

Gedatolisib, a multitarget PI3K/AKT/mTOR inhibitor, plus fulvestrant with or without palbociclib for second-line treatment of patients with HR+/HER2-/PIK3CA-WT advanced breast cancer: updated results from the randomized, phase 3 VIKTORIA-1 trial

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Disclosure Information

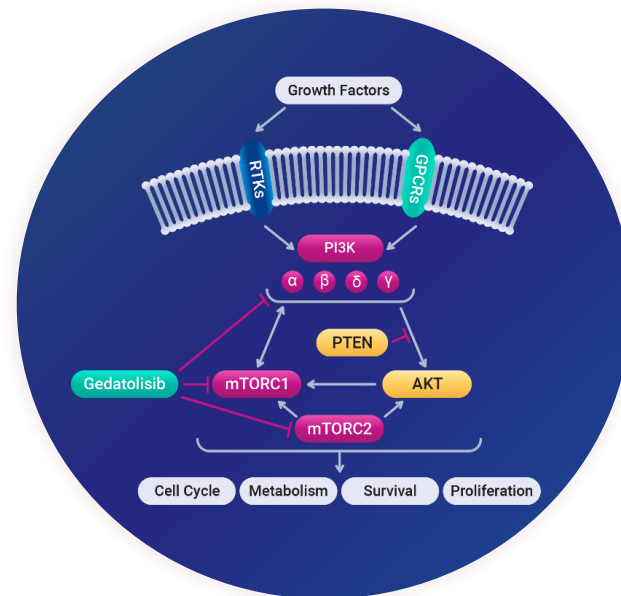
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I have the following relevant financial relationships to disclose:

- **Consulting fees:** AstraZeneca (institutional), Seagen (institutional), Gilead (institutional), Novartis (institutional), Lilly (institutional), MSD (institutional), Pierre Fabre (personal), Daiichi Sankyo (institutional/personal), Olema (institutional)
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Background

- The PI3K/AKT/mTOR (PAM) pathway drives breast cancer growth and contributes to ET and CDK4/6i resistance
 - Most available therapies are indicated only for patients with PI3K-pathway activation^{1,2}
 - **There remains a need for safe, effective therapies for *PIK3CA*-WT disease**
- In **VIKTORIA-1 trial**, gedatolisib, a highly potent multitarget PAM inhibitor, demonstrated statistically significant and clinically meaningful efficacy in patients with HR+, HER2-negative, *PIK3CA*-WT ABC, who received prior CDK4/6i³
 - **Gedatolisib + palbo + fulvestrant, mPFS 9.3 mo. (HR, 0.24; 95% CI, 0.17-0.35; $P < 0.0001$)**
 - **Gedatolisib + fulvestrant, mPFS 7.4 mo. (HR, 0.33; 95% CI, 0.24-0.48; $P < 0.0001$)**
- Treatment-related adverse events associated with gedatolisib were mainly grade 1-2³
 - Hyperglycemia and diarrhea were relatively uncommon
 - Grade 3 stomatitis: triplet, 19.2%; doublet, 12.3%



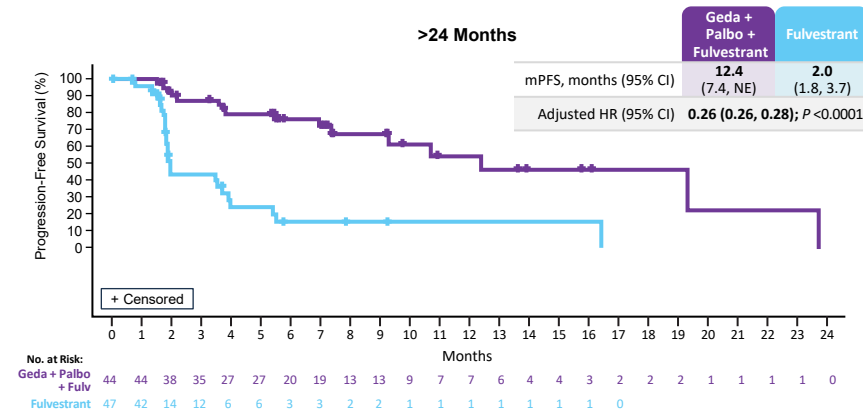
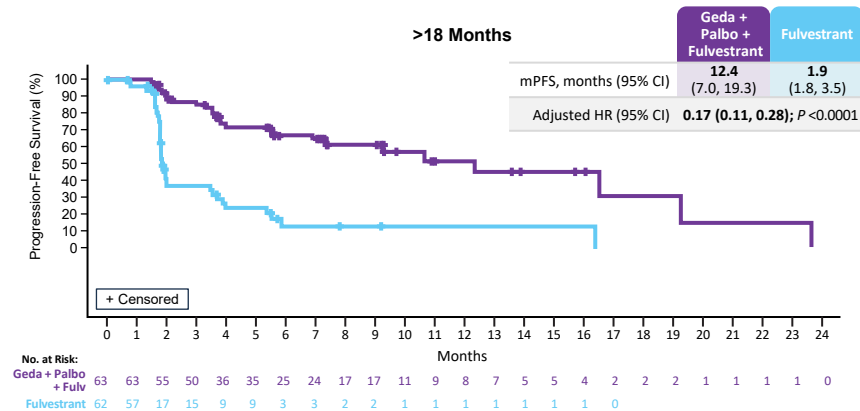
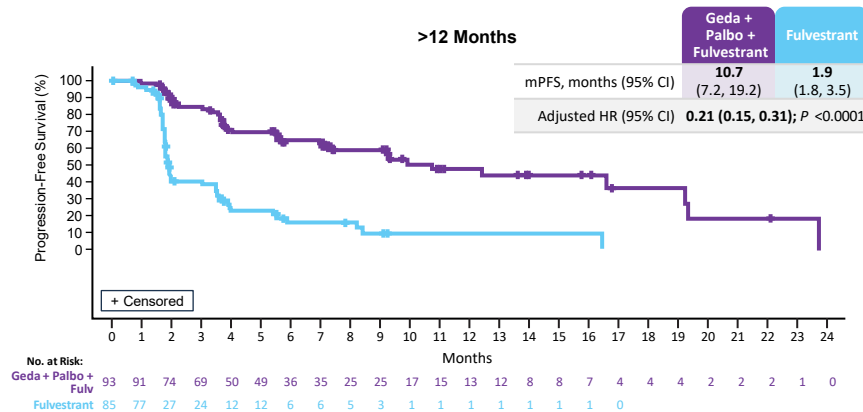
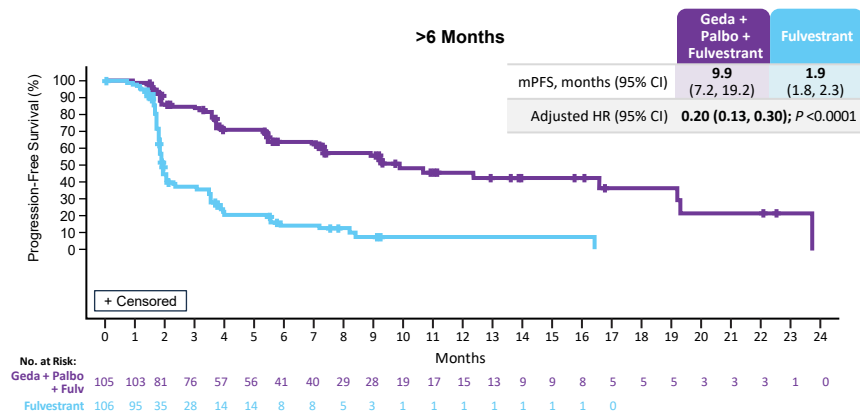
Here we examine additional subgroups, expanded safety, and initial patient-reported outcomes

