

# WHITE PAPER: THE BENEFIT ASSESSMENT OF NEW METASTATIC BREAST CANCER (MBC) TREATMENTS



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# ABBREVIATIONS

<b>ABC</b>	Advanced Breast Cancer
<b>CADTH</b>	Canadian Agency for Drugs and Technologies in Health
<b>CODE</b>	Collaboration for Oncology Data in Europe
<b>EC</b>	European Commission
<b>EMA</b>	European Medicines Agency
<b>EORTC</b>	European Organisation for Research and Treatment of Cancer
<b>ESO</b>	European School of Oncology
<b>ESMO</b>	European Society for Medical Oncology
<b>EU</b>	European Union
<b>EUnetHTA</b>	European Network for Health Technology Assessment
<b>EUSOMA</b>	European Society of Breast Cancer Specialists
<b>HER2</b>	Human Epidermal Growth Factor Receptor 2
<b>HR</b>	Hormone receptor
<b>HRQoL</b>	Health Related Quality of Life
<b>HTA</b>	Health Technology Assessment
<b>MBC</b>	Metastatic Breast Cancer
<b>MDT</b>	Multidisciplinary Team
<b>MTB</b>	Multidisciplinary Tumour Board
<b>NICE</b>	National Institute for Health and Care Excellence
<b>ODN</b>	Oncology Data Network
<b>OS</b>	Overall Survival
<b>PBAC</b>	Pharmaceutical Benefits Advisory Committee
<b>PFS</b>	Progression-Free Survival
<b>PRO</b>	Patient-Reported Outcome
<b>PROM</b>	Patient-Reported Outcome Measure
<b>RWD</b>	Real World Data
<b>RWE</b>	Real World Evidence
<b>SMC</b>	Scottish Medicine Consortium
<b>QoL</b>	Quality of Life

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# EXECUTIVE SUMMARY

Metastatic Breast Cancer (MBC) places a major humanistic and economic burden on patients and their caregivers, along with issues of equity in access to quality care. It is recognised that various health systems are facing difficult prioritisation decisions when introducing new MBC treatments. The introduction of new MBC treatments may be hindered by several elements including the availability of relevant evidence of value. Therefore, in a multi-stakeholder collaboration, this White Paper aims to place MBC on the agenda of national policy makers and provide policy recommendations and solutions to current challenges in decision-making processes within access to MBC care and treatment in several countries from Europe, Australia and Canada.

The focus of this White Paper is two-fold; i) the challenges in the overall benefit assessment of new MBC treatments, ii) the role of multi-stakeholder collaboration in MBC decision-making. This White Paper builds on the multi-stakeholder collaboration [A Policy Roadmap on Addressing Metastatic Breast Cancer](#) (2017). The Policy Roadmap (2017) made a call for action addressed to EU and national level policymakers, healthcare professionals, academia, advocates, patients and members of the MBC community, requiring a collaborative approach to close gaps in provision of care in MBC.

In addition to the findings from the Policy Roadmap (2017), this White Paper is informed by a targeted literature review and expert discussions with patient advocacy representatives, members of the academia and oncologists held in 2018.

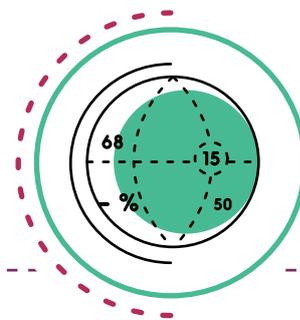
It is proposed that decision-makers should begin to consistently consider MBC patient needs, patient relevant outcomes and attributes in the overall benefit assessment of MBC treatments.

The two over-arching policy recommendations are:

- ✓ Include MBC-specific patient priorities and outcomes in the overall benefit assessment of new MBC treatments
- ✓ Enhance multi-stakeholder collaboration in order to improve MBC patient outcomes

More specific policy recommendations are provided in section 3 of this White Paper.

# 1. INTRODUCTION



## Burden of metastatic breast cancer

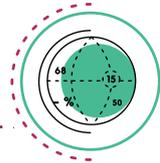
Breast cancer (BC) is the most common cancer in women worldwide, with 2.09 million new cases diagnosed in 2018 (GLOBOCAN, 2018a). Metastatic breast cancer (MBC) is responsible for the majority of the 0.6 million deaths from BC every year globally (Cardoso et al 2018; GLOBOCAN, 2018). MBC is a stage of BC where the disease has spread to distant sites beyond the axillary lymph nodes. While patients can be treated via chemotherapy, hormonal therapy or targeted agents, MBC is incurable.

Globally, BC takes second place in terms of incidence and prevalence among cancers. Covering 11.6% of all new cancer cases in both sexes and with 24.2% of the female cases, BC is the leading cause of cancer death among females (GLOBOCAN, 2018b). In 2015, there were 2.4 million estimated new BC cases and 523,000 estimated deaths worldwide in women (Fitzmaurice et al 2017). Moreover, 5-10% of newly diagnosed patients with BC will present with metastatic disease globally. However, there are regional variations; in high income countries fewer than 8% of patients are initially diagnosed with MBC. The highest burden of MBC is carried by low and middle-income countries where up to 60% are initially diagnosed with MBC (El Saghir et al 2007; Cardoso et al 2018).

MBC survival rates are poor. The 5-year survival rate for MBC is approximately 25%, compared to 98% for non-metastatic BC (Cardoso et al 2018). Based on data gathered during the Epidemio Strategy Medical Economical (ESME) MBC observational cohort study in France and Tumour Registry Breast Cancer in Germany the median overall survival (OS) in developed countries is approximately 2-3 years (Gobbini et al 2018; Fietz et al 2017), but lower in developing countries. Median survival is highly influenced by MBC subtype, patient characteristics, and access to optimal treatment (Cardoso et al 2018). Although there has been progress in the treatment of MBC over the past decade, it remains an incurable, but treatable disease (Cardoso et al 2018b).

