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The evolving landscape of hormone receptor-positive/HER2-negative metastatic breast cancer (EVOLVE): An Italian Delphi consensus report

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ABSTRACT

Background: The expanding treatment landscape for patients with hormone receptor-positive, HER2-negative (HR+/HER2-) metastatic breast cancer (mBC) has led to the emergence of new "grey areas" not covered by international guidelines, where treatment decision making is particularly challenging.
Methods: Sixteen relevant statements regarding the management of HR+ /HER2- mBC were formulated by an Executive Board and validated by a Scientific Board, composed by internationally recognized experts in the field of BC. Subsequently, 50 Italian oncologists were surveyed between May 2024 and June 2024 through the modified Delphi method, in order to capture their rate of agreement and disagreement on the proposed statements.
Results: The consensus was reached for all 16 statements: 4 were related to resistance and sensitivity to CDK4/6 inhibitors and endocrine therapy, 6 to biomarkers for HR+ /HER2- mBC, and 6 to treatment algorithm of HR+ /HER2- mBC. The Panel critically and comprehensively discussed the most relevant results, especially regarding the statements with lower level of agreement (which ranged from 85.4 % to 100 %).
Conclusions: The treatment of HR+ /HER2- mBC is currently being reshaped due to the expansion of its pharmacopoeia, the better understanding of its molecular determinants and the validation of biomarkers for patient selection. This consensus addressed the most controversial questions related to treatment decision and reached the agreement in all statements.

1. Introduction

Breast cancer (BC) is the most prevalent solid tumor in women, with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) representing the most common subtype (65–75 % of all new cases) (Siegel et al., 2024; Loibl et al., 2021). Although the continuous diagnostic improvements and the pharmacopoeia expansion have significantly enhanced curability rates, a minority of patients with HR+ /HER2- BC still experience metastatic recurrence or present *de novo* metastatic disease, which represent virtually incurable conditions (Gennari et al., 2021).

The prognosis of patients with HR+ /HER2- metastatic or advanced inoperable BC (mBC) is improving year by year, due to the access to high quality multidisciplinary care, as well as the continuous development of innovative systemic therapies (Cardoso et al., 2024). Notably, the addition of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) to endocrine therapy (ET) as a first-line treatment has dramatically enhanced progression-free survival (PFS) in all key studies, with further significant improvements in overall survival (OS) observed with abemaciclib (in combination with fulvestrant) and ribociclib (with fulvestrant or an aromatase inhibitor) (Gao et al., 2020). In parallel, many targeted agents (with or without ET) have been approved in the post-CDK4/6i setting, where guidelines provide a biomarker-driven treatment algorithm which includes: PARP inhibitors for patients with a germline *BRCA1* or *BRCA2* pathogenic variant, fulvestrant plus alpelisib in case of phosphatidyl inositol-3 kinase (*PIK3CA*)-mutant tumors, fulvestrant plus capivasertib for patients with PI3K pathway–altered tumors (*PIK3CA or* protein kinase B [*AKT1]* activating mutations*, or* phosphatase and tensin homolog [*PTEN*] inactivating alterations), elacestrant for patients harboring activating mutations in the estrogen receptor gene ligand-binding domain (*ESR1*) (Gennari et al., 2021; Valenza et al., 2024a). Furthermore, the treatment landscape has evolved substantially also for endocrine-refractory patients, after the introduction of innovative chemotherapy-based strategies, namely antibody-drug conjugates (ADCs), such as trastuzumab deruxtecan and sacituzumab govitecan (Modi et al., 2022; Bardia et al., 2024a; Rugo et al., 2023).

However, the concomitant regulatory approval of multiple treatment options with partially overlapping clinical indications, as well as the anticipation of the most active treatments in the non-metastatic setting, such as CDK4/6is, have led to the emergence of new clinical conditions where treatment decisions are particularly challenging and which currently represent "grey areas" not covered by the international guidelines (Gennari et al., 2021; Cardoso et al., 2024; Johnston et al., 2023; Slamon et al., 2024a).

Within this framework, a panel composed of internationally recognized Italian oncologists (expert in BC) formulated several relevant statements regarding the management of patients with HR+ /HER2- mBC, aiming to describe the agreement of the Italian oncology community on the most relevant and controversial treatment scenarios.

2. Methods

The development and validation of the statements followed a structured methodology aimed at ensuring transparency, scientific rigor, and expert representativeness. Topic selection was informed by both gaps in the literature and emerging needs in Italian clinical settings, with the goal of addressing areas of uncertainty or variability in prescribing practices.

Based on these priorities, sixteen relevant statements regarding the management of HR+ /HER2- mBC were formulated by an Executive Board and validated by a Scientific Board, each composed of 8 internationally recognized experts in the field of BC, thus ensuring a high level of clinical expertise to develop clinically relevant statements. During a dedicated virtual meeting, the faculty reviewed, revised, and validated each statement, resulting in the final version. Statement generation and validation took place between January 2024 and March 2024. The statements addressed 3 major areas: resistance and sensitivity to CDK4/6i and ET, biomarkers for HR+ /HER2- mBC, treatment algorithm of HR+ /HER2- mBC.

The finalized statements were subsequently submitted for voting via an online questionnaire, distributed through a private link. Access was restricted to eligible participants, including board members, faculty, and coordinators of Italian Breast Units (from either hub or spoke centers, and identified through official regional oncology networks and relevant scientific societies). The survey was conducted entirely online, asynchronously, within a predefined time window. Data were exported and analyzed using standard statistical methods to calculate agreement rates. Consensus was predefined as $\geq$ 66.6 % agreement or disagreement for each statement.

