III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026

PROTACS EN CÁNCER DE MAMA

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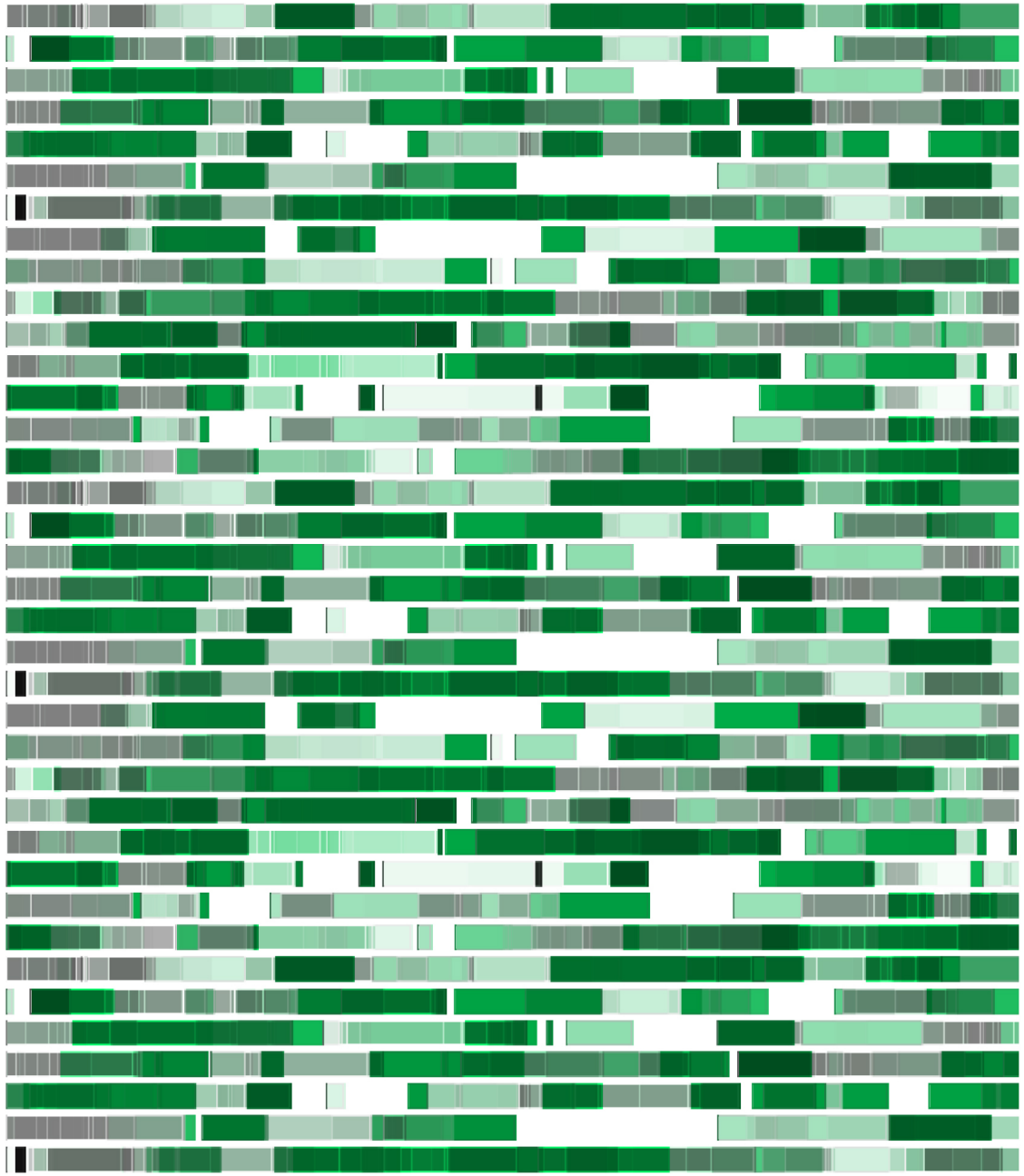
Organizador por:

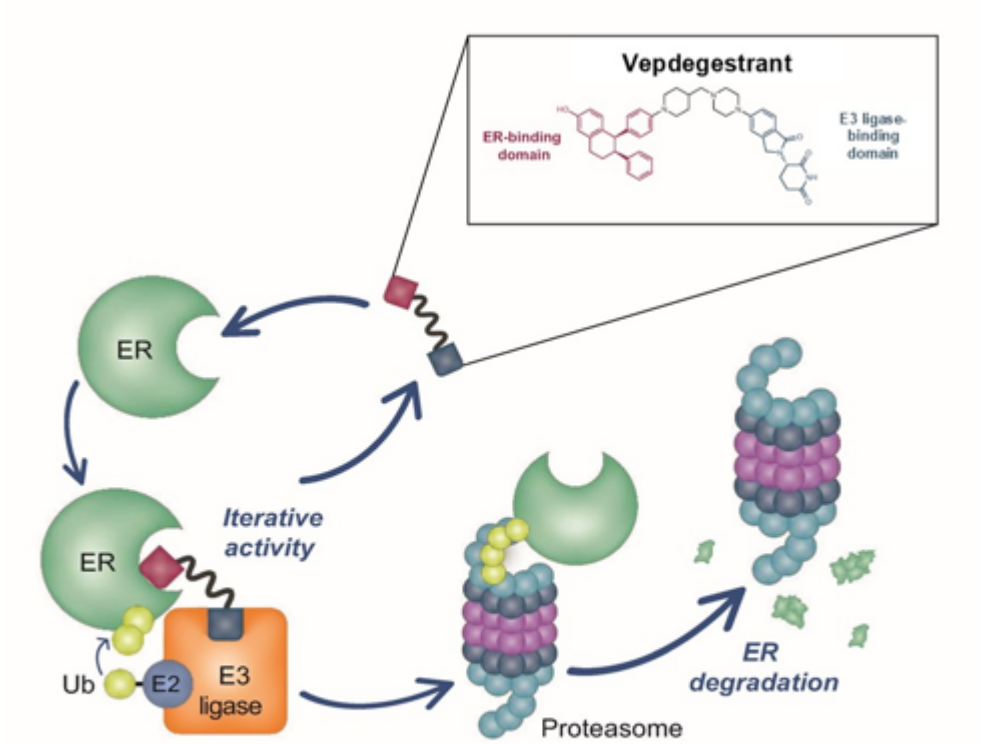
HENDERE HEALTHCARE



PROTACS

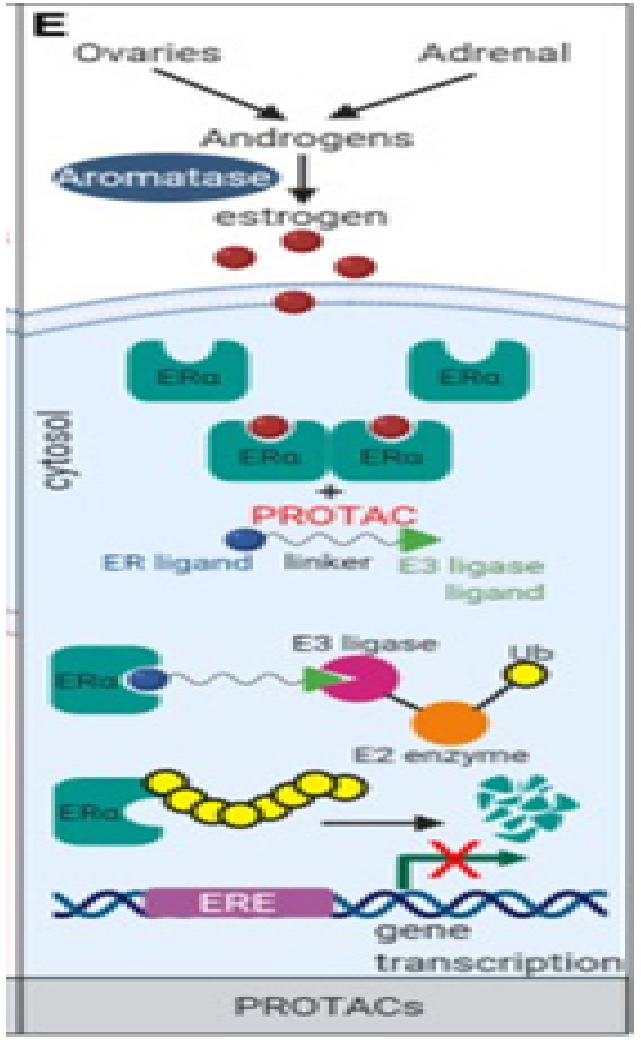
INTRODUCCIÓN Y MECANISMO DE ACCIÓN

MECANISMO DE ACCIÓN



Vepdegestrant has a unique MOA that directly harnesses the ubiquitin-proteasome system to degrade ER[8]

Hamilton EA, ASCO 2025



Hanker et al. Cancer Cell 2020

MECANISMO DE ACCIÓN

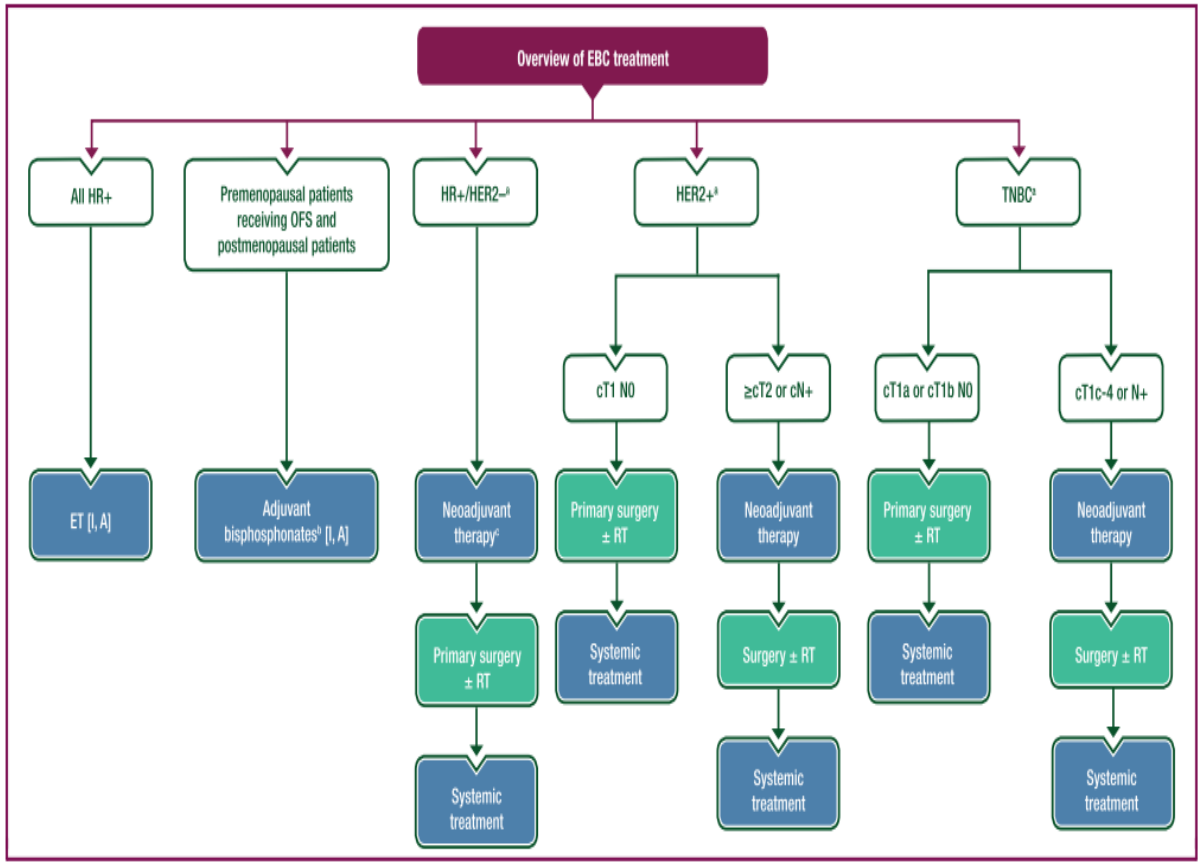
SERD VS PROTAC: MECHANISM OF ACTION

Feature	Oral SERD	PROTAC
ER binding	Direct ER LBD	ER binding + E3 ligand binding
Degradation trigger	Conformational destabilization	Forced ubiquitination
Role of E3 ligase	Indirect/endogenous	Directly recruited
Pharmacology	Occupancy-driven	Event-.driven (catalytic)
Ability to overcome ER mutations	Moderate	High (often mutation-agnostic)
Molecular size	Small molecule	Large bufunctional moleculeSelect
Selectivity risk	Lower	Higher (off-target degradation possible)

