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TITLE: : Clinical investigations of GLP-1 RA induced weight loss in early-stage triple negative breast cancer and impact on treatment outcomes.

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BACKGROUND AND RATIONALE

In obesity, breast adipose tissue undergoes significant hormonal and inflammatory changes that creates an environment that promotes cancer development (1). Genomic instability, inflammation or immune responses in the tumor microenvironment are major underlying hallmarks of cancer (2) and the interaction between the cancer genome and immune reactions have important implications for early and late phases of cancer development. The effect of obesity on the immune microenvironment can lead to deleterious inflammation that result in cancer causing mutations (3, 4). A large-scale study from more than 180,000 women across 10 prospective studies found that sustained weight loss in women over age 50 was significantly associated with lower breast cancer risk compared with women who did not lose weight (5). In the U.S, obesity rates are at epidemic proportions and affect Black women disproportionately, with 57.2% of Black women being obese vs. 38.2% Non-Hispanic (NHW) women (6). In particular, obesity disproportionately affects Black women, with 57.2% of Black women being obese vs. 38.2% Non-Hispanic (NHW) women (6). Disparities in income, lack of access to nutritious food and healthcare, unsafe neighborhoods, and lack of physical activity can promote co-morbid diseases such as obesity and diabetes for Black women. Over 60% of adults are overweight and obese by Body Mass Index (BMI): 25–29.9 and >30 kg/m2, respectively (6,7). The prevalence of class 3 obesity (BMI> 40) in Black women was 16.8% vs. 9.7% in NHW women (6). TNBC is negative for, ie, does not express the estrogen receptor, progesterone receptor or have the amplification of HER2 all of which help guide targeted treatment if present, and thus there are limited treatment options for this disease. These TNBC are high-grade cancers with an overall poor prognosis and is an aggressive disease which affects Black women at a higher rate and contributes to the 41% worse survival outcomes compared to White women. A link exists between a higher BMI and TNBC in Black women, but not in NHW women, and with the prevalence of TNBC in overweight/obese Black women 2-fold compared to that in normal weight Black women while the incidence remained the same (7).

Obesity at time of breast cancer diagnosis and following treatment in survivorship years, is associated with poorer overall and breast cancer survival (5,8). In particular, a higher central body fat as measured by waist-to-hip ratio was associated with a higher risk of all-cause and breast cancer-specific death among Black women with triple negative breast cancer (9). This chronic, inflammatory state of obesity creates a breast tissue environment that promotes cancer development and may drive signaling pathways and genomic alterations associated with TNBC, underscoring the need for research in this area. There is a preponderance of evidence of an association with obesity and response to neoadjuvant chemotherapy (NAC) and correlation with survival (10,11). In one study, obesity was an important independent prognostic factor which had an adverse effect on pCR. Moreover, it decreased recurrence free survival and overall survival (OS) in breast cancer patients who had received NAC (12). In another study, 8,872 patients with early-stage BC from eight neoadjuvant trials were categorized according to BMI. Mean disease-free survival and OS were shorter in obese patients compared with normal weight patients and was consistent in luminal-like and TNBC (13). In a pooled analysis of 18,702 women, higher BMI was associated with lower pCR and had a negative impact on survival (14). In yet another study, a higher BMI was associated with worse pCR to NAC and these obese patients were more likely to have hormone-negative tumors, stage III tumors, and worse overall survival at a median follow-up time of 4.1 years (11).

The landscape for weight loss changed dramatically with the development of glucagon-like-peptide-1 (GLP-1) receptor agonists. GLP-1 receptor agonists (GLP-1 RA) are incretin mimetic drugs that facilitate fasting and postprandial glycemic control by increasing glucose-dependent insulin secretion, reducing glucagon release, suppressing hepatic gluconeogenesis, and slowing gastric emptying (15). These agents were initially developed for managing type 2 diabetes but now are proven to be remarkably effective weight loss drugs. Retrospective studies of GLP-1 RA in breast cancer are conflicting regarding benefit and may be breast cancer subtype dependent (15). While these studies report participant demographics such as race, age, and gender, there is a lack of analysis on the influence of socioeconomic status, race/ethnicity, and age on treatment outcomes.

