RADIATION ONCOLOGY—REVIEW ARTICLE

Clinical evidence for synergy between immunotherapy and radiotherapy (SITAR)

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Summary

Previous preclinical and clinical trials have shown promising antitumour activity and toxicity profile when employing the 'Synergy between Immunotherapy and Radiotherapy' (SITAR) strategy. Approximately, one in seven radiation therapy studies currently recruiting is investigating SITAR. This article reviews the range of cancers known to respond to immunotherapy and publications analysing SITAR. It sets the background for work that needs to be done in future clinical trials. It also reviews the potential toxicities of immunotherapy and discusses areas where caution is required when combining treatments.

Key words: checkpoint inhibitor; immunotherapy; radiotherapy; SABR; stereotactic.

Introduction

In 1979, Stone *et al*.[1] proved an association between radiation therapy and the immune system by showing that a higher dose of radiation therapy was needed to control sarcoma in mice following thymectomy or total body irradiation. Furthermore, clinically, we occasionally see metastases regress outside the irradiated volume, a phenomenon called the abscopal effect.[2] Various mechanisms have been proposed based on preclinical models which may lead to tumour 'rejection' by the immune system.[3] The anti-tumour immune response is tightly regulated by immune checkpoints, whereby immune-cell surface receptors control either the activation or the inhibition of immune responses.[4] Examples of immune checkpoint inhibitors include PD-1/PD-L1 axis inhibitors, such as atezolizumab, avelumab, nivolumab, pembrolizumab, and durvalumab or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, such as ipilimumab.[5–18] Table 1 summarises the target, type of antibody, approved uses, response rates, and the toxicity rates of the most common immune checkpoint inhibitors used in practice. Table 1 also highlights that immunotherapy is currently proven effective in selected cancers only. Even in cancers where it provides a survival benefit, many patients still do not respond. Table 1 highlights the rates of grades 3 and 4 toxicities with immunotherapy alone and stresses the importance of having future randomised controlled trials to evaluate the safety of immunotherapy–radiation therapy combination treatment.

This review covers the most clinically available immunotherapy agents, the cancers they are active in, and we discuss published radiation therapy–immunotherapy studies. It summarises the current clinical evidence for 'Synergy between Immunotherapy and Radiotherapy' (SITAR). A summary of SITAR publications is provided in Table 2, including the year, cancer type, intent, number of patients, phase of the study, sequencing of treatment, the dose of radiation therapy and results and toxicity.

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Table 1. Agent and comparator, target, antibody type, clinical uses of common immune checkpoint inhibitors, outcomes and toxicity rates

Agent and comparator	Target	Ig type	Clinical use	Outcomes (finding of the study)	Rate of Grade 3–4 toxicity in the immunotherapy group
Atezolizumab monotherapy[5]	PD-L1	IgG1	2nd line phase 2 metastatic bladder cancer	ORR 15–26% (depending on PD-L1 expression)	Grade 3–4 in 5% (mainly pneumonitis, increased LFT, rash and dyspnoea)
Chemotherapy +/−atezolizumab (IMpower 133)[6]	PD-L1	IgG1	1st line RCT ES-SCLC	CR 2.5% vs 1%, PR 58% vs 63% (NS) OS 12.3 vs 10.3 months	Grade 3–4 in 40% (mainly rash and hypothyroidism)
Avelumab monotherapy[7]	PD-L1	IgG1	1st line phase 2 Merkel cell carcinoma	ORR 40% (with 30% experiencing durable response)	Grade 3–4 in 18.1%
Nivolumab vs chemotherapy[8]	PD1	IgG4	2nd line RCT NSCLC	ORR 19% vs 12%	Grade 3–4 in 10%
Nivolumab vs everolimus[9]	PD1	IgG4	2nd or 3rd line RCT metastatic renal cancer	ORR 25% vs 5%	Grade 3–4 in 19%
Ipilimumab and nivolumab vs chemotherapy (Checkmate 743)[10]	CTLA-4 and PD1	IgG1 kappa and IgG4	1st line RCT mesothelioma	ORR 40% vs 43%. OS 18 vs 14 months	Grade 3–4 in 30%
Nivolumab plus ipilimumab vs nivolumab vs ipilimumab[11]	CTLA-4 and PD1	IgG1kappa and IgG4	1st line RCT metastatic melanoma	ORR 58%, 45% and 19%	Grade 3 or 4 in 59% vs 23% vs 28% (relatively higher dosing schedule for ipilimumab compared to other lung and mesothelioma studies)
Nivolumab plus ipilimumab vs nivolumab vs ipilimumab (CheckMate 040)[12]	CTLA-4 and PD1	IgG1kappa and IgG4	2nd line RCT advanced hepatocellular cancer	ORR 32% vs 27% vs 29%	Grade 3–4 in 53% vs 29% vs 31%
Pembrolizumab vs chemotherapy (KEYNOTE-024)[13]	PD1	IgG4 kappa	1st line RCT metastatic NSCLC PDL1+ >50%	ORR 45% vs 28%	Grade 3–5 in 26.6%
Pembrolizumab–axitinib vs sunitinib[14]	PD1	IgG4 kappa	1st line RCT metastatic renal cancer	ORR 59% vs 36%	Grade 3–5 in 76%
Pembrolizumab vs ipilimumab[15]	PD1	IgG4 kappa	1st line RCT metastatic melanoma	ORR 33% vs 12%	Grade 3–5 toxicity in 10.1%
Pembrolizumab vs chemotherapy[16]	PD1	IgG4 kappa	2nd line RCT metastatic urothelial carcinoma	ORR 21% vs 11%	Grade 3–5 toxicity in 15.0%
Durvalumab vs placebo (PACIFIC study)[17]	PD-L1	IgG1κ	1st line RCT Stage 3 NSCLC	ORR 28.4% vs 16.0%	Grade 3–4 in 30%
Ipilimumab monotherapy[18]	CTLA-4	IgG1kappa	Metastatic melanoma	ORR 10.9%	Grade 3–4 in 10–15%, 1% grade 5 toxicity

CR, complete response rate; ES-SCLC, Early stage small-cell lung cancer; LFT, liver function tests; NS, not statistically different; ORR, overall response rate; OS, median overall survival; PR, partial response rate; RCT, randomised controlled trial.

Lung cancer

The double-blinded phase III PACIFIC clinical trial demonstrated the efficacy of durvalumab sequentially after chemoradiotherapy (CRT) in stage III NSCLC. The 18-month progression-free survival (PFS) rate was increased from 27.0% to 44.2%, and durvalumab significantly prolonged the overall survival compared with placebo with a hazard ratio of 0.68.[42] Patients who had previously experienced Grade 2 or higher pneumonitis from CRT were excluded. In patients who received durvalumab, as compared with those who received placebo, pneumonitis or radiation pneumonitis of any grade occurred in 33.9% and 24.8% and pneumonitis or radiation pneumonitis of grade 3 or 4 occurred in 3.4% and 2.6%, that is, pneumonitis was more common in patients receiving subsequent immunotherapy, but was primarily low grade.[17] The next step for stage III lung cancer is to evaluate concurrent immunotherapy and radiotherapy. NICOLAS is a phase-II trial evaluating the safety and efficacy of nivolumab combined with CRT in stage III NSCLC.[43] Patients received platinum-based CRT, 66 Gy in 33 fractions. Eighty-two patients were recruited with a median follow-up of 13.4 months. For the first 21 patients, no grade-≥3-pneumonitis was observed by the end of the 3-month post-radiation therapy follow-up period. Radiation therapy was found to be an independent prognostic marker of favourable prognosis in NSCLC patients after treatment with nivolumab.