The Delphi method (Milholland et al., 1973) represents a survey approach aiming at quantifying the agreement and disagreement levels to develop a consensus. For each statement, the voters were asked to express a preference among the following options: a) completely disagree (contributing to the “disagreement”); b) partially disagree

(contributing to the "disagreement"); c) partially agree (contributing to the "agreement"); d) agree (contributing to the "agreement"); e) completely agree (contributing to the "agreement").

Agreement or disagreement was deemed achieved if more than 66.6 % of the responses aligned in either direction. If this threshold was not met, consensus was considered unattained.

The findings of this survey were later discussed during a meeting (June 2024), which involved the Executive and Scientific Boards, as well as a faculty composed of 21 highly-profiled oncologists dedicated to BC, utilizing the Nominal Group Technique (NGT).

Data were analyzed applying descriptive statistics.

3. Results

Overall, 50 Italian oncologists were surveyed: 42 (84 %) worked in a hub oncology department and 15 (30 %) served as breast unit director.

The statements were divided into 3 main topics, as follows:

Resistance and sensitivity to CDK4/6 inhibitors and endocrine therapy

1. In patients with early-stage BC treated with adjuvant CDK4/6 inhibitors (CDK4/6i), primary endocrine resistance is defined as invasive disease relapse while on CDK 4/6i + endocrine therapy (ET) or within 12 months from CDK4/6i completion
2. In patients with early-stage BC treated with adjuvant CDK4/6i, secondary endocrine resistance is defined as invasive disease relapse after 12 months from CDK4/6 inhibitor completion
3. In patients with advanced or metastatic BC treated with first-line ET plus CDK 4/6i, primary endocrine resistance is defined as progression of disease (PD) within the first 6 months of first-line treatment (while on ET+CDK 4/6i)
4. In patients with advanced or metastatic BC treated with first-line ET+CDK4/6i, secondary endocrine resistance is defined as PD after at least 6 months from ET+CDK4/6i initiation

Biomarkers for HR+/HER2- metastatic BC

5. In patients with BC progressed on first-line CDK4/6i plus ET, PIK3CA and AKT activating mutations, and PTEN inactivating alterations (i.e., PI3K/PTEN/AKT pathway alterations), germline BRCA mutational status and ESR1 mutational status should be assessed, preferably by next generation sequencing techniques (validated assays) covering all clinically relevant alterations, to determine second line treatment access (PI3K/AKT inhibitor+fulvestrant, elacestrant, PARP-inhibitor) according to the respective label indications
6. PIK3CA mutational status may be tested on any available tissue sample (primary or metastasis) or on ctDNA. In case of PIK3CA not detected on ctDNA, PIK3CA should be re-tested on tissue
7. ESR1 mutational status should be assessed at PD on ET-based treatment (+/- CDK4/6i) on ctDNA, also in case of availability of a previous ESR1-wild type report
8. In patients progressing within 12 months from first-line CDK4/6i+ET initiation, ESR1 mutational status assessment should not be prioritized given the limited expected efficacy of elacestrant in this subgroup
9. If technically minimally invasive, hormone receptor and HER2 status should be reassessed through repeated biopsy in case of aggressive clinical course (unusual metastatic pattern, early disease relapse from adjuvant ET initiation or early PD from ET initiation for metastatic BC) only if clinically meaningful
10. HER2-low status may be assessed on primary and/or metastatic samples. In case of HER2-null only available, a revision of the stained sample (if of sufficient quality) or a new sampling should be recommended, when feasible

Treatment algorithm of HR+ /HER2- metastatic BC

11. In patients with metastatic BC, CDK 4/6i+ET is the actual preferred first-line treatment option and may be considered even in case of aggressive disease (symptomatic visceral metastases, rapid disease progression or impending visceral compromise, markedly symptomatic non visceral disease)
12. The choice of the CDK4/6i to be prioritized should be based on: magnitude of clinical benefit, toxicity profile, country-specific availability and patient preferences
13. In the absence of evidence, patients with metastatic BC relapsed on adjuvant CDK4/6i or within 12 months from CDK4/6i completion should not be considered for further CDK 4/6i
14. After progression on first line CDK4/6i+ET, in case of multiple druggable alterations, the choice of second line treatment should be guided by the expected magnitude of clinical benefit, the toxicity profile, country-specific availability and patient's preferences
15. In patients with metastatic BC progressing within 6 months from first-line CDK4/6i+ET initiation, chemotherapy should be preferred over ET-based treatment
16. In patients with HER2-low BC already treated with at least one prior line of chemotherapy, trastuzumab deruxtecan should be prioritized over other chemotherapy

The consensus was reached for all 16 statements (Table 1, Fig. 1), of whom 4 related to resistance and sensitivity to CDK4/6i and ET (from 1 to 4), 6 to biomarkers for HR+ /HER2- mBC (from 5 to 10), and 6 to treatment algorithm of HR+ /HER2- mBC (from 11 to 16).

The level of agreement ranged from 85.4 % to 100 %.

4. Discussion

4.1. Resistance and sensitivity to CDK4/6 inhibitors and endocrine therapy

The first topic that was addressed was the definition of primary and secondary endocrine resistance, which is radically changing by the widespread use of CDK4/6i in the metastatic and early setting, with consequences in terms of treatment decision-making and design of clinical trial for novel ET agents (Gao et al., 2020; Johnston et al., 2023; Slamon et al., 2024a; Lambertini et al., 2023).

