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The evolution of non-surgical management in stage III non-small cell lung cancer

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The management of unresectable stage III non-small cell lung cancer (NSCLC) continues to evolve with the integration of immunotherapy and targeted agents into treatment paradigms. The PACIFIC trial established consolidation durvalumab following concurrent chemoradiotherapy (CRT) as the standard of care in many settings. However, emerging evidence challenges the one-size-fits-all approach, particularly for molecularly defined subsets and specific patient populations. This debate article examines the evolving landscape of non-surgical stage III NSCLC management, presenting evidence-based arguments for refining treatment strategies based on molecular biomarkers, novel immunotherapy combinations, and alternative sequencing approaches.

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INTRODUCTION

Stage III NSCLC represents approximately 20-30% of newly diagnosed lung cancer cases, encompassing a heterogeneous population with varying tumor burden, nodal involvement, and molecular characteristics [1]. For decades, the standard treatment paradigm consisted of platinum-based concurrent chemoradiotherapy (CRT), yielding 5-year survival rates of only 15-32% [2, 3]. The therapeutic landscape transformed dramatically following the PACIFIC trial, which demonstrated that consolidation durvalumab —a programmed death-ligand 1 (PD-L1) inhibitor—significantly improved progression-free survival (PFS) and overall survival (OS) compared to placebo [4, 5]. The PACIFIC regimen established a new benchmark: median PFS of 16.9 months versus 5.6 months with placebo (HR 0.55, 95% CI 0.45-0.68, $p < 0.001$), and 5-year OS rates of 42.9% versus 33.4% [5, 6]. These results fundamentally altered clinical practice guidelines worldwide. However, as our understanding of tumor biology deepens and novel therapeutic agents emerge, critical questions arise regarding optimal patient selection, treatment sequencing, and the role of molecular biomarkers in guiding therapy. This debate article examines seven key controversies in the non-surgical management of stage III NSCLC: (1) the essential role of multimodality therapy integration, (2) consolidation immunotherapy strategies, (3) molecular-targeted approaches for oncogene-driven disease, (4) novel immunotherapy combinations, (5) chemotherapy-sparing regimens, (6) neoadjuvant strategies for converting unresectable disease, and (7) biomarker-directed patient selection. Key trials are summarized in Table 1.

THE INDISPENSABLE ROLE OF RADIATION THERAPY: TIMING AND SEQUENCING MATTER

Position

Radiation therapy remains a cornerstone of curative-intent treatment for stage III NSCLC, but the sequence and timing of RT delivery influence outcomes when combined with systemic therapies.

The integration of radiation therapy with systemic agents presents both opportunities and challenges. Preclinical evidence demonstrates that radiotherapy induces immunomodulatory changes, including upregulation of PD-L1 expression and enhancement of tumor antigen presentation [7, 8]. However, radiation also exhibits immunosuppressive effects through lymphocyte depletion and upregulation of regulatory T cells and transforming growth factor-beta (TGF-β) [9]. The PACIFIC trial mandated completion of concurrent CRT 1-42 days before randomization [4], with durvalumab benefit observed across all timing subgroups when durvalumab was initiated after completing radiotherapy [10]. Post-hoc analyses suggested that median PFS was numerically longest among patients who started durvalumab ≤14 days after RT completion, though durvalumab improved outcomes regardless of time from CRT completion [10]. This observation aligns with preclinical data suggesting that the immunostimulatory effects of radiation are transient and may be optimally captured by immediate immunotherapy administration [8]. Real-world evidence from the PACIFIC-R study, encompassing 1,399 patients across 11 countries, corroborates these findings [11]. The median time from CRT completion to durvalumab initiation dropped to 31 days overall, and to just 21 days for patients treated since 2020, reflecting updated clinical practice [12]. Despite these improvements, 18% of eligible patients failed to initiate durvalumab, most commonly due to toxicity, poor performance status, and disease progression [12]. Patients unable to start durvalumab were distinguished by significantly higher baseline lactate dehydrogenase, greater cumulative toxicity, worse post-CRT ECOG performance status, and elevated C-reactive protein, as well as lung diffusion capacity, underlining the need for tailored supportive care and prehabilitation strategies to improve treatment completion [12]. Median real-world PFS was 21.7 months (95% CI 19.1-24.5), with 48.2% of patients remaining progression-free at 24 months [11]. Notably, rwPFS (real-world