There is significant data suggesting that SITAR may be beneficial in stage IV lung cancer. The PEMBRO-RT phase 2 randomised clinical trial for 92 patients with advanced

Table 2. Immune checkpoint inhibitors used in combination with RT in recent clinical trials

Trial/author	Site	Year	Metastatic vs curative intent	Number of patients	Phase of study	Sequencing of treatment	Dose of RT	Endpoints and results	Toxicity
Atezolizumab									
Qin[19]	Metastatic NSCLC	2020	Metastatic	12	Phase 2	Concurrent	3 × 8 Gy or 5 × 6 Gy	ORR = 25%. OS = 6.9 months	5/12 had a grade 3 immune-related adverse event
Van den ende (PERFECT)[20]	In resectable oesophageal adenocarcinoma	2021	Curative	40	Phase 2	Concurrent	CROSS regimen combined with five cycles of atezolizumab	pCR in 25%. Baseline expression of an established IFNγ signature was higher in responders than non-responders	6/40 had any grade immune-related adverse events
Avelumab									
Kwan (ICE-PAC)[21]	Prostate	2021	Metastatic	31	Phase 2	SABR was administered to one or two disease sites within 5 d before the first and second avelumab treatments	20 Gy in one fraction	48% achieved CR or PR, or SD for ≥6 months	Grade 3–4 treatment-related adverse events occurred in six patients (16%), with three (10%) requiring high-dose corticosteroid therapy
Shamseddine[22]	Rectal	2020	Curative	13	Phase 2	Preop short-course radiation followed by six cycles of FOLFOX with avelumab in locally advanced rectal cancer patients	25 Gy in five fractions	3/13 achieved pCR, and another 3/13 had near pCR	The protocol regimen was well-tolerated, with no reported serious adverse events of grade 4
Lee[23]	Head and neck SCC	2021	Curative	697	Phase 3	Concurrent CRT +/− 2 weekly avelumab	70 Gy in 35 fractions	Median PFS not reached in both groups	Serious treatment-related adverse events occurred in 124 (36%) patients in the avelumab group and in 109 (32%) patients in the placebo group
Ipilimumab									
Chicas-Sett[24]	Melanoma	2018	Metastatic	451	Systematic review	Various	Various	The median reported abscopal effect and OS were 26.5% and 19 months, respectively	The median toxicity ≥ Grade 3 was 18.3%, ranged from 10% to 20%
Formenti[25]	NSCLC	2018	Metastatic	39	Phase 2	Concurrent	RT to one metastasis (palliative dose, 6 Gy × 5 or 9 Gy × 3)	ORR in 18% with 2 CR and 5 PR	Adverse events were consistent with ipilimumab-induced side effects, and the addition of RT did not modify them

Table 2. (continued)

Trial/author	Site	Year	Metastatic vs curative intent	Number of patients	Phase of study	Sequencing of treatment	Dose of RT	Endpoints and results	Toxicity
Fizazi[26]	Prostate	2014	Metastatic	799	Phase 3	Concurrent	8 Gy single fraction to one or more bone metastases	OS rates were higher in the ipilimumab versus placebo arms at 2 years (25.2% vs 16.6%), 3 years (15.3% vs 7.9%), 4 years (10.1% vs 3.3%), and 5 years (7.9% vs 2.7%)	In seven patients (1.8%) in the ipilimumab arm and one (0.3%) in the placebo arm, the primary cause of death was reported as study drug toxicity. No long-term safety signals were identified
Nivolumab									
Masini (Nives)[27]	Renal	2021	Metastatic	69	Phase 2	Concurrent	30Gy in three fractions	The ORR was 17%. The median PFS was 5.6 months, no evidence better than nivolumab alone	No new safety concerns arose
Peters (ETOP NICOLAS)[28]	Lung	2021	Curative	79	Phase 2	Concurrent nivolumab and CRT	66 Gy in 33 fractions	OS of 38.8 months and a 2-year survival rate of 63.7% (numerically higher than other studies for the same population)	Nine (11.7%) pneumonitis events of grade ≥3 occurred among the 79 patients. All happened within 1-year of follow-up. Half of all patients experienced adverse events
McBride[29]	Head and neck	2021	Metastatic	62	Phase 2 randomised	Nivolumab alone vs Concurrent	SABR to metastasis 9 Gy X 3 fractions	ORR in non-irradiated lesions was 34.5 vs 29%.	Grade 3–5 toxicities were similar (13.3% v 9.7%; $P = 0.70$)
Sundahl[30]	Melanoma	2019	Metastatic	20	Phase 2	Concurrent	SABR 8 Gy × 3	ORR in non-irradiated lesions of 45% was noted with three complete and six partial responses. Three patients experienced stable disease, and 7 had progressive disease as best response	Three patients experienced grade 3 AEs (lymphopenia, gastroenteritis, and bullous pemphigoid). No grade 4 to 5 AEs occurred
Voorwerk (TONIC)[31]	Triple-negative breast cancer	2019	Metastatic	67	Phase 2 randomised to five arms	Concurrent	8 Gy X3	ORR was higher in the cisplatin (ORR23%) and doxorubicin (ORR 35%) and not the RT group	Not reported
Pembrolizumab									
Liniker[32]	Melanoma	2016	Metastatic	53	Retrospective	Mixed sequential or concurrent.	Various	Response in irradiated extracranial/intracranial SRS lesions was 44% for sequential treatment and 64% for concurrent treatment ($P = 0.448$)	There was no excessive anti-PD-1 or RT toxicity observed in patients receiving extracranial RT

Table 2. (continued)

Trial/author	Site	Year	Metastatic vs curative intent	Number of patients	Phase of study	Sequencing of treatment	Dose of RT	Endpoints and results	Toxicity
Ho[33]	Triple-negative breast cancer	2020	Metastatic	17	Phase 2	Concurrent	30 Gy in five fractions	3/17 achieved CR. 17.6% had a reduction in tumour outside the treated area	29% experienced grade 1 or 2 dermatitis. 4/17 had a grade 3 adverse event
Shaverdian[34]	NSCLC	2017	Metastatic	98	Retrospective analysis of a phase 3 trial	Radiotherapy prior to immunotherapy	Various	OS 10.7 months vs 5.3 months ($P = 0.034$)	15 (63%) of 24 patients who had previously received thoracic radiotherapy had any recorded pulmonary toxicity versus 29 (40%) of 73 patients with no previous thoracic radiotherapy
Zhu[35]	Pancreatic	2021	Post-operative locally recurrent pancreatic cancer.	170	Phase 2 randomised	Concurrent.	35–40 Gy in five fractions	OS was 24.9 months vs 22.4 months $P = 0.0012$	22% vs 14% had a severe adverse event with and without immunotherapy
Rahma[36]	Rectal cancer	2021	Curative preoperative	185	Phase 2 randomised	Concurrent	50.4 Gy in 28 fractions	pCR rate was 31.9% vs 29.4% ($P = 0.75$)	Grade 3 to 4 adverse events were slightly increased 48.2% vs 37.3%
Li (PALACE-1)[37]	Oesophageal	2021	Curative preoperative	20	Phase 2	Concurrent	41.4 Gy in 23 fractions	pCR in 55.6%	Grade 3 + AEs 13/20, 65%, and one patient had a grade 5 AE
Fukushima[38]	Bladder	2020	Metastatic	98	Retrospective	History of radiotherapy to the primary tumour.	Various.	OS 77% vs 50% at 12 months; $P = 0.02$.	Not reported.
Tree (PLUMMB)[39]	Bladder	2018	Mixed	5	Phase 1	Concurrent	36 Gy in six fractions	Stopped early after five patients due to toxicity	3 grade 3, 1 grade 4
Siva (RAPPORT)[40]	Renal	2021	Metastatic	30	Phase 1/2	Sequential (5 days after radiotherapy)	20 Gy single fraction SABR (or, if not feasible, 10 fractions of 3 Gy) was given to all metastatic sites	Local control at 2 years was 92%. ORR was 63%, and DCR was 83%. Estimated 1- and 2-yr OS were 90% and 74%, respectively, and PFS was 60% and 45%	Four patients (13%) had grade 3 treatment-related AEs
Durvalumab									
Antonia (PACIFIC)[17]	Stage 3 NSCLC	2017	curative	713	Phase 3	Sequential	60 Gy in 30 fractions	18-month PFS was 44.2% versus 27.0%	Grade 3 or 4 adverse events occurred in 29.9% of the patients who received durvalumab and 26.1% of placebo
Xie.[41]	Pancreatic cancer	2020	metastatic	59	Phase 1	Sequential	SABR 8 Gy in one fraction or 25 Gy in five fractions	The ORR was 5.1%	No dose-limiting toxicities were seen

CR, complete response; ORR, overall response rate; OS, median overall survival; pCR, pathological complete response; PFS, progression-free survival; PR, partial response.

