Review Article on Oligometastasis- Fallacy or Real Deal?

The role of immunotherapy in combination with oligometastasis-directed therapy: a narrative review

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Abstract: Metastatic disease is a significant cause of morbidity and mortality among patients with cancer. Patients with oligometastatic cancer represent a subset of the metastatic population with a limited amount of disease that has metastasized distantly and progresses at a slow pace and thus has the potential to be cured with metastasis-directed local therapy. Recent studies examining the role of metastasis-directed therapy in patients with oligometastatic disease have primarily focused upon treatment with ablative doses of radiation, commonly referred to as stereotactic body radiation therapy (SBRT). While the use of SBRT to treat oligometastases has increased considerably in recent years, the benefit of this approach has yet to be confirmed in phase III randomized controlled trials; moreover, distant failure remains a significant problem in patients with oligometastatic disease treated with SBRT. Given the propensity for distant failure in patients with oligometastatic disease treated with SBRT, there is growing interest in the utility of combining SBRT with systemic agents such as immunotherapy. Immunotherapy, and specifically immune checkpoint blockade (ICB), represents a rapidly evolving systemic therapy option with a growing number of indications among patients with metastatic disease; however, despite its promise, only a minority of patients respond to ICB and among those who do, the majority eventually progress. SBRT and ICB are both dependent upon, and have the ability to shift, the balance between antitumor immune surveillance and immunosuppressive states in the tumor and tumor microenvironment. As a result, it has been speculated that SBRT and ICB have the potential to act synergistically when used in combination. SBRT has been demonstrated to be safe in combination with ICB in studies with short-term follow-up and although additional research is needed, preliminary prospective data support the potential efficacy of this approach. In addition to confirming the safety and efficacy of SBRT in combination with immunotherapy, further studies are needed to determine how to maximize the therapeutic ratio of this treatment paradigm for the full potential of immunotherapy in the oligometastatic population to be realized.

Keywords: Immunotherapy; oligometastatic; radiation therapy; stereotactic body radiation therapy (SBRT); stereotactic ablative radiation therapy (SABR)

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Appeal of immunotherapy for treatment of patients with oligometastatic disease

Oligometastatic disease

Among patients afflicted with cancer, metastatic disease is a significant cause of morbidity and mortality; it has been estimated that metastases account for up to 90% of cancer-related mortality (1). Historically, it was believed that metastatic disease is characterized by a predictable pattern of progression that portends a consistently poor prognosis for patients, though an increasingly nuanced understanding of the biology of cancer metastasis has challenged this myopic view. Long before the development of contemporary models of cancer metastasis, Halsted proposed that metastatic progression occurs in an orderly fashion in which primary tumor cells first spread regionally to draining lymph nodes, where tumor cells accumulate until capacity in the lymph nodes is reached and tumor cells spill out to the next region of drainage (2). This idea was directly challenged by the theory that cancer metastasis does not occur in an orderly fashion and that distant spread occurs early in its natural history, which was most famously articulated by Fisher (3). These theories were subsequently reconciled by Hellman who proposed the spectrum hypothesis, which postulated the existence of a continuum of metastatic progression ranging from disease with a tendency to remain local to that with a propensity for early distant metastasis (4). Shortly thereafter, this hypothesis was refined by Hellman and Weichselbaum who proposed the existence of an oligometastatic state in which patients present with a limited amount of disease that has metastasized distantly, but is unlikely to progress rapidly (5).

While it is not well-characterized in the historical literature, recent data suggest that presentation with oligometastatic disease is not uncommon. A review of several first-line systemic therapy trials for patients with metastatic breast cancer found that approximately 50% of enrolled patients initially had two or fewer metastatic sites and up to 75% had four or fewer (6). Similar findings have been reported in several other common histologies including non-small cell lung cancer (NSCLC) (7), prostate cancer (8), and renal cell carcinoma (9) suggesting that the oligometastatic state may be relatively common. Given its seeming ubiquity across multiple histologies, the oligometastatic state represents an area that is both amenable to further research and where the results of such inquiry have the potential to significantly improve outcomes for a large number of patients. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1528).

Metastasis-directed therapy for oligometastatic disease

As a result of the hypothesized frequency of the oligometastatic state, there has been significant interest in the optimal management of patients who fall into this category. Given the inherently limited burden of disease in patients with oligometastases, local therapy has been attempted as a therapeutic option dating back to a pulmonary metastasectomy following the resection of a chest wall sarcoma, as described by Weinlechner *et al*. in 1882 (10). Since that time, surgery has been utilized extensively in patients with limited metastatic disease with curative intent, primarily among patients with pulmonary, liver, and adrenal metastases and less commonly among patients with other sites of extracranial metastasis. In fact, the most robust long-term survival data available among patients with limited metastatic disease come from patients with colorectal cancer who have undergone metastasectomy of liver metastases (11). Moreover, multiple other reported experiences have demonstrated the potential for significant rates of long-term (>10 years) overall survival (OS) with complete resection of metastatic disease (12-14).

