Journal of Translational Science

Review Article

ISSN: 2059-268X

Locally advanced non-small-cell lung cancer (NSCLC): The potential role of concurrent immunotherapy and radiotherapy

Muto M*, Sgambato A, Maione P, Spagnuolo A and Gridelli C

Division of Radiotherapy, S. G. Moscati, Hospital, Avellino, Italy

Abstract

Locally advanced non-small cell lung cancer (NSCLC) disease includes a wide spectrum of clinical presentation and requires an interdisciplinary approach to optimize cure. Phase III PACIFIC trial represents a significant breakthrough in locally-advanced NSCLC treatment paradigm. PACIFIC study findings have established 1-year maintenance durvalumab after definitive concurrent chemo-radiotherapy as the standard of care in unresectable locally advanced NSCLC tumors with PD-L1 expression level ≥ 1%.

Promising preclinical and early clinical data on the potential synergistic effects of combining immune checkpoint inhibitors with radiation therapy have encouraged to carry out studies aiming to explore how to optimize the addition of immunotherapy to multimodality treatment in order to further advance the field of unresectable stage III NSCLC.

In this review we discuss the available evidences on concurrent immunotherapy and radiotherapy combined or not with concurrent chemotherapy in unresectable locally advanced NSCLC.

Introduction

Locally advanced non-small cell lung cancer (NSCLC) disease includes a wide spectrum of clinical presentations and requires an interdisciplinary approach to optimize cure. Majority of patients with stage III NSCLC are deemed unresectable due to disease extension and multi-modality therapy is considered as the standard treatment. Historically, unresectable patients were candidates to receive platinum-based chemotherapy concurrent with thoracic radiotherapy (60 Gy given in 2-Gy once-daily fractions over 6 weeks; concurrent chemoradiotherapy, cCRT) [1]. Unfortunately, the prognosis is severe with a 5-year overall survival (OS) rate of about 20%. The strategies of intensification of radiation dose and induction or consolidation chemotherapy failed in increasing survival, while adding significant toxicity [2].

New hope to improve these results comes from the success of immune checkpoint inhibitors (ICI) in metastatic setting and their potential synergistic antitumor effect in combination with chemotherapy and radiotherapy [3,4].

Ionizing radiation targets DNA leading, directly or indirectly (through free radical oxygen), to the breakage of the single or double helix. The DNA enzymatic repair is efficient in healthy cells while deficient or slow in highly or moderately radiosensitive tumor cells, resulting in potential and fatal cell death and consequent regression of the irradiated tumor [5]. In addition to cytoreductive effect, recent preclinical and early clinical evidences suggest that ionizing radiation can generate anti-tumor immunity through induction of immunogenic cell death (ICD) and modulation of tumor microenviroment (TME).

Radiotherapy has been shown to induce all the three essential components which orchestrate ICD and that are required for immune priming and activation: increased expression of ecto-calreticulin on tumor cells (a potent dendritic cells "eat-me" signal), extracellular release from dying tumor cells of both high mobility group box 1 (HMGB1, a nuclear protein agonist of toll-like receptor 4 that promotes the transcription of proinflammatory genes) and adenosine-5'-triphosphate (ATP, involved in activation of immune cells via the P2XR7 purinergic receptor pathway). These "danger signals" promote antigen presentation by antigen presenting cells (APC), such as dendritic cells (DC), and this turn in leads to priming of tumor antigen-specific T-cell responses [6].

Moreover, the accumulation of cytosolic DNA stimulates the production of type I interferons (IFN-1) by DCs through activating the stimulator of interferon genes (STING) pathway. Radiotherapy amplifies this pathway of IFN-I production by enhancing tumor DNA delivery to DCs, thus promoting the priming of antitumor T cells [7]. It has also been shown that radiation therapy increases the expression level of major histocompatibility complex (MHC) class I molecules, which may lead to enhanced antigen presentation to

Correspondence to: Matteo Muto, MD, Division of Radiotherapy, "S. G. Moscati" Hospital, Avellino, Italy, E-mail: mattomuto@gmail.com

Key words: *concurrent chemoradiation therapy, concurrent immunoradiation therapy, concurrent immuno-and chemoradiation therapy, locally-advanced non-small-cell lung cancer*

Received: December 16, 2020; **Accepted:** December 30, 2020; **Published:** January 04, 2021

immune effector cells (like DC or CD8+ T-lymphocytes) and supports the recruitment of CD8+ T cells by the increase of the natural killer cell group 2 member D (NKG2D) ligands [8]. Furthermore, radiotherapy induces the generation of pro-inflammatory cytokines (such as tumor necrosis factor [TNF], interleukin [IL]-1a, and IL-6) and generation of tumor-derived antigens (including neoantigens) recognized by APC (such as DC and macrophages) [8]. The release of inflammatory cytokines together with immunomodulatory changes in TME and increased permeability, due to endothelial cell dysfunction, result in the infiltration of activated CD8+ T cells that can promote an antitumor effect local and outside the irradiated field, known as abscopal effect [9].

