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## New challenges in the combination of radiotherapy and immunotherapy in non-small cell lung cancer

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### Abstract

Immunotherapy has represented one of the main medical revolutions of recent decades, and is currently a consolidated treatment for different types of tumors at different stages and scenarios, and is present in a multitude of clinical trials. One of the diseases in which it is most developed is non-small cell lung cancer. The combination of radiotherapy and immunotherapy in cancer in general and lung cancer in particular currently represents one of the main focuses of basic and clinical research in oncology, due to the synergy of this interaction, which can improve tumor response, resulting in improved survival and disease control. In this review we present the biochemical and molecular basis of the interaction between radiotherapy and immunotherapy. We also present the current clinical status of this interaction in each of the stages and cases of non-small cell lung cancer, with the main results obtained in the different studies both in terms of

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tumor response and survival as well as toxicity. Finally, we mention the main studies underway and the challenges of this interaction in the coming years, including how these treatments should be combined to achieve the greatest efficacy with the fewest possible side effects (dose, type of radiotherapy and drugs, sequence of treatments).

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**Core Tip:** Immunotherapy has revolutionised cancer treatment. Its association with radiotherapy has synergistic effects studied at a preclinical and clinical level, especially in metastatic patients. Currently, clinical research in this field is very prolific, and no doubt, as with the PACIFIC trial in non-small cell lung cancer (NSCLC), we will see further changes in the standard of care in the coming years. This review highlights the most important published work in NSCLC in the field of radio-immunotherapy, listing the clinical trials currently existing in each stage of NSCLC.

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## INTRODUCTION

Immunotherapy, especially in the form of immune checkpoint inhibitors (ICI), is becoming a revolution in the understanding and treatment of cancer. Their interaction with radiotherapy (RT) generates synergistic effects that have been thoroughly described in preclinical studies. In the clinical setting, the benefits of combining RT and ICI have been evidenced mostly in metastatic patients. However, this concept has evolved since the publication of the PACIFIC trial, which has modified clinical practice in unresectable stage III non-small-cell lung cancer (NSCLC) by demonstrating a significant benefit derived from the addition of sequential durvalumab to standard definitive chemoradiotherapy (CRT). Research on the association of RT and ICI in NSCLC is currently an extraordinarily active field with numerous ongoing clinical trials.

## IMMUNOTHERAPY IN LUNG CANCER

The development of ICI has become a turning point in the standard of care (SoC) of NSCLC through a significant increase in overall survival (OS) in these patients. ICI were initially approved as second-line therapy for patients who had received combination chemotherapy (CT) including platinum following the results of a number of trials: CheckMate 017 and 057 for nivolumab, Keynote-010 for pembrolizumab and the OAK trial for atezolizumab. These studies showed increased OS in comparison to docetaxel, both in squamous and non-squamous NSCLC[1-4]. In particular, Keynote-10[3] was the first to select patients with a programmed death cell protein ligand 1 (PD-L1) expression in tumor cells  $\geq 1\%$ , showing that a higher expression of PD-L1 tends to produce better responses.

In the following years, ICI were tested as first-line treatments. Keynote-024 was the first study to evidence that those patients with advanced NSCLC and PD-L1  $> 50\%$  receiving pembrolizumab obtained an OS significantly longer than those treated with a platinum doublet. In the updated analysis, with a median follow-up of 25.2 mo (mo), the median OS was 30.0 mo with pembrolizumab and 14.2 mo with chemotherapy [Hazard ratio (HR), 0.63; 95%CI: 0.47 to 0.86][5,6].

Moreover, the addition of pembrolizumab to platinum plus paclitaxel/nab-paclitaxel *vs* CT alone was assessed in two trials: Keynote-189 (for non-squamous) and Keynote-407 (for squamous NSCLC). A benefit in the pembrolizumab arm was observed in both trials: Progression-free survival (PFS) was 9 mo *vs* 4.9 mo (HR 0.48) and 8 mo *vs* 5.1 mo (HR 0.57), respectively. OS was 22 mo *vs* 10.7 mo (HR 0.56) and 17.1 mo *vs* 11.6 mo (HR 0.71), respectively[7-10]. These benefits were evidenced in all subgroups and were independent of PD-L1 status.

