SA–CME Information

THE SAFETY AND EFFICACY OF COMBINED IMMUNOTHERAPY AND RADIATION THERAPY

Description
To date, there is little consensus on how to best combine radiation and immune checkpoint blockade (ICB) to maximize therapeutic gains while minimizing the potential for serious overlapping toxicities. This review summarizes relevant clinical data related to both safety and efficacy of the combination of ICB and radiation.

Learning Objectives
After completing this activity, participants will be able to:

1. Better quantify the risk of toxicity when using combined immunotherapy and radiation based on current published studies.
2. Put into practice the rationale for recommending combined immunotherapy and radiation.

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The safety and efficacy of combined immunotherapy and radiation therapy

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Evasion of the host immune system is critical to the development and spread of cancer. Through aberrant activation of immune checkpoints, tumor cells have identified a potent strategy of immune escape.[1] When activated by foreign antigens, T-cells upregulate inhibitory receptors such as cytotoxic T-cell lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1). These immune checkpoints normally serve as protective homeostatic mechanisms to quell the immune response, thereby limiting immunopathology and promoting self-tolerance.[2] However, chronic antigenic stimulation without antigen clearance can drive effector T-cells into an abnormal state known as exhaustion. T-cell exhaustion mediated via the PD-1 pathway is one hypothesized mechanism by which the immune system fails to eradicate tumor cells.[3]

Inhibiting immune checkpoints has emerged as a promising anti-neoplastic therapy, reshaping treatment paradigms in oncology. The enthusiasm around immune checkpoint blockade (ICB) appears threefold. First, ICB has displayed superior survival in phase III trials over conventional therapies, making previously elusive outcomes now possible.[4-6] Second, responses achieved by ICB are durable. Third, ICB can be implemented across a wide range of heterogeneous cancer types. In a 2010 pivotal phase III trial of patients with metastatic melanoma, ipilimumab (antibody targeting CTLA-4) resulted in unprecedented long-term overall survival (OS) of 20% and, subsequently, became the first checkpoint inhibitor approved for clinical use in oncology.[4] A pooled analysis of several trials conducted in patients with metastatic melanoma validated durable long-term survival in 20% of ipilimumab-treated patients.[7] Furthermore, antibodies targeting the PD-1/PD-L1 axis, specifically nivolumab and pembrolizumab, have also demonstrated groundbreaking responses in 35% to 40% of patients with metastatic melanoma.[8,9] In addition to the success in melanoma, ICB, most notably anti-PD-1/PD-L1 therapies, have demonstrated activity in numerous other malignancies.[5,10-23]

Despite the clinical success of anti-CTLA-4 and anti-PD-1/ PD-L1 antibodies, only a minority of patients respond to immune checkpoint inhibitors. As such, novel strategies to enhance the efficacy and durability of ICB are needed. One such strategy is to utilize radiation therapy to augment the anti-tumor immune response. The immune-modulatory effects of radiation remain poorly understood and are summarized elsewhere.[24] The ability of radiation to specifically improve response to ICB was identified in early mice studies when Demaria and colleagues added radiation to CTLA-4 inhibition and witnessed regression of both irradiated and un-irradiated ("abscopal") tumors,[25] a phenomenon that has been replicated by other investigators.[26-28] This phenomenon of an abscopal response with combination radiation and ICB was later noted in several patient case reports in a variety of malignancies, revealing radiation's immune stimulatory properties and capacity to aid in systemic anti-tumor effects.[29-31] Perhaps the most compelling evidence of the synergy of radiation and ICB comes from the retrospective analysis of patients on KEYNOTE-001, a phase 1 trial of pembrolizumab in patients with metastatic non-small cell lung cancer (NSCLC). Specifically, in the subset of patients in this trial treated at the University of California, Los Angeles (UCLA) (n = 97), those who had radiation at some point in their oncological care appeared to have improved OS and progression-free survival (PFS) compared with those who never received radiation.[32] Overall, the combination of exciting preclinical data and intriguing

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case reports of the synergy of radiation and immunotherapy has led to dozens of ongoing clinical trials examining the combination of radiation and ICB in a variety of malignancies in the definitive, adjuvant and metastatic setting. This review aims to bridge the gap by highlighting our current clinical experience with radiation and ICB combination in regard to toxicity and efficacy in the treatment of solid tumors.

