A First-In-Man Phase 1/2 Study of OBI-3424, an AKR1C3-Selective Bis-Alkylating Agent Prodrug, in Subjects With Advanced Cancer, Including Hepatocellular Carcinoma (HCC) and Castrate-Resistant Prostate Cancer (CRPC)

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BACKGROUND

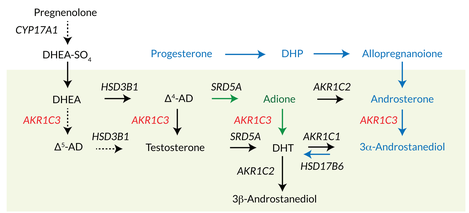
Aldo-keto reductase family 1 member C3 (AKR1C3):

- Reduces aldehydes and ketones to their corresponding primary and secondary alcohols
- Plays a role in carbonyl metabolism of a broad range of endogenous and exogenous substrates [1]
- Is expressed in normal tissues
- Overexpressed at high levels in the majority of hepatocellular carcinomas (when assessed by IHC, 91% of HCC samples had an AKR1C3 score of ≥ 4)[2], castrate-resistant prostate cancer (CRPC)[3], endometrial cancer[4], adenocarcinomas and squamous cell carcinomas[5] including non-small cell lung cancer[6], and leukemias[7]
- Associated with poor patient survival[6] and resistance to both radiation[8] and chemotherapy[9]

Role of AKR1C3 in CRPC

- Global gene expression analysis showed that AKR1C3 was significantly elevated in enzalutamide resistant cells and that overexpression of AKR1C3 confers resistance to enzalutamide[9]
- The role that AKR1C3 plays in the classical and salvage (alternative and backdoor) pathways of intra-tumoral androgen biosynthesis in castrate prostate cancer cells is illustrated in Figure 1[10]

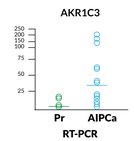
Figure 1. Role of AKR1C3



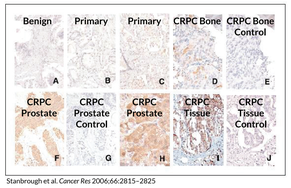
Names of genes (in italics). The classical pathway to DHT synthesis is indicated by black arrows, the alternative pathway to DHT synthesis is indicated by green arrows, and the backdoor pathway to DHT synthesis is indicated by blue arrows.

- Assessment of both AKR1C3 mRNA and protein expression confirm that AKR1C3 is adaptively upregulated in prostate cancers in response to castration
- At both the mRNA and protein level, AKR1C3 overexpression was uncommon in samples from primary tumors (prior to castration) and common in androgen-independent tumor samples, including samples from the prostate, soft tissue, and bone

Figure 2. Expression of AKR 1C3 Protein



AKR1C3 mRNA expression (RT-PCR) from 10 primary tumors and 32 androgen-independent bone marrow metastases

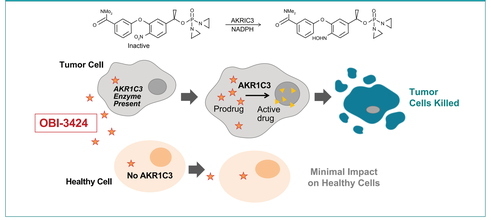


Stanbrough et al. *Cancer Res* 2006;66:2815–2825

Intermediate strong AKR1C3 staining:
– 1/18 primary tumors
– 11/19 Androgen-Independent tumors (CRPC)

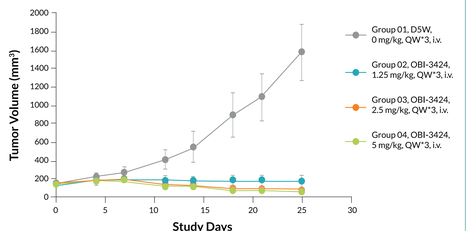
AIPCa, androgen-independent prostate cancer (bone marrow metastases); CRPC, castrate-resistant prostate cancer; mRNA, messenger RNA; PR, primary; RT-PCR, reverse transcription polymerase chain reaction