## Challenges in policy and clinical decision-making in MBC

Many MBC patients face challenges in access to new treatments. For a new MBC treatment to become available to a patient, it will need to be assessed for safety and efficacy by medicines regulatory bodies, and thereafter appraised for relative value by Health Technology Assessments (HTA) or reimbursement bodies. The decisions that determine which treatments are made available for patients are extremely important and need to combine the clinical and economic evidence with ethical judgments (Pujolras & Cairns 2015 p. 21).



There are currently different approaches to assessing the relative treatment benefit in HTA appraisals (Akehurst et al 2017; Holmstrom et al 2015; Schoenherr et al 2015; Shah et al 2013; Efthymiadou et al 2017). Pujolras & Cairns (2015) investigated differences in oncology drug appraisals across 10 European countries, and identified several factors that contribute to varying appraisal outcomes, such as differences in reimbursement system characteristics, particularities of the drugs appraised and the socioeconomic status of the country. In MBC specifically, prior studies have highlighted that the different approaches to HTA appraisals have led to varying appraisal outcomes and reimbursement decisions of the same product (Akehurst et al 2017; Holmstrom et al 2015; Schoenherr et al 2015; Shah et al 2013).

Additional challenges in policy decision-making are the knowledge gaps on the humanistic and economic burden of MBC for patients and the society (Jönsson et al 2016; Jönsson et al 2016b). The humanistic burden entails the impact of MBC on a patient's quality of life, activities of daily living, treatment satisfaction and adherence to treatment regimens, but also caregiver wellbeing. This situation impacts directly the prioritisation and the decision-making at multiple levels of the health system (Expert discussions 2018).

Despite ongoing efforts to implement existing international guidelines in MBC at the local level, a vast proportion of MBC patients around the world are not treated according to existing guidelines. Diversion from these guidelines is often the result of organisational, administrative or behavioural barriers (The Policy Roadmap 2017 p.13), including financial constraints. Frequently, reimbursement policies are not updated to the new scientific developments nor aligned with the guidelines as they do not favour the use of oral medications or shorter courses of radiation therapy even though those treatments are cost-effective or considered to have an acceptable budget impact and are much more convenient to patients (Cardoso & Gennari 2017). Standardised clinical decision-making by means of adhering to treatment guidelines is considered to promote better patient outcomes. Another challenge pertains to the role and participation of patients in decision-making, both in clinical practice and at policy level.

This White Paper aims to discuss the challenges in MBC decision-making identified in the multi-stakeholder Policy Roadmap (2017), a targeted literature review and expert discussions with patient advocacy representatives, members of the academia and oncologists held in 2018. Moreover, this White Paper proposes policy recommendations to tackle the challenges identified in decision-making in MBC.

## 2. DECISION-MAKING IN THE CONTEXT OF MBC



### 2.1. ATTRIBUTES OF OVERALL BENEFIT ASSESSMENT OF MBC TREATMENT

Assessing the overall benefit of a new treatment for MBC is key to decision-makers, both clinicians and payers, and it is of undoubted value also for the patient. MBC as a severe and life-threatening disease has very specific implications on the assessment of the overall benefit of new MBC treatments. There is a growing understanding, as science evolves, that different cancer types require different approaches to treatment, especially for metastatic stages.

Regulators, payers and HTA bodies tend to use different endpoints to assess whether a new treatment should become available to patients. Overall survival (OS) and progression-free survival (PFS) are key endpoints used in oncology trials, and have different aims. OS is defined as time from randomisation to death from any cause (EMA 2016), and it is considered to be the “gold standard” to assess the benefit of a treatment. At times, regulators will accept surrogate endpoints e.g. PFS, defined as time from randomisation to objective tumour progression or death from any cause (EMA 2016), for the purposes of regulatory approval of the safety and efficacy of a new therapy. In contrast, payers and HTA bodies focus almost exclusively on OS to evaluate the benefit of a therapy (The Policy Roadmap 2017).

From a clinical perspective, OS allows an assessment of efficacy in the controlled trial setting and effectiveness in a real life setting. Verma et al (2011) state that OS is favored due to its objectivity, clear indication of benefit, and ease and reliability of measurement. However, there are challenges with OS as an endpoint as it requires a large sample size, a longer follow-up period and may in some cases be influenced by therapies used after patient participation in a given trial has ended, including crossover to the experimental arm. (Verma et al 2011)

Moreover, given the nature of MBC and the need to allow patients to access new treatments until mature data on overall survival becomes available, progression-free survival can be considered an appropriate endpoint for initial approval in MBC, but only if a re-evaluation is made once overall survival data is available (Pazdur 2017). Further reviews of reimbursement decisions should then take place once newer data, including data on overall survival and new safety data, become available (The Policy Roadmap 2017).

Given the severe and progressive nature of MBC, the focus of this section of the White Paper is on the attributes of the overall benefit assessment. Attributes that are relevant to MBC patients are not considered to be consistently reflected in current decision-making. These include: overall survival, time-to-event endpoints, such as PFS, considerations of MBC patients’ priorities, burden of disease, MBC-specific quality of life (QoL), value in delay of chemotherapy, route of administration, drug toxicities and the supportive evidence of benefit of the treatment provided in real world settings. In particular, route of administration in terms of oral and subcutaneously administered therapies that do not require hospital admission are considered important to patient decision-making (Expert discussions 2018). As such, the assessments of the overall benefit of MBC treatments are considered most valuable when informed by the MBC patients’ needs and priorities: QoL, real world data (RWD) regarding long-term outcomes, being able to participate in daily life activities; work, take care of the children, in addition to considering length of life.



