Diagnosis and Treatment of Leptomeningeal Disease – Where are we in 2024?

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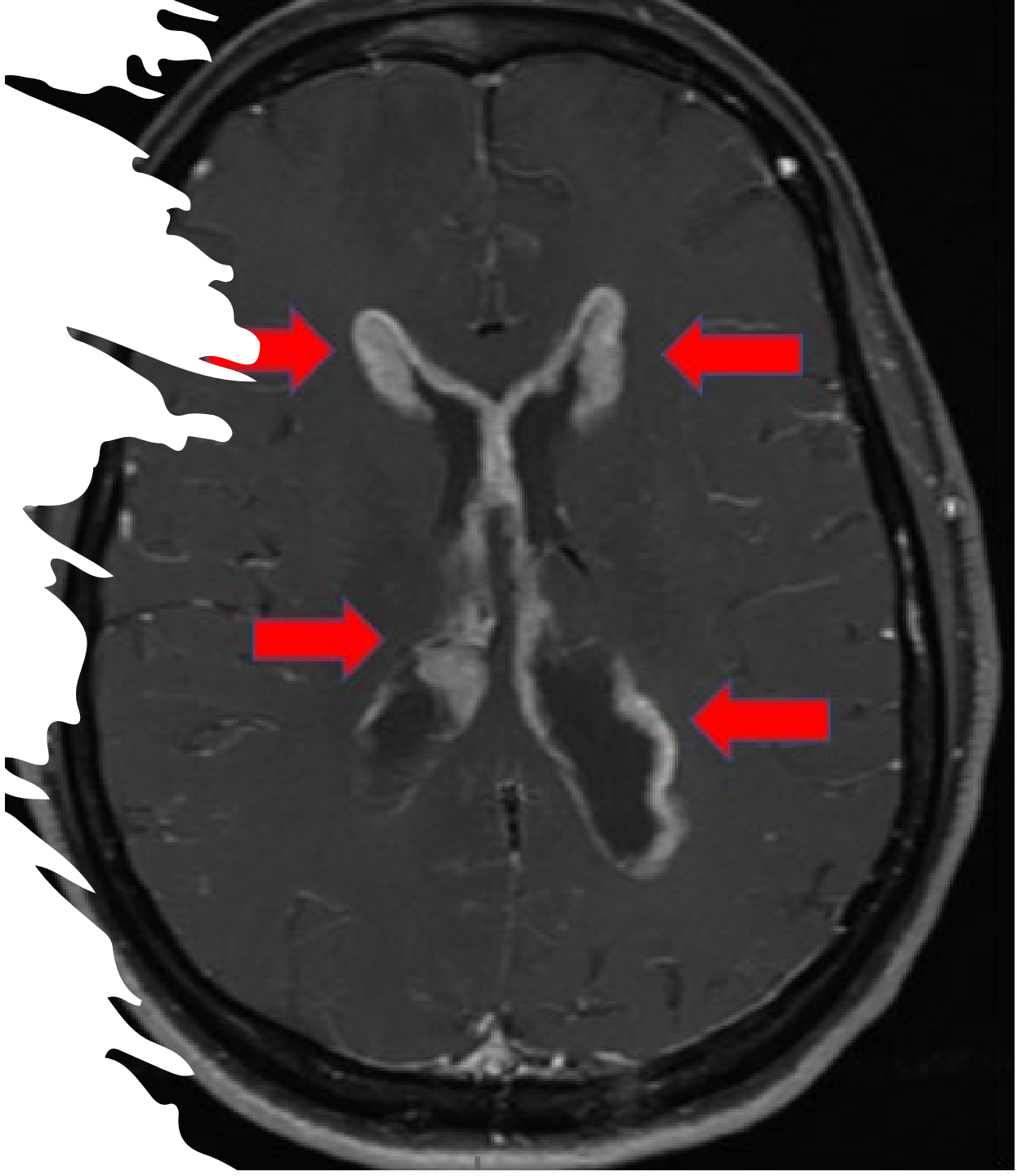
Disclosures

Speaker/Consultant:
Pfizer, Novartis, Biodexa, Everclear(

Advisory Board:
Bristol Myers Squibb, Novartis, Pfizer



Incidence

Type of cancer	Frequency of LM (%)
Melanoma	22-46
Small-cell lung cancer	10-25
Breast carcinoma	5
Nonsmall-cell lung cancer	1
Head and neck cancer	1

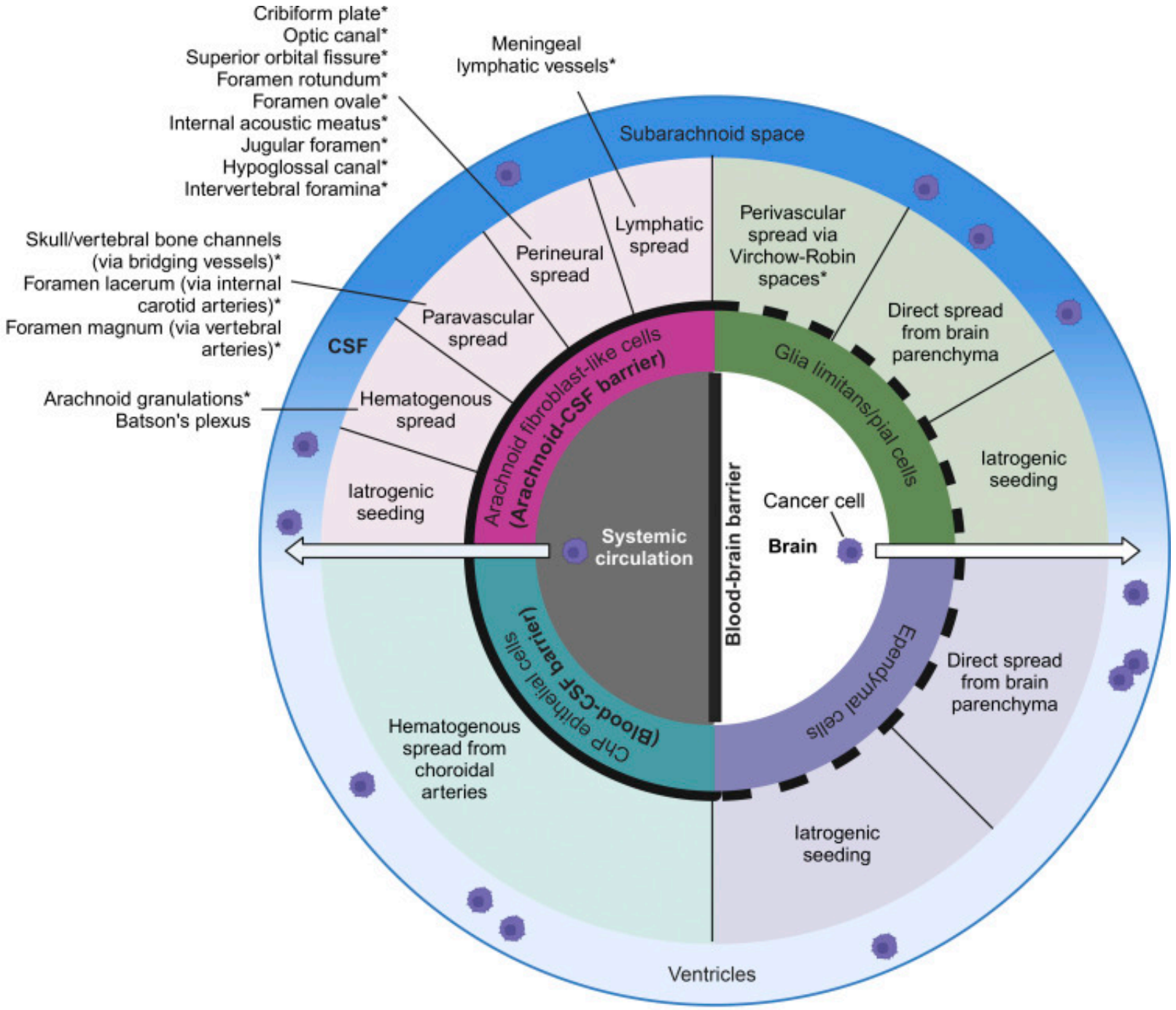
- **Late in disease course**
- **Brain parenchymal metastases may be associated with LMD in up to 82%**

- Reported incidence of LMD is rising across all tumor types
  - Improved detection
  - Better controlled systemic disease

Lack of sufficient clinical trial options for melanoma patients with LMD (and other cancers)

Surg Neurol Int. 2013 May 2;4(Suppl 4):S265-88. doi: 10.4103/2152-7806.111304. Print 2013. **Carcinomatous meningitis: Leptomeningeal metastases in solid tumors.** Le Rhun E[1], Taillibert S, Chamberlain M

LMD-Pathogenesis



Freret ME, Boire A. The anatomic basis of leptomeningeal metastasis. J Exp Med. 2024 Apr 1;221(4

LMD- Overall Survival across tumor types

- The median overall survival (OS) of untreated patients with LM is 4-6 weeks.
- Despite aggressive treatment, LM has a poor prognosis.
- The survival of patients with combined treatment is usually less than 8 months with a median OS of 2-3 months

Table 4: Median OS in the main cohorts of LM according to the primary type of tumor

Type of the primitive tumor	References	Recruitment of the patients	Median overall survival (
All types	Wasserstrom *et al*., 1982	90 patients from 1975 to 1980	5.8 months (1-29)
	Hitchins *et al*., 1987	44 patients	8 weeks
	Liaw *et al*.,[179] 1992	41 patients from 1984 to 1990	4 weeks
	Grossman *et al*., 1993	52 patients	14.1-15.9 weeks
	Chamberlain 2002	22 patients from 1995-2001	16 weeks
	Glantz *et al*., 1999	61 patients from 1994 to 1996	78-105 days
	Kim *et al*., 2003	55 patients from 1995 to 2002	11.9 weeks (2.7-28.7)
	Herrlinger *et al*., 2004	155 patients from 1980 to 2002	4.8 months
	Lassman *et al*.,[174] 2006	32 patients from 1999 to 2003	19.9 weeks (2.9-135.4)
	Groves *et al*., 2008	62 patients from 2001 to 2006	15 weeks (95% CI, 13-24w
	Waki *et al*., 2009	85 patients from 1995 to 2005	51 days (3-759 days)
	Clarke *et al*., 2010	187 patients from 2002 to 2004	2,4 months (95% IC 1.9-3.
	Oeschle *et al*., 2010	135 patients from 1989 to 2005	2.5 months
	Jimenez Mateos *et al*.,[153] 2011	37 patients from 1990 to 2008	12.6 weeks
	Gani *et al*.,[106] 2012	27 patients	8.1 weeks
	Segura *et al*., 2012	19 patients	43 days (95% IC 28-57.3)
Breast cancer	Boogerd *et al*., 2004	35 patients from 1991 to 1998	18.3-30.3 weeks
	Grossman 1982	52 patients	14.1-15.9 weeks
	Clamon *et al*.,[71] 1987	22 patients	21-150 days
	Boogerd 1991	58 patients	12 weeks
	Jayson[152] 1994	35 patients	77 days
	Chamberlain 1997	32 patients	7.5 months (1.5-16)
	Jaeckle 2001	43 patients from 1994 to 1999	7 weeks
	Regierer[231] 2008	27 patients from 1998 to 2005	9 weeks
	Rudnicka *et al*., 2007	67 patients from 2000 to 2005	16 weeks (1-402)
	De Azevedo *et al*., 2011	60 patients from 2003 to 2009	3.3 months (0.03-90,4)
	Clatot *et al*., 2009	24 patients from 1999 to 2008	150 days (9-561)
	Gauthier *et al*., 2010	91 patients from 2000 to 2007	4.5 months (0-53)
	Lee *et al*., 2011	68 patients from 1995 to 2008	4.1 months (2.2-5.8 month
	Kim *et al*.,[163] 2012	30 patients from 1981 to 2009	8 months
Melanoma	Chamberlain *et al*., 1996	16 patients from 1986-1995	4 months
	Harstad 2008	110 patients from 1944 to 2002	10 weeks (95% IC, 8-14)
Lung cancer	Rosen *et al*., 1982	60 patients from 1969 to 1980	7 weeks
	Chamberlain *et al*., 1998	32 patients	5 months (1-12)
	Hammerer[135] 2005	26 patients	57 weeks (NA)
	Sudo *et al*.,[272] 2006	37 patients from 2001 to 2005	106 days (10-392)
	Chuang *et al*.,[70] 2008	34 patients from 1992 to 2002	5.1 weeks (1 day-82 week
	Morris 2012	50 patients from 2003 to 2009	3 months (95% IC, 2.0-4.0
	Park 2012	125 patients from 2002 to 2009	4.3 months (1.5-6.7)

Le Rhun E, Taillibert S, Chamberlain MC. Carcinomatous meningitis: Leptomeningeal metastases in solid tumors. Surg Neurol Int. 2013 May 2;4(Suppl 4):S265-88.