Atezolizumab has also shown good results in the first-line setting. In the IMpower 150 trial, patients with advanced non-squamous NSCLC who received a combination of carboplatin, paclitaxel, bevacizumab and atezolizumab presented higher PFS (8.3 mo *vs* 6.8 mo, HR 0.62) and OS (19.8 mo *vs* 14.9 mo, HR 0.62) when compared to carboplatin plus paclitaxel plus bevacizumab[11]. This benefit was also independent of PD-L1 expression. Interestingly, this has been the only study at this point that included patients with epidermal growth factor receptor and anaplastic lymphoma kinase mutations that had progressed to a tyrosine kinase inhibitor, although OS was not significant in this subgroup. In squamous NSCLC, the IMpower 130 study evidenced that the combination of atezolizumab, carboplatin and nab-paclitaxel improves PFS (7 mo *vs* 5.5 mo, HR 0.64) and OS (13.9 mo *vs* 8.6 mo, HR 0.79) compared to CT alone[12].

In unresectable stage III NSCLC, ICI have also changed the SoC. The results of the PACIFIC trial have led to the approval of one year of consolidative durvalumab in patients who have not progressed after definitive CRT and have a PD-L1  $\geq 1\%$  [13,14].

Finally, in small-cell lung cancer, atezolizumab and durvalumab in combination with a doublet of platinum and etoposide have been recently approved after showing a modest improvement in PFS and OS[15,16].

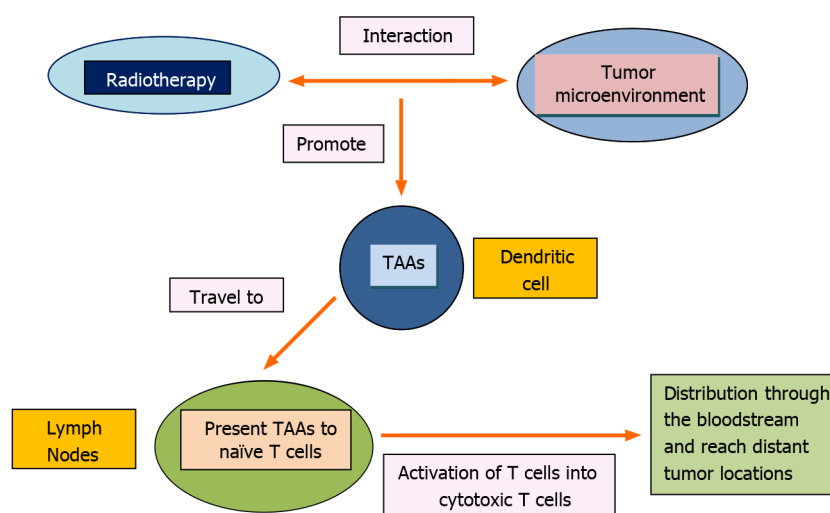
## INTERACTION BETWEEN RADIOTHERAPY AND THE IMMUNE SYSTEM

RT plays a role in all stages of NSCLC, both in the radical and palliative settings[17]. Even though RT has traditionally been considered as an exclusively local treatment, limited to the tissues involved in the radiation field, a number of cases reporting the “abscopal effect” (AE) of RT have been published since its first definition by Mole in 1953, who described it as an antitumor effect taking place outside the radiation field [18]. Recent investigations on this matter have shown that the AE might have an immunological explanation. Several preclinical data have evidenced that RT induces immunogenic cell death through the interaction of tumor-associated antigens (TAAs), damage-associated molecular patterns, high mobility group box 1, heat shock proteins, interferon type I (IFN-I), IFN- $\gamma$  and other immune mediators[19]. This microenvironment favors the incorporation of TAAs by dendritic cells, which transport these to the lymph nodes in order to present them to naïve T cells through the major histocompatibility complex I. This causes the activation of T cells into cytotoxic T cells, which can then be distributed through the bloodstream and reach distant tumor locations[20, 21]. This process is summarized in Figure 1.

For many years, this preclinical data has been difficult to translate into the clinical setting, as reports of the AE have been extremely rare[22]. However, since the introduction of ICI, abscopal responses have become much more frequent, with studies reporting up to 65% rates of AE in patients with metastatic NSCLC and melanoma[23]. This is due to the fact that RT and ICI seem to have a synergistic effect: while ICI “take the brakes off” the immune system by blocking inhibitory signals [such as upregulation of PD-1 and cytotoxic T-lymphocyte antigen 4 (CTLA4)-CD28 inhibition of T cell activation], RT serves as an in-situ vaccination that drives immune cells towards the tumor[24,25].