Clinical Experience

Retrospective Studies

A variety of retrospective studies have evaluated the combination of radiation and anti-CTLA-4 and anti-PD-1 therapy. Overall the combination appears to be safe with no significant increase in toxicity compared with monotherapy. Many of these studies have assessed the combination of ICB with stereotactic radiosurgery (SRS) for brain metastases. In 2015, Memorial Sloan Kettering Cancer Center published a retrospective study examining outcomes of combined SRS and ipilimumab ($n = 46$).[33] Patients were treated with a single fraction of 15 to 24 Gy and divided into 3 groups: SRS prior to, concurrent with, or after ipilimumab. Patients treated with SRS prior to or concurrently with ipilimumab had an apparent survival advantage and lower regional recurrence rates compared with patients treated with SRS after ipilimumab (1-year OS 65% vs 56% vs 40%, $p = 0.008$; 1-year regional recurrence 69% vs 64% vs 92%, $p = 0.003$). The treatment was overall well tolerated, where 20% of patients developed grade 3 to 4 adverse events (AEs), none of which prevented the therapy completion. Typical systemic immune-related AEs (irAEs) associated with ipilimumab remained unaffected by SRS. Seven patients (15%) experienced central nervous system (CNS)-specific grade 3 to 4 AEs, and these were slightly more frequent in those receiving concurrent therapy. These findings demonstrate that combined SRS and ipilimumab is relatively safe with a possible immune stimulatory effect of concurrent SRS.

A similar retrospective analysis conducted at the University of Virginia evaluated 46 patients with metastatic melanoma with brain metastases who received ipilimumab and SRS to a median dose of 20 Gy. Patients were divided into 2 groups: 1) SRS with concurrent ipilimumab or ipilimumab following SRS; and 2) SRS after completion of ipilimumab. Group 1 had substantially improved local tumor control at 1 year (54.4% vs 16.5%, $p = 0.005$) and a nonstatistically significant improvement in survival (59% vs 33%, $p = 0.118$) compared with group 2. However, the authors reported a higher incidence of radiation necrosis in group 1 (19.4% vs 9.7%, $p = 0.066$), calling into question the safety of concurrent ipilimumab and SRS.[34]

In a retrospective study between Yale and MD Anderson, patients ($n = 99$) with metastatic melanoma who received SRS within 5.5 months after their ipilimumab therapy had significantly better intracranial disease control than those who received SRS later (HR 2.07, $p = 0.041$). This benefit was more prominent in patients with higher baseline lymphocyte count (>1000/μL). Intriguingly, the 1-year intracranial control rate for the early SRS group was nearly 50%, a rate nearing that achieved by SRS plus whole-brain irradiation (WBRT), whereas the intracranial control rate for the late-SRS group was 20% to 30%, similar to the historical rate achieved by SRS alone. The toxicities were not reported in this study.[35]

In another retrospective analysis, Chen et al examined the safety and efficacy of concurrent ICB (ipilimumab, nivolumab, or pembrolizumab) and radiation in patients with metastatic NSCLC, melanoma, and RCC who had brain metastases treated with SRS without prior WBRT. Patients were treated with SRS ($n = 181$), SRS with nonconcurrent ICB ($n = 51$), or SRS with concurrent ICB ($n = 28$). Among patients who received ICB, no grade 4 irAEs were reported, and there was no significant difference in rates of irAEs among those who received concurrent (ie, within 2 weeks) vs. noncurrent ICB with SRS. Furthermore, with a median SRS dose of 20 Gy, there were no differences in any grade acute CNS toxicity or in the rate of pathologically confirmed radionecrosis (3% total) across groups. In addition to its demonstrated safety, concurrent ICB with SRS predicted for a decreased likelihood of the development of ≥ 3 new brain metastases after SRS (OR 0.337, $p = 0.045$). Median OS for patients treated with SRS, SRS with nonconcurrent ICB, and SRS with concurrent ICB was 12.9 months, 14.5 months, and 24.7 months, respectively. Furthermore, SRS with concurrent ICB had improved OS compared with SRS alone (HR 2.69, $p = 0.002$) and SRS with nonconcurrent ICB (HR 2.40, $p = 0.006$). The OS benefit of concurrent SRS and ICB was significant in comparison with patients treated with SRS before (HR 3.82, $p = 0.002$) or after ICB (HR 2.64, $p = 0.02$).[36]

