NCCN Guidelines: Systemic Therapy for Patients with *EGFR* Exon 20 Insertion Mutated Advanced NSCLC

First line (PS 0-1)

Preferred	Other recommended	Useful in certain circumstances
Pembrolizumab + chemotherapy as appropriate for histology*	Additional combination regimens involving: • Atezolizumab**, • Nivolumab/ipilimumab, • Cemiplimab-rwlc, or • Tremelimumab-actl/durvalumab, as appropriate for histology*	Contraindications to PD-1/PD-L1 inhibitors • Chemotherapy as appropriate for histology* • Bevacizumab + chemotherapy for adenocarcinoma*

*Bevacizumab and pemetrexed not recommended for SCC
**Atezolizumab not recommended for first line treatment of SCC

Subsequent therapy

Second line	Later lines	
• **Amivantamab-vmjw** • **Mobocertinib**	If not received previously: • **Amivantamab-vmjw** • **Mobocertinib** Amivantamab-vmjw can be used if patients have previously received mobocertinib and vice versa, because these agents have different MoAs.	Or other systemic therapy: Preferred (no previous IO) • Nivolumab • Pembrolizumab • Atezolizumab Other (no previous or previous IO) • Chemotherapy as appropriate for histology

See guidelines for full recommendations. EGFR, epidermal growth factor receptor; PS, performance status; PD-1, programmed death protein 1; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma; MoAs, mechanisms of action; IO, immunotherapy.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3.2023. Updated April 13, 2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450.

Amivantamab-vmjw in *EGFR* Exon 20 Insertion Mutated Advanced NSCLC

Efficacy Results

CHRYSALIS

Phase 1/2 multicohort open label dose-escalation/dose expansion trial

- Metastatic or unresectable NSCLC
- Activating or resistance *EGFR* or *MET* mutations or amplifications (*EGFR* exon 20 insertion mutations reported here)
- Failed or ineligible for standard of care therapy
- Previously treated or asymptomatic brain metastases allowed
- Results reported for Phase 2 post-platinum patients treated with 1050 mg dose (1400 mg ≥ 80 kg)

MoA: Bispecific EGFR and MET receptor monoclonal antibody

Long term results reported at ELCC 2022

	N = 114
Objective response, % (95% CI)	37 (28–46)
Median duration of response, mo (95% CI)	12.5 (6.9–19.3)
Median PFS, mo (95% CI)	6.9 (5.6–8.8)
Median OS, mo (95% CI)	23 (18.5–29.5)

Data cutoff date: June 8, 2020 (median follow-up 19.2 mo)

ORR across subgroups:	
Older patients	
≥65 years	32%
≥75 years	33%
Heavily pretreated	
>2 prior lines	53%
Prior IO	42%
Prior EGFR TKI	52%
Platinum sensitive	36%
Platinum resistant	31%

FDA approved May 2021 for patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations that progressed on or after platinum-based chemotherapy

EGFR, epidermal growth factor receptor; MoA, mechanism of action; ELCC, European Lung Cancer Conference; CI, confidence interval; PFS, progression-free survival; mo, months; OS, overall survival; IO, immunotherapy; TKI, tyrosine kinase inhibitor.

Garrido Lopez P et al. Presented at ELCC 2022. Abstract 30; Park K et al. *J Clin Oncol*. 2021;39:3391-3402; FDA Approved Drugs: Oncology (Cancer) / Hematologic Malignancies Approval Notifications /Oncology (Cancer) Approvals & Safety Notifications. Reviewed June 20, 2023. Accessed June 20, 2023. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm.

