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Expert consensus on the prevention of brain metastases in patients with HER2-positive breast cancer

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ABSTRACT

Background: Patients with HER2-positive breast cancer have a significant risk of developing brain metastases (BrM), which have detrimental effects on survival outcomes and quality of life. Although there are several systemic treatment options available that may delay the appearance of BrM and secondary progression of previously treated BrM, there are still substantial unmet needs for this patient population and primary prevention remains elusive.

Methods: A group of experts created consensus statements, through a modified Delphi process, to bridge the gap between current unmet needs, available evidence, and international guidelines.

Results: The steering committee reviewed all relevant literature and formed research questions to be answered by the subsequent consensus statements. In total, 61 contributors provided feedback on the consensus statements, with 34 statements reaching agreement out of the 55 statements that were voted on altogether. Statements with consensus aimed to define BrM primary and secondary prevention, screening procedures, assessment of symptoms, treatment efficacy, and preventing the occurrence and progression of BrM, while acknowledging the possibilities and limitations in daily clinical practice. Some statements did not reach agreement for a variety of reasons, mostly due to lack of evidence.

Conclusions: The consensus statements outlined in this publication provide a point of reference for daily clinical practice and can act as recommendations for clinical trial procedures and future guidelines.

Introduction

The treatment landscape for HER2-positive breast cancer (BC) has evolved as clinical research and technology have improved; however, the delay in occurrence and treatment of brain metastasis/metastases (BrM) remains a significant unmet need. HER2–positive BC tumour cells exhibit central nervous system (CNS) tropism, with approximately 30–55 % of patients with HER2-positive metastatic BC (MBC)

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developing BrM, which has a detrimental effect on overall survival (OS) and health-related quality of life (HR-QoL) [1–3].

Treatment for BrM in patients with HER2-positive MBC includes locally directed therapy with neurosurgical resection and/or stereotactic radiation therapy, or whole brain radiotherapy (WBRT) although the indications for WBRT are limited [4]. European Association of Neuro-Oncology – European Society for Medical Oncology (EANO-ESMO) guidelines recommend that systemic treatment of asymptomatic or minimally symptomatic BrM should be considered to delay WBRT in patients with HER2-positive MBC with a preserved general status [4,5]. The management of BrM requires a multidisciplinary approach, involving multimodal treatment based on the clinical and radiological scenario. One challenge in treating patients with HER2-positive MBC and BrM is inconsistent drug delivery across the blood–brain barrier/blood–tumour barrier, resulting in discordant intracranial versus extracranial drug sensitivity to HER2-targeted agents [1,6]. This issue becomes even more relevant in the field of BrM prevention: while available treatments are effectively reducing extracranial recurrence risk in patients with early-stage HER2-positive BC, the rate of BrM as first site of recurrence is yet to improve [7].

In HER2-positive MBC, most previous clinical trials have excluded patients with any history of BrM (e.g., CLEOPATRA) or active CNS metastases (e.g., EMILIA, DESTINY-Breast03) [8–10], hindering therapy development. HER2CLIMB was the first registrational trial allowing inclusion of patients with both active (untreated or treated but progressing BrMs) and stable BrM [11]. Just recently, the efficacy of T-DXd in patients with active brain metastases has also been confirmed in a larger dataset from the non-randomised DESTINY-Breast12 trial[12]. A limitation of the majority of clinical trials which do include patients with HER2-positive MBC with BrM is that they do not usually include pre-specified endpoints but report post-hoc analyses of CNS outcomes [13].

This publication aims to establish consensus regarding: defining BrM prevention, screening procedures, assessing symptoms and treatment efficacy, and preventing the primary and secondary progression of BrM, whilst acknowledging the possibilities and limitations in daily clinical practice. Although leptomeningeal disease may also occur in patients with advanced BC, it was agreed by the steering committee that this would not be considered in the development of this consensus as it is a separate entity of CNS involvement.

Methods

A modified Delphi process (a well-established and reliable means of achieving consensus within a structured process [14]) was used to collect opinions from experts who manage and/or treat patients who have HER2-positive MBC with BrM. Consensus was established using the following steps:

- Recruitment of steering committee members
- Literature screening and evidence grading
- Using research questions, defining and drafting consensus statements
- Voting on draft statements using a 5-point Likert scale
- Consensus meeting to discuss survey findings and second survey development

An expert consensus group was gathered to review the prevention and systemic treatments of BrM in patients with HER2-positive MBC. The international group (consisting of co-chairs [n = 2], steering committee members [n = 10], contributors [n = 61] and a patient advocate [n = 1]) covered a variety of specialties, involved in the diagnosis and management of patients with HER2-positive MBC with BrM. These included medical oncology, radiation oncology, gynecology, neuro-radiology, neuro-surgery, neuro-oncology, neurology, pathology, psycho-oncology and translational research. The co-chairs and steering committee members were selected based on their relevant expertise and recent publications in the field.

