



# Is radiotherapy the missing link to enhancing the outcomes in non-small cell lung cancer patients treated with immunotherapy?

Ritchell van Dams<sup>1</sup>, David Raben<sup>2</sup>, Percy Lee<sup>1</sup>

<sup>1</sup>Department of Radiation Oncology, University of California, Los Angeles, USA; <sup>2</sup>Department of Radiation Oncology, University of Colorado, Denver, USA

**Contributions:** (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Percy Lee, MD. 200 UCLA Medical Plaza, Suite B265, Los Angeles, CA 90095, USA. Email: PercyLee@mednet.ucla.edu.

**Abstract:** Significant improvements in outcomes for locally advanced and metastatic non-small cell lung cancer (NSCLC) have been seen with increased use of immune checkpoint inhibitors (ICIs), and their role in the treatment of early-stage NSCLC is a subject of active investigation. Mounting evidence from preclinical and clinical trials involving immunotherapy for NSCLC has demonstrated the importance of understanding the tumor microenvironment (TME) and the host anti-tumor response. Incorporation of radiation, specifically in hypofractionated regimens, may potentiate the anti-tumor response stimulated by ICIs and thereby improve the efficacy of immunotherapy for these patients. Additional studies are in progress to determine the optimal sequence, dose, fractionation, and duration of combination therapy.

**Keywords:** Non-small cell lung cancer (NSCLC); immunotherapy; stereotactic body radiotherapy (SBRT); immune checkpoint inhibitors (ICIs)

Received: 08 November 2018; Accepted: 17 December 2018; Published: 30 December 2018.

doi: 10.21037/tro.2018.12.08

**View this article at:** <http://dx.doi.org/10.21037/tro.2018.12.08>

## Introduction

Although lung cancer remains the leading cause of cancer death worldwide, significant advances in outcomes have been achieved with the introduction and increased use of immunotherapy for non-small cell lung cancer (NSCLC) in particular. Despite these improvements, currently, there are still substantial cohorts of patients who do not respond to these therapies, resulting in active research efforts to identify and enhance the mechanism of response to these immune checkpoint inhibitors (ICIs). Clinical evidence has shown that the tumor microenvironment (TME), and specifically the type, ratio, and location of key immune cells can have a dramatic impact on patient survival (1). This has led to a framework of classifying tumors by their immunogenic profile, into “hot” tumors with a high proportion of infiltrating cytotoxic T cells (CTLs) compared to “cold” tumors with limited T cell

infiltration (2). In this review we discuss the evolving nature of the TME and its effect on tumor progression, the role of radiation in altering the immunologic profile of the TME, and preclinical and clinical data supporting the use of radiation as a tool to convert “cold” tumors to “hot” ones, thereby potentially increasing the efficacy of ICIs.

## Biology of stereotactic body radiation therapy (SBRT) and the immune system

### *The TME and immune checkpoint inhibition*

A growing body of evidence supports the concept of a complex and ever-changing interaction between the host immune system and the tumor within the TME. This interplay is thought to progress through phases described by the three *Es* of cancer immunoediting: (I) cancer immunosurveillance and attempts at tumor *elimination*; (II)

selection of tumor clonogens with lower immunogenicity that exist in *equilibrium*; and (III) the emergence of immune-resistant clonogens that ultimately *escape* attempts by the host immune system (3).

The elimination phase is thought to be a two-part process involving the innate and adaptive host immune system. The innate system begins with identification of early tumor clonogens by natural killer cells and  $\gamma\delta$ -T cells, leading to cytotoxic destruction of these cells (4,5). This pathway of cytotoxic destruction releases damage-associated molecular patterns (DAMPs), including HMGB1 and RAGE, which go on to activate the dendritic cells (DCs) and antigen-presenting cells (APCs) that stimulate the adaptive immune response (6). Mice lacking both B and T cells have been shown to develop spontaneous adenocarcinoma at a higher rate, highlighting the importance of the adaptive immune system for cancer immunosurveillance and elimination (7). These findings have been recapitulated in large cohort analyses of immunosuppressed patients post solid-organ transplant, with increased risk ratios for a variety of cancers with a non-viral etiology, including colon, lung, bladder, and melanoma skin cancers (8,9).

