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Tumour Review

The evolving landscape of stage III unresectable non-small cell lung cancer "between lights and shadows"

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ABSTRACT

Despite PACIFIC set a new milestone in the clinical management of unresectable stage III non-small cell lung cancer (NSCLC), it left some critical questions pending for clinical research: the efficacy of durvalumab in the real-world setting; the activity of less intensive regimens for frail populations; the role of targeted therapies in oncogene-addicted tumors; the selection of subsequent strategies at immunotherapy failure; the efficacy of novel and intensified treatments; the role of molecular biomarkers for patients' selection. This review aims to describe the evolving landscape of unresectable stage III NSCLC and provides an updated overview of the available evidence, analyzing lights and shadows emerging from recent clinical trials and discussing the most relevant challenges of post-PACIFIC era.

Introduction

Locally advanced non-small cell lung cancer (LA-NSCLC) is a highly heterogeneous disease that often displays an intricate clinical profile and includes a wide spectrum of tumours characterized by different prognosis as well as therapeutic strategies [1]. Multidisciplinary discussion is mandatory to define tumour operability as well as best treatment approaches considering the characteristics of the disease, local expertise, as well as patient's comorbidities and preferences [2].

Historically, resectable LA-NSCLC has been managed with multimodality treatment including surgery and neo-adjuvant chemo(radio) therapy [3]. However, the recent advent of enhanced strategies (i.e. perioperative chemo-immunotherapy and adjuvant targeted therapies) is radically changing the therapeutic paradigm in the field, albeit raising new questions regarding the optimal management of these patients [4–10].

In 2018 the practice-changing PACIFIC trial established definitive concurrent chemoradiotherapy (cCRT) followed by a 1-year durvalumab consolidation as new standard of care for unresectable LA-NSCLCs [11–13]. PACIFIC randomised 2:1 713 unresectable LA-NSCLC patients, regardless of mutational and programmed death-ligand 1 (PD-L1) status, to receive durvalumab 10 mg/kg versus placebo within 42 days

Abbreviations: cCRT, concurrent chemoradiotherapy; HypoRT, Hypo-fractionated radiotherapy; CT, chemotherapy; RT, radiotherapy; ICI, immunotherapy agents; pts, patients; EFS, event free survival; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TGF-β, transforming growth factor beta; PARP, poly ADP-ribose polymerase; KRAS, kirsten rat sarcoma virus; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1; RET, rearranged during transfection.

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from cCRT completion [11]. Durvalumab showed a clear superiority over placebo in terms of median progression-free survival (mPFS, 16.8 vs. 5.6 months; HR 0.52, 95 % CI 0.42–0.65; p < 0.001), with only 30 % of patients experiencing a grade 3 or worse adverse event (AE) and 15 % of them discontinuing the study drug for AEs [11]. The updated analysis confirmed that durvalumab improved landmark PFS and OS rates at 3, 4 and 5 years of follow-up in all prespecified subgroups, with a median overall survival (mOS) of 47.5 vs. 29.1 months at a five-year follow up (HR 0.72, 95 % CI 0.59–0.89) [11,14–17]. However, durvalumab approval in Europe was restricted to LA-NSCLCs with PD-L1 tumour proportion score (TPS) ≥ 1 % following an unplanned post-hoc subgroup analysis mandated by the European Medicines Agency (EMA) showing a lack of benefit in patients with a PD-L1 TPS < 1 % (HR 1.14, 95 % CI 0.71–1.84) [18,19].

Although the PACIFIC trial established a new milestone in the clinical management of unresectable LA-NSCLC, data revealed that approximately 50 % of patients experienced disease progression between 12 and 18 months after initiating durvalumab, and only 33 % were alive at five years, leaving several unresolved questions for clinical research. This review describes the evolving landscape of unresectable LA-NSCLC and provides an updated overview of available evidence regarding the efficacy of durvalumab in the real-world setting, the activity of less intensive regimens for frail populations, the role of targeted therapies in oncogene-addicted tumors, and the selection of subsequent strategies at immunotherapy failure. Novel therapeutic strategies aiming to enhance the survival plateau of LA-NSCLC patients as well as molecular biomarkers for personalized treatments will be also addressed, highlighting the most relevant challenges characterizing the post-PACIFIC era.

PACIFIC clinical studies

Durvalumab consolidation after sequential CRT

Although cCRT is preferably recommended for its superiority in terms of survival gain and local control for LA-NSCLC, many patients continue to receive sequential CRT (sCRT) in daily practice, due to advanced age, comorbidities, burden of disease and clinicians' choice [12,20–36].

PACIFIC-6 is a single arm phase II trial that enrolled 117 unresectable LA-NSCLCs after completion of at least 2 cycles of platinum-based chemotherapy and sequential standard-dose radiotherapy (60 Gy in 30 fractions) to receive consolidation durvalumab 1500 mg every 4 weeks for up to 24 months [37]. As compared to PACIFIC, a higher proportion of patients had ≥ 65 years old (65.8 % vs. 45.2 %) and a performance status more than 0 (59.8 % vs. 50.8 %), while a lower proportion had a stage IIIA disease (37.6 % vs. 52.9 %) [37]. The mPFS was 10.9 months, with about half of patients being alive and progression-free at 12 months, while OS rates were 84 % at 12 months and 70 % at 24 months [37]. Nearly 65 % of patients discontinued durvalumab compared to 50 % of PACIFIC, and patients received a median of eight 4-weekly infusions versus twenty 2-weekly infusions of PACIFIC [37]. The most common reasons for discontinuation were disease progression (29.9 %) and AEs (21.4 %), with interstitial lung disease (ILD) reported as the most frequent AE leading to treatment discontinuation ($n = 12$) [37].

PACIFIC-5 (NCT03706690) is a global phase III randomized study assessing the efficacy and safety of durvalumab consolidation in a broader population of patients with unresectable stage III NSCLC regardless of PD-L1 level who did not progress after either cCRT or sCRT [38]. Modified intention-to-treat population only included epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) wild type participants ($n = 381$), who were randomised 2:1 to receive durvalumab 1500 mg Q4W ($n = 252$) or placebo ($n = 129$) until disease progression [38]. Wu et al. have recently presented the results of the first interim analysis at the ESMO Asia Congress 2024 [38]. Most patients in both arms were male (88–92 %), with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 1 (55–68 %), PD-L1 TPS ≥ 1 % (60 %), and squamous histology (66–69 %) [38]. Overall, 30 % of patients received sCRT [38]. Approximately 80 % of participants in both arms discontinued the study treatment, of those, 30 % in durvalumab arm (versus 15 % in placebo arm) discontinued after at least 12 months of treatment [38]. The most common reasons for discontinuation of durvalumab/placebo were progressive disease (53 vs. 66 %) and AEs (14 vs. 7 %), with pneumonitis (40 %), pneumonia (18 %) and hypothyroidism (18 %) being the most common AEs of all grades in the experimental arm [38]. At a median follow up of 30 months, durvalumab demonstrated a statistically significant PFS benefit compared to placebo (14 vs. 6.5 months; HR 0.75, 95 % CI 0.58–0.99; p = 0.038) [38]. Subgroup analysis suggested a consistent PFS benefit after both cCRT (HR 0.76, 95 % CI 0.55–1.06; p = 0.103) and sCRT (HR 0.75, 95 % CI 0.49–1.18; p = 0.213) [38]. A trend towards improved OS with durvalumab was observed (mOS 38.3 vs. 32.5 months), however, the results did not reach statistical significance (HR 0.87, 95 % CI 0.66–1.17; p = 0.346) [38].

Even if cCRT remain the backbone treatment for patients with unresectable LA-NSCLCs and should be always preferred when clinically feasible, these data, along with recent real-world evidence, currently support the efficacy of durvalumab consolidation also in those patients who receive sCRT in clinical practice due to performance status or physicians' preference.

Durvalumab consolidation in the real-world

Several studies have assessed the use, effectiveness, and tolerability of durvalumab consolidation in real-world practice, seeking to bridge the gap between trial data and daily practice.

PACIFIC-Real is an international retrospective study based on patients receiving durvalumab through an expanded access program (EAP) started once the primary results of PACIFIC had been available to provide ethical access to durvalumab [39]. The study aimed to deliver real-world data on the use and effectiveness of consolidation durvalumab. In contrast with PACIFIC, participants could have received either cCRT or sCRT and commenced durvalumab later than 42 days after CRT completion [40]. The full analysis set comprised 1399 patients from 11 countries who received durvalumab between September 2017 and December 2018 for a median time of 11 months. Median PFS (counted from the first dose of durvalumab) was 21.7 months in the overall population, 23.7 months in patients treated with cCRT (77 %), and 19.4 months in patients treated with sCRT (14 %) [41]. PFS was also numerically longer among patients with PD-L1 expression ≥ 1 % (73 %) as compared with PD-L1 < 1 % patients (18 %; 22.4 vs. 15.6 months) [41]. At the most recent 3-year follow-up update, survival data were still immature (mOS: 95 % CI 46.3 months-NE) and the 2- and 3-year OS rates were 72.3 % (95 % CI 69.7 %-74.8 %) and 63.2 % (95 % CI 60.3 %-65.9 %), respectively. Three-year OS rates were numerically higher among patients with PD-L1 expression ≥ 1 % (67.0 %, 95 % CI 63.0 %-70.8 %) as compared with PD-L1 < 1 % (54.4 %, 95 % CI 45.7 %-62.4 %). Similarly, 3y-OS was numerically higher among patients receiving cCRT (64.8 %, 95 % CI 61.5 %-67.9 %) versus sCRT (57.9 %, 95 % CI 49.8 %-65.2 %), amongst patients starting durvalumab within 42 days (66.0 %, 95 % CI 61.1 %-70.5 %) versus > 42 days (61.8 %, 95 % CI 58.1 %-65.2 %), and for non-squamous (68.0 %, 95 % CI 64.5 %-71.2 %) versus squamous histology (53.2 %, 95 % CI 48.0 %-58.1 %) [42]. Following the lead of PACIFIC-Real, several retrospective real-world studies have explored the use of durvalumab in other countries including heterogeneous cohorts of patients. Outcomes were broadly consistent with PACIFIC, reporting a mPFS ranging from 16 to 25 months [43–54].

ALLSTAR is an Austrian multicentre prospective registry designed to document the diversity of treatment schedules used in daily clinical practice [51]. Patients with ECOGPS > 1 and those receiving sCRT (69 % of the whole cohort) were also allowed to participate [51]. Among the

188 recruited patients, 113 received durvalumab consolidation between 1 and 65 days from the end of CRT (median time: 14 days) [51]. Patients treated with durvalumab had longer mPFS (25.8 months, 95 % CI 21.9-not reached, NR) than those without durvalumab (15.7 months, 95 % CI 13.2–27.8; HR 1.88, 95 % CI 1.16–3.05; p = 0.009) [51]. ALLSTAR included also 25 patients with PD-L1 expression less than 1 % or unknown [51]. In contrast to PACIFIC-Real, there was no difference in PFS after stratification according to PD-L1 status [51].