AIMS

We established feasibility in a prior AHEPA funded pilot project and we will build on our findings, expanding to a large multi-ethnic cohort of early-stage TNBC patients to further examine differences in patients with earl-stage TNBC and assess treatment outcomes in the setting of GLP-1 RA drug intervention for weight loss. For this study, we have identified across our large Rutgers Cancer Institute /RWJ Barnabas health system, about 770 early-stage TNBC patients, defined as Stage I, II or III, TNBC (ER-/PR-/Her2-) and ER/PR < 10% cut off is considered negative. Obese patients will be identified according to FDA approved criteria for use of GLP-1 RA medication which is a BMI of >30 kg/m2 or > 27 kg/m2 with an obesity related co-morbidity. This cohort includes a diverse population of ~ 50% Non-Hispanic White and 50% non-White patients, including Asian/Pacific Islander, Black and Hispanic/Latino. We will:

1) Determine the rates of pathologic complete response (pCR) versus residual disease for patients who received
neoadjuvant chemotherapy.
2) Determine the percent body weight reduction in patients using GLP-1 RA for weight loss management.
3) Assess the 3-year invasive disease-free survival (IDFS), disease free survival (DFS) and distant relapse free survival (DRFS) for all non-obese and obese patients and in patients using GLP-1 RA for weight loss management.
4) Assess influence of socioeconomic status, race/ethnicity, and age on treatment outcomes in Aims 1-3.

We identified across our large Rutgers Cancer Institute /RWJ Barnabas health system, over 750 early-stage TNBC Pts treated in the past 5 years, defined as Stage I, II or III, TNBC (ER-/PR-/Her2-) where ER/PR < 10% cut off is considered negative. The exclusion criteria: <18 years old, Stage IV TNBC, ER+, > 10%/and/or PR+, >10% or Her2 + BC. A pCR is defined as ypT0/Tis ypN0 (i.e., no invasive residual cancer in the breast or lymph nodes; noninvasive breast residual cancer e.g DCIS is allowed). pCR as determined by the local pathologist at time of surgery will be abstracted from pathology reports. Obese Pts will be identified according to FDA approved criteria for use of GLP-1 agonist medication which is a BMI of >30 kg/m^2 or > 27 kg/m^2 with an obesity related co-morbidity. This identified cohort includes a diverse population of Non-Hispanic White (47%), Asian/Pacific Islander (7%), Black (29%), Hispanic/Latino (12%), and Unknown (4%).

Data Abstraction from our Health system wide, unified Electronic Medical Record (EMR) is being performed by our Biomedical Imaging and Data Analytics team in the Division of Bioinformatics (Led by Dr. Wenjin Chen, Director, Academic computing) and will provide de-identified data. This will be abstracted from the Rutgers Clinical and Research Data Warehouse (CRDW) and our unified EMR across the health system. Data extracted from the EMR among others will include diagnosis, BC receptor status, stage, stage, gender, race, weight, height, chemotherapy regimen, GLP-1 use (any brand, type, oral or injectable), dates of treatment, death, imaging studies, pathology reports, and review of additional deidentified text reports to collect/verify disease progression.

BMI will be calculated from height and weight at the start of NAC and BMI of 30 kg/m2 or greater is considered obese. Social determinants of health data, e.g., zip code, county, town, and type of insurance plan will be abstracted. These elements are required to enable accurate longitudinal analysis of treatment timelines and outcomes, and to examine potential geographic or socioeconomic patterns related to TNBC care. ZIP code is used for regional analysis and linking with area-level socioeconomic indicators. Insurance type will be important for evaluating access and payer-related outcomes. Treatment dates/death dates are needed to establish sequence, duration, and survival metrics.