Figure 3. Structure and Mechanism of Action of OBI-34244



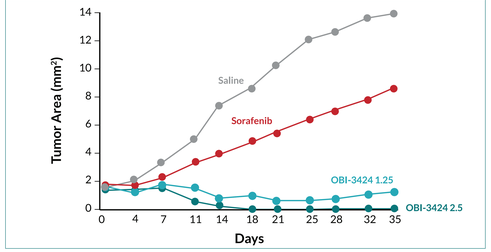
- OBI-3424 is a nitro-benzene prodrug of a nitrogen mustard that can be selectively cleaved in the presence of AKR1C3 enzyme into a bis-alkylating agent capable of forming intra- and inter-strand cross-links with DNA, thereby resulting in cell death (**Figure 3**)
- OBI-3424 has received orphan drug designation for hepatocellular carcinoma

Figure 4. Liver Cancer Preclinical Model (1.25mg/kg and 2.5mg/kg)



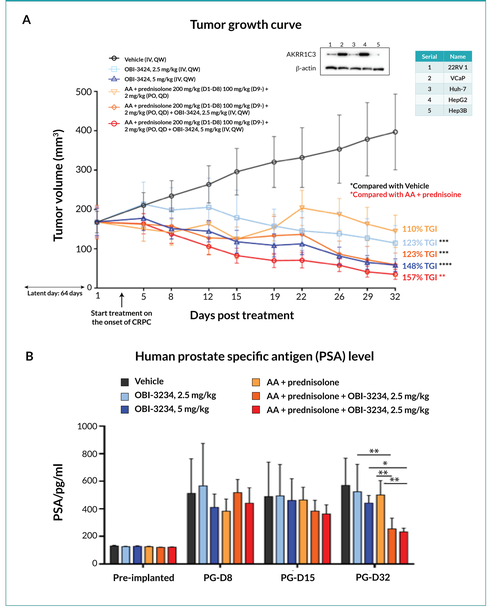
- OBI-3424 efficacy evaluation in human hepatoma patient-derived xenograft (PDX) tumor model in Balb/c nude mice (**Figure 4**)

Figure 5. Orthotopic Xenograft Liver Cancer Animal Model



- OBI-3424 efficacy evaluation in human hepatoma cell line, HepG2-GFP, derived xenograft (CDX) orthotopic tumor model in Balb/c nude mice (**Figure 5**)

Figure 6. Human Prostate Cancer Cell Line Derived Xenograft Tumor Model



- OBI-3424 efficacy evaluation in human prostate cancer cell line, VCaP, derived xenograft tumor model in castrated male Balb/c nude mice (**Figure 6**)

STUDY OBJECTIVES

Primary Objectives

Dose Escalation and Expansion Phases:

- Safety and tolerability of single agent OBI-3424 when administered intravenously (IV)

Dose Escalation Phase:

- Dose-limiting toxicities (DLTs), maximum tolerable dose (MTD), and Recommended Phase II dose (RP2D) of OBI-3424 administered as a single agent
- PK of OBI-3424 in plasma and urine

Expansion Phase:

- Preliminary assessment of the activity of OBI-3424 as determined by ORR, DOR, and PFS in defined patient groups considered potentially responsive to OBI-3424 treatment, i.e., subjects with HCC and CRPC

Secondary Objectives:

- To explore association between tumor AKR1C3 expression by IHC and CTC counts, and clinical activity
- To determine impact of OBI-3424 on immune cell populations relevant for immune response to tumors as determined by lymphocyte immunophenotyping

METHODS

Main Inclusion Criteria

- Recovered from toxicities of prior therapy to Grade 0 or 1
- Measurable disease by RECIST version 1.1 criteria or for rising PSA
- PSA according to the Prostate Cancer Working Group 3 (PCWG3) criteria for subjects with CRPC
- Available tissue (including archival tissue) for retrospective AKR1C3 expression analysis (except for subjects with CRPC)
- ECOG performance status of 0 or 1
- Cardiac QTcF interval ≤ 450msec for males and ≤470 msec for females
- Acceptable liver and renal function and acceptable hematologic status

Dose Escalation Phase Subjects Only

- Histologically or cytologically confirmed solid malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective
- Tumor progression after most recent therapy