The equilibrium phase is hypothesized to be the result of elimination of the most immunogenic clonogens as above, with resultant selection for cells that can evade detection for prolonged periods of time (10). This hypothesis is supported by a range of clinical findings, including years-long periods of remission followed by eventual relapse, as in cases of MGUS, low-grade B cell lymphoma, and acute myeloid leukemia as well as in cases of transmission of solid tumor from donor to recipient after transplantation (11).

The escape phase is characterized by the development of clonogens that are capable of evading immune detection or downregulation of an effective host response. These clonogens can produce directly suppressive cytokines, such as IL-10 and TFG- $\beta$ , that are capable of suppressing DC maturation and the activation and proliferation of lymphocytes, respectively (12). These tumor cells also demonstrate the ability to alter the ratio of regulatory T cells (Tregs) compared to CTLs, thereby maintaining an immunosuppressive microenvironment (13).

Two mechanisms for this have been identified and targeted in clinical practice to improve host tumor immune rejection. CTLA-4 is a potent negative regulator of T cell activation that interferes with the typical activation signaling pathway between APCs and T cells, limiting the overall pool of activated T cells (14). Anti-CTLA-4 therapy

releases this negative regulation, changing the ratio between activated *vs.* inactivated CTLs (15). The PD-1/PD-L1 axis is perhaps even more central to the maintenance of an immunosuppressive TME. PD-1 is another inhibitory receptor that suppresses T cells that have already been activated, and upregulation of its ligand (PD-L1) by tumor cells has been shown to be a key characteristic of an immunosuppressed TME (16). Targeting of these pathways by anti-CTLA-4 (ipilimumab), anti-PD-1 (pembrolizumab, nivolumab), and anti-PD-L1 (durvalumab, atezolizumab, avelumab) antibodies have shown promise in the treatment of advanced NSCLC (17-19).

### *Radiation-induced immunogenic cell death*

As described above, the mature TME in the escape phase is predominantly immunosuppressive, resulting in uncontrolled growth despite an overall normal host immune system. Radiation, and specifically SBRT, may be able to shift the balance toward immune stimulation as opposed to suppression. This shift in balance may increase the efficacy of ICIs such as ipilimumab, pembrolizumab, and others.

Ionizing radiation effects cell death by directly or indirectly ionizing DNA, leading to single-strand or double-strand breaks that trigger cell death through apoptosis or mitotic catastrophe (20). Cell death in this manner can be immunostimulatory, in a process known as immunogenic cell death (21). These dying tumor cells participate in three key steps that prime an immunostimulatory response: translocation of calreticulin to the cell surface, extracellular release of HMGB1, and extracellular release of ATP (22). The end result of this process is the release of DAMPs that recruit DCs and APCs to activate CD8+ CTLs as part of the adaptive immune response. Notably, this immunostimulatory cascade has been found to be triggered by radiation in a dose-dependent manner (22).

The immunogenic cell death cascade and its resultant activation of CTLs offers a potential synergy with existing drugs that modify immune checkpoint pathways. CTLA-4 and PD-1 are T cell receptors that exhibit a potent inhibitory response, with a hypothesized physiologic role of prevention of autoimmunity (14). Overstimulation of CTLA-4 and upregulated production of the PD-1 ligand (PD-L1) leads to an immunosuppressive TME (14). A potential synergy between the immunostimulatory effect of immunogenic cell death and ICIs is the subject of active preclinical and clinical research.

## Preclinical evidence

There is substantial evidence for a synergistic interaction between radiation and immunotherapy in preclinical models. Due to their approval for human use and active use in clinical practice, it is most instructive to examine the preclinical data as it pertains to anti-CTLA-4 and anti-PD-1/PD-L1 therapies.

