Leptomeningial carcinomatosis: standards of care

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Disclosures

MP has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen.

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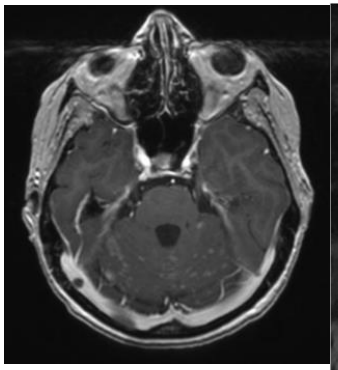
Definition of LM

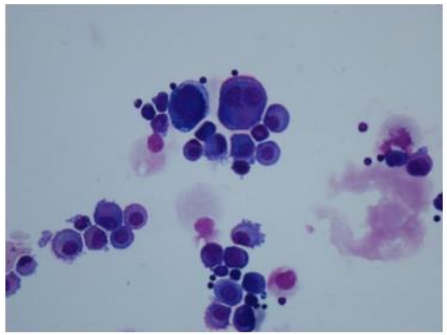
- LM is defined as the spread of tumor cells within the leptomeninges and the subarachnoid space
- LM is synonymous with neoplastic meningitis and can be further denoted by primary tumor as leptomeningeal carcinomatosis, gliomatosis or lymphomatosis



Axial brain gadolinium enhanced MRI

Sagittal spinal gadolinium enhanced MRI

Lumbar puncture

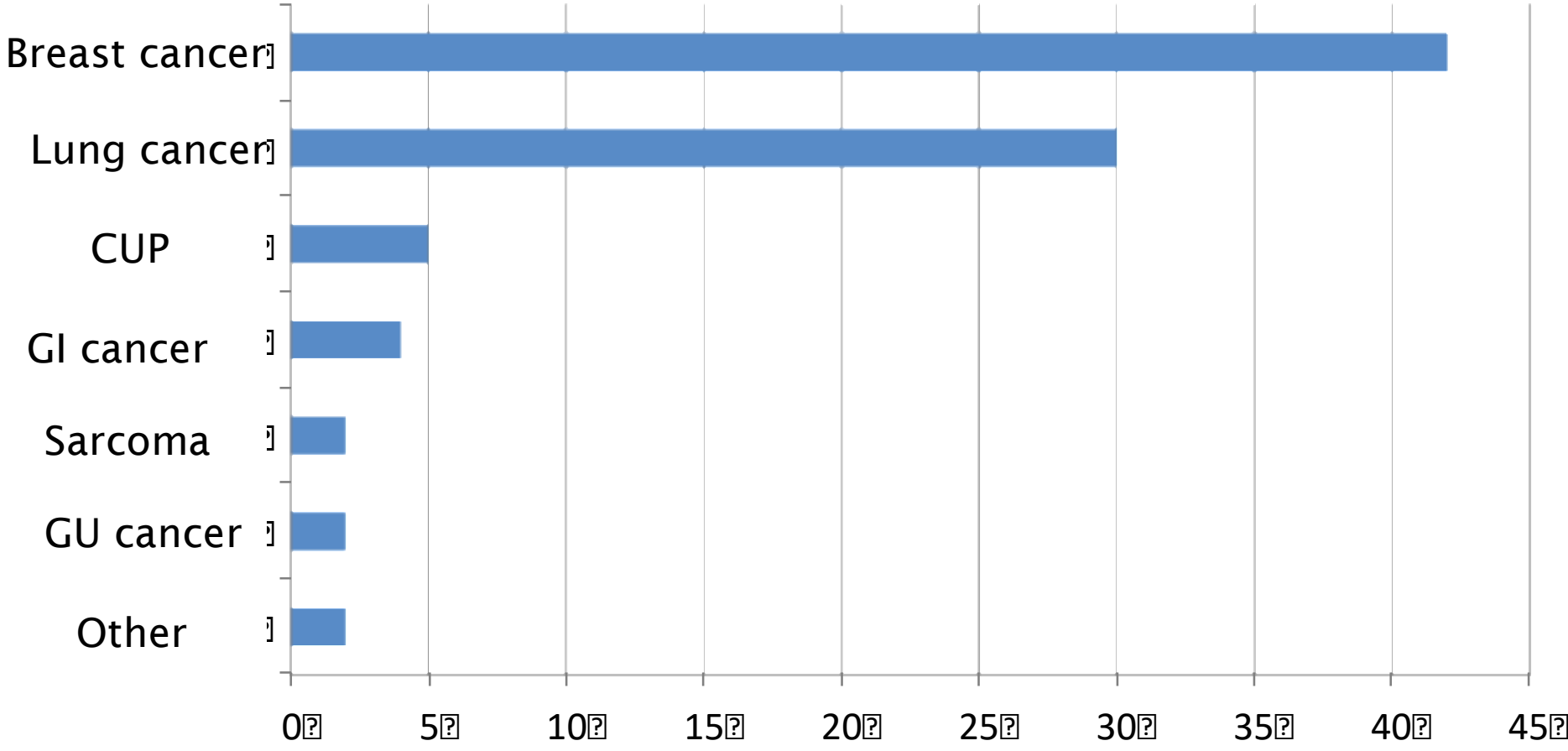


Invasive lobular carcinoma
MGG X40

Background

- Leptomeningeal metastasis (LM) affects up to 10% of patients with solid tumors
- The median survival is limited to 2-3 months, with a 1-year survival rate below 10%
- Only a few prospective clinical trials are available
- Treatment strategies include intra-CSF chemotherapy, systemic pharmacotherapy, and focal or large volume radiotherapy and vary widely across centers

Epidemiology



Levels of evidence in LM

No standards for:

- Neurological examination
- Neuro-imaging assessment
- CSF diagnosis
- No trial on systemic treatment
- No trial on radiotherapy
- Only 5 trials on intra-CSF therapy….

Neuro-Oncology

19(4), 484–492, 2017 | doi:10.1093/neuonc/now183 | Advance Access date 30 December 2016

Leptomeningeal metastases: a RANO proposal for response criteria

Marc Chamberlain, Larry Junck, Dieta Brandsma, Riccardo Soffietti, Roberta Rudà, Jeffrey Raizer, Willem Boogerd, Sophie Taillibert, Morris D. Groves, Emilie Le Rhun, Julie Walker, Martin van den Bent, Patrick Y. Wen, and Kurt A. Jaeckle.

