Leptomeningeal metastasis from solid tumours: EANO–ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TEXT

SECTION 1. INCIDENCE AND EPIDEMIOLOGY

Incidence and risk factors

The incidence of leptomeningeal metastasis (LM) remains uncertain since the clinical diagnosis is challenging and the diagnostic work-up often remains incomplete in clinical practice. Despite this, the sensitivity of diagnostic methods is steadily improving. In an autopsy study published in 1979, 73 of 363 (20%) patients with a primary brain tumour, an extra-central nervous system (CNS) tumour or a hematological malignancy with suspicion of CNS involvement (either during the course of the disease or raised by the prosector) had leptomeningeal involvement.[1] In this cohort, parenchymal brain metastases were noted in 142 (39%) patients, and among these, were associated with LM in 44 (31%) patients. The best estimate available in the literature is that up to 10% of patients with metastatic cancer will develop LM during the course of the disease.[2]

In cohort studies comprising more than 100 patients with breast cancer diagnosed after 2000, the development of LM appeared to vary according to breast cancer subtype [ductal carcinoma: 65%-84%, lobular carcinoma: 10%-29%, human epidermal growth factor receptor-2 (HER2)-positive tumours: 20%-25%, triple-negative tumours: 15%-23%].[3-4] According to Surveillance, Epidemiology, and End Results (SEER) data for 2010-2016, which included 225,417 female patients with breast cancer, the distribution among the different breast subtypes was: 78% of ductal carcinoma, 10% of lobular carcinoma, 15% of HER2-positive tumours and 11% of triple-negative tumours.[5] Thus, there may be a moderately increased LM risk for patients with HER2-positive and triple-negative breast cancer. In lung cancer, LM was reported in 78%-96% of patients with adenocarcinomas.[6-7] In a cohort of 171 patients with lung cancer and LM, an oncogenic driver mutation was identified in 84

of 160 (52%) patients, including an epidermal growth factor receptor (*EGFR*) mutation in 63 (75%) patients, an anaplastic lymphoma kinase (*ALK*) mutation in 8 (10%) patients and *HER2* alterations in 7 (8%) patients.[8] Among patients with non-small-cell lung cancer (NSCLC) across Europe, the incidence of an *EGFR* mutation is approximatively 15%, an ALK rearrangement is approximatively 4% and a HER2 amplification is approximatively 1%,[9] suggesting an increased lifetime risk of developing LM in patients with tumours expressing oncogenic driver mutations. Only a few large cohorts of patients with melanoma and LM have been reported. In the largest of these cohorts, *BRAF* mutations were identified in 69 of 103 (67%) patients[10] whereas they are found in 47% of the general population of patients with melanoma.[11] *BRAF* mutations are also observed more frequently in metastatic compared with non-metastatic melanoma.[12]

The surgical technique employed for the resection of brain metastasis may impact on the risk of developing LM. A meta-analysis of 13 retrospective studies reported that ventricle opening during surgery and a subtotal or piecemeal resection were associated with an increased risk of developing LM.[13] Proximity of brain metastases to cerebrospinal fluid (CSF) spaces and infratentorial location of brain metastases were also associated with a risk of developing LM. However, in most studies assessing risk factors of LM,[14,15] no CSF cytology work-up was reported to confirm the diagnosis of LM.

Pathogenesis

The invasion of the leptomeninges by tumour cells may occur by (i) haematogenous spread via the arterial or venous circulation through the venous plexus of Batson, (ii) direct extension from contiguous tumour deposits in the brain or spine parenchyma, (iii) centripetal migration from extra-CNS tumours along perineural, endoneural or perivascular spaces or (iv) via the lymphatic system. Iatrogenic spread may occur after neurosurgical interventions. *De novo* tumours originating in the leptomeninges with melanoma histology represent a distinct disease entity.[16] Once seeded in the meninges, tumour cells may disseminate along the meningeal and ependymal surfaces or with the CSF flow, with a predilection of colonising regions with slow CSF flow and gravity-dependent locations, e.g. the posterior fossa, basilar cisterns and

lumbar cistern.[17] Tumour deposits may impair the function of the arachnoid granulations leading to CSF flow obstruction and hydrocephalus.

