CLINICAL INVESTIGATION

Implications of *BRCA1* and *BRCA2* status for cancer clinical study outcomes

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Germline mutations of the *BRCA1* and *BRCA2* genes are associated with higher risk of breast, ovarian, prostate and pancreatic cancers. Initial conventional treatment is largely the same as for non-*BRCA1/2*-mutated cancers although there is increasing evidence in a variety of cancer types to suggest that *BRCA1* or *BRCA2* mutation or inactivation has a role in predicting response to DNA-damaging chemotherapy. The development of PARP inhibitors promises an exciting new therapy in germline *BRCA1/2* mutated cancers that directly exploits the genetic mutation. Studies in both germline *BRCA1/2* mutation carriers and in platinum-sensitive, high-grade, serous ovarian cancer have demonstrated impressive efficacy when given either as a single agent or maintenance treatment following platinum-based chemotherapy. Initial studies in pancreatic and prostate cancer also suggest significant efficacy. In breast cancer, although efficacy has been demonstrated, the optimal patient population remains to be defined.

Keywords: BRCAness phenotype • homologous recombination DNA repair • PARP inhibitors • platinum sensitivity/hypersensitivity • synthetic lethality

Background

The *BRCA1* gene on chromosome 17q, and the *BRCA2* gene on chromosome 13q were identified in 1994 [1] and 1995 [2], respectively. Germline mutations of *BRCA1* or *BRCA2* (g*BRCA1/2*) have been shown to confer a higher risk of breast, ovarian, pancreatic and prostate cancer [3,4], with a breast cancer lifetime risk of 57–72% for g*BRCA1* and 42–96% for g*BRCA2* mutation carriers [5,6], and an ovarian cancer risk of 40% for g*BRCA1* and 18% for g*BRCA2* mutation carriers [5]. Estimates place the prevalence of *BRCA1* mutations in the UK population at 0.11%, with *BRCA2* prevalence at 0.12% [7], although these figures are considerably higher in certain populations, such as Ashkenazi Jews.

Diagnosis of a g*BRCA1/2* mutation carries a number of implications, including consideration of risk-reducing surgery, cancer screening, and both genetic counseling and testing for family members.

Amongst other roles, functional BRCA1 and BRCA2 proteins are crucial in the homologous recombination DNA repair pathway [8,9]. In response to DNA damage, phosphorylated BRCA1 and BRCA2 assemble with PALB2, BRIP1 and RAD51 in DNA-repair foci to participate in homologous recombination DNA repair (Figure 1), allowing repair of double strand breaks and interstrand cross-links. The tumors of g*BRCA1/2* mutation carriers have impaired homologous recombination (by virtue of the second hit sustained during tumorigenesis) resulting in increased sensitivity to both conventional and novel DNA damaging anticancer therapies [10,11]. Homologous recombination may also be impaired by somatic mutation of *BRCA1/2* or methylation of *BRCA1* [12].

This article aims to summarize the current role of *BRCA1* and *BRCA2* status in the treatment of solid malignancies, looking at the significance of germline and somatic *BRCA1/2* mutations and BRCA1/2 protein

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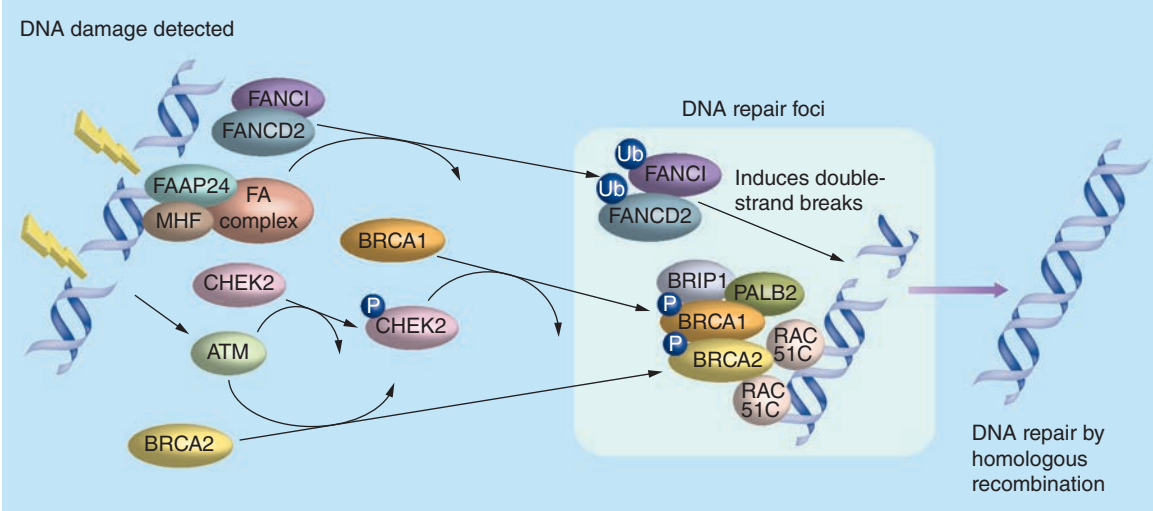

Figure 1. Fanconi Anaemia-BRCA DNA repair pathway. Recognition of inter-strand crosslinks results in binding of FAAP24, MHF and recruitment of the proteins of the FA complex. The FA complex catalyses mono-ubiquitination of FANCI and FANCD2, which translocates to chromatin and DNA-repair foci and induces double stranded DNA breaks. DNA damage triggers ATM to induce phosphorylation of BRCA2 and CHEK2, with CHEK2 in turn phosphorylating BRCA1. Phosphorylated BRCA1 and BRCA2 then assemble with PALB2, BRIP1 and RAD51 in DNA repair foci to participate in homologous DNA repair [8–9,13–14].
FA: Fanconi Anaemia complex.

expression. The role of *BRCA1* mRNA expression as a potential biomarker for patients receiving anti-cancer therapy, tailored treatments for patients with g*BRCA1/2* mutations and novel treatments in development will also be covered. Screening programs and risk-reducing interventions for g*BRCA1/2* mutation carriers without a cancer diagnosis are outside the scope of this review.

Methods

An electronic database search was performed of MEDLINE, EMBASE and PubMed to identify all studies published by October 2013 related to *BRCA1*, *BRCA2* or the BRCAness phenotype. Search terms included 'BRCA', 'BRCA1', 'BRCA2', 'BRCA1/2' and 'BRCAness'. Articles related to the treatment of cancer or the BRCAness phenotype were retrieved and reviewed, with the reference lists for each article reviewed to identify additional relevant studies.