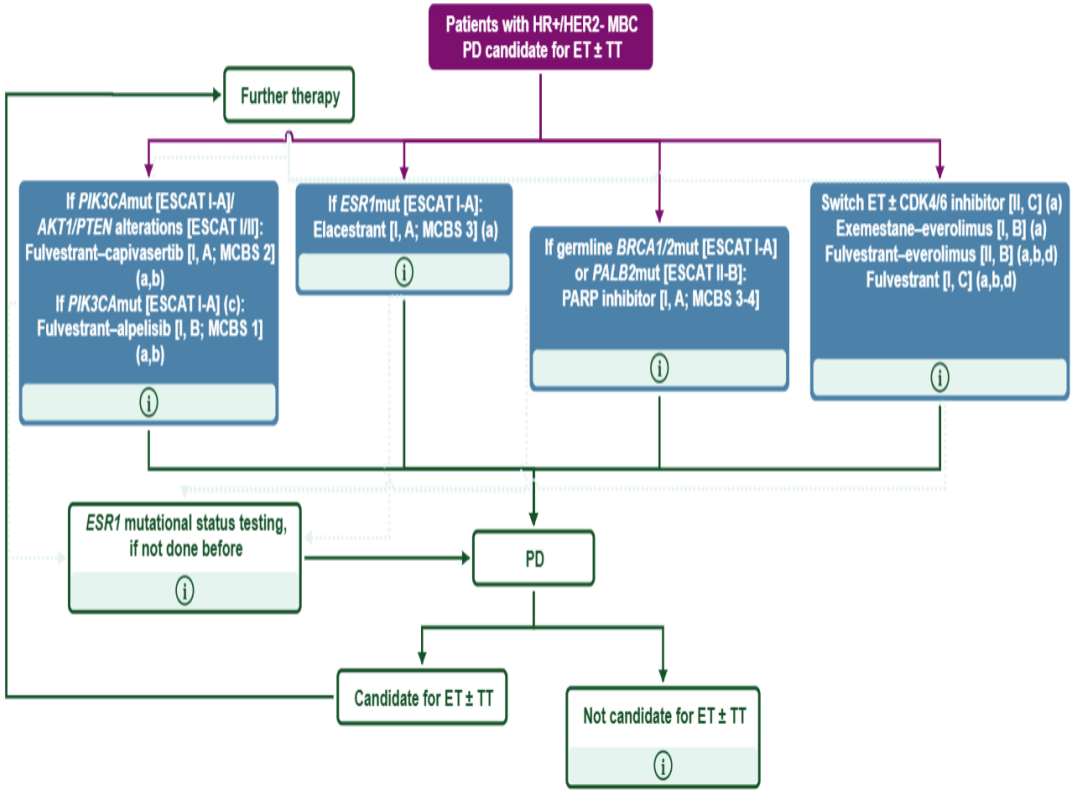
Oral selective estrogen receptor degraders (SERDs) induce ERα antagonism and occupancy-dependent, incomplete receptor degradation. PROTACs are bifunctional molecules that recruit an E3 ubiquitin ligase to ERα, forming a ternary complex that triggers direct, catalytic ubiquitination and proteasomal degradation. This event-driven mechanism results in **deeper and more sustained ER suppression**, including in endocrine-resistant disease.
LBD: ligand-binding domain

Del Mastro L, ESMO Asia 2025

UTILIDAD CLÍNICA RH+



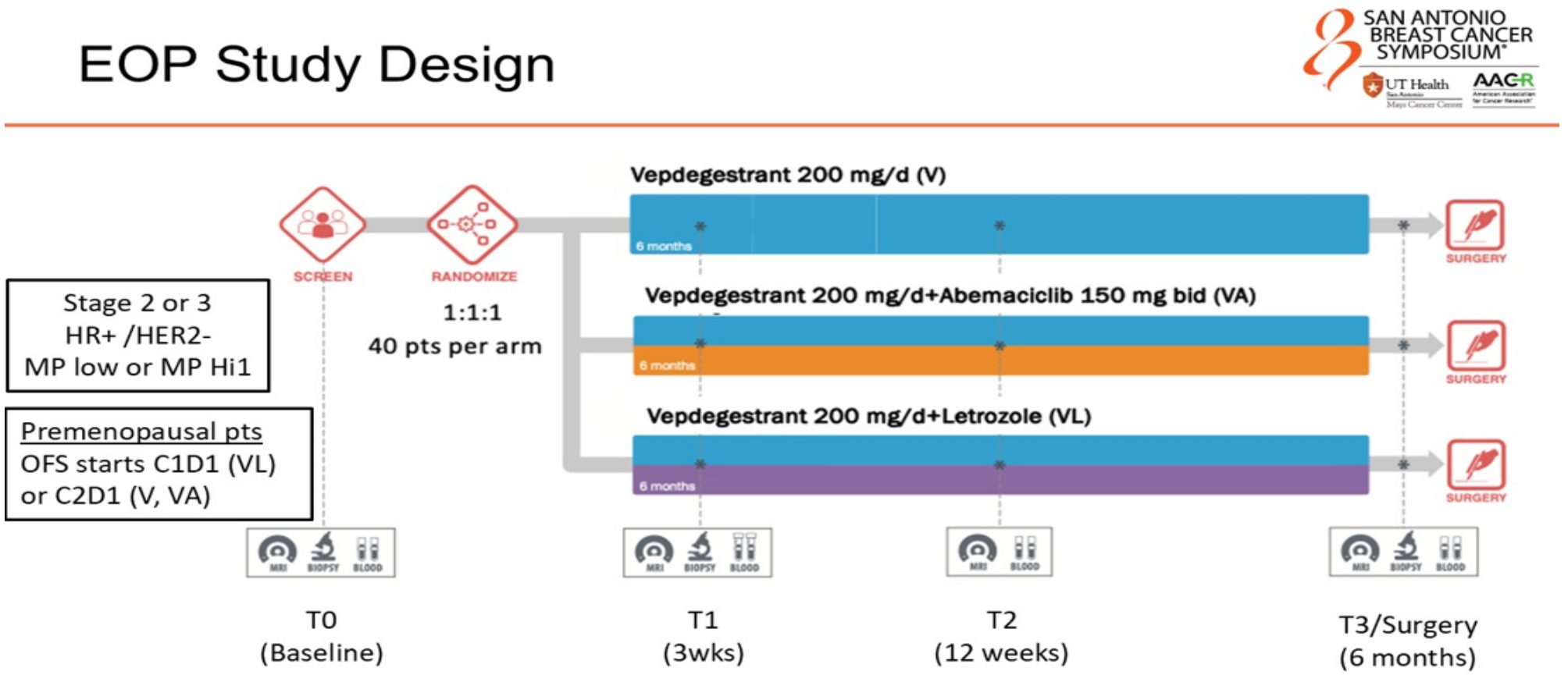
Loibl S et al. Ann Oncol 2024



ESMO living guidelines v1.2 April 2025

PROTACS EN CÁNCER DE MAMA PRECOZ

I-SPY2 ENDOCRINE OPTIMIZATION PILOT (EOP)



Chien J, SABCS 2025

I-SPY2 ENDOCRINE OPTIMIZATION PILOT (EOP)

RESULTS: Patient characteristics and tolerability

SAN ANTONIO BREAST CANCER SYMPOSIUM®

- Enrolled 121 patients
- Baseline Patient/Tumor characteristics:
  - Median age 55
  - 50% premenopausal
  - 85% MammaPrint Low
  - 56% cN+ at screening
  - 45% Baseline Ki67 ≥ 10%
  - 38% lobular or mixed histology

	V (N=40)	VA (N=40)	VL (N=41)
Completed ≥ 75% study therapy	35 (88%)	34 (85%)	37 (90%)
Early discontinuation	6 (15%)	8 (20%)	4 (10%)

- All 3 arms met the primary endpoint of feasibility

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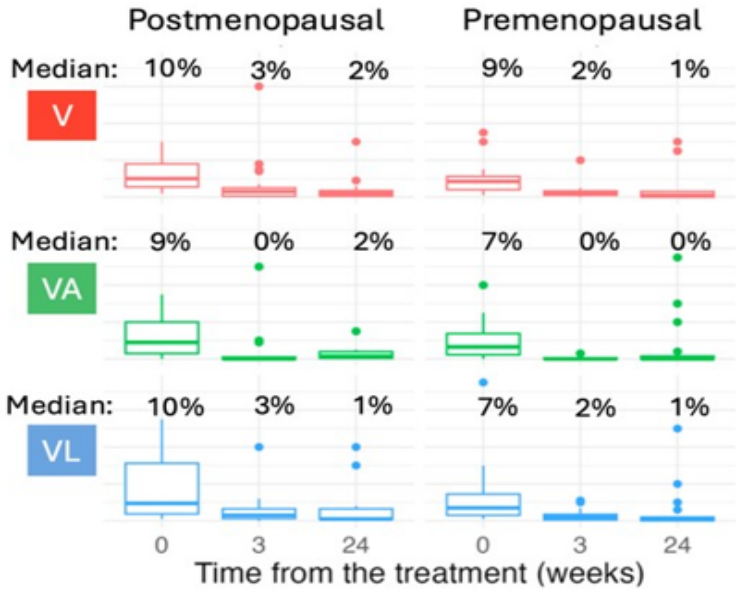
I-SPY2 ENDOCRINE OPTIMIZATION PILOT (EOP)

RESULTS: Ki67

SAN ANTONIO BREAST CANCER SYMPOSIUM®

- Ki67 suppression in all 3 arms was similar between postmenopausal and premenopausal pts, including premenopausal pts who started OFS at C2 (V and VA arms)

	V (N=40)	VA (N=40)	VL (N=41)
Baseline Ki67 Median [Min, Max]	9.00 [1,50]	8.00 [0, 40]	7.50 [1, 75]
3 weeks Ki67 Median [Min, Max]	2.00 [0, 60]	0 [0, 50]	3.00 [0, 40]
Ki67 <10%	35/40 (88%)	32/33 (97%)	36/39 (92%)
Ki67 <2.7%	21/40 (53%)	28/33 (85%)	17/39 (42%)
Surgery % Ki67 Median [Min, Max]	1.00 [0, 30]	1.00 [0, 55]	1.00 [0, 50]
Ki67 <10%	29/33 (88%)	27/31 (87%)	27/31 (87%)
Ki67 <2.7%	19/33 (58%)	22/31 (71%)	22/31 (71%)



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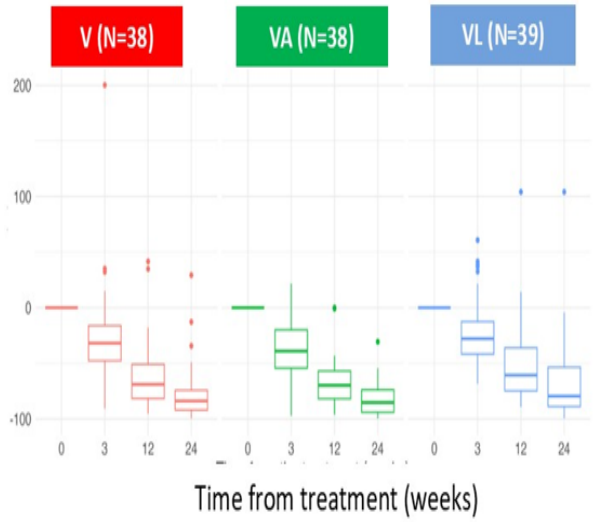
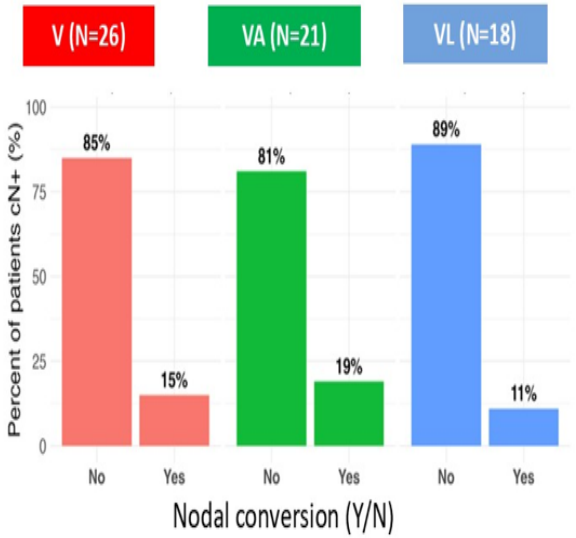
I-SPY2 ENDOCRINE OPTIMIZATION PILOT (EOP)

RESULTS: MRI FTV and Nodal conversion

MRI Functional Tumor Volume (FTV) change (T0→T3)

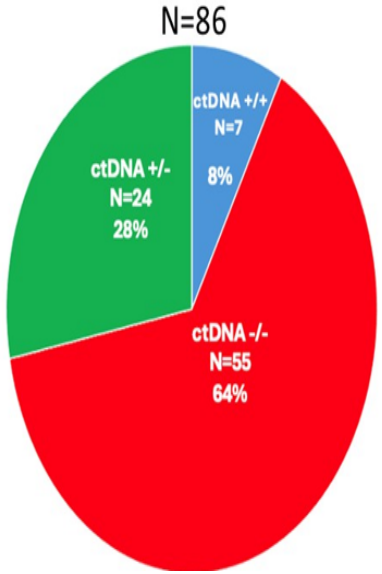


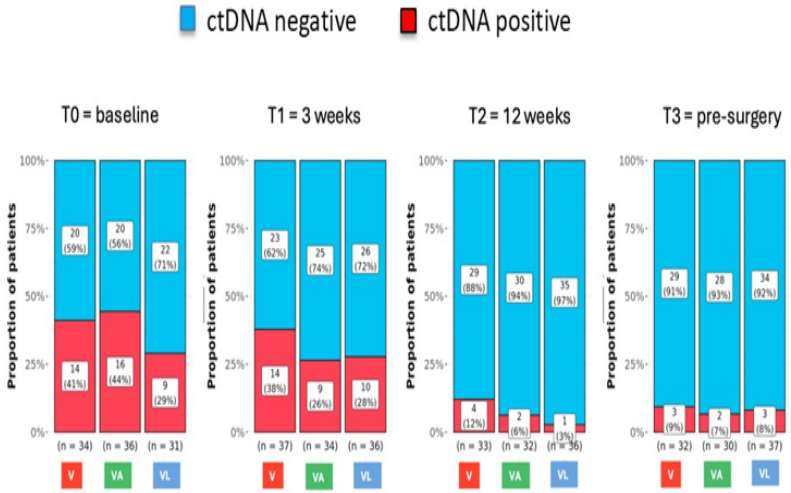
Nodal conversion (cN+ → ypN0)



RESULTS: ctDNA dynamics (Baseline T0 → Pre-surgery T3)

- 31/86 (36%) ctDNA+ at baseline
- 24/31 (77%) clear ctDNA by surgery
- No patients were ctDNA negative at baseline and ctDNA+ at pre-op (T3).





