Journal for ImmunoTherapy of Cancer

Abscopal effects in patients with malignant melanoma treated with radiotherapy and immune checkpoint inhibition: analysis of a large observational multicenter study

Simone Ferdinandus ,[1,2] Alexander Rühle,[3,4] Allison Lamrani,[5] Charlotte Frei,[5,6] Justus Kaufmann ,[7] Matthias Mäurer,[8,9] Georg Wurschi,[8,10] Ping Jiang,[11] Felix Ehret ,[12,13] Andrea Baehr,[14] Annika Hardt,[15] Raphael Bodensohn,[16,17] Lukas Käsmann,[16] Maria Waltenberger,[18] Davide Scafa,[19] Julian P Layer,[19,20] Esther G C Troost,[21,22] Sally A Elkhamisy,[21,22] Danny Jazmati,[23] Cindy Franklin ,[2,24] Sebastian Neppl,[1] Anna Hagemeier,[25] Maike Trommer [2,19]

To cite: Ferdinandus S, Rühle A, Lamrani A, *et al*. Abscopal effects in patients with malignant melanoma treated with radiotherapy and immune checkpoint inhibition: analysis of a large observational multicenter study. *Journal for ImmunoTherapy of Cancer* 2025;**13**:e012717. doi:10.1136/jitc-2025-012717

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jitc-2025-012717).

Accepted 15 September 2025

For numbered affiliations see end of article.

Correspondence to
Dr Simone Ferdinandus; simone.wegen@uk-koeln.de

ABSTRACT

Background Abscopal effect (AbE), the regression of non-irradiated metastatic lesions (NILs) following radiotherapy (RT), is relevant in patients with malignant melanoma (MM) with progressive disease (PD) under immune checkpoint inhibition (ICI) as resistance to immunotherapy. In the "ARTIC" trial, we assessed the incidence of AbE in patients with progressive MM by evaluating the effect of RT on NILs.

Methods ARTIC (Abscopal effects in metastasized cancer patients treated with RadioTherapy and Immune Checkpoint inhibition) (ARO (Arbeitsgemeinschaft Radiologische Onkologie) 2022–10, DRKS00032390) retrospectively screened clinical records of patients with stage IV MM with PD under ICI. Patients received RT for metastases and had ≥1 NIL outside the RT field (=control lesion). NILs were evaluated according to iRECIST (immune Response Evaluation Criteria in Solid Tumors): abscopal response (AR): size reduction ≥30%, abscopal progression (AP): size increase ≥20%, abscopal control (AC): all others. Patients with AR and/or AC were categorized as abscopal benefit (AB), patients with AP and/or mixed response=no AB. RT details and factors influencing AR were analyzed.

Results After screening clinical records of 3773 patients with stage IV tumor from 12 oncological centers in Germany, we identified 47 patients with MM with 115 NILs. RT targeted metastases in brain (38.3%) and lung (19.1%), primarily using stereotactic RT (29.8%). The mean time interval between the end of ICI and RT was 3.53±5.67 months. AR was achieved in 19.1% of patients and 29.1% of lesions. Compared with stereotactic RT, normofractionated or other (non-stereotactic) RT regimens significantly reduced the probability of AB (OR=0.092, p=0.04, 95% CI: (0.007 to 0.758)). Longer ICI-to-RT intervals were associated with reduced mortality risk (HR=0.703, p=0.007, 95% CI: (0.544 to 0.908)). Patients with AB had a longer median overall (17 vs 9 months) and a longer median progression-free survival (4 vs 2 months).

Conclusions RT can induce AR in patients with MM with PD under ICI, particularly with hypofractionated regimens and long ICI-to-RT intervals. Our findings can serve as a reference for designing prospective trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Abscopal effects (AbE) in metastatic malignant melanoma (MM) can be observed in patients with malignant melanoma progressive under immune checkpoint inhibition (ICI) after radiotherapy (RT) of target lesions, but the true incidence of AbE remains uncertain.

WHAT THIS STUDY ADDS

⇒ In a multicenter analysis of 3773 patients from 12 German cancer centers, 47 patients with MM with 115 non-irradiated lesions (NILs) were identified. Abscopal response was observed in 19.1% of patients and 29.1% of NILs. Factors associated with abscopal benefit were stereotactic RT regimens and longer ICI-to-RT intervals, correlating with numerically improved median overall survival (17 vs 9 months) and progression-free survival (4 vs 2 months).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings may serve as a reference for designing prospective trials on AbE in patients with ICI-refractory MM.

INTRODUCTION

Increasing knowledge about the immune system and the availability of a variety of different immunotherapies for numerous solid tumors raises the question of to what

extent an immune response can be triggered by radiotherapy (RT). This is especially relevant in patients progressing during immune checkpoint inhibition (ICI). The most common tumor entities treated with ICI are lung cancer, renal cell carcinoma, hepatocellular carcinoma, malignant melanoma (MM), and head and neck cancer.[1–3] More than 60% of patients with cancer receive at least one course of RT for either curative or palliative purposes.[4] In most cases, RT alone can locally inhibit the proliferation of tumor cells but cannot induce durable systemic antitumor immune responses. Multimodal cancer therapies consisting of RT and ICI to either boost immune response or dampen immunosuppression have shown promising results in preclinical studies.[5] RT applied simultaneously to ICI is safe and may induce immune-mediated effects. Preclinical data and clinical case series support the hypothesis of synergistic effects on unirradiated distant tumors,[6 7] especially for highly hypofractionated RT (>5 Gy/fraction) combined with anti-programmed cell death protein-1 (PD-1) ICIs.[8] Abscopal effects (AbE) are defined as regression of non-irradiated (tumorous) lesions (NILs) following RT, most likely mediated by immune response. Yet, the actual probability of the occurrence of AbE has not been systematically assessed.

MM is one of the most immunogenic solid tumors. About 15% of patients with MM have metastatic disease at first diagnosis or will develop metastases during their treatment course.[9] Survival of patients with stage III and IV MM has been significantly prolonged with the implementation of ICI therapy.[10 11] However, there are various hypothesized mechanisms explaining primary and secondary resistance to immunotherapy.[6–11] RT might be able to interact at those points and reactivate the immune system by inducing different types of cell death and releasing neoantigens and damage-associated molecular patterns (DAMPs), facilitating immune recognition of cancer cells.[12–14] The existence of AbE in patients with MM has been described before.[15] One of the first clinical cases of AbE after RT in the context of ICI was reported in a patient with metastasized MM, followed by a few small retrospective studies.[3 16 17] Here we present the occurrence and pattern of AbE in a real-world cohort of patients with MM from 12 national cancer centers.

PATIENTS AND METHODS

The current analysis, ARTIC (Abscopal effects in metastasized cancer patients treated with RadioTherapy and Immune Checkpoint inhibition), builds on a pilot study from the University Hospital Cologne, Germany, published in 2019, with an AbE rate of 29% (7/24 patients[18]). Based on this pilot study, we assumed an AbE rate of ≥20% with a corresponding statistical estimation of 62 required patients. The study concept was presented at the annual spring retreat of the young German Radiation Oncologists working group (young DEGRO (jDEGRO)) in Berlin in February 2022. Here, 12 centers agreed on contributing patients for a nationwide analysis. The trial was registered in the German working group for radiation oncology (Arbeitsgemeinschaft Radiologische Onkologie (ARO), ARO 2022–10 and DRKS (Deutsches Register für Klinische Studien, DRKS00032390).

