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Review

Current challenges of unresectable stage III NSCLC: are we ready to break the glass ceiling of the PACIFIC trial?

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***Abstract*:** Consolidation anti-programmed death-ligand 1 has become a new standard of care in unresectable stage III non-small cell lung cancer (NSCLC) following chemo-radiotherapy (CTRT), based on the results of two phase III trials. Advances remain however needed, in particular to reduce the risk of distant relapse and for treatment personalization. Newer strategies are currently being tested, including consolidation with dual immune checkpoint inhibitors (ICIs), concurrent chemo-radioimmunotherapy and (chemo)-immunotherapy induction before CTRT. One randomized phase II reported better outcomes with a double ICI consolidation as compared with durvalumab alone. Three nonrandomized phase II trials also suggested that concurrent ICI-CTRT was feasible. Within this review, we summarize the current evidence, highlight ongoing trials and discuss challenges that will ideally lead to a cure for more patients with unresectable stage III NSCLC.

Keywords: stage III non-small cell lung cancer, PACIFIC, concurrent chemo-radiotherapy, immune checkpoint inhibitors stage III, oleclumab

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Introduction

Stage III non-small cell lung cancer (NSCLC) remains a heterogenous disease, as there is no homogeneous definition of 'resectable N2-disease' and all such cases should be evaluated within an experienced multidisciplinary team to choose the optimal treatment approach,[1] especially for defining resectable disease and local treatment decisions. Lymph node volume and extent should be taken into consideration before proceeding to surgery.[2] In the wild-type metastatic NSCLC, the immune checkpoint inhibitors (ICIs) have emerged as the new standard of care (SoC) in the first-line setting regardless of the histological subtype and the programmed death-ligand 1 (PD-L1) expression,[3] opening a new opportunity for testing these drugs in earlier stages of the disease. In the last 5 years, the introduction of ICI in the early-stage setting has shifted the treatment paradigm, thereby impacting the outcomes for resectable as well as unresectable stage III disease.

Briefly, in resectable stage IB-IIIA NSCLC, neoadjuvant ICI plus chemotherapy has been reported to improve the event-free survival *versus* chemotherapy,[4] leading approval of this strategy by the US Food and Drug Administration (FDA) on March 2022; whereas in the adjuvant setting, atezolizumab *versus* best supportive care[5] and pembrolizumab *versus* placebo[6] after surgery and adjuvant chemotherapy significantly improved the disease-free survival (DFS). For instance, adjuvant atezolizumab is approved by the FDA in patients with completely resected stage II-IIIA NSCLC with PD-L1 expression $\geqslant$1% in tumor cells[5] since October 2021, whereas the European Medicines Agency (EMA) approved adjuvant atezolizumab but only for stage II-IIIA tumors with PD-L1 expression $\geqslant$50% in June 2022. Finally, in resected stage III, two major randomized controlled trials (lung-ART and PORT-C trial) do not support adjuvant postoperative radiotherapy (RT) in pN2 disease, as they did not improve the DFS *versus* no postoperative RT.[7–9]

Stage III NSCLC accounts for approximately 20% of NSCLC cases at the time of diagnosis.[10] For decades, based on an improvement in overall survival (OS) compared with a sequential strategy, concurrent chemo-radiotherapy (cCTRT) followed by observation has been considered the SoC for selected patients who fulfilled the eligibility criteria in terms of disease stage, age, pulmonary function and performance status (PS).[11] Despite multiple interventions, such as adding induction or consolidation chemotherapy; incorporating monoclonal antibodies or tyrosine kinase inhibitors (TKI), namely anti-epidermal growth factor receptor (*EGFR*, mostly unselected population); testing third-generation chemotherapy drugs or increasing the dose of RT, none have demonstrated to improve the OS over the SoC treatment.[12–17] In the most recent cCTRT RTOG 0617 trial with the SoC strategy before the immunotherapy era, the median OS was 28.7 months, with a 5-year OS rate of 32%,[13] and this outcome remained largely unchanged.

Preclinical evidence suggests that chemotherapy and RT may upregulate PD-L1 expression in tumor cells,[18–20] which is a predictive biomarker for a response to ICI. Radiotherapy may also increase the production and presentation of tumor antigens and induce interferon signaling that enhances the antitumor immune responses elicited by ICI.[21,22] In the light of this knowledge, it was hypothesized that ICI might work synergistically with the chemo-radiotherapy (CTRT) strategy. In this review, we summarize the current therapeutic approach, the ongoing clinical trials and the challenges of this strategy for daily clinical practice in unresectable stage III NSCLC.

PACIFIC trial and beyond

In the phase III PACIFIC study, 713 patients with unresectable stage III NSCLC and no disease progression after two cycles of platinum-based cCTRT were randomized in 2:1 ratio to receive either durvalumab (10 mg/kg intravenously; once every 2 weeks for up to 12 months) or placebo, starting 1–42 days after cCTRT. The results of PACIFIC trial changed the SoC in this population, as durvalumab achieved both co-primary endpoints and improved the progression-free survival (PFS, as assessed by independent review) and the OS. The last update with exploratory long-term survival data was consistent with the primary analysis.[23] Durvalumab consolidation was found to be associated with 28% of reduction in risk of death compared with placebo [hazard ratio (HR), 0.72; 95% confidence interval (CI), 0.59–0.89; median, 47.5 *versus* 29.1 months], with 5-year OS rates of 42.9% and 33.4%, respectively. Similarly, a 45% reduction in the risk of disease progression was reported with durvalumab *versus* placebo (HR, 0.55; 95% CI, 0.45–0.68; median, 16.9 *versus* 5.6 months), with 5-year PFS rates of 33.1% and 19%, respectively.[23] The survival benefit of durvalumab was mainly driven by the more substantial control in the extrathoracic disease, including brain metastases (detected in 6.5% *versus* 11.8% of patients, respectively for durvalumab *versus* placebo)[23]; however, brain metastases incidence was low in both arms compared with historical data.[24,25] Safety outcomes from PACIFIC trial reported that all-causality adverse events (AEs) of grade 3/4 occurred in 30.5% and 26.1% (and fatal AEs in 4.4% and 6.4%) of patients receiving durvalumab and placebo, respectively, and 15.4% and 9.8% discontinued durvalumab and placebo because of AEs, mostly pneumonitis, radiation pneumonitis and pneumonia.[23,26] Of note, for the immune-related adverse events (ir-AEs), a post hoc analysis reported that the time elapsed from completion of prior RT to trial randomization (<14 *versus* $\geqslant 14$ days) did not impact either incidence or severity of immune-related AEs.[26] Indeed, there were no apparent associations of pneumonitis with baseline respiratory disorders, prior RT dose (RT volumes were not detailed) or prior cisplatin or carboplatin use.[27] The benefit of durvalumab occurred without detrimental effect on patient-reported outcomes.[28] Durvalumab has been shown to improve survival in almost all subgroups, including a post hoc analysis regarding CTRT variables.[29] However, an unplanned post hoc analysis reported that OS did not improve in tumors with PD-L1 expression $\leqslant 1\%$ (HR, 1.15; 95% CI, 0.75–1.75).[23,30] The uncertainties identified in this subgroup provided the basis for the EMA decision of restricted approval of durvalumab for tumors with PD-L1 expression in tumor cells $\geqslant 1\%$ in September 2018. In contrast, the FDA approved durvalumab as a new SoC in February 2018 regardless of PD-L1 expression based on the statistical design of the trial and the OS benefit reported in the intention to treat population.

