# 4 Genetic Alterations in Ovarian Cancer as Prognostic and Predictive Biomarkers of Therapy Response and Surgical Outcomes

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**Abstract**

The emergence of precision medicine and our latest understanding of the biological characteristics of ovarian cancer (OC) have led to the discovery of drug targets, novel anticancer agents, and their predictive biomarkers. The genetics of OC is an evolving biomarker for predicting outcomes. Several completed and ongoing clinical trials used this concept for better patients' selection and stratification. The exploitation of specific molecular vulnerabilities in OC for drug development such as *BRCA* and *BRCA*ness is a milestone in the current management of this women's cancer. Without a doubt, OC is one of the solid cancers that have benefited from genetic biomarkers for the implementation of targeted agents such as PARP inhibitors in clinical practice. This progress is discussed in this chapter based on recent studies and clinical trials.

**Keywords**

Genetics · Ovarian cancer · Biomarkers · Survival · Surgery

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## 4.1 Introduction

Few therapeutic advances were achieved in improving survival outcomes in the first-line therapy of ovarian cancer (OC). However, predictive and prognostic biomarkers have considerably changed outcomes in some settings in women with this aggressive cancer (Le Page et al. 2020a; b; El Bairi et al. 2017a, b; Madariaga et al. 2020). An illustrative example is the important number of clinical trials, prospective studies, and retrospective real-world cohorts that have demonstrated the favorable impact of *BRCA* mutations on therapy response and prognosis in OC (Madariaga et al. 2019; Lorusso et al. 2020). Moreover, *BRCA* mutations and other variants in homologous recombination repair (HRR) genes are now used for OC patients' selection for poly-ADP-ribose polymerase inhibitors (PARPi). *BRCA*, *BRCA*ness, and HRR are associated with genomic instability and synthetic lethality in OC and are potential predictors of pharmacological sensitivity to platinum agents and PARPi (Konstantinopoulos and Matulonis 2018). Remarkably, as a result of the relevant success of cancer genetics in the field of translational oncology, there is an increasing number of clinical trials in OC that use genetic alterations as biomarkers for patient's selection, stratification, and prediction of drug response; particularly using umbrella and basket trial designs (Tsimberidou et al. 2020). As described in the other chapters of this book, some of their results provided considerable information for clinical use and it is not surprising to see other starting and ongoing trials in this highly active research area of OC. The current chapter focuses on the impact of genetic variants on outcomes in OC.

## 4.2 Ovarian Cancer Genetics as a Biomarker of Response to Chemotherapy and Survival Outcomes

Platinum-based chemotherapy is currently considered the backbone of OC therapy. Carboplatin and cisplatin bind to DNA and induce structural adducts which in turn cause considerable damages to cancer cells, and therefore driving cell cycle arrest and mitochondrial apoptosis (Galluzzi et al. 2012). Enhanced response to these anticancer drugs is observed in patients with mutated *BReast Cancer* 1 and 2 genes (*BRCA1/2*) which confer impairment of DNA repair mechanisms (Quinn et al. 2009; Madariaga et al. 2019). Several preclinical reports have shown that cells harboring *BRCA* variants have superior sensitivity to platinum-based chemotherapy (Madariaga et al. 2019). This loss of function is considered the key driver of responsiveness to these agents and is a well-established predictive biomarker in OC. Clinically, women with both germline and somatic mutated *BRCA* were found to have increased response to platinum-based chemotherapy (Alsop et al. 2012; Gorodnova et al. 2015; Vencken et al. 2011; Pennington et al. 2014; Leunen et al. 2009) (for detailed review, see: Le Page et al. 2020a, b). During a relapse, these improved outcomes were also observed in platinum-resistant OC with *BRCA* mutations (Alsop et al. 2012). Thus, platinum re-challenge is an approach for recurrent OC patients with germline mutated *BRCA* carriers (Madariaga et al.

2019). In addition to high immune infiltrates, increased mutational burden, and loss of heterozygosity, *BRCA* mutations are considered as key determinants of exceptional long-term OC survival (Yang et al. 2018; Hoppenot et al. 2018). This was further confirmed by several meta-analyses of survival outcomes in OC (summarized in Table 4.1). Remarkably, a large study that enrolled 316 high-grade serous OC patients found that *BRCA2*, but not *BRCA1*, was associated with superior

**Table 4.1** Summary of recent meta-analyses of the impact of *BRCA* mutations on prognosis and survival

| Author/ year | Number of enrolled studies (patients) | Prognostic endpoints | Findings |
|---|---|---|---|
| Huang (2018) | 33 (7745) | Overall survival (OS) and progression-free survival (PFS), complete response rate (CRR), partial response rate (PRR), and overall response rate (ORR) | –Mutated *BRCA*1/2 are associated with improved OS (HR: 0.75; 95%; CI: 0.64–0.88) and PFS (HR: 0.80; 95% CI: 0.64–0.99).<br>–Presence of *BRCA*1/2 mutated status is associated with better ORR, higher CRR, and lower PRR but mutated *BRCA1* or *BRCA2* alone were not associated with ORR. |
| Xu et al. (2017) | 34 (18396) | OS and PFS | Mutated *BRCA1* and *BRCA2* demonstrated improved OS and PFS in ovarian cancer patients (HR: 0.73; 95% CI: 0.63–0.86 and HR, 0.57; 95% CI, 0.45–0.73, respectively) and PFS (HR: 0.68; 95% CI: 0.52–0.89 and HR: 0.48; 95% CI: 0.30–0.75, respectively). |
| Zhong et al. (2014) | 14 (9588) | OS and PFS | Ovarian cancer patients with mutated *BRCA1* and *BRCA2* had better OS (HR: 0.76; 95% CI: 0.70–0.83 and HR: 0.58; 95% CI: 0.50–0.66, respectively) and PFS (HR: 0.65; 95% CI: 0.52–0.81 and HR: 0.61; 95% CI: 0.47–0.80, respectively) than non-mutated status |
| Sun et al. (2014) | 35 | OS and PFS | Mutated *BRCA* status had a favorable impact on OS (HR: 0.69; 95% CI: 0.61–0.79). Similarly, patients with *BRCA*-mutated had longer PFS (based on 18 studies) (HR: 0.69, 95% CI: 0.63–0.76) |

