2026 ESMO TAT

Targeted Anticancer Therapies

Dose Optimization of Zovegalisib, a Novel PI3Kα Inhibitor, in Patients with *PIK3CA*-Mutant HR+/HER2− Advanced Breast Cancer

Results from the First-In-Human Study to Support the Recommended Phase III Dose

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Declaration of Interests

Institutional clinical trial contract: Alterome, BeiGene, Boehringer Ingelheim, BridgeBio, OnKure Therapeutics, Relay Therapeutics, Synovation Therapeutics, Totus Medicines

Institutional sponsor research agreement: OnKure Therapeutics, Relay Therapeutics

Travel: Roche

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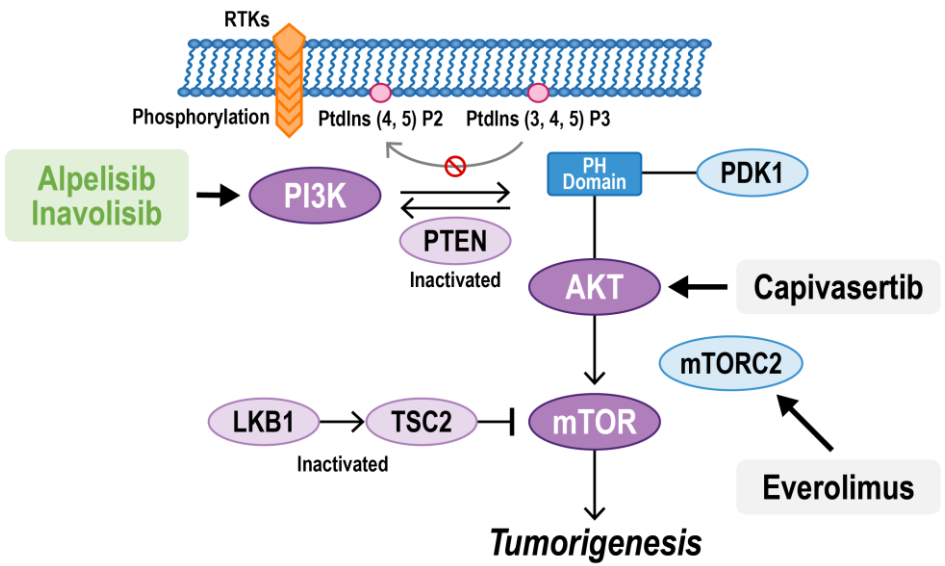
Zovegalisib (RLY-2608) – 1st Mutant-Selective PI3Kα Inhibitor for HR+/HER2- Breast Cancer

Mutant PI3Kα Drives ~40% of HR+/HER2- BC[1-3]

The PI3K pathway[5]



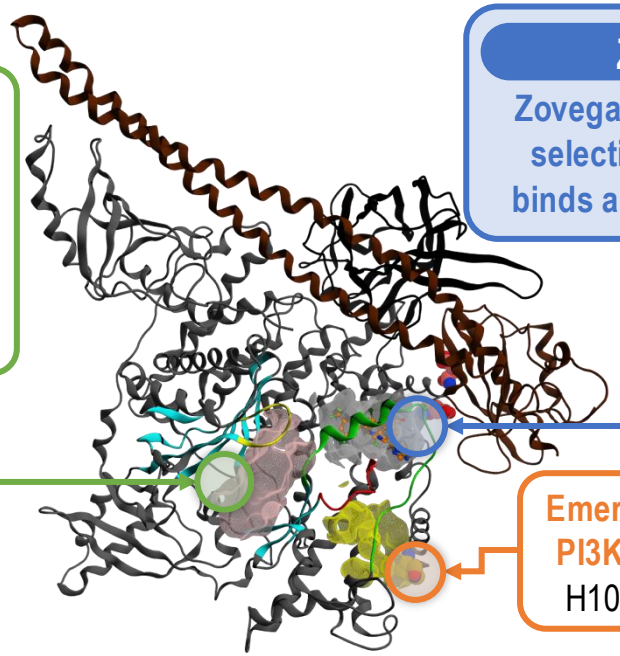
Less-selective pathway inhibitors have side effects (e.g., hyperglycemia, rash, diarrhea, stomatitis) that limit efficacy (mPFS ~5.5 – 7.5 months with ET doublet)

Zovegalisib's Novel MOA Selectively Targets Mutant PI3Kα[4]

Non–mutant-selective PI3Kα inhibitors (alpelisib, inavolisib) bind the orthosteric (active) site and inhibit both WT and mutant PI3Kα

Zovegalisib

Zovegalisib, a pan-mutant–selective PI3Kα inhibitor, binds a novel allosteric site



Emerging H1047R-specific PI3Kα inhibitors bind only H1047R hotspot mutation

Non-selective downstream pathway inhibitors (capivasertib, everolimus) do not bind PI3Kα