Clinical evaluation

- **Typical clinical features include:** headache, nausea and vomiting, mental changes, gait difficulties, cranial nerve palsies with diplopia, visual disturbances, hearing loss, sensorimotor deficits of extremities, cauda equina syndrome, radicular, neck and back pain

➢ Standardized neurological evaluation that needs validation

Table 1 Neurological examination (adapted from RANO Neurological Assessment group)

Domain	Level of Function Score				Key Considerations
	0	1	2	3	
Gait	Normal	Abnormal but walks without assistance	Abnormal and requires assistance (companion, cane, walker, etc.)	Unable to walk	1. Walking is ideally assessed by at least 10 steps.
Strength	Normal	Movement present but decreased against resistance	Movement present but none against resistance	No movement	1. Each limb should be tested separately. 2. Recommend assess proximal (above knee or elbow) and distal (below knee or elbow) major muscle groups. 3. Score should reflect worst performing area. 4. Patients with preexisting level 3 function in one major muscle group/limb at baseline can be scored based on assessment of other major muscle groups/limb.
Sensation	Normal	Decreased but aware of sensory modality	Unaware of sensory modality	---------	1. Recommend evaluating major body areas separately (face, limbs, and trunk). 2. Score should reflect worst performing area. 3. Sensory modality includes but is not limited to light touch, pinprick, temperature, and proprioception. 4. Patients with preexisting level 2 function in one major body area at baseline can be scored based on assessment of other major body areas.
Vision	Normal	Partial monocular visual loss	Complete monocular visual loss	Bilateral visual loss	1. Patients who require corrective lenses should be evaluated while wearing corrective lenses. 2. Each eye should be evaluated, and score should reflect worst performing eye.
Eye movements	Normal	Abnormality noted in 1 direction of gaze	Abnormality noted in more than 1 gaze direction, but not all	Unable to move the eye in any gaze direction	1. Test eye movements for each eye individually. 2. The score will reflect the worst performing eye (ie, the highest score).
Facial strength	Normal	Mild facial weakness (nasolabial fold flattening, asymmetric smile, decreased forehead contraction, or partial eye closure)	Severe facial weakness (severe nasolabial fold flattening, asymmetric smile with limited or no movement of face, incomplete eye closure, or labial incompetence	Bilateral facial weakness	1 Weakness includes nasolabial fold flattening, asymmetric smile, and difficulty elevating eyebrow.
Hearing	Normal	Impaired but residual serviceable hearing	Absent unilateral hearing	Bilateral hearing loss	1. Each ear should be evaluated and score should reflect worst performing ear.
Swallowing	Normal	Impaired but not requiring change in diet formulation, not aspirating by bedside testing	Unable to swallow without risk of aspiration by bedside testing	----------	1. Bedside testing comprising a swallow test with a small glass of water.
Level of consciousness	Normal	Drowsy (easily arousable & responsive)	Somnolent (difficult to arouse & poorly responsive)	Coma (unarousable & unresponsive)	
Behavior	Normal	Mild/moderate alteration	Severe alteration	---------	1. Alteration includes but is not limited to apathy, disinhibition, and confusion. 3. Consider subclinical seizures for significant alteration.
Other	Normal	Occasional or mild	Persistent, moderate to severe	----------	

Legend: "Other": Neurological findings not otherwise defined in the current examination, for example ataxia.

RANO grid, Chamberlain et al., 2017

Imaging evaluation

Slice thickness 1 mm or less

Gadolinium injected 10 min before data acquisition (EANO ESMO) at a dose of 0.1 mmol/kg

Standardized and validated grid

Follow-up on the same device

MRI prior to lumbar puncture

Table 3. Scorecard for radiographic assessment in leptomeningeal metastases

MRI Findings	Present (1) or Absent (0) or Non-evaluable (NE)	Dimensions Of Measurable Nodules Defined as >5 x 10 mm (orthogonal diameters)	Change from Previous MRI (–3 to +3)
BRAIN			
Nodules (subarachnoid or ventricular)			
Leptomeningeal enhancement*			
Cranial nerve enhancement			
Hydrocephalus^			
Parenchymal (brain metastases)^			
SPINE			
Nodules (subarachnoid)			
Leptomeningeal enhancement			
Nerve root enhancement			
Parenchymal(intramedullary metastases)^			
Epidural metastasis ^			
TOTAL SCORE			

Legend:
*Leptomeningeal enhancement may include pia, cerebellar folia, ventricular ependyma or cerebral sulci.
^Both hydrocephalus and parenchymal metastases, either brain or spine, are noted as present or absent but not used for LM response determination.
Column 2: scored as 1 (present) or 0- (absent) or non-evaluable (NE). A maximum of 5 radiographic target lesions are selected from baseline imaging to score on follow-up.
Column 3: scores each measurable lesion (at least 5 × 10 mm) excluding parenchymal as 1 (present with maximum orthogonal diameters) or 0 (absent).
Column 4: change from baseline or prior image scored as same (0), probable improvement (+1), definite improvement (+2), no evidence of disease (+3) or probable worsening (–1), definite worsening (–2), new site(s) of disease (–3). Measurable nodules defined as ≥5 × 10 mm are scored as same (0), resolved (no evidence of disease, complete response), definitely better (+2, partial response) [decrease by >50% in the summed product of orthogonal diameters], definite worsening (–2, progressive disease) [increase by >25% in the summed product of orthogonal diameters]. A composite score (total score) is calculated and compared with the baseline total score. A 25% worsening in the current score relative to baseline defines radiographic progressive disease. A 50% improvement in the current score defines a radiographic partial response. Resolution of all baseline radiographic abnormalities defines a complete response. All other situations define stable disease.

RANO grid, Chamberlain et al., 2017

	EANO ESMO
Brain	axial, coronal and sagittal T1 without and with contrast enhancement, axial T2, axial and coronal FLAIR
Spine	sagittal T2 and T1 without and with contrast

Imaging methodology

Table 2. MRI parameters in leptomeningeal disease

MRI prerequisites
1.5T and 3T MR scanners only
Use of same MRI at baseline and follow-up
MRI to be performed prior to lumbar puncture
Recommended MRI sequences
Brain
Volumetric 3DT1 (magnetization-prepared rapid acquisition with gradient echo [MPRAGE] or spoiled gradient [SPGR]) postcontrast image with isotropic 1-mm voxels to permit reformatting in 3 planes (axial, coronal, and sagittal)
Reformatted slice thickness 3 mm to obtain good signal to noise ration and manageable number of slices for full brain coverage
IV contrast dose = 0.1 mmol/kg of gadolinium-based agent.
Spine
Volumetric 3DT1 (MPRAGE or SPGR) postcontrast image in sagittal plane with isotropic 1 mm voxels to permit reformatting in 3 planes (axial, coronal, and sagittal) with a 2–3 mm reformatted slice thickness without gap.

LM patterns

- Diffuse/fluid

- Solid

- Adherent

Imaging evaluation: RANO grid

Table 3. Scorecard for radiographic assessment in leptomeningeal metastases

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Nerve root enhancement			
Parenchymal(intramedullary metastases)^			
Epidural metastasis ^			
TOTAL SCORE			

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Annals of Oncology 28 (Supplement 4): iv84–iv99, 2017
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CLINICAL PRACTICE GUIDELINES

EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours†

E. Le Rhun[1,2,3], M. Weller[4], D. Brandsma[5], M. Van den Bent[6], E. de Azambuja[7], R. Henriksson[8,9], T. Boulanger[10], S. Peters[11], C. Watts[12], W. Wick[13,14], P. Wesseling[15,16], R. Rudà[17] & M. Preusser[18], on behalf of the EANO Executive Board and ESMO Guidelines Committee*

