Abstract # 4633

EZN-3042, a novel locked nucleic acid oligonucleotide specifically inhibits survivin expression and confers Taxol sensitivity

Puja Sapra, Jennifer Malaby, Mary Mehlig, Maoliang Wang, Baisong Liao, Krishnan Subbiah, Lee M. Greenberger, Yixian Zhang, Ivan D. Horak
Enzon Pharmaceuticals Inc., Piscataway, NJ

email: puja.sapra@enzon.com

Introductions

Survivin plays a pivotal role as a functional checkpoint for both mitosis and apoptosis (Figure 1A) in cancer cells. Since survivin is highly and selectively expressed in numerous cancers and linked to poor clinical outcome [1,2], survivin is considered one of the most promising cancer targets [3]. A potent, specific locked nucleic acid antisense oligonucleotide (LNA-ON) EZN-3042, has been identified [4] that down-regulates survivin mRNA and protein expression in cancer cells.

Objective

The objective of this study was to evaluate the efficacy of EZN-3042 in vitro and in human cancer xenograft animal models, including a chemo-sensitizer (CC(3)-induced liver regeneration model.

Inhibition of survivin expression and cell growth

EZN-3042 demonstrated potent in vivo knockdown of survivin mRNA by qRT-PCR and growth inhibition by MTS assay in several transfected tumor cell lines (Table 1).

Figure 5A. Figure 5B. Figure 5C.

A representative figure in A549 cells is given below (Figure 3: A-B):

Table 1

<table>
<thead>
<tr>
<th>Oligonucleotide</th>
<th>Growth inhibition (IC50 nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EZN-3042</td>
<td>8</td>
</tr>
<tr>
<td>EZN-3046</td>
<td>18</td>
</tr>
<tr>
<td>Saline</td>
<td>60</td>
</tr>
<tr>
<td>Taxol</td>
<td>80</td>
</tr>
</tbody>
</table>

Conclusions

1) EZN-3042 displayed potent and specific in vivo knockdown of survivin mRNA (IC50 <8 nM) and growth inhibition of several human cancer cell lines (IC50 <8 to 16 nM).
2) Treatment with EZN-3042 as a single agent or in combination with Taxol® induced growth and improved survival in cancer xenograft models.
3) In a liver regeneration model, treatment with SPC-3836, the murine homolog of EZN-3042, resulted in potent and specific knockdown of survivin mRNA.
4) EZN-3042 is a potent and selective LNA–RNA antagonist of survivin in preclinical models and optimal dose and schedule will be identified in an ongoing clinical trial.

References and Acknowledgements

5) For further details on LNA technology see Poster #4630.

For additional information on Enzon's LNA technology, see Poster #4630.