# Safety, Pharmacokinetics, and Clinical Activity of OBI-3424, an AKR1C3 Activated Prodrug, in Patients With Advanced or Metastatic Solid Tumors: A Phase 1 Dose-Escalation Study

Apostolia Maria Tsimberidou[1], Claire F. Verschraegen[2], Henry Hiep Vo[1], Jennifer Beck[1], Chi-Sheng Sia[3], Pei Hsu[3], Tillman E. Pearce[4]

[1]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Division of Medical Oncology, The Ohio State University James Cancer Hospital, Columbus, Ohio, USA; [3]OBI Pharma Inc., Taipei City, Taiwan; [4]OBI Pharma USA, Inc., San Diego, CA, USA

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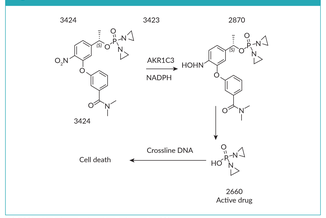
## INTRODUCTION

- Aldo-keto reductases (AKRs) are a superfamily of NAD(P)(H)-dependent oxidoreductases that primarily catalyze the reduction of aldehydes and ketones to their corresponding alcohols.[1-3]
- AKR family 1 member C3 (AKR1C3) is involved in the synthesis of steroid hormones and prostaglandins, activating mechanisms that are involved in cell proliferation.[1-3]
- AKR1C3 is overexpressed in various solid tumors (breast, prostate, endometrium, gastrointestinal, pancreas, liver, and kidney) and hematologic malignancies, and the intensity of AKR1C3 expression is strikingly elevated in certain tumors relative to normal tissues.[2]
- AKR1C3 plays a role in carbonyl metabolism and has the capability of reducing carbonyl-containing anticancer drugs, such as doxorubicin, into the related alcohols, thereby destroying their anticancer effect.[1,4,5]
- OBI-3424 is a highly potent DNA-alkylating prodrug that is selectively activated by AKR1C3 (**Figure 1**).
- In the presence of NADPH, OBI-3424 is reduced by AKR1C3 to an intermediate that spontaneously hydrolyzes to the cytotoxic moiety OBI-2660, an aziridine bisalkylating agent that causes cross-linking of DNA at the N7 (or O6) position of guanine and subsequent tumor cell death.[1]
- The cytotoxicity of OBI-3424 is highly AKR1C3 dependent, and this selective mode of activation distinguishes OBI-3424 from traditional prodrug alkylating agents.
- We report the results of a Phase 1, first-in-human trial of OBI-3424 in patients with advanced solid tumors (NCT03592264).

**Figure 1. Structure and Mechanism of Action of OBI-3424**




AKR1C3, aldo-keto reductase family 1 member C3.

### Study Objectives

- Safety and tolerability of single-agent OBI-3424 administered intravenously (IV).
- Dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D) of OBI-3424 administered as a single agent.
- Pharmacokinetics of OBI-3424 in plasma and urine.

## PATIENTS AND METHODS

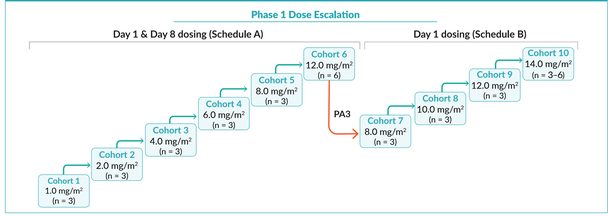
### Eligibility Criteria

- Patients ≥18 years of age.
- Histologically or cytologically confirmed advanced solid tumors for which standard curative or palliative measures did not exist or were no longer effective.
- Exclusion criteria included prior radiotherapy to >25% of the bone marrow; symptomatic brain metastases; other malignancies treated within the last 3 years; active infection; radiation therapy, surgery, chemotherapy, targeted therapy, hormones, or investigational drug/device within 28 days of study entry; or concomitant use of strong cytochrome P450 family 3 subfamily A member 4 inhibitors/inducers or naproxen.

### Study Design

- The initial dose escalation part of the study (OBI-3424 1, 2, 4, 6, 8 and 12 mg/m$^2$ IV on days 1 and 8 every 3 weeks, Schedule A) was followed by an amended dose escalation phase (OBI-3424 8, 10, 12, and 14 mg/m$^2$ IV on day 1 every 3 weeks, Schedule B) (**Figure 2**).

**Figure 2. Study Design: A standard 3+3 dose-escalation design was used.**




PA3, Protocol amendment #3

- "3+3" design.
- The MTD was defined as the dose level where <2 of 6 patients experienced a DLT.
- Treatment was discontinued if there was clinically significant deterioration of the patient's condition; disease progression; noncompliance/protocol violation; pregnancy; unacceptable toxicity, or consent withdrawal.

