# Metastatic Non-Small Cell Lung Cancer With *EGFR* Mutations: Treatment Patterns and Outcomes From a Systematic Literature Review

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## PURPOSE

- To identify and summarize the current treatment patterns and outcomes in *EGFR*-mutated NSCLC

## CONCLUSIONS

- Treatment options after third-generation EGFR TKIs remain limited, and, with no standard of care in later lines of therapy, patient outcomes are suboptimal
  - In the second-line setting, PBC- and IO-based regimens have only demonstrated an mPFS benefit of ~5 months
  - In the third-line+ setting, the benefit of salvage regimens (eg, other chemotherapy regimens, such as bevacizumab + carboplatin + paclitaxel; pemetrexed; gemcitabine, docetaxel; docetaxel + bevacizumab; and paclitaxel) is even less, with mPFS below 3 months
  - Safety findings were in line with what has been reported in literature, eg, EGFR TKIs generally have fewer serious adverse events than standard chemotherapy
- The poor outcomes seen in published trials, along with the paucity of current trials in later-line settings, highlighting a significant need for new effective and tolerable treatment options, especially for patients progressing on EGFR TKIs

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## ABBREVIATIONS

AE, adverse event; ALK, anaplastic lymphoma kinase; BRAF, B-raf serine/threonine protein kinase; CT, chemotherapy; EGFR, epidermal growth factor receptor; *EGFRm*, *EGFR*-mutated; IHC, immunohistochemistry; ILD, interstitial lung disease; IO, immuno-oncology therapy; *KRAS*, kirsten rat sarcoma viral oncogene homolog mutation; mAb, monoclonal antibody; MET, mesenchymal-epithelial transcription; mo, month(s); mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; PICOTS, population, intervention, comparator, outcome, timing, and study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCT, randomized control trial; *RET*, ret proto-oncogene; RoB 2, Revised Cochrane Risk of Bias tool; *ROS1*, ROS proto-oncogene 1; TKI, tyrosine kinase inhibitor; TP53, tumor protein p53; TT, targeted therapy.

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## BACKGROUND

- Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers[2]
- Absence or presence of genomic alterations in NSCLC, including activating mutations in the epidermal growth factor receptor (EGFR) gene or other actionable molecular alterations (such as *ALK*, *ROS1*, *BRAF*), influences responses to some therapies and can guide treatment decisions[3]
- Estimated prevalence of *EGFR* mutations in patients with NSCLC ranges from 12.8% in Europe to 15.4% in North America and 49.1% in Asia[4]
- Although EGFR tyrosine kinase inhibitors (TKIs) have transformed the treatment of patients with *EGFR*-mutated (*EGFRm*) advanced or metastatic NSCLC in earlier lines of therapy, disease progression is inevitable[3,5]
- Treatment approaches in later lines are fragmented, and the clinical benefits of these subsequent therapies are limited[3,5]
- **Objective:** To identify and summarize the current treatment patterns and outcomes in *EGFRm* NSCLC

## METHODS

- We performed a systematic literature review (SLR), following standard methods adapted from the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020)[6,7]
- Study eligibility was based on specific population, intervention, comparator, outcome, timing, and study design (PICOTS) criteria (**Table 1**)
  - Publications were limited to English language, but without geographic restrictions
- A comprehensive search strategy was executed across multiple databases (including EMBASE and MEDLINE®), clinical trial registries, and manual searches
  - Supplemental searches included abstracts from 6 relevant congresses (in both 2021 and 2022) and 10 bibliographies of relevant reviews (published in 2020-2022)
- Data extraction was performed for included studies, with extraction of data related to study design, population, intervention, comparisons, and outcomes as specified in the protocol
- Quality assessments were performed using the Revised Cochrane Risk of Bias tool (RoB 2) for randomized control trials (RCTs) and the Newcastle-Ottawa Scale for observational studies[8,9]

### Table 1. PICOTS eligibility criteria

| Criterion | Description[a] |
|---|---|
| **Population** | Adults with metastatic NSCLC within the following patient populations:<br>• *EGFR* mutation, including activating and resistance mutations, as reported by the study authors<br>• *EGFR* wild type |
| **Intervention** | Any pharmacotherapy (with or without radiotherapy) |
| **Comparators** | Any standard of care or emerging therapy |
| **Outcome domains** | • Epidemiology<br>• Treatment pathways<br>• Clinical management<br>• Clinical and safety outcomes<br>• Co-mutations |
| **Timing** | January 1, 2017, to September 7, 2022 |
| **Study design** | • Phase 3/4 clinical trials (≥50 participants)<br>• Observational/real-world studies (≥200 participants)<br>• Clinical practice guidelines or preferred practice patterns |
| **Other** | • Limited to English language only<br>• No geographical limit |

