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Overview

The Abscopal Effect of Stereotactic Radiotherapy and Immunotherapy: Fool's Gold or El Dorado?

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Abstract

An 'abscopal' effect if often used to refer to distant tumour regression after localised irradiation. Since the first report of the abscopal effect in the 1950s, well-documented cases with radiotherapy alone are very rare. It is widely accepted that the immune response plays an important role in the abscopal effect, although the mechanism is still unclear. With the recent success of cancer immunotherapy, there is growing interest in combining immunotherapy with radiotherapy to boost abscopal response rates. Compared with conventional radiotherapy, stereotactic ablative radiotherapy (SABR) not only delivers ablative dose to the tumour, but may also induce robust immune responses. In this review we examine studies that combine SABR and immunotherapy. We review the preclinical rationale for SABR and immunotherapy combinations, the case for and against abscopal effects, and the current landscape of clinical trials.

Key words: Abscopal; immunotherapy; oligometastatic; radiotherapy; stereotactic

Statement of Search Strategies Used and Sources of Information

We carried out a structured search of peer-reviewed articles on MEDLINE between January 2000 and December 2018. We also searched the registered clinical trials on clinicaltrials.gov and anzctr.org.au. The search terms included stereotactic ablative body radiotherapy, stereotactic radiosurgery, immunotherapy, immune checkpoint inhibitors, abscopal effect.

Introduction

Radiotherapy plays a crucial role in cancer treatment, especially for local control of disease recurrence or progression. However, there is accumulating evidence that locally applied radiotherapy can induce a systemic antitumour effect, as evidenced by the regression of tumour in distant non-irradiated sites [1]. The systemic effect of radiotherapy, or 'abscopal effect' (from the Latin *ab scopus*, away from the target), was first introduced by Mole in 1953 [2] to describe the phenomenon of regression of metastatic cancer 'at a distance from the irradiated volume but within the same organism'. It is currently accepted that immune mechanisms are the underlying driving forces [3], although some components of DNA damage effects have been implicated [4]. Clinical cases of abscopal effects secondary to conventional radiotherapy (i.e. 1.8–2 Gy per fraction) are rare [1,5]. With the advance in radiotherapy technology, we are now able to deliver short courses of very large dose per fraction radiotherapy to the target with acceptable toxicity to normal tissue. Stereotactic ablative radiotherapy (SABR) is a modern radiation technique to deliver one to five fractions of doses above 6 Gy per fraction to small target volumes. Ablative doses have more potential to generate systemic antitumour immune responses compared with conventional radiotherapy [1,6]. With increasing utilisation of immunotherapy [7], abscopal effects are being increasingly observed, and efforts to exploit this effect are increasing [8]. Here we will briefly outline the mechanism

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of SABR-induced immune response and its synergistic effect with an immune modulator. We will present and discuss the latest clinical reports and data on the combination of SABR and immunotherapy in both the metastatic and non-metastatic settings.

Statement of Search Strategies

For this review we carried out a structured search of peer-reviewed articles on MEDLINE between January 2000 and December 2018. We also searched the registered clinical trials on clinicaltrials.gov and anzctr.org.au. The search terms included stereotactic ablative body radiotherapy, stereotactic radiosurgery, immunotherapy, immune checkpoint inhibitors, abscopal effect.

Radiation and Immune Responses

Classic radiation biology has been focused on radiation-induced DNA damage resulting in cell cycle inhibition as well as cell death through apoptosis, necrosis and autophagy [9]. There is substantial evidence that locally applied radiation can also stimulate systemic immune responses, leading to enhanced tumour cell recognition and tumour death by the immune system [10]. Radiation, especially SABR, not only causes lethal damage of tumour cell to release tumour-associated antigens [11], but also enhances major histocompatibility complex class I surface expression [12], calreticulin expression [13] and the release of HMGB1, a damage-associated molecular pattern. These events lead to dendritic cell activation [14]. Radiation-induced cytokine release, principally type I and type II interferons, also plays a role in dendritic cell activation [15]. The activated dendritic cells migrate to lymph nodes to present the antigen to T cells [12] and result in tumour-specific T cell activation and proliferation [16]. T cell activation alone is not sufficient for tumour eradication. Radiation can also lead to lymphocytes infiltrating into the tumour by two main mechanisms: (i) normalising tumour vasculature [17] and increasing expression of endothelial adhesion molecules [18] to enhance immune cell extravasation; (ii) releasing chemokine to attract immune cell migration and invasion [19]. A schematic of these events is illustrated in Figure 1.

With the emergence of immune checkpoint inhibitor (ICI) there has been a renewed interest in the abscopal response [20]. Although immunotherapy has been associated with impressive response rates in several cancer entities, the overall response rate for monotherapy is modest, e.g. 11% with ipilimumab monotherapy in metastatic melanoma [21], and ICIs may be associated with severe toxic effects. Responses to immunotherapy preferentially occur in tumours with a rich infiltration of dendritic cell and CD8+ T cells, which have been described as the T cell 'inflamed phenotype' or 'hot' tumour [22]. Unfortunately, 'cold' tumours (i.e. tumours with a poor infiltration of T lymphocytes) constitute the most frequent phenotype among solid tumours. The radiation-induced immune response may be able to turn a 'cold' tumour into a 'hot' tumour.

Selected Preclinical Data of Immune Therapy and Radiotherapy Combination

Preclinical studies have exploited different immune response pathways to enhance the immune system and increase the radiation abscopal response. In a metastatic Lewis lung carcinoma model, combined treatment of a single dose of 60 Gy to one tumour site and Fms-like tyrosine kinase receptor 3 ligand, a growth factor for dendritic cells, reduced non-irradiated pulmonary metastasis and improved disease-free survival at 20 weeks by 56% [23]. The dendritic cell-mediated abscopal response was further confirmed in a poorly immunogenic mammary carcinoma model [3]. This abscopal effect was lost in athymic mice, indicating a T cell-mediated mechanism [24]. The systemic effect of radiation can also be achieved by directly enhancing T cell function by interleukin-2 (IL-2) [25]. Demaria *et al.* [26] used a combination of CTLA-4 blockade and radiotherapy in preclinical models. This combination

