Targeted therapies for Ovarian Cancer

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Abstract:

Epithelial ovarian cancer has the highest mortality rate of all gynaecological malignancies. Most women present with advanced disease and develop a recurrence after radical surgery and chemotherapy. Improving the results of first- or subsequent line chemotherapy has been slow and novel approaches to systemic treatment are needed. Ovarian cancer is a heterogeneous disease with complex molecular and genetic changes. Understanding these better will provide information on the mechanisms of resistance and opportunities to target therapy more rationally, exploiting specific changes in the tumour. Here we review targeted approaches to therapy, focussing on targeting angiogenesis and inhibition of DNA repair, two areas that show promising activity. Additionally, we review studies that are underway targeting the cell cycle and signalling pathwayYs as well as immunotherapeutic strategies. Many of these innovative approaches already demonstrate promising activity in ovarian cancer, and have the potential to improve the outcome in women with ovarian cancer.

Keywords: targeted therapy, ovarian cancer, anti-angiogenesis, PARP inhibitor, immunotherapy

Introduction:

Epithelial ovarian cancer (EOC) is one of the most common gynaecological malignancies and most women present with advanced disease. It has a high mortality rate and is the 5th most common cause of cancer death in women [1]. Whilst the survival of patients with advanced ovarian cancer has increased over the last two decades through better surgery and more chemotherapy options, cytotoxic drug therapy has been non-selective often resulting in significant toxicity and short-lived anti-tumour responses. Most women with ovarian cancer will suffer a tumour recurrence after first-line therapy and in almost all of them, resistance to chemotherapy will eventually develop leading to death from ovarian cancer. There has been a significant increase in the knowledge of molecular and genetic changes in ovarian, and this has led to the development and evaluation of targeted therapies in this disease. Here we review how these new drugs are being used and investigated in women with ovarian cancer, and their contribution thus far to improving the response to therapy and disease outcome.

1.Angiogenesis

Solid tumour growth and progression is reliant on neovascularisation [2]. Angiogenesis is complex and is regulated by several different endogenous pro-angiogenic and anti-angiogenic factors. Key angiogenic molecules include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and angiopoietin (Ang 1 and 2) [3]. The Ang 1/2 –Tie 2 receptor axis is a VEGF independent signalling pathway, which mediates vascular re-modelling [3]. Folkman et al proposed that a fine balance exists between angiogenic inhibitory and stimulatory factors. In normal tissues angiogenesis is turned off. However, an '*angiogenic switch'* can occur in tumours leading to the production

of pro-angiogenic stimuli causing growth of the tumour and its vasculature [4]. These new blood vessels often have defective basement membranes, are thin walled and leaky, allowing cancer cells to enter the circulation and metastasise [5].

In EOC, angiogenesis plays a role in tumour growth, formation of ascites and metastasis. The vasculature within the tumour is more structurally and functionally abnormal, with tortuous, leaky, dilated and immature blood vessels with poor flow. The endothelial cells within these vessels are more dependent on VEGF for survival when compared to more mature blood vessels elsewhere in the body [6].

The VEGF family of growth factors and its receptors are the most important signalling pathways in tumour angiogenesis [6]. VEGF-A is the best-characterised VEGF ligand and appears to play a dominant role in angiogenesis by binding to VEGF receptor tyrosine kinases (VEGFR). In angiogenesis the two most important members of the VEGFR family are VEGFR1 (Flt-1) and VEGFR2 (Flk-1). VEGFR2 has the most direct effect on angiogenesis, by mediating the angiogenic and permeability enhancing effects of VEGF. The role of VEGFR1 is less direct, and may play a role in angiogenesis by recruiting bone marrow derived cells and monocytes into the tumour vasculature [7].

2. Vascular Endothelial Growth Factor (VEGF) inhibition

Inhibition of VEGF restores the balance between pro-angiogenic and anti-angiogenic factors, thereby normalising tumour blood vessel structure and function [8]. This influences tumour growth and is thought to improve the delivery of chemotherapy drugs to tumours and to decrease their metastatic potential.

There is a high expression of VEGFR in ovarian cancer and many tumours produce high levels of VEGF. Inhibitors of VEGF signalling such as the recombinant monoclonal antibody, bevacizumab that binds to circulating VEGF-A and aflibercept, a fusion protein that binds directly to VEGF preventing it from binding to its receptors, have been extensively evaluated in ovarian cancer treatment. Another strategy that has been explored is to use a peptide-Fc fusion protein, trebananib, which binds to Ang 1 and Ang 2, preventing its interaction with the Tie 2 receptor [3].

2.1 Bevacizumab

In ovarian cancer, bevacizumab has been explored as a single agent, in combination with chemotherapy, and as maintenance treatment post chemotherapy. It has been studied extensively in the setting of first-line platinum-based chemotherapy, 'platinum-sensitive' (relapse > 6months following completion of platinum based treatment) and in 'platinum-resistant' disease (relapse ≤6 months of completing platinum based treatment). For a summary the pivotal trials described below see table 1.

ICON7 [9] and GOG 218 [10] are the two key first-line studies investigating the addition of bevacizumab to chemotherapy following surgery for advanced ovarian cancer. In ICON7, patients were randomised to standard 6 cycles of three-weekly carboplatin and paclitaxel with or without intravenous bevacizumab 7.5mg/kg every three weeks followed by maintenance bevacizumab for up to 12 months. The median progression free survival (PFS) was 17.5 months with standard therapy alone versus 19.9 months in the bevacizumab arm (HR 0.87; p=0.04). The benefit from bevacizumab was greater in women at higher risk of progression due to incomplete cytoreductive surgery (≥1 cm residual disease) or FIGO stage IV disease.

In this group the PFS was 14.5 compared to 18.1months in women receiving bevacizumab. No difference was seen in the median overall survival (OS), which was 58 months. However, in the higher risk subgroup there was a 9.5 month difference in the median OS, 30.2 vs 39.7 months (p=0.03) in women receiving bevacizumab [11]. The second trial GOG 218 was a US-led 3-arm randomised placebo-controlled study. Each arm received 6 cycles of standard three-weekly carboplatin and paclitaxel. Arm 1 received chemotherapy with placebo, and placebo maintenance for 15 months, arm 2 chemotherapy plus bevacizumab (15mg/kg) from cycle 2-6 then switching to placebo maintenance as above, and women in arm 3 received chemotherapy plus bevacizumab from cycle 2-6 followed by bevacizumab maintenance. Compared to the control (arm 1) a significant improvement in PFS was seen only in women receiving bevacizumab with chemotherapy and as maintenance. The difference in median PFS in this group compared to placebo was 3.9 months and there was no difference in OS (table 1 for details) [10].