The 'BRCAness' phenotype

As well as informing genetic counseling for relatives of mutation carriers, g*BRCA1/2* mutations have both prognostic and predictive value for patients with ovarian cancer. g*BRCA1/2* mutations are common in ovarian cancer, occurring in 14% of all non-mucinous ovarian cancer patients, and 22% of patients with high-grade serous cancer in one Australian study of 1001 women [11]. Patients with g*BRCA1/2* mutations and ovarian cancer have greater sensitivity to both platinum and non-platinum chemotherapy [11,15], often maintaining platinum sensitivity through multiple lines of therapy [16] with significantly longer treatment-free intervals and overall survival having been demonstrated [11,15–16]. Interestingly, a component of this improved prognosis may be independent of chemotherapy sensitivity, particularly in patients with g*BRCA2* mutations [10,17]. However, recent work suggests the survival advantage seen in g*BRCA1/2* carriers is short-term only, with no difference in overall survival between hereditary and non-hereditary ovarian cancer cases at 10 years from diagnosis [18]. Improved survival of g*BRCA1/2* patients was also seen in multivariate analysis regardless of stage, extent of debulking or age [11]. Patients without germline mutations who experienced good response to treatment are more likely to have a somatic mutation of *BRCA1* or *BRCA2* [11]. Patients with g*BRCA1* mutations were significantly younger although patients with g*BRCA2* mutations were no younger than non-mutation carriers [10]. Tumors are more likely to be of serous histology [16] and have an increased risk of visceral metastases [19]. Together these features comprise the 'BRCAness' phenotype in ovarian cancer, which describes features some sporadic cancers share with *BRCA1/2* mutated ovarian cancers [20].

One study reported a gene expression profile of 'BRCAness' that correlated with response to platinum chemotherapy and PARP inhibitors in ovarian cancer [21]. This has not been validated in subsequent studies and the search for a robust and practical test of homologous recombination deficiency (HRD) remains a major goal (in order to reliably identify patients

with deficient homologous repair in the absence of a germline mutation).

In breast cancer, the BRCAness phenotype is seen in most triple negative (estrogen receptor, progesterone receptor and HER-2 negative) breast cancers [22]. This may be a surrogate for the basal phenotype seen in g*BRCA1*-associated breast cancers [23]. Patients tend to be younger at diagnosis, with grade 3 tumors that are node negative [22,24]. A trend to improved responses to anthracycline and platinum chemotherapy has been reported [22].

Data concerning the possible existence of a BRCAness phenotype in prostate cancer is limited, but a retrospective analysis of 2019 patients with prostate cancer, including 79 patients with confirmed g*BRCA1/2* mutations, identified poor prognostic features associated with g*BRCA1/2* mutations [25]. Patients with g*BRCA1/2* mutations were more likely to have higher grade tumors (Gleason grade ≥8), higher tumor stage (T3/4), nodal involvement and metastatic disease than non-carriers. Contrary to the picture in ovarian cancer, prognosis was significantly worse in g*BRCA1/2* prostate cancer patients, with reduced metastasis-free and cause-specific survival. A Phase II trial of satraplatin in metastatic prostate cancer will be used to assess whether a 'BRCAness' genetic signature for prostate cancer, derived from the genomic profiles of *BRCA1/2* breast cancers, could be used to predict response to platinum therapy [26].

BRCA1 expression as a predictive & prognostic marker

The BRCA1 protein has been shown in preclinical studies to mediate sensitivity to chemotherapy-induced apoptosis in response to antimicrotubule agents, while conversely inducing resistance to DNA-damaging agents [27]. Retrospective analyses in a number of tumor types have shown a potential role for *BRCA1* mRNA or protein expression as predictive or prognostic markers, with low BRCA1 expression repeatedly indicating sensitivity to DNA-damaging chemotherapy agents (see below). These findings require prospective validation.

The potential predictive and prognostic role of *BRCA1* mRNA expression was first reported in 55 patients receiving neo-adjuvant cisplatin and gemcitabine chemotherapy for non-small-cell lung cancer (NSCLC) [28]. Reduced *BRCA1* mRNA expression was associated with more radiological responses to neo-adjuvant chemotherapy, more complete tumor resections, and more lobectomies as opposed to pneumonectomies.

In breast cancer, reduced expression of the BRCA1/BRCA2/Rad51 complex has been shown to be a prognostic marker for increased risk of local recurrence, but also a predictive marker for improved outcomes following adjuvant radiotherapy [29].

Low expression of both *ERCC1* and *BRCA1* mRNA was associated with improved response to cisplatin chemotherapy in patients with stage 4 NSCLC, gastric cancer or gynecological cancers, with greatest sensitivity to cisplatin seen in patients whose tumors expressed low levels of both [30].

Increased expression of *BRCA1*, and reduced levels of *RRM2* mRNA were associated with a significant increase in response to Docetaxel and gemcitabine chemotherapy and a lower risk of progression in a study in advanced NSCLC [31]. Conversely, in the second-line setting where most patients (90.2%) received cisplatin-based therapy, reduced *BRCA1* expression was associated with a reduced risk of progression.

A comparative genomic hybridization (CGH) based BRCA1-like classifier, designed to differentiate between *BRCA1* mutated and sporadic breast cancers [32], has been evaluated in adjuvant breast cancer therapy. A subgroup of an adjuvant breast cancer trial was analyzed retrospectively according to this BRCA1-like^{CGH} status [33], with 41 of 230 samples analyzed scored as BRCA1-like. The initial study had randomized patients to standard treatment (five cycles of fluorouracil, epirubicin and cyclophosphamide [FEC]), or high-dose, platinum-based treatment (four cycles of FEC, followed by one cycle of high-dose chemotherapy with cyclophosphamide 6000 mg/m^2, thiotepa 480 mg/m^2 and carboplatin 1600 mg/m^2) [34]. In non-BRCA1-like cases, no benefit was seen in the high dose arm, but in the BRCA1-like cases, risk of recurrence was reduced eightfold in patients who were treated within the high-dose arm (hazard ratio [HR]: 0.12). A clinical trial is currently recruiting to explore this treatment prospectively in triple negative breast cancer in the Netherlands [35].

A non-randomized trial of personalized treatment in advanced *EGFR* wild-type lung adenocarcinomas [36] treated patients according to tumor *BRCA1* expression levels, with cisplatin/gemcitabine for low *BRCA1* expression, cisplatin/docetaxel for intermediate *BRCA1* expression docetaxel for high *BRCA1* expression. Although patients in the low *BRCA1* expressing group had significantly lower response rates to first-line chemotherapy, 2-year survival was significantly better in this group, with the best survival seen in patients whose tumor expressed low levels of both *BRCA1* and RAP80. The design of this study does not allow conclusions to be drawn about the efficacy of personalized treatment schedules, but may identify a subgroup of NSCLC patients with low *BRCA1* and RAP80 expression with a significantly improved prognosis. However, a subsequent trial by this group that randomized

patients with metastatic NSCLC to standard treatment with cisplatin/docetaxel, or experimental treatment determined by their BRCA1 and RAP80 expression, demonstrated worse progression-free and overall survival in the experimental arm after an interim analysis [37] and accrual to the study has now closed.

