Published in final edited form as:
Curr Med Chem. 2012 August 1; 19(23): 3907–3921.

Role of PARP Inhibitors in Cancer Biology and Therapy

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Abstract

Deeper understanding of DNA repair mechanisms and their potential value as therapeutic targets in oncology heralded the clinical development of poly (ADP-ribose) polymerase (PARP) inhibitors. Although initially developed to exploit synthetic lethality in models of cancer associated with defective DNA repair, our burgeoning knowledge of PARP biology has resulted in these agents being exploited both in cancer with select chemotherapeutic agents and in non-malignant diseases. In this review article, we briefly review the mechanisms of DNA repair and pre-clinical development of PARP inhibitors before discussing the clinical development of the various PARP inhibitors in depth.

Keywords

Base excision repair (BER); BRCA1; BRCA2; CEP-9722; DNA repair; GPI-21016; INO-1001; iniparib; MK-4827; LT-673; olaparib; poly(ADP-ribose) polymerase (PARP) inhibitors; rucaparib; synthetic lethality; triple negative breast cancer; veliparib

INTRODUCTION

1.1. DNA Repair

DNA continually sustains damaging alterations under a constant barrage of environmental insults, toxic products of metabolism, and erroneous DNA replication. These alterations can be divided into: 1) base modifications; 2) single strand breaks (SSB); 3) double strand breaks (DSB); and 4) intrastrand or interstrand cross-links. Several DNA repair mechanisms

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CONFLICTS OF INTEREST

The authors report no competing interests concerning the validity of research or for financial gain.

have evolved to repair these lesions and maintain genomic integrity. Given the large array of potential lesions and the importance of high-fidelity repair, DNA repair mechanisms are generally complex, highly redundant, and to a large extent conserved across phylogenetic classes [1].

Canonical DNA repair mechanisms include: 1) base excision repair (BER); 2) nucleotide excision repair (NER); 3) mismatch repair (MMR); 4) recombinational repair comprising homologous recombination (HR) and non-homologous end-joining (NHEJ); and 5) direct repair mechanisms. SSB repair mechanisms include BER, NER, or MMR pathways whilst DSB repair mechanisms consist of HR and NHEJ pathways. Direct repair of, for example, guanine base methylation, is affected by the protein O6-methylguanine-DNA methyltransferase (MGMT). Full details of these mechanisms are beyond the scope of the review and readers are referred to detailed recent reviews on the topic [2–5].

1.2. Role of PARP in DNA Repair

Amongst the various DNA insults, single strand alterations occur most often at a rate of approximately 10^4 per day and are repaired through a combination of BER, NER and MMR mechanisms using the intact DNA strand as a template. The predominant pathway of SSB repair is the BER utilizing a family of related enzymes termed poly-(ADP-ribose) polymerases (PARP).

Following the initial description by Chambon *et al* in 1963 of a DNA-dependent polyadenylic acid synthesizing nuclear enzyme, 17 different enzymes have since been characterized based on sequence homology within the catalytic domain [6]. Of the 17 known members of the PARP super-family in humans, PARP-1, PARP-2, tankyrase1, tankyrase2, and vPARP are thought to have roles in DNA repair but PARP-1 accounts for more than 90% cellular PARP activity and remains the most studied. PARP enzymes are thought to have 4 domains – an N-terminal DNA-binding domain that comprises two zinc finger motifs, a C-terminal catalytic domain, a central auto-modification domain and a caspase-cleaved domain [7].

1.2.1. PAR-ylation as Dynamic Equilibrium—PARP enzymes are found in the cellular nucleus and are activated by DNA damage [8]. PARP-1 acts as a “molecular sensor” to identify DNA SSBs; it is recruited and activated by SSBs as a homodimer in a fast reaction which is amplified 10 to 500-fold with formation of poly-(ADP-ribose) (PAR) polymers within 15 to 30 seconds. Upon binding to a damaged strand *via* its zinc finger DNA-binding domain, PARP-1 undergoes a conformational change inducing the C-terminal catalytic domain to transfer ADP-ribose moieties from cellular nicotinamide-adenine-dinucleotide (NAD+) to protein acceptors, including the central auto-modification domain of PARP1 itself.

The major mechanism that limits the PAR-ylation of protein acceptors is PAR hydrolysis by poly-(ADP-ribose) glucohydrolase (PARG). The amount of PAR present in the cell depends on the balance between PARP1 (and to a lesser extent PARP 2) on the one hand, and PARG on the other. PARP-1 function is restored by the degradation of PAR. In case of small to moderate damage, PARP-1 allows for the restoration of genomic integrity and the return to normal cellular function. However, emerging evidence has implicated PARP-1 over-activation in unregulated PAR synthesis, depleting NAD, and consequently ATP, eventually leading to widespread cell death. In this recently characterized model, PARP-1 over-activation results in the synthesis of numerous long branched PAR polymers which triggers the translocation of apoptosis-inducing factor (AIF) from mitochondria to the nucleus resulting in caspase-independent cell death [9]. This mechanism of cell death has been termed *parthanatos*. PARP-1-dependent cell death has been implicated in a wide variety of

disease models ranging from neurological illnesses like stroke and Parkinson's disease to the acute coronary syndrome.

1.2.2. Base Excision Repair—The lengthening PAR chain builds up a large negatively charged structure at the SSB which recruits other DNA repairing enzymes. These include DNA ligase III (LigIII), DNA polymerase beta (polβ), and scaffolding proteins such as x-ray cross complementing gene 1 (XRCC1), that collectively form the base excision repair (BER) multi-protein complex. Among the proteins it recruits, 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. As it dissociates from DNA, PARP-1 becomes inactive and no further synthesis of the PAR polymer occurs [10].

1.2.3. The Role of PARP in DNA Repair Pathways Other Than BER—In addition to its involvement in BER and SSB repair, PARP-1 appears to aid in the NHEJ and HR pathways of DSB repair. NHEJ directly ligates the broken ends of a damaged DNA chain often resulting in a loss of genetic material whilst HR repairs DSBs by using information derived from a homologous sequence, often the sister chromatid, as a blueprint. Recent studies suggest that NHEJ and HR are competing pathways – with the outcome being dependent on the initial event following DSB formation. NHEJ is initiated by the Ku heterodimer (consisting of Ku70 and Ku80) and DNA-PK complex binding to the DSB whilst HR results when an exonuclease creates a 3' single strand tail that is subsequently covered by RAD51 [11].

Work from a group at the Mayo Clinic suggests that PARP inhibition may have direct effects on NHEJ. Patel *et al* previously reported that PARP inhibition results in NHEJ deregulation and that NHEJ mediated sensitivity of HR-deficient cells to PARP inhibitors. This implies that PARP-mediated genomic instability may be secondary to error-prone NHEJ in addition to BER inhibition [12].

1.2.4. PARP Function Other Than DNA Repair—Poly-(ADP) ribosylation modulates the function of many proteins and functions as a signaling mechanism akin to phosphorylation or acetylation. Therefore, PARP-1 appears to have broad genome-wide functions. Recent work has intimated a role for PARP-1 in the generation of normal antibody responses and in the formation of long-term memory in mammals [13–14]. When mice were exposed to several different learning stressors, PAR chain buildup was immediately noted in their cerebral cortices and hippocampi. Subsequently, when PARP activity in the CNS was suppressed by the inter-ventricular injection of PJ-34, a potent PARP inhibitor, long-term memory formation was impaired without commensurate effects on short-term memory formation suggesting a role for PARP-1 activation in long-term memory formation.

1.3. Effect of PARP Inhibition in Cells with Aberrant DNA Repair Mechanisms

Despite the critical role for PARP-1 in the maintenance of genomic integrity, PARP-1 deficiency does not result in embryonic lethality. In a Polβ knockout mouse model extensive neuronal apoptosis was noted during neurogenesis followed by neonatal mortality. In contrast, PARP-1 knockout mice were viable but did appear to be highly sensitive to genomic instability caused by DNA-alkylating agents or γ-irradiation [15]. This is not surprising given the multiple redundant DNA repair mechanisms present in eukaryotic cells – unrepaired SSBs can possibly be converted into DSBs at replication forks allowing subsequent repair by unaffected HR mechanisms.

However, if cells have a deficient HR repair mechanism, PARP-1 inhibition can be expected to result in unsalvageable DNA damage and consequent lethality. This was elegantly described in 2 papers in Nature published in 2005. First, Bryant *et al.* showed that BRCA2-deficient cells - in which the homologous recombination mechanism is defective - were exquisitely sensitive to PARP-1 inhibition [16]. Subsequently, Farmer and colleagues demonstrated that small molecule PARP-1 inhibition in embryonic stem cells lacking wild-type BRCA1 and BRCA2 resulted in early cell death [17].