MEDICAL UNIVERSITY OF VIENNA
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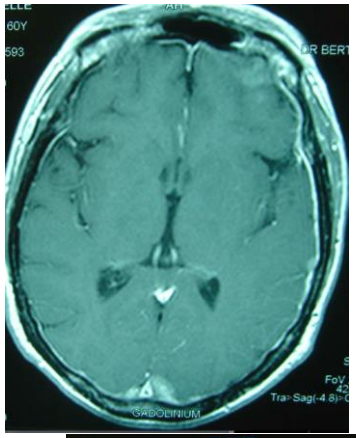
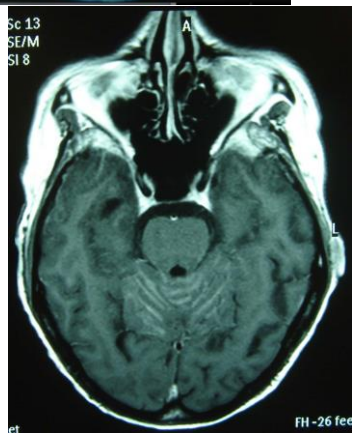
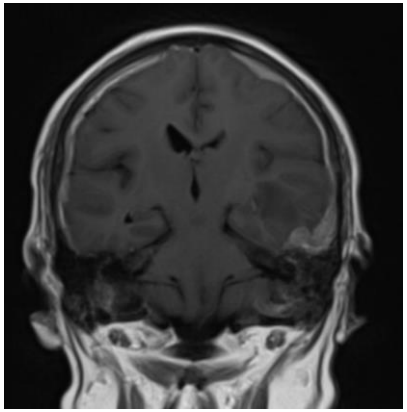
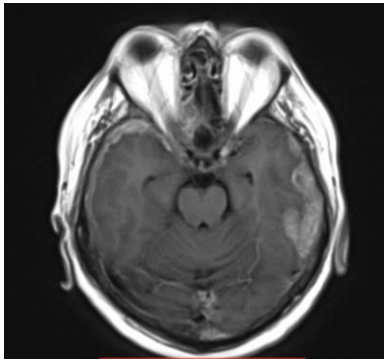
Imaging subtypes

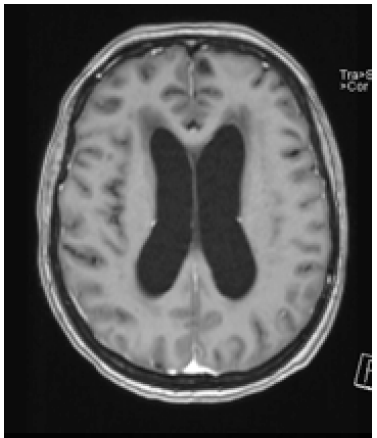
Type A: LM with typical linear MRI abnormalities	**Type B**: LM with nodular disease only	**Type C**: LM with both linear and nodular disease	**Type D**: LM without MRI abnormalities, except possibly hydrocephalus

