# Clinical Development in Challenging Cancers: Ovarian Clear Cell Carcinoma (OCCC)

Ovarian clear cell carcinoma (OCCC) is a rare histological subtype of epithelial ovarian cancers (EOCs), with an incidence, among EOCs, of 4–12% in western countries[1–3] and a higher ratio of over 20% in Japan[4,5]. Histologically, EOCs are classified into serous, mucinous, endometroid, clear cell and undifferentiated subtypes. Ovarian cancer is already the leading cause of death among gynaecological malignancies in the US[6]; in addition, the OCCC subtype presents a lower response rate to traditional platinum-based chemotherapy and is generally associated with poorer prognosis across all stages compared to other EOC subtypes[2,4,7–9].

In 1973, the World Health Organization (WHO) strictly defined ovarian clear cell carcinomas (OCCCs) as lesions characterised by clear cells growing in solid, glandular, tubular, papillary or microcystic patterns or combinations thereof, as well as hobnail cells lining tubules and cysts[10].

## Current Clinical Management

The peak age group of incidence of EOC is 55–64 years[11]. OCCC generally presents as an observable pelvic mass[12–14], and is associated with endometriosis1,[4,15,16] and an increased risk of thromboembolic complications[4,15,17,18], and more than half of patients are diagnosed early in Stage I[2,18].

Although chemoresistence is a significant challenge in OCCC management, no specific first-line treatment has been established to address this, and standard EOC treatment is used, which is summarised in Figure 1. Primary management is based on initial surgery[19,20] with a goal of optimal cytoreduction, followed by adjuvant chemotherapy. Surgical interventions include total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy; however, there is currently no strong evidence that systematic nodal dissection improves survival[21]. In a meta-analysis, which included 835 patients with stage III and IV ovarian cancer, the incremental increase in chemotherapy cycles in the neoadjuvant setting was associated with a decrease in median overall survival compared to initial surgery[22].

Chemotherapy historically comprised a combination of cisplatin plus cyclophosphamide[23], and later, cisplatin-paclitaxel doublet, due to evidence of superiority in effectiveness[24]. Finally, carboplatin was found to be an equally effective, but safer, alternative to cisplatin[25], thus the current standard of care comprises carboplatin-paclitaxel combination.

Several studies concluded that the use of VEGF (Vascular Endothelial Growth Factor) inhibitor bevacizumab, in addition to platinum-based chemotherapy, is beneficial to patients in late stages (III and IV), for patients with recurrent diseases, as well as patients in early stages with a high risk of recurrence[26,27]. Bevacizumab has been approved as first-line treatment, in the mentioned settings, by EMA[28] and FDA[29].

Additionally, since December 2016, three different target therapy agents from the PARP (Poly ADP-Ribose Polymerase) inhibitor group were granted approval by FDA in second-line treatment: rucaparib[30], niraparib[31] and olaparib[32]. While niraparib and olaparib were also approved by EMA[33,34], rucaparib is pending approval. Theoretically, PARP inhibitors express most effectiveness in cells with deleterious BRCA mutations, thus the indication of rucaparib is restricted to these cases; niraparib and olaparib showed benefit to PFS (progression-free survival) regardless of BRCA status[35,36]. Although patients with identified germline BRCA1/2 mutations showed increased response to olaparib and niraparib treatment, the observed effect on patients without BRCA mutations can be explained by other deficiencies of the HR (homologous recombination) system in cancer cells, leading to susceptibility to PARP inhibition[37–39]. As these agents primarily demonstrated effectiveness in platinum-sensitive EOCs, and taking into consideration the lower BRCA mutation rates in the clear cell subtype[40], their role in the management of OCCC is yet to be confirmed.

