Clinical & Experimental Metastasis (2024) 41:863–875
https://doi.org/10.1007/s10585-024-10312-3

REVIEW

Local treatment for oligoprogressive metastatic sites of breast cancer: efficacy, toxicities and future perspectives

Filippo Merloni[1] · Michela Palleschi[1] · Caterina Gianni[1] · Marianna Sirico[1] · Riccardo Serra[1] · Chiara Casadei[1] · Samanta Sarti[1] · Lorenzo Cecconetto[1] · Giandomenico Di Menna[1] · Marita Mariotti[1] · Roberta Maltoni[1] · Daniela Montanari[1] · Antonino Romeo[2] · Ugo De Giorgi[1]

Received: 9 July 2024 / Accepted: 8 September 2024 / Published online: 23 September 2024

Abstract

Metastatic breast cancer (MBC) is still an incurable disease, which eventually develops resistance mechanisms against systemic therapies. While most patients experience widespread disease progression during systemic treatment (ST), in some cases, progression may occur at a limited number of metastatic sites. Evidence from other malignancies suggests that local treatment with stereotactic ablative radiotherapy (SABR) of oligoprogressive disease (OPD) may allow effective disease control without the need to modify ST. Available evidence regarding local treatment of oligoprogressive breast cancer is limited, mostly consisting of retrospective studies. The only randomized data come from the randomized CURB trial, which enrolled patients with oligoprogressive disease, including both small cell lung cancer and breast cancer patients, and did not show a survival benefit from local treatment in the latter group. However, local treatment of oligoprogressive MBC is still considered in clinical practice, especially to delay the switch to more toxic STs. This review aims to identify patients who may benefit from this approach based on the current available knowledge, focusing also on the potential risks associated with the combination of radiotherapy (RT) and ST, as well as on possible future scenarios.

Keywords Breast cancer · Oligoprogressive · Local treatment · Radiotherapy · Toxicities

Abbreviations

MBC	Metastatic breast cancer
ST	Systemic treatment
OPD	Oligoprogressive disease
OMD	Oligometastatic disease
SBRT	Stereotactic body radiotherapy
SABR	Stereotactic ablative radiotherapy
RT	Radiotherapy
PET	Positron emission tomography
FES	Fluoroestradiol
ER	Estrogen receptor
HR	Hormone receptor
TKI	Tyrosine-kinase inhibitors
NSCLC	Non-small cell lung cancer
PFS	Progression free survival
OS	Overall survival
TTST	Time to subsequent therapy
SOC	Standard of care
HER-2	Human epidermal growth factor receptor 2 (HER2)
NEST	Time to delay the next systemic therapy
tPMC	Time to polymetastatic conversion
CDK4/6i	Cyclin-dependent kinase 4 and 6 inhibitors
SRS	Stereotactic radiosurgery
ADC	Antibody-drug conjugate
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand-1
PARPi	Poly (ADP-ribose) polymerase inhibitors
ctDNA	Circulating tumor DNA
CTCs	Circulating tumor cells
WB-MRI	Whole-body magnetic resonance imaging

✉ Filippo Merloni
filippo.merloni@irst.emr.it

[1] Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Via P.Maroncelli 40, 47014 Meldola, Italy

[2] Radiotherapy Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Via P.Maroncelli 40, 47014 Meldola, Italy

Introduction

Metastatic breast cancer (MBC) patients constitute a heterogeneous population, with great variability of disease presentation and prognosis. The majority of patients with MBC will face widespread disease progression, while a lower percentage of them will experience oligoprogression [1]. Oligoprogressive disease (OPD) is a relatively recent clinical concept characterized by disease progression limited to a few specific sites during systemic treatment (ST). OPD must be differentiated from oligometastatic disease (OMD), an intermediate state between localized and widespread disease. The latter one denotes a metastatic disease empirically constrained to a maximum of five sites, which can occur synchronously or metachronously to the primary tumor. In this context, Guckenberger et al. have proposed a classification of OMD that can elucidate the relationship between these two entities [2]. Occasionally, OPD may represent a subset of OMD, as seen in patients developing oligometastatic disease during active ST; at the same time patients with OMD could experience oligoprogression. OPD and OMD are different entities, but they can co-exist. While OMD may represent an "earlier" state of metastatic disease associated with a better prognosis, oligoprogression is a manifestation of the development of resistance mechanisms to ST and, consequently, may imply greater aggressiveness [3]. Some retrospective studies include both BC patients with OMD and OPD treated with stereotactic body radiotherapy (SBRT). Only two of these studies have separately analyzed these two groups, revealing thatpatients with OMD experience better local control and improved progression-free survival (PFS), as additional confirmation of the higher biological aggressiveness of OPD and the diversity between these two entities [4]. However, also in the OPD scenario, local ablative therapy, such as SBRT targeted at progressing metastases, could eradicate the cellular clones that have developed resistance to ST. This may prevent widespread disease progression and extend the therapeutic efficacy of the ongoing ST [3]. Furthermore, certain mechanisms of resistance, such as the emergence of an ESR1 mutation or the selection of a clone with a different phenotype, could be countered with specific therapies [5, 6]. Non-small cell lung cancer (NSCLC), and to a lesser extent, prostate carcinoma, and renal cell carcinoma, are the malignancies with the most data regarding the local ablative treatment of oligoprogression [3, 7–12]. These studies demonstrate that the treatment of OPD can be an effective strategy, especially in patients who received a limited number of therapeutic lines for metastatic disease, with oligoprogression during tyrosine-kinase inhibitors (TKI) therapy and without visceral metastases. Furthermore, in retrospective studies on NSCLC, prolonged disease control during ST before oligoprogression and ablative local treatment, constitute a positive prognostic factor [3, 13, 14]. However, prospective data are limited and heterogeneous and the appropriate therapeutic approach to OPD is not established yet. This is particularly evident in the BC context, where the lack of consistent data makes the management of OPD extremely challenging [15]. In this review, we will discuss the available data regarding the locally ablative treatment of oligoprogression in patients with BC, its implications in current clinical practice, and potential future perspectives that could shed light on this topic.

Oligoprogression definition

Typically, OPD is defined by progression at four or fewer sites, although some studies include up to five lesions [16]. However, this definition is empirical and involves several critical issues. First of all, it is important to consider that the RECIST criteria v1.1, which represent the standard methodology for interpreting the response to oncological treatments, are not suitable for assessing oligoprogression and could interpret it as stability or even partial response of the disease [3, 17]. Additionally, the RECIST criteria do not allow for an adequate assessment of patients with predominantly sclerotic bone disease. Bone is the most common metastatic site in patients with breast cancer, especially in HR-positive disease [18, 19]. Although bone lesions are generally lytic at diagnosis, the use of ST and bone target therapy can convert them into sclerotic ones [20, 21].

Advanced imaging modalities that allow for both functional and morphological assessment could represent one solution to this problem. In this regard, 18 F-fluoride Positron Emission Tomography (PET/CT) could enable a more accurate and timely identification of oligoprogression [22, 23]. PET/CT can also be used in combination with more innovative tracers, such as 18-fluoro-16-alpha-fluoroestradiol (FES), which has demonstrated high diagnostic accuracy in detecting metastases from estrogen receptor (ER)-positive breast cancer [24, 25]. In a prospective study, the 18 F-FES uptake of biopsied lesions was correlated with the immunohistochemical expression of the ER, showing a sensitivity and specificity of 91% and 69%, respectively [26]. Thus, 18 F-FES PET/CT could also represent an alternative to tissue biopsy for determining ER status. An ongoing study is currently evaluating the use of FES-PET/CT specifically in patients with oligoprogressive ER-positive breast cancer [27]. Whole-body Magnetic Resonance Imaging (WB-MRI) is a radiological technique that has the potential to identify additional metastatic sites (especially bone metastases) compared to standard imaging methods. In a retrospective study analyzing 101 breast cancer patients,

WB-MRI revealed additional disease sites compared to Chest, Abdomen, and Pelvis Computed Tomography (CT-CAP) in 53.3% of cases. Moreover, in 18.9% of cases, WB-MRI detected disease progression during ST, while CT-CAP showed stability [86]. Of note, WB-MRI's ability to detect disease progression before standard imaging methods seems higher in cases of BC with lobular histology [87].