Another real-world retrospective study conducted in Korea stratified 286 patients according to age, with 42 % being 70 years or older [54]. The proportion of patients who completed durvalumab was lower in elderly (≥70 years) patients (27.5 % vs. 39.2 %; p = 0.040), however mPFS (17.7 vs. 19.4 months; p = 0.43) and mOS (35.7 months vs. NR; p = 0.13) were similar between the two groups [54]. In elderly patients, a good ECOG-PS was associated with an improved PFS, while a cisplatin-based regimen was associated with worse OS [54]. In patients aged less than 70 years, a PD-L1 expression equal or above 50 % was associated with improved survival outcomes [54]. Elderly patients experienced more treatment-related AEs (TRAEs), serious AEs, permanent discontinuation of durvalumab, and treatment-related deaths [54]. Among the AEs leading to permanent discontinuation or death, pulmonary AEs were significantly higher in elderly patients [54].

Treatment strategies at durvalumab progression

The optimal treatment strategy at durvalumab progression remains uncertain and available options are limited due to the prior administration of platinum-chemotherapy and immunotherapy.

In the PACIFIC study, durvalumab re-treatment was permitted for patients who achieved a disease control at the end of 1-year consolidation period [11]. Also, in the 5-year follow-up analysis, authors reported that nearly 50 % of patients received a subsequent anticancer therapy after discontinuation of durvalumab [17]. Specifically, approximately 35 % in both durvalumab and placebo arms were treated with chemotherapy, however the type of cytotoxic treatment was not specified [17]. Rechallenge of immunotherapy, mainly nivolumab or pembrolizumab, was adopted in 30 % of patients receiving placebo versus 12 % of patients receiving durvalumab [17]. As for the other participants, about 20–25 % received further radiotherapy, and 11–14 % other systemic treatments including tyrosine kinase inhibitors (TKIs) [17]. Authors also reported that time from study randomisation to first subsequent anticancer treatment initiation was improved with durvalumab as compared with placebo (HR 0.65, 95 % CI 0.53–0.79), with a median time of 21.2 months (95 % CI 17.1–25.8) versus 10.4 months (95 % CI 8.4–12.5) [17].

More recently, a retrospective real-world clinical study on 127 patients receiving subsequent treatments after progression to durvalumab showed that platinum-based chemotherapy was the most frequently administered, whereas patients rechallenged with immunotherapy mostly progressed after 1 year from durvalumab initiation [55]. Another retrospective multicentre analysis in the Japanese population confirmed that platinum-based treatment was the most common strategy conferring a median second PFS of 5.5 months [56]. Within this subgroup, patients with a durvalumab PFS longer than 1 year had a significantly longer second PFS from platinum-based treatment (13.2 vs. 4.7 months, HR 0.45) [56]. On the other hand, among the 20 % of patients rechallenged with immunotherapy, median second PFS was 10.2 months [56]. After stratifying participants according to the durvalumab PFS, the proportion of patients who received immunotherapy rechallenge was significantly higher in the group reaching a mPFS longer than 1 year (32 % vs. 15 %; p = 0.03) [56].

These studies highlight the potential for tailored treatment strategies based on responses to durvalumab consolidation. However, further research is essential to establish the feasibility of immunotherapy rechallenge and to identify robust biomarkers that can guide personalized therapeutic approaches.

Oncogene-addicted LA-NSCLC

The role of immunotherapy

The efficacy of consolidation immunotherapy with durvalumab in oncogene addicted LA-NSCLC is questionable and largely dependent from the specific molecular alteration.

In the PACIFIC trial, only 43 out of 188 patients had a confirmed epidermal growth factor receptor mutation, while information regarding other molecular biomarkers (e.g. ALK, ROS1, RET, BRAF, KRAS) was not available [11,14]. Naidoo et al. published an exploratory subgroup analysis showing no significant differences in terms of both PFS and OS between durvalumab and placebo in the small subgroup of patients harboring an EGFR activating mutation [57]. Subsequently, Aredo et al showed that EGFR-TKI administred either before or after CRT were associated with a significantly longer mPFS compared to either CRT followed by durvalumab or CRT alone (log-rank p = 0.023) in 37 patients with stage III unresectable EGFR-mutant NSCLC. These data, although limited by a small sample size, confirmed that durvalumab might not be the best option for EGFR-driven LA-NSCLC and suggested for the first time a potential role of targeted therapy in this context [58]. Looking beyond EGFR-activating mutations, different studies investigated the efficacy of durvalumab consolidation across different molecular subtypes (ALK, ROS1, BRAF, KRAS, etg) [59], overall showing that not all molecular drivers are the same and suggesting a potential survival benefit in patients with KRAS mutations and uncommon EGFR alterations, to be confirmed in larger prospective studies [60].

The role of targeted therapies

The role of targeted therapy as consolidation treatment in this context has been recently investigated by the LAURA trial, a phase III, randomised, double-blind study designed to compare osimertinib versus placebo until disease progression in patients with EGFR-mutated LA-NSCLC who had previously received cCRT [61]. A total of 216 patients were enrolled, with 143 assigned to the osimertinib arm and 73 to the placebo arm [61]. The mPFS was 39.1 months vs. 5.6 months (HR 0.16, 95 % CI 0.10–0.24; p < 0.001), while the 12-month PFS rates were 74 % (95 % CI 65–80) and 22 % (95 % CI 13–32) for osimertinib vs. placebo, respectively. The 36-month OS (with 20 % maturity) was 84 % (95 % CI 75–89) for osimertinib vs. 74 % (95 % CI 57–85) for placebo, while the median duration of exposure to osimertinib treatment was 24 months versus 8.3 months with placebo [61]. Adverse events of grade 3 or higher were 35 % with osimertinib (vs. 12 % with placebo). The most common adverse event, regardless of cause, was radiation pneumonitis (48 % with osimertinib vs. 38 % with placebo), diarrhea (36 % vs. 14 %) and rash (24 % vs. 14 %). Overall, adverse events were responsible for 56 % dose interruptions and 13 % discontinuation with osimertinib [61]. These data indicate a significant benefit in terms of PFS, which have already changed the standard of care for this specific subgroup of patients [36]. However, a longer follow-up will be necessary to obtain additional survival data and also to monitor long-term toxicities and the financial aspect related to a therapy administered until disease progression or discontinuation. More recently, the authors presented the intracranial efficacy of osimertinib in this setting and reported a median central nervous system (CNS) PFS not reached for osimertinib, compared to 14.9 months in the control group (HR 0.17, 95 % CI 0.09–0.32) [62]. The cumulative incidence of CNS progression at 12 months was 9 % with osimertinib (95 % CI 5–14) versus 36 % with placebo (95 % CI 24–47) [62]. One limitation of the LAURA trial was that baseline PET-CT staging was not required for all the patients at diagnosis (55 % in the osimertinib and 45 % in the placebo group) [62], thus leading to a potential misclassification of stage IV disease that could explain the poor prognosis in the placebo group [62]. However, a consistent PFS benefit was observed with osimertinib in both patients

who underwent (HR 0.24, 95 % CI 0.14–0.40) or not (HR 0.23, 95 % CI 0.13–0.38) a PET scan-based staging at baseline, further supporting the role of systemic TKI treatment in this context [62].

The phase II ASCENT trial, evaluated the combination of afatinib and CRT as induction therapy in EGFR-mutated LA-NSCLC [63]. Overall, 19 patients were enrolled, with those having resectable disease after induction treatment undergoing surgery [63]. All participants were offered 2 years of consolidation treatment with afatinib. The primary endpoint was reached with an objective response rate (ORR) to the induction TKI of 63 %. After a median follow-up of 5.0 years, the mPFS was 2.6 years (95 % CI 1.4–3.1) and mOS was 5.8 years (95 % CI 2.9-NR) [63]. Among 10 patients who underwent lobectomy and nodal dissection following induction therapy with TKI and cCRT, a major pathological response was observed in 5, while a pathologic complete response (pCR) was identified in only one patient. Notably, the single pCR occurred in a patient initially classified as having unresectable disease [63]. Sixteen patients experienced recurrence or death, with 6 having isolated CNS recurrences [63]. Median time to progression after discontinuing consolidation TKI was 2.9 months (95 % CI 1.1–7.2). Four patients developed grade 2 pneumonitis, but no treatment-related death was reported [63].

The POLESTAR randomized study demonstrated a significant superiority of another third-generation EGFR-TKI, aumolertinib, over placebo in patients with EGFR exon 19 deletions or L858R exon 21 mutations following CRT. Aumolertinib achieved a mPFS (primary endpoint) of 30.4 months (95 % CI 17.2-NR) compared to 3.8 months (95 % CI 3.7–5.6) for placebo. The mOS was NR in both groups while the ORR was 57 % with aumolertinib and 22 % with placebo (OR 4.58; 95 % CI 2.07–10.14; $p < 0.0001$). Regarding safety, the rates of grade 3 or higher TRAEs were 9.6 % and 1.9 %, respectively [64].

Nassar et al. published the results of a retrospective multicenter study that investigated the role of ALK-TKIs as consolidation therapy compared with either durvalumab or observation in patients with unresectable stage III ALK-positive NSCLC treated with CRT [65]. Sixty-seven patients were enrolled, of whom 15 received a consolidation ALK targeted agent, 30 durvalumab, and 22 observation alone [65]. Results showed a real-world mPFS not reached (95 % CI 22.7-NR) in the ALK TKI arm, 11.3 months in the durvalumab arm (95 % CI 8.9–18.5; HR 0.12, 95 % CI 0.026–0.5; p-adjusted = 0.006), and 7.2 months in the observation arm (95 % CI 3.4–10.6; HR 0.04, 95 % CI 0.009–0.2; p-adjusted < 0.0001) [65]. A benefit in terms of mOS was also reported for ALK TKI and durvalumab versus observation [65].

These data suggest that consolidation ALK-TKI could also be appropriate in this setting. Currently the phase III HORIZON-01 trial (NCT05170204) is currently randomizing patients with unresectable stage III NSCLC and ALK rearrangements post-CRT to receive either consolidation durvalumab or a three-year course of alectinib. The primary endpoint is median PFS (Table 1).

This data support the shift of precision medicine in the locally advanced unresectable disease, suggesting that targeted therapies rather than immunotherapy should be the new standard of care for molecularly selected patients undergoing CRT.

New therapeutic strategies

The success of PACIFIC trial paved the way for the development of new therapeutic strategies to improve the outcomes of patients with unresectable LA-NSCLC, including consolidation-treatment intensification, immunotherapy concurrently with cCRT, as well as induction immunotherapy with or without chemotherapy followed by CRT.

Consolidation immunotherapy intensification

The combination of monoclonal antibodies with different and complementary mechanisms of action is a therapeutic approach to overcome resistance to anti-PD-(L)1, maximizing the potential benefit of these drugs with the possibility of achieving long-lasting response.