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Table 1. Summary of Key Clinical Trials Guiding the Treatment of Unresectable Stage III NSCLC

Trial Acronym	Study Start	Country of Origin	Patient Count	Patient Population	Intervention Arms	Primary Endpoint	Key Result (Median PFS and Hazard Ratio)
PACIFIC [6].	05/2014	United States of America	713	Unresectable Stage III NSCLC, post-cCRT	Durvalumab vs. Placebo	PFS, OS	Median PFS: 16.9 vs. 5.6 months; HR 0.55
LAURA [20].	07/2018	United States of America	216	Unresectable Stage III EGFRm NSCLC, post-CRT	Osimertinib vs. Placebo	PFS	Median PFS: 39.1 vs. 5.6 months; HR 0.16
COAST [24].	01/2019	United States of America	189	Unresectable Stage III NSCLC, post-cCRT	Durvalumab vs. Durvalumab + Oleclumab vs. Durvalumab + Monalizumab	ORR, PFS	PFS HRs vs. Durvalumab alone: 0.59 (Oleclumab), 0.63 (Monalizumab)
DOLPHIN [31].	09/2019	Japan	35 (efficacy); 74 enrolled	Unresectable Stage III PD-L1 + NSCLC	Concurrent Durvalumab + Radiotherapy	12-month PFS Rate	12-month PFS rate: 72.1%; Median PFS: 25.6 months

cCRT concurrent chemoradiotherapy, *EGFRm* epidermal growth factor receptor-mutated, *HR* hazard ratio, *NSCLC* non-small-cell lung cancer, *ORR* objective response rate, *OS* overall survival, *PD-L1 +* programmed death ligand-1 positive, *PFS* progression-free survival.

progression-free survival) was numerically longer among patients who received concurrent versus sequential CRT (23.7 vs 19.3 months), reinforcing the importance of treatment intensity [11]. These findings highlight that, beyond timing, patient fitness and inflammation are pivotal barriers to consolidation therapy and long-term outcomes. The mechanistic rationale for optimal RT-immunotherapy sequencing continues to evolve. Radiation induces a spectrum of effects: DNA damage, vascular injury, cytokine release, and alteration of the tumor microenvironment [7]. The challenge lies in harnessing the immunostimulatory effects while minimizing immunosuppression and responding to how these associations play out in the clinical setting. Emerging data suggest that total RT dose, fractionation schedule, and field size all influence the immune response, though optimal parameters remain under investigation [9].

CONSOLIDATION IMMUNOTHERAPY

Position

Consolidation durvalumab following definitive CRT has fundamentally transformed stage III NSCLC outcomes and represents a significant therapeutic advance in this setting.

At 5-year follow-up, durvalumab durvalumab demonstrated sustained clinical benefit with median OS of 47.5 months versus 29.1 months for placebo (HR 0.72, 95% CI 0.59–0.89), and a 5-year OS rate of 42.9% versus 33.4% [6]. The 5-year PFS rates of 33.1% versus 19.0% translate to an absolute improvement of 14.1 percentage points—a magnitude rarely observed in thoracic oncology [6]. Critically, the PFS benefit was observed across prespecified subgroups, including patients regardless of PD-L1 expression level, disease stage, histology, and smoking status [4]. Among patients with PD-L1 tumor cell expression ≥1%, median PFS was 17.8 months versus 5.6 months with placebo (HR 0.46, 95% CI 0.33–0.64) [13]. Even in the PD-L1 < 1% subgroup, durvalumab demonstrated benefit with median PFS of 10.7 months versus 5.6 months (HR 0.73, 95% CI 0.48-1.11), though the magnitude was attenuated [13]. The safety profile proved manageable, with grade 3-4 adverse events occurring in 29.9% of durvalumab-treated patients versus 26.1% with placebo [4]. Pneumonitis or radiation pneumonitis of any grade occurred in 33.9% versus 24.8%, with grade 3-4 events in 3.4% versus 2.6% [4]. Importantly, the incidence was similar to historical rates with CRT alone, suggesting that durvalumab did not substantially exacerbate radiation-related toxicity. Patient-reported outcomes further supported the clinical benefit, with durvalumab demonstrating either maintenance or improvement in health-related quality of life measures compared to placebo [14]. Time to deterioration in global health status, physical functioning, and lung cancer symptoms favored durvalumab, underscoring that survival gains were not achieved at the expense of patient well-being [4]. The real-world PACIFIC-R study validated these findings in routine clinical practice [11]. Among 1,399 patients who received durvalumab through an early access program, median rwPFS of 21.7 months and 24-month OS rate of 71.2% confirmed that the benefits observed in the controlled trial environment translate to heterogeneous patient populations [11]. Notably, 47.1% of patients completed the intended 12-month durvalumab treatment course, comparable to PACIFIC trial completion rates [11].

