Safety and efficacy of concurrent immune checkpoint inhibitors and hypofractionated body radiotherapy

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ABSTRACT
Integration of hypofractionated body radiotherapy (H-RT) into immune checkpoint inhibitor (ICI) therapy may be a promising strategy to improve the outcomes of ICIs, although sufficient data is lacking regarding the safety and efficacy of this regimen. We, hereby, reviewed the safety and efficacy of this combination in 59 patients treated with H-RT during or within 8 weeks of ICI infusion and compared results with historical reports of ICI treatment alone. Most patients had RCC or melanoma. Median follow-up was 11 months. Most patients received either Nivolumab alone or with Ipilimumab; 83% received stereotactic RT and 17% received conformal H-RT. Any grade adverse events (AEs) were reported in 46 patients, and grade 3–4 in 12 patients without any treatment-related grade 5 toxicity. The most common grade 3 AEs were fatigue and pneumonitis. Grade 3–4 toxicities were higher with ICI combination and with simultaneous ICIs. Overall, most any-grade or grade ≥ 3 AEs did not differ significantly from historically reported rates with single-agent or multi-agent ICIs. Toxicity did not correlate with H-RT site, dose, fraction number, tumor type, or ICI and H-RT sequencing. Median progression-free survival was 6.5 months. Objective response rate (ORR) was 26%; 10% had complete response (CR). Median duration of response was 9.4 ± 4.6 months. H-RT of lung lesions was more likely to achieve CR than other sites. H-RT of bone lesions had a lower ORR than non-bone H-RT. In conclusion, combining body H-RT with ICIs is safe and promising. Prospective validation is warranted.

Introduction
Immune checkpoint inhibitors (ICIs) have improved outcomes for several metastatic cancers, including melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), and bladder cancer, leading to their FDA approval. Despite promising outcomes in phase III clinical trials, complete responses are infrequent, and most patients who respond eventually progress. Thus, outcomes can be improved in these patients. Strategies under investigation to improve ICI response rates include simultaneous ICI therapy and combination with radiotherapy (RT).

Preclinical studies have shown that the combination of RT with ICIs is more effective than either treatment modality alone. Despite the hype, such treatment combinations are still far from standard clinical practice, because the optimal timing, dosing, and fractionation of RT to yield the best synergistic outcomes remain uncertain. Moreover, data on the safety of such combinations are scarce. ICIs are associated with serious and potentially fatal adverse events (AEs), with grade ≥ 3 AEs ranging between 5–15% in monotherapies and about 50% in simultaneous combinations.

The few studies that have evaluated the combination of ICIs with RT have shown that these combinations are probably safe for conventional RT and brain stereotactic radiosurgery (SRS).

Evidence shows that hypofractionated RT (H-RT) is more immunogen than conventional regimens and may synergize better with ICIs. However, only a few patients in the reported combination studies received stereotactic ablative body RT (SABR). Multiple clinical trials are currently investigating the combination of RT and ICIs, with many combining body H-RT or stereotactic ablative RT (SABR) with limited supporting data. Our study analyzes toxicity and efficacy data for patients who received extra-cranial H-RT or SABR concurrently or within 8 weeks of ICI infusion and compares the results with historically reported data of ICI alone treated patients.

Results
Patient characteristics
We identified 59 patients who received at least one ICI infusion and at least one H-RT course (SABR or conformal RT; C-RT) concurrently or within 8 weeks of each other between 2012 and
Table 1. Patient characteristics and treatments.

