Leptomeningial carcinomatosis: standards of care

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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.

The following for-profit companies have supported clinical trials and contracted research conducted by MP with payments made to his institution: Böhringer-Ingelheim, Bristol-Myers Squibb, Roche, Daiichi Sankyo, Merck Sharp & Dome, Novocure, GlaxoSmithKline, AbbVie.
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

Breast cancer
Lung cancer
CUP
GI cancer
Sarcoma
GU cancer
Other
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....
Leptomeningeal metastases: a RANO proposal for response criteria

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>
<thead>
<tr>
<th>Domain</th>
<th>Level of Function Score</th>
<th>Key Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait</td>
<td>Normal</td>
<td>3. Walking is likely assessed by at least 10 steps.</td>
</tr>
<tr>
<td>Strength</td>
<td>Normal</td>
<td>3. Each limb should be tested separately.</td>
</tr>
<tr>
<td>Sensation</td>
<td>Normal</td>
<td>3. Sensory modality includes but is not limited to touch, proprioception, and pain.</td>
</tr>
<tr>
<td>Vision</td>
<td>Normal</td>
<td>3. Patients who require corrective lenses should be evaluated while wearing corrective lenses.</td>
</tr>
<tr>
<td>Eye movements</td>
<td>Normal</td>
<td>2. The score will reflect the worst performing eye (i.e., the high test ear).</td>
</tr>
<tr>
<td>Facial strength</td>
<td>Normal</td>
<td>1. Weakness includes nasolabial fold flattening, asymmetric smile, and difficulty elevating eyebrow.</td>
</tr>
<tr>
<td>Hearing</td>
<td>Normal</td>
<td>1. Each ear should be evaluated and score should reflect worst performing ear.</td>
</tr>
<tr>
<td>Swallowing</td>
<td>Normal</td>
<td>1. Bicarbonate testing comprising swallowing test with a small glass of water.</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Normal</td>
<td>1. Alteration includes but is not limited to aphasia, disorientation, and confusion.</td>
</tr>
<tr>
<td>Behavior</td>
<td>Normal</td>
<td>3. Consider subclinical features for significant alteration.</td>
</tr>
<tr>
<td>Other</td>
<td>Normal</td>
<td>1. No other neurological findings.</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th><strong>EANO ESMO</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain</strong></td>
<td>axial, coronal and sagittal T1 without and with contrast enhancement, axial T2, axial and coronal FLAIR</td>
</tr>
<tr>
<td><strong>Spine</strong></td>
<td>sagittal T2 and T1 without and with contrast</td>
</tr>
</tbody>
</table>

RANO grid, Chamberlain et al., 2017
# Imaging methodology

## Table 2. MRI parameters in leptomeningeal disease

<table>
<thead>
<tr>
<th>MRI prerequisites</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5T and 3T MR scanners only</td>
</tr>
<tr>
<td>Use of same MRI at baseline and follow-up</td>
</tr>
<tr>
<td>MRI to be performed prior to lumbar puncture</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended MRI sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain</strong></td>
</tr>
<tr>
<td>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)</td>
</tr>
<tr>
<td>Reformatted slice thickness 3 mm to obtain good signal to noise ration and manageable number of slices for full brain coverage</td>
</tr>
<tr>
<td>IV contrast dose = 0.1 mmol/kg of gadolinium-based agent.</td>
</tr>
<tr>
<td><strong>Spine</strong></td>
</tr>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>
LM patterns

- Diffuse/fluid
- Solid
- Adherent
# Imaging evaluation: RANO grid

## Table 3. Scorecard for radiographic assessment in leptomeningeal metastases

<table>
<thead>
<tr>
<th>MRI Findings</th>
<th>Present (1) or Absent (0) or Non-evaluable (NE)</th>
<th>Dimensions Of Measurable Nodules Defined as &gt;5 x 10 mm (orthogonal diameters)</th>
<th>Change from Previous MRI (−3 to +3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAIN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodules (subarachnoid or ventricular)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptomeningeal enhancement*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial nerve enhancement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus^</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenchymal (brain metastases)^</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SPINE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodules (subarachnoid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptomeningeal enhancement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve root enhancement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenchymal(intramedullary metastases)^</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidural metastasis ^</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL SCORE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL PRACTICE GUIDELINES