A large retrospective review from MD Anderson Cancer Center was conducted of 137 patients with metastatic melanoma with brain metastases to predict the risk of radiation necrosis after SRS and ICB. Patients received ipilimumab (87%), pembrolizumab (9%), or both (4%). The crude rate of radionecrosis was 27% with a median time to radiation necrosis of 6 months. In those who received ipilimumab, pembrolizumab, or both, the respective radionecrosis rates were 13%, 7%, and 27%. On multivariate analysis, the authors found immunotherapy type and timing of immunotherapy to SRS (whether administered within 3, 6, or 12 months before or after) was not clearly associated with a differing radiation necrosis risk.[37]

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Martin et al recently published the largest series of patients treated with SRS with or without ICB to help define the risk or radiation necrosis with combination therapy. Specifically, this study retrospectively assessed 480 patients with brain metastases from melanoma, RCC, and NSCLC. The authors found that those who received ICB and SRS had higher rates of symptomatic radiation necrosis than those who received SRS alone (20% vs 7%, HR 2.56, p = 0.004). Their results also indicated that patients with metastatic melanoma were prone to increased rates of symptomatic radiation necrosis (HR 4.70, $p = 0.01$).[38]

Given numerous retrospective studies of SRS and ICB, there have been recent attempts to consolidate data. Lehrer et al published a meta-analysis to better elucidate the safety and efficacy of SRS with ICB. They reported an overall radiation necrosis rate of 5.3%, which was more notable in patients receiving ipilimumab over pembrolizumab or nivolumab. Their analysis indicated a 1-year OS of 64.6% vs 51.6% for concurrent (ie, SRS and ICB within 4 weeks of each other) and nonconcurrent therapy, respectively ($p < 0.001$).[39]

Taken together, these retrospective analyses of brain-directed radiation and ICB show that the combination is generally safe with a possible increase in risk of symptomatic radiation necrosis, and there are enticing signs of synergy between the two therapies. Other retrospective studies also indicate that the combination of ipilimumab and radiation to extracranial sites is overall well tolerated.[40-41]

Prospective Data

In addition to the plethora of the retrospective studies, in recent years prospective data has emerged evaluating the safety and efficacy of combined radiation and ICB. A number of these trials have evaluated the combination of radiation with ipilimumab. Investigators at the University of Pennsylvania completed a phase I trial of 22 patients with metastatic melanoma combining stereotactic body radiation (SBRT) with 4 cycles of adjuvant ipilimumab. The trial was designed with multiple dose levels. Liver and subcutaneous lesions were treated with 6 Gy x 2 or 3 fractions while lung and bone lesions were treated with 8 Gy x 2 or 3 fractions. Importantly, no dose-limiting toxicities (DLTs), defined as grade ≥ 4 irAEs or grade ≥ 3 non-irAEs, were observed. In fact, the observed toxicities were no different than one would expect from ipilimumab monotherapy, indicating radiation can safely be added to ipilimumab. Unirradiated lesions were assessed for an abscopal response; 18% of patients had a partial response (PR), 18% had stable disease (SD), and 64% had progressive disease (PD). With a median follow-up of 18 months, the median PFS was 3.8 months and median OS was 10.7 months.[26] Similar to preclinical studies, tumor PD-L1 expression correlated with inferior responses, suggesting that dual checkpoint blockade may enhance outcomes. Furthermore, results from another phase I trial in 35 patients with metastatic solid malignancies also demonstrated the combination of hypofractionated radiation (50 Gy in 4 fraction or 60 Gy in 10 fractions) and ipilimumab was safe.[42] Specifically, 34% of patients developed grade 3 toxicity (most frequently colitis) and there were 2 DLTs in those treated with liver-directed radiation. In terms of efficacy, 23% of patients derived a clinical benefit in abscopal tumors.[42] In addition, Williams et al recently published a phase I trial of 16 patients with metastatic melanoma and brain metastases with ipilimumab combined with SRS or whole-brain radiation. The combination was safe with no DLTs. Only one patient experienced a grade 3 neurotoxicity, but this occurred prior to administration of ipilimumab.[43] Furthermore, a phase I/II trial of patients with metastatic prostate cancer ($n = 71$) treated with ipilimumab with or without bone-directed radiation (8 Gy in 1 fraction) revealed that the combination was tolerable, and there were no increased toxicities in those who received radiation.[44] Similar safety results were seen in a phase III study comparing radiation with or without ipilimumab.[45]

