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Impact of a preceding radiotherapy on the outcome of immune checkpoint inhibition in metastatic melanoma: a multicenter retrospective cohort study of the DeCOG

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ABSTRACT

Background Immune checkpoint inhibition (ICI) is an essential treatment option in melanoma. Its outcome may be improved by a preceding radiation of metastases. This study aimed to investigate the impact of a preceding radiotherapy on the clinical outcome of ICI treatment.

Methods This multicenter retrospective cohort study included patients who received anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or anti-programmed cell death protein 1 (PD-1) ICI with or without preceding radiotherapy for unresectable metastatic melanoma. ICI therapy outcome was measured as best overall response (BOR), progression-free (PFS) and overall survival (OS). Response and survival analyses were adjusted for confounders identified by directed acyclic graphs. Adjusted survival curves were calculated using inverse probability treatment weighting.

Results 835 patients who received ICI (anti-CTLA-4, n=596; anti-PD-1, n=239) at 16 centers were analyzed, whereof 235 received a preceding radiotherapy of metastatic lesions in stage IV disease. The most frequent organ sites irradiated prior to ICI therapy were brain (51.1%), lymph nodes (17.9%) and bone (17.9%). After multivariable adjustment for confounders, no relevant differences in ICI therapy outcome were observed between cohorts with and without preceding radiotherapy. BOR was 8.7% vs 13.0% for anti-CTLA-4 (adjusted relative risk (RR)=1.47; 95% CI=0.81 to 2.65; p=0.20), and 16.5% vs 25.3% for anti-PD-1 (RR=0.93; 95% CI=0.49 to 1.77; p=0.82). Survival probabilities were similar for cohorts with and without preceding radiotherapy, for anti-CTLA-4 (PFS, adjusted HR=1.02, 95% CI=0.86 to 1.25, p=0.74; OS, HR=1.08, 95% CI=0.81 to 1.44, p=0.61) and for anti-PD-1 (PFS, HR=0.84, 95% CI=0.57 to 1.26, p=0.41; OS, HR=0.73, 95% CI=0.43 to 1.25, p=0.26). Patients who received radiation last before ICI (n=137) revealed no better survival than those who had one or more treatment lines between radiation and start of ICI (n=86). In 223 patients with brain metastases, we found no relevant survival differences on ICI with and without preceding radiotherapy.

Conclusions This study detected no evidence for a relevant favorable impact of a preceding radiotherapy on anti-CTLA-4 or anti-PD-1 ICI treatment outcome in metastatic melanoma.

BACKGROUND

The systemic therapy of metastatic melanoma recently underwent considerable changes due to the introduction of antibodies blocking the immune checkpoints CTLA-4 and PD-1.[1 2] Both CTLA-4 (ipilimumab) and PD-1 (nivolumab, pembrolizumab) immune checkpoint inhibitors (ICIs) have been shown to induce durable tumor responses and long-term survival in a subset of patients.[3–5] Immunological conditions reflecting an inflamed state of a patient's tumor such as expression of PD-L1 or presence of tumor-infiltrating lymphocytes were identified as predictive markers of ICI treatment response.[6 7] Due to the high proportion of patients with melanoma presenting a primary resistance to ICI therapy, various strategies have been considered to enhance the tumor's upfront ICI sensitivity. Herein, one promising approach that has been discussed vigorously is the enhancement of tumor immunogenicity by radiation. For various cancer entities including non-small-cell lung cancer (NSCLC),[8 9] head-and-neck cancer,[10] colon carcinoma[11] and sarcoma,[12] it has been demonstrated that radiotherapy

of tumor lesions generates immune-related abscopal antitumor effects. These effects have been assumed to be mediated by the modulation of the tumor and its microenvironment toward an increased antigen presentation and recognition, leading to an overall improvement of antitumorous immune responses.[13 14] In this regard, radiation and ICI therapy were shown to act synergistically in mouse models as well as in clinical trials.[9 15–17] A subgroup analysis of the KEYNOTE-001 trial cohort investigating pembrolizumab in metastatic NSCLC showed prolonged survival times in patients who received a radiotherapy of tumor lesions at any time preceding the start of pembrolizumab.[8] In melanoma, a variety of small studies and case series led to contradictory results with regard to an effect of radiotherapy on ICI treatment outcome (for review see Ref. 18 and tables 1 and 2). Statistical analyses of larger patient populations that address confounding are lacking, and randomized controlled trials (RCTs) on this topic are difficult to implement.

The present study aimed at investigating the impact of a preceding therapeutic radiation of metastatic lesions on ICI treatment outcome in terms of response and survival on CTLA-4 or PD-1 inhibition in a large multicenter cohort of patients with metastatic melanoma. Since radiotherapy for melanoma is mainly applied to prognostically poor patient groups with advanced metastatic disease such as metastasis to the brain or bone, this study carefully addressed confounding by the use of directed acyclic graphs (DAGs) and inverse probability treatment weighting (IPTW).

METHODS

We performed a PubMed search for articles published from January 2011 until April 2019. Our search focused on clinical studies investigating a combination or sequencing of radiotherapy and ICI in patients with metastatic melanoma. We selected studies which investigated at least 20 patients, and which reported tumor response, progression-free survival (PFS) or overall survival (OS) as a study endpoint. The used search terms were “melanoma” AND “radiotherapy”, “radiation”, “radiosurgery” AND “PD-1”, “CTLA-4”, “ipilimumab”, “nivolumab”, and “pembrolizumab”. The hereby found reported evidence on radiotherapy combined or sequenced with ICI in melanoma was based on a variety of small clinical studies with low patient numbers (tables 1 and 2). The study results were contradictory, and multivariable adjustments to confounders were lacking in the majority of studies. Data from retrospective studies led to heterogeneous results with some studies finding a beneficial effect of radiotherapy on the outcome of ICI and others do not. Data from RCTs comparing patients treated with immune checkpoint inhibitors with and without radiotherapy were missing. Thus, the clinical impact of a preceding radiotherapy on the treatment outcome of ICI in metastatic melanoma was unclear.

Study design

This multicenter retrospective cohort study was designed to analyze the impact of a preceding radiotherapy on the treatment outcome of ICI with either anti-CTLA-4 or anti-PD-1 monotherapy in patients with advanced metastatic melanoma. The secondary objective was to analyze this impact in a subgroup of patients with brain metastases. Patient selection criteria were histologically proven diagnosis of melanoma, treatment with single agent anti-CTLA-4 or anti-PD-1 ICI for unresectable metastatic disease of stage IV according to American Joint Committee on Cancer (AJCC)-v8 criteria,[19] ICI therapy start between January 2010 and June 2017, complete documentation of all treatment lines applied before ICI, and at least one documented follow-up visit after start of ICI therapy. The participating study centers were skin cancer centers of the German Dermatologic Cooperative Oncology Group (DeCOG).