It is therefore of utmost importance to recognise the specificities of MBC and how these aspects should be reflected in the overall benefit assessment of MBC treatments. This multi-stakeholder White Paper calls for alignment on concrete patient relevant evidence requirements in MBC and a common definition for overall treatment benefit. The alignment between stakeholders would benefit patients, health systems and society in general.

### 2.1.1. MBC patient needs

MBC is an incurable, yet treatable disease. It is important to recognise that there is a major difference in the MBC patient's needs compared to those of an early breast cancer patient, not only due to the severity and incurable nature of the disease, but also due to the emotional burden. The 5-year survival rate for MBC is very low, approximately 25% (Cardoso et al 2018). In addition to being an incurable disease, there are other distinct challenges compared to early stage breast cancer, such as need for continuous treatment and monitoring which carries not only an enormous emotional burden, but also a physical burden from the treatment side effects (Harding et al 2013).

The side effects associated with various forms of MBC therapy have led researchers to explore the role of patient preferences in decision-making in terms of treatment goals and desired outcomes. An aggressive cancer treatment may maximise the duration of survival or progression free survival but it may also be associated with significant and burdensome side effects that have a negative impact on quality of life (daCosta DiBonaventura 2014).

The MBC patient is considered to be the best informant of their individual preferences and needs. The identification and consideration of patient preferences and needs allow to minimise the burden of MBC in terms of better engaging the patient in the care process and thereby increase adherence to the treatment. Eliciting these priorities can be done using questionnaires and surveys (daCosta DiBonaventura 2014). Fallowfield and Fleissig (2012) highlight that further research is needed to understand cancer patients' experiences using standardised measures alongside traditional clinical outcomes in trials, but also to understand the value that patients may place on treatments that stabilize disease even though survival might not increase substantially. Moreover, it is important to recognise that each MBC patient has individual needs and characteristics, be it clinical, social and/or financial. All of these should be fully understood and considered routinely in the overall benefit assessment of new MBC treatments; they should be recognised in both clinical and policy decision-making with the support of appropriate instruments (Expert discussions 2018).

### 2.1.2. Quality of life

Improved health-related QoL (HRQoL) or non-deterioration of HRQoL combined with robust evidence of efficacy or effectiveness may be considered to be the overall benefit of a treatment (Angelis et al 2017; Expert discussions 2018). HRQoL is defined as the effect of a medical condition and the subsequent therapy upon a patient (Cella 1995; Schipper et al 1996). HRQoL as a concept is multi-dimensional and includes domains related to a person's physical, mental, emotional, and social functioning. More often MBC patients face difficulties balancing between the HRQoL and benefit in PFS. An aggressive cancer treatment may lengthen PFS but it may also be associated with significant and burdensome side effects that have a negative effect on HRQoL (daCosta DiBonaventura 2014; Expert discussions 2018).



HRQoL and other patient reported outcomes (PRO) data can be useful to differentiate treatments with similar efficacy or comparable toxicity profiles. According to Zagadailov et al (2013), PROs present an opportunity to incorporate patient-perceived effects as an addition to clinical efficacy measures in situations where there are therapies offering equivalent survival or other clinical endpoints (Zagadailov et al 2013).

MBC patients may receive treatment in sequential regimens or in combination. While combination therapies may improve some measures of efficacy, such as response rates, the improvement is usually counterbalanced by increased toxicity (Dear et al 2013). Consequently, new MBC combination therapies, in particular of different types of therapies (i.e. endocrine + targeted therapy or chemotherapy + targeted therapy) that are able to maintain or improve an MBC patient's HRQoL should be seen as presenting value to patients as well as decision-makers. In the presence of a significant survival (OS) benefit, most patients accept an increase of toxicity of a given treatment regimen although it is acknowledged that based on personal milestones, MBC patients may interpret the extent of the survival benefit differently (Expert discussions 2018).

HRQoL is recognised by policy decision-makers, as a highly relevant endpoint. As an example, in Canada, the pan-Canadian Oncology Drug Review (pCODR) is transparent in their requirements and consideration of HRQoL data when assessing the benefit of new oncology treatments (pCODR 2013; pCODR 2018; Expert discussions 2018). A challenge persists in decision-makers ability to consider HRQoL improvements in HTA processes due to the absence of effective measurement tools in the MBC treatment setting. Most of the available QoL instruments have not been developed for MBC, but for early breast cancer and the available complementary tools for MBC QoL are often not used in clinical trials (Expert discussions 2018).

From the patient perspective, the patient's judgment and assessment of the patient utility and effects of the treatment are highly valuable for decision-making. Promoting the development and subsequent use of MBC-specific HRQoL instruments is a priority. Currently, there is work underway to develop an MBC-specific QoL tool, by the European Organisation for Research and Treatment of Cancer (EORTC) in collaboration with the European School of Oncology (ESO) and ABC Global Alliance.

### 2.1.3. Delay of chemotherapy

In MBC patients with hormone-receptor (HR) positive and human epidermal growth factor receptor 2 (HER2)-negative MBC, there is significant value in being able to delay the initiation of chemotherapy. From the patient perspective, delaying chemotherapy is considered a crucially relevant aspect of the overall benefit of treatment. It was discussed among experts (2018) that the advantage that an MBC treatment may have in delaying the start of chemotherapy, is that it may translate into positive outcomes, such as improvements in HRQoL or a reduction in side effects; the value of this delay depends on the safety profile of alternative treatments (Expert discussions 2018). Moreover, the benefits of delaying chemotherapy among MBC patients, and the subsequent negative impact of the side effects including emergency and hospital visits, may also translate into cost-savings for the health system when these highly costly visits can be avoided (Rodriguez-Monguio et al 2003; Magdelijns et al 2014).