In bladder cancer, low or intermediate *BRCA1* mRNA expression was associated with significantly longer median and overall survival, and more pathological responses to neo-adjuvant platinum based chemotherapy than high *BRCA1* mRNA expressing tumors [38].

In gastric cancer, negative BRCA1 expression as assessed by immunohistochemistry has been shown to be associated with more advanced tumor stage, nodal stage and the presence of perineural invasion, as well as reduced 5-year overall survival [39]. However, adjuvant chemotherapy resulted in a significant benefit for BRCA1 non-expressing tumors, particularly when DNA damaging agents were used in addition to fluoropyrimidines, with increased disease-free and overall survival observed in BRCA1 non-expressing, but not BRCA1 expressing tumors.

A further study in advanced NSCLC looked at the predictive role of ERCC1, BRCA1 and XPG expression by immunohistochemistry observed improved survival and response to chemotherapy in ERCC1 negative patients, but no significant findings related to BRCA1 were identified [40]. A large, randomized, multinational Phase III trial comparing intravenous with intraperitoneal paclitaxel and cisplatin in advanced ovarian cancer was analyzed retrospectively according to BRCA1 expression [41]. BRCA1 expression was quantified by immunohistochemistry in archival tumor of 393 patients, with low BRCA1 expression observed in 189 tumors (48%), and normal BRCA1 expression in 204 tumors (52%). Overall, there was no significant overall survival difference between aberrant or normal BRCA1 expressing tumors. However, when the low BRCA1 expression group was analyzed according to route of administration of chemotherapy, patients treated with intraperitoneal chemotherapy had a significantly longer survival than patients who received intravenous chemotherapy (84 vs 48 months, $p = 0.0002$). No significant survival advantage for intraperitoneal chemotherapy was observed in patients whose tumors had normal BRCA1 expression. In the cohort treated with intraperitoneal therapy, aberrant BRCA1 expression was an independent prognostic factor for overall survival.

Together these findings suggest reduced BRCA1 expression in a variety of cancers is associated with increased sensitivity to DNA-damaging agents, whereas increased BRCA1 expression is associated with resistance to DNA-damaging agents but sensitivity to agents such as taxanes. One potential explanation for these findings is that the low BRCA1 expression group contains germline mutation carriers that, by definition, will be homologous recombination deficient and therefore much more sensitive to DNA damaging agents. What is as yet unclear is the extent to which epigenetic reduction in BRCA1 expression contributes to increased sensitivity to DNA damaging agents but this may also contribute to the explanation. Although prospective validation of these findings is awaited, there may be a role for personalizing chemotherapy based on tumor BRCA1 expression. However, the only prospective trial of personalized chemotherapy conducted to date closed early due to poor performance of the personalized arm.

Conventional treatment of *BRCA1/2*-mutation-associated cancers

Standard primary treatment of localized *gBRCA1/2*-mutated cancers is currently the same as for non-germline-mutation carriers. This usually comprises a combination of surgery, cytotoxic chemotherapy and radiotherapy depending on the site and stage of the cancer, and the fitness and wishes of the patient. Prophylactic surgery for female carriers of *gBRCA1/2* mutations, and intensive screening programs are considered after treatment of the primary cancer.

Ovarian cancer

In advanced or relapsed ovarian cancer, platinum-based chemotherapy has a crucial role in treatment, with patients often deriving benefit from multiple lines of treatment. Ovarian cancer patients with *gBRCA1/2* mutations have been shown to have tumors with significantly greater platinum sensitivity, often maintained through multiple lines of therapy [16].

One retrospective review has suggested that pegylated liposomal doxorubicin (PLD) may also be more effective in *gBRCA1/2* mutation carriers with ovarian cancer than in nonhereditary ovarian cancer [42]. However, although survival in the *gBRCA1/2* group was significantly prolonged (56.8 vs 22.6 months), this was not a pure analysis of PLD sensitivity as platinum-containing combinations were also included and, as such, further confirmatory evidence is required.

Concern that *gBRCA1/2*-mutated cancers may be inherently resistant to taxane monotherapy has been raised by preclinical studies showing BRCA1 expression confers sensitivity to spindle poisons [27], while BRCA1 down-regulation confers resistance to paclitaxel in breast cancer cell lines [43]. However, a small, retrospective study assessing the efficacy of paclitaxel monotherapy in 26 patients with *gBRCA1/2*-mutated, relapsed ovarian cancer [44] observed responses in 12 patients (46%) suggesting g*BRCA*-mutation-associated ovarian cancer retains sensitivity to taxane therapy.

Breast cancer

A large, matched, case-control study designed to assess the efficacy of adjuvant chemotherapy and endocrine therapy in reducing the risk of asynchronous contralateral breast cancer, reported a substantial reduction in the relative risk of contralateral breast cancer [45]. Within the study population, 109 mutations in *BRCA1* and 72 mutations in *BRCA2* were detected and results incorporating *gBRCA1/2* status were reported separately [46]. A similar relative risk reduction in contralateral breast cancer was seen in both *gBRCA1/2* mutation carriers and non-carriers who received adjuvant chemotherapy or adjuvant tamoxifen therapy, although the authors noted that the significantly higher risk of breast cancer in g*BRCA* mutation carriers would conceivably result in a much greater absolute risk reduction in this group. Analysis of the efficacy of tamoxifen was limited by the small proportion of women with *BRCA1/2* mutations and estrogen receptor positive tumors.

The same study group reported on the risk of contralateral breast cancer in *gBRCA1/2 patient*s receiving adjuvant radiotherapy, due to a concern that *gBRCA1/2* mutations may predispose patients to a higher risk of secondary malignancies after DNA-damaging adjuvant radiotherapy [47]. A modestly elevated risk of contralateral breast cancer was seen in *gBRCA1/2* mutation carriers who received radiation compared with those who did not receive radiation (18.5 vs 13.3%), this risk was not statistically significant.

A small, non-controlled trial evaluated the frequency of pathological complete responses with neo-adjuvant cisplatin-based therapy in *gBRCA1* mutation carriers with breast cancer [48]. Ten patients received cisplatin 75 mg/m^2, 3-weekly for four cycles before proceeding to mastectomy and axillary node dissection. Five patients had T1 tumors, four had T2 tumors and one patient had a T4 tumor. Of the nine patients who had immunohistochemistry studies, all were triple negative. All ten patients had a clinical and pathological complete response to cisplatin in the breast tissue. Three patients had clinical nodal disease, with a clinical and pathological complete response in two of these patients in the axilla. The overall complete response rate was therefore 90% with one partial response.

