PARP inhibitors in ovarian cancer: where are we now?

More than 1 million women globally are diagnosed with breast or ovarian cancer every year, and 5–10% of them carries a germline mutation in *BRCA1* or *BRCA2* [1–3]. Inside the complex of DNA repair machinery, the BRCA proteins play a crucial role via homologous recombination, while poly(ADP)-ribose polymerase (PARP) is the key component in base-excision repair of DNA. Preclinical studies showed that inhibition of PARP would lead to selective and significant killing of *BRCA*-mutated cancer cells, a phenomenon described as synthetic lethality that is not observed in cells with intact *BRCA* function [4]. These findings contribute to the evolving concept of genetic classification of cancer. Traditionally, we rely on histology and site of origin to classify and treat cancers. With emerging targeted agents aimed at specific molecular defects (e.g. rituximab for CD20-positive lymphoma, trastuzumab for HER2-overexpressed breast cancer etc.), molecular classification of cancer will become more informative than conventional classification for the guidance of targeted therapies and *BRCA* mutation might be integrated into the classification of breast and ovarian cancer. Marchetti et al. described a complete overview about the state of the art of PARP inhibitors in ovarian cancer, showing a great potential as a valid treatment opportunity for ovarian cancer patients. Although PARP inhibitors have shown striking responses in germline *BRCA*-associated tumors, there are still several challenges for the clinical development of these agents and today's results might not reflect the complete picture. This point reflects our incomplete understanding of the complexity of DNA repair mechanisms in human cancers, in fact the synthetic lethality depends on the joint inhibition of PARP together with defective homologous recombination (HR) DNA repair. On the other hand, the benefits of a PARP inhibitor as reported today might not be restricted only to patients with germline *BRCA* mutation. Recent data show that a subset of sporadic breast and ovarian cancers also harbour homologous recombination repair abnormalities as a result of epigenetic silencing of *BRCA1* or deficiencies in other components of such repair [5]. This clinical syndrome, called "BRCAness", indicates the potential clinical benefits of PARP inhibitors for these sporadic cancers. There are already some preliminary data reporting clinical responses of olaparib in ovarian cancer without *BRCA* mutation at tumour biopsy [6]. This observation indicates that *BRCA* germline mutation is too restrictive as predictive biomarker for PARP inhibitors. Consequently, identification of sporadic patients who harbor HR-deficient tumors without *BRCA1* or *BRCA2* mutations and who may respond to PARP inhibitors is an important challenge. Unfortunately, there is currently no prospectively validated biomarker of HR-deficient ovarian cancers that accurately predicts defective HR and responsiveness to PARP inhibitors, and this is an area of high priority for ovarian cancer research.

Second, despite the excellent responses of PARP inhibitors in HR deficient

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tumors, a substantial fraction of patients does not respond or develops resistance to these agents suggesting that *de novo* and acquired resistance to PARP inhibitors may be a significant clinical problem. Several mechanisms of resistance exist but the most important include: a) secondary genetic and epigenetic events (such as secondary *BRCA1/2* mutations) that restore functional HR in HR deficient tumors, b) suppression of NHEJ via loss of 53BP1 or other mechanisms which leads to PARP inhibitor resistance but not platinum resistance and c) increased expression of p-glycoprotein efflux transporter mediating multi-drug resistance [7]. Elucidation of the mechanisms of PARP inhibitor resistance and how these relate to resistance to platinum and other chemotherapeutics may aid the development of novel therapies to overcome PARP inhibitor resistance and may also help optimize the sequence of how these agents are incorporated in the clinical management of both *BRCA*-associated and sporadic ovarian cancers. This is another challenge for the development of these agents as it is currently unclear when they should be incorporated in the management of ovarian cancer, i.e. before or after platinum, first line or advanced setting, maintenance or not. In addition, another challenge will be the rational development of combinations of chemotherapy and PARP inhibitors given their overlapping toxicities.

Actually, BRCA mutation test is recommended for patients with familiar history of ovarian and breast cancer, but considering the great potential of PARP inhibitors in ovarian cancer target therapy, BRCA genetic test should be considered as an option in all high-grade serous ovarian cancer patients.

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