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Patients with Biallelic BRCA1/2 Inactivation Respond to Olaparib Treatment Across Histologic Tumor Types

Hanneke van der Wijngaart^{1,2}, Louisa R. Hoes^{2,3}, J. Maxime van Berge Henegouwen^{2,4}, Daphne L. van der Velden⁵, Laurien J. Zeverijn^{2,3}, Paul Roepman⁶, Erik van Werkhoven⁷, Wendy W.J. de Leng⁸, Anne M.L. Jansen⁸, Niven Mehra⁹, Debbie G.J. Robbrecht¹⁰, Mariette Labots¹, Derk Jan A. de Groot¹¹, Ann Hoeben¹², Paul Hamberg¹³, Hans Gelderblom⁴, Emile E. Voest^{2,3}, and Henk M.W. Verheul⁹



ABSTRACT

Purpose: To assess the efficacy of olaparib, a PARP inhibitor (PARPi) in patients with tumors with *BRCA1/2* mutations, regardless of histologic tumor type.

Patients and Methods: Patients with treatment-refractory *BRCA1/2*-mutated cancer were included for treatment with off-label olaparib 300 mg twice daily until disease progression or unacceptable toxicity. In Drug Rediscovery Protocol (DRUP), patients with treatment-refractory solid malignancies receive off-label drugs based on tumor molecular profiles while whole-genome sequencing (WGS) is performed on baseline tumor biopsies. The primary endpoint was clinical benefit (CB; defined as objective response or stable disease \geq 16 weeks according to RECIST 1.1). Per protocol patients were enrolled using a Simon-like two-stage model.

Results: Twenty-four evaluable patients with nine different tumor types harboring *BRCA1/2* mutations were included, 58%

had CB from treatment with olaparib. CB was observed in patients with complete loss of function (LoF) of *BRCA1/2*, while 73% of patients with biallelic *BRCA* LoF had CB. In 17 patients with and seven without current labeled indication, 10 and four patients had CB, respectively. Treatment resistance in four patients with biallelic loss might be explained by an additional oncogenic driver which was discovered by WGS, including Wnt pathway activation, *FGFR* amplification, and *CDKN2A* loss, in three tumor types.

Conclusions: These data indicate that using PARPis is a promising treatment strategy for patients with non-*BRCA*-associated histologies harboring biallelic *BRCA* LoF. WGS allows to accurately detect complete LoF of *BRCA* and homologous repair deficiency (HRD) signature as well as oncogenic drivers that may contribute to resistance, using a single assay.

Introduction

Homologous recombination repair (HRR) is a crucial DNA repair pathway, essential for the repair of DNA double-strand breaks (DSBs; ref. 1) that the genome is continuously subjected to (2). It allows for

error-free restoration of DNA integrity and sequence, even when the genomic damage is extensive. The breast cancer susceptibility genes *BRCA1* and *BRCA2* are two of the most extensively studied tumor suppressor genes and are key players in the homologous recombination (HR) pathway (3). Deleterious alterations in *BRCA1* or *BRCA2*, both germline (4–6) and somatic (7, 8), result in deficient HRR (dHRR; refs. 9, 10) and a high risk of developing cancer. dHRR due to biallelic loss of function (LoF) mutations in *BRCA1* or *BRCA2* is seen in 4.9% of patients with cancer across tumor types (11–13).

Tumor cells with dHRR can be specifically targeted by drugs inducing multiple DNA strand breaks. Inhibitors of PARP specifically target the weakness of dHRR tumor cells (14–16) by synthetic lethality (17, 18) leading to selective cytotoxicity and apoptosis.

Olaparib, an oral inhibitor of *PARP1*, is approved by the FDA and European Medicines Agency (EMA) for several indications, among which the maintenance treatment of ovarian, fallopian tube, and primary peritoneal cancer with germline or somatic *BRCA* mutations after response to first-line platinum-based chemotherapy and, regardless of *BRCA* status, for recurrent ovarian, fallopian tube, and primary peritoneal cancer after response to platinum-based chemotherapy. Olaparib was most recently approved as monotherapy for patients with metastatic castration-resistant prostate cancer with germline or somatic *BRCA* mutations (EMA) and mutations in other homologous repair deficiency (HRD) genes (FDA; refs. 19–21). Several other PARP inhibitors (PARPis) have been registered for the treatment of epithelial ovarian, fallopian tube, and primary peritoneal cancer (rucaparib, ref. 22; niraparib, ref. 23) and gBRCAm breast cancer (talazoparib; ref. 24).

The majority of the phase II to III clinical trials performed focused on efficacy of PARPi monotherapy in *BRCA*-associated cancer types,

¹Department of Medical Oncology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands. ²Oncode Institute, Utrecht, the Netherlands. ³Department of Molecular Oncology & Immunology, Netherlands Cancer Institute, Amsterdam, the Netherlands. ⁴Department of Medical Oncology, Leiden University Medical Center, Rapenburg, Leiden, the Netherlands. ⁵Department of Radiology and Nuclear Medicine, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands. ⁶Hartwig Medical Foundation, Amsterdam, the Netherlands. ⁷Department of Biometrics, Netherlands Cancer Institute, Amsterdam, the Netherlands. ⁸Department of Pathology, University Medical Center Utrecht, Utrecht, the Netherlands. ⁹Department of Medical Oncology, Radboud University Medical Center, Nijmegen, the Netherlands. ¹⁰Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands. ¹¹Department of Medical Oncology, University Medical Center Groningen, Groningen, the Netherlands. ¹²Department of Medical Oncology, Maastricht University Medical Center, Maastricht, the Netherlands. ¹³Department of Internal Medicine, Franciscus Gasthuis and Vlietland, Rotterdam, the Netherlands.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

Corresponding Author: Henk M.W. Verheul, Department of Medical Oncology, Radboud University Medical Center, P.O. Box 9101, Nijmegen 6500 HB, the Netherlands. Phone: 31-24-3610353; E-mail: henk.verheul@radboudumc.nl

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Translational Relevance

In tumors with *BRCA1/2* mutations, homologous repair deficiency (HRD) causes inability to repair DNA double-strand breaks. PARP inhibitors (PARPis) specifically target this weakness of tumor cells by disabling single-strand break repair, leading to accumulation of double-strand breaks causing selective cytotoxicity. PARPis have already proven to be effective in *BRCA*-mutated ovarian, breast, pancreatic, and prostate cancer. We hypothesized that olaparib may also be effective in other tumor types with *BRCA1/2* mutations and found that biallelic inactivation of *BRCA1/2* is important for selecting patients with non-*BRCA*-associated histologies to reach treatment benefit. These results support the clinical value of whole-genome sequencing (WGS) of tumor tissue for treatment selection in patients with cancer.

