Phase 1 study of safety and tolerability of Selinexor in Asian patients with advanced solid cancers

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Selective Inhibitors of Nuclear Export (SINE)

- Tumor Suppressor Proteins (TSPs) exert anti-neoplastic effects in the nucleus.

- Cancer cells can inactivate TSPs via the nuclear export mechanism.

- Exportin 1 (XPO1) is the nuclear exporter of most TSPs.

- Blockade of XPO1 leads to nuclear retention and activation of multiple TSPs and reduced translation of key oncogenes (myc, BCL2/BCL6).

- Selinexor is a covalent, oral selective inhibitor of nuclear export against XPO1.

- First in class Asian patients, phase 1 study.
Study design

• Objectives
  • Primary: Safety, tolerability and Recommended Phase 2 Dose (RP2D) of selinexor in Asian patients with solid tumour and lymphoma
  • Secondary: Pharmacokinetics (PK), pharmacodynamics (PDn), anti-tumor response

• Modified 3+3 design

• Major eligibility criteria:
  • Advanced or metastatic solid tumour and lymphoma
  • ECOG 0-1
  • Documented progression at study entry
  • Stable brain metastases permissible
Treatment schedules

**Schedule 1 (S1):**
- Twice weekly continuous 28 day cycle at 40 mg/m²
- S1 was stopped due to persistent drug-related adverse events (AEs) – two additional schedules were subsequently explored:

**Schedule 2 (S2):**
- Once weekly for a 28 day cycle, starting at 50 mg/m²

**Schedule 3 (S3):**
- Twice weekly for 2 weeks of a 21 day cycle, starting at 40 mg/m²

**DLT criteria**

- Discontinuation of a patient due to toxicity in cycle 1
- Non Hematologic: Gd ≥3 (nausea/vomiting, diarrhea, fatigue > 5 days, AST/ALT > 7 days, electrolyte abnormalities despite adequate supplements)
- Hematologic: Gd 4 neutropenia ≥ 7 days, febrile neutropenia, Gd 4 thrombocytopenia ≥ 5 days or Gd 3 associated with bleeding
Patient demographics and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>60 (25 – 76)</td>
</tr>
<tr>
<td>Male /Female</td>
<td>25 /15</td>
</tr>
<tr>
<td>Median prior lines of treatment (range)</td>
<td>4 (1 – 9)</td>
</tr>
<tr>
<td>ECOG performance status, 0/1</td>
<td>22/18</td>
</tr>
</tbody>
</table>

Disease site
- Colorectal                                        | 15           |
- Lymphoma                                          | 7            |
- Lung                                              | 4            |
- Pancreas                                          | 4            |
- Head & Neck                                       | 3            |
- Ovarian                                           | 2            |
- Liver                                             | 2            |
- Other (esophagus, thymic, RCC, sarcoma)           | 4            |
### Dose levels, DLT and MTD

#### Schedule 1: Twice a week continuous schedule

<table>
<thead>
<tr>
<th>Dose Level (mg/m²)</th>
<th>DLT Evaluable Patients (n=6)</th>
<th>Pts with DLT</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>6</td>
<td>1</td>
<td>G3 diarrhea</td>
</tr>
</tbody>
</table>

Ceased due to chronic, persistent drug related toxicity

#### Schedule 2: Once weekly continuous

<table>
<thead>
<tr>
<th>Dose Level (mg/m²)</th>
<th>DLT Evaluable Patients (n=12)</th>
<th>Pts with DLT</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>60</td>
<td>3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>70</td>
<td>6 (+4)</td>
<td>1/6 + (0/4)</td>
<td>G3 fatigue &gt; 5 days</td>
</tr>
</tbody>
</table>

#### Schedule 3: Twice a week, 2 out of 3 weeks

<table>
<thead>
<tr>
<th>Dose Level (mg/m²)</th>
<th>DLT Evaluable Patients (n=9)</th>
<th>Pts with DLT</th>
<th>DLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>3</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>50</td>
<td>6 (+4)</td>
<td>1/6 + (1/4)</td>
<td>G3 N/V; G3 fatigue &gt; 5 days</td>
</tr>
</tbody>
</table>
## Most common treatment-related AEs