In women with 'platinum-sensitive' recurrent disease, the OCEANS trial [12] evaluated the addition of bevacizumab to chemotherapy and then as maintenance post chemotherapy until disease progression. Patients were randomised to three-weekly chemotherapy (gemcitabine 1000mg/m^2 D1,8 and carboplatin AUC 4) with bevacizumab 15mg/kg or placebo. A 4 month improvement in median PFS was seen that was statistically significant, but there was no OS benefit [13]. Similar results were seen in GOG 0213 that compared three-weekly carboplatin and paclitaxel with or without bevacizumab. In this trial there was a 3.4 month significant difference in median PFS. Preliminary results reported a trend towards an improvement in median OS and the benefit was unaffected by prior use of bevacizumab [14].

In women with ‘platinum-resistant’ relapse, the phase III randomised AURELIA trial [15] evaluated the addition of bevacizumab to a choice of chemotherapy regimens (weekly paclitaxel, pegylated liposomal doxorubicin [PLD] or topotecan, given either over five days, or weekly). Overall, there was a 3.3month improvement in median PFS when bevacizumab was added to chemotherapy which was significant (table 1). Bevacizumab was not continued as maintenance therapy but the benefit in PFS and quality of life was seen consistently across all subgroups, particularly in patients with ascites, which is associated with a poorer prognosis [16]. The greatest difference in PFS was seen in patients receiving weekly paclitaxel [17]. There was no statistically significant improvement in OS but the trial was not designed to show a difference in OS and 40% of patients receiving chemotherapy alone were subsequently treated with bevacizumab.

Toxicities of VEGF-Inhibitors include hypertension, impaired wound healing, proteinuria, increase risk of thromboembolism and gastrointestinal toxicities. This includes the rare but serious complications of perforation and fistulae and a decision to use bevacizumab needs to take note of the volume of serosal disease, particularly thickening of the sigmoid colon due to tumour, as the risk of perforation is greater in patients with large amounts of serosal disease.

Despite evidence of activity in different phases of the treatment pathway, there is no international consensus about when the value of bevacizumab therapy is greatest. This is reflected in the license, with indications varying across the world.

2.2 Aflibercept

Intravenous aflibercept has been evaluated in recurrent ovarian cancer both as a single agent and in combination with chemotherapy. In 'platinum-resistant' disease the response rate to single-agent aflibercept is <5% [18], although in combination with docetaxel, the response rate has been reported to be 54%. However, these patients were not as heavily pre-treated as those enrolled in the single agent phase II study and 13/46 (28%) patients had 'platinum-sensitive' disease [19]. Aflibercept prolongs the time to repeat paracentesis in women with recurrent symptomatic ascites, when compared to placebo, with a median time to repeat paracentesis of 55.1 days and 31.8 days respectively [20]. However, the risk of fatal bowel perforation is increased with aflibercept and the risk-benefit balance needs to be carefully considered [20].

2.3 Trebananib

Trebananib has been evaluated in a series of trials: TRINOVA-1, a randomised phase III trial combining trebananib with weekly paclitaxel in 919 women with recurrent ovarian cancer relapsing after a platinum-free interval of <12 months. Compared to placebo, trebananib significantly prolonged the median PFS (7.2 vs 5.4 months respectively; HR 0.66; $p<0.0001$) but no OS advantage was seen (19.3 vs 18.3 months; HR 0.95; $p=0.55$). The main toxicity observed was oedema [21]. Results from two other phase III studies of trebananib in ovarian cancer are pending; TRINOVA-2 (NCT01281254) a study of PLD with or without trebananib also in recurrent ovarian cancer, and TRINOVA-3 (NCT01493505) a study in which trebananib was combined with first-line chemotherapy.

3. Multi-targeted anti-angiogenic agents

Tyrosine kinase inhibitors (TKIs) are multi-targeted, low-molecular weight drugs, which bind to the ATP-binding catalytic site of the tyrosine kinase domains of VEGF-R and other tyrosine kinases. These oral agents often target more than one receptor tyrosine kinase [4]. Examples include sorafenib, cediranib, pazopanib and nintedinib, all of which have been shown to have activity in ovarian cancer [3]. It is attractive to use a drug that targets more than one pathway, as this could lead to a greater inhibition of angiogenesis compared with single pathway inhibitors such as bevacizumab. However, while the therapeutic response may be greater, their more complex mechanism of action may increase toxicity [4] (table 2).

3.1 Pazopanib

Pazopanib targets several angiogenic receptors including downstream signals of VEGFR 1,2,3, PDGFR and c-kit [22, 23]. Pazopanib has been evaluated in recurrent ovarian cancer and as maintenance therapy in the first-line setting. In MITO11 [24], an open-label phase II trial, patients with 'platinum-resistant' ovarian cancer were randomised to weekly paclitaxel with or without pazopanib. There was a 2.9 month improvement in PFS in the combination arm (median 6.3 vs 3.4 months) that was statistically significant. In the phase III study, AGO-OVAR-16, patients who did not have tumour progression at the end of first-line therapy, were randomised to maintenance pazopanib or placebo for up to 24 months. There was an improvement of 5.6 months in the median PFS in patients on pazopanib compared to placebo, however this did not translate into an OS benefit and there were much higher grade 3/4 adverse event rates in patients on pazopanib, for example, hypertension, neutropenia, liver toxicity, diarrhoea, fatigue, thrombocytopenia and palmar-plantar erythema. The dose of

pazopanib was reduced in 58%, and 33.3% discontinued treatment secondary to toxicity compared to 5.6% in the placebo arm [25]. Consequently, the drug has not been submitted for Market Authorisation.

3.2 Nintedanib

Nintedanib (BIBF 1120) is a triple angiokinase inhibitor, inhibiting VEGFR, FGFR and PDGFR, which all contribute to tumour angiogenesis [26]. Activity of the drug in a randomised phase II trial [27] led to a phase III study in first-line therapy.

In the AGO-OVAR 12 nintedinib or placebo was combined with carboplatin and paclitaxel and then continued as maintenance for up to 120 weeks. There was a 1.2 month difference in median PFS, significantly longer in patients receiving nintedanib compared with placebo but this small difference was thought to be insufficient for further development in this indication [28]. Hypertension is uncommon with this drug and most of the adverse events were gastrointestinal, with 21% of patients in the nintedanib arm experiencing ≥ grade 3 diarrhoea [28]. Trials continue in patients with 'platinum-resistant' ovarian cancer and in patients with clear cell tumours of the ovary or endometrium.

