# Systematic Review and Meta-analysis of Immunotherapy Effectiveness for Pretreated Patients With Non–Small Cell Lung Cancer Harboring *EGFR* Exon 20 Insertions

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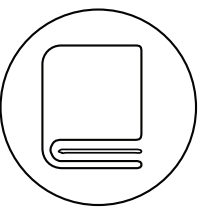
Introduction

- Epidermal growth factor receptor gene (*EGFR*) exon 20 insertion (ex20ins) mutations are rare, accounting for up to 12% of EGFR-mutated non–small cell lung cancer (NSCLC) tumors and 2% of all NSCLC[1,2]
- Current treatment options for patients with NSCLC with *EGFR* ex20ins mutations include epidermal growth factor receptor (EGFR) inhibitors, monoclonal antibodies, and chemotherapy
- Data on clinical outcomes with immuno-oncology (IO) therapy in this patient population are not conclusive
- IO monotherapy is not recommended over targeted therapies for patients with NSCLC with an oncogenic driver[3]
- A systematic review and meta-analysis of real-world data were conducted to determine the efficacy of IO monotherapy in the second-line setting and beyond (≥2nd-line) for *EGFR* ex20ins+ NSCLC
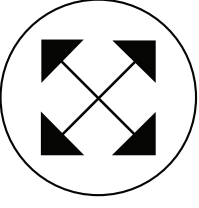
Methods

Data Sources

- Data on patient treatment and clinical outcomes were abstracted from 3 sources:
1. Sources identified in a comprehensive PubMed literature search conducted in November 2020
   - Search terms included "EGFR", "exon 20 insertion mutation", "NSCLC", "immunotherapy", "second-line setting"
   - Only English-language publications with either abstracts or full text available were included
   - A manual search of reference lists in the articles was conducted
   - Data on patient treatment and relevant clinical outcomes (eg, overall response rate [ORR], disease control rate [DCR], duration of response [DoR], progression-free survival [PFS]) were abstracted for inclusion
2. Real-world (rw) data
   - Retrospective observational cohort study using longitudinal data from patients with advanced NSCLC with *EGFR* ex20ins mutations from the Flatiron Health Database, a nationwide electronic health record database in the United States
     - Prior platinum study–aligned patients included those whose baseline characteristics were aligned with key eligibility criteria of Part 3 of mobocertinib study AP32788-15-101 (NCT02716116), who initiated the next treatment after a confirmed advanced NSCLC diagnosis, who had documented *EGFR* ex20ins mutations, who received ≥1 prior line of therapy in the advanced setting, and who were previously treated with platinum-based chemotherapy in the advanced setting. Index date was defined as start date of the next treatment initiated immediately after confirmed locally advanced/metastatic NSCLC diagnosis, documented *EGFR* ex20ins mutations, and ≥1 prior line of therapy in the advanced setting
   - Retrospective chart review with longitudinal data from patients with NSCLC with *EGFR* or human epidermal growth factor receptor-2 gene (*HER2*) ex20ins from 12 German academic thoracic oncology centers
     - Included patients with histologic diagnosis of NSCLC who received systemic treatment for stage IV NSCLC and were evaluable for response
     - Patients with *EGFR* ex20ins were included in meta-analysis
3. Mobocertinib clinical study AP32788-15-101[4,5]
   - Open-label, multicenter, global, single-agent, single-arm, continuously conducted, 3-part phase 1/2 study
     - Part 1: Phase 1 first-in-human dose-escalation study
     - Part 2: Expansion phase in distinct disease cohorts
     - Part 3: Pivotal global extension cohort designed to further explore the safety, activity, and clinical benefit of mobocertinib in patients with previously treated NSCLC whose tumor harbored an *EGFR* ex20ins mutation
   - Prior anti–programmed death ligand 1 (anti–PD-L1) monotherapy and combination therapy and responses in ≥2nd-line therapy setting were assessed in patients enrolled in the study

Data Analysis

- Meta-analysis
  - ORR information from patients with ≥2 lines of IO therapy was combined from the 6 data sources (Takeda M, et al. *Oncotarget*. 2018; Udagawa H, et al. *J Thorac Oncol*. 2019 [LC-SCRUM-JAPAN]; Yang G, et al. *Lung Cancer*. 2020; Flatiron database; German chart review; mobocertinib AP32788-15-101 study)
  - Sources in which the treatment setting was a combination of first- and second-line treatments or in which the line of therapy was not clear were excluded

Results

Literature Review

- Because *EGFR* ex20ins+ NSCLC is rare and use of anti–PD-L1 therapy is limited in this population, most reported efficacy results involve small numbers of patients and do not typically distinguish between the first-line versus second-line or greater treatment settings
- Studies identified in the literature that met criteria for inclusion in the meta-analysis are summarized in **Table 1**