A systematic literature review was conducted using PubMed with agreed search terms and related MeSH terms (medical subject headings; HER2-positive, breast cancer, brain metastasis, prevention, treatment). Inclusion and exclusion criteria were considered and confirmed during the first steering committee meeting. Inclusion criteria included English language articles, published between January 2013 and February 2023, HER2-positive BC with and without BrM, publication types covering clinical trials, reviews, meta-analyses and preclinical studies. Exclusion criteria included non-English language, publication date before 2013, cancers other than breast, HER2-negative BC, leptomeningeal metastasis as the only CNS disease, and non-included article types. Congress abstracts were also manually searched from ASCO (American Society of Clinical Oncology), ESMO and ESMO-BC (ESMO – Breast Cancer) dated from 2018 to 2022. Articles were retrieved from these systematic searches, with duplicates removed, then screened for relevance and identified for grading by members of the steering committee (Fig. 1).

Articles were graded according to Infectious Diseases Society of America (IDSA) level of evidence and grades of recommendation, used in the ESMO standard operating procedures for clinical practice guidelines (Table 1) [15]. Each article was graded by two members of the steering committee and was considered highly rated if graded A or B, or the level of evidence was rated I or II. Where grading was not agreed, the co-chairs were asked to adjudicate and provide the final rating. The literature review was used to support and develop the initial research questions.

Following refinement of the research questions, initial consensus statements were agreed by the steering committee and formed the content for the group-wide survey. Contributors were asked to agree, strongly agree, disagree or strongly disagree (or select 'neutral') with proposed consensus statements (known as the 5-point Likert scale). Consensus was defined based on responses, with agreement reached at $\geq$ 75 %.

In June 2023, invited contributors attended a virtual consensus meeting to discuss the survey results. Statements close to achieving consensus (defined as 65–75 % agreement) were revised and presented for live voting. Statements that did not achieve consensus (defined as $<$ 65 % agreement) were presented in breakout groups, where experts discussed how to revise these statements. Statements that reached consensus at the survey stage did not require further discussion in the consensus meeting. The outcomes of these discussions were used to guide the final statement amendments. In July 2023, contributors received a second survey of revised statements as a result of the consensus meeting and steering committee feedback.

Results

The systematic literature search generated 1,256 articles for consideration. Following removal of articles not written in English and within time range restrictions, 908 articles remained. The literature was screened against the inclusion/exclusion criteria, resulting in the exclusion of 323 articles. The remaining 585 articles and 78 screened abstracts were graded by the steering committee (Fig. 1).

For the first round of the consensus survey, 28 consensus statements were generated to address each research question, supported by evidence from the literature search. Of these 28 initial statements, 16 reached consensus; therefore, following polling and feedback during the consensus meeting, interim adjustments were made to the remaining statements by the steering committee members and contributors. A second survey was circulated with an additional 27 statements, of which 19 reached consensus. Overall, 35 statements reached consensus, although one was removed by the steering committee due to repetitive wording, resulting in 34 statements with consensus presented in this manuscript. Eight statements from the second survey of amended statements did not reach consensus (Supplementary material).

