# Immunotherapy combined with radiotherapy for advanced non-small cell lung cancer: Current status and challenge (Review)

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**Abstract.** Immunotherapy, particularly immune checkpoint inhibitors (ICIs), has revolutionized the treatment landscape for advanced non-small cell lung cancer (NSCLC) in previous years. However, not all patients achieve a satisfactory objective response and long-term benefits, leading to growing interest in combining immunotherapy with radiotherapy (RT) to enhance therapeutic outcomes. The present review explored the rationale, efficacy and safety of combining RT with immunotherapy in advanced NSCLC. RT can potentiate immune responses through various mechanisms, such as immunogenic cell death and modification of the tumor microenvironment. The addition of RT to immunotherapy has notable synergistic antitumor effects to improve systemic control as RT can induce diverse immunomodulatory effects. The present review assessed the efficacy and safety of combining ICIs with RT and examined the optimal timing, dose and fraction strategies of RT for enhancing immune activation while minimizing toxicity. Additionally, the potential of RT to overcome primary and acquired resistance to immunotherapy was discussed. Despite encouraging findings, challenges such as optimal patient selection and biomarkers, treatment-related toxicity and precise timing of interventions remain unresolved. The present review aimed to provide a comprehensive analysis of current evidence, as well as the key considerations for integrating RT and immunotherapy into clinical practice.

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*Abbreviations:* AEs, adverse events; ATP, adenosine triphosphate; CALR, calreticulin; CRT, chemoradiation therapy; cGAS, cyclic GMP-AMP synthase; CTLs, cytotoxic T lymphocytes; DAMPs, damage-associated molecular patterns; ICD, immunogenic cell death; ICIs, immune checkpoint inhibitors; IFN, interferon; IGRT, image guided radiotherapy; IMRT, intensity modulated radiotherapy; HMGB1, high mobility group box 1; MDSCs, myeloid-derived suppressor cells; MMR, mismatch repair; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; RT, radiotherapy; SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiotherapy; SRT, stereotactic radiotherapy; STING, stimulator of interferon genes; TAMs, tumor-associated macrophages; TMB, tumor mutational burden; TME, tumor microenvironment; Tregs, regulatory T cells

*Key words:* immunotherapy, immune checkpoint inhibitor, radiotherapy, immunotherapy combined with radiotherapy, non-small cell lung cancer

**Contents**



## 1. Introduction

The global incidence rate of non-small cell lung cancer (NSCLC) is notable, accounting for ~85% of newly diagnosed cases of lung cancer annually and contributing to a large number of cancer-associated mortalities worldwide (1,2). The 5-year overall survival (OS) rate for NSCLC remains relatively low at ~15%, due to the high proportion of cases diagnosed at advanced stages (3). For patients with unresectable advanced NSCLC, the standard treatment is concurrent chemoradiotherapy (CRT). However, the long-term prognosis for this treatment remains limited. According to previous studies, the 5-year OS rate for concurrent CRT in these patients is 15-30% (4,5). Immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) axis have markedly improved the survival rates of patients with advanced NSCLC. Numerous clinical trials have demonstrated the clinical advantages of these therapies (6-9). Various ICIs

such as nivolumab, pembrolizumab, durvalumab and atezolizumab have already been approved for NSCLC treatment by the US Food and Drug Administration (10). However, the efficacy of ICIs for NSCLC remains limited, as the majority of patients have no tumor response and the objective response rates is only ~20% in previously treated patients (6,11,12). In order to improve efficacy, a number of studies are exploring the combination of immunotherapy and radiotherapy (RT) for advanced NSCLC (13-15), usually referred to as 'combined radio-immunotherapy'.

Local RT can induce the regression of metastatic cancer at a distance from the field of radiation, known as the abscopal effect (16,17). Although it has been recognized for several years, the abscopal effect remains a rare event (18). RT modulates the immune system through complex mechanisms including local tumor cell death, antigen release, activation of dendritic cells (DCs), recruitment of cytotoxic T lymphocytes (CTLs) and promotion of the antitumor response (17). On other hand, ICIs help to mitigate the immunosuppressive tumor microenvironment (TME), allowing for a more robust and sustained antitumor immune response. Combination strategies with RT and immunotherapy, especially ICIs such as PD-1/PD-L1 and CTL associated protein 4 (CTLA-4) inhibitors, can lead to a mutual synergistic effect by unleashing the full potential of the immune system (19-22).

Moreover, it seems that the timing and sequence is important for the beneficial synergic activity of ICIs plus RT according to previous research. The randomized PACIFIC trial recommended that immunotherapy treatment is initially performed with subsequent RT (13). Certain studies support the concurrent use of RT and immunotherapy (23-25). When administered together, RT not only directly kills tumor cells but also boosts the efficacy of ICIs (23). However, concurrent therapy requires careful monitoring for adverse effects, such as pneumonitis and other immune-related adverse events (AEs) (24). Furthermore, a phase 1 trial of a randomized comparison of concurrent or sequential immunotherapy and stereotactic body RT (SBRT) in patients with stage IV NSCLC reports that administering immunotherapy concurrently with SBRT is not more toxic compared with sequential therapy, allowing for systemic therapy to be initiated earlier in the patient's treatment plan (25). Therefore, the optimal timing of combining ICIs with RT to maximize synergistic effects needs to be further investigated.

In previous years, the complex integration of immunotherapy and RT has advanced rapidly, with a greater expectation of further therapeutic benefit. With the advent of new efficient immunotherapeutic agents, a large area of active research has emerged, following considerable interest in treating RT as a potential combination partner for immunotherapy. The present review discusses the current status of combining immunotherapy and RT for advanced NSCLC, the optimal combination strategies, the utility of RT for overcoming resistance to immunotherapy and summarizes the main problems as well as future perspectives.

