Cost-effectiveness of 'ROS1-testing' strategy compared to a 'no-ROS1-testing' strategy in advanced NSCLC in Spain

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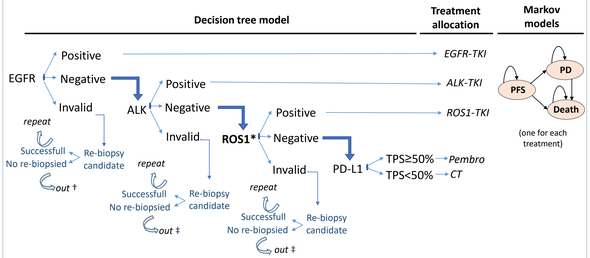
INTRODUCTION AND OBJECTIVES

- Rearrangements of the *c-ros oncogene 1* (*ROS1*) gene have been described as oncogenic drivers of NSCLC (present in 1%-2% of NSCLC cases) [1,2]
- Molecular testing of *ROS1* rearrangements in advanced or metastatic NSCLC patients for therapy decision is considered mandatory[1-4], however this detection is not yet fully widespread (with only 58% of the samples of NSCLC patients determined for *ROS1* according to *LungPath* registry)[5]
- The objective of this analysis is to estimate the clinical and economic impact of *ROS1* determination in patients with advanced NSCLC in Spain, comparing a 'ROS1-testing' strategy with sequentially testing *ROS1* in addition to *EGFR* and *ALK* versus a 'no-testing-ROS1' strategy without *ROS1* testing.

METHODS

- A joint model combining a decision-tree with Markov models was developed (figure 1) (in line with a previous model in ALK testing)[6]

Figure 1: Joint model diagram



EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; ROS1: c-ros oncogene 1; PD-L1: programmed death-ligand 1; pembro: pembrolizumab monotherapy; CT: Chemotherapy; TKI: Tyrosine kinase inhibitors; PFS: progression free survival; PD: progression disease. *ROS1 is determined by IHC, FISH, reflex or NGS in 'ROS1-testing' scenario and not determined in 'no-ROS1-testing' scenario.
†When molecular diagnosis of EGFR is unknown, patients receive doublet of chemotherapy; ‡ When molecular diagnosis of ALK or ROS1 is unknown but the diagnosis of EGFR is known and negative, patients receive chemo-immunotherapy

- **Base case analysis** used a lifetime horizon (20 years), a 3% discount for both costs and effects and a payer's perspective were considered.
- A multidisciplinary group of oncologists and pathologists validated all parameters, assumptions made, and clinical feasibility of the results.

Target population

- A hypothetical cohort of patients with advanced/metastatic NSCLC, who were 'theoretical' candidates for the molecular diagnosis according to the current clinical guidelines for molecular diagnosis in NSCLC was initially estimated. Of these patients, only those finally tested for *EGFR* were defined as the **target population** and entered the model.

Model structure (Figure 1)

- The **decision-tree model** comprise the sequential determination of *EGFR, ALK, ROS1* and PD-L1. The diagnostic results can be informative (positive or negative) or invalids, in which case patients would be direct candidates for re-biopsy. In the 'no-ROS1 testing' strategy, the sequence of determination in the Figure 1 excludes only *ROS1* determination.
- A **Markov model** was developed for each specific treatment allocated depending on the molecular diagnosis result. A partitioned-survival model structure (PFS, PD and death states) with 1-month cycles length were used.

Parameters

- Table 1 lists all inputs included in the **decision-tree model**.
- The direct costs (€, 2021) related to the decision-tree model are:
  - Test costs (IHC: € 70; FISH: € 110; NGS: € 455; *EGFR* test: € 120; *ALK* test: € 76; PD-L1 test: € 70) were agreed by the expert panel.
  - Biopsy costs (€ 385.41) were obtained from eSalud database[7]

Table 1. Decision-tree inputs

	Input	References
Invalid results and positivity rate in selected biomarkers		
***EGFR* (% positive / % invalid)**	13.6% / 1.70%	*Lungpath*[6]
***ALK* (% positive / % invalid)**	3.4% / 2.60%	*Lungpath*[6]
***ROS1* (% positive / % invalid)**	1.0% / 3.30%	*Lungpath*[6]
PD-L1 (% positive* / % invalid)	32.5% / 1.00%	*Expert panel / Lungpath*[6]
Distribution of ROS1 determination strategies in Spain		
IHC	10.0%	*Expert panel*
FISH	30.0%	*Expert panel*
REFLEX to FISH	55.0%	*Expert panel*
NGS	5.0%	*Expert panel*
Probability of re-biopsy		
Percentage of invalid results re-biopsied	33.3%	*Expert panel*

EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; ROS1: c-ros oncogene 1; PD-L1: Programmed Death-ligand 1; IHC: immunohistochemistry; FISH: fluorescent in situ hybridization; NGS: next-generation sequencing;
*Assumed TPS>50% as the threshold for PD-L1 positivity.

