SYD985 Synergizes with PARP Inhibitors (PARPi) in Human Tumor Cell Lines and Patient-Derived Xenografts (PDxS)


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INTRODUCTION

SYD985 is a HER2 targeting antibody-drug conjugate (ADC) comprised of a degradable linker and the produg duocarmycinate, which, upon release, spontaneously rearranges to form the active toxin duocarmycin. Duocarmycine analogues, DUBA covalently binds adenine residues in the DNA spontaneously rearranges to form the active toxin DUBA, a synthetic PARP trapping, i.e. the formation of non-covalent protein–DNA adducts and/or inhibition of fork degradation. The cytotoxicity of PARPi depends on PARP trapping, i.e. the formation of non-covalent protein–DNA adducts composed of inhibited PARP bound to DNA lesions of cleaved and uncleared PARP1 bound to DNA lesions of clear and unclear activity in HER2-negative cells. SYD985 showed potent anti-tumor activity in clinical studies, including HER2 positive and HER2 low expressing breast cancer and is currently in a Phase III trial in HER2-positive metastatic breast cancer (TULIP trial) as stand-alone therapy in last line.

IN VITRO STUDIES

Tumor cell lines were from breast (BT-474, AU-565, UACC-893) or ovarian (TOV-112D, NIH:OVCAR-3) origin. Cytotoxicity was established by measuring DNA content of living cells (CyQUANT assay) and by measuring metabolic activity of cells ( PrestoBlue assay). For both PARPi the highest non-cytotoxic concentration for each tumor cell line was established. This concentration was subsequently used to measure the potential potency shift of the SYD985 concentration-response curve by means of comparing SYD985 IC50 values in the absence and presence of PARPi. PARPi-induced fold change in IC50 was selected for each tumor cell line in two to three independent experiments, each experiment performed in triplicate.

In vitro SYD985 concentration-response curves for niraparib (A) and olaparib (B) are shown in figure 1. In these cell lines, niraparib co-treatment reveals a biphasic concentration-response curve to SYD985 in both PrestoBlue and CyQUANT assays (figure 1). This is in line with the fact that BT-474 cells express high levels of HER2 and are known to respond to naked trastuzumab at concentrations slightly above those of SYD985.

In a breast cancer PDX mouse clinical trial in immunodeficient mice that lack carboxylesterase 1c (Ces1c) we studied the combination of SYD985 (1 mg/kg, IV, SD) and niraparib (40-50 mg/kg Q1DX21, PO) or olaparib (50 mg/kg Q1DX21, IP). In order to be able to detect potential additive and/or synergistic effects of SYD985 and the PARPi, a suboptimal dose of SYD985 (1 mg/kg) was selected based on observations in previous studies. PARPi doses were chosen which are known to inhibit tumor growth in tumors with a defective DNA repair mechanism. These data clearly show that the combination of SYD985 and PARPi is more effective in tumor volume reduction in a selection of mostly HER2-negative breast cancer PDxs than the respective monotherapies alone (figures 2 and 3).

REFERENCES


IN VIVO STUDIES

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CONCLUSION

SYD985 synergizes with PARPi niraparib and olaparib in killing HER2-high and HER2-low expressing human tumor cell lines in vitro. In vivo such synergistic activity translates in improved inhibition of tumor growth of various breast cancer PDxs. These data warrant further clinical studies. A combination study of SYD985 plus niraparib will start later this year.

Table 1

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Niraparib</th>
<th>Olaparib</th>
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<tbody>
<tr>
<td>Conc. (µM)</td>
<td>PrestoBlue</td>
<td>CyQUANT</td>
</tr>
<tr>
<td>Conc. (µM)</td>
<td>PrestoBlue</td>
<td>CyQUANT</td>
</tr>
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<td>BT-474</td>
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</tr>
<tr>
<td>AU-565</td>
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<td>7.5</td>
</tr>
<tr>
<td>TOV-112D</td>
<td>1</td>
<td>7.5</td>
</tr>
<tr>
<td>NIH:OVCAR-3</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>UCSC-609</td>
<td>1</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* Intersection: not enough data to conclude on a potency shift for olaparib in NIH:OVCAR-3 cells.

Figure 1

In vitro SYD985 concentration-response curves for niraparib (A) and olaparib (B). Dashed vertical lines indicate IC50 for SYD985 in absence (black) and presence (red) of a non-cytotoxic concentration of niraparib for ovarian TOV-112D and breast BT-474 tumor cells. Large dash (·) horizontal red lines indicate the survival of cells at the non-cytotoxic concentration of niraparib used in that particular study. Small dash (···) horizontal red lines indicate the survival of cells at the non-cytotoxic concentration of olaparib used in that particular study. Small dash (···) horizontal red lines indicate the survival of cells at the non-cytotoxic concentration of olaparib used in that particular study.

Figure 2

In vivo responses to SYD985 ± PARPi. In a mouse clinical trial setting olaparib improves the response to a single 1 mg/kg dose of SYD985 in PDX models of breast cancer.

Figure 3

In vivo responses to SYD985 ± PARPi. In a mouse clinical trial setting olaparib improves the response to a single 1 mg/kg dose of SYD985 in PDX models of breast cancer.