## 2. Immunomodulatory effects of RT

Preclinical evidence has demonstrated that focal RT has diverse immunomodulatory effects (26-28). The mechanism of action of RT is complex and involves both direct cytotoxic effects of RT on cancer cells and immunomodulatory components (29). The therapeutic effect of RT is mediated by the generation of ROS resulting direct breakage of DNA, which serves an important role in changes of molecular signaling pathways (30). RT enhances the release of tumor-associated antigens from tumor cell apoptosis and necrosis, which are subsequently taken up by antigen-presenting cells. This upregulates major histocompatibility complex class I and adhesion molecule expression and increases chemokine secretion, leading to APC recruitment, thereby rendering tumor cells more susceptible to recognition by T cells and augmenting the antitumor effect (22,31,32).

The immune response must be initiated with a unique type of programmed cell death commonly known as immunogenic cell death (ICD). RT induces ICD which involves the release of various immunogenic signals, known as damage-associated molecular patterns (DAMPs), including calreticulin (CALR) exposure on the cell membrane, extracellular adenosine triphosphate (ATP) and high mobility group box 1 (HMGB1) (33-35). In the TME, ICD could also trigger a pathogen response with the co-release of chemokines such as C-X-C motif chemokine ligand 10, TNFα and type I interferon (IFN) (36). Mechanistically, IFN produced by $CD8^+$ T cells serves a key role in driving the upregulation of PD-L1 on tumor cells after delivery of fractionated RT (37). In addition, the TME is remodeled by vascular, stromal and immunological changes that are induced by irradiation and contribute to an antitumor response (27,38). The reprogrammed TME induced by RT contributes to turning 'cold' tumors lacking lymphocytic infiltration into 'hot' tumors with high levels of immune cell infiltration and raises response rates achievable with ICIs (39-41).

*Abscopal effect*. The combined treatment of RT and ICIs appears to be an optimal tool to treat cancer as RT has notable synergistic antitumor effects with systemic ICIs. This immune priming signal can be translated into systemic immune tumor control, known as the abscopal effect (42). The abscopal response has been observed in multiple immunocompetent mouse cancer models (43,44). In a mouse model of melanoma, RT with either concurrent or sequential anti-CTLA4 treatment improved survival and inhibited total tumor growth compared with anti-CTLA4 or RT alone (45). A preclinical study demonstrated that stereotactic RT (SRT) combined with immune checkpoint blockade can enhance antitumor immune responses by cross-presentation of tumor antigen in a mouse model, markedly improving local tumor control (46). In line with these findings, the ability of this combination to induce effective antitumor immune responses was reported in mouse models of NSCLC. After conventionally fractionated radiation, PD-L1 expression increased both *in vivo* and *in vitro*. The combination of RT with an anti-PD-L1 antibody synergistically enhanced antitumor immunity mediated by $CD8^+$ T-cells in a mouse model (47). In a study of Kras-driven murine NSCLC, RT induced adaptive upregulation of PD-L1 expression in tumor cells, and the concurrent administration of an anti-PD-1 antibody elicited robust antitumor immune responses, leading to sustained tumor control (48).

Notably, when RT is combined with immunotherapy, rational selection of radiation dose and fraction are acquired

to achieve the most pronounced systemic effect. The DNA exonuclease, three prime repair exonuclease 1 (TREX1), was identified as an upstream regulator of radiation-induced antitumor immunity and served as a marker for the optimal dose determination (49). When radiation is administrated beyond a threshold dose in a single fraction, Trex1-induced DNA degradation and accumulation of irradiated cancer cells precludes activation of the IFN-I pathway mediated by cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING) (50,51). By contrast, a radiation dose below the dose threshold for Trex1 induction is optimal for the IFNβ stimulation required for recruitment of DCs and $CD8^+$ T-cells to the tumor site. In this context, adding ICIs may mediate complete durable regression of the irradiated and non-irradiated tumor (abscopal effect).

Together, these findings demonstrate the capability of RT to initiate an endogenous antigen-specific immune response and provide additional mechanistic rationale for combining RT with immunotherapy in the clinic.

*Efficacy and safety of RT combined with immunotherapy.* Focusing on locally advanced and metastatic NSCLC, several clinical trials and secondary or retrospective analyses have investigated the efficacy and safety of combination therapy using RT and ICIs (24,52-55). The main prospective data associated with the efficacy of ICI-RT combination are summarized in Tables I and II. Some clinical studies have demonstrated that the administration of combined radio-immunotherapy could improve survival outcome with an acceptable safety profile (54,56-58).

## 3. Locally advanced NSCLC

The phase 3 randomized clinical trial PACIFIC study compared durvalumab vs. placebo in 713 patients with locally advanced NSCLC with no progressive disease after ≥2 rounds of platinum-based CRT. Progression free survival (PFS) was significantly improved in the durvalumab arm vs. placebo [16.8 months vs. 5.6 months; hazard ratio (HR), 0.52; 95% CI, 0.42-0.65; P<0.001], as well as the median time to mortality or distant metastasis (28.3 months vs. 16.2 months; HR 0.53; 95% CI, 0.41-0.68; P<0.001) (13,52). Updated OS data from the PACIFIC trial reported a long-term clinical benefit in the durvalumab group vs. placebo with a 36-month OS rate (57.0% vs. 43.5%) (53). AEs of any cause were similar in durvalumab vs. placebo for any grade (96.8% vs. 94.9%), grade 3 or 4 AEs (29.9% vs. 26.1%) and serious AEs (28.6% vs. 22.6%). The most frequent AEs leading to discontinuation of durvalumab and placebo were pneumonitis (in 6.3 and 4.3%, respectively) and pneumonia (in 1.1 and 1.3%, respectively), and mortality due to AEs occurred in 4.4 and 6.4%, respectively (13,52). Hence, the safety profile was similar between the groups.

