Exploration of immunotherapy modalities in stage III unresectable non-small cell lung cancer (Review)

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Abstract. In recent years, the treatment of stage III unresectable non-small cell lung cancer (NSCLC) has witnessed notable progress due to the application of immune checkpoint inhibitors, which markedly improved patient prognosis. On the basis of pivotal studies such as PACIFIC and GEMSTONE-301, immune consolidation therapy has become the standard regimen. Durvalumab consolidation therapy extended the median progression-free survival (mPFS) from 5.6 to 16.9 months [hazard ratio (HR)=0.55] and the median overall survival from 29.1 to 47.5 months (HR=0.72), thus increasing the 5-year survival rate by ~10%. Sugemalimab demonstrated similar benefits (mPFS, 9.0 vs. 5.8 months; HR=0.64). Currently, immune consolidation therapy serves as the core treatment strategy, whereas induction therapy and treatment de-escalation strategies provide novel options for specific patient populations. The optimization of treatment sequencing is being integrated with dynamic circulating tumor DNA (ctDNA) monitoring. ctDNA clearance after chemoradiotherapy indicates further remission and notably improved survival outcomes. Furthermore, emerging therapeutic modalities such as antibody-drug conjugates and bispecific antibodies are potentially expected to further reshape the treatment landscape in the future. The present review aimed to provide an evidence-based framework for individualized precision treatment for stage III unresectable NSCLC.

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1. Introduction

Lung cancer is the leading cause of cancer burden in China, accounting for 22.0% of all novel malignant tumor cases and 28.5% of all cancer-related mortalities (1). According to the classification of the World Health Organization, lung cancer is divided into non-small cell lung cancer (NSCLC) and SCLC. NSCLC accounts for ~85% of cases and includes subtypes such as squamous cell carcinoma, adenocarcinoma and large cell carcinoma. At the time of diagnosis, ~70% of patients with NSCLC present with distant metastasis, thus resulting in a relatively low overall survival (OS) rate (2).

It has been reported that ~30% of patients with NSCLC, which is one of the most common malignant tumors worldwide, are diagnosed at a locally advanced stage (stage III). Stage III NSCLC exhibits notable heterogeneity, with 5-year survival rates of 36, 26 and 13% for stages IIIA, IIIB and IIIC (3), respectively; this highlights the difficulty of treatment and the urgency of unmet clinical needs (4). In terms of resectability, stage III NSCLC can be categorized into three groups (3): i) Resectable (e.g., stage IIIA with N0/N1 status, certain single-station N2 cases); ii) unresectable (e.g., certain stage IIIA and IIIB cases and all stage IIIC cases) and iii) potentially resectable (e.g., certain stage IIIA and IIIB cases) (5-7).

The Robinson classification is widely adopted in clinical practice to precisely guide treatment and assess prognosis. This classification stratifies stage IIIA NSCLC into four subgroups on the basis of the involvement pattern of the mediastinal lymph nodes (N2) (single-station vs. multi-station) and the size and extent of invasion of the primary tumor (bulky vs. non-bulky) (8). Typically, N2 disease with

'single-station, non-bulky' features is more likely to benefit from multimodal therapy incorporating surgery; by contrast, N2 disease with 'multi-station, bulky' characteristics is clearly indicated for definitive chemoradiotherapy (CRT) followed by subsequent immune consolidation therapy. This classification facilitates the implementation of individualized treatment decisions.

Traditional CRT has limited efficacy, high recurrence rates and poor long-term survival outcomes in unresectable stage III NSCLC. This paradigm was transformed by the PACIFIC trial, in which durvalumab consolidation therapy significantly improved outcomes, demonstrating a higher objective response rate (ORR by BICR) of 29.8% compared to 18.3% in the placebo group (9). The treatment of this subtype faces multiple complex challenges because it is necessary to not only effectively control the local tumor burden but also inhibit the occurrence and progression of distant micrometastases. Although traditional treatment modalities, such as radiotherapy or chemotherapy, can alleviate the disease to a certain extent, their overall efficacy remains limited, the recurrence rates are high and the long-term survival prognosis of patients remains unsatisfactory.

In recent years, the advent of immune checkpoint inhibitors (ICIs) has revolutionized the landscape of cancer treatment, particularly for NSCLC, by offering patients novel therapeutic options. By reactivating the host antitumor immune response, ICIs [e.g., programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors] have not only demonstrated notable efficacy in advanced NSCLC but have also been gradually extended to the treatment of locally advanced and early-stage disease (10). Compared with traditional radiotherapy and chemotherapy, immunotherapy delivers more durable antitumor effects while markedly reducing the incidence of severe chemotherapy-related adverse events (AEs) (11). However, the key focus of current research is on how to effectively combine immunotherapy with existing treatment modalities to achieve synergistic benefits in patients with stage III unresectable NSCLC.

Since 2017, the PACIFIC trial has pioneered a novel treatment paradigm for stage III unresectable NSCLC: Durvalumab consolidation therapy following concurrent CRT (CCRT), which has markedly improved patient survival (12,13). On the basis of the findings, the 'PACIFIC model' has established a novel standard for the treatment of this patient population. Nevertheless, molecular analysis in this cohort revealed that patients with driver gene alterations, particularly those harboring epidermal growth factor receptor (*EGFR*) gene mutations, derived limited benefits from immune consolidation therapy (14).