Since the mechanisms of drug resistance underlying disease progression include the emergence of mutations (such as the ESR1 mutation) and the selection of clones with different genotype and phenotype [28, 29], the definition of OPD cannot overlook biological data. The use of circulating tumor DNA (ctDNA) allows the determination of the tumor mutational profile and the onset of resistance mutations, potentially impacting treatment management. The PADA-1 study, which enrolled patients with metastatic hormone receptor (HR)-positive HER2-negative BC on first-line treatment with an aromatase inhibitor and cyclin-dependent kinase 4 and 6 inhibitors (CDK 4/6i), demonstrated that an early switch from the aromatase inhibitor to fulvestrant in case of ESR1 mutation emergence can provide a significant PFS benefit [30]. On the other hand, circulating tumor cells (CTCs) determination allows for the detection of molecular subtype conversion (evaluating HR and HER2 expression), enabling targeted adjustments to ST [31]. Furthermore, the determination of CTCs [32–34] and ctDNA biomarkers could help distinguish between a disease in real oligoprogression from a situation where few progressive lesions underlie a diffuse microscopic progression. The assessment of ctDNA allows for the identification of disease progression even if not radiologically visible. A relatively recent study highlighted how continuing the same ST in case of ctDNA progression often leads to rapid clinical-radiological progression [35]. However, liquid biopsy is not yet a clinical practice tool. In this scenario, tissue biopsy (a more invasive technique) of one site of oligoprogression, can be used in daily practice to verify a potential conversion of the tumor phenotype. If the site of oligoprogression is singular, surgical intervention could also be considered. This approach would allow both the determination of the tumor phenotype and the local treatment of oligoprogression.

Local treatment of oligoprogression: is it worth?

The rationale for local treatment of metastatic lesions in the context of OPD is to eliminate resistant cellular clones that have developed during ST. This can be achieved through either surgery or radiotherapy. There is some data on the surgical treatment of metastases in BC, but it mainly pertains to OMD rather than OPD disease [36]. Surgical treatment is an invasive approach, but it allows histological and immunophenotypic reassessment of the lesions. However, there has been increasing interest in SBRT for metastatic sites both in OMD and OPD.

SBRT is a technique that allows the delivery of high radiation doses to small-volume lesions while minimizing the exposure of healthy tissues. Higher doses per fraction can lead to indirect cell death due to ischemia, unlike traditional radiotherapy. SBRT is administered in small number of sessions compared to traditional therapy, but doses and number of sessions can vary based on the metastatic site and the histological characteristics of the underlying disease (radio-resistant tumors require a higher dose per fraction) [37]. Studies focused on oligoprogressive BC reported SBRT doses ranging from 24 to 60 Gy in 1 to 10 fractions (Table 1) depending on the site and size of the metastasis, with overall good tolerance [15]. SBRT in OPD is generally preferred over surgery, both in clinical practice and clinical trials, as it allows non-invasive local disease control.

SBRT can be delivered using various techniques, including intensity-modulated radiation therapy, which allows the modulation of the radiation beam, enabling the irradiation of tumors with complex and irregular shapes near sensitive organs; CyberKnife, a robotic system that uses robotic arms to deliver radiation from numerous angles; the Gamma Knife, which uses multiple gamma radiation beams and is specifically designed for the treatment of brain lesions; and stereotactic proton therapy, a technique that uses protons instead of conventional photons to deliver the dose [38].

Prospective evidence

The first prospective randomized evidence regarding the local treatment of OPD in patients with mBC is provided by the recently published results of the CURB study (Table 1). This phase II study randomized patients with mBC or metastatic NSCLC experiencing oligoprogression, between the standard of care plus SBRT at the sites of oligoprogression and standard of care (SOC) alone. The primary endpoint of the study was progression-free survival (PFS). Out of the 106 randomized patients, 47 had BC. The median PFS was longer in the SBRT-treated group compared to the SOC alone group (7.2 months vs. 3.2 months, HR 0.53, p 0.0035). However, analyzing only BC patients, no difference was observed between the two treatment groups (4.4 months vs. 4.2 months, HR 0.78, $p = 0.43$). The time to initiation of a new therapy was also longer in patients with NSCLC compared to those with BC (11.0 months vs. 3.9 months). However, no benefit in overall survival (OS) was observed in either the entire cohort or in the different subgroups. This study has several limitations that prevent definitive conclusions. Firstly, the BC patient sample is too small, and more

Table 1 Prospective and retrospective studies of local treatment for oligoprogressive breast cancer patients

Study	Design	Intervention	Oligo definition	No. of oligoprogressive lesions	No. of metastatic lesions	Staging	Lines of ST received (before RT)	CNS disease	Change of ST	RT regimen	Treatment sites	Primary endpoint	Secondary endpoints	No. patients	BC subtypes	Grade≥2 toxicity
CURB trial [39]	Phase II randomized	SOC + SBRT vs. SOC	≤5	SOC + SBRT 1 (17%) 2–5 (83%) SOC 1 (22%) 2–5 (78%)	SOC + SBRT ≤5 (55%) >5 (46%) SOC ≤5 (34%) >5 (65%)	CT or PET or MRI	SOC + SBRT ≤4) SOC ≤5	Permitted (not in PD) 26%	Permitted	From 27–30 Gy in 3 fractions to 30–50 Gy in 5 fractions	N/A	mPFS 4.4 vs. 4.2 motnhs; HR 0.78, $p = 0.43$	OS NEST	47	HR+/HER2- negative HR+/HER2+ HER-enriched Triple negative (34%)	SOC + SBRT 41% of pts SOC 62% of pts
AVATAR trial [40]	Phase II single arm	Endocrine therapy + SBRT	≤5	1 (41%) 2 (31%) 3 (22%) 4 (6%)	N/A	CT or PET/CT 18-FDG + brain MRI	≤1 line	Permitted (not leptomeningeal)	Not permitted	− 1 dose of 20 Gy − 3 dose of 10 Gy -5 dose of 7 Gy	Bone (77%) Nodes (18%) Other (5%)	mEFS (5.2 months) ≥6 months in 47% of pts	PFS (5.2 months) mmodified-PFS (10.4 months) OS	32	HR+/HER2- negative	13% (no grade 3 or 4)
Nicosia L et al. [42]	Retrospective	Single arm (SBRT + ST continuation)	≤5	1 (43%) 2–3 (19%) 4–5 (38%)	N/A	CT or PET	≤2	N/A	Not permitted	Minimum effective dose 48 Gy	Bone (34.6%) Liver (18.3%) Lung (22.9%) Nodes (20.9%) Others (3.3%)	Median NEST 8 months	Median tPMC 10 months	79	Luminal A (39%) Luminal B (37%) HER2 enriched (15.5%) Triple negative (8.5%)	N/A
Tan H et al. [43]	Retrospective	Single arm (SBRT)	≤5	N/A	N/A	CT/MRI	*0 (5.2%) 1 (25.9%) 2 (36.8%) 3 (13.9%) >4 (17.1%) Unknown (1%)	N/A	N/A	From 24 Gy in 2 fractions to 30–60 Gy in 5 fractions	Bone (58.5%) Liver (20.2%) Lung (18.7%) Others (2.6%)	*1- and 2 year OS (78.5% and 57.7%) *1- and 2-year PFS (19.6% and 8%) *1- and 2-year incidence of SCT (39.7% and 57.9%)		120 (total) 36 (OPD)	*Luminal A (63.3%) Luminal B (10%) Triple positive (10%) HER2 enriched (4.2%) Triple negative (12.5%)	4.2% (only grade 3)
Weykamp et al. [4]	Retrospective	Single arm (SBRT)	1	1 (100%)	≤3 (OMD) >3 (OPD)	CT	N/A	*Permitted (not in PD) 4%	N/A	From a single fraction of 24–30 Gy to 10 fractions of 5 Gy	Bone (32.8%) Liver (32.8%) Lung (32.8%) Adrenal gland (2.0%	*2-year OS (62.1%) *2-year PFS (16.6%) *2-year Local control (88.5%)		46 (total) 14 (OPD)	*Luminal (72%) HER2 enriched (20%) Triple negative (8%)	1.7%
Wijetunga et al. [44]	Retrospective	Single arm (SBRT)	1	1 (100%)	≤5 (100%)	N/A	*0 (20%) ≥1 (80%)	Permitted	N/A	From 8–10 Gy in 3 fractions to 5 Gy in 8 fractions	Bone (93%) Lung (2%) Lymph node (4%) Others (1%)	mOS (86 months) mPFS (33 months) mTTST (28 months)		79 (total) 37 (OPD)	*HR+/HER2- negative (84%) HR+/HER2+ (9%) HER-2 enriched (1%) Triple negative (6%%)	N/A

