INTRODUCTION

Molecular Activity of TRC253 Determined in Receptor Binding or Reporter Assays

<table>
<thead>
<tr>
<th>Androgen Receptor</th>
<th>IC50 (µM)</th>
<th>Method</th>
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</thead>
<tbody>
<tr>
<td>AR wild type</td>
<td>0.0099</td>
<td>binding assay</td>
</tr>
<tr>
<td>AR-F877L</td>
<td>0.099</td>
<td>Reporter assay</td>
</tr>
<tr>
<td>AR-H875Y</td>
<td>6.81</td>
<td>Reporter assay</td>
</tr>
<tr>
<td>AR-W742C</td>
<td>19</td>
<td>Reporter assay</td>
</tr>
<tr>
<td>AR-T878A</td>
<td>12.3</td>
<td>Reporter assay</td>
</tr>
<tr>
<td>AR-L702H</td>
<td>16.8</td>
<td>Reporter assay</td>
</tr>
</tbody>
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Abbreviation: IC50 = estimated 50% inhibitory concentration

TRC253

- Is a potent, high affinity competitive binder of wild type and mutated AR.
- Blocks AR nuclear translocation as well as AR binding to DNA and is an antagonist of transcription for wild type and mutated AR including AR F877L.
- Does not have agonist activity towards either wild type or mutated ARs.

Clinical Validation of AR F877L Mutation^9

- Plasma collected from Janssen’s AR-N509 Phase 1 trial.
- 29 patients analyzed: Pre-treatment and as late in treatment as possible.
- 3/29 samples had detectable AR F877L mutation.
- Mutation not detected in T1 samples (0/29).

METHODS – Study Design Part 1

Part 1: Dose Escalation

Starting Dose

1 patient per cohort

3+3 Dose Escalation

MTD or MED

Part 2 Dose Expansion

Cohort 1: mCRPC with acquired resistance to enzalutamide or apalutamide (n=30 patients)

- Must have received enzalutamide or apalutamide.
- Must have had shown acquired resistance to enzalutamide or apalutamide defined as: a decline in serum PSA ≥ 50% compared to baseline serum levels by week 12 (±4 weeks) of treatment followed by disease progression using PCWG3 PSA criteria or PCWG3 radiographic criteria.
- Circulating tumor DNA will be used to define cohort assignment.
- RP2D selected from part 1.
- TRC253 capsules are taken once daily in the morning starting on cycle 1 day 1 (28-day cycles).

REFERENCE


NCT02987829