In the ongoing Drug Rediscovery Protocol (DRUP, NCT02925234), patients are treated based on tumor molecular profiles with off-label targeted- or immunotherapy, while WGS is performed on baseline tumor biopsies. Here, we report the cohort “Olaparib for *BRCA1/2* mutated tumors.”

often only based on the presence of a germline *BRCA* mutation, and lacking detailed biomarker information such as confirmation of biallelic *BRCA* LoF in tumor tissue. Data on the effectivity of PARPis in patients with somatic *BRCA* mutations are scarce.

In the Drug Rediscovery Protocol (DRUP, NCT02925234; ref. 25) patients are being treated based on their tumor molecular profile with registered targeted treatments outside their labeled indications, systematically recording efficacy and safety data. Moreover, the DRUP creates opportunities for extensive biomarker analysis by performing whole-genome sequencing (WGS) on baseline tumor biopsies. Within DRUP, we initiated a cohort in which patients were treated with olaparib based on a germline or somatic *BRCA1* or *BRCA2* LoF genomic event. Patients with a malignancy for which olaparib was not available as standard treatment were considered for this cohort. We hypothesized that a PARPi may be an effective treatment option for patients with malignant tumors harboring *BRCA1/2* LoF mutations, both germline and somatic, independent of histology.

Here, we show that using PARPis is a potentially effective treatment strategy for patients with complete LoF of *BRCA1/2* in the DRUP cohort of 24 patients “Olaparib for tumors with a *BRCA1/2* mutation.” The importance of WGS, performed on baseline biopsies, is demonstrated by the correlation between complete LoF of *BRCA1/2* and clinical benefit from olaparib. WGS provides information on both germline and somatic mutations, and genomic mutational signatures, allowing for optimal patient selection using a single assay.

Patients and Methods

Study design

The DRUP is an ongoing prospective, multicenter, nonrandomized basket trial in which patients with advanced solid malignancies are being treated on the basis of their tumor molecular profile, with targeted- or immunotherapy outside their registered indications (25). The basket trial design allows for an unlimited number of parallel cohorts consisting of patients with the same histologic tumor type, molecular target (defined at gene level), and study drug. Patients enrolled in the histology-agnostic cohort “Olaparib for tumors with a *BRCA1* or *BRCA2* mutation” received olaparib tablets 300 mg twice

daily (26) in 28-day cycles until occurrence of disease progression or intolerable side effects. Dose reductions were allowed up to a minimum dose of 200 mg twice daily. Patients were enrolled in nine out of the 32 DRUP-participating hospitals in the Netherlands, between September 2016 and October 2019. To date, accrual in other cohorts of the DRUP is still ongoing.

This study is registered with ClinicalTrials.gov, number NCT02925234.

Patients

Adult patients with advanced solid malignancies, for which standard treatment options were exhausted, and with no option for on-label or phase III study treatment with PARPis, were enrolled. Expansion of the reimbursed indications of olaparib during the course of the trial resulted in exclusion of patients with the new “on-label” histologies from that moment on. Patients with those histologies who were already enrolled in DRUP were not excluded, but continued treatment within the trial and were included in the efficacy analysis. Preenrollment, patients needed to have a pathogenic, inactivating *BRCA1* or *BRCA2* mutation or deletion confirmed in their tumor tissue, identified using any validated genetic test within the context of routine diagnostics or using WGS in the context of the Dutch CPCT-02 study (27). At the start of the trial, confirmation of biallelic LoF of *BRCA* was not a requirement for eligibility yet. During the course of the trial, literature emerged reporting on the importance of complete LoF for response to PARPis. Therefore, we added biallelic LoF of *BRCA* as a second requirement for eligibility in this cohort. In all submitted cases, the variant was reviewed by two independent clinical molecular biologists, assessing the actionability of the variant. Actionable variants were homozygous deletions and inactivating biallelic somatic mutations or inactivating germline mutations with LOH. They advised the study team on the driver likelihood, after which the decision to include the patient was made by the study team.

For this cohort in DRUP, the general DRUP inclusion and exclusion criteria applied (25). Additionally, patients were not eligible if they had previously been treated with a PARPi, if they were immunocompromised, or if they had features suggestive of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Patients were considered evaluable for the primary endpoint if at least one cycle of olaparib was completed. Nonevaluable patients were excluded for the efficacy analysis, but included in the safety analysis.

The study is conducted in accordance with the International Conference of Harmonization of Good Clinical Practice and the Declaration of Helsinki, and was approved by the independent ethics committee and by the institutional review boards in every participating hospital. Patients provided written informed consent upon enrollment.

Study endpoints

The primary end point of this study is the clinical benefit rate (CBR), defined as confirmed complete or partial response or stable disease for 16 weeks or more, according to RECIST 1.1 and measured at least twice, at least 28 days apart in a particular cohort. Tumor response was reported by the local investigator in the electronic case record form (eCRF).

Tumor assessments were done at baseline and after every second treatment cycle. If patients were on treatment ≥ 6 months, tumor assessments were performed after every three cycles. Secondary endpoints include: objective response rate (ORR, defined as partial or complete response), duration of response, progression-free survival (PFS), overall survival (OS), and treatment related Common

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Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 adverse events. Exploratory endpoints include biomarker analysis on fresh frozen tumor biopsies.

Safety is assessed by documentation of serious and study treatment-related grade ≥ 3 adverse events according to CTCAE v.4.03, and followed up until 1 month after the last dose of study drug. Safety within the trial is monitored by an Independent Data Monitoring Committee (IDMC) who is blinded for response rates per cohort during accrual.

Statistical analysis

Cohorts are monitored using a Simon-like two-stage “admissible” monitoring plan (28, 29) to identify cohorts with evidence of activity. Clinical benefit (CB) of $\geq 30\%$ is considered of sufficient clinical interest to warrant further study in a confirmatory expansion cohort (stage III within the DRUP; ref. 30). The cohorts are evaluated in a two-stage design, if there would be no patients with CB in the first eight participants in the cohort, the cohort would be closed. Otherwise, an additional 16 patients would be included in the cohort. Four or fewer patients with CB out of 24 would suggest a lack of (clinically meaningful) activity, whereas 5 or more patients with CB would suggest that further investigation of the drug in the tumor/variant cohort is warranted. The null hypothesis and alternative hypothesis to be tested are defined as CBR of 10% versus $\geq 30\%$. This monitoring rule has 85% power to reject the null hypothesis of a CBR of 10% when the true CBR is 30%, with a one-sided alpha error rate of 7.8%. Exact 95% confidence intervals (CIs) were calculated using the Clopper–Pearson method.

