TACTIVE-N: Phase 2 Study of Neoadjuvant Vepdegestrant, a PROTAC Estrogen Receptor (ER) Degrader, or Anastrozole in Postmenopausal ER+/Human Epidermal Growth Factor Receptor 2-Negative Localized Breast Cancer

PA Fasching[1], B Bermejo de las Heras[2], E Arkania[3], N Martinez Jañez[4], M Ruíz-Borrego[5], S Blau[6], SA Hurvitz[7], G Spera[8], M Lachowicz[9], E Duperret[9], W Wu[9], X. Zhi[9], J Parameswaran[9], O Valota[10], I Blancas[11]

[1]University Hospital Erlangen and Comprehensive Cancer Center Erlangen, Erlangen, Germany; [2]Hospital Clínico Universitario de Valencia, Valencia, Spain; [3]Israeli-Georgian Multiprofile Medical Center "Healthycore", Tbilisi, Georgia; [4]Hospital Univeritario Ramón y Cajal, Madrid, Spain; [5]Hospital Virgen del Rocío, Seville, and Grupo Español de Investigación en Cáncer de Mama, Spanish Breast Cancer Group, Madrid, Spain; [6]Northwest Medical Specialties, Tacoma, WA; [7]Fred Hutchinson Cancer Center, University of Washington, Seattle, WA; [8]Translational Research in Oncology, Montevideo, Uruguay; [9]Arvinas Operations, Inc., New Haven, CT; [10]Pfizer Srl, Milan, Italy; [11]Hospital Universitario Clínico San Cecilio, Granada and Grupo Español de Investigación en Cáncer de Mama, Spanish Breast Cancer Group, Madrid, Spain

Declaration of Interests

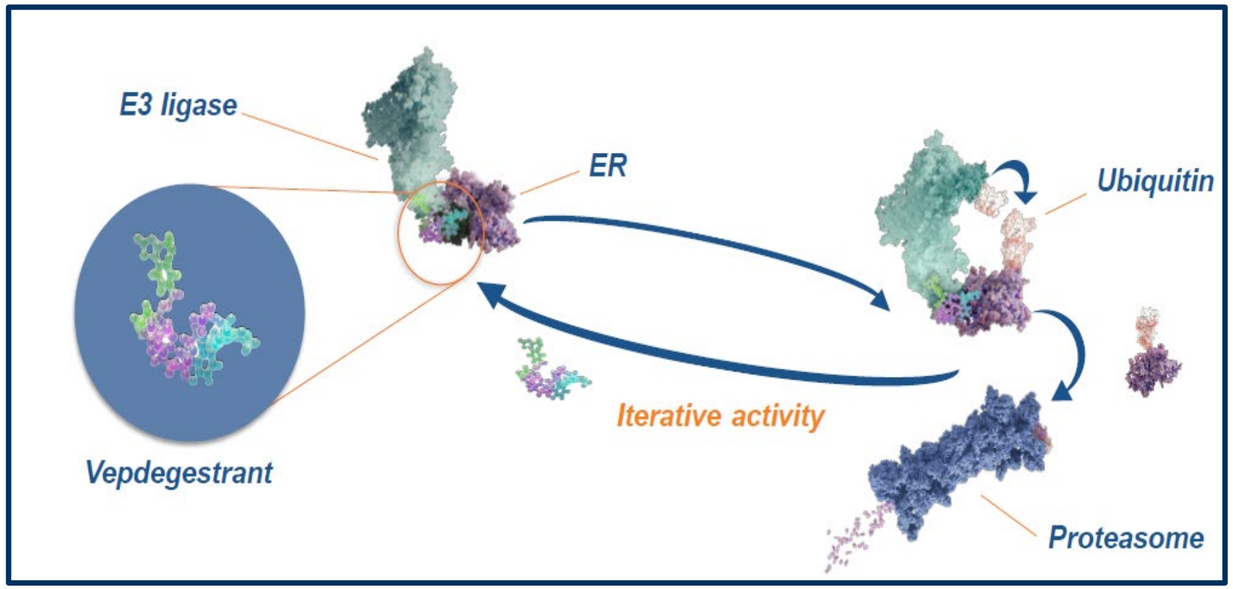
Invited speaker and/or advisory board member for: Agendia, AstraZeneca, Daiichi-Sankyo, Eisai, Gilead, Guardant Health, Hexal, Lilly, Medac, Menarini, Merck, Sharp & Dohme, Mylan, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi Aventis, Seagen, Veracyte.

