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## Drug interactions between tyrosine-kinase inhibitors and acid suppressive agents

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multiple doses of esomeprazole. Importantly, the mean steady-state trough concentration of pazopanib was reduced to 17 µg/mL, which is similar to the minimal threshold for therapeutic efficacy (15 µg/mL). In view of these results, and the substantial between-subject pharmacokinetic variability, proton-pump inhibitors appear to diminish the systemic exposure of pazopanib in targeted patients, and so might compromise therapeutic efficacy in some individuals. Due to the persistent acid suppression of proton-pump inhibitors, staggering their dosing will not mitigate the magnitude of such drug-drug interactions. Based on these considerations, the FDA updated the safety information of pazopanib with regard to drug-drug interactions with acid-suppressive agents in June 2014, recommending the avoidance of concomitant use of pazopanib with proton-pump inhibitors or H<sub>2</sub>-antagonists.<sup>9</sup> The FDA recommendations differ substantially from those of van Leeuwen and colleagues.<sup>3,9</sup> Although the EMA has not changed the label of pazopanib, which still allows concomitant use with proton-pump inhibitors or H<sub>2</sub>-antagonists when administered in a staggered manner, it mentions that the recommendations for how to use proton-pump inhibitors or H<sub>2</sub>-antagonists in conjunction with pazopanib are based on physiological considerations.<sup>4</sup>

A drug-drug interaction study of nilotinib with esomeprazole was performed in healthy volunteers by the sponsor of nilotinib.<sup>5</sup> In the presence of the steady-state level of esomeprazole, the average AUC after a single dose of nilotinib was reduced by 34% (90% CI 21–46). The sponsor subsequently concluded that the systemic exposure of nilotinib was only modestly reduced by esomeprazole, and thus that there was no reason for nilotinib to not be taken concurrently with proton-pump inhibitors.<sup>6</sup> Unlike the EMA, the FDA did not agree with the sponsor. After reviewing this new trial, the FDA does

not recommend the concomitant use of proton-pump inhibitors with nilotinib.<sup>7</sup> There are at least two efficacy concerns. First, greater inter-patient variability of the reduced AUC might be expected in patients with cancer, leading to suboptimal nilotinib exposure in individual patients. Second, the loss of nilotinib exposure following steady-state administration might be larger than that after single-dose administration, along with administration of esomeprazole.

The sponsor of lapatinib did a drug-drug interaction study of lapatinib with esomeprazole in patients with metastatic ErbB2-positive breast cancer (ClinicalTrials.gov, number NCT00849329). Maximum acid suppression was achieved after giving patients multiple doses of esomeprazole, at which point the average steady-state AUC of lapatinib was decreased by only 26% (90% CI 18–34), after correcting for age. Therefore, the FDA approved a lapatinib label alteration, recommending that acid suppressive agents can be administered concurrently with lapatinib because the steady-state exposure of lapatinib (therapeutic dose) did not decrease substantially, even in the worst-case scenario (ie, multiple dosing of tyrosine kinase inhibitors with multiple dosing of proton pump inhibitors in the target patients).<sup>5</sup> However, the EMA does not recommend the concomitant use of acid-suppressive agents with lapatinib.<sup>4</sup>

Although we identified inconsistencies and controversies surrounding drug-drug interactions between tyrosine kinase inhibitors and acid-suppressive agents when we compared and revisited the recommendations for tyrosine kinase inhibitors from the FDA, EMA, and the review of Leeuwen and colleagues, we believe that the recommendations from the FDA are the most reasonable prescribing guidance for coadministration with acid-suppressive agents during tyrosine kinase inhibitors treatment.

We declare no competing interests.

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### Authors' reply

We appreciate the opportunity to respond to the Letter of Guo Yu and colleagues,<sup>1</sup> about our Review.<sup>2</sup> The number of tyrosine-kinase inhibitors is rapidly increasing, and physicians

are faced with many drug–drug interactions in clinical practice.<sup>3</sup> As therapeutic drug monitoring for most tyrosine-kinase inhibitors is not standard practice, or might not be appropriate, many of these drug–drug interactions cannot be managed by adjusting the dose based on drug exposure monitoring.<sup>4</sup> In individual patients, the treating physicians will need to decide, supported by clinical pharmacists and pharmacologists, whether or not it is better to start a particular drug at all, to choose another dose, or aim for an alternative drug.