Abbreviations: ABC, advanced breast cancer; AKT, protein kinase B; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; ET, endocrine therapy; GPCRs, G protein-coupled receptors; HER2-negative, human epidermal growth factor receptor 2-negative; HR, hazard ratio; HR+, hormone receptor-positive; mo., months; mPFS, median progression-free survival; mTORC, mechanistic target of rapamycin complex; PAM, PI3K/AKT/mTOR; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin entity; RTKs, receptor tyrosine kinases; TRAE, treatment-related adverse event; WT, wild-type

1. Andre F. *N Engl J Med.* 2019;380:1929-40; 2. Turner NC. *N Engl J Med.* 2023;388:2058-70; 3. Hurvitz SA, et al. *ESMO* 2025. LBA17.

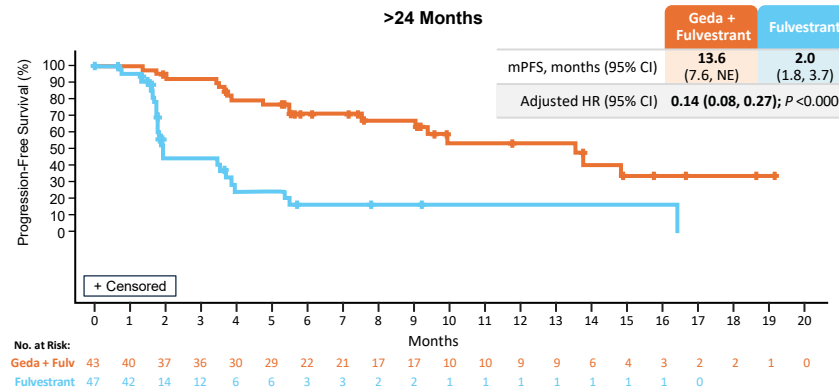
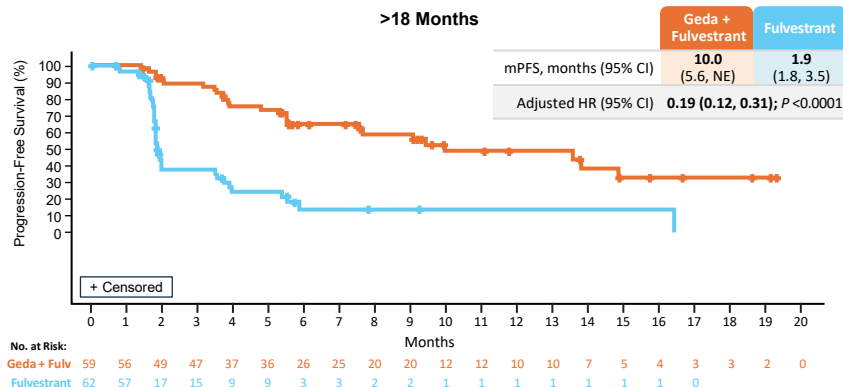
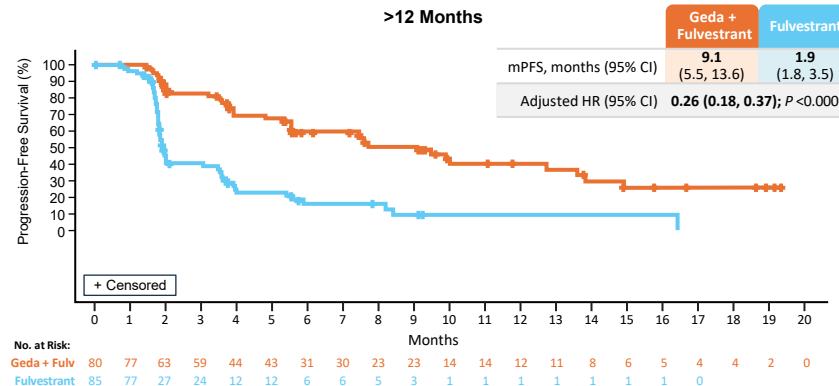
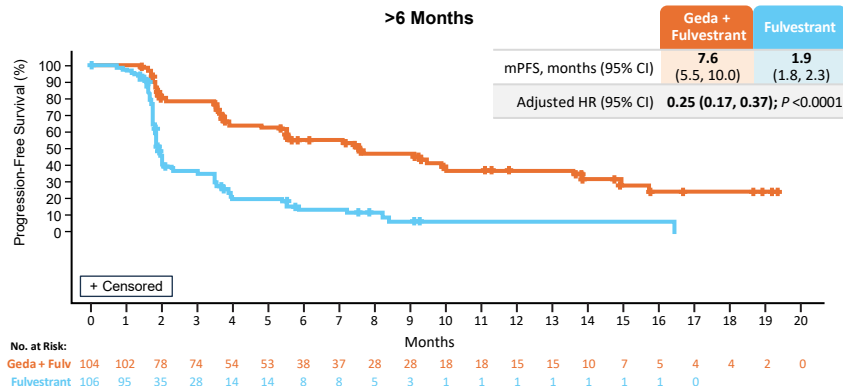
PFS by TTP on Immediate Prior Therapy:

Gedatolisib Triplet vs. Fulvestrant



PFS by TTP on Immediate Prior Therapy:

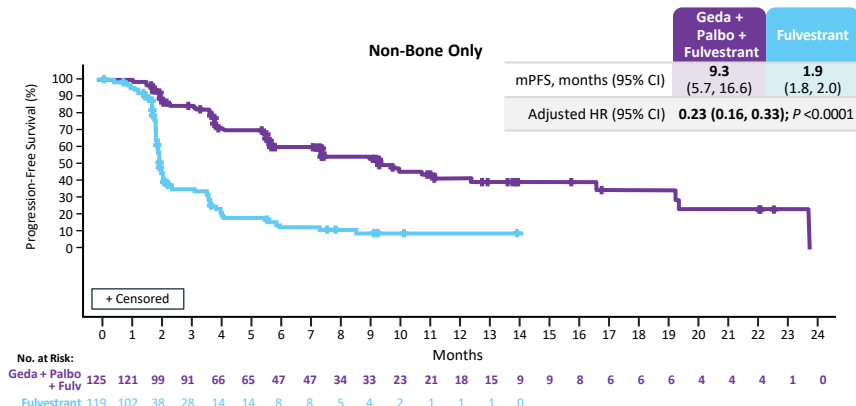
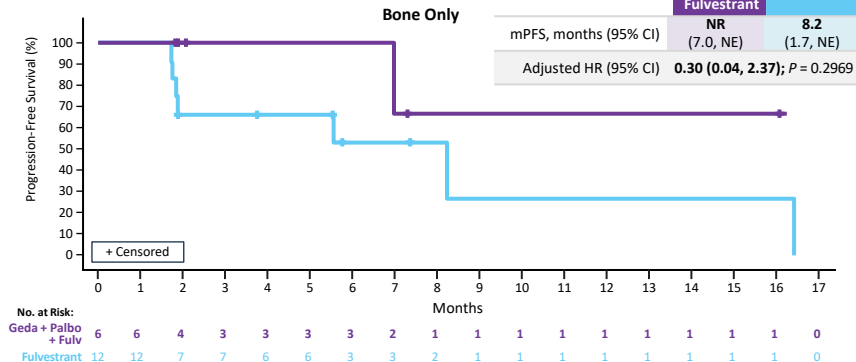
Gedatolisib Doublet vs. Fulvestrant



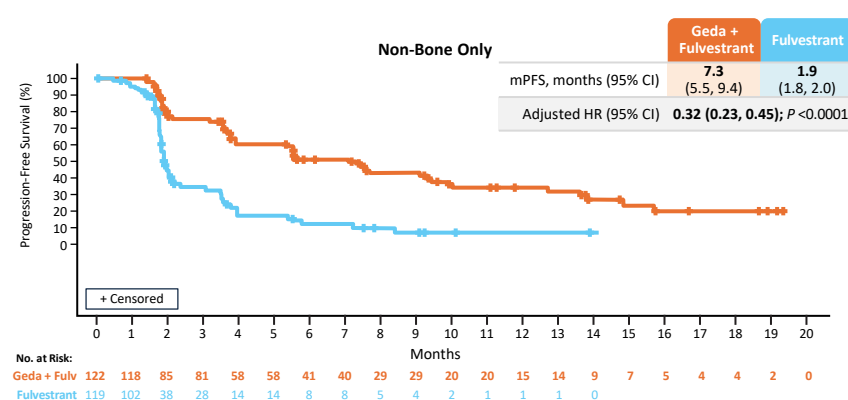
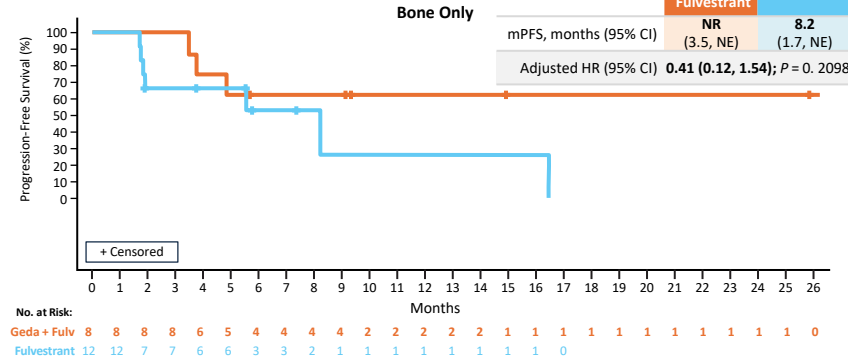
PFS by Bone Metastases Status:

Bone Only vs. Non-Bone Only

Gedatolisib Triplet



Gedatolisib Doublet



Stomatitis: Time to First Onset

Event	Gedatolisib + Palbo + Fulvestrant (n=130)		Gedatolisib + Fulvestrant (n=130)	
Pts with treatment-related stomatitis*†, n (%)	90 (69.2%)		74 (56.9%)	
Median time to onset (first instance), days (range)	7.5 (1-259)		4.0 (1-524)	
Grade 1	n=57	8.0 (1-259)	n=48	4.5 (1-524)
Grade 2	n=24	7.5 (1-146)	n=16	3.5 (1-158)
Grade 3	n=9	4.0 (1-20)	n=10	3.5 (2-87)

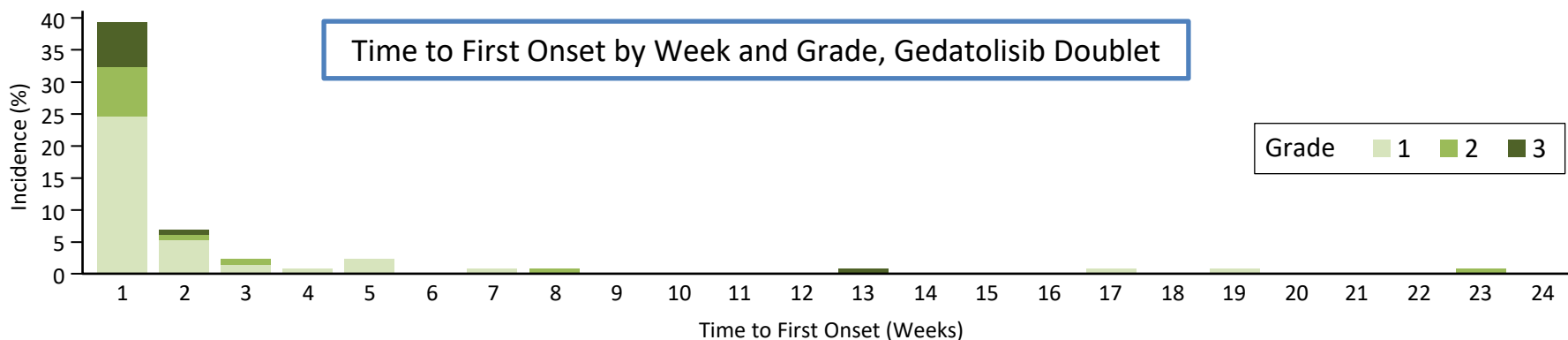
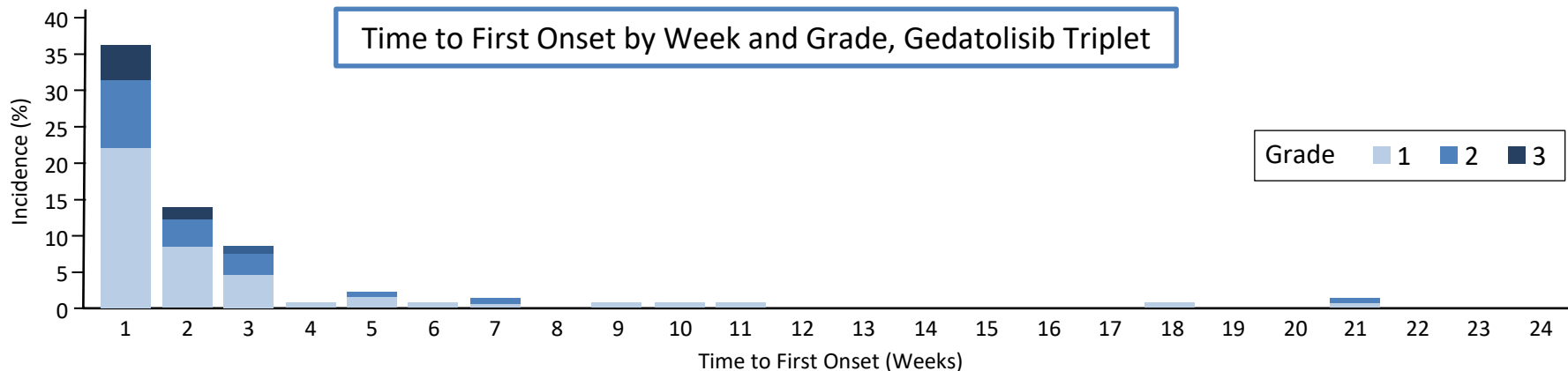
*Stomatitis is a combination of the following terms: aphthous ulcer; gingival pain; gingivitis; lip ulceration; oral mucosal inflammation; mouth ulceration; stomatitis

†Dexamethasone “swish-and-spit” mouthwash, provided by the sponsor, was required prophylactic treatment for gedatolisib, starting prior to first infusion and continued daily for 8 weeks, and as clinically indicated thereafter

The majority of patients experienced Grade 1 stomatitis as the first event

Stomatitis: Time to First Onset

Safety Analysis Set, Weeks 1-24



Stomatitis: Time to Improvement

Event	Gedatolisib + Palbo + Fulvestrant (n=130)		Gedatolisib + Fulvestrant (n=130)	
Pts with treatment-related stomatitis*†, n (%)	90 (69.2%)		74 (56.9%)	
Median time to improvement (from worst grade), days (range)				
Grade 3 to lower	n=25	12.0 (3-103)	n=16	7.5 (2-112)
Grade 2 to lower	n=25	14.0 (4-229)	n=18	9.0 (3-41)
Grade 1 to lower	n=40	27.5 (1-402)	n=40	17.5 (1-317)

*Stomatitis is a combination of the following terms: aphthous ulcer; gingival pain; gingivitis; lip ulceration; oral mucosal inflammation; mouth ulceration; stomatitis

