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Authors' reply

We read the Correspondence by Genevieve Neal-Perry and colleagues on our analysis reporting an increased risk of neoplasm with the neurokinin 3 receptor antagonist fezolinetant. Their conclusion is in line with the US Food and Drug Administration (FDA) Clinical Review suggesting that the incidence rate of malignancy treatment emergent adverse events is within the normal background rate of cancer. However, the FDA document states that the background incidence rate of cancer for the age group 50–59 years is 0·56%.[1] The annual rate of neoplasms with fezolinetant at 45 mg is 1·48%.[2] This prompted our in-depth analysis.

Neal-Perry and colleagues concluded that a drug effect is not supported on the basis of the evaluation of fezolinetant structural properties, non-clinical data, and an epidemiological literature review. They suggest that the short latency period to diagnosis, heterogeneity of tumour type, previous neoplastic or risk factor history, and presence of alternative baseline causes support their assessment.

First, any relevant pre-existing factors should be equally distributed among the different arms of the studies. A proper analysis of such pre-existing factors in the SKYLIGHT programme is not publicly available. Second, we reported a dose-dependent increase of the risk of neoplasm, suggesting that these treatment emergent adverse events could be associated with the pharmacodynamic properties of fezolinetant. Third, there is at least one potential underlying mechanism supporting a possible association with the observed increased risk of neoplasm. Indeed, neurokinin B is responsible for the release of kisspeptin. Kisspeptin can delay the metastatic cascade by preventing growth and colonisation of different metastatic cells in distant sites.[3] By antagonising the neurokinin 3 receptor, fezolinetant could alleviate the dormancy of cancer cells.[3]

Neal-Perry and colleagues mentioned that the Peto method used to compute the odds ratio is not appropriate for investigating rare events. Our use of the Peto method was guided by the Cochrane Statistical Methods Group and others who report that this method works well when intervention effects are small, events are not particularly common, and the studies have similar numbers in experimental and comparator groups.[4,5] The two other fixed-effect methods (ie, inverse variance and Mantel–Haenszel) lead to a similar conclusion (sensitivity analysis available on Open Science Framework), strengthening the robustness of our findings.

In conclusion, our data indicate an association between fezolinetant and the risk of neoplasm. The causal link of such an association is not established but we strongly believe that additional non-clinical mechanistic studies and a careful monitoring of such events with real-world evidence are needed to further characterise this risk.

JD reports personal fees from Daiichi-Sankyo, Diagnostica Stago, Gedeon Richter, GyneBio Pharma, Mithra Pharmaceuticals, Norgine, Roche, Roche Diagnostics, Technoclone, Werfen, and YHLO outside the submitted work. All other authors declare no competing interests.

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Published **Online** April 19, 2024 https://doi.org/10.1016/S0140-6736(24)00824-9

For the **sensitivity analysis** see https://osf.io/cn9re/

Department of Error

GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet *2024; published online April 3. https://doi.org/10.1016/S0140-6736(24)00367-2*—In this Article, the key in figure 1 has been corrected, the URL for the GBD data sources has been corrected, and the appendix has been updated. These changes have been made to the online version as of April 19, 2024 and the printed version is correct.