Patient registry

Patients were identified at the participating centers according to the abovementioned selection criteria. Data were extracted from patient files, collected on standardized electronic case record forms, and merged in one central electronic registry. The following known prognostic factors of stage IV melanoma were collected: sites of metastasis categorized by AJCC-v8,[19] patients’ overall performance status (OPS) graded by Eastern Cooperative Oncology Group categories, and serum lactate dehydrogenase activity at baseline of ICI therapy. All treatment lines received in stage IV disease prior to the investigated ICI therapy were assessed and categorized by type of treatment (radiotherapy, chemotherapy, kinase inhibition, immunotherapy). Details on radiotherapy were recorded including the type of radiation and the irradiated organ site. Outcome parameters of ICI treatment were collected, including best overall response (BOR), PFS, and OS survival. BOR was defined as best response recorded from the start of ICI until disease progression and was evaluated according to response evaluation criteria in solid tumors (RECIST)v1.1.[20] PFS and OS were measured from ICI therapy start until disease progression or death, respectively; if no such event occurred, the date of last patient contact was used as endpoint of survival assessment (censored observation).

Data analysis

Survival curves and median survival times with 95% CIs were calculated using the Kaplan-Meier method for censored failure time data. The multivariable Cox proportional hazards model was applied to estimate the raw and the multivariably adjusted effects of a preceding radiotherapy on PFS and OS of patients treated with ICI in terms of HRs. Adjustment for multiple confounders was done by IPTW.[21] To illustrate the effect of IPTW on the baseline characteristics of patient groups being compared, see online supplementary tables 1 and 2. The proportional hazards assumption was tested using the

Table 1 Clinical studies on combining or sequencing RT and anti-CTLA-4 checkpoint inhibition in melanoma

Author(s) (year)	ICI agent	Study design	n	RT target	RT type	Cohorts/ comparators	RT timing	OS (median)	PFS (median)	Response	Benefit of combination/ sequencing
Anti-CTLA-4											
Knisely *et al* (2012)[30]	Ipilimumab	Retrospective	77	Brain	Stereotactic (SRS)	Two cohorts: RT+ICI (n=27); RT (n=50)	Sequential (RT before ICI, n=11; RT after ICI, n=16)	6.7 months (all patients); 21.3 months (RT+ICI) vs 4.9 months (RT), p=0.04	NR	NR	Yes (RT+ICI superior to RT; OS)
Barker *et al* (2013)[31]	Ipilimumab	Retrospective	29	Various, non-brain	Various (stereotactic and conventional)	Single cohort (RT+ICI); no comparator	Concurrent	9.0 months (RT within 16 weeks after start of ICI); 39.0 months (RT later than 16 weeks after start of ICI)	5 months (RT within 16 weeks after start of ICI); 39 months (RT later than 16 weeks after start of ICI)	NR	NA
Mathew *et al* (2013)[32]	Ipilimumab	Retrospective	58	Brain	Stereotactic (SRS)	Two cohorts: RT+ICI (n=25); RT (n=33)	Concurrent	5.9 months (all patients); 6 months OS 56% (RT+ICI) vs 46% (RT), p=ns	NR	Local tumor control (brain) 65% (RT+ICI) vs 63% (RT), p=ns	No (local tumor control; OS)
Silk *et al* (2013)[33]	Ipilimumab	Retrospective	70	Brain	Various (stereotactic and conventional)	Two cohorts: RT+ICI (n=33); RT (n=37)	Sequential (RT before ICI, n=21; RT after ICI, n=12)	18.3 months (RT+ICI) vs 5.3 months (RT), p=0.002	2.7 months (RT+ICI) vs 3.3 months (RT), p=0.55	NR	Yes (RT+ICI superior to RT; OS); SRS+ICI superior to WBRT+ICI
Chandra *et al* (2015)[34]	Ipilimumab	Retrospective	47	Various	Various (stereotactic and conventional)	Single cohort (RT+ICI); no comparator	Concurrent	28.0 months	NR	Lesion response in hyperfractionated (81%) vs hypofractionated (52%) RT, p=0.014	NA
Kiess *et al* (2015)[35]	Ipilimumab	Retrospective	46	Brain	Stereotactic (SRS)	Three cohorts on different timings: RT before ICI, n=19; RT concurrent to ICI, n=15; RT after ICI, n=12	Concurrent or sequential (RT before ICI, n=19; RT concurrent to ICI, n=15; RT after ICI, n=12)	1-year OS RT before (56%) vs concurrent (65%) vs after (40%) ICI, p=0.008	1 year regional recurrence RT before (64%) vs concurrent (69%) vs after (92%) ICI, p=0.003	NR	Yes (RT before or concurrent to ICI superior to RT after ICI; PFS, OS)

Continued

Table 1 Continued

Author(s) (year)	ICI agent	Study design	n	RT target	RT type	Cohorts/ comparators	RT timing	OS (median)	PFS (median)	Response	Benefit of combination/ sequencing
Tazi *et al* (2015)[36]	Ipilimumab	Retrospective	31	Brain	Stereotactic (SRS)	Two cohorts: RT+ICI, n=10 (brain metastases); ICI, n=21 (no brain metastases)	Concurrent or sequential	16.5 months (RT+ICI) vs 24.5 months (ICI), p=0.93	NR	NR	No (OS)
Twyman-Saint Victor *et al* (2015)[37]	Ipilimumab	Prospective, phase 1 (NCT01497808)	22	Various, non-brain	Stereotactic body radiation	Single cohort (RT before ICI); no comparator	Sequential (RT before ICI)	10.7 months	3.8 months	BOR 18% (18% PR, 18% SD, 64% PD)	NA
Hiniker *et al* (2016)[38]	Ipilimumab	Retrospective	22	Various, including brain	Various (stereotactic and conventional)	Single cohort (RT+ICI); no comparator	Concurrent	13.8 months	6.5 months	BOR 27% (14% CR, 14% PR, 27% SD, 45% PD)	NA
Qian *et al* (2016)[39]	Ipilimumab	Retrospective	54	Brain	Stereotactic (SRS)	Three cohorts: RT concurrent to ICI, n=19; RT before/after ICI, n=19; RT concurrent and sequential, n=16	Concurrent or sequential (RT before/after ICI)	19.1 months (RT concurrent to ICI) vs 8.0 months (RT sequential to ICI), p=0.086	NR	NR	NA
Qin *et al* (2016)[40]	Ipilimumab	Retrospective	88	Various, including brain	Various (stereotactic and conventional)	Two cohorts: RT+ICI, n=44; ICI, n=44	Sequential (RT before ICI, n=20; RT after ICI, n=24)	17.9 months (RT+ICI) vs 24.8 months (ICI), p=0.67	NR	NR	No (OS)
Theurich *et al* (2016)[41]	Ipilimumab	Retrospective	127	Various, including brain	Various (stereotactic and conventional)	Two cohorts: RT+ICI, n=45; ICI, n=82	Concurrent or sequential	23.3 months (RT+ICI) vs 10.5 months (ICI), p=0.0028	NR	BOR 58% (RT+ICI) vs 39% (ICI), p=0.05	Yes (RT before, concurrent to, or after ICI superior to ICI; BOR, OS)
Koller *et al* (2017)[42]	Ipilimumab	Retrospective	101	Various, including brain	Various (stereotactic and conventional)	Two cohorts: RT+ICI, n=70; ICI, n=31	Concurrent	19.0 months (RT+ICI) vs 10.0 months (ICI), p=0.01	5.0 months (RT+ICI) vs 3.0 months (ICI), p=0.20	BOR 37% (RT+ICI) vs 19% (ICI), p=0.11; CR 26% (RT+ICI) vs 7% (ICI), p=0.04	Yes (RT+ICI superior to ICI; BOR, OS)

