ESMO GUIDELINES:
REAL WORLD CASES

LEPTOMENINGEAL METASTASIS

FROM SOLID TUMOURS

Lizza Hendriks

Chair

Maastricht University Medical Center, Maastricht

ESMO WEBINAR SERIES

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Programme

30 October 2024

10 min	**Welcome and introduction** Lizza Hendriks
10 min	**Case Presentation** Eugenia Cella
20 min	**Presentation of the ESMO Clinical Practice Guideline for Critical Analysis of the Case** Giuseppe Minniti
10 min	**Considerations Related to Guideline Implementation in Everyday Clinical Practice and Discussion** Henk van Halteren
10 min	**Live Q&A and Discussion** All speakers, Wolfgang Wick


Lizza Hendriks


Eugenia Cella


Giuseppe Minniti


Henk Van Halteren


Wolfgang Wick

In this webinar's discussion, we will also be joined by a multidisciplinary expert – Prof Wolfgang Wick, who will provide different perspectives to the discussion, for a more comprehensive approach.

LEARNING OBJECTIVES

- Promote evidence-based quality cancer care by disseminating the ESMO Clinical Practice Guidelines (CPG) in the oncology community.
- Present a clinical case for each of the selected topics for discussion in the context of the ESMO CPG recommendations.
- Present and critically review the ESMO CPG recommendations for each selected cancer type.
- Discuss the case, the ESMO CPG recommendations, their impact on care and implementability in the daily practice setting under the guidance of a moderator senior expert, with participation of the guideline authors, practicing oncologists and young oncologists.
- Audit the fulfillment of the learning objectives and acceptability of the ESMO CPG recommendations by means of an online questionnaire.

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CLINICAL CASE

HER2+ Metastatic Breast Cancer with Leptomeningeal Disease

Eugenia Cella,MD

University of Genoa - IRCCS Policlinico San Martino Hospital, Genoa (Italy)

Aiom
Associazione Italiana di Oncologia Medica

EANO

Università di Genova

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

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DISCLOSURES

No disclosures to declare

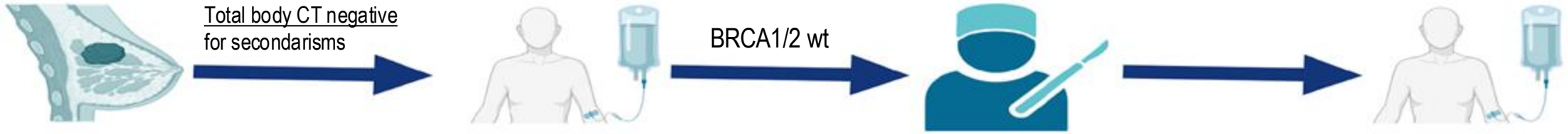
CANCER DIAGNOSIS and PATIENT JOURNEY

50-year-old female

No relevant medical history

Oncological family history: mother breast cancer at the age of 88, maternal cousin deceased from breast cancer at the age of 40, maternal aunt breast cancer > 60 year old.

March 2023 | **April-September 2023** | **September 2023** | **October 2023- June 2024**



NST breast cancer ER 5%, PgR neg, HER2 3+, ki67 25-30% cT1cN1M0 (AJCC 8th Ed **Stage IIA**)

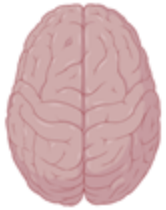
Neoadjuvant
EC x4 cycles followed by paclitaxel x 12 cycles, plus Trastuzumab

Quadrantectomy+ LS
ypTisG3ypN0 (0/4)

Adjuvant
Trastuzumab

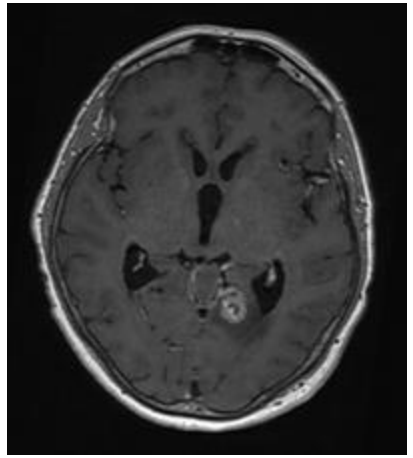
CNS disease recurrence: presentation

July 2024



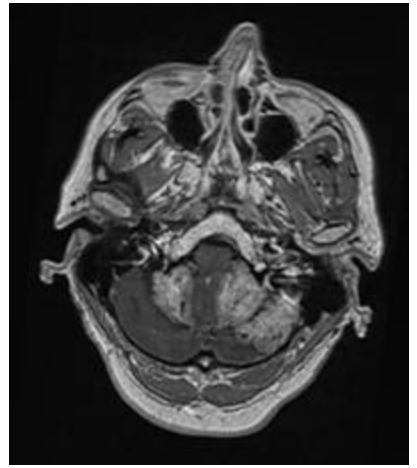
Clinical presentation: headache, nausea and vomiting, neurocognitive changes and loss of consciousness

25 Jul 2024 admitted to the emergency room



Brain CT scan (25 Jul 2024): occurence of multiple secondary lesions with compression at the level of 4th ventricle and tonsillar herniation

Brain MRI (27 Jul 24): confirmed TC finding an evidence of *leptomeningeal dissemination (linear+nodular) and hydrocephalus.*



CNS disease recurrence: initial approach

July 2024

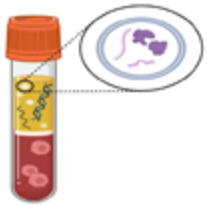
During hospitalization started:

-Mannitol 18% every 8 hours

-Dexamethasone 8mg/bid ev.

-Sulfamethoxazole + Trimethoprim 160+800 mg (profilaxy) 1 tablet every other day

Neurosurgery (26 Jul 24): ventriculostomy



CSF analysis: equivocal (only 3 mL) presence of blood cells

LM diagnosis probable (type IID) [1]

1)Le Rhun E, et al, «Leptomeningeal metastasis from solid tumours: EANO/ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up" ESMO Open 2023

RISK FACTORS [1,2,3]

