

Advances in Immunotherapy for Non-Small-Cell Lung Cancer

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Abstract: *Treatment strategies for non-small-cell lung cancer (NSCLC) have achieved unprecedented revolutionary breakthroughs. Represented by programmed cell death protein-1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors, immunotherapy has been applied across all therapeutic stages of NSCLC. Surgical resection remains a preferred intervention for resectable NSCLC. The advent of immune-checkpoint-inhibitor-based therapies has substantially improved clinical outcomes of NSCLC. Accumulating evidence has demonstrated favorable safety and feasibility profiles of immune checkpoint inhibitors in NSCLC management. Nevertheless, authoritative prognostic assessment tools, optimized therapeutic regimens and standardized treatment durations are still lacking. This review elaborates on the developmental process, mechanism of action and current research status of neoadjuvant immunotherapy for resectable NSCLC. Continuous discovery of novel targets, mechanisms and advanced therapeutic modalities will further satisfy clinical demands for long-term survival of NSCLC patients.*

Keywords: Non-small-cell lung cancer, Immunotherapy, Immune checkpoint inhibitors.

1. Introduction

Over the last decade, treatment modalities against lung cancer have achieved remarkable progress, particularly in the population diagnosed with non-small cell lung cancer (NSCLC). Numerous studies have investigated immunotherapy in multiple treatment settings, and various combinatorial treatment strategies have yielded encouraging therapeutic effects. In the same vein, immunotherapy has begun to be utilized in early-stage tumors as a component of perioperative treatment protocols [1]. Immune checkpoint inhibitors (ICIs) represent the foundation that forms the modern treatment paradigm for NSCLC. Regardless of treatment line—initial or subsequent—and whether delivered as monotherapy or a multi-agent regimen, this applies to both early-stage and advanced NSCLC. Immune checkpoint inhibitors (ICIs) offer meaningful clinical benefits and broaden the range of therapeutic options for affected patients. We offer an overview of the most important recent advances in NSCLC immunotherapy, and aims to provide evidence-based insights to guide clinical decision-making and everyday patient care [2].

2. The Evolution of Immunotherapy for Advanced NSCLC: Key Milestones and Clinical Impact

By interrupting the engagement of immune checkpoint molecules with their cognate ligands, ICIs exert their therapeutic effects. This process reverses tumor-induced immune suppression and reinstates immune cell function to trigger anti-tumor activity. Accumulated data derived from clinical trials and real-world practice demonstrate that inhibition of PD-1/PD-L1 produces prominent overall survival advantages in individuals with metastatic NSCLC. Currently, PD-1/PD-L1 targeted agents are included within routine first-line treatment strategies for the bulk of NSCLC cases. An increasing number of studies have demonstrated that first-line immunotherapy, whether delivered alone or in

conjunction with chemotherapy, commonly results in better long-term survival outcomes.

2.1 Advances in Neoadjuvant Therapeutic Research of Nivolumab for NSCLC

Existing clinical data demonstrate that the combination of nivolumab and ipilimumab yields a 4-year survival rate of 29%. In contrast, dual immunotherapy centered on nivolumab combined with chemotherapy achieves a 2-year survival rate of 38% in NSCLC treatment [3]. In the broad range of immune checkpoint therapeutic targets, programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) remain the most extensively investigated biomarkers in current research. CheckMate 159, a single-arm clinical study focusing on neoadjuvant immunotherapy enrolled 21 stage I–IIIA NSCLC cases, every patient was given two cycles of single-agent nivolumab for neoadjuvant treatment, and 20 of these subjects completed radical surgery, corresponding to a major pathological response (MPR) rate of 45%. The median follow-up was one year, during which recurrence remained comparatively uncommon, with the 18-month recurrence-free survival rate amounting to 73%. Nivolumab demonstrated a favorable safety profile, with patients tolerating the treatment well and no surgical delays reported [4]. The NADIM trial evaluated whether integrating neoadjuvant nivolumab into conventional chemotherapy was feasible and safe for patients with resectable stage IIIA NSCLC, and defined 24-month progression-free survival (PFS) as its primary endpoint. Of the 46 patients enrolled, Surgical resection was performed in 41 patients (89%), all of whom had their tumors completely removed. According to the findings, the 24-month PFS rate in the intention-to-treat (ITT) cohort was 77.1%. A total of 83% of patients attained major pathological response (MPR), and 63% exhibited a pathological complete response (pCR). Among the participants, 93% (43/46) experienced treatment-related adverse events attributable to neoadjuvant immunochemotherapy, with grade 3 or severe toxicities observed in 30% of the overall cohort. Fatigue (50%),