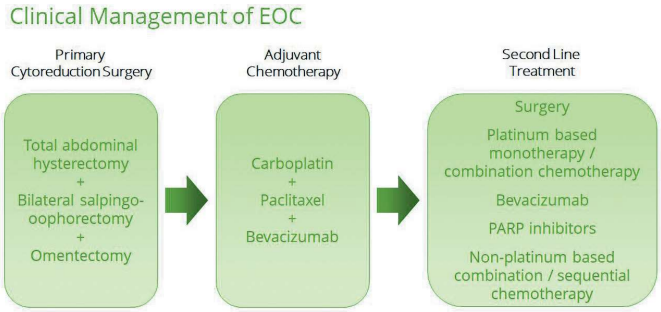


*Figure 1: Overview of approved treatment options in EOC*

## Therapeutic Challenges

OCCC is known to be less sensitive to platinum-based front-line chemotherapy and is associated with a worse prognosis. Crotzer *et al.* (2007)[41] retrospectively analysed 51 patients with OCCC and concluded that OCCC is particularly chemoresistant and advocated for more active research on target identification. Another aspect in the clinical management of OCCC is the lack of effective chemotherapy for recurrent disease after front-line treatment with platinum-based chemotherapy. It was reported after a retrospective study in 75 OCCC patients[42] that the response rate for various regimens in the setting of second-line chemotherapy for recurrent platinum-resistant OCCC was only 1%, and suggested that recurrent or resistant OCCC is extremely chemoresistant, and there is only a small benefit of long treatment-free periods in OCCC patients.

Conventionally, the OCCCs were considered as a homogenous subtype of EOC at the molecular level until 2011, when Tan *et al.*[43]

subjected 50 archival OCCCs to high-resolution microarray-based comparative genomic hybridisation analysis that revealed OCCC are indeed genetically heterogenous, and can be further subdivided into distinct patterns of copy number aberration. Based on this, two distinct genomic subgroups of OCCCs (cluster-1 and cluster-2) that did not significantly differ in terms of their clinicopathological and histological features were identified. Subsequent survival analysis revealed that patients from cluster-1 had a significantly shorter median progression-free survival (PFS) than those from cluster-2 (11 vs 65 months, P=0.009) and subsequent multivariate analysis revealed that genomic cluster was an independent prognostic factor for PFS.

Distinction of OCCC from high-grade serous carcinomas (HGSCs) was a diagnostic challenge. In 2006, Kato *et al.*[44] presented that hepatocyte nuclear factor-1beta (HNF-1beta) was significantly upregulated in OCCC, and proposed HNF-1beta as an excellent biomarker for OCCC. This was later confirmed by Kobel *et al.*[45], by examining 133 OCCC samples. However, a specific antibody for HNF-1beta was not developed and its potential as a therapeutic target in such tumours of high expression remains unexplored.

Various studies were conducted to understand carcinogenesis in OCCC, and multiple OCCC-specific genetic mutations and altered protein expressions were identified, leading the way to the discovery of molecular pathways that could shed light on potential therapeutic targets. Unlike serous ovarian cancers, OCCCs show low frequency of BRCA1 and BRCA2 mutations, but harbour important alterations in AT-rich interactive domain 1A (*ARID1A*), phosphatase and tensin homolog (*PTEN*), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (*PIK3CA*) mutations[46].

Here, we will discuss some of the key pathways and agents tested with clinical studies in recent years.

## Clinical Development in OCCC

Published results from recent clinical studies of OCCC patients are seen in Table 1, while there are several other ongoing clinical trials.

## mTOR Inhibitors

mTORC1 (mammalian target of rapamycin complex 1) was shown by immunohistochemical analysis to be more frequently activated in OCCC than in serous adenocarcinomas (86.6% versus 50%)[47]. Additionally, various studies have shown that ovarian CCCs often exhibit genetic alterations in one or more components of the PI3K/AKT/mTOR signalling pathway[46].

## VEGFR Inhibitors

The most successful VEGFR inhibitor, bevacizumab, an anti-angiogenic humanised monoclonal antibody that inhibits the binding of both VEGFR-1 and VEGFR-2 is already approved in the treatment of ovarian cancers. Recently Sunitinib, an oral multi-targeted tyrosine kinase inhibitor against vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) pathways was evaluated by a Phase II study in 30 subjects with persistent or recurrent OCCC. Five (16.7%) patients had PFS ≥ 6 months (90% CI: 6.8%, 31.9%). Two (6.7%) patients had a partial or complete response (90% CI: 1.2%–19.5%). The median PFS was 2.7 months and the median overall survival was 12.8 months, and it was concluded that Sunitinib demonstrated minimal activity in the second- and third-line treatments of persistent or recurrent clear cell ovarian carcinoma[48]. Nintedanib, which is also an inhibitor of FGFR (fibroblast growth factor receptor) and PDGFR (platelet-derived growth factor receptor) in addition to VEGFR is examined in a Phase II study comparing efficacy to standard second-line chemotherapy in recurrent or advanced ovarian clear cell carcinomas, with no results to date[49].

