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Metastases-directed Radiotherapy in Addition to Standard Systemic Therapy in Patients with Oligometastatic Breast Cancer: Study protocol for a randomized controlled multi-national and multi-center clinical trial (OLIGOMA)



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ABSTRACT

Background: Several recent randomized therapeutic exploratory trials demonstrated improvement of progression-free survival and in some even overall survival using stereotactic body radiotherapy in patients with oligometastatic disease. However, only very few patients enrolled in these trials had breast cancer, and results from confirmatory trials are lacking.

Methods/design: The OLIGOMA-trial is a randomized controlled multi-national multi-center therapeutic confirmatory trial studying the role of local ablative radiotherapy as an additive treatment in patients with oligometastatic breast cancer receiving standard systemic therapy. Patients will be randomized 1:1 to standard systemic therapy according to national guidelines with or without radiotherapy to all metastatic sites. Randomization will be stratified according to type and line of systemic therapy, which has to be determined by a multidisciplinary tumor board before enrollment. Patients with up to five metastatic lesions are eligible, including patients with up to three brain metastases (only in case of extracranial disease) and with locoregional recurrence (only in case of additional metastatic lesions). In the standard arm, palliative radiotherapy to symptomatic metastases is permitted if at least one lesion remains untreated. The co-primary endpoints are progression-free survival and quality of life. The primary hypothesis is that progression-free survival in the experimental arm will be superior to the standard arm while simultaneously demonstrating non-inferiority of quality of life at 12 weeks after randomization. Secondary endpoints are feasibility, overall survival, toxicity, quality of life and patient satisfaction. A translational sub-study with collection of ctDNA will be conducted.

Discussion: The OLIGOMA-trial will provide high level evidence on the use of and benefit from local ablative radiotherapy for patients with oligometastatic breast cancer.

Trial registration: The OLIGOMA-trial is registered at clinicaltrials.gov under the identification NCT04495309. The related information was first posted on July 31st 2020.

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Introduction/Rationale

The concept of oligometastatic disease as a transitional state between locally confined disease and widespread metastatic disease was first defined by Hellman and Weichselbaum in the

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1990 s [1,2]. This was guided by the observation that there are patients with limited metastatic disease who achieve long lasting-remissions or even cure after local therapy of metastases (i.e. surgery, radiotherapy, radiofrequency ablation). Up to this point, there were two main competing hypotheses of breast cancer. In the late 19th century, William Halsted proposed that breast cancer spreads in an orderly fashion with serial involvement from the primary tumor to lymph nodes and distant organs. This led to the establishment of radical breast cancer surgery as a means of achieving long term cure. Based on experiments of tumor biology and metastatic spread, Fisher et al. established the alternative hypothesis (or systemic hypothesis) in the 1960 s. This hypothesis states that there is no orderly metastatic spread and that breast cancer is a systemic disease even in patients with early stage breast cancer (for review see [3]). The hypothesis by Hellman and Weichselbaum which defined the term “oligometastases” is also referred to as the spectrum hypothesis as it refers to breast cancer representing a spectrum of diseases ranging from diseases that remain local during the course of the disease to those that are characterized by early systemic spread [1–3]. Fig. 1.

There is no uniform definition of oligometastases, but most authors have defined this disease state as a maximum of 3–5 metastatic lesions (for review [4]). Recently, a consensus statement by the European Society of Radiotherapy and Oncology (ESTRO) and the American Society of Radiation Oncology (ASTRO) was published [4]. Here, the authors argue against the use of a threshold but instead recommend to determine the maximum number of metastases individually based on the possibility to safely deliver ablative radiotherapy to all lesions.

For prognostic purposes, additional clinical factors need to be considered, among them the disease-free interval since the last oncologic treatment, previous lines of treatment and response to these treatments, timing of metastatic disease (synchronous vs. metachronous), pattern of organ involvement, and histology. The ESTRO and the European Organisation for Research and Treatment of Cancer (EORTC) have recently developed the first systematic classification of oligometastatic disease [5].