Baseline tumor biopsies and biomarker analysis

At baseline, a new fresh frozen tumor biopsy was obtained from each patient. Biopsies were harvested and collected by the participating hospitals and sent to the Hartwig Medical Foundation (HMF), together with a 10-mL blood sample to determine the background variation of the germline DNA of the patient. For WGS, a minimum tumor-cell percentage of 30% is required. A 6- μm section was collected for hematoxylin and eosin (H&E) staining and estimation of tumor cellularity by an experienced pathologist. If the sample tumor cellularity was $\geq 30\%$ and the DNA yield was ≥ 300 ng, WGS was performed.

WGS data were analyzed using an optimized, high-quality bioinformatic pipeline (31), and per patient a summarizing report of all relevant findings was created, including information on tumor purity, ploidy, somatic variants, copy-number variations, mutational load, and more complex genomic features such as gene fusions, Catalogue of Somatic Mutations in Cancer (COSMIC) mutational signatures (32) and microsatellite (in)stability. A Classifier of Homologous Recombination Deficiency (CHORD) for pancreatic HRD detection, as recently developed by HMF, was computed for each sample, hereafter referred to as “HRD score” (33). Biallelic status of point mutations and the driver likelihood were assessed as described in previously published work (31). All code and scripts used for analysis of the WGS data are available at GitHub (<https://github.com/hartwigmedical/>).

Before biomarker analysis was performed, all WGS samples (baseline study samples and preenrollment WGS samples) were reanalyzed using the most recent HMF bioinformatics pipeline, including computation of the HRD score for each sample. The investigators and an independent clinical molecular biologist reviewed the baseline biopsy WGS results and confirmed presence of the qualifying BRCA mutation, assessed biallelic status of BRCA LoF and explored other identified oncogenic-driver alterations. In cases where no baseline WGS

data were available (i.e., failed sequencing due to low tumor cellularity), the call for biallelic or mono-allelic BRCA LoF was made based on the preenrollment molecular data. If preenrollment WGS data was available, an HRD score was computed from that sample. Recent reports show a high spatiotemporal preservation of genomic-driver alterations (34) which justifies this approach.

Role of funding source

This investigator-initiated study receives funding from the Dutch Cancer Society (KWF), Barcode for Life and receives equal funding from a number of pharmaceutical companies, including AstraZeneca. WGS was performed free of charge at HMF. Study medication was made available free of charge by the manufacturer.

AstraZeneca had no role in the design or execution of the study and no influence on the study report.

Results

Accrual in the cohort “olaparib for tumors with a BRCA1 or BRCA2 mutation”

Between September 2016 and November 2019, 68 patients with advanced cancer harboring a BRCA1 or BRCA2 alteration, who had exhausted standard treatment options, were submitted to the study team for evaluation for potential study participation in the cohort “Olaparib for tumors with a BRCA1 or BRCA2 mutation.” Forty-five patients were approved by the study team to be screened for treatment with olaparib, 18 patients were ineligible for study participation (Supplementary Fig. S1). Twenty-seven patients with nine tumor types were found eligible and started study treatment, of which the majority (41%, $N = 11$) had prostate cancer. Nineteen patients were included despite their current labeled indication (prostate, $n = 11$; breast $n = 3$; ovarian, $n = 3$; and pancreatic cancer, $n = 2$), because at the time of enrollment PARPi treatment was still off-label and not reimbursed for their tumor type. Patients had a median number of four prior lines of systemic treatment (Table 1; Supplementary Table S1). The regimens varied greatly due to the different tumor types enrolled. Fifteen of 27 patients were treated with a platinum-containing regimen (carboplatin, $n = 11$; oxaliplatin, $n = 3$; and cisplatin, $n = 1$). Seven patients who were previously platinum resistant had clinical benefit of olaparib treatment. Three patients were not evaluable for the primary endpoint according to our protocol definition of evaluability and were excluded in the efficacy analysis (2 had clinical progression and rapid deterioration (within 4 weeks) before finishing the first complete cycle, one patient suffered from intolerable side effects and stopped study treatment after 6 days). All 27 patients who received at least one dose of study medication were included in the safety analysis. Baseline characteristics are presented in Table 1. Twenty-four patients were evaluated in the efficacy analysis. From here on, only the results and characteristics of these 24 patients are described.

Preenrollment molecular characteristics

Seventeen patients were included based on a BRCA2 mutation, and seven patients had a BRCA1 mutation. In 14 of 24 patients, the BRCA alteration was discovered by WGS, performed as part of the Dutch CPCT-02 study (27). In five patients, the target was found using an NGS panel (single molecular inversion probe–based sequencing analysis and/or multiplex ligation-dependent probe amplification). Four patients were included based on a germline test only, and in one patient, a germline test combined with two functional HRD tests was performed. This patient with breast cancer had a germline mono-allelic

Table 1. Baseline characteristics of patients enrolled in the cohort “Olaparib for tumors with a BRCA1 or BRCA2 mutation.”

	<i>n</i> = 27	
Gender		
Male	17	63%
Female	10	37%
Age (approximately at consent)		
Median (range)	57	(37–79)
WHO performance status		
WHO 0	7	26%
WHO 1	18	67%
Not available	2	7%
Primary tumor types		
Prostate cancer	11	41%
Breast cancer	4	15%
Pancreatic cancer	3	11%
Ovarian cancer	2	7%
Colorectal cancer	2	7%
Cholangiocarcinoma	2	7%
Renal cell carcinoma	1	4%
Adrenal gland carcinoma	1	4%
Endometrial cancer	1	4%
Number of prior systemic therapy lines		
Median (range)	4	(1–6) ^a

^aAll patients were required to have exhausted standard therapies, but six patients refused standard chemotherapy due to fear of toxicity. In addition, occasionally the treating physician had well-argued reasons to refrain from certain standard therapies (i.e., low response rate to standard therapies in specific patient subgroups).

BRCA2 c.9104A>C mutation that was classified as a variant of uncertain significance. Functional characterization of this variant using embryonic stem cell complementation showed 50% reduction in HR functionality (35). In addition, a Recombination Capacity (RECAP) test (36) showed negative RAD51 staining after *ex vivo* irradiation of the tumor tissue, which is highly suggestive of HRD. On the basis of these results, the study team granted a waiver to include the patient. Twelve patients had a germline *BRCA* mutation. Six of them also had a somatic event in *BRCA*, or LOH in tumor tissue, resulting in complete *BRCA* LoF. Twelve patients were included based only on somatic *BRCA* alterations. In six of them, complete LoF of *BRCA* was confirmed preenrollment or based on the baseline WGS data (Supplementary Table S1).

Baseline biopsies and WGS results

Baseline study biopsies were performed in 22 out of 24 patients. For two patients, a biopsy was not possible for medical reasons. Thirteen (59%) biopsies were successfully sequenced. Eight biopsies could not be sequenced due to a low tumor cellularity (<30%) and one was sequenced despite a tumor cellularity below the threshold, confirming the qualifying *BRCA* mutation, but HRD score and biallelic call could not be extracted (Supplementary Table S1).

