relevant studies after an accurate screening, including completed trials with available results.

3 | CLINICAL TRIALS THAT INCLUDED ADJUVANT AND NEOADJUVANT IMMUNOTHERAPY IN PATIENTS WITH RESECTABLE NSCLC

3.1 | Neoadjuvant immunotherapy in resectable NSCLC

The benefit of neoadjuvant therapy has been investigated and reported, including a reduction in tumor size and an increased rate of R0 resection. The MPR and pCR rates

were found to be promising surrogate endpoints for long-term survival in studies of neoadjuvant therapy [15, 16]. An MPR is usually defined by ≥90% tumor necrosis in the surgical specimen, and a pCR is defined as no viable tumor cells found in the resected samples. A randomized Phase 3 study showed that the pCR and MPR rates were associated with improved event-free survival (EFS) with neoadjuvant ICI-based therapy, and the depth of pathological regression also appeared to be predictive of improved EFS [17]. Other endpoints include recurrence-free survival (RFS), EFS, and the objective response rate (ORR). Multiple studies have shown a favorable safety profile and durable antitumor responses of ICI therapy compared with standard platinum-based chemotherapy [18, 19]. Therefore, ICI monotherapy was then initially designed in a neoadjuvant setting in preliminary Phase I/II studies. We review the most representative data, such as the CheckMate159 trial, Lung Cancer Mutation Consortium (LCMC) 3 study, and NEOSTAR study (Table 1).

CheckMate159 was one of the first pilot studies that investigated the efficacy and safety of neoadjuvant ICI monotherapy in patients with Stage I–IIIA (AJCC version 7) resectable NSCLC [20]. The PD-1 inhibitor nivolumab was administered at a dose of 3 mg/kg of body weight every 2 weeks for 1–2 cycles, approximately 4 weeks before the planned surgery. This trial showed an MPR of 45% (9/20 resected tumors, 95% confidence interval [CI]: 23%–68%). The radiological response rate was not completely parallel to pathological responses, with an ORR of 10%. Newly released data showed no correlation between the MPR and RFS, although at a median follow-up of 30 months, RFS was not matured (with only five recurrent events out of 20 patients) and the 24-month RFS rate was 69% (95% CI: 51%–93%) [21]. No treatment-related surgical delays or any previously unreported toxic events were reported, indicating a favorable safety profile [20]. Another trial, ChiCTR-OIC-17013726, which evaluated the safety of neoadjuvant PD-1 inhibitors as the primary endpoint, reported that 52.5% (21/40) of enrolled patients had treatment-related adverse events after two doses of sintilimab [22]. Only 10.0% (4/40) of patients experienced Grade 3 or higher treatment-related adverse events, and one patient had Grade 5 treatment-related adverse event, which indicated that neoadjuvant sintilimab was well tolerated. In this study, the MPR rate was 40.5% in 37 patients who underwent R0 resection, which was also promising [22].

LCMC3 was a Phase 2 study of the neoadjuvant PD-L1 inhibitor atezolizumab in patients with Stage IB–IIIB NSCLC (AJCC version 7) in whom two cycles of atezolizumab 1200 mg every 3 weeks was administered before surgery [23]. In a preliminary study, the MPR rate

TABLE 1 Representative and ongoing trials of neoadjuvant immunotherapy or chemoimmunotherapy for resectable NSCLC.

Trial name/NCT number	Phase	Stage	Treatment	Sample size	MPR	pCR
CheckMate159 (NCT02259621)	I	I-IIIA	Nivolumab	22	45%	10%
LCMC3 (NCT02927301)	II	IB-IIIA	Atezolizumab	101	20.4%	6.8%
NEOSTAR (NCT03158129)	II	I-IIIA	Nivolumab ± ipilimumab	44	24% versus 50%	10% versus 38%
NADIM (NCT03081689)	II	IIIA	Nivolumab + carboplatin/paclitaxel	46	83%	63%
NADIM II (NCT03838159)	II	IIIA	Nivolumab + carboplatin/paclitaxel	87	52%	36.2%
SAKK 16/14 (NCT02572843)	II	IIIA	Durvalumab + cisplatin/docetaxel	67	62%	18%
CheckMate816 (NCT02998528)	III	IB-IIIA	Nivolumab + platinum-doublet chemotherapy/ platinum-doublet chemotherapy alone	358	36.9% versus 8.9%	24% versus 2.2%
HCRN LUN17-321 (NCT03871153)	II	III	Durvalumab + carboplatin/paclitaxel + radiation	25	Not reported	Not reported
NCT04061590	II	I-IIIA	Pembrolizumab + cisplatin/pemetrexed	NA	Not reported	Not reported
IMpower030 (NCT03456063)	III	II–IIIB	Atezolizumab + platinum-based chemotherapy	453	Not reported	Not reported