After launching the new SoC strategy in unresectable stage III NSCLC, the international observational PACIFIC-R trial (NCT03798535) assessed the real-world data (RWD) for

effectiveness of durvalumab in patients from an expanded access program. In the 1399 included patients (median age 66 years, only 10% aged ⩾75 years; 67% males, 98% ECOG PS 0–1), the median time to durvalumab initiation after the end of RT was 56 days, and overall durvalumab treatment duration was approximately 11 months. The median PFS with durvalumab was 21.7 months, which was consistent with the stage (IIIA: 23.7 months and IIIB/C: 19.2 months), prior CTRT approach (cCTRT: 23.7 months and sequential CTRT, sCTRT: 19.4 months), histology (25.3 months in nonsquamous and 14.7 months in squamous) and PD-L1 status (only assessed in 967 patients, 22.4 months in PD-L1 ⩾1% and 16.3 months in PD-L1 <1% tumors). Rates of durvalumab discontinuation due to AEs (16.7%) and disease progression (26.9%) were consistent with the results from PACIFIC trial. In the PACIFIC-R trial, occurrence of any-grade pneumonitis was reported in 17.9% of patients who receive durvalumab, being severe in only 2.9% of cases.[31] However, other real-world series reported an incidence up to 15% of grade 3 pneumonitis.[32]

Other anti-PD-L1 has also been tested as consolidation therapy in stage III NSCLC. The phase III GEMSTONE-301 trial tested the efficacy and safety of sugemalimab (an anti-PD-L1 antibody, 1200 mg or matching placebo, intravenously, Q3W for up to 24 months) *versus* placebo in 381 eligible Chinese patients with unresectable wild-type (*EGFR*, *ALK* and *ROS1* negative) stage III NSCLC whose disease had not progressed after cCTRT or sCTRT. After a limited median follow-up of 14.3 months, the PFS by independent review was significantly longer with sugemalimab than with placebo (9.0 months *versus* 5.8 months; stratified HR 0.64; 95% CI: 0.48–0.85, $p = 0.0026$). The PFS benefit with sugemalimab was seen across most of the prespecified subgroups, including cCTRT and sCTRT subgroups. The OS data is still immature, but initial analysis shows a HR of 0.4 (95% CI: 0.27–0.73; $p = 0.0009$), favoring sugemalimab. Grade 3–4 treatment-related AEs occurred in 9% and 6% of the patients in the sugemalimab and placebo arm, respectively, the most common being pneumonitis or immune-mediated pneumonitis (3% in the sugemalimab arm *versus* <1% of in the placebo arm).[33] Although this trial endorses the role of a consolidation ICI strategy after CTRT, a significant limitation of the GEMSTONE-301 trial is regarding data about PD-L1 expression, as it is missing in half of the patients enrolled, due to PD-L1 expression testing was not an obligatory inclusion step. Finally, the single-arm phase II LUN 14-179 trial (NCT02343952)[34] reported that consolidation pembrolizumab after cCTRT improved time to metastatic disease, PFS, and OS in comparison with historical controls of chemoradiation alone. Rates of grade 3–5 pneumonitis ($N = 6/93$, 6.5%) were similar to those reported with cCTRT alone. Despite the limitations like lack of baselines in brain MRI and Positron emission tomography–computed tomography (PET-CT) assessment for majority of enrolled patients, short follow-up in some trials like GEMSTONE 301 and unspecified RT volumes/doses, data from these trials support the use of consolidation strategy with ICI to improve the outcomes of patients with unresectable stage III NSCLC.

Crossing the borders of PACIFIC

Further advances are needed to build upon the success of cCTRT and immunotherapy to ultimately cure more patients with unresectable stage III NSCLC. New approaches are being investigated and dual combination of immune strategies in the consolidation setting is one of the potential therapeutic approaches as well as is the administration of ICI as induction treatment or with cCTRT (Figures 1 and 2).

ICI consolidation intensification

The COAST trial was a phase II study of consolidation durvalumab alone (1500 mg Q4W, control) or in combination with the anti-CD73 monoclonal antibody oleclumab (3000 mg IV Q2W for cycles 1 and 2, and Q4W thereafter, arm A) or the anti-NKG2A monoclonal antibody monalizumab (750 mg IV Q4W, arm B). Although the objective RR (ORR) after RT is sometimes difficult to assess, the primary endpoint of the trial was ORR assessed by investigator and 189 patients were included. The median age was 65 years, almost half had squamous cell histology and tumor PD-L1 expression was available for 68.7%, 50.0% and 51.6% of patients, respectively. After a limited median follow-up of 11.5 months, ORR was achieved in 17.9%, 30.0% and 35.5% in the control arm, arm A and arm B, respectively. The PFS was significantly prolonged with both combinations *versus* durvalumab alone [stratified HR of 0.44 (95% CI, 0.26–0.75) for durvalumab plus oleclumab and stratified HR of 0.42 (95% CI,

