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

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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. Initial chemo-sensitive, recurrent disease ultimately becomes chemo-resistant 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.

11 March 2016

Received 23 October 2015
Accepted 17 February 2016
Published online

Germline deleterious BRCA1/2 mutation; chemical and contextual synthetic lethality; poly(adenosine diphosphate-ribose) polymerase inhibitor; DNA repair defect; homologous recombination repair; high grade serous ovarian cancer; vascular endothelial growth factor receptor inhibitor
suppressor genes recognized for their association with familial breast and ovarian cancers.[17,18] Germ-line deleterious mutations in BRCA1/2 (gBRCAm) occur in approximately 17% of newly diagnosed high-grade serous epithelial ovarian cancers (HGSOCs).[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 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 nonmalignant cells, this causes apoptotic cell death, but in abnormal, premalignant 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 an 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 PARP, as has been observed.[23–27] A series of PARPi (Box 1) are under clinical investigation; currently, only olaparib (AZD2281/ Lynparza™) is approved for use.[29] 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.[25,26,30]

Angiogenesis, the process of new blood vessel formation and vessel sprouting, is necessary for tumor growth and dissemination.[31] Hollingsworth et al. showed in 1995 that ovarian cancers with high microvessel numbers had a worse outcome.[32] Subsequently, many preclinical, clinical, and translational studies have continued to confirm a role for angiogenesis in the malignant biology of HGSOC.[31] 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.[33,34] Hypoxia is a major inducer of VEGFA, and a major consequence of antiangiogenic therapy is induction of local hypoxia.[35] 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,[36,37] similar to that of single-agent bevacizumab, and shows greater activity than was demonstrated for sorafenib or sunitinib.[38,39] Bevacizumab has recently been approved for recurrent platinum-resistant ovarian cancer when given in combination with chemotherapy.[40]

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 microvascular tube development in vitro was seen in preclinical studies using cediranib in combination with olaparib.[39] 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.[41] In the randomized phase 2 portion of the study comparing olaparib against olaparib and cediranib in platinum-sensitive HGSOC patients (NCT01116648), an overall PFS of 17.7 months in the combination therapy group and 9.0 months in the single-agent olaparib group was observed.[42] 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.[42] 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.

**Box 1. PARP inhibitors (PARPi) in clinical development**

| Name                  | Catalytic inhibition (IC<sub>50</sub> nM) | Cytotoxicity (IC<sub>50</sub> 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 cytotoxicity: talazoparib >> naraparib, olaparib >> veliparib

Adapted with permission from reference [28].
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. 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 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 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 1). 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,[44,45] unlike monoclonal antibodies. This review will focus on the treatment of HGSOC with the combination of cediranib and olaparib in platinum-sensitive and -resistant disease.

3. Introduction to the compounds

Cediranib (AZD2171) is a highly potent oral VEGFR-1,-2, and -3 inhibitor that also targets c-Kit.[46–49] Cediranib inhibits human umbilical vein endothelial cell (HUVEC) proliferation and diminishes microvessel density while causing reversible epithelial cell hyperplasia in rodent animal models.[49] 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.[50]

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 HR deficiency (HRD). Olaparib is an orally administered agent that is clinically active as a single-agent or in combination with other small-molecule
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 $C_{25}H_{27}FN_4O_3$. Its melting point is 197°C.

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 2).

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. [51] 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 and 20 mg doses, cediranib levels are sufficient to cover the half maximal inhibitory concentration ($IC_{50}$) for VEGFRs 1,
Figure 3. Augmenting DNA damage and inhibiting repair as a therapeutic direction. 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 endjoinig; 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, RAD52 homolog; MSH2, mutS homolog 2; MSH6, mutS homolog 6; gBRCA1/2m, germline mutation in BRCA1 or BRCA2; HRD, homologous recombination deficiency.
2, and 3. At these exposures it will also inhibit c-Kit.\[46,49\] Although cediranib has activity against platelet-derived growth factor receptors (PDGFRs) \textit{in vitro}, the free drug levels achieved in patients are not sufficient to achieve effective inhibition of PDGFR signaling.\[46,49\] 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 (Box 1); by trapping PARP1/2 in DNA complexes, leading to PARP inactivation; and by relieving inhibition of NHEJ.\[22,52\] 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.\[52\]

### 5.3. Olaparib and cediranib

Inhibition of angiogenesis causes induction of circulating proangiogenic cytokines, such as VEGFA, interleukin (IL)-6, and IL-8.\[53\] It also has been shown to induce production of circulating endothelial cells (CECs) and endothelial cell precursors.\[54,55\] Preclinical antiangiogenic 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.\[52,56\] 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 the 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 end points will be examined prospectively in soon-to-open randomized phase 3 trials (NCT02446600 and NCT02502266).

