NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Amivantamab and Lazertinib in *EGFR*-mutated CNS Cancers

Amivantamab-vmjw in combination with either lazertinib or carboplatin and pemetrexed has not been specifically approved for patients with *EGFR*–sensitizing mutation-positive NSCLC brain metastases. Per MARIPOSA and MARIPOSA-2 protocols, patients with brain metastases were eligible provided intracranial disease was clinically stable, asymptomatic, and previously treated.

EGFR–sensitizing mutation-positive NSCLC brain metastases[a]

NCCN Guidelines® for CNS recommend amivantamab-vmjw + lazertinib as a preferred[a] combination regimen for patients with NSCLC harboring exon 19 deletions or exon 21 L858R mutations with brain metastases[1]

Systemic therapy recommendations[1,b]

Preferred[c] (Category 2A)[1]

- Amivantamab-vmjw + lazertinib[d,e] *
- Amivantamab-vmjw + carboplatin/pemetrexed[e] *
- Osimertinib

Other recommended[1]

- Carboplatin/ osimertinib/ pemetrexed (Category 1)
- Cisplatin/ osimertinib/ pemetrexed (Category 1)
- Erlotinib (Category 2A)
- Afatinib (Category 2B)
- Gefitinib (Category 2B)

*Amivantamab-vmjw recommendations included in V2.2026[1] based on findings from the phase 3 MARIPOSA[2] and MARIPOSA-2[3] studies

MARIPOSA and MARIPOSA-2 studies[2,3]

MARIPOSA[2]

Study design

Patient population:
- Treatment- naive
- *EGFR* Ex19del/ L858R
- Asymptomatic/ previously treated and stable brain metastases

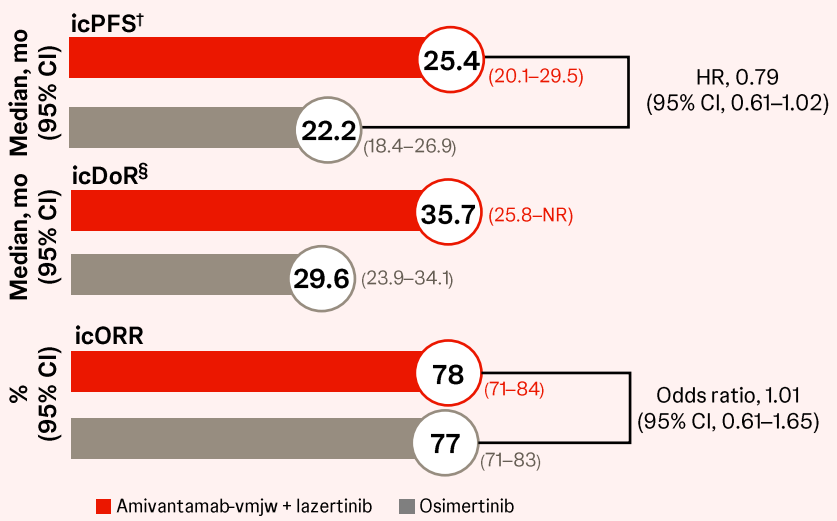
2:2:1
- Amivantamab-vmjw + lazertinib (n=429)
- Osimertinib (n=429)
- Lazertinib (n=216)[4]

Prespecified intracranial endpoints as assessed by BICR:
- icPFS
- icDOR
- icORR

Intracranial efficacy summary

Median follow-up: **37.8 months**[f]

OS in patients with baseline brain metastases:
HR = 0.67 (95% CI, 0.50–0.90)[2]



Note: icPFS, icDoR, and icORR were prespecified secondary analyses and were not powered to show statistical significance. †icPFS was defined as the time from randomization to intracranial disease progression or death, whichever occurred first, based on BICR using RECIST v1.1 in participants with a history of brain metastasis. §icDOR was defined as the time from first documented intracranial objective response to documented intracranial progression or death, whichever occurred first, in participants with a history of brain metastasis.

Safety summary

	Amivantamab-vmjw + lazertinib (n=421)	Osimertinib (n=428)
Grade ≥3 AEs	80%	52%
AEs of special interest (any grade)		
Paronychia	69%	30%
IRR	65%	0
Rash	64%	32%
VTE[i]	40%	11%

MARIPOSA-2[3]