These radiation-induced immunostimulatory effects are countered by immunosuppressive signals, including transforming growth factor β (TGFβ) activation and colony stimulating factor 1 (CSF-1) induction, which turn in leads in increased infiltration by myeloid-derived suppressor cells (MDSCs, a subset of bone cells responsible for sustaining chronic immunosuppression in the TME) and by Tregs (more radiation resistant than conventional T cells) [10]. Moreover, the durability of the antitumor immune response to radiotherapy is restricted by immune escape phenomenon. Programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) are immune checkpoint molecules involved in escaping tumor cells to the host immune response which inhibit effector T-cell function and induct T-cell exhaustion [11]. Radiation leads to an adaptive upregulation of tumor cell PD-L1 expression that seems to be secondary to CD8+ T-cell production of interferon-gamma and may attenuate the immune response [12]. Besides, the sensitivity of antitumor immune response seems to be attenuated by radiation-induced local inflammatory response and simultaneous PD-L1 expression in the tumor microenvironment [3].

In this scenario, immunotherapy combined to radiotherapy can be used to modulate antitumor immune response and block cancer cells evading the immunosurveillance, [3,13]. It has been shown that radiotherapy works synergistically with anti-PD-L1 antibody to enhance the generation of durable T cell responses and anti-cancer immunity by eradicating the local accumulation of iTregs and MDSCs and stimulating CD8-positive T-cell infiltration [13].

Finally, also chemotherapy has been shown not only a direct cytotoxicity (DNA lethal and sublethal damage) but it can also promote tumor immunogenicity and tumor immune response by inducing ICD, disrupting immune suppressive pathways and enhancing effector T-cell response [8].

These evidences provide a rationale for the combination of immunotherapy and radiotherapy or of all three treatment modalities concurrently. The synergistic effects of double or triple combination (increase of cytotoxicity, enhancement of ICD, enhancement of tumor necrosis, and neoantigen creation) is under investigation in several clinical trials.

In this review we discuss the available evidences on concurrent immunotherapy and radiotherapy combined or not with concurrent chemotherapy in unresectable locally advanced NSCLC.

Combining immunotherapy and chemo-radiotherapy in locally-advanced NSCLC

In metastatic setting, a single-arm phase II feasibility study examined clinically the effect of given radiotherapy to a metastatic lesion (6.0 or 9.5 Gy) in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor ipilimumab in 21 chemotherapy-refractory NSCLC patients, reporting an objective response (ORR) of 33% with a disease control rate (DCR) of 31% and showed the correlation between disease response and radiation-induced higher levels of IFNβ and T-cell clones [14]. A retrospective review of the phase I KEYNOTE-001 trial, assessing the safety of pembrolizumab in advanced melanoma or NSCLC, evaluated the potential difference in outcome between patients receiving radiation and ICIs or ICIs alone. A longer progression-free survival (PFS) and overall survival (OS) was observed in patients who had received prior radiation compared to those who had never received radiation (media PFS: 4.4 vs. 2.1 months; median OS: 10.7 vs. 5.3 months) [15].

In unresectable locally-advanced setting, first convincing results of consolidation immunotherapy after cCRT were achieved with the anti-PD-L1 durvalumab (10 mg/kg every 2 weeks for up to 12 months) in phase III PACIFIC trial [16]. At 4 years update, approximately half of patients who received maintenance durvalumab was alive and about a third both alive and progression free almost 3 years after the end of study treatment (median PFS: 17.2 vs. 5.6 months, PFS Hazard Ratio [HR] 0.55, 48-months PFS rates: 35.3% vs. 19.5% with durvalumab and placebo, respectively; median OS: 47.5 vs. 29.1 months, OS HR 0.71, 48-month OS rates: 49.6% vs. 36.3% with durvalumab and placebo, respectively). This impressive and durable clinical benefit led to approval of 1 year maintenance durvalumab after definitive cCRT for NSCLC tumors with PD-L1 expression ≥1% [17]. To note, an improved response rate, with a PFS HR of 0.39 favoring durvalumab treatment, has been reported in patients receiving ICI within 14 days of completing radiation in a subset analysis of PACIFIC trial [16]. However, it was only a retrospective analysis and it need to be confirmed. Similarly to PACIFIC study, the phase II LUN 14-179 trial evaluated consolidation pembrolizumab (200 mg intravenously every 3 weeks for up to 12 months) after cCRT in 93 patients (92 for efficacy) reporting an improvement in time to metastatic disease or death (TMDD, 30.7 vs. 12 months; $P < 0.0001$), PFS (18.7 months), and OS (35.8 months; 12-, 24-, and 36-month OS estimate rate: 81.2%, 62.0%, and 48.5%, respectively) in comparison with historical controls of cCRT alone, albeit with a slightly higher risk of pulmonary toxicity (grade 2: 17.2% of which 5.4% had grades 3 to 4 pneumonitis and 1 died of pneumonitis-related causes) [18].

Of note, concomitant, but not sequential, administration of a PD-L1 blockade with fractionated radiotherapy has been shown to improve treatment outcomes in mice models [12].

These promising preclinical and early clinical data on the potential synergistic effects of combining ICI with radiation therapy have encouraged to carry out studies aiming to explore how to optimize the addition of immunotherapy to multimodality treatment (chemoradiation or radiation therapy) in order to further advance the field of unresectable stage III NSCLC (Table 1).

Phase I clinical trials

Among trials combining all three modalities concurrently, preliminary data of phase I CLOVER trial showed that durvalumab in combination with cCRT was generally well tolerated in solid tumors, including a cohort of 19 stage III NSCLC patients. Only 1 dose-limiting toxicitiy (DLT) was reported in the NSCLC cohort with overall similar high rate of grade 3/4 adverse events (AEs) to historical data of CRT [19].