Abbreviation: NSCLC, non-small cell lung cancer.

was 20.4% (30/147 patients without *EGFR/ALK* mutations; 95% CI: 14%–28%) and the pCR rate was 6.8% (10/147; 95% CI: 3%–12%) [23]. The presurgery ORR (RECISTv1.1) was 7% [24], which did not reflect the MPR rate, similar to the results from the CheckMate159 study. The NEOSTAR study was a Phase 2 trial of neoadjuvant nivolumab or nivolumab plus ipilimumab in patients with Stage IA–IIIA NSCLC (AJCC version 7) [25]. An MPR rate of 22% and a pCR rate of 10% (2/21) was observed in 21 (5/21) patients who received R0 resection in the nivolumab arm. The ORR was 19% with nivolumab (4/21 complete response [CR]/partial response [PR]), and was positively associated with the pathological tumor response. Notably, some patients with radiographical stable disease also achieved marked pathological regression, similar to all patients with a CR/PR, which indicated that radiographical assessment might not comprehensively reflect tumor regression. This study also showed higher MPR and pCR rates, and less viable tumors in resected specimens in the nivolumab + ipilimumab arm than with nivolumab alone. Therefore, PD-1 inhibitor-based neoadjuvant therapy is promising and merits further investigation on the combination strategies for patients with operable NSCLC.

3.2 | Neoadjuvant chemoimmunotherapy in resectable NSCLC

Preclinical studies have shown that chemotherapy may work synergically with ICIs in promoting antitumor responses [26]. The mechanistic rationale is that chemotherapy inhibits the proliferation of tumor cells and also exerts immunostimulatory effects by increasing T-cell infiltration or reducing the immunosuppressive tumor microenvironment [27]. The efficacy of combining immunotherapy and standard chemotherapy has been shown by multiple prospective Phase 3 trials in advanced or metastatic NSCLC, with an ideal response rate in patients, regardless of PD-L1 expression levels [11, 28]. The strategy of chemoimmunotherapy is more promising for a larger population, with a controllable safety profile, than ICI monotherapy which benefits a subset of patients with high PD-L1 expression [10, 29]. Phase 1–2 studies have shown that monotherapy of neoadjuvant ICI has an encouraging MPR, which varies from 14% to 40.5% [22, 30]. Additionally, the combination of chemotherapy and an ICI in the neoadjuvant setting is emerging as a novel strategy. The efficacy outcomes from the Phase 2 NADIM study, Swiss cooperative group for Cancer Research (SAKK) 16/14 study, and phase 3 CheckMate 816 study are shown in Table 1.

The NADIM trial assessed the safety and feasibility of the neoadjuvant nivolumab plus paclitaxel-carboplatin regimen for three cycles before resection, followed by adjuvant treatment with nivolumab until month 12, in 46 patients with stage IIIA (AJCC version 7) NSCLC [31]. The ORR was 76% in 46 patients (2 CRs and 33 PRs), and the progression-free survival (PFS) rate at 24 months was 77.1%. A total of 89% (41/46) of the study population underwent R0 resection, without any treatment interruption or delay in surgery, and an MPR was achieved in 83% (34/41) of patients, and a pCR was achieved in 63% of patients (26/41). Long-term follow-up has also shown a consistent benefit in survival [32, 33]. Notably, the 24-month PFS rate was 88.4% in 34 patients who achieved an MPR/pCR, 96.2% in 26 who achieved a pCR, and 57.1% in patients with an incomplete pathological response. A significant difference was identified in PFS and OS between patients with a pCR and those with an incomplete pathological response, but not between patients with an MPR and those with an incomplete pathological response [32]. This finding indicated the importance of increasing the proportion of patients with resectable NSCLC who achieve a pCR.

The NADIM II study (NCT03838159) showed a significantly higher pCR rate in the neoadjuvant chemoimmunotherapy group than in the chemotherapy group (36.2% vs. 6.8%, $p = 0.0071$), and also an improved MPR (52% vs.14%) and ORR (74% vs. 48%) [34]. After a median follow-up of 26.1 months, the PFS rate at 12 and 24 months reached 89.3% and 66.6% in the chemoimmunotherapy group, which was superior to the chemotherapy group (60.7% and 42.3%), respectively [35]. Additionally, the median PFS was not reached and was 18.3 months in each group (hazard ratio [HR] = 0.48, 95% CI: 0.25–0.91, $p = 0.025$). The OS rate at 12 and 24 months was 98.2% and 84.7% in the chemoimmunotherapy group, and 82.1% and 63.4% in the chemotherapy group, respectively, and the median OS was not reached in either group (HR = 0.40, 95% CI: 0.17–0.93, $p = 0.034$) [35]. Overall, neoadjuvant chemoimmunotherapy has benefited the response rate and long-term survival, which provides more evidence for its application in the perioperative setting.

