**Name of Journal:** *World Journal of Clinical Oncology*

**Manuscript NO:** 63832

**Manuscript Type:** MINIREVIEWS

**Mechanisms of acquired resistance of BRCA1/2-driven tumors to platinum compounds and PARP inhibitors**

Imyanitov E *et al*. Drug resistance in BRCA1/2-driven tumors

Evgeny Imyanitov, Anna Sokolenko

**Evgeny Imyanitov, Anna Sokolenko,** Department of Tumor Growth Biology, N.N. Petrov Institute of Oncology, Saint-Petersburg 197758, Russia

**Evgeny Imyanitov, Anna Sokolenko,** Department of Medical Genetics, St.-Petersburg Pediatric Medical University, Saint-Petersburg 194100, Russia

**Evgeny Imyanitov,** Department of Oncology, I.I. Mechnikov North-Western Medical University, Saint-Petersburg 191015, Russia

**Author contributions:** Imyanitov E designed the concept of the paper and prepared the draft; Sokolenko A collected the data for the paper, designed the figures and contributed to the manuscript writing.

**Supported by** The Ministry of Science and Higher Education of the Russian Federation, No. 075-15-2020-789.

**Corresponding author: Evgeny Imyanitov, MD, Professor,** Department of Tumor Growth Biology, N.N. Petrov Institute of Oncology, Pesochny, Leningradskaya str. 68, Saint-Petersburg 197758, Russia. evgeny@imyanitov.spb.ru

**Received:** February 3, 2021

**Revised:** April 4, 2021

**Accepted:** June 3, 2021

**Published online:** July 24, 2021

**Abstract**

Molecular pathogenesis of tumors arising in *BRCA1/2* germ-line mutation carriers usually includes somatic inactivation of the remaining allele of the involved gene. Consequently, BRCA1/2-driven cancers are sensitive to platinum-based therapy and poly (ADP-ribose) polymerase inhibitors (PARPi). Long-term exposure to these drugs may result in the emergence of secondary *BRCA1/2* mutations, which restore the open-reading frame of the affected allele. This platinum/PARPi cross-resistance mechanism applies both for *BRCA1* and *BRCA2* genes and has been repeatedly validated in various laboratory models and multiple clinical studies. There are some other routes associated with the partial rescue of *BRCA1/2* function or the development of BRCA1/2-independent pathways for genomic maintenance; however, their actual clinical relevance remains to be established. In addition, studies on the short-term neoadjuvant therapy for ovarian cancer revealed that even chemonaive BRCA1-driven tumors contain a small proportion of BRCA1-proficient cells. These pre-existing cells with retained *BRCA1* heterozygosity rapidly repopulate the tumor mass during platinum exposure, but become outcompeted by BRCA1-deficient cells during therapy holidays. Understanding of the platinum/PARPi resistance pathways has led to the development of novel therapeutic approaches, which aim to improve the management of BRCA1/2-related cancers and are currently undergoing preclinical and clinical evaluation.

**Key Words:** *BRCA1/2* mutations; Platinum-based therapy; Poly (ADP-ribose) polymerase inhibitors; Drug resistance; Secondary mutations; Intratumoral heterogeneity; Neoadjuvant therapy

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Imyanitov E, Sokolenko A. Mechanisms of acquired resistance of BRCA1/2-driven tumors to platinum compounds and PARP inhibitors. *World J Clin Oncol* 2021; 12(7): 544-556

**URL:** https://www.wjgnet.com/2218-4333/full/v12/i7/544.htm

**DOI:** https://dx.doi.org/10.5306/wjco.v12.i7.544

**Core Tip:** BRCA1/2-associated tumors are highly sensitive to platinum compounds and poly (ADP-ribose) polymerase inhibitors; however, they eventually acquire resistance to this type of therapy. Restoration of *BRCA1/2* function *via* the second mutation is the most known mechanism of tumor adaptation to the therapeutic pressure. Some studies demonstrate that even chemonaive BRCA1-driven tumors contain a small fraction of BRCA1-proficient cells suggesting that the loss of the remaining allele of this gene is not the first event in tumor pathogenesis. These pre-existing platinum-resistant cells rapidly repopulate tumor mass during neoadjuvant therapy for ovarian cancer and explain inevitability of the disease relapses after seemingly successful surgical debulking.

**INTRODUCTION**

Germ-line mutations in *BRCA1* and *BRCA2* genes are the most well-known cause of hereditary cancer predisposition. *BRCA1/2* pathogenic variants contribute to approximately 5%-10% and 15%-30% breast and ovarian cancer morbidity, respectively[1-6]. In addition, both mentioned genes are involved in the pathogenesis of a subset of stomach cancers, and the inheritance of *BRCA2* inactive alleles is associated with an increased risk of prostate and pancreatic malignancies[7,8]. BRCA1/2-driven tumors tend to have particular clinical characteristics, being associated with younger age at onset and highly malignant phenotype[9,10]. Breast carcinomas (BCs) occurring in *BRCA1* mutation carriers usually lack the expression of estrogen and progesterone receptors, and BRCA1/2-associated ovarian cancers (OCs) are characterized by serous high-grade histological appearance[10,11].

Breast and ovarian tumors arising in patients with BRCA1/2-associated hereditary cancer syndrome usually develop *via* somatic inactivation of the remaining allele of the involved gene. *BRCA1* and *BRCA2* play a key role in the maintenance of genomic integrity. Consequently, cancers lacking functional *BRCA1* or *BRCA2* proteins are deficient in DNA repair by homologous recombination (HR). Platinum compounds and poly (ADP-ribose) polymerase inhibitors (PARPi) induce massive DNA damage, which requires an HR-mediated repair. BRCA1/2-null cells are deficient for HR and consequently die upon the action of platinum salts or PARPi. This drug sensitivity is tumor-selective, as the normal cells of the patient retain one functional copy of *BRCA1/2* gene and therefore remain capable of coping with the DNA damage[12-14].

As mentioned above, BRCA1/2-related hereditary tumors constitute a significant portion of OCs. In addition, many high-grade serous OCs have other causes of HR deficiency, *e.g.*, somatic biallelic inactivation of *BRCA1/2* genes or the presence of germ-line mutations in other members of DNA repair pathways[1,15]. This explains the high efficacy of platinum-based chemotherapeutic regimens in OC, which were developed empirically before the discovery of *BRCA1/2* genes and constitute a standard-of-care for OC management. As expected, platinum therapy demonstrates increased efficacy in hereditary *vs* sporadic ovarian tumors[2,16]. In contrast to OC, *BRCA1/2* deficiency is characteristic only for a minority of breast tumors; therefore, platinum compounds are not incorporated in the conventional treatment schemes for non-selected BC patients. Several trials demonstrated that platinum salts might outperform other chemotherapeutic agents when applied to BRCA1/2-driven BCs[17-19]. PARPi have been developed specifically for targeting tumors characterized by *BRCA1/2* and/or HR deficiency. There are several PARPi approved for clinical use with slightly varying medical indications[20,21].

Although BRCA1/2-driven tumors have a clear-cut vulnerability, the use of platinum salts or PARPi does not usually result in a cure from metastatic disease. Platinum- and PARPi-exposed cancers eventually manage to escape from the action of BRCA1/2-specific therapy. Multiple preclinical and clinical studies have identified various BRCA1/2-restoring mechanisms or bypass pathways, which resume resistance to DNA damage in initially HR-deficient tumor cells. Recent investigations also provided evidence for an alternative scenario, where the emergence of the platinum-resistant tumor clone is attributed to a selection of pre-existing BRCA1-proficient cells; these therapy-resistant cells persist in small amounts in chemonaive tumors but are enriched in the residual lesion. This paper provides a brief overview of the mechanisms of acquired platinum and PARP-resistance in BRCA1/2-driven tumors.

