



# Homologous recombination deficiency in epithelial ovarian cancer

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**Summary** Since the introduction of poly-ADP-ribose polymerase (PARP) inhibitor therapy for epithelial ovarian cancer (EOC) patients, testing for aberrations of homologous recombination (HR) repair as a predictive biomarker of therapy response has become an area of particular clinical interest. As HR represents a crucial repair pathway of otherwise possibly lethal DNA double strand breaks, its deficiency triggers a phenotypic behavior of tumor cells resulting in the accumulation of genetic damage. PARP inhibitors target this emerging genomic instability by fostering DNA strand breaks. Whereas testing for mutations of the tumor-suppressor genes *BRCA 1* and *BRCA 2* as a pivotal part of the HR apparatus has entered clinical routine, approximately 30% more high-grade EOC patients harbor aberrations of the HR pathway other than *BRCA* mutations and may therefore respond to PARP inhibition therapy. In recent years, several double-blind, placebo-controlled trials investigating sizeable patient cohorts have reported positive results of PARP inhibitor therapy response in HR-positive patient subgroups. Therefore, introducing HR testing in both the primary and recurrent setting as a biomarker for PARP inhibitor response may expand the range of patients who may profit from this therapeutic option beyond *BRCA*-mutated tumors.

**Keywords** Ovarian cancer · PARP inhibitor · Homologous recombination · Double strand break

## Abbreviations

DSB	Double strand breaks
EOC	Epithelial ovarian cancer
HR	Homologous recombination repair
HRd	Homologous recombination repair deficient
PARP	Poly-ADP-ribose polymerase
PFS	Progression-free survival

## Rationale of homologous repair deficiency in epithelial ovarian cancer

DNA double strand breaks (DSB) are considered to be among the most cytotoxic DNA lesions, triggering chromosomal aberration and ultimately cell death if not adequately repaired. The ability to restore DSBs depends on the activity of the homologous recombination repair (HR) apparatus, which copies the respective undamaged, homologous DNA of the sister chromatid to reconstruct the corrupted double strand during S and G2 phase. The functionality of this apparatus relies on the interaction of a complex set of proteins, such as the gene products of *BRCA 1*, *BRCA 2* and *RAD 51*, among others. Any dysfunctional protein involved may induce phenotypical HR deficiency, as around 20% of all high-grade serous epithelial ovarian cancers (EOC) are observed to harbor a *BRCA 1* or *BRCA 2* germline or somatic mutation. Approximately 30% more, however, show *BRCA* wild-type status, but are associated with alterations of the HR apparatus which result in the phenotypical deficient cell behavior [1]. If HR fails, the process is ended by so-called non-homologous end joining, an error-prone process of random end-to-end fusion of damaged strands, leading to information loss and subsequently genomic instability. HR deficient (HRd) cells refer DSBs to non-homologous end joining more often and are therefore more likely to suffer fatal DNA damage. Introduction of poly-ADP-ribose polymerase (PARP)

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**Table 1** Recent clinical trials assessing homologous recombination deficiency in ovarian cancer

Author	Study name	Agent	Phase/Size	Patient cohort	BRCAm tumors treatment vs. placebo PFS (months, 95% CI)	HRd tumors treatment vs. placebo PFS (months, 95% CI)
Coleman et al. (2017) [8]	ARIEL-3	Rucaparib 600 mg BID	Phase III n= 564	Recurrent disease, platinum sensitive	16.6 vs. 5.4 months <sup>a</sup> HR 0.23 (0.16–0.34)	13.6 vs. 5.4 months <sup>c</sup> HR 0.32 (0.24–0.42)
Mirza et al. (2016) [9]	NOVA	Niraparib 300 mg qDay	Phase III n= 553	Recurrent disease, platinum sensitive	21.0 vs. 5.5 months <sup>b</sup> HR 0.27 (0.17–0.41)	12.9 vs. 3.8 months <sup>e</sup> HR 0.38 (0.24–0.59)
Ray-Coquard et al. (2019) [13]	PAOLA-1	Olaparib 300 mg BID + bevacizumab 15 mg/kg qw3	Phase III n= 806	First line, platinum sensitive	37.2 vs. 21.7 months <sup>a</sup> HR 0.31 (0.20–0.47)	37.2 vs. 17.7 months <sup>a</sup> HR 0.33 (0.25–0.45)
González-Martín et al. (2019) [11]	PRIMA ENGOT-OV26 GOG-3012	Niraparib 300 mg qDay	Phase III n= 733	First line, platinum sensitive	19.6 vs. 8.2 months <sup>a</sup> HR 0.50 (0.31–0.83)	22.1 vs. 10.9 months <sup>d</sup> HR 0.40 (0.27–0.62)
Coleman et al. (2019) [12]	VELIA GOG-3005	Veliparib 150/300/400 mg BID	Phase III n= 1140	First line	34.7 vs. 22.0 months <sup>a</sup> HR 0.44 (0.28–0.68)	31.9 vs. 20.5 months <sup>d</sup> HR 0.57 (0.43–0.76)

