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Combined immune checkpoint inhibitors and ablative radiotherapy in metastatic cancers: a meta-analysis of prospective clinical trials

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ABSTRACT

Objective To pool data from prospective clinical trials investigating combined stereotactic ablative radiotherapy (SABR) with immune checkpoint inhibitors (ICI) in patients with metastatic cancers.

Methods and analysis PubMed, Scopus and EMBASE were queried for full-length articles of prospective clinical trials involving patients with metastatic solid tumours. Random-effects meta-analysis was performed with the Knapp-Hartung method. Multilevel regression analyses with primary cancers used as random effects and pairwise comparisons with two-tailed test adjusted with Benjamini-Hochberg method were performed. Regression coefficients (β) were calculated to assess the correlation between dose and outcomes.

Results We identified 30 trials and 35 individual treatment arms with a total of 951 patients with at least one outcome metric reported. Large heterogeneity was identified for all outcomes measured (I^2 range: 75%–86%). The pooled rate of grade 3+ treatment-related adverse events was 18% (95% CI 11% to 24%). The progression-free survival (PFS) and overall survival (OS) at 6 months were 27% (95% CI 19% to 36%) and 67% (95% CI 59% to 76%), respectively. On multilevel regression, we identified improvement in 6-month PFS (β=0.6, p=0.003) and OS (β=1.6, p=0.04) with increasing BED10Gy doses. Combined-target ICI correlated with better 6-month OS when compared with αPD-1/PD-L1 alone.

Conclusion We report a safety profile of combined ICI with SABR in patients with metastatic cancer that is comparable to that of ICI alone. We identified higher doses of radiotherapy and dual-target ICI to be associated with better OS at 6 months. Large heterogeneity and the lack of a control group limit the interpretation of our findings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Stereotactic ablative radiotherapy (SABR) can increase the immunogenicity of tumours through modulation of the tumour and its environment. Several, mostly small, non-randomised trials have investigated combining SABR with immune checkpoint inhibitors (ICI) to increase their therapeutic potential.

WHAT THIS STUDY ADDS

⇒ This study provides a comprehensive view of all prospective clinical trials and pooled analyses of important clinical outcomes. The combination seemed safe with promising outcomes. Higher doses of radiotherapy and combined-target ICI were identified to correlate with longer survival, although with a higher incidence of adverse events with the latter.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study should influence clinical practice and clinical trial design, given the favourable safety profile found, and the identification of higher doses of radiotherapy and combined-target ICI as treatment variables associated with better survival.

INTRODUCTION

The advent of immunotherapy has revolutionised cancer therapeutics. In the clinical space, immune checkpoint inhibitors (ICI) have gained the strongest presence among the different immunotherapeutic drugs.[1] In 2011, the FDA approved ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (αCTLA-4) monoclonal antibody, for use in patients with metastatic melanoma after a landmark trial showed improved overall survival (OS) associated with its use.[2] Since then, several more ICIs have been approved for different indications including seven anti-programmed cell death protein 1 (αPD-1) or anti-programmed cell death ligand 1 (αPD-L1) and one anti-lymphocyte-activation gene 3 in combination with nivolumab.[1 3 4] Despite notable examples of clinical trials showing clinical response with the use of ICIs, the majority of patients with advanced cancers do not experience durable responses to ICIs. The development of strategies to increase and sustain this response is an active topic of research today.[5 6]

Radiotherapy (RT) remains a cornerstone of cancer treatment, with nearly half of all patients receiving this treatment modality during their therapeutic journey. Beyond its established role in local tumour control, growing evidence has highlighted the immunomodulatory effect of radiation with potential systemic effects. Specific doses and regimens have emerged that result in an activation of distinct damage signalling pathways and induction of immunogenic cell death, which may lead to a robust systemic, tumour-specific immune response.[7 8] The 'abscopal effect', wherein untreated metastatic lesions outside the RT field shrink following treatment, is a notable phenomenon engaging type I interferons, tumour-infiltrating dendritic cells for cross-presentation of tumour-associated antigens.[9–11] These discoveries prompt a critical exploration for improved therapeutic outcomes, including, potentially, in patients with metastatic disease. Recent phase II clinical trials have reported improved progression-free survival (PFS) and, in some cases, OS in patients with metastatic solid tumours treated with ablative RT doses.[12–18] Motivated by these encouraging data, international societies have sought to issue clinical guidance on the role of SABR for metastases.[19–22] A compelling hypothesis for how a local treatment like RT might lead to improved OS in metastatic disease is that RT leads to a systemic anticancer cellular immune response.[23] This body of evidence highlights the potential of combined immune checkpoint therapy and RT for more effective cancer treatment strategies.

A number of clinical studies have been published in recent years investigating the combination of ICI with RT in patients with metastatic cancers. These trials were small, often with the primary endpoint of safety. For the present study, we sought to pool the data on safety and clinical outcomes from all published prospective trials in this space. We hypothesised that the use of combined ICI and RT would result in acceptable toxicity profiles and favourable oncologic outcomes. We evaluated whether different variables such as the type of cancer, sequencing of therapies and dose of RT were associated with improved outcomes or increased toxicity.