Furthermore, real-world data indicated that only 50% of patients with stage III NSCLC receive definitive treatment in routine clinical practice. Among patients who undergo CRT, approximately two-thirds receive CCRT, whereas one-third receive sequential CRT (SCRT) (15). A subset of patients treated with CCRT are ineligible for durvalumab consolidation therapy due to residual toxicity, impaired performance status (PS), disease progression or PD-L1 expression <1% (in the European Union) (16). There is an urgent need for novel treatment approaches for patients who have not been cured or are ineligible for consolidation therapy. By contrast, ~20% of patients are cured after CCRT and do not require durvalumab consolidation (17). Therefore, identifying this cured subgroup is key to avoiding unnecessary immunotherapy-related toxicities and reducing healthcare costs.

Immunotherapy has transformative potential for unresectable stage III NSCLC; however, its full clinical effect remains to be elucidated. Emerging strategies, including novel immune targets and multimodal therapeutic approaches, may further enhance patient survival and quality of life (18,19). The present review synthesizes current evidence to guide the evolution of precision medicine in this complex clinical landscape.

2. Mechanisms of immunotherapy

Fundamental principles and current developments. Immunotherapy has emerged as a transformative approach for NSCLC treatment by targeting the activation of the host immune system to specifically recognize and eliminate tumor cells (20). Unlike traditional therapies, immunotherapy exploits the durability and memory of the immune system, thus offering the potential for long-term survival in patients with advanced-stage cancer. Current treatment strategies include: i) ICIs; ii) chimeric antigen receptor T-cell therapy; iii) cancer vaccines; and iv) cytokine therapy (21,22).

Molecular mechanisms of ICIs

PD-1/PD-L1 pathway. PD-1 (also known as CD279) is primarily expressed on the surface of activated T cells, whereas its ligand, namely PD-L1 (also known as B7-H1 or CD274), is highly expressed in various tumor cells. Upon the binding of PD-1 to PD-L1, inhibitory signals are transmitted, thus leading to T-cell exhaustion, which is a key mechanism underlying tumor immune escape (23). PD-1/PD-L1 inhibitors restore the antitumor activity of T cells by blocking this interaction. PD-L1 expression has an 'immune switch' indication function: PD-L1 expression ≥50% indicates a strong potential for immune response, which supports single-agent immunotherapy or combination strategies, whereas PD-L1 expression <1% suggests a high likelihood of primary resistance, which necessitates intensified combination therapies (e.g., chemotherapy plus immunotherapy).

Cytotoxic T lymphocyte-associated protein 4 (CTLA-4) pathway. CTLA-4 functions during early immune activation by competitively binding B7 molecules (CD80/CD86) on antigen-presenting cells (APCs), thus inhibiting T-cell activation and IL-2 secretion (24). Furthermore, CTLA-4 upregulation in regulatory T cells (Tregs) induces dendritic cell tolerance and indoleamine 2,3-dioxygenase-mediated immunosuppression (25).

Combinatorial blockade strategies. Clinical studies have reported that blocking both the PD-1 and CTLA-4 pathways simultaneously can produce a synergistic effect (19,26,27). Tregs reduce the expression levels of CD80/CD86 in APCs through CTLA-4-dependent macrophage effects, thereby inhibiting the T cell-stimulating activity of APCs. The decrease in CD80/CD86 on APCs can have a dual inhibitory effect on the T-cell immune response by restricting the co-stimulation of CD80/CD86 T cells and increasing the amount of free PD-L1 available to inhibit the expression level of PD-1 on effector T cells (28). This combination strategy can comprehensively

relieve immunosuppression in the tumor microenvironment and markedly improve the therapeutic effect. However, this may increase the incidence of immune-related adverse reactions (29). Although single-agent CTLA-4 inhibitor therapy has not demonstrated notable activity in stage III NSCLC, its combination with PD-1/PD-L1 inhibitors has emerged as a key clinical research strategy, as exemplified by trials such as BTCRC-LUN16-081 and CheckMate 9LA, which will be discussed in the following sections.

3. Distinct therapeutic modalities for stage III unresectable NSCLC

In recent years, the use of immunotherapeutic agents for unresectable stage III NSCLC has emerged as a frontier area of research (30). Findings from multiple randomized controlled trials (RCTs) have provided novel treatment options for this patient population, which have effectively prolonged the survival of a subset of patients with advanced NSCLC (31,32). However, not all patients respond well to ICI therapy and certain patients may even develop severe AEs. Therefore, different ICIs should be selected for different subtypes of patients with NSCLC to achieve optimal therapeutic outcomes (13,33).

Sequential therapeutic modality: Immunotherapy consolidation post-CRT. In the treatment of stage III unresectable NSCLC, CRT serves as the standard treatment approach and includes two main methods: CCRT and SCRT (27). After completing CRT, immune consolidation therapy is regarded as a key strategy to further improve the therapeutic effect and can be divided into two modalities: Single-agent immunotherapy and a combination of immunotherapy with other drugs (Table I) (34).

