**Background**

Localization of p27 within a cell determines its function. Cytoplasmic sequestration of p27 promotes oncogenic activity while its nuclear retention inhibits tumorigenesis. RAS activation in tumours indirectly causes cytoplasmic sequestration of p27 via the activation of its effectors PI3K/AKT and Raf/MEK/ERK pathway. Selinexor is a potent XPO1 inhibitor that forces nuclear retention of multiple proteins including p27 resulting in tumour cell death.

**Aims**

To assess the predictive value of RAS and PI3KCA/AKT/mTOR pathway mutations in tumours following treatment with selinexor

**Methods**

Selinexor was administered orally to patients with advanced solid cancers. The phase 1 dose escalation study was initiated in a 3 + 3 design on:

- **Schedule 1**
  - Twice weekly continuous 28 day cycle at 40mg/m²
- **Schedule 2**
  - Once weekly continuous every 28 days, starting at 50mg/m²
- **Schedule 3**
  - Twice weekly for 2 weeks of a 21 day cycle, starting at 40mg/m²

Patients were screened for ~2,800 COSMIC mutations in 50 cancer genes which included members of the RAS and PI3KCA/AKT/mTOR pathway using the Ion AmpliSeq™ Cancer Hotspot Panel v2

**Tumour PD:**

Nuclear-cytoplasmic localisation of p27 in RAS and/or AKT pathway activated tumours from tumour biopsies pre and post selinexor were determined together with other XPO1 cargo proteins including ki67, apotag, cleaved caspase 3, and c-myc using immunohistochemistry.

**Results**

**Table 1. Patient demographics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>62.5 (58 - 79)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>15/7</td>
</tr>
<tr>
<td>Median prior lines of treatment (range)</td>
<td>3.5 (2 – 9)</td>
</tr>
<tr>
<td>ECOG performance status, 0/1</td>
<td>11/71</td>
</tr>
<tr>
<td>Colon / rectal carcinoma</td>
<td>19/13</td>
</tr>
</tbody>
</table>

**Table 2. Mutations detected in RAS and PI3KCA/AKT/mTOR pathway**

**Clinical activity: best response and duration on study**

**Figure 3: Percentage change in size of target lesion from baseline at best response (n=19 evaluable patients)**

**Figure 4: Tumor response for patients with colorectal cancer according to RAS and PI3KCA/AKT pathway mutation (n=19)**

**Figure 5: Duration on study according to RAS and PI3KCA/AKT pathway mutation (n=19)**

**Figure 6: Increased nuclear retention of p27 and other XPO1 cargos, induction of apoptosis and reduction in proliferation in patients with KRAK mutant colorectal cancer pre and post selinexor treatment**

**Conclusion**

- **RAS and AKT pathway activated CRC appear to have a longer DCR with an increased number of patients achieving DCR of >3 months compared to WT tumours.**
- **Cytoplasmic translocation of p27 could be a key oncogenic mechanism in RAS and/or AKT pathway activated tumours and can be targeted by inhibition of XPO1**
- **Dose expansion cohort ongoing in patients with RAS and PI3KCA/AKT/mTOR pathway mutations in colorectal cancer as well as other solid malignancies**

**References**

1. Tan et al., Cancer Discov: 4(3), S27–37, 2014
3. Chin Cancer Res; 17(1); 12–8. 2010 AACC
4. This study is supported by research grants from Karyopharm Therapeutics, Inc. and the National Medical Research Council Singapore