In the past decade, there has been a rapidly increasing interest in oligometastatic disease due to advances in imaging and ablative treatment modalities. Prospective and retrospective studies have shown that approximately 50% of patients with metastatic breast cancer present with ≤ 2 metastatic sites [6]. Thus, there is consid-

erable potential in terms of eligibility for local ablative treatment strategies in patients with metastatic breast cancer.

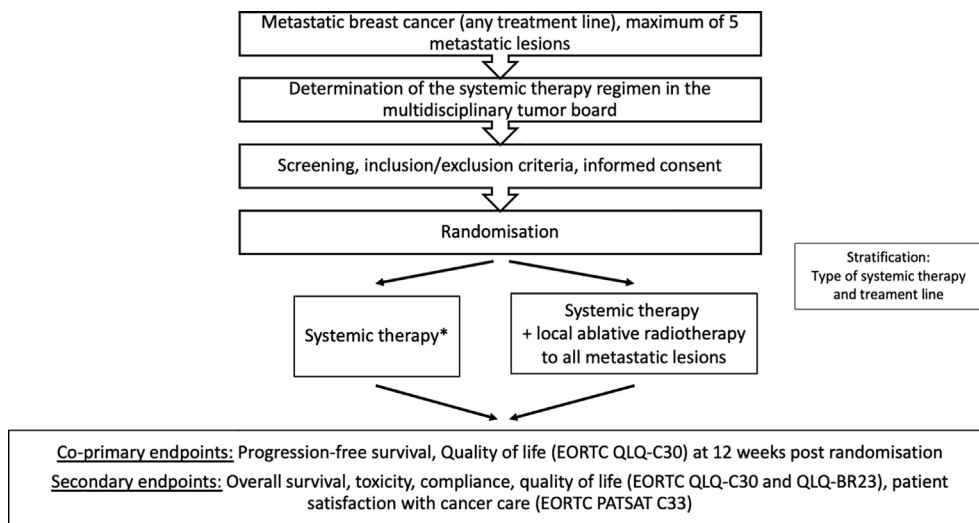
Numerous local ablative treatment modalities are available, among them surgery, radiofrequency ablation, irreversible electroporation, microwave ablation, and radiotherapy.

Stereotactic radiosurgery (SRS) has been used for intracranial tumors since the 1950 s and represents the standard of care for patients with limited brain metastases. While the available randomized controlled trials comparing SRS alone to SRS plus whole-brain irradiation for brain metastases have included patients with up to 4 brain metastases [7–10], prospective data on patients treated with SRS for up to 10 brain metastases have been published [11].

Stereotactic body radiotherapy (SBRT) was first introduced in the clinic in the 1990 s and has been extensively studied in patients with pulmonary, osseous and hepatic metastases. Several prospective and retrospective studies have analyzed the outcome of patients with oligometastatic disease treated with SBRT (for review see [12,13]) and have shown promising local control and low rates of grade ≥ 2 adverse events.

The SABR-COMET trial was the first randomized controlled trial of SBRT in patients with oligometastatic disease [14]. Patients were eligible if they had up to 5 metastatic lesions with a good performance status (ECOG 0-1) and a life expectancy > 6 months. 99 patients were randomized 2:1 to SBRT or palliative standard of care. The overwhelming majority (92%) of patients had 1–3 metastatic lesions and 18% suffered from metastatic breast cancer. Progression-free survival (PFS) was 12 months in patients treated with SBRT and 6 months in patients treated with palliative care alone (p = 0.001). There was an improvement in median overall survival (OS) in patients treated with SBRT (41 months vs. 28 months; p = 0.09) that was statistically significant at the pre-defined level of 0.2. Grade ≥ 2 adverse events occurred significantly more often in the SBRT-arm (30% vs. 9%; p = 0.022). There were 3 grade 5-events in the SBRT-arm. Long term results were recently published and confirmed the OS-benefit without additional safety concerns [15].

Furthermore, two randomized controlled trials have shown a significant improvement in PFS [16,17] and one also in OS [18] with local ablative therapy to all metastatic sites in patients with de novo oligometastatic non-small cell lung cancer who had stable disease or partial response after first-line systemic therapy.



