



Royal College of  
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# Targeted Therapies for the Management of Ovarian Cancer

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# Targeted Therapies for the Management of Ovarian Cancer

This is the second edition of this paper, which was published in 2008 under the same title.

## 1. Introduction

In the United Kingdom each year, ovarian cancer is diagnosed in over 6500 women and causes approximately 4400 deaths.<sup>1</sup> Many women present with advanced disease with little prospect of cure. The 5 year survival rate for advanced ovarian cancer between 2005–2009 was 43%.<sup>1</sup> The current standard of care consists of the combination of radical surgery and platinum-based chemotherapy. Though key advances in surgical and chemotherapeutic strategies have led to small improvements in outcome, there still remains a significant risk of recurrence and resistance to therapy and a need to improve current treatment options.

Novel biologically targeted agents have proven successful in a variety of malignancies such as leukaemia, colon, renal and breast cancers. These agents target tumour cells and/or the microenvironment by exploiting specific molecular abnormalities in the tumour; an approach which holds the promise of greater selectivity and lower toxicity than traditional modalities such as chemotherapy. Advances in our understanding of the biology of ovarian cancer have led to clinical trials of targeted agents,<sup>2</sup> of which approaches, angiogenesis inhibitors and polyadenosine diphosphate-ribose polymerase (PARP) inhibitors are the most developed (Appendix 1).

Epithelial ovarian cancer has previously been treated as a single disease. However, it is a heterogeneous disease consisting of several histological subtypes with distinct clinical behaviour and defects in molecular pathways (high grade serous- p53, BRCA, homologous recombination deficiency; low grade serous- BRAF, KRAS, NRAS, HER2); clear cell-PIK3CA, PTEN; endometrioid PIK3CA, PTEN; and mucinous KRAS, HER2). The developments of clinical trials directed at specific subtypes of ovarian cancer are underway.

Multiple components of signalling cascades are aberrant in ovarian cancer and targeted agents have entered phase I–III clinical trials. Drug targets include molecules associated with the tumour cell (for example, folate receptor, mTOR inhibitors, MEK inhibitors) and the endothelial cell (for example, bevacizumab, vascular disrupting agents (VDAs). Antiangiogenic agents (for example, bevacizumab and VEGFR inhibitors) and PARP inhibitors are the most developed novel treatments.

## 2. Stem cells from reproductive tissues

Angiogenesis, the formation of new blood vessels, is a critical component of cancer growth and metastasis. Bevacizumab, a monoclonal antibody against Vascular Endothelial Growth Factor (VEGF) has shown very encouraging activity in ovarian cancer. Two phase II clinical trials of bevacizumab provided evidence that single-agent anti-VEGF therapy is a promising strategy in recurrent ovarian cancer.<sup>3,4</sup> Two randomised, phase III trials, the Gynaecologic Oncology Group (GOG) trial 0218<sup>5</sup> and International Collaborative Ovarian Neoplasm (ICON) 7 trials<sup>6</sup> have addressed the issue of adding bevacizumab to the combination of carboplatin and paclitaxel followed by maintenance therapy as first-line treatment for advanced epithelial ovarian cancer. The dose of bevacizumab used in ICON7 was half (7.5 mg/kg) the dose used in GOG-0218 (15 mg/kg). Both studies demonstrated highly significant improvements in progression-free-survival (PFS) (GOG-0218 HR 0.72, 10.3 (chemotherapy) vs 14.1 months (bevacizumab throughout),  $p < 0.001$ ; ICON7 HR 0.81, median PFS 17.3 (chemotherapy) vs 19 months (bevacizumab throughout),  $p = 0.004$ ) for the use of concurrent and maintenance bevacizumab. Furthermore, in ICON7, preliminary analyses have shown a significant improvement in OS with bevacizumab (28.8 months vs 36.6 months, HR = 0.64,  $p < 0.01$ )<sup>6</sup> in the high-risk subgroup of patients (high-risk group defined as FIGO stage IV disease or FIGO stage III disease with > 1.0 cm of residual disease after debulking surgery). An overall survival benefit was not evident in GOG-0218. The

proportion of patients in the chemotherapy alone arm who subsequently received bevacizumab means that a potential overall survival benefit would have been difficult to demonstrate. Mature survival data from ICON7 are expected in 2014. However, the initial demonstration of a survival benefit of almost 8 months in patients with a poor prognosis is very encouraging.