In the PACIFIC trial (35), compared with the control arm (placebo), the experimental arm (durvalumab) reported markedly prolonged OS and progression-free survival (PFS). Specifically, in the durvalumab group (12), the median OS was 47.5 months, which is markedly higher compared with the 29.1 months in the placebo group, with a hazard ratio (HR) of 0.68 (95% CI, 0.53-0.87). The 5-year OS rate was 42.9% in the durvalumab group vs. 33.4% in the placebo group. In terms of disease control, the median PFS in the durvalumab group was 16.8 months (95% CI, 13.1-23.9), which is markedly higher compared with 5.6 months (95% CI, 4.6-7.8) in the placebo group, with an HR of 0.52 (95% CI, 0.42-0.65). The 5-year PFS rates in the durvalumab and placebo groups were 33.1 and 19.0%, respectively. Furthermore, the therapeutic effect of durvalumab was independent of PD-L1 expression levels: Similar survival benefits were observed in both subgroups with PD-L1 expression <25% and ≥25% (Table II). Further subgroup analysis indicated that in patients with PD-L1 expression ≥1%, durvalumab demonstrated highly consistent benefits in terms of PFS (HR=0.46) and OS (HR=0.68) compared with placebo (13). For patients with PD-L1 expression <1%, the PFS benefit was consistent with that in the overall population (HR=0.73); however, the initial OS analysis revealed no statistically significant difference (HR=1.14). Regulatory agencies held differing stances on the basis of these data: The US Food and Drug Administration (FDA) considered the OS and PFS benefits in the overall intention-to-treat population to be of high clinical significance and deemed that the PFS benefits and eventual OS trend observed in the PD-L1 <1% subgroup to be sufficient to support durvalumab use in this population (36). By contrast, the European Medicines Agency (EMA) and certain other regulatory authorities required PD-L1 expression ≥1%. The EMA emphasized the uncertainty of initial OS data in the PD-L1 <1% subgroup and restricted approval to patients with PD-L1$^+$ tumors as a precautionary measure. This discrepancy implies regional variations in clinical practice (37). Nevertheless, international consensus and guidelines generally recommend the following (17,38,39): i) PD-L1 analysis should be performed for all patients; ii) patients with PD-L1 ≥1% should be strongly recommended to receive durvalumab consolidation therapy; and iii) for patients with PD-L1 <1%, individualized decisions should be made on the basis of multidisciplinary team (MDT) discussions; considerations of clinical characteristics [e.g., disease burden, depth of response to CRT and circulating tumor DNA (ctDNA) clearance status], potential benefits and risks; and collaborative decision-making with patients. In terms of safety, durvalumab exhibited an acceptable toxicity profile. The incidence of grade 3 or higher all-cause AEs was 30.5% in the durvalumab group vs. 26.1% in the placebo group, thus confirming the controllable toxicity of immunotherapy (13) (Table III). These results demonstrated that durvalumab, as a consolidation therapy for patients with stage III unresectable NSCLC who have completed CCRT, markedly improves long-term survival, thus establishing its pivotal role as a standard treatment regimen (40). As a major milestone in immunotherapy for stage III NSCLC, it is the first to validate the efficacy of durvalumab consolidation therapy after CCRT, to the best of our knowledge. However, despite notable improvements in the 5-year survival rate, most patients still fail to achieve long-term survival (12), thus highlighting the need for further optimization of this treatment modality. Several large-scale real-world studies have further verified the efficacy and safety of durvalumab in routine clinical practice (41,42).

The PACIFIC-R study (43), which utilized real-world data, validated the long-term survival benefit of durvalumab administered after CCRT, with a 3-year OS rate of 64.8%. As the first phase III RCT that enrolled patients who received SCRT, the GEMSTONE-301 study (44) demonstrated that sugemalimab markedly prolonged PFS compared with placebo, thereby expanding the clinical applicability of immune consolidation therapy. Single-arm investigations revealed the following: In PACIFIC-6, among older/infirm patients (45) following SCRT, the median OS was 39.0 months with a 3-year OS rate of 56.5% and the incidence of grade 3/4 treatment-related AEs (TRAEs) remained as low as 6.0% throughout the treatment course. The LUN14-179 study (46), which employed pembrolizumab as maintenance therapy, reported a median time to disease metastasis or mortality of 30.7 months and a 2-year OS rate of 61.5%, thus indicating the therapeutic potential of PD-1 inhibitors in this clinical setting. It is key to note that variations in the median PFS across studies (ranging from 9.0 to 25.6 months) are likely associated with differences in the inclusion criteria and treatment protocols. Collectively, these findings demonstrated

Table I. Sequential treatment modalities: Immune consolidation after chemoradiotherapy.

First author, year	Study name	Treatment protocol	Median PFS	OS rate	ORR	(Refs.)
Spigel *et al*, 2022	PACIFIC	CCRT → durvalumab vs. placebo (12 months)	16.8 vs. 5.6 months	5-year, 42.9% vs. 33.4% (HR=0.72)	NA	(12)
Filippi *et al*, 2024	PACIFIC-R	CCRT → durvalumab (real-world clinical data)	25.6 months	3-year, 64.8%	NA	(43)
Zhou *et al*, 2022	GEMSTONE-301	CRT → sugemalimab vs. placebo (24 months)	9.0 vs. 5.8 months (HR=0.64)	NA	NA	(44)
Garassino *et al*, 2022	PACIFIC-6	SCRT → durvalumab (elderly/infirm patients)	NA	3-year, 56.5%	NA	(45)
Durm *et al*, 2020	LUN14-179	CCRT → pembrolizumab (12 months)	15 months	2-year, 61.5%	NA	(46)
Weismann *et al*, 2024	BTCRC-LUN16-081	CCRT → nivolumab ± ipilimumab (6 months)	Dual-immunotherapy group, 67% vs. single-agent, 62.3%	NA	NA	(49)
Herbst *et al*, 2022	COAST	CCRT → durvalumab ± oleclumab/monalizumab	NA	NA	Oleclumab group ORR, 35.5% vs. single-agent, 17.9%	(29)

PFS, progression-free survival; OS, overall survival; ORR, objective response rate; NA, not available; CRT, chemoradiotherapy; CCRT, concurrent CRT; SCRT, sequential CRT; HR, hazard ratio.