NSCLC compared pembrolizumab alone or after three doses of 8 Gy radiation therapy to a single tumour site showed an improvement in response rate at 12 weeks which was 18% in the control arm vs 36% in the experimental arm ($P = 0.07$). Median PFS was 1.9 months vs 6.6 months ($P = 0$ 0.19), and OS was 7.6 months vs 15.9 months, more so for the patients with PD-L1 negative tumours.[44] Two further retrospective studies support SITAR. A non-randomised retrospective analysis of 95 consecutive patients with advanced NSCLC who received radiation therapy treatment either during or within 60 days of nivolumab showed a median overall survival (OS) of 22.4 months vs 8.6 months.[45] The definition of radiation therapy within 60 days after immunotherapy as concurrent was used because of the long half-life of nivolumab, a feature common to immune checkpoint inhibitors. A subgroup analysis of the KEYNOTE-001 trial showed that OS after pembrolizumab was significantly longer in patients who had received previous radiation therapy than in those who were radiation therapy naïve (HR 0.58 $P = 0.026$; OS 10.7 months vs 5.3 months).[34]

There are several other smaller studies also suggesting a potential synergy between radiotherapy and nivolumab,[46] ipilimumab[25] and combined nivolumab and ipilimumab.[47] In the randomised multisite SABR phase 1 COSINR study for newly diagnosed stage IV NSCLC, no dose-limiting toxicity occurred in the concurrent cohort ($n = 18$), but the sequential cohort required a dose reduction in those participants with central lung lesions due to two patients (2/19) developing grade 4 pneumonitis.[47]

Atezolizumab established itself in extensive-stage small-cell lung cancer in the IMpower 133 study.[6] However, the investigators did not evaluate the possible benefit of combining it with radiotherapy, despite, in this population, where radiotherapy is a standard of care. It is not surprising that immunotherapy works in small-cell lung cancer. These patients have a history of prolonged tobacco exposure leading to high tumour mutational burden, often leading to natural immune phenomena such as paraneoplastic syndromes and high T-lymphocyte tumour infiltration. More work on SITAR in small-cell lung cancer is required.

Head and neck cancer

A phase 3 trial of 697 patients with locally advanced head and neck squamous cell carcinoma (HNSCC) were randomised to avelumab or placebo plus CRT found no benefit to the combination.[23] The stratified hazard ratio was 1.21, favouring the placebo group. The primary endpoint was PFS, but because of the short follow-up of 15 months in both groups, the median PFS was not reached in either group. In addition, treatment-related severe adverse events occurred in 36% of patients in the avelumab group and 32% in the placebo group, which suggests minimal increased toxicity, if any. In a phase Ib study, 59 HNSCC patients were treated with concurrent CRT and pembrolizumab. Safety was the primary endpoint, and the study found that pembrolizumab in combination with weekly cisplatin-based CRT was safe and did not impair the delivery of curative radiation therapy or chemotherapy and that early efficacy data support further investigation.[48] Currently active, the KEYNOTE-412 study is a randomised, double-blind, phase 3 trial investigating pembrolizumab or placebo administered concurrently with CRT and as maintenance treatment in patients with locally advanced HNSCC.[49]

In metastatic HNSCC, McBride *et al*. reported on a randomised clinical trial comparing nivolumab alone or combined with SABR, delivered in three fractions of 9 Gy to one metastatic lesion alone, leaving at least one other untreated lesion to evaluate the abscopal response. This study reported no evidence of an abscopal effect.[29] In other cancers, a delayed crossing over of the survival curves has been found to be a feature of anti-PD-1 therapy, and so longer follow-up may be required.[50]

Prostate cancer

Significant data support SITAR for prostate cancer. Kwon *et al*. conducted a randomised phase III trial of 799 patients with mCRPC following docetaxel chemotherapy. All patients had 8 Gy single fraction to between one and five metastases, but not necessarily to all metastases. After radiotherapy, patients were randomly allocated to receive ipilimumab or placebo until progression or intolerable side effects. The study found SITAR led to an improvement in OS at 2 years (25.2% vs 16.6%), 3 years (15.3% vs 7.9%), 4 years (10.1% vs 3.3%), and 5 years (7.9% vs 2.7%).[26,51,52]

Avelumab with stereotactic ablative body radiotherapy (SABR) was tested in a prospective phase 2 study called the ICE-PAC trial, which enrolled 31 men with progressive metastatic castrate-resistant prostate cancer (mCRPC) after at least one prior androgen receptor directed therapy.[21] Avelumab was administered every 2 weeks for 12 cycles. A single 20 Gy fraction of SABR was administered to one or two disease sites 5 days before the first and second avelumab treatments. The primary endpoint, disease control rate (DCR), was defined as the complete or partial response of any duration or stable condition for ≥6 months. The DCR rate was 48%, and it was higher in patients with lymph node predominant disease. Median OS was 14 months. Grade 3–4 treatment-related adverse events occurred in six patients (16%), with three (10%) requiring high-dose corticosteroid therapy. It is uncertain if this combination provided additional benefit to avelumab alone, and a phase 3 trial investigating this combination would be needed to demonstrate an advantage definitively. Of note, baseline androgen receptor alterations, MYC gain, and high baseline circulating tumour DNA fraction was possibly associated with poorer outcomes.[21]

Higa *et al*. found a high PSA response or stabilisation in approximately half of 31 mCRPC patients who received pembrolizumab with or without SABR with a trend for benefit with concomitant SABR. A PSA response was more common in men who had begun pembrolizumab with a lower PSA level, fewer bone metastases, fewer mutations and those who had not received previous chemotherapy, suggesting possible selection criteria for future studies.[53]

Urothelial cancer

Urothelial cancers are relatively uncommon cancers, but more common in elderly patients, and so a shorter course of radiotherapy is conceptually attractive. The PLUMMB trial (pembrolizumab in muscle-invasive/metastatic bladder cancer) was a phase I study addressing this concept. In the first dose-cohort, patients received pembrolizumab starting 2 weeks before weekly adaptive bladder radiation therapy to a dose of 36 Gy in six fractions. However, the trial was stopped after five enrolments because three patients experienced grade 3 urinary toxicities and one patient experienced a grade 4 rectal perforation.[39]

Nevertheless, early data does support the SITAR approach for urothelial cancer. A Japanese study retrospectively reviewed 98 advanced urothelial cancer patients treated with pembrolizumab, of whom 17% had prior radiation therapy to the primary tumour. The radiation therapy group showed a significantly higher objective response ratio than did the non-radiation therapy group (65% vs 19%; $P < 0.001$).[38] In a small study of 10 patients, durvalumab also has also shown activity in bladder cancer.[54]

Renal cancer

Paraneoplastic manifestations are present in up to 20% of patients with renal cell carcinoma, and a significant proportion of patients may survive several years with only slowly progressing metastatic disease, which is presumably a sign the immune system can keep the disease in check naturally.[55] Both nivolumab and pembrolizumab are standard treatments in stage IV disease.[9,14] The NIVES study in metastatic renal carcinoma investigated nivolumab's activity and safety with SABR, 30 Gy in three fractions to one lesion only, 7 days after the first nivolumab infusion. In these second- and third-line pretreated patients, the response rate in non-irradiated lesions was 17%, PFS was 5.6 months, and OS was 20 months.[27] The authors felt this result to be similar to cohorts of patients treated with nivolumab alone, without SABR.

The RAPPORT study is a progressive study where the researchers have attempted to treat all metastatic sites with single fraction 20 Gy SABR or 30 Gy in 10 fractions for one to five oligometastatic clear cell renal cell carcinoma followed 5 days later by pembrolizumab every 3 weeks for eight cycles.[40] The RAPPORT study included only patients who had up to two lines of prior systemic therapy. For 30 patients, local control at 2 years was 92%. Estimated 1- and 2-year OS was 90% and 74%, respectively, and PFS was 60% and 45%.[56] A phase III trial with this protocol could confirm the benefit compared with pembrolizumab alone.

