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
In the late 19th century, William Halsted proposed that breast cancer spreads in an orderly fashion 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 1960s. 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].

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 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. 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 considerable 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 1950s 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 1990s 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 predefined 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.

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**Fig. 1.** Workflow for the OLIGOMA trial.

- Metastatic breast cancer (any treatment line), maximum of 5 metastatic lesions
- Determination of the systemic therapy regimen in the multidisciplinary tumor board
- Screening, inclusion/exclusion criteria, informed consent
- Randomisation
- Systemic therapy
- Systemic therapy + local ablative radiotherapy to all metastatic lesions
- Co-primary endpoints: Progression-free survival, Quality of life (EORTC QLQ-C30) at 12 weeks post randomisation
- Secondary endpoints: Overall survival, toxicity, compliance, quality of life (EORTC QLQ-C30 and QLQ-BR23), patient satisfaction with cancer care (EORTC PATSAT C33)

*pPalliative radiotherapy to symptomatic metastases is allowed, however patients requiring palliative radiotherapy to all metastases are not eligible.*
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 oligoresistance 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    | ≤ 5 met.          | 10x5 Gy @ 80%-isodose  | median 50 months | 4 y 89% | 2 y 44% | 2 y 76% |
| Scorsetti 2016 | ≤ 5 met.           | 3x19-25 Gy @ 95%-isodose, 4x12 Gy @ 95%-isodose | median 24 months | 2 y 90% | 2 y 38% | 2 y 59% |
| Trovo 2018     | ≤ 5 met.  | 3x10-15 Gy, 25x2.4 (IMRT) | median 30 months | 2 y 97% | 2 y 53% | 2 y 95% |
| David 2019     | ≤ 1–3 bone met.   | 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
Randomized controlled trials of local treatment in patients with oligometastatic breast cancer.

**Inclusion criteria:**

- **Primary tumor**
  - Locoregional recurrence allowed as target lesion* Allowed**
- **Brain metastases**
  - 5 (any number of involved organs)
- **Maximum number of metastatic lesions**
  - 5 (any number of involved organs)
- **Setting**
  - Any line, any tumor biology
- **Type of local therapy**
  - Radiotherapy
- **Primary endpoint**
  - PFS
- **Primary hypothesis**
  - Median PFS 12 months → 16 months (HR 0.75)
- **Sample size**
  - 564 patients

**Exclusion criteria:**

- **Patient age**
  - 18 years
- **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**
- **Patient’s inability to understand or comply with the trial procedures**
- **Pregnancy or lactation**

**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...
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 D98%). For intensity-modulated radiotherapy (IMRT) and 3D-conformal radiotherapy (3D-CRT), dose will be prescribed to the PTV D95.

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 regimens 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 PAT-SAT 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. **Denise Oblich:** Conceptualization, Project administration, Writing - review & editing. **Julia Richter:** Writing - review & editing. **Claudia Schmalz:** Writing - review & editing. **Achim Rödy:** Writing - review & editing. **Nicolai Maass:** Writing - review & editing. **Dirk Bauerschlag:** Conceptualization, Writing - review & editing. **Nicole Heßler:** 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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