

# The Next Frontier in Non–Small Cell Lung Cancer: Synergizing Radiation Therapy and Immune Checkpoint Blockade

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**Abstract:** Immune checkpoint blockade (ICB), which harnesses the body's immune system to recognize and kill cancer cells, has transformed the management landscape for patients with advanced non–small cell lung cancer (NSCLC). Building on the success of this approach, clinical and translational researchers are attempting to augment the benefit of anti–programmed death 1/programmed death ligand 1 monotherapy through the addition of other therapies, such as conventional cancer treatments. This article reviews the potential use of immunotherapeutic strategies combined with radiation therapy in patients with NSCLC, focusing on ICB. It describes the mechanism of action of immune checkpoint inhibitors, summarizes published studies that demonstrate the benefit of immune checkpoint inhibitors in advanced NSCLC, and provides the preclinical and clinical rationale supporting the potential immunologic synergy of radiation and ICB.

## Introduction

As a treatment approach for cancer, immunotherapy has many features that support the potential for long-term benefit. These include, but are not limited to: (1) the specificity of a T cell to a particular tumor antigen; (2) the adaptability of the T-cell response to ongoing genomic/epigenomic changes in tumors; (3) the universality of the presence of a T-cell response as a cancer therapy regardless of tumor type; and (4) the memory of T-cell responses, to maintain long-term immunity against cancer antigens.<sup>1,2</sup>

Anti–cytotoxic T-lymphocyte–associated protein 4 (anti–CTLA-4) antibodies were the first immune checkpoint inhibitors to receive US Food and Drug Administration (FDA) approval, after a late-phase clinical trial demonstrated improved survival with ipilimumab (Yervoy, Bristol-Myers Squibb) in patients with advanced melanoma.<sup>3</sup> This clinical study provided proof of principle for a number of concepts that are central to cancer immunotherapy. For example, a subset of patients derived durable long-term responses, consistent with the phenomenon of immunologic memory.<sup>3</sup>

From here, the immune checkpoint programmed death 1 (PD-1) receptor and its ligand, programmed death ligand 1 (PD-L1), were therapeutically targeted in seminal phase 1 studies that

## Keywords

Abscopal effect, immunotherapy, radiation therapy, SABR, SBRT, stereotactic ablative radiation therapy

demonstrated promising activity in multiple tumor types.<sup>4,5</sup> These findings led to later-phase studies that demonstrated overall survival (OS) benefits for patients with advanced non-small cell lung cancer (NSCLC) in both the second-line setting<sup>6-9</sup> and the first-line setting.<sup>10</sup> Immune checkpoint blockade (ICB) agents that are currently approved or in the late phases of clinical development for NSCLC include two CTLA-4 antibodies (ipilimumab and tremelimumab), two PD-1 antibodies (nivolumab [Opdivo, Bristol-Myers Squibb] and pembrolizumab [Keytruda, Merck]) and three PD-L1 antibodies (atezolizumab [Tecentriq, Genentech], durvalumab [Imfinzi, AstraZeneca], and avelumab [Bavencio, EMD Serono/Pfizer]).

With the recent success of ICB in patients with advanced NSCLC, the next set of clinical and translational studies in this field is focused on achieving greater clinical benefit by combining ICB with other cancer treatments.

Radiation therapy (RT) has several clinical indications in patients with NSCLC. RT may be used as palliative therapy in patients with symptomatic metastatic disease,<sup>11</sup> alongside systemic therapy in patients with non-operable stage II and III NSCLC, and as an alternative ablative therapy for the management of stage I NSCLC when surgery is either declined or not possible.<sup>12</sup> Preclinical studies and clinical case reports offer support for the synergistic effects of RT in enhancing immune response when combined with ICB.<sup>13-16</sup>

This article reviews the potential for combining ICB with different modalities of RT in NSCLC. It describes the mechanism of action of immune checkpoint inhibitors, summarizes the therapeutic benefit demonstrated in clinical trials for anti-PD-1/PD-L1 monotherapy in advanced NSCLC, and provides the preclinical and clinical rationale for combining RT and ICB, sometimes referred to as *immunoRT*. It also provides an overview of the current studies investigating the role of combining these 2 modalities.

## The Mechanism of Action of Immune Checkpoint Inhibitors

Tumors in a host's immune system initially are either eliminated, or maintained in equilibrium or in a dormant state. They need to circumvent the effects of the immune system, however, in order to form clinically apparent cancer, a phase termed *immune escape*.<sup>17-19</sup> ICB tips the balance toward immune-mediated tumor elimination by increasing cytotoxic T-cell activation within the tumor microenvironment. T-cell activation and tumor cell death require 2 signals. The first is T-cell receptor interaction with a tumor antigen (signal 1), and the second is appropriate positive costimulation (signal 2).<sup>1</sup>

In signal 1, the tumor antigen has to be presented to a T-cell receptor bound to a major histocompatibility complex (MHC) molecule of an antigen-presenting cell (APC) or tumor cell. It is postulated that specific tumor types may release larger amounts of tumor antigens for a variety of reasons that may be implicated in the achievement of therapeutic response to ICB.<sup>20,21</sup>

After signal 1 is achieved, signal 2 involves the achievement of a positive costimulation signal between APCs, such as dendritic cells, and T cells to induce T-cell activation at the level of the tumor microenvironment. Specifically, signal 2 involves engagement of the B7 family of protein receptors on APCs to the CD28 receptor present on T cells. The combination of both signal 1 and signal 2 then induces T cells to become activated, such that they proliferate and functionally differentiate. Activated T cells also simultaneously induce coexpression of proteins involved in inhibitory pathways that govern signal 2, such as CTLA-4 and PD-1 on T cells, as a negative feedback to prevent continued immune stimulation and to ensure that T-cell activation does not continue unchecked within the host tissues.