Adverse effects from drugs are usually divided into four grades depending on severity: Grade 1, (Mild) Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required. Grade 2 (Moderate), normal daily activity is affected mild to moderately – some assistance may be needed and no or minimal medical intervention/therapy required. Grade 3 (Severe), normal daily activity is markedly reduced – some assistance usually required; medical intervention/therapy is required, hospitalisation or hospice care may become necessary. Grade 4, (Potentially life threatening). There is extreme limitation to daily activity, significant assistance is required; significant medical intervention/therapy, hospitalisation or hospice care are very likely.

Adverse effects from bevacizumab include hypertension ( $\geq$  grade 2, ICON7 18% (bevacizumab arm) vs 2% (chemotherapy)), thromboembolism ( $\geq$  grade 3, ICON7 7% (bevacizumab arm) vs 3% (chemotherapy)). It is recognised that bevacizumab may increase the likelihood of gastrointestinal (GI) perforation and fistula formation. However, in ICON7 and GOG-0218, the reported rates of GI perforation are low ( $\geq$  grade 3 ICON7 1% bevacizumab arm) but higher than the control arms. The impact of maintenance bevacizumab therapy on quality of life (QoL) is important. ICON7 showed that bevacizumab maintenance was associated with a small but significant reduction in QoL compared with standard chemotherapy<sup>7</sup> and more QoL data for angiogenesis inhibitor clinical trials are required.

The OCEANS study, a phase III trial in which patients with recurrent platinum-sensitive disease were treated with bevacizumab in combination with chemotherapy (carboplatin with gemcitabine), also reported a significant improvement in the primary endpoint, PFS, with the addition of bevacizumab (8.4 months vs 12.4 months, HR = 0.48,  $p < 0.0001$ ).<sup>8</sup> Furthermore, the recently reported AURELIA study,<sup>9</sup> a phase III trial in which patients with recurrent platinum-resistant disease were treated with bevacizumab in combination with chemotherapy, also demonstrated a statistically significant improvement in PFS (3.4 months vs 6.7 months, HR = 0.48,  $p < 0.001$ ).<sup>9</sup> Final overall survival (OS) data are expected next year. Clinical trial data presented in the AURELIA study, and the aforementioned OCEANS study, support a role for bevacizumab in the setting of recurrent disease.

The European Medicines Agency (EMA) has approved the use of bevacizumab in combination with carboplatin and paclitaxel as first-line therapy and for the treatment of first platinum-sensitive relapse in combination with carboplatin and gemcitabine. However, bevacizumab has not received FDA approval for these indications because overall survival advantages have not been observed so far.

Bevacizumab is currently under evaluation in combination with other targeted agents (eg. sorafenib, everolimus). Other angiogenesis inhibitors have entered clinical trials in ovarian cancer and include cedirinib (ICON 6), pazopanib, sorafenib, BIBF1120 (Nintedanib), AMG 386 (trebananib, an angiopoietin-Tie2 inhibitor)<sup>10</sup> and aflibercept (VEGF-Trap)<sup>11</sup> (Appendix 1).

### 3. Poly (ADP) Ribose Polymerase (PARP) Inhibitors

Carriers of BRCA mutations harbour DNA repair pathway homologous recombination defects (HRD) and are at risk of developing ovarian cancer (10–40% lifetime risk). PARP inhibitors work by generating specific DNA lesions that require functional BRCA1 and BRCA2 for DNA repair. Patients with BRCA associated cancers lack wild type BRCA1 or BRCA2 in tumour cells but normal cells retain a single wild type copy of the relevant gene. This difference between tumour and normal cells means that PARP inhibitors can kill tumour cells specifically whilst sparing normal cells. This concept is termed ‘synthetic lethality’ (Appendix 1).<sup>12</sup> A phase II study of the PARP inhibitor, olaparib, demonstrated low toxicities and encouraging radiological and serological clinical responses in ovarian cancer patients with BRCA1 or BRCA2 mutations (57.6% RECIST and CA-125 criteria).<sup>13</sup> The promising activity of PARP inhibitors

