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Hot Topic

Oligometastatic breast cancer: Dissecting the clinical and biological uniqueness of this emerging entity. Can we pursue curability?

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ABSTRACT

Metastatic breast cancer represents an incurable condition, however, the increasing interest towards the oligometastatic entity is now challenging this assumption. Up to 20% of patients with metastatic breast cancer present with oligometastatic disease, which refers to metastatic breast cancer presenting or recurring with limited metastatic burden. In the last years, progressive advancements in imaging techniques, the growing availability of minimally invasive locoregional treatments, alongside the increasing expectations from a patient perspective, have contributed to rising the awareness towards this emerging entity. In the present work we comprehensively reviewed available evidence regarding oligometastatic breast cancer, focusing on clinical and biological notions virtually supporting the adoption of a curative approach when treating this condition. We also discussed main areas of uncertainties, providing a research agenda that may guide and fine-tune the future investigation in this field.

Introduction

In the last years we have witnessed unprecedented improvements of breast cancer (BC)-related survival, mostly driven by the progressive enhancement of the therapeutic armamentarium with increasingly effective treatment strategies [1]. Approximately 20–30 % of patients with early-stage disease will eventually experience disease relapse and 5 % are diagnosed with de-novo stage IV disease [2,3]. Once metastatic, BC is traditionally considered an incurable condition, where treatment choices, although potentially aimed at prolonging survival, are typically driven by palliative motives. This paradigm has remained undisputed for long time, however, the increasing interest towards the oligometastatic (OM)-BC entity is now challenging this assumption. Indeed, up to 20 % of patients with metastatic BC (MBC) present with OM disease (OM-BC), referring to MBC presenting or recurring with limited metastatic burden. Advancements in imaging techniques - becoming increasingly sensitive, the growing availability of minimally invasive locoregional treatments, alongside the increasing expectations from a patient perspective, have all contributed to rising the awareness towards this emerging entity.

According to the Hellman's spectrum theory (1995)[4] the metastatic spread is a continuum, reflecting a step-wise process which leads to the transformation of a localized disease into a widespread one. Against this backdrop, the OM disease represents an intermediate state – both quantitatively and qualitatively – between localized tumor and overt metastatic disease, possibly representing the epiphenomenon of a restricted virulence, resulting in a limited metastatic capacity. In fact, in a limited tumor, the properties needed to achieve dissemination (reduced cellular adhesion, increased mobility, survival into the blood or lymphatic stream, reimplant and proliferation in a secondary tissue) develop gradually and possibly in a restricted fashion, thus resulting in the outgrowth of a limited number of metastases[4–7].

In the present work we comprehensively reviewed available evidence regarding OM-BC, focusing on clinical and biological notions virtually supporting the adoption of a curative approach, as well as on main areas of uncertainties.

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Clinical landscape of OM-BC

The European Society for Radiotherapy and Oncology (ESTRO) and European Organization for Research and Treatment of Cancer (EORTC) consensus recommendations differentiate between a state of genuine OM disease (patients without a previous history of polymetastatic disease) and a state of induced OM disease (patients with a history of polymetastatic disease)[6]. Indeed, although the definition of OM-BC may potentially be extended to patients presenting with disseminated MBC subsequently converted to OM-BC under the exposure of systemic treatment, the present review is focused on the most genuine entities of OM-BC. In particular, synchronous or *de novo* OM-BC, referring to *de novo* stage IV disease presenting as oligometastatic at initial presentation and oligoreccurence, where BC relapses as OM-BC after treatment for early-stage primary BC are addressed in the present review. Features of OM-BC definition are shown in Fig. 1.

No unanimous definition currently exists when referring to OM-BC in terms of number of metastatic sites and/or number and type of site/organ involved. However, the most accepted definition, currently endorsed by ESMO guidelines, is a maximum of 5 metastatic lesions, not necessarily located in the same site/organ, all potentially susceptible to ablative local treatment[5].

It should be noted that the cutoff of 5 metastatic lesions has been arbitrarily set based on multi-histology studies and suggested within the wider definition of OM cancer[6], with no specific focus on BC. In terms of prognostic correlation, in a real-world cohort of 3447 patients with de-novo MBC, patients with more than 5 metastases experienced more unfavorable OS as compared to those with 1–3 metastatic sites, with, however, similar OS as compared to patients with 4–5 lesions. Of note, 3 metastatic sites as cutoff maintained an independent negative prognostic value[8]. Interestingly, in a large retrospective study of more than 400 HER2 + de-novo MBC patients treated with anti-HER2-based treatments with or without multimodality approaches, the subgroup achieving a "no-evidence of disease" (NED) status experienced excellent long-term outcome, with 100 % and 98 % of 5-year PFS and OS rates, respectively, that were maintained at 10 years. Conversely, patients failing to achieve a NED status experienced substantially more dismal prognosis, with 12 % and 45 % 5-year PFS and OS, respectively, collapsing to 0 % and 4 %, respectively at 10-year. In this context, the number of metastatic sites was significantly associated with the likelihood of achieving a NED status, and the most solid odd-ratio for NED at the logistic regression analysis has been observed when setting 3 metastatic sites as cutoff[9]. A similar association has been observed in a smaller retrospective series of 73 unselected OM-BC patients (≤5 metastatic sites, ≤2 organs involved, ≤5 cm lesion dimeter), where ≤ 3 lesions were significantly associated with the probability of achieving a complete response after first-line chemotherapy[10,11]. Taken together, these data suggest that the cutoff of 3 metastatic lesions may better recapitulate the OM definition for BC patients.