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

E. Le Rhun¹,²,³, M. Weller⁴, D. Brandsma⁵, M. Van den Bent⁶, E. de Azambuja⁷, R. Henriksson⁸,⁹, T. Boulanger¹⁰, S. Peters¹¹, C. Watts¹², W. Wick¹³,¹⁴, P. Wesseling¹⁵,¹⁶, R. Rudà¹⁷ & M. Preusser¹⁸, on behalf of the EANO Executive Board and ESMO Guidelines Committee*
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)

<table>
<thead>
<tr>
<th>Technical aspects</th>
<th>EANO ESMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>- fresh CSF samples processed within 30 minutes after sampling; alternatively, fresh CSF samples fixed with Ethanol-Carbowax</td>
<td></td>
</tr>
<tr>
<td>- CSF volume &gt; 10 ml (at least 5 ml)</td>
<td></td>
</tr>
<tr>
<td>- routine stainings: Papanicolaou and Giemsa; additional immunocytochemical stainings (upon indication and availability of material)</td>
<td></td>
</tr>
<tr>
<td>- a second CSF sample should be analyzed if the initial CSF sample is negative for diagnosis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interpretation of the results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- positive (presence of tumor cells)</td>
<td></td>
</tr>
<tr>
<td>- equivocal (suspicious or atypical cells)</td>
<td></td>
</tr>
<tr>
<td>- negative (absence of tumor cells)</td>
<td></td>
</tr>
</tbody>
</table>
## Classification of LM: EANO ESMO Proposal

### Table 2. Diagnostic criteria for LM

<table>
<thead>
<tr>
<th></th>
<th>Cytology/biopsy</th>
<th>MRI</th>
<th>Confirmed</th>
<th>Probable&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Possible&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Lack of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I:</strong> positive</td>
<td>IA +</td>
<td>Linear</td>
<td>yes</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>CSF cytology or biopsy</td>
<td>IB +</td>
<td>Nodular</td>
<td>yes</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>IC +</td>
<td>Linear + nodular</td>
<td>yes</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>ID +</td>
<td>Normal</td>
<td>yes</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Type II:</strong> clinical findings and neuroimaging only</td>
<td>IIA − or equivocal</td>
<td>Linear</td>
<td>n/a</td>
<td>With typical clinical signs</td>
<td>Without typical clinical signs</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>IIB − or equivocal</td>
<td>Nodular</td>
<td>n/a</td>
<td>With typical clinical signs</td>
<td>Without typical clinical signs</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>IIC − or equivocal</td>
<td>Linear + nodular</td>
<td>n/a</td>
<td>With typical clinical signs</td>
<td>Without typical clinical signs</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>IID − or equivocal</td>
<td>Normal</td>
<td>n/a</td>
<td>With typical clinical signs</td>
<td>Without typical clinical signs</td>
<td>n/a</td>
</tr>
</tbody>
</table>

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.

<sup>a</sup>Requires a history of cancer.

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

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without tumour-specific treatment</td>
<td>6-8 weeks</td>
</tr>
<tr>
<td>Breast cancer with treatment</td>
<td>1.5-4.5 months</td>
</tr>
<tr>
<td>Lung cancer with treatment</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Melanoma with treatment</td>
<td>1.7-2.5 months</td>
</tr>
</tbody>
</table>