†Dexamethasone “swish-and-spit” mouthwash, provided by the sponsor, was required prophylactic treatment for gedatolisib, starting prior to first infusion and continued daily for 8 weeks, and as clinically indicated thereafter

Grade 2/3 events generally improved to a lower grade within 1-2 weeks

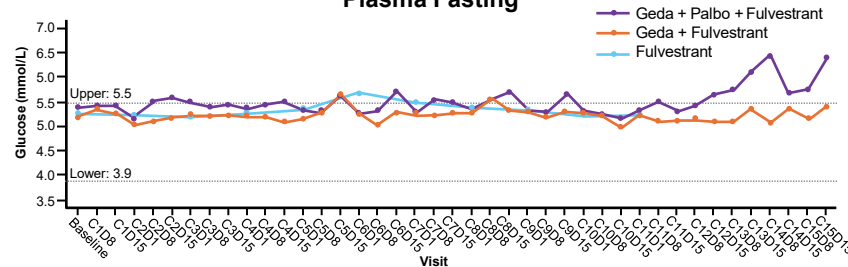
Median Glucose Levels Were Stable

Hyperglycemia, n (%)	Geda + Palbo + Fulvestrant (n=130)	Gedatolisib + Fulvestrant (n=130)	Fulvestrant (n=123)
All grades	12 (9.2)	15 (11.5)	0
HbA1c (%), median (range)	n=91	n=89	n=72
Baseline (B)	5.4 (4.1-6.4)	5.4 (4.0-6.3)	5.3 (4.0-6.3)
End of treatment (EOT)	5.9 (4.3-8.8)	5.9 (4.5-14.1)	5.5 (4.6-6.8)
Change, B to EOT	0.5 (-1.6 - 2.9)	0.6 (-0.7 - 8.2)	0.2 (-0.6 - 1.3)

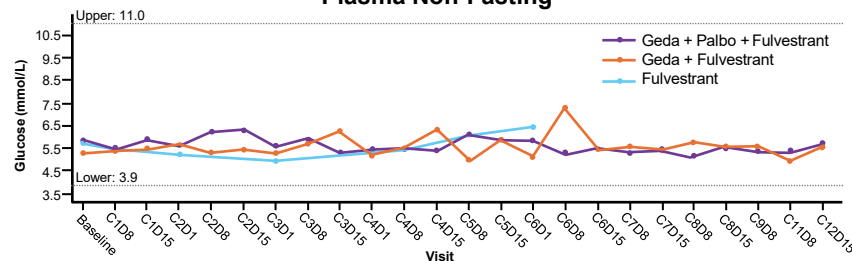
Gedatolisib did not produce clinically relevant hyperglycemia and had no dose reductions or withdrawals due to hyperglycemia

Abbreviations: B, baseline; C, cycle; EOT, end of treatment; Geda, gedatolisib; HbA1c, hemoglobin A1c; Palbo, palbociclib

Median Fasting Glucose Levels Over Time
Plasma Fasting

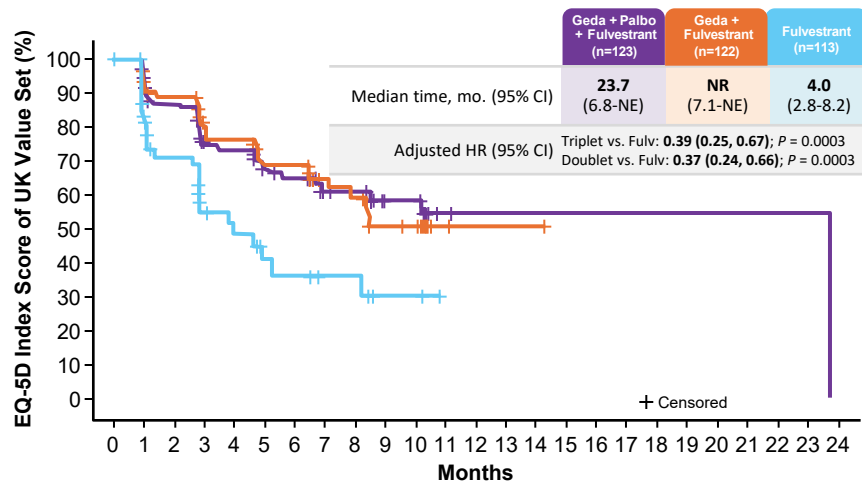


Median Non-Fasting Glucose Levels Over Time
Plasma Non-Fasting



PRO: Temporal and Mean Change, EQ-5D-5L

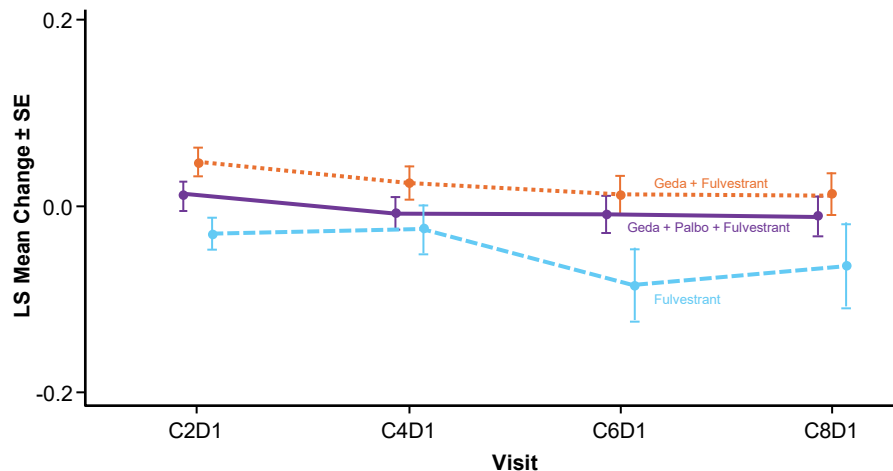
Time to Definitive Deterioration in EQ-5D-5L