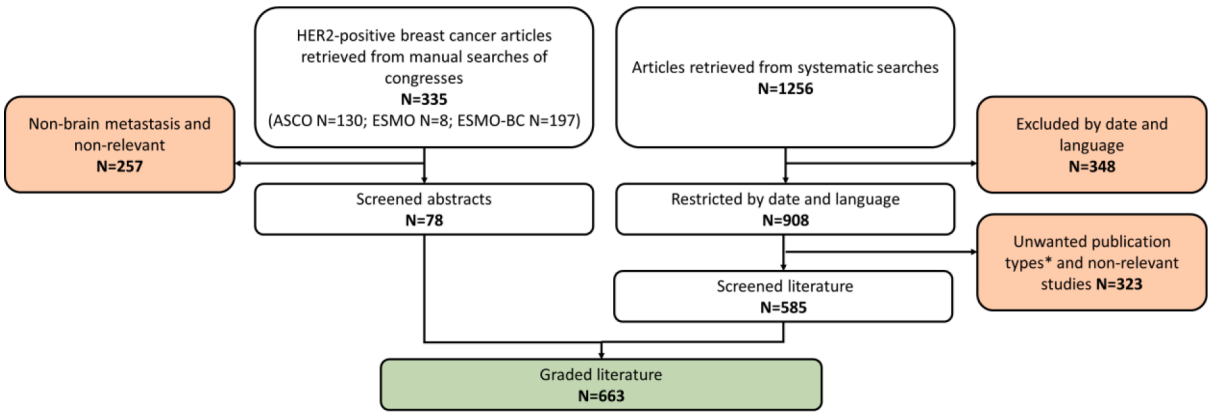

Fig. 1. Breakdown of systematic literature review screening for evidence grading. *Unwanted publication types included editorial, addresses biography, comment, directory, festschrift, interview, lectures, legal cases, legislation, news, newspaper article, patient education handout, popular works, and consensus development conference. ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; ESMO-BC, ESMO Breast Cancer; HER2, human epidermal growth factor receptor 2.

Table 1
Criteria used by the expert steering committee to grade identified literature and evidence.

Level of evidence	Criteria
I	Large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta–analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
Grade of recommendation	**Criteria**
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

*What is the definition of BrM prevention in HER2-positive BC? (Table 2**A**)*

Our literature review identified that studies rated highly by the steering committee often use incidence and time to CNS metastases as first site of disease progression, and progression-free survival (PFS) and OS as a measure of treatment efficacy [11,16–18].

As noted in the EANO-ESMO 2021 guidelines, treatment of patients with HER2–positive MBC and BrM predominantly aims to prevent or delay neurological deterioration, extending survival while offering an acceptable QoL [4]. However, no clear direction is given around how to define which time interval reflects an acceptable delay of BrM diagnosis to define the concept of BrM prevention, and this remains inconsistent among the literature. Therefore, the committee aimed to provide more clarity on this topic. A total of six statements were formed to establish definitions of delay and/or prevention of BrM in early and metastatic BC, with consideration to the fact that delaying progression of an established BrM does not qualify as prevention.

*What is the most appropriate method for BrM screening? (Table 2**B**)*

EANO-ESMO 2021 guidelines state that neurological testing and imaging should be performed in cancer patients experiencing new symptoms potentially suggesting the presence of BrM, and that screening may be justified in specific subpopulations at risk of BrM, e.g., HER2-positive MBC or triple-negative MBC [4]. As highlighted in the guidelines, magnetic resonance imaging (MRI) is considered the gold-standard for screening, whereas computed tomography (CT) and positron emission tomography (PET) are deemed less sensitive [4].

Our literature search identified high-quality evidence that concurs with current guidelines. Further insights on timings of BrM screening were provided by contributors. Clinical trials, considered to be of most relevance by the steering committee, utilised MRI or CT scans for BrM screening [11,16,19]. Although studies investigating the validity of circulating tumor deoxyribonucleic acid (ctDNA) detection through plasma DNA sampling were noted as interesting, experts felt that there was not enough evidence to justify using ctDNA as the main method of BrM detection, particularly for relapse within the brain that has reportedly been detected by ctDNA in only 17 % of patients [20]. Some evidence suggests that ctDNA detection in cerebrospinal fluid may be able to facilitate BrM diagnosis, but this requires further exploration [21]. Experts felt it was important to acknowledge that not all centers have equal access to resources and therefore some screening techniques chosen may be below gold-standard, but wherever possible highly sensitive imaging should be used.

One statement that was close to reaching consensus (supported by 70.6 % of respondents) was '*Following the diagnosis of HER2-positive BC, asymptomatic patients should be screened for BrM with a contrast-enhanced brain MRI*' (Supplementary Q2). This topic was raised as an interesting point during the steering committee meetings; guidelines currently do not recommend asymptomatic screening as part of standard practice but advise that it could potentially be justified for patients with a high risk of developing BrM, such as those with HER2-positive and triple-negative MBC [4]. Although there is not enough evidence to support screening for asymptomatic BrM, patient preference should be considered, alongside the prospect that changes in this practice may be anticipated given increasing evidence of intra-cranial activity of systemic therapies (especially HER2-targeted therapies); ongoing research in this area may lead to wider expert agreement in future e.g. NCT04030507 [22–24].

*What is the minimum clinically relevant measure for treatment efficacy regarding BrM prevention? (Table 3**A**)*

Our literature review identified common measures of treatment

Table 2
Statements with consensus, to address research questions 2A and 2B.