METHODS

Literature search

Pubmed, Embase and Cochrane Central databases were queried on 30 November 2024. Full search criteria in the online supplemental data. Full-length manuscripts of prospective studies published in English were selected without restriction on date of publication. Resulted studies were then individually examined for the following inclusion criteria: prospective studies including patients with metastatic cancer treated with ICIs and RT within 21 days, with a minimum fractional dose of radiation of 6 Gy and a minimum total dose of 15 Gy to non-brain targets of RT reporting on at least one of our outcomes of interest. We excluded studies investigating any other modality of treatment, including other non-ICI immunomodulators.

Outcome measures

A meta-analysis was conducted for the six outcome measures of interest: grade 3 or higher treatment-related adverse events (AE), disease control rate (DCR, defined as systemic stable disease, partial response or complete response as best response after treatment), PFS at 6 and 12 months, and OS at 6 and 12 months. These time points were chosen since they are routinely reported in trials and facilitated analysis. AEs were analysed as the total number of patients experiencing any grade ≥3 AE, rather than the total number of individual events. For studies with more than one treatment arm meeting our inclusion criteria, each arm was included as an individual entry for the meta-analysis. The estimates of individual treatment arms were modelled as proportions, calculated as the total number of evaluable patients in the study over the number of patients experiencing the outcome of interest. Plot Digitizer (SourceForge) was used to extract survival rates from Kaplan-Meier curves.

Data analysis

Statistical analyses were performed using RStudio V.2023.09.0. The packages *meta* (V.7.0–0) and *metafor* (V.4.4–0) were used for generation of meta-analysis of proportions, forest plots, test for heterogeneity, Peter's regression test, funnel plot for publication bias and nested regression analyses. Random-effects modelling was used to produce an overall summary estimate (pooled estimate) for each outcome measure and its 95% CI. In addition, 95% prediction interval (PI) was constructed to provide an insight into the prediction region for a hypothetical future study.[24] Model parameters were estimated using maximum likelihood (ML) for common-effect modelling; and restricted ML and Hartung-Knapp SE adjustment for random-effects modelling. Hartung-Knapp method was chosen given the expected high heterogeneity of included studies. To quantify heterogeneity, our analysis computed I^2—the percentage of variability in the estimates that is not caused by sampling error. Heterogeneity was considered to be substantial if I^2>75% or moderate if I^2>50%.[25] The SD of random effect, τ, was calculated using an arcsine transformation; and then an inverse transformation, $sin\left(\frac{\tau}{2}\right)^2$, was applied to express this statistic as a proportion.[26 27] Cochran's Q-test was performed to examine if the variance of the estimates exceeds the amount that would be expected under the null hypothesis of no heterogeneity.[28] The presence of publication bias was investigated via funnel plot asymmetry via Peter's regression test.[29]

Multivariate meta-regression models were performed to evaluate the effect of different treatment characteristics on outcomes of interest (6-month PFS and OS rates and G3+AEs), accounting for differences in prognoses across cancer types. A nested structure was implemented using a mixed-effects model with a random intercept for cancer type to account for between-study variability and clustering of trials within cancer types. The following variables were independently tested as fixed effects with

this model: BED10Gy (biologically effective dose with α/β=10 Gy), immunotherapy target and sequencing of treatments. The linear-quadratic model was used to calculate the BED10Gy for different radiation doses and fractionation schedules, as it is widely used to predict biologic responses to radiation.[30] To assess the dose–response relationship between BED10Gy and outcomes of interest, we performed a multivariable meta-regression using a mixed-effects model with a random intercept for primary cancer type. The model included BED10Gy as a continuous moderator, and significance was evaluated using a t-test. Pairwise comparisons between treatment groups were performed using a multivariate random-effects meta-regression model in pooled proportions and their associated SEs. P values were computed using a two-sided t-test. Given the multiple comparisons for timing of therapies and target of ICI, the false discovery rate was controlled using the Benjamini-Hochberg procedure to reduce the risk of type I error. A threshold of BED10Gy ≥ or <45 Gy allowed for a more equitable distribution of patients in each group and was therefore chosen for comparison. For analysis of the sequencing of therapies, three categories were defined: concurrent if the interval between therapies was ≤7 days, or RT first or ICI first if therapies were separated by >7 days. A p value<0.05 was considered statistically significant.

RESULTS

Study characteristics

Table 1 shows the included treatment arms and table 2 presents a summary of patient and treatment details. A study selection flow diagram is found in online supplemental figure S1. Thirty prospective interventional clinical trials with a total of 35 individual treatment arms meeting inclusion criteria were identified. Outcome data were available for at least one endpoint for a total of 951 patients. The primary cancers enrolled in these studies included non-small cell lung cancer (NSCLC; n=257, 27%), mixed cancers (n=235, 25%), pancreatic (n=101, 11%), renal cell carcinoma (RCC; n=69, 7%), biliary tract (n=61, 6%), melanoma (n=59, 6%), colorectal (37, 4%), head and neck (32, 3%), prostate (n=31, 3%), breast (29, 3%), urothelial carcinoma (n=18, 2%), anaplastic thyroid (n=12, 1%) and adenoid cystic carcinoma (n=10, 1%). The majority of studies allowed the target of RT to be any extracranial metastatic site.