Demaria *et al.* identified a synergy between anti-CTLA-4 therapy and high-dose radiation in a mouse model for mammary carcinoma (23). Mice were treated with either an anti-CTLA-4 therapy alone, radiation alone, or both therapies. There was a statistically significant survival advantage and a reduction in lung metastases in the combined therapy group (23). In murine models for melanoma and renal cell carcinoma, wild-type expression of PD-1 was found to compromise the efficacy of SBRT (24). Mice lacking functional PD-1 expression experienced prolonged survival compared to their wild-type counterparts, and notably the introduction of exogenous PD-1 blockade was able to compensate for intact PD-1 expression and recapitulate the survival advantage in the wild-type mice (24).

The most compelling evidence for a synergistic response can be found in a preclinical trial involving blockade of both pathways in combination with radiation. By sampling murine tumors resistant to combined anti-CTLA-4 and radiation therapy, Twyman-Saint Victor *et al.* identified a relationship between tumor resistance and upregulation of PD-L1 on the tumor cells, which was hypothesized to lead to T cell exhaustion within the TME (25). Subsequent PD-L1 blockade was able to reverse this T cell exhaustion phenomenon and improve the overall response rate. They hypothesize that each arm of this combined immunoradiotherapy treatment acts through a distinct mechanism: anti-CTLA-4 therapy for expansion of the overall T cell population, radiation for inducing a favorable ratio between CTLs and Tregs, and anti-PD-L1 therapy to reverse T cell exhaustion (25).

Although the above findings represent a promising frontier of potentially synergistic multi-therapy treatment regimens, much work remains to elucidate optimal dosing, fractionation, and timing of the various interventions. Preclinical trials have identified conflicting results regarding the effect of fractionation, notably with regard to single-fraction “ablative” doses versus fractionated treatment schema. Dewan *et al.* compared three fractionation regimens

(1×20 Gy, 3×8 Gy, and 5×6 Gy) in combination with anti-CTLA4 therapy in a mouse model for breast carcinoma and found 3×8 Gy to be more effective at inducing immune cell infiltration than either the “ablative” single fraction dose or the five fraction regimen with a lower dose per fraction (26). In contrast, a comparison of 1×30 Gy, 10×3 Gy, or 1×30 Gy followed by 10×3 Gy in a murine model for colon tumors not only found increased CTL activation with the single fraction regimen, but found that the addition of extended radiation (i.e., 10×3 Gy) negatively affected survival (27). These apparently contradictory findings are potentially reconciled by a study of dose-fractionation on infiltrating CTLs and suppressor Tregs in a murine melanoma model. In this study, 15 Gy was delivered in 1, 2, 3, or 5 fractions. Notably, CTL infiltration was only induced above 7.5 Gy per fraction, but at 15 Gy in a single fraction suppressor Tregs were also induced, attenuating tumor control (28). An alternative mechanism for this dose-dependence is posited by Vanpouille-Box *et al.*, who identified Treg1 as a DNA exonuclease with an induction threshold above 12–18 Gy (29). At a dose of 8 Gy, below the proposed induction threshold of Treg1, radiation stimulated cytosolic DNA generation with a downstream effect of increased interferon- $\beta$  (IFN $\beta$ ) and CTL recruitment (29). Above this threshold, the exonuclease Treg1 was induced with subsequent degradation of cytosolic DNA and attenuation of IFN $\beta$  production and CTL infiltration (29). Importantly, while one fraction of 8 Gy was shown to increase IFN $\beta$  production, repeated doses below the threshold (e.g., 3×8 Gy) further increased IFN $\beta$  production without inducing Treg1, underscoring a mechanism whereby CTLs could be recruited optimally without the abrogating effects seen at doses >12 Gy (29).