While metastasectomy does have a history of success in a select population of patients with low burden metastatic disease, many patients with metastatic cancer are not able to undergo metastasectomy as a result of their medical comorbidities and/or disease that is not amenable to resection. As previously noted, while frequently used for pulmonary, liver, and adrenal metastases, metastasectomy has not typically been utilized in patients with other sites of extracranial metastasis; moreover, metastasectomy has typically been reserved for patients with one site of metastatic disease rather than several. Thus, the search for other methods of effective local therapy in patients who are not candidates for metastasectomy drove the development of hypofractionated courses of precisely-delivered, ablative doses of radiation therapy, often referred to as stereotactic body radiation therapy (SBRT) or stereotactic ablative radiation therapy (SABR). In recent years, SBRT/SABR (hereinafter referred to simply as "SBRT") has become a popular and increasingly utilized option for metastasis-directed therapy (15). Although several prospective series with long-term follow-up have examined the role of SBRT in patients with oligometastatic disease (16-20), the

randomized data supporting the role of metastasis-directed SBRT remain scarce. SABR-COMET, a phase IIR screening trial, which randomized 99 patients with a controlled primary tumor and 5 or fewer distant metastases to standard of care (SOC) therapy with or without SBRT in a 2:1 ratio demonstrated significant improvements in median progression-free survival (PFS) and OS with the addition of metastasis-directed SBRT to SOC therapy (21,22). While the results of SABR-COMET are undoubtedly exciting, several caveats should be considered in its interpretation, including the variety of histologies treated and imbalances between the SBRT and SOC arms (21,22). Moreover, it is of paramount importance to be mindful of its intent as a phase II screening trial, to identify potentially significant outcomes for further testing in confirmatory phase III trials (23).

Although the results of SABR-COMET are encouraging and strengthen the conclusions of smaller, disease-specific, phase II studies that demonstrate PFS, and in some cases OS, benefits among patients treated with SBRT to low volume metastatic disease (24-27) further validation of these results in the form of disease-specific, phase III randomized trials is needed. Moreover, given the relatively limited number of histologies represented in the current phase II studies along with the fact that the vast majority of patients represented in the currently reported experiences had a low burden of disease relative to upper limit of 5 metastases commonly used to define the oligometastatic state (28) further work is needed to establish optimal management for many patients with limited burden metastatic disease. Finally, given the propensity for long-term distant failure despite local therapy, additional strategies are needed in order to attain durable disease control in patients with oligometastatic disease. One such strategy is the combination of SBRT with systemic agents such as immunotherapy.

The rapidly evolving landscape of immunotherapy

Immunotherapy has been utilized to treat patients with cancer for several decades. Its indications and utilization have expanded massively over the last few years with the largest gains achieved in the use of immune checkpoint blockade (ICB) to block cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1) along with its ligand (PD-L1). Since ipilimumab, a monoclonal antibody that targets CTLA-4, was first approved for use in patients with advanced melanoma in 2011 (29) the proportion of patients with advanced or metastatic disease eligible for treatment with ICB has increased from approximately 1.5% to greater than 40%, as of 2018 (30). Moreover, immunotherapy has been demonstrated to improve outcomes and in some instances produce long-term disease-free intervals, not only in melanoma, but in a variety of different advanced malignancies (30-38). Though the data supporting the benefit of ICB in patients with metastatic disease have increased rapidly, the role of ICB remains uncertain in many histologies. Moreover, despite its triumphs, only approximately 20–25% of patients with metastatic disease respond to ICB (32,39-42) and among those who do, the majority eventually progress (43-46), underscoring the need to continue to improve upon the advances that the have been made in the use of immunotherapy to treat patients with metastatic disease. One such strategy is the liaison of immunotherapy with local therapy in order to improve response rates.

Perhaps one of the largest advances in the use of ICB in the treatment of cancer patients has come in the form of durvalumab as a consolidative therapy following definitive chemoradiation for patients with non-metastatic, unresectable, NSCLC. In this setting ICB has been shown to provide a significant PFS and OS benefit (47,48). Given its demonstrated efficacy in the eradication of microscopic disease following chemoradiation in the locally advanced setting, the combination of ICB with radiation therapy represents a logical strategy to maximize therapeutic response in patients with low-volume metastatic disease. The potential benefit of this combination is further supported by the fact that immunotherapy has been demonstrated to be most efficacious in the setting of low-volume disease (49), while ablative doses of radiation are capable of significant cytoreduction (50,51). Moreover, the abscopal effect, which describes the response of tumors outside of the irradiated field following radiation therapy, further bolsters the rationale for the union of immunotherapy and radiation therapy.

First described in 1953 by Mole *et al.* (52) the abscopal effect remained somewhat of an enigma for decades, rarely and unpredictably occurring in patients treated with radiation therapy (53). One hypothesis attempting to explain the abscopal effect postulated that it was, at least in part, a T-cell-dependent, immune-mediated event (54). Accordingly, abscopal effects were described by Postow *et al.* in 2012 in a patient with metastatic melanoma with progression of disease on maintenance ipilimumab who was

treated with 28.5 Gy over 3 fractions to a painful paraspinal metastasis. Following radiation therapy, the patient was noted to have regression of not only her treated paraspinal lesion, but also other metastatic lesions that were not irradiated (55). This and other reports of robust abscopal effects following the combination of ICB with SBRT has invigorated interest in this liaison as a potential means to induce widespread response to SBRT in patients with oligometastatic disease.

