

CORRESPONDENCE

Reply to comments on: Drug-drug interactions between palbociclib and proton pump inhibitors may significantly affect clinical outcome of metastatic breast cancer patients



We thank Beechinor RJ et al. and Altundag K for their constructive comments on our recent article about the concomitant use of proton-pump inhibitors (PPIs) and their effect on progression-free survival (PFS) in patients with metastatic breast cancer treated with palbociclib.¹

Regarding the first point raised by Beechinor RJ et al., it should be made clear that the effect of PPIs on cancer mortality has been evaluated within observational studies,² which cannot exclude residual confounding factors including disease stage, treatment delivered to patients, sociodemographic or lifestyle characteristics; moreover, the link between PPI use and increased risk of mortality is not supported by evidence of causality. A significant bias is the use of PPIs within different clinical settings as well as the lack of information about the specific indications for PPIs and other drugs used during hospitalization, as stated by the authors themselves.² Moreover, the effect of specific disease may be relevant, such as in the case of colorectal cancer mortality of PPI users versus non-users.³

Secondly, regarding the magnitude of the reduction in PFS, we invite the authors to consider the PFS in the population stratified by endocrine status and not the overall population. The PALOMA-2 study reported a difference in PFS of 24.8 versus 14.5 months ($\Delta = 10.3$), and the relative cohort of patients in our study had a PFS of not reached versus 20 months.⁴ Considering the PALOMA-3 trial, median PFS was 11.2 versus 4.6 months ($\Delta = 6.6$), whereas it was 16.4 versus 6.3 months ($\Delta = 10.1$) in the population of our study.⁵ Obviously, with our population being numerically smaller and mirroring real-life practice, a slight difference in survival data is reasonable.

Regarding the criteria used to enroll patients, all centers included subjects given palbociclib capsules as per approved label and with complete clinical data available for analysis.

As pointed out by Altundag K, we are pleased to clarify that the number of metastatic sites has been considered in the univariate analysis reported in Table 2 and it was not found to significantly impact on patient survival.

Few additional data have been published about the class-effect of PPIs on cyclin-dependent kinase 4/6 (CDK4/6) inhibitors and are in agreement with our findings; furthermore, preliminary unpublished data from our group suggest that PPIs have no effect on the PFS of ribociclib-treated patients. Considering the small number of subjects and the limitations that retrospective studies may have, however, the effect of PPIs on CDK4/6 inhibitors deserves further investigations.

In conclusion, our article highlights the importance of carefully assessing the implications of polypharmacy in cancer patients and the need of eradicating the overuse and off-label prescription of PPIs, to avoid the potential drug-drug interactions with orally co-administered anticancer agents.

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