- Table 2 lists the distribution of 13 possible **first-line specific treatments assigned** (established by the panel of experts).
- Other parameters included in the **Markov model**:
  - Median progression free survival (PFS) and overall survival (OS) for each treatment were obtained from clinical trials [8-16], and exponential models based on those medians were developed (in line with previous model) [6]
  - Utility values for PFS and PD states were obtained from Carlson et al. (2018)[17] (in line with the previous model developed) [6].

Table 2. Distribution of first line treatments

Molecular diagnosis		Treatment	Distribution
ALK+		Alectinib	95%
		Crizotinib	5%
EFGR+		Erlotinib	3,3%
		Gefitinib	6,7%
		Afatinib	11.7%
		Osimertinib	76.3%
		Dacomitinib	2%
ROS1+		Crizotinib	95% (40%*)
		Clinical trials	5%
		Entrectinib	0% (55%*)
WT	**TPS ≥50%**	Pembrolizumab monotherapy	90%
		Cisp+pmtrx	5%
		Clinical trials	5%
	TPS <50%	Cisp+pmtrx	25%
		Carb+paclitx+beva	5%
		Cisp+pmtrx+pembrolizumab	60%
		Carb+ paclitx +beva+atezolizumab	10%

ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; ROS1: c-ros oncogene 1; WT: wild-type; TPS: tumour proportion score; Cisp: cisplatin; pmtrx: pemetrexed; Carb: carboplatin; paclitx; paclitaxel; beva: bevacizumab.
*Distribution considered in the alternative scenario in which entrectinib is a treatment alternative in *ROS1*-positive patients

- The direct costs (€, 2021) related to the markov models are:
  - Drug acquisition costs (first and second line) expressed as the ex-factory price considering the corresponding deductions [18,19] and vial sharing.
  - Administration costs of € 211 (intravenous administration)[7]

Sensitivity analyses

- Deterministic (scenarios and one-way) and probabilistic sensitivity analyses were carried out.

RESULTS

- 9,578 NSCLC patients with non-squamous histology and those with squamous histology who are never-smokers were 'theoretical' candidate for first-line treatment. 8,755 of those patients that were finally tested for *EGFR* were defined as the target population entering the model.

Base case

- In the target population, the 'ROS1-testing' strategy provided **a gain of 121.3 quality-adjusted life years (QALYs)** compared with 'no-ROS1-testing' strategy over a 20-year horizon, although with an increase in direct costs (Table 3).
- The incremental cost-effectiveness ratio (ICER) shows that **'ROS1-testing' strategy in Spain is cost-effective**, as it was below the cost-effectiveness thresholds commonly considered [20,21] (Table 3).

Table 3. Results for health outcomes and costs, base case

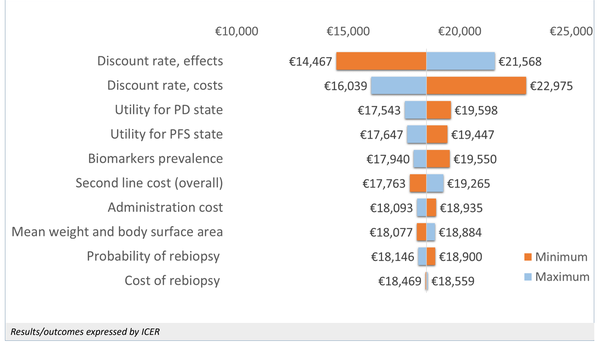
	'Testing ROS1'	'No-testing ROS1'	Difference
Cost of testing	*€ 2,843,608*	*€ 2,149,256*	*€ +694,352*
Cost of re-biopsy	*€ 72,543*	*€ 45,451*	*€ +27,093*
Cost of treatment	*€ 1,045,898,644*	*€ 1,044,375,352*	*€ +1,523,292*
Total costs	**€ 1,048,814,795**	**€ 1,046,570,058**	**€ +2,244,737**
LY	*23,226.07*	*23,068.58*	*+157.49*
QALYs	*16,171.87*	*16,050.62*	*+121.25*
ICER (€/LY gained)			**€ 14,254/LY**
ICUR (€/QALY gained)			**€ 18,514/QALY**

ROS1: c-ros oncogene 1; LY: Life-years; QALY: Quality Adjusted Life Year; ICER: incremental cost effectiveness ratio; ICUR: incremental cost utility ratio

Sensitivity analysis

- In a potential future scenario where entrectinib is available in *ROS1*-positive patients, the 'testing ROS1' vs. 'no-testing ROS1' strategy remains cost-effective (€ 17,652/QALYs: ICUR slightly lower than in the base case).
- Variables modified for the one-way sensitivity analysis and its results are shown in figure 2. The tornado diagram shown that discount rate (for both cost and effects) followed by utilities have the greatest impact on base case ICUR.

Figure 2. One-way sensitivity analysis results, ICER



Results/outcomes expressed by ICER

- Means obtained from the 1,000 simulations (€ +2,209,967 and 18,456 QALYs gained with respect to 'no-testing ROS1' strategy) are in line with the base case.

CONCLUSIONS

1. Testing ROS1 in patients with NSCLC in Spain increases and improves patients' lives and that it is a cost-effective strategy for the Spanish National Health System.

2. This analysis should encourage that not a single ROS1-positive patient goes undiagnosed

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