Abbreviations: *BRCA* Breast Cancer gene, *CI* confidence interval, *HR* hazard ratio

chemotherapy response and also improved survival outcomes (Yang et al. 2011). Mechanistically, both *BRCA1* and *BRCA2* are important complementary members of the genes involved in DNA damage repair. However, accumulating evidence suggests that the principal function of *BRCA2* is the regulation of RAD51 that has a pivotal role in double-strand break repair (Davies et al. 2001) rather than tumor suppression ensured particularly by *BRCA1*. Functions of BRCA1 encompass cell cycle arrest checkpoint control (Yarden et al. 2002; Sharma et al. 2018), mitotic spindle assembly (Joukov et al. 2006; Xiong et al. 2008), and centrosome duplication (Mullee and Morrison 2016; Kais et al. 2012; Sankaran et al. 2007; Hsu and White 1998) and their failure can predispose to cancer initiation rather than conferring sensitivity to platinum DNA-crosslink agents. Therefore, these fundamental data may explain this difference in survival and drug response in this previous study. Importantly, the "mutator phenotype" hypothesis in OC patients with mutations beyond *BRCA1* is a potential driver of chemotherapy response in this setting as well. Despite these important observations, the acquisition of reversion mutations in *BRCA* genes can restore BRCA proteins expression and induce resistance to platinum-based therapy and also PARPi (Milanesio et al. 2020). Therapeutically, a recent meta-analysis documented that pharmacological blockade of DNA end-joining repair signaling may improve the stability of drug response by preventing the acquisition of reversion *BRCA* mutations (Tobalina et al. 2021). Promisingly, detection of these reversion mutations can be performed using real-time liquid biopsy approaches. Based on massively parallel targeted sequencing, Weigelt et al. showed recently that prospective evaluation of circulating-free DNA has the potential to non-invasively identify putative *BRCA1* or *BRCA2* reversion mutations with restored functions in women with OC and breast cancer (Weigelt et al. 2017). Similarly, two other recent reports confirmed these findings and showed that detected *BRCA* mutations using liquid biopsy in OC patients are associated with acquired resistance to treatments (Christie et al. 2017; Lin et al. 2019). Methylation phenomena in *BRCA1* promoter were also suggested as a biomarker of chemosensitivity in OC (Ignatov et al. 2014). However, a meta-analysis of individual data ($n = 2636$) demonstrated that patients with BRCA1-methylated OC had similar survival outcomes as compared to those with non-BRCA1-methylated tumors (Kalachand et al. 2020). Other mutated genes outside the *BRCA* family (Table 4.2) such as members of the HRR pathway particularly *RAD51,* which are found in approximately 50% of high-grade serous OC, were also found to predict chemosensitivity (Fuh et al. 2020; da Costa et al. 2019). Moreover, this HRR deficiency has also a value for prognostic stratification of OC patients (Takaya et al. 2020; Morse et al. 2019). Patients with this fundamental vulnerability had high infiltration of immune cells particularly tumor-infiltrating lymphocytes (TILs) which correlate with better survival and may make these women highly responsive to immune-checkpoint blockade (Ledermann 2019; Morse et al. 2019; Konstantinopoulos et al. 2015) (*see Chap. 3 for details*). Currently, this biomarker is used for predicting response to PARPi rather than platinum-based

**Table 4.2** Other emerging and potential single gene variants or panels with impact on prognosis and survival of ovarian cancer

| Genes | Functions/pathways | Clinical impact | References |
|---|---|---|---|
| *RAD51B* | Repair of DNA double-strand breaks | Acquired chemotherapy resistance | Patch et al. (2015) |
| *RAD51C* | Repair of DNA double-strand breaks | Acquired resistance to PARP inhibitors via secondary somatic reversion mutations | Kondrashova et al. (2017) |
| | | Improved overall survival (OS) and sensitivity to platinum | Pennington et al. (2014) |
| *RAD51D* | Repair of DNA double-strand breaks | Acquired resistance to PARP inhibitors via secondary somatic reversion mutations | Kondrashova et al. (2017) |
| *TP53* | Cell cycle regulation, cell death, and DNA repair | Resistance to platinum- and taxane-based chemotherapy (oncomorphic mutations) | Brachova et al. (2014) (for review, see: Brachova et al. 2013) |
| | | Sensitivity to chemotherapy and improved survival | Wong et al. (2013) |
| *RB1* | Cell cycle regulation | Long OS and PFS, and durable response | Garsed et al. (2018) |
| *ADAMTS* | Tissue development and maintenance, tumor progression and metastasis (cell migration and angiogenesis) | Significant association with better OS, progression-free survival (PFS), and platinum-free survival | Liu et al. (2015) |
| *CCNE1* | Regulation of cell cycle | Poor OS | The Cancer Genome Atlas Research Network, (2011); Nakayama et al. (2010) |
| *CHEK2* | Regulation of cell cycle after DNA damage | Poor OS and therapy response | Ow et al. (2014) |
| *KRAS* | Proliferative signaling pathways | Resistance to platinum-based therapy | Ratner et al. (2012) |
| | | Sensitivity to decitabine agent | Stewart et al. (2015) |
| | | Improved cancer-specific survival | Nodin et al. (2013) |
| *BRAF* | Signal transduction, cell division, and differentiation | Improved OS as compared to *KRAS* mutant or *KRAS*/wild-type *BRAF* tumors | Grisham et al. (2013) |
| *NF1* | Regulation of cell cycle | Acquired resistance to chemotherapy | Patch et al. (2015) |

(continued)

**Table 4.2** (continued)

| Genes | Functions/pathways | Clinical impact | References |
|---|---|---|---|
| *TAP1* | Antigen presentation | Association with OS | Millstein et al. (2020) |
| *ZFHX4* | Cell differentiation | | |
| *CXCL9* | Mediation of T cells recruitment | | |
| *FBN1* | Extracellular matrix protein | | |
| *PTGER3* | Receptor of prostaglandin E2 | | |

chemotherapeutics. The European Society for Medical Oncology (ESMO) stated that assays for clinical evaluation of HRR deficiency are useful in predicting the likely magnitude of benefit from PARP inhibition but additional biomarkers with improved accuracy are needed to better stratify patients (Miller et al. 2020).

