

## HER2-Targeted Antibody Treatment for Ovarian Cancer – Future Opportunities

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### Editorial

There are an estimated 240,000 new cases of ovarian cancer diagnosed worldwide each year [1]. Due to late presentation, in many parts of the world it remains the most lethal gynecological cancer [2]. In 2004, a new model description of this disease was proposed that combined both histopathological and molecular features and which classified epithelial ovarian cancers into two broad categories designated Type I and Type II tumors [3]. Type I tumors tend to be low grade and are exemplified by clear cell, mucinous, low-grade serous and endometrioid histologies with associated molecular alterations characterised by mutations in genes including HER2, KRAS, BRAF, CTNNB1, PTEN, PIK3CA, ARID1A and PPP1A [3]. More recently, profiling studies have attempted to further stratify ovarian cancer into molecular subtypes, although these have largely focused on Type II, high grade serous ovarian tumors which frequently contain mutations in p53 and the BRCA genes [3-5]. These genetic abnormalities can help define the response of cancers to specific treatments, hence the widespread use of platinum containing drugs which have useful efficacy particularly in type II disease. Platinum containing regimens are the standard of care in first line treatment of this disease [2]. However, resistance frequently develops and there is an ongoing need for improved second line options.

The observation that HER2 is amplified and overexpressed, especially in clear cell and mucinous tumors suggests possible use of HER2 based therapies in selected ovarian cancers [6,7]. In fact, increased expression of HER2 has been observed in small groups of tumors across all the histological subtypes including Type II disease [8]. HER2 (or erbB2) is a member of the HER (erbB) family of cell surface receptors. In breast cancer, 15-20% cancers have amplification and high expression that enables these tumors to be treated with HER2-targeted antibodies such as trastuzumab (Herceptin) [9].

In ovarian cancer, trastuzumab was the first HER2 targeted antibody to be trialled and the phase II trial indicated a response rate of 7.3% in a cohort of HER2+ cancer patients [10]. In 2006, another humanised anti-HER2 antibody (pertuzumab, Perjeta) underwent clinical evaluation in ovarian cancer and this demonstrated clinical benefit in 14.5% of patients in a monotherapy Phase II trial [11]. These modest response rates are typical of active second line agents in ovarian cancer demonstrating the difficulty of treating advanced resistant disease. The pertuzumab monotherapy trial was followed by a clinical trial of pertuzumab in combination with chemotherapy in a platinum-resistant group of patients [12]. In this study, there was an indication of improved benefit when pertuzumab was given alongside chemotherapy particularly in patients whose tumors had low HER3 mRNA expression levels. These clinical studies support the view that a

subgroup of ovarian cancers do benefit from HER2-targeted treatment, but it would be helpful to enhance the level of activity further.

Over the last decade, several developments have identified more effective treatments targeting HER2+ disease for breast cancer. Firstly, use of the combination of trastuzumab with pertuzumab has demonstrated superiority of the combination over the single agents in a large scale Phase III clinical trial (CLEOPATRA) [13]. This led to the drug combination being approved for treatment of HER2+ metastatic breast cancer and more recently for neoadjuvant treatment. Secondly, the antibody-drug conjugate ado-trastuzumab emtansine (Kadcyla, trastuzumab-DM1) has shown marked activity against HER2+ breast cancer and has been approved for treatment of HER2+ disease [14]. This is a conjugate of trastuzumab with a cytotoxic moiety emtansine (DM1) which is particularly effective against tubulin. Ado-trastuzumab emtansine is now FDA approved for treatment of HER2+ breast cancer disease. These approaches now merit consideration in ovarian cancer.

Preclinical experimental studies have demonstrated that HER2+ ovarian cancer xenografts are responsive to combination of trastuzumab and pertuzumab and furthermore, the two antibodies are more effective together than either one alone, producing very marked and prolonged growth inhibition [15,16]. Similarly, interesting results have been obtained for ado-trastuzumab emtansine in preclinical models of ovarian cancer, again producing marked tumour regression in experimental models [17,18]. Together, these data support the view that HER2+ ovarian cancer cells can show strong responsiveness to these enhanced HER2-targeting strategies in an experimental setting and merit consideration for future ovarian cancer trials. If these trials go ahead, it will be important to analyse biomarkers to identify features of responding tumours. Markers such as HER2 or HER3 expression levels may be useful to help identify sensitive ovarian cancers and further biomarkers are currently being sought within preclinical models [15,16].

In conclusion, these data support continued clinical investigation of HER2-targeted antibody evaluation in chemotherapy insensitive/resistant ovarian cancer. The likely limited number of responding patients will necessitate the need for biomarkers to help predict which patients are most likely to benefit. If these hurdles can be overcome, then HER2-targeted antibodies could find a role in the treatment of selected ovarian cancers.

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