Analogous to the combination of radiation and ipilimumab, phase I studies evaluating the combination of radiation and PD-1 blockade have demonstrated safety with signs of clinical efficacy. First, investigators from the University of Chicago conducted a phase I study evaluating the safety of pembrolizumab with multisite SBRT in patients with metastatic solid tumors ($n = 73$). At least 2 sites of metastatic disease were targeted with radiation. Radiation fractionation schedules for this trial included 30 Gy in 3 fractions for osseous disease, 50 Gy in 5 fractions for central lung tumors and mediastinal disease, and 45 Gy in 3 fractions for other sites. The therapy was overall well tolerated, but 6 out of 62 patients experienced grade 3 toxicities, corresponding to a DLT rate of 9.7%. When toxicity occurred, it tended to occur at the site of radiation. This trial also demonstrated possible synergism of radiation and pembrolizumab. The abscopal response rate was 13.2% in a population of heavily pre-treated patients. This population was unselected for PD-L1 expression and was enriched for histologies not associated with a significant response rate to pembrolizumab. Furthermore, the authors found that the expression of interferon-γ-associated genes from post-SBRT tumor biopsies significantly correlated with nonirradiated tumor response, albeit in a small sample size.[46]

Similarly, investigators from the University of Pennsylvania recently reported the initial results of a phase I trial combining SBRT and pembrolizumab for patients with metastatic solid tumors ($n = 24$). This trial included a cohort of patients who progressed on prior PD-1 blockade to better delineate

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the synergistic role of radiation therapy with ICB vs the effect of ICB alone. The investigators hypothesized that if patients demonstrated tumor shrinkage despite prior progression, this effect was likely due to the immune stimulatory effects of radiation. Overall, the trial had 2 stratums: 1) patients with melanoma or NSCLC who progressed on prior anti-PD-1 therapy and 2) patients with diverse solid malignancies that were anti-PD-1/PD-L1 therapy naïve. Every patient received 6 cycles of pembrolizumab, starting 1 week before radiation. Each group was evenly split to receive either 8 Gy x 3 fractions or 17 Gy x 1 fraction to the index lesion. All treatment-related toxicities were grade 1 and 2, suggesting that either fractionation with pembrolizumab was well-tolerated. Furthermore, this trial demonstrated signals of possible synergy. Within stratum 1 (n = 12), 2 patients (16.7%) who progressed on prior PD-1 inhibition demonstrated prolonged responses of 9.2 and 28.1 months. Within stratum 2 (n = 12), 1 patient achieved a complete response (CR) and 2 patients experienced prolonged SD of approximately 7 months. Interestingly, 2 irAEs (hypothyroidism and pneumonitis) occurred following radiation to a lung metastasis in the same patient who achieved a CR.[47]

As discussed, several single-arm phase I trials have been published establishing the safety of combined radiation and ICB, with encouraging signs of efficacy. However, to date no randomized or comparative trials combining ICB with or without radiation have been published, and to our knowledge only 3 such trials have been reported in abstract form. These trials have all combined anti-PD-1 therapy with or without radiation therapy in the metastatic setting and thus far have failed to show a definitive benefit of adding radiation therapy to anti-PD-1 therapy. At the 2018 American Society of Clinical Oncology (ASCO) annual meeting, Theelen et al reported on a multicenter trial randomizing 74 patients with metastatic NSCLC to pembrolizumab vs SBRT (8 Gy x 3 fractions) plus pembrolizumab. Although no results met statistical significance, there are encouraging signs of efficacy. Particularly in the combination arm, there was an increased objective response rate (39% vs 21%, p = 0.28), improvement in median PFS (7.1 vs 2.8 months) with a hazard ratio of 0.61 (95% CI 0.35-1.06, p = 0.08), and improvement in median OS (19.2 vs 7.6 months) with a hazard ratio of 0.58 (95% CI 0.31-1.1, p = 0.1). Importantly, the combination regimen was safe and there were no grade 3 or higher toxicities related to the addition of SBRT.[48] Furthermore, although not randomized, at the 2018 World Conference on Lung Cancer, Moreno et al presented comparative data of the anti-PD-1 antibody cemiplimab with or without SBRT (9 Gy × 3 fractions) in metastatic NSCLC. This study was a comparison of two phase 1 expansion cohorts, one with cemiplimab alone (n = 20) and the other in combination with SBRT (n = 33). Although, the combination arm had a similar safety profile, there did not appear to be any benefit of adding SBRT to cemiplimab.[49] Lastly, at the 2018 ASCO annual meeting McBride et al presented results from a phase II trial randomizing patients with metastatic head and neck squamous cell carcinoma (n = 53) to nivolumab with or without SBRT (9 Gy x 3). Although, the addition of radiation therapy did not increase the rate of ≥ grade 3 toxicities, SBRT did not enhance the efficacy of nivolumab with comparable objective response rates in the monotherapy vs combination arm (26.9% vs 22.2 %, p = 0.94).[50]

