

Niraparib in ovarian cancer: results to date and clinical potential

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Ther Adv Med Oncol

1–10

DOI: 10.1177/
1758834017718775

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Abstract: Ovarian cancer is the first cause of death from gynaecological malignancy. Germline mutation in *BRCA1* and *2*, two genes involved in the mechanisms of reparation of DNA damage, are showed to be related with the incidence of breast and ovarian cancer, both sporadic and familiar. PARP is a family of enzymes involved in the base excision repair (BER) system. The introduction of inhibitors of PARP in patients with *BRCA*-mutated ovarian cancer is correlated with the concept of synthetic lethality. Among the PARP inhibitors introduced in clinical practice, niraparib showed interesting results in a phase III trial in the setting of maintenance treatment in ovarian cancer, after platinum-based chemotherapy. Interestingly, was niraparib showed to be efficacious not only in *BRCA*-mutated patients, but also in patients with other alterations of the homologous recombination (HR) system and in patients with unknown alterations. These results position niraparib as the first PARP-inhibitor with clinically and statistically significant results also in patients with no alterations in *BRCA 1/2* and other genes involved in the DNA repair system. Even if the results are potentially practice-changing, the action of niraparib must be further studied and deepened.

Keywords: *BRCA* mutations, BRCAness, epithelial ovarian cancer, high-grade serous ovarian cancer, homologous recombination deficiency (HRD), niraparib, poly(ADP-ribose) polymerase inhibitors (PARPis), synthetic lethality concept, target therapy

Received: 20 February 2017; revised manuscript accepted: 9 June 2017

Introduction

Epithelial ovarian cancer (EOC) accounts for 90% of all ovarian tumours and typically presents in post-menopausal women.¹ It is the second most common malignant gynaecological disease and first cause of death from gynaecological malignancy.^{2,3}

According to histopathological characteristics and to next-generation sequencing, EOC has been found to consist of a complex set of diseases. Several genetic or epigenetic alterations, strategic for tumorigenesis and progression, have been identified in heterogeneous subsets of patients.⁴

For example, *BRCA* mutations are most commonly associated with HGSOC (high-grade serous ovarian cancer).⁵ *BRCA1* and *BRCA2* are well known tumour suppressor genes, involved in

the response to DNA damage. The prevalence of germline *BRCA* mutations (gBRCAm) in EOC has historically been estimated to be around 10–15%.⁶ Recent reports suggest that this may be an underestimated phenomenon, especially in women with HGSOC.⁷ The inhibition of PARP in the presence of homologous recombination deficiency (HRD) leads to cell death from gross genetic disarray due to a process called ‘synthetic lethality’.^{8,9}

The emergence of the DNA repair pathway as a rational target in various cancers led to the development of the PARP inhibitors (PARPis).¹⁰

Such data support the use of routine evaluation of *BRCA* status in all patients with HGSOC, regardless of family history. This expansion in *BRCA* testing will require changes to the traditional

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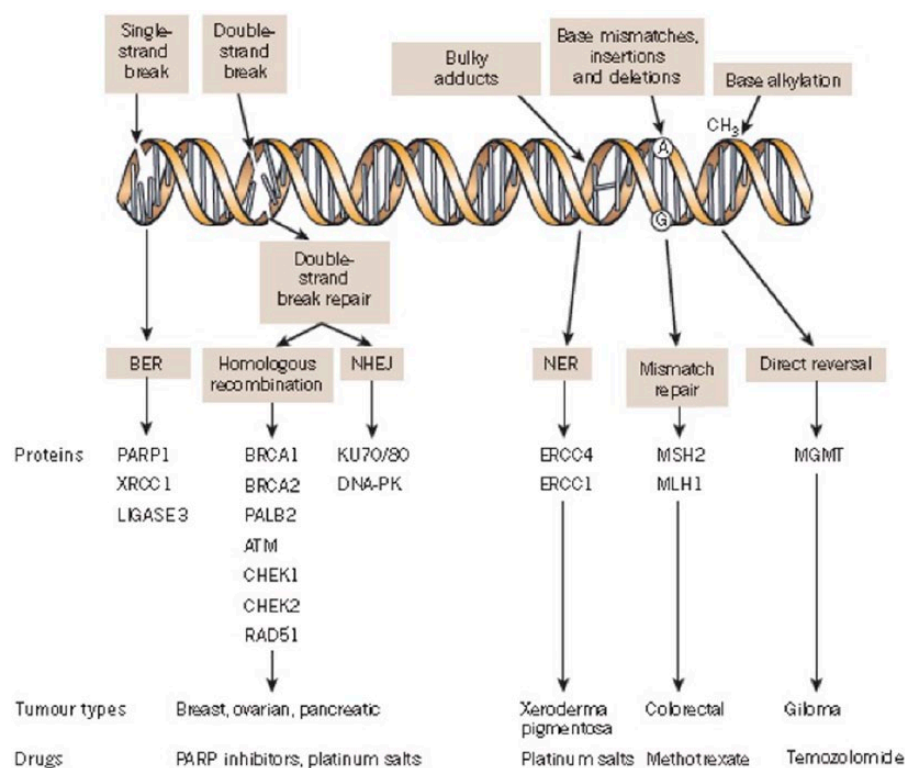