From seven of 13 patients with successful baseline biopsy WGS, preenrollment WGS data were also available. Additionally, from eight patients with failed baseline study WGS, preenrollment WGS data were available, and from three patients no WGS data were available and information on biallelic status and HRD score from these patients could not be retrieved. Based on a consensus of findings from the preenrollment and the baseline study biopsies, 15 out of 24 patients had confirmed biallelic *BRCA* LoF and a high HRD score (Supplementary Table S1). In two patients with prostate cancer the call for

biallelic loss could not be made due to low tumor purity, but in one of them, the high HRD score suggests complete LoF of *BRCA2*. In six other patients, baseline WGS showed a low HRD score and only mono-allelic loss (*n* = 4) or no *BRCA* variant at all (*n* = 2, 9%; Supplementary Table S1).

Clinical benefit

Fourteen of 24 patients (58%, 95% CI, 37%–78%) had CB upon treatment with olaparib. The objective response rate was 29% (7/24 patients), median time on treatment was 5.8 months (95% CI, 1.8–9.2 months). At data cutoff (November 5, 2020), one patient was still on treatment. The median PFS in this cohort was 7 months (95% CI, 2–8 months) and the median OS was 13 months (95% CI, 7–NA months; Fig. 1). CB was observed across tumor types, including non-*BRCA* histologies such as cholangiocarcinoma, and in patients with both germline and somatic *BRCA* alterations (Fig. 2; Supplementary Table S1). In the group of patients with CB, the median treatment duration was 9.1 months (95% CI, 8.4–NA months). The difference in outcome between biallelic LoF of *BRCA1* and *BRCA2* was not statistically significant (Fisher exact value 0.2445).

CB was predominantly observed in patients with tumors harboring a biallelic LoF alteration of *BRCA1* or *BRCA2*, and with an HRD genomic signature, with few exceptions: one patient with prostate cancer had prolonged stable disease, while having no signs of genomic biallelic *BRCA* loss. The preenrollment molecular data showed a somatic *BRCA2* mutation with 24% variant allele frequency (VAF), while in the baseline study biopsy WGS data, no evidence of a *BRCA* alteration or HRD was found. As indicated before, the most likely cause of this discordance is tumor heterogeneity. It is known that patients with *BRCA*-associated tumor types can benefit from PARPi even if the tumor has only mono-allelic *BRCA* LoF (13). Another possible explanation for the clinical benefit in this patient may be that the dominant tumor clone indeed had a *BRCA2* alteration, in combination with a posttranslational silencing of *BRCA2*, resulting in functional HRD. CB was also observed in two patients whose details regarding biallelic LoF and HRD score were unknown. Both patients had *BRCA*-associated tumor types and were included based on a germline test only, with no WGS results available to confirm the target. None of the four patients with confirmed mono-allelic loss had CB. Of the 15 patients with confirmed biallelic *BRCA1/2* LoF, 11 had CB (73%).

Non-*BRCA*-associated histologies

Seven patients in this cohort had non-*BRCA*-associated tumor types. Of these, four (57%) had clinical benefit: two patients with cholangiocarcinoma, one with renal cell carcinoma, and one with endometrial cancer. WGS data showed biallelic LoF of *BRCA* (Supplementary Table S1). Three patients with non-*BRCA*-associated histologies had no benefit from olaparib. The WGS data from the two patients with colorectal cancer clearly showed no biallelic LoF of *BRCA* and no evidence of HRD. This suggests that the *BRCA* mutations found in these patients are likely neutral passenger mutations and a consequence rather than a cause of tumorigenesis, in line with previous reports (13). Both patients had *TP53*, *APC*, and *KRAS* mutations and one also had a *SMAD4* mutation. One patient with adrenal gland carcinoma had biallelic *BRCA* LoF and HRD, however, a *CTNNB1* (*β-catenin*) p.Ser45Pro mutation was found, suggestive for WNT pathway activation, which is a known mechanism of PARPi resistance via N⁶-methyladenosine modification of *FZD10* mRNA, correlating with increased HR activity and reduced PARPi sensitivity (37). Additionally, this patient had a *TP53* mutation and *RB1* deletion (Supplementary Table S1).

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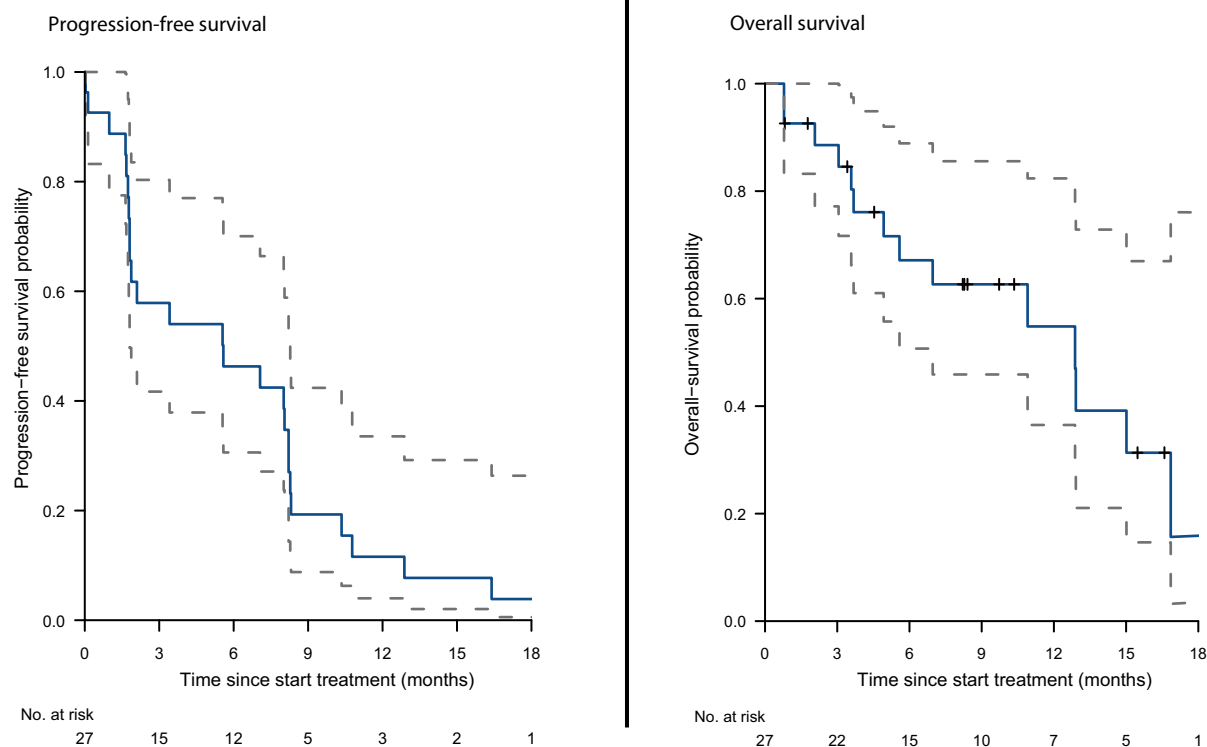


Figure 1. PFS and OS in the cohort "Olaparib for tumors with *BRCA1/2* mutations". Kaplan-Meier curves for estimated PFS (left) and OS (right), with 95% CI (dashed lines).