Continued

Table 1 Continued

Author(s) (year)	ICI agent	Study design	n	RT target	RT type	Cohorts/ comparators	RT timing	OS (median)	PFS (median)	Response	Benefit of combination/ sequencing
Patel *et al* (2017)[43]	Ipilimumab	Retrospective	54	Brain	Stereotactic (SRS)	Two cohorts: RT before ICI, n=20; RT, n=34	Sequential (RT before ICI, n=20)	1 year OS: 37.1% (RT before ICI) vs 38.5% (RT), p=0.84	NR	1 year intracranial control: 12.7% (RT before ICI) vs 29.1% (RT), p=0.59	NA
Minniti *et al* (2019)[44]	Ipilimumab	Retrospective	45	Brain	Stereotactic (SRS)	Single cohort (RT before ICI, n=45); no comparator	Sequential (RT before ICI)	14.7 months	6.0 months (intracranial PFS)	NR	NA
Knispel *et al**	Ipilimumab	Retrospective	596	Various, including brain	Various (stereotactic and conventional)	Two cohorts: RT+ICI, n=150; ICI, n=446	Sequential (RT before ICI)	6.8 months (RT before ICI) vs 9.6 months (ICI), p=0.61 (adjusted for confounders)	2.8 months (RT before ICI) vs 3.1 months (ICI), p=0.74 (adjusted for confounders)	BOR 9% (RT before ICI) vs 13% (ICI), p=0.20 (adjusted for confounders)	No (BOR, PFS, OS)

Published clinical studies on RT and ICI are presented with their outcomes in terms of tumor response and patient survival. Only studies investigating a cohort >20 patients are shown.
*Data of the present study.
BOR, best overall response; CR, complete response; ICI, immune checkpoint inhibition; NA, not applicable; NR, not reported; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RT, radiotherapy; SD, stable disease; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

Table 2 Clinical studies on combining or sequencing RT and anti-PD-1 checkpoint inhibition in melanoma

Author(s) (year)	ICI agent	Study design	n	RT target	RT type	Cohorts/comparators	RT timing	OS (median)	PFS (median)	Response	Benefit of combination/ sequencing
Anti-PD-1											
Ahmed *et al* (2016)[45]	Nivolumab	Retrospective	26	Brain	Stereotactic (SRS)	Single cohort (RT+ICI); no comparator	Concurrent or sequential (RT before/ after ICI)	12.0 months	NR	NR	NA
Liniker *et al* (2016)[46]	Nivolumab or pembrolizumab	Retrospective	53	Various, including brain	Various (stereotactic and conventional)	Four cohorts: RT before ICI, n=11; RT concurrent to ICI, n=16; RT at progression to ICI, n=15; WBRT, n=11	Concurrent, sequential, or at progression	6.4 months (RT concurrent to ICI) vs 8.6 months (RT sequential to ICI), p=0.77	NR	BOR in irradiated lesions 64% (RT concurrent to ICI) vs 44% (RT sequential to ICI), p=0.45; BOR in non-irradiated lesions 46% (RT concurrent to ICI) vs 52% (RT sequential to ICI), p=0.88	NA
Aboudaram *et al* (2017)[47]	Nivolumab or pembrolizumab	Retrospective	59	Various, including brain	Various (stereotactic and conventional)	Two cohorts: RT+ICI, n=17; ICI, n=42	Concurrent or sequential (RT before ICI)	12.1 months (RT+ICI) vs 8.3 months (ICI), p=0.42	7.8 months (RT+ICI) vs 5.9 months (ICI), p=0.32	BOR 65% (RT+ICI) vs 33% (ICI), p=0.027	Yes (RT+ICI superior to ICI; BOR)
Anderson *et al* (2017)[48]	Pembrolizumab	Retrospective	21	Brain	Various (stereotactic and conventional)	Single cohort (RT+ICI); no comparator	Concurrent or sequential (RT after ICI)	NR	NR	BOR in irradiated lesions 70%	NA
Pike *et al* (2017)[49]	Nivolumab or pembrolizumab	Retrospective	48	Various, including brain	Various (stereotactic and conventional)	Two cohorts: RT before ICI, n=26; RT concurrent to ICI, n=22	Concurrent or sequential	14.1 months	NR	NR	NA
Maity *et al* (2018)[50]	Pembrolizumab	Prospective, phase 1 (NCT02303990)	24 (various tumor entities, thereof n=4 melanoma)	Various, including brain	Various (stereotactic and conventional)	Two cohorts: RT at progression to ICI, n=12; RT concurrent to ICI, n=12	Concurrent	NR	NR	BOR 16.7%	NA
Nardin *et al* (2018)[51]	Pembrolizumab	Retrospective	25	Brain	Stereotactic (SRS)	Single cohort (RT+ICI); no comparator	Concurrent or sequential (RT before, concurrent to, or after ICI)	15.3 months	4.0 months (intracranial PFS)	Local tumor control (brain) 68%	NA

Continued

Table 2 Continued

Author(s) (year)	ICI agent	Study design	n	RT target	RT type	Cohorts/comparators	RT timing	OS (median)	PFS (median)	Response	Benefit of combination/ sequencing
Roger *et al* (2018)[52]	Nivolumab or pembrolizumab	Retrospective	25	Various, including brain	Stereotactic body radiation; SRS (brain)	Two cohorts: RT concurrent to ICI, n=15; RT at progression to ICI, n=10	Concurrent or at progression	9.9 months (RT concurrent to ICI), 18.9 months (RT at progression to ICI)	3.0 months (RT concurrent to ICI), 16.2 months (RT at progression to ICI)	BOR 36% (all patients)	NA
Trommer-Nestler *et al* (2018)[53]	Nivolumab or pembrolizumab	Retrospective	26	Brain	Stereotactic (SRS)	Two cohorts: RT+ICI, n=13; RT, n=13	Concurrent	NR	NR	BOR in irradiated lesions 43% (RT+ICI) vs 20% (RT), p=0.028	NA
Minniti *et al* (2019)[44]	Nivolumab	Retrospective	35	Brain	Stereotactic (SRS)	Single cohort (RT before ICI); no comparator	Sequential (RT before ICI)	22.0 months	10.0 months (intracranial PFS)	NR	NA
Knispel *et al**	Nivolumab or pembrolizumab	Retrospective	239	Various, including brain	Various (stereotactic and conventional)	Two cohorts: RT+ICI, n=85; ICI, n=154	Sequential (RT before ICI)	10.8 months (RT before ICI) vs 17.5 months (ICI), p=0.26 (adjusted for confounders)	4.0 months (RT before ICI) vs 4.2 months (ICI), p=0.41 (adjusted for confounders)	BOR 17% (RT before ICI) vs 25% (ICI), p=0.86 (adjusted for confounders)	No (BOR, PFS, OS)

Published clinical studies on RT and ICI are presented with their outcomes in terms of tumor response and patient survival. Only studies investigating a cohort >20 patients are shown.
*Data of the present study.
BOR, best overall response; ICI, immune checkpoint inhibition; NA, not applicable; NR, not reported; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy.