alopecia (35%), and nausea (33%) emerged as the most frequently documented low-grade (grade 1–2) treatment-related adverse events. For grade 3 or higher TRAEs, the most common were elevated lipase and febrile neutropenia, each reported in 7% of patients [5]. In 2022, the PFS and OS findings, as secondary endpoints of the NADIM II study [6], were updated at the WCLC. TT analysis revealed consistent PFS rates of 69.6% at both 36 and 42 months, while the PP cohort yielded equivalent 36-month and 42-month PFS values of 81.1%. Long-term overall survival (OS) data obtained from over three years of follow-up demonstrated that patients with resectable stage IIIA NSCLC achieved 36-month OS rates of 81.9% and 91.0% in the ITT and PP cohorts, respectively. Such superior survival outcomes in patients with stage IIIA NSCLC have never been documented in prior neoadjuvant therapy studies. The combination of neoadjuvant nivolumab and chemotherapy is therefore anticipated to further improve long-term survival benefits for this patient population. In another phase III trial, CheckMate 816, which investigated neoadjuvant nivolumab plus chemotherapy [7]. In this trial, 358 stage IB (tumor ≥ 0.4 cm) to IIIA NSCLC patients without EGFR or ALK genomic alterations were randomly assigned to three cycles of neoadjuvant nivolumab combined with platinum-based chemotherapy or single-agent chemotherapy. The study adopted event-free survival (EFS) and pathological complete response (pCR) as its dual primary endpoints. At the data cutoff, the neoadjuvant nivolumab combined with chemotherapy group achieved significant improvements in both EFS and pCR relative to the chemotherapy monotherapy arm. The median EFS was 31.6 months versus 20.8 months (HR = 0.63, 95% CI: 0.43–0.91, $P = 0.005$). Patients treated with preoperative nivolumab plus chemotherapy achieved a pCR rate of 24%, which was markedly higher than the 2.2% observed in the chemotherapy monotherapy group (OR = 13.94, 95% CI: 3.49–55.75, $P < 0.001$). Notably, the incorporation of nivolumab into neoadjuvant chemotherapy failed to elevate adverse event rates and did not affect the feasibility of subsequent surgery. As evidenced by the phase III CheckMate 227 study, dual immunotherapy with nivolumab plus ipilimumab yields persistent long-term therapeutic superiority over chemotherapy in previously untreated metastatic NSCLC populations, independent of PD-L1 expression status [8]. The body of clinical evidence emerging from the trials discussed above highlights the marked therapeutic effectiveness of nivolumab in non-small cell lung cancer.

2.2 Exploration of Pembrolizumab in Adjuvant Therapy for NSCLC

Yang Yan-qing et al. mentioned in a retrospective study that [9], immune checkpoint inhibitors represented by PD-1/PD-L1 monoclonal antibodies have been proven to improve survival outcomes in patients with advanced non-squamous non-small-cell lung cancer. Paz-Ares L et al. [10] recruited 559 treatment-naïve patients suffering from metastatic squamous non-small-cell lung cancer. All participants were randomized to receive 200 mg pembrolizumab or matched placebo throughout a standardized treatment cycle. All participants concurrently received four initial cycles of carboplatin combined with either paclitaxel or nab-paclitaxel. The study set overall survival (OS) and progression-free survival (PFS) as its dual