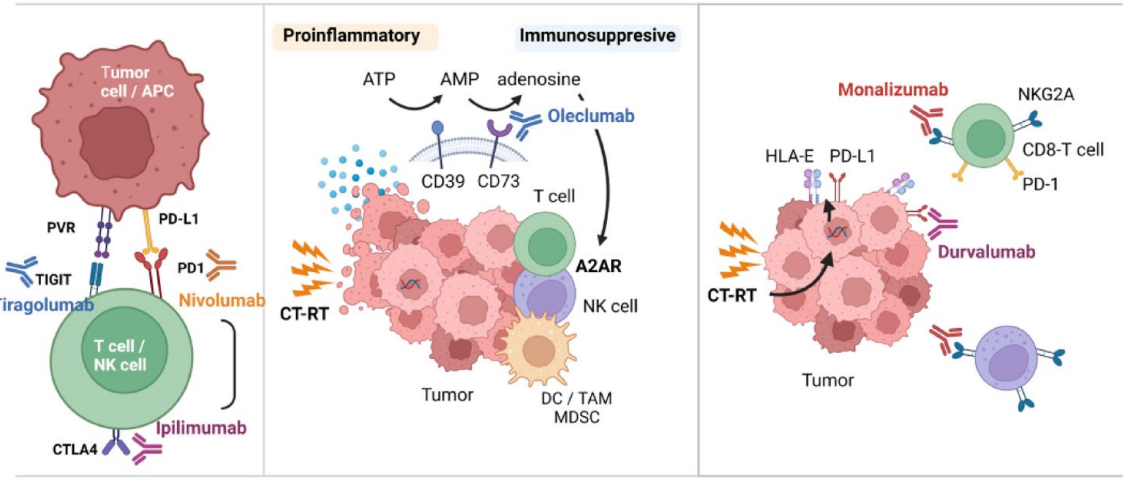

Figure 1. Potential immune strategies' combinations in unresectable stage III non-small cell lung cancer. (Figure realized by BioRender).

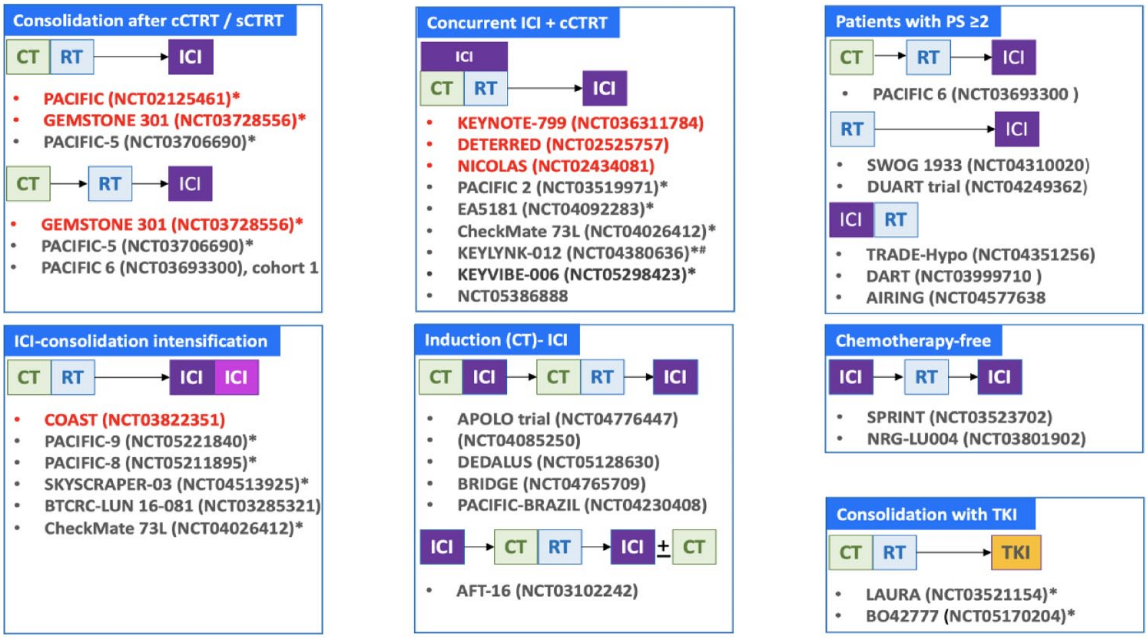

Figure 2. Phase II and III clinical trials testing immune checkpoint inhibitors in unresectable stage III non-small cell lung cancer.
In red, trials already published.
*Phase III trials. #In the consolidation patients receive pembrolizumab ± olaparib.
CT, chemotherapy; cCTRT, concurrent chemo-radiotherapy; sCTRT, sequential chemo-radiotherapy; ICI, immunotherapy; RT, radiotherapy.

0.24–0.72) for durvalumab plus monalizumab *versus* durvalumab alone]. The median PFS was not reached in arm A, 15.1 months in arm B and 6.3 months with durvalumab alone. In an exploratory subgroup analysis, the clinical benefit from the combinations appeared to be persistent among patients regardless of their PD-L1 status, although this was limited by the number of patients available. All-cause grade ⩾3 treatment AEs occurred in 40.7% (arm A), 27.9% (arm B) and 39.4% (durvalumab), respectively. All-grade rates of pneumonitis were similar in the three arms (18.6%, 16.4%

and 16.7%, respectively) as well as the treatment discontinuation rates (15.3%, 14.8% and 16.7%, respectively).[35] Although durvalumab arm in COAST trial underperformed compared to the PACIFIC trial, mainly related to different patient characteristics, the results of COAST trial support that combination approaches are feasible, safe and may in the future potentially shift again the prognosis of patients in this setting. Therefore, results of COAST trial support further evaluation of these combinations in the currently recruiting phase III PACIFIC-9 trial (NCT05221840).

