

EGFR-Mutated Advanced NSCLC: Standard of Care Overview



Clinical Significance of EGFR Mutations

- EGFR mutations occur in ~20% to 30% of patients with non-small-cell lung cancer (NSCLC) globally¹⁻⁴
 - More common in never smokers, adenocarcinomas, women, and Asian patients
 - Predominantly located in EGFR exons 18-21
- The specific EGFR mutation is important because it affects sensitivity/resistance to EGFR-targeted agents (**Table 1**)⁵
 - FDA-approved indications, dosing, and safety profiles differ between agents targeting EGFR point mutations and/or exon 19 deletions (**Table 2**) compared with those targeting EGFR exon 20 insertion mutations (**Table 3**)

Table 1. FDA-Approved and Key Investigational Agents for EGFR-Mutated Advanced NSCLC: Activity by EGFR Mutation Categories⁵⁻¹⁴

Mutation Category	Active Agents	FDA-Approved Settings
Classical mutation (EGFR exon 19 deletion or exon 21 L858R)	• Afatinib	• 1L • 2L+ (squamous)
	• Dacomitinib	• 1L
	• Erlotinib ± ramucirumab	• 1L+
	• Gefitinib	• 1L
	• Osimertinib*	• 1L
EGFR S768I, L861Q, G719X†	• Afatinib	• 1L • 2L+ (squamous)
	• Osimertinib*	• N/A (recommended by NCCN for 1L)
EGFR exon 20 insertions	• Amivantamab	• 2L+
	• Mobocertinib	• 2L+
EGFR atypical mutations (exons 18-21)	• Emerging targets with no clear guidance on treatment; patients often should be offered an EGFR tyrosine kinase inhibitor or consider a clinical trial	• N/A

1L, first line; 2L, second line; N/A, not applicable; NCCN, National Comprehensive Cancer Network.

*Osimertinib is also approved as adjuvant therapy and in 2L+ setting if EGFR T790M mutation present with disease progression on or after an EGFR TKI. †Most common atypical EGFR mutations.

Table 2. FDA-Approved Agents for EGFR Mutation-Positive NSCLC⁶⁻¹¹

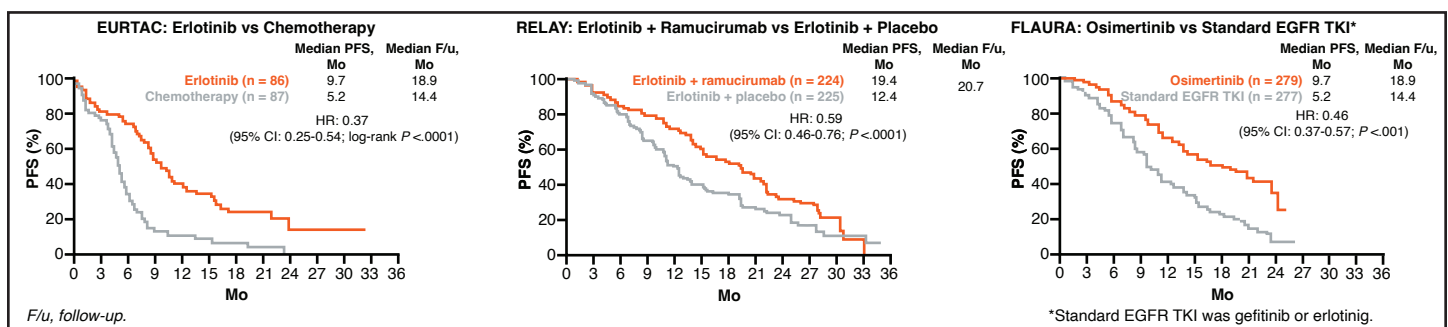
Agent	Indication	Dosing	Key Adverse Events
Afatinib	• 1L metastatic NSCLC with nonresistant EGFR mutations • 2L metastatic squamous NSCLC progressing after platinum-based chemotherapy	40 mg once daily, 1 hr before or 2 hr after meal	Warnings and precautions: bullous and exfoliative skin disorders, diarrhea, ILD, hepatic toxicity, GI perforation, keratitis, embryo-fetal toxicity Common: diarrhea, dermatitis, stomatitis, paronychia, dry skin, decreased appetite, nausea, vomiting, pruritus
Dacomitinib	• 1L metastatic NSCLC with EGFR L858R or exon 19 deletion	45 mg once daily with or without food	Warnings and precautions: ILD, diarrhea, dermatologic adverse reactions, embryo-fetal toxicity Common: diarrhea, rash, paronychia, stomatitis, decreased appetite, dry skin, decreased weight, alopecia, cough, pruritus
Erlotinib	• 1L+ and as maintenance for metastatic NSCLC with EGFR L858R or exon 19 deletion after progression following ≥1 chemotherapy regimen	150 mg once daily on empty stomach	Warnings and precautions: ILD, renal failure, hepatotoxicity, GI perforations, bullous and exfoliative skin disorders, cerebrovascular accident, microangiopathic hemolytic anemia, ocular disorders, hemorrhage in patients taking warfarin, embryo-fetal toxicity Common: diarrhea, rash, anorexia, fatigue, dyspnea, cough, nausea, vomiting
Erlotinib ± ramucirumab	• 1L metastatic NSCLC with EGFR L858R or exon 19 deletion	Daily erlotinib plus ramucirumab 10 mg/kg every 2 wk	Erlotinib: see above Ramucirumab: Warnings and precautions: hemorrhage, GI perforations, impaired wound healing, arterial thromboembolic events, hypertension, infusion-related reactions, worsening of preexisting hepatic impairment, posterior reversible encephalopathy syndrome, proteinuria including nephrotic syndrome, thyroid dysfunction, embryo-fetal toxicity Common (when given with erlotinib): infections, hypertension, stomatitis, proteinuria, alopecia, epistaxis
Gefitinib	• 1L metastatic NSCLC with EGFR L858R or exon 19 deletion	250 mg once daily with or without food	Warnings and precautions: ILD, hepatotoxicity, GI perforation, diarrhea, ocular disorders including keratitis, bullous and exfoliative skin disorders, embryo-fetal toxicity Common: diarrhea, skin reactions
Osimertinib	• Adjuvant therapy after tumor resection for NSCLC with EGFR L858R or exon 19 deletion • 1L metastatic NSCLC with EGFR L858R or exon 19 deletion • 2L+ metastatic NSCLC with EGFR T790M mutation that progressed on or after EGFR TKI	80 mg once daily with or without food	Warnings and precautions: ILD/pneumonitis, QTc interval prolongation, cardiomyopathy, keratitis, erythema multiforme and Stevens-Johnson syndrome, cutaneous vasculitis, embryo-fetal toxicity Common: diarrhea, rash, musculoskeletal pain, nail toxicity, dry skin, stomatitis, fatigue, cough

