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SPECIAL ARTICLE

EANO—ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours☆

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INTRODUCTION

The present joint European Association of Neuro-Oncology (EANO)—European Society for Medical Oncology (ESMO) recommendations for the diagnosis and treatment of parenchymal brain metastasis (BM) from solid cancers complement the first joint EANO—ESMO guideline on leptomeningeal metastasis from solid cancers.[1] These recommendations address BMs from solid tumours, but do not address BMs from primary brain tumours or BMs from lymphoma or leukaemia. The recommendations cover prevention, diagnosis, therapy and follow-up, but not differential diagnosis, adverse effects of therapeutic measures or supportive or palliative care. Given the low level of evidence, the recommendations are often based on expert opinion and consensus rather than on evidence from informative clinical trials. Still, the EANO—ESMO multidisciplinary recommendations shall serve as a valuable source of information for physicians and other health care providers, as well as informed patients and relatives.

INCIDENCE AND EPIDEMIOLOGY

Details on epidemiology and pathogenesis are covered in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.07.016.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Clinical presentation

The clinical history is commonly short with development of neurological symptoms and signs within weeks. BMs may cause headaches, epileptic seizures or motor deficits such as hemiparesis, hemisensory loss, personality changes, aphasia, visual disturbances or symptoms and signs of

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raised intracranial pressure. The risk of epilepsy probably depends on proximity to the cortex and on the presence of tumoural haemorrhage. Focal symptoms and signs depend on BM location. Haemorrhage, typically with BMs from melanoma or chorionic carcinoma, or obstructive hydrocephalus, notably with cerebellar BMs, can cause rapid neurological deterioration. A detailed neurological examination using a standard evaluation form, e.g. as proposed by the Response Assessment in Neuro-Oncology (RANO) group,[2] should be carried out and documented when BMs are diagnosed and during follow-up.[3]

Diagnostic procedures

Neuroimaging at diagnosis. New neurological symptoms and signs in a cancer patient should trigger a neurological work-up including neuroimaging to distinguish BMs from other aetiologies of neurological morbidity, notably side-effects of cancer therapy. Furthermore, subgroups of cancer patients have a high risk of BM, probably justifying screening at diagnosis of their cancer, including lung cancer in general, notably non-squamous lung cancers, with the possible exception of stage I non-small-cell lung cancer (NSCLC). Screening should also be considered in stage IV melanoma, notably because early BM diagnosis may impact clinical decision making and improve outcome. Screening at diagnosis is also potentially justified in metastatic human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer [EANO: IV, n/a; ESMO: IV, B].[4,5] This approach will result in a higher rate of detection of asymptomatic brain metastases.

About 75% of BMs are located in the cerebral hemispheres, 21% in the cerebellum and up to 3% in the brain stem. Fewer than half of all BMs are single, i.e. there is only one brain lesion,[6] and very few are solitary, i.e. the only metastasis detected in the body. Cranial magnetic resonance imaging (MRI), without and with contrast agent administration carried out with at least 1.5-T field strength, is the gold standard for neuroradiological assessment of patients with suspected BMs.[7] The diagnostic work-up of patients with suspected BM should include at minimum cranial MRI with pre- and post-contrast T_1-weighted, T_2-weighted and/or T_2-fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences [EANO III, C; ESMO IV, B]. Characteristic MRI findings include solid or ring enhancement, perifocal oedema and a predilection for the grey–white matter junction and vascular border zones. Magnetic resonance spectroscopy (MRS) as well as perfusion and DWI may offer supportive findings, such as tumour-specific metabolites, unrestricted diffusion of cystic content and low perfusion. However, there is no combination of imaging features that distinguishes BM from other pathologies with absolute certainty. Although differential diagnosis is beyond the scope of this guideline, a biopsy should be considered if lesions, notably of cystic nature, cannot be distinguished with certainty from primary brain tumours, abscesses or inflammatory lesions. The sensitivity of MRI for the detection of BM depends on the technique employed, with influencing factors being field strength, contrast agent type and dose, delay between contrast agent administration and data acquisition and in- and through-plane resolution. Three-dimensional acquisition is preferred because of its thinner slices.[8,9] With double-dose contrast agent, imaging sensitivity is increased, but this comes at the cost of a decrease in specificity and should be reserved for those instances when it is essential to optimise sensitivity. There should be at least a several-minute delay between contrast agent administration and image acquisition, typically achieved by performing an additional sequence between contrast agent administration and the post-contrast T_1-weighted acquisition.[10,11] Cranial computed tomography (CT) is markedly less sensitive than MRI for BM detection and should be limited to patients with contraindications for MRI.

Positron emission tomography using [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG–PET) represents the most widely used tracer in extracranial oncological PET imaging and is of value in improving the accuracy of staging by detecting more extracranial metastases than CT, especially in BM patients with cancers of unknown primary (CUP).[12] However, the regionally high FDG uptake in the normal brain limits substantially the sensitivity of FDG–PET for BM detection.[13] PET using radiolabelled amino acids has an additional diagnostic value compared with anatomical MRI and is superior to FDG–PET for patients with brain tumours including BMs.[13,14]

Pathology and liquid biopsies. Details on pathology and liquid biopsies are covered in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.07.016.

An efficient algorithm allows for identification of the source of BM in most patients (Table 1 and Figure 1).

Table 1. Predictive markers

Entity	Molecular markers/targets
Breast	HER2, ER/PR, BRCA1/2 ('BRCAness'), PIK3CA, PD-L1
Non-small-cell lung	EGFR, ROS1, NTRK, ALK, RET, MET, KRAS, BRAF, PD-1/PD-L1
Squamous cell	FGFR1
Melanoma	BRAF, KIT, NF1, NRAS, PD-L1
Colorectal	KRAS, BRAF, NRAS, PD-L1, MSI
Upper gastrointestinal	HER2, MET
Urothelial/transitional Cell	PD-L1
Endometrium	MSI
Ovarian (serous)	ER/PR, MSI
Ovarian (mucinous)	MSI

Predictive value for treatment guidance of these markers may depend on the overall clinical setting (localisation and extent of manifestations, subsequent identification of primary) and is thus only provided for orientation.
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ER/PR, estrogen/progesterone receptor; FGFR1, fibroblast growth factor receptor 1; HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; NF1, neurofibromin 1; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3KCA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