Pembrolizumab in combination with cCRT (weekly carboplatin and paclitaxel plus 60 Gy radiation therapy in 30 daily 2-Gy fractions)

Table 1. Main concomitant immunotherapy and chemo-radiotherapy trials in locally-advanced NSCLC

Trial	NCT	Phase	Stage	Patients	Trial Design	Radiotherapy	Results (P.E)
Jabbour [20]	02621398	I	Unresectable II – III	21/23 evaluable	cCRT→pembrolizumab *(cohort 1: 4 pts)* cCRT+ pembrolizumab→ pembrolizumab *(cohorts 2–6: 19 pts)*	60 Gy (2 Gy/day)	Active, not recruiting No DLTs mPFS (2 cycles): 21 months 6-months PFS rate: 81.0% 12-months PFS rate: 69.7%
CLOVER NSCLC (Arms 1-3) [19]	03509012	I	III NSCLC	300 solid tumors (19 NSCLC)	cCRT + durvalumab *Arm 1*: CIS + ETO *Arm 2*: CBDCA + PTX *Arm 3*: CIS or CBDCA + PEM	-	1 DLT G3/4 AEs Arm 1: 83.3% Arm 2: 100% Arm 3: 66.7%
H. Lee Moffitt Cancer Center	03663166	I/II	III	50	cCRT + 2 x ipilimumab → nivolumab	60 Gy	Recruiting (P.E.: 8-weeks unacceptable toxicity, 12-month PFS)
KEYNOTE-799 [21]	03631784	II	III	216	1 x CT + pembrolizumab→ cCRT + pembrolizumab→ pembrolizumab *Cohort A*: CBDCA + PTX, 112 pts *Cohort B*: CIS + PEM, 73 pts	60 Gy (2 Gy/day)	Active, not recruiting Cohort A/B G≥3 AEs: 64.3/41.1% G≥3 pneumonitis: 8/5.5% (4 cases of G5 in cohort A) ORR: 67/56.6% 6-mo PFS rate: 81.4/85.2% 6-mo OS rate: 87.2/94.8%
DETERRED [22]	02525757	II	III	52	cCRT→ CT + atezolizumab → atezolizumab *(10 pts)* cCRT + atezolizumab→ CT + atezolizumab → atezolizumab *(30 pts)*	60-66 Gy (30-33 fractions)	Active, not recruiting Any G≥3 AEs: 80% for each part G≥2 pneumonia: 10/16% in part ½ Part 1, mPFS/mOS: 12.5/22.8 months Part 2, mPFS/mOS: 13.2 months/NR
NICOLAS (ETOP) [23, 24]	02434081	II	IIIA/B	82/94 per protocol	cCRT + nivolumab→ nivolumab *(cCRT arm of v3.0)*	cCRT: 66 Gy (2 Gy/day) (cCRT arm of v3.0)	Completed No case of 3-months G≥3 pneumonia Primary efficacy analysis cohort: 1-year PFS rate ≤45% not rejected Full cCRT cohort: 1-year PFS rate 53.7%, mPFS: 12.7 months 1-year OS: 75.7%, mOS: 38.8 months Grade≥3 pneumonitis: 11.7%
EMD Serono	03840902	II	III	Safety run-in: 42 pts Expansion: 308 pts	cCRT + placebo→ durvalumab or cCRT + MK7824→ MK7824	60 Gy (2 Gy/day)	Recruiting (PFS)

PACIFIC 2	03519971	III	III	328	cCRT + placebo→ placebo or cCRT + durvalumab→ durvalumab	60 Gy (2 Gy/day)	Recruiting (PFS)
EA5181	04092283	III	III	660	cCRT + durvalumab→ durvalumab or cCRT + placebo→ durvalumab	-	Recruiting (OS)
CheckMate 73L	04026412	III	III	1400	cCRT + nivolumab→ nivolumab+ipilimumab or cCRT + nivolumab→ nivolumab or cCRT→ durvalumab	-	Recruiting (PFS and OS)
NCI Study	04092283	III	III	660	cCRT + durvalumab→ durvalumab or cCRT→ durvalumab	-	Recruiting (OS)

AEs: Adverse events; CBDCA: Carboplatin; cCRT: Concurrent chemoradiotherapy; CIS: Cisplatin; CT: Chemotherapy; DLT: Dose-Limiting toxicity; ETO: Etoposide; NR: Not reached; ORR: Objective response rate; OS: Overall survival; P.E.: Primary endpoint; PEM: Pemetrexed; PFS: Progression-free survival; PTX: Paclitaxel; sCRT: Sequential chemoradiotherapy.