The phase III PACIFIC trial redefined the standard of care for unresectable Stage III NSCLC and showed an improvement 2 months after concurrent CRT as shown by PFS (i.e. 16.9 months with durvalumab vs 5.6 months with placebo) and OS (47.5 months vs 29.1 months), so the 5-year OS significantly increased to 43% [6]. Thus, the PACIFIC-R trial demonstrated the efficacy of durvalumab after concurrent CRT; however, many patients can be unfit for concurrent CRT, and sequential CRT (sCRT) is commonly used [15]. The PACIFIC-6 trial, a phase II, open-label study that enrolled 117 patients with unresectable Stage III NSCLC who had completed platinum-based sCRT with no

progression, demonstrated that durvalumab may be safe to utilize with sequential CRT. Of the patients in the trial, 27.4% had grade 3 or grade 4 adverse events, with 6.0% possibly related to the treatment, and one patient (0.9%) experienced a fatal adverse event possibly related to treatment (pneumonitis), though three patients (2.6%) experienced fatal adverse events of any cause, and 27.4% discontinued durvalumab due to adverse events [15, 16]. These adverse event and discontinuation data compare to the PACIFIC trial data of 30.5% grade ≥3 adverse events and 4.4% fatal adverse events, with 15.4% discontinuation of durvalumab due to adverse events [4], although inter-study comparisons must be made cautiously, especially since, in PACIFIC-6, durvalumab could be administered for up to 2 years versus only one year in PACIFIC, giving more time for patients to decide to discontinue therapy in the PACIFIC-6 trial, and patients in the PACIFIC-6 study were generally more frail (and thus required sequential CRT). In terms of efficacy, durvalumab with sequential CRT resulted in a median overall survival of 39 months, a median PFS of 13.1 months, and a 2-year PFS of 35.3%, with a confirmed objective response in 24 out of 117 patients [15, 16].

MOLECULAR-TARGETED THERAPY: PROMISING ADVANCES IN EGFR-DRIVEN DISEASE

Position

For patients with EGFR-mutated stage III NSCLC, targeted therapy with osimertinib represents superior consolidation treatment compared to immunotherapy, fundamentally altering the treatment algorithm for this molecular subset.

