symposium article

The clinical development of inhibitors of poly(ADP-ribose) polymerase

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A number of inhibitors of DNA repair have been evaluated or are undergoing development as potential cancer treatments. Inhibitors of poly(ADP-ribose) polymerase (PARP) are of particular interest in treating hereditary breast cancers occurring in patients who are carriers of BRCA1 or BRCA2 mutations. *In vitro* PARP inhibitors are highly cytotoxic to cell lines carrying BRCA mutations while only minimally toxic to cell lines without these mutations. This is thought to be due to a phenomenon known as synthetic lethality where the accumulation of single-strand breaks consequent on PARP inhibition are converted to double-strand breaks on cell division. Cancer cells in BRCA carriers are uniquely unable to repair the consequent double-strand breaks that result during cell division. PARP inhibitors were initially developed as possible chemo-potentiating agents but have now been evaluated clinically in BRCA-related tumors, showing remarkable single-agent activity. The potential future development and use is reviewed.

introduction

DNA repair is a process essential to life. It has been estimated that each cell sustains many thousand of episodes of DNA damage every day. Normally these are repaired by a wide variety of specific single- and double-strand break repair mechanisms [1]. There are many examples of hereditary defects in DNA repair enzymes associated with predisposition to cancer. Defects in mismatch repair (MMR) are associated with hereditary non-polyposis colon cancer (HNPCC) [2]. The gene that is mutated in ataxia telangetactasia (ATM), a cancer-prone disease, is involved in DNA repair [3] as are the Fanconi proteins, which are characteristically mutated in the Fanconi syndromes [4].

The BRCA1 and BRCA2 genes were originally discovered by studying families with hereditary breast and ovarian cancer [5]. It is now known that both of these are involved in a form of DNA repair known as homologous recombination (HR) repair. HR is a form of double-strand break repair that occurs in the G2 phase of the cell cycle where the second double-stranded copy of the DNA is used as a template to form an error-free repair. Individuals who are carriers of BRCA1 or BRCA2 mutations are heterozygous, with one mutated, non-functional allele and one wild-type, functional allele. The single allele is sufficient to allow HR to take place normally, so they are phenotypically normal. However, the loss of the second allele due to a chance mutation or other event will lead to a cell not capable of HR repair. In this event a process of non-homologous end-joining catalyzed by DNA protein kinase takes place. Since this process is error prone further mutations may accumulate leading to a high possibility of oncogenesis [6]. Women who are carriers of BRCA1 and BRCA2 mutations have a very high lifetime risk of developing breast or ovarian cancer. Men may develop prostate cancer and both sexes are known to be at an increased risk of pancreatic cancer [7]. Other cancers are also likely to be associated with BRCA1 and BRCA2 mutation carriers [8].

Since many anticancer drugs act by damaging DNA there has been a long-standing interest in using inhibitors of DNA repair as chemo-potentiating agents. Trials of two inhibitors of O6-alkyl guanine alkyl transferase (O6-benzylguanine and lomaguetrib) have largely been unsuccessful probably on account of the potentiation of normal tissue toxicity [9]. However, trials of inhibitors of poly(ADP-ribose) polymerase (PARP) have been more promising. In the early 1980s Durkacz et al. [11, 12] showed that PARP was involved in the repair of single-strand breaks in DNA and that the toxicity of certain DNA-damaging agents was enhanced by 3-aminobenzamide, an inhibitor of PARP. An overall pattern emerged (to be reviewed later) that, *in vitro*, PARP inhibition consistently potentiated the cytotoxicity of monomethylating agents (such as temozolomide) and topoisomerase I inhibitors (such as camptothecin). Results with bifunctional alkylating agents and platinum drugs were less consistent [13]. [Note: it is now known that there are at least 17 homologues of PARP [10], for many of which the physiological function is not clear. The discussion in this article is confined to PARP-1, although the less abundant PARP-2 can probably function in a similar way.]