Amivantamab-vmjw in *EGFR* Exon 20 Insertion Mutated Advanced NSCLC

Safety Results

CHRYSALIS

Patients treated at the recommended phase 2 dose: 1050 mg (1400 mg ≥ 80 kg) (n = 258)

	n (%)
Any adverse event	267 (100)
Grade ≥3	101 (39)
Adverse event leading to dose reduction	26 (10)
Adverse event leading to dose interruption	88 (34)
Adverse event leading to discontinuation of therapy	17 (7)
Adverse event leading to death	13 (5)

AEs in ≥20% of patients, n (%)

	Any grade	Grade 1	Grade 2	Grade ≥3
Rash	202 (78)	101 (39)	94 (36)	7 (3)
Infusion-related reaction	167 (65)	21 (8)	140 (54)	6 (2)
Paronychia	104 (40)	50 (19)	51 (20)	3 (1)
Hypoalbuminemia	63 (24)	21 (8)	38 (15)	4 (2)
Constipation	58 (23)	36 (14)	22 (9)	0
Nausea	55 (21)	40 (16)	14 (5)	1 (0.4)
Dyspnea	52 (20)	28 (11)	13 (5)	11 (4)

EGFR, epidermal growth factor receptor; AE, adverse event.

Park K et al. *J Clin Oncol*. 2021;39:3391-3402.

Mobocertinib in *EGFR* Exon 20 Insertion Mutated Advanced NSCLC

Efficacy Results

Study 101/EXCLAIM

Phase 1/2 global multicohort open label trial

- Stage IIIB or IV NSCLC
- *EGFR* exon 20 insertion or HER2 exon 20 mutations
- Results shown here for overlapping PPP and EXCLAIM cohorts:
  - **PPP cohort** = all platinum-treated patients with *EGFR* exon 20 insertions from the dose-escalation, expansion, and EXCLAIM extension cohorts
  - **EXCLAIM cohort** = extension cohort including only patients with *EGFR* exon 20 insertions; includes 10 patients not pretreated with platinum
- All patients received mobocertinib 160 mg once daily

MoA: Small molecule tyrosine kinase inhibitor

	PPP N = 114	EXCLAIM N = 96
Objective response, n (%) (95% CI)	32 (28) (28–46)	24 (25) (17–35)
Disease control rate, n (%) (95% CI)	89 (78) (66–84)	73 (76) (66–84)
Median duration of response, mo (95% CI)	17.5 (7.4–20.3)	NR (5.6–NR)
Median PFS, mo (95% CI)	7.3 (5.5–9.2)	7.3 (5.5–9.1)
Median OS, mo (95% CI)	24.0 (14.6–28.8)	NR (13.1–NR)

IRC-assessed results shown. Data cutoff date: Nov. 1, 2020.

FDA approved Sept. 2021 for patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy

EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; PPP, platinum-pretreated patients; MoA, mechanism of action; CI, confidence interval; mo, months; PFS, progression-free survival; OS, overall survival; NR, not reached; IRC, independent review committee.

Zhou C et al. *JAMA Oncol*. 2021;7:e214761; FDA Approved Drugs: Oncology (Cancer) / Hematologic Malignancies Approval Notifications /Oncology (Cancer) Approvals & Safety Notifications. Reviewed June 20, 2023. Accessed June 20, 2023. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm.

Mobocertinib in *EGFR* Exon 20 Insertion Mutated Advanced NSCLC

Safety Results

Study 101 and EXCLAIM

PPP cohort shown

	n (%)
Any adverse event	114 (100)
Any treatment related	113 (99)
Serious adverse events	56 (49)
Adverse event leading to dose reduction	29 (25)
Adverse event leading to discontinuation	19 (17)

AEs in ≥20% of patients, n (%)		
	Any grade	**Grade ≥3**
Diarrhea	104 (91)	24 (21)
Rash	51 (45)	0
Paronychia	43 (38)	1 (<1)
Decreased appetite	40 (35)	1 (<1)
Nausea	39 (34)	5 (4)
Dry skin	35 (31)	0
Vomiting	34 (30)	3 (3)
Blood creatinine increased	29 (25)	2 (2)
Stomatitis	27 (24)	5 (4)
Pruritus	24 (21)	1 (<1)

EGFR, epidermal growth factor receptor; PPP, platinum-pretreated patients; AEs, adverse events.

Riely GJ et al. *Cancer Discov*. 2021;11:1688-1699; Zhou C et al. *JAMA Oncol*. 2021;7:e214761.