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# Tackling Leptomeningeal Disease (LMD) in NSCLC

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19th Annual

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# Tackling Leptomeningeal Disease in NSCLC

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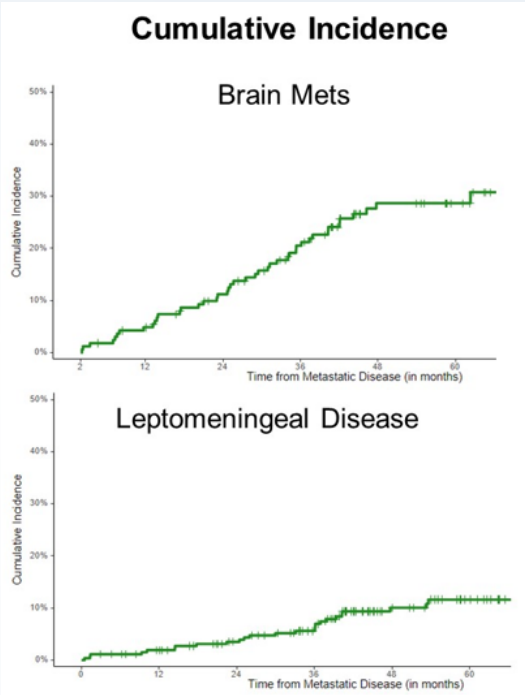
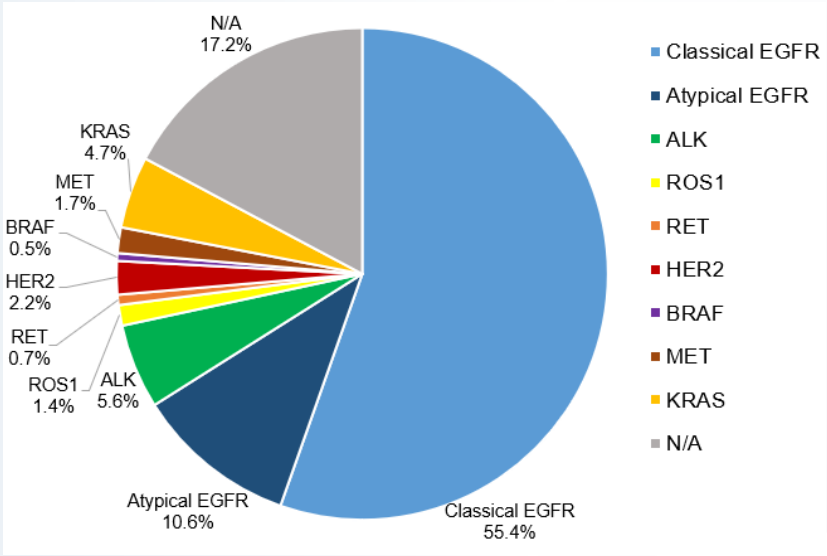
# Overview

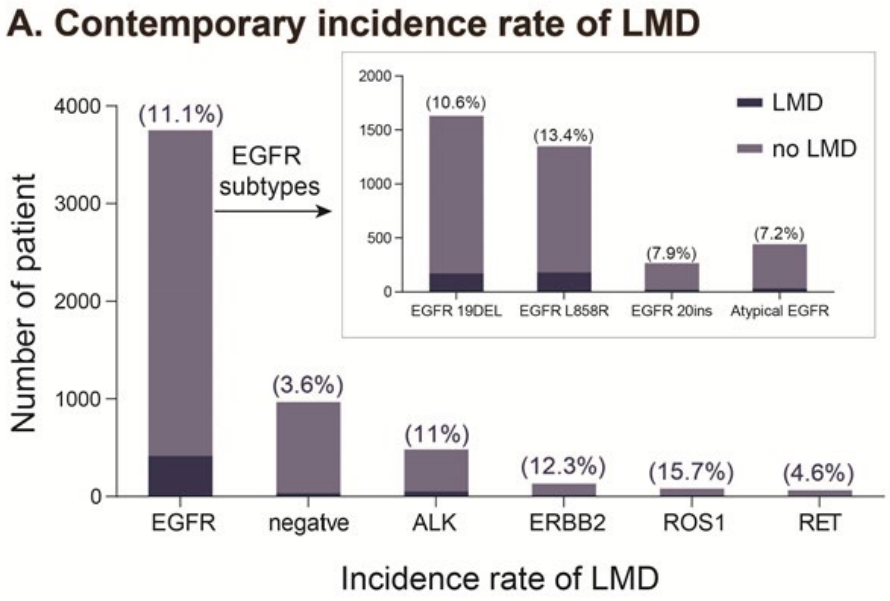
1. Epidemiology of LMD in NSCLC
2. Diagnostic approaches and prognosis
3. Current and emerging treatments:
    1. Systemic therapies
    2. Radiotherapy
    3. Intrathecal therapies
4. Ongoing clinical trials/ future directions

# Background and Epidemiology

- Leptomeningeal disease (LMD) occurs in 3-5% of advanced NSCLC
- Increasing incidence with improved survival and CNS-penetrant systemic therapies
- Strongly associated with oncogene-driven subtypes (EGFR, ALK, HER2, ROS1)
- Median OS ~3-12 mo, but improving in era of targeted therapies