According to the updated 6th and 7th international consensus guidelines for the management of advanced BC (ABC), primary ET resistance is defined by disease relapse during the first 2 years of adjuvant ET, or progressive disease within the first 6 months of first line ET-based treatment, regardless the use of additional companion drugs (including CDK4/6i) (Cardoso et al., 2024). Instead, secondary endocrine resistance consists of: disease relapse after the second year of adjuvant ET, disease progression after at least 6 months of first-line endocrine-based therapy, disease progression after a second or subsequent line of endocrine-based therapy for mBC (any duration), or identification of *ESR1* mutation. While the current ABC definitions of endocrine sensitivity/resistance undoubtedly represent a significant step forward towards the dissection of the complexity of the contemporary treatment landscape of HR+ /HER2- BC, their omission of prior exposure to CDK 4/6 inhibitors as a variable in the equation of endocrine resistance has created a zone of uncertainty—a gap that this panel sought to address in the present work, especially in the scenario of recurrent disease after previous exposure to adjuvant CDK4/6i, where the selection of patients for CDK 4/6i re-challenge represents a critical issue. Consensus was reached to define primary resistance as invasive disease relapse on or within 12 months from adjuvant CDK4/6i plus ET in early-stage BC, and secondary resistance as invasive disease relapse after 12 months from adjuvant CDK4/6i completion. The cut-off to distinguish primary from secondary resistance refers to the end of the adjuvant CDK4/6i therapy, whose duration depends on the specific agent (2 years for abemaciclib and 3 years for ribociclib) (Johnston et al., 2023; Slamon et al., 2024a). Instead, as far as patients with mBC treated with first-line ET plus CDK4/6i are concerned, primary

Table 1
Statements and level of consensus.

Statement	Preferences					Consensus reached?	Level of agreement
	Completely disagree	Partially disagree	Partially agree	Agree	Completely agree		
Resistance and sensitivity to CDK4/6 inhibitors and endocrine therapy							
1. In patients with early-stage BC treated with adjuvant CDK4/6 inhibitors (CDK4/6i), primary endocrine resistance is defined as invasive disease relapse while on CDK 4/6i + endocrine therapy (ET) or within 12 months from CDK4/6i completion	2.1 %	6.3 %	4.2 %	**50.0 %**	37.5 %	Yes	91.7 %
2. In patients with early-stage BC treated with adjuvant CDK4/6i, secondary endocrine resistance is defined as invasive disease relapse after 12 months from CDK4/6 inhibitor completion	2.1 %	6.3 %	10.4 %	**54.2 %**	27.1 %	Yes	91.7 %
3. In patients with advanced or metastatic BC treated with first-line ET plus CDK 4/6i, primary endocrine resistance is defined as progression of disease (PD) within the first 6 months of first-line treatment (while on ET+CDK 4/6i)	0 %	6.3 %	14.6 %	**47.9 %**	33.3 %	Yes	95.8 %
4. In patients with advanced or metastatic BC treated with first-line ET+CDK4/6i, secondary endocrine resistance is defined as PD after at least 6 months from ET+CDK4/6i initiation	0 %	4.2 %	22.9 %	**52.1 %**	20.8 %	Yes	95.8 %
Biomarkers for HR+ /HER2- metastatic breast cancer							
5. In patients with BC progressed on first-line CDK4/6i plus ET, *PIK3CA* and *AKT* activating mutations, and *PTEN* inactivating alterations (i.e., *PI3K/PTEN/AKT* pathway alterations), germline *BRCA* mutational status and *ESR1* mutational status should be assessed, preferably by next generation sequencing techniques (validated assays) covering all clinically relevant alterations, to determine second line treatment access (*PI3K/AKT* inhibitor+fulvestrant, elacestrant, PARP-inhibitor) according to the respective label indications	0 %	0 %	6.2 %	41.7 %	**52.1 %**	Yes	100 %
6. *PIK3CA* mutational status may be tested on any available tissue sample (primary or metastasis) or on ctDNA. In case of *PIK3CA* not detected on ctDNA, *PIK3CA* should be re-tested on tissue	0 %	2.1 %	12.5 %	37.5 %	**47.9 %**	Yes	97.9 %
7. *ESR1* mutational status should be assessed at PD on ET-based treatment (+/- CDK4/6i) on ctDNA, also in case of availability of a previous *ESR1*-wild type report	0 %	4.1 %	10.2 %	37.5 %	**47.9 %**	Yes	95.6 %
8. In patients progressing within 12 months from first-line CDK4/6i+ET initiation, *ESR1* mutational status assessment should not be prioritized given the limited expected efficacy of elacestrant in this subgroup	2.0 %	12.5 %	33.3 %	**39.6 %**	12.5 %	Yes	85.4 %
9. If technically minimally invasive, hormone receptor and HER2 status should be reassessed through repeated biopsy in case of aggressive clinical course (unusual metastatic pattern, early disease relapse from adjuvant ET initiation or early PD from ET initiation for metastatic BC) only if clinically meaningful	2.0 %	4.1 %	12.5 %	**43.8 %**	37.5 %	Yes	93.8 %
10. HER2-low status may be assessed on primary and/or metastatic samples. In case of HER2-null only available, a revision of the stained sample (if of sufficient quality) or a new sampling should be recommended, when feasible	0 %	0 %	6.2 %	39.6 %	**54.2 %**	Yes	100 %
Treatment algorithm of HR+ /HER2- metastatic breast cancer							
11. In patients with metastatic BC, CDK 4/6i+ET is the actual preferred first-line treatment option and may be considered even in case of aggressive disease (symptomatic visceral metastases, rapid disease progression or impending visceral compromise, markedly symptomatic non visceral disease)	0 %	4.1 %	14.6 %	**43.8 %**	37.5 %	Yes	95.9 %
12. The choice of the CDK4/6i to be prioritized should be based on: magnitude of clinical benefit, toxicity profile, country-specific availability and patient preferences	0 %	0 %	4.1 %	39.6 %	**56.3 %**	Yes	100 %
13. In the absence of evidence, patients with metastatic BC relapsed on adjuvant CDK4/6i or within 12 months from CDK4/6i completion should not be considered for further CDK 4/6i	2.0 %	4.1 %	25.0 %	**45.8 %**	22.9 %	Yes	93.7 %
14. After progression on first line CDK4/6i+ET, in case of multiple druggable alterations, the choice of second line treatment should be guided by the expected magnitude of clinical benefit, the toxicity profile, country-specific availability and patient's preferences	0 %	0 %	4.2 %	35.4 %	**60.4 %**	Yes	100 %
15. In patients with metastatic BC progressing within 6 months from first-line CDK4/6i+ET initiation, chemotherapy should be preferred over ET-based treatment	2.0 %	10.4 %	18.8 %	**50.0 %**	18.8 %	Yes	87.6 %
16. In patients with HER2-low BC already treated with at least one prior line of chemotherapy, trastuzumab deruxtecan should be prioritized over other chemotherapy	0 %	2.0 %	6.3 %	31.3 %	**60.4 %**	Yes	98.0 %