Table II. Efficacy of durvalumab by PD-L1 expression level.

PD-L1 expression level, %	5-year OS rate (durvalumab), %	5-year OS rate (placebo), %	HR (95% CI)
<1 (n=105)	33.1	17.0	0.72 (0.51-1.01)
1-24 (n=201)	45.2	26.1	0.59 (0.43-0.82)
≥25 (n=170)	43.3	29.6	0.63 (0.45-0.88)

Durvalumab significantly improved OS across all PD-L1 expression subgroups (all HR<1) without statistical heterogeneity (interaction P=0.29). PD-L1, programmed death-ligand 1; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.

Table III. PACIFIC 5-year follow-up data.

Safety parameters	Durvalumab, %	Placebo, %
Any-grade AEs	96.8	94.9
Grade 3-4 AEs	30.5	26.1
Immune-related AEs	24.3	8.1

Pneumonia characteristics: Grade 3-4 pneumonia incidence, 4.4 vs. 3.8%; median onset time, 4.8 months; 92% of cases controlled with treatment discontinuation + corticosteroids. AE, adverse event.

that immunotherapy, when used as maintenance therapy after CRT for stage III NSCLC, exhibits favorable efficacy and safety profiles and is capable of prolonging both PFS and OS. Although pembrolizumab has exhibited notably increased efficacy to durvalumab in certain studies, further RCTs are necessary to definitively validate this advantage (47,48). These investigations provide key evidence for the clinical implementation of immunotherapy in patients with stage III NSCLC and highlight the need to optimize treatment strategies, identify appropriate patient populations and explore the potential of additional immunotherapeutic agents to further improve patient outcomes.

The BTCRC-LUN16-081 study (49) pioneered the exploration of dual-immunotherapy consolidation (nivolumab ± ipilimumab) after CCRT and achieved 18-month PFS rates of 62.3-67.0% and 24-month OS rates >80%; this suggested that short-course dual-immunotherapy regimens may serve as a viable alternative to traditional single-agent consolidation. The COAST study (29), through combination with the CD73 inhibitor oleclumab or the natural killer cell activator monalizumab, reduced the PFS HR to 0.42-0.44 and increased the objective response rate (ORR) to 35.5%, thus offering novel strategies for targeting the tumor immunosuppressive microenvironment. Notably, the discrepancies in median PFS between these two phase II studies (25.8 vs. 6.3 months) and data from the PACIFIC series may be attributed to the synergistic effects of combination therapies and variations in patient selection criteria. The results of BTCRC-LUN16-081 and COAST further

Table IV. Concurrent treatment modalities: Immunotherapy combined with chemoradiotherapy.

First author, year	Study name	Treatment protocol	Median PFS	OS rate	ORR	(Refs.)
Peters *et al*, 2021	NICOLAS	CCRT concurrent with nivolumab → nivolumab maintenance (12 months)	1-year PFS rate, 53.7%	NA	NA	(51)
Liu *et al*, 2022	DETERRED	CCRT concurrent with atezolizumab → atezolizumab maintenance (12 months)	1-year PFS rate, 55%	NA	NA	(53)
Jabbour *et al*, 2021	KEYNOTE-799	Pembrolizumab + CCRT → pembrolizumab maintenance (12 months)	30.6 months	NA	Cohort A/B ORR, 70.5/ 56.6%	(55)
Jabbour *et al*, 2022	KEYLYNK-012	Pembrolizumab + CCRT → pembrolizumab ± olaparib maintenance	Ongoing	Ongoing (NCT04815997)	NA	(56)

CRT, chemoradiotherapy; CCRT, concurrent CRT; SCRT, sequential CRT; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; NA, not available.

underscore the potential of combination regimens to enhance survival outcomes, particularly the notable benefits observed in 2-year survival rates. The ongoing PACIFIC-9 trial (50) is a double-blind, randomized, placebo-controlled phase III study that was designed to validate the efficacy of dual-target combinations (durvalumab + oleclumab/monalizumab) in patients after CCRT. With a planned enrollment of 720 patients across global multi-centers and the use of PFS and OS as primary endpoints, the trial results may directly support future clinical decision-making on combination therapy modalities. All the aforementioned studies are prospective controlled trials (BTCRC-LUN16-081 and COAST as phase II RCTs), which carry evidence levels that are markedly higher compared with those of historical control studies. Although single-arm studies project a 2-year OS rate of 85.5% for sequential dual immunotherapy, data from RCTs remain the cornerstone in guiding clinical practice.

Concurrent treatment modalities: Immunotherapy combined with CRT. A triple therapy combining immunotherapy, chemotherapy and radiotherapy aims to prevent delays in initiating immunotherapy due to toxicity or disease progression after CRT while potentially exploiting the synergies between immunotherapy and chemotherapy. The NICOLAS, DETERRED, KEYNOTE-799 and KEYLYNK-012 trials have evaluated the synergistic effects of immunotherapy combined with CCRT (Table IV).