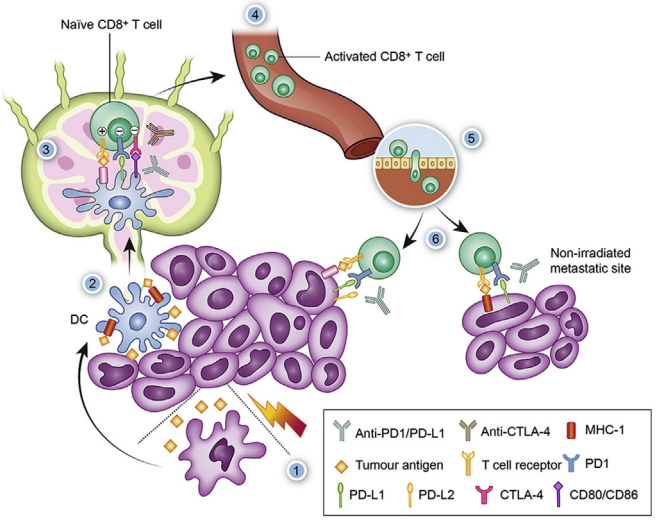

Fig 1. Mechanism of radiation-induced immune response. (1) Tumour cells release tumour antigens after irradiation; (2) tumour antigen can be taken up by dendritic cells (DC, i.e. antigen-presenting cells), which travels to regional lymph nodes; (3) this leads to priming and activation of naive T cells in regional nodes via the interaction of T cell receptors on T cells and major histocompatibility complex class I (MHC-I) on dendritic cells. In parallel to this stimulation, programmed death-ligand 1 (PD-L1) ligands bind to the PD-1 T cell receptor and sends an inhibitory signal to the same T cells suppressing their immune response. On the dendritic cells, an additional inhibitory signal can occur with CD80/CD86 and CTLA-4 receptors on T cells. Therapies with monoclonal antibodies anti-PD-1/anti-PD-L1 and anti-CTLA-4 block these inhibitory signals; (4) trafficking of activated tumour-specific T cells; (5) infiltration of T cells into tumour in both irradiated sites and non-irradiated metastatic sites; (6) recognition of cancer cells by T cells and killing of cancer cells.

significantly improved tumour control, reduced lung metastases and increased survival of a metastatic mouse mammary carcinoma model compared with monotherapy [26]. In the subsequent study [27], this group showed that CTLA-4 blockade enhanced the abscopal response using a bilateral flank model in which the primary flank tumour was irradiated and a smaller secondary flank tumour was shielded from radiation. Programmed death-ligand 1 (PD-L1) is upregulated in the tumour microenvironment after irradiation. Administration of anti-PD-L1 antibody improved local control by radiotherapy through a cytotoxic T cell-dependent mechanism [28]. Using the small animal radiation research platform, stereotactic radiotherapy combined with anti-PD-1 therapy significantly improved tumour control and enhanced the development of T cell and B cell antitumour responses [12]. Park *et al.* [29] also reported that this strategy not only induces near complete regression of the irradiated primary tumour, but also elicited a 66% reduction in size of non-irradiated tumour independent of tumour histology or host genetic background. The abscopal response is further enhanced by concurrent administration of bone marrow-derived dendritic cells *in vivo* [30].

Case Reports of the Abscopal Effect of Radiotherapy with Immunotherapy

The incidence of abscopal effects of radiotherapy alone is very low. There were no more than 50 well-documented cases reported in the literature between 1960 and 2014, despite millions of patients being treated with radiotherapy worldwide [1,5,31]. Since the seminal case report of a sustained complete response in a patient with metastatic melanoma treated with a combination of stereotactic radiotherapy to a single paraspinal mass and ipilimumab by Postow *et al.* [32], the abscopal response has been recognised in an increasing number of case reports of patients receiving radiotherapy and immunotherapy for melanoma [33–37], non-small cell lung cancer (NSCLC) [38], breast cancer [39,40], gastrointestinal malignancies [41–43], renal cell carcinoma [44,45], cervical cancer [46] and lymphoma [47]. Interestingly, abscopal effects occur not only in scenarios of radiotherapy to single or multiple extracranial metastatic sites but can be induced by stereotactic radiosurgery (SRS) for cranial metastasis [35,36].

Combining Radiotherapy and Immunotherapy in the Metastatic Setting

Current indications for immunotherapy mostly relate to use in the metastatic setting, in which palliative radiotherapy also plays an important role. To address the benefit of the combination of radiotherapy and immunotherapy, several retrospective analyses has been published recently. In the secondary analysis KEYNOTE-001 (a phase I study to evaluate the safety and antitumour activity of pembrolizumab in advanced NSCLC patients progressing on palliative chemotherapy [48]), Shaverdian *et al.* [49] reported that prior radiotherapy in patients with metastatic NSCLC was associated with increased progression-free survival (PFS) and overall survival compared with treatment with pembrolizumab alone. A similar finding was also reported in a systemic review of 127 consecutive melanoma patients treated with combined ipilimumab and radiotherapy compared with ipilimumab therapy alone [50]. In a recent meta-analysis of 17 studies of a combination of SRS and ICI for brain metastases, 1-year overall survival was 64.6% with concurrent therapy and 51.6% with non-concurrent therapy ($P < 0.001$). Regional brain control at 1 year was 38.1% with concurrent administration and 12.3% with immunotherapy given prior to SRS ($P = 0.049$) [51].

These results have set the stage for multiple phase I/II studies to investigate the efficacy and to evaluate the safety of the combination of treatment. In the studies published this far, it seems that the combination of SABR and ICI is tolerable (Table 1). Most grade 3 or 4 side-effects were related to immunotherapy and the addition of radiotherapy did not modify them. CTLA-4 blockade has not shown activity in NSCLC as a single agent, but its combination with SABR to a single disease site led to an 18% (7/39) objective response rate (ORR) in a recently published phase II study, including two complete responses and five partial responses [52]. The ORR was between 10 and 13.2% in the cohort of mixed tumour entities when SABR was delivered in combination with ipilimumab [53]. The ORR is similar to that observed in the KEYNOTE-28 study (9–33% response rate) of unselected patients who were tested with pembrolizumab alone [54]. Other phase I/II trials testing various SABR and immunotherapy strategies in the metastatic setting are listed in Table 2.

One strategy to combine SABR with immunotherapy in the metastatic setting is to deliver SABR to a single index lesion before the start of immunotherapy as an *in vivo* vaccination. The preliminary data from the PEMBRO-RT trial [82], which was recently presented at ASCO 2018, showed significant benefit in patients with metastatic NSCLC who progressed on second-line chemotherapy. In the experimental arm, patients received SABR 24 Gy in three fractions to a single metastatic lesion 7 days before the treatment with pembrolizumab. The control arm received pembrolizumab alone. The ORR at 12 weeks was 19% in the control arm ($n = 32$) versus 41% in the experimental arm ($n = 32$). In the experimental arm, one patient had a complete response and 12 patients had a partial response. There was no complete response in the control arm. The ORR of combined therapy was higher than the non-selected PD-L1 expression NSCLC cohort who received PD-1 immunotherapy alone [48]. The median PFS was 1.8 months in the control arm versus 6.4 months in the experimental arm (hazard ratio 0.55, confidence interval 0.31–0.98, $P = 0.04$). The combination therapy was well tolerated. On the contrary, in a similar phase II study in metastatic head and neck squamous cell carcinoma, including nasopharyngeal squamous cell carcinoma, the combination of SABR and ICI failed to improve ORR and PFS [83]. In this study, the experimental arm received 27 Gy in three fractions to a single metastatic

Table 1
Phase I and II studies of stereotactic ablative radiotherapy (SABR) or fractionated radiotherapy to the metastatic sites in combination with immunotherapy