3-Aminobenzamide is a comparatively weak inhibitor of PARP and is not sufficiently potent for *in vivo* use. Because of interest in the potential of PARP inhibitors, both as
chemo-potentiating agents for cancer and in other areas of medicine, various groups developed high-potency PARP inhibitors for in vivo, and subsequently clinical, use. PARP-1 is activated by DNA strand breaks, uses nicotinamide–adenine dinucleotide (NAD) as a substrate and forms polymers of ADP-ribose attached to histone proteins and itself. Since these polymers are negatively charged they cause dissociation of the histone proteins from the DNA, thus permitting specific DNA repair enzymes to access the DNA backbone. Most of the inhibitors of PARP-1 that have been developed (including 3-aminoobenzamide) have a structural mimic of nicotinamide to permit binding to the enzyme. One of the first high-affinity PARP inhibitors (NU1085) was developed by a group at Newcastle University (UK), and a subsequent collaboration between Newcastle and Agouron Pharmaceuticals led to the selection of AG014699 for clinical development (Figure 1). This was the first PARP inhibitor to enter clinical trials for cancer [14, 15].

In 2005 two independent groups published observations showing a remarkably high cytotoxic potency of PARP inhibitors towards cell lines that lacked BRCA functionality compared with isogenic lines that were heterozygous with one functional BRCA gene or wild type with two functional genes. Bryant et al. [16] used BRCA2-deficient cell lines (V-C8) and the PARP inhibitor AG014361 (closely structurally related to AG014699). AG014361 was ~250-fold more potent against the BRCA2-deficient cell lines than against the heterozygote or wild type, and cured a xenograft model of the deficient cell line while having no effect on the heterozygote or wild type. Farmer et al. [17] used both BRCA1- and BRCA2-deficient cell lines and PARP inhibitors developed by Kudos and showed the same substantial difference in cytotoxicity for both BRCA1 and BRCA2 cell lines. These remarkable results are thought to be the result of a phenomenon known as synthetic lethality, in which two molecular lesions combine to have a lethal effect on the cell, although neither of them is harmful individually. In an editorial published in the New England Journal of Medicine, Iglehart and Silver [18] clearly emphasized the potential clinical validity of synthetic lethality in cancer treatment. The theoretical principle is that two genes are in a synthetic lethal relationship if the mutation in each gene is by itself not lethal, while the simultaneous presence causes cell death. Applied in drug research, this hypothesis has been applied to cells deficient in BRCA1 and BRCA2 (resulting in defective homologous DNA repair recombination) that should be extremely sensitive to drugs that inhibit PARP, an essential component for the repair of single-strand breaks through the base excision repair pathways. In fact, exposure of the cells to a PARP inhibitor led to the accumulation of spontaneously occurring single-strand breaks in DNA, since these cannot be repaired. When the cell divides and DNA replication takes place, these single-strand breaks are converted to double-strand breaks in one of the daughter strands. In cells that have functional HR these double-strand breaks are repaired without errors, explaining the lack of toxicity of the PARP inhibitors towards the heterozygote and wild-type cell lines. However, if HR is deficient, as it is in the BRCA-negative cell lines, these double-strand breaks cannot be repaired, leading to collapse of the replication fork and cell death.

**in vitro studies using PARP-1 inhibitors in combination with chemotherapy**

Suppression of PARP activity increases cell susceptibility to DNA-damaging agents and inhibits strand break rejoining. PARP is essential for the repair of single-strand breaks through the base excision repair pathways indicating a potential amplifier role for this cellular target that may enhance the effectiveness of chemotherapy [19–21]. Briefly, in this section in vitro evidence of chemopotentiation by PARP inhibitors is summarized focusing on compounds that are already in phase I/II clinical trials, mostly in combination with chemotherapy.