| Characteristic                                      | Total # of patients (%; n = 59) |
|-----------------------------------------------------|----------------------------------|
| Sex                                                 |                                  |
| Male                                                | 38 (64%)                         |
| Female                                              | 21 (36%)                         |
| Primary diagnoses                                   |                                  |
| Renal cell carcinoma                                | 27 (46%)                         |
| Melanoma                                            | 18 (31%)                         |
| Non-small cell lung cancer                          | 5 (9%)                           |
| Bladder carcinoma                                   | 7 (12%)                          |
| Pancreas adenocarcinoma                             | 1 (%)                            |
| Head and neck squamous cell carcinoma               | 1 (%)                            |
| Prior treatments for primary tumor                  |                                  |
| Oncologic surgery                                   | 44 (75%)                         |
| Chemotherapy                                        | 16 (27%)                         |
| Targeted therapy                                    | 37 (63%)                         |
| Immune therapy                                      | 6 (10%)                          |
| Brain metastasis                                    |                                  |
| Yes                                                 | 21 (36%)                         |
| s/p surgical resection                              | 8                                |
| s/p SRS                                             | 17                               |
| Observation                                         | 1                                |
| No                                                  | 38 (64%)                         |
| Metastasis status prior to treatment                |                                  |
| Widely metastatic                                   | 45 (76%)                         |
| Oligo-metastatic                                    | 13 (22%)                         |
| Non-metastatic                                      | 1 (2%)                           |
| ECOG PS at the initiation of ICI                   |                                  |
| 0                                                   | 19 (32%)                         |
| 1                                                   | 31 (53%)                         |
| 2                                                   | 5 (8%)                           |
| ≥3                                                  | 0 (0%)                           |
| Unavailable                                         | 4 (7%)                           |
| ICI type (single vs. multiple)                      |                                  |
| Nivolumab alone                                     | 27 (46%)                         |
| Ipilimumab alone                                    | 4 (7%)                           |
| Pembrolizumab alone                                 | 4 (7%)                           |
| Atezolizumab alone                                  | 5 (8%)                           |
| > 1 ICI                                             | 19 (32%)                         |
| Any simultaneous combination of ICIs                | 14 (24%)                         |
| Median duration of ICI treatment, in months         |                                  |
| All patients                                        | 5                                |
| Single agent                                        | 4                                |
| > 1 ICI                                             | 7.5                              |
| ICI status                                          |                                  |
| Ongoing treatment at last follow-up                | 22 (37%)                         |
| Stopped d/t progressive disease                     | 24 (41%)                         |
| Stopped d/t toxicity                                | 6 (10%)                          |
| Stopped d/t patient’s death                         | 5 (8%)                           |
| Stopped d/t hospice enrollment                      | 1 (2%)                           |
| Stopped because patient finished planned course     | 1 (2%)                           |
| Radiation Character                                 |                                  |
| # of treatments (%)                                 |                                  |
| Total # of concurrent radiation courses             | 137                              |
| # of RT courses before ICI                         | 35 (26%)                         |
| # of RT courses simultaneous with ICI              | 77 (56%)                         |
| # of RT courses after ICI                          | 25 (18%)                         |
| Treatment sites (out of 137 courses)                |                                  |
| Pelvis                                              | 24                               |
| Head/neck including brain                           | 36                               |
| Cervical spine                                      | 4                                |
| Thoracic spine                                      | 10                               |
| Lumbar spine                                        | 8                                |
| Chest wall                                          | 13                               |
| Lungs/mediastinum                                  | 21                               |
| Extremities                                         | 12                               |
| Abdomen                                            | 14                               |
| Treatment technique                                 |                                  |
| SABR                                                | 77 (56%)                         |
| 3D-CRT or IMRT                                     | 22 (16%)                         |
| Conventional 3D                                     | 17 (12.5%)                       |

(Continued on next column)

Table 1. (Continued).

| Characteristic                                      | Total # of patients (%; n = 59) |
|-----------------------------------------------------|----------------------------------|
| SRS                                                 | 17 (12.5%)                       |
| Superficial                                         | 4 (3%)                           |
| Number of patients with:                           |                                  |
| At least one hypofractionated RT (excluding SRS)    | 59 (100%)                        |
| At least one SABR                                   | 49 (83%)                         |
| C-RT (3D-CRT or IMRT) but not SABR                  | 10 (17%)                         |
| Did patient receive concurrent RT courses other than |                                  |
| hypofractionated body RT                            |                                  |
| Yes                                                 | 21 (36%)                         |
| No                                                  | 38 (64%)                         |
| Fractionation schemes                               |                                  |
| SABR or C-RT                                        |                                  |
| Medium dose in Gy (range)                           | 30 (6-54)                        |
| Mean fraction # (range)                             | 3 (1-5)                          |
| Mean target volume (cc)                             | 141                              |
| Other concurrent RT (non-SRS)                       |                                  |
| Medium dose (range)                                 | 30 (15–60)                       |
| Median fraction # (range)                           | 10 (5–20)                        |
| SRS§                                                |                                  |
| Medium dose (range)                                 | 24 (13–40)                       |
| Median fraction # (range)                           | 1 (1–5)                          |
| Did patient receive other non-concurrent RT courses beyond above time limits? | | |
| Yes                                                 | 34 (58%)                         |
| No                                                  | 25 (42%)                         |

Abbreviations: #, number; %, percentage; yrs, years; ICI, immune checkpoint inhibitor; s/p, status post; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; d/t, due to; RT, radiotherapy; SABR, stereotactic ablative radiotherapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity modulated radiotherapy; C-RT, hypofractionated conformal radiotherapy; Gy, Gray; cc, cubic centimeters.

*Oligometastatic was defined as ≤5 lesions at the time of initiation of therapy.

*aOne Nivolumab alone patient received simultaneous Cabozantinib.

*bThis included patients who received sequential or simultaneous ICIs.

*cSome treatments overlap sites.

*dThis included conventional RT or SRS.