2A. What is the definition of BrM prevention in HER2-positive BC?	
Consensus statement	**Level of contributor agreement (%)***
In patients with a history of early BC, prevention of first BrM is defined as the lack of radiologically detectable brain lesion suggestive of BrM, prior to death	81
In patients with a history of early BC, delay to first BrM is defined as a prolonged time to radiologically detectable brain lesion suggestive of BrM	94
In patients with known MBC, primary prevention of BrM is defined as the lack of development of radiologically detectable BrM, or radiologically detected BrM occurrence, prior to death	89
In patients with known MBC, primary delay of BrM is defined as a prolonged time to development of radiologically detectable BrM, or radiologically detected BrM occurrence	92
In patients with pre-existing BrM, secondary prevention of BrM is defined as the lack of development of new brain lesions suggestive of BrM	98
In patients with pre-existing BrM, secondary delay of BrM is defined as a prolonged time to development of new brain lesions suggestive of BrM	96
2B. What is the most appropriate method for BrM screening?	
Consensus statement	**Level of contributor agreement (%)***
Contrast-enhanced brain MRI is the standard/optimal method for screening and surveillance of BrM among patients with MBC and pre-existing BrM	98
Contrast enhanced CT is inferior to contrast-enhanced brain MRI for BrM screening	88
PET scans alone are not suitable for BrM screening	94
Blood testing and ctDNA analyses are not suitable for BrM screening	77
CSF analyses are not suitable for BrM screening	83
Radiological suspicion of BrM determined using less sensitive methods (i.e., CT, PET) should be confirmed using contrast-enhanced brain MRI	96
There is not enough evidence to support screening for BrM at stage 1–3 BC. An appropriate clinical trial is warranted to provide supporting evidence for screening of the brain with contrast-enhanced brain MRI for BrM in asymptomatic patients	88
If there is uncertainty regarding BrM in a brain MRI scan, such as due to its small size (<5mm), a subsequent MRI examination should be scheduled after a period of 8–12 weeks	96

BC, breast cancer; BrM, brain metastases; CSF, cerebrospinal fluid; CT, computed tomography; ctDNA, circulating tumor deoxyribonucleic acid; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; MRI, magnetic resonance imaging; PET, positron emission tomography.
* Proportion of contributors agreeing (strongly agree/agree combined) with a survey statement.

Table 3
Statements with consensus, to address research questions 3A and 3B.

3A. What is the minimum clinically relevant measure for treatment efficacy regarding BrM prevention?	
Consensus statement	**Level of contributor agreement (%)***
The clinically relevant measure for the primary delay of BrM (with treatment) is defined as "delay of at least 6 months in the development of first brain lesion"	78
The clinically relevant measure for the primary prevention of BrM (with treatment) is defined as "no evidence of brain lesion(s) prior to death"	84
The clinically relevant measure for treatment efficacy in secondary prevention of new BrM occurrence (among patients with a history of BrM) is defined as "no evidence of new BrM occurrence prior to death"	84
3B. In patients with HER2-positive MBC, how can we prevent the progression of BrM?	
Consensus statement	**Level of contributor agreement (%)***
When local intervention to treat active BrM is indicated by the multidisciplinary team, surgical resection and/or stereotactic radiotherapy is preferred, but whole brain radiotherapy may be necessary in some cases	94
What is the current outlook of treatments for the primary prevention of BrM in HER2-positive MBC?	
More evidence is required to determine the optimal therapeutic strategy for the primary/secondary prevention of BrM among patients with HER2-positive MBC	98
Compounds that are thought to penetrate the blood–brain barrier, with promise for intracranial activity, should be evaluated in clinical trials with the aim of preventing BrM	100
Recommendations for systemic second-line treatment of HER2-positive BC with BrM	
When local intervention is not indicated, evidence-based practice supports systemic therapy for patients with HER2-positive MBC and active BrM	94
In clinical practice, systemic treatment could be used to delay local therapy after diagnosis of asymptomatic BrM and prevent intracranial progression in HER2-positive MBC in some cases	82
Evidence-based clinical practice suggests that systemic treatment using tucatinib + trastuzumab + capecitabine may have an added benefit of reducing risk of further intracranial relapse among patients with HER2-positive MBC and a history of BrM	76

BC, breast cancer; BrM, brain metastases; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer.
* Proportion of contributors agreeing (strongly agree/agree combined) with a survey statement.

efficacy within highly rated studies. However, no clear guidance was given regarding measures of treatment efficacy required to establish delay or prevention of BrM in clinical trials or routine clinical practice; therefore, the steering committee suggested that clearer definitions are required.