It must be noted, however, that RT can also unleash immunosuppressive effects in certain conditions. A prime example is transforming growth factor beta, which participates in regulatory T cell differentiation. Studies have shown that high levels of this substance are associated with diminished antitumor responses, and its blockade is currently being investigated as a way of improving outcomes[26,27]. Although it is considered that RT generally favors a more immunostimulatory state, more data on various treatment variables that might have an influence on this balance (dose, fractionation, treatment sequence) are still required[28,29].





**Figure 1** Interaction between radiotherapy and the immune system - Abscopal effect. TAAs: Tumor-associated antigens.

## RADIO-IMMUNOTHERAPY IN EARLY-STAGE NSCLC

In the last few years, the results of translational and clinical studies have evidenced the synergistic effects obtainable through the combination of immunotherapy with radiotherapy (iRT) in NSCLC[30,31]. Most of these studies are focused on advanced disease. For instance, this combination has been a paradigm shift in the treatment of unresectable stage III NSCLC following the results of the PACIFIC trial, where an improvement in OS and PFS was observed[13,30].

The management of early-stage NSCLC is generating considerable interest in this setting of combined therapies. Although surgery and stereotactic ablative radiotherapy (SABR) have reported good local control rates (70%-92%) in stage I tumors[32], distant failures can represent up to 30%-60% of cases[33,34]. Moreover, many patients at this stage are inoperable due to comorbidities or refuse surgery. In this scenario, ICI may be an alternative to CT given their comparatively better toxicity profile[31]. The main problem, however, is the poor overall response rate (ORR) of ICI in monotherapy in NSCLC (19% for anti-PD-1 and 4.8% for anti-CTLA-4). For this reason, ICI are being combined with other treatments to achieve better results[35]. Forde *et al*[36] reported a pathological down-staging rate of 40% in patients receiving nivolumab prior to surgical resection (stages I-III). Furthermore, pathological response rates were approximately 10% and no grade  $\geq 4$  toxicities were observed.

In stage IV NSCLC, iRT in the form of SABR has already achieved an ORR of 36%-41.7% and PFS of 9 mo with a good safety profile[37]. Currently, there are several ongoing clinical trials evaluating iRT in stage I-II NSCLC (Table 1)[38-45]. Although there is still no consensus on the optimal fractionation, ICI agent and treatment sequence, most studies prescribe doses  $\geq 6.5$  Gy per fraction (fx). The ICI agents include nivolumab, durvalumab, atezolizumab and avelumab. Almost 50% of the registered studies are randomized and evaluate similar primary objectives, such as PFS, local control and toxicity. Among the studies that are already recruiting patients, two of them are randomized phase III studies. The NCT03833159 (PACIFIC-004) trial evaluates sequential durvalumab and SABR in patients with stage I-II NSCLC who are not candidates for surgery. Patients in this study will receive either durvalumab or placebo every four weeks for two years or until treatment discontinuation is necessary [38]. In the NCT04214262, patients will be treated with atezolizumab concurrently with SABR[39]. The exact SABR doses are not specified in either study, but a range of 1-8 fractions will be administered. Great expectations have been placed on these phase III studies, as they could set a new standard in inoperable stage I-II NSCLC.

## RADIO-IMMUNOTHERAPY IN STAGE III NSCLC

Stage III NSCLC represents a heterogeneous group of patients with variable prognosis. It includes both resectable tumors in which surgery is the primary curative treatment and CT and RT are administered with neoadjuvant/adjuvant intent, and unresectable tumors in which the SoC is definitive CRT. The suboptimal results of these available



**Table 1** Ongoing clinical trials of stereotactic ablative radiotherapy and immune checkpoint inhibitors combination in early-stage non-small cell lung cancer

Ref.	Phase	n	Stage	SABR dose	ICI agent	ICI sequence	Status
NCT03833154[38]	III randomized	706	I-II	NM; 3-8 fx	Durvalumab	Sequential	Recruiting
NCT04214262[39]	III randomized	460	I-II	NM; 3-5 fx	Atezolizumab	Concurrent	Recruiting
NCT03110978[40]	II randomized	140	I-IIA	50 Gy/4 fx; 70 Gy/10 fx	Nivolumab	Concurrent	Recruiting
NCT03446547[41]	II randomized	216	I	NM; 3-4 fx	Durvalumab	Sequential	Recruiting
NCT03148327[42]	I-II randomized	105	I-IIA	54 Gy/3 fx; 50 Gy/4 fx; 65 Gy/10 fx	Durvalumab	Concurrent	Recruiting
NCT03050554[43]	I-II	56	I	48 Gy/4 fx; 50 Gy/5 fx	Avelumab	Concurrent	Not recruiting
NCT03383302[44]	I-II	31	I-II	54 Gy/3 fx; 55 Gy/5 fx	Nivolumab	Sequential	Recruiting
NCT02599454[45]	I	33	I	50 Gy/4 fx; 50 Gy/5 fx	Atezolizumab	Induction	Not recruiting