has been resulted tolerable with promising 12-months PFS in another non-randomized phase I trial [20]. This study used a 3 plus 3 design to assess the safety of timing and dosing of pembrolizumab sequentially or concurrently with CRT in 23 inoperable stage III NSCLC patients (of which 21 received at least 1 dose and were evaluable). Patients were divided into 5 dose cohorts: full-dose pembrolizumab (200 mg intravenously every 3 weeks) at 2 to 6 weeks after cCRT (cohort 1); reduced-dose pembrolizumab (100 mg intravenously every 3 weeks) starting from day 29 (cohort 2); full-dose pembrolizumab starting from day 29 (cohort 3); reduced-dose pembrolizumab starting from day 1 (cohort 4); and full-dose pembrolizumab starting from day 1 after CRT (cohort 5). Pembrolizumab was continued every 3 weeks for up to 1 year. A safety expansion cohort of 6 patients was planned using the maximum tolerated dose of pembrolizumab (MTD). There was no DLT in any cohort (defined as grade ≥ 4 pneumonitis within cycle 1 of ICI). Pneumonitis of at least grade 2 occurred in 7 patients (33%), of which one case of grade 5 pneumonitis was reported in the safety expansion cohort with cohort 5. Median PFS in patients receiving at least 2 doses of pembrolizumab (n = 19) was 21.0 months with a promising 12-months PFS of 69.7% in comparison with 12-months PFS of 55.7% reported in PACIFIC study. To note, these data should be interpreted with caution because they derived from a limited sample size and limited follow-up [20].

Phase II clinical trials

The phase II KEYNOTE-799 confirmed the promising antitumor activity emerged in the phase I study. A total of 185 patients were enrolled into two cohorts: patients in cohort A (n=112) received 1 cycle of pembrolizumab plus chemotherapy (paclitaxel 200 mg/m2 and carboplatin AUC 6 intravenously every 3 weeks), 2 cycles of immunochemotherapy (paclitaxel 45 mg/m2 and carboplatin AUC 2 intravenously once weekly) plus concurrent radiotherapy, followed by up to 14 cycles pembrolizumab; patients in cohort B (n=73) received 1 cycle of pembrolizumab plus chemotherapy (pemetrexed 500 mg/m2 and cisplatin 75 mg/m2 intravenously every 3 weeks; nonsquamous only), 2 cycles of immunochemotherapy plus concurrent radiotherapy followed by up to 14 cycles pembrolizumab. Pembrolizumab was administered at fixed-dose of 200 mg intravenously every 3 weeks and radiotherapy were delivered in 30 daily 2-Gy fractions (60 Gy totally). At data cut-off, the combination of all three treatment modalities concurrently achieved an ORR of 67% in cohort A and 56.6% in cohort B. Most responses continued for at least 6 months: the 6-month PFS rates in cohort A and B were 81.4% and 85.2%, respectively, while the corresponding OS rates were 87.2% and 94.8%. The co-primary endpoint of grade ≥3 pneumonitis occurred in 8.0% and 5.5% of patients, respectively (interstitial lung disease in one patient in cohort B; grade 5 pneumonitis in 4 patients in Cohort A and none in Cohort B) [21].

Atezolizumab, another PD-L1 inhibitor, is being examined in locally-advanced NSCLC in two phase II trials, DETERRED (PD-L1 blockadE To Evaluate the safety of Lung CanceR therapy using Carboplatin, Paclitaxel, and Radiation combined with MPDL3280A) [22] and Alliance Foundation Trial (NCT03102242). The first trial consists of two parts: 10 patients enrolled into part 1 received conventionally fractionated cCRT (60-66 Gy in 30-33 fractions combined with weekly low dose of carboplatin AUC 2.0 plus paclitaxel 50 mg/m2) followed by consolidation full-dose chemotherapy (carboplatin AUC 6.0 and paclitaxel 200 mg/m2) plus atezolizumab 1200 mg intravenously every 3 weeks for 2 cycles and then sequential maintenance atezolizumab for up to 1 year; 30 patients enrolled into part 2 received concurrent atezolizumab with cCRT followed by the same consolidation and maintenance as in part 1. The addition of concurrent atezolizumab to cCRT demonstrated to be safe without increased toxicities compared to sequential strategy: overall grade ≥3 AEs was seen in 80% (comparable

to sequential strategy), with a 20% grade ≥3 AEs immune-related AE rate (vs. 30% in part 1) and grade ≥2 pneumonia of 16% (vs. 10% in part 1; grade 2 and 3: 13% and 3%, respectively). Early efficacy analysis showed promising results (mPFS and mOS: 12.5 and 22.8 months in part 1, 13.2 and not reached in part 2, respectively) with no difference in cancer recurrence regardless PD-L1 status (in 34 evaluable patients: 56.3% vs. 38.9% for PD-L1 <1% and ≥1%; 53.8% vs. 25% for the PD-L1 cutoff of <50% and ≥50%, respectively, p value not statistically significant for both); further follow-up is needed [22].

On the other hand, atezolizumab as induction strategy is under evaluation in The Alliance Foundation trial (NCT03102242): atezolizumab followed by cCRT (carboplatin AUC2 + paclitaxel 50 mg/m2 intravenously weekly for 6 weeks plus radiation at dose of 60 Gy in 30 daily 2-Gy fractions), after that, consolidation chemotherapy for 2 cycles (carboplatin AUC6 + paclitaxel 200 mg/m2 intravenously every 3 weeks beginning 3-5 weeks after completion of radiation) and then additional atezolizumab for up to 1 year. Results are pending.