Immune checkpoint inhibitors have distinct pathways. Anti-CTLA-4 antibodies, such as ipilimumab, interfere with the positive costimulation of naive and resting T-cell clones early in the T-cell activation cascade.<sup>22</sup> CTLA-4 receptors are expressed on T cells as a result of early T-cell activation and interleukin 2 production.<sup>23,24</sup> The CTLA-4 receptor is highly homologous to CD28 and binds with high affinity to the B7 molecule on APCs, thus breaking the positive costimulatory signal early in the activation process.<sup>23,25</sup>

PD-1/PD-L1 blockade affects T-cell activation later in the cycle than does CTLA-4 blockade. The PD-1 receptor that may be found on both T cells and tumor cells has 2 ligands, PD-L1 and PD-L2, which are also molecules in the B7 family. Activated T cells limit uncontrolled cytotoxic T-cell attack by producing interferon gamma, which induces PD-L1 expression on other APCs and nonimmune cells (epithelial and endothelial cells).<sup>26</sup> In a preclinical chronic viral infection model, blockade of the immunosuppressive PD-1/PD-L1 pathway restored functionally exhausted cytotoxic T cells, where PD-1 receptor upregulation was present.<sup>27</sup> PD-1 also may be constitutively expressed on T cells and tumor cells through a variety of mechanisms.<sup>28</sup>

## Trials of ICB in Advanced NSCLC

The success of ICB was recently demonstrated in advanced NSCLC. This discussion is limited to the currently approved immune checkpoint agents in advanced NSCLC.

Regarding PD-1 inhibitors, nivolumab resulted in a 3-month (9.2 vs 6.0 months) median OS benefit and a 1-month (3.5 vs 2.8 months) median progression-free survival (PFS) benefit in the second-line setting in patients with advanced squamous cell lung cancer compared with docetaxel.<sup>6</sup> In a subset analysis, all patient groups benefited regardless of PD-L1 expression on tumor specimens. Subsequently, a phase 3 trial of nivolumab administered in the second-line setting to patients with nonsquamous NSCLC also demonstrated a 3-month median OS benefit in this population compared with docetaxel.<sup>7</sup> The objective response rates with nivolumab were 19% and 20% in the respective studies, with an incidence of grade 3 or 4 toxicity of 7% and 10%, respectively.<sup>6,7</sup>

In KEYNOTE-010 (Study of Two Doses of Pembrolizumab Versus Docetaxel in Previously Treated Participants With Non-Small Cell Lung Cancer), a randomized phase 2/3 study, pembrolizumab was first studied at 2 dose levels (2 mg/kg and 10 mg/kg) in the second-line setting for previously-treated NSCLC with a PD-L1 expression of at least 1%.<sup>8</sup> Pembrolizumab 2 mg/kg and 10 mg/kg resulted in a 2- to 4-month (10.4 and 12.7 vs 8.5 months) median OS benefit compared with docetaxel in all patients, without a difference in median PFS. In a subset analysis of tumors with at least 50% PD-L1 expression, the corresponding doses of pembrolizumab resulted in a 7- to 9-month (14.9 and 17.3 vs 8.2 months) OS benefit, and an approximate 1-month (5.0 and 5.2 vs 4.1 months) benefit compared with docetaxel, with a 13% to 15% adverse event rate. The FDA subsequently approved first-line pembrolizumab in October 2016 for the treatment of advanced NSCLC with at least 50% PD-L1 expression.<sup>29</sup> In a phase 3 trial, pembrolizumab given in a fixed dose resulted in a 6-month (10.3 vs 6.0 months) PFS benefit compared with platinum doublet chemotherapy. Median OS data from KEYNOTE-024 (Study of Pembrolizumab Compared to Platinum-Based Chemotherapies in Participants With Metastatic Non-Small Cell Lung Cancer) have not yet matured, but the 1-year OS rate was superior with pembrolizumab than with standard chemotherapy (70% vs 55%).<sup>10,30</sup> Pembrolizumab also demonstrated a 17% (45% vs 28%) improvement in the objective response rate, with a 27% rate of grade 3 or greater adverse events compared with 53% for chemotherapy.

Regarding PD-L1 inhibitors, atezolizumab demonstrated a 4-month (15.6 vs 11.2 months) median OS benefit compared with second-line docetaxel in patients with nonsquamous NSCLC, and a 2-month (8.9 vs 7.7 months) median OS benefit in patients with squamous NSCLC.<sup>31</sup> The majority of patients (52%) who responded to atezolizumab demonstrated an ongoing response at the time of data analysis, with grade 3 or

greater treatment-related adverse events occurring in 15% of patients.

