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Can sequencing of TKI-inhibitors improve clinical outcomes and cost of treatment in first line advanced non-small cell lung cancer with common EGFR+ mutations in Spain?

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Presented at XXXIX Jornada Economía de la Salud, Albacete (12-14th June 2019)

INTRODUCTION

ESMO guidelines recommend the use of 1st, 2nd and 3rd generation tyrosine kinase inhibitors (TKI) as first line options for patients with epidermal growth factor receptor mutation-positive (EGFR+) non-small cell lung cancer (NSCLC). Even though TKI treatments are effective interventions, resistance ultimately develops, most commonly due to T790M mutations. For these patients, osimertinib is the only targeted therapy available. No targeted therapy is available after failure of osimertinib in first line. In the absence of a RCT, it is currently unclear what the optimal treatment sequence is for patients with EGFR+ NSCLC.

OBJECTIVE

The model aims to compare the time on treatment (ToT) and the TKI treatment-related costs of sequential treatment with afatinib vs. first-line osimertinib treatment, in patients with EGFR+ NSCLC in Spain.

METHODS

- **Model design:** A decision-analytic model was developed to compare the results of two treatment options:
  - Sequential treatment with afatinib plus osimertinib *(Scenario 1)*: Patients received first-line afatinib treatment. Upon disease progression, T790M+ patients received second-line osimertinib, and subsequent chemotherapy upon further disease progression. T790M- patients received second line chemotherapy.
  - First-line osimertinib treatment plus chemotherapy *(Scenario 2)*: Patients received first-line osimertinib treatment. Upon disease progression, patients received second line chemotherapy.
- **Population:** EGFR+ mutation NSCLC patients[1,2].
- **Time horizon:** Time period from initiation of first-line TKI treatment to best supportive care (BSC) or death health state.
- **Perspective:** Spanish National Health System (NHS).
- **Model inputs:** EGFR T790M mutation rate and successive-line treatment rates are described in Figure 1.

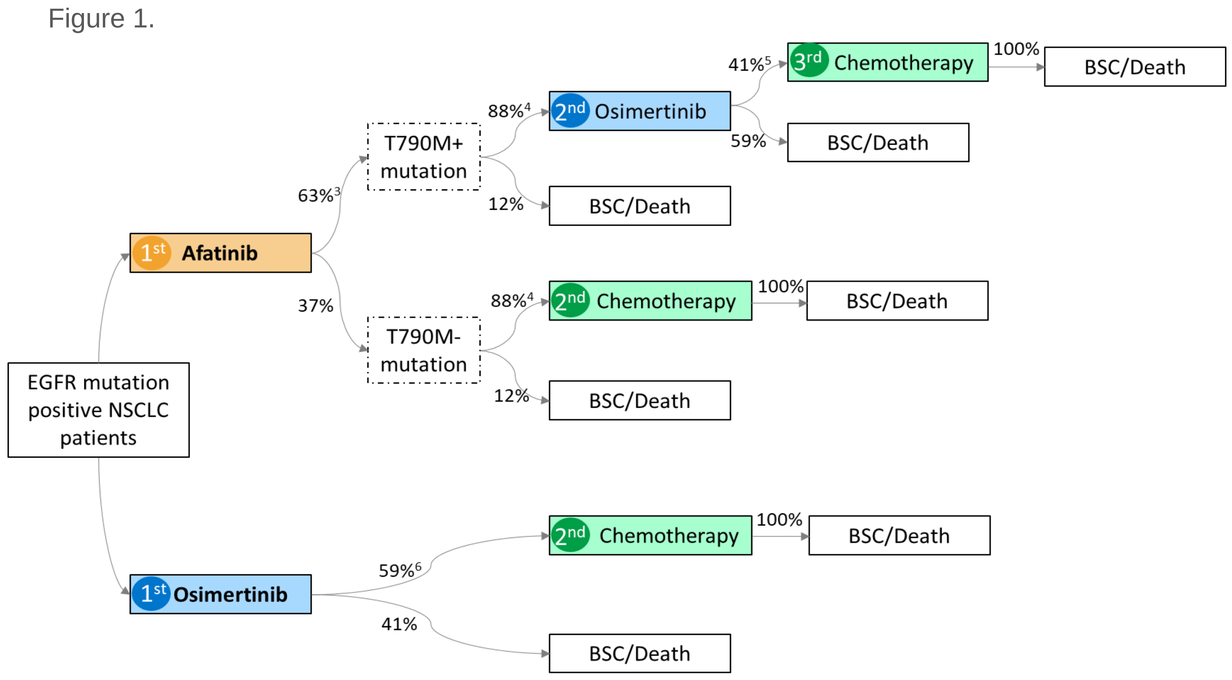

Figure 1. *Decision analytic model of 1st line treatment in advanced or metastatic NSCLC with EGFR mutations.*

- **Clinical input:**
  - ToT was estimated using individual patient level data reconstructed from published progression free survival (PFS) curves[7-10], using the Guyot method[11]. The relative effectiveness measures between the interventions were estimated using adjusted indirect treatment comparison (ITC). The mean ToT was extrapolated to a common time horizon using the Weibull distribution.
  - Adverse event (AE) frequencies for anemia, diarrhea, dyspnea, fatigue, leukopenia, neutropenia, paronychia, rash and stomatitis were obtained from the literature[8,12-14]. Only grade ≥3 AE were considered.
  - In addition to ToT, the model also calculated quality adjusted life months (QALM). The QALM calculation was based on progression status, treatment line and AE profile.
- **Cost input:** Only direct costs were included (Table 1). They were obtained from the literature and updated to € 2019 according to the consumer price index[15], when applicable.
- **Sensitivity analyses:** A sensitivity analysis was performed to analyze the impact of osimertinib potential price change (25% and 40% discount vs. current list price) expected with the approval of the new indication (1st line in EGFR+ NSCLC patients) in Spain.