Importantly- Survival has not improved over the last decade

	Ferguson et al	Chorti et al	Foppen et al	Tetu et al	Glitza et al
Year of Diagnosis	**2009-2015**	**2011-2019**	**2010-2015**	**2013-2020**	**2015-2020**
# of patients	178	52	39	29	172
Male Gender	62%	58%	59%	62%	60%
Median Age at LMD diagnosis	**51** (18-89)	**58** (32-85)	**52.9** (26–84)	**55** (50-67)	**53** (range: 20-79)
BRAF Mutant	67%	65%	14 pts received BRAF/MEKi	45%	66%
% of patients with prior therapy	79%	81%	71%	52%	84%
Median Overall Survival	**3.5 months**	**2.9 months**	**6. 9 weeks**	**5.1 months**	**4.9 months**

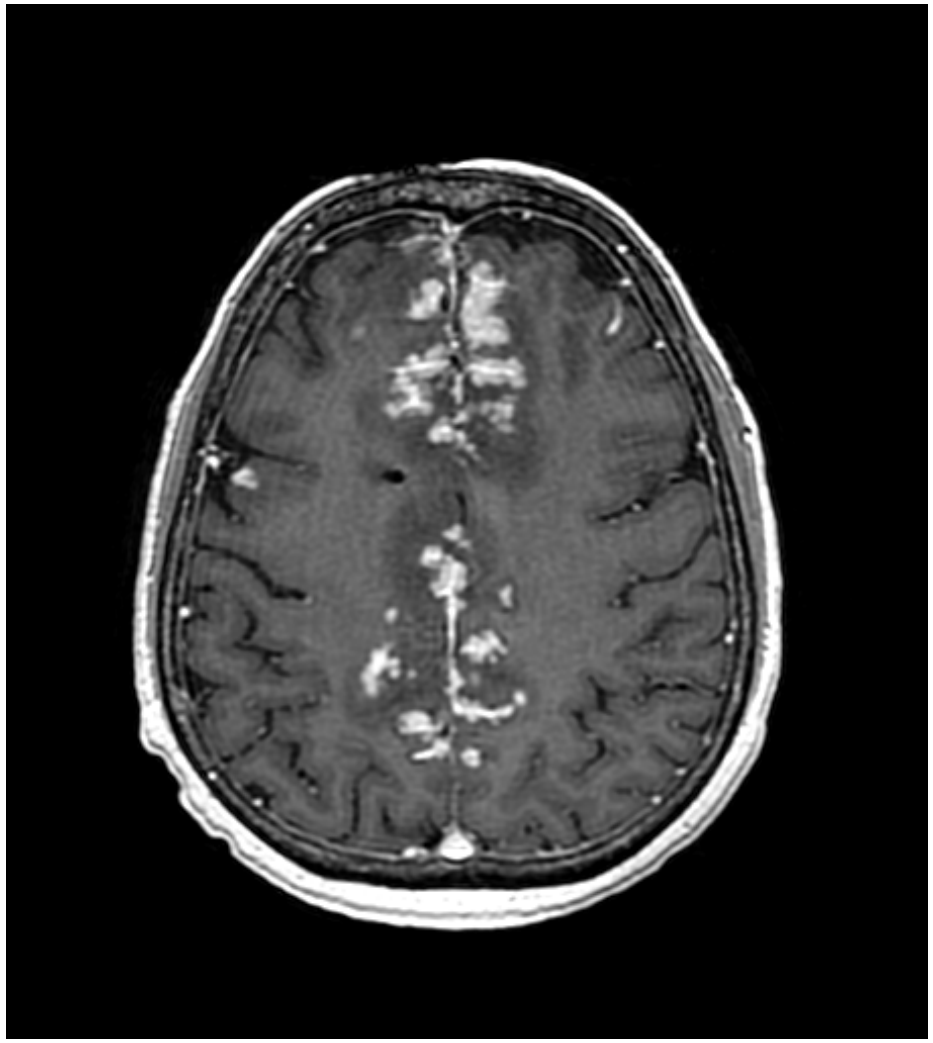
Melanoma patients only

Chorti E et al. *Eur J Cancer*. 2021;148:395-404
Ferguson SD et al. *J Neurooncol*. 2019;142(3):499
Geukes Foppen MH et al. Ann Oncol. 2016 Jun;27(6):1138-1142
Tétu P,et al. Cancers (Basel). 2020 Sep 16;12(9):2635
Glitza et al. ESMO 2022

Some of the areas we need to think about..

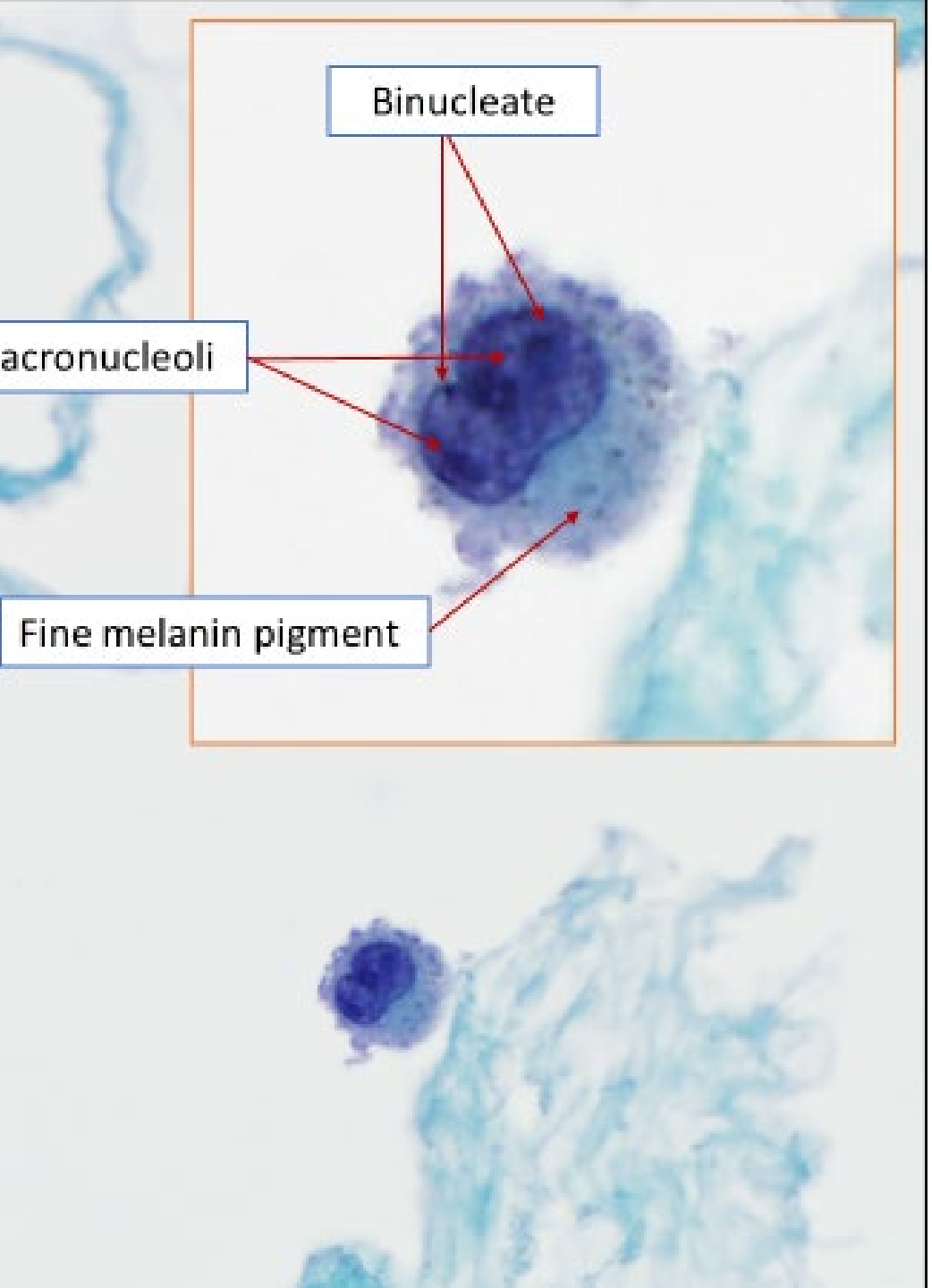
Diagnosis

Patient and Primary Tumor



The leptomeningeal microenvironment

Treatment



Conventional CSF Analysis

Cytology remains Gold-standard

- High specificity >95%
- Low Sensitivity, <50%
- Only ~50% show initially positive cytology
- Up to 3 LPs recommended