In the phase II BTCRC-LUN 16–081 trial, nivolumab plus ipilimumab versus nivolumab alone as consolidation therapy following CRT were compared, both administered for a duration of six months [66]. Results showed similar mPFS (25.4 months vs. 25.8 months) and 2-year OS rate (81 % vs. 78 %) [67]. A higher toxicity rate was reported in the combination arm, especially in terms of pneumonitis (17.6 % vs. 9.3 %) [67]. A recent update compared safety and efficacy among the young (< 65 years) and the elderly (≥ 65 years) patients. Safety was similar, while the OS estimate in combination arm was higher in younger patients as compared with the older ones ($p = 0.029$) [67].

The randomized phase II COAST study evaluated the combination of durvalumab with the anti-CD73 monoclonal antibody oleclumab (arm A) and the NKG2A inhibitor monalizumab (arm B) versus durvalumab alone (arm C) in patients not progressing after cCRT [68]. At a median follow-up of 11.5 months, ORR were 30.0 % (95 % CI 18.8 %-43.2 %), 35.5 % (95 % CI 23.7 %-48.7 %) and 17.9 % (95 % CI 9.6 %-29.2 %) in arm A, B and C, respectively [68]. Furthermore, the 12-month PFS were 62.6 % (95 % CI 48.1 %-74.2 %), 72.7 % (95 % CI, 58.8 %-82.6 %) and 33.9 % (95 % CI, 21.2 %-47.1 %), respectively [68]. The clinical benefit of the two experimental arms was demonstrated independently of PD-L1 status [68]. The incidence of any grade pneumonitis and serious TRAEs was similar in the three treatment arms [68]. A 30-month follow-up update was recently presented at the ASCO 2024 congress, with a 2-year OS rate of 76.8 % (95 % CI 63.3 %-85.8 %), 72.1 % (95 % CI 58.6 %-81.9 %) and 61.5 % (95 % CI 47.4 %-72.9 %) in arm A, B, and C, respectively [69]. Based on this data, randomized phase III PACIFIC-9 trial (NCT05221840), comparing durvalumab plus either oleclumab or monalizumab versus durvalumab alone, with the primary endpoint of PFS. The phase III study PACIFIC-8 (NCT05211895) is investigating the combination of durvalumab and domvanalimab (anti-TIGIT) versus durvalumab and placebo for a duration of one year post cCRT with the primary endpoint of PFS in patients with PD-L1 ≥ 50 %. Several other ongoing studies investigating novel immunotherapy combinations will inform us about the impact of intensified consolidation strategies on patients' clinical outcomes (Table 1).

Immunotherapy concurrently with cCRT

Several chemotherapeutic agents have been shown to promote immunogenic cell death and enhance antigenic presentation, stimulating the anti-tumor immune response [70]. This rationale supports the combination of immunotherapy and chemoradiation in patients with unresectable stage III NSCLC.

In the phase II NICOLAS trial, 79 stage IIIA-B unresectable NSCLC patients received three cycles of platinum-based chemotherapy combined with concurrent radiotherapy (66 Gy) and, from the second cycle of chemotherapy, concomitant nivolumab followed by consolidation nivolumab for 12 months [71]. At a median follow-up of 21 months, mPFS was 12.7 months (95 % CI 10.1–22.8 months) with a 1-year PFS rate of 53.7 % (95 % CI 42 %-64 %). At a follow-up of 32.6 months, mOS was 38.8 months (95 % CI 26.8 %-NE) with a 2-year OS rate of 63.7 % (95 % CI 51.9 %-73.4 %) statistically significantly higher for stage IIIA patients than for stage IIIB patients (81 % vs. 56 %; $p = 0.037$) [71]. Furthermore, the ORR was 73.4 % (95 % CI 62.3 %-82.7 %) with a total of 5 complete responses (6.3 %). Nine patients (11.7 %) experienced grade 3 or higher pneumonitis, all attributed to nivolumab and four of them also to radiotherapy [71].

The DETERRED trial used atezolizumab as immunotherapy. In part 1, 10 patients received carboplatin AUC 2 and paclitaxel 50 mg/mq weekly with concomitant radiotherapy (60–66 Gy in 30–33 fractions) and after 3 weeks continued with carboplatin AUC 6, paclitaxel 200 mg/mq and atezolizumab every three weeks for 2 cycles followed by atezolizumab maintenance for 12 months [72]. At a median follow-up of 22.5 months, a mPFS of 18.6 months and a mOS of 22.8 months were reported. In the second part of the study, 30 patients received

Table 1
Ongoing phase II/III trials in unresectable stage III NSCLC.

NCT number (name)	Phase	Treatment Arms (experimental arm vs control arm)	Mechanism of action	N (estimated enrollment)	Primary endpoints	Status
Consolidation after CRT						
NCT05414630	2	Envafolimab for up to 2 years post CRT	Anti PD-L1	30	PFS	Not yet recruiting
NCT03379441 (MP-LALC)	2	Pembrolizumab Vs. Observation post CRT for up to 2 years regardless PD-L1 status	Anti PD-1	126	OS	Recruiting
NCT03706690 (PACIFIC-5)	3	Durvalumab q4w Vs. Placebo post CRT until PD	Anti PD-L1 Vs. Placebo	407	PFS	Active,not recruiting
NCT05718297 (BOUNCE)	2 (ALK-fusion)	Brigatinib (for up 3 years) Vs. Durvalumab post CRT	ALK inhibitor Vs. Anti PD-L1	44	PFS	Recruiting
NCT04951635	3 (EGFR mutated)	Almonertinib Vs. Placebo post CRT	Anti EGFR mutation	150	PFS	Recruiting
NCT05170204 (HORIZON-01, BO42777)	3 (ALK rearrangement)	Cohort A1: Alectinib (for up 3 years) Vs. Durvalumab (ALK +) post CRT	Anti ALK Vs. Anti PD-L1	121	PFS	Recruiting
NCT05338619 (PLATINUM)	2 (EGFR mutated)	Lazertinib post CRT	Anti EGFR mutation	77	PFS	Recruiting
Neoadjuvant intent						
NCT05611879	2	Tislelizumab + CT (neoadjuvant)	Anti PD-1	30	Resectability Rate	Recruiting
NCT05306847	2	Sintilimab + Anlotinib (neoadjuvant)	Anti PD-1 + Anti VEGFR	93	Surgical conversion rate	Not yet recruiting
NCT05940532	2	Sugemalimab + CT▶(RT or surgery) ▶Sugemalimab for up to 2 years	Anti PD-L1	41	ORR	Recruiting
ICI-consolidation intensification						
NCT04325763	3	TQB2450 + Anlotinib Vs. TQB2450 + Placebo Vs. Placebo post CRT	Anti PD-L1 + Anti VEGFR Vs. Placebo	315	PFS	Recruiting
NCT04513925 (SKYSCRAPER-03)	3	Atezolizumab + Tiragolumab Vs. Durvalumab For up to 13 cycles post cCRT	Anti PD-L1 + Anti TIGIT Vs. Anti PD-L1	829	PFS in PD-L1 + pts and overall population	Active,not recruiting
NCT05211895 (PACIFIC-8)	3	Durvalumab + Domvanalimab Vs. Durvalumab + Placebo for up to 1 year post cCRT	Anti PD-L1 + Anti TIGIT Vs. Anti PD-L1 + Placebo	860	PFS in PD-L1 $\geq$ 50 %	Recruiting
NCT05221840 (PACIFIC-9)	3	Durvalumab + Oleclumab Vs. Durvalumab + Monalizumab Vs. Durvalumab + Placebo for up to 1 year post cCRT	Anti PD-L1 + Anti CD-73 Vs. Anti PD-L1 + Anti NKG2A receptors Vs. Anti PD-L1	999	PFS	Recruiting
Concurrent ICI + cCRT						
NCT05386888	2	GFH018 + Toripalimab + cCRT▶GFH018 + Toripalimab for up to 1 year	TGF-βRI kinase inhibitor + Anti PD-1	65	ORR	Active,not recruiting
NCT04380636 (KEYLYNK-012)	3	Pembrolizumab + cCRT▶Pembrolizumab + Placebo for up to 1 year Vs. Pembrolizumab + cCRT▶Pembrolizumab + Olaparib for up 1 year Vs. cCRT▶Durvalumab for up to 1 year	Anti PD-1 + cCRT▶ Anti PD-1 + Placebo Vs. Anti PD-1 + cCRT▶ Anti PD-1 + PARP inhibitor Vs. cCRT▶Anti PD-L1	870	PFS and OS	Active,not recruiting
NCT04092283 (EA5181)	3	Durvalumab + cCRT▶Durvalumab Vs. cCRT▶Durvalumab for up to 12 cycles	Anti PD-L1 + cCRT▶Anti PD-L1 Vs. cCRT▶Anti PD-L1	660	OS	Active,not recruiting
NCT01386385	2	Veliparib + cCRT▶Veliparib + CT Vs. Placebo + cCRT▶Placebo + CT	PARP inhibitor + cCRT▶ PARP inhibitor + CT Vs. Placebo + cCRT▶Placebo + CT	53	PFS	Active,not recruiting
Induction (CT)-ICI						
NCT05128630 (DEDALUS)	2	Durvalumab + CT▶Durvalumab + Hypo-RT▶Durvalumab	Anti PD-L1	45	Safety	Recruiting
NCT04765709 (BRIDGE)	2	Durvalumab + CT▶Durvalumab + RT▶Durvalumab for up to 2 years	Anti PD-L1	10	% pts who did not progressed and who achieved a mean lung dose < 20 Gy and/or a lung V20 < 35 % (response) after part 1	Active,not recruiting
NCT05798663 (AFT-57)	2	ArmA: Atezolizumab▶cCRT + Atezolizumab▶Atezolizumab ArmB:Atezolizumab + Tiragolumab▶cCRT + Atezolizumab▶Atezolizumab + Tiragolumab ArmC: Atezolizumab + Tiragolumab ▶cCRT + Atezolizumab + Tiragolumab▶ Atezolizumab + Tiragolumab	Anti PD-L1 + Anti TIGIT	178	PFS	Recruiting
Concurrent ICI + RT						

(*continued on next page*)

Table 1 (*continued*)

NCT number (name)	Phase	Treatment Arms (experimental arm vs control arm)	Mechanism of action	N (estimated enrollment)	Primary endpoints	Status
NCT04351256 (TRADE-hypo)	2	Durvalumab + HypoRT Vs. Durvalumab + conventionally RT	Anti PD-L1	88	ORR and toxicity (pneumonitis)	Recruiting
RT followed by ICI						
NCT04310020 (SWOG 1933)	2	HypoRT▶Atezolizumab for up to 1 year	Anti PD-L1	47	Safety	Recruiting
Others trial						
NCT05398094 (MERIT-lung)	2 (KRAS G12C and ineligible for CRT)	Sotorasib	Anti KRAS G12C	43	PFS	Recruiting
NCT06194448 (NEOLA)	2 (EGFR mutated)	Osimertinib▶CRT▶Osimertinib	Anti EGFR mutation	70	PFS	Recruiting
NCT04580498	2	SHR-1701 + CT Vs. CT	Anti PD-L1 and Anti TGF-β + CT Vs. CT	107	ORR and EFS	Active,not recruiting

concomitant cCRT followed by the same consolidation and maintenance regimen as in part 1. Authors reported a mPFS of 13.2 months while mOS was not reached [72]. Furthermore, there was no difference in the risk of recurrence between those with PD-L1 < 1 % and those with PD-L1 ≥ 1 % (56.3 % vs. 38.9 %; p = not significant) as well as between those with levels below 50 % and ≥ 50 % (53.8 % vs. 25 %; p = not significant) [72]. Safety was the primary endpoint of the study and was achieved with grade ≥ 2 pneumonia rates of 10 % and 16 %, respectively [72].