Reference/study name/NCT number	Cancer type	Intervention	No. patients	Radiotherapy technique/ fractionation	ORR (%)	Complete response (*n*)	Partial response (*n*)	Stable disease (*n*)	Grade 3/4 toxicity (*n*/ total no. patients)
iMOSART [55]/NCT 02608385	Mixed	SABR → pembrolizumab within 7 days	79	SABR to 2 metastatic lesions with 30–50 Gy in 3–5 fractions	13.2	1	8	21	6/73
Tang *et al.* [53]/ NCT02239900	Mixed	SABR + concurrent/ sequential ipilimumab	31	SABR 50 Gy/4 fractions or 60 Gy/10 fractions	10	0	3	7	12/35
Sundahl *et al.* [56]	Urothelial carcinoma	SABR + concurrent/ sequential pembrolizumab	18	SABR 27 Gy/3 fractions to 1 metastatic lesion	44 (concurrent arm)	1	3	NR	1/18
Formenti *et al.* [52]/ NCT02221739	NSCLC	SABR + concurrent ipilimumab	39	SABR 24 Gy/4 fractions or 27 Gy/3 fractions to single disease site	18	2	5	5	14/39
RADVAX™ [57]/ NCT01497808	Melanoma	SABR → ipilimumab	22	SABR to single index lesion Lung/bone, 16 Gy/2 fractions or 24 Gy/3 fractions Liver/subcutaneous, 12 Gy/2 fractions or 18 Gy/3 fractions	18	NR	NR	NR	NR
Hiniker *et al.* [58]	Melanoma	Radiotherapy + concurrent ipilimumab	22	SABR, 3DCRT and IMRT to 1 or 2 lesions	22	3	3	5	3/22
Williams *et al.* [59]/ NCT01703507	Melanoma with brain metastasis	SRS → ipilimumab WBRT + concurrent ipilimumab	16	SRS ($n = 11$), WBRT ($n = 5$)	NR	0	1	5	2/16
Seung *et al.* [60]	Melanoma and RCC	SABR → IL-2	12	1, 2 or 3 doses of 20 Gy/ fraction	66.7	1	7	1	NR

3DCRT, three-dimensional conformal radiotherapy; IL-2, interleukin-2; IMRT, intensity-modulated radiotherapy; NSCLC, non-small cell lung cancer; ORR, objective response rate; RCC, renal cell carcinoma; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

Table 2
Proposed and ongoing clinical trials testing stereotactic ablative radiotherapy (SABR) in combination with immunotherapy

Trial number [reference]	Trial status	Phase	Estimated enrolment (n)	Immunotherapy agents	Dose fractionation	Time of immunotherapy	Study arms	Primary end point
Stage IV non-small cell lung cancer								
ACTRN12616000352404 [61]	Recruiting	II	120	Nivolumab	18–20 Gy/1 fraction to ≥1 metastasis	Sequential	SABR → immunotherapy versus immunotherapy	PFS at 6 months, ORR
NCT03307759 [62]	Recruiting	Ib	32	Pembrolizumab	18–20 Gy/1 fraction to 1–3 metastases	Sequential	SABR → immunotherapy versus immunotherapy → SABR	Safety
NCT02839265 [63]	Recruiting	II	29	FLT3 ligand (CDX-301)	34 Gy/1 fraction (lesion <2 cm); 54 Gy/3 fractions and 50 Gy/5 fractions (central lesion)	Concurrent	Single	PFS, toxicity
NCT03223155 [64]	Recruiting	I	80	Nivolumab/ ipilimumab	2–4 sites within 2 weeks		Concurrent versus sequential immunotherapy	Toxicity
NCT03705403 [65]	Not open	II	130	L19-IL2*	SABR to all sites (maximum 3)	Sequential	SABR versus SABR + L19-IL2	PFS, overall survival
NCT03275597 [66]	Recruiting	Ib	21	Durvalumab + tremelimumab	SABR to all sites (maximum 3) 30 –50 Gy/5 fractions	Sequential	Single	Safety and feasibility
NCT03391869 [67]	Recruiting	III	270	Nivolumab + ipilimumab		Concurrent	Nivolumab + ipilimumab versus nivolumab + ipilimumab + LCT (RO versus surgery)	Overall survival, PFS
Stage IV melanoma								
NCT03340129 [68]	Not open	II	155	Nivolumab + ipilimumab	SRS 16–22 Gy in 1 fraction	Concurrent	SRS + nivolumab + ipilimumab versus nivolumab + ipilimumab	Intracranial response to immunotherapy
NCT01416831 [69]	Active, not recruiting	II	43	High dose IL-2	SABR up to 3 sites	Concurrent	SABR + IL-2 versus SABR	Change in diameter of target lesions
Stage IV breast cancer								
NCT02303366 [70]	Complete	Ib	15	Pembrolizumab	SABR to 1–5 metastases	Sequential	Single	Safety
NCT03464942 [71]	Not open	II	52	Atezolizumab	20 Gy/1 fraction or 24 Gy/3 fractions to 1–4 metastases	Sequential	20 Gy/1 fraction versus 24 Gy/3 fractions	Safety, PFS
NCT01862900 [72]	Active, not recruiting	I/II	14	MEDI6469 (anti-OX40)	30 or 40 Gy in 2 fractions	Concurrent	Single	Tolerance and safety
Head and neck squamous cell carcinoma								
NCT03283605 [73]	Recruiting	I/II	45	Duralumab + tremelimumab	SABR to 2–5 sites	Sequential	Single	Tolerance and safety
NCT03546582 [74]	Recruiting	II	102	Pembrolizumab	SABR to recurrence or second head and neck malignancy	Sequential	SABR + pembrolizumab versus SABR alone	PFS and overall survival
NCT02684253 [75]	Active, not recruiting	II	65	Nivolumab	27 Gy/3 fractions to single lesion	Concurrent	SABR + nivolumab versus SABR	Overall response rate
Mixed solid tumour								

NCT03693014 [76]	Recruiting	II	60	Ipilimumab/ nivolumab/ Pembolizumab/ atezolizumab	SABR 27 Gy/3 fractions to 1–3 sites	Concurrent	Single arm (SABR as salvage)	ORR
NCT02843165 [77]	Recruiting	II	146	PD-1/PD-L1 blockade	28.5 Gy/3 fractions	Concurrent	SABR + immunotherapy versus immunotherapy	ORR
NCT03431948 [78]	Recruiting	II	60	Nivolumab/ cabiralizumab/ urelumab	SABR 30–50 Gy to multiple lesions	Concurrent	Arm 1: SABR + nivolumab + urelumab Arm 2: SABR + nivolumab + cabiralizumab	Dose fractionation
NCT02710253 [79]	Recruiting	II	150	Multiple immunotherapy	50 Gy/4 fractions; 60–70 Gy/10 fractions; 20–30 Gy/5 fractions; 30–45 Gy/ 10–15 fractions	Concurrent	Single	Systemic disease control
Prostate cancer								
ACTRN12618000954224 [80]	Recruiting	II	25	Avelumab	18–20 Gy/1 fraction to 2–3 metastases	Sequential	Single	Radiological PFS at 24 weeks
NCT03007732 [81]	Recruiting	II	42	Pembrolizumab	35 Gy/5 fractions	Concurrent	SABR versus conventional radiotherapy	Change rate of PSA

FLT3, Fms-like tyrosine kinase receptor 3; IL-2, interleukin-2; LCT, local control treatment; ORR, objective response rate; PFS, progression-free survival; PSA, prostate-specific antigen; SRS, stereotactic radiosurgery.