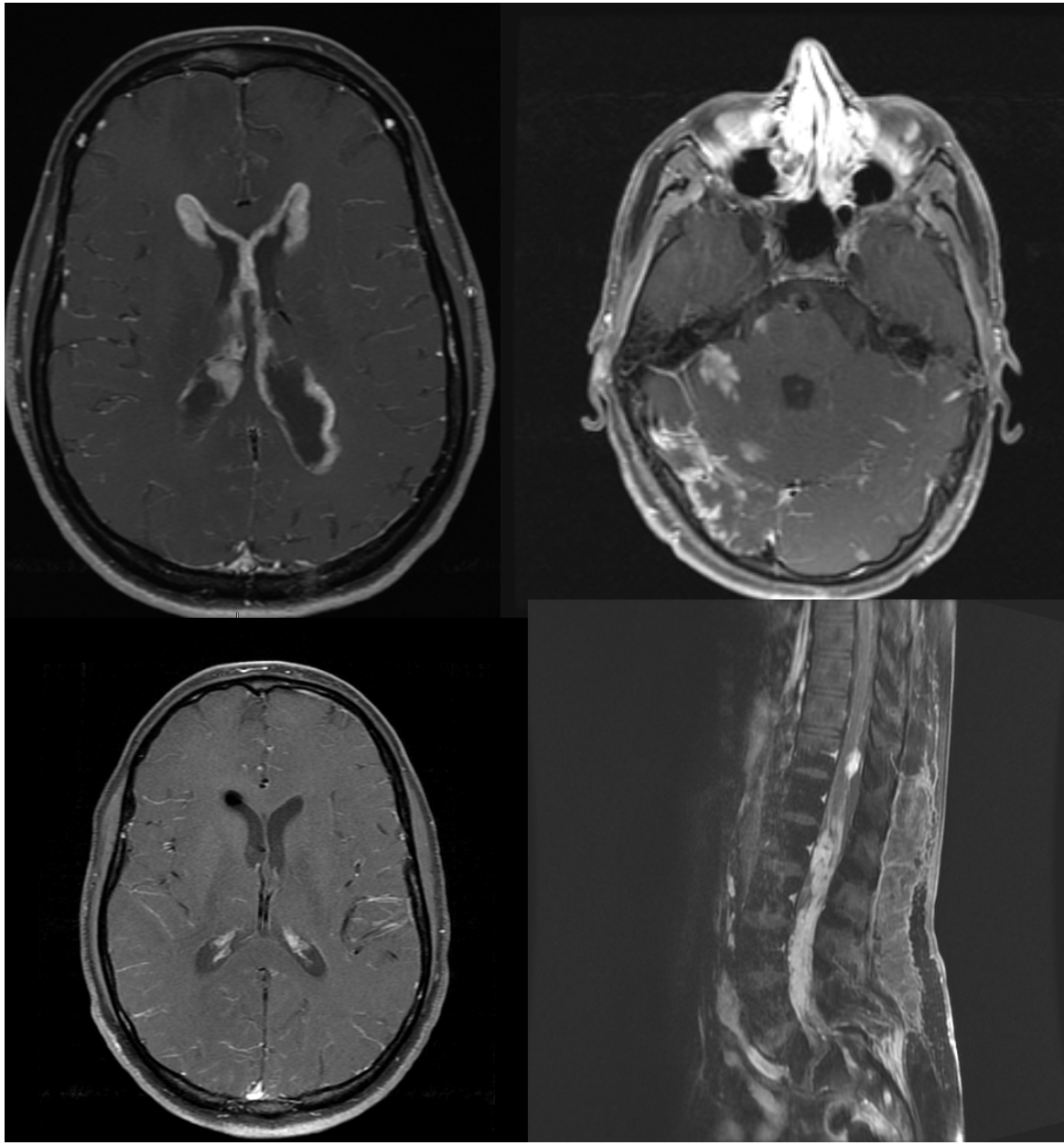
Le Rhun E, Taillibert S, Chamberlain MC. Carcinomatous meningitis: Leptomeningeal metastases in solid tumors. Surg Neurol Int. 2013 May 2;4(Suppl 4):S265-88.

MRI Brain and Spine

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Leptomeningeal Metastases

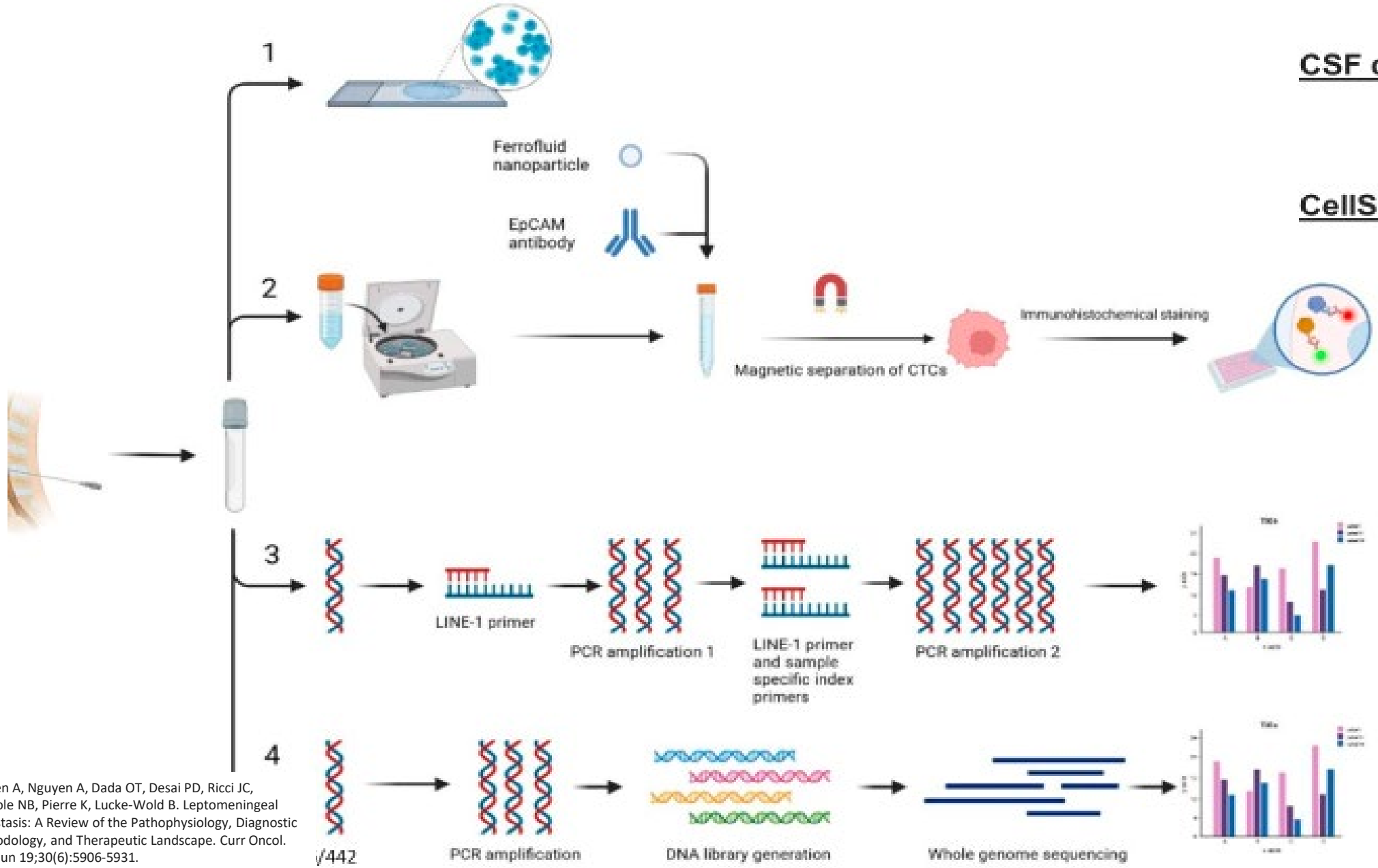
WORKUP		DIAGNOSIS
Signs and symptoms suggestive of leptomeningeal disease[a]	→ • Physical exam with careful neurologic evaluation • Brain and spine MRI if patient is a candidate for active treatment[b] • CSF analysis[c,d,e]	→ CSF positive for tumor cells or Positive radiologic findings with supportive clinical findings or Signs and symptoms with suggestive CSF[f] in a patient known to have a malignancy



- Contrast enhanced T1-weighted and FLAIR sequences are the most sensitive to detect LMD
- Lumbar puncture can cause a meningeal reaction
- Sensitivity varies from 20% to 91%
- A normal MRI does not exclude the diagnosis of LMD

Le Rhun E, Taillibert S, Chamberlain MC. Carcinomatous meningitis: Leptomeningeal metastases in solid tumors. Surg Neurol Int. 2013 May 2;4(Suppl 4):S265-88.

LMD CSF based diagnostic tools



CSF cytology

CellSearch Technology

mFAST-SeqS

ulpWGS

Nguyen A, Nguyen A, Dada OT, Desai PD, Ricci JC, Godbole NB, Pierre K, Lucke-Wold B. Leptomeningeal Metastasis: A Review of the Pathophysiology, Diagnostic Methodology, and Therapeutic Landscape. Curr Oncol. 2023 Jun 19;30(6):5906-5931.

Patient/Primary Tumor

Facts

- Patients develop LMD typically later in the course of their disease
- Had exposure to the currently available agents- mechanism of resistance?
- Performance status
  - Poor overall survival, rapid deterioration
- LMD disease burden can not be compared with extracranial disease

Some risk factors are known

- **Tumor type specific:**
  - Breast: ER/PR/HER2 neg tumors, infiltrating lobular
  - Lung: SCLC
  - Melanoma: BRAF+ mutation
- **Iatrogenic risk:**
  - Piecemeal resection
  - Cerebellar met resection
  - Supratentorial resection with violation of the ventricular system
- Use of medication with **poor CNS penetration**

Unanswered Questions

- How to best monitor patients at high risk?
- How to avoid spread (not just iatrogenic)
  - Is there a role for prophylaxis?
- Should certain medication be avoided?
- How to improve/stabilize performance status for trial enrollment?
- Who are the patients that do better than expected?
- How to best monitor response
  - RANO-LM criteria

