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Review Article

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TITLE PAGE

TITLE: Toxicity in combination immune checkpoint inhibitor and radiation therapy: a systematic review and meta-analysis

RUNNING TITLE: Toxicity of ICI + RT vs ICI alone

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Key words: toxicity, immune checkpoint inhibitors, radiotherapy, stereotactic radiosurgery, brain metastases, meta-analysis

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ABSTRACT

Background and purpose: Immune checkpoint inhibitor with radiation therapy (ICI + RT) is under investigation for improved patient outcome, so we performed a systematic review/meta-analysis of toxicities for ICI + RT compared to immune checkpoint inhibitor (ICI) therapy alone.

Materials and methods: A PRISMA-compliant systematic review of studies in MEDLINE (PubMed) and in the National Comprehensive Cancer Network guidelines was conducted, with primary outcome grade 3+ toxicity. Criteria for ICI alone were: phase III/IV trials that compared immunotherapy to placebo, chemotherapy, or alternative immunotherapy; and for ICI + RT: prospective/retrospective studies with an arm treated with ICI + RT. Meta-analysis was performed by random effects models using the DerSimonian and Laird method. The I^2 statistic and Cochran's Q test were used to assess heterogeneity, while funnel plots and Egger's test assessed publication bias.

Results: This meta-analysis included 51 studies (n=15,398), with 35 ICI alone (n=13,956) and 16 ICI + RT studies (n=1,442). Our models showed comparable grade 3-4 toxicities in ICI + RT (17.8%; 95% CI, 12.0-24.5%) and ICI alone (22.3%; 95% CI, 18.1-26.9%). Stratification by timing of radiation and irradiated site showed no significant differences, but anti-CTLA4 therapy and melanoma showed increased toxicity. The grade 5 toxicities were 1.1% and 1.9% for ICI alone and ICI + RT respectively. There was significant heterogeneity, but not publication bias.

Conclusions: The random effects model showed comparable grade 3-4 toxicity in using ICI + RT compared to ICI alone in CNS melanoma metastases, NSCLC, and prostate cancer. ICI + RT is safe for future clinical trials in these cancers.

Keywords: combination therapy, radiation, immune checkpoint inhibitor, toxicity

INTRODUCTION

Recent rising use of immune checkpoint inhibitors (ICIs) in metastatic and recurrent cancers

leverages their systemic activity to eradicate disseminated malignancies. For example, the

current National Comprehensive Cancer Network (NCCN) guidelines (version 1.2019) for newly

diagnosed metastatic melanoma to the brain recommend four treatment options: ipilimumab with

nivolumab, nivolumab alone, pembrolizumab, or BRAF/MEK inhibitors.[1] Similarly, radiation

therapy (RT) may be used for palliation or definitive treatment of oligoprogressive disease.[1]

However, ICI use results in well-characterized accompanying toxicities.[2] Targets of ICI therapy

include cytotoxic T lymphocyte antigen 4 (CTLA4), programmed cell death protein 1 (PD1), and

programmed death-ligand 1 receptor (PDL1).[3]

There is interest in combining ICI with RT in order to increase efficacy of therapy and

reduce rate of recurrence,[4-21] as well as to explore the possibility of enhancing an abscopal effect.

However, there are few data regarding the toxicity of this combination therapy in humans. The

proinflammatory effects of ICI and RT may be additive, resulting in unacceptable toxicity. A

recent meta-analysis found that in patients treated for brain metastases by ICI and SRS,

ipilimumab was associated with greater risk of radionecrosis.[7, 22, 23] There is evidence that PD-1

signaling is significantly involved in radiation-induced cardiac toxicity.[24] Finally, it is not known

what timeline of ICI and RT maximizes efficacy without sacrificing safety, though some

evidence suggests concurrent therapy is superior to non-concurrent.[6, 25, 26]

There are currently limited data available across disease sites regarding the safety of

combination ICI + RT, with respect to ICI target, RT fractionation, timing of therapy, and region

irradiated. We sought to compare toxicity of ICI + RT to ICI alone, review evidence for

differences in timing of ICI + RT administration, and to examine other factors which may affect

toxicity. We hypothesized there is no increase in toxicity due to ICI + RT therapy compared to

ICI alone.