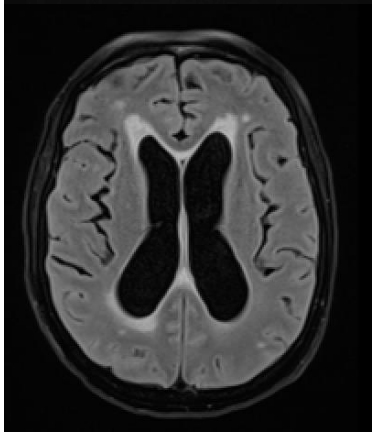




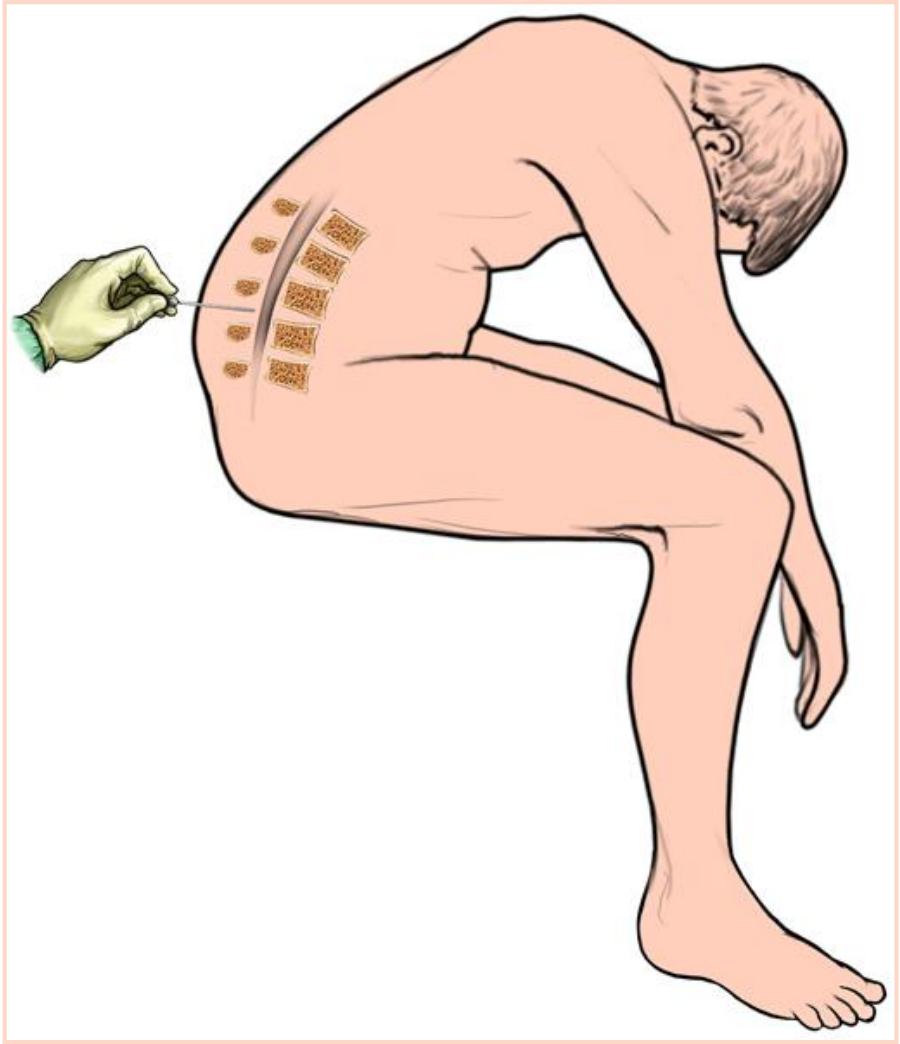








Lumbar puncture



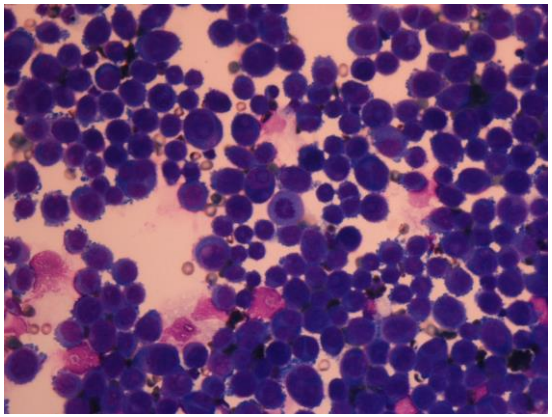
CSF analysis

Specificity >95%

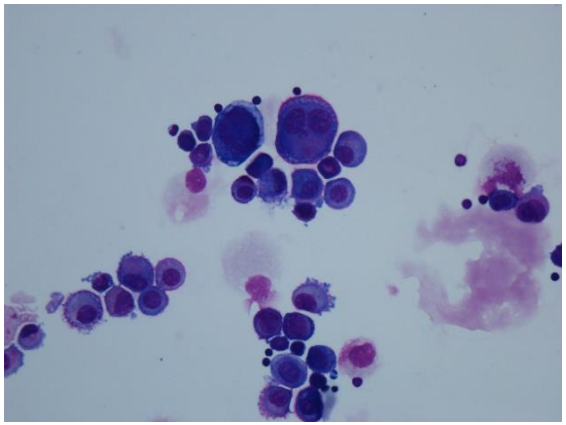
Sensitivity: first lumbar puncture: 55%

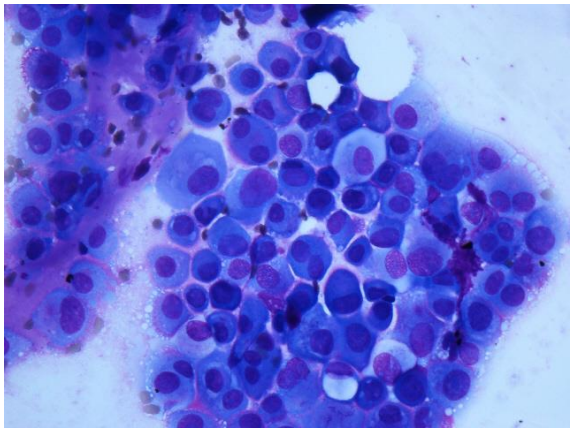
second lumbar puncture: 80%

In recent large cohorts of LM patients, CSF cytology was considered positive in 66%-90%.



Melanoma - MGG X40





Invasive Lobular Carcinoma - MGG X40

CSF analysis

In presence of tumor cells, the diagnosis is confirmed **(type I)**
In other cases the diagnosis can only be probable or possible **(type II)**

	EANO ESMO
Technical aspects	- **fresh CSF samples processed within 30 minutes after sampling; alternatively, fresh CSF samples fixed with Ethanol-Carbowax** - **CSF volume > 10 ml (at least 5 ml)** - routine stainings: Papanicolaou and Giemsa; additional immunocytochemical stainings (upon indication and availability of material) - a second CSF sample should be analyzed if the initial CSF sample is negative for diagnosis
Interpretation of the results	**- positive (presence of tumor cells)** **- equivocal (suspicious or atypical cells)** **- negative (absence of tumor cells)**

Classification of LM: EANO ESMO Proposal

Table 2. Diagnostic criteria for LM

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

Type A: LM with typical linear MRI abnormalities; Type B: LM with nodular disease only as type B; Type C: LM with both linear and nodular disease; Type D: LM without MRI abnormalities except possibly hydrocephalus.

[a]Requires a history of cancer.

+, positive; −, negative; CSF, cerebrospinal fluid; LM, leptomeningeal metastasis; MRI, magnetic resonance imaging; n/a, not applicable.

Prognosis

	Median OS
Without tumour-specific treatment	6-8 weeks
Breast cancer with treatment	1.5-4.5 months
Lung cancer with treatment	3-6 months
Melanoma with treatment	1.7-2.5 months

Chamberlain 2009, Groves 2010, Grossman 1982, De Angelis 1998 , Gauthier 2010, Rudnicka 2007, Clatot 2009, De Azevedo 2011, Le Rhun 2013, Harstad 2008, Papadopoulos 2002, Geukes Foppen 2016, Grossman 1999 , Hammerer 2005, Morris 2011, Park 2011, Gwak 2013, Lee 2013, Kuiper 2015

Prognostic factors

- performance status at diagnosis of LM
- primary tumour type
- cerebrospinal fluid (CSF) protein levels
- administration of combined modality treatment, systemic treatment, or intra-CSF treatment
- initial clinical or CSF responses to treatment