The leptomeningeal microenvironment

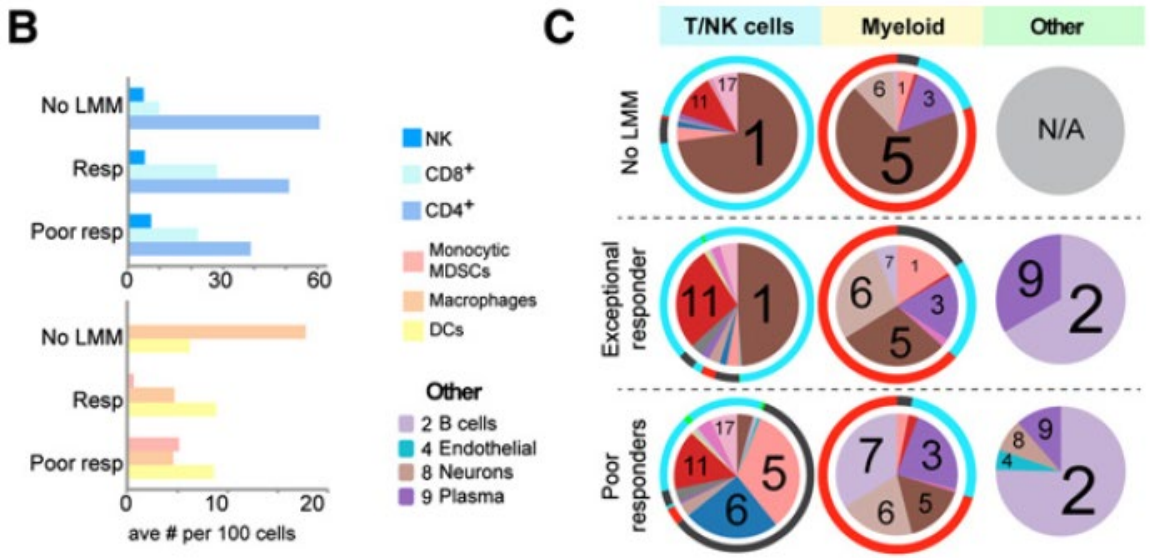
What we know

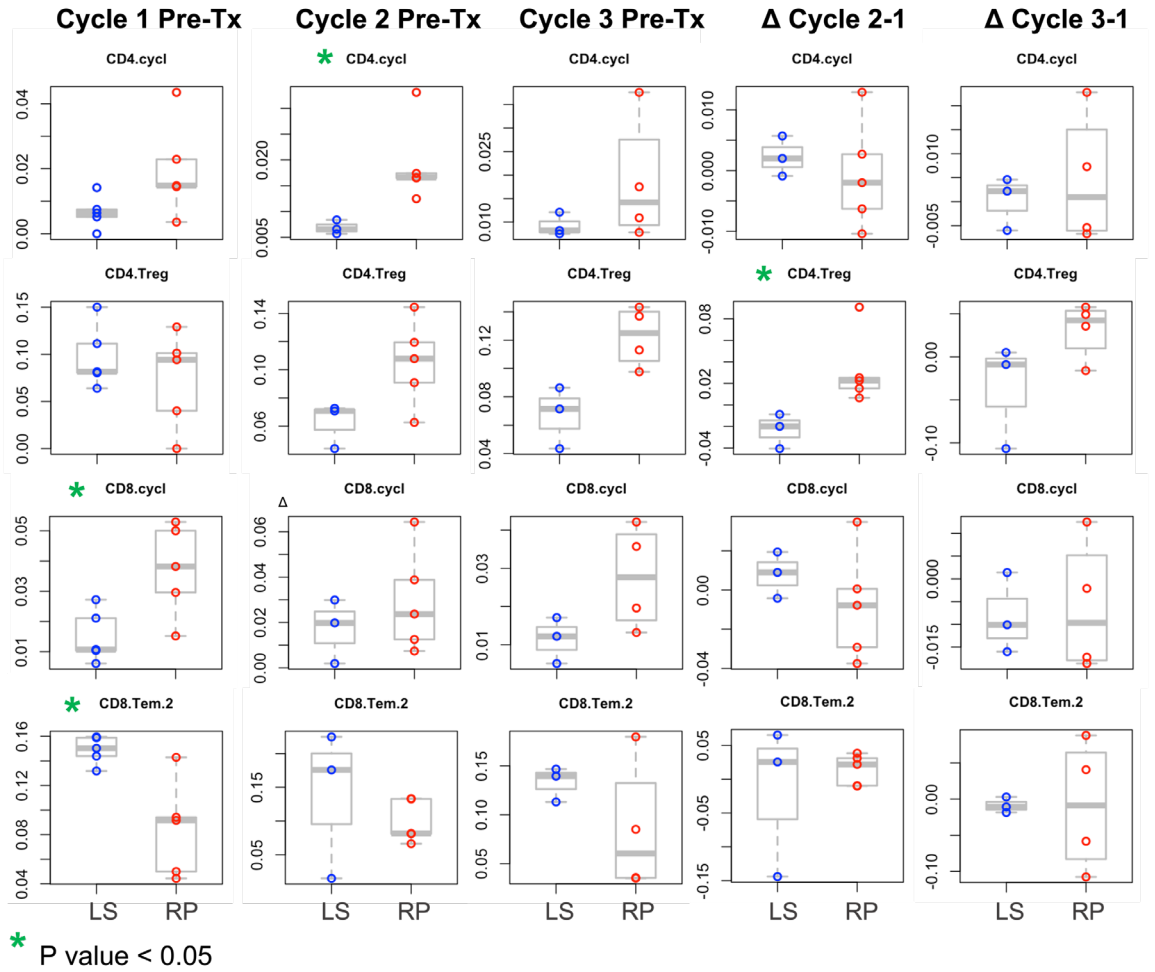
- Immune Cell Population
  - CSF generally cell poor environment
    - But recent data shows T Cells can migrate in and out of the CSF
  - Role of the choroid plexus
- Role of cytokines in the intrathecal space
  - IT Interleukin-2 can increase inflammatory cytokines
- Cancer cells deploy lipocalin-2 to collect limiting iron in leptomeningeal metastasis

Unanswered Questions

- Immune Cell Population and Cytokines in intrathecal space
  - Is this predefined or can we alter it with our treatment?
- How can we enhance the migration of immune cells into the CFS
  - Direct injection of T Cells?
  - Role of Radiation
- Role of cytokines in the intrathecal space
- Do LMD cancer cell use any other resistance/metabolic mechanism for survival?

Baseline CSF microenvironment





LMD patient with long-term OS

- immune repertoire distinct from that of poor survivors
  - more similar to normal cerebrospinal fluid (CSF)
- Upon response to PD-1 showed **increased levels of T cells and dendritic cells in their CSF**, whereas poor survivors showed little improvement in their T-cell responses.

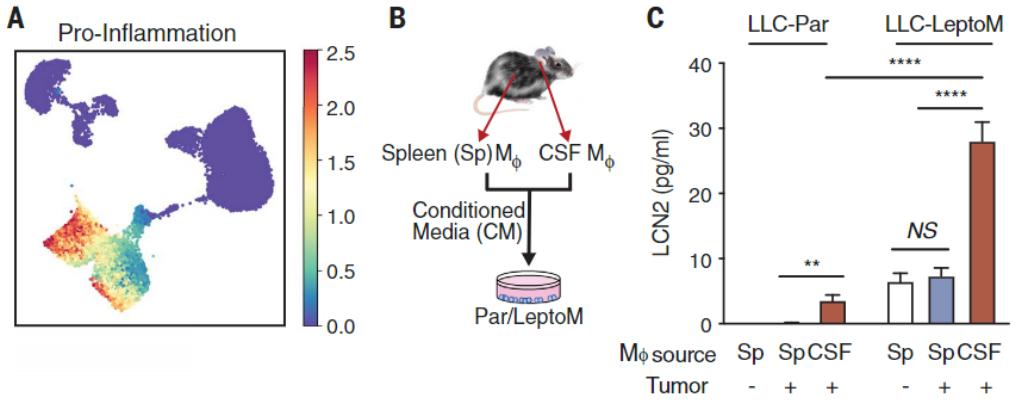
Exploratory single cell analysis of longitudinal CSF samples of LMD patients suggests that **baseline and early on-treatment immune features** may predict **outcomes with intrathecal Nivolumab**

Smalley I et al. Single-Cell Characterization of the Immune Microenvironment of Melanoma Brain and Leptomeningeal Metastases. Clin Cancer Res. 2021 Jul 15;27(14):4109-4125.

Morad et al. J Clin Oncol 41, 2023 (suppl 16; abstr 2015)

The role of iron-binding protein lipocalin-2 (LCN2) and its receptor SCL22A17

- Cancer cells, but not macrophages, within the CSF express the iron-binding protein lipocalin-2(LCN2) and its receptor SCL22A17.
- These macrophages generate inflammatory cytokines that induce cancer cell LCN2 expression but do not generate LCN2 themselves.
- In mouse models of LM, cancer cell growth is supported by the LCN2/SLC22A17 system and is inhibited by iron chelation therapy.



Cancer cells generate LCN2 in response to inflammatory cytokines

Cancer cells appear to survive in the CSF by outcompeting macrophages for iron.

Chi Y et al. Cancer cells deploy lipocalin-2 to collect limiting iron in leptomeningeal metastasis. Science. 2020 Jul 17;369(6501):276-282

The drugs

Unanswered Questions

What is the ”best” route of administration?

- Intrathecal versus systemic
- Half-life of agents used for IT administration
- Formulation for IT administration not available (e.g. BRAF inhibitors)

What if patients have flow obstruction?

Increased CNS penetration of agents- ongoing clinical trials

Combining different treatment modalities (radiation and intrathecal or systemic?)

CNS/CSF Penetration of contemporary agents

Rituximab

Rituximab was detectable after the first infusion in serum and CSF although the CSF rituximab concentration was found to be 400- to 1000-fold lower.

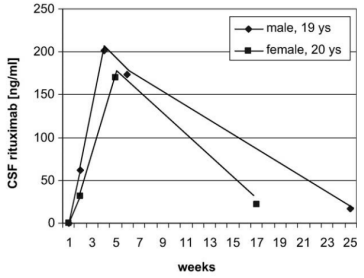


Figure 1 Cerebrospinal fluid concentration of rituximab in two patients with multiple sclerosis.

Interleukin- 2

- Appearance of rIL-2 in lumbar CSF 4 to 6 hours after the first intravenous dose
- Rise over 2 to 4 hours to a plateau of 3 to 9 U/ml

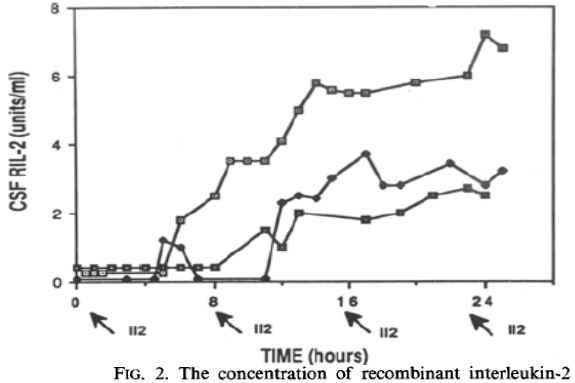
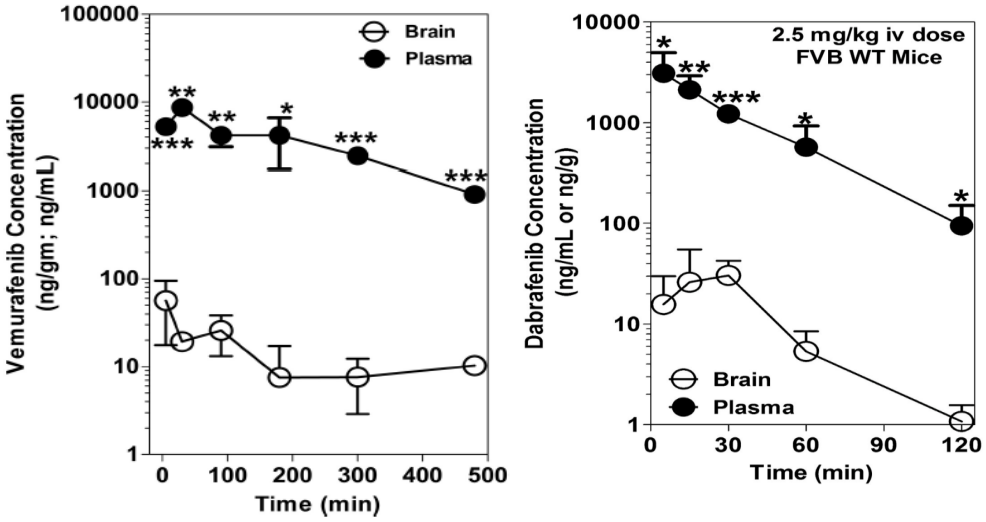


FIG. 2. The concentration of recombinant interleukin-2 (RIL-2) in the lumbar cerebrospinal fluid (CSF) plotted against time in three patients who began treatment with intravenous RIL-2 at time 0. *Arrows* (II2) indicate the times of intravenous drug injections.

BRAF Inhibitors

Vemurafenib **Dabrafenib**



Vemurafenib: After steady state: 80-fold lower
Dabrafenib: 10-fold better than vemurafenib

Intrathecal Checkpoint Inhibitors

Measured nivolumab concentrations in serum and CSF from 5 patients receiving the indicated dose of nivolumab at day 1 of every course. In addition, melanoma patients received 3 mg/kg ipilimumab. Results are the average of three replicate measurements ± SD. CSF = cerebrospinal fluid; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; C = course; D = day; q2w and q3w = administration of nivolumab every 2 and 3 weeks, respectively.

patient #	tumor type	nivolumab dosing regime	PK sample	dose mg/kg	dose mg	measured nivolumab concentration ± SD in ng/mL		ratio
						serum	CSF	serum/CSF
137	breast cancer	q3w	C1D16	1	61	4481 ± 287	15 ± 0.9	299
123	melanoma	q3w	C1D21	1	80	1831 ± 138	35 ± 0.9	52
113	melanoma	q3w	C1D21	1	77	4410 ± 324	39 ± 1.9	113
135	melanoma	q2w	C1D12	3	245	13,759 ± 311	150 ± 2.5	92
114	NSCLC	q3w	C3D14	3	240	33,454 ± 705	304 ± 11	110

Pluim D, Ros W, van Bussel MTJ, Brandsma D, Beijnen JH, Schellens JHM. Enzyme linked immunosorbent assay for the quantification of nivolumab and pembrolizumab in human serum and cerebrospinal fluid. J Pharm Biomed Anal. 2019 Feb 5;164:128-134. doi: 10.1016/j.jpba.2018.10.025. Epub 2018 Oct 17. PMID: 30368118.