### 6. Pharmacokinetics and metabolism

#### 6.1. Pharmacokinetics – cediranib

Pharmacokinetic (PK) evaluations of cediranib supported once-daily (QD) oral dosing.\[57–59\] 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, which 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 twofold differences in any parameters, including area under the plasma concentration-time curve (AUC) at steady-state (AUC$_{\text{ss}}$) or maximum plasma concentrations ($C_{\text{max}}$).\[60\]

![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 tube 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.](image-url)
6.2. Metabolism – cediranib

Following single- and multiple-daily dosing of cediranib, cediranib was absorbed with $C_{\text{max}}$ typically observed within 1 to 8 hours post-dose.[50] Coadministration of cediranib with a high-fat meal reduced the cediranib AUC by 24% and $C_{\text{max}}$ 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 bound to serum albumin and alpha 1-acid glycoprotein.

Following a single dose of cediranib, AUC and $C_{\text{max}}$ increased proportionally with doses ranging from 0.5 to 60 mg.[50] Following multiple-daily dosing, the accumulation index ranged from one- to threefold, 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 oxidized 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 monoxygenase (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.

Coadministration 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 ($C_{\text{ss,max}}$): 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.

Coadministration of 600 mg rifampycin, a potent inducer of CYP3A4 and glucurononidation (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. rifampycin, carbamazepine, phenobarbital, phenytoin, and St John’s Wort) should be avoided, if possible, with cediranib.

6.3. Pharmacokinetics – olaparib capsule formulation

Olaparib was rapidly absorbed following capsule oral dosing in cancer patients.[28] At the 400 mg twice daily (BID) capsule dose, the apparent volume of distribution, apparent plasma clearance, and estimated terminal half-life ($t_{1/2}$) were 167 L, 8.6 L/h, and 11.9 hours, respectively. 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] Coadministration of a potent CYP3A inhibitor increased the mean $C_{\text{max}}$ 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); coadministration of a potent CYP inducer decreased the mean $C_{\text{max}}$ 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 on the development of these drugs and this drug combination in HGSC are detailed below.

7.1. Phase 1 studies

7.1.1. Cediranib

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 to 45 mg oral administered on a QD 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 noncompliant with antihypertensive treatment regimens. Regimens to manage hypertension, such as antihypertensive therapy, have been developed.[50] However, patients undergoing antihypertensive therapy at baseline are at an increased risk for elevated blood pressure and may require more than one drug or more antihypertensive 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 nine experienced a Response Evaluation Criteria in Solid Tumors (RECIST) response.[24]

7.1.3. Cediranib and olaparib combination
The examination was combined in a phase 1 (NCT01116648) study as detailed and shown to be generally antiparable and manageable, tolerable, and with preliminary evidence of antitumor 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 BRCAm 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 BRCAm 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 and platinum-resistance at <10%.[23,26,27,29,61,62] 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 capsule monotherapy at 400 mg 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).[63] Women with first-recurrence platinum-sensitive ovarian cancer (n = 456) were randomized (2:3:3) to receive platinum-based chemotherapy with either placebo,[63] 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 end point was PFS in the reference versus concurrent + maintenance arms. Secondary end points 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
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.[64] SOLO3 (NCT02282020) has also recently opened and randomized 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/
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. 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 ICON9 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. 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 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 preexisting hypertension may be at a 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-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 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/anticancer 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, NCT0494234, NCT02006622, NCT02032823, NCT00572364, NCT00516373, NCT00777582, NCT01078662, NCT02184195, NCT00516724), investigator-sponsored (e.g. NCT02208375, NCT02398058, NCT01623349, NCT01562210, NCT02533765, NCT0227082, NCT02485990, NCT01650376, NCT02338622, NCT02446704, NCT01682727, NCT02308072, NCT02121990, NCT01758731, NCT02418624), and NCI-sponsored NCTN (e.g. NCT00116648, NCT02345265, NCT02498613, NCT01237067, NCT01298763, NCT01445418, NCT02484404) studies.[28,67] The tablet formulation recommended dose is lower due to greater bioavailability and a higher $C_{max}$ despite little if any change in $t_{1/2}$.[67] 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 AEs.