Figure 1. A panoply of DNA repair mechanisms maintains genomic stability. DNA is continually exposed to a series of insults that cause a range of lesions, from single-strand breaks (SSBs) to base alkylation events. The choice of repair mechanism is largely defined by the type of lesion, but factors such as the stage of the cell cycle also have a role. Key proteins involved in each DDR mechanism, the tumour types usually characterized by DDR defects and the drugs that target these defects are shown. Figure modified, with permission, from Lord and colleagues 2012.

BER, base excision repair; DDR, DNA damage response; NER, nucleotide excision repair; NHEJ, non-homologous end joining.

genetic service indications, because today patients are screened for and referred according to family history. This diagnostic change will lead to tailored genetic testing, according to definite germline characteristics.

Determining the molecular events driving HGSOC progression and diffusion could advance the understanding of tumorigenesis and facilitate individualized treatment strategies for this lethal disease.

BRCA and PARP role in the DNA stability system

DNA continually undergoes structural alterations. These alterations can be divided into: base modifications; single-strand breaks (SSBs); double strand breaks (DSBs); and intrastrand or interstrand crosslinks.¹¹ Fortunately, cells have evolved different mechanisms to maintain genomic integrity.¹²

There are at least five DNA repair mechanisms. Homologous recombination (HR) and non-homologous end joining (NHEJ) are responsible for DSB repair. The BRCA1 and BRCA2 proteins are important in maintaining genomic stability by promoting efficient and precise repair of DSB.^{13,14}

SSB repair mechanisms include base excision repair (BER), nucleotide excision repair (NER) and mismatch repair (MMR) pathways.¹⁵ The PARP family is involved in BER, which is the predominant pathway of the SSB repair system (Figure 1).¹⁶

Poly(ADP-ribose) polymerase (PARP) is a family of nuclear proteins that sense and bind to DNA SSB and subsequently activate the BER pathway by recruiting additional repair factors, modifying target proteins with ADP-ribose units. Of the 17 known members of the PARP superfamily in humans, PARP-1 accounts for

>90% of cellular DNA repair activity and remains the most studied.^{17,18}

When an SSB occurs, PARP-1 is recruited, undergoing a conformational change inducing the C-terminal catalytic domain to transfer ADP-ribose moieties from cellular (NAD⁺) to protein acceptors. This activation leads to addition of PAR chains, that results in a relaxation of chromatin and subsequent recruitment of DNA repair factors, such as XRCC1. XRCC1 is crucial for DNA repair, initially assembling and activating the BER machinery through the modification of several proteins such as histones and topoisomerases, but subsequently ‘switching off’ the BER machinery by decreasing the affinity of both histones and PARP-1 to DNA.¹⁹

In cases of small to moderate damage, PARP-1 allows restoration of the genomic integrity and the return to normal cellular function. However, emerging evidence has implicated PARP-1 overactivation in unregulated PAR synthesis, depleting NAD, and consequently ATP, eventually leading to widespread cell death.²⁰

PARP inhibitors in *BRCA*-mutated EOC and synthetic lethality concept

PARPis mediate their anti-cancer effects as catalytic inhibitors able to block repair of DNA SSBs by the BER/SSBR pathway. The initial clinical development of PARPis focused on their role as chemo-sensitizers, while their single-agent activity was unknown. Ten years ago, two articles published in *Nature* reported that *BRCA1/2* heterozygote or wild-type cell lines were 100- to 1000-fold less sensitive to PARP inhibitors than cells deficient in *BRCA1* and 2.^{8,9} The conclusion of both studies was that the *BRCA*-deficient cells were selectively sensitive to PARP inhibition by a mechanism of ‘synthetic lethality’: cancer cells are selectively sensitive to the inactivation of two genes or pathways when inactivation of either gene or pathway alone is non-lethal.²¹