Served as a local PI for BioNTech and Cepheid.

Background

- Surgery is the cornerstone of treatment for early and locally advanced BC
  - SOC for HR+ HER2- disease includes neoadjuvant chemotherapy to increase surgical options[1]
- Neoadjuvant ET provides an effective and less toxic alternative to chemotherapy for patients with localized ER+/HER2- disease[2]
- Vepdegestrant is a selective, oral PROTAC ER degrader that targets WT and mutant ER[3,4]
- Vepdegestrant has demonstrated a favorable tolerability profile in previously treated ER+/HER2− advanced breast cancer,[5-7] supporting evaluation earlier in the disease course, including the treatment-naïve, neoadjuvant setting

Vepdegestrant, an oral PROTAC ER degrader, has a unique MOA that directly harnesses the ubiquitin-proteasome system to degrade ER[8]



1. Cardoso F, et al. Ann Oncol. 2019;30(8):1194-1220. 2. Spring LM, et al. JAMA Oncol. 2016;2(11):1477. 3. Békés M, et al. Nat Rev Drug Discov 2022;21(3):181-200. 4. Gough SM, et al. Clin Cancer Res. 2024;30(16):3549-3563. 5. Campone M, et al. N Engl J Med. 2025;Epub ahead of print. 6. Hamilton EP, et al. ESMO. 2023; 390P. 7. Hurvitz SA, et al. SABCS. 2023; PO3-05-08. 8. Hamilton EP, et al. Futur Oncol. 2024;20(32):2447–55

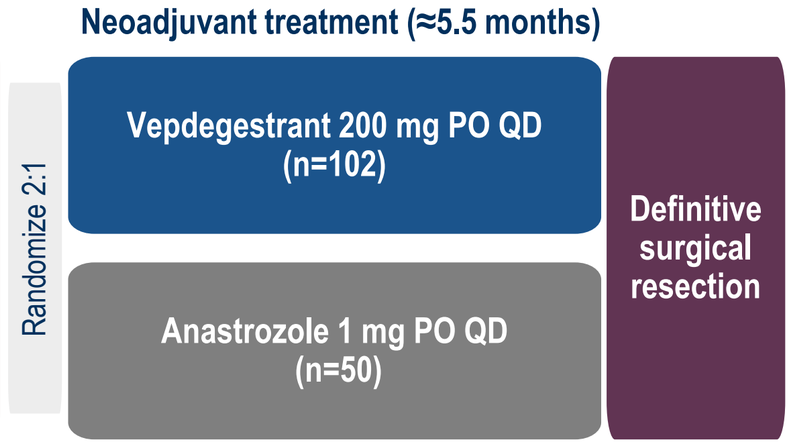
BC=breast cancer; ER=estrogen receptor; *ESR1m*=estrogen receptor 1 gene mutation; ET=endocrine therapy; HER2-=human epidermal growth factor receptor; HR=hormone receptor; MOA=mechanism of action; PROTAC=PROteolysis TArgeting Chimera; SOC=standard of care; WT=wild type.