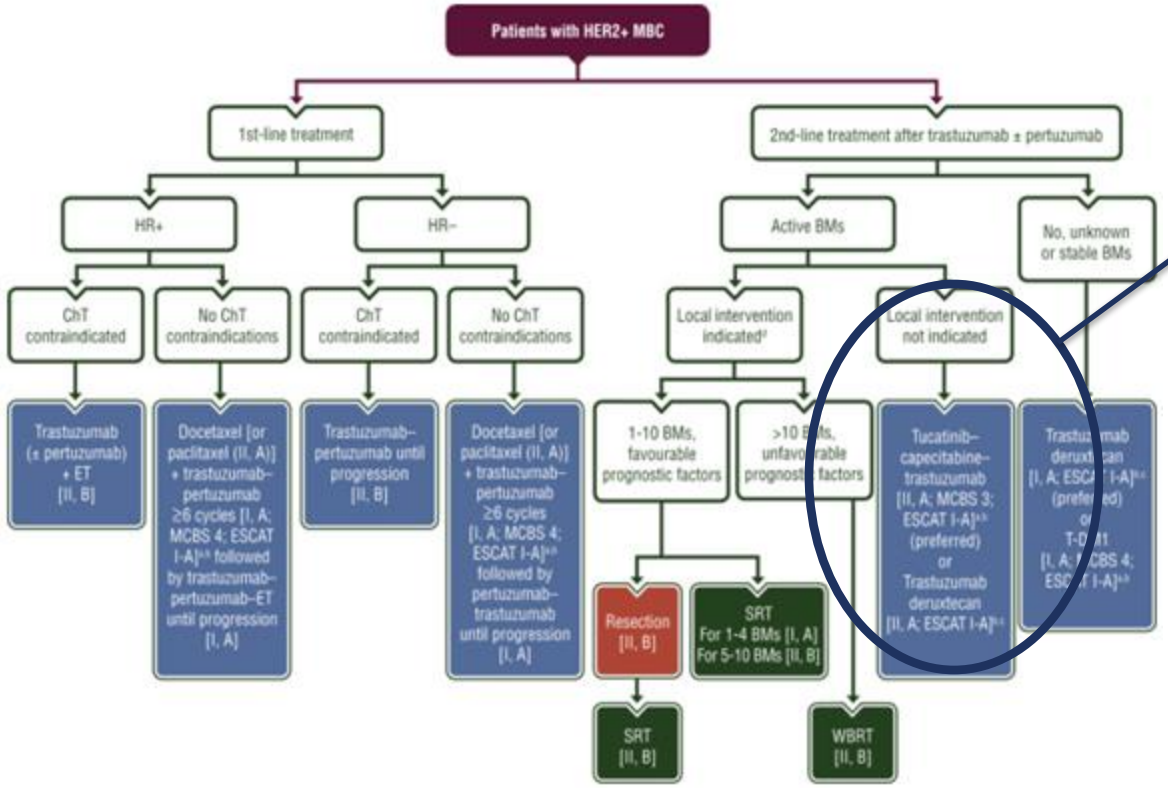
1) ER receptor negativity→ **ER 5%**
2) High histological grade→ **G3**
3) HER 2 overexpression→**3+**
4) Time interval from diagnosis to development of metastatic disease ≤ 6 months since the end of adjuvant treatment→ **1 month**
5) The incidence of CNS involvement is independent of PCR[3]

Brain metastases (BM) cumulative incidence HER2+ Breast Cancer: 31%

Leptomeningeal disease (LM) cumulative incidence HER2+ Breast Cancer: 10%

1)Kuksis M, et al. "The incidence of brain metastases among patients with metastatic breast cancer: a systemic reviw and metanalysis"Neuro Oncol. 2021
2) Darlix A, et al. "Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a larger multicentre real-life cohort."Br J Cancer 2019
3) Ferraro E, et al. "Incidence of brain metastases in patients with early HER2-positive breast cancer receiving neoadjuvant chemotherapy with trastuzumab and pertuzumab"NPJ Breast Camcer 2022

MANAGEMENT



Neurosurgical controindicated for LM

Radiotherapy controindicated for tonsillar erniation

cxx Aug 24 (2 months after the end of adjuvant treatment)

. . . . .

Trastuzumab Deruxtecan

Gennari A, et al. « ESMO Clinical Practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Annals of Oncology 2021

OUTCOMES

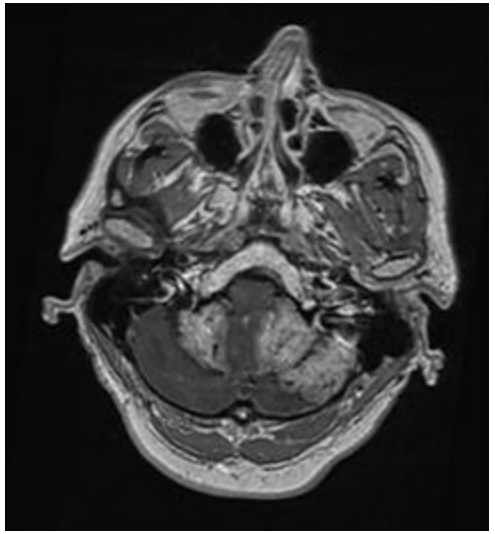
Clinical complete regression of neurological symptoms

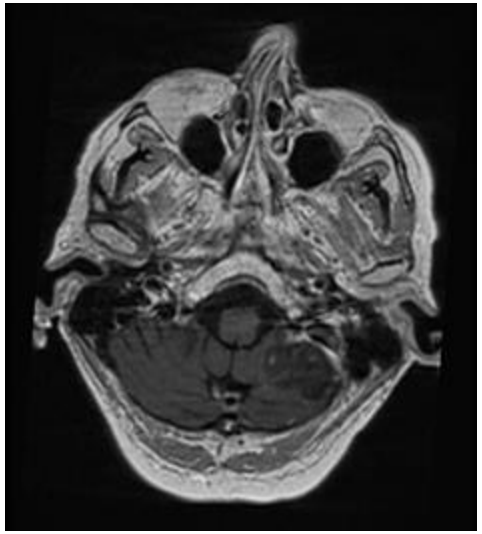
MRI after 3 cycles of Trastuzumab Deruxteca→RP

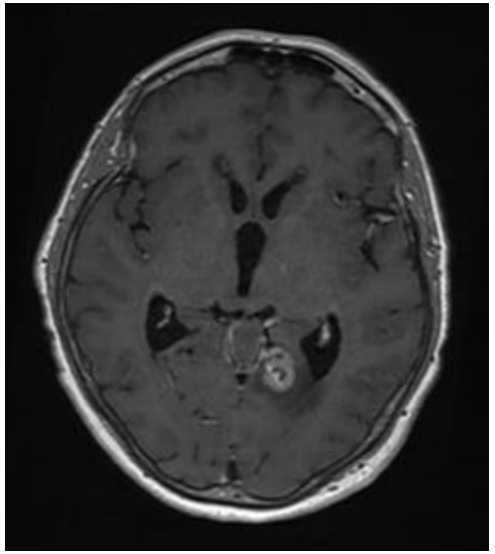
CSF not repeated

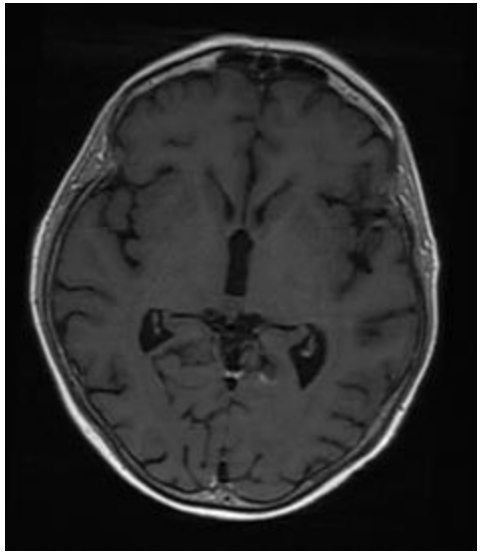
Baseline MRI (25.07.24)

After 3 cycles MRI (30.09.24)









OUTCOMES and COMPLICATIONS

22th September 2024

After 3 cycles of Trastuzumab Deruxtecan…

G2 pancytopenia with a finding of **hypogammaglobulinemia and CMV infection** (CMV DNA 4.67x10^5 UI/ml) treated with:

– Hemotransfusion

– Ganciclovir 5 mg/kg bid

– Immunoglobulin 30 g EV

DISCUSSION

1) Role of baseline CNS MRI for high risk patients ?

