Editorial Commentary

Efficacy of stereotactic ablative radiotherapy (SABR) during anti-PD-1 in oligoprogressive non-small cell lung cancer and melanoma—a prospective multicenter observational study pointing out new unmet needs

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Metastatic non-small cell lung cancer (NSCLC) and melanoma remains one of the main causes of cancer-related death (1). Until recently, standard of treatment consisted of palliative chemotherapy (2,3). The introduction of immunotherapy has significantly changed the prognosis of patients with metastatic NSCLC and melanoma, especially treatment with programmed cell death protein 1 (anti-PD-1) immune checkpoint inhibitors (ICIs), like nivolumab and pembrolizumab. An increasing number of studies demonstrate effectiveness of ICIs over other palliative systemic treatments (2,3). Unfortunately, the actual benefit remains low due to multiple resistance mechanisms (4). To overcome these resistance mechanisms and increase response rates, combination therapies with ICI are investigated. A growing number of reports show that the combination of stereotactic ablative radiotherapy (SABR) and ICI is safe and could increase progression-free survival (PFS) and overall survival (OS) (5-9). There are even reports of spontaneous regression of non-target lesions, also known as the abscopal effect, possibly due to a synergistic effect between SABR and ICI leading to immunogenic cell death (5,10). However, several questions remain unanswered, for example the optimal timing of SABR in combination with ICI, in what patient subgroups it is most effective and what type of response measurement should be used.

In the *International Journal of Radiation Oncology*, *Biology*, *Physics*, Chicas-Sett *et al.* report the results of a prospective multicenter observational study on the combination of SABR with anti-PD-1 ICI in 31 (62%) NSCLC and 19 (38%) melanoma patients (11). All patients were treated concurrently with SABR for 1–5 oligoprogressive lesions during treatment with pembrolizumab or nivolumab, and continued the same anti-PD-1 treatment until further progression, unacceptable toxicity, or medical/patient decision. With a median follow-up of 33 months, they showed an overall response rate of 42%, median PFS of 14.2 months [95% confidence interval (CI): 6.9–29 months] and median OS of 37.4 months (95% CI: 22.9 months–not reached). Abscopal response evaluation was possible in 40 patients and they report an abscopal response (AR) rate of 65%. Grade ≥3 toxicities were seen in 3 patients (6%). The authors conclude that combined anti-PD-1 and SABR in oligoprogressive metastatic NSCLC and melanoma can lead to high response rates and can further extent the

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clinical benefit of immunotherapy by delaying progression and switch of systemic therapy.

The results of this study are noteworthy for several reasons. First, this seems to be the only prospective study to evaluate the efficacy of SABR after progression to anti-PD-1 in patients with metastatic NSCLC and melanoma. So far, only retrospective series evaluated this (7,9,12). The only prospective trials treated patients with SABR at the start of ICI, to potentially increase response rates by boosting the anti-tumor immunity by radiotherapy (6,13,14). In addition, the timing of SABR concurrently with ICI seems to be in line with current literature. For anti-PD-1 inhibitors, like pembrolizumab or nivolumab used in this study, preclinical data suggests that SABR at initiation or concurrently with ICI is critical for the generation of an effective antitumor immune response (15). Furthermore, the authors show a promising overall response rate of 42%, which seems to be comparable to 2 prospective studies treating patients with SABR at the start of ICI, the PEMBRO-RT (8) and MD Anderson Cancer Center (MDACC) trial (6), with response rates of 36% and 38%, respectively. However, this comparison should be done with great caution, as the study of Chicas-Sett *et al.* reports the overall response rate (including irradiated lesions), and the PEMBRO-RT and MDACC trials report the out-of-field response rate. Furthermore, in the PEMBRO-RT trial only 1 lesion and in the MDACC trial up to 4 lesions were irradiated, whereas in this current study up to 5 metastatic lesions where irradiated. A comparison between these response rates is therefore very unreliable and could lead to an overestimation of the response rate of Chicas-Sett *et al.* (11). Nevertheless, their overall response rate of 42% remains auspicious and could be of real clinical importance.