PFS rate at 6 and 12 months

Twenty-eight treatment arms with a total of 779 patients reported rates of 6-month PFS, which ranged from 0% to 75% and varied widely across treatment arms (I^2=86% (81% to 90%), p<0.01; figure 1A). The pooled PFS was 27% (95% CI 18% to 37%) with a 95% PI of 0% to 77%. There were significant differences in outcomes depending on the primary cancer (p<0.01), with prostate cancer and NSCLC having the highest 6-month PFS. Twenty-six treatment arms with a total of 772 patients reported 12-month PFS rates, which ranged from 0% to 67% (online supplemental figure S3). The PFS rates varied widely across the studies (I^2=83% (76% to 88%), p<0.01). The pooled 12-month PFS was 16% (95% CI 10% to 23%) with a 95% PI of 0%–46%. Linear regression of discrete BED10Gy values, nested by primary cancer, revealed a strong correlation between 6 and 12-month PFS rates and increasing BED10Gy (figure 1E, online supplemental figure S3C). No publication bias was detected on funnel plot Egger's test or Peter's linear regression test for 6-month or 12-month OS rates (p>0.05 for all, figure S2, figure S3).

Figure 1B–D shows the results of a pairwise comparison of 6-month PFS proportion estimates derived from nested meta-regression analyses using primary cancer as random variable. We found better PFS in patients treated with RT first as opposed to concurrent treatment (32% (95% CI 20% to 44%) vs 17% (95% CI 5% to 28%), p=0.034).

OS rate at 6 and 12 months

Twenty-eight treatment arms including 798 patients reported rates of OS at 6 months, which ranged from 25% to 100% and varied widely across treatment arms (I^2=84% 78% to 88%), p<0.01; figure 2A). The pooled OS rate at 6 months was 67% (95% CI 58% to 76%) with a 95% PI 22% to 98%. There were significant differences in outcomes depending on the primary cancer (p<0.01), with adenoid cystic carcinoma and NSCLC having the highest 6-month OS. Twenty-nine arms with a total of 808 patients reported 12-month OS rates, which ranged from 0% to 90% (online supplemental figure S4). The OS rates varied widely across the studies (I^2=87% (82% to 90%), p<0.01). The pooled 12-month OS was 43% (95% CI 32% to 54%) with a 95% PI of 3% to 91%. Linear regression of discrete BED10Gy values, nested by primary cancer, revealed a strong correlation between 6 and 12-month OS rates and increasing BED10Gy (figure 2E, online supplemental figure S4C). No publication bias was detected on funnel plot Egger's test or Peter's linear regression test for 6-month or 12-month OS rates (p>0.05 for all, figure S2, figure S4).

Figure 2B–D shows the results of a pairwise comparison of 6-month OS proportion estimates derived from nested meta-regression analyses using primary cancer as random variable. We found better OS in patients treated with BED10Gy ≥45 Gy than with <45 Gy (75% (95% CI 63% to 87%) vs 57% (95% CI 44% to 70%), p=0.005). Combined-target ICIs were also associated with superior OS compared with αPD-1/PD-L1 monotherapy (80% (95% CI 63% to 96%) vs 61% (95% CI 46% to 77%), p<0.001).

Disease control rate

Twenty-six treatment arms including 704 patients reported DCR, which ranged from 0% to 80% and varied widely across treatment arms (I^2=85% 78% to 89%), p<0.01; online supplemental figure S5A). The pooled DCR was