EGFR mutations occur in approximately 17% of Western patients and 48% of Asian patients with NSCLC [17, 18]. The role of immunotherapy in EGFR-mutated tumors remains controversial, with retrospective analyses suggesting diminished benefit compared to EGFR wild-type disease [19]. This biological observation prompted investigation of EGFR tyrosine kinase inhibitors (TKIs) as consolidation therapy following definitive CRT. The phase 3 LAURA trial randomized 216 patients with unresectable stage III EGFR-mutated (exon 19 deletion or L858R) NSCLC who had not progressed after platinum-based CRT to receive osimertinib 80 mg daily versus placebo [20]. The results were striking: median PFS by blinded independent central review was 39.1 months with osimertinib versus 5.6 months with placebo (HR 0.16, 95% CI 0.10-0.24, $p < 0.001$) [20]. The 24-month PFS rate was 65% versus 13%, representing an absolute improvement of 52 percentage points [20]. The magnitude of benefit with osimertinib compared with placebo in LAURA substantially exceeds that observed with durvalumab in PACIFIC (cognizant of the limitations of cross-trial inferences), even among PD-L1-positive patients; of note, retrospective series suggest that in the setting of EGFR-mutated NSCLC, consolidative durvalumab may not improve outcomes compared with observation, qualifying the control arm in LAURA [21]. This difference likely reflects the biology of EGFR-mutated tumors, which typically harbor lower tumor mutational burden, reduced PD-L1 expression, and less robust immune infiltration compared to EGFR wild-type tumors [22]. Furthermore, osimertinib's CNS penetration addresses the high propensity for brain metastases in EGFR-mutated NSCLC [23]. The safety profile of osimertinib in LAURA was consistent with its established tolerability in the metastatic and adjuvant settings [20]. Grade 3 adverse events occurred in 35% of osimertinib-treated patients versus 12% with placebo, with no unexpected toxicities [20]. Radiation pneumonitis occurred in 48% versus 38%, predominantly grade 1–2; 87% of osimertinib-treated patients with radiation pneumonitis continued or restarted therapy per protocol. Overall discontinuation of trial regimen due to any AE occurred in 13% and 5%, respectively [20]. These findings establish osimertinib as the standard of care for EGFR-mutated stage III NSCLC, representing a precision medicine approach that tailors consolidation therapy to tumor molecular characteristics. The LAURA results underscore the importance of comprehensive molecular profiling at diagnosis and challenge the notion of universal immunotherapy-based consolidation.

NOVEL IMMUNOTHERAPY COMBINATIONS: EXPANDING THE BENEFIT

Position

Combination immunotherapy strategies targeting complementary immune checkpoints demonstrate enhanced clinical activity compared to PD-L1 inhibition alone and warrant further investigation in phase 3 trials.

Despite the success of durvalumab monotherapy, substantial room for improvement remains—approximately 54% of patients experience disease progression or death within 2 years [6]. Preclinical rationale suggests that addressing additional immunosuppressive mechanisms may enhance antitumor immunity and expand the population of responders. The phase 2 COAST trial evaluated durvalumab combined with either oleclumab (anti-CD73 antibody) or monalizumab (anti-NKG2A antibody) versus durvalumab alone following definitive CRT in unresectable stage III NSCLC [24]. Both combinations demonstrated superior efficacy: confirmed objective response rate was 30.0% with durvalumab plus oleclumab and 35.5% with durvalumab plus monalizumab versus 17.9% with durvalumab alone [24]. Final results from the COAST trial show that objective response rates remained numerically higher with durvalumab plus oleclumab (35.0%) and durvalumab plus monalizumab (40.3%) compared to durvalumab monotherapy (23.9%), but these differences were not statistically significant [25]. Disease control rates at 16 weeks were 80.0% and 79.0% for the combinations versus 58.2% for durvalumab alone [25]. Median progression-free survival was 21.1 months for durvalumab plus oleclumab, 19.8 months for durvalumab plus monalizumab, and 7.3 months for durvalumab alone (hazard ratios 0.59 and 0.63), with 12-month PFS rates of 63.5% and 73.2% for the combinations and 37.6% for monotherapy [25]. The 12-month PFS rates of 62.6% and 72.7% with the combination regimens compared favorably to 33.9% with durvalumab alone [24]. Critically, the safety profiles were comparable across arms, with no new or significant safety signals identified with either combination [24]. In the final analysis, grade 3 or higher treatment-emergent adverse event rates remained similar across arms—40.7% with durvalumab plus oleclumab, 34.4% with durvalumab plus monalizumab, and 45.5% with durvalumab alone [25]. Serious adverse event rates, immune-mediated adverse events, and rates of pneumonitis all remained comparable, with no new significant safety signals [25]. The incidence of pneumonitis, the most concerning toxicity, was similar across all three arms (18-20%) [24]. CD73, an ectonucleotidase expressed on tumor and immune cells, converts AMP to immunosuppressive adenosine [26]. Radiotherapy upregulates CD73 expression, providing rationale for combining anti-CD73 therapy with CRT and PD-L1 blockade [27]. Similarly, NKG2A is an inhibitory receptor on natural killer cells and CD8 + T cells that binds HLA-E, which is upregulated by radiation [28]. Blocking this axis with monalizumab enhances both innate and adaptive antitumor immunity [28]. The consistent PFS benefit across subgroups in COAST, including patients with PD-L1 < 1% and those who received sequential CRT, suggests that these combinations may overcome resistance mechanisms to single-agent PD-L1 blockade [24]. The phase 3 PACIFIC-9 trial (NCT05221840) is currently evaluating these combinations, which may establish new standards of care if positive results are confirmed.