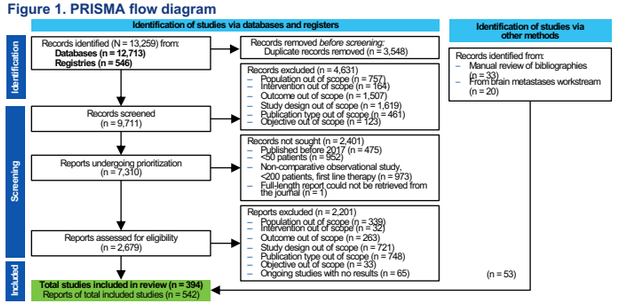
EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer, PICOTS, population, intervention, comparator, outcome, timing, and study design; SLR, systematic literature review.
[a]During the course of the SLR, amendments were made to the protocol in order to refine the eligibility criteria and focus on the most relevant and robust information available. All amendments were made prior to the data extraction phase and were applied universally across all records:
- Specified start date (January 1, 2017), based on actual search date
- Study eligibility sample size thresholds were applied: ≥50 patients for clinical trials; ≥200 patients for observational studies
- Phase 1 or 2 clinical trials were excluded
- Conference abstracts were excluded

## RESULTS

### Search Output

- Based on searches of various data sources, 13,312 records were identified; following deduplication, title/abstract screening, and full article screening, 542 publications on 394 unique studies were included in the review (Figure 1)
- Most randomized control trials (RCTs; 69%) and observational studies (58%) were conducted in Asia (Figure 2)
- Of the 394 unique studies,134 included data on patients with *EGFR*m NSCLC (26 randomized control RCTs, 103 observational studies, and 5 single-arm trials) (The full supplemental SLR reference list is accessible via the QR Code)
  - Among those with *EGFR* mutations in first-line therapy, most patients had activating mutations corresponding to exon 19 deletion or L858R substitution in exon 21, with breakdowns aligned with the rates observed in published literature[10]

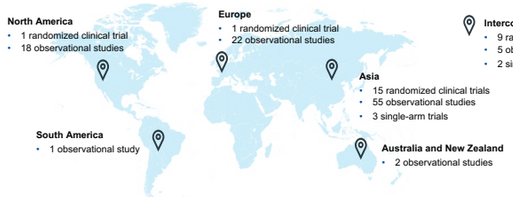
### Figure 1. PRISMA flow diagram




PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

## RESULTS (cont'd)

### Figure 2: Geographic distribution summary of *EGFRm* studies (N = 134)




### Patient Characteristics

**Age and Sex (Table 2)**

- **RCTs**[S1-S26]
  - Based on available data, the median age was 62 years, and the median percentage of males was 37.5%
- **Single-arm studies**[S27-S31]
  - The median age of patients was 61 years, and median percentage of males was 47%
- **Observational studies**[S32-S98]
  - Based on available data, the median age was 66 years, and the median percentage of males was 37%

**Race Breakdown Across 9 International RCTs Reporting Data (Figure 3)**[S1,S6-S8,S15,S18,S19,S22]

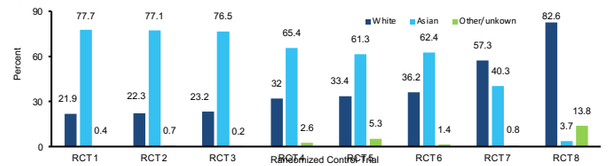
- The median percent of patients who were categorized as White were 32.7% (range, 21.9%-82.6%)
- The median percent of patients who were categorized as Asian were 61.9% (range, 3.7%-77.7%)
- In the international RCTs with additional race breakdowns, Blacks were reported in 6 studies (0.2%-2.4%); American Indians/Alaska Natives in 2 studies (0.2%-0.8%); and Native Hawaiians/Pacific Islanders in 1 study (0.2%)

### Table 2: Patient characteristics by study type

| Study type | Median age, years (range) | Median % male (range) |
|---|---|---|
| RCTs | 61.5 (54-67.5) | 37.5 (22-65) |
| Single-arm | 61 (58-70.5) | 47 (19-48) |
| Observational[a] | 66 (57.5-84) | 36 (26-56) |

[a]Sixty-seven (67) of 103 observational studies reported age and sex data.

