Implementing a CTC-Based Clinical Trial Assay for Selecting AR-V7+ Patients for Enrollment in a Pivotal Phase 3 Study (ARMOR3-SV)

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Abstract

Background: ARMOR3-SV is a randomized phase 3, multi-center study comparing galeterone to enzalutamide in men with metastatic (M1) castrate resistant prostate cancer (CRPC) expressing androgen receptor splice variant-7 mRNA (AR-V7) who have not yet received chemotherapy, or other second generation androgen signaling inhibitors. AR-V7 is a truncated, constitutively active splice variant of the androgen receptor (AR) that lacks the ligand binding domain (LBD) and has been implicated in prostate cancer progression. Recently, the presence of AR-V7 in circulating tumor cells (CTCs) has been associated with a lack of responsiveness to both abiraterone and enzalutamide, whereas galeterone, a selective small molecule that potently degrades the androgen receptor, has demonstrated activity in preclinical model systems expressing AR-V7 and clinically in patients with C-terminal loss, of which AR-V7 is the most common form.

Methods: Utilizing the lab test developed at JHU as a model system, we sought to develop a clinical trial assay utilizing immunomagnetic bead isolation of CTCs followed by mRNA isolation and cDNA generation. We then developed a duplexed PCR assay using Taqman chemistry to detect the full-length AR (AR-FL) and AR-V7. Negative patient samples were used to establish the limit of blank and assay cut-off and synthetic oligonucleotides to establish the limit of detection.

Results: The AR-FL and AR-V7 assay shows linear response to template dilution to the assay cut-off Ct. Blood spiked with LNCaP and LNCaP95 cells were used to demonstrate assay suitability and sensitivity. We have successfully detected AR-FL and AR-V7 in select CRPC patient samples. We have also demonstrated assay reproducibility and have shown that the assay remains consistent in the presence of select interfering substances.

Conclusions: For the ARMOR3-SV trial, this clinical trial assay is being utilized globally at central laboratories to screen patient blood samples for AR-V7 expression in evaluable CTCs as the first criterion for inclusion in this study.

Conflicts of Interest: DTD is an employee of Tokai Pharmaceuticals, GB is an employee of QIAGEN, JL has received support from Tokai Pharmaceuticals

Funding Support: Tokai Pharmaceuticals

Galeterone

- First-in-Class oral Androgen Receptor Degrader
- Clinically meaningful PSA50 responses observed in mCRPC patients with C-terminal loss
  - AR-V7 is the most common form of C-terminal loss, and is a biomarker for primary resistance to currently-approved oral therapies for mCRPC
- Well-tolerated safety profile
- Pivotal Phase 3 clinical trial of treatment-naïve, AR-V7+ mCRPC patients ongoing
  - Screening eligibility determined using proprietary assay for AR-V7+
  - Primary endpoint: rPFS vs. enzalutamide

ARMOR3-SV: First Precision Medicine Prostate Cancer Pivotal Trial

Unique trial design finalized in consultation with FDA and EMA

Key Inclusion:
- Progressive metastatic (M1) disease on androgen deprivation therapy based on PCWG2
- Detectable AR-V7 from CTCs
- ECOG 0 or 1

Key Exclusion:
- Prior treatment with second generation anti-androgens (e.g. Zytiga, Xtandi)
- Prior treatment with chemotherapy for CRPC