Research in this area of biomarkers discovery has also provided other perspectives for non-platinum chemotherapy such as the natural compound trabectedin and pegylated liposomal doxorubicin (PLD) (Madariaga et al. 2019; El Bairi et al. 2019). Trabectedin (known as Yondelis®) is a marine compound isolated from the colonial tunicate *Ecteinascidia turbinate* that acts as a cytotoxic alkylating agent and also as a vascular disruptor (El Bairi et al. 2019). It was approved in several countries of the European Union for the treatment of OC as a late-line therapy in combination with PLD for recurrent platinum-sensitive disease. The efficacy of trabectedin was found associated with deficient HRR systems in various clinical trials (El Bairi et al. 2018; Ventriglia et al. 2018). Previously, an exploratory analysis of the randomized phase 3 OVA-301 study that compared the efficacy of trabectedin and PLD versus PLD alone in women with recurrent OC showed that germline *BRCA1* mutant tumors had improved median PFS (13.5 vs. 5.5 months, $p = 0.0002$), OS (23.8 versus 12.5 months, $p = 0.0086$), and higher response rates (49 vs. 28%) (Monk et al. 2015). Moreover, women with *BRCA* wild-type OC had no improvements in median OS (19.1 versus 19.3 months; $p = 0.9377$) (Monk et al. 2015). *BRCA* status and *BRCA*ness were also used for patients' selection in the MITO-15 phase II study that investigated trabectedin in women with recurrent OC (Lorusso et al. 2016). *BRCA* status was not associated with response to trabectedin nor with survival (Lorusso et al. 2016). However, the recent findings of another randomized phase III trial that compared the efficacy of trabectedin combined with PLD in the same previous setting showed significant overall survival (OS) benefits for patients harboring *BRCA* mutations (34.2 vs. 20.9 months; HR: 0.54, 95% CI: 0.33–0.90; $p = 0.016$) (Monk et al. 2020). Similarly, improved outcomes for median PFS were also noticed for patients with *BRCA* mutant tumors (HR: 0.72, 95% CI: 0.48–1.08; $p = 0.039$) (Monk et al. 2020). The DNA damaging agent PLD used in the recurrent setting was also found to be more effective in tumors with *BRCA* mutations. Two previous retrospective studies demonstrated that *BRCA*-associated

OC women had improved sensitivity to PLD, greater PFS (Adams et al. 2011), and also OS (Safra et al. 2014). Regarding taxane chemotherapy which is used in combination with carboplatin in the first-line setting as a standard of care and as a single agent for recurrent platinum-resistant disease; data on *BRCA* as a predictor of response are sparse. In prostate cancer, the correlation between mutated *BRCA* and poor response to docetaxel was noticed (Nientiedt et al. 2017). In addition, mutated *BRCA1*-associated breast cancer was found less sensitive to taxane chemotherapy (Kriege et al. 2012). In OC, the inhibition of endogenous BRCA1 expression was reported to be associated with decreased sensitivity to antimicrotubule agents (Quinn et al. 2007). Moreover, median OS in patients with higher BRCA1-expression was found improved after treatment with taxanes (23 vs. 18.2 months; HR: 0.53; $p = 0.12$) (Quinn et al. 2007). Other emerging genes that might impact drug response and prognosis in OC can be found in Tables 4.2 and 4.3.

## 4.3 Ovarian Cancer Genetics and Response to PARP Inhibitors

DNA damage response pathway is one of the invested targets in drug discovery for OC. PARP 1 and PARP2 are the principal enzymes of this pathway and are recruited during DNA lesions to orchestrate repair effectors activity (Lord and Ashworth 2017). PARP bound to damaged DNA and transfer poly-ADP-ribose units to various target proteins (PARylation process) required for DNA breaks repair such as topo-isomerase and DNA ligase (for review, see: Franzese et al. 2019). Inhibition of PARP mediated DNA repair appeared to be a potential strategy that is widely known as synthetic lethality (Lord et al. 2015; Lord and Ashworth 2017) and has moved successfully into clinical trials several PARPi including rucaparib (Rubraca®), olaparib (Lynparza®), veliparib (ABT-888), niraparib (Zejula®) as well as the next-generation of this category such as talazoparib (Talzenna®). In 2005, two preclinical reports were published in *Nature* by Farmer et al. and Bryant et al. showed that mutant cancer cells with *BRCA* dysfunction are highly sensitive to PARP inhibition (Farmer et al. 2005; Bryant et al. 2005). Based on these substantial findings, this new concept was used as a rationale for developing trial designs of several PARPi for various cancers harboring this signature. In OC, many clinical studies that investigated oral PARPi have achieved their primary objectives and showed positive results from phase II-III trials in the front-line, for recurrent disease, or maintenance settings following platinum-based chemotherapy (Table 4.4).

### 4.3.1 Olaparib

Olaparib was the first-in-class developed PARPi and approved by the FDA and EMA in 2014 for treating OC (Franzese et al. 2019). Early trials (NCT00516373 and NCT00494442) showed favorable safety and tolerability profile which were represented mainly by reversible fatigue, anemia, and mild gastrointestinal symptoms (Fong et al. 2009, 2010; Audeh et al. 2010). Interestingly, these dose-