**AG014699 (PF-01367338) (Pfizer)**

AG014699 is the phosphate salt of AG14447, which results in improved aqueous solubility rendering it more suitable for clinical trials. It has been shown in preclinical models to potentiate the cytotoxicity of several chemotherapeutic drugs. Briefly, Thomas et al. [22] carried out the first characterization of a new class of PARP inhibitors with the aim of identifying a compound suitable for clinical use. They analyzed the relationships between the in vitro efficacy of the inhibitors, alone or in combination with the monofunctional alkylating agent, temozolomide (TMZ), and the topoisomerase I poison, topotecan, determining their intrinsic growth-inhibitory potential and in vivo anticancer efficacy. This screening identified AG14447 as the most promising drug with a 10-fold more potent activity than the lead compound, when given in single or multiple doses. In the same study, the authors reported that this compound increased TMZ and topotecan effectiveness in their colon cancer in vitro model. In vivo validation of the results has led to the selection of AG14447, administered as its prodrug AG014699, being considered their most promising compound for clinical trials. In 2009, Ali et al. [23] showed that AG014699 did not enhance TMZ-induced growth inhibition in vitro but strongly increased the activity of chemotherapeutic drug against SW620 xenografts. They explained this discrepancy by suggesting that mechanisms other than inhibition of DNA repair were contributing to the observed effects of AG014699 in vivo. They introduced the

![Figure 1. Structure of the PARP inhibitor AG014699.](https://academic.oup.com/annonc/article-abstract/22/suppl_1/i53/243877/53)
suggestion that AG014699 and AG14361 increased the extent of tumor drug exposure by enhancing vascular perfusion. This hypothesis opened the way for the possible use of this class of compounds as enhancers of chemotherapeutics effectiveness, not only by their ability to inhibit the classical mechanisms of DNA repair, but also by actions to enhance in vivo distribution of some conventional drugs.

Preliminary data from our lab indicates that AG14699 may act as an enhancer of chemotherapeutics effectiveness by combining it with carboplatin, oxaliplatin and gemcitabine in ovarian, breast and pancreas cancers, respectively; in vitro [24, data unpublished]. We have shown that the effectiveness of the conventional drugs increased in the presence of the PARP inhibitor by ~30% as inhibition of both cell growth and colony formation—in experiments carried out by Azzariti et al. [25]. In tumor models of breast and pancreas, where cell lines both mutated for BRCA and wild type were available, the phenomenon was more evident in cells with BRCA1 or BRCA2 mutations. In in vitro models of ovarian cancer, our data confirmed the potentiation of chemotherapy reported by Curtin et al. [26], albeit with a drug other than TMZ. Finally, Daniel et al. [27] extended the in vitro model to evaluate the ability of AG014699 as an enhancer of TMZ and topotecan activity; they used an in vitro model of human neuroblastoma and confirmed the ability of this PARP inhibitor to increase TMZ’s and topotecan’s ability to reduce cell growth and cloning efficiency.

**olaparib (AZD2281; KU-0059436) (Kudos/ AstraZeneca)**

Olaparib (AZD2281; KU-0059436) is a nanomolar inhibitor of both PARP-1 and PARP-2 that shows activity against BRCA1-deficient breast cancer cell lines [28].

The increasing interest in PARP inhibitors utilization in tailored anticancer therapy led to investigation of their application directed towards selected tumors. In 2008, Rottenberg et al. [29] hypothesized a promising utilization of AZD2281 in triple-negative breast cancer patients based on the knowledge that these tumors frequently harbor defects in DNA double-strand break repair through HR, related to BRCA1 dysfunction, rendering these tumors more susceptible to inhibition by PARP inhibitors. In a newly established in vivo BRCA1-deficient mammary tumor model, the same authors demonstrated that tumors responded to AZD2281 treatment even after acquired drug resistance related to increased expression of drug transporters, Abcb1a/b. In their article, Rottenberg et al. [29] reported that AZD2281 plus platinum compounds such as cisplatin and carboplatin, significantly prolonged recurrence-free survival and overall survival.