### Figure 3: Reported race breakdowns in international RCTs




RCT, randomized control trial.

### Treatments Evaluated in *EGFRm* NSCLC

**RCTs**

- Of the 26 RCTs: 18 evaluated first-line therapy (16 with targeted therapy [TT] and 2 with immunotherapy [IO] + monoclonal antibodies [mAbs]), 1 evaluated first-line or second-line TT, 3 evaluated second-line TT, and 4 evaluated second-line or later lines (3 with TT and 1 with IO + mAbs)
  - In studies in second-line or later-line therapy settings, most patients had been treated with prior TKIs, chemotherapy (CT), and/or radiotherapy (RT). CT or other targeted therapy were the most common comparators across RCTs

**Single arm studies**

- All 5 single-arm trials evaluated TT in first line, second-line, and later-line settings

**Observational studies**

- Of the 103 reported observational studies: 79 evaluated TT (30 in the first-line only setting), 3 evaluated IO, and 21 evaluated any type of treatment without separating results by type of treatment (5 in the first-line only)

### Survival

**Median progression-free survival (mPFS) (Table 3)**

- Both RCTs and observational studies found that mPFS was longer in patients who received second- or third-generation EGFR TKIs (14.7-20.8 months) compared with first-generation EGFR TKIs or other TTs (8.6-13.2 months), regardless of line of therapy[S5,S16,S19,S22,S79]
- In the first-line setting, third-generation EGFR TKIs demonstrated mPFS of 18.9-20.8 months in RCTs and 16.8 months in an observational study of osimertinib[S5,S16,S19,S34]
- Across first-line setting RCTs, with first- and second-generation EGFR TKIs, longer mPFS was observed with:
  - Combination of EGFR TKIs (13.7 months) or EGFR TKI + CT (up to 16 months) vs EGFR TKI only (up to 10.2 months) or CT only (3.9 months)[S2,S11,S26]
  - EGFR TKIs + mAbs (up to 19.4 months) vs EGFR TKIs only (up to 12.4 months)[S9,S13,S14]
- In 2 second-line post-EGFR TKI RCTs, platinum-based chemotherapy (PBC) regimens demonstrated mPFS of 4.3-5.4 months in RCTs[S6,S8]
  - Recent clinical trials of immune checkpoint inhibitors + PBC failed to demonstrate an improvement over PBC alone (mPFS, 5.6 vs ~5.5 months, respectively)[11,12]
- In a third-line+ post-EGFR TKI, post-PBC RCT, mPFS was up to 2.95 months with salvage regimens[S10]

**Median overall survival (mOS)**

- In the first-line setting, in RCTs with mature OS data, mOS reached 38.6 months with osimertinib, with a range of 9.2-34.1 months for first- and second-generation TKIs[S19,S22]
- In RCTs in the second-line post-EGFR TKI setting, in patients who developed *T790M* and were treated with osimertinib, mOS reached 26.8 months[S7]
  - Across retrospective studies evaluating the second-line post-EGFR TKI setting, in patients who developed *T790M* and were treated with osimertinib, mOS reached 61.8 months[S39]
  - In 1 observational study, in patients who received a second-line CT regimen, mOS was 34.6 months[S39]
- In RCTs in third-line+ settings, mOS was 10.7 months for anlotinib, a novel multitarget TKI (post-CT/post-either RT or TT), and 15.9 months with osimertinib (post-TKI/post-CT)[S2,a]

**Co-mutations frequency and survival**[S34,S35,S43,S58,S59,S69,S74,S81,S83,S90,S99-S109]

- The distribution of co-mutations with primary *EGFR* mutations varied substantially across studies. The most frequently reported co-mutations at diagnosis were *TP53* (4%-65.7%), *KRAS* (0%-35.8%), *MET* (2%-33.3%), and *RET* (1.3%-33.3%)
  - With first-line therapy, patients with co-mutations had worse OS and PFS than those with single mutations

[a]Post-TKI/post-CT mOS data comes from CheckMate 722 results; Mok TSK, et al. ESMO Asia Congress2022, LBA8.