One statement which did not reach consensus but had a notable level of agreement (supported by 54.9 % of respondents) was *'The clinically relevant measure for treatment efficacy in secondary delay of new BrM occurrence (among patients with a history of BrM) is defined as a delay of 4–8 months in the development of new BrM'* (Supplementary Q7). In comparison, delays of at least 4 months or over 8 months received 19.6 % and 25.5 % agreement, respectively. During the steering committee meeting, some experts stated that delays of as little as 2–3 months would be clinically relevant and valuable to the patient. Others felt that length of delay should be determined by recent trial data, or that a numerical value would over-simplify the task of delaying BrM occurrence and that lack of presentation before death would be a more realistic common goal.

The steering committee experts and contributors also considered the possibility of a hazard ratio to establish clinically relevant treatment efficacy but were unable to agree on a range to recommend (Supplementary Q8). Of the 51 experts who responded to the second survey, in primary prevention of BrM (among patients without a history of BrM) a hazard ratio of 0.50–0.70 was considered indicative of a clinically relevant delay by 52.9 % of respondents. Similarly, in secondary prevention of BrM (among patients with a history of BrM) a hazard ratio of 0.50–0.70 was considered indicative of a clinically relevant delay by 74.5 % of respondents. Upon reflection, experts felt that statements of this nature could not be included due to lack of agreement across both scenarios.

How can we prevent the progression of BrM?

(Table 3**B**) Current EANO-ESMO guidelines state that WBRT should only be considered in patients with multiple BrM that are not amenable to stereotactic radiosurgery, although this is patient dependent [4]. This is further supported by studies reporting that OS was not improved by WBRT [25–28]. During the expert meetings, it was generally agreed that while WBRT is not the preferred treatment of choice, it can be used in selected patient cases within the guidelines and at the treating clinician's discretion.

Research on preventing the progression of BrM is limited, due to the lack of treatment options that can cross the blood–brain barrier and few clinical trials including patients with MBC and identifiable BrM. The HER2CLIMB trial of tucatinib in pre-treated HER2-positive MBC patients included patients with active and stable BrM [11]. The study concluded that both PFS and OS were improved with this treatment combination, including those with BrM, with a significant increase in PFS for patients with BrM when compared with patients who received placebo (24 % vs 0 % at one year) [11]. An exploratory analysis in patients with BrM found that the risk of intracranial progression or death was reduced by 68 % in the tucatinib arm [29]. Accordingly, the experts agreed that tucatinib + trastuzumab + capecitabine may reduce the risk of further intracranial relapse (76 % agreement). However, the optimal sequencing of local and systemic therapies is unclear.

The HER2CLIMB trial also included a subgroup of patients with untreated BrM, who chose to defer radiation treatment, and ultimately saw improvements in CNS-PFS and OS. Furthermore, among all randomized patients, the risk of developing new brain lesions as the site of first progression or death was 45.1 % less in the tucatinib arm with a median new brain lesion-free survival that was 11.1 months longer for the tucatinib-combination group than for the placebo-combination group (exploratory analysis: 24.9 vs 13.8 months; 95 % CI, 17.8 to inestimable vs 9.6 to inestimable) [30]. In the CEREBEL trial, the incidence of CNS metastases as first site of progression was 3 % in the lapatinib-capecitabine arm and 5 % in the trastuzumab-capecitabine (the difference was not statistically significant) with a numerically longer median time to first CNS progression in the lapatinib-capecitabine compared to the trastuzumab-capecitabine arm (5.7 and 4.4 months, respectively) [31]. In the LANDSCAPE trial, which evaluated lapatinib combined with capecitabine in patients with HER2-positive MBC with BrM not previously treated with WBRT, the median time to WBRT was 8.3 months with a median time to CNS progression of 5.5 months [5]. The evidence discussed supports the consensus statement agreed by this group of experts: 'In clinical practice, systemic treatment could be used to delay local therapy after diagnosis of asymptomatic BrM and prevent intracranial progression in HER2-positive MBC in some cases' (Table 3).

Generally, data are not currently available to confirm the best approach to treatment and multiple anti-HER2 therapies such as trastuzumab deruxtecan (T-DXd) are available or undergoing further research [32,33]. Intracranial response was observed in the TUXEDO-1 phase 2, single-arm study; 15 patients with MBC and active BrM receiving T-DXd experienced a median PFS of 21 months, and median OS was not reached [34]. Intracranial efficacy was also investigated in the DESTINY-Breast12 phase 3b/4 study. A 12-month PFS of 61.6 % was observed in previously treated patients with HER2 + MBC with stable/active BrM treated with T-DXd; 12-month CNS PFS was 58.9 % with similar outcomes in patients with stable and active BrM [12],

A number of highly rated articles outlining early and encouraging research suggests that other compounds of interest should be evaluated further in clinical trials, with the aim of identifying their potential to prevent BrM [19,35].