Deficiency in BRCA2 results in complex genomic rearrangements that are often the hallmark of tumors caused by such mutations [30]. Evers et al. [31] characterized the ability of AZD2281 to potentiate cisplatin effectiveness in BRCA2-deficient mammary tumor, demonstrating that this PARP inhibitor synergized the platinum compound in BRCA2-deficient mammary tumor cells whereas the combination was additive in BRCA2-proficient tumor cells. In 2009, similar results were also reported by Hay et al. [32]. In their experiments, a BRCA2/p53-deficient mammary tumor in vivo model was exposed to the PARP inhibitor in combination with carboplatin and there was no significant difference between the two therapeutic regimens after 28 days of drug treatment. Conversely, prolonged (>100 days) and continued PARP inhibition enhanced carboplatin effectiveness in terms of tumor relapse and mouse survival. More recently, Evers et al. [33] expanded the panel of chemotherapeutics drugs that increased their activity when given in combination with AZD2281, to three alkylators, chlorambucil, melphalan and nimustine. They demonstrated that there was a synergic drugs interaction, with a combinatorial index of less than −0.15, in the BRCA2-deficient cell lines whereas combinations of alkylating agents with AZD2281 in the BRCA2-proficient model resulted in additive effects. Furthermore, Zander et al. [34] reported data on the in vivo evaluation of combined administration of AZD2281 plus the topoisomerase I inhibitor topotecan in BRCA1/p53-deficient mouse mammary tumors. Their results showed that AZD2281 substantially increases topotecan’s activity even if none of the tumors were completely eradicated.

**veliparib (ABT-888) (Abbott)**

Veliparib (ABT-888) is an orally active PARP-1 and PARP-2 inhibitor. ABT-888 potentiated the action of various chemotherapeutic drugs as reported by Donawho et al. [35]. They combined ABT-888 with TMZ in orthotopic rat glioma and melanoma models, with cisplatin or carboplatin in a breast carcinoma xenograft model and with cyclophosphamide in a lymphoma and human breast carcinoma xenograft models. Their results showed that this PARP inhibitor acts as a broad-spectrum enhancer of DNA-damaging agents. Similar results were obtained by other authors, who demonstrated in vitro the capability of ABT-888 to potentiate TMZ in several cancer models, such as colon cancer, cervical carcinoma and melanoma and leukemia cell lines. They confirmed this promising drug combination in in vivo B-cell lymphoma, melanoma, glioma, small-cell lung carcinoma, non-small-cell lung carcinoma, pancreatic, ovarian, breast and prostate cancer xenografts [36–38]. Later, Clarke et al. [39] demonstrated that the capability to sensitize glioblastoma xenografts to TMZ by ABT-888 was dependent on the status of tumors, i.e. whether they had been already exposed to TMZ, which may cause acquired resistance. These results indicated that patients with newly diagnosed glioblastoma may be more likely to respond to combined TMZ/ABT-888 therapy than patients with recurrent disease. Other evidence concerning acquired resistance to combination treatment with TMZ and ABT-888 in an in vitro colon carcinoma model was provided by Liu et al. [40]. The authors explained this phenomenon by the upregulation of the HR DNA repair pathway to compensate for the loss of base excision repair.

**INO-1001 (Inotek/Genentech)**

INO-1001 is an isothidolinone derivative and a potent inhibitor of PARP with chemosensitization and radiosensitization properties.

Since 2005, Cheng et al. [41] have underscored the ability of INO-1001 to increase the efficacy of TMZ in both in vitro and...
in vivo models of malignant glioma tumor. Their tumor models allowed them to investigate the possibility that one could overcome tumor resistance to TMZ due to base excision repair (responsible for removing the N-methylpurine adducts created by temozolomide). They utilized cells to obtain xenografts with both proficiency and deficiency in DNA mismatch: their results demonstrated that the inhibition of PARP, using the highly potent inhibitor INO-1001, restores some degree of temozolomide sensitivity in a resistant human glioblastoma multiforme model.