Table 1 Treatment arms included and select study descriptions

Study	Country	Primary cancer	ICI	Radiation dose	BED10Gy	Sequencing of therapies	Patients available for analysis
Mahmood *et al*[33]	USA	Adenoid cystic carcinoma	Pembrolizumab	30 Gy in 5 fx	48	ICI	10
Lee *et al*[46]	USA	Anaplastic thyroid	Durvalumab+tremelimumab	27 Gy in 3 fx	51.3	ICI	12
Markussen *et al*[47]	Denmark	Biliary tract carcinoma	Nivolumab	15 Gy in 1 fx	37.5	Concurrent	19
Markussen *et al*[47]	Denmark	Biliary tract carcinoma	Nivolumab+ipilimumab	15 Gy in 1 fx	37.5	Concurrent	42
Ho *et al*[48]	USA	Breast	Pembrolizumab	30 Gy in 5 fx	48	Concurrent	17
Voorwerk *et al*[49]	Netherlands	Breast	Nivolumab	24 Gy in 3 fx	43.2	RT	12
Monjazeb *et al*[50]	USA	Colorectal	Durvalumab+tremelimumab	24 Gy in 3 fx	43.2	ICI	10
Parikh *et al*[51]	USA	Colorectal	Nivolumab+Ipilimumab	24 Gy in 3 fx	43.2	ICI	27
McBride *et al*[34]	USA	Head and neck	Nivolumab	27 Gy in 3 fx	51.3	ICI	32
Postow *et al*[52]	USA	Melanoma	Nivolumab+Ipilimumab	27 Gy in 3 fx	51.3	ICI	10
Ratnayake *et al*[53]	Australia	Melanoma	Allowed any	15 Gy in 1 fx	37.5	ICI	14
Sundahl *et al*[54]	Belgium	Melanoma	Ipilimumab	24 Gy in 3 fx, 30 Gy in 3 fx, or 36 Gy in 3 fx	43–79	ICI	13
Twyman-Saint Victor *et al*[55]	USA	Melanoma	Ipilimumab	12 Gy in 2 fx, 16 Gy in 2 fx, 18 Gy in 3 fx, or 24 Gy in 3 fx	19–43	RT	22
Luke *et al*[56 57]	USA	Mixed primary cancer	Pembrolizumab	30 Gy in 3 fx, 45 Gy in 3 fx, 50 Gy in 5 fx	60–100	RT	73
Maity *et al*[58 59]	USA	Mixed primary cancer	Pembrolizumab	17 Gy in 1 fx or 24 Gy in 3 fx	43–46	ICI	24
Tang *et al*[60]	USA	Mixed primary cancer	Ipilimumab	50 Gy in 4 fx or 60 Gy in 10 fx	96–110	NA	32
Welsh *et al*[61 62]	USA	Mixed primary cancer	Ipilimumab	50 Gy in 4 fx or 60 Gy in 10 fx	96–110	NA	106
Bassetti *et al*[63]	USA	NSCLC	Tremelimumab+durvalumab	30–50 Gy in 5 fx	48–100	RT	15
Bestvina *et al*[64]	USA	NSCLC	Nivolumab+ipilimumab	30 Gy in 3 fx, 45 Gy in 3 fx, 50 Gy in 5 fx	60–100	ICI	28
Bestvina *et al*[64]	USA	NSCLC	Nivolumab+ipilimumab	30 Gy in 3 fx, 45 Gy in 3 fx, 50 Gy in 5 fx	60–100	RT	24
Formenti *et al*[65]	USA	NSCLC	Ipilimumab	28.5 Gy in 3 fx or 30 Gy in 5 fx	48–56	Concurrent	39
Horndalsveen *et al*[66]	Norway	NSCLC	Atezolizumab	24 Gy in 3 fx	43.2	ICI	21
Mattes *et al*[67]	USA	NSCLC	Any allowed	Any SBRT in 3–5 fx dose allowed	N/A	ICI	34
Miyamoto *et al*[68]	Japan	NSCLC	Nivolumab	Any allowed, range 25.5/3 fx - 48 Gy/4 fx	47–106	RT	6
Qin *et al*[69]	USA	NSCLC	Atezolizumab	24 Gy in 3 fx, 30 Gy in 5 fx	43–48	ICI	12
Schoenfeld *et al*[35]	USA	NSCLC	Durvalumab+tremelimumab	24 Gy in 3 fx	43.2	ICI	26
Theelen *et al*[36]	Netherlands	NSCLC	Pembrolizumab	24 Gy in 3 fx	43.2	RT	36
Welsh *et al*[37]	USA	NSCLC	Pembrolizumab	50 Gy in 4 fx	112.5	NA	16
Chen *et al*[70]	Denmark	Pancreatic adenocarcinoma	Nivolumab+ipilimumab	15 Gy in 1 fx	37.5	Concurrent	43
Chen *et al*[70]	Denmark	Pancreatic adenocarcinoma	Nivolumab	15 Gy in 1 fx	37.5	Concurrent	41
Parikh *et al*[51]	USA	Pancreatic adenocarcinoma	Nivolumab+Ipilimumab	24 Gy in 3 fx	43.2	ICI	17

Continued

Table 1 Continued

Study	Country	Primary cancer	ICI	Radiation dose	BED10Gy	Sequencing of therapies	Patients available for analysis
Kwan *et al*[71]	Australia	Prostate	Avelumab	20 Gy in 1 fx	60	NA	31
Masini *et al*[72]	Italy	RCC	Nivolumab	30 Gy in 3 fx	60	ICI	69
Sundahl *et al*[73]	Belgium	Urothelial carcinoma	Pembrolizumab	24 Gy in 3 fx	43.2	RT	9
Sundahl *et al*[73]	Belgium	Urothelial carcinoma	Pembrolizumab	24 Gy in 3 fx	43.2	ICI	9
						Total	951

ICI, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; RT, radiotherapy.

Table 2 Summary of cancer types and treatment characteristics from the included studies

	Studies	Patients, n (%)
Primary cancer		
NSCLC	11	257 (27)
Mixed primary cancer	4	235 (24.7)
Pancreatic adenocarcinoma	3	101 (10.6)
RCC	1	69 (7.3)
Biliary tract carcinoma	2	61 (6.4)
Melanoma	4	59 (6.2)
Colorectal	2	37 (3.9)
Head and neck	1	32 (3.4)
Prostate	1	31 (3.3)
Breast	2	29 (3)
Urothelial carcinoma	2	18 (1.9)
Anaplastic thyroid	1	12 (1.3)
Adenoid cystic carcinoma	1	10 (1.1)
BED10Gy		
< 45 Gy	16	348 (36.6)
≥ 45 Gy	15	520 (54.7)
Other	4	83 (8.7)
ICI target		
PD-1/PD-L1	19	497 (52.3)
Combined	10	228 (24)
CTLA-4	5	212 (22.3)
Either target	1	14 (1.5)
Sequencing		
ICI first	15	326 (34.3)
RT first	7	173 (18.2)
Concurrent	8	239 (25.1)
Other	5	213 (22.4)

CTLA-4, anti-cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PD-1, anti-programmed cell death protein 1; PD-L1, anti-programmed cell death ligand 1; RCC, renal cell carcinoma; RT, radiotherapy.