ST, systemic therapy; CNS, central nervous system; BC, breast cancer; SOC, standard of care; SBRT, stereotactic body radiotherapy; CT, computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression free survival; HR, hormone receptor; OPD, oligoprogressive disease; OMD, oligometastastic disease; NEST, time to delay the next systemic therapy; tPMC, time to polymetastatic conversion; PD, progressive disease; TTST, time to subsequent therapy

*Data on ITT population of the study (not only oligoprogressive pts)

than a third of it comprises triple-negative BC, which is inherently more aggressive than other BC phenotypes and may not represent the ideal candidate for ablative therapy of oligoprogressive sites. Additionally, the representation of other phenotypes is not specified, especially the prevalence of human epidermal growth factor receptor 2 (HER2) expression in the study population is not reported. The STs used are also not detailed; it is only emphasized that 15% of patients in the SBRT arm and 25% in the SOC arm changed ST at the time of enrollment. The fact that the decision regarding ST change at randomization was at the discretion of the clinician reflects current clinical practice but complicates the interpretation of the results. Finally, it should be noted that the BC patients had received a greater number of previous STs on average compared to NSCLC patients, reflecting a population with more advanced disease [39].

The AVATAR study a phase II single-arm trial recruited 32 patients with HR-positive, HER2-negative BC undergoing endocrine therapy in combination with a CDK4/6i, with progressive disease in a maximum of 5 sites. These patients received stereotactic RT at the sites of progression in addition to the mentioned ST. The primary endpoint was the event-free survival (EFS), defined as a change in systemic therapy, progression within 6 months of enrollment, or progression in more than 3 lesions. Data from a median follow-up of 15.8 months were presented at the 2023 ASTRO Annual Meeting. The primary endpoint was achieved, with 47% (95% CI: 29–65) of patients remaining event-free for ≥ 6 months. The median PFS was 5.2 months (95% CI, 3.1–6.8), but 33% of these progressing patients were eligible for a second course of SABR to further delay the modification of ST [40]. Despite the limitations due to the small sample size (32 patients), these results suggest that patients with HR-positive/HER2-negative BC undergoing therapy with CDK4/6i may benefit from local treatment with SABR in the case of oligoprogression, maintaining the same ST. This subgroup of patients may emerge as a promising candidate population for the ablative treatment of oligoprogression. Firstly, the combination of CDK4/6i and endocrine therapy represents a targeted therapy. Progression during this kind of therapy may more frequently be associated with the development of resistant clones in a limited number of sites, thus more often configuring a true oligoprogression [1, 3]. Of note, the patients enrolled in the study must have stable or responsive disease to a CDK 4/6i-based treatment for at least 6 months. This criterion likely helped to select patients with true oligoprogression, excluding those with potentially more aggressive and microscopic widespread progression. Furthermore, it is well-established that the combination of CDK4/6i and endocrine therapy is well-tolerated, especially in comparison to the chemotherapeutic agents used in subsequent lines [41]. Therefore, the concept of time to change or cessation of ST (applied to the definition of EFS in this study) holds undeniable value. Even if the local treatment of progression does not lead to an increase in OS, extending a well-tolerated treatment would result in improved quality of life.

Retrospective evidence

The remaining evidence regarding the treatment of oligoprogression in patients with BC consists of retrospective studies (Table 1).

A study conducted by Nicosia et al. included 79 patients with BC patients experiencing oligoprogression treated with SBRT. Local control of treated metastases was associated with time to polymetastatic conversion (tPMC) in both univariate and multivariate analysis (HR 2.726, $p = 0.02$). This highlights the importance of achieving local control through the administration of an appropriate radiation dose, identified as a BED greater than 70 Gy in the mentioned study [42].

The remaining retrospective studies include both patients with OPD and OMD.

A study conducted by Tan et al. included a total of 120 mBC patients treated with SBRT, of which only 36 underwent ablative therapy for oligoprogression. Patients treated for oligometastases showed more favorable outcomes, corroborating the higher biological aggressiveness of OPD. Although it is specified that the best survival patterns were observed in patients with Luminal A and triple-positive disease, specific subgroup analysis for patients with OPD was not conducted [43].

In a retrospective study conducted by Weykamp et al., among the 46 patients included (treated with SBRT), 32 had OMD, and 14 had OPD. The presence of bone metastases proved to be a favorable prognostic factor for both PFS and OS. Although these data pertain to the entire study population, the authors emphasize that PFS and OS did not significantly differ in patients with OPD. However, the fact that OPD was associated with lower local control confirms its increased aggressiveness and likely indicates the need for higher SBRT doses than those used in oligometastatic patients [4].

In a retrospective study by Wijetunga et al., all 79 patients undergoing stereotactic ablative radiotherapy (SABR) had OMD, but 37 of them were treated for oligoprogression. Like the previous study, no substantial difference was observed between oligometastatic and oligoprogressive patients, although it should be noted that even the latter had OMD. It is interesting to note that a shorter time from BC diagnosis to SABR (< 5 years) was associated with lower OS and time to subsequent therapy (TTST) [44].

Table 2 Ongoing trials of local treatment for oligoprogressive breast cancer patients

Trial	Design	Intervention	Number of patients	RT dose and fractions (fr)	Previous lines of systemic therapy	Tumor type	BC subtype	Oligoprogressive definition	Staging	Primary endpoint	Completion date (estimated)
NCT06055881 (BOSS)	Observational	RT	45	Not specified	first line (for at least 12 months) second line (for at least 6 months)	BC	ER+, PR + and/or HER2+	1–3 extracranial sites	CT	No change in systemic therapy at 6 months after RT PFS at 6 months.	October 30, 2025
NCT06260033	Phase II	SABR	18	30 to 40 Gy 3–5 fr	≤3 lines	BC	ER+ (any HER2 or PR status)	1–4 extracranial sites	FES PET/CT	No change in systemic therapy at 24 weeks post SBRT treatment	December 11, 2025
NCT05301881 (COSMO)	Phase II	LAT: Surgery, SBRT or RFA	118	Not specified	.≤ 2 lines	BC	All	1–2 distant metastatic lesions, limited to one organ	PET/CT	PFS at 6 months	April 1, 2035
NCT06103669 (VALOROUS)	Phase II Pragmatic	SABR or IR ablation therapy	250	Not specified	≥ 1 line of systemic therapy for metastatic disease	BC Other malignancies	All	1–5 sites	N/A	Disease control at 3 months	December 5, 2025

BC, breast cancer; SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiation therapy; RT, radiotherapy; RF, radiofrequency ablation; LAT, local ablative therapy; SERMs, selective estrogen receptor modulators; SERDs, selective estrogen receptor degraders; ER, estrogen receptor; PR, progesterone receptor; FES PET/CT, F-18 16 Alpha-Fluoroestradiol PET/CT; TNBC, triple negative breast cancer; SD, stable disease; PR, partial response; CR, complete response; IR, interventional radiology; CDK, cyclin-dependent kinase; AI, aromatase inhibitor

While in the study by Nicosia et al. OPD was treated with SBRT maintaining the same ST, this information is not clearly reported in the other studies. Additionally, while the aforementioned study and the one by Tan et al. allowed for up to 5 progressing lesions, the other two studies evaluated patients with just one progressing lesion. This is an important difference, since in the study by Nicosia et al. the number of metastases was found to be an associated factor with NEST in multivariate analysis (HR 1.765, $p < 0.01$). Specifically, patients with 1, 2–3, and 4–5 active metastases showed a median NEST of 13.4, 10.2, and 5.8 months, respectively. Furthermore, while the study by Nicosia et al. allowed for a maximum of 2 prior lines of ST, this limitation was not present in the other studies. The retrospective nature of these studies together with their heterogeneity, affect the chance of drawing impactful conclusions for our clinical practice.