INPUT	COST (€ 2019)	UNIT	REFERENCE
Drug acquisition (list ex-factory price plus mandatory discounts when applicable)[16]			
Afatinib	€1,918.25	Month	17
Osimertinib	€5,689.92	Month	17
Chemotherapy*	€1,892.19	Month	17
Testing (for all patients progressing on 1st line afatinib)			
T790m test	€407.07	Per test	18
AE management			
Anemia	€511.13	Per episode	19
Diarrhea	€1,582.05	Per episode	19
Dyspnea	€4,038.95	Per episode	20
Fatigue	€178,71	Per episode	19
Leukopenia	€1,633.76	Per episode	19
Neutropenia	€1,941.87	Per episode	19
Paronychia	€0	Per episode	19
Rash	€2.15	Per episode	19
Stomatitis	€1,378.17	Per episode	19

Table 1. *Costs considered in the model (expressed in € 2019).* * *without drug wastage adjustment.*

RESULTS

The model showed that sequential treatment results in:

- **A gain in efficacy**: sequential treatment may lead to improved tumour control with an additional 4.4 months in expected ToT in comparison to osimertinib plus chemotherapy (29.1 vs. 24.8 months, respectively) (Figure 2).
- **Improved quality and quantity of life**: the ToT benefit is translated into a gain of 3 quality adjusted-life months (QALM) (sequential treatment 20.5 vs. first-line osimertinib 17.4 months), suggesting a favourable risk benefit profile for the sequence.
- **Reduced costs**: sequential treatment offers potential cost-savings when compared to first-line osimertinib treatment (€37,338 per patient), in the base case scenario. In the sensitivity analysis, cost-savings are still observed with sequential treatment (Figure 3).

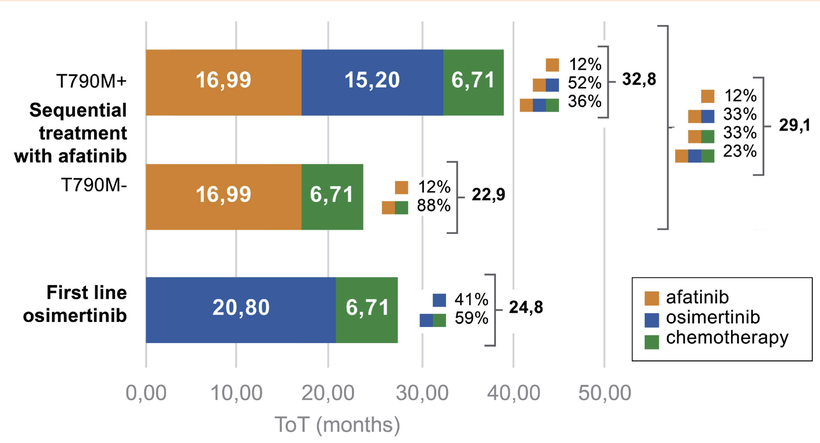

Figure 2. *ToT and weighted average ToT of each treatment option.*

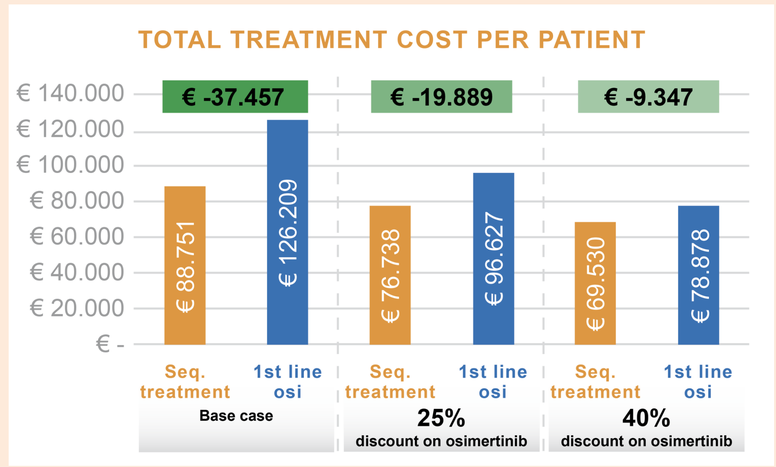

Figure 3. *Total treatment-related cost per patient in the three price scenarios analysed.*

CONCLUSION

The model showed that TKI sequencing could lead to an increase of ToT and QALM in first-line treatment in NSCLC EGFR+. Additionally, utilizing first-line afatinib may result in a total treatment–related cost reduction, generating potential cost-savings for the Spanish NHS. Further clinical research is required to assess the relative benefit of the two treatment strategies. In addition, more comprehensive economic evaluations should be considered when mature overall survival is reported for osimertinib.

LIMITATIONS

- There are currently no head-to-head clinical trials comparing the sequential therapy with afatinib vs. first-line osimertinib treatment. Hence, mean PFS data had to be obtained from their respective pivotal trials.
- The model assumed that TKI treatment is discontinued upon disease progression. This may not reflect the clinical practice. Also, ToT may be underestimated.
- The model was based on TKI list price. As hospital drugs have dual price in Spain, cost of treatment for TKI could be lower than described.
- As AE rates were not reported by mutation type in the respective trials, the frequency of AE were assumed to be constant across the different EGFR mutation subpopulations.
- T790m test was based on data from one region. Cost may vary in other regions.

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MA.11020.052019

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