

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 ALTT0 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 ALTT0 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.

Leah Puklin, MPH^{a,t};
Melinda L. Irwin, PhD, MPH^{a,b};
Tara Sanft, MD^{b,c}; and
Leah M. Ferrucci, PhD, MPH^{a,b}
^aYale School of Public Health,
^bYale Cancer Center, and
^cYale School of Medicine, Yale University,
New Haven, Connecticut
[†]Email: Leah.puklin@yale.edu

doi: 10.6004/jnccn.2021.7052

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 ALTT0 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, Lofffield 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.

Letter to the Editor

Lapatinib Confounds Post-Hoc Weight Loss Analysis in the ALTT0 Trial

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 ALTT0 BIG 2-06 trial. *J Natl Compr Canc Netw* 2021;19(2):181–189.

In the February 2021 issue of *JNCCN*, Martel et al¹ reported an exploratory analysis of the ALTT0 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 ALTT0? The toxicity profile of lapatinib presents a unique confounder. Specifically, 35% of patients in the ALTT0 trial had grade 3/4 toxicity, 14.7% withdrew due to toxicity, and these rates were higher in obese participants. The

rate of all-grade diarrhea was 75%, with 15% of patients experiencing ≥ 7 stools per day requiring hospitalization.^{4,5} Thus, weight loss in obese ALTO participants may well be a surrogate indicator of ineffective treatment due to accentuated toxicity leading to treatment discontinuation. This theory is supported by 2 observations: (1) the association between weight loss and worse outcomes was primarily significant in the lapatinib-alone arm in ALTO, and (2) weight loss was not associated with outcomes in trastuzumab-treated patients in HERA. Information from ALTO regarding the relationships among weight loss, toxicity, and treatment discontinuation would be helpful in assessing this source of potential confounding.

The presence of undiagnosed meta-static disease or other comorbid conditions can also confound analyses of weight change and cancer outcomes. In this analysis of ALTO, the authors acknowledge that they were unable to discern purposeful versus involuntary weight loss. Prospective

randomized control trials are needed to overcome these multiple sources of unavoidable confounding.

Should weight loss be approached cautiously in patients with HER2-positive breast cancer as the authors suggest? Given the above considerations, and that lapatinib is not part of standard adjuvant treatment, we would not use these post hoc observational analyses for the basis of clinical recommendations.

Neil M. Iyengar, MD,^{a,*} and
Jennifer A. Ligibel, MD^{b,†}

^aDepartment of Medicine,
Memorial Sloan Kettering Cancer Center,
New York, New York; and

^bDepartment of Adult Oncology,
Dana-Farber Cancer Institute,
Boston, Massachusetts

*Email: iyengarn@mskcc.org

†Email: jennifer_ligibel@dfci.harvard.edu

doi: 10.6004/jnccn.2021.7082

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 ALTO BIG 2-06 trial. *J Natl Compr Canc Netw* 2021;19:181–189.
2. Lohmann AE, Soldera SV, Pimentel I, et al. Association of obesity with breast cancer outcome in relation to cancer subtypes: a meta-analysis. *J Natl Cancer Inst* 2021;djab023.
3. Yerushalmi R, Dong B, Chapman JW, et al. Impact of baseline BMI and weight change in CCTG adjuvant breast cancer trials. *Ann Oncol* 2017;28:1560–1568.
4. Piccart-Gebhart M, Holmes E, Baselga J, et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. *J Clin Oncol* 2016;34:1034–1042.
5. Piccart-Gebhart MJ, Holmes AP, Baselga J, et al. First results from the phase III ALTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone, trastuzumab alone, their sequence, or their combination in the adjuvant treatment of HER2-positive early breast cancer [abstract]. *J Clin Oncol* 2014;32(Suppl):Abstract LBA4.

Authors' Reply

To the Letters to the Editor by Puklin et al and by Iyengar and Ligibel

Our work published in the February 2021 issue of *JNCCN* showed that in patients with HER2-positive early breast cancer, obesity at baseline is a poor prognostic factor and that weight loss during treatment and follow-up negatively impact on clinical outcomes.¹ Therefore, dietary counseling should be part of survivorship care programs.