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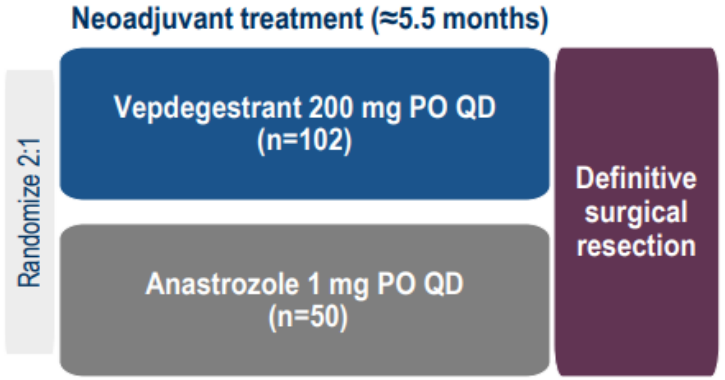
TACTIVE-N

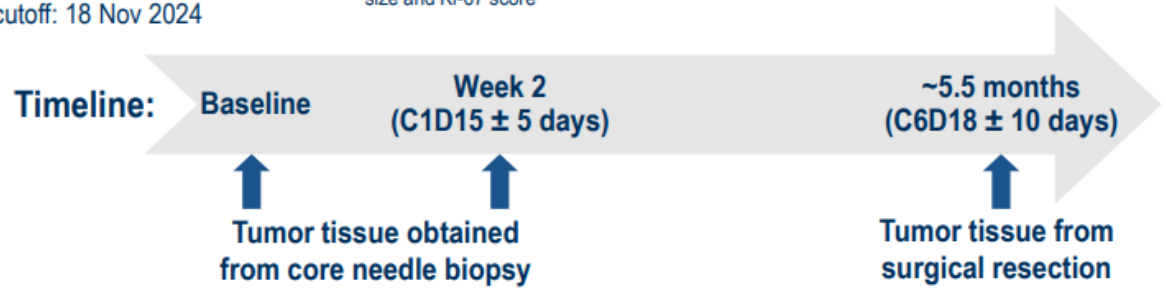
Study Design

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

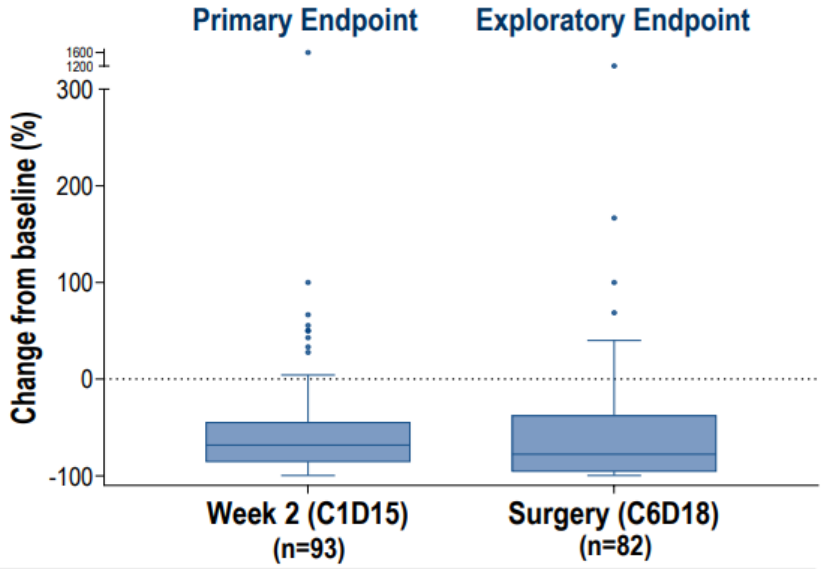
Parameter	Vepdegestrant (n=102)	Anastrozole (n=50)
Age, years, median (range)	66.0 (50, 88)	66.0 (46, 88)
ECOG PS 0, %	83	90
Ki-67 score <20%, %[c]	51	50
PgR H score ≥1%, %[c]	87	77
Primary tumor size, %		
≤2 cm	35	32
>2 to <5 cm	52	58
≥5 cm	13	10
Disease stage, %		
IA/B	29	20
IIA/B	55	64
IIIA/B	16	16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

Fasching PA, ESMO 2025

TACTIVE-N

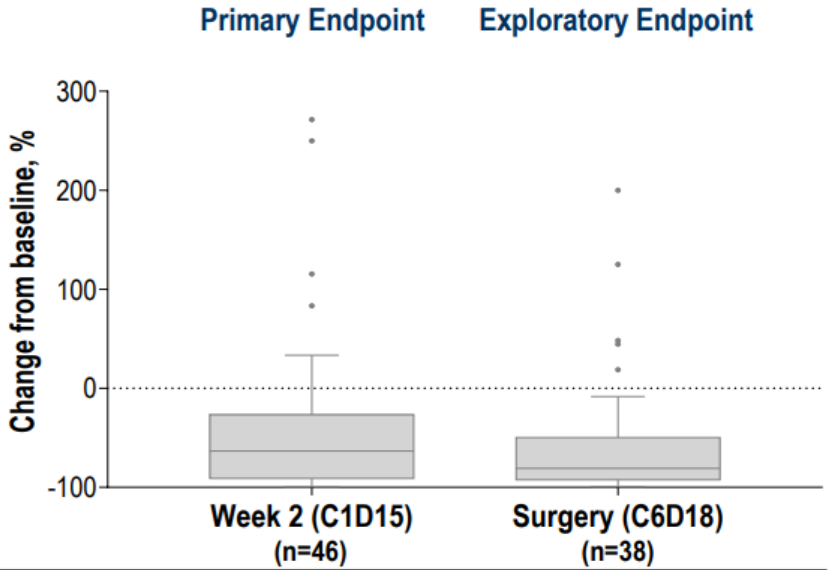
Change in Tumor Ki-67 Expression

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)

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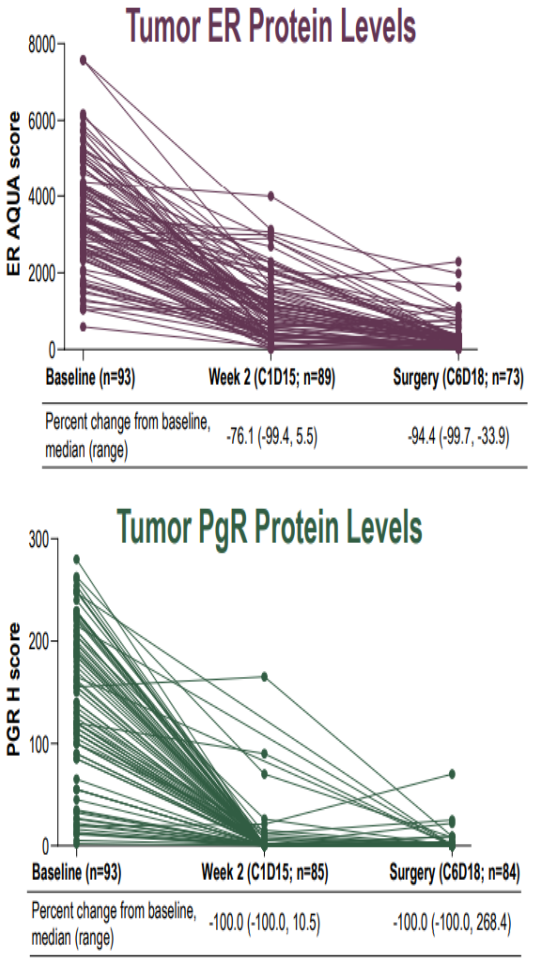
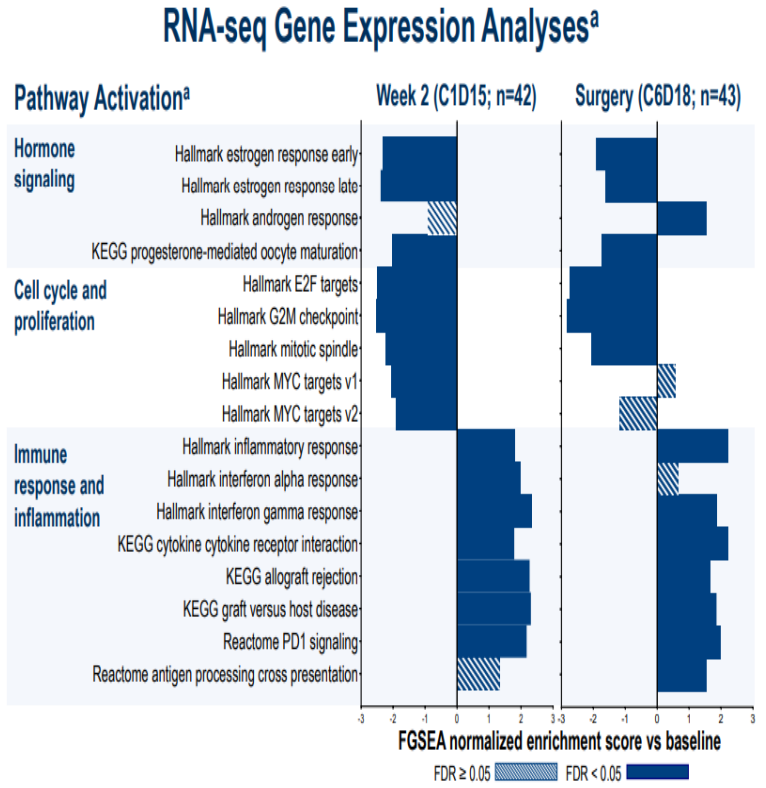
TACTIVE-N

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)





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

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TACTIVE-N

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

	Vepdegestrant (n=101)		Anastrozole (n=48)	
TRAEs (≥5%), %	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

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VERITAC-1

Phase 1/2 Study Design[a]

First-in-human, open-label, 3-part study of ARV-471 alone or in combination with palbociclib in patients with ER+/HER2- locally advanced/metastatic breast cancer

Phase 1 dose escalation (Part A)	Phase 2 cohort expansion (Part B; VERITAC)	Phase 1b combination (Part C)
Treatment • ARV-471 orally	**Treatment** • ARV-471 orally	**Treatment** • ARV-471 plus palbociclib orally
Primary objective • Evaluate the safety and tolerability of ARV-471 in order to estimate the MTD and select the RP2Ds	**Primary objective** • Assess the antitumor activity of ARV-471	**Primary objective** • Evaluate the safety and tolerability of ARV-471 plus palbociclib and select the RP2D of the combination

[a]ClinicalTrials.gov: NCT04072952
ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; MTD=maximum tolerated dose; RP2D=recommended phase 2 dose

Hurvitz SA, SABCS 2022

VERITAC-1

DOSE ESCALATION RESULTS

- As of September 30, 2021, 60 patients received ARV-471
  - Total daily doses ranged from 30–700 mg
- ARV-471 was well tolerated at all doses, with no DLTs or grade ≥4 TRAEs; most TRAEs were grade 1/2
- The CBR[a] was 40% (95% CI: 26–56) in 47 evaluable patients
- 3 patients had confirmed PRs
- Preliminary PK data showed dose-related increases for AUC_{24} and C_{max} from 30–500 mg daily doses
- At the 200-mg and 500-mg doses, mean exposure on day 15 exceeded the nonclinical efficacious range by >2-fold and >5-fold, respectively[2]
- ER degradation up to 89% was observed; median and mean ER degradation across dose levels was 67% and 64%, respectively

DOSE EXPANSION:

57.7% MUT ESR1
54.9% enf visceral
Tratamientos previos:
- 100% iCDK
- 90.1% IA previo
- 79.8% FULV
- 45.1% QT en M1