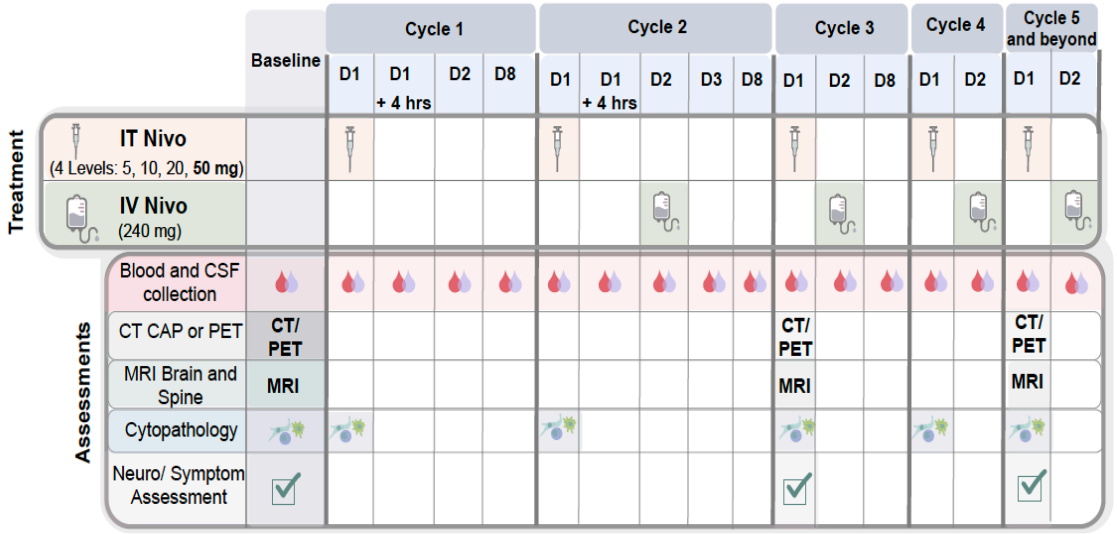
Petereit HF, Rubbert-Roth A. Rituximab levels in cerebrospinal fluid of patients with neurological autoimmune disorders. Mult Scler. 2009 Feb;15(2):189-92

Mittapalli RK, et al. *J Pharmacol Exp Ther.* 2013;344:655–664.

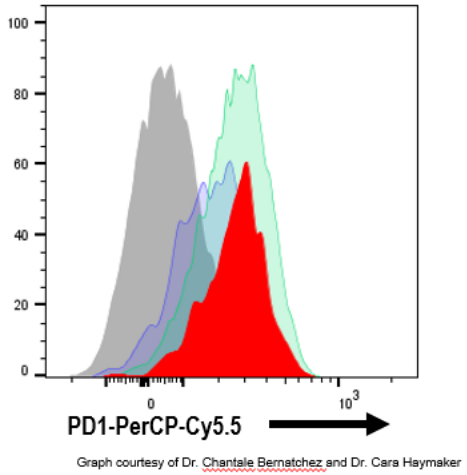
Mittapalli RK, et al. *J Pharmacol Exp Ther.* 2012;342(1):33-40.

Saris SC, Rosenberg SA, Friedman RB, Rubin JT, Barba D, Oldfield EH. Penetration of recombinant interleukin-2 across the blood-cerebrospinal fluid barrier. J Neurosurg. 1988 Jul;69(1):29-34

IT/IV Nivolumab for LMD Demographics and Study



PD-1 is expressed on the surface of immune cells in the CSF



Graph courtesy of Dr. Chantale Bernatchez and Dr. Cara Haymaker

Number of patients treated at each IT Nivo dose level

5 mg= 2 patients
10 mg= 3 patients
20 mg= 14 patients
50 mg= 31 patients

Factor	Value	Number	%
Total patients	No.	50	**100**
Age, years, at 1st dose IT Nivo	Median (range):	**49.3 years (19-75)**	
Sex	Female	23	**46**
Site of Primary	Cutaneous	22	**44**
	Acral Lentiginous	1	**2**
	Primary CNS	4	**8**
	Mucosal	1	**2**
	Uveal	3	**6**
	Lung Cancer- NSCLC	2	**4**
	Unknown primary	17	**34**
Mutation	BRAF V600 (E/K)	33	**6**
	NRAS	3	**6**
	GNAQ/GNA11	4	**8**
	Other or BRAF/NRAS wildtype	8	**16**
	Not done, unknown	1	**2**
ECOG performance at baseline	0	24	**48**
	1	20	**40**
	2	6	**12**
Baseline LDH Level	above normal limit	18	**36**
LMD detection method at baseline	CSF Cytopathology	31	**62**
	MRI Brain	43	**86**
	MRI Spine	28	**56**
Prior Therapies	Immunotherapy	42	**88**
	Targeted Therapy	34	**68**
	Radiation (WBXRT, SRS, SBRT)	40	**80**
	Intrathecal IL-2	7	**14**
	Median Number of prior systemic therapies (range)	**3 (0-7)**	
Concurrent Therapy	Targeted Therapy	27	**54**
	Dexamethasone (Dexa, patient taking at baseline)	18	**36**
	Median Dose of Dexa (range)	**2 mg (0.9-4)**	

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Summary of Outcome- IT/IV Nivolumab

This First-in-human study

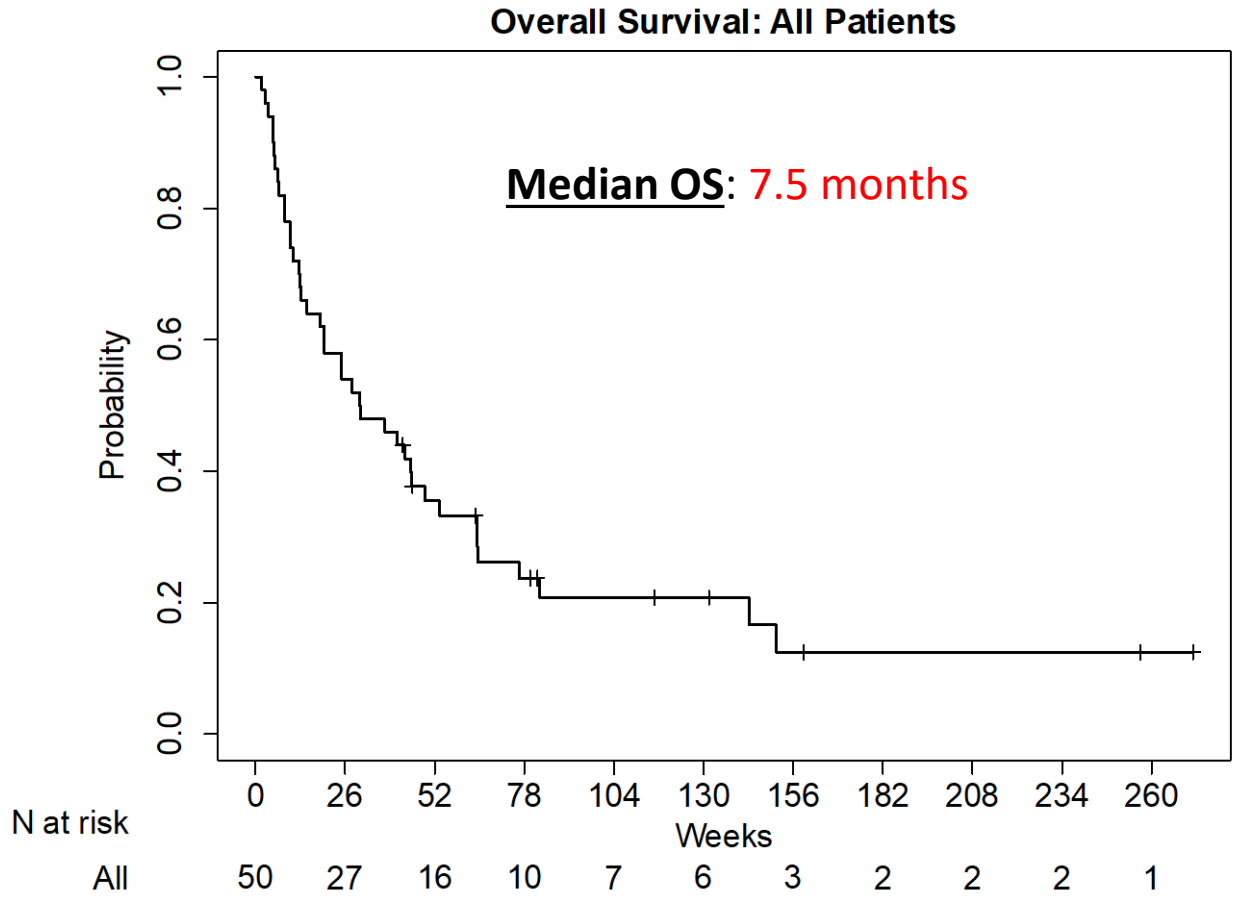
- **Demonstrate safety and efficacy, including at the recommended IT Nivo of 50mg**
- Confirmation of feasibility of prospective clinical trial in patients with LMD
- Largest prospective clinical trial to date in melanoma patients with LMD
- Benefit in patients previously treated with anti-PD1 based regimen(s), including Nivo+ Ipi

Evidence of clinical activity

- Median OS 7.5 months
- Landmark OS: 3-month OS = 68 %, 6-month OS 54%, 12-month OS 35%

Awaiting the results from

- IT Ipi and Nivo (Switzerland, NCT05598853)
- IT Nivo (Germany, NCT05112549)



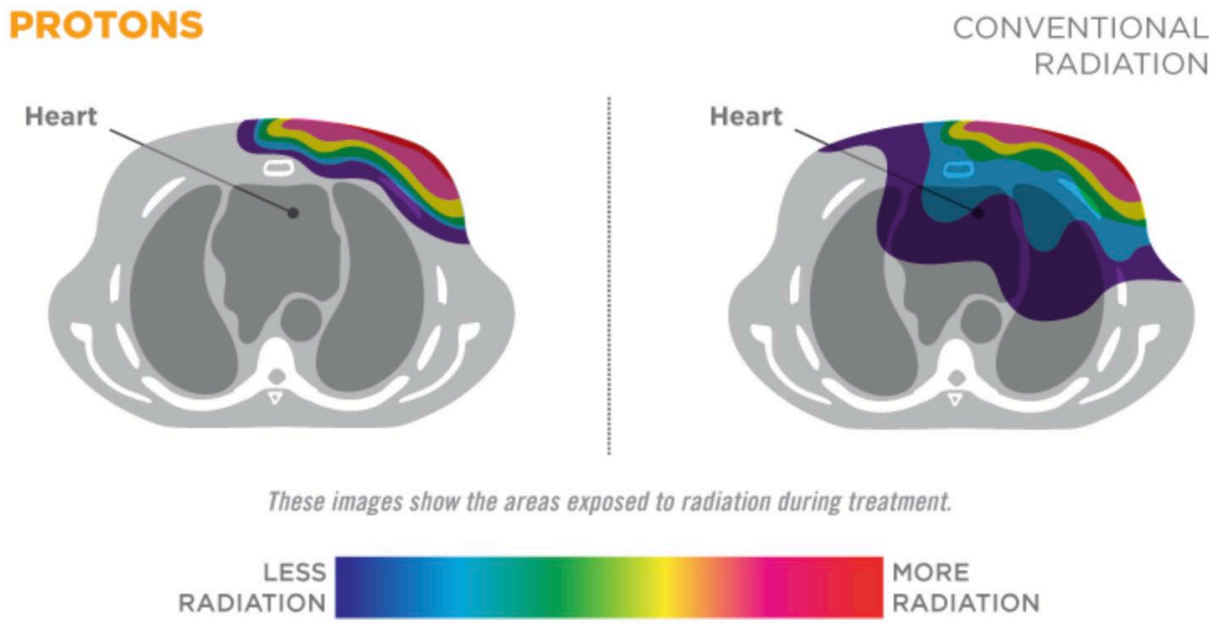
Ongoing translational work and additional trials evaluating IT immune checkpoint blockade are needed to further improve outcomes for patients with LMD

Glitza et al. ESMO 2023

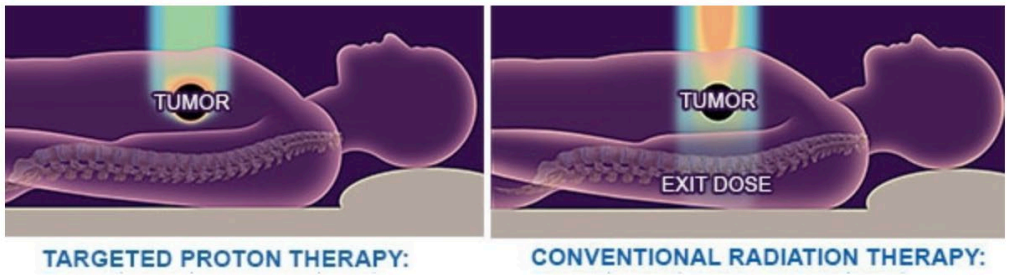
Checkpoint inhibitor in LMD-
Do we know which route is the most beneficial one?

