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ARV-471, an estrogen receptor (ER) PROTAC degrader, combined with palbociclib in advanced ER+/human epidermal growth factor receptor 2 negative breast cancer: phase 1b cohort (part C) of a phase 1/2 study

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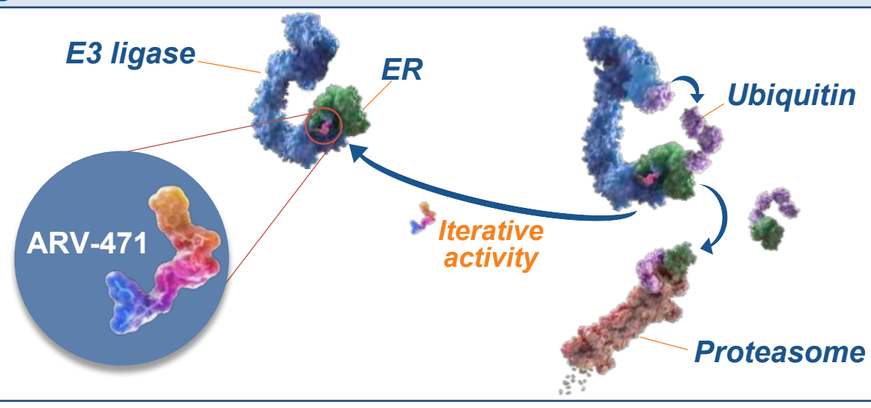
Background and Rationale

- ARV-471 is a novel, potent, orally bioavailable PROteolysis TArgeting Chimera (PROTAC) protein degrader that selectively targets the ER (**Figure 1**)
- ARV-471 degraded ERα and blocked cell proliferation in multiple ER-positive (ER+) cell lines[1]
- In patient-derived xenograft breast cancer models, ARV-471 induced substantially greater ER degradation and tumor growth inhibition compared with the selective ER degrader fulvestrant[1]

Figure 1: ARV-471 mechanism of action



ER=estrogen receptor

- ARV-471 is being evaluated in patients with ER+/human epidermal growth factor receptor 2 negative (HER2-) locally advanced or metastatic breast cancer in a first-in-human phase 1/2 study (**Figure 2**)
  - In part A (dose escalation), ARV-471 showed a manageable safety profile in patients who had previously received endocrine therapy and a cyclin-dependent kinase (CDK) 4/6 inhibitor[2]
  - The clinical benefit rate (rate of confirmed complete or partial response or stable disease ≥24 weeks) was 40% (95% CI: 26%-56%) in 47 evaluable patients
  - Part B (cohort expansion; VERITAC) is further evaluating recommended phase 2 doses of ARV-471 in this patient population
- Palbociclib, a CDK4/6 inhibitor, plus fulvestrant is a standard treatment option for patients with ER+/HER2- breast cancer and disease progression on endocrine therapy
- ARV-471 plus palbociclib had substantially greater antitumor activity in a xenograft model vs palbociclib plus fulvestrant (**Figure 3**)[1]

Figure 2: Phase 1/2 study

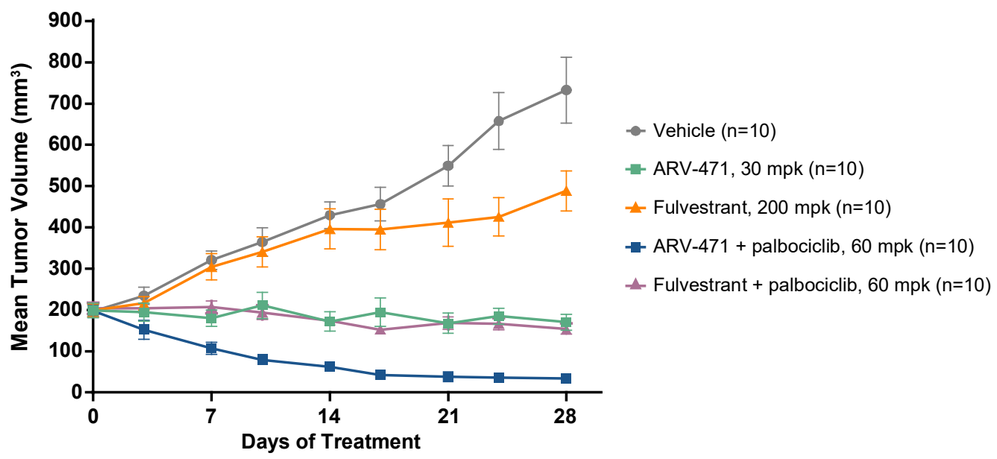
Part A: Phase 1 dose escalation[a]