Colorectal cancer

Only phase 2 studies in colorectal cancer have tested SITAR in both the neoadjuvant setting and the metastatic setting but results have not shown a benefit so far.

Shamseddine *et al*. conducted a phase 2 trial for locally advanced rectal cancer (T2N+ or T3 or T4a) of short-course radiation (25 Gy in five fractions) followed by six cycles of FOLFOX plus avelumab and total mesorectal excision and found a CR rate of 25%.[22] Rahma *et al*. reported on 185 rectal cancer patients, CR after neoadjuvant CRT +/− pembrolizumab did not show any difference, although long-term survival data are awaited. Grade 3–4 adverse events were slightly increased in the pembrolizumab arm (48.2%) vs the control arm (37.3%) during CRT.[36]

In microsatellite high (MSI-H) metastatic colorectal cancer, pembrolizumab was superior to chemotherapy in the KEYNOTE-177 randomised study, with a median PFS of 16.5 vs 8.2 months, most likely due to increased neo-antigen load associated with microsatellite instability.[57] Future studies may benefit from selecting MSI-H stage 3 or stage 4 colorectal cancer for SITAR, as these patients appear to benefit from immunotherapy the most.

Oesophageal cancer

The benefit of SITAR in oesophageal cancer is unconfirmed. Van den Ende *et al*. treated 40 patients with resectable oesophageal adenocarcinoma with neoadjuvant chemoradiation (CRT) therapy according to the CROSS regimen (paclitaxel, carboplatin, and 41.4 Gy/23 fractions) combined with five cycles of atezolizumab. Of these 40 patients, 6 experienced immune-related side effects. The pathologic complete response (CR) rate was 25%, no different from a historical propensity score-matched cohort with the CROSS regimen alone. In most cancers, patients who have a pathological CR after neoadjuvant therapy have longer event-free survival, however, pathological CR may not be a good surrogate for long-term survival in this situation because immunotherapy works slowly compared with for example chemotherapy. Baseline expression of an established IFNγ signature was higher in responders compared with non-responders suggesting that high inflammation in the sample at baseline predicted therapeutic benefit, including high PD-L1 combined positivity scores (CPS) $\geq$25.[20]

The PALACE-1 trial recruited 20 patients with oesophageal squamous cell carcinoma who underwent preoperative pembrolizumab, carboplatin, and paclitaxel CRT with 41.4 Gy in 23 fractions.[37] Grade 3 and higher adverse events were observed in 13 patients (65%), mainly lymphopenia. One patient had a grade 5 event due to a significant oesophageal haemorrhage. The pathological CR rate was higher than expected at 56%, but a larger phase III study is required to show that the benefit did not occur by chance. A future randomised SITAR study with prospective stratification by CPS may help select patients who benefit from SITAR.

Melanoma

Melanoma is a highly immunogenic tumour as shown by its response to immunotherapy.[11,15] Chicas-Sett *et al*. conducted a systematic review of the incidence of the abscopal effect among 451 patients with metastatic melanoma from 16 studies in which radiation therapy and ipilimumab were combined. They found that eight of 16 studies reported abscopal reactions, and for the eight studies, the median reported proportion of patients experiencing an abscopal effect was very high at 26.5%.[24] As expected, the median survival for patients with abscopal responses was significantly longer, 22.4 months, compared with 8.3 months in subjects who did not manifest an abscopal reaction. They reported median toxicity $\geq$ Grade 3 of 18.3% in patients with combined radiation therapy and ipilimumab. Furthermore, Koller *et al*.[58] report improved survival and CR rates in patients with stage IV melanoma treated with concurrent ipilimumab and radiation therapy versus ipilimumab alone. Other small non-comparative studies are referenced in Table 2.[30,32,59] A definitive phase 3 trial comparing SITAR to immunotherapy alone in stage IV melanoma is needed, especially with emerging evidence from the SABR-COMET study and similar studies for oligometastatic cancer.[60]

Pancreatic cancer

Zhu *et al*. investigated if SITAR was useful in locally advanced pancreatic cancer. They conducted an open-label phase 2 study randomised study of 170 patients with mutant KRAS and PD-L1 positive, to SABR plus pembrolizumab and trametinib (n = 85) or SABR plus gemcitabine (n = 85). OS was 24.9 months with SABR plus pembrolizumab and trametinib and 22.4 months with SABR plus gemcitabine (hazard ratio 0.60; P = 0.0012). Serious adverse events were reported by 19 (22%) participants in the SABR plus pembrolizumab and trametinib group and 12 (14%) in the SABR plus gemcitabine group, but no treatment-related deaths occurred.[35]

Xie *et al*. attempted SITAR in stage IV pancreatic cancer as a second-line treatment. In this study, 59 patients received 8 Gy in one fraction or 25 Gy in five fractions with durvalumab.[41] This study provided evidence suggesting that the acute safety profile was acceptable, but the median survival following treatment was only 3.3 months. With such short survival, it was impossible to identify any benefit signal, signifying that studies in metastatic cancer should investigate SITAR at an earlier time-point in the course of treatment, particularly in aggressive cancers such as pancreatic cancer, because immunotherapy can work slowly and it may take months to show if it is beneficial.

Breast cancer

The FDA has approved neoadjuvant pembrolizumab and palliative atezolizumab for triple-negative breast cancer patients, but data for the use of SITAR in breast cancer are limited. A recent review of the clinical studies using SITAR in breast cancer was conducted by Nguyen *et al*.[61] At present, there are only a few phase 2 studies.[31,33] In one phase 2 study, 17 patients received SABR to a single site with pembrolizumab, of these, three had a complete response, one stable disease and 13 progressed, which is apparently a favourable response rate compared with pembrolizumab alone which has a response rate of about 5%.[33,61] Future studies should focus on triple-negative breast cancer patients, as these patients are more likely to benefit from immunotherapy.

Gliomas

A phase I study of stereotactic reirradiation 30 Gy in five fractions with pembrolizumab and bevacizumab in 32 patients with recurrent high-grade gliomas showed that this regime was reasonably well-tolerated.[62]

Idiosyncratic toxicity of immune checkpoint inhibitors in combination with radiation therapy

Immune checkpoint inhibitors can cause varied and unpredictable immune-related adverse events whereby the immune-inflammatory response acts against the host's normal tissues. Different immune checkpoint inhibitors cause similar toxicities, as the toxicities are a class effect. These immune-inflammatory responses affect the skin, gastrointestinal tract, lungs, liver, thyroid, pituitary, and joints. They can rarely affect the central nervous system, kidneys, heart or haematological system.[63] There are reports of severe but rare interactions when immunotherapy is combined with radiation therapy. This stresses the importance of properly conducted randomised controlled trials of radiation therapy and immunotherapy agents to elucidate the risks and benefits of the strategy. However, immunotherapy combined with radiation therapy can result in idiosyncratic reactions, which would not be easily teased from data in large randomised trials because the absolute incidence is

low. It is worth bearing in mind that current immune checkpoint antibodies have long half-lives, and toxicity can occur months after the last dose of immunotherapy. For example, durvalumab infused intravenously every 2 weeks achieves a steady-state after 16 weeks and has a half-life of 18 days; once it reaches a steady state, it would take 3 months to clear from the system. Hence, radiation therapy given following the recent cessation of checkpoint blockade is, in effect, being given in combination.

Pneumonitis is a known risk with immunotherapy and hence leads to concerns about combining immunotherapy with thoracic radiation due to overlapping toxicity. It is uncertain if radiation therapy to the lung in the setting of planned immunotherapy could increase the likelihood of pneumonitis. In a retrospective review of 101 patients with lung cancer who received treatment with immunotherapy, 22 were diagnosed with pneumonitis, of which 73% (16/22) had a history of radiation therapy.[64] This relatively high incidence of pneumonitis makes it attractive to identify predictive biomarkers of severe toxicity aside from radiation dosimetric factors. In one study of 27 patients who received palliative thoracic radiation therapy (30 Gy in 10 fractions) followed by pembrolizumab (n = 17), nivolumab (n = 8) or atezolizumab (n = 4) immunotherapy, pre-radiotherapy levels of sialylated carbohydrate antigen KL-6 were shown to predict the likelihood of pneumonitis.[65] Pneumonitis events were grade 1 (n = 10; 34%), grade 2 (n = 4; 14%) and grade 3 (n = 3; 10%) after a median follow-up of 10 months. In that study, dosimetric factors, such as lung V5, V10, V20, V30, and mean lung dose (MLD) did not significantly differ between the grade $\leq$1 and grade $\geq$2 pneumonitis groups.

