### Rigosertib Background

**Rigosertib:** PLK-1 & PI3K Pathway Inhibitor

- **Mechanism of action:**
  - PLK-1 inhibitor
  - PI3K inhibitor
- **Cytotoxic to tumor but not to normal cells**
- **PK formulation currently in clinical trials**
- **Effective as single agent and in combination with other chemotherapeutic agents in animal models**
- **Mutational status acquired in 26/36 patients**
  - A hausman test is unrelated to urinary toxicity
- **Mechanisms of action:**
  - Downregulation of c-Myc
  - Induction of apoptosis in tumor cells
- **Bioavailability & Metabolism:**
  - Oral rigosertib is active and well tolerated
  - MTD declared to 560 mg twice daily
  - Further confirmation of the MTD is ongoing
  - Urinary toxicity is dose limiting and independent of urinary and plasma PK
  - A significant number of patients experienced stable disease or a partial response

### Dose Escalation & Treatment Duration

<table>
<thead>
<tr>
<th>Dose Level (mg)</th>
<th>Number Patients</th>
<th>Range of Doses of Treatment (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>3</td>
<td>2-42</td>
</tr>
<tr>
<td>140</td>
<td>2</td>
<td>12-30</td>
</tr>
<tr>
<td>280</td>
<td>1</td>
<td>1-61</td>
</tr>
<tr>
<td>560</td>
<td>1</td>
<td>2-37</td>
</tr>
<tr>
<td>700</td>
<td>1</td>
<td>7-12</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>1-51</td>
</tr>
</tbody>
</table>

### Plasma Pharmacokinetics

- **At 560 mg dosing**
  - AUC (ng-h/ml) = 11875 ± 60ng/ml
  - Cmax (ng/ml) = 5707 ± 50

### Mutational Testing

- **Mutational status acquired in 26/36 pts**
  - 17 completed
  - 2 PXS3A point mutations (both with PK)
  - 19 xs mutations (at study on for 42 PK)
  - 6 in process
  - 1 rejected due to inadequate tissue

### CONCLUSIONS

- **Rigosertib is active and well tolerated**
- **MTD declared to 560 mg twice daily**
- Further confirmation of the MTD is ongoing
- Urinary toxicity is dose limiting and independent of urinary and plasma PK