Lack of benefit due to other dominant non-HRD mutational processes

Apart from the patient with adrenal gland carcinoma described above, three other patients had no CB, despite having *BRCA*-associated tumor types, confirmed biallelic *BRCA* LoF and a high HRD score. We analyzed WGS data to search for indicators of primary resistance to PARPi. In each patient, WGS analysis showed the presence of another (strong) oncogenic driver mutation that was not previously implied as possible PARPi resistance mechanism. One patient had breast cancer with an amplification (18 copies) of fibroblast growth factor receptor 1 (*FGFR1*), which is found in 6.9% to 19.7% of patients with metastatic breast cancer (31, 38) and has been reported as a possible driver alteration and potential therapeutic target in breast cancer (39–41). Another patient with pancreatic cancer had a homozygous loss of *CDKN2A* and a duplication of exons 3 to 6 of *TGFBR2*, likely leading to inactivation. *CDKN2A* (p16) is deleted or inactivated in 67% of patients with metastatic pancreatic cancer (31). If expressed, it compromises efficient *BRCA1*-dependent DNA repair (42) and it is associated with better radiosensitivity *in vitro* (43), while we hypothesize that the opposite may result in lower sensitivity to PARPi. Inactivation of *TGFBR2* may also contribute to decreased sensitivity to PARPi because active TGF β signaling in tumors enhances sensitivity to PARPi *in vitro* (44). In the third patient, also with pancreatic cancer, a *KEAP* p.Cys434* inactivating mutation, which is associated with drug resistance by regulation of expression of plasma membrane efflux pumps and detoxifying enzymes (45), and a *KRAS* p.Gly12Arg activating hotspot mutation were detected. *In vitro* cell line data have indicated a role of *KRAS* mutation for PARPi resistance (46), but the clinical relevance remains uncertain. In all these patients, it is likely

that the tumors were not dependent on *BRCA*, but rather on another dominant non-HRD mutational process.

Safety

Serious adverse events (SAEs) occurred in 37% of the enrolled patients (Table 2). No unexpected toxicity or CTCAE grade ≥ 4 events were reported. Review of SAEs by the IDMC raised no safety concerns.

Discussion

Precision medicine holds great promise for the future of patients with (advanced) cancer, but is hampered by many challenges, including target identification, prioritization and funding/reimbursement of biomarker identification and treatment, due to extremely low numbers of patients with similar molecular profiles. This makes established methods of randomized trials to generate solid evidence for determination of treatment benefit difficult. To circumvent this challenge, the innovative design of the DRUP allows evaluation of small groups of patients with rare cancer subtypes to determine the potential benefit of a targeted agent in a group of patients with a specific tumor molecular profile.

In patients with cancer harboring deleterious *BRCA1/2* mutations, regardless of histologic tumor type, we here report that olaparib monotherapy is an effective and tolerable treatment option, for both germline and somatic alterations. The majority of patients (58%) derived CB from olaparib treatment. CB was almost exclusively observed in patients who had biallelic *BRCA* LoF and a high HRD score, confirming the absence of a functional homologous-repair system. Posthoc selection of only those patients with confirmed biallelic loss of *BRCA1/2* ($N = 15$) revealed a CBR of 73% ($N = 11$).

Olaparib Is an Effective Treatment for BRCA-mutated Tumors

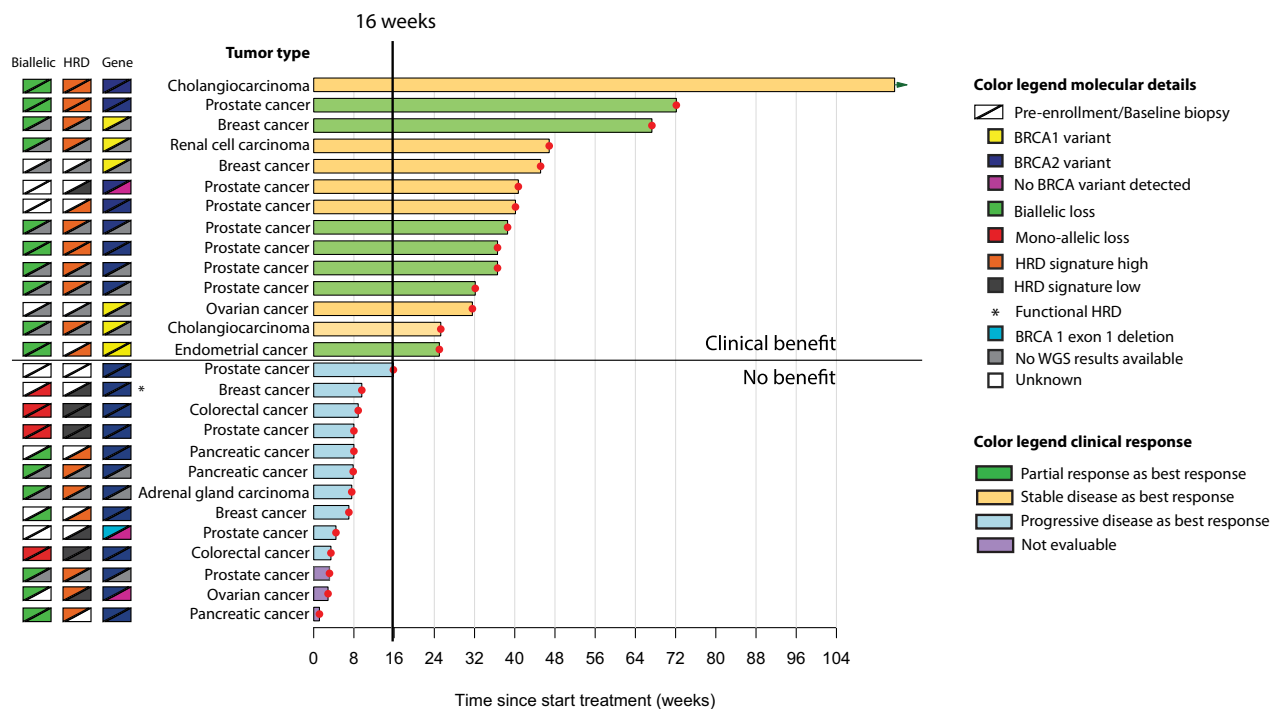


Figure 2.