42% (95% CI 33% to 51%) with a 95% PI 0% to 83%. There were significant differences depending on the primary cancer (p<0.01), with NSCLC and RCC having the highest DCR. No dose-dependent effect was seen with linear regression of BED10Gy nested by primary cancer (online supplemental figure S5C). No publication bias was detected on funnel plot Egger's test or Peter's linear regression test (p>0.05 for both).

Online supplemental figure S6 shows the results of a pairwise comparison of DCR estimates derived from nested meta-regression analyses using primary cancer as random variable. We found better DCR in patients treated with combined-ICI target than with αCTLA-4

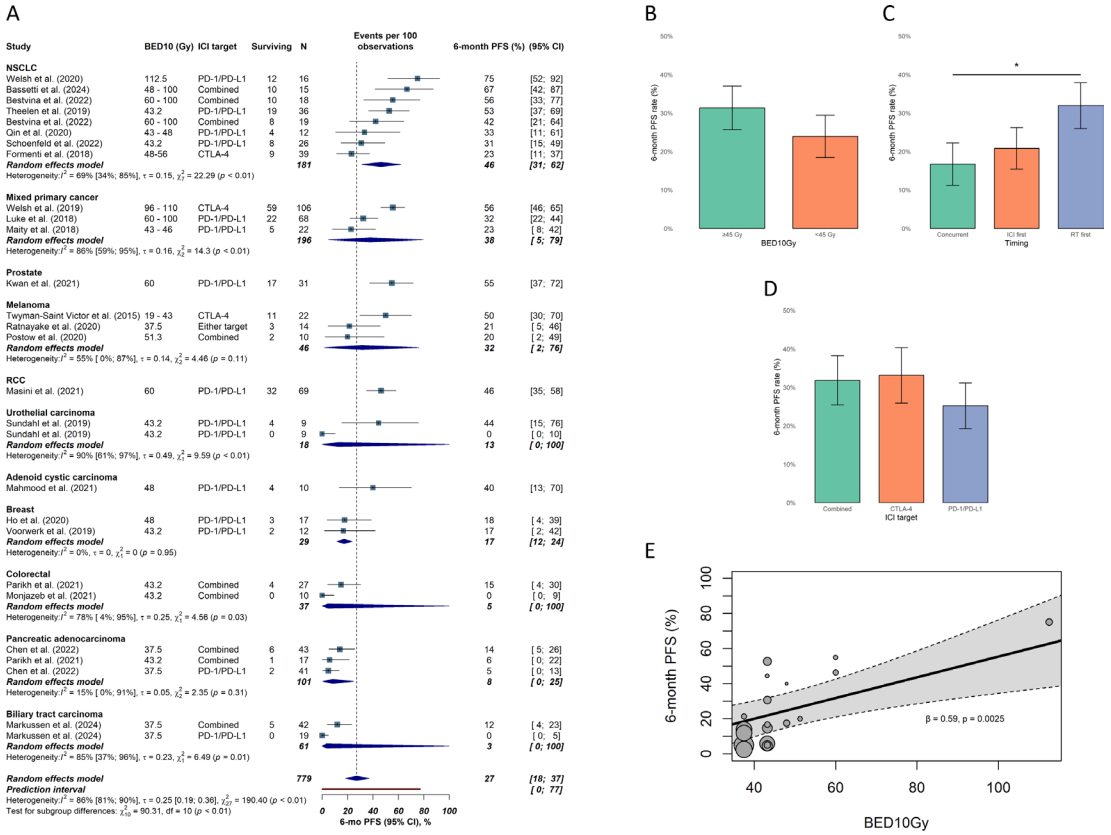

Figure 1 (A) Forest plot for 6 month progression-free survival (PFS). Proportion estimates calculated with nested meta-regression analyses with primary cancer used as random effect for 6-month PFS for (B) BED10Gy, (C) timing of therapies and (D) ICI target. The differences of sublevels were assessed via pairwise comparisons; statistically significant comparisons are identified with a horizontal line. Vertical bars represent SE. (E) Regression model with primary cancers used as groups for random effects testing BED10Gy as a continuous variable for 6-month PFS rates; only studies that had a single radiotherapy regimen were included. β refers to the regression coefficient (per cent change in survival per unit dose) and the p value was derived from a t test. *p<0.05. CTLA-4, anti-cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; PD-1, anti-programmed cell death protein 1; PD-L1, anti-programmed cell death ligand 1; OS, overall survival; BED10Gy, biologically effective dose with α/β=10 Gy.

alone (45% (95% CI 30% to 59%) vs 25% (95% CI 9% to 40%), p=0.013).

Grade 3–5 AE rate

Twenty-three treatment arms including 595 patients reported G3+AEs, which ranged from 0% to 40% and varied widely across treatment arms (I^2=75% (62% to 83%), p<0.01; figure 3A). The pooled G3+AE was 18% (95% CI 12% to 24%) with a 95% PI 0% to 41%. There were significant differences depending on the primary cancer (p<0.01), with NSCLC and pancreatic cancer having the highest pooled AE rates. No dose-dependent effect was seen with linear regression of BED10Gy (figure 3E). No publication bias was detected on funnel plot Egger's test or Peter's linear regression test (p>0.05 for both, figure S2).