Methods

The primary objective of this narrative review was to characterize the current role of SBRT in combination with immunotherapy among patients with oligometastatic disease as well as potential future directions in this area. Specifically, we aimed to review the data supporting the biologic basis for combining SBRT with immunotherapy. We subsequently assessed the current data to support the safety and efficacy of this approach. Finally, we reviewed emerging data to support potential future methods to improve the therapeutic ratio of this liaison. Using MeSH terms and keywords including, but not limited to: immunotherapy, ICB, oligometastatic, radiation therapy, SBRT, and SABR, we constructed search terms, which were used to query PubMed as well as Google Scholar. Data in the narrative portion of the review included English-language publications between 1999 and 2020. ClinicalTrials.gov, which is an online registry of clinical trials run by the United States National Library of Medicine at the National Institute of Health, was also used to identify relevant ongoing prospective studies.

Biologic basis for the combination of immunotherapy with oligometastasis-directed therapy

Role of T-cells in antitumor response

In order to improve the efficacy of immunotherapy in combination with oligometastasis-directed therapy, an understanding of the underlying biologic effects of these therapies is required. The role of the immune system in response to treatment is well established; immune-excluded tumors, which are characterized by lack of T-cell infiltration, including low levels of helper (TH1) and cytotoxic (CD8+) T-cells, have been shown to be associated with decreased therapeutic response (56). Using patient-derived xenografts, Lee *et al*., demonstrated the importance of cytotoxic T-cells for tumors to respond to ablative doses of radiation. In their experiments, Lee *et al*. demonstrated that immunocompetent murine xenografts treated with ablative doses of radiation responded to treatment, while nude mice and cytotoxic T-cell-depleted wild-type mice did not (57). Others have similarly shown the importance of T-cell infiltration (58,59) for response to radiation therapy and accordingly, levels of tumor infiltrating lymphocytes (TILs) have been demonstrated to be prognostic in patients treated with radiation across multiple histologies (60-63). Unsurprisingly, T-cell infiltration has also been demonstrated to play a significant role determining response to ICB, as heavily T-cell infiltrated or "hot" tumors have been demonstrated to have a higher rate of response to ICB compared to less T-cell infiltrated or "cold" tumors (64). Thus, T-cells play an important role in antitumor surveillance and degree of T-cell infiltration is a significant determinant of therapeutic response to both radiation therapy and immunotherapy.

Mechanisms of ICB

Within the tumor microenvironment, T-cell activation is regulated by tumor cells, macrophages, and antigen presenting cells (APCs), such as dendritic cells (DCs), all of which have the ability to form ligand-receptor interactions with T-cells resulting in either immune-stimulation or immunosuppression. These ligand-receptor interactions are known as immune checkpoints and blockade of these checkpoints (ICB) has revolutionized the role of immunotherapy in the treatment of cancer. Currently approved ICB agents have one of two targets, CTLA-4 or PD-1/PD-L1 (65). CTLA-4 is expressed constitutively on immunosuppressive, regulatory T-cells (Tregs) and is upregulated in activated T-cells. CTLA-4 binds the same ligands as the co-stimulatory T-cell receptor CD28; however, with greater affinity allowing it to outcompete CD28. Following activation, T-cells upregulate CTLA-4 resulting in an increase in inhibitory signals and a decrease in stimulatory signals, ultimately decreasing immune surveillance (66). As such, CTLA-4 blockade with antagonistic antibodies can decrease immunosuppression and increase antitumor immune surveillance. PD-1, which is also expressed on T-cells, transmits pro-apoptotic signals in activated T-cells and anti-apoptotic signals in Tregs in response to its ligand PD-L1. PD-L1 is frequently upregulated in cancer cells as a mechanism of immune

evasion (66). As such, antibodies targeting PD-1/PD-L1 are another frequently used form of ICB. Overall, the efficacy of ICB relies upon several relationships within the tumor microenvironment. Similarly, multiple important interactions within the tumor microenvironment underlie tumor response to radiation therapy.

Immune response to ionizing radiation

Following treatment with ionizing radiation, a complex cascade of events occurs within tumors and the surrounding tumor microenvironment with the potential to either increase or suppress antitumor immune surveillance. Radiation and resulting cell death results in cytosolic release of DNA, which is recognized by cyclic GMP-AMP synthase (cGAS), resulting in type I interferon (IFN) production via the stimulator of interferon genes (STING) pathway (67). In addition to toll-like receptor-dependent stimulation, STING promotes IFN production, which has a number potentially immunostimulatory actions, including the recruitment of CD8+ T-cells and activation of DCs, which prime CD8+ T-cells for antitumor response (68). However, prolonged IFN exposure may stimulate tumor survival factors (69) and can also upregulate tumor PD-L1 expression resulting in immunosuppression (70,71). In fact, increased expression of PD-L1 following irradiation has previously been recognized as a significant cause of resistance to radiation therapy that can potentially be overcome with PD-L1 blockade (72). Consequently, radiation therapy-induced activation of the STING pathway has multiple effects, some of which bolster antitumor response, while others, such as upregulation of PD-L1 contribute to immune evasion and could potentially be targeted by ICB to increase therapeutic response.