Importantly, the practice changing PACIFIC trial also provides unique insight into the safety of fractionated thoracic radiation with concurrent chemotherapy followed by ICB. Specifically, this trial, which randomized patients (n = 713) with stage III NSCLC to standard chemoradiation with or without adjuvant durvalumab (PD-L1 inhibitor), demonstrated a significant PFS and OS benefit with the addition of adjuvant durvalumab. The overall toxicity profile was similar between the durvalumab and placebo group with similar rates of any grade 3 to 4 AE (30% vs 26%).[51]

Conclusion

Based on promising preclinical data and enticing clinical case reports, there are more than 100 accruing clinical trials combining radiation therapy with various forms of immune checkpoint inhibitors. These trials span numerous malignancies in a variety of disease circumstances (metastatic, adjuvant, neoadjuvant or definitive) using different radiation doses, fractionation schedules, targets, and timing of ICB and radiation. These studies, along with ongoing and future basic and translational laboratory research, will undoubtedly provide more insight underlying the interaction of radiation and immunotherapy, and better define its safety and efficacy.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144(5):646-674.
2. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell.* 2015;27(4):450-461.
3. Pauken KE, Wherry EJ. Overcoming T cell exhaustion in infection and cancer. *Trends Immunol.* 2015;36(4):265-276.
4. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363(8):711-723.
5. Herbst RS, Baas P, Dong-Wan K, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet.* 2016;387(10027):1540-1550.
6. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med.* 2016; 375(19):1823-1833.
7. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III Trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol.* 2015;33(17):1889-1894.
8. Hodi FS, Kluger H, Sznol M, et al. Durable, long-term survival in previously treated patients with advanced melanoma (MEL) who received nivolumab

