Cediranib, a pan-VEGFR inhibitor, and olaparib, a PARP inhibitor, in combination therapy for high grade serous ovarian cancer

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Abstract

Introduction:

An estimated 22,000 women are diagnosed annually with ovarian cancer in the United States. Initially chemo-sensitive, recurrent disease ultimately becomes chemoresistant and may kill ~14,000 women annually. Molecularly targeted therapy with cediranib (AZD2171), a vascular endothelial growth factor receptor (VEGFR)-1, 2, and 3 signaling blocker, and olaparib (AZD2281), a poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, administered orally in combination has shown anti-tumor activity in the treatment of high grade serous ovarian cancer (HGSOC). This combination has the potential to change the treatment of HGSOC.

Areas covered:

Preclinical and clinical studies of single agent cediranib and olaparib or their combination are reviewed. Data are presented from peer-reviewed published manuscripts, completed and ongoing early phase clinical trials registered in ClinicalTrials.gov, National Cancer Institute-sponsored clinical trials, and related recent abstracts.

Expert opinion:

Advances in the treatment of HGSOC that improve progression-free and overall survival have proven elusive despite examination of molecularly targeted therapy. HGSOC patients with deleterious germline or somatic mutations in *BRCA1* or *BRCA2* (BRCAm) are most responsive to PARP inhibitors (PARPi). PARPi combined with angiogenesis inhibition improved anti-cancer response and duration in both BRCAm and BRCA wild type HGSOC patients, compared to olaparib single agent treatment, demonstrating therapeutic chemical and contextual synthetic lethality.

1. **Introduction**

It is estimated that approximately 22,000 women are diagnosed annually with ovarian

cancer in the United States, and an estimated 14,000 women die annually from this

disease [1]. Initial treatment with platinum/taxane-based chemotherapy will result in a

nearly 80% response rate; however, with a 31% 5-year survival rate, almost all will

relapse, and become treatment resistant succumbing to disease [2, 3]. New treatments are

needed to prolong overall survival (OS), progression-free survival (PFS), and ameliorate

side effects of chemotherapy. Combination therapy with small molecule inhibitors of

angiogenesis and poly(adenosine diphosphate [ADP]-ribose [PAR]) polymerase (PARP)

holds promise for treating cancers that harbor DNA repair defects.

Intrinsic DNA repair pathways have evolved across all normal cells to allow those

cells to tolerate and repair DNA damage associated with normal cellular function and

exposure, and DNA damage caused by extrinsic injury such as ambient radiation, reactive

oxygen species, and chemical agents [4-8]. These DNA repair pathways can be

detrimental when they are used by tumor cells to survive DNA damage from

chemotherapy, radiotherapy, and other anti-cancer treatments [9]. Two major forms of

injury can occur: single strand breaks (SSBs) and double strand breaks (DSBs) (Figure

1). There are multiple and redundant mechanisms for DNA repair that fall into two

categories: SSB and DSB targeted pathways. DSBs are repaired predominantly by the

low fidelity non-homologous end joining (NHEJ) program during G1/S; replication-

associated and secondary DSBs are repaired by the high fidelity homologous

recombination (HR) repair pathway in G2 (Figure 2) [10]. Alkylating agent-induced

DNA adducts cause covalent intra- and inter-strand cross-linking of DNA, resulting in

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stalled replication forks. These may be excised and repaired by base excision repair (BER) or nucleotide excision repair (NER) (Figure 1) [11]. PAR polymerization (PARylation) is a unique post-translational modification of histones and other nuclear proteins that contributes to the survival of cells following SSB damage. The enzyme PARP1 is stimulated by DNA strand breakage, and mediates BER by recruiting its scaffolding proteins XRCC1 and DNA polymerase ß [12]. Increased PARP1 expression and/or activity in tumor cells has been demonstrated in many tumor types, and thus it has been hypothesized that inhibition of PARP should sensitize tumor cells to cytotoxic agents that induce SSB DNA damage. Pre-clinical testing of several PARP inhibitors (PARPi) demonstrated anti-tumor activity both alone and in combination with DNA damaging chemotherapy [13-15]. PARPi has been shown to increase cytotoxic activity and apoptosis in cisplatin-resistant ovarian cancer cell lines when given in combination with cisplatin [16].

HR is a complex repair program requiring a cascade of proteins that include *BRCA1* and *BRCA2 (BRCA1/2)*, the tumor suppressor genes recognized for their association with familial breast and ovarian cancers [17, 18]. Germline deleterious mutations in *BRCA1/2* (gBRCAm) occur in approximately 17% of newly diagnosed high grade serous epithelial ovarian cancers (HGSOC) [19]. HGSOC tumors have lost their second copy of *BRCA1*/2, leaving the tumor homozygous deficient in BRCA1/2 function, and thus having a loss of function of the DSB HR repair pathway. Other potential methods of developing HR repair deficiency include somatic homozygous loss of *BRCA1/2*, and loss of lower frequency and lower penetrance DNA repair genes, such as *RAD51c* and *PALB2* [20]. Methylation of *BRCA1* with resultant BRCA1 protein

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reduction has not been shown conclusively to cause an HR repair-deficient phenotype [21]. Inability to repair DSBs causes the cell to accumulate further somatic mutations; in non-malignant cells, this causes apoptotic cell death, but in abnormal, pre-malignant cells, this may augment cell survival and promote malignancy (Figures 1 and 3).

PARP1 has been shown to have at least two major functions in DNA repair (Figure 3). The first is to inhibit PARylation, an event that signals the presence of a SSB and recruits repair proteins. Second, PARP1 is involved in keeping the low fidelity NHEJ DNA repair program in check. Functional PARP1 inhibits phosphorylation of DNA-dependent protein kinase catalytic subunit (DNA-PKcs) and subsequent activation of NHEJ [22]. Loss of *BRCA1/2* function causes cells to default to other DNA repair pathways such as the BER repair pathway, which is modulated by PARP proteins, and NHEJ, which is regulated by PARP1. Loss of PARP1 activity in a background where the HR repair pathway is compromised by *BRCA1/2* genomic loss has been shown to create a synthetic lethal event *in vitro* [13, 15]. This data suggests that gBRCAm breast and ovarian cancers would be selectively or differentially sensitive to PARPi, as has been observed [23-27]. A series of PARPi (Box 2) are under clinical investigation; currently, only olaparib (AZD2281/Lynparza™) is approved for use [28]. In the United States, olaparib was granted approval for the capsule formulation for fourth line or later therapy in patients with gBRCAm ovarian cancer, and in the European Union, for maintenance of second or later clinical response in patients with platinum-sensitive relapsed gBRCAm or sBRCAm HGSOC who had a complete or partial response to platinum-based chemotherapy. Activity of olaparib is greatest in platinum-sensitive gBRCAm carriers

with decrements in activity as a function of loss of platinum-sensitivity and absent

mutation status [25, 26, 29].

Angiogenesis, the process of new blood vessel formation and vessel sprouting, is

necessary for tumor growth and dissemination [30]. Hollingsworth *et al.* showed in 1995

that ovarian cancers with high microvessel numbers had a worse outcome [31].

Subsequently, many preclinical, clinical, and translational studies have continued to

confirm a role for angiogenesis in the malignant biology of HGSOC [30]. Vascular

endothelial growth factors (VEGFs A through E) are the ligands to the VEGF receptor

(VEGFR) 1-3 family. VEGFA, also known as vascular permeability factor, was initially

identified in the malignant ascites of a human ovarian cancer xenograft [32, 33]. Hypoxia

is a major inducer of VEGFA, and a major consequence of anti-angiogenic therapy is

induction of local hypoxia [34]. VEGFA was the first, and perhaps the most successful,

non-oncogene-specific target for onco-therapeutics. VEGFA has been targeted with

selective monoclonal antibodies, such as bevacizumab, and its receptor family with

numerous kinase inhibitors, many of which have received approval in other cancers.

Cediranib, an inhibitor predominantly of the VEGFRs 1-3, has a 14-17.0% response rate

in ovarian cancer [35, 36], similar to that of single agent bevacizumab, and shows greater

activity than was demonstrated for sorafenib or sunitinib [37, 38]. Bevacizumab has

recently been approved for recurrent platinum-resistant ovarian cancer when given in

combination with chemotherapy [39].

