ARV-766, a PROTAC Androgen Receptor Degradator, Combined With Abiraterone in Novel Hormonal Agent–Naïve Metastatic Prostate Cancer: Phase I/II Study

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Key Points

• ARV-766, a PROTAC Androgen Receptor (AR) degrader, was well tolerated as monotherapy in patients with metastatic castration-resistant prostate cancer (mCRPC) who had received prior novel hormonal agent (NHA) therapy (eg, abiraterone or enzalutamide) in parts A and B of a phase 1/2 study
• Part C of the study will assess the safety, tolerability, and antitumor activity of ARV-766 with abiraterone in men with NHA-naive metastatic prostate cancer

Background

ARV-766 is a PROTAC AR degrader that creates a trimeric complex with AR and an E3 ubiquitin ligase to directly trigger ubiquitination and subsequent degradation of AR by the proteasome (Figure 1)

ARV-766 showed degradation activity against wild-type AR as well as clinically relevant mutants in preclinical experiments and robust tumor growth inhibition in mouse models of prostate cancer

In the first-in-human study of ARV-766 (NCT05067140), parts A (dose escalation) and B (cohort expansion) are assessing ARV-766 monotherapy in men with mCRPC

• Abiraterone is an NHA that is used to treat patients with mCRPC or metastatic castration-sensitive prostate cancer (mCSPC)
• Abiraterone acts upstream of AR by depleting androgen biosynthesis, and patients may become resistant to abiraterone through AR upregulation, AR mutations or splice variants, and/or alternative oncogenic signaling pathways
• Due to its ability to degrade wild-type and mutant AR and act on the AR pathway downstream of abiraterone, ARV-766 might enhance abiraterone efficacy when the 2 drugs are combined

Safety of ARV-766 Monotherapy (Parts A and B)

• Parts A and B of the study are evaluating ARV-766 monotherapy in patients with mCRPC and prior NHA treatment (Figure 2)
• Part A (dose escalation) assessed the safety and tolerability of ARV-766 to select recommended phase 2 doses (RP2Ds)
• Part B (cohort expansion) is evaluating the antitumor activity of the RP2Ds
• As of August 23, 2023, 84 patients with mCRPC were treated with ARV-766 monotherapy in parts A and B
• There were no grade ≥4 TRAEs with ARV-766 monotherapy

ARV-766 + Abiraterone Study Design (Part C)

• In part C, patients will receive ARV-766 in combination with abiraterone (Figure 2)
• Patients eligible for part C have confirmed metastatic prostate cancer (mCRPC) and no prior treatment with abiraterone
• Dose escalation will follow a 3+3 cohort design based on safety and pharmacokinetic parameters
• The primary objective and endpoints are shown in Table 3

Table 1: TRAEs with ARV-766 monotherapy reported in ≥20% of patients (N=84)

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Any grade</th>
<th>Grade 3</th>
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</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>24 (29)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (11)</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>9 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>8 (10)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Patients were treated in TRAEs first recorded at their dose level

Table 2: Key eligibility criteria for part C

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
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<tbody>
<tr>
<td>• Men ≥18 years</td>
<td>• Prior treatment with an NHA (abiraterone, enzalutamide, darolutamide, or apalutamide)</td>
</tr>
<tr>
<td>• Histologically, pathologically, or cytologically confirmed diagnosis of adenocarcinoma of the prostate</td>
<td>• Symptomatic brain metastases requiring steroids above physiologic replacement doses</td>
</tr>
<tr>
<td>• ECOG performance status of 0 or 1</td>
<td>• Active inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease, or previous gastric resection or lap band surgery</td>
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Table 3: Outcome measures for part C

Primary objective: Evaluate the safety and tolerability of ARV-766 in combination with abiraterone

Primary endpoints:
• DLTs during the first cycle
• Type, frequency, severity, and relationship to study drug of adverse events
• Type, frequency, and severity of laboratory abnormalities

Figure 1: Mechanism of action of ARV-766

Figure 2: Study schema

References

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