A non-randomized controlled phase 1 trial of pembrolizumab administered concurrently with CRT for locally advanced NSCLC showed that the 12-month PFS rate was 81.0% (95% CI, 49.3-90.2%). Among the 21 patients included in the analysis, no dose-limiting toxic effects in any cohort were observed, and 18% of patients (4/21) experienced immune-related AEs of grade ≥3 (54). These results indicate that combined treatment with PD-1 inhibitors and RT for locally advanced NSCLC is tolerable. The comparable randomized trial, RTOG 3505 (NCT02768558), on nivolumab in unresectable stage III NSCLC patients was terminated and the results have not been reported (55).

## 4. Metastatic NSCLC

In a secondary analysis of the KEYNOTE-001 trial, patients with advanced NSCLC received pembrolizumab after previous RT treatment. The PFS and OS with pembrolizumab were significantly longer in patients who previously received any RT compared with in patients without previous RT (PFS, 4.4 months vs. 2.1 months; P=0.019; OS, 10.7 months vs. 5.3 months; P=0.026). Pulmonary toxicity was recorded in 15 patients of 24 patients (63%) with previous thoracic RT vs. 29 patients of 73 patients (40%) with no previous thoracic RT. A total of 3 patients (13%) with previous thoracic RT developed immune-related pulmonary toxicity compared with 1 patient (1%) without previous RT. The safety profile was considered to be acceptable.

The PEMBRO-RT randomized trial of 76 patients with advanced NSCLC reported that pembrolizumab combined with SBRT produced a greater overall response rate (ORR) at 12 weeks compared with pembrolizumab alone (36% vs. 18%; P=0.07), particularly in PD-L1-negative patients. Grade 3 to 5 immune-related AEs were reported in 12 patients (17%), with no notable differences between arms (56). A pooled analysis including PEMBRO-RT and MDACC trials was performed to evaluate the responses of pembrolizumab with or without RT for metastatic NSCLC. Overall, 148 patients were included in the pooled analysis. The abscopal response rate was markedly higher in the pembrolizumab plus RT cohort vs. in the pembrolizumab alone group (41.7% vs. 19.7%; P=0.0039), as was the abscopal disease control rate (65.3% vs. 43.4%, P=0.0071). Compared with pembrolizumab alone, adding RT to pembrolizumab significantly increased survival outcomes, with a longer PFS (9.0 months vs. 4.4 months; HR, 0.67; 95% CI, 0.45-0.99; P=0.045) and OS (19.2 months vs. 8.7 months; HR, 0.67; 95% CI, 0.54-0.84; P=0.0004) (24). These findings indicate that adding PD-1inhibitors to RT for advanced NSCLC can provide survival benefits.

Numerous retrospective studies have evaluated the benefit and safety of combining ICIs with RT. In a multicenter retrospective cohort study of patients with NSCLC treated with nivolumab after the second line systemic chemotherapy, there was no difference in PFS between those without past RT and those who received RT in the past 6 months (adjusted HR 0.65; 95% CI, 0.37-1.14) (57). Efficacy and toxicity of immunotherapy with SRT for brain metastases from NSCLC were evaluated in a previous multicentric retrospective study from the Italian Association of RT and Clinical Oncology. Patients receiving SRT with immunotherapy vs. SRT-alone had a significantly higher 1-year intracranial local progression-free survival rate (83.9% vs. 53.5%, respectively; P=0.007). The combined treatment immunotherapy and SRT was well tolerated, and no notable differences in radio-necrosis rates between patients who received SRT + immunotherapy and patients who received SRT-alone were observed (58).

Taken together, these studies suggest that combining RT and immunotherapy is associated with improved survival

Table I. Completed or ongoing clinical trials with ICI/RT combinations in locally-advanced NSCLC.

| Trial name | Trial phase | Sequence | Trial design | Estimated/actual study completion date | Status | (Refs.) |
|---|---|---|---|---|---|---|
| NCT03519971 PACIFIC-2 | 3 | Concurrent | Durvalumab + concurrent CRT vs. CRT | March 2025 | Active, not recruiting | (119) |
| NCT04597671 NVALT28 | 3 | Concurrent | Durvalumab with low-dose PCI (15 Gy in 10 fractions) vs. durvalumab with observation | December 2032 | Recruiting | (120) |
| NCT03801902 ARCHON-1 | 1 | Sequential | Durvalumab + ACRT (60 Gy in 15 fractions) vs. durvalumab + standard RT (60 Gy in 30 fractions) | March 2025 | Recruiting | (121) |
| NCT04892953 | 2 | Concurrent | Durvalumab + consolidation RT | November 2024 | Recruiting | (122) |
| NCT04013542 | 1 | Concurrent | Ipilimumab + nivolumab + RT | December 2026 | Active, not recruiting | (123) |
| NCT03818776 | 1 | Concurrent | Durvalumab + proton beam therapy RT (60 CGyE in 20 fractions) vs. durvalumab + proton beam therapy RT (69 CGyE in 23 fractions) | January 2022 | Active, not recruiting | (124) |
| NCT04765709 BRIDGE | 2 | Concurrent | Durvalumab + platinum-based chemotherapy vs. durvalumab + RT | June 2026 | Active, not recruiting | (125) |
| NCT03663166 | 1 | Sequential | Ipilimumab with thoracic radiation therapy followed by nivolumab monotherapy | October 2021 | Completed | (126) |
| NCT04577638 AIRING | 2 | Concurrent | Nivolumab + accelerated IMRT (66 Gy in 24 fractions) + 6 months nivolumab maintenance | April 2023 | Completed | (127) |
| NCT03631784 KEYNOTE-799 | 2 | Concurrent | Pembrolizumab + concurrent CRT | March 2024 | Completed | (128) |
| NCT03589547 | 2 | Concurrent | Durvalumab + SBRT (20 Gy in 2 fractions) | October 2026 | Active, not recruiting | (129) |
| NCT04230408 PACIFIC BRAZIL | 2 | Concurrent | Concurrent chemo-immuno-radiotherapy | September 2024 | Active, not recruiting | (130) |
| NCT04003246 | 2 | Concurrent | Thoracic RT + durvalumab + consolidative durvalumab | August 2026 | Active, not recruiting | (131) |
| NCT03999710 | 2 | Concurrent | RT (60 Gy in 30 fractions) + durvalumab | July 2025 | Active, not recruiting | (132) |