Optimizing combination therapy with cediranib and olaparib is an important

objective for the treatment of patients with HGSOC, based on preclinical and clinical data

where enhanced efficacy was exhibited. A greater than interactive inhibition of

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microvascular tube development *in vitro* was seen in preclinical studies using cediranib in

combination with olaparib [38]. In patients with recurrent epithelial ovarian cancer and

triple negative breast cancer, this combination was examined in a phase 1/2 study

(NCT01116648) and shown to be safe with preliminary evidence of activity in recurrent

epithelial ovarian cancer [40]. In the randomized phase 2 portion of the study comparing

olaparib against olaparib and cediranib in platinum-sensitive HGSOC patients

(NCT01116648), an overall progression-free survival (PFS) of 17.7 months in the

combination therapy group and 9.0 months in the single agent olaparib group was

observed [41]. An unplanned post-hoc analysis showed equal distribution of gBRCAm

carriers on each arm and demonstrated that the combination was active in both the

gBRCAm and the wild type/unknown groups [41]. A PFS of 5.7 months was observed

for single agent olaparib in non-mutation carriers compared to a PFS benefit of 16.5

months (p=0.008) with combination therapy. A benefit of 16.5 months was seen for

single agent olaparib in mutation carriers compared to 19.4 months (p=0.16) with the

combination.

2. Overview of the treatment options

HGSOC remains a serious, chronic, and lethal malignancy in the 70% of women

diagnosed with advanced disease. Women who present with advanced disease will

receive initial therapy with a platinum-taxane combination treatment regimen [42]. They

will ultimately relapse on one or many more occasions, although their cancer may

continue to remain responsive to platinum-based therapy. Eventually, however, their

disease will become resistant or refractory to platinum-based therapy and, at that time,

their survival diminishes to 15 months or less. The primary goal for treatment of ovarian

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cancer remains improvement in OS, maintenance of a good quality of life and activities of daily living, prolongation of the interval between platinum-based therapies, and amelioration of treatment-based side effects. Recurrent disease occurs in nearly all advanced staged HGSOC, such that approximately half of the newly diagnosed 22,000 patients per year could at some point in their treatment be eligible for this combination therapy. Both of these agents are orally bioavailable and can be administered with careful monitoring of blood pressure and diarrhea. Thus, this combination therapy may conceivably be applicable in a wide variety of settings beyond tertiary care and hospital/inpatient settings.

Olaparib is now licensed in the United States for the treatment of ovarian cancer in fourth line or later treatment of gBRCAm patients, and in the European Union for the maintenance treatment of platinum-sensitive relapsed BRCAm ovarian cancer. Cediranib remains an investigational agent with activity in a wide variety of clinical settings, including platinum sensitive and resistant ovarian cancer. Multiple PARPi are currently in clinical development (see Box 2). A vast array of VEGFR2 small molecule inhibitors are licensed for the treatment of renal cell cancer (sunitinib, sorafenib, pazopanib, and axitinib) and sarcomas (pazopanib and sunitinib), and some have shown activity in ovarian cancer (pazopanib); however, none are indicated for the treatment of ovarian cancer [43, 44], unlike monoclonal antibodies. This review will focus on treatment of HGSOC with the combination of cediranib and olaparib in platinum-sensitive and -resistant disease.

3. Introduction to the compounds

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Cediranib (AZD2171) is a highly potent oral VEGFR-1,-2, and -3 inhibitor that also targets c-Kit [45-48]. Cediranib inhibits human umbilical vein endothelial cell (HUVEC) proliferation and diminishes microvessel density while causing reversible epiphyseal zone hypertrophy in rodent animal models [48]. Also, cediranib is active in a wide variety of human tumor xenografts. It has demonstrated single agent clinical activity in ovarian cancer and is also active in combination with other small molecule inhibitors or chemotherapy [49].

Olaparib (Lynparza™, AZD2281, KU-0059436) is a highly potent PARP1/2 and tankyrase inhibitor that induces chemical synthetic lethality, particularly in combination with loss of BRCA1/2 function and BRCA-like context, when tumors have DNA homologous recombination deficiency (HRD). Olaparib is an orally administered agent that is clinically active as a single agent or in combination with other small molecule inhibitors or chemotherapy. Olaparib is active in solid tumors including ovarian cancer, with greater activity in platinum-sensitive gBRCAm ovarian cancer than in platinum-resistant gBRCAm, platinum-refractory gBRCAm, or platinum-sensitive BRCA wild type ovarian cancer (see box 1).

4. Chemistry

The chemical name for cediranib is 4-[(4-Fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline maleate (International Union of Pure and Applied Chemistry). It is an achiral compound, and it has a molecular weight of 566.59 as a maleate salt (450.52 as a free base). It appears as an off-white crystal powder. Its molecular formula is $C_{25}H_{27}FN_4O_3 \cdot C_4H_4O_4$ with a melting point of 197°C.

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Olaparib, 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one, is a non-chiral, crystalline solid with an off-white to pale yellow-orange appearance. Its molecular weight is 434.46, and its molecular formula is $C_{24}H_{23}FN_4O_3$. Its melting point is 210-211°C.

5. Pharmacodynamics

5.1 Cediranib

Induction of VEGF in response to angiogenesis inhibitors is well recognized and is in response to generation of local hypoxia. VEGF and soluble VEGFR2 (sVEGFR2) concentrations were measured in serum of all patients on AstraZeneca-sponsored studies and the results showed an increase in VEGF levels with cediranib treatment and a decrease in sVEGFR2 [50]. To date, no biomarkers predictive of response to antiangiogenic therapy have been confirmed.

Cediranib is commonly administered as 20 or 30 mg tablets once a day (Figure 4). At the free drug exposure achieved at the 30 mg and 20 mg doses, cediranib levels are sufficient to cover the half maximal inhibitory concentration (IC_{50}) for VEGFRs 1, 2, and 3. At these exposures it will also inhibit c-kit [45, 48]. Although cediranib has activity against platelet-derived growth factor receptors (PDGFRs) *in vitro*, the free drug levels achieved in patients are not sufficient to achieve effective inhibition of PDGFR signaling [45, 48]. Therefore, cediranib, at doses used clinically, has a selective pharmacology profile delivering pan-VEGFR pathway inhibition and activity against c-kit.

5.2 Olaparib

PARPi exert their effects by blocking DNA repair of SSBs through catalytic inhibition of the PARP enzyme inhibiting DNA PARylation blockade required for SSB recognition

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(Box 2), by trapping PARP1/2 in DNA complexes leading to PARP inactivation, and by

relieving inhibition of NHEJ [22, 51]. DNA PARylation occurs at sub- and low-

therapeutic drug concentrations and has not correlated with clinical activity. PARP

trapping may be a key element for cytotoxicity. PARPi are functionally categorized into

two classes based on their catalytic inhibition and ability to trap PARP on DNA [51].

5.3 Olaparib and cediranib

Inhibition of angiogenesis causes induction of circulating pro-angiogenic cytokines, such

as VEGFA, interleukin (IL)-6 and IL-8 [52]. It also has been shown to induce production

of circulating endothelial cells (CECs) and endothelial cell precursors [53, 54].

Preclinical anti-angiogenic interaction of olaparib and cediranib led to pharmacodynamic

evaluation in a partially randomized phase 2 trial (NCT01116648). Lee *et al.* studied

serial blood samples from a small subset of participants, equal proportions having

received olaparib or olaparib with cediranib, and equal numbers of wild type/unknown

and gBRCAm [51, 55]. Patients on combination therapy had a greater decrease in

circulating IL-8 concentration and a larger fold-increase in CECs than those receiving

single agent olaparib (p=0.026, p=0.032, respectively). The fold increase in CECs from

pretreatment to day 3 was positively associated with duration of PFS (R^2=0.77, 95% CI

0.55-0.97, p<0.001). Changes in circulating IL-8 concentrations over that same 72 hours

also correlated with PFS (p=0.028). These findings demonstrate pharmacodynamic

effects of the combination and foreshadow potential predictive value. These endpoints

will be examined prospectively in soon-to-open randomized phase 3 trials

(NCT02446600 and NCT02502266).

6. Pharmacokinetics and metabolism

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6.1 Pharmacokinetics-cediranib

Pharmacokinetics (PK) evaluations of cediranib supported once daily (QD) oral dosing

[56-58]. Cediranib was well-absorbed with apparently linear PK for single and multiple

doses ranging from 0.5 to 60 mg. The absolute bioavailability of cediranib was not

determined clinically. Steady-state plasma concentrations were achieved by ~7 days with

continuous oral daily dosing. The single-dose PK predicted steady-state plasma

concentrations; accumulation was limited, and there were no time-dependent changes in

PK. Cediranib was cleared by moderate hepatic metabolism that was approximated as

41% of nominal hepatic plasma flow.

A number of chemotherapy regimens have been combined with cediranib [50].