Database prescreening

Participating centers were requested to perform a database prescreening of all patients with Union for International Cancer Control (UICC) stage IV/metastatic tumor (all entities) having ever received ICI and RT between June 2015 and June 2021. The local ethics board at the principal investigation center and the respective ethics committees of each participating center approved the trial. Centers could decide on how to perform the above-mentioned prescreening: one common method was to request a list of all patients with UICC stage IV cancer who have ever received ICI at each center's corresponding hospital pharmacy/institutional pharmacy. These patients were compared with all patients having received RT in the same time span at the respective RT institution. This adjustment could be carried out manually; centers were also offered to use a self-programmed script, which was created at the principal investigation center (SN), automatically pre-sorting the list of patients with ICI and RT in the relevant time span. Other centers already had preexisting lists as their patients were enrolled in clinical trials on the role of RT+ICI, mostly for specific tumor entities, requiring an update and completion of this list for inclusion in ARTIC database analysis.

Screening and data collection

Patients who passed the initial database pre-screening were screened for inclusion/exclusion criteria. Patients were included when they had stage IV/metastatic MM with radiologically confirmed tumor progression under ICI (programmed cell death ligand-1 (PD-L1)/PD-1/cytotoxic T-lymphocyte-associated protein 4 inhibitors). ICI was initiated at least 4 weeks prior to RT and continuously applied during the analysis time (RT+180 days) or discontinued before RT. Any switch to another systemic treatment due to tumor progression (between the time point of progression and beginning of RT) and lack of cross-sectional imaging data (CT, MRI or positron emission tomography (PET)) were exclusion criteria. For NIL measurement, patients needed to have at least two images prior to RT to rule out undefined response or complete/partial response as effects of ICI only. After RT, patients needed to have at least one CT/MRI scan (preferably two scans) of the NILs (within 7 and 180 days after RT) for follow-up measurements. For ARTIC inclusion/exclusion criteria, please see figure 1 and online supplemental table 1.

We collected clinical information on smoking status, PD-L1 status/tumor proportion score (TPS), beta-blockers, and antibiotics 30 days prior to RT, dates of beginning and end of ICI, type of ICI and on RT

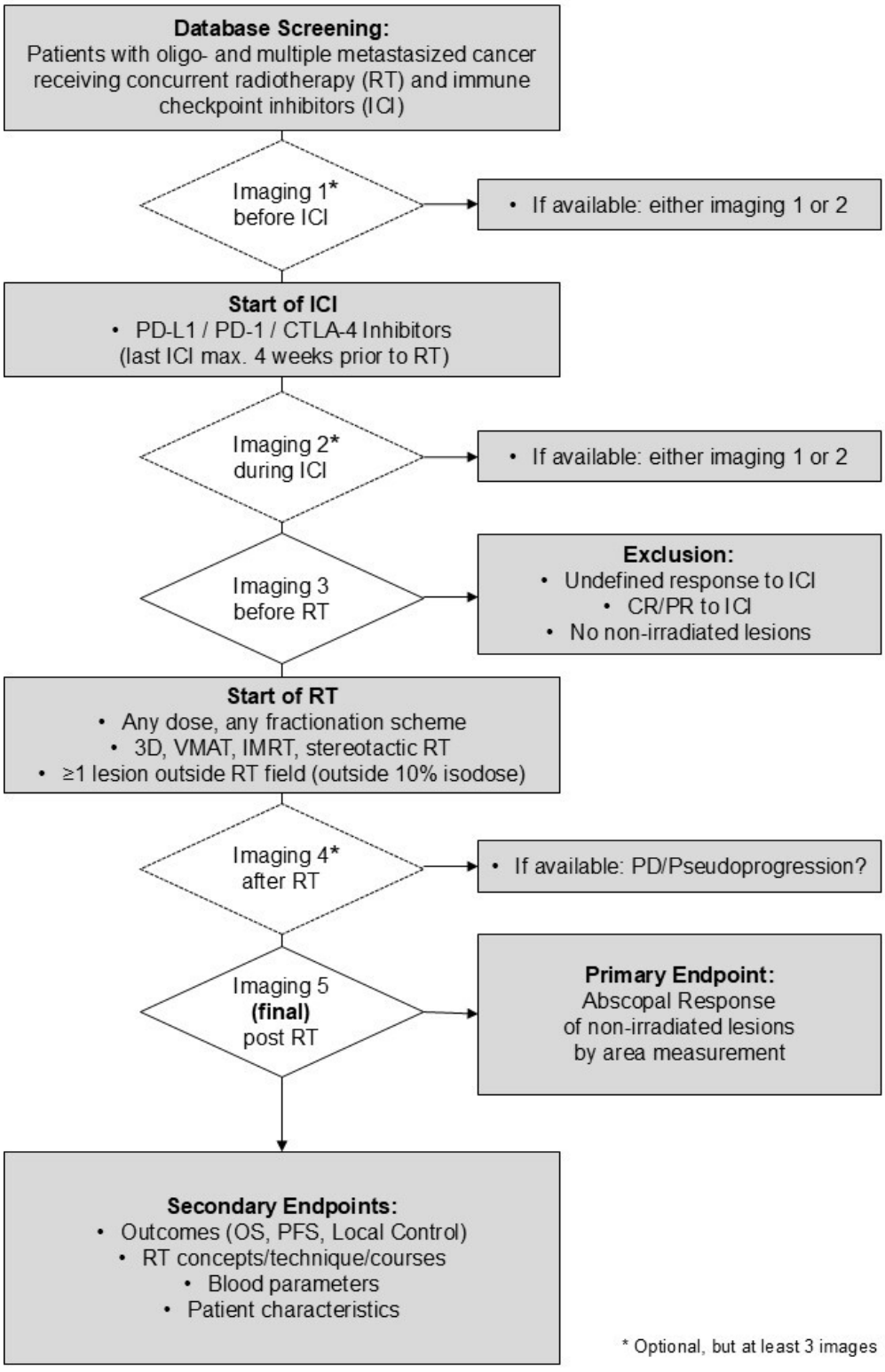


Figure 1 ARTIC screening: Study design and imaging timeline for evaluating abscopal effects in patients receiving RT and ICI. Patients with metastatic cancer treated with concurrent RT and ICI were retrospectively screened. Imaging was performed at multiple time points: before ICI, during ICI, before RT (if available) and after RT (minimum of three imaging time points required). Inclusion required ≥1 non-irradiated lesion and progressive disease after ICI. The primary endpoint was abscopal response of non-irradiated lesions; secondary endpoints included survival, local control, RT parameters, and patient characteristics. ARTIC, Abscopal effects in metastasized cancer patients treated with RadioTherapy and Immune Checkpoint inhibition; CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; IMRT, intensity-modulated radiation therapy; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PR, partial response; Pts, patients; RT, radiotherapy; VMAT, Volumetric Intensity Modulated Arc Therapy; 3D, three-dimensional.

fractionation schemes. All collected parameters are available in the supplements (online supplemental table 2).

Imaging requirements and NIL measurements

For the assessment of NILs, we initially determined up to five lesions, which were radiologically confirmed metastatic lesions and which were clearly visible in the first two (pre-RT) scans. Lesions had to be outside the irradiation field (outside the 10% isodose) and could be distant or lymph node metastases.