*Palliative radiotherapy to symptomatic metastases is allowed, however patients requiring palliative radiotherapy to all metastases are not eligible.

Fig. 1. Workflow for the OLIGOMA trial.

For prostate cancer patients, two randomized controlled phase II-trials demonstrated improvements in PFS or androgen-deprivation therapy-free survival with metastasis-directed treatment, however, both trials were small and did not use an active comparator [19,20].

There are only few studies specifically addressing the outcome of patients with oligometastatic breast cancer (for review see [6,21,22]).

Several retrospective and prospective reports of SBRT in patients with oligometastatic disease have suggested that patients with breast cancer have a favorable prognosis compared to other tumor types and achieve higher rates of local and distant control [23–27].

There are several small, single arm prospective trials of SBRT in patients with oligometastatic breast cancer (Table 1).

Milano et al. conducted a prospective trial of SBRT in patients with up to 5 metastatic sites, including 40 patients with 85 lesions from breast cancer treated with curative intent [28]. The most common fractionation regimen was 10x5 Gy to the 80%-isodose. >70% of breast cancer patients had 1–2 metastatic lesions, with involvement of the liver, lung or bone. Overall, the 4-year local control, PFS and OS were 80%, 38% and 59%, respectively. Milano et al. recently published an updated analysis of breast cancer patients from different prospective trials [29]. They demonstrated that patients with bone-only oligometastases had a significantly better overall survival and freedom from widespread metastatic disease on multivariate analysis. Patients with bone-only oligometastases had a 10-year OS of 75%.

From 2010 to 2014, Scorsetti et al. enrolled 33 patients with 47 lung or liver metastases who were treated with 48–75 Gy in 3–4 fractions [30]. At 2 years, local control, PFS and OS were 90%, 27% and 66%, respectively. No acute or chronic toxicity ≥ grade 2 were observed.

Trovo et al. conducted a single-arm trial of patients with up to 5 extracranial metastases on FDG-PET/CT and a controlled primary tumor [31]. 54 patients with 92 lesions were treated with SBRT consisting of 30–45 Gy in 3 fractions or intensity-modulated radiotherapy consisting of 60 Gy in 25 fractions. 50% of patients had only one metastatic lesion, 74% had synchronous metastatic disease and 60 and 23 lesions were bone and lymph node metastases, respectively. 89% of patients received concomitant systemic therapy. After a median follow-up of 30 months, 2-year PFS and local control were 53% and 95%, respectively. Neither number of metastatic lesions, nor pattern or timing of metastatic disease were significantly associated with PFS. There was no grade ≥ 3-toxicity.

A prospective trial enrolling patients with bone-only oligometastatic disease was recently published by David [32]. All patients received a sodium fluoride positron emission tomography and

were treated with a single fraction of 20 Gy to the 80%-isodose. 15 patients with 19 metastases were enrolled. 73% of patients had luminal breast cancer. At two years, no local progression or death from any cause had been observed. PFS was 65% at two years. There was no grade ≥ 3-toxicity.

In summary, local control rates of ≥ 90% can be achieved with SBRT in patients with oligometastatic breast cancer with PFS at 2 years ranging between 27% and 65%.

Notwithstanding these excellent results, the value of local therapy in oligometastatic disease has been questioned due to the efficacy of systemic therapy for most breast cancer subtypes.

Key differences between the OLIGOMA trial and three other ongoing randomized controlled trials are listed in Table 2.

The OLIGOMA-trial is the only trial enrolling patients with locoregional recurrence and patients with brain metastases. However, enrolment in both situations will only be possible in the case of concurrent extracranial metastatic disease. While most other trials exclusively treat patients with de novo oligometastatic disease, OLIGOMA will enroll patients from all treatment lines. Since radiotherapy is currently the only local treatment modality with consistent improvement in PFS, and in some cases OS, in clinical trials of patients with oligometastatic disease of different primaries [14–20], it was chosen as the only local treatment modality for the OLIGOMA-trial. Surgery of large brain metastases or spine metastases with postoperative radiotherapy is allowed in selected cases.