The T-cell immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) is a novel inhibitory immune checkpoint present on activated T cells and natural killer cells in multiple cancers. Based on the initial synergistic effect reported with anti-TIGIT agents plus anti-PD-L1 in the metastatic NSCLC setting, two randomized phase III clinical trials are conducted, that is, testing this approach in unresectable stage III NSCLC: the PACIFIC-8 (NCT05211895) with domvanalimab (AB154) plus durvalumab and the SKYSCRAPER-03 (NCT04513925) with tiragolumab plus atezolizumab as consolidation treatment after CTRT. In both arms, the control arm is durvalumab and the primary endpoint is PFS. However, after the first anti-TIGIT enthusiasm, optimism has decreased as the combination of atezolizumab plus tiragolumab has neither reported to improve the PFS primary endpoint in the first-line setting in PD-L1 ⩾50% NSCLC (SKYSCRAPER-01, NCT04294810) nor PFS and OS in advanced small cell lung cancer (SKYSCRAPER-02, NCT04256421).[36] Finally, a consolidation combination with anti-PD1 and anti-CTLA4 has also been tested. The phase II BTCRC-LUN 16-081 trial (NCT03285321) was designed to explore shorter treatment duration (6 months) and combination of ICI as consolidation treatment.[37] One hundred five patients were randomized after completion of CRT to nivolumab (480 mg Q4W, Arm A) or to nivolumab (3 mg/kg Q2W) plus ipilimumab (an anti-CTLA4, 1 mg/kg Q6W, arm B). The percentage of patients completing the full treatment was 70.4% on arm A and 56.9% on arm B ($p = 0.15$). Both arms demonstrated improved 18-month PFS (63.7% and 67.6%, respectively) compared with historical controls (18-month PFS of 30%) despite a shortened interval (6 months) of treatment, with a median PFS of 25.8 months and 25.4 months, respectively. The 2-year OS in arm A was of 78% and in arm B was 81%. However, the grade ⩾3 AEs were higher in arm B *versus* A (52.9% *versus* 38.9%) as well as, the grade ⩾3 treatment-related adverse events (TRAEs: 27.5% *verus* 18.5%), with higher incidence of grade ⩾3 pneumonitis in arm B *versus* A (17.6% *versus* 9.3%).[37] Despite the potential limitation regarding toxicity with the combination of nivolumab plus ipilimumab and the fact that nivolumab alone overperformed, which makes combination not appearing better than monotherapy, the phase III CheckMate 73L (NCT04026412) trial assesses the PFS and OS with nivolumab plus cCTRT, followed by nivolumab plus ipilimumab, or nivolumab plus cCTRT, followed by nivolumab consolidation, *versus* the standard PACIFIC strategy in unresectable stage III NSCLC.

Concurrent chemo-radioimmunotherapy

Similarly, new approaches for applying ICI in unresectable stage III NSCLC have been reported, especially in combination with cCTRT (Table 1). It is worthwhile to highlight that direct comparison with PACIFIC is difficult, given that PACIFIC randomization was performed after cCTRT. Pembrolizumab in combination with cCTRT has been tested in the nonrandomized phase II KEYNOTE-799 trial (NCT03631784) enrolling two cohorts according to the histologic subtype (cohort A squamous and non-squamous and cohort B non-squamous).[38,39] The trial enrolled 216 patients, with pembrolizumab being started along with the first chemotherapy injection and pursued up to 1 year after cCTRT. The primary endpoints were ORR assessed by independent review committee (BIRC) per RECIST v1.1 and the percentage of grade 3 or higher pneumonitis. The ORR was approximately 70% in both cohorts regardless of tumor histology and PD-L1 expression (although only available in 155 patients, including 32% with PD-L1 < 1%), with a 12-month PFS and OS of approximately 70% and 80%, respectively.[39] In most recent updated data, median PFS was 30.6 months in cohort A and not reached in cohort B, with a 2-year OS of 64.3% and 71.2%, respectively. The grade ⩾3 TRAEs occurred in 64.3% and 51.0% of patients in cohort A and B, respectively.[40] Grade ⩾3 pneumonitis occurred in 16 patients, with 9/112 (8%) in the cohort A and 7/102 (6.9%) in the cohort B, and there were 5 patients (2.3%) died due to pneumonitis-related death.[39,40] Although the percentage of patients who receive intensity-modulated radiation therapy (IMRT) is not

Table 1. Outcome and safety data reported in phase II trials with concurrent administration of immunotherapy and chemo-radiotherapy, compared to the chemo-radiotherapy alone.

Trial	ADK	Stage IIIB/C	PET	PD-L1 <1%	Dose RT	IMRT	Chemo	Conc. ICI	Med. FU	1y PFS	1y OS	PNP ⩾ G3	G5 PNP
RTOG 0617[13] (SD arm)	39%	34%	91%	ND	60	59.2%	Carbo Tx	None	5.1 y	49.2%	80%	7%**	1%
KEYNOTE-799[39]	39% (A)	63.4% (A)	ND*	18.8% (A)	60	ND	Carbo Tx (A)	Pembro	1.1 y (A)	67.1% (A)	81.3% (A)	8% (A)	2.3%
	100% (B)	61.8% (B)		27.5% (B)			Cis Pem (B)		1.5 y (B)	76.6% (B)	87% (B)	6.9% (B)	
DETERRED[42] (part 2+)	67%	44%	ND*	8%	66	80%	Carbo Tx	Atezo	1.3 y	52%*	80%*	3%	0%
						20% protons							
NICOLAS[43,44]	59.5%	63.3%	ND*	ND	66	ND	82% Cis-based doublet	Nivo	1.8 y	53.7%	75.7%	11.7%	0%

ADK, adenocarcinomas; atezo, atezolizumab; Carbo, carboplatin; Chemo, chemotherapy; Cis, cisplatin; conc., concurrent; FU, follow-up; G, grade; ICI, immune checkpoint inhibitor; IMRT, intensity-modulated RT; ND, not described; nivo, nivolumab; OS, overall survival; PD-L1, programmed death-ligand 1; pem, pemetrexed; Pembro, pembrolizumab; PET, whole body positron emission tomography/computed tomography (PET/CT) scan; PFS, progression-free survival; PNP, pneumonitis; RT, radiation therapy; SD, standard dose; Tx, paclitaxel; y, year.
+Concurrent ICI part.
*Inclusion criteria.
*ND, based on curves.
***7.9% (Three dimensional (3D) conformal radiation therapy* 3DRT) *versus* 3.5% (IMRT) in the whole trial.

described in the trial, these numbers are globally similar to those reported by the RTOG 0617 trial, with a grade ⩾3 pneumonitis of 7%, being less common when using IMRT than conventional RT (3.5% *versus* 7.9%; $p = 0.039$).[41]