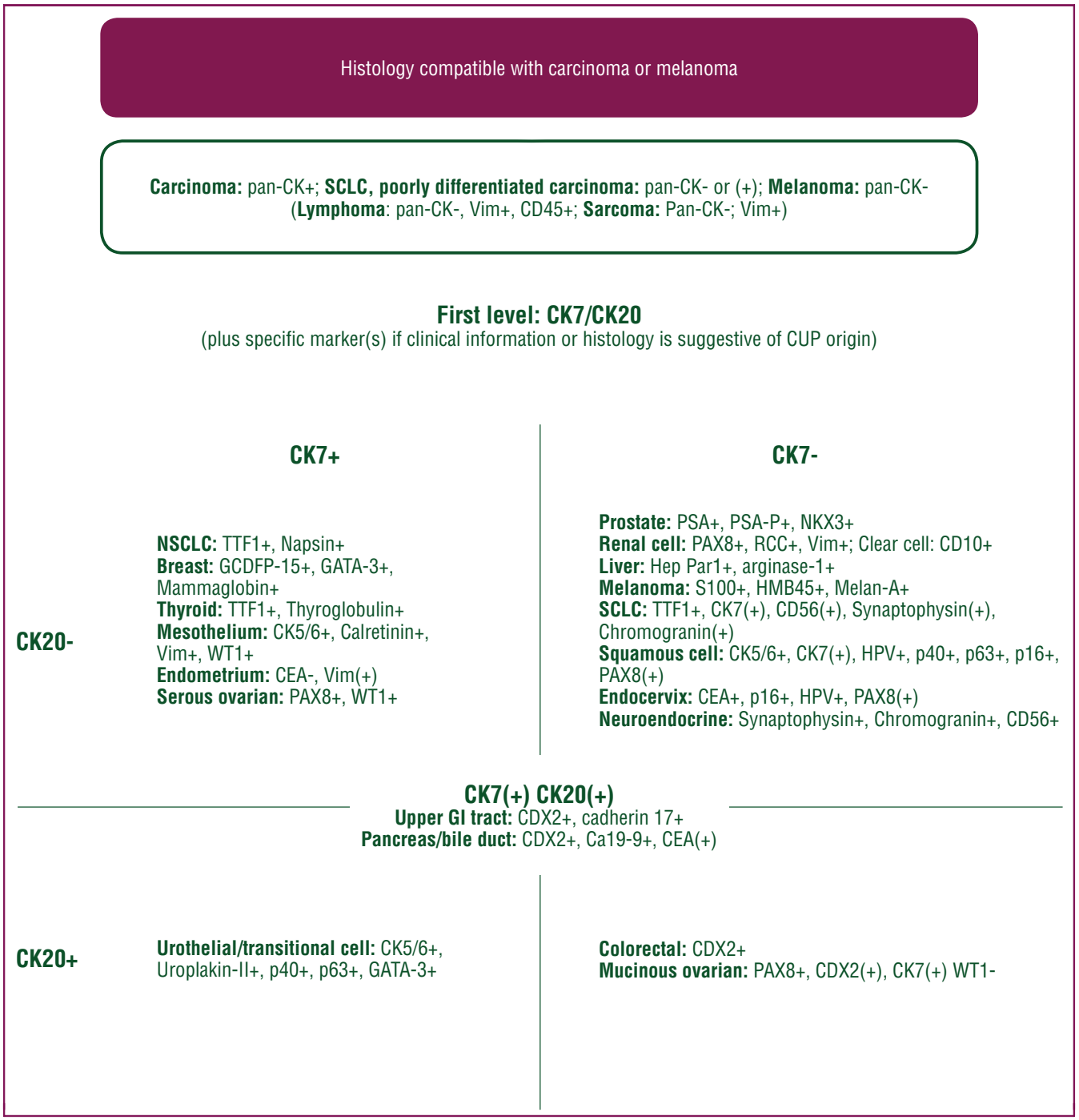

Figure 1. Immunohistochemical markers for evaluation of metastatic carcinoma of unknown primary (CUP). Typical expression profiles often greatly facilitate the identification of the tissue of origin. However, the combinations depicted here represent the most common marker profiles and various exceptions can occur (e.g. in less differentiated tumours, as is often the case for CUPs). Also, metastases of squamous cell and neuroendocrine carcinoma are particularly challenging in this respect because they often lack immunohistochemical markers indicating the tissue of origin. More recently developed diagnostic platforms such as DNA methylation, RNA or microRNA (miRNA) analysis hold great potential for the identification of the tissue of origin of CUPs but have not yet entered clinical routine. (+): tends to be positive. Ca19-9, cancer antigen 19-9; CD, cluster of differentiation; CDX, caudal type homeobox transcription factor; CEA, carcinoembryonic antigen; CK, cytokeratin; GATA-3, member 3 of transcription factor family binding to DNA sequence GATA; GCDFP, gross cystic disease fluid protein; GI, gastrointestinal; Hep Par 1, hepatocyte paraffin 1; HMB, human melanoma black; HPV, human papilloma virus; Melan-A, melanoma antigen recognised by T cells, MART1; NKX3, homeobox protein Nkx 3.1; NSCLC, non-small-cell lung carcinoma; p16/p40/p63, tumour protein 16/40/63; PAX, paired-box gene transcription factor; PSA, prostate-specific antigen; PSA-P, prostate-specific acidic phosphatase; RCC, renal cell carcinoma; SCLC, small-cell lung carcinoma; TTF, thyroid transcription factor; Vim, vimentin; WT1, Wilms tumour protein 1.

Recommendations

- Screening for BM should be considered for patients with lung cancer with the possible exception of stage I NSCLC, and for stage IV melanoma, and potentially also for patients with metastatic HER2-positive and triple-negative breast cancer [EANO: IV, n/a; ESMO: IV, B].
- The presence of BMs should be explored by neuroimaging in all patients with cancer who present with clinical

symptoms or signs of raised intracranial pressure, seizures and new neurological deficits [EANO III, B; ESMO III, B].
- The diagnostic work-up of patients with suspected BM should include cranial MRI with pre- and post-contrast T1-weighted, T2-weighted and/or T2-FLAIR and diffusion-weighted sequences [EANO: III, C; ESMO: IV, B].
- Histopathological and immunohistochemical work-up of BM should follow local institutional algorithms [EANO: IV, n/a; ESMO: V, B].
- In patients undergoing neurosurgical resection, treatment-relevant predictive biomarkers detected in the primary tumour or extra-central nervous system (CNS) metastasis should be reconfirmed in the BM [EANO: IV, n/a; ESMO: V, B].
- Cell-free tumour DNA in the blood or cerebrospinal fluid (CSF) analyses should not be routinely requested for the characterisation or monitoring of BM [EANO: IV, n/a; ESMO: IV, C].
- CSF studies including cytology should be carried out to rule out leptomeningeal metastasis if suspected based on clinical or neuroimaging findings [EANO: III, C; ESMO: IV, B].

THERAPEUTIC STRATEGIES: GENERAL CONSIDERATIONS

For the majority of patients, the goal of treatment of BM is to prevent or delay neurological deterioration and to prolong survival with acceptable quality of life. A minority of patients, notably with small and few lesions, may experience long-term survival or even cure. Several tumour-specific approaches are commonly used in combination.

Surgery

Diagnostic considerations. Neurosurgical interventions with diagnostic intention are required in several clinical scenarios, including patients where neuroimaging leaves doubt that lesions represent BMs, where no primary tumour is known, where more than one tumour is known, where the primary tumour rarely generates BM or where changes in molecular profile compared with the primary tumour may impact clinical decision making [EANO: III, C; ESMO: IV, B]. The diagnostic value of biopsy to distinguish progression from therapy-induced changes after stereotactic radiotherapy (SRT) remains limited because active tumour- and therapy-induced changes like necrosis may coexist, but not adequately be represented in the biopsy material.

Therapeutic considerations. The therapeutic value of neurosurgical resection at least of single BMs in patients with controlled systemic disease remains undisputed. Extent of resection is associated with local control of BM[15,16] [EANO: I, A; ESMO: II, A]. *En bloc* resections may result in lower recurrence rates and lower risk of leptomeningeal dissemination than piecemeal resections.[17] The likelihood of gross total BM resection with low morbidity can be increased using preoperative functional MRI, intraoperative neuronavigation, fluorescence-guided resection and cortical mapping.[18-21] A post-operative MRI should be carried out within 48 h after surgery to determine the extent of resection.

The randomised clinical trials that demonstrated improved survival when surgical resection was followed by whole-brain radiotherapy (WBRT), compared with WBRT alone in patients with single BMs, were conducted decades ago at a time when surgical and imaging techniques were different and when no active systemic treatments were available. These trials also commonly pooled patients with BMs from different primary tumours.[22,23] Extrapolating these data to modern neurosurgery has led to the assumption that similar improvements in outcome may be achieved with surgical interventions in patients with more than one BM if a gross total resection is feasible.

There are specific scenarios where surgery should be considered for its immediate therapeutic effect in patients with multiple BMs. This includes large BMs (>3 cm diameter) causing raised intracranial pressure or neurological impairment when located in eloquent brain regions. Posterior fossa location often constitutes a surgical indication because of the risk of obstructive hydrocephalus. Cystic or necrotic BMs are another indication since these may respond less well to SRT than solid BMs. Prior cyst aspiration followed by radiosurgery may also be considered.[24,25] Surgical resection, more than any other intervention, allows rapid steroid tapering and optimises the therapeutic efficacy of ensuing therapy, notably immune checkpoint inhibition.[26] Surgery is less often indicated for patients with recurrent BM, although the above-mentioned individual considerations may apply, notably if further promising systemic treatment options are available.

Laser interstitial thermal therapy is a novel intervention mostly for recurrent brain tumours as well as for radiation necrosis, with encouraging local control data,[27] but the definition of its role in the management of BM requires further study.[28]

All indications for surgical interventions in BM, except emergency situations, should be assessed for risk and benefit in a multidisciplinary tumour board since the majority of BM patients die of systemic disease and not of BM. Specifically, the role of surgery versus SRT needs to be weighted and it has to be determined which kind of molecular neuropathology work-up is required, to secure that an adequate amount and quality of tissue is obtained to maximise benefit for the patients.

Radiotherapy

Stereotactic radiosurgery. Whereas WBRT has been the historical mainstay of radiotherapy (RT) for treatment of BM, stereotactic radiosurgery (SRS) has today become the standard of care in many clinical situations. In general, SRS is defined as the delivery of high doses of radiation via stereotactic or image guidance with ~1 mm targeting accuracy to intracranial targets. It is commonly given as single fraction utilising doses between 15 and 24 Gy. Fractionated

SRS given in two to five fractions typically delivered with 27 Gy in three fractions or 30 Gy in five fractions[29] is preferred in patients with larger lesions (>3 cm diameter) or lesions in proximity of structures at risk, e.g. the brain stem or in pre-irradiated patients.

SRS added to WBRT improves overall survival (OS) in patients with 1-3 BMs.[30] SRS has been increasingly used in patients with >3 BMs. A prospective multicentre study (JLGK0901) of 1194 patients with 1-10 BMs who received SRS alone showed a similar survival of 10.8 months in patients with 2-4 versus 5-10 BMs.[31] Treatment-related toxicity was low, with neurocognitive function assessed by the mini-mental state examination being similar between groups when cumulative tumour volume was <15 ml.[32]

Because of high local recurrence rates after neurosurgical resection alone, two randomised trials evaluated SRS to the resection cavity after neurosurgical resection of BMs. Brown et al. randomised 194 patients to post-operative WBRT or SRS.[33] There was no difference in OS and the decline in cognitive function was more frequent after WBRT. Mahajan et al. randomised 132 patients to either post-operative SRS or observation.[34] Freedom from local recurrence was significantly improved by post-operative SRS. In case of larger resection cavities, a risk-adapted fractionation is encouraged where the total dose is distributed over three to five fractions.