Ultimately, the efficacy of radiation and ICIs is likely dependent on a multitude of factors. In general, however, there is at least moderate evidence that hypofractionated regimens (e.g., 7–8 Gy per fraction) may be more effective than either conventionally fractionated (e.g., 2–3 Gy per fraction) or single fraction regimens for inducing a favorable balance of CTLs to Tregs (30). Ultimately, the findings above are subject to confounding regarding the unknown effect of total treatment dose on the relative recruitment of CTLs and suppressor Tregs into the TME. Beyond these technical hurdles lays the arguably more challenging task of translating these findings in preclinical murine models to effective clinical treatment regimens in human subjects.

## Clinical evidence

Prospective clinical evidence for a potential interaction between radiation and immunotherapy is limited. Most data are from case reports and retrospective analyses. Two reports identify cases of the abscopal effect, in which radiation induces a response in tumor outside the treated field. Two patients with NSCLC and documented treatment resistance to nivolumab were subsequently treated with radiation to limited sites and thereafter experienced reduction not only in the burden of disease at the irradiated site, but at several other lesions outside the treatment field (31,32). These responses are dramatic and promising, but are unfortunately not typical. Significant uncertainties exist regarding optimal induction of the abscopal effect, including single *vs.* multiple/all site irradiation, visceral *vs.* bony treatment sites, and dose/fractionation of irradiation (33).

Larger retrospective analyses of a potential interaction between immunotherapy and radiation have had more muted results. A retrospective study of 146 patients with NSCLC identified no difference in progression-free survival (PFS) associated with radiation prior to nivolumab (34). In contrast, a secondary analysis of patients in the KEYNOTE-001 study identified a cohort of patients treated with pembrolizumab who had also received prior extracranial radiation. Although these patients received prior extracranial irradiation at a median 9.5 months prior to receipt of pembrolizumab, they had significantly longer PFS and overall survival (OS) compared to those who had received pembrolizumab alone and importantly there was no significant difference in grade  $\geq 3$  pulmonary toxicity (35). These findings of the safety and efficacy of prior radiation and ICIs are supported by a single-institution retrospective review of 164 patients, 73 of whom had received prior thoracic radiation. They identified no difference in all-grade or grade  $\geq 2$  pneumonitis as well as a trend toward reduced all-cause mortality in patients who had received prior radiation (HR =0.66, P=0.06) (36). Intriguingly, multivariable analysis revealed reduced all-cause mortality in patients who experienced grade  $\geq 2$  immune-related adverse events (HR =0.45, P=0.03), suggesting a potential overlap between antitumor and auto-immune responses (36).

Secondary analysis of the practice-changing PACIFIC trial in locally advanced NSCLC offers additional evidence regarding the potential for radiation to enhance the effectiveness of ICIs. In this randomized phased 3 trial, patients with stage III NSCLC were randomized to durvalumab (an anti-PD-L1 antibody) or placebo

shortly after standard-of-care chemoradiotherapy, with a hypothesis that prior chemoradiotherapy would upregulate PD-L1 expression and thereby increase the efficacy of subsequent ICI use (37). The trial identified a tripling of median PFS (5.6 *vs.* 17.2 months for durvalumab) and a significant increase in the OS rate at 2 years (55.6% *vs.* 66.3% for durvalumab, P=0.005) as well as median OS (28.7 months *vs.* not reached for durvalumab) (37). Importantly, an unplanned post-hoc analysis of PD-L1 expression in evaluable samples identified a significant benefit in the combined endpoint of disease progression or death for all levels of PD-L1 expression  $>1\%$  (37). In addition, post-hoc analysis of the interval between completion of chemoradiotherapy and initiation of durvalumab also identified improved outcomes in OS (HR 0.42 *vs.* 0.81 for interval  $\geq 14$  days) and PFS (HR 0.39 *vs.* 0.63 for interval  $\geq 14$  days) for patients receiving durvalumab within 14 days of completion of radiation (37,38). These findings potentially support the hypothesis that prior chemoradiotherapy as part of the trial protocol enhanced the efficacy of subsequent ICI therapy, and that a possible synergy exists between early initiation of ICI therapy after radiation. Caution must be exercised in the interpretation of these findings, as they are the results of post-hoc analyses and are subject to hidden imbalances between cohorts (e.g., younger age, higher performance status, and/or lower stage disease in patients receiving early durvalumab).