Little or no effect of cediranib has been found on the steady-state plasma concentrations

of paclitaxel, cisplatin, carboplatin, oxaliplatin, 5-fluorouracil (5-FU) (given as part of the

mFOLFOX6 regimen), docetaxel, pemetrexed, irinotecan, +SN38, gefitinib, or

gemcitabine (<1.5-fold change). Steady-state PK parameters of cediranib in combination

with the chemotherapy agents were comparable to those seen previously with cediranib

monotherapy. Comparison of the PK in Japanese and Western populations yielded less

than two-fold differences in any parameters, including area under the plasma

concentration-time curve (AUC) at steady-state [AUC_{ss}] or maximum plasma

concentrations (C_{max}) [59].

6.2 Metabolism-cediranib

Following single and multiple daily dosing of cediranib, cediranib was absorbed with

C_{max} typically observed within 1 to 8 hours post-dose [50]. Co-administration of

cediranib with a high fat meal reduced the cediranib area under the plasma concentration-

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time curve (AUC) by 24% and the C_{max} by 33%. Therefore, it is recommended that

cediranib be taken on an empty stomach at least 1 hour before or 2 hours after a meal.

Mean apparent volume of distribution at steady state of cediranib ranged from 429

to 1290 L, indicating extensive distribution into tissues [50]. Plasma protein binding was

~95%. Cediranib binded to serum albumin and alpha 1-acid glycoprotein.

Following a single dose of cediranib, AUC and C_{max} increased proportionally

with doses ranging from 0.5 to 60 mg [50]. Following multiple daily dosing, the

accumulation index ranged from 1- to 3-fold, and the PK of cediranib was linear over

time. Based on the mean terminal half-life of cediranib of 22 hours, steady-state cediranib

plasma concentrations should be achieved ~5 days after starting or changing the dose of

cediranib.

Following a single oral dose of radiolabeled cediranib, unchanged cediranib and

oxidised metabolites were detected in plasma, urine, and feces [50]. Excretion was

predominantly via the feces (59%), with renal elimination of metabolites accounting for

about 21% of the administered dose and with less than 1% of the administered dose

excreted as unchanged drug in the urine.

An N-glucuronide conjugate of cediranib was the major circulating metabolite but

represented only 11% of cediranib in plasma [50]. Cediranib oxidative metabolism

appeared to be mediated by flavin containing monooxygenase (FMO)1 and FMO3, while

phase 2 metabolism was mediated primarily via glucuronidation by uridine 5'-

diphosphosphate (UDP)-glucuronosyltransferase (UGT)1A4.

In vitro data indicated that cediranib was not metabolized by cytochrome P450

(CYP450), and was unlikely to cause interactions with a CYP450 inhibitor or inducer

[50]. Cediranib was a substrate of multidrug resistance protein 1 (MDR1)/P-glycoprotein (P-gp), but not of breast cancer resistance protein (BCRP). While cediranib was not an inhibitor of MDR1, it was found to have a low potential in inhibiting BCRP; however, the clinical impact of this finding is unknown.

Administration of cediranib with chemotherapy showed little or no apparent effect (≤1.5-fold change) on the exposure to carboplatin, cisplatin, docetaxel, gefitinib, gemcitabine, paclitaxel, or pemetrexed [50]. Cediranib exposure with carboplatin, cisplatin, docetaxel, gefitinib, gemcitabine, paclitaxel, or pemetrexed was also comparable to exposure with cediranib monotherapy.

Co-administration of cediranib 20 mg and ketoconazole 400 mg, a potent CYP 3A4 enzyme and MDR1/P-gp transporter inhibitor, for 3 days caused a modest increase in cediranib exposure (AUC_{ss}: 21% [confidence interval (CI)=9% to 35%]; maximum plasma concentration at steady state [$C_{ss,max}$]: 26% [CI=10% to 43%]) [50]. Given that cediranib was not metabolized by CYP450 enzymes *in vitro*, this increase was most likely due to P-gp inhibition. Since the increase in exposure was small, no *a priori* dose adjustment is required when cediranib is given with a potent CYP3A4/P-gp inhibitor.

Co-administration of 600 mg rifampicin, a potent inducer of CYP3A4 and glucuronidation (UGT) and an MDR1/P-gp transporter, for 6 days prior to administration of cediranib decreased cediranib exposure (AUC_{ss}: 39%[CI: 34% to 43%] and $C_{ss,max}$: 23% [CI: 16% to 30%]) [50]. This decrease was most likely due to UGT/P-gp induction. Use of potent inducers of UGT/P-gp (*e.g.*, rifampicin, carbamazepine, phenobarbital, phenytoin, and St John's Wort) should be avoided, if possible, with cediranib.

6.3 Pharmacokinetics-olaparib capsule formulation

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Olaparib was rapidly absorbed following capsule oral dosing in cancer patients [28]. Apparent volume of distribution was 167 L, apparent plasma clearance was 8.6 L/h, and the estimated terminal half-life ($t_{1/2}$) was between 11.9 hours. Steady state exposures were achieved within ~3 to 4 days, and significant drug accumulation was not observed with multiple dose administration.

6.4 Metabolism-olaparib

The metabolism of olaparib is extensive. The majority is attributable to oxidation with a number of products undergoing subsequent glucuronidation or sulfation. The majority of olaparib is excreted as metabolites. CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib [28]. Co-administration of a potent CYP3A inhibitor increased the mean C_{max} of olaparib 1.42-fold (90% CI: 1.33-1.52) and increased the mean AUC 2.70-fold (90% CI: 2.44-2.97); co-administration of a potent CYP inducer decreased the mean C_{max} by 71% (treatment ratio: 0.29; 90% CI: 0.24-0.33) and the mean AUC by 87% (treatment ratio: 0.13; 90% CI: 0.11-0.16). Therefore, it is recommended that potent CYP3A inhibitors and inducers are not given with olaparib. Olaparib can also inhibit CYP3A4 *in vitro* [28].

7. Clinical efficacy

Both cediranib and olaparib have demonstrated single agent activity in ovarian cancer, and the activity of these drugs in combination has now been reported in both Phase 1 and Phase 2 studies. Key studies in the development of these drugs and this drug combination in HGSOC are detailed below.

7.1 Phase 1 studies

7.1.1 Cediranib

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Multiple AstraZeneca-sponsored phase 1 studies of single agent cediranib were

conducted to determine the dose and schedule as well as the safety and tolerability of

cediranib (NCT00501605, NCT00502385, NCT00502164, NCT00243347,

NCT00503412, NCT00750425, NCT00503477, NCT00750841, NCT00981721). The

recommended phase 2 dose was determined and ranged from 20-45 mg oral administered

on a once daily schedule. One notable adverse event (AE) observed was mechanism-

based hypertension, which ranged from grade 1 to 4 with grade 3 and 4 hypertension

observed in patients in the phase 1 investigation or in those who were non-compliant with

anti-hypertensive treatment regimens. Regimens to manage hypertension, such as anti-

hypertensive therapy, have been developed[50]. However, patients undergoing anti-

hypertensive therapy at baseline are at an increased risk for elevated blood pressure and

may require more than one drug or more anti-hypertensive therapy than previously

indicated. Diarrhea was the most common cause for dose modification after hypertension.

Early intervention with loperamide and subsequent dose reduction allowed continuation

of therapeutic dosing, although dose reductions were necessary in those patients still

having diarrhea despite addition of anti-diarrheal agents. Overall, the most commonly

occurring toxicities were fatigue, diarrhea, nausea, dysphonia, and hypertension [50].

7.1.2 Olaparib

Fong *et al.* first reported the single agent activity of olaparib, including 23 BRCAm

patients, of whom 9 experienced a Response Evaluation Criteria in Solid Tumors

(RECIST) response [24].

7.1.3 Cediranib and olaparib combination

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The combination was examined in a phase 1 (NCT01116648) study as detailed and shown to be generally anticipatable and manageable, tolerable, and with preliminary evidence of anti-cancer activity in HGSOC [40].

7.2 Phase 2 studies

7.2.1 Cediranib and olaparib monotherapy

The activity in ovarian cancer and minimally overlapping toxicity observed in single agent phase 2 studies (NCT00501605, NCT00243347, NCT00750425, and NCT00516373) led to the randomized phase 2 study of the combination of olaparib and cediranib for women with platinum-sensitive HGSOC or gBRCAm ovarian cancer (NCT01116648). Single agent cediranib resulted in response rates of 17% in a single arm study; the response rate increased to 26% in platinum-sensitive patients [35, 36]. Single agent olaparib activity was observed in both treatment and maintenance of response designs, in single agent and combination studies, and in gBRCAm and unselected ovarian cancer patients. Responses to olaparib monotherapy are hierarchically best in gBRCAm platinum-sensitive women at >45% and worst in those without HRD deficiency and platinum-resistance at <10% [23, 26, 27, 29, 60, 61]. The results of the maintenance of response study (NCT00753545) served as the basis for the European Medicines Agency (EMA) approval of olaparib as maintenance therapy post platinum therapy in patients with continued platinum-sensitive HGSOC ovarian cancer.