CHEMOTHERAPY-SPARING APPROACHES: REDUCING TOXICITY WHILE MAINTAINING EFFICACY

Position

For selected patients with PD-L1-positive tumors, concurrent radiotherapy plus immunotherapy without chemotherapy represents a

rational strategy that may reduce treatment-related toxicity while preserving efficacy.

The tolerability of concurrent CRT remains a significant clinical challenge. In real-world practice, a significant proportion of patients do not proceed to consolidation durvalumab due to adverse events or performance status decline following CRT [11, 12]. Chemotherapy-related toxicities, including neutropenia (grade ≥3 in 18-53%) and treatment interruptions, compromise RT delivery and may limit subsequent therapy [29, 30]. Thus efforts to examine ways to treat without chemotherapy are merited.

The phase 2 DOLPHIN trial investigated durvalumab plus concurrent radiotherapy (60 Gy) without chemotherapy in 35 patients with PD-L1-positive (tumor proportion score ≥1%) unresectable stage III NSCLC [31]. The primary endpoint—12-month PFS rate—was 72.1% (90% CI 59.1-85.1%), substantially exceeding the predefined threshold of 50% [31]. Median PFS was 25.6 months (95% CI 13.1-NE), comparable to outcomes observed with full-intensity CRT plus durvalumab in PACIFIC [31]. Remarkably, 97.1% of patients completed the planned radiotherapy, and the treatment completion rate was 57.6% [31]. Grade 3-4 adverse events occurred in 52.9% of patients, lower than typical rates with concurrent CRT [31]. Pneumonitis or radiation pneumonitis of grade 3–4 occurred in 11.8%, with no grade 5 pneumonitis, although 2 patients (5.9%) experienced fatal AEs from other causes (lung infection following steroids for an immune-related AE, and a bronchoesophageal fistula at the irradiated site) [31]. The confirmed objective response rate was 90.9%, with 33.3% achieving complete response [31]. The high complete response rate in DOLPHIN is particularly noteworthy, as pathologic complete response correlates strongly with long-term survival outcomes [32, 33]. The absence of disease progression during concurrent treatment suggests synergistic activity between radiotherapy and immunotherapy, consistent with preclinical models demonstrating enhanced antitumor immunity when PD-L1 blockade is administered concurrently with radiation [7, 8]. This chemotherapy-sparing approach warrants validation in randomized trials. The strategy may be particularly relevant for elderly patients, those with comorbidities limiting chemotherapy tolerance, or patients with high PD-L1 expression who derive maximal benefit from immunotherapy. However, patient selection criteria require careful definition, as the DOLPHIN trial excluded patients with PD-L1 < 1%, and generalizability to unselected populations remains uncertain.

NEOADJUVANT STRATEGIES: CONVERTING UNRESECTABLE TO RESECTABLE DISEASE

Position

Neoadjuvant immunotherapy combined with chemotherapy achieves high pathological response rates and may facilitate surgical resection in select patients with initially unresectable stage III NSCLC.