**Table 4.3** Genetic biomarkers of response to other anticancer drugs used in ovarian cancer therapy

| References | Drugs/ regimens | Enrollment | Phase | Biomarkers | Clinical endpoints | Findings |
|---|---|---|---|---|---|---|
| Monk et al. (2017) | Motolimod + pegylated liposomal doxorubicin (PLD) | 297 [arm 1: motolimod + PLD ($n = 149$), arm 2: PLD + placebo ($n = 149$)] | Randomized phase II | ***TLR8* (SNPs), *BRCA*–Fanconi anemia mutational status** | **PFS and OS** | *TLR8* (SNPs), mutated *BRCA* and did not correlate with PFS or OS |
| Harter et al. (2016) (AGO-OVAR 16) | Pazopanib | 664 (pazopanib, $n = 335$; placebo, $n = 329$) | Randomized phase III (exploratory analysis) | ***BRCA1/2*** | **Median PFS: Pazopanib arm** –*BRCA*(+): 30.2 months –*BRCA* (−): 17.7 months HR: 0.64; 95% CI: 0.40–1.03; $p = 0.069$ **Median PFS: Placebo arm** –*BRCA*(+): 30.3 months –*BRCA* (−): 14.1 months HR: 0.48; 95% CI: 0.29–0.78; $p = 0.0031$ | OC patients with *BRCA1/2* carriers treated with antiangiogenic pazopanib had longer PFS |
| Monk et al. (2015) (OVA-301) For review, see: Ventriglia et al. (2018) | Trabectedin + PLD | 264 [arm 1: trabectedin + PLD ($n = 135$), arm 2: PLD alone ($n = 129$)] | Randomized phase III (exploratory analysis) | ***BRCA1*** ***XPG*** | **Response rate (RR):** –*BRCA* (+): 49% –*BRCA* (−): 28% ***BRCA* (+):** –**Median PFS:** arm 1: 13.5 vs. 5.5 months for arm | Recurrent OC patients with *BRCA* mutated status treated with trabectedin + PLD had better survival outcomes compared with single-arm PLD |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | 2, $p = 0.0002$.<br>–**Median OS:** arm 1: 23.8 vs. 12.5 months for arm 2, $p = 0.0086$.<br>***BRCA* (−):**<br>–**Median PFS:** arm 1: 6.0 vs. 5.4 months for arm 2, $p = 0.2185$<br>–**Median OS:** arm 1: 19.1 vs. 19.3 months for arm 2, $p = 0.9377$.<br>***XPG* status:** no significant difference in the two arms | |
| Hyman et al. (2011) | Topotecan (topoisomerase I inhibitor) | 50 | Retrospective | ***BRCA*** | **Median PFS:**<br>–*BRCA* (+): 1.7 months (95% CI: 1.0–2.8)<br>–*BRCA* (−): 2.5 months (95% CI: 1.9–2.8) $p = 0.057$ | Topotecan did not demonstrate superiority in platinum-resistant OC patients with *BRCA* positive status |

**Table 4.4** Landmark completed phase III trials of PARP inhibitors in ovarian cancer

| Trial name | Investigated predictive biomarker | Sample size | Anticancer drug | Comparator | Randomization | Setting |
|---|---|---|---|---|---|---|
| NOVA | *BRCA* mutations | 553 | Niraparib | Placebo | 2:1 | Maintenance for recurrent platinum-sensitive |
| SOLO-2 | *BRCA* mutations | 295 | Olaparib | Placebo | 2:1 | |
| ARIEL-3 | *BRCA* mutations and homologous recombination deficiency (HRD) | 564 | Rucaparib | Placebo | 2:1 | |
| SOLO-1 | *BRCA* mutations | 391 | Olaparib | Placebo | 2:1 | Maintenance in newly diagnosed |
| PAOLA-1 | *BRCA* mutations and HRD | 806 | Olaparib | Bevacizumab or placebo | 2:1 | |
| VELIA | *BRCA* mutations and HRD | 1140 | Veliparib | Placebo or carboplatin and paclitaxel | 1:1:1 | First-line and maintenance |
| PRIMA | *BRCA* mutations and HRD | 733 | Niraparib | Placebo | 2:1 | First-line |
| SOLO-3 | Germline *BRCA* mutations | 266 | Olaparib | Pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan | 2:1 | Recurrent platinum-sensitive |

finding trials demonstrated significant antitumor response in OC patients with *BRCA* mutations (Fong et al. 2010; Audeh et al. 2010). In a second interim analysis of OS and a preplanned analysis of data by *BRCA* mutation status of a randomized and double-blind phase II study (NCT00753545) that used olaparib as maintenance treatment for recurrent platinum-sensitive OC, Ledermann et al. found that patients with mutated *BRCA* had significantly longer PFS as compared with wild-type subjects (11.2 vs. 7.4 months) (Ledermann et al. 2014). However, in terms of OS, no significant difference was seen between the two groups (HR: 0.73; 95% CI: 0.45–1.17; $p = 0.19$ for *BRCA* mutated status and (HR: 0.99; 95% CI: 0.63–1.55; $p = 0.96$) for wild-type *BRCA*) (Ledermann et al. 2014). Moving from this immature evidence, the greatest clinical benefit was observed in *BRCA*-mutated recurrent and platinum-sensitive OC patients in another randomized phase II trial (NCT01081951) combining olaparib with standard chemotherapy (Oza et al. 2015). PFS in patients with mutated *BRCA* was significantly improved (HR: 0.21; 95% CI: 0.08–0.55; $p = 0.0015$) (Oza et al. 2015). These data were supported by an updated analysis of OS of NCT00753545 trial and showed that *BRCA*-mutated platinum-sensitive recurrent OC patients appear to have longer OS despite it did not achieve the planned level for statistical significance ($p < 0.0095$) (Ledermann et al. 2016). Confirmatory results from two randomized phase III trials (SOLO-1 and SOLO-2/ENGOT-Ov21) using olaparib as maintenance therapy for OC were reported recently. Pujade-Lauraine et al. conducted a phase III randomized, double-blind and placebo-controlled and multicenter trial to evaluate the efficacy of olaparib as maintenance treatment for platinum-sensitive, relapsed and *BRCA* mutated OC (Pujade-Lauraine et al. 2017). This study (NCT01874353; SOLO-2/ENGOT-Ov21) enrolled 295 patients including 196 in the olaparib arm and showed significantly higher PFS as compared with the placebo arm (19.1 months vs. 5.5 months $p < 0.0001$ respectively) (Pujade-Lauraine et al. 2017). More recently, results from SOLO-1 (NCT01844986) phase III trial that assessed olaparib ($n = 260$) versus placebo ($n = 131$) as maintenance therapy this time for newly diagnosed OC with *BRCA* mutations and after first-line standard chemotherapy demonstrated a gain of 3 years in PFS (despite not reached) in the group who received olaparib after 41 months of follow-up (HR: 0.30; 95% CI: 0.23–0.41; $p < 0.001$) (Moore et al. 2018). Remarkably, a recent meta-analysis that enrolled 8 randomized trials (1957 patients) including SOLO-2 found that patients with *BRCA* carriers exhibited significant survival benefits from olaparib and thus showing decisive additional evidence for this genetic biomarker but with an increased risk of severe anemia which requires regular hematologic surveillance (Guo et al. 2018). Promisingly, further evidence will be released by the ongoing SOLO3 phase III trial that randomizes relapsed OC patients who have received at least 2 prior lines of platinum-based chemotherapy and with *BRCA* carriers to receive olaparib versus standard of care (NCT02282020). Moving beyond *BRCA* biomarkers, it seems that a subset of OC patients with mutations in HRR genes other than traditional *BRCA* may also benefit from olaparib which can expand the use of this drug in the future (Hodgson et al. 2018). Similarly, findings