If the cell cannot initiate HR, as is the case with *BRCA1/2*-mutant tumours, it resorts to more error-prone pathways, such as NHEJ or single-strand annealing, which can cause gross chromosomal mutations, growth inhibition and eventual cell death.²²

Then, patients with EOC with germline mutations in either *BRCA1* or *BRCA2* genes exhibit

impaired ability to repair DNA DSB *via* HR, and show a heightened sensitivity to inhibitors of the BER pathway.^{23,24}

Sometimes, sporadic EOC share pathological and clinical traits of *BRCA* mutation-associated cases, in the absence of a gBRCAm. This condition is termed ‘BRCAness’.^{23,25} Genes possibly involved in HR include *PALB2*, *RAD51C*, *RAD51D*, *BRIP1*, *BARD1*, *Chk2Mre11A*, *MSH6*, *NBN* and *RAD50*.^{25,26}

Niraparib in ovarian cancer treatment

Niraparib (MK-4827) is a potent PARP-1 and PARP-2 inhibitor, with *in vitro* IC₅₀ = 3.8 and 2.1 nM. Niraparib was shown to selectively inhibit proliferation of *BRCA1* and *BRCA2* deficient cell lines. Like for other PARPis, also niraparib induces cell cycle arrest in the G₂/M phase, followed by apoptosis and mitosis dysregulation. Correlations between niraparib, *BRCA* mutation status and DNA damage was evaluated in HGSOC patient-derived xenograft models. These xenograft model showed interesting results, both in niraparib monotherapy and niraparib maintenance after combination of niraparib and chemotherapy. Other genes, involved in HR mechanisms, seemed to be related with niraparib action.²⁷ Niraparib showed activity also in a CAPAN-1 pancreatic cancer xenograft model. In preclinical models, PARP-1/2 showed efficacy in combination with platinum, alkylating and methylation agents, radiation therapy and topoisomerase inhibitors.²⁸ Niraparib enhanced efficacy of radiation therapy in breast and lung cancer models.²⁹

The genomic analysis by the Cancer Genome Atlas evaluated the rate of mutations in 489 patients with HGSOC, finding 9% germline mutations in *BRCA1*, 8% germline mutations in *BRCA2* and 3% somatic mutations in both genes. Other significant mutations were highlighted in other HR genes: *EMSY* (8%), *PTEN* (7%), *RAD51* (3%), *ATM* or *ATR* (3%) and Fanconi anaemia genes (5%). Overall, HRD could be present in about half of HGSOC cases.³⁰ Other data from Pennington and colleagues showed the presence of germline and somatic loss-of-function mutations in 30 genes, involved in the HR pathway, in 390 cases of ovarian carcinoma. In this case, 367 individuals and 390 carcinomas were evaluated: 87 (24%) had a germline HR mutation; 32 (9%) had a somatic mutation. Four

Table 1. Published trials with niraparib.

Authors	Drug	Ph	Pts	Lines of therapy	BRCA status		PL Sens.	ORR (%)	mPFS (m)		
					Mt n (%)	Wt n (%)			Mt	Wt	HRD+
Sandhu and colleagues ³²	NIR	I	100	II–IV	29 (29)	71 (71)	S	40 (in gBRCAm)			
Mirza and colleagues ³³	NIR	III	372	III	136	231	S	Nr	21	9.3	12.9
	PLA		181		65 ()	114	S	Nr	5.5	3.9	3.8

gBRCAm, germline BRCA mutated; HRD+, homologous recombination deficiency positive; mPFS, median progression-free survival; Mt, mutated; NIR, niraparib; ORR, overall response rate; Ph, phase; PLA, placebo; Pts, patients; Wt, wild-type; PL Sens, Platinum sensitivity; S, sensitive.

patients (1.1%) had both a somatic and germline mutation. In particular, 68 mutations occurred in *BRCA1*, 23 in *BRCA2* and 32 in another 11 genes (*ATM*, *BARD1*, *BRIP1*, *CHEK1*, *CHEK2*, *FAM175A*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*, and *RAD51D*). Mutations of HR-related genes were present also in non-squamous ovarian cancer.³¹