Table I. Continued.

| Trial name | Trial phase | Sequence | Trial design | Estimated/actual study completion date | Status | (Refs.) |
|---|---|---|---|---|---|---|
| NCT03523702 | 2 | Sequential | Pembrolizumab + RT in patients with high (≥50%) PD-L1 expression vs. concurrent CRT in patients with PD-L1 expression <50% | November 2026 | Active, not recruiting | (133) |
| NCT04245514 | 2 | Concurrent | Durvalumab + RT (arm A, 20x2 Gy weekdaily; arm B, 5x5 Gy weekdaily; and arm C, 3x8 Gy q2d) | December2031 | Recruiting | (134) |
| NCT03285321 | 2 | Sequential | Concurrent CRT + nivolumab vs. concurrent CRT + nivolumab + ipilimumab | December2024 | Active, not recruiting | (135) |
| NCT03693300 | 2 | Sequential | CRT + durvalumab | April 2023 | Completed | (136) |
| NCT04085250 | 2 | Sequential | Neoadjuvant therapy + concurrent CRT + nivolumab vs. neoadjuvant therapy + concurrent CRT + observation | January 2025 | Active, not recruiting | (137) |
| NCT03706690 PACIFIC-5 | 3 | Sequential | CRT + durvalumab vs. CRT + placebo | March 2027 | Active, not recruiting | (138) |
| NCT04026412 | 3 | Sequential | Arm A, nivolumab + CCRT + ipilimumab vs. arm B, nivolumab + CCRT vs. arm C, CCRT + durvalumab | September 2024 | Active, not recruiting | (139) |
| NCT02434081 | 2 | Concurrent | CRT + concurrent nivolumab | March 2020 | Completed | (140) |
| NCT05128630 | 2 | Concurrent | Chemotherapy + durvalumab + hypofractionated RT + concurrent durvalumab + durvalumab maintenance | November 2025 | Recruiting | (141) |
| NCT03141359 | 2 | Sequential | SBRT + concurrent mediastinal chemoradiation +/- consolidation chemotherapy/ adjuvant durvalumab | July 2027 | Active, not recruiting | (142) |

CRT, chemoradiotherapy; CCRT, concurrent chemoradiotherapy; ICI, immune checkpoint inhibitor; RT, radiotherapy; NSCLC, non-small cell lung cancer; PCI, prophylactic cranial irradiation; ACRT, accelerated hypofractionated radiation therapy; IMRT, intensity modulated radiotherapy; SBRT, stereotactic body radiotherapy; PD-L1, programmed cell death ligand-1.

Table II. Completed or ongoing clinical trials with ICI/RT combinations in metastatic NSCLC.

| Trial name | Trial phase | Sequence | Trial design | Estimated/ actual study completion date | Trial name | (Refs.) |
|---|---|---|---|---|---|---|
| NCT02492568 PEMBRO-RT | 2 | Sequential | Pembrolizumab after SBRT (24 Gy in 3 fractions) vs. pembrolizumab alone | June 2018 | Completed | (143) |
| NCT02940990 | 2 | Concurrent | Chemotherapy + clinical observation or maintenance chemotherapy vs. chemotherapy + SBRT concurrent with GM-CSF | December 2019 | Completed | (144) |
| NCT03158883 | 1 | Sequential | Avelumab with SAR (50 Gy in 5 fractions) | June 2020 | Completed | (145) |
| NCT03867175 | 3 | Concurrent | Pembrolizumab with SBRT vs. pembrolizumab only | December 2027 | Active, not recruiting | (146) |
| NCT02444741 | 1/2 | Concurrent | Pembrolizumab with SBRT (50 Gy in 4 fractions) vs. pembrolizumab with traditional RT (45 Gy in 15 fractions). | September 2025 | Active, not recruiting | (147) |
| NCT03774732 NIRVANA-lung | 3 | Concurrent | Pembrolizumab + chemotherapy vs. pembrolizumab + chemotherapy with 3D-CRT (18 Gy in 3 fractions)/SBRT | December 2026 | Recruiting | (148) |
| NCT03391869 LONESTAR | 3 | Sequential | Nivolumab + ipilimumab vs. nivolumab + ipilimumab with LCT | December 2025 | Recruiting | (149) |
| NCT03168464 | 1/2 | Concurrent | Ipilimumab and nivolumab with RT (30 Gy in 5 fractions) | March 2022 | Recruiting | (150) |
| NCT04081688 | 1 | Sequential | Varlilumab and atezolizumab with SBRT | April 2024 | Active, not recruiting | (151) |
| NCT03176173 | Not applicable | Concurrent | Immunotherapy + concurrent IGRT vs. immunotherapy | May 2026 | Active, not recruiting | (152) |
| NCT02696993 | 1/2 | Concurrent | Nivolumab + ipilimumab + RT (SBRT or WBRT) vs. nivolumab + RT | December 2024 | Active, not recruiting | (153) |
| NCT03825510 | 2 | Sequential | Nivolumab/pembrolizumab + SBRT | March 2022 | Completed | (154) |
| NCT03812549 | 1 | Sequential | SBRT + LDRT+ sintilimab | July 2022 | Completed | (155) |
| NCT04929041 | 2/3 | Concurrent | Arm A, immunotherapy +/- chemotherapy; arm B, immunotherapy +/- chemotherapy, SBRT | December 2027 | Recruiting | (156) |
| NCT03705806 | Not applicable | Sequential | RT (30 Gy in 10 fractions) combined with immunotherapy | September 2024 | Recruiting | (157) |
| NCT04513301 | 2 | Concurrent | Sintilimab + RT vs. sintilimab alone | December 2022 | Recruiting | (158) |
| NCT05222087 | 1 | Sequential | Pembrolizumab +/- carboplatin or paclitaxel + SBRT | April 2025 | Recruiting | (159) |