Whole-brain radiotherapy. WBRT, typically 20-30 Gy in 5-10 fractions, has been used either as a consolidating treatment after local therapy or as the primary treatment modality primarily for patients with multiple BMs. WBRT after neurosurgical resection or SRS of limited BMs improved local and distant brain control, but not OS, and was associated with a detrimental effect on neurocognitive function.[35-37] In addition, no benefit for WBRT was demonstrated in a randomised phase III trial in melanoma patients already locally treated for one to three BMs.[37]

When used as initial treatment for patients with multiple BMs, WBRT is associated with a median survival of 3-6 months, with 10%-15% of BM patients alive at 1 year.[38] The QUARTZ trial, which randomised NSCLC patients not eligible for surgery or SRT to receive optimal supportive care or optimal supportive care plus WBRT (20 Gy in five fractions), showed similar median survival of ∼9 weeks in both arms,[39] with no significant reduction in quality of life for patients receiving supportive care only. Yet, WBRT may still have a role for the management of patients with multiple large unresectable BMs in the context of a recent diagnosis of cancer, in younger patients and in patients in good general performance status (PS).

New WBRT-based approaches have also been evaluated in patients with multiple BMs. The simultaneous integrated boost technique allows an additional focal dose escalation in macroscopic BMs compared with WBRT alone. Radiation Therapy Oncology Group (RTOG) 0614 showed a trend towards neurocognitive protection by memantine when combined with WBRT.[40] The NRG CC001 trial compared WBRT plus memantine with hippocampal avoiding (HA)-WBRT plus memantine and reported significantly preserved patient-reported quality of life and prevention of cognitive decline throughout the follow-up period.[41] The implications of these data for the use of memantine remain unclear because memantine alone was not active when combined with WBRT and whether it helped HA-WBRT to be active cannot be determined.

Prophylactic cranial irradiation. Prophylactic cranial irradiation (PCI) has been established as a standard of care in small-cell lung cancer (SCLC), both in limited[42] and extensive disease.[43] However, PCI is currently being challenged due to its toxicity in extensive-stage SCLC by the introduction of serial MRI-based follow-up[44,45] and immune checkpoint inhibition.[46] A randomised phase III trial showed no lower probability of cognitive decline in patients treated with PCI associated with hippocampal avoidance when compared to standard PCI. No difference in incidence rate of BM at 2 years or in survival was observed either.[47] Hippocampal sparing can thus not be considered standard of care in this setting.

Pharmacotherapy

Most BMs exhibit uptake of contrast on MRI or CT and are thus characterised by the lack of a functional blood—brain barrier. Intravenously (i.v.) administered drugs are predicted to distribute in the same way as i.v. administered contrast agents for neuroimaging, suggesting that systemic pharmacotherapy could be as efficient for contrast-enhancing BMs as for other systemic tumour manifestations. However, to what extent uptake of a gadolinium-based contrast agent truly allows prediction of adequate penetration of larger molecules (like monoclonal antibodies or antibody—drug conjugates) remains uncertain. The choice of agent is primarily determined by histological and molecular tumour type and not by the metastasis location in the brain. If feasible, molecular genetic work-up of BMs rather than primary tumour should be considered for selecting targeted therapy and immunotherapy in a tumour-specific manner [EANO: IV, C; ESMO: IV, B]. Drugs with better blood—brain barrier penetration are predicted to provide superior tumour control, notably in tumour areas that are partially protected by the blood—brain barrier. Previous lines of treatment should also be considered in the decision making. In the situations of multiple systemic treatment options, CNS and extra-CNS disease activity as well as toxicity profile of the respective treatment options should be considered in the decision-making process for the optimal systemic treatment strategy [EANO: IV, A; ESMO: IV, B].

Preliminary evidence suggests that steroid use has a negative impact on outcome of immunotherapy in BM patients.[48]

BM from breast cancer. Systemic therapy plays an important role in the control of BM from breast cancer. Different drugs have been used for the treatment of BM including classical chemotherapy agents such as capecitabine,

cyclophosphamide, 5-fluorouracil, methotrexate, vincristine, cisplatin, etoposide, vinorelbine and gemcitabine, most of them with response rates >30%.

Patients with BM from HER2-positive metastatic breast cancer are particularly likely to benefit from targeted therapy. In patients without neurosurgical indication and with preserved neurological status (PS 0-2), previously treated with trastuzumab but capecitabine—lapatinib-naïve, the combination of lapatinib and capecitabine produced a brain response rate of 38% in patients with pre-irradiated BM and of 66% in patients with treatment-naïve BM.[49,50] The NALA study compared neratinib plus capecitabine to lapatinib plus capecitabine in second/third line. One hundred and thirty patients had asymptomatic and stable BM at study entry and 'overall cumulative incidence' of intervention for BM (mostly RT) was decreased from 29% to 23% in the neratinib arm ($P = 0.04$).[51] The combination of neratinib and capecitabine showed a control rate approaching 50% (22 partial response, 16 stable disease) for patients with BM pre-treated with any combination of surgery and RT and with a stable steroid dose who had received mainly more than two lines of systemic treatment in a phase II study.[52] A secondary analysis of the second-line EMILIA study evaluating trastuzumab emtansine (T-DM1) in patients previously treated with trastuzumab and a taxane was carried out on patients retrospectively identified with asymptomatic CNS metastases ($n = 95$). This analysis showed an improved OS in the T-DM1 group compared with the lapatinib and capecitabine group (median, 26.8 months, $n = 45$ versus 12.9 months, $n = 50$).[53] A retrospective analysis of T-DM1 in BM breast cancer patients, including 92% of patients pre-treated with local treatment, showed a response rate of up to 44%.[54] The combination of tucatinib, capecitabine and trastuzumab was tested in a third-line phase III trial with half of the patients presenting with BM (HER2CLIMB). In the sub-analysis among the 291 patients with BM, median OS was significantly prolonged in the tucatinib combination group compared with the trastuzumab and capecitabine combination group (18.1 versus 12.0 months).[55] Few studies have specifically assessed systemic therapy for BM from HER2-negative luminal or triple-negative breast cancer. Abemaciclib showed an intracranial clinical benefit rate defined as complete response plus partial response plus stable disease persisting for ≥6 months of 25% and a median progression-free survival (PFS) of 4.4 months in heavily pre-treated patients with BM from estrogen receptor-positive/HER2-negative breast cancer.[56]

Prevention of BM by systemic treatment is an emerging topic in the management of breast cancer. In the CLEOPATRA study, patients did not have BM at diagnosis but 13% relapsed in the brain at first recurrence. In this subpopulation, median time to develop BM was increased from 12 to 15 months with the addition of pertuzumab to trastuzumab and docetaxel.[57] The CEREBEL study did not show that the combination of lapatinib and capecitabine was more efficient than trastuzumab plus capecitabine for BM prevention in the first-line or second-line setting.[58]

BM from lung cancer. For patients with advanced NSCLC without actionable oncogenic driver alterations, monotherapy with anti-programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors in case of PD-L1 positivity (>50%) or combination of immune checkpoint inhibition with platinum-based combination chemotherapy has become standard of care. Further combination immunotherapies, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibition, with or without chemotherapy, have recently reached clinical practice.[59,60] Only scarce data are available regarding the role of immune checkpoint inhibition specifically in the treatment of asymptomatic BM. Early data suggested that pembrolizumab is safe and effective for untreated NSCLC BMs with CNS response rates in the range of 30%.[61] The efficacy of nivolumab has been retrospectively confirmed in NSCLC patients with asymptomatic BMs.[62] Subgroup analyses from combination trials using anti-PD-1 and anti-CTLA-4, with or without chemotherapy, suggest a significant efficacy against BMs, with similar benefit irrespective of the presence of CNS lesions.[63] Most immunotherapy trials have only enrolled patients with controlled and treated, e.g. with RT, BMs, and the lack of prospective data limits the level of evidence for immunotherapy in the management of asymptomatic BM. A multicentre pooled analysis reported immunotherapy efficacy in a variety of settings. Among patients with 'active' BM ($n = 73$), the intracranial response rate was 27.3%.[64]

NSCLC patients with oncogenic driver alterations such as epidermal growth factor receptor (*EGFR*) mutation and anaplastic lymphoma kinase (*ALK*), c-ros oncogene 1 (*ROS1*) or Ret proto-oncogene (*RET*) rearrangements are characterised by a higher cumulative incidence of BM than those without driver oncogenes. These patients achieve favourable median survival times of >3 years in *EGFR*-mutated NSCLC[65] and >5 years with *ALK* rearrangement.[66] Tyrosine kinase inhibitors (TKIs) have thus become a standard treatment component of the multimodality management because of increased response rates for extracranial as well as intracranial metastases compared with classical chemotherapy. CNS response rates are influenced by the potency of the TKIs as well as their blood—brain barrier penetration, including their specific P-glycoprotein interaction.[67] Specific TKIs have shown significant CNS activity, notably in the presence of *EGFR* mutations as well as *ALK, ROS1, RET,* neurotrophic tyrosine receptor kinase (*NTRK*), Neuregulin 1 (*NRG1*) rearrangements, as well as exon 14 skipping mutations of *MET,* also called tyrosine-protein kinase Met or hepatocyte growth factor receptor. Only limited data are available regarding targeted therapy for *KRAS* G12C and *BRAF* mutations.