### Patient Monitoring

- Radiologic assessments of tumor response by computed tomography (CT) scan were conducted at baseline and after every 2 cycles.
- Tumor response was measured using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
- Toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 5.
- A DLT was defined as the occurrence of any event within the first cycle of treatment that was considered possibly related to OBI-3424.

## RESULTS

### Patient Demographics

The most common tumor types were prostate cancer (8 of 39, 21%) and colorectal cancer (5 of 39, 13%) (**Table 1**).

**Table 1. Patient Demographics and Baseline Characteristics**

| | Day 1 and Day 8 Dosing | | | | | | Day 1 Dosing | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | Cohort 1 1.0 mg/m$^2$ (n=3) | Cohort 2 2.0 mg/m$^2$ (n=3) | Cohort 3 4.0 mg/m$^2$ (n=3) | Cohort 4 6.0 mg/m$^2$ (n=3) | Cohort 5 8.0 mg/m$^2$ (n=3) | Cohort 6 12.0 mg/m$^2$ (n=6) | Cohort 7 8.0 mg/m$^2$ (n=3) | Cohort 8 10.0 mg/m$^2$ (n=3) | Cohort 9 12.0 mg/m$^2$ (n=6) | Cohort 10 14.0 mg/m$^2$ (n=6) | Total (N=39) |
| **Females, n (%)** | 1 (33.3) | 1 (33.3) | 3 (100.0) | 1 (33.3) | 0 | 1 (16.7) | 1 (33.3) | 3 (100.0) | 3 (50.0) | 3 (50.0) | 17 (43.6) |
| **Age, n** | 3 | 3 | 3 | 3 | 3 | 6 | 3 | 3 | 6 | 6 | 39 |
| Mean, yr (SD) | 71.3 (2.08) | 64.3 (9.07) | 58.3 (17.21) | 53 (5.57) | 65 (8.89) | 68.3 (7.99) | 54.7 (13.65) | 60.7 (11.02) | 59.8 (11.36) | 68.2 (6.62) | 63.1 (10.25) |
| Median, yr | 72 | 68 | 64 | 54 | 68 | 67.5 | 57 | 66 | 60 | 68.5 | 67 |
| Min, max, yr | 69, 73 | 54, 71 | 39, 72 | 47, 58 | 55, 72 | 55, 78 | 40, 67 | 48, 68 | 45, 75 | 59, 76 | 39, 78 |
| **ECOG PS, n (%)** | | | | | | | | | | | |
| 0 | 0 | 0 | 1 (33.3) | 0 | 0 | 1 (16.7) | 2 (66.7) | 0 | 1 (16.7) | 2 (33.3) | 7 (17.9) |
| 1 | 3 (100.0) | 2 (66.7) | 2 (66.7) | 3 (100.0) | 3 (100.0) | 5 (83.3) | 1 (33.3) | 3 (100.0) | 5 (83.3) | 4 (66.7) | 31 (79.5) |
| Missing | 0 | 1 (33.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.6) |
| **Tumor Type, n (%)** | | | | | | | | | | | |
| Breast | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 1 (2.6) |
| Colorectal | 0 | 0 | 0 | 1 (33.3) | 0 | 0 | 0 | 0 | 1 (16.7) | 3 (50.0) | 5 (12.8) |
| Hepatocellular carcinoma | 2 (66.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 3 (7.7) |
| Lung | 0 | 0 | 1 (33.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.6) |
| Melanoma | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 1 (2.6) |
| Ovarian | 0 | 1 (33.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.6) |
| Prostate | 0 | 2 (66.7) | 0 | 0 | 1 (33.3) | 3 (50.0) | 2 (66.7) | 0 | 0 | 0 | 8 (20.5) |
| Squamous cell carcinoma | 0 | 0 | 0 | 0 | 2 (66.7) | 0 | 0 | 0 | 0 | 0 | 2 (5.1) |
| Other | 1 (33.3) | 0 | 2 (66.7) | 2 (66.7) | 0 | 3 (50.0) | 1 (33.3) | 3 (100.0) | 3 (50.0) | 2 (33.3) | 17 (43.6) |
| **Stage, n (%)** | | | | | | | | | | | |
| Stage 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 1 (2.6) |
| Stage 4 | 3 (100.0) | 2 (66.7) | 3 (100.0) | 3 (100.0) | 3 (100.0) | 6 (100.0) | 3 (100.0) | 3 (100.0) | 5 (83.3) | 6 (100.0) | 37 (94.9) |
| Unknown | 0 | 1 (33.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.6) |

ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; yr, year.