Table II. Continued.

| Trial name | Trial phase | Sequence | Trial design | Estimated/ actual study completion date | Trial name | (Refs.) |
|---|---|---|---|---|---|---|
| NCT03223155 | 1 | Concurrent/ sequential | Nivolumab/ipilimumab+ SBRT | December 2027 | Active, not recruiting | (160) |
| NCT04291092 | 2 | Concurrent | Camrelizumab + WBRT | June 2023 | Recruiting | (161) |
| NCT04167657 STAR | 2 | Sequential | Sintilimab + RT | April 2023 | Recruiting | (162) |
| NCT03589339 | 1 | Sequential | NBTXR3 + SABR + nivolumab/pembrolizumab | May 2028 | Recruiting | (163) |
| NCT03965468 CHESS | 2 | Concurrent | Durvalumab + chemotherapy + SBRT | December 2026 | Recruiting | (164) |
| NCT03035890 | Not applicable | Concurrent | Hypofractionated RT + nivolumab/pembrolizumab/ atezolizumab | June 2022 | Completed | (165) |
| NCT04549428 | 2 | Concurrent | Atezolizumab + palliative RT (8 Gy in 1 fraction) | December 2024 | Active, not recruiting | (166) |
| NCT03275597 | 1 | Concurrent | SBRT + durvalumab + tremelimumab | July 2020 | Active, not recruiting | (167) |
| NCT05034055 | 2 | Sequential | Atezolizumab/tiragolumab + SBRT | December 2023 | Not yet recruiting | (168) |
| NCT04889066 | 2 | Concurrent | Durvalumab+ PULSAR vs. durvalumab + standard fSRT | January 2025 | Not yet recruiting | (169) |
| NCT04786093 | 2 | Concurrent | SBRT + durvalumab vs. PULSAR + durvalumab | May 2027 | Recruiting | (170) |
| NCT04364776 | Observational | Sequential | CRT + durvalumab | December 2024 | Active, not recruiting | (171) |
| NCT04238169 | 2 | Concurrent | SBRT + toripalimab vs. SBRT + bevacizumab + toripalimab | December 2023 | Completed | (172) |

SBRT, stereotactic body radiotherapy; GM-CSF, granulocyte-macrophage colony-stimulating factor; SAR, stereotactic ablative radiotherapy; RT, radiotherapy; CRT, chemoradiotherapy; LCT, local consolidation therapy; IGRT, image-guided radiation therapy; WBRT, whole-brain radiotherapy; LDRT, low dose radiotherapy; SABR, stereotactic ablative radiotherapy; PULSAR, personalized ultra-fractionated stereotactic adaptive radiotherapy; fSRT, fractionated stereotactic radiotherapy.

benefit and does not increase toxicities beyond each administrated strategy independently. However, the combination therapy needs to be further optimized using the results of numerous ongoing clinical trials.

## 5. Optimal timing for combination of RT with immunotherapy

The sequence of administration of combined radio-immunotherapy is a crucial factor for its efficacy. However, currently, the optimal sequence remains unclear. Since different types of ICIs target different stages of the immune response and activate multiple immune cells, the ideal sequence and timing must be meticulously planned to achieve synergistic effects (59-61).

A few preclinical studies have demonstrated that concurrent therapeutic strategies have been associated with superior therapeutic activity. In preclinical models of melanoma, colorectal and breast cancer, concurrent but not sequential PD-1/PD-L1 blockade and RT was shown to be more effective at improving local tumor control and survival (37). The mechanistic hypothesis was that RT leads to upregulation of PD-L1 expression secondary to $CD8^+$ T cell production of IFN. A comprehensive meta-analysis of treatment of brain metastases with stereotactic radiosurgery and ICIs suggested that concurrent administration RT and ICIs may be associated with improved safety and efficacy over sequential

therapy (62). However, data from a mouse model of colorectal cancer demonstrated that an anti-CTLA-4 inhibitor was the most efficient when given before RT (63). In addition, a meta-analysis of 20 clinical trials that enrolled 2,027 patients with NSCLC who received combination therapy using PD-1/PD-L1 inhibitors and RT demonstrated that PD-1/PD-L1 inhibitor administration following RT outperformed concurrent treatment (64). This finding was in line with the theory established by preclinical studies which demonstrated that RT could regulate PD-L1 expression in cancer cells through the repair of DNA double-strand breaks and induce enrichment of $CD8^+$ T-cells. The upregulation of PD-L1 expression has been shown to improve the efficacy of ICIs and increase $CD8^+$ T-cell infiltration (65,66). Thus, the different results between various studies suggest that the optimal schedule depends on a number of factors, such as tumor type and the mechanics of action of immunotherapy agents, which should be considered when designing clinicals trials.