The phase II NICOLAS trial, conducted by the European Thoracic Oncology Platform, is examining the PD-1 inhibitor nivolumab combined with cCRT: (Nivolumab Combination with Standard First-Line Chemotherapy and Radiotherapy in Locally Advanced Stage IIIA/B Non-Small Cell Lung Carcinoma) [23,24]. Nivolumab could be originally administered both after concurrent CRT (3 cycles of cis- or carboplatin combined with vinorelbine, etoposide or pemetrexed; radiotherapy at dose of 66 Gy in 33 daily 2-Gy fractions beginning from 2nd and 3th chemotherapy cycles) or sequential CRT (radiotherapy at dose of 66 Gy in 24 daily fractions of 2.75 Gy) [23]. After two amendments, the administration of nivolumab was allowed only concurrent with cCRT (nivolumab 360 mg every three weeks for 4 cycles, starting from the first day of cCRT, followed by 480 mg every 4 weeks for up to 1 year) and efficacy evaluation focused only on patients receiving this treatment. The early interim safety analysis in 21 patients provided the evidence that CRT in combination with concurrent and maintenance nivolumab was safe and tolerable regarding the 6-month rate of pneumonitis grade ≥3 (primary outcome): no grade-≥3-pneumonitis was observed at 3 months post-radiation therapy [23]. Beyond the safety evaluation, the primary endpoint was 1-year PFS rate improvement compared to historical data of at least 15%, from 45% to 60%. For testing this efficacy hypothesis, a sample size of 74 evaluable patients provided power 83%, using an exact binomial test at 1-sided alpha 5%. So, primary efficacy analysis was performed on the 74 first evaluable patients on cCRT who either completed 1-year of follow-up without an event or had a PFS event up to that timepoint. Among those patients, only 37 patients (instead of at least 41 patients) were free of progression at one year, thus a 1-year PFS rate of ≤45% could not be rejected (p-value=0.23). After follow-up of 21 months, for the full cCRT cohort, including 79 patients, a 1-year PFS of 53.7% and a median PFS of 12.7 months has been reported. At longer follow-up (32.6 months), median OS was 38.8 months, with 1- and 2-year OS of 75.7% and 63.7%. Grade 1-4 serious AEs were observed in almost half of the patients in the safety cohort (77 patients, 48.1%), of which 47.5% of grade 3. Grade≥3 pneumonitis were reported in nine patients (11.7%), six of which occurred within 6 months post-radiotherapy [24].

Another phase II trial (EMD Serono study, NCT03840902) is combining a novel agent, M7824, with cCRT. M7824 is an innovative first-in-class bifunctional fusion protein composed of a fully human IgG1 monoclonal antibody against PD-L1 linked to the extracellular domain of the human TGF-β receptor 2 protein (a TGF-β "trap"). Upon administration, the PD-L1 monoclonal antibody part of M7854 binds PD-L1 while the TGF-β part binds to and neutralizes TGF-β receptor 2 protein. In this way, M7824 blocks TGF-β- and PD-L1-mediated signaling and increases T-cell-mediated immune response against cancer cells, thus inhibiting tumor cell growth. After manageable safety and encouraging long-term survival in metastatic setting, especially in patients with high PD-L1 expression, this double-blind randomized phase II trial is evaluating safety and efficacy of cCRT plus M7824 followed by M7824 compared to PACIFIC regimen (cCRT followed by maintenance durvalumab) in unresectable stage III NSCLC; results are pending.

Focusing on KEYNOTE-799, DETERRED and NICOLAS trials, the clinical benefit of cCRT with nivolumab and pembrolizumab therapy in NICOLAS and KEYNOTE-799 studies, respectively, was achieved at the cost of higher-than-expected rate of pneumonitis (grade ≥3 of 11.7% in NICOLAS; grade ≥3 pneumonitis of 8.0% and 5.5% in cohort A and B of KEYNOTE-799). On the contrary, patients treated with atezolizumab concurrently with cCRT in DETERRED study experimented grade 2 and 3 pneumonitis in 13% and 3%, respectively, comparable to those treated only with cCRT in historical controls and with PACIFIC regimen. Jabbour *et al.* observed in their phase I trial an increased rate of pneumonitis with pembrolizumab (grade ≥ 2 pneumonitis: 24% with one case of grade 3 and grade 5 pneumonitis) that was higher than reported in PACIFIC regimen (grade 3 and 5 of 5% for each vs. grade 3 and 4 of 3.4% and 2.5%, respectively, in PACIFIC). However, it is important remember that in PACIFIC trial patients who presented with signs of grade ≥ 2 pneumonia after CRT were excluded. Two recent meta-analysis reported higher rates of pneumonitis in advanced NSCLC patients treated with anti-PD1 compared to anti-PD-L1 agents (3-4% vs. 1-2%) [25,26]. This finding could be one of the possible explanations of difference in toxicities observed in locally-advanced NSCLC trials, although it has never been confirmed in locally advance setting. On the other hand, DETERRED trial reported an higher overall grade ≥3 AEs (80% for each strategy) compared to other studies, but this result must be evaluated considering the further planned consolidation full-dose chemotherapy after cCRT. To date, consolidation chemotherapy is no longer recommended due to the lack of data and after the publication of PACIFIC results.

Regarding predictive biomarkers, the role of PD-L1 expression level remains doubtful in locally-advance NSCLC, unlikely the higher ORRs observed at higher levels of PD-L1 expression in metastatic setting. In unplanned exploratory post-hoc analysis in a small subset of PACIFIC trial, lack of improved survival was observed with consolidation durvalumab in PD-L1 negative patients, but it must remember that the PD-L1 testing was not mandatory for accrual and PD-L1 status was unknown for 37% of the patients. Jabbour *et al.* in the phase I trial did not detect difference in PFS based on PD-L1 status or tumor-infiltrating lymphocytes. In DETERRED trial, a non-statistically significant trend in improved 1-year PFS rate was reported with higher baseline tumor PD-L1 expression level but there was no difference in cancer recurrence according to PD-L1 status.