2) Loco-regional treatment for LM disease ?

3) Adverse events of prolonged corticosteroid treatment ?

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ESMO Guidelines Webinar Series, on the topic of Leptomeningeal Metastasis from Solid Tumours

Critical Analysis of the Case and Parallel presentation of the ESMO CPG recommendations, flow charts, MCBS, section by section

Giuseppe Minniti

Department of Radiological Sciences, Oncology, and Anatomical Pathology

Sapienza University of Rome, Roma

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DECLARATION OF INTERESTS

Giuseppe Minniti

Honoraria fees: Brainlab, Accuray

Advisory Board: Servier, GlaxoSmithKline, Astra Zeneca, Novocure

QUESTIONS ARISED FROM THE CLINICAL CASE

1- How to diagnose LM?

2- Which (standard) systemic and loco-regional treatment for LM?

3- How to assess treatment response?

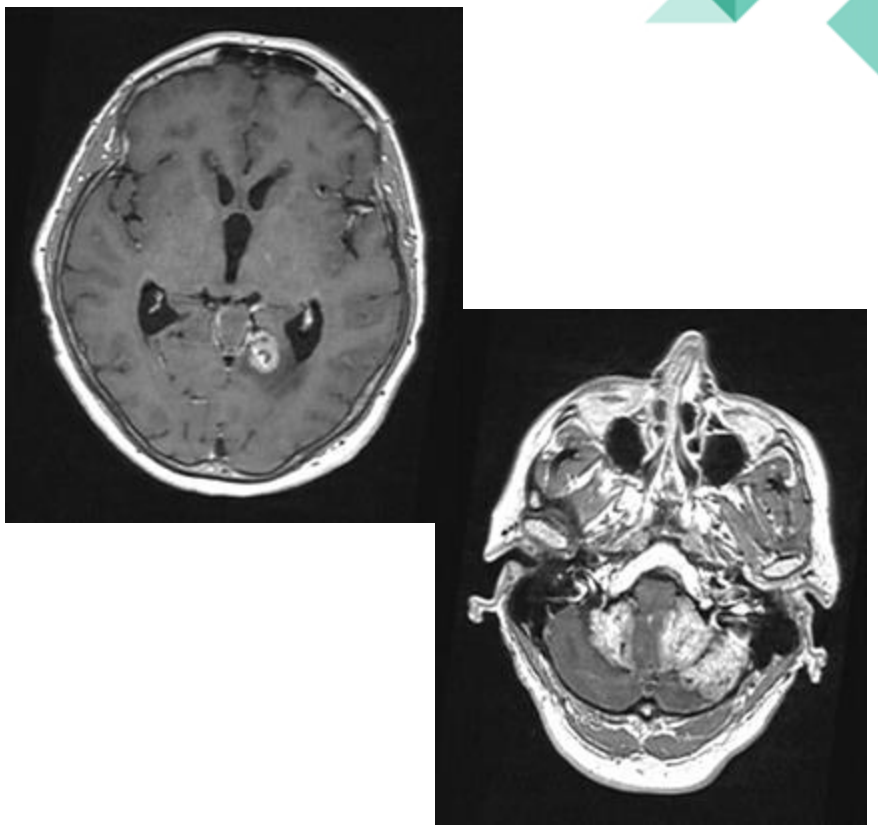
How was LM disease diagnosed?

Clinical presentation: headache, nausea and vomiting, neurocognitive changes and loss of consciousness

Brain CT scan: occurence of multiple secondary lesions with compression at the level of 4th ventricle and tonsillar herniation

Brain MRI: confirmed TC finding an evidence of *leptomeningeal dissemination (linear+nodular) and hydrocephalus.*

CSF analysis: equivocal (only 3 mL) presence of blood cells



LM diagnosis probable (type IID) [1]

1)Le Rhun E, et al, «Leptomeningeal metastasis from solid tumours: EANO/ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up" ESMO Open 2023

How to diagnose LM disease?

Diagnostic criteria and level of evidence for LM

		Cytology/biopsy	MRI	Confirmed	Probable[a]	Possible[a]	Lack of evidence[b]
Type I: positive CSF cytology or biopsy	IA	+	Linear	+	NA	NA	NA
	IB	+	Nodular	+	NA	NA	NA
	IC	+	Linear + nodular	+	NA	NA	NA
	ID	+	Hydrocephalus	+	NA	NA	NA
	ID	+	Normal	+	NA	NA	NA
Type II: clinical findings and neuroimaging only	IIA	− or equivocal	Linear	NA	With typical clinical signs	Without typical clinical signs	NA
	IIB	− or equivocal	Nodular	NA	With typical clinical signs	Without typical clinical signs	NA
	IIC	− or equivocal	Linear + nodular	NA	With typical clinical signs	Without typical clinical signs	NA
	IID	− or equivocal	Hydrocephalus	NA	NA	With typical clinical signs	Without typical clinical signs
	IID	− or equivocal	Normal	NA	NA	With typical clinical signs	Without typical clinical signs

Type A: LM with typical linear MRI abnormalities; type B: LM with nodular disease; type C: LM with both linear and nodular disease; type D: LM without MRI abnormalities (except hydrocephalus).
CSF, cerebrospinal fluid; LM, leptomeningeal metastasis; MRI, magnetic resonance imaging; NA, not applicable.
"Requires a history of cancer with a reasonable risk of LM and consideration of alternative diagnoses.
•Including in patients with a history of cancer.

1)Le Rhun E, et al, «Leptomeningeal metastasis from solid tumours: EANO/ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up" ESMO Open 2023

DIAGNOSIS OF LM

Recommended evaluation of suspected LM to establish the level of evidence for the diagnosis

	Recommended protocols of evaluation	Results
Clinical evaluation	Thorough neurological examination focused on abnormalities typically seen in patients with LM	Presence of typical clinical signs of LM[a] Any other neurological abnormality[b] Normal neurological evaluation
Neuroimaging	Field strength of 1.5 or preferably 3 T Gadolinium should be injected 10 min before data acquisition at a dose of 0.1 mmol/kg. The slice thickness should be ≤1 mm at the brain level and ≤3 mm at the spinal level Brain: 3D pre-contrast T1-weighted, 2D or 3D FLAIR, 2D diffusion-weighted imaging, 2D pre-contrast T2-weighted, post-gadolinium 3D T1-weighted. Post-gadolinium 3D FLAIR sequences should be considered Spinal axis: sagittal fat-suppression T2-weighted sequences, sagittal pre-contrast T1-weighted sequences, T1-weighted post-gadolinium sagittal fat-suppressed sequence	Typical MRI findings of linear LM (type A)[c] Typical MRI findings of nodular LMD (type B) Both (type C) Hydrocephalus only (type D—hydrocephalus) Equivocal leptomeningeal findings or absence of leptomeningeal MRI findings (type D—normal)
CSF cytology	Fresh CSF samples should ideally be processed within 30 min after sampling CSF volume is ideally >10 ml but at least 5 ml After centrifugation, cytospins can be air-dried and subsequently May-Grünwald-Giemsa (MGG = Pappenheim) stained Alternatively, fresh CSF samples can be fixed with Ethanol-Carbowax (CSF—fixative ratio 1:1) to reduce time pressure, followed by Papanicolaou staining of the cytospins Upon indication and availability of material, additional immunocytochemical stainings for epithelial and melanocytic markers should be considered A second CSF sample should be analysed if the initial CSF sample is negative	Positive: presence of tumour cells Equivocal: suspicious or atypical cells Negative: absence of tumour cells

1)Le Rhun E, et al, «Leptomeningeal metastasis from solid tumours: EANO/ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up" ESMO Open 2023

DIAGNOSIS OF LMD

Recommendations

A detailed neurological evaluation, cerebrospinal MRI and CSF studies using optimised analysis conditions [**EANO: III, B; ESMO: IV, B**].