7.2.2 Cediranib and olaparib combination

A phase 2 trial (NCT01116648) was conducted comparing cediranib and olaparib in combination to olaparib alone in women with recurrent platinum-sensitive ovarian cancer (see also above) [41]. Ninety women were enrolled, with 46 receiving olaparib

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capsule monotherapy at 400 mg twice daily (BID) and 44 patients receiving

cediranib/olaparib combination with cediranib 30 mg tablets QD and olaparib 200 mg

capsules BID. The median PFS in the combination arm was 17.7 months, compared to

9.0 months in the single agent arm. A post-hoc analysis by gBRCAm status, a predefined

stratification variable, found in women with a known gBRCAm that median PFS

increased from 16.5 to 19.4 months (p=0.16), while an increase from 5.7 to 16.5 months

(p=0.008) was observed in women who were not gBRCAm or whose germline *BRCA*

status was unknown.

7.3 Proposed phase 3 studies

7.3.1 Cediranib in ovarian cancer

ICON6 is a phase 3, international three-arm, double-blind placebo-controlled randomized

trial (NCT00532194) [62]. Women with first recurrence platinum-sensitive ovarian

cancer (n=456) were randomized (2:3:3) to receive platinum-based chemotherapy with

either placebo [62], cediranib 20 mg/day during chemotherapy followed by placebo for

up to 18 months (concurrent), or cediranib 20 mg/day followed by maintenance cediranib

(concurrent + maintenance). The primary endpoint was PFS in the reference versus

concurrent + maintenance arms. Secondary endpoints were OS, toxicity and quality of

life. Improved PFS was demonstrated in both the concurrent cediranib and the concurrent

+ maintenance cediranib arms compared to chemotherapy + placebo (median PFS

[mPFS] 8.7 months), with the greatest impact in the concurrent + maintenance arm

(mPFS 11.0 months, p<0.001) [50]. OS data also showed potential benefit (26.3 months

on concurrent + maintenance cediranib versus 20.3 months on chemotherapy + placebo).

7.3.2 Olaparib

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Two pivotal phase 3 trials of olaparib maintenance therapy following either initial

adjuvant chemotherapy (SOLO1; NCT01844986) or platinum-based chemotherapy in

platinum-sensitive recurrence (SOLO2; NCT01874353) in women with *BRCA*-related

ovarian cancer have now completed accrual and are awaiting maturation of results [63].

SOLO3 (NCT02282020) has also recently opened and randomizes patients with

gBRCAm recurrent platinum sensitive ovarian cancer to olaparib versus physician's

choice of single agent standard of care non-platinum based chemotherapy. Patients on

SOLO3 must have received at least two prior platinum-based lines of chemotherapy.

7.3.3 Combination of cediranib and olaparib

The activity of the cediranib/olaparib combination observed in the phase 2 study

(NCT01116648) has led to the development of two pivotal phase 3 studies

(NCT02446600 and NCT02502266) exploring this combination in ovarian cancer. A

Cancer Therapy Evaluation Program (CTEP)-sponsored three-arm study (NRG-GY004;

NCT02446600) to be conducted in the National Cancer Institute National Clinical Trials

Network (NCTN) will randomize recurrent platinum-sensitive HGSOC or any histology

gBRCAm patients to receive combination cediranib/olaparib, olaparib monotherapy, or

standard platinum-based chemotherapy (carboplatin/paclitaxel, carboplatin/pegylated

liposomal doxorubicin [PLD], or carboplatin/gemcitabine). Women will be stratified for

this trial by gBRCAm status as an integral biomarker. PFS is the primary endpoint. NRG-

GY005 (NCT02502266) is a phase 2/3 study that will randomize patients with recurrent

platinum-resistant or refractory HGSOC to receive combination cediranib/olaparib, non-

platinum based standard of care chemotherapy (weekly paclitaxel, topotecan, or PLD), or

either olaparib or cediranib monotherapy. PFS is the primary endpoint for the phase 2

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component, and OS and PFS are the two primary endpoints for phase 3. Resistant and

refractory ovarian cancer is enriched for non-gBRCAm patients leading to the

development of this study based upon the greater clinical benefit observed with

olaparib/cediranib in women with *BRCA* wild type or unknown *BRCA* status in the phase

2 study [41]. In addition, responses have been observed in platinum-resistant ovarian

cancer in the phase 1 study and the formulation bridge study [40, 64]. ICON9, sponsored

by Cancer Research UK, will investigate platinum-based chemotherapy with cediranib,

followed by the cediranib/olaparib combination or cediranib single agent as maintenance

therapy following platinum-based chemotherapy in platinum-sensitive recurrent HGSOC,

endometrial histology, or clear cell ovarian cancer.

8.   Safety and tolerability

8.1 Safety and tolerability-cediranib

Over 5,800 patients have received cediranib to date on AstraZeneca or NCI-sponsored

studies [50]. Early clinical data demonstrated that the most common cediranib AEs

included fatigue, diarrhea, nausea, vomiting, hoarseness, hand-foot syndrome, and

hypertension. With the development and implementation of hypertension management

protocol, grade 4 hypertension and end organ damage decreased significantly. In the

ICON6 trial, mild bleeding events were reported.

Hypertension is an expected AE seen with all agents that inhibit VEGF signaling,

and is the major cardiovascular AE associated with cediranib treatment [65]. Common

Terminology Criteria for Adverse Events (CTCAE) grade 4 hypertension and end-organ

damage related to hypertension, such as cerebrovascular events or left ventricular

dysfunction and heart failure have been observed with cediranib. Therefore, clinical trials

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include rigorous monitoring of blood pressure (BP) and renal function (creatinine, creatinine clearance, and urinary protein). A hypertension management protocol is incorporated into all clinical study protocols. Patients with pre-existing hypertension may be at particularly high risk of developing moderate or severe hypertension on cediranib and should have their BP management optimized prior to starting the drug. Left ventricular dysfunction, in some cases leading to cardiac failure, has been observed in patients with risk factors for left ventricular dysfunction (including prior or concomitant anthracycline treatment). Patients should be instructed to measure their BP at home and alert their medical team if BP readings are abnormally high.

Additional VEGF inhibitor class toxicities have been seen with cediranib and include bleeding and hemorrhagic episodes, clotting, gastrointestinal perforation, hoarseness, fatigue, hand-foot syndrome, and reversible posterior leukoencephalopathy syndrome (rare) [50]. Bleeding episodes, such as central nervous system (CNS) bleeding, may also be a result of hypertension. Some hemorrhagic events were fatal, but causality could not be unequivocally assigned to cediranib. Gastrointestinal perforation, sometimes associated with fistula formation, has been observed in patients receiving cediranib. Some events of gastrointestinal perforation have been fatal.

Diarrhea, nausea, and vomiting are commonly occurring AEs in cediranib studies. Dehydration has been observed in clinical studies as a consequence of cediranib- or chemotherapy-related diarrhea or vomiting; chemotherapy-associated anorexia or reduced oral intake may be contributing factors. Muscle weakness, dry mouth, and oral mucosal inflammation resembling gingivitis or mucositis have been observed in cediranib studies. Increases in transaminases, which are sometimes associated with increases in

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total bilirubin, have also been seen. Thrombocytopenia, predominantly of CTCAE grade

1 or 2, has also been observed with cediranib monotherapy or in combination treatment.

Additionally, cediranib has been associated with increases in thyroid stimulating

hormone (TSH); in a small number of patients, clinical hypothyroidism has been reported

and may require oral thyroid replacement. The maximum tolerated dose (MTD) of

cediranib, as determined in company phase 1 studies, was originally 45 mg QD [50].

However, due to the toxicities observed at that level, 30 mg QD is now considered the

starting single agent dose.

8.2 Safety and tolerability-olaparib

More than 3,800 patients with ovarian, breast, pancreatic, gastric and a variety of other

solid tumors are estimated to have received treatment with olaparib, predominantly as

monotherapy, but also in combination with other chemotherapy/anti-cancer agents. More

than 1,800 have received the capsule formulation of olaparib, and 2,000 patients have

received the tablet formulation. Olaparib is generally well tolerated at monotherapy doses

up to 400 mg BID capsule formulation and 300 mg BID tablet formulation in patients

with solid tumors in AstraZeneca-sponsored (*e.g.*, NCT00494442, NCT00628251,

NCT00753545, NCT00679783, NCT01874353, NCT01844986, NCT02282020,

NCT00494234, NCT02000622, NCT02032823, NCT00572364, NCT00516373,

NCT00777582, NCT01078662, NCT02184195, NCT00516724) investigator-sponsored

(*e.g.*, NCT02208375, NCT02398058, NCT01623349, NCT01562210, NCT02533765,

NCT02227082, NCT02485990, NCT01650376, NCT02338622, NCT02446704,

NCT01682772, NCT02308072, NCT02121990, NCT01758731, NCT02418624) and

NCI-sponsored NCTN (*e.g.*, NCT01116648, NCT02345265, NCT02498613,

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NCT01237067, NCT01296763, NCT01445418, NCT02484404) studies [28, 66]. The

tablet formulation recommended dose is lower due to greater bioavailability and a higher

C_{max} despite little if any change in $t_{1/2}$ [66]. The AE profile in this dose range

recapitulates that seen with the capsule formulation.