Because of the small patient numbers on these trials and the limited follow up time, we would be cautious to draw conclusions on PD-L1 as predictive biomarker to select patients with local-regionally advanced NSCLC candidate to receive immunotherapy treatment.

Phase III clinical trials

To better define the role of immunotherapy in combination with cCRT in locally-advanced NSCLC, several ongoing phase III are currently ongoing.

The phase III, randomized, double-blind, PACIFIC 2 trial (NCT03519971) aims to assess whether durvalumab concurrent with cCRT followed by consolidation durvalumab until disease progression provides additional benefit, in terms of PFS and ORR, compared with cCRT alone. Durvalumab has been administered intravenously at flat dose of 1500 mg every 4 weeks in approximately 300 patients with unresectable stage III NSCLC. Study enrollment began in March 2018 and recruitment is completed.

The synergistic effects of combination of all three treatment modalities arised the question if t durvalumab concurren with cCRT, followed by consolidative durvalumab, is a more effective treatment approach than PACIFIC regimen. The phase III randomized EA5181 trial (NCT04092283) aims to enroll 660 unresectable stage III NSCLC patients to evaluate whether there is an improvement in OS in the group that receives concurrent and consolidative therapy with durvalumab.

Similar to durvalumab, the safety and tolerability of nivolumab concomitantly with cCRT reported in stage III NSCLC in NICOLAS study [24] together with the longer median OS nivolumab plus ipilimumab compared to chemotherapy in advanced NSCLC expressing PD-L1 ≥1% in the phase III CheckMate 227 study [27] and clinical benefit achieved in the PACIFIC trial [16,17], led to the phase III Checkmate 73 L (NCT04026412). This randomized trials is assessing whether the administration of nivolumab concurrently with cCRT followed by nivolumab alone or combined to ipilimumab consolidation for up ≤1 year performs better than PACIFIC regimen, in term of PFS.

Replacing chemotherapy with immunotherapy in locally-advanced NSCLC

To date, we known that cCRT is superior to sequential therapy or radiation alone and no consolidation chemotherapy nor consolidation/maintenance targeted therapy trials in an unselected population have provided a survival benefit. So, the standard of care remains cCRT followed by 1 year consolidation immunotherapy. However, chemotherapy regimens in combination with radiotherapy do not achieve systemic therapy dosing and their main benefit may be to provide radiosensitization. Given the potential radiosensitizing effect of immunotherapy, an additional major shift in locally-advanced disease treatment strategy might to be replace concurrent chemotherapy with immunotherapy as radiosensitizer with the aim of achieving the same clinical benefit at less toxicity. This treatment paradigm is supported by several findings: first, the results of KEYNOTE-024 [28] trial

Table 2. Main replacing chemotherapy with immunotherapy trials in locally-advanced NSCLC

Trial	NCT	Phase	Stage	Patients	Trial Design	Radiotherapy	Note (P.E.)
NRG LU004	03801902	I	IIA-IIIC	24	Durvalumab + ACRT or Durvalumab + standard RT	ACRT (60 Gy/15 fractions) Standard RT (60 Gy/30 fractions)	Recruiting Biomarkers PD-L1≥50% (Incidence AEs)
MDACC	04013542	I	II-III	20	Ipilimumab+nivolumab+RT→nivolumab	60-66Gy	Recruiting (Incidence AEs)
SPRINT	03523702	II	II-III	63	Pembrolizumab x 3→ RT→pembrolizumab *(PD-L1 ≥ 50%)* cCRT *(PD-L1 <50%)*	Dose-painted RT: 55Gy in 20 fractions if metabolic tumor volume > 20 cc on FDG-PET 48 Gy if smaller	Recruiting Biomarker PD-L1 status (PFS)
Cleveland Medical Center	03818776	I	IIA-IIIC	27	Durvalumab + 60 CGyE proton beam RT→ durvalumab *(Arm 1)* or Durvalumab + 69 CGyE proton beam RT→ durvalumab *(Arm 2)*	*Arm 1*: 60 CGyE in 20 fractions (3+3 participants, 3-6 total) *Arm 2*: 69 CGyE in 23 fractions (3+3 participants, 3-6 total)	Recruiting Poor PS (Safety)
TRADE-hypo	04351256	II	III	88	Durvalumab + 55Gy RT→ durvalumab *(Arm A)* or Durvalumab + 60Gy RT→ durvalumab *(Arm B)*	*Arm A*: 55 Gy (20 x 2,75 Gy) in 4 weeks or *Arm B:* 60 Gy (30 x 2 Gy) in 6 weeks	Recruiting Elderly and/or frail unfit for chemo Durvalumab fixed-dose (Toxicities and ORR)
SPIRAL-RT study [30]	-	II	III	33	RT→ durvalumab	Completed RT (54–66 Gy)	In progress Poor PS or elderly unfit for CRT (12-mos PFS rate)

ACRT: Accelerated hypofractionated radiation therapy; AEs: Adverse events; CRT: Chemo-radiotherapy; PD-L1: Programmed death ligand 1; P.E.: Primary endpoints; PFS: Progression-free survival; PS: Performance status; ORR: Objective response rate; RT: Thoracic radiotherapy.

which allowed immunotherapy to replace chemotherapy in frontline metastatic NSCLC tumor with PD-L1 expression 50% or as added to chemotherapy in tumor expressing PD-L1 <50%; second, the PFS and OS improvement in locally-advanced NSCLC achieved for the first time with the addition of consolidation durvalumab; third, the better safety profile of immunotherapy compared to chemotherapy; lastly, the previously described potential abscopal effect of immunotherapy in combination with radiotherapy [29].