Given the success of immune checkpoint inhibitors compared with first-line and second-line chemotherapy in the above phase 3 trials, clinical studies are now evaluating the potential role of combination immunotherapy and conventional chemotherapy. KEYNOTE-021 (A Study of Pembrolizumab in Combination With Chemotherapy or Immunotherapy in Participants With Lung Cancer) was a phase 2 randomized study that tested the efficacy of adding pembrolizumab to standard carboplatin/pemetrexed doublet chemotherapy in untreated stage IIIB or advanced NSCLC vs chemotherapy alone.<sup>32</sup> KEYNOTE-021 demonstrated a signal for combinatorial immunotherapy, improving median PFS by 5.9 months, with a 26% improved objective response rate, but similar OS. This further supports evaluating the combination of immunotherapy and other conventional therapies, such as chemotherapy.<sup>33</sup>

### Preclinical Rationale for Radiation-Induced, Immune-Mediated Tumor Rejection

Classical radiobiology has attributed the likelihood of success of RT-induced cell death to the 4 Rs: (1) the inability of tumor cells to *repair* DNA damage; (2) *redistribution* of tumor cells into the G2/M radiosensitive portion of the cell cycle; (3) *repopulation* with radio-resistant clones; and (4) *reoxygenation* of hypoxic and resistant tumor regions.<sup>34</sup> A potential new radiobiological principle, or a “fifth R”—RT-induced immune-mediated tumor *rejection*—has been proposed.<sup>35-37</sup> In support of RT-induced immune-mediated tumor rejection, an intact immune system was shown to be necessary for successful RT-induced tumor cell death. Lee and colleagues demonstrated that RT resulted in inferior tumor control and survival in immunodeficient mice and in mice with depleted CD8-positive T cells.<sup>38</sup> These investigators then showed that in wild-type mice with intact immune systems, RT provided complete local tumor control that translated into improved survival when compared with immunodeficient mice.<sup>38</sup> RT-induced double-strand DNA damage alone was shown here to be insufficient for tumor kill. Consequently, an intact immune system is needed for RT-induced cell death.

RT has been linked to immune activation in preclinical models through: (1) increasing signal 1 by boosting the release of tumor antigens; (2) increasing signal 2 by enhancing APC presentation of tumor antigens; and (3) activating downstream effector T cells (Table 1). Below is a summary of the preclinical evidence supporting RT-induced immune activation leading to downstream immune-mediated tumor cell death.

### ***Radiation Increases T-Cell Activation Signal 1***

RT-induced double-strand DNA breaks lead to tumor cell death via apoptosis, mitotic catastrophe, and necrosis.<sup>39</sup> RT-induced cell death in turn releases tumor peptides that may be foreign to the host's immune system, and thus may increase signal 1. For example, Reits and colleagues demonstrated in a mouse model that RT increased the number of peptides found in intracellular peptide pools, as well as the presentation of new tumor antigen peptides.<sup>40</sup> RT increased the expression of MHC class I molecules, which bind to and present bound antigens to CD8-positive cytotoxic T cells, at the cell surface days after RT in a dose-dependent fashion.<sup>40</sup> Lung cancers, like melanomas, are found to have a tumor mutational load of approximately 175 nonsynonymous mutations per tumor, which is approximately 3 to 5 times higher than the average mutational load (-30–70) in solid tumors.<sup>20</sup> These mutations include somatic DNA mutations that, when translated, provide novel protein sequences—or *neoantigens*—not previously recognized by the immune system. The body develops immune tolerance to unique protein sequences present during fetal development.<sup>41</sup> Somatic DNA mutations that develop after the neonatal learning of self-antigens vs non-self-antigens may generate neoantigens. In patients with metastatic melanoma, an increased neoantigen load of greater than 100 nonsynonymous mutations demonstrated a correlation with clinical benefit in patients treated with anti-CTLA-4 checkpoint blockade in a retrospective study of 25 patients.<sup>21</sup> In patients with NSCLC, a higher nonsynonymous mutational burden was also shown to correlate with an improved response to anti-PD-1 checkpoint inhibition with pembrolizumab.<sup>42</sup> Thus, there is preclinical support for RT to enhance signal 1, or “prime” the immune system, by inducing release of potential cancer neoantigens stored in the tumor and increasing exposure of these neoantigens to the immune system when presented bound to an MHC molecule.

In addition, RT has been shown to enhance APCs' presentation of tumor antigens bound to MHC molecules. RT-induced release of danger-associated molecular patterns (DAMPs) and pro-inflammatory cytokines has been shown to recruit APCs.<sup>43,44</sup> For example, a single high dose of RT was linked to DNA damage-dependent ataxia-telangiectasia mutated (ATM) protein kinase activation and phosphorylation of nuclear factor  $\kappa$ B (NF- $\kappa$ B) essential modulator (NEMO). These signaling pathways were linked to downstream APC functional maturation and activation in preclinical models.<sup>45</sup>

### ***Radiation Increases T-Cell Activation Signal 2 and Downstream Effector T-Cell Recruitment***

As mentioned earlier, signal 2 (the synchronous positive costimulation signal arising from the interaction of the