TACTIVE-N: Open-Label, Noncomparative Phase 2 Study

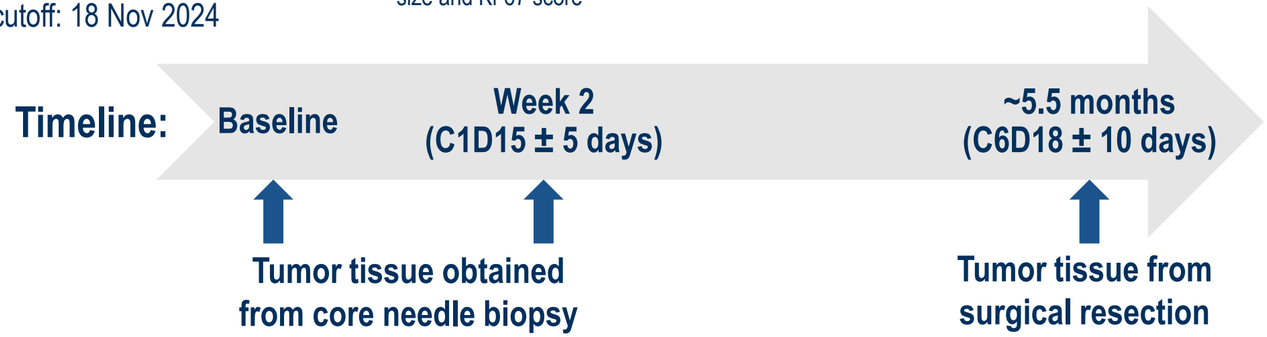
Study Design

Key eligibility criteria:

- ER+/HER2- localized BC
- Postmenopausal women
- Clinical T1c-T4c (≥1.5 cm), N0-N2, M0 amenable to surgical resection
- No prior therapy
- ER expression ≥10% (local IHC)
- Ki-67 ≥5% (local lab)



NCT05549505
Data cutoff: 18 Nov 2024



Primary endpoint[b]: Ki-67 expression in tumors at week 2 (C1D15)

Key secondary endpoints[b]: Safety; clinical and pathological responses; mPEPI score at surgery; BCS rate; radiographic response during C6

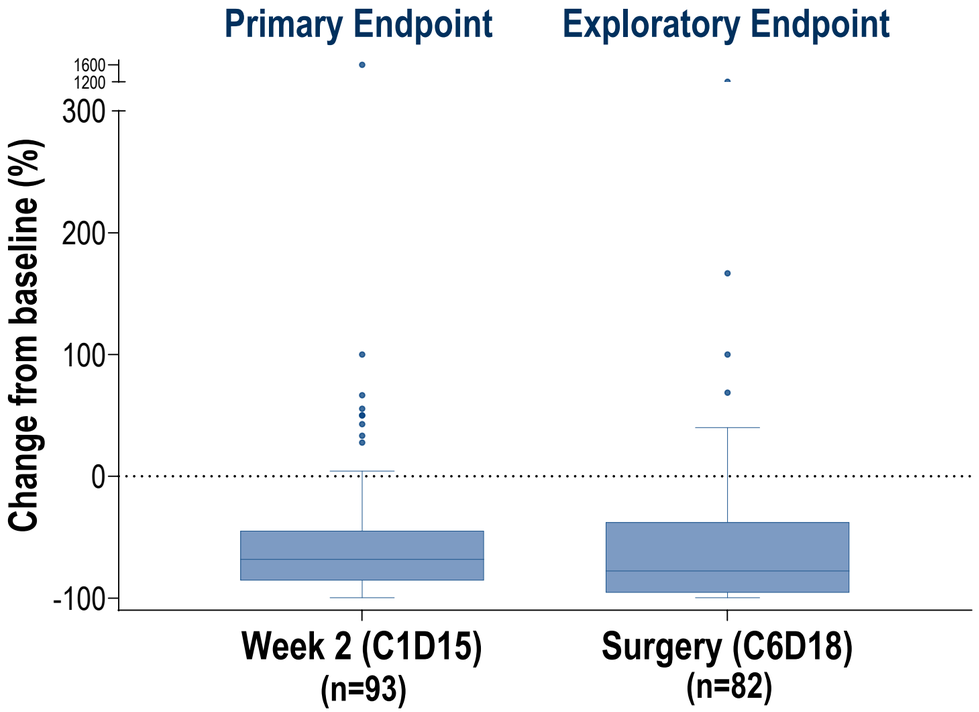
Baseline Characteristics

Parameter	Vepdegestrant (n=102)	Anastrozole (n=50)
Age, years, median (range)	66.0 (50, 88)	66.0 (46, 88)
ECOG PS 0, %	83	90
Ki-67 score <20%, %[c]	51	50
PgR H score ≥1%, %[c]	87	77
Primary tumor size, %		
≤2 cm	35	32
>2 to <5 cm	52	58
≥5 cm	13	10
Disease stage, %		
IA/B	29	20
IIA/B	55	64
IIIA/B	16	16
Lymph node involvement, %		
cN0	68	52
cN1	26	44
cN2a/b	6	4
***ESR1m* positive**, %[d]	2	0