The distinction between resectable and unresectable stage III NSCLC has traditionally been rigid, but emerging evidence suggests that effective systemic therapy may convert initially unresectable disease to surgically amenable presentations. The phase 3 CheckMate 816 trial evaluated neoadjuvant nivolumab plus chemotherapy versus chemotherapy alone in resectable stage IB-IIIA NSCLC [34]. Among 358 patients, neoadjuvant nivolumab plus chemotherapy resulted in significantly higher pathological complete response (pCR) rates—24.0% versus 2.2% (OR 13.94, 99% CI 3.49-55.75, $p < 0.001$) [34]. Median event-free survival was 31.6 months with the combination versus 20.8 months with chemotherapy alone (HR 0.63, 97.38% CI 0.43-0.91, $p = 0.005$) [34]. Critically, the addition of nivolumab did not increase surgical complications or impede surgical feasibility—83.2% of nivolumab-treated patients versus 75.4% of chemotherapy-alone patients underwent surgery [34]. The depth of pathological response correlated with survival outcomes. Patients achieving pCR had superior event-free survival compared to those without pCR, regardless of treatment arm [34]. This observation aligns with accumulating evidence that pathological response serves as a surrogate endpoint for long-term survival in NSCLC [32, 33]. Translational analyses revealed that circulating tumor DNA (ctDNA) clearance before surgery occurred more frequently with neoadjuvant nivolumab plus chemotherapy (56% vs 35%) [34]. Patients with ctDNA clearance demonstrated longer event-free survival in both treatment arms, suggesting that molecular response assessment may guide treatment decisions [34]. While CheckMate 816 enrolled patients with resectable disease, the principles may extend to marginally unresectable stage III presentations. Radiographic downstaging occurred in 30.7% of nivolumab-treated patients versus 23.5% with chemotherapy alone [34]. For patients with borderline resectability, neoadjuvant immunotherapy-chemotherapy might enable surgical consolidation, potentially improving cure rates beyond what is achievable with definitive CRT.

BIOMARKER-DIRECTED PATIENT SELECTION: PRECISION APPROACHES TO STAGE III NSCLC

Position

Integration of molecular biomarkers, including PD-L1 expression, oncogenic driver mutations, tumor mutational burden, and ctDNA dynamics, enables personalized treatment selection and optimizes outcomes in stage III NSCLC.

The heterogeneity of stage III NSCLC mandates precision medicine approaches. While the PACIFIC trial demonstrated PFS benefit across PD-L1 subgroups, the magnitude of benefit varied substantially [13]. Among patients with PD-L1 ≥ 1%, the median PFS was 17.8 months versus 5.6 months with placebo (HR 0.46), whereas in the PD-L1 < 1% subgroup, median PFS was 10.7 versus 5.6 months (HR 0.73) [13]. This difference in median PFS suggests that PD-L1 expression identifies patients most likely to derive durable benefit from immunotherapy. However, PD-L1 as a biomarker has limitations. Expression is heterogeneous, dynamic, and influenced by prior treatments including radiation [35]. Pre-CRT PD-L1 levels may not accurately reflect post-CRT tumor immunogenicity [35]. Furthermore, approximately 30-40% of patients in clinical trials have unknown PD-L1 status due to inadequate tissue, highlighting practical implementation challenges [11]. Oncogenic driver mutations represent another critical biomarker dimension. As demonstrated by the LAURA trial, EGFR-mutated tumors derive substantially greater benefit from targeted therapy than immunotherapy [20]. Similar considerations apply to ALK rearrangements, ROS1 fusions, and other actionable alterations. Comprehensive next-generation sequencing at diagnosis enables identification of these subsets and appropriate therapy selection. Additionally, emerging work suggests that within EGFR-driven tumors, response to TKIs such as Osimertinib can vary based on type of mutation (e.g. L858R or exon 19 deletion) [36]. Efforts are needed to further understand the biology underlying these differences. Tumor mutational burden (TMB) has emerged as a predictive biomarker in metastatic NSCLC, with higher TMB correlating with immunotherapy benefit [37]. In the PACIFIC trial, patients with TMB ≥ 10 mutations/megabase had numerically longer PFS with durvalumab versus placebo compared to TMB < 10 patients, though the difference was not statistically significant in this subgroup analysis [13]. The role of TMB in stage III disease requires further validation. Circulating tumor DNA (ctDNA) analysis offers dynamic assessment of treatment response. In CheckMate 816, ctDNA clearance predicted superior event-free survival and correlated with pathological response [34]. In the consolidation setting, ctDNA monitoring might identify patients at high risk of recurrence who could benefit from treatment intensification or alternative strategies. Ongoing trials are exploring ctDNA-guided therapy adaptation. Patient-intrinsic factors also influence outcomes. Advanced age