### Safety and Tolerability

- The median number of doses administered was 4 (range, 1-38).
- Treatment-related adverse events (TEAEs) occurred in 32 (82%) of the 39 patients (**Table 2**).
- The most common AEs were anemia (25/39, 64%), thrombocytopenia/platelet count decreased (21/39, 54%), nausea (10/39, 26%), and fatigue (8/39, 21%).
- There were no fatal TEAEs; 5 patients reported a treatment-related serious AE; 4 patients with Grade >3 anemia in Cohort 6 (12 mg/m$^2$) and 1 patient in Cohort 8 (10mg/m$^2$)

**Table 2. Patient Incidence* of Treatment-Emergent Adverse Events (AEs)**

| | Day 1 and Day 8 Dosing | | | | | | Day 1 Dosing | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Preferred Term, n (%) | Cohort 1 1.0 mg/m$^2$ (n=3) | Cohort 2 2.0 mg/m$^2$ (n=3) | Cohort 3 4.0 mg/m$^2$ (n=3) | Cohort 4 6.0 mg/m$^2$ (n=3) | Cohort 5 8.0 mg/m$^2$ (n=3) | Cohort 6 12.0 mg/m$^2$ (n=6) | Cohort 7 8.0 mg/m$^2$ (n=3) | Cohort 8 10.0 mg/m$^2$ (n=3) | Cohort 9 12.0 mg/m$^2$ (n=6) | Cohort 10 14.0 mg/m$^2$ (n=6) | Total (N=39) |
| Patients reporting any treatment-emergent AE | 2 (66.7) | 0 | 2 (66.7) | 1 (33.3) | 3 (100.0) | 6 (100.0) | 3 (100.0) | 3 (100.0) | 6 (100.0) | 6 (100.0) | 32 (82.1) |
| Patients reporting any grade ≥3 treatment-emergent AE | 0 | 0 | 1 (33.3) | 1 (33.3) | 1 (33.3) | 6 (100.0) | 2 (66.7) | 2 (66.7) | 2 (33.3) | 4 (66.7) | 19 (48.7) |
| **Treatment-emergent AEs in >10% of patients** | | | | | | | | | | | |
| Anemia | 0 | 0 | 1 (33.3) | 1 (33.3) | 1 (33.3) | 6 (100.0) | 3 (100.0) | 2 (66.7) | 5 (83.3) | 6 (100.0) | 25 (64.1) |
| Thrombocytopenia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (33.3) | 2 (5.1) |
| Platelet count decreased | 0 | 0 | 0 | 0 | 2 (66.7) | 6 (100) | 1 (33.3) | 1 (33.3) | 4 (66.7) | 5 (88.3) | 19 (48.7) |
| Lymphocytopenia | 0 | 0 | 0 | 1 (33.3) | 0 | 2 (33.3) | 1 (33.3) | 1 (33.3) | 0 | 2 (33.3) | 7 (17.9) |
| Leukopenia | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 3 (50.0) | 3 (50.0) | 7 (17.9) |
| Neutropenia | 0 | 0 | 1 (33.3) | 0 | 0 | 1 (16.7) | 0 | 0 | 2 (33.3) | 2 (33.3) | 6 (15.4) |
| Nausea | 1 (33.3) | 0 | 1 (33.3) | 1 (33.3) | 0 | 0 | 1 (33.3) | 2 (66.7) | 2 (33.3) | 2 (33.3) | 10 (25.6) |
| Diarrhea | 0 | 0 | 0 | 0 | 0 | 2 (33.3) | 0 | 0 | 2 (33.3) | 1 (16.7) | 5 (12.8) |
| Vomiting | 0 | 0 | 1 (33.3) | 0 | 0 | 3 (50.0) | 0 | 0 | 0 | 1 (16.7) | 5 (12.8) |
| Fatigue | 1 (33.3) | 0 | 0 | 1 (33.3) | 1 (33.3) | 1 (16.7) | 0 | 2 (66.7) | 2 (33.3) | 0 | 8 (20.5) |
| Decreased appetite | 0 | 0 | 0 | 0 | 0 | 3 (50.0) | 0 | 0 | 0 | 1 (16.7) | 4 (10.3) |
| Dyspnea | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 1 (33.3) | 0 | 2 (33.3) | 4 (10.3) |

*Patients reporting multiple AEs in the same System Organ Class or Preferred Term are counted only once in that row