The NICOLAS study (51) assessed the efficacy and safety of nivolumab combined with CCRT for unresectable stage III NSCLC. The treatment protocol involved the addition of nivolumab starting from the second cycle of platinum-based chemotherapy during radiotherapy, followed by nivolumab consolidation for 1 year. Results demonstrated a 6-month incidence of grade ≥3 pneumonitis of 11.7% without a notable increase in radiation pneumonitis risk (52). Survival outcomes included a median PFS of 12.7 months, 1-year PFS rate of 53.7%, median OS of 38.8 months and 2-year OS rate of 63.7%. Patients with stage IIIA disease had a markedly higher 2-year OS rate compared with those with stage IIIB disease (81 vs. 56%; P=0.037). This study confirmed the safety and feasibility of concurrent immunotherapy, which offers a novel treatment option for inoperable patients in the future.

The DETERRED study (53) employed a design similar to that of NICOLAS, namely, a combination of atezolizumab with CCRT followed by 1-year immune maintenance therapy. This study met its primary endpoint (safety), with 20% of patients experiencing grade ≥3 immune-related AEs (54). irAEs encompass a spectrum of side effects resulting from immune checkpoint inhibitor-induced overactivation of the immune system, which can lead to autoimmune-like attacks on normal tissues. These events can affect virtually any organ system. Common and clinically significant examples include immune-mediated pneumonitis (presenting as cough and dyspnea), colitis (causing diarrhea and abdominal pain),

Table V. Induction-consolidation modalities: Integrating immunotherapy across the treatment continuum.

First author, year	Study name	Treatment protocol	Median PFS	OS rate	DCR	(Refs.)
Ross *et al*, 2024	AFT-16	Atezolizumab induction → CCRT → atezolizumab (12 months)	30.0 months	NA	12-week DCR, 74.2%	(59)
Paz-Ares *et al*, 2021	CheckMate 9LA	Nivolumab (360 mg once every 3 weeks) + ipilimumab (1 mg/kg once every 6 weeks) + 2 cycles of chemotherapy → immune maintenance (≤2 years) vs. 4 cycles of chemotherapy + pemetrexed (non-squamous NSCLC)	NA	Median OS, 15.8 vs. 11.0 months (HR=0.72); 2-year OS rate, 38 vs. 26%; 4-year OS rate, 21 vs. 16%; 1-year OS rate in Asian patients, 93% ; HR in patients with PD-L1 <1%, 0.62	NA	(60)

DCR, disease control rate; PFS, progression-free survival; OS, overall survival; NSCLC, non-small cell lung cancer; HR, hazard ratio; PD-L1, programmed death-ligand 1; CCRT, concurrent chemoradiotherapy.

hepatitis (often asymptomatic, detected via liver enzyme elevation), endocrinopathies such as thyroiditis and hypophysitis, and dermatologic toxicities like rash and pruritus. The median PFS was 13.2 months, the 1-year OS rate was 80% and the 1-year PFS rate was 55%.

The phase II KEYNOTE-799 trial (55) adopted a sequential immune strategy: Patients received upfront immune induction, followed by CCRT combined with pembrolizumab and then 1 year of pembrolizumab consolidation. The primary endpoint, namely, ORR, was 70.5% in groups A (squamous and non-squamous NSCLC) and B (squamous NSCLC). The median PFS was 30.6 months in group A and was not reached in group B (including the induction phase).

The phase III KEYLYNK-012 study (56), which was sponsored by Merck Sharpe & Dohme, aimed to evaluate three maintenance therapy regimens, namely, pembrolizumab alone (group A), pembrolizumab plus the poly(adenosine diphosphate-ribose) polymerase inhibitor olaparib (group B) and durvalumab (group C), after pembrolizumab combined with CCRT for unresectable locally advanced stage III NSCLC.

Furthermore, ongoing investigations of immunotherapy-CRT combinations have focused on optimizing the treatment sequence and dosage to maximize efficacy while minimizing toxicity. A post-hoc analysis of KEYNOTE-799 suggested that different administration sequences may markedly affect patient immune responses, with upfront immunotherapy potentially enhancing the efficacy in tumors with high PD-L1 expression (57). Collectively, these studies demonstrated the notable survival benefits of immunotherapy-CRT combinations, particularly in achieving a favorable balance between safety and efficacy. This provides strong support for the treatment of unresectable stage III NSCLC and potentially lays the foundation for the further optimization of therapeutic strategies in the future.

Induction-consolidation modalities: Integrating immunotherapy across the treatment continuum. The administration of immunotherapy before CRT (e.g., the immune induction strategy) (57,58) aims to expand access to immunotherapy for more patients while enhancing the efficacy of subsequent treatments. Related studies have explored the feasibility and efficacy of this strategy for the treatment of unresectable stage III NSCLC (Table V).

The phase II AFT-16 trial (59) investigated atezolizumab induction followed by CCRT in stage III NSCLC. The protocol consisted of two cycles of atezolizumab induction, two cycles of consolidation, CCRT and 1 year of immune maintenance. The short-term outcomes demonstrated a 12-week disease control rate of 74.2%, ORR of 66.2%, median PFS of 30.0 months and 24-month OS rate of 73.7%. Notable tumor regression was observed in certain patients, although the major pathological response rate was not reported. These findings suggested that immune induction may enhance CRT sensitivity. However, phase II trials are required to validate this generalizability in the future.

In the randomized phase III CheckMate 9LA study (NCT03215706) (60), first-line nivolumab plus ipilimumab plus two cycles of chemotherapy markedly improved OS, PFS and ORR compared with chemotherapy alone (four cycles). Clinical benefits were observed irrespective of the PD-L1 expression level or tumor histology.

Table VI. Treatment de-escalation strategies.

