Marked therapeutic efficacy of a novel poly(ethylene-glycol) conjugated SN38 conjugate in xenograft models of breast and colorectal cancers

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Abstract # 145

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Therapeutic efficacy

SN38 (10-hydroxy-7-ethyl-camptothecin) is the active moiety of CPT-11 (Camptosar®). The clinical utility of SN38 has been severely limited due to its poor solubility. We have generated a novel water soluble conjugate, PEG-SN38 (EZN-2208), by linking SN38 with a multi-arm high molecular weight polyethylene-glycol (PEG). EZN-2208 conjugates is readily soluble and has in vivo potency equivalent to that of the free drug on a panel of tumor cell lines. Here we evaluate the pharmacokinetics and therapeutic efficacy of EZN-2208 in xenograft models of human breast, colorectal and pancreatic cancers.

Test compound (EZN-2208)

EZN-2208 is a novel water soluble prodrug of SN38, generated by conjugating SN38 to multi-arm PEG (4-arm-PEG) via a glycine linker. EZN-2208 is readily soluble in saline (180 mg/ml). (For details on synthesis of compounds, refer poster #154).

In MX-1 xenografts, treatment with either a single dose of 20 mg/kg or multiple doses of 5 mg/kg (q2d x 5) EZN-2208, led to 100% tumor growth inhibition and complete cures of all the animals. At equivalent dose levels, treatment with CPT-11 caused a 26 and 44% tumor growth inhibition when given as a single dose or multiple injections, respectively.

In HT-29 (colorectal) and MiaPaCa-2 (pancreatic) xenograft models, EZN-2208 demonstrated significantly better therapeutic efficacy than CPT-11 at their respective MTDs as well as equivalent dose levels.

In vivo cytotoxicity (IC₅₀ μM)

In MX-1 xenografts, mice were dosed with lower doses than MTDs both for EZN-2208 and CPT-11. As controls, mice received CPT-11 at its MTD and equivalent dose level as EZN-2208. In MX-1 model, mice were dosed with lower doses than MTDs both for EZN-2208 and CPT-11.

In HT-29 and MiaPaCa-2 models, mice received EZN-2208 at its maximum tolerated dose (MTD). As controls, mice received CPT-11 at its MTD and equivalent dose level as EZN-2208. In MX-1 model, mice were dosed with lower doses than MTDs both for EZN-2208 and CPT-11.

In vitro cytotoxicity (IC₅₀ μM)

Maximum tolerated dose in nude mice

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose level (mg/kg)</th>
<th>Survival/Total</th>
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<tbody>
<tr>
<td>EZN-2208</td>
<td></td>
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<tr>
<td>Single dose</td>
<td>10</td>
<td>10/10</td>
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<tr>
<td>Multiple doses</td>
<td>5</td>
<td>5/5</td>
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<tr>
<td>CPT-11</td>
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<tr>
<td>Single dose</td>
<td>10</td>
<td>10/10</td>
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<tr>
<td>Multiple doses</td>
<td>5</td>
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</tbody>
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Conclusions

1) EZN-2208 (PEG-SN38) is a novel water soluble prodrug of SN38 for direct parental applications
2) EZN-2208 displayed potent in vitro cytotoxicity against a panel of human cancer cell lines
3) EZN-2208 demonstrated excellent antitumor activity in xenograft models of human breast, colorectal and pancreatic cancer
4) Treatment with a single or multiple small doses of EZN-2208 led to complete cures of animals in MX-1 (breast) xenograft model
5) In HT-29 (colorectal) and MiaPaCa-2 (pancreatic) xenograft models, EZN-2208 demonstrated significantly better therapeutic efficacy than CPT-11 at their respective MTDs as well as equivalent dose levels.
6) In naive (tumor-free) mice, EZN-2208 provided a long circulation half-life and exposure to the parent drug, SN38.
7) EZN-2208 has demonstrated excellent preclinical properties that merit its further evaluation in the clinic.

Refer Abstract #154 for chemistry and in vitro properties of EZN-2208.