Pharmacogenomic and Pharmacokinetic Assessment of Liposome Encapsulated SN-38 (LE-SN38) in Advanced Cancer Patients

Irinotecan (CPT-11)

- Topoisomerase I inhibitor
- Significant anticancer activity
- Prodrug hydrolized to active metabolite SN-38
  - Conversion rate ~3-12%
SN-38

- *In vitro* ~250-1000x more cytotoxic than CPT-11 against tumor cell lines
- Poorly soluble
  - Delivery requires use of prodrug CPT-11
SN-38 Metabolism

• Metabolized to inactive SN-38G by hepatic enzyme UGT1A1
• Enzyme promoter polymorphisms
  – ↓ UGT1A1 expression
  – ↑ neutropenia and diarrhea after CPT-11 administration

UGT1A1 = uridine diphosphate glucuronosyltransferase isoform 1A1
**UGT1A1*28 Variants Decrease SN-38 Glucuronidation**

**WT/WT**

**WT/*28**

***28/*28**

**UGT1A1**

**SN-38**

**β-glucuronidase**

**SN-38 G**
**UGT1A1*28 Variants Increase SN-38 AUC**

Average SN-38 AUC after 300 mg/m² CPT-11:

- **WT/WT:** 205.13 ng·hr/mL
- **WT/*28:** 288.61 ng·hr/mL
- ***28/*28:** 531.37 ng·hr/mL


Iyer et al. 2002 *Pharmacogenomics J.* 2:43-47
LE-SN38

- Novel liposomal formulation
  - Overcomes poor solubility of SN-38
- Drug entrapment >95%
- Broader antitumor activity than CPT-11 in preclinical models
Phase I Study of LE-SN38 in Advanced Cancer Patients

- Pharmacogenomics
- Pharmacokinetics
- Safety
- Antitumor activity
Inclusion Criteria

• Patients with advanced solid tumors
• ECOG PS 0-2
• Laboratory values:
  – ANC $\geq$ 1,500/mm$^3$
  – Platelets $\geq$ 100,000/mm$^3$
  – Hgb $\geq$ 9 g/dL
  – Creatinine $\leq$ 2.0 mg/dL
  – Bilirubin $\leq$ 2.0 mg/dL
  – ALT and AST $\leq$ 1.5x ULN
Exclusion Criteria

- Known CNS metastasis
- On agents interfering with SN-38 metabolism
- Known HIV infection
- Pregnant or nursing
LE-SN38 Phase I Study Design

UGT1A1 Genotype Screening

- WT/WT
- WT/*28
- *28/*28

90 min infusion q 3 weeks until progression or toxicity

Determine MTD for each genotype
Dose-limiting Toxicity

- Neutropenia Gr 4 for ≥3 days, Gr 3 + fever
- Thrombocytopenia Gr 4, Gr 3 for ≥7 days
- Diarrhea Gr ≥3 for ≥24 hours despite treatment
- Nausea/vomiting Gr ≥3 for ≥24 hours despite treatment
- Hepatic transaminase Gr 4, Gr 3 for ≥7 days
- Infusion-related reaction Gr ≥3, Gr 2 + broncospasm
### Dose Escalation Plan

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>Increment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
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<tr>
<td>10</td>
<td>100</td>
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<td>20</td>
<td>100</td>
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<tr>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>62.5</td>
<td>25</td>
</tr>
<tr>
<td>75</td>
<td>20</td>
</tr>
<tr>
<td>90</td>
<td>20</td>
</tr>
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</table>

Current dose: *28/*28
**UGT1A1 Genotyping Results**

- **WT/WT**: 43%
- **WT/*28**: 45%
- ***28/*28**: 10%
- **Other**: 2%

*n = 144 Screened*
## Patient Characteristics

(n=56)