Recently, decision-makers in England and Germany have considered and acknowledged the additional value of a new MBC treatment in terms of delaying the need for chemotherapy (NICE TA495, 2017; Institute for Quality and Efficiency in Health Care, IQWiG 2017). For example, one MBC treatment appraisal by NICE in England (NICE TA495 2017), took into account patient input emphasising how MBC patients value delaying both disease progression and the need for chemotherapy: agreeing “that people value delaying progression of the disease and an important consideration is delaying the time to chemotherapy” (NICE TA495 2017, 4.2).

Given the above described benefits, decision-makers should consistently consider the benefit of a new MBC treatment in terms of postponing disease progression and delaying the need for chemotherapy, and thereby reducing the number of people who are exposed to the toxicities and side effects in the sub group of MBC patients where targeted therapies are indicated. However, not all targeted therapies are alike and a correct evaluation of their side effects as well as direct comparisons with chemotherapy both in terms of efficacy and tolerability and HRQoL are crucial to make decisions.

### 2.1.4. Patient heterogeneity

Patient heterogeneity, defined by Ramaekers et al (2013) as the part of the natural variation between patients that can be attributed to characteristics of those patients, is incorporated in health economic guidelines in European countries (Ramaekers et al 2013). Considering patient heterogeneity, such as by conducting sub group analyses, allows to target treatments based on patients’ demographic and clinical characteristics, preferences, as well as it may bring about additional benefits in terms of adherence to treatment. It was highlighted in expert discussions that the clinical characteristics of MBC patients, such as severity of the disease and comorbidities, should be further incorporated in the overall benefit assessment of MBC treatments to account for differences across sub-populations and the trajectory of the disease (Expert discussions 2018). Due to the evolving science in personalised medicine, a greater understanding will be gained in the future with respect to disease heterogeneity allowing to target MBC treatments for those patients that will benefit from it the most.

### 2.1.5. Side effects and toxicities

Consideration of treatment-related side effects and toxicities is an important part of the overall benefit assessment of a new MBC treatment. In addition to being a significant physical and emotional burden to the MBC patient, treatment-related side effects also incur costs for society and patients.

There is a scarcity in the literature in how MBC patients view the relative importance of improved survival versus greater treatment toxicity (Harding et al 2013). Previous studies in lung cancer and renal cell carcinoma (Wong et al 2012; Bridges et al 2012) have suggested that some patients would be willing to accept greater toxicity for modest improvements in survival or to live long enough to see a milestone event in their lives, whereas other patients may not consider the toxicities as acceptable. It has been underscored in expert discussions (2018) that MBC patients have varying preferences for the tolerability of treatment toxicities. Some MBC patients may consider hair loss as intolerable whereas others consider other side effects such as neuropathy to be worse.



In essence, side effects may be well tolerated by MBC patients if there is an extension of life of good quality (Expert discussions 2018). The key is to inform MBC patients of the actual benefits and risks related to the treatment in order to make an informed decision, and for policy decision-makers to become aware and recognise the value of different treatment toxicity profiles in relation to achieved benefits. For the choice among treatments with similar efficacy, the type of side effects that a specific patient wants to avoid, may be the determinant factor (Expert discussions 2018).

### 2.1.6. Treatment adherence

Treatment adherence behaviour is considered to have a direct relationship with oncology outcomes (Shingler et al 2014; Huang et al 2016). There are many attributes that may contribute to the treatment adherence of MBC patients. The preference for a specific mode of administration (i.e. oral versus intravenous) is important for cancer patients, and can be associated with numerous factors such as convenience or perception of efficacy (Eek et al 2016). Other attributes include patient beliefs and values that have been identified as having moderating effect on treatment adherence (Shingler et al 2014). Side effects and also the schedule of treatment administration, may have an impact on patients' adherence to treatment. Real World Evidence (RWE) could provide further insights into the influence of side effects in treatment adherence (Expert discussions 2018). It is considered of high importance to provide MBC patients with adequate support and information to be able to adhere to treatments. The role of oncology nurses to provide support for adherence as well as advice and education in the MBC cancer care setting is invaluable. (Expert discussions 2018)

In expert discussions with patient advocacy groups and oncologists, patient adherence was considered a key aspect of MBC care. The different attributes, as outlined above, that contribute to a better treatment adherence, should be further incorporated in the treatment overall benefit assessment.

### 2.1.7. Role of real world evidence in overall benefit assessment

RWE has the potential to provide additional evidence of the overall benefit of a MBC treatment to decision-makers allowing for more informed decisions to be made in an environment of scarce resources. RWD is defined by the ISPOR Real-World Data Task Force as "data used for decision-making that are not collected in conventional randomised controlled trials, generated during routine clinical practice" (Garrison et al 2007; Berger et al 2017). RWE is obtained from analysing RWD (Berger et al 2017).

RWE can support HTA bodies and payers, in addressing gaps in evidence, such as population effects in the real world, including long-term safety, how dosing and compliance translate to effectiveness, use of the treatment in broader populations, and how new medicines perform compared to current standard of care. More specifically, RWE can support decision makers in providing data on areas of uncertainty such as the burden of illness, natural history of the disease, the needs in the patient population in real life versus the trial population with a specific focus on older patients who are generally underrepresented in clinical trials, comparator treatments, and how trial surrogate endpoints link with outcomes measured in real life. (IHE 2017) The supportive evidence of the treatment overall benefit provided in real world settings decreases the uncertainty in decision-making for payers and HTA bodies in terms of addressing the gaps outlined earlier. This, in turn, may support more informed decisions and allows more efficient allocation of resources in the health systems.