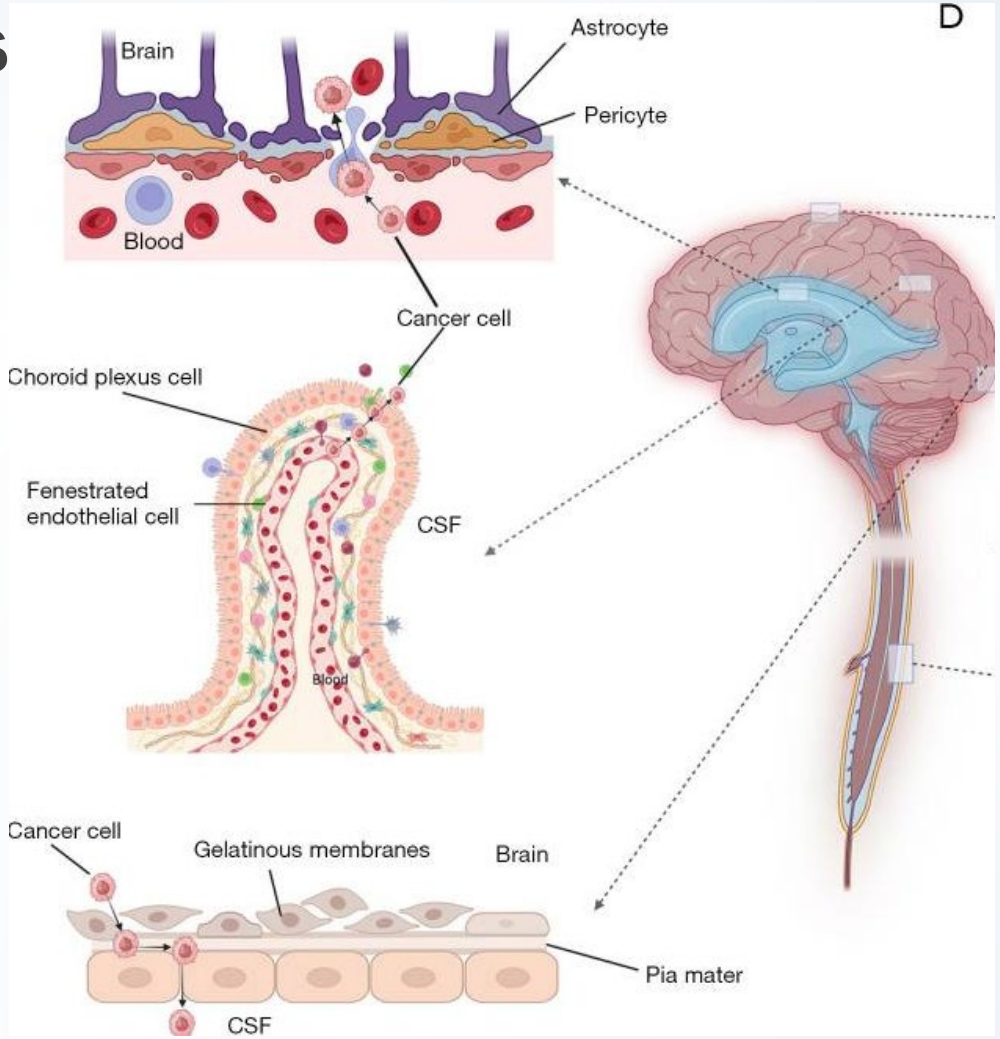




Yu et al., ASCO 2024
Pan et al., TTLC 2024
Zheng et al., Annals of Oncology 2025

# Pathophysiology and Clinical Features

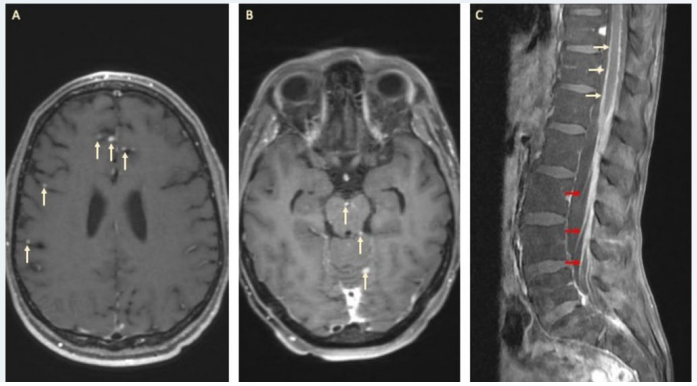
- Dissemination of tumor cells into the CSF, subarachnoid space, or leptomeninges (pia and arachnoid membranes)
- Symptoms:
  - Headache, fatigue, nausea/ vomiting
  - Altered mentation, lightheadedness
  - Cranial neuropathies, radiculopathy



# Diagnostic Approach

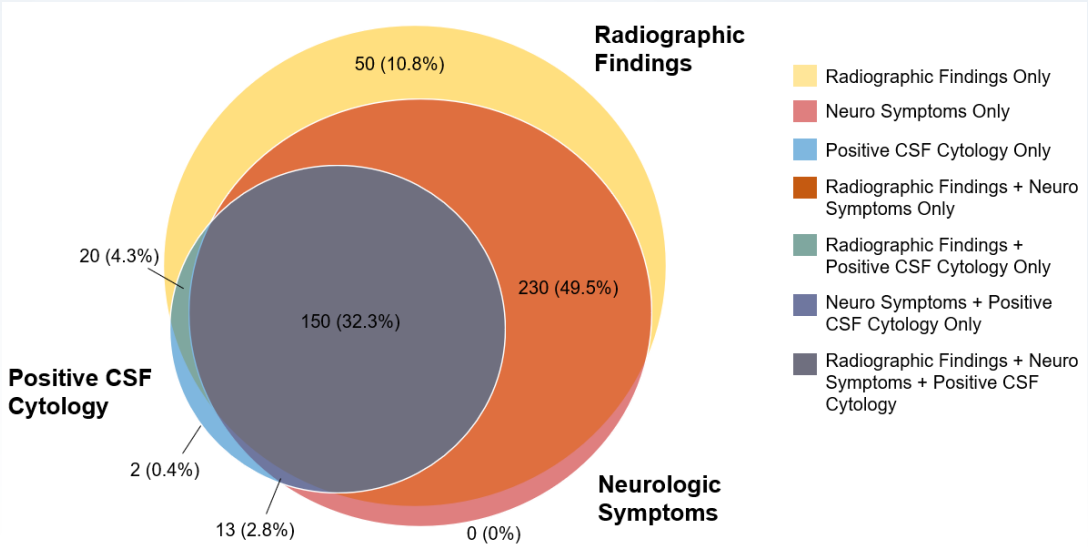
## 1. Imaging

- MRI brain/ spine with contrast
- Sensitivity limited; low concordance between radiologists




**A. Including All Raters** **Concordance goal 0.8**

| | NO + NR (*n* =19) | | | NO (*n* = 10) | | | NR (*n* =9) | | |
|---|---|---|---|---|---|---|---|---|---|
| **Item** | **ICC** | **LCL** | **UCL** | **ICC** | **LCL** | **UCL** | **ICC** | **LCL** | **UCL** |
| **Change score 1** | 0.48 | 0.32 | 0.70 | 0.35 | 0.18 | 0.59 | 0.66 | 0.50 | 0.81 |
| **Change score 2** | 0.48 | 0.33 | 0.66 | 0.37 | 0.22 | 0.58 | 0.59 | 0.43 | 0.76 |
| **Change score 3** | 0.48 | 0.34 | 0.67 | 0.37 | 0.23 | 0.58 | 0.59 | 0.44 | 0.76 |




## 2. CSF analysis

- Cytology (gold standard, sensitivity ~50-60%)
- Circulating tumor cells (CTCs), ctDNA

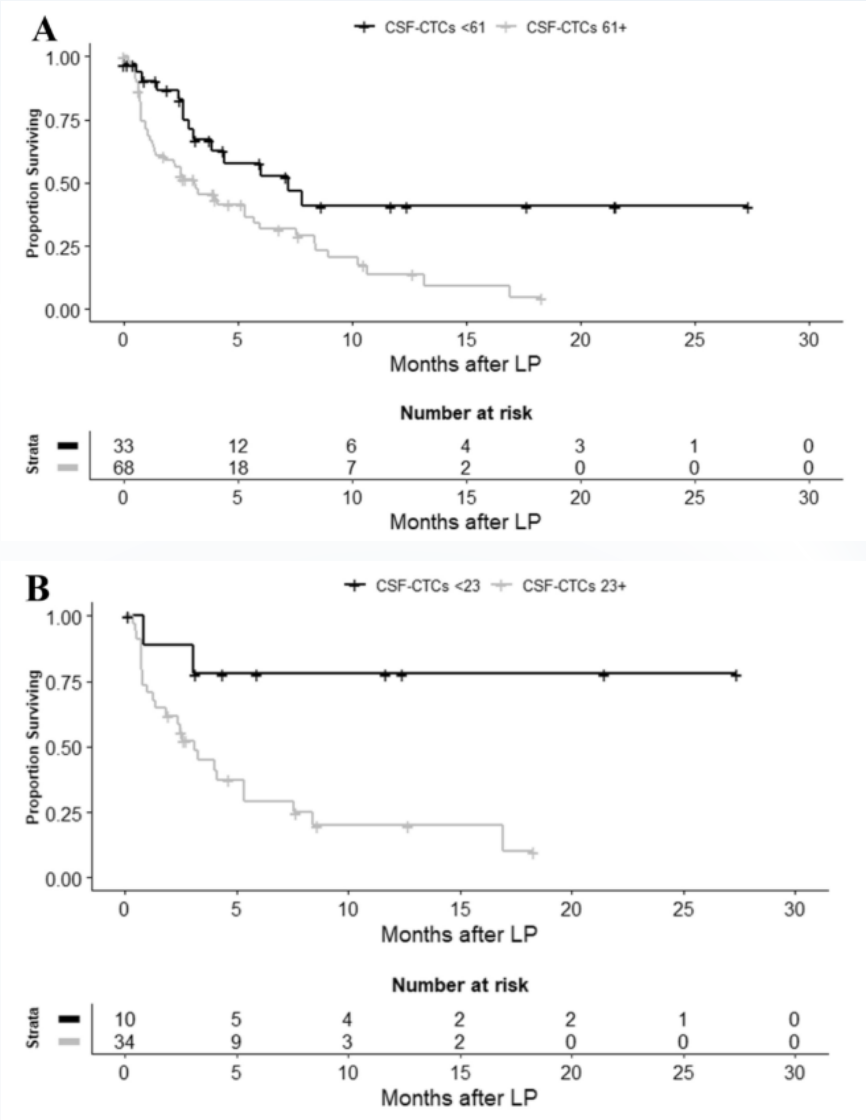
## 3. Clinical symptoms

- Only 1/3 of pts have all 3!