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 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 hold 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.[65]

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 the patients on combination therapy and in 74% of the 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 was randomized to receive olaparib/cediranib therapy. The patient responded with a partial response despite dose reductions, and after approximately 1 year of continuous therapy, was diagnosed with MDS.

The risk of MDS/acute myeloid leukemia (AML) in ovarian cancer patients increases with the dose and duration of cytotoxic chemotherapy.[68] The role of gBRCAm status in the risk of secondary MDS/AML is unknown, as was the BRCA status of the patient who experienced 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 in 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 (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 1 and 2 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 13 patients on the phase 2 component indicate that early vascular injury, as assessed by Day 3 CEC and IL-8 concentrations, is associated with PFS response and bears 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.[69–72]

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,[73] 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 disease. [74] 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 [75,76] 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 druggable target. The 2005 observations by Bryant et al. and Farmer et al. of the unique susceptibility of cells with BRCAm to PARPi [13,15] have 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 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.[33,77,78] 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,[79,80] and has been shown to provide added benefit in PFS when used in combination with chemotherapy for newly diagnosed ovarian cancer patients,[81,82] for first-recurrence platinum-sensitive ovarian cancer,[83] and has most recently received registration for use with chemotherapy for recurrent ovarian cancer patients.[84]

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 lethalties

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., [85] describes 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 the development of more DNA SSBs 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.[86] This has been borne out further by observations that hypoxia causes transcriptional inhibition of RAD51, BRCA1, and BRCA2, thus reducing protein production and DNA repair potential, among other findings. [87] Additional preclinical studies showed that PARPi exerted increased cytotoxicity against multiple cancer cells under hypoxic conditions, compared to normoxic conditions.[70] Use of antiangiogenic 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 [66] tested in vitro the effects of inhibition of microvascular endothelial cell growth and reorganization into vascular tubes with cediranib, recapitulating its recognized antiangiogenic 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 reached a PFS of 11–14 months were considered advances in the treatment of HGSOC.[62,83] 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.[41,61] The wild-type/unknown patient outcome of ~5 months for single-agent olaparib was consistent with prior observations. The nearly threefold 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, was unexpected. 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 end points to further dissect the mechanisms of success and to identify predictive biomarkers are planned in these trials.

10.3. Leveraging contextual and chemical synthetic lethalities 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 the successful collaboration of chemical and contextual synthetic lethalities in the clinic, and further demonstrated that this approach could improve upon the previously identified selective predictiveness of gBRCAm for PARPi benefit.[85] This opportunistic approach overcame the requirement for underlying high-level HRD. This important observation argues for the examination of this contextual/chemical combination, such as chemotherapies and/or radiation, in other cancers sensitive to DNA damage 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.[40,41,71]

Acknowledgments

The authors thank Kristie Magee, Technical Resources International, for her editorial and formatting help and Melissa Maher, Technical Resources International, for her help with the preparation of figures.

Declaration of interest

This paper has been supported by the National Cancer Institute, Bethesda, and Harvard Medical School, Boston. JD Liu is a consultant for AstraZeneca and Genentech, and has acted as principal investigator for clinical trials sponsored by AstraZeneca, Genentech, Merrimack Pharmaceuticals, Boston Biomedical and Atara Pharmaceuticals. U Matulonis has participated in advisory boards for AstraZeneca and Tesaro. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016 Jan;66(1):7–30.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin. 2009 Jul-Aug;59(4):225–249.
3. Korkmaz T, Seber S, Basaran G. Review of the current role of targeted therapies as maintenance therapies in first and second line treatment of epithelial ovarian cancer; In the light of completed trials. Crit Rev Oncol Hematol. 2016 Feb;98:180–188.
4. Curtin NJ. DNA repair dysregulation from cancer driver to therapeutic target. Nature Reviews Cancer. 2012 Dec;12(12):801–817.