The phase II DETTERRED trial was conducted in two parts to assess CTRT (78% IMRT and 22% protons) with sequential or concurrent ICI. The part 1 ($n = 10$) involved administration of cCTRT followed by two cycles of consolidation chemotherapy plus atezolizumab followed by maintenance atezolizumab for up to 1 year. Part 2 ($n = 30$) involved administration of cCTRT with atezolizumab followed by the same consolidation and maintenance therapies as in part 1. The primary endpoint was safety, defined by the time any grade ⩾3 non-hematologic treatment-related toxicity monitored over the first 15 weeks from the start of the first dose of atezolizumab. The PD-L1 status was <1% in 11 patients (28%; unknown status: $n = 6/40$). The median follow-up times were 22.5 and 15.1 months in each trial parts, respectively. In part 1, the median PFS and OS were 18.6 months and 22.8 months, whereas in part 2 these were 13.2 months and not reached, respectively. Grade ⩾2 pneumonitis occurred in 10% of patients in part 1 and in 16% in part 2, respectively.[42] The third published single-arm phase II trial is the European Thoracic Oncology Platform NICOLAS study (NCT02434081) that evaluated nivolumab concomitant with cCTRT in 79 patients.[43,44] This was a two-step design with grade ⩾3 pneumonitis in the first 6 months, a first step toxicity endpoint, then 1-year PFS as second efficacy step endpoint (target improvement compared with historical data of at least 15%, from 45% to 60%). PD-L1 status and IMRT percentage were not reported. At a median follow-up of 21.0 months, the median PFS was 12.7 months (1-year PFS: 53.7%) and the median OS was 38.8 months (so the 1-year PFS assumption was not reached) at an extended median follow-up of 32.6 months. Grade ⩾3 pneumonitis occurred in nine patients (11.7%).

These three nonrandomized phase II trials suggested that concurrent administration of ICI and cCTRT is feasible and safe. Results are again not directly comparable with those of PACIFIC (randomization after cCTRT), but the first reported 1-year PFS seems comparable to prior SoC trial without immunotherapy, except for KEYNOTE-799 (Table 1). Several ongoing phase III clinical are exploring this strategy such

as the PACIFIC2 trial (NCT03519971, concurrent and consolidation durvalumab), the EA5181 (NCT04092283, concurrent and consolidation durvalumab) and the CheckMate 73L (NCT04026412, concurrent nivolumab followed by nivolumab with or without ipilimumab). Finally, the KEYLINK-012 (NCT04380636) trial is assessing pembrolizumab with cCTRT followed by pembrolizumab with or without olaparib and the KEYVIBE-006 (NCT05298423) evaluating MK-7684A (co-formulation of vibostolimab – anti-TIGIT plus pembrolizumab) plus cCTRT, followed by MK-7684 *versus* cCTRT followed by durvalumab. The results of these trials may help to elucidate whether more intensive treatment improves the outcome without compromising the safety.

Any role for induction (chemo)-immunotherapy?

Neoadjuvant chemo-immunotherapy has shown impressive results in resectable patients,[4] so it was logical to test the strategy in unresectable disease.

The phase II APOLO trial (NCT04776447) is testing neoadjuvant atezolizumab plus chemotherapy followed by cCTRT and consolidation atezolizumab for 1 year. The same strategy is being assessed with nivolumab in another phase II trial (NCT04085250), but this trial also includes a comparator arm that will not receive consolidation nivolumab. Finally, three single-arm phase II trials (DEDALUS: NCT05128630; BRIDGE: NCT04765709 and PACIFIC-BRAZIL: NCT04230408) are testing induction chemotherapy plus durvalumab, followed by concurrent RT (cCTRT in PACIFIC-BRAZIL) with durvalumab subsequently durvalumab consolidation.

Sparing chemotherapy induction approaches have also been tested. In the AFT-16 trial (NCT03102242), patients received four cycles of atezolizumab 1200 mg every 3 weeks followed by cCTRT and then consolidation chemotherapy and adjuvant atezolizumab for 1 year. The median PFS with this strategy was 23.7 months, with 84% of patients alive at 18 months,[45] suggesting that neoadjuvant ICI monotherapy approaches merit further evaluation. Similarly, the SPRINT trial (NCT03523702) evaluates in PD-L1 ⩾50% tumors, sequential three cycles of pembrolizumab followed by risk-adapted thoracic RT and followed by up to 12 additional injections of pembrolizumab.[46] The trial also enrolls patients with tumors with PD-L1 <50% who are treated with standard cCTRT to serve as a nonrandomized comparison group (N=38). In the first 25 subjects with PD-L1 ⩾50% tumors, 48% achieved an RR after pembrolizumab, with 1-year PFS and OS rates of 73% and 91%, respectively. Similarly, the NRG-LU004 trial (NCT03801902) assesses the combination of durvalumab concomitantly with RT followed by durvalumab for 1 year in subjects with PD-L1 ⩾50% NSCLC.

Challenges in unresectable NSCLC

Although there is little doubt that the consolidation treatment strategy with durvalumab has changed the treatment paradigm for patients with unresectable stage III NSCLC, but still some challenges remain to be resolved (Figure 3).

Sequential CTRT

Although cCTRT improves survival compared with sCTRT, more than half of the patients with stage III NSCLC are not eligible for cCTRT.[47] Following the feasibility assessment of durvalumab after sCTRT in PACIFIC-R trial[31] and sugemalimab in the GEMSTONE-301 trial [HR for PFS in sCTRT 0.59 (95% CI: 0.39–091) and in cCTRT 0.66 (0.44–0.99)],[33] the cohort 1 of the PACIFIC-6 trial (NCT03693300) also assessed the safety and tolerability of durvalumab (1500 mg every 4 weeks, Q4W up to 2 years) after sCTRT in patients with ECOG PS ≤2. The primary endpoint was ssafety defined, as the incidence of treatment related AE grade ≥3. In the primary analysis of 117 patients (only 2.6% with PS 2). Overall, 18.8% developed a grade 3-4 AE, leading to discontinuation in 21.4% of patients, and pneumonitis (10.3%) was the most common AE leading to treatment discontinuation. The median PFS and OS were 13.1 and 25.0 months, respectively.[48] These results mirror data reported in PACIFIC-R.[31] The ongoing phase III PACIFIC-5 trial (NCT03706690) will assess the efficacy and safety of consolidation durvalumab (1500 mg Q4W) after either cCTRT or sCTRT.