Another non-randomized phase 2 study (KEYNOTE-799) included unresectable stage IIIA-C NSCLCs [73,74]. In cohort A (squamous and non-squamous) patients received carboplatin AUC 6 plus paclitaxel combined with pembrolizumab for one cycle, followed by weekly carboplatin AUC 2 plus paclitaxel for 6 weeks and two cycles of pembrolizumab combined with standard radiotherapy (60 Gy) [73]. In cohort B (non-squamous), 3 cycles of cisplatin, pemetrexed and pembrolizumab combined with radiotherapy in the second and third cycles were administered [73]. At a 2-year update, ORR was 71.4 % (62.1 %-79.6 %) in cohort A, similar by histology, and 75.5 % (66 %-83.5 %) in cohort B; mOS was not reached in both cohorts while mPFS was 30.6 months and NR, respectively [74]. Serious treatment-related AEs were reported in 64.3 % in cohort A and 51 % of patients in cohort B [74].

The phase III randomized PACIFIC-2 trial failed to demonstrate the superiority of an intensified strategy over the standard chemoradiation [75]. Overall, 327 patients were randomised 2:1 to receive cCRT concurrently with durvalumab or placebo, followed by durvalumab/placebo consolidation until progression and/or toxicity [75]. There was a high number patients with unknown EGFR mutational status within the study population (45.7 % in the durvalumab arm and 40 % in the placebo arm). In addition, the durvalumab arm contained a higher number of patients with ECOG PS of 1, T4 tumors, squamous histology, and PD-L1 expression < 1 %. At a median follow-up of 30.5 months, mPFS was 13.8 months in the experimental arm and 9.4 months in the control arm (HR 0.85, 95 % CI 0.65–1.12; p = 0.247), while mOS was 36.4 months and 29.5 months, respectively (HR 1.03, 95 % CI 0.78–1.39; p = 0.823). Safety was similar in the two arms, with the same rate of pneumonitis/radiation pneumonitis [76].

Recently, the CheckMate 73L phase III randomized trial investigated the combination of nivolumab with cCRT, followed by nivolumab plus ipilimumab (Arm A) or nivolumab alone (Arm B), versus PACIFIC regimen (Arm C). Patients' characteristics were well balanced across the three treatment arms, while mutational status was not reported. The trial did not meet the primary endpoint, with mPFS of 16.7 months vs. 15.6 months for Arm A vs C (HR 0.95, 95 % CI 0.77–1.19; p = 0.646). The subgroup analysis suggested a trend toward a mPFS improvement in the PD-L1 ≥ 50 % subset (25.5 months vs. 19.4 months), not reaching a statistical significance (HR 0.74, 95 % CI 0.50–1.11). There was no difference also in terms of mOS (HR 1.12, 95 % CI 0.87–1.43). The comparison between arm B and C failed to show any benefit in terms of both mPFS (HR 0.84, 95 % CI 0.69–1.04) and mOS (HR 0.97, 95 % CI 0.76–1.24), with a higher rate of pneumonitis and treatment discontinuation due to AEs in the experimental arm (41 % Arm A vs. 39 % Arm B vs. 36 % Arm C) [77].

Finally the Keyvibe-006 study (NCT05298423) comparing the combination of pembrolizumab plus vibostolimab concurrently with cCRT versus the standard PACIFIC regimen has been definitively discontinued on December 2024.

Overall, this data do not support this intensified strategy for our clinical practice and emphasize the need to investigate novel efficacious treatment options for patients with unresectable stage III NSCLC.

Induction immunotherapy with or without chemotherapy

The biological rationale for the induction strategies with immunotherapy followed by CRT is based on the possibility of exploiting a larger pool of neoantigens to activate the immune system [78].

The phase II study AFT-16 enrolled 64 patients with stage III NSCLC. After two cycles of atezolizumab, re-staging was performed and, in absence of disease progression, additional two cycles of atezolizumab followed by cCRT without anti-PD-L1 were administered [79]. Subsequently, consolidation atezolizumab was performed for 1-year [79]. Disease control rate (DCR) at 12 weeks (primary endpoint) was 74.2 % (80 % CI 65.7–81.4 %). Median PFS was 30 months (95 % CI 15.8 months-NR) and OS at 24 months was 73.7 % (95 % CI 63.4 %-85.7 %) [79]. Seventeen patients experienced grade 3 or higher immune-related adverse events [79].

The GASTO-1091 trial (NCT04085250) is a phase II, randomized, multicenter study evaluating the role of consolidation nivolumab in patients with stage IIIA-C NSCLC [80]. Out of a total of 264 enrolled patients, 172 were treated with neoadjuvant chemoimmunotherapy, hypofractionated radiotherapy (40 Gy in 10 fractions or 30 Gy in 6 fractions plus a boost to 24–30 Gy in 6 fractions), and concurrent chemotherapy, and subsequently randomized to receive consolidation nivolumab or observation [80]. With a median follow up of 22.8 months, patients treated with nivolumab had a statistically significant benefit in mPFS compared to patients in the observation arm (NR vs. 12.2 months; HR 0.49, 95 % CI 0.31–0.79; p = 0.002) [80]. The 12-month and 18-month PFS rates were 72.6 % and 64.8 % in the nivolumab arm, versus 52.5 % and 42.3 % in the control arm, and OS data are still immature [80].

At the 2024 WCLC, Provencio et al. presented the results of the phase II APOLO study (NCT04776447), investigating an induction strategy with atezolizumab combined with chemotherapy followed by chemoradiotherapy and then maintenance atezolizumab for up to 16 cycles [81]. After a median follow-up of 29.6 months, mPFS was 20.8 months (95 % CI 12.6-NR); in particular, PFS in ITT population at 12 and 18 months was 68.4 % (95 % CI 51.1–80.6 %) and 60.5 % (95 % CI 43.3–74 %), respectively. The OS (secondary endpoint) in the ITT population was 86.8 % (95 % CI 71.2–94.3) at 12 months and 60.5 % (95 % CI 43.3–74) at 24 months, respectively [81]. Equally interesting were the results of

the phase II PACIFIC-BRAZIL trial (NCT04230408) [82]. Forty-nine patients received two cycles of induction with durvalumab and chemotherapy, followed by combination immunotherapy and chemo-radiotherapy, and then maintenance durvalumab for 12 cycles [82]. The primary endpoint of 12-month PFS was achieved, reaching 68.1 % (95 % CI 56–82.8) in the study population [82].

Although preliminary, these findings appear promising and overall support the exploration of induction chemoimmunotherapy to enhance the effectiveness of existing treatments in this setting.

De-escalation strategies

Several trials explored de-escalation strategies for unfit or clinically selected patients.

DUART is a phase II single arm multicentre study designed to evaluate safety and tolerability of durvalumab following radiotherapy in patients with unresectable stage III NSCLC deemed ineligible for chemotherapy [83]. Patients were stratified according to the dose of radiotherapy: cohort A comprised participants treated with standard radiotherapy (60 Gy ± 10 % or hypofractionated biologically equivalent dose) and cohort B included those who received palliative radiotherapy (between 40 and 54 Gy) [83]. The median age of patients enrolled in the trial was 79 years and about 80 % had an ECOG PS 1–2. The updated results were recently presented at the ESMO Immuno-Oncology Congress 2024 [84]. At the final analysis data cutoff, 102 patients received durvalumab ($n = 53$ in cohort A and $n = 49$ in cohort B) with a median total treatment duration of 36 weeks [84]. Median PFS was 9.2 months [cohort A: 10.3 months (95 % CI 7.5–16.6); cohort B: 7.6 months (95 % CI 5.6–11.0) in cohort B) and ORR was 29.4 % [(cohort A: 34 % (95 % CI 21.5–48.3); cohort B 24.5 % (95 % CI 13.3–38.9)] [84]. Overall, 9.8 % had a severe possibly-related AE (PRAE) within 6 months after the first dose, of which 9.4 % in cohort A and 10.2 % in cohort B [84], and the most common PRAE leading to discontinuation was pneumonitis [84].

The SPRINT study evaluated a chemotherapy-free schedule in 25 patients with PD-L1 ≥ 50 % [85]. Three cycles of induction with pembrolizumab were followed by hypofractionated radiotherapy (48 to 55 Gy in 20 fractions) and then another 12 cycles of immunotherapy [85]. The 1-year PFS rate was 76 %, and the 1- and 2-year OS rates were 92 % and 76 %, respectively. Overall, 48 % of patients achieved either a partial or complete response following pembrolizumab induction, with gastrointestinal toxicity (colitis and esophagitis) being the most commonly reported adverse events [85].

Another phase II trial (DOLPHIN) evaluated the same study design with durvalumab in 32 patients with PD-L1 > 1 % [86]. At a median follow-up of 22.8 months, the mPFS was 25.6 months (95 % CI 13.1 months-NE) and the ORR 90.9 % (95 % CI 75.7 %-98.1 %) [86].

The phase I trial NRG-LU004 investigated both safety and efficacy of durvalumab Q4 weeks and thoracic radiotherapy, within 2 weeks of the first infusion, and subsequent durvalumab for one year in stage III unresectable NSCLC patients with PD-L1 ≥ 50 % [87]. Patients received either accelerated fractionated RT with 60 Gy in 15 fractions (ACRT) or conventional RT with 60 Gy in 30 fractions (CONV) [87]. Among the 24 evaluable patients enrolled, one dose limiting toxicity (DLT) event (unrelated bronchopulmonary haemorrhage leading to discontinuation of durvalumab) was reported [87]. At preliminary analysis, patients in ACRT cohort had 4 grade 3 AEs, 1 grade 4 AE (lymphopenia), and 1 grade 5 AE (lung infection, assessed as unrelated to therapy) [87]. In CONV cohort, there were 8 grade 3 AEs, and 1 grade 5 AE (respiratory failure, unrelated to therapy). For feasibility, 85 % of patients in the ACRT cohort and 75 % of patients in the CONV cohort received the second dose of durvalumab [87].

The preliminary results obtained with these strategies suggested that chemotherapy-free approaches could be a valuable strategy for frail, ECOG PS ≥ 2, elderly and PD-L1 selected patients, while the results of ongoing clinical studies are awaited (Table 1).

The potential impact of neoadjuvant immunotherapy

In recent years, the role of immunotherapy in the neoadjuvant and/or adjuvant setting for resectable stage III NSCLC has gained increasing relevance. Several studies investigated the role of PD-1 inhibitors in combination with chemotherapy as neoadjuvant/perioperative treatment in upfront resectable NSCLC [4,6,9,88–90], showing promising outcomes in terms of pathological complete resposne (pCR), major pathological response (MPR), event-free survival (EFS), and OS, compared to chemotherapy alone [4,6,9,88–90].