from a comparative molecular analysis of the NCT00753545 trial showed that long-term responders to olaparib maintenance may be multifactorial and related to HRR profile (Lheureux et al. 2017). In the confirmatory SOLO-3 phase III trial, patients with *BRCA* mutated status were randomly assigned to receive olaparib or a non-platinum drug for the platinum-sensitive setting for which objective response rate was the primary endpoint as mandated by the FDA (Penson et al. 2020). The superiority of olaparib was noticed and reached 72.2 as compared to 51.4% in patients treated with standard of care (Penson et al. 2020). The addition of olaparib to bevacizumab for the first-line maintenance therapy was investigated in the PAOLA-1 phase III trial (Ray-Coquard et al. 2019). This study randomized 806 OC patients with mutated *BRCA* to receive olaparib and bevacizumab or bevacizumab + placebo in a 2:1 fashion. A significant hazard ratio of 0.59 resulted in the comparison for PFS. In patients with HRR deficiency, the hazard ratio for progression or death reached a value of 0.33 suggesting the clinical benefits of adding olaparib to anti-angiogenesis in this setting (Ray-Coquard et al. 2019).

### 4.3.2 Rucaparib

Women with OC who have *BRCA* mutant tumors that were enrolled in the ARIEL-3 randomized and controlled phase III ($n = 564$) for the recurrent platinum-sensitive disease had superior median PFS (HR: 0.23, 95% CI: 0.16–0.34, $p < 0.0001$) (Coleman et al. 2017). Similarly, patients with HRR deficiency had also improved PFS (HR: 0.32, 0.24–0.42, $p < 0.0001$). In the ARIEL-2 phase II trial for the recurrent platinum-sensitive setting that stratified patients into multi-cohorts including those with *BRCA* status, median PFS was also improved in the group treated with rucaparib and having *BRCA* mutations (HR: 0.27, 95% CI: 0.16–0.44, $p < 0.0001$) (Swisher et al. 2017). Notably, *RAD51C* and *RAD51D* genetic variants were found associated with acquired resistance to this PARP inhibitor in OC (Kondrashova et al. 2017). Furthermore, reversion mutations in *BRCA* were also identified in circulating tumor DNA of OC patients with reduced rucaparib PFS as compared to women with no reversion mutations at baseline (median 1.8 vs. 9 months; HR: 0.12; $p < 0.0001$). Thus, combinatorial approaches may be promising to overcome drug resistance to rucaparib (Lin et al. 2019).

### 4.3.3 Niraparib

To the best of our knowledge, niraparib has been investigated in two randomized phase III trials for OC, NOVA ($n = 553$) and PRIMA ($n = 733$) (*see Chap. 3*). In the NOVA study that explored the efficacy of niraparib in the recurrent platinum-sensitive setting, 203 women had germline mutated *BRCA* and had superior PFS as compared to those treated with placebo (HR: 0.27; 95% CI: 0.17–0.41)

(Mirza et al. 2016). Remarkably, women with HRR deficiency had also improved PFS (HR: 0.38; 95% CI: 0.24–0.59) (Mirza et al. 2016). When niraparib was investigated as a monotherapy in the maintenance setting after response to front line therapy in NOVA study, enrolled women with HRR deficient tumors had clinically and statistically improved PFS (HR: 0.43; 95% CI: 0.31–0.59; $p < 0.001$) (González-Martín et al. 2019). In late lines of recurrent OC therapy, the QUADRA phase II trial explored the efficacy of niraparib in heavily pre-treated patients and showed a clinical activity of this PARPi in women with HRR deficiency including those with or without *BRCA* mutations (Moore et al. 2019).

### 4.3.4 Veliparib

Veliparib is a new synthetically lethal therapeutic approach for treating OC (Boussios et al. 2020). Previously and based on early signs of efficacy in a phase II trial (Coleman et al. 2015), veliparib as a single agent was studied for platinum-resistant or partially sensitive recurrent OC in a combined phase I/II trial (Steffensen et al. 2017). Veliparib was given to women that have exclusively germline mutated *BRCA* showed clinical activity in this heavily pretreated population including 65% of overall response rate, PFS of 5.6 months, and OS of 13.7 months (Steffensen et al. 2017). VELIA ($n = 1140$) was a landmark three arms phase III trial that explored the efficacy of veliparib in the first-line therapy of OC (Coleman et al. 2019). Women with *BRCA* mutant and HRR deficient tumors treated with veliparib in combination with carboplatin/paclitaxel doublets had favorable outcomes including superior PFS (HR: 0.44 and HR: 0.68 respectively, $p < 0.001$ for both) (Coleman et al. 2019). In a recent biomarker analysis of a phase II study, homeobox A9 (*HOXA9*) promoter methylation in circulating tumor DNA was demonstrated to confer resistance to veliparib (Rusan et al. 2020). Longitudinal monitoring of OC patients based on this liquid biopsy approach showed that methylated *HOXA9* at baseline was significantly correlated with worse outcomes included reduced PFS and OS ($p < 0.0001$ and $p = 0.002$, respectively) (Rusan et al. 2020). Therefore, this may provide perspectives for real-time monitoring using this potential predictive biomarker.

