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TACTIVE-N: Phase 2 study of neoadjuvant vepdegestrant, a PROteolysis Targeting chimera (PROTAC) estrogen receptor (ER) degrader, or anastrozole in postmenopausal ER+/human epidermal growth factor receptor 2 (HER2)- localized breast cancer (BC)

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Background

This open-label, noncomparative phase 2 study (TACTIVE-N; NCT05549505) evaluated neoadjuvant vepdegestrant, an oral PROTAC ER degrader, or anastrozole in postmenopausal women with ER+/HER2- localized BC amenable to surgical resection.

Methods

Patients (pts) were randomized 2:1 to vepdegestrant 200 mg QD or anastrozole 1 mg QD until surgical resection ~5.5 months later. Tumor tissue was taken at screening, week 2 (C1D15), and surgery (C6D18). Primary endpoint was Ki67 score % change from baseline (CFB) to C1D15. Secondary endpoints included pathologic complete response (pCR), modified pre-operative endocrine prognostic index (mPEPI) score 0, breast-conserving surgery rate, radiographic response, and safety. Assessments of ER and progesterone receptor (PgR) protein levels were exploratory.

Results

As of 19 Nov 2024, 152 pts (median age: 66 y; tumor >2 cm: 66%; Ki-67 <20%: 49%) were randomized (vepdegestrant n=102; anastrozole n=50). Key results are in the Table below. In pts receiving vepdegestrant, the % geometric mean CFB in Ki67 score was -71% at C1D15 and -85% at C6D18. Vepdegestrant reduced median tumor ER protein levels by 76% at C1D15 and by 94% at C6D18. Treatment-emergent adverse events (AEs) led to vepdegestrant dose reduction in 7 pts (not permitted for anastrozole) and to discontinuation of vepdegestrant in 3 pts and anastrozole in 4 pts. The most common treatment-related AEs (TRAEs) in patients receiving vepdegestrant were hot flush (24%), asthenia (19%), and constipation (14%); 3% had grade 3 TRAEs and 0 had grade 4/5 TRAEs.Table: 293MO

Summary of outcome measures

	Vepdegestrant (n=102)	Anastrozole (n=50)
Ki67 score, geometric mean CFB, % (95% CI) ^a C1D15 (primary endpoint)C6D18	-71 (-79, -61)-85 (-90, -76)	-73 (-83, -58)-83 (-91, -67)
pCR, %	1	0
mPEPI 0, %	21	20
Breast-conserving surgery, %	70	54
Radiographic response, % ^b	41	42
ER (AQUA), median CFB, % (range)C1D15C6D18	-76 (-99, 6)-94 (-100, -34)	Not evaluated
PgR H-score, median CFB, % (range)C1D15C6D18	-100 (-100, 11)-100 (-100, 268)	-78 (-100, 1186)-98 (-100, 1543)

Not all pts had assessments at each timepoint.AQUA, automated quantitative analysis.^aBased on ANCOVA with baseline Ki67 (< vs ≥20%) and

tumor size (≤ 2 , >2 to <5 , or ≥ 5 cm) as covariates.^bPer modified RECIST.

Conclusions

Neoadjuvant vepdegestrant was well tolerated and demonstrated biological and clinical activity in postmenopausal women with ER+/HER2-localized BC. Vepdegestrant led to robust ER protein degradation in tumor tissue, supporting its pharmacodynamic effect in pts with BC.

Clinical trial identification

NCT05549505.

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Legal entity responsible for the study

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Disclosure

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