The standard of care for patients with extensive SCLC disease is based on platinum and etoposide combination chemotherapy together with immune checkpoint inhibition,[46] [EANO: II, B; ESMO: II, B]. The added value of immune checkpoint inhibition remains to be formally demonstrated in SCLC patients with brain metastases, with or without symptoms or dedicated local treatment.

BM from melanoma. Systemic chemotherapy using classical agents such as temozolomide, dacarbazine or fotemustine has only limited efficacy in melanoma patients with BM.[68] Monotherapy using the BRAF inhibitors vemurafenib or dabrafenib in *BRAF*-mutated patients with melanoma BM achieved intracranial response rates between 15% and 40%;[69-71] and improved intracranial response rates up to 60% were observed with the combination of vemurafenib and dabrafenib in asymptomatic untreated BM, similar to the response rate in other organ sites with, however, overall short duration of response.[72] Anti-PD-1 monotherapy or ipilimumab plus nivolumab has been investigated in patients with BM: in patients with asymptomatic BM, current data favour the combination with an overall response rate of ~50%,[73,74] reasonable response duration and PFS of >50% at 18 months. However, the inclusion criteria in these trials were stringent resulting in asymptomatic or oligosymptomatic patient populations with low CNS tumour burden. Based on these data, ipilimumab—nivolumab combination therapy is the preferred first-line treatment also in *BRAF*-mutated asymptomatic patients with BMs [EANO: II, B; ESMO: II, B]. Importantly, efficacy of ipilimumab—nivolumab combination seems to be lower in patients with symptomatic BM requiring steroids with 21%[74] intracranial response rates.

Recommendations

Surgery

- Surgery should be considered when there is doubt on the neoplastic nature of a brain lesion, when no primary tumour is known, when more than one tumour is known, when the primary tumour rarely generates BM or when changes in molecular profile compared with the primary tumour may impact clinical decision making [EANO: III, C; ESMO: IV, B].
- Single BMs should be considered for surgical resection [EANO: I, A; ESMO: II, A].
- Multiple resectable BMs may be considered for surgical resection [EANO: IV, C; ESMO: V, C].
- Surgery may be considered for patients requiring steroids, who are candidates for immune checkpoint inhibition [EANO: III, n/a; ESMO: IV, B].
- Surgery should be considered when there are acute symptoms of raised intracranial pressure [EANO: III, C; ESMO: IV, B].
- A post-operative MRI should be carried out within 48 h after surgery to determine the extent of resection [EANO: IV, C; ESMO: V, C].

Radiotherapy

- SRS is recommended for patients with a limited number (1-4) of BMs [EANO: I, A; ESMO: I, A].
- SRS may be considered for patients with a higher number of BMs (5-10) with a cumulative tumour volume <15 ml [EANO: II, B; ESMO: II, B].
- SRS to the resection cavity is recommended after complete or incomplete resection of BMs [EANO: I, A; ESMO: I, A].
- Post-operative WBRT after neurosurgical resection or after SRS should be discouraged [EANO: I, A; ESMO: I, E].
- WBRT should be considered for treatment of multiple BMs not amenable to SRS, depending on the presence of neurological symptoms, size, number and location of BMs and the choice and availability of CNS-active systemic therapy [EANO: III, B; ESMO: III, B].
- Supportive care with omission of WBRT should be considered in patients with multiple BMs not eligible for SRS and poor PS [EANO: I, B; ESMO: I, B].
- Despite scepticism, PCI is still recommended for patients with limited and extensive-stage SCLC with complete response to chemoradiotherapy [EANO: I, A; ESMO: I, A].

Pharmacotherapy

- Systemic pharmacotherapy based on histological and molecular characteristics of the primary tumour and previous treatment should be considered for most patients with BMs [EANO: IV, n/a; ESMO: IV, B].
- If feasible, molecular genetic work-up of BMs rather than primary tumour should be considered for selecting targeted therapy and immunotherapy in a tumour-specific manner [EANO: IV, C; ESMO: IV, B].
- Systemic treatment of asymptomatic or oligosymptomatic BMs should be considered to delay WBRT in HER2-positive breast cancer patients with a preserved general status [EANO: III, C; ESMO: III; B].
- For HER2-negative breast cancer patients with progressive BM after local treatment, standard chemotherapy, such as capecitabine, eribulin or carboplatin and bevacizumab, may be considered [EANO: III, C; ESMO: III, B].
- Patients with NSCLC without actionable oncogenic driver alterations with asymptomatic or oligosymptomatic BM should be treated by upfront immune checkpoint inhibition alone (PD-L1 ≥50%) or systemic chemotherapy combined with immune checkpoint inhibition (PD-L1 <50%) [EANO: II, B; ESMO: III, B].
- Patients with NSCLC with actionable oncogenic driver alterations such as *EGFR* or *ALK* or *ROS1* rearrangement and asymptomatic or oligosymptomatic BM should be treated by upfront systemic targeted therapy [EANO: II, B; ESMO: III, B].
- Patients with SCLC should be treated by platinum-based chemotherapy without or with immune checkpoint inhibition [EANO: II, B; ESMO: II, B].
- The combination of ipilimumab and nivolumab should be the preferred first-line treatment option not only in *BRAF* wild-type, but also in *BRAF*-mutated asymptomatic patients [EANO: II, B; ESMO: II, B].
- Patients with multiple symptomatic *BRAF*-mutated BMs or patients requiring 4 mg dexamethasone or more eligible for further treatment should receive dabrafenib plus trametinib [EANO: IV, B; ESMO: IV, B].

INTEGRATED THERAPEUTIC APPROACHES

The best combination of the different therapeutic approaches should be identified according to the general and

neurological status, comorbidities, neuroimaging findings, histology and molecular status of the primary tumours (if possible updated) and previous treatments (Figure 2). The multimodality treatment of BMs requires a careful individualised estimation of the different contributions from surgery, radiation oncology and medical oncology. Ideally, therapeutic decisions should be discussed at a dedicated BM board or at a disease-specific tumour board with participation of colleagues experienced in the management of CNS tumours [EANO: IV, n/a; ESMO: V, B].

To obtain local control, surgery and SRT can be competitive as well as complementary approaches. The role of WBRT is declining, considering the modest benefit–risk ratio and the development of SRS. The following factors favour neurosurgical resection: unknown primary tumour, neuroradiologically uncertain lesion, large cystic or necrotic lesion, need for high-dose steroids, mass effect and need for molecular profiling to guide clinical decision making. Factors favouring SRS alone over surgery commonly followed by SRS or systemic therapy include a surgically less accessible location, increased surgical risk and preference for a non-invasive outpatient treatment.

Systemic therapy should primarily follow the histology and molecular characteristics of the primary tumour and prior treatment.

In the specific case of BM from cancer of unknown primary tumour (BM-CUP), after extensive diagnostic work-up including notably PET, no data from controlled trials are available. Surgical resection should be followed by RT of the cavity, but not by any tumour-agnostic systemic treatment in the absence of further tumour manifestations unless an actionable driver mutation is detected.

When combining systemic pharmacotherapy and RT, the risk of adverse events should be considered for each new drug, e.g. BRAF inhibitors and WBRT cause severe dermatitis that is usually managed by avoiding concomitant treatment.[75]

For patients with asymptomatic or oligosymptomatic BM, no prospective trials have addressed the question of optimal combined modality treatment with systemic therapy, including TKI or immune checkpoint inhibition, and surgery or SRS. Such a trial would have to consider survival endpoints as well as quality of life including neurocognitive endpoints.

In breast cancer, no study has defined the best timing of systemic treatment and RT combinations and most of the trials focus on the role of systemic pharmacotherapy alone. In NSCLC patients without activating driver mutations and limited asymptomatic BM, systematic meta-analysis of mostly uncontrolled data suggests improved OS after early combination of immune checkpoint inhibitors and SRS compared with a sequential approach.[76] For NSCLC with activating *EGFR* mutations, several retrospective studies, including mainly studies on first-generation EGFR inhibitors characterised by a poor CNS tumour penetration, also suggest that the best survival may be achieved with combined upfront TKI and SRT compared with a sequential strategy.[77-79] Adequately designed controlled clinical trials are required to determine whether novel, potent brain-penetrant TKIs, including the third-generation TKI osimertinib, can obviate the need for early SRS. Fewer data are available about optimal sequencing of TKI and local therapy in patients with *ALK* translocations where several potent CNS-penetrating compounds are available. However, there is widespread consensus that upfront WBRT should not be delivered in patients with *EGFR* mutation or *ALK* translocation. In case of BM from SCLC, the decision to add SRS or WBRT and the timing of such interventions depend on symptoms and disease burden. Replacement of WBRT by SRS appears to compromise time to progression in the CNS, but not OS.[80] Although melanoma is known as a radioresistant tumour, durable local control may be achieved after SRS.[81] The optimal timing of SRT in the multimodal therapeutic approach to BM from melanoma remains to be determined, although data from uncontrolled cohort studies also support early combination.[82]

Data from randomised trials to confirm the superiority of initial combined modality treatment have not been published. To what extent patient selection introduced bias into the published cohort studies suggesting superiority of combined modality treatment remains controversial. For patients with symptomatic BM, systemic therapy is also considered, but commonly not as a single modality treatment.