On this basis, several trials are evaluating if replacing chemotherapy with immunotherapy can actually result in an equally efficacy outcome with less toxicity in local-regionally advanced NSCLC (Table 2). Two of these studies are working to evaluate biomarker-driven strategies to optimize treatment in PD-L1–high tumors: NRG LU004 and SPRINT trial.

The phase I NRG LU004 ARCHON-1 (NCT03801902) trial is assessing how well giving accelerated hypofractionated (60 Gy in 15 fractions, cohort 1) or conventionally fractionated radiation therapy (60 Gy in 30 fractions, cohort 2) and concurrent durvalumab, followed by 1 year of durvalumab, works in treating patients with stage II-III NSCLC expressing high levels of PD-L1 (≥ 50%). If the treatments will be tolerated (safety/tolerability and feasibility is the primary endpoint), a randomized phase II study is already planned.

The safety and efficacy of dose-painted thoracic radiotherapy in combination with immunotherapy without chemotherapy in stage II-III NSCLC with high PD-L1 immunohistochemistry (IHC) expression (≥ 50%) is the primary end point of the phase II trial SPRINT (selective personalized radioimmunotherapy for locally advanced NSCLC trial; NCT03523702). The enrollment will include 25 patients who will receive three cycles of induction pembrolizumab (pembrolizumab 200 mg every 3 weeks) followed by dose-painted radiotherapy (20 fractions: 55Gy if metabolic tumor volume of lesions exceeding 20 cc on FDG-PET; 48 Gy if smaller) and, after that, 12 additional cycles of pembrolizumab. Approximatively 38 patients with PD-L1–low (TPS < 50%) tumors will receive cCRT alone.

A phase I pilot trial (NCT04013542) is evaluating how the combination of two immunotherapies (ipilimumab and nivolumab) plus radiation therapy works in treating locally-advanced NSCLC patients. Twenty patients will receive nivolumab every 3 weeks for up to 8 cycles and ipilimumab every 6 weeks for up to 4 cycles concurrently with radiation therapy followed by maintenance nivolumab up to 8 cycles. An exploratory analysis on tumor tissue/blood biomarkers, microbiome, tumor mutational burden and PD-L1 IHC is planned. Safety and feasibility of double immunotherapy combination is the primary objective.

The same strategy of replacing concurrent chemotherapy with immunotherapy is currently underway evaluation alsco in the elderly and/or poor performance patient population not eligible for cCRT treatment. Durvalumab will be tested in combination with two different schemes for accelerated fractionation proton radiation in patients unable to tolerate cCRT (such as proton based external beam radiation therapy, NCT03818776) or concurrently with conventionally fractionated or hypofractionated thoracic radiotherapy in elderly and/or frail unfit for chemotherapy (TRADE-hypo, NCT04351256), or following radiation monotherapy in poor PS/elderly patients unfit for CRT (SPIRAL-RT study [30]).

The radiosensitizing effect of immunotherapy has stimulated the development of studies combining immunotherapy and radiotherapy also in unresected stage I/II NSCLC. Two phase III, randomized, placebo-controlled, double-blind trials are actually assessing the safety and efficacy in term of PFS (as primary endpoint) of this combination: PACIFIC-4/RTOG-3515 (NCT03833154) and KEYNOTE-867 (NCT03924869). The first is testing durvalumab (1500 mg intravenously every 4 weeks) for 24 months or until discontinuation following definitive stereotactic body radiation therapy (SBRT) in approximately

Table 3. Main recruiting Trials on Consolidation/Maintenance Immunotherapy in Stage II/III NSCLC

Trial	NCT	Phase	Stage	Patients	Trial Design	Radiotherapy	Note (P.E.)
Alliance Foundation Trial	03102242	II	IIIA/B	64	2-4 x atezolizumab→ cCRT→ 2 x CT→ atezolizumab	Completed cCRT 60 Gy (2 Gy/day)	Active, not recruiting (12-weeks DCR)
BTCRC-LUN16–081 [31]	03285321	II	IIIA/B	105 planned (50 enrolled)	cCRT→ 6 x nivolumab or cCRT→ 4 x nivolumab/ipilimumab	Completed cCRT (59.4-66.6 Gy)	Recruiting G>3 AEs: 32% vs 44% (PFS)
PACIFIC-6	03693300	II	III	150	sCRT→ durvalumab fixed-dose	Completed sCRT (54-66 Gy)	Recruiting No biomarker selection Durvalumab 1500 mg every 4 weeks (G3-4 AEs rate)
COAST	03822351	II	III	189	cCRT→ durvalumab or cCRT→ durvalumab + anti-CD73 agent oleclumab or cCRT→ durvalumab + anti-NKG2A agent monalizumab	Completed cCRT	Active, not recruiting (ORR)