AKT, protein kinase B; BC, breast cancer; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; MOA, mode of action; mTORC, mammalian target of rapamycin kinase; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol-4, 5-bisphosphate; PIP3, phosphatidylinositol-3, 4, 5-triphosphate; PTEN, phosphatase and tensin homolog; RTK, receptor tyrosine kinase; WT, wild type. 1. The Cancer Genome Atlas Network. Nature. 2012;490:61–70; 2. Mollon L, et al. Presented at AACR 2018. Poster 1207; 3. Varkaris A, et al. Cancer Discovery. 2024;14:240–257; 4. Saura C, et al. Poster presented at SABCS 2024, PS7-01; 5. Saal LH, et al. Proc Natl Acad Sci U S A. 2007;104:7564–7569

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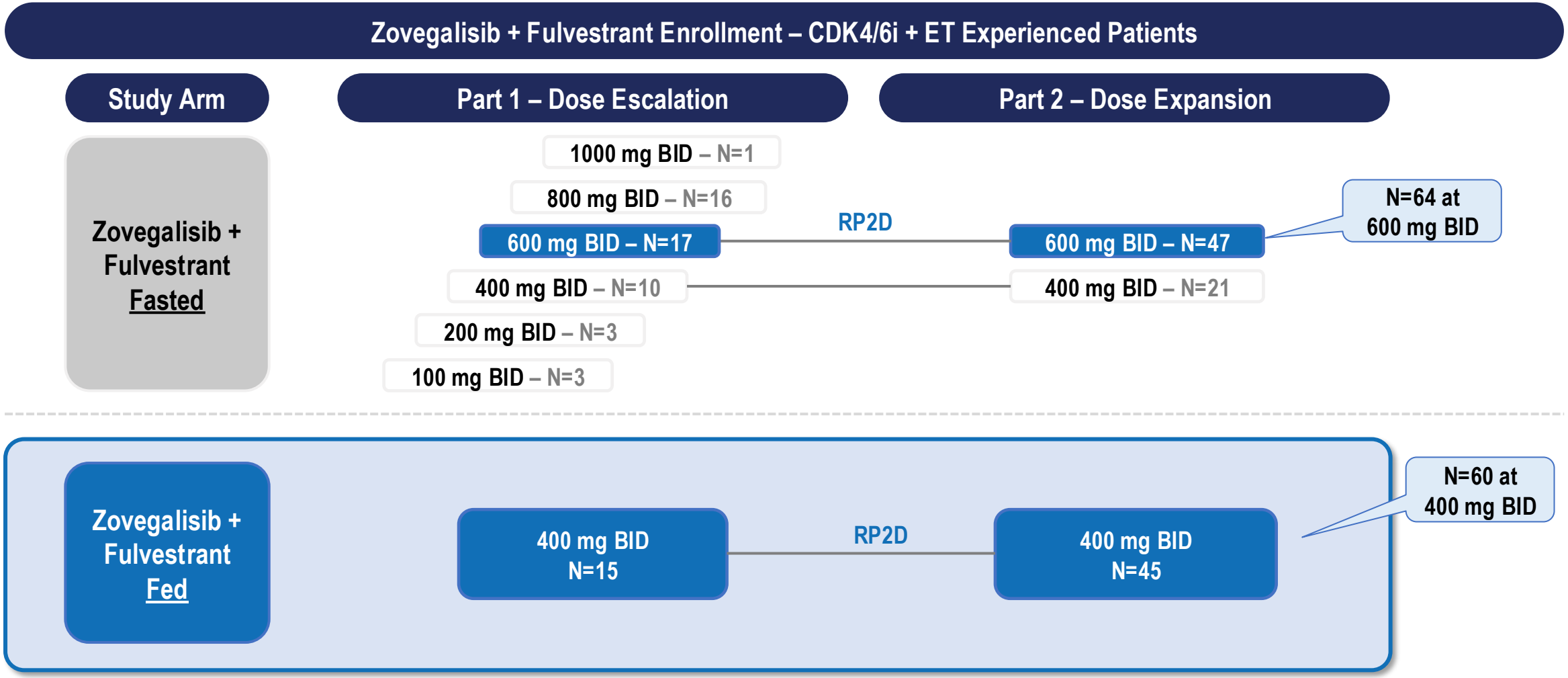
ReDiscover First-in-Human Study – *PIK3CA*m HR+/HER2- Advanced Breast Cancer