The PACIFIC trial showed marked improvements in both PFS and OS for patients treated with the sequential use of durvalumab after CRT compared with those receiving a placebo (13). As shown in the study, the sequential approach has notable benefits in NSCLC, with a manageable toxicity profile. Similarly, the clinical trials assessing the safety and efficacy of pembrolizumab and nivolumab recommended administration as adjuvant therapy after CRT (55,67). Furthermore, the updated data from PACIFIC study suggest that administering immunotherapy within 14 days of completing concurrent CRT seemed to have markedly greater PFS compared with starting immunotherapy after 14-42 days (14). However, a retrospective study of patients with stage IV NSCLC from the National Cancer Database reported a different optimal time for combined radio-immunotherapy. The study demonstrated patients treated with immunotherapy ≥21 days after start of SBRT had a longer OS compared with those treated thereafter (median OS, 19 months vs. 15 months; P=0.0335) (68). This finding suggests that the synergistic effect is not only associated with the sequence, but also with the time interval between RT and ICI administration.

Sequential administration of immunotherapy after RT has previously been assessed, and several studies have begun investigating whether the use of concurrent administration would achieve improved results. The KEYNOTE-799 study, a phase-II trial evaluating the safety and efficacy of pembrolizumab plus concurrent CRT in patients with unresectable, locally advanced, stage III NSCLC, reported an incidence rate of 4.0% for grade ≥3 pneumonitis, which was slightly higher compared with the 3.4% reported in the PACIFIC trial (15). This indicates that concurrent use of ICIs with CRT or RT may lead to an elevated risk of immune-related pneumonitis. The balance between efficacy and safety is crucial when combining ICIs with RT or CRT. A single center prospective trial of concurrent anti-PD-L1 durvalumab and palliative RT demonstrated an acceptable safety profile of the combined treatment (23). Furthermore, the ETOP NICOLAS phase II clinical trial assessed treatment with nivolumab concurrently with standard first line CRT regimen in unresectable locally advanced NSCLC and provided evidence that the addition of nivolumab to concurrent CRT is safe and tolerable (69). The increasing experimental evidence indicates that concurrent immunotherapy and RT is more effective compared with sequential therapy (37). In addition, there are ongoing clinical trials investigating the concurrent administration of ICIs and RT in NSCLC to determine if this approach can provide superior outcomes compared with sequential treatment. The PACIFIC 2 (NCT03519971) study was designed to assess the benefit and safety of concurrent durvalumab and platinum-based CRT in patients with unresectable stage III NSCLC (70). Similarly, another trial (NCT03589547) is exploring the effects of concurrent pembrolizumab with RT in stage III NSCLC. Until more conclusive data is available, the choice between concurrent and sequential administration remains individualized, based on patient factors, such as tumor characteristics and treatment goals.

*Optimizing the dose and fractionation*. At present, a wide range of RT doses and fractionation schedules are applied in clinical studies and the appropriate regimen to elicit an immune response safely remains unknown. Notably, a rational selection of RT dose and fraction is required to achieve the most synergistic effects. Preclinical studies in NSCLC suggest that combination therapy using hypofractionated RT, such as SBRT or SRT, and ICIs may be more effective in promoting the release of tumor antigens and DAMPs (such as HMGB1 and ATP) and enhancing the immune response compared with conventional fractionation (71-73). However, high-dose RT may potentially increase the proportion of splenic regulatory T cells (Tregs) suppressing the antitumor immune response (74). Other preclinical studies have reported that conventional fractionation might have improved efficacy compared with combined radio-immunotherapy (49). It is accepted currently that the optimal radiation dose appears to be somewhere between 8 and 10 Gy per fraction in one to three fractions, which induces an effective antitumor response (75). Nevertheless, clinical trials comparing different RT doses and fractionation alongside ICIs is limited.

The subgroup analysis of the PACIFIC study demonstrated that patients may get a notable survival benefit regardless of the total radiation doses used (76). However, The PEMBRO-RT trial showed that the largest benefit from the addition of SBRT was observed only in patients with PD-L1-negative subgroup, which indicates SBRT has a potential augmenting effect through altering PD-L1 expression, thereby improving the efficacy of ICIs (56). The review proposed that both conventional radiotherapy and SBRT are capable of inducing an immune response (77). However, an exploratory analysis revealed that compared with conventional RT, SBRT improved the out-of-field ORRs (38% vs. 10%; P=0.11) and median PFS (21.1 months vs. 6.8 months; P=0.03), suggesting responses may be enhanced by SBRT (78). While hypofractionation shows promise for maximizing the synergistic effects of RT and immunotherapy in NSCLC, the optimal dose and fractionation schedule remain under investigation. Currently, there is a hypothesis that low-dose RT serves a distinct role in the antitumor immune response combined with ICIs. A number of preclinical studies have investigated the immunomodulatory effect of low-dose RT (79-82), and this subject will be the focus of future research. Several ongoing trials (such as NCT02444741 and NCT03391869) are investigating the impact of varying RT regimens on immune response and overall outcomes. These trials are warranted to determine the best approach, with the ultimate goal of improving patient outcomes while minimizing toxicity.