Later, Toshimitsu et al. [42] demonstrated that this promising combination could be effective also in a rat model of extremity malignant melanoma. They carried out their experiments both in MMR-deficient and MMR-proficient xenografts. In the first model, treatment with TMZ plus INO-1001 induced an increase in tumor volume at day 40 after therapy of ~22.6% with respect to 322.8% obtained after TMZ alone. In the MMR-proficient model, there was only little improvement in TMZ efficacy with INO-1001 treatment; in fact, the tumor volume increase was from 152.4% to 257%. Furthermore, Mason et al. [43] expanded the panel of chemotherapeutic agents whose activity could be amplified by INO-1001. They showed that also the effectiveness of an anthracycline, such as doxorubicin, could be enhanced by INO-1001 in models of p53-deficient breast cancer.

Iniparib (BSI-201) (BiPar Sciences)
Iniparib (BSI-201) is a PARP inhibitor that has been demonstrated to potentiate antitumor effects of carboplatin and gemcitabine in a triple-negative breast cancer cell line [44]. Subsequently, the randomized clinical trial in breast cancer utilizing gemcitabine + carboplatin chemotherapy demonstrated superior results when the chemotherapy was given with BDI-201 [45]. Also, Ossovskaya et al. [46] reported that the combination of BSI-201 and topotecan produced significant antitumor activity and increased the percentage of complete tumor regression compared with topotecan alone in an ovarian in vivo model. The same authors demonstrated that this potentiation did not occur in a prostate cancer model.

GPI21016 (MGI Pharma/Eisai)
GPI21016 is a PARP inhibitor that has been shown to enhance cisplatin effectiveness in an in vivo leukemia model [47]. Lapidus and coauthors [47] demonstrated that this PARP inhibitor increased the survival benefit from cisplatin, with an increase in life span of 160% compared with the chemotherapeutic drug alone, and reduced deficits in nerve conduction velocity induced by the platinum agent, thus limiting platinum-induced neuropathy.

CEP-9722 (Cephalon)
CEP-9722 is the prodrug of CEP-8983, which has been demonstrated to be a PARP inhibitor able to potentiate the cytotoxicity of TMZ and SN-38, the active metabolite of irinotecan, in several cell lines of glioblastoma, neuroblastoma and colon cancer [48]. The prodrug has been shown to enhance both TMZ and irinotecan effectiveness, with a reduction in tumor growth of ~60% and ~80%, respectively, in in vivo models of glioblastoma and colon carcinoma [48].

clinical results using PARP-1 inhibitors strategies
At least nine PARP-1 inhibitors are in clinical or late preclinical development. These are summarized in Table 1. These have a variety of pharmacophores but for the most part are inhibitors of PARP-1 because they possess a mimic of nicotinamide. The exception to this is the BiPar/Sanoﬁ Aventis compound, where the mechanism is less clear. Despite the similarity in their mechanism of action the clinical development strategies that have been adopted are quite variable, depending on the proposed clinical application. There are a number of different roles that PARP inhibitors may have in oncology: (i) they may potentiate speciﬁc drugs, such as monomethylating agents or topoisomerase I inhibitors, as has been characterized in vitro; (ii) they may potentiate radiation therapy (as has been demonstrated in experimental systems [49]; (iii) they may be used as single agents in the treatment of tumors that arise in patients who are carriers of a mutant BRCA1 or BRCA2 gene, and whose tumors are therefore deficient in HR; (iv) they may be used in combination with DNA-damaging drugs that are not necessarily potentiated by PARP inhibition in vitro. Trials conducted to date have focused on cancers that are likely to be deﬁcient in HR, although not necessarily have BRCA mutation. In addition there is the possibility that PARP-1 inhibitors might be used in the future for chemoprevention of cancer in known carriers of BRCA mutations.