Ionizing radiation also results in the secretion of numerous cytokines and chemokines into the tumor microenvironment, which similarly can have conflicting effects on antitumor immune surveillance. Factors secreted into the tumor microenvironment following radiation recruit a host of immune-related cells to the tumor microenvironment including DCs, macrophages, and CD8+ T-cells, all of which have the potential to enhance antitumor response (73,74). Given its ability to promote the migration of effector T cells, SBRT also has the ability increase tumor T-cell infiltration, turning "cold" tumors "hot" (73-78), without eliminating resident T-cells in inflamed tumors (79). In addition, ionizing radiation upregulates cellular adhesion molecules in endothelial cells, which can further increase T-cell infiltration (73,76). Conversely, factors secreted into the tumor microenvironment following radiation also have the potential to result in the efflux of potentially immunostimulatory cell populations and attract Tregs and myeloid-derived suppressor cells (MDSCs) (54,78,80-84). Tregs secrete TGF-β and IL-10, have the ability to suppress effector T-cell function (85,86), and have been demonstrated to be associated with suppressed antitumor immune response and poor clinical outcomes (87,88). Moreover, Tregs enhance the function of MDSCs, which have been demonstrated to have important roles in promoting tumor invasion and metastasis (89) and also induce Tregs (90). Tregs notably constitutively express CTLA-4 and selective depletion of Tregs in the tumor microenvironment has been demonstrated in response to ipilimumab (91). Thus, given the prominent role that Tregs play in inhibiting antitumor surveillance following radiation therapy, ICB-mediated depletion of Tregs represents an additional opportunity to improve therapeutic response to radiation therapy.

Another important component of the tumor microenvironment, tumor-associated macrophages (TAMs), are a highly plastic class of cells that have been implicated in tumor immune surveillance. Historically, TAMs have been described as polarized into either M1 or M2 subtypes, with M1 macrophages acting in a pro-inflammatory, antitumor fashion, and M2 macrophages acting in an immunosuppressive fashion (92). While it has recently been suggested that this binary classification is not entirely accurate and that a spectrum of activation of TAMs exists (93), high doses of radiation have been demonstrated to induce an M2-like phenotype (94,95) and depletion of TAMs prior to radiation has been demonstrated to increase antitumor activity (96), while M1-like macrophages promote recruitment and activation of CD8+ T-cells following radiation (76). As such, there is interest in the combination of radiation therapy with, cabiralizumab a monoclonal antibody antagonist of colony-stimulating factor 1 receptor (CSF-1R), which has been demonstrated to skew TAM populations towards an M2-like phenotype (97). In summary, ionizing radiation results in several changes in the tumor microenvironment, some of which promote antitumor immune surveillance, while others inhibit antitumor response; in many cases these effects are targetable via immunotherapy. Thus, the utilization of immunotherapy to skew the tumor microenvironment towards an immunostimulatory, antitumor phenotype and away from an immunosuppressive protumor phenotype

represents an enticing strategy to improve therapeutic response to radiation therapy.

In addition to its aforementioned effects on the tumor microenvironment, radiation releases tumor antigens as well as damage-associated molecular patterns (DAMPs) which are well-established to have an important role in improved DC function and T-cell priming (98,99). Moreover, cytoreduction following SBRT represents another potentially important means by which radiation can increase immune surveillance and improve outcomes with ICB. Given that TILs have been demonstrated to be relatively radioresistant (79), SBRT provides a potential mechanism for the selective elimination of tumor cells. SBRT has been show to decrease the ratio of tumor cells to non-exhausted effector T-cells, which has been demonstrated to correlate directly with PFS (100). Moreover, given that increasing antigen burden has been demonstrated to promote T-cell exhaustion, cytoreduction provides a possible means by which to lower antigen burden and potentially increase T-cell re-invigoration (50,51). Given that immunotherapy has been demonstrated to be most efficacious in the setting of low-volume disease (49), the cytoreductive properties of SBRT provide an important mechanism by which SBRT and immunotherapy may act synergistically.

Prospective data evaluating combination of immunotherapy with oligometastasis-directed therapy

Safety of ICB with SBRT

Given the relatively novel concept of combining ICB with SBRT in patients with metastatic disease, the safety of combination therapy is of significant concern, especially given the uncertain clinical benefit of this regimen. Notably, SABR-COMET reported significantly more treatment-related grade 2 or higher adverse events among patients treated with SBRT (29%) compared to those treated with SOC therapy only (9%). Moreover, 3 patients (5%) treated with SBRT experienced grade 5 treatment-related adverse events (one patient with radiation pneumonitis, one patient with a post-treatment pulmonary abscess, and one patient with a subdural hemorrhage after surgical repair of a SBRT-related perforated gastric ulcer), while no patients in the SOC arm experienced treatment-related death (21). Additionally, immunotherapy is associated with its own set of potential complications, with the most common immune-related adverse events (irAEs) being dermatitis (101) and colitis (102) followed by endocrinopathy (103) and hepatotoxicity (104). A less common, but potentially serious irAE is pneumonitis. Pneumonitis related to ICB is well-documented and has the potential to cause significant morbidity and in some instances mortality (105-109). Moreover, given that pneumonitis is a potentially fatal complication of metastasis-directed SBRT (21) and radiation recall pneumonitis has been reported in patients who receive ICB well after completion of radiation therapy (110) the potential for serious toxicity related to the combination of ICB with SBRT exists driving the need for clinical trials.