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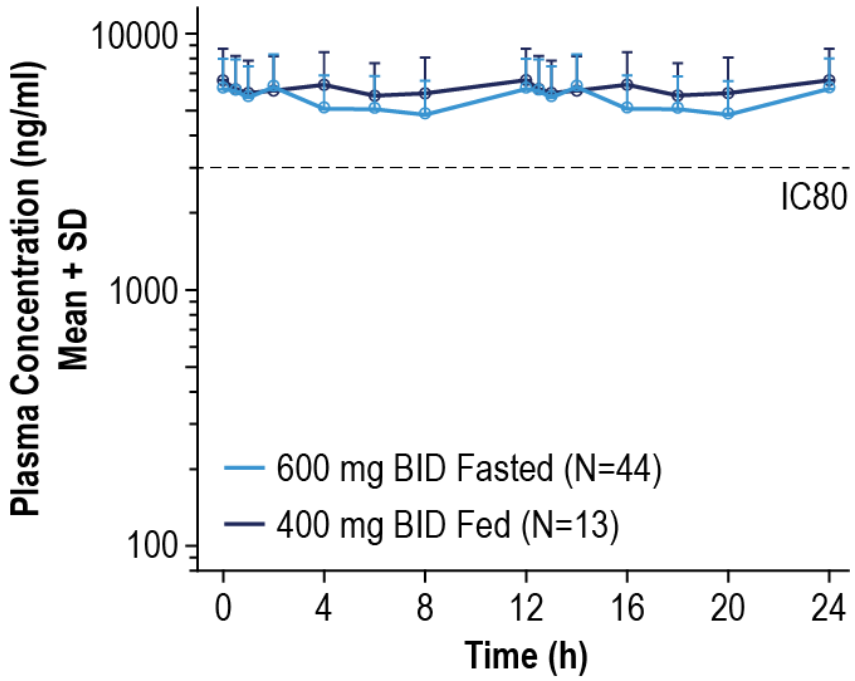
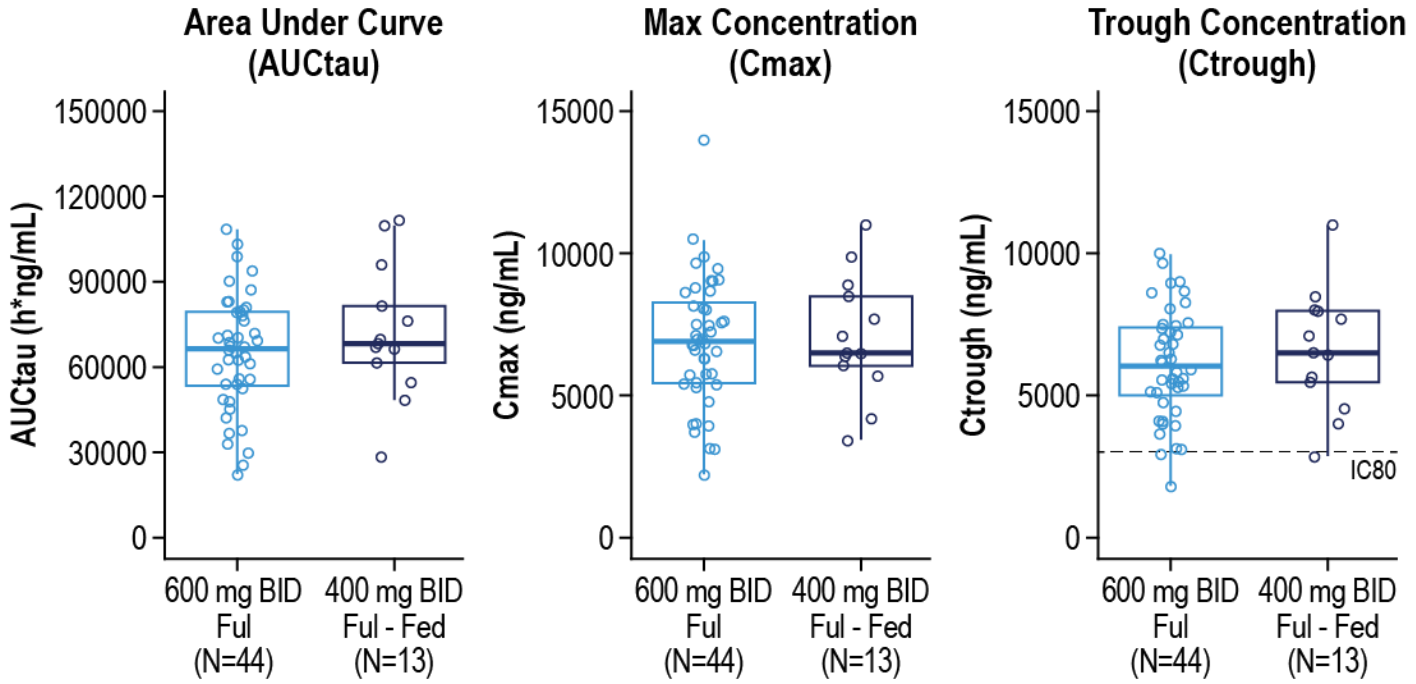
Zovegalisib Exposures Comparable Between 400 mg BID Fed and 600 mg BID Fasted Doses

Mean Concentration vs Time (Cycle 1 Day 15)



Pharmacokinetic Parameter (Cycle 1 Day 15)



Following 400 mg BID fed dosing, mean zovegalisib concentrations remain above IC80 throughout the dosing interval

Ful: Fulvestrant

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ReDiscover preliminary data as of 10/28/2025