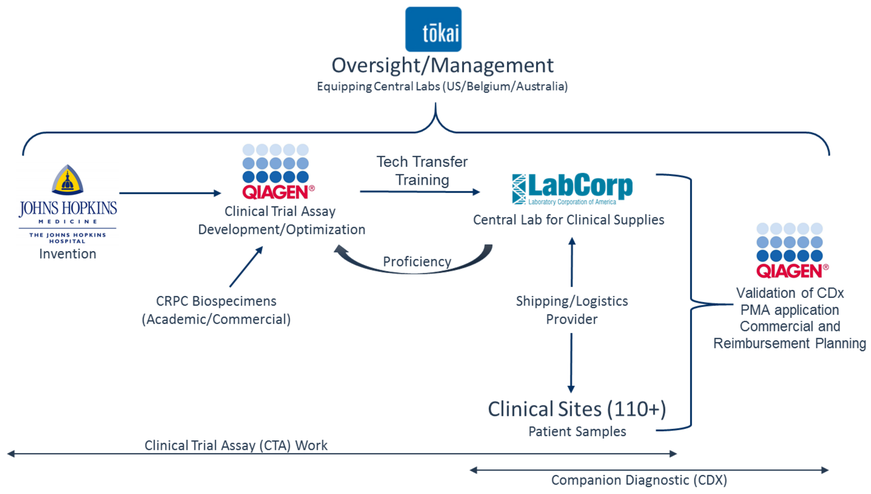
Randomize 1:1 N = 148

- Galeterone 2550mg/day
- Xtandi 160mg/day

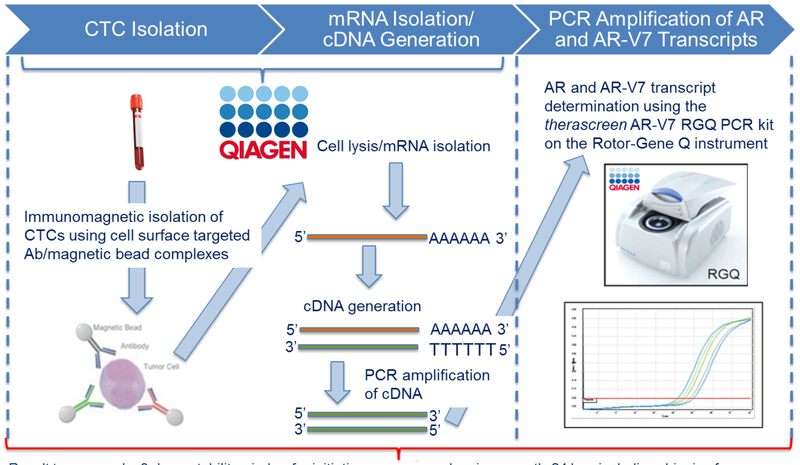
Primary Endpoint:
- Radiographic Progression Free Survival (rPFS)

Secondary Endpoints:
- Time to cytotoxic therapy
- Overall Survival (OS)
- PSA Changes
- Safety

Clinical Trial Assay and CDx

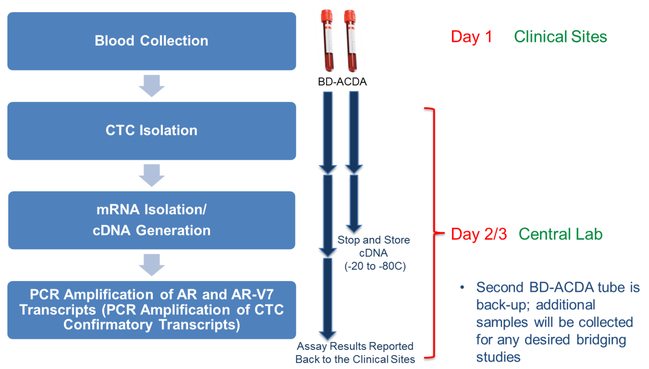


Clinical Trial Assay Overview



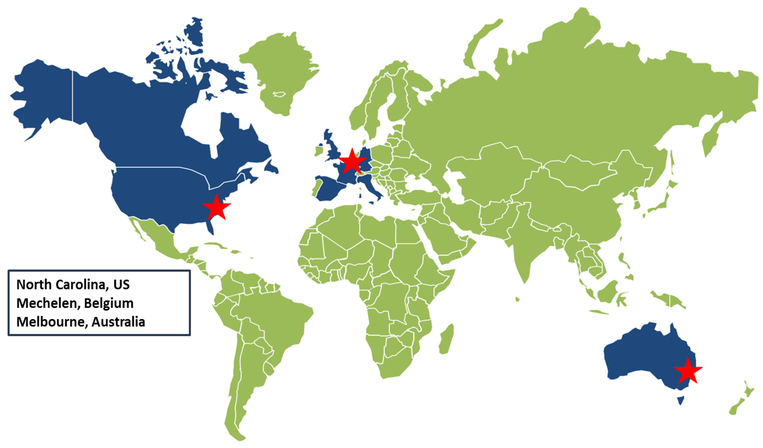
Result turn around ≤ 3 days; stability window for initiating assay procedure is presently 24 hrs, including shipping from clinical sites to central lab sites

Clinical Trial Assay Sample Flow Chart



- Second BD-ACDA tube is back-up; additional samples will be collected for any desired bridging studies

ARMOR3-SV: Clinical Trial Assay Central Lab Sites



Sampling Schedule for AR-V7 Determination and CTC Characterization

	Pre-screening	Enrollment	Study Visit	First Scan	End of Treatment
AR-FL/AR-V7 Transcript Determination	✓			✓	✓
CTC Collection, Enumeration and Characterization		✓	✓	✓	✓

Summary

- Identification of a high unmet need sub-population of mCRPC patients harboring a specific splice variant of the androgen receptor led to a unique opportunity for an efficient pivotal trial design (ARMOR3-SV) utilizing a patient selection strategy for enrollment
- Required development of a clinical trial assay to detect the AR-V7 splice variant in CTCs
- Sample acquisition during clinical trial assay development utilized to ensure workflow, demonstrate reproducibility, and lack of an effect of interfering substances, and finalize technical aspects of the assay
- Executed trial runs for all steps in the process prior to opening ARMOR3-SV
- Development of a companion diagnostic underway
- Ongoing ARMOR3-SV trial utilizing a clinical trial assay to select patients with AR-V7 is the first ever “precision medicine” pivotal trial in CRPC

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