**INTRODUCTION**

- Chronic myeloid leukaemia (CML) is one of the white blood cancers in which there is an overproduction of one type of white blood cell (WBC), the granulocytes, by the bone marrow. The typical CML progression curve is triphasic: the initial chronic phase (CML-CP) during which the disease is stable and slow to progress is followed after a variable interval by progression through an accelerated phase (CML-AP) to a rapidly fatal blast crisis (CML-BC). In approximately one-third of patients there is no demonstrable AP, with the disease progressing directly from CP to BC. Transition between the phases may be gradual or rapid.[1,2]

- The incidence of CML ranges between 1 and 2 cases/100,000/year [age adjusted] with no major geographic or ethnic differences. The median age of diagnosis ranges between 65 and 75 years in Europe. The prevalence of CML is slowly rising due to the very substantial prolongation of survival that has been achieved with targeted therapy.[3]

- CML was the first malignant disease in which an acquired genetic anomaly was demonstrated as the final trigger in a chronic myeloproliferative syndrome characterized by a translocation between chromosomes 9 and 22, giving rise to the formation of the so-called Philadelphia chromosome (Ph) and the creation of a new fused gene, BCR-ABL. This gene codifies a chimeric BCR-ABL protein that elevates tyrosine kinase (TK) activity, which increases the survival and proliferation of cells and inhibits apoptosis.[4,5]

- With the advent of a new class of drugs for the treatment of CML known as tyrosine kinase inhibitors (TKIs), the natural history of the disease has markedly changed. The current clinical practice of CML therapy is to treat patients indeﬁnitely with a TKI and current evidence suggests that patients whose disease responds favourably to treatment with TKIs may remain essentially symptom free for at least 10 years.[6,9]

- Several clinical trials have reported successful treatment-free remission (TFR) in patients with sustained deep molecular response (MR) on TKIs.[7,8]

- The on the other hand, considering drug costs, it is important to underline that imatinib will lose patent protection in December 2016, with a considerable price reduction.

**OBJECTIVES**

- The aim of this study is to assess the cost-utility of first-line nilotinib vs imatinib in patients with chronic CML eligible to start the TFR phase in the Italian healthcare setting (NHS), taking into account the loss of patent protection for imatinib.

**METHODS**

- A previous cost-utility model in MSExcel® and EVA² was adapted to the Italian NHS, using a bottom-up approach, consistent with the methodology of the activity based costing. (9-12)

**MODEL STRUCTURE AND ASSUMPTIONS**

- The model, an individual patient simulation model (IPS) based on a Markov framework model, simulates a cohort of 20,000 computer “patients” individually followed over time. Each “patient” has his own trajectory guided by the parameters associated with Sokal category, age, and gender and random variation, simulating real-life experience. Simulation outputs are clinical and economic outcomes averaged over all patients.

- Patients traverse through several CML health states (Figure 1) and time in TFR is the key feature of the disease progression simulation.

- 1st-line discontinuation probabilities are estimated from patient-level ENesti-trial data.

- All of the patients remaining on 1st-line treatment at 36 months are “long-term responders”: • BCR-ABL trajectories always decreases with time.
  - Long-term responders who have BCR-ABL under the threshold of MR 4.5 for 2 years enter in TFR.

- Table 1: shows the results of TFR from estimated from STIM data. Patients return to 1st-line treatment and are no longer eligible for TFR.

- After discontinuation from initial treatment, patients go to 2nd-line TKI therapy or no therapy.

- After 2nd line, patients are removed from TKI therapy (i.e., treated with hydroxyurea) and are eligible for stem cell transplant.

**MODEL ADOPTION**

- An advisory board of clinicians expert in the management of the disease, provided information on: treatment pathways, patients routine healthcare resource consumption, health care resource costs (routine visits and instrumental tests etc.), adverse events (SAE) management and utilities.