The response to prior systemic therapy is not an inclusion criterion. Thus, patients with oligoprogression or patients with oligopersistence may be enrolled. Patients with de novo oligometastatic breast cancer are eligible, however, it is recommended to complete treatment of the primary tumor before enrollment. While one might argue that including patients with various courses of disease is problematic [42] and these different presentations certainly have a prognostic impact [43,44], we believe that it is important to gather clinical data across all situations. Disease state according to the ESTRO/EORTC-classification of oligometastatic disease [5] will be collected, and randomization is stratified for line and type of systemic treatment. Systemic therapy has to be specified by a multidisciplinary tumor board prior to enrollment, thus reducing the risk of bias related to different intensity of systemic therapy between the trial arms. While normofractionated and moderately hypofractionated regimens are allowed in the case of large metastases or proximity to critical organs at risk, there is a clear preference for using hypofractionated regimens as SRS/SBRT with single doses > 5 Gy.

Since cross-over is allowed after progression, we believe that an improvement in OS is not realistic and PFS was hence chosen as the primary endpoint. OS will be reported as a secondary endpoint. However, we chose to include quality of life at 12 weeks after ran-

Table 1
Prospective trials of stereotactic body radiotherapy for patients with oligometastatic breast cancer.

	Patient number	Inclusion criteria	Dose and fractionation	Follow up	Local control	PFS	OS
Milano 2008	40 pat./85 met.	<ul style="list-style-type: none"> • ≤ 5 met. • KI ≤ 70% 	10x5 Gy @ 80%-isodose	median 50 months (survivors)	4 y 89%	2 y 44% / 4 y 38%	2 y 76% / 4 y 59%
Scorsetti 2016	33 pat./47 met.	<ul style="list-style-type: none"> • ≤ 5 met. (only lung/liver lesions) • ECOG-PS ≤ 2 	3x19-25 Gy @ 95%-isodose, 4x12 Gy @ 95%-isodose	median 24 months	2 y 90%	2 y 27%	2 y 66%
Trovo 2018	54 pat./92 met.	<ul style="list-style-type: none"> • ≤ 5 met. • ECOG-PS < 2 • FDG-PET/CT 	3x10-15 Gy, 25x2.4 (IMRT)	median 30 months	2 y 97%	2 y 53%	2 y 95%
David 2019	15 pat. / 19 met.	<ul style="list-style-type: none"> • 1–3 bone met. • ECOG-PS < 2 • NaF-PET/CT 	1x20 Gy @ 80%-isodose	minimum 24 months	2 y 100%	2 y 65%	2 y 100%

PFS = progression-free survival; OS = overall survival; KI = Karnofsky index, Gy = Gray; ECOG-PS = Eastern Cooperative Oncology Group-Performance Score; NaF = Sodium fluoride; y = year

Table 2
Randomized controlled trials of local treatment in patients with oligometastatic breast cancer.

	OLIGOMA (NCT04495309)	NRG-BR002 (NCT02364557)	Fudan University (NCT04413409)	STEREO-SEIN (NCT02089100)	Chinese Academy of Sciences (NCT04646564)
Primary tumor	Locoregional recurrence allowed as target lesion*	Controlled	Local recurrence not allowed	Treated with curative intent	Controlled
Brain metastases	Allowed**	Not allowed	Not allowed	Not allowed	Not allowed
Maximum number of metastatic lesions	5 (any number of involved organs)	2	3 (only lung or liver metastases, < 5 cm)	5 (≤10 cm / ≤ 50 ml)	5 (≤5 cm)
Setting	Any line, any tumor biology	First line palliative therapy, ≤ 365 days after diagnosis of metastatic breast cancer, any tumor biology	First line metastatic setting, any tumor biology	First line metastatic setting, hormone-receptor positive	Metachronous recurrence > 3 months after surgery, any tumor biology
Type of local therapy	Radiotherapy	Radiotherapy or surgery	Surgery	Radiotherapy	Radiotherapy
Primary endpoint	PFS	PFS/OS	OS	PFS	PFS
Primary hypothesis	Median PFS 12 months → 16 months (HR 0.75)	Phase IIR: Median PFS 10.5 months → 19 months (HR 0.55) Phase III: 5-year OS 28% →42.5% (HR 0.67)	n.s.	n.s.	n.s.
Sample size	564 patients	Phase IIR: 146 patients Phase III: 256 patients	172 patients	280 patients	170 patients

PFS = progression-free survival, OS = overall survival, HR = hazard ratio, n.s. = not stated.

