Editorial Commentary

Increased abscopal responses after radiation therapy for oligoprogressive patients receiving immune checkpoint inhibitors?

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The definition of oligometastatic disease has been recently refined by national societies (1). With advances in systemic treatments, drug exposition time tends to be longer, and a subsequent proportion of patients develop limited acquired resistance or "oligoprogression" while receiving systemic treatments. In this setting, local ablative treatments with stereotactic ablative radiation therapy (SABR) could allow maintaining responses by inducing tumor subclones elimination without modifying systemic treatments. Moreover, some systemic treatments such as immune-checkpoint inhibitors (ICI) and SABR could work together with possible stimulation of radiation immune-stimulatory effects, counteraction of radiation immune-suppressive effects and possible immune-resistance tackling (2). SABR could reinvigorate anti-tumoral immunity by (I) the presentation of new tumoral antigen to the immune system/expansion of neoantigen-reactive CD8 T cells [described in patients by Postow *et al.* (3) and Formenti *et al.* (4)], (II) the increase of immunogenic cell death, (III) the increase of the viral mimicry and (IV) the reversal of vascular barrier as reviewed by Charpentier *et al.* (5). This could ultimately lead to increased radiated out-of-field "abscopal" responses.

The observational study of Chicas-Sett *et al.* (6) is one of the first to prospectively report the efficacy of SABR in advanced melanoma or non-small cell lung cancer (NSCLC) patients showing oligoprogression while on ICI with anti-programmed cell death protein 1 (anti-PD1) (nivolumab and pembrolizumab). SABR was administered concurrently at a dose of 35 Gy (5 fractions) or 24 Gy (3 fractions). Interestingly, brain lesions, partial tumor irradiation (if >65 cc, but % not described afterwards) and patients with oncogenic driver mutations (although low proportion: 8%) could be enrolled. It should also be highlighted that further course of SABR after new oligoprogression was allowed if the patient maintained clinical benefit, and if so, earlier disease progression was not counted. Endpoints included objective response rate (ORR), overall (OS) and progression-free survival (PFS) and an abscopal response was defined as a ≥30% reduction in 1 to 2 predefined non-irradiated lesions at 2 months.

In total, 50 previously treated (median of 2 prior lines of systemic therapy) patients with 76 irradiated lesions were analyzed. Positron emission tomography was performed in 64% of patients [n=32; brain magnetic resonance imaging (MRI) not reported]. The majority (64%) of patients presented more than 5 metastases (polymetastatic disease) but with five or fewer progressive tumor sites while on ICI (median of 6 cycles of ICI; range, 2–43) (6). Halve patients were considered "primary refractory" to ICI. Main irradiated lesions were nodes, lung and bones (83%) and one third of patients (38%) had more than one course of SABR.

Outcomes reported by Chicas-Sett *et al.* are promising. At a median follow-up of 32.8 months, 42% ORR (30%

complete response rate, 12% partial responses) and 10% stabilizations while maintaining anti-PD1 were observed (6). The median OS and PFS, calculated from SABR delivery, were respectively 37.4 and 14.2 months (2-year PFS: 36%). Some non-irradiated tumor sites that presented no further tumor response before SABR also decreased in size or were stabilized after SABR. This abscopal effect was observed in 26/40 (65%) evaluable patients, with improved outcome in this subgroup of patients as compared to other patients (median PFS of 21.2 *vs.* 3 months, respectively; P<0.0001).

Although it may not be directly compared, Results of Chicas-Sett et al. exceeded outcomes observed with single agent ICI in pre-treated patients or retrospective reports in oligoprogressive patients (7,8). Only one early report of a randomized trial (CURB) is available in this setting (9). Tsai *et al.* evaluated in advanced NSCLC or breast cancer with five or fewer oligoprogressive lesions standard of care with systemic therapy (almost 50% patients with ICI) +/– SBRT to oligoprogressive sites. PFS was increased in the 59 patients with NSCLC after SBRT (44 *vs.* 9 weeks; P=0.001) but no difference was observed in the 47 patients with breast cancer (P=0.48).