Early results of one prospective trial are encouraging. This randomized phase II study enrolled 74 patients with advanced NSCLC (64 of which were evaluable) to either pembrolizumab alone or combined therapy with SBRT (3 $\times$ 8 Gy) prior to pembrolizumab (39). They identified a doubling of overall response rate (39% *vs.* 21% in the control group) as well as an increased proportion of responders with 0% PD-L1 expression in the experimental arm (22% *vs.* 5% in the control) (39).

There are several ongoing trials investigating the combined use of SBRT and ICIs. They span a clinical range from early stage NSCLC to locally advanced or metastatic disease, and include both single-agent and dual-agent trials. *Table 1* highlights some ongoing trials examining the combined use of SBRT and ICIs in early-stage NSCLC. Most trials are phase I/II and are nonrandomized investigations of PD-1 or PD-L1 inhibitors in combination with radiation. For example, the trial NCT03050554 (UC San Diego), is a phase I/II nonrandomized study of a non-FDA approved anti-PD-L1 therapy avelumab with lung SBRT in inoperable stage I NSCLC. Another trial,



**Table 1** Ongoing studies of immunotherapy in combination with RT in early-stage NSCLC

Identifier	Phase	Trial name	Radiation	ICI	Center/collaborator
NCT02599454	I/I	Atezolizumab and stereotactic body radiation therapy in treating patients with non-small cell lung cancer	4×12.5 Gy, 5×10 Gy	Atezolizumab (PD-L1)	University of California, Davis; Genentech
NCT02904954	II	Durvalumab (MEDI4736) with or without SBRT in clinical stage I, II and IIIA non-small cell lung cancer	SBRT in 3 daily fractions	Durvalumab (PD-L1)	Weill Medical College of Cornell University; AstraZeneca
NCT03050554	I/II	Stereotactic body radiation therapy (SBRT) combined with avelumab (anti-PD-L1) for management of early stage non-small cell lung cancer (NSCLC)	4×12.5 Gy, 5×10 Gy	Avelumab (PD-L1)	University of California, San Diego; Pfizer
NCT03110978	II	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	4×12.5 Gy, 10×7 Gy	Nivolumab (PD-1)	M.D. Anderson Cancer Center; Bristol-Myers Squibb
NCT03148327	I/II	Astra Zeneca (immune-stereotactic ablative body radiotherapy) ISABR study: randomized phase I/II study of stereotactic body radiotherapy	3×18 Gy, 4×12.5 Gy, 10×6.5 Gy	Durvalumab (PD-L1)	University of California, Los Angeles; AstraZeneca
NCT03217071	II	Pembrolizumab with and without radiotherapy for non-small cell lung cancer	1×12 Gy	Pembrolizumab (PD-L1)	University of California, San Francisco; Merck
NCT03383302	I/II	SBRT with immunotherapy in early stage non-small cell lung cancer: tolerability and lung effects (STILE)	3×18 Gy, 5×11 Gy	Nivolumab (PD-1)	Royal Marsden NHS Foundation Trust; Bristol-Myers Squibb