Baseline Demographics Reflect Previously Treated FIH Population

	Zovegalisib + Fulvestrant RP2D	
	600 mg BID (RP2D, N=64)	400 mg BID fed (RP2D, N=60)
Median age (range), years	59.0 (34, 80)	60.0 (32, 78)
ECOG 0/1, n (%)	38 (59.4) / 26 (40.6)	33 (55.0) / 27 (45.0)
Local *PIK3CA* baseline results		
Kinase mutation, n (%)	31 (48.4)	33 (55.0)
Non-kinase mutations, n (%)	33 (51.6)	27 (45.0)
BMI ≥30 or HbA1c ≥5.7%, n (%)	22 (34.4)	29 (48.3)
Measurable disease, n (%)	42 (65.6)	37 (61.7)
Patients with visceral metastases[1], n (%)	39 (60.9)	43 (71.7)
Prior lines of therapy in advanced setting, n (%)		
0	0	2 (3.3)
1,	35 (54.7)	36 (60.0)
2+	29 (45.3)	22 (36.7)
Prior therapies in advanced setting, n (%)		
CDK4/6i[2]	64 (100.0)	59 (98.3)
Fulvestrant or novel SERD	33 (51.6)	26 (43.3)
Chemo/ADC	17 (26.6)	11 (18.3)
ESR1 mutation[3], n (%)	18 (28.6)	23 (40.4)
PTEN or *AKT1* E17K mutation[3], n (%)	12 (19.0)	3 (5.3)

400 mg BID fed cohort has higher rate of pre-diabetes and visceral disease

In 400 mg BID fed (n=60) cohort:
- Still on treatment: 17 (28.3%)
- Discontinued: 43 (71.1%) – predominantly due to progressive disease

1. Visceral metastatic sites include brain, lung, liver, pleural, peritoneal involvement; 2. 5 (3@600 and 2@400) patients received prior CDK4/6 in the adjuvant setting which is allowed per protocol; 1 subject @400 received "other CDK4 inhibitor"; 3. Percentage was based on pts with evaluable ctDNA data at baseline; ECOG = Eastern Cooperative Oncology Group performance status

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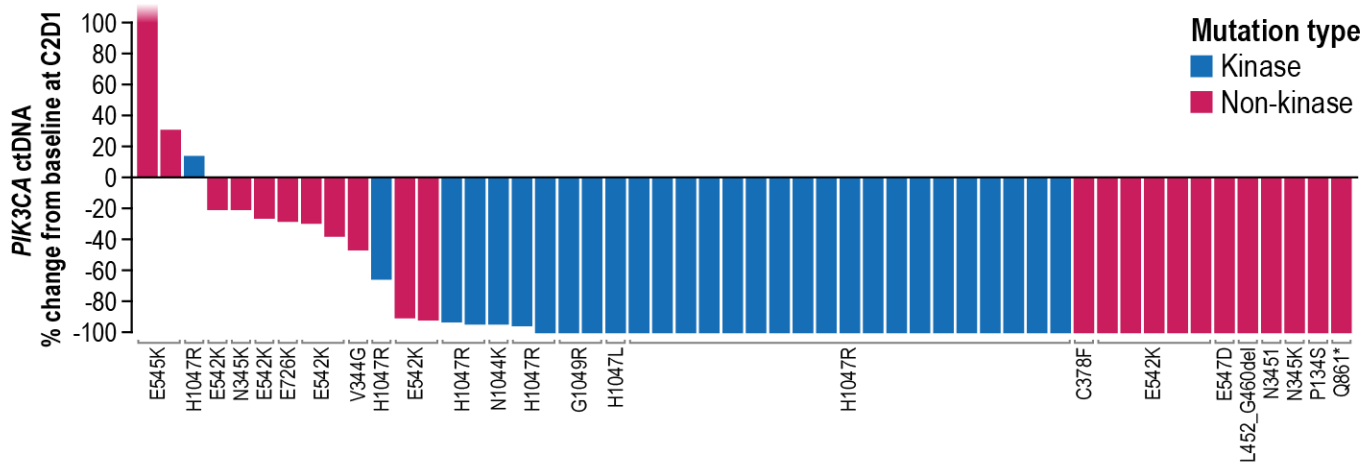
Zovegalisib + Fulvestrant – Rapid Decline in *PIK3CA* and *ESR1* ctDNA Across Mutations

Circulating Tumor DNA Clearance – Zovega 400 mg BID Fed + Fulvestrant

***PIK3CA* ctDNA: Percent Change from Baseline**

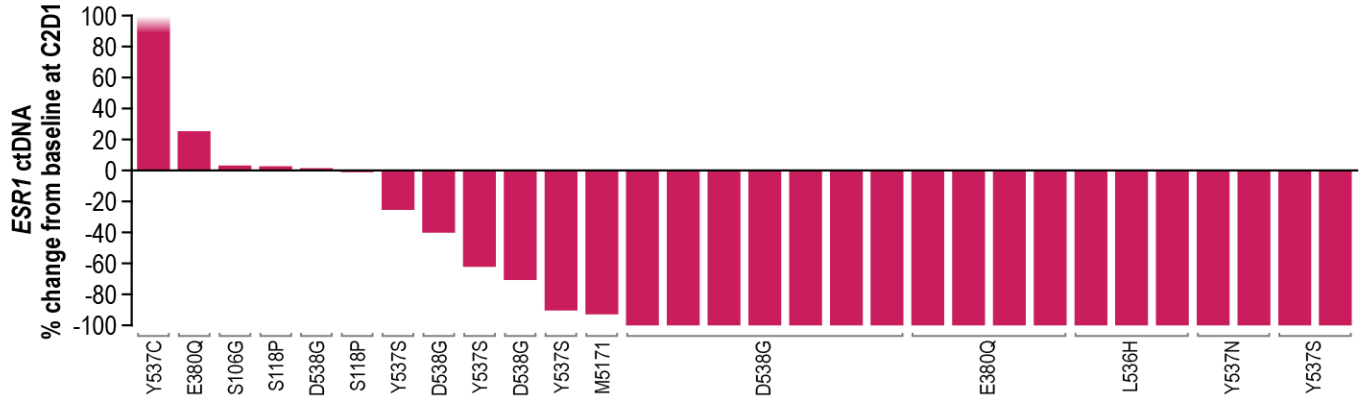
N=46



- 46 patients had detectable *PIK3CA* mutations at baseline and a paired result
  - 6 patients had ≥1 mutation
- 93.5% of patients experienced a decline or clearance in ctDNA by C2D1