Pan et al., TTLC 2025
Senur et al., Curr Neurol Neurosci Rep 2025
Clarke et al., Neurology 2011

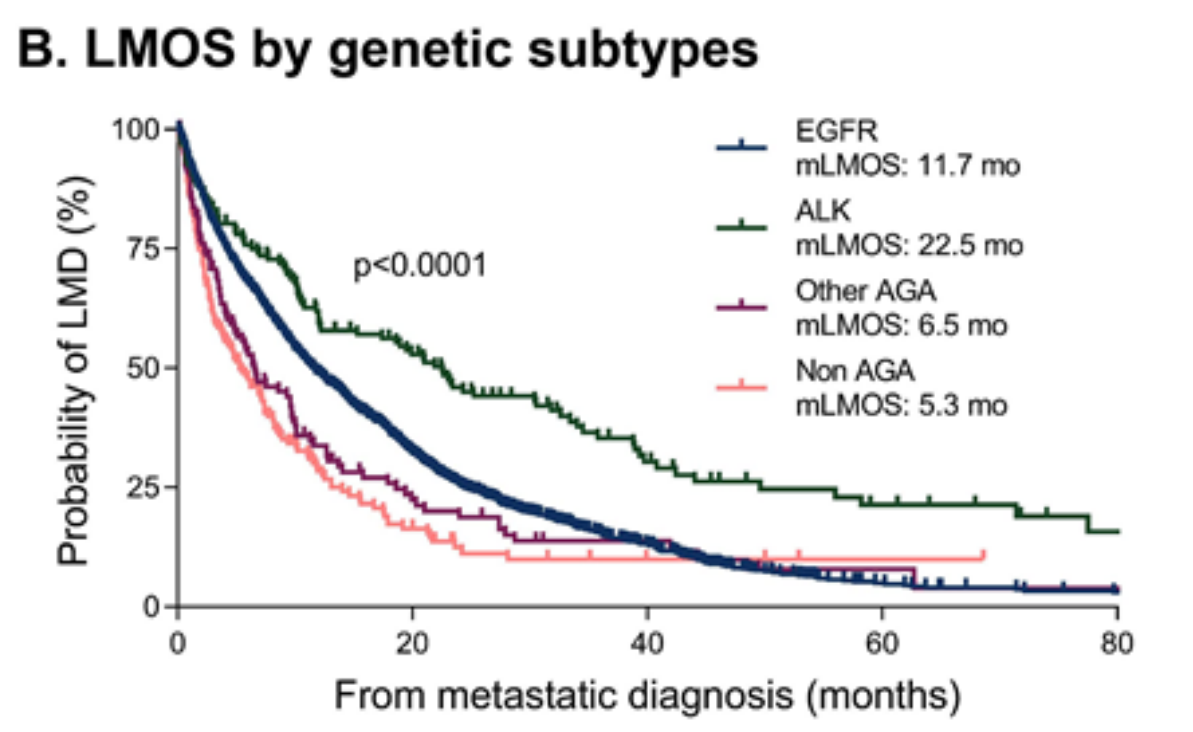
# Prognostic Factors

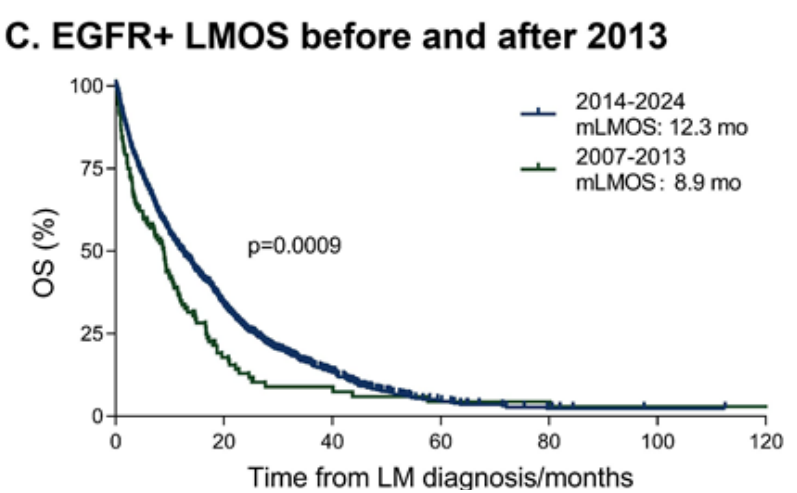
- Molecular subtypes
  - Availability of CNS-penetrant TKI
- CSF cytology
  - (+) cytology, higher CTCs→ associated with worse prognosis
- Radiographic features/ extent of involvement?
  - Under investigation → potential integration of radiomics