Legend: CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitors; ctDNA; circulating tumor DNA; ET, endocrine therapy; ESR1, estrogen receptor gene ligand-binding domain; HER2-, HER2-negative; HR+ , hormone receptor-positive; PD, progression of disease.

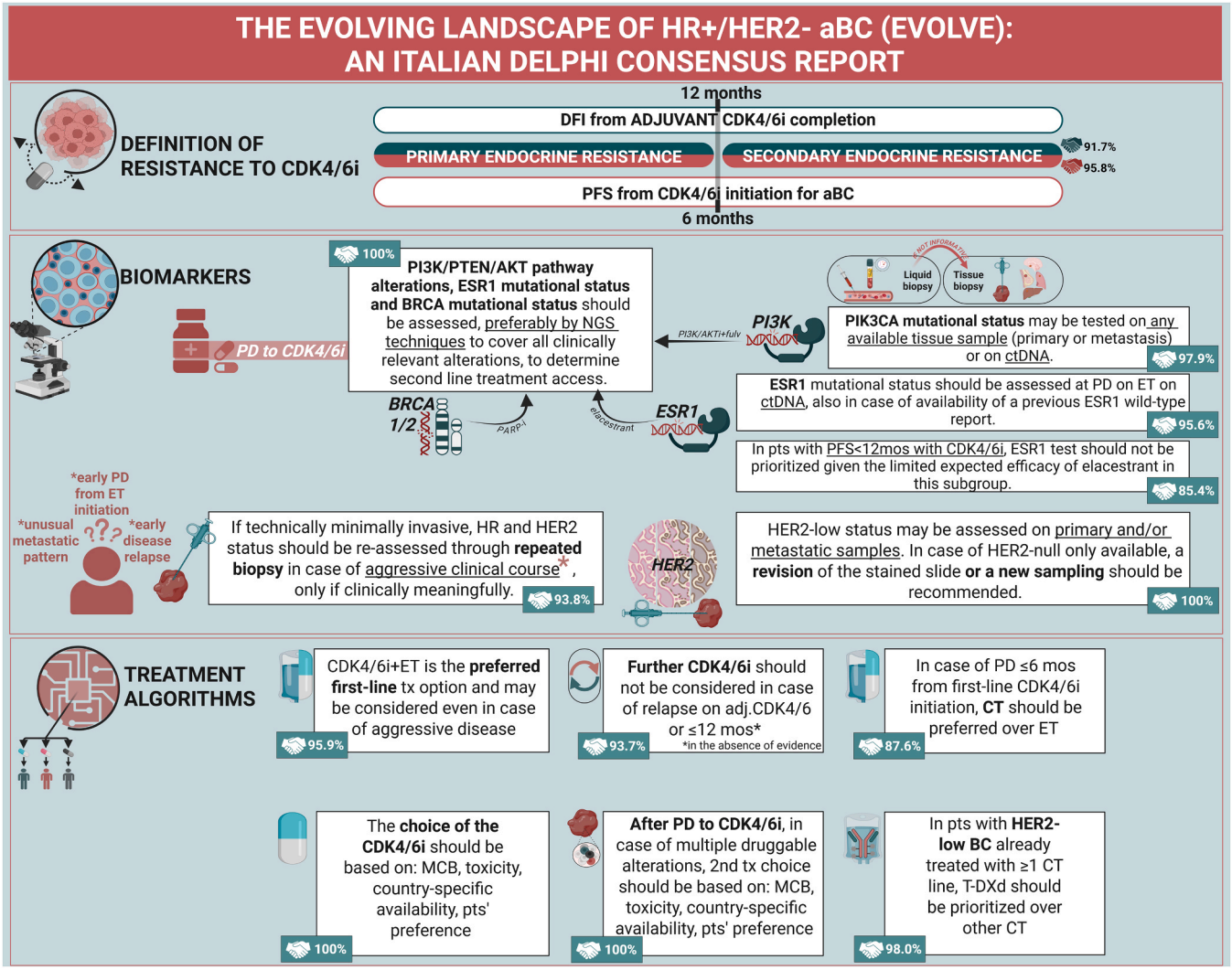

Fig. 1. The evolving landscape of hormone receptor-positive, HER2-negative metastatic breast cancer: statements and level of consensus. **legend**: aBC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitors; ctDNA; circulating tumor DNA; DFI, disease-free interval; ET, endocrine therapy; ESR1, estrogen receptor gene ligand-binding domain; HER2-, HER2-negative; HR+ , hormone receptor-positive; MCB, magnitude of clinical benefit; mos, months; NGS, next-generation sequencing; PD, progression of disease; PFS, progression-free survival; tx, therapy.

resistance is defined as progression of disease within the first 6 months of therapy and secondary resistance after at least 6 months.