*eThis included all radiation treatments during or ± 8 weeks from ICI start.

fTwo patients received hypofractionated CyberKnife to 40 Gy in 5 fractions.

2017. Table 1 summarizes patient characteristics, including diagnoses, prior treatments, and characteristics of ICI and H-RT therapies. Most patients were male (64%), and most had RCC or melanoma (76%). Seventy-six percent of patients had widely metastatic disease, and 24% had locally advanced or oligo-metastatic disease. Median age was 64 (range 14–84) years at diagnosis of metastasis. Fifty patients (85%) had received prior systemic therapy. The remaining 9 patients (8 with melanoma, 1 with RCC) received ICIs in the first-line setting. Four patients received only a single infusion; their treatments were stopped due to toxicity (2), death (1), or patient preference for hospice enrollment (1). Most patients received Nivolumab alone (46%) or a combination of ICIs. Combination ICIs were sequential, simultaneous, or both. 14 patients (24%) received a simultaneous combination of ICIs, all of which consisted of Nivolumab and Ipilimumab.

All patients received at least one SABR (83%) or hypofractionated C-RT (17%) treatment, either concurrently or within 8 weeks of the ICI (Table 1). Thirty-five patients (59%) received multiple RT treatments within the study’s 8-week time constraint, making a total of 137 courses of radiation (56% SABR) with a median of 2 RT courses per patient (range 1–8).
Toxicity

Forty-six patients (78%) experienced any treatment-related AE, mostly grade 1–2 (Table 2). The most common AEs were fatigue (37%), nausea (19%), transaminitis (17%), and rash/dermatitis (17%). Grade 3–4 treatment-related AEs occurred in 12 patients (20%). Only one patient, who did not receive liver RT, had a grade 4 AE (asymptomatic elevation of liver enzymes), but eventually recovered after the ICI was withheld. The most common grade 3 AEs were fatigue and pneumonitis (3 patients, 5% each). All patients with grade 3 pneumonitis had RCC, and only one received lung RT during or within 8 weeks of ICI. Four patients (7%) developed more than one grade 3 AE; two of whom received only Nivolumab, one had sequential Pembrolizumab and Ipilimumab, and one had simultaneous Nivolumab and Ipilimumab followed by Nivolumab only. No treatment-related grade 5 toxicities were observed. Median (average) times from treatment initiation to grade 1–2 or grade ≥3 toxicity were 32 days (65 days) or 98 days (107 days), respectively. Immune-related AEs were treated by cessation or holding of ICIs and usually steroids.

Forty-five patients (76%) in our cohort received single or sequential ICI, and 14 (24%) received simultaneous ICIs. We compared treatment-related grade ≥3 AEs in each subgroup to historical controls of cutaneous melanoma patients receiving Nivolumab only,40 RCC patients receiving Nivolumab only (CheckMate 025),10 NSCLC patients receiving Nivolumab only (CheckMate 057),17 cutaneous melanoma patients receiving Nivolumab + Ipilimumab,40 and recurrent small cell lung cancer (SCLC) patients receiving Nivolumab + Ipilimumab in different doses (CheckMate 032).13 Overall, there was no difference in most grade ≥3 toxicities compared to the historical controls. For patients receiving single-agent ICI, we observed a statistical increase in the risk of grade ≥3 fatigue (7% vs. 0.6%; p = 0.007) and grade ≥3 pneumonitis (4% vs. 0.2%; p = 0.01) between our study and the pooled analysis of cutaneous melanoma, and a statistical increase in the risk of grade ≥3 fatigue (7% vs. 1%; p = 0.03) between our study and CheckMate 057. For patients receiving simultaneous Nivolumab and Ipilimumab, we observed a statistical increase in the risk of grade ≥3 transaminitis (14% vs. 0%; p = 0.03) between our study and CheckMate 032 (Nivo 1 mg/kg and Ipi 3 mg/kg arm).

We next analyzed correlations between different treatment parameters and any grade or grade ≥3 AEs (Table 4). We found more grade ≥3 AEs in patients who received multiple ICIs (whether sequential or simultaneous) than in those who only received a single ICI (36.8% vs 12.5%, p = 0.04) and more grade ≥3 AEs in patients who received simultaneous ICI combinations than in those who received single or multiple but sequential ICIs (42.9% vs. 13.3%, p = 0.03). Otherwise, there was no correlation between toxicity and diagnoses, treatment sequence, RT site, RT dose (BED, biologically equivalent dose), RT fraction number, receiving other concurrent RT (conventional fractionation or brain SRS) or number and duration of ICI infusions.

We grouped patients according to radiation site for every treatment-related AE (Table 5). Despite the small numbers, there was no clear correlation between particular toxicities and RT to or near the corresponding sites. For example, 5.4% of patients who received RT to the chest, including the lungs, chest wall, mediastinum, and T-spine, developed grade 3 pneumonitis, compared to 4.5% in those who did not receive RT to the chest (p = 1.00).

