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Method for Determining PARP Inhibitor Responsiveness and Improving PARP Inhibitor Therapy

This method allows for determining a cancer patients responsiveness to treatment with a PARP inhibitor. Further, the method allows for the treatment of a new patient population with PARP inhibitors, and provides the opportunity for a combination therapy using both a PARP inhibitor as well as an inhibitor of the new biomarker.

Keywords Determining PARP Inhibitor Responsiveness, new PARP inhibitor patient populations

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Background Poly(ADP-ribose) polymerase 1 (PARP1) is an abundant chromatin associated enzyme, whose activity is strongly induced in response to genotoxic stress. While PARP inhibitors (PARPi) protect cells from PARP1-mediated NAD+ depletion, their clinical use is primarily associated with causing synthetic lethality in BRCA1/2-deficient tumors. The tumour suppressors BRCA1 and BRCA2 are critical components of the homology-directed repair (HDR) pathway, which promotes error-free repair of DNA double-strand breaks (DSBs). Accordingly, the majority of PARP inhibitors on the market are approved for the treatment of patients with cancers harbouring inherited BRCA1/2 mutations. Beyond BRCA1/2-deficiency predicting PARPi sensitivity of tumors has remained challenging due to the lack of good biomarkers, and thus, additional markers for PARPi efficiency are needed.

Invention This invention is based on the identification of a mechanistically distinct relationship between PARP and a newly identified cancer biomarker. Correlation of PARP with the new biomarker has been analyzed using matched multiomics data in breast and ovarian cancer patient's cohorts. The new biomarker allows for determining a cancer patients responsiveness to treatment with a PARP inhibitor independent of BRCA1/2-deficiency, extends the so far to BRCA1/2-deficiency limited patient population for treatment with PARP inhibitors to other patients correlating with the new biomarker. Additionally, the invention provides the opportunity for a combination therapy using both a PARP inhibitor as well as an inhibitor of the new biomarker, as shown in cell culture experiments. Otherwise the feasibility of the concept has not yet been proven in an animal model system.

Fields of Use Diagnosing cancer patient's responsiveness to treatment with a PARP inhibitor, extending patient populations to treatment by PARP inhibitors, and providing for combination cancer therapy using both a PARP inhibitor as well as an inhibitor of the new biomarker.

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