Administration of olaparib in AstraZeneca-sponsored trials in recurrent ovarian

cancer patients has been commonly associated with mild to moderate (CTCAE grade 1 or

2) intermittent nausea, diarrhea, vomiting, headache, and fatigue, which are manageable

using standard care without interrupting treatment. Mild to moderate myelotoxicity

(anemia, neutropenia, and thrombocytopenia) has also been observed; grade 3 and 4

anemia, an uncommon finding, has been managed by withholding or reducing olaparib

and providing blood transfusions. Nausea and fatigue have been the most common AEs

leading to early dose reduction, whereas anemia and occasional myelosuppression have

been more commonly late causes of dose modification. Other important potential risks

such as pneumonitis events, which have no consistent clinical pattern in a small number

of patients, and myelodysplasia/leukemia, which is included in the informed consent as

possibly associated with olaparib therapy, are not considered by the sponsor AstraZeneca

as clearly drug-associated, as the incidence has not exceeded that of patients receiving

platinating or alkylating agents. Future trials will provide more information on causality

of these adverse events.

8.3 Safety and tolerability-cediranib/olaparib combination

Combination cediranib/olaparib has been associated most frequently with fatigue,

diarrhea, hypertension, and nausea as compared to either single agent. All 28 patients in

the phase 1 study of cediranib tablets and olaparib capsules experienced at least one

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treatment-related AE [40]. Overall, 93% of patients experienced fatigue (18% at grade 3),

86% diarrhea (7% at grade 3), and 46% hypertension (25% at grade 3). Grade 3 or 4

treatment-related AEs occurred in 21 of 28 patients (75%) [40]. AEs were generally

managed with drug holds or dose reductions with close observation and early

intervention. In a recent phase 1 formulation bridging trial (NCT01116648), the olaparib

tablet formulation in combination with cediranib tablets showed a similar toxicity profile,

with nausea (79%), fatigue (75%), diarrhea (58%), and hypertension (42%) among the

most frequent toxicities [64].

A similar distribution of toxicities was noted in 44 patients receiving combination

cediranib/olaparib in the seminal phase 2 study (NCT01116648), with the most common

AEs being fatigue (86%; 27% ≥grade 3), diarrhea (93%; 23% ≥grade 3), and

hypertension (77%; 39% ≥grade 3) [41]. Nausea was seen in 73% of patients on

combination therapy and in 74% of patients receiving olaparib monotherapy.

Differentially occurring grade 3 or 4 toxicities between the cediranib/olaparib

combination and olaparib monotherapy arms included fatigue (27% *vs.* 11%), diarrhea

(23% *vs.* 0%), and hypertension (41% *vs.* 0%). There were two grade 4 events, both in

the cediranib/olaparib arm: hypertension and myelodysplastic syndrome (MDS). Grade 4

hypertension occurred in a patient who was not fully compliant with BP monitoring or

treatment. As in the phase 1 study, close observation and early intervention for any

observed toxicities via drug holds or dose reductions were important for optimal

management. MDS occurred in a patient with multiple prior lines of platinum-based

chemotherapy who randomized to receive olaparib/cediranib therapy. The patient

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responded with a partial response despite dose reductions, and after approximately one year of continuous therapy, was diagnosed with MDS.

The risk of MDS/acute myeloid leukemia (AML) in ovarian cancer patients increases with dose and duration of cytotoxic chemotherapy [67]. The role of gBRCAm status on the risk of secondary MDS/AML is unknown, as was the *BRCA* status of the patient that experience MDS in the phase 2 combination study. The occurrence of secondary MDS/AML has been noted as a potential risk of olaparib treatment with 21 reports of secondary MDS/AML out of 3,862 patients who received olaparib, a cumulative incidence of 0.5% [28]. There were two cases of MDS in patients who had received placebo or comparator in olaparib clinical trials (0.6% incidence, including patients receiving placebo/comparator).

9. Conclusion

The phase 1 combination trial of cediranib and olaparib (NCT01116648) established an MTD of cediranib tablets at 30 mg QD and olaparib capsules at 200 mg BID. The AE profile for this combination of agents was recapitulated from previous studies with the majority of events (primarily diarrhea, fatigue, nausea, and hypertension) being manageable and reversible with supportive care. Only two treatment-related grade 4 AEs were reported on the combination arm (during phase 2), and nearly two-thirds of all patients receiving the combination experienced a maximum of a grade 3 AE. The formulation bridging study (NCT01116648) identified the same recommended dosing when using the olaparib tablet formulation. Thus, the soon-to-open pivotal studies

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(NCT02446600 and NCT02502266) will use 30 mg cediranib QD and 200 mg olaparib tablets BID.

Phase 2 results from an ongoing clinical trial (NCT01116648) indicate that the combination of cediranib (30 mg QD) and olaparib (200 mg BID) shows significant PFS improvement over single agent olaparib (400 mg BID) in patients with recurrent ovarian, fallopian tube, or peritoneal cancer. The estimated median PFS for patients receiving the combination of cediranib/olaparib is 16.5 months (Arm B) compared to 8.2 months on olaparib alone (Arm A/dose level 1A) [50]. The stratified PFS hazard ratio (HR) at this time is estimated to be 2.44 (p=0.0028; 95% confidence interval [CI] 1.36-4.38), consistent with benefit on the combination arm.

Statistically significant between-arm differences were seen in patients who were known to be *BRCA* wild type or who had not undergone testing, as well as in a group of patients with a platinum-free interval of 6-12 months, although this evaluation is underpowered for subgroup analysis,. Both subsets are those expected to be less susceptible to DNA damaging agents and shown to have less benefit from single agent olaparib. These results suggest that the addition of cediranib to olaparib alters the biology of the disease and thus the susceptibility to intervention. Treatment advances are urgently needed for platinum-resistant and BRCA wild type women with ovarian cancer.

The combination therapy was associated with AEs requiring dose modification as described above. Patients continued to experience durable benefit despite such dose reductions, with some patients continuing beyond one and two years, on dosing as low as cediranib 15 mg QD with olaparib. The trial has also examined use of olaparib tablets in combination with cediranib and now is enrolling for a detailed PK analysis of this dose

and formulation. Further, women on the combination therapy consistently said they preferred the simpler oral regimen; a quality of life element has been included in upcoming pivotal trials to examine this potential.

No predictive biomarkers of response to antiangiogenic therapy have been confirmed. Correlative results in a subset of 10 patients on the phase 2 component (5 from each arm) indicate that early vascular injury, as assessed by Day 3 CEC and IL-8 concentrations, are associated with PFS response and bear further exploration. In addition, preclinical evidence suggests that cediranib may sensitize tumor cells to olaparib treatment by downregulating BRCA1 protein expression; future trials may assess BRCA protein expression as a biomarker of benefit in patients without a known gBRCAm [68-71].

10. Expert opinion

10.1 Perspective on evolving treatment of HGSOC

Advanced stage HGSOC is rarely cured, with fewer than half of affected women alive at 5 years despite recent advances. This is, nonetheless, a marked improvement in quality and duration of life over a two decade period. The advent of combination chemotherapy with taxanes starting in the 1990s, as well as the addition of intraperitoneal therapy and improved surgery and supportive care, has increased median OS from less than 2 years in the 1980s to nearly 5 years in the 2010s. Early detection has not fared as well, although we now have data indicating the fallopian tube as the source of serous cancers [72], and the potential for serial cancer antigen (CA)-125 sampling and triggered use of transvaginal ultrasound to identify lower tumor burden disease, though not earlier stage

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disease [73]. This underscores the urgent unmet need for new and different therapeutic modalities targeting the vulnerabilities in the biology of epithelial ovarian cancer.

Dissection of the molecular biology of ovarian cancer through the Cancer Genome Atlas (TCGA) project [19], the Ovarian Cancer Australian Consortium (OCAC), and other studies [74, 75] has led to new understanding of the disease, but has not uncovered new molecular drivers for therapeutic targeting. The only validated molecular driver, and now recognized predictive biomarker and therapeutic director, is BRCAm. These mutational events were found to predispose to development of ovarian (and breast) cancer. Ovarian cancers with BRCAm tend to be highly platinum-sensitive and retain this sensitivity through several rounds of treatment. Patients with BRCAm have an improved OS, which can be attributed at least in part to loss of function of the highly important HR DNA repair pathway function.