* Enrollment is only possible in case of additional metastatic sites.

** Only patients with 1–3 asymptomatic brain metastases and extracranial disease activity are eligible.

domization as a co-primary endpoint. The goal is to show that local ablative radiotherapy improves PFS without a detrimental effect on quality of life.

Design

The OLIGOMA trial (NCT04495309) is a randomized controlled multi-national multi-center therapeutic confirmatory-trial studying the role of local ablative radiotherapy as an additive treatment in patients with oligometastatic breast cancer. Patients will be recruited at 50 sites in Germany and Austria. Inclusion and exclusion criteria are shown in Table 3. Patients will be randomized 1:1 to systemic therapy either with or without ablative radiotherapy. Systemic therapy is administered according to national guidelines [33,34] and will be determined before enrollment by a multidisciplinary tumor board.

Central randomization (permuted blocks of variable length) will be stratified according to systemic therapy and line of treatment

(first-line endocrine therapy vs. ≥ second-line endocrine therapy vs. first-line chemotherapy +/- HER2-targeted therapy vs. ≥ second line chemotherapy +/- HER2-targeted therapy). Endocrine-based therapy with CDK4/6-inhibitors or mTOR-inhibitors will be considered as endocrine therapy for this purpose.

Assessment with a CT of chest and abdomen (contrast-enhanced MRI or ultrasonography of the abdomen is also allowed), mammography (within the last 6 months) and a bone scintigraphy are required for enrollment. Staging with FDG-PET/CT is optional. MRI of the brain is only recommended in patients with clinical suspicion of brain metastases.

Treatment description

Ablative radiotherapy should preferentially be administered as SRS or SBRT, if technically feasible. Typical dose and fractionation regimens are listed in Table 4. For brain metastases, SRS is recommended, although fractionated stereotactic radiotherapy may be

Table 3
Inclusion and exclusion criteria.

Inclusion criteria:
<ul style="list-style-type: none"> • Metastatic breast cancer • Up to 5 metastatic lesions during the course of disease (locoregional lymph node metastases or local recurrence will be treated as a metastatic lesion), including up to three brain metastases. Histologic confirmation of metastases is not required. • Indication for palliative systemic therapy given according to guidelines (endocrine therapy, chemotherapy, targeted therapy, immunotherapy etc. without a preference for any specific regimen) • ECOG performance status ≤ 2 • Feasibility of local radiotherapy to all metastatic sites • Written informed consent • Patient age ≥ 18 years
Exclusion criteria
<ul style="list-style-type: none"> • Previous radiotherapy compromising local radiotherapy to any of the metastatic sites • Symptomatic metastases that require palliative radiotherapy to all metastatic sites (palliative treatment of symptomatic metastases is not an exclusion criterion, however there has to be at least one evaluable lesion without an indication for immediate local treatment) • More than three brain metastases (indication for whole-brain radiotherapy according to national guidelines) or brain as the only metastatic site • Regional nodal recurrence as the only metastatic site • Multiple metastases in one organ with a high likelihood of violation of organ dose constraints • Relevant comorbidity, if this results in restrictions for further treatment • Patient's inability to understand or comply with the trial procedures • Pregnancy or lactation

Table 4
Recommended dose and fractionation regimens.

