# Prognostic Factors and Outcomes of Patients With Advanced Non–Small Cell Lung Cancer While on Osimertinib Treatment: A Retrospective Database Study

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## BACKGROUND

- Advanced non–small cell lung cancer (NSCLC) with common epidermal growth factor receptor (*EGFR*) mutations (ie, Exon 19 deletions [Ex19del] or Exon 21 L858R mutations)[1] is a noncurable disease
- The current standard of care for first-line (1L) treatment of advanced NSCLC with common *EGFR* mutations is osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI)[2,3]
- Despite initial efficacy, not all patients benefit from treatment with osimertinib and most inevitably develop resistance[4,5]
- Platinum-based chemotherapy is the guideline-recommended next line of therapy after treatment failure or progression on osimertinib and represents the standard of care[2,3]
  - Studies of platinum-based chemotherapy in patients with disease progression after treatment with TKIs have shown poor outcomes[6-9]
- There are currently few targeted therapies approved for advanced NSCLC with common *EGFR* mutations,[1] highlighting an unmet need in this patient population

## OBJECTIVE

- This retrospective, real-world study aimed to characterise the profile of patients with advanced NSCLC with common *EGFR* mutations and describe the existing unmet medical need

## METHODS

### Study design and patient population

- This was a retrospective observational cohort study using secondary data from the Epidemiological Strategy and Medical Economics (ESME; France; ClinicalTrials.gov Identifier: NCT03848052) and the Rigshospitalet (RH; Denmark) databases
- The index date was defined as the date of osimertinib initiation
- Patients were followed up until death or end of data coverage, whichever occurred first
- Patients were included in the study if they met the following criteria:
  - ≥18 years of age at treatment initiation
  - Histologically confirmed locally advanced or metastatic NSCLC
  - Diagnosis of an *EGFR* Ex19del- or L858R-activating mutation, either alone or in combination with other *EGFR* mutations
  - Treatment with 1L or second-line (2L) osimertinib
  - Had available baseline information within the baseline period before osimertinib initiation
- Patients were excluded if they had any of the following:
  - Concurrent chemotherapy or immuno-oncology treatment
  - Evidence of prior osimertinib exposure before the index date

### Objectives

- The primary objective was to describe patient profiles and outcomes and identify characteristics that are potential prognostic factors for:
  - Overall survival (OS)
  - Real-world progression-free survival (rwPFS)
    - Progression was defined as either death or disease progression (including central nervous system metastases), whichever occurred first
  - Time to next therapy (TTNT)
  - Time to treatment discontinuation (TTD)
- One of the secondary objectives was to describe the treatment pathway taken after osimertinib treatment initiation

### Statistical analyses

- The proportion of patients at risk for the event of interest (progression/death for rwPFS, initiation of next therapy line or death for TTNT, treatment discontinuation for TTD, and death for OS) was estimated using the Kaplan-Meier method
- The prognostic value of baseline characteristics was analysed using univariate Cox proportional hazards regression
  - *P*<0.05 was used as a threshold for the prognostic significance of each characteristic

## RESULTS

### Patients

- A total of 757 patients were included in the analysis (ESME, n=624; RH, n=133), as described in **Table 1**
- Median (range) follow-up time was 30.2 months (95% confidence interval [CI], 27.6-34.5) for patients in the ESME database and 27.7 months (95% CI, 23.8-30.9) for patients in the RH database