Evaluating patient outcomes

Median follow-up was 11.1 months (IQR: 6.5-15.8; mean 11.8±8.1). The most common reason for discontinuing ICI was disease progression (24 patients, 41%). Treatment-related AEs prompted treatment discontinuation in 6 patients (10%). At last follow-up, 22 patients (37%) continued to receive ICIs, 31 patients (53%) were alive, 22 patients (37%) had died, and 6 (10%) had been lost to follow-up. All deceased patients died of disease progression and/or its complications. Among evaluable patients (n = 39), median follow-up was 13.5 months (IQR: 8.9-16.6; mean 13.5±6.6). Overall response rate (ORR) was 26% (10/39), including 10% (4/39) with complete response (CR); 6 patients had partial response (PR), 10 had stable disease (SD), and 19 had progressive disease (PD). All patients with CR (3 with melanoma and 1 with NSCLC) received SAbR to a lung lesion concurrently with Nivolumab alone and are still alive receiving it at last follow-up. One-year overall survival (OS) was 69.8% (95% CI 55.8-80.1) (Supplementary Table 1). Median OS was not reached. Median progression-free survival (PFS) was 6.5 months (3.4-12.3) for all evaluable patients (17.1 months for CR patients and 12.6 months for CR+PR+SD patients). Median duration of
response was 9.4 ± 4.6 months for patients with PR and CR; 5 of whom were ongoing responses at last follow up. All patients with CR had oligometastatic disease involving ≤5 lesions in 1–3 organ systems, who received SABR to the lung concurrently with Nivolumab only and are still alive receiving it at last follow-up.

We analyzed the relationship between different treatment parameters and tumor responses (Table 6 and supplementary Table 2). Patients who received H-RT to bones tended to have less objective responses (CR+PR) (Table 6: 10.5% vs. 40%, p = 0.065). Otherwise, there was no correlation between tumor response and diagnoses, number of ICIs, treatment sequence, RT site, RT dose (BED), RT fraction number, receiving other concurrent RT (conventional fractionation or brain SRS) or number and duration of ICI infusions. Comparing CR with non-CR responses (PR+SD+PD), we found that RT of lung lesions was significantly more likely to induce CR than RT of any other site (Table 6: 26.7% vs. 0%; p = 0.0166).

### Discussion

This study has limitations associated with a retrospective study with a relatively small and heterogeneous sample of patients, which can be subject to bias. While the short median follow-up of 11.1 months is adequate to cover short-term toxicity, ORR, and PFS, longer follow-up is needed to cover long-term outcomes and late toxicities. We also lack a proper comparison group for comparing outcomes and toxicities. However, the focus of this study, looking exclusively at the toxicities and outcomes of concurrent (within 8 weeks) ICIs with extra-cranial H-RT, makes the results applicable and relevant to ongoing clinical trials.

ICIs are overall well tolerated, with grade ≥3 toxicities ranging from 5–15% in single ICIs and >50% in simultaneous ICIs. Our study’s toxicity profile, with 78% any grade toxicity and 20% grade ≥3 toxicity, fits well within the reported values, given that 24% of our patients received simultaneous ICIs. H-RT, thus, did not increase treatment-related immune-related AEs of ICI therapy, indicating that H-RT, thus, did not increase treatment-related immune-related AEs of ICI therapy, indicating that H-RT does not augment immunity against self-antigens. This was independent of irradiation site, suggesting that this is an immune-related rather than an RT-induced toxicity. When compared to different historical controls from multiple landmark studies using single or simultaneous ICIs, we did not notice any significant increase in grade ≥3 toxicities, despite the acknowledged controversy of such a statistical comparison. Interestingly, we noticed a minimal but statistically significant increase in the rate of grade ≥3 pneumonitis, fatigue, and transaminitis in some of these comparisons. Admittedly, the historical control cohorts we chose are not ideal, but they have a large number of patients treated for different metastatic disease using single...
Table 4. Relationship of treatment parameters with occurrence of adverse events.