A retrospective study by the same group reported outcomes of neo-adjuvant therapy in breast cancer for 102 *gBRCA1* mutation carriers [49]. A pathological complete response was seen in 24 (24%) patients although this varied widely according to treatment regime. Complete response was achieved in 7% of patients treated with cyclophosphamide, methotrexate and fluorouracil, 8% of those receiving doxorubicin/docetaxel, 22% for adriamycin and cyclophosphamide and 83% of those treated with cisplatin. A Phase II, non-randomized, open label trial of cisplatin in *gBRCA1*-mutated metastatic breast cancer was conducted in Poland [50]. In total, 20 patients were enrolled in the study, 18 of whom had previously received non-platinum chemotherapy. All enrolled patients were HER-2 negative, with 70% triple negative. Cisplatin 75 mg/m^2 was administered 3-weekly for six cycles with response assessed by RECIST criteria. The response rate was 80%, with a complete response seen in 45% of patients. Seven of 14 patients with triple negative disease showed a complete response.

The efficacy of taxane monotherapy in *gBRCA1/2* mutation metastatic breast cancer has been evaluated in a retrospective case-control study [51]. 32 *gBRCA1* and 13 g*BRCA2* carriers were matched to 90 controls, with poorer response (Odds ratio [OR]: 25 vs 38% first line; 24 vs 36% ≥ second line; $p \leq 0.001$) and poorer disease free survival (2.0 vs 4.7 months; $p = 0.03$) in *gBRCA1 patient*s. No difference was noted in g*BRCA2 patient*s.

Two retrospective analyses have evaluated the efficacy of neo-adjuvant chemotherapy in *gBRCA1/2* carriers with breast cancer. A study of 80 *gBRCA1/2* carriers and 237 patients who tested negative for a *gBRCA* mutation, reported higher pathological complete response rates in *gBRCA1* carriers (46 vs 22%, $p \leq 0.001$) although not in *gBRCA2* carriers (13%) [52]. *BRCA1* mutation remained a predictor of a pathological complete response in a multivariate analysis (OR: 3.16; $p = 0.002$) but no correlation between type of neo-adjuvant systemic therapy and pathological complete responses was seen. Another retrospective study of 23 *gBRCA1/2* mutation carriers, 64 *gBRCA* negative patients and 87 matched controls receiving neo-adjuvant chemotherapy for breast cancer also reported improved responses to chemotherapy in *gBRCA1/2* carriers [53]. Pathological complete responses were seen in 39.1% of *gBRCA1/2 patient*s compared with 20.3% of *BRCA* negative patients and 17.1% of controls although this was not significant ($p = 0.07$). However, *gBRCA1/2* carriers had significantly higher rates of local recurrence (HR: 7.86; $p = 0.002$) and distant metastases (HR: 4.57; $p = 0.01$) than the control group.

The UK TNT trial, which was originally two parallel trials (one for *gBRCA1/2* breast cancer and one for triple negative breast cancer), is comparing docetaxel with single agent carboplatin in first-line metastatic breast cancer. This should provide good prospective evidence regarding the impact of *BRCA1/2* status on sensitivity to platinum and taxanes.

Prostate cancer

One retrospective case-control study, analyzing 43 *gBRCA1/2* carriers with early prostate cancer and 129 matched controls, has reported reduced biochemical

Table 1. Results of interventional studies in breast cancer.

Tumor type	Type of study	Patients (n)	BRCA status	Treatment	Outcome	Ref.
Breast (neo-adjuvant)	Prospective non-randomized Phase II	10	*gBRCA 1* mutation	Cisplatin 75 mg/m^2	90% pathological CR	[48]
Breast (neo-adjuvant)	Prospective, non-randomized Phase II	80	19 *gBRCA1/2* mutations	Iniparib 5.6 mg/kg on days 1, 4, 8, 11; Gemcitabine 100 mg/m^2 on days 1, 8; Carboplatin AUC2 days 1, 8	Pathological CR in 20 of 61 (33%) non-BRCA patients, and nine of 19 (47%) *gBRCA1/2* mutation carriers	[58]
Breast (advanced)	Prospective, non-randomized Phase II	20	*gBRCA1* mutation	Cisplatin 75 mg/m^2	80% response rate, 45% CR	[50]
Breast (metastatic)	Prospective, non-randomized Phase II	122	35 *gBRCA1/2* mutations	Trabectedin 1.3 mg/m^2 every 21 days	PR in four of 29 *gBRCA1/2* mutation carriers, four of 35 HER-2 positive cancers, 0 of 43 triple negative cancers	[59]
Breast (metastatic)	Sequential cohort Phase II	54	*gBRCA1/2* mutation	Olaparib 400 mg b.i.d.; Olaparib 100 mg b.i.d.	41% RR at 400 mg b.i.d., 22% RR at 100 mg b.i.d.	[60]
Breast (metastatic)	Phase I	22	*gBRCA1/2* mutation	Veliparib dose escalation; Carboplatin AUC6	CR in three patients, PR in nine patients and SD in seven patients, clinical benefit rate of 74%	[61]
Breast (metastatic), ovarian (relapsed)	Prospective, non-randomized Phase II	91	*gBRCA1/2* mutations in 17/65 ovarian cancer patients; 10/26 breast patients	Olaparib 400 mg b.i.d.	41% PR in *gBRCA1/2* ovarian patients, 28% PR rate in non-BRCA ovarian patients, No responses in breast patients	[62]
Breast (metastatic), ovarian (relapsed)	Prospective, non-randomized Phase II	41	*gBRCA1/2* mutation	Rucaparib 18 mg/m^2 on days 1–5	PR in two patients, SD in ten patients, clinical benefit rate of 32%	[63]
Multiple tumor types (dose escalation), ovarian (relapsed) and prostate (metastatic; extension)	Phase I dose escalation study and extension study	100	29 *gBRCA1/2* mutations	Niraparib dose escalation – MTD 300 mg daily	PR in nine of 20 *gBRCA1/2* ovarian cancer, and two of four *gBRCA1/2* breast cancer patients SD for >6 months in nine of 21 prostate cancer patients Antitumor activity also seen in NSCLC	[64, 65]

b.i.d.: Twice daily; CR: Complete response; *gBRCA1/2*: germline *BRCA1/2*; MTD: maximum-tolerated dose; NSCLC: Non-small-cell lung cancer; PR: Partial response; RR: Response rate; SD: Stable disease.

progression-free survival (PFS) in *gBRCA1/2* patients treated with radical radiotherapy (39 vs 65 months; p = 0.023). No difference in biochemical PFS was seen in patients treated with radical prostatectomy (3-year PFS: 73% *gBRCA1/2* vs 76% controls) [54]. While this suggests a potential role for tailoring treatment in *gBRCA1/2* carriers, its findings are yet to be validated.

