PCN148

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COST-UTILITY OF ENTRECTINIB VERSUS CRIZOTINIB IN ROS1+ NSCLC PATIENTS: AN AUC MODEL ADAPTED TO ITALIAN CLINICAL PRACTICE

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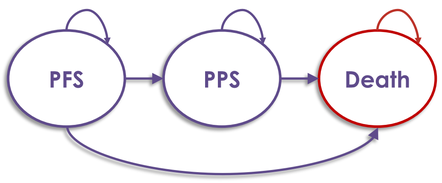
Objective

- Better understanding of oncogenic signaling processes and subsequent therapy targeting specific alterations represent the real frontline of cancer treatment.
- Lung cancer has one of the highest rates of genetic aberrations in cancer and these aberrations have led to molecularly distinct diseases. The frequency of ROS1 rearrangements in Non Small Cell Lung Cancer (NSCLC) patients is estimated at 1-3% (1), approximately 5-fold lower than ALK rearrangements.
- Entrectinib is a new potent inhibitor of the tyrosine kinases (TKI) encoded by the gene ROS1 (2,3).
- An international Area Under the Curve (AUC) model — or partitioned survival model — has been adapted to Italian clinical practice in order to estimate entrectinib cost-utility in the treatment of ROS1+ NSCLC, with respect to crizotinib, currently TKI approved in Italy for ROS1+ rearrangements.

Methods

- A partitioned survival model with weekly cycles is used to model clinical outcomes and costs over the lifetime of Italian patients with ROS1+ NSCLC treated with entrectinib or crizotinib.
- Health states are based on partitioning NSCLC patient overall survival (OS) into progression-free survival (PFS) and post-progression (PPS) (fig 1).
- Main clinical drivers are PFS and OS curves, estimated by parametric extrapolation with exponential function — selection was based on goodness-of-fit, assessed statistically and visually — to observed data from the pooled entrectinib trials; given the lack of head-to-head studies, a Matched Adjusted Indirect Comparison (MAIC) has been carried out to estimate hazard ratios of entrectinib vs. crizotinib.
- Utilities are generated from the STARTRK-2 EQ5D-3L questionnaire data (3) valued with Italian tariffs (4).
- Considered costs are for mutation test (mandatory to start TKIs), oral drug acquisition, adverse events management, and supportive care; unit costs are based on national literature data and current tariffs, from NHS perspective (5-9). Drugs are costed based on protocol/label planned dose, observed length of treatment and parity price assumption (Tab 1).
- Costs, updated to 2018 Euro, and health gains occurring after the first year are discounted at an annual 3.5% rate (10). A half cycle correction is applied.

Figure 1 Model structure



All patients in PFS state may move to PPS or death states at the end of each cycle. At specific discrete points in time, the proportion of patients in PPS state is assumed to be the difference between OS and PFS (progression = OS – PFS)

The estimated PFS utility (0.82) is used for all the compared therapies in the ROS1 indication, in the absence of further data. As post progression utility for the ROS1 therapies, the estimate of 0.66 is used, based on the chemotherapy arm of the PROFILE 1007 study (11) for Crizotinib in the ALK+ NSCLC population. The rationale behind the selection of the post progression utility is the potential consistency of ALK and ROS1 NSCLC population as well as the consistency with the estimated PFS utility from the entrectinib trials.
In the model, the estimated utilities are adjusted for age over time: utility decrements due to age are based on data regression of utility values clustered by age in Italian general population(12).

Table 1 Details of main input costs;

Cost item	Cost
Entrectinib (weekly /patient) - assumption	€ 1,381
Crizotinib (weekly /patient)	€ 1,381
Mutation test (unit /patient)*	€ 226
Supportive care PFS (weekly /patient)	€ 8
Supportive care PPS (weekly /patient)	€ 68
Post progression treatment (weekly/patient)	€ 628
AE management (weekly /patient)	€ 5

** Testing cost is based on reimbursement tariff for FISH (Fluorescence in situ hybridization) assay, the core methodology generally used for ROS1 testing in Italy.*

Supportive care cost for PFS health state includes clinical visit, CT, bronchoscopy test, ECG, spirometry test and complete blood counts. Annual frequencies derive from AIOM guidelines and summary of product characteristics (SPC) (5,8).
Supportive care cost for PPS health state includes medical care and home artificial nutrition, valued by Italian study (9).

Patients discontinuing front-line therapy receive a second line therapy (chemotherapy) or palliative care. Therapeutic sequences are based on expert opinion and Italian clinical practice. Costs for chemotherapy derive from official source (6), whilst the palliative care costs derive from Italian study (9).