Phase 2 cohort expansion (Part B; VERITAC)

Key eligibility criteria
- Histologically or cytologically confirmed ER+ and HER2- advanced breast cancer
- Measurable or nonmeasurable disease per RECIST criteria v1.1
- ≥1 prior endocrine regimen (≥1 regimen for ≥6 months in the locally advanced or metastatic setting)
- ≥1 prior CDK4/6 inhibitor
- ≤1 prior chemotherapy regimen in the locally advanced or metastatic setting

ARV-471 200 mg orally QD[a] (n=35)

ARV-471 500 mg orally QD[a] (n=36)

Primary endpoint
- CBR (rate of confirmed CR or PR or SD ≥24 weeks)[b]

Secondary endpoints
- ORR, DOR, PFS, and OS
- AEs and laboratory abnormalities
- PK parameters

Exploratory endpoints
- *ESR1* mutational status
- ER protein levels

Data cutoff date for this analysis
- June 6, 2022

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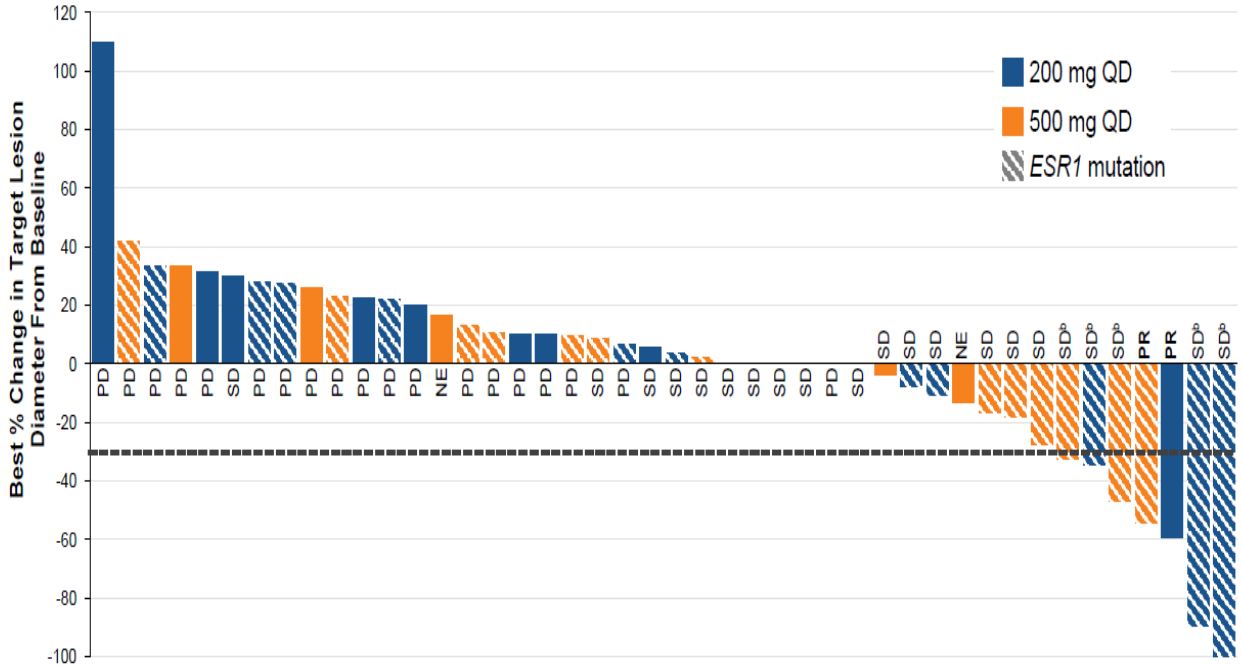
VERITAC-1

Primary Endpoint: Clinical Benefit Rate[a] (VERITAC)

	200 mg QD (n=35)	500 mg QD (n=36)	Total (N=71)
CBR, % (95% CI)	37.1 (21.5–55.1)	38.9 (23.1–56.5)	38.0 (26.8–50.3)
Patients with mutant *ESR1*	(n=19)	(n=22)	(n=41)
CBR, % (95% CI)	47.4 (24.4–71.1)	54.5 (32.2–75.6)	51.2 (35.1–67.1)

Tumor Response[a] (VERITAC)



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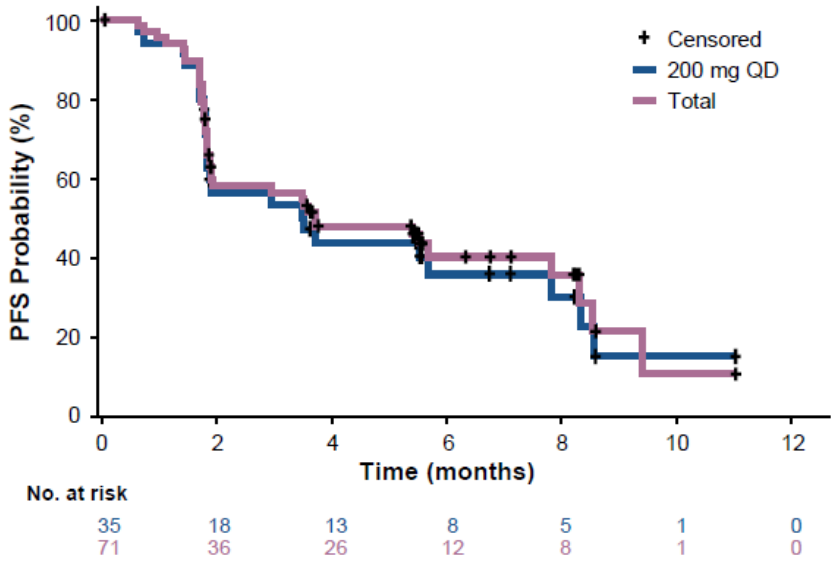
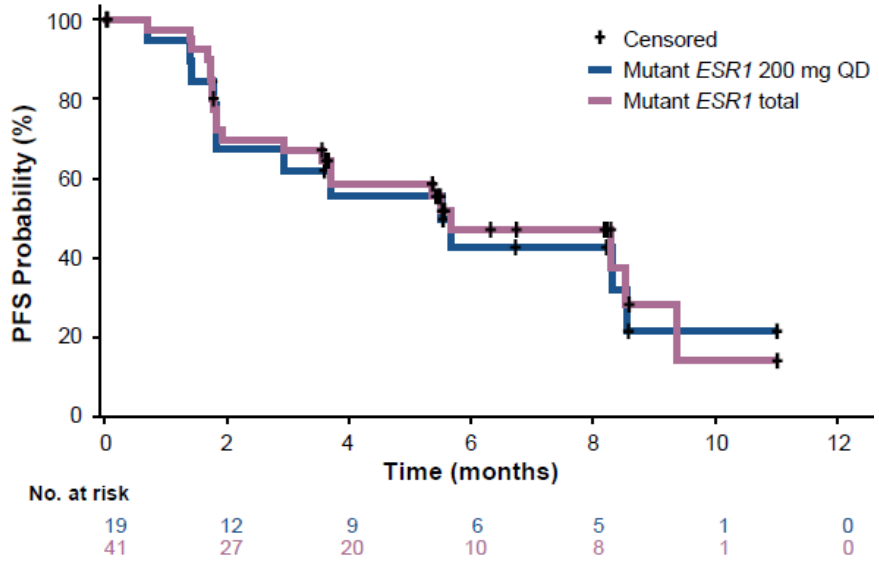
VERITAC-1

Progression-Free Survival[a] (VERITAC)

	All Patients	
	200 mg QD (n=35)	Total (N=71)
Events, n (%)	24 (68.6)	41 (57.7)
mPFS, mo (95% CI)	3.5 (1.8–7.8)	3.7 (1.9–8.3)



	Mutant *ESR1*	
	200 mg QD (n=19)	Total (n=41)
Events, n (%)	12 (63.2)	22 (53.7)
mPFS, mo (95% CI)	5.5 (1.8–8.5)	5.7 (3.6–9.4)



[a]Limited follow-up in 500-mg QD cohort led to ≥50% of patients censored for PFS (curve not shown)
ESR1=estrogen receptor 1 gene; mPFS=median progression-free survival; PFS=progression-free survival; QD=once daily

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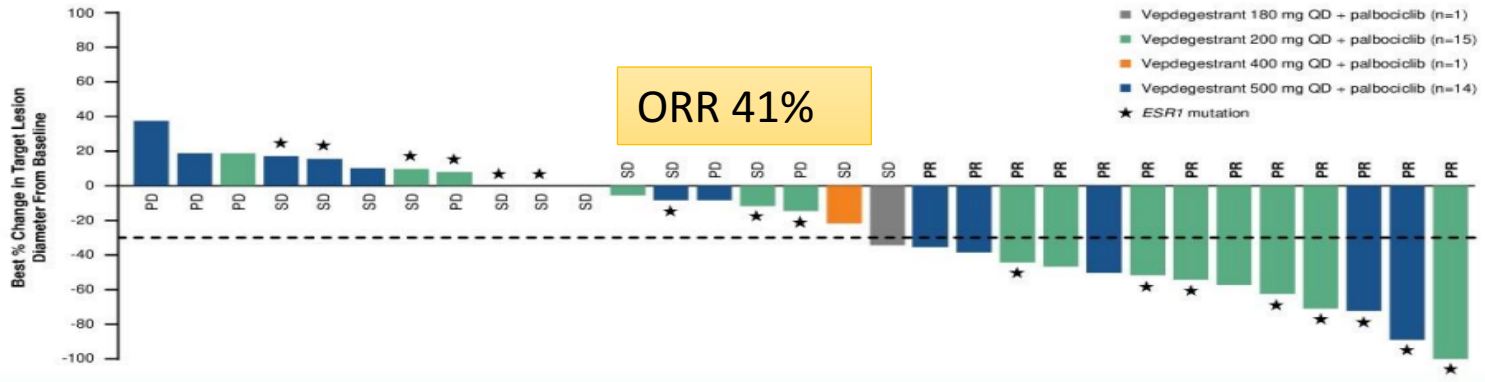
VERITAC-1: PARTE C (+PALBOCICLIB)

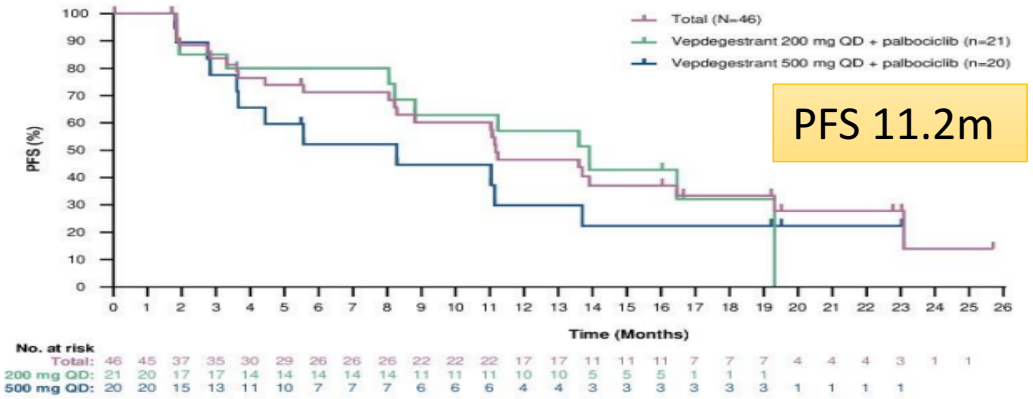
Characteristic	Total (N=46)
Baseline *ESR1* status, n (%)[a]	
Mutant	29 (63)
Wild type[b]	15 (33)
Prior regimens, median (range)	
Any setting	4 (1–11)
Metastatic setting	3 (0–7)
Type of prior therapy, n (%)	
CDK4/6 inhibitor	40 (87)
Palbociclib	36 (78)
Aromatase inhibitor	45 (98)
Fulvestrant	37 (80)
Chemotherapy	
Any setting	36 (78)
Metastatic setting	22 (48)

Figure 1: Antitumor activity (best percentage change from baseline in sum of target lesions) in response-evaluable patients (n=31)



ESR1=estrogen receptor 1 gene; PD=progressive disease; PR=confirmed partial response; QD=once daily; SD=stable disease.

Figure 2: PFS analysis



Overall	Total (N=46)	200-mg QD cohort (n=21)	500-mg QD cohort (n=20)
Events, n (%)	27 (59)[a]	12 (57)	12 (60)
mPFS, months (95% CI)	11.2 (8.2–16.5)	13.9 (8.1–NR)	8.3 (3.6–13.7)
Mutant *ESR1*			
	Total (n=29)	200-mg QD cohort (n=14)	500-mg QD cohort (n=12)[b]
Events, n (%)	16 (55)	7 (50)	7 (58)
mPFS, months (95% CI)	13.7 (8.2–NR)	13.9 (8.1–NR)	8.3 (2.8–13.7)
Wild-type *ESR1*			
	Total (n=15)	200-mg QD cohort (n=7)	500-mg QD cohort (n=6)[b]
Events, n (%)	10 (67)	5 (71)	4 (67)
mPFS, months (95% CI)	11.1 (2.8–19.3)	11.2 (1.8–NR)	7.4 (1.8–NR)

[a]2 (100%) events occurred in patients who received vepdegestrant 180 mg QD and 1 (33%) event occurred in a patient who received vepdegestrant 400 mg QD. [b]Baseline *ESR1* status was missing for 2 patients who received vepdegestrant 500 mg QD.
ESR1=estrogen receptor 1 gene; mPFS=median PFS; NR=not reached; PFS=progression-free survival; QD=once daily.