* L19-IL2 is a recombinant fusion protein composed of two moieties: L19, a human monoclonal antibody fragment in the single chain Fv (scFv) format, bound via a flexible linker to IL-2.

lesion (59% are pulmonary metastasis) between the first and second dose of nivolumab. Kwon *et al.* [84] conducted a phase III randomised placebo-controlled trial (CA184-043) to assess the ability of ipilimumab to extend overall survival in patients with metastatic castration-resistant prostate cancer who had progressed after docetaxel. A single dose (8 Gy) of bone-directed radiotherapy was delivered in all patients prior to ipilimumab or placebo. Addition of ipilimumab to radiotherapy improved PFS, but not overall survival, although there was a trend towards an improvement in overall survival. In an unplanned subgroup analysis, patients with favourable metastatic prostate cancer as defined by three baseline factors (low alkaline phosphatase concentration, haemoglobin >110 g/l and no visceral metastases) appeared to derive benefit from ipilimumab therapy followed single 8 Gy bone-directed radiotherapy (median overall survival 22.7 versus 15.8 months, hazard ratio 0.62) [84]. As illustrated by these studies, response rates vary quite significantly for immunotherapy and SABR combinations in different tumour entities and this may reflect the tumour biology (e.g. 'cold' tumour versus 'hot' tumour) in response to immunotherapy.

Another strategy to combine radiotherapy and immunotherapy is to introduce the radiotherapy as salvage when the patients progress on the immunotherapy. It has been detailed in several case reports that SABR to single tumour sites has resulted in a systemic response in patients with metastatic melanoma progressing on immunotherapy [32,33]. The ongoing phase II trial (NCT02710253) [85] was designed to test the hypothesis in mixed tumour entities. Salvage radiotherapy utilised in this trial consisted of standard dose SABR (50 Gy in four fractions or 60–70 Gy in 10 fractions) or conventional external beam radiation. The ABC-X study (NCT03340129) [68] is an open-label, non-randomised study of ipilimumab and nivolumab with salvage radiotherapy (SRS or whole-brain radiotherapy) in patients with stage IV melanoma progressing intracranially on immunotherapy; the results of this study are awaited.

Maximising the Likelihood of Abscopal Effects: are Two Targets Better than One?

Although previous studies have focused on irradiating only one site in order to maximise the number of unirradiated measurable disease sites for response assessment, there is biological rationale for irradiating multiple sites. Through multisite irradiation, tumoural heterogeneity may result in additional exposure of tumour-associated antigens, and certain organs may be more favourable in mounting an immune response than others. For example, a phase I study showed that liver irradiation is associated with greater systemic immune activation than lung irradiation [53].

Two studies in the pre-ICI era showed modest synergistic response when combining radiotherapy with immunomodulatory agents. Golden *et al.* [86] reported an abscopal effect rate of 25% (11/41 patients) in a prospective single-arm study (NCT02474186) of the combination of chemoradiotherapy with granulocyte-macrophage colony-stimulating factor in patients with metastatic solid cancer. In another early phase I study, concurrent SABR (20 Gy × 1, 2 or 3) with IL-2 achieved an ORR of 66.6% (one complete response; seven partial responses) in 12 patients with metastatic melanoma and renal cell cancer [60]. Historically, the ORR of single IL-2 treatment was about 20% [87]. Results of two phase I trials of combination with ipilimumab and SABR in patients with metastatic melanoma have been published so far. Twyman-Saint Victor *et al.* [88] reported an 18% ORR in 22 patients when a single index lesion was irradiated. The radiotherapy doses were 16 Gy in two fractions for pulmonary lesions, 24 Gy in three fractions for bony lesions, 12 Gy in two fractions for liver lesions and 18 Gy in three fractions for subcutaneous lesions. There were no complete abscopal responses observed, but a durable partial response was achieved without added toxic effects. On the contrary, a relatively higher ORR of 27% was reported by Hiniker *et al.* [58] when one to two disease sites were irritated. In this cohort, 11 of 22 evaluable patients achieved a clinical benefit. Three patients had a complete response at a median follow-up of 55 weeks, three patients had a partial response for a median of 40 weeks and five patients had stable disease for a median of 39 weeks.

The complete response rate in all the studies mentioned above is low and this raises the question of whether the abscopal effect of radiation is a meaningful clinical entity [89]. In a phase II study of a heavily pretreated advanced solid tumour population (iMOSART, NCT02608385), multi-site SABR followed by pembrolizumab led to excellent tumour control in both partially and fully irradiated tumours. Luke *et al.* [55] observed a median overall survival of 9.6 months despite a PFS of 3.1 months. They interpreted the comparatively long overall survival being achieved as the result of tumour debulking by irradiating the largest tumours or those likely to cause injury or death to the patient, relieving the immunosuppressive effects of large tumours and affording immunotherapy agents sufficient time to generate an effect. There was only one complete response and eight partial responses in 68 patients, as per RECIST criteria, in this study. Thus, the benefit of adding radiation to immunotherapy might be mediated through effects other than the abscopal response.

Combining Immunotherapy with Radiotherapy in the Curative Setting: Moving Beyond Abscopal Effects

Immunotherapy has shown significant benefits in patients with metastatic NSCLC in multiple phase III trials [90,91]. There is growing interest in integrating immunotherapy in definitive radiotherapy in NSCLC. In the landmark PACIFIC trial, adjuvant therapy with durvalumab following radical chemoradiotherapy in patients with stage III NSCLC significantly improved medial PFS (17.2 versus 5.6 months) and overall survival at 24 months (66.3%, confidence interval 61.7–70.4 versus. 55.6%, confidence interval 48.9–61.8, $P = 0.005$) [92]. Furthermore, durvalumab

therapy resulted in a longer time to death or distant metastasis, suggesting that the drug not only works at the local level but also at the distant level. Interestingly, a subgroup analysis showed that patients who started durvalumab within 14 days after radical chemoradiotherapy benefited more, indicating a plausible synergistic effect of radiotherapy and immunotherapy if delivered in a timely manner. The combination therapy had similar high-grade all-causality adverse events compared with chemoradiotherapy alone. The other area that is being investigated at the moment is the incorporation of immunotherapy after SABR in the treatment of early stage NSCLC. A retrospective study reporting outcomes following SABR for early stage NSCLC reported that distant failure accounted for over 66% of recurrence after treatment with SABR alone [93]. It is hypothesised that anti-PD therapy in combination with SABR may sterilise subclinical disease and increase cure rates. Two phase II trials are open at the early enrolment stage to test this hypothesis to compare adding nivolumab (I-SABR, NCT03110978) [94] or durvalumab (ASTEROID, NCT03446547) [95] after SABR with SABR alone. Other similar trials are summarised in Table 3. Given the propensity of NSCLC to metastasise, it is unclear whether early systemic immunotherapy enhances the radiation-related immune response on occult metastatic sites (early abscopal effect) or works synergistically with radiotherapy in the adjuvant setting. In the PACIFIC trial there was minimal crossover to the immunotherapy arm and positron emission tomography staging was not mandated. Future studies with true crossover will help to answer this question.