Author	Brastianos et al.	Brastianos et al.	Naidoo et al.	Glitza et al.
Total number of patients	20	18	13	**50**
Cancer Subtype	Breast, n=17	Breast, n=8	NSCLC, n=3	**Melanoma, n=48**
	NSCLC, n=1	**Melanoma, n=2**	H/N Squam, n=1	NSCLC, n=2
	SCLC, n=1	Ana. Astrocytoma, n=1	Cut. Squam, n=1	
	Ovarian, n=1	Esophageal Adeno, n=1	Breast, n=5	
		Ependymoma, n=1	Glioma, n=3	
		GE junction adeno, n=1		
		Glioblastoma, n=1		
		NSCLC, n=1		
		Ovarian, n=1		
		SCLC, n=1		
Phase	II	II	II	I/IB
Immunotherapy used	Pembrolizumab	Ipilimumab and Nivolumab	Pembrolizumab	Nivolumab
Prior Checkpoint inhibitor	No	No	No	**Yes**
Administration route	Intravenous	Intravenous	Intravenous	**Intrathecal** and intravenous
Concurrent Steroids allowed	Yes; up to 2mg	Yes	Yes	Yes, up to 4mg
% of patients on steroids	n=6 (30%)	n=7 (38%)	n=5 (38%)	n=18 (36%)
Primary endpoint	OS at 3 months	OS at 3 months	CNS response after 4 cycles	**Safety**
Median OS	3.6 months	2.9 months	4.9 months	**7.5 months**

Craniospinal Proton Radiation

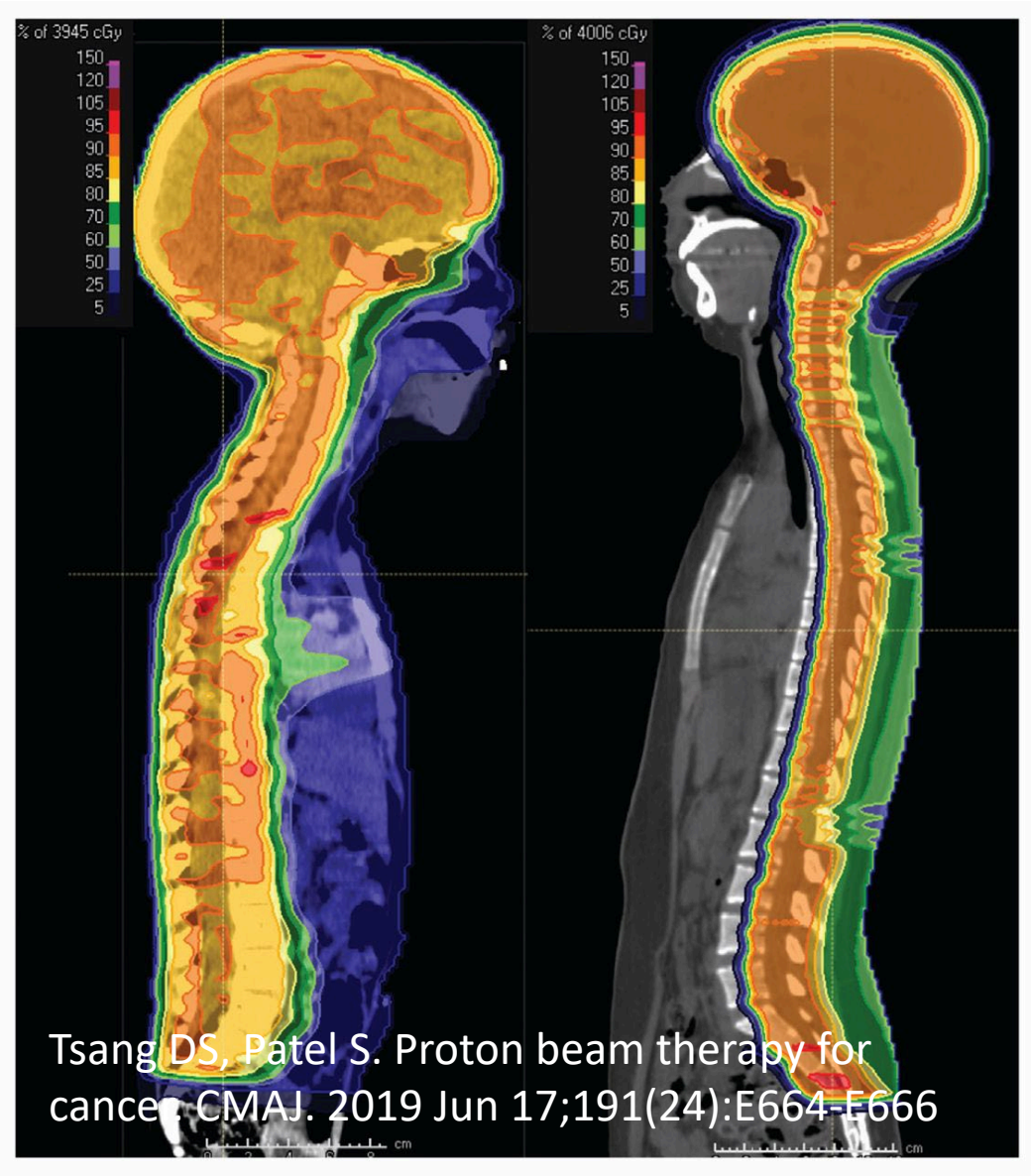


Images from https://www.provisionproton.com



UF Health proton therapy institute

Floridaproton.org



Tsang DS, Patel S. Proton beam therapy for cancer. CMAJ. 2019 Jun 17;191(24):E664-E666

Phase II trial of pCSI versus IFRT in patients with non–small-cell lung cancer and breast cancers with LMD

Initially only breast and NSCLC, additional exploratory cohort, n=35
Melanoma: only 6 patients total included in this analysis

TABLE 2. Multivariate Cox Proportional Hazard Regression With CNS PFS and OS as Outcomes

Variables	HR	95% CI	P
CNS PFS			
pCSI (reference: photon IFRT)	0.15	0.07 to 0.33	< .001
			.049
			.025
			.020

active)

Abbreviations: HR, hazard ratio; IFRT, involved-field radiotherapy; OS, overall survival; pCSI, proton craniospinal irradiation; PFS, progression-free survival.

In the exploratory pCSI group, 35 patients enrolled:

- **the median CNS PFS was 5.8 months (95% CI, 4.4 to 9.1 months)**
- **OS was 6.6 months (95% CI, 5.4 to 11 months)**

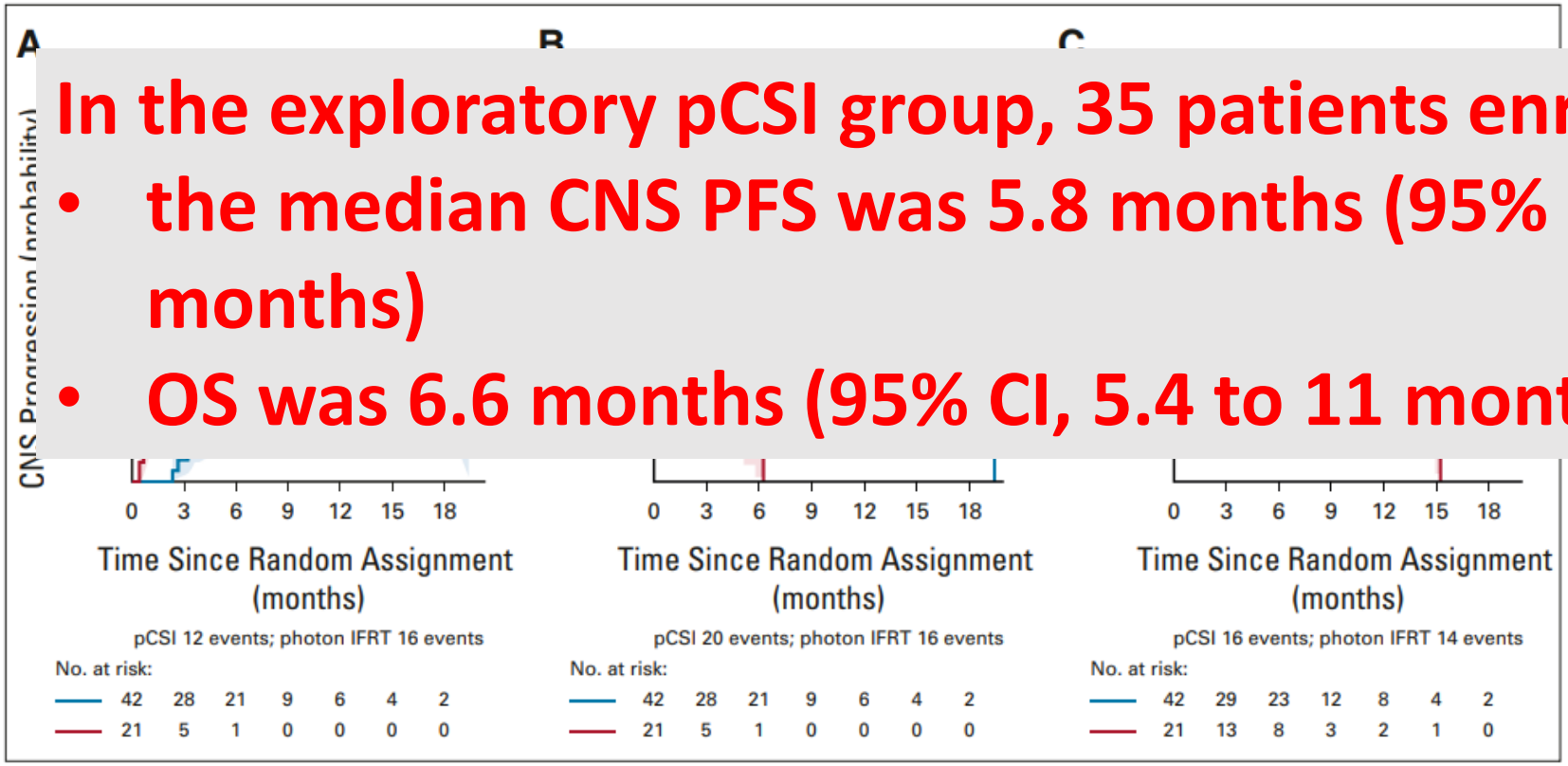


FIG 2. Patients who were randomly assigned to pCSI had significantly improved (A) CNS time to progression, (B) CNS PFS, and (C) OS. IFRT, involved-field radiotherapy; OS, overall survival; PFS, progression-free survival; pCSI, proton craniospinal irradiation.