MATERIALS AND METHODS

Evidence acquisition

The inclusion criteria for the literature search was defined using the Population,

Intervention, Control, Outcome, Study Design (PICOS), per **Table 1**.[27-29] The Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) literature selection

protocol was used for article selection, per **Figure 1**.[30] The Meta-analyses Of Observational

Studies in Epidemiology (MOOSE) guidelines were followed.

Medical literature including clinical trials, clinical studies, comparative studies, and

multicenter studies published in English was searched in PubMed, Google Scholar, and the 2019

NCCN guidelines. For ICI alone, the search terms used were: (nivolumab or ipilimumab or

pembrolizumab or durvalumab or cemiplimab or atezolizumab or avelumab or tremelimumab or

ctla4 or pd1 or pdl1). For ICI + RT, the search terms used were the same along with: and

("radiation therapy" or radiotherapy or radiosurgery); the ICI alone results were limited to phase

III/IV clinical trials in humans. 703 ICI + RT studies and 93 ICI alone studies from PubMed

were found and screened based on title to exclude non-relevant studies such as basic science and

non-human studies; 12 additional non-duplicate ICI + RT records were identified from the

NCCN guidelines. The studies were checked for completeness by coauthors who are both

medical and radiation oncologists (EL, NZ, DT, CH). Of the 618 ICI + RT and 93 ICI alone non-

duplicate remaining studies, 29 ICI + RT and 66 ICI alone full-text articles passing the title

screening were reviewed for inclusion of relevant treatment and toxicity data. An additional 13

ICI + RT articles were excluded for not including grade 3-4 adverse event data, and 27 ICI alone

articles excluded as subgroup analyses of trials already included (**Figure 1**).

Data extraction

51 full-text articles (16 ICI + RT and 35 ICI alone) were reviewed and coded into a database by two authors (CMS and EL); discrepancies were discussed with three other authors (NZ, DT, CH). Extracted data included number of patients, disease site, therapy (radiation method and/or ICI used), timing of radiation with respect to immunotherapy, radiation dose and fractionation, radionecrosis incidence, and toxicities (grade 3-4 and/or grade 5). Each study arm was coded separately, and RT alone control arms in the ICI + RT studies were excluded.

Intervention and endpoints

The intervention was radiation therapy alone (RT), immunotherapy alone (ICI), or combination radiation and immunotherapy (ICI + RT). Included ICI + RT studies could have multiple arms comparing therapies or could be single-arm studies of each intervention alone.

The primary endpoint was worst reported grade 3-4 toxicities for each patient. One study did not provide this information, and we reached out to the corresponding author for patient adverse event logs.[11] In this case, we coded a grade 3-4 toxicity if the toxicity was "probably" or "definitely" caused by treatment.

We classified timing RT relative to ICI administration into four categories: "before" in which RT was given and completed before an ICI; "mixed" in which RT was given before the ICI and continued during ICI administration; "concurrent" in which RT was administered within 4 weeks after ICI; and "after" in which RT was administered past 8 weeks after the last ICI. We provide this timing data in **Supplemental Table 3**. Data were discussed by all authors to maintain reporting accuracy.

Statistical Analysis

RStudio version 3.6.1 (Boston, MA) and The Meta-Analysis Package for R (metafor v. 2.1.0) version were used to conduct the meta-analyses.[31, 32] The General Package for Meta-Analysis was used to generate the forest plots. The DerSimonian and Laird method was used to perform meta-analysis of grade 3-4 toxicities.[33] Univariate meta-regression of toxicities was also performed with respect to concurrency of ICI + RT, RT target, immune signaling axis targeted by ICI, malignant histology, and ICI used. Heterogeneity was assessed using the I^2 statistic and the Cochran Q-Test, with significance if $I^2 > 50\%$ and $p < 0.10$ respectively.[34]

Random effects models were used over fixed effects models to mitigate heterogeneity. Forest plots were generated for ICI alone and ICI + RT. Graphing of meta-regression intercepts, 95% confidence intervals, and statistical significance by Wald test were also performed. A Bonferroni correction was applied to the p-values of the Wald-type tests for each categorical variable, so that the null hypothesis was rejected with $p < 0.05$.