Unanswered Questions: Future Research Areas for Radiotherapy and Immunotherapy Combinations

Optimising Dose per Fractionation

The optimal radiation dose and fractionation for enhancing the abscopal effect or the interaction with an ICI is yet to be determined. Some preclinical data suggest that single-fraction radiation is better than multiple fractionation [11], but others suggest that fractionated radiotherapy works better [27]. In a recent seminar paper by Vanpouille-Box *et al.* [99], a single dose in excess of 10–12 Gy induced DNA exonuclease Trex1, which abrogated the dendritic cell activation pathways. This study also proposed that 24 Gy in three fractions is the optimal dose to induce the abscopal effect *in vivo*. By contrast, Filatenkov *et al.* [100] reported that a single 30 Gy ablative dose induced a more robust tumour immune response compared with a fractionated radiation regimen in a murine colon cancer model. Clinical data that directly compare different doses and fractionations are lacking. The Trans-Tasman Radiation Oncology Group (TROG) phase II AZTEC study (NCT 03464942) is currently recruiting to compare the efficacy of 24 Gy in

Table 3
Trials of stereotactic ablative radiotherapy (SABR) in combination with anti-PD therapy in early stage non-small cell lung cancer in set-up or recruiting

Study name [reference]/NCT number	Trial status	Phase	Estimated enrolment (n)	Immunotherapy agents	Dose fractionation	Time of immunotherapy	Study arms	Primary end point
I-SABR [94]/NCT03110978	Recruiting	II	140	Nivolumab	50 Gy/4 fractions or 70 Gy/10 fractions	Before and after first SABR; every 2 weeks for a total of 7 doses	SABR + immunotherapy versus SABR alone	Event-free survival
ASTEROID [95]/NCT03446547	Recruiting	II	216	Durvalumab	NA	After radiotherapy	SABR + immunotherapy versus SABR alone	Time to progression
NCT03050554 [96]	Active, not recruiting	I/II	56	Avelumab	48 Gy/4 fractions or 50 Gy/5 fractions	After radiotherapy	Single	Safety and tolerability; relapse-free survival
STILE [97]/NCT03383302	Not open	I/II	31	Nivolumab	54 Gy/4 fractions or 55 Gy/5 fractions	After final radiotherapy within 24 h	Single	Assessment of lung toxicity
NCT03574220 [98]	Not open	I	15	Pembrolizumab	50 Gy/5 fractions or 60 Gy/3 fractions	After radiotherapy	Single	Tolerability

three fractions versus single 20 Gy SABR in combination with atezolizumab in metastatic triple-negative breast cancer.

Single-site versus Multisite Irradiation

Brooks and Chang [101] proposed comprehensive irradiation of multiple/all lesions in order to enhance the likelihood of obtaining a meaningful clinical outcome. As discussed earlier, irradiating multiple sites of disease may maximise exposure of the tumour antigen and overcome the immune suppressant microenvironment of each tumour site. The preliminary data of the PEMBO-RT trial showed a meaningful clinical outcome (i.e. PFS benefit) when SABR was delivered to three sites [82]. By contrast, the phase III CA184-043 trial [84] failed to show an overall survival benefit of a combination of single-site bone irradiation and CTLA-4 blockade. Furthermore, the SABR-COMET trial [102], which was just presented at ASTRO 2018, showed an overall survival benefit of ablative radiotherapy alone to multiple metastatic tumour sites (up to five sites). It is yet to be confirmed whether the overall survival benefit derived from maximising local control by treating multiple disease sites or another underlying mechanism (i.e. enhancing the immune system).

The Promise of Stereotactic Ablative Radiotherapy as a Partner for Immunotherapy

Compared with conventional radiotherapy, SABR induces a more robust immune response by releasing a large amount of tumour-associated antigens [12] and enhancing CD8+ T cell infiltration [16]. SABR is able to spare the radiation dose to the drainage lymph nodes, allowing T cell priming [103]. The high and durable local control with SABR can lead to a decrease in the likelihood of metastases causing harm and allow the immunotherapy agents sufficient time to generate an effect. Compared with other cytotoxic agents or targeted agents, radiotherapy is unique as a partner for immunotherapy in that it is readily available, well tolerated, as shown in multiple phase I and II trials, and part of the standard of care for most cancers.

Conclusions

There is mounting evidence that an immune response-mediated cell kill is one of the key mechanisms of effect in radiotherapy. Radiotherapy, and specifically SABR, in combination with immunotherapy is a promising strategy to enhance the effect of immunotherapy with tolerable side-effects and there is increasing evidence of a synergistic benefit to this combination. A number of clinical studies are now in progress that are examining both the disease setting and the optimal sequence of SABR and immunotherapy combinations.

Conflicts of Interest

S. Siva received speaker honoraria from Astra Zeneca, had a consulting or advisory role with Astra Zeneca, received research funding from Merck Sharp and Dohme, Merck Serono and AstraZeneca and travel sponsorship from Astra Zeneca. G.G. Hanna received honoraria from AstraZeneca, Roche, Pfizer, Bristol-Myers Squibb and Novartis, had a consulting or advisory role with Pfizer, received research funding from Dermal Laboratories and AstraZeneca and travel sponsorship from Roche, Boehringer Ingelheim and Astra Zeneca. The authors report no direct conflict of interest in preparing this manuscript from any of the above funding scources.