Hamilton EP, SABCS 2022

VERITAC-1: PARTE C (+PALBOCICLIB)

Characteristic	Total (N=46)
Baseline *ESR1* status, n (%)[a]	
Mutant	29 (63)
Wild type[b]	15 (33)
Prior regimens, median (range)	
Any setting	4 (1–11)
Metastatic setting	3 (0–7)
Type of prior therapy, n (%)	
CDK4/6 inhibitor	40 (87)
Palbociclib	36 (78)
Aromatase inhibitor	45 (98)
Fulvestrant	37 (80)
Chemotherapy	
Any setting	36 (78)
Metastatic setting	22 (48)

Table 2: TEAE summary

n (%)	Total (N=46)[a]	200-mg QD cohort (n=21)	500-mg QD cohort (n=20)
Any grade	46 (100)	21 (100)	20 (100)
Grade 3/4	43 (93)	19 (90)	19 (95)
Grade 5	0	0	0
Vepdegestrant dose reduction	5 (11)	2 (10)	3 (15)
Vepdegestrant discontinuation	7 (15)	5 (24)	2 (10)
Palbociclib dose reduction	36 (78)	16 (76)	16 (80)
Palbociclib discontinuation	10 (22)	7 (33)	3 (15)

[a]Includes 2 patients who received vepdegestrant 180 mg QD and 3 patients who received vepdegestrant 400 mg QD.
QD=once daily; TEAE=treatment-emergent adverse event.

Hamilton EP, SABCS 2022

VERITAC-2

Key Eligibility Criteria

- Age ≥18 years old
- ER+/HER2- advanced or metastatic breast cancer
- Prior therapy:
  - 1 line of CDK4/6i + ET
  - ≤1 additional ET
  - Most recent ET for ≥6 months
  - No prior SERD (eg, fulvestrant, elacestrant)
  - No prior chemotherapy for advanced or metastatic disease
- Radiological progression during or after the last line of therapy

Randomization (1:1)

28-day Treatment Cycles

Vepdegestrant (n=313)
200 mg orally (once daily)

Fulvestrant (n=311)
500 mg IM
(days 1 and 15 of cycle 1; day 1 of subsequent cycles)

Stratification Factors:
- *ESR1* mutation[a] (yes vs no)
- Visceral disease (yes vs no)

Primary Endpoint:
- PFS by BICR in
  - *ESR1*m population
  - All patients

Secondary Endpoints:
- OS (key secondary)
- CBR and ORR by BICR
- AEs

Data cutoff date: Jan 31, 2025
Clinicaltrials.gov: NCT05654623

[a]*ESR1*m status was assessed in ctDNA by Foundation Medicine, except in China, where Origmed testing was used.
AE=adverse event; BICR=blinded independent central review; CBR=clinical benefit rate; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; *ESR1*m=estrogen receptor 1 gene mutation; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; IM=intramuscularly; ORR=objective response rate; OS=overall survival; PFS=progression-free survival, SERD=selective estrogen receptor degrader.

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VERITAC-2

VERITAC-2: Baseline Characteristics

Characteristic	Patients With *ESR1*m		All Patients	
	Vepdegestrant (n=136)	Fulvestrant (n=134)	Vepdegestrant (n=313)	Fulvestrant (n=311)
Median age (range), y	60 (26–87)	60 (34–85)	60 (26–89)	60 (28–85)
Female, %	99	100	99	100
Postmenopausal, %	79	79	78	78
Race, %				
White	43	51	47	46
Black or African American	3	4	2	2
Asian	45	37	39	41
Unknown/NR	9	7	12	9
ECOG PS, %				
0	57	57	61	64
1	43	43	39	36
*ESR1*m, %[a]	100	100	43	43
Sites of disease, %				
Visceral disease	68	68	63	63
Liver metastasis	46	44	40	36
Bone-only disease	18	18	18	20

Characteristic, %	Patients With *ESR1*m		All Patients	
	Vepdegestrant (n=136)	Fulvestrant (n=134)	Vepdegestrant (n=313)	Fulvestrant (n=311)
Measurable disease[b]	71	75	71	71
Prior lines of therapy in advanced/metastatic setting[c]				
1	82	80	82	76
2	18	20	18[d]	23[d]
Prior endocrine therapy	100	100	100	100[e]
Aromatase inhibitor	99	100	99	99
SERM	15	16	16	20
Prior CDK4/6 inhibitor	100	100	100	100
Palbociclib	50	54	46	52
Ribociclib	38	28	36	31
Abemaciclib	16	25	20	21
Other[f]	1	5	4	4

CDK4/6=cyclin-dependent kinase 4/6; ECOG PS=Eastern Cooperative Oncology Group performance status; *ESR1*m=estrogen receptor 1 gene mutation; NR=not reported; SERD= selective estrogen receptor degrader; SERM=selective estrogen receptor modulator.
[a]*ESR1*m status was assessed in pretreatment circulating tumor DNA. [b]Measurable disease assessed by blinded independent central review using Response Evaluation Criteria for Solid Tumors v1.1. [c]Disease progression during or within 12 months from the end of adjuvant therapy was counted as a line of therapy in the advanced/metastatic setting. [d]1 additional patient in the vepdegestrant group and 3 additional patients in the fulvestrant group received 3 prior lines of therapy. [e]1 patient received a prior SERD. [f]Other CDK4/6 inhibitors included birociclib, dalpiciclib, lerociclib.

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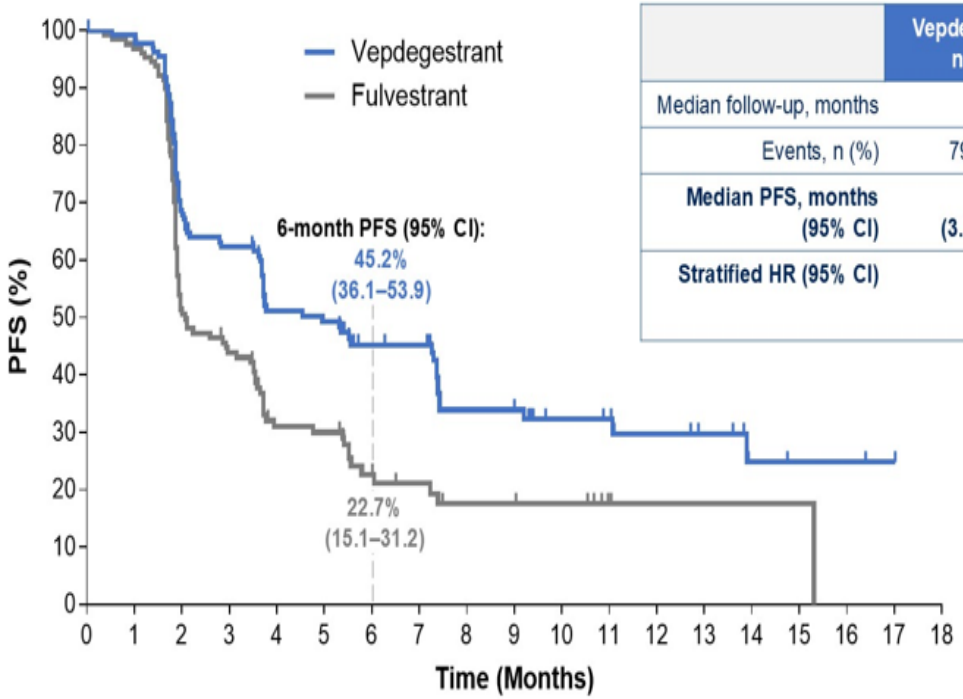
VERITAC-2: OBJETIVO PRIMARIO

PFS by BICR in Patients With *ESR1*m



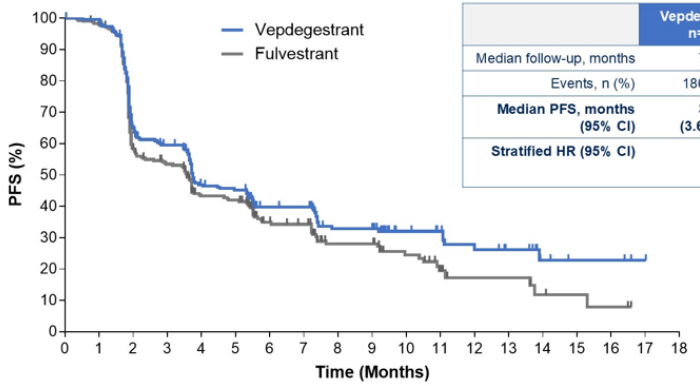
	Vepdegestrant n=136	Fulvestrant n=134
Median follow-up, months	7.4	6.0
Events, n (%)	79 (58)	95 (71)
Median PFS, months (95% CI)	**5.0 (3.7–7.4)**	**2.1 (1.9–3.5)**
Stratified HR (95% CI)	**0.57 (0.42–0.77)**	
	2-sided *P*<0.001	

No. at risk

Vepdegestrant	136	134	87	78	55	53	38	37	22	22	15	14	10	8	4	3	3	2	0
Fulvestrant	134	125	62	52	30	29	15	12	8	8	7	2	1	1	1	1	0	0	0

BICR=blinded independent central review; *ESR1m*=estrogen receptor 1 gene mutation; HR=hazard ratio; PFS=progression-free survival.

PFS by BICR in All Patients



	Vepdegestrant n=313	Fulvestrant n=311
Median follow-up, months	7.4	7.2
Events, n (%)	186 (59)	198 (64)
Median PFS, months (95% CI)	**3.7 (3.6–5.3)**	**3.6 (2.2–3.8)**
Stratified HR (95% CI)	**0.83 (0.68–1.02)**	
	2-sided *P*=0.07	

No. at risk

Vepdegestrant	313	306	189	168	113	108	74	72	46	46	28	24	15	12	6	4	4	2	0
Fulvestrant	311	292	162	143	101	98	58	54	36	36	23	12	7	7	4	3	2	0	0

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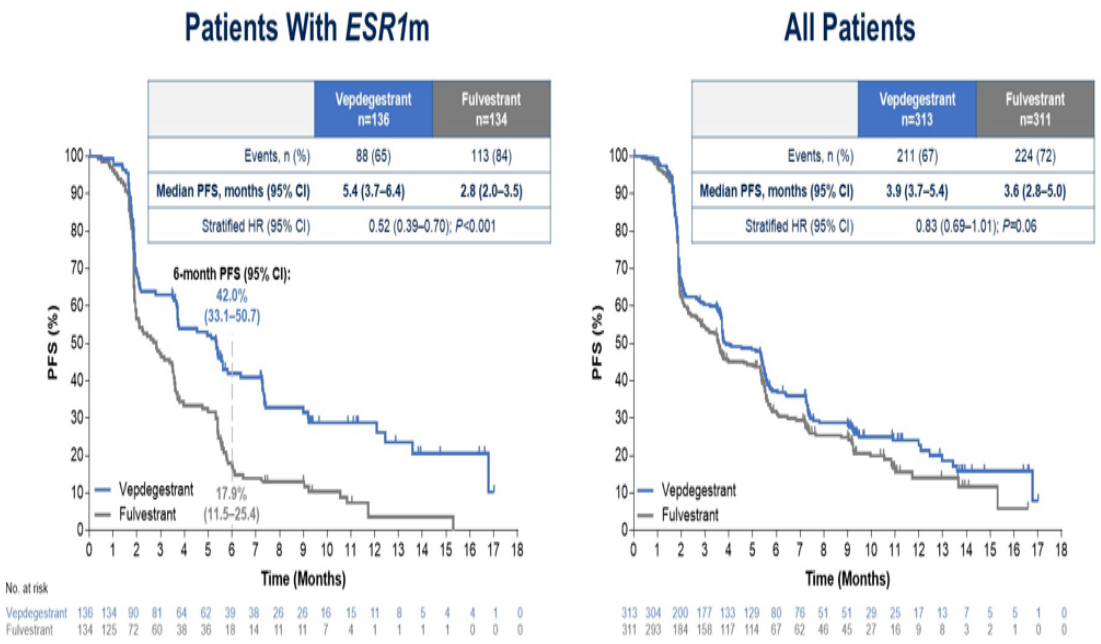
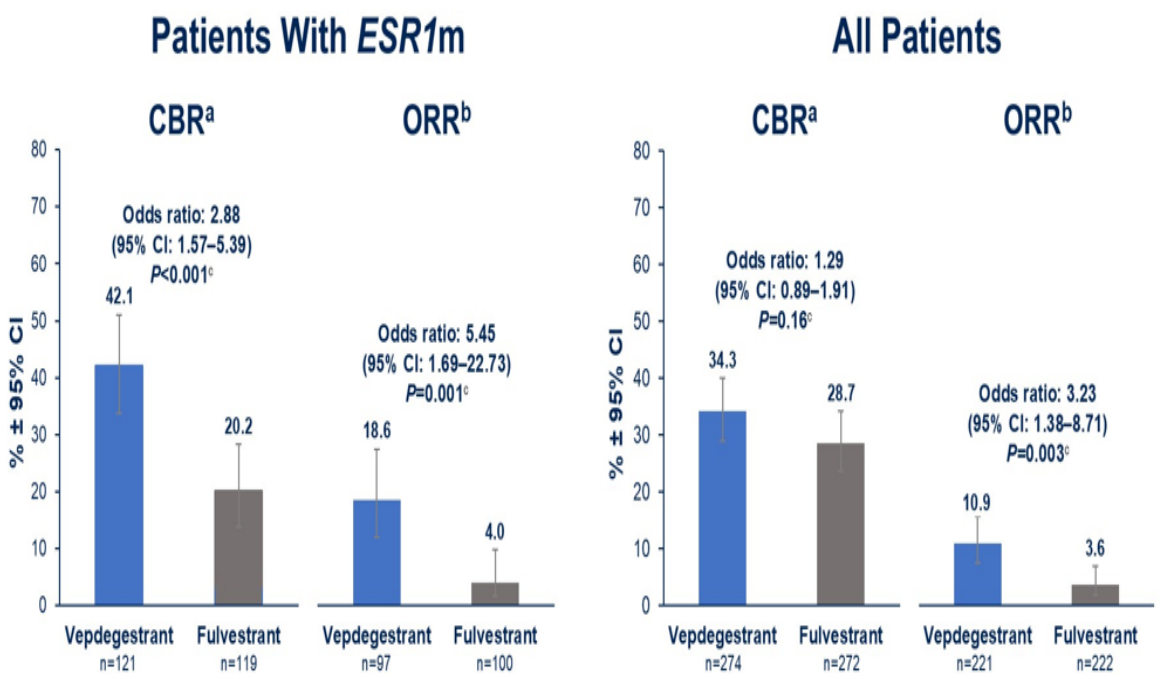
VERITAC-2: OBJETIVOS SECUNDARIOS