SABR: Stereotactic ablative body radiotherapy; ICI: Immune checkpoint inhibitor; Gy: Gray; NM: Not mentioned.

treatments have led to the investigation of new therapeutic approaches, such as induction/consolidation CT, RT dose escalation, vaccines or targeted therapies. However, none of these have demonstrated significant improvements over standard treatments. For this reason, recent research is evaluating if the incorporation of ICI could improve results, both as consolidation therapy after CRT or surgery, as well as definitive treatment and neoadjuvant therapy.

### Neoadjuvant setting

Even though there is currently no evidence on its clinical efficacy, the results of ongoing trials combining ICI with RT prior to surgery in resectable tumors could potentially change clinical practice in the years to come (Table 2). At the moment, there are some data on the combination of ICI with CT. For instance, Forde *et al*[36] reported a 45% of pathological responses in 23 patients with stage I-IIIA NSCLC receiving nivolumab monotherapy, independent of PD-L1 expression. Moreover, the recent NADIM study has observed even higher rates of major pathological response (84.6%) and complete pathological response (71%) with the combination of neoadjuvant nivolumab plus CT[46].

### Adjuvant or consolidation setting

The PACIFIC trial was the first randomized double-blinded phase III study to evaluate maintenance durvalumab for 12 mo after definitive CRT in unresectable stage III NSCLC in patients who had not progressed to CRT. A significant increase in PFS (16.8 mo *vs* 5.6 mo) and a manageable toxicity profile (G3-4 30.5% *vs* 26.1%) made this approach the new SoC[13]. Its most recent update in February 2020 reported, with a median follow-up of 33 mo, a 3-year OS of 57% *vs* 43.5% and a 31% reduction in mortality risk[14]. These results were independent of PD-L1 expression, CT regimen and RT dose. In Europe, durvalumab was approved in September 2018, but only in patients with PD-L1  $\geq 1\%$  based on a post-hoc analysis. This debate on PD-L1 status will be addressed in the PACIFIC 5 trial, as the original trial was not designed with this issue in mind[47]. In contrast, the sequence of administration does seem to be relevant, as an improvement in PFS and OS was reported in those patients that started durvalumab within 14 d after CRT.

On the other hand, the LUN 14-179 study, testing consolidative pembrolizumab 4-8 wk after CRT in 93 patients, showed that ICI can also be effective in delivered with a certain delay after concomitant definitive therapy[48]. With a median follow-up of 18.6 mo, the median time to metastatic disease or death was 22.4 mo, while PFS was 17 mo, with a 2-year OS of 61.9%. In regard to toxicity, only 5.4% of patients developed G3-4 pneumonitis.

Consolidative therapy with nivolumab was also being studied in the RTOG 3505 trial (NCT02768558), a randomized phase III study that was prematurely closed after the results of the PACIFIC trial were published[49]. Among the ongoing clinical trials (Table 3), some are investigating dual ICI and the potential side effects of this combination. An interim analysis of the first 20 patients of the NCT03285321 study has reported higher G  $\geq 3$  toxicity rates in the nivolumab plus ipilimumab arm, but still

**Table 2 Ongoing clinical trials of radiotherapy and immune checkpoint inhibitors combination in locally advanced stage non-small-cell lung cancer in the neoadjuvant setting**