First author, year	Study name	Treatment protocol	Median PFS	OS rate	ORR	(Refs.)
Ohri *et al*, 2024	SPRINT	Pembrolizumab + radiotherapy (PD-L1 ≥50%)	1-year PFS rate, 76%	1-year OS rate, 92%	NA	(62)
Mouri *et al*, 2024	NEJ039A	Low-dose chemotherapy + radiotherapy → durvalumab (elderly patients)	10.2 months	NA	NA	(63)
Bozorgmehr *et al*, 2023	TRADE-hypo	Durvalumab + conventional vs. hypofractionated radiotherapy	2-year PFS rate, 48% (hypofractionated) vs. 42% (conventional)	NA	NA	(64)

PFS, progression-free survival; OS, overall survival; ORR, objective response rate; NA, not available; PD-L1, programmed death-ligand 1.

By priming the immune system through upfront immunotherapy, this induction strategy offers a novel option for the comprehensive management of stage III NSCLC in the future (61). AFT-16 provided initial evidence of its feasibility, demonstrating robust disease control, prolonged PFS and promising pathological response rates. CheckMate 9LA further explored the potential of combining induction immunotherapy with maintenance treatment and offers key insights into optimizing future protocols. However, defining the patient populations that are most suitable for immune induction and refinement of treatment sequences remain key areas for future research.

Treatment de-escalation strategies. Treatment de-escalation strategies aim to reduce toxicity by replacing or minimizing chemotherapy and CRT doses, particularly in patients with poor PS, advanced age or high PD-L1 expression. However, dose reduction may compromise efficacy; therefore, studies are limited to specific patient populations (Table VI).

The SPRINT study (NCT03523702) evaluated a chemotherapy-free regimen in patients with PD-L1 expression ≥50% (62). The participants received 3 cycles of pembrolizumab induction, followed by radiotherapy and 12 cycles of pembrolizumab consolidation. Interim analysis demonstrated a 1-year PFS rate of 76% and a 1-year OS rate of 92%. For patients with PD-L1 <50%, restaging positron emission tomography-CT indicated that the 1-year PFS rate reached 100% in partial responders compared with 61% in those with stable disease or progressive disease, thus highlighting the importance of early adaptive treatment assessment. The NEJ039A study (jRCTs031190070) explored the feasibility of de-escalation by evaluating durvalumab after daily carboplatin-based concurrent radiotherapy in patients with a PS score of 2 and/or age of >74 years (63). The TRADE-hypo trial (NCT04351256), which is an open-label randomized phase II study (64), assessed durvalumab combined with conventional fractionated (30 fractions of 2 Gy) and hypofractionated (20 fractions of 2.75 Gy) thoracic radiotherapy in chemotherapy-ineligible patients.

These studies suggested that treatment de-escalation holds promise in selected populations. However, its efficacy and safety require further validation, particularly on early adaptive assessments and individualized treatment adjustments.

Debate regarding consolidation vs. induction therapy modalities. In the treatment landscape of stage III unresectable NSCLC, immune consolidation following CCRT is the standard regimen and is supported by the highest level of evidence and an optimal risk-benefit ratio (12,17). However, to further overcome efficacy bottlenecks, researchers have begun exploring the upfront use of immunotherapy in the neoadjuvant setting (induction therapy), sparking a 'debate between consolidation and induction modalities' (65). Despite promising results in phase II studies, the addition of immune induction therapy was negated by negative findings from the phase III CHECKMATE-73L trial (66), thus indicating that increasing the treatment intensity and phases is inadvisable. This phase III study compared two strategies: Induction with nivolumab plus ipilimumab followed by CCRT and nivolumab consolidation vs. CCRT followed by durvalumab consolidation. The results demonstrated that PFS and OS in the experimental arm (induction + consolidation) were not notably increased compared with those in the control arm (PACIFIC modality), whereas incidences of grade 3-4 TRAEs and treatment-discontinuing events were higher. Consolidation therapy is suitable for the majority of patients with stage III unresectable NSCLC, particularly those with PD-L1 positivity, who could successfully complete CCRT and maintain a good PS score. For PD-L1$^-$ patients, MDT discussions are required before making decisions. The failure of CHECKMATE-73L may stem from an overly aggressive regimen (toxicity overlap from dual immunotherapy plus CRT), thus highlighting the need to explore short-course induction modalities using single-agent immunotherapy or immunotherapy combined with chemotherapy. Notably, the aforementioned COAST and PACIFIC-9 trials explored combination strategies based on consolidation

therapy rather than upfront induction. This 'consolidation intensification' approach may hold more promise compared with the 'induction + consolidation' model in the future.

Treatment for special populations: Patients with EGFR mutations. For patients with NSCLC harboring *EGFR* mutations, the efficacy of single-agent immunotherapies is generally limited (67). Previous studies have reported that patients with *EGFR* mutations have relatively low response rates to PD-1/PD-L1 inhibitors, which may be attributed to factors such as a low tumor mutational burden (TMB), reduced T-cell infiltration, increased infiltration of immunosuppressive cells and downregulated expression levels of major histocompatibility complex class I molecules. First-line single-agent ICI therapy has limited efficacy in patients with *EGFR*-mutated NSCLC and may even be harmful (e.g., hyperprogression). Current treatment strategies primarily focus on *EGFR* tyrosine kinase inhibitor (TKI)-based targeted therapy (17,68,69). Results from the LAURA trial demonstrated that the study met its primary PFS endpoint: The median PFS as assessed by blinded independent central review was 39.1 months in the osimertinib group vs. 5.6 months in the placebo group (P<0.001), with an HR for disease progression or mortality of 0.16 (95% CI, 0.10-0.24; P<0.001). The PFS curves diverged from the initiation of treatment, thus indicating that osimertinib, a third-generation *EGFR*-TKI, markedly improved the PFS in patients with *EGFR*-mutated stage III unresectable NSCLC following definitive CRT and reduced the risk of disease progression or mortality by 84%. These findings confirmed the notable efficacy of osimertinib as consolidation therapy in patients with *EGFR*-mutated stage III unresectable NSCLC (70).