**RESTORATION OF *BRCA1/2* function BY SECONDARY SOMATIC MUTATIONS**

The vast majority of *BRCA1/2* inherited pathogenic alleles are represented by small alterations in the nucleotide sequence, which cause a frameshift and emergence of premature stop-codons. The open reading frame (ORF) can be rescued by a nearby second mutation if it restores an original 3-letter genetic code, or by small deletion, which excises the pathogenic allele and reconstitutes the ORF, or by the true back mutation (Figure 1)[22-24]. A secondary ORF-restoring *BRCA2* mutation was first described in an acute myeloid leukemia cell line obtained from a patient with Fanconi anemia[25]. The discovery of PARPi and the recognition of BRCA1/2-specific action of platinum compounds stimulated intense investigations of the mechanisms of tumor resistance to these drugs. A series of studies revealed that the emergence of secondary *BRCA1/2* mutations is the most reproducible hallmark of the acquisition of a drug-resistant phenotype. Indeed, the reversion mutations have been repeatedly observed in the experiments with cell lines, patient-derived xenografts (PDX) and clinical samples[26,27].

For the time being, the development of secondary ORF-restoring mutations in *BRCA1/2* genes is the only clinically proven mechanism of the tumor adaptation to the therapy, which is relevant both to platinum compounds and PARPi, characteristic both for *BRCA1* and *BRCA2* genes, and has been convincingly validated in patient samples. The true incidence of secondary *BRCA1/2* mutations is difficult to presently define due to various selection biases and technical limitations of available molecular genetic assays: They appear to be found in approximately a quarter of PARPi/platinum-resistant tumors, although some studies provide even higher estimates. Importantly, many reports describe the emergence of multiple distinct *BRCA1/2* ORF-restoring mutations in independent drug-resistant clones obtained from the same patient, thus providing evidence for the functional convergence of tumor adaptation pathways[26,27].

Some data suggest that the genetic reversion is somewhat more characteristic for BRCA2- than for BRCA1-driven tumors. Distinct pathogenic variants of *BRCA1* and *BRCA2* may differ in their ability to be rescued by the second mutation: It is hypothesized that the genetic reversion is more acceptable for non-conservative regions of the above genes, which are more or less dispensable for their function. Indeed, in all cases, except genuine back mutations, the involved region of *BRCA1* and *BRCA2* genes undergoes subtle alterations (*i.e*. the deletion of a few coding nucleotides or the change of the sequence for a few amino acids); therefore, highly conserved parts of these genes may not tolerate this mechanism of genetic adaptation[14,26,27].

In addition to secondary mutations affecting the coding sequence of *BRCA1/2* genes, there are functionally similar events resulting in the production of hypomorphic but still functional protein. For example, loss of exon 11 is compatible with the participation of *BRCA1* in HR; consequently, alternative splicing resulting in the *BRCA1* exon 11 skipping may contribute to the acquired drug resistance[28]. The mutation located in the N-terminal portion of the *BRCA1* gene can be bypassed by the production of a hypomorphic protein, whose translation starts after the frameshift[29]. Another mechanism of the partial rescue of *BRCA1* function involves gene rearrangements, which terminate *BRCA1* translation before the mutation-containing BCRT domain, consequently preventing the proteasomal degradation of *BRCA1*. These truncated versions of *BRCA1* are capable of maintaining HR and mediate PARPi resistance[30]. Upregulation of HSP90 may stabilize some BRCA1-mutant proteins and thus support their function[31]. Amplification of mutated *BRCA2* was shown to compensate for partial loss of *BRCA2* function and rendered PARPi resistance in cell line experiments[32].

Some *BRCA1/2* germ-line pathogenic alleles are represented by so-called large gene rearrangements (LGRs), which may involve deletions of multiple exons. By definition, these tumors cannot be repaired by the second ORF-restoring mutation. One would expect that these tumors are likely to demonstrate a more pronounced and prolonged response to BRCA1/2-specific therapy. *BRCA1/2* LGRs are not specifically considered in the studies on tumor drug sensitivity. However, there are case reports supporting exceptional responsiveness of *BRCA1/2* LGR-associated tumors to PARPi[33].

**BYPASS MECHANISMS**

There are two key mechanisms of the repair of DNA double-strand breaks (DSB). Accurate correction of DNA sequence can be achieved exclusively by HR. In the absence of functional HR, error-prone non-homologous end-joining (NHEJ) becomes a prevailing mechanism of DSB repair. The choice between HR and NHEJ is mediated by the balance between their regulators, *BRCA1* and *53BP1*. When *BRCA1* is inactivated by mutation, NHEJ-driven DNA repair prevails. This results in the accumulation of multiple DNA lesions and eventual cell death. BRCA1-deficient cells may adapt to the platinum or PARPi pressure by down-regulation of *53BP1*. As a result of consequent NHEJ suppression, tumor cells re-activate HR and eventually become resistant to the drug exposure[31,34,35]. Down-regulation of *53BP1* has been observed in some clinical samples that failed platinum-based or PARPi therapy[31,36,37]. *In vitro* studies revealed several other proteins whose loss also contributes to the switch from NHEJ to HR or to other bypass pathways. Noticeably, the involvement of *53BP1* exemplifies the differences between BRCA1- and BRCA2-mutated tumors, as the loss of *53BP1* or related proteins is relevant only for the treatment escape of BRCA1-deficient cancers[34]. Preclinical studies also identified HR-independent platinum/PARPi resistance mechanisms, which involve stabilization of replication forks[38].

**BRCA1/2-NON-RELATED MECHANISMS OF ACQUIRED RESISTANCE TO PLATINUM COMPOUNDS AND PARP**i

The above-described mechanisms of acquired therapy resistance are more or less specific for the BRCA1/2-associated action of platinum salts and PARPi. There are also general mechanisms for the adaptation of tumor cells to the therapy, which are indirectly related to the targeted biological pathway and may involve activation of the drug efflux, down-deregulation of apoptosis, preservation of tumor cancer stem cells (CSCs) and epithelial-mesenchymal transition (EMT)[39]. Up-regulation of *ABCB1* (MDR1) transporter has been implicated in multidrug resistance. Therapy-resistant ovarian and breast carcinomas are characterized by gene fusions, which result in increased expression of the *ABCB1* gene[40]. The translational implications of these observations are not immediately clear: Drug transporters are involved in multiple physiological processes and are characterized by significant redundancy, so their targeting may be associated with significant adverse events and insufficient clinical efficacy[41]. There are reports demonstrating the selection of CSCs upon PARPi exposure[42]. The role of EMT in the development of PARPi resistance has been shown in preclinical studies involving BRCA2-deficient cells[43].

**SELECTION OF PRE-EXISTING BRCA1-PROFICIENT CELLS DURING PLATINUM-BASED THERAPY**

A significant portion of OC patients present with the inoperable disease; therefore, they undergo neoadjuvant (first-line) therapy aimed to reduce the tumor burden and permit surgical excision of the remaining cancer lumps. BRCA1-driven cancers are particularly sensitive to systemic platinum-based treatment; hence, this category of OC is usually amenable to complete surgical debulking. Despite that presumably efficient platinum-based therapy is administered again after the surgery, it apparently cannot eliminate the residual cancer cells, given that almost all OC treated by this scheme eventually relapse[44].

Comparison of tumor specimens obtained before the start of the treatment and after a few weeks of neoadjuvant therapy revealed surprising findings (Figure 2). While chemonaive BRCA1-associated OCs are characterized by somatic loss of heterozygosity (LOH) of the remaining allele, the residual tumors obtained after a few weeks of neoadjuvant therapy often show the retention of the wild-type *BRCA1* copy. This “restoration of heterozygosity” occurs due to the selection of preexisting BRCA1-proficient cells, which persist in small amounts in chemonaive tumors; these isolated tumor cells with retained *BRCA1* function can be visualized by various imaging techniques. Importantly, both primary cancers and residual tumor masses were shown to retain the same mutation in the *TP53* gene. Loss of *BRCA1* in normal cells triggers apoptosis, while cells with inactive *TP53* may survive *BRCA1* deficiency. It appears that *TP53* mutation must be acquired in the very initial stages of the tumor evolution, while *BRCA1* LOH, being a key event in the pathogenesis of BRCA-driven cancers, can emerge and be tolerated only after *TP53* inactivation. The persistence of isolated BRCA1-proficient cells within a gross tumor mass is common for BRCA1-driven cancers, as the “restoration” of *BRCA1* heterozygosity is observed approximately in two-thirds of BRCA1-associated OCs[45].