A minimum of three images (preferably: four) was required. Images were labeled as follows: "Image 1": pre-ICI, serving as baseline scan, "Image 2": during ICI (with radiological progression in our cohort), "Image 3" (optional); second CT imaging during ICI or RT planning CT, not considered for analysis, "Image 4": first imaging after RT, >7 days (up to 180 days) after last RT appointment. Lesions were measured to their largest extent (lymph nodes in their short axis diameter) with a digital linear using each center's routinely used radiological imaging software. Measurements were taken by the corresponding radiation oncologist in the respective center, and unclear findings were discussed with a radiologist.

NIL assessment was performed according to immune Response Evaluation Criteria in Solid Tumors (iRECIST) criteria:[19 20] diameter of lesions showing ≥30% decrease in size: "response", diameter of the lesion showing ≥20% increase in size: "progression", diameter of the lesion showing between <30% decrease and <20% increase in size: "stable". Measurements and iRECIST classification were performed in the images prior to RT (Image 1 vs Image 2, to exclude complete responders prior to RT (see exclusion criteria) and between Image 4 (first response after RT) vs Image 2. If available, centers could measure lesions in an additional post-RT image ("Image 5", within 180 days after RT) and compare it to Image 2). Of the two latter (Image 4 vs Image 2 and Image 5 vs Image 2), the more favorable ratio (greater reduction in size after RT) was used to determine abscopal response (AR) in NILs ("best abscopal response", BAR).

Patient-based/lesion-based analysis and abscopal benefit

Every lesion from each patient was collected and categorized according to iRECIST as described above. Still, one patient could have lesions with different responses (eg, two lesions with tumor response, one lesion with progression, and one stable lesion). We predefined the AR group to only consist of patients with AR in all lesions, the group of ≥1 AR to only have AR and abscopal control (AC) in lesions but not progressive lesions (AP), and the AC group to only consist of patients with "control" in all lesions. Patients with AR, AC, and AP at the same time were categorized as "mixed response". From a clinical perspective, this classification distinguishes best between patients with tumor response and tumor progression.

To simplify these categories, we summed up the groups "AR", "≥1 AR" and "AC" as abscopal benefit (AB). The reason for adding "AC" to the AB group is that we considered tumor control (AC) in patients with stage IV melanoma with progressive disease under immunotherapy (poor prognosis) as a considerable clinical benefit for this patient group. The "no abscopal benefit" group, consequently, consisted of patients with a mixed response, where at least one metastatic lesion showed progression (AP). For a better understanding of this complex stratification, please see figure 2.

Another aspect investigated was the tumor burden per patient. For this purpose, the volumetric sum of the measured metastases was added up. Here, changes in the metastatic sum were categorized into response (≥30% decrease), progression (≥20% increase), and stable (all in between). The approach of assessing changes in total (non-irradiated) tumor burden (sum of all lesions) is described in the iRECIST criteria.[19 20]

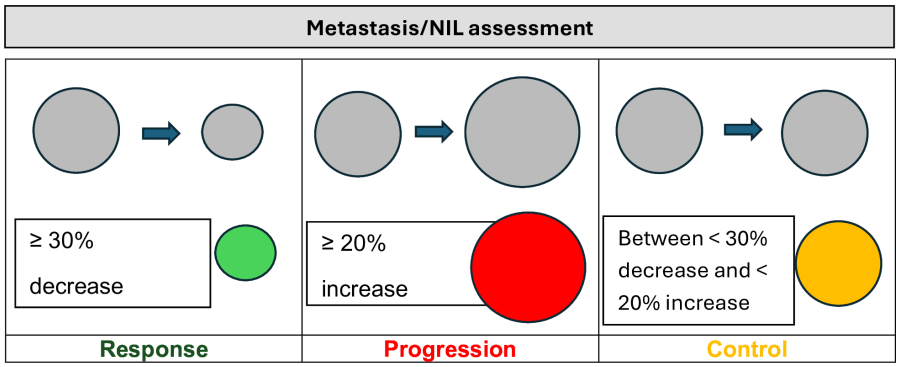
Statistical analysis

Descriptive analyses provided an overview of the study population. Categorical variables are given as absolute and relative frequencies. For continuous variables, mean with standard deviation (±SD) or median with IQR are given. A logistic regression assessed AB (yes/no), selecting variables based on clinical relevance with insufficient categories summarized or excluded to ensure the stability and reliability of the model. In addition to gender and age, the variables included in the logistic regression model were as follows: ICI-to-RT time, RT type (stereotactic, hypofractionated, other), Eastern Cooperative Oncology Group performance status (ECOG; 0 vs ≥1), and prior ICI therapy (yes/no). Kaplan-Meier curves were generated for overall survival (OS) and progression-free survival (PFS) grouped according to the abscopal benefit (yes/no). A Cox regression identified factors influencing the OS. In addition to age and gender, the variables ICI-to-RT-time, RT-type, RT-dose, ECOG (0 vs ≥1), lactate dehydrogenase (LDH) before RT, C-reactive protein (CRP) before RT, and whether there was prior ICI therapy (yes/no) were included in the final Cox regression model. The proportional hazards assumption was verified using Schoenfeld residuals and the global Schoenfeld test. Comparison tests (log-rank tests) were only calculated if the assumption was fulfilled. A p value of <0.05 ($p<0.05$) was considered significant, though all p values are exploratory. Analyses were performed using R V.4.4.0.[21]

RESULTS

Patient characteristics

At data closure in April 2024, 12 centers contributed data for the ARTIC trial. A total of 3773 cases were screened to identify 47 patients with MM. The mean age at first tumor diagnosis was 60.2±15.0 years, 55.3% (26/47) patients were men, 44.7% (21/47) were women. 36.2% (17/47) of patients had ECOG 0, 57.4% (27/47) ECOG 1, 6.4% (3/47) ECOG 2. Mean



Patient stratification

Measured lesions	Categorized lesions	Response summary (patient-level)	Interpretation (patient-level)
	Response in all NILs	Abscopal Response (AR)	ABSCOPAL BENEFIT (AB)
	At least one lesion with response + control in all other lesions	At least one AR (≥ 1 AR)	
	Control in all lesions	Abscopal control (AC)	
	Progression, Control and/or response	Mixed Response	NO ABSCOPAL BENEFIT (no AB)
	Only progression	Abscopal Progression (AP)	

Figure 2 NIL assessment and patient stratification. Criteria for lesion-level response assessment and patient-level stratification of abscopal effects. NILs were classified as response (≥30% decrease), progression (≥20% increase), or control (changes between −30% and +20%). Patients were stratified based on lesion responses: AR, AC, or AP. AB was defined as AR in all lesions or at least one AR plus AC in all other lesions or AC in all lesions. The no abscopal benefit (no AB) group consisted of patients with mixed response (among the measured lesions, at least one lesion had to be progressive) or progression in all lesions (AP). AB, abscopal benefit; AC, abscopal control; AP, abscopal progression; AR, abscopal response; NIL, non-irradiated lesions.

LDH values prior to ICI were 318±255 (range=(3.03–1240)). The mean BMI was 26.5±5.38. The most frequently applied ICI was nivolumab (25/47, 53.2%), followed by pembrolizumab (21/52, 44.7%), and one patient received durvalumab (2.1%). 48.9% of patients (23/47) did not receive any RT prior to the RT series being examined in our analysis. For patient characteristics, please see table 1 and the supplementary online supplemental appendix- table 2.