Niraparib has been studied in a phase I dose-escalation trial.³² In part A of the trial, eligible patients had several kinds of malignancies, not suitable for standard treatments. Enrichment for germline *BRCA1* and *BRCA2* mutations was conducted prospectively, to detect whether administration of niraparib could be more effective in patients with defective HR function. Mutations were established using Myriad Genetics *BRCA* mutation testing. In part B of the trial only patients with sporadic platinum-resistant EOC and castration-resistant prostate cancer were enrolled. At the end of part A, 400 mg was found to be the maximum tolerated dose (MTD) due to grade 4 reversible thrombocytopenia; 300 mg was defined as the recommended dose in phase II trials, evaluated in an additional 10 patients. All toxicities were manageable and reversible.

Overall, 77 patients showed a response according to RECIST criteria. Among the patients in part A, 29 showed mutations in *BRCA1* or *BRCA2*. Twenty-two patients had ovarian cancer. Twenty of these 22 patients had measurable disease; partial response (PR) was observed in eight patients (40%), using doses between 80 mg and 400 mg. Three of nine patients with platinum-resistant EOC showed RECIST and Ca125 responses; another patient had stable disease (SD) for 120 days. Five patients of the 22 with *BRCA* wild-type serous ovarian cancer

achieved a durable PR. Two of these responding patients were platinum-resistant, three were platinum-sensitive.

Combination of niraparib with temozolomide was evaluated in an open-label phase I trial in 19 patients [ClinicalTrials.gov identifier: NCT01294735]. MTD was found to be 40 mg/day plus temozolomide 150 mg/m²/die. The most frequent adverse events were thrombocytopenia, leukopenia, nausea and fatigue. A patient with glioblastoma achieved PR after four cycles, while SD was achieved in two patients (a malignant melanoma and a serous ovarian cancer patient).

Other combination attempts were evaluated in three trials: a phase I trial in which niraparib was associated with carboplatin or carboplatin/paclitaxel or carboplatin/liposomal doxorubicin [ClinicalTrials.gov identifier: NCT01110603]; a phase Ib trial evaluated niraparib in combination with pegylated liposomal doxorubicin [ClinicalTrials.gov identifier: NCT01227941]; and a phase I study, started in Japan, in patients with advanced solid tumours [ClinicalTrials.gov identifier: NCT01226901]. None of these trials are yet completed.

NOVA trial³³ is a phase III randomized double-blind trial, in which niraparib was evaluated versus placebo in patients with platinum-sensitive ovarian cancer expressing *BRCA* mutation or high-grade histology (Table 1).

In the NOVA trial all patients enrolled had platinum-sensitive disease, with at least two platinum-based chemotherapy regimens in their clinical history. Patients, divided in two cohorts on the basis of the *BRCA* mutation, determined with BRAC analysis testing (Myriad Genetics, Salt

Lake City, USA), were assigned a 2:1 ratio of niraparib 300 mg or placebo once daily in 28-day cycles. Before the database lock, tissue samples in the non-BRCA cohort were analysed using the myChoice HRD test (Myriad Genetics) to determine the status of the HR system. A tumour with a score >42 was considered HRD-positive. Primary endpoint was progression-free survival (PFS); secondary endpoints were patient-reported outcome (Functional Assessment of Cancer Therapy – Ovarian Symptom Index questionnaire and the European Quality of Life Scale, the EQ-5D-5L questionnaire), chemotherapy-free interval (time from the last platinum dose until initiation of the next anti-cancer therapy), time to first and second subsequent therapy (time from treatment randomization in the current study to the start date of the first or second subsequent anti-cancer therapies, respectively), PFS2 (time from randomization until progression to subsequent treatment after study treatment or death), time to second subsequent therapy and overall survival (OS).

A total of 553 patients were enrolled, with a median age from 57 to 63 years; 203 in the gBRCAm cohort, 350 in the non-gBRCAm cohort, of whom 201 and 345 received the treatment. Among the non-gBRCAm patients, 162 were HRD-positive and 134 were HRD-negative. Of the 162 HRD-positive patients, 47 exhibited a somatic mutation of *BRCA*. Treatment with niraparib was associated with significantly longer PFS than placebo in gBRCAm patients: 21 months *versus* 5.5 months (HR 0.27). PFS was longer also in the HRD-positive subgroup of the non-gBRCA cohort (12.9 *versus* 3.8 months, HR 0.38) and in the overall non-gBRCAm cohort (9.3 *versus* 3.9 months, HR 0.45).