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

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

CSF, cerebrospinal fluid; thioTEPA, thiotriethylene phosphoramid.
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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Population</th>
<th>Primary endpoint</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grossman 1993</td>
<td>IT MTX versus IT thiotepa</td>
<td>Solid tumors (n=40), CUPS (n=1) and lymphomas (n=10)</td>
<td>Neurological response rate</td>
<td>IT MTX vs. IT thiotepa: Neurological response rate: none, Neurological stabilization: 32% vs. 12.5%, Survival: 15.9 weeks vs. 14.1 weeks</td>
<td>IT MTX vs. IT thiotepa: Serious toxicities similar in both groups, Mucositis (p=0.04) and neurological complications (p=0.008) more frequent in MTX arm</td>
</tr>
<tr>
<td>Hitchins 1997</td>
<td>IT MTX versus IT MTX + cytarabine</td>
<td>Solid tumors (n=30), cancers of unknown primaries (n=7) and lymphomas (n=7)</td>
<td>Response rate</td>
<td>IT MTX vs. MTX + cytarabine: Response rate: 61 vs. 45% (p&lt;0.05), Median survival: 12 vs. 7 weeks (p&lt;0.05)</td>
<td>IT MTX vs. MTX + cytarabine: Nausea and vomiting: 36% vs. 50%, Septicemia, neutropenia: 9% vs. 15%, Mucositis: 14% vs. 10%, Pancytopenia: 9% vs. 10%</td>
</tr>
<tr>
<td>Glantz 1999</td>
<td>IT liposomal cytarabine versus IT MTX</td>
<td>Solid tumors (n=61)</td>
<td>Response rate at the end of the induction period</td>
<td>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)</td>
<td>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)</td>
</tr>
<tr>
<td>Boogerd 2004</td>
<td>IT MTX versus no IT</td>
<td>Breast cancers (n=35)</td>
<td>Overall survival: time from randomization until death</td>
<td>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)</td>
<td>IT MTX vs. no IT: Neurological complications: 47% vs 6% (p = 0.0072)</td>
</tr>
<tr>
<td>Shapiro 2006</td>
<td>solid tumors: IT liposomal cytarabine versus IT MTX (lymphomas: IT liposomal cytarabine versus IT aracytine)</td>
<td>Solid tumors (n=103) and lymphomas (n=25)</td>
<td>Progression free survival: randomized to neurological progression or death</td>
<td>IT liposomal cytarabine versus IT MTX or aracytine: Median progression free survival: 35 vs. 43 days (p=0.7321)</td>
<td>IT liposomal cytarabine versus IT control: Drug related AE: 48% vs. 60% of the serious AE: 86 vs. 77%</td>
</tr>
</tbody>
</table>
Intrathecal liposomal cytarabine plus systemic therapy versus systemic chemotherapy alone for leptomeningeal metastasis from breast cancer - a randomized study. Final results

DESIGN OF DEPO-SEIN (NCT01645839)

- Phase III randomised controlled open-label trial

Patients with newly diagnosed LM from breast cancer

Control arm
systemic treatment* alone

R
(1:1)

Depocyte arm
systemic treatment* combined with intra-CSF liposomal cytarabine**

* 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
Patients recruited between 08/2011 and 02/2018
N=74

Allocated to the control arm, N=37

Included in the control arm, N=37

Treated according to the protocol, N=35
Did not receive systemic treatment, N=1
Received Intra-CSF injections, N=1

Intention-to-treat analysis, N=37
Per protocol analysis, N=35

Allocated to the Depocyte arm, N=37

Consent withdrawal, N=1

Included in the Depocyte arm, N=36
Including 1 patient with WHO-PS=4

Treated according to the protocol, N=33
Did not receive systemic treatment, N=3

Intention-to-treat analysis, N=36
Per protocol analysis, N=32
## BASELINE CHARACTERISTICS

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

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

HR = 0.61
(95% CI: 0.38 – 0.98)
P = 0.04
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
Life expectancy < 1 month

Palliative approach

Type I LM
positive CSF or biopsy

CSF cytology positive

No active BM
Stable ECD

Progressive ECD

Active BM
Stable ECD
Progressive ECD

Life expectancy ≥ 1 month

Type II LM
clinical findings and neuroimaging only

CSF cytology negative
(LM confirmed by biopsy)

No active BM
Stable ECD
Progressive ECD

Active BM
Stable ECD
Progressive ECD

Type IA
• IT therapy +
• Modification of systemic therapy (+)
• WBRT (+)

Type IB
• IT therapy +
• Modification of systemic therapy +
• Focal RT (+)