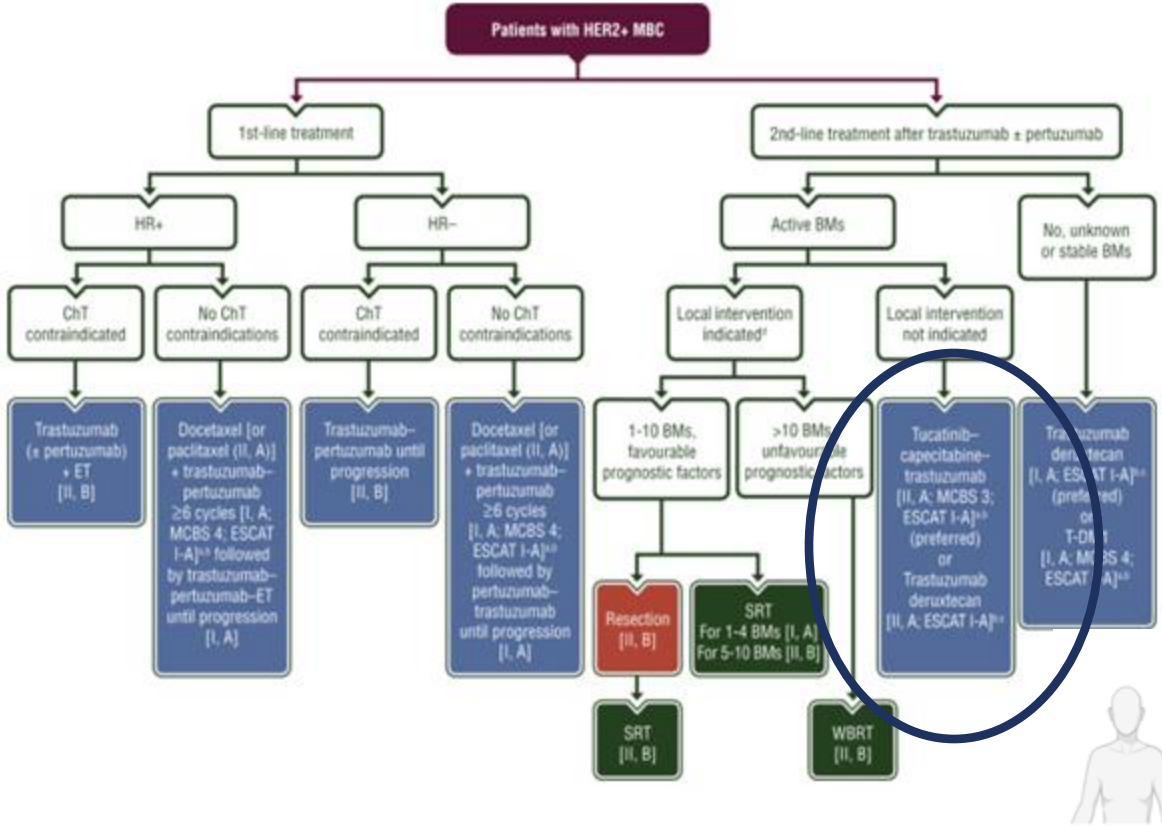
Typical clinical signs of LM, such as headache, nausea and vomiting, mental changes, gait difficulties, cranial nerve palsies with diplopia, visual disturbances, hearing loss, sensorimotor deficits of extremities and cauda equina syndrome, radicular, neck and back pain, especially in a patient with cancer, should alert clinicians to consider LM [**EANO: III, B; ESMO: IV, B**].

Brain MRI should include axial T1-weighted, axial FLAIR, axial diffusion-weighted, axial T2-weighted, postgadolinium 3D T1-weighted and post-gadolinium 3D FLAIR sequences. Spinal MRI should include post-gadolinium sagittal T1-weighted sequences. Spine sagittal T1- weighted sequences without contrast and sagittal fatsuppression T2-weighted sequences, combined with axial T1-weighted images with contrast of regions of interest, may also be considered [**EANO: III, B; ESMO: III, B**].

One repeat lumbar puncture with optimised analysis conditions should be carried out in patients with suspected LM and initial negative or equivocal cytological CSF studies [**EANO: IV, NA; ESMO: V, NA**].

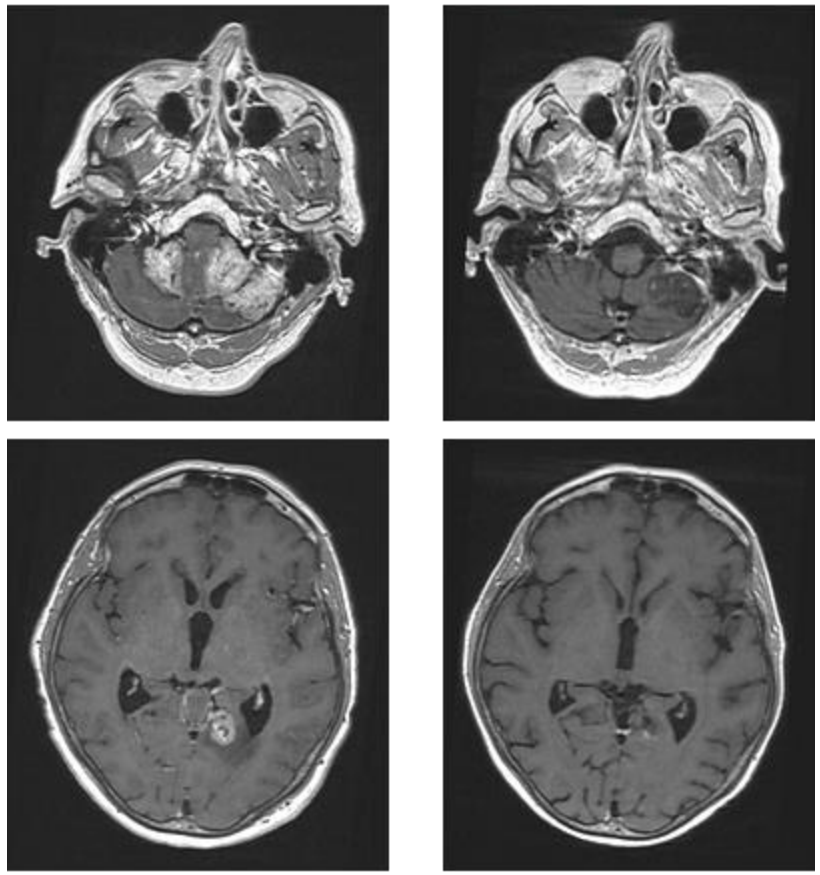
1)Le Rhun E, et al, «Leptomeningeal metastasis from solid tumours: EANO/ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up" ESMO Open 2023

MANAGEMENT of LM (clinical case)



Trastuzumab Deruxtecan

After 3 cycles MRI (30.09.24)



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Gennari A, et al. « ESMO Clinical Practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Annals of Oncology 2021

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TREATMENT OF LM (RECOMMENDATIONS)

- Intra-CSF pharmacotherapy should be considered for patients with type IA/C LM [EANO: III, B; ESMO: III, B].
- ventricular rather than lumbar route [EANO: IV, NA; ESMO: V, NA].