Chemotherapy-free interval and time to first subsequent therapy were significantly longer in the niraparib group. Although data were not completely mature, results about PFS2 showed that niraparib was better than the placebo group. Data about time to second subsequent therapy and OS were not mature for analysis. Exploratory analysis was conducted to detect the effect of somatic BRCA mutations in the HRD-positive population. HRD-positive *BRCA* wild-type patients showed a median PFS of 9.3 months, while PFS for placebo was only 3.7 months (HR 0.38). The HR was similar to that of the overall HRD-positive population. Patients with HRD-positive and somatic *BRCA* mutation disease achieved

similar results to the gBRCAm cohort (20.9 mo *versus* 11 mo; HR 0.27). Also, for HRD-negative sBRCA wild-type the administration of niraparib led to an increase in median PFS (6.9 months *versus* 3.8 months; HR 0.58).

All patients in the niraparib group showed almost an adverse event. No death occurred during study treatment. Follow-up analysis showed that three patients (one patient in the niraparib group and two in the placebo group) died from myelodysplastic syndrome of acute myeloid leukaemia. Five patients (1.4%) in the niraparib group developed myelodysplastic syndrome; while two patients in the placebo group developed myelodysplastic syndrome and acute myeloid leukaemia. Incidence of grade 3–4 adverse events was 77.4% in the niraparib group and 22.9% in the placebo group.

Companion diagnostics

All developing biopharmaceutical and biotechnological companies developing PARPis have interests in the development of companion diagnostics to identify PARPis-selective patients. Myriad's BRCAAnalysis CDxTM is the only FDA-approved test to determine olaparib treatment eligibility. The same test is used for veliparib, while niraparib and talazoparib eligibility is determined with myChoice HRD.TM Rucaparib uses Foundation Medicine's NGS-based CDx.

While BRCAAnalysis CDxTM, as the name explains, evaluates only *BRCA*, myChoiceHRDTM, developed by the same company, evaluates loss of heterozygosity (LOH) beyond *BRCA* and can be considered an enhancement of BRCAAnalysis CDxTM. It is an NGS-based assay that assesses *BRCA1/2* sequences, and genomic scarring (HRD score), composed by LOH, telomeric allelic balance (TAI) and large-scale transitions (LST). HRD is correlated with alterations in *BRCA1/2*, *PTEN*, *FANCM* and *RAD51C*.³¹ High levels of TAI are correlated with DNA repair defects. All *BRCA1/2* mutated cancer have high levels of LST. It seems that LST scores indicate HRD better than BRCA status. In addition, LST signature is inexpensive. Recently, retrospective data from an ovarian cancer cohort showed that dichotomized individual components (LST, TAI, LOH) to the combined biomarkers have a significant correlation for the combined HRD score with PFS and OS.³⁰ HR threshold of myChoice HRDTM can identify 95% of patients with

mutations in *BRCA1/2* and other HR genes, and who have a higher likelihood of responding to treatment with DNA-damaging agents. In a study by Telli and colleagues,³⁴ a positive myChoice HRD™ result with a threshold of 42 was showed to be related with response to neoadjuvant chemotherapy in patients with triple-negative breast cancer (TNBC) or *BRCA1/2* mutated breast cancer. Using the same validated endpoint of the trial by Telli and colleagues, the myChoice HRD™ test was used to predict response to chemotherapy in a Geparsixto population: patients with positive myChoice HRD™ test had a higher rate of tumour response.³⁵ The same threshold was used in the niraparib phase III trial: all the BRCAm patients were identified except one, supporting the use of this companion diagnostic to select sensitive patients.³⁶

Discussion

Niraparib and olaparib are the main PARPis studied in ovarian cancer. In trials both drugs have showed to improve PFS in women with recurrent platinum-sensitive disease, with manageable side effects. However, beneficial effects in terms of OS have not been adequately demonstrated by the addition of olaparib, while data about OS with niraparib are still immature. More data are required to decide on the clinical application and strategies for the use of these drugs.

The European Medicines Agency (EMA) approved olaparib for monotherapy for maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) HGSOc, fallopian tube or primary peritoneal cancer who are in response (complete response (CS) or PR) to platinum-based chemotherapy in 2014. Meanwhile, niraparib has received label by the FDA in all platinum-sensitive patients (PR and CR) regardless of histology, *BRCA* and HRD status.

