Clinically relevant biomarkers of PARP1 inhibitor resistance and indicators of targeted combinatorial treatments

Synopsis

Tumours with defective DNA repair by the homologous recombination repair (HRR) pathway are exquisitely sensitive to DNA damaging agents and to novel agents that block parallel pathways, including PARP inhibitors (PARPi). PARPi have been approved for the treatment of metastatic ovarian cancer (OvC) or breast cancer (BC). Currently used selection biomarkers to enrich the population of patients (pt) most likely to respond, namely the platinum-sensitive or BRCA1/2-mutated pts, have limited predictive capacity. There is a need for more specific biomarkers to guide personalized treatment. Genomic scar signatures have been proposed as a putative biomarker associated with DNA repair deficiency. A major limitation of these assays is the lack of specificity in HRR-altered tumours once they have restored the HRR function as mechanism of drug resistance. Instead, RAD51 foci formation is a functional and dynamic biomarker of HRR that correlates with PARPi response. In this lecture, we will review the current knowledge on PARPi sensitivity and resistance in breast cancer, response biomarkers and the potential of hypothesis-based therapeutic combinations.