primary endpoints. Study data showed that with a median follow-up of 7.8 months, the median overall survival was 15.9 months (95% CI, 13.2–not-reached) in the pembrolizumab-plus-chemotherapy group versus 11.3 months (95% CI, 9.5–14.8) in the placebo-plus-chemotherapy group (hazard ratio for death = 0.64; 95% CI, 0.49–0.85; $P < 0.001$). The overall-survival benefit was consistent regardless of PD-L1 expression levels. The median progression-free survival was 6.4 months (95% CI, 6.2–8.3) in the pembrolizumab-combined group versus 4.8 months (95% CI, 4.3–5.7) in the placebo-combined group (hazard ratio for disease progression or death = 0.56; 95% CI, 0.45–0.70), indicating significant prolongation of both overall survival and progression-free survival [11]. Meanwhile, Tong et al. conducted the phase II TOP1501 trial in 2019. This trial recruited 30 patients with operable stage IB–IIIA NSCLC. All participants were administered two cycles of neoadjuvant pembrolizumab prior to surgical resection, followed by four cycles of adjuvant pembrolizumab after surgery. Ultimately, R0 resection was successfully achieved in 22 patients. Eleven patients exhibited tumor shrinkage, whereas disease progression precluded surgical resection in 5 cases. Over half of the patients attained pathological tumor regression, which accounted for 80% of all enrolled participants, 28% of patients attained MPR and 12% achieved pCR [12]. In the KEYNOTE-024 trial investigating first-line pembrolizumab monotherapy for PD-L1-positive NSCLC, the 5-year overall survival (OS) rate was 31.9% in the pembrolizumab group, which doubled that of the chemotherapy-alone group [13], Reck M et al. [14], compared pembrolizumab with chemotherapy. This trial randomized 305 treatment-naïve patients with advanced NSCLC characterized by PD-L1 expression $\geq 50\%$ on tumor cells and wild-type EGFR/ALK status. Participants were allocated to either 200 mg pembrolizumab administered every three weeks or investigator-selected platinum-based chemotherapy. Crossover to the pembrolizumab group was permitted upon disease progression. The median progression-free survival was 10.3 months (95% CI, 6.7–not-reached) in the pembrolizumab group versus 6.0 months (95% CI, 4.2–6.2) in the chemotherapy group (hazard ratio for disease progression or death = 0.50; 95% CI, 0.37–0.68; $P < 0.001$). The estimated 6-month overall survival rate was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (hazard ratio for death = 0.60; 95% CI, 0.41–0.89; $P = 0.005$). The response rate was higher in the pembrolizumab group (44.8% vs. 27.8%), together with a longer median duration of response (not-reached [range, 1.9+–14.5+ months] vs. 6.3 months [range, 2.1+–12.6+ months]). The incidence of any-grade treatment-related adverse events was lower in the pembrolizumab group (73.4% vs. 90.0%), and the rate of grade 3–5 treatment-related adverse events was 26.6% versus 53.3%. For advanced NSCLC patients with tumor PD-L1 expression of at least 50%, pembrolizumab significantly improved both progression-free survival and overall survival, while demonstrating a more favorable safety profile than platinum-based chemotherapy. This prospective study led by Reck M assessed the safety outcomes of pembrolizumab across 1010 enrolled patients. After completing the 6-week preliminary screening run-in period, 86.8% of the overall cohort (877/1010) were incorporated into the final efficacy analysis set. This study assessed the potential association

between immune-related adverse events (irAEs) and clinical outcomes in the enrolled cohort. Among all participants, any-grade irAEs occurred in 333 patients (32.9%), while grade 3/4 irAEs were observed in 101 patients (10.0%). This study confirmed the feasibility and safety of first-line pembrolizumab monotherapy in a large clinical cohort of PD-L1-positive non-small-cell lung cancer patients [15]. According to data reported by Chen Y et al. [16], stereotactic body radiation therapy (SBRT) shows promising advances and acceptable safety in the treatment of non-small-cell lung cancer. NSCLC patients treated with SBRT achieve significantly improved local control rate and overall survival (OS) rate (2-year local failure rate: 10 % versus 40 %). Additionally, a propensity-matched cohort analysis of 497 patients revealed that SBRT was linked to improved local failure rates and 3-year overall survival outcomes relative to conventional radiotherapy (13.6% vs. 34.1% and 53.1% vs. 38.9%, respectively). Currently, SBRT has been widely recognized as an optimal alternative to surgical resection for patients with early-stage NSCLC. SBRT delivers high-dose radiation precisely to tumor lesions via small fractional doses, thereby minimizing radiation injury to adjacent healthy normal tissues (Velcheti V et al.). reported three-year follow-up data of patients with advanced NSCLC. The findings demonstrated that among US real-world patients with advanced non-small-cell lung cancer, favorable ECOG performance status (PS 0–1), PD-L1 TPS $\geq 50\%$, and wild-type EGFR/ALK/ROS1, the median real-world time on treatment (rwToT) reached 7.4 months. This value was comparable to the treatment duration observed in clinical trials. In addition, 22 % of patients remained on first-line pembrolizumab monotherapy at 24 months [17]. Study results have demonstrated that [18] compared with chemotherapy, pembrolizumab as first-line therapy for metastatic NSCLC patients with a tumor proportion score (TPS) of $\geq 50\%$ delivers durable and clinically meaningful long-term overall survival (OS) benefits. The KEYNOTE-042 trial expanded the population eligible to benefit from pembrolizumab. Among patients with advanced NSCLC and TPS $>1\%$ without sensitizing epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) alterations, pembrolizumab yielded superior OS compared with chemotherapy. Nevertheless, patients with PD-L1-high tumors derived the greatest survival benefit (TPS $\geq 50\%$, HR = 0.69, 95 %CI: 0.56-0.85). At the 5-year follow-up [median follow-up duration of 61.1 (50.0-76.3) months], pembrolizumab maintained favorable OS benefits relative to chemotherapy. The estimated 5-year survival rates were 21.9 %, 19.4 % and 16.6 %, and no new safety signals were identified, Carbone DP et al. reported 4-year overall survival (OS) follow-up data demonstrating that, compared with chemotherapy, the survival benefit conferred by dual immunotherapy combined with chemotherapy in metastatic NSCLC was independent of PD-L1 expression level and histologic subtype. The median OS was 11.0 months and 15.8 months, respectively [19].