References

[1] Siva S, MacManus MP, Martin RF, Martin OA. Abscopal effects of radiation therapy: a clinical review for the radiobiologist. *Cancer Lett* 2015;356:82–90.
[2] Mole RH. Whole body irradiation; radiobiology or medicine? *Br J Radiol* 1953;26:234–241.
[3] Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, *et al*. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *Int J Radiat Oncol Biol Phys* 2004;58:862–870.
[4] Siva S, Lobachevsky P, MacManus MP, Kron T, Moller A, Lobb RJ, *et al*. Radiotherapy for non-small cell lung cancer induces DNA damage response in both irradiated and out-of-field normal tissues. *Clin Cancer Res* 2016;22:4817–4826.
[5] Reynders K, Illidge T, Siva S, Chang JY, De Ruysscher D. The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant. *Cancer Treat Rev* 2015;41:503–510.
[6] Siva S, Callahan J, MacManus MP, Martin O, Hicks RJ, Ball DL. Abscopal effects after conventional and stereotactic lung irradiation of non-small-cell lung cancer. *J Thorac Oncol* 2013;8:e71–e72.
[7] Couzin-Frankel J. Cancer immunotherapy. *Science* 2013;342:1432–1433.
[8] Hanna GG, Coyle VM, Prise KM. Immune modulation in advanced radiotherapies: targeting out-of-field effects. *Cancer Lett* 2015;368:246–251.
[9] Amaravadi RK, Thompson CB. The roles of therapy-induced autophagy and necrosis in cancer treatment. *Clin Cancer Res* 2007;13:7271–7279.
[10] Demaria S, Golden EB, Formenti SC. Role of local radiation therapy in cancer immunotherapy. *JAMA Oncol* 2015;1:1325–1332.
[11] Lugade AA, Moran JP, Gerber SA, Rose RC, Frelinger JG, Lord EM. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J Immunol* 2005;174:7516–7523.
[12] Sharabi AB, Nirschl CJ, Kochel CM, Nirschl TR, Francica BJ, Velarde E, *et al*. Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. *Cancer Immunol Res* 2015;3:345–355.
[13] Gameiro SR, Jammeh ML, Wattenberg MM, Tsang KY, Ferrone S, Hodge JW. Radiation-induced immunogenic modulation of tumor enhances antigen processing and

calreticulin exposure, resulting in enhanced T-cell killing. *Oncotarget* 2014;5:403–416.
[14] Gupta A, Probst HC, Vuong V, Landshammer A, Muth S, Yagita H, *et al.* Radiotherapy promotes tumor-specific effector CD8+ T cells via dendritic cell activation. *J Immunol* 2012;189:558–566.
[15] Gerber SA, Sedlacek AL, Cron KR, Murphy SP, Frelinger JG, Lord EM. IFN-gamma mediates the antitumor effects of radiation therapy in a murine colon tumor. *Am J Pathol* 2013;182:2345–2354.
[16] Lee Y, Auh SL, Wang Y, Burnette B, Wang Y, Meng Y, *et al.* Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. *Blood* 2009;114:589–595.
[17] Ganss R, Ryschich E, Klar E, Arnold B, Hammerling GJ. Combination of T-cell therapy and trigger of inflammation induces remodeling of the vasculature and tumor eradication. *Cancer Res* 2002;62:1462–1470.
[18] Hallahan D, Kuchibhotla J, Wyble C. Cell adhesion molecules mediate radiation-induced leukocyte adhesion to the vascular endothelium. *Cancer Res* 1996;56:5150–5155.
[19] Matsumura S, Wang B, Kawashima N, Braunstein S, Badura M, Cameron TO, *et al.* Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells. *J Immunol* 2008;181:3099–3107.
[20] Turgeon GA, Weickhardt A, Azad AA, Solomon B, Siva S. Radiotherapy and immunotherapy: a synergistic effect in cancer care. *Med J Aust* 2019;210:47–53.
[21] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–723.
[22] Trujillo JA, Sweis RF, Bao R, Luke JJ. T cell-inflamed versus non-T cell-inflamed tumors: a conceptual framework for cancer immunotherapy drug development and combination therapy selection. *Cancer Immunol Res* 2018;6:990–1000.
[23] Chakravarty PK, Alfieri A, Thomas EK, Beri V, Tanaka KE, Vikram B, *et al.* Flt3-ligand administration after radiation therapy prolongs survival in a murine model of metastatic lung cancer. *Cancer Res* 1999;59:6028–6032.
[24] Chakravarty PK, Guha C, Alfieri A, Beri V, Niazova Z, Deb NJ, *et al.* Flt3L therapy following localized tumor irradiation generates long-term protective immune response in metastatic lung cancer: its implication in designing a vaccination strategy. *Oncology* 2006;70:245–254.
[25] Yasuda K, Nirei T, Tsuno NH, Nagawa H, Kitayama J. Intratumoral injection of interleukin-2 augments the local and abscopal effects of radiotherapy in murine rectal cancer. *Cancer Sci* 2011;102:1257–1263.
[26] Demaria S, Kawashima N, Yang AM, Devitt ML, Babb JS, Allison JP, *et al.* Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clin Cancer Res* 2005;11:728–734.
[27] Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, *et al.* Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res* 2009;15:5379–5388.
[28] Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, *et al.* Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* 2014;124:687–695.
[29] Park SS, Dong H, Liu X, Harrington SM, Krco CJ, Grams MP, *et al.* PD-1 restrains radiotherapy-induced abscopal effect. *Cancer Immunol Res* 2015;3:610–619.
[30] Wang Y, Zenkoh J, Gerelchuluun A, Sun L, Cai S, Li X, *et al.* Administration of dendritic cells and anti-PD-1 antibody converts X-ray irradiated tumors into effective in situ vaccines. *Int J Radiat Oncol Biol Phys* 2019;103:958–969.
[31] Abuodeh Y, Venkat P, Kim S. Systematic review of case reports on the abscopal effect. *Curr Probl Cancer* 2016;40:25–37.
[32] Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, *et al.* Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* 2012;366:925–931.
[33] Hiniker SM, Chen DS, Reddy S, Chang DT, Jones JC, Mollick JA, *et al.* A systemic complete response of metastatic melanoma to local radiation and immunotherapy. *Transl Oncol* 2012;5:404–407.
[34] Okwan-Duodu D, Pollack BP, Lawson D, Khan MK. Role of radiation therapy as immune activator in the era of modern immunotherapy for metastatic malignant melanoma. *Am J Clin Oncol* 2015;38:119–125.
[35] Karbach J, Gnjatic S, Biskamp M, Atmaca A, Weidmann E, Brandt K, *et al.* Long-term complete remission following radiosurgery and immunotherapy in a melanoma patient with brain metastasis: immunologic correlates. *Cancer Immunol Res* 2014;2:404–409.
[36] Stamell EF, Wolchok JD, Gnjatic S, Lee NY, Brownell I. The abscopal effect associated with a systemic anti-melanoma immune response. *Int J Radiat Oncol Biol Phys* 2013;85:293–295.
[37] Tsui JM, Mihalcioiu C, Cury FL. Abscopal effect in a stage IV melanoma patient who progressed on pembrolizumab. *Cureus* 2018;10:e2238.
[38] 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.
[39] Deipolyi AR, Bromberg JF, Erinjeri JP, Solomon SB, Brody LA, Riedl CC. Abscopal effect after radioembolization for metastatic breast cancer in the setting of immunotherapy. *J Vasc Interv Radiol* 2018;29:432–433.
[40] Leung HW, Wang SY, Jin-Jhih H, Chan AL. Abscopal effect of radiation on bone metastases of breast cancer: a case report. *Cancer Biol Ther* 2018;19:20–24.
[41] Joe MB, Lum JJ, Watson PH, Tonseth RP, McGhie JP, Truong PT. Radiation generates an abscopal response and complete resolution of metastatic squamous cell carcinoma of the anal canal: a case report. *J Gastrointest Oncol* 2017;8:E84–E89.
[42] Sato H, Suzuki Y, Yoshimoto Y, Noda SE, Murata K, Takakusagi Y, *et al.* An abscopal effect in a case of concomitant treatment of locally and peritoneally recurrent gastric cancer using adoptive T-cell immunotherapy and radiotherapy. *Clin Case Rep* 2017;5:380–384.
[43] Shi F, Wang X, Teng F, Kong L, Yu J. Abscopal effect of metastatic pancreatic cancer after local radiotherapy and granulocyte-macrophage colony-stimulating factor therapy. *Cancer Biol Ther* 2017;18:137–141.
[44] Xie G, Gu D, Zhang L, Chen S, Wu D. A rapid and systemic complete response to stereotactic body radiation therapy and pembrolizumab in a patient with metastatic renal cell carcinoma. *Cancer Biol Ther* 2017;18:547–551.
[45] Van de Walle M, Demol J, Staelens L, Rottey S. Abscopal effect in metastatic renal cell carcinoma. *Acta Clin Belg* 2017;72:245–249.