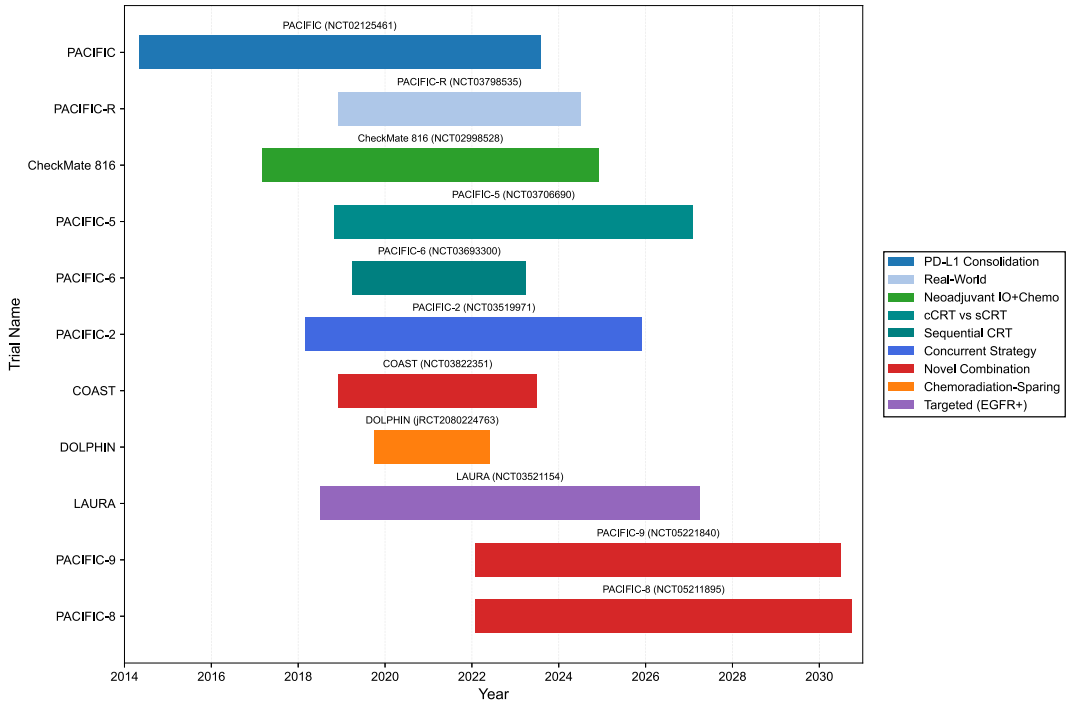

Fig. 1 Timeline of clinical trials for unresectable stage III NSCLC. This Gantt chart illustrates the chronological timeline of key clinical trials shaping the treatment landscape for unresectable stage III non-small cell lung cancer (NSCLC). Each bar represents the duration from study start to estimated completion, with trial registration identifiers annotated. Trials are color-coded by therapeutic strategy: PD-L1 consolidation (PACIFIC), real-world evidence (PACIFIC-R), neoadjuvant immunotherapy-chemotherapy (CheckMate 816), concurrent versus sequential chemoradiotherapy evaluation (PACIFIC-5), sequential CRT approaches (PACIFIC-6), concurrent immunotherapy with CRT (PACIFIC-2), novel immunotherapy combinations targeting CD73 and NKG2A (COAST, PACIFIC-9, PACIFIC-8), chemoradiation-sparing regimens (DOLPHIN), and EGFR-targeted consolidation therapy (LAURA). Trial dates were sourced from ClinicalTrials.gov (API v2) for NCT-registered trials and from the Japan Registry of Clinical Trials (jRCT) for the DOLPHIN trial (jRCT2080224763).

(≥75 years) was associated with numerically shorter rwPFS in PACIFIC-R (19.2 months versus 22.4-22.8 months for younger patients) [11]. Smoking status, performance status, and comorbidity burden all impact treatment tolerance and efficacy. Integration of clinical, molecular, and genomic data through multidisciplinary tumor boards enables individualized treatment recommendations that balance efficacy and tolerability.

The timeline of key trials is presented in Fig. 1.