- Systemic pharmacotherapy based on the primary tumour and previous treatment should be considered for most patients with type B/C LM [EANO: IV, NA; ESMO: V, NA].

- RT (IFRT/CSI) should be considered for focal symptomatic lesions and extensive nodular or symptomatic linear LM [EANO: IV, NA; ESMO: V, NA]. NA; ESMO: V, NA].

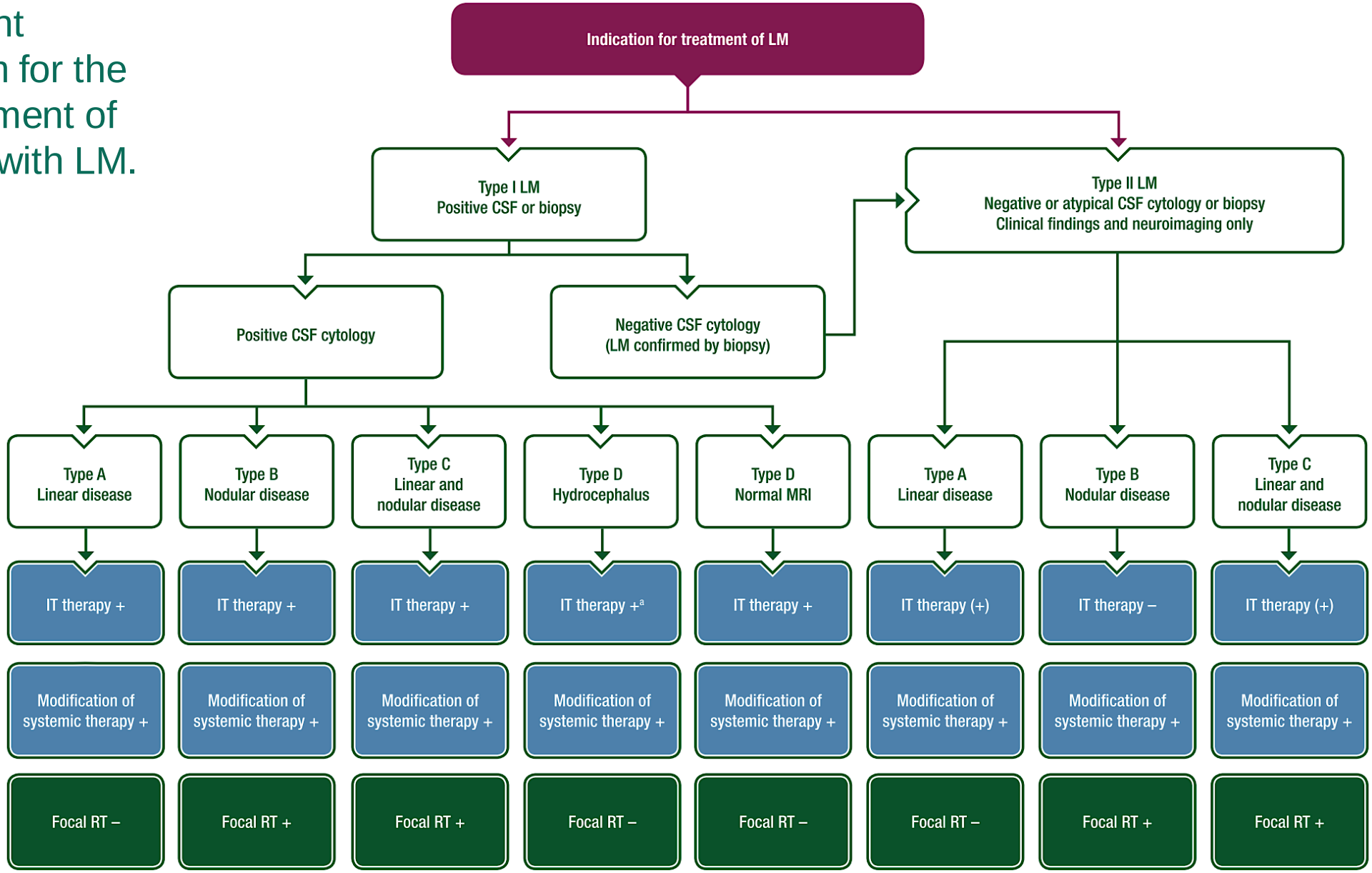
- MTX, Cytarabine, Lyposomal cytarabine, Thiotepa

- oral abemaciclib (n=1);
- intravenous paclitaxel trevatide (n=1);
- oral lapatinib (n=1);
- oral tucatinib in combination with capecitabine and trastuzumab (n=1);
- intravenous trastuzumab deruxtecan (n=1)
- intravenous pembrolizumab (n=2);
- intravenous nivolumab and ipilimumab (n=1);
- bevacizumab, etoposide, and cisplatin (n=1);
- oral temozolomide as monotherapy (n=1) or in combination with intravenous irinotecan (n=1)

- WBRT and/or focal spine RT
- CSI
- SRS/SRT

1) 1)Le Rhun E, et al, «Leptomeningeal metastasis from solid tumours: EANO/ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up" ESMO Open 2023
2) Bartsch R et al., Pharmacotherapy for leptomeningeal disease in breast cancer :Cancer Treatment Reviews, 2024

Treatment algorithm for the management of patients with LM.