Expansion Phase - Castrate Resistant Prostate Cancer Cohort Only

- Histologically confirmed diagnosis of adenocarcinoma of the prostate
- Documented evidence of metastatic CRPC
- Progressive disease according to the PCWG3 criteria for rising PSA or according to RECIST version 1.1 for measurable soft tissue disease
- Receipt of two or more lines of systemic standard of care treatment
- Castrate due to prior bilateral orchiectomy or ongoing LHRH analog therapy (with or without an androgen synthesis inhibitor)
- Serum testosterone concentration of 50 ng/dL or less

Expansion Phase - Hepatocellular Carcinoma Cohort Only

- Histologically confirmed advanced HCC not amenable to curative surgery or local treatment
- Prior treatment with an FDA-approved systemic therapy
- Child-Pugh Classification with score ≤6 points within 7 days of the first study dose

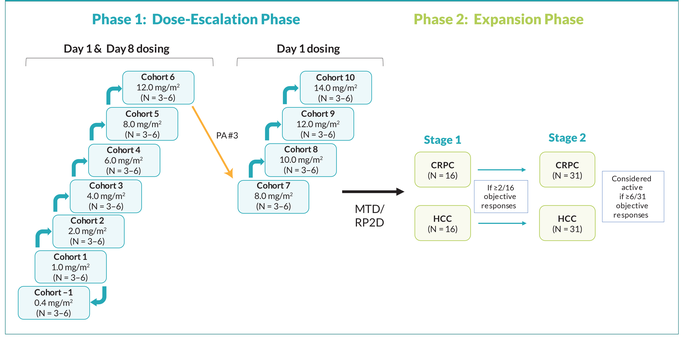
Exclusion Criteria

- Prior radiotherapy to more than 25% of the bone marrow
- Symptomatic brain metastases
- Concomitant use of strong CYP3A4 inhibitors/inducers
- Subjects with chronic hepatitis B virus (HBV) infection, unless Screening viral load <100 IU/mL on stable doses of antiviral therapy

Study Design (Figure 7)

- OBI-3424 will be administered by IV infusion over 30 minutes on Days 1 of each 21-day cycle
- Thrombocytopenia was seen as a dose limiting toxicity at 12 mg/m^2 on the day 1 and 8 Q 21 dosing schedule and the protocol has been modified to administer doses on Day 1 of a Q 21 day schedule (protocol amendment #3)

Figure 7. Study Design NCT03592264



CRPC, castrate-resistant prostate cancer; HCC, hepatocellular carcinoma; MTD, maximum tolerable dose; PA, protocol amendment; RP2D, recommended Phae II dose

Endpoints

Primary Endpoints:

- Incidence and severity of adverse events (AEs)
- Changes in electrocardiogram (ECG), lab parameters, vital signs, and weight
- DLTs
- MTD/RP2D of single agent OBI-3424
- Standard PK parameters
- ORR, DOR, and PFS in subjects recruited in the Dose Escalation cohorts as well as in the HCC and CRPC Expansion Cohorts

Secondary Endpoints:

- Determination of tumor AKR1C3 expression from archival biopsy tissue and circulating tumor cells
- Determination of changes in CTC counts and CTC AKR1C3 expression after treatment with OBI-3424
- Exploration of potential association between tumor AKR1C3 expression (from archival biopsy tissue and CTCs) and clinical activity of OBI-3424
- Assessment of changes in immune cell populations by flow cytometry after treatment with OBI-3424

CONCLUSIONS

- Tumor expression of the enzyme AKR1C3 has been associated with resistance to chemotherapy and radiotherapy
- AKR1C3 overexpression is present in the majority of HCCs and CRPCs
- OBI-3424, an AKR1C3-activated prodrug, exploits the potential differential in expression of AKR1C3 in tumors relative to normal tissue to achieve high levels of activation selectively within tumors
- This study is designed in 2 phases; Phase 1 will establish the MTD and RP2D; Phase 2 will use a validated IHC assay developed in collaboration with NeoGenomics Laboratories to select patients whose tumors over-express the enzyme that activates the prodrug

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