2.3 Exploration of Durvalumab in Neoadjuvant Therapy for NSCLC

In the IONESCO trial, a multicenter neoadjuvant immunotherapy study, patients with stage IB (≥ 4 cm only)-IIIA NSCLC received three cycles of preoperative

durvalumab monotherapy. Forty-three out of 46 patients underwent surgery. The primary endpoint was complete (R0) resection, which was achieved in 89 % of operated patients. The trial was halted because the 90-day postoperative mortality rate exceeded 9 %. Nevertheless, this study demonstrated that the percentage of residual viable tumor (RVT) was significantly correlated with OS and disease-free survival (DFS). Patients with higher RVT had worse OS and DFS; the 12-month DFS rate was 78 %, and the 12-month OS rate was 89 % [20-21]. Observation group: 18 males and 15 females; aged 42–75 years, with a mean age of (58.12 ± 7.39) years; 17 patients had an ECOG score of 1, and 16 patients had an ECOG score of 2. According to TNM clinical staging, 7 patients were stage IIIA, 6 were stage IIIB, and 20 were stage IIIC. Control group: 22 males and 11 females; aged 40–73 years, with a mean age of (55.37 ± 8.14) years; 21 patients had an ECOG score of 1, and 12 patients had an ECOG score of 2. According to TNM clinical staging, 9 patients were stage IIIA, 8 were stage IIIB, and 16 were stage IIIC. There was no statistically significant difference in baseline characteristics between the two groups ($P > 0.05$), indicating comparability. Methods: The control group received the PP chemotherapy regimen. On day 1, intravenous infusion of pemetrexed disodium for injection was administered at a dose of 500 mg/m² calculated based on pemetrexed (C₂₀H₂₁N₅O₆). On days 1–3, intravenous infusion of cisplatin injection (2 mL:10 mg) was given at 25 mg/m². Each cycle lasted 28 days, and treatment was continued for 3 cycles (12 weeks). The observation group received durvalumab injection (AstraZeneca UK Limited, 120 mg/2.4 mL) in combination with the above chemotherapy regimen. Durvalumab was administered intravenously over more than 60 minutes at a dose of 10 mg/kg per dose once every two weeks for a total treatment duration of 12 weeks. Comparison of disease response rates between the two groups: The disease response rate in the observation group was 60.61 %, which was significantly higher than 36.36 % in the control group, and the difference was statistically significant ($P < 0.05$). Yang Xiaozun et al. [22] evaluated the efficacy of neoadjuvant durvalumab combined with cisplatin and docetaxel in the treatment of locally advanced non-small-cell lung cancer, all patients received neoadjuvant therapy with durvalumab combined with cisplatin and docetaxel before surgery. The regimen was as follows: durvalumab (AstraZeneca UK, 120 mg/vial) was administered intravenously at a dose of 10 mg/kg once every two weeks for a total of 3 doses. Cisplatin (Qilu Pharmaceutical Co., Ltd., 20 mg/ampoule) was given intravenously at 100 mg/m² once every three weeks for a total of 2 doses. Docetaxel (Qilu Pharmaceutical Co., Ltd., 40 mg/ampoule) was administered intravenously at 85 mg/m² once every three weeks for a total of 2 doses. Surgical resection was performed 4 weeks after the completion of neoadjuvant therapy. After postoperative recovery, patients received adjuvant therapy with durvalumab monotherapy or durvalumab combined with cisplatin and docetaxel for no less than 2 cycles (3 weeks per cycle). The primary endpoint of this study was the pathological response rate. All enrolled patients (n = 25) underwent pathological examination of resected tumors to assess pathological response. The results showed that 56.00 % of patients achieved MPR and 24.00 % achieved CPR. The median follow-up duration was 10.9 (3.2–16.9) months, with the last follow-up date on August 30, 2021. All patients were

