Letter to the Editor

Inclusive and Adequate Care Overcoming All Health Care Gaps: The Need to Specifically Look to the LGBTQI+ Population

Re: Stabellini N, Dmukauskas M, Bittencourt MS, et al. Social determinants of health and racial disparities in cardiac events in breast cancer. J Natl Compr Canc Netw 2023; 21(7):705–714.e17.

We read with great interest the work by Stabellini et al[1] on social determinants of health (SDOH) and racial disparities in cardiac events in breast cancer, recently published in *JNCCN*. The authors masterfully examined in women with breast cancer the impact of individual and neighborhood-level SDOH on the racial disparities in major adverse cardiovascular events (MACE). They concluded that the most important SDOH predictors for 2-year MACE are neighborhood and built environment variables, and that non-Hispanic Black patients were more likely to have unfavorable SDOH conditions.

Furthermore, in their accompanying commentary, Corianò et al[2] emphasized that the study's findings highlight the importance of social constructs and, due to the importance of the objectives set and the results obtained, suggested the need to broaden the scenarios in which to carry out these studies to make research more inclusive, and to ensure that study results are applicable to broader patient groups.

In this regard, sex and gender minorities represent a multiplicity of populations in which a particular vulnerability to cancer is widely documented,[3] and unfortunately, many investigations reflect the invisibility of the LGBTQI+ population.[4] Sadly there are significant disparities in the cardiovascular and oncologic health of these groups of people due to variety of causes, many of which are now well identified and described in several studies. However, the implementation of significant actions by the different players in the system to overcome these disparities and make health care truly inclusive is still lacking. Among the many, we recall some differences in the risk for some types of cancer within the LGBTQI+ population, cardiovascular health that could be undermined by greater exposure to traditional risk factors, greater difficulty in accessing treatment, the lack of specific data to support the personalization of care, a greater exposure to stressful factors, and the development of psychiatric conditions in turn capable of influencing the development and outcome of oncologic and cardiovascular diseases.[5] Actionable strategies must be implemented within cardio-oncology research, clinical practice, and community engagement to reduce these disparities.

In conclusion, we hope that our reflections may offer additional topics to the discussion and contribute to sensitizing researchers, clinicians, and all possible actors involved on the need to broaden their perspective for truly inclusive research and care.

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Letter to the Editor

Re: Influence of Food With Different Fat Concentrations on Alectinib Exposure: A Randomized Crossover Pharmacokinetic Trial

Re: Lanser DAC, de Leeuw SP, Oomen-de Hoop E, et al. Influence of food with different fat concentrations on alectinib exposure: a randomized crossover pharmacokinetic trial. J Natl Compr Canc Netw 2023;21(6):645–651.e1.

We read with great interest the article by Lanser et al,[1] which sought to explore dietary approaches affecting alectinib's exposure–response threshold in treating altered anaplastic lymphoma kinase–positive (ALK+) advanced non–small cell lung cancer (NSCLC). We applaud the authors' pioneering efforts, given that little research has been done to explore diet–drug interactions in oncology care. Moreover, study strengths include rigor in assessing alectinib exposure, careful monitoring of adverse events, and a solid double-crossover study design. However, we were disheartened by the conclusion that "Patients and physicians should be warned of the detrimental food–alectinib interaction when taken with low-fat yogurt" given that confounders associated with the study design and methodology make it difficult to draw these conclusions. Caloric and volumetric content of yogurt compared with the other test meals differed substantially, because calories were at least 3 times higher in the latter. Additionally, although total daily caloric intake and macronutrient composition were not reported, these also are likely confounders.

Most concerning, however, is the authors' exclusive focus on the low-fat nature of yogurt, while completely overlooking its function as a probiotic food.[2] Yogurt is a potent short-term beneficial modulator of the gut microbiome, and one that may exert downstream effects in altering the intestinal epithelial barrier, stimulating immune response, and reducing inflammation.[3] This may have contributed to the lower occurrence of adverse events compared with the continental breakfast treatment reported by the authors. Given that alectinib is lipophilic and it has been established previously that absorption is increased with meals compared with fasting,[4] a cleaner approach to determine the contribution of fat in moderating drug uptake would be to compare low- versus high-fat yogurt (though again, caloric intake would need to be standardized).