Elderly population and patients with poor PS

There is a potential concern suggesting that anticancer immunity may be compromised in the elderly population due to their low amounts of naïve T cells (potentially leading to holes in the repertoire for neoantigens), the 'exhaustion' of potentially tumor-specific memory T cells and

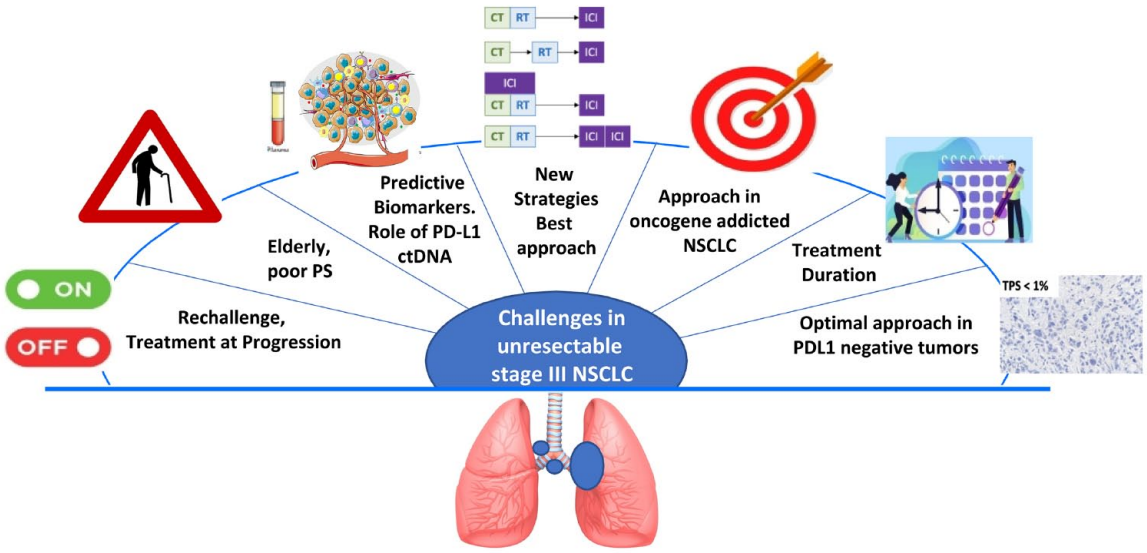

Figure 3. Current challenges with immune checkpoint inhibitors in unresectable stage III non-small cancer.

higher amounts of suppressive cells.[49] However, in a recent study, it was reported that although circulating T cell immunosenescence is observed in up to 28% of patients with advanced NSCLC and correlates with lack of benefit from ICI, this phenotype is independent of patients' age.[50] Therefore, efficacy of durvalumab in the elderly population (⩾70 years) is of special relevance as RWD suggest that the median age of patients with stage III is 67 years. In general, treatment tolerance for both cCRT and sCRT are decreasing with an increasing number of comorbidities, even for fit patients.[51] In a post hoc analysis from the PACIFIC trial, with a 70-year age threshold cutoff (only 22% of all patients enrolled), durvalumab was found to improve PFS and OS among patients, aged ⩾70 [PFS: HR, 0.62 (95% CI, 0.41–0.95); OS: HR, 0.78 (95% CI, 0.50–1.22)] and <70 [PFS: HR, 0.53 (95% CI, 0.42–0.67); OS: HR, 0.66 (95% CI, 0.51–0.87)]. Elderly patients treated with durvalumab had higher incidence of grade 3–4 AEs (41.6% *versus* 31.2%) leading to discontinuation (21.8% *versus* 13.6%) and serious AEs (42.6% *versus* 25.4%) compared with patients <70 years. However, the profile was manageable and did not detrimentally affect the patient-reported outcomes compared with placebo.[52] Of note, these elderly patients had to be fit within 42 days of completing cCTRT without major comorbidities to be eligible for enrollment in the PACIFIC trial. This is not reflective of the daily practice patient population. Unfortunately, in the PACIFIC-R trial, efficacy according to the age was not reported.[31] Clinical frailty index and comprehensive geriatric assessment are increasingly used to supplement patient selection and guide informed decision-making but this requires further clinical validation.[53] Indeed, in this subgroup of elderly and poor PS patients, it is important to assess the impact of polypharmacy, as these patients have higher rate of polypharmacy (⩾5 concomitant medicaments), which is an independent poor prognostic factor in patients with advanced NSCLC treated with ICI.[54,55]

Likewise, patients with PS ⩾2 were excluded from the PACIFIC trial, and in real world, this population represent up to 14% of patients with stage III NSCLC.[56,57] Although in the PACIFIC-6 patients with PS 2 were allowed, only 2.6% of enrolled patients actually had PS 2. Several ongoing phase II clinical trials are aiming to determine whether consolidation ICI improves outcomes in patients with ECOG PS2, such as the S1933 trial (NCT04310020), is testing hypofractionated radiation alone, 60 Gy in 15 fractions, followed by atezolizumab (1200 mg Q3W for 17 cycles), and finally the DUART trial (NCT04249362) is testing durvalumab (1500 mg Q4W for 12 cycles) after RT (60 Gy). Other phase II trials will evaluate concurrent radioimmunotherapy without the incorporation of chemotherapy: TRADE-hypo [NCT04351256, hypofractionated (55 Gy/20

fractions) *versus* conventional (60 Gy 30 fractions) thoracic radiation therapy and concurrent durvalumab, pursued for a total of 12 cycles], DART (NCT03999710; 60 Gy/30 fraction with durvalumab, followed by 1-year maintenance), and AIRING (NCT04577638, hypofractionated irradiation at a dose of 66 Gy/24 fractions with nivolumab, then pursued for 6 months)

Need for better patients' selection: the PD-L1-negative tumors illustration

The evaluation of efficacy of consolidation ICI in PD-L1-negative NSCLC can be hindered by the small sample size as PD-L1 status was not required for enrollment in majority of trials, as well as by the post hoc analysis or exploratory analysis regarding the efficacy according to the PD-L1 status.[23,35] Although the PACIFIC-R study reported that durvalumab was feasible in PD-L1-negative tumors, the median PFS was shorter than PD-L1 ⩾1% tumors,[31] raising the issue of optimal consolidation approach in PD-L1-negative NSCLC.