It was highlighted in the expert discussions (2018), that there are multiple aspects to why RWE is beneficial in the overall benefit assessment of MBC treatments. RWE allows to contribute to the efficacy-effectiveness gap, by capturing the true value of a treatment in everyday clinical practice compared to a clinical trial setting, in terms of treatment effectiveness, sequence of treatments, providing data on side effects, inappropriate prescribing and adherence (Eichler et al 2011). Regarding the efficacy-effectiveness gap, Nordon et al. (2016) highlight the importance of identifying the real life contextual factors either patient related, healthcare related or provider related, that have an impact on the effect estimates for medications (Nordon et al 2016). MBC patients may also indirectly benefit from robust RWE, as access to new treatments could be improved through reducing payer uncertainty around decisions to adopt a new treatment. Moreover, increased certainty also avoids wasting scarce healthcare resources, which represent opportunities for other patients. (IHE 2017)

There is interest from decision-makers, including HTA bodies and payers, to use robust RWE to support decision-making, however, current uptake of RWE may be hindered by several barriers. Among those, the lack of clear standards in study designs, and the infrastructure to collect patient-level data in MBC (IHE 2017). In addition, the International Society for Pharmacoeconomics and Outcomes (ISPOR) and International Society for Pharmacoepidemiology (ISPE) taskforce on RWE recommend to ensure validity and reduce potential bias to inform decision making (Berger et al 2017). The majority of the existing cancer registries only capture aggregate level data such as diagnosis and death but not relapse data, making it impossible to know with certainty the number of advanced cancer patients (Expert discussions 2018). These barriers hinder the potential that RWE has in informing payer and HTA agency decisions, and reducing uncertainty in the environment of scarce resources.

There are several initiatives to address these gaps, among them the Collaboration for Oncology Data in Europe (CODE). CODE is an initiative of IQVIA and several pharmaceutical companies and aims to study the use of anti-cancer medicines by supporting the development of the Oncology Data Network (ODN). ODN aims to collate up to date, comparable information on the use of anti-cancer medicines to help inform patient care and help address the challenges of financial sustainability. (CODE 2018)

### **2.1.8. Other attributes in overall benefit of an MBC treatment**

In a recent event in the European Parliament, the members of ABC Global Alliance called for decision-makers to provide better conditions for people with advanced breast cancer to return to work (European School of Oncology Press Release 2018). The overall benefit assessment of MBC treatments would be more valuable when informed by patient experience and HRQoL in terms of capacity to continue to work, being able to take care of the children, keeping autonomy in every day activities. (Expert discussion 2018). It is unclear if decision-makers consider the patient contribution to society when they assess a new treatment, as their focus often lies with the direct clinical outcomes.



## 2.2. MULTI-STAKEHOLDER COLLABORATION IN MBC DECISION-MAKING

### 2.2.1. Multi-stakeholder collaboration in clinical decision-making

It is well understood that patients' input into their care is considered invaluable. However, it should also be recognised that there may be cultural reasons for MBC patients to not actively seek participation in decision-making. Nevertheless, patients should be encouraged to collaborate with clinicians and other decision-makers. The development of e-health tools used during clinical trials and care outside of the trial setting may support patients that are not able or willing to participate in decision-making. These new tools could bring the insights from the patient experience to the decision-makers and provide evidence of the real added benefit of a treatment. (Expert discussions 2018)

Multidisciplinary teams (MDTs) and Multidisciplinary Tumor Boards (MTBs), as forums of multidisciplinary management of cancer patients, have long presented an integrated approach to collaborative cancer care in many countries worldwide (Saini et al 2012; El Saghir et al 2014). The main benefit of MDT and specialised breast units is that they provide consistent, continuous, coordinated, and cost-effective cancer care and allow BC patients to have access to the best available care and treatments (Blamey et al 2000; Blamey & Cataliotti 2006; Saini et al 2012). The role and involvement of the patient and general practitioner (primary care physicians) in the overall care, including MDT and MTB discussions, was highlighted in expert discussions (2018). The inclusion of primary care physicians was considered to be valuable from the perspective of being the healthcare provider who can be involved at different stages of BC management, from diagnosis to end of life.

In clinical decision-making, treatment guidelines are key to providing evidence-based and standardised quality care, however as mentioned in the previous chapter, challenges still persist in MBC. It is believed that enhanced collaboration between the stakeholder groups, that is MBC patients, physicians, researchers, policy makers and reimbursement bodies would promote the adherence to treatment guidelines and subsequently improve care outcomes. It is crucial to include the MBC patient perspective and values in treatment guidelines, for example, as it is done in the ESO-ESMO ABC Guidelines (Cardoso et al 2018a).

### 2.2.2. Multi-stakeholder collaboration in policy decision-making

There is inherent value in multi-stakeholder engagement between patients, physicians, companies, and regulatory and HTA bodies; not least in providing support for timely patient access to transformative medicines and in the potential to improve patient outcomes. Gannedahl et al (2017) propose that early and enhanced dialogue with extended stakeholder groups is a crucial element in supporting the introduction of breakthrough medicines responding to an unmet need with sufficient evidence to ensure accelerated access while balancing this with affordability for payers.



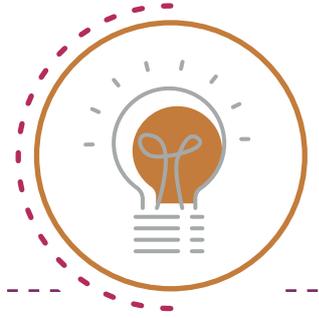
Recently, to support ongoing collaboration between HTA bodies in the European Union, the European Commission (EC) proposed a new regulation, COM [2018] 51, for future co-operation in HTA that envisages for a joint clinical assessment of medicinal products undergoing the centralised marketing authorisation process (EC Proposal for Directive 2011/24/EU). The joint clinical assessments have the aim to address the challenges in variation and duplications in assessment methods between EU Member States' HTA bodies. Such an approach may translate into more streamlined and more consistent clinical assessments to MBC treatments across the EU.