3.3 Cediranib

Cediranib, an oral inhibitor of VEGFR-1, 2 and 3 is also active in recurrent ovarian cancer. The magnitude of response of this drug was modest but sufficient for exploration in a phase III trial [29]. Cediranib was evaluated in ICON6, an academic-led randomised, three arm, double-blind placebo-controlled trial in 'platinum-sensitive' ovarian cancer. The design

allowed comparison of the effect of cediranib with chemotherapy, and as maintenance therapy [30]. The original trial design was changed when the manufacturer temporarily ceased production of the drug, and the main comparison using a smaller number of patients was between chemotherapy and concurrent cediranib followed by maintenance cediranib with chemotherapy and placebo throughout. There was a significant improvement in median PFS, from 8.7 to 11 months (HR 0.56; $p<0.0001$). OS data were immature at the time of publication. However, toxicity, principally fatigue, diarrhoea and hypertension were significant with 32% of patients discontinuing cediranib during treatment. This was most evident when cediranib was given with chemotherapy [30]. A submission for Market Authorisation in patients was recently withdrawn by the manufacturer. However, cediranib is an active drug and continues to be evaluated in ovarian cancer (see below).

4. Targeting the folate receptor

The folate cycle maintains essential metabolic reactions required for rapidly growing cells. Once folates enter a cell, they have a crucial role in the biosynthesis of purines and thymidine, required for DNA synthesis, repair and methylation [31-34]. The alpha isoform of the FR (αFR) transports folates by receptor-mediated endocytosis [35] and is selectively overexpressed in a number of solid tumours, including non-mucinous ovarian cancers [36]

Farletuzumab (MORAb-003), a humanised monoclonal antibody to αFR leads to cell-mediated cytotoxicity, complement dependent killing and non-immune mediated αFR-dependent inhibition of growth under folate limiting conditions [36, 37]. An initial phase II study looking at the addition of farletuzumab to chemotherapy followed by maintenance therapy in 'platinum-sensitive' ovarian cancer showed promising activity with an improved

overall response rate compared to historical controls [38]. However, the benefit was not confirmed in a subsequent phase III trial [39].

In a different folate-targeting strategy, vintafolide (EC145), a folate-conjugated vinca alkaloid that targets FR-expressing cells was explored in a randomised phase II trial in 'platinum-resistant' ovarian cancer. In the PRECEDENT trial patients were randomised to PLD alone, or in combination with vintafolide [40]. The study met its primary end point, demonstrating a 2.3 month improvement in median PFS in the experimental arm (5.0 versus 2.7 months; HR 0.63; p=.031]) but the subsequent randomised phase III trial (PROCEED) [41] was stopped early because a pre-specified interim analysis showed no benefit.

5. Homologous recombination deficiency (HRD) and ovarian cancer

Normal cellular function and genomic stability is maintained by recognition and subsequent repair of DNA damage that occurs in all cells [42]. There are 450 known genes implicated in DNA damage response and repair [43] and they are sub-divided into 5 distinct pathways which are responsible for repair of specific types of DNA damage [44]. Double stranded DNA breaks (DSB) are the most lethal insult to the genome and if left unrepaired, genomic instability and cell death will occur [45]. They can be repaired by several different pathways, the main one being homologous recombination repair (HRR). A large proportion of DSB arise during DNA replication when a replication fork encounters an unrepaired single strand break (SSB). The HRR pathway, together with PARP-1, a nuclear enzyme, is especially important in repairing these collapsed replications forks [46, 47]. If HRR is defective (HRD), cells are dependent on alternative pathways for repair. These are significantly impaired by inhibition of PARP enzymes. BRCA1 and BRCA2 proteins play an important role in HRR,

and when mutated, cells have HRD that can be selectively exploited by PARP inhibitors, leading to unrepaired, or poorly repaired DNA and tumour synthetic lethality [48].

6. Ovarian cancer and PARP inhibitors (PARPi)

Germline mutations of BRCA1 and BRCA2 genes are present in about 15% of high-grade serous ovarian cancer (HGSOC), the most common histological subtype. Whilst this is the most common cause of HRD, somatic mutations of the BRCA genes are found in about 5% of these tumours as well as mutations of other key HRR genes, such as RAD51. It has been estimated that approximately 50 % of HGSOC tumours have HRD [49, 50] sometimes referred to as 'BRCAness' [51]. Targeting HRD with PARPi, in both $BRCA^{mut}$ (BRCA mutated) and $BRCA^{wt}$ (BRCA wild-type) ovarian cancer is an important therapeutic approach that is being developed in high-grade ovarian cancers. Several oral PARPi are being developed, and are summarised in table 3.

6.1 Olaparib

Much of the initial investigations with PARPi and the greatest body of information comes from studies with olaparib (AZD2281). Frequent and sometimes durable responses were seen in Phase I trials in patients with $BRCA^{mut}$ cancers [52, 53]. Subsequent phase II trials in $BRCA^{mut}$ advanced breast and ovarian cancer confirmed the activity of olaparib monotherapy [54, 55].

The first randomised trial, Study 12 compared olaparib with PLD in women with a $BRCA^{mut}$ recurrent ovarian cancer [56]. It was a small trial with three arms (two different doses of

olaparib, 200mg bd and 400mg bd,) continuously were compared with PLD (50mg/m^2 IV) every four weeks in patients with a $BRCA^{mut}$ relapsing ≤ 12 months after prior therapy. There was no statistically significant difference in PFS between the olaparib and PLD arms. Olaparib was active, as predicted but the outcome of patients treated with PLD was better than expected and confounded the ability to see a benefit in favour of olaparib [56].

Clear activity of single-agent olaparib in $BRCA^{mut}$ was also demonstrated in Study 42, a multicentre phase II trial that enrolled 298 patients with germline BRCA1/2 mutations and recurrent breast, ovarian, pancreatic or prostate cancers [57]. Within this trial there were 193 patients who had received ≥ 3 lines for chemotherapy for ovarian cancer and the overall response rate was 34%, median duration of response 7.9 months [58].On the basis of these data the US FDA granted approval for single agent olaparib in this group.