Study design

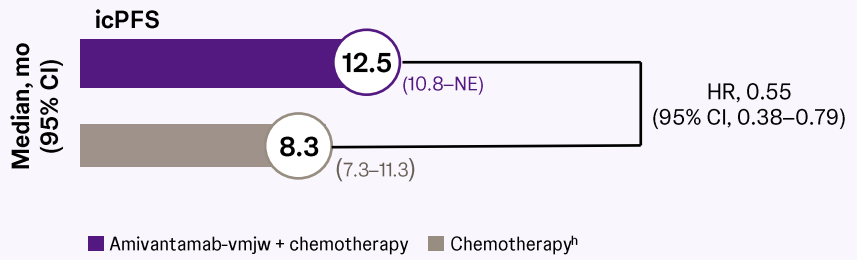
Patient population:
- Post-osimertinib
- *EGFR* Ex19del/ L858R
- Asymptomatic/ stable intracranial disease and on a low steroid dose

2:2:1
- Amivantamab-vmjw + chemotherapy (n=131)
- Amivantamab-vmjw + chemotherapy + lazertinib (n=263)
- Chemotherapy (n=263)

Prespecified intracranial endpoints:
- icPFS by BICR

Intracranial efficacy summary

Median follow-up: **8.7 months**[g]



Note: icPFS was a prespecified secondary analysis and was not powered to show statistical significance.

Safety summary

	Amivantamab-vmjw + chemotherapy (n=130)	Chemotherapy (n=243)
Grade ≥3 TEAEs	72%	48%
TEAEs of special interest (any grade)		
Paronychia	58%	<1%
IRR	43%	5%
Rash	37%	<1%
VTE[i]	10%	5%

AE, adverse event; BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HR, hazard ratio; icDoR, intracranial duration of response; icORR, intracranial overall response rate; icPFS, intracranial progression-free survival; IRR, infusion-related reaction; IV, intravenous; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NE, not estimable; NR, not reached; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event; VTE, venous thromboembolism.

[a]If an active agent exists (eg, cytotoxic, targeted, immune modulating), trial of systemic therapy with good CNS penetration may be considered in select patients (eg, for patients with small asymptomatic brain metastases it is reasonable to hold on treating with radiation to see if systemic therapy can control the brain metastases). Consultation with a radiation oncologist and close MRI surveillance is strongly recommended. There are no data from prospective clinical trials comparing the two strategies to assess what the impact of delayed radiation would be in terms of survival or in delay of neurologic deficit development. [b]An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. [c]Preferred therapy: interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. [d]For exon 19 deletion or L858R. [e]Amivantamab and hyaluronidase subcutaneous injection may be substituted for IV amivantamab-vmjw. Amivantamab and hyaluronidase has different dosing and administration instructions compared to IV amivantamab. [f]Data cut off date: December 4, 2024. [g]Data cut off date: July 10, 2023. [h]Chemotherapy was carboplatin-pemetrexed. [i]VTE is a grouped term that included pulmonary embolism, deep-vein thrombosis, limb venous thrombosis, venous thrombosis, thrombosis, superficial-vein thrombosis, thrombophlebitis, embolism, venous embolism, jugular-vein thrombosis, sigmoid-sinus thrombosis, axillary-vein thrombosis, pulmonary infarction, vena cava thrombosis, central venous catheterization, portal-vein thrombosis, the post-thrombotic syndrome, pulmonary thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, pelvic venous thrombosis, and the superior vena cava syndrome. [j]VTE is a grouped term that included pulmonary embolism, deep-vein thrombosis, embolism, renal vein thrombosis, venous thrombosis limb, embolism venous, jugular vein thrombosis, superficial vein thrombosis, thrombophlebitis, and thrombosis.

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NCCN Guidelines for Amivantamab and Lazertinib in *EGFR*-mutated CNS Cancers

Amivantamab-vmjw in combination with lazertinib has not been specifically approved for patients with NSCLC harboring leptomeningeal metastases.

NSCLC leptomeningeal metastases

NCCN Guidelines for CNS recommend Amivantamab-vmjw + lazertinib as an "other recommended" combination regimen for patients with NSCLC harboring exon 19 deletions or exon 21 L858R mutations with leptomeningeal metastases[1]

Systemic therapy recommendations[1]

Other recommended (Category 2A)[1]

- Amivantamab-vmjw + lazertinib[a,*]
- Osimertinib[b]
- Erlotinib (Category 2B)[c]
- Pemetrexed[d]

Useful in certain circumstances (Category 2A)[1]

- Tepotinib[e]

*Amivantamab recommendations included in V2.2026,[1] citing evidence from NCT04965090[2] and an individual case study[3]

Amivantamab-vmjw + lazertinib as a systemic therapy option for *EGFR*-mutated NSCLC and leptomeningeal metastases[a]

NCT04965090[2]

Study design[f]

Single-center MSKCC study in participants who previously received:

- Osimertinib for *EGFR* alterations sensitive to TKIs (ex19 del, L858R, ex20ins, and uncommon *EGFR* alterations)
- Platinum-based chemotherapy for exon 20 insertions

Also, have:

- Had an extracranial biopsy
- Have positive CSF cytology or the presence of CTCs in the CSF

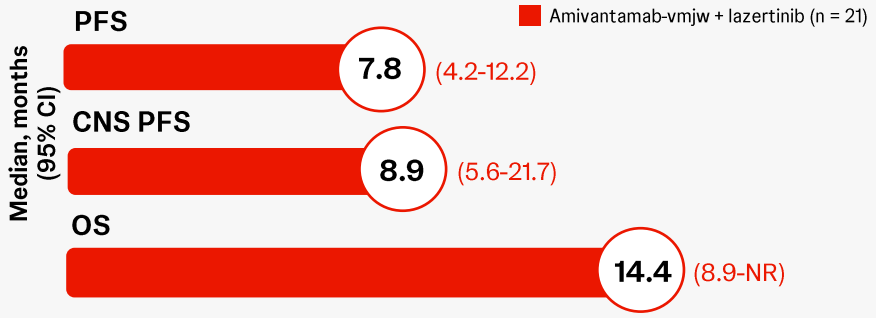
Primary endpoint:

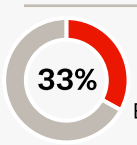
- ORR by systemic and CNS ORR by RECIST and RANO-BM or RANO-LM[g]

Treatment:

- IV amivantamab was administered weekly for Cycle 1 and Q2W thereafter + oral lazertinib daily
- Treatment was deemed active if ≥3 responses were observed in ≤6 months in each cohort

Systemic efficacy in patients with leptomeningeal metastases





ORR, n/N (95% CI)
7/21 (15–57)
Evaluable responses included 7 PR, 8 SD, and 1 PD[h]

Median time on treatment,
8.3 months
(range, 1.1–25.3)

ORR for LMD was based on a composite of systemic and CNS ORR using RECIST 1.1 and RANO-LM criteria, which include neurologic examination, CSF results, and CNS imaging[g]

Safety summary

- No new safety signals were identified
- In the overall population, treatment discontinuations, dose reductions, and dose interruptions were reported in 7%, 17%, and 50%, respectively
- The most common TRAEs (all grade) were rash, IRR, and paronychia

Individual case study[3]

Case presentation

- 67-year-old Asian male with stage IV squamous cell lung carcinoma poorly differentiated with a PD-L1 IHC score of 70%
- A spiculated 7.7 cm lesion in the right upper lung, along with hilar and subcarinal lymphadenopathy
- Uncommon EGFR mutations G719A and A289V
- No initial CNS involvement
- Disease progression after osimertinib, chemotherapy, and immunotherapy, including development of leptomeningeal disease

After 6 weeks of amivantamab-vmjw:

- Follow up scans showed a PR with a 32.2% decrease in tumor size per RECIST 1.1
- MRI showed reduction in parenchymal lesions and decreased leptomeningeal enhancement

After 6 months of amivantamab-vmjw:

- 100% resolution of CNS disease, including leptomeningeal enhancement
- No evidence of circulating tumor cells in the CSF
- Patient regained ability to walk and perform activities of daily living independently
- Durable response at 19 months, as measured by RECIST 1.1 with CT scan

Limitations

Moderately sized participant populations from a single-center or case report may preclude generalizability, and bias may be introduced due to data collection from a single-center

Johnson & Johnson

AE, adverse event; CI, confidence interval; CNS, central nervous system; CSF, cerebrospinal fluid; CTC, circulating tumor cells; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; IRR, infusion-related reaction; IV, intravenous; LMD, leptomeningeal disease; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; NR, not reached; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; Q2W, every 2 weeks; RANO-BM, Response Assessment in Neuro-Oncology brain metastases; RANO-LM, Response Assessment in Neuro-Oncology leptomeningeal metastases; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TKI, tyrosine kinase inhibitor; TRAE, treatment-related adverse event.

[a]Amivantamab and hyaluronidase subcutaneous injection may be substituted for IV amivantamab-vmjw. Amivantamab and hyaluronidase has different dosing and administration instructions compared to IV amivantamab. [b]*EGFR* mutation positive, either single or double dose. [c]Weeklypulse erlotinib for *EGFR* exon 19 deletion or exon 21 L858R mutation. [d]Intrathecal pemetrexed for *EGFR* mutation positive. [e]*MET* exon 14 mutated. [f]A cohort of 20 patients with brain metastases was included. [g]Because radiographic findings in LMD can be unmeasurable or subjective, a dedicated neuroradiologist assigned response assessments according to modified RANO-LM scorecard, which assesses nodules, leptomeningeal enhancement, cranial nerve enhancement, and parenchymal brain metastases on a predesignated scale. [h]5 patients had clinical PD that was not evaluable.

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