However, none of the previously mentioned studies included patients with upfront unresectable stage III NSCLC, thus the benefits of neoadjuvant chemo-immunotherapy in this context are less clear. Additionally, there is some overlap between patient populations enrolled in neoadjuvant/perioperative trials versus the PACIFIC trial, highlighting the need to optimize patients' selection within the multidisciplinary team to define the best approaches in clinical practice [4,6,9,11,14,88–90].

Zhou et al. have recently investigated the role of neoadjuvant chemo-immunotherapy in unresectable stage III NSCLC through a proof-of-concept phase II study, evaluating the efficacy of SHR-1701, a bifunctional anti-PD-L1/TGF-βRII fusion protein, either alone or in combination with chemotherapy [91]. Following initial treatment, patients either underwent surgery or radiotherapy according to the multidisciplinary team evaluation, eventually followed by maintenance with SHR-1701 [91]. In the primary cohort of patients receiving the neoadjuvanttherapy ($n = 97$), both primary endpoints were achieved, with a post-induction ORR of 58 % (95 % CI 47–68) and an 18-month EFS rate of 56.6 % (95 % CI 45.2–66.5) [91]. Of these, 27 patients (25 %) underwent surgery and all of them achieved R0 resection. Among the surgically resected patients, 12 (44 %) had major pathological responses and 7 (26 %) achieved pathological complete responses [91]. The 18-month EFS rate was 74.1 % (95 % CI 53.2–86.7) for surgical patients and 57.3 % (95 % CI 43.0–69.3) for those treated with radiotherapy [91]. The results of this study were intriguing, demonstrating the potential for downstaging and improving outcomes with the introduction of neoadjuvant chemoimmunotherapy in stage III unresectable NSCLC [91].

MDT-BRIDGE (NCT05925530) is an ongoing phase II, multicenter study enrolling patients with non-oncogene addicted NSCLC at stages IIB-IIIB (N2), including both resectable and unresectable disease [92]. All patients receive 2 cycles of durvalumab combined with neoadjuvant chemotherapy, followed by re-evaluation of resectability within MTD [92]. Patients deemed resectable (group 1) then receive additional 2 cycles of chemo-immunotherapy followed by surgical resection, whilst patients deemed unresectable (group 2) undergo definitive CRT [92]. Subsequently, both groups receive durvalumab consolidation for 1 year [92]. The primary endpoint is the resection rate in the overall study population [92].

Several other studies are investigating the role of neoadjuvant immunotherapy in unresectable stage III NSCLC (Table 1).

Biomarkers for treatment personalization

To date, the only predictive biomarker for consolidation immunotherapy in unresectable LA-NSCLC approved in clinical practice is PD-L1 expression [18]. Preliminary data from a small cohort reveal that both density of tumor-infiltrating CD8 + lymphocytes (TILs) and tumor expression of PD-L1 are significantly increased after CRT treatment, regardless of baseline PD-L1 levels [93]. Similarly, an increased density level of CD8 + TILs is a favorable prognostic factor [93]. In a retrospective cohort study of 328 patients treated with standard CRT and durvalumab consolidation, high PD-L1 TPS (≥90 %) and increased tumor mutational burden (TMB) were independent factors associated with better DCR [94]. In multivariate analysis, both PD-L1 ≥ 90 % and high TMB were independent favorable factors in terms of PFS (HR 0.43

with p = 0.032 and HR 0.32 with p = 0.001, respectively) [94]. Furthermore, the mutation of KEAP1 (Kelch-like ECH-associated protein) was independently associated with worse OS (HR 0.42; p = 0.04) [94]. In a cohort of 81 unresectable stage III patients undergoing CRT and durvalumab consolidation, those with high TMB (≥10 mutations per megabase) demonstrated lower locoregional failure (LRF) rates at 24 months (9 % vs. 51 %; p = 0.001) and better PFS at 24 months (66 % vs. 27 %; p = 0.003) [95]. The role of KEAP1/NFE2L2 was also evaluated in the same analysis; patients with mutated status had higher rates of LRF at one year compared to wildtype (52 % vs. 27 %; p = 0.05) [95].

In recent years, with the advent of liquid biopsy, multiple plasma biomarkers have been evaluated, including both ctDNA and circulating cytokines. Moding et al., demonstrated that in unresectable stage III NSCLC patients with minimal residual disease (MRD) positive after CRT, a survival benefit could be derived from consolidation with immunotherapy; conversely, in the MRD-negative cohort, there was no difference between receiving or not immunotherapy consolidation [96]. Moreover, those patients who experienced early ctDNA clearance under durvalumab consolidation had a 1-year FFP (freedom from progression) of 100 %, (p = 0.003) [96]. Recently, a study of 139 patients with unresectable LA-NSCLC and detectable ctDNA at baseline, showed that ctDNA level reduced during CRT and that delayed ctDNA clearance was associated to a worse prognosis [97]. Another recent translational analysis conducted within the BTCRC LUN 16–081 trial, showed that ctDNA detection predicts worse PFS after the end of CRT (PFS at 24 months 29 % vs. 65 %; p = 0.0048), before day 1 cycle 2 of consolidation immunotherapy (PFS at 24 months 0 % vs. 72 %; p < 0.0001) and at the end of immunotherapy (PFS at 24 months 15 % vs. 67 %; p = 0.0011) [98]. Furthermore, patients with either a decreasing or undetectable ctDNA after one cycle of immunotherapy had longer PFS at 24 months than patients with increasing ctDNA levels (72 % vs. 0 %; p < 0.0001) [98]. Based on this rationale, a phase 3 trial was developed to validate the role of MRD in guiding a personalized escalation treatment consolidation following chemotherapy and immunotherapy. Patients with detectable ctDNA (Cohort 1 minimal residual disease positive) will receive four cycles of platinum-based dual chemotherapy, tremelimumab and durvalumab, followed by durvalumab for up to one year; instead, patients with undetectable ctDNA (Cohort 2 minimal residual disease negative) will receive durvalumab alone as standard of care (NCT04585490).

At ESMO Congress 2024, Filippi et al. presented the ctDNA analysis from the DUART study. Detectable ctDNA at cycle 1 of durvalumab was associated with a trend toward a worse PFS regardless of the dose of radiotherapy delivered (HR 1.60, 95 % CI 0.89–2.86; p = 0.11); furthermore, the PFS was 25.5 versus 9.2 months for patients with undetectable versus detectable ctDNA at cycle 7 of immunotherapy (HR 4.43, 95 % CI 1.55–12.72; p = 0.0026) [99].

Evaluation of ctDNA levels could also guide de-escalation approaches for stage III NSCLC patients with target mutations undergoing consolidation TKI therapy in order to reduce long-term toxicities, as already demonstrated in the advanced setting [100].

Wei et al. developed a machine-learning-based platform, called Cytokine-based ICI Response Index (CIRI), which evaluated the role of 93 plasma cytokines from patients with stage III and IV NSCLC in predicting OS-related immunotherapy response [101]. Fourteen and 19 cytokines at baseline and during the treatment course, respectively, were selected to generate two corresponding CIRI models, both of which were found to identify patients with worse OS in 2 completely independent cohorts [101]. The authors also pointed out that PD-L1 at baseline did not correlate with OS and that combining cytokine profile with clinical features as well as other circulating factors improved predictive performance [101]. In addition, the recent GASTO-1091 trial, presented at ASCO 2024, demonstrated the negative prognostic role of high IL-6 and low CD3 + lymphocyte levels in this treatment context [80].

Recent research evaluated the role of aneuploidy as predictive biomarkers in a cohort of 197 patients with stage III NSCLC treated with cCRT and durvalumab consolidation; tumors with high aneuploidy had higher incidence of distant metastasis and shorter median distant-metastasis free survival (p = 0.04 and p = 0.048, respectively), while in multivariate analysis low tumor aneuploidy was independently associated with better PFS (HR 0.63, 95 % CI 0.41–0.95; p = 0.03) and OS (HR 0.50, 95 % CI 0.27–0.92; p = 0.03) [102].

Concerning the emerging field of radiomics, a study conducted by Jazieh et al. on 133 patients with unresectable stage III NSCLC undergoing either CRT plus durvalumab or CRT alone, generated a radiomic risk score (RRS), based on pre-treatment intra-tumoural and peri-tumoural radiological features [103]. RRS was statistically significantly associated with both PFS and OS in the analysez population [103]. Even if preliminary this data highlights the potential applications of radiomics not only in predicting treatment response but also in discerning immunotherapy-related pneumonitis in LA-NSCLC patients [104,105].

Conclusion

To date, CRT followed by durvalumab consolidation remains the standard of care for unresectable LA-NSCLC. However, despite its impressive results, the use of PACIFIC regimen needs to be reconsidered based on several critical issues. Firstly, according to the results of real-world studies, the efficacy of durvalumab is influenced by patient's characteristics, type of CRT and tumour hallmarks. Also, for the majority of patients who develops disease progression during or at completion of durvalumab consolidation, a definite treatment strategy has not been established yet. Secondly, the indiscriminate use of immunotherapy as consolidation treatment for all LA-NSCLCs has recently been questioned by the results of the LAURA study, which showed for the first time the efficacy of targeted therapies for oncogene-addicted patients. This data emphasized the role of molecular testing in the locally advanced disease, paving the way for additional investigations in other molecular drivers. Also, the utility of immunotherapy in the perioperative management of stage III resectable NSCLC has been firmly established with some overlap between patient cohorts included in the neoadjuvant/perioperative studies and those included in the PACIFIC trial. Therefore, defining the role of chemo-immunotherapy for unresectable or borderline resectable disease is mandatory and ongoing studies are addressing this critical question. Novel therapeutic strategies have been developed in the post-PACIFIC era. Preliminary promising results come from the intensification of immunotherapy-consolidation [66–69], while we are still awaiting the results of phase III PACIFIC-9 trial. Conversely, based on the negative results of different randomized studies, the anticipation of immunotherapy concurrently with CRT remain quite controversial [71–77], leaving some doubts about the biological rational underlying this combination strategy. Promising results were observed with the induction of chemo-immunotherapy, but more mature results from randomized studies are needed to confirm the role of this approach in the unresectable disease (Table 1) [79–82]. Lastly, in the future, the implementation of ctDNA will likely help to overcome the limitations of tissue biomarkers and to optimize patients' selection in the real-world.

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References

[1] Cortiula F, Reymen B, Peters S, Van Mol P, Wauters E, Vansteenkiste J, et al. Immunotherapy in unresectable stage III non-small-cell lung cancer: state of the art and novel therapeutic approaches. Ann Oncol 2022;33. https://doi.org/10.1016/j.annonc.2022.06.013.

[2] Catania C, Piperno G, Russo A, Greco C, Agustoni F, Scotti V, et al. Open issues in the therapeutic management of unresectable stage III NSCLC in the immunotherapy era. Crit Rev Oncol Hematol 2022;174. https://doi.org/10.1016/j.critrevonc.2022.103684.