We analyzed the studies for publication bias using funnel plots (funnelR) and tested for asymmetry with Egger's test, significant if $p < 0.05$.[35]

RESULTS

The meta-analysis included 15,398 patients across 51 studies published during the years 2004-2019.[4-7, 9-12, 14-16, 18, 20, 21, 36-71] The ICI + RT studies were mainly from the United States, with two studies done in France,[7, 12] one study in Italy,[15] one in Australia,[18] and one between Belgium and Canada.[21] The ICI alone studies included multi-national/multi-center randomized clinical trials with patients from the United States, the United Kingdom, France, Spain, Poland, Denmark, Germany, Hungary, Austria, Canada, Australia, and other countries.

There were 35 studies with ICI alone arms totaling 13,956 patients (**Supplemental Table 3**).[36-71] Disease sites include cancers of head and neck,[41, 42] stomach,[49, 68] melanoma,[46, 47, 50, 51, 56, 58, 59, 61, 62, 67, 70, 71] lung,[38-40, 43-45, 55, 57, 60, 63, 64, 69] kidney,[12, 53, 54, 65] prostate,[36] and urothelial origin.[37, 52, 66] Four studies compared ICI alone regimens to other ICI alone regimens.[58, 63, 70, 71] Three studies assigned multiple ICI therapy to an arm (combination nivolumab with ipilimumab).[63, 65, 71] The ICIs used were: anti-CTLA4 (ipilimumab[36, 46, 47, 58, 59, 61, 63, 65, 70, 71]), anti-PD1 (nivolumab,[38-40, 42, 44, 51, 54, 63, 65, 67, 69-71] pembrolizumab[37, 41, 43, 45, 50, 55, 58, 62, 64, 68]), and anti-PDL1 (atezolizumab,[53, 57, 66] avelumab,[60] durvalumab[52]).

There were 16 studies with ICI + RT arms totaling 1,442 patients (**Supplemental Table 3**).[4-7, 9, 11-21] Of these, 507 patients were given concurrent RT and ICI,[7, 13, 16] 456 were given RT courses ending before ICI administration,[9, 17, 20] and the remaining 479 patients were give a combination of timings of RT with respect to ICI administration.[4-6, 11, 12, 14, 15, 18, 19, 21] Most studies reported a disease site of melanoma metastases to the brain;[4-6, 9, 11, 12, 14, 16, 18, 19] other disease sites included cancers of lung,[5, 13-15] kidney,[5, 14, 15, 19] prostate,[17, 20] and urothelial origin.[21] The ICIs used were: anti-CTLA4 (ipilimumab[5, 6, 11, 16, 17, 19, 20], tremelimumab[56]), anti-PD1 (nivolumab,[5, 12, 15, 18, 19] pembrolizumab[4, 5, 12, 18, 21]), and anti-PDL1 (durvalumab[7, 13]). Median

radiation dosage for all ICI + RT patients was 22.5 Gy / 1 fraction. One study included 473

patients who received 60 Gy in multiple fractions to the lungs,[13] and two other studies totaling

434 patients delivered 8 Gy / 1 fraction to bony lesions from the prostate.[17, 20, 31]

We assessed for publication bias using funnel plots and Egger's test (**Supplemental**

Figure 1). For ICI alone, Egger's test gave p=0.698 while for ICI + RT, Egger's test gave

p=0.258. Since p>0.05 in both cases, we did not reject the null hypothesis that the funnel plots

are symmetric.

According to our weighted random effects model, worst reported grade 3-4 toxicities are

observed in 22.3% (95% confidence interval: 18.1-26.9%) of ICI alone patients and 17.8% (95%

CI: 12.0-24.5%) of ICI + RT patients. Forest plots are in **Figures 2A** and **2B**, with side-by-side

comparison in **Figure 2C**.