NCT02599454 (UC Davis) is exploring the anti-PD-L1 drug atezolizumab in a dose escalation trial with SBRT to identify the maximum tolerated dose (MTD) for this combination therapy. In this trial, the anti-PD-L1 therapy is given 24–48 hours before the first fraction of radiation. A larger randomized phase I/II trial, NCT03148327 (UC Los Angeles), is investigating the combination of SBRT with the anti-PD-L1 drug previously shown to increase OS in the setting of stage III NSCLC, durvalumab. Here, the ICI is scheduled for infusion approximately 5 days prior to delivery of SBRT. The use of a randomized control arm in this study and use of similar fractionation schema between these trials will potential allow for post-hoc meta-analyses to determine not only the potential synergistic efficacy of SBRT and ICIs for early-stage NSCLC, but may offer insights into the optimal timing and duration of ICI infusion before and after SBRT. The results of these trials will contribute invaluable to our understanding of the safety

profile and efficacy of lung SBRT and ICIs for early stage NSCLC. Future investigations will undoubtedly build on this body of knowledge to inform yet-unanswered questions about the effects of dose, fractionation, and relative benefit of combined immune blockade.

## Conclusions

Within the span of a few years, our advancing understanding of the TME and its interaction with radiation has opened the door to dozens of new lines of investigation regarding the best use of these interventions. Many questions remain unanswered, including the optimal sequencing of radiation and ICIs, dose fractionation of radiation, and whether a combination of ICIs leads to increased efficacy. There are also critical questions regarding the safety and toxicity profile in the combined use of ICIs and radiation, as evidenced by the predominance of phase I and phase

II studies in this field. Results from these studies will undoubtedly have a profound impact on future practice patterns for the treatment of NSCLC, from early stage to metastatic disease.

## Acknowledgments

*Funding:* None.

## Footnote

*Conflicts of Interest:* D Raben—Merck: Advisory board, AstraZeneca: Advisory board, consultant, Genentech: Advisory board, Nanobiotix: Advisory board, EMD Serono: Advisory board. P Lee—AstraZeneca: Advisory board, speaker bureau, research grant, Viewray: Consultant, educational speaker, Varian: Consultant, educational speaker, Brainlab: educational speaker. R van Dams has no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

1. Galon J, Costes A, Sanchez-Cabo F, et al. Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome. *Science* 2006;313:1960-4.
2. Demaria S, Coleman CN, Formenti SC. Radiotherapy: Changing the Game in Immunotherapy. *Trends in Cancer* 2016;2:286-94.
3. Dunn GP, Old LJ, Schreiber RD. The Three Es of Cancer Immunoeediting. *Annu Rev Immunol* 2004;22:329-60.
4. Girardi M, Oppenheim DE, Steele CR, et al. Regulation of cutaneous malignancy by  $\gamma\delta$  T cells. *Science* 2001;294:605-9.
5. Smyth MJ, Crowe NY, Godfrey DI. NK cells and NKT cells collaborate in host protection from methylcholanthrene-induced fibrosarcoma. *Int Immunol* 2001;13:459-63.
6. Sims GP, Rowe DC, Rietdijk ST, et al. HMGB1 and RAGE in Inflammation and Cancer. *Annu Rev Immunol* 2010;28:367-88.
7. Shankaran V, Ikeda H, Bruce AT, et al. IFN $\gamma$ , and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature* 2001;410:1107-11.
8. Birkeland SA, Storm HH, Lamm LU, et al. Cancer risk after renal transplantation in the nordic countries, 1964-1986. *Int J Cancer* 1995;60:183-9.
9. Penn I. Malignant melanoma in organ allograft recipients. *Transplantation* 1996;61:274-8.
10. Formenti SC, Demaria S. Radiation therapy to convert the tumor into an in situ vaccine. *Int J Radiat Oncol Biol Phys* 2012;84:879-80.
11. Swann JB, Smyth MJ. Immune surveillance of tumors. *J Clin Invest* 2007;117:1137-46.
12. Khong HT, Restifo NP. Natural selection of tumor variants in the generation of “tumor escape” phenotypes. *Nat Immunol* 2002;3:999-1005.
13. Sakaguchi S, Sakaguchi N, Shimizu J, et al. Immunologic tolerance maintained by CD25+ CD4+ regulatory T cells: Their common role in controlling autoimmunity, tumor immunity, and transplantation tolerance. *Immunol Rev* 2001;182:18-32.
14. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252-64.
15. Ribas A. Releasing the Brakes on Cancer Immunotherapy. *N Engl J Med* 2015;373:1490-2.
16. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. *Sci Transl Med* 2016;8:328rv4.
17. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: Results from a randomized, double-blind, multicenter phase II study. *J Clin Oncol* 2012;30:2046-54.
18. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* 2016;375:1823-33.
19. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N Engl J Med* 2017;376:2415-26.
20. Eriksson D, Stigbrand T. Radiation-induced cell death

