CLR 180099, a lipid raft targeted phospholipid-drug conjugate, shows potent improved safety and efficacy against colorectal tumors

Longcor J, Hoover R, Pinchuk A
Celloctar Biosciences, Inc.

INTRODUCTION

CLR 180099 is a phospholipid drug conjugate (PDC) composed of a uniquely designed phospholipid after conjugated to a flavagline (FLV) analogue via a cleavable linker. FLVs are potent cytotoxins that inhibit translation, cell cycle progression and induce apoptosis.

AIM OF THIS STUDY

Characterization of the in vitro uptake, release and cytotoxicity, in vivo efficacy, maximum tolerated dose (MTD) and pharmacokinetics (PK) of CLR 180099.

Materials & Methods

In vitro uptake and release was assessed using A549 tumor cell line and normal human dermal fibroblasts (NHDF) cells and measured via LC/MS/MS. Cells were incubated with 1 uM of drug and reported and normal human dermal fibroblasts (NHDF) cells and measured via cytotoxicity was determined by Cell Titer-Glo® assay.

Tumor volume was monitored for efficacy and body weight for tolerability.

In vivo efficacy was assessed in athymic nude mice bearing HCT 116 xenografts. Two doses (2 mg/kg given 2 times or 2 mg/kg given 3 times) of CLR 180099 were assessed. Each group contained 10 mice.

Study was initiated when group mean tumor volume reached ~120 mm3 (Day 1). CLR 180099 was dosed iv at 2 mg/kg on either day 1 and 4 or day 1, 3 and 5. Docetaxel was dosed at 10 mg/kg on day 1 and 4. CLR 180099 demonstrated similar or better reduction in tumor volume than docetaxel and demonstrated dose dependent effect. Docetaxel arm experienced multiple deaths starting day 18 and ending day 26.

In vivo pharmacokinetic data was collected from 5 mice per group. Both PDCs were tolerated up to dose of 10 mg/kg with all mice alive and showing no end organ toxicities. The Payload alone was not tolerated at doses above 0.5 mg/kg as all mice died at 0.3 mg/kg.

CONCLUSIONS

• CLR 180099 demonstrates significant uptake and release of payload (~40% of exposed drug) in tumor cell lines while minimal uptake occurs in normal cells.
• CLR 180099 shows potent in vitro activity against various solid tumors, including lung cancer (A549), breast cancer (MCF7), and melanoma (A375), as well as other tumor types (data not shown).
• In vivo two or three doses of CLR 180099 showed similar or better activity to docetaxel in colorectal cancer. Additionally, CLR 180099 demonstrated significantly improved survival benefit at both doses as compared to docetaxel.
• Tolerability assessment demonstrated that CLR 180099 was well tolerated in both tumor bearing and normal animals. The FLV payload was toxic in both normal and bearing mice.
• CLR 180099 showed no toxicity as compared to the FLV analogue payload alone demonstrating that this payload would benefit from targeted delivery with a phospholipid ether (PLE).
• Together these data demonstrate the potent in vitro and in vivo activity of CLR 180099 against a series of solid tumors and warrants the continued development of this PDC.

Table 1: in vivo tolerability

<table>
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<tr>
<th>Compound</th>
<th>MTD (mg/kg)</th>
<th>Day 1</th>
<th>Day 4</th>
<th>5</th>
<th>10</th>
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<tbody>
<tr>
<td>Docetaxel</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FLV</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
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<td>CLR 180099A</td>
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<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>CLR 180099B</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

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Figure 1: Characterization of uptake and release of CLR 180099A and CLR 180099B in A549 and NHDF cells.

Figure 2: in vitro uptake in A549 and NHDF of CLR 180099A and CLR 180099B.

Figure 3: in vitro Release of Payload in A549.

Figure 4: in vitro cytotoxicity of CLR 180099A in lung cancer, breast cancer and melanoma.

Figure 5: in vivo antitumor efficacy in implanted colorectal cancer xenograft model.

Figure 6: Kaplan-Meier survival curve in colorectal cancer xenograft model.

Figure 7: Kaplan-Meier curve shows that treatment with CLR 180099 at 2 mg/kg day 1 and 4 or day 1, 3, and 5 resulted in significant increase in survival as compared to docetaxel (log-rank test, p ≤ 0.01).