The concept of "synthetic lethality", first articulated by Dobzhansky in 1946 as a situation in which mutations in two genes have little or no effect individually but the combination results in cell death, is thus well illustrated by PARP inhibition in BRCA deficient cells [18]. Inhibition of PARP allows single strand breaks to progress to DSBs. In the absence of functioning HR, this leads to activation of the more error-prone NHEJ. Disabling NHEJ rescues the lethality of PARP inhibition or down-regulation in cell lines lacking BRCA2 or BRCA1. Therefore, NHEJ can be viewed as a requisite cytotoxic effector pathway of inhibition PARP in the absence of functional HR [12]. An anti-tumor strategy based on this approach would specifically target cells with the primary defect and spare healthy cells. Hence, it stands to reason that PARP inhibition will be similarly effective in cells in which HR is deficient or impaired – i.e. cells that share a "BRCA phenotype" or "BRCAness".

The human BRCA-1 gene located on 17q21, encodes the breast cancer type 1 susceptibility protein that interacts with RAD51 to repair DNA DSBs. In addition, its association with the Mre11/Rad50/Nbs1 (nibrin) complex suggests that it may be involved in the NHEJ repair process. Mutations in the BRCA-1 gene result in a predisposition towards breast and ovarian cancer in women and gremlin mutations are associated with the basal epithelial phenotype [19]. Although breast cancer is common in women with BRCA-1/2 mutations (60% risk of developing breast cancer by age 90), it is rare for these genes to be inactivated by mutation in sporadic cancers. However, up to 14% of sporadic breast cancers and 31% of sporadic ovarian cancers are associated with aberrant methylation of the BRCA1 promoter region that results in gene inactivation [20]. Acquired loss of BRCA expression confers a similar clinicopathological phenotype - morphological high grade, aggressive clinical behavior, poor prognosis and a similar genetic profile, i.e. "BRCAness" [21]. The current state of clinical development of various agents in summarized in Table 1 (see Table 1 – PARP Inhibitors in Development) while the development of agents in unselected patients as well as in BRCA-1/2 deficient patients is chronicled in the next section.

1.4. Synergy of PARP Inhibition with Cytotoxic Chemotherapy and Radiotherapy

It can be extrapolated that PARP inhibition may be synergistic with other agents that cause DNA damage including cytotoxic chemotherapy and ionizing radiation. Ionizing radiation therapy (RT) exerts an anti-tumor effect through the induction of hydroxyl free radicals which cause DSBs and is a cornerstone of loco-regional control in diseases such as head and neck cancer (HNC).

The PARP inhibitors ABT-888 and AZD-2281 have demonstrated synergism in combination with ionizing radiation in cell line modes of HNC and lymphoma [22–23]. 2 phase I trials are currently investigating combinations of ABT-888 and radiation: with whole brain radiation in brain metastases (NCT00649207) and with chest wall/nodal irradiation in patients with inflammatory or loco-regionally recurrent breast cancer (NCT01477489). Analogously, PARP inhibition has demonstrated synergy when combined with other DNA damaging agents in sporadic tumors with no intrinsic DNA repair defects including breast cancer (platinum-agents, topotecan and cyclophosphamide), melanoma (temozolomide and dacarbazine) and glioblastoma (temozolomide). These studies are summarized in Table 2 (see Table 2 – Phase I Trials of PARP Inhibitors) [24–37].

MATERIALS AND METHODS

2.1. Search Strategy and Selection Criteria

A systematic search strategy was utilized to interrogate the MEDLINE, EMBASE, Cancerlit, Cochrane, ISI and Web of Science databases for articles published between January 1, 2002, and January 1, 2012. MeSH headings used included “PARP”, “PARP inhibitor”, “PARP inhibition” and “DNA repair mechanisms” to look for pertinent articles discussing clinical development of PARP inhibitors and clinical trials utilizing PARP inhibitors.

Searches were limited to clinical trials and publications in English or with available English translations. The “related articles” feature of PubMed was used for all reports that met the requested criteria as an additional means of identifying potentially relevant investigations. Data from recently published and ongoing Phase I/II/III trials were gathered by searching clinical trial databases. The abstract databases of the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology annual congresses were also searched for recently released clinical trial data. Additionally, the references in reviewed articles were analyzed to find further relevant publications.

DISCUSSION

3.1. Pre-Clinical Development of the PARP Inhibitors

PARP enzymes catalyze the transfer of ADP-ribose moieties from cellular NAD+ to nuclear proteins forming ADP-ribose polymers which led the first inhibitors to be structural analogues of NAD+ blocking the binding of NAD+, thereby inhibiting PARP activity. Nicotinamide was the first PARP inhibitor identified in 1971. Subsequently, second-generation agents were identified by empirical screening of drug libraries looking for structural analogues of a 3-aminobenzamide structure – including the tricyclicindoles (Pfizer), ideno[1,2-c]isoquinolinones (Inotek), benzimidazoles (Abbott) and pthalazinones (KuDOS).

Before “synthetic lethality” was identified as an outcome of PARP inhibition in a background of BRCA mutation in 2005, PARP inhibitors were developed primarily as chemosensitizers in combination with other cytotoxic agents in a wide variety of pre-clinical models. PARP inhibition potentiated the clinical efficacy of alkylating agents (temozolomide), topoisomerase inhibitors (irinotecan and topotecan) and ionizing radiation [38] but not the anti-metabolites. This data has been reviewed elsewhere [39].

Bryant *et al* and Farmer *et al* demonstrated the increased sensitivity of BRCA-deficient cells to PARP inhibition and the subsequent resistance to PARP inhibition that developed on restoration of BRCA2 functionality thereby illustrating the concept of "synthetic lethality". This observation provided a strong rationale for the use of PARP inhibitors in patients with BRCA1/2-associated cancers. Subsequently, it was determined that certain cancers had defective homologous recombination (HR) mechanisms that resulted from acquired defects in HR rather than germline BRCA mutations - referred to as "BRCAness". Defective HR can result from epigenetic modifications of BRCA 1/2 and/or mutations in various proteins critical to HR pathways such as RAD51, RAD54, DSS1, RPA1, ATM, CHK2 and PTEN [40–42] and has been associated with several malignancies including triple-negative breast cancer and sporadic serous ovarian cancer.

Whilst selective PARP-1 and PARP-2 inhibitors have been identified, most of the PARP inhibitors under clinical investigation are not selective for PARP-1 and 2 as both PARP-1 and PARP-2 share significant sequence homology in their catalytic domains. Highly

selective inhibitors are being investigated in other disease states, particulary neurodegenerative disease where selective PARP-1 over-activity following DNA damage has been implicated in models of neuronal damage following focal ischemia. PARP-1 specific inhibitors (INO-1001 and MP-124) are being studied in animal models of cardiac [43] and neuronal ischemia [44] as protective agents from reperfusion injury.

3.2. Clinical Development of PARP Inhibitors

PARP inhibitors are currently being investigated either as single agents in BRCA1/2 deficient cancers and cancers with "BRCAness", or in combination therapy with other DNA-damaging agents including ionizing radiation in a wider variety of malignancies. There are a total of 9 agents in various stages of the drug development pipeline from phase 0 to III. These agents, their developments and the stage of current evaluation are detailed below and reviewed in Table 3 (Table 3 – Selected Phase II/III trials of PARP Inhibitors) [45–61].

3.2.1. Clinical Development of PARP Inhibitors - AG-014699 (PF-01367338, Rucaparib)—AG-014699 is the water-soluble phosphate salt of AG-014447, a potent intravenous tricyclicindole PARP inhibitor and has been shown to the cytotoxicity of temozolomide (TMZ) and irinotecan in pre-clinical models [62]. In the first-in-human phase I clinical trial of AG-014699 [24], AG-014699 was combined with TMZ in 32 adults with a variety of malignancies although patients with brain metastases were excluded. In the dose-escalation portion of the study, the dose of the PARP inhibitor was increased sequentially using the standard three-patient cohort dose escalation design. The PARP inhibitory dose (PID) was determined to be 12 mg/m^2 with a fixed dose of TMZ at 100 mg/m^2/d. Once the PID was reached, the dose of TMZ was sequentially increased till the maximal tolerated dose (MTD) was established or dose-level 200 mg/m^2/d was reached. MTD of the combination was determined to be 12 mg/m^2 AG-014699 and 200 mg/m^2/d TMZ.

The combination was deemed to have preliminary evidence for antitumor efficacy - with 1 complete response (CR), 2 partial responses (PRs) and 7 cases of prolonged disease stabilization (SD) (≥6 months) for an overall disease control rate of 31%. PARP inhibition was also observed at the tissue level. In the second part of the study, 15 patients with therapy-naive melanoma and tumor deposits amenable to pretreatment and post-treatment biopsy were dosed at 200 mg/m^2/d TMZ with AG-014699 at PID or 18 mg/m^2. Paired tumor biopsies obtained revealed >50% PARP inhibition observed in all biopsies.

Whilst no dose-limiting toxicities (DLTs) were observed at the MTD, when the dose of AG-014699 was increased to 18mg/m^2 (in part 2), 4 of 6 patients experienced grade 3 or greater hematological toxicity (1 case of pancytopenia and 3 causes of delayed recovery of neutropenia). Whilst TMZ has a steep dose-response curve, myelosuppression is unusual even at the 200 mg/m^2/d dose-level. Moreover, pharmacokinetic (PK) analyses suggested that neither drugs' PK variables were affected by co-administration. However, COMET analyses of DNA damage in PBMC indicated dose-dependent increases in DNA damage with increasing doses of AG-014699, especially above 12 mg/m^2 suggesting that the enhanced myelotoxicity may, in part, be mediated by the effects of AG-014699 on myeloid precursors in bone marrow.