Type IC
• IT therapy +
• Modification of systemic therapy +
• Focal RT (+), WBRT (+)

Type ID
• IT therapy +
• Modification of systemic therapy +
• RT -

Type IA
• IT therapy +
• Modification of systemic therapy +
• WBRT (+)

Type IB
• IT therapy +
• Modification of systemic therapy +
• Focal RT +

Type IC
• IT therapy +
• Modification of systemic therapy +
• WBRT or SRT (+)

Type ID
• IT therapy +
• Modification of systemic therapy +
• WBRT (+)

Type IA
• IT therapy (+)
• Modification of systemic therapy +
• WBRT (+)

Type IB
• IT therapy +
• Modification of systemic therapy +
• Focal RT +

Type IC
• IT therapy +
• Modification of systemic therapy +
• WBRT and/or Focal RT +

Type ID
• IT therapy +
• Modification of systemic therapy +
• WBRT (+)

Type IA
• IT therapy +
• Modification of systemic therapy or
• WBRT or both +

Type IB
• IT therapy +
• Modification of systemic therapy +
• Focal RT +

Type IC
• IT therapy +
• Modification of systemic therapy +
• Focal RT +

Type ID
• IT therapy +
• Modification of systemic therapy +
• RT -

Type IA
• IT therapy (+)
• Modification of systemic therapy or
• WBRT or both +

Type IB
• IT therapy -
• Modification of systemic therapy +
• Focal RT +

Type IC
• IT therapy +
• Modification of systemic therapy +
• WBRT or SRT (+)

Type ID
• IT therapy +
• Modification of systemic therapy +
• RT -

Type IA
• IT therapy (+)
• Modification of systemic therapy +
• WBRT (+)

Type IB
• IT therapy -
• Modification of systemic therapy +
• Focal RT +

Type IC
• IT therapy +
• Modification of systemic therapy +
• WBRT and/or Focal RT +

Type ID
• IT therapy +
• Modification of systemic therapy +
• WBRT (+)

Type IA
• IT therapy (+)
• Modification of systemic therapy +
• WBRT (+)

Type IB
• IT therapy -
• Modification of systemic therapy +
• Focal RT +

Type IC
• IT therapy +
• Modification of systemic therapy +
• WBRT +

Type ID
• IT therapy +
• Modification of systemic therapy +
• RT -
Follow-up of LM

| EANO ESMO | Neurological assessment: LANO grid  
| | Cerebrospinal MRI: standardized grid  
| | CSF cytology: positive, negative, equivocal  
| | Evaluation every 2-3 months |
## Table 5. EANO–ESMO response assessment in LM

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Imaging</th>
<th>CSF</th>
<th>Response determination</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved or stable</td>
<td>Improved</td>
<td>Improved or stable</td>
<td>Response</td>
<td>Continue treatment</td>
</tr>
<tr>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Stable</td>
<td>Continue treatment</td>
</tr>
<tr>
<td>Worse</td>
<td>Improved or stable</td>
<td>Improved or stable</td>
<td>Suspicion of progression</td>
<td>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</td>
</tr>
<tr>
<td>Improved or stable</td>
<td>Improved or stable</td>
<td>Worse</td>
<td>Suspicion of progression, or progression in case of <em>de novo</em> appearance of tumour cells in the CSF</td>
<td>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</td>
</tr>
<tr>
<td>Worse</td>
<td>Improved or stable</td>
<td>Worse</td>
<td>Suspicion of progression, or progression in case of <em>de novo</em> appearance of tumour cells in the CSF</td>
<td>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</td>
</tr>
<tr>
<td>Improved or stable</td>
<td>Worse</td>
<td>Improved or stable</td>
<td>Progression</td>
<td>Change treatment</td>
</tr>
<tr>
<td>Improved or stable</td>
<td>Worse</td>
<td>Worse</td>
<td>Progression</td>
<td>Change treatment</td>
</tr>
<tr>
<td>Worse</td>
<td>Worse</td>
<td>Improved or stable or worse</td>
<td>Progression</td>
<td>Change treatment</td>
</tr>
</tbody>
</table>
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