- **Discussion that includes transition to potential patient care.**

5. Friedberg EC, Walker GC, Siede W, et al. DNA repair and mutagenesis. Second. Washington, DC: ASM Press; 2006.
6. Glazer PM, Hegan DC, Ly U, et al. Hypoxia and DNA repair. Yale J Biol Med. 2013 Dec;86(4):443–451.
7. Sancar A, Lindsey-Boltz LA, Unsal-Kacmaz K, et al. Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. Annu Rev Biochem. 2004;73:39–85.

- **Good review of DNA repair and checkpoints**

8. Wood RD, Mitchell M, Sgroi J, et al. Human DNA repair genes. Science 2001 Feb;291(5507):1284–1289.
9. Hoeyemakers JH. Genome maintenance mechanisms for preventing cancer. Nature. 2001 May 17;411(6835):366–374.
10. Morgan MA, Parsels LA, Maybaum J, et al. Improving the efficacy of chemoradiation with targeted agents. Cancer Discov. 2014 Mar;4(3):280–291.
11. Lord RV, Brabender J, Gandara D, et al. Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2002 Jul;8(7):2286–2291.
12. Meng AX, Jalali F, Cudditty A, et al. Hypoxia down-regulates DNA double strand break repair gene expression in prostate cancer cells. Radiother Oncology: Journal Eur Soc Ther Radiol Oncol. 2005 Aug;76(2):168–176.
13. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005 Apr 14;434(7035):913–917.
14. De Soto JA, Wang X, Tominaga Y, et al. The inhibition and treatment of breast cancer with poly (ADP-ribose) polymerase (PARP-1) inhibitors. Int J Biol Sci. 2006;2(4):179–185.
15. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005 Apr 14;434(7035):917–921.
16. Ngueua PA, Fuertes MA, Cepeda V, et al. Poly(ADP-ribosyl)polymerase-1 inhibitor 3-aminobenzamide enhances apoptosis induction by platinum complexes in cisplatin-resistant tumor cells. Med Chem. 2006 Jan;21(1):47–53.
17. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unsellected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003 May;72(5):1117–1130.
18. King M-C, Marks JH, Mandell JB, et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003 Oct 24;302(5645):643–646.
19. Cancer Genome Atlas Research N. Integrated genomic analyses of ovarian carcinoma. Nature. 2011 Jun 30;474(7353):609–615.
20. Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal cancer identified by massively parallel sequencing. Proc Natl Acad Sci U S A. 2011 Nov 1;108(44):18032–18037.
21. Drews Y, Mulligan EA, Vong W-T, et al. Therapeutic potential of poly (ADP-ribose) polymerase inhibitor AG014699 in human cancers with mutated or methylated BRCA1 or BRCA2. J Natl Cancer Inst. 2011 Feb 16;103(4):334–346.
22. Patel AG, Sarkaria JN, Kaufmann SH. Nonhomologous end joining drives poly(ADP-ribose) polymerase (PARP) inhibitor lethality in homologous recombination-deficient cells. Proc Natl Acad Sci U S A. 2011;108(8):3406–3411.
23. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet. 2010 Jul 24;376(9737):245–251.
24. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med. 2009 Jul 9;361(2):123–134.

- **Seminal paper describing initial benefit of PARP inhibition and relationship to germline deleterious BRCA mutation and platinum-sensitivity.**