***ESR1* ctDNA: Percent Change from Baseline**

N=21



- 21 patients had detectable *ESR1* mutations at baseline and a paired result
  - 7 patients had ≥1 mutation
- 81.0% of patients experienced a decline or clearance in ctDNA by C2D1

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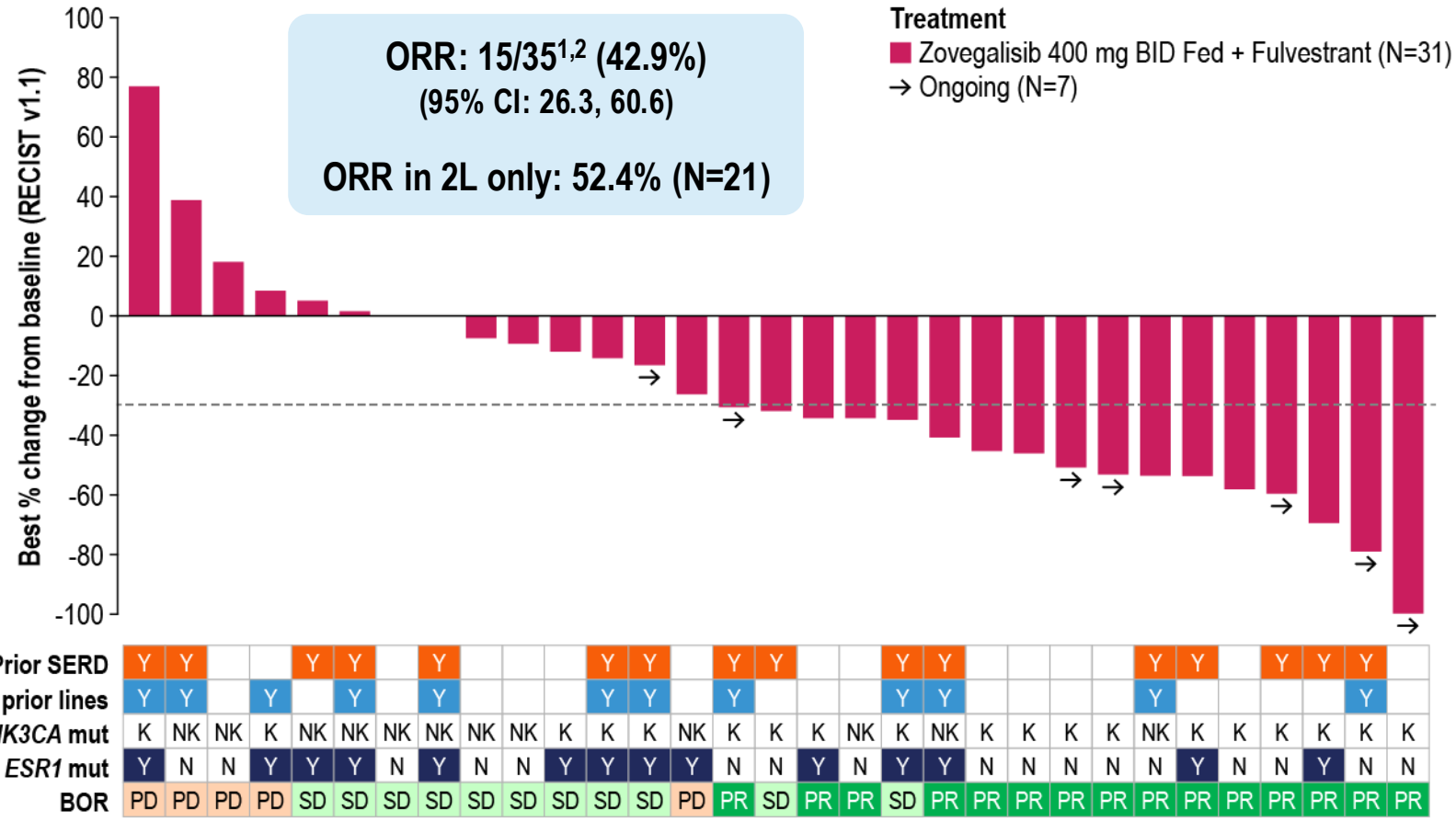
ReDiscover preliminary data as of 1/13/2026

Zovegalisib + Fulvestrant Demonstrates Clinically Meaningful Anti-Tumor Activity

Zovegalisib 400 mg BID Fed (RP2D) + fulvestrant – Radiographic Tumor Reduction and Response per RECIST v1.1 (N=35)[1]