Multiple prospective studies aimed at evaluating the safety of ICB in combination with SBRT have been performed. Our institution performed a phase I study evaluating the combination of pembrolizumab with SBRT in patients with advanced solid tumors that had progressed on SOC therapy. In this study, 73 of 79 enrolled patients received SBRT and at least one cycle of pembrolizumab, which began within 7 days of completion of SBRT. A total of 2–4 metastases were treated per patient with each metastasis receiving 30–50 Gy in 3–5 fractions (identical to the doses and normal tissue constraints employed with NRG BR001), with dose and fractionation dependent upon metastasis location. Notably, as opposed to other trials evaluating the role of SBRT, metastases greater than 65 mL were partially-irradiated with only 65 mL of any tumor receiving the prescription dose in an attempt to minimize toxicity. With a median follow up of 5.5 months, dose-limiting toxicity (DLT) was seen in only 6 patients (9.7%; n=3 grade 3 pneumonitis, n=2 grade 3 colitis, and n=1 grade 3 hepatic toxicity), with no dose reductions required (111). The overall objective response rate (ORR) of non-irradiated metastases was 13.2%. With additional follow-up, it was determined that the degree of irradiated tumor response was correlated with outcome, with median overall survivals of 17.8, 9.1, and 3.4 months among patients with complete/partial local response, stable local disease, and progressive local disease, respectively (112). Thus, these results suggest not only that metastasis-directed SBRT was well-tolerated, but also that degree of local response to SBRT is prognostic of survival.

Additional smaller, non-randomized, prospective studies evaluating the safety of ICB in combination with SBRT have been reported with similar results. For instance, a phase I study performed at the University of Pennsylvania enrolled 22 patients with metastatic melanoma who received SBRT (6–8 Gy per fraction for 2–3 fractions,

Table 1 Comparative studies of ICB with SBRT in patients with oligometastatic disease

Study/sponsor	Design	Histology (enrollment)	ORR	Toxicity
PEMBRO-RT/Netherlands Cancer Institute (NCT02492568)	Phase 2 RCT; pembrolizumab ± SBRT	NSCLC (n=76)	36% *vs.* 18% (P=0.07)	17% G3+ (NS between groups)
MDACC (NCT02444741)	Phase 1/2 RCT; pembrolizumab ± SBRT	NSCLC (n=20/n=80)	22% *vs.* 25% (P=0.99)	Phase 1: 30% G3+; no G4+; phase 2: 11% G3+; two G4 cardiac AEs in 1 patient
MSKCC (NCT02684253)	Phase 2 RCT; nivolumab ± SBRT	HNSCC (n=53)	26.9% *vs.* 22.2% (P=0.94)	15% *vs.* 11% (P=0.96)
Regeneron (NCT02383212)	Phase 1, 2 ECs; cemiplimab ± SBRT	NSCLC (n=33, n=20)	40% *vs.* 18.2% (NS)	NS between groups; one patient with G5 pneumonitis

ICB, immune checkpoint blockade; SBRT, stereotactic body radiation therapy; RCT, randomized controlled trial; ECs, expansion cohorts; NSCLC, non-small-cell lung cancer; HNSCC, head and neck squamous cell carcinoma; ORR, overall response rate; NS, non-significant; G3, grade 3 adverse event; G4, grade 4 adverse event; G5, grade 5 adverse event

dependent upon site of metastasis) in combination with ipilimumab with no DLTs and a partial response, as best response, in 18% by RECIST (75). An additional study performed at MD Anderson Cancer Center (MDACC) reported only 2 DLTs (n=1 grade 3 pancreatitis and lipase elevation and n=1 grade 3 increase in bilirubin and aspartate aminotransferase) and an ORR of 23% in patients with advanced solid malignancies treated with 50–60 Gy in 4–10 fractions followed by ipilimumab (113). On the whole, the results of these and other, phase I/II, prospective, non-randomized studies demonstrate that the combination of ICB with SBRT is seemingly safe with encouraging rates of response (114-118). Moving forward, the results of additional studies investigating the role of SBRT in combination with ICB will be important to further establish the safety of this approach. Moreover, the results of ongoing phase III studies investigating this combination in the definitive setting will likely be informative. Currently, PACIFIC-4 (NCT03833154) and SWOG/NRG S1914 (NCT04214262), both of which randomize patients with early-stage NSCLC with high-risk features to treatment with SBRT with or without consolidative ICB, are currently enrolling (119,120). Notably, patients treated on the experimental arms of these studies receive radiation therapy with biologically effective doses (BEDs) in excess of 100 Gy in combination with ICB and as a result, the outcomes of these trials will likely provide additional valuable information on the safety of combining ablative doses of radiation with ICB.

Comparative studies evaluating the addition of SBRT to ICB

Although most of the evidence evaluating the role of ICB in combination with SBRT is limited to retrospective series and small, single-arm prospective studies, randomized data are beginning to emerge in this area. The currently reported comparative studies of ICB ± SBRT in patients with oligometastatic disease are shown in *Table 1*. The first of these to be published, was the PEMBRO-RT trial reported by Theelen *et al*. in 2019. This multicenter study included 76 patients with metastatic NSCLC randomized to receive pembrolizumab ± SBRT. Patients in the SBRT arm were treated to a single metastatic site, every other day, with 24 Gy in 3 fractions; pembrolizumab began 7 days after the completion of SBRT. Despite a doubling of ORR at 12 weeks, improvement in 12-week ORR did not reach the prespecified benchmark for meaningful clinical benefit and as a result the trial was negative (36% *vs*. 18% 12-week ORR in the experimental *vs*. control arm, P=0.07) (121). The trial also reported median a PFS of 6.6 months in the experimental arm *vs*. 1.9 months in the control arm (P=0.19) and median OS of 15.9 months in the experimental arm *vs*. 7.1 months in the control arm (P=0.16). The authors did note that upon subgroup analysis by PD-L1 status, the addition of SBRT seemed to drive benefits in median PFS (P=0.03) and median OS (P=0.05) in the PD-L1 negative subgroup (121). Perhaps more importantly, no increase in adverse events was observed in the experimental arm. Overall, though a negative trial, PEMBRO-RT supports the

safety of SBRT in combination with ICB and provides some insight regarding directions for future trials investigating the clinical utility of this combined-modality therapeutic approach.