The same authors [45] had presented the results of the phase II AG-014699/TMZ combination at the 2006 ASCO Annual Meeting. This trial enrolled 40 patients with metastatic melanoma at the recommended phase II dose (RP2D) of 12 mg/m^2 AG-014699 and 200 mg/m2/d TMZ. Whilst 20 patients were deemed too early for evaluation, in the remaining 20 patients, 4 PRs and 4 SDs were noted. Myelotoxicity was significantly greater than in the phase I study - with 1 death and 3 hospitalizations related to myelosupp-ression and 12 patients (30%) requiring 25% TMZ dose reductions. The authors concluded that

although the combination appeared active in metastatic melanoma, synergistic myelosuppression remained an issue.

More recently, the utility of single-agent AG-014699 in HR-deficient tumors was presented at the 2011 ASCO Annual Meeting [46]. This multi-center, single-arm phase II trial enrolled patients with known BRCA 1/2-deficient advanced ovarian and/or breast cancer to treatment with single-agent AG-014699 dosed at 18mg/m^2 5 days a week every 21 days. At the time of presentation, 41 patients had been enrolled. Although the overall response rate (ORR) was only 5% with response being evaluable in 38 patients, the disease control rate (DCR) of 32% (12/38) was encouraging. Moreover, no DLTs were observed at any dose level with the most common toxicities being grade 1/2 fatigue, nausea and diarrhea in 20–39% of patients.

The activity of AG-014699 in the central nervous system (CNS) is unknown and most trials have excluded patients with brain and/or ocular metastases as a result. Recently, using xenograft models and pre-clinical cell line models of medulloblastoma, a British group [63] has demonstrated PARP uptake into the CNS across an intact blood-brain barrer in mice and significant and sustained PARP inhibition in brain tissue. Whilst CNS penetration of PARP inhibitors is known, and is actually the basis of utilizing PARP-1 selective inhibitors in neuro-protective models of stroke, this work represented the first demonstration of AG-014699's CNS activity and its ability to potentiate the effects of TMZ in DNA repair protein-competent D384Med xenografts.

In addition to known effects on PARP-1/2, AG-014699 may have additional effects that may be exploited for therapeutic benefit. Experiments utilizing tumor xenografts have demonstrated that AG-014699 increases vascular perfusion possibly by inhibition of myosin light chain kinase (MLCK) [64]. This suggests an alternative mechanism for the chemo-potentiating effects of AG-014699 and provokes interest in rational combinations of AG-014699 with other cytotoxic agents including ionizing radiation. Recently published data utilizing NF-κB p65(−/−) cells revealed that AG-014699 is able to sensitize cells to ionizing radiation by downstream inhibition of NF-κB activation rather than overt SSB repair inhibition. Not only may AG-014699 be synergistic with ionizing radiation, it may be possible to exploit AG-014699’s abrogation of NF-κB signaling that is constitutively activated in tumorigenesis in a wide variety of cancers [65].

3.2.2. Clinical Development of PARP Inhibitors - AZD2281 (Olaparib)—Olaparib (AZD-2281) is a potent oral inhibitor of PARP1/2 and TNKS that is well absorbed (peak plasma concentration observed between one and three hours after administration) and rapidly eliminated (terminal-elimination half-life of approximately five to seven hours).

In the first-in-human phase I trial [66] 60 patients with a variety of advanced solid tumors were accrued; the MTD was established as 400 mg twice daily. Although initially the patients were not selected for BRCA1/2 mutations, the cohort was subsequently BRCA1/2 mutation enriched following protocol amendment. At the 400 mg dose level, one out of eight patients in the cohort developed grade 3 mood disturbance and fatigue. At the maximal allowed dose of 600 mg twice daily, two out of five patients in this cohort developed DLTs - grade 4 thrombocytopenia and grade 3 somnolence. These toxicities tended to resolve upon drug cessation but recurred upon restarting therapy. The toxicity profiles of responders and non-responders were similar. Overall, an objective RR of 47% and DCR of 63% were observed in the group of 19 patients with BRCA mutations and breast, ovarian or prostate cancers.

The same authors subsequently published data on the phase I expansion study evaluating olaparib at 200 mg twice daily in a cohort of patients with ovarian, peritoneal and fallopian

tube cancer carrying BRCA 1/2 mutations [67]. Of the 50 patients treated, RR of 40% [95% CI, 26%-55%] and DCR of 46% [95% CI, 32%–61%] were observed with responses primarily in the platinum-sensitive group. The toxicity profile was favourable. Interestingly, the authors reported a statistical association between clinical response and platinum sensitivity suggesting that PARP inhibitor resistance and platinum resistance may be mechanistically related.

Two subsequent phase II studies followed evaluating single-agent olaparib therapy in BRCA1/2 mutation carrying patients with chemotherapy-refractory breast and ovarian cancer – the results of which were presented at the 2009 ASCO Annual Meeting and subsequently published in the Lancet [43, 49, 68–69]. 54 patients with breast cancer and 57 patients with ovarian cancer were treated with 100 mg or 400 mg of olaparib twice daily. In the breast cancer study, the overall RR was 41% [95% CI, 25–59%] at the 400 mg dose level and 22% [95% CI, 11–41%] at the 100 mg dose level. In the ovarian cancer study, the overall RR was 33% [95% CI, 20–51%] at the 400 mg dose level and 13% [95% CI, 4–31%] at the 100 mg dose level.

Recently published data however was not consistent with this experience and raised concerns over the utility of monotherapy with olaparib in BRCA-positive patients. In a phase II study [51], pre-treated patients with advanced breast and mostly serous ovarian cancer were enrolled and later divided into separate groups based on BRCA status - Group A (TNBC, BRCA unknown/negative), Group B (breast cancer, BRCA positive), Group C (ovarian cancer, BRCA positive) and Group D (ovarian cancer, BRCA unknown/negative). Patients received 400 mg olaparib twice daily for 4 weeks until progression. No objective responses were recorded in any of the breast cancer patients. Whilst the lack of response in BRCA-negative patients was not unexpected, the absence of recorded responses in BRCA-positive patients was rather surprising. DCR at 8 weeks was 70% [95% CI, 40–89%] in BRCA-positive and 19% [95% CI, 7–43%] in BRCA-negative patients. Conversely, responses in patients with ovarian cancer were noted even in the BRCA-negative group - overall objective response rate (ORR) of 29% [95% CI, 19–41%] with RR of 41% [95% CI, 22–64%] in BRCA-positive and 24% [95% CI, 14–38%] in BRCA-negative patients. The lack of response among the breast cancer patients, in contrast to earlier studies, was notable - and may be secondary to chance given the small numbers enrolled or the heavy pre-treatment many patients received, and poses interesting questions for the design of planned phase III trials.

Several combinations of olaparib with cytotoxic chemotherapy have been explored [48, 70–72]. Initial combinations have been plagued by significant myelosuppression - even at olaparib dose levels of 100 mg twice daily. More recently, two phase I studies evaluating olaparib in combination with cediranib (AZD2171) in ovarian cancer/TNBC and in combination with carboplatin in BRCA1/2 mutated breast/ovarian cancer are nearing completion. Although accrual was small at 18 patients, the unconfirmed RR of 56% is encouraging. Phase II trials results are currently pending.

Cediranib (AZD-2171) is a potent oral inhibitor of VEGF signalling with activity against c-Kit and VEGFR1-3 and broad antitumour activity both singly and in combination with certain chemotherapy regimens. Mechanistically, attempting to concurrently inhibit DNA repair and angiogenesis seems attractive and the results of this trial are eagerly awaited. Other combinations undergoing evaluation at present include olaparib/cediranib (NCT01116648), olaparib/carboplatin (NCT012-37067), olaparib/paclitaxel (NCT01063517), olaparib/TMZ (NCT01390571) and olaparib/radiotherapy (NCT01460888).

3.2.3. Clinical Development of PARP Inhibitors - ABT-888 (Veliparib)—ABT-888 (veliparib) is an oral PARP 1/2 inhibitor with good oral bioavailability and demonstrable CNS penetration. Preclinical models had demonstrated that ABT-888 significantly potentiated the anti-neoplastic effect of several cytotoxic agents including temozolomide, platinum, irinotecan, and ionizing radiation. The initial first-in-human phase 0 trial showed that ABT-888 was well tolerated at single doses ranging from 10 to 50 mg, in addition to being rapidly absorbed and cleared and the 50mg twice daily dose resulted in 55% reduction in PAR in peripheral blood mononuclear cells (PBMCs) and 95% in tumors [29].

Two phase I studies have looked at ABT-888 in combination with irinotecan [73] and doxorubicin/cyclophosphamide [74]. ABT-888 dose levels ranged from 10–50mg twice daily in the former and 50–150 mg twice daily in the latter. MTDs of ABT-888 were 40 mg twice daily and 100 mg twice daily respectively. Myelosuppression was the most frequent DLT and RP2Ds should be predicated on the anticipated overall myelosuppressive effect of the combination. Disease control rates were approximately 60% in both studies with the majority of the responses in the latter study occurring in BRCA mutated patients. BRCA mutation status for the irinotecan /ABT-888 combination was not available.