In the absence of more refined understanding of PARPis action, *BRCA1/2* mutation status has been the most extensively studied predictor of PARPis sensitivity to date.

However, trials of maintenance treatment of olaparib and niraparib are quite different. In the olaparib phase II trial by Lederman and colleagues,³⁷ patients were enrolled only on the basis of their platinum sensitivity; indeed there was no initial selection for *BRCA* mutations, and

mutation status was initially unknown in the majority of cases (64%). However, retrospective analysis indicated that 136 patients (51%) were positive for *BRCA1* or 2; this group achieved a PFS of 11.2 months, while the placebo-only group achieved 4.3 months (HR 0.18). In wild-type *BRCA* patients, olaparib showed more modest results, as expected: mPFS 7.4 months *versus* 5.5 months (HR 0.54). No significant differences were seen in OS analysis.³⁸

The other phase II trial by Oza and colleagues³⁹ was different, because olaparib was introduced in the treatment with chemotherapy and continued in monotherapy after the completion of chemotherapy: so, one arm had a standard chemotherapy treatment with carboplatin and paclitaxel and another had carboplatin, paclitaxel and olaparib. In this case, *BRCA* status was known for few patients at the beginning of the trial but, as expected, the addition of olaparib had very good effect on BRCAm patients. Overall, olaparib plus chemotherapy resulted in an mPFS of 12.2 *versus* 9.6 months for chemotherapy alone. For BRCAm patients the HR was 0.21. No differences were seen in OS.

In the NOVA trial, the population was initially selected for *BRCA1/2* mutations and also the evaluation of HRD was introduced to investigate the effect of the drug in all potentially sensitive patients. Inclusion criteria required that patients have received at least four cycles of platinum-based chemotherapy, with the possible addition of bevacizumab,^{41,42} with CR or PR before starting niraparib. Among the patients enrolled in the trial, only about 25% in each cohort have had a previous treatment with bevacizumab. Data about efficacy of niraparib are biased by these strategies; moreover, it is not correct to talk of niraparib maintenance therapy, but rather of switch maintenance. What we have seen is that niraparib showed very interesting results in gBRCAm patients, but also showed to be effective in wtBRCA HRD-positive patients and in wtBRCA HRD-negative patients, with an HR similar to that of the olaparib trial (HR 0.58). Results in the HRD-positive population with sBRCA mutation need to be further investigated, because this population was small in the trial.

Some considerations have to be made: somatic mutation testing is more laborious and less reproducible than germline testing; while in germline testing genes are evaluated in healthy cells, in somatic testing the evaluation is carried out in

cancer cells, which are very heterogeneous. Obtaining high-quality DNA from tumour cells is quite difficult and depends on well-preserved and well-sized specimens. Finally, as we have said before, cancer cells are heterogeneous by definition and intra-tumour heterogeneity could lead to a change in biomarkers, like sBRCA, over time. Further evaluations are needed.

In the NOVA trial, initial division was used with germline evaluation, while HRD was evaluated in tissue samples using myChoice; all the evaluations made about differences between germline and somatic testing have to be kept in mind.

Surprisingly, even if the population was selected in a different way – to have a greater population who could benefit from PARPis treatment, not only gBRCAm but also a HRD-positive subgroup – patients receiving niraparib had a significantly longer PFS than those receiving placebo regardless of gBRCA mutations or HRD status. The effect of niraparib in the BRCAwt population is clearly visible; indeed 20% of this population showed more than 18 months of benefit from niraparib administration.

However, authors did not report how many cycles (average/ranging) were administered; moreover, in the study a dose reduction was allowed (300 → 200 → 100 mg), but, unlike the olaparib trial, efficacy was not reported at different doses: data about dose reductions are awaited.

These results could be an important success for the drug, making niraparib the first choice in the treatment of EOC, not only in gBRCAm EOC, but also in BRCAwt. However, some patients with BRCAm EOC do not respond or develop resistance. A possible explanation could be the following: secondary genetic and epigenetic events (such as secondary *BRCA1/2* mutations) that restore functional HR in HR-deficient tumours; suppression of NHEJ *via* loss of 53BP1 or other mechanisms which leads to PARPis resistance but not platinum resistance; increased expression of p-glycoprotein efflux transporter mediating multi-drug resistance. On the other hand, we have a BRCAwt HR-non-deficient population that responds to niraparib: how can this happen?