Similarly, a phase I/II randomized controlled trial of pembrolizumab ± radiation therapy in patients with metastatic NSCLC was performed at MDACC with results recently reported by Welsh *et al*. This study randomized 20 patients in the phase I portion and subsequently 80 patients in the phase II portion. Unlike the PEMBRO-RT trial, pembrolizumab was given concurrently in combined-modality arm. Moreover, patients randomized to receive radiation therapy in this trial were treated with 50 Gy in 4 fractions if deemed feasible, which constitutes a significantly higher BED than the 24 Gy in 3 fractions used in the PEMBRO-RT trial. (However, it should be noted that approximately half of the patients randomized to radiation therapy were deemed to have metastatic lesions that were not amenable SBRT and as a result were treated with a moderately hypofractionated course of 45 Gy in 15 fractions.) Overall, the ORR in the combined-modality arm was not significantly different than that of patients treated with pembrolizumab alone (22% *vs*. 25%, P=0.99), nor was median PFS significantly different (9.1 *vs*. 5.1 months, P=0.52) (122). Like PEMBRO-RT, the authors noted that upon subgroup analysis by PD-L1 status, the addition of radiation therapy seemed to result in a benefit in median PFS (20.8 *vs*. 4.6 months, P=0.004) in the low PD-L1 subgroup. Notably, rates of grade 3 or higher toxicity were 30% and 11% in the combined-modality arms of the phase I and II portions of the trial, respectively. Moreover, two grade 4 cardiac adverse events (myocardial infarction and subsequent ventricular tachycardia) were noted in one patient treated with combined-modality therapy in the phase II portion of the trial (122). While like PEMBRO-RT, the MDACC trial was negative, this study did importantly add to the data supporting the safety of combined-modality treatment with pembrolizumab. Moreover, it is of note that a recently published pooled analysis of these two randomized trials did demonstrate improved PFS (4.4 *vs*. 9.0 months, P=0.045) and OS (8.7 *vs*. 19.2 months, P=0.0004) and no new safety concerns with the addition of radiation therapy to pembrolizumab (123). Although these findings are hypothesis-generating, they support the need for future, phase III randomized studies evaluating the role of radiation therapy in combination with ICB.

In another trial of ICB ± SBRT, 62 patients with metastatic head and neck squamous cell carcinoma were randomized to receive nivolumab ± SBRT (27 Gy in 3 fractions, delivered every other day to one metastatic lesion). As reported in the aforementioned series, the addition of ICB to SBRT was safe, with no increase in grade 3 or higher toxicity in the experimental arm (13.3% *vs*. 9.7%, P=0.70); however, SBRT did not improve ORR in this study (34.5% *vs*. 29.0%, P=0.86), nor were median PFS (1.9 *vs*. 2.6 months, P=0.79) or OS (14.2 *vs*. 13.9 months, P=0.75) improved with the addition of SBRT (124). Moreno *et al*. also reported the results of a comparative study of patients with metastatic NSCLC treated with cemiplimab ± SBRT at the 19th World Conference on Lung Cancer in 2018. This study was not randomized, but rather was comprised of a comparison of two separate phase I expansion cohorts in which patients either received cemiplimab alone (n=20) or cemiplimab in combination with SBRT (27 Gy in 3 fractions; n=33). As was the case in the aforementioned studies, the addition of SBRT to ICB did not appear to result in a significantly higher rate of toxicity, though it is important to note that one patient in the experimental arm experienced grade 5 pneumonitis, which was attributed to treatment; furthermore, the addition of SBRT to ICB once again failed to improve ORR (125).

Overall, the results of the currently reported comparative studies investigating the addition of SBRT to ICB support the safety of combined-modality therapy; however, the data to support the efficacy of this approach remains hypothesis-generating in nature. It is important to note that the doses of radiation used in these trials (with the exception of the patients in the MDACC trial randomized to combined-modality therapy in whom 50 Gy in 4 fractions was deemed feasible) resulted in BEDs that are well below that of ablative approaches in which BEDs of 100 Gy and greater are delivered. Given that ablative BEDs have been demonstrated to be imperative for optimal local control of irradiated metastases (126-129) and that degree of local response to SBRT is an important predictor of survival (112) future randomized studies investigating the role of SBRT in combination with ICB should utilize ablative doses of radiation therapy in an attempt to maximize the potential for therapeutic response with this liaison. Although the currently reported randomized studies do support the safety of SBRT in combination with ICB, it is important that future studies utilizing higher doses of SBRT evaluate this further as these, along with ongoing phase III studies investigating the combination of ablative doses of radiation with ICB in the definitive setting, will help to determine the safety of this approach. However, prospective non-

randomized data do support the safety of multi-site ablative dose radiation therapy in combination with ICB (111,112).