SECTION 2. MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

2.1 Systemic pharmacotherapy for breast cancer

A single arm phase II study of ANG1005, a taxane derivative comprising three paclitaxel molecules covalently linked to Angiopep-2, yielded a response rate of 8% on central review and a median overall survival (OS) of 8.0 months among 28 patients with clinical and magnetic resonance imaging (MRI) features of LM without CSF analysis.[18] A pilot study of eight patients with LM from breast cancer evaluated bevacizumab combined with etoposide and cisplatin. A response was noted in three of five evaluable patients, but the other three patients survived for only 0.7-1.6 months after treatment initiation; the median OS was 4.7 months.[19] Ten patients with hormone receptor-positive breast cancer and a diagnosis of European Association of Neuro-Oncology (EANO)–European Society for Medical Oncology (ESMO) probable LM were enrolled into a dedicated arm of a phase II study evaluating the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, abemaciclib. No objective responses were observed and only the median OS for the 7 patients with HER2-negative tumours was reported (8.4 months).[20] Few patients with LM (*n* = 2-5) have been enrolled into other CNS metastases trials evaluating EGFR/HER2 or HER2 inhibitors and no meaningful conclusions can be derived.

In a study evaluating the efficacy of tucatinib–trastuzumab–capecitabine for the treatment of LM in patients with HER2-positive breast cancer, the authors reported a median tucatinib CSF to plasma ratio of 83% (range 19%–21%) and similar values for the metabolite, ONT-993, after administration of 300 mg tucatinib twice daily (BID).[21] Only 17 of the 30 initially planned patients were enrolled, five (29%) of whom had confirmed LM. No response rate was reported. The median time to CNS progression was 6.9 months (95% CI 2.8-13.8) and the median OS was 11.9 months [95% CI 4.1-not reached (NR)].[22]

In a phase II study, intravenous (i.v.) pembrolizumab 200 mg was administered every 3 weeks to a cohort of 20 patients with LM, including 17 patients with breast cancer, four of whom also received other concomitant systemic treatment. The median OS was 3.6 months for the whole cohort, 4.4 months for patients with HER2-positive tumours, 3.4 months for patients with HER2-negative tumours, 5.1 months for patients who were not treated with steroids at baseline and 2.4 months for patients who were treated with steroids at baseline.[23] In another study, i.v. pembrolizumab 200 mg was administered every 3 weeks to 13 patients (including five with breast cancer) with confirmed (*n* = 6) or probable (*n* = 7) LM. Most patients enrolled had a primary cancer not usually considered responsive to immune checkpoint inhibition [e.g. breast cancer (*n* = 5) and 'high-grade' glioma (*n* = 3)]. One patient received concomitant trastuzumab and tamoxifen. A CNS response was reported in three patients. The median OS for the whole cohort was 4.9 months.[24] Eighteen patients with various primary cancers (including eight patients with breast cancer), 13 of whom had EANO–ESMO confirmed LM, were enrolled in a phase II study of nivolumab and ipilimumab. Six patients had one or more grade 3/4 adverse events (AEs). One patient had a complete response and seven had stable disease. The median OS was 2.9 months.[25]

2.2 Systemic pharmacotherapy for NSCLC

In a phase II study of 21 patients with confirmed LM from NSCLC, including 17 patients with tumours harbouring classical *EGFR* activating and sensitising mutations (without *T790M*), a median OS of 3.4 months was reported following treatment with erlotinib 150 mg/day. The OS was 4.0 months for the *EGFR*-mutated subgroup and 1.2 months for patients with EGFR wildtype tumours.[26]

In the AURA studies, 22 patients with LM from NSCLC and *EGFR* sensitising and resistance *T790M* mutations who had progressed on EGFR tyrosine kinase inhibitor (TKI) therapy received osimertinib 80 mg/day.[27] In this subgroup, a median OS of 19 months was reported. Of note, the diagnosis of LM was based on MRI criteria only and LM specific diagnostic work-up was not mandated. Of note, the AURA phase I study compared varying doses of osimertinib (20-240 mg/day) with no impact on efficacy but increasing toxicity[28].