The results of 3 phase II trials of ABT-888 are available for analysis. In the phase II trial of ABT-888 with TMZ for metastatic colorectal cancer, 47 patients received ABT-888 (40 mg orally twice daily) on days 1–7 and TMZ (150 mg/m2 daily) on days 1–5 of each 28-day cycle [55]. Patients were heavily pre-treated with an average of 4 prior therapies each. DCR was 23% with 2 PRs and although the median TTP was 11 weeks, TTP in disease-control group was more than double at 23 weeks. Tumor tissues were archived for planned immunohistochemical analysis to assess mismatch repair enzyme (MMR) and PTEN protein expression but this data is still not available.

A phase II trial of ABT-888 with TMZ enrolled patients with metastatic breast cancer and used a similar dose regimen but ABT-888 was dose-reduced to 30 mg twice daily following greater than expected grade 4 thrombocytopenia [54]. Responses in this study however were limited to BRCA mutation carriers - 37.5% RR and 62.5% DCR in the 8 patients with BRCA mutations. Median PFS was 5.5 months in BRCA mutation carriers vs. 1.8 months in non-carriers.

In the phase II study of the ABT-888/TMZ combination in advanced melanoma, 346 patients with metastatic or unresectable stage III melanoma were randomized in a double-blinded fashion to TMZ/placebo or TMZ/ABT-888 in 2 dose levels (20 mg and 40 mg BID). Median PFS in the study cohort was nearly twice that of the placebo arm (110–113 days vs. 60 days) though this difference was not statistically significant and the median OS was similar in all 3 cohorts (327–412 days). Notably, in addition to the inability of this study to demonstrate statistically significant improvements in PFS and OS differences, there was also low overall response rate of 8.7–10.3% [75].

Multiple other early phase studies are in active accrual and include ABT-888/TMZ combination in liver cancer (NCT01205828) and prostate cancer (NCT01085422); ABT-888/carboplatin combination in HER2-negative metastatic breast cancer [76]; ABT-888 plus 5-fluorouracil and oxaliplatin (modified FOLFOX-6) in patients with metastatic pancreatic cancer (57, NCT01489865); ABT-888/cisplatin/paclitaxel in advanced cervical cancer (NCT01281852); ABT-888/topotecan in advanced solid tumors (NCT01012817); ABT-888/gemcitabine in advanced solid tumors (NCT01154426); ABT-888/liposomal doxorubicin in advanced breast/ovarian (NCT01145430); ABT-888/ bendamustine/ rituximab in advanced lymphoma and myeloma (NCT01326702); ABT-888/ whole brain radiation in patients with CNS metastases (NCT00649207); ABT-888/

gemcitabine/cisplatin (NCT01282333) in patients with advanced biliary, pancreatic, urothelial, or non-small cell lung cancer (NSCLC); and ABT-888/carboplatin /paclitaxel combination in multiple settings including phase I in advanced solid tumors (NCT01281150), phase II in unresectable NSCLC (NCT01386385) and phase I in patients with advanced solid tumors and liver and/or kidney dysfunction (NCT01366144).

3.2.4. Clinical Development of PARP Inhibitors - BSI-201 (Iniparib)—BSI-201 (iniparib) is an intravenous agent that is mechanistically different from the other PARP inhibitors – by interacting with the DNA binding domain of PARP-1, it functions as a non-competitive inhibitor of PARP-1 [77].

In the first-in-human phase I study in advanced solid tumors, BSI-201 was given at dose levels ranging from 0.5 mg/kg to 8.0 mg/kg IV twice weekly. At the 2.8 mg/kg dose level, PARP inhibition in PBMCs was greater than 50% after a single dose with multiple dosing resulting in 80% inhibition. Overall the regimen appeared well tolerated with no DLTs and gastrointestinal toxicity noted in 39% [31].

Subsequently, 2 phase Ib trials, a randomized phase II trial and a non-randomized phase II trial were carried out testing various combinations of cytotoxic chemotherapy with BSI-201 in a variety of different malignancies. In the phase Ib trial that combined BSI-201 with topotecan, gemcitabine, temozolomide, and carboplatin /paclitaxel in patients with advanced solid tumors, BSI-201 was dosed at dose levels 1.1 thru 8.0 mg/kg twice weekly [32]. The toxicity profile was excellent with none of the 21 serious adverse events being attributed to study drug. Responses were seen in 6 patients (1 CR, 5 PR) and 19 patients had SD. A more recent phase I study evaluated the combination of BSI-201 with standard-of-care carboplatin/paclitaxel in patients with advanced non-small cell lung cancer [34]. Again, BSI-201 appeared to confer clinical benefit with minimal additive toxicity - ORR 23% (3/13) and DCR 85% (11/13).

These results appeared consistent with the phase II studies. In the randomized phase II in patients with TNBC, BSI-201 (5.6 mg/kg, i.v. twice weekly) in combination with gemcitabine/ carboplatin had improved DCR (52% vs 12%), PFS (HR 0.30, 95% CI 0.15–0.59) and OS (HR 0.24, 95% CI 0.09–0.61) compared to gemcitabine/carboplatin alone with minimal additive toxicity attributable to the PARP inhibitor [58]. Updated DCR, PFS, and OS for all 120 patients and exploratory correlative analyses of PARP expression and clinical response are pending. Another non-randomized phase II compared evaluated the same BSI-201 with gemcitabine/carboplatin combination in patients with platinum-sensitive recurrent ovarian cancer [60]. Compared to standard gemcitabine/carboplatin alone, the addition of BSI (5.6 mg/kg, i.v. twice weekly) resulted in ORR 71% with no additional toxicities in the first 17 patients treated (12/17 responses). Updated response data from all 41 enrolled patients is awaited.

Based on the encouraging phase I/II data, Sanofi-Aventis/BiPar Sciences sponsored a randomized phase III study of BSI with gemcitabine/carboplatin against the gemcitabine/ carboplatin combination alone. Although the formal trial results have yet to be released, a recent press release from Sanofi-Aventis/BiPar Sciences indicated that the triplet did not meet the pre-specified criteria for significance for the co-primary endpoints of overall survival and progression-free survival though it increased PFS and OS with minimal additional toxicity. Ji *et al.* recently demonstrated that BSI-201 neither decreased PAR levels nor inhibited PARP-1 in BRCA-deficient cell lines but rather resulted in telomere-centric DNA damage raising questions as to whether BSI-201 is even a PARP inhibitor at all and may explain the lack of synergism observed in the phase III trial [78].

Currently, multiple trials assessing combinations of cytotoxic chemotherapy with BSI-201 are in active accrual including BSI-201 with gemcitabine/carboplatin in patients with platinum-resistant recurrent ovarian cancer (NCT01033292); gemcitabine/carboplatin in patients with TNBC prior to surgery (neo-adjuvant setting) (NCT00813956); with TMZ in patients with newly diagnosed malignant glioma (NCT00687765); with irinotecan in patients with TNBC brain metastases (NCT01173497); and with paclitaxel in patients with TNBC (NCT01204125). Two randomized multi-center phase III trials of gemcitabine/carboplatin with or without BSI-201 are being conducted - in patients with TNBC (NCT00938652) and in patients with previously untreated stage IV squamous non-small cell lung cancer (NSCLC) [79, NCT0108-2549].

3.2.5. Clinical Development of PARP Inhibitors - MK-4827—MK-4827 is an orally bioavailable PARP inhibitor with potent PARP-1 and PARP-2 inhibitory capacity [80]. The initial phase I data was presented at the 2010 ASCO Annual Meeting [35]. This trial enrolled 60 patients with advanced solid tumors but was enriched for BRCA1/2 mutations and sporadic cancers associated with HR repair defects. MTD was identified at 300 mg daily and grade 3 DLTs included fatigue, anorexia and pneumonitis with nausea/vomiting and myelosuppression occurring commonly. Notably, responses were observed in both BRCA-deficient and sporadic cancers. Response data updated at ASCO in 2011 [36] showed 12 PRs and 8 SDs of which 7 (3 PR and 4 SD) occurred in patients without BRCA mutations.

Several phase I studies evaluating MK-4827 both singly (NCT01226901 and NCT00749502) and in combination with TMZ (NCT01294735) in a variety of malignancies are currently underway. MK-4827 may also be synergistic with radiotherapy - MK-4827 mediated PARP inhibition enhances radiation in neuroblastoma cell lines and the combination decreased tumor burden and prolonged survival in an *in vivo* murine neuroblastoma model [81].

3.2.6. Clinical Development of PARP Inhibitors - CEP-9722—CEP-9722 is an oral PARP-1/2 inhibitor that is a prodrug of CEP-8983. Preclinical studies [82] have shown that CEP-8983 is able to sensitize tumor cells to TMZ, irinotecan and radiation without significant increase in myelosuppression although antitumor efficacy for CEP-9722 was observed in xenografts.