In closing, we appreciate the authors' groundbreaking efforts to investigate dietary approaches that impact the absorption and exposure of alectinib in the treatment of ALK+ NSCLC. However, the conclusion that alectinib and low-fat yogurt have a detrimental food–drug interaction is not soundly supported by the results presented. Furthermore, the conjecture that eating low-fat yogurt is equivalent to eating a low-fat diet is an overstatement, because the consumption of a single food item cannot represent a dietary pattern. Indeed, the effect of low-fat yogurt on absorption of alectinib must be rigorously tested in future studies controlling for energy intake, meal timing, and appropriate comparison groups before these results can be considered conclusive.

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Authors' Reply

Reply To the Letter to the Editor by Frugé et al

We are pleased that our study[1] has captured the attention of Frugé et al, who are specialized in the field of nutritional science.

First and foremost, the objective of our study was to investigate the potential for a significant food–drug interaction when alectinib is coadministered with food that patients are consuming in daily practice. We deem this to be of great relevance, given that evidence shows that exposure to alectinib impacts the effectiveness of this treatment.[2] Furthermore, our clinical observations revealed a substantial portion of patients frequently opting for alectinib consumption alongside a modest snack, with the intention of maintaining a precise 12-hour interval between their twice-daily dosages. Consequently, the imperative to consume alectinib with a substantial meal, particularly in the morning, seemed to be of reduced importance to patients compared with adhering rigorously to the prescribed dosing schedule. Throughout the study, this was accentuated by the disparity in caloric intake between the 2 study groups. Although it is well-established that food significantly influences the pharmacokinetics of several oncology drugs,[3] the potential harm associated with alectinib's use in daily practice, as described earlier, remained unknown prior to the executing of our trial.

The rationale behind opting for low-fat yogurt was to mirror a common low-fat breakfast choice, thereby simulating a real-world scenario. Yogurt consumption is a prevalent habit in the Netherlands, possibly also for its healthy effects as mentioned by Frugé et al. We agree to the suggestions of these authors that a fourth arm in the study, to also study the effects of high-fat yogurt, could have been interesting. However, this would have extended beyond the primary objective of our study.

The main conclusion of our paper, which asserts that "Patients and physicians should be warned of the detrimental food–alectinib interaction when taken with low-fat yogurt" is, in our opinion, a logical deduction based on the available data. The data clearly demonstrate a significant and clinically meaningful distinction in alectinib exposure between low-fat yogurt and the other meals. Because we cannot prove that this food effect is exclusively the result of the fat difference between the tested diets, we also did not assert this in our paper. In our discussion, we have delved into potential mechanisms for this study outcome, and the chemical properties (eg, lipophilic nature) of alectinib seemed to best align with our findings. Frugé et al have suggested that the reduced incidence of alectinib-related adverse events when taken with yogurt, as opposed to the other meals, might be linked to yogurt's potential positive effects on the gut microbiome. However, based on our results, we neither endorse nor invalidate this hypothesis, given that lower exposure to alectinib may also lead to fewer side effects. We appreciate the positive influence of yogurt in a balanced diet and want to emphasize that our study does not caution patients treated with alectinib against yogurt consumption. We solely proved that coadministration of alectinib with low-fat yogurt alone is not suitable for an adequate absorption, and patients should opt for higher-fat alternatives.

We wholeheartedly support further research in this area, and in drug interaction studies in general. Informing patients about the impact of food, drugs, herbal supplements, or other influencing factors on drug efficacy and toxicity is important for optimizing pharmacologic treatment. Consequently,

we are currently conducting a follow-up study to assess the safe coadministration of semaglutide, a glucagon-like peptide 1 receptor agonist, alongside alectinib.[4] Given that clinical relevant weight gain is a common side effect of alectinib, this popular new drug might present a potential solution or prevention for weight gain.[5] Should our new study reveal no drug–drug interactions, there is no reason to anticipate negative effects of semaglutide on alectinib treatment from a pharmacological perspective.

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ERRATUM

Erratum to: NCCN Clinical Practice Guidelines in Oncology: Non–Small Cell Lung Cancer, Version 3.2022

In the May 2022 issue of *JNCCN*, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non–Small Cell Lung Cancer, Version 3.2022 (J Natl Compr Canc Netw 2022;20[5]:497–530. doi:10.6004/jnccn.2022.0025) were published with an error.

An incorrect study was cited as reference #29. The correct reference for #29 should have been:

Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078–2092.

This has been corrected online. The editors and publisher apologize for this error.

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