25. Fong PC, Yap TA, Boss DS, et al. Poly(ADP-ribose) polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol. 2010;28(15):2512–2519.
26. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol. 2011 Sep;12(9):852–861.
27. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010 Jul 24;376(9737):235–244.
28. Murai J, Pommier Y. PARP inhibitors for cancer therapy. Cham: Springer International; 2015.
29. Investigator’s Brochure for Olaparib, Polyadenosine 5′-diphosphoryl-ribosyl polymerase (PARP) inhibitor (AZD2281, KU-0059436), Ed. 12. Nature. 2011 Jul;15(2):852–861.
30. Kassis NJ, Cohen JG, Rasool N, et al. Models for Angiogenesis. The Cancer Handbook. 2007.
31. Hollingsworth HC, Kohn EC, Steinberg SM, et al. Tumor angiogenesis in advanced stage ovarian carcinoma. Am J Pathol. 1995 Jul;147(1):33–41.
32. Dvorko HF, Brown LF, Detmar M, et al. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. Am J Pathol. 1995 May;146(5):1029–1039.
33. Senger DR, Galli SJ, Dvorko AM, et al. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science. 1983 Feb 25;219(4587):983–985.
34. Forsythe JA, Jiang BH, Iyer NV, et al. Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. Mol Cell Biol. 1996 Sep;16(9):4604–4613.
35. Hirte H, Lheureux S, Fleming GF, et al. A phase 2 study of cediranib in recurrent or persistent ovarian, peritoneal or fallopian tube cancer: a trial of the princess margaret, Chicago and California Phase II consortia. Genecol Oncol. 2015;138(1):55–61.

- **Describes single-agent activity of cediranib in recurrent ovarian cancer**

36. Matulonius UA, Berlin S, Ivey P, et al. Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. J Clinical Oncology: Official Journal Am Soc Clin Oncol. 2009 Nov 20;27(33):5601–5606.
37. Matei D, Sill MW, Lankes HA, et al. Activity of sorafenib in recurrent ovarian cancer and primary peritoneal carcinomatosis: a gynecologic oncology group trial. J Clinical Oncology: Official Journal Am Soc Clin Oncol. 2011 Jan 1;29(1):69–75.
38. Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2003 Jan;9(1):327–337.
40. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the aurelia open-label randomized phase III. Trial J Clin Oncol. 2014;32(13):1302–1308.

41. Liu JF, Tolany SM, Birrer M, et al. A Phase 1 trial of the poly(ADP-ribose) polymerase inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cediranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer. Eur J Cancer. 2013;49 (14):2972–2978.

- Describes dose finding of cediranib and olaparib combination therapy and preliminary evidence of activity in recurrent ovarian cancer

42. Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol. 2014;15 (11):1207–1214.

- Seminal randomized phase 2 trial showing superiority of cediranib/olaparib combination in platinum-sensitive ovarian cancer

43. Jayson GC, Kohn EC, Kitchener HC, et al. Ovarian cancer. Lancet 2014 Oct 11;384(9955):1376–1388.

- Comprehensive review of epithelial ovarian cancer

44. Du Bois A, Floquet A, Kim J-W, et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. J Clinical Oncology: Official Journal Am Soc Clin Oncol. 2014 Oct 20;32(30):3374–3382.

45. Ivy SP, Wick JY, Kaufman BM. An overview of small-molecule inhibitors of VEGF signaling. Nat Reviews Clin Oncology. 2009 Oct;6 (10):569–579.

46. Brave SR, Ratcliffe K, Wilson Z, et al. Assessing the activity of cediranib, a VEGF-R-2/3 tyrosine kinase inhibitor, against VEGF-R-1 and members of the structurally related PDGFR family. Mol Cancer Ther. 2011 May;10(5):861–873.

47. Heckman CA, Holopainen T, Wirzenius M, et al. The tyrosine kinase inhibitor cediranib blocks ligand-induced vascular endothelial growth factor receptor-3 activity and lymphangiogenesis. Cancer Res. 2008 Jun 15;68(12):4754–4762.

48. Smith NR, James NH, Oakley I, et al. Acute pharmacodynamic and antivascular effects of the vascular endothelial growth factor signalin inhibitor AZD2171 in Calu-6 human lung tumor xenografts. Mol Cancer Ther. 2007 Aug;6(8):2198–2208.

49. Wedge SR, Kendrew J, Hennesquin LF, et al. AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. Cancer Res. 2005 May 15;65(10):4389–4400.

50. Decio A, Cesca M, Bizzaro F, et al. Cediranib combined with chemotherapy reduces tumor dissemination and prolongs the survival of mice bearing patient-derived ovarian cancer xenografts with different responsiveness to cisplatin. Clin Exp Metastasis. 2015 Oct;32(7):647–658.