According to the European Network for Health Technology Assessment (EUnetHTA), patient engagement is considered essential in the future collaboration in HTA, in terms of gaining the patients' perspective on setting the scope for joint assessments, and in providing experiential knowledge of living with the condition and available treatments. Moreover, there is importance in patients advising on the signs and symptoms that have the greatest impact on their functional and emotional well-being. (EUnetHTA 2018) Currently, some HTA agencies, such as NICE, SMC, CADTH and PBAC, consider patient representatives and patient organisations input on their experiences with the disease and the health technology that is being assessed (Scott et al 2017). Although formal training on the HTA process is limited, some HTA agencies (e.g. CADTH and SMC) provide support to patient representatives participating in HTA committees and writing dossier submissions. However, this type of support is not extended to the broader patient organisations (Scott et al 2017) and there is room for improvement for HTA agencies to be more supportive, inclusive and provide feedback to consumer groups regarding the extent of their influence on decision-making.

MBC patient needs should also be reflected in early clinical development plans of new treatments. The proposed collaboration in the EC proposal for a Regulation (HTA COM [2018] 51), in early joint scientific consultations with HTA bodies and the option to include regulators, builds on existing multi-stakeholder early dialogue processes. In the EU, patients have been routinely invited to participate in integrated (i.e. combined regulatory and HTA) scientific advice processes since 2014, and a notable increase has been observed in patient participation (Udechuku & Bending 2017).

To support these positive trends in multi-stakeholder collaboration in HTA, it is crucial to further engage MBC patients and their caregivers in early dialogue processes, integrated scientific advice and joint clinical assessments. Such collaboration would allow for consideration of MBC patient priorities, more informative choices in regards to trial designs and endpoints, support companies in MBC-specific PRO and PROMS development and allow early alignment on the requirements for the overall treatment benefit assessment in MBC to ensure that the needs of all key decision-makers are met. There is work done by the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) to identify a more standardised way of assessing elements of value (The Policy Roadmap 2017). For example, the ESMO Magnitude of Clinical Benefit Scale (MCBS) provides an objective scale to classify new therapies based on their impact on efficacy and toxicity/HRQoL (Cherny et al 2017).

# 3. POLICY RECOMMENDATIONS



## 3.1. KEY RECOMMENDATION FOR GOVERNMENT AGENCIES, HTA DECISION-MAKERS AND PAYERS

### **Include MBC-specific patient priorities and outcomes in the overall benefit assessment of new MBC treatments**

- ✓ Incorporate MBC patient needs in the overall benefit assessment of an MBC treatment
- ✓ Provide an agreement on the appropriate endpoints in MBC, including the use of surrogate endpoints such as PFS, with re-evaluation once OS data is available
- ✓ Ensure MBC patient involvement and, where relevant, voting rights in clinical assessments of MBC treatments both at national and /or regional levels
- ✓ Provide means to educate policy decision-makers on understanding the MBC patient needs
- ✓ Incorporate the value placed in delaying the start of chemotherapy in the overall benefit assessment, where applicable
- ✓ Support the development and incorporate MBC-specific HRQoL and MBC-specific PRO measures into decision-making and establish one standardised MBC-specific PRO measure that is accepted and used by all HTA agencies
- ✓ Support and use observational data collection initiatives in MBC to acquire patient-level data for long-term outcomes
- ✓ Recognise and use Real World Evidence as supportive evidence in the overall benefit assessment of MBC treatments
- ✓ Recognise MBC patients' ability to return or maintain work or studies, and capacity to participate in daily activities as part of the overall benefit assessment of MBC treatments
- ✓ Consider objective value framework tools as one of the several sources of information in the decision making process to assess the clinical benefit of new treatments, such as the ESMO Magnitude of Clinical Benefit Scale (MCBS) or the ASCO Value Framework. These tools' methodologies are in constant update according to the experience in the field
- ✓ Address value in oncology by considering issues such as affordability and value based pricing, healthcare systems adaptability to the rate of innovation in cancer treatment, including waste and the wider healthcare spending



### 3.2. KEY RECOMMENDATION FOR MBC MULTI-STAKEHOLDER GROUPS

#### **Enhance multi-stakeholder collaboration in order to improve MBC patient outcomes**

- ✓ Enforce the importance of multidisciplinary specialized teams (MDTs) and Multidisciplinary Tumor Boards (MTBs) in MBC care
  - ✓ Make sure all MBC patients are discussed in these boards
  - ✓ Ensure the patient perspective is integrated into treatment guidelines and enforce the implementation of high quality, international and national MBC management guidelines
  - ✓ Further promote MBC patient participation in formal early dialogues, integrated scientific advice engagements and (joint) clinical assessments in the EU and beyond
  - ✓ Provide means and support initiatives to educate patients on understanding the general HTA processes
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# REFERENCES

- Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *Eur J Health Econ*. 2018;19(1):123-52.
- Akehurst RL, Abadie E, Renaudin N, Sarkozy F. Variation in Health Technology Assessment and Reimbursement Processes in Europe. *Value in Health*. 2017;20(1):67-76.
- A Policy Roadmap on addressing metastatic breast cancer – multistakeholder collaboration. 2017. Available from: <https://lillypad.eu/WP/wp-content/uploads/MBC-Policy-Roadmap-Report.pdf>.
- Berger ML, Sox H, Willke RJ, Brixner DL, Eichler HG, Goettsch W, et al. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2017;20(8):1003-8.
- Blamey R, Blichert-Toft M, Cataliotti L, Costa A, Greco M, Holland R, et al. The requirements of a specialist breast unit. *European Journal of Cancer*. 2000;36(18):2288-93.
- Blamey RW, Cataliotti L. EUSOMA accreditation of breast units. *Eur J Cancer*. 2006;42(10):1331-7.
- Bridges JF, Mohamed AF, Finnern HW, Woehl A, Hauber AB. Patients' preferences for treatment outcomes for advanced non-small cell lung cancer: a conjoint analysis. *Lung cancer (Amsterdam, Netherlands)*. 2012;77(1):224-31.
- Cardoso F, Spence D, Mertz S, Corneliussen-James D, Sabelko K, Gralow J, et al. Global analysis of advanced/metastatic breast cancer: Decade report (2005-2015). *Breast (Edinburgh, Scotland)*. 2018;39:131-8.
- Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, Andre F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Ann Oncol*. 2018b;29(8):1634-57.
- Cardoso F, Gennari A. Why are guidelines not followed in clinical practice? *The Breast*. 2017 Apr 1;32:245-6.
- Cella DF, editor Measuring quality of life in palliative care. *Seminars in oncology*; 1995.
- CODE. Website. 2018. [Accessed 24-10-2018] Available from: <https://www.code-cancer.com/>.
- daCosta DiBonaventura M, Copher R, Basurto E, Faria C, Lorenzo R. Patient Preferences and Treatment Adherence Among Women Diagnosed with Metastatic Breast Cancer. *American Health & Drug Benefits*. 2014;7(7):386-96.
- Doward LC, Gnanasakthy A, Baker MG. Patient reported outcomes: looking beyond the label claim. *Health and Quality of Life Outcomes*. 2010;8:89. 1-9.
- Dear RF, McGeechan K, Jenkins MC, Barratt A, Tattersall MH, Wilcken N. Combination versus sequential single agent chemotherapy for metastatic breast cancer. *The Cochrane database of systematic reviews*. 2013(12):Cd008792.
- Eek D, Krohe M, Mazar I, Horsfield A, Pompilus F, Friebe R, et al. Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: a review of the literature. *Patient preference and adherence*. 2016;10:1609-21.
- Efthymiadou O, Mills M, Kanavos P. Are Accelerated Approval Mechanisms A Predictor To Early Access And Coverage? A Global Study Of Cancer Drugs. *Value in Health*. 2017 Nov 30;20(9):A458.
- El Saghir NS, Keating NL, Carlson RW, Khoury KE, Fallowfield L. Tumor boards: optimizing the structure and improving efficiency of multidisciplinary management of patients with cancer worldwide. *American Society of Clinical Oncology educational book American Society of Clinical Oncology Annual Meeting*. 2014:e461-6.
- El Saghir NS, Khalil MK, Eid T, El Kinge AR, Charafeddine M, Geara F, et al. Trends in epidemiology and management of breast cancer in developing Arab countries: a literature and registry analysis. *Int J Surg*. 2007;5(4):225-33.
- EUnetHTA. Patient, Consumer and Health Care Provider Involvement in EUnetHTA JA3 April 2018. Available from: [https://www.ema.europa.eu/documents/presentation/presentation-patient-consumer-health-care-provider-involvement-eunetha-ja3-emas-pcwp-hcpwp-joint\\_en.pdf](https://www.ema.europa.eu/documents/presentation/presentation-patient-consumer-health-care-provider-involvement-eunetha-ja3-emas-pcwp-hcpwp-joint_en.pdf).
- European Commission. Proposal for a Regulation of the European Parliament and of the Council on Health Technology Assessment and Amending Directive 2011/24/EU. Available from: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52018PC0051>.
- European Medicines Agency (EMA). Regulatory perspective on real world evidence (RWE) in scientific advice. April 2018. Available from: [https://www.ema.europa.eu/documents/presentation/presentation-regulatory-perspective-real-world-evidence-rwe-scientific-advice-emas-pcwp-hcpwp-joint\\_en.pdf](https://www.ema.europa.eu/documents/presentation/presentation-regulatory-perspective-real-world-evidence-rwe-scientific-advice-emas-pcwp-hcpwp-joint_en.pdf).

