First-in-human safety and activity of ARV-471, a novel PROTAC® estrogen receptor degrader, in ER+/HER2- locally advanced or metastatic breast cancer

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References

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Background

• There is an unmet need for better treatments for ER+ advanced breast cancer: resistance to CDK4/6 inhibitors and endocrine therapy remain a particular challenge for patients who have progressed on or after these agents.

  – The CBR with fulvestrant plus venetoclax vs fulvestrant alone was only 11.8% vs 13.7% in the randomized phase 2 VERICOM study in patients with breast cancer prior to ARV-471 treatment and endocrine therapy.

  – 26% of patients with metastatic breast cancer treated with CDK4/6 inhibitors develop a genomic alteration representing an ER-independent mechanism of resistance.

  – Although fulvestrant is a standard-of-care option for patients with ER+ advanced breast cancer, it has limitations, including its intramuscular route of administration and only 40–50% degradation of ER at its optimal dose.

Results

Baseline Characteristics

As of September 30, 2021, 55 patients were enrolled in the trial; 52 patients received the study drug (250 mg BID) and 3 patients received 700 mg daily for 24 weeks. All patients received prior CDK4/6 inhibitors, 80% received prior fulvestrant, and 78% received prior endocrine therapy. 10 patients had disease progression on prior CDK4/6 inhibitor.

Objective

• To evaluate the safety and clinical activity of ARV-471, an oral estrogen receptor (ER) PROTAC® targeting Chimeric PROTAC® (PROTAC®) protein degrader, in patients with ER+positive/human epidermal growth factor receptor 2-negative (ER+/HER2-) locally advanced or metastatic breast cancer who had previously received cyclin-dependent kinase (CDK) inhibitors.

Key Findings

• ARV-471 was well tolerated at all dose levels, with no dose-limiting toxicities (DLTs) reported.

• Most treatment-related adverse events (TRAEs) were grade 1/2: ARV-471 showed antitumor activity in CDK4/6 inhibitor–pre-treated patients with ER+/HER2- breast cancer, with a clinical benefit rate (CBR) of 42% (95% CI: 29–56%).

• Overall response rate was 56% (95% CI: 39–73%) in 47 evaluable patients; 3 patients had confirmed PRs (Figure 1).

Conclusions

• ARV-471 has a manageable safety profile, with mostly low-grade TRAEs.

• Pharmacokinetics of ARV-471 were dose-related up to 500 mg daily.

• Clinical activity and pharmacodynamic data suggest ARV-471 may have superior ER degradation to fulvestrant; it has the potential to fill an unmet need for patients with ER+/HER2- breast cancer and prior treatment with CDK4/6 inhibitors.

Methods

• This is a phase 2, multicenter, first-in-human, open-label study (NCT04729522) of ARV-471 in patients with ER+/HER2- breast cancer.

  – In the phase 1 dose escalation portion (3+3 design with beakoff), patients had received 1 prior CDK4/6 inhibitor, 2 prior endocrine therapies, and 3 prior lines of chemotherapy; ARV-471 was administered orally with food at a starting dose of 30 mg daily.

  – Introspective dose escalation was conducted before the phase 2 optimal dose was selected.

  – The primary objective of the phase 1 dose escalation study was to evaluate the safety and tolerability of ARV-471 in order to estimate the maximum tolerated dose (MTD) and select the recommended phase 2 doses.

  – Other objectives were to assess pharmacokinetics and pharmacodynamics and explore ARV-471’s antitumor activity.

  – CBR (rate of confirmed complete response [CR] or partial response [PR] or stable disease [SD] ≥24 weeks) was analyzed in patients enrolled ≥24 weeks prior to the data cutoff.

Safety

• No DLT or grade 3 TRAEs were observed; the MTD was not reached.

• Of 60 patients, 37 had grade 1 TRAEs and 57 had grade ≤2 (Table 2).

• There were six grade 3 TRAEs in four patients (headache lasting 1 day, single occurrence of asymptomatic increased alanine aminotransferase, grade 3 diabetes, and grade 3 vomiting, each reported by 1 patient). The patient with grade 3 venous embolism was the only patient who discontinued ARV-471 due to a TRAE, and the patient with grade 3 nausea was the only patient with a dose reduction due to ADR (500 mg to 400 mg).

Efficacy

• The CBR (rate of confirmed CR or PR or SD ≥24 weeks) was 40% (95% CI: 26–56%) in 47 evaluable patients; 3 patients had confirmed PRs (Figures 1–3).

• 14 patients were ongoing at the time of data cutoff, including 2 who have been on treatment for >18 months.

Pharmacokinetics

• Pharmacokinetic data showed dose-related increases for ARV-C and Cmax up to 500 mg to daily doses (Table 3); mean exposure on Day 15 exceeded the nonclinical efficacious range at doses ≥300 mg daily.

Biomarkers

• Robust ER degradation (up to 89%) was observed at all dose levels up to 500 mg daily, regardless of ESR1 mutation status (Figure 4).

• Median and mean ER degradation across dose levels were 67% and 64%, respectively.

Table 1: Preliminary ARV-471 pharmacokinetic parameters on Day 15

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (n=10)</th>
<th>90% CI</th>
<th>Mean (n=10)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARV-471 Cmax (ng/mL)</td>
<td>180</td>
<td>(150, 200)</td>
<td>360</td>
<td>(300, 420)</td>
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<tr>
<td>ARV-471 AUC24 (ng/mL min)</td>
<td>560</td>
<td>(440, 680)</td>
<td>1120</td>
<td>(900, 1360)</td>
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<tr>
<td>ARV-471 MRT (hours)</td>
<td>3.1</td>
<td>(2.7, 3.5)</td>
<td>6.3</td>
<td>(5.6, 7.1)</td>
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<tr>
<td>ARV-471 mean exposure (hAUC24)</td>
<td>2960</td>
<td>(2440, 3560)</td>
<td>5920</td>
<td>(4800, 7040)</td>
</tr>
</tbody>
</table>


Compliance with ethical standards

The study protocol was reviewed and approved by local institutional review boards as applicable. This study was conducted in accordance with the principles of the Declaration of Helsinki (1964), its later revision, and International Conference on Harmonization Good Clinical Practice guidelines. All enrolled patients provided written informed consent.

Plain Language Summary

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