6.2 Olaparib maintenance therapy

Most of the studies with olaparib and other PARPi have focussed on using these drugs as maintenance therapy following chemotherapy. The original trial, study 19, included patients with platinum-sensitive HGSOC who had responded to platinum-based therapy. The trial was designed to investigate maintenance olaparib in a broad setting, including patients with or without a $BRCA^{mut}$. The inclusion of the latter group was based on emerging data showing single agent activity of olaparib in patients without a BRCA mutation [59]. Study 19 randomly assigned 265 patients to olaparib capsules (400mg BD) or placebo within 8 weeks of completing platinum-based therapy. There was a significant difference in PFS with olaparib compared to placebo, measured from the start of maintenance therapy (8.4 vs 4.8 months, HR 0.35; p<.001]) [60].

At study entry, the BRCA mutation status was known for only 98 (37%) of the patients. A later analysis of BRCA status in germline and or tumour was carried out and BRCA status became available for 254 (96%) of patients. A pre-specified retrospective analysis of all efficacy endpoints was done [61]. In the mutated-BRCA (germline or somatic $BRCA^{mut}$) group of 136 patients there was an even greater increase in the median PFS from start of maintenance with olaparib compared to the placebo group (11.2 vs 4.3 months; HR 0.18; p<0.0001]). However, there was also a benefit in the $BRCA^{wt}$ group (HR 0.54; p=0.0075).

Exploratory end-points such as the time to first subsequent therapy or death (TFST) and time to second subsequent therapy or death (TSST) were significantly improved with olaparib [61], adding weight to the overall clinical value of this therapy in the absence of a significant OS benefit. It is noteworthy that in patients with a $BRCA^{mut}$ the start of the next line of therapy was delayed by a median of 9.4 months (median PFS 15.6 versus 6.2 months; HR 0.32; p<0.0001). In the third interim survival analysis, there is a trend for a survival benefit in the $BRCA^{mut}$ group but it does not reach statistical significance (34.9 vs 30.2 months; HR 0.62; p=0.02). The reasons for this include the small sample size, multiple survival analyses, and most importantly crossover to a PARPi by 23% of patients [62]. However, the longer follow up at this analysis identified that 13% of all patients (15% of $BRCA^{mut}$ patients) received maintenance olaparib for at least 5 years. The most common toxicities, with an incidence of ≥10% in the olaparib group, were nausea, vomiting, fatigue and anaemia, most of which were grade ≤2 [60].

Based on the results of this trial, the drug received marketing authorisation as maintenance therapy in mutated-BRCA HGSOC from the EMA and many other international regulatory

authorities. Two phase III trials of olaparib maintenance have now been completed, using tablets, 300mg bd, rather than capsules. SOLO-1 (NCT01844986) recruited patients with newly diagnosed $BRCA^{mut}$ ovarian cancer, who responded to first line platinum therapy; the results are pending. The top-line results for SOLO-2 (NCT01874353) in $BRCA^{mut}$ high-grade 'platinum-sensitive' ovarian cancer after ≥2 lines of platinum therapy have reported a favourable outcome but the results have not yet been presented.

6.3 Olaparib combination with molecularly targeted therapies

After showing promising activity in a phase I trial [63], the combination of cediranib with olaparib was tested in a phase II trial [64]. Patients with 'platinum-sensitive' ovarian cancer were randomly assigned to receive olaparib capsules alone (400mg BD) or olaparib (200mg BD) and cediranib (30mg od). The trial, without intravenous cytotoxic chemotherapy resulted in a significant improvement in PFS in the combination arm. The median PFS was 17.7 months versus 9.0 months; HR 0.42; p=0.005). A post-hoc analysis suggested the greatest benefit was in the subgroup of $BRCA^{wt}$ or unknown. However, 70% of patients in the combination arm experienced ≥grade 3 AEs, including diarrhoea, fatigue and hypertension. Nevertheless, the encouraging results have led to randomised trials in recurrent ovarian cancer, comparing this combination with chemotherapy NRG-GY004 (NCT02446600), and as maintenance in the planned ICON9 trial. A first-line trial, PAOLA-1 is comparing the combination of olaparib and bevacizumab to bevacizumab maintenance alone following carboplatin/paclitaxel and bevacizumab (NCT02477644).

6.4 Niraparib

The recently reported results of the maintenance trial, NOVA using niraparib (MK4827), an active oral, selective PARP1 and 2 inhibitor [65] have confirmed the value of maintenance therapy and added weight to the broader use of PARPi in both germline $BRCA^{mut}$ ($gBRCA^{mut}$) and non-$gBRCA^{mut}$ HGSOC cohorts who have responded to their most recent platinum-based chemotherapy. The NOVA trial (NCT01847274) is a double-blind controlled phase III maintenance study of niraparib vs placebo and enrolled these two cohorts, randomising patients 2:1 to niraparib 300mg once daily or placebo. In the 203 patients with $gBRCA^{mut}$ niraparib led to a significant prolongation in the PFS (median PFS after enrolment 21 months versus 5.5 months with placebo; HR 0.27; $p< 0.001$). Similarly, in the 350 non-$gBRCA^{mut}$ patients there was a significant benefit for niraparib (median PFS 3.9 versus 9.3 months; HR 0.45; $p<0.001$) [66].In an exploratory analysis, tumours were tested for HRD using the MyChoice assay (Myriad Genetics). Significant benefit in PFS was seen across all subgroups, including somatic $BRCA^{mut}$, (HRD positive), $BRCA^{wt}$ HRD positive and non-$gBRCA^{mut}$ HRD negative groups. The effect of niraparib was less in HRD negative tumours and it remains to be seen whether the sensitivity of this assay is sufficient for it to distinguish patients who may or may not have a clinically meaningful benefit from niraparib. The most common adverse effects were thrombocytopenia, often occurring early, anaemia and neutropenia, which could usually be managed by dose reductions.

As with olaparib, combination studies of niraparib with bevacizumab have started and there are plans to conduct studies in the first-line setting. The drug has yet to be licensed in ovarian cancer, but the results of the NOVA trial have confirmed the significant benefit of PARPi in

the treatment of recurrent ovarian cancer and value of this drug in patients without a germline or somatic BRCA mutation.