In the last decades multiple efforts were conducted to better characterize the emerging entity of OM-BC from a prognostic point of view.

Intuitively, among OM-BC, a positive association between decreasing number of metastatic sites and improved prognosis has been consistently reported. In a retrospective dataset of 122 OM-BC patients (≤5 metastatic sites), fewer metastatic sites were significantly associated with improved OS, with patients with an isolated metastatic lesion exhibiting the most favorable prognosis as compared to those with 2–4 metastases, especially when considering luminal and HER2 + BC subtypes. The positive prognostic impact of isolated metastatic site has been also confirmed across different sites/organs involved, including lymph nodes, lung, liver and bone[12,13].

Besides the disease burden, several other factors have emerged as capable of providing prognostic information in patients with OM-BC. In detail, younger age at diagnosis, favorable performance status, longer DFI from surgery, non-triple negative subtype and no-CNS/liver involvement, have been consistently associated with improved OS in unselected BC patients[8,12,13]. Notably, the prognostic impact of specific metastatic sites has been also confirmed specifically in HER2 + MBC, where patients with bone or CNS involvement exhibited poorer OS than those with no-bone or no-CNS disease[9].

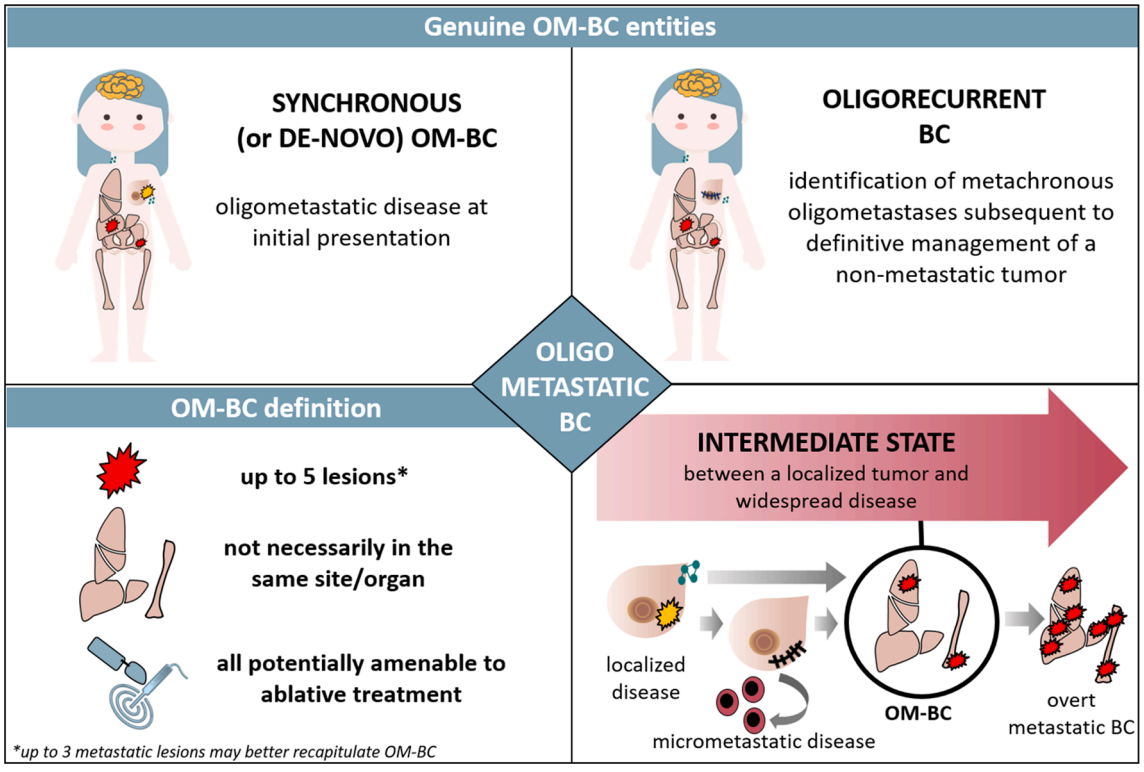

Fig. 1. Oligometastatic breast cancer definition and main features. Abbreviations: OM, oligometastatic; BC, breast cancer.

Clinical and biological rationale for pursuing curative intents in OM-BC

One of the most debated issues is represented by the actual clinical value of integrating a locoregional approach into the framework of OM-BC management. A growing body of evidence suggest that OM-BC patients undergoing multimodal treatments, including locoregional strategies, may experience excellent prognosis.

Interestingly, one of the pivotal evidence in this regard comes from a retrospective report of 45 patients with limited stage IV disease who underwent local excision of all evaluable disease, subsequent doxorubicin-based chemotherapy, followed by a late-consolidation with a non-cross-resistant regimen. At a median follow-up of 44 months, more than a half of patients with stage IV NED status were alive and disease-free[14]. Similarly, in a subsequent retrospective series of OM-BC patients treated with systemic therapy with or without locoregional treatment, approximately 25 % of them were relapse-free at 25-year thus suggesting that a substantial proportion of OM-BC receiving multimodal treatment may achieve a sustained NED status[10]. Subsequently, other retrospective reports were consistent in suggesting favorable long-term outcome of OM-BC receiving multimodality approach encompassing both locoregional and systemic treatments [12,13].