The SAKK 16/14 study included patients with Stage IIIA (AJCC version 7) NSCLC who were treated with neoadjuvant cisplatin and docetaxel every 3 weeks for two cycles, followed by two cycles of the PD-L1 inhibitor durvalumab every 2 weeks preoperatively, and continued for 1 year post-peratively [36]. This strategy led to a further increase in the pathological response rate compared with previous studies of neoadjuvant ICI

alone. Among 68 patients enrolled, 55 underwent surgical resection after neoadjuvant sequential chemoimmunotherapy, of whom 34 (62%) achieved an MPR of 62% (34/55) and a pCR of 18% (10/55) [37]. With a median follow-up of 28.6 months, the EFS at 1 year was 73%, while the median EFS and OS were not reached.

The CheckMate 816 study was the first randomized Phase 3 trial to evaluate the clinical outcome of neoadjuvant chemoimmunotherapy versus chemotherapy as neoadjuvant treatment for Stage IB (≥4 cm)–IIIA (AJCC version 7) NSCLC [38]. Nivolumab (360 mg) plus platinum-doublet chemotherapy or chemotherapy alone was administered every 3 weeks for three cycles before planned surgery, followed by up to four cycles of adjuvant chemotherapy, radiotherapy, or both. The baseline characteristics were generally similar in both groups (each with 179 patients), with >60% patients diagnosed with stage IIIA disease, and approximately 50% of patients had pretreatment tumor PD-L1 expression ≥1% in each group. The median EFS was 31.6 months with chemoimmunotherapy and 20.8 months with chemotherapy alone ($p = 0.005$) [39]. The pCR rate was 24.0% with nivolumab plus chemotherapy in all of the patients in the primary analysis population, and this was significantly higher than that with chemotherapy alone (2.2%). However, this result was not as remarkable as data from previous sing-arm Phase 2 studies [31, 37]. A growing number of clinical trials intend to further determine the role of single-agent immunotherapy or combination therapy in the neoadjuvant setting (Table 1). Although there have been no reports comparing neoadjuvant chemoimmunotherapy and immunotherapy alone, the response rates in current studies appeared to favor the combination strategy. Therefore, currently, there is interest in neoadjuvant chemoimmunotherapy regarding the study design and clinical practice.

3.3 | Adjuvant immunotherapy in resectable NSCLC

Adjuvant platinum-based chemotherapy has been the standard of care for resected stage IB–IIIA NSCLC in past years, with an improvement in OS of 4%–5% 5 years compared with observation [5, 40]. The primary goal of adjuvant therapy is to treat micrometastatic disease as early as possible after surgery to prevent recurrence or distant metastasis. In recent years, the investigation of adjuvant targeted therapy in early stage (Stage IB–IIIA) patients harboring *EGFR*-activating mutations has shown a promising benefit of DFS compared with placebo [7]. However, a novel adjuvant treatment for resected NSCLC without *EGFR/ALK* mutations is still urgently required. Some trials are ongoing, such as the ANVIL study, which randomizes patients with Stage IB–IIIA NSCLC without *EGFR/ALK* mutations to receive 1 year of nivolumab or observation post-resection (Table 2).

IMpower010 was the first Phase 3 randomized study that showed a promising benefit of DFS with atezolizumab versus best supportive care (BSC) after adjuvant chemotherapy in patients with resected Stages IB–IIIA (AJCC version 7) NSCLC [14]. One to four cycles of platinum-based chemotherapy were administered in 1280 patients, followed by 1200 mg atezolizumab for up to 16 cycles (or 1 year) or BSC, after randomization stratified on the basis of PD-L1 expression. The primary endpoint DFS was tested hierarchically in three populations. [41] The first population was the PD-L1 expression tumor cell (TC) ≥ 1% subgroup with Stage II–IIIA disease, the second was randomized patients with stage II-IIIA disease, and the third was the intention-to-treat (ITT) population, defined as all randomized patients with Stage IB–IIIA disease. Initial data at a median follow-up of 32.2 months met the primary endpoints. The DFS of adjuvant atezolizumab was significantly longer than that of BSC in

TABLE 2 Selected trials of adjuvant immunotherapy for resectable NSCLC.