(Rudnicka 2007, Gauthier 2010, Lee 2011, de Azevedo 2011, Niwinska 2013, Yust Katz 2013, Le Rhun 2013, Clarke 2010, Oechsle 2010, Herrlinger 2004, Clatot 2009, Hyun 2016)

Radiotherapy

- No randomized clinical trial to assess the efficacy and tolerance of RT in LM has been conducted.
- **Focal RT** (involved-field or stereotactic RT or radiosurgery) can be used to treat nodular disease and symptomatic cerebral or spinal sites.
- **WBRT** may be considered for extensive nodular or symptomatic linear LM or co-existing brain metastases.
- **Cerebrospinal RT** is rarely an option for adult patients with LM from solid cancers because of risk of bone marrow toxicity, enteritis and mucositis, and the usual co-existence of systemic disease.

Systemic pharmacotherapy

- *a priori* no reason to believe that systemic pharmacotherapy for contrast-enhancing manifestations of LM should be less efficient than for other systemic manifestations of cancer
- increased CSF protein levels in most LM patients confirm that the blood-CSF barrier is commonly disrupted in LM
- no specific prospective trials reported on systemic treatment of LM, but retrospective series suggest some activity of systemic chemotherapy
- the best systemic treatment for LM is determined by:
  - the primary tumour
  - its molecular characteristics or the molecular characteristics of tumour cells of the CSF when available
  - and prior treatment of the underlying malignancy

Intra-CSF therapy

Table 3. Characteristics and schedules of administration of intra-CSF therapy

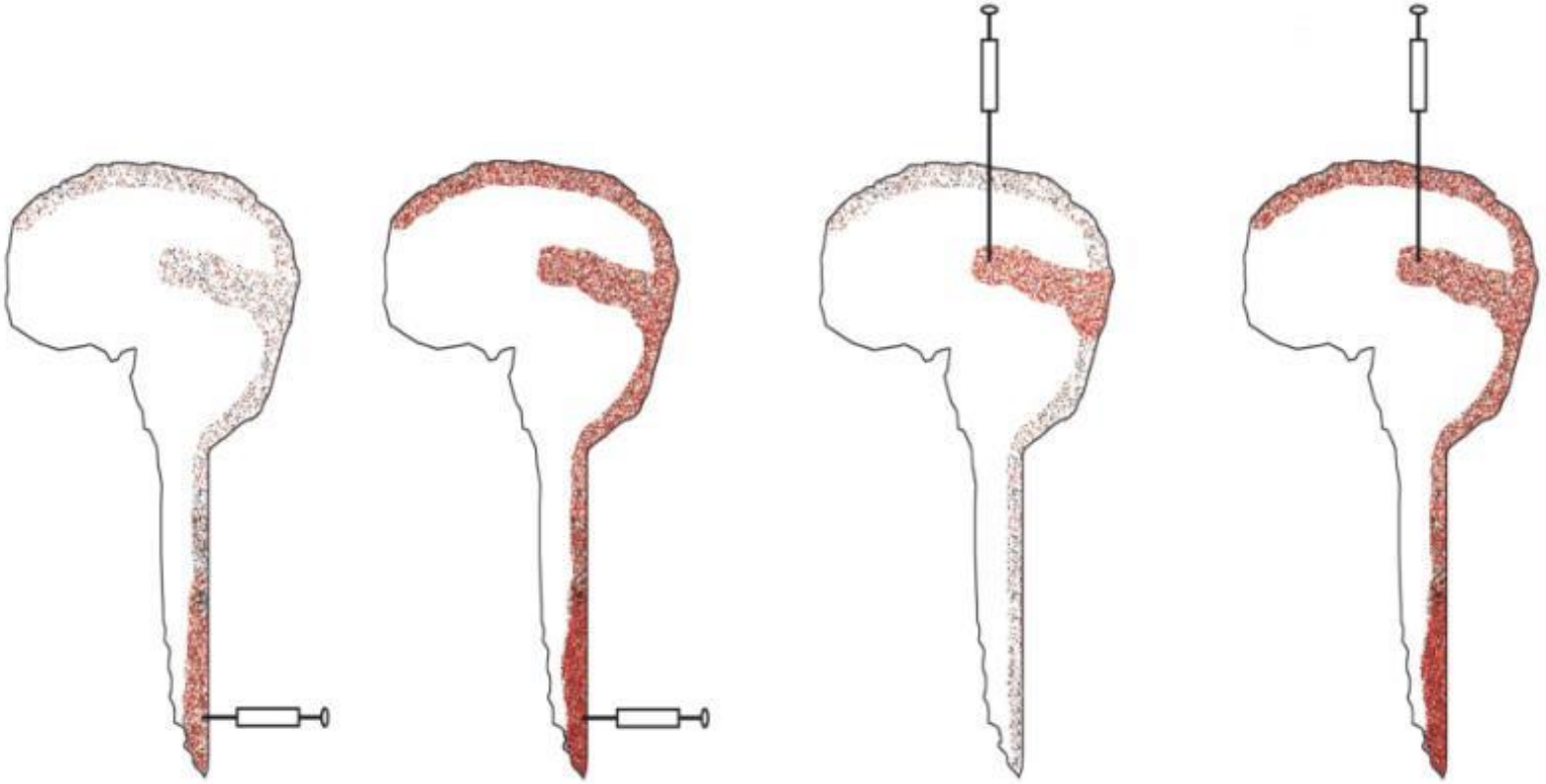
Agent	Description	Half-life in the CSF	Recommended schedules of administration	Prophylaxis of adverse events
Methotrexate	Folate anti-metabolite, cell cycle specific	4.5–8 h	10–15 mg twice weekly (total, 4 weeks), then 10–15 mg once weekly (total, 4 weeks) then 10–15 mg once monthly	Folinic acid rescue, 25 mg × 6 h for 24 h starting 6 h after administration
Cytarabine	Pyrimidine nucleoside analogue, cell cycle specific	< 1 h	10 mg twice weekly (total, 4 weeks) then 10 mg once weekly (total, 4 weeks) then 10 mg once a month	None
Liposomal cytarabine	Pyrimidine nucleoside analogue, cell cycle specific	14–21 days	50 mg every 2 weeks (total, 8 weeks) then 50 mg once a month	Oral steroids, e.g. 6 mg dexamethasone equivalent daily (d1–d4)
ThioTEPA	Alkylating ethyleneimine compound, cell cycle non-specific	3–4 h	10 mg twice weekly (total, 4 weeks) then 10 mg once weekly (total, 4 weeks) then 10 mg once a month	None