**Table 1.** Immunogenic Properties of Radiation

<b>Pro-immunogenic Properties of Radiation</b>
1. Increases release of tumor antigens
2. Enhances antigen-presenting cells' presentation of tumor antigens
3. Enhances effector cytotoxic T cells' activation pathways
<b>Immunoradiation Parameters Pending Clarification</b>
1. Exact mechanism of radiation's effect on the immune system
2. Optimal radiation parameters: dose, fraction number, volume, targets
3. Ideal sequencing of radiation with checkpoint blockade agent(s)
4. Ideal patient population to benefit from immunoradiation
5. Incidence of toxicity with immunoradiation
6. Potential biomarkers for immunoradiation response and toxicity

B7 family of proteins located on APCs and the CD28 receptor on T cells) is needed in order to achieve effector cytotoxic T-cell activation. The expression of the costimulatory B7 family of proteins, such as PD-L1, is typically limited to APCs and is less commonly expressed on tumor cells. RT-induced tumor neoantigen release may also overcome the lack of signal 2 within and outside of the tumor microenvironment by recruiting and allowing APCs to take up and present tumor antigens to naive T cells, along with providing a positive costimulatory B7 signal.<sup>2</sup>

Shirabi and colleagues demonstrated in vitro that a single high dose of 12 Gy RT increased antigen-MHC complexes in irradiated cells.<sup>46</sup> Next, they eloquently confirmed in vivo that: (1) RT was associated with an increase in dendritic cell antigen-MHC I complexes in draining lymph nodes; and that (2) APC presentation and signal 2 were needed for RT-induced T-cell activation. By using *MHCI* knockout mice, which could only provide direct antigen presentation and could not provide the costimulatory signal 2 with APCs, RT could not effectively activate T cells. These results supported RT-induced increased uptake of tumor antigens by APCs in the tumor, as well as possible post-RT efflux of APCs to draining lymph nodes to cross-prime T cells. RT is thus being explored as an adjunctive therapy to convert a nonimmunogenic, “cold” tumor to an immunogenic, “hot” tumor, through proposed mechanisms such as increasing tumor antigen release, leading to T-cell receptor engagement needed for signal 1 and increasing signal 2 within the body's immune's system.

Lastly, RT has been associated with downstream T-cell activation. In a mouse model, RT increased the migration of activated tumor-specific T cells into the

tumor microenvironment 7 days after a single, high-dose RT treatment of 10 Gy.<sup>47</sup> RT also has been shown to induce the expression of chemokines, such as C-X-C motif chemokines, which have been associated with T-cell recruitment into the tumor microenvironment.<sup>48</sup>

### ***Preclinical Support for Combined Radiation and ICB***

RT alone is insufficient to induce sustained antitumor immunity as demonstrated by distant relapses in patients with stage I NSCLC treated with ablative RT. RT has been shown to upregulate PD-L1 expression in the tumor microenvironment.<sup>14</sup> The presence of PD-1 expression in the tumor has also been shown to reduce ablative RT tumor control, which does not occur in PD-1-deficient knockout mice.<sup>13</sup> Thus, a next rational step was to investigate the addition of RT to ICB to enhance effector T-cell activation. RT and anti-PD-L1 antibody combinations have been shown to reduce negative regulatory myeloid-derived suppressor cells, which suppress effector T-cell function, in the tumor microenvironment.<sup>14</sup>

In summary, RT has been shown to increase the release of tumor antigens and cytokines as well as to augment antigen presentation and APC priming of effector CD8-positive T cells. RT may be used as an adjunctive stimulus to create a pro-immunogenic tumor microenvironment that, when combined with ICB, may lead to an improved local and systemic cancer response.

## **Clinical Evidence Supporting Immunoradiation in NSCLC**

The ability to induce a concurrent systemic cancer kill for a traditionally local cancer treatment modality adds an exciting role for RT. This is important in tumors such as NSCLC, given that the overwhelming majority of patients with locally advanced NSCLC (>75%) develop distant, recurrent disease that leads to death within 5 years. Additionally, in early-stage disease, high relapse rates translate into a 5-year survival rate of only 70%.<sup>12</sup> The abscopal effect, an immune-mediated systemic cancer kill in areas away from the irradiated site, is a phenomenon that has been postulated and may have been demonstrated in a single patient with melanoma treated with the combination of ipilimumab and RT.<sup>15</sup> However, the abscopal effect is not common and has not been confirmed with RT alone. It is typically reported when RT is combined with immune checkpoint inhibitors or immune-modulating therapies that increase that ability of RT to prime downstream effector T cells.<sup>49</sup>

In NSCLC, the abscopal effect was first demonstrated in a patient with treatment-refractory disease approximately 3 months after combined delivery of palliative RT (30 Gy in 5 treatments) plus concurrent ipilimumab to a

liver metastasis. An excised lymph node not located near the site of irradiation demonstrated a significant reduction in size. Pathologic analysis showed a significant increase in both lymphocyte CD8-positive T cells and a cytotoxic CD8-positive/regulatory forkhead box P3 (FOXP3)-positive T-cell ratio within the excised lymph node.<sup>16</sup>