Across all ICI + RT studies, only 2 patients in one multi-arm study and 1 patient in a case

series were reported to experience grade 3-4 radionecrosis.[5, 18] The authors did not find

significant differences in radionecrosis among the RT, concurrent ICI + RT, or non-concurrent

ICI + RT groups.[6]

From univariate categorical meta-regression, no statistically significant differences in

grade 3-4 toxicity were seen in either the timing or irradiated site for the ICI + RT studies

(**Figures 3A and 3B**). Variables which resulted in significant differences in grade 3-4 toxicity

were: the axis targeted (e.g. anti-PD1 vs anti-CTLA4, **Figure 3C**), the histological origin of the

malignancy (e.g. HNSCC vs melanoma, **Figure 3D**), and the specific ICI used in the study (e.g.

durvalumab vs ipilimumab, **Figure 3E**).

A statistically significant effect on grade 3-4 toxicity was seen with histological origin of the malignancy in the ICI alone studies (**Figure 3D**). Treatment of melanoma was associated with greater toxicity than treatment of NSCLC. However, this result may be confounded by the effects of anti-CTLA4 therapy, with 9 melanoma arms out of 19 total treated with ipilimumab;[46, 47, 58, 59, 61, 70, 71] one additional arm was treated with the anti-CTLA4 agent tremelimumab.[56] No such effect was seen for the ICI + RT studies.

Anti-CTLA4 therapy increased grade 3-4 toxicity compared to anti-PD1 therapy and anti-PDL1 therapy in the ICI alone studies (**Figure 3C**). The breakdown of specific ICIs reflects this trend in the ICI alone studies, with the anti-CTLA4 ipilimumab and tremelimumab showing increased toxicity compared to the anti-PD1 nivolumab and pembrolizumab and the anti-PDL1 atezolizumab and durvalumab (**Figure 3E**).

There were twenty-eight grade 5 toxicities (deaths related to treatment) observed in the phase III ICI + RT studies. Grade 5 toxicities were observed at a rate of 4.4% (21 deaths) for non-small cell lung cancer (NSCLC treated with adjuvant durvalumab and definitive platinum-based chemoradiotherapy,[13] and 1.0% (7 deaths) for castration-resistant prostate cancer treated with concurrent ipilimumab and directed radiotherapy for bone metastases.[17] No other ICI + RT study included in this meta-analysis reported any grade 5 toxicities, giving an overall grade 5 toxicity incidence of 1.9% (28 deaths out of 1,442 treated) for the ICI + RT studies. This rate was similar to the overall grade 5 toxicity incidence of the ICI alone studies, which was 1.1% (158 deaths out of 13,956 treated).[36-47, 49-71]

DISCUSSION

ICI + RT is currently being investigated as a treatment strategy for cancers of various origin, however there are few clinical trials with characterize the toxicity of ICI + RT compared to ICI alone. This meta-analysis indicates that around 1 in 5 patients treated with ICIs experienced treatment-related grade 3-4 toxicity, a rate paralleled in ICI + RT patients regardless of timing of ICI + RT administration. Incidence of treatment-related grade 5 toxicity was slightly higher for ICI + RT than for ICI alone, at 1.9% and 1.1% respectively. Due to the similar toxicities between ICI + RT and ICI alone, it appears that ICI + RT is a viable treatment option and warrants further study.

In the ICI alone studies, the significant heterogeneity observed may be due to differences in adverse event grading, ICI agent used, and disease site. There were some study arms with significantly higher rates of grade 3-4 toxicity.[12, 46, 47, 61, 65, 70, 71] The disease sites (i.e. melanoma, renal cell carcinoma) and ICI agents used (i.e. ipilimumab, tremelimumab, nivolumab) in these studies are similar to other studies with far lower grade 3-4 toxicity. The study by Ribas et al. reported all grade 3-4 toxicities and not treatment-related grade 3-4 toxicities.[56] One study by Hodi et al. from 2014 did have high treatment-related grade 3-4 toxicities.[47] Trials involving combination nivolumab with concurrent ipilimumab showed high toxicity,[63, 65, 71] a result confirmed in **Figure 3E**, where nivolumab + ipilimumab shows significant increase in toxicity compared to all other ICIs except ipilimumab and tremelimumab alone.