may not be limited to tumours harbouring germline BRCA mutations. Up to 50% of high-grade serous, sporadic ovarian cancers may have homologous recombination defects (including somatic BRCA mutations, BRCA methylation) which confer sensitivity to PARP inhibition.<sup>14</sup> A randomised phase II trial has shown that maintenance therapy with olaparib extended progression-free survival by almost 4 months (median 8.4 months vs. 4.8 months, HR 0.35,  $p < 0.001$ ), in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer with or without BRCA1 or BRCA2 germline mutations.<sup>15</sup> Clinical trials of a number of other PARP inhibitors (for example rucaparib or niraparib) are in progress. In view of the significant clinical activity of PARP inhibitors, and that BRCA germline mutation status is a biomarker of response, knowledge of the BRCA status for an individual patient is likely to have therapeutic implications in ovarian cancer. In a population-based study of over 1000 women with non-mucinous invasive ovarian cancer, germline BRCA1/2 mutations were identified in 14% of all cases and in 17% of all women diagnosed with high grade serous histology.<sup>16</sup> Over 40% of all women identified to have BRCA1/2 mutations did not have a significant family cancer history and therefore would not have routinely undergone BRCA testing. More wide-scale BRCA testing in groups of patients at high-risk of harbouring BRCA mutations, such as high grade serous histology, should be considered.

#### 4. Epidermal Growth Factor Receptor and Human Epidermal Growth Factor 2 Receptor Inhibitors

The epidermal growth factor receptor (EGFR) and human epidermal growth factor 2 receptor (HER2) are tyrosine kinase receptors involved in cell proliferation and survival. Preclinical evidence suggested that EGFR and HER2 were potential targets in ovarian cancer. However, results from trials of erlotinib, gefitinib (EGFR inhibitors), trastuzumab (targeting HER2) and pertuzumab (HER2 dimerisation inhibitor) have all been relatively disappointing (Appendix 1). The effectiveness of anti-HER2 therapies may have been limited by a lower than expected level of HER2 expression in ovarian cancer. The EORTC55041/OVO7 phase III trial demonstrated that maintenance erlotinib after first-line treatment in ovarian cancer did not improve progression-free or overall survival.<sup>17</sup> HER2 overexpression or amplification has been reported in 18% of mucinous ovarian carcinomas<sup>18</sup> and HER2 directed treatment for this subgroup of patients is under exploration.

#### 5. Other signalling molecules

Multiple components of signalling cascades are aberrant in ovarian cancer resulting in activation of critical oncogenic pathways involved in processes such as cell proliferation, survival, migration and angiogenesis (Appendix 1). These cellular changes are implicated in tumour growth and metastasis and so are likely to affect patient outcome. Examples of critical signalling molecules include phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), insulin growth factor receptor (IGFR), Src, Wee-1 kinase and the folate receptor, which is over expressed in > 90% of ovarian cancers. Farletuzumab (MORab-003, Morphotek), a monoclonal antibody directed against the  $\alpha$ -folate receptor and EC145, a conjugate of a vinblastine analogue to folate, are being investigated in phase III trials of ovarian cancer. The Ras/MEK/ERK pathway is an attractive therapeutic target in low grade serous ovarian carcinoma (LGSOC). This is a rare subtype of ovarian cancer with disappointing response rates following standard systemic treatment options. A phase II trial of the MEK 1/2 inhibitor, Selumetinib has shown promising results in recurrent LGSOC with an overall response rate of 15.4%, disease stabilisation of 65% and median PFS of 11 months.<sup>19</sup> Phase II/III studies of this approach are planned.

#### 6. Relevance to other gynaecological cancers

Some of the approaches described above have been used in other gynaecological cancers. For example, internationally, there are ongoing trials of angiogenesis inhibitors in cervical and endometrial cancers and EGFR inhibitors in vulval cancer. There is particular interest in mammalian target of rapamycin (mTOR) inhibitors (Temsorilimus-CCI779, Everolimus-RAD001) in the treatment of endometrial cancer.