Sun Yat-sen University	04085250	II	III	264	CT + nivolumab→ cCRT or CT + nivolumab→ cCRT→nivolumab	SIB-IMRT	Recruiting (PFS)
NEJ039A [32]	In progress	II	III	70 pts PS = 2 and/or aged > 75 years	cCRT→durvalumab	60 Gy (30 fraction)	In progress (12-mos PFS)
SKYSCRAPER-03	04513925	III	III	800	cCRT→ atezolizumab + tiragolumab or cCRT→ durvalumab	Completed cCRT (54-66 Gy)	Recruiting (PFS)
PACIFIC-5	03706690	III	III	360	cCRT/sCRT→ durvalumab fixed-dose or cCRT/sCRT→placebo	Completed cCRT or sCRT (54-66 Gy)	Recruiting Durvalumab 1500 mg every 4 weeks (PFS)
CONSIST	03884192	III	III	162	cCRT→anti-PD1 sintimab (IBI308) or cCRT alone	Completed cCRT	Recruting (PFS)
CStone Pharmaceuticals	03728556	III	III	702	sCRT/cCRT→CS1001 mAb or sCRT/cCRT→placebo	Completed cCRT or sCRT	Recruiting (PFS)

AEs: Adverse events; cCRT: Concurrent chemoradiotherapy; DCR: Disease control rate; G: Grade; ORR: Objective response rate; PD-1: Programmed death 1; P.E.: Primary endpoints; PFS: Progression-free survival; PTX: Paclitaxel; sCRT: Sequential chemoradiotherapy; SIB-IMRT: Simultaneous integrated boost intensity-modulated radiation therapy.

630 clinical stage I/II node-negative NSCLC. The second aims to recruit 530 medically inoperable Stage I/IIA NSCLC who will be randomized to receive SBRT alone or in combination with pembrolizumab.

Consolidation/maintenance immunotherapy trials in stage II/III NSCLC

Other studies, such as PACIFIC 6 (NCT03693300, durvalumab fixed-dose up to 24 months after sequential CRT), PACIFIC 5 (NCT03706690, likely PACIFIC 6 but after concurrent CRT), GO41854 (NCT04513925, atezolizumab and tiragolumab up to 13 cycles after cCRT, SKYSCRAPER-03), and BTCRC-LUN16–081 by the Big Ten Cancer Research Consortium [31] are enrolling stage III unresectable NSCLC patients after CRT is completed. Those patients will receive consolidation immunotherapies for 1 to 2 years afterward (Table 3).

The RTOG 3505 phase III (NCT02768558), testing consolidation nivolumab up to 1-year after cCRT with cisplatin/etoposide chemotherapy similar to PACIFIC trial, has been early terminated due to a change in the treatment landscape.

Consolidation nivolumab (480 mg intravenously every 4 weeks up to six cycles) or nivolumab/ipilimumab (3 mg/kg intravenously every 2 weeks + ipilimumab 1 mg/kg intravenously every 6 weeks up to four cycles) following the standard of care CRT has been assessed in BTCRC-LUN16–081 trial [31]. In the first 50 patients, the incidence of > grade 3 toxicity was greater in the consolidative nivolumab/ipilimumab arm (32% vs. 44%) which resulted in a higher rate of treatment discontinuation than nivolumab alone [32].

Finally, the multidrug, randomized, COAST study (NCT03822351) is a platform trial that aims to identify potential combinations of durvalumab with novel agents oleclumab (MEDI9447) and monalizumab (IPH2201) to improve response rates over monotherapy.

Conclusion

In conclusion, stage III NSCLC is a heterogeneous disease and personalized therapy is essential. PACIFIC trial represents a significant breakthrough in locally-advanced NSCLC treatment paradigm. Nowadays, many questions on how to optimize this strategy remain unanswered, such as the better timing of the delivery of immunotherapy relative to cCRT (tri-modality or neoadjuvant or adjuvant), the duration of maintenance immunotherapy, the type of radiation therapy (hypofractionated versus conventional), whether if possible, replace chemotherapy with immunotherapy, and the use of concomitant medication (such as steroids, antibiotics, or proton pump inhibitors). Finally, the development of biomarkers to predict the response to combination therapy would help to identify the patients who are most likely to benefit from treatment. Hypothetical future strategy could include neoadjuvant systemic therapy with chemo-immunotherapy to reduce radiation field size in NSCLC patients with unresectable large T or bulky or multi-station N2 nodal disease, or with at least some PD-L1 expression (≥1%). In those patients with significant responses and minimal disease burden, immunotherapy-radiation followed by 1 year immunotherapy could be sufficient. On the other hand, NSCLC patients with small T and small multi-station N2 could receive concurrent immunotherapy-radiation if PD-L1 IHC high or cCRT if PD-L1 low, and then 1 year immunotherapy. The results of ongoing trials evaluating the efficacy of immunotherapy with SBRT, concurrent with chemo-radiation, maintenance/consolidation, and replacement of chemotherapy are eagerly awaited to further reshape our standard practice.

Competing interest

Muto M: honoraria as speaker bureau for Astra Zeneca.

Sgambato A: no competing interests.

Maione P: no competing interests.

Spagnuolo A: no competing interests.

Gridelli C: honoraria as speaker bureau, advisory board member or consultant for MSD, BMS, Roche, Astra Zeneca, Pfizer, Novartis, Menarini.

Authorship

*Muto M, Sgambato A, Maione P, Spagnuolo A, Gridelli C.

Acknowledgments

None.

Founding information

None.

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