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Author's reply

Response to letter entitled re: UGT1A1 genotype-guided dosing of irinotecan: A prospective safety and cost analysis in poor metaboliser patients
Is it time for everyone treated with irinotecan to be tested for UGT1A1 gene polymorphism?

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Dear Editor,

We would like to thank Dr. Kong and colleagues for their letter in support of the importance of *UGT1A1* genotype-guided dosing of irinotecan. Our recently published study showed that *UGT1A1* genotype-guided dosing of irinotecan strongly decreased the incidence of severe adverse events, provided therapeutic systemic drug exposure, and was also cost-saving [1]. We fully agree with the recommendation of Kong *et al.* that *UGT1A1* genotype testing to be incorporated in clinical treatment guidelines as an essential test to be carried out before the start of therapy.

To elaborate on the study findings, Kong *et al.* had further remarks regarding the chosen design, our analysis, and the interpretation of our data.

First, they asked for more detail with regard to the applied genotype groupings for *UGT1A1**28 and *UGT1A1**93. Specifically, they state that the exposure to irinotecan in patients with two homozygous or heterozygous mutations – also called compound heterozygous – and only one mutation, will be different, which would be finally reflected in a toxicity difference. However, on this point, we disagree. Namely, it is known that *UGT1A1**28 and *UGT1A1**93 are in high linkage disequilibrium (LD), with a $r^2 = 0.83$ (https://ldlink.nci.nih.gov/). The high degree of LD means that the majority of patients were both homozygous for *28 as well as for *93. Concretely, in our study, 25 out of

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31 UGT1A1 poor metaboliser patients (PMs) were homozygous for both *28 and *93, and only six patients were homozygous for *28 but heterozygous for *93. For UGT1A1 intermediate metabolisers (IMs), 141 out of 158 patients were heterozygous for both *28 and *93. Homozygosity for *93 and heterozygosity for *28 or heterozygosity for *93 and wild type for *28 did not occur. This means that all our homozygous variant allele carriers were truly PM phenotype. In addition, from a clinical perspective, it is in essence not of direct importance which of the two polymorphisms is the driver for the PM phenotype. Moreover, no additive effect is described or can be expected, given the high degree of LD. In case the LD would be lower, then further research would be required to assess whether there is a difference between compound and single mutation carriers. However, in this case, our genotyping groupings did not lead to intragroup differences in toxicity profile.

Second, Kong *et al.* suggested an additional subgroup analysis, specifically to test for differences in haematological toxicity between monotherapy versus combination therapy in the UGT1A1 IM and EM groups. Although our study was not specifically designed and powered to compare toxicity profiles between monotherapy versus combination therapy regimens in IM and extensive metaboliser (EM) patients, the proposed subgroup analysis may indeed provide additional data of clinical relevance. Table 1A–C provides the incidences of