Figure 3B–D shows the results of a pairwise comparison of G3+AE proportion estimates derived from nested meta-regression analyses using primary cancer as random variable. Patients receiving combined-target ICIs experienced more frequent AEs than those receiving αPD-1/PD-L1 monotherapy (32% (95% CI 22% to 41%) vs 11% (95% CI 5% to 17%), p<0.001). Concurrent treatment of ICI and RT was associated with higher AE rate compared with ICI-first (24% (95% CI 13% to 35%) vs 11% (95% CI 3% to 18%), p= 0.03).

DISCUSSION

This is the first meta-analysis of prospective clinical trials investigating the combination of ICIs with ablative RT in patients with metastatic cancers. We found substantial heterogeneity across the different treatment arms analysed, which limits the reliability of our results. Main findings include a 6-month PFS of 27%, 6-month OS of 67% and a DCR of 40%. Grade 3 or higher adverse effects were observed in 18% of patients, which is similar to the rate of 16% found in a meta-analysis that included retrospective studies of concurrent ICI and RT.[31] In comparison, a meta-analysis of studies with patients treated with ICI monotherapy reports rates of grade 3–5 AE rates of 27%, while another meta-analysis with patients with metastatic cancers treated with SBRT showed a pooled grade 3–5

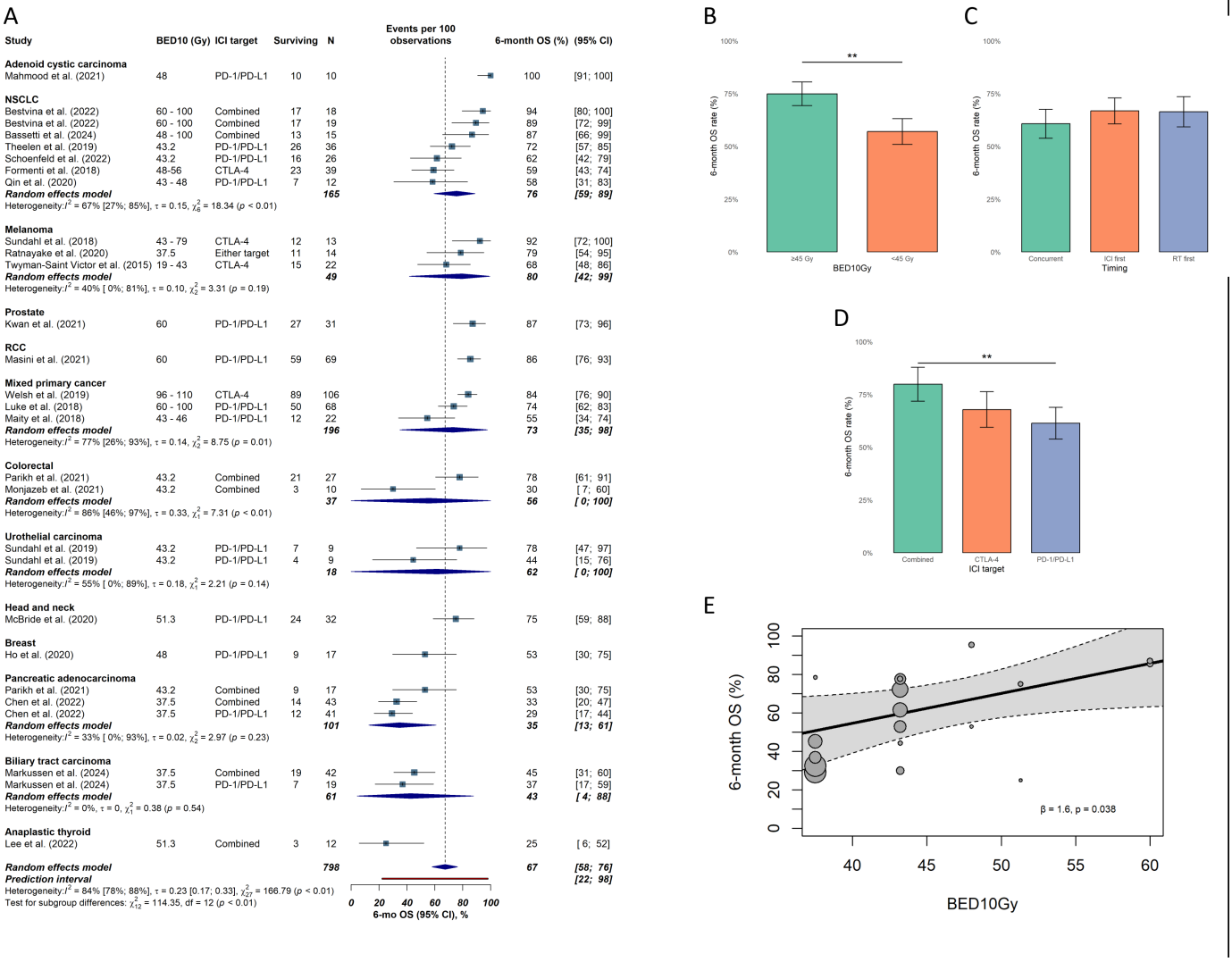

Figure 2 (A) Forest plot for 6-month overall survival (OS). Proportion estimates calculated with nested meta-regression analyses with primary cancer used as random effect for 6-month OS for (B) BED10Gy, (C) timing of therapies and (D) ICI target. The differences of sublevels were assessed via pairwise comparisons; statistically significant comparisons are identified with a horizontal line. Vertical bars represent SE. (E) Regression model with primary cancers used as groups for random effects testing BED10Gy as a continuous variable for 6-month OS rates; only studies that had a single radiotherapy regimen were included. β refers to the regression coefficient (per cent change in survival per unit dose) and the p value was derived from a t test. **p<0.01. CTLA-4, anti-cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; PD-1, anti-programmed cell death protein 1; PD-L1, anti-programmed cell death ligand 1; RCC, renal cell carcinoma; BED10Gy, biologically effective dose with α/β=10 Gy.

AE rate of 1%.[16 32] These combined results suggest that the addition of ablative RT to ICI does not significantly contribute to high-grade toxicity.

Given the substantial heterogeneity in outcomes with different primary cancers, we performed nested meta-regression analyses using primary cancers as groups for random effects. Better OS and PFS were observed with increasing BED10Gy in a linear regression model, including, for example, an absolute increase in 6-month OS rate of 1.6% with every BED10Gy unit increment. In a categorical analysis, BED10Gy≥45 Gy was also associated with better OS. As explained in the Methods section, 45 Gy was selected to enable meaningful statistical categorical analysis, rather than to identify an optimal dose. There was no evidence of an increase in grade 3–5 AEs with higher doses of RT. Six-month OS and G3+AE rates were numerically higher with combined-target ICI compared with αCTLA-4 alone, and significantly higher than αPD-1/PD-L1 alone. Better PFS was observed with patients receiving RT first as opposed to concurrent treatment. Finally, higher AE rates were seen when treating with concurrent therapy compared with sequencing ICI first.

Recently published phase II randomised controlled clinical trials have failed to show a survival benefit to the addition of SABR to ICI in patients with advanced, relapsed