[a]Randomization was stratified by size of primary breast tumor (T-stage: ≤2 cm, >2 to <5 cm, or ≥5 cm) and Ki-67 score (<20% or ≥20%). [b]No formal statistical comparisons were planned. [c]By central assessment in evaluable patients (vepdegestrant, n=100; anastrozole, n=48).[d]*ESR1m* were detected by RNA-seq of tumor tissue in evaluable patients (vepdegestrant, n=92; anastrozole, n=40). BCS=breast conserving surgery; C=cycle; D=day; ER=estrogen receptor; *ESR1m*=estrogen receptor 1 gene mutation; HER2=human epidermal growth factor receptor 2; mPEPI=modified pre-operative endocrine prognostic index; PgR=progesterone receptor; PO=orally; QD=once daily; RNA-seq=RNA sequencing.

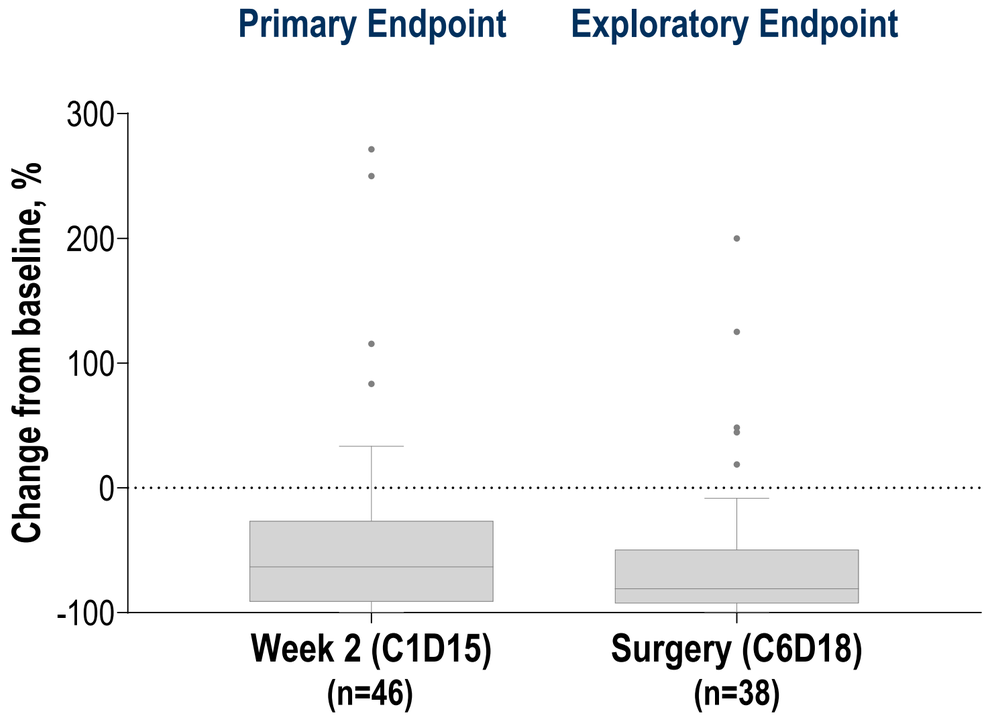
Change in Tumor Ki-67 Expression

Vepdegestrant



	Week 2 (C1D15) (n=93)	Surgery (C6D18) (n=82)
Geometric mean ratio (95% CI)[a]	0.286 (0.207, 0.394)	0.155 (0.098, 0.244)
% change from baseline (95% CI)	-71.4 (-60.6, -79.3)	-84.5 (-75.6, -90.2)

Anastrozole



	Week 2 (C1D15) (n=46)	Surgery (C6D18) (n=38)
Geometric mean ratio (95% CI)[a]	0.271 (0.174, 0.422)	0.172 (0.091, 0.0326)
% change from baseline (95% CI)	-72.9 (-57.8, -82.6)	-82.8 (-67.4, -90.9)

[a]Based on an ANCOVA model with baseline Ki-67 score (assessed centrally: <20% vs ≥20%) and tumor size (≤2 cm, >2 to <5 cm, or ≥5 cm) as covariates for treatment. Geometric mean ratios are back-transformed LSM values from the ANCOVA.
ANCOVA=analysis of covariance; C=cycle; LSM=least square mean.