No. at Risk:

Geda + Palbo + Fulvestrant	123	102	82	62	60	46	43	29	27	16	16	2	1	1	1	1	1	1	1	1	0
Geda + Fulvestrant	122	94	78	60	57	41	41	25	23	17	16	2	1	1	1	0					
Fulvestrant	113	55	34	18	15	9	8	6	6	3	3	0									

Mean Changes from BL in EQ-5D-5L



No. at Risk:

Geda + Palbo + Fulvestrant	95	75	63	50
Geda + Fulvestrant	98	75	58	49
Fulvestrant	88	29	15	10

Median time to definitive deterioration was meaningfully delayed in the gedatolisib arms as compared with fulvestrant

Conclusions

- VIKTORIA-1 is the first study to demonstrate a statistically significant and clinically meaningful improvement in PFS with PAM inhibition in patients with *PIK3CA*-WT disease, all of whom received prior CDK4/6i
- Significant efficacy was observed irrespective of the duration of prior treatment.
- Measures to mitigate stomatitis were effective; most patients experienced resolution to a lower grade of stomatitis in about 2 weeks
- Notably, hyperglycemia was low in both gedatolisib arms, and HbA1c levels were stable over time
- Both gedatolisib regimens delayed time to definitive deterioration of well-being (EQ-5D-5L) vs fulvestrant

Gedatolisib plus fulvestrant, with or without palbociclib, represents a potential new standard of care for patients with HR+, HER2-negative, *PIK3CA*-WT ABC whose disease progressed on or after treatment with a CDK4/6 inhibitor

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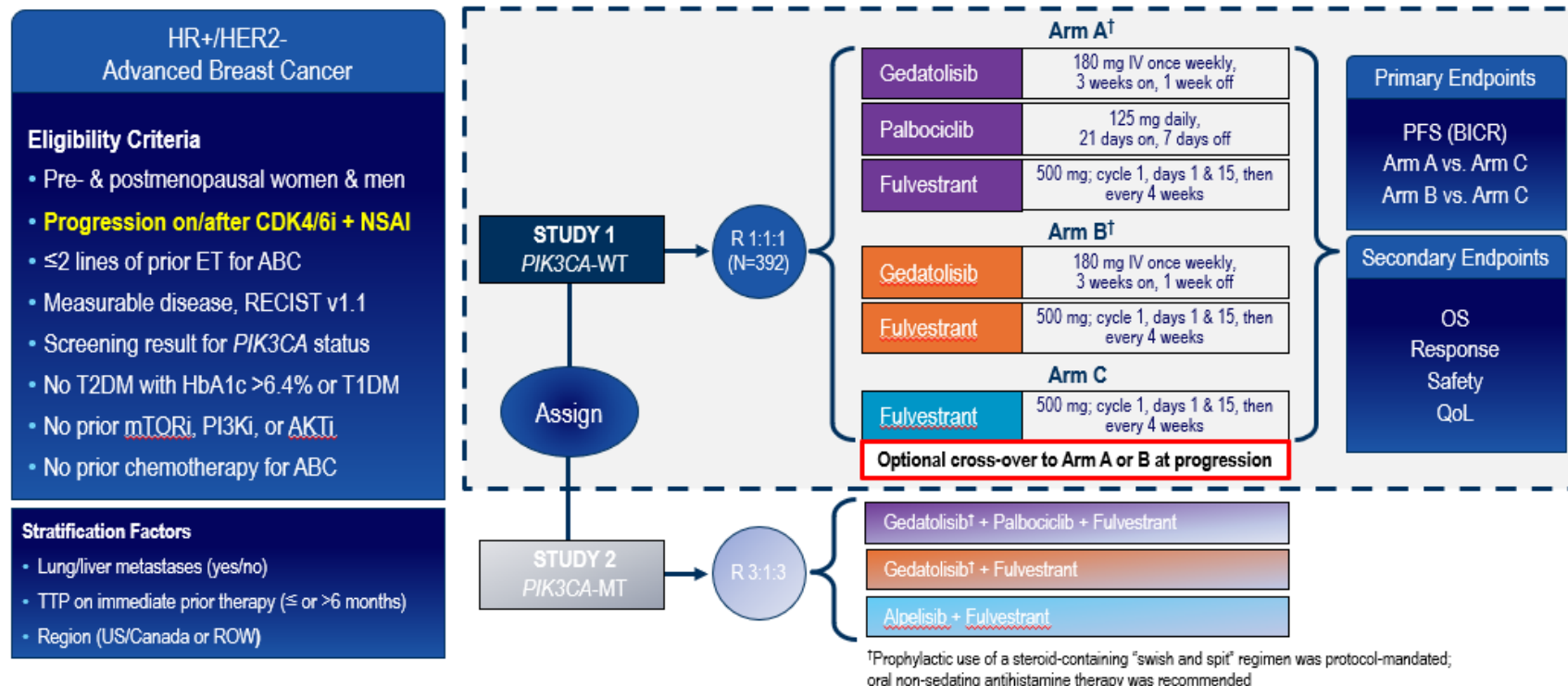
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Supplementary Material