The ICI + RT studies showed high heterogeneity and a smaller sample size than the ICI alone studies. Our meta-regression showed no differences in grade 3-4 toxicities with respect to timing of ICI + RT administration or the irradiated site (**Figures 3A and 3B**). There was an

outlier for ICI + RT grade 3-4 toxicity at 68.2%, 2-3 times as high as similar studies with anti-CTLA4 + RT treatment.[9]

The trend toward targeted immune checkpoint inhibitors has significantly improved outcomes in malignancies once solely treated by radiation therapy or chemotherapy, with fewer severe side effects than chemotherapy.[3] By blocking anti-inflammatory signals from malignant cells, ICIs increase helper and CD8+ T cell activation, allowing for recognition and destruction of malignant cells.[72] At the same time, ICIs are systemic agents and the haphazard activation of immune cells throughout the body by ICIs explains their toxicities. This may even be a target for personalized medicine, as some patients may be predisposed to certain toxicities.[73]

There are several proposed mechanisms by which combination ICI + RT therapy can enhance the activity of the ICI resulting in a synergistic effect. In addition to RT causing radiation-induced damage to malignant cell DNA and other cellular components, the resultant clearance of damaged tumor cells by antigen-presenting cells (APCs) increases subsequent activation of T cells by APCs, facilitated by disruption of inhibitory CTLA4 and PDL/PDL1 signals.[10] For instance, stereotactic radiosurgery (SRS) is theorized to sensitize CD8+ T cells to tumor-specific antigens, and thus act as an *in vivo* "vaccine."[72] An immune response can sometimes be induced systemically, leading to the so-called abscopal effect.[22] We may also ask if there is an "abscopal toxicity" due to sensitization of CD8+ T cells to self-antigens; this would be one possible way RT could enhance ICI toxicity.[74] As subjective and clinician-dependent as toxicity grading already is, singling out toxicities caused by the combination of ICI + RT may be infeasible.

Hypofractionated or ablative RT are being investigated for increased pro-immunogenic properties and enhancing the abscopal effect, however there may be risks for increased toxicity

as discussed above. There are several case reports of an abscopal effect when ICI is combined with RT in the human and animal models.[24, 75, 76] There are also preclinical studies which show that conventional RT may have anti-immunogenic properties through induction of regulatory T cells, so further investigation of the fractionation of RT is needed to explore its effect on the immune response.[77] Unfortunately, we were unable to evaluate the effect of various fractionation schemes as we did not have patient-level data. There is evidence that fractionation plays a role in toxicity, however this conclusion was made for cetuximab + RT and not ICI + RT.[78] This highlights the need for high quality randomized controlled trials with various fractionations of RT in ICI + RT to further investigate the effect of fractionation on toxicities.

There were numerous other limitations to our studies. There was high heterogeneity in the studies included in our meta-analysis. However, our aim was to assess all possible toxicity from all permutations of combination ICI + RT, so this heterogeneity is expected. We addressed the heterogeneity by using a random effects model over a fixed effects model. There were no individual patient-level data. Many of the studies of ICI + RT treatment were primarily concerned with melanoma metastases to the brain, whereas the ICI alone data pooled results from a variety of cancer sites, thus we are unable to confidently generalize our ICI + RT results to other cancers and ICI + RT regimens. Another possible source of bias in our analysis could be under-reporting of toxicity in retrospective compared to prospective studies. We also were not able to control for the effect of ICI agent or dosage, and this may have affected the toxicities of experimental treatments such as the nivolumab + ipilimumab trials,[65, 71] or trials which focused on effects of ICI dosing.[59] Some of the differences we observed (e.g. higher rates of toxicity in melanoma vs NSCLC trials) may be related to the greater use of CTLA4-targeted therapy in melanoma trials. There were almost ten times as many patients in the ICI alone studies (13,956)

as in the ICI + RT studies (1,442). We thus may not have had sufficient statistical power to distinguish effects of various factors on ICI + RT toxicity. Clinicians await the results of clinical trials such as NCT03601455 (durvalumab/tremelimumab with RT) and NCT03604991 (nivolumab/ipilimumab with RT).