Beside randomized trial, the strategy of adding a local treatment in oligoprogressive patients is also the only, scientific way to prove that the abscopal effect exist. The definition of the abscopal response is however not standardized. Many non-randomized report-initiated ICI and SABR concurrently with uncertainties regarding additional abscopal responses. Formenti *et al.*, Saiag *et al.*, and Sumodhee *et al.* observed a 18%, 31.5% and 9.5% abscopal response rates, respectively, and a 10%, 0% and 9.5% stable disease rates, respectively (4,10,11).

The high abscopal response rate observed by Chicas-Sett *et al.* could be partially biased since authors included few patients (median: 6 cycles) that only received 2 ICI cycles (6). For such patients, progression could have been pseudoprogression and not true progression, reflecting delayed response on ICI. The pseudoprogression rate among solid tumors is around 10–15% [reviewed by Wang *et al.* (12)], which is consequently not a frequent event. The use of stereotactic technique as compared to conventional radiotherapy or limited volume/partial irradiation may have also played a role since the limited dose delivered to healthy organs could decrease radiation-induced lymphopenia (RIL) (13). Correlation between survival and RIL was demonstrated in many cancers (14). Techniques such as lymph-node sparing radiotherapy, proton therapy or the use of fewer (15) fractions (less than 5) could potentially limit RIL since lymphocytes are highly radiosensitive [0.95 Gy causing 37% of cell death (16)]. The best dose per fraction is anyway unknown. According to Vanpouille-Box *et al.* the amount of cytosolic DNA which reflects the immunogenicity of tumor cells, depends on the dose per fraction (17). Interestingly, most studies that reported abscopal response used dose per fraction less than 10 Gy: 9.5 Gy for Postow *et al.* (3), 6–9.5 Gy for Formenti *et al.* (4), 7–8 Gy for Chicas-Sett *et al.* (6), 6 Gy for Saiag *et al.* (10) and Sumodhee *et al.* (11). Of note, in these studies abscopal response was not only observed after SABR but also after conventional 3-dimensional conformal radiotherapy.

Only few randomized trials assessed the addition of SABR in patient's receiving ICI. A pooled analysis of two phase 2 randomized studies already demonstrated survival benefit in advanced NSCLC if pembrolizumab was combined with radiotherapy, concurrently with pembrolizumab (18). At the opposite, two randomized phase II trial showed no additional effects of SABR. In 62 patients with advanced head and neck squamous cell carcinoma (HNSCC) the addition of 3×9 Gy was assessed on 1 target between the first and second cycle of nivolumab: no survival benefit was observed (19). Another randomized phase II trial assessed nivolumab-ipilimumab +/– SABR (3×8 Gy to one lesion) in 50 patients (50% ICI naïve only) advanced Merkel cell carcinomas (20). No difference of ORR was observed between the two arms. Although the dose per fraction and number of fractions seemed appropriate, the limited number of radiated targets could have limited he efficacy of SABR given it did not consider the tumor heterogeneity (21,22). Some primary tumors such as HNSCC carcinomas could not be a good model for this association yet suggested in earlier stages (23). Finally, the best ICI-SABR sequence is unknown. Preclinical data suggest indeed that irradiation after the beginning of ICI reduces lymphocyte infiltration and the magnitude of the abscopal effect (24).

Several phase III trials are ongoing (25), testing the association of radiotherapy with ICI (NCT03391869, NCT03774732, NCT04929041, NCT04402788, NCT04944914, NCT04747054) with some focusing on oligoprogression (CURB, STOP: NCT02756793). Prospectively clinical and surrogate predictive biomarkers are eagerly needed for selecting oligoprogressive patients that could best benefit from additional local treatments.

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Footnote

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