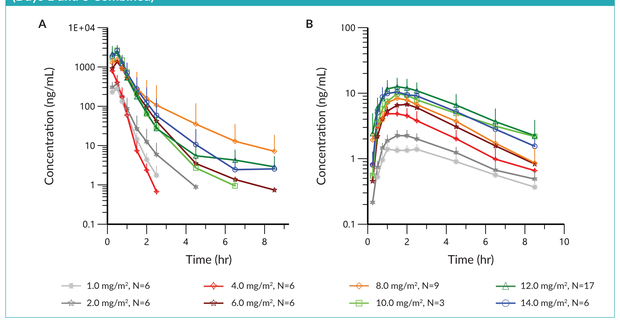
### Dose-Limiting Toxicity and Maximum Tolerated Dose

- In Schedule A (days 1 and 8 every 3 weeks), OBI-3424 was well tolerated at doses of up to 8.0 mg/m$^2$. Given that the platelet count nadirs were occurring on day 15 or day 21, the schedule of administration was modified for Schedule B (day 1 every 3 weeks) (**Figure 2**).
- Treatment with OBI-3424 at doses of ≥8 mg/m$^2$ using Schedule A and 12 mg/m$^2$ using Schedule B was associated with clinically significant decreases in hemoglobin levels and platelet counts, corresponding to the observed increase in the incidence of anemia and thrombocytopenia in these dosing cohorts.
- OBI-3424 administered on day 1 every 3 weeks was tolerated at doses up to 14 mg/m$^2$; the MTD was not reached.
- The RP2D and regimen of OBI-3424 were determined to be 12 mg/m$^2$ on day 1 every 3 weeks (**Schedule B**).

### Pharmacokinetics

- OBI-3424 and OBI-2660 (a circulating metabolite of OBI-3424) concentrations were analyzed from blood samples collected on day 1 of cycle 1 (pretreatment); 15 minutes after infusion begins; at the end of infusion (EOI); and 15, 30, 60, and 90 minutes and 2, 4, 6, and 8 hours post-treatment.
- Mean plasma concentration versus time profiles of single doses of OBI-3424 and OBI-2660 are illustrated in **Figure 3**.
- OBI-3424 and OBI-2660 pharmacokinetic parameters are summarized in **Table 3**.
- Maximum serum concentrations ($C_{max}$) of OBI-3424 generally occurred at the end of the 30-minute drug infusion. Time to maximum concentration of OBI-2660 was observed to be slightly delayed compared with OBI-3424, with $C_{max}$ achieved between 1.33 and 1.75 hours after the start of drug infusion.
- The half-life of OBI-3424 was short (0.20 to 0.74 hours), while OBI-2660 had a longer half-life (1.87 to 3.48 hours).
- Mean clearance ranged from 4.8 to 8.8 L/h/m$^2$ and volume of distribution ranged from 2.4 to 4.3 L/m$^2$ for OBI-3424.
- No accumulation of exposure ($C_{max}$ and area under the concentration-time curve) between 2 doses (cycle 1 day 1 and cycle 1 day 8) was observed for either OBI-3424 and OBI-2660.

**Figure 3. Pharmacokinetic Profiles of OBI-3424 (A) and OBI-2660 (B) During Cycle 1 (Days 1 and 8 Combined)**




OBI-3424 and OBI-2660 pharmacokinetic parameters are summarized in **Table 3**.

