LEUKOPREDICT:

an in vitro system predicting and monitoring the therapeutic response of patients in the cure of Chronic Myeloid Leukemia (CML)

Summary of the context and overall objectives of the project

Before the introduction of imatinib, the first drug in the family of Tyrosine-Kinase Inhibitors (TKIs) approved for the treatment of Chronic Myelogenous Leukemia (CML) in year 2001, a diagnosis of CML amounted in most cases to a death sentence through the progression from the chronic phase, to the accelerated phase, to the blast crisis phase.
The treatment of CML with imatinib has been highly successful in controlling the disease. However, it is estimated that approximately 20% to 30% of patients will eventually develop resistance to imatinib. Moreover, the responses obtained in patients with advanced CML are low and typically short-lived.

2nd generation TKIs demonstrated a superior efficacy as compared to imatinib as first-line treatment for newly diagnosed CML patients in inducing rapid and deep responses. Moreover, patients treated with 2nd generation TKIs had a reduced probability of progression to accelerated and blastic phase. Despite this favourable results, a broad use of 2nd generation TKIs upfront is matter of debate, and imatinib is still considered a valuable option of first-line treatment since it has determined significant, not yet overcomed benefits on survival, and there are no reports of worrying organ toxicities after more than a decade of use. The overall tolerability profile of 2nd generation TKI is comparable to that of imatinib, but the long-term complications are not yet fully understood and evaluable.
One of the major arguments against the use of imatinib first line is that superior rates of progression to accelerated and blastic phase (and consequently death) can not be completely reverted by switching to another TKI at a subsequent timepoint. The main reason of this disappointing circumstance is that a treatment switch is tipically made after many months of treatment, when full resistance to imatinib is displayed.
On the other hand, due to patent expiration, generic imatinib is available since 2016. The average per-person total cost of treatment with generic imatinib is expected to drop to about $46.000 per year, while that of 2nd generation TKIs Dasatinib or Nilotinib is $87.000-$92.000/year

Therefore, the possibility to early evaluate the effectiveness of a given TKI-based therapy is a valuable and highly prized goal.

The main project objective is the development and placing on the market of the first In Vitro Diagnostic (IVD) Medical Device capable of predicting the response to the treatment of patients affected by CML with TKIs by measuring Tyrosine Kinase activity, thus assisting the physician in the choice of a treatment with optimal efficacy and low probability of adverse effects and onset of resistance, both in newly diagnosed CML patients and on therapy switch due to acquired resistance, as well as when resuming therapy after failure of TKI discontinuation attempts.

Horizon 2020
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Duration: 01.02.16 – 31.07.16
Project costs: 71.429,00
EU contribution: 50.000,00

The device will also support the adoption of the less expensive treatment with generic imatinib, thus freeing substantial resources of the Healthcare System which can be redirected to other needs.

Work performed from the beginning of the project to the end of the period

A feasibility study has been completed whose main results are:

- ✓ The design of a clinical trial aimed at demonstrating the utility of the IVD device; the clinical trial is currently under Ethics Committee approval ;
- ✓ An analysis of potential infringement of existing Intellectual Property Rights aimed at ensuring commercial exploitation while preventing legal controversies (Freedom-To-Operate Analysis), and consequent IPR strategy;
- ✓ A regulatory compliance analysis specifically taking into account the issues arising from the intended use of the IVD device, which, being targeted to assist in personalized therapy selection, may be classified in or be considered close to the category of Companion Diagnostics;
- ✓ A detailed financial plan.

Progress beyond the state of the art and expected potential impact

The development of an assay capable of predicting the response to the treatment of patients affected by CML with TKI is an outstanding result in itself which has been sought for by many researchers. In the framework of the activities which have been planned in the LeukoPredict project, in addition to the outstanding scientific and technical result, the assay will be brought to actual widespread adoption as a marketable In Vitro Diagnostic (IVD) Medical Device, backed up by industrial capability and worldwide commercial availability.

The growth impact for the company embraces many aspects:

- ✓ Increased revenue, leading to a doubling of the current revenue already two years after project completion (1.1 M€ to 2.2 M€);
- ✓ Increased employment, leading to 6 additional stable people hired within two years after project completion (Production 2 units, Research&Development 2 units, Sales&Marketing 1 unit, Administration 1 unit);
- ✓ Adoption of a new technology adding to the two main technologies on which current molecular diagnostics products are based (Reverse Line Blot and Real Time PCR);
- ✓ Establishment of company know-how and best practices for carrying out successful radical innovation in addition to the incremental innovation on which the company has built its gradual but steady growth since startup in 1987.

The main societal impact is expected to come from huge cost savings for Healthcare Systems, allowing them to redirect their increasingly limited resources to other needs different from CML patient care.

For most CML patients in the chronic phase physicians are able to keep the disease under control with TKI treatment.

For these patients the device will increase quality of life thanks to the timely support to:

- first-line therapy optimization in terms of efficacy and reduction of both adverse effects and probability of onset of primary resistance;
- therapy optimization on therapy switch mandated by acquired resistance.

Patients attempting therapy discontinuation will also benefit from therapy optimization in case of failure and therapy resuming.
There is also a potential to be investigated for therapy optimization in the accelerated and blastic phase.

In the recent European clinical practice guideline (European LeukemiaNet recommendations for the management of chronic myeloid leukemia:2013) the importance of quality of life improvement is acknowledged, including the issue of therapy discontinuation.
This is particularly relevant to fertile women who may have achieved an optimal response, because conception and pregnancy are contraindicated during TKI treatment.
The quality of life is also affected by the very fact that living together with a potentially fatal disease—CML is a cancer, after all—has emotional and social consequences affecting family and career planning and is accompanied by a variable level of uncertainty and fear. It was not surprising that both physical and mental health were reported to be better and closer to normal in the older than in the younger patients, because younger have more and different expectations, not only of a normal life, but also of a life free from leukemia and from treatment.
Currently, the major goal of therapy is survival, but it is acknowledged that living without treatment and without detectable leukemia will be a major issue for clinical investigation, requiring the achievement of a deeper molecular response.

An entirely new development can also be envisaged in the prediction of TKI response in general, i.e. also when treating diseases different from CML.
Numerous TKIs aiming at various tyrosine kinases have been proven to be effective anti-tumor agents and anti-leukemic agents, e.g. gefitinib and erlotinib aiming at the EGF receptor which are used for the therapy of non-small cell lung cancer (NSCLC), a lung cancer type accounting for about 80% to 85% of lung cancers.
Targeted therapies which are revolutionizing cancer therapy generally require so-called Companion Diagnostics (CDx) to check if the patient is a potential responder to the therapy. Various approaches are adopted in such IVD tests, resulting in different types of test, including e.g. mutation tests and immunohistochemistry tests, but generally some specific molecular feature correlated to response is detected.
For TKI drugs the more general approach adopted in this project of measuring the Tyrosine Kinase activity could be a generally applicable alternative, independently from proven correlations between specific molecular features and response, and as such capable of providing correct indications even when the response is driven by less frequent molecular features whose correlation is not yet proven or discovered.
Such development would open the application of the method to the prediction of response of tumors with much larger incidence than CML.