In the phase I BLOOM study, 41 patients with cytologically confirmed LM who had progressed under previous EGFR TKIs received osimertinib 160 mg/day. The median OS was 11 months.[29] Among the 21 patients not assessed for the *T790M* mutation at inclusion and with stable non-CNS disease, the median OS was 16.6 months, whereas for the 20 patients with the *T790M* mutation who were not required to have stable non-CNS disease, the median OS was 8.1 months. The clinical benefit of osimertinib was also shown by neurological improvements in neurological performance in 57% of patients. Of note, in this study, the median time from LM diagnosis to the initiation of osimertinib was 37 months in the unselected cohort and 32 months in the *T790M* cohort.

In the subsequent phase II study, 40 patients with LM from *EGFR T790M*-positive NSCLC (38 cytologically confirmed) received osimertinib 160 mg/day after prior EGFR TKI failure. A subset of patients had received prior treatment for LM, including osimertinib 80 mg/day or intrathecal methotrexate. The median OS (including patients with prior treatment for LM) was 13.3 months (95% CI 9.1-NR).[30] Of note, current evidence does not support increasing the osimertinib dose to 160 mg/day for patients who develop leptomeningeal disease while receiving osimertinib 80 mg/day. Very few prospective clinical trials evaluating EGFR TKI monotherapy or in combination with antiangogenic agents in *EGFR*-mutated NSCLC are ongoing (e.g. NCT04425681).

In the ASCEND-7 phase II trial, a median OS of 7.2 months was reported for 18 patients with confirmed or probable LM from *ALK*-positive NSCLC who received ceritinib.[31] Various case reports and case series of patients with LM have shown significant and durable radiological responses with both standard (600 mg BID) and increased dose (900 mg BID) alectinib. Brigatinib and lorlatinib have also shown activity in a few LM patient cases to date.

No prospective trials evaluating the use of systemic immunotherapy in patients with LM from lung cancer have been published. Programmed death-ligand 1 (PD-L1) expression is a predictive factor for response to immune checkpoint inhibitors (ICIs) but its expression in LM remains unknown. Case reports and retrospective series have reported neurological improvement and disease responses/stabilisations after treatment with nivolumab. In a prospective clinical trial, 19 patients with LM from

NSCLC (including six confirmed, 12 probable and one case diagnosed based on PET imaging data) and a time between LM diagnosis and initiation of immunotherapy of 0-16.6 months received nivolumab (*n* = 13) or pembrolizumab (*n* = 6). The median PFS was 3.7 months from ICI initiation, and the 6- and 12-month OS was 36.8% and 21.1%, respectively.[32]

Very few patients with LM from NSCLC treated with ICIs at the time of LM diagnosis have been evaluated, and clinical trials evaluating anti-PD-(L)1 monotherapy (e.g. NCT03091478) or in combination with radiotherapy (e.g. NCT04356222) or chemotherapy (e.g. NCT04356222) in this setting are ongoing or awaiting results.

TABLES

Supplementary Table S1. Randomised clinical trials in patients with LM from solid tumours[a]

Reference	Design	Population	Primary endpoint	Efficacy	Toxicity (selected data)
Grossman et al. 1993[33]	IT MTX versus IT thiotepa[b]	*N* = 52 Solid tumours (*n* = 41) Lymphoma (*n* = 10) CUP (*n* = 1)	Neurological response rate	IT MTX versus IT thiotepa: **No neurological improvements** Neurological stabilisation: 32% versus 12.5% Median OS: 15.9 versus 14.1 weeks	IT MTX versus IT thiotepa: Serious AEs: 16 patients (58%) versus 8 patients (34%) Among serious toxicities: • Grade 4 seizure: 1 patient versus 0 patients • Leukoencephalopathy: 1 patient versus 0 patients • Grade 4 haematotoxicity: 3 patients versus 2 patients
Hitchins et al. 1997[34]	IT MTX versus IT MTX–Ara-C[b]	*N* = 44 Solid tumours (*n* = 30)	Response rate	IT MTX versus IT MTX–Ara-C: **RR: 61% versus 45%** **(*P* <0.10)**	IT MTX versus IT MTX–Ara-C: Nausea/vomiting: 8 (36%) versus 11 (50%) patients