**Table 3. Mean Plasma Pharmacokinetic Parameters for OBI-3424 and OBI-2660 in Cycle 1 – Days 1 and 8 Combined**

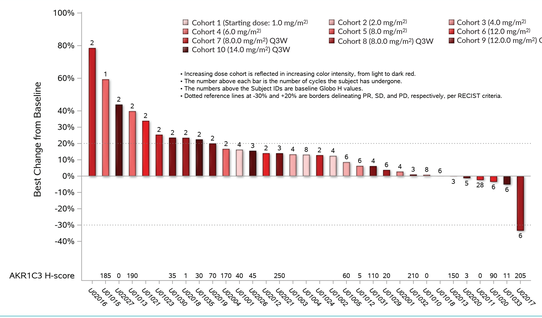
| Dose Level | $T_{max}$ (h) | | $C_{max}$ (ng/mL) | | $AUC_{0-t}$ (h*ng/mL) | | $T_{1/2}$ (h) | | CL (L/h/m$^2$) | $Vd_{ss}$ (L/m$^2$) |
|---|---|---|---|---|---|---|---|---|---|---|
| (mg/m$^2$) | OBI-3424 | OBI-2660 | OBI-3424 | OBI-2660 | OBI-3424 | OBI-2660 | OBI-3424 | OBI-2660 | OBI-3424 | OBI-3424 |
| 1 | 0.46 (0.10) | 1.75 (0.61) | 289.30 (56.10) | 1.70 (0.80) | 217.10 (46.10) | 7.30 (1.90) | 0.29 (0.04) | 3.08 (1.21) | 4.74 (0.87) | 2.45 (0.40) |
| 2 | 0.50 0.00 | 1.67 (0.26) | 375.80 (161.40) | 2.30 (0.50) | 298.00 (156.50) | 10.00 (2.20) | 0.31 (0.14) | 2.48 (0.76) | 8.85 (5.25) | 4.13 (1.67) |
| 4 | 0.33 (0.13) | 1.33 (0.41) | 803.50 (500.70) | 5.00 (1.10) | 650.90 (391.60) | 19.30 (6.70) | 0.21 (0.04) | 2.00 (0.24) | 7.74 (3.29) | 2.68 (1.69) |
| 6 | 0.50 0.00 | 1.75 (0.27) | 1360.30 (247.10) | 6.80 (0.40) | 1278.10 (230.00) | 27.40 (3.50) | 0.74 (0.39) | 2.09 (0.44) | 4.84 (1.03) | 3.72 (0.83) |
| 8 | 0.42 (0.13) | 1.44 (0.30) | 1613.10 (419.80) | 8.50 (1.60) | 1678.40 (1302.00) | 32.80 (8.90) | 0.67 (0.33) | 1.87 (0.35) | 6.53 (2.92) | 3.97 (1.06) |
| 10 | 0.50 0.00 | 1.67 (0.29) | 2654.70 (426.40) | 10.10 (1.10) | 2037.00 (316.20) | 29.20 (18.30) | 0.57 (0.24) | 2.99 (0.10) | 4.92 (0.83) | 3.06 (0.50) |
| 12 | 0.44 (0.17) | 1.53 (0.37) | 2481.90 (1132.70) | 13.10 (4.20) | 2159.40 (1089.10) | 56.60 (21.40) | 0.55 (0.34) | 2.41 (0.69) | 8.20 (7.98) | 4.33 (4.67) |
| 14 | 0.42 (0.13) | 1.75 (0.52) | 2619.20 (878.00) | 11.20 (2.70) | 2131.80 (955.10) | 45.60 (9.80) | 0.55 (0.27) | 2.46 (0.78) | 8.49 (5.67) | 4.31 (1.22) |

Data expressed as mean (SD).
CL, clearance; $AUC_{0-t}$, area under the concentration-time curve from time 0 to the last measurable concentration; $C_{max}$, time to maximum concentration; SD, standard deviation; $T_{1/2}$, half-life; $T_{max}$ , time to maximum concentration; Vdss, volume of distribution at steady state.

### Antitumor Activity

- Best response by RECIST v1.1 is shown in Figure 4. Of 33 patients who were evaluable for response assessment, one patient with cholangiocarcinoma in Cohort 8 (10 mg/m$^2$ Q3W) had a partial response (PR), 21 (54%) had stable disease (SD), and the remaining 11 (28%) patients had progressive disease. Six patients ended the study before the first post-treatment response assessment.
- AKR1C3 expression was assessed by a validated automated immunohistochemistry assay in tumor tissue of 32 patients. In nine patients, tumor cells were insufficient for testing. AKR1C3 H-scores are listed in **Figure 4**.

**Figure 4. Antitumor Activity in Patients Treated With OBI-3424 at Post-Baseline Scans**




AKR1C3, aldo-keto reductase family 1 member C3; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; Q3W, every 3 weeks.

## CONCLUSIONS

- OBI-3424 was tolerated at doses of up to 14.0 mg/m$^2$ on day 1 every 3 weeks. No DLT occurred at the maximum administered dose, and thus MTD was not determined.
- All patients who received OBI-3424 at the dose of 12.0 mg/m$^2$ on days 1 and 8 every 3 weeks experienced anemia and/or thrombocytopenia, requiring dose reductions and blood transfusions.
- The most common AEs were anemia (64%), thrombocytopenia/platelet count decreased (48.7%), nausea (26%), and fatigue (21%); including 5 patients who experienced a treatment-emergent serious AE (Grade >3 anemia).
- OBI-3424 exhibited linear pharmacokinetics and dose proportionality from 1.0 mg/m$^2$ to 14.0 mg/m$^2$ without marked accumulation after repeated dosing, indicating that there was no evidence of cumulative toxicity.
- Best confirmed response to OBI-3424 treatment was PR.
- A Phase 2 dose-expansion study of single-agent OBI-3424 is currently enrolling patients with locally advanced/metastatic hepatocellular carcinoma, pancreatic cancer, and other epithelial carcinomas with high AKR1C3 expression.

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