Results

- Lifetime model results estimated that entrectinib, when compared to crizotinib, induces a survival gain of 2.2 life years in the post-progression phase, corresponding to 1.4 QALYs (Tab 2).
- The incremental costs associated to entrectinib are 117K €, mainly due to the improvement of life expectancy (paradox effect) and to longer TKI treatment duration (TTOT of entrectinib was estimated at 103 weeks vs. 74 of crizotinib).
- Estimated clinical and cost outcomes lead to an ICER of 54 K€/LY and an ICUR around 80 K€/QALY (Tab 3 and Fig 2).

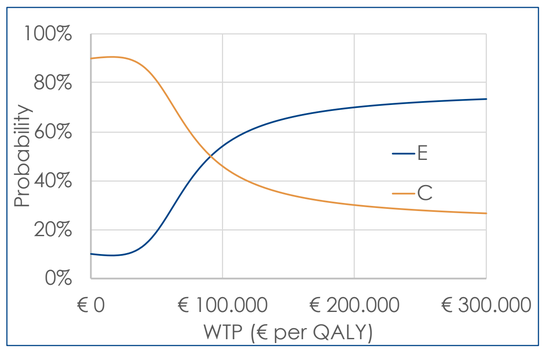
Table 2 Summary of results - Values are discounted. Costs are in €.

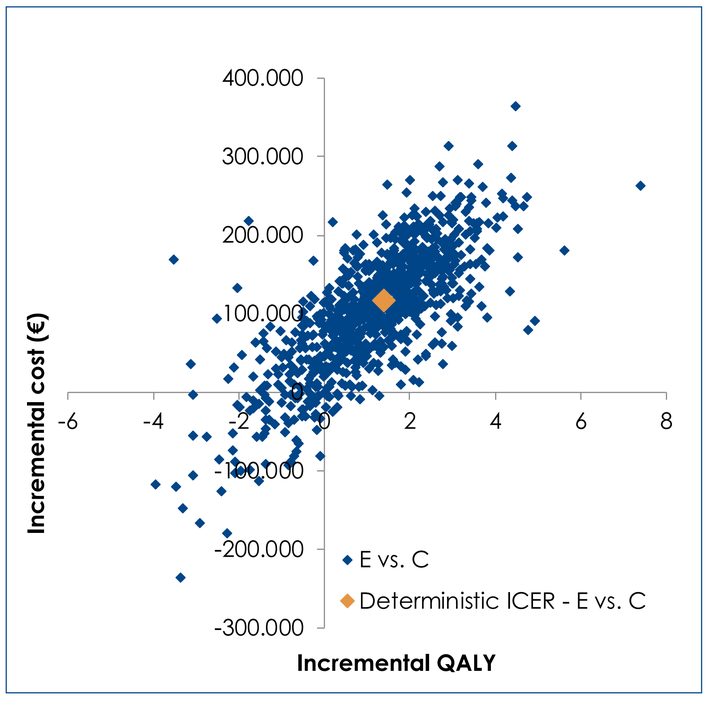
Item	E	C	Δ E vs. C
Total LYs	**6.02**	**3.85**	**2.17**
In PFS	2.02	2.05	-0.04
In progression	4.00	1.79	2.21
Total QALYs	**4.21**	**2.83**	**1.39**
In PFS	1.64	1.67	-0.03
In progression	2.57	1.16	1.41
Overall costs	**282,639**	**165,442**	**117,197**
Mutation test	226	226	0
Front-line therapy	135,741	98,864	36,877
Adverse events	508	370	138
Supportive care	845	861	-16
PPS cost	145,318	65,121	80,198

Table 3 ICER and ICUR

Description	Δ E vs. C	ICER/ICUR
LYs	2.17	€ 53,988 /LY gained
QALYs	1.39	€ 84,828 /QALY gained
Costs	€ 117,197	

Figure 2 (right side) Incremental Cost-Effectiveness Plane; Figure 3 (below) Cost-Effectiveness Acceptability Curve





Conclusions

- Entrectinib increases expected survival in ROS1+ NSCLC patients with an incremental cost-utility that can be considered acceptable, especially considering the approximation of ROS1-NSCLC to a rare disease (13). Main limitations are the ineluctable indirect comparison approach, that together with the poor knowledge on the natural history of the ROS1-NSCLC population make the analysis subject to considerable uncertainty.

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ISPOR Copenhagen 2019