Trial name/NCT number	Phase	Stage	Regimen	Estimated sample Size	Primary endpoints	Median PFS
IMpower010 (NCT02486718)	III	IB-IIIA	Atezolizumab	1280	DFS	42.3 months
ANVIL (NCT02595944)	III	IB-IIIA	Nivolumab	903	DFS and OS	Not reported
PEARLS (NCT02504372)	II	IB-IIIA	Pembrolizumab	1177	DFS	Not reported
BTCRC LUN18- 153 (NCT04317534)	II	I	Pembrolizumab	NA	DFS	Not reported
NCT04585477	II	I-III	Durvalumab	80	Decrease in ctDNA level	Not reported
BR31 (NCT02273375)	III	IB-IIIB	Durvalumab	1415	DFS	Not reported

Abbreviation: NSCLC, non-small cell lung cancer.

patients with Stages II–IIIA and PD-L1 TC ≥ 1% and in those with stage II–IIIA, with a favorable safety profile with no new safety signals [41]. Based on these results, adjuvant atezolizumab was officially recommended for PD-L1 TC ≥ 1% in NSCLC without *EGFR*-sensitizing mutations in guidelines. Further analysis of the benefit of OS and predictive biomarkers is still undergoing, whereas the application of PD-L1 inhibitors after adjuvant chemotherapy in early-stage NSCLC is promising. The clinical benefit of 1%–49% and ≥50% in patients with PD-L1 expression is shown below to review the predictive value of the PD-L1 status.

Another Phase 3 study called the PERALS/KEYNOTE-091 trial compared the efficacy and safety of pembrolizumab and placebo as adjuvant therapy after complete resection in Stage IB–IIIA (AJCC version 7) NSCLC [42]. An interim study showed that adjuvant pembrolizumab prolonged DFS compared with placebo (53.6 vs. 42.0 months, HR = 0.76, 95% CI: 0.63–0.91; $p = 0.0014$) in the overall population [43]. PD-L1 testing by an immunohistochemistry 22C3 assay was performed with resected tumors. Adjuvant chemotherapy was considered for stage IB patients and recommended for Stage II–IIIA patients. A subgroup analysis showed that pembrolizumab benefitted DFS in patients who received adjuvant chemotherapy (HR = 0.73 in patients who received chemotherapy and HR = 1.25 in those who did not) [44]. This study provided further evidence for the application of PD-1 inhibitors in the adjuvant setting for patients with Stage IB–IIIA NSCLC after complete resection and adjuvant chemotherapy if indicated by guidelines.

4 | PREDICTIVE BIOMARKERS FOR ADJUVANT AND NEOADJUVANT IMMUNOTHERAPY

4.1 | PD-L1/TMB

The ligand of immune checkpoint receptor PD-1 is expressed in immune cells and tumor cells, and is highly expressed on the surface of activated lymphocytes, thus inducing suppression of effector immune responses [45]. Therefore, ICIs targeting the PD-1 pathway may enhance antitumor responses by diminishing suppressive activity in T cell activation within tumors. The utility of PD-L1 as a biomarker of response to first-line PD-1/PD-L1 inhibitors in NSCLC is widely accepted. In patients with metastatic NSCLC, tumor PD-L1 expression levels predict responses and outcomes to anti-PD-L1 treatment [46, 47] The TMB is also an emerging biomarker in immunotherapy in advanced or metastatic NSCLC. The TMB is a measurement of the number of somatic mutations via next-generation sequencing derived from tissue or peripheral blood. A high TMB status increases the probability of immune recognition and killing tumor cells, and may indicate an ICI response and clinical outcomes [48]. Despite the theoretical benefit, previous studies have shown controversial results regarding the correlation of TMB and outcomes in patients treated with ICIs. A high tissue TMB status was considered to be correlated with favorable tumor response to pembrolizumab monotherapy in the KEYNOTE-158 study with previously treated solid tumors [49]. Additionally, a benefit of long-term survival was observed in patients with advanced NSCLC who received nivolumab plus ipilimumab as the first-line therapy, regardless of the TMB status in the CheckMate227 study [50]. An updated version of the NCCN guidelines has removed TMB as an emerging immune biomarker for patients with metastatic NSCLC because of the lack of supporting data and concerns of challenges in standardizing laboratory measurements. The investigation of TMB in conjunction of PD-L1 expression is still on-going in patients with resectable NSCLC who receive adjuvant and neoadjuvant immune-based therapies.