Table 1. PARP inhibitors in clinical development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Company</th>
<th>Route</th>
<th>Clinical status</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG014699/</td>
<td>Pfizer</td>
<td>iv (oral)</td>
<td>Phase I/II combos</td>
</tr>
<tr>
<td>PF-01367338</td>
<td></td>
<td></td>
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<tr>
<td>KU59436/AZD2281/</td>
<td>AstraZeneca/Kudos</td>
<td>oral</td>
<td>Phase II/III combos</td>
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<tr>
<td>olaparib</td>
<td></td>
<td></td>
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<tr>
<td>Veliparib/ART888</td>
<td>Abbott</td>
<td>oral</td>
<td>Phase II/III combos</td>
</tr>
<tr>
<td>Iniparib BSI-201</td>
<td>BiPar/Sanoﬁ-Aventis</td>
<td>iv</td>
<td>Phase II/III combos</td>
</tr>
<tr>
<td>INO-1001</td>
<td>Inotek</td>
<td>iv</td>
<td>Phase 2b complete</td>
</tr>
<tr>
<td>GPI21016</td>
<td>MGI Pharma/Eisai</td>
<td>oral</td>
<td>Phase 1</td>
</tr>
<tr>
<td>CEP-9722</td>
<td>Cephalon</td>
<td>oral</td>
<td>Phase 1</td>
</tr>
<tr>
<td>MK4827</td>
<td>Merck &amp; Co.</td>
<td>oral</td>
<td>Phase 1</td>
</tr>
<tr>
<td>BMN-673</td>
<td>Biomarin/Lead Pharmaceuticals</td>
<td></td>
<td>Preclinical</td>
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iv, intravenous.
mononuclear cells and tumor biopsies. Once a PARP inhibitory dose of AG014699 had been established the dose of temozolomide was successfully escalated to the standard single-agent dose for temozolomide (200 mg/m² per day for 5 days) [15]. Subsequently a phase II trial of AG014699 in combination with temozolomide was conducted in patients with metastatic melanoma [50], documenting a partial response rate of 17.3%, progression-free survival of 3.5 months and overall survival of 9.9 months. There were no discernible side-effects attributable directly to the PARP inhibitor, although there was some increase in the myelosuppression related to temozolomide. These results compared favourably with previous results using temozolomide alone documented by the same investigators. At the current time there are few data available on the combination of PARP inhibitors with topo-isomerase I inhibitors.

**Role 2: Potentiation of radiotherapy.** There are currently no results available on this indication although a number of trials are planned.

**Role 3: Use in BRCA-related tumors.** Olaparib (AZD 2281) was developed by Kudos and AstraZeneca. A phase I study was conducted using oral administration of the single agent with patients who were known to be BRCA carriers being selected. The end point was dose-limiting toxicity. Mood alteration, somnolence, thrombocytopenia and fatigue were reported. Responses were observed in BRCA carriers with breast, ovarian and prostate cancer [51]. Subsequently phase II studies were conducted in BRCA-related breast [52] and ovarian [53] cancer. The schedule of olaparib was the same, with each patient group divided into two sequential cohorts, the first receiving continuous oral olaparib at the maximum tolerated dose (400 mg twice daily), and the second a lower dose (100 mg twice daily). The primary end point of the studies was the objective response rate (ORR) and secondary end points included efficacy of olaparib, progression-free survival and duration of response. In breast cancer patients, results showed that the ORR was 41% in the cohort receiving the highest dose and 22% in the other one [52]. In ovarian cancer patients, ORR was 33% in the cohort receiving the highest dose and 13% in the other one [53]. Toxic effects were mainly of low grade in both studies (fatigue, nausea, vomiting and anemia) [52, 53]. These two phase II trials provide positive evidence of the efficacy and tolerability of olaparib treatment in BRCA-mutated advanced breast and ovarian cancer at a dose of 400 mg twice a day. Notably, responses were seen in patients with ovarian cancer resistant to cisplatin.