Prior SERD	Y	Y			Y	Y		Y				Y	Y		Y	Y			Y	Y					Y	Y		Y	Y	Y	
≥2 prior lines	Y	Y		Y		Y		Y				Y	Y		Y				Y	Y					Y					Y		
PIK3CA mut	K	NK	NK	K	NK	NK	NK	NK	NK	NK	K	K	K	NK	K	K	K	NK	K	NK	K	K	K	K	NK	K	K	K	K	K	K
ESR1 mut	Y	N	N	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	N	N	Y	N	Y	Y	N	N	N	N	N	Y	N	N	Y	N	N
BOR	PD	PD	PD	PD	SD	SD	SD	SD	SD	SD	SD	SD	SD	PD	PR	SD	PR	PR	SD	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR	PR

[1] Excludes patients with PTEN or AKT1 E17K co-mutation at baseline. [2] Includes 4 pts discontinued treatment prior to 1st post-baseline scan: 1 with scan performed at outside institution, it was assessed as PD, but no image was available, 1 withdrew consent, 1 AE (creatinine increased) and 1 Clinical PD

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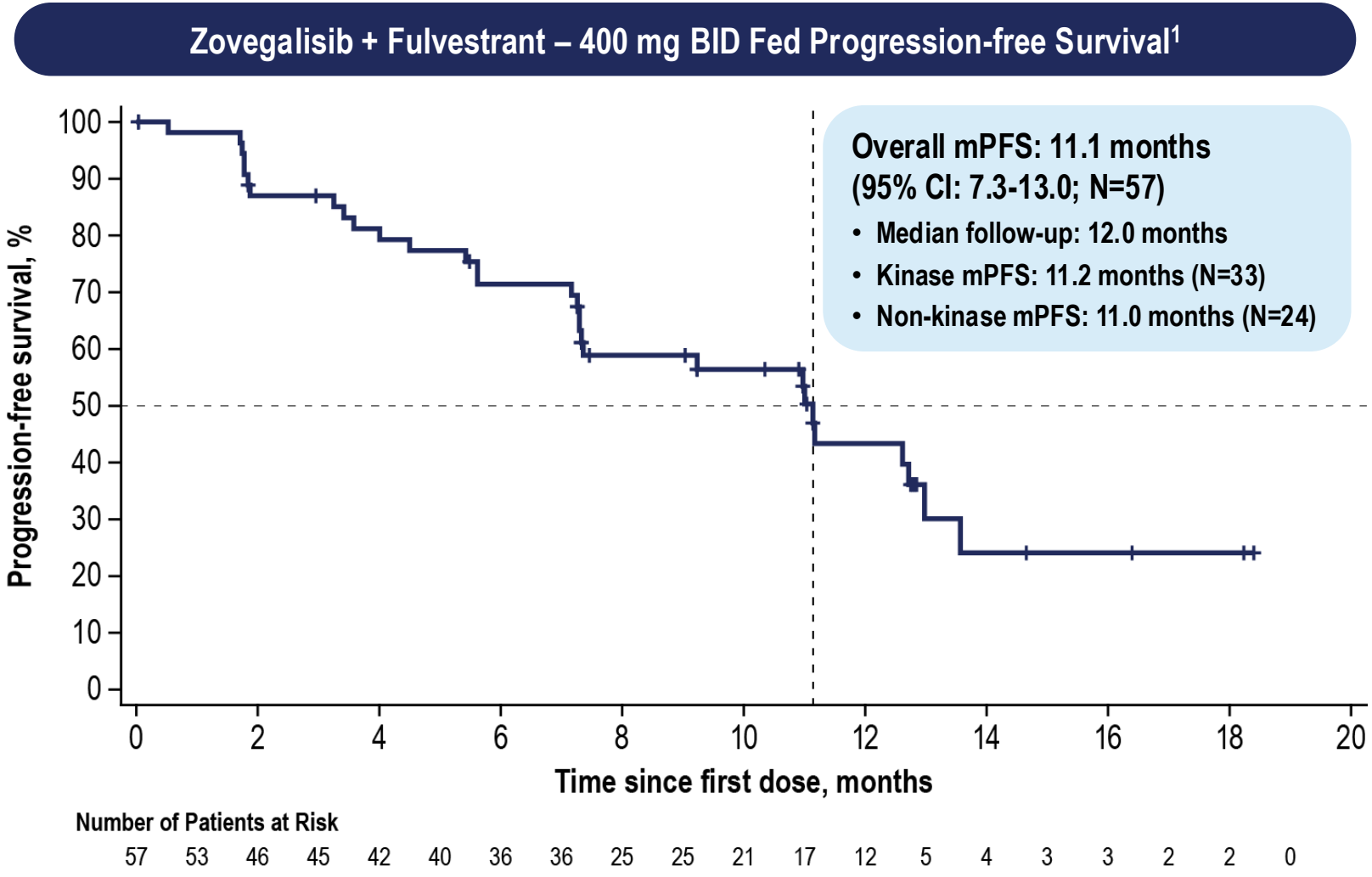
ReDiscover preliminary data as of 1/13/2026

Zovegalisib + Fulvestrant Achieves Progression-free Survival of 11.1 months



[1] Excludes patients with PTEN or AKT1 E17K co-mutation at baseline.