Radiotherapy

In the analyzed cohort, 70% of patients (33/42) received one irradiation series (=RT for one metastatic region, "target lesion"), while 14/47 patients (29.8%) received two parallel series. RT, in most cases, had been applied as single-fraction stereotactic (n=23, 48.9%) or hypofractionated RT (n=17, 36.2%), 7/47 patients (14.9%) received other RT fractionation schemes, usually normofractionation. The most

Table 1 Patient characteristics and RT details

Patient characteristics	Abscopal benefit (AR, AC, at least one AR)	No abscopal benefit (AP, mixed)	Overall
N (%) or median (IQR) or mean±SD	(**n=31**)	(**n=16**)	(**n=47**)
Sex			
Female	14 (45.2%)	7 (43.8%)	21 (44.7%)
Male	17 (54.8%)	9 (56.3%)	26 (55.3%)
Age (median)	59.5(48.8–68.0)	72.0(52.5–80.0)	62.0(51.0–71.5)
Age (mean±SD)	57.3±13.4	65.5±17.0	60.2±15.0
BMI (median)	27.3(22.6–29.5)	26.2(21.8–27.7)	27.1(22.4–28.9)
UICC tumor stage at first diagnosis			
I	4/30 (13.3%)	1/15 (6.7%)	5/45 (11.1%)
II	9/30 (30%)	7/15 (46.7%)	16/45 (35.6%)
III	4/30 (13.3%)	4/15 (26.7%)	8/45 (17.8%)
IV	13/30 (43.3%)	3/15 (20%)	16/45 (35.6%)
ECOG performance status at start RT			
0	11 (35.5%)	6 (37.5%)	17 (36.2%)
1	20 (64.5%)	7 (43.8%)	27 (57.4%)
2	0 (0%)	3 (18.8%)	3 (6.4%)
Smoking status			
Current smoker	3/31 (9.7%)	0/13 (0%)	3/47 (6.4%)
Former smoker	0/31 (0%)	3/16 (18.8%)	3/47 (6.4%)
Never smoker	25/31 (80.6%)	10/16 (62.5%)	35/47 (74.5%)
Missing	3/31 (9.7%)	3/16 (12.8%)	6/47 (1.8%)
TPS score			
≥50%	2/31 (6.5%)	0/5 (0%)	2/47 (4.3%)
1–49%	4/31 (12.9%)	0/5 (0%)	4/47 (8.5%)
<1%	3/31 (9.7%)	5/16 (31.3%)	8/47 (17%)
Missing	22/31 (71%)	11/16 (68.8%)	33/47 (70.2%)
Prior RT			
Yes	18/31 (58.1%)	5/16 (31.3%)	23/47 (48.9%)
No	12/31 (38.7%)	11/16 (68.8%)	23/47 (48.9%)
Missing	1/31/3.2%)	0/16 (0%)	1/47 (2.1%)
ICI			
Nivolumab	18 (58.1%)	7 (43.8%)	25 (53.2%)
Pembrolizumab	13 (41.9%)	8 (50.0%)	21 (44.7%)
Durvalumab	0 (0%)	1 (6.3%)	1 (2.1%)
LDH (pre ICI) (median)	216 (176–315)	268 (248–439)	248 (193–335)
LDH (pre ICI) (mean)	265±206	420±315	318±255
LDH (pre RT) (median)	218 (141–246)	326 (252–584)	240 (183–410)
LDH (pre RT) (mean)	244±224	461±361	334±304
RT location			
Bone	3 (9.7%)	1 (6.3%)	4 (8.5%)
Brain	13 (41.9%)	5 (31.3%)	18 (38.3%)
Lung	8 (25.8%)	1 (6.3%)	9 (19.1%)
Lymph node	4 (12.5%)	6 (40.0%)	10 (21.3%)
Other visceral organs	1 (3.2%)	1 (6.3%)	2 (4.3%)

Continued

Table 1 Continued

Patient characteristics	Abscopal benefit (AR, AC, at least one AR)	No abscopal benefit (AP, mixed)	Overall
Spine (myelon)	0 (0%)	1 (6.3%)	1 (2.1%)
Soft tissue	1 (3.2%)	0 (0%)	1 (2.1%)
Lymphatic system	4 (12.9%)	6 (37.5%)	10 (21.3%)
Other	1 (3.2%)	1 (6.3%)	2 (4.3%)
RT type (grouped)			
Hypofractionated	12/31 (38.7%)	5/16 (31.3%)	17/47 (36.2%)
Normofractionated/other	2/31 (6.5%)	5/16 (31.3%)	7/47 (14.9%)
Stereotactic*	17/31 (54.8%)	6/16 (35.7%)	23/47 (48.8%)
PTV of RT target volume (mL) (mean±SD)	368±596	541±552	434±579
Total physical dose (Gy) (mean±SD)	34.0±15.3	32.9±13.5	33.6±14.6
Physical dose per fraction (Gy) (mean±SD)	8.51±7.22	8.50±8.43	8.51±7.56
EQD2† (Gy) (mean±SD)	64.0±36.2	58.8±28.4	62.2±33.5
BED† (Gy) (mean±SD)	55.7±29.3	52.3±14.5	54.6±25.5
Ablative dose			
Yes (>50 Gy EQD2)	17/31 (54.8%)	5/14 (35.7%)	22/45 (48.9%)
No (<50 Gy EQD2)	15/31 (48.4%)	8/14 (57.1%)	23/45 (51.1%)

*=≥4 Gy single-dose fraction.
†=assuming an alpha/beta value of 2.
AC, abscopal control; AP, abscopal progression; AR, abscopal response; BED, biologically effective dose; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; EQD2, equivalent dose in 2 Gy fractions; Gy, gray; ICI, immune checkpoint inhibition; LDH, lactate dehydrogenase; ml, milliliter; PTV, planning target volume; RT, radiotherapy; TPS, tumor proportion score; UICC, Union for International Cancer Control.

common irradiated metastatic sites were the brain (n=18, 38.3%) and lung (n=9, 19.1%). The mean total physical RT dose applied was 33.60 Gy±14.60, mean single dose was 8.51 Gy±7.56 Gy.

Total non-irradiated tumor burden

As described in the methods section, we compared the last image before the start of RT ("Image 2", see figure 1) to the follow-up imaging timpoints (imaging timepoints 4 and 5, see figure 1). Of the two latter, as defined per study protocol, we used the smaller value for NIL analysis each ("best abscopal response"). The maximum time span of the last Image 5 was 180 days after RT. We were able to assess 117 lesions at Image 2 and added up the volumes of all NILs available (total non-irradiated tumor volume). We compared these results to the tumor volumes at final imaging (115 lesions at Image 5) and performed both a patient-based and a lesion-based analysis: patient-based defined as the sum of all NILs measurable before and after RT for each patient (n=47), lesion-based as size reduction for each lesion measured (n=115) as one patient can have more than one NIL. A description of the lesion-based analysis is provided in the supplements (figure 1).

Patient-based and lesion-based analysis

On a patient basis, we found a >30% decrease of all NILs per patient of total abscopal tumor burden (response) in 9/47 patients (19.1%). The majority of patients (34.0% (16/47)) showed abscopal tumor control (volumes between ≤20% increase and ≤30% decrease), while 8.5% (4/47) had AP (>20% increase) and a quarter (n=12, 25.5%) had a mixed response. Lesion-based, 34/115 lesions (29.6%) showed >30% decrease in size (BAR) (see figure 3).