| Diagnosis        | No AE (n = 13) | Any AE (n = 46) | p       | No Grade ≥ 3 AE (n = 47) | Grade ≥ 3 AE (n = 12) | p       |
|------------------|----------------|-----------------|---------|--------------------------|----------------------|---------|
| Bladder          | 3 (42.9%)      | 4 (57.1%)       | 0.0659  | 7 (100%)                 | 0 (0%)               | 0.4952  |
| Melanoma         | 3 (16.7%)      | 15 (83.3%)      |         | 14 (77.8%)               | 4 (22.2%)            |         |
| NSCLC            | 0 (0%)         | 5 (100%)        |         | 5 (100%)                 | 0 (0%)               |         |
| Pancreas         | 1 (100%)       | 0 (0%)          |         | 1 (100%)                 | 0 (0%)               |         |
| RCC              | 5 (18.5%)      | 22 (81.5%)      |         | 19 (70.4%)               | 8 (29.6%)            |         |
| SCC HN           | 1 (100%)       | 0 (0%)          |         | 1 (100%)                 | 0 (0%)               |         |
| No. of ICI       |                |                 |         |                          |                      |         |
| Single           |                |                 |         |                          |                      |         |
| > 1 ICI          | 2 (10.5%)      | 17 (89.5%)      | 0.1893  | 12 (63.2%)               | 7 (36.8%)            |         |
| ICI status       |                |                 |         |                          |                      |         |
| Simultaneous     | 1 (7.1%)       | 13 (92.9%)      | 0.1591  | 8 (57.1%)                | 6 (42.9%)            | 0.0260  |
| Other            | 12 (26.7%)     | 33 (73.3%)      |         | 39 (86.7%)               | 6 (13.3%)            |         |
| Treatment order  |                |                 |         |                          |                      |         |
| ICI → RT (ICI first) | 3 (27.3%)   | 8 (72.7%)      | 0.9153  | 11 (100%)                | 0 (0%)               | 0.1765  |
| RT + ICI (simultaneous) | 6 (20.0%) | 24 (80.0%) | 0.7365  | 23 (76.7%)               | 7 (23.3%)            |         |
| RT → ICI (RT first) | 4 (22.2%)  | 14 (77.8%)     |         | 13 (72.2%)               | 5 (27.8%)            |         |
| Single fractions |                |                 |         |                          |                      |         |
| 1 fraction       | 1 (16.7%)      | 5 (83.3%)       | 1.0000  | 5 (83.3%)                | 1 (16.7%)            | 1.0000  |
| > 1 fraction     | 8 (25.8%)      | 23 (74.2%)      |         | 26 (83.9%)               | 5 (16.1%)            |         |
| 1-3 fractions    |                |                 |         |                          |                      |         |
| > 3 fractions    | 3 (16.7%)      | 15 (83.3%)      | 1.0000  | 13 (72.2%)               | 5 (27.8%)            | 0.2320  |
| Other concurrent RT | 6 (28.6%)  | 15 (71.4%)     | 0.5131  | 16 (76.2%)               | 5 (23.8%)            | 0.7386  |
| Head and Neck RT |                |                 |         |                          |                      |         |
| No               | 9 (25.0%)      | 27 (75.0%)      | 0.4916  | 29 (80.6%)               | 7 (19.4%)            | 0.8309  |
| Yes              | 4 (17.4%)      | 19 (82.6%)      |         | 18 (78.3%)               | 5 (21.7%)            |         |
| Bone RT          |                |                 |         |                          |                      |         |
| No               | 8 (29.4%)      | 12 (70.6%)      | 0.4620  | 23 (74.2%)               | 8 (25.8%)            | 0.2723  |
| Yes              | 5 (17.9%)      | 23 (82.1%)      |         | 24 (85.7%)               | 4 (14.3%)            |         |
| Lung and Chest RT|                |                 |         |                          |                      |         |
| No               | 8 (25.8%)      | 23 (74.2%)      | 0.4213  | 27 (81.8%)               | 6 (18.2%)            | 0.6428  |
| Yes              | 5 (17.9%)      | 23 (82.1%)      |         | 24 (85.7%)               | 4 (14.3%)            |         |
| Below Diaphragm RT|             |                 |         |                          |                      |         |
| No               | 6 (18.2%)      | 27 (81.8%)      | 0.0102  | 27 (81.8%)               | 6 (18.2%)            | 0.5157  |
| Yes              | 7 (26.9%)      | 19 (73.1%)      |         | 20 (76.9%)               | 6 (23.1%)            |         |
| Median BED (Gy), total (IQR) | 127.3 (83.5-160.0) | 131.8 (77.5-206.5) | 0.5043  | 127.3 (75.4-201.0)     | 146.0 (97.3-185.4)   | 0.5157  |
| Median infusions (IQR) | 4 (2-8)    | 8 (4-15)       | 0.0102  | 8 (4-15)                 | 4 (3.5-7.5)          | 0.0632  |
| Median ICI duration (mos), months (IQR) | 2.7 (1.0-4.5) | 3.8 (2.1-8.3) | 0.1798  | 3.8 (2.1-8.3)           | 3.2 (1.7-4.1)        | 0.2247  |

Abbreviations: AE, adverse events; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCC HN, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; RT, radiotherapy; BED, biologically equivalent dose; IQR, inter-quartile range.