Treatment efficacy of olaparib in patients with tumors harboring *BRCA1/2* alterations. Swimmer plot of the time on treatment (in weeks) for each patient ($n = 27$). Patients marked with an arrow were still on treatment (as per November 5th, 2020). On the left side of the figure, the molecular tumor profiles of pre-enrollment biopsies and DRUP baseline-study biopsies and the histologic tumor types are annotated.

A considerable proportion of patients in this cohort had *BRCA*-associated tumor types (i.e., prostate, ovarian, breast, and pancreatic cancer), of which we now know that olaparib is an effective treatment option (47–51). Ten out of 15 evaluable patients with *BRCA*-associated histologies had CB, which may in part contribute to the success of the cohort. Seven of 24 patients had non-*BRCA*-associated tumor types, of whom four (57%) had clinical benefit (Supplementary Table S1). These results indicate that patients with tumor types other than the known

BRCA associated histologies can benefit from treatment with PARPis, provided that they have biallelic LoF of *BRCA*, resulting in HRD. It also emphasizes the importance of extensive molecular tumor profiling by means of WGS or large-panel sequencing for all patients. Small tumor-specific sequencing panels would, in all seven patients in this cohort, not have identified the *BRCA* mutations, as *BRCA* diagnostics is not part of the regular reimbursed care for these tumor types.

An important limitation of this study is the small sample size of 24 patients. Nine different tumor types were enrolled in this histology-agnostic cohort, resulting in a heterogeneous population with large variations in biological tumor features and previous treatments. The number of patients per tumor type is low, there is a relative underrepresentation of patients with non-*BRCA*-associated tumor types and since some important tumor types (i.e., non-small cell lung cancer) are not represented in our cohort, the results cannot simply be extrapolated to all patients with cancer. Though we find a clinically relevant signal of activity here, confirmation of our findings in a larger cohort is essential, with special emphasis on patients with non-*BRCA* tumor types.

Six patients ultimately did not have biallelic *BRCA* loss (mono-allelic loss: $N = 4$; no *BRCA* variant: $N = 2$). In two patients with prostate cancer, the qualifying *BRCA* variant could not be reidentified in the baseline biopsy WGS data, the exact reason for this discordance is unclear. No evidence for reversion of HRD (for example due to platinum-based chemotherapy) was found in the WGS data. A possible explanation in both cases could be inter or intratumor heterogeneity. Alternatively, in the first patient the low VAF of 24% may suggest that *BRCA2* LoF was not the major driver of tumorigenesis and that the variant was lost in clonal evolution. However, the short time between

Table 2. SAEs in the cohort “Olaparib for tumors with a *BRCA1* or *BRCA2* mutation.”

SAE	N	Grade ≥ 3	
		N	%
Dehydration	1		3.7
Fatigue	2		7.4
Enterocolitis	1		3.7
Hydronephrosis	1		3.7
GGT increased	2		7.4
Spinal cord compression	1		3.7
Pain	2		7.4
Pneumonitis	1		3.7
Tachycardia	1		3.7
Anemia	1		3.7
Dyspnea	2		7.4
Pulmonary embolism	1		3.7

Note: SAEs: 16 SAEs occurred in 10 of 27 patients. No grade ≥ 4 SAEs were reported. Grading according to CTCAE 5.0.

Abbreviation: GGT, gamma glutamyltransferase.

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preenrollment biopsy and baseline study biopsy did not support this. In the other patient with a *BRCA1* exon-1 deletion, an alternative explanation could be that the deletion of exon 1, which is located outside the open reading frame and contains the *BRCA1* promoter, could not be picked up by the bioinformatics pipeline. However, the low HRD score suggests that there was no functional HRD, which points toward the more likely hypothesis of tumor heterogeneity. In three other patients, the information regarding biallelic status of *BRCA* could not be retrieved. In the early days of the trial, confirmation of complete LoF of *BRCA* was not a requirement for eligibility. The initial inclusion of patients without complete LoF of *BRCA1* or *BRCA2* in this cohort may be considered a weakness but we regard it as an unintentional strength, as it underlines the importance of a sharply defined biomarker. Our data illustrate the contrast between the groups with and without complete LoF, in terms of CB to PARPi treatment (73% versus 17%). Clearly, this study is not powered to demonstrate a significant difference between these subgroups within the cohort due to the small number of patients. However, we noted this as an interesting signal that warrants confirmation in a larger independent cohort. Currently, pathologists and molecular biologists struggle to reliably call loss-of-heterogeneity and biallelic *BRCA* LoF using the available standard large NGS panels. Experts are able to circumvent some of the struggles by adding a custom design of polymorphous single-nucleotide polymorphisms (SNPs) around the *BRCA1/2* genes, but this requires experience and expertise that is not widely available yet, and an uncertainty margin remains when NGS panels are used, especially for samples with lower tumor percentages. Due to the reliable detection of tumor purities, WGS facilitates the diagnostic process by accurately informing physicians on tumor-specific biallelic LoF of *BRCA1/2* and HRD, as well as on the presence of additional mutations potentially causing resistance to PARPis, using a single assay. Prompt availability of this information allows for better patient selection for treatment with PARPis, preventing overtreatment of patients who will likely not benefit.

The availability of WGS data also allowed to explore possible reasons for unexplained lack of clinical benefit upon PARPi treatment in patients with HRD and biallelic *BRCA* LoF. As described, in the four patients who had no CB despite having a favorable HRD molecular profile, another dominant non-HRD mutational process was identified as possible explanation for the lack of benefit. Pan-cancer, it is known that tumors have a mean number of 5.7 candidate genomic driver events per patient (31), likely occurring at different stages of tumor evolution. Some tumors may have multiple drivers occurring as early events in tumor development. In tumors with HRD, not responding to PARPis, one could also hypothesize that biallelic *BRCA* LoF and HRD may simply manifest as a consequence of genomic instability rather than being an early driving genomic event, especially in late-stage cancers such as in our cohort. Although we did find potential underlying tumor biology contributing to resistance in these patients, it is still hypothetical and needs further investigation.

Although an association between clinical benefit from olaparib and platinum sensitivity has been described (52, 53), we here found that platinum-refractory tumors can still respond to PARPi treatment. Seven out of 12 patients previously treated with platinum-containing chemotherapy had CB upon olaparib treatment; one patient was primary resistant to carboplatin, which indicates that platinum-sensitivity alone may not be a good predictive biomarker for olaparib treatment outcome.

Baseline WGS was successfully performed on all biopsies that had sufficient tumor cellularity ($N = 15$; 60%). This is consistent with the

overall WGS success rate within DRUP (25) and within the Dutch CPCT-02 study (31). Currently, the minimum required tumor cellularity for clinical-grade WGS analysis has been further downscaled from 30% to 20% due to ongoing technical improvements and optimized data analysis (bioinformatics; ref. 54), resulting in a current successful analysis of 71% (55).