With neoadjuvant immunotherapy emerging as a novel strategy in recent years, the predictive role of PD-L1 to responses of neoadjuvant ICI is also under investigation. The MPR has been accepted as a surrogate endpoint for evaluating the feasibility of immunotherapy in the neoadjuvant setting. Therefore, the relationship between pretreatment/posttreatment PD-L1 expression and the MPR rate has been investigated in multiple studies. The results of the CheckMate159 trial were not different regarding the MPR between PD-L1-positive and PD-L1-negative tumors [20]. A relatively small sample size of pretreatment biopsy underwent PD-L1 expression testing by the Dako 28-8 assay. Therefore, the evidence provided by subgroup analysis did not appear to be strong enough. However, a significant correlation between the MPR and pretreatment TMB in 11 resected specimens using whole-exome sequencing in this trial was observed, but there was no significant correlation between TMB and PD-L1 expression. Interim analysis of biomarkers in the LCMC3 study showed no correlation between the MPR and TMB rates or tumor PD-L1 expression [51]. Nevertheless, newly released data from the LCMC3 study have shown a positive association between the MPR and PD-L1 status (clone 22C3), and also showed a positive correlation between the TMB and pathological response [52]. A phase 1b trial examined the safety and efficacy of the neoadjuvant PD-1 inhibitor sintilimab in 40 patients with Stage IA–IIIB NSCLC [22].

This trial showed a positive correlation between baseline PD-L1 expression in stromal cells and pathological regression ($p = 0.0471$), which provides a novel aspect of underlying mechanisms.

The NEOSTAR study showed no association between posttherapy tumor PD-L1 expression by immunohistochemistry and the pathological response, and a radiographic or pathological response was observed in patients with pretreatment tumor specimens lacking PD-L1 expression [25]. Similarly, no significant association was observed between pretreatment PD-L1 expression and the MPR or EFS at 1 year in a multicenter, single-arm, Phase 2 trial (SAKK16/14), despite a higher pCR rate in patients with PD-L1 expression levels ≥25% [37]. Moreover, there was no association between the TMB and EFS, MPR, or nodal clearance in another study [53]. In a molecular analysis in the NADIM and NADIM II studies, the PD-L1 tumor proportion score was significantly higher in patients who had a pCR than in those with an incomplete pathological response [31, 34]. Additionally, increasing categories of PD-L1 tumor proportion score (TPS) showed an increase in the pCR rate (TPS < 1%, pCR: 14.3%; TPS of 1%–49%, pCR: 41.7%; TPS ≥ 50%, pCR: 61.1%; $p = 0.008$). However, no similar association was observed in those with an MPR and an incomplete pathological response, or between the PD-L1 tumor proportion score and PFS or OS [31]. A subgroup analysis of the CheckMate 816 study showed a benefit in the pCR with neoadjuvant nivolumab plus chemotherapy, regardless of tumor PD-L1 expression levels [39]. However, patients with tumor PD-L1 expression levels of at least 1% appeared to benefit more than those with levels <1%. The predictive value of PD-L1 expression and TMB is still debatable, as they are in immunotherapy for advanced diseases, and more biomarkers beyond PD-L1 expression and TMB need to be investigated.

In the adjuvant setting, the correlation between PD-L1 expression and the efficacy of the PD-L1 inhibitor atezolizumab was analyzed with the SP263 immunohistochemistry assay in the IMpower010 study [14]. This study met the primary endpoint DFS in patients with Stage II–IIIA and PD-L1 TC ≥ 1% (HR = 0.66, 95% CI: 0.50–0.88) and the secondary endpoint DFS in patients with Stage II–IIIA and PD-L1 TC ≥ 50% (HR = 0.43, 95% CI: 0.27–0.68). An exploratory analysis in the Stage II–IIIA population with PD-L1 TC of 1%–49% also showed a benefit of DFS (HR = 0.87, 95% CI: 0.60–1.26). The safety profile and clinical benefit with atezolizumab were also consistent across most subgroups in an exploratory analysis of the subpopulation of PD-L1 TC of ≥50% [54]. The KEYNOTE-091 study showed that the adjuvant PD-1 inhibitor pembrolizumab benefited patients with Stage IB–IIIA NSCLC regarding DFS, regardless of PD-L1 expression after stratification by PD-L1 levels (<1%, 1%–49%, and ≥50%) [43]. Despite these informative findings, further investigation on the prognostic value of PD-L1 expression on adjuvant immune-based therapies is required. Moreover, the challenges in defining the threshold of a high TMB and standardizing the sequencing approach in assessing the TMB still need to be taken into consideration.

4.2 | ctDNA/MRD

ctDNA shows a genetic profile in tumors and has emerged as a noninvasive liquid biopsy tool. The genomic changes shown by monitoring ctDNA has provided evidence for assessing tumor responses to antitumor therapies and thus helped guide clinical treatments [55, 56]. In patients with early-stage NSCLC who undergo complete resection, the detection of ctDNA in peripheral blood helps to identify molecular residual disease (MRD), which might develop in distant metastatic sites. The prospective study LUNGCA-1 included patients with pathological Stage I–III (AJCC version 8) NSCLC and showed that MRD was an independent factor to predict the risk of relapse after resection [57]. Additionally, the presence of postoperative ctDNA-based MRD was strongly correlated with a higher rate of disease relapse, and patients who were MRD-positive and received adjuvant therapies had better RFS than their counterparts without adjuvant therapy [7].