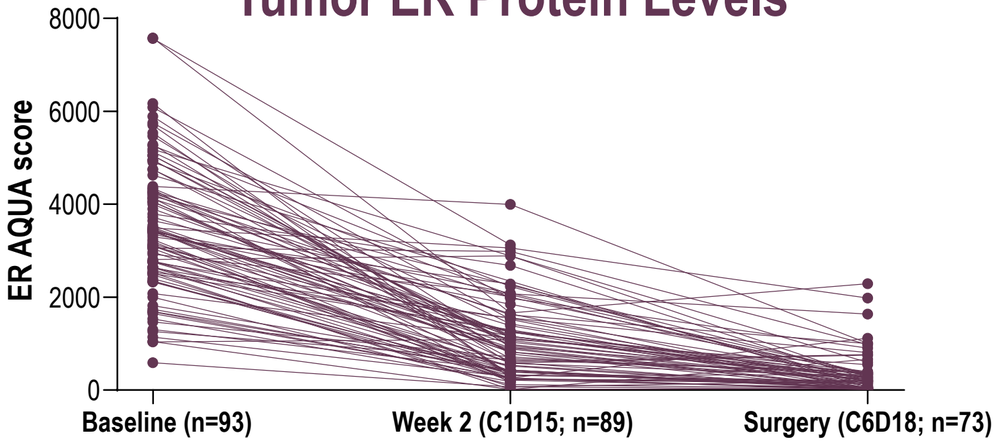
Secondary and Exploratory Endpoints

Secondary Endpoints	Vepdegestrant (n=102)	Anastrozole (n=50)
Pathological complete response, %	1	0
mPEPI score 0 at surgery, % (95% CI)[a]	21 (14, 29)[b]	20 (11, 33)[c]
Breast-conserving surgery at C6D18, % (95% CI)[a]	70 (60, 78)[b]	54 (40, 67)[c]
Radiographic response[d], %	41	42
Complete response	5	8
Partial response	36	34
Stable disease	37	32
Exploratory Endpoints		
PgR H score, % change from baseline, median (range)		
Week 2	-100.0 (-100.0, 10.5)	-78.1 (-100.0, 1185.7)
Surgery	-100.0 (-100.0, 268.4)	-97.5 (-100.0, 1542.9)

[a]95% Wilson CI. [b]90 patients (88%) received surgery as scheduled; 7 (7%) did not undergo surgery; 5 (45%) had unscheduled surgery. [c]40 patients (80%) received surgery as scheduled; 9 (18%) did not undergo surgery; 1 (20%) had unscheduled surgery. [d]Complete response or partial response per mRECIST during C6.
C=cycle; mRECIST=modified Response Evaluation Criterion in Solid Tumors; mPEPI=modified pre-operative endocrine prognostic index.