- According to the clinicians, CML patients could start treatment with nilotinib or imatinib, at the age of 60 years while for both arms a second-line with nilotinib 800 mg is expected according to the Italian clinical practice.

- Model outcomes are expressed in Quality-Adjusted-Life-Years (QALYs) and years-lived (YLD). Costs - Euros (€) 2015 - were quantified using hospital national tariffs (in-patient and outpatient): For drugs, the maximum prices that the Italian National Healthcare Service (NHS) reimburses were considered.

- The model considers for nilotinib the cost-sharing according agreements with the National Drug Agency (AIFA) and that generic imatinib and nilotinib become available as of December 2016 and July 2017, respectively with a consequent 74% price discount for both drugs.

- The analysis, according to the clinicians, was performed with a time horizon of 15 years and costs and outcomes were discounted at 3% according to Italian Guidelines for Economic Evaluations.[13]

- Incremental cost-effectiveness ratios (ICERs) were calculated to estimate the incremental cost of a TKI patient with nilotinib.

**SENSITIVITY ANALYSIS**

- To test the robustness of the results we considered also a scenario with no price reduction, after generic entry for nilotinib.

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**RESULTS**

**BASE CASE**

- Table 1 shows the unitary costs modelled in the analysis.

<table>
<thead>
<tr>
<th>Drugs &amp; Transplant Costs</th>
<th>Management Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib (Cost Sharing – 3 months)</td>
<td>Management Costs</td>
</tr>
<tr>
<td>Variable</td>
<td>€/month/episode</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>1,204K</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>2,408K</td>
</tr>
<tr>
<td>Generic Nilotinib</td>
<td>626K</td>
</tr>
<tr>
<td>Imatinib</td>
<td>1,907K</td>
</tr>
<tr>
<td>Generic Imatinib</td>
<td>496K</td>
</tr>
<tr>
<td>ALL</td>
<td>Transplant</td>
</tr>
<tr>
<td>59,806K</td>
<td>Peripheral Edema</td>
</tr>
</tbody>
</table>

- According to a different proportion of patients reaching MR 4.5 (Figure 2), an incremental number of 3,773 patients are eligible to TFR with nilotinib vs imatinib (11,980 vs 8,207).

- Table 2 shows very important clinical outcomes with nilotinib with +1.06 L/H (12.03 L/H vs 10.97 L/H) and good results regarding also progression free survival of +3.49 L/H (11.32 L/H vs 9.81 L/H). Considering different utilities related to health states and used for the Italian scenario, according to clinicians, the model shows for nilotinib an average increase of 0.85 QALY (8.22 QALY vs 7.38 QALY).

- Despite the higher monthly cost for nilotinib, an early loss of price for imatinib: and a very high discount for generic drugs (Table 1), the average cost per patient for nilotinib is close to imatinib (Table 2), with an incremental drug cost, in a time horizon of fifteen years, of €61,692 (€201,937 vs €140,244 ), but with a total increase in healthcare costs of €53,748 (€257,611 vs €223,863).

- The model, according to the variables considered, estimated a very favourable [17,18] ICERs for nilotinib vs imatinib with a value of €39,935/QALY and €31,969/LY.

**CONCLUSIONS**

- The model shows that a greater number of patients enter TFR with nilotinib with a better clinical profile in terms of overall survival, progression free survival and number of patients in TFR with and an acceptable ICERs vs imatinib.

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**REFERENCES**

9. TFR: 45,000/85,000
17. Horvath K, the cost-sharing according agreements with the National Drug Agency (AIFA) and that generic imatinib and nilotinib become available as of December 2016 and July 2017, respectively with a consequent 74% price discount for both drugs.
18. Sensitivity Analysis: Considering the scenario with no price reduction for nilotinib, the results are still favourable for nilotinib, with an ICER of €44,351/QALY and €35,505/LY.

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**DISCLOSURE**

This analysis was a collaboration between Creativo-Ceutical and Novartis Farma. Funding was provided by Novartis Farma.