## 4.4 Ovarian Cancer Genetics and Surgical Outcomes

Usually, cytoreductive debulking surgery is performed for OC patients after primary diagnosis and staging, followed by adjuvant platinum-based chemotherapy or after receiving neoadjuvant chemotherapy (NACT) for women with poor performance status, large tumors, and important volumes of ascites (Vitale et al. 2013). Furthermore, secondary debulking surgery can be performed during recurrences but its role in improving outcomes is still controversial (Lorusso et al. 2012). Resectability and

optimal cytoreduction are influenced by several factors such as disease location, the expertise of surgeons as well as probably genetic status such as *BRCA* mutations (Narod 2016; Ponzone 2021). Interestingly, to see whether OC patients with *BRCA* mutations have superior surgical outcomes as compared with those with wild status, some recent reports looked into this matter based on different observational study designs. Earlier in 2012, a retrospective report of 367 stage IIIC-IV high-grade serous OC from the Memorial Sloan Kettering Cancer Center investigated germline *BRCA* mutation status as a predictor of optimal cytoreduction compared to wild-type tumors (Hyman et al. 2012). OC patients with mutated *BRCA* and who underwent surgery had relatively superior rates of optimal debulking as compared with wild-type patients (84.1% vs. 70.1% respectively, $p = 0.02$) (Hyman et al. 2012). However, based on multivariate analysis, this study demonstrated that mutated *BRCA* status is not associated with residual tumor volume (OR: 0.63; 95% CI: 0.31–1.29; $p = 0.21$) suggesting that optimal cytoreduction may be due to surgery alone instead of OC genetics (Hyman et al. 2012). In another retrospective study that enrolled 27 cases with recurrent OC treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) and 84 matched controls treated with systemic chemotherapy alone, women with positive *BRCA* carriers were found to have longer PFS in the HIPEC group as compared with the controls (20.9 vs. 12.6 months, $p = 0.048$) (Safra et al. 2014). Consequently, this confirms the recently published data supporting the impact of the emerging HIPEC in treating OC (van Driel et al. 2018; Spiliotis et al. 2015; Cascales-Campos et al. 2015) especially in patients with *BRCA* mutational status. However, an opposing conclusion from a recent study found that patients with *BRCA1* mutated OC are less likely to achieve no residual disease after debulking surgery than wild-type patients (19% vs. 39%; $p < 0.0001$) (Kotsopoulos et al. 2016). Importantly, the same study found that improved survival outcomes observed in OC patients with mutated *BRCA* status may be due to higher initial sensitivity to platinum-based therapy and, notably, no residual disease at debulking is the strongest predictive factor of long-term survival (Kotsopoulos et al. 2016). Recently, Petrillo et al. evaluated the impact of *BRCA* mutational status on outcomes including optimal debulking in a large multicenter report of women with newly diagnosed high-grade serous OC with stage IIIc and IV disease (Petrillo et al. 2017). Patients with mutated *BRCA* had significantly higher peritoneal tumor load but without having different median PFS when treated with NACT or debulking surgery ($p = 0.268$). Remarkably, patients with wild-type *BRCA* status and who benefited from primary debulking surgery had superior median PFS as compared to those treated with NACT (26 vs. 18 months; $p = 0.003$) (Petrillo et al. 2017). Similarly, Marchetti et al. showed in their recent retrospective cohort that women with *BRCA* wild-type ovarian tumors who underwent complete secondary cytoreductive surgery had superior 5-year post-recurrence survival as compared to those with no surgical intervention (54% vs. 42%; $p = 0.048$) (Marchetti et al. 2018). However, Naumann et al. showed that optimally resected high-grade OC had frequent *BRCA* mutations and

dramatically improved median OS (110.4 vs. 67.1 months; HR: 0.28, 95% CI: 0.11–0.73, $p = 0.009$) when treated with HIPEC compared with patients wild type tumors (Naumann et al. 2018). More recently, Gordonova et al. analyzed the medical record of 283 consecutive women who underwent complete or optimal debulking and compared their outcomes based on *BRCA* status (Gorodnova et al. 2019). Again, this study showed that *BRCA* status did not predict outcomes in patients subjected to primary surgery ($p = 0.56$) (Gorodnova et al. 2019). To the best of our knowledge, only one report has prospectively assessed the impact of *BRCA* status on optimal debulking. This was a cohort report that enrolled 107 OC patients including 51.4% of *BRCA* mutated cases (Rudaitis et al. 2014). No significant difference between OC patients harboring *BRCA* mutations and those with wild-type status was seen in terms of optimal debulking surgery (58.2% vs. 53.9%, $p = 0.6994$). However, *BRCA* mutated OC patients had improved median PFS (19 months, 95%; CI: 13–25) compared with wild-type subjects (13 months, 95%; CI: 10–16) ($p = 0.039$) (Rudaitis et al. 2014). In conclusion, it seems that *BRCA* carriers have no impact on optimal debulking for OC patients. However, most of these studies are retrospective in their design and thus, should be commented with caution because of the high risk of biases. Until to date, no definitive answers were provided and most current studies especially clinical trials are investigating *BRCA* as biomarkers for chemotherapy and targeted therapies.

## 4.5 Conclusion

The genetics of OC is becoming actionable with the arrival of precision medicine in gynecologic oncology. This progress is also supported by the recent development of sequencing technology. To date, several therapies require genetic information of OC patients before their use. Remarkably, this approach has deeply improved outcomes in some settings of this aggressive women's cancer. More research on biomarkers is needed to ensure that patients can achieve maximal clinical benefits from the emerging targeted agents in OC. In this perspective, the currently active clinical trials using *BRCA* status for patients' selection and stratification can improve personalized medicine in the near future (Tables 4.5 and 4.6). For additional reading, see Box 4.1.

**Table 4.5** Summary of active clinical trials assessing *BRCA* mutations as prognostic biomarkers in ovarian cancer for patients' selection and stratification

| Trial identifier[‡] | Objective | Enrollment[@] | Sponsor |
|---|---|---|---|
| NCT02341118 | Genomic profiling of *BRCA1/2* mutational status to predict clinical outcomes | 2000 | University Health Network, Toronto |
| NCT02321228 (TUBA)[§] | To determine whether an early salpingectomy and a delayed oophorectomy in mutated *BRCA* subjects will improve menopause-related quality of life without increasing OC incidence | 510 | University Medical Center Nijmegen |
| NCT00579488 | Assessment of clinical outcomes in OC patients with mutated *BRCA* | 20,000 | Memorial Sloan Kettering Cancer Center in collaboration with Cold Spring Harbor Laboratory |
| NCT03296826 | Identification of clinicopathological features in Japanese women with mutated *BRCA* undergoing RRSO (risk-reducing salpingo-oophorectomy) | 600 | Translational Research Center for Medical Innovation, Kobe, Hyogo, Japan |
| NCT03159572 (HITOMI) | Investigation of association between PFS/sensitivity to platinum and germline mutation *BRCA* in breast cancer and OC | 700 | Translational Research Center for Medical Innovation, Kobe, Hyogo, Japan |
| NCT03510689 (Gene-HEART study) | Investigation of association between pathogenic *BRCA* mutations in hereditary breast and OC treated with anthracycline-based chemotherapy and the risk to develop cardiovascular disease | 150 | Abramson Cancer Center of the University of Pennsylvania |
| NCT01167842 | Correlation between molecular findings (*BRCA* mutational status and other mutated genes) with response to treatment, recurrence data and survival | 180 | University of Washington |