How to combine radiotherapy and systemic treatment

Identifying patients most likely to benefit from local treatment of oligoprogressive sites is not the only obstacle to overcome. Once the patient is considered for this strategy, the issue of potential toxicity associated with the concomitant administration of ST and radiotherapy (RT) arises.

The treatment of metastatic BC is rapidly evolving with the introduction of novel drugs. However, safety data regarding the concomitant administration with RT remains limited. Most of the data concerning the concurrent use of SBRT and ST involves CDK 4/6i, while other drugs have been primarily evaluated with conventional radiotherapy. Therefore, these observations should be interpreted with caution.

The CDK4/6i have become the standard of care for HR-positive and HER2-negative MBC [45, 46]. The concurrent use of palliative RT and CDK4/6i was specifically examined in a prospective clinical context only for a subset of patients enrolled in the PALOMA trials [47], where palbociclib was suspended from the day before RT. Therefore, we have no information regarding the combination of RT and the CDK4/6i [48]. Becherini C. et al. conducted a meta-analysis that incorporated eleven retrospective studies, encompassing a total of 382 patients who underwent concurrent RT and CDK4/6i, to examine the safety profile of this combination [48]. SBRT or Stereotactic Radiosurgery (SRS) was employed in 96 patients, with Intensity-Modulated Radiotherapy or Volumetric-Modulated Arc Therapy documented in 79 patients, and 3-Dimensional Conformal Radiation Therapy used in 286 patients. The pooled incidence of all grade 3 + toxicity was 22% (95% CI, 0.08–0.39), the pooled

incidence of grade 3 + hematologic toxicity rate was 14% (95% CI, 0.03–0.30) and was mostly represented by neutropenia (58.8% of events). However, only four patients required definitive discontinuation of CDK4/6i treatment. A retrospective study on MBC patients treated with CDK4/6i, with or without RT, found no evidence of increased pulmonary toxicity in patients who underwent SBRT for lung or bone metastases [49]. Several ongoing trials are currently assessing the combination of CDK4/6i and RT in breast cancer [50, 51].

Regarding HER2-positive disease, which accounts for approximately 25% of all breast cancers, the use of first-line double-blockade with humanized monoclonal antibodies, directed against the extracellular domain of the HER2 receptor, trastuzumab and pertuzumab in combination with taxane, has been shown to provide long-term survival for approximately one-third of treated patients becoming the gold standard first-line therapy for this subgroup of patients [52]. In the adjuvant setting, trastuzumab is commonly used concomitantly to RT [53]. Since both trastuzumab and locoregional RT can cause cardiotoxicity [54, 55] their concomitant use could result in higher cumulative cardiac events. However, several retrospective studies showed no increased pulmonary, skin or cardiac toxicity [56, 57]. Retrospective studies in the adjuvant setting also support the safety of HER2-double blockade (Pertuzumab plus trastuzumab) and RT combination [58, 59]. Evidence for the concomitant use of dual HER2 blockade and SBRT for metastatic lesions is lacking, but there is no reason to suspect higher rates of adverse events.

TDM-1 is an antibody-drug conjugate (ADC) consisting of the humanized monoclonal antibody trastuzumab covalently linked to the cytotoxic agent DM1, currently approved both in the adjuvant and metastatic setting [60, 61]. In concurrently with RT compared to patients treated with trastuzumab and RT and more ≥ grade 3 events were observed in patients who underwent irradiation compared to those treated only with TDM-1 [60]; but there is also clinical evidence supporting the safety of this combination [62, 63].

Trastuzumab-deruxtecan is an ADC consisting of the humanized monoclonal antibody trastuzumab covalently linked to the topoisomerase I inhibitor deruxtecan. This agent is reshaping the treatment of both HER2-positive and HER2-low metastatic breast cancer, providing impressive survival benefit in comparison to standard therapy, also in heavily pretreated patients [64, 65]. Trastuzumab deruxtecan is associated with a significant risk of drug-related interstitial lung disease or pneumonitis (10.5% incidence in Destiny-Breast03 study) and with higher rates of gastrointestinal toxicity [64]. Data regarding the combination of trastuzumab deruxtecan and RT are lacking, but the aforementioned toxicities pose questions about the feasibility of concomitant treatment with thoracic and abdominal RT.

There is also lack of data regarding the use of TKIs, such as lapatinib and tucatinib targeting HER2 /neu pathways. However, tucatinib showed important gastrointestinal toxicity which could potentially be enhanced by concomitant abdominal RT [66].

Immune checkpoint inhibitors targeting programmed cell death 1 (PD-1) and its ligand 1 (PD-L1) are currently used in triple negative breast cancer patients both in the neoadjuvant and metastatic setting [67–69]. Clinical trials conducted in metastatic patients with different tumor types support the use of immunotherapy with concomitant RT in terms of toxicity [70–73]. Clinical evidence in BC patients is still lacking but prospective trials are ongoing [74, 75]. A phase II trial investigated the efficacy and safety of concurrent RT and pembrolizumab in metastatic triple-negative breast cancer patients. Among the 17 patients enrolled in the trial, dermatitis was the most common low-grade toxicity (29%); four grade 3 were reported [76]. Overall, the combination of immunotherapy and RT seem safe, since it increases the rate of grade 1 and 2 toxicities, but with rare grade 3 or 4 adverse events [77]. However, we suggest caution. Since immunotherapy can present a wide spectrum of toxicities and long-term side effects, larger studies with extended follow-up are needed [78].

Poly (ADP-ribose) polymerase inhibitors (PARPi) are a novel class of anti-cancer therapies targeting the DNA damage response, currently approved in adjuvant and metastatic setting for BC patients carrying a BRCA 1/2 mutation [79–81]. A phase I trial evaluated Olaparib and breast RT combination in triple-negative BC patients with inflammatory, locoregionally advanced, or metastatic disease, or with residual disease after neoadjuvant chemotherapy. Among the 24 patients enrolled in the study, at 1-year follow-up, no treatment-related grade ≥ 3 toxicity was reported [82]. However, data are still limited to consider the concomitant administration of PARPi and RT as a safe strategy.

However, some metastatic BC patients are treated with conventional chemotherapy instead of target therapy. In such cases, the interval between chemotherapy administration and radiotherapy should be determined based on the pharmacokinetics and pharmacodynamics of the drug, as well as the site to be irradiated. However, it should be noted that the prescription of local treatment for oligoprogression is less common in this subgroup and may be reserved for cases with limited therapeutic alternatives.

Discussion

A retrospective study highlighted that approximately 21% of patients with HR-positive MBC treated with endocrine therapy, exhibit oligoprogressive disease [1]. Even though the percentage of oligoprogression is higher in other malignancies, such as NSCLC treated with TKIs, it is important to note that BC data refer to a population not treated with modern targeted therapies (e.g. CDK 4/6i). Therefore, it may be underestimated compared to the current reality. Furthermore, patients with MBC are much more numerous than those with NSCLC ALK/EGFR mutations and the absolute incidence of OPD is likely higher within the context of BC, warranting special attention [1]. Therefore, defining a treatment strategy for MBC patients with oligoprogression represents an everyday clinical challenge.

While it is challenging to determine whether local treatment of oligoprogressive sites can result in an OS benefit, endpoints such as PFS or NEST also hold particular significance in evaluating this strategy. Being able to extend disease control during a well-tolerated ST, thus delaying the switch to a more toxic therapy, represents a clinically relevant outcome with a direct impact on the patient's quality of life. We can pursue this goal with SBRT, which allows for an excellent local response without high levels of toxicity [15, 83, 84].

However, it is not easy to compare data regarding OPD management, as both published and ongoing studies (Tables 1 and 2) use different endpoints, ranging from PFS to the percentage of patients who have not changed treatment after a certain period (with these concepts being expressed through various endpoints). Future studies should standardize endpoints to ensure a correct interpretation of results and should a thorough evaluation of quality of life.

