BIOVALID Report Summary

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Periodic Reporting for period 2 - BIOVALID (Clinical validation of the DiviTum assay in two high profile clinical studies in Europe)

Reporting period: 2016-09-01 to 2017-08-31

Summary of the context and overall objectives of the project

Clinicians need better predictive and monitoring tools to administer optimal treatments for cancer patients and evaluate who actually responds to therapy. Drug developers face high risk of regulatory failure due to not being able to use better tools for selection and evaluation of drugs in early development and later for patients in clinical development programs. Biovica have developed a state-of-the-art assay kit for measuring cell proliferation rate - DiviTumTM, for the serum-based detection of Thymidine Kinase (TK) activity – a key enzyme involved in cell proliferation and DNA synthesis. There is compelling scientific rationale to use TK as a biomarker for drugs that disrupt cell cycle regulation, such as Cyclin Dependent Kinase (CDK) inhibitors. As part of the previously conducted SME Instrument Phase 1 feasibility study, our company has identified the clinical study & research market segment, comprised of pharma companies that develop CDK inhibitors, as a current target for the commercialization of DiviTumTM. The first CDK 4/6 inhibitor to be approved by the FDA is Ibrance (palbociclib) in February 2015 and an application for approval in the EU was approved by EMA in November 2016. Our company has successfully negotiated to be part of two high-profile clinical studies involving a novel CDK inhibitor with leading oncology institutes in Europe. Overall objectives: A clinically validated DiviTumTM has the potential to become the gold standard predictive and efficacy biomarker for CDK 4/6-inhibitors like Ibrance and other cell cycle regulating drugs in selected, metastatic, solid tumors. This will benefit patients through improved utilization of current and novel treatments; payers by saving costs on ineffective treatments; clinicians by providing a guiding clinical decision tool; and drug developers by improving clinical trial success rates through optimized cohort selection, shorter time to market and decreased risk of regulatory failure.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

• PREDIX and PYTHIA studies have started and are including patients. First payment for inclusion in the PYTHIA study made to IBCSG/BIG.
• Communication/PR of our collaboration with IBCSG/BIG have been issued.
• Produced an initial investigative Health Economic report as foundation for future reimbursement arguments, strategy and marketing plan.
• Published a White Paper with the scientific rationale for using Biovicas technology in cell cycle regulating drugs like CDK 4/6 inhibitors.
• First results from a study including CDK 4/6 inhibitors with a US university have been accepted for presentation at scientific congress before the end of 2016.
• Biovica have produced all kits needed for full analysis of all samples from the PYTHIA and PREDIX studies.
The PREDIX and PYTHIA studies, evaluating the addition of palbociclib (trade name Ibrance; Pfizer) to standard endocrine therapy have started and inclusion of patients is ongoing. The fact that these studies are ongoing and the first DiviTum results from a US study of palbociclib that soon will be presented, have resulted in increased interest and inclusion in new projects & trials with US cancer institutes. In total DiviTum have been able to initiate interest and be included in 5 US studies addressing CDK 4/6 inhibitors. The first of these collaborations is a clinical study that will report before the end of the year at a major US cancer congress, supporting the use of DiviTum as an efficacy biomarker for CDK 4/6 inhibitors. With the potential in the US and the imminent study results that will be presented, Biovica have chosen to expand in the US and contract a full time consultant responsible for US Business Development (from 1 January 2016).

The value and interest in the studies in BIOVALID was boosted by the approval of palbociclib in EU in November 2016. With that comes the need for authorities to negotiate price and reimbursement of the drug, making the fundamental questions asked in BIOVALID highly actual. The price for palbociclib in the US is approx. USD 120,000 per patient and year making the drug highly expensive. We assume that all EU member states will have a significant interest in the pricing of palbociclib in EU. The addition of an efficacy biomarker for the drug would be a significant contribution and aid in administration guidance for the drug to those who actually respond. The results from PYTHIA & PREDIX studies and the other ongoing CDK 4/6 trials where DiviTum is included will provide evidence and reimbursement information on how to best use DiviTum as a tool for evaluating efficacy in this class of new drugs. At the recent ESMO meeting (www.esmo.org) biomarker data from the PALOMA-2 study (palbociclib in addition to standard endocrine therapy) was presented (Finn R et al). In summary, none of the markers looked at in the study revealed any correlation to the efficacy of palbociclib, yet again underlining the need to find a biomarker for early identification of patients responding to palbociclib.

A collaboration has been initiated with a high profile European Cancer Research Institute to look at another drug in the class of CDK 4/6 compounds, demonstrating the interest for DiviTum as a biomarker for this class of drugs. Biovica have also built on the collaboration with the PYTHIA Principal Investigator to provide data for DiviTum as a tool in early development and preclinical model rationale for endocrine therapy and cell cycle regulating drugs.

**Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)**

The expected final results will make DiviTum a biomarker for efficacy for the CDK 4/6-inhibitor palbociclib in combination with endocrine therapy for women with metastatic breast cancer. Approximately 450,000 women are affected by the disease every year of whom 80% are eligible for treatment with palbociclib (hormone receptor positive tumors). The cost of palbociclib is approx $ 100,000/year (in the US) so the need for a biomarker to predict and monitor efficacy is great amongst payers. CHMP gave a positive opinion to the EC for approving palbociclib in the EU on September 16, 2016 meaning that the approval of the drug can be imminent. The price of palbociclib in EU is not yet known but being able to identify which patients benefits from treatment will avoid over-treatment and side effects of the therapy as well as save money for payers. Palbociclib is only the first drug in the class, two others have filed for approval and others can follow.

In total DiviTum have been able to initiate interest and be included in 5 US studies addressing CDK 4/6 inhibitors and 7 in total. The first of these collaborations is a clinical study that will report before the end of the year at a major US cancer congress, supporting the use of DiviTum as an efficacy biomarker for CDK 4/6 inhibitors (SABCS 2016, Thomas S et al, Poster 5-04-02). This collaboration and the promising first data have resulted in a follow-up study with the same University and Biovica aim to publish more clinical results in the first half of 2017 with an abstract submitted to the AACR annual meeting in April.

**Related information**