1 Publishable summary

1.1 Summary description of project context and objectives

The RESPONSIFY project has the overall goal to identify and create standardised, clinically implementable predictive biomarkers, which will eventually form an CE-marked IVD test to better select breast cancer patients for anti-HER2 treatment and anti-angiogenesis therapy. This overall aim will be reached by reaching the following objectives.

1. Identification and discovery of predictive biomarkers using novel and established genome-wide based techniques to take forward for further validation and functional characterization
2. Identification of genes modulating HER2-inhibitor sensitivity by whole genome siRNA screening.
3. Transfer of novel and established genome-wide based techniques to a diagnostic platform to take forward for further validation and functional characterization
4. Validation of candidate biomarker assays in large clinical trial cohorts
5. Formal development of CE-marked IVD (in vitro diagnostics) tests
6. To establish a commercialisation and dissemination plan for validated diagnostic tests
7. Set up of a commercially available web-based centralised database for clinical & biomarker data management within clinical trials.
8. To establish a core health economic model (Markov model) for several European countries as a basis for evaluating and comparing different testing strategies for various biomarkers in breast cancer
9. To further improve and develop a functioning research infrastructure which is demanded by such a high level multinational project including SOPs, central sample management and integrated bioinformatics.

In order to achieve this, the RESPONSIFY structure is composed of two logical periods:

During period 1 (Month1-18), the functional identification of biological markers modulating HER2 inhibitors will be performed by whole genome siRNA screening using cell-lines. In parallel the identification of biomarker candidates for anti-HER2 and anti-angiogenic using novel genome based technologies will be performed based on tumour tissue (WP3). Candidate biomarkers from the literature or previous projects will be evaluated (WP5) and transferred to a diagnostic platform by the SMEs (WP4).

1.2 Description of the work performed so far and main results

At the very beginning of the project the backbone and logistics have been built and strengthened. We identified the possible cohorts with the appropriate biomaterial and set up standard operating procedures how these biomaterials will further be prepared and distributed from the central biobank from the German Breast Group. In parallel the biomaterial collection in various neoadjuvant studies is continued. In an ongoing neoadjuvant study we implemented a window of opportunity study, where the patients receive only the anti-HER2 treatment before they enter the main study (Geparsepto study NCT01583426). This will be an additional source for fresh frozen material. To seek other collaborations and to make the project visible, RESPONSIFY was continuously presented at various meetings ,e.g. EORTC pathobiology meeting.
In parallel to these efforts, new biomarker candidates are currently investigated in different sources. On the cell level novel genes for anti-HER2 therapy resistance are currently been searched, because the treatment of HER2-positive tumours involves the use of multiple agents targeting HER2 and its family members, and includes both antibody-based therapies, such as Trastuzumab (TR) and Pertuzumab, and tyrosine kinase inhibitors (so called small molecule), such as Lapatinib (LAP) and Afatinib (AF). Understanding the mechanisms of resistance to these compounds is essential to be able to develop alternative strategies for tumour treatment.

As part of the Responsify consortium, we are performing both genome-wide loss-of-function (shRNA screens) and gain-of-function (transposon screens) studies to identify novel genes that determine resistance and/or sensitivity to HER2 inhibition using breast cancer cell lines. Comparing the targets among different cell lines will allow to identify common modulators that could represent potential therapeutic targets and will be further validated in tumour tissues by our partners. In addition the group has developed and functionally validated the novel transposon construct for the gain-of-function genome-wide screens.

Different datasets have been identified to perform the identification of biomarker candidates for anti-HER2 & anti-angiogenic therapy using novel genome-wide analysis, which is currently in progress. Based on previous work of several partners of the consortium the quantity and location (stromal or intra-tumoural) of lymphocytic infiltration (TILs) has been evaluated. In additional studies candidate genes have been identified in order to start establishing a FFPE based IVD test using qRT-PCR. Our results show that immunological parameters are linked to therapy response for classical chemotherapy as well as targeted therapy.
We will now focus on immune markers in tumor tissue that are evaluated by RT-PCR to investigate the cellular pathways involved and to define molecular tests for evaluation of immune response.
A health economic project is integrated into RESPONSIFY to finally decide if selecting patients responding from a certain therapy based on the tests developed during the project is really cost-effective. Three core combined decision tree and Markov cohort state-transition models were constructed to cover patient paths of breast cancer patients in the adjuvant, neo-adjuvant and metastatic settings, respectively. In parallel to these research focused tasks a web based ECD system has been further developed to be able to become a study management tool. During the first part of the project additional functions have been implemented as a role and access for the central pathology to enter the data of the central

assessment of HER2, ER, PgR, Ki67, TILs. The next step would be to upgrade this part into a biomaterial tracking system. The second important function is the possibility to enter, assess and manage serious adverse events (SAEs). The RESPONSIFY project has been disseminated through several channels. At the upcoming San Antonio breast cancer meeting three projects from RESPONSIFY have been selected for oral presentations. Several papers have been submitted to high impact peer reviewed journals. This underlines the scientific success of the consortium.

1.3 The expected final results and their potential impact and use

The overall aim of this proposal is to develop FFPE based predictive IVD tests for anti-HER2 and antiangiogenic therapy in breast cancer to improve risk to benefit ratio for women diagnosed with cancer as well as cost to benefit ratio. If this will be successful these tests will provide a better opportunity to stratify patients according to predictive factors for therapy response.

RESPONSIFY Website: www.RESPONSIFY-FP7.eu