Pancreatic cancer

A case series presented at the American Society of Clinical Oncology (ASCO) in 2012 has suggested a role for platinum based chemotherapy in *gBRCA1/2* associated pancreatic cancer [55]. In total, 14 patients with *gBRCA1/2* mutations and locally advanced pancreatic cancer were identified, five of whom received platinum-based chemotherapy and six non-platinum

based chemotherapy. All five patients treated with platinum responded, with three partial and two complete responses. Only one of six patients treated with non-platinum chemotherapy had a partial response. Overall survival was prolonged in patients receiving platinum (33.0 vs 7.3 months).

Another retrospective study has analyzed 63 patients with pancreatic cancer and *gBRCA1/2* mutations [56]. In this series, the 12 patients who received platinum-based chemotherapy did not experience a survival benefit compared with 18 patients who received non-platinum chemotherapy (PFS: 90 vs 92 days). However, two patients with locally advanced disease were rendered resectable with gemcitabine/cisplatin chemotherapy. A further case series of 16 patients with pancreatic cancer and *gBRCA1/2* mutations, reported partial responses in five out of six patients treated with platinum-based chemotherapy, and three of four patients treated with a PARP inhibitor [57].

The unifying message from these studies of conventional chemotherapy in *gBRCA1/2* mutation carriers is that in multiple tumor types (ovarian, breast and pancreas) there is evidence of markedly increased sensitivity to DNA damaging agents, particularly platinum. This results from the fact that these tumors are homologous recombination deficient and therefore cannot repair double strand breaks in DNA with the same efficiency as *BRCA1/2* wild-type cells. While this increased platinum sensitivity is well accepted within the ovarian cancer community, research is ongoing in breast cancer and the high levels of platinum sensitivity seen in admittedly small studies in *gBRCA1/2*-mutated pancreatic cancer are very exciting given the fact that this malignancy is otherwise very resistant to systemic therapy.

Emerging therapies in *BRCA1/2*-deficient cancers

Interventional studies dependent on BRCA1/2 expression or mutation status are listed in Table 1 (breast cancer), Table 2 (ovarian cancer) and Table 3 (other cancers).

PARP inhibitors

PARP inhibitors have recently been investigated in a number of solid tumors. The PARPs are involved in the repair of DNA single-strand breaks. By inhibiting PARP, these single strand breaks accumulate, leading to double strand breaks that would usually be repaired by homologous recombination. The BRCA1 and BRCA2 proteins are crucial for homologous recombination. In patients with *gBRCA1* or *gBRCA2* mutations, the non-cancer cells in their bodies are heterozygous for the wild-type *BRCA1* or *BRCA2* gene whereas the tumor cells have no functional copy. As a result this pathway is deficient in these tumor cells and PARP inhibition results in the accumulation of double strand breaks leading to cell death as part of a strategy known as synthetic lethality [78–83]. The non-tumor cells, by virtue of having one functional copy of the gene are homologous recombination proficient, can repair the double strand breaks and as a consequence, are much more resistant to PARP inhibition.

The efficacy of PARP inhibitors in the *BRCA1/2*-deficient population was first shown in a Phase I trial of olaparib in a population enriched for *gBRCA1* or *gBRCA2* mutation carriers [71]. In total, 60 patients were enrolled in the study, 22 of whom had *gBRCA1* or *gBRCA2* mutations and one of whom had a strong family history of BRCA-associated cancers but declined mutation testing. The initial dose escalation phase identified 400 mg twice dailiy (b.i.d.) as the maximum-tolerated dose. The second phase of the trial tested the hypothesis that tumors associated with *gBRCA1* or *gBRCA2* mutations (ovarian, breast and prostate cancer) would show an antitumor response to single agent olaparib. Of 23 *gBRCA1/2* carriers within the trial, 19 had evaluable disease. Of the 19 patients, 12 (63%) had a clinically meaningful response to olaparib, nine of which were responses according to RECIST criteria. No objective antitumor responses were seen in patients without a *gBRCA1/2* mutation. The study was extended in a population of *gBRCA1/2* mutated ovarian cancer patients [67], with 50 patients included in an analysis performed to evaluate any association between platinum sensitivity and response to olaparib. A total of 20 patients (40%) had a RECIST partial response or complete response, a Ca125 response by Gynecologic Cancer Intergroup criteria or both, with responses seen in 61.5% of patients with platinum-sensitive disease (eight of 13), 41.7% of patients with platinum resistant disease (ten of 24) and 15.4% of patients with platinum refractory disease (two of 13).

A non-randomized, sequential cohort, Phase II trial of olaparib was conducted in 54 patients with *gBRCA1* or *gBRCA2* mutations and metastatic or incurable locally advanced breast cancer [60]. Of the 54 patients, 27 received olaparib 400 mg b.i.d. and 27 received 100 mg b.i.d., with objective responses seen in 11 of the 27 patients (41%) treated at 400 mg b.i.d. compared with six of the 27 patients (22%) treated at 100 mg b.i.d. Similar results were seen in a proof of concept Phase II trial of olaparib in 57 patients with advanced ovarian cancer and *gBRCA1* or *gBRCA2* mutations [84]. Objective responses were seen in 11 of 33 patients (33%)

Table 2. Results of interventional studies in ovarian cancer.

Tumor type	Type of study	Patients (n)	BRCA status	Treatment	Outcome	Ref.
Breast (metastatic), ovarian (relapsed)	Prospective, non-randomized Phase II	91	*gBRCA1/2* mutations in 17/65 ovarian cancer patients; 10/26 breast patients	Olaparib 400 mg b.i.d.	41% PR rate in *gBRCA1/2* ovarian patients, 28% PR rate in non-*BRCA* ovarian patients, No responses in breast patients	[62]
Breast (metastatic), ovarian (relapsed)	Prospective, non-randomized Phase II	41	*gBRCA1/2* mutation	Rucaparib 18 mg/m^2, days 1–5	PR in two patients, SD in ten patients, clinical benefit rate of 32%	[63]
Ovarian (relapsed)	Randomized Phase II	97	*gBRCA1/2* mutation	Olaparib 200 mg b.i.d., Olaparib 400 mg b.i.d., Pegylated liposomal doxorubicin	Improved ORR with olaparib 400mg, no difference in PFS	[66]
Ovarian (relapsed)	Phase I extension study	50	*gBRCA1/2*mutation	olaparib 200 mg b.i.d.	40% RR	[67]
Ovarian (relapsed)	Randomized, prospective Phase II	265	136 *gBRCA1/2* mutations identified *post hoc*	Maintenance olaparib 400 mg b.i.d. or placebo	PFS 8.4 months in olaparib group, 4.8 months in placebo group; PFS 11.2 vs 4.1 months in *gBRCA1/2* patients treated with olaparib vs placebo	[68, 69]
Ovarian (relapsed)	Prospective, non-randomized Phase II	6	Not assessed	*BRCA1* gene therapy	Vector rapidly cleared from peritoneal fluid, all six patients progressed within 3 months, study terminated	[70]
Multiple tumor types (dose escalation), ovarian (relapsed) and prostate (metastatic; extension)	Phase I dose escalation study and extension study	100	29 *gBRCA1/2* mutations	Niraparib dose escalation – MTD 300 mg daily	PR in nine of 20 *gBRCA1/2* ovarian cancer, and two of four *gBRCA1/2* breast cancer patients; SD for >6 months in nine of 21 prostate cancer patients; Antitumor activity also seen in NSCLC	[64, 65]