51. Investigator’s Brochure for Cediranib, AZD2171, Ed. 17. AstraZeneca Corp. September 11, 2015.

52. Murali J, Huang SY, Das BB, et al. Differential Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. Cancer Res. 2013 21(1):5588–5599.

53. Azad N, Yu M, Davidson B, et al. Translational predictive biomarker analysis of the phase 1b sorafenib and bevacizumab study expansion cohort. Molecular Cellular Proteomics: MCP. 2013 Jun;12 (6):1621–1631.

54. Ning Y-M, Gulley JL, Arlen PM, et al. Phase II trial of bevacizumab, thalidomide, docetaxel, and prednisone in patients with metastatic castration-resistant prostate cancer. J Clinical Oncology: Official Journal Am Soc Clin Oncol. 2010 Apr 20;28 (12):2070–2076.

55. Park SR, Speranza G, Piekarz R, et al. A multi-histology trial of fostamatinib in patients with advanced colorectal, non-small cell lung, head and neck, thyroid, and renal cell carcinomas, and pheochromocytomas. Cancer Chemother Pharmacol. 2013 Apr;71 (4):981–990.

56. Lee JM, Trepel JB, Choyke P, et al. CECs and IL-8 Have Prognostic and Predictive Utility in Patients with Recurrent Platinum-Sensitive Ovarian Cancer: Biomarker Correlates from the Randomized Phase-2 Trial of Olaparib and Cediranib Compared with Olaparib in Recurrent Platinum-Sensitive Ovarian Cancer. Front Oncol. 2015;5:123.

- Exploratory biomarker findings from seminal randomized phase 2 of olaparib and cediranib versus olaparib study

57. Reid A, Tang A, Spicer J, et al. An open pharmacokinetic (PK) and mass balance study of 14C-AZD2171, incorporating DCE-CT evaluations. Proc Am Soc Clin Oncol. 2007;25:A14140.

58. Ryan CJ, Stadler WM, Roth B, et al. Phase I dose escalation and pharmacokinetic study of AZD2171, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinase, in patients with hormone refractory prostate cancer (HRPC). Invest New Drugs. 2007 Oct;25(5):445–451.

59. Yamamoto N, Tamura T, Yamamoto N, et al. Phase I, dose escalation and pharmacokinetic study of cediranib (RECENTINI), a highly potent and selective VEGF signaling inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol. 2009 Nov;64(6):1165–1172.

60. Satoh T, Yamaguchi K, Boku N, et al. Phase I results from a two-part Phase I/II study of cediranib in combination with mFOLFOX6 in Japanese patients with metastatic colorectal cancer. Invest New Drugs. 2012 Aug;30(4):1511–1518.

61. Kaye SB, Lubinski J, Matulonis UA, et al. Phase II, Open-Label, Randomized, Multicenter Study Comparing the Efficacy and Safety of Olaparib, a Poly (ADP-Ribose) Polymerase Inhibitor, and Pegylated Liposomal Doxorubicin in Patients With BRCA1 or BRCA2 Mutations and Recurrent Ovarian Cancer. J Clin Oncol. 2012;30(4):372–379.

62. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012 Apr 12;366(15):1382–1392.

63. Ledermann J, Perren T, Raja FE, et al. Randomised double-blind phase III trial of cediranib (AZD 2171) in relapsed platinum sensitive ovarian cancer: Results of the ICON6 trial. Eur J Cancer. 2013;49 (Supplement3):LBA10.

- Abstract report of seminal positive randomized phase 3 trial introducing cediranib to carboplatin and paclitaxel treatment of first recurrence platinum-sensitive ovarian cancer patients

64. Moore KN, DiSilvestro P, Lowe ES, et al. SOLO1 and SOLO2: Randomized phase III trials of olaparib in patients (pts) with ovarian cancer and a BRCA1/2 mutation (BRCAm). J Clin Oncol. 2014;32(5s):TPS5616.

65. Liu J, Lee J-M, Luo W, et al. A phase 1 study optimizing the dosing of olaparib tablet formulation combined with cediranib in recurrent ovarian cancer. J Clin Oncol. 2015;33;A5559.

