

INTRODUCTION

- We evaluated real-world CNS treatment patterns and outcomes in patients with stage IV non-small cell lung cancer (NSCLC) harboring actionable molecular alterations who developed CNS metastases, in the era of CNS-active targeted therapies.

METHODS

- We retrospectively analyzed patients at MedStar Georgetown University Hospital with stage IV NSCLC and an actionable alteration diagnosed between January 2018 and July 2024, who had CNS metastases at diagnosis or while on frontline systemic therapy.
- Overall survival (OS) was estimated using the Kaplan-Meier method.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- In this real-world cohort of molecularly selected NSCLC patients with CNS metastases, management varied, with approximately half receiving local therapy and most receiving targeted systemic treatment.
- A subset of patients, including those with CNS symptoms, achieved meaningful intracranial responses with systemic therapy alone, and survival was similar regardless of symptom status.
- These findings support individualized treatment strategies in the era of CNS-active targeted therapies.

Future Direction for Research

- Larger, prospective studies are needed to define optimal management of CNS metastases in molecularly selected NSCLC, including which patients can safely defer local CNS-directed therapy.

RESULTS

Table 1. Baseline Characteristics (N=106)

Characteristic	N (%)
Median age, years (range)	63 (32–82)
Female	71 (67)
Never smoker	64 (60)
Adenocarcinoma	104 (98)
CNS metastasis timing	
Present at diagnosis	93 (88)
Developed on frontline therapy	13 (12)
Molecular alteration	
EGFR exon 19 deletion	25 (24)
EGFR L858R	19 (18)
ALK fusion	11 (10)
ROS1 fusion	9 (8)
HER2 mutation	8 (8)
KRAS G12C	7 (7)
BRAF V600E	7 (7)
EGFR exon 20 insertion	6 (6)
RET fusion	6 (6)
EGFR atypical	6 (6)
EGFR compound	2 (2)
Symptom status at CNS diagnosis	
Asymptomatic	61 (58)
Symptomatic	42 (40)
Unknown	3 (3)
CNS-directed local therapy	
Radiation only	38 (36)
Surgery only	7 (7)
Radiation and surgery	11 (10)
SRS (% of total radiated)	45 (92)
WBRT (% of total radiated)	2 (4)
Proton craniospinal (% of total radiated)	1 (2)
Systemic therapy	104 (98)
Targeted therapy	75 (72)
Chemotherapy	8 (8)
Chemoimmunotherapy	8 (8)
Immunotherapy	6 (6)
Clinical trial treatment	7 (7)