<sup>a</sup>BRCAm BRCA mutated, *HR* (95%CI) hazard ratio (95% confidence interval), *HRd* homologous recombination repair deficient, *PFS* progression-free survival  
<sup>b</sup>BRCAm was defined as a detected germline or somatic mutation of the BRCA 1 and/or BRCA 2 gene  
<sup>c</sup>BRCAm was defined as a BRCA 1 and/or 2 germline mutation  
<sup>d</sup>HRd was defined as a detection of a whole-genome loss of heterozygosity of at least 16% in a next-generation sequencing assay  
<sup>e</sup>HRd was defined as a tumor score of ≥42 on the myChoice HRD Plus assay (Myriad Genetics) and/or BRCA tumor or germline mutation  
<sup>f</sup>HRd was defined as a tumor score of ≥42 on the myChoice HRD Plus assay (Myriad Genetics) and and/or BRCA tumor mutation

inhibitors rendered HR repair both a possible target and biomarker in the treatment of EOC. As HRd cancer cells are more sensitive to lesser DNA damages favoring subsequent DSBs, PARP inhibition-induced excess of single strand breaks leads to accumulation of DSB HRd tumor cells cannot repair [2].

### Defining and diagnosing homologous recombination deficiency

Whereas testing *BRCA* mutation status as a predictive biomarker for response to PARP inhibition has entered clinical routine, selecting *BRCA* wildtype patients who express an HRd phenotype poses a clinical challenge. Sometimes termed BRCAness, manifold steps of the HR pathway apart from *BRCA* mutations may contribute to its deficiency and therefore have to be considered for testing. Three methodically different approaches to test for HR deficiency have been proposed to date:

First, “genomic scarring” assays aim to quantify large genomic aberrations by next generation whole genome sequencing. Whereas the “CDx BRCA LOH” (Foundation Medicine, Cambridge, MA, USA) detects the percentage of loss of heterozygosity throughout the genome as well as mutations in *BRCA 1* or *BRCA 2*, the “myChoice” HR deficiency test (Myriad Genetics Inc., Salt Lake City, UT, USA) calculates a score based on the presence of loss of heterozygosity, large scale transitions, telomeric allelic imbalance. All trials depicted in Table 1 relied on genomic scarring assays [3]. Second, big data analyses of somatic point mutations and large-scale genomic alterations allow for the definition of gene signatures characteristic for HRd carcinoma. The so-called HRDetect test was designed upon such gene signature analyses and thereby detects *BRCA* pathway-related HRd tumors with high

sensitivity [4]. Third, assessing point mutations in HR deficiency-related genes using DNA sequencing panels combined with immunostaining of respective genes may be predictive for HR deficiency, e.g. *RAD51* expression as a crucial step of HR. Approaches solely depicting *BRCA* pathway-related HR deficiency, however, may be of limited clinical applicability since they may fail to identify tumors with functional mutations in other HR deficiency-related genes, such as *ATM*, *CHEK* and *ATR* [5].

Whereas several approaches of detecting HR deficiency are available, no specific assay may be generally recommended since all proposed methods lack broad prospective validation. Advantages and limitations of each assay should be considered carefully according to the specific clinical question and the framework conditions of the respective center.

### Recent clinical trials assessing homologous recombination deficiency in ovarian cancer

As depicted in Table 1, several prospective trials evaluating clinical efficacy of PARP inhibitors in sizeable cohorts provide evidence on survival benefits for progression-free survival (PFS) in patients with HRd EOC in both the first-line and recurrent setting. Heterogeneous definitions of HR deficiency, *BRCA*-mutated study subgroups and different methods of HR deficiency assessment pose a challenge if study results are to be compared directly or translated into clinical practice. Other large trials evaluating PARP inhibitor efficacy such as SOLO-2 or Study 19 did not assess HR deficiency and were therefore not considered for the present review [6, 7].

The ARIEL-3 trial, a phase 3, randomized, double-blind study of rucaparib 600 mg BID maintenance in a cohort of 564 patients with recurrent, platinum

sensitive high-grade serous or endometrioid EOC observed a significantly increased PFS of 13.6 months for patients with HRd tumors in the treatment arm versus 5.4 months in the placebo arm (HR 0.32; 95%CI 0.24–0.42). In patients with BRCA-mutated tumors, PFS was 16.6 months in the treatment arm versus 5.4 months in the placebo arm (HR 0.23; 95%CI 0.16–0.34) [8].

This result was supported by the NOVA trial, a phase 3, randomized, double-blind study of niraparib 300 mg daily maintenance in a cohort of 553 patients with platinum sensitive high-grade serous EOC. For patients with HRd but germline BRCA wild-type tumors, authors reported a PFS of 12.9 months in the treatment arm compared to 3.8 months in the placebo arm (HR 0.38; 95%CI 0.24–0.59). In patients with BRCA germline-mutated tumors PFS was 21.0 months in the treatment arm versus 5.5 months in the placebo arm (HR 0.27; 95% CI 0.17–0.41) [9].