Reference	Design	Population	Primary endpoint	Efficacy	Toxicity (selected data)
		CUP (*n* = 7) Lymphoma (*n* = 7)		Median OS: 12 versus 7 weeks (*P* <0.05)	Meningitis: 4 (18%) versus 2 (10%) patients Septicaemia, neutropenia: 2 (9%) versus 3 (15%) patients Uncomplicated pancytopenia: 2 (9%) versus 2 (10%) patients
Glantz et al. 1999[35]	IT liposomal cytarabine versus IT MTX[b]	*N* = 61 Solid tumours	Neurological RR at the end of the induction period	IT liposomal cytarabine versus IT MTX: **RR: 26% versus 20% (*P* = 0.76)** OS: 105 versus 78 days (*P* = 0.15) TTP: 58 versus 30 days (*P* = 0.007) LM-specific OS: 343 versus 98 days (*P* = 0.074)	IT liposomal cytarabine versus IT MTX: Headache grade 3/4: 4 (13%) versus 2 (7%) patients Drug related meningitis: 5 (16%) versus 2 (7%) patients Nausea/vomiting: 3 (10%) versus 2 (7%) patients

Reference	Design	Population	Primary endpoint	Efficacy	Toxicity (selected data)
Boogerd et al. 2004[36]	IT MTX versus no IT MTX	*N* = 35 Breast cancer	OS	IT MTX versus no IT MTX: Improvement or stabilisation: 59% versus 67% Median TTP: 23 versus 24 weeks **Median OS: 18.3 vs. 30.3 weeks (*P* = 0.32)**	IT MTX versus no IT MTX: Serious headache: 2 (18%) versus 4 (23%) patients Serious cognitive impairment: 3 (18%) versus 2 (11%) patients Serious gait disturbances: 11 (65%) versus 5 (28%) patients Reservoir revision: 3 patients (18%)
Shapiro et al. 2006[37]	IT liposomal cytarabine versus IT MTX, or IT liposomal cytarabine versus cytarabine[b,c]	*N* = 103 Solid tumours	PFS	IT liposomal cytarabine versus IT MTX and cytarabine combined: **PFS: 35 versus 43 days (*P* = 0.7321)**	Not specified for solid tumours

Reference	Design	Population	Primary endpoint	Efficacy	Toxicity (selected data)
				Liposomal cytarabine was non inferior to MTX in solid tumours (HR 0.94, 95%CI 0.58-1.53)	
Le Rhun et al. 2020[38]	Systemic treatment versus IT liposomal cytarabine + systemic treatment	*N* = 73 Breast cancer	LM-PFS	Systemic treatment versus IT liposomal cytarabine + systemic treatment: **LM-PFS: 2.2 versus 3.8 months (*P* = 0.04)** OS: 4.0 versus 7.3 months	Systemic treatment versus IT liposomal cytarabine + systemic treatment: Serious AEs in 22 (61%) versus 30 (81%) patients; QoL up to progression did not differ between groups

AE, adverse event; Ara-C, cytarabine; ChT, chemotherapy; CI, confidence interval; CSF, cerebrospinal fluid; CUP, cancer of unknown primary; HR, hazard ratio; IT, intrathecal; LM, leptomeningeal metastasis, MTX, methotrexate; PFS, progression-free survival, OS, overall survival, QoL, quality of life; RR, response rate; TTP, time to progression.

[a] All randomised trials explored the role of IT ChT and systemic therapy was commonly allowed but not controlled for.

[b] Compared two intra-CSF pharmacotherapies.

[c] Published as a conference abstract only. Patients with neoplastic meningitis from solid tumours (*n* = 103) were randomised to IT liposomal cytarabine or IT MTX and patients with lymphomatous neoplastic meningitis (*n* = 25) were randomised to IT liposomal cytarabine or cytarabine. Toxicities were reported for the whole cohort.