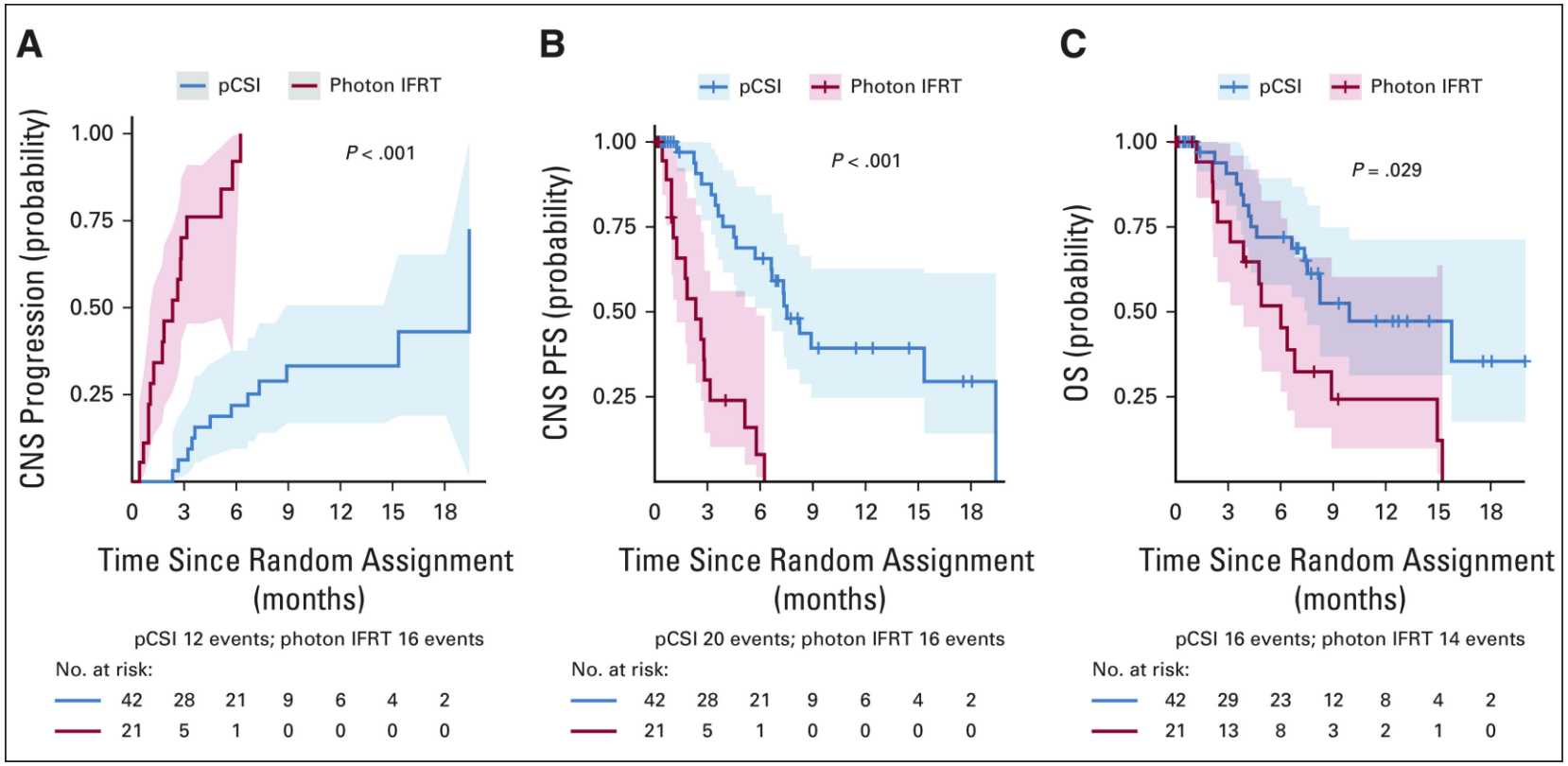
1)Le Rhun E, et al,

WHICH SYSTEMIC AND INTRA-CSF TREATMENTS FOR HER2+ LM?

- **oral abemaciclib** (n=1); phase II study in 10 patients with breast cancer (7 with HER2–/HR+ disease), median PFS and OS 5.9 and OS 8.4 months, Grade ≥ 3 AE in ≥ 10 %
- **intravenous paclitaxel trevatide** (n=1); 28 had LMD (16 HER2+, 17 ER+, 15 PR+, and four TNBC), median PFS and OS 3.4 and 8.0 months, Grade ≥ 3 AE in ≥ 10 %
- **oral lapatinib** (n=1); phase I study, 11 pts (5 LMD), one PR
- **oral tucatinib in combination with capecitabine and trastuzumab** (n=1); 17 pts Her2+, median f-up 17 months, median time to CNS progression 6.9 and median OS 11.9 months. G3 in ≥ 10 % of patients
- **intravenous trastuzumab deruxtecan** (n=1); 19 patients with HER2+ LMD, median PFS and OS were not reached at a median f-up of 17 m., IC objective response rate in 78%; 8 patients with HER2+ with a clinical response; after MRI 4 PR and 4 SD
- **intravenous pembrolizumab** (n=2); 20 patients in Brastianos et al. [32], CNS responses (per Immunotherapy RANO) included 11 with stable disease (55 %)
- **Lyposomal cytarabine** (n=1); 27 patients with HER2+ and 68 HER2- LMD; median PFS and OS 2.4 and OS 3.8 months

Bartsch R et al., Pharmacotherapy for leptomeningeal disease in breast cancer :Cancer Treatment Reviews, 2024

WHICH LOCO-REGIONAL TREATMENT FOR LM DISEASE?



CNS PFS of 7.5 months vs 2.3 months ($P < .001$

OS benefit with pCSI: median OS of 9.9 months vs 6.0 months (95%, $P = .029$

Yang et al.:Randomized Phase II Trial of Proton Craniospinal Irradiation Versus Photon Involved-Field Radiotherapy for Patients With Solid Tumor Leptomeningeal Metastasis, J Clin Oncol. 2022 Jul 8;40(33):3858–3867

HOW TO ASSESS TREATMENT RESPONSE?

Monitoring and follow-up: Recommendations

- ✓ The use of standardised scorecards for the assessment of clinic status, as well as imaging and CSF cytology data, are recommended for patient follow-up [EANO: IV, NA; ESMO: V, NA].
- ✓ A detailed neurological examination using a standard evaluation form should be carried out every 2 months for the first 6 months and every 3 months thereafter in stable patients or at radiological progression or when new neurological symptoms or signs are reported [EANO: IV, NA; ESMO: V, NA].
- ✓ Cerebrospinal MRI should be carried out every 6-12 weeks and at any timepoint where clinical progression is suspected [EANO: IV, NA; ESMO: V, NA].
- ✓ CSF studies should be carried out every 6-12 weeks in patients undergoing intra-CSF pharmacotherapy [EANO: IV, NA; ESMO: V, NA]

1)Le Rhun E, et al, «Leptomeningeal metastasis from solid tumours: EANO/ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up" ESMO Open 2023

MONITORING AND FOLLOW-UP

LM overall response assessment

Clinical	Cerebrospinal imaging	CSF cytology	Response determination	Action
Improved or stable	Improved	Improved or stable	Response	Continue treatment
Stable	Stable	Stable	Stable	Continue treatment
Worse	Improved or stable	Improved or stable	Suspicion of progression	Consider alternative neurological diagnoses or other reasons for clinical deterioration, change treatment only if there is no other explanation and if there is significant worsening of clinical signs for >2 weeks
Improved or stable	Improved or stable	Worse	Suspicion of progression[a] or progression in case of *de novo* appearance of tumour cells in the CSF[b]	[a]Continue treatment with close follow-up (e.g. for 4 weeks) [b]Change treatment for *de novo* appearance of tumour cells from the same CSF site (lumbar or ventricular)
Worse	Improved or stable	Worse	Suspicion of progression[a] or progression in case of *de novo* appearance of tumour cells in the CSF[b]	[a]Consider alternative neurological diagnoses; continue treatment with close follow-up (e.g. for 4 weeks) [b]Change treatment if there is worsening of clinical signs for >2 weeks or if there is appearance of tumour cells from the same CSF site (lumbar or ventricular)
Improved or stable	Worse	Improved or stable	Progression	Change treatment
Improved or stable	Worse	Worse	Progression	Change treatment
Worse	Worse	Improved or stable or worse	Progression	Change treatment

1)Le Rhun E, et al, «Leptomeningeal metastasis from solid tumours: EANO/ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up" ESMO Open 2023

SUMMARY

Patients with LM should undergo high quality brain and spine MRI with and without contrast at the time of diagnosis and for routine disease monitoring.

CSF cytology remains the gold standard for LM diagnosis. CSF sampling should be performed in all patients with suspicious leptomeningeal enhancement to confirm the diagnosis of LM.