Figure 1. Overall Survival

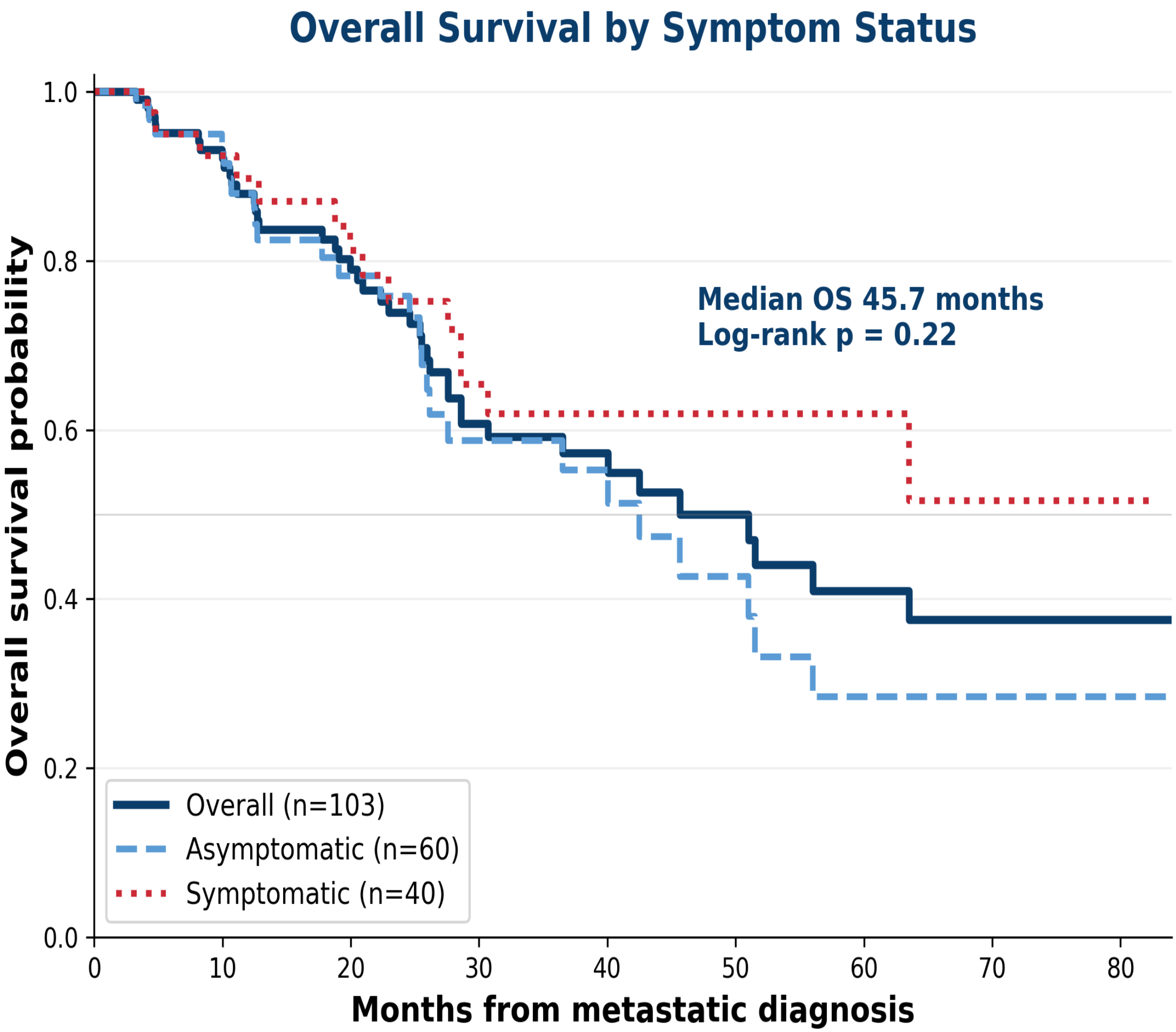


Table 3. Symptomatic Patients Treated with Systemic Therapy Alone (n=6)

Mutation	Age	Sex	Systemic Therapy	CNS Response
EGFR exon 19 del	69	F	Osimertinib	CR
EGFR ex19del/C797S + MET amp	78	M	Osimertinib	PR
EML4::ALK fusion	38	M	Lorlatinib	CR
HMBBOX1::ALK fusion	55	M	Lorlatinib	CR
EGFR L858R	72	F	Osimertinib	SD
BRAF V600E	63	F	Dabrafenib + trametinib	PD

CNS objective response rate 66% by RECIST. All patients had symptomatic CNS metastases and received no CNS-directed radiation or surgery. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 2. Treatment Patterns and Outcomes by Molecular Subtype

Molecular Alteration	n	CNS at diagnosis	Local therapy	Systemic alone	CNS ORR	12-mo OS	24-mo OS
EGFR exon 19 del	25	96%	44%	56%	19/21	100%	90%
EGFR L858R	19	84%	42%	58%	14/16	83%	64%
ALK	11	82%	27%	73%	8/9	100%	100%
ROS1	9	56%	67%	33%	3/5	89%	76%
HER2	8	100%	88%	12%	4/4	67%	44%
KRAS G12C	7	86%	86%	14%	3/5	71%	29%
BRAF V600E	7	100%	57%	43%	3/4	54%	54%
EGFR exon 20	6	83%	33%	67%	4/4	100%	80%
RET	6	100%	67%	33%	3/4	100%	75%
EGFR atypical	6	83%	67%	33%	1/4	100%	80%
EGFR compound	2	100%	50%	50%	2/2	100%	100%

EGFR compound mutations (n=2): exon 19 deletion + G719S/R574L; exon 19 deletion + C797S with MET amplification.
EGFR atypical mutations (n=6): G719A/S768I; G719S; exon 18 G719C then L861Q; exon 19 indel E746_L747delinsIP; H773_V774 insertion; L747 (with BRAF V600).