6.5 Rucaparib

In addition to inhibition of PARP 1 and 2 rucaparib also inhibits other PARP isoforms, tankyrase 1 and 2 (TNKS1/2) [67]. Phase I studies identified 600mg BD as the optimal dose [68] that has been taken forward in ovarian cancer patients. The drug has been given 'breakthrough' designation by the FDA for use as a single agent in patients with $BRCA^{mut}$ who have had at least 2 lines of platinum-based chemotherapy [69]. ARIEL 2 (NCT01891344), is a phase II study designed to identify patients who are likely to respond to rucaparib, based on biopsies to characterise a biomarker test for HRD that measures the degree of genomic scarring, expressed as Loss of Heterozygosity (LOH), a marker of tumour HRD. Three pre-defined HRD subgroups, tumour $BRCA^{mut}$, BRCA-like ($BRCA^{wt}$/LOHhigh) and biomarker negative ($BRCA^{wt}$/LOHlow) were identified. Two-hundred and six patients were enrolled and the median PFS was 9.4 vs 7.1 vs 3.7 months, with ORR of 82%, 45% and 21% in the $BRCA^{mut}$, BRCA-like and biomarker negative groups respectively. Robust activity was seen in both germline and somatic $BRCA^{mut}$ patients and the median duration of response was 9.3 months, but is still ongoing [70]. Rucaparib is generally well tolerated, with the most common adverse events being nausea, fatigue and increase in ALT/AST [70]. The HRD algorithm will be applied prospectively to ARIEL 3 (NCT01968213), a randomised phase III maintenance study of rucaparib vs placebo in high grade ovarian cancer, $BRCA^{mut}$ or $BRCA^{wt}$ who have responded to $\geq$2 platinum regimens

6.6 Veliparib

Veliparib (ABT-888) is an orally bioavailable small molecule that inhibits PARP1 and 2 and is able to penetrate the blood brain barrier [71]. Phase I studies have evaluated its activity in combination with cytotoxic chemotherapy, with myelosuppression being the most common toxicity [72-74]. Responses were observed in $BRCA^{mut}$ cancers [74]. Single agent veliparib is active in $BRCA^{mut}$ recurrent ovarian cancer as shown in a multicentre phase II clinical trial [75]. However, a phase II trial conducted to evaluate its activity in combination with oral cyclophosphamide in $BRCA^{mut}$ ovarian cancer revealed no improvement in response rate or median PFS compared to cyclophosphamide alone [76]. A three-arm phase III placebo controlled trial of carboplatin and paclitaxel with placebo, or veliparib followed by maintenance placebo, or the combination followed by veliparib maintenance in first line treatment of advanced HGSOC is currently recruiting patients (NCT02470585).

6.7 Talazoparib

Talazoparib (BMN 673) inhibits PARP1/2 and pre-clinical studies have shown it to be more potent than other PARPi [77]. In a phase I dose escalation study, responses were seen in 11/17 $BRCA^{mut}$ ovarian cancers. The recommended dose is 1000mcg/day due to dose-limiting thrombocytopenia [78]. A phase II study for single agent talazoparib in patients with $BRCA^{mut}$ advanced solid tumours is currently underway (NCT01989546) and importantly, the drug is being examined in patients who have previously been treated with a PARPi (NCT02326844).

7. Ovarian cancer and the immune system

The success of immune checkpoint inhibition in melanoma and lung cancer [79-83] has inspired further investigation of these agents in multiple other solid tumours, including ovarian cancer. Tumour cells are able to 'escape' the immune system and one of the most important components is an immunosuppressive co-signal (immune checkpoint) facilitated by programmed cell death 1 (PD-1) and it's ligand PDL-1 [84]. PD-1 is mainly expressed on T-cells and PDL-1 is expressed on numerous types of cancer cells and on tumour infiltrating immune cells in the tumour microenvironment [84]. In ovarian cancer, the presence of tumour infiltrating lymphocytes (TILs) is associated with a better outcome [85]. Nivolumab, pembrolizumab and avelumab are checkpoint inhibitors being trialled in ovarian cancer.

Intravenous nivolumab, an anti-PD-1 antibody was given to 20 patients with 'platinum-resistant' ovarian cancer using either 1mg/kg or 3mg/kg two-weekly infusions. The overall response rate was 15%. No correlation was found between clinical response and PDL-1 expression [86].

A phase Ib trial with the humanized monoclonal anti-PD-1 antibody, pembrolizumab included patients with ovarian cancer (KEYNOTE-028) (NCT02054806). In PDL-1+ve (PDL-1 expression $\geq$ 1%) there were 26 patients with advanced ovarian cancer and the overall response rate was 11.5% [87]. Pembrolizumab is undergoing further evaluation in a phase II trial in ovarian cancer (KEYNOTE-100) (NCT02674061).

Avelumab (MSB0010718C), a fully human anti-PDL-1 antibody, has been evaluated in the JAVELIN Solid tumour phase Ib study (NCT01772004). One hundred and twenty-four

unselected patients with heavily pre-treated 'platinum-resistant' ovarian cancer patients were enrolled, making this the largest reported dataset of patients with ovarian cancer and immune checkpoint inhibitors. The overall response rate was 9.7% [88]. The most common treatment related adverse events were fatigue, nausea/vomiting, diarrhoea/constipation, chills, infusion-related reactions, rash and hypothyroidism. Whilst tumour response rates are modest, some patients experience long responses to all these checkpoint inhibitors. Phase III trials with avelumab in ovarian cancer are currently underway. JAVELIN Ovarian 200 (NCT02580058) is a trial of avelumab +/- PLD vs PLD alone in 'platinum-resistant' ovarian cancer and JAVELIN Ovarian 100 (NCT02718417) is a three-arm trial evaluating avelumab in combination with and/or following first line chemotherapy for advanced ovarian cancer.

9. Phosphatidylinositol 3-Kinase (PI3K) inhibitors

The PI3K/AKT/mTOR is a complex pathway that regulates a number of crucial cellular functions, including cell growth, migration, survival and angiogenesis [89]. Changes in the pathway and molecular alterations, such as gene mutations and amplifications contribute to oncogenesis and resistance to anti-cancer drugs. It is an important therapeutic target in cancer, however, there has been little success of these agents in ovarian cancer to date [90].

10. Wee1 inhibitors

When DNA is damaged, there are various checkpoints that arrest the cell cycle to allow for this damage to be repaired. The G1 checkpoint is mainly regulated by the p53, which is commonly mutated in cancer cells. p53-deficient tumours therefore rely on the G2/S checkpoint for DNA damage repair [91]. If the G2 checkpoint is impeded, then p53 deficient cells may become more sensitive to DNA-damaging drugs [92]. Wee1 is a tyrosine kinase that phosphorylates CDC2, which inactivates the CDC2/cyclin B complex required for the

normal functioning of the G2 checkpoint. AZD1775 (formally MK-1775) is a potent Wee1 inhibitor. In combination with carboplatin, it has been shown to have promising activity in 'platinum-resistant' disease (relapse <3 months following completion of first line therapy) with p53 mutations. The most common toxicities reported were myelosuppression, fatigue, diarrhoea, nausea and vomiting [93].