Ref.	Phase	Design	No.ofpatients	Tumor stage	RT	ICI agent	Sequence	Status
CASE4516, NCT02987998[72]	1	Neoadjuvant CRT (CDDP-etoposide) + ICI followed by surgery and consolidative ICI	20	Resectable IIIA	45 Gy/25 fx (1.8 Gy/fx)	Pembrolizumab	Concomitant (neoadjuvant) + adjuvant ICI	Active, not recruiting
NCT03237377[73]	2	Neoadjuvant RT-ICI followed by surgery +/-adjuvant CT	32	Resectable IIIA	45 Gy/25 fx (1.8-2 Gy/fx)	Durvalumab ± tremelimumab	Concomitant(neoadjuvant)	Recruiting
NCT04245514, SAKK 16/18[74]	2 3 RT arms	Neoadjuvant RT-ICI followed by surgery	90	Resectable IIIA	Randomized 1:1:1; A: 20 × 2 Gy; B: 5 × 5 Gy; C: 3 × 8 Gy (non - consecutive days)	Durvalumab	Concomitant (neoadjuvant)	Recruiting
INCREASE, NL8435[75]	2 single arm	Neoadjuvant CRT (platinum doublet) + ICI followed by surgery	29	Resectable IIB-III (T3-4 N0-1)	50 Gy/25 fx	Ipilimumab + Nivolumab	Concomitant (neoadjuvant)	Recruiting
NCT02904954[76]	2 randomized	Neoadjuvant ICI +/- SBRT followed by surgery and adjuvant maintenance ICI	60	Resectable I-IIIa	SBRT 24 Gy/3 fx	Durvalumab	Concomitantneoadjuvant + adjuvant ICI	Active, not recruiting
NCT03871153[77]	2 single arm	Neoadjuvant CRT (Carbo-taxol) + ICI followed by surgery and adjuvant ICI	25	Resectable IIIA N2	45-61.2 Gy (25-34 fx a 1.8-2 Gy/fx)	Durvalumab	Concomitant (neoadjuvant) + adjuvant ICI	Recruiting
CHIO3, NCT04062708[78]	2single arm	Concomitant neoadjuvant CT (platinum doublet + ICI followed by surgery + adjuvant RT followed by ICI	55	Resectable IIIA- IIIB	54 Gy	Durvalumab	Concomitant CT-ICI (neoadjuvant) + adjuvant ICI (after adjuvant RT)	Not yet recruiting
NCT03102242[79]	2singlearm	Induction ICI followed by definitive CRT (Carbo-Taxol followed by consolidation CT- ICI	63	Unresectable IIIA-IIIB	60 Gy/30 fx	Atezolizumab	Neoadjuvant + consolidative ICI	Active, notrecruiting
NCT02572843[80]	2	Neoadjuvant CT (platinum + docetaxel) + ICI followed by surgery +/-RT + ICI	68	Resectable IIIA N2	Conventional RT if R1-R2 and before adjuvant ICI	Durvalumab	Neoadjuvant + adjuvant	Active, not recruiting

RT: Radiotherapy; CRT: Chemoradiotherapy; CT: Chemotherapy; ICI: Immune checkpoint inhibitor; Gy: Gray.

manageable according to the authors[50].

### Definitive setting

Given the good results as consolidation therapy, concomitant ICI with definitive CRT is being investigated in order to further improve clinical outcomes while maintaining an adequate toxicity profile. This has been the case for nivolumab and atezolizumab in the ETOP NICOLAS and DETERRED trials, respectively.

The PACIFIC2 phase III study with durvalumab and the KEYNOTE-799 study with pembrolizumab (Table 4) put a focus on toxicity after the previous studies with nivolumab[51] and pembrolizumab[52], which offered promising outcomes but with an increased risk of pneumonitis. In the first one, the ETOP NICOLAS phase II trial [51], nivolumab is added to standard CRT both as concomitant and consolidation therapy. An interim analysis of the initial 21 patients showed a 1-year OS of 79% with

**Table 3 Ongoing clinical trials of radiotherapy and immune checkpoint inhibitor combination in locally advanced stage non-small cell lung cancer in the adjuvant/consolidation setting**

Ref.	Phase	Design	No. of patients	Tumor stage	RT	ICI agent	Sequence	Status
BTCRC-LUN16-081, NCT03285321[50]	2 randomized	Concomitant definitive CRT followed by consolidative ICI (3 CT regimens: CDDP-VP16 <i>vs</i> Carbo-Taxol <i>vs</i> Cisplatin- Pemetrexed)	108	Unresectable IIIA-IIIIB	59.4-66.6 Gy	Nivolumab +/- Ipilimumab	Consolidation after definitive treatment	Recruiting
NCT03589547[81]	2	CRT followed by consolidative ICI and SABR	25	III	60 Gy followed by SBRT 20 Gy/2-3 fx	Durvalumab	Consolidation after definitive treatment (ICI prior to SABR)	Recruiting
PACIFIC 6, NCT03693300[82]	2	ICI after sequential CRT	150	Unresectable III	Conventional RT; 60 Gy/30 fx	Durvalumab	Consolidation after definitive treatment (within 28 d after RT)	Active, not recruiting
MK-3475, NCT03379441[83]	2	Maintenance ICI after definitive CRT	126	Unresectable IIIA-IIIIB	Conventional RT	Pembrolizumab	Consolidation after definitive treatment	Not recruiting
DUART, NCT04249362[84]	2 single arm	RT followed by ICI	150	Unresectable III	Conventional RT 60 Gy Hypofractionated RT 40-54 Gy	Durvalumab	Consolidation after RT (no CT)	Recruiting
PACIFIC 5, NCT03706690[47]	3 randomized, double-blinded	Consolidative ICI <i>vs</i> placebo after definitive CRT radical (concomitant or sequential)	360	Unresectable III	Conventional RT	Durvalumab	Consolidation after definitive treatment	Recruiting

