ASCO GU

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A PHASE 1/2 STUDY OF ONCT-534, A DUAL-ACTION ANDROGEN RECEPTOR INHIBITOR (DAARI), IN SUBJECTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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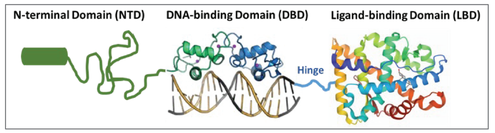
BACKGROUND

- Current therapeutic strategies for metastatic castration-resistant prostate cancer (mCRPC) include treatment with next-generation androgen receptor pathway inhibitors (ARPIs), which target the ligand-binding domain (LBD) of the AR.
- Approximately 5% to 10% of patients will have primary resistance to ARPIs and most initial responders will develop resistance within 1 to 3 years.
- Eventually, nearly all men with prostate cancer treated with ARPIs develop resistance via several mechanisms including:
  - Activation of AR genomic alterations
  - Epigenetic alterations
  - Expression of truncated constitutively active AR splice variants
- Treatment with another ARPI after developing ARPI resistance yields only modest clinical benefits.
- Other salvage therapies are more toxic and impact quality of life.

There is substantial unmet need for treatment of men with mCRPC resistant to at least one next-generation ARPI.



Androgen Receptor Structure

- ONCT-534 is a Dual-Action Androgen Receptor Inhibitor (DAARI) with a novel mechanism of action that combines inhibition of AR function with degradation of the AR protein.
- This activity includes interaction with both the LBD and the N-terminal domain (NTD) of the AR, rendering it effective against splice variants and LBD mutants, unlike existing ARPIs, while also active against native AR.

METHODS

Study Design: Schema

Key Eligibility:
- Progressing mCRPC
- R/R to next-gen AR pathway inhibitor
- Prior chemo allowed
- PSA ≥ 10 ng/mL or ≥ 2 ng/mL (≥ 50% increase)
- ECOG 0-2
- No CNS mets or seizure history
- No neuroendocrine or small cell histology

→ Dose Level 1: 40 mg oral daily
→ Dose Level 2: 80 mg oral daily
→ Dose Level 3: 160 mg oral daily
→ Dose Level 4: 300 mg oral daily
→ Dose Level 5: 600 mg oral daily

→ Dose Level A
- N = 9-16 evaluable

Dose Level B
- N = 9-16 evaluable

Phase 1 Adaptive BOIN* design
- Safety & tolerability, DLT
- PK, Activity (PSA)
- Identify MTD
- Select Phase 2 doses/schedule
- N = ~27

Phase 2 Simon 2-stage design
- Compare safety & tolerability
- Select optimal dose
- Estimate ORR, CRR, DOR, PFS
- Correlate efficacy with AR phenotype
- PK/PD and AR levels

mCRPC: metastatic castrate resistant prostate cancer; AR: androgen receptor; AR pathway inhibitor: enzalutamide, darolutamide, apalutamid e, abiraterone; MTD: Maximum Tolerated Dose; ORR: Objective Response Rate; CRR:Complete Response Rate; DOR: Duration of Response; PFS: Progression Free Survival; BOIN: Bayesian optimal interval; PK: pharmacokinetics; PD: pharmacodynamics.

*Phase 1 Adaptive BOIN Design

- A Bayesian Optimal Interval (BOIN) design is being implemented, applying an accelerated titration design for the first 2 dose levels.
- The BOIN design finds the MTD by incorporating features of the traditional 3+3 design and being more flexible with superior operating characteristics.
- The target DLT rate for a cohort is φ = 0.3 with a cohort size of 3 (beginning with third dose level) and planned maximum sample size of 27.

KEY ELIGIBILITY CRITERIA

- Histologically documented metastatic adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features
- R/R disease following treatment with at least 1 next-generation ARPI
- At least 1 measurable lesion per RECIST v1.1 or evaluable bony disease
- Continuing LHRH therapy or bilateral orchiectomy
- Progressing disease:
  - Increasing PSA as defined by PCWG3 determined by 2 consecutive measurements 7 days apart OR
  - Progression of measurable disease by RECIST v1.1 or progression of bony disease by PCWG3
- Lowest of
  - PSA ≥ 10 ng/mL OR
  - PSA ≥ 2 ng/mL and ≥ 50% increase from nadir on prior therapy
- Adequate renal, hepatic and pulmonary function

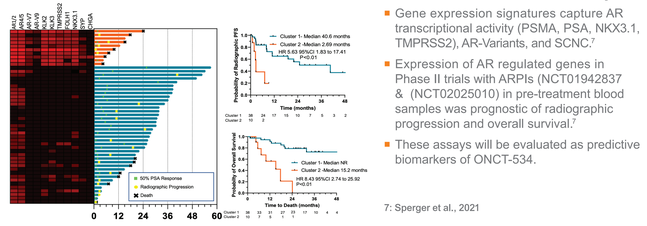
Exclusion Criteria

- Metastases to brain or CNS
- Major surgery within 30 days
- Concurrent, untreated pathologic long-bone fracture or risk thereof
- Current or imminent spinal cord compression
- Active or history of seizure disorder
- Abnormal ECG
  - QTcF > 450 ms
  - Torsade de Pointes
- Active HIV, HBV, HCV
- Active infection requiring IV antibiotics within 1 week
- Other significant conditions:
  - Active cardiac disease
  - Pulmonary disease requiring oxygen
  - GI condition
  - Other malignancies

