



Harnessing Wnt signaling as a targetable therapy in epithelial ovarian cancer

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Epithelial ovarian cancer (EOC) is the deadliest of gynecologic malignancies and the majority of patients are diagnosed at an advanced stage. The 5-year survival for women with stage IIIC EOC, which is the most common stage at the time of diagnosis, remains less than 50% (1) and the 5-year relative survival for all advanced stage EOC is approximately 30% (2). Even following a complete clinical response to initial chemotherapy in conjunction with optimal surgical cytoreduction, the vast majority of these patients will experience a recurrence, thus necessitating continued investigation of beneficial therapies and consideration of novel approaches. Chemotherapy with a platinum/taxane doublet has long been the standard of care for treatment of EOC; this regimen is used in current practice as the typical choice for first-line chemotherapy and for the treatment of recurrent disease when the progression-free interval is at least six months. Following this regimen, various options exist for treating recurrent disease, though there is no pure “gold standard” due to largely inconsistent responses to treatment between patients. In relatively recent years, the angiogenesis inhibitor bevacizumab and poly (ADP-ribose polymerase) (PARP) inhibitors have been approved for maintenance therapies in select groups of patients with EOC; while PARP inhibitors are most efficacious in patients with either somatic or germline *BRCA* mutations, as of yet there are no predictive biomarkers for which patients may derive the most benefit from bevacizumab maintenance therapy (3).

Thus, while these therapies offer promising options in select groups of patients, a treatment gap persists for many women with recurrent or progressive disease.

Wnt signaling is markedly complex and has roles in human development and organogenesis in addition to its implication in certain cancers. Alterations in the Wnt signaling pathway have been identified in multiple cancer subtypes, including EOC (4), and are associated with promoting tumor growth. Ongoing studies investigating the efficacy of targeting the Wnt pathway have shown promising results in patients harboring Wnt signaling mutations in various cancers (5,6). While the exact mechanism of how Wnt signaling alterations contribute to tumorigenesis is unknown, it is postulated that targeting Wnt may have effects on tumor immunogenicity in addition to direct cell cytotoxicity (7). As immunotherapies overall have seen modest success in EOC, developing new therapies that can harness the host’s immune system as another route of attack would open new avenues of treatment for many patients.

Ipafricept (IPA) is a recombinant protein that serves as a Wnt inhibitor through blocking the interaction of Frizzled (FZD) with the FZD8 receptor (8,9), a necessary component in the Wnt signaling pathway. Previous work in mouse models demonstrated that IPA was associated with a decrease in specific cell populations with the ability to reconstitute tumor cells (akin to cancer stem cells). Additionally, results from a xenograft model of EOC

suggested that a combined therapeutic approach of IPA with a taxane-containing regimen in a sequential rather than a concurrent fashion had superior efficacy (10). Moore and colleagues report the results of a phase 1b study of IPA (OMB-54F28) in combination with carboplatin and paclitaxel in recurrent platinum-sensitive EOC.

The primary objectives in this study were to determine the safety and tolerability of IPA in combination with carboplatin and paclitaxel, dose-limiting toxicities (DLT), the maximum tolerated dose (MTD), and the recommended phase 2 dosing regimen. Secondary objectives included characterization of the drug's pharmacokinetic profile, immunogenicity, and clinical activity in combination with carboplatin/paclitaxel. Importantly, during the dose escalation phase, IPA was discontinued in two cohorts (those receiving IPA at 5 and 10 mg/kg q3w) as fragility fractures were observed in phase 1 programs of IPA as well as vantictumab, an antibody that inhibits Wnt signaling by binding to various FZD receptors. The remaining cohorts received IPA at lower doses (2, 4, and 6 mg/kg q3w) and carboplatin and paclitaxel were administered at AUC = 5 mg/mL*min and 175 mg/m², respectively on day 3 of each cycle (as opposed to day 1 in cohorts 1 and 2) due to the superior efficacy of this regimen in prior studies as described above.

In this study, no DLTs were identified. The MTD was not determined as following implementation of the revised bone safety plan no patients experienced any treatment related adverse events (TRAE) qualifying as a DLT or fragility fracture. Notably, however, all serum bone turnover markers decreased compared to baseline levels. Consequently, the study was prematurely discontinued and the development of IPA was ceased due to the incidence of fragility fractures in both IPA (6%) and vantictumab (12%) programs (11); prior to study discontinuation, 75.7% of enrolled patients had either a complete or partial response.

As mentioned, there is an unmet need for further therapeutic options in recurrent platinum-sensitive ovarian cancer, specifically targeted therapies, as well as therapies harnessing the host's immune system. This need is likely to further increase due to the fact that EOC patients will likely be receiving maintenance therapy in the upfront setting, particularly with PARP inhibitors, which will increase the population of patients with platinum-sensitive ovarian cancer. Targeted therapies have begun to infiltrate the oncology landscape in recent years and have seen success in many instances. Within EOC specifically, the introduction of PARP inhibitors has arguably yielded the most success

and possibly had the most immediate effect on treatment practices, but as only roughly 15% of EOC patients harbor *BRCA* mutations (12), identifying other targetable pathways is highly indicated. Moore and colleagues provide compelling evidence that targeting Wnt signaling may prove to have notable clinical efficacy in such patients given an overall response rate of 75.7% in their study, though they did not include specific testing for Wnt target mutations. The discontinuation of IPA and vantictumab due to poor bone safety profiles should not dampen investigation into other Wnt-targeting therapies. Currently, there is an ongoing phase 2 clinical trial investigating DKN-01, a monoclonal antibody targeting Dickkopf-1 (DKK1), as monotherapy or in combination with paclitaxel in advanced gynecologic malignancies, including EOC (NCT03395080). DKK1 itself, via a negative feedback loop, inhibits the Wnt pathway, particularly in the setting of Wnt upregulation; however, despite its role in negative feedback, increased DKK1 levels are poorly prognostic in several cancers, including ovarian cancer (13), and in nonclinical models increased DKK1 has been shown to promote cancer cell migration, tumor growth, metastasis and angiogenesis and may play an immune-modulatory role.

Moving forward, the Wnt pathway remains a promising therapeutic target in advanced ovarian cancers and has gained increased enthusiasm lately given its potential role in immune evasion. While IPA development has been discontinued due to a poor bone safety profile, the clinical efficacy reported by Moore and colleagues speaks to the potential utility of targeting Wnt signaling in this patient population. Available clinical and pre-clinical data investigating other modulators of Wnt signaling suggests that perhaps the key to their therapeutic benefit in EOC and other advanced gynecologic cancers lies in an immunomodulatory role. Continued work to unravel the mechanistic underpinnings of how altered Wnt signaling creates an avenue for these cancers to potentially escape immunosurveillance and translate this into an effective anti-cancer targeted therapy is highly warranted.

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Footnote

Conflicts of Interest: RCA: Advisory board, Clovis, Tesaro, AstraZeneca, Leap. JW has no conflicts of interest to declare.

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