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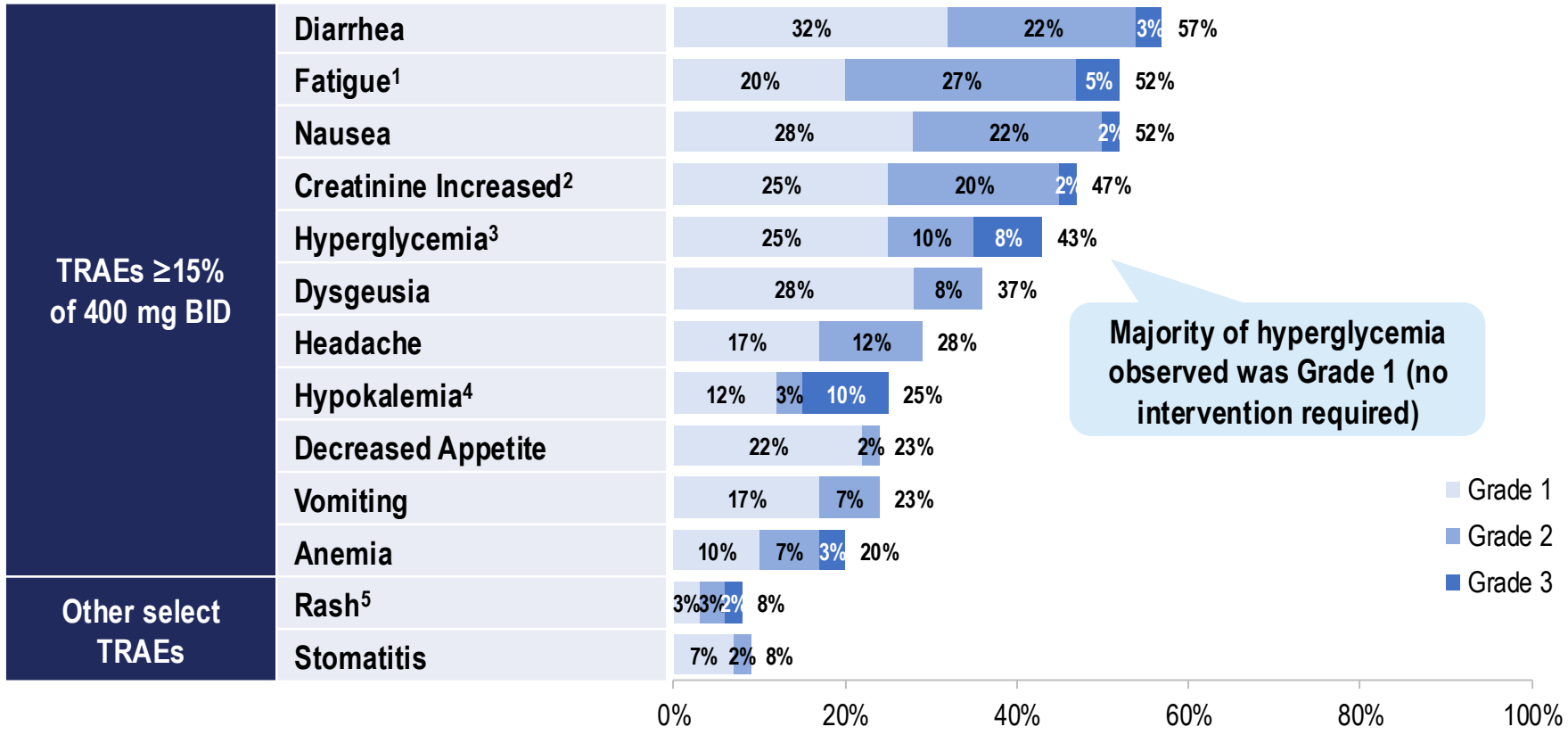
Zovegalisib – Treatment-related Adverse Events Largely Low-grade and Reversible

ReDiscover – Zovega 400 mg BID Fed + Fulvestrant (n=60): 33.4 weeks mDOE (Range: 2.9 – 80.1)



Zovegalisib has a favorable safety profile consistent with mutant-selective PI3Kα inhibition

[1] Fatigue includes the PTs: Fatigue, Asthenia; [2] Creatinine Increased includes the PTs: Blood creatinine increased, hypercreatininaemia; [3] Hyperglycemia includes the MedDRA v28.0 Preferred Terms (PT): Hyperglycemia, Blood Glucose Increased; [4] Hypokalemia includes the PTs: Hypokalemia and blood potassium decreased; [5] Rash includes the PTs: Rash, Rash Macular, Rash Maculo-Papular. Note: 4 dose discontinuations due to:(1) Chronic kidney disease, Gr2; (1) Creatinine increase, Gr2; (1) neutropenia, Gr3; (1) Severe cutaneous adverse reaction DRESS syndrome, Gr3.