Supplementary Table S2. EORTC RANO Scorecard for imaging assessment

Patient identification Number Sex, date of birth	Reference scan		Follow-up scan		Response assessment
Dates of MRI	Brain: DD-MM-YYYY Spine: DD-MM-YYYY		Brain: DD-MM-YYYY Spine: DD-MM-YYYY		
Date of last CSF sampling prior to MRI	DD-MM-YYYY		DD-MM-YYYY		
MRI findings	Present or absent or non-evaluable	Individual dimensions (dimension 1, dimension 2, dimension 3: X x Y mm) of 3 largest measurable nodules (measurable defined as ≥5 x 5 mm (orthogonal diameters in 2 planes)	Present or absent or non-evaluable	Individual dimensions (dimension 1, dimension 2, dimension 3: X x Y mm) of 3 largest measurable nodules (measurable defined as ≥5 x 5 mm (orthogonal diameters in 2 planes)	**Change from previous MRI**
ITEMS RELATED TO ASSESSMENT OF LEPTOMENINGEAL METASTASIS					
BRAIN					
Nodules (subarachnoid or ventricular)[a]	☐ **present** ☐ measurable ☐ non-measurable	**For measurable nodules[b]** N1: size: (2 largest perpendicular diameters in mm) ... x ...	☐ **present** ☐ measurable ☐ new measurable nodule ☐ non-measurable	**For measurable nodules[b]** N1: size (2 largest perpendicular diameters in mm) ... x ...	☐ improved ☐ CR ☐ PR

	☐ **absent** ☐ **not evaluable**	location: ☐ right hemisphere ☐ left hemisphere ☐ frontal ☐ parietal ☐ temporal ☐ insular ☐ occipital ☐ midline ☐ cerebellar ☐ brainstem ☐ ventricular ☐ other free text N2: size (2 largest perpendicular diameters in mm) ... x ... location: ☐ right hemisphere ☐ left hemisphere ☐ frontal ☐ parietal ☐ temporal ☐ insular ☐ occipital ☐ midline ☐ cerebellar ☐ brainstem ☐ ventricular ☐ other free text N3: size: (2 largest perpendicular diameters in mm) ... x ... location:	☐ **absent** ☐ **not evaluable**	N2: size (2 largest perpendicular diameters in mm) ... x ... N3: size (2 largest perpendicular diameters in mm) ... x ... **For <u>new largest</u> measurable nodule[b]** NN1: size (2 largest perpendicular diameters in mm) ... x ... location: ☐ right hemisphere ☐ left hemisphere ☐ frontal ☐ parietal ☐ temporal ☐ insular ☐ occipital ☐ midline ☐ cerebellar ☐ brainstem ☐ ventricular ☐ other free text	☐ no change ☐ worse ☐ not evaluable

		☐ right hemisphere ☐ left hemisphere ☐ frontal ☐ parietal ☐ temporal ☐ insular ☐ occipital ☐ midline ☐ cerebellar ☐ brainstem ☐ ventricular ☐ other free text			
Leptomeningeal enhancement[c]	☐ **present** ☐ **absent** ☐ **not evaluable**		☐ **present** ☐ *de novo* linear enhancement ☐ **absent** ☐ **not evaluable**		☐ improved ☐ CR ☐ PR ☐ no change ☐ worse ☐ not evaluable
Hydrocephalus[d]	☐ **present** ☐ **absent** ☐ **not evaluable**		☐ **present** ☐ **absent** ☐ **not evaluable**		☐ improved ☐ no change ☐ worse ☐ not evaluable

Evan's index		A1: ... mm B1: ... mm E1=A1/B1: ...		A2: ... mm B2: ... mm E2=A2/B2: ...	(E1/E2) x 100: ... ☐ improved or no change <25%) ☐ worse (≥25%) ☐ not evaluable
SPINE					
Nodules (subarachnoid)	☐ **present** ☐ measurable ☐ non-measurable ☐ **absent** ☐ **not evaluable**	**For measurable nodules[b]** N1: size: (2 largest perpendicular diameters in mm) ... x ... location: ☐ cervical ☐ thoracic ☐ lumbar N2: size: (2 largest perpendicular diameters in mm) ... x ... location: ☐ cervical ☐ thoracic ☐ lumbar	☐ **present** ☐ measurable ☐ new measurable nodule ☐ non-measurable ☐ **absent** ☐ **not evaluable**	**For measurable nodules[b]** N1: size (2 largest perpendicular diameters in mm) ... x ... N2: size (2 largest perpendicular diameters in mm) ... x ... N3:	☐ improved ☐ CR ☐ PR ☐ no change ☐ worse ☐ not evaluable