Intriguingly, the relapse OC tissues obtained from the same patients after therapy holidays show *BRCA1* LOH again, thus providing a mechanistic explanation for the platinum sensitivity of recurrent BRCA1-associated cancers (Figure 2). Exome sequencing revealed that only *TP53* mutation is stably maintained throughout the natural history of BRCA1-driven cancers, while the profiles of somatic point mutations and chromosome number alterations show some variations between chemonaive, post-neoadjuvant and recurrent tumor specimens. Overall, it appears that BRCA1-driven tumors present an ecosystem: While the gross majority of tumor mass is BRCA1-deficient, there are apparently some biological reasons to maintain the persistence of small amounts of BRCA1-proficient cells. In the absence of external hazards, BRCA1-deficient cells clearly outcompete cells with retained *BRCA1* function. However, these cells are sensitive to platinum exposure and perhaps to some other kinds of unfavorable environment, so the maintenance of the reservoir of invulnerable (BRCA1-proficient) cells is important for warranting tumor plasticity. Upon drug pressure, BRCA-proficient cells take advantage and increase their relative fraction in residual tumor mass; however, they again lose the competition after the cessation of the systemic treatment[46]. The above observations fit very well with the concept of tumor “stem cells” as a cause of acquired drug resistance.

The platinum-induced selection of pre-existing BRCA-proficient cells has been demonstrated only for the *BRCA1* gene, while similarly designed studies have not been performed yet for BRCA2-associated tumors. It is not self-explanatory that the same phenomenon is applicable to BRCA2-driven cancers. Indeed, although both *BRCA1* and *BRCA2* proteins are involved in the response to DNA damage, they have essential dissimilarities in their structure and function[14]. Consequently, they demonstrate differences regarding the spectrum of associated tumors, with prostate and pancreatic cancer been strongly linked to *BRCA2* but not to *BRCA1* heterozygosity[7]. Breast carcinomas arising in *BRCA1* germ-line mutation carriers are usually triple-negative with regard to the receptor status (ER, PgR and HER2), while *BRCA2* pathogenic alleles are generally associated with the development of tumors expressing steroid hormone receptors[10,11]. *BRCA1* but not *BRCA2* is essential for taxane-mediated cell death, so the resistance to taxanes is characteristic for BRCA1- but not for BRCA2-deficient cells[12]. The emergence of ORF-restoring secondary mutations in heavily pretreated tumors appears to be somewhat more common for *BRCA2* than for *BRCA1* gene[26,27]. *BRCA1* deficiency is lethal for normal cells; therefore, the development of cancers in *BRCA1* germ-line mutation carriers always involves mutation-driven inactivation of the *TP53* gene, which results in down-regulation of apoptosis and provides the ground for the survival of BRCA1-null cells. In contrast, *BRCA2* inactivation is compatible with cell viability, so BRCA2-associated tumors often have wild-type *TP53* status[47]. While the persistence of BRCA1-proficient cells in chemonaive BRCA1-driven tumors is essential for the adaptation of OC to platinum-based therapy, it is unclear how this intratumoral heterogeneity supports the maintenance of tumor mass in “natural” conditions. This intratumoral heterogeneity may not necessarily be characteristic for the cancers arising in *BRCA2* germ-line mutation carriers. Further studies are needed to reveal whether the persistence of isolated HR-proficient “stem” cells is relevant for BRCA2-driven tumors or sporadic OCs with BRCAness phenotype.

**CONTROVERSIAL AND UNRESOLVED ISSUES**

Platinum compounds and PARPi converge in their mechanisms with regard to targeting HR-deficient cells; however, there are also some differences in their action. For example, platinum salts appear to target tumors with deficient nucleotide excision repair[34]. Consequently, while secondary *BRCA1/2* mutations or other HR-restoring events are likely to result in cross-resistance between platinum and PARPi, other modes of tumor adaptation to the therapy may be more drug-specific. Platinum is commonly used for the treatment of ovarian cancer, and the clinical trials demonstrated that the use of PARPi results in significantly better outcomes in platinum-sensitive *vs* platinum-resistant disease[48,49]. Similarly, the advantage of talazoparib was more pronounced in BRCA1/2-driven breast cancer patients who did not receive prior cisplatin or carboplatin[50]. However, some presumably platinum-resistant ovarian tumors still demonstrate some sensitivity to PARPi[48,49]. On the other hand, PARPi therapy may result, for example, in the emergence of mutations in the PARP1 gene, which alter PARP1 trapping to DNA but are unlikely to affect tumor sensitivity to drugs other than PARPi[51]. It needs to be stressed that in the clinical setting, the platinum sensitivity of ovarian cancer is usually defined not by the actual tumor response to carboplatin or cisplatin but by the time interval exceeding 6 mo since the last platinum exposure. It is not impossible that some tumors may actually restore HR deficiency within a shorter period of time, so their response to PARPi could be explained by conventional PARPi-associated biological mechanisms. While the use of PARPi after chemotherapy has been evaluated in many clinical trials[49], we are unaware of a systematic analysis of chemotherapy response in PARPi-resistant tumors.

*BRCA1* and *BRCA2* germ-line mutations are usually viewed as equivalent in all clinical trials involving DNA damaging treatments. Although this approach is generally well justified, some differences between these two genes need to be acknowledged. Preclinical experiments have demonstrated mechanisms for therapy escape that are relevant for BRCA1- but not for BRCA2-driven tumors[34]. The spectrum of associated cancers is somewhat different for these two genes; for example, the analysis of PARPi-resistant prostate malignancies is almost entirely limited to *BRCA2* mutation carriers, as *BRCA1* plays a negligible role in the predisposition to this disease[26].

The regimens of administration of platinum salts and PARPi significantly differ. Cisplatin or carboplatin are usually administered in several cycles, so there are peak drug concentrations and significant intervals between chemotherapy infusions. In contrast to this intermittent drug administration of platinum drugs, PARPi are used at a continuous dose for a prolonged period of time. It is very likely that the mode of drug administration may influence the pathways of tumor adaptation to therapeutic intervention. Furthermore, published clinical experiments included very heterogeneous groups of patients with regard to the duration of prior treatment. It appears that the majority of secondary *BRCA1/2* mutations were detected mainly in heavily pretreated patients, while the initial cycles of chemotherapy rarely resulted in the genetic reversion of the *BRCA1/2* sequence[26,27,46,52].

Cell and animal experiments cannot fully recapitulate the complexity of intratumoral heterogeneity, tumor microenvironment, interplay with the immune system, drug dosing, *etc.*, characteristic for a clinical setting. The investigation of biological material obtained from cancer patients is challenging, particularly when it comes to the analysis of acquired therapy resistance. Tumor re-biopsy, by definition, requires sound clinical and ethical justification; therefore, some studies relied on circulating tumor DNA (ctDNA). Liquid biopsy is capable, in theory, to uncover the entire spectrum of subclonal secondary mutations, although it may underestimate the frequency of back mutations and does not account for the proportion of BRCA1/2-restored cells within a tumor mass. Current technologies for gene sequencing, which are utilized for the detection of secondary mutations, may miss some large deletions of genetic material[26]. It is highly desirable to continue the collection of platinum- and PARPi-resistant tumor samples from cancer patients, to subject these specimens to comprehensive molecular profiling, and to monitor the response of these tumors to subsequent treatment modalities. This effort may identify gene-response correlation and help to guide the clinical management of BRCA1/2-related cancers after the failure of the standard therapy.

**CONCLUSION**

BRCA1/2-driven tumors have a number of in-built mechanisms of adaptation to conventional schemes of platinum-based therapy and PARPi (Figure 3). Nowadays, an increasing number of OC patients are subjected to long-term PARPi maintenance therapy, which certainly affects the biological and clinical properties of recurrent tumors. It is somewhat surprising that the available medical research literature does not put an emphasis on the potential treatment options for tumors arising on the background of continuous PARPi exposure, despite that multiple lines of preclinical and clinical data suggest the involvement of cross-resistance mechanisms[34].

Genome profiling of drug-resistant tumors obtained from *BRCA1/2* mutation carriers has not identified recurrent actionable molecular lesions[46]. However, despite the restoration of HR proficiency or the emergence of bypass pathways, these tumors continue to contain the genomic scar of BRCAness, *i.e.* the existence of multiple genomic rearrangements. These genetic lesions may underlie an increased antigenicity of BRCA1/2-driven tumors. Interestingly, second mutations, which are the cause of drug resistance, are often associated with the emergence of additional antigenic epitopes[26]. The feasibility of the use of immune therapy against platinum/PARPi-resistant OCs has not been evaluated systematically, although case series support the promise of this option[53].