There are reports of CNS toxicity when radiation therapy is combined with immunotherapy.[66] In one case report, transverse myelitis occurred in the radiation field following 30 Gy in 10 fractions to T7-T10 spine.[67] The patient received a combination of ipilimumab and nivolumab during spine radiation therapy but was switched to pembrolizumab approximately 3 months later; and he developed new ataxia within 2 weeks of switching. Methylprednisolone, plasmapheresis, and cyclophosphamide were tried. However, infliximab was then given with a dramatic imaging response after one dose. There is also a case report of subacute monophasic multifocal inflammatory CNS disorder occurring after standard radiation therapy-TMZ plus nivolumab in a young GBM patient.[68]

Skin complications, such as erosive lichen planus and bullous pemphigoid have been reported in patients on nivolumab who had radiation therapy.[69,70] Radiation recall dermatitis after atezolizumab has been reported.[71]

Combining cellular immunotherapies with radiation therapy

Sipuleucel-T for prostate cancer is one example of a cancer vaccine which stimulates the T-cell immune response targeted against prostatic acid phosphatase (PAP) – an antigen that is highly expressed on prostate cancer cells.[72] Sipuleucel-T is manufactured by leukapheresis followed by ex vivo culture with a protein composed of PAP and GM-CSF, producing activated antigen-presenting cells which are then reinfused into the patient. In 2010, the IMPACT trial compared sipuleucel-T (341 patients) or placebo (171 patients) administered intravenously every 2 weeks, for a total of three infusions in patients with mCRPC and showed that the 36-month survival probability was 31.7% in the sipuleucel-T group versus 23.0% in the placebo group.[72]

Twardowski *et al*. reported a randomised Phase 2 study on 51 patients comparing sipuleucel-T alone versus sipuleucel-T initiated 1 week after completing sensitising radiation therapy to a single metastatic site at 30 Gy in 10 fractions.[73] There was a slight non-significant improvement in median progression-free survival of 2.5 months versus 3.6 months (P = 0.06). Sinha *et al*.[74] looked at a combination of sipuleucel-T and ipilimumab in patients with metastatic castration-resistant prostate cancer. The multivariate analysis found that patients with prior radiation treatment appeared to have improved radiographic progression-free survival.

Chimeric antigen receptor T cells, or CAR-T therapy, refers to a treatment where T cells are harvested from the patient or donor, extra genetic information tailor-made to recognise cancer cells from the patient is added to the T cells, and then the CAR-T cells are reinfused into the patient.[75] There are currently five FDA-approved CAR-T therapies; idecabtagene vicleucel for relapsed multiple myeloma, axicabtagene ciloleucel, and lisocabtagene maraleucel for relapsed or refractory large B-cell lymphoma, tisagenlecleucel for acute lymphoblastic leukaemia (ALL) and brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma and ALL. In haematological cancers, radiation therapy can act as bridging treatment while waiting for CAR-T therapy, radiation therapy can be used to prime CAR-T-cell-mediated death, radiation therapy can debulk and reduce tumour burden, and radiation therapy can be used for early salvage for patients at high risk of CAR-T therapy failure.[76] These are all additive benefits of radiation therapy and CAR-T therapy; however, evidence for synergy, whereby the combined use of two treatments outweighs the use of each of its components, is scarce in this setting.

For solid tumours, Hauth *et al*.[75] recently reviewed the role of radiation therapy in combination with CAR-T treatment. CAR-T-cell therapies for solid tumours are associated with unique challenges. The reason for this is that in hematologic malignancies, a common antigen is often uniformly expressed on the surface of all malignant cells, making them amenable to CAR-T therapies. Solid tumours lack such an antigen or undergo natural selection when exposed to therapeutic interventions such as monoclonal antibodies.[77] In solid tumours, radiation therapy increases the local expression of multiple

cytokines, including IFN-γ and its inducible chemokines, such as CXCL9, CXCL10, CXCL11 or CXCL16, which could chemoattract lymphocytes, including CAR-T cells, making it an attractive potential catalyst in the process.[78] In a glioblastoma mouse model, a subtherapeutic dose of local radiation therapy combined with chNKG2D T-cell treatment resulted in synergistic activity by promoting migration of CAR-T cells to the tumour site increased effector functions.[79] CAR-T therapy for triple-negative breast cancer is of interest because of the high mutational burden commonly seen in this particular type of breast cancer.[80]

What have we learned, where are the deficiencies, and what work is underway?

Just as immunotherapy works in some cancers and not others, SITAR appears to work in lung cancer and prostate cancer, but is less likely to be effective in head and neck cancers, as shown in randomised trials hitherto. Turchan *et al*. suggested that elective nodal irradiation in head and neck cancer may elicit an immunosuppressive effect and thus potentially explain the lack of benefit so far for SITAR in head and neck cancer.[81] Many current clinical SITAR studies are phase 2 studies, having been sequentially developed after the relatively recent phase 3 confirmation of efficacy of immunotherapy in many settings. However, there is a wealth of preclinical work in this area. In urothelial cancer, renal cancer and melanoma, promising results have been seen. So far, only a few studies have been done in pancreatic cancer, colorectal cancer, oesophageal cancer, breast cancer, and gliomas and these have as yet to demonstrate a synergistic effect.

One deficiency in several published studies at the moment is in the paucity of comparison of SITAR with the current standard of care. Secondly, several studies add both immunotherapy and radiotherapy simultaneously, making it difficult to ascertain if either treatment alone may have led to the same benefit.

Moving forward, a deeper understanding of reasons for success or failure within the clinical trials is required, and several authors have put forward theoretical suggestions. Masini *et al*.[27] suggested that several negative studies in the metastatic setting have used radiation therapy to only a fraction of the disease in the hope of eliciting an abscopal effect; but perhaps, treating all sites of disease or oligoprogressive lesions only may in the future prove to be more effective. The SABR-COMET trial showed that ablating all oligometastases prolongs survival.[60] It is tempting to combine the recent expansion in experience with SABR with expansion in immunotherapy treatments. The RAPPORT study has been quick to adopt this approach by offering SITAR treatment, either SABR or fractionated radiotherapy to all visible metastases in oligometastatic renal cancer patients, and this study demonstrated a relatively high local control and 2-year survival.[40,56] Turchan *et al*.[81] also promote this approach, suggesting that immunotherapy may be more effectivewhen there is a lower volume of residual tumour burden.

Future planned clinical trials will answer some of these questions. According to clinicaltrials.gov, approximately, one in seven radiation therapy studies currently recruiting is investigating SITAR. Priority areas being studied currently include biomarkers, patient selection, dose and fractionation, sequencing, and there is interest in combining with SABR, especially in the first-line setting.