Identification of variables associated with abscopal response

Favorable outcomes (AB, as defined in the methods section) appear in non-smoking patients ("never smokers": 80.6% vs 62.5%, Fisher's exact test, p=0.029) at younger age (mean age: 57.3±13.4 years vs 65.5±17.0 in the AP group (analysis of variance test, p=0.091). Most patients in the AB group had oligometastatic disease (29% vs 6.3%) and tumors with a higher PD-L1 expression: a TPS≥50% occurred in 6.5% versus 0%, a TPS<50% in 12.9% versus 0% of patients.

The group of patients with AB was characterized by a high percentage of pre-irradiated patients (58.1% vs 31.3%, p=0.122) with stereotactic RT schemes (54.8% vs 37.5%), application of a higher biologically effective

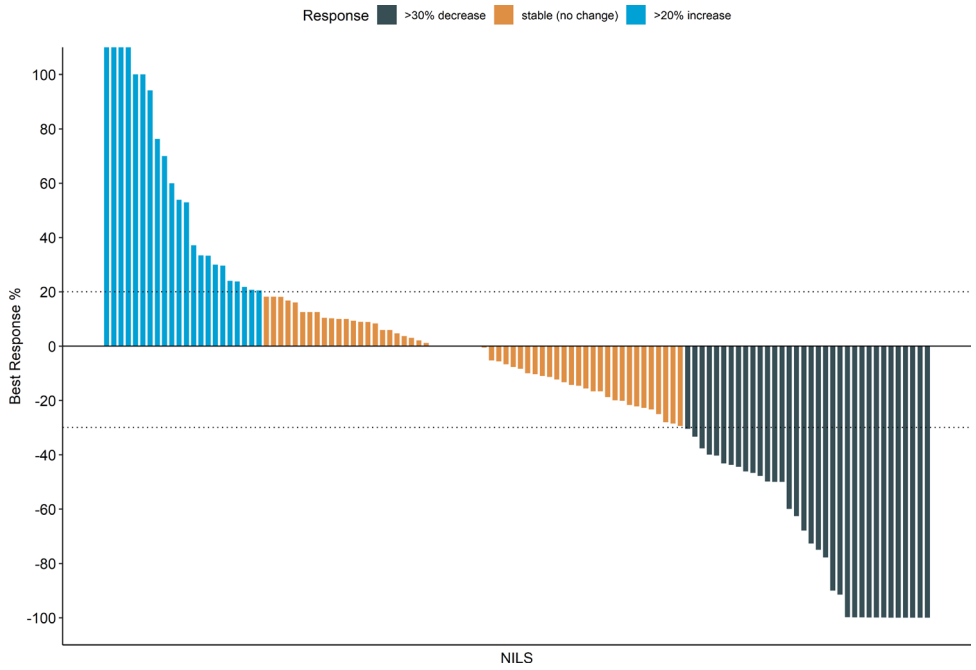


Figure 3 Best response of NILs. Waterfall plot showing the best percentage change in size of NILs (sum of all NILs) for individual patients, n=113. Gray=lesions with >20% increase in size (progressive lesions, 22/115, 19.1%), yellow=lesions between 20% increase and 30% decrease (stable lesions, 59/113, 51.3%), blue=lesions with >30% decrease in size (responding lesions, 34/115, 29.6%). Each bar represents one patient's best NIL response. NIL, non-irradiated lesion.

dose/equivalent dose in 2 Gy fractions doses (55.7 Gy±29.3 vs 52.3 Gy±14.5 and 64.0 Gy±36.2 vs 58.8 Gy±28.4, respectively) and smaller irradiation volumes (mean planning target volume (PTV) (mL): 368±596 vs 541±552, respectively). The proportion of stereotactic brain RT was higher in the AB group (41.9% vs 31.3%). For further RT details, please see table 1 and the supplementary online supplemental table 2 and figure 2.

For laboratory values, we observed lower LDH levels pre-ICI and pre-RT in the AB group compared with the no AB group: 265±206 vs 420±315 and 244±224 vs 461±361, respectively (p=0.0457 and p=0.015) (see table 1 and online supplemental table 2).

Logistic regression

The logistic regression for abscopal benefit only showed a significant influence for "normofractionated" (and "other") versus "stereotactic" RT type. The OR here is <1 (whereby the sign of the estimate (−2.39) was correspondingly negative), that is, the relative probability that a person has an abscopal benefit decreases significantly (p=0.04, 95% CI: (0.007 to 0.758)) by 90.8% (0.092–1=−0.908) for the RT type "normofractionated" compared with the reference category "stereotactic". Other variables had no significant influence on the outcome (p>0.05). For further details from the Cox regression, please see online supplemental figures 3 and 4.

Survival analysis (Kaplan-Meier and Cox regression)

Figure 4 shows the Kaplan-Meier curves for OS and PFS grouped by abscopal benefit. In both OS and PFS, patients with AB survived longer than in the group without AB (median OS: 17 months vs 9 months; median PFS: 4 months vs 2 months). However, the difference was not significant in either case (log-rank p=0.12 (OS); p=0.09 (PFS).

The Cox regression for n=29 patients with MM with 21 events shows a significant influence for the variable time interval between ICI and RT therapy in months (p=0.007, 95% CI: (0.544 to 0.908)). A longer time interval between the end of ICI and the start of RT therapy was associated with a lower risk of death. The HR (HR=0.703) shows that each additional month reduced the risk of death by approximately 29.7% (1−HR=1−0.703=0.297).

DISCUSSION

To our knowledge, ARTIC is one of the largest retrospective analyses on AbE in patients with MM. It benefits from a high number of screened patients (n=3773) and strict inclusion criteria (ICI before RT, no start of other systemic treatment during the assessed time, sufficient number of images at fixed time points), making it a final cohort of 47 patients eligible for analysis. Data for this trial do not only come from university hospitals but also from smaller peripheral hospitals and therefore help to obtain a comprehensive overview of a real-world cohort. Limitations certainly stem from its retrospective design, a certain sampling bias and a high amount of missing data in some specific areas of patient characteristics (such as PD-L1/TPS score or smoking status). Still, our results for AR are in line with previous case series reporting an AR rate between 18% and 52% (for various tumor entities,