Part B: Phase 2 cohort expansion[a]

Part C: Phase 1b combination[b]

[a]ARV-471 monotherapy; [b]ARV-471 plus palbociclib

Figure 3: Tumor growth inhibition[a] with ARV-471 plus palbociclib[1]



[a]Orthotopic MCF7/estradiol xenograft model

Objective

- This phase 1b cohort (part C) of a phase 1/2 study (NCT04072952) is evaluating the safety and clinical activity of ARV-471 plus palbociclib in patients with ER+/HER2- breast cancer after prior endocrine therapy

Study Design

- In part C of this open-label, multicenter study, ARV-471 and palbociclib will be given orally in 28-day cycles
  - ARV-471 will be administered daily continuously
  - Palbociclib will be administered for 21 days followed by 7 days off treatment
- Eligible patients have ER+/HER2- advanced breast cancer and previous treatment with ≥1 prior endocrine therapy (**Table 1**); prior CDK4/6 inhibitor therapy is permitted
- Key outcomes of part C of this study are shown in **Table 2**

Table 1: Key eligibility criteria

Inclusion criteria	Exclusion criteria
• ≥18 years of age • Histologically or cytologically confirmed ER+ and HER2- advanced breast cancer • Measurable or nonmeasurable disease per RECIST criteria v1.1 • Willingness to undergo a biopsy of accessible tumor for ER IHC testing and pharmacodynamic studies ≤4 weeks prior to the study treatment initiation and on treatment • Women must be postmenopausal due to surgical or natural menopause • ≥1 prior endocrine therapy • ≤2 prior chemotherapy regimens for advanced disease	• Known symptomatic brain metastases requiring steroids • Receipt of prior anticancer or other investigational therapy ≤14 days of start of treatment • Radiation therapy ≤4 weeks of start of treatment or prior irradiation to >25% of the bone marrow

ER+=estrogen receptor positive; HER2-=human epidermal growth factor receptor 2 negative; IHC=immunohistochemistry; RECIST=Response Evaluation Criteria In Solid Tumors

Table 2: Key outcome measures

Primary objective	Endpoints
Evaluate the safety and tolerability of ARV-471 plus palbociclib and select the RP2D and schedule of the combination	• Dose-limiting toxicities during the first cycle • Frequency and severity of adverse events and laboratory abnormalities
Secondary objectives	**Endpoints**
Assess preliminary antitumor activity of ARV-471 plus palbociclib	• Overall response rate per RECIST v1.1 • Clinical benefit rate[a] • Progression-free survival • Duration of response
Assess pharmacokinetic parameters of ARV-471 after a single dose and after multiple doses	• Area under the concentration-time curve (AUC) • Maximum concentration (C_{max}) • Minimum concentration (C_{min}) • Time to maximum concentration (T_{max})

[a]Rate of confirmed complete or partial response or stable disease ≥24 weeks
RECIST=Response Evaluation Criteria In Solid Tumors; RP2D=recommended phase 2 dose

References

1. Flanagan JJ, et al. SABCS 2018. Poster #P5-04-18.
2. Hamilton E, et al. SABCS 2021. Spotlight Poster Discussion #PD13-08.

Acknowledgments

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