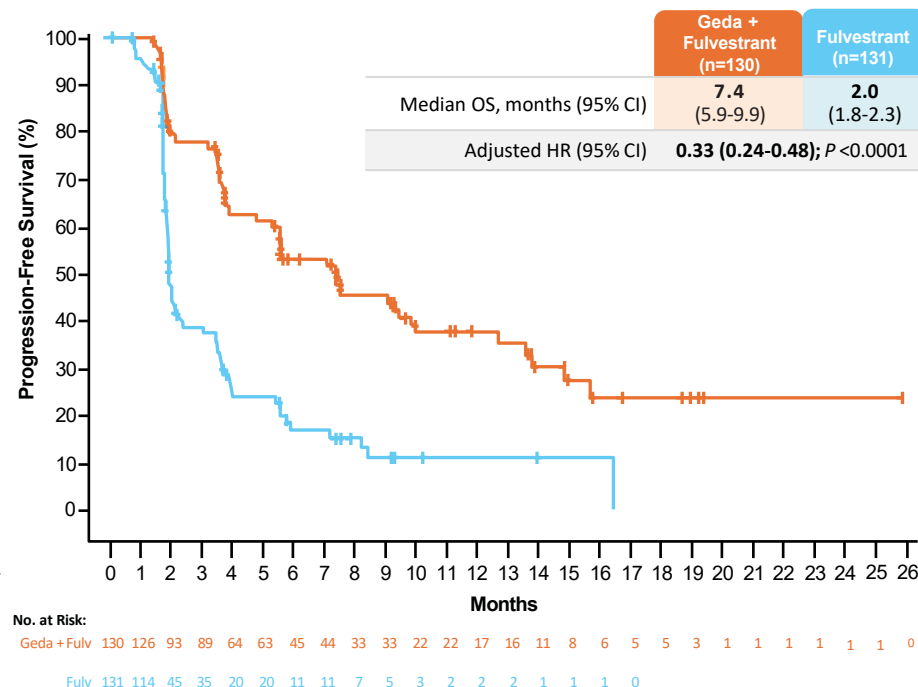
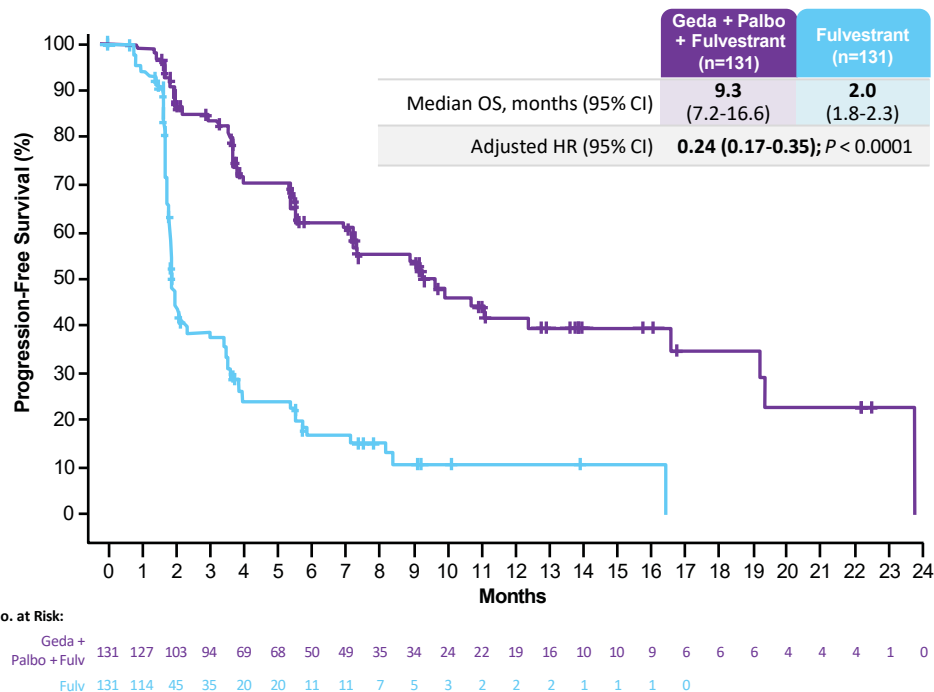
VIKTORIA-1 Study Design



Abbreviations: ABC, advanced breast cancer; AKTi, protein kinase B inhibitor; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; ET, endocrine therapy; HbA1c, hemoglobin A1c; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; IV, intravenous; MT, mutated; mTORi, mechanistic target of rapamycin inhibitor; NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PFS, progression-free survival; PI3Ki, phosphatidylinositol 3-kinase inhibitor; QoL, quality of life; R, randomization; ROW, rest of world; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TTP, time to progression; WT, wild-type