Ongoing phase I studies evaluating CEP-9722 include a dose-finding study (NCT01311713), CEP-9722 in combination with gemcitabine and cisplatin in advanced solid tumors and mantle cell lymphoma (NCT01345357) and CEP-9722 singly and in combination with temozolomide in advanced solid tumors (NCT00920595).

3.2.7. Clinical Development of PARP Inhibitors - E7016 (GPI-21016)—E7016 (formerly known as GPI-21016) is an orally bioavailable PARP inhibitor. When tested in a murine leukemia model, E7016 concurrently enhanced cytotoxicity and limited cisplatin-induced neuropathy suggesting that the pleiotropic effects of PARP inhibition may be exploited in multiple ways to improve the therapeutic potential of a particular cytotoxic agent [83]. Like CEP-9722 and MK-4827, E7016 appears to enhance tumor radiosensitivity and may synergize with TMZ [84]. A phase I dose-escalation trial (NCT01127178) in combination with temozolomide in patients with advanced solid tumors and gliomas has accrued and results are pending. We are conducting a Phase II study of this combination in patients with metastatic melanoma who are wild-type for BRAF.

3.2.8. Clinical Development of PARP Inhibitors - INO-1001—INO-1001 is an isoindolinone derivative and a potent PARP 1 inhibitor [85]. INO-1001 does not have any significant single-agent cytotoxic effects but may have use as a chemo- and radio- sensitizer.

INO-1001 administration increased the anti-tumor effects of doxorubin in cell lines of p53 deficient tumors [86]. In a phase IB trial in advanced melanoma patients, the INO-1001/TMZ combination resulted in 5 responses (4 SD and 1 PR) – including a PR that lasted nearly 2 years [37]. Significant toxicities included TMZ-related myelosuppression and transaminitis attributed to INO-1001.

More recently, INO-1001 has been investigated for a putative cardioprotective role. When tested in a randomized, placebo-controlled trial of patients undergoing percutaneous coronary intervention, INO-1001 administration was associated with a significant reduction in inflammatory markers CRP and IL-6 [87]. Although the *in vivo* effects were not assessed in the former study, INO-1001 use demonstrably improved functional recovery without affecting infarct size in a porcine model of myocardial reperfusion injury [88]. At present, there are no ongoing or planned cancer trials of INO-1001 either singly or in combination with cytotoxic therapy to the authors' knowledge.

3.2.9. Clinical Development of PARP Inhibitors - LT-673—BMN-673 (formerly LT-673) is an orally bioavailable PARP inhibitor manufactured by Lead Therapeutics and subsequently acquired by Biomarin Pharmaceuticals. In preclinical studies it has demonstrated greater PARP inhibition than other agents. Data recently presented at the 2011 meeting of the American Society of Hematology (ASH) showed that a subset of patients with myeloid malignancies (AML and MDS) possessed microsatellite instability (MSI) in DNA repair genes that conferred-increased sensitivity to LT-673 likely due to enhanced inhibition of functional HR mechanisms of DNA repair [89]. Two phase I trials are at present underway in patients with hematological malignancies (NCT01399840) and advanced solid tumors with defects in DNA repair pathways (NCT01286987).

3.3. Resistance to PARP Inhibition

As PARP inhibitor use becomes more prevalent and widespread, resistance is likely to develop and become clinically significant. As such, it is important to elucidate the mechanisms by which resistance develops. Preclinical data suggests that resistance to PARP inhibition can be created in cell lines through constant high-level exposure to PARP inhibitors. In a model utilizing the CAPAN1 pancreatic cancer cell line that lacks BRCA2 and has a defective HR mechanism which is intrinsically sensitive to PARP inhibition, exposure to increasing levels of a PARP inhibitor resulted in the development of PARP inhibitor resistant clones. These clones demonstrated an ability to form RAD51 foci indicating a competent HR mechanism and additionally expressed new BRCA2 isoforms likely secondary to restoration of the open reading frame of the BRCA2 allele – an example of "reverse mutation" [90].

Evidence gathered from analyzing the mechanism of platinum-resistance in patients with BRCA-2 mutated ovarian carcinoma suggests that the mechanism of acquired resistance to cisplatin involves intragenic mutations in BRCA2 that restore the wild-type BRCA2 reading frame [91]. The same group subsequently demonstrated that a similar mechanism is responsible for platinum-resistance and PARP resistance in patients with BRCA-1 mutated ovarian carcinoma [92]. This observation was validated in large set of patient samples from the University of Washington tumor bank [93]. This may be because the restoration of the wild-type BRCA1/2 open reading frame provides an alternative means of HR repair not otherwise inhibited by PARP.

Clinical trials of PARP inhibitors are still too immature to provide information to assess mechanisms of resistance. That said, the mechanism of acquired resistance *ipso facto* suggests potential solutions. Firstly, it would be important to identify resistant clones early in therapy – and the presence of wild-type BRCA-1/2 and/or functional assays to assess HR

competence (RAD51 foci formation) may be useful in this regard. Additionally, assessing for presence of wild-type BRCA-2 may be important in distinguishing tumors with secondary intragenic BRCA-2 mutations from platinum-resistant tumors which may still be sensitive to PARP inhibition. Finally, it may be possible to abrogate this functional resistance by inhibiting RAD51 foci formation through the use of proteasome inhibitors.

3.4. Cytoprotective Effects of PARP Inhibitors

While the focus of this article is on the role of PARP inhibitors in treating malignancies, recent advances have implicated the PARP family of proteins in a wide range of cellular functions from inflammation [94] and to embryonic development [95] to atherosclerosis [96]. PARP-1 is required for the activation of NF-κB - a transcription factor critical to multiple aspects of the inflammatory response. In a murine model of cortical ischemia-reperfusion injury, the experimental PARP inhibitor PJ-34 suppressed the microglia-mediated cellular brain inflammatory response resulting in a significant reduction in neuronal death suggesting that PARP inhibitor use following coronal ischemia may prevent neuronal death [97]. Other authors have suggested that PARP activation may be implicated in models of neuropathy - as evidenced by the amelioration of oxaliplatin-induced acute cold allodynia in rats treated with BSI-401 [98].

Similarly, PARP activation has been implicated in the pathogenesis of myocardial reperfusion injury. Animal studies have demonstrated that PARP inhibition may retard the early and late consequences of myocardial ischemic injury [99] and administration of INO-1001 in myocardial ischemia has been shown to reduce inflammation and preserve cardiac function [87–88].

3.5. Future Questions

The development of PARP inhibitor therapy has paralleled paradigm shifts in our understanding of cancer therapeutics and therapies targeted at a particular cancer's unique molecular alterations. Although the synthetic lethality concept was first advanced in the 1940s, it took nearly a half-century to develop efficacious agents that exploited this concept in clinical practice. New therapies are always accompanied by new challenges to tackle and PARP inhibitors are no exception.

At present, the crop of PARP inhibitors is heterogeneous – varying in routes of administration, toxicity profiles, efficacy, and resistance mechanisms. Commensurately, the early phase trials evaluating the PARP inhibitors were quite different in their design and scope – involving PARP inhibitors used singly and/or in combination with a diverse array of cytotoxic agents leading to a range of inconsistent results in terms of tumor control and survival benefit. Although these early phase trials have by and large established reasonable dosing strategies of the various PARP inhibitors, no phase III data is presently available to guide clinical decision-making. Moreover, for any specific PARP inhibitor, the optimal dose and schedule of the allied chemotherapeutic regimen that will maximize clinical benefit while minimizing toxicity has yet to be elucidated.

The allied chemotherapeutic regimens in PARP inhibitor trials were chosen based on their potential for causing DNA damage and include methylating/alkylating agents (TMZ, dacarbazine, cyclophosphamide), topoisomerase I inhibitors (topotecan, irinotecan), platinum agents (carboplatin and cisplatin) in addition to ionizing radiation. However, not all DNA damaging agents are synergistic with the PARP inhibitors – the data regarding synergism between PARP inhibitors and anti-metabolites is conflicting. Pre-clinical studies have reported that disruption of the BER pathway (by either PARP-1 inhibition or XRCC1 inactivation) sensitizes cells to 5-fluorodeoxyuridine but not 5-fluorouracil (5-FU) [100].

These divergent results suggest that although 5-FU clearly causes DNA damage, its primary cytotoxicity may be secondary to a different cellular process (possibly RNA disruption following incorporation of 5-FU into RNA). Hence, PARP inhibitors may only be synergistic with agents that cause DNA damage that requires an intact BER mechanism and conversely, agents that cause such defects (confer a phenotype of "BRCAness") may be synergistic with PARP inhibitors – "contextual synthetic lethality" – as illustrated by the synergism between bortezomib and ABT-888 in a multiple myeloma model [101].

An alternative approach to combination therapy was noted with the use of E7016 (formerly known as GPI- 21016) – which when combined with cisplatin, enhanced cytotoxicity and limited cisplatin-induced neuropathy in a murine leukemia model [70]. Similarly, AGO-14699's vasoactive properties may explain its ability to ameliorate doxorubicin-mediated cardiotoxicity without any allied synergism [102]. This suggests another avenue for PARP inhibitors might lie in improving the toxicity profile of the chemotherapeutic combination with minimal or no added anti-tumor effect.