Tumors with PD-L1 expression <1% may unravel two distinct tumor microenvironments: (i) a tumor-lacking T cell infiltration (TILs) in a 'cold' tumor microenvironment and (ii) a tumor with TILs, but expressing co-inhibitory checkpoints, other than PD-L1.[58] In the first situation, treatment strategies should try to bring T cells into the tumor before blocking PD-L1. In this regard, CTLA4 blockade has been shown to induce frequent increases in TILs irrespective of tumor responses.[59] Of note, in the first-line setting in advanced NSCLC, in the CheckMate 227 trial the combination of nivolumab plus ipilimumab reported similar long-term survival regardless of the PD-L1 status (4-year OS 29% and 24% in PD-L1 positive and negative NSCLC, respectively).[60] However, the safety of this combination strategy as consolidation approach reported in the BTCRC-LUN 16-081 trial[37] may limit the general clinical applicability of this strategy and also efficacy according to PD-L1 expression remains unknown. Results from the CheckMate 73L trial may shed light in this setting as PD-L1 expression (<1% vs ≥1%) is a stratification criteria.

In the second scenario, the combination between anti-PD(L)1 blockers and a tailored immune checkpoint blockade based on the expression patterns of co-inhibitory checkpoints should be ideally used.[35] However, a challenge specific to stage III NSCLC is that tumor biopsies are performed at baseline, before starting the chemoradiation. Therefore, biomarker analysis will not take into account the potential changes induced by the treatment. Alternative noninvasive methods, such as circulating tumor cells (CTC) and circulating white blood cells, may be used to evaluate immune checkpoint expression[61] and their dynamic variation under treatment. The concordance between PD-L1 expression in tissue and CTC was reported to be as high as 93% in advanced NSCLC.[61] Nevertheless, the isolation of CTC would risk having a low detection rate considering the reduced CTC shedding of a low tumor volume, especially in already treated localized disease.

Treatment duration

The optimal treatment duration for the consolidation strategy is unknown, especially as only 43% of patients enrolled in PACIFIC trial were able to complete the planned 1-year of therapy.[62] For GEMSTONE 301, the percentage of patients completing the 2 years of therapy is still unknown, as at data cutoff, 43% of patients in the sugemalimab arm were still on treatment.[33] This is of particular relevance as in the first-line metastatic setting treatment is up to 2 years in some trials or until disease progression in others.[3] Indeed, it remains unknown whether longer treatment duration correlates with higher benefit from ICI (or is due to bias as patients who progress will have a shorter course of ICI) and whether CTRT modulates the immune system in such a way that a shorter duration of treatment is also feasible. The role of biomarkers others than PD-L1 expression, such as the dynamic evolution of circulating tumor DNA (ctDNA), is of relevance. The dynamic ctDNA may facilitate personalization of the duration of ICI, enable early intervention in patients at high risk for progression[63] and personalize consolidation ICI strategy after CTRT according to the minimal residual disease (MRD) status.[64] In a recent study, ctDNA analysis of 218 samples from 65 patients receiving CTRT for locally advanced NSCLC, including 28 patients receiving consolidation ICI, revealed that those patients with undetectable ctDNA after CTRT (no MRD) had excellent outcomes whether or not they received consolidation ICI. In contrast, patients with detectable ctDNA obtained significant benefit with the consolidation ICI strategy.[65] Similarly, in the BTCRC LUN 16-081 phase II

trial, patients with MRD positive after completion of CRT demonstrated significantly inferior PFS than patients who were MRD negative (1-year PFS 29% *versus* 76% and 2-year PFS: 29% *versus* 68%, respectively, $p = 0.003$). Indeed, patients with undetectable MRD at the end of consolidation ICI strategy achieved a 2-year OS of 91%. However, progression of disease occurred within 10.8 months of starting ICI in all patients with uncreasing ctDNA levels after two cycles of ICI.[66] All these data confirm the prognostic value of MRD detection in patients with NSCLC after definitive CTRT, which might help to select cured population *versus* the population who requires more intensive treatment and might obtain benefit from escalate treatment to consolidation strategies, as well as ctDNA could be an early marker of disease progression risk among those patients without clearance of ctDNA under treatment with consolidation immunotherapy. In the ongoing clinical trial (NCT04585490), will personalise the consolidation ICI after CTRT according to MRD. Those with MRD-positive will receive 4 cycles of platinum doublet chemotherapy and durvaluma, whereas those with MRD negative will receive durvaluamb monotherapy.

Rechallenge

There is a lack of biomarkers to guide the choice of therapy at progression after durvalumab consolidation. An exploratory study of relapse patterns from PACIFIC revealed that for 80.6% of patients the first relapse occurred as intrathoracic disease, 15.3% patients developed recurrence only as extrathoracic metastasis and 4.2% patients developed both intrathoracic and extrathoracic recurrence.[67] While local ablative treatment is a potential option in patients with oligo-progressive disease,[68,69] data regarding the optimal therapeutic approach, including rechallenge, at widespread systemic progression on durvalumab is limited. In advanced NSCLC, few trials support the feasibility and antitumor activity of rechallenge strategy, especially among those patients who receive a second course of treatment at least 1 year after the last dose of the previous ICI.[70–72] However, the recent WJOG9616L trial reported that even in patients who initially responded to prior ICI and had ICI-free interval, once resistance occurred, retreatment with nivolumab had limited efficacy.[73] In contrast, a previous study assessed the role of durvalumab rechallenge in previously treated patients with several advanced tumor types who stopped durvalumab without disease progression. Of the 70 retreated patients, more than 70% experienced clinical benefit (11.4% and 60.0% with partial response or stable disease, respectively, including patients with NSCLC), with a median duration of response of 16.5 months and median OS of 23.8 months.[74] These data may suggest that rechallenge restores antitumor activity on some patients and result in a meaningful clinical rate of durable disease control. In a post hoc analysis from the PACIFIC trial,[23] a small subset of 34 patients who completed the 1-year consolidation and the disease progressed during the follow-up were retreated with durvalumab. Retreatment was successful for several of them as 51% of these patients were estimated to be alive and without second progression at 4 years. However, second progression was investigator assessed as per local practice and only a small number of patients received retreatment, further limiting interpretation. The duration of response and the time elapsed since the last dose of durvalumab would be crucial for adopting a rechallenge strategy, which appears to be more suitable for patients with recurrence after an extended time period, especially for those with progression occurring >6 months since the last treatment with ICI.[75] Identifying patients who may obtain benefit from this strategy, based on clinical or biologic parameters, remains a future challenge.