[3] Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28. https://doi.org/10.1093/annonc/mdx222.

[4] Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386. https://doi.org/10.1056/nejmoa2202170.

[5] Wakelee H, Liberman M, Kato T, Tsuboi M, Lee S-H, Gao S, et al. Perioperative pembrolizumab for early-stage non–small-cell lung cancer. N Engl J Med 2023;389. https://doi.org/10.1056/nejmoa2302983.

[6] Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, et al. Perioperative durvalumab for resectable non–small-cell lung cancer. N Engl J Med 2023;389. https://doi.org/10.1056/nejmoa2304875.

[7] Wu Y-L, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in resected EGFR -mutated non–small-cell lung cancer. N Engl J Med 2020;383. https://doi.org/10.1056/nejmoa2027071.

[8] Wu Y-L, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, et al. Alectinib in resected ALK -positive non–small-cell lung cancer. N Engl J Med 2024;390:1265–76. https://doi.org/10.1056/nejmoa2310532.

[9] Lu S, Zhang W, Wu L, Wang W, Zhang P, Fang W, et al. Perioperative toripalimab plus chemotherapy for patients with resectable non-small cell lung cancer: the neotorch randomized clinical trial. JAMA 2024;331. https://doi.org/10.1001/jama.2023.24735.

[10] Cascone T, Awad MM, Spicer JD, He J, Lu S, Sepesi B, et al. Perioperative nivolumab in resectable lung cancer. N Engl J Med 2024;390:1756–69. https://doi.org/10.1056/nejmoa2311926.

[11] Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. N Engl J Med 2017;377. https://doi.org/10.1056/nejmoa1709937.

[12] Daly ME, Singh N, Ismaila N, Antonoff MB, Arenberg DA, Bradley J, et al. Management of stage III non-small-cell lung cancer: ASCO guideline. J Clin Oncol 2022;40. https://doi.org/10.1200/JCO.21.02528.

[13] Remon J, Soria JC, Peters S. Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical practice guidelines focusing on diagnosis, staging, systemic and local therapy. Ann Oncol 2021;32. https://doi.org/10.1016/j.annonc.2021.08.1994.

[14] Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379. https://doi.org/10.1056/nejmoa1809697.

[15] Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Three-Year Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC—update from PACIFIC. J Thorac Oncol 2020;15. https://doi.org/10.1016/j.jtho.2019.10.002.

[16] Faivre-Finn C, Vicente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, et al. Four-Year Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC—an Update From the PACIFIC Trial. J Thorac Oncol 2021;16. https://doi.org/10.1016/j.jtho.2020.12.015.

[17] Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40. https://doi.org/10.1200/JCO.21.01308.

[18] Paz-Ares L, Spira A, Raben D, Planchard D, Cho BC, Özgüroğlu M, et al. Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. Ann Oncol 2020;31:798–806. https://doi.org/10.1016/J.ANNONC.2020.03.287.

[19] Peters S, Dafni U, Boyer M, De Ruysscher D, Faivre-Finn C, Felip E, et al. Position of a panel of international lung cancer experts on the approval decision for use of durvalumab in stage III non-small-cell lung cancer (NSCLC) by the committee for medicinal products for human use (chmp). Ann Oncol 2019;30. https://doi.org/10.1093/annonc/mdy553.

[20] Curran WJ, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs concurrent chemoradiation for stage iii non-small cell lung cancer: Randomized phase III trial RTOG 9410. J Natl Cancer Inst 2011;103. https://doi.org/10.1093/jnci/djr325.

[21] Patel SR, Jenkins J, Papadopolous N, Andrew Burgess M, Plager C, Gutterman J, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B nonsmall cell lung carcinoma: A modified phase I/II trial. 5<1213 ::AID-CNCR1440>3.0.CO;2-0 Cancer 2001;92. https://doi.org/10.1002/1097-0142(20010901)92.

[22] Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 1999;17. https://doi.org/10.1200/jco.1999.17.9.2692.

[23] Aupérin A, Le Péchoux C, Pignon JP, Koning C, Jeremic B, Clamon G, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): A meta-analysis of individual data from 1764 patients. Ann Oncol 2006;17. https://doi.org/10.1093/annonc/mdj117.

[24] Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non - small-cell lung cancer. J Clin Oncol 2010;28. https://doi.org/10.1200/JCO.2009.26.2543.

[25] Walraven I, Damhuis RA, ten Berge MG, Rosskamp M, van Eycken L, de Ruysscher D, et al. Treatment Variation of Sequential versus Concurrent Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer Patients in the Netherlands and Belgium. Clin Oncol 2017;29. https://doi.org/10.1016/j.clon.2017.07.012.

[26] Driessen EJM, Bootsma GP, Hendriks LEL, van den Berkmortel FWPJ, Bogaarts BAHA, van Loon JGM, et al. Stage III Non-Small Cell Lung Cancer in the elderly: Patient characteristics predictive for tolerance and survival of chemoradiation in daily clinical practice. Radiother Oncol 2016;121. https://doi.org/10.1016/j.radonc.2016.07.025.

[27] Girard N, Perol M, Simon G, Audigier Valette C, Gervais R, Debieuvre D, et al. Treatment strategies for unresectable locally advanced non-small cell lung cancer in the real-life ESME cohort. Lung Cancer 2021;162. https://doi.org/10.1016/j.lungcan.2021.10.017.

[28] Zheng Z, Rengan R, Zhao J, Sineshaw HM, Chun SG, Han X, et al. Concurrent and sequential chemoradiation therapy are associated with improved survival among unresected stage III non-small cell lung cancer patients in the United States. J Clin Oncol 2020;38. https://doi.org/10.1200/jco.2020.38.15_suppl.7043.

[29] Provencio M, Carcereny E, Castro RL, Calvo V, Abreu DR, Cobo M, et al. Real-world treatment patterns and survival outcomes for patients with stage III non-small cell lung cancer in Spain: a nationwide cohort study. Transl Lung. Cancer Res 2023;12. https://doi.org/10.21037/tlcr-23-176.

[30] Jazieh AR, Onal HC, Tan DSW, Soo RA, Prabhash K, Kumar A, et al. Real-World Treatment Patterns and Clinical Outcomes in Patients With Stage III NSCLC: Results of KINDLE, a Multicountry Observational Study. J Thorac Oncol 2021;16. https://doi.org/10.1016/j.jtho.2021.05.003.

[31] Spencer A, Williams J, Samuel R, Boon IS, Clarke K, Jain P. Concurrent versus sequential chemoradiotherapy for unresectable locally advanced stage III non-small cell lung cancer: Retrospective analysis in a single United Kingdom cancer centre. Cancer Treat Res Commun 2021;29. https://doi.org/10.1016/j.ctarc.2021.100460.

[32] Zatloukal P, Petruzelka L, Zemanova M, Havel L, Janku F, Judas L, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: A randomized study. Lung Cancer 2004;46. https://doi.org/10.1016/j.lungcan.2004.03.004.

[33] Fournel P, Robinet G, Thomas P, Souquet PJ, Léna H, Vergnenégre A, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Français de Pneumo-Cancérologie NPC 95-01 Study. J Clin Oncol 2005;23. https://doi.org/10.1200/JCO.2005.03.070.

[34] Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16. https://doi.org/10.1016/S1470-2045(14)71207-0.

[35] Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. iv1 –21 Ann Oncol 2017;28. https://doi.org/10.1093/annonc/mdx222.

[36] Daly ME, Singh N, Ismaila N, Daly ME, Singh N, Ismaila N, et al. Management of Stage III Non-Small Cell Lung Cancer: ASCO Guideline Rapid Recommendation Update. J Clin Oncol 2024;42:3058–60. https://doi.org/10.1200/JCO-24-01324/ASSET/CFF92843-3599-463C-B979-B866CFC38D4B/ASSETS/IMAGES/LARGE/JCO-24-01324F1.JPG.

[37] Garassino MC, Mazieres J, Reck M, Chouaid C, Bischoff H, Reinmuth N, et al. Durvalumab After Sequential Chemoradiotherapy in Stage III, Unresectable NSCLC: The Phase 2 PACIFIC-6 Trial. J Thorac Oncol 2022;17. https://doi.org/10.1016/j.jtho.2022.07.1148.

[38] Wu Y-L, Wu L, Bi N, Cil T, Ge H, Zhu Z, et al. PACIFIC-5: a Phase 3 Study of Consolidation Durvalumab in Patients with Unresectable Stage III NSCLC and No Progression After Concurrent or Sequential Chemoradiotherapy. n.d.

[39] Girard N, Mornex F, Christoph DC, Fietkau R, Filippi AR, Field J, et al. PACIFIC-R: First real-world study of patients with unresectable, stage III NSCLC treated with durvalumab after chemoradiotherapy. Ann Oncol 2019;30. https://doi.org/10.1093/annonc/mdz067.017.

[40] Girard N, Smit HJM, Sibille A, McDonald F, Mornex F, Garassino MCC, et al. 1171MO PACIFIC-R real-world study: Treatment duration and interim analysis of progression-free survival in unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. Ann Oncol 2021;32. https://doi.org/10.1016/j.annonc.2021.08.1775.

[41] Girard N, Bar J, Garrido P, Garassino MC, McDonald F, Mornex F, et al. Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study. J Thorac Oncol 2023;18. https://doi.org/10.1016/j.jtho.2022.10.003.

[42] Filippi AR, Bar J, Chouaid C, Christoph DC, Field JK, Fietkau R, et al. Real-world outcomes with durvalumab after chemoradiotherapy in patients with