The role *BRCA1/2* plays in the repair and maintenance of damaged DNA is still being fully elucidated. The dysregulation of DNA repair that occurs in BRCAm tumors leads to accumulation of DNA damage and ultimately cell susceptibility to DNA damaging therapy and tumor cell death. PARP enzymes were known to play a pivotal role in the repair of DNA SSBs, leading to the observation that PARP was an excellent and drugable target. The 2005 observations by Bryant *et al.* and Farmer *et al.* of the unique susceptibility of cells with BRCAm to PARPi [13, 15] has now been validated in patients and supported by the approval of the first selective PARPi in ovarian cancer patients with BRCAm. Several PARPi are currently in development for the treatment of patients who carry BRCAm with breast and ovarian cancer and other tumor types. How

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to capitalize on this important discovery and apply it more broadly to ovarian cancer patients remains a challenge.

Concurrent with PARPi development in the early 2000s was the exploding field of angiogenesis inhibitors for the treatment of a wide variety of malignancies. Targeting angiogenesis in cancer hinged on the pivotal observations of Judah Folkman, Lance Liotta, Harold Dvorak, and many others [33, 76, 77]. Antibodies were developed to target VEGFA, and small molecule inhibitors were developed to inhibit signaling from VEGFRs 1, 2, and 3 affecting angiogenesis and lymphangiogenesis. Bevacizumab, the Food and Drug Administration (FDA)-approved monoclonal anti-VEGFA antibody, has been shown to have single agent activity in ovarian cancer [78, 79], and has been shown to provide added benefit in PFS when used in combination with chemotherapy for newly diagnosed ovarian cancer patients [80, 81], for first recurrence platinum-sensitive ovarian cancer [82], and most recently receiving registration for use with chemotherapy for recurrent ovarian cancer patients [83].

Cediranib is a particularly potent blocker of VEGFR-1, -2, and -3 signaling, which inhibited signaling in low-single digit nanomolar concentrations and showed single agent activity against ovarian cancer in two single arm phase 2 studies (reviewed above). Use of VEGFA or VEGFR inhibitors has been shown to cause or augment local tumor hypoxia, which results in upregulated VEGFA production, a recognized cellular homeostatic response to hypoxia. These studies of angiogenesis inhibitors demonstrated an important role for modulation of the ovarian cancer tumor microenvironment as part of therapeutic strategy.

10.2 Optimizing targeted therapy in ovarian cancer: Chemical and contextual synthetic lethality

Improving therapy for ovarian cancer can now be advanced rationally, building upon the scaffolding of knowledge of tumor cell dysfunction in DNA repair, application of the new class of DNA repair inhibitory drugs such as PARPi, and the ability to cause genotoxic stress in the microenvironment through its regulation with agents such as angiogenesis inhibitors. Creating an opportunity for synthetic lethality outside of genomic complementarity provides the leverage for development of new, potentially truly, synergistic treatment combinations.

Chemical and contextual synthetic lethality, as coined by McLornan *et al.* [84], describe the capitalization upon drug or microenvironmental changes that, when combined together and/or with standard treatments, augment therapeutic gain. The application of PARPi on a backbone of platinum-sensitivity as seen with gBRCAm ovarian cancer is an example of chemical synthetic lethality. This may be due to development of more DNA SSB from inhibition of BER by PARP, increase in conversion of SSBs to DSBs caused by DNA replication stress, and/or the release from inhibition of NHEJ with increase in its poor fidelity DNA repair, propagating DNA damage.

The increase in DNA damage observed in a hypoxic environment, likewise, augments injury through contextual synthetic lethality. This has been demonstrated in preclinical models where the genetic depletion of histone *H2AX*, and the associated dysfunctional DNA damage response, was greatest when the experimental animals or cells were subjected to gross or relative hypoxia [85]. This has been borne out further by

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observations that hypoxia causes transcriptional inhibition of *RAD51*, *BRCA1*, and *BRCA2*, thus reducing protein production and DNA repair potential, among other findings [86]. Additional preclinical studies showed that PARPi exerted increased cytotoxicity against multiple cancer cells under hypoxic conditions, compared to normoxic conditions [70]. Use of anti-angiogenic agents, alone or in combination with agents that result in increased DNA damage, then yields therapeutic contextual lethality.

The logical next step in ovarian cancer, then, was to solve the sum of chemical synthetic lethality + contextual synthetic lethality (Figure 4). Preclinical work by Kohn and Kim [65] tested *in vitro* the effects of inhibition of microvascular endothelial cell growth and reorganization into vascular tubes with cediranib, recapitulating its recognized anti-angiogenic activity. They then added the PARPi olaparib, demonstrating a statistically significant and more than additive inhibition of vasculogenesis at nanomolar concentrations. Following this observation was the demonstration of successful clinical combination therapy with these two oral agents in women with recurrent ovarian cancer or triple-negative breast cancer [40]. Remarkable responses were seen in patients with ovarian cancer regardless of gBRCAm status, leading to a randomized phase 2 study of olaparib/cediranib versus olaparib in platinum-sensitive HGSOC (NCT01116648) [41]; gBRCAm status was collected where known, but was not an eligibility criterion.

The overall response rate of the randomized phase 2 study was notably high at 80% in the cediranib/olaparib combination treatment arm with an equally notable PFS of 17.7 months in the combination cohort compared with 9 months for single agent olaparib. Randomized phase 2 and 3 trials of patients with platinum-sensitive ovarian cancer that

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reached a PFS of 11-14 months were considered advances in the treatment of HGSOC

[61, 82]. The trial conducted by Liu *et al.* accrued nearly equal numbers of gBRCAm and

wild type/unknown status women leading to an unplanned post hoc analysis of the

interaction between gBRCAm status and PFS. First, the gBRCAm patients treated with

single agent olaparib had a better than expected outcome with a PFS of 16.5 months,

compared to the ~8-month outcomes in the company-sponsored pivotal single agent

olaparib trials [41, 60]. The wild type/unknown patient outcome of ~5 months for single

agent olaparib was consistent with prior observations. Unexpected was the nearly 3-fold

increase in PFS in the patients with wild type/unknown *BRCA* status, 16.5 months for the

combination versus 5.7 months for single agent olaparib. Two pivotal phase 3 trials,

opening in early 2016, will examine the superiority of the olaparib/cediranib combination

over standard of care chemotherapy in women with platinum-sensitive (NRG-GY004;

NCT02446600) and resistant/refractory (NRG-GY005; NCT02502266) HGSOC. Key

translational endpoints to further dissect the mechanisms of success and to identify

predictive biomarkers are planned in these trials.

10.3 Leveraging contextual and chemical synthetic lethality for other cancers

The results from the randomized phase 2 study in platinum-sensitive HGSOC comparing

cediranib/olaparib to olaparib alone were the first to illustrate successful collaboration of

chemical and contextual synthetic lethality in the clinic, and further demonstrated this

approach could improve upon the previously identified selective predictiveness of

gBRCAm for PARPi benefit [84]. This opportunistic approach overcame the requirement

for underlying high level HRD. This important observation argues for the examination of

this contextual/chemical combination in other cancers sensitive to DNA damage, such as

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chemotherapies and/or radiation, or to local micro-environmental modulation with angiogenesis inhibitors. Accumulating evidence shows that somatic partial or total loss of BRCA1/2 protein occurs in many solid tumors, including non-small cell and small cell lung cancer, prostate cancer, serous endometrial cancer, mesothelioma, triple negative breast cancer, and glioblastoma multiforme, to name a few. Many of these are cancers known for rapid recurrence and frequent progression while on cytotoxic therapies. The tumor microenvironment is often already somewhat hypoxic and acidic, promoting DNA damage. Interaction of PARPi with radiation is known to be successful, as is the interaction of radiation with angiogenesis inhibition. The demonstration that the olaparib/cediranib combination was surprisingly active in the non-gBRCAm ovarian cancers, supports the application of this combination in other settings where creating a DNA repair failure environment may be therapeutically optimal [40, 41, 70].