There is substantial evidence supporting the local ablative treatment of OPD in patients with NSCLC, but BC data are scarce and have numerous limitations. The main limitations of these studies lie in their retrospective nature, the small number of patients and their heterogeneity, both in terms of BC phenotype and STs. This complicates the identification of a population that could derive more benefit from a locoregional approach to oligoprogression. In addition, the CURB study, which is the only randomized trial available, highlighted that this approach could be beneficial in patients with NSCLC but not in those with BC [39].

However, before deeming local treatment of OPD as ineffective in BC, we must consider the high heterogeneity of this disease. In fact, the recent results of the phase II AVATAR study, which enrolled only patients with HR-positive/HER2-negative disease undergoing therapy with CDK 4/6i, achieved its primary endpoint, suggesting a potential benefit in this patient setting. Patients with HR-positive BC can be excellent candidates for local treatment of OPD: a more indolent progression generally characterizes this subtype and they can be managed with drugs that are typically well-tolerated, allowing for a good quality of life. In contrast, triple-negative breast cancer is usually more aggressive [85]. Delaying a change in systemic therapy in the event of OPD may result in rapid disease progression, leading to symptom onset and organ failure. Moreover, despite recent advances, we have fewer well-tolerated targeted drugs for this subtype [86]. However, it might be worthwhile to further explore the role of OPD treatment in triple-negative BC patients with OMD (and thus at lower risk of organ failure) during immune checkpoint inhibitor therapy. Although HER2-positive disease is biologically aggressive, it is also effectively treated with anti-HER2 targeted therapies, which are well-tolerated and allow for durable disease control [52]. Thus, patients with HER2-positive tumors could also be good candidates for local treatment of OPD.

Future studies may provide the answers we are looking for, some of which are currently in progress (Table 2). The COSMO study is a phase 2 trial with 6-month PFS as the primary endpoint. Local treatment can include RT, surgery, and radiofrequency. Moreover, this study aims to enroll a larger number of patients, specifically 118, although they may be less selected, as various types of STs (endocrine therapy, targeted therapy, chemotherapy, and immunotherapy) are allowed. At the same time, the definition of oligoprogression is more selective, considered as the progression of 1–2 metastatic lesions limited to a single organ. Among the exploratory endpoints, the study also includes an analysis of the prognostic value of circulating tumor DNA (ctDNA), assessed both at the occurrence of oligoprogression and during treatment [74]. This study could contribute to redefining the concept of oligoprogression by integrating radiological imaging with ctDNA assessment. The BOSS study is an observational trial that could also contribute to clarifying some aspects of local treatment for oligoprogression in BC. In this study, oligoprogression is defined as the progression of 1–3 extracranial lesions, and an analysis of CTCs is planned [75]. These studies could provide us a more comprehensive definition of oligoprogressive that integrates biological data with imaging. Considering a disease as oligoprogressive when there is a maximum of 3–5 progressing lesions is utterly arbitrary as the presence of a limited number of progressing lesions may still underlie the development of widespread progression, and the evaluation of ctDNA and CTCs could precisely discern cases where ablative local treatment might be futile.

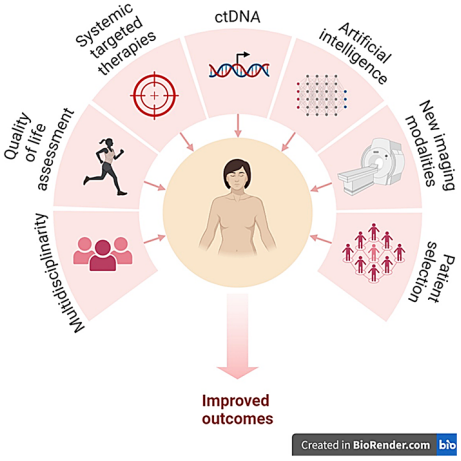
The aforementioned CURB study included the measurement of ctDNA at pre-randomization and 8 weeks. While in NSCLC patients SBRT led to a reduction in allelic fraction, no change in ctDNA was observed in BC patients

after ablative therapy. This evidence is consistent with the progression pattern observed in the two subgroups. While in NSCLC patients progression mostly occurred in pre-existing lesions (non-irradiated), BC patients showed a greater propensity to develop new lesions [39]. These data seem to confirm that imaging alone may not be sufficient to distinguish between BC patients in real oligoprogression, potentially candidates for ablative therapy, and those with diffuse progression. It is also important to note that in both the AVATAR and BOSS trials, the duration of the response to the ongoing ST represents one of the inclusion criteria. In the AVATAR trial, patients must have stable or responsive disease to a CDK 4/6i-based treatment for at least 6 months, while in the BOSS study, patients can be enrolled only if responsive to first-line treatment for at least 12 months. The presence of a durable response to the ongoing ST along with the evaluation of biological biomarkers, could help identify a population less prone to developing widespread disease progression and, therefore, suitable for ablative therapy.

Moreover, the use of liquid and tissue biopsy allows the determination of resistance mutations and BC phenotype, potentially impacting treatment management. For example, ctDNA could help categorize 3 groups of patients: those in true oligoprogression without targetable mutation, who may benefit from a local approach; those with widespread progression and no targetable resistance mutation, who could be candidates for an ST change; patients with true oligoprogression and emergence of targetable resistance mutation, who may benefit from both local approach and ST change. We need to define oligoprogression also from a biological perspective, which is necessary to plan a targeted treatment that may not necessarily involve only radiotherapy.

However, it should be noted that the current radiological definition of oligoprogression may also evolve with the adoption of new imaging techniques. WB-MRI and PET are promising techniques that could define the presence of oligoprogression with greater precision and timeliness and should be included in future trials evaluating the management of oligoprogression. Surprisingly, in the AVATAR study, patients with bone-only progression showed a worse PFS (multivariable HR, 0.3; 95% CI, 0.1–0.9; $P=0.021$). One of the causes might have been the underestimation of the progressing lesions before SABR, leading to an incorrect definition of oligoprogression due to the limitations of standard imaging techniques [40].

To summarize, we need randomized trials able to enroll a larger number of patients, undergoing well-tolerated targeted therapy, such as double anti-HER2 blockade or CDK4/6i, with a durable response. The incorporation of CTCs and ctDNA biomarkers and modern imaging techniques should be mandatory for an advanced definition of oligoprogression. Additionally, if oligoprogression coincides with the emergence of a targetable resistance mutation or subclonal selection, a treatment arm that includes a switch to the specific drug alongside SBRT should also be considered (as previously described) (Image 1).



While this kind of studies could represent a turning point in the management of OPD, we urgently need to identify criteria for the management of oligoprogressive BC patients in everyday clinical practice. Referring to the available data, HR-positive/HER2-negative or HER2-positive patients undergoing first-line target therapy that has provided prolonged disease control (especially CDK 4/6i), experiencing non-visceral oligoprogression (especially in a single site), may be potential candidates for local treatment of OPD, in addition to current ST continuation. It is also crucial that the ongoing ST is well-tolerated, justifying the delay in changing ST. If the few progressing sites are also symptomatic, local ablative treatment should be strongly considered, as it would have a potential dual benefit. In any case, tissue biopsy of the progressive lesions must be considered, as it enables tailoring of the ST in case of phenotype change, instead of continuing the same therapy.

Once a patient is considered for local OPD treatment, it is important to consider the risks associated with the concurrent use of SABR and ST, as discussed earlier. For this purpose, guidelines resulting from a Delphi consensus involving 28 members of the European Society for Radiotherapy (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC) Oligocare consortium were published in 2023. These guidelines focus on the suspension of modern STs during SBRT [87]. In any case, both the indication for local treatment of oligoprogression and the timing of the ST suspension, should be evaluated within a multidisciplinary team composed of an oncologist, radiologist, and radiation oncologist, as available data does not allow us to draw definitive conclusions for clinical practice.

Acknowledgements This work was partly supported by "Ricerca Corrente", by the Italian Ministry of Health within the research line

"Appropriateness, outcomes, drug value and organizational models for the continuity of diagnostic-therapeutic pathways in oncology".