Toxicity, especially myelosuppression, remains a major concern moving forward into the phase III trial paradigm, particularly with continuous rather than intermittent dosing of PARP inhibitors. As yet uninvestigated are the long-term consequences of PARP inhibition. PARP-1 may have a tumor-suppressor role as demonstrated in experiments on PARP-1/p53 double-null mice in which a heightened incidence of aggressive brain tumors was observed [103] although PARP-1 absence singly results in a high degree of genomic instability but not overt tumorigenesis [104]. Given the wide scope of PARP-1 signaling, it is not surprising that the toxicity profile may be broader than initially supposed. de Murcia *et al.* [105] reported that adult PARP double-null mice in their experiments weighed significantly less than wild-type counterparts. Conversely, other authors have reported that PARP double-null mice were more likely to become obese despite a normal diet [106–107] and have an increased predisposition towards insulin resistance [108]. These considerations are especially important given the interest in developing PARP inhibitor combinations in the neo-adjuvant setting or for long-term use in BRCA mutation carriers.

PARP inhibitors can be used as single agents in tumors with DNA repair defects on the basis of synthetic lethality. Early phase studies have demonstrated the validity of this concept in treating BRCA1/2 mutated tumors with olaparib and MK-4827 and phase III validation data is eagerly awaited. The next phase of trials will likely expand the scope of PARP inhibitor use in patients with defects in HR repair beyond BRCA1/2 mutations including Fanconi's anemia protein defects, ATM abnormalities, PTEN defects, Rad51 dysfunction, EMSY defects, and TNKS abnormalities. Identifying clinical, biochemical or pathogenetic features that indicate tumor susceptibility to PARP inhibitors would expand the scope of clinical utility and broaden the inclusion pool for PARP inhibitor trial enrollment.

Recent PARP inhibitor trials have utilized reductions in PAR levels in PBMCs and tumor tissue as surrogate markers of PARP inhibitor activity and clinical pharmacodynamic endpoints – based on the initial phase 0 trial conducted by the National Cancer Institute (NCI) that utilized an immunoassay to quantify PAR. Most trials have designated reductions in PAR levels of 50–55% in PBMCs and 90–95% in tumor tissue as the threshold for assigning significance. There are several issues with this approach – firstly cells have different basal levels of PAR reflecting their relative capacity for DNA repair and unless changes in PAR levels pre- and post- PARP inhibitor administration are quantified, a low level of PAR *per se* may not mean a great deal. Secondly, although there is abundant data to suggest that PARP-1 activity is greater in tumor cell lines and in several tumor types including TNBC compared to healthy tissue, no correlation in PAR levels has hitherto been reported between patient tumor and PBMC samples [109–110]. At present, assessing the

correlation between reductions in PAR levels in PBMCs post PARP inhibitor administration and PAR levels in tumor tissue is an area of great interest. Also of interest is assessing whether changes in PAR levels in PBMCs following *ex-vivo* administration of PARP inhibitor can be predictably correlated with *in vivo* effects and if so this approach may be utilized to screen for patients most likely to benefit from PARP inhibitor treatment and for clinical trial enrollment [111].

While the focus of this article is on the role of PARP inhibitors in treating malignancies, one cannot ignore the recent advances that have established neuro-protective and cardio-protective roles for PARP inhibitors. This underscores the limited understanding we have regarding the fundamentals surrounding the PARP family of enzymes. These proteins have been implicated in a wide range of cellular functions from inflammation [94], to embryonic development [95] to atherosclerosis [96]. Unanswered questions that would benefit from further clarification include the full length structure of PARP, mechanism of PARP activation, range of proteins recruited by PARP and the roles of other members of the PARP super-family. For example, recently published work has suggested that Tankyrase 1 (PARP 5a) targeting may be selectively lethal in BRCA mutated cell lines and establishes another therapeutic target that can be pursued [112].

Acknowledgments

FUNDING SUPPORT

This work was supported by P50-CA121973 (HT), U01-CA099168 (HT and JHB) and P30-CA47904 (HT and JHB) from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

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Table 1

PARP inhibitors in Development

Name	Current Development Stage
AG-014699/PF-01367338 (Rucaparib)	Phase II - single agent in BRCA-associated breast or ovarian cancer. Phase I - combination with chemotherapy in advanced solid tumors.
AZD2281 (Olaparib)	Phase I/II - singly or combination with chemotherapy in various cancer types including breast, ovarian and colorectal cancers.
ABT-888 (Veliparib)	Phase II - combination with chemotherapy in various cancer types including breast cancer, colorectal cancer, glioblastoma multiforme (GBM) and melanoma. Phase I: combination with radiation.
BSI-201 (Iniparib)	Phase III - gemcitabine and ±BSI-201 in breast and lung cancers. Phase I/II - single agent or combination with chemotherapy in various cancer types including glioma and ovarian cancer.
MK-4827	Phase I - single agent; combination with carboplatin-containing regimens.
CEP-9722	Phase I - combination with temozolomide in advanced solid tumors.
E7016 (GPI-21016)	Phase I - combination with temozolomide in advanced solid tumors.
INO-1001	Phase II in cardiovascular disease. Phase I - combination with temozolomide in melanoma (completed) without further investigation in oncology.
LT-673	Preclinical.
MP-124	Phase I in acute ischemic stroke.
NMS-P118	Preclinical.
XAV939	Preclinical, highly selective against PARP-5 (tankyrase).

Table 2

Phase I Trials of PARP Inhibitors

PARP Inhibitor	Study Reference	No Of Patients	Disease	Dose and Schedule	Response	Toxicity (DLT, Grade ≥ III, SAE)
AG-014699/PF-01367338 (Rucaparib)	Plummer (2008)[24]	32	Part 1 (dose-finding): Advanced solid malignancies Part 2: Chemo-naïve metastatic melanoma	AG-014699 + temozolomide (TMZ) Part 1 (dose-finding): Escalating AG-014699 daily up to PID (PARP inhibitory dose – 12 mg/m^2/d) + TMZ 100 mg/m^2/d Part 2: AG-014699 at PID + TMZescalating dose up to 200 mg/m^2/d	CR: 1/32 (melanoma) PR: 2/32 (melanoma, desmoid tumor) SD: 7/32 (melanoma, prostatic cancer, pancreatic cancer and leiomyosarcoma)	DLT –nil Overall grade ≥ III 3% (18/200 AG-014699/TMZ) Myelosuppression – 13% patients at the maximum dose of AG014699 evaluated - 18 mg/m^2/d given with TMZ 200 mg/m^2/d
AZD2281 (Olaparib)	Khan (2011)25	40	Advanced melanoma (11 – stage IV, 1 – stage III unresectable)	Olaparib + dacarbazine (DTIC) Olaparib in escalating dose levels from 10 to 40 mg twice daily DTIC 600 to 800 mg/m^2	CR: 0/40 PR: 2/40 SD: 8/40	DLTs 7.5% Grade 3 hypophosphatemia and leucopenia – 1pt (40/800 olaparib/DTIC); Grade 4 neutropenia – 2 pts (20/600 olaparib/DTIC) Overall grade ≥ III 72.5% Anemia – 5% Neutropenia – 22.5% Thrombocytopenia – 7.5% Hyponatremia – 5.0% Hypophosphatemia – 10% Lethargy –5.0%
	Yamamoto (2011)26	12	Advanced solid malignancies	Olaparib in escalating dose levels from 100 to 400 mg twice daily MTD – 400 mg twice daily	CR: 0/12 PR: 1/12 (breast - unknown BRCA status) SD: 4/12 (unknown BRCA status)	DLT – nil Overall grade ≥ III 16% AST elevation– 8% Anemia– 8%
	Samol (2011)[27]	19	Advanced solid malignancies	Olaparib + topotecan in 4 cohorts Olaparib escalating dose levels from 50 to 200 mg twice daily Topotecan - 0.5 mg/m^2/d × 3 days or 1.0 mg/m^2/d × 3 days MTD – Olaparib 100 mg twice daily + Topotecan 1.0 mg/m^2/d	CR: 0/12 PR: 1/12 (breast - unknown BRCA status) SD: 4/12 (unknown BRCA status)	DLTs 16% Grade 3 thrombocytopenia – 1 pt (0.5/100 topotecan/olaparib) Grade 4 neutropenia – 2 pts (1.0/100 topotecan/olaparib) 1 treatment related death – pneumonia (1.0/200 topotecan/olaparib) Overall grade ≥ III 47.4% Neutropenia – 42.1%
	Dean (2012)[28]	12	Advanced solid malignancies	Olaparib + bevacizumab Olaparib in escalating dose levels from 100 to 400 mg twice daily Bevacizumab 10 mg/kg every 2 weeks	Not reported	DLT – nil Overall grade ≥ III 33% Pathological fracture –8% Intestinal obstruction – 8% Dyspnea – 16%