CSF, cerebrospinal fluid; thioTEPA, thiotriethylenephosphoramide.

CSF distribution

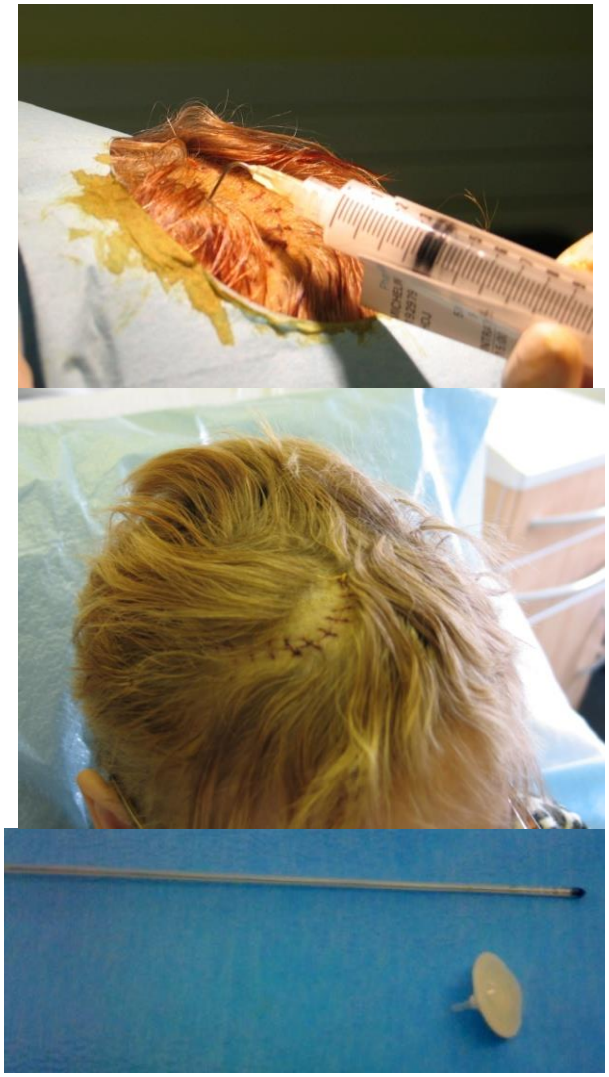
Intralumbale Injektion

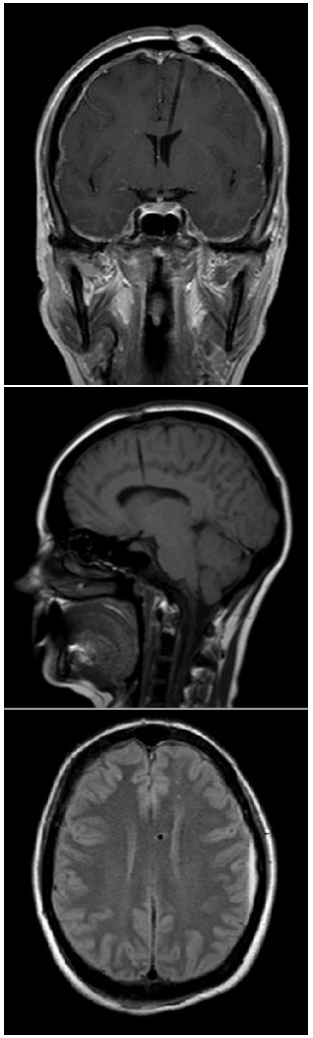
Intraventrikuläre Injektion



Cytarabin **Liposomal cytarabin** **Cytarabin** **Liposomal cytarabin**

Route of administration of intra-CSF therapy





Randomized trials assessing the response to intra-CSF treatment in LM

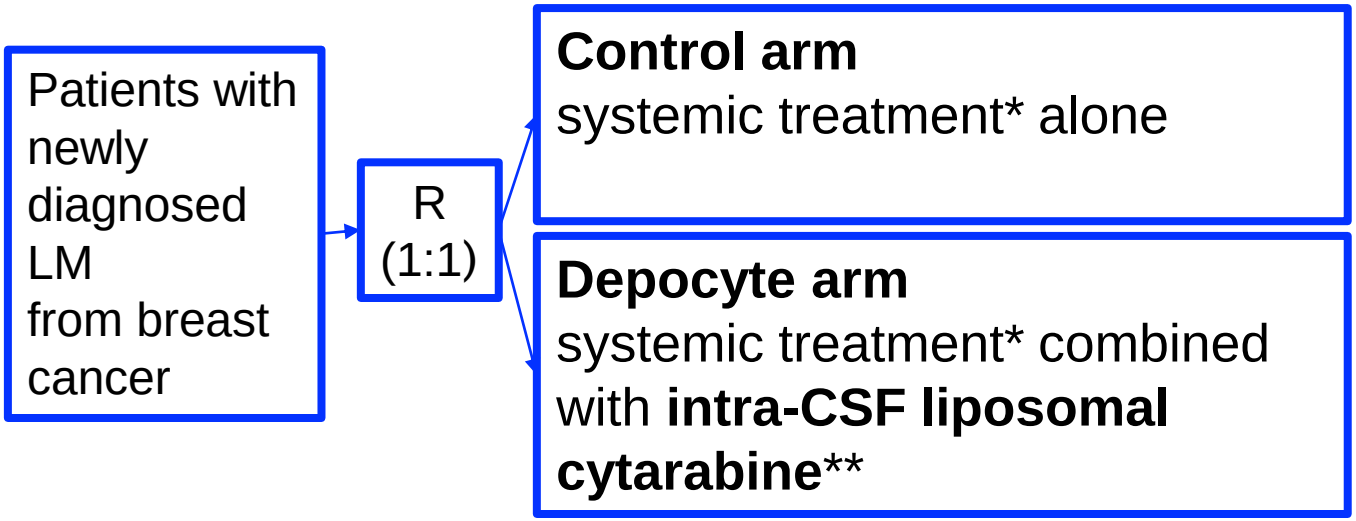
Trial	Design	Population	Primary endpoint	Efficacy	Safety
Grossman 1993	IT MTX versus IT thiotepa	Solid tumors (n=40), CUPS (n=1) and lymphomas (n=10)	Neurological response rate	IT MTX vs. IT thiotepa Neurological response rate: none Neurological stabilization: 32% vs. 12.5% Survival: 15.9 weeks vs. 14.1 weeks	IT MTX vs. IT thiotepa Serious toxicities similar in both group Mucositis (p=0.04) and neurological complications (p=0.008) more frequent in MTX arm
Hitchins 1997	IT MTX versus IT MTX + cytarabine	Solid tumors (n= 30), cancers of unknown primaries (n=7) and lymphomas (n=7)	Response rate	IT MTX vs. MTX + cytarabine Response rate : 61 vs. 45% (p<0.05) Median survival : 12 vs. 7 weeks (p<0.05)	IT MTX vs. MTX + cytarabine Nausea and vomiting : 36% vs. 50% Septicemia, neutropenia : 9% vs. 15% Mucositis : 14% vs. 10% Pancytopenia : 9% vs. 10%
Glantz 1999	IT liposomal cytarabine versus IT MTX	Solid tumors (n=61)	Response rate at the end of the induction period	IT liposomal cytarabine vs. IT MTX Responses rate : 26% vs. 20% (p = 0.76) Median survival : 105 days vs. 78 days (p *P* = 0.15) Time to neurological progression : 58 vs. 30 days (p = 0.007) Neoplastic meningitis-specific survival : 343 *vs.* 98 days (p = 0.074)	IT liposomal cytarabine vs. IT MTX Sensory/motor dysfunction : 4% vs. 10% (p = 0.021) Visual impairment 0% vs. 13% (p = 0.066) Chemical meningitis of any grade : 23% vs. 19% (*p*=0.57)
Boogerd 2004	IT MTX versus no IT	Breast cancers (n=35)	Overall survival: time from randomization until death	IT MTX vs. no IT Overall survival :18.3 weeks vs. 30.3 weeks (p = 0.32) Neurological improvement or stabilisation : 59% vs. 67% (p = NR) Median time to progression of 23 weeks and 24 weeks (p = NR)	IT MTX vs. no IT Neurological complications : 47% vs 6% (p = 0.0072)
Shapiro 2006	solid tumors: IT liposomal cytarabine versus IT MTX (lymphomas: IT liposomal cytarabine versus IT aracytine)	Solid tumors (n=103) and lymphomas (n=25)	Progression free survival: randomized to neurological progression or death	IT liposomal cytarabine versus IT MTX or aracytine Median progression free survival: 35 vs. 43 days (p=0.7321)	IT liposomal cytarabine versus IT control Drug related AE: 48% vs. 60% of the serious AE: 86 vs. 77%

Intrathecal liposomal cytarabine plus systemic therapy versus systemic chemotherapy alone for leptomeningeal metastasis from breast cancer - a randomized study. Final results

E Le Rhun, J Wallet, A Mailliez, M Le Deley, I Rodrigues, T Boulanger, V Lorgis, J Barriere, Y Robin, M Weller, J Bonneterre

DESIGN OF DEPO-SEIN (NCT01645839)

- Phase III randomised controlled open-label trial



* In both groups: systemic treatment selected by the treating physician prior to randomisation

** Intra-CSF liposomal cytarabine: 50 mg every 14 days for 2 months (5 injections) followed by monthly injections of 50 mg until progression, unacceptable toxicity or for a total of one year.
Oral steroids recommended for 5 days from the day of intra-CSF injection to prevent chemical meningitis.
In case of severe toxicity, the dose of cytarabine could be reduced to 25 mg.

TRIAL OBJECTIVES

Primary endpoint

To demonstrate superior LM-related progression-free survival (LM-PFS) in the experimental group

Secondary endpoints

- PFS (progression at any site)
- Overall Survival (death from any cause)
- Quality of life (QLQ-C30)
- Safety

MAIN INCLUSION CRITERIA

- Female >18 years, with histologically confirmed **breast cancer**
- **Newly diagnosed LM** based on
  - the presence of malignant cells in the CSF, or
  - the combination of clinical symptoms and typical signs and MRI findings
- **Meningeal nodules < 5 mm** if no focal radiotherapy (RT) planned; could be larger if focal RT planned. Irradiated nodules not used as target lesions to define response.
- ECOG-Performance Status between 0 and 2 with a life expectancy of at least 2 months
- **Candidates for systemic chemotherapy**
- Brain metastases allowed if asymptomatic and not considered to require whole brain radiation therapy (WBRT)
- Prior WBRT for brain metastases allowed, but prior cranio-spinal radiation therapy not allowed
- Prior intra-CSF chemotherapy or prior systemic treatment with high-dose cytarabine or methotrexate not allowed
- Patients with ventriculo-peritoneal shunts not eligible

STATISTICAL CONSIDERATIONS SAMPLE SIZE

- **Sample size calculation**:

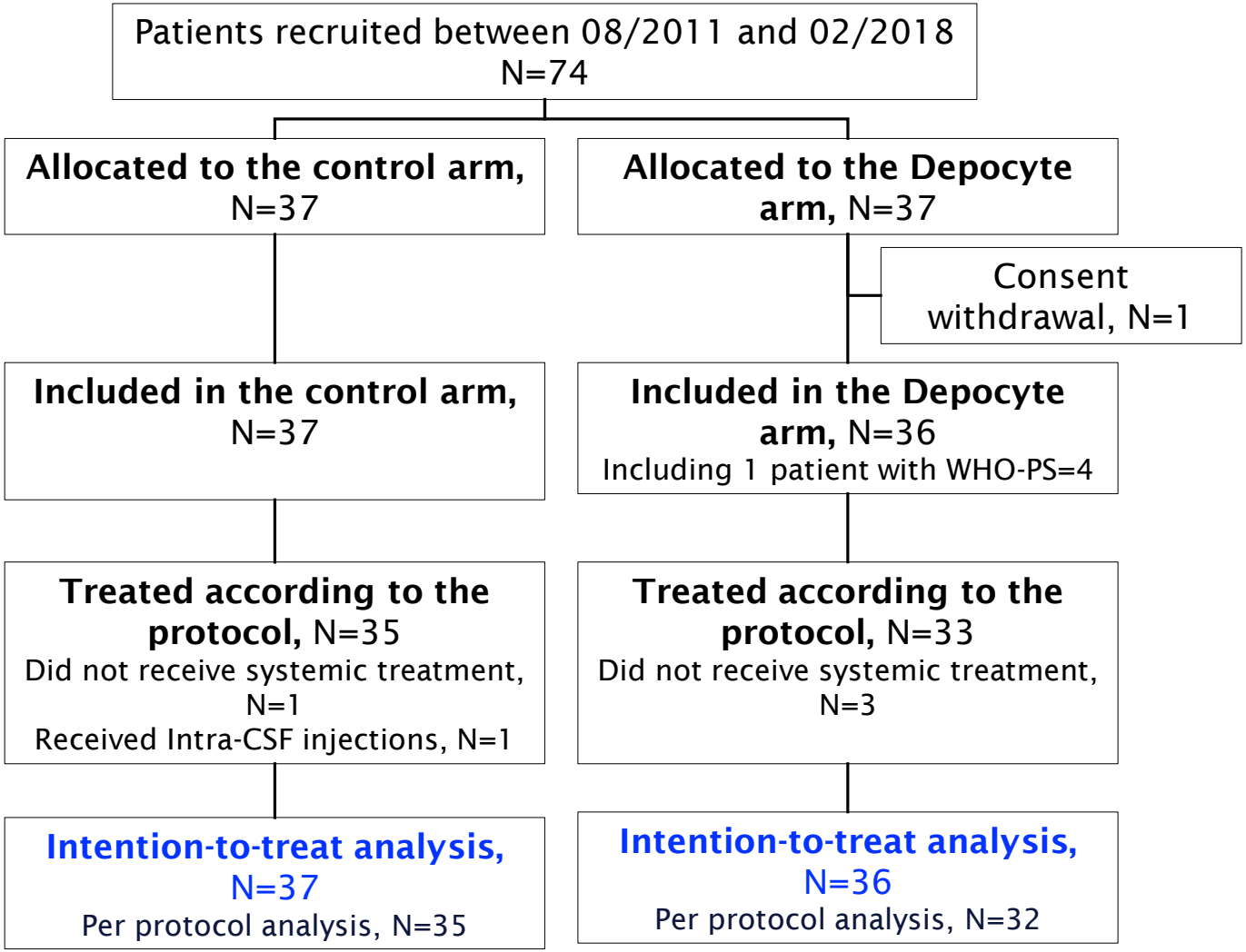
- 80%-power for a hazard ratio = 0.50 (median LM-PFS 1 mo ⇨ 2 mo)

- logrank test, 2-sided alpha=5%

⇨ **66 events required**

- Main analysis on the **intention-to-treat population**

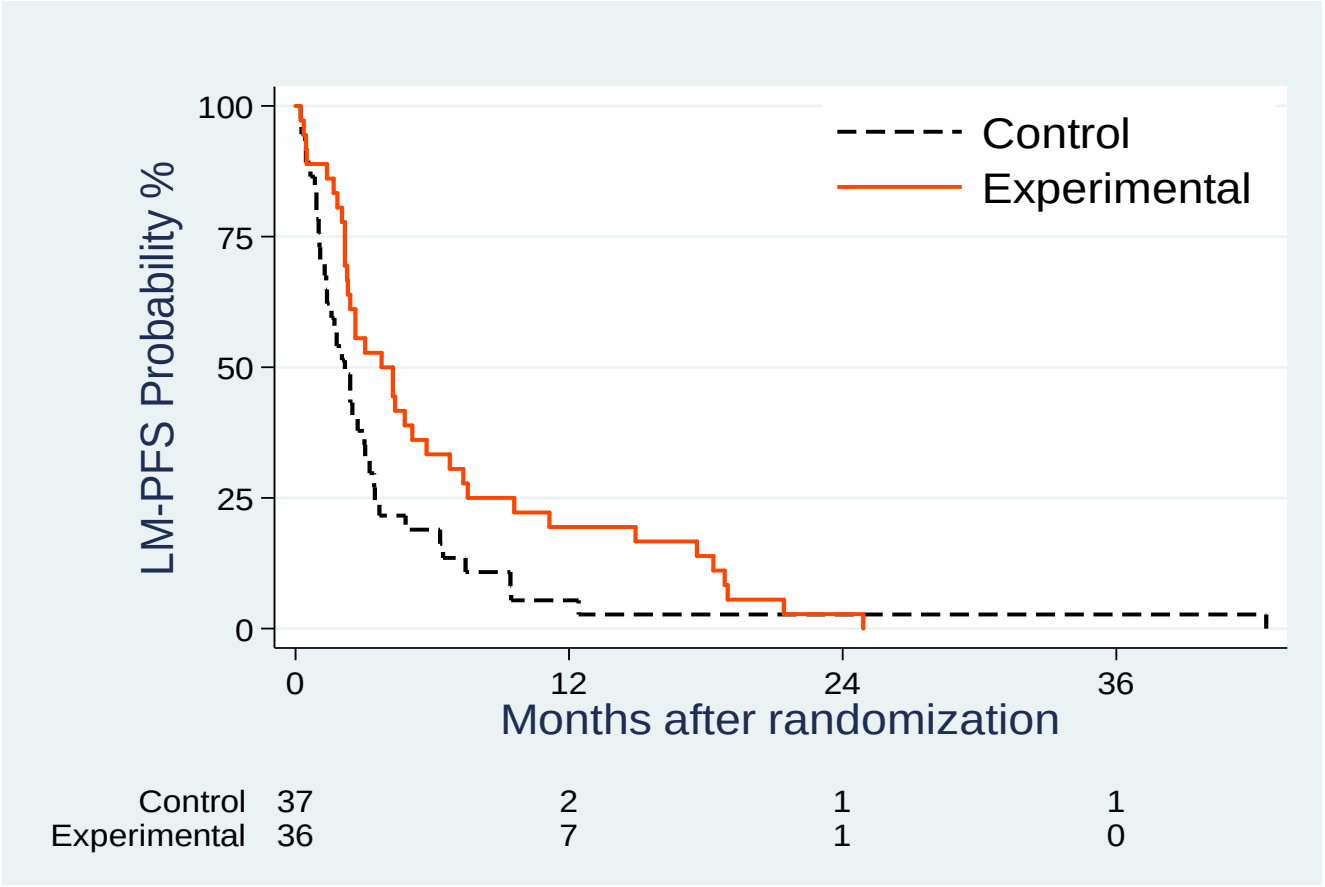
CONSORT CHART



BASELINE CHARACTERISTICS

	Control (n=37)	Depocyte (n=36)
Breast cancer history		
Age at breast cancer (BC) diagnosis in years, median (range)	48 (30 – 84)	51 (30 – 75)
Invasive ductal carcinoma / invasive lobular carcinoma, n (%)	23 (62%) / 9 (24%)	22 (61%) / 9 (25%)
Triple-negative tumors, n (%) (8 pts with incomplete data)	5 (16%)	4 (12%)
Metastases at breast cancer diagnosis, n (%)	5 (14%)	8 (22%)
Time interval between BC diagnosis and LM diagnosis in years, median (range)	4.5 (0.4 – 25)	7.3 (0.1 – 24)
Number of lines of systemic therapy before LM diagnosis, median (range)	3 (1 – 11)	2 (0 – 8)
LM presentation		
Age at LM diagnosis in years, median (range)	59 (31 – 87)	57 (41 – 76)
Neurological symptoms or signs, n (%)	33 (89%)	34 (94%)
MRI findings suggestive of LM diagnosis, n (%)	37 (100%)	34 (94%)
CSF cytology at LM diagnosis prior to randomisation, n (%) - Positive - Equivocal - Negative	 28 (76%) 3 (8%) 6 (16%)	 25 (69%) 2 (6%) 9 (25%)
Patient characteristics at LM diagnosis		
WHO-PS at LM diagnosis: 3-4, n (%)	0	1 (3%)
Brain metastases at LM diagnosis, n (%)	8 (22%)	6 (17%)
Other known non-CNS metastatic sites at LM diagnosis, n (%)	35 (95%)	34 (94%)
LM as the first site of metastasis one of the initial sites of metastasis, n (%)	1 (3%)	1 (3%)

