Medical University of Graz

Biomarker and resistance mechanisms of metastatic Her2 positive breast cancer treated in the NerHer clinical trial

Summary

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Supervisor:	Dr. Marija Balic
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 03, 2022 00:00 and September 20, 2022 23:59 (Europe/Zurich)

Description

Background:

HER2-positive breast cancer (BC) is characterized by the overexpression of the HER2 protein as determined by immunohistochemistry or by the amplification of *HER2/neu* gene as determined by in-situ hybridization. HER2 overexpression was traditionally associated with poor prognosis. However, the treatment of HER2 positive disease has vastly improved over the last two decades, starting with the introduction of the monoclonal antibody trastuzumab as the first HER2-directed targeted treatment. Its implementation in the treatment of mBC patients with HER2 overexpression led to significant improvements in progression-free survival (PFS) and overall survival (OS). NerHer 1 is an investigator initiated clinical study in patients with metastastic breast cancer

In this study proposal, we suggest evaluating the efficacy of neratinib with two possible combination partners as 3rd-line or beyond 3rd-line therapy. Combination partners for neratinib will be at the discretion of treating physicians, enabling 2 possible treatment options: Neratinib + Trastuzumab + Vinorelbine or Neratinib + Trastuzumab

Hypothesis and Objectives:

We hypothesise that with implementation of biomarker analyses including ctDNA longitudinal trajectories, mutational profile and epigenomic changes we may establish correlation with response and resistance and translate this knowledge into the evaluation of resistance mechanisms with in vitro modelling.

Methodology:

Exploratory endpoints of the NerHer study will be focus of the thsis and involve evaluation of biomarkers potentially predicting for response to neratinib + combination partners and/ or resistance:

We will perform assessment of HER2 gene copy numbers (primary tumor, if indicated; optionally cell-free tumor DNA (ctDNA)), HER2/neu mutation status, and PIK3Ca mutation status (ctDNA)

Mutational profile of ctDNA will be performed with Avenio kit. WGS will be performed for evaluation of novel resistance mechanisms and methylation profile of ctDNA will be evaluated in good responders vs. patients with very short progression free survival in order to evalute potential of methylation profiles for prediction of response and prognosis.

Assessment of baseline and longitudinal trajectories of circulating ctDNA fraction as assessed by mFAST-Seq (so-called Z-score).

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