Once progression of BMs has been diagnosed using appropriate imaging examinations or tissue analysis, further treatment options should ideally be discussed in a multidisciplinary board (Figure 2). On an individual case-by-case consideration, surgery, (repeat) SRS, change of systemic treatment and combinations thereof may be considered.

Randomised trials in the BM population are needed to confirm the optimal timing of the different interventions, e.g. surgery before immunotherapy, SRS at BM diagnosis concomitant with systemic pharmacotherapy or at progression. Considering the high unmet need, enrolment into trials should be considered whenever possible.

Recommendations

- The multimodality treatment of BMs should be based on a careful individualised estimation of the different contributions from surgery, radiation oncology and medical oncology [EANO: IV, n/a; ESMO: V, B].
- Ideally, therapeutic decisions should be discussed at a dedicated BM board or at a disease-specific tumour board with participation of colleagues experienced in the management of CNS tumours [EANO: IV, n/a; ESMO: V, B].
- Randomised trials in patients with asymptomatic or oligosymptomatic BM should be conducted to identify the optimal combined modality treatment of systemic therapy, including TKI or immune checkpoint inhibition, with surgery or SRS [EANO: IV, n/a; ESMO: V, B].

MONITORING AND FOLLOW-UP

Patients with a history of BM should be followed up by neurological assessment and neuroimaging in 3-monthly

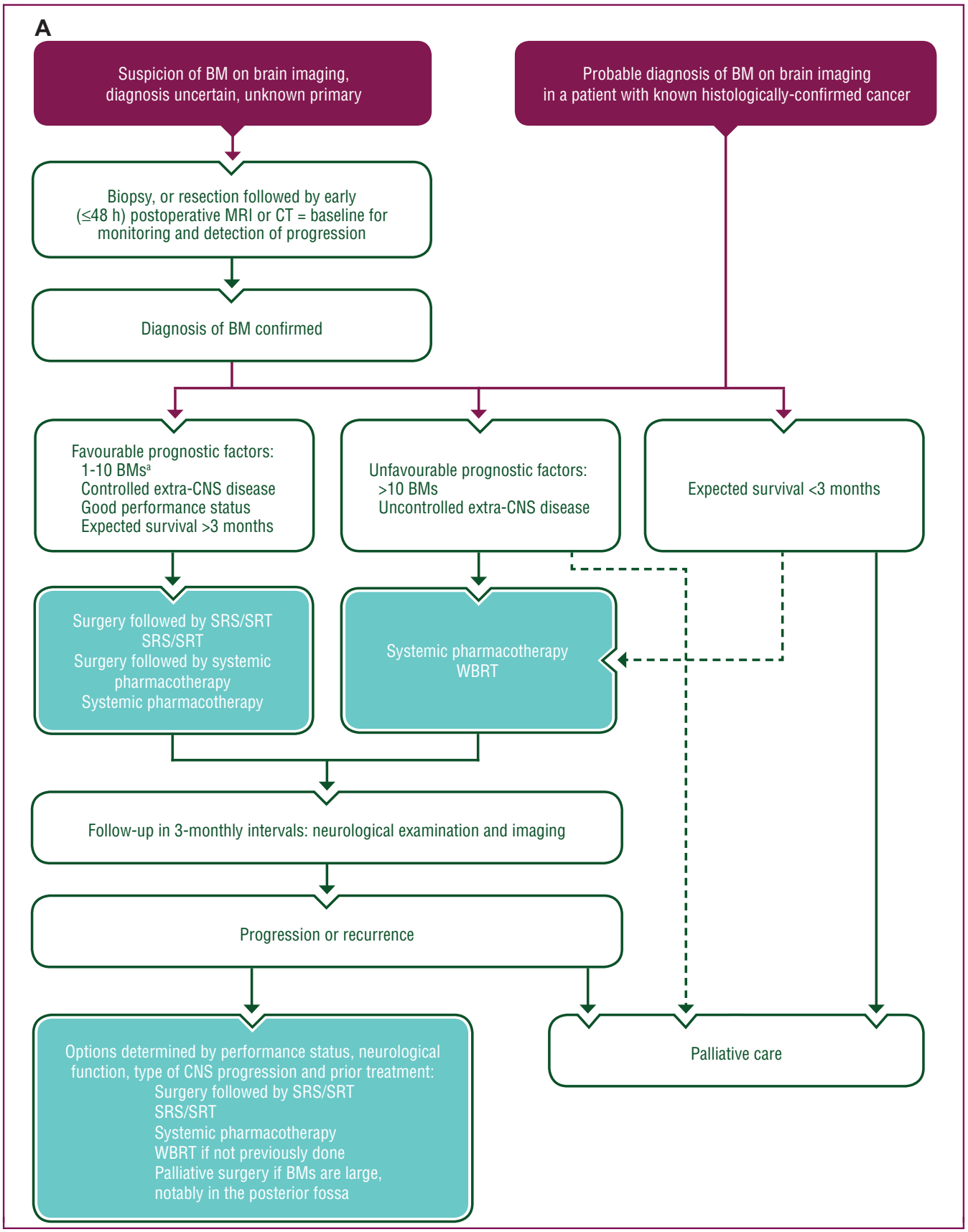

Figure 2. Proposed combination of the different therapeutic approaches for patients diagnosed with BM.
(A) In general. (B) For SCLC patients. (C) For melanoma patients.
Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management. Straight line: preferred option; dotted line, alternative option.
BM, brain metastasis; CNS, central nervous system; CT, computed tomography, GI, gastrointestinal; mucin, mucinous; MRI, magnetic resonance imaging; PCI, prophylactic cranial irradiation; SCLC, small-cell lung cancer; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; WBRT, whole-brain radiotherapy.
[a] Depending on the total volume of BM.