*What are the best tools for symptom evaluation and patient QoL (quality of life) assessment among patients with in HER2-positive BC and BrM? (Table 4**A**)*

As evidenced by the literature, QoL is a valuable parameter for assessment in both daily clinical practice and clinical trials using appropriate tools, e.g., European Organisation for Research and Treatment (EORTC) questionnaires and Eastern Cooperative Oncology Group (ECOG) performance status scales [36,37]. Experts felt that clinicians may be limited by time and/or resources available to provide regular HR-QoL questionnaires and neurocognitive function assessment. However, they also acknowledged that HR-QoL changes and neurocognitive symptom improvement noted during regular clinic visits should be considered alongside the traditional imaging and assessments to provide a better overview of the patient's condition. Indeed, QoL and neurocognitive function could greatly affect patients' perception of their health status [38]. In the opinion of the experts, questionnaires often do not address the patient's capabilities to conduct specific tasks that are relevant to their daily life. While validated tools e.g., EORTC QLQ-C30 and BN-20, are of interest for assessing QoL as part of clinical trials, regular and relevant questions should be asked routinely by clinicians to ascertain treatment efficacy.

It was noted, within clinical trials of patients with HER2-positive MBC, that the reduction in size of BrM is often associated with improved neurological and neurocognitive symptoms; however, this was not consistently assessed in the clinical trial setting [17]. Accordingly, contributors highlighted that each patient's neuropsychological profile should be composed by neuropsychological assessment, as well as patient-specific recommended treatments. Therefore, neurocognitive tests that can be completed quickly should be adapted to cancer care context and subsequently validated; existing tools are often lengthy, potentially enhancing participants' burden within clinical trials [39].

Additional assessments (as outlined in the consensus statements, Table 4**A**) could be useful to fully evaluate symptoms, cognitive functions and QoL both in clinical trials and daily clinical practice.

Conclusions

Current guidelines on screening, diagnosis, as well as primary and secondary prevention are in many aspects limited by the lack of evidence from clinical trials. Experts agreed on several statements, covering definitions for the prevention of BrM, optimal methods and guidance on the appropriate timing for the screening of BrM, and guidance on the most valuable symptom and QoL assessments for clinical trials and daily clinical practice. Consensus on clinically relevant measures of treatment efficacy, the prevention of BrM in the current landscape, systemic treatment options, and the direction of future research was also achieved. Some statements did not reach consensus, for reasons such as lack of evidence around the most relevant and applicable QoL assessment tools and promising future therapies. Other statements did not reach consensus due to limitations of individual clinical practice, as resources available to clinicians vary considerably both nationally and internationally.

Statements covered a broad range of topics within the HER2-positive MBC with BrM landscape. Experts are often knowledgeable in one or some specific areas, but not all, and naturally experts within the same niche fields will have different perspectives. This could be seen as a limitation of the consensus statement survey format, as some experts may have felt unable to respond with confidence on specific topics outside of their expertise, others may have chosen to vote for the option of best fit. While current guidelines do not generally recommend screening for BrM in an asymptomatic BC population, a surprisingly high rate of experts (70.6 %) considered BrM screening as a potential standard approach for patients with HER2-positive disease, highlighting the clinical interest in BrM screening and the urgent need for further clinical investigation in this field.

Table 4
Statements with consensus, to address research question 4A.

4A. What are the best tools for symptom evaluation and patient QoL (quality of life) assessment among patients with in HER2-positive MBC with BrM?	
Consensus statement	**Level of contributor agreement (%)***
QoL improvement should be considered as a valuable endpoint for assessing the efficacy of interventions for the treatment of BrM in those with HER2-positive MBC	100
Clinical neurological assessment of the patient is valuable in evaluating treatment efficacy in HER2-positive MBC with BrM	86
Neurocognitive symptoms improvement should be considered as a valuable endpoint for assessing the efficacy of interventions for the treatment of BrM in those with HER2-positive MBC	92
Neurocognitive function assessment of the HER2-positive BC patient with BrM should ideally be conducted using validated tools, but may not be suitable for daily clinical practice due to time restrictions	100
Neurological symptoms improvement should be considered as a valuable endpoint for assessing the efficacy of interventions for the treatment of BrM in those with HER2-positive MBC	94
Treatment efficacy endpoints (such as risk of relapse or brain-specific progression-free survival) should be assessed in conjunction with QoL	98
A lack of decline (stability) in QoL is a valuable measurement of treatment efficacy for patients with BrM	85
In clinical trials, symptom assessment should include specific function-related validated tools when comparing outcomes in patients with HER2-positive MBC and BrM (e.g., patient diary and symptom history, ECOG PS, and neurological assessment and function)	96
In clinical trials, QoL assessment should include specific function-related validated tools when comparing outcomes among HER2-positive MBC patients with BrM, such as EORTC QLQ-C30 and EORTC QLQ-BN20	84
In clinical trials, evaluation of neurological status should include specific validated tools when comparing outcomes in patients with HER2-positive MBC and BrM, such as NANO and the UK MRC neurological status scale	80
In daily clinical practice (depending on available resources), valuable/practical tools for symptom evaluation in patients with HER2-positive MBC and BrM include, but are not limited to, patient diary, symptom history and ECOG PS	92