		N3: size: (2 largest perpendicular diameters in mm) ... x ... location: ☐ cervical ☐ thoracic ☐ lumbar		size (2 largest perpendicular diameters in mm) ... x ... **For <u>new largest</u> measurable nodule[c]** NN1: size (2 largest perpendicular diameters in mm) ... x ... location: ☐ cervical ☐ thoracic ☐ lumbar	
Leptomeningeal enhancement[b]	☐ **present** ☐ **absent** ☐ **not evaluable**		☐ **present** ☐ *de novo* linear enhancement ☐ **absent** ☐ **not evaluable**		☐ improved ☐ CR ☐ PR ☐ no change ☐ worse ☐ not evaluable
Progression is diagnosed - if there is at least one new measurable nodule, or - if at least one measurable nodule that does not reach 10 mm in its two largest perpendicular diameters, increases in the product of the largest perpendicular diameters by 50% or more, or					**OVERALL RESPONSE**

- if at least one nodule of at least 10 mm diameter in its two largest perpendicular diameters increases in the product of the largest perpendicular diameters by 25% or more, or - if the Evan's index increases by at least 25% - *de novo* linear leptomeningeal contrast enhancement alone also qualifies for progression unless attributable to lumbar puncture **Partial response** requires regression of all nodules by 50% or more, without an increase in ventricular size. **Complete response** requires resolution of all contrast-enhancing, LM-related measurable lesions, without an increase in ventricular size assessed by Evan's index of more than 25%. All other situations are considered **stable disease.** LM without measurable nodules can only remain stable as its best response. Linear enhancement cannot be quantified and is thus only noted as absent or present, but not used for response assessment unless developing *de novo* or affecting leptomeningeal regions not previously affected – then this constitutes **progressive disease.** Deterioration in any one item qualifying for progression will be sufficient to call progression. **Not evaluable** refers to scans that cannot be assessed for poor quality or incomplete sequences or if the assessment is uncertain and requires a new follow-up imaging.	☐ **CR** ☐ **PR** ☐ **SD** ☐ **PD** ☐ **not evaluable**

ITEMS NOT RELATED TO ASSESSMENT OF LEPTOMENINGEAL METASTASIS[e]					
BRAIN					
Parenchymal (brain) metastases	☐ **present** ☐ measurable ☐ non-measurable	**For measurable metastases[b]** M1: size: (2 largest perpendicular diameters in mm) ... x ...	☐ **present** ☐ measurable ☐ new measurable metastasis	**For measurable metastases[b]** M1: size: (2 largest perpendicular diameters in mm) ... x ...	☐ improved ☐ CR ☐ PR

	☐ **absent** ☐ **not evaluable**	location: ☐ right hemisphere ☐ left hemisphere ☐ frontal ☐ parietal ☐ temporal ☐ insular ☐ occipital ☐ midline ☐ cerebellar ☐ brainstem ☐ other free text M2: size: (2 largest perpendicular diameters in mm) ... x ... location: ☐ right hemisphere ☐ left hemisphere ☐ frontal ☐ parietal ☐ temporal ☐ insular ☐ occipital ☐ midline ☐ cerebellar ☐ brainstem ☐ other free text M3: size: (2 largest perpendicular diameters in mm) ... x ... location:	☐ non-measurable ☐ **absent** ☐ **not evaluable**	M2: size: (2 largest perpendicular diameters in mm) ... x ... M3: size: (2 largest perpendicular diameters in mm) ... x ... **For <u>new largest</u> measurable metastasis[b]** **NM1:** size (2 largest perpendicular diameters in mm) ... x ... location: ☐ right hemisphere ☐ left hemisphere	☐ no change ☐ worse ☐ not evaluable