A proof-of-principle trial showed an abscopal effect in patients who received granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine that stimulates APCs, in addition to RT. In this trial, 41 patients with stable or progressing advanced solid tumors (including NSCLC) receiving chemotherapy also received RT and immune-modulating GM-CSF. Before enrollment, patients had 3 measurable target sites, of which 2 were sequentially irradiated. Twenty-seven percent of the patients had at least a 30% reduction in the size of the third, nonirradiated target lesion, located in a site away from the irradiated areas, with the addition of an immune-stimulating cytokine to RT.<sup>50</sup> In a phase 1/2 trial determining the dose-limiting toxicity of ablative RT given with or 7 days after ipilimumab treatment in patients with solid metastatic tumors, in which the most common malignancy was NSCLC, there was a sign of immunologic memory in sites away from the irradiation area after immunoRT. Twenty-three percent of patients demonstrated a partial response or stable disease in areas outside the irradiated area lasting longer than 6 months with receipt of immunoRT. Laboratory correlates showed an increase in peripheral CD8-positive T cells and the CD8-positive/CD4-positive T-cell ratio in the patients with this immunoRT-induced additional systemic response.<sup>51</sup> Future studies would need to evaluate whether there is an increased systemic response of nontarget lesions in patients with NSCLC who receive immunoRT vs checkpoint blockade alone.

## **Current Trials Investigating Combinatorial Immunoradiation**

Based on the exciting preclinical data and preliminary clinical data summarized earlier, therapeutic clinical trials investigating the role of immunoRT are actively recruiting patients with NSCLC. Here we summarize immunoRT trials in advanced (stage IV), locally advanced (stage III), and early-stage (stage I/II) populations with NSCLC.

### ***Advanced NSCLC Immunoradiation Trials***

In the advanced NSCLC population, the majority of immunoRT trials are an attempt to build upon the demonstrated benefit of checkpoint inhibitors in this population. These immunoRT trials are mainly directed toward either determining the safety and feasibility of the combined immunoRT regimens or investigating the

**Table 2.** Clinical Trials With Radiation and Immune Checkpoint Blockade in Stage IV NSCLC

Identifier	Phase	Trial Name	Radiation	Immune Checkpoint Inhibitor (Target)	Center; Collaborator
NCT02221739	2	Study of Combined Ionizing Radiation and Ipilimumab in Metastatic Non-small Cell Lung Cancer	6 Gy × 5 9.5 Gy × 3	Ipilimumab (CTLA-4)	New York University; BMS
NCT02239900	1/2	Ipilimumab and Hypofractionated Stereotactic Body Radiation Therapy in Advanced Solid Tumors	Hypofractionated SABR 12.5 Gy × 4	Ipilimumab (CTLA-4)	MD Anderson Cancer Center; BMS
NCT02831933	2	Trial of Stereotactic Body Radiation and Gene Therapy Before Nivolumab for Metastatic Non-Small Cell Lung Carcinoma (ENSIGN)	SABR 6 Gy × 5	Nivolumab (PD-1)	Methodist Hospital System
NCT02318771	1	Radiation Therapy and MK-3475 for Patients With Recurrent/Metastatic Head and Neck Cancer, Renal Cell Cancer, Melanoma, and Lung Cancer	8 Gy × 1	Pembrolizumab (PD-1)	Thomas Jefferson University; Merck
NCT02303990	1	RADVAX: A Stratified Phase I Trial of Pembrolizumab With Hypofractionated Radiotherapy in Patients With Advanced and Metastatic Cancers	Hypofractionated RT	Pembrolizumab (PD-1)	University of Pennsylvania
NCT02587455	1	Pembrolizumab and Palliative Radiotherapy in Lung (PEAR)	Palliative RT	Pembrolizumab (PD-1)	Royal Marsden NHS Foundation Trust
NCT02608385	1	Study of PD1 Blockade by Pembrolizumab With Stereotactic Body Radiotherapy in Advanced Solid Tumors	SABR 3-5 fractions	Pembrolizumab (PD-1)	University of Chicago
NCT02444741	1/2	MK-3475 and Stereotactic Body Radiation Therapy (SBRT) in Patients With Non-Small Cell Lung Cancer (NSCLC)	SABR 12.5 Gy × 4	Pembrolizumab (PD-1)	MD Anderson Cancer Center; Merck
NCT02407171	1/2	Evaluating the Combination of MK-3475 and Stereotactic Body Radiotherapy in Patients With Metastatic Melanoma or NSCLC	SABR 6 Gy × 5 10 Gy × 3 10 Gy × 1	Pembrolizumab (PD-1)	Yale University
NCT02658097	2	A Randomized Two Arm Phase II Trial of Pembrolizumab Alone or Sequentially Following Single Fraction Non-ablative Radiation to One of the Target Lesions, in Previously Treated Patients With Stage IV NSCLC	8 Gy × 1	Pembrolizumab (PD-1)	Case Comprehensive Cancer Center
NCT02492568	2	Pembrolizumab After SBRT Versus Pembrolizumab Alone in Advanced NSCLC (PEMBRO-RT)	SABR 8 Gy × 3	Pembrolizumab (PD-1)	Netherlands Cancer Institute; Merck
NCT02463994	1	A Pilot Study of MPDL3280A and HIGRT in Metastatic NSCLC	Hypofractionated RT	Atezolizumab (PD-L1)	University of Michigan
NCT02400814	1	MPDL3280A and Stereotactic Ablative Radiotherapy in Patients With Non-small Cell Lung Cancer	SABR 5 fractions	Atezolizumab (PD-L1)	UC Davis; Genentech