Notably, results from several prospective single-arm trials where patients with OM-BC underwent an integrated approach of ablative locoregional treatments (surgery and/or radiotherapy) and systemic therapy overall strengthened the notion that a not negligible proportion of OM-BC patients may experience prolonged DFS and OS with combined-modality treatment, with also a subgroup of them potentially accomplishing curability.

In detail, in a pooled analysis of 3 prospective trials of anthracycline-based chemotherapy (n = 259) in patients with stage IV NED status after radical resection of isolated recurrence (surgery +/- radiotherapy), 5-year DFS and OS were 41 % and 56 % respectively, with even 26 % of 20-year DFS and OS[15]. Consistently, a prospective trial of sequential anthracycline-docetaxel chemotherapy conducted in a similar population and setting reported 34 % and 59 % of 5-year DFS and OS, respectively[15].

Noteworthy, Milano et al. prospectively treated 48 BC patients with 1–5 extracranial oligometastases with hypofractionated stereotactic body radiotherapy (SBRT) to all sites of disease, obtaining a 5- and 10-year OS rates of 83 % and 75 %, respectively, for patients with bone-only disease in respect to 31 % and 17 %, respectively, for patients with non-bone-only disease[16].

A phase II single arm trial conducted by Trovò et al enrolled 54 BC patients with up to 5 extracranial metastases to receive SBRT or treatment with intensity modulated radiation therapy (IMRT) in addition to systemic therapy in 89 % of cases. At a median follow-up of 30 months, authors reported 1- and 2-year PFS rates of 75 % and 53 %, respectively, while 2-year local control and OS were 97 % and 95 %, respectively. Radiation therapy was well tolerated, with no reported grade $\geq$ 3 adverse events[17].

Of course, it should be noted that in the abovementioned studies the allocation to ablative locoregional approach was not driven by randomization, but rather clinical considerations, and subsequently the presence of a selection bias should be acknowledged as inevitable. However, overall, based on these data it can be postulated that women with limited disease burden have a different and more favorable natural history as compared to those with overt metastatic disease, thus uncovering the possibility to aspire to curability.

From a biological point of view, several efforts have been made in order to shed light on the phylogenetic evolution of metastatic BC progression. However, a comprehensive and reliable elucidation of this issue have been mostly limited in scope by the difficulty to have access to all the metastases for each patient, thus downsizing the representativeness of analyzed samples. Nonetheless, in the last years, some insights have been uncovered, generating compelling and enlightening hypotheses. In more detail, whole-genome sequencing-based studies have attempted to phylogenetically reconstruct BC progression[18,19], revealing that 2 possible scenarios may be outlined, as summarized in Fig. 2: a) the most common highlights the crucial evolutionary role of the primary tumor, which represents the main parental seeding source. According t this model, the primary tumor triggers the metastasis-to-metastasis dissemination; in this context, the genomic features of the primary tumor may be a reliable proxy of clones subsequently generating overt metastases, with the majority of parental driver alterations detected in the primary tumor being also detectable in the context of distant sites. However, it has been reported a much wider genomic heterogeneity within the metastatic lesions than the matched primary tumor, thus suggesting that after dissemination, the clonal evolution proceeds, resulting in an additional burden of private somatic mutations. b) The second scenario implies that metastases themselves may represent an additional source of seeding, with multiple parallel seeding events occurring from both the primary tumor and metastases, with these latter triggering daughter metastasis-to-metastasis dissemination.

Overall, this clinical and biological framework generates several orders of hypotheses and considerations regarding the rationale of pursuing a curative intent for the management of OM-BC (Fig. 3). Firstly, the wider genomic variability of metastatic disease as compared to the primary tumor strengthens the importance of distant site re-sampling in order to capture additional alterations that would otherwise be missed if focusing only on the primary tumor profile[5,20–23]. This consideration acquires a crucial importance within the contemporary therapeutic landscape of MBC, where the access to several highly effective treatment strategies is contingent to the ascertainment of a positive result for the matched actionable biomarker. Secondly, it could be postulated that surgery of the primary tumor in case of de-novo OM-BC diagnosis may allow to disrupt the metastatic dissemination cascade triggered by the primary tumor itself, thus limiting the clonal selection of aggressive and treatment-resistant clones. Thirdly, based on the assumption that metastases represent an additional source of seeding and contribute to increasing the genomic heterogeneity of metastatic disease, ablative locoregional treatments of all metastatic sites may limit this further clonal evolution. This may be crucial in the context of OM-BC, in order to prevent the acquisition of a full metastatic potential. Fourthly, given the consistency of evidence supporting OM-BC as a distinct entity characterized by a more indolent nature as compared to disseminated metastatic disease, it is questionable whether the diagnosis of OM-BC should be “forced” by promoting the implementation of an intensive follow-up for EBC patients at high risk of relapse.

Primary tumor resection in de-novo OM-BC

In the last few years, the role of the primary tumor surgery in de-novo stage IV BC patients has been object of intense debate in the light of the controversial results from several clinical trials[24–27], which are summarized in Table 1.