Author contributions All the authors contributed equally to this work. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

Funding No funding.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests Dr. De Giorgi received honoraria for advisory boards or speaker fees for Pfizer, BMS, MSD, PharmaMar, Astellas, Bayer, Ipsen, Roche, Novartis, Clovis, GSK, AstraZeneca, Institutional research grants from AstraZeneca, Sanofi and Roche. Dr. Michela Palleschi has received advisory board or speaker fees from Novartis, Lilly, Astrazeneca. Dr. Filippo Merloni has received advisory board or speaker fees from Novartis, Lilly, Astrazeneca.

References

1. Kelly P, Ma Z, Baidas S, Moroose R, Shah N, Dagan R et al (2017) Patterns of progression in metastatic estrogen receptor positive breast Cancer: an argument for local therapy. Int J Breast Cancer 2017:1367159. https://doi.org/10.1155/2017/1367159
2. Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM et al (2020) Characterisation and classification of oligometastatic disease: a european society for radiotherapy and oncology and european organisation for research and treatment of cancer consensus recommendation. Lancet oncol 21(1):e18–e28. https://doi.org/10.1016/S1470-2045(19)30718-1
3. Patel PH, Palma D, McDonald F, Tree AC (2019) The dandelion dilemma revisited for oligoprogression: treat the whole lawn or weed selectively? clin oncol 31(12):824–833. https://doi.org/10.1016/j.clon.2019.05.015
4. Weykamp F, König L, Seidensaal K, Forster T, Hoegen P, Akbaba S et al (2020) Extracranial stereotactic body radiotherapy in oligometastatic or oligoprogressive breast cancer. Front oncol 26:10:987. https://doi.org/10.3389/fonc.2020.00987. eCollection 2020
5. Raheem F, Karikalan SA, Batalini F, El Masry A, Mina L (2023) Metastatic ER + breast cancer: mechanisms of resistance and future therapeutic approaches. Int J Mol Sci 24(22):16198. https://doi.org/10.3390/ijms242216198
6. Mavrommati I, Johnson F, Echeverria GV, Natrajan R (2021) Subclonal heterogeneity and evolution in breast cancer. NPJ Breast Cancer 7(1):155. https://doi.org/10.1038/s41523-021-00363-0
7. Kim C et al (2018) Abstract CT106: local ablative therapy for oligoprogressive, EGFR-mutant, non-small cell lung cancer (NSCLC) after treatment with osimertinib. Cancer Res 78(13 Supplement):CT106–CT106. https://doi.org/10.1158/1538-7445.am2018-ct106
8. Iyengar P, Kavanagh BD, Wardak Z, Smith I, Ahn C, Gerber DE et al (2014) Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. J Clin Oncol 32(34):3824–3830. https://doi.org/10.1200/JCO.2014.56.7412
9. Berghen C, Joniau S, Rans K, Poels K, Devos G, Haustermans K et al (2021) Metastasis-directed therapy for oligoprogressive castration-resistant prostate cancer — preliminary results of the prospective, single-arm MEDCARE trial. IJROBP 111(3):E265–E266. https://doi.org/10.1016/j.ijrobp.2021.07.869
10. Pezzulla D, Macchia G, Cilla S, Buwenge M, Ferro M, Bonome P et al (2021) Stereotactic body radiotherapy to lymph nodes in oligoprogressive castration-resistant prostate cancer patients: a post hoc analysis from two phase I clinical trials. clin exp metastasis 38(6):519–526. https://doi.org/10.1007/s10585-021-10126-7
11. Cheung P, Patel S, North SA, Sahgal A, Chu W, Soliman H et al (2021) Stereotactic radiotherapy for oligoprogression in metastatic renal cell cancer patients receiving tyrosine kinase inhibitor therapy: a phase 2 prospective multicenter study. eur urol 80(6):693–700. https://doi.org/10.1016/j.eururo.2021.07.026
12. Hannan R, Christensen M, Hammers H, Christie A, Paulman B, Lin D et al (2022) Phase II trial of stereotactic ablative radiation for oligoprogressive metastatic kidney cancer. eur urol oncol 5(2):216–224. https://doi.org/10.1016/j.euo.2021.12.001
13. Chan OSH, Lee VHF, Mok TSK, Mo F, Chang ATY, Yeung RMW (2017) The role of Radiotherapy in epidermal growth factor receptor mutation-positive patients with oligoprogression: a matched-cohort analysis. clin oncol 29(9):568–575. https://doi.org/10.1016/j.clon.2017.04.035
14. Qiu B, Liang Y, Li QW, Liu GH, Wang F, Chen ZL et al (2017) Local therapy for oligoprogressive disease in patients with advanced stage non–small-cell lung cancer harboring epidermal growth factor receptor mutation. clin lung cancer 18(6):e369–e373. https://doi.org/10.1016/j.cllc.2017.04.002
15. Yan B, Ramadan S, Jerzak KJ, Louie AV, Donovan E (2023) The effectiveness and safety of stereotactic body Radiation Therapy (SBRT) in the treatment of oligoprogressive breast cancer: a systematic review. curr oncol 30(7):6976–6985. https://doi.org/10.3390/curroncol30070505
16. Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA et al (2012) Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. J Thora Oncol 7(12):1807–1814. https://doi.org/10.1097/JTO.0b013e3182745948
17. Schwartz LH, Litière S, De Vries E, Ford R, Gwyther S, Mandrekar S et al (2016) RECIST 1.1 - update and clarification: from the RECIST committee. Eur J Cancer 62:132–137. https://doi.org/10.1016/j.ejca.2016.03.081
18. Shao H, Varamini P (2022) breast cancer bone metastasis: a narrative review of emerging targeted drug delivery systems. cells 11(3):388. https://doi.org/10.3390/cells11030388