(Table continues on next page)

**Table 2.** (Continued) Clinical Trials With Radiation and Immune Checkpoint Blockade in Stage IV NSCLC

Identifier	Phase	Trial Name	Radiation	Immune Checkpoint Inhibitor (Target)	Center; Collaborator
NCT02383212	1	Study of REGN2810 (Anti-PD-1) in Patients With Advanced Malignancies	Hypofractionated RT	REGN2810 (PD-1)	Regeneron Pharmaceuticals
NCT03035890	N/A	Hypofractionated Radiation Therapy to Improve Immunotherapy Response in Non-Small Cell Lung Cancer	Hypofractionated RT 8-15 Gy × 3 6-10 Gy × 5	Nivolumab (PD-1) Pembrolizumab (PD-1) Atezolizumab (PD-L1)	West Virginia University
NCT02696993	1/2	Trial of Nivolumab With Radiation or Nivolumab and Ipilimumab With Radiation for the Treatment of Intracranial Metastases From Non-Small Cell Lung Cancer	Brain SRS or whole-brain RT	Ipilimumab (CTLA-4) Nivolumab (PD-1)	MD Anderson Cancer Center; BMS

BMS, Bristol-Myers Squibb; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HIGRT, hypofractionated image-guided radiotherapy; N/A, not applicable; NHS, National Health Service; NSCLC, non-small cell lung cancer; PD-1, programmed death 1; PD-L1, programmed death ligand 1; RT, radiation therapy; SABR, stereotactic ablative RT (also known as SBRT, stereotactic body RT); SRS, stereotactic radiosurgery.

potential increased systemic efficacy of ICB with the addition of RT (Table 2).

Trials investigating immunoRT in patients with advanced NSCLC who have brain metastases deserve further mention. Brain metastases develop in up to 44% of patients with advanced NSCLC.<sup>52</sup> Noninvasive stereotactic brain RT or whole-brain RT is often considered the preferred treatment modality for these patients in light of: (1) the frequency of multiple lesions at presentation; (2) the worse prognosis of these patients; and (3) the poor brain penetration of standard chemotherapeutic agents. A phase 2 study showed a promising response to the anti-PD-1 agent pembrolizumab in patients with PD-L1-positive NSCLC and brain metastases (33%; 6/18). Of note, these patients had untreated or progressive nonsymptomatic brain metastases.<sup>53</sup> The ongoing efficacy of ICB in patients with central nervous system involvement is being investigated. A phase 2 trial is assessing pembrolizumab in patients with advanced solid tumors and leptomeningeal disease who did not receive prior PD-1 checkpoint blockade, with a primary outcome of radiographic response.<sup>54</sup> As a class, brain immunoRT trials will help to clarify the safety of combined ICB and RT of the brain. With the brain being the neurologic and endocrine command center of the body, patients with advanced NSCLC who have spread of disease to the brain may have increased neurologic toxicity as well as potential for extracranial disease progression and may benefit from synchronous local treatment to the brain and continued immunotherapy to the body. If safe, the potential ability of brain immunoRT to increase an extracranial systemic response is an exciting treatment combination. Johns Hopkins has a clinical trial in development for patients with NSCLC who have 1 to 5

brain metastases that is evaluating the role of stereotactic radiosurgery combined with the anti-CTLA-4 agent tremelimumab and the anti-PD-L1 agent durvalumab.

#### **Locally Advanced NSCLC Immunoradiation Trials**

Although thoracic RT is delivered as a standard treatment in patients with unresectable locally advanced NSCLC, it is unknown whether it is safe and feasible to deliver thoracic RT alongside ICB, or to deliver consolidation ICB after definitive chemoradiation. There is concern for potential increased immunotherapy-related pneumonitis when ICB is combined with thoracic RT. Less than 10% of patients who receive anti-PD-1/PD-L1 agents experience a grade 3 or 4 adverse event, with 1% to 5% developing treatment-related pneumonitis.<sup>6,29,55,56</sup> An increase in grade 3 or greater pneumonitis was seen in only 4% of those treated with combined anti-PD-L1/CTLA-4 checkpoint blockade in a phase 1 study.<sup>57</sup> Only 4% to 8% of patients receiving definitive chemoradiation developed grade 3 or greater RT-related pneumonitis in the most recent trials evaluating definitive chemoradiation, although 20% to 30% experienced grade 2 or greater RT pneumonitis.<sup>58,59</sup>

Five of the open clinical trials in locally advanced NSCLC are currently evaluating the feasibility of current or adjuvant ICB (Table 3). There is only one ongoing phase 3 trial, RTOG 3505 from the Radiation Therapy Oncology Group, which is evaluating the survival benefit of consolidation anti-PD-1 treatment compared with placebo.<sup>60</sup>

In patients with resectable stage IIIA NSCLC, induction chemoradiation for patients with mediastinal node involvement improved PFS as well as OS in the subset of patients undergoing lobectomy.<sup>61</sup> Johns Hopkins has a pending pilot trial evaluating induction immunoRT in a

carefully selected cohort of patients with resectable stage IIIA NSCLC. Safety and feasibility of neoadjuvant immunoRT with the anti-PD-L1 agent durvalumab (cohort 1) with or without the anti-CTLA-4 agent tremelimumab (cohort 2) during and after thoracic RT and prior to surgical resection are being studied.