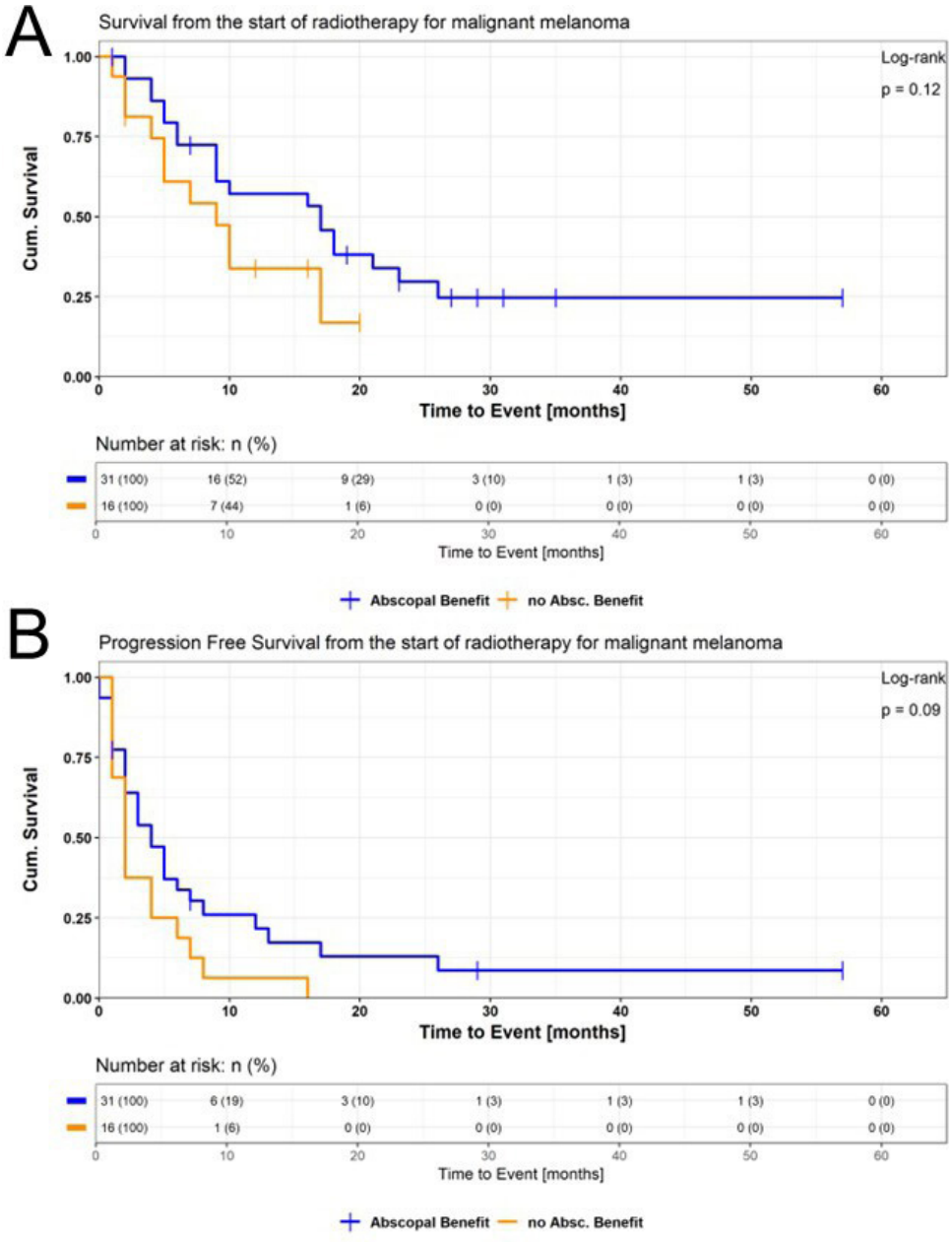


Figure 4 Cumulative overall (A) and progression-free (B) survival in patients with malignant melanoma**,** stratified by abscopal benefit. Kaplan-Meier analysis of (A) overall survival and (B) progression-free survival from the start of radiotherapy, comparing patients with abscopal benefit (blue) versus no abscopal benefit (yellow). Survival probabilities were calculated from the start of radiotherapy, and group differences were assessed using the log-rank test. The number of patients at risk over time is shown below each plot.

not specifically in melanoma).[7] In our analysis, RT led to AR/>30% size reduction in 19.1% of patients (9/47) (patients with >30% decrease in size in all lesions) and in 29.1% of lesions (34/115). These results are consistent with results from the corresponding 2019 pilot trial from the University Hospital Cologne, reporting an AbE rate of 29% (7/24 patients) in patients with different tumor entities.

Similarly, Backlund *et al* reported in their retrospective single-center analysis consisting of 55 patients with MM that patients treated with a combination of RT and ICI exhibited superior tumor responses in both irradiated and non-irradiated lesions compared with the RT-only group. The study categorized patients into three groups: those receiving RT at the start of ICI treatment (RT+ICI (start)), those receiving RT on progression during ICI therapy (RT+ICI (salvage)), and those receiving RT without ICI (RT (only)). The overall response rates in non-irradiated metastases were 36.1% (RT+ICI (start)), 14.8% (RT+ICI (salvage)), and 0.0% (RT (only)), respectively.[22] In our cohort, we have mostly included patients with RT+ICI (salvage), according to this nomenclature, for pragmatic reasons, as stated above. Importantly, median OS was also higher in the combination therapy

groups and the addition of ICI did not lead to a significant increase in grade ≥3 adverse events. These results are in line with our findings and another hint—based on a retrospective cohort—that combining RT with ICI enhances antitumor responses in metastatic melanoma without substantially increasing toxicity.

Patients with AB in the ARTIC trial had a numerically longer median OS and PFS than those in the group without AB (OS: M=17 months vs 9 months; PFS: M=4 months vs 2 months, log-rank p>0.05), even though statistical significance was not reached. In our cohort, response to RT in NILs especially occurred in patients with stereotactic fractionation schemes (p=0.075) and smaller PTVs, strengthening well-described synergistic effects of immunotherapy and RT in literature,[18 23 24] leading to improved outcomes, especially in stereotactic and focal high-dose cerebral irradiation.[25–27] The proportion of stereotactic brain RT was higher in the AB group (45.2% vs 37.5%).

Patients showed progression during treatment with ICI and, therefore, needed RT to symptomatic or progressive sites (clinical indication). There are various reasons for treatment failure and progression in patients with MM under immunotherapy. These include immune escape mechanisms such as defective recognition of melanoma cells, inhibition of T-cell function (by upregulation of the immune checkpoints and its ligands), release of pro-apoptotic molecules by tumor cells, and changes in the tumor microenvironment (TME), especially release of protumorigenic/pro-angiogenic factors (transforming growth factor (TGF)-beta, vascular endothelial growth factor (VEGF), interleukin-6).[28–31] Escaping from the regular immune system control, a complex pathway of intracellular and extracellular signals is activated, called "immune editing". It describes the relationship between the tumor cells and the immune system and is made up of three phases: elimination, equilibrium, and escape.[32] Recent works suggest two categories of tumor escape based on cellular and molecular characteristics of the TME, one being a T cell-inflamed phenotype, and the other one is a T-cell lacking phenotype. These two major phenotypes of TME may require distinct immunotherapeutic interventions for maximal therapeutic effects.[33]

The immunomodulatory effects of RT form the theoretical foundation for combination therapies, especially combination with ICI. These effects consist of the release and presentation of tumor antigens, increasing the number of tumor-infiltrating lymphocytes, stimulating priming and activation of immune cells, and aiding T cells in recognizing cancer cells.[34–36] RT also alters the TME by changing stromal, immunological, and vascular components, thereby promoting an antitumor response.[37 38]

In their review of patients with melanoma treated with RT and ipilimumab, Chandra *et al* identified multiple fraction radiation regimens as more favorable for tumor response of the target lesion.[15] In our cohort, fractionation had a significant effect on NIL response. Hypofractionated RT with 2.5 Gy or higher per fraction is now standard for the treatment of metastasis in MM due to its effectiveness, convenience, and low risk of late effects.[39] Patients with UICC stage IV cancer, despite recent advantages in immunotherapy, are in a palliative treatment setting. Thus, long fractionation schemes should only be carried out with caution to not place additional strain on patients with a very limited life expectancy. This might be different for oligometastatic disease (OMD) or oligoprogressive MM. OMD takes a special role in modern cancer therapy, as it might provide a curative approach for a tumor formally characterized as stage IV disease.[40] In the era of ICI, it is unclear if all metastases of a patient with MM in an oligometastatic setting should be treated locally (with RT or surgery) and if they should be treated upfront, after or during the systemic treatment.[41 42] In our study, there were 10 patients with MM with OMD with a higher percentage of OMD in the AB group (29%) compared with the no AB group (6.3%, p=0.33).