## PD-1 Inhibition

Multiple molecules were developed inhibiting interaction between Programmed Cell Death Ligand 1 (PD-L1) and PD-1. PD-L1 may be expressed or overexpressed by tumour cells, leading to decreased T-cell response from the immune system and subsequent decreased anti-tumour activity. By inhibiting this interaction, anti-tumour activity may be increased. It is notable that in previous studies examining the safety and efficacy of PD-1 receptor antibody Nivolumab[50] and PD-L1 antibody Avelumab[51], in refractory or recurrent ovarian cancer patients, best results were achieved in patients with the OCCC subtype[52]. Although no OCCC-specific study has started as of now, it may be a promising direction toward target therapy in the treatment. A recent Phase II study is recruiting patients with recurrent OCCC comparing Durvalumab to any second-line standard chemotherapy[53].

## Multi-kinase Inhibitors

ENMD-2076, a multi-kinase inhibitor, with effect demonstrated on Aurora-A kinases, VGFRs, FGFRs and other targets, is examined in a Phase II clinical study for OCCC treatment[54]. The study concluded with 40 patients and demonstrated a PFS of 20% after six months. However, patients with ARID1A loss demonstrated better results, despite loss of ARID1A being a negative prognostic factor[55]. Although additional molecular profiling for interpretation of results is still underway, further research will not be continued by the current manufacturer to demonstrate efficacy of ENMD-2076 as a monotherapy[56].

| Investigational Drug | Target | Regimen | Indication | Phase | Results |
|---|---|---|---|---|---|
| Temsirolimus | mTORC1 | Temsirolimus+ Carboplatin +Paclitaxel | Newly diagnosed stage III-IV OCCC | II (90 subjects) | PFS of >12 months shown by optimally debulked subjects. No statistically significant increase in PFS at 12 months in all cases when compared to historical controls[57] |
| Temsirolimus | mTORC1 | Temsirolimus+ Trabectedin | Recurrent platinum-resistant OCCC | II (21 subjects) | 43% subjects achieved clinical benefit rate (CR+PR+SD>3 months)[58] |
| Sunitinib | VEGFR | Sunitinib monotherapy | Recurrent OCCC | II (30 subjects) | Median PFS was 2.7 months and the median OS was 12.8 months[59] |
| ENMD-2076 | AURORA-A, VEGFR, FGFR | ENMD-2076 monotherapy | Recurrent OCCC with previous platinum therapy | II (40 subjects) | Loss of ARID1A, a known negative prognostic factor, was correlated with better PFS on ENMD-2076[55] |

OCCC: ovarian clear cell carcinoma, mTORC1: mammalian target of rapamycin complex 1, PFS: progression-free survival, CR: complete response, PR: partial response, SD: stagnating disease, VEGFR: vascular endothelial growth factor receptor, OS: overall survival, FGFR: fibroblast growth factor receptor

*Table 1: Overview of recent OCCC-specific studies with published results*

## Conclusion

As demonstrated, the clinical management of OCCC remains to be a significant challenge for clinicians to this day. This specific subtype of EOCs is not only primarily chemoresistant, but is genetically heterogenous and no effective therapy has yet been identified to overcome this obstacle. Even the promising results of some of the newer treatment options for EOCs, like the PARP inhibitors, cannot be extrapolated to OCCCs due to the difference in tumorigenesis and genetic mutations. It can be observed that current clinical studies do not routinely focus on stratification by histological subtype and therefore the advancements in overall EOC management often overshadow the fact that OCCC treatment, especially in an advanced setting, is still unresolved.

To facilitate the advancement of OCCC management, further genetic research is needed to define the potential target points for emerging future treatment options and the currently ongoing

clinical studies need to be more focused on examining the effects of the experimental treatments based on histological subtypes. The question also arises if there is a need to define a separate first-line treatment protocol for OCCC management based on the high ratio of platinum-resistant diseases.

There have been minor improvements in recent years to the treatment of advanced OCCC, but the results need to be further verified on larger patient groups. There are also some promising pathways waiting to be explored, like the PD-1 checkpoint inhibition or the potential benefit from PARP inhibitor therapy.

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