*Other included those who received single or > 1 sequential but no concurrent ICIs.
*Patients who only received 1 fraction versus patients who only received more than 1 fraction to all treated sites.
*Patients who only received 1–3 fractions versus patients who only received more than 3 fractions to all treated sites.
*This included conventional RT or brain SRS.

Table 5. Relationship of radiotherapy treatment site to occurrence of adverse events.

| Radiotherapy Treatment Site | Any Grade AE | Grade ≥ 3 AE |
|----------------------------|--------------|-------------|
|                            | No RT to/near organ | RT to/near organ | p       | No RT to/near organ | RT to/near organ | p       |
| Lung                       | n = 22       | n = 37      | 1.0000  | n = 22       | n = 37      | 1.0000  |
| Pneumonitis                | 2 (9.1%)     | 4 (10.8%)   |         | 1 (4.5%)     | 2 (5.4%)   |         |
| Abdomen                    | n = 26       | n = 33      | 0.7365  | n = 26       | n = 33      | 0.0000  |
| Transaminitis              | 5 (19.2%)    | 5 (15.2%)   |         | 1 (3.8%)     | 1 (3.0%)   |         |
| AKI                        | 3 (11.5%)    | 2 (6.1%)    | 0.6458  | 1 (3.8%)     | 0 (0%)     | 0.4407  |
| Adrenal insufficiency      | 1 (3.8%)     | 1 (3.0%)    | 1.0000  | 1 (3.8%)     | 0 (0%)     | 1.0000  |
| Pancreatitis               | 0 (0%)       | 1 (3.0%)    | 1.0000  | 0 (0%)       | 0 (0%)     |         |
| Colon                      | n = 17       | n = 42      | 0.0795  | n = 17       | n = 42      | 0.2881  |
| Colitis                    | 2 (11.8%)    | 0 (0%)      |         | 1 (5.9%)     | 0 (0%)     |         |
| Thyroid                    | n = 22       | n = 37      | 0.3513  | n = 22       | n = 37      |         |
| Hypo/hyper-thyroidism      | 3 (13.6%)    | 2 (5.4%)    | 0.3513  | —           | —          | —       |
| Head                       | n = 25       | n = 42      | 0.5607  | n = 22       | n = 37      |         |
| Hypophysitis               | 1 (2.9%)     | 2 (8.3%)    |         | 1 (2.9%)     | 0 (0%)     |         |

Abbreviations: AE, adverse events; RT, radiotherapy.
or simultaneous ICIs. While the population is small and heterogeneous and the comparison group is not ideal, vigilant monitoring of these patients is warranted.

We report an ORR of 26% (28% for single-agent ICIs), a median PFS of 6.5 months for all evaluable patients, and a duration of response of 9.4±4.6 months for patients who responded. It is difficult, however, to formulate clear conclusions given the heterogeneity in diagnoses and treatments. Interestingly, bone RT was the only site that trended towards a lower ORR compared to non-bone RT (Table 5). This may suggest that bones are the least immunogenic site, which agrees with the clinical understanding that bone lesions are often lytic and may contain fewer tumor cells available for antigen presentation when irradiated than soft tissue metastases. On the other hand, all patients with CR had a relatively small burden of disease and received SAbR to a lung lesion. This notion of organ-specific differences in immune-modulatory properties is well known in the field of transplant immunology, where kidney and liver transplants require far less immune-suppression than lungs and hearts to prevent rejection.43 Therefore, it is feasible that the immune-modulatory response from RT is also organ-dependent, as our analysis suggests. Notably, three of the CRs had primary melanoma, yielding a 30% CR rate (3 of 10 evaluable patients) for melanoma patients (0-22% in prior reports3,10,35).