**TABLE 1: Demographics and baseline disease characteristics**

| Characteristic | 1L osimertinib (n=319) | 2L osimertinib (n=438) | Overall (N=757) |
|---|---|---|---|
| **Age at diagnosis, median (range), y** | 70.8 (32.0, 94.3) | 67.1 (27.0, 91.0) | 69.0 (27.0, 94.3) |
| **Female, n (%)** | 240 (75.2) | 317 (72.4) | 557 (73.6) |
| **ECOG PS, n (%)** | | | |
| 0-1 | 166 (52.0) | 139 (31.7) | 305 (40.3) |
| 2+ | 61 (19.1) | 45 (10.3) | 106 (14.0) |
| Unknown | 92 (28.8) | 254 (58.0) | 346 (45.7) |
| **Smoking status, n (%)** | | | |
| Current smoker | 24 (7.5) | 38 (8.7) | 62 (8.2) |
| Ex-smoker | 130 (40.8) | 132 (30.1) | 262 (34.6) |
| Never smoked | 143 (44.8) | 241 (55.0) | 384 (50.7) |
| Unknown | 22 (6.9) | 27 (6.2) | 49 (6.5) |
| **Type of *EGFR* mutation, n (%)** | | | |
| L858R | 157 (49.2) | 173 (39.5) | 330 (43.6) |
| Ex19del | 164 (51.4) | 268 (61.2) | 432 (57.1) |
| Non-*EGFR* comutations[a] | 68 (21.3) | 26 (5.9) | 94 (12.4) |
| **Other biomarkers,[b] n (%)** | | | |
| *TP53* positive | 74 (56.1) | 37 (67.3) | 111 (59.4) |
| *PDL1* positive | 133 (52.2) | 103 (49.8) | 236 (51.1) |
| **Most common metastatic site, n (%)** | | | |
| Bone | 157 (49.2) | 270 (61.6) | 427 (56.4) |
| Brain | 106 (33.2) | 204 (46.6) | 310 (41.0) |
| Lung | 113 (35.4) | 170 (38.8) | 283 (37.4) |
| Liver | 48 (15.0) | 111 (25.3) | 159 (21.0) |
| **Number of metastatic locations, n (%)** | | | |
| 0-1 | 130 (40.8) | 108 (24.7) | 238 (31.4) |
| 2-4 | 168 (52.7) | 287 (65.5) | 455 (60.1) |
| ≥5 | 21 (6.6) | 43 (9.8) | 64 (8.5) |
| **Comorbidities, n (%)** | | | |
| None | 194 (60.8) | 247 (56.4) | 441 (58.3) |
| High blood pressure[c] | 72 (22.6) | 109 (24.9) | 181 (23.9) |
| Diabetes mellitus[c] | 30 (9.4) | 11 (2.5) | 19 (2.5) |
| High blood pressure plus diabetes mellitus[c] | 54 (16.9) | 17 (3.9) | 37 (4.9) |
| Other | 25 (7.8) | 26 (5.9) | 51 (6.7) |

1L, first-line; 2L, second-line; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; *PDL1*, programmed death-ligand 1.
[a]Includes *ALK*, *BRAF*, *KRAS*, *MET* (mutations, amplifications, and fusions), and *ROS1* positivity. [b]Among tested patients with contributive results (*TP53*: n=132/757; *PDL1*: n=255/2074&2). [c]Patients in each category may have other comorbidities besides high blood pressure and/or diabetes mellitus.

### Treatment pathway

- The treatment pathways for both lines can be seen in **Figure 1**
- For both 1L and 2L osimertinib, treatment with an EGFR TKI was continued beyond progression by many patients (percentages calculated among patients receiving subsequent therapy; 1L osimertinib: EGFR TKI monotherapy, 5.6%; EGFR TKI combination, 31.0%; 2L osimertinib: EGFR TKI monotherapy, 1.9%; EGFR TKI combination, 15.6%), despite limited evidence of efficacy for this approach