Yu and colleagues<sup>1</sup> have identified several examples of drugs for which the official recommendations of the US Food and Drugs Administration (FDA) and European Medicines Agency (EMA) are not the same, often based on different interpretations of the studies on which these recommendations are based. Similarly, some of the recommendations that we gave in our tables are not identical to those from the FDA or EMA, although we made the same considerations as these agencies did. When writing our Review it was not our intention to position ourselves as a third regulatory agency. As is clear from our title, we aimed for a clinical perspective. As clinical pharmacologists, it is our daily routine to give advice on complex clinical cases. Additionally, we participate in a Dutch national expert group on anticancer drug interactions for translation of research data to recommendations for clinical practice.<sup>5</sup> Instead of aiming for the lowest possible risk strategy, we chose to identify practical solutions for drug–drug interactions. These solutions were based on physiological and pharmacological principles.

Changes in tyrosine-kinase inhibitor exposure as a result of combined treatment with acid-suppressive treatments contribute only in part to the substantial inter-patient pharmacokinetic variability that is inherent to tyrosine-kinase inhibitors.<sup>6</sup> More studies are needed that investigate the concentration–effect

relation of tyrosine-kinase inhibitors. Several clinical trials are ongoing. When ranges for therapeutic target concentrations have been defined, physicians will be able to better individualise the drug dose in their patients, including patients co-treated with interacting drugs.

We declare no competing interests.

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## Epidemiological differences in haematological malignancies between Europe and China

In *The Lancet Oncology*, Sant and colleagues<sup>1</sup> reported results of the EURO CARE-5 study that show 5-year

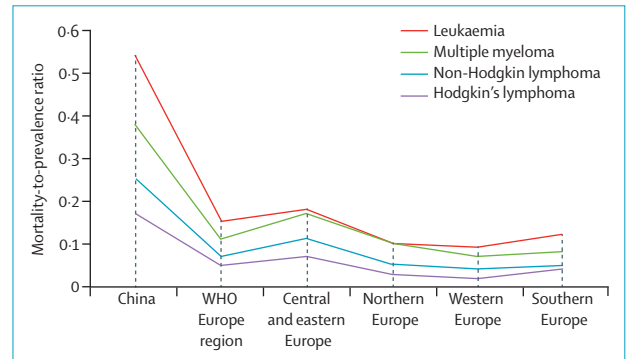


Figure: Comparison of mortality-to-prevalence ratio of leukaemia, non-Hodgkin lymphoma, Hodgkin's lymphoma, and multiple myeloma between Europe and China

survival for European patients with haematological malignancies has improved over the past decade, probably because of new drugs such as rituximab and imatinib.<sup>2</sup> In China, despite the great burden of lung, liver, stomach, and oesophageal cancers, the prevalence, incidence, and mortality of haematological malignancies are relatively low.<sup>3</sup> According to the GLOBOCAN 2012 report, the 5-year prevalence of leukaemia, non-Hodgkin lymphoma, Hodgkin's lymphoma, and multiple myeloma are 6.7, 6.3, 0.6, and 1.3 per 100 000 persons in China, respectively.<sup>3</sup> These rates are lower than those in Europe, especially northern, western, and southern Europe (appendix). In China, the incidence and mortality of these four haematological malignancies are also lower than those in Europe (appendix). According to the Chinese National Central Cancer Registry, the age-specific and sex-specific mortality of leukaemia (all classifications) did not significantly change from 2003 to 2007 (appendix). Similar to the EURO CARE-5 study, those older than 50 years had a higher risk of mortality from leukaemia in China (appendix). However, comparison of mortality-to-prevalence ratios showed that survival outcomes for leukaemia, lymphoma, and multiple myeloma are worse in China than those in Europe (figure). In particular, the mortality-to-prevalence

See Online for appendix