Besides the practical implications, the definitions of primary and secondary resistance aim to distinguish distinct disease settings, with peculiar clinical, genomic and prognostic features, which have been demonstrated to evolve according to the type and duration of previous treatments (Bar et al., 2024). In this regard, these definitions should progressively adapt to the evolution over time of the therapeutic landscape. Furthermore, from a purely clinical standpoint, patients with primary endocrine resistance exhibit more unfavorable baseline characteristics (greater stage at diagnosis, poorly differentiated tumors, younger age) and in the presence of these features, a close clinical monitoring when initiating ET may be strategical (Cardoso et al., 2024; Lambertini et al., 2023; Guerrero et al., 2024).

From a molecular perspective, the formal introduction of the *ESR1* mutation as a criterion to define endocrine resistance represents a significant step forward. Nevertheless, a growing body of evidence suggests that endocrine-resistant tumors may exhibit distinct genomic profiles beyond *ESR1* mutations, also depending on the type of endocrine therapy that shaped their resistance (Wander et al., 2020; O'Leary et al., 2018; Condorelli et al., 2018; Herrera-Abreu et al., 2016; Saatci et al., 2021; Goetz et al., 2024a; Chaudhary et al., 2024). In this context, as an example, the Italian experience of the BIOITALEE study proposed serum thymidine kinase 1 (TK1) activity and dynamics (sTKa) as a new biomarker for primary endocrine resistance (Malorni et al., 2023).

These data underscore the evolving nature of endocrine resistance and demonstrate how its integration into clinical practice could aid in optimizing therapeutic strategies for patients with mBC.

4.2. *Biomarkers for HR+/HER2- metastatic breast cancer*

The second part of the survey addressed the role of biomarkers for the management of patients with HR+/HER2 mBC, arising insights that warrant critical discussion.

In the scenario of patients progressing on first-line CDK4/6i plus ET, a total consensus was reached for the statement regarding the

assessment of *PI3K/PTEN/AKT* pathway alterations (*PIK3CA-AKT* activating mutations/*PTEN* inactivating alterations), germline *BRCA* pathogenic variants and *ESR1* mutational status, to determine second line treatment access, highlighting next-generation sequencing (NGS) as the preferred technique for this purpose. This level of agreement appears fully aligned with the most recent recommendations by the ESMO Precision Medicine Working Group, which advocate for the use of NGS as standard of care in patients with HR+ /HER2- mBC after resistance to ET (Mosele et al., 2024). This recommendation builds on several assumptions: i) based on the EMERALD trial, *ESR1* mutations have been reclassified/upgraded to ESCAT level IA; ii) although the well-established actionable role of PI3K pathway alterations is mainly propelled by *PIK3CA* mutations which retain ESCAT level IA, based on the CAPItello-291 trial, the determination of *AKT1/PTEN* alterations may have therapeutic consequences in terms of drug access, thus driving the recommendation for their assessment as well, despite a remaining degree of uncertainty regarding the most appropriate classification in ESCAT level I versus level II (Turner et al., 2023; Mateo et al., 2018).

The panel nonetheless acknowledged the possibility that technical, logistical, and economic barriers could hinder the widespread use of NGS, especially at the level of small-medium sized laboratories (Goodwin et al., 2016). In this context, it is reasonable to hypothesize a strategic integration/sequence of multigene with single-gene testing (e.g. polymerase chain reaction), aiming to define an accessible diagnostic path without excluding therapeutic options for patients.

As far as the detection of germline *BRCA* mutations is concerned, the ESMO Precision Medicine Working Group endorses tissue NGS as substitute of germline *BRCA1/2* testing in patients with endocrine-resistant HR+/HER2- mBC, given the high performance of tissue sequencing, and recommends reflex germline test in patients with no tumoral alteration and a high probability of harboring a germline *BRCA1/2* pathogenic variant (7 % risk of undetected *BRCA*-mutations by NGS) (Mosele et al., 2024; Terraf et al., 2022). Despite the ESMO Precision Medicine Working Group's recommendations, regulatory barriers still exist that currently prevent full alignment with these positions. For example, in Italy, access to PARP inhibitors is restricted to patients with a *BRCA* mutation determined by germline testing, according to the registration trials (Robson et al., 2019; Litton et al., 2018). Therefore, the implementation of NGS as a screening test for drug access purposes would require a flexible interpretation of the label and this certainly warrants a place in future discussions at the decision-making table.

An almost unanimous level of agreement was also achieved in the statement about the technical assessment of *PIK3CA* mutational status. Panelists agreed that primary or metastatic tumor samples are equally informative in this regard, since *PIK3CA* mutations represent a parental event rather than an acquired one (André et al., 2019; Rugo et al., 2021), and, consequently, there is no need to retest a new sample in case of a previously established wild-type status. As far as the sampling source for *PIK3CA* testing is concerned, SOLAR1 and plasma-MATCH trials showed a significant concordance between tissue or plasma samples (André et al., 2019; Turner et al., 2020), which has led to the regulatory approval of alpelisib in patients with tumor or blood *PIK3CA* mutations. However, while liquid biopsy demonstrated high specificity, its sensitivity remains suboptimal (Turner et al., 2020). Consequently, in case of non-informative liquid biopsy, tissue testing is advisable to intercept false negative cases. Importantly, according to the panel, this statement provided an opportunity to further enhance the cooperation between the clinician who prescribes the test and the laboratory that performs it, to avoid the risk of interpreting an "inconclusive" result as a "negative" one.