followed up continuously after surgery to evaluate disease-free survival (DFS) and overall survival (OS). By the last follow-up, tumor recurrence occurred in 3 patients (12.00 %) and 1 patient (4.00 %) died. The incidence of adverse events in this study was 100 %. The most common adverse events included alopecia (1 patient), fatigue (10 patients), nausea and vomiting (9 patients), neutropenia (7 patients); anemia, diarrhea, leukopenia, and rash were reported in 6 patients each; peripheral neuropathy in 5 patients; constipation, thrombocytopenia, anorexia, and elevated transaminases in 4 patients each; and elevated bilirubin and hypothyroidism in 3 patients each. Xu Mengmin et al. [23] enrolled a total of 38 eligible patients with an age range of 43–74 years and a mean age of (62.08 ± 7.95) years. All patients received two cycles of neoadjuvant therapy with durvalumab plus paclitaxel/carboplatin followed by surgical resection. After postoperative recovery, patients continued to receive adjuvant therapy consisting of durvalumab monotherapy combined with paclitaxel/carboplatin for at least two cycles. Durvalumab (specification: 120 mg/vial, batch number: S20190039, AstraZeneca UK Limited) was administered intravenously at a dose of 10 mg/kg once every two weeks with an infusion duration longer than 60 minutes per administration. Paclitaxel (specification: 60 mg/ampoule, batch number: H20083848, Jiangsu Aosaikang Pharmaceutical Co., Ltd.) was intravenously infused at 100 mg/m² on days 1 and 8. Carboplatin (specification: 50 mg/ampoule, batch number: H20020181, Qilu Pharmaceutical Co., Ltd.) was administered intravenously on day 1 at an area under the curve (AUC) of 5 mg·mL·min. Paclitaxel and carboplatin were administered on a 21-day cycle. After neoadjuvant therapy with durvalumab combined with chemotherapy, patients were assessed per RECIST criteria: 0 (0.0%) achieved complete response (CR), 25 (65.78%) achieved partial response (PR), 12 (31.58%) had stable disease (SD), and 1 (2.63%) had progressive disease (PD). The overall objective response rate (ORR) was 65.78%, Antonia S J et al. reported that the 12-month overall survival rate was 83.1 % in the durvalumab group versus 75.3 % in the placebo group. The 24-month overall survival rate was 66.3 % (95 %CI, 61.7-70.4) in the durvalumab group and 55.6 % in the placebo group. Durvalumab significantly prolonged overall survival compared with placebo. In addition, as assessed by blinded independent central review, the incidence of new lesions was 22.5 % in the durvalumab group and 33.8 % in the placebo group. The rate of new brain metastases was lower in the durvalumab group than in the placebo group (6.3 % vs. 11.8 %). The study demonstrated that overall survival was significantly longer with durvalumab treatment than with placebo [24].

2.4 Exploration of Atezolizumab in Neoadjuvant Therapy for NSCLC

LCMC3 is an open-label, single-arm phase II trial in which 181 treatment-naïve patients with resectable stage IB–IIIB NSCLC received neoadjuvant atezolizumab monotherapy. Obtaining the final overall survival (OS) results requires a long follow-up period [25]. Obtaining the final overall survival (OS) results requires a long follow-up period [26]. A total of 159 patients in this study underwent surgical resection. The primary endpoint was major pathological response (MPR), defined as $\leq 10\%$ viable tumor cells at surgery, in

patients without EGFR/ALK mutations. In the primary efficacy cohort, 20% of participants attained a major pathological response. MPR exhibited a positive correlation with PD-L1 expression and a negative association with EGFR/ALK genomic alterations. Neoadjuvant atezolizumab was well tolerated, with a low incidence of grade ≥ 3 treatment-related adverse events. The most common adverse event associated with atezolizumab was fatigue (20%) [27]. PD-1/PD-L1 checkpoint inhibitors still have certain limitations at present, with response rates of only 20 %–30 % in solid tumors. Accordingly, combination therapy has emerged as a potent strategy to broaden the beneficiary population of immunotherapy and overcome or postpone therapeutic drug resistance. Supported by pivotal findings from the IMpower150 and IMpower130 phase III trials, the quadruple regimen consisting of atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP) has been clinically approved as a first-line therapeutic option for patients with metastatic non-squamous NSCLC. Given the short clinical application history of such combination regimens, current data are insufficient to draw definitive conclusions, and further studies are warranted to elucidate their intrinsic molecular mechanisms [28].