Although existing research has furnished evidentiary support for immunotherapy in stage III NSCLC, notable variability in patient populations, trial designs and real-world applicability has undermined the reliability and extrapolability of the evidence (15,55). A systematic review is imperative to delineate the boundaries of clinical decision-making. Nevertheless, phase III trials such as PACIFIC and GEMSTONE-301 have established the role of anti-PD-L1 consolidation therapy, the marked disparities in the inclusion and exclusion criteria of patient populations have imposed limitations on cross-study comparisons and real-world generalizations. The PACIFIC trial expressly excluded patients with *EGFR*/anaplastic lymphoma kinase mutations (constituting ~15-20% of stage III NSCLC cases) and those with baseline interstitial lung disease. By contrast, while GEMSTONE-301 incorporated an *EGFR* mutation subgroup, no notable PFS benefit was observed (HR=0.83; 95% CI, 0.49-1.42) (13,44). This implies that the standard conclusion of 'consolidation immunotherapy' may not be applicable to patients with positive driver gene mutations. Furthermore, population representativeness bias has exacerbated the limitations of the evidence. In trials led by the United States and Europe, such as CheckMate 9LA, white patients accounted for 70-80% of the study population (60). By contrast, GEMSTONE-301, which predominantly enrolled Asian patients, reported a 2-year OS rate of 64.1%, notably higher compared with 57.0% in the PACIFIC trial. This discrepancy may be attributed to ethnicity-related tumor biological characteristics (such as TMB levels) or variances in treatment tolerance. The heterogeneity in trial designs has further complicated the interpretation of the evidence. PACIFIC employed 'central radiological review' to adjudicate PFS, whereas single-arm trials such as BTCRC-LUN16-081 relied on 'local investigator assessment'. In accordance with FDA guidelines, local assessment may overestimate the ORR by 10-15%, potentially introducing bias into the reported 38% ORR in BTCRC-LUN16-081. Simultaneously, KEYNOTE-799 designated 'ORR' as the primary endpoint, which cannot be directly compared with the 'OS/PFS' endpoints of PACIFIC, rendering it arduous to discern the superiority between 'induction immunotherapy 'and 'consolidation immunotherapy' (55,71). Numerous early combination therapy studies (e.g., ipilimumab + durvalumab) utilized single-arm designs, lacked placebo controls and failed to report key real-world endpoints such as 'time to treatment failure (TTF)' (55,71,72). TTF takes into account both treatment efficacy and treatment discontinuation due to toxicity. By contrast, single-arm studies primarily focus on ORR/PFS, potentially obscuring the risk of treatment interruption attributable to immune-related toxicities (e.g., grade 3 pneumonia), thereby undermining the assessment of treatment feasibility (73,74).

These limitations suggest that future reviews should place further emphasis on 'the applicable scenarios of evidence' rather than merely aggregating conclusions, in order to more effectively guide individualized treatment.

4. Biomarker-guided treatment decisions: Current status and challenges

PD-L1 expression. Currently, the expression level of PD-L1 is the most extensively studied biomarker and the only one incorporated into clinical practice guidelines (75). A post-hoc analysis of the PACIFIC trial demonstrated that durvalumab conferred definite survival benefits in patients with PD-L1 expression ≥1%, whereas the benefit became more uncertain in those with PD-L1 <1% (76). This finding directly led to discrepancies in regulatory approvals: The FDA has no restriction on PD-L1 status, whereas the EMA requires PD-L1 ≥1%. However, the predictive value of PD-L1 is associated with notable limitations: i) Spatial and temporal heterogeneity (discrepancies may exist between primary and metastatic lesions as well as between biopsy and surgical specimens); and ii) lack of unified interpretation criteria [the coexistence of different detection antibodies (e.g., 22C3 and SP263) (77,78) and interpretation cut-offs (1 vs. 50%) creates confusion regarding clinical decision-making].

ctDNA. Dynamic ctDNA monitoring has demonstrated notable potential as a promising 'liquid biopsy' tool for the diagnosis of stage III NSCLC. Previous studies have indicated that ctDNA clearance after CRT or during consolidation immunotherapy is strongly associated with a markedly prolonged PFS and OS (79,80). By contrast, persistent ctDNA positivity or reappearance may indicate minimal residual disease (MRD) and treatment resistance, thus providing opportunities for early intervention or therapeutic strategy adjustment (81). Nevertheless, its clinical application still faces challenges: Information remains insufficient regarding the optimal

monitoring timing (post-CRT, pre-consolidation therapy or during treatment), standardized detection techniques and prospective clinical trial evidence supporting interventions based on ctDNA results, which represent key directions for future research.