Biomarkers and future directions

Only 20–40% of patients with selected cancers derive benefit from immunotherapy. PD-L1 immunohistochemistry assays may be helpful as a biomarker to guide the selection of patients to receive anti-PD-L1 inhibitors. In KEYNOTE-001, patients with advanced NSCLC treated with pembrolizumab with a PD-L1 tumour proportional score (TPS) of ≥50% had a response rate of 45.2%, versus 16.5% and 10.7% among patients with a TPS of 1–49% and <1%, respectively.[82] In the CheckMate 227 study, which compared first-line nivolumab plus ipilimumab versus chemotherapy in metastatic NSCLC, patients receiving immunotherapy had an improved OS regardless of a PD-L1 TPS of <1% or ≥1%.[83] In melanoma, PD-L1 TPS of ≥5% or <5% did predict response rates of 52.7% vs 33.1%, but the response rate of DTIC, the standard at the time, was relatively poor, that it was approved without restrictions on PD-L1 positivity.[84] In triple-negative breast cancer, PD-L1 staining also appears to be useful.[85]

Tumour mutational burden may predict response to immunotherapy independent of PD-L1 expression.[86] Other factors that may predict response to treatment include baseline clinical parameters, including the neutrophil to lymphocyte ratio, previously shown to be higher in patients without abscopal response to radiation therapy and granulocyte-macrophage colony-stimulating factor.[87]

Intratumour heterogeneity can confound the determination of PD-L1 expression in biopsy samples. For example, the TPS can vary depending on which part of a tumour is sampled, whether primary or metastases, at what time-point biopsies are taken, that is, before or after therapy, the assay used and inter-observer variability due to limits of human perception of a biomarker located within a complex visual environment.[88]

A phase 1 study in 35 patients with liver or lung metastases who initiated ipilimumab with SABR dose radiation therapy found that clinical benefit correlated with an increase in peripheral CD8+ T cells, CD8+/CD4+ T-cell ratio and proportion of CD8+ T cells expressing 4-1BB and PD1, suggesting the potential use of peripheral T-cell ratios as a biomarker for future studies.[89]

Future trials should pay attention to the unwanted radiation therapy effect in increasing regulatory T-cell (Treg) infiltration into tumours, which dampens the immune response.[90,91] Methods to downregulate Treg could pave the way in the future for more successful outcomes with SITAR combinations.

Future studies should analyse the appropriate outcome measures to assess new immunotherapy and radiation therapy combinations. For example, pseudoprogression on imaging is seen in 2–10% of patients treated with immunotherapy and can cloud the clinical picture.[92] There is an urgent clinical need for molecular assays that identify patients more likely to respond. For example, circulating tumour DNA or T-cell receptor levels may better predict responses earlier so that treatment can be modified if required. Imaging biomarkers such as 89-Zr-durvalumab may also be able to identify PD-L1 expression in the tumour as a whole rather than in biopsy specimens only, making them another promising potential biomarker.[93]

Insights gained from preclinical studies regarding optimal radiation dose

It has been recently reported that both fractionated and hypofractionated radiation therapy can produce abscopal responses[2]; however, hypofractionation is not always feasible. For example, in the PLUMMB trial, immune checkpoint inhibition potentiated the side effects of hypofractionated radiation therapy, resulting in unacceptable side effects and the discontinuation of that study.[39] Furthermore, it is uncertain if higher doses of radiotherapy may be more likely to produce the abscopal effect. As such, several studies have used preclinical models to further elucidate the optimal radiation dose to elicit a robust immune response.

One exemplary study compared three regimes on mouse breast tumours, 20 Gy in one fraction, 8 Gy in three fractions or 6 Gy in five fractions over consecutive days.[94] They found that fractionated radiation therapy-induced a better abscopal effect when combined with anti-CTLA-4 antibody, with the three 8 Gy fractions protocol being the most effective. Other studies have shown that low-dose radiation therapy (0.5–1 Gy per fraction) is sufficient to increase CD4+ and CD8+ T-cell infiltration into tumours, although this is also associated with an increase in T regulatory cell infiltration which may prevent effective anti-tumour immunity.[95] High-dose radiation therapy on the other hand is hypothesised to be required for an efficient immune response by showering the immune system with antigen; although there is preclinical evidence that dose ranges above 10 Gy may reduce radiation therapy-induced immune response via induction of the DNA exonuclease TREX1.[96]

A meta-analysis of preclinical data indicates that the probability of revealing the abscopal effect was 50% when a biologically equivalent dose (BED) of 60 Gy is generated with an assumed α/β ratio of 10 Gy.[97] However, most publications in the field have only examined the immune response after delivery of a single fraction and there is an overall lack of preclinical experiments that accurately mimic clinical doses. Moreover, older studies have used equipment incapable of stereotactically delivering radiation. With the development of radiotherapy platforms capable of delivering precise and conformal radiation therapy to small animals, such as the SAARP or XRAD SmART, it is essential that future preclinical research on combining immunotherapy with radiation therapy employ dosing methods to ensure they are as clinically applicable as possible.

Conclusion

This review describes the current data available for radiation in combination with immunotherapy. Immunotherapy has been a great advance in cancer therapy across multiple cancer subtypes. Despite this, not all patients derive benefit and there is significant scope for improvement. It is hoped that SITAR can be used to improve responses and long-term outcomes. To date, the data on the utilisation of SITAR are limited but there is provisional evidence to suggest synergy exists. Future well-designed larger scale studies are needed to determine the relevant clinical scenarios that would benefit from this approach moving forward.

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Data availability statement

Data sharing does not apply to this article as no new data were created or analysed in this study.

References

1. Stone HB, Peters LJ, Milas L. Effect of host immune capability on radiocurability and subsequent transplantability of a murine fibrosarcoma. *J Natl Cancer Inst* 1979; **63**: 1229–35.
2. 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.
3. Keam S, Gill S, Ebert MA, Nowak AK, Cook AM. Enhancing the efficacy of immunotherapy using radiotherapy. *Clin Transl Immunol* 2020; **9**: e1169.
4. Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor

immunotherapy. *Cancer Immunol Immunother* 2005; **54**: 307–14.
5. Rosenberg JE, Hoffman-Censits J, Powles T *et al*. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016; **387**: 1909–20.
6. Horn L, Mansfield AS, Szczesna A *et al*. First-line Atezolizumab plus chemotherapy in extensive-stage Small-cell lung cancer. *N Engl J Med* 2018; **379**: 2220–9.
7. D'Angelo SP, Lebbé C, Mortier L *et al*. First-line avelumab in a cohort of 116 patients with metastatic Merkel cell carcinoma (JAVELIN Merkel 200): primary and biomarker analyses of a phase II study. *J Immunother Cancer* 2021; **9**: e002646.
8. Borghaei H, Gettinger S, Vokes EE *et al*. Five-year outcomes from the randomized, phase III trials CheckMate 017 and 057: nivolumab versus docetaxel in previously treated non-Small-cell lung cancer. *J Clin Oncol* 2021; **39**: 723–33.
9. Motzer RJ, Escudier B, McDermott DF *et al*. Nivolumab versus Everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015; **373**: 1803–13.
10. Baas P, Scherpereel A, Nowak AK *et al*. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet* 2021; **397**: 375–86.
11. Larkin J, Chiarion-Sileni V, Gonzalez R *et al*. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med* 2019; **381**: 1535–46.
12. Yau T, Kang YK, Kim TY *et al*. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. *JAMA Oncol* 2020; **6**: e204564.
13. Reck M, Rodriguez-Abreu D, Robinson AG *et al*. Pembrolizumab versus chemotherapy for PD-L1-positive non-Small-cell lung cancer. *N Engl J Med* 2016; **375**: 1823–33.
14. Rini BI, Plimack ER, Stus V *et al*. Pembrolizumab plus Axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019; **380**: 1116–27.
15. Robert C, Schachter J, Long GV *et al*. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015; **372**: 2521–32.
16. Bellmunt J, de Wit R, Vaughn DJ *et al*. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017; **376**: 1015–26.
17. Antonia SJ, Villegas A, Daniel D *et al*. Durvalumab after chemoradiotherapy in stage III non-Small-cell lung cancer. *N Engl J Med* 2017; **377**: 1919–29.
18. Hodi FS, O'Day SJ, McDermott DF *et al*. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; **363**: 711–23.
19. Qin A, Rengan R, Lee S *et al*. A pilot study of Atezolizumab plus Hypofractionated image guided radiation therapy for the treatment of advanced non-Small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2020; **108**: 170–7.
20. van den Ende T, de Clercq NC, van Berge Henegouwen MI *et al*. Neoadjuvant chemoradiotherapy combined with Atezolizumab for Resectable esophageal adenocarcinoma: a single-arm phase II feasibility trial (PERFECT). *Clin Cancer Res* 2021; **27**: 3351–9.
21. Kwan EM, Spain L, Anton A *et al*. Avelumab combined with stereotactic ablative body radiotherapy in metastatic castration-resistant prostate cancer: the phase 2 ICE-PAC clinical trial. *Eur Urol* 2021; **81**: 253–62.
22. Shamseddine A, Zeidan YH, Kreidieh M *et al*. Short-course radiation followed by mFOLFOX-6 plus avelumab for locally-advanced rectal adenocarcinoma. *BMC Cancer* 2020; **20**: 831.
23. Lee NY, Ferris RL, Psyrri A *et al*. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol* 2021; **22**: 450–62.
24. Chicas-Sett R, Morales-Orue I, Rodriguez-Abreu D, Lara-Jimenez P. Combining radiotherapy and ipilimumab induces clinically relevant radiation-induced abscopal effects in metastatic melanoma patients: a systematic review. *Clin Transl Radiat Oncol* 2018; **9**: 5–11.
25. Formenti SC, Rudqvist NP, Golden E *et al*. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. *Nat Med* 2018; **24**: 1845–51.
26. Fizazi K, Drake CG, Beer TM *et al*. Final analysis of the ipilimumab versus placebo following radiotherapy phase III trial in Postdocetaxel metastatic castration-resistant prostate cancer identifies an excess of Long-term survivors. *Eur Urol* 2020; **78**: 822–30.
27. Masini C, Iotti C, De Giorgi U *et al*. Nivolumab in combination with stereotactic body radiotherapy in pretreated patients with metastatic renal cell carcinoma. Results of the phase II NIVES study. *Eur Urol* 2021; **81**: 274–82.
28. Peters S, Felip E, Dafni U *et al*. Progression-free and overall survival for concurrent nivolumab with standard concurrent chemoradiotherapy in locally advanced stage IIIA-B NSCLC: results from the European thoracic oncology platform NICOLAS phase II trial (European thoracic oncology platform 6-14). *J Thorac Oncol* 2021; **16**: 278–88.
29. McBride S, Sherman E, Tsai CJ *et al*. Randomized phase II trial of nivolumab with stereotactic body radiotherapy versus nivolumab alone in metastatic head and neck squamous cell carcinoma. *J Clin Oncol* 2021; **39**: 30–7.
30. Sundahl N, Seremet T, Van Dorpe J *et al*. Phase 2 trial of nivolumab combined with stereotactic body radiation therapy in patients with metastatic or locally advanced inoperable melanoma. *Int J Radiat Oncol Biol Phys* 2019; **104**: 828–35.
31. Voorwerk L, Slagter M, Horlings HM *et al*. Immune induction strategies in metastatic triple-negative breast

cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. *Nat Med* 2019; **25**: 920–8.
32. Liniker E, Menzies AM, Kong BY *et al*. Activity and safety of radiotherapy with anti-PD-1 drug therapy in patients with metastatic melanoma. *Onco Targets Ther* 2016; **5**: e1214788.
33. Ho AY, Barker CA, Arnold BB *et al*. A phase 2 clinical trialassessing theefficacy and safety of pembrolizumab and radiotherapy in patients with metastatic triple-negative breast cancer. *Cancer* 2020; **126**: 850–60.
34. Shaverdian N, Lisberg AE, Bornazyan K *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.
35. Zhu X, Cao Y, Liu W *et al*. Stereotactic body radiotherapy plus pembrolizumab and trametinib versus stereotactic body radiotherapy plus gemcitabine for locally recurrent pancreatic cancer after surgical resection: an open-label, randomised, controlled, phase 2 trial. *Lancet Oncol* 2021; **22**: 1093–102.
36. Rahma OE, Yothers G, Hong TS *et al*. Use of Total neoadjuvant therapy for locally advanced rectal cancer: initial results from the pembrolizumab arm of a phase 2 randomized clinical trial. *JAMA Oncol* 2021; **7**: 1225–30.
37. Li C, Zhao S, Zheng Y *et al*. Preoperative pembrolizumab combined with chemoradiotherapy for oesophageal squamous cell carcinoma (PALACE-1). *Eur J Cancer* 2021; **144**: 232–41.
38. Fukushima H, Kijima T, Fukuda S *et al*. Impact of radiotherapy to the primary tumor on the efficacy of pembrolizumab for patients with advanced urothelial cancer: a preliminary study. *Cancer Med* 2020; **9**: 8355–63.
39. Tree AC, Jones K, Hafeez S *et al*. Dose-limiting urinary toxicity with pembrolizumab combined with weekly Hypofractionated radiation therapy in bladder cancer. *Int J Radiat Oncol Biol Phys* 2018; **101**: 1168–71.
40. Pryor D, Bressel M, Lawrentschuk N *et al*. A phase I/II study of stereotactic radiotherapy and pembrolizumab for oligometastatic renal tumours (RAPPORT): clinical trial protocol. *Contemp Clin Trials Commun* 2021; **21**: 100703.
41. Xie C, Duffy AG, Brar G *et al*. Immune checkpoint blockade in combination with stereotactic body radiotherapy in patients with metastatic pancreatic ductal adenocarcinoma. *Clin Cancer Res* 2020; **26**: 2318–26.
42. Antonia SJ, Balmanoukian A, Brahmer J *et al*. Clinical activity, tolerability, and Long-term follow-up of Durvalumab in patients with advanced NSCLC. *J Thorac Oncol* 2019; **14**: 1794–806.
43. Peters S, Felip E, Dafni U *et al*. Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-radiotherapy regimen in stage III non-small cell lung cancer-the ETOP NICOLAS trial. *Lung Cancer* 2019; **133**: 83–7.
44. Theelen W, Peulen HMU, Lalezari F *et al*. Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-Small cell lung cancer: results of the PEMBRO-RT phase 2 randomized clinical trial. *JAMA Oncol* 2019; **5**: 1276–82.
45. Bassanelli M, Ricciuti B, Giannarelli D *et al*. Systemic effect of radiotherapy before or after nivolumab in lung cancer: an observational, retrospective, multicenter study. *Tumori* 2022; **108**: 250–7.
46. Yamaguchi O, Kaira K, Hashimoto K *et al*. Radiotherapy is an independent prognostic marker of favorable prognosis in non-small cell lung cancer patients after treatment with the immune checkpoint inhibitor, nivolumab. *Thorac Cancer* 2019; **10**: 992–1000.
47. Bestvina CM, Pointer KB, Karrison T *et al*. A phase I trial of concurrent or sequential ipilimumab, nivolumab, and stereotactic body radiotherapy in patients with stage IV non-Small cell lung cancer (COSINR study). *J Thorac Oncol* 2021; **17**: 130–40.
48. Powell SF, Gold KA, Gitau MM *et al*. Safety and efficacy of pembrolizumab with chemoradiotherapy in locally advanced head and neck squamous cell carcinoma: a phase IB study. *J Clin Oncol* 2020; **38**: 2427–37.
49. Machiels JP, Tao Y, Burtness B *et al*. Pembrolizumab given concomitantly with chemoradiation and as maintenance therapy for locally advanced head and neck squamous cell carcinoma: KEYNOTE-412. *Future Oncol* 2020; **16**: 1235–43.
50. Seiwert TY, Kiess AP. Time to debunk an urban myth? The "abscopal effect" with radiation and anti-PD-1. *J Clin Oncol* 2021; **39**: 1–3.
51. Kwon ED, Drake CG, Scher HI *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**: 700–12.
52. Heidegger I, Necchi A, Pircher A *et al*. A systematic review of the emerging role of immune checkpoint inhibitors in metastatic castration-resistant prostate cancer: will combination strategies improve efficacy? *Eur Urol Oncol* 2021; **4**: 745–54.
53. Higa J, Wilenius K, Savino S, Larsen C, Scholz M, Vogelzang N. Real world experience with pembrolizumab in recurrent or advanced prostate cancer. *Clin Genitourin Cancer* 2020; **18**: e397–401.
54. Levy A, Massard C, Soria JC, Deutsch E. Concurrent irradiation with the anti-programmed cell death ligand-1 immune checkpoint blocker durvalumab: single Centre subset analysis from a phase 1/2 trial. *Eur J Cancer* 2016; **68**: 156–62.
55. Gold PJ, Fefer A, Thompson JA. Paraneoplastic manifestations of renal cell carcinoma. *Semin Urol Oncol* 1996; **14**: 216–22.
56. Siva S, Bressel M, Wood ST *et al*. Stereotactic radiotherapy and short-course pembrolizumab for oligometastatic renal cell carcinoma-the RAPPORT trial. *Eur Urol* 2022; **81**: 364–72.

