Characterisation of CCS1477: A novel small molecule inhibitor of p300/CBP for the treatment of castration resistant prostate cancer

Neil Pegg, Nigel Brooks, Jenny Worthington, Barbara Young, Amy Prosser, Jordan Lane, David Taddei, Richard Brown, Gareth Harbottle, Jonathan Shannon, Silvia Paolotta, Karen E. Knudsen

CellCentric Ltd, Cambridge UK; *Axis Bioservices, Coleraine, UK; †Sgnature Discovery, Nottingham UK; ‡The Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, USA

Introduction
- Targeted degradation of androgen receptor (AR) and androgen receptor variant (AR-V) remains an important therapeutic opportunity for patients with castration resistant prostate cancer.
- E1A binding protein (p300) and CBP binding protein (CBP) are two closely related homologous transcriptional co-activators of AR.
- We have developed potent, selective and orally active small molecule inhibitors of the bromodomain of p300/CBP and here report their impact on AR, AR-V and c-Myc expression and function.
- We have also examined their effects in xenograft models of castration resistant prostate cancer as monotherapy and in combination with standard of care agents.

1. CCS1477 potency and selectivity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mean EC50 [nM]</th>
<th>SI</th>
<th>Selectivity</th>
<th>Kd [nM]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCS1477</td>
<td>0.25</td>
<td>175</td>
<td>1/175</td>
<td>3.7</td>
</tr>
</tbody>
</table>

2. Inhibition of in vitro proliferation

3. CCS1477 degrades AR-Rl, AR-SV & c-Myc protein: Including time course of AR-Rl, AR-SV reduction

4. CCS1477 reduces expression of AR-target genes in 22Rv1 cells

5. Good oral exposure in mouse: blood levels exceed 22Rv1 proliferation IC50 for several hours

6. In vivo efficacy in 22Rv1 xenograft: Including continued tumour growth block following drug withdrawal

7. Protein biomarkers are reduced in 22Rv1 tumour bearing animals treated with CCS1477 for 7 and 28 days

8. Plasma PSA is reduced in 22Rv1 tumour bearing animals treated with CCS1477

Conclusions
- Small molecule inhibition of the bromodomain of p300/CBP, leads to down regulation of AR, AR-V and c-Myc, as well as inhibiting key downstream genes, including PSA and TMPRSS2.
- CCS1477, a clinical candidate, causes complete tumour growth inhibition in a 22Rv1 xenograft model at doses which are well tolerated. The tumour growth inhibition caused by CCS1477 is sustained following drug withdrawal.
- CCS1477 is also efficacious in a bilateral castrate-resistant LNCaP xenograft model as monotherapy or in combination with bicalutamide, demonstrating a more sustained effect.
- CCS1477 is a potential first-in-class p300/CBP inhibitor for the treatment of CRPC, and potentially in the future, of tumours harbouring p300 and CBP mutations.