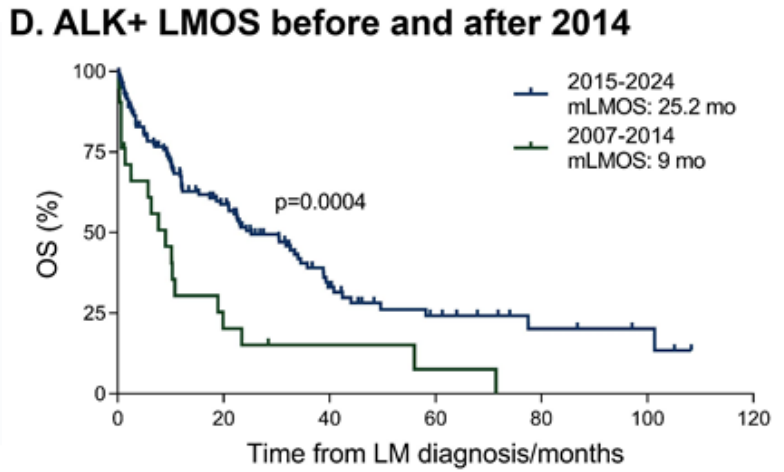



Diaz et al., J Neuro Onc 2022

# EGFR- and ALK (+) LMD associated with improved LMOS, largely due to improved, CNS-penetrant targeted therapies

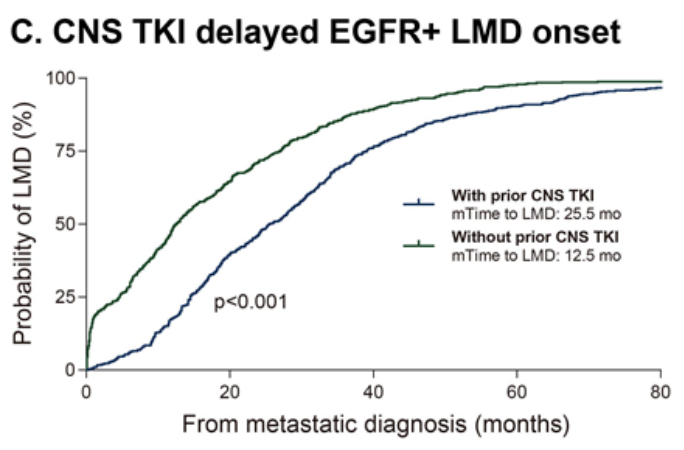


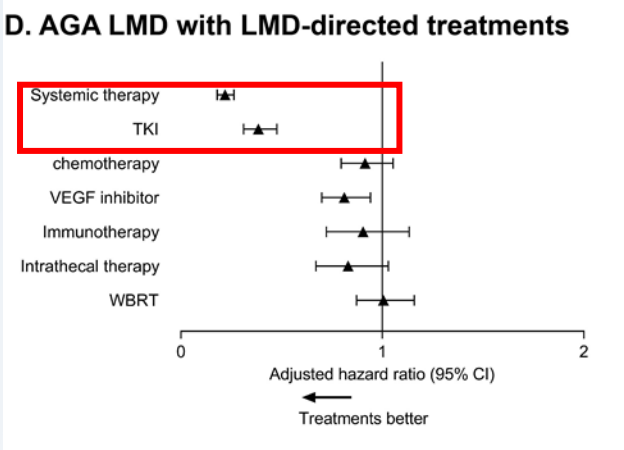



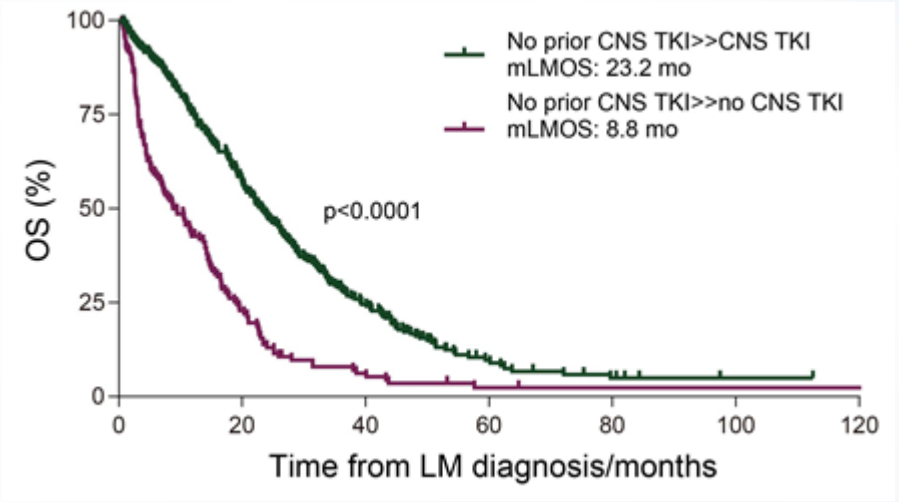

Zheng et al., Annals of Oncology 2025

# Highly CNS-penetrant TKIs associated w/ delayed onset of LMD and improved LMOS in EGFRm NSCLC

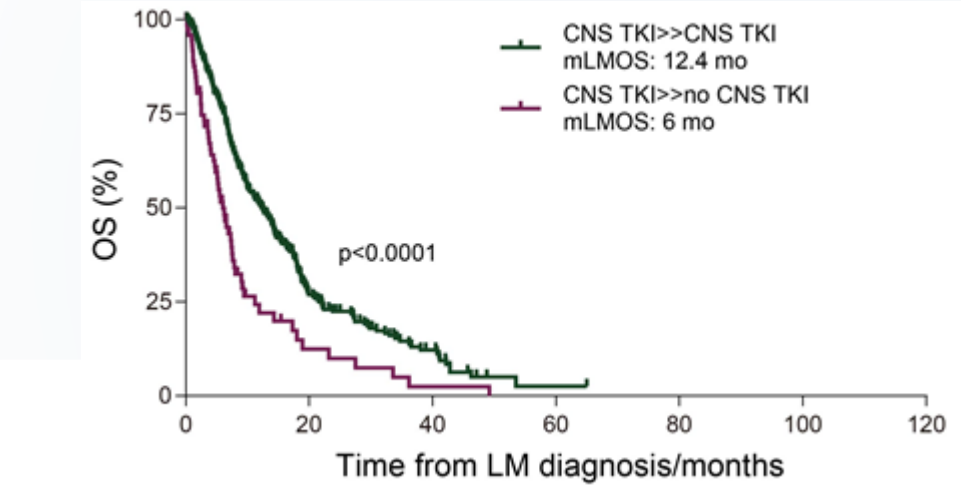



**No prior CNS TKI:**



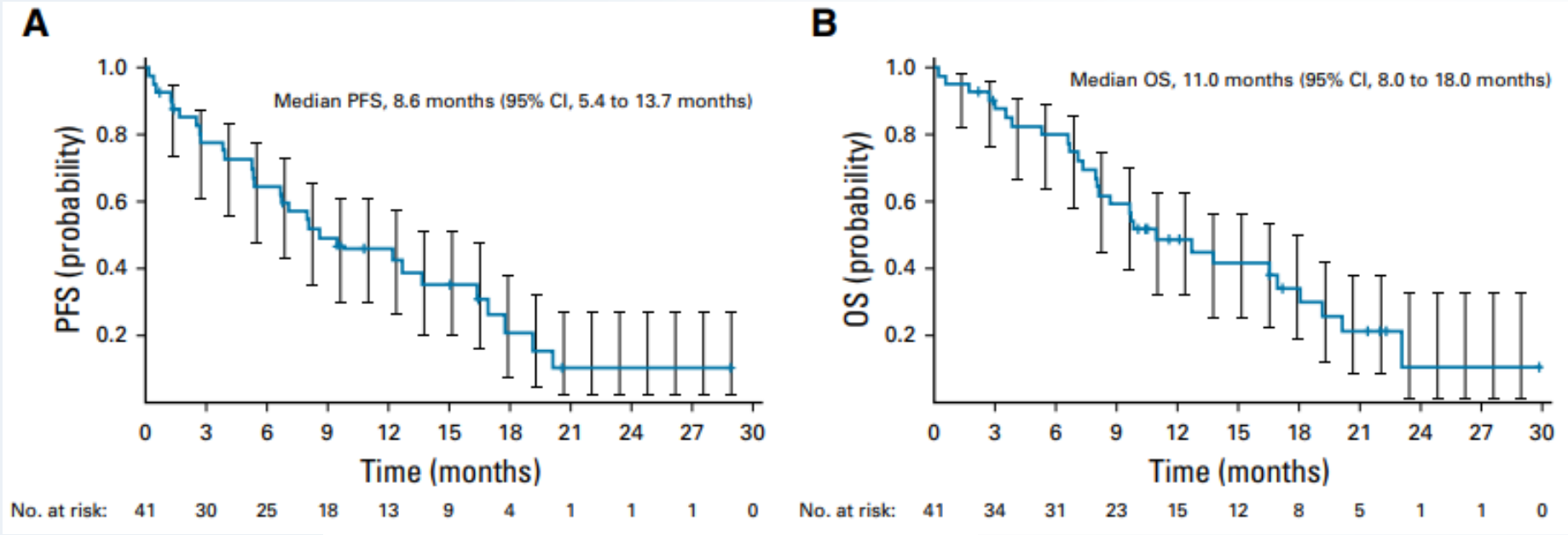

**Prior CNS TKI:**

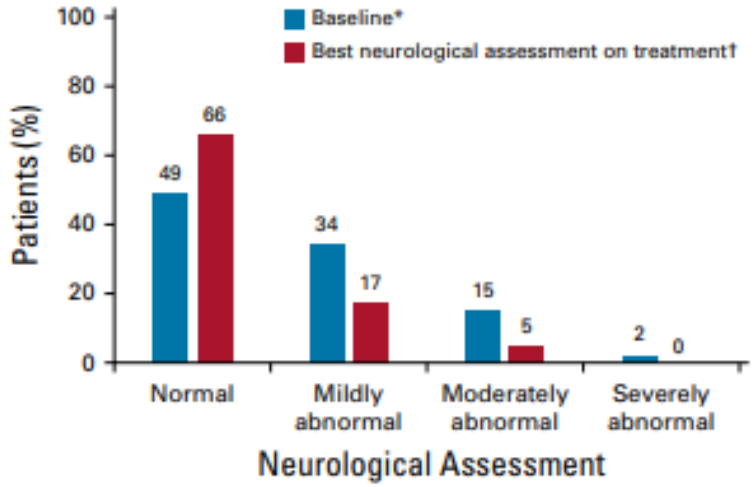



- Systemic tx and TKI associated w/ improved LMOS in LMD with actionable driver
- In EGFRm LMD, use of 3rd gen EGFR TKI → improved LMOS in pts who are both CNS TKI-naïve and previously treated

Zheng et al., Annals of Oncology 2025

# EGFRm LMD: Osimertinib 160 mg is SOC




Phase I BLOOM Study:
- ORR 41%, mPFS 8.6 mo, mOS 11.0 mo
- CSF tumor cell clearance in 28%
- Improved neuro function in 57%