[46] Sharabi A, Kim SS, Kato S, Sanders PD, Patel SP, Sanghvi P, *et al*. Exceptional response to nivolumab and stereotactic body radiation therapy (SBRT) in neuroendocrine cervical carcinoma with high tumor mutational burden: management considerations from the Center For Personalized Cancer Therapy at UC San Diego Moores Cancer Center. *Oncologist* 2017;22:631–637.

[47] Michot JM, Mazeron R, Dercle L, Ammari S, Canova C, Marabelle A, *et al*. Abscopal effect in a Hodgkin lymphoma patient treated by an anti-programmed death 1 antibody. *Eur J Cancer* 2016;66:91–94.

[48] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, *et al*. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015;372:2018–2028.

[49] Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, *et al*. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* 2017;18:895–903.

[50] Theurich S, Rothschild SI, Hoffmann M, Fabri M, Sommer A, Garcia-Marquez M, *et al*. Local tumor treatment in combination with systemic ipilimumab immunotherapy prolongs overall survival in patients with advanced malignant melanoma. *Cancer Immunol Res* 2016;4:744–754.

[51] Lehrer EJ, Peterson J, Brown PD, Sheehan JP, Quinones-Hinojosa A, Zaorsky NG, *et al*. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: an international meta-analysis of individual patient data. *Radiother Oncol* 2019;130:104–112.

[52] Formenti SC, Rudqvist NP, Golden E, Cooper B, Wennerberg E, Lhuillier C, *et al*. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. *Nat Med* 2018;24:1845–1851.

[53] Tang C, Welsh JW, de Groot P, Massarelli E, Chang JY, Hess KR, *et al*. Ipilimumab with stereotactic ablative radiation therapy: phase I results and immunologic correlates from peripheral T cells. *Clin Cancer Res* 2017;23:1388–1396.

[54] Hansen AR, Massard C, Ott PA, Haas NB, Lopez JS, Ejadi S, *et al*. Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. *Ann Oncol* 2018;29:1807–1813.

[55] Luke JJ, Lemons JM, Karrison TG, Pitroda SP, Melotek JM, Zha Y, *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.

[56] Sundahl N, De Wolf K, Kruse V, Meireson A, Reynders D, Goetghebeur E, *et al*. Phase 1 dose escalation trial of ipilimumab and stereotactic body radiation therapy in metastatic melanoma. *Int J Radiat Oncol Biol Phys* 2018;100:906–915.

[57] RADVAX™: A stratified phase I/II dose escalation trial of hypofractionated radiotherapy followed by ipilimumab in metastatic melanoma. Available at: https://clinicaltrials.gov/ct2/show/NCT01497808?term=NCT01497808&rank=1.

[58] Hiniker SM, Reddy SA, Maecker HT, Subrahmanyam PB, Rosenberg-Hasson Y, Swetter SM, *et al*. A prospective clinical trial combining radiation therapy with systemic immunotherapy in metastatic melanoma. *Int J Radiat Oncol Biol Phys* 2016;96:578–588.

[59] Williams NL, Wuthrick EJ, Kim H, Palmer JD, Garg S, Eldredge-Hindy H, *et al*. Phase 1 study of ipilimumab combined with whole brain radiation therapy or radiosurgery for melanoma patients with brain metastases. *Int J Radiat Oncol Biol Phys* 2017;99:22–30.

[60] Seung SK, Curti BD, Crittenden M, Walker E, Coffey T, Siebert JC, *et al*. Phase 1 study of stereotactic body radiotherapy and interleukin-2 – tumor and immunological responses. *Sci Transl Med* 2012;4:137ra74.

[61] Mitchell P, Siva S, Kok P, O'Byrne K, Yeung A, Livingstone A, *et al*. NIVORAD: a randomised phase 2 trial of nivolumab and stereotactic ablative body radiotherapy in advanced non-small cell lung cancer, progressing after first or second line chemotherapy. *J Clin Oncol* 2017;35. TPS9097-TPS.

[62] Sequencing of stereotactic ablative body radiotherapy in combination with PD-1 blockade using pembrolizumab in metastatic non-small cell lung carcinoma (SABRseq). Available at: https://clinicaltrials.gov/ct2/show/NCT03307759?term=NCT03307759&rank=1.

[63] FLT3 ligand immunotherapy and stereotactic radiotherapy for advanced non-small cell lung cancer (FLT3). Available at: https://clinicaltrials.gov/ct2/show/NCT02839265?term=NCT02839265&rank=1.

[64] Concurrent or sequential immunotherapy and radiation therapy in patients with metastatic lung cancer (COSINR). Available at: https://clinicaltrials.gov/ct2/show/NCT03223155?term=NCT03223155&rank=1.

[65] IMMUNOtherapy and Stereotactic ABlative Radiotherapy (IMMUNOSABR): a phase II study (IMMUNOSABR2). Available at: https://clinicaltrials.gov/ct2/show/NCT03705403?term=NCT03705403&rank=1.

[66] Phase Ib study of stereotactic body radiotherapy (SBRT) in oligometastatic non-small lung cancer (NSCLC) with dual immune checkpoint inhibition. Available at: https://clinicaltrials.gov/ct2/show/NCT03275597?term=NCT03275597&rank=1.

[67] Trial of local consolidation therapy (LCT) after nivolumab and ipilimumab (LONESTAR). Available at: https://clinicaltrials.gov/ct2/show/NCT03391869?term=NCT03391869&rank=1; 2017.

[68] Anti-PD 1 brain collaboration + radiotherapy: the ABC-X Study. Available at: https://clinicaltrials.gov/ct2/show/NCT03340129?term=NCT03340129&rank=1.

[69] Comparison of high-dose IL-2 and high-dose IL-2 with radiation therapy in patients with metastatic melanoma (SBRT/IL-2). Available at: https://clinicaltrials.gov/ct2/show/NCT01416831?term=NCT01416831&rank=1.