The best approach would be to implement treatment that would prevent the appearance of drug-resistant clones. There is a number of ongoing trials evaluating the efficacy of combinations of PARPi with other drugs[34,54]. Several studies demonstrated the potentially curative impact of high-dose chemotherapy for *BRCA1/2* mutation carriers; however, the use of this treatment is associated with excessive adverse effects[55]. Neoadjuvant combination of cisplatin and mitomycin C resulted in complete pathological responses, *i.e.* in the elimination of all detectable cancer cells, in some BRCA1/2-driven OCs[44].

There are several recent breakthroughs in the management of BRCA1/2-driven tumors, which resulted in significant improvement of disease outcomes. Continued understanding of the mechanisms of platinum/PARPi resistance inspired the development of a multitude of novel therapeutic approaches, which are likely to contribute to further advances in cancer treatment. BRCA1/2-associated carcinomas have well-defined vulnerabilities and are characterized by pronounced drug sensitivity. They are similar in this respect to germ-cell tumors and some hematological malignancies, which are generally curable by already available therapeutic tools. There are reasonable chances that cure rates for BRCA1/2-associated malignancies will significantly increase in the near future.

**ACKNOWLEDGEMENTS**

We appreciate greatly the contribution of Dr. Ekatherina Kuligina (N.N. Petrov Institute of Oncology) in the preparation of Figures. We are cordially thankful to Dr. Barbara Vona (University of Tuebingen) for critical reading of this manuscript.

**REFERENCES**

1 **Walsh T**, Casadei S, Lee MK, Pennil CC, Nord AS, Thornton AM, Roeb W, Agnew KJ, Stray SM, Wickramanayake A, Norquist B, Pennington KP, Garcia RL, King MC, Swisher EM. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci USA* 2011; **108**: 18032-18037 [PMID: 22006311 DOI: 10.1073/pnas.1115052108]

2 **Alsop K**, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, Dobrovic A, Birrer MJ, Webb PM, Stewart C, Friedlander M, Fox S, Bowtell D, Mitchell G. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol* 2012; **30**: 2654-2663 [PMID: 22711857 DOI: 10.1200/JCO.2011.39.8545]

3 **Kast K**, Rhiem K, Wappenschmidt B, Hahnen E, Hauke J, Bluemcke B, Zarghooni V, Herold N, Ditsch N, Kiechle M, Braun M, Fischer C, Dikow N, Schott S, Rahner N, Niederacher D, Fehm T, Gehrig A, Mueller-Reible C, Arnold N, Maass N, Borck G, de Gregorio N, Scholz C, Auber B, Varon-Manteeva R, Speiser D, Horvath J, Lichey N, Wimberger P, Stark S, Faust U, Weber BH, Emons G, Zachariae S, Meindl A, Schmutzler RK, Engel C; German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC). Prevalence of BRCA1/2 germline mutations in 21 401 families with breast and ovarian cancer. *J Med Genet* 2016; **53**: 465-471 [PMID: 26928436 DOI: 10.1136/jmedgenet-2015-103672]

4 **Hauke J**, Horvath J, Groß E, Gehrig A, Honisch E, Hackmann K, Schmidt G, Arnold N, Faust U, Sutter C, Hentschel J, Wang-Gohrke S, Smogavec M, Weber BHF, Weber-Lassalle N, Weber-Lassalle K, Borde J, Ernst C, Altmüller J, Volk AE, Thiele H, Hübbel V, Nürnberg P, Keupp K, Versmold B, Pohl E, Kubisch C, Grill S, Paul V, Herold N, Lichey N, Rhiem K, Ditsch N, Ruckert C, Wappenschmidt B, Auber B, Rump A, Niederacher D, Haaf T, Ramser J, Dworniczak B, Engel C, Meindl A, Schmutzler RK, Hahnen E. Gene panel testing of 5589 BRCA1/2-negative index patients with breast cancer in a routine diagnostic setting: results of the German Consortium for Hereditary Breast and Ovarian Cancer. *Cancer Med* 2018; **7**: 1349-1358 [PMID: 29522266 DOI: 10.1002/cam4.1376]

5 **Beitsch PD**, Whitworth PW, Hughes K, Patel R, Rosen B, Compagnoni G, Baron P, Simmons R, Smith LA, Grady I, Kinney M, Coomer C, Barbosa K, Holmes DR, Brown E, Gold L, Clark P, Riley L, Lyons S, Ruiz A, Kahn S, MacDonald H, Curcio L, Hardwick MK, Yang S, Esplin ED, Nussbaum RL. Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle? *J Clin Oncol* 2019; **37**: 453-460 [PMID: 30526229 DOI: 10.1200/JCO.18.01631]

6 **Gorodnova T**, Sokolenko A, Ni V, Ivantsov A, Kotiv K, Petrik S, Amelina I, Berlev I, Imyanitov E. BRCA1-associated and sporadic ovarian carcinomas: outcomes of primary cytoreductive surgery or neoadjuvant chemotherapy. *Int J Gynecol Cancer* 2019; **29**: 779-786 [PMID: 30839285 DOI: 10.1136/ijgc-2018-000175]

7 **van Asperen CJ**, Brohet RM, Meijers-Heijboer EJ, Hoogerbrugge N, Verhoef S, Vasen HF, Ausems MG, Menko FH, Gomez Garcia EB, Klijn JG, Hogervorst FB, van Houwelingen JC, van't Veer LJ, Rookus MA, van Leeuwen FE; Netherlands Collaborative Group on Hereditary Breast Cancer (HEBON). Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. *J Med Genet* 2005; **42**: 711-719 [PMID: 16141007 DOI: 10.1136/jmg.2004.028829]

8 **Avanesyan AA**, Sokolenko AP, Ivantsov AO, Kleshchev MA, Maydin MA, Bizin IV, Raskin GA, Shelekhova KV, Gorodnova TV, Bessonov AA, Anisimova EI, Volynshchikova OA, Romanko AA, Ni VI, Broyde RV, Tkachenko OB, Whitehead AJ, Scherbakov AM, Imyanitov EN. Gastric Cancer in BRCA1 Germline Mutation Carriers: Results of Endoscopic Screening and Molecular Analysis of Tumor Tissues. *Pathobiology* 2020; **87**: 367-374 [PMID: 33161400 DOI: 10.1159/000511323]

9 **Antoniou A**, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003; **72**: 1117-1130 [PMID: 12677558 DOI: 10.1086/375033]

10 **Hodgson A**, Turashvili G. Pathology of Hereditary Breast and Ovarian Cancer. *Front Oncol* 2020; **10**: 531790 [PMID: 33117676 DOI: 10.3389/fonc.2020.531790]

11 **Mavaddat N**, Barrowdale D, Andrulis IL, Domchek SM, Eccles D, Nevanlinna H, Ramus SJ, Spurdle A, Robson M, Sherman M, Mulligan AM, Couch FJ, Engel C, McGuffog L, Healey S, Sinilnikova OM, Southey MC, Terry MB, Goldgar D, O'Malley F, John EM, Janavicius R, Tihomirova L, Hansen TV, Nielsen FC, Osorio A, Stavropoulou A, Benítez J, Manoukian S, Peissel B, Barile M, Volorio S, Pasini B, Dolcetti R, Putignano AL, Ottini L, Radice P, Hamann U, Rashid MU, Hogervorst FB, Kriege M, van der Luijt RB; HEBON, Peock S, Frost D, Evans DG, Brewer C, Walker L, Rogers MT, Side LE, Houghton C; EMBRACE, Weaver J, Godwin AK, Schmutzler RK, Wappenschmidt B, Meindl A, Kast K, Arnold N, Niederacher D, Sutter C, Deissler H, Gadzicki D, Preisler-Adams S, Varon-Mateeva R, Schönbuchner I, Gevensleben H, Stoppa-Lyonnet D, Belotti M, Barjhoux L; GEMO Study Collaborators, Isaacs C, Peshkin BN, Caldes T, de la Hoya M, Cañadas C, Heikkinen T, Heikkilä P, Aittomäki K, Blanco I, Lazaro C, Brunet J, Agnarsson BA, Arason A, Barkardottir RB, Dumont M, Simard J, Montagna M, Agata S, D'Andrea E, Yan M, Fox S; kConFab Investigators, Rebbeck TR, Rubinstein W, Tung N, Garber JE, Wang X, Fredericksen Z, Pankratz VS, Lindor NM, Szabo C, Offit K, Sakr R, Gaudet MM, Singer CF, Tea MK, Rappaport C, Mai PL, Greene MH, Sokolenko A, Imyanitov E, Toland AE, Senter L, Sweet K, Thomassen M, Gerdes AM, Kruse T, Caligo M, Aretini P, Rantala J, von Wachenfeld A, Henriksson K; SWE-BRCA Collaborators, Steele L, Neuhausen SL, Nussbaum R, Beattie M, Odunsi K, Sucheston L, Gayther SA, Nathanson K, Gross J, Walsh C, Karlan B, Chenevix-Trench G, Easton DF, Antoniou AC; Consortium of Investigators of Modifiers of BRCA1/2. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol Biomarkers Prev* 2012; **21**: 134-147 [PMID: 22144499 DOI: 10.1158/1055-9965.EPI-11-0775]