None of these trials was specifically focused on OM-BC, however, some insights may be extrapolated. Briefly, considering the open label randomized trial by the Tata Memorial Centre[24] and the phase III randomized MF07-01[26], ABCSG-POSYTIVE[25] and ECOG-ACRIN 2108[27] trials, 972 patients were collectively included and randomized to receive systemic therapy with or without primary tumor resection. While the MF07-01 and the ABCSG-POSYTIVE trials included purely treatment naïve stage IV BC populations, the Tata Memorial Centre study allowed the inclusion of patients with not-resectable tumors responding to induction chemotherapy and the ECOG-ACRIN 2108 included patients exhibiting no progression of distant disease after 4/8 months of first-line systemic therapy. Overall, they all failed to meet their primary endpoint of OS improvement with primary tumor resection as compared to systemic therapy alone. Notably, the MF07-01 trial formally designed to test 3-yr OS, suggested a signal of better OS with

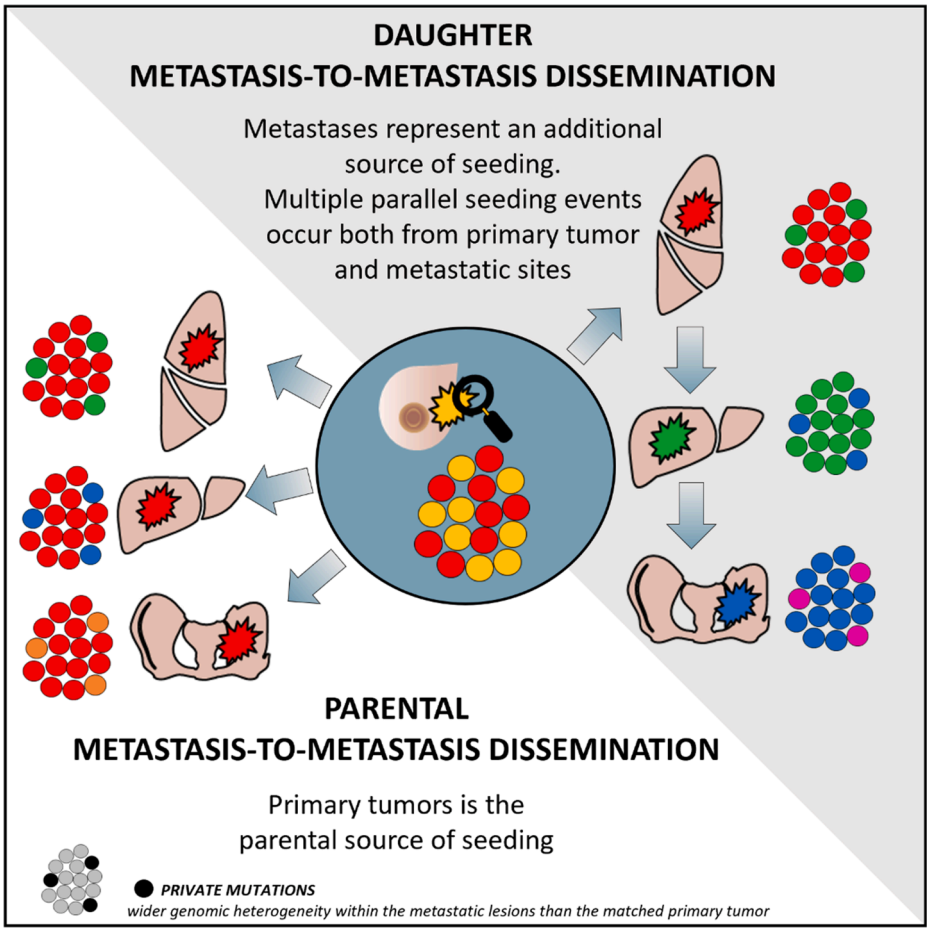

Fig. 2. Main scenarios of the phylogenetic evolution of metastatic BC progression.

the locoregional approach at longer follow up (5 year). Regarding the role of tumor phenotype, a possible benefit in favor of the locoregional approach was observed in the MF07-01 trial within the subpopulation with HR+/HER2- phenotype. On the other hand, ECOG-ACRIN 2108 trial described a detrimental effect for the triple-negative subgroup. It should however be noted that all these trials were not biology-driven (unselected patients' populations in terms of tumor biology/BC phenotype), the type of systemic therapy was in most cases left to the investigator's choice[25–27] (according to local standards), resulting in a wide heterogeneity, and systemic treatments adopted across trials are mostly no longer representative of the current standard of care. In addition, ablative therapy of metastases was not required and, when reported, the proportion of patients receiving locoregional approaches targeted to metastatic lesions was lower than one third, with no mention in terms of locoregional treatment intent (curative vs palliative). Subgroup analyses also showed a consistent lack of OS benefit within the locoregional treatment arms across subgroups defined by the metastatic burden (when reported), with the only exception of a possible signal of benefit for patients with isolated bone metastases[26]. Although data from these studies may suggest that the lack of clinical benefit derived from the primary tumor resection might be generalized to the OM-BC subgroup, this extrapolation deserves caution. In particular, two of the four trials did not report the proportion of patients with OM-BC and even those reporting data on subgroups defined by the metastatic burden, did not adopted the currently accepted definition of OM-BC (25 % of patients from the Tata Memorial Centre had $\leq$ 3 metastatic lesions, approximately 30 %[24] of MF07-01 patients exhibited an isolated lesion[26], and data are missing for the ABCSG-POSYTIVE[25] and ECOG-ACRIN2108[27] trials).

Based on these observations, primary tumor resection for de-novo stage IV BC patients, including those with OM-BC, should not be considered as a standard approach (Fig. 3). However, given the important trial limitations discussed above, there might be still room for improvement, especially in the subgroup of patients with limited tumor burden. In this context, results from more recent ongoing trials are highly awaited[28].