Future developments in the role of immunotherapy in the treatment of patients with oligometastatic disease

Manipulation of the tumor microenvironment

Although the data reviewed herein support the safety of ICB in combination with SBRT additional data are needed to determine its efficacy. In addition to the need to investigate the use of metastasis-directed ablative doses of radiation therapy in combination with ICB in the prospective, randomized setting, novel strategies are needed to attempt to improve the therapeutic ratio of this combination. One approach to improve outcomes involves utilizing knowledge of the pro-immune surveillance and immunosuppressive actions of SBRT and manipulating the tumor microenvironment such that this balance is favorably shifted.

Given their plastic nature, TAMs represent a component of the tumor microenvironment that have the potential to be targeted in order to shift the balance away from immunosuppression in favor of immune surveillance. Specifically, attempts to polarize TAMs towards an M1-like antitumor phenotype and away from an M2-like pro-tumor growth phenotype could potentially enhance the effect of ICB and radiation therapy; granulocyte-macrophage colony-stimulating factor (GM-CSF), has been investigated in combination with radiation therapy in this capacity, with initially promising results. In a trial at New York University, patients with metastatic solid tumors were treated with GM-CSF concurrently with radiation therapy (35 Gy in 10 daily fractions) with abscopal responses noted in non-treated metastases in 11 (26.8%, 95% CI: 14.2–42.9%) of the 41 accrued patients (130). Given that a M2-like phenotype has been demonstrated to be induced in response to high doses of radiation (94,95), attempts to manipulate TAM polarization may be even more effective in combination with SBRT. Moreover, given that increased CD8+ T-cell response and resulting increased IFN production has the potential to upregulate tumor expression of PD-L1 (70), the addition of anti-PD-1 therapy to this treatment regimen is logical. As such, our institution, is currently investigating the role of SBRT and nivolumab in combination with cabiralizumab (NCT03431948), a monoclonal antibody antagonist of colony-stimulating factor 1 receptor (CSF-1R), which has been demonstrated to skew TAM populations towards an M2-like phenotype (97). Cabiralizumab has also notably been studied previously in combination with nivolumab in patients with pancreatic cancer (131). Thus, future studies should continue to investigate the polarization of TAMs towards an antitumor phenotype to increase the therapeutic ratio of SBRT in combination with ICB. Another potential opportunity to shift the balance of the tumor microenvironment in favor of antitumor response exists in the form of targeting 4-1BB, a transmembrane glycoprotein on activated effector T-cells, which promotes CD8+ T-cell activity and survival and inhibits Tregs, in response to 4-1BB ligand (4-1BBL, CD137) on APCs. Pre-clinical data support the potential benefit of targeting 4-1BB; the addition of agonistic 4-1BB monoclonal antibodies to radiation therapy has been demonstrated to significantly increase rates of response in murine breast and lung carcinoma models (132). Moreover, 4-1BB monoclonal antibodies combined with PD-1 blockade and SBRT have been studied in murine melanoma models with encouraging rates of response (133). In addition, impressive responses have been reported clinically following the combination of a 4-1BBL agonist with radiation therapy (134) and PD-1 blockade (135), individually. As result, another strategy to improve the therapeutic response of SBRT in combination with ICB exists in the form of targeting 4-1BB on activated effector T-cells. Accordingly, our institution is currently investigating the addition of a 4-1BBL agonist, urelumab, to nivolumab and SBRT in patients with advanced solid tumors (NCT03431948).

Beyond CSF-1R antagonistic and 4-1BB agonistic approaches, additional methods of targeting the tumor microenvironment in order to maximize antitumor activity are currently under investigation. For instance, TGF-β has been demonstrated to induce an immune-excluded phenotype and resulting resistance to PD-L1 (136) and as such, inhibition of TGF-β and bispecific antibodies targeting both PD-1 and TGF-β (137,138) have been investigated as a potential mechanism of overcoming PD-L1 resistance. Moreover, numerous approaches utilizing PD-1/PD-L1 blockade with other agents targeting effector T-cells and chemokine inhibition have been investigated in addition to a wide variety of combinatory approaches joining PD-1/PD-L1 blockade with cytotoxic chemotherapy, small molecule inhibitors, hormone therapy, vaccine therapy, and other ICB agents in order to overcome PD-L1 resistance (139). Overall, strategies to induce a more favorable antitumor,

pro-immune surveillance tumor microenvironment have the potential to increase the efficacy of combined SBRT and ICB.

Innovations in metastasis-directed SBRT

In addition to attempts to increase the therapeutic ratio of SBRT and ICB, by altering the tumor microenvironment, improvements in metastasis-directed SBRT have the potential to significantly improve the efficacy of this treatment approach. As previously discussed, given that ablative BEDs are crucial for optimizing the local control of irradiated metastases (126-129) and that local response to SBRT has been correlated with survival (112), randomized studies investigating the role of ablative doses of SBRT in combination with ICB are needed. Historically, technical and practical considerations have largely limited the feasibility of multi-site SBRT using ablative doses for patients with metastatic disease, though several recent innovations have significantly decreased these limitations. First, improvements in image-guided radiation therapy (IGRT) have allowed metastases to be treated with smaller margins (140), increasing the ability to treat multiple metastases in close proximity to high doses safely. Additionally, volumetric modulated arc therapy (VMAT) has been demonstrated to improve treatment conformality, increasing the ability to deliver ablative doses to multiple metastases with sharp dose gradients and highly conformal dose distributions (141). VMAT has also been shown to significantly decrease treatment times, increasing the practicality of treating several metastases in one course of treatment and decreasing the risk of intrafraction motion, which has allowed further reduction of target volume margins (141). On the whole, these technical innovations combined with the realization that partial irradiation of large metastases with ablative doses does not seem to comprise efficacy (111,112) have contributed significantly to the ability to safely deliver ablative-dose SBRT to multiple metastases, which is likely necessary to increase the efficacy of combined SBRT and ICB. Notably, retrospective analysis of patients treated on protocol with multi-site ablative SBRT and ICB using the aforementioned approaches suggests that much higher BEDs, in excess of 360 Gy, can be achieved while respecting normal tissue constraints, and thus, further dose-escalation beyond standard ablative doses may be a feasible method of improving the efficacy of combined SBRT and ICB (142).