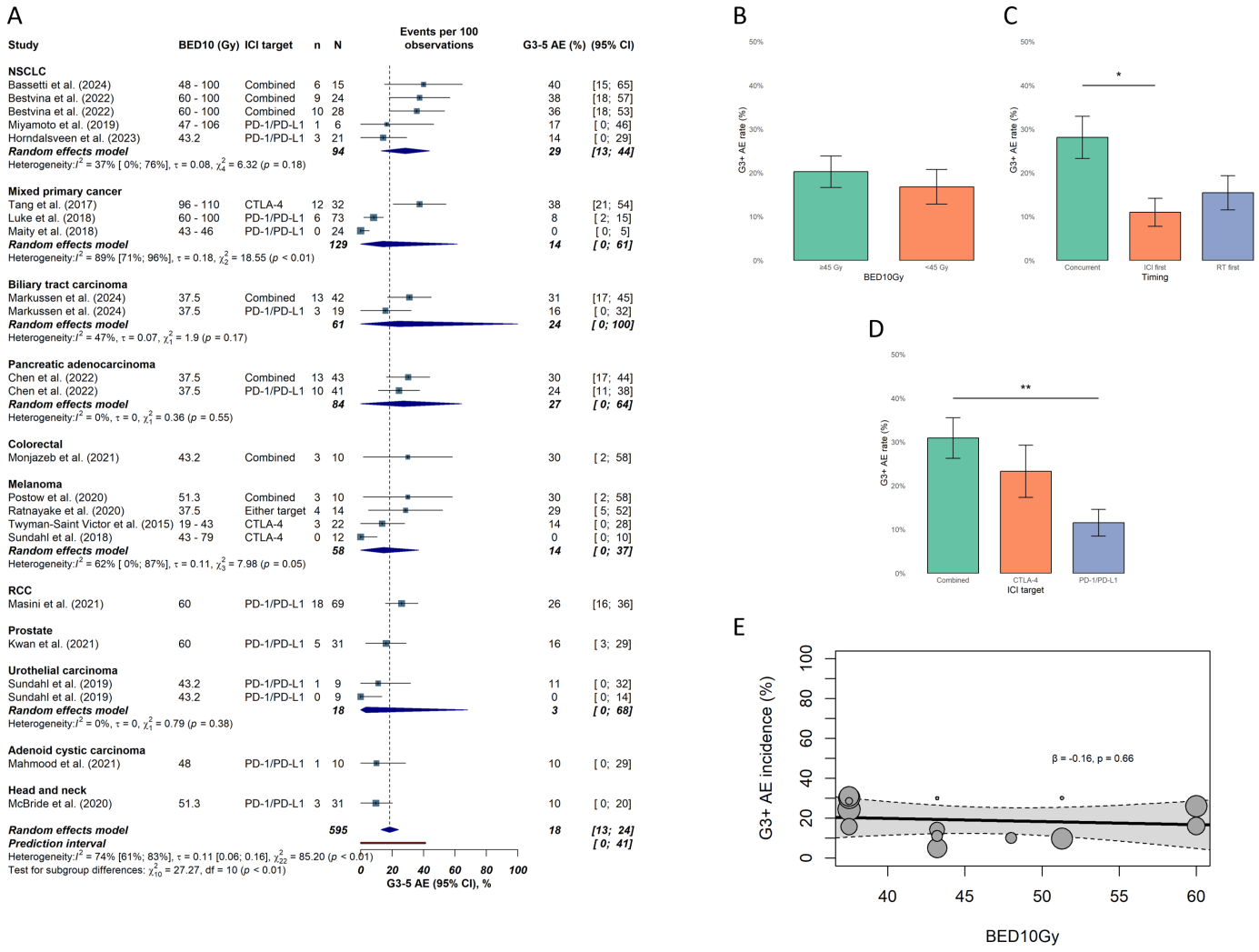

Figure 3 (A) Forest plot for rates of grade 3+ adverse events (G3+AE). Proportion estimates calculated with nested meta-regression analyses with primary cancer used as random effect for G3+AE rates for (B) BED10Gy, (C) timing of therapies and (D) ICI target. The differences of sublevels were assessed via pairwise comparisons; statistically significant comparisons are identified with a horizontal line. Vertical bars represent SE. (E) Regression model with primary cancers used as groups for random effects testing BED10Gy as a continuous variable for G3+AE rates; only studies that had asingle radiotherapy regimen were included. β refers to the regression coefficient (per cent change in survival per unit dose) and the p value was derived from a t test. *p<0.05, **p<0.01. CTLA-4, anti-cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; PD-1, anti-programmed cell death protein 1; PD-L1, anti-programmed cell death ligand 1; RCC, renal cell carcinoma; BED10Gy, biologically effective dose with α/β=10 Gy.

and/or metastatic cancers.[33–39] Notably, the BED10Gy in these studies ranged from 43 Gy to 51 Gy, with Welsh *et al* being the exception allowing regimens corresponding to BED10Gy of 59 Gy or 113 Gy. Our linear regression analyses revealed no ceiling effect of BED10Gy and its correlation with survival, supporting the use of higher doses than those employed in most randomised trials, especially since there is no concomitant increase in AEs.

The low toxicity from combined therapy in our study is consistent with prior studies.[31 40] Special concern exists that combination therapy may increase the risk of pneumonitis, as both ICIs and RT to the chest are known risk factors for this complication. The studies in our analysis seldom reported individual patient data, precluding an assessment of correlation between RT to the thorax and pneumonitis. However, we found that grade ≥3 pneumonitis was not a commonly reported AE overall, occurring in only 4% of patients (Table S1). Prior studies have suggested that the risk of grade ≥3 pneumonitis from combined ICI and ablative RT to lungs is around 10%.[41 42] In contrast, the risk of grade 3+ pneumonitis is low for ICI monotherapy, as suggested in a meta-analysis that found incidence rates of less than 1%.[43] The risk of pneumonitis with ICI and thoracic RT for metastases warrants prospective evaluation; meanwhile, current data support individualized risk–benefit assessment based on factors such as cardiopulmonary comorbidities, prior thoracic RT, and expected response to ICI+RT.

OS in our analysis was numerically lower than that reported in a prior meta-analysis of stereotactic ablative RT to oligometastatic cancers.[16] Both meta-analyses allowed any primary cancer; however, differences in the

