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 ALTTO 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 ALTTO, and (2) weight loss was not associated with outcomes in trastuzumab-treated patients in HERA. Information from ALTTO regarding the relationships among weight loss, toxicity, and treatment discontinuation would be helpful in assessing this source of potential confounding.

The presence of undiagnosed metastatic disease or other comorbid conditions can also confound analyses of weight change and cancer outcomes. In this analysis of ALTTO, 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.

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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 ≥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 ALTTO 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 ALTTO, which was prematurely stopped due to futility 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.

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