Letter to the Editor

Differentiating Between Intentional Versus Unintentional Weight Loss

Re: Martel S, Lambertini M, Agbor-Tarh D, et al. Body mass index and weight change in patients with HER2-positive early breast cancer: exploratory analysis of the ALTTO BIG 2-06 trial. *J Natl Compr Canc Netw* 2021;19(2):181–189.

We read with particular interest the article by Martel et al¹ exploring associations between obesity, weight change, and survival in patients with HER2-positive early breast cancer in the ALTTO trial. The authors' main findings were 2-fold: (1) obesity at randomization was associated with worse distant disease-free survival (DDFS) and overall survival (OS), and (2) weight loss $\geq 5\%$ at 2 years after randomization was associated with poorer DFS, DDFS, and OS. Although the first finding is consistent with previously published meta-analyses,² we have concerns regarding the authors' discussion of the second result and believe a more thorough explanation is warranted to minimize misinterpretations that could negatively impact clinical recommendations.

The authors noted that intentional versus unintentional weight loss would have been informative for this study, but was unavailable. We wanted to clarify that not differentiating between how weight loss was achieved is a crucial missing data point that ultimately obscures their conclusion. Weight loss after diagnosis among patients with breast cancer, induced by healthy diet and exercise, has favorably impacted treatment-related adverse effects, quality of life, body composition measures, and serum inflammatory and

metabolic biomarkers.^{3,4} Comparatively, weight loss potentially from underlying disease can result in sarcopenia (loss of muscle mass), which is associated with increased risk of mortality among patients with early breast cancer.⁵ It is also important to note the significant impact of weight loss was only observed among premenopausal women, and therefore any clinical implications these results may have should be carefully considered in this context.

Based on their results, the authors also called for "caution if weight loss trials, such as the ongoing phase III Breast cancer WEight Loss study (BWEL), are to be conducted in survivors of HER2-positive breast cancer." However, because BWEL is a supervised weight loss intervention, we do not believe the results by Martel et al¹ should be directly extrapolated to BWEL nor similar lifestyle interventions exploring the impact of intentional weight loss on DFS.

We commend the authors for investigating these associations among a lesser studied breast cancer subtype and agree that dietary and exercise counseling should be part of survivorship care programs. However, we felt it was necessary to express our concerns about some of the conclusions, because they may unintentionally impact evidence-based research promoting weight loss through exercise and diet for patients with breast cancer and obesity. We hope future studies can differentiate how weight loss is achieved to further clarify these results.

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References

1. Martel S, Lambertini M, Agbor-Tarh D, et al. Body mass index and weight change in patients with HER2-positive early breast cancer: exploratory analysis of the ALTTO BIG 2-06 trial. *J Natl Compr Canc Netw* 2021;19:181–189.
2. Chan DSM, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer: systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol* 2014;25:1901–1914.
3. Harrigan M, Cartmel B, Lofftfield E, et al. Randomized trial comparing telephone versus in-person weight loss counseling on body composition and circulating biomarkers in women treated for breast cancer: the Lifestyle, Exercise, and Nutrition (LEAN) study. *J Clin Oncol* 2016;34:669–676.
4. Demark-Wahnefried W, Colditz GA, Rock CL, et al. Quality of life outcomes from the Exercise and Nutrition Enhance Recovery and Good Health for You (ENERGY)-randomized weight loss trial among breast cancer survivors. *Breast Cancer Res Treat* 2015;154:329–337.
5. Zhang XM, Dou QL, Zeng Y, et al. Sarcopenia as a predictor of mortality in women with breast cancer: a meta-analysis and systematic review. *BMC Cancer* 2020;20:172.

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Lapatinib Confounds Post-Hoc Weight Loss Analysis in the ALTTO Trial

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In the February 2021 issue of *JNCCN*, Martel et al¹ reported an exploratory analysis of the ALTTO BIG 2-06 trial in which baseline body mass index ≥ 30 and weight loss $\geq 5.0\%$ were associated with decreased survival in patients with HER2-positive breast

cancer. The authors conclude that weight loss recommendations and trials should be approached cautiously.

These observations add to a growing literature demonstrating an association between obesity and increased risk of recurrence and mortality in HER2-positive breast cancer. In a recent meta-analysis, which included patients treated with trastuzumab, obesity was associated with worse disease-free and overall survival in HER2-positive breast cancer.² This meta-analysis did not include

information about weight change, but a prior report from the HERA trial did not show a relationship between weight change and survival in individuals treated with trastuzumab.³

So what is driving the relationship between weight loss and poor outcomes in this analysis of ALTTO? The toxicity profile of lapatinib presents a unique confounder. Specifically, 35% of patients in the ALTTO trial had grade 3/4 toxicity, 14.7% withdrew due to toxicity, and these rates were higher in obese participants. The