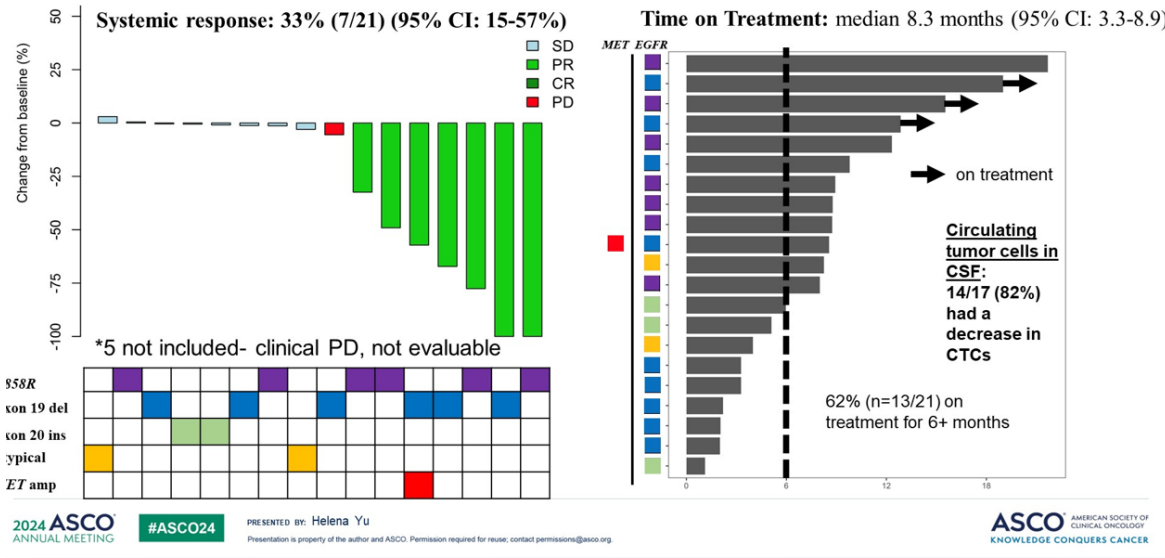
Yang et al, JCO 2019

# LMD subsets do better than we think in trials of novel TKIs

**TABLE 4.** Characteristics, CNS PFS, and CNS Objective Response Rates in Patients With Leptomeningeal Metastases at Baseline

| Characteristic or Outcome | Osimertinib Plus Platinum-Pemetrexed (n = 13) | Osimertinib Monotherapy (n = 5) |
|---|---|---|
| Age, years, median | 57 | 54 |
| Baseline WHO PS, No. (%) | | |
| 0 | 6 (46) | 2 (40) |
| 1 | 7 (54) | 3 (60) |
| *EGFR* mutation, No. (%) | | |
| Ex19del | 10 (77) | 3 (60) |
| L858R | 3 (23) | 2 (40) |
| Total exposure, months, median | 25.2 | 12.0 |
| CNS PFS event or censoring description, No. (%) | | |
| RECIST progression | 3 (23) | 5 (100) |
| Alive and progression-free | 8 (62) | 0 |
| Censored death | 1 (8) | 0 |
| Death | 1 (8) | 0 |
| Best objective CNS response, No. (%) | | |
| Patients with response | 9 (69) | 2 (40) |
| CR | 5 (38) | 1 (20) |
| PR | 4 (31) | 1 (20) |

## Results – Efficacy Leptomeningeal Cohort

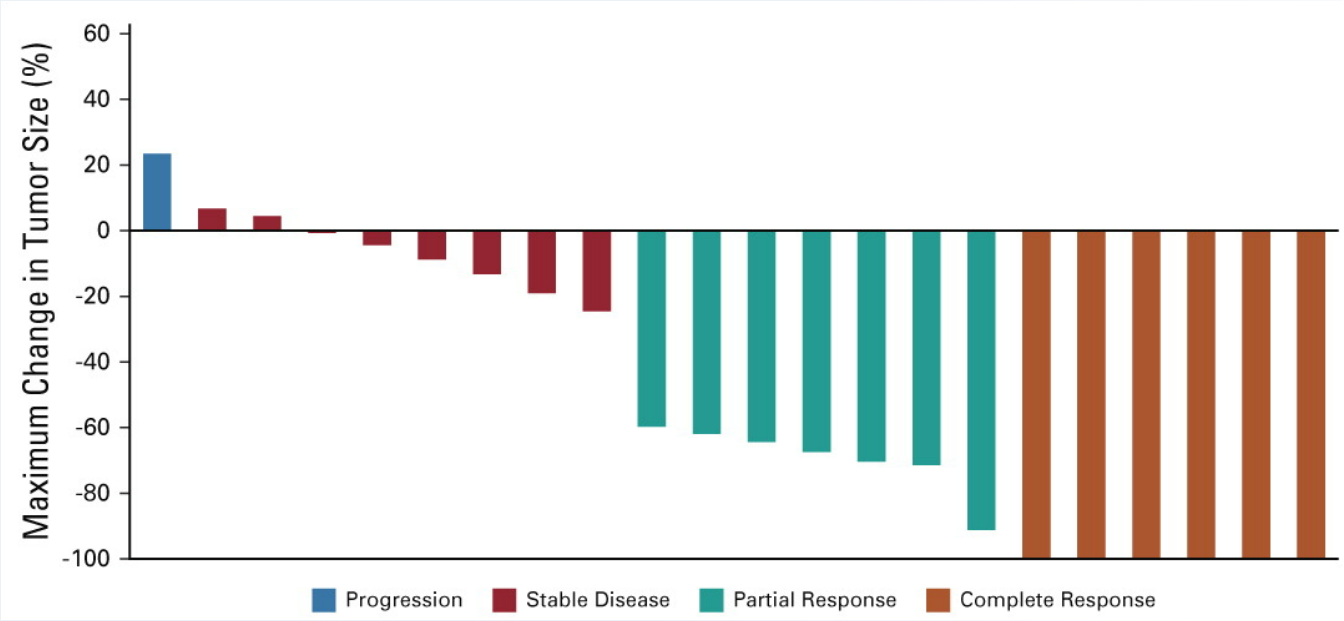


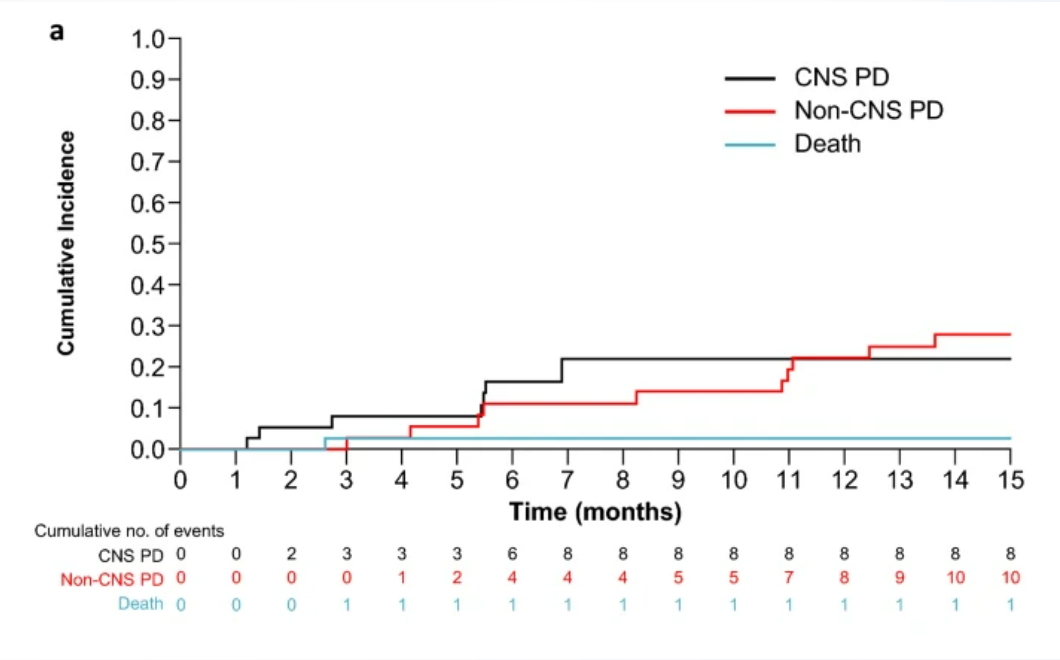

FLAURA2: 18 pts with baseline LMD
- CNS ORR 69% vs. 40%
- 62% vs. 0% alive and CNS progression-free
- Treatment exposure: 25.2 vs. 12.0 mo

Amivantamab + Laz in EGFRm NSCLC: 21 pts with LMD
- 8.3 mo PFS
- 14.4 mo OS
- 33% systemic response