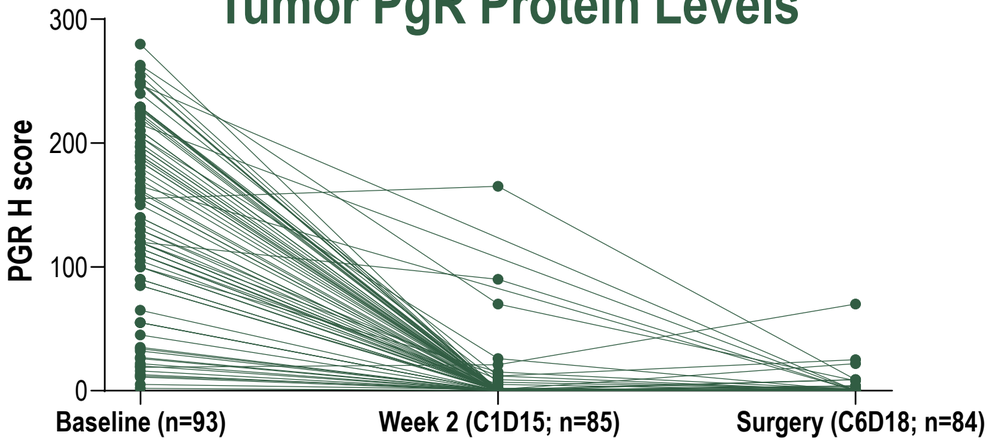
Vepdegestrant Pharmacodynamic Results

Tumor ER Protein Levels



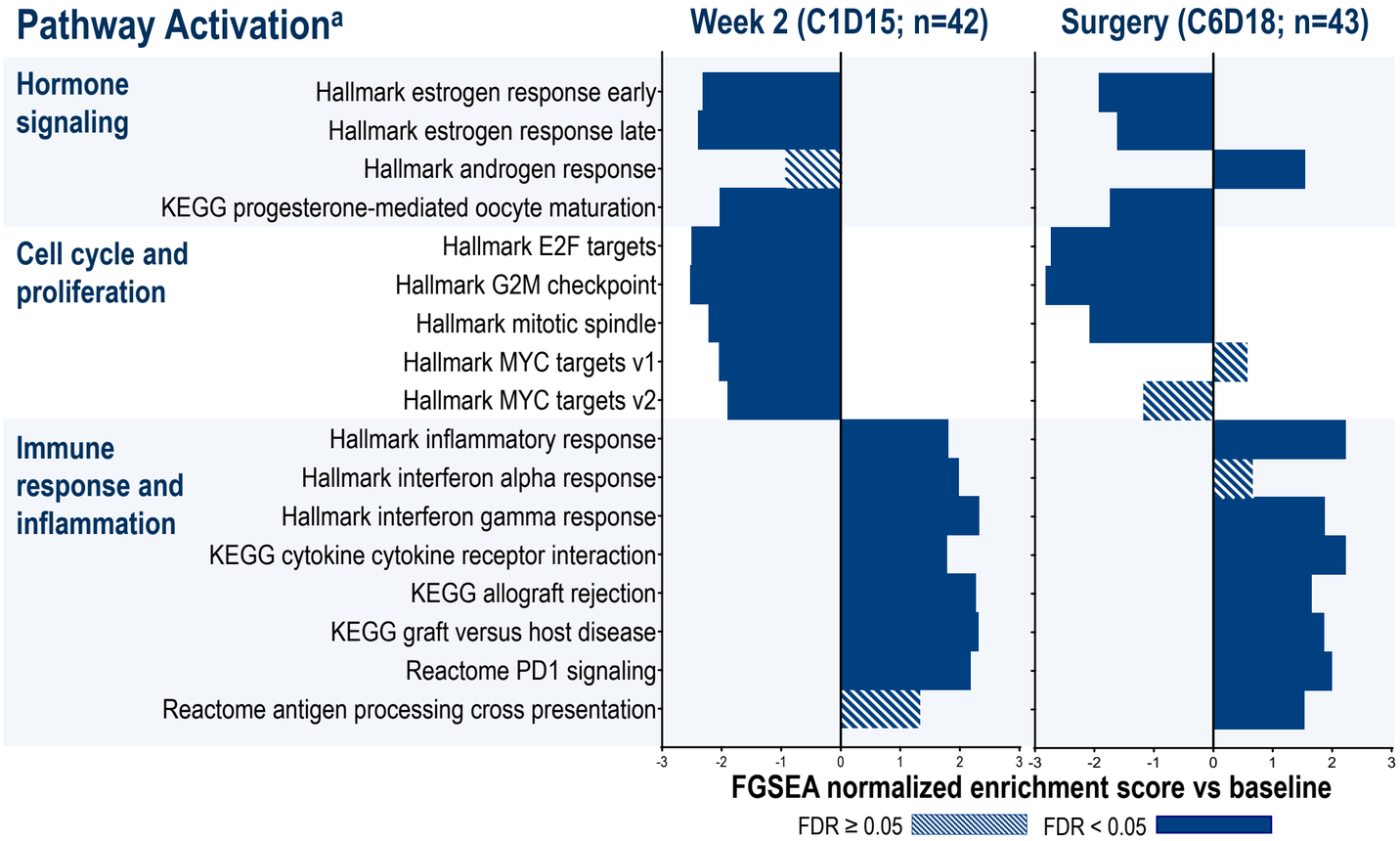
Percent change from baseline, median (range)	-76.1 (-99.4, 5.5)	-94.4 (-99.7, -33.9)