11. Summary

This review highlights the paradigm shift in the treatment of ovarian cancer. Although chemotherapy remains the backbone of treatment, novel targeted therapies, both in combination with chemotherapy and alone, have demonstrated significant improvements in PFS and the 'one size fits all' treatment approach for ovarian cancer is no longer applicable. Bevacizumab are olaparib are two drugs directed against the angiogenic and DNA damage response pathways that have been approved for treatment of ovarian cancer. Olaparib is the first drug directed against a predictive marker which allows the selection of patients likely to achieve the greatest benefit. Encouraging results are emerging from studies with other PARP inhibitors and these are likely to widen the use of these drugs in ovarian cancer. A benefit is seen not only in patients with a BRCA mutation, but also in a larger number of patients within an HRD positive group. Combinations of PARP inhibitors with other molecularly targeted therapies, especially anti-angiogenic drugs are also showing promise. The most recent development in therapeutics has been investigation of immune checkpoint inhibitors. Their role in treatment of ovarian cancer is unclear, but many trials are in progress and there is hope that the benefit of these drugs seen in other tumours may extend into the treatment of ovarian cancers.

Table 1: Phase III trials of bevacizumab in advanced ovarian cancer.

Study	Population	Treatment	Median PFS (months)	Median OS (months)
ICON7 [9]	First-line high risk stage I-IIA or stage IIB-IV ovarian cancer (n=1528)	CP vs CP + bevacizumab (7.5mg/kg) followed by maintenance bevacizumab	22.4 vs 24.1 (HR 0.87; p=0.04)	58.6 vs 58.0 (p=0.85) Poor prognosis group: 30.2 vs 39.7 (p=0.03)
GOG 218 [10]	First-line stage III (incompletely resected) and stage IV ovarian cancer (n=1873)	CP vs CP + bevacizumab (15mg/kg) + maintenance + PL vs CP + bevacizumab (15mg/kg) + maintenance bevacizumab	10.3 vs 11.2 vs 14.1 (HR 0.72; p<0.001)	39.3 vs 38.7 vs 39.7 (HR 0.95; p=0.45)
OCEANS [13]	PSROC (n=484)	GC + PL vs GC + bevacizumab (15mg/kg)	8.4 vs 12.4 (HR 0.48; p<.0001)	32.9 vs 33.6 (HR 0.95; p=0.65)
GOG 0213 [14]	PSROC (n=674)	CP vs CP + bevacizumab (15mg/kg)	10.4 vs 13.8 (HR 0.61; p<.0001)	37.7 vs 42.2 (HR 0.83; p=0.056)
AURELIA [15]	PRROC (n= 361)	CT vs CT + bevacizumab (10mg/kg q2/52 or 15mg/kg q3/52)	3.4 vs 6.7 (HR 0.48; p<.001)	13.3 vs 16.6 (HR 0.85; p<.174)

PSROC – 'platinum-sensitive' recurrent ovarian cancer; PRROC – 'platinum-resistant recurrent' ovarian cancer; CP – carboplatin/paclitaxel;

PL – placebo; GC – gemcitabine/carboplatin; CT – chemotherapy [choice of weekly paclitaxel, PLD, topotecan];

q2/52 – 2 weekly; q3/52 – 3 weekly;

Table 2: VEGFR-Inhibitors in ovarian cancer

Agent	Trial	Line of treatment	PFS (months)
Sorafenib	**Randomised phase II [94]** CP +/- sorafenib followed by maintenance sorafenib for a total of 1yr	First line	15.4 vs 16.3 (p=0.38)
Pazopanib	**Randomised Phase II: MITO 11 [24]** Pazopanib + paclitaxel vs paclitaxel alone **Phase III maintenance study: AGO-OVAR-16 [25]** Pazopanib v placebo maintenance	PRROC First line	6.3 vs 3.4 17.9 vs 12.3 HR 0.77; p=0.0021
Nintedanib	**Phase III: AGO-OVAR-12 [28]** CP +/- nintedanib followed by maintenance nintedinib or placebo	First line	17.2 vs 16.6 HR 0.84; p=0.024
Cediranib	**Phase III: ICON 6 [30]** 3 arm study: CT with placebo vs CT + cediranib followed by placebo maintenance vs CT + cediranib followed by cediranib maintenance	First relapse PSROC	11.0 vs 8.7 HR 0.56; p<0.0001

CP – carboplatin /paclitaxel; CT – platinum-based chemotherapy; PRROC – 'platinum-resistant' recurrent ovarian cancer;

PSROC – 'platinum-sensitive' recurrent ovarian cancer

Table 3: PARPi trials in ovarian cancer (results awaited)

Agent	Trial	Population	Line of treatment
Olaparib (Astrazeneca)	**SOLO-1 (NCT01844986):** Phase III maintenance (olaparib vs placebo) **SOLO-2 (NCT01874353):** Phase III maintenance (olaparib vs placebo) **SOLO-3 (NCT02282020):** Phase III olaparib vs physician choice CT (standard of care non-platinum based)	$BRCA^{mut}$; AOC $BRCA^{mut}$; PSROC $BRCA^{mut}$; PSROC	First line After ≥2 lines platinum based CT After ≥2 lines of platinum based CT
Rucaparib (Clovis)	**ARIEL 2 (part 2) (NCT01891344):** Single arm study **ARIEL 3 (NCT01968213):** Phase III maintenance (rucaparib vs placebo) **ARIEL 4 (NCT02855944):** Phase III rucaparib vs chemotherapy	HGROC HGROC $BRCA^{mut}$; ROC	Received ≥2 prior lines of CT After ≥2 lines of platinum based CT Received ≥2 lines prior CT
Niraparib (Tesaro)	**QUADRA study (NCT02354586):** Single arm phase II study **PRIMA study (NCT02655016):** Phase III maintenance (niraparib vs placebo) **AVANOVA study (NCT02354131):** Phase I/II niraparib +/- bevacizumab	HGROC HRD +ve; AOC HRD+ve; PSROC	Must have had 3/4 prior lines of CT First line No limits on number of previous lines of CT
Veliparib (AbbVie)	Phase III combination CT followed by maintenance **(NCT02470585)**	$BRCA^{mut}$; AOC	First line
Talazoparib (Medivation/ Pfizer)	Phase I/II study **(NCT01989546)** Phase II study **(NCT02326844)**	$BRCA^{mut}$ solid tumours $gBRCA^{mut}$; ROC	After ≥ 1 standard CT OR no standard Rx options Progression following a PARPi

CT – chemotherapy; Ph – phase; gBRCAm – germline BRCA mutation; PSROC – 'platinum sensitive' recurrent ovarian cancer; HGROC – high grade recurrent ovarian cancer; HRD – homologous recombination deficient; AOC – advanced ovarian cancer; Rx – treatmen

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Table

Table 1: Phase III trials of bevacizumab in advanced ovarian cancer.