FUTURE DIRECTIONS AND UNRESOLVED QUESTIONS

Several critical questions remain unanswered and represent priorities for ongoing investigation:

Optimal treatment duration

The 12-month durvalumab treatment cap in PACIFIC was empirically derived rather than biologically justified. Whether longer durations provide additional benefit or shorter courses suffice for responders remains unknown. Real-world data from PACIFIC-R showed that only 19.8% of patients received durvalumab beyond 12 months [11], suggesting that protocol-mandated duration may already exceed what most patients tolerate.

Concurrent versus sequential CRT

PACIFIC mandated concurrent CRT, yet real-world practice frequently employs sequential CRT for patients with comorbidities or extensive disease [11]. The phase 2 PACIFIC-6 trial demonstrated encouraging outcomes with durvalumab after sequential CRT (median PFS 13.1 months) [15], and the ongoing phase 3 PACIFIC-5 trial (NCT03706690) is definitively evaluating this question. If positive, PACIFIC-5 would expand the eligible population for consolidation immunotherapy.

Concurrent immunotherapy with CRT

The phase 3 PACIFIC-2 trial (NCT03519971) is investigating durvalumab administered concurrently with CRT rather than as consolidation. Preclinical data suggest that concurrent administration optimally captures radiation-induced immune activation [7, 8]. However, concerns about additive toxicity, particularly pneumonitis, require careful safety monitoring.

Role of chemotherapy

The DOLPHIN trial demonstrated promising activity with RT plus durvalumab without chemotherapy in PD-L1-positive patients [31]. This approach requires validation in phase 3 trials but could substantially improve tolerability for elderly or frail patients. Conversely, intensified chemotherapy regimens merit investigation in fit patients with high-risk features.

Adjuvant therapy after progression

In PACIFIC, the median time to death or distant metastasis was 23.2 months with durvalumab versus 14.6 months with placebo [4], suggesting that consolidation therapy delays but does not prevent systemic recurrence in many patients. The optimal systemic therapy after progression on durvalumab—whether rechallenge with immunotherapy, chemotherapy, or targeted agents—remains undefined.

Salvage therapy and oligoprogression

Patients who progress on durvalumab frequently exhibit oligoprogressive patterns amenable to local ablative therapies. Integration of stereotactic body radiotherapy, surgical resection, or radiofrequency ablation for limited sites of progression may prolong survival and defer systemic therapy escalation.

CONCLUSIONS

The management of unresectable stage III NSCLC has undergone revolutionary transformation over the past decade. Consolidation durvalumab following concurrent CRT established a new standard of care, with 5-year survival rates approaching 43%, outcomes previously achievable only with surgical resection. However, the field continues to evolve rapidly, with emerging evidence challenging universal application of a single treatment paradigm. For EGFR-mutated tumors, osimertinib consolidation achieves median PFS exceeding 3 years, substantially surpassing immunotherapy outcomes and establishing molecular biomarker-directed therapy selection as essential. Novel immunotherapy combinations targeting CD73 and NKG2A demonstrate enhanced activity in phase 2 trials and may further improve outcomes if validated in phase 3 studies. Chemotherapy-sparing approaches warrant investigation in carefully selected PD-L1-positive populations, potentially reducing toxicity while maintaining efficacy. Neoadjuvant strategies achieve remarkable pathological response rates and may convert borderline-unresectable disease to surgical candidacy. The integration of precision medicine principles, including comprehensive molecular profiling, PD-L1 assessment, ctDNA monitoring, and clinical risk stratification, enables individualized treatment recommendations that optimize the therapeutic ratio. As the armamentarium expands to include targeted therapies, immunotherapy combinations, antibody-drug conjugates, and bispecific antibodies, the complexity of treatment decision-making increases proportionally. Future progress requires rigorous clinical trial evaluation of novel strategies, robust biomarker development and validation, and real-world evidence generation to inform implementation in heterogeneous patient populations. The ultimate goal remains clear: transform stage III NSCLC from a disease with historically dismal outcomes into a curable condition for the majority of patients. The data reviewed herein demonstrate substantial progress toward this ambitious objective and illuminate the path forward.

DATA AVAILABILITY

No datasets were generated or analysed during the current study.

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AUTHOR CONTRIBUTIONS

MSP wrote the main manuscript and prepared all of the figures, and all authors reviewed the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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