*RT target volume*. The irradiated target volume is likely to have a crucial influence on the ability of RT to elicit immunostimulatory effects. The size and extent of the irradiated target volume can influence both the local tumor response and the systemic immune effects, including the potential for immune-mediated abscopal effects. Larger irradiated volumes can lead to a higher risk of lymphopenia (reduction in circulating lymphocytes), which can negatively impact the effectiveness of ICIs (83). Strategies to minimize the occurrence of lymphopenia include reduction in the volume of the radiation field and using advanced RT techniques. The KEYNOTE-001 trial highlights that irradiating only a portion of the tumor might be sufficient to trigger an effective immune response (84-86). This notion challenges the traditional approach to RT, which typically aims to target the entire tumor volume. Partial tumor irradiation could offer a way to maximize immune activation while minimizing toxicity, potentially leading to improved outcomes for patients with NSCLC (87). However, more clinical evidence is needed to fully understand the best application of this approach and to identify the patient populations most likely to benefit. The use of advanced RT techniques such as SBRT, proton therapy and particle beam RT can help reduce the dose to targeted areas to minimize radiation exposure to normal tissues and critical immune structures while effectively targeting the tumor. This sparing of immune cells is particularly important when combining RT with ICIs (88). Thus, these modern RT techniques could provide notable benefits in reducing radiation-induced toxicities, particularly radiation pneumonitis, when combined with ICIs.

## 6. Combining RT to overcome resistance to immunotherapy

Immunotherapy has emerged as a breakthrough treatment for NSCLC by enhancing the immune system's ability to recognize and destroy cancer cells. ICIs have provided durable responses in some patients. However, resistance to immunotherapy, whether primary or acquired, remains a notable challenge, limiting its overall effectiveness in the majority of patients (89,90). Primary resistance, which is associated with various intrinsic and extrinsic tumor factors, occurs when patients fail to respond to immunotherapy from the outset (91). Intrinsic factors that lead to primary resistance include a lack of antigenic mutations, loss of tumor antigen and human leukocyte antigen (HLA) expression, alterations in antigen processing machinery, alterations of several signaling pathways (MAPK, PI3K, WNT, IFN, EGFR or anaplastic lymphoma kinase) and constitutive PD-L1 expression (89,92).

The major extrinsic factors which contribute to immunotherapy resistance include immunoregulatory factors within the TME. The TME serves a critical role in shaping the immune response to cancer. In NSCLC, the TME often contains a high density of immunosuppressive cells, such as Tregs and myeloid-derived suppressor cells (MDSCs). These cells inhibit the activity of cytotoxic T cells and promote an environment that supports resistance to ICIs and tumor growth (93). Besides, tumor-associated macrophages (TAMs) may also contribute to immune suppression by secreting anti-inflammatory cytokines and promoting immune evasion (94,95). In addition, tumors can evade immune detection by upregulating immune checkpoint molecules such as PD-L1, which binds to PD-1 on T cells, leading to T cell exhaustion and an impaired immune response (96). The acquired resistance may be associated with loss of the target antigen and HLA expression and altered IFN signaling, as well as loss of T-cell functionality (89). These mechanisms contribute to the complex and multifactorial nature of immunotherapy resistance in NSCLC, highlighting the need for novel approaches to overcome these challenges. A study included patients with advanced NSCLC who developed acquired resistance to PD-1 inhibitor and demonstrated that acquired resistance to PD-1 inhibitors is often limited to one or two sites and lymph nodes metastases appear to be particularly susceptible to acquired resistance (97). Therefore, when patients develop oligo-progression after responding to PD-1 inhibitor, local therapy to oligoprogressive disease may prolong ICI effectiveness.

RT is traditionally used for local tumor control by directly damaging DNA and causing cell death in targeted cancer cells. However, previous evidence suggests that RT has notable immunomodulatory effects that extend beyond the immediate vicinity of the irradiated tumor, affecting both local and distant immune responses. A primary immunomodulatory effect of RT is the induction of ICD. When cancer cells die in response to RT, they release danger signals known as DAMPs, such as CALR, IFN-I and HMGB1 (50,98,99). These DAMPs serve as signals to the immune system, alerting DCs and other antigen-presenting cells to process and present tumor antigens, thereby activating cytotoxic T cells (100). When combined with ICIs, these T cells are more equipped to recognize and eliminate tumor cells, overcoming one of the key mechanisms of immunotherapy resistance.

The immunosuppressive nature of the TME is a notable contributor to immunotherapy resistance. RT could remodel the TME by reducing the population of immunosuppressive cells such as Tregs, MDSCs and TAMs. Additionally, RT increases the infiltration of effector immune cells, such as cytotoxic T cells and natural killer (NK) cells, into the tumor, further enhancing the antitumor immune response (101,102). By shifting the balance of immune cells within the TME, the combination of RT and immunotherapy can overcome the immunosuppressive barrier that often limits the effectiveness of ICIs.

Traditionally, a phenomenon known as the abscopal effect has garnered notable interest in the context of RT and immunotherapy. The abscopal effect refers to the observation that, following local irradiation, distant (non-irradiated) tumors may shrink or become more responsive to immune attack (16). This systemic effect is considered to occur due to RT's ability to stimulate a systemic antitumor immune response, mediated by activated T cells that circulate and target cancer cells at distant sites (73,103). It is widely accepted that CTLs induced by RT migrate to the irradiated tumor and eliminate residual cancer cells and also to metastatic sites, a key mechanism transforming local effects into abscopal responses (104,105). Several preclinical trials have demonstrated high-dose RT causes ICD and leads to a systemic antitumor response. The endogenous cytosolic DNA can be sensed by the cGAS-STING pathway leading to IFN production along this pathway which has a crucial role in T-cell cross-priming to initiate an antitumor response (20,106). Local RT triggers the systemic antitumor immune response through these pathways.