Janne et al., JCO 2023, Yu et al, ASCO 2024

# LMD subsets do better than we think in trials of novel TKIs



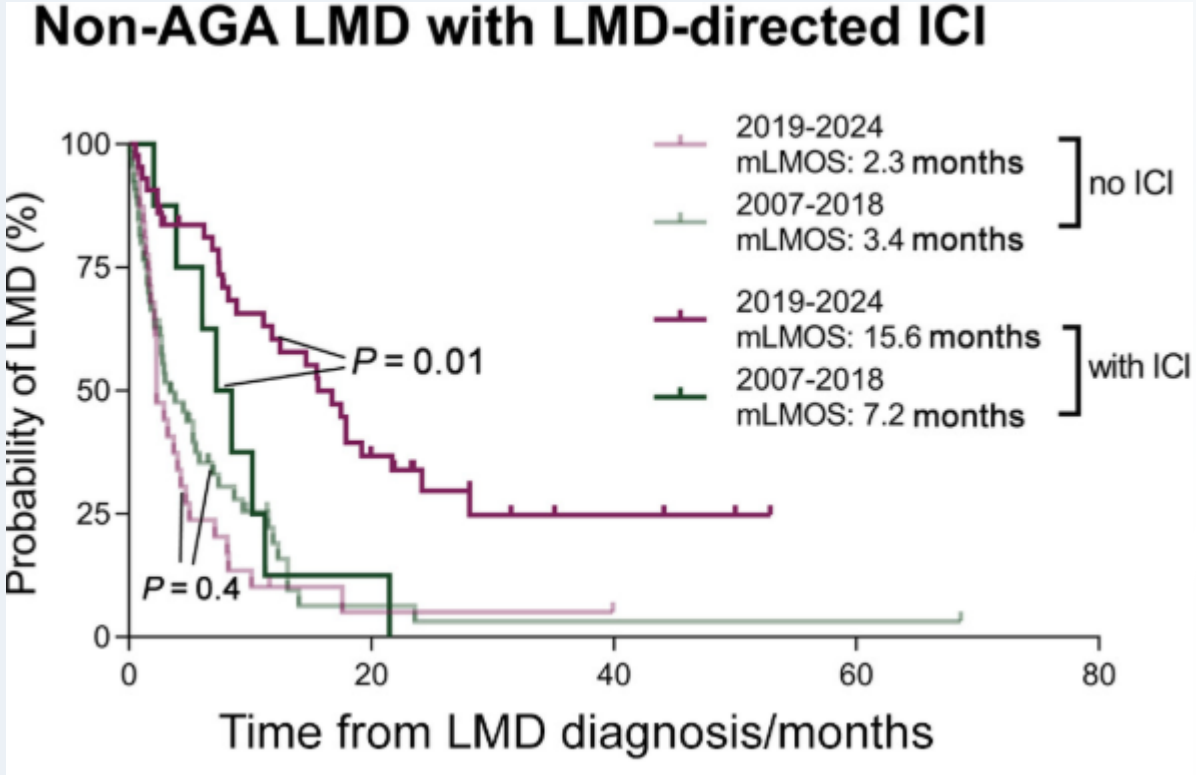



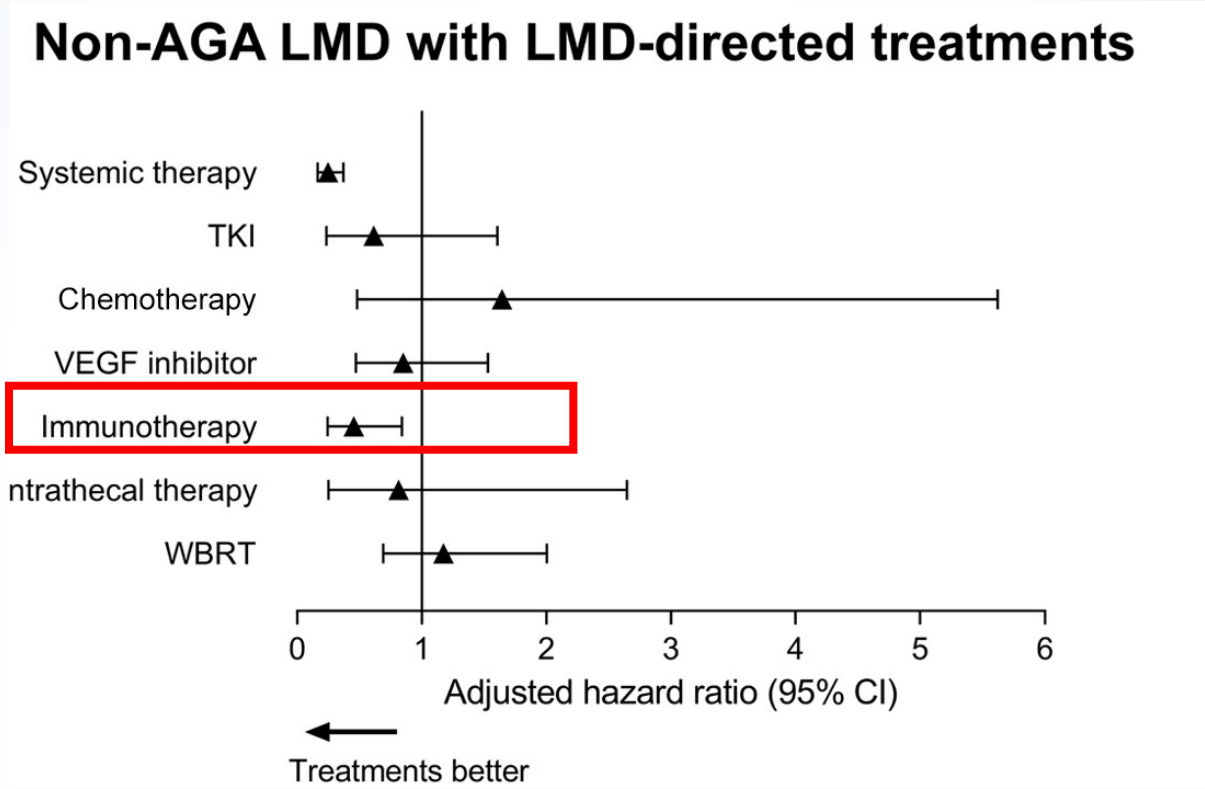

Phase II study of Lorlatinib in ALK+ NSCLC with CNS-progression: 4 pts with LMD
- Best response was SD

Another phase II study of ALK+ NSCLC treated w/ Lorlatinib: 2 pts with LMD
- 1 CR (mPFS 21.9 mo), 1 PR (mPFS 11 mo)