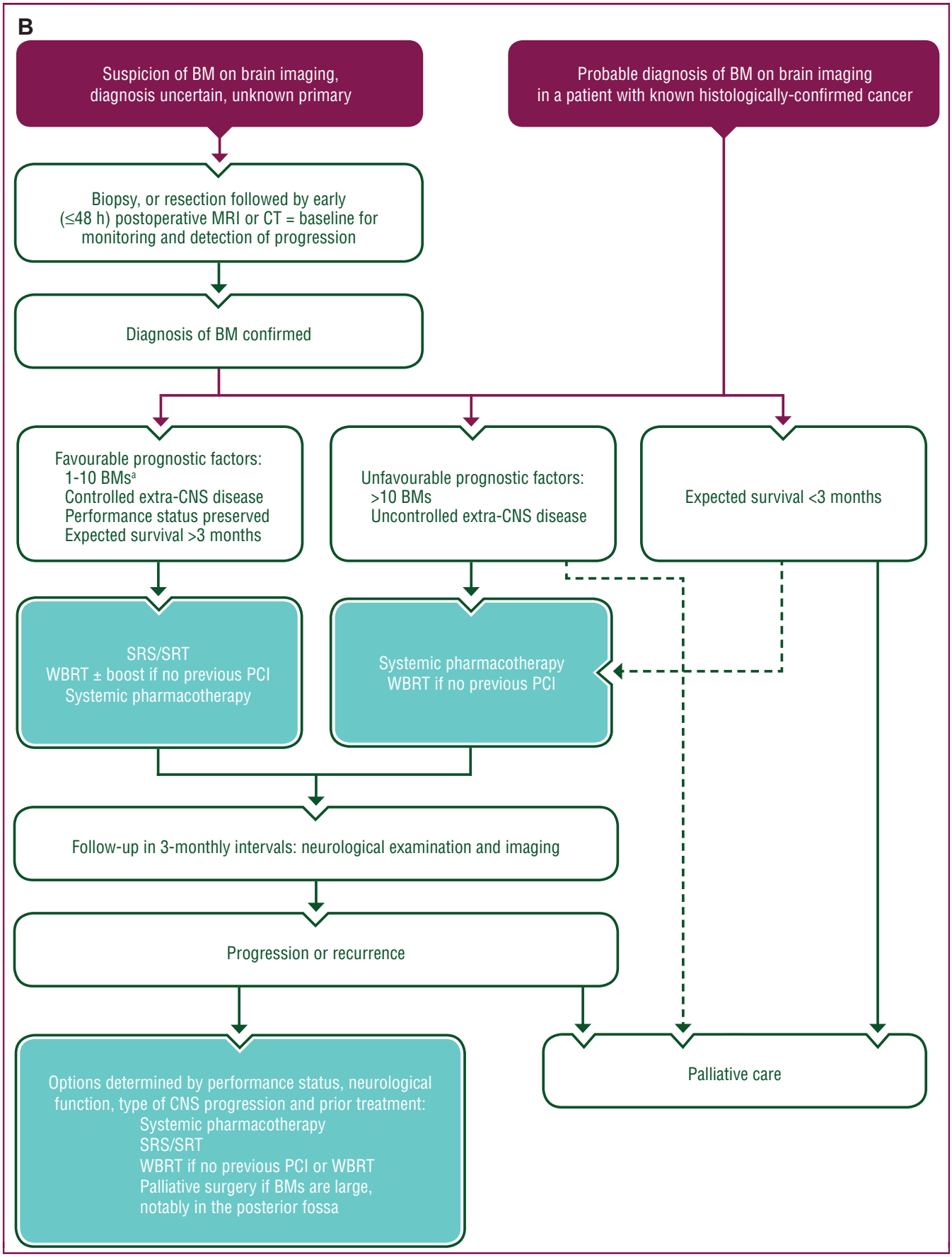

Figure 2. **Continued.**

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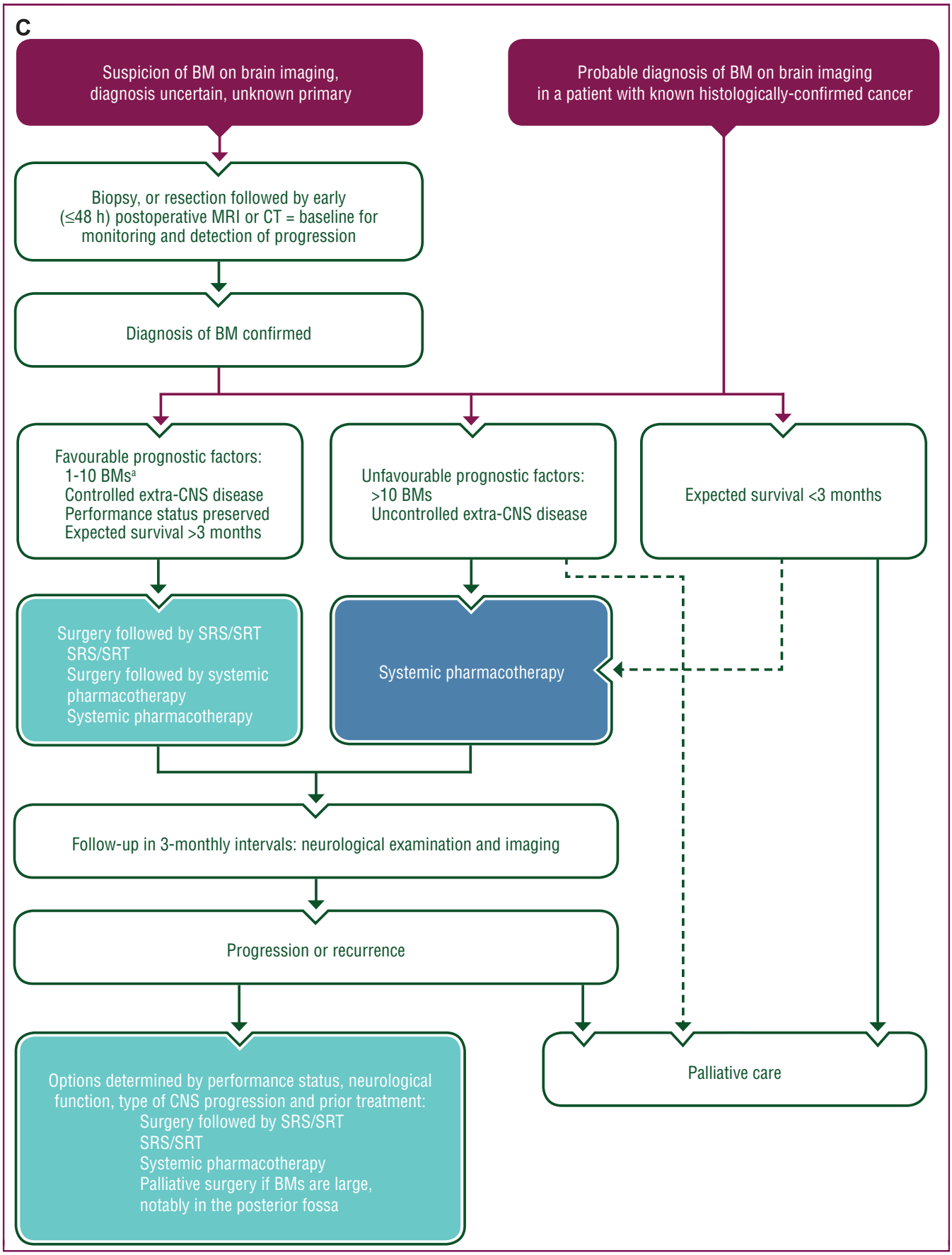

Figure 2. **Continued.**

intervals and whenever clinically indicated. The evaluation of response to treatment in clinical trials on BM is increasingly based on RANO criteria, which consider changes in target and non-target lesions on conventional contrast-enhanced MRI, neurological status and steroid use,[83] and such criteria are also increasingly used in clinical practice.

The neurological status should be regularly documented using a standardised procedure, e.g. the neurologic assessment in neuro-oncology scale.[2] Cognitive function should be assessed at baseline and in the course of disease and ability to consent should regularly be re-evaluated [EANO: IV, n/a; ESMO: V, B]. Brain MRI should be carried out every 2-3 months or at any instance of suspected neurological progression [EANO: IV, n/a; ESMO: V, B]. MRI is the standard method for response assessment and follow-up.[83] The MRI should be repeated on the same device or at least a device with an identical field strength. However, conventional MRI may not always reliably distinguish between treatment-related abnormalities, notably pseudoprogression, radionecrosis and tumour progression. Perfusion MRI and MRI spectroscopy are increasingly used in this setting, but evidence for their ability to aid in differential diagnosis remains low.[84-86]

Amino acid PET tracers such as [^{11}C]-methyl-L-methionine, 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine or O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) have been most frequently evaluated for the differentiation of BM relapse from radiation injury following RT. Across all these amino acid PET tracers, both the sensitivity and specificity for correct differentiation are in the range of 80%-90%.[87] Furthermore, amino acid PET using FET is also of value for the diagnosis of treatment-related changes following immunotherapy, using immune checkpoint inhibitors or targeted therapy, with or without RT [EANO III, C; ESMO IV, C].[88]

The immunotherapy RANO criteria[89] have been designed to assess delayed responses and prevent that progression is assumed too early in patients treated with immunotherapy, as long-term survival and tumour regression can occur following initial progression in these patients. The rate of pseudoprogression with immunotherapy alone appears to be low. Further studies are required to determine how to distinguish treatment-related changes from progression after SRT with or without systemic therapy.[82] For BM patients, whose primary tumour is still unknown after a first work-up at diagnosis, whole-body FDG—PET in the follow-up may be useful.

Liquid biopsies assessing circulating tumour cells or cell-free DNA in blood or CSF have not yet been integrated into the response assessment and follow-up of BM patients.[90]

Recommendations

- A detailed neurological examination should be carried out every 2-3 months or earlier when radiological progression is suspected and/or neurological symptoms or signs develop [EANO: IV, n/a; ESMO: V, B].
- Neurocognitive function and ability to consent should be regularly assessed [EANO: IV, n/a; ESMO: IV, B].
- Brain MRI should be carried out every 2-3 months or at any instance of suspected neurological progression [EANO: IV, C; ESMO: IV, B].
- Advanced MRI techniques, such as MRS and perfusion imaging and amino acid PET, should be considered for distinguishing treatment-related changes from tumour progression [EANO: III, C; ESMO: IV, C].

SUPPORTIVE CARE

This guideline does not aim to comprehensively describe palliative and supportive care for BM patients. Therefore, general considerations for brain tumour patients apply.[91] When required clinically for control of raised intracranial pressure, the lowest dose of steroids should be used for the shortest time possible [EANO: IV, n/a; ESMO: IV, B]. The risk of *Pneumocystis jirovecii* pneumonia is increased in patients treated with steroids for more than a few weeks, and prophylaxis with trimethoprim—sulfamethoxazole should be considered in such circumstances if additional immunosuppressive systemic therapy is administered. Bevacizumab is probably the best agent for the treatment of radionecrosis after SRT.[92] It exhibits superior activity compared with steroids and does probably not interfere with the efficacy of immunotherapy. Patients who experienced a seizure should receive secondary anticonvulsant prophylaxis, at least transiently. Primary prophylaxis is not recommended because it has not been shown to be effective in preventing a first-ever seizure [EANO: I, A; ESMO: I, A]. Seizures should be managed with anticonvulsant drugs that do not exhibit drug—drug interactions, e.g. levetiracetam, lamotrigine and lacosamide are preferred over phenytoin, carbamazepine or valproic acid. Primary thromboprophylaxis should be considered in patients hospitalised for an acute illness or who are confined to bed. Low-molecular-weight heparin (LMWH) or unfractionated heparin is recommended for primary prophylaxis as well as for the treatment of venous thromboembolism (VTE) [EANO: II, B; ESMO: II, C]. Risk factors for thromboembolic events in BM patients include specific primary tumours, steroid use, administration of chemotherapy, high body mass index and immobilisation. The risk of intracranial bleeding is probably not increased in BM patients in general treated with therapeutic doses of LMWH. Other risk factors of bleeding should be considered. Data on direct oral anticoagulants in BM patients are lacking.

Recommendations

- Steroids should only be considered in symptomatic patients [EANO: IV, n/a; ESMO: IV, B].
- Primary anticonvulsant prophylaxis should not be given [EANO: I, A; ESMO: I, A].
- If indicated, LMWH should be considered as the first-line treatment for primary or secondary thromboprophylaxis and for the therapeutic treatment of VTE in BM patients [EANO: II, B; ESMO: II, C].

