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TACTIVE-N: open-label, randomized, noncomparative neoadjuvant phase 2 study of ARV-471, a PROteolysis TArgeting Chimera (PROTAC) estrogen receptor (ER) degrader, or anastrozole in postmenopausal women with ER+/human epidermal growth factor receptor 2 (HER2)- localized breast cancer

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Objective

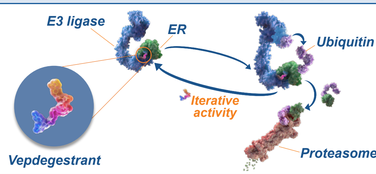
- The phase 2, noncomparative, proof-of-concept TACTIVE-N study (NCT05549505) will evaluate the safety and clinical activity of neoadjuvant vepdegestrant (ARV-471) or anastrozole in patients with breast cancer amenable to definitive surgical resection

Background and Rationale

- Neoadjuvant endocrine therapy, such as the aromatase inhibitor anastrozole, is a standard treatment option for postmenopausal patients with ER+/HER2- localized breast cancer[1,2]
  - However, in patients with ER+ tumors treated with neoadjuvant anastrozole therapy, the 6-month response rate was only 56%, breast-conserving surgery was achieved in 60% of patients, and 5-year relapse-free survival was approximately 84%[3]
  - The IMPACT study reported an overall response rate of 37% after 3 months of neoadjuvant anastrozole treatment and breast-conserving surgery in 44% of patients[4]
- New ER-targeted therapies with novel mechanisms of action are needed to improve outcomes in patients with ER+ breast cancer[5]
- Vepdegestrant (ARV-471) is a selective, orally administered PROTAC protein degrader that targets ER[6]
- Vepdegestrant creates a trimer complex with ER and the cereblon E3 ubiquitin ligase, which directly induces ubiquitination and subsequent proteasomal degradation of ER (**Figure 1**)
  - In preclinical studies, vepdegestrant demonstrated potent ER degradation and tumor growth inhibition, including tumor regression (**Figure 2**)[6]
- Vepdegestrant monotherapy once daily (QD) showed antitumor activity and was well tolerated in the phase 2 expansion (VERITAC) of a phase 1/2 study (NCT04072952) in heavily pretreated patients with ER+/HER2- advanced breast cancer[7]
  - Clinical benefit rate[a] was 37.1% (95% CI: 21.5–55.1) at 200 mg QD (n=35)
  - Most adverse events were grade 1/2
  - Vepdegestrant 200 mg QD was selected as the recommended phase 3 monotherapy dose based on results from this study

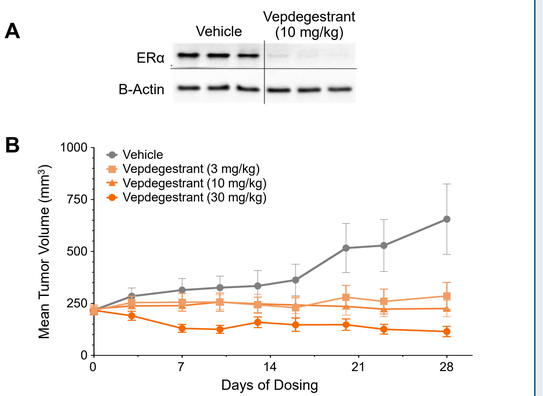
[a]Rate of confirmed complete response, partial response, or stable disease ≥24 weeks; evaluable patients were enrolled ≥24 weeks prior to the data cutoff

Figure 1: Mechanism of action of vepdegestrant[a]



[a]General PROTAC protein degrader is shown
ER=estrogen receptor; PROTAC=PROteolysis TArgeting Chimera

Figure 2: ER degradation (A) and tumor growth inhibition/regression (B) with vepdegestrant in an estradiol-dependent MCF7 xenograft model[6]

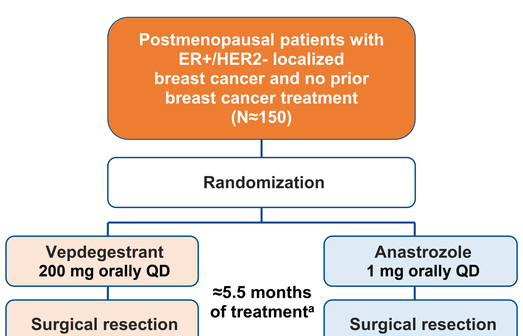


ER=estrogen receptor

Study Design

- In this open-label, randomized, noncomparative, multicountry, phase 2 study, postmenopausal women with ER+/HER2- localized breast cancer receive neoadjuvant vepdegestrant 200 mg or anastrozole 1 mg orally QD until surgical resection approximately 5.5 months after starting treatment (**Figure 3**)
- Eligible patients have confirmed ER+/HER2- breast cancer amenable to surgical resection (**Table 1**)
- Outcome measures are shown in **Table 2**
- Enrollment is ongoing

Figure 3: TACTIVE-N trial schema



[a]Cycle 6, day 18±10 days
ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; QD=once daily

Table 1: TACTIVE-N key eligibility criteria

Inclusion criteria	Exclusion criteria
• Postmenopausal women aged ≥18 years • Histologically or cytologically confirmed ER+/HER2- breast cancer per local assessment – ER+ with ER staining of ≥10% of tumor cell nuclei – Ki-67 score ≥5% • Clinical T1c-T4c, N0-N2, M0 breast cancer amenable to definitive surgical resection • Primary tumor ≥1.5 cm by imaging • ECOG performance status of 0 or 1 • Willingness to undergo a screening biopsy, an on-treatment biopsy, and surgical resection	• Bilateral breast ductal carcinoma in situ or invasive breast cancer • Prior treatment for breast cancer

ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2

Table 2: TACTIVE-N outcome measures

Primary objective	Endpoint
• Evaluate the effects of vepdegestrant or anastrozole on Ki-67 expression in tumors after 2 weeks of treatment	• Percent change in Ki-67 expression in tumors
Secondary objectives	**Endpoints**
• Evaluate the safety and tolerability of vepdegestrant or anastrozole	• Incidence of AEs, SAEs, and AEs leading to discontinuation
• Evaluate the pathologic response at time of surgical resection	• Pathologic stage • Pathologic complete response rate • Modified preoperative endocrine prognostic index score
• Evaluate the clinical response at time of surgical resection	• Rate of breast-conserving surgery • Rate of radiographic response during cycle 6 • Best percentage change in caliper measurement on cycle 6, day 1

AE=adverse event; SAE=serious AE

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Disclosure

Dr Fasching has served as an invited speaker and/or on advisory boards for Agendia, AstraZeneca, Daiichi Sankyo, Eisai, Gilead, Hexal, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi Aventis, and Seagen. He serves as Principal Investigator for BioNTech and Cepheid, and has received compensation for medical writing support from Roche.

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Please scan this QR code with your smartphone app to view a **video of the mechanism of action of vepdegestrant**

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