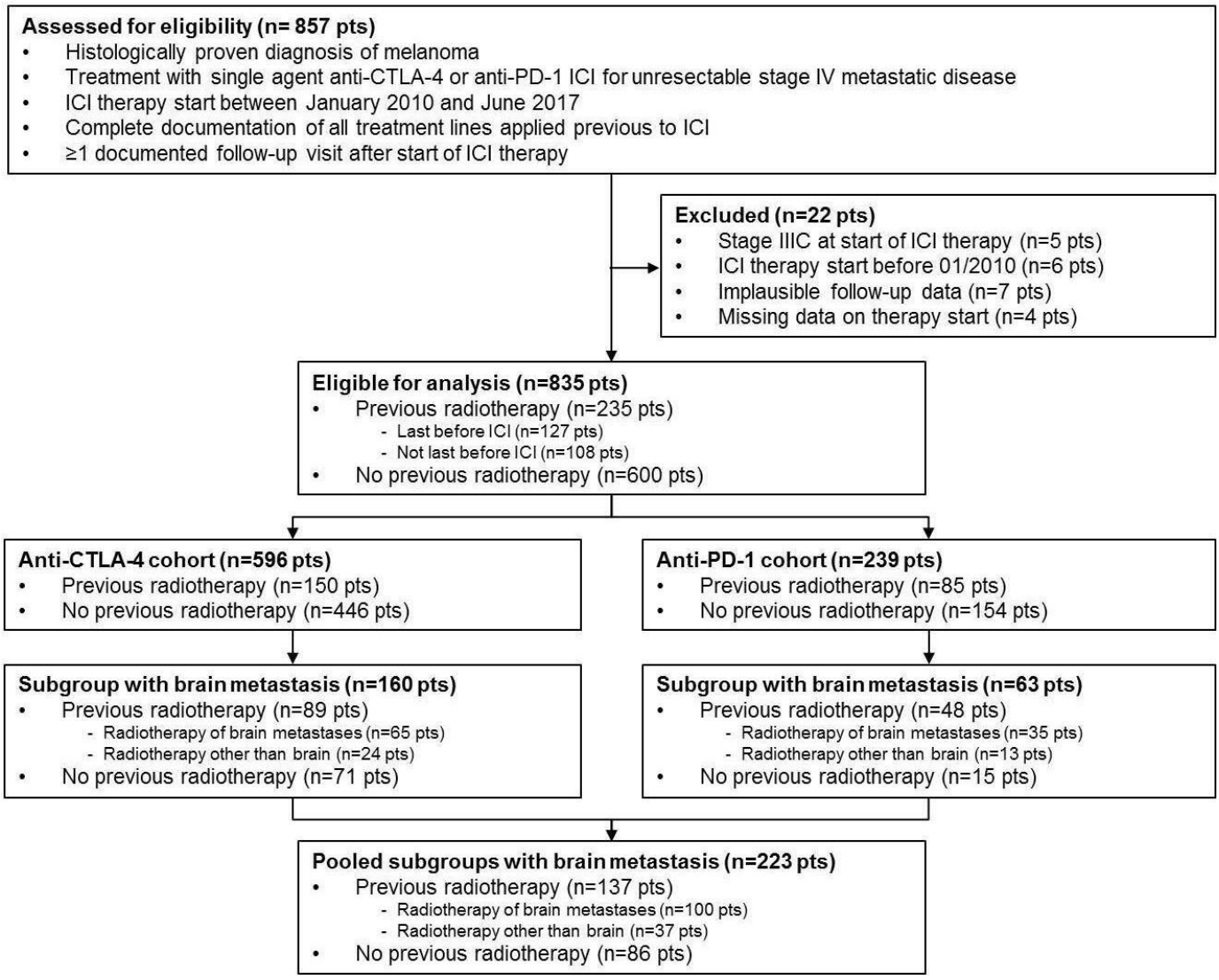

Figure 1 Schematic presentation of the patient selection flow. Eight hundred and fifty-seven patients were identified at 16 clinical centers. Thereof, 835 patients were eligible for analysis, including a subgroup of 223 patients with brain metastasis. ICI, immune checkpoint inhibition.

supremum test. Log-binomial regression models were used to estimate crude and multivariably adjusted relative risks (RR) and 95% CI for BOR. To define the confounder adjustment sets, we used DAGs.[22] The adjusted survival curves were estimated using IPTW in the Cox models. We calculated and reported CIs to assess the precision of our estimates. All presented p-values are two-tailed and unadjusted for potential multiple comparisons to allow a hypothesis-generating exploratory data analysis.

RESULTS

Patient characteristics

Data of 857 consecutive patients from 16 centers were entered into the central registry. Thereof, 22 patients had to be excluded from analysis (figure 1). The remaining patient population (n=835) was used for all further analysis. Detailed patient characteristics at ICI therapy start are presented in table 3. Data on the patients' systemic pretreatment in stage IV are given in online supplementary table 3.

Radiotherapy

Of all patients eligible for analysis, 235 (28.2%) received radiotherapy of at least one metastatic lesion in stage IV at any time preceding the start of the investigated ICI. Radiotherapy applied in an adjuvant setting to lymph node basins in stage III disease was not considered. Patients who received radiotherapy concurrent to ICI treatment were not eligible. The most frequent organ sites irradiated prior to ICI therapy were brain (51.1%), lymph nodes (17.9%), and bone (17.9%). Among patients with a preceding radiotherapy of the brain (n=100), the most common radiation type was whole brain radiation (44.0%), followed by stereotactic radiation (33.0%). With regard to ICI therapy type, 150 (25.2%) of 596 patients who received anti-CTLA-4, and 85 (35.6%) of 239 patients treated with anti-PD-1, respectively, received a preceding