In the NADIM study, which showed 69.8% (30/43) of ctDNA in pretreatment plasma samples, showed that a low baseline ctDNA level was an independent predictive factor for PFS and OS after neoadjuvant chemotherapy plus nivolumab (PFS: HR = 0.20, 95% CI: 0.06–0.63, $p = 0.006$; OS: HR = 0.07, 95% CI: 0.01–0.39, $p = 0.002$) [58]. In this study, patients also had low ctDNA levels at baseline had a significantly longer PFS and OS after neoadjuvant chemoimmunotherapy than those with high ctDNA levels [59]. These findings suggest the prognostic value of baseline ctDNA, which is consistent with other studies on advanced cancer treated with ICIs in which a correlation between pretreatment ctDNA and long-term survival was observed [60].

In contrast, the CheckMate 159 trial, which assessed longitudinal molecular data in peripheral blood for ctDNA, showed that the presence of ctDNA at diagnosis was not associated with RFS. Additionally, clearance of detectable ctDNA before surgery was observed in all patients with a reduction ≥30% in the viable tumor in response to nivolumab [21]. This result shows potential of ctDNA monitoring in predicting the efficacy of

neoadjuvant immunotherapy. The Phase 3 trial CheckMate816 provided further evidence in the predictive value of ctDNA clearance in neoadjuvant chemotherapy plus nivolumab treatment using whole-exome sequencing (before and after two cycles of neoadjuvant thearpy [38]. A ctDNA clearance rate of 56% and 35% was observed in the nivolumab plus chemotherapy group (24/43) and the chemotherapy group (15/44), respectively [39]. Additionally, there was a higher pCR rate in patients with ctDNA clearance in both treatment groups than in those in the groups without ctDNA clearance [39]. This informative data suggests that ctDNA clearance reflects the pathological response and EFS in the therapy used. However, because baseline ctDNA can also identify patients at high risk of progression and death, the assessment of baseline ctDNA may be more feasible than longitudinal surveillance of ctDNA during perioperative immunotherapy.

Investigation on the role of ctDNA to identify patients with MRD after resection who might benefit from adjuvant immunotherapy has provided limited evidence. In 600 patients with evaluable ctDNA before adjuvant therapy after surgery, adjuvant atezolizumab resulted in better DFS than BSC (19.1 vs. 7.9 months, HR = 0.61, 95% CI: 0.39–0.94) in the IMpower010 study [61]. After stratification by the ctDNA status, a benefit in DFS was primarily observed in PD-L1 TC ≥ 1% in the ctDNA-positive and ctDNA-negative groups. Despite the absolute increase in DFS benefit shown in the ctDNA-positive subpopulation, there are insufficient data on whether postoperative ctDNA shows a benefit in DFS. Therefore, additional studies using post-chemotherapy and longitudinal time points are required. There are ongoing biomarker studies on the relevance of ctDNA clearance at several designed time points and early relapse in patients with stage IB–IIIA NSCLC treated with adjuvant chemotherapy plus atezolizumab followed by atezolizumab [62].

4.3 | Specific gene mutations

The discovery of driver genes, such as *EGFR*, *ALK*, and *KRAS,* has stimulated research on targeted therapy to these signal pathways [63]. This has to an improvement in the prognosis of the patient subgroup with advanced NSCLC harboring these mutations [64]. While *KRAS* and *BRAF V600E* mutations show a superior clinical benefit from immunotherapy [65], multiple studies have shown no long-term benefit of ICI therapy in patients with driver genes, such as *EGFR* and *ALK* alterations [18, 66]. Therefore, first-line ICIs are recommended only in the subset of *EGFR/ALK* wild-type patients with advanced NSCLC. The LCMC4 study is also ongoing and aims to determine the proportion of patients with Stage IA2–III lung cancer who harbor targetable driver genes, such as *EGFR* mutations and *ALK* rearrangements for selection of neoadjuvant strategies [67]. Besides the driver genes that are frequently mutated in NSCLC, inhibitory mutations, such as *STK11* and *KEAP1,* often co-occur with the *KRAS* mutation, and help to define a subgroup of patients who have a poor response and survival to chemoimmunotherapy [68]. The role of driver genes and inhibitors genes in adjuvant and neoadjuvant ICI therapy for early-stage NSCLC is still under investigation, and the results in perioperative immuno-based strategies are discussed below.