12 **Iyevleva AG**, Imyanitov EN. Cytotoxic and targeted therapy for hereditary cancers. *Hered Cancer Clin Pract* 2016; **14**: 17 [PMID: 27555886 DOI: 10.1186/s13053-016-0057-2]

13 **Maxwell KN**, Wubbenhorst B, Wenz BM, De Sloover D, Pluta J, Emery L, Barrett A, Kraya AA, Anastopoulos IN, Yu S, Jiang Y, Chen H, Zhang NR, Hackman N, D'Andrea K, Daber R, Morrissette JJD, Mitra N, Feldman M, Domchek SM, Nathanson KL. BRCA locus-specific loss of heterozygosity in germline BRCA1 and BRCA2 carriers. *Nat Commun* 2017; **8**: 319 [PMID: 28831036 DOI: 10.1038/s41467-017-00388-9]

14 **Le Page C**, Amuzu S, Rahimi K, Gotlieb W, Ragoussis J, Tonin PN. Lessons learned from understanding chemotherapy resistance in epithelial tubo-ovarian carcinoma from BRCA1and BRCA2mutation carriers. *Semin Cancer Biol* 2020 [PMID: 32827632 DOI: 10.1016/j.semcancer.2020.08.005]

15 **Jonsson P**, Bandlamudi C, Cheng ML, Srinivasan P, Chavan SS, Friedman ND, Rosen EY, Richards AL, Bouvier N, Selcuklu SD, Bielski CM, Abida W, Mandelker D, Birsoy O, Zhang L, Zehir A, Donoghue MTA, Baselga J, Offit K, Scher HI, O'Reilly EM, Stadler ZK, Schultz N, Socci ND, Viale A, Ladanyi M, Robson ME, Hyman DM, Berger MF, Solit DB, Taylor BS. Tumour lineage shapes BRCA-mediated phenotypes. *Nature* 2019; **571**: 576-579 [PMID: 31292550 DOI: 10.1038/s41586-019-1382-1]

16 **Gorodnova TV**, Sokolenko AP, Ivantsov AO, Iyevleva AG, Suspitsin EN, Aleksakhina SN, Yanus GA, Togo AV, Maximov SY, Imyanitov EN. High response rates to neoadjuvant platinum-based therapy in ovarian cancer patients carrying germ-line BRCA mutation. *Cancer Lett* 2015; **369**: 363-367 [PMID: 26342406 DOI: 10.1016/j.canlet.2015.08.028]

17 **Byrski T**, Gronwald J, Huzarski T, Grzybowska E, Budryk M, Stawicka M, Mierzwa T, Szwiec M, Wisniowski R, Siolek M, Dent R, Lubinski J, Narod S. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. *J Clin Oncol* 2010; **28**: 375-379 [PMID: 20008645 DOI: 10.1200/JCO.2008.20.7019]

18 **Tutt A**, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P, Owen J, Abraham J, Barrett S, Barrett-Lee P, Brown R, Chan S, Dowsett M, Flanagan JM, Fox L, Grigoriadis A, Gutin A, Harper-Wynne C, Hatton MQ, Hoadley KA, Parikh J, Parker P, Perou CM, Roylance R, Shah V, Shaw A, Smith IE, Timms KM, Wardley AM, Wilson G, Gillett C, Lanchbury JS, Ashworth A, Rahman N, Harries M, Ellis P, Pinder SE, Bliss JM. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med* 2018; **24**: 628-637 [PMID: 29713086 DOI: 10.1038/s41591-018-0009-7]

19 **Garutti M**, Pelizzari G, Bartoletti M, Malfatti MC, Gerratana L, Tell G, Puglisi F. Platinum Salts in Patients with Breast Cancer: A Focus on Predictive Factors. *Int J Mol Sci* 2019; **20** [PMID: 31295913 DOI: 10.3390/ijms20143390]

20 **Patel M**, Nowsheen S, Maraboyina S, Xia F. The role of poly(ADP-ribose) polymerase inhibitors in the treatment of cancer and methods to overcome resistance: a review. *Cell Biosci* 2020; **10**: 35 [PMID: 32180937 DOI: 10.1186/s13578-020-00390-7]

21 **Rose M**, Burgess JT, O'Byrne K, Richard DJ, Bolderson E. PARP Inhibitors: Clinical Relevance, Mechanisms of Action and Tumor Resistance. *Front Cell Dev Biol* 2020; **8**: 564601 [PMID: 33015058 DOI: 10.3389/fcell.2020.564601]

22 **Patch AM**, Christie EL, Etemadmoghadam D, Garsed DW, George J, Fereday S, Nones K, Cowin P, Alsop K, Bailey PJ, Kassahn KS, Newell F, Quinn MC, Kazakoff S, Quek K, Wilhelm-Benartzi C, Curry E, Leong HS; Australian Ovarian Cancer Study Group, Hamilton A, Mileshkin L, Au-Yeung G, Kennedy C, Hung J, Chiew YE, Harnett P, Friedlander M, Quinn M, Pyman J, Cordner S, O'Brien P, Leditschke J, Young G, Strachan K, Waring P, Azar W, Mitchell C, Traficante N, Hendley J, Thorne H, Shackleton M, Miller DK, Arnau GM, Tothill RW, Holloway TP, Semple T, Harliwong I, Nourse C, Nourbakhsh E, Manning S, Idrisoglu S, Bruxner TJ, Christ AN, Poudel B, Holmes O, Anderson M, Leonard C, Lonie A, Hall N, Wood S, Taylor DF, Xu Q, Fink JL, Waddell N, Drapkin R, Stronach E, Gabra H, Brown R, Jewell A, Nagaraj SH, Markham E, Wilson PJ, Ellul J, McNally O, Doyle MA, Vedururu R, Stewart C, Lengyel E, Pearson JV, Waddell N, deFazio A, Grimmond SM, Bowtell DD. Whole-genome characterization of chemoresistant ovarian cancer. *Nature* 2015; **521**: 489-494 [PMID: 26017449 DOI: 10.1038/nature14410]

23 **Lin KK**, Harrell MI, Oza AM, Oaknin A, Ray-Coquard I, Tinker AV, Helman E, Radke MR, Say C, Vo LT, Mann E, Isaacson JD, Maloney L, O'Malley DM, Chambers SK, Kaufmann SH, Scott CL, Konecny GE, Coleman RL, Sun JX, Giordano H, Brenton JD, Harding TC, McNeish IA, Swisher EM. *BRCA* Reversion Mutations in Circulating Tumor DNA Predict Primary and Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma. *Cancer Discov* 2019; **9**: 210-219 [PMID: 30425037 DOI: 10.1158/2159-8290.CD-18-0715]

24 **Carneiro BA**, Collier KA, Nagy RJ, Pamarthy S, Sagar V, Fairclough S, Odegaard J, Lanman RB, Costa R, Taxter T, Kuzel TM, Fan A, Chae YK, Cristofanilli M, Hussain MH, Abdulkadir SA, Giles FJ. Acquired Resistance to Poly (ADP-ribose) Polymerase Inhibitor Olaparib in *BRCA2*-Associated Prostate Cancer Resulting From Biallelic *BRCA2* Reversion Mutations Restores Both Germline and Somatic Loss-of-Function Mutations. *JCO Precis Oncol* 2018; **2** [PMID: 31501807 DOI: 10.1200/PO.17.00176]