Leptomeningeal Progression-Free Survival



HR=0.61
(95%CI: 0.38 – 0.98)
P=0.04

Median (95% CI)
2.2 (1.3 – 3.1)
4.3 (2.3 – 5.7)

DEPOSEIN- CONCLUSIONS

- Significant reduction in the risk of LM-progression with Intra-CSF liposomal cytarabine

- Trend for a benefit also in terms of PFS when considering progression at any site

- Study underpowered to demonstrate a benefit in terms of OS

- Manageable toxicity

- Quality of life preserved despite more intensive therapy

Limits

- Open-label study with unblinded evaluation

- LM-PFS questionable as main endpoint, even though intra-CSF liposomal cytarabine is a local treatment

- Challenge to assess the leptomeningeal response without validated tools

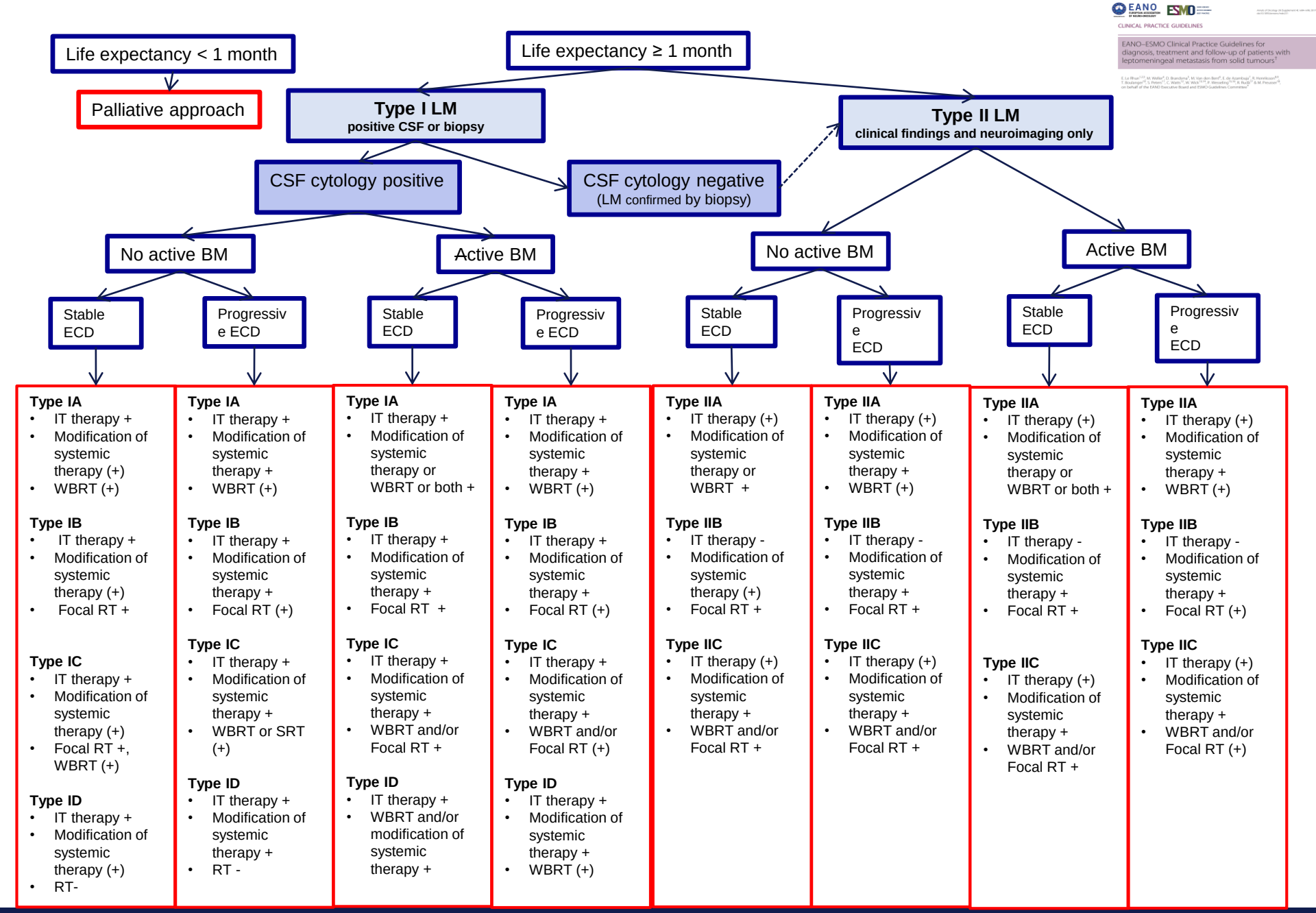
- Liposomal cytarabine no longer available at the moment. Can these findings be extrapolated to standard cytarabine?

Supportive care

- When required clinically, the lowest dose of steroids should be used for the shortest time possible.

- Seizures should be managed using drugs that do not interact with systemic treatments. Primary prophylaxis is not recommended.

- Ventriculoperitoneal shunting may provide durable relief from symptomatic hydrocephalus



EANO ESMO
CLINICAL PRACTICE GUIDELINES
EANO–ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours

Follow-up of LM

EANO ESMO	**Neurological assessment: LANO grid** **Cerebrospinal MRI: standardized grid** **CSF cytology: positive, negative, equivocal** **Evaluation every 2-3 months**

Response Assessment

Table 5. EANO–ESMO response assessment in LM[a]

Clinical	Imaging	CSF	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 more than 2 weeks
Improved or stable	Improved or stable	Worse	Suspicion of progression, or progression in case of *de novo* appearance of tumour cells in the CSF[b]	Continue treatment, change treatment if appearance of tumour cells is confirmed on two consecutive CSF studies from the same CSF site (lumbar or ventricular) at least 4 weeks apart
Worse	Improved or stable	Worse	Suspicion of progression, or progression in case of *de novo* appearance of tumour cells in the CSF[b]	Consider alternative neurological diagnoses, continue treatment; change treatment if there is worsening of clinical signs for more than 2 weeks and if appearance of tumour cells is confirmed on two consecutive CSF studies from the same CSF site (lumbar or ventricular) at least 4 weeks apart
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

Conclusions

- Different subtypes of LM should be considered according to the results of cytology and MRI
- Management strategies for individual patients should be derived by integrating:
    - general and neurological health status
    - CSF findings
    - neuroimaging findings
    - absence or presence of solid brain and systemic metastases
    - histology and molecular status of the primary tumor
    - previous treatments
- A standardized follow-up should be considered