Radiotherapy plus immune checkpoint blockade in PD(L)-1-resistant metastatic NSCLC

Jonathan D Schoenfeld and colleagues[1] report the findings of a randomised phase 2 clinical trial, in which two radiotherapy regimens known to modulate immune response in preclinical models were tested in patients with metastatic non-small-cell lung cancer (NSCLC) that was resistant to previous PD-(L)1 inhibitor therapy. Radiotherapy was given in combination with dual immune checkpoint blockade (ICB). We commend the authors for incorporating these preclinical notions into a well designed phase 2 trial. Unfortunately, none of the radiotherapy schemes enhanced the overall response rate, and both progression-free survival and overall survival remained unchanged.

The results from this study are clearly disappointing and require some reflection. Translation of preclinical immunoradiotherapy findings into the clinic is more complicated than anticipated.

In Schoenfeld and colleagues' trial, one group tested a hyperfractionated low-dose irradiation scheme of 0·5 Gy administered twice a day for two consecutive days, repeated for each of the first four cycles of therapy (total dose 8 Gy). In the other group, patients received a hypofractionated radiotherapy scheme consisting of three 8 Gy fractions every other day (total dose 24 Gy) during the first cycle of therapy only. Radiotherapy in both groups was started 1 week after initial durvalumab–tremelimumab administration. Importantly, in both groups, radiotherapy was targeted to one or two metastases per patient. The rationale to irradiate a small number of metastases during ICB treatment is based on exciting preclinical findings that show that this strategy triggers distant immune-mediated tumour regression (abscopal effect). Unfortunately, the occurrence of abscopal effects might have been overestimated in patients, and randomised clinical trials have now convincingly proved that they are inherently incidental. Therefore, alternative approaches should be sought to leverage the immune effects of radiotherapy for combination treatments.

Recent clinical data suggest that low-dose irradiation delivered diffusely to multiple or all tumour metastases, combined with ICB and stereotactic body radiotherapy (SBRT) to one or two metastatic deposits, elicits a tumour response in low-dose irradiated lesions,[2] suggesting that the effect of the radiation is due to local immunological reprogramming of the tumour microenvironment while SBRT induces in-situ vaccination.[2] Schoenfeld and colleagues delivered low-dose irradiation to a low number of metastases and presumably did not sufficiently reprogramme the tumour microenvironment in non-irradiated lesions to facilitate an effective antitumour immune response.

Importantly, Schoenfeld and colleagues delivered irradiation 1 week after ICB. Preclinical models indicate that the immunomodulatory effects of radiotherapy are schedule-dependent, and the immunological effects can differ when delivering radiotherapy before or after anti-PD1.[3] Immune reprogramming might be time sensitive, especially when radiotherapy is delivered at low doses, where its immune effects can be short lived as we recently showed in an ovarian cancer mouse model.[4] Similarly, SBRT increases response to tumour neoantigens, which are crucial determinants of ICB response. As a result, T-cell reinvigoration by anti-PD1 should be carefully timed to coincide with the peak of tumour antigen release following radiotherapy.[5] Because therapy sequencing and schedule seem to be particularly important, it is possible that the widely spaced delivery of radiotherapy used by Schoenfeld and colleagues was insufficient to maintain the proinflammatory effects of radiotherapy.

In light of these considerations, what lessons could be learned for future clinical trial development? Hypofractionated radiotherapy delivered to obtain abscopal effects should be best combined with orthogonal systemic approaches to reprogramme the tumour microenvironment. In order to reprogram the tumor microenvironment, all lesions should be irradiated, in which case low-dose irradiation could be a rational choice. Given the short-lived effects, frequent low-dose irradiation could be applied, although the optimal delivery schedules remain to be determined. Indeed, there is a long way to go to determine the optimal radiation dose, fractionation, volumes, and sequencing to trigger strong immune-mediated tumour responses.

We declare no competing interests.

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1 Schoenfeld JD, Giobbie-Hurder A, Ranasinghe S, et al. Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non-small-cell lung cancer refractory to previous PD(L)-1 therapy: an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol* 2022; **23:** 279–91.

2 Barsoumian HB, Ramapriyan R, Younes AI, et al. Low-dose radiation treatment enhances systemic antitumor immune responses by overcoming the inhibitory stroma. *J Immunother Cancer* 2020; **8:** e000537.

3 Wei J, Montalvo-Ortiz W, Yu L, et al. Sequence of αPD-1 relative to local tumor irradiation determines the induction of abscopal antitumor immune responses. *Sci Immunol* 2021; **6:** eabg0117.

4 Herrera FG, Ronet C, Ochoa de Olza M, et al. Low dose radiotherapy reverses tumor immune desertification and resistance to immunotherapy. *Cancer Discov* 2022; **12:** 108–33.

5 Formenti SC, Rudqvist NP, Golden E, et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. *Nat Med* 2018; **24:** 1845–51.