The CBR observed in this cohort needs confirmation in a larger independent cohort. Currently, we are preparing an expansion cohort within DRUP. After the first example of a third-stage cohort “nivolumab for MSI tumors,” which is the first pilot of the new Dutch personalized reimbursement model that has been previously described (30), negotiations with the manufacturer, payers, and health authorities are currently ongoing to work toward a second expansion cohort in DRUP to study olaparib in *BRCA1/2*-mutated tumors. On the basis of our current findings and previous reports (13), we have refined the qualifying biomarker to biallelic (somatic or germline) LoF of *BRCA1* or *BRCA2*, and only off-label tumor types (non-*BRCA* histologies) will be eligible. In this expansion cohort, the financial risk will be shared between the manufacturer of olaparib and the insurance companies. For the first 16 weeks of treatment, the study drug is provided by the manufacturer. Upon confirmation of clinical benefit at 16 weeks, the subsequent treatment will be reimbursed by the health care insurance on an individual basis while efficacy and safety data collection continues to ultimately support expansion of the existing labeled indications of the drug.

Conclusion

Olaparib is an effective treatment option for patients with cancer harboring somatic and germline deleterious *BRCA1/2* alterations regardless of tumor type, who exhausted other treatment options. The CBR in this cohort was 58%, and CB was predominantly observed in patients harboring tumors with biallelic LoF of *BRCA* and HRD. In patients with non-*BRCA*-associated tumor types, 57% had clinical benefit, suggesting PARPis as a promising treatment strategy and justifying a broad molecular diagnostic approach in all patients. In patients in this cohort who had complete LoF of *BRCA* and HRD in tumor tissue, but without clinical benefit of olaparib, another potential oncogenic driver was discovered by WGS. Further investigation and confirmation of this CBR in patients with non-*BRCA* histologies in an independent expansion cohort is warranted, and is currently in preparation within DRUP for patients with biallelic *BRCA* LoF.

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Authors' Contributions

H. van der Wijngaart: Data curation, formal analysis, investigation, visualization, writing—original draft, project administration. **L.R. Hoes:** Data curation, investigation, project administration, writing—review and editing. **J.M. van Berge Henegouwen:** Data curation, investigation, project administration, writing—review and editing. **D.L. van der Velden:** Data curation, investigation, project administration, writing—review and editing. **L.J. Zevenij:** Data curation,

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investigation, project administration, writing–review and editing. **P. Roepman:** Formal analysis, writing–review and editing. **E. van Werkhoven:** Data curation, software, formal analysis, visualization, methodology, writing–review and editing. **W.W.J. de Leng:** Formal analysis, writing–review and editing. **A.M.L. Jansen:** Formal analysis, writing–review and editing. **N. Mehra:** Resources, writing–review and editing. **D.G.J. Robbrecht:** Resources, writing–review and editing. **M. Labots:** Resources, writing–review and editing. **D.J.A. de Groot:** Resources, writing–review and editing. **A. Hoeben:** Resources, writing–review and editing. **P. Hamberg:** Resources, writing–review and editing. **H. Gelderblom:** Conceptualization, supervision, investigation, writing–review and editing. **E.E. Voest:** Conceptualization, supervision, funding acquisition, investigation, methodology, writing–review and editing. **H.M.W. Verheul:** Conceptualization, formal analysis, supervision, investigation, writing–original draft.

References

- Liang F, Han M, Romanienko PJ, Jasin M. Homology-directed repair is a major double-strand break repair pathway in mammalian cells. *Proc Natl Acad Sci U S A* 1998;95:5172–7.
- Hoeijmakers JH. DNA damage, aging, and cancer. *N Engl J Med* 2009;361:1475–85.
- Gudmundsdottir K, Ashworth A. The roles of BRCA1 and BRCA2 and associated proteins in the maintenance of genomic stability. *Oncogene* 2006;25:5864–74.
- Foulkes WD, Knoppers BM, Turnbull C. Population genetic testing for cancer susceptibility: founder mutations to genomes. *Nat Rev Clin Oncol* 2016;13:41–54.
- King MC, Marks JH, Mandell JB, New York Breast Cancer Study G. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 2003;302:643–6.
- Nielsen FC, van Overeem Hansen T, Sorensen CS. Hereditary breast and ovarian cancer: new genes in confined pathways. *Nat Rev Cancer* 2016;16:599–612.
- Cancer Genome Atlas Research N. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011;474:609–15.
- Robinson D, Van Allen EM, Wu Y-M, Schultz N, Lonigro RJ, Mosquera J-M, et al. Integrative clinical genomics of advanced prostate cancer. *Cell* 2015;161:1215–28.
- Moynahan ME, Chiu JW, Koller BH, Jasin M. Brca1 controls homology-directed DNA repair. *Mol Cell* 1999;4:511–8.
- Moynahan ME, Pierce AJ, Jasin M. BRCA2 is required for homology-directed repair of chromosomal breaks. *Mol Cell* 2001;7:263–72.
- Riaz N, Bleuca P, Lim RS, Shen R, Higginson DS, Weinhold N, et al. Pan-cancer analysis of bi-allelic alterations in homologous recombination DNA repair genes. *Nat Commun* 2017;8:857.
- Levy-Lahad E, Friedman E. Cancer risks among BRCA1 and BRCA2 mutation carriers. *Br J Cancer* 2007;96:11–5.
- Jonsson P, Bandlamudi C, Cheng ML, Srinivasan P, Chavan SS, Friedman ND, et al. Tumour lineage shapes BRCA-mediated phenotypes. *Nature* 2019;571:576–9.
- Farmer H, McCabe N, Lord CJ, Tutt ANJ, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005;434:917–21.
- Gallmeier E, Kern SE. Absence of specific cell killing of the BRCA2-deficient human cancer cell line CAPAN1 by poly(ADP-ribose) polymerase inhibition. *Cancer Biol Ther* 2005;4:703–6.
- Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 2005;434:913–7.
- Hartwell L. Theoretical biology. A robust view of biochemical pathways. *Nature* 1997;387:855,7.
- Kaelin WG Jr. The concept of synthetic lethality in the context of anticancer therapy. *Nat Rev Cancer* 2005;5:689–98.
- Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-Repair defects and olaparib in metastatic prostate cancer. *New Engl J Med* 2015;373:1697–708.
- Mateo J, Porta N, Bianchini D, McGovern U, Elliott T, Jones R, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* 2020;21:162–74.
- Sandhu SK, Hussain M, Mateo J, Fizazi K, Saad F, Shore N, et al. PROfound: Phase III study of olaparib versus enzalutamide or abiraterone for metastatic castration-resistant prostate cancer (mCRPC) with homologous recombination repair (HRR) gene alterations [abstract]. Late-Breaking Abstract Genitourinary Tumours, Prostate 2006; 30 Suppl 9:IX188–9.
- Coleman RL, Oza AM, Lorusso D, Investigators A. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial (vol 390, pg 1949, 2017). *Lancet* 2017;390:1948.
- González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *New Engl J Med* 2019;381:2391–402.
- Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee K-H, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *New Engl J Med* 2018;379:753–63.
- van der Velden DL, Hoes LR, van der Wijngaart H, van Berge Henegouwen JM, van Werkhoven E, Roepman P, et al. The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs. *Nature* 2019;574:127–31.
- Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017;18:1274–84.
- Bins S, Cirkel GA, Gadellaa-Van Hooijdonk CG, Weeber F, Numan IJ, Bruggink AH, et al. Implementation of a multicenter biobanking collaboration for next-generation sequencing-based biomarker discovery based on fresh frozen pretreatment tumor tissue biopsies. *Oncologist* 2017;22:33–40.
- Jung SH, Lee T, Kim K, George SL. Admissible two-stage designs for phase II cancer clinical trials. *Stat Med* 2004;23:561–9.
- Simon R. Optimal 2-stage designs for Phase-II clinical-trials. *Control Clin Trials* 1989;10:1–10.
- van Waalwijk van Doorn-Khosrovani SB, Pisters-van Roy A, van Saase L, van der Graaff M, Gijzen J, Sleijfer S, et al. Personalised reimbursement: a risk-sharing model for biomarker-driven treatment of rare subgroups of cancer patients. *Ann Oncol* 2019;30:663–5.
- Priestley P, Baber J, Lolkema MP, Steeghs N, de Bruijn E, Shale C, et al. Pan-cancer whole-genome analyses of metastatic solid tumours. *Nature* 2019;575:210–6.
- Forbes SA, Beare D, Boutselakis H, Bamford S, Bindal N, Tate J, et al. COSMIC: somatic cancer genetics at high-resolution. *Nucleic Acids Res* 2017;45:D777–D83.
- Nguyen L, Martens JWM, Van Hoeck A, Cuppen E. Pan-cancer landscape of homologous recombination deficiency. *Nat Commun* 2020;11:5584.
- Van De Haar J, Hoes LR, Roepman P, Cuppen E, Wessels LF, Voest EE. Genomic evolution of metastatic tumours under therapeutic pressure. *Ann Oncol* 2020;31:S274–S.
- Shimelis H, Mesman RLS, Von Nicolai C, Ehlen A, Guidugli L, Martin C, et al. BRCA2 hypomorphic missense variants confer moderate risks of breast cancer. *Cancer Res* 2017;77:2789–99.
- Naipal KAT, Verkaik NS, Ameziane N, van Deurzen CHM, ter Brugge P, Meijers M, et al. Functional ex vivo assay to select homologous