Due to practical considerations and the retrospective study design, ICI was given upfront, followed by RT (only) to progressive lesions under ICI. In this setting, a remarkable number of patients with MM benefited from RT, with AR observed in 19.1% of patients and 29.1% of all measured lesions. As shown in previous studies, we observed a significant influence for the variable time interval between ICI: a longer time interval between the end of ICI and the start of RT therapy is associated with a lower risk of death (HR=0.703).[43] Our study results serve as a reference for designing prospective trials evaluating AbE. Here, the growing consensus is that combining RT with immunotherapy is safe and provides an opportunity to boost tumor response rates.[38 44 45]

Author affiliations
[1]Department of Radiation Oncology, Cyberknife and Radiotherapy, University Hospital Cologne, Cologne, Germany
[2]University Hospital Cologne, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, CIO ABCD, Cologne, Germany
[3]Department of Radiation Oncology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[4]Department of Radiation Oncology, University of Leipzig Medical Center, Leipzig, Germany
[5]Department of Radiation Oncology, Universitätsklinikum Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
[6]Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany
[7]Department of Radiation Oncology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany
[8]Department of Radiotherapy and Radiation Oncology, Jena University Hospital, Jena, Germany
[9]Clinician Scientist Program OrganAge, Jena University Hospital, Jena, Germany
[10]Clinician Scientist Program, Interdisciplinary Center for Clinical Research (IZKF), Jena University Hospital, Jena, Germany
[11]Clinic for Radiation Oncology and Radiotherapy, Luedenscheid Clinic, Luedenscheid, Germany
[12]Department of Radiation Oncology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
[13]German Cancer Consortium (DKTK), partner site Berlin, a partnership between DKFZ and Charité – Universitätsmedizin Berlin, Berlin, Germany
[14]Department of Radiation Oncology, University Medical Hospital, Hamburg-Eppendorf, Hamburg, Germany
[15]Department of Radiotherapy and Radiation Oncology, Outpatient Center of the University Medical Hospital Hamburg-Eppendorf, Hamburg, Germany

[16]Department of Radiation Oncology, University Hospital, LMU Munich, Munich, Germany
[17]Department of Radiation Oncology, University Hospital Tübingen, Tübingen, Germany
[18]Department of Radiation Oncology, Hospital of Bolzano (SABES-ASDAA); Teaching Hospital of Paracelsus Meodical University Salzburg, Salzburg, Austria, Bolzano-Bozen, Italy
[19]Department of Radiation Oncology, University Hospital Bonn, Bonn, Germany
[20]Institute of Experimental Oncology, University Hospital Bonn, Bonn, Germany
[21]OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany
[22]Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[23]Department of Radiation Oncology, University Hospital Dusseldorf, Medical Faculty, Heinrich-Heine-University Dusseldorf, Dusseldorf, Germany
[24]Department of Dermatology and Venereology, Faculty of Medicine and University Hospital Cologne, Cologne, Germany
[25]Institute of Medical Statistics and Computational Biology, Medical Faculty and University Hospital, University of Cologne, Cologne, Germany

Acknowledgements ARTIC was performed via the network of the German Society for Radiation Oncology (DEGRO) and the "young DEGRO (jDEGRO)" and depended on a high personal commitment of our jDEGRO members at each participation site.

Contributors MT, SF, AR, AL, CS, JK, MM, GW, PJ, FE, AB, AH, RB, LK, MW, JPL, DS and DJ collected data. SN created a script for data comparison between ICI and RT patients. AH performed statistical analysis. SW and MT drafted the manuscript. All authors read, carefully revised, and approved the final version of the manuscript. The guarantors for this study are SF and MT. They take full responsibility for the integrity of the data and the accuracy of the data analysis.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests FE has received honoraria and travel support from ZAP Surgical Systems, Inc. and Accuray, Inc., and acknowledges research funding from the German Cancer Aid and Accuray, Inc., all unrelated to the submitted work. RB received honoraria from NovoCure for participating in invited meetings of specialized centers. JPL reports stocks and travel expenses from TME Pharma AG, travel expenses and honoraria from Carl Zeiss Meditec AG, stocks and honoraria from Siemens Healthineers AG, advisory board membership and honoraria from OncoMAGNETx Inc., and stocks from Bayer AG and BioNTech AG, all unrelated to this work. AR reports speaking fees and research grants from Novocure, consulting fees from Johnson & Johnson, and speaker fees from Merck Healthcare Germany and AstraZeneca, all outside the submitted work. AR is supported by a Clinician Scientist Program of the Medical Faculty of the University of Leipzig. GW acknowledges support by a Clinician Scientist Program of the Interdisciplinary Center for Clinical Research at Jena University Hospital. CF has been on the advisory board or has received honoraria from Bristol Myers Squibb, Immunocore and Novartis and received travel grants from Bristol Myers Squibb, Novartis and Pierre Fabre. All others have nothing to disclose. Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Patient consent for publication Not applicable.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent: Informed consent to undergo imaging and RT was obtained from all individual participants included in the study. The local institutional review board (Cologne, Germany) approved this study and waived the requirement to obtain consent for retrospective data analysis (22-1230-retro). Contact data: Ethics Committee University Hospital Cologne, Head of Department: Professor Dr Raymond Voltz, Kerpener Str. 62, 50937 Köln, Germany, mail: ek-pool@uni-koeln.de.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. De-identified individual participant data—including the full baseline laboratory panel underlying Supplementary Table 2—are available from the corresponding author upon reasonable request, subject to institutional approvals.

ORCID iDs
Simone Ferdinandus http://orcid.org/0000-0002-0361-728X
Justus Kaufmann http://orcid.org/0000-0003-0189-3499
Felix Ehret http://orcid.org/0000-0001-6177-1755
Cindy Franklin http://orcid.org/0000-0001-9142-5423
Maike Trommer http://orcid.org/0000-0003-2864-4273