VERITAC-2: Investigator-Assessed PFS



Secondary Endpoints: CBR and ORR by BICR



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VERITAC-2: SEGURIDAD Y TOLERABILIDAD

Overview

TEAEs, %	Vepdegestrant (n=312)	Fulvestrant (n=307)
Any grade	87	81
Grade ≥3	23	18
Serious	10	9
Leading to treatment discontinuation	3	1
Leading to dose reduction	2	NA
TRAEs, %		
Any grade	57	40
Grade ≥3	8	3

QT prolongation

- TEAEs: vepdegestrant,10%; fulvestrant, 1%
- A QT interval sub-study (n=88) confirmed a mild increase (11.1 ms) from baseline in mean QTcF, with upper 90% CI (13.7 ms) <20 ms,[f] **indicating no large QT-prolonging effect**

TEAEs in >10% of Patients in Either Group

TEAE, %	Vepdegestrant (n = 312)		Fulvestrant (n = 307)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Fatigue[a]	27	1	16	1
ALT increased[b]	14	1	10	1
AST increased[b]	14	1	10	3
Nausea	13	0	9	1
Anemia[b, c]	12	2	8	3
Neutropenia[d]	12	2[e]	5	1[e]
Back pain	11	1	7	<1
Arthralgia	11	1	11	0
Decreased appetite	11	<1	5	0

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GI=gastrointestinal; QTcF=corrected QT interval using Fridericia's method; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event.
[a]Includes fatigue and asthenia. [b]No between-group differences were observed for ALT/AST increases or anemia based on laboratory values. [c]Includes anemia, hemoglobin decreased, and iron deficiency anemia. [d]Includes neutropenia and neutrophil count decreased. No events led to dose reductions or treatment discontinuation in either treatment group. There were no events of febrile neutropenia in the vepdegestrant group and 1 event of grade 2 febrile neutropenia in the fulvestrant group. [e]1 patient with grade 4 event. [f]Based on a concentration-QTc population modeling analysis.

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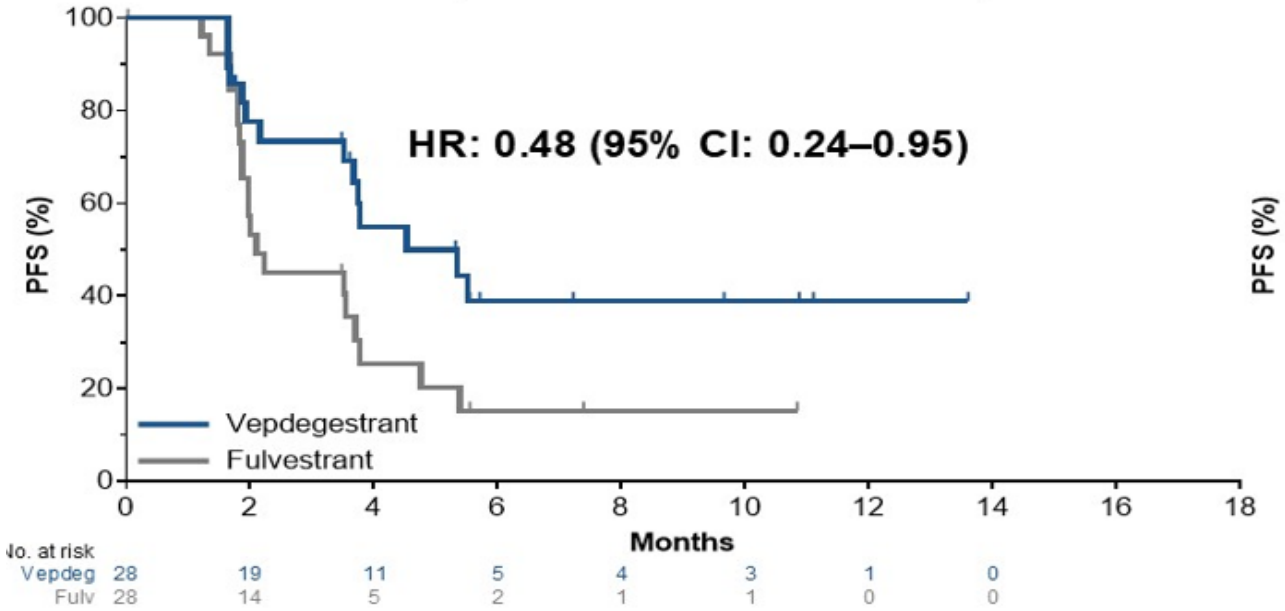
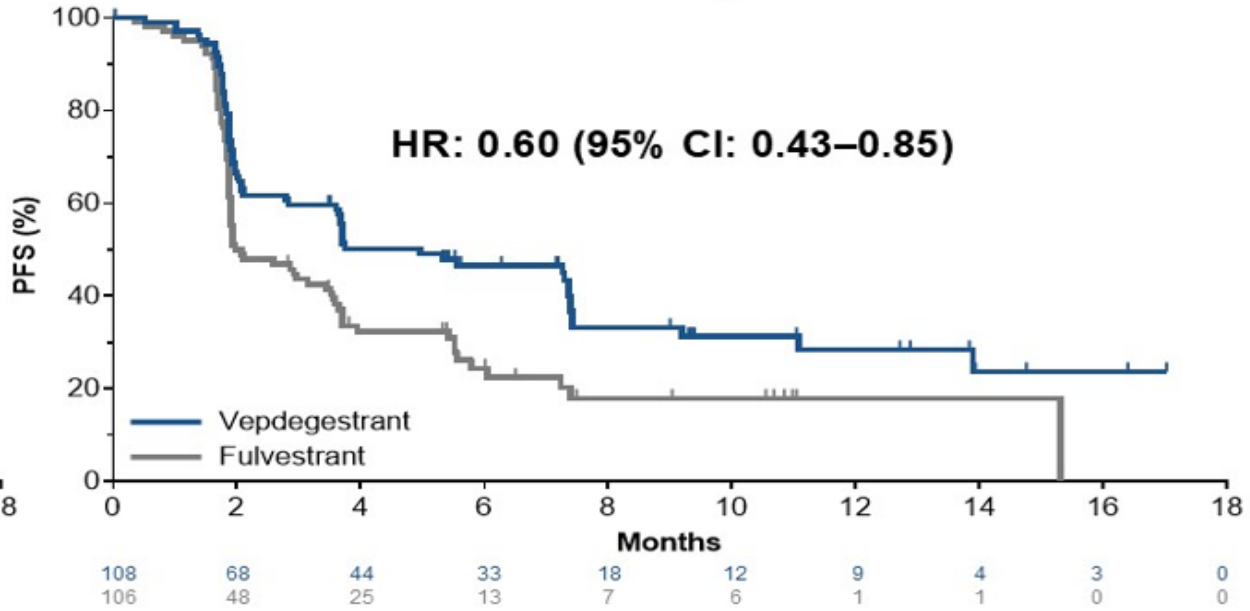
VERITAC-2: ANÁLISIS SUBGRUPOS EN POBLACIÓN ESR1-MUT

Premenopausal or Perimenopausal[a]



	Vepdegestrant (n=28)	Fulvestrant (n=28)
Events, %	50	71
Median PFS (95% CI)	4.5 (3.7–NE)	2.1 (1.9–3.7)

Postmenopausal



Vepdegestrant (n=108)	Fulvestrant (n=106)
60	71
5.0 (3.6–7.4)	2.0 (1.9–3.5)

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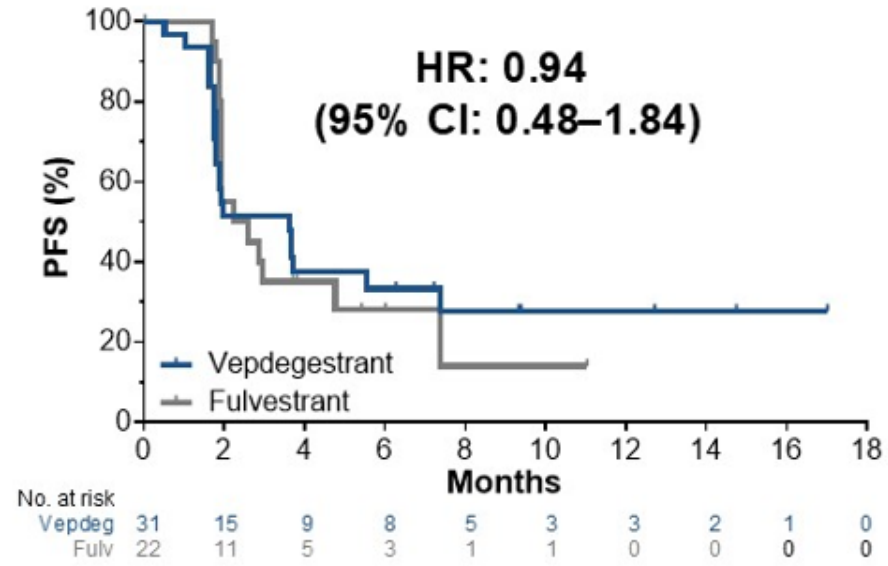
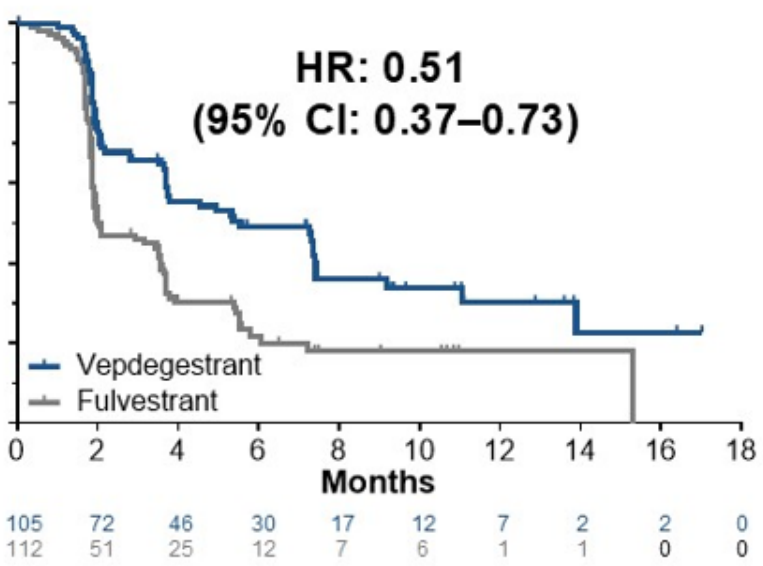
VERITAC-2: ANÁLISIS SUBGRUPOS EN POBLACIÓN ESR1-MUT