		☐ right hemisphere ☐ left hemisphere ☐ frontal ☐ parietal ☐ temporal ☐ insular ☐ occipital ☐ midline ☐ cerebellar ☐ brainstem ☐ other free text		☐ frontal ☐ parietal ☐ temporal ☐ insular ☐ occipital ☐ midline ☐ cerebellar ☐ brainstem ☐ other free text	
SPINE					
Parenchymal (intramedullary) metastases	☐ **present** ☐ measurable ☐ non-measurable ☐ **absent** ☐ **not evaluable**	**For measurable metastases[b]** M1: size: (2 largest perpendicular diameters in mm) ... x ... location: ☐ cervical ☐ thoracic ☐ lumbar M2: size: (2 largest perpendicular diameters in mm) ... x ... location: ☐ cervical ☐ thoracic ☐ lumbar M3: size: (2 largest perpendicular diameters in mm) ... x ...	☐ **present** ☐ measurable ☐ new measurable metastasis ☐ non-measurable ☐ **absent** ☐ **not evaluable**	**For measurable metastases[b]** M1: size: (2 largest perpendicular diameters in mm) ... x ... M2: size: (2 largest perpendicular diameters in mm) ... x ... M3: size: (2 largest perpendicular diameters in mm) ... x ... **For <u>new largest</u> measurable metastasis[b]**	☐ improved ☐ CR ☐ PR ☐ no change ☐ worse ☐ not evaluable

		location: ☐ cervical ☐ thoracic ☐ lumbar		NM1: size (2 largest perpendicular diameters in mm) ... x ... location: ☐ cervical ☐ thoracic ☐ lumbar	
Epidural metastasis	☐ **present** ☐ measurable ☐ non-measurable ☐ **absent** ☐ **not evaluable**	**For measurable metastases[b]** M1: size: (2 largest perpendicular diameters in mm) ... x ... location: ☐ cervical ☐ thoracic ☐ lumbar M2: size: (2 largest perpendicular diameters in mm) ... x ... location: ☐ cervical ☐ thoracic ☐ lumbar M3: size: (2 largest perpendicular diameters in mm) ... x ... location: ☐ cervical ☐ thoracic ☐ lumbar	☐ **present** ☐ measurable ☐ new measurable metastasis ☐ non-measurable ☐ **absent** ☐ **not evaluable**	**For measurable metastases[b]** M1: size: (2 largest perpendicular diameters in mm) ... x ... M2: size: (2 largest perpendicular diameters in mm) ... x ... M3: size: (2 largest perpendicular diameters in mm) ... x ... **For <u>new largest</u> measurable metastasis[b]** NM1:	☐ improved ☐ CR ☐ PR ☐ no change ☐ worse ☐ not evaluable

				size (2 largest perpendicular diameters in mm) ... x ... location: ☐ cervical ☐ thoracic ☐ lumbar	

Technical considerations: MRI scans should be carried out on the same scanner or at least a device of identical field strength during follow-up using the same imaging protocol at all timepoints during follow-up. Standardised MRI protocols should be used. Contrast agent should be injected ideally 10 minutes, but not less than 5 minutes, before acquisition of T1-weighted sequences and the slice thickness should be ≤1 mm in the brain and ≤3 mm for the spinal cord, as the leptomeningeal enhancement may have complex aspects and is commonly linear.[39] As lumbar punctures may induce leptomeningeal enhancement, the date(s) of the last CSF analysis carried out before MRI acquisition should be documented on the grid.

CR, complete response; CSF, cerebrospinal fluid; DD, day; EORTC, European Organisation for Research and Treatment of Cancer; LM, leptomeningeal metastasis; M, metastasis; MM, month; MR, magnetic resonance; MRI, magnetic resonance imaging; N, nodule; NM, new metastasis; NN, new nodule; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-oncology; SD, stable disease; YYYY, year.

[a] A nodule is a contrast-enhancing lesion that is defined as LM-related as opposed to parenchymal if there is direct contact (<2 mm distance) between the outer edge of the nodule and the leptomeninges on contrast-enhanced scans.

[b] Measurable nodules or metastases should be ordered by size, starting with the largest nodule.

[c] Leptomeningeal linear enhancement may include cranial nerve or spinal nerve root, cerebellar folia, ventricular ependymal or cerebral sulcal enhancement.