Tumor PgR Protein Levels



Percent change from baseline, median (range)	-100.0 (-100.0, 10.5)	-100.0 (-100.0, 268.4)

RNA-seq Gene Expression Analyses[a]



Vepdegestrant led to robust reductions in ER and PgR protein levels, reduced activation of ER and cell-cycle pathways, and increased activation of immune response pathways at both timepoints

[a]RNA-seq data was only available in a subset of participants with sufficient biopsy tissue remaining. The n values reflect the number of patients with paired biopsies at baseline and the post-baseline timepoint. Statistical significance between time points was calculated using pathway scores (FDR by adjusted *p* value) for selected KEGG, REACTOME and HALLMARK pathways.

AQUA=automated quantitative analysis; ER=estrogen receptor; FDR, false discovery rate; FGSEA, fast gene set enrichment analysis; KEGG=Kyoto Encyclopedia of Genes and Genomes; PgR=progesterone receptor; RNA-seq, RNA sequencing.

Safety

Event, % of patients	Vepdegestrant (n=101)	Anastrozole (n=48)
TEAE		
Any grade	81	77
Grade ≥3	12	15
Serious	4	10
Leading to:		
Treatment discontinuation	3	8
Treatment interruption	15	4
Dose reduction	7	NA
TRAE		
Any grade	64	48
Grade 3	3[a]	2[b]

- Most TEAEs were grade 1/2; no grade 4 TEAEs occurred with vepdegestrant
- No deaths occurred during the study

TRAEs (≥5%), %	Vepdegestrant (n=101)		Anastrozole (n=48)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hot flush	24	0	19	0
Asthenia	19	0	6	0
Constipation	14	0	0	0
Arthralgia	13	0	23	0
Nausea	11	0	2	0
Fatigue	9	0	4	0

[a]Grade 3 TRAEs in the vepdegestrant group were hypertension (n=2) and QT interval prolonged (n=1). [b]Grade 3 TRAEs in the anastrozole group were ALT and AST increased in 1 patient.
ALT=alanine aminotransferase; AST=aspartate aminotransferase ;TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.

Conclusions

- Neoadjuvant vepdegestrant demonstrated biological and clinical activity in this treatment-naïve, predominantly *ESR1* WT population of postmenopausal women with ER+/HER2- localized BC
- Robust ER protein degradation and suppression of ER signaling was observed in tumor tissue from patients treated with vepdegestrant, supporting the pharmacodynamic effect and MOA of a PROTAC ER degrader in patients with BC
- Neoadjuvant vepdegestrant was well tolerated in patients with treatment-naive localized BC, as evidenced by low rates of discontinuation and grade 3 TRAEs

Acknowledgements: We thank the patients who participated in this study and their caregivers, and all investigators, researchers, and coordinators who contributed to TACTIVE-N.

This study is sponsored by Arvinas Estrogen Receptor, Inc, in collaboration with Pfizer, Inc. Medical writing support was provided by Lela Creutz, PhD and Bina Patel, PharmD, of Arvinas Operations, Inc

View a plain language summary of this presentation

BC=breast cancer; ER=estrogen receptor; ESR1=estrogen receptor 1 gene; HER2=human epidermal growth factor receptor 2; MOA=mechanism of action; ; PROTAC=PROteolysis TArgeting Chimera; TRAE=treatment-related adverse event; WT=wild type.