[‡]Titles of clinical trials were copied as shown by the database (with recruiting or enrolling by invitation studies), [@]Actual or estimated. Data from ClinicalTrials.gov (accessed 12/10/18). [§]Results published, see Harmsen et al.: https://bmccancer.biomedcentral.com/articles/10.1186/s12885-015-1597-y

**Table 4.6** Summary of active clinical trials assessing mutated *BRCA* as a predictive biomarker in ovarian cancer for patients' selection and stratification

| Trial identifier[‡] | Objective | Phase | Primary endpoints | Status[†] | Enrollment[@] | Sponsor |
|---|---|---|---|---|---|---|
| NCT03117933 (OCTOVA trial) | Comparison of olaparib and cediranib with standard paclitaxel-based chemotherapy in *BRCA* mutated platinum resistant ovarian cancer (OC) | II | Progression-free survival (PFS) | Recruiting | 132 | University of Oxford in collaboration with AstraZeneca |
| NCT03402841 (OPINION trial) | Use of olaparib maintenance treatment as monotherapy in platinum sensitive and relapsed OC with non-germline mutated *BRCA* | III | PFS | Recruiting | 265 | AstraZeneca |
| NCT03509636 | Evaluation of efficacy and safety profile of fluzoparib in *BRCA* mutated and relapsed OC | II | Objective response rate (ORR) | Recruiting | 112 | Jiangsu HengRui Medicine Co., Ltd. |
| NCT02203513 | Evaluation of LY2606368 (prexasertib, an inhibitor of checkpoint kinase 1 and 2 (Chk1/2) proteins) in *BRCA* mutated OC | II | ORR | Recruiting | 153 | National Cancer Institute (NCI) |
| NCT02983799 | Assessment of olaparib in platinum-sensitive and relapsed, OC with mutated *BRCA* or aberrations in homologous recombination deficiency (HRD) | II | ORR | Recruiting | 260 | AstraZeneca |
| NCT02903004 (MITO23) | Evaluation of safety and efficacy of trabectedin (yondelis) in mutated *BRCA1* and *BRCA2* and BRCAness phenotype advanced OC | III | Overall survival (OS) | Recruiting | 244 | Fondazione IRCCS Istituto Nazionale dei Tumori, Milano |

(continued)

**Table 4.6** (continued)

| Trial identifier[‡] | Objective | Phase | Primary endpoints | Status[†] | Enrollment[@] | Sponsor |
|---|---|---|---|---|---|---|
| NCT02855944 (ARIEL4) | Assessment of rucaparib versus platinum-based chemotherapy in OC patients harboring mutated *BRCA* | III | PFS | Recruiting | 345 | Clovis Oncology, Inc. in collaboration with Foundation Medicine |
| NCT03470805 | Study of olaparib in OC patients with BRCA mutations after response to trabectedin and pegylated liposomal doxorubicin | II | PFS | Recruiting | 66 | Grupo Español de Investigación en Cáncer de Ovario in collaboration with AstraZeneca and Apices Soluciones S.L. |
| NCT02855697 (MOLTO) | Determination of the feasibility of a second course administration of maintenance olaparib for more than 6 months to recurrent platinum-sensitive and BRCA mutated OC | I | PFS (as secondary outcome measure) | Recruiting | 26 | Rozalia Lubiatowska, The Christie NHS Foundation Trust |
| NCT03382574 | Comparison of denosumab effects versus not treatment on the fimbrial and fallopian tube tissues of premenopausal *BRCA* mutated OC subjects undergoing risk-reducing salpingo-oophorectomy (RRSO) | I | Ki67 proliferation index after RRSO | Not yet recruiting | 60 | NCI |
| NCT02950064 | Evaluation of safety, pharmacokinetics, and anticancer activity of BTP-114 in advanced *BRCA* mutated solid tumors including OC | I | Maximum tolerated dose (MTD), PFS, ORR | Recruiting | 95 | Placon Therapeutics |

| | | | | | | |
|---|---|---|---|---|---|---|
| NCT01989546 | Investigation of BMN 673 (talazoparib, a PARP inhibitor) in patients with advanced solid neoplasms including OC and with mutated *BRCA* status | I/II | – | Recruiting | 24 | NCI |
| NCT03106987 (OReO trial) | Investigation of safety-efficacy olaparib maintenance re-treatment in patients with relapsed non-mucinous OC based on *BRCA* status as a biomarker | III | PFS | Recruiting | 416 | AstraZeneca in collaboration with European Network of Gynaecological Oncological Trial Groups (ENGOT) |
| NCT02489058 (OLALA study) | Assessment of long-term response to olaparib in OC patients based on *BRCA* status and other biomarkers | Observ-ational | – | Recruiting | 100 | University Health Network, Toronto |
| NCT03598270 (ANITA) | Double-blinded study of platinum-based chemotherapy +/− atezolizumab followed by niraparib maintenance +/− atezolizumab in subjects with recurrent OC and correlation of *BRCA* mutational status with PFS | III | PFS | Not yet recruiting | 414 | Grupo Español de Investigación en Cáncer de Ovario in collaboration with Hoffmann-La Roche and Apices Soluciones S.L. |
| NCT02953457 | Evaluation of olaparib combined with durvalumab (Medi4736) and tremelimumab for treating recurrent platinum sensitive or resistant or refractory OC subjects with mutated *BRCA* status | I/II | PFS | Recruiting | 39 | NCI in collaboration with Roswell Park Cancer Institute |

(continued)