### Table 6. Relationship of treatment parameters with treatment response.

| | CR versus PR, SD, and PD | CR and PR versus SD and PD |
|-----------------|--------------------------|---------------------------|
| Diagnosis       | CR (n = 4) PR+SD+PD (n = 35) p | CR+PR (n = 10) SD+PD (n = 29) p |
| Bladder         | 0 (0%) 3 (100%) 0.0449       | 0 (0%) 3 (100%) 0.4186     |
| Melanoma        | 3 (30.0%) 7 (70.0%)         | 4 (40.0%) 6 (60.0%)        |
| NSCLC           | 1 (25.0%) 3 (75.0%)         | 2 (50.0%) 2 (50.0%)        |
| Pancreas        | 0 (0%) 1 (100%)             | 0 (0%) 1 (100%)            |
| RCC             | 0 (0%) 21 (100%)            | 4 (19.0%) 17 (81%)         |
| No. of ICI      |                           |                           |
| Single          | 2 (8.0%) 23 (92.0%)         | 7 (28.0%) 18 (72.0%)       |
| > 1 ICI         | 2 (14.3%) 12 (85.7%)        | 3 (21.4%) 11 (78.6%)       |
| ICI status      |                           |                           |
| Simultaneous    | 2 (18.2%) 9 (81.8%)         | 2 (18.2%) 9 (81.8%)        |
| Other           | 2 (7.1%) 26 (92.9%)         | 8 (28.6%) 20 (71.4%)       |
| Treatment order |                           |                           |
| ICI → RT (ICI first) | 0 (0%) 6 (100%) 0.2555 | 1 (16.7%) 5 (83.3%) 0.1658 |
| RT → ICI (simultaneous) | 4 (19.0%) 17 (81.0%) | 8 (38.1%) 13 (61.9%)       |
| Single fractions |                           |                           |
| 1 fraction      | 1 (50.0%) 1 (50.0%)         | 1 (50.0%) 1 (50.0%)        |
| > 1 fraction    | 3 (15.0%) 17 (85.0%)        | 7 (35.0%) 13 (65.0%)       |
| 1–3 fractions   | 3 (25.0%) 9 (75.0%)         | 5 (41.7%) 7 (58.3%)        |
| > 3 fractions   | 0 (0%) 12 (100%)            | 4 (33.3%) 8 (66.7%)        |
| Other concurrent RT |                           |                           |
| Yes             | 1 (7.1%) 13 (92.9%)         | 2 (14.3%) 12 (85.7%)       |
| No              | 3 (12.0%) 22 (88.0%)        | 8 (32.0%) 17 (68.0%)       |
| Bone RT         |                           |                           |
| No              | 4 (20.0%) 16 (80.0%)        | 8 (40.0%) 12 (60.0%)       |
| Yes             | 0 (0%) 19 (100%)            | 2 (10.5%) 17 (89.5%)       |
| Lung RT         |                           |                           |
| No              | 0 (0%) 24 (100%)            | 4 (16.7%) 20 (83.3%)       |
| Yes             | 4 (26.7%) 11 (73.3%)        | 6 (40.0%) 11 (60.0%)       |
| Brain RT        |                           |                           |
| No              | 4 (13.8%) 25 (86.2%)        | 9 (31.0%) 20 (69.0%)       |
| Yes             | 0 (0%) 10 (100%)            | 1 (10.0%) 9 (90.0%)        |
| Head & Neck RT  |                           |                           |
| No              | 4 (12.1%) 29 (87.9%)        | 9 (27.3%) 24 (72.7%)       |
| Yes             | 0 (0%) 6 (100%)             | 1 (16.7%) 5 (83.3%)        |
| Soft Tissue RT  |                           |                           |
| No              | 4 (11.8%) 30 (88.2%)        | 8 (23.5%) 26 (76.5%)       |
| Yes             | 0 (0%) 5 (100%)             | 2 (40.0%) 3 (60.0%)        |
| Adrenal RT      |                           |                           |
| No              | 4 (10.5%) 34 (89.5%)        | 9 (23.7%) 29 (76.3%)       |
| Yes             | 0 (0%) 1 (100%)             | 1 (100%) 0 (0%)            |

**Abbreviations:** AE, adverse events; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; ICI, immune checkpoint inhibitor; RT, radiotherapy; BED, biologically equivalent dose; IQR, inter-quartile range; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

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*Other included those who received single or > 1 sequential but no concurrent ICIs.

*Patients who only received 1 fraction versus patients who only received more than 1 fraction to all treated sites.

*Patients who only received 1–3 fractions versus patients who only received more than 3 fractions to all treated sites.

*This included conventional RT or brain SRS.
Only a few studies have evaluated combinations of ICIs and RT. While these combinations were deemed safe, these studies focused on brain SRS or conventional radiotherapy, and the number of patients who received H-RT or SAbR was minimal. Moreover, many patients received RT several months prior to ICIs, making them less relevant to the ongoing trials. For example, in a study of patients who had previous radiotherapy and received Pembrolizumab for NSCLC, very few patients received H-RT, and the median time between RT and the first infusion of Pembrolizumab was 9.5 months. In a recently published phase I trial of patients (with multiple primary histologies) receiving SAbR to liver or lung lesions concurrently with Ipilimumab, grade 3 toxicities were observed in 34% of patients and no CRs were observed. The authors concluded that the combination was safe and that immune activation, measured using assays of CD8\(^+\) and CD4\(^+\) T cells, was greater after liver irradiation. This is contrasted to our study where liver RT did not increase response rate (Supplementary Table 2). In another prospective study of patients with metastatic melanoma receiving Ipilimumab concurrently with RT (8/22 received SAbR), authors concluded that the combination was safe and promising. Interestingly, of the 3 CR observed, 2 had SAbR to lung lesions. Overall, similar to these reports, our study adds to the evidence that combining RT with immunotherapy is probably safe and, at least, promising in terms of response.