Based on our random effects models, adding RT to ICI therapy does not increase incidence of grade 3-4 toxicities and the combination treatment is safe for use across a variety of ICI agents and for CNS melanoma metastases, NSCLC, and prostate cancer. The safety of concurrent administration of ICI + RT is of interest, as there is preliminary clinical evidence that concurrent administration improves overall survival over non-concurrent ICI + RT. For patients receiving an ICI, anti-CTLA4 agents such as ipilimumab and tremelimumab are associated with worse grade 3-4 toxicities. Existing data and this analysis support combining ICI and SRS in certain patient populations. Due to the hypothesis-generating nature of this study, further prospective studies are needed to validate this treatment combination.

REFERENCES

1. Central Nervous System Cancers (Version 1.2019). Available from URL: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf [accessed March 27, 2019].

2. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of Immunotherapy for the Practitioner. J Clin Oncol. 2015;33: 2092-2099.

3. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015;27: 450-461.

4. Anderson ES, Postow MA, Wolchok JD, et al. Melanoma brain metastases treated with stereotactic radiosurgery and concurrent pembrolizumab display marked regression; efficacy and safety of combined treatment. J Immunother Cancer. 2017;5: 76.

5. 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: 916-925.

6. 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 Phys. 2015;92: 368-375.

7. 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: 156-162.

8. Pilones KA, Vanpouille-Box C, Demaria S. Combination of radiotherapy and immune checkpoint inhibitors. Semin Radiat Oncol. 2015;25: 28-33.

9. Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015;520: 373-377.

10. Wang Y, Deng W, Li N, et al. Combining Immunotherapy and Radiotherapy for Cancer Treatment: Current Challenges and Future Directions. Front Pharmacol. 2018;9: 185.

11. 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: 22-30.

12. 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: 485-491.

13. 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: 1919-1929.

14. Bang A, Wilhite TJ, Pike LRG, et al. Multicenter Evaluation of the Tolerability of Combined Treatment With PD-1 and CTLA-4 Immune Checkpoint Inhibitors and Palliative Radiation Therapy. Int J Radiat Oncol Biol Phys. 2017;98: 344-351.

15. Desideri I, Francolini G, Scotti V, et al. Benefit of ablative versus palliative-only radiotherapy in combination with nivolumab in patients affected by metastatic kidney and lung cancer. Clin Transl Oncol. 2018.

16. Hiniker SM, Reddy SA, Maecker HT, et al. A Prospective Clinical Trial Combining Radiation Therapy With Systemic Immunotherapy in Metastatic Melanoma. Int J Radiat Oncol Biol Phys. 2016;96: 578-588.

17. 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: 700-712.

18. 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: e1214788.

19. Mohamad O, Diaz de Leon A, Schroeder S, et al. Safety and efficacy of concurrent immune checkpoint inhibitors and hypofractionated body radiotherapy. Oncoimmunology. 2018;7: e1440168.

20. 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: 1813-1821.

21. Sundahl N, Vandekerkhove G, Decaestecker K, et al. Randomized Phase 1 Trial of Pembrolizumab with Sequential Versus Concomitant Stereotactic Body Radiotherapy in Metastatic Urothelial Carcinoma. Eur Urol. 2019;75: 707-711.

22. Demaria S, Ng B, Devitt ML, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. Int J Radiat Oncol Biol Phys. 2004;58: 862-870.

23. Harary M, Reardon DA, Iorgulescu JB. Efficacy and safety of immune checkpoint blockade for brain metastases. CNS Oncol. 2019.

24. Du S, Zhou L, Alexander GS, et al. PD-1 Modulates Radiation-Induced Cardiac Toxicity through Cytotoxic T Lymphocytes. J Thorac Oncol. 2018;13: 510-520.

25. 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.

26. Qian JM, Yu JB, Kluger HM, Chiang VL. Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. Cancer. 2016;122: 3051-3058.

27. Ebell M. Information at the point of care: answering clinical questions. J Am Board Fam Pract. 1999;12: 225-235.

28. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. ACP J Club. 1995;123: A12-13.

29. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. AMIA Annu Symp Proc. 2006: 359-363.

30. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6: e1000097.

31. RStudio: Integrated Development Environment for R: Team R, 2019.

32. Viechtbauer W. Conducting meta-analyses in R with the metafor package   Journal of Statistical Software, 2010.

33. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7: 177-188.

