Medical University of Graz

Bioinformatic characterization of the molecular background affecting treatment response in early-stage and metastatic breast cancer

Summary

Division of Clinical Oncology, Department of Internal Medicine, Medical University of Graz

Supervisor:	Dr. Marija Balic
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 15, 2022 00:00 and March 28, 2022 23:59 (Europe/Zurich)

Description

Background:

Breast cancer is the most frequent malignancy in women worldwide and is a heterogeneous disease on the molecular level. Molecular features include activation of hormone receptors (oestrogen receptor and progesterone receptor), activation of human epidermal growth factor receptor 2 (HER2, encoded by the ERBB2 gene), and/or BRCA gene mutations and have an impact on treatment strategies [1]. Hormone-receptor-positive (HR+) breast cancer represents the largest subset of this disease, affecting more than 1 million patients annually worldwide. Breast cancer that has not developed metastatic lesions or that has only spread to the axillary lymph nodes is considered early stage with chances for cure in about 70–80% of patients. While adjuvant endocrine therapy provides substantial benefits in the treatment of HR+ early breast cancer by reducing disease recurrence and the risk of death from breast cancer, considerable risk of recurrence persists over several decades. Although the addition of the CDK4/6 inhibitor Palbociclib to endocrine therapy in metastatic HR+/HER2- breast cancer improves progression-free survival, this effect could not be observed in the early-stage setting [2].

Hypothesis and Objectives:

The aim of the project is to investigate the molecular profiles of breast cancer patients with respect to the response towards endocrine therapy in combination with and without Palbociclib. Given the advantage of adding Palbociclib in the metastatic setting, we aim at identifying patients with early stage breast cancer that are likely to also benefit from this form of treatment. Moreover, it is aimed to describe therapeutically targetable aberrant molecular mechanisms driving carcinogenesis and metastasis formation as well as to describe molecular signatures which may serve as predictive biomarkers for individual treatment combinations in early stage and metastatic breast cancer.

Approaches and methods:

Molecular profiles of more than 5,000 breast cancer patients are available, as well as comprehensive clinical records. Patients were treated according to treatment protocol within global clinical trials [2, 3]. Molecular characterization includes profiling of gene mutations and gene expression of primary tumor samples as well as metastatic lesions and blood samples. Individual computational approaches which are needed to analyze this unique data collection will be developed during the project and will be combined with state-of-the-art bioinformatic pipelines for the analysis of DNA- and RNA-sequencing data [4, 5]. The development of computational methods includes custom machine learning approaches, well-tailored for this exclusive collection of molecular profiles of breast cancer patients. Candidate mechanisms can be subsequently evaluated in vitro using cutting edge molecular approaches such as the CRISPR/Cas9 system.

During this PhD project, the candidate will use modern computational approaches to characterize and correlate mutational and transcriptional profiles with respect to cancer development and treatment response in retrospective cohorts of breast cancer patients. The successful completion of the project will contribute to our understanding of the biology of breast cancer progression and pave the way for more effective treatment approaches for early stage and metastatic breast cancer patients.

References:

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[2] Mayer EL, Dueck AC, Martin M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2021 Feb;22(2):212-222. doi: 10.1016/S1470-2045(20)30642-2.

[3] Aftimos P, Oliveira M, Irrthum A, et al. Genomic and transcriptomic analyses of breast cancer primaries and matched metastases in AURORA, the Breast International Group (BIG) molecular screening initiative. Cancer Discov. 2021 Jun 28:candisc.1647.2020. doi: 10.1158/2159-8290.CD-20-1647.

[4] Greif PA*, Hartmann L*, Vosberg S*, et al. Evolution of Cytogenetically Normal Acute Myeloid Leukemia During Therapy and Relapse: An Exome Sequencing Study of 50 Patients. Clin Cancer Res. 2018 Apr 1;24(7):1716-1726. doi: 10.1158/1078-0432.CCR-17-2344. *authors contributed equally

[5] Kerbs P, Vosberg S, Krebs S, et al. Fusion gene detection by RNA sequencing complements diagnostics of acute myeloid leukemia and identifies recurring NRIP1-MIR99AHG rearrangements. Haematologica. 2021 Jun 17. doi: 10.3324/haematol.2021.278436.