### ***Early-Stage NSCLC Immunoradiation Trials***

Stereotactic ablative RT (also known as SBRT [stereotactic body RT] or SABR) provides greater than 90% primary tumor control and offers a curative treatment option in patients with early-stage NSCLC who are medically inoperable or decline surgery.<sup>62</sup> Preliminary 5-year long-term results show persistent primary tumor control of greater than 90%, but a high 5-year rate of locoregional failure (38%) and distant failure (31%).<sup>63</sup> Thus, even in early-stage NSCLC, there is a potential for immunoRT to enhance local control and increase cross-priming and activation of T cells to improve systemic cancer control. Preliminary results of a phase 2 trial showed that preoperative anti-PD-1 inhibition was safe to administer in patients with earlier-stage NSCLC prior to surgical resection, and resulted in major pathologic responses in just under half of patients.<sup>64</sup> There are currently three open phase 1/2 trials evaluating SBRT together with ICB in stage I NSCLC, with endpoints of maximum tolerated dose of atezolizumab given concurrently with SBRT (NCT02599454), event-free survival benefit owing to the addition of nivolumab to SBRT compared with SBRT alone (NCT03110978), and safety and tolerability of concurrent and adjuvant use of the anti-PD-L1 agent avelumab with SBRT (NCT03050554; Table 3).

### **Outstanding Questions When Combining RT and ICB**

Although immunoRT has both preclinical and clinical data that would support ongoing clinical investigation, several unanswered questions remain that deserve further consideration (Table 1). These include: (1) What are the mechanisms of immunologic synergy with RT and ICB in a patient receiving this combination? (2) What are the optimal RT parameters, including dose, fractionation, volume, and targets that would best synergize RT and ICB? (3) What is the ideal sequencing of RT with ICB? (4) What is the ideal patient population in which immunoRT may achieve a synergistic effect that will translate into a clinical benefit? (5) What will the incidence be of toxicity with these combinations, and will this limit the ability to use immunoRT in clinical practice? (6) Finally, what are the potential biomarkers for response with this combination, and will their assessment in human biospecimens be limited by RT fibrosis or scar tissue formation?

The immune system is complex owing to an interplay of a multitude of coinhibitory signals (LAG-3, TIM-3, BISTA, and BTLA-4) and costimulatory signals (including but not limited to ICOS, OX40, and 41BB).<sup>2</sup> Our understanding of the mechanistic interactions between RT and the immune system is crude. In addition to preclinical studies that have linked RT with enhancement of the immune-mediated antitumor effect, RT has anti-immunogenic properties. For example, RT activates transforming growth factor beta, an immunosuppressive cytokine in the tumor microenvironment,<sup>65</sup> and can attract immunosuppressive cells such as regulatory T cells to the tumor.<sup>46</sup> These contradictory immune effects found to be induced by RT may be akin to the dual costimulatory and coinhibitory signals found in the process of cytotoxic T-cell activation, with signals tipping the immune system's balance of positive and negative feedbacks toward immune activation. The anti-immunogenic effects of RT also point to a need to optimize RT parameters to promote the pro-immunogenic and to reduce the anti-immunogenic effects induced by RT alone and when RT is combined with ICB.

The optimal RT parameters needed to best synergize immunoRT are unknown. This is highlighted by the presence of 16 open early-phase trials investigating immunoRT in patients with advanced NSCLC (Table 2). In terms of RT dose, it is not known whether lower total-dose, palliative RT is as effective as higher-dose, curative or ablative RT in inducing an immune response. RT also can be delivered in a single treatment or over many treatments, known as fractions. Fractionated RT allows for normal tissue repair between treatments and decreased long-term side effects. In a mouse model, fractionated RT (but not single-dose ablative RT) induced an abscopal effect when combined with an anti-CTLA-4 antibody.<sup>66</sup>

Regarding RT volume, it needs to be determined whether large-volume RT should be avoided. Large-volume RT has been shown to lower blood counts, as seen in total body RT, which was used as a priming mechanism for bone marrow transplants. Circulating white blood cells also are exquisitely radiosensitive.<sup>67</sup> It is possible that large-volume RT depletes the pool of circulating lymphocytes needed to mount a systemic immune response. However, large-volume RT—targeting both the primary tumor and involved lymph node(s)—is needed for curative treatment in patients with nonoperable, locally advanced NSCLC. Nearby draining lymph nodes are often included in these RT targets, or are otherwise exposed to low-dose RT. As noted in preclinical studies, the draining lymph node is a site of T-cell cross-priming.<sup>46</sup> It is unknown whether large-volume RT, which may include draining nodal basins, should be avoided. SBRT provides an opportunity to deliver