Statistical Analysis will be provided by the Biostatistics core lab (Dr. Hao Liu, Dir. of Biostatistics).

Sample Size and Power: Obesity may be associated with lower rates of pathologic complete response (pCR) for TNBC Pts treated with neoadjuvant chemotherapy. In the published literature, the average pCR rate for normal-weight TNBC patients is approximately 50%. A meta-analysis indicated overweight operable BC Pts are less likely to achieve a pCR compared to normal-weight Pts, with an odds ratio of .68. We hypothesize that a similar association may be observed in obese TNBC Pts. We therefore propose using 750 Pts with early-stage TNBC treated with neoadjuvant chemotherapy at Rutgers from 2021 to 2025 to evaluate the impact of obesity on treatment outcomes. According to recent studies, the average percentage of TNBC Pts who are obese is about

40%. Thus, we expect to have approximately 300 obese and 450 non-obese TNBC patients in our cohort. We suppose that the pCR rate is 50% in non-obese TNBC patients, with a total sample size of 750 patients (300 obese and 450 non-obese), we will have over 81.8% power to detect an OR of 0.65, with a two-sided type-I error of 0.05 (21). The percentage of women who used glucagon-like peptide-1 (GLP-1) injectables in 2024 was 27.2% and higher, up to 32.4% for those using it for obesity (2024 National Health Interview Survey (NHIS).

Data analysis plan: pCR rates will be compared between obese and non-obese TNBC Pts using Chi-square or Fisher's exact test. Similarly, pCR rates will be compared between obese TNBC Pts using GLP-1 and obese TNBC Pts not on GLP-1. Logistic regression models will assess association between obesity status and GLP-1 use and pCR, adjusting for potential confounding factors, including age, tumor stage, and treatment regimen. We will employ propensity score and inverse probability weighting to adjust for potential confounding factors related to obesity and GLP-1 use. Survival outcomes (BCSS, IDFS, DFS, and DRFS) will be analyzed using Kaplan-Meier methods and compared using log-rank tests. Cox proportional hazards models will be used to evaluate impact of obesity on survival outcomes, adjusting for relevant covariates.

We have begun applying for larger grants based on Abstracted data which this funding has allowed us to do to continue this work. Our proposal once completed will build on our findings from our preliminary data and in this multi-ethnic cohort could generate important hypotheses for larger investigations that can help generate treatment strategies in early-stage TNBC, reduce disparities and improve survival outcomes for patients with this aggressive disease.