**Table 4.6** (continued)

| Trial identifier[‡] | Objective | Phase | Primary endpoints | Status[†] | Enrollment[@] | Sponsor |
|---|---|---|---|---|---|---|
| NCT03414047 | Evaluation of safety/efficacy of prexasertib in women with platinum-resistant or refractory recurrent OC based on *BRCA* mutational status | II | ORR | Recruiting | 180 | Eli Lilly and Company |
| NCT03604315 | Determination of correlation between *BRCA* mutational status and fluorine F18-fluorthanatrace ([18F] FTT) in OC treated with PARP inhibitors | I | [18F] Fluorthanatrace PET/CT uptake measure | Not yet recruiting | 120 | M.D. Anderson Cancer Center in collaboration with NCI |
| NCT03326193 | Evaluation of safety/efficacy of niraparib in combination with bevacizumab as maintenance treatment for OC patients based on BRCA status after front-line platinum-based therapy | II | PFS | Recruiting | 90 | Tesaro, Inc. |
| NCT03534453 (L-MOCA trial) | Assessment of olaparib as maintenance therapy in *BRCA* mutated status and platinum sensitive relapsed OC patients | III | PFS | Recruiting | 300 | AstraZeneca |
| NCT03428802 | Evaluation of response rate of pembrolizumab in patients with solid cancers with mutated *BRCA* including OC | II | ORR | Recruiting | 40 | Rutgers, The State University of New Jersey in collaboration with NCI |

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|---|---|---|---|---|---|---|
| NCT03161132 (ROLANDO) | Impact of olaparib combined with pegylated liposomal doxorubicin on PFS in patients with platinum-resistant advanced OC with mutated *BRCA* | II | PFS | Recruiting | 32 | Grupo Español de Investigación en Cáncer de Ovario in collaboration with AstraZeneca |
| NCT02567253 (OvIP1 trial) | Assessment of gene expression of selected genes including *BRCA*, *ERCC1* and *CTR1* as predictive biomarkers for intraoperative intraperitoneal chemoperfusion to treat peritoneal minimal residual disease in stage III OC | II | Peritoneal recurrence free survival (PRFS), DFS and OS (as secondary outcome measures) | Recruiting | 48 | University Hospital, Ghent |
| NCT03522246 (ATHENA) | Evaluation of rucaparib in combination with nivolumab as maintenance treatment following response to front-line treatment in newly diagnosed OC with a focus on *BRCA* as a predictor of response | III | PFS | Recruiting | 1012 | Clovis Oncology, Inc. |
| NCT03552471 | Determination of recommended dose, safety and tolerability of mirvetuximab soravtansine combined with rucaparib in patients with endometrial cancer and OC with mutated *BRCA* status | I | PFS and ORR | Recruiting | 42 | Ohio State University Comprehensive Cancer Center in collaboration with ImmunoGen, Inc. and Clovis Oncology, Inc. |

(continued)

**Table 4.6** (continued)

| Trial identifier[‡] | Objective | Phase | Primary endpoints | Status[†] | Enrollment[@] | Sponsor |
|---|---|---|---|---|---|---|
| NCT03394885 (AdORN trial) | –Study of atezolizumab in combination with neoadjuvant chemotherapy for newly diagnosed and advanced OC<br>–Analysis of association between *BRCA* mutational status and tumor infiltrating lymphocytes (TILs), immune checkpoint receptor, cytokines and PD-L1 expressions and PFS | I/II | OS, PFS and ORR (as secondary outcomes measure) | Recruiting | 40 | Duke University in collaboration with Johns Hopkins University, Genentech, Inc. and Kaiser Permanente |
| NCT03586661 | Investigation of niraparib in association with copanlisib in treating recurrent endometrial cancer and OC with mutated *BRCA* status | I | PFS (as a secondary outcome measure) | Not yet recruiting | 44 | M.D. Anderson Cancer Center in collaboration with NCI |
| NCT02684318 | Assessment of predictive capacity and prognostic impact of some selected biomarkers including *BRCA*, *PTEN* and HRD panel in a phase Ib/II evaluating the efficacy and tolerability of PM01183 (lurbinectedin) combined with olaparib for treating advanced tumors including OC | I/II | Dose limiting toxicity (DLT), maximum tolerated dose (MTD) PFS and ORR (as secondary outcomes measure) | Recruiting | 100 | AstraZeneca and PharmaMar |

| | | | | | | |
|---|---|---|---|---|---|---|
| NCT02734004 (MEDIOLA) | Determination of *BRCA* and *ATM* mutations, and overall mutation burden in a phase I/II evaluating safety/efficacy of MEDI4736 combined with olaparib in advanced cancer patients including OC | I/II | Disease control rate (DCR) and ORR | Recruiting | 288 | AstraZeneca in collaboration with IQVIA (formerly QuintilesIMS) |

[‡]Titles of clinical trials were copied as shown by the database (with recruiting or enrolling by invitation studies), [@]Actual or estimated. Data from ClinicalTrials.gov (accessed 12/10/18). [†] These studies are still ongoing at the time of manuscript writing

**Box 4.1 Recommended reading of particular interest**

| | DOI |
|---|---|
| Kuroki L, Guntupalli SR. **Treatment of epithelial ovarian cancer**. BMJ. 2020;371:m3773. | 10.1136/bmj.m3773 |
| Mirza MR, et al. **The forefront of ovarian cancer therapy: update on PARP inhibitors**. Ann Oncol. 2020;31(9):1148–1159. | 10.1016/j.annonc.2020.06.004 |
| Chan JK, et al. **Selecting new upfront regimens for advanced ovarian cancer with biomarker guidance**. Gynecol Oncol. 2020;159(3):604–606. | 10.1016/j.ygyno.2020.09.017 |
| Haunschild CE, Tewari KS. **The current landscape of molecular profiling in the treatment of epithelial ovarian cancer**. Gynecol Oncol. 2020:S0090-8258(20)33953-6. | 10.1016/j.ygyno.2020.09.043 |
| Byrum AK, et al. **Defining and Modulating 'BRCAness'**. Trends Cell Biol. 2019;29(9):740–751. | 10.1016/j.tcb.2019.06.005 |
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| Lheureux S, et al. **Epithelial ovarian cancer: Evolution of management in the era of precision medicine**. CA Cancer J Clin. 2019;69(4):280–304. | 10.3322/caac.21559 |

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