Table 3 Patient characteristics at start of ICI

	Anti-CTLA-4 (n=596)				Anti-PD-1 (n=239)				All (N=835)			
	No preceding RT		Preceding RT		No preceding RT		Preceding RT		No preceding RT		Preceding RT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total	446	100	150	100	154	100	85	100	600	100	235	100
Age (years), mean±SD	62.7 (±13.1)		57.8 (±14.6)		59.1 (±14.6)		58.2 (±14.1)		61.8 (±13.6)		57.9 (±14.4)	
Sex												
Male	265	59.4	93	62.0	88	57.1	51	60.0	353	58.8	144	61.3
Female	181	40.6	57	38.0	66	42.9	34	40.0	247	41.2	91	38.8
Primary site												
Skin	332	74.4	109	72.7	112	72.7	63	74.1	444	74.0	172	73.2
Occult (MUP)	43	9.6	28	18.7	21	13.6	10	11.8	64	10.7	38	16.2
Mucosa	37	8.3	6	4.0	17	11.1	8	9.4	54	9.0	14	6.0
Uvea	32	7.2	6	4.0	3	2.0	3	3.5	35	5.8	9	3.8
Missing data	2	0.5	1	0.6	1	0.6	1	1.2	3	0.5	2	0.8
BRAF V600 mutational status												
Wild type	267	59.9	75	50.0	108	70.1	52	61.2	375	62.5	127	54.0
Mutation	135	30.3	55	36.7	36	23.4	29	34.1	171	28.5	84	35.7
Missing data	44	9.8	20	13.3	10	6.5	4	4.7	54	9.0	24	10.3
Overall performance status												
ECOG=0	167	37.4	38	25.3	74	48.1	27	31.8	241	40.2	65	27.7
ECOG≥1	83	18.6	39	26.0	36	23.4	28	32.9	119	19.8	67	28.5
Missing data	196	43.9	73	48.7	44	28.6	30	35.3	240	40.0	103	43.8
Serum LDH												
Normal	173	38.8	55	36.7	64	41.6	27	31.8	237	39.5	82	34.9
Elevated ≤twofold ULN	132	29.6	52	34.7	49	31.8	33	38.8	181	30.2	85	36.2
Elevated >twofold ULN	64	14.3	24	16.0	26	16.9	13	15.3	90	15.0	37	15.7
Missing data	77	17.3	19	12.6	15	9.7	12	14.0	92	15.3	31	13.2
M stage												
M1a (skin, lymph node)	71	15.9	5	3.3	16	10.4	4	4.7	87	14.5	9	3.8
M1b (lung)	110	24.7	16	10.7	45	29.2	9	10.6	155	25.8	25	10.6
M1c (other organ)	185	41.5	39	26.0	77	50.0	23	27.1	262	43.7	62	26.4
M1d (brain)	71	16.0	89	59.3	15	9.8	48	56.5	86	14.3	137	58.3
Missing data	9	2.0	1	0.7	1	0.6	1	1.1	10	1.7	2	0.9
Bone metastases												
No	377	84.5	103	68.7	140	90.9	56	65.9	517	86.2	159	67.7
Yes	69	15.5	47	31.3	14	9.1	29	34.1	83	13.8	76	32.3
Missing data	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Number of organ sites involved												
≤3	343	76.9	87	58.0	111	72.1	40	47.1	454	75.7	127	54.0
>3	94	20.1	62	41.3	42	27.3	44	51.8	136	22.7	106	45.1
Missing data	9	2.0	1	0.7	1	0.6	1	1.1	10	1.7	2	0.9

Continued

Table 3 Continued

	Anti-CTLA-4 (n=596)				Anti-PD-1 (n=239)				All (N=835)			
	No preceding RT		Preceding RT		No preceding RT		Preceding RT		No preceding RT		Preceding RT	
	n	%	n	%	n	%	n	%	n	%	n	%
Systemic pretreatment in stage IV												
No	138	30.9	27	18.0	28	18.2	11	13.0	166	27.7	38	16.2
Yes	291	65.2	123	82.0	123	79.8	72	84.7	414	69.0	195	83.0
Missing data	17	3.9	0	0.0	3	2.0	2	2.3	20	3.3	2	0.8
Duration of stage IV disease at start of ICI (months) Median (p10; p90)	6.0 (0.8; 26.6)		9.8 (2.2; 42.4)		13.7 (1.4; 36.2)		14.2 (2.5; 43.8)		8.2 (1.4; 26.5)		14.7 (4.5; 68.2)	

The given patient characteristics refer to the start of the investigated ICI therapy. Percentages are given per column for each individual patient cohort. M stage categories refer to the AJCC v8 classification system; the number of organ sites refer to organs involved with metastasis; systemic pretreatment describes systemic therapies received by the patient for inoperable stage IV disease (not adjuvant) prior to the investigated ICI therapy.
BRAF, v-raf murine sarcoma viral oncogene homolog B1; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibition; LDH, lactate dehydrogenase; MUP, melanoma of unknown primary; p10, 10th percentile; p90, 90th percentile.; RT, radiotherapy; ULN, upper limit of normal.

radiotherapy (online supplementary table 4). The patient cohorts with and without preceding radiotherapy differed markedly in important prognostic factors such as OPS, sites of metastasis (particularly brain), number of metastatic sites, and systemic pretreatment in stage IV, revealing a less favorable prognosis for patients who received radiotherapy before start of ICI in both the anti-CTLA-4 and the anti-PD-1 therapy groups.

Statistical adjustment sets

After application of DAGs, separate adjustment sets of confounders were defined for PFS and OS, each for the total patient population as well as for the subgroup of patients with brain metastases (online supplementary figure 1). The adjustment set for the response parameter BOR equals than that for PFS. For the total patient population, the adjustment set included brain metastases (yes vs no), bone metastases (yes vs no), primary site of disease (categorical), and systemic pretreatment (yes vs no) for PFS and BOR, and duration in stage IV (continuous), brain metastases, bone metastases, primary site of disease, BRAF mutational status (yes vs no), and systemic pretreatment for OS. For patients with brain metastases, the confounders were primary site of disease and systemic pretreatment for PFS and BOR, and duration in stage IV, primary site of disease, BRAF mutational status, and systemic pretreatment for OS.

Survival outcome of ICI therapy

The closing date for the patient registry was February 15, 2018. At that time, the total study population had a median follow-up time of 13.1 months. 78.7% of the patients had experienced disease progression and 55.7% had died.

For patients treated with anti-CTLA-4, the median PFS was 2.9 months (95% CI=2.0 to 5.4 months), and the median OS was 6.2 months (95% CI=2.8 to 12.0 months). After multivariable adjustment for confounders, no difference could be detected for PFS (HR=1.02; 95% CI=0.86 to 1.25; p=0.74; figure 2A) and OS (HR=1.08; 95% CI=0.81 to 1.44; p=0.61; figure 2D) between patients who received a preceding radiotherapy before CTLA-4 inhibition and patients who did not.

For patients treated with anti-PD-1, the median PFS was 3.8 months (95% CI=1.9 to 6.2 months), and the median OS was 13.0 months (95% CI=3.7 to 18.0 months). A radiotherapy preceding anti-PD-1 treatment had no impact on PFS (HR=0.84; 95% CI=0.57 to 1.26; p=0.41; figure 2B) or OS (HR=0.73; 95% CI=0.43 to 1.25; p=0.26; figure 2E) after adjustment for confounders. Subgroup analysis of patients with (n=192) or without (n=45) pretreatment with anti-CTLA-4 prior to anti-PD-1 ICI revealed a possible survival benefit of a previous radiotherapy in patients treated with anti-PD-1 without prior treatment with anti-CTLA-4 after adjustment for confounders (online supplementary figure 2B,D). This benefit was more visible in OS (HR 0.36; 95% CI 0.08 to 1.57; p=0.17) than in PFS (HR 0.91; 95% CI 0.47 to 1.75; p=0.78); however, due to the small sample size, the effect estimation did not provide meaningful results. In patients treated with anti-CTLA-4 prior to anti-PD-1 ICI, no differences were visible for PFS and OS between patients with or without preceding radiotherapy (online supplementary figure 2A,C).