Yang JT 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 Nov 20;40(33):3858-3867

Intrathecal Chelators

Deferoxamine

- prospective, open-label, single center phase Ia dose escalation study of IT-DFO
- 9 dosing cohorts (IT-DFO dose range 10mg to 495mg)
- Phase Ib will further explore the safety of IT-DFO at the RP2D in 20 patients with NSCLC LMD
- NCT05184816

Intrathecal Radioisotope

Rhenium (^{186}Re) obisbemeda

- short half-life, beta energy for destroying cancer cells, and gamma energy for real-time imaging
- completed dosing in Cohort 5 of the ReSPECT-LM Phase 1 dose escalation clinical trial
  - total to 18 patients
  - no DLTS observed to date at RT doses up to 66.14 millicuries in Cohort 5, a ten-fold increase over Cohort 1
- Ongoing clinical trial

Response Assessment changes over time- RANO- LM

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.

Table 4. Response determination in leptomeningeal metastases

Assessment	Response	Progressive or refractory disease				Stable Disease
		Neurological Examination Defined Progression	CSF Defined Disease Progression	Radiologic Defined Disease Progression	Symptoms^	
Neurological Exam	**Improved**	**Worse**	**Stable**	**Stable**	**Stable**	**Stable**
CSF cytology (all cancers)	Negative	Negative	Positive (lack consensus)	Negative	Negative	Negative or positive (solid tumors only)
CSF flow cytometry (in hematologic cancers only)	Negative	Negative	Positive (lack consensus)	Negative	Negative	Negative or positive
CNS imaging	Definite improvement	Stable	Stable	Definite worsening	Stable	Stable or equivocally worsening or improved
Steroid dose (in hematologic cancers only)	None or decreased	Stable or increased	Stable or increased	Stable or increased	Stable	Stable or decreased
Symptom assessment	Improved	Worse or stable	Worse or stable	Worse or stable	Worse	Stable

Legend:
CSF cytology negative Defined as either true negative or atypical
CSF cytology positive Defined as true positive or suspicious
Stable Defined as stable or indeterminate
Symptoms^Stable; no change (–1 to +1 in symptom inventory
Worse; –2 to –3 in symptom inventory
Improved; +2 to +3 in symptom inventory

Chamberlain M, Junck L, Brandsma D, Soffietti R, Rudà R, Raizer J, Boogerd W, Taillibert S, Groves MD, Le Rhun E, Walker J, van den Bent M, Wen PY, Jaeckle KA. Leptomeningeal metastases: a RANO proposal for response criteria. Neuro Oncol. 2017 Apr 1;19(4):484-492

Response Assessment changes over time- EANO-ESMO

Table 2. 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

Table 5. Overall EANO—ESMO response assessment and guidance for LM treatment

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

Le Rhun E, Weller M, van den Bent M, Brandsma D, Furtner J, Rudà R, Schadendorf D, Seoane J, Tonn JC, Wesseling P, Wick W, Minniti G, Peters S, Curigliano G, Preusser M; EANO Guidelines Committee and ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Leptomeningeal metastasis from solid tumours: EANO-ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. ESMO Open. 2023 Oct;8(5):101624.

Intrathecal Studies in NSCLC and LMD

Table 2
Published studies of intrathecal chemotherapy in NSCLC patients with LM.

Study	Year	Type	Patients (n)	BM (n)	Previous therapy	IT Regimen	Concurrent therapy	Median PFS	Median OS	Response rate	Toxicity
Park JH, et al [108]	2012	R	50 NSCLC	28	5 WBRT 34 Chemotherapy 9 EGFR TKIs	48 ITC	22 Radiotherapy 12 Chemotherapy 14 EGFR TKIs	NA	4.3 *m*	Cytological response rate: 52 %	NA
Lee SJ, et al [1]	2013	R	149 NSCLC	98	34 WBRT 53 EGFR TKIs	109 ITC	47 WBRT 23 VP shunt 25 Chemotherapy 24 EGFR TKIs	NA	14.0 weeks 17.0 weeks in ITC group vs 8 weeks in non-ITC group ($P < 0.001$)	NA	NA
Pan Z, et al [48]	2016	II	59 (32 NSCLC) (20 SCLC)	NA	NA	56 IT MTX	51 WBRT 5 CSI	NA	6.5 *m* 6.7 m for NSCLC 4.5 m for SCLC	CRR: 86.4 % NSCLC CRR:87.5 % SCLC CRR: 90 %	G3-4: 20.3 %
Pan Z, et al [50]	2019	I	13 NSCLC	NA	11 IFRT + ITC 5 Chemotherapy 10 EGFR TKIs 1 ALK TKIs	11 IT Pemetrexed 10 mg 2 IT Pemetrexed 15 mg	6 EGFR TKIs 1 ALK TKI	2.5 m*	3.8 *m*	CRR: 31 % DCR: 54.0 %	SAEs: 31 %
Pan Z, et al [51]	2020	I/II	34 (21 NSCLC) (5 SCLC)	6	19 Systemic therapy 13EGFR TKIs	34 IT Pemetrexed 10 mg	31 WBRT 3 CSI 1 Systemic therapy 11 EGFR TKIs	3.5 m*	5.5 *m* 7.3 m for NSCLC 3.5 m for SCLC	CRR: 68 % DCR: 74 % NSCLC CRR:67 % SCLC CRR:80 %	Total AEs: 53 % G3-4: 21 %
Miao Q, et al [52]	2020	R	23 NSCLC	12	4 Brain radiotherapy 18 Chemotherapy 15 EGFR TKIs	12 IT Pemetrexed 10 mg	1 WBRT 9 Chemotherapy 10 Antiangiogenic therapy 1 Immunotherapy 19 EGFR TKIs	9.6 *m*	NR	CRR: 34.8 %	Total AEs: 60.9 % G3-4: 21 %
Pan C, et al [34]	2021	II	30 NSCLC	20	8 WBRT 5 ITC 30 EGFR TKIs	30 IT Pemetrexed 50 mg	9 Chemotherapy 15 EGFR TKIs	NA	9.0 *m*	CRR: 84.6 %	G3: 26.7 %
Geng D, et al [53]	2022	R	34 Lung cancer	23	3 Bevacizumab 5 Chemotherapy 24 EGFR TKIs 3 ALK TKIs	34 IT Pemetrexed	5 Bevacizumab 7 Chemotherapy 24 EGFR TKIs 4 ALK TKIs	NA	20.0 *m*	NA	G3-4: 0

IT, intrathecal treatment; LM, leptomeningeal metastasis; NSCLC, non-small cell lung cancer; BM, brain metastasis; PFS, progression-free survival; OS, overall survival; R, retrospective; WBRT, whole brain radiation therapy; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitors; ITC, intrathecal chemotherapy; NA, not applicable; m, months; VP shunt, ventriculo-peritoneal shunt; SCLC, small cell lung cancer; MTX, methotrexate; CSI, craniospinal irradiation; CRR, clinical response rate; G, grade of toxicity; IFRT, involved field radiation therapy; ALK, anaplastic lymphoma kinase; DCR, disease control rate; SAE, serious adverse event; NR, not reached. *Median neurological progression-free survival.

Wang Y, Yang X, Li NJ, Xue JX. Leptomeningeal metastases in non-small cell lung cancer: Diagnosis and treatment. Lung Cancer. 2022 Dec;174:1-13.

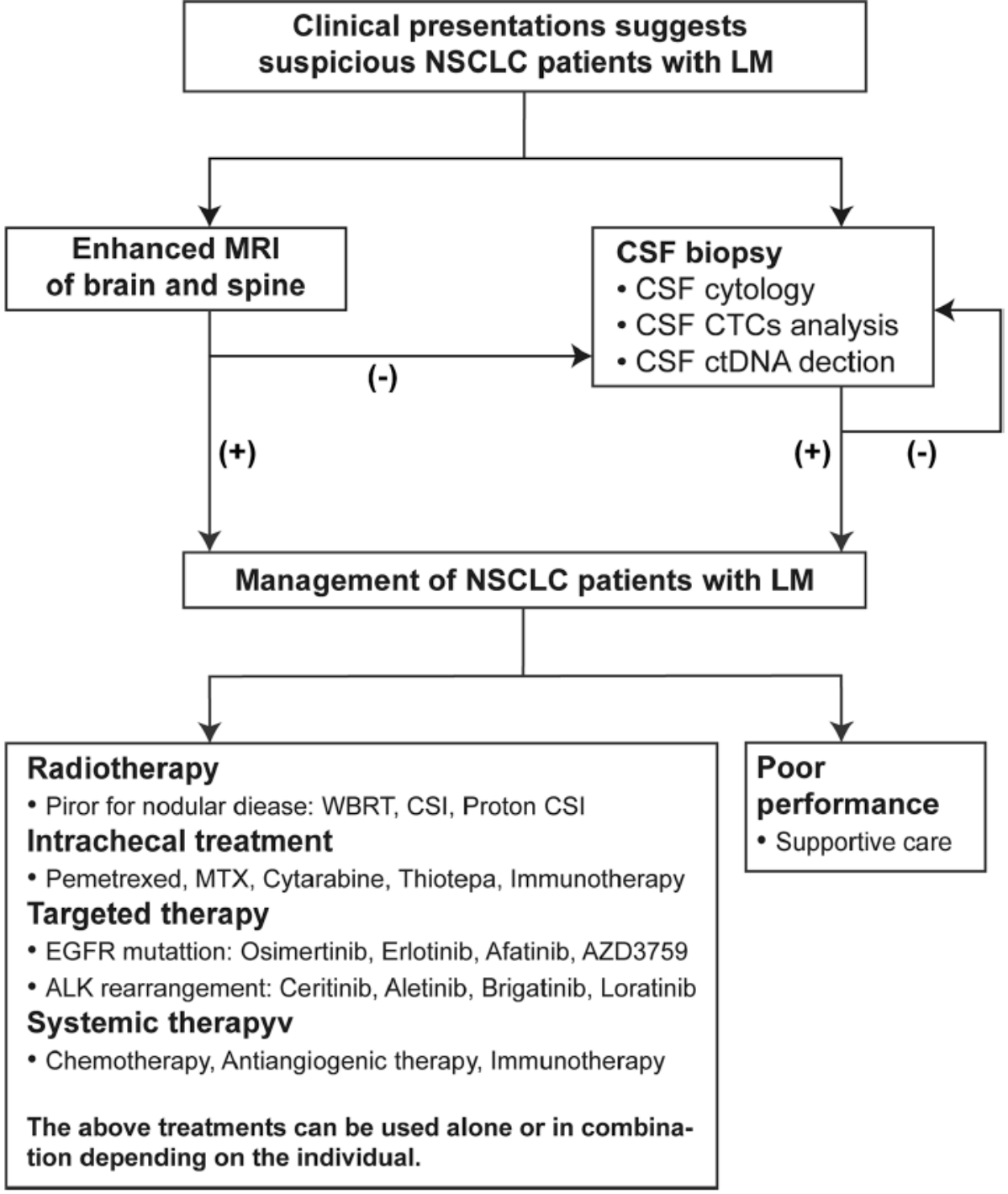


Fig. 3. The algorithm for the diagnosis and management of NSCLC patients with LM (-) indicates that the corresponding result is negative. (+) indicates that the corresponding result is positive. NSCLC, non-small cell lung cancer; LM, leptomeningeal metastasis; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; CTCs, circulating tumor cells; ctDNA, circulating tumor deoxyribonucleic acid; WBRT, whole brain radiation therapy; CSI, craniospinal irradiation; MTX, methotrexate; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Proposed Clinical Algorithm in NSCLC and LMD

Wang Y, Yang X, Li NJ, Xue JX. Leptomeningeal metastases in non-small cell lung cancer: Diagnosis and treatment. Lung Cancer. 2022 Dec;174:1-13.

