

**Letter to the Editor****Introduction to the special edition on immunotherapy and radiation oncology****Sophia Bornstein MD, PhD, Silvia C. Formenti MD\****Department of Radiation Oncology, Weill Cornell Medicine, Weill Cornell Medical College, New York, New York*

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This special edition of *Advances in Radiation Oncology* is focused on the role of radiation therapy in the context of immunotherapy. Radiation therapy has been used for more than 50 years as an effective modality to eradicate gross and microscopic cancer. Over the past few decades, a distinct role for radiation from that of directly killing tumor cells has emerged. Tumor responses outside of the radiated field, or abscopal effects (ab scopus = outside the target), have been described, although they are rare with radiation alone.<sup>1</sup> However, when combined with immunotherapy, abscopal responses are more common.

With the wider use of immunotherapy, multiple case reports have demonstrated dramatic abscopal responses (eg, in patients with melanoma and non-small cell lung cancer).<sup>2,3</sup> Preclinical tumor models demonstrate that radiation exerts distant effects linked to activation of the immune system by inducing tumor-specific effector T-cells through the generation of an in situ vaccine.<sup>4</sup> This mechanism may explain why combinations of radiation and immune-modulating systemic therapies have yielded higher rates of abscopal responses. In the current era of immuno-oncology, in which stimulating the immune system holds the promise of extending survival for patients with advanced cancer, radiation is taking on a new role, that of an “adjuvant” to immunotherapy.<sup>5</sup> This

new role warrants revisiting many of the principles that guide radiation therapy decisions. This issue of the journal consists of a series of critical reviews that outline the goals and challenges of combining radiation and immunotherapy, with a focus on clinical strategies to enhance responses and minimize toxicity.

The first article focuses on the role of radiation dose and fractionation. Historically, radiation was given over several weeks in small daily doses. However, it is now clear that larger fractional doses are needed to prime the immune system,<sup>6</sup> with recent preclinical data indicating there may be an optimum fraction size with a threshold beyond which immunogenicity is hampered.<sup>7,8</sup> To date, there has been little consensus on the optimum dose and fractionation to employ in clinical trials that combine radiation and immunotherapy. Thus, ongoing trials use a range of fractionation schedules including standard fractionation, hypofractionation,<sup>9</sup> and ablative regimens.<sup>10</sup>

The second article focuses on the sequencing of radiation and immunotherapy (whether to deliver them concurrently or sequentially), which is a potentially important consideration in maximizing the therapeutic ratio. Preclinical models have demonstrated that appropriate timing is related to the mechanism of action of the immunotherapy agent used<sup>11</sup> and should inspire translation to the clinic. The third article focuses on the common toxicity of radiation therapy and immunotherapy, as we move into an era in which concurrent treatment will be increasingly common.

The fourth article discusses the role of field size, specifically with regard to how it affects toxicity to circulating normal lymphocytes. As combinations of immunotherapy and radiation progress to trials in the

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\* Corresponding author. Weill Cornell Medicine, 525 East 68th Street, N-046, Box 169, New York, NY 10065-4885.

E-mail address: [formenti@med.cornell.edu](mailto:formenti@med.cornell.edu) (S.C. Formenti).

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curative setting, where traditional larger field sizes are still standard, this issue has significant relevance. To justify a reduction of the margins applied for traditional curative treatments, the prevailing concept of eradication of tumor cells will need to be challenged by the rationale of effectively harnessing the immune system. The risk of compromising some cures will understandably concern most radiation oncologists. Only rigorously conducted prospective clinical trials can address this dilemma.

Another strategy to improve immune responses to radiation involves blocking local immunosuppressive signals, which is the topic of the fifth review. Although recent efforts have largely focused on checkpoint inhibition, promising data targeting novel immunosuppressive cells and molecules are accumulating, with multiple clinical trials evaluating new combinations.<sup>5,12</sup> The responses associated with checkpoint inhibitors are unfortunately restricted to a minority of patients who respond. Even fewer patients have lasting responses, encouraging investigation on overcoming these other immunosuppressive mechanisms, either alone or in combination with checkpoint inhibitors.

The sixth article discusses the importance of DNA damage response in eliciting immune responses to radiation. This includes a description of emerging biomarkers because DNA repair defects and mutational burden are strong predictors of response to immunotherapy. The final article reviews the role of noninvasive molecular imaging in determining response to radiation. As liquid biopsies are beginning to dynamically guide systemic treatment in a patient-specific way, improved noninvasive imaging is likely to further advance radiation treatment planning.

In summary, immunotherapy is a much-needed paradigm shift in cancer treatment with more progress in the past decade affecting tumor response, overall survival, and quality of life than in the several decades prior. Radiation can enhance the proportion of patients who derive a benefit from cancer immunotherapy and the duration of their response. Radiation oncology planning

and delivery is traditionally highly individualized: elucidating patient-specific factors that control tumor response in combination with immunotherapy will advance personalized cancer care.

## References

1. Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. *Curr Probl Cancer*. 2016;40:25-37.
2. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med*. 2012;366:925-931.
3. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. *Cancer Immunol Res*. 2013;1:365-372.
4. Formenti SC, Demaria S. Radiation therapy to convert the tumor into an in situ vaccine. *Int J Radiat Oncol Biol Phys*. 2012;84:879-880.
5. Kang J, Demaria S, Formenti S. Current clinical trials testing the combination of immunotherapy with radiotherapy. *J Immunother Cancer*. 2016;4:51.
6. Golden EB, Frances D, Pellicciotta I, Demaria S, Helen Barcellos-Hoff M, Formenti SC. Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death. *Oncoimmunology*. 2014;3:e28518.
7. Vanpouille-Box C, Formenti SC, Demaria S. TREX1 dictates the immune fate of irradiated cancer cells. *Oncoimmunology*. 2017;6:e1339857.
8. Vanpouille-Box C, Formenti SC, Demaria S. Toward precision radiotherapy for use with immune checkpoint blockers. *Clin Cancer Res*. 2018;24:259-265.
9. Crittenden M, Kohrt H, Levy R, et al. Current clinical trials testing combinations of immunotherapy and radiation. *Semin Radiat Oncol*. 2015;25:54-64.
10. Luke JJ, Lemons JM, Karrison TG, et al. Safety and clinical activity of pembrolizumab and multisite stereotactic body radiotherapy in patients with advanced solid tumors. *J Clin Oncol*. 2018;36:1611-1618.
11. Young KH, Baird JR, Savage T, et al. Optimizing timing of immunotherapy improves control of tumors by hypofractionated radiation therapy. *PLoS One*. 2016;11:e0157164.
12. O'Donnell JS, Long GV, Scolyer RA, Teng MW, Smyth MJ. Resistance to PD1/PDL1 checkpoint inhibition. *Cancer Treat Rev*. 2017;52:71-81.