Table 1. Studies Identified In Literature Review Included in Meta-Analysis

Study	Study Description	No. of Patients Included in Meta-analysis	ORR (%)
Takeda M, et al. (*Oncotarget*. 2018)[6]	Observational study that examined efficacy outcomes of patients with NSCLC harboring *EGFR/HER2* ex20ins mutations at an academic hospital in Japan	7	14.3
LC-SCRUM-JAPAN/ Udagawa H, et al. (*J Thorac Oncol*. 2019)[7]	Evaluation of treatment outcomes of patients with NSCLC harboring *EGFR/HER2* ex20ins mutations in the Lung Cancer Genomic Screening Project for Individualized Medicine in Japan (LC-SCRUM-JAPAN)	21	0
Yang G, et al. (*Lung Cancer*. 2020)[8]	Retrospective analysis of real-world treatment outcomes in patients from 99 hospitals across China with NSCLC harboring *EGFR* ex20ins mutations	2	0

Real-World Data

German Chart Review Study

- A total of 14 patients with *EGFR* ex20ins+ NSCLC received 2nd-line IO therapy, 10 as monotherapy (included in the meta-analysis) and 4 in combination with chemotherapy
- Clinical outcomes are summarized in **Table 2**

Table 2. Clinical Outcomes in Patients From German Chart Review Study Receiving 2nd-Line IO Therapy

Endpoint	IO Monotherapy (n=10)	IO/Chemotherapy Combination (n=4)
Confirmed ORR (%)	0	0
DCR (%)	30	75
PFS (months)	2.3	6.3

DCR, disease control rate; IO, immuno-oncology; ORR, objective response rate; PFS, progression-free survival.

US Flatiron Electronic Health Database

- Clinical outcomes in 20 patients who were study-aligned to Part 3 of the mobocertinib Study AP32788-15-101 and had received prior platinum therapy are summarized in **Table 3**

Table 3. Clinical Outcomes in Patients From the US Flatiron Database Who Initiated IO Monotherapy

Endpoint	Prior Platinum Study-Aligned Patients* (N=20)
Confirmed rwORR	
n (%)	1 (5.0)
95% CI (%)	0.1, 24.9
rwDCR	
n (%)	5 (25.0)
95% CI (%)	8.7, 49.1
Overall survival (months), median (95% CI)	7.1 (2.5, 10.1)
rwPFS (months), median (95% CI)	2.2 (1.7, 3.0)
rwTime to discontinuation (months), median (95% CI)	2.3 (1.0, 2.9)

*Defined as patients whose baseline characteristics were aligned with the key eligibility criteria of Part 3 of mobocertinib Study AP32788-15-101, who initiated the next treatment after a confirmed diagnosis of advanced NSCLC, had documented *EGFR* ex20ins mutations, and had ≥1 prior line of therapy in the advanced setting.
CI, confidence interval; rwDCR, real-world disease control rate; rwORR, real-world objective response rate; rwPFS, real-world progression-free survival.
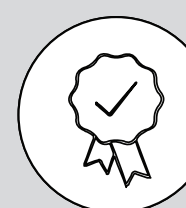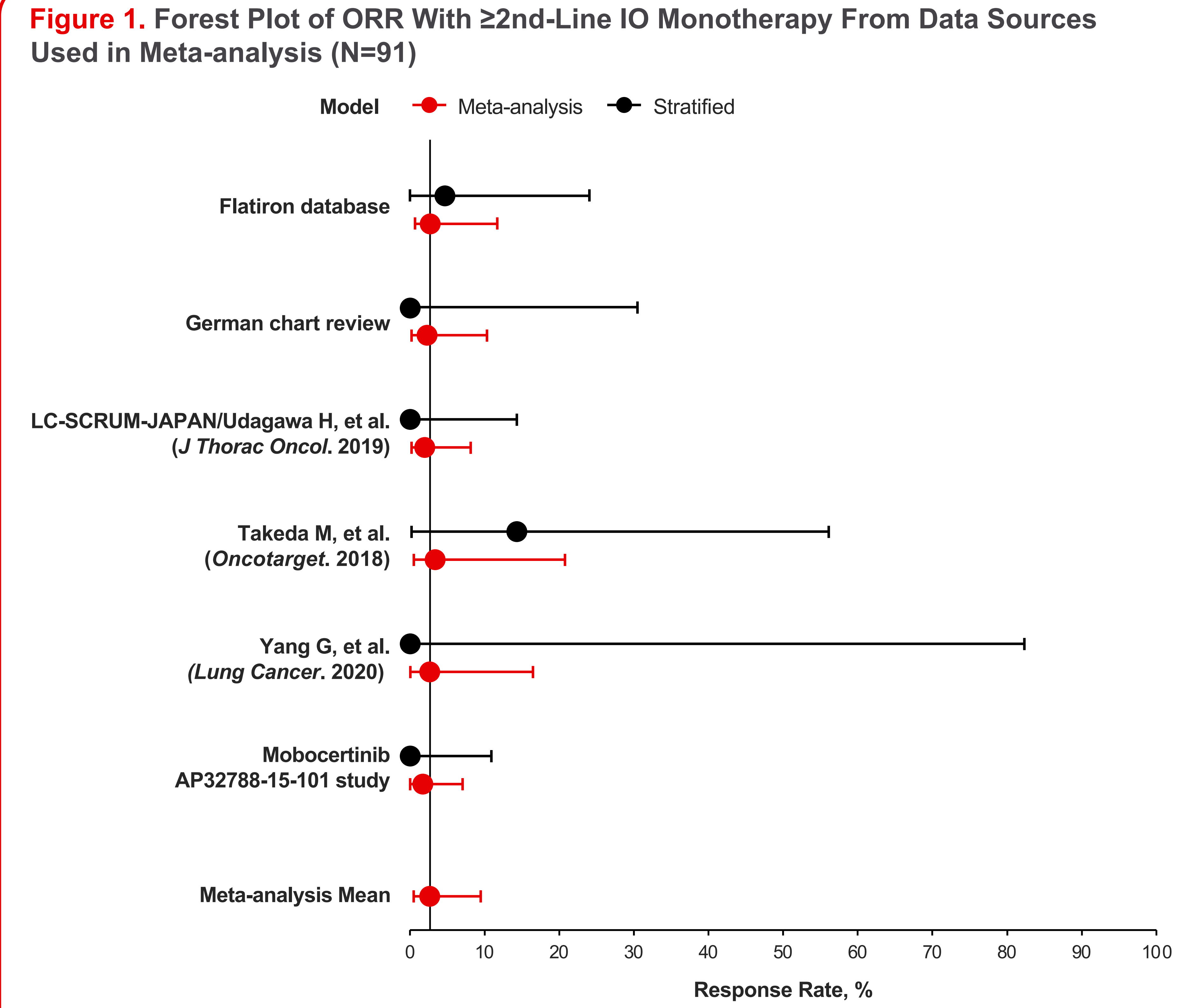
Mobocertinib Study AP32788-15-101