In consideration of the setting in which niraparib is administered, which is maintenance treatment, BRCA status and HRD, even if they may provide

essential information about treatment efficacy, do not meet the clinical definition of platinum sensitivity. Maybe the myChoice test does not investigate some other gene involved in the HR system – that, we still do not know. Other studies are awaited to confirm this result.

In a future scenario, PARPis will be administered to all EOC patients, and BRCA and HRD testing will not be the indicators of eligibility, but biomarkers of treatment efficacy. Our opinion is that initial evaluation should be somatic testing on tumour samples. If a mutation is found, patients will be referred for genetic counselling to investigate whether this mutation is somatic or germline. We want to underline that a germline mutation also has consequences for the lives of the patient's relatives.

In consideration of the manageable side effects of long-term administration, niraparib could be considered a well-tolerated drug to use in combination treatment: a possible strategy to improve outcomes in EOC could be the combination with another maintenance treatment that has already showed some results, like bevacizumab; the creation of neo-antigens could potentiate the action of immunotherapy (Table 2). It is confirmed that checkpoint inhibitors, and in particular anti-PD1 antibodies, are well tolerated and effective in EOC. Immunotherapy may play a significant role in future clinical management, improving the prognosis of EOC. First results about efficacy in platinum-resistant EOC with nivolumab have already been published.⁴⁰

Efficacy of anti-PD1 is well established in other tumours, like lung cancer, kidney cancer, urothelial cancer and melanoma; moreover, high mutational loads are associated with improved survival in melanoma patients but are not predictive of response to anti-PD-1 therapy, suggesting that other genomic and non-genomic features also contribute to response patterns on PD-1 checkpoint blockade therapy. Hugo and colleagues analysed the somatic mutanomes and transcriptomes of pre-treatment melanoma biopsies to identify factors that may influence innate sensitivity or resistance to anti-PD-1 therapy, finding that overall high mutational load is associated with improved survival, and tumours from responding patients are enriched for mutations in the DNA repair gene *BRCA2*. Thus, *BRCA2* loss-of-function mutations, which are expected to produce defects in HR and DNA DSB repair,

Table 2. Ongoing trials with niraparib.

Trial (ClinicalTrials.gov identifier)	Title	Recruitment
NCT01847274	A maintenance study with niraparib <i>versus</i> placebo in patients with platinum sensitive ovarian cancer	Completed
NCT02354131	Niraparib and/or niraparib-bevacizumab combination against bevacizumab alone in HRD platinum sensitive ovarian cancer	Recruiting
NCT01227941	MK-4827 in combination with pegylated liposomal doxorubicin in participants with advanced solid tumors and ovarian cancer (MK-4827-011)	Terminated
NCT02655016	A study of niraparib maintenance treatment in patients with HRD-positive advanced ovarian cancer following response on front-line platinum-based chemotherapy	Recruiting
NCT02354586	A study of niraparib in patients with ovarian cancer who have received three or four previous chemotherapy regimens	Recruiting
NCT02657889	Study of niraparib in combination with pembrolizumab (MK-3475) in patients with triple-negative breast cancer or ovarian cancer	Recruiting
NCT00749502	A study of MK4827 in participants with advanced solid tumors or hematologic malignancies (MK-4827-001 AM8)	Completed

may produce specific mutational signatures or unknown effects (e.g. induction of cell death) that contribute to anti-PD-1 responsiveness.^{41,42}

Moreover, considering PARPis mechanism of action, their use could further increase the mutational loads in BRCAm EOC patients; therefore, it would be very interesting to evaluate the effectiveness of the combination of PARPis and anti-PD1 in BRCAm EOC patients, as is ongoing in some trials.

Our knowledge about all mechanisms involved in the control of DNA damage is still incomplete. PARP are ubiquitous enzymes in the nucleus of the cells and we can certainly state that it is the first line of defence when DNA is damaged. Inhibiting the PARP family could cause more DNA damage than we want to, having some carcinogenic consequences, as we saw with the incidence of myelodysplastic syndrome in patients under olaparib or niraparib. In our opinion, it could be interesting to understand backup pathways that could cause less DNA damage, causing cell death. Particularly, it could be fascinating to target backup pathways that are less active in normal cells; in this area of investigation one possible backup pathway could be driven by the Rad52 protein.^{43–45}

Acknowledgements

This work was realized on behalf of Consorzio Interuniversitario Nazionale per la Bio-Oncologia

(CINBO) – Via dei Vestini, 31, 66100 Chieti, Italy.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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