In addition to permitting safe dose-escalation of metastasis-directed SBRT, these advancements have also increased the feasibility of simultaneously treating multiple metastases within the same radiation therapy course. Like dose-escalation, the treatment of multiple metastases has the potential to significantly increase response to combined SBRT and ICB. Many of the studies examining the combination of the ICB with SBRT have done so under the premise that radiation can act as an adjuvant that stimulates the activity of ICB, with the goal of achieving abscopal responses at unirradiated sites. However, recent attempts to induce this type of abscopal response with non-ablative doses of radiation in combination with ICB have failed to produce robust therapeutic responses (121,125,143). While, SBRT certainly has the potential for synergy with immunotherapy resulting in effects outside of the irradiated field, the local benefits of ablative radiation suggest that it plays an important role beyond acting as an adjuvant. Given that radiation increases T-cell infiltration of tumors locally (73-78) and is able to re-prime resident T-cells (73,74,79), as well as kill resistant tumor clones (144), targeting all sites of metastasis may be beneficial in patients with oligometastatic disease. Also, given that increasing antigen burden has been demonstrated to promote T-cell exhaustion, maximal cytoreduction through multi-site SBRT has the potential to further lower antigen burden and potentially increase T-cell re-invigoration (50,51). Moreover, increased volume and diversity of the tumor antigens released following multi-site SBRT makes this approach potentially appealing. On the whole, these theoretical advantages of multi-site SBRT along with the fact that immunotherapy has been demonstrated to be most efficacious in the setting of low-volume disease (49) support the potential utility of treating several metastatic sites in an attempt to improve the efficacy of SBRT combined with ICB.

In summary, recent advancements in the understanding, planning, and delivery of metastasis-directed radiation therapy have increased the feasibility of treating multiple metastatic sites with ablative doses of radiation. Continued innovations in treatment planning and delivery, such as autonomous contouring (145) and biology-guided radiation therapy (146) have the potential to continue increase the feasibility of treating multiple metastases with ablative doses. Moreover, given data that the decreased absolute lymphocyte count (ALC) at the completion of SBRT is associated decreased rates of response to ICB (147), treatment planning approaches which limit "low dose bath" to surrounding tissues may be employed in order to decrease post-treatment lymphopenia (148). Future studies

utilizing these techniques are needed in order to further investigate how to optimize rates of response to combined SBRT and ICB.

Defining the population likely to benefit from SBRT and ICB

Another potential strategy to improve the therapeutic ratio of combined SBRT and ICB in patients with oligometastatic disease is to identify the subpopulation of patients most likely to benefit from this approach. Clinical factors associated with a favorable long-term prognosis among patients with oligometastatic disease treated with metastasis-directed therapy are well-established (11,12). More recently, molecular factors associated with oligo- versus polymetastatic progression have been identified (149) providing the potential to discern which patients are likely to be cured by metastasis-directed therapy, versus those who are likely to fail diffusely. Notably, Pitroda *et al*. recently proposed an integrated molecular classification in patients with hepatic metastases from colorectal cancer that successfully stratified patients by risk of failure following metastasectomy (150). Not only does this study provide a potentially useful framework upon which patients with curable oligometastatic disease could be successfully identified, but given that patients in whom microsatellite instability-independent immune activation was exhibited had the most favorable long-term outcome in this analysis, this framework has potentially important implications for the use of immunotherapy in patients with oligometastatic disease. Overall, efforts to further define the population most likely to benefit from the combination of SBRT and ICB are needed for this therapeutic approach to be utilized in a manner that maximizes its benefit to risk ratio.

Conclusions

Patients with oligometastatic cancer represent a subset of the metastatic population with a limited amount of disease that has metastasized distantly but is unlikely to progress rapidly and thus has the potential to be cured with metastasis-directed local therapies, such as SBRT. While initial evidence suggests that SBRT may provide significant benefit in patients with oligometastatic disease, high rates of distant failure following local therapy continue to preclude long-term disease control in this population as a whole. ICB has proven benefits in many metastatic cancers and may be beneficial in combination with SBRT in the oligometastatic population. Based upon short-term follow-up from prospective studies, the combination of SBRT with ICB appears to be safe with preliminary, hypothesis-generating data suggesting potential efficacy; however, longer follow-up and additional studies are needed investigate this further. Going forward, prospective, randomized studies evaluating the utility of multi-site, metastasis-directed SBRT utilizing ablative doses in combination with ICB are needed to better evaluate the efficacy of this approach and how the therapeutic ratio of combined-modality therapy can be maximized.

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