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(NIVO) monotherapy in a phase I trial [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16-20; New Orleans, LA. Philadelphia (PA): AACR; *Cancer Res.* 2016;76(14 Suppl):Abstract nr CT001.
9. Robert C, Ribas A, Hamid O, et al. Three-year overall survival for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. *J Clin Oncol.* 2016;34:15(Suppl)9503.
10. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med.* 2015;373(17):1627-1639.
11. Brahmer J, Reckamp KL, Baas, P, et al. Nivolumab versus Docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med.* 2015;373(2):123-135.
12. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med.* 2015;372(21):2018-2028.
13. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol.* 2016;17(7):883-895.
14. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in advanced renal-cell carcinoma. *N Engl J Med.* 2015;373(19):1803-1813.
15. 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(10031):1909-1920.
16. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol.* 2016;17(7):956-965.
17. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med.* 2015. 372(4):311-319.
18. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol.* 2018;4(5):e180013.
19. Frenel JS, Le Tourneau C, O'Neil B, et al. Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: results from the phase Ib KEYNOTE-028 trial. *J Clin Oncol.* 2017;35(36):4035-4041.
20. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet.* 2017;389(10088):2492-2502.
21. Diaz LA, Uram JN, Wang H, et al. Programmed death-1 blockade in mismatch repair deficient cancer independent of tumor histology. *J Clin Oncol.* 2016;34:15(suppl)3003-3003.
22. Le DT, Yoshino T, Jager D, et al. KEYNOTE-164: Phase II study of pembrolizumab (MK-3475) for patients with previously treated, microsatellite instability-high advanced colorectal carcinoma. *J Clin Oncol.* 2016;34:4(Suppl)TPS787-TPS787.
23. Diaz L, Marabelle A, Kim TW, et al. 386P Efficacy of pembrolizumab in phase 2 KEYNOTE-164 and KEYNOTE-158 studies of microsatellite instability high cancers. *Ann Oncol.* 2017;28(Suppl5).
24. Shabason JE, Minn AJ. Radiation and immune checkpoint blockade: from bench to clinic. *Semin Radiat Oncol.* 2017;27(3):289-298.
25. Demaria S, Kawashima N, Yang AM, 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(2 Pt 1):728-734.
26. Twyman-Saint VC, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature.* 2015;520(7547):373-377.
27. Park SS, Dong H, Liu X, et al. PD-1 restrains radiotherapy-induced abscopal effect. *Cancer Immunol Res.* 2015;3(6):610-619.
28. Rodriguez-Ruiz ME, Rodriguez I, Garasa S, et al. Abscopal effects of radiotherapy are enhanced by combined immunostimulatory mAbs and are dependent on CD8 T cells and crosspriming. *Cancer Res.* 2016;76(20):5994-6005.
29. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med.* 2012;366(10):925-931.
30. Hiniker SM, Chen DS, Knox SJ. Abscopal effect in a patient with melanoma. *N Engl J Med.* 2012;366(21):2035; author reply 2035-2036.
31. Siva S, Callahan J, MacManus MP, Martin O, Hicks RJ, Ball DL. Abscopal [corrected] effects after conventional and stereotactic lung irradiation of non-small-cell lung cancer. *J Thorac Oncol.* 2013;8(8):e717-712.
32. 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(7):895-903.
33. Kiess AP, Wolchok JD, Barker CA, et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. *Int J Radiat Oncol Biol Phy.* 2015;92(2):368-375.
34. Cohen-Inbar O, Shih HH, Xu Z, Schlesinger D, Sheehan JP. The effect of timing of stereotactic radiosurgery treatment of melanoma brain metastases treated with ipilimumab. *J Neurosurg.* 2017;127(5):1007-1014.
35. An Y, Jiang W, Kim BYS, Qian JM, et al. Stereotactic radiosurgery of early melanoma brain metastases after initiation of anti-CTLA-4 treatment is associated with improved intracranial control. *Radiother Oncol.* 2017;125(1):80-88.
36. Chen L, Douglass J, Kleinberg L, et al. Concurrent immune checkpoint inhibitors and stereotactic radiosurgery for brain metastases in non-small cell lung cancer, melanoma, and renal cell carcinoma. *Int J Radiat Oncol Biol Phys.* 2018;100(4):916-925.
37. Fang P, Jiang W, Allen P, et al. Radiation necrosis with stereotactic radiosurgery combined with CTLA-4 blockade and PD-1 inhibition for treatment of intracranial disease in metastatic melanoma. *J Neurooncol.* 2017;133(3):595-602.
38. Martin AM, Cagney DN, Catalano PJ, et al. Immunotherapy and symptomatic radiation necrosis in patients with brain metastases treated with stereotactic radiation. *JAMA Oncol.* 2018;4(8):1123-1124.
39. Lehrer EJ, Peterson J, Brown PD, 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.
40. Liniker E, Menzies AM, Kong BY, et al. Activity and safety of radiotherapy with anti-PD-1 drug therapy in patients with metastatic melanoma. *Oncoimmunology.* 2016;5(9):e1214788.
41. Aboudaram A, Modesto A, Chaltiel L, Gomez-Roca C, 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(5):485-491.
42. 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(6):1388-1396.
43. Williams NL, Wuthrick EJ, Kim 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(1):22-30.
44. Slovin SF, Higano CS, Hamid O, et al. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. *Ann Oncol.* 2013;24(7):1813-1821.
45. 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(7):700-712.
46. Luke JJ, Lemons JM, Karrison TG, et al. Safety and clinical activity of pembrolizumab and multisite stereotactic body radiotherapy in patients with advanced solid tumors. *J Clin Oncol.* 2018;36(16):1611-1618.
47. Maity A, Mick R, Huang AC, et al. A phase I trial of pembrolizumab with hypofractionated radiotherapy in patients with metastatic solid tumours. *Br J Cancer.* 2018;119(10):1200-1207.
48. Theelen W, Peulen H, Lalezari F, 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;36:15(Suppl)9023-9023.
49. Moreno V, Gil-Martin M, Johnson M, et al. Cemiplimab, a human monoclonal anti-pd-1, alone or in combination with radiotherapy: phase 1 NSCLC expansion cohorts [abstract MA04. 01]. *J Thorac Oncol.* 2018;13:10(Suppl).S366.
50. McBride SM, Sherman EJ, Tsai CJ, 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;36:15(Suppl)6009-6009.
51. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med.* 2018;379(24):2342-2350.