[70] Pilot study of stereotactic ablation for oligometastatic breast neoplasia in combination with the anti-PD-1 antibody MK-3475 (BOSTON II). Available at: https://clinicaltrials.gov/ct2/show/NCT02303366?term=NCT02303366&rank=1.

[71] Stereotactic radiation and immunotherapy in patients with advanced triple negative breast cancer (AZTEC). Available at: https://clinicaltrials.gov/ct2/show/NCT03464942?term=NCT03464942&rank=1.

[72] Stereotactic body radiation and monoclonal antibody to OX40 (MEDI6469) in breast cancer patients with metastatic lesions (OX40 Breast). Available at: https://clinicaltrials.gov/ct2/show/NCT01862900?term=NCT01862900&rank=1.

[73] Immunotherapy and SBRT for metastatic head and neck carcinomas. Available at: https://clinicaltrials.gov/ct2/show/NCT03283605?term=NCT03283605&rank=1.

[74] SBRT +/- pembrolizumab in patients with local-regionally recurrent or second primary head and neck carcinoma (KEYSTROKE). Available at: https://clinicaltrials.gov/ct2/show/NCT03546582?term=NCT03546582&rank=1.

[75] Screening trial of nivolumab with image guided, stereotactic body radiotherapy (SBRT) versus nivolumab alone in patients with metastatic head and neck squamous cell

carcinoma (HNSCC). Available at: https://clinicaltrials.gov/ct2/show/NCT02684253?term=NCT02684253&rank=1.
[76] A study of several radiation doses for patients with progression on immunotherapy/checkpoint inhibitors. Available at: https://clinicaltrials.gov/ct2/show/NCT03693014?term=NCT03693014&rank=1.
[77] Checkpoint blockade immunotherapy combined with stereotactic body radiation in advanced metastatic disease. Available at: https://clinicaltrials.gov/ct2/show/NCT02843165?term=NCT02843165&rank=1.
[78] Stereotactic body radiotherapy (SBRT) plus immunotherapy for cancer (C4-MOSART). Available at: https://clinicaltrials.gov/ct2/show/NCT03431948?term=NCT03431948&rank=1.
[79] Trial of salvage radiation therapy to induce systemic disease regression after progression on systemic immunotherapy. Available at: https://clinicaltrials.gov/ct2/show/NCT02710253?term=NCT02710253&rank=1.
[80] A phase II study of avelumab + stereotactic ablative body radiosurgery (SABR) for metastatic castration-resistant prostate cancer (mCRPC). Available at: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374725.
[81] Pembrolizumab in combination with intratumoral SD-101 therapy. Available at: https://clinicaltrials.gov/ct2/show/NCT03007732?term=NCT03007732&rank=1.
[82] Theelen W, Peulen H, Lalezari F, de Vries J, De Langen J, Aerts J, *et al*. Randomized phase II study of pembrolizumab after stereotactic body radiotherapy (SBRT) versus pembrolizumab alone in patients with advanced non-small cell lung cancer: the PEMBRO-RT study. *J Clin Oncol* 2018;36:9023.
[83] McBride SM, Sherman EJ, Tsai CJ, Baxi SS, Aghalar J, Eng J, *et al*. A phase II randomized trial of nivolumab with stereotactic body radiotherapy (SBRT) versus nivolumab alone in metastatic (M1) head and neck squamous cell carcinoma (HNSCC). *J Clin Oncol* 2018;36:6009.
[84] Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJ, *et al*. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2014;15:700–712.
[85] Phase II trial of salvage radiation therapy to induce systemic disease regression after progression on systemic immunotherapy. Available at: https://clinicaltrials.gov/ct2/show/NCT02710253?term=NCT02710253&rank=1.
[86] Golden EB, Chhabra A, Chachoua A, Adams S, Donach M, Fenton-Kerimian M, *et al*. Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. *Lancet Oncol* 2015;16:795–803.
[87] Escudier B, Ravaud A, Fabbro M, Douillard JY, Negrier S, Chevreau C, *et al*. High-dose interleukin-2 two days a week for metastatic renal cell carcinoma: a FNCLCC multicenter study. *J Immunother Emphasis Tumor Immunol* 1994;16:306–312.
[88] Twyman-Saint Victor C, Rech AJ, Maity A, Rengan R, Pauken KE, Stelekati E, *et al*. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature* 2015;520:373–377.
[89] Luke JJ, Chmura SJ. Reply to S.C. Formenti et al. *J Clin Oncol* 2018;36:2662–2663.
[90] Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, *et al*. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015;373:123–135.
[91] Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, *et al*. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017;389:255–265.
[92] Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, *et al*. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 2018;379:2342–2350.
[93] Senthi S, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol* 2012;13:802–809.
[94] Chang JY, Feng L, Lin SH, Welsh JW, Antonoff M, Gomez DR, *et al*. Phase II randomized clinical trial comparing immunotherapy plus stereotactic ablative radiotherapy (I-SABR) versus SABR alone for stage I, selected stage IIa or isolated lung parenchymal recurrent non-small cell lung cancer: I-SABR. *J Clin Oncol* 2018;36. TPS8580-TPS.
[95] Ablative STEreotactic RadiOtherapy wIth Durvalumab (MEDI4736) (ASTEROID). Available at: https://clinicaltrials.gov/ct2/show/NCT03446547?term=NCT03446547&rank=1.
[96] Stereotactic body radiation therapy (SBRT) combined with avelumab (anti-PD-L1) for management of early stage non-small cell lung cancer (NSCLC). Available at: https://clinicaltrials.gov/ct2/show/NCT03050554?term=NCT03050554&rank=1.
[97] SBRT with immunotherapy in early stage non-small cell lung cancer: tolerability and lung effects (STILE). Available at: https://clinicaltrials.gov/ct2/show/NCT03383302?term=NCT03383302&rank=1.
[98] Pembrolizumab after lung SBRT for medically inoperable early stage non-small cell lung cancer. Available at: https://clinicaltrials.gov/ct2/show/NCT03574220?term=NCT03574220&rank=1.
[99] Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, *et al*. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. *Nat Commun* 2017;8:15618.
[100] Filatenkov A, Baker J, Mueller AM, Kenkel J, Ahn GO, Dutt S, *et al*. Ablative tumor radiation can change the tumor immune cell microenvironment to induce durable complete remissions. *Clin Cancer Res* 2015;21:3727–3739.
[101] Brooks ED, Chang JY. Time to abandon single-site irradiation for inducing abscopal effects. *Nat Rev Clin Oncol* 2019;16:123–135.
[102] Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, *et al*. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019. Published April 11, 2019 online ahead of press. https://doi.org/10.1016/S0140-6736(18)32487-5.
[103] Marciscano AE, Ghasemzadeh A, Nirschl TR, Theodros D, Kochel CM, Francica BJ, *et al*. Elective nodal irradiation attenuates the combinatorial efficacy of stereotactic radiation therapy and immunotherapy. *Clin Cancer Res* 2018;24:5058–5071.