- A total of 34 patients previously received anti–PD-L1 therapy in second-line setting
  - Included 31 patients who received anti–PD-L1 monotherapy and 3 patients who received anti–PD-L1 therapy in combination with platinum-based chemotherapy
  - ORR to prior anti–PD-L1 therapy was 0% for both monotherapy and combination therapy
  - Stable disease was best response to prior anti–PD-L1 therapy in 26% (9/34) of patients (monotherapy, 26% [8/31]; combination therapy, 33% [1/3])

Meta-analysis

- The mean ORR (2.5%, 97.5%) for ≥2nd-line IO monotherapy was 3.5% (0.6%, 9.9%; **Table 4**; **Figure 1**)

Table 4. ORR With ≥2nd-Line IO Monotherapy From Data Sources Used in Meta-analysis (N=91)

Data Source	Reported ORR, n/N (%)	Evaluation by RECIST v1.1
Takeda M, et al. (*Oncotarget*. 2018)	1/7 (14.3%)	✓
LC-SCRUM-JAPAN/Udagawa H, et al. (*J Thorac Oncol*. 2019)	0/21 (0%)	-
Yang G, et al. (*Lung Cancer*. 2020)	0/2 (0%)	-
Flatiron database	1/20 (5%)	-
German chart review	0/10 (0%)	✓
Mobocertinib AP32788-15-101 study	0/31 (0%)	✓
Meta-analysis	Mean ORR (2.5%, 97.5%), 3.5% (0.6%, 9.9%)	

Figure 1. Forest Plot of ORR With ≥2nd-Line IO Monotherapy From Data Sources Used in Meta-analysis (N=91)

Conclusions

- Results of this meta-analysis suggest that IO monotherapy is not effective in the ≥2nd-line setting for patients with *EGFR* ex20ins+ NSCLC, with a mean ORR of 3.5%
  - Across sources, reported ORRs ranged from 0% to 14.3% (1 of 7 patients in a single source), with 2 total responses among 91 patients
  - Analyses of reported data were limited by the small number of patients and studies reporting mixed lines of therapy
  - Real-world ORR results were comparable across series, regardless of whether RECIST v1.1 criteria were used
- The poor response of patients with *EGFR* ex20ins+ NSCLC to ≥2nd-line IO monotherapy highlights the need for novel treatment options in this patient population

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Abbreviations

anti–PD-L1, programmed death ligand 1; CI, confidence interval; DCR, disease control rate; EGFR, epidermal growth factor receptor; *EGFR*, epidermal growth factor receptor gene; ex20ins, exon 20 insertion; *HER2*, human epidermal growth factor receptor 2 gene; IO, immuno-oncology; LC-SCRUM-JAPAN, Lung Cancer Genomic Screening Project for Individualized Medicine in Japan; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; rw, real-world; ≥2nd-line, second-line setting and beyond.

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Disclosures

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