Puklin et al rightfully raise concerns regarding the clinical implication of our surprising finding that weight loss $\geq 5\%$ at 2 years after randomization is associated with poorer breast cancer outcomes. The presented results of the prognostic impact of baseline body mass index (BMI) and weight change in patients with HER2-positive early breast cancer was unplanned and exploratory. In this regard, any conclusion should be viewed only as hypothesis-generating. We agree that not knowing whether weight loss was intentional versus unintentional is an additional limitation in interpreting these findings. However, we hope that our analysis and this intriguing finding will raise interest for future studies to collect this type of information to allow a better understanding of the relationship

between BMI and outcomes in patients with breast cancer. As acknowledged in our discussion, obesity has been associated with increased mortality and impacts negatively on health outcomes^{2,3} and our findings further support the current recommendations for dietary counseling in breast cancer survivorship programs.

Additionally, Iyengar and Ligibel provide a valuable hypothesis explaining the relationship between weight loss and poor outcomes in our ALTO analysis. Indeed, the association between weight loss and worse outcomes was primarily significant in premenopausal patients or hormone receptor-positive tumors and was restricted to the lapatinib-alone arm in ALTO, which was prematurely stopped due to fertility analysis. We agree that the adverse effects associated with lapatinib, which include diarrhea, may impact on treatment completion, which then may lead to worse breast cancer outcomes. However, this association was not seen in the trastuzumab followed by lapatinib arm or in the trastuzumab and lapatinib combination arm. A possible confounder variable within an exploratory unplanned analysis may also be an

explanation. Weight loss interventions for breast cancer survivors conducted within clinical trials such as the ongoing phase III Breast cancer WEight Loss study (BWEL) will provide more solid evidence in this regard by minimizing the potential effect of confounding factors.

Samuel Martel, MD^{a,†};
Matteo Lambertini, MD, PhD^{b,c}; and
Evandro de Azambuja, MD, PhD^d

^aDepartment of Hemato-Oncology,
CISSS Montréal Centre, and
Hôpital Charles Lemoyne,
Université de Sherbrooke,

Greenfield Park, Quebec, Canada;
^bDepartment of Medical Oncology,

Clinica di Oncologia Medica,
IRCCS Ospedale Policlinico San Martino, and

^cDepartment of Internal Medicine and
Medical Specialties, School of Medicine,
University of Genova, Genova, Italy; and

^dInstitut Jules Bordet,
Université Libre de Bruxelles (U.L.B.),
Brussels, Belgium

†Email: samuel.martel3@usherbrooke.ca

doi: 10.6004/jnccn.2021.7110

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 ALTO BIG 2-06 trial. *J Natl Compr Canc Netw* 2021;19:181–189.
2. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010;363:2211–2219.
3. National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity, and health risk. *Arch Intern Med* 2000;160:898–904.

CALL FOR CORRESPONDENCE

JNCCN is committed to providing a forum to enhance collaboration between academic medicine and the community physician. We welcome comments about the NCCN Guidelines, articles published in the journal, or any other topic relating to cancer prevention, detection, treatment, supportive care, or survivorship.

Please submit correspondence to www.editorialmanager.com/JNCCN.

Letters should be no more than 400 words, with no more than 5 references if included. NCCN reserves the right not to publish correspondence for any reason it deems appropriate. All letters are subject to editing and/or abridgment.



FREE Patient Webinars

People with cancer, their caregivers, and their families can join experts as they discuss treatment options and answer questions.

Small Cell Lung Cancer

Monday, January 24, 2022

11:15 AM – 12:30 PM EST

Wednesday, January 26, 2022

3:15 – 4:30 PM EST

Kidney Cancer

Monday, February 28, 2022

12:15 – 1:30 PM EST



Register Now!

[NCCN.org/patientwebinars](https://www.nccn.org/patientwebinars)

JNCCN-N-0306-0122