b.i.d.: Twice daily; ***gBRCA1/2:*** germline ***BRCA1/2***; MTD: Maximum-tolerated dose; NSCLC: Non-small-cell lung cancer; ORR: Overall response rate; PFS: Progression-free survival; PR: Partial response; RR: Response rate; SD: Stable disease.

treated at 400 mg b.i.d., and three of 24 patients (11%) treated at 100 mg b.i.d.

A total of 91 patients were recruited in another non-randomized, Phase II trial of olaparib in triple-negative breast cancer or high grade serous ovarian cancer, and were stratified according to *BRCA* mutation status [62]. Patients received olaparib 400 mg b.i.d. until progression. Responses were seen in seven of 17 ovarian cancer patients (41%) with *gBRCA1/2* mutations, and 11 of 46 ovarian cancer patients (24%) without *gBRCA1/2* mutations but no objective responses were seen in the 26 breast cancer patients treated within this trial.

Recently a randomized, double-blind, placebo controlled Phase II trial of maintenance olaparib therapy was performed in patients with platinum sensitive recurrent ovarian, primary peritoneal or fallopian tube cancer [68]. A sample of 265 patients, who had received at least two previous courses of platinum-based chemotherapy, and had an objective response to their most recent course of chemotherapy (by RECIST or Gynecologic Cancer Intergroup Ca125 criteria), were randomized to receive either maintenance olaparib at 400 mg b.i.d. or placebo within 8 weeks of completing chemotherapy. Patients were not selected according to their *gBRCA1/2* mutation status (rather platinum sen-

sitivity was used as an enrichment factor for HRD) but they were stratified according to their ancestry (Jewish vs non-Jewish) in an attempt to balance the distribution of *gBRCA1/2* mutation carriers in each arm. Patients were also stratified according to response to most recent treatment and platinum- free interval prior to most recent chemotherapy. Treatment continued until disease progression, with no crossover to olaparib allowed for placebo patients on progression within the context of the study. The primary analysis demonstrated a significant PFS advantage for patients treated within the olaparib arm (median 8.4 versus 4.8 months from randomization; HR: 0.35; 95% CI: 0.25–0.49; $p < 0.001$). Nausea, fatigue, vomiting and anemia were observed more frequently in the olaparib arm. Mature survival data and a preplanned subgroup analysis of patients according to *BRCA1/2* mutation status were presented at the ASCO conference in Chicago in 2013 [69]. *BRCA1/2* status was determined retrospectively, with a germline or somatic *BRCA1/2* mutation identified in 136 (51%) patients, wild type *BRCA1* and *BRCA2* sequence in 118 (45%) patients and unknown *BRCA1/2* mutation status in 11 (4%) patients. Patients with a *BRCA1/2* mutation (either germline or somatic) had a greater benefit from olaparib than the population as a whole (median PFS: 11.2 vs 4.3 months; HR: 0.18; 95% CI: 0.11–0.31; $p < 0.00001$). Interestingly, in the non-*BRCA1*/2 mutation carriers there was a significant benefit for patients receiving olaparib (HR: 0.53; 95% CI: 0.33–0.84; $p = 0.007$) although the unusual shape of the curves do bring them close together around the median before separating out again (median PFS: 5.6 vs 5.5 months). There was no significant difference in overall survival in this analysis, but these data may be confounded by the fact that 13 of 37 *BRCA1/2* mutation carriers who progressed on placebo subsequently received a PARP inhibitor off-trial.

In an open label Phase II trial, olaparib monotherapy has shown efficacy in heavily pretreated patients with *gBRCA1/2* mutation carriers regardless of tumor type [73]. In total, 298 patients were treated within the study, with objective responses seen in ovarian, breast, prostate and pancreatic cancers. The 1-year survival ranged from 40.2% in pancreatic cancer to 64.4% in ovarian cancer.

A further randomized Phase II trial compared olaparib at two doses (200 or 400 mg b.i.d.) to PLD in patients with recurrent ovarian cancer within 12 months of platinum-based chemotherapy, and *gBRCA1/2* mutations [66]. Crossover from PLD to olaparib 400 mg b.i.d. was allowed on progression. A total of 97 patients were randomized in a 1:1:1 ratio to the three arms of the study. Although there was a greater overall response rate in the olaparib 400 mg b.i.d. arm, PFS was not significantly different between the three arms. It was noted however, that the PFS for the PLD group was significantly longer than expected, consistent with data suggesting that *BRCA1/2*-deficient tumors are more sensitive to PLD [42].

Another PARP inhibitor, veliparib, has been assessed in a Phase I trial in combination with metronomic cyclophosphamide in refractory solid tumors and lymphoid malignancies [72]. A sample of 35 patients was enrolled in the study and a *gBRCA1/2* mutation was not required to enter the study. Seven patients had a partial response to treatment, six of whom carried *BRCA1/2* mutations. A further six patients had prolonged stable disease (for more than six cycles), three of whom carried *BRCA1/2* mutations. A Phase I trial has also assessed single agent veliparib in 63 patients with advanced solid tumors, 38 of whom carried *gBRCA1/2* mutations [74]. Two *gBRCA1/2 patient*s had a partial response, with stable disease for over 4 months in a further ten patients. Activity was also seen in *BRCA1/2* wild-type patients, with one partial response and seven cases of stable disease for over 4 months. Activity in combination with fluorouracil and oxaliplatin has also been shown in a Phase I trial [77]. In total, 22 patients with metastatic pancreatic cancer were treated with escalating doses of ABT-888 (veliparib) with a standard 14-day schedule of oxaliplatin and fluorouracil. Response rate was 14%, but both patients with *gBRCA2* mutations responded, with one partial response and one complete response. In total, 28 patients with *gBRCA1/2* mutations and metastatic breast cancer were treated with veliparib and carboplatin in a Phase I trial [61]. Three (12%) complete and nine (35%) partial responses were seen, with unconfirmed partial responses or stable disease seen in a further seven patients (27%) resulting in an overall clinical benefit rate of 74%.

