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

1L Therapy: *EGFR* exon 19 deletion or L858R mutation-positive NSCLC

NCCN Guidelines® recommend **lazertinib + amivantamab** as an **NCCN Category 1, preferred**[a] treatment option for 1L *EGFR* exon 19 deletion or exon 21 L858R mutation positive advanced or metastatic NSCLC

EGFR mutation discovered prior to 1L systemic therapy

Preferred[a] (Category 1)

- Osimertinib[b]
- (Carboplatin or cisplatin) /osimertinib/pemetrexed[c]
- Lazertinib + amivantamab-vmjw[d] 1

Updates as of V1.2026:

1 Lazertinib + amivantamab upgraded to preferred status

Based on OS analysis from the phase 3, open-label,[e] randomized MARIPOSA study with findings from the phase 2, open-label, COCOON (randomized) and SKIPPirr studies

2 Lazertinib monotherapy added

Based on the phase 3, double-blind, randomized LASER301 study and exploratory analysis from the MARIPOSA study

Useful in certain circumstances

- Afatinib[b] (Category 1)
- Dacomitinib[b] (Category 1)
- Gefitinib[b] (Category 1)
- Erlotinib[b] (Category 1)
- Erlotinib + bevacizumab
- Erlotinib + ramucirumab
- Lazertinib[b] (Category 2A) 2

2L+ Therapy: *EGFR* exon 19 deletion or L858R mutation-positive NSCLC with disease progression

Progression[f] on osimertinib or lazertinib ± amivantamab-vmjw[d]

Asymptomatic

- Consider definitive local therapy (SABR or surgery) for limited lesions[g,h]
- Continue osimertinib or lazertininb ± amivantamab-vmjw[d] 3

Symptomatic

Systemic

Multiple lesions[i]

Preferred[a,k]

- Carboplatin/pemetrexed + **amivantamab-vmjw**[c,d,l]

Useful in certain circumstances

- Lazertinib + amivantamab-vmjw[d,l] 4

Limited progression[j]

- Consider definitive local therapy (SABR or surgery)[g]
- Continue osimertinib or lazertininb ± amivantamab-vmjw[d] 3
- See therapy for multiple lesions

Brain

- Consider definitive local therapy (SRS)[j]
- Continue osimertinib or lazertininb ± amivantamab-vmjw[d] 3

Progression

Preferred (*EGFR* mutations)

- Datopotamab deruxtecan-dlnk

Other recommended (*EGFR* exon 19 deletion or L858R mutation)

- Lazertinib + amivantamab-vmjw[l,m] 5

NCCN Guidelines for 2L+ *EGFR* exon 19 deletion or exon 21 L858R mutation positive advanced or metastatic NSCLC recommend:

- Amivantamab + carboplatin/pemetrexed as a Category 1, preferred[a] subsequent treatment option for symptomatic, systemic disease with multiple lesions[c,l]
- Lazertinib + amivantamab as a Category 2A, useful in certain circumstances treatment option for symptomatic, systemic disease with multiple lesions[l]
- Lazertinib + amivantamab as a Category 2A, other recommended subsequent therapy treatment option[c,l,m]

Updates as of V1.2026:

3 Lazertinib monotherapy added as subsequent therapy option

4 Lazertinib + amivantamab added as useful in certain circumstances and as other recommended following progression

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Based on findings from the phase 1, open-label CHRYSALIS Cohort E and the phase 3, open-label, randomized PALOMA-3 studies

Prophylaxis management recommendations: *EGFR* exon 19 deletion or L858R mutation-positive NSCLC

Updates as of V1.2026:

Dermatologic adverse events

Lazertinib + amivantamab (1L+); amivantamab + chemotherapy (2L+)

ADDITION OF prophylactic oral antibiotics,[n] clindamycin lotion to the scalp, chlorhexidine to the nails, and a ceramide-based non-comedogenic moisturizer

Based on findings from the phase 2, open-label, randomized COCOON study

Venous thromboembolism

Lazertinib + amivantamab (1L+)

ADDITION OF prophylactic anticoagulants at the time of initiation

Infusion-related reactions

Lazertinib + amivantamab (1L+); amivantamab + chemotherapy (2L+)

ADDITION OF prophylactic oral dexamethasone (8 mg) for 2 days prior to first treatment dose

Based on findings from the phase 2, open-label SKIPPirr study

1L, first-line; 2L, second-line; CNS, central nervous system; EGFR, epidermal growth factor receptor; HSCLC, human small cell lung cancer; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; SABR, stereotactic ablative radiotherapy; SCLC, small cell lung cancer; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor.
[a]Preferred therapy: interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. [b]For performance status 0-4.[c]Nonsquamous. [d]See prophylaxis section for management recommendations. [e]MARIPOSA was open-label for the lazertinib + amivantamab treatment arm only; other arms were double-blind. [f]Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI. [g]Image-guided tumor ablation therapy (cryotherapy, microwave, radiofrequency) may be an option for select patients. [h]Clinical trials have included up to 3-5 progressing sites. [i]Consider a biopsy at time of progression to rule out SCLC transformation and biopsy or plasma testing to evaluate mechanisms of resistance. [j]Definitive local therapy of CNS disease can include asymptomatic lesions at risk for symptomatic progression based on site, location, and edema. [k]Not an option for EGFR S768I, L861Q, and/or G719X mutations. [l]If not previously given. [m]If progression on (carboplatin or cisplatin)/osimertinib/pemetrexed. [n]Doxycycline or minocycline.

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Last updated: Feb 2026
US-SFM-7515