RT: Radiotherapy; CRT: Chemoradiotherapy; CT: Chemotherapy; ICI: Immune checkpoint inhibitor; Gy: Gray.

no  $G \geq 3$  pneumonitis, which led to the recruitment of additional patients up to a total number of 80. In this case, the analysis of these 80 patients evidenced 10%  $G \geq 3$  pneumonitis. 1-year OS in this new cohort has not been published yet.

The phase II trial DETERRED[53] with concomitant atezolizumab has completed recruitment and reported better PFS in the ICI arm (57% *vs* 50%), with no significant increase in toxicity but with no benefit in OS at this point (79% in both arms).

In addition, several ongoing studies are investigating if CT can be excluded from radical treatment by combining RT and ICI. The SPRINT trial[54] is evaluating the efficacy of induction pembrolizumab in monotherapy and RT in patients with PD-L1  $\geq 50\%$ . Moreover, the DART study[55] is testing the safety and efficacy of concomitant RT and durvalumab followed by consolidative durvalumab in patients who are not candidates for CT. Other strategies include combinations of ICI with different mechanisms, such as anti-CTLA-4 in the NCT03663166 study (Table 4).

## RADIO-IMMUNOTHERAPY IN STAGE IV NSCLC

As mentioned above, the irruption of ICI has been shifted the treatment paradigm in metastatic NSCLC by increasing survival both as first and second-line therapy[2,3,5,7,

**Table 4 Ongoing clinical trials of radiotherapy and immune checkpoint inhibitor combination in locally advanced stage non-small cell lung cancer in the concomitant setting**

Ref.	Phase	Design	No.of patients	Tumor stage	RT	ICI agent	Sequence	Status
ARCHON-1, NCT03801902[85]	1; 2 RT arms	ICI + RT	24	Unresectable II-III	Conventional RT (60 Gy/30 fx); Hypofractionated RT (60 Gy/15 fx)	Durvalumab	Concomitant with definitive RT	Recruiting
PARTICLE-D, NCT03818776[86]	1; 2 RT arms (proton beam therapy)	ICI + RT	27	Unresectable III	RT 60 Gy/20 fx; RT 63 Gy/23 fx	Durvalumab	Concomitant with definitive RT	Recruiting
NCT04013542[87]	1	ICI + RT	20	II-III	Conventional RT	Ipilimumab + Nivolumab	Concomitant with definitive RT and consolidation (nivolumab)	Recruiting
NCT03663166[88]	1; 2	Concomitant CRT + ICI +/- consolidative ICI	50	Unresectable III	60 Gy/30 fx	Ipilimumab +/- Nivolumab	Concomitant definitive treatment +/- consolidative ICI	Recruiting
SPRINT, NCT03523702 [54]	2	ICI + RT (if PD-L1 $\geq$ 50%) ; CRT (if PD-L1 < 50%)	63	Unresectable III	Conventional RT	Pembrolizumab	Concomitant with definitive RT	Recruiting
KEYNOTE-799, NCT03631784[89]	2	Concomitant ICI + CRT (platinum doublet) followed by ICI	216	Unresectable III	60 Gy/30 fx	Pembrolizumab	Concomitant and consolidative	Active, not recruiting
NCT04092283[90]	3 randomized	Concomitant CRT + ICI <i>vs</i> CRT followed by ICI (CT: Cisplatin + VP16/ Taxol + Carboplatin/ Cisplatin + Pemetrexed)	660	Unresectable III	60 Gy/30 fx	Durvalumab	Concomitant with definitive treatment <i>vs</i> adjuvant ICI	Recruiting
PACIFIC 2, NCT03519971[91]	3 randomized, double-blinded	ICI <i>vs</i> placebo concomitant to CRT (CDDP-VP16 <i>vs</i> Carbo-Taxol <i>vs</i> Cisplatin or Carbo + Pemetrexed)	328	Unresectable III	Conventional RT (60 Gy in 30 fx)	Durvalumab	Concomitant +/- consolidative	Active, not recruiting
NCT04026412[92]	3 randomized	ICI (nivolumab) + CRT followed by ICI (nivolumab + ipilimumab) <i>vs</i> ICI (nivolumab) + CRT followed by ICI (nivolumab) <i>vs</i> CRT followed by durvalumab	1400	Unresectable/inoperable III	Conventional RT	Nivolumab; Ipilimumab; Durvalumab	Concomitant + 2 consolidation regimens <i>vs</i> consolidation after CRT	Recruiting