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- recombination-deficient breast tumors for PARP inhibitor treatment. *Clin Cancer Res* 2014;20:4816–26.
37. Fukumoto T, Zhu HR, Nacarelli T, Karakashev S, Fatkhutdinov N, Wu S, et al. N6-methylation of adenosine of Fzd10 mRNA contributes to parp inhibitor resistance. *Cancer Res* 2019;79:2812–20.
 38. Angus L, Smid M, Wilting SM, van Riet J, Van Hoeck A, Nguyen L, et al. The genomic landscape of metastatic breast cancer highlights changes in mutation and signature frequencies. *Nat Genet* 2019;51:1450–8.
 39. André F, Bachelot T, Campone M, Dalenc F, Perez-Garcia JM, Hurvitz SA, et al. Targeting FGFR with dovitinib (TKI258): preclinical and clinical data in breast cancer. *Clin Cancer Res* 2013;19:3693–702.
 40. Brunello E, Brunelli M, Bogina G, Calìo A, Manfrin E, Nottegar A, et al. FGFR-1 amplification in metastatic lymph-nodal and haematogenous lobular breast carcinoma. *J Exp Clin Cancer Res* 2012;31:103.
 41. Turner N, Pearson A, Sharpe R, Lambros M, Geyer F, Lopez-Garcia MA, et al. FGFR1 amplification drives endocrine therapy resistance and is a therapeutic target in breast cancer. *Cancer Res* 2010;70:2085–94.
 42. Wang L, Zhang P, Molkentine DP, Chen C, Molkentine JM, Piao H, et al. TRIP12 as a mediator of human papillomavirus/p16-related radiation enhancement effects. *Oncogene* 2017;36:820–8.
 43. Molkentine JM, Molkentine DP, Bridges KA, Xie T, Yang L, Sheth A, et al. Targeting DNA damage response in head and neck cancers through abrogation of cell cycle checkpoints. *Int J Radiat Biol* 2021;97:1121–8.
 44. Liu L, Zhou W, Cheng C-T, Ren X, Somlo G, Fong MY, et al. TGFbeta induces "BRCAness" and sensitivity to PARP inhibition in breast cancer by regulating DNA-repair genes. *Mol Cancer Res* 2014;12:1597–609.
 45. Singh A, Misra V, Thimmulappa RK, Lee H, Ames S, Hoque MO, et al. Dysfunctional KEAP1-NRF2 interaction in non-small-cell lung cancer. *Plos Med* 2006;3:1865–76.
 46. Sun C, Fang Y, Yin J, Chen J, Ju Z, Zhang D, et al. Rational combination therapy with PARP and MEK inhibitors capitalizes on therapeutic liabilities in RAS mutant cancers. *Sci Transl Med* 2017;9:eal5148.
 47. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med* 2020;382:2091–102.
 48. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012;366:1382–92.
 49. Moore K, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *New Engl J Med* 2018;379:2495–505.
 50. Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *New Engl J Med* 2017;377:523–33.
 51. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. *N Engl J Med* 2019;381:317–27.
 52. Fong PC, Yap TA, Boss DS, Carden CP, Mergui-Roelvink M, Gourley C, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol* 2010;28:2512–9.
 53. Jiang X, Li X, Li W, Bai H, Zhang Z. PARP inhibitors in ovarian cancer: Sensitivity prediction and resistance mechanisms. *J Cell Mol Med* 2019;23:2303–13.
 54. Roepman P, de Bruijn E, van Lieshout S, Schoenmaker L, Boelens MC, Dubbink HJ, et al. Clinical validation of whole genome sequencing for routine cancer diagnostics. *J Mol Diagn* 2021;23:816–33.
 55. Monkhorst K, Samsom K, Schipper L, Roepman P, Bosch L, de Bruijn E, et al. Validation of whole genome sequencing in routine clinical practice. *Ann Oncol* 2020;31:S784–S.

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Patients with Biallelic BRCA1/2 Inactivation Respond to Olaparib Treatment Across Histologic Tumor Types

Hanneke van der Wijngaart, Louisa R. Hoes, J. Maxime van Berge Henegouwen, et al.

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