57. Andre T, Shiu KK, Kim TW *et al*. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med* 2020; **383**: 2207–18.
58. Koller KM, Mackley HB, Liu J *et al*. Improved survival and complete response rates in patients with advanced melanoma treated with concurrent ipilimumab and radiotherapy versus ipilimumab alone. *Cancer Biol Ther* 2017; **18**: 36–42.
59. Aboudaram A, Modesto A, Chaltiel L *et al*. Concurrent radiotherapy for patients with metastatic melanoma and receiving anti-programmed-death 1 therapy: a safe and effective combination. *Melanoma Res* 2017; **27**: 485–91.
60. Palma DA, Olson R, Harrow S *et al*. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: Long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol* 2020; **38**: 2830–8.
61. Nguyen AT, Shiao SL, McArthur HL. Advances in combining radiation and immunotherapy in breast cancer. *Clin Breast Cancer* 2021; **21**: 143–52.
62. Sahebjam S, Forsyth PA, Tran ND *et al*. Hypofractionated stereotactic re-irradiation with pembrolizumab and bevacizumab in patients with recurrent high-grade gliomas: results from a phase I study. *Neuro Oncol* 2021; **23**: 677–86.
63. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin* 2020; **70**: 86–104.
64. Barron F, Sanchez R, Arroyo-Hernandez M *et al*. Risk of developing checkpoint immune pneumonitis and its effect on overall survival in non-small cell lung cancer patients previously treated with radiotherapy. *Front Oncol* 2020; **10**: 570233.
65. Saito S, Abe T, Iino M *et al*. Incidence and risk factors for pneumonitis among patients with lung cancer who received immune checkpoint inhibitors after palliative thoracic radiotherapy. *J Radiat Res* 2021; **62**: 669–75.
66. Guenole M, Lucia F, Bourbonne V *et al*. Impact of concomitant systemic treatments on toxicity and intracerebral response after stereotactic radiotherapy for brain metastases. *BMC Cancer* 2020; **20**: 991.
67. Chang VA, Simpson DR, Daniels GA, Piccioni DE. Infliximab for treatment-refractory transverse myelitis following immune therapy and radiation. *J Immunother Cancer* 2018; **6**: 153.
68. Di Stefano AL, Savatovsky J, Feuvret L *et al*. CNS inflammatory disorder after concurrent radiotherapy-temozolomide and nivolumab in a glioblastoma patient. *Neuro Oncol* 2019; **21**: 139–41.
69. Katsuo K, Honda T, Komori T, Kaku Y, Kabashima K. Erosive lichen planus on the extremities during combination therapy with nivolumab and radiation: a second case report. *Acta Derm Venereol* 2020; **100**: adv00100.
70. Tanita K, Fujimura T, Kambayashi Y *et al*. Intensity-modulated radiotherapy triggers onset of bullous pemphigoid in a patient with advanced melanoma treated with nivolumab. *Case Rep Oncol* 2018; **11**: 114–8.
71. Nakashima K, Saruwatari K, Sato R *et al*. Non-small-cell lung cancer with severe skin manifestations related to radiation recall dermatitis after Atezolizumab treatment. *Intern Med* 2020; **59**: 1199–202.
72. Kantoff PW, Higano CS, Shore ND *et al*. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010; **363**: 411–22.
73. Twardowski P, Wong JYC, Pal SK *et al*. Randomized phase II trial of sipuleucel-T immunotherapy preceded by sensitizing radiation therapy and sipuleucel-T alone in patients with metastatic castrate resistant prostate cancer. *Cancer Treat Res Commun* 2019; **19**: 100116.
74. Sinha M, Zhang L, Subudhi S *et al*. Pre-existing immune status associated with response to combination of sipuleucel-T and ipilimumab in patients with metastatic castration-resistant prostate cancer. *J Immunother Cancer* 2021; **9**: e002254.
75. Hauth F, Ho AY, Ferrone S, Duda DG. Radiotherapy to enhance chimeric antigen receptor T-cell therapeutic efficacy in solid tumors: a narrative review. *JAMA Oncol* 2021; **7**: 1051–9.
76. Fang PQ, Gunther JR, Wu SY *et al*. Radiation and CAR T-cell therapy in lymphoma: future Frontiers and potential opportunities for synergy. *Front Oncol* 2021; **11**: 648655.
77. Esfahani K, Roudaia L, Buhlaiga N, Del Rincon SV, Papneja N, Miller WH Jr. A review of cancer immunotherapy: from the past, to the present, to the future. *Curr Oncol* 2020; **27** (Suppl 2): S87–97.
78. Schaue D, Kachikwu EL, McBride WH. Cytokines in radiobiological responses: a review. *Radiat Res* 2012; **178**: 505–23.
79. Weiss T, Weller M, Guckenberger M, Sentman CL, Roth P. NKG2D-based CAR T cells and radiotherapy exert synergistic efficacy in glioblastoma. *Cancer Res* 2018; **78**: 1031–43.
80. Dees S, Ganesan R, Singh S, Grewal IS. Emerging CAR-T cell therapy for the treatment of triple-negative breast cancer. *Mol Cancer Ther* 2020; **19**: 2409–21.
81. Turchan WT, Pitroda SP, Weichselbaum RR. Radiotherapy and immunotherapy combinations in the treatment of patients with metastatic disease: current status and future focus. *Clin Cancer Res* 2021; **27**: 5188–94.
82. Dang TO, Ogunniyi A, Barbee MS, Drilon A. Pembrolizumab for the treatment of PD-L1 positive advanced or metastatic non-small cell lung cancer. *Expert Rev Anticancer Ther* 2016; **16**: 13–20.
83. Hellmann MD, Rizvi NA, Goldman JW *et al*. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol* 2017; **18**: 31–41.
84. Robert C, Long GV, Brady B *et al*. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; **372**: 320–30.

85. Schmid P, Rugo HS, Adams S *et al*. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2020; **21**: 44–59.
86. Strickler JH, Hanks BA, Khasraw M. Tumor mutational burden as a predictor of immunotherapy response: is more always better? *Clin Cancer Res* 2021; **27**: 1236–41.
87. Golden EB, Chhabra A, Chachoua A *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.
88. Vitale I, Shema E, Loi S, Galluzzi L. Intratumoral heterogeneity in cancer progression and response to immunotherapy. *Nat Med* 2021; **27**: 212–24.
89. Tang C, Welsh JW, de Groot P *et al*. Ipilimumab with stereotactic ablative radiation therapy: phase I results and immunologic correlates from peripheral T cells. *Clin Cancer Res* 2017; **23**: 1388–96.
90. Kachikwu EL, Iwamoto KS, Liao YP *et al*. Radiation enhances regulatory T cell representation. *Int J Radiat Oncol Biol Phys* 2011; **81**: 1128–35.
91. Qinfeng S, Depu W, Xiaofeng Y, Shah W, Hongwei C, Yili W. In situ observation of the effects of local irradiation on cytotoxic and regulatory T lymphocytes in cervical cancer tissue. *Radiat Res* 2013; **179**: 584–9.
92. Dromain C, Beigelman C, Pozzessere C, Duran R, Digklia A. Imaging of tumour response to immunotherapy. *Eur Radiol Exp* 2020; **4**: 2.
93. Smit J, Borm FJ, Niemeijer AN *et al*. PD-L1 PET/CT imaging with radiolabeled durvalumab in patients with advanced stage non-small cell lung cancer. *J Nucl Med* 2021; **63**: 686–93.
94. Dewan MZ, Galloway AE, Kawashima N *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**: 5379–88.
95. Herrera FG, Ronet C, Ochoa de Olza M *et al*. Low dose radiotherapy reverses tumor immune desertification and resistance to immunotherapy. *Cancer Discov* 2021; **12**: 108–33.
96. Vanpouille-Box C, Alard A, Aryankalayil MJ *et al*. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. *Nat Commun* 2017; **8**: 15618.
97. Marconi R, Strolin S, Bossi G, Strigari L. A meta-analysis of the abscopal effect in preclinical models: is the biologically effective dose a relevant physical trigger? *PLoS One* 2017; **12**: e0171559.