Ablative therapy of metastatic lesions

The increasing knowledge about the biological drivers of OM-BC as well as the constant improvement of locoregional techniques with minimally-invasive impact have fueled the interest towards the clinical value of pursuing an eradication intent when treating BC metastases. As already mentioned, available evidence overall generated the hypothesis that OM-BC patients receiving locoregional treatment with curative purposes may experience favorable long-term outcome.

However, concerns regarding the solidity of results derived from retrospective reports or single-arm prospective trials prevented such approach to be formally included in OM-BC treatment framework.

In this context, evidence gathered from phase 2 randomized trials conducted in OM patients with other cancer types (Non Small Cell Lung Cancer [NSCLC][29,30], colorectal cancer with liver metastases[31]) highlighted that the integration of metastases-directed ablative therapy to standard-of-care systemic therapy may enhance progression-free survival (PFS)[30] or overall survival (OS)[29,31], thus furnishing the urgency to assess the clinical value of such approach also (or specifically) in BC. Noteworthy, one of the pivotal evidences in this regard comes from the histology agnostic phase II SABR-COMET trial[32,33],

Table 1
Randomized trials of primary BC surgery in MBC.

	Treatment arms (n)	BC phenotype			Metastatic sites			Systemic treatment		Locoregional treatment on metastases		Main results
		HR	HER2	ER-/HER2-	OM-BC	Bone-only	Visceral	CT	ET	RT	Surgery	
Tata Memorial Trial[24]	LC (173)	HR+, 102 HR-, 71	HER2+, 45 HER2-, 124	NA	44***	50	123	166	7	0	0	No difference in OS
	NO LC (177)	HR+, 106 HR-, 71	HER2+, 62 HER2-, 108	NA	45***	50	127	170	7	0	0	
ABCSG-28 POSYTIVE Trial[25]	ST + LC (45)	HR+, 28 HR-, 17	HER2+, 12 HER2-, 32	4	NA	18	27	15	30	18	2	No difference in OS
	ST (45)	HR-, 30 HR-, 15	HER2+, 8 HER2-, 34	4		16	29	17	28	12	3	
MF07-01[26]	ST + LC (134)	HR+, 115 HR-, 19	HER2+, 40 HER2-, 94	10	46****	100	134	124**	NA	34		No difference in 3-y OS (primary endpoint) Better 5-y OS in LC + ST vs ST Signal for better OS: HR+/HER2-, age < 55, bone-only solitary metastasis
	ST (131)	HR + 95 HR-, 36	HER2+, 37 HER2-, 94	23	35****	88	131	115**	NA	42		
ECOG-ACRIN 2108[27]	ST + LC (125)	HR+, 73 HR-, 52	HER2+, 38 HER2-, 82	9	NA	47	14*	NA	NA	0	0	No difference for OS Signal for worse OS for TNBC
	ST (131)	HR+, 73 HR-, 58	HER2+, 41 HER2-, 84	11		56	13*			0	0	

* visceral only.
** anthracycline-based CT.
*** ≤3 sites.
**** isolated metastases (bone or visceral).

investigating whether the non-invasive radiation technique of stereotactic ablative radiotherapy (SABR or SBRT) associated to standard palliative therapy may enhance outcome in patients with OM solid tumors, including BC (up to 5 metastatic lesions). Among 99 cancer patients included in the study, 18 patients presented with OM-BC, 5 of whom were assigned to the SBRT/SABR arm. Importantly, all patients had their primary tumor removed at least 3 months before trial enrollment with no evidence of local progression. Overall, the trial met its primary endpoint by demonstrating an OS advantage with SBRT/SABR combined to standard palliative approach (HR 0.57, p = 0.09, with a two-sided alpha of 0.20). The trial was amended in 2016 to extend follow-up to 10 years, and the results beyond 5 years confirmed durable improvements in OS and PFS, with a proportion of patients (21.3 %) achieving more than 5 years of survival without recurrence[34]. However, it should be mentioned the occurrence of 3 treatment-related deaths in the SBRT/SABR arm (4.5 %), which was higher than expected despite the implementation of stringent preventive measures, highlights a gap of knowledge regarding the maximum number of metastatic lesions to be irradiated with acceptable risk. Reassuringly, no new major toxicity signals were captured with extended follow-up. In addition, the transferability of SABR-COMET results to general OM-BC population may be limited by the small number of BC patients included in this pivotal study.

Starting from these considerations, the randomized phase II/III NRG-BR002 trial was conducted with the aim of investigating the role of metastasis-directed therapy specifically in OM-BC patients receiving first-line standard of care systemic treatment[35]. In particular BC patients with up to 4 metastatic lesions (≤5 cm), all amenable to SBRT/SABR or surgical resection, with controlled locoregional disease and who have received up to 12 months of first-line systemic therapy with no evidence of progression were included. Stringent protocols for SBRT/SABR derived from the early-stage NRG-BR001 study[36] were adopted in order to deliver the highest biological doses without hampering safety. Among 125 OM-BC patients, the majority had isolated metastatic lesions and exhibited HR+/HER2- BC phenotype. First-line systemic therapy consisted on chemotherapy, endocrine-based treatment and targeted therapy in 27 %, 76 % and 67 % patients, respectively. Unexpectedly, the trial failed to meet the primary endpoint of PFS, showing 19.5 months and 23 months of median PFS with first line systemic therapy with and without SABR/SBRT, respectively. Consistently, no OS benefit was captured. In addition, while the locoregional approach appeared to have a preventing effect in terms of development of new lesions inside the index area as first site of failure, no effect was observed for the occurrence of new lesions outside the index area. Reassuringly, only one grade 4 and no grade 5 toxicity events were reported.