The third and fourth statements focused on the detection of *ESR1* mutations, which are acquired under the pressure of ET and therefore represent a molecular and real-time surrogate of endocrine resistance. This notion is entirely consistent with the two key messages conveyed by the third statement, which reached a high level of consensus: liquid biopsy represents the tool that most effectively captures *ESR1* dynamics and it should be performed after disease progression on every ET line, even in case of a previous *ESR1* negative test.

The fourth statement was more controversial and garnered a lower level of consensus, although agreement was ultimately reached. It dealt with the subgroup analysis from the EMERALD trial, which clearly demonstrated that the magnitude of benefit provided by elacestrant compared to standard ET was largely driven by the subset of patients with a PFS on CDK4/6i of 12 months or more (Bardia et al., 2024b). However, approximately 48 % of panelists were only partially in agreement or even in disagreement, and their position was supported by the following considerations: i) a prior PFS on CDK4/6i of 6–12 months does not always qualify a status of endocrine resistance where a benefit from further ET can be automatically excluded; ii) in addition, despite its role in predicting elacestrant benefit, the well-established negative prognostic value of *ESR1* mutations should not be overlooked (Brett et al., 2021). In this context, a portion of the disagreement may stem from the fact that while it is unquestionable that *ESR1* testing for determining elacestrant access should be prioritized in those patients that have derived substantial benefit from prior CDK4/6i, the intrinsic value of the test stands and extends beyond the therapeutic access.

The last two statements addressed the issue of tissue resampling. International guidelines endorse tissue resampling in patients with newly diagnosed or recurrent mBC to confirm the histology and reassess HR and HER2 status (Gennari et al., 2021; Wolff et al., 2023). This recommendation may broadly apply to all patients with mBC and is based on the well-known phenomenon of phenotypic switch from primary to metastatic disease (Curigliano et al., 2011; Morganti et al., 2023; Dieci et al., 2013). Interestingly, although the panelists agreed with this recommendation, a more conservative approach was suggested in the specific setting of HR+ /HER2- mBC. In particular, three nuances that can be captured when analyzing the statement should guide the decision of whether or not to consider tissue resampling in a patient with a newly diagnosed or recurrent HR+ /HER2- mBC: the clinical need ("when clinically indicated"), the presence of specific clinical features ("unusual/aggressive clinical course") and the invasiveness of the interventional approach ("if technically minimally invasive").

Finally, the last statement specifically dealt with HER2-low disease (Tarantino et al., 2020). In particular, there are two considerations worthy of discussion: the choice of the tumor sample to assess HER2 and instability of this predictive biomarker. In more detail, in the DESTINY-Breast04 trial, which demonstrated the superiority of trastuzumab deruxtecan over standard chemotherapy in terms of PFS and OS in patients with HR+ /HER2low mBC, the most recent tumor sample was required for centralized HER2 evaluation: 90 % of the samples were archival, 75 % derived from metastatic lesions, and half was collected prior to 2019 (Modi et al., 2022). An exploratory analysis of the study clearly revealed that the benefit from trastuzumab deruxtecan was consistent regardless of sample characteristics, whether primary versus metastatic, biopsy versus surgical excision, or the sample's time of collection (Prat et al., 2023). Secondly, the well-known HER2 expression instability throughout the course of the disease (specifically from HER2-null in primary tumor to HER2-low upon recurrence) provides the rationale to reassess HER2 status in patients with HER2-null tumors, to allow the access to a highly effective treatment (Miglietta et al., 2021; Valenza et al., 2024b); from this, the 100 % agreement among patients with only HER2-null status availability follows. An alternative approach to achieve the same goal is revising archival samples classified as HER2-null in the pre-HER2-low era (i.e., 0 by immunohistochemistry per ASCO/CAP recommendations): indeed, at that time, the distinction between HER2-null and HER2-low was burdened by a very high level of inter-pathologist discordance, mainly due to the lack of treatment consequences when these samples were collected and analyzed (Fernandez et al., 2022). Accordingly, where analytical issues do not preclude it, archival tissue revision offers an alternative approach to re-label a previous HER2-null result by capturing the HER2-low phenotype with hindsight in terms of potential therapeutic implications.

A further evolution of the concept of HER2-low disease has been triggered by the DESTINY-Breast06 study, which has brought to light HER2-ultralow disease as a new targetable entity (Bardia et al., 2024a). Since the last statement has been voted and discussed before the availability of DESTINY-Breast06 trial results, the concept of HER2-ultralow disease has not been addressed in this specific survey, however, within this upcoming landscape, this novel pathological entity will require meticulous consideration from both analytical and regulatory perspectives to ensure equitable access to therapy.

4.3. Treatment algorithm of HR+/HER2- metastatic breast cancer

The third topic was treatment sequence, with particular emphasis on challenging clinical scenarios.