### Table 3. Median progression-free survival in *EGFRm* NSCLC from RCTs and observational studies[S2,S5-S8,S10,S12,S16-S19,S34,S44]

| | Treatment regimen | | | |
|---|---|---|---|---|
| **mPFS by line of therapy, mo** | **Third-generation EGFR TKIs** | **Platinum-based chemotherapy** | **Immune checkpoint inhibitor-based regimens** | **Other chemotherapy regimens[a]** |
| **First-line** | 16.8-20.8 | 5.6-7.9 | 10.2 | 6.9 |
| **Second-line** | 10.1 (after first-/second-generation EGFR TKI) | 4.3-5.4 | 5.6[b]-7.2 | 4.5-6.9 |
| **Third-line+** | NA | NA | NA | 2.95 |

EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; *EGFRm*, epidermal growth factor receptor-mutated; mo, month; mPFS, median progression-free survival; NA, not available; NSCLC, non-small cell lung cancer; RCT, randomized control trial.
[a]Other chemotherapies include bevacizumab + carboplatin + paclitaxel; pemetrexed; gemcitabine, docetaxel; docetaxel + bevacizumab; and paclitaxel. [b]Data from CheckMate 722 results; Mok TSK, et al. ESMO Asia Congress 2022, LBA8 and KEYNOTE-789 results; Yang JCH, et al. ASCO Annual Meeting 2023, LBA9000.

### Safety

**Safety summary**

- The most commonly reported any-grade adverse events (AEs) with third-generation EGFR TKIs were diarrhea, rash, and paronychia; nausea, decreased appetite, and anemia with PBC regimens; and nausea, fatigue, and peripheral neuropathy with IO regimens
- Any-grade AEs were lower among patients treated with:
  - EGFR TKI only vs chemotherapy
  - First-generation vs third-generation EGFR TKIs
- Grade ≥3 AEs were lower in patients treated with:
  - EGFR TKI only vs chemotherapy
  - EGFR TKI only vs EGFR TKI + mAb
  - First-generation vs second-generation TKIs
- Discontinuation due to AEs varied across regimens evaluated in RCTs (**Table 4**)[S4-S17,S19,S21-S24,S26,S28,S29,S33,S50,S67]

**Interstitial lung disease (ILD)**[S4-S7,S10,S11,S14, S17,S19,S21,S22,S24,S26,S40,S47,S62-S63,S67,S74]

- Fifteen RCTs and 5 observational studies reported rates of ILD (and/or pneumonitis)
- In most studies, ILD was reported as an AE or a serious AE
- Overall, the occurrence of any-grade ILD was low, ranging from 0% to 4%

### Table 4. Discontinuation due to AEs in RCTs across regimens and all LOTs

| Regimens in RCTs across all LOTs | Studies, n[a] | Discontinuation rates (%) |
|---|---|---|
| First-/second-generation EGFR TKI monotherapies | 16 | 0.7-18.5 |
| Third-generation EGFR TKI monotherapies | 7 | 3.7-22.7 |
| PBC | 4 | 7.0-17.5[b] |
| Combinations | | |
| First-generation EGFR TKI + mAb | 2 | 8.0, 13.8, 30[c] |
| First-/second-generation EGFR TKI + chemotherapy | 2 | 8.3, 16.7[d] |
| First-/second-generation EGFR TKI + MET inhibitor | 1 | 17.9 |
| First-/second-generation EGFR TKI + VEGFR inhibitor | 1 | 5.1 |
| First-/second-generation EGFR TKI + radiotherapy | 1 | 2.9 |

EGFR, epidermal growth factor receptor; LOT, line of therapy; mAb, monoclonal antibody; MET, mesenchymal-epithelial transcription factor; PBC, platinum-based chemotherapy; RCT, randomized control trial; TKI, tyrosine kinase inhibitor.
[a]Some studies are included in the n across regimens. [b]One study reported non-platinum-based chemotherapy discontinuation rate of 8.0%.[S23] [c]In the combination arm, discontinuation rate of erlotinib was 13.8%, and of bevacizumab was 30%.[S13] [d]16.7% was discontinuation rate of pemetrexed only.[S11]

### Limitations

- Inherent limitations of SLR exist including:
  - There is no accounting for prognostic factors and effect modifiers that may have impacted the OS and PFS beyond line of therapy
  - The duration of exposure is not accounted for; thus, it is difficult to compare safety



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