To analyze a potential effect of different timings of radiation in relation to the investigated ICI, the total number of patients who received radiotherapy prior to anti-CTLA-4 or anti-PD-1 (n=235) were divided into those

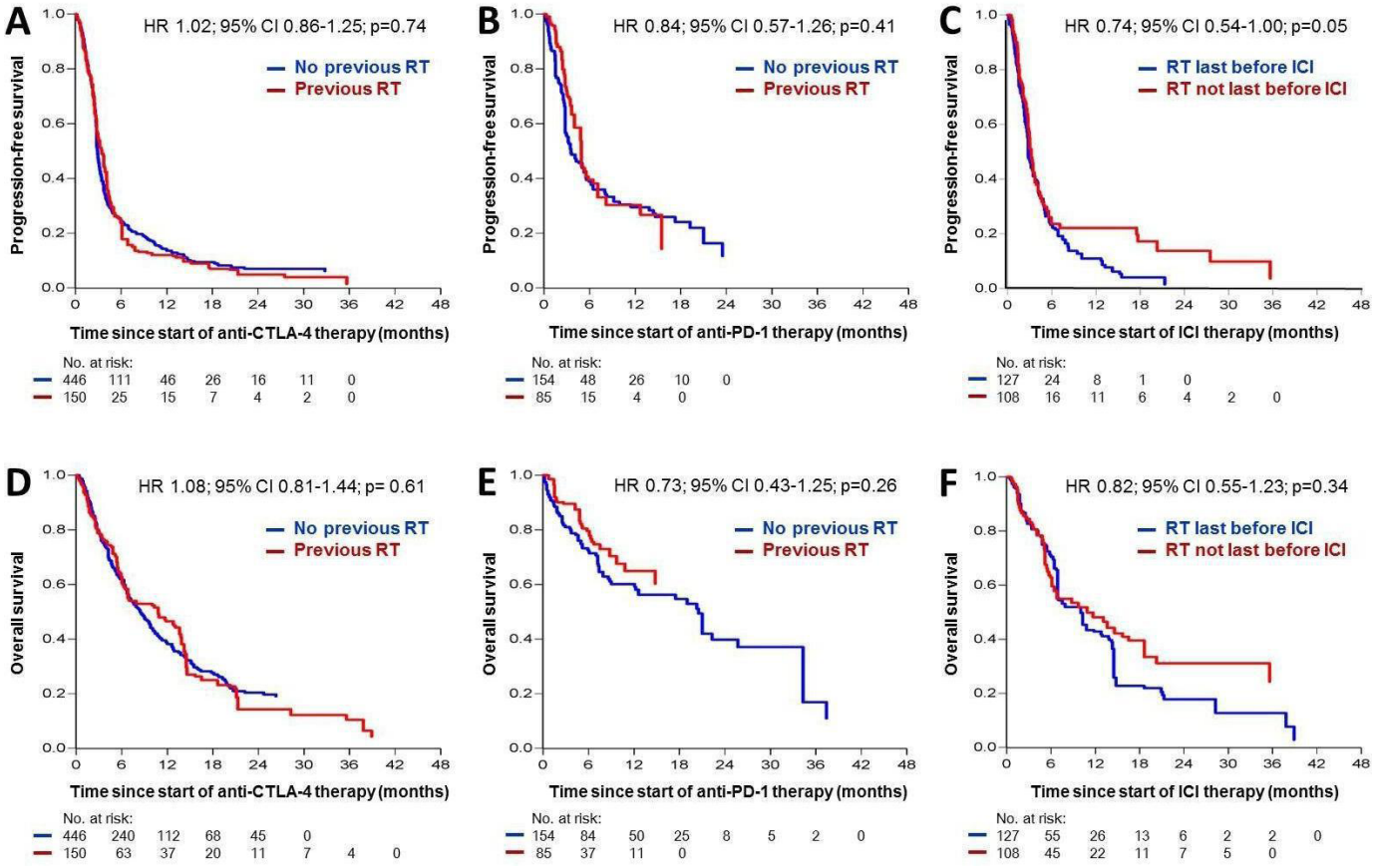

Figure 2 Kaplan-Meier curves showing the probability of progression-free (A–C) and overall survival (D–F) adjusted for confounding factors in patients with metastatic melanoma treated with immune checkpoint inhibitors (ICIs). A and D: n=596 patients treated with anti-CTLA-4 ICI with or without preceding radiotherapy; B and E: n=239 patients treated with anti-PD-1 ICI with or without preceding radiotherapy; C and F: n=235 patients treated with anti-CTLA-4 or anti-PD-1 ICI and preceding radiotherapy, either last before ICI or with at least one treatment line between radiotherapy and start of ICI. RT, radiotherapy.

who had radiotherapy last before start of ICI (n=127; 54%), and those who had one or more treatment lines between radiation and ICI (n=108; 46%). Within the first 6 months after ICI start, no difference was observed for multivariably adjusted PFS and OS between both groups. However, at 6 months or later, those patients who received radiotherapy last before ICI showed a poorer survival outcome (PFS, HR=0.74, 95% CI=0.54 to 1.00, p=0.05; OS, HR=0.82, 95% CI=0.55 to 1.23, p=0.34), figure 2C,F).

Response outcome of ICI therapy

After multivariable adjustment for confounders, no relevant differences were observed for objective response (CR+PR) between patients who underwent a preceding radiotherapy and patients who did not, both in the anti-CTLA-4 (8.7% vs 13.0%; RR=1.47; 95% CI=0.81 to 2.65; p=0.20) and in the anti-PD-1 ICI therapy cohort (16.5% vs 25.3%; RR=0.93; 95% CI=0.49 to 1.77; p=0.82); table 4. Also, the individual categories of BOR showed no differences between groups with or without preceding radiotherapy (table 4).

Patients with brain metastases

26.7% (n=223) of the total patient population had brain metastases at start of the investigated ICI, whereof 61% (n=137) received a preceding radiotherapy (table 3, figure 1). Due to the clinical relevance of the presence of brain metastases and the high frequency of radiotherapy applied in these patients, this subgroup was investigated separately for a potential impact of a preceding radiotherapy on ICI treatment outcome. After multivariable adjustment for confounders, no relevant differences were observed for PFS (HR=0.85; 95% CI=0.63 to 1.15; p=0.29; figure 3A) or OS (HR=0.77; 95% CI=0.53 to 1.13; p=0.18; figure 3C). With regard to the type of brain radiation, we found no survival differences between whole brain radiation and stereotactic brain radiation (PFS, HR=0.97, 95% CI=0.80 to 1.17, p=0.74; OS, HR=1.05, 95% CI=0.72 to 1.52, p=0.80; figure 3B,D). Moreover, patients with brain metastases showed no difference in objective response to ICI between groups with and without preceding radiation (8.8% vs 3.5%; RR=2.54; 95% CI=0.73 to 8.75; p=0.14; table 4).