RT has been shown to modulate the expression of immune checkpoint molecules, such as PD-L1 on tumor cells. While

increased PD-L1 expression can contribute to immune escape, when combined with PD-1/PD-L1 inhibitors, the upregulation of these checkpoints by RT can actually enhance the effectiveness of ICIs (107,108). By blocking the PD-1/PD-L1 pathway, ICIs prevent tumor cells from evading immune detection, leading to a more robust and sustained antitumor response. A clinical study provided early evidence that the combination of RT and ICIs can overcome resistance in NSCLC. The NRG-LU002 study is investigating the use of SBRT combined with ICIs in patients with oligometastatic NSCLC. Preliminary data indicates that this combination leads to improved PFS, especially in patients with resistance to initial immunotherapy (109). As this field evolves, combination strategies may also include the use of other immunomodulatory agents, such as vaccines, oncolytic viruses or targeted therapies, to further enhance the immune response and overcome resistance.

## 7. Challenges and considerations

While the combination of RT and immunotherapy offers potential, several challenges and considerations must be addressed to ensure safe and effective implementation in clinical practice. For instance, the treatment approach of combing ICIs with RT could potentially be utilized for any stage of NSCLC. However, it is unclear which stage of NSCLC patients benefit most from this strategy. In addition to locally advanced and metastatic NSCLC, there is randomized evidence to support that patients with early-stage disease also benefit from this combination treatment. A recent study reported the addition of immunotherapy to SABR in patients with early (stage I-II) or recurrent NSCLC with negative lymph node involvement led to notable improvements in event-free survival with tolerable toxicity (110). For early-stage NSCLC, patients have high survival benefit from postresection adjuvant therapy and post SBRT maintenance therapy, and there are numerous ongoing randomized trials to evaluate safety and efficacy of the combination of SBRT with adjuvant immunotherapy.

Not all patients with NSCLC will benefit equally from the combination of RT and immunotherapy. Identifying predictive biomarkers that can guide patient selection is a key area of research. Assessment of PD-L1and PD-1 expression as biomarkers is currently required to determine clinical decisions on use of treatment strategies targeting ICIs (111,112). Since patients with high PD-L1 expression often have an improved response to ICIs, adding RT may not provide a notable benefit compared with patients with low PD-L1 levels, where RT might stimulate an immune response, making them more responsive to ICIs (24,107). The inter- and intra-tumoral heterogeneity of PD-L1 expression, variability in assay platforms and cut-off thresholds and the lack of standardized assessment methods reduce reproducibility and predictive accuracy. Therefore, the utility of PD-L1 testing in the context of combination immunotherapy with RT remains limited.

Preclinical studies have demonstrated that tumor mutational burden (TMB), tumor-infiltrating lymphocytes and DNA mismatch repair (MMR) deficiency are additional important biomarkers of immunotherapy response (113,114). However, the biomarkers are currently under investigation to determine their role in predicting response to combination therapy. Patients with a higher TMB, particularly those with MMR repair deficiency, may be particularly sensitive to RT-induced cellular damage (115). Although the TMB is a promising biomarker, it is less validated and less widely used compared with PD-L1, and its utility for guiding patient selection remains uncertain. There are still advantages and disadvantages associated with the clinical utility of TMB. Personalized treatment approaches based on biomarker analysis may improve outcomes by selecting patients who are most likely to benefit from the combination of RT and immunotherapy, while avoiding unnecessary toxicity in non-responders.

A major challenge in combining RT and immunotherapy is distinguishing between beneficial immune activation and harmful inflammation (116,117). Radiation can stimulate immune responses, but it can also lead to inflammation and tissue damage, particularly in sensitive organs such as the lungs. Thus, it is essential to guard the patients from immune-, radiation- or combined therapy-associated toxicities during combined treatment. With the latest imaging technology, such as image-guided RT for intensity modulated RT, volumetric modulated arc therapy and adaptive radiation therapy, it is possible to detect clinically relevant changes in lung tissue at the early stages of the disease (118-172). Careful monitoring of side effects and the development of strategies to enhance antitumor immunity without triggering excessive inflammation are crucial for the success of this approach.

Designing clinical trials that adequately evaluate the combination of RT and immunotherapy presents unique challenges. These trials need to account for variations in RT dose, fractionation, timing and sequence relative to immunotherapy administration. Furthermore, the heterogeneity of NSCLC, with its diverse molecular subtypes and immune landscapes, complicates the interpretation of trial results. Trial endpoints, such as PFS and OS, must also be carefully selected, particularly in light of the delayed responses often seen with immunotherapy.

Addressing these challenges is essential for optimizing the combination of RT and immunotherapy for clinical use and ensuring that patients receive the maximum benefit from this promising treatment strategy.

## 8. Conclusions

Currently available preclinical and clinical data support the pairing of ICIs with RT. This strategy offers new hope for patients who have not responded to immunotherapy alone. Based on the existing literature, the present review systematically integrated and analyzed the latest clinical research progress in the combined use of immunotherapy and RT for advanced NSCLC in previous years. Firstly, the present review assessed the rationale, safety challenges and management strategies of combined therapy and suggestions for optimizing treatment options were put forward. Secondly, this review comprehensively evaluated the effects of different RT doses and fractionation methods on the efficacy of immunotherapy and proposed strategies for individualized adjustment of RT regimens. Thirdly, the present review explored the mechanism of RT-induced immunomodulatory effects and its potential role in overcoming immune resistance. Furthermore, exploring the mechanistic interaction between RT and immunotherapy, and analyzing optimal sequencing of therapies and RT dose, fraction and target volume may provide new treatment perspectives for patients with advanced NSCLC in the future.

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**Authors' contributions**

Conception and design was performed by QL and SHW. YQC, LHS and YXQ provided administrative support. QL, LYG, HXS and YMD collected and assembled the data. QL, YQC, LHS, YXQ, LYG, HXS, YMD, and SHW performed data analysis and interpretation and wrote the manuscript. All authors read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

Not applicable.

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Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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