BC, breast cancer; BrM, brain metastases; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC, European Organisation for Research and Treatment of Cancer; HER2, human epidermal growth factor receptor 2; MBC; metastatic breast cancer; MRC, Medical Research Council; NANO, Neurologic Assessment in Neuro-Oncology; QoL, quality of life.

* Proportion of contributors agreeing (strongly agree/agree combined) with a survey statement.

The steering committee felt that good quality clinical trials, inclusive of patients with BrM utilising a variety of treatments and outcome assessments are sparse, and that these studies, alongside the current consensus statements, may contribute to updated, in-depth clinical guidelines in future. This work aimed to build on the current guidelines, with the inclusion of statements that can be referenced in daily practice and planning future clinical trials.

Conflict of interest

VM: Speaker/consultancy honoraria for AstraZeneca, Daiichi-Sankyo, Eisai, Pfizer, MSD, Medac, Novartis, Roche, Seagen, Onkowissen, high5 Oncology, Medscape, Gilead, Pierre Fabre, iMED Institut, PINK, ClinSol, MSD, Lilly, Seagen, Stemline; institutional research support from Novartis, Roche, Seagen, Genentech, AstraZeneca and travel grants from AstraZeneca, Roche, Pfizer, Daiichi Sankyo and Gilead.

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GC: Advisory board participation/fees from Roche, Novartis, Lilly, Pfizer, AstraZeneca, Daichii Sankyo, Ellipsis, Veracyte, Exact Science, Celcuity, Merck, BMS, Cilead, Sanofi and Menarini.

EdeA: Honoraria and/or advisory board participation/consultancy for Roche/GNE, Novartis, Seagen, Zodiac, Libbs, Pierre Fabre, Eli Lilly, AstraZeneca, MSD, Gilead Sciences; travel grants from AstraZeneca and Gilead Sciences; research grants to institution from Roche/GNE, AstraZeneca, GSK/Novartis, Gilead Sciences; non-financial - ESMO Director of Membership 2023–2025 and BSMO President 2023–2026.

JF: Honoraria for lectures and consultation from Novartis and Seagen.

JG: Speaker/consultancy and/or advisory board participant for Seagen, Zeiss and BrainLab.

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Appendix B. Supplementary material

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References

[1] Lin NU, et al. CNS metastases in breast cancer: Old challenge, new frontiers. Clin Cancer Res 2013;19(23):6404–18.
[2] Chen W, et al. Organotropism: new insights into molecular mechanisms of breast cancer metastasis. NPJ Precis Oncol 2018;2(1):4.
[3] Kuksis M, et al. The incidence of brain metastases among patients with metastatic breast cancer: A systematic review and meta-analysis. Neuro Oncol 2021;23(6):894–904.
[4] Le Rhun E, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol 2021;32(11):1332–47.
[5] Bachelot T, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): A single-group phase 2 study. Lancet Oncol 2013;14(1):64–71.
[6] Zimmer AS, Van Swearingen AED, Anders CK. HER2-positive breast cancer brain metastasis: A new and exciting landscape. Cancer Reports 2022;5(4):e1274.
[7] von Minckwitz G, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019;380(7):617–28.
[8] Baselga J, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366(2):109–19.
[9] Verma S, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367(19):1783–91.
[10] Hurvitz SA, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: Updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet 2023;401(10371):105–17.
[11] Murthy RK, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med 2020;382(7):597–609.
[12] Harbeck N, et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. Nat Med 2024. https://doi.org/10.1038/s41591-024-03261-7. Online ahead of print.
[13] Bhogal T, Cameron D, Palmieri C. Central nervous system disease in phase III studies for advanced HER2 positive breast cancer: A review. Breast 2022;63:85–100.
[14] Boulkedid R, et al. Using and reporting the Delphi method for selecting healthcare quality indicators: A systematic review. PLoS One 2011;6(6):e20476.
[15] ESMO Guidelines Committee. ESMO Standard Operating Procedures (SOPs) for Clinical Practice Guidelines (CPGs) and ESMO Magnitude of Clinical Benefit (ESMO-MCBS) and ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) scores. 2022 September 2023]; Available from: https://www.esmo.org/content/download/77789/1426712/file/ESMO-Clinical-Practice-Guidelines-Standard-Operating-Procedures.pdf.
[16] Krop IE, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: A retrospective, exploratory analysis in EMILIA. Ann Oncol 2015;26(1):113–9.
[17] Montemurro F, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial(☆). Ann Oncol 2020;31(10):1350–8.
[18] Swain SM, et al. Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: Results from the randomized phase III study CLEOPATRA. Ann Oncol 2014;25(6):1116–21.
[19] Macpherson IR, et al. A phase I/II study of epertinib plus trastuzumab with or without chemotherapy in patients with HER2-positive metastatic breast cancer. Breast Cancer Res 2019;22(1):1.