Table 4 Therapy outcome of ICI

	Total patient population (N=835)								Patients with brain metastases (N=223)			
	Anti-CTLA-4 (n=596)				Anti-PD-1 (n=239)				Anti-CTLA-4 (n=160)/anti-PD-1 (n=63)			
	No preceding RT		Preceding RT		No preceding RT		Preceding RT		No preceding RT		Preceding RT	
	n	%	n	%	n	%	n	%	n	%	n	%
Total	446	100	150	100	154	100	85	100	86	100	137	100
Best overall response												
CR	16	3.6	2	1.3	6	3.9	2	2.4	0	0	1	0.7
PR	42	9.4	11	7.3	33	21.4	12	14.1	3	3.5	11	8.0
SD	59	13.2	18	12.0	24	15.6	23	27.6	9	10.5	22	16.0
PD	305	68.4	110	73.3	79	51.3	41	48.2	70	81.4	95	69.4
Missing data	24	5.4	9	6.0	12	7.8	7	8.2	4	4.6	8	5.9
Objective response												
Responders (CR/PR)	58	13.0	13	8.7	39	25.3	14	16.5	3	3.5	12	8.8
Non-responders (SD/PD)	364	81.6	128	85.3	103	66.9	64	75.3	79	91.9	117	85.4
Missing data	24	5.4	9	6.0	12	7.8	7	8.3	4	4.7	8	5.9
RR (95% CI); p value	1.47 (0.81 to 2.65); p=0.20				0.93 (0.49 to 1.77); p=0.86				2.54 (0.73 to 8.75); p=0.14			
PFS												
Median (months) (95% CI)	3.1 (2.0 to 5.9)		2.8 (1.5 to 4.6)		4.2 (2.3 to 17.3)		4.0 (2.4 to 8.2)		2.7 (1.4 to 3.5)		2.8 (1.5 to 5.1)	
HR (95% CI); p value	1.02 (0.86 to 1.25); p=0.74				0.84 (0.57 to 1.26); p=0.41				0.85 (0.63 to 1.15); p=0.29			
OS												
Median (months) (95% CI)	9.6 (4.2 to 21.3)		6.8 (3.3 to 15.7)		17.5 (4.6 to 34.3)		10.8 (5.2 to NR)		4.6 (2.4 to 9.8)		6.4 (2.7 to 14.8)	
HR (95% CI); p value	1.08 (0.81 to 1.44); p=0.61				0.73 (0.43 to 1.25); p=0.26				0.77 (0.53 to 1.13); p=0.18			

Therapy outcome of CI is shown separately for patients treated with anti-CTLA-4 and for patients treated with anti-PD-1, as well as for a subgroup of patients with brain metastases (M1d) treated with either anti-CTLA-4 or anti-PD-1. The effect of a preceding radiotherapy on response to ICI is given as RR to achieve an objective response; the effect of a preceding radiotherapy on survival on ICI therapy is given as HR to attain a progression (PFS) or death (OS). All RR, HR, and p values result from multivariable analyses adjusted for confounders.
ICI, immune checkpoint inhibition; NR, not reached; OS, overall survival; PFS, progression-free survival; RR, relative risk.

DISCUSSION

Radiation is a common treatment modality in metastatic melanoma, primarily aimed at the control of difficult to treat or symptomatic metastatic sites such as brain or bone. Since there are no detrimental side effects of interaction described, radiotherapy is often combined or sequenced with immunotherapy in these patients. This combination or sequencing approach gained additional attention from the hypothesis of radiation to act as means of converting immunologically "cold" into "hot" tumor microenvironments, herein functioning as a sensitizer for ICI therapy.[16 23] Whether the radiation of tumor lesions prior to the start of ICI can increase ICI treatment efficacy in patients with melanoma currently is a matter of ongoing investigation and intense debate.

For both CTLA-4 and PD-1 inhibition, several case reports exist on patients with melanoma who experienced impressive tumor responses to ICI when combined or sequenced with radiotherapy.[24 25] The current evidence on ICI and radiotherapy in melanoma provided by clinical studies on cohorts of >20 patients differs between the two types of inhibitors, anti-CTLA-4 and anti-PD-1 (tables 1 and 2). For anti-CTLA-4, out of 15 studies, 7 did not compare cohorts with and without radiation. Of the remaining eight studies, five demonstrated a prolonged OS (n=5) or an increased BOR (n=3) in patients treated with