3. Progress of Immunotherapy for Early-Stage Non-Small-Cell Lung Cancer

Surgery remains the most common treatment modality for early-stage NSCLC, yet the overall prognosis remains relatively modest. In an effort to lower postoperative recurrence and reduce mortality, a large body of clinical research has sought to enhance outcomes for early-stage NSCLC patients through the integration of adjuvant or neoadjuvant therapeutic strategies. Nevertheless, traditional chemotherapy-centered adjuvant and neoadjuvant regimens confer only modest survival benefits in NSCLC, improving 5-year OS rates by merely 5.4% and 5.0%, respectively [29]. The impressive therapeutic efficacy of immune checkpoint inhibitors (ICIs) in advanced NSCLC has opened novel therapeutic avenues for early-stage disease. Current research primarily focuses on whether the upfront application of immunotherapy can deliver comparable survival benefits for patients with early-stage NSCLC.

3.1 Advances in Neoadjuvant Immunotherapy

3.1.1 PD-1 Monoclonal Antibody (Pembrolizumab)

In a study by Eichhorn F [30], 30 patients with stage II/IIIA NSCLC who were eligible for curative-intent surgery were enrolled. The investigational agent was pembrolizumab. Following two cycles of immunotherapy (200 mg administered intravenously every 3 weeks), tumor resection was subsequently carried out. The trial primarily aimed to validate the safety profile and clinical feasibility of neoadjuvant immunotherapy, while evaluating pembrolizumab-mediated antitumor activity based on clinical and pathological tumor response endpoints. Disease-free survival and overall survival served as the secondary endpoints. All patients achieved successful R0 resection. Despite favorable surgical outcomes, TRAEs prompted the discontinuation of immunotherapy among three enrolled patients. Of note, two individual participants attained MPR

and pCR separately after neoadjuvant treatment. Guan Yelan et al. [31] interpreted the long-term follow-up data from KEYNOTE-021G cohort, a phase II, randomized, open-label study comparing pembrolizumab combined with pemetrexed and carboplatin versus pemetrexed plus carboplatin as first-line therapy for advanced non-squamous non-small-cell lung cancer. In this combination therapy trial, 60 patients (49%) were administered pembrolizumab combined with pemetrexed and carboplatin, whereas 63 patients (51%) received pemetrexed plus carboplatin alone (Table 1). Updated long-term survival outcomes with a median follow-up of 49.4 months were reported in the Journal of Thoracic Oncology in 2020. Across the overall population, irrespective of PD-L1 expression levels, the immunotherapy-chemotherapy combination arm (n=60) achieved an objective response rate (ORR) of 58% and a median duration of response (DOR) of 36.3 months, versus 33% and 22.8 months in the chemotherapy-only cohort (n=63). The median progression-free survival (PFS) was 24.5 months versus 9.9 months (HR=0.54, 95%CI: 0.35–0.83), and the median overall survival (OS) was 34.5 months versus 21.1 months (HR=0.71, 95%CI: 0.45–1.12) (Figure 2). The 3-year OS rates were 50% and 37%, respectively. In terms of adverse events, the most frequently observed immune-related adverse events (irAEs) in the pembrolizumab plus chemotherapy arm included hypothyroidism, hyperthyroidism and pneumonitis, with multiple cases documented for each condition. Sundar R et al. [32] reported that in a phase I human study, the objective response rate (ORR) was 17%, with a median duration of response of 74 weeks (range, 6.1–133.9 weeks). Tumor volume reduction occurred within the first 2 months of treatment in 50% of patients who achieved a response. By histology, response rates were 33% (6 of 18) for squamous tumors and 12% (7 of 56) for non-squamous tumors.

3.1.2 Nivolumab

Schuler M et al. [33] reported updated data from a randomized phase II trial investigating neoadjuvant nivolumab with or without relatlimab for resectable non-small-cell lung cancer. The median follow-up duration was 12 months. The disease-free survival rate and overall survival (OS) rate were 89% and 93% in the nivolumab monotherapy arm, and 93% and 100% in the nivolumab plus relatlimab combination arm, respectively. To date, no patients who achieved MPR have experienced recurrence. One patient with MPR died of pulmonary embolism during extended follow-up. Regarding adverse events, the most common immune-related adverse events were hyperthyroidism and hypothyroidism. Pneumonitis was observed in patients in Arm AB. One patient developed cryptogenic liver failure several days after treatment and subsequently died; a causal relationship with nivolumab could not be ruled out. Gettinger S N et al. [34] conducted a retrospective study comparing nivolumab combined with ipilimumab versus nivolumab monotherapy in previously treated patients with stage IV squamous cell lung cancer. Nivolumab plus ipilimumab was superior to platinum-based chemotherapy in treatment-naïve patients with advanced non-small-cell lung cancer (NSCLC). Nivolumab is superior to docetaxel in the treatment of advanced non-small-cell lung cancer [35].

