CHEMOSENSITIZATION TO CARBOPLATIN AND PACLITAXEL BY IAP INHIBITOR DEBIO 1143 IN OVARIAN CANCER CELL LINES: SIGNATURE IDENTIFICATION FOR POTENTIAL PATIENT STRATIFICATION

INTRODUCTION

Resistance to apoptosis is a typical hallmark of cancer. Inhibition of Apoptosis Proteins (IAP) block caspase activation, evade Wnt/β-catenin signaling, and are involved in resistance to standard chemotherapeutic agents. IAP inhibitors such as Debio 1143 can reverse this effect and lead to apoptosis (Figure 1). A phase II trial of IAP inhibitor Debio 1143 in combination with standard of care chemotherapy was recently completed, with signs of activity observed in patients with heavily pretreated epithelial ovarian cancer (SOC).

This study assessed the potential of Debio 1143 to sensitize to paclitaxel in in vitro models of human SOC, and provides a basis for the identification of biomarkers for response in a combination therapy setting.

MATERIALS AND METHODS

Figure 2: Methods and Results Workflow

High-throughput drug combination screening at 48 ovarian cancer cell lines was performed at Horizon Discovery using 48-well plate format. Sensitization to paclitaxel and carboplatin was determined using a clonogenic assay. For each agent, IC50s were calculated, and synergy cutoffs based on the observed distribution were selected to evaluate combinations (Table 1). The cell line drug combination sensitivities are shown in Figure 3. Figure 4 shows the synergy scores for the combinations that were sensitive to paclitaxel or carboplatin, and indicates that several lines were found to have a synergistic effect (Figure 4). Genomic data from in vitro sensitization to paclitaxel and carboplatin was acquired using a biochemistry approach and was derived from libraries by combining response and gene expression data from the cell lines with data from the Cancer Cell Line Encyclopedia.

Figure 3: Single agent IC50 distribution – Debio 1143 and SOCs

Table 1: Number of cell lines with available genomic data in the platform used for genomic analysis

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Number of Genomic Data</th>
<th>Avg.</th>
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<tbody>
<tr>
<td>Debio 1143</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>9</td>
<td>5</td>
</tr>
</tbody>
</table>

Figure 4: Synergy Score for Growth Inhibition

The synergy scores for combination were calculated by Chacolet Analysis using growth inhibition (SI).

SYNERGY AND SENSITIZATION

Figure 5: Example of a sensitization

1. Sensitization to paclitaxel and/or carboplatin viability was calculated for Debio 1143 combined with paclitaxel (log(C Carboplatin) vs. log(IC50 Debio 1143)), with a cut-off of 20% sensitization in comparison to single-agent IC50 values (Figure 5).

CONCLUSIONS

Prognostic in vitro data of response to Debio 1143, SOC (carboplatin and paclitaxel) and their combinations was acquired in 48 ovarian cancer cell lines using a drug combination sensitivity to Debio 1143 in about a quarter of the cell lines, suggesting that Debio 1143 is a good candidate for combination with 50-70% SOC.

A signature based on genomic expression was derived from in vitro data of response and was subsequently validated in patient samples from clinical Phase I trial. This confirms potential clinical relevance for selection of responsive patients, and will be verified in an ongoing Phase II trial in view of patient selection.

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