EXPLORATORY BIOMARKER ANALYSIS

AR phenotype and AR levels of each subject's disease will be evaluated pre- and post-treatment based on:
- **Circulating Tumor Cells –** determine AR levels and identify AR variants by immunohistochemical staining, RNA sequencing, protein analysis
- **ctDNA –** serial and quantitative measurement of point mutations of AR genes and the expression of genes involved in androgen-driven regulation or tumor progression
- **Tumor biopsies –** characterize AR protein expression, AR gene abnormalities and expression of AR-driven genes

CTC Biomarker Analysis

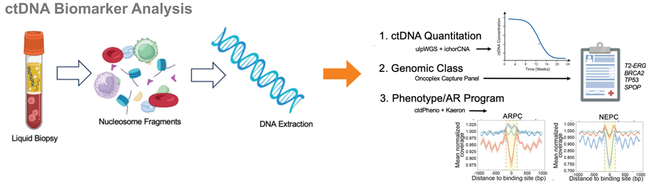


Validation methods for CTC analysis[7]

- Gene expression signatures capture AR transcriptional activity (PSMA, PSA, NKX3.1, TMPRSS2), AR-Variants, and SCNC.[7]
- Expression of AR regulated genes in Phase II trials with ARPIs (NCT01942837 & (NCT02025010) in pre-treatment blood samples was prognostic of radiographic progression and overall survival.[7]
- These assays will be evaluated as predictive biomarkers of ONCT-534.

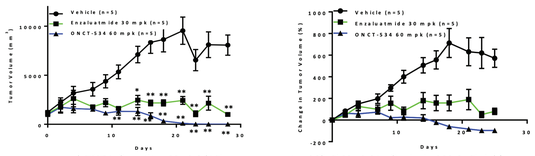
7: Sperger et al., 2021

ctDNA Biomarker Analysis

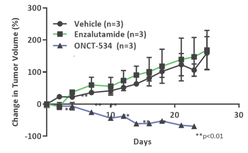


PRECLINICAL STUDIES

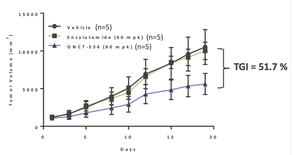
ONCT-534: Anti-tumor Activity in Preclinical Models



a) ENZA-Sensitive Model (AR-overexpressing VCaP Model in Castrated Male Rats)[1]



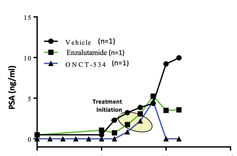
b) ENZA-Resistant MDVR VCaP Model in Uncastrated Male Rats[2]



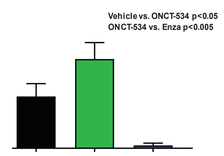
c) AR-V7-Splice Variant Positive 22Rv1 CRPC Model[2*]

*Note: model is mixed AR dependent and AR independent, 50% represents maximal AR dependent growth

ONCT-534: Serum PSA Reduction in Preclinical Models[2,3,4,5]

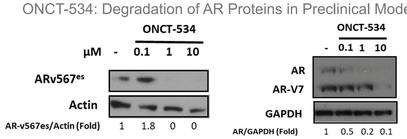


d) ENZA-Resistant MDVR VCaP Model in Uncastrated Male Rats



e) AR-V7-Splice Variant Positive 22Rv1 CRPC Model

ONCT-534: Degradation of AR Proteins in Preclinical Models



f) ONCT-534 Induces Degradation of full-length AR and AR-SV Proteins in Prostate Cancer Cells (D567es and 22RV1)[6]

Figure 1. ONCT-534 demonstrates antitumor activity and PSA reduction in multiple animal models, including enzalutamide-resistant and AR-V7 splice variant tumors.

1: Ponnusamy et al., 2021; 2: Narayanan, 2021; 3: Compagno et al., 2007; 4: Li et al., 2013; 5: Dehm et al., 2008; 6: Nyquist et al., 2013

OBJECTIVES & ENDPOINTS

Phase 1

- Primary Objectives
  - To assess the safety, tolerability, and dose-limiting toxicity (DLT) of ONCT-534 at escalating doses.
  - To determine the MTD of ONCT-534 and inform the 2 dose levels or schedules to be tested in Phase 2.
- Secondary Objectives
  - To assess the preliminary antitumor activity of ONCT-534.
  - To assess the PK of ONCT-534.

Phase 2

- Primary Objectives
  - To assess the safety and tolerability of ONCT-534.
  - To compare 2 dose levels or schedules of ONCT-534 and select the optimal dose for further study.
  - To assess the preliminary antitumor activity of ONCT-534.
- Secondary Objectives
  - To correlate antitumor activity of ONCT-534 with AR phenotype.
  - To assess the pharmacodynamics of ONCT-534.

We humbly and sincerely thank patients, their families and caregivers, and the investigators, study staff and institutions for their involvement in and commitment to this study

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SUMMARY AND STATUS

- There is substantial unmet need for treatment of men with mCRPC resistant to a next-generation ARPI.
- ONCT-534 is a Dual-Action Androgen Receptor Inhibitor (DAARI) with a novel mechanism of action that combines inhibition of AR function with degradation of the AR protein.
- ONCT-534 has demonstrated preclinical activity in prostate cancer models against unmutated AR and multiple forms of AR alteration, including amplification, mutations in the LBD, and splice variants with loss of LBD.
- ONCT-534-101 is a phase 1/2, multi-center study to evaluate the safety, tolerability, antitumor activity, and pharmacokinetics of ONCT-534 in subjects with histologically confirmed mCRPC without neuroendocrine differentiation or small cell features who have relapsed or are refractory (R/R) to at least one next-generation ARPI.
- ONCT-534-101 is currently active and enrolling patients in the Phase 1 dose escalation portion of the study.

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