PARP Inhibitor	Study Reference	No Of Patients	Disease	Dose and Schedule	Response	Toxicity (DLT, Grade ≥ III, SAE)
				RP2D - Olaparib 400 mg BID + bevacizumab 10 mg/kg every 2 weeks		
ABT-888 (Veliparib)	Kummar (2009)[29]	14	Advanced solid malignancies	ABT-888 alone at escalating dose levels from 10, 25, 50, 100, to 150 mg daily MTD - veliparib 60 mg daily	No efficacy reported – phase 0 study	DLTs - nil Overall grade ≥ III 0% 1 pt – recurrent nausea and dizziness 1 pt – mild dysgeusia
	Kummar (2012)[30]	35	Advanced solid tumors and lymphoid malignancies	ABT-888 + metronomic cyclophosphamide ABT-888 daily for 7, 14, or 21 days in escalating doses Cyclophosphamide once daily in 21 day cycles MTD - veliparib 60 mg daily + cyclophosphamide 50 mg daily	CR – 0 PR – 7/35 (6 BRCA mutation) SD – 6/35 (3 BRCA mutation)	DLTs 6% Grade 4 respiratory failure resulting in death – 1pt; Grade 3 ileus – 1 pt (both at ABT-888/ cyclophosphamide80/50) Overall grade ≥ III 42.9% Lymphopenia – 34.3% Fatigue – 3% Hypophosphatemia – 3% Urinary tract obstruction – 3%
BSI-201 (Iniparib)	Kopetz (2008)[31]	23	Advanced refractory solid tumors	BSI-201 only BSI-201 at 0.5 mg/kg to 8.0 mg/kg in 7 dose levels twice weekly MTD – not identified	CR+PR – 0 SD – 6/23	DLTs – not reported Overall grade ≥ III – not reported GI toxicity – 39% (unknown severity) Respiratory – 7% (unknown severity)
	Mahany (2008)[32]	55	Advanced refractory solid tumors	BSI-201 in combination with topotecan, gemcitabine, TMZ, or carboplatin/paclitaxel in a non-randomized fashion BSI-201 at 5.1 mg/kg to 6.8 mg/kg twice weekly Topotecan, gemcitabine and carboplatin/paclitaxel at standard doses TMZ -75 mg/m^2 daily×42 days or 150–200 mg/m^2 for 5/28 days	CR – 1/55 (ovarian cancer) PR – 5/55 (renal, breast, uterine, sarcoma) SD – 19/55	DLTs – not reported Overall grade ≥ III – not reported 21 SAE in 38% of pts deemed unrelated to BSI-201
	Blakeley (2010)[33]	30	Newly diagnosed GBM	BSI-201 in combination with TMZ and RT BSI-201 at 1.1 mg/kg to 8.0 mg/kg twice weekly MTD – not reached	Not evaluable	DLTs – not reported Overall grade ≥ III – not reported Grade 4 thrombosis – 2 pts (BSI-201/TMZ 5.1/75) Grade 3 lymphopenia – 2 pts (6.1/75) Grade 3 thrombocytopenia – 2 pts (5.1/150–200) Grade 3 LFT elevation – 1 pt (6.8/150–200)
	Mita (2011)[34]	18 (13 evaluable)	Advanced non-small cell lung cancer (NSCLC)	BSI-201 + carboplatin + paclitaxel BSI-201 5.6 mg/kg D1, 4, 8, 11	CR – 0 PR – 3/13 (23%) SD – 8/13 (62%)	DLTs - nil Overall grade ≥ III 17% Neutropenia – 17%

Curr Med Chem. Author manuscript; available in PMC 2012 August 17.

PARP Inhibitor	Study Reference	No Of Patients	Disease	Dose and Schedule	Response	Toxicity (DLT, Grade ≥ III, SAE)
			(IIIB-IV)	of 21 day cycle Carboplatin AUC 6 D1 + paclitaxel 200 mg/m^2 D1 MTD – phase Ib trial		Anemia – 17%
MK-4827	Sandhu (2010)[35] and Schelman (2011)[36]	60	Advanced solid tumors enriched for BRCA-mutation carriers (BRCA-MC) and non-BRCA HR defects	MK-4827 alone MK-4827 30-400 mg in 10 dose levels once daily D1-21 of 28 day cycle followed by continuous dosing MTD – 300mg once daily	CR – 0 PR – 12/60 (20%) (7 BRCA mutation carriers with ovarian cancer, 3 sporadic ovarian cancers, 2 BRCA mutation carriers with breast cancer) SD – 8/60 (13.3%) (2 BRCA mutation carriers with ovarian cancer, 2 sporadic ovarian cancers, 2 NSCLC, 2 BRCA mutation carriers with breast cancer)	DLTs 4/60 – Grade 3 fatigue – 1 pt (30 mg); Grade 3 pneumonitis – 1 pt (60 mg); Grade 3 thrombocytopenia – 2 pt (400 mg); Overall grade ≥ III – not reported SAE data – not reported
INO-1001	Bedikian (2009)[37]	12	Advanced melanoma	INO-1001 + TMZ INO-1001 at escalating dose levels from 100–400 mg twice daily for 5 days per 28 day cycle TMZ 200 mg/m^2/d for 5 days per 28 day cycle MTD - INO-1001 200 mg twice daily + TMZ 200 mg/m^2/d	CR – 0 PR – 1/12 (melanoma) SD – 4/12	DLT (2/12) – Grade 3 myelosuppression – 1 pt; Grade 3 hepatotoxicity – 1 pt (both 400 mg twice daily) Overall grade ≥ III – 15.3% Grade 4 hematologic 58% Grade 4 hepatotoxicity 8% Grade 4 fatigue 17%

Key: CR – complete response; PR – partial response; SD – stable disease; MTD – maximal tolerated dose; DLT – dose limiting toxicity; SAE – serious adverse events; RP2D - recommended phase II dose.

Table 3

Selected Phase II/III Trials of PARP Inhibitors

PARP Inhibitor	Study Reference	Design	Participants	Dose and Schedule	Results
AG-014699/PF-01367338 (Rucaparib)	Plummer (2006)[45]	Multi-center open-label non-randomized phase II 1^0 endpoint(s) – BORR, toxicity 2^0 endpoint(s) – PFS	N = 40; advanced malignant melanoma	(1) AG-014699 12 mg/m^2 + TMZ 200 mg/m^2 D1-5 of 28 day cycle	Responses (at time of reporting): ORR (all PR) 10% (4/40) SD 10% (4/40) Survival: median PFS unknown
	Drew (2011)[46]	Multi-center open-label non-randomized Phase II 1^0 endpoint(s) – BORR, toxicity 2^0 endpoint(s) – PFS	N = 41 (38 evaluable); advanced breast and ovarian carcinoma (17 breast, 24 ovary; 22 BRCA1 deficient, 19 BRCA2 deficient)	(1) AG-014699 18 mg/m^2 D1-5 of 21 day cycle	Responses: ORR (all PR) 5% (2/38) SD 26% (10/38) Survival: median PFS unknown
AZD2281 (Olaparib)	Leichman (2010)[47]	Open-label non-randomized phase II	N = 32 (10 MSI-H, 22 non-MSI-H); metastaic colorectal cancer (mCRC) failing standard treatment Pts stratified by microsatellite status (MSs) status. If ≥ 3/17 responses in non-MSI-H pts, enrollment to continue. If <3/17 responses in the 1st 17 pts, enrollment to be restricted to 15 MSI-H pts.	(1) olaparib 400 mg twice daily	Responses/Survival: Not available
	Dent (2010)[48]	Open-label non-randomized phase I/II	N = 19; metastatic triple negative breast cancer (TNBC)	(1) olaparib 200 mg twice daily + paclitaxel 90 mg/m^2 weekly for 3 of 4 weeks	Responses: PR (no CR) 53% (10/19) confirmed + unconfirmed SD unknown Survival: median PFS unknown
	Tutt (2010)[49]	Multi-center open-label non-randomized phase II 1^0 endpoint(s) – ORR 2^0 endpoint(s) – PFS, clinical benefit rate, duration of response	N = 57; recurrent, advanced epithelial ovarian, peritoneal or fallopian tube carcinoma; germline BRCA mutations (1 – 40, 2 – 17); median prior chemotherapy regimens = 3–4	Cohort 1: olaparib 400 mg twice daily (MTD) Cohort 2: olaparib 100 mg twice daily (PARP inhibitory dose)	Responses: CR+PR 33% (11/33) (cohort 1) vs. 13% (3/24) (cohort 2) SD 36% (12/36) (cohort 1) vs. 29% (7/24) (cohort 2) Survival: median PFS 9.7 mths (cohort 1) vs. 9.0 mths (cohort 2)
	Audeh (2010)[50]	Multi-center open-label non-randomized phase	N = 57; recurrent, advanced breast cancer; germline BRCA mutations (1 – 33, 2 –	Cohort 1: olaparib 400 mg twice daily (MTD)	Responses: CR+PR 41% (cohort 1 – 9/18 BRCA1, 2/9 BRCA2,