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GOG 218 [10]	First-line stage III (incompletely resected) and stage IV ovarian cancer (n=1873)	CP vs CP + bevacizumab (15mg/kg) + maintenance + PL vs CP + bevacizumab (15mg/kg) + maintenance bevacizumab	10.3 vs 11.2 vs 14.1 (HR 0.72; p<0.001)	39.3 vs 38.7 vs 39.7 (HR 0.95; p=0.45)
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GOG 0213 [14]	PSROC (n=674)	CP vs CP + bevacizumab (15mg/kg)	10.4 vs 13.8 (HR 0.61; p<.0001)	37.7 vs 42.2 (HR 0.83; p=0.056)
AURELIA [15]	PRROC (n= 361)	CT vs CT + bevacizumab (10mg/kg q2/52 or 15mg/kg q3/52)	3.4 vs 6.7 (HR 0.48; p<.001)	13.3 vs 16.6 (HR 0.85; p<.174)

PSROC – ‘platinum-sensitive’ recurrent ovarian cancer; PRROC – ‘platinum-resistant recurrent’ ovarian cancer; CP – carboplatin/paclitaxel;

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Table 2: VEGFR-Inhibitors in ovarian cancer

Agent	Trial	Line of treatment	PFS (months)
Sorafenib	**Randomised phase II [94]** CP +/- sorafenib followed by maintenance sorafenib for a total of 1yr	First line	15.4 vs 16.3 (p=0.38)
Pazopanib	**Randomised Phase II: MITO 11 [24]** Pazopanib + paclitaxel vs paclitaxel alone **Phase III maintenance study: AGO-OVAR-16 [25]** Pazopanib v placebo maintenance	PRROC First line	6.3 vs 3.4 17.9 vs 12.3 HR 0.77; p=0.0021
Nintedanib	**Phase III: AGO-OVAR-12 [28]** CP +/- nintedanib followed by maintenance nintedinib or placebo	First line	17.2 vs 16.6 HR 0.84; p=0.024
Cediranib	**Phase III: ICON 6 [30]** 3 arm study: CT with placebo vs CT + cediranib followed by placebo maintenance vs CT + cediranib followed by cediranib maintenance	First relapse PSROC	11.0 vs 8.7 HR 0.56; p<0.0001

CP – carboplatin /paclitaxel; CT – platinum-based chemotherapy; PRROC – 'platinum-resistant' recurrent ovarian cancer;

PSROC – 'platinum-sensitive' recurrent ovarian cancer

Table 3: PARPi trials in ovarian cancer (results awaited)

Agent	Trial	Population	Line of treatment
Olaparib (Astrazeneca)	**SOLO-1 (NCT01844986):** Phase III maintenance (olaparib vs placebo) **SOLO-2 (NCT01874353):** Phase III maintenance (olaparib vs placebo) **SOLO-3 (NCT02282020):** Phase III olaparib vs physician choice CT (standard of care non-platinum based)	$BRCA^{mut}$; AOC $BRCA^{mut}$; PSROC $BRCA^{mut}$; PSROC	First line After ≥2 lines platinum based CT After ≥2 lines of platinum based CT
Rucaparib (Clovis)	**ARIEL 2 (part 2) (NCT01891344):** Single arm study **ARIEL 3 (NCT01968213):** Phase III maintenance (rucaparib vs placebo) **ARIEL 4 (NCT02855944):** Phase III rucaparib vs chemotherapy	HGROC HGROC $BRCA^{mut}$; ROC	Received ≥2 prior lines of CT After ≥2 lines of platinum based CT Received ≥2 lines prior CT
Niraparib (Tesaro)	**QUADRA study (NCT02354586):** Single arm phase II study **PRIMA study (NCT02655016):** Phase III maintenance (niraparib vs placebo) **AVANOVA study (NCT02354131):** Phase I/II niraparib +/- bevacizumab	HGROC HRD +ve; AOC HRD+ve; PSROC	Must have had 3/4 prior lines of CT First line No limits on number of previous lines of CT
Veliparib (AbbVie)	Phase III combination CT followed by maintenance **(NCT02470585)**	$BRCA^{mut}$; AOC	First line
Talazoparib (Medivation/ Pfizer)	Phase I/II study **(NCT01989546)** Phase II study **(NCT02326844)**	$BRCA^{mut}$ solid tumours $gBRCA^{mut}$; ROC	After ≥ 1 standard CT OR no standard Rx options Progression following a PARPi

CT – chemotherapy; Ph – phase; gBRCAm – germline BRCA mutation; PSROC – 'platinum sensitive' recurrent ovarian cancer; HGROC – high grade recurrent ovarian cancer; HRD – homologous recombination deficient; AOC – advanced ovarian cancer; Rx – treatment

PRACTICE POINTS:

- Bevacizumab is licensed for use in ovarian cancers. Variation in precise indications in the ovarian cancer treatment pathway exist in different parts of the world but the drug will increase tumour response rate and extend progression-free survival.
- There are no predictive markers for benefit but one trial, ICON7 in the first-line setting demonstrated a survival benefit in patients with a poorer prognosis.
- In 'platinum-resistant' disease, the addition of bevacizumab to chemotherapy improves the tumour response rate, progression-free survival and patient-reported outcomes.
- BRCA mutations are the first predictive markers for response to PARP inhibitors in ovarian cancer. Olaparib is the first-in-class drug to be licensed for the treatment of ovarian cancer as maintenance therapy in platinum-sensitive ovarian cancer with a BRCA mutation.
- In USA the drug is licensed as a single agent, in patients with a BRCA mutation who have received ≥3 lines of chemotherapy

RESEARCH AGENDA:

There has been a rapid expansion of new drugs targeting tumour cell growth and survival pathways. Whilst chemotherapy continues to be a valuable therapeutic approach, the incorporation of these new molecularly targeted drugs into treatment is a research priority This will involve:

- Having a better understanding of the pathway control mechanisms
- Developing trials to evaluate activity rapidly, using newer endpoints. Dose escalation is being replaced by target activation and novel response endpoints
- Identification of markers predictive of response is a priority
- Molecularly targeted agents, sequentially or in combination are likely to be most effective and designing trials to evaluate these are challenging

Multiple Choice Questions:

1. Which of the following statements about bevacizumab are true:
    a. It is a fusion protein that binds to VEGF
    b. Has been shown to improve progression free survival in women with high risk disease when given in combination with first line chemotherapy followed by 12 months maintenance therapy
    c. Trials failed to show benefit in 'platinum-resistant' recurrent ovarian cancer
    d. Toxicities of bevacizumab include increased risk of bowel perforation, fistulae formation, impaired wound healing, increased risk of thromboembolism and hypertension
    e. Measurement of predictive markers allow the selection of patients who will benefit.

Answers:

a) F – bevacizumab is a recombinant monoclonal antibody that binds to circulating VEGF-A; Aflibercept is a fusion protein that binds to VEGF preventing it from binding to its receptors

b) T –ICON7 and GOG 218 are the two key first-line studies investigating the addition of bevacizumab to chemotherapy following surgery. High-risk disease is defined as incomplete cytoreductive surgery (>1cm residual disease) or FIGO stage IV disease. PFS for this population was 14.5 months in the chemotherapy alone arm vs 18.1 months in the chemotherapy plus bevacizumab arm. No OS benefit was seen in these trials.

c) F – AURELIA study adding bevacizumab to chemotherapy in 'platinum-resistant' relapse showed significant improvement in tumour response rate, progression free survival and patient-reported outcome.

d) T – these are the main toxicities of all VEGF inhibitors. It is important to carefully select patients for treatment with bevacizumab as those with extensive serosal disease are at high risk of bowel perforation.

e) F – There are no predictive markers to select which patients will benefit.

2. Which of the following are considered to be novel targets in ovarian cancer?
    a. Oestrogen and progesterone receptors
    b. Folate receptor
    c. Wee 1
    d. BRAF
    e. PARP

Answers:

a) F – oestrogen and progesterone receptors are targets for inhibition in the treatment of breast cancer. Tamoxifen and aromatase inhibitors can be used in the treatment of ovarian cancer, particularly low-grade serous cancers. However, it is unclear whether oestrogen/progesterone receptor status in these tumours influences the benefit of these drugs

b) *T – Farletuzumab and vintafolide both target the folate receptor and have been evaluated in the treatment of ovarian cancer. However, they have not been shown to improve survival.*

c) *T - Wee1 is a tyrosine kinase that is required for normal functioning of the G2 checkpoint in the cell cycle. Wee1 inhibitors, when combined with carboplatin, have shown promising activity in 'platinum-resistant' ovarian cancer with p53 mutations.*

d) *F – BRAF mutations lead to activation of the MAPK signalling pathway and are commonly found in a number of cancers. BRAF inhibitors are approved in the treatment of malignant melanoma and are being investigated in clinical trials for other BRAF-mutant cancers. BRAF inhibitors are currently not being evaluated in the treatment of ovarian cancer.*

e) *T – Poly ADP ribose polymerase (PARP) is an enzyme involved in DNA damage repair. PARP inhibitors have been shown improve outcomes in ovarian cancers with homologous recombination deficiency, particularly those with BRCA mutations.*

3. Which of the following statements related to homologous recombination deficiency (HRD) in ovarian cancer are true?
    a. Single strand DNA breaks are the most lethal insult to the genome
    b. Germline BRCA mutations are present in 50% of high grade serous ovarian cancer
    c. Olaparib only improves PFS in BRCA mutated ovarian cancer, but has no activity in $BRCA^{wt}$ cancer
    d. PARP inhibitors are well tolerated, with the most common toxicities being nausea, vomiting, fatigue and anaemia
    e. The most evidence for the use of PARP inhibitors is in the 'platinum- sensitive' setting

Answers:

a) F – Double strand DNA breaks (DSB) are the most lethal insult to the genome and if left unrepaired, cell death will occur.

b) F – germline BRCA mutations are found in 10-15% of high-grade serous ovarian cancers. Approximately 50% of high-grade serous tumours have HRD and behave like BRCA mutated cancer ('BRCAness')

c) F – study 19 is the original trial evaluating the use of olaparib as maintenance therapy in high-grade serous ovarian cancer after completion of platinum based

therapy. BRCA status was unknown at the time of study entry, but was analysed retrospectively in a pre-specified analysis. In the BRCA mutated (germline or somatic) group of patients, the median PFS was significantly longer in the olaparib group compared to the placebo group. However, there was also a benefit seen in the BRCA wild-type group.

d) *T – PARP inhibitors are oral tablets, which are generally well tolerated.*

e) *T*

4. **The role of immunotherapy in ovarian cancer is currently being evaluated in multiple trials. Which of the following statements are true?**

    a. PD-1 and PDL-1 enable cancer cells to 'escape' the immune system

    b. Tumour infiltrating cells are poor prognostic indicators in ovarian cancer

    c. Pembrolizumab is a humanized monoclonal anti-PD-1 antibody,

    d. Immune checkpoint inhibitors have shown encouraging response rates of > 20% in patients with 'platinum-sensitive' recurrent ovarian cancer

    e. Common adverse events include fatigue, flu-like symptoms, infusion-related reactions, rash and hypothyroidism.

Answers:

a) *T - Tumour cells are able to 'escape' the immune system and one of the most important components is an immunosuppressive co-signal (immune checkpoint) facilitated by programmed cell death 1 (PD-1) and it's ligand PDL-1*

b) *F - In ovarian cancer, the presence of tumour infiltrating lymphocytes (TILs) is prognostic for better survival; a high number of immunosuppressive regulatory T-cells (Tregs) are associated with a poor prognosis*

c) *T – Pembrolizumab and nivolumab are anti-PD-1 antibodies and avelumab is a fully humanised anti-PDL-1 antibody*

d) *F – The JAVELIN Solid tumour phase Ib (avelumab) study in multiple tumours reported an overall response rate of 9.7% in patients with heavily pre-treated 'platinum-resistant' ovarian cancer. KEYNOTE-028 study with pembrolizumab reported an overall response rate of 11.5%.*

e) T