Biomarker analysis in the LCMC3 study suggested that patients with *STK11/LKB1* and *KEAP1* were more likely to be pathological non-responders to neoadjuvant ICI [24]. Similarly, the NADIM study showed a shorter PFS after neoadjuvant chemoimmunotherapy in patients with *STK11*, *KEAP1*, *RB1*, and *EGFR* mutations ($n = 9$) than in those without these mutations ($n = 20$) [31]. The absence of these mutations appeared to be prognostic for neoadjuvant immunotherapy rather than predictive of the pathological response. However, a subgroup analysis in the IMpower010 study showed a similar benefit of DFS from adjuvant atezolizumab in patients with Stage II–IIIA and PD-L1 TC ≥ 1% who were *EGFR*-positive, *EGFR*-negative, or an unknown status [14]. This finding may have been due to the small number of patients with a positive *EGFR* status ($n = 43$). When patients with known *EGFR/ALK* mutations were excluded, the HRs for DFS improved in all PD-L1 subgroups, except for TC ≥ 50% [61]. The evidence from the subgroups is limited owing to the relatively small sample size. Therefore, whether molecular biomarkers can be used before perioperative immunotherapy in expert consensus remains controversial [69].

4.4 | TME-related biomarkers

The investigation of TME-related biomarkers has shown predictive value of PD-L1 expression, tumor-infiltrating lymphocytes, and T-cell receptor (TCR) in response to immunotherapy. In perioperative therapy, the monitoring of TME-related biomarkers via pretreatment and posttreatment tissues and blood samples has shown the potential to predict a therapeutic response. However, whether the dynamic changes in tumor infiltration of specific T cells and TCR repertoires are correlated with the tumor response to adjuvant and neoadjuvant therapy in early-stage patients remains controversial. The presentation and recognition of neoantigen peptides by TCR

bound to major histocompatibility molecules is essential in the immunogenic process [60]. TCR features of diversity, evenness, and clonality are being explored as markers in ICI therapy. A study showed a correlation between dynamic changes in TCR clonality and acquired resistance after an initial response to PD-1 inhibitors, which was induced by neoantigen loss, in patients with stage IIB–IV NSCLC [70]. However, there is less evidence regarding the predictive role of intratumoral and peripheral TCR features in neoadjuvant ICI treatments in resected NSCLC.

In the CheckMate159 trial of neoadjuvant nivolumab therapy, TCR sequencing was performed in tumors and peripheral blood at the time of resection in nine patients. A higher TCR clonality was observed in tumors with an MPR than in their counterparts [20]. The surveillance of peripheral T cell expansion to identify responders and non-responders to PD-1 blockade has also suggested potential biomarkers for response and survival [21]. Similarly, TCR richness and clonality were greater in resected tumors followed neoadjuvant nivolumab or nivolumab + ipilimumab therapy than in matched, tumor-adjacent, uninvolved lung samples in the NEOSTAR study [25]. However, the number of tested samples was limited in these studies. TCR repertoire assessment in the SAKK 16/15 study showed its potential in predicting the risk of recurrence after neoadjuvant sequential chemoimmunotherapy with durvalumab in stage IIIA/N2 NSCLC. The TCR evenness in pretreatment peripheral blood samples was associated with the 1-year EFS rate, and an increased TCR richness in posttreatment tissue was correlated with the 1-year EFS rate, MPR, and nodal clearance [53]. In the exploration of biomarkers in the NADIM study, TCR repertoires in primary tumors or lymph nodes from pretreatment biopsy tissue and posttreatment resected tissue of 19 patients with NSCLC were analyzed in relation to convergence, diversity, evenness, and clonality [71]. Larger scale studies on TME-related biomarkers are required to verify the predictive role of these features.

Intratumoral and peripheral immunophenotypes may dynamically change in patients who receive pathological regression after neoadjuvant ICI therapy. In the CheckMate159 study, only a few intratumoral macrophages expressing PD-L1 were observed in pretreatment tissue, whereas CD8 + and PD-1+ immune cells were infiltrated in posttreatment samples in a patient who received an MPR from neoadjuvant nivolumab [20]. The LCMC3 study showed that patients who received an MPR from neoadjuvant atezolizumab had a decreased number of late-activated CD4 + and CD8 + T lymphocytes in peripheral blood [72]. The changes in CD3 + T lymphocytes from pretreatment specimens and posttreatment tumors were significantly greater in patients treated with nivolumab + ipilimumab than in those treated with nivolumab alone in the NEOSTAR study [25]. This result indicated that the dynamic alternation in CD3 + T lymphocytes potentially correlated with a better response to neoadjuvant ICIs. Patients with stage IIIA NSCLC who achieved a pCR after neoadjuvant nivolumab and chemotherapy showed downregulation on the levels of activated peripheral CD4 + T cells and NK cells, and a reduction in PD-L1 expression on immune cells in the NADIM study [73].