PARP Inhibitor	Study Reference	Design	Participants	Dose and Schedule	Results
		II 1^0 endpoint(s) – ORR 2^0 endpoint(s) – efficacy, PFS, duration of response	20, 1&2 – 1); median prior chemotherapy regimens = 3	Cohort 2: olaparib 100 mg twice daily (PARP inhibitory dose)	7/13 TNBC, 4/14 non-TNBC) vs. 22% (cohort 2 – 3/16 BRCA1, 3/11 BRCA2, 4/16 TNBC, 2/11 non-TNBC) SD 44% (cohort 1 – 7/18 BRCA1, 5/9 BRCA2, 4/13 TNBC, 8/14 non-TNBC) vs. 44% (cohort 2 – 9/16 BRCA1, 3/11 BRCA2, 7/16 TNBC, 4/11 non-TNBC) Survival: median PFS 4.8 mths (cohort 1) vs. 4.7 mths (cohort 2)
	Gelmon (2011)[51]	Multi-center open-label non-randomized phase II 1^0 endpoint(s) – ORR 2^0 endpoint(s) – DCR, PFS	N = 92 (86 evaluable); advanced high-grade serous and/or undifferentiated ovarian carcinoma or TNBC; germline BRCA mutations [ovarian – 11(1), 5(2), 1(both); breast – 4(1), 6(2), 0(both)]	(1) olaparib 400 mg twice daily	Responses: CR+PR Ovarian – 29% total 41% (7/17) (BRCA mutated) vs. 24% (11/46) (non-BRCA) Breast - 0% total 0% (0/8) (BRCA mutated) vs. 0% (0/15) (non-BRCA) NE patients – 5 (ovarian) and 1 (breast) SD Ovarian – 38% total 35% (6/17) (BRCA mutated) vs. 39% (18/46) (non-BRCA) Breast - 30% total 63% (5/8) (BRCA mutated) vs. 13% (2/15) (non-BRCA) Survival: median PFS Ovarian - 7.4 mths (BRCA mutated) vs. 6.4 mths (non-BRCA) Breast – 3.6 mths (BRCA mutated) vs. 1.8 mths (non-BRCA)
	Ledermann (2011)[52]	Multi-center double-blinded placebo-controlled randomized phase II 1^0 endpoint(s) – PFS 2^0 endpoint(s) – TTP (GCIG criteria), OS, safety	N = 265; previously treated serous ovarian cancer in CR+PR	(1) olaparib 400 mg twice daily (2) placebo	Responses: CR+PR (RECIST), ORR, SD Too immature to analyse Survival: median PFS 8.4 mths (olaparib) vs. 4.8 mths (placebo) TTP 8.3 mths (olaparib) vs. 3.7 mths (placebo)
	Kaye (2012)[53]	Multi-center open-label randomized phase II 1^0 endpoint(s) – PFS 2^0 endpoint(s) – ORR, safety	N = 97; recurrent, advanced epithelial ovarian, peritoneal or fallopian tube carcinoma; germline BRCA mutations (1 – 84%; 2 – 16%)	(1) olaparib 200 mg twice daily (2) olaparib 400 mg twice daily (3) pegylated liposomal doxorubicin (PLD)50 mg/m^2 intravenously every 28 days	Responses: CR+PR (RECIST) 25% (200 mg) vs. 31% (400 mg) and 18% (PLD) ORR (GCIG using CA-125) 34% (200 mg) vs. 56% (400 mg) and 33% (PLD) SD 47% (200 mg) vs. 59% (400 mg) and 52% (PLD)

PARP Inhibitor	Study Reference	Design	Participants	Dose and Schedule	Results
					Survival: median PFS 8.4 mths (olaparib) vs. 4.8 mths (placebo)
ABT-888 (Veliparib)	Isakoff (2010)[54]	Open-label non-randomized phase II 1^0 endpoint(s) – ORR 2^0 endpoint(s) – PFS, OS, safety, and toxicity	N = 41 (24 evaluable); metastatic breast cancer TNBC 37% (15/41)]; BRCA mutation status (unknown)	(1) ABT-888 (40 mg twice daily D1-7) + TMZ (150 mg/m^{2}daily D1-5) in a 28 day cycle * dose of ABT-888 reduced to 30 mg daily D1-7 after higher than expected incidence of thrombocytopenia	Responses: ORR (CR+PR) 12.5% (3/24) SD 29% (7/24) Survival: median PFS unknown
	Pishvaian (2011)[55]	Open-label non-randomized phase I/II 1^0 endpoint(s) – DCR 2^0 endpoint(s) – RR, TTP	N = 47; heavily pretreated (mean no. of prior therapies – 4), metastatic colorectal cancer	(1) ABT-888 (40 mg twice daily D1-7) + TMZ (150 mg/m^{2}daily D1-5) in a 28 day cycle	Responses: ORR (CR+PR) 5% (2 PRs, no CR) DCR (CR+PR+SD) 23% Survival: median TTP 11 weeks overall (23 in pts with disease control)
	Andreopoulou/ NYCC P8853 (2011)[56]	Multi-center double-blinded controlled randomized phase II 1^0 endpoint(s) – PFS	N = 62 (based on α=0.10, β=0.90) Eligibility: chemotherapy-resistant (≥2 prior regimens including taxane and capecitabine); ER/PRpositive, HER2/neu-negative metastatic breast cancer	(1) low-dose metronomic cyclophosphamide 50 mg daily + ABT-888 60mg daily (2) low-dose metronomic cyclophosphamide 50 mg daily + placebo	Responses/Survival: Results awaited (trial in progress)
	Pishvaian (2011)[57]	Open-label non-randomized phase I/II 1^0 endpoint(s) – ORR 2^0 endpoint(s) – DCR, PFS, OS	N = 3+3 dose escalation in phase I; Simon's two-stage design in phase II with 9 pts/Arm in 1st stage and up to 24 in 2nd stage Eligibility: metastatic, unresectable pancreatic cancer	(1) ABT-888 + mFOLFOX-6 mFOLFOX-6: oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 and 5-FU 400 mg/m^2 on D1, followed by a continuous infusion of 5-FU 2400 mg/m^{2}over 46 hours on D1-3 of each 14 day cycle Phase I portion: ABT-888 40–100 mg twice daily D1-7 of each 14 day cycle Phase II portion: Arm A – previously untreated pts Arm B - ≥1 prior therapies	Responses/Survival: Results awaited (trial in progress)

PARP Inhibitor	Study Reference	Design	Participants	Dose and Schedule	Results
BSI-201 (Iniparib)	O'Shaughnessy (2009 – ASCO plenary)[58] (2011 – NEJM publication)[59]	Multi-center open-label non-randomized phase II 1^0 endpoint(s) – clinical benefit rate (OR + PR + SD) 2^0 endpoint(s) – OR, PFS, OS	N = 123; metastatic TNBC; percentage of pre-treated pts (40% in G/C group and 43% in G/C + BSI-201 group)	(1) gemcitabine + carboplatin (2) gemcitabine + carboplatin + iniparib Gemcitabine 1000 mg/m^2 + carboplatin AUC2 on D1,8 of each 21 day cycle Iniparib 5.6 mg/kg D1,4,8,11 of each 21 day cycle	Responses: Clinical benefit rate (CR+PR+SD) 34% (G/C alone) vs. 56% (G/C + BSI-201) ORR (CR+PR) 32% (G/C alone) vs. 52% (G/C + BSI-201) Survival: median PFS 3.6 mths (G/C alone) vs. 5.9 mths (G/C + BSI-201) median OS 7.7 mths(G/C alone) vs. 12.3 mths (G/C + BSI-201)
	Penson (2011)[60]	Multi-center single-arm phase II 1^0 endpoint(s) – ORR 2^0 endpoint(s) – PFS and safety	N = 17 (41 planned); recurrent platinum sensitive ovarian, fallopian tube or peritoneal carcinoma; BRCA mutation status not reported N = 41 based on Simon's two-stage design in phase II with 17 in 1st stage and up to 24 in 2nd stage	(1) gemcitabine + carboplatin (2) gemcitabine + carboplatin + iniparib Gemcitabine 1000 mg/m^2 D1 and D8 Carboplatin AUC4 D1 Iniparib 5.6 mg/kg D1,4,8,11 of each 21 day cycle	From 17 patients in 1st stage: Responses: ORR (CR+PR) 70.6% (12/17 CR) Survival: Data not reported
	O'Shaughnessy (2011)[61]	Multi-center open-label randomized phase III 1^0 endpoint(s) – OS, PFS 2^0 endpoint(s) – ORR, safety	N = 519; metastatic TNBC	(1) gemcitabine + carboplatin (2) gemcitabine + carboplatin + iniparib Gemcitabine 1000 mg/m^2 + carboplatin AUC2 on D1,8 of each 21 day cycle Iniparib 5.6 mg/kg D1,4,8,11 of each 21 day cycle	Responses: ORR (CR+PR) 57% (1st line) vs. 43% (2nd or 3rd line) Survival: median PFS 4.1 mths (G/C alone) vs. 5.1 mths (G/C + BSI-201) *(p = 0.284)* median OS 11.1 mths(G/C alone) vs. 118 mths (G/C + BSI-201) *(p = 0.027)*

Key: ORR – objective response rate; BORR – best observed response rate; CR – complete response; PR – partial response; SD – stable disease; PFS – progression free survival; DCR - disease-control rate (CR, PR or SD according to RECIST); TNBC – triple negative breast cancer; GCIG - Gynecologic Cancer Intergroup; mCRC – metastatic colorectal cancer.