**Table 3.** Clinical Trials With Radiation and Immune Checkpoint Blockade in Locally Advanced and Earlier-Stage NSCLC

Identifier	Phase	Trial Name	Radiation	Immune Checkpoint Inhibitor	Center; Collaborator
<b>Stage III NSCLC</b>					
NCT02434081	2	Nivolumab Consolidation With Standard First-line Chemotherapy and Radiotherapy in Locally Advanced Stage IIIA/B Non-Small Cell Lung Carcinoma (NICOLAS)	EBRT	Nivolumab (PD-1)	European Thoracic Oncology Platform; BMS
NCT02768558	3	Cisplatin and Etoposide Plus Radiation Followed by Nivolumab/Placebo for Locally Advanced NSCLC (RTOG 3505)	EBRT	Nivolumab (PD-1)	RTOG Foundation; BMS
NCT02621398	1	Pembrolizumab, Paclitaxel, Carboplatin, and Radiation Therapy in Treating Patients With Stage II-III B Non-Small Cell Lung Cancer	EBRT 6 wk	Pembrolizumab (PD-1)	Rutgers; National Cancer Institute; Merck
NCT02343952	2	Consolidation Pembrolizumab Following Chemoradiation in Patients With Inoperable/Unresectable Stage III NSCLC (HCRN LUN14-179)	EBRT 6-8 wk 1.8 Gy × 33-37	Pembrolizumab (PD-1)	Hoosier Cancer Research Network; Genentech
NCT03102242	2	Atezolizumab Immunotherapy in Patients With Advanced NSCLC	EBRT	Atezolizumab (PD-L1)	Alliance Foundation Trials
NCT02525757	2	MPDL3280A With Chemoradiation for Lung Cancer (DETERRED)	EBRT 6-7 wk 2 Gy × 30-33	Atezolizumab (PD-L1)	MD Anderson Cancer Center; Genentech
<b>Stage I/II NSCLC</b>					
NCT03110978	2	Clinical Trials Comparing Immunotherapy Plus Stereotactic Ablative Radiotherapy (I-SABR) Versus SABR Alone for Stage I, Selected Stage IIa or Isolated Lung Parenchymal Recurrent Non-small Cell Lung Cancer: I-SABR	SABR 12.5 Gy × 4 7 Gy × 10	Nivolumab (PD-1)	MD Anderson Cancer Center; BMS
NCT02599454	1	Atezolizumab and Stereotactic Body Radiation Therapy in Treating Patients With Non-small Cell Lung Cancer	SABR 12.5 Gy × 4 10 Gy × 5	Atezolizumab (PD-L1)	UC Davis; Genentech
NCT03050554	1/2	Stereotactic Body Radiation Therapy (SBRT) Combined With Avelumab (Anti-PD-L1) for Management of Early Stage Non-Small Cell Lung Cancer (NSCLC)	SABR 12 Gy × 4 10 Gy × 5	Avelumab (PD-L1)	UC San Diego; Pfizer

BMS, Bristol-Myers Squibb; EBRT, external beam radiation therapy; NSCLC, non-small cell lung cancer; PD-1, programmed death 1; PD-L1, programmed death ligand 1; RTOG, Radiation Therapy Oncology Group; SABR, stereotactic ablative RT (also known as SBRT, stereotactic body RT); wk, weeks.

high-dose RT to small-volume targets, with rapid RT dose fall-off. SBRT may significantly reduce possible detrimental exposure of draining lymph nodes and circulating hematopoietic cells to RT, and therefore may be a preferred RT treatment modality for investigating

synergy between RT and ICB.

In terms of radiation targets, the effect of visceral vs nonvisceral RT targets<sup>68</sup> in inducing an immune response needs to be clarified. A phase 1 study in stage IV NSCLC found that ablative RT of liver targets among visceral

organ targets included in the study was associated with improved systemic responses.<sup>51</sup>

In addition, the ideal patient population for immunoRT needs to be identified. Some outstanding questions include: In which stage of NSCLC would immunoRT be most beneficial? For example, would the greatest immunoRT benefit be among patients with a low burden of advanced disease, such as those with limited (1 to 3 sites) oligometastatic involvement? Is immunoRT beneficial in the subset of patients with advanced NSCLC who have brain metastases, in whom the blood-brain barrier traditionally prevents penetration of standard chemotherapeutics?

Finally, it is unknown if RT to the chest will increase the risk of clinical pneumonitis and limit delivery of immunoRT, given the known risks of immunotherapy-related pneumonitis and RT-related pneumonitis. Biomarkers for immunoRT response and toxicity have yet to be explored.

There is a clear need to systematically study RT parameters to best synergize RT with ICB.

## Conclusion

Identifying how RT can improve clinical outcomes seen with ICB in patients with NSCLC is an area under active study. With the emergence of ICB in patients with advanced NSCLC, and its demonstrated response and survival benefits, the next frontier is to clarify how RT can be combined with ICB to further synergize immune response. A systematic approach is clearly needed for studying RT-induced immune-mediated tumor rejection, changes in immunologic parameters as a result of immunoRT, and optimal clinical combinations of RT with ICB. Indeed, with the growing field of immunotherapy and other immunotherapeutic strategies—including the use of adoptive T-cell therapy, cancer vaccines, and chimeric antigen receptor T-cell therapy—various combinations are under active study in different solid tumors and hematologic malignancies. Future studies will examine combinations of these agents and RT, with the intent of improving clinical outcomes for patients with many types of cancer.

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