Oncogenic addicted tumors

In the PACIFIC study, a post hoc exploratory analysis assessed the efficacy and safety of durvalumab in 35 patients with *EGFR*-mutant NSCLC.[76] In this subgroup, durvalumab ($N = 24$) compared with placebo ($N = 11$) did neither improve the PFS (11.2 *versus* 10.9 months; HR, 0.91; 95% CI, 0.39–2.13) nor the OS (46.8 *versus* 43.0 months; HR, 1.02; 95% CI, 0.39–2.63). The safety profile for durvalumab was consistent with the overall population. In the durvalumab and placebo arms, radiation pneumonitis was reported in 42% *versus* 36% of patients and pneumonitis was reported in 17% *versus* 18% of patients (one grade 3 in placebo arm), respectively.[76] Therefore, the benefit of immune strategy as monotherapy in this population or in patients with oncogenic-driven stage III NSCLC remains unclear. Unfortunately, there is no current SoC for these patients, and although some authors argue for continuing the use of durvalumab consolidation until concise prospective evidence arises,[77] the fact is that these patients face a consistently underwhelming prognosis

according to recently published data.[78] Indeed, in a recent ESMO consensus, there were 90.3% level of consensus regarding that 'in EGFR-positive disease, the use of consolidation ICI therapy after curative-intent CRT is not recommended'.[79] This is even more relevant as existing data suggests that there is an immune-inert phenotype among some oncogenic-driven NSCLC such as *EGFR*-mutant, possibly due to the low mutation burden,[80] and overexpression of CD47,[81] among others. Indeed, some groups have suggested that stage III NSCLC with selected gene alterations may be associated with shorter PFS with CRT than wild-type NSCLC,[82,83] probably due to the higher risk of distant metastases, especially brain, for tumors with oncogenic drivers,[82,84] questioning the best consolidative strategy in this setting. Furthermore, the risk of severe ir-AEs is higher with sequential ICI treatment followed by targeted therapies such as EGFR TKI[85] and also existing higher risk of interstitial lung disease when combining osimertinib plus durvalumab.[86]

Evidence against the use of durvalumab consolidation in this setting comes from a small retrospective analysis ($N=36$) reporting a significantly shorter DFS with durvalumab consolidation in *EGFR*/*ERBB2*-mutant tumors compared with wild-type tumors (7.5 *versus* not reached; $p=0.04$), and in *EGFR*/*ERBB2*-mutant tumors, the lack of benefit was independent of PD-L1 expression.[87] Similarly, another small retrospective analysis ($N=37$) reported again that patients with *EGFR*-mutant NSCLC did not obtain benefit with consolidation durvalumab (PFS: 10.3 months *versus* 6.9 months for those who only received CTRT *versus* 26.1 months for those who received an EGFR TKI after TKI, $p=0.023$) and experienced a high frequency of ir-AEs. Finally, RWD including 61 patients (16 had *EGFR*-mutations) who received consolidation durvalumab reported in the multivariate analysis that the presence of an *EGFR*-mutation was the only independently predictive factor for unfavorable PFS after consolidative durvalumab (6.5 *versus* 33.63 months in EGFR wild-type or unknown tumors; HR, 10.47, 95% CI, 4.55–24.07; $p<0.001$), suggesting that better consolidative strategy for patients with *EGFR*-mutations and other oncogenic drivers is adamantly needed, such as the role of targeted therapies in this setting.[88]

However, not all genomic alterations might display this limitation. Recently, a retrospective study was reported, including 323 patients treated with CTRT and consolidation durvalumab, of which the genomic profiling was available for 186: 43 (23%) had an oncogenic driver genetic alteration, mainly *KRAS* ($n=26$) followed by *EGFR*, *BRAF* and *ALK*. Similar to the metastatic setting, only those tumors with a *KRAS* mutation seemed to derive benefit from consolidation durvalumab (PFS not reached *versus* 8.1 months in patients with *EGFR*-mutations). Indeed, *KEAP1-NFE2L2*-mutated tumors correlate with a chemo-radiation-resistant phenotype, with higher risk of locoregional failure. However, this risk disappears when durvalumab is added as consolidation strategy (1-year regional failure of 62% *versus* 25%, $p=0.021$, for KEAP1-NFE2L2-mutant tumors with cCTRT and durvalumab *versus* cCTRT alone, respectively).[89] These interesting findings will add to the complexity regarding who should be selected for this treatment strategy among a growingly complex genomic profile which includes rare mutations, co-mutations and other specifics.[90] Further studies are needed to evaluate the role of the PACIFIC scheme in *ALK*, *ROS1* and others, subgroups in which evidence is limited but concludes a worse prognosis.[90] Finally, the role of TKI and cCTRT in oncogenic-addicted NSCLC could be also of interest and feasibility of this strategy has been reported in *EGFR*-mutant NSCLC[91,92]; however, the limited sample size does not allow to obtain firm conclusions.

In conclusion, the PACIFIC trial was not powered to perform subgroup analyses in patients with oncogene-driven disease, but retrospective data from small cohorts do not support this strategy except for *KRAS*-mutant tumors, and these retrospective studies have consistently shown a hindered survival outcome and an unfavorable safety profile for this population. Although EGFR-TKI have improved OS in the metastatic setting, currently there is no evidence to support the administration of EGFR-TKIs for consolidation or induction in this setting and one we should await the results from the ongoing clinical trials (NCT03521154 and NCT05170204) with targeted therapies.

Conclusions

Although several challenges are still pending, PACIFIC trial remains the SoC. Exploring new ICI strategies may break the glass ceiling reported with consolidation durvalumab, shifting the treatment paradigm in the coming future.

Declarations

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Not applicable.

Consent for publication
Not applicable.

Author contribution(s)
Jordi Remon: Conceptualization; Data curation; Formal analysis; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing.

Antonin Levy: Formal analysis; Supervision; Writing – original draft.

Pawan Singh: Resources; Validation; Writing – original draft.

Lizza E. L. Hendriks: Supervision; Writing – original draft; Writing – review & editing.

Mihaela Aldea: Validation; Writing – original draft.

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