34. Cochran WG. The comparison of percentages in matched samples. Biometrika. 1950;37: 256-266.

35. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315: 629-634.

36. Beer TM, Kwon ED, Drake CG, et al. Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer. J Clin Oncol. 2017;35: 40-47.

37. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017;376: 1015-1026.

38. 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: 1627-1639.

39. 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: 123-135.

40. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med. 2017;376: 2415-2426.

41. Cohen EEW, Soulieres D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet. 2019;393: 156-167.

42. Ferris RL, Blumenschein G, Jr., Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016;375: 1856-1867.

43. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372: 2018-2028.

44. Gettinger S, Rizvi NA, Chow LQ, et al. Nivolumab Monotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2016;34: 2980-2987.

45. Herbst RS, Baas P, Kim DW, 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: 1540-1550.

46. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363: 711-723.

47. Hodi FS, Lee S, McDermott DF, et al. Ipilimumab plus sargramostim vs ipilimumab alone for treatment of metastatic melanoma: a randomized clinical trial. Jama. 2014;312: 1744-1753.

48. Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2016;17: 1558-1568.

49. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390: 2461-2471.

50. Kluger HM, Chiang V, Mahajan A, et al. Long-Term Survival of Patients With Melanoma With Active Brain Metastases Treated With Pembrolizumab on a Phase II Trial. J Clin Oncol. 2019;37: 52-60.

51. Larkin J, Minor D, D'Angelo S, et al. Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. J Clin Oncol. 2018;36: 383-390.

52. Massard C, Gordon MS, Sharma S, et al. Safety and Efficacy of Durvalumab (MEDI4736), an Anti-Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer. J Clin Oncol. 2016;34: 3119-3125.

53. McDermott DF, Sosman JA, Sznol M, et al. Atezolizumab, an Anti-Programmed Death-Ligand 1 Antibody, in Metastatic Renal Cell Carcinoma: Long-Term Safety, Clinical Activity, and Immune Correlates From a Phase Ia Study. J Clin Oncol. 2016;34: 833-842.

54. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373: 1803-1813.

55. 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: 1823-1833.

56. Ribas A, Kefford R, Marshall MA, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol. 2013;31: 616-622.

57. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389: 255-265.

58. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372: 2521-2532.

59. Ascierto PA, Del Vecchio M, Robert C, et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2017;18: 611-622.

60. Barlesi F, Vansteenkiste J, Spigel D, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. Lancet Oncol. 2018;19: 1468-1479.

61. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. N Engl J Med. 2016;375: 1845-1855.

62. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med. 2018;378: 1789-1801.

63. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med. 2018;378: 2093-2104.

64. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019;393: 1819-1830.

65. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018;378: 1277-1290.

66. Powles T, Duran I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2018;391: 748-757.

67. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372: 320-330.

68. Shitara K, Ozguroglu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet. 2018;392: 123-133.

69. Waterhouse D, Horn L, Reynolds C, et al. Safety profile of nivolumab administered as 30-min infusion: analysis of data from CheckMate 153. Cancer Chemother Pharmacol. 2018;81: 679-686.

70. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med. 2017;377: 1824-1835.

71. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2017;377: 1345-1356.

72. Lehrer EJ, McGee HM, Peterson JL, et al. Stereotactic Radiosurgery and Immune Checkpoint Inhibitors in the Management of Brain Metastases. Int J Mol Sci. 2018;19.

73. Maciejko L, Smalley M, Goldman A. Cancer Immunotherapy and Personalized Medicine: Emerging Technologies and Biomarker-Based Approaches. J Mol Biomark Diagn. 2017;8.

74. Hwang WL, Pike LRG, Royce TJ, Mahal BA, Loeffler JS. Safety of combining radiotherapy with immune-checkpoint inhibition. Nat Rev Clin Oncol. 2018;15: 477-494.

75. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res. 2013;1: 365-372.

76. Zeng J, Harris TJ, Lim M, Drake CG, Tran PT. Immune modulation and stereotactic radiation: improving local and abscopal responses. Biomed Res Int. 2013;2013: 658126.

77. Kachikwu EL, Iwamoto KS, Liao YP, et al. Radiation enhances regulatory T cell representation. Int J Radiat Oncol Biol Phys. 2011;81: 1128-1135.