Niraparib is an inhibitor of PARP-1 and PARP-2 that has shown efficacy in solid tumors in a Phase I trial [64], with mature data presented at ASCO in 2013 [65]. In the first, dose-escalation phase of the study, 300 mg/day was established as the maximum-tolerated dose. The second phase of the study assessed activity in sporadic, platinum resistant ovarian cancer and castrate refractory prostate cancer. Between the two phases of the study, 100 patients were enrolled with 20 ovarian cancer patients and four breast cancer patients with *gBRCA1/2* mutations. Of the patients with *gBRCA1/2* mutations, nine ovarian cancer patients (45%) and two breast cancer patients (50%) had objective partial responses to treatment. In prostate cancer, stable disease for >6 months was seen in nine of 21 patients (43%). The authors have proposed

further investigation in cancers with homologous recombination DNA repair deficiencies.

A single-arm Phase II study of 80 breast cancer patients receiving neoadjuvant chemotherapy evaluated the efficacy of gemcitabine, carboplatin and iniparib therapy [58]. In total, 19 patients had *gBRCA1/2* mutations, with a pathological complete response seen in nine (47%), including one patient with bilateral breast cancer who had a pathological complete response in both tumors. However, Phase III results in triple-negative breast cancer were negative and iniparib has subsequently been shown not to be a true PARP inhibitor [85]. Development of iniparib has since ceased.

Another PARP inhibitor, rucaparib, has shown activity in a Phase II trial of 41 patients with *gBRCA1/2* mutations and advanced breast or ovarian cancer [63]. Although overall response rate was only 5% (two of 38 evaluable by RECIST), a further ten patients experienced stable disease for over 4 months giving a clinical benefit rate of 32%. Phase III trials in the maintenance setting are ongoing.

BMN 673 is a new PARP inhibitor currently in early-phase clinical development. Preclinical work suggests this is the most potent PARP inhibitor reported to date, exhibiting antitumor cell responses and eliciting DNA repair biomarkers at much lower concentrations than existing PARP inhibitors such as olaparib, veliparib and rucaparib [86].

Concern had been raised in preclinical work that exposure to and the development of resistance to PARP inhibition could be associated with subsequent resistance to chemotherapy. However, a review of 89 patients with *gBRCA1/2* mutations and epithelial ovarian cancer who received olaparib, demonstrated response rates of up to 45% to post-olaparib chemotherapy, including response rates to platinum chemotherapy of up to 49%, suggesting different mechanisms of resistance to PARP inhibitors and chemotherapy [87].

Therefore, there is clear evidence in a number of tumor types of selective benefit to PARP inhibition in *gBRCA1/2* mutation carriers. There is also some evidence of benefit in non-*gBRCA1/2* mutation carriers. Clinical tests that can detect homologous recombination repair defects have considerable potential to identify this latter group of patients. Development of these tests continues, with one study reporting a DNA-based HRD score that appears capable of detecting homologous recombination defects regardless of mechanism or etiology [88]. The score was developed in epithelial ovarian cancer, and validated in independent epithelial ovarian cancer datasets, and breast and pancreatic cancer cell lines. This HRD score is currently being evaluated in breast and pancreatic cancer, and in studies to evaluate its ability to predict response to platinum and PARP inhibitors, potentially expanding the use of PARP inhibitors to other tumor types.

Olaparib and bevacizumab

Olaparib has also been assessed in combination with bevacizumab in a small Phase I study without assessment of *BRCA1/2* status [89]. In total, 12 patients received olaparib at doses of 100, 200 or 400 mg b.i.d. in combination with bevacizumab 10 mg/kg. All three arms were well tolerated with no overlapping toxicities, and olaparib 400 mg b.i.d. was identified as a tolerable dose to take forward into a Phase II combination study of olaparib and bevacizumab.

Trabectedin

A retrospective analysis of mRNA expression of *BRCA1, ERCC1* and *XPG* was performed in 245 patients with soft tissue sarcomas treated with the DNA damaging antineoplastic agent trabectedin [90]. Low *BRCA1* mRNA expression was associated with a significantly improved response to trabectedin, particularly when associated with high *ERCC1* or *XPG* expression.

On the background of these results, a Phase II trial of trabectedin was performed in non-small-cell lung cancer patients with overexpression of *XPG* and/or *ERCC1*, and repression of *BRCA1* [76]. Of the 18 screened patients with the appropriate gene expression signature, only two achieved the primary end point of PFS at 3 months, with no objective RECIST responses, and the study was terminated.

A Phase II trial of trabectedin in 122 patients with pretreated metastatic breast cancer reported results in a cohort of *gBRCA1/2 patient*s, with partial responses seen in four of 29 patients (13.8%) [59].

Nucleoside analogs with CDK inhibitors

A combination of sapacitabine, a nucleoside analog, and seliciclib, an inhibitor of CDK2, 7 and 9 has shown antitumor activity in *gBRCA1/2* mutation associated tumors in a Phase I trial [75]. In total, 27 patients with advanced solid tumors were recruited, with partial responses seen in two patients, one with pancreatic and one with breast cancer, both of whom carried *gBRCA1/2* mutations.

Gene therapy

After promising activity in animal models and a Phase I trial [91], a Phase II trial of *BRCA1* gene therapy with a viral vector was performed in patients with relapsed ovarian cancer of unknown *gBRCA1/2* mutation status [70]. Patients had received standard debulk-

Table 3. Results of interventional studies in other and multiple cancers.