Bauer et al., Target Oncol 2020, Dagogo-Jack et al, JCO Precis Oncol 2022

# What about in patients withOUT actionable genomic alteration?

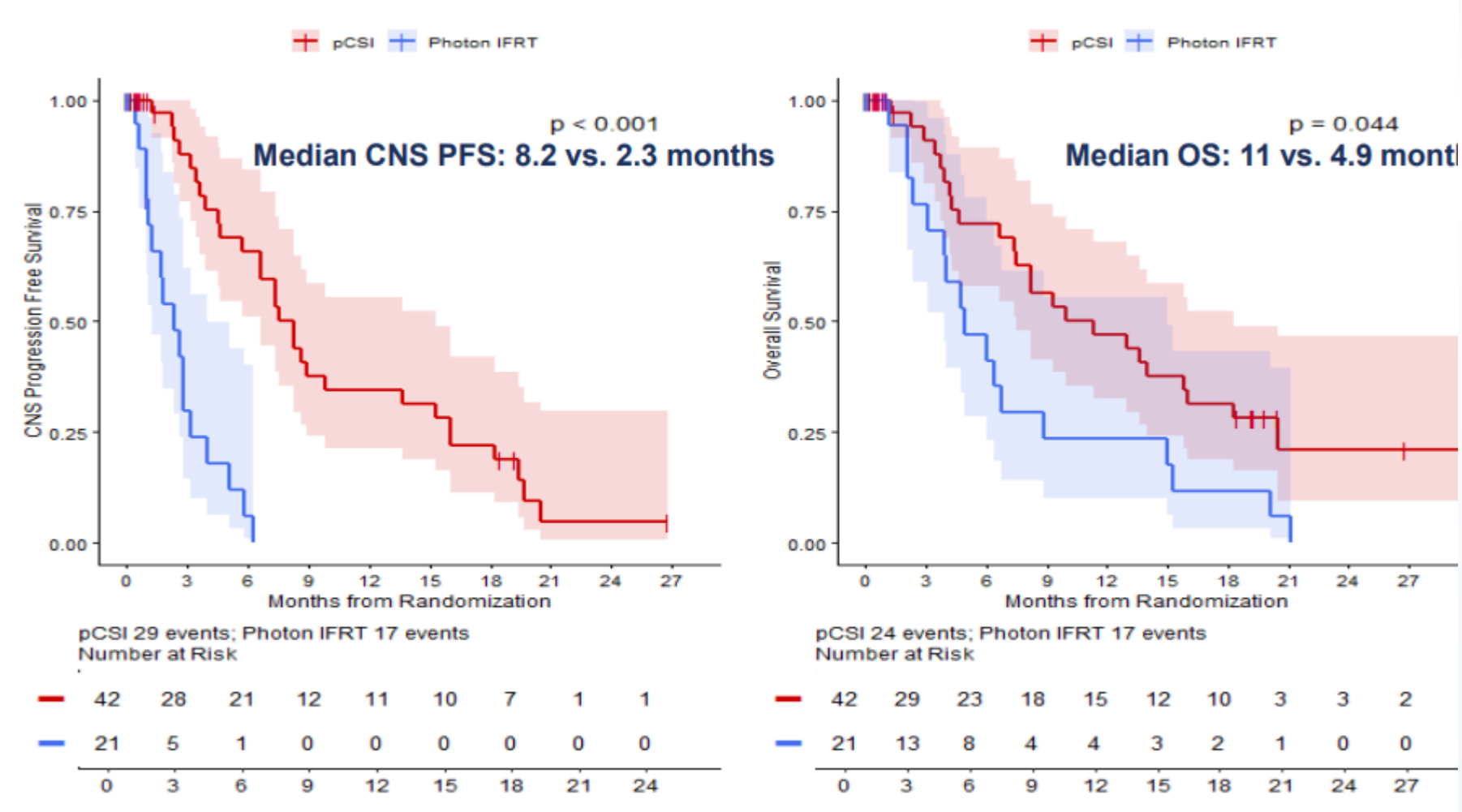



Treatment with immunotherapy was associated with improved LMOS in pts w/o AGA

Zheng et al., Annals of Oncology 2025

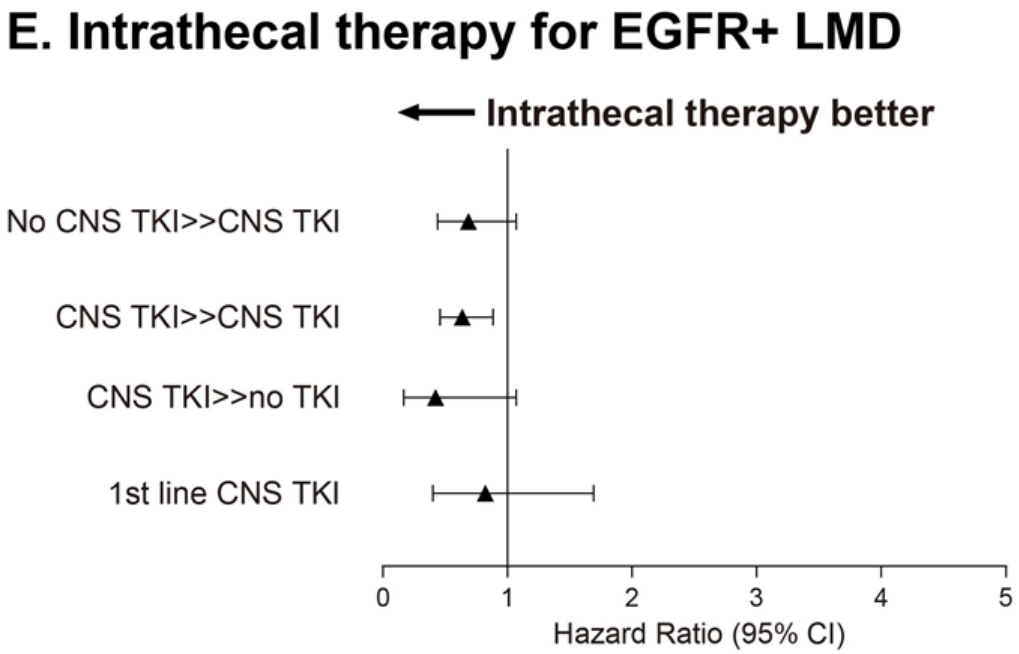
# Proton CSI has demonstrated CNS PFS and OS benefit in LMD

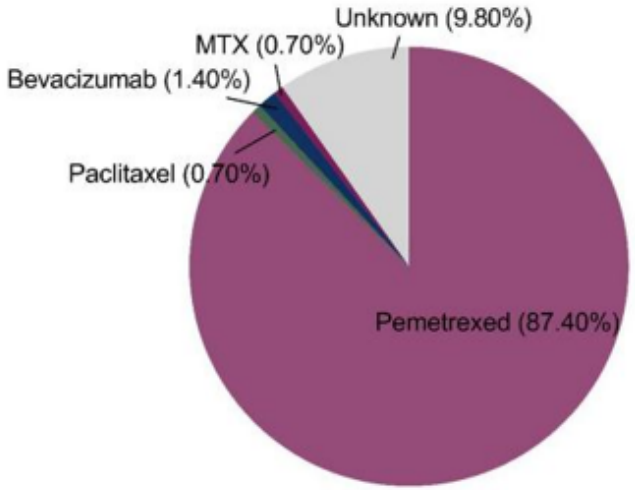



Yang et al, ASTRO 2024

Yang et al, JCO 2022

# There could be a role of intrathecal therapy, but prospective studies are needed




Trend towards improved LMOS with IT, particularly in those who received CNS TKI before and after LMD diagnosis