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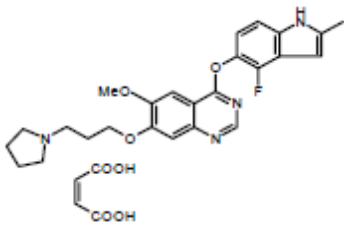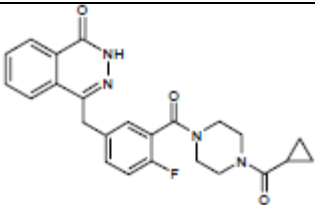
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**Boxes**

| Box 1: Drug summary Box		
Drug name	Cediranib + Olaparib	
Phase of development	III	
Indication	High grade serous ovarian cancer	
	Cediranib	Olaparib
Pharmacology	Pan-vascular-endothelial growth factor receptor (VEGFR) 1, 2, and 3 tyrosine kinase inhibitor	Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor
Route of administration	Oral	Oral
Chemical name/ Structure	4-[(4-Fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline maleate	4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2H)-one
Pivotal trial(s)	NRG-GY004 (NCT02446600), NRG-GY005 (NCT02502266), ICON9	

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Box 2. PARP inhibitors (PARPi) in clinical development

Name	Catalytic inhibition (IC_{50} nM)	Cytotoxicity (IC_{90} µM)	PARP-trapping potency (relative to olaparib)	Class
veliparib (ABT-888)	30	>50	<0.2	1
talazoparib (BMN673)	4	0.04	~100	2
olaparib (AZD2281, KU-0059436, CO-CE42)	6	4.5	1	2
rucaparib (CO-338, PF-01367338, AG-014699)	21	3	1	2
niraparib (MK4827)	60	2.3	~2	2

- Class 1: catalytic inhibition >>PARP trapping

- Class 2: PARP trapping (stabilization of toxic PARP1/2-DNA complexes) correlates with cytoxicity: talazoparib>>naraparib, olaparib>>veliparib

Adapted with permission from reference [88].

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Figure Legends:

Figure 1. <u>The universe of DNA damage and repair</u>. Central is the development of DNA damage of either SSBs (left) or DSBs (right). Stalled replication forks or repair dysfunction, causing DNA strain can result in second strand breakage and conversion to double strand breaks. Methods of DNA repair are shown for each side. Common causes of cell death are due to breakage induction of apoptosis or accumulation of mal-repaired DNA due to failed DNA repair and ultimate mitotic catastrophe. **Abbreviations:** P, phosphorylation; H2AX, histone 2AX; RAD50, RAD50 homolog; NBS1, Nijmegen breakage syndrome 1 (nibrin); MRE11, meiotic recombination (S. cerevisiae) 11; NHEJ, non-homologous endjoining; HRR, homologous recombination repair; MRN, MRE11–RAD50–NBS1; BER, base excision repair; NER, nucleotide excision repair; MMR, mismatch repair; PAR, poly (adenosine diphosphate-ribose); PARP, PAR polymerase.
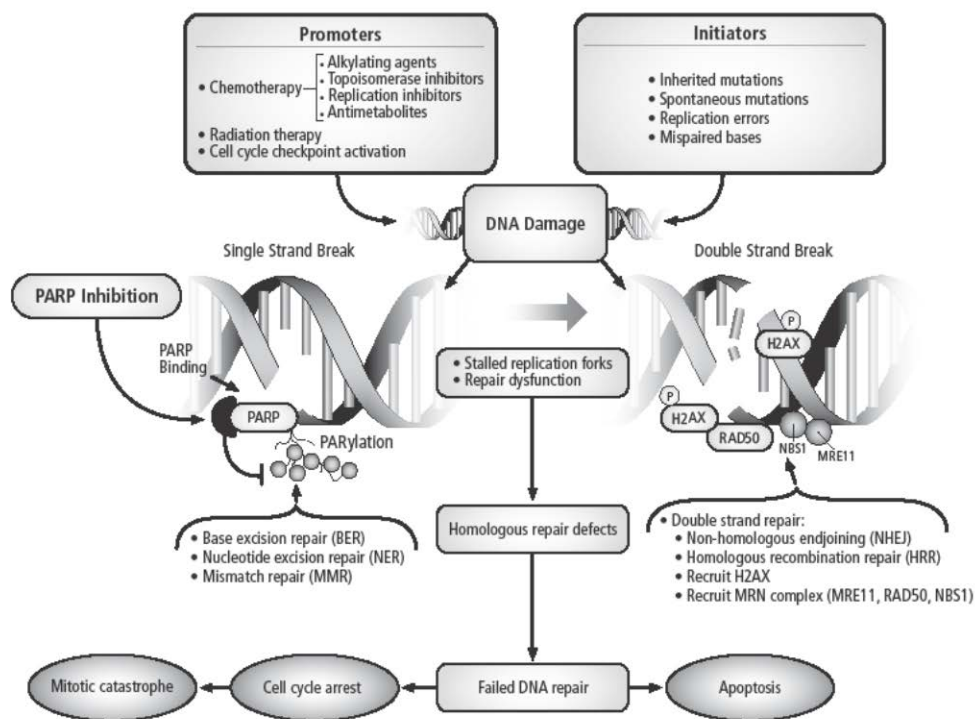
Figure 2. The six major forms of DNA repair. NER, MMR, BER, and translesion synthesis are the leading forms of SSB repair and have selectivity to the type of single strand event, ranging from intra- and inter-strand crosslinking (NER) to single base errors (BER). Homologous recombination (top) is the high fidelity DSB repair system, and is the most complex in terms of the many proteins in its cascade. It functions selectively in G2. NHEJ, both classical and alternate, are lower fidelity mechanisms, essentially gluing loose ends together and potentially introducing new DNA errors. **Abbreviations:** BRCA1/2, breast cancer 1 and 2, early onset; FANCs, fanconi anemia complementation group genes; ATM, ataxia telangiectasia mutated serine/threonine kinase; ATR, ataxia telangiectasia and Rad3 related serine/threonine kinase; RAD51, RAD51 recombinase; MRN, MRE11–RAD50–NBS1; CHEK 1 and 2, checkpoint kinases 1 and 2; G2/M, gap 2/mitosis phase; G1/S, gap 1/synthesis phase; Wee1, Wee1 G2 checkpoint kinase; HR, homologous recombination; SDSA, synthesis-dependent strand annealing; DSB, double strand break; DSBR, DSB repair; NHEJ, non-homologous endjoining; 53bp1, p53 binding protein 1; DNA PKcs, DNA-dependent protein kinase, catalytic subunit; POL-θ, polymerase (DNA directed), theta; PARP, poly (adenosine diphosphate-ribose) polymerase; XRCC1, X-ray repair complementing defective repair in Chinese hamster cells 1; BER, base excision repair; MMR, mismatch repair; MSH2, mutS homolog 2; MSH6, mutS homolog 6; MLH1, mutL homolog 1; PMS1, PMS1 homolog 1, mismatch repair system component; NER, nucleotide excision repair; ERCC1, excision repair cross-complementation group 1; XPs, Xeroderma pigmentosum complementation groups.

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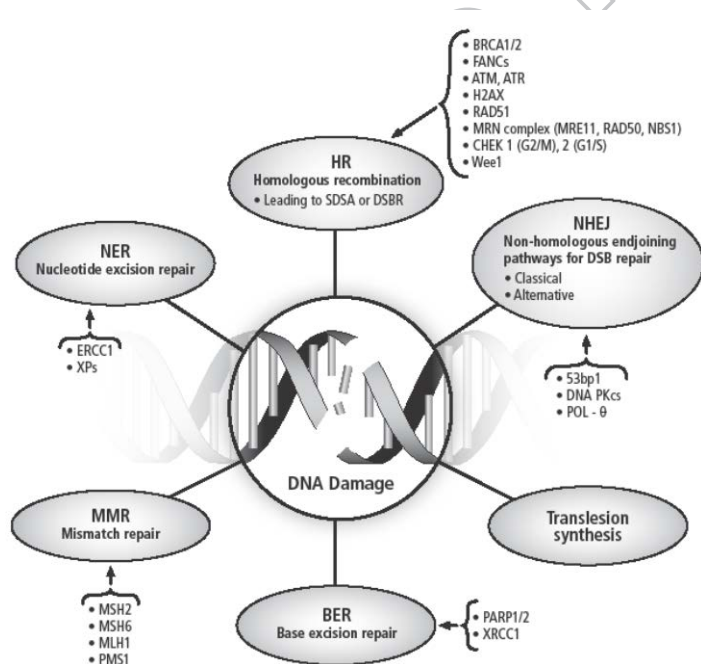
Figure 3. <u>Augmenting DNA damage and inhibiting repair as a therapeutic direction</u>. PARP affects DNA damage repair in several ways. Normal function includes PARylation of DNA core histones as a signal for SSB recognition. Loss of PARylation impedes recognition of SSB and permits transition to DSBs. PARP activity is important in telomere maintenance, cellular energetics, and to keep low fidelity NHEJ activation in check. In addition, PARP can be trapped at the DSB by PARP inhibitors, preventing repair processes. PARP inhibition thus leads to reduced or failed DNA repair that is compounded in the setting of germline and somatic genomic HR dysfunction. Local hypoxia due to tumor outgrowing its blood supply and/or with agents inhibiting angiogenesis, as with VEGFR-1-3 inhibitors, further augments failed DNA repair by reducing quantities of key homologous recombination repair proteins. **Abbreviations:** PAR, poly (adenosine diphosphate-ribose); PARP, PAR polymerase; PARPi, PARP inhibitor; XRCC1, X-ray repair complementing defective repair in Chinese hamster cells 1; DNA PKcs, DNA-dependent protein kinase, catalytic subunit; NHEJ, non-homologous endjoining; single strand break, SSB; P, phosphorylation; BRCA1, breast cancer 1, early onset; BRCA2, breast cancer 2, early onset; BRCA1/2, breast cancer 1 and 2, early onset; BARD1, BRCA1 associated RING domain 1; ATM, ataxia telangiectasia mutated serine/threonine kinase; CHK2, checkpoint kinase 2; H2AX, histone 2AX; VEGFR, vascular endothelial growth factor; RAD51, RAD51 recombinase; RAD52, RAD 52 homolog; MSH2, mutS homolog 2; MSH6, mutS homolog 6; gBRCA1/2m, germline mutation in *BRCA1* or *BRCA2*; HRD, homologous recombination deficiency