## 7. Opinion

Ovarian cancer remains a treatment challenge. The success of targeted therapies in other cancers has encouraged the development of these agents for ovarian cancer. Numerous targeted therapies are currently being evaluated in phase I-III studies and should clarify their potential clinical use. The most promising strategies developed so far use the anti-angiogenic approach and PARP inhibitors. Further challenges facing the success of targeted therapy include the identification of biomarkers to guide management and assess response, overcoming drug resistance, toxicities and choosing the correct target population. Issues to address when designing clinical trials include whether combination therapy is superior to monotherapy and the role for maintenance therapy. More research focussing on predictive biomarker for targeted therapies is critical. Circulating short VEGFA isoforms, expression of neuropilin-1 and VEGF receptor 1 and genetic variants in VEGFA are potential biomarkers for angiogenesis inhibitors.<sup>20</sup> Translational clinical trials are essential; understanding the molecular abnormalities involved in ovarian cancer is critical in developing appropriate candidate agents and for the success of these agents in improving clinical outcome. Cancer therapy is currently moving ever closer towards personalised medicine and the first stages of stratification of this in ovarian cancer means that patients with different tumour characteristics can benefit from suitable but different targeted therapies.

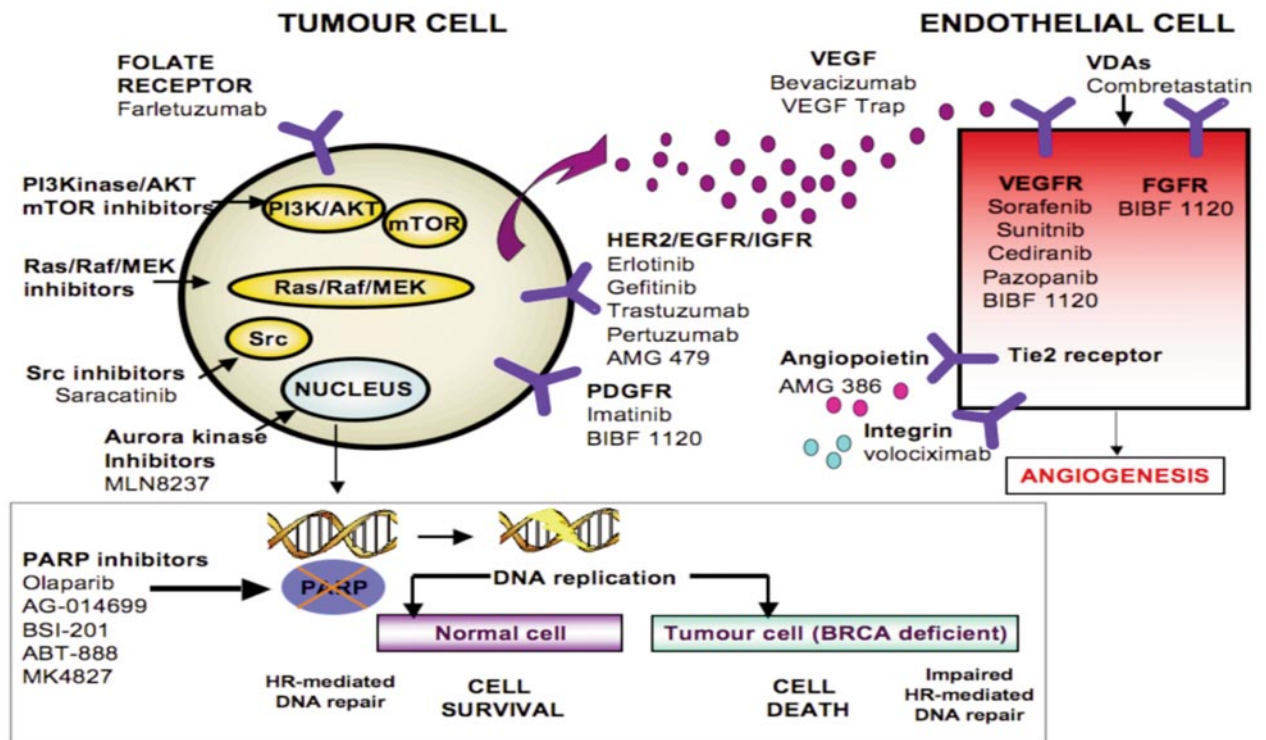
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## Appendix 1

Targeted approaches in Ovarian Cancer.<sup>2</sup>



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