78. Kroeze SG, Fritz C, Hoyer M, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review. Cancer Treat Rev. 2017;53: 25-37.

FIGURE CAPTIONS

Figure 1: PRISMA flow diagram

Figure 2: Forest plots and summary

A. The grade 3-4 toxicities for ICI therapy alone, with 95% confidence intervals. Each row represents a different prospective clinical trial which used an ICI (Therapy) for a malignancy (Histology). An overall random effects estimate is provided in bold. Test statistics are shown on the bottom left. Our meta-analysis shows 22.3% (95% CI: 18.1-26.9%) of patients receiving ICI alone experience grade 3-4 toxicities. Note the high heterogeneity present, with I^2=97% and Cochran's Q-test showing significance at the $p < 0.01$ level.

B. The grade 3-4 toxicities for ICI + RT, with 95% confidence intervals. Each row represents an arm of a given study which used an ICI (Therapy) for a malignancy (Histology) as well as radiation (Irradiated Sites) with varying timing of ICI administration with respect to radiation (Timing). An overall random effects estimate is provided in bold. Test statistics are shown on the bottom left. Our meta-analysis shows 16.3% (11.1-22.3%) of patients receiving ICI + RT experience grade 3-4 toxicities. High heterogeneity is also present here, with I^2=84% and Cochran's Q-test showing significance at the $p < 0.01$ level.

C. 95% confidence intervals for grade 3-4 toxicities for ICI alone and ICI + RT (blue). ICI + RT is further stratified by concurrency of ICI and RT administration (orange). I^2, χ are shown, with * indicating significant heterogeneity ($p<0.05$). Full numerical values with summary of data are shown in **Supplemental Table 1**. Note that the 95% confidence interval of ICI + RT grade 3-4 toxicities lies well within that of the ICI alone estimates.

Figure 3: Stratification by factors

Blue bars indicate ICI + RT while orange bars indicate ICI alone. * indicates statistical significance to the level of $\alpha < 0.05$. Full data are shown in **Supplemental Table 2**. We show the meta-regression estimates of grade 3-4 toxicities with errorbars showing 95% confidence intervals) stratified by:

A. timing of RT with respect to ICI administration. All the 95% confidence intervals overlap and there were no significant differences.

B. site which was irradiated. This variable was coded with a focus on radiation directed at the brain and radiation directed elsewhere. All the 95% confidence intervals overlap and there were no significant differences.

C. immune signaling axis targeted by the ICI used. There are significant differences in the ICI alone groups ($\alpha<0.05$), with treatments including anti-CTLA4 therapy causing increased toxicity compared to treatments without anti-CTLA4 therapy.

D. histologically determined origin of the malignancy. There are no significant differences except for between NSCLC and melanoma ($\alpha<0.05$). Histology does not appear to play a significant role in toxicity experienced.

E. the specific ICI agent(s) used. There are significant differences between therapies that contain anti-CTLA4 agents (i.e. ipilimumab, tremelimumab) compared to those that do not ($\alpha<0.05$).

Table 1: PICOS	
ICI alone	
Population	Cancer patients undergoing treatment of cancer by ICI
Intervention	Any ICI
Comparison	Studies had an ICI group and at least one comparison placebo, chemotherapy, or alternative ICI control group
Outcome	Grade 3-4 toxicities per the CTCAE or RTOG guidelines
Study design	All prospective phase III/IV clinical trials
ICI+RT	
Population	Cancer patients undergoing treatment of cancer by ICI+RT
Intervention	Any combination of ICI with RT
Comparison	Studies could have no control group (single-arm study), or could be multi-arm studies comparing therapies (e.g. ICI vs ICI+RT, ICI vs tyrosine kinase inhibitors)
Outcome	Grade 3-4 toxicities per the CTCAE or RTOG guidelines
Study design	All prospective or retrospective studies with one or more arms

- Few studies characterize combined immunotherapy and radiation
- Toxicities similar after adding radiation to immunotherapy
- Anti-CTLA4 associated with more toxicity than anti-PD1/PDL1
- No significant difference based on timing of immunotherapy and radiation