[d] Hydrocephalus is assessed by determining the Evan's index calculated on T1-weighted axial MR images. It represents the ratio of the largest diameter at the maximal width of the frontal horns relative to the largest internal diameter of the cranium on the same slide.[40] The most appropriate cut-off value must be predefined in the protocol considering the studied population.

[e] These items should be documented as present or absent but are not used for LM response assessment. In the context of LM, measurable lesions for parenchymal brain or spinal metastases and for epidural metastases should measure at least 5 x 5 mm for standardisation.

Reproduced from Le Rhun et al.[41]

Supplementary Table S3. EANO–ESMO CSF response assessment[a]

Baseline	Follow-up 1	Follow-up 2	Response for follow-up 1	Response for follow-up 2
Negative	Negative	Negative	SD	SD
Negative	Negative	Equivocal	SD	SD
Negative	Negative	Positive	SD	PD
Negative	Equivocal	Negative	SD	SD
Negative	Equivocal	Equivocal	SD	SD
Negative	Equivocal	Positive	SD	PD
Negative	Positive	Negative	PD	NA
Negative	Positive	Equivocal	PD	PD
Negative	Positive	Positive	PD	PD
Equivocal	Negative	Negative	SD	SD
Equivocal	Negative	Equivocal	SD	SD
Equivocal	Negative	Positive	SD	PD
Equivocal	Equivocal	Negative	SD	SD
Equivocal	Equivocal	Equivocal	SD	SD
Equivocal	Equivocal	Positive	SD	SD
Equivocal	Positive	Negative	SD	NA
Equivocal	Positive	Equivocal	SD	SD
Equivocal	Positive	Positive	SD	SD

Positive	Negative	Negative	NA	CR
Positive	Negative	Equivocal	NA	SD
Positive	Negative	Positive	NA	SD
Positive	Equivocal	Negative	SD	SD
Positive	Equivocal	Equivocal	SD	SD
Positive	Equivocal	Positive	SD	SD
Positive	Positive	Negative	SD	NA
Positive	Positive	Equivocal	SD	SD
Positive	Positive	Positive	SD	SD

CR, complete response; CSF, cerebrospinal fluid; EANO, European Association of Neuro-Oncology; ESMO, European Society for Medical Oncology; NA, not applicable; PD, progressive disease; SD, stable disease.

[a] The follow-up examinations described here should be at least 4 weeks apart from the preceding examination. If a response is achieved, this becomes the new baseline.

Adapted from Le Rhun et al.[38]

Supplementary Table S4. Levels of evidence and grades of recommendation for a diagnostic measure and therapeutic intervention (using the European Federation of Neurological Societies criteria as recommended by EANO)

Evidence classification for a diagnostic measure

Class I	A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy
Class II	A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared with a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy
Class III	Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation
Class IV	Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Rating of recommendations for a diagnostic measure

Level A	Established as useful/predictive or not useful/predictive Requires at least one convincing class I study or at least two consistent, convincing class II studies
Level B	Established as probably useful/predictive or not useful/predictive

	Requires at least one convincing class II study or overwhelming class III evidence
Level C	Established as possibly useful/predictive or not useful/predictive Requires at least two convincing class III studies

Evidence classification for a therapeutic intervention

Class I	An adequately powered prospective, randomised, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomised controlled clinical trials with masked outcome assessment in representative populations. The following are required: (a) Randomisation concealment (b) Primary outcome(s) is/are clearly defined (c) Exclusion/inclusion criteria are clearly defined (d) Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias (e) Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class II	Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a-e above or a randomised, controlled trial in a representative population that lacks one criteria a-e
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV	Evidence from uncontrolled studies, case series, case reports or expert opinion

Rating of recommendations for a therapeutic intervention

Level A	Established as effective, ineffective or harmful Requires at least one convincing class I study or at least two consistent, convincing class II studies
Level B	Probably effective, ineffective or harmful Requires at least one convincing class II study or overwhelming class III evidence
Level C	Possibly effective, ineffective or harmful Requires at least two convincing class III studies

EANO, European Association of Neuro-Oncology.

Supplementary Table S5. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System)[a]

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

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

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