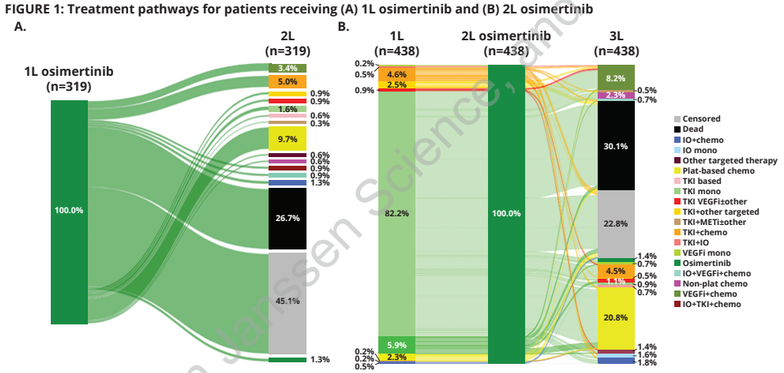
### Outcomes

- For 1L and 2L osimertinib, respectively:
  - Median OS was 26.2 and 18.6 months (**Figure 2A**)
  - Median rwPFS was 11.9 and 7.4 months (**Figure 2B**)
  - Median TTNT was 19.5 and 12.0 months (**Figure 2C**)
  - Median TTD was 16.9 and 11.5 months (**Figure 2D**)

### Prognostic factors

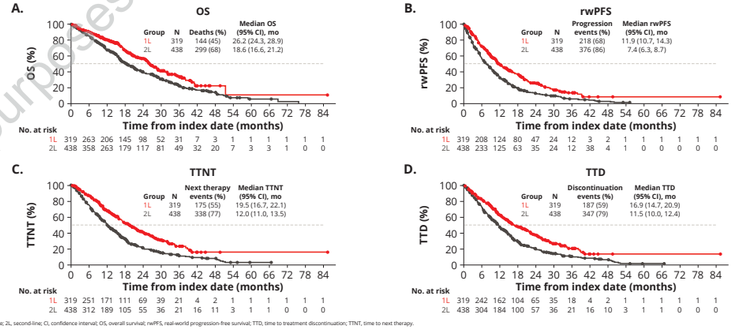
- A summary of significance for all prognostic factors across outcomes and lines of therapy can be found in **Figure 3** and **Figure 4**
- ECOG performance status (2+ vs 0-1), the presence of liver metastases, and the presence of L858R mutations were significantly associated with shorter OS and rwPFS in both the 1L and 2L settings
- The presence of *TP53* mutations and bone metastases were significantly associated with poorer outcomes in the 1L and 2L settings, respectively

**FIGURE 1: Treatment pathways for patients receiving (A) 1L osimertinib and (B) 2L osimertinib**



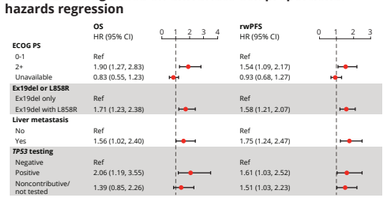

1L, first-line; 2L, second-line; chemo, chemotherapy; IO, immuno-oncology; MET, mesenchymal epithelial transition inhibitor; mono, monotherapy; plat, platinum; TKI, tyrosine kinase inhibitor; VEGFi, vascular endothelial growth factor inhibitor.
Of the 319 patients who received 1L osimertinib, 45.1% were censored (18.8% did not initiate 2L, 7.8% were lost to follow-up, and 18.5% were still on treatment at the last follow-up date). Of the 438 patients who received 2L osimertinib, 22.8% were censored (10.3% did not initiate 3L, 11.4% were lost to follow-up, and 1.1% were still on treatment at the last follow-up date).
For patients who received osimertinib in both the 1L and 2L, only 1L data were considered in the analysis.

**FIGURE 2: Kaplan-Meier estimates for 1L and 2L osimertinib for (A) OS, (B) rwPFS, (C) TTNT, and (D) TTD**



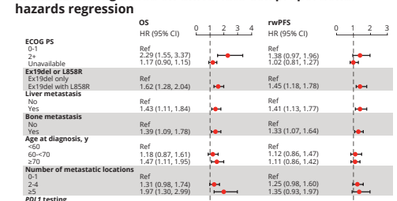

1L, first-line; 2L, second-line; CI, confidence interval; OS, overall survival; rwPFS, real-world progression-free survival; TTD, time to treatment discontinuation; TTNT, time to next therapy.