- mechanisms. *Tumour Biol* 2010;31:363-72.
21. Galluzzi L, Maiuri MC, Vitale I, et al. Cell death modalities: classification and pathophysiological implications. *Cell Death Differ* 2007;14:1237-43.
  22. Golden EB, Apetoh L. Radiotherapy and Immunogenic Cell Death. *Semin Radiat Oncol* 2015;25:11-7.
  23. Demaria S, Kawashima N, Yang AM, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clin Cancer Res* 2005;11:728-34.
  24. Park SS, Dong H, Liu X, et al. PD-1 Restrains Radiotherapy-Induced Abscopal Effect. *Cancer Immunol Res* 2015;3:610-9.
  25. Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature* 2015;520:373-7.
  26. Dewan MZ, Galloway AE, Kawashima N, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res* 2009;15:5379-88.
  27. Filatenkov A, Baker J, Mueller AMS, et al. Ablative tumor radiation can change the tumor immune cell microenvironment to induce durable complete remissions. *Clin Cancer Res* 2015;21:3727-39.
  28. Schae D, Ratikan JA, Iwamoto KS, et al. Maximizing Tumor Immunity With Fractionated Radiation. *Int J Radiat Oncol Biol Phys* 2012;83:1306-10.
  29. Vanpouille-Box C, Alard A, Aryankalayil MJ, et al. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. *Nat Commun* 2017;8:15618.
  30. Demaria S, Formenti SC. Radiation as an immunological adjuvant: current evidence on dose and fractionation. *Front Oncol* 2012;2:153.
  31. Yuan Z, Fromm A, Ahmed KA, et al. Radiotherapy Rescue of a Nivolumab-Refractory Immune Response in a Patient with PD-L1-Negative Metastatic Squamous Cell Carcinoma of the Lung. *J Thorac Oncol* 2017;12:e135-6.
  32. Komatsu T, Nakamura K, Kawase A. Abscopal Effect of Nivolumab in a Patient with Primary Lung Cancer. *J Thorac Oncol* 2017;12:e143-4.
  33. Brooks ED, Chang JY. Time to abandon single-site irradiation for inducing abscopal effects. *Nat Rev Clin Oncol* 2018. [Epub ahead of print].
  34. Kataoka Y, Ebi N, Fujimoto D, et al. Prior radiotherapy does not predict nivolumab response in non-small-cell lung cancer: A retrospective cohort study. *Ann Oncol* 2017;28:1402.
  35. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* 2017;18:895-903.
  36. Hwang WL, Niemierko A, Hwang KL, et al. Clinical Outcomes in Patients With Metastatic Lung Cancer Treated With PD-1/PD-L1 Inhibitors and Thoracic Radiotherapy. *JAMA Oncol* 2018;4:253.
  37. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med* 2018. [Epub ahead of print].
  38. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med* 2017;377:1919-29.
  39. Theelen W, H.Peulen@Nki.Nl, Lalezari F, et al. Randomized phase II study of pembrolizumab after stereotactic body radiotherapy (SBRT) versus pembrolizumab alone in patients with advanced non-small cell lung cancer: The PEMBRO-RT study. *J Clin Oncol* 2018;36:abstr 9023.

doi: 10.21037/tro.2018.12.08

**Cite this article as:** van Dams R, Raben D, Lee P. Is radiotherapy the missing link to enhancing the outcomes in non-small cell lung cancer patients treated with immunotherapy? *Ther Radiol Oncol* 2018;2:66.