3.1.3 Sintilimab

Published studies including CAMEL, CAMEL-sq, ORIENT-11, ORIENT-12 and CHOICE-01 have demonstrated that chemotherapy combined with sintilimab or toripalimab significantly improves progression-free survival (PFS) and overall survival (OS) compared with chemotherapy alone in patients with advanced NSCLC [36]. In 2018, Forde et al. first published the CheckMate-159 study on the application of neoadjuvant immunotherapy in NSCLC, which aimed to evaluate the feasibility and safety of neoadjuvant therapy with the PD-1 inhibitor nivolumab. This study enrolled 22 treatment-naïve patients with resectable stage I-IIIa NSCLC. Twenty patients received preoperative nivolumab; one patient developed grade 3 pneumonitis during treatment and underwent surgery after receiving only one cycle of nivolumab. The results showed that patients had relatively good tolerability, with an adverse event rate of only 23% (5/22), including only one case of grade 3 adverse event, which did not affect the surgical procedure. In addition, up to 45% (9/20) of patients achieved major pathological response (MPR), among whom 3 patients attained pathological complete response (pCR). At a median follow-up of 12 months after surgery, 80% (16/20) of patients had no evidence of recurrence. Jiang H et al. conducted a study aiming to evaluate the safety and efficacy of the PD-1 inhibitor sintilimab plus chemotherapy in first-line (1L) patients with non-squamous and squamous non-small-cell lung cancer (nsqNSCLC/sqNSCLC). Sintilimab combined with pemetrexed-cisplatin or gemcitabine-cisplatin demonstrated manageable toxicity and encouraging antitumor activity in patients with nsqNSCLC and sqNSCLC [37]. On the other hand, Zhang et al. [38] from Shanghai Pulmonary Hospital published the results of a clinical trial of neoadjuvant chemotherapy combined with sintilimab. This trial enrolled 50 patients with stage IIIa NSCLC. After receiving 2 to 4 cycles of neoadjuvant therapy, partial response was observed in 46% (23/50) of patients, and stable disease in 48% (24/50). Thirty patients underwent R0 resection; 43% (13/30) achieved MPR and 20% (6/30) achieved pCR. This study further demonstrates the potential benefits of the neoadjuvant therapeutic strategy for patients with NSCLC.

3.1.4 Toripalimab Combined with Chemotherapy

Current clinical evidence for toripalimab in NSCLC includes a phase II trial published in 2021, which evaluated toripalimab plus chemotherapy in patients with resectable stage IIIa or T3–4N2 stage IIIB NSCLC. This study enrolled 33 patients, all of whom received three cycles of toripalimab combined with chemotherapy. In the 29 patients with successful R0 surgical resection, MPR and pCR were achieved in 20 and 15 individuals, respectively. Additionally, 24 patients presented with significant postoperative TNM downstaging. Yang Ning et al. [39] conducted a retrospective study enrolling 87 patients with stage III NSCLC, who were divided into a conventional chemoradiotherapy group (43 patients) and a toripalimab combination group (44 patients). As immunotherapeutic agents have gained successive regulatory approvals, their clinical application in NSCLC has broadened. Toripalimab, a domestically developed immunotherapy agent, when combined with chemotherapy for advanced NSCLC patients who have failed prior EGFR tyrosine kinase inhibitor (TKI) therapy, has demonstrated notable efficacy and substantially improved the 5-year survival rate in this

population. Jiang T et al. [40], conducted a multicenter phase II trial investigating toripalimab plus chemotherapy as second-line therapy for patients with EGFR-mutated advanced non-small-cell lung cancer who had previously received EGFR-TKI treatment. The median overall survival (OS) was 23.5 months (95%CI, 18.0 to NR). Among the 29 patients who finished induction therapy, the objective response rate (ORR) reached 69.0%. The predominant adverse event observed in this study was leukopenia.