REFERENCES

1 Garon EB, Rizvi NA, Hui R, *et al*. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015;372:2018–28.
2 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;375:1856–67.
3 Grimaldi AM, Simeone E, Giannarelli D, *et al*. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. *Oncoimmunology* 2014;3:e28780.
4 Warren JL, Yabroff KR, Meekins A, *et al*. Evaluation of trends in the cost of initial cancer treatment. *J Natl Cancer Inst* 2008;100:888–97.
5 Irianto T, Gaipl US, Rückert M. Immune modulation during anti-cancer radio(immuno)therapy. *Int Rev Cell Mol Biol* 2024;382:239–77.
6 Yin L, Xue J, Li R, *et al*. Effect of Low-Dose Radiation Therapy on Abscopal Responses to Hypofractionated Radiation Therapy and Anti-PD1 in Mice and Patients With Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* 2020;108:212–24.
7 Ribeiro Gomes J, Schmerling RA, Haddad CK, *et al*. Analysis of the Abscopal Effect With Anti-PD1 Therapy in Patients With Metastatic Solid Tumors. *J Immunother* 2016;39:367–72.
8 Saiag P, Lahmi L, Funck-Brentano E. Extra-cranial radiotherapy in anti-PD-1-treated melanoma patients: A systematic review. *EJC Skin Cancer* 2024;2:100258.
9 Tazi K, Hathaway A, Chiuzan C, *et al*. Survival of melanoma patients with brain metastases treated with ipilimumab and stereotactic radiosurgery. *Cancer Med* 2015;4:1–6.
10 Larkin J, Chiarion-Sileni V, Gonzalez R, *et al*. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med* 2019;381:1535–46.
11 Blank CU, Lucas MW, Scolyer RA, *et al*. Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma. *N Engl J Med* 2024;391:1696–708.
12 D'Andrea MA, Reddy GK. Systemic Effects of Radiation Therapy-Induced Abscopal Responses in Patients with Advanced Lung Cancer. *Oncology (Williston Park, NY)* 2021;99:1–14.
13 Carvalho H de A, Villar RC. Radiotherapy and immune response: the systemic effects of a local treatment. *Clinics (Sao Paulo)* 2018;73:e557s.
14 Sevenich L. Turning "Cold" Into "Hot" Tumors-Opportunities and Challenges for Radio-Immunotherapy Against Primary and Metastatic Brain Cancers. *Front Oncol* 2019;9:163.
15 Chandra RA, Wilhite TJ, Balboni TA, *et al*. A systematic evaluation of abscopal responses following radiotherapy in patients with metastatic melanoma treated with ipilimumab. *Oncoimmunology* 2015;4:e1046028.
16 Postow MA, Callahan MK, Barker CA, *et al*. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* 2012;366:925–31.
17 Takahashi J, Nagasawa S. Immunostimulatory Effects of Radiotherapy for Local and Systemic Control of Melanoma: A Review. *Int J Mol Sci* 2020;21:9324.

18 Trommer M, Yeo SY, Persigehl T, *et al*. Abscopal Effects in Radio-Immunotherapy-Response Analysis of Metastatic Cancer Patients With Progressive Disease Under Anti-PD-1 Immune Checkpoint Inhibition. *Front Pharmacol* 2019;10:511.
19 Seymour L, Bogaerts J, Perrone A, *et al*. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017;18:e143–52.
20 Persigehl T, Lennartz S, Schwartz LH. iRECIST: how to do it. *Cancer Imaging* 2020;20:2.
21 R Core Team (2024. R: a language and environment for statistical computing. r foundation for statistical computing, vienna, austria. 2024. Available: https://www.R-project.org
22 Backlund E, Grozman V, Egyhazi Brage S, *et al*. Radiotherapy with or without immunotherapy in metastatic melanoma: efficacy and tolerability. *Acta Oncol* 2023;62:1921–30.
23 Sharabi AB, Lim M, DeWeese TL, *et al*. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *Lancet Oncol* 2015;16:e498–509.
24 Deloch L, Derer A, Hartmann J, *et al*. Modern Radiotherapy Concepts and the Impact of Radiation on Immune Activation. *Front Oncol* 2016;6:141.
25 Trommer-Nestler M, Marnitz S, Kocher M, *et al*. Robotic Stereotactic Radiosurgery in Melanoma Patients with Brain Metastases under Simultaneous Anti-PD-1 Treatment. *Int J Mol Sci* 2018;19:2653.
26 Tétu P, Allayous C, Oriano B, *et al*. Impact of radiotherapy administered simultaneously with systemic treatment in patients with melanoma brain metastases within MelBase, a French multicentric prospective cohort. *Eur J Cancer* 2019;112:38–46.
27 Layer JP, Shiban E, Brehmer S, *et al*. Multicentric Assessment of Safety and Efficacy of Combinatorial Adjuvant Brain Metastasis Treatment by Intraoperative Radiation Therapy and Immunotherapy. *Int J Radiat Oncol Biol Phys* 2024;118:1552–62.
28 Passarelli A, Mannavola F, Stucci LS, *et al*. Immune system and melanoma biology: a balance between immunosurveillance and immune escape. *Oncotarget* 2017;8:106132–42.
29 Champiat S, Ferté C, Lebel-Binay S, *et al*. Exomics and immunogenics: Bridging mutational load and immune checkpoints efficacy. *Oncoimmunology* 2014;3:e27817.
30 Snyder A, Makarov V, Merghoub T, *et al*. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med* 2014;371:2189–99.
31 Le DT, Uram JN, Wang H, *et al*. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015;372:2509–20.
32 Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol* 2004;22:329–60.
33 Gajewski TF, Schreiber H, Fu YX. Innate and adaptive immune cells in the tumor microenvironment. *Nat Immunol* 2013;14:1014–22.
34 Lin W, Xu Y, Chen X, *et al*. Radiation-induced small extracellular vesicles as "carriages" promote tumor antigen release and trigger antitumor immunity. *Theranostics* 2020;10:4871–84.
35 Gupta A, Probst HC, Vuong V, *et al*. Radiotherapy promotes tumor-specific effector CD8+ T cells via dendritic cell activation. *J Immunol* 2012;189:558–66.
36 Kwilas AR, Donahue RN, Bernstein MB, *et al*. In the field: exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer. *Front Oncol* 2012;2:104.
37 McLaughlin M, Patin EC, Pedersen M, *et al*. Inflammatory microenvironment remodelling by tumour cells after radiotherapy. *Nat Rev Cancer* 2020;20:203–17.
38 Chen J, Levy A, Tian A-L, *et al*. Low-dose irradiation of the gut improves the efficacy of PD-L1 blockade in metastatic cancer patients. *Cancer Cell* 2025;43:361–79.
39 Sause WT, Cooper JS, Rush S, *et al*. Fraction size in external beam radiation therapy in the treatment of melanoma. *International Journal of Radiation Oncology*Biology*Physics* 1991;20:429–32.
40 Cho HL, Balboni T, Christ SM, *et al*. Is Oligometastatic Cancer Curable? A Survey of Oncologist Perspectives. *Decision Making, and Communication Adv Radiat Oncol* 2023;8:101221.
41 Salim N, Tumanova K, Popodko A, *et al*. Second Chance for Cure: Stereotactic Ablative Radiotherapy in Oligometastatic Disease. *JCO Glob Oncol* 2024;10:e2300275.
42 Ch'ng S, Uyulmaz S, Carlino MS, *et al*. Re-defining the role of surgery in the management of patients with oligometastatic stage IV melanoma in the era of effective systemic therapies. *Eur J Cancer* 2021;153:8–15.
43 Zhang Z, Liu X, Chen D, *et al*. Radiotherapy combined with immunotherapy: the dawn of cancer treatment. *Sig Transduct Target Ther* 2022;7:258.
44 Ngwa W, Irabor OC, Schoenfeld JD, *et al*. Using immunotherapy to boost the abscopal effect. *Nat Rev Cancer* 2018;18:313–22.
45 Welsh JW, Tang C, de Groot P, *et al*. Phase II Trial of Ipilimumab with Stereotactic Radiation Therapy for Metastatic Disease: Outcomes, Toxicities, and Low-Dose Radiation-Related Abscopal Responses. *Cancer Immunol Res* 2019;7:1903–9.