Multiple additional analysis in molecular biomarkers has also indicated the potential of immune cells in predicting the pathological response to neoadjuvant immunotherapy in resected NSCLC. A higher frequency of tumor-infiltrating lymphocytes and effector memory T cells were found by flow cytometry in resected specimens after nivolumab + ipilimumab than after nivolumab monotherapy in the NEOSTAR study [25], which indicated a better pathological response. However, no further investigation of the value of tumor-specific T cells was performed in this study. A decrease in T lymphocytes in tissue, except for regulatory and regulatory T cells, was observed after neoadjuvant nivolumab and chemotherapy [31], but no similar trend was found in peripheral mononuclear cells [74]. Immune cell analysis in the NADIM study showed a significantly decreased number of activated CD4 + T cells and NK cells in posttreatment blood samples in patients who achieved a pCR, with no reduction in cytokines (e.g., interleukin [IL]-2, IL-15, IL-6, IL-13, and IFN-γ) after neoadjuvant treatment in this subpopulation [74]. Despite the informative findings reviewed above, the determination of cellular and cytokine biomarkers in neoadjuvant immunotherapies still requires further investigation in larger patient cohorts.

4.5 | Fluorine-18-fluorodeoxyglucose positron emission tomography-computed tomography parameters

Fluorine-18-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) scans show potential predictive value in the evaluation of therapeutic response to immuno-based strategies for patients with advanced NSCLC [75]. In resected NSCLC, elevated fluorine-18-fluorodeoxyglucose maximum standardized uptake (SUVmax) values are correlated with an immunosuppressive and poorly immune infiltrated tumor microenvironment, and also indicate poor clinical outcomes following immunotherapy [76]. The predictive role of SUVmax changes in the pathological response to

neoadjuvant ICI treatment has not been fully investigated. Gao et al. reported that a reduction in SUVmax of primary lesions after anti-PD-1 (sintilimab) treatment was significantly correlated with the MPR rate [22]. However, in the NEOSTAR study, the phenomenon of nodal immune flare [77] has been observed in a few cases. An invasive pathological examination of the flared nodes with an increased SUVmax showed changes in immune cell infiltration instead of malignancy [25]. The evidence for the predictive value of changes in SUVmax by positron emission tomography-computed tomography remains controversial and requires further confirmation in larger studies.

5 | CURRENT CHALLENGES AND FUTURE PERSPECTIVES

The application of immunotherapy has revolutionized the treatment of patients with advanced NSCLC and those with resected NSCLC who have a high risk of recurrence. Perioperative therapies eliminate micrometastases, prevent postoperative recurrence, and lead to long-term benefits. An increasing number of studies have shown a clinical benefit from neoadjuvant immunotherapy by promoting pathological regression and prolonging postoperative survival. Further investigation on the combination of ICI and chemotherapy or ICI dual therapy in the neoadjuvant setting has shown a high rate of pathological responses. Our article is the most up-to-date review of the primary results of represented trials and of the potential markers for adjuvant and neoadjuvant ICI-based therapies.

Despite the encouraging results of multiple studies, there are still current challenges for clinical feasibility. Unsolved controversies in the study design of perioperative immunotherapy remain. These challenges include the timing for resection after neoadjuvant therapy, the optimal therapeutic mode including the choice of drugs and the application cycle, and the duration of postoperative therapies. A recent Phase 2 study showed that three cycles of neoadjuvant sintilimab plus chemotherapy treatment achieved a higher MPR rate than two cycles in resectable Stage IB–IIIA NSCLC [78]. Moreover, most of the previous studies were Phase 1–2 exploratory trials, with a single cohort and limited sample size. Therefore, the existing data provide limited evidence for the long-term benefit of ICI-based therapy in the neoadjuvant setting. The selection of predictive markers is also an issue for perioperative immunotherapy and chemoimmunotherapy. The role of tissue-based biomarkers (e.g., PD-L1/TMB) and blood-based biomarkers (e.g., ctDNA) has been investigated, and large cohort studies are required to provide sufficient evidence. Other potential biomarkers, such as the microbiome, are also under investigation. Collectively, the existing data are promising for adjuvant and neoadjuvant ICI-based strategy for patients with resectable NSCLC without driver gene mutations, and also suggest multiple potential molecular biomarkers for efficacy and survival.

AUTHOR CONTRIBUTIONS

Ziyi Xu: Conceptualization (equal); methodology (equal); writing—original draft (lead). **Zihua Zou**: Project administration (supporting); writing—original draft (supporting); writing—review & editing (supporting). **Xuezhi Hao**: Conceptualization (supporting); project administration (supporting); writing—review & editing (supporting). **Puyuan Xing**: Project administration (equal); supervision (equal); writing—review & editing (equal). **Junling Li**: Project administration (lead); supervision (equal); writing—review & editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable – no new data is generated.

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