19. Sihto H, Lundin J, Lundin M, Lehtimäki T, Ristimäki A, Holli K et al (2011) Breast cancer biological subtypes and protein expression predict for the preferential distant metastasis sites: a nationwide cohort study. Breast cancer Res 13(5):R87. https://doi.org/10.1186/bcr2944
20. Yin JJ, Pollock CB, Kelly K (2005) Mechanisms of cancer metastasis to the bone. Cell Res 15(1):57–62. https://doi.org/10.1038/sj.cr.7290266
21. Lu J, Hu D, Zhang Y, Ma C, Shen L, Shuai B (2023) Current comprehensive understanding of denosumab (the RANKL neutralizing antibody) in the treatment of bone metastasis of malignant tumors, including pharmacological mechanism and clinical trials. Fron Oncol 13:1133828. https://doi.org/10.3389/fonc.2023.1133828
22. Cook GJR, Goh V (2020) Molecular imaging of bone metastases and their response to therapy. J Nucl Med 61(6):799–806. https://doi.org/10.2967/jnumed.119.234260
23. Peterson LM, O'Sullivan J, Wu Q, Novakova-Jiresova A, Jenkins I, Lee JH et al (2018) Prospective study of serial18F-FDG PET and18F-fluoride PET to predict time to skeletal-related events, time to progression, and survival in patients with bone-dominant metastatic breast cancer. J Nucl Med 59(12):1823–1830. https://doi.org/10.2967/jnumed.118.211102
24. Liu C, Xu X, Yuan H, Zhang Y, Zhang Y, Song S et al (2020) Dual Tracers of 16α-[18F]fluoro-17β-Estradiol and [18F]fluorodeoxyglucose for prediction of progression-free survival after fulvestrant therapy in patients with HR+/HER2- metastatic breast cancer. Front oncol. https://doi.org/10.3389/fonc.2020.580277
25. Kurland BF, Peterson LM, Lee JH, Schubert EK, Currin ER, Link JM et al (2017) Estrogen receptor binding (18F-FES PET) and glycolytic activity (18F-FDG PET) predict progression-free survival on endocrine therapy in patients with ER + breast cancer. Clin Cancer Res 23(2):407–415. https://doi.org/10.1158/1078-0432.CCR-16-0362
26. Van Geel JJL, Boers J, Elias SG, Glaudemans AWJM, De Vries EFJ, Hospers GAP et al (2020) Clinical validity of 16α-[18F] Fluoro-17β-Estradiol positron emission tomography/computed tomography to assess estrogen receptor status in newly diagnosed metastatic breast Cancer. J Clin Oncol 40(31):3642–3652. https://doi.org/10.1200/JCO.22.00400
27. Stereotactic Body Radiation Therapy and FES PET/CT Imaging for the Treatment of Oligoprogressive Estrogen Receptor Positive Metastatic Breast Cancer ClinicalTrials.gov. Available: https://clinicaltrials.gov/study/NCT06260033
28. Brett JO, Spring LM, Bardia A, Wander SA (2021) ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Res 23(1):85. https://doi.org/10.1186/s13058-021-01462-3
29. Talmadge JE (2007) Clonal selection of metastasis within the life history of a tumor. Cancer Res 67(24):11471–11475. https://doi.org/10.1158/0008-5472.CAN-07-2496
30. Bidard FC, Hardy-Bessard AC, Dalenc F, Bachelot T, De La Pierga Jy T et al (2022) Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 23(11):1367–1377. https://doi.org/10.1016/S1470-2045(22)00555-1
31. Grigoryeva ES, A.Tashireva L, Alifanov VV, Savelieva OE, Vtorushin SV, Zavyalova MV et al (2022) Molecular subtype conversion in CTCs as indicator of treatment adequacy associated with metastasis-free survival in breast cancer. Sci Rep ;12(1)
32. Giuliano M, Giordano A, Jackson S, De Giorgi U, Mego M, Cohen EN et al (2014) Circulating tumor cells as early predictors of metastatic spread in breast cancer patients with limited metastatic dissemination. Breast Cancer Res 16(5):440. https://doi.org/10.1186/s13058-014-0440-8
33. De Giorgi U, Valero V, Rohren E, Mego M, Doyle GV, Miller MC et al (2010) Circulating tumor cells and bone metastases as detected by FDG-PET/CT in patients with metastatic breast cancer. Ann Oncol 21(1):33–39. https://doi.org/10.1093/annonc/mdp262
34. De Giorgi U, Mego M, Rohren EM, Liu P, Handy BC, Reuben JM et al (2010) 18F-FDG PET/CT findings and circulating tumor cell counts in the monitoring of systemic therapies for bone metastases from breast cancer. J Nuc Med 51(8):1213–1218. https://doi.org/10.2967/jnumed.110.076455
35. Gouda MA, Huang HJ, Piha-Paul SA, Call SG, Karp DD, Fu S et al (2022) Longitudinal monitoring of circulating Tumor DNA to predict treatment outcomes in advanced cancers. JCO Precis Oncol 6:e2100512. https://doi.org/10.1200/po.21.00512
36. Ueno T (2022) Surgical management of metastatic breast cancer: a mini review. Front oncol 12:910544. https://doi.org/10.3389/fonc.2022.910544
37. Terlizzi M, Limkin E, Sellami N, Louvel G, Blanchard P (2023) Is single fraction the future of stereotactic body radiation therapy (SBRT)? A critical appraisal of the current literature. Clin transl radiat oncol 39:100584. https://doi.org/10.1016/j.ctro.2023.100584
38. Tsang MWK (2016) Stereotactic body radiotherapy: current strategies and future development. J Thorac Dis 8(Suppl 6):S517–S527. https://doi.org/10.21037/jtd.2016.03.14
39. Tsai CJ, Yang JT, Shaverdian N, Patel J, Shepherd AF, Eng J et al (2023) Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (consolidative use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study. Lancet 403(10422):171–182. https://doi.org/10.1016/S0140-6736(23)01857-3
40. David SP, Siva S, Bressel M, Tan J, Hanna GG, Alomran RK et al (2023) Stereotactic ablative body radiotherapy (SABR) for oligoprogressive ER-positive breast cancer (AVATAR): a phase II prospective multicenter trial. IJROBP https://doi.org/10.1016/j.ijrobp.2023.08.033
41. Di Lauro V, Barchiesi G, Martorana F, Zucchini G, Muratore M, Fontanella C et al (2022) Health-related quality of life in breast cancer patients treated with CDK4/6 inhibitors: a systematic review. ESMO Open 7(6):100629. https://doi.org/10.1016/j.esmoop.2022.100629
42. Nicosia L, Figlia V, Ricottone N, Cuccia F, Mazzola R, Giaj-Levra N et al (2022) Stereotactic body radiotherapy (SBRT) and concomitant systemic therapy in oligoprogressive breast cancer patients. Clin exp metastasis 39(4):581–588. https://doi.org/10.1007/s10585-022-10167-6
43. Tan H, Cheung P, Louie AV, Myrehaug S, Niglas M, Atenafu EG et al (2021) Outcomes of extra-cranial stereotactic body radiotherapy for metastatic breast cancer: treatment indication matters. Radiother Oncol 161:159–165. https://doi.org/10.1016/j.radonc.2021.06.012
44. Wijetunga NA, dos Anjos CH, Zhi WI, Robson M, Tsai CJ, Yamada Y et al (2021) Long-term disease control and survival observed after stereotactic ablative body radiotherapy for oligometastatic breast cancer. Cancer Med 10(15):5163–5174. https://doi.org/10.1002/cam4.4068
45. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Hart L et al Overall survival with ribociclib plus letrozole in advanced breast cancer. N Eng J Med 386(10):942–950 https://doi.org/10.1056/NEJMoa2114663
46. Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X et al (2019) The Effect of Abemaciclib Plus Fulvestrant on overall survival in hormone Receptor–Positive, ERBB2-Negative breast Cancer