unresectable stage III NSCLC: interim analysis of overall survival from PACIFIC-R. ESMO Open 2024;9. https://doi.org/10.1016/j.esmoop.2024.103464.
[43] Faehling M, Schumann C, Christopoulos P, Hoffknecht P, Alt J, Horn M, et al. Durvalumab after definitive chemoradiotherapy in locally advanced unresectable non-small cell lung cancer (NSCLC): Real-world data on survival and safety from the German expanded-access program (EAP). Lung Cancer 2020;150. https://doi.org/10.1016/j.lungcan.2020.10.006.
[44] Jung HA, Noh JM, Sun JM, Lee SH, Ahn JS, Ahn MJ, et al. Real world data of durvalumab consolidation after chemoradiotherapy in stage III non-small-cell lung cancer. Lung Cancer 2020;146:23–9. https://doi.org/10.1016/j.lungcan.2020.05.035.
[45] Huang Y, Zhao JJ, Soon YY, Wong A, Aminkeng F, Ang Y, et al. Real-world experience of consolidation durvalumab after concurrent chemoradiotherapy in stage III non-small cell lung cancer. Thorac Cancer 2022;13:3152–61. https://doi.org/10.1111/1759-7714.14667.
[46] Taugner J, Käsmann L, Eze C, Rühle A, Tufman A, Reinmuth N, et al. Real-world prospective analysis of treatment patterns in durvalumab maintenance after chemoradiotherapy in unresectable, locally advanced NSCLC patients. Invest New Drugs 2021;39. https://doi.org/10.1007/s10637-021-01091-9.
[47] Bruni A, Scotti V, Borghetti P, Vagge S, Cozzi S, D'Angelo E, et al. A Real-World, Multicenter, Observational Retrospective Study of Durvalumab After Concomitant or Sequential Chemoradiation for Unresectable Stage III Non-Small Cell Lung Cancer. Front. Oncol 2021;11. https://doi.org/10.3389/fonc.2021.744956.
[48] Abe T, Saito S, Iino M, Aoshika T, Ryuno Y, Ohta T, et al. Effect of durvalumab on local control after concurrent chemoradiotherapy for locally advanced non-small cell lung cancer in comparison with chemoradiotherapy alone. Thorac. Cancer 2021;12. https://doi.org/10.1111/1759-7714.13764.
[49] Sankar K, Bryant AK, Strohbehn GW, Zhao L, Elliott D, Moghanaki D, et al. Real World Outcomes versus Clinical Trial Results of Durvalumab Maintenance in Veterans with Stage III Non-Small Cell Lung Cancer. Cancers (Basel) 2022;14. https://doi.org/10.3390/cancers14030614.
[50] Gómez Rueda A, Taus Á, Álvarez Álvarez R, Bernabé-Caro R, Chara L, López-Brea M, et al. The S-REAL study: Spanish real-world data on unresectable stage III NSCLC patients treated with durvalumab after chemoradiotherapy. Clin Transl Oncol 2024;26:1779–89. https://doi.org/10.1007/s12094-024-03404-9.
[51] Zehentmayr F, Feurstein P, Ruznic E, Langer B, Grambozov B, Klebermass M, et al. Durvalumab impacts progression-free survival while high-dose radiation >66 Gy improves local control without excess toxicity in unresectable NSCLC stage III: Real-world data from the Austrian radio-oncological lung cancer study association registry (ALLSTAR). Radiother Oncol 2024;196. https://doi.org/10.1016/j.radonc.2024.110294.
[52] Stevens S, Nindra U, Shahnam A, Wei J, Bray V, Pal A, et al. Real world efficacy and toxicity of consolidation durvalumab following chemoradiotherapy in older Australian patients with unresectable stage III non-small cell lung cancer. J Geriatr Oncol 2024;15. https://doi.org/10.1016/j.jgo.2024.101705.
[53] Vrankar M, Stanic K, Jelercic S, Ciric E, Vodusek AL, But-Hadzic J. Clinical outcomes in stage III non-small cell lung cancer patients treated with durvalumab after sequential or concurrent platinum-based chemoradiotherapy - Single institute experience. Radiol Oncol 2021;55:482–90. https://doi.org/10.2478/raon-2021-0044.
[54] Park JE, Hong KS, Choi SH, Lee SY, Shin KC, Jang JG, et al. Durvalumab Consolidation After Chemoradiotherapy in Elderly Patients With Unresectable Stage III NSCLC: A Real-World Multicenter Study. Clin Lung Cancer 2024;25:354–64. https://doi.org/10.1016/j.cllc.2024.02.006.
[55] Hasegawa T, Ariyasu R, Tanaka H, Saito R, Kawashima Y, Horiike A, et al. Subsequent treatment for locally advanced non-small-cell lung cancer that progressed after definitive chemoradiotherapy and consolidation therapy with durvalumab: a multicenter retrospective analysis (TOPGAN 2021-02). Cancer Chemother Pharmacol 2023;92. https://doi.org/10.1007/s00280-023-04547-2.
[56] Kawachi H, Tamiya M, Oya Y, Saito G, Taniguchi Y, Matsumoto H, et al. Real-World Outcomes of Subsequent Chemotherapy after Progression Following Chemoradiation and Consolidative Durvalumab Therapy in Locally Advanced Non-small Cell Lung Cancer: An Exploratory Analysis from the CRIMSON Study (HOPE-005). Clin Lung Cancer 2024. https://doi.org/10.1016/j.cllc.2024.07.014.
[57] Naidoo J, Antonia S, Wu YL, Cho BC, Thiyagarajah P, Mann H, et al. Brief Report: Durvalumab After Chemoradiotherapy in Unresectable Stage III EGFR-Mutant NSCLC: A Post Hoc Subgroup Analysis From PACIFIC. J Thorac Oncol 2023;18. https://doi.org/10.1016/j.jtho.2023.02.009.
[58] Aredo JV, Mambetsariev I, Hellyer JA, Amini A, Neal JW, Padda SK, et al. Durvalumab for Stage III EGFR-Mutated NSCLC After Definitive Chemoradiotherapy. J Thorac Oncol 2021;16. https://doi.org/10.1016/j.jtho.2021.01.1628.
[59] Riudavets M, Auclin E, Mosteiro M, Dempsey N, Majem M, Lobefaro R, et al. Durvalumab consolidation in patients with unresectable stage III non-small cell lung cancer with driver genomic alterations. Eur J Cancer 2022;167:142–8. https://doi.org/10.1016/j.ejca.2022.02.014.
[60] Cortiula F, De Ruysscher D, Steens M, Wijsman R, van der Wekken A, Alberti M, et al. Adjuvant durvalumab after concurrent chemoradiotherapy for patients with unresectable stage III NSCLC harbouring uncommon genomic alterations. Eur J Cancer 2023;184. https://doi.org/10.1016/j.ejca.2023.02.013.
[61] Lu S, Kato T, Dong X, Ahn M-J, Quang L-V, Soparattanapaisarn N, et al. Osimertinib after Chemoradiotherapy in Stage III EGFR -Mutated NSCLC. N Engl J Med 2024;391:585–97. https://doi.org/10.1056/NEJMOA2402614/SUPPL_FILE/NEJMOA2402614_DATA-SHARING.PDF.
[62] Lu S, Ahn MJ, Reungwetwattana T, Özgüroğlu M, Kato T, Yang JCH, et al. Osimertinib after definitive chemoradiotherapy in unresectable stage III epidermal growth factor receptor-mutated non-small-cell lung cancer: analyses of central nervous system efficacy and distant progression from the phase III LAURA study. Ann Oncol 2024;35:1116–25. https://doi.org/10.1016/j.annonc.2024.08.2243.
[63] Chang AEB, Piper-Vallillo AJ, Mak RH, Lanuti M, Muzikansky A, Rotow J, et al. The ASCENT Trial: a phase 2 study of induction and consolidation afatinib and chemoradiation with or without surgery in stage III EGFR-mutant NSCLC. Oncologist 2024;29:609–18. https://doi.org/10.1093/ONCOLO/OYAE107.
[64] Meng X, Ge H, Ning F, et al. Aumolertinib after chemoradiotherapy in unresectable stage III non-small-cell lung cancer with EGFR mutation: interim analysis of the phase III POLESTAR study. Abstract presented at: 2024 International Association for the Study of Lung Cancer World Conference on Lung Cancer; September 7-10, 2024; San Diego, CA. Abstract PL04.13.
[65] Nassar AH, Jayakrishnan R, Feng J, Shepherd F, Adib E, Cheung JM, et al. Consolidation ALK Tyrosine Kinase Inhibitors versus Durvalumab or Observation After Chemoradiation in Unresectable Stage III ALK+ Non-Small Cell Lung Cancer. J Thorac Oncol 2024. https://doi.org/10.1016/j.jtho.2024.09.1379.
[66] Durm GA, Mamdani H, Althouse SK, Jabbour SK, Ganti AK, Jalal SI, et al. Consolidation nivolumab plus ipilimumab or nivolumab alone following concurrent chemoradiation for patients with unresectable stage III non-small cell lung cancer: BTCRC LUN 16-081. J Clin Oncol 2022;40. https://doi.org/10.1200/jco.2022.40.16_suppl.8509.
[67] Shahani S, Althouse SK, Hanna NH, Durm GA. Updated safety and efficacy analysis comparing elderly vs nonelderly patients treated with consolidation nivolumab or nivolumab plus ipilimumab after chemoradiation for unresectable stage III NSCLC from the BTCRC LUN 16-081 clinical trial. J Clin Oncol 2024;42:e13770–. https://doi.org/10.1200/JCO.2024.42.16_SUPPL.E13770.
[68] Herbst RS, Majem M, Barlesi F, Carcereny E, Chu Q, Monnet I, et al. COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination with Oleclumab or Monalizumab in Patients with Unresectable, Stage III Non-Small-Cell Lung Cancer. J Clin Oncol 2022;3. https://doi.org/10.1200/JCO.22.00227.
[69] Aggarwal C, Martinez-Marti A, Majem M, Barlesi F, Carcereny E, Chu QS, et al. Updated results from COAST, a phase 2 study of durvalumab (D) ± oleclumab (O) or monalizumab (M) in patients (pts) with stage III unresectable non-small cell lung cancer (uNSCLC). J Clin Oncol 2024;42:8046. https://doi.org/10.1200/JCO.2024.42.16_SUPPL.8046.
[70] Wang Q, Ju X, Wang J, Fan Y, Ren M, Zhang H. Immunogenic cell death in anticancer chemotherapy and its impact on clinical studies. Cancer Lett 2018;438. https://doi.org/10.1016/j.canlet.2018.08.028.
[71] Peters S, Felip E, Dafni U, Tufman A, Guckenberger M, Álvarez R, et al. Progression-Free and Overall Survival for Concurrent Nivolumab With Standard Concurrent Chemoradiotherapy in Locally Advanced Stage IIIA-B NSCLC: Results From the European Thoracic Oncology Platform NICOLAS Phase II Trial (European Thoracic Oncology Platform 6-14). J Thorac Oncol 2021;16. https://doi.org/10.1016/j.jtho.2020.10.129.
[72] Lin SH, Lin Y, Yao L, Kalhor N, Carter BW, Altan M, et al. Phase II Trial of Concurrent Atezolizumab With Chemoradiation for Unresectable NSCLC. J Thorac Oncol 2020;15. https://doi.org/10.1016/j.jtho.2019.10.024.
[73] Jabbour SK, Lee KH, Frost N, Breder V, Kowalski DM, Pollock T, et al. Pembrolizumab plus Concurrent Chemoradiation Therapy in Patients with Unresectable, Locally Advanced, Stage III Non-Small Cell Lung Cancer: The Phase 2 KEYNOTE-799 Nonrandomized Trial. JAMA. Oncol 2021;7. https://doi.org/10.1001/jamaoncol.2021.2301.
[74] Reck M, Lee KH, Frost N, Breder VV, Kowalski D, Levchenko E, et al. Two-year update from KEYNOTE-799: Pembrolizumab plus concurrent chemoradiation therapy (cCRT) for unresectable, locally advanced, stage III NSCLC. J Clin Oncol 2022;40. https://doi.org/10.1200/jco.2022.40.16_suppl.8508.
[75] Bradley JD, Nishio M, Okamoto I, Newton MD, Trani L, Shire NJ, et al. PACIFIC-2: Phase 3 study of concurrent durvalumab and platinum-based chemoradiotherapy in patients with unresectable, stage III NSCLC. J Clin Oncol 2019;37. https://doi.org/10.1200/jco.2019.37.15_suppl.tps8573.
[76] Bradley JD, Sugawara S, Lee KHH, Ostoros G, Demirkazik A, Zemanova M, et al. LBA1 Durvalumab in combination with chemoradiotherapy for patients with unresectable stage III NSCLC: Final results from PACIFIC-2. ESMO Open 2024;9:102986. https://doi.org/10.1016/J.ESMOOP.2024.102986.
[77] ESMO Immuno-Oncology Congress 2024 | OncologyPRO n.d. https://oncologypro.esmo.org/meeting-resources/esmo-immuno-oncology-congress-2024/checkmate-73l-phase-3-study-comparing-nivolumab-n-concurrent-chemoradiotherapy-ccrt-followed-by-n-_-ipilimumab-i-v-ccrt-followed-by-durval (accessed December 15, 2024).
[78] Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. Science 1979;2020:367. https://doi.org/10.1126/science:aax0182.
[79] Ross HJ, Kozono D, Wang XF, Urbanic JJ, Williams TM, Nelson GD, et al. Atezolizumab Before and After Chemoradiation for Unresectable Stage III Non–Small Cell Lung Cancer: A Phase II Nonrandomized Controlled Trial. JAMA Oncol 2024;10:1212–9. https://doi.org/10.1001/JAMAONCOL.2024.1897.
[80] Liu H, Qiu B, Zhao Y, He W, Feng W, Zeng W, et al. A phase II randomized trial evaluating consolidative nivolumab in locally advanced non-small cell lung cancer post neoadjuvant chemotherapy plus nivolumab and concurrent chemoradiotherapy (GASTO-1091). J Clin Oncol 2024;42:8008. https://doi.org/10.1200/JCO.2024.42.16_SUPPL.8008.