Tumor type	Type of study	Patients (n)	BRCA status	Treatment	Outcome	Ref.
Multiple tumor types (dose escalation); Ovarian (relapsed) and prostate (metastatic; extension)	Phase I dose escalation study and extension study	100	29 *gBRCA1/2* mutations	Niraparib dose escalation – MTD 300 mg daily	PR in nine of 20 *gBRCA1/2* ovarian cancer, and two of four *gBRCA1/2* breast cancer patients; SD for >6 months in nine of 21 prostate cancer patients; Antitumor activity also seen in NSCLC	[64, 65]
Multiple tumor types	Phase I dose escalation study	60	23 *gBRCA1/2* mutations	Dose escalation olaparib	PR in 12 of 19 evaluable *gBRCA1/2* patients, no responses in non-*BRCA* patients	[71]
Multiple tumor types	Phase I dose escalation study	35	13 *gBRCA1/2* mutations, 22 unknown	Veliparib dose escalation with metronomic cyclophosphamide MTD 60 mg veliparib q.d., 50 mg cyclophosphamide q.d.	PR in six *gBRCA* patients, prolonged SD in three *gBRCA* patients	[72]
Multiple tumor types	Open label, non-randomized Phase II	298	*gBRCA1/2* mutations	Olaparib 400 mg b.i.d.	RR 31.1% ovarian (60/193), 12.9% in breast cancer (8/62), 21.7% in pancreatic cancer (5/23), 50% in prostate cancer (4/8)	[73]
Multiple tumor types	Phase I dose escalation	63	38 *gBRCA1/2 mutations*	Veliparib dose escalation	PR in two *gBRCA1/2* patients, SD >4 months in ten patients, PR in one non-*BRCA* patient, SD >4 months in seven patients	[74]
Multiple tumor types	Phase I dose escalation	27	Not required	Sapacitabine and seliciclib dose escalation	PR in two patients, both *gBRCA1/2* mutation carriers (one pancreatic cancer, one breast cancer)	[75]
NSCLC (advanced)	Prospective, non-randomized Phase II	18	Under-expression *BRCA1* mRNA, over-expression *XPG/ERCC1*	Trabectedin 1.3 mg/m^2 every 21 days	No objective responses, study terminated early	[76]
NSCLC (advanced, EGFR wt)	Prospective, non-randomized Phase II	111	Stratified and treated according to *BRCA1* mRNA expression	Gemcitabine/cisplatin in low *BRCA1* expressing tumorsdocetaxel cisplatin in intermediate *BRCA1* expressing tumorsdocetaxel in high *BRCA1* expressing tumors	Reduced ORR in low *BRCA1* gemcitabine/cisplatin group compared with high *BRCA1* docetaxel group (25 vs 41.9%), but significantly increased 2-year OS (41.2% vs 0%)	[36]
NSCLC (advanced, EGFR wt)	Prospective, randomized Phase II	391	Stratified and treated according to *BRCA1* and *RAP80* mRNA expression in study arm	Docetaxel/cisplatin in controls study arm assigned to gemcitabine/cisplatin, docetaxel/ cisplatin or docetaxel according to *RAP80* and *BRCA1* expression	Worse survival in study arm (OS 8.52 vs 12.66 months) and study closed	[37]
Pancreatic (metastatic)	Dose escalation Phase I	22	Two *gBRCA1/2* mutations	Dose escalation veliparib; oxaliplatin 85 mg/m^2, 5-FU 400mg/m^2 bolus, 2400 mg/m^2 over 3 days, every 14 days	RR 14% but both *gBRCA* mutation carriers responded (1 PR, 1 CR)	[77]

5-FU: Fluorouracil; b.i.d.: Twice daily; CR: Complete response; EGFR: EGF receptor; *gBRCA1/2*: Germline *BRCA1/2*; MTD: Maximum-tolerated dose; NSCLC: Non-small-cell lung cancer; ORR: Overall response rate; OS: Overall survival; PR: Partial response; q.d.: Once daily; RR: Response rate; SD: Stable disease; wt: Wild type.

ing surgery and at least one line of chemotherapy with platinum and paclitaxel, and were not eligible if any tumors were >3 cm in size. Patients received the retroviral vector intra-peritoneally for 4 consecutive days every 4 weeks. Six patients were enrolled into the study before it was terminated, with all 6 patients developing a neutralizing antibody response to the vector, rapidly clearing the vector from peritoneal fluid. All six patients progressed during the first 3 months of therapy. Future *BRCA1 or BRCA2* gene therapy trials may require either a less immunogenic vector or concurrent immunosuppression.

Future perspective

Historically, identifying *gBRCA1/2* mutations was important for determining future cancer risk in patients, prompting discussions about prophylactic surgery, and genetic testing for family members. Recent work has demonstrated that *gBRCA1/2* mutation carriers (and possibly also patients with low *BRCA1* expression or inactivation of other homologous recombination genes) are more sensitive to platinum-based chemotherapy although at present standard treatment regimes are little different for *gBRCA1/2* mutation carriers compared with non-mutation carriers. Further work is required in order to determine whether choice of chemotherapy in *gBRCA1/2* mutation carriers should be tailored in order to exploit this apparent platinum hypersensitivity. Potential examples include trials of intraperitoneal chemotherapy explicity in ovarian cancer patients with *gBRCA1/2* mutations and trials of high-dose chemotherapy explicitly in breast cancer patients with *gBRCA1/2* mutations.

Unquestionably, the biggest recent advance in the treatment of *gBRCA1/2* mutation carriers has been the development of PARP inhibitors. High levels of efficacy have been demonstrated in relapsed ovarian cancer and efficacy has also been shown in breast, prostate and pancreatic cancer. Maintenance studies following first-line chemotherapy are currently underway in patients with advanced ovarian cancer who have *gBRCA1/2* mutations. If the efficacy in the relapsed setting translates into the first line setting then hopefully this will have a significant impact on the disease course for these individuals. Trials are also underway in the maintenance setting in patients with metastatic breast cancer and *gBRCA1/2* mutations. In triple negative breast cancer, a trial is underway in the neoadjuvant setting in combination with chemotherapy, although *BRCA* mutations are not required to enter this trial.

Future trials will also investigate the potential for PARP inhibition in the adjuvant setting for breast cancers and clarify its utility in prostate and pancreatic cancer. One of the limitations of these efforts will be the ability to identify *gBRCA1/2* mutation carriers and sequencing should be made more widely available in order to facilitate this.

A further challenge will be identifying the patients without *gBRCA1/2* mutations who also stand to benefit from PARP inhibition through somatic mutation of *BRCA1*, *BRCA2* or other HRD genes, or through methylation of *BRCA1*. Clinically applicable tests of HRD are being actively sought and the validation of any of these would be hugely beneficial.

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Executive summary

- Germline *BRCA1/2* mutation carriers have a significantly increased risk of breast, ovarian and other solid cancers.
- A recognised 'BRCAness' phenotype for ovarian cancer consists of young age at diagnosis, high-grade serous histology, sensitivity to platinum-based chemotherapy, significantly prolonged survival but higher risk of visceral metastases.
- The breast BRCAness phenotype is of grade 3, triple-negative, node negative cancers presenting in younger patients.
- Tumor *BRCA1* mRNA expression has been shown to predict response to platinum-based cytotoxic chemotherapy.
- *gBRCA1/2*-associated ovarian cancer is very platinum sensitive, with clinical trials also suggesting a role for platinum in *gBRCA1/2*-associated breast cancer.
- PARP inhibitors have shown considerable promise in *BRCA1/2*-deficient advanced ovarian cancer and are under investigation in the adjuvant setting in breast and ovarian cancer.
- Evidence of PARP inhibitor efficacy have also been identified in *gBRCA1/2*-muitation carriers with prostate and pancreatic cancer.
- Impressive efficacy for the PARP inhibitor olaparib has been demonstrated when it was used as a maintenance therapy in patients with relapsed platinum-sensitive high grade serous ovarian cancer. The patients who benefited most from olaparib were those with *BRCA1* or *BRCA2* mutations.

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