Overall, data from the phase II part of the NRG-BR002 trial do not support ablative locoregional treatment for OM-BC receiving standard first-line treatment, thus representing a “no-go” signal for the originally planned phase III part of the trial. However, results from this study provided interesting insights. Firstly, OM-BC is overall associated with relatively favorable long-term outcome with approximately 70 % of OS probability at 3 years, thus further solidifying OM-BC as a more indolent entity as compared to widespread MBC. Secondly, median PFS with systemic therapy-only over-performed than expected (23 months versus

the expected 10.5 months), thus suggesting that the contemporary landscape of first-line treatment for MBC may provide a substantial beneficial effect in terms of delay of progression. In this context, an intriguing implication of this observation may be represented by the possibility of pursuing curative goals with systemic therapy alone for de-novo stage IV BC by disengaging from the approach traditionally adopted in MBC, privileging the sequential administration of the most-effective treatments to enhance the progression-free interval, rather than switching them at disease progression. In this context, the ideal experimental scenario to test the clinical value of this approach could be represented by the HER2 + disease, characterized by an exceptionally wide availability of highly effective targeted strategies for MBC, and efforts in this regard are already underway. Thirdly, the exploratory subgroup analysis for PFS of the NRG-BR002 trial captured a trend for improved PFS in favor of the addition of ablative strategies in patients with more than one metastasis, while an effect in the opposite direction was instead captured for TN subgroup. Although the substantial under-representation of these subgroups in the NRG-BR002 trial imposes caution in the interpretation of results, they overall generate some interesting hypotheses that may guide and fine-tune the future investigation of ablative metastasis-directed treatment.

Within this uncertainty, the adoption of a more selected biology-driven approach appears crucial in order to prioritize the investigation of ablative metastasis-directed therapy in the subgroups of patients more likely to derive long-term benefit with such approach. Other randomized phase II-III trials evaluating local ablative approaches in combination to systemic therapy in BC patients are ongoing (Table 2), and first results are eagerly awaited in the next few years.

For the time being, global ablative approach for OM-BC should only be reserved to highly selected OM-BC patients, after ascertaining response to biology-driven standard first-line treatment and after entering a careful discussion with the patient regarding the risk benefit-ratio of such approach (Fig. 3).

Should we force the diagnosis of OM-BC?

For EBC patients entering the follow up period, there is strong evidence supporting routine breast radiological examination (mammography, breast US and MRI in selected cases) in order to detect early local relapses or contralateral tumors[37]. Conversely, no solid data from randomized trials area currently available supporting the association between early detection of distant relapse and survival benefit. For this reason, international EBC guidelines do not recommend the implementation of specific follow up procedures in asymptomatic patients [37], namely imaging and laboratory tests including serum tumor markers, intended for this specific purpose. However, the lack of data regarding the value of an intensive follow up in a contemporary scenario, characterized by unprecedented availability of effective systemic treatments and technical advancements of locoregional approaches, imposes a rethinking of follow up recommendations.

Within this uncertainty, it may provocatively be speculated that anticipating MBC diagnosis at the stage of OM disease may be beneficial to enhance treatment activity and efficacy (Fig. 3). This aproach may acquire a well-timed relevance if focusing on one of the most challenging clinical settings, namely metastatic TN BC[38]. Indeed, the current standard of care for newly diagnosed TN BC patients with PD-L1 positive status is represented by immune checkpoint inhibition (atezolizumab/pembrolizumab) plus chemotherapy, based on the results from the Impassion130[39] and Keynote355[40] phase III trials. Data from pivotal trials of immunotherapy for TN MBC overall suggest a strong inverse association between the pre-treatment status of TN MBC patients and benefit from immunotherapy, with an enhanced effect observed when immunotherapy was administered in earlier lines[41–46]. This clinical observation finds its biological rationale in the well-accepted notion that the metastatic progression is accompanied by a progressive acquisition of an immune-restricted status (immune evasion), characterized by a less hostile and more permissive environment for tumor growth, sustained by both cancer cell-intrinsic and -extrinsic features. In particular, the evolution towards an overt metastatic phenotype is associated with progressively inefficient antigen presentation mechanisms, increased tumor clonality and heterogeneity, as well as an enrichment of tumor microenvironment for immunosuppressive subpopulations and its contextual pauperization for cells with a cytotoxic polarization[47–52].

Based on these observations, and based on the assumption that the immuno-editing process leading to immune evasion is a continuum[53], the implementation of an intensive follow-up in high-risk TN EBC patients, may serve for the purpose of distant metastasis early detection, thus potentially maximizing the benefit from immunotherapy in this specific subpopulation.

In this connection, another question deserving to be answered is: how far can we go in terms of OM-BC definition? (Fig. 3).

As widely discussed above, the general definition of OM-BC traditionally refers to the presence of a limited burden of macrometastatic disease. However, it has been recently demonstrated the clinical validity of ctDNA monitoring for molecular relapse detection in BC patients completing curative treatment for early-stage disease, including TNBC. In particular, it has been consistently reported that tracking tumor somatic mutations through ctDNA monitoring may allow the identification of molecular relapse ahead of clinically-overt relapse, with a lead time ranging from approximately 10 to 24 months across studies[54,55]. Interestingly, residual molecular disease at diagnosis was significantly

Table 2
Ongoing randomized phase II/III trials of local ablative therapy + systemic therapy in BC.

