

WEE1 Inhibitor AZD1775 as a Promising Therapeutic Approach for Ovarian Cancer



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Submission: September 18, 2017; **Published:** September 27, 2017

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Opinion

Epithelial ovarian cancer is the most deadly of the gynecologic malignancies. The asymptomatic nature of the disease and a high rate of chemo resistance result in a long-term survival rate of only 30%. Despite the high response rate to initial treatments, most women diagnosed with advanced ovarian cancer will eventually have a recurrence. Women with Type II ovarian cancers (e.g., HGSC) are likely to have higher rates of recurrence. Patients with cancers that are not responsive to front-line therapy are typically treated with other agents (e.g., gemcitabine or etoposide), but the overall response to these agents remains poor and the median PFS is only 3 months on average. Inadequate sensitivity to chemotherapy and in tratumoral heterogeneity is the primary cause of therapeutic failure in ovarian cancer patients [1]. To improve patient outcomes, there is a critical need to identify more appropriate molecularly targeted agents to combine with chemotherapy to overcome drug resistance. The use of next-generation sequencing (NGS) has led to the development of targeted therapies for various solid tumors, and these data may also lead to new indications for already approved cancer drugs if identical mutations exist in other cancer types. The NCI-MATCH trial represents a new method for evaluating targeted therapies, which is needed for precision medicine initiatives [2]. The molecular analysis of HGSC by TCGA revealed the presence of TP53 mutations in 96% tumors and germ line or somatic mutations of BRCA1 and BRCA2 in 20% tumors [3]. However, HGSC patients have limited actionable mutations for targeted therapy. Varying types of p53 mutant proteins exist with different implications for chemo sensitivity. Some mutations are relatively inconsequential from the perspective of p53 function, and proteins of this type retain wild type activity. Other mutations are loss of function (LOF) or p53-null in which single amino acid changes completely inactivate or destabilize the protein. Another category is the gain of function (GOF) or "oncogenic" TP53 mutations that convert p53 from a tumor suppressor to an oncogene. Oncogenic p53 mutations predict for poor response to treatment [4]. Using stringent criteria to define oncogenic

TP53 mutations, 21.2% of patients in the TCGA cohort have an oncogenic p53 mutation, whereas 18.9% are LOF [5].

In response to chemotherapy, cancer cells with wild-type p53 activate G1/S checkpoint by inducing p21 Cdkn1a /Cip1/Waf1. Cancer cells with TP53 LOF mutations or p53-null are sensitive to tyrosine kinase inhibitors gefitinib or BIBF1120 combination with paclitaxel [6,7]. BRCA1 and BRCA2 mutations are actionable genetic mutations in ovarian cancer. The PARP inhibitor olaparib has been approved as a mono therapy for recurrent ovarian cancer patients with BRCA1/2 mutations who have had three prior chemotherapy treatments [8]. The p53-reactivating compound APR-246 is currently investigated in ovarian cancer clinical trial (Aprea AB, 2014) [9]. Avastin (bevacizumab), a recombinant humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF), is another recently approved targeted agent in combination with carboplatin and paclitaxel for the treatment of patients with recurrent ovarian cancer resistant to platinum by the FDA [10]. Synthetic lethal studies will provide more treatment options to help circumvent acquired and de novo chemo resistance.

Overcome resistance to standard chemotherapy by targeting WEE1 is a promising therapeutic strategy. Entry into mitosis is regulated by the CDK1/cyclin B complex, whose activity is regulated by kinase WEE1 and MYT1, and phosphatase CDC25. WEE1 gene is overexpressed in cancer cells. WEE1 inhibition leads to forced CDK1 activation and inhibition to HR repair [11]. H3K36me3-deficient is identified as a potential actionable mutation biomarker for WEE1 inhibitor AZD1775 single drug treatment [12]. The target of this synthetic lethal interaction is the ribonucleotide reductase subunit RRM2. H3K36me3 facilitates RRM2 expression through transcription initiation factor recruitment and WEE1 inhibition degrades RRM2 through untimely CDK1 activation. WEE1 inhibition in H3K36me3-deficient cells results in RRM2 reduction, dNTP depletion, S-phase arrest, and apoptosis. Cancer cells with low MYT1

*This work was supported by NIH R01CA184101 (XM, KKL).

expression is sensitive to AZD1775, indicating that low MYT1 is another potential response marker for AZD1775 monotherapy [13].

H3K36me3-deficient or low PKMYT1 expression will be promising prediction biomarkers for Wee1 targeted therapy. Proteomic analysis for targets of AZD1775 indicates that PLK1 is another critical target for inhibiting tumor growth in addition to Wee1 [12,13]. AZD1775 can stimulate early mitotic entry in cancer cells by overriding cell cycle G2/M checkpoint, delay mitotic exit by targeting PLK1 and impair homologous recombination. AZD1775 has shown effect in ovarian cancer cells with wild type BRCA genes when combined with PARP inhibitor olaparib in preclinical study [14]. WEE1 inhibitor AZD1775 and WEE1 siRNA have been confirmed to increase sensitivity to cisplatin and gemcitabine by overriding G2/M checkpoint to allow cancer cells with defect of DNA replication inappropriately entrance to mitosis and cause mitotic catastrophe [15]. Novel synergistic and efficacious combination of AZD1775 with the mTOR inhibitor (ridaforolimus) was identified by a high-throughput platform [16]. AZD1775 in combination with chemotherapy is investigating in several clinical trials. Various preclinical and clinical studies showed that increasing sensitivity to chemotherapy was achieved with AZD1775 [17,18]. Promising combination schedules are currently being investigated, e.g. combining AZD1775 with Gemcitabine, Carboplatin or PARP inhibitor.

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DOI: [10.19080/IJCSMB.2017.03.555614](https://doi.org/10.19080/IJCSMB.2017.03.555614)

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