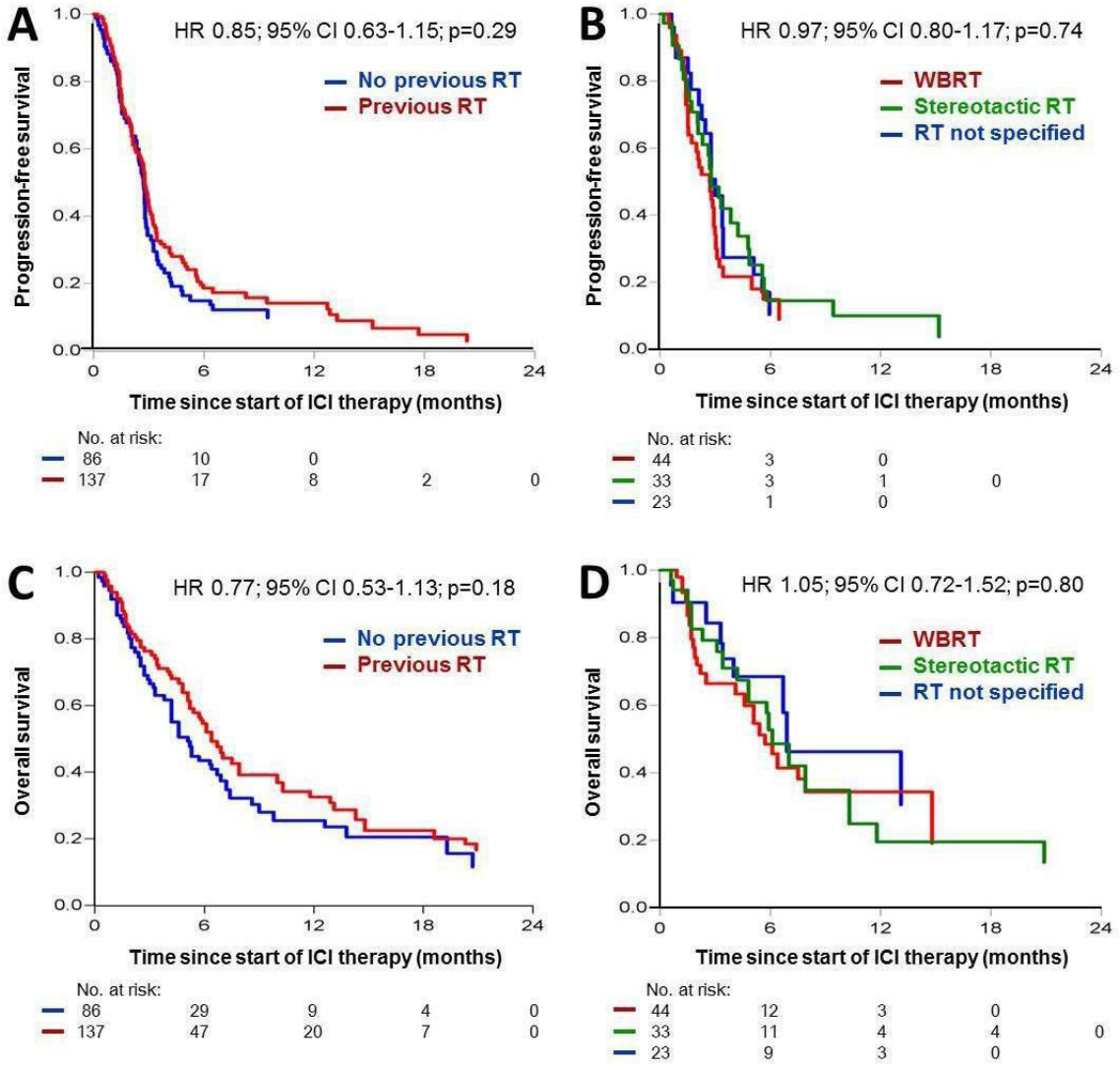

Figure 3 Kaplan-Meier curves showing the probability of progression-free (A, B) and overall survival (C, D) adjusted for confounding factors in patients with melanoma with brain metastases (AJCC stage M1d) treated with anti-CTLA-4 or anti-PD-1 immune checkpoint inhibitors (ICIs). A and C: n=223 M1d patients treated with ICI with or without preceding radiotherapy; B and D: n=100 M1d patients treated with ICI and preceding radiotherapy of the brain displayed by the radiation technique used (whole brain radiotherapy (WBRT), stereotactic radiotherapy, or not further specified radiation therapy of brain metastases). RT, radiotherapy.

radiotherapy and ICI combined or sequenced, whereas three studies did not detect such a beneficial effect. For anti-PD-1 ICI combined or sequenced with radiation, out of 10 published studies only 1 compared patient cohorts with and without radiation, revealing a positive impact on BOR but no relevant differences in PFS or OS. The other nine studies investigated different timings and modalities of radiation in relation to anti-PD-1. Notably, approximately half of all studies on radiation and ICI (8/15 anti-CTLA-4; 4/10 anti-PD-1) investigated brain metastases as the only target of radiation, with the majority of these studies focusing on stereotactic radiosurgery. Additionally important, of these 25 clinical studies all but 2 were retrospective. The remaining two prospective studies included small patient numbers only and had no comparator arms. Statistical analyses addressing the important issue of confounders are lacking, mainly due to the small patient numbers analyzed in most of these studies. Taken together, the current clinical data comparing ICI with or without combined or sequenced radiotherapy rely on relatively small retrospective studies, with no implementation of multivariable adjustment for confounders. Results from RCTs adressing this subject are completely missing.

Our present study comprises by far the largest patient cohorts on ICI plus or minus radiation in melanoma to date. In contrast to some of the abovementioned smaller studies, we detected no relevant impact of a preceding radiotherapy on ICI treatment outcome, neither in patients treated with anti-CTLA-4 nor in patients treated with anti-PD-1. In patients treated with anti-PD-1 with no pretreatment with anti-CTLA-4, a possible survival benefit of a previous radiotherapy could not be excluded, while in patients treated with anti-CTLA-4 prior to anti-PD-1, a precedent radiotherapy led to no relevant difference

in survival. Regarding tumor response in terms of BOR, our results revealed broad CIs indicating a wide range of potential effects of a preceding radiation. In contrast, for survival in terms of PFS and OS, the narrow CIs found by us showed no evidence that radiotherapy relevantly influenced the rate of progression or death.

The observed discrepancy between published data showing a beneficial impact of a preceding radiation on ICI treatment outcome at least in some clinical studies, and our own data revealing no evidence for such an effect can be primarily explained by the small patient numbers investigated within the previously reported studies (see tables 1 and 2). The largest study comprised 127 patients with only 45 thereof receiving radiotherapy; the majority of the remaining studies investigated cohorts of 10 to 30 patients only. These small patient numbers probably led to unreliable results and hampered the application of multivariable adjustment for confounders. Confounder adjustment is of essential importance to obtain valid effect estimates, as it was applied in our present study. Additionally, the multicenter design of our present study reduces center-induced bias, rendering the present study results superior to those emerging from the previously reported oligocentric or monocentric studies. However, the conclusions drawn by us require validation in RCTs. This is particularly true for the further investigation of sequencing and timing of radiotherapy, since the present study included patients with radiotherapy before ICI therapy only, herein excluding patients with radiotherapy concurrent to ICI.

Notably, different from other cancer entities, melanoma has been demonstrated to react to irradiation not only with unrestricted immune activation leading to beneficial abscopal tumor regressions but also with rapidly evolving resistance mechanisms. Thus, Twyman-Saint Victor and coworkers demonstrated that irradiation of melanoma metastases led to an upregulation of PD-L1 expression of tumor cells and to an increased exhaustion of tumor-infiltrating lymphocytes within these lesions, which both are mechanisms enabling the escape of tumor cells from immune recognition.[26]

ICI therapy of melanoma has recently been shown to exert high efficacy also in patients with brain metastases.[27 28] Our present study cohort comprised a relevant number of patients with brain metastases with or without radiotherapy prior to ICI, allowing us to perform separate analyses of this clinically highly relevant patient population using appropriate adjustment sets of confounders. We did not find a relevant impact of a preceding intracranial radiation on response and survival outcomes of ICI therapy. Moreover, subgroup analyses with regard to the type of preceding intracranial radiotherapy, in terms of conventional whole brain radiation compared with stereotactic radiation, revealed no relevant differences in ICI therapy outcome. However, the wide CIs resulting from our analysis suggest that a possible advantage of a preceding radiotherapy for this patient subgroup cannot be excluded.

Notably, the conclusions drawn from our study results are limited because of its observational nature. The groups of patients with and without previous radiotherapy compared by us differed markedly in their patient and treatment characteristics, which we tried to compensate by multivariate adjustment for confounders. Also, nearly half of the investigated patients who received a preceding radiotherapy had this radiation applied not immediately before start of ICI therapy, but earlier in stage IV disease with at least one intermittent treatment line. However, a comparison of both groups did not show a benefit in ICI treatment outcome for those patients who were irradiated immediately before ICI, but rather revealed that these patients had a poorer ICI therapy outcome. Additionally, it is apparent that the patient cohorts investigated by us are characterized by a shorter PFS and OS compared with survival rates from landmark clinical trials. This can mainly be explained by the inferior treatment outcomes in real-world patient populations compared with the highly selected populations investigated in RCTs.[29]

CONCLUSIONS

The results of the present study indicate no relevant impact of a preceding radiotherapy of metastatic lesions on the therapy outcome of anti-CTLA-4 or anti-PD-1 ICI in metastatic melanoma. Based on our data, the intended use of radiation as a sensitizer for ICI therapy of melanoma can currently not be recommended for routine clinical use. Instead, patients should be preferentially treated within prospective clinical trials adressing the question of synergistic beneficial effects of radiotherapy and ICI, either simultaneously or sequentially applied. There are various RCTs planned or already activated investigating this effect (for overview see Refs 15–17 and https://clinicaltrials.gov/). However, recruitment of patients into these trials is difficult, leading to a slow trial progress with results pending for a longer term. Until data from RCTs become available, the results of our present multicenter cohort study is the most valid information to guide clinicians toward the sequencing of radiotherapy and ICI in metastatic melanoma.

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