GI, gastrointestinal; ILD, interstitial disease; TKI, tyrosine kinase inhibitor.

Table 3. FDA-Approved Agents for *EGFR* Exon 20 Insertion Mutation–Positive Advanced NSCLC^{13,14}

Agent	Indication	Dosing	Key Adverse Events
Amivantamab	Advanced NSCLC with <i>EGFR</i> exon 20 insertion mutations with disease progression on or after platinum-based chemotherapy	- Dose determined by baseline body weight: <80 kg, 1050 mg; ≥80 kg, 1400 mg - Administer weekly for 4 wk with initial dose given as split infusion in Wk 1 on Day 1 and Day 2, then administer every 2 wk	<i>Warnings and precautions:</i> infusion-related reactions, ILD/pneumonitis, dermatologic adverse reactions, ocular toxicity, embryo-fetal toxicity <i>Common:</i> rash, infusion-related reactions, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, vomiting
Mobocertinib	Advanced NSCLC with <i>EGFR</i> exon 20 insertion mutations with disease progression on or after platinum-based chemotherapy	160 mg once daily with or without food	<i>Warnings and precautions:</i> infusion-related reactions, ILD/pneumonitis, cardiac toxicity, diarrhea, embryo-fetal toxicity <i>Common:</i> diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, musculoskeletal pain

- EGFR tyrosine kinase inhibitors offer improved progression-free survival (PFS) compared with chemotherapy, with the third-generation EGFR TKI osimertinib now being the 1L standard of care for these patients (**Figure**)^{12,15,16}
 - Osimertinib achieved an overall survival benefit compared with first-generation EGFR TKIs (38.6 vs 31.8 months, respectively; HR: 0.80; 95% CI: 0.64-1.00; $P=.046$)¹⁷
- Combination therapy with the first-generation EGFR TKI erlotinib plus the VEGFR2 inhibitor ramucirumab is also a 1L approved option (**Figure**)^{12,18}
 - Biologic rationale: increased EGFR signaling in *EGFR*-mutated disease upregulates VEGF, a key mediator of angiogenesis that supports tumorigenesis and contributes to the development of EGFR TKI resistance, suggesting that combining EGFR TKIs with antiangiogenic agents in the 1L setting may delay or prevent development of EGFR TKI resistance¹⁹
 - Evidence of a PFS benefit with erlotinib plus the VEGF inhibitor bevacizumab suggests a class effect of antiangiogenic agents (**Table 4**)

Figure. PFS benefit in the 1L setting for registrational trials of erlotinib monotherapy, erlotinib plus ramucirumab, and osimertinib.^{15,16,18}**Table 4. Class Effect of VEGF Inhibition With Erlotinib Plus Bevacizumab in Select Phase III Trials^{20,21}**

Phase III Trial	Trial Population	Median F/u, Mo	Median PFS, Mo	HR (95% CI)
NEJ026	Japanese patients with advanced or recurrent nonsquamous NSCLC with <i>EGFR</i> L858R or exon 19 deletion, no prior chemotherapy	12.4 (range: 7.0-15.7)	- Erlotinib plus bevacizumab: 16.9 - Erlotinib alone: 13.3	0.605 (0.417-0.877; $P = .016$)
BEVERLY	Italian patients with advanced nonsquamous NSCLC with <i>EGFR</i> L858R or other <i>EGFR</i> activating mutations, no prior chemotherapy	36	- Erlotinib plus bevacizumab: 15.4 - Erlotinib alone: 9.6	0.66 (0.47-0.92; $P = .015$)

- The standard of care is evolving internationally with recently approved third-generation EGFR TKIs (**Table 5**)

Table 5. Third-Generation EGFR TKIs with Recent Global Approvals^{22,23}

Approved Agent	Location Approved	Date Approved
Aflutininib	China	March 2021
Almonertinib	China	March 2020
Lazertinib	Korea	January 2021

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