Number of fractions	Preferred dose	Accepted dose	Protocol violation
1	20–27 Gy	16–19 Gy / 28–30 Gy	<16 Gy or > 30 Gy
3	30–42 Gy	24–29 Gy / 43–45 Gy	<24 Gy or > 45 Gy
5	35–50 Gy	30–34 Gy / 51–55 Gy	<30 Gy or > 55 Gy
10	45–60 Gy	35–44 Gy / 61–65 Gy	<35 Gy or > 65 Gy
15	45 Gy	37.5–75 Gy	<37.5 Gy or > 75 Gy
25	50 Gy	45–75 Gy	<45 or > 75 Gy

used for larger lesions or for lesions with close proximity to organs at risk. SBRT in 3–5 fractions is the recommended regimen for bone, lung and liver metastases. If SBRT is not feasible due to the size of the lesion or proximity to organs at risk, hypo- or normofractionated intensity-modulated or 3D-conformal radiotherapy is allowed. The minimal total dose should be 45 Gy administered in 25 fractions over 5 weeks. Surgery of large brain metastases or spine metastases with postoperative radiotherapy is allowed in selected cases.

Regarding SRS/SBRT, dose will be prescribed to the 60–80% isodose encompassing the planning target volume (PTV), with at least 98% of the PTV receiving the prescription dose (PTV $D_{98\%}$). For intensity-modulated radiotherapy (IMRT) and 3D-conformal radiotherapy (3D-CRT), dose will be prescribed to the PTV $D_{50\%}$. The use of a simultaneous integrated boost is allowed.

The margin from gross tumor volume (GTV) to the clinical target volume (CTV) should be kept to a clinically acceptable minimum. Larger CTV-margins of up to 5 mm may be used if clinically necessary. The CTV-to-PTV margin should be chosen according to the technique, immobilization as well as image guidance and motion management strategies. The CTV-to-PTV margin should be no > 1–2 mm for intracranial targets. For target volume delineation of brain, liver and bone metastases, an additional MRI should be performed.

4D-planning CT should be performed for pulmonary and hepatic metastases and the use of motion compensation techniques such as gating or tracking is highly recommended for targets in the lower lung or liver.

Radiotherapy should be started as early as possible after enrollment, usually within 2–4 weeks after initiation of endocrine therapy or after the first or second chemotherapy cycle. Usually, no > 3 metastatic lesions should be treated simultaneously. SRS or SBRT with a fraction dose ≥ 5 Gy should not be administered on the same day as chemotherapy. Radiotherapy has to be started within 4–6 weeks after randomization.

The indication for systemic therapy as well as the specific regimen have to be determined by a multidisciplinary tumor board according to national guidelines [33,34] before enrollment. Systemic therapy may include endocrine therapy, chemotherapy, targeted therapy or immunotherapy without preference for any specific regimen. Delay of systemic therapy due to radiotherapy should be avoided.

Follow-up assessments will be conducted according to national guidelines [33,34]. They will take place every 12 weeks and include a brief medical history with physical examination, imaging with CT or MRI (same diagnostic tool as at enrollment), assessment of toxicity using Common Terminology Criteria For Adverse Effects, version 5.0 [35], ECOG performance status and quality of life with the EORTC QLQ-C30 [36] and BR23 [37] questionnaires. At 12 weeks and starting from week 60, Radiation Therapy and Oncology Group-classification [38] is used to assess late toxicity. At 12 and 36 weeks after randomization, patient satisfaction with cancer care will be evaluated using the EORTC PAT-SAT C33 questionnaire [39].

When patients have disease progression, the use of ablative radiotherapy to new or progressive metastases is allowed in both arms. The use of radiotherapy and further systemic therapy after progression will be documented.

Endpoints

There are two co-primary endpoints, PFS during 1–4 years and quality of life at 12 weeks after randomization. The hypothesis is that the experimental arm is superior in terms of PFS and non-inferior in terms of quality of life 12 weeks after randomization.

Progression will be determined according to RECIST 1.1 [40]. The primary assessment will be performed by the local investigator at the treating site. In case of suspected progression, the trial leadership should be contacted. Regular virtual study meetings will be conducted to discuss exemplary cases. Central radiology assessment of all events of progression with final assessment of the primary endpoint is planned. Observations will be considered censored at the last visit with sufficient examinations and imaging to assess progression, if two or more visits in a row are missed, regardless of negative findings later that will be used for secondary analyses. If later examinations show a progression, its date is set at six weeks into the hiatus of follow-ups and at the day of imaging otherwise.