RT: Radiotherapy; CRT: Chemoradiotherapy; CT: Chemotherapy; ICI: Immune checkpoint inhibitor; Gy: Gray.

11,56,57]. Furthermore, RT in stage IV has evolved from a merely palliative intent to having a key role when associated with ICI. Reports of objective responses in distant locations not included in the radiation field (AE) have multiplied in the era of immunotherapy[31,58].

Preclinical and clinical data suggest that the antitumor efficacy of ICI increases when combined with RT, with a possible impact in survival, which could be the base for designing new combinations that can maximize this synergistic effect[58-65]. Even though most published studies on the combination of RT and ICI in stage IV NSCLC

are phase I/II trials with a limited number of patients (Table 5), they have laid the foundation for the possible benefits of this strategy that are being determined in ongoing phase III studies.

Although retrospective data had been the only evidence available for years, phase I studies evaluating the safety of the combination recently started to surface. For instance, Tang *et al*[66] treated 21 patients with pembrolizumab and RT (SABR or hypofractionated RT) and reported an ORR of 32% while maintaining a good toxicity profile (14% G  $\geq$  3).

The safety of anti-CTLA-4 agents has also been addressed. Formentiet *al*[67] designed a phase I/II study with 39 patients treated with ipilimumab plus SABR (28.5 Gy in 3 fx or 30 Gy in 5 fx). ORR was 31%, PFS was 7.1 mo and OS was 13 mo, with only 10.3% G  $\geq$  3 toxicity[67]. The safety of multisite irradiation was evaluated in the oligometastatic setting by Bauml *et al*[68], who included 45 patients with oligometastatic NSCLC and delivered local ablative therapy (surgery or SABR) followed by sequential pembrolizumab, showing promising results in terms of PFS (19.1 mo) and OS (41.6 mo), with low toxicity rates.

With the safety of the combination established and the promising survival data reported in these initial studies, randomized evidence on the combination of ICI and RT (mainly in the form of SABR, also known as I-SABR) is finally starting to emerge. At the moment, three randomized trials have published their results. Not only are these reinforcing the idea that a benefit in survival exists, but they are also starting to contemplate some questions regarding the optimal treatment delivery. For instance, the COSINR study by Patel *et al*[69] is a phase I trial that randomized 35 patients to receive dual ICI (ipilimumab plus nivolumab) and either concurrent or sequential SABR. Global ORR was 68%, while PFS was 6.2 mo in the concomitant arm and 5.9 mo in the sequential arm. Welsh *et al*[70] recently reported the results of a phase II study that randomized 72 patients to receive RT plus pembrolizumab *vs* pembrolizumab monotherapy. In the experimental arm, patients received either SABR (50 Gy in 4 fx or 70 Gy in 10 fx) or conventional RT (45 Gy in 15 fx). Globally, there were no significant differences in response or PFS between the combination arm and the pembrolizumab arm, with an ORR of 22% *vs* 25 and PFS of 9.1 *vs* 5.1 ( $P = 1.00$ ). However, in the subanalysis of patients treated in the combination arm, ORR was higher in the SABR group than in the conventional RT group (38% *vs* 10%), as well as PFS (20.8 mo *vs* 6.8 mo,  $P = 0.03$ )[70]. Finally, the PEMBRO-RT phase II study included 76 patients and randomized them in two arms: sequential pembrolizumab after SABR to a single lesion (24 Gy in 3 fx) *vs* pembrolizumab monotherapy. ORR was 36% and 18%, respectively. Furthermore, PFS favored the I-SABR arm (6.6 mo *vs* 1.9 mo), as well as OS (15.6 mo *vs* 7.6 mo), even though these were not statistically significant[71].