<12 Months



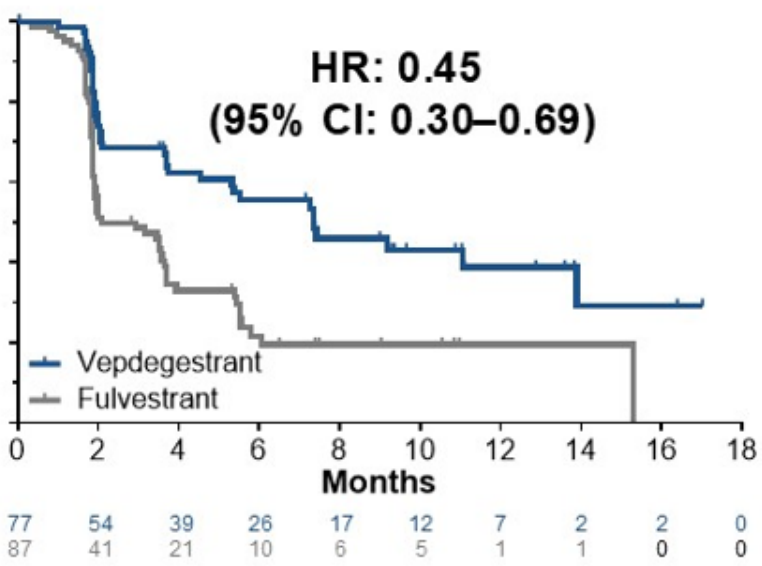
	Vepdegestrant (n=31)	Fulvestrant (n=22)
Events, %	68	68
Median PFS (95% CI)	3.6 (1.8–7.4)	2.4 (1.9–4.8)

≥12 Months



	Vepdegestrant (n=105)	Fulvestrant (n=112)
Events, %	55	71
Median PFS (95% CI)	5.5 (3.7–7.4)	2.0 (1.9–3.5)

≥18 Months



	Vepdegestrant (n=77)	Fulvestrant (n=87)
Events, %	49	70
Median PFS (95% CI)	7.4 (4.5–13.9)	2.1 (1.9–3.6)

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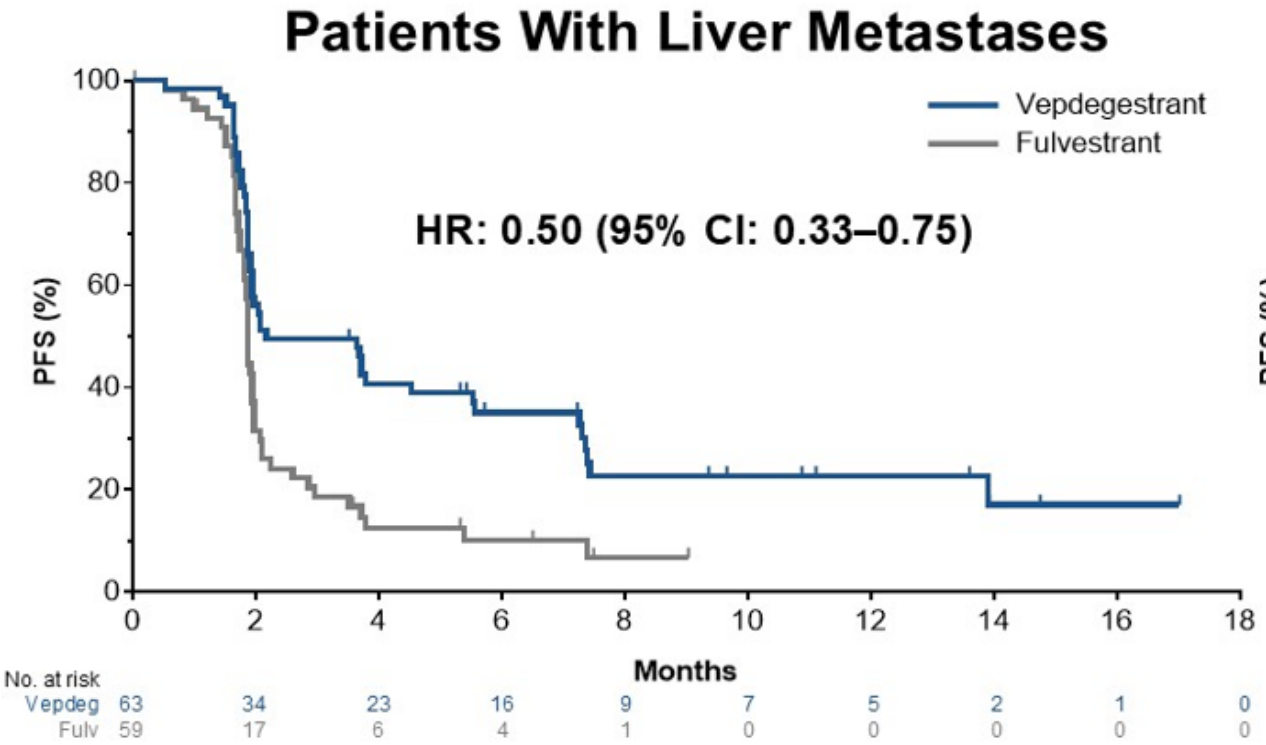
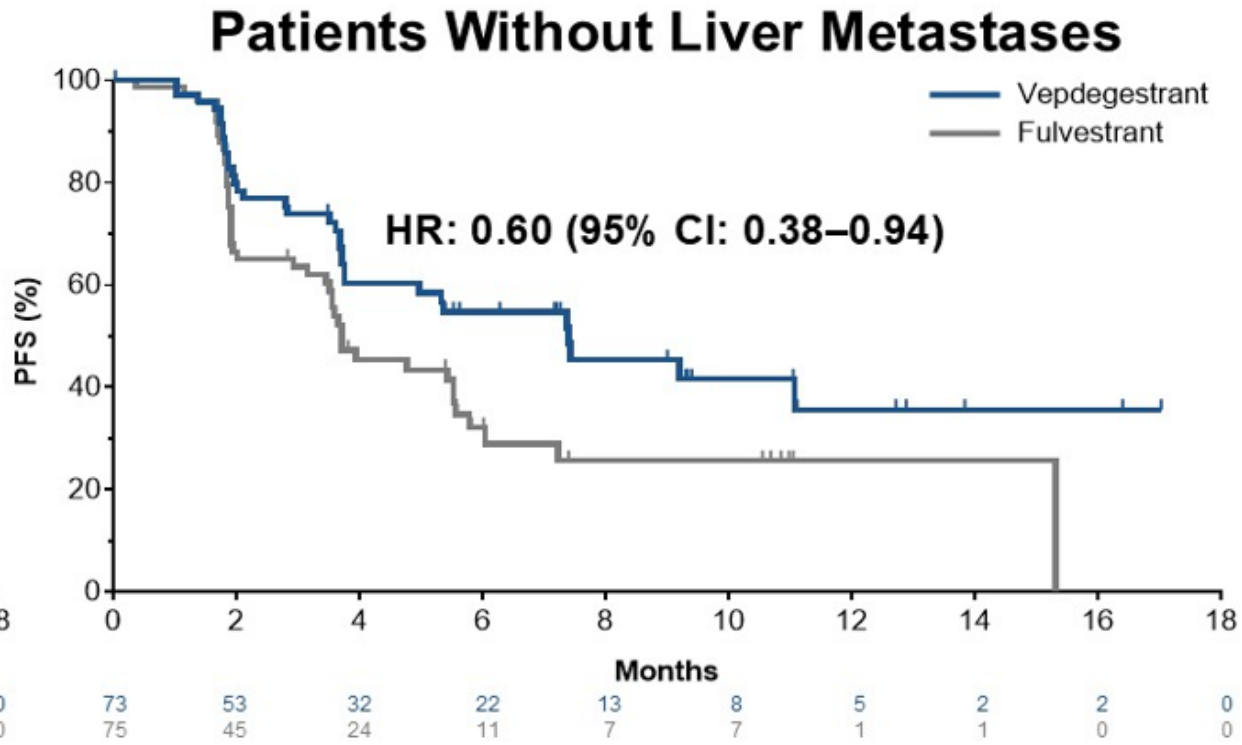
VERITAC-2: ANÁLISIS SUBGRUPOS EN POBLACIÓN ESR1-MUT



	Vepdegestrant (n=63)	Fulvestrant (n=59)
Events, %	71	83
Median PFS (95% CI)	2.2 (1.9–5.5)	1.9 (1.8–1.9)



Vepdegestrant (n=73)	Fulvestrant (n=75)
47	61
7.4 (3.7–NE)	3.7 (3.4–5.5)

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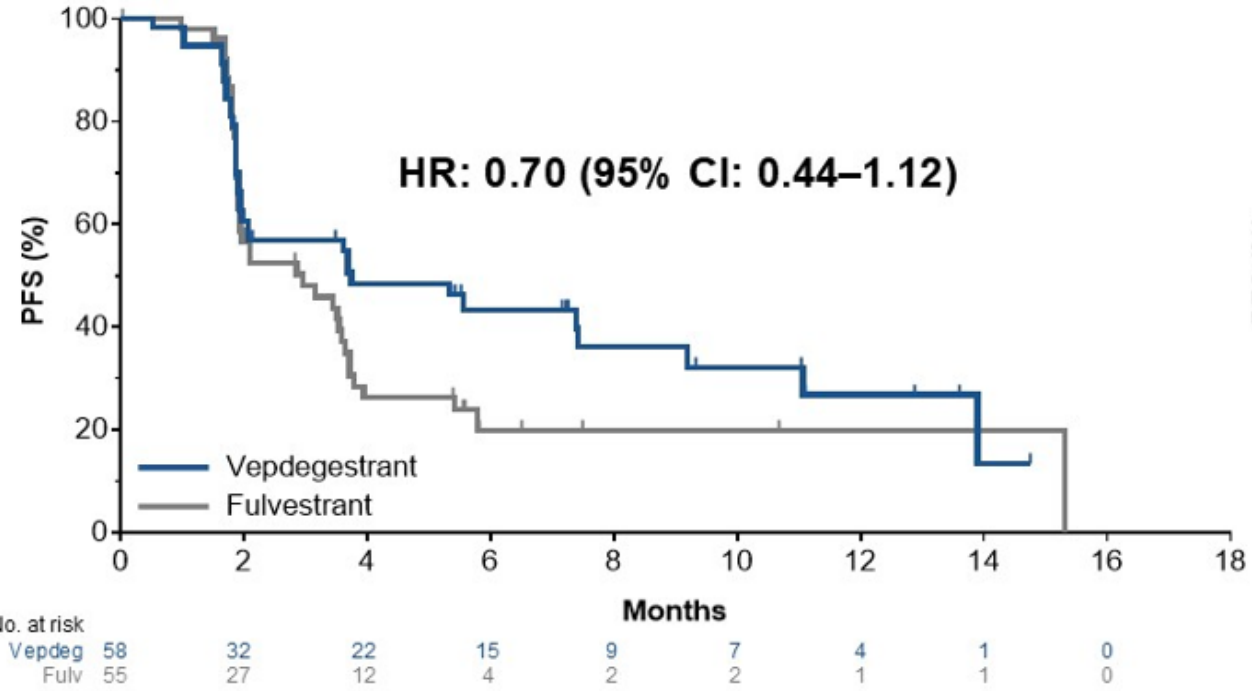
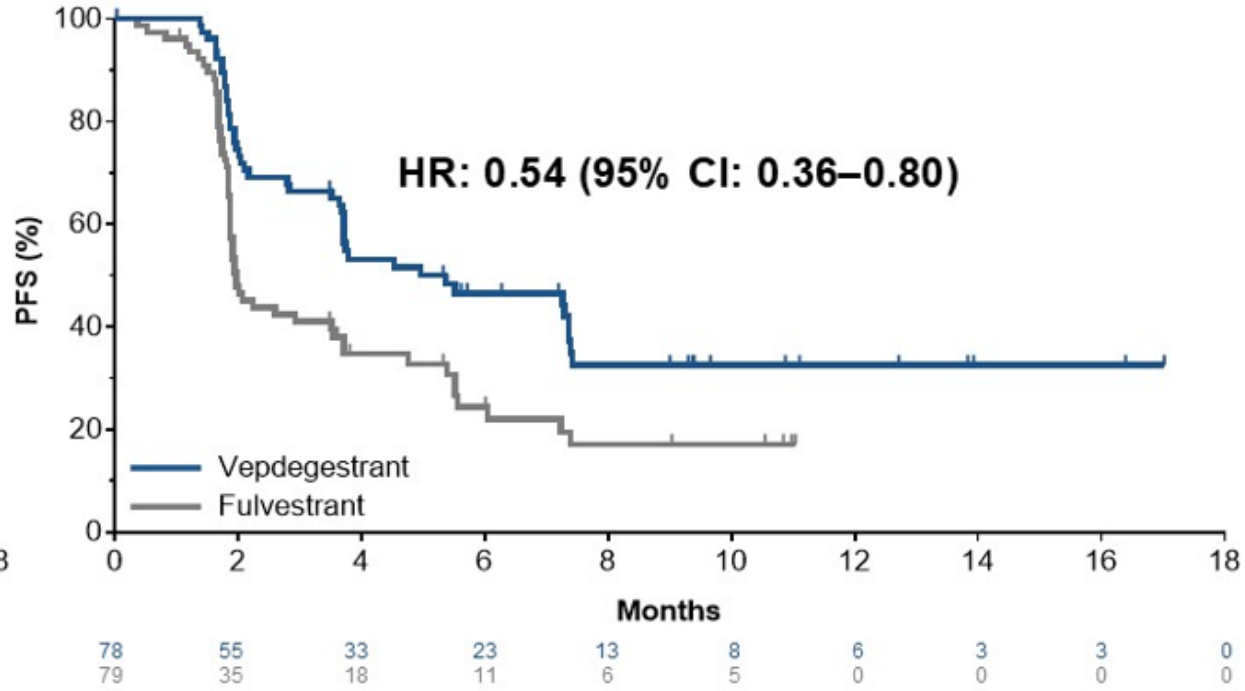
VERITAC-2: ANÁLISIS SUBGRUPOS EN POBLACIÓN ESR1-MUT

