DPYD genotype-guided dose individualisation of fluoropyrimidine therapy: who and how?

Authors' reply

We appreciate that Ka On Lam and colleagues agree that *DPYD* genotype-guided dosing should be a new standard of care, and we recognise that some minor issues need to be addressed for full universal implementation.

Our study tested the four *DPYD* variants (four single nucleotide polymorphisms [4SNP]), for which evidence-based dosing guidelines are available in the literature.[1] However, patients not carrying one of these four variants still had a 23% risk of developing severe fluoropyrimidine-related toxicity.[2] In search of novel variants, the results of *DPYD* sequencing and whole-genome SNP genotyping in our study are awaited. We are in the process of designing a new prospective trial in which we plan to recruit at least 1000 patients with 4SNP-guided dosing and additional dosage guiding by endogenous uracil levels, employing experience from our latest, as well as a previous, prospective trial.[3,4] We will consult international researchers in the field about this trial, to reach consensus on the best way to identify dihydropyrimidine dehydrogenase-deficient patients, and set a global standard for individualised treatment with fluoropyrimidines.

We previously showed that exposure to 5-fluorouracil, a driver of both therapeutic as well as toxic effects, is similar in the dose-reduced *DPYD* variant allele carriers and wild-type patients. We also provided evidence, in a matched-pair analysis of *DPYD**2A variant allele carriers and wild-type patients,[5] that effectiveness is not negatively affected by dose reductions in *DPYD* variant allele carriers.

We agree with Lam and colleagues about the high clinical need of studies on *DPYD* genotyping in populations other than those of European origin. We are also about to start a prospective clinical trial in the Netherlands in which we will recruit patients of non-white descent to help solve this gap in knowledge. Additionally, in 2019, we plan to open an international online project collaboration, sharing our dataset with other researchers, with the aim of maximising patient benefit from this dataset.

LMH and CATCL report grants from the Dutch Cancer Society (Alpe d'HuZes/KWF-fund, project number NKI2013-6249) during the conduct of the study. CATCL was previously supported by an unrestricted grant from Roche Pharmaceuticals. There was no involvement in the study design, data collection, analysis, interpretation or writing of the report by any of the funding sources. JHMS reports personal fees from Modra Pharmaceuticals bv and Debiopharm outside the submitted work and is a part-time employee of Modra Pharmaceuticals bv. The other authors declare no potential conflicts of interest.

*Linda M Henricks, Carin A T C Lunenburg, Annemieke Cats, Ron H J Mathijssen, Henk-Jan Guchelaar, *Jan H M Schellens*

j.schellens@gmail.com

Division of Pharmacology (LMH, JHMS), and Department of Gastrointestinal Oncology, Division of Medical Oncology (AC), The Netherlands Cancer Institute, Amsterdam, Netherlands; Department of Clinical Chemistry and Laboratory Medicine (LMH), Department of Medical Oncology (CATCL), and Department of Clinical Pharmacy and Toxicology (H-JG), Leiden University Medical Center, Leiden, Netherlands; Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, Netherlands (RHJM); and Department of Pharmaceutical Sciences, Faculty of Science, Utrecht University, 3584 CG Utrecht, Netherlands (JHMS)

1 Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. *Clin Pharmacol Ther* 2018; **103:** 210–16.

2 Henricks LM, Lunenburg CATC, de Man FM, et al. *DPYD* genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol* 2018; **19:** 1459–67.

3 Deenen MJ, Meulendijks D, Cats A, et al. Upfront genotyping of *DPYD**2A to individualize fluoropyrimidine therapy: a safety and cost analysis. *J Clin Oncol* 2016; **34:** 227–34.

4 Meulendijks D, Henricks LM, Jacobs BA, et al. Pretreatment serum uracil concentration as a predictor of severe and fatal fluoropyrimidine-associated toxicity. *Br J Cancer* 2017; **116:** 1415–24.

5 Henricks LM, van Merendonk LN, Meulendijks D, et al. Effectiveness and safety of reduced-dose fluoropyrimidine therapy in patients carrying the *DPYD**2A variant: a matched pair analysis. *Int J Cancer* 2018; published online Nov 28. DOI:10.1002/ijc.32022.