Identifier	Phase	Patients	End of Study	Primary Endpoint(s)	Local treatment	Number and site of metastases allowed	Tumour biology
NCT04413409 (OMIT)	Phase III randomized	172	2025	OS	Surgery	≤3 metastatic lesions, involving 1–2 organs, single lesion ≤ 5 cm	Any
NCT04495309 (OLIGOMA)	Phase III randomized	564	2025	PFS HRQoL	SBRT	Up to 5 clinically manifest metastases (maximum 3 CNS lesions)	Any
NCT04698252 (LARA)	Phase II randomized	74	2031	PFS	SBRT, surgery, RFA	1–4 bone lesions; 1–4 lung and/ or liver lesions	HR+/HER2-
NCT04424732	Phase II single arm	50	2026	PFS	SBRT	1–3 bone metastases	Any
NCT03750396 (CLEAR)	Phase II single arm	110	2025	PFS	Palliative RT, SBRT, surgery, RFA	≤2 lesions in single organ or site (lung, bone, liver, adrenal glands, nodal)	HR+/HER2-
NCT02089100 (STEREO-SEIN)	Phase III randomized	280	2023	PFS	SBRT	≤5 metastatic lesions	HR+ (HER2+/-)
NCT05301881 (COSMO)	Phase II single arm	118	2040	PFS	SBRT, surgery, RFA	Oligoprogression defined as 1–2 metastatic lesions, limited to one organ, or the primary tumour or regional nodes	Any
NCT05377047 (TAORMINA)	Phase III randomized	345	2027	OS	SBRT	1–5 lesions in 1–2 organs	Any

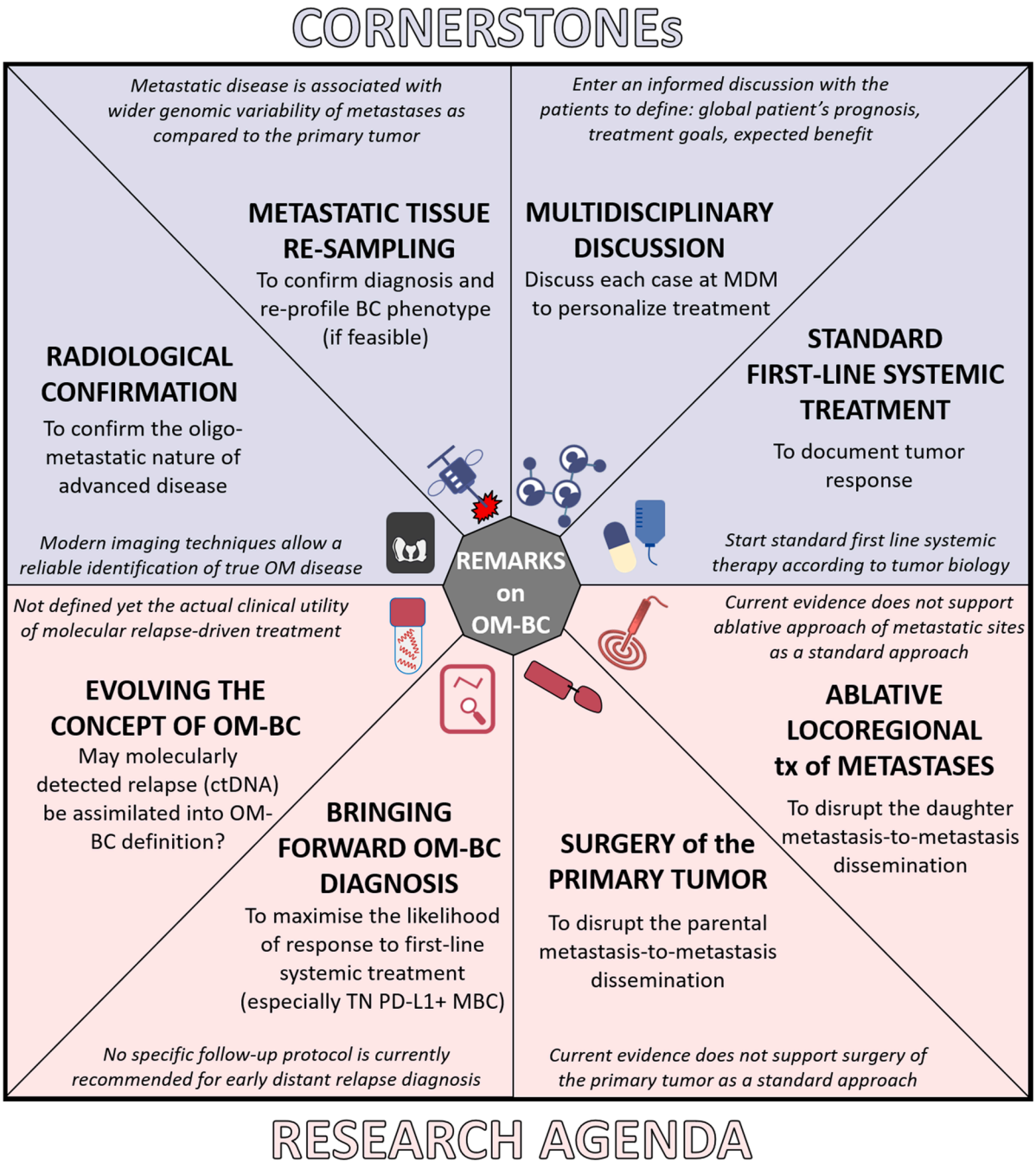

Fig. 3. Cornerstones and main areas of uncertainties regarding oligometastatic breast cancer management. Abbreviations: OM, oligometastatic; BC, breast cancer; MDM, multidisciplinary meeting; TN, triple-negative.