**Role 4: Use in combination with standard chemotherapy regimens.** Iniparib (BSI-201) is being developed by BiPar Sciences and Sanofi Aventis. A randomized phase II trial was conducted recruiting patients who had triple-negative breast cancer [negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)] who had received at least two previous regimens of chemotherapy. Patients received a combination regimen of gemcitabine + carboplatin and were randomized to receive or not to receive BSI-201. The addition of BSI-201 significantly improved median survival from 7.7 to 12.2 months ($P = 0.005$) [45].

**Other clinical trials in cancer treatment**

Since there are so many PARP-1 inhibitors in development, a wide variety of clinical trials are ongoing. These have been comprehensively reviewed elsewhere [54]. The trials mentioned above have been chosen to exemplify the ways in which PARP-1 inhibitors may be integrated into clinical practice in the future, rather than being an exhaustive list of current activity.

**Resistance to PARP-1 inhibitors**

Resistance to PARP-1 inhibitors used to treat BRCA1 or BRCA2-related cancers certainly occurs. Preclinical data have demonstrated that it is possible for a second mutation in the BRCA gene to restore its functionality [55], thus documenting one possible mechanism of resistance. It is likely that other mechanisms will become apparent in the future.

**Potential future use of PARP-1 inhibitors for cancer prevention**

Individuals who are carriers of a BRCA1 or BRCA2 mutation are known to be at a high risk of developing various cancers. Current management consists of screening with the option of prophylactic surgery—mastectomy or oophorectomy. While these measures reduce the risk of cancers developing they do not eliminate it and also carry their own risks and morbidity. This raises the possibility of using PARP-1 inhibitors for cancer prevention in known carriers. Engineered cell lines that lack BRCA1 or BRCA2 are exquisitely sensitive to PARP-1 inhibition [16, 17]. These may be compared to the potential tumor cell in a patient who is a carrier immediately after it has lost its second allele. The genetic instability that follows, and the acquisition of downstream mutations that reinforce the malignant phenotype [6], is likely to render the tumor more capable of developing resistance to PARP-1 inhibitors. It is therefore possible that a short course of a PARP-1 inhibitor could eliminate transforming cells before an overt tumor was formed and that intermittent short course might reduce, or prevent, the emergence of BRCA-related tumors. Clearly a significant database on the safety of PARP-1 inhibitors would be necessary before such an approach could be justified. So far the symptomatic side-effects of PARP-1 inhibitors at PARP-inhibitory doses have been minimal or absent [15, 51]. However, the role of PARP-1 in DNA repair indicates that their use could be genotoxic and raises the possibility that they might increase the risk of some cancers due to this. Such a risk, if it exists, will probably be small. Short-term treatment of patients with (genotoxic) adjuvant chemotherapy for breast cancer is associated with only a very small risk of the development of chemotherapy-related tumors. The risk of developing leukemia during the 10 years following adjuvant therapy including anthracyclines has been estimated at 0.5% if no radiotherapy is given and 2% if radiotherapy is administered [56]. These data indicate that the risk from short-term exposure to genotoxic agents in the absence of radiotherapy is very low. If a risk of this sort is induced by the use of PARP-1 inhibitors it would have to be weighed against the known high risk of BRCA carriers developing cancers.
discussion
PARP-1 inhibitors have great potential for the treatment of metastatic or advanced cancer occurring in patients who are carriers of BRCA1 or BRCA2 mutations. Existing data show clearly that they are extremely well tolerated and have significant anticancer activity, even in patients resistant to conventional chemotherapy. The use of PARP-1 inhibitors as chemo-potentiators, either in patients receiving certain DNA-damaging drugs or in those who may have a HR-deficient phenotype is also extremely promising. The development of a predictive test for HR functionality would greatly facilitate the development of PARP inhibitors in a wide variety of tumor types. PARP-1 inhibitors may also turn out to be useful potentiators of radiotherapy but at the current time clinical data are lacking. Further indications in cancer prevention remain speculative.

disclosures
The authors declare no conflict of interest.

references