25 **Ikeda H**, Matsushita M, Waisfisz Q, Kinoshita A, Oostra AB, Nieuwint AW, De Winter JP, Hoatlin ME, Kawai Y, Sasaki MS, D'Andrea AD, Kawakami Y, Joenje H. Genetic reversion in an acute myelogenous leukemia cell line from a Fanconi anemia patient with biallelic mutations in BRCA2. *Cancer Res* 2003; **63**: 2688-2694 [PMID: 12750298]

26 **Pettitt SJ**, Frankum JR, Punta M, Lise S, Alexander J, Chen Y, Yap TA, Haider S, Tutt ANJ, Lord CJ. Clinical *BRCA1/2* Reversion Analysis Identifies Hotspot Mutations and Predicted Neoantigens Associated with Therapy Resistance. *Cancer Discov* 2020; **10**: 1475-1488 [PMID: 32699032 DOI: 10.1158/2159-8290.CD-19-1485]

27 **Tobalina L**, Armenia J, Irving E, O'Connor MJ, Forment JV. A meta-analysis of reversion mutations in BRCA genes identifies signatures of DNA end-joining repair mechanisms driving therapy resistance. *Ann Oncol* 2021; **32**: 103-112 [PMID: 33091561 DOI: 10.1016/j.annonc.2020.10.470]

28 **Wang Y**, Bernhardy AJ, Cruz C, Krais JJ, Nacson J, Nicolas E, Peri S, van der Gulden H, van der Heijden I, O'Brien SW, Zhang Y, Harrell MI, Johnson SF, Candido Dos Reis FJ, Pharoah PD, Karlan B, Gourley C, Lambrechts D, Chenevix-Trench G, Olsson H, Benitez JJ, Greene MH, Gore M, Nussbaum R, Sadetzki S, Gayther SA, Kjaer SK; kConFab Investigators, D'Andrea AD, Shapiro GI, Wiest DL, Connolly DC, Daly MB, Swisher EM, Bouwman P, Jonkers J, Balmaña J, Serra V, Johnson N. The BRCA1-Δ11q Alternative Splice Isoform Bypasses Germline Mutations and Promotes Therapeutic Resistance to PARP Inhibition and Cisplatin. *Cancer Res* 2016; **76**: 2778-2790 [PMID: 27197267 DOI: 10.1158/0008-5472.CAN-16-0186]

29 **Drost R**, Dhillon KK, van der Gulden H, van der Heijden I, Brandsma I, Cruz C, Chondronasiou D, Castroviejo-Bermejo M, Boon U, Schut E, van der Burg E, Wientjens E, Pieterse M, Klijn C, Klarenbeek S, Loayza-Puch F, Elkon R, van Deemter L, Rottenberg S, van de Ven M, Dekkers DH, Demmers JA, van Gent DC, Agami R, Balmaña J, Serra V, Taniguchi T, Bouwman P, Jonkers J. BRCA1185delAG tumors may acquire therapy resistance through expression of RING-less BRCA1. *J Clin Invest* 2016; **126**: 2903-2918 [PMID: 27454287 DOI: 10.1172/JCI70196]

30 **Wang Y**, Bernhardy AJ, Nacson J, Krais JJ, Tan YF, Nicolas E, Radke MR, Handorf E, Llop-Guevara A, Balmaña J, Swisher EM, Serra V, Peri S, Johnson N. BRCA1 intronic Alu elements drive gene rearrangements and PARP inhibitor resistance. *Nat Commun* 2019; **10**: 5661 [PMID: 31827092 DOI: 10.1038/s41467-019-13530-6]

31 **Johnson N**, Johnson SF, Yao W, Li YC, Choi YE, Bernhardy AJ, Wang Y, Capelletti M, Sarosiek KA, Moreau LA, Chowdhury D, Wickramanayake A, Harrell MI, Liu JF, D'Andrea AD, Miron A, Swisher EM, Shapiro GI. Stabilization of mutant BRCA1 protein confers PARP inhibitor and platinum resistance. *Proc Natl Acad Sci USA* 2013; **110**: 17041-17046 [PMID: 24085845 DOI: 10.1073/pnas.1305170110]

32 **Park PH**, Yamamoto TM, Li H, Alcivar AL, Xia B, Wang Y, Bernhardy AJ, Turner KM, Kossenkov AV, Watson ZL, Behbakht K, Casadei S, Swisher EM, Mischel PS, Johnson N, Bitler BG. Amplification of the Mutation-Carrying BRCA2 Allele Promotes RAD51 Loading and PARP Inhibitor Resistance in the Absence of Reversion Mutations. *Mol Cancer Ther* 2020; **19**: 602-613 [PMID: 31575654 DOI: 10.1158/1535-7163.MCT-17-0256]

33 **Moiseyenko VM**, Chubenko VA, Moiseyenko FV, Zagorskaya LA, Zaytseva YA, Gesha NE, Zykov EN, Ni VI, Preobrazhenskaya EV, Sokolenko AP, Imyanitov EN. "Lazarus Response" to Olaparib in a Virtually Chemonaive Breast Cancer Patient Carrying Gross BRCA2 Gene Deletion. *Cureus* 2018; **10**: e2150 [PMID: 29651367 DOI: 10.7759/cureus.2150]

34 **McMullen M**, Karakasis K, Madariaga A, Oza AM. Overcoming Platinum and PARP-Inhibitor Resistance in Ovarian Cancer. *Cancers (Basel)* 2020; **12** [PMID: 32560564 DOI: 10.3390/cancers12061607]

35 **Belotserkovskaya R**, Raga Gil E, Lawrence N, Butler R, Clifford G, Wilson MD, Jackson SP. PALB2 chromatin recruitment restores homologous recombination in BRCA1-deficient cells depleted of 53BP1. *Nat Commun* 2020; **11**: 819 [PMID: 32041954 DOI: 10.1038/s41467-020-14563-y]

36 **Hurley RM**, Wahner Hendrickson AE, Visscher DW, Ansell P, Harrell MI, Wagner JM, Negron V, Goergen KM, Maurer MJ, Oberg AL, Meng XW, Flatten KS, De Jonge MJA, Van Herpen CD, Gietema JA, Koornstra RHT, Jager A, den Hollander MW, Dudley M, Shepherd SP, Swisher EM, Kaufmann SH. 53BP1 as a potential predictor of response in PARP inhibitor-treated homologous recombination-deficient ovarian cancer. *Gynecol Oncol* 2019; **153**: 127-134 [PMID: 30686551 DOI: 10.1016/j.ygyno.2019.01.015]

37 **Waks AG**, Cohen O, Kochupurakkal B, Kim D, Dunn CE, Buendia Buendia J, Wander S, Helvie K, Lloyd MR, Marini L, Hughes ME, Freeman SS, Ivy SP, Geradts J, Isakoff S, LoRusso P, Adalsteinsson VA, Tolaney SM, Matulonis U, Krop IE, D'Andrea AD, Winer EP, Lin NU, Shapiro GI, Wagle N. Reversion and non-reversion mechanisms of resistance to PARP inhibitor or platinum chemotherapy in BRCA1/2-mutant metastatic breast cancer. *Ann Oncol* 2020; **31**: 590-598 [PMID: 32245699 DOI: 10.1016/j.annonc.2020.02.008]

38 **Ray Chaudhuri A**, Callen E, Ding X, Gogola E, Duarte AA, Lee JE, Wong N, Lafarga V, Calvo JA, Panzarino NJ, John S, Day A, Crespo AV, Shen B, Starnes LM, de Ruiter JR, Daniel JA, Konstantinopoulos PA, Cortez D, Cantor SB, Fernandez-Capetillo O, Ge K, Jonkers J, Rottenberg S, Sharan SK, Nussenzweig A. Replication fork stability confers chemoresistance in BRCA-deficient cells. *Nature* 2016; **535**: 382-387 [PMID: 27443740 DOI: 10.1038/nature18325]

39 **Aleksakhina SN**, Kashyap A, Imyanitov EN. Mechanisms of acquired tumor drug resistance. *Biochim Biophys Acta Rev Cancer* 2019; **1872**: 188310 [PMID: 31442474 DOI: 10.1016/j.bbcan.2019.188310]