Systemic therapies with CNS bioactivity and blood-CSF barrier permeability should be prioritized in all patients with LM. Current intrathecal therapies (eg, methotrexate, cytarabine, thiotepa, topotecan) have showed a median survival around 4 months.

LM disease is a disseminated neuraxial process. IFRT (WBRT or focal cranial or spinal RT) are palliative interventions and have not been proven to improve survival. CSI may be a therapeutic option in selected patients.

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ESMO GUIDELINES WEBINAR SERIES, ON THE TOPIC OF LEPTOMENINGEAL METASTASIS FROM SOLID TUMOURS

Implementation Issues from the Practising Oncologists` standpoint

Henk van Halteren, Medical Oncologist

Department of Medical Oncology

ADRZ hospital, Goes, the Netherlands

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

The ESMO POWG serves to identify the practice needs of oncologists who are hospital and office-based by developing educational services, practice tools and quality indicators that will facilitate the implementation of best practice at the point of care.

The POWG members are relevant stakeholders to the ESMO Guidelines Webinars as experts who are consulting and implementing the guidelines in their daily practices

For more information about the ESMO POWG visit **esmo.org**

ESMO > About ESMO > Organisational Structure > Educational Committee

ESMO PRACTISING ONCOLOGISTS WORKING GROUP

Don't miss:

- The «ESMO Checklists» on OncologyPRO

The ESMO/EANO (European Association of Neuro-Oncology) Guideline: A Major Effort But mainly based on a retrospective series of 254 patients diagnosed and treated in a time span of 23 years in 7 centers

Le Rhun et al. ESMO Open 2023; Volume 8: Issue 5
Le Rhun et al. Neuro-Oncology 2021; 23: 1100- 12

41% of patients had Breast Cancer, 26% of patients had Lung cancer, 20% of patients had Melanoma
Study Population heterogeneity expected to be high

Levels of Evidence and Grades of Recommendation

Guideline Chapter	Level of Evidence	Grade of Recommendation
Diagnostic Work Up and Staging	≥ III	≥ A
Treatments	≥ III	≥ B
Treatment Response Assessment	V	Not Applicable

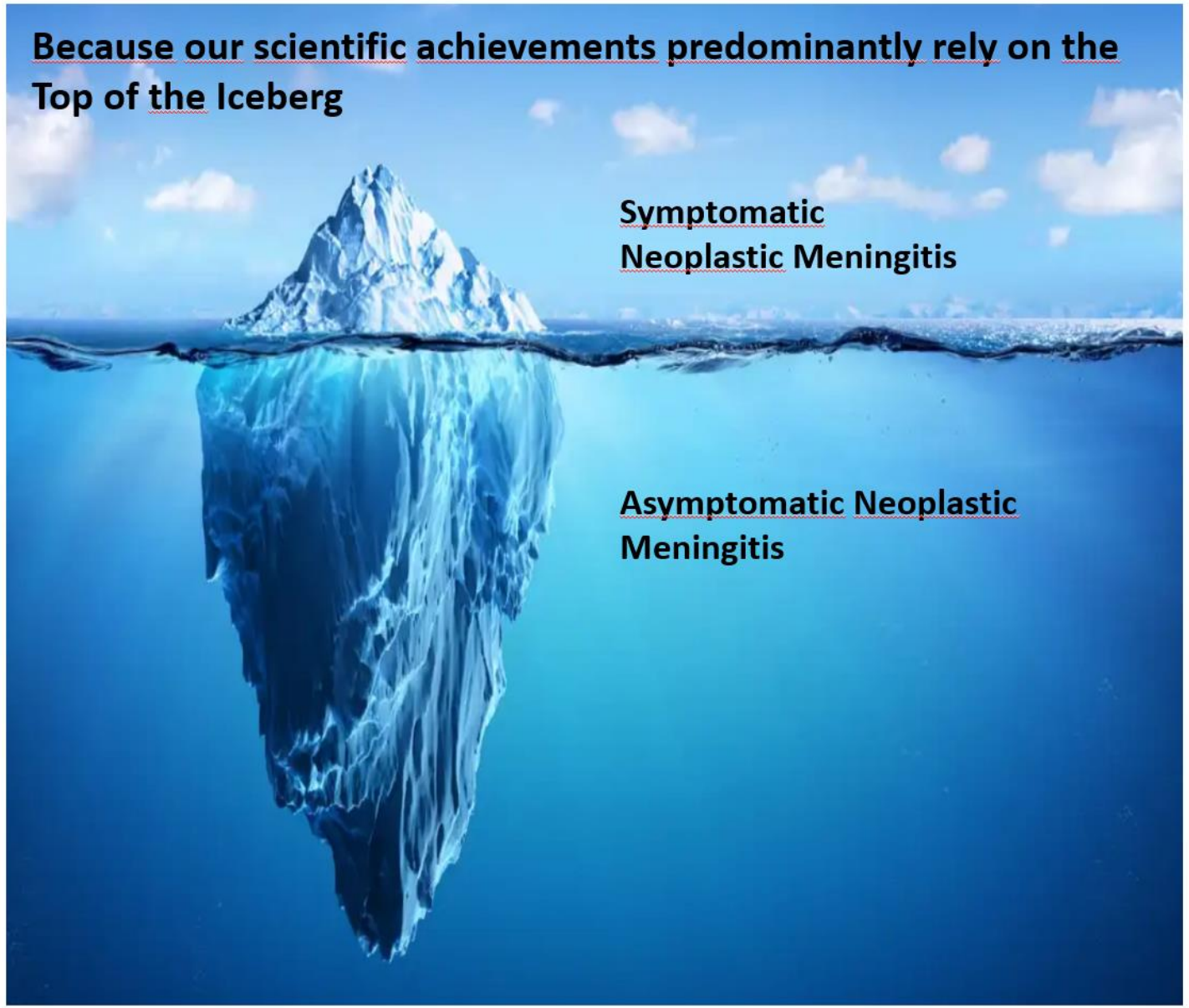
Levels of evidence

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 with 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

Why is it, that we need to rely on such limited data?



The NM diagnosis is usually made in later stages of cancer, when it has become symptomatic

Outcome is usually dismal with a median survival of only a few months

Main Roads towards NM

1. Direct invasion through surrounding structures, s.a. Dura Mater, Bone and Nerves
2. Hematogenous venous spread
3. Entry through the fenestrated pores of the choroid plexus

It is to be expected, that asymptomatic NM may occur quite often

Top 3 of Solid Cancers Affected

Melanoma, Lung Cancer, Breast Cancer

How could we catalyse our scientific achievements?