that progressed on endocrine Therapy—MONARCH 2: a Randomized Clinical Trial. JAMA Oncol 6(1):116–124. https://doi.org/10.1001/JAMAONCOL.2019.4782
47. Turner NC, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N et al (2018) Overall survival with Palbociclib and fulvestrant in advanced breast Cancer. N Eng J Med 379(20):1926–1936. https://doi.org/10.1056/nejmoa1810527
48. Becherini C, Visani L, Caini S, Bhattacharya IS, Kirby AM, Nader Marta G et al (2023) Safety profile of cyclin-dependent kinase (CDK) 4/6 inhibitors with concurrent radiation therapy: a systematic review and meta-analysis. Canc Treat Rev 119:102586. https://doi.org/10.1016/j.ctrv.2023.102586
49. Visani L, Livi L, Ratosa I, Orazem M, Ribnikar D, Saieva C et al (2022) Safety of CDK4/6 inhibitors and concomitant radiation therapy in patients affected by metastatic breast cancer. Radiother Oncol 177:40–45. https://doi.org/10.1016/j.radonc.2022.10.023
50. Radiation Therapy Palbociclib, and Hormone Therapy in Treating Breast Cancer Patients With Bone Metastasis. ClinicalTrials.gov. Available:https://classic.clinicaltrials.gov/ct2/show/study/NCT03691493
51. Local Treatment in ER-positive/HER2-negative Oligo-metastatic Breast Cancer. ClinicalTrials.gov. Available: https://clinicaltrials.gov/ct2/show/NCT03750396
52. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V et al (2020) Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol 21(4):519–530. https://doi.org/10.1016/S1470-2045(19)30863-0
53. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E et al (2017) 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin adjuvant (HERA) trial. Lancet 389(10075):1195–1205. https://doi.org/10.1016/S0140-6736(16)32616-2
54. Lidbrink E, Chmielowska E, Otremba B, Bouhlel A, Lauer S, Liste Hermoso M et al (2019) A real-world study of cardiac events in > 3700 patients with HER2-positive early breast cancer treated with trastuzumab: final analysis of the OHERA study. Breast Cancer Res Treat. https://doi.org/10.1007/s10549-018-5058-6
55. Bergom C, Bradley JA, Ng AK, Samson P, Robinson C, Lopez-Mattei J et al (2021) Past, Present, and Future of Radiation-Induced Cardiotoxicity: refinements in Targeting, Surveillance, and risk stratification. JACC CardioOncol 3(3):343–359. https://doi.org/10.1016/j.jaccao.2021.06.007
56. Meattini I, Cecchini S, Muntoni C, Scotti V, De Luca Cardillo C, Mangoni M et al (2014) Cutaneous and cardiac toxicity of concurrent trastuzumab and adjuvant breast radiotherapy: a single institution series. Med Oncol 31(4):891. https://doi.org/10.1007/s12032-014-0891-x
57. Halyard MY, Pisansky TM, Dueck AC, Suman V, Pierce L, Solin L et al (2009) Radiotherapy and adjuvant trastuzumab in operable breast cancer: tolerability and adverse event data from the NCCTG phase III trial N9831. J Clin Oncol 27(16):2638–2644. https://doi.org/10.1200/JCO.2008.17.9549
58. Ajgal Z, de Percin S, Diéras V, Pierga JY, Campana F, Fourquet A et al (2017) Combination of radiotherapy and double blockade HER2 with pertuzumab and trastuzumab for HER2-positive metastatic or locally recurrent unresectable and/or metastatic breast cancer: Assessment of early toxicity. Cancer Radiother 21(2):114–118. https://doi.org/10.1016/j.canrad.2016.10.002
59. Ben Dhia S, Loap S, Loirat P, Vincent-Salomon D, Cao A, Escalup K L, et al (2021) Concurrent radiation therapy and dual HER2 blockade in breast cancer: Assessment of toxicity. Cancer Radiother 25(5):424–431. https://doi.org/10.1016/j.canrad.2020.06.037
60. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M et al (2019) Trastuzumab Emtansine for residual invasive HER2-Positive breast Cancer. N Eng J Med 380(7):617–628. https://doi.org/10.1056/nejmoa1814017
61. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J et al (2012) Trastuzumab Emtansine for HER2-Positive advanced breast Cancer. N Engl J Med 367(19):1783–1791. https://doi.org/10.1056/nejmoa1209124
62. Zolcsák Z, Loirat D, Fourquet A, Kirova YM (2020) Adjuvant Trastuzumab Emtansine (T-DM1) and concurrent radiotherapy for residual invasive HER2-positive breast Cancer: single-center preliminary results. Am J Clin Oncol 43(12):895–901. https://doi.org/10.1097/COC.0000000000000769
63. Krop IE, Suter TM, Dang CT, Dirix L, Romieu G, Zamagni C et al (2015) Feasibility and cardiac safety of trastuzumab emtansine after anthracycline-based chemotherapy as (neo)adjuvant therapy for human epidermal growth factor receptor 2-positive early-stage breast cancer. J Clin Oncol 33(10):1136–1142. https://doi.org/10.1200/JCO.2014.58.7782
64. Hurvitz SA, Hegg R, Chung WP, Im SA, Jacot W, Ganju V et al (2023) Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet 401(10371):105–117. https://doi.org/10.1016/S0140-6736(22)02420-5.)
65. Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E et al (2022) Trastuzumab Deruxtecan in previously treated HER2-Low advanced breast Cancer. N Eng J Med 387(1):9–20. https://doi.org/10.1056/NEJMoa2203690
66. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA et al (2020) Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive metastatic breast Cancer. N Eng J Med 382(7):597–609. https://doi.org/10.1056/nejmoa1914609
67. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J et al (2020) pembrolizumab for early triple-negative breast cancer. N Eng J Med 382(9):810–821. https://doi.org/10.1056/nejmoa1910549
68. Cortes J, Rugo HS, Cescon DW, Im SA, Yusof MM, Gallardo C et al (2022) pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. N Eng J Med 387(3):217–226. https://doi.org/10.1056/nejmoa2202809
69. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H et al (2018) atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Eng J Med 379(22):2108–2121. https://doi.org/10.1056/nejmoa1809615
70. Mattes MD, Eubank TD, Almubarak M, Wen S, Marano GD, Jacobson GM et al (2021) A prospective trial evaluating the safety and systemic response from the concurrent use of radiation therapy with checkpoint inhibitor immunotherapy in metastatic non–small cell lung cancer. Clin Lung Cancer 22(4):268–273. https://doi.org/10.1016/j.cllc.2021.01.012
71. Bang A, Wilhite TJ, Pike LRG, Cagney DN, Aizer AA, Taylor A et al (2017) Multicenter evaluation of the tolerability of combined treatment with pd-1 and ctla-4 immune checkpoint inhibitors and palliative radiation therapy. Int J Radiat Oncol Biol Phys 98(2):344–351. https://doi.org/10.1016/j.ijrobp.2017.02.003
72. Bestvina CM, Pointer KB, Karrison T, Al-Hallaq H, Hoffman PC, Jelinek MJ et al (2022) A phase 1 trial of concurrent or sequential Ipilimumab, Nivolumab, and stereotactic body radiotherapy in patients with stage IV NSCLC Study. In: J Thorac Oncol
73. Spaas M, Sundahl N, Kruse V, Rottey S, De Maeseneer D, Duprez F et al (2023) checkpoint inhibitors in combination with stereotactic body radiotherapy in patients with advanced solid tumors. JAMA Oncol 9(9):1205–1213. https://doi.org/10.1001/jamaoncol.2023.2132

74. Pre-op pembro + radiation therapy in breast cancer (P-RAD)-clinicaltrials.gov. Available: https://clinicaltrials.gov/study/NCT04443348
75. Evaluate the Clinical benefit of a post-operative treatment associating radiotherapy + Nivolumab + ipilimumab versus radiotherapy + capecitabine for triple negative breast cancer patients with residual disease. ClinicalTrials.gov. Available: https://clinicaltrials.gov/study/NCT03818685?cond=NCT03818685&rank=1
76. Ho AY, Barker CA, Arnold BB, Powell SN, Hu ZI, Gucalp A et al (2020) A phase 2 clinical trial assessing the efficacy and safety of pembrolizumab and radiotherapy in patients with metastatic triple-negative breast cancer. Cancer 126(4):850–860. https://doi.org/10.1002/CNCR.32599
77. Zhang Z, Liu X, Chen D, Yu J (2022) Radiotherapy combined with immunotherapy: the dawn of cancer treatment. Signal Transduct Target Therapy 17. https://doi.org/10.1038/s41392-022-01102-y
78. Gumusay O, Callan J, Rugo HS (2022) Immunotherapy toxicity: identification and management. Breast Cancer Res Treat 192(1):1–17. https://doi.org/10.1007/s10549-021-06480-5
79. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P et al (2021) Adjuvant olaparib for patients with BRCA1 - or BRCA2 -mutated breast cancer. N Eng J Med 384(25):2394–2405. https://doi.org/10.1056/nejmoa2105215
80. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N et al (2017) Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 377(6):523–533. https://doi.org/10.1056/nejmoa1706450
81. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH et al (2018) Talazoparib in patients with advanced breast Cancer and a germline BRCA mutation. N Eng J Med 379(8):753–763. https://doi.org/10.1056/nejmoa1802905
82. Loap P, Loirat D, Berger F, Cao K, Ricci F, Jochem A et al (2021) Combination of olaparib with radiotherapy for triple-negative breast cancers: one-year toxicity report of the RADIOPARP phase I trial. Int J cancer 149(10):1828–1832. https://doi.org/10.1002/ijc.33737
83. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C et al (2020) Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol 38(25):2830–2838. https://doi.org/10.1200/JCO.20.00818
84. Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA et al (2013) Stereotactic body radiotherapy for oligometastases. Lancet Oncol 14(1):e28–37. https://doi.org/10.1016/S1470-2045(12)70510-7
85. Hu M, Shao B, Ran R, Li H (2021) Prognostic factors for patients with metastatic breast cancer: a literature review. Transl Cancer Res 10(4):1644–1655. https://doi.org/10.21037/tcr-20-2119
86. Huppert LA, Gumusay O, Rugo HS (2022) Emerging treatment strategies for metastatic triple-negative breast cancer. Ther Adv Med Oncol 14:17588359221086916. https://doi.org/10.1177/17588359221086916
87. Kroeze SGC, Pavic M, Stellamans K, Lievens Y, Becherini C, Scorsetti M et al (2023) Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: systematic review and consensus recommendations by the EORTC–ESTRO OligoCare consortium. Lancet Oncol 24(3):e121–e132. https://doi.org/10.1016/S1470-2045(22)00752-5