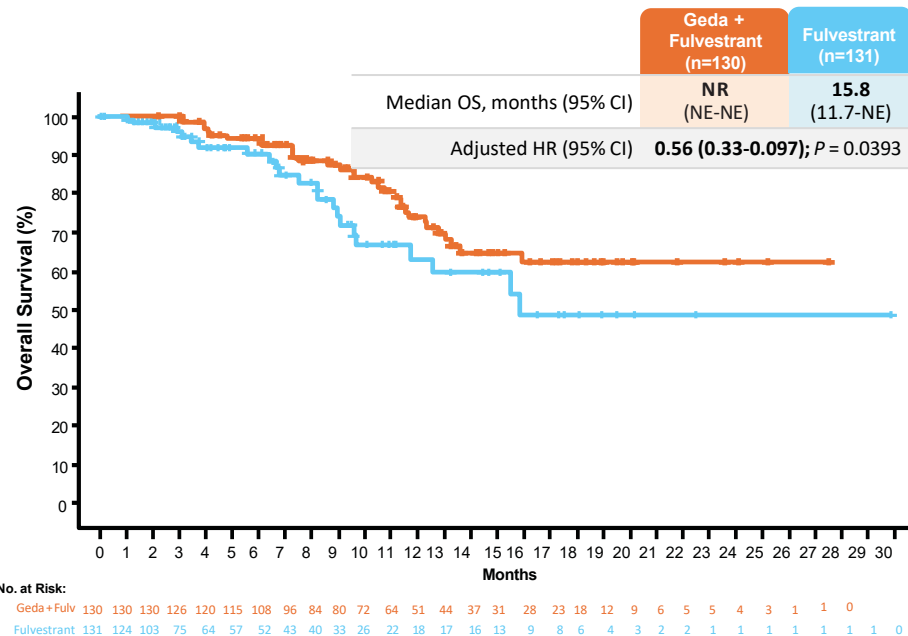
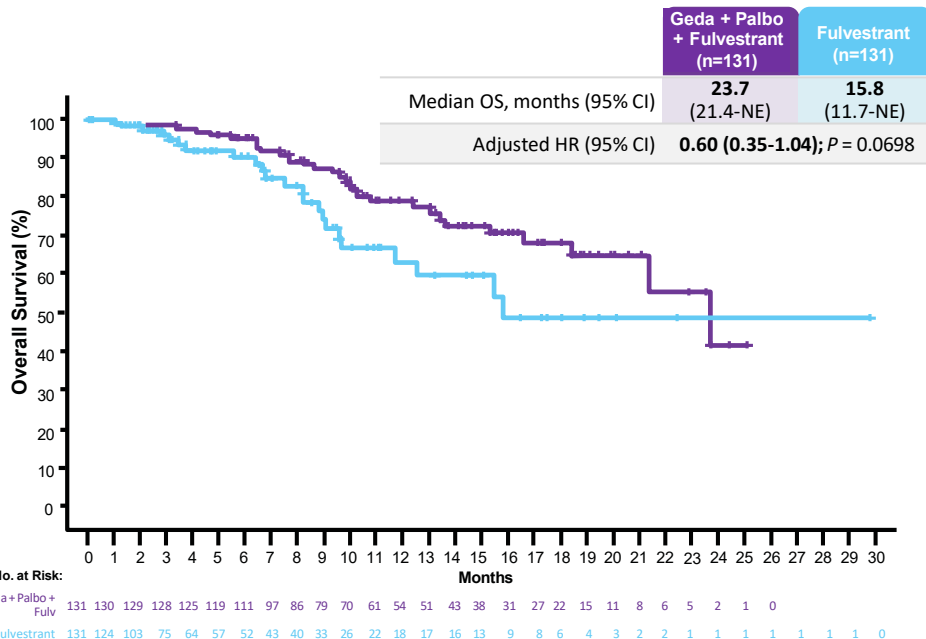
Co-Primary Endpoints: Progression-Free Survival (BICR)

Gedatolisib triplet and gedatolisib doublet vs. fulvestrant



Interim OS, Censored at Cross-Over

Gedatolisib triplet and gedatolisib doublet vs. fulvestrant

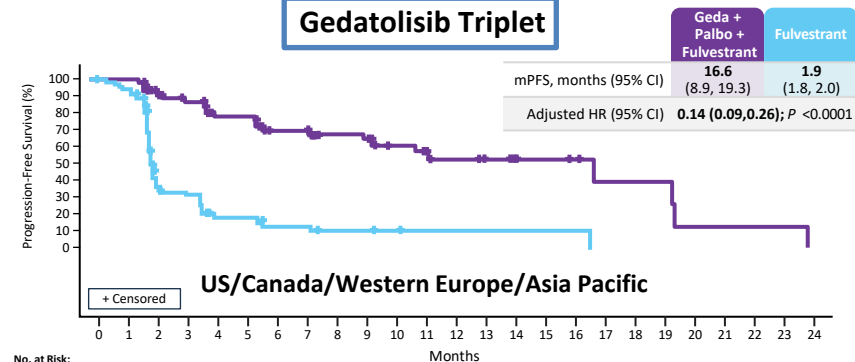


63 patients in the fulvestrant arm who crossed over to one of the gedatolisib regimens were censored in this sensitivity analysis

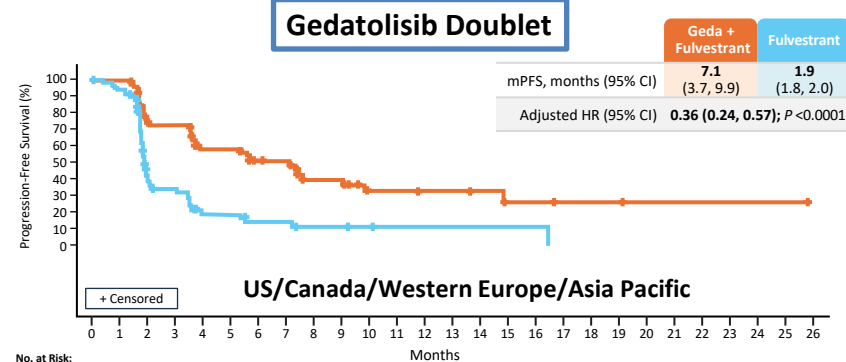
PFS by Region

US/Canada/Western Europe/Asia Pacific vs. Rest of World

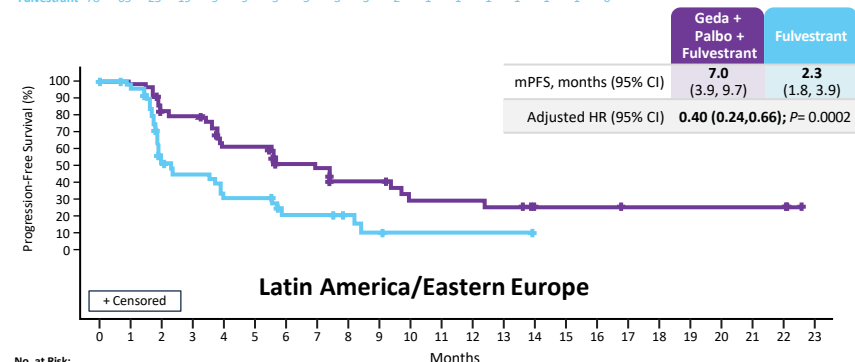
Gedatolisib Triplet



Gedatolisib Doublet



Latin America/Eastern Europe



Latin America/Eastern Europe

