An Open-label Phase 1/2A Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of TRC253, an Androgen Receptor Antagonist, in Patients With Metastatic Castration-resistant Prostate Cancer

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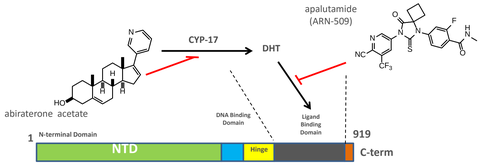
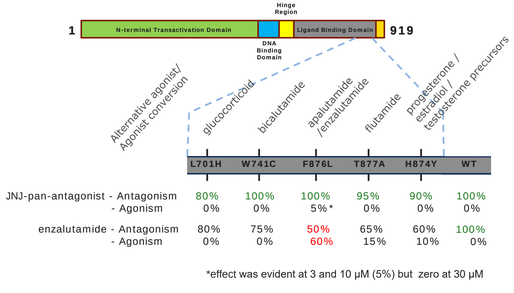
INTRODUCTION

- Androgen receptor (AR) inhibitors enzalutamide and apalutamide (ARN-509) potently inhibit the wild type (WT) AR receptor through binding to the ligand binding domain



- Single amino acid mutations of the AR ligand binding domain may mediate resistance to current second generation AR inhibitors, including enzalutamide. The F877L mutation is found in approximately 10% of cases of metastatic castrate resistant prostate cancer (mCRPC)[1]

- The development of potent inhibitors of wild-type (WT) AR as well as mutated AR, including F877L mutant AR, is a priority



	L701H	W741C	F876L	T877A	H874Y	WT
JNJ-pan-antagonist - Antagonism	80%	100%	100%	95%	90%	100%
- Agonism	0%	0%	5%*	0%	0%	0%
enzalutamide - Antagonism	80%	75%	50%	65%	60%	100%
- Agonism	0%	0%	60%	15%	10%	0%

*effect was evident at 3 and 10 μM (5%) but zero at 30 μM

Molecular Activity of TRC253 Determined in Receptor Binding or Reporter Assays

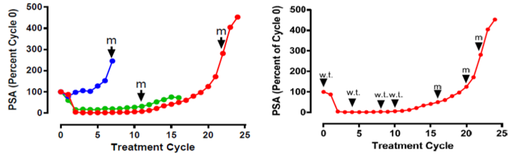
Androgen Receptor	IC_{50} (μM)	Method
AR wild type	0.0069	Binding assay
AR Mutations		
AR-F877L	0.099	Reporter assay
AR-T878A	6.81	Reporter assay
AR-L702H	10	Reporter assay
AR-W742C	12.3	Reporter assay
AR-H875Y	16.8	Reporter assay

Abbreviation: IC_{50} = estimated 50% inhibitory concentration

TRC253

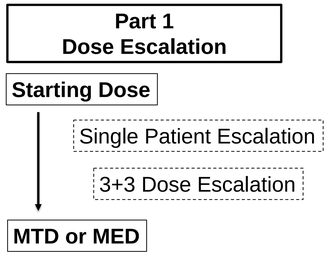
- Is a potent, high affinity competitive binder of wild type and mutated AR
- Blocks AR nuclear translocation as well as AR binding to DNA and is an antagonist of transcription for wild type and mutated AR including AR F877L
- Does not have agonist activity towards either wild type or mutated ARs

Clinical Validation of AR F877L Mutation[1]



- Plasma collected from Janssen's ARN-509 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 T_0 samples (0/29)

METHODS – Study Design Part 1



Primary Objectives
- Assess the safety of TRC253
- Determine the recommended phase 2 dose (RP2D) of TRC253
- Evaluate prostate-specific antigen (PSA) response at week 12 according to Prostate Cancer Working Group 3 (PCWG3) criteria

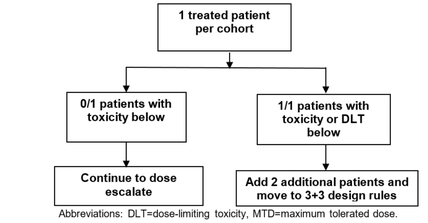
Secondary Objectives
- Evaluate PK/PD relationships
- Determine the extent of receptor occupancy (FDHT-PET)
- Evaluate preliminary anti-tumor effects of TRC253

Exploratory Objective
- Determine effect of treatment on resistance markers

Part 1 Dose Escalation

- Proposed doses: 40 mg, 80 mg, 160 mg, 240 mg, 320 mg, 400 mg
- A single dose of TRC253 will be taken on the first day (cycle 1 day 1) of a 7-day cycle to investigate the pharmacokinetic characteristics of TRC253.
- Starting with cycle 2, TRC253 will be administered orally once daily in the morning of 28-day cycles.
- Patients must have received at least 2 prior therapies for CRPC, including a prior AR inhibitor (enzalutamide or apalutamide).

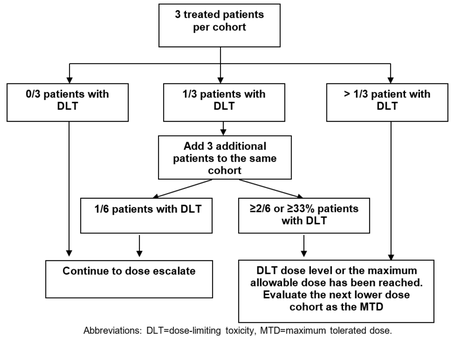
Single Patient Dose Escalation Schematic



Abbreviations: DLT=dose-limiting toxicity, MTD=maximum tolerated dose.

Single Patient Dose Escalation Will Proceed in the Absence of the Following Toxicities:
- Grade ≥ 3 hematologic toxicity
- Grade ≥ 2 non-hematological toxicity unless responsive to symptomatic treatment or the Investigator does not believe is clinically significant

3+3 Dose Escalation Schematic



Abbreviations: DLT=dose-limiting toxicity, MTD=maximum tolerated dose.

DLT Criteria:
- Grade 4 or select grade 3 hematologic toxicity
- Grade 4 or grade 3 non-hematological toxicity
- Grade ≥ 1 seizure
- Missing > 7 days of doses due to toxicity in cycle 2 (cycle 2 is the first 28-day cycle)

METHODS – Study Design Part 2

Part 2
Dose Expansion

Cohort 1: mCRPC with acquired resistance to enzalutamide or apalutamide with AR F877L mutation (n=30 patients)

Cohort 2: mCRPC with acquired resistance to enzalutamide or apalutamide by other mechanisms (n=30 patients)

Part 2 Dose Expansion

- Patients must have received enzalutamide or apalutamide.
- Patients must have 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).

REFERENCES

[1]Joseph *et al*, Cancer Dis 3:1020-9, 2013

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