- Decisions on the competency to drive should take into account epilepsy but also cognitive and other neurological functions and need to adhere to national guidelines and law [EANO: IV, n/a; ESMO: V, n/a].

OUTLOOK

Guidelines reflect knowledge and consensus at a given timepoint. Updates on these recommendations will be announced on the websites of EANO (www.eano.org) and ESMO (www.esmo.org). Conclusions derived from secondary analyses on patients with BM defined as 'active' or 'inactive', which are poorly defined concepts, are not suitable to derive treatment algorithms. Dedicated trials for BM patients based on well-defined diagnostic and inclusion criteria, ideally enriched for molecular genetic signatures where feasible and with adequate criteria of evaluation, are required to improve the outcome of BM in a primary cancer-specific manner.

METHODOLOGY

This Clinical Practice Guideline was developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. References were identified through searches of PubMed with the search terms 'CNS', 'brain', 'metastasis', 'trial', 'clinical', 'surgery', 'radiotherapy', 'chemotherapy', 'targeted therapy', 'immunotherapy', 'imaging', 'MRI' and 'PET' in various combinations from 1 January 2011 to 30 August 2020. Articles were also identified through searches of the authors' own files. Only papers in English were reviewed. The final reference list was generated by consensus of the authors and based on originality and relevance to the broad scope of this guideline. Levels of evidence and grades of recommendation were applied using the European Federation of Neurological Societies criteria as recommended by EANO (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.07.016)[93] as well as using an adapted version of the Infectious Disease Society of America-United States Public Health Service Grading System as recommended by ESMO (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.07.016).[94] Statements without grading were considered justified standard clinical practice by the experts.

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REFERENCES

1. Le Rhun E, Weller M, Brandsma D, et al. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours. *Ann Oncol*. 2017;28(suppl 4):iv84-iv99.
2. Nayak L, DeAngelis LM, Brandes AA, et al. The Neurologic Assessment in Neuro-Oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria. *Neuro Oncol*. 2017;19(5):625-635.
3. Soffietti R, Abacioglu U, Baumert B, et al. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). *Neuro Oncol*. 2017;19(2):162-174.
4. Cagney DN, Martin AM, Catalano PJ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro Oncol*. 2017;19(11):1511-1521.
5. Singh R, Stoltzfus KC, Chen H, et al. Epidemiology of synchronous brain metastases. *Neurooncol Adv*. 2020;2(1):vdaa041.
6. Wolpert F, Lareida A, Terziev R, et al. Risk factors for the development of epilepsy in patients with brain metastases. *Neuro Oncol*. 2020;22(5):718-728.
7. Kaufmann TJ, Smits M, Boxerman J, et al. Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases (BTIP-BM). *Neuro Oncol*. 2020;22:757-772.
8. Suh CH, Jung SC, Kim KW, et al. The detectability of brain metastases using contrast-enhanced spin-echo or gradient-echo images: a systematic review and meta-analysis. *J Neurooncol*. 2016;129(2):363-371.
9. Nagao E, Yoshiura T, Hiwatashi A, et al. 3D turbo spin-echo sequence with motion-sensitized driven-equilibrium preparation for detection of brain metastases on 3T MR imaging. *AJNR Am J Neuroradiol*. 2011;32(4):664-670.
10. Yuh WT, Tali ET, Nguyen HD, et al. The effect of contrast dose, imaging time, and lesion size in the MR detection of intracerebral metastasis. *AJNR Am J Neuroradiol*. 1995;16(2):373-380.
11. Jeon J-Y, Choi JW, Roh HG, et al. Effect of imaging time in the magnetic resonance detection of intracerebral metastases using single dose gadobutrol. *Korean J Radiol*. 2014;15(1):145-150.
12. Wolpert F, Weller M, Berghoff AS, et al. Diagnostic value of 18F-fluordesoxyglucose positron emission tomography for patients with brain metastasis from unknown primary site. *Eur J Cancer*. 2018;96:64-72.
13. Galldiks N, Langen K-J, Albert NL, et al. PET imaging in patients with brain metastasis-report of the RANO/PET group. *Neuro Oncol*. 2019;21(5):585-595.
14. Albert NL, Weller M, Suchorska B, et al. Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas. *Neuro Oncol*. 2016;18(9):1199-1208.
15. Kamp MA, Rapp M, Slotty PJ, et al. Incidence of local in-brain progression after supramarginal resection of cerebral metastases. *Acta Neurochir (Wien)*. 2015;157(6):905-910;discussion 910-911.
16. Yoo H, Kim YZ, Nam BH, et al. Reduced local recurrence of a single brain metastasis through microscopic total resection. *J Neurosurg*. 2009;110(4):730-736.
17. Patel AJ, Suki D, Hatiboglu MA, et al. Impact of surgical methodology on the complication rate and functional outcome of patients with a single brain metastasis. *J Neurosurg*. 2015;122(5):1132-1143.
18. Kamp MA, Munoz-Bendix C, Mijderwijk H-J, et al. Is 5-ALA fluorescence of cerebral metastases a prognostic factor for local recurrence and overall survival? *J Neurooncol*. 2019;141(3):547-553.
19. Höhne J, Hohenberger C, Proescholdt M, et al. Fluorescein sodium-guided resection of cerebral metastases-an update. *Acta Neurochir (Wien)*. 2017;159(2):363-367.
20. Chua TH, See AAQ, Ang BT, et al. Awake craniotomy for resection of brain metastases: a systematic review. *World Neurosurg*. 2018;120:e1128-e1135.
21. Sanmillan JL, Fernández-Coello A, Fernández-Conejero I, et al. Functional approach using intraoperative brain mapping and neurophysiological monitoring for the surgical treatment of brain metastases in the central region. *J Neurosurg*. 2017;126(3):698-707.
22. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med*. 1990;322(8):494-500.
23. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol*. 1993;33(6):583-590.
24. Lee SR, Oh JY, Kim S-H. Gamma Knife radiosurgery for cystic brain metastases. *Br J Neurosurg*. 2016;30(1):43-48.
25. Wang H, Liu X, Jiang X, et al. Cystic brain metastases had slower speed of tumor shrinkage but similar prognosis compared with solid tumors that underwent radiosurgery treatment. *Cancer Manag Res*. 2019;11:1753-1763.
26. Alvarez-Breckenridge C, Giobbie-Hurder A, Gill CM, et al. Upfront surgical resection of melanoma brain metastases provides a bridge toward immunotherapy-mediated systemic control. *Oncologist*. 2019;24(5):671-679.
27. Shah AH, Semonche A, Eichberg DG, et al. The role of laser interstitial thermal therapy in surgical neuro-oncology: series of 100 consecutive patients. *Neurosurgery*. 2020;87(2):266-275.
28. Bastos DCA, Weinberg J, Kumar VA, et al. Laser interstitial thermal therapy in the treatment of brain metastases and radiation necrosis. *Cancer Lett*. 2020;489:9-18.
29. Lehrer EJ, Peterson JL, Zaorsky NG, et al. Single versus multifraction stereotactic radiosurgery for large brain metastases: an international meta-analysis of 24 trials. *Int J Radiat Oncol Biol Phys*. 2019;103(3):618-630.
30. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004;363(9422):1665-1672.
31. Yamamoto M, Serizawa T, Higuchi Y, et al. A multi-institutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901 study update): irradiation-related complications and long-term maintenance of mini-mental state examination scores. *Int J Radiat Oncol Biol Phys*. 2017;99(1):31-40.
32. Sahgal A, Aoyama H, Kocher M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys*. 2015;91(4):710-717.
33. Brown PD, Ballman KV, Cerhan JH, 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):1049-1060.

34. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1040-1048.
35. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *J Am Med Assoc*. 1998;280(17):1485-1489.
36. Kocher M, Soffietti R, Abacioglu U, 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):134-141.
37. Hong AM, Fogarty GB, Dolven-Jacobsen K, et al. Adjuvant whole-brain radiation therapy compared with observation after local treatment of melanoma brain metastases: a multicenter, randomized phase III trial. *J Clin Oncol*. 2019;37(33):3132-3141.
38. Tsao M, Xu W, Sahgal A. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer*. 2012;118(9):2486-2493.
39. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet*. 2016;388(10055):2004-2014.
40. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol*. 2013;15(10):1429-1437.
41. Brown PD, Gondi V, Pugh S, et al. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG oncology CC001. *J Clin Oncol*. 2020;38(10):1019-1029.
42. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 1999;341(7):476-484.
43. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357(7):664-672.
44. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(5):663-671.
45. De Ruysscher D, Dingemans A-MC, Praag J, et al. Prophylactic cranial irradiation versus observation in radically treated stage III non-small-cell lung cancer: a randomized phase III NVALT-11/DLCRG-02 study. *J Clin Oncol*. 2018;36(23):2366-2377.
46. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394(10212):1929-1939.
47. Belderbos JSA, De Ruysscher DKM, De Jaeger K, et al. Phase 3 randomized trial of prophylactic cranial irradiation with or without hippocampus avoidance in SCLC (NCT01780675). *J Thorac Oncol*. 2021;16(5):840-849.
48. Petrelli F, Signorelli D, Ghidini M, et al. Association of steroids use with survival in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Cancers (Basel)*. 2020;12(3):546.
49. Lin NU, Diéras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res*. 2009;15(4):1452-1459.
50. Bachelot T, Romieu G, Campone M, 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.
51. Saura C, Oliveira M, Feng Y-H, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with $\geq$ 2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol*. 2020;38(27):3138-3149.
52. Freedman RA, Gelman RS, Anders CK, et al. TBCRC 022: a phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J Clin Oncol*. 2019;37(13):1081-1089.
53. Krop IE, Lin NU, Blackwell K, 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):113-119.
54. Jacot W, Pons E, Frenel J-S, et al. Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases. *Breast Cancer Res Treat*. 2016;157(2):307-318.
55. Lin NU, Borges V, Anders C, 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):2610-2619.
56. Tolaney SM, Sahebjam S, Le Rhun E, et al. A phase 2 study of abemaciclib in patients with brain metastases secondary to hormone receptor positive breast cancer. *Clin Cancer Res*. 2020;26(20):5310-5319.
57. Swain SM, Baselga J, Miles D, 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):1116-1121.
58. Pivot X, Manikhas A, Żurawski B, 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):1564-1573.
59. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078-2092.
60. Gadgeel SM, Lukas RV, Goldschmidt J, et al. Atezolizumab in patients with advanced non-small cell lung cancer and history of asymptomatic, treated brain metastases: Exploratory analyses of the phase III OAK study. *Lung Cancer*. 2019;128:105-112.
61. Goldberg SB, Schalper KA, Gettinger SN, et al. Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2020;21(5):655-663.
62. Gauvain C, Vauléon E, Chouaid C, et al. Intracerebral efficacy and tolerance of nivolumab in non-small-cell lung cancer patients with brain metastases. *Lung Cancer*. 2018;116:62-66.
63. Paz-Ares L, Ciuleanu T-E, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):198-211.
64. Hendriks LEL, Henon C, Auclin E, et al. Outcome of patients with non-small cell lung cancer and brain metastases treated with checkpoint inhibitors. *J Thorac Oncol*. 2019;14(7):1244-1254.
65. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med*. 2020;382(1):41-50.
66. Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Ann Oncol*. 2020;31(8):1056-1064.
67. Tan AC, Itchins M, Khasraw M. Brain metastases in lung cancers with emerging targetable fusion drivers. *Int J Mol Sci*. 2020;21(4):1416.
68. Gutzmer R, Vordermark D, Hassel JC, et al. Melanoma brain metastases—interdisciplinary management recommendations 2020. *Cancer Treat Rev*. 2020;89:102083.
69. Dummer R, Goldinger SM, Turtschi CP, et al. Vemurafenib in patients with BRAF(V600) mutation-positive melanoma with symptomatic brain metastases: final results of an open-label pilot study. *Eur J Cancer*. 2014;50(3):611-621.
70. McArthur GA, Maio M, Arance A, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. *Ann Oncol*. 2017;28(3):634-641.

71. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(11):1087-1095.
72. Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol*. 2017;18(7):863-873.
73. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med*. 2018;379(8):722-730.
74. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol*. 2018;19(5):672-681.
75. Anker CJ, Grossmann KF, Atkins MB, et al. Avoiding severe toxicity from combined BRAF inhibitor and radiation treatment: consensus guidelines from the Eastern Cooperative Oncology Group (ECOG). *Int J Radiat Oncol Biol Phys*. 2016;95(2):632-646.
76. Lehrer EJ, Peterson J, Brown PD, et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: an international meta-analysis of individual patient data. *Radiother Oncol*. 2019;130:104-112.
77. Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol*. 2017;35(10):1070-1077.
78. Miyawaki E, Kenmotsu H, Mori K, et al. Optimal sequence of local and EGFR-TKI therapy for EGFR-mutant non-small cell lung cancer with brain metastases stratified by number of brain metastases. *Int J Radiat Oncol Biol Phys*. 2019;104(3):604-613.
79. Lee J-H, Chen H-Y, Hsu F-M, et al. Cranial irradiation for patients with epidermal growth factor receptor (EGFR) mutant lung cancer who have brain metastases in the era of a new generation of EGFR inhibitors. *Oncologist*. 2019;24(12):e1417-e1425.
80. Rusthoven CG, Yamamoto M, Bernhardt D, et al. Evaluation of first-line radiosurgery vs whole-brain radiotherapy for small cell lung cancer brain metastases: the FIRE-SCLC cohort study. *JAMA Oncol*. 2020;6(7):1028-1037.
81. Yaeh A, Nanda T, Jani A, et al. Control of brain metastases from radioresistant tumors treated by stereotactic radiosurgery. *J Neurooncol*. 2015;124(3):507-514.
82. Le Rhun E, Wolpert F, Fialek M, et al. Response assessment and outcome of combining immunotherapy and radiosurgery for brain metastasis from malignant melanoma. *ESMO Open*. 2020;5(4):e000763.
83. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16(6):e270-e278.
84. Knitter JR, Erly WK, Stea BD, et al. Interval change in diffusion and perfusion MRI parameters for the assessment of pseudoprogression in cerebral metastases treated with stereotactic radiation. *AJR Am J Roentgenol*. 2018;211(1):168-175.
85. Chuang M-T, Liu Y-S, Tsai Y-S, et al. Differentiating radiation-induced necrosis from recurrent brain tumor using MR perfusion and spectroscopy: a meta-analysis. *PLoS One*. 2016;11(1):e0141438.
86. Lai G, Mahadevan A, Hackney D, et al. Diagnostic accuracy of PET, SPECT, and arterial spin-labeling in differentiating tumor recurrence from necrosis in cerebral metastasis after stereotactic radiosurgery. *AJNR Am J Neuroradiol*. 2015;36(12):2250-2255.
87. Ceccon G, Lohmann P, Stoffels G, et al. Dynamic O-(2-18F-fluoroethyl)-L-tyrosine positron emission tomography differentiates brain metastasis recurrence from radiation injury after radiotherapy. *Neuro Oncol*. 2017;19(2):281-288.
88. Galldiks N, Abdulla DSY, Scheffler M, et al. Treatment monitoring of immunotherapy and targeted therapy using 18F-FET PET in patients with melanoma and lung cancer brain metastases: initial experiences. *J Nucl Med*. 2021;62(4):464-470.
89. Okada H, Weller M, Huang R, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. *Lancet Oncol*. 2015;16(15):e534-e542.
90. Seoane J, De Mattos-Arruda L, Le Rhun E, et al. Cerebrospinal fluid cell-free tumour DNA as a liquid biopsy for primary brain tumours and central nervous system metastases. *Ann Oncol*. 2019;30(2):211-218.
91. Pace A, Dirven L, Koekkoek JAF, et al. European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. *Lancet Oncol*. 2017;18(6):e330-e340.
92. Levin VA, Bidaut L, Hou P, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys*. 2011;79(5):1487-1495.
93. Brainin M, Barnes M, Baron J-C, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces—revised recommendations 2004. *Eur J Neurol*. 2004;11(9):577-581.
94. Dykewicz CA. Centers for Disease Control and Prevention (U.S.), Infectious Diseases Society of America, American Society of Blood and Marrow Transplantation. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. *Clin Infect Dis*. 2001;33(2):139-144 (Adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis*. 1994:18:421).

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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).

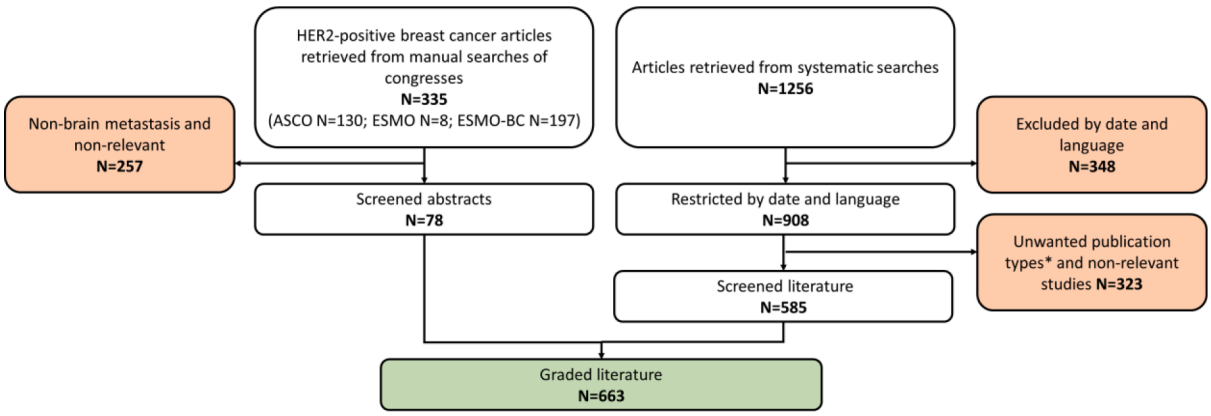

Fig. 1. Breakdown of systematic literature review screening for evidence grading. *Unwanted publication types included editorial, addresses biography, comment, directory, festschrift, interview, lectures, legal cases, legislation, news, newspaper article, patient education handout, popular works, and 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.

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Declaration of competing interest

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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).