TMB. Although higher TMB levels have been confirmed to be associated with higher immunotherapy efficacy for advanced NSCLC, data on its predictive role in stage III NSCLC are limited and controversial (82). Late-phase studies, such as CheckMate 227, have supported the value of TMB; however, an exploratory analysis of the phase III PACIFIC trial failed to validate the predictive effect of the TMB (12,83,84). This highlights a major challenge in TMB applications, namely, the lack of standardization. The transition from whole-exome sequencing to targeted sequencing panels, variations in calculation methods and undefined thresholds have not been unified, thus severely restricting the routine clinical use of TMB in stage III NSCLC.

5. Conclusion and future perspectives

The treatment of stage III unresectable NSCLC has established a standard paradigm that is centered on immune consolidation therapy following CCRT. Among these approaches, durvalumab has become the standard regimen on the basis of the results of the PACIFIC trial, thus markedly improving PFS and OS. Despite this progress, >50% of patients still experience disease progression (12), thus highlighting the unmet clinical needs and limitations of current treatment strategies. Despite the existing evidence, the clinical management of stage III NSCLC still faces multiple challenges.

Future breakthroughs will depend on a shift toward individualized precision treatment strategies. First, the dynamic monitoring of ctDNA for the assessment of MRD and early treatment responses will provide a basis for early intervention in 'molecular recurrence' and personalized management of treatment duration. Second, the development of novel combination therapies targeting resistance mechanisms, such as immunotherapy combined with agents targeting the tumor microenvironment (e.g., CD73 and natural killer group 2 member A) (29) or strategies addressing specific resistance mutations, will be key. Bispecific antibodies (BsAbs) and antibody-drug conjugates (ADCs) represent promising novel directions (85). BsAbs (e.g., the PD-L1/TGF-β trap M7824) aim to block multiple immunosuppressive pathways simultaneously (86), but their clinical development has been hindered by overlapping toxicities (e.g., hepatotoxicity and cutaneous events) and failure to meet efficacy expectations. By contrast, ADCs (e.g., trophoblast cell surface antigen 2-DXd, human *EGFR* 2-DXd and human *EGFR* 3-DXd) have demonstrated efficacy in advanced NSCLC via a 'precision chemotherapy' mechanism (87) and their use is now being explored to intensify consolidation therapy in stage III patients or for combination with immunotherapy (the 'CCRT → ADC + immune consolidation' model), particularly in high-risk populations identified via biomarkers (e.g., ctDNA positivity or high expression levels of specific antigens) (79,88). For instance, the amivantamab regimen has emerged as one of the standard treatment options for patients with *EGFR* ex20ins mutations and resistance to osimertinib (89). Multiple phase I/II studies are currently exploring the combination of bispecific antibodies (e.g., KN046) with chemotherapy or PD-1 inhibitors for first-line treatment (90-92), with the aim of offering more efficacious and safer combination regimens for subsets of patients who may benefit. Datopotamab deruxtecan (Dato-DXd), when compared with docetaxel in patients with previously treated NSCLC, markedly prolonged PFS and demonstrated notably improved safety profiles. In the final analysis of the TROPION-Lung02 trial, the combination of Dato-DXd and pembrolizumab ± platinum-based chemotherapy exhibited durable antitumor activity in patients with advanced NSCLC. The ORR was 54.8% in the two-drug combination group and 55.6% in the three-drug combination group and therapeutic efficacy was evident across all PD-L1 expression level subgroups (93). In terms of safety, the tolerability of this combination regimen was consistent with the previously reported safety profiles of each individual drug and no novel toxicities were identified. Furthermore, through exploratory retrospective TROP2 QCS-NMR analysis, it was observed that for patients with positive biomarker results, both the two-drug and three-drug combination groups demonstrated a tendency towards prolonged PFS (93,94). These findings supported the evaluation of the efficacy of Dato-DXd in combination with immunotherapeutic agents ± platinum-based chemotherapy vs. standard treatment regimens in the ongoing phase III pivotal studies, namely TROPION-Lung07, TROPION-Lung08 and the AVANZAR study (94,95). Key toxicities include BsAb-mediated TGF-β inhibition (e.g., edema, which can be managed with diuretics) and ADC-associated payload toxicity (e.g., trastuzumab-DXd-induced interstitial lung disease, monitored through monthly chest CT scans). Prophylactic administration of corticosteroids (low-dose prednisone) reduces the incidence of overlapping immune-related AEs between ICIs and ADCs by ~30% (96).

The success of these strategies will ultimately rely on innovative biomarker-driven clinical trial designs (e.g., umbrella/basket trials) to efficiently identify optimal patient populations and validate novel regimens. Future research should focus on actively targeting the 'abscopal effect', wherein local radiotherapy induces immunogenic cell death to release tumor antigens, triggering a systemic antitumor immune response that leads to the regression of non-irradiated lesions (97). This effect forms the cornerstone of synergy between radiotherapy and immunotherapy. By optimizing radiotherapy regimens, combining them with novel immune agonists (e.g., stimulator of interferon genes agonists) (98,99) and integrating ctDNA monitoring, it may be possible to transform this uncommon phenomenon into a predictable and potent therapeutic strategy, thus enabling a paradigm shift from 'post-treatment consolidation' to 'intra-treatment synergy'. Integrating the latest advances in immunology, genomics and clinical medicine through interdisciplinary collaboration is expected to drive further breakthroughs in the treatment of stage III unresectable NSCLC, thus potentially providing patients with individualized, effective and safe treatment regimens in the future.

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JJ and JM conceived and designed the present study. JJ provided helpful suggestions. JM was responsible for the initial manuscript drafting and conducted the literature search and selection. JJ was responsible for critical revision and editing of the manuscript for important intellectual content. Both authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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