Osimertinib in NSCLC and LMD

Table 2 Key efficacy data for osimertinib as post prior EGFR-TKI treatment for leptomeningeal metastases in EGFRm advanced NSCLC

Study	LM efficacy endpoints	Osimertinib ($n=37$[a])	
BLOOM (NCT02228369) [67]	Primary: Safety	LM ORR	62% (45–78)
BGFRm advanced NSCLC with progression on previous EGFR-TKI therapy	Secondary: LM ORR, LM DoR, LM DCR, PFS, OS	LM DCR	35% (82–99)
Osimertinib 160 mg QD[b]		LM DoR	15.2 months (7.5–17.5)
		PFS	8.6 months (5.4–13.7)
		OS	11.0 months (8.0–18.0)
		Osimertinib ($n=40$)	
(NCT03257124) [53]	Primary LM cohort with/without BM: OS	OS	13.3 months (9.1–NR)
BGFRm with CNS progression on previous EGFR-TKI therapy (LM cohort: with LM with/without BM)	Secondary LM cohort: LM DCR	LM DCR (LM CR)	92.5% (12.5%)
Osimertinib 160 mg QD			
		Osimertinib ($n=22$)	
AURA LM [68]	LM ORR, LM DoR, LM DCR, LM PFS, OS	LM ORR	55% (32–76)
AURA extension (NCT01802632)/AURA2 (NCT02094261)/AURA17 (NCT02442349)/ AURA3 (NCT02151981)		LM DCR	91%
		LM DoR	NR (2.8–NC)
BGFRm T790M-positive advanced NSCLC with progression on previous EGFR-TKI therapy		LM PFS	11.1 (4.6–NC)
		OS	18.8 (6.3–NC)
Osimertinib 80 mg QD			

Data are presented as % or median (95% CI); CNS ORR and CNS DCR data are presented as % (95% CI) and CNS PFS and CNS DoR are median in months (95% CI)

BICR blinded independent central neuroradiology review, *BM* brain metastases, *CI* confidence interval, *CNS* central nervous system, *CR* complete response, *DCR* disease control rate, *DoR* duration of response, *EGFRm* epidermal growth factor receptor mutation positive, *LM* leptomeningeal metastases, *NC* not calculable, *NR* not reached, *NSCLC* non-small-cell lung cancer, *OR* odds ratio, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *QD* once daily, *TKI* tyrosine kinase inhibitors

[a]Data shown are for patients with BICR assessments

[b]Data shown for patients from both the T790M-positive cohort and the T790M unselected cohort

Popat S, Ahn MJ, Ekman S, Leighl NB, Ramalingam SS, Reungwetwattana T, Siva S, Tsuboi M, Wu YL, Yang JC. Osimertinib for EGFR-Mutant Non-Small-Cell Lung Cancer Central Nervous System Metastases: Current Evidence and Future Perspectives on Therapeutic Strategies. Target Oncol. 2023 Jan;18(1):9-24.

Intrathecal Agents used in Breast LMD

Agent	Description	Half-Life in the CSF	Recommended Schedules of Administration	Recommended Prophylaxis of Adverse Events
Cytarabine	Pyrimidine nucleoside analogue	<1 h	10 mg twice weekly (total 4 weeks), then 10 mg once weekly (total 4 weeks), then 10 mg once monthly	None
Liposomal cytarabine *	Pyrimidine nucleoside analogue	14–21 days	50 mg every 2 weeks (total 8 weeks), then 50 mg once monthly	Oral steroids [40]
Methotrexate	Folate antimetabolite	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 [41]
Topotecan	Topoisomerase 1 inhibitor	1.3 h [42,43]	0.4 mg twice weekly × 4–6 weeks, then weekly × 4, then every other weekly × 4 then monthly	
Thiotepa	Alkylating ethyleneimine compound	3–4 h	10 mg once every other week	Given with methylprednisone 40 mg [44]
Trastuzumab	Monoclonal antibody		80 mg twice weekly or 150 mg weekly	None [45,46]

* Currently not commercially available.

Warrior S, Cohen-Nowak A, Kumthekar P. Modern Management and Diagnostics in HER2+ Breast Cancer with CNS Metastasis. Cancers (Basel). 2023 May 25;15(11):2908

Summary of HER2+ TKI trials for BM and LMD patients

Table 1. Summary of HER2+ TKI trials for BM and leptomeningeal metastasis patients (original)

Study drug	Phase	No. of patients	LM patients allowed	Primary endpoint	Primary endpoint met	Median PFS (months)	Median OS (months)
Lapatinib + capecitabine (LANDSCAPE) [23]	2	45	No	CNS ORR	Yes (65% CNS ORR)	5.5 (95% CI 4.3 - 6.0)	17.0
Neratinib + capecitabine [24]	2	49	Yes (3 with LM)	CNS ORR	Yes (49% CNS ORR)	5.5 (range 0.8–18.8)	13.3 (range 2.2–27.6)
Tucatinib + capecitabine + trastuzumab (HER2CLIMB) [25]	3	480 (291 with BM)	No	PFS	Yes	7.6 versus 5.4 Hazard ratio 0.48, 95% CI (0.34– 0.69) $P<0.001$	21.9 versus 17.4 Hazard ratio 0.66, 95% CI (0.5 – 0.88) $P=0.005$

BM, brain metastases; CI, confidence interval; CNS, central nervous system; HER2, human epidermal growth factor receptor 2; LM, leptomeningeal metastasis; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitors

Chew SM, Seidman AD. New strategies for the treatment of breast cancer with leptomeningeal metastasis. Curr Opin Oncol. 2023 Nov 1;35(6):500-506.

Summary of T-DXd trials for BM and LMD patients

Table 2. Summary of T-DXd trials for BM and leptomeningeal metastasis patients (original)

Trial name	Phase	No. of patients	Patient cohort	Primary endpoint (s)	Primary endpoint met	Median PFS (months)	Median OS (months)
DESTINY-Breast03 [28▪▪]	3	524	HER2+ MBC (114 patients had treated BM. LM excluded)	PFS	Yes	28.8 versus 6.8 Hazard ratio 0.33, 95% CI (0.26– 0.43) $P<0.0001$)	NA
TUXEDO-1 [29▪▪]	2	15	HER2+ active BM LM excluded	CNS ORR	Yes (CNS ORR 73.3%)	14 (95% CI 11.0-NR)	NA
DEBBRAH (cohort 1–3) [30▪▪]	2	21	HER2+ treated and active BM (Cohort 5 which includes LM patients is ongoing)	16-week PFS rate CNS ORR	Yes (16-week PFS rate 87.5%. CNS ORR 46.2%)	NA	NA
DESTINY-Breast01 [31]	2	184	HER2+ MBC (24 patients had treated BM. LM excluded)	ORR	Yes (ORR 60.9%)	16.4 (95% CI 12.7-NR)	NA
DESTINY-Breast02 [32▪]	3	608	HER2+ MBC (110 patients had treated BM. LM excluded)	PFS	Yes	17.8 versus 6.9 Hazard ratio 0.36, 95% CI (0.28 - 0.45) $P<0.0001$)	39.2 versus 26.5 Hazard ratio 0.66, 95% CI (0.50 – 0.86) $P<0.002$)
DESTINY-Breast04 [33▪▪]	3	557	HER2low MBC (32 patients had treated BM. LM excluded)	PFS	Yes	9.9 versus 5.1 Hazard ratio 0.50, 95% CI (0.40–0.63) $P<0.001$)	23.9 versus 17.5 Hazard ratio 0.64, 95% CI (0.48–0.86) $P<0.003$)
DAISY [34]	2	179	Her2 non, low and high expressing MBC (24 patients had treated BM. LM excluded)	Best overall response	Ongoing	NA	NA

BM, brain metastases; CI, confidence interval; CNS, central nervous system; HER2, Human epidermal growth factor receptor 2; LM, leptomeningeal metastasis; MBC, metastatic breast cancer; NA, not available; NR, not reached; ORR, overall response rate; OS, overall survival; T-Dxd, Trastuzumab deruxtecan.

Chew SM, Seidman AD. New strategies for the treatment of breast cancer with leptomeningeal metastasis. Curr Opin Oncol. 2023 Nov 1;35(6):500-506.

Conclusion

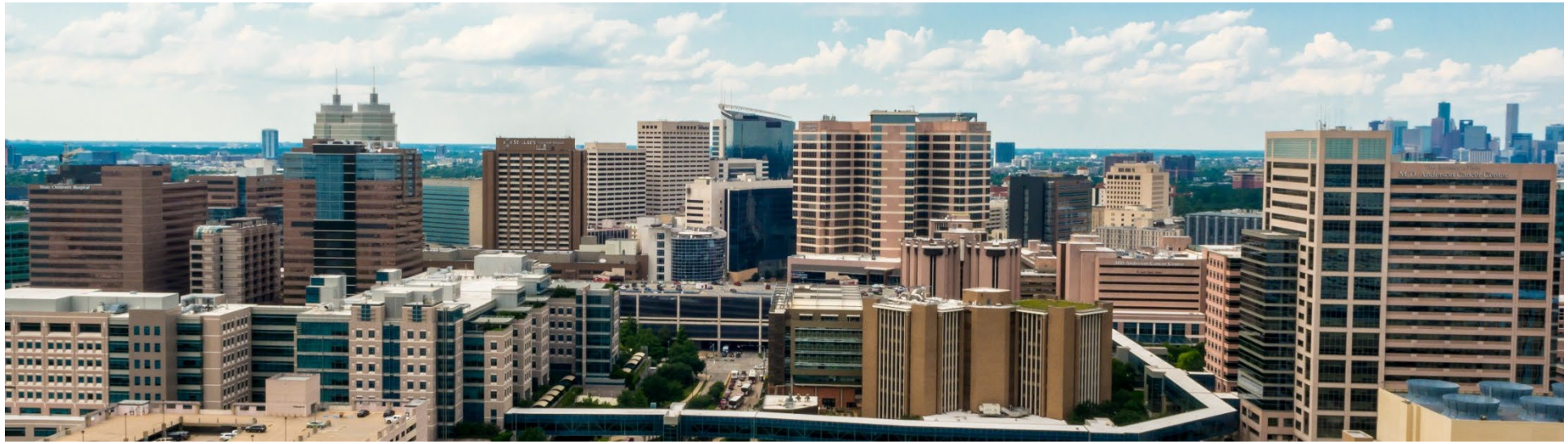
- **LMD remains a significant unmet need**
- **Survival still overall very poor**
- **Diagnosis and response assessment remain challenging**
- **Clinic trials are sparse and progress historically has been slow**
- **Unclear ‘best practice’ in sequencing ongoing clinical trial/ treatment options**

More Questions than answers!

- **But:**

- **Progress is being made**
- **More clinical trials are happening**
- **Long term survival is possible!**

Thank you for your attention!



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