Quality of life at 12 weeks after randomization (at least two weeks after the end of radiotherapy) will be assessed using the sum score of the EORTC QLQ-C30 [41].

The two co-primary hypotheses will be tested at multiple significance level 5% in a Bonferroni-Holm procedure while adjusting for the stratification used in randomization.

Secondary endpoints are feasibility (proportion of patients treated per protocol), toxicity (CTCAE/RTOG), quality of life using the EORTC QLQ-C30 and QLQ-BR23 throughout the course of the trial and patient satisfaction with cancer care using the EORTC PATSAT C33.

A translational sub-study will evaluate the prognostic and predictive value of circulating tumor DNA, which will be collected at randomization and 12 weeks as well as 36 weeks after randomization.

Statistics

Estimated PFS in the control arm is 12 months based on published literature for metastatic breast cancer (a list of publications used for PFS estimation can be found in Supplementary Material 1). The trial is designed to show an improvement in PFS from 12 to 16 months with a hazard ratio of 0.75 at a two-sided significance level of 0.05 with power of 0.8. This requires a total number of 380 PFS-events.

We assumed that the difference in the quality of life sum score between treatment arms is 5 points and that the standard deviation of the sum score of all patients is 20 points. The non-inferiority margin (the minimal clinically relevant difference) is defined as 10 points in the sum score of the EORTC QLQ-C30. 508 evaluations are needed to show non-inferiority with a one-sided level of 0.025 with power of 0.8.

Assuming a dropout rate of 5%, a censoring rate of 5% per year for PFS and a dropout rate of 10% for quality of life, 564 patients need to be randomized.

All statistical analyses will be described in detail in the statistical analysis plan which will be finalized before the randomization of the last patient. Reporting and visualization comply with the CONSORT guidelines.

The primary analysis will be performed on the full analysis set based on the intention to treat principle. The per protocol popula-

tion will consist of patients treated according to treatment protocol. For safety purposes, patients will be analyzed as treated and being irradiated at least once. No interim analysis is planned.

Explorative subgroup analyses are planned for number of metastatic lesions (1 vs. 2–3 vs. 4–5), number and type of involved organs (lung, liver, bone, brain, others; 1 vs. 2 vs. 3 or more), systemic therapy and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1–2).

Planned timeline

The estimated duration of recruitment is 36 months. Minimum follow-up will be 12 months. The estimated end of study will be 2024. A preliminary discontinuation of the trial is possible in case of unforeseen toxicity, insufficient recruitment or if new scientific data show that the study hypothesis is invalid.

Ethical and legal considerations

The study protocol was approved by the DEGRO-expert commission and the leading institutional review board at the University of Kiel (ID D500/20). Approval by the respective institutional review board relevant to each site will be collected before opening new sites. Written informed consent will be obtained by each participant. The study is monitored by ZKS Lübeck. The trial is supported by the Arbeitsgemeinschaft Radiologische Onkologie.

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Author contributions

David Krug: Conceptualization, Writing - Initial draft, Writing - review & editing. **Reinhard Vonthein:** Conceptualization, Methodology, Writing - review & editing. **Alicia Illen:** Conceptualization, Project administration, Writing - review & editing. **Denise Olbrich:** Conceptualization, Project administration, Writing - review & editing. **Jörg Barkhausen:** Writing - review & editing. **Julia Richter:** Writing - review & editing. **Wolfram Klapper:** Writing - review & editing. **Claudia Schmalz:** Writing - review & editing. **Achim Rody:** Writing - review & editing. **Nicolai Maass:** Writing - review & editing. **Dirk Bauerschlag:** Conceptualization, Writing - review & editing. **Nicole Heßler:** Methodology, Writing - review & editing. **Inke R.König:** Conceptualization, Methodology, Writing - review & editing. **Kathrin Dellas:** Conceptualization, Funding acquisition, Writing - review & editing. **Jürgen Dunst:** Conceptualization, Funding acquisition, Writing - Initial draft, Writing - review & editing.

Declaration of Competing Interest

DK has received honoraria from Merck Sharp & Dome outside the submitted work. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2021.03.012>.

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