At present, a great number of clinical trials combining RT and ICI in stage IV NSCLC are ongoing (Table 5). These include multiple ICI agents (atezolizumab, avelumab, nivolumab, pembrolizumab, sintilimab, tremelimumab), different combinations, various treatment sequences (induction, sequential or concomitant) and several fractionations and RT techniques such as conventional RT, hypofractionation, SABR, intensity-modulated RT and proton beam RT.

## CONCLUSION

Radio-immunotherapy represents a dynamic area of preclinical and clinical investigation in lung cancer. The synergy between RT and ICI to achieve a greater tumor response has been shown to be a promising option for the treatment of NSCLC. The positive experiences reported with the combination of RT and ICI in early stage, unresectable stage III and stage IV NSCLC have reinforced the interest in the association of these two treatments. In the years to come, the results of ongoing clinical trials will continue to evolve clinical practice in NSCLC.

**Table 5 Ongoing clinical trials involving radiotherapy and immunotherapy in stage IV non-small cell lung cancer**

Ref.	Phase	ICI agent	RT dose	Design	Primary endpoints
NCT03158883[93]	I	Avelumab	50 Gy/5 fx	ICI + SABR	ORR
NCT03224871[94]	I	Nivolumab; Pembrolizumab; Intratumor IL-2	8 Gy/3 fx	ICI + IL-2 + RT	MTD
NCT03436056, PRIMING [95]	I	Pembrolizumab	SABR 30 Gy-3 fx SABR 54 Gy/3 fx	ICI + SABR	MTD
NCT03812549[96]	I	Sintilimab	SABR 30 Gy/3 fx; LD (low dose)-RT: 2 Gy/1 fx or 4 Gy/2 fx or 10 Gy/5 fx	ICI + SABR; ICI + LD-RT	MTD
NCT03223155, COSINR [69]	I	Nivolumab; Ipilimumab	SABR 3-5 fx, 2-4 sites	ICI + SABR	MTD
NCT02639026[97]	I	Durvalumab; Tremelimumab	HFRT 24 Gy/3 fx, 17 Gy/1 fx	ICI + HFRT	MTD
NCT03275597[98]	I	Durvalumab; Tremelimumab	SABR 30-50 Gy/5 fx	ICI + SABR	MTD
NCT03168464[99]	I-II	Nivolumab; Ipilimumab	RT 30 Gy/5 fx	ICI + RT	ORR
NCT02239900[100]	I-IIR	Ipilimumab	SABR 50 Gy/4 fx or 60 Gy/10 fx; 1-4 lesions	ICI + SABR	MTD
NCT02444741[101]	I-IIR	Pembrolizumab	SABR 4 fx or IMRT, PBRT, 3D-CRT 15 fx	ICI + SABR or IMRT, PBRT, 3D-CRT	MTD, ORR
NCT03176173, RRADICAL [102]	II	Nivolumab; Pembrolizumab; Atezolizumab	SABR 1-10 fx	ICI +/- SABR	PFS
NCT03965468, CHESS[103]	II	Durvalumab	SABR 1-10 fx	ICI + SABR + CT	PFS
NCT03044626, FORCE [104]	II	Nivolumab	RT 20 Gy/5 fx	ICI + RT	ORR
NCT02221739[105]	II	Ipilimumab	IMRT or 3D-CRT 30 Gy/5 fx	ICI + RT	ORR
NCT02658097[106]	II	Pembrolizumab	RT 8 Gy/1 fx	ICI + RT	ORR
NCT03391869, LONESTAR [107]	III	Nivolumab; Ipilimumab	LCT	ICI +/- SABR	OS
NCT03867175[108]	III	Pembrolizumab	SABR 3-10 fx	ICI +/- SABR	PFS
NCT03774732, NIRVANA-LUNG[109]	III	Pembrolizumab	SABR or 3D-CRT 18 Gy/3 fx	ICI + RT + CT	OS

ICI: Immune checkpoint inhibitors; Fx: Fraction; SABR: Stereotactic ablative radiotherapy; RT: Radiotherapy; LD-RT: Low dose radiotherapy; HFRT: Hypofractionated radiotherapy; IMRT: Intensity modulated radiotherapy; PBRT: Proton beam radiation therapy; 3D-CRT: 3D conformal radiation therapy; LCT: Local consolidation therapy; CT: Chemotherapy; ORR: Overall response rate; MTD: Maximum tolerated dose.

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