While the exact mechanisms of the combination are not well understood, several studies indicate the cumulative benefits of combining RT with immune-related treatments to create an enhanced immunologic response. The optimal fractionation required for tumor killing and immune response, however, remains debatable, though most studies suggest the benefit of hypofractionation and larger doses per fraction. We found no difference in toxicity or outcome between different numbers of H-RT fractions or biologically equivalent doses (BED). While this might be attributable to the heterogeneous patient population, dose regimens, and relatively small population size in this study, the lack of any trend towards significance suggests that there may be no universal optimal immune-modulatory radiation dose. Prospective and cancer site-specific clinical trials are required to adequately answer this question.

We have shown that combining immune checkpoint inhibitors with extra-cranial H-RT, such as SAbR, is safe and well tolerated with no significant increase in toxicity, no temporal or spatial relationships between toxicities and radiation timing or sites, and a possible association between lung SAbR and complete responses.

**Patients and methods**

**Patient selection**

With institutional review board approval (IRB # STU 042017-028), we retrospectively reviewed medical records of patients with pathologically-confirmed metastatic RCC, melanoma, NSCLC, bladder, pancreatic, and head and neck cancers. All patients were treated using ICIs combined with hypofractionated SAbR or conformal radiation therapy (C-RT) delivered to extra-cranial site(s) during or within 8 weeks of the start or end of ICI infusions at the University of Texas Southwestern Medical Center. Patients who only received brain SRS, conventional, superficial, or electron RT were excluded. The 8-week cut-off was selected to enrich our population with patients having a close temporal association between ICIs and RT. A multi-disciplinary team of medical oncologists, radiation oncologists, and surgeons treated each patient.

**Radiotherapy and immune checkpoint inhibitors**

H-RT is defined as regimens of 1–5 fractions with \( \geq 5 \) Gy per fraction and includes SAbR and C-RT. C-RT includes intensity modulated radiotherapy (IMRT) and 3-dimensional conformal radiation therapy (3D-CRT). Patients were included even if they received other concurrent RT (stereotactic brain RT or conventionally fractionated RT) as long as they received at least one course of SAbR or hypofractionated C-RT. Computed tomography (CT) simulation was performed per institutional guidelines. All SAbR treatments used a stereotactic body frame. The treating physician chose motion management and immobilization setups as needed. Image guidance was used where applicable. Planning target volume (PTV) expansion differed depending on RT technique. All RT plans were optimized to ensure adequate PTV coverage by the prescription dose. BED was calculated using the universal survival model. Our institutional normal tissue constraints are published elsewhere. Inhibitors of PD-1 (Nivolumab and Pembrolizumab), PD-L1 (Atezolizumab), and CTLA-4 (Ipilimumab) were administered according to FDA-approved guidelines.

**Evaluating treatment toxicity and outcomes**

We analyzed AEs based on CTCAE 4.0. We defined time to toxicity from treatment initiation (ICI or H-RT, whichever came first) until a particular toxicity developed. We analyzed toxicities against H-RT site, dose, tumor type, or ICI and H-RT sequencing. We defined best overall response as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) from ICI therapy initiation until disease progression or last follow-up, as evaluated by a board-certified radiologist, based on the immune-related (ir)-RECIST criteria. Radiated lesions were excluded from response evaluation. Objective response rate (ORR) included patients with CR or PR. We excluded from our outcome analysis patients who did not receive appropriate follow-up imaging (i.e. the two sets of imaging required for irRECIST) or did not have at least 1 non-radiated measurable lesions for response evaluation. We considered these patients non-evaluable for outcome analysis but evaluable for toxicity. We calculated overall survival (OS) from treatment initiation until death or last known date of survival. Patients lost to follow-up were censored at last follow-up. We calculated progression-free survival (PFS) from ICI therapy initiation until death or first dated progression, as defined by irRECIST criteria.

**Statistical considerations**

We used the Kaplan-Meier method to estimate OS and PFS. Fisher’s exact test was used to compare data to historical
controls. Correlation between treatment or patient variables and toxicity (or response to treatment) was assessed using Fisher’s exact test for categorical parameters and Kruskal-Wallis test for continuous measures. All statistical tests were two-sided, and a p-value of ≤0.05 was considered statistically significant for all comparisons. We used SAS 9.4 (SAS Institute Inc., Cary, NC) for analysis.

Conflicts of interest
All authors report no conflicts of interest except 1) Dr. James Brugarolas who receives research funding from Genentech, is an advisory board member with Bethyl Laboratories and is a consultant with Nektar and 2) Dr. Hans Hammers who is an advisory board member with BMS and receives trial funding from BMS.

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