40 **Christie EL**, Pattnaik S, Beach J, Copeland A, Rashoo N, Fereday S, Hendley J, Alsop K, Brady SL, Lamb G, Pandey A, deFazio A, Thorne H, Bild A, Bowtell DDL. Multiple ABCB1 transcriptional fusions in drug resistant high-grade serous ovarian and breast cancer. *Nat Commun* 2019; **10**: 1295 [PMID: 30894541 DOI: 10.1038/s41467-019-09312-9]

41 **Lhommé C**, Joly F, Walker JL, Lissoni AA, Nicoletto MO, Manikhas GM, Baekelandt MM, Gordon AN, Fracasso PM, Mietlowski WL, Jones GJ, Dugan MH. Phase III study of valspodar (PSC 833) combined with paclitaxel and carboplatin compared with paclitaxel and carboplatin alone in patients with stage IV or suboptimally debulked stage III epithelial ovarian cancer or primary peritoneal cancer. *J Clin Oncol* 2008; **26**: 2674-2682 [PMID: 18509179 DOI: 10.1200/JCO.2007.14.9807]

42 **Bellio C**, DiGloria C, Foster R, James K, Konstantinopoulos PA, Growdon WB, Rueda BR. PARP Inhibition Induces Enrichment of DNA Repair-Proficient CD133 and CD117 Positive Ovarian Cancer Stem Cells. *Mol Cancer Res* 2019; **17**: 431-445 [PMID: 30401718 DOI: 10.1158/1541-7786.MCR-18-0594]

43 **Ordonez LD**, Hay T, McEwen R, Polanska UM, Hughes A, Delpuech O, Cadogan E, Powell S, Dry J, Tornillo G, Silcock L, Leo E, O'Connor MJ, Clarke AR, Smalley MJ. Rapid activation of epithelial-mesenchymal transition drives PARP inhibitor resistance in *Brca2*-mutant mammary tumours. *Oncotarget* 2019; **10**: 2586-2606 [PMID: 31080552 DOI: 10.18632/oncotarget.26830]

44 **Gorodnova TV**, Kotiv KB, Ivantsov AO, Mikheyeva ON, Mikhailiuk GI, Lisyanskaya AS, Mikaya NA, Guseynov KD, Bondarev NE, Matveyeva NS, Nekrasova EA, Sidoruk AA, Roman LD, Manikhas GM, Belyaev AM, Sokolenko AP, Berlev IV, Imyanitov EN. Efficacy of Neoadjuvant Therapy With Cisplatin Plus Mitomycin C in BRCA1-Mutated Ovarian Cancer. *Int J Gynecol Cancer* 2018; **28**: 1498-1506 [PMID: 30247247 DOI: 10.1097/IGC.0000000000001352]

45 **Sokolenko AP**, Savonevich EL, Ivantsov AO, Raskin GA, Kuligina ES, Gorodnova TV, Preobrazhenskaya EV, Kleshchov MA, Tiurin VI, Mukhina MS, Kotiv KB, Shulga AV, Kuznetsov SG, Berlev IV, Imyanitov EN. Rapid selection of BRCA1-proficient tumor cells during neoadjuvant therapy for ovarian cancer in BRCA1 mutation carriers. *Cancer Lett* 2017; **397**: 127-132 [PMID: 28377179 DOI: 10.1016/j.canlet.2017.03.036]

46 **Sokolenko AP**, Bizin IV, Preobrazhenskaya EV, Gorodnova TV, Ivantsov AO, Iyevleva AG, Savonevich EL, Kotiv KB, Kuligina ES, Imyanitov EN. Molecular profiles of BRCA1-associated ovarian cancer treated by platinum-based therapy: Analysis of primary, residual and relapsed tumors. *Int J Cancer* 2020; **146**: 1879-1888 [PMID: 31693165 DOI: 10.1002/ijc.32776]

47 **Park S**, Lee E, Park S, Lee S, Nam SJ, Kim SW, Lee JE, Yu JH, Kim JY, Ahn JS, Im YH, Park WY, Park K, Park YH. Clinical Characteristics and Exploratory Genomic Analyses of Germline BRCA1 or BRCA2 Mutations in Breast Cancer. *Mol Cancer Res* 2020; **18**: 1315-1325 [PMID: 32554602 DOI: 10.1158/1541-7786.MCR-19-1108]

48 **Madariaga A**, Lheureux S, Oza AM. Tailoring Ovarian Cancer Treatment: Implications of *BRCA1/2* Mutations. *Cancers (Basel)* 2019; **11** [PMID: 30909618 DOI: 10.3390/cancers11030416]

49 **Veneris JT**, Matulonis UA, Liu JF, Konstantinopoulos PA. Choosing wisely: Selecting PARP inhibitor combinations to promote anti-tumor immune responses beyond BRCA mutations. *Gynecol Oncol* 2020; **156**: 488-497 [PMID: 31630846 DOI: 10.1016/j.ygyno.2019.09.021]

50 **Litton JK**, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH, Fehrenbacher L, Yerushalmi R, Mina LA, Martin M, Roché H, Im YH, Quek RGW, Markova D, Tudor IC, Hannah AL, Eiermann W, Blum JL. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med* 2018; **379**: 753-763 [PMID: 30110579 DOI: 10.1056/NEJMoa1802905]

51 **Pettitt SJ**, Krastev DB, Brandsma I, Dréan A, Song F, Aleksandrov R, Harrell MI, Menon M, Brough R, Campbell J, Frankum J, Ranes M, Pemberton HN, Rafiq R, Fenwick K, Swain A, Guettler S, Lee JM, Swisher EM, Stoynov S, Yusa K, Ashworth A, Lord CJ. Genome-wide and high-density CRISPR-Cas9 screens identify point mutations in PARP1 causing PARP inhibitor resistance. *Nat Commun* 2018; **9**: 1849 [PMID: 29748565 DOI: 10.1038/s41467-018-03917-2]

52 **Lambrechts S**, Smeets D, Moisse M, Braicu EI, Vanderstichele A, Zhao H, Van Nieuwenhuysen E, Berns E, Sehouli J, Zeillinger R, Darb-Esfahani S, Cacsire Castillo-Tong D, Lambrechts D, Vergote I. Genetic heterogeneity after first-line chemotherapy in high-grade serous ovarian cancer. *Eur J Cancer* 2016; **53**: 51-64 [PMID: 26693899 DOI: 10.1016/j.ejca.2015.11.001]

53 **Matsuo K**, Spragg SE, Ciccone MA, Blake EA, Ricker C, Pham HQ, Roman LD. Nivolumab use for *BRCA* gene mutation carriers with recurrent epithelial ovarian cancer: A case series. *Gynecol Oncol Rep* 2018; **25**: 98-101 [PMID: 29998185 DOI: 10.1016/j.gore.2018.06.011]

54 **Lee EK**, Matulonis UA. PARP Inhibitor Resistance Mechanisms and Implications for Post-Progression Combination Therapies. *Cancers (Basel)* 2020; **12** [PMID: 32722408 DOI: 10.3390/cancers12082054]

55 **Boudin L**, Gonçalves A, Sabatier R, Moretta J, Sfumato P, Asseeva P, Livon D, Bertucci F, Extra JM, Tarpin C, Houvenaeghel G, Lambaudie E, Tallet A, Resbeut M, Sobol H, Charafe-Jauffret E, Calmels B, Lemarie C, Boher JM, Viens P, Eisinger F, Chabannon C. Highly favorable outcome in BRCA-mutated metastatic breast cancer patients receiving high-dose chemotherapy and autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2016; **51**: 1082-1086 [PMID: 27042835 DOI: 10.1038/bmt.2016.82]

**Footnotes**

**Conflict-of-interest statement:** The authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Corresponding Author's Membership in Professional Societies:** European Society for Medical Oncology, No. 6102