<table>
<thead>
<tr>
<th></th>
<th>WT/WT</th>
<th>WT/*28</th>
<th>*28/*28</th>
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<tbody>
<tr>
<td>Enrolled</td>
<td>28</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>13</td>
<td>12</td>
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<tr>
<td></td>
<td>Female</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Age</td>
<td>Median</td>
<td>60.5</td>
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</tr>
<tr>
<td></td>
<td>Range</td>
<td>40-75</td>
<td>40-84</td>
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<tr>
<td>ECOG PS</td>
<td>0-1</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Prior Chemos</td>
<td>0-3</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>≥4</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Tumor Type</td>
<td>Number of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WT/WT</td>
<td>WT/*28</td>
<td>*28/*28</td>
</tr>
<tr>
<td>Colorectal</td>
<td>10</td>
<td>3</td>
<td>--</td>
</tr>
<tr>
<td>Lung</td>
<td>4</td>
<td>6</td>
<td>--</td>
</tr>
<tr>
<td>Breast</td>
<td>4</td>
<td>2</td>
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<tr>
<td>Pancreatic</td>
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<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Thyroid</td>
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<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Melanoma</td>
<td>--</td>
<td>3</td>
<td>--</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>9</td>
<td>2</td>
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</table>
## DLTs by Dose Level

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>DLTs / No. of Pts</th>
<th>WT/WT</th>
<th>WT/*28</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>0/3</td>
<td>0/4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1/6</td>
<td>0/6</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0/3</td>
<td>0/4</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0/3</td>
<td>0/4</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0/6</td>
<td>0/6</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>*2/5</td>
<td>0/3</td>
<td></td>
</tr>
</tbody>
</table>

*One patient with a DLT had received 9 prior regimens*
All Adverse Events WT/WT Patients

Number of AEs

Grade 1

Grade 2

Grade 3

Grade 4

Grade 5

Dose (mg/m²)

2.5 (n=3)

5 (n=6)

10 (n=3)

20 (n=4)

30 (n=6)

40 (n=5)
## Most Frequent AEs Regardless of Attribution

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of Patients</th>
<th></th>
<th></th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WT/WT n=28</td>
<td>WT/*28 n=25</td>
<td>*28/*28 n=3</td>
<td>n=56</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>15</td>
<td>3</td>
<td>32 (57%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13</td>
<td>12</td>
<td>2</td>
<td>27 (48%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>12</td>
<td>2</td>
<td>27 (48%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>5</td>
<td>1</td>
<td>22 (39%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
<td>8</td>
<td>1</td>
<td>20 (36%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>6</td>
<td>8</td>
<td>2</td>
<td>16 (29%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>15 (27%)</td>
</tr>
<tr>
<td>Cough</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td>12 (21%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>12 (21%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>11 (20%)</td>
</tr>
</tbody>
</table>
SN-38 Plasma PK - WT/WT Pts
2.5 to 40 mg/m² LE-SN38

SN-38 Plasma PK - WT/WT Pts
2.5 to 40 mg/m² LE-SN38

SN-38 (ng/mL)

Time (Hrs)

40 mg/m² (n=2)
30 mg/m² (n=3)
20 mg/m² (n=3)
10 mg/m² (n=3)
5 mg/m² (n=6)
2.5 mg/m² (n=3)
SN-38 Plasma PK By Genotype
10 mg/m² LE-SN38
SN-38 Plasma AUC By Genotype
10 mg/m² LE-SN38

AUC 0-48hrs (ng*hr/mL)
AUC 0-∞ (ng*hr/mL)

AUC (ng*hr/mL)

WT/WT  WT/*28  *28/*28

373  684  1098
393  711  1369
SN-38 & SN-38G Plasma PK
10.0 mg/m² LE-SN38

WT/WT Patients
(n=3)

*28/*28 Patients
(n=3)
LE-SN38 Summary

- Multiple cycles safely administered with >35% of patients receiving >2 cycles
- Dose-limiting toxicity of neutropenia
- No severe diarrhea observed
- SN-38 AUC in WT/WT < WT/*28 < *28/*28
- PK profile of SN-38 and SN-38G altered in *28/*28 patients
- No apparent PK/PD safety correlation for WT/WT and WT/*28 patients to date
Next Steps

• Dose escalation continues in patients with \( \leq 3 \) prior chemotherapy regimens
• Phase II planning underway
  – SCLC (NCCTG)
  – NSCLC (NeoPharm)
  – CRC (CALGB)
Participants

- **Study Centers**
  - Ohio State University, Columbus, OH
  - H. Lee Moffitt Cancer Center, Tampa, FL
  - Karmanos Cancer Institute, Detroit, MI

- **PK Collaborator**
  - Cognigen Corp., Buffalo, NY

- **Pharmaceutical Sponsor**
  - NeoPharm, Inc., Lake Forest, IL