[20] Garcia-Murillas I, et al. Assessment of molecular relapse detection in early-stage breast cancer. JAMA Oncol 2019;5(10):1473–8.
[21] De Mattos-Arruda L, et al. Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma. Nat Commun 2015;6:8839.
[22] Jerzak, K.J., et al. MRI screening versus symptom-directed surveillance for brain metastases among patients with triple negative or HER2+ metastatic breast cancer: A pilot study (NCT03881605). Cancer Res 2022;82(4_Supplement):Abstract OT1-07-01.
[23] National Library of Medicine (U.S.). Brain Monitoring for High Risk of Brain Metastases in Metastatic Breast Cancer. ClinicalTrials.gov identifier: NCT03617341. 2020. Available from: https://clinicaltrials.gov/study/NCT03617341. Last accessed November 2024.
[24] National Library of Medicine (U.S.). Screening Magnetic Resonance Imaging of the Brain in Patients With Breast Cancer. ClinicalTrials.gov identifier:NCT04030507.-2023. Available from: https://clinicaltrials.gov/study/NCT04030507. Last accessed November 2024.
[25] Gori S, et al. The HERBA study: A retrospective multi-institutional italian study on patients with brain metastases from HER2-positive breast cancer. Clin Breast Cancer 2019;19(4):e501–10.
[26] Kocher M, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011;29(2):134–41.
[27] Brown PD, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: A randomized clinical trial. JAMA 2016;316(4):401–9.
[28] Brown PD, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): A multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 2017;18(8):1049–60.
[29] Lin NU, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. J Clin Oncol 2020;38(23):2610–9.
[30] Lin NU, et al. Tucatinib vs placebo, both in combination with trastuzumab and capecitabine, for previously treated ERBB2 (HER2)-positive metastatic breast cancer in patients with brain metastases: Updated exploratory analysis of the HER2CLIMB randomized clinical trial. JAMA Oncol 2023;9(2):197–205.
[31] Pivot X, et al. CEREBEL (EGF111438): A phase III, randomized, open-label study of lapatinib plus capecitabine versus trastuzumab plus capecitabine in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer. J Clin Oncol 2015;33(14):1564–73.
[32] Wynn CS, Tang SC. Anti-HER2 therapy in metastatic breast cancer: many choices and future directions. Cancer Metastasis Rev 2022;41(1):193–209.
[33] Bartsch R, et al. Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: A single-arm, phase 2 trial. Nat Med 2022;28(9):1840–7.
[34] Bartsch R, et al. Final outcome analysis from the phase II TUXEDO-1 trial of trastuzumab-deruxtecan in HER2-positive breast cancer patients with active brain metastases. Neuro Oncol 2024:noae123.
[35] Nounou MI, et al. Anti-cancer antibody trastuzumab-melanotransferrin conjugate (BT2111) for the treatment of metastatic HER2+ breast cancer tumors in the brain: An in-vivo study. Pharm Res 2016;33(12):2930–42.
[36] Saura C, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Phase III NALA trial. J Clin Oncol 2020;38(27):3138–49.
[37] Li Y, et al. Incidence, risk factors and survival of patients with brain metastases at initial metastatic breast cancer diagnosis in China. Breast 2021;55:30–6.
[38] Li J, et al. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. Int J Radiat Oncol Biol Phys 2008;71(1):64–70.
[39] Matsui JK, et al. Quality of life and cognitive function evaluations and interventions for patients with brain metastases in the radiation oncology clinic. Cancers (Basel) 2022;14(17).