66. Chiou VL, Kohn EC, Darvapanah N, et al. Novel Therapeutic Strategies For Angiogenesis Inhibition In Recurrent Ovarian Cancer. Curr Angiogenesis. 2015;3(4):179–192.

67. Plummer R, Swaisland H, Leunen K, et al. Olaparib tablet formulation: effect of food on the pharmacokinetics after oral dosing in patients with advanced solid tumours. Cancer Chemother Pharmacol. 2015 Oct;76(4):723–729.

68. Travis LB, Holowaty EJ, Bergfeldt K, et al. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. N Engl J Med. 1999 Feb 4;340(5):351–357.

69. Bindra RS, Gibson SL, Meng A, et al. Hypoxia-induced down-regulation of BRCA1 expression by E2Fs. Cancer Res. 2005 Dec 15;65 (24):11597–11604.

70. Bindra RS, Schaffer PJ, Meng A, et al. Down-regulation of Rاد51 and decreased homologous recombination in hypoxic cancer cells. Mol Cell Biol. 2004 Oct;24(19):8504–8518.

71. Lu Y, Chu A, Turker MS, et al. Hypoxia-induced epigenetic regulation and silencing of the BRCA1 promoter. Mol Cell Biol. 2011 Aug;31(16):3339–3350.

72. Tentori L, Lacal PM, Muzi A, et al. Poly(ADP-ribose) polymerase (PARP) inhibition of PARP-1 gene deletion reduces angiogenesis. Eur J Cancer. 2007 Sep;43(14):2124–2133.

73. Mehra K, Mehrad M, Ning G, et al. STICS, SCOUTs and p53 signatures: a new language for pelvic-serous carcinogenesis. Front Biosciience. 2011;6:325–634.

74. Menon U, Ryan A, Kalsi J, et al. Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom
75. Patch AM, Christie EL, Etemadmoghadam D, et al. Whole-genome characterization of chemoresistant ovarian cancer. Nature. 2015 May 28;521(7553):489–494.

76. Tothill RW, Tinker AV, George J, et al. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2008 Aug 15;14(16):5198–5208.

77. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971 Nov 18;285(21):1182–1186.

78. Liotta LA, Kleinerman J, Saidel GM. Quantitative relationships of intra-vascular tumor cells, tumor vessels, and pulmonary metastases following tumor implantation. Cancer Res. 1974 May;34(5):997–1004.

79. Burger RA, Sill MW, Monk BJ, et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clinical Oncology: Official Journal Am Soc Clin Oncol. 2007 Nov 20;25(33):5165–5171. Erratum in: J Clin Oncol. 2014 Nov;32(32):3686.

80. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clinical Oncology: Official Journal Am Soc Clin Oncol. 2007 Nov 20;25(33):5180–5186. Erratum in: J Clin Oncol. 2008 Apr 1;26(10):1773.

81. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011 Dec 29;365(26):2473–2483.

82. Oza AM, Cibuła D, Benzaquen AO, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. Lancet Oncol. 2015 Jan;16(1):87–97.

83. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clinical Oncology: Official Journal Am Soc Clin Oncol. 2012 Jun 10;30(17):2039–2045.

84. Poveda AM, Selle F, Hilpert F, et al. Bevacizumab combined with weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan in platinum-resistant recurrent ovarian cancer: analysis by chemotherapy cohort of the randomized phase III AURELIA trial. J Clin Oncol. 2015;33:3836–3838.

85. McLoman DP, List A, Mufti GJ. Applying synthetic lethality for the selective targeting of cancer. N Engl J Med. 2014 Oct 30;371(18):1725–1735.

* Review discussing mechanisms for interactive synthetic lethality.

86. Economopoulou M, Langer HF, Celeste A, et al. Histone H2AX is integral to hypoxia-driven neovascularization. Nat Med. 2009 May;15(5):553–558.

87. Scanlon SE, Glazer PM. Multifaceted control of DNA repair pathways by the hypoxic tumor microenvironment. DNA Repair. 2015 Aug;32:180–189.

* Review describing the interactions between hypoxia and DNA damage and repair.