Zheng et al., Annals of Oncology 2025

# IT pemetrexed in EGFRm NSCLC with LMD

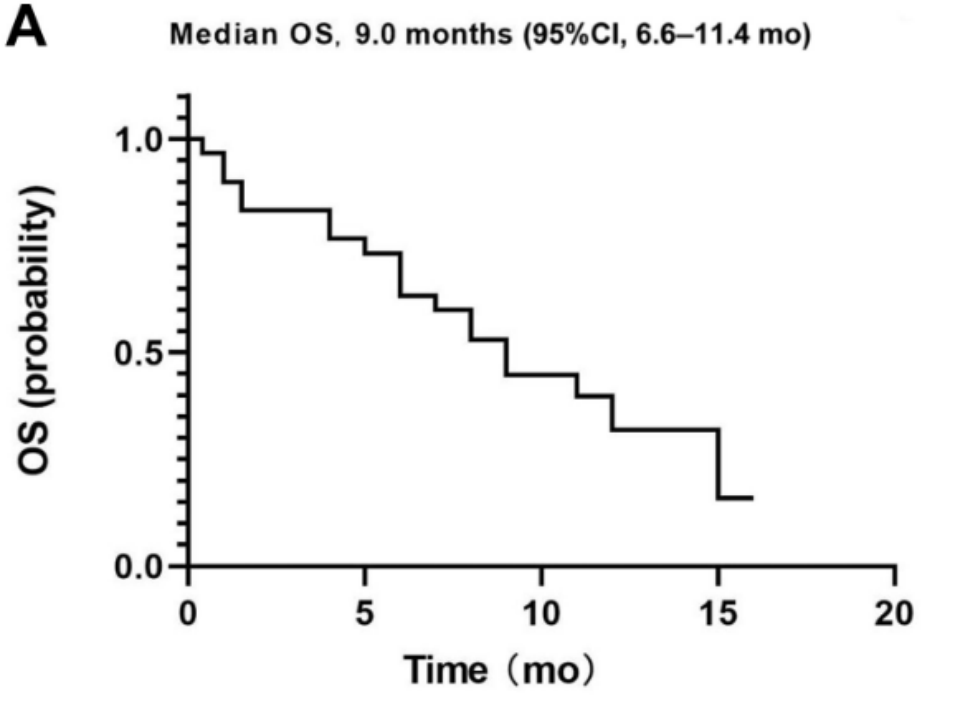



Table2. Clinical Response Rate and Patient Survival

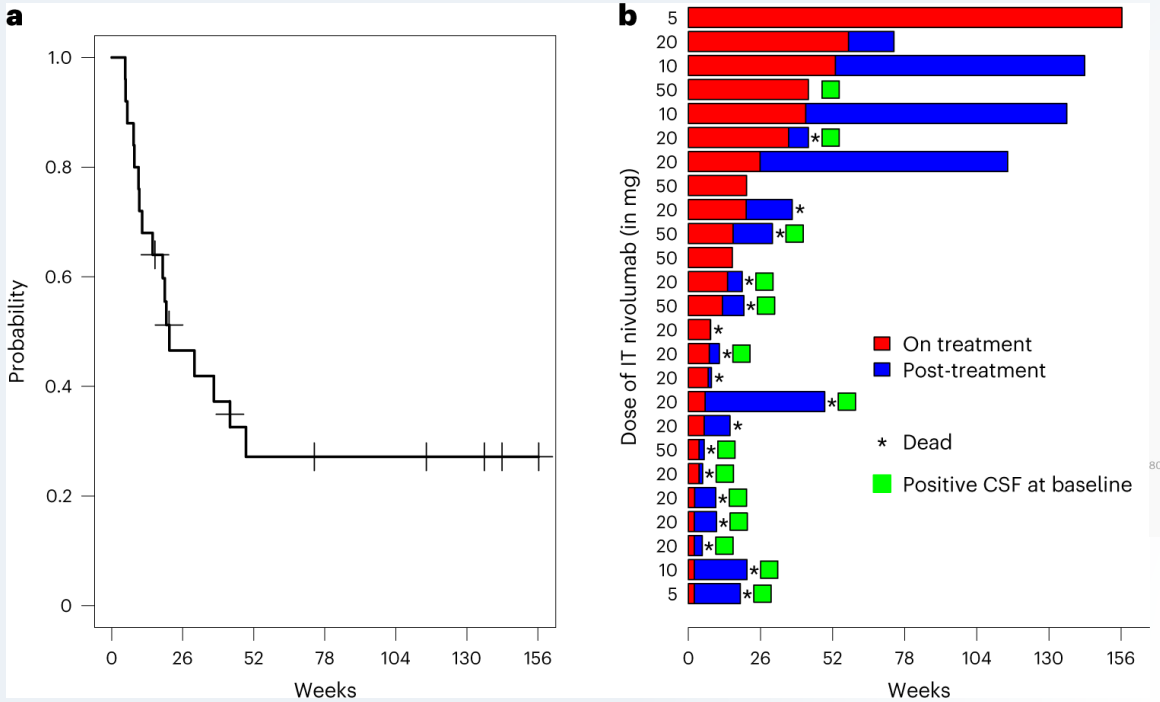
| Response | n (%) | OS (mo) | Median OS (mo) |
|---|---|---|---|
| CR | 2 (7.7) | 8.0-NR | NR |
| Obvious response | 13 (50.0) | 6.0~16.0 | 12.0 |
| PR | 7 (26.9) | 4.0~15.0 | 9.0 |
| Stable disease | 3 (11.5) | 4.0~6.0 | 5.0 |
| PD | 1 (3.8) | 1.5 | NR |
| Effective | 22 (84.6) | 4.0~16.0 | 12.0 |
| Noneffective | 4 (15.4) | 1.5~6.0 | 4.5 |

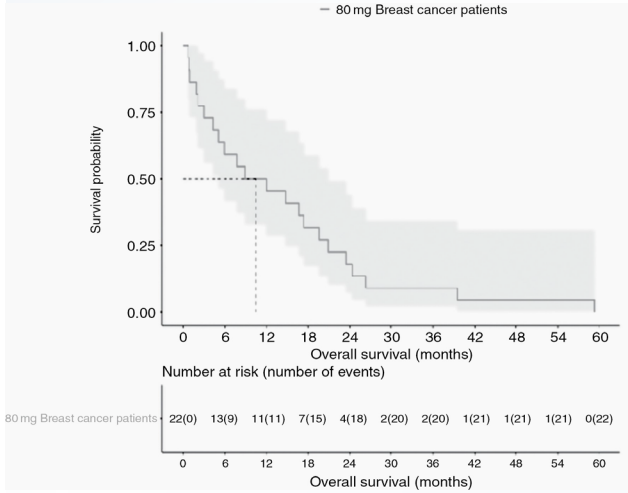
Abbreviations: CR, complete response; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response.

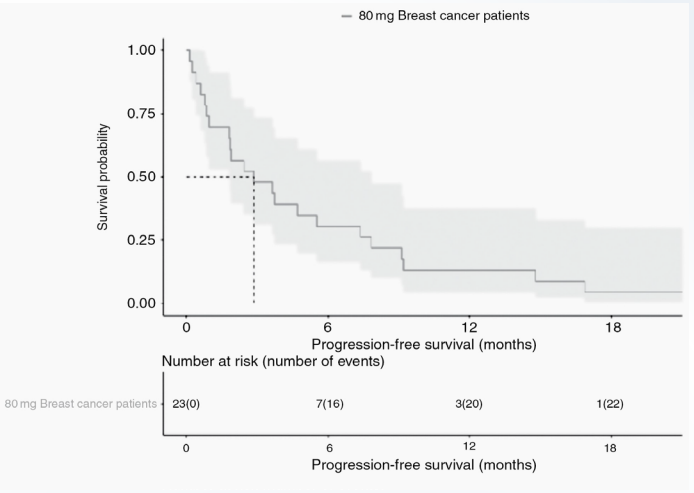
Phase I/II study of IT pemetrexed in EGFRm NSCLC with LMD: ORR 84.6%, mOS 9.0 mo

Fan et al., ESMO Open 2024

# IT as an emerging treatment for LMD in other solid malignancies




Phase I/Ib study of IT and IV nivolumab in melanoma pts with LMD: mOS 4.9 mo

Phase I/II study of IT trastuzumab in HER2+ breast cancer pts with LMD: mPFS 2.8 mo, mOS 10.5 mo

Glitza et al, Nature Medicine 2023; Kumthekar et al, Neuro-Oncology 2023

# Active Trials in NSCLC LMD:

| Study Treatment | Study Population | Location |
|---|---|---|
| IT deferoxamine | LMD from any solid tumor | Memorial Sloan Kettering |
| Furmonertinib + Chemo | LMD from EGFRm NSCLC, post 3rd gen EGFR TKI | Nanjing, Jiangsu, China |
| Trilaciclib + Chemo (Phase II) | LMD from NSCLC | Suzhou, Jiangsu, China |
| IT Pemetrexed + Bev | LMD from NSCLC | Shanghai, China |
| IT Pemetrexed | LMD from EGFR, ALK and ROS1+ NSCLC | Changsha, Hunan, China |
| IT Pemetrexed + IT Nivo (Phase II) | LMD from refractory non-squamous NSCLC | Shanghai, China |
| High-dose Furmonertinib + Bev + Pemetrexed | LMD from EGFRm NSCLC | Zhengzhou, Henan, China |
| IT + IV Nivolumab + Ipilimumab (Phase I) | Newly dx LMD from non-AGA NSCLC or Melanoma | University of Zurich |
| IT + IV Nivolumab | LMD from lung cancer or melanoma | MD Anderson Cancer Center |
| IT Pemetrexed + Osimertinib vs. Osimertinib alone | LMD from EGFRm NSCLC | Huizhou, Guandong, China |

# Future Directions

- More prospective studies and dedicated clinical trials of systemic and intrathecal therapies are needed to expand current treatment options in patients with LMD
  - Broader inclusion of patients with active brain mets and LMD in trials
  - Dedicated CNS cohorts
- IT options for LMD from non-AGA NSCLC
- Early pCSI for LMD
- Developing improved response assessment criteria and endpoints for LMD
  - CTCs and ctDNA

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