PIK3CA/AKT1/PTEN Alteration Detected



	Vepdegestrant (n=58)	Fulvestrant (n=55)
Events, %	60	71
Median PFS (95% CI)	3.7 (1.9–9.2)	3.0 (1.9–3.6)

No *PIK3CA/AKT1/PTEN* Alteration Detected



Vepdegestrant (n=78)	Fulvestrant (n=79)
56	71
5.0 (3.7–7.4)	2.0 (1.9–3.5)

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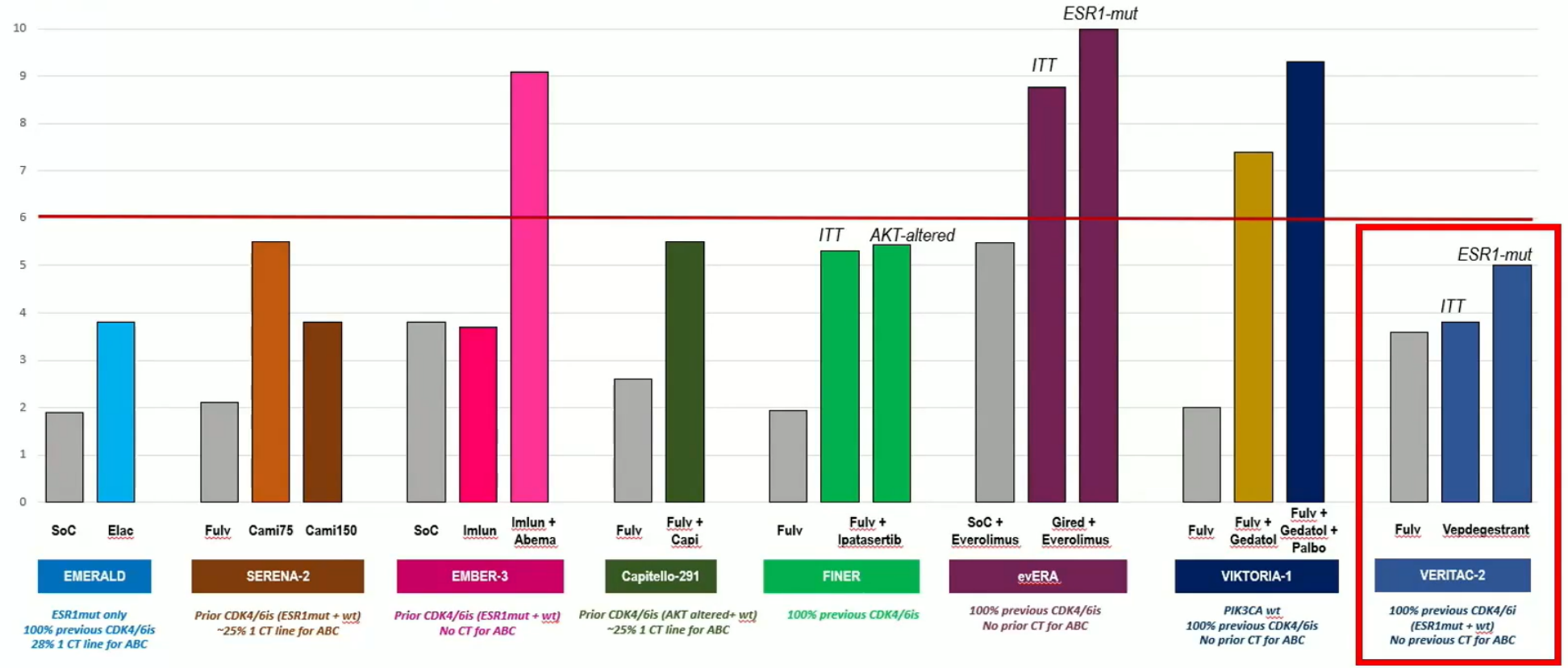
Pushing beyond the 6-month PFS ceiling after CDK4/6 inhibitors

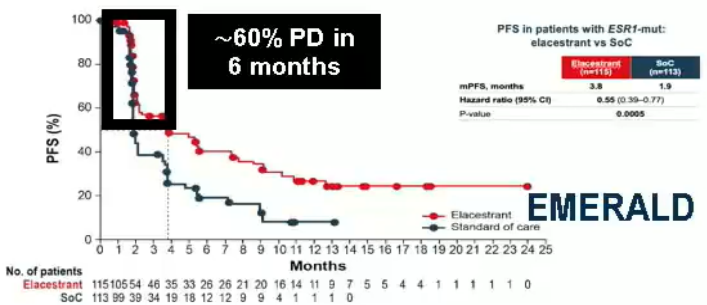
Combination of SERDs/SERMs with targeted therapies including PI3Ki and CDK4/6i represents the future of ET-based treatment in CDK4/6i-pretreated population

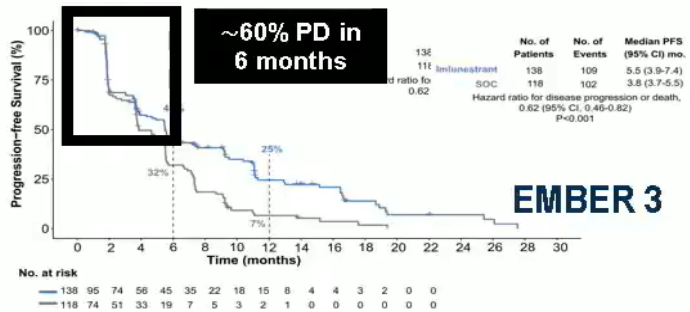


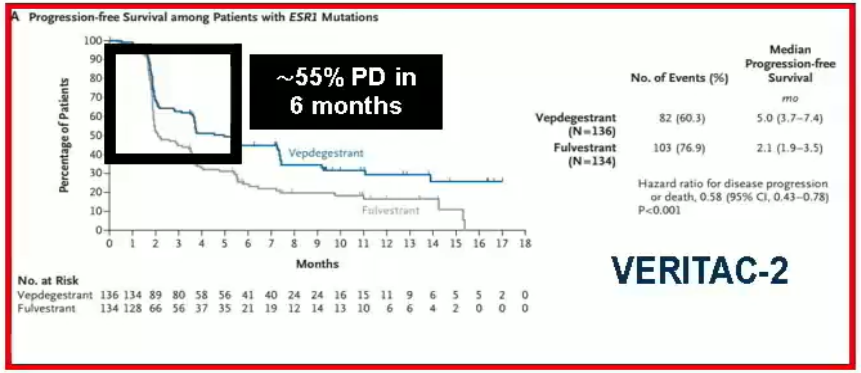
Bardia A et al SBACS 2021; Bidard FC et al JCO 2022; Oliveira M et al Lancet Oncol 2024; Jhaveri et al SABCS 2024 & NEJM 2024; Turner NC et al NEJM 2023; Chia S et al ASCO 2025; Mayer E et al ESMO 2025; Hurvitz S et al ESMO 2025 ; Campone M et al N Engl J Med 2025

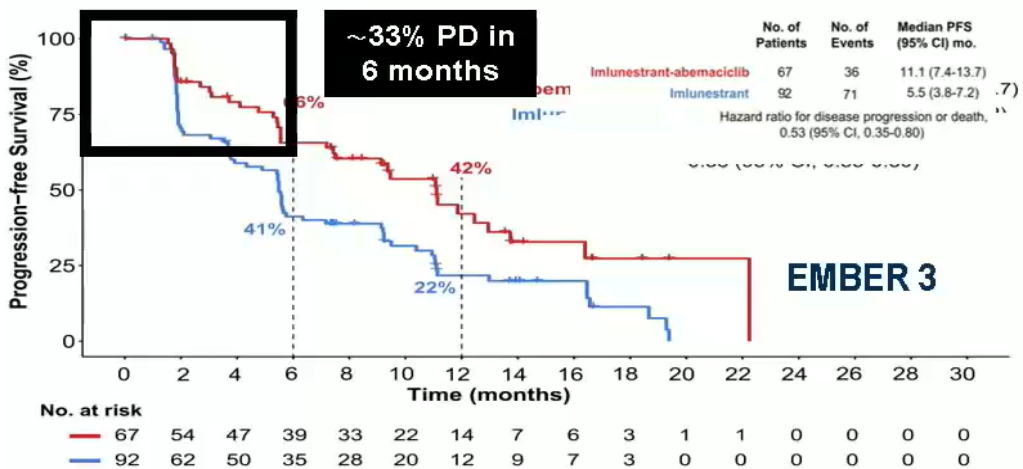
A.Gennari, ESMO 2025

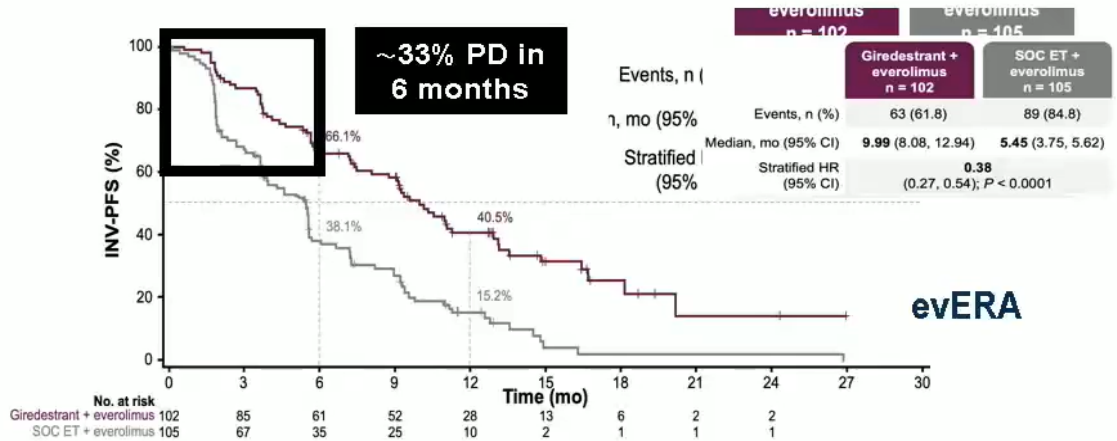
Early progression in ESR1 mut: single agent ET vs SERD + targeted therapy











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Mayer EL et al, ESMO 2025. Bidard FC et al. J Clin Oncol. 2022. Jhaveri KL et al. N Engl J Med. 2025.

PROTACS PERSPECTIVAS FUTURAS

ENFERMEDAD PRECOZ

ARV-471 en adyuvancia (pipeline Arvinas)

ENFERMEDAD AVANZADA

VERITAC-3 (NCT05909397)

- Fase III, 1ªLínea, IA + Palbociclib vs Vepdegestrant + Palbociclib

TACTIVE-E (NCT05501769)

- Fase Ib, ≥2ªLínea, Vepdegestrant + Everolimus

TACTIVE-K (NCT06206837)

- Fase Ib-II, ≥2ªLínea, Vepdegestrant + PF-07220060 (iCDK4)

TACTIVE-U (NCT05548127, NCT05573555, NCT06125522)

- Fase Ib-II, ≥2ªLínea, Vepdegestrant + Abemaciclib o Ribociclib o Samuraciclib

Otros fármacos en estudio preclínico: AC 0682, ERD-3111

CONCLUSIONES

- PROTACs en enfermedad precoz:
  - I-SPY2 (Vepdegestrant): Supresión significativa ki67, disminuye FTV en RM, aclaramiento ctDNA y conversión nodal.
  - TACTIVE-N (Vepdegestrant): Supresión similar ki67 frente a Anastrozol, perfil toxicidad levemente diferente, supresión de RE, RP y aumento de expresión inmune.
- PROTACs en enfermedad avanzada:
  - VERITAC-2 (Vepdegestrant): PFS en ESR1-mut 5 meses, OS inmadura, <5% AEs que discontinúen tto.
- PREGUNTAS CLAVE:
  - ¿Cómo revertir mejor la resistencia iCDK? (SERDs, PROTACs, nuevos iCDK, iPI3KCA, iKAT6, combinaciones…)
  - ¿Biomarcadores más allá de ESR1 y PI3KCA/PTEN/AKT?
  - En la clínica … ¿Podemos definir a la paciente rápidamente progresora que va a precisar uso precoz de ADCs o QT?

GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025