associated with higher risk of clinical relapse. In particular, patients with positive ctDNA status experienced poorer relapse-free survival as compared to those who were ctDNA-negative and this prognostic association was consistent across subgroup defined by BC subtype and disease burden at diagnosis. Based on this promising pivotal evidence, the phase II c-TRACK TN trial was conducted aiming to assess the proof of principle of the clinical utility of ctDNA assays in guiding therapy for high-risk TNBC molecular relapser[56]. In particular, 208 patients completing treatment for TN EBC, exhibiting residual disease after neoadjuvant therapy or either pT2 or pN + tumors at the primary surgery, underwent active ctDNA surveillance and those found to be ctDNA-positive were randomized to either observation or immunotherapy with pembrolizumab. Although data regarding the clinical value of starting pembrolizumab in patients with isolated molecular relapse are pending, preliminary results uncover interesting insights. In particular, it has been reported that the proportion of patients with positive ctDNA was significantly higher in patients defined as belonging to the higher risk category, based on the burden of either residual disease or primary tumor at surgery, thus outlining a subgroup of patients were the investigation of the clinical utility of serial ctDNA monitoring-based surveillance may deserve to be prioritized in future trials. In addition, overt clinical metastatic disease was found in more than 70 % of patients at the time of ctDNA detection (greater than70 %), thus suggesting that the rate of undiagnosed metastatic disease in asymptomatic patients with high-risk TN EBC may be more meaningful than expected.

Overall, available evidence hints that OM-BC definition is expected to undergo a substantial revolution in the near future, progressively switching from a merely quantitative clinically-based definition

(macrometastatic disease) to a more molecularly-based definition, to incorporate clinical risk factors, tumour biology, host biology and novel biomarkers (mainly blood-based biomarkers such as ctDNA) to define the metastatic spectrum and select OM patients with truly limited metastatic capacity that can potentially derive a higher benefit from the addition of local therapies[57] (Fig. 3)..

Unluckily, due to the scarcity of currently available biomarkers, the diagnosis is still only based on imaging findings. In this context, rapid advances in imaging landscape is allowing the identification of small metastases and consequently a better differentiation between oligometastatic and polymetastatic disease, excluding patients with more widespread disease from unnecessary local treatment and potentially leading to systemic therapy de-escalation in patients with a low burden of lesions[58].

Within this framework, promising - albeit preliminary - hints have been captured across studies adopting a more qualitative approaches to investigate OM disease. Interestingly, some hypothesis-generating studies analyzed specific microRNAs from patients who underwent lung resection for oligometastases from any primary site[59] or SBRT to any site[60–62]. MicroRNAs can differentiate oligometastatic to polymetastatic phenotypes, and select microRNAs able to convert stable oligometastases to polymetastatic progression in xenograft model. Furthermore, immunologic and inflammatory markers may predict outcomes of BC patients undergoing SBRT[63–65] and the use of this locoregional approach may contribute to break local tolerance and release tumour-associated antigens (TAAs), improving the efficiency of host antitumor immunity. Interestingly, in a study in which 21 BC patients with up to six metastases were treated with three daily doses of 10 Gy, and whose blood samples for immune profiling were collected before and after treatment, a boosting or even the de novo appearance of polyfunctional CD4 + and CD8 + T cell responses against known BC TAAs (survivin, mammaglobin-A, HER2) were reported in a third of cases, one month after SBRT. In addition, half of patients showed increased numbers of activated natural killer (NK) cells, immediately after the first fraction of SBRT. Liquid biopsy might thus represent a useful resource to monitor the potential immunogenic effects of SBRT [64].

Conclusions

To conclude, the oligometastatic status still represents one of the main burning and multidisciplinary challenge for BC treatment. Available evidence currently does not support the systematic adoption of ablative locoregional treatment for OM-BC as a standard approach. However, results of ongoing clinical trials as well as a further understanding of the value of locoregional approach in different BC biological subtypes might be crucial to fully capture the uniqueness of OM-BC entity.

Indeed, conflicting results from available literature push forward a higher-level research scenario, where treatment techniques, patient- and tumour- characteristics, together to translational evidence and modern diagnostic imaging strategies integration and selection are crucial.

Competing interests

FM reports personal fees from Novartis,Roche and Gilead, outside the submitted work. GG reports personal fees from EliLilly and Novartis, outside the submitted work. MVD reports personal fees from EliLilly, Exact Sciences, Novartis, Pfizer, Seagen, outside the submitted work. IM reports occasional speaker honoraria supported by Eli Lilly, Novartis, Pfizer, Accuray, and Seagen, outside the submitted work. VG reports personal fees from Eli-Lilly, Novartis, MSD, GSK, Gilead, EISAI, Amgen, outside the submitted work. The remaining authors declare no competing interests.

CRediT authorship contribution statement

Federica Miglietta: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Luca Visani:** Methodology, Investigation, Writing – original draft, Writing – review & editing. **Sabrina Marini:** Writing – original draft, Writing – review & editing. **Gaia Griguolo:** Writing – original draft, Writing – review & editing. **Grazia Maria Vernaci:** Writing – original draft, Writing – review & editing. **Michele Bottosso:** Writing – original draft, Writing – review & editing. **Maria Vittoria Dieci:** Conceptualization, Methodology, Writing – review & editing. **Icro Meattini:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Valentina Guarneri:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

The 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.

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