3.2 PD-L1-Targeted Neoadjuvant Immunotherapy

3.2.1 Atezolizumab

Atezolizumab, a potent inhibitor targeting the PD-L1 checkpoint, can specifically recognize and interact with PD-L1 proteins distributed on tumor cells and immune-suppressive stromal cells in the tumor microenvironment. Through disruption of the PD-L1/PD-1 interaction, this agent reverses T-cell exhaustion, enhances T-cell activation, and induces tumor cell apoptosis. Activated T cells release cytokines that further recruit other immune cells, leading to an augmented anti-tumor immune response [41]. In a study reported by Liu and colleagues [42], the therapeutic effects of atezolizumab versus sintilimab were evaluated among patients diagnosed with non-small cell lung cancer. A total of enrolled subjects were divided into two arms: 32 cases in the control arm receiving sintilimab, and 35 cases in the observation arm treated with atezolizumab. Outcomes measured consisted of cell growth factors (VEGF, bFGF, MMP-9), tumor biomarkers (CEA, CA125, CA19-9), CYFRA21-1, and immune parameters including CD4⁺, CD8⁺ and CD4⁺/CD8⁺ ratio. Data from this research revealed that either agent could ameliorate the levels of cell growth factors and tumor markers, lower CYFRA21-1 and enhance immune status in patients with intermediate-advanced NSCLC, while atezolizumab yielded better clinical responses. In the pharmacoeconomic analysis conducted by Zhang and colleagues, adjuvant atezolizumab was associated with improved quality-adjusted life years (3.81 vs. 3.36 QALYs) but increased treatment costs (CNY 96, 606 vs. CNY 79, 819) when benchmarked against routine supportive care. The resulting incremental cost-effectiveness ratio (ICER) was CNY 37, 304 per QALY. From an economic standpoint, atezolizumab demonstrated a favorable cost-effectiveness profile and can be regarded as a cost-effective therapeutic strategy [43].

4. Existing Challenges of Neoadjuvant Immunotherapy

Several limitations exist in this trial, including its limited sample size and the overrepresentation of squamous cell carcinoma cases, which may potentially induce analytical bias in final clinical results. In addition, despite consistent telephone follow-up performed during the research period, the predefined endpoints of progression-free survival (PFS) and overall survival (OS) have not been reached so far. Therefore, further high-quality investigations are required to elucidate the long-term survival benefits and prognostic impacts of neoadjuvant chemoimmunotherapy regimens. Additionally, precise screening of ideal treatment responders remains a critical unsolved problem in current neoadjuvant

immunotherapy studies. At present, tumor proportion score (TPS), calculated based on preoperative biopsy specimens, acts as the predominant clinical biomarker for PD-L1 expression evaluation and immunotherapy guidance. Hence, exploring more stable and sensitive predictive biomarkers for neoadjuvant chemoimmunotherapy is of great clinical significance, representing a core research focus for subsequent clinical trials. Overall, accumulating clinical evidence demonstrates that neoadjuvant chemoimmunotherapy yields remarkable therapeutic benefits for patients with locally advanced NSCLC, supporting its widespread clinical application [43].

5. Conclusion

Synthesized clinical evidence from the aforementioned investigations demonstrates that perioperative immune checkpoint inhibitor therapy can elicit robust anti-tumor efficacy with tolerable safety profiles in patients with resectable stage I–IIIA NSCLC. Mature data from these prospective trials are expected to profoundly reshape the therapeutic paradigm for resectable NSCLC. Nevertheless, the optimal therapeutic regimen for immune checkpoint inhibitors—encompassing dosage, treatment duration, routes of administration, and timing of intervention—remains to be fully elucidated. Further basic investigations and clinical trials are warranted to resolve these unresolved clinical issues [44]. The predictive performance of current tumor markers for NSCLC is inconsistent. As precision therapy becomes mainstream for advanced NSCLC, constructing comprehensive biomarker panels has become an important approach to enhance the predictive performance of immunotherapy biomarkers [45]. Corticosteroids serve as the primary intervention for immune-related adverse events. Even when low-dose corticosteroids are applied briefly, ICI therapeutic potency remains unimpaired; however, long-term or high-dose corticosteroid intervention is generally associated with suboptimal clinical prognosis. As such, the current diagnostic standards for immune-related adverse events remain in need of further optimization, while proactive research priorities should focus on discovering reliable predictive biomarkers for therapeutic efficacy [46]. In addition, in-depth comprehension of how immune checkpoint inhibitors exert therapeutic effects can guide the formulation of rational clinical regimens. Furthermore, elucidating the functional mechanisms of immune checkpoint inhibitors is conducive to formulating individualized and rational clinical therapeutic regimens. Moreover, a deeper understanding of how immune checkpoint inhibitors function at the molecular level enables clinicians to design more individualized and evidence-based therapeutic regimens.

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