Second generation AR antagonists enzalutamide and apalutamide (AR 509) partially inhibit the wild-type (WT) AR receptor through binding to the ligand binding domain of AR.

Single amino acid mutations of the AR ligand binding domain, including the F876L mutation, may mediate resistance to current second generation AR inhibitors, including enzalutamide, in approximately 10% of cases of metastatic castrate resistant prostate cancer (mCRPC).

The development of potent antagonists of wild-type (WT) AR as well as mutated AR, including F876L mutant AR, is a priority.

METHODS

Small molecule inhibitors were developed by Janssen to bind WT AR and AR containing ligand binding domain mutations. Inhibitors were studied in vitro to determine affinity and quantify antagonism and possible agonism towards WT AR and mutated AR.

Inhibitors were also studied in vivo in xenograft models of prostate cancer cell lines and patient derived tumors containing WT AR and F876L mutated AR.

RESULTS - Pharmacology Studies

Pan-AR Antagonist Potency and Selectivity

<table>
<thead>
<tr>
<th>Compound</th>
<th>JNJ-pan-AR</th>
<th>enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50 (nM)</td>
<td>Ki (nM)</td>
<td>IC50 (nM)</td>
</tr>
<tr>
<td>AR</td>
<td>19</td>
<td>8.4</td>
</tr>
<tr>
<td>GR</td>
<td>20,000</td>
<td>9,900</td>
</tr>
<tr>
<td>ER</td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

Pan-AR Antagonist Inhibits WT AR and Mutant AR Translocation

Xenograft Studies

Agonism

0% 0% 5%* 0% 0%

Pan-AR Antagonist is active in AR F876L-Driven Xenograft Models that are Resistant to Enzalutamide

CONCLUSIONS

A Pan-AR Antagonist has been developed with potential best-in-class properties:

- Potent competitive binder of AR: antagonizes WT AR and all mutations tested (including F876L) without demonstrating agonism
- Inhibits AR translocation, DNA binding and AR dependent proliferation
- Active in F876L driven models that are resistant to enzalutamide
- High oral bioavailability, favorable PK, with low seizure risk (data not shown)
- Companion diagnostic in development to identify F876L AR mutations using circulating tumor DNA

REFERENCES

Janssen Pharmaceuticals, Springhouse, PA; TRACON Pharmaceuticals, Inc., San Diego, CA

Development of a Small Molecule Inhibitor Targeting Androgen Receptor (AR) Mutations Associated with Resistance to Current AR Antagonists

Gilles Bignan, Ian Hickson, James Bischoff, Jonathan Branch, Janine Ondrus, Charles Theuer, Marco Gottardis

Janssen Pharmaceuticals, Springhouse, PA; TRACON Pharmaceuticals, Inc., San Diego, CA