## REFERENCES

---

- A policy roadmap on addressing metastatic breast cancer – multistakeholder collaboration. 2017. Available from: <https://lillypad.eu/WP/wp-content/uploads/MBC-Policy-Roadmap-Report.pdf>
- European School of Oncology Press Release. Campaigners call for stronger rights to work for people living with breast cancer. November 7th 2018. Available from: <https://medicalxpress.com/news/2018-11-campaigners-stronger-rights-people-breast.html>.
- Expert discussions (individual discussions) with Steering Committee members held between August and October 2018, and group discussion held in Steering Committee meeting on October 15th 2018.
- Fallowfield L, Fleissig A. Fallowfield LJ, Fleissig A The value of progression-free survival to patients with advanced-stage cancer. *Nat Rev Clin Oncol*. 9: 41-47 2012. 41-7 p.
- Fietz T, Tesch H, Rauh J, Boller E, Kruggel L, Janicke M, et al. Palliative systemic therapy and overall survival of 1,395 patients with advanced breast cancer - Results from the prospective German TMK cohort study. *Breast*. 2017;34:122-30.
- Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and National Cancer Incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 Cancer groups, 1990 to 2015. *JAMA Oncol*. 2017;3:524.
- Gannedahl M, Udechuku A, Bending MW. Initiatives driving accelerated access to medicines in Europe: Review of recent concepts and developments. *Medicine Access @ Point of Care*. 2018;2.
- Garrison LP, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. *Value in Health*. 2007;10(5):326-35.
- GLOBOCAN, 2018a. Breast factsheet. Available from: <https://gco.iarc.fr/today/data/factsheets/cancers/20-Breast-fact-sheet.pdf>.
- GLOBOCAN, 2018b. World factsheet. Available from: <http://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf>.
- Gobbini E, Ezzalfani M, Dieras V, Bachelot T, Brain E, Debled M, et al. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. *Eur J Cancer*. 2018;96:17-24.
- Harding V, Afshar M, Krell J, Ramaswami R, Twelves CJ, Stebbing J. 'Being there' for women with metastatic breast cancer: a pan-European patient survey. *British journal of cancer*. 2013;109(6):1543-8.
- Holmstrom S, Kooreman PJ, Van Engen A, Heemstra L, Novak A, Naidoo S. Payer/Hta Requirements In Metastatic Breast Cancer. *Value in Health*. 2015;18(7):A490.
- Huang W-C, Chen C-Y, Lin S-J, Chang C-S. Medication adherence to oral anticancer drugs: systematic review. *Expert Review of Anticancer Therapy*. 2016;16(4):423-32. Available from: <https://www.tandfonline.com/doi/full/10.1586/14737140.2016.1159515?src=recsys>.
- Institute for Quality and Efficiency in Health Care, IQWiG, Palbociclib (breast cancer) – Addendum to Commission A16-74, 2017. Accessed October 3rd 2018. Available from: <https://www.iqwig.de/en/search.1029.html>.
- Institute of Health Economics (IHE), Alberta Canada. Summary report of the IHE Roundtable. 2017. Available from: <https://www.ihe.ca/publications/real-world-evidence-what-role-can-it-play-in-real-world-decision-making-summary-report>.
- Jönsson B, Hofmarcher T, Lindgren P, Wilking N. The cost and burden of cancer in the European Union 1995-2014. *European journal of cancer (Oxford, England: 1990)*. 2016;66:162-70.
- Jönsson B et al. (b) Comparator report on patient access to cancer medicines in Europe revisited, The Swedish institute for Health Economics, 2016:4. Available from: [http://ihe.se/wp-content/uploads/2016/08/IHE-Report\\_2016\\_4.pdf](http://ihe.se/wp-content/uploads/2016/08/IHE-Report_2016_4.pdf).
- Magdelijns FJH, Stassen PM, Stehouwer CDA, Pijpers E. Direct health care costs of hospital admissions due to adverse events in the Netherlands. *European Journal of Public Health*. 2014;24(6):1028-33.
- NICE TA495 Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Accessed October 3rd 2018. Available from: <https://www.nice.org.uk/guidance/ta495/resources/palbociclib-with-an-aromatase-inhibitor-for-previously-untreated-hormone-receptorpositive-her2negative-locally-advanced-or-metastatic-breast-cancer-pdf-82605088634821>.
- Nordon C, Karcher H, Groenwold RHH, Ankarfeldt MZ, Pichler F, Chevrou-Severac H, et al. The Efficacy-Effectiveness Gap: Historical Background and Current Conceptualization. *Value in Health*. 2016;19(1):75-81.
- Paris V, Belloni A. Value in Pharmaceutical Pricing. OECD Health Working Papers, No. 63. 2013.
- pan-Canadian Oncology Drug Review (pCODR) 2018. Submission Guidelines. Available from: <https://www.cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pcodr-submission-guidelines.pdf>.

## REFERENCES

pan-Canadian Oncology Drug Review (pCODR) 2013. A guide for patient advocacy groups: how to provide patient and caregiver input for a pCODR drug review. Available from: <https://cadth.ca/sites/default/files/pcodr/pCODR%27s%20Drug%20Review%20Process/pcodr-patient-guide.pdf>.

Pujolras L.M., Cairns J. Why do some countries approve a cancer drug and others don't? *Journal of Cancer Policy* 4 (2015) 21–25.

Ramaekers BLT, Joore MA, Grutters JPC. How Should We Deal with Patient Heterogeneity in Economic Evaluation: A Systematic Review of National Pharmacoeconomic Guidelines. *Value in Health*. 2013;16(5):855-62.

Rodriguez-Monguio R, Otero MJ, Rovira J. Assessing the economic impact of adverse drug effects. *PharmacoEconomics*. 2003;21(9):623-50.

Saini KS, Taylor C, Ramirez AJ, Palmieri C, Gunnarsson U, Schmoll HJ, et al. Role of the multidisciplinary team in breast cancer management: results from a large international survey involving 39 countries. *Annals of oncology: official journal of the European Society for Medical Oncology*. 2012;23(4):853-9.

Schoenherr N, Gordon J. Analysis Of Differences In Hta Reimbursement Decisions Of Stage Iv (Metastatic) Breast Cancer Medications Across Different Countries. *Value in Health*. 2015;18(7):A490.

Scott AM, Wale JL, On behalf of the HP, Citizen Involvement in Hta Interest Group PI, Education Working G. Patient advocate perspectives on involvement in HTA: an international snapshot. *Research Involvement and Engagement*. 2017;3(1):2.

Schipper H, Clinch JJ, Olweny CLM. Quality of life studies: definitions and conceptual issues. *Quality of Life and Pharmacoeconomics in Clinical Trials*. Philadelphia: Lippincott-Raven Publishers; 1996. p. 11-23.

Shah KK, Mestre-Ferrandiz J, Towse A, Smyth EN. A review of health technology appraisals: case studies in oncology. *International journal of technology assessment in health care*. 2013;29(1):101-9.

Shingler SL, Bennett BM, Cramer JA, Towse A, Twelves C, Lloyd AJ. Treatment preference, adherence and outcomes in patients with cancer: literature review and development of a theoretical model. *Current Medical Research and Opinion*. 2014;30(11):2329-41.

Udechuku A, Bending MW. The Value of Health Technology Assessment Scientific Advice. *RASP Regulatory Focus*. Published 23 August 2017.

Verma S, McLeod D, Batist G, Robidoux A, Martins IR, Mackey JR. In the end what matters most? A review of clinical endpoints in advanced breast cancer. *The oncologist*. 2011;16(1):25-35.

Wong MK, Mohamed AF, Hauber AB, Yang JC, Liu Z, Rogerio J, et al. Patients rank toxicity against progression free survival in second-line treatment of advanced renal cell carcinoma. *J Med Econ*. 2012;15(6):1139-48.

Zagadailov E, Fine M, Shields A. Patient-Reported Outcomes Are Changing the Landscape in Oncology Care: Challenges and Opportunities for Payers. *American Health & Drug Benefits*. 2013;6(5):264-74.



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