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Effects of 6 Months of Tirzepatide on Risk Biomarkers for Development of Breast Cancer

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Summary

Background: Tirzepatide is a dual agonist of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors. It is FDA-approved for obesity treatment, but little is known about effects on biomarkers for breast cancer risk or breast cancer incidence.

Objectives 1) ≥1 enrollee/month cohort model where participant bears part of drug cost 2) >70% completion of study including biomarker procurement; 3) Determination of proportion of women with detected GIPR in breast epithelium; and 4) Identification of reliably modulated biomarkers.

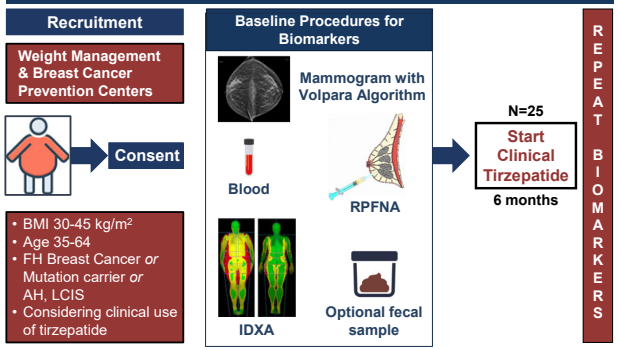
Methods: Women with obesity and additional risk factors for breast cancer considering clinical use of tirzepatide were approached for study participation. Inclusion criteria were age 35-64, BMI ≥30 kg/m^2, ≥2x population risk for breast cancer, and self-pay or insurance coverage for tirzepatide. Exclusion criteria included prior invasive cancer or current insulin or antiestrogens. Prior to tirzepatide initiation, women signed consent and underwent a fasting blood draw, 3D mammography, iDXA, random periareolar fine needle aspiration (RPFNA), and optional stool for microbiome. Tirzepatide was started at a dose of 2.5 mg/week, escalated every 4 weeks to a maximum of 15 mg. Imaging risk biomarkers assessed are glandular volume (FGV) via Volpara™ and visceral fat via iDXA. Tissue markers include Ki-67, adipocyte size, GIPR and estrogen response gene expression, Blood biomarkers include adipocytokines, circulating microRNA, and Klotho. Change in microbiome is also being assessed.

Results: 25 enrolled in 11 months (15 pre,10 postmenopausal). Of 19 completing study to date, median base BMI was 35.5 kg/m^2. Change in BMI -15%, visceral fat -19%, FGV -20%, and HOMA-IR -34%. Median relative change in Ki-67 is -0.74 for the nine women with baseline Ki-67 ≥ 2%. 7/12 entrants tested to date have evidence of *GIPR* in breast epithelium at baseline by spatial genomics.

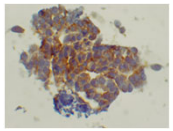
Conclusions: Feasibility of a convenient cohort study design is demonstrated and initial biomarker results support expansion to a larger Phase II trial where the magnitude of biomarker change can be evaluated with greater precision and confidence.

Methods and Materials

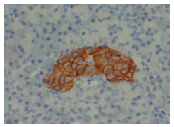
Pilot of Convenient Cohort Design Assessing Tirzepatide Effects on Breast Cancer Risk Biomarkers in Women with Obesity (NCT06485089)



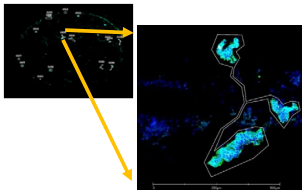
Detection of GIPR by IHC in RPFNA



Pancreatic Islets Positive control for GIPR staining



Detection of *GIPR* in 7/12 participants assessed to date was performed using Digital Spatial Profiling transcriptomic analysis (Nanostring's GeoMx platform)



Median Values for Participants Completing Trial (N=19)

Parameter	Baseline	6-month	Absolute Change	Relative Change
BMI, kg/m^2	35.5	31.1	-5.5	-0.15
FGV, cm^3	139.9	115.6	-32.4	-0.20
Visceral fat, Kg	1.91	1.70	-0.46	-0.19
Ki-67, %	1.9	2.0	-1.15	-0.46
Ki-67 (baseline >2%) [N=9]	6.6	1.6	-6.1	-0.74
Insulin, mcU/mL	10.6	7.6	-3.0	-0.26
Glucose, mg/dL	95.0	85.0	-8.0	-0.08
HOMA-IR	2.53	1.67	-0.90	-0.34
Estradiol, pg/ml	22.83	13.51	-2.74	-0.18
Estrone, pg/ml	23.42	19.40	5.57	0.23
Testosterone, nmol/L	1.03	1.02	0.02	0.02
SHBG, nmol/L	43.39	71.41	16.67	0.29
Bioavailable Estradiol, pM	1.41	0.74	-0.26	-0.15
Bioavailable Testosterone, pM	44.11	37.82	-5.57	-0.25
FSH, mIU/ml	31.31	45.38	4.79	0.14
Progesterone, ng/ml	0.38	0.37	0.00	0.04
IGF-1, ng/mL	99.48	100.84	4.58	0.05
IGFBP3, ng/mL	2.35	2.19	-0.17	-0.07
IGF-1 : IGFBP3 molar ratio	0.14	0.17	0.01	-0.07

Discussion

Feasibility objectives:

1) **The benchmark of recruitment success (≥1 enrollee/month) has been surpassed with recruitment at 2.5 enrollees/month.**
2) **The benchmark of 70% completion of study with biomarker procurement at baseline and off-study has already been achieved (19/25, 76%) with remaining participants still on schedule.**
3) **Proportion of women with detected GIPR in breast epithelium appears >50% on initial results**
4) **Visceral adipose, measures of insulin resistance, and Ki-67 in women with 1% or higher at baseline appear to be favorably modulated over the treatment interval. Results of other biomarkers are pending.**

Contact

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