REFERENCES

1. Bhardwaj P, Brown KA. Obese Adipose Tissue as a Driver of Breast Cancer Growth and Development: Update and Emerging Evidence. Front Oncol. 2021 Mar 30;11:638918. doi: 10.3389/fonc.2021.638918. PMID:
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144(5):646- 74. doi: 10.1016/j.cell.2011.02.013. PMID: 21376230.
3. Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013 Jan;137(1):307-14. doi: 10.1007/s10549-012-2339-3. Epub 2012 Nov 20. PMID: 23179600.
4. Dietze EC, Chavez TA, Seewaldt VL. Obesity and Triple-Negative Breast Cancer: Disparities, Controversies, and Biology. Am J Pathol. 2018 Feb;188(2):280-290. doi: 10.1016/j.ajpath.2017.09.018. Epub 2017 Nov 9. PMID: 29128565; PMCID: PMC5785535.
5. Teras LR, Patel AV, Wang M, Yaun S-S, Anderson K, Brathwaite R, et al.. Sustained Weight Loss and Risk of Breast Cancer in Women 50 Years and Older: A Pooled Analysis of Prospective Data. JNCI: J Natl Cancer Inst (2020) 112(9):929–37. 10.1093/jnci/djaa026.
6. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in Obesity Among Adults in the United States, 2005 to 2014. JAMA. 2016 Jun 7;315(21):2284-91. doi: 10.1001/jama.2016.6458. PMID: 27272580.
7. Gershuni V, Li YR, Williams AD, So A, Steel L, Carrigan E, Tchou J. Breast cancer subtype distribution is different in normal weight, overweight, and obese women. Breast Cancer Res Treat. 2017 Jun;163(2):375-381. doi: 10.1007/s10549-017-4192-x. Epub 2017 Mar 14. PMID: 28293912.
8. Raghavendra A, Sinha AK, Valle-Goffin J, Shen Y, Tripathy D, Barcenas CH. Determinants of Weight Gain During Adjuvant Endocrine Therapy and Association of Such Weight Gain With Recurrence in Long-term Breast Cancer Survivors. Clin Breast Cancer. 2018 Feb;18(1):e7-e13. doi: 10.1016/j.clbc.2017.11.006. Epub 2017 Nov 9. PMID: 29239836; PMCID: PMC5937690.
9. Bandera EV, Qin B, Lin Y, Zeinomar N, Xu B, Chanumolu D, Llanos AAM, Omene CO, Pawlish KS, Ambrosone CB, Demissie K, Hong CC. Association of Body Mass Index, Central Obesity, and Body Composition With Mortality Among Black Breast Cancer Survivors. JAMA Oncol. 2021 Jun 4;7(8):1–10. doi: 10.1001/jamaoncol.2021.1499. Epub ahead of print. PMID: 34086040; PMCID: PMC8377573.
10. Usiskin I, Li F, Irwin ML, Cartmel B, Sanft T. Association between pre-diagnosis BMI, physical activity, pathologic complete response, and chemotherapy completion in women treated with neoadjuvant chemotherapy for breast cancer. Breast Cancer. 2019 Nov;26(6):719-728. doi: 10.1007/s12282-019- 00974-3. Epub 2019 May 22. PMID: 31119682.
11. Litton JK, Gonzalez-Angulo AM, Warneke CL, Buzdar AU, Kau SW, et al. Relationship between obesity

and pathologic response to neoadjuvant chemotherapy among women with operable breast cancer. J Clin Oncol. 2008 Sep 1;26(25):4072-7. doi: 10.1200/JCO.2007.14.4527. PMID: 18757321; PMCID: PMC6557586.
12. Karatas F, Erdem GU, Sahin S, Aytekin A, Yuce D, Sever AR, Babacan T, Ates O, Ozisik Y, Altundag K. Obesity is an independent prognostic factor of decreased pathological complete response to neoadjuvant chemotherapy in breast cancer patients. Breast. 2017 Apr; 32:237-244. doi: 10.1016/j.breast.2016.05.013. Epub 2016 Jun 16. PMID: 27318645.
13. Fontanella C, Lederer B, Gade S, Vanoppen M, Blohmer JU, Costa SD, Denkert C, Eidtmann H, Gerber B, Hanusch C, Hilfrich J, Huober J, Schneeweiss A, Paepke S, Jackisch C, Mehta K, Nekljudova V, Untch M, Neven P, von Minckwitz G, Loibl S. Impact of body mass index on neoadjuvant treatment outcome: a pooled analysis of eight prospective neoadjuvant breast cancer trials. Breast Cancer Res Treat. 2015 Feb;150(1):127-39. doi: 10.1007/s10549-015-3287-5. Epub 2015 Feb 13. PMID: 25677740.
14. Wang H, Zhang S, Yee D, Basu S, Beckwith H, Potter D, Blaes A. Impact of body mass index on pathological complete response following neoadjuvant chemotherapy in operable breast cancer: a metaanalysis.
Breast Cancer. 2021 May;28(3):618-629. doi: 10.1007/s12282-020-01194-w. Epub 2021 Jan 2. PMID: 33387284.
15. Parsons K, Montalvo M, Fischbach N, Taylor M, Alfaro S, Lustberg M. The Impact and Safety of GLP-1 Agents and Breast Cancer. Cancer Med. 2025 Jun;14(12):e70932. doi: 10.1002/cam4.70932. PMID: 40552446; PMCID: PMC12186097.