distribution of primary cancers with varying prognoses may account for some of the observed differences in survival. Another major difference is that study limited the selection criteria to oligometastatic disease (≤5 metastases), whereas we had no limitation, consistent with recent trials investigating SABR for polymetastatic disease.[44 45] Moreover, 11 out of the 21 studies included by Lehrer *et al* involved patients with ≤3 metastases. Most studies included in our analysis did not exclude patients based on number of metastases, nor did many studies report the number of metastases per patient. Thus, a measure of central tendency in our analysis would not accurately represent the burden of disease in the included patients. Based on the wide inclusion criteria of different cancers, sites treated, and no limit on the burden of metastatic disease, we posit that the clinical outcomes in our analysis are promising and merit further study.

There are several elements of our study that limit the generalisability of our findings. First, we observed large heterogeneity for every outcome reported, which contributed to broad PIs that make our pooled estimates less reliable. Moreover, our analysis is based on single-arm prospective data without a control group. As a study-level meta-analysis, important confounding variables were not modelled or accounted for (eg, age, performance status, prior therapies, systemic disease burden). We performed regression analyses that show better PFS and OS with increasing doses of RT; however, this analysis was restricted to trials testing a single radiotherapy regimen (whereas many trials allowed more than one), which decreased the number of participants in the analysis. Finally, despite no publication bias seen on our analyses, meta-analyses are subjected to overestimation of clinical benefit since positive trials are more likely to be published than negative trials.

In conclusion, this is the first meta-analysis on safety and efficacy of prospective clinical trials investigating the role of combined ICI with ablative RT in patients with metastatic solid malignancies. We report promising clinical outcomes with acceptable toxicity rates that are, comparatively, not higher than rates reported for ICI alone. We identified higher doses of radiation and use of dual-target ICI to be associated with better survival. Pursuant to the commitment to advance precision medicine, our data calls for further and more comprehensive studies, inclusive of immunological and molecular parameters, to better tailor therapeutic approaches for the diverse landscape of metastatic cancers.

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