The QUADRA trial, a phase 2, single-arm study of niraparib 300 mg daily monotherapy in a cohort of 463 patients with platinum-sensitive high-grade serous EOC who received at least three prior lines of chemotherapy observed a median overall survival of 26.0 months (18.1–not estimable) in patients with BRCA-mutated tumors, 19.0 months (14.5–24.6) in patients with HRd tumors and 15.5 months (11.6–19.0) in HR proficient tumors, indicating HR deficiency to maintain its predictive value for response in heavily pretreated patients [10].

To date, three trials reported positive results for olaparib, niraparib, and veliparib in first-line maintenance therapy:

The PRIMA trial, a phase 3, randomized, double-blind study of 300 mg niraparib daily maintenance versus placebo in a cohort of 733 patients with response to first-line platinum-based chemotherapy for advanced high-grade serous or endometrioid EOC observed a PFS of 22.1 months in patients with HRd tumors in the treatment arm versus 10.9 months in the placebo arm (HR 0.40; 95%CI 0.27–0.62). In patients with BRCA-mutated tumors, PFS was 19.6 months in the treatment arm versus 8.2 months in the placebo arm (HR 0.50; 95%CI 0.31–0.83) [11].

The VELIA trial, a phase 3, randomized, double-blind study of veliparib 400 mg twice daily maintenance versus placebo in a cohort of 1140 patients with response to first-line platinum-based chemotherapy for advanced high-grade serous EOC observed a PFS of 31.9 months in patients with HRd tumors in the treatment arm versus 20.5 months in the placebo arm (HR 0.57; 95%CI 0.43–0.76). In the BRCA mutated cohort, PFS was 34.7 months in the treatment arm versus 22.0 months in the placebo arm (HR 0.44; 95%CI 0.28–0.68) [12].

The PAOLA-1 trial, a phase 3, randomized, double-blind study of a combinatory olaparib 300 mg twice daily versus placebo and bevacizumab 15 mg/kg q3weeks maintenance therapy in a cohort of 806

patients with response to first-line platinum-based chemotherapy for advanced platinum-sensitive high-grade serous EOC reported in patients with HRd tumors a PFS of 37.2 months in the olaparib arm compared to 17.7 months in the control arm (HR 0.38; 95% CI 0.24–0.45). In patients with BRCA-mutated tumors, PFS was 37.2 months in the treatment arm versus 21.7 months in the placebo arm (HR 0.31; 95%CI 0.20–0.47) [13].

Of note, no clinical evidence exists for PARP inhibitor therapy in other histologic EOC subtypes to date. Since associated by different driver mutations and rarely harboring HR deficiency, they were not included into recent studies for PARP inhibitor efficacy [14, 15].

HR deficiency testing appears to be a promising predictive biomarker for the efficacy of PARP inhibitor therapy in high-grade serous EOC patients in the first-line and recurrent setting. Since patients without HRd tumors also seem to benefit from PARP inhibition to some extent, it may be assumed that HRd assays lack accuracy or do not depict certain tumors with non *BRCA* pathway-related HRd phenotypes [11]. Nevertheless, introducing HRd testing in addition to *BRCA* mutation analysis for both primary and recurrent therapy may thereby aid greatly to select patients who will most likely profit from PARP inhibitor therapy.

### Future prospects of PARP inhibitor combination trials

The combined use of PARP inhibitors with other active agents is of increasing interest in the treatment of EOC. Relating to the positive results of the PAOLA-1 trial, it has been hypothesized that antiangiogenic agents induce a hypoxic environment, resulting in down-regulation of genes of HR [16, 17]. Thereby, tumor cells otherwise not sensitive to PARP inhibition could be sensitized and a synergistic activity could be exploited. Particularly, the oral VEGF inhibitor cediranib showed promising results in a 2019 phase II study by Liu et al. [18]. A combination of 30 mg cediranib daily with 200 mg olaparib twice daily compared to 400 mg olaparib twice daily only in relapsed platinum-sensitive ovarian cancer including 90 patients reported significant prolonged overall survival of 37.8 versus 23.0 months in patients with BRCA-mutated tumors. However, no HRd subgroup analysis has been published to date. To address this question, the phase III trial ICON-9 (NCT03278717) is currently evaluating a combination of cediranib with olaparib in relapsed platinum-sensitive ovarian cancer. Final results, however, are not expected before the year 2023.

### Take home message

HR deficiency defines a subset of high-grade serous EOC patients who are most likely to benefit from PARP

inhibitor therapy in the first-line and recurrent setting. Thereby, the scope of targeting solely *BRCA*-mutated tumors may be expanded significantly to approximately 50% of all high-grade EOC patients. Whereas different approaches of testing for HR deficiency are available to date, further research will be necessary to improve HR assay accuracy. Moreover, combining PARP inhibitors with antiangiogenic agents seems to be a promising concept which may expand the indication of PARP inhibition even beyond current HR deficiency.

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