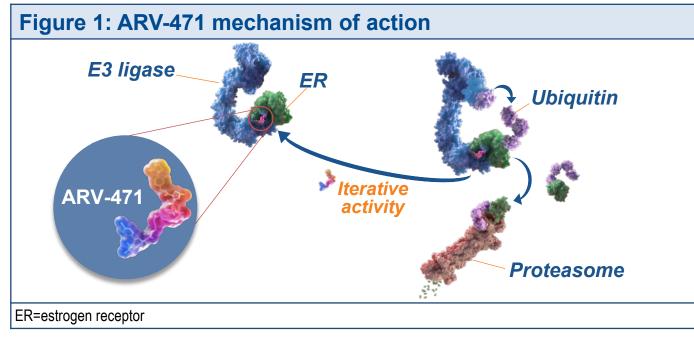
ARV-471, an estrogen receptor (ER) PROTAC degrader, combined with palbociclib in advanced ER+/human epidermal growth factor receptor 2 negative breast cancer: phase 1b cohort (part C) of a phase 1/2 study

Erika P Hamilton¹, Anne F Schott², Rita Nanda³, Haolan Lu⁴, Chi F Keung⁴, Richard Gedrich⁴, Janaki Parameswaran⁴, Hyo S Han⁵, Sara A Hurvitz⁶

¹Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; ²Rogel Cancer Center, University of Michigan Health, Ann Arbor, MI; ³University of Chicago Medicine, Chicago, IL; ⁴Arvinas, Inc., New Haven, CT; ⁵Moffitt Cancer Center, Tampa, FL; ⁶UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA

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 lines¹
- In patient-derived xenograft breast cancer models, ARV-471 induced substantially greater ER degradation and tumor growth inhibition compared with the selective ER degrader fulvestrant¹



 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)

| -ig | ure 2: Phase 1/2 study |
|-----|--|
| Pa | rt A: Phase 1 dose escalation ^a |
| Pa | rt B: Phase 2 cohort expansion ^a |
| Ра | rt C: Phase 1b combination ^b |

- In part A (dose escalation), ARV-471 showed a manageable safety

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

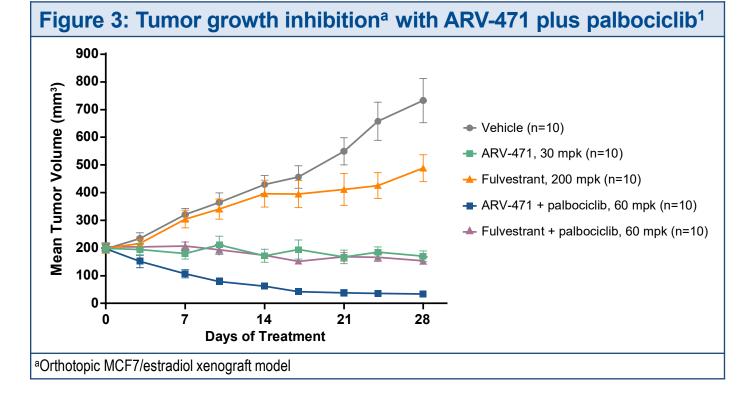
≤2 prior chemotherapy regimens for advanced disease

- 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 | 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

- profile in patients who had previously received endocrine therapy and a cyclin-dependent kinase (CDK) 4/6 inhibitor²
- 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



| 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}) | | |

References

1. Flanagan JJ, et al. SABCS 2018. Poster #P5-04-18.

RECIST=Response Evaluation Criteria In Solid Tumors; RP2D=recommended phase 2 dose

2. Hamilton E, et al. SABCS 2021. Spotlight Poster Discussion #PD13-08.

Acknowledgments

This study is sponsored by Arvinas Estrogen Receptor, Inc. Poster development support was provided by Apollo Medical Communications and funded by Arvinas, Inc.



Plain Language Summary

Please scan this Quick Response (QR) code with your smartphone app to view a plain language summary of the poster

Contact

Erika Hamilton, MD; ehamilton@tnonc.com

Presented at the American Society for Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, June 3–7, 2022