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>All (N=40) N (%)</th>
<th>Schedule 1 (twice weekly continuous)</th>
<th>Schedule 2 (weekly continuous)</th>
<th>Schedule 3 (twice a week 2 out of 3 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>40mg/m² (n=6)</td>
<td>50mg/m² (n=3)</td>
<td>60mg/m² (n=3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ Grade 3 N(%)</td>
<td>≥ Grade 3 N(%)</td>
<td>≥ Grade 3 N(%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (82.5)</td>
<td>2 (33.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (42.5)</td>
<td>0</td>
<td>0</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>25 (62.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (30.0)</td>
<td>0</td>
<td>0</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>10 (25.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (27.5)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (27.5)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>10 (25)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>30 (75)</td>
<td>5 (83.3)</td>
<td>0</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3 (7.5)</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypomagnesiemia</td>
<td>11 (27.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (5.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Plasma Pharmacokinetics: Mean ± SD plasma selinexor concentration vs. time following oral administration at 40 - 60 mg/m² to Asian patients with solid tumor malignancies, Day 1

Plasma PK:
- Median $T_{\text{max}}$ values of 1 – 4 hours, followed by a more prolonged distribution phase,
- Dose proportional increases in exposure, and rapid elimination with a mean $t_{1/2}$ of ~6 hours.
- No plasma KPT-330 accumulation following repeated oral administration over a dose range of 40 – 60 mg/m² in a twice-weekly regimen for up to 8 weeks.
Tumour Pharmacodynamics: Reduced proliferation and increased nuclear staining of XPO1 cargos and major tumor suppressor proteins post selinexor treatment

**Ki67**
- Baseline: Pt. 023, Lymphoma
- Post-Selinexor: Pt. 023, Lymphoma

**Cleaved caspase 3**
- Baseline: Pt. 011, CRC
- Post-Selinexor: Pt. 011, CRC

**P27**
- Baseline: Pt. 011, CRC
- Post-Selinexor: Pt. 011, CRC

**Apoptag**
- Baseline: Pt. 019, Thymoma
- Post-Selinexor: Pt. 019, Thymoma

**FAS**
- Baseline: Pt. 012, Lung CA
- Post-Selinexor: Pt. 012, Lung CA

**P53**
- Baseline: Pt. 012, Lung CA
- Post-Selinexor: Pt. 012, Lung CA
Clinical activity: best tumour response and duration of best response

Percentage change in size of target lesion from baseline at best response (n=34 evaluable)

- Duration of best response for PR and SD (days)

* Treatment ongoing
Biomarker – RAS mutants/ cytoplasmic p27

ORIGINAL ARTICLE
Cytoplasmic p27 is oncogenic and cooperates with Ras both in vivo and in vitro

MP Serres¹,²,³, E Zlotek-Zlotkiewicz¹,²,³, C Concha¹,²,³, M Gurian-West⁴, V Daburon¹,²,³, JM Roberts⁴ and A Besson¹,²,³

¹INSERM UMR1037-Cancer Research Center of Toulouse, Toulouse, France; ²Université de Toulouse, Toulouse, France; ³CNRS ERL5294, Toulouse, France and ⁴Fred Hutchinson Cancer Research Center, Division of Basic Sciences, Seattle, WA, USA
Biomarker – RAS mutants/ cytoplasmic p27

Tumor response for patients with colorectal cancer according to RAS mutation (n=10)

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锺响 percentage of tumor change from baseline (%)

-20 0 20 40 60

Weeks

PD with new lesion  Consent withdrawal

Dual KRAS_G12D and AKT1_G37D mutation
Tumor response for patients with colorectal cancer according to RAS mutation (n=10)

- PD with new lesion
- Consent withdrawal

Dual KRAS_G12D and AKT1_G37D mutation

Biomarker – RAS mutants/ cytoplasmic p27

P27 IHC: Pt 037 with CRC, AKT_G37D and KRAS_G12D mutation treated with selinexor

Hua Chang
Conclusion

• Inhibition of the nuclear-cytoplasmic export pathway is a viable anti-cancer strategy

• XPO1 inhibitor selinexor given weekly or twice weekly is tolerable with manageable toxicities at current escalated dose levels

• Schedule 2 (weekly): Current recommended phase 2 dose (RP2D) at 70 mg/m$^2$
• Schedule 3 (2 x weekly/ 3 weeks): Current RP2D at 50 mg/m$^2$
• 3 times a week at 20 mg/m$^2$ currently being explored → Phase 1b expansion

• Proof of mechanism in peripheral blood cells and tumours

• Promising antitumor activity was observed in Asian patients with highly refractory tumours

• → Predictive Biomarkers: ?p27 cytoplasmic expression
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