We have the (Phase1/Phase2) basics at hand already
We know which drugs breach the Blood Brain Barrier
There are even approaches to increase Blood Brain Barrier permeability
We are acquainted with the safety issues of treatments

But treatment appraisals are still based on small selected Patient Series

We need **more patients** and a **lengthier therapeutic window**

What if
We would screen high risk patients for asymptomatic NM in order to
1. Increase the number of patients to be included in studies
2. Lengthen the Treatment Duration Window, which may increase the chance of Treatment Success

And of course the burden of the diagnostic work up (MRI/CSF-aspiration and their sensitivity/specificity, Number Needed to Screen) in relation to arising opportunities for treatment needs to be investigated in **prospective trials** with an **adaptive design**

Test Performance

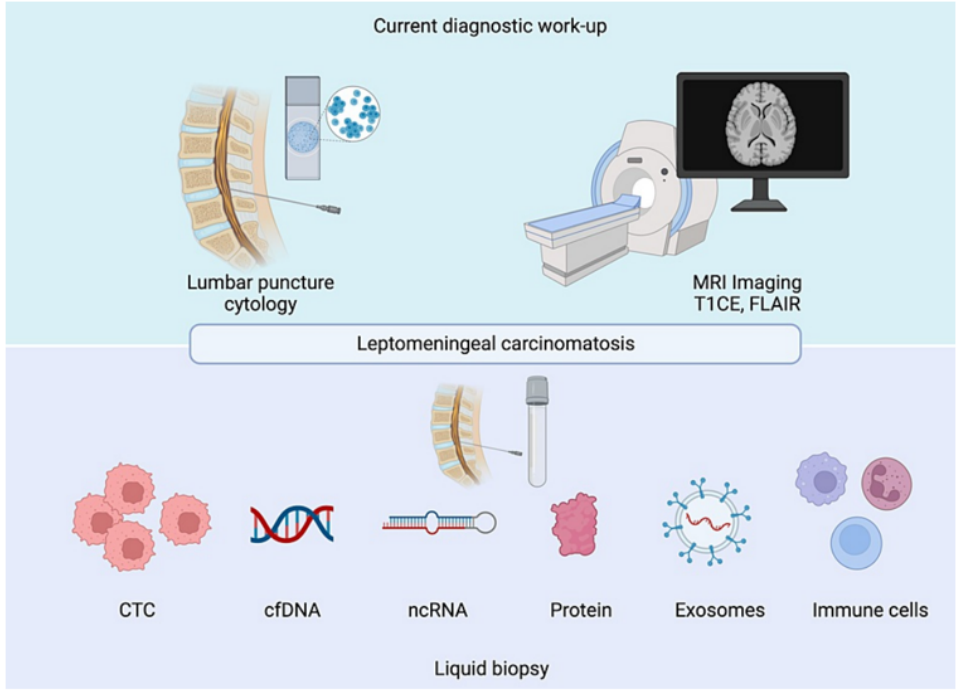


FIGURE 2: Methods to diagnose leptomeningeal carcinomatosis.

Note: This image is created by Biorender.com.

Procedure	Sensitivity	Specificity
Contrast-enhanced T1-weighted MR images	59%	93%
Contrast-enhanced FLAIR images	41%	88%
Cerebrospinal Fluid Cytology	75%	100%
Cerebrospinal Fluid Circulating Tumor Cells	87%	94%

CSF Cytology and CTC`s to be tested in High-Risk Groups may prove Cost-Effective

Goldberg et al. Cureus 2024; 16: e55187
Shah et al. Int J Surg Oncol 2011; 2011: 769753
Le Rhun et al. Ann Oncol 2021; 32: 1332- 47
Nakasu et al. Neuro-oncol Adv. 2023; 5: vdad002
Singh et al. Am J Neuroradiol 2022; 23: 817- 21

Example 1: Which patients with advanced Lung Cancer are at increased risk for NM?

Variable	Hazard Risk (95% CI)	P-value
Headache/Dizziness	18.695 (4.335- 80.628)	<0.001
Cranial Nerve Paralysis	18.127 (2.299- 142.951)	0.006
EGFR Mutation	5.80 (1.699- 19.929)	0.005
Surgery for Primary Tumor	7.742 (1.825- 32.846)	0.006
N3 stage (cervical nodes)	23.321 (3.067- 177.331)	0.002

Consider investigating the impact/benefit of CSF screening in patients with Advanced lung Cancer, who

- Have undergone surgery for the primary tumor and/or
- Have N3 stage and/or
- Have an EGFR-mutated tumor

Hua et al. Cancer Medicine 2024; 13: e7206

Example 2: Which patients with advanced Breast Cancer are at increased risk for NM?

A large Population-based study of patients with early breast cancer and 15 years of follow up
Kennecke et al. J Clin Oncol 2010; 20: 3271- 7

Cancer Subtype	% of patients developing Brain Metastases	% of patients with metastases developing Brain Metastases
Luminal A	2.2%	7.6%
Luminal B	4.7%	10.8%
Luminal B/HER2-enriched	7.9%	15.4%
HER2-enriched	14.3%	28.7%
Basal-like	10.9%	25.2%
Triple Negative Non-Basal	7.2%	22.0%

Consider investigating the impact/benefit of CSF-screening in patients with Advanced Breast Cancer, who Have a HER2-enriched or Triple Negative cancer subtype

Screening for NM in high risk groups: Two Examples

Example 1 (Freret et al. Advances in Radiation Oncology 2023; 8: 101154)

495 patients referred for stereotactic radiosurgery of solid organ spinal bone metastases

4 mL of CSF obtained, 8 patients with asymptomatic NM found, Number Needed to Screen 62

But the more precise the Risk Profiling is performed, the Lower the Number Needed to Screen could be

Example 2: ESMO Guidance for High Grade Malignant Lymphomas

ESMO Consensus Conference on malignant lymphoma: management of 'ultra-high-risk' patients

Annals of Oncology 29: 1687–1700, 2018
doi:10.1093/annonc/mdy167
Published online 19 June 2018

Table 4. Covariates Associated With CNS Recurrence in Final Multivariate Logistic Regression Analysis

	P Value	Relative Risk (95% CI)
LDH elevated at diagnosis	.0008	7.0 (2.0-38.0)
Involvement of more than one extranodal site at diagnosis	.0005	5.5 (2.1-14.9)

Guidelines statement	LoE	GoR	Consensus
1. How to predict, prevent and treat early CNS relapse after first-line treatment of DLBCL			
Recommendations:			
1.1 IPI parameters (age >60 years, high LDH levels, poor PS, advanced disease stage and more than one extra-nodal site) are risk factors for early CNS relapse following first-line treatment of DLBCL, with a direct relationship between the number of unfavourable features and the CNS risk. The involvement of the testes, kidneys, adrenals, breast, bone marrow and bone has also been reported to increase the risk of CNS disease.	II	B	100% yes (18 voters)

Levels of evidence

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 with demonstrated heterogeneity

Grades of recommendation

B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

Van Besien et al. Blood 1998; 91: 1178- 84

Conclusions

In order to improve **the outcome of patients with Leptomeningeal Metastases** we need **Intervention Studies** with a **Higher Number of Patients** and a **Lengthier Therapeutic Window**

Screening for Asymptomatic Leptomeningeal Metastases in High Risk Groups may serve both purposes

This approach has been adopted before:
Just Check the current ESMO Guideline for High Risk lymphomas, which clearly indicates which patients should undergo CSF-screening and what the therapeutic consequences of tumor-positive CSF-cytology should be

"And – just as a principle of thought- we do not postpone treatment of colon cancer liver metastases until they have become symptomatic, but we screen actively to Lengthen the Therapeutic Window and to increase the chance of Treatment Success"

Therefore,
The Cost Efficacy of CSF-screening
of **High Risk patients with Breast Cancer, Lung Cancer and Melanoma**
deserves to be estimated in **future prospective trials with an adaptive design**

ESMO GUIDELINES: REAL WORLD CASES

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