[81] Provencio M, Campos B, Guirado M, Vilà L, Campelo MRG, Dorta M, et al. OA12.05 APOLO: Phase II Trial of Induction Chemo-Immunotherapy Plus Chemoradiotherapy and Maintenance Immunotherapy in Stage III NSCLC. J Thorac Oncol 2024;19:S37. https://doi.org/10.1016/J.JTHO.2024.09.067.
[82] William WN, Junior GC, Matias D d. A, Araújo LH d. L, Reis TV, Teixeira VBG, et al. OA12.06 Intensified Chemo-Immuno-Radiotherapy with Durvalumab for Stage III NSCLCs: A Single Arm Phase II Study - PACIFIC-BRAZIL (LACOG 2218). Journal of Thoracic Oncology 2024;19:S37–8. https://doi.org/10.1016/J.JTHO.2024.09.068.
[83] Filippi AR, Dziadziuszko R, Garciá Campelo MR, Paoli JB, Sawyer W, Díáz Pérez IE. DUART: Durvalumab after radiotherapy in patients with unresectable, stage III NSCLC who are ineligible for chemotherapy. Future Oncol 2021;17:4657–63. https://doi.org/10.2217/fon-2021-0952.
[84] Filippi ARR, García-Campelo MR, Paoli J-B, Kowalski D, Bennati C, Borghetti P, et al. LBA62 Durvalumab after radiotherapy (RT) in patients with unresectable stage III NSCLC ineligible for chemotherapy (CT): Primary results from the DUART study. Ann Oncol 2023;34. https://doi.org/10.1016/j.annonc.2023.10.058.
[85] Ohri N, Jolly S, Cooper BT, Kabarriti R, Bodner WR, Klein J, et al. Selective Personalized RadioImmunotherapy for Locally Advanced Non-Small-Cell Lung Cancer Trial (SPRINT). J Clin Oncol 2024;42. https://doi.org/10.1200/JCO.23.00627.
[86] Tachihara M, Tsujino K, Ishihara T, Hayashi H, Sato Y, Kurata T, et al. Durvalumab Plus Concurrent Radiotherapy for Treatment of Locally Advanced Non-Small Cell Lung Cancer: The DOLPHIN Phase 2 Nonrandomized Controlled Trial. JAMA. Oncol 2023;9. https://doi.org/10.1001/jamaoncol.2023.3309.
[87] Lin SH, Pugh SL, Tsao AS, Edelman MJ, Doemer A, Simone CB, et al. Safety results of NRG-LU004: Phase I trial of accelerated or conventionally fractionated radiotherapy combined with durvalumab in PD-L1–high locally advanced non-small cell lung cancer. J Clin Oncol 2022;40. https://doi.org/10.1200/jco.2022.40.16_suppl.8513.
[88] Cascone T, Awad MM, Spicer JD, He J, Lu S, Sepesi B, et al. LBA1 CheckMate 77T: Phase III study comparing neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) vs neoadjuvant placebo plus chemo followed by surgery and adjuvant NIVO or placebo for previously untreated, resectable stage II–IIIb NSCLC. Ann Oncol 2023;34. https://doi.org/10.1016/j.annonc.2023.10.050.
[89] Wakelee H, Liberman M, Kato T, Tsuboi M, Lee S-H, Gao S, et al. Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer. N Engl J Med 2023;389:491–503. https://doi.org/10.1056/NEJMOA2302983/SUPPL_FILE/NEJMOA2302983_DATA-SHARING.PDF.
[90] Yue D, Wang W, Liu H, Chen Q, Chen C, Zhang J, et al. LBA58 Pathological response to neoadjuvant tislelizumab (TIS) plus platinum-doublet (PtDb) chemotherapy (CT) in resectable stage II-IIIA NSCLC patients (pts) in the phase III (Ph3) RATIONALE-315 trial. Ann Oncol 2023;34. https://doi.org/10.1016/j.annonc.2023.10.054.
[91] Zhou Q, Pan Y, Yang X, Zhao Y, Han G, Pang Q, et al. Neoadjuvant SHR-1701 with or without chemotherapy in unresectable stage III non-small-cell lung cancer: A proof-of-concept, phase 2 trial. Cancer Cell 2024;42:1258–1267.e2. https://doi.org/10.1016/J.CCELL.2024.05.024.
[92] Reck M, Nadal E, Girard N, Filippi AR, Martin LW, Gay CM, et al. MDT-BRIDGE: Neoadjuvant Durvalumab Plus Chemotherapy Followed by Either Surgery and Adjuvant Durvalumab or Chemoradiotherapy and Consolidation Durvalumab in Resectable or Borderline-resectable Stage IIB-IIIB NSCLC. Clin Lung Cancer 2024;25:587–593.e3. https://doi.org/10.1016/J.CLLC.2024.06.007.
[93] Yoneda K, Kuwata T, Kanayama M, Mori M, Kawanami T, Yatera K, et al. Alteration in tumoural PD-L1 expression and stromal CD8-positive tumour-infiltrating lymphocytes after concurrent chemo-radiotherapy for non-small cell lung cancer. Br J Cancer 2019;121. https://doi.org/10.1038/s41416-019-0541-3.
[94] Alessi JV, Ricciuti B, Wang X, Pecci F, Di Federico A, Lamberti G, et al. Impact of TMB/PD-L1 expression and pneumonitis on chemoradiation and durvalumab response in stage III NSCLC. Nat Commun 2023;14. https://doi.org/10.1038/s41467-023-39874-8.
[95] Lebow ES, Shepherd A, Eichholz JE, Offin M, Gelblum DY, Wu AJ, et al. Analysis of Tumor Mutational Burden, Progression-Free Survival, and Local-Regional Control in Patents with Locally Advanced Non-Small Cell Lung Cancer Treated with Chemoradiation and Durvalumab. JAMA Netw Open 2023;6. https://doi.org/10.1001/jamanetworkopen.2022.49591.
[96] Moding EJ, Liu Y, Nabet BY, Chabon JJ, Chaudhuri AA, Hui AB, et al. Circulating Tumor DNA Dynamics Predict Benefit from Consolidation Immunotherapy in Locally Advanced Non-Small Cell Lung Cancer. Nat. Cancer 2020;1. https://doi.org/10.1038/s43018-019-0011-0.
[97] Pan Y, Zhang JT, Gao X, Chen ZY, Yan B, Tan PX, et al. Dynamic circulating tumor DNA during chemoradiotherapy predicts clinical outcomes for locally advanced non-small cell lung cancer patients. Cancer Cell 2023;41. https://doi.org/10.1016/j.ccell.2023.09.007.
[98] Jun S, Shukla NA, Durm G, Hui AB, Cao S, Ganti AK, et al. Analysis of Circulating Tumor DNA Predicts Outcomes of Short-Course Consolidation Immunotherapy in Unresectable Stage III NSCLC. J Thorac Oncol 2024;19. https://doi.org/10.1016/J.JTHO.2024.06.024.
[99] Filippi AR, Garcia-Campelo MR, Paoli J-B, Kowalski DM, Bennati C, Borghetti P, et al. LBA51 Circulating tumor DNA (ctDNA) dynamics and treatment responses in chemotherapy-ineligible patients (pts) with unresectable stage III NSCLC from the phase II DUART trial. Ann Oncol 2024;35:S1241. https://doi.org/10.1016/J.ANNONC.2024.08.2292.
[100] Dong S, Wang Z, Zhang JT, Yan B, Zhang C, Gao X, et al. Circulating Tumor DNA-Guided De-Escalation Targeted Therapy for Advanced Non-Small Cell Lung Cancer: A Nonrandomized Controlled Trial. JAMA Oncol 2024 Jul 1;10(7):932–40. https://doi.org/10.1001/jamaoncol.2024.1779.
[101] Wei F, Azuma K, Nakahara Y, Saito H, Matsuo N, Tagami T, et al. Machine learning for prediction of immunotherapeutic outcome in non-small-cell lung cancer based on circulating cytokine signatures. J Immunother Cancer 2023;11. https://doi.org/10.1136/jitc-2023-006788.
[102] Alessi JV, Price A, Richards AL, Ricciuti B, Wang X, Elkrief A, et al. Multi-institutional analysis of aneuploidy and outcomes to chemoradiation and durvalumab in stage III non-small cell lung cancer. J Immunother Cancer. 2024 Jan 30;12(1):e007618corr1. doi: 10.1136/jitc-2023-007618corr1.
[103] Jazieh K, Khorrami M, Saad A, Gad M, Gupta A, Patil P, et al. Novel imaging biomarkers predict outcomes in stage III unresectable non-small cell lung cancer treated with chemoradiation and durvalumab. J Immunother Cancer 2022;10. https://doi.org/10.1136/jitc-2021-003778.
[104] Kawahara D, Imano N, Nishioka R, Ogawa K, Kimura T, Nakashima T, et al. Prediction of radiation pneumonitis after definitive radiotherapy for locally advanced non-small cell lung cancer using multi-region radiomics analysis. Sci Rep 2021;11. https://doi.org/10.1038/s41598-021-95643-x.
[105] Chen X, Sheikh K, Nakajima E, Lin CT, Lee J, Hu C, et al. Radiation Versus Immune Checkpoint Inhibitor Associated Pneumonitis: Distinct Radiologic Morphologies. Oncologist 2021;26. https://doi.org/10.1002/onco.13900.