**Peer-review started:** February 3, 2021

**First decision:** March 31, 2021

**Article in press:** June 3, 2021

**Specialty type:** Oncology

**Country/Territory of origin:** Russia

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

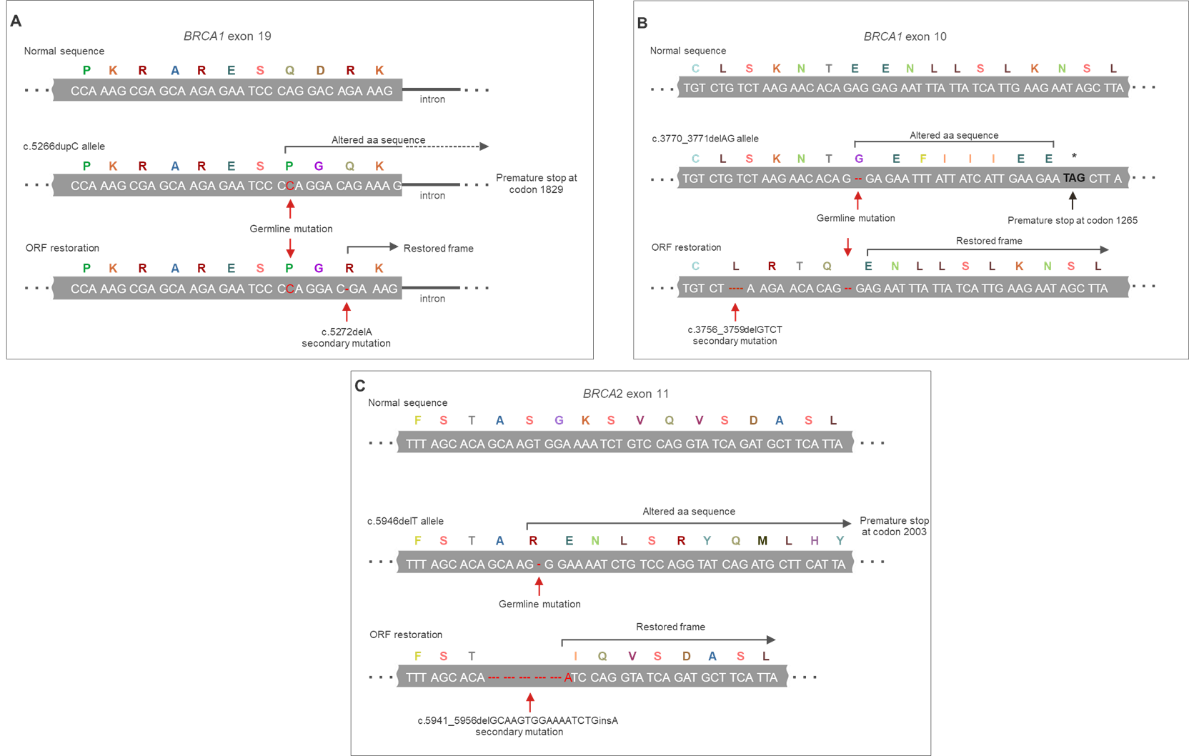
Grade C (Good): 0

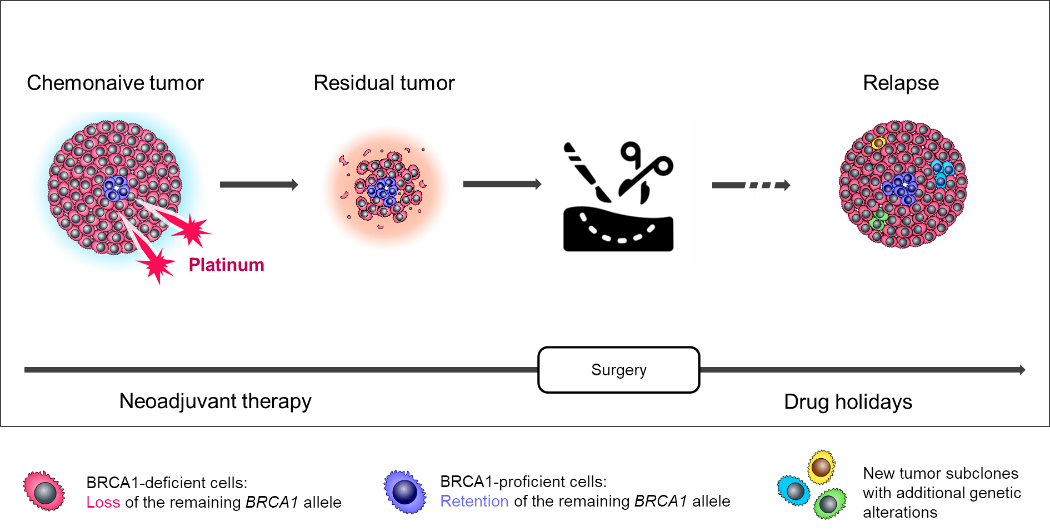
Grade D (Fair): 0

Grade E (Poor): 0

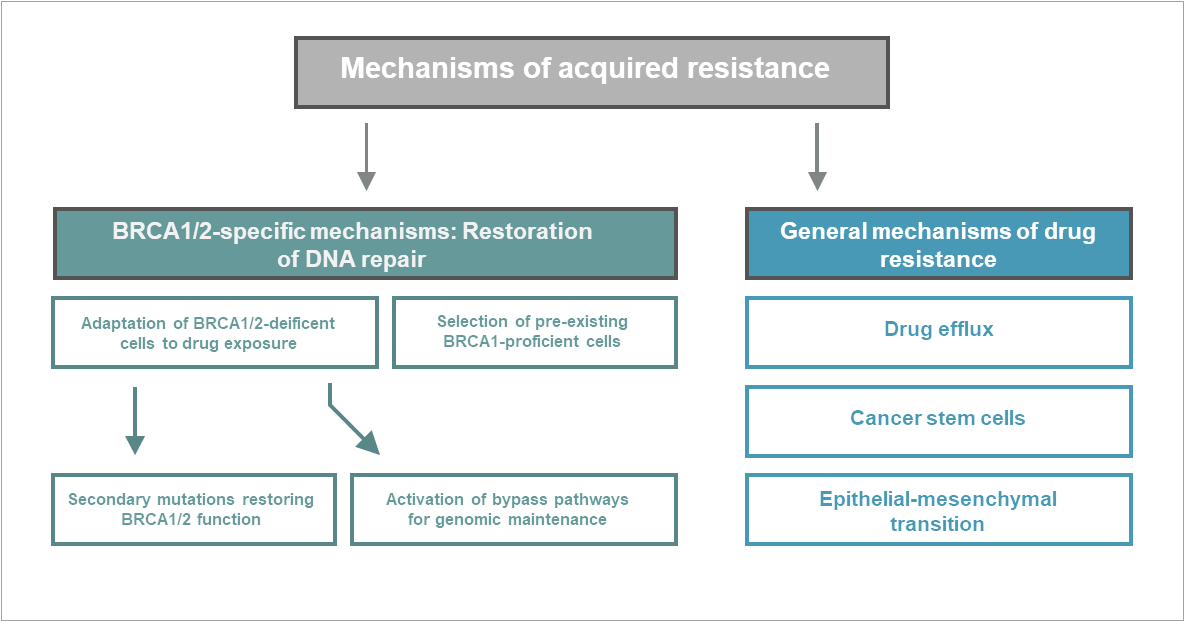
**P-Reviewer:** Zheng Z **S-Editor:** Liu M **L-Editor:** Filipodia **P-Editor:** Yuan YY

**Figure Legends**



**Figure 1 Examples of *BRCA1/2* open-reading frame restoration in BRCA1/2-mutated tumors during systemic therapy.** A: Secondary 1-bp deletion occurring downstream to the germline mutation (*BRCA1* c.5266dupC; described in[22]); B: Secondary 4-bp deletion located upstream to the germline mutation (*BRCA1* c.3770\_3771delAG; an example from[23]); C: Secondary in-frame deletion/insertion excising the mutation-containing gene fragment (*BRCA2* c.5946delT; an example from[24]). ORF: Open-reading frame.

**Figure 2 Selection of pre-existing BRCA1-proficient cells during platinum-based therapy.** Loss of the remaining *BRCA1* allele is observed in the majority of cells forming the tumor; however, even chemonaive BRCA1-driven ovarian cancers contain a small fraction of transformed cells with retained *BRCA1* heterozygosity. These cells are platinum-resistant and rapidly repopulate tumor mass during neoadjuvant therapy for ovarian cancer. During platinum-free interval, which occurs after the completion of the adjuvant therapy, these BRCA1-proficient cells become outcompeted by cells carrying *BRCA1* LOH. Therefore, ovarian cancer relapses resemble primary tumors with regard to the *BRCA1* status, as they demonstrate again the *BRCA1* deficiency and the sensitivity to platinum compounds.



**Figure 3 Mechanisms of acquired resistance of BRCA1/2-driven tumors to platinum compounds and PARP inhibitors.**



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**