An important emerging clinical question is whether 7 Gy in 5 fractions (fx), with an equivalent dose in 2 Gy fractions (EQD2) (α/β=3) of 70, is the right SABR dose used to treat the progressive lesions (11). Although the authors report that most lesions were thoracic, with corresponding dose-limiting constraints, it can be debated if this is the optimal dose. The pooled results of the PEMBRO-RT and MDACC trial showed that 12.5 Gy in 4 fx, with an EQD2 (α/β=3) of 155, gave the best out-of-field response (13), which is significantly higher compared to the 7 Gy in 5 fx used. However, as stated by a recent review of the literature on this topic, a lack of evidence prevents us from understanding the best fractionation schedule and it might be questionable if there is only one optimal fractionation schedule as the effect might be dependent on the specific drug or on other patient-related factors (16).

The evaluation of ARs was possible in 40 patients, and a considerable number of 26 patients (65%) is reported to show an AR. This number seems to be notably higher compared to the 41.7% AR found in the pooled PEMBRO-RT and MDACC trial (13). One explanation for this difference could be that Chicas-Sett *et al.* also included melanoma patients, who are known to be more immunogenic (3). A question that arises is if all out-of-field regressive lesions are indeed ARs. As these lesions are not biopsy-proven metastases, non-metastatic lesions could be mistakenly regarded as metastases. Infections, sarcoidosis, sarcoid-like reactions or aspergillosis are examples of lesions that could mimic an AR by regressing spontaneously or due to treatments with antibiotics or glucocorticoids (17-21). These doubts are strengthened by the fact that the participating centers only used Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to define response during follow-up. Although this study was a beautiful opportunity to do so, the authors state that the immune-RECIST (iRECIST) (22), the consensus guideline for immunotherapy trials, was not validated yet. As shown by recent qualitative retrospective analysis of 16 metastatic NSCLC and melanoma patients treated with (stereotactic) radiotherapy for oligoprogression during anti-PD-1 treatment, 6 patients (38%) were suspected of an AR by determining with RECIST (12). However, after better assessment of earlier scans and volumetric measurement of these lesions, only 1 lesion (6%) remained suspected of an AR. This data shows the importance of meticulous response measurement in immunotherapy studies and argues that volumetric measurements should be incorporated in future studies.

Another point that should be commented is that they were unable to collect tumor or blood samples during their study, prohibiting evaluation of biomarkers. One interesting biomarker could be the absolute lymphocyte count (ALC), standard blood test in this patient group. More and more reports show that radiotherapy can induce lymphopenia and that this subsequently leads to worse outcomes (23). Recent reports have shown that a reduction in the number of lymphocytes also appears to result in a reduction in the effectiveness of lymphocyte-activating immunotherapeutic agents, like anti-PD-1 treatment (24,25). It would have been very interesting to evaluate the association between response rates in their study and lymphopenia. In addition, the tumors programmed death-ligand 1 (PD-L1) expression may be of interest as a biomarker. In the PEMBRO-RT

trial, subgroup analysis showed that the largest benefit from the addition of radiotherapy was seen in the PD-L1 negative group (hazard ratio 0.49, 95% CI: 0.26–0.94), and they stated that their imbalance between experimental and control groups in terms of PD-L1 expression positive patients (50% *vs.* 60%, respectively) might have influenced their results (8). Unfortunately, information on PD-L1 expression is missing in 68% of patients in the trial of Chicas-Sett *et al.* (11).

In summary, the results of this first prospective trial add further evidence on the efficacy and safety of combining SABR concurrently with anti-PD-1 in oligoprogressive metastatic NSCLC and melanoma patients. However, several questions remain unanswered including the optimal SABR dose, most reliable response evaluation and identification of useful predictive biomarkers of response, like ALC. These unmet medical needs should be addressed in future prospective randomized clinical trials.

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