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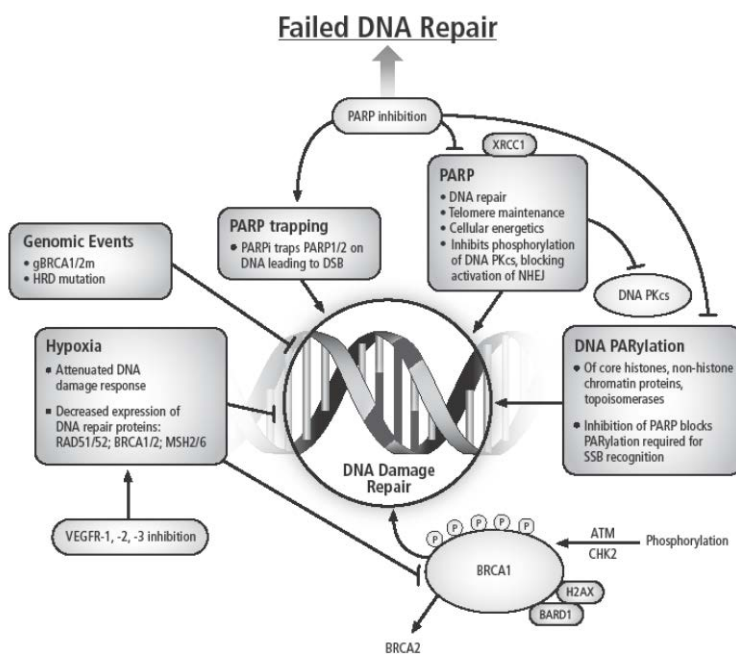
Figure 4. Representation of the average exposure of cediranib across a population of patients when administered once daily at 20 and 30 mg. R-P represents the IC_{50} for inhibition of the phosphorylation of the receptor (VEGFR-1, 2, or 3 as indicated). C-P represents the half maximal growth inhibition concentration (GI_{50}) of inhibition of proliferation of VEGFA induced HUVEC growth. T-G represents the IC_{50} of inhibition of endothelial tubule formation in an *in vitro* co-culture assay; the inhibition of total tubule areas, branch points, and vessel length are shown. **Abbreviations:** VEGFR, vascular endothelial growth factor; HUVEC, human umbilical vein endothelial cell.
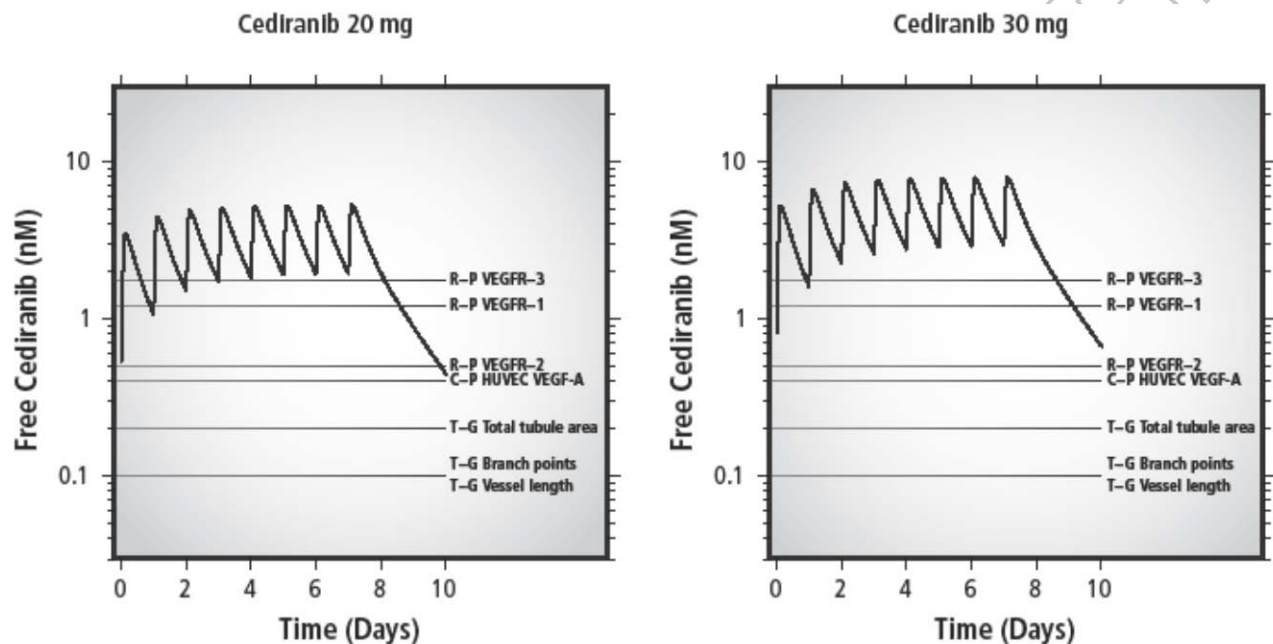
Abbreviation   Definition

5-FU   5-fluorouracil

ADP   adenosine diphosphate

AE   adverse event

AML   acute myeloid leukemia

AUC   area under the plasma concentration-time curve

AUC$_{ss}$ AUC at steady state

BCRP   breast cancer resistance protein

BER   base excision repair

BID   twice daily

BP   blood pressure

BRCAm germline or somatic mutation in *BRCA1* or *BRCA2*

CA   cancer antigen

CBR   clinical benefit rate

CEC   circulating endothelial cell

CI   confidence interval

C$_{max}$ maximum plasma concentration

C$_{ss,max}$ maximum plasma concentration at steady state

CNS   central nervous system

CTCAE   Common Terminology Criteria for Adverse Events

CTEP   Cancer Therapy Evaluation Program

CYP   cytochrome P450

DNA-PKcs   DNA-dependent protein kinase, catalytic subunit

DNA-Ri DNA repair inhibitor

DSB   double strand break

EMA   European Medicines Agency

FDA   Food and Drug Administration

FMO   flavin containing monooxygenase

gBRCAm   germline mutation in *BRCA1* or *BRCA2*

GI$_{50}$ half maximal growth inhibition concentration

HGSOC high-grade serous ovarian cancer

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HR   hazard ratio

HRD   homologous recombination deficiency

HR   homologous recombination

HUVEC human umbilical vein endothelial cell

IC_{50} half maximal inhibitory concentration

IL   interleukin

MDR1 multidrug resistance protein 1

MDS   myelodysplastic syndrome

mPFS median PFS

MTD   maximum tolerated dose

NCTN National Clinical Trials Network

NER   nucleotide excision repair

NHEJ non-homologous end joining

OCAC Ovarian Cancer Australian Consortium

OS   overall survival

PAR   poly (ADP-ribose)

PARP   PAR polymerase

PARPi PARP inhibitors or PARP inhibition

PARylation   PAR polymerization

PDGFR platelet-derived growth factor receptor

P-gp   P-glycoprotein

PFS   progression-free survival

PK   pharmacokinetics

PLD   pegylated liposomal doxorubicin

QD   once daily

48

RECIST   Response Evaluation Criteria in Solid Tumors

sBRCAm   somatic mutation in *BRCA1* or *BRCA2*

SSB   single strand break

sVEGFR2   soluble VEGFR2

$t_{1/2}$ terminal half-life

TCGA   The Cancer Genome Atlas

TSH   thyroid stimulating hormone

UDP   uridine 5'-diphosphate

UGT   UDP-glucuronosyltransferase

VEGF   vascular endothelial growth factor

VEGFR   VEGF receptor