**FIGURE 3: Summary of significant prognostic factors in the 1L setting based on univariate Cox proportional hazards regression**




1L, first-line; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; OS, overall survival; *PDL1*, programmed death-ligand 1; Ref, reference; rwPFS, real-world progression-free survival.
Potential prognostic factors that were tested but were not significant (*P*>0.05): age at diagnosis, age at line of treatment, body mass index, sex, smoking status, bone metastasis, brain metastasis, lung metastasis, number of metastatic locations, and *PDL1* positive. Non-*EGFR* comutations (*ALK*, *BRAF*, *KRAS*, *MET*, *ROS1* positive) were found to be significant for OS only when combined together and, therefore, were not informative.

**FIGURE 4: Summary of significant prognostic factors in the 2L setting based on univariate Cox proportional hazards regression**




2L, second-line; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; OS, overall survival; *PDL1*, programmed death-ligand 1; Ref, reference; rwPFS, real-world progression-free survival.
Factors that were significant for OS only: ECOG PS, age at diagnosis, number of metastatic locations, and *PDL1* positive. Potential prognostic factors that were tested but were not significant (*P*>0.05): age at line of treatment, body mass index, sex, smoking status, brain metastasis, lung metastasis, *ALK* positive, *BRAF* positive, *KRAS* positive, *MET* positive (mutations, amplifications, and fusions), *ROS1* positive, *TP53* positive, and other non-*EGFR* comutations (*ALK*, *BRAF*, *KRAS*, *MET*, *ROS1* positive).

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## KEY TAKEAWAY

This retrospective analysis based on real-world data of 1L and 2L osimertinib efficacy in patients with advanced NSCLC with common *EGFR* mutations revealed poorer outcomes for osimertinib than those shown in clinical trials and highlighted the unmet need for new treatment options to improve long-term outcomes in this patient population

## CONCLUSIONS

Based on this real-world analysis, 26.7% of patients who received 1L osimertinib died before receiving a 2L treatment; however, a significant proportion (45.1%) of patients were censored, and therefore longer follow-up would be needed to confirm the rate of patients dying before receiving 2L; with longer follow-up, this percentage is expected to increase

In this study, platinum-based doublet chemotherapy was the most common follow-up therapy after 1L osimertinib (34.4% of patients among those receiving subsequent treatment)

For both 1L and 2L osimertinib, OS and rwPFS in this real-world population were substantially lower than those reported in clinical trials[4,8,10,11]

While different sets of prognostic factors were observed for different outcomes and lines of treatment, ECOG PS, the presence of liver metastases, and the presence of L858R mutations were consistently prognostic across all settings

- In addition, the presence of *TP53* mutations was prognostic in the 1L setting and the presence of bone metastases was prognostic in the 2L setting

The results of this retrospective analysis underscore the unmet need for new treatment options for patients with advanced NSCLC with common *EGFR* mutations

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## DISCLOSURES

**MP** received consulting fees from AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Eisai, GSK, Ipsen, Janssen, Merck Sharp & Dohme, Novocure, Pfizer, Roche, and Takeda; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AnHeart Therapeutics, AstraZeneca, Bristol Myers Squibb, Janssen, Merck Sharp & Dohme, Pfizer, Sanofi, and Takeda; received payment for expert testimony from AstraZeneca, Bristol Myers Squibb, Janssen, and Roche; received support for attending meetings and/or travel from AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Pfizer, Roche, and Takeda; and participated on a data safety monitoring board or advisory board for PharmaMar and Roche. **CC** received grants or contracts, consulting fees, and support for attending meetings and/or travel from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, GSK, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Sanofi Aventis, and Takeda. **AB** received grants or contracts from his institution from Eli Lilly, Novartis, and Roche; and received support for attending meetings and/or travel from Gilead. **LB** has no conflicts of interest to declare. **JC**, **IL**, and **NP** are employees and stockholders of Janssen. **JE** is an employee of Janssen and a stockholder of AstraZeneca.

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