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ReDiscover preliminary data as of 1/13/2026

ReDiscover-2 – Phase III Registrational Trial for Post-CDK4/6 inhibitor HR+/HER2- Advanced Breast Cancer with a *PIK3CA* Mutation[1,2]

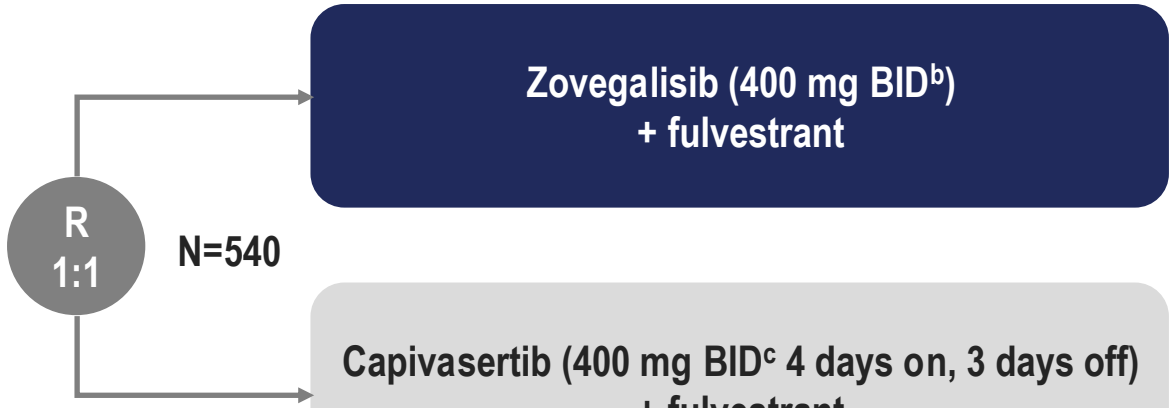
Key Eligibility Criteria:

Inclusion criteria

- *PIK3CA*-mutated HR+/HER2- ABC
- No concomitant *PTEN* or *AKT* tumor alterations
- Measurable disease or evaluable bone-only disease
- Progression in ABC or adjuvant[a] setting on or after:
  - 1-2 lines ET, and
  - 1 line CDK4/6i

Exclusion criteria

- Prior PI3Ki, AKTi, mTORi, ADC, IO, or investigational CDKi, CDK2i, CDK4i
- Progression on ≤6 mo ET-based regimen for ABC
- Type 1 diabetes, or type 2 diabetes requiring antihyperglycemic medication
- Fasting plasma glucose ≥140 mg/dL, or HbA1c ≥7.0% (≥53 mmol/mol)



Stratification:
- *PIK3CA* mutation type
- Visceral disease
- Geography

- Primary endpoint: PFS (kinase, overall population)
- Key secondary endpoint: OS (kinase, overall population)
- Additional secondary endpoints: ORR, DoR, CBR, QoL

Phase 3 trial initiated mid-2025

[a] Disease progression during or within 12 mo of completing adjuvant therapy; [b] Zovegalisib administered with food; [c] Capivasertib administered with or without food
ABC, advanced breast cancer; ADC, antibody-drug conjugate; AKT, protein kinase B; BID, twice daily; CBR, clinical benefit rate;CDK, cyclin-dependent kinase; DoR, duration of response; ET, endocrine therapy; HbA1c, glycated hemoglobin; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; i, inhibitor; IO, immuno-oncology therapy; mo, months; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; QoL, quality of life; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.
1. Rugo, H et al. Poster presented at SABCS; Dec 9-12J, 2025. Abstract 852; 2. https://clinicaltrials.gov/study/NCT06982521. Accessed Jan 27, 2026.

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Conclusions

Zovegalisib is the first oral, pan-mutant-selective PI3Kα inhibitor for patients with HR+/HER2– advanced breast cancer harboring PIK3CA mutations[1]

Prior data with zovegalisib 600 mg BID + fulvestrant in fasted patients demonstrated clinically meaningful activity and tolerability, establishing the value of mutant-selective PI3Kα inhibition in this population[2,3]

The 400 mg BID fed dose of zovegalisib taken with food achieves comparable exposures to 600 mg BID fasted, enabling a more convenient and patient-friendly dosing option

At 400 mg BID fed, zovegalisib + fulvestrant maintains robust efficacy, with PFS consistent across kinase and non-kinase *PIK3CA* mutation subtypes

Consistent with its mutant-selective MOA, the fed 400 mg BID zovegalisib + fulvestrant regimen continues to demonstrate a favorable and differentiated safety profile

These results support the Phase III ReDiscover-2 trial evaluating zovegalisib 400 mg BID fed + fulvestrant versus capivasertib + fulvestrant in post-CDK4/6 inhibitor, *PIK3CA*-mutated, HR+/HER2– advanced breast cancer[4]

Zovegalisib + fulvestrant has received FDA Breakthrough Therapy Designation for the Phase III ReDiscover-2 trial population

1. Varkaris A, et al. Cancer Discovery. 2024;14:240–257; 2. Sammons SL, et al. Poster presented at ASCO 2025, Abstract 1086; 3. Saura, C et al. Poster presented at SABCS 2025. Abstract 799;4. Rugo, H et al. Poster presented at SABCS 2025, Abstract 852

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