The first statement dealt with the superiority of the combination of CDK4/6i and ET over ET al.one also in patients with poor prognostic features and in scenarios traditionally considered unsuitable for ET, such as symptomatic visceral metastases, rapid disease progression, impending visceral compromise or a markedly symptomatic non-visceral disease (Gao et al., 2020). Indeed, growing retrospective and prospective evidence supports the use of CDK4/6i also in this setting (De la Haba Rodriguez et al., 2024; Dawood and Brzozowski, 2021). In particular, the phase 2 RIGHT Choice trial compared ribociclib plus ET to chemotherapy doublets in patients with untreated HR+ /HER2- mBC and aggressive behavior, demonstrating a significant improvement within the CDK4/6i arm in terms of PFS, with superimposable performance to CT in terms of time to response and objective response rate (ORR) (Lu et al., 2024). The ABIGAIL trial assessed a similar question, evaluating abemaciclib plus ET with or without a short course of induction paclitaxel in patients with previously untreated HR+ /HER2- mBC with aggressive disease criteria: this trial showed that first-line abemaciclib plus ET achieved higher rates of 12-week ORR compared to paclitaxel (De la Haba Rodriguez et al., 2024).This data questions the historical approach of upfront chemotherapy for patients with clinically aggressive disease even in case of HR+ /HER2- mBC, and suggests a more efficient and less toxic strategy. However, in the RIGHT Choice trial, the definition of "true visceral crisis" largely depended on clinical judgment and was partially arbitrary, and only 48 % of patients enrolled had visceral crisis by investigators' assessment. Furthermore, the trial was limited by the small sample size, the absence of anthracycline as chemotherapy regimen, the exclusion of patients with liver impairment, thus preventing the generalization of these findings to the clinical practice. Similarly, the ABIGAIL study's inclusion criteria appear more conservative compared to the true definition of visceral crisis, thus preventing the possibility of considering this approach as a new standard in this specific context. Based on this, although the role of first-line chemotherapy is progressively narrowing, a degree of residual uncertainty remains.

The second statement regarded the choice across the available CDK4/6is and outlined all the criteria that should guide the decision-making process: magnitude of clinical benefit, toxicity profile falling outside the class-effects, country-specific availability and patient preferences. Indeed, although the three available CDK4/6is combined with ET have demonstrated their superiority over ET in terms of PFS (Gao et al., 2020), differences in OS and toxicity profile have been reported. Specifically, both ribociclib and abemaciclib have shown a clinically significant OS benefit when compared to ET, unlike palbociclib (Goetz et al., 2024b; Hortobagyi et al., 2022; Slamon et al., 2024b). Furthermore, abemaciclib is more frequently associated with nausea and diarrhea, ribociclib with QT prolongation and liver enzyme abnormalities, palbociclib with neutropenia (Gao et al., 2020). However, given the lack of direct comparisons among the three CDK4/6i, and the differences in patient populations and statistical plans across studies, no definitive conclusions can be drawn regarding the formal superiority of one agent over the others. It is the gaps left by clinical trials that well-conducted real-world studies are well-suited to fill. PALMARES represents a multicenter study which compared the real-world efficacy of abemaciclib, ribociclib, and palbociclib in 1850 patients with HR+ /HER2- mBC, treated in 18 Italian centers between 2016 and 2023 (40 % received palbociclib; 35 % ribociclib; 25 % abemaciclib) (Vernieri et al., 2024). Despite the retrospective comparison, in this study abemaciclib and ribociclib were independently associated with improved real-world PFS compared to palbociclib, while no significant differences were observed between abemaciclib and ribociclib. Specifically, abemaciclib and ribociclib outperformed palbociclib in patients with endocrine resistance, luminal B-like tumors, and in pre-menopausal patients. Abemaciclib showed superior efficacy in patients with *de novo* metastatic disease, while ribociclib was more effective in those with liver metastases. In contrast, all three CDK4/6i performed equally well in patients with bone-only disease. These data overall provide important insights that could assist the decision-making in a clinical practice setting.

Subsequently, the panel explored retreatment with CDK4/6i. In the advanced setting, the available evidence does not solidly support the use of CDK4/6i beyond progression while switching the ET backbone, as most studies, mainly involving patients receiving first-line palbociclib, have failed to demonstrate a clinically meaningful benefit (Kalinsky et al., 2023; Mayer et al., 2024; Llombart-Cussac et al., 2023). In more detail, the only phase III study available at the time of this consensus development was the post-MONARCH trial, which randomized patients progressing on CDK 4/6i + AI or relapsing on or after adjuvant CDK 4/6i + endocrine therapy, to receive fulvestrant in association with either abemaciclib or placebo, with approximately 60 % of patients having received prior palbociclib as initial therapy for mBC. The trial met its primary endpoint, with however a modest PFS delta of 1.7 months between treatment arms (Kalinsky et al., 2024). Subsequently, the results from the phase III EMBER-3 trial were also made available (Jhaveri et al., 2025). In particular, the EMBER-3 trial enrolled patients who had progressed either within 12 months of completion of adjuvant AI ± CDK4/6i or following first-line AI+ -/ CDK4/6i (approximately 60 % of patients had previously received a CDK 4/6i). The trial showed that the oral SERD imlunestrant, as single agent, led to significantly longer PFS than standard of care ET in the ESR1-mutated population. Moreover, the combination of imlunestrant + abemaciclib led to superior OFS than imlunestrant alone in the overall population and across all major subgroups. However, no formal comparison between standard ET versus imlunestrant + abemaciclib has been provided and the trial lacked a direct comparison of imlunestrant–abemaciclib with fulvestrant–abemaciclib. In addition, as observed in the post-MONARCH trial, in the EMBER-3 trial as well, approximately 60 % of patients had received palbociclib as their prior CDK4/6i.

Based on this, before considering treatment with CDK 4/6 inhibitors beyond progression, the panel considers it essential to address the following questions: in addition to switching the endocrine partner (while also understanding which agent may represent the best option in this setting), is it also necessary to switch the CDK4/6i? Within this framework, the treatment landscape could further evolve since the preliminary evidence of clinical utility in switching the endocrine partner while continuing the CDK inhibitor at the point of preclinical molecular progression (emergence of ESR1 mutation) suggested by the PADA-1 trial has already been confirmed by the recently reported positive results of the interim analysis of SERENA-6 trial. Furthermore, data generated within the post-MONARCH and EMBER-3 trials cannot even be transposed to patients who relapse on adjuvant CDK4/6i, as only 2 % and 4 % of patients from the post-MONARCH and EMBER-3 trial, respectively, were in this subgroup. Accordingly, the panel agreed that patients relapsing on or within 12 months from adjuvant CDK4/6i should not be considered for further CDK4/6i.

Instead, according to the fourth statement which reached a very high level of agreement, treatment decisions in the post-CDK4/6i setting should be guided by the expected magnitude of clinical benefit, toxicity profile, country-specific availability and patient's preferences, in the context of a biomarker-driver treatment algorithm, where a formal

hierarchical prioritization of treatment options cannot be established (Gennari et al., 2021; Valenza et al., 2024a). In particular, the major grey-areas in the context of the post-CDK 4/6i scenario is the presence of multiple co-existing targetable mutations. This does not represent a rare phenomenon since it has been reported that 10–15 % of patients may exhibit the coexistence of a *ESR1* mutation and a *PIK3CA/AKT/PTEN* pathway alteration (Dempsey et al., 2024). In this context, the lack of head-to-head comparisons of PI3K/AKT inhibitors vs elacestrant in patients with molecular alterations in both targets precludes the possibility of outlining a formal hierarchy. However, subgroup analyses from pivotal trials can provide some insights: in the EMERALD trial elacestrant showed clinical activity also in patients with a *PIK3CA*-mutant tumor (39 % of patients with a *ESR1* mutation), with an absolute increase in median PFS of 3.6 months compared to standard ET (Bardia et al., 2024b); the analysis of capivasertib efficacy according to *ESR1* mutation in the CAPItello-291 trial is pending (however it can be estimated that nearly 40 % of patients included harbored an *ESR1* mutation) (Turner et al., 2023).

Once endocrine strategies or their anticipated benefits have been exhausted, clinical guidelines suggest the sequencing of chemotherapy (e.g., capecitabine, taxanes, eribulin, gemcitabine) and ADCs (trastuzumab deruxtecan and sacituzumab govitecan) (Gennari et al., 2021). In this regard, the panel reached consensus in defining primary endocrine resistance to CDK4/6i (i.e., progression within the first 6 months of first-line treatment with ET plus CDK 4/6i) as a scenario where chemotherapy is preferable over an additional ET-based approach. However, more than 10 % of panelists disagreed with this statement, considering PFS on CDK4/6i to be an insufficient factor alone in the decision to switch to chemotherapy: in their opinion, molecular characteristics (e.g., *PI3K/AKT/PTEN* alternations and/or *ESR1* mutations) and the extent/magnitude of progression (oligo-progression vs massive progression, predominantly visceral involvement, associated symptom burden) are equally important factors to be taken into account. The last statement addressed the clinical positioning of trastuzumab deruxtecan in patients progressed on at least one line of chemotherapy, outlining that this ADC should be preferred over a further conventional chemotherapy line with more than 90 % of agreement, due to the clinically meaningful survival benefit emerged in the DESTINY-Breast04 trial (Modi et al., 2022). However, approximately 8 % of panelists partially dis-/agreed with this statement, mainly due to the toxicity profile of trastuzumab deruxtecan which included gastrointestinal events, alopecia and the risk of ILD, with the potential of even fatal outcome, thus preventing from the use of trastuzumab deruxtecan without discrimination in all patients (Powell et al., 2022). Indeed, the panel acknowledges the fact that a subset of endocrine refractory patients may be candidates to better tolerable alternatives (i.e., capecitabine).

Although this consensus was conducted prior to the presentation of the DESTINY-Breast06 trial results, the panel believes that considerations raised in this and the previous statements could also apply to the earlier use of trastuzumab deruxtecan as the first chemotherapy-based treatment (Bardia et al., 2024a).

5. Conclusions

The treatment of HR+/HER2- mBC is currently being reshaped due to the expansion of its armamentarium, the better understanding of its molecular determinants and the validation of biomarkers for patient selection. This consensus addressed the most controverse questions related to treatment decision, including the grey areas not covered by current guidelines. The following criteria were adopted to guide treatment decisions when two concomitant options or more are available: magnitude of clinical benefit, toxicity profile, country-specific availability, benefit derived by previous treatment, disease characteristics and patient preferences. The agreement was reached in all 16 statements. The nation-based nature of this work may limit the generalizability of the considerations raised throughout the consensus development process. However, the clinical grey areas that have been addressed are broadly relevant to the global management of HR+ / HER2- BC. Moreover, we acknowledge that some of therapeutic innovations discussed may not be equally accessible across healthcare systems, particularly in low- and middle-income countries. Nonetheless, we believe that this work adequately addresses issues of sustainability and feasibility, especially with regard to the evolving biomarker landscape. Finally, given the rapidly evolving treatment landscape of HR+ / HER2- advanced BC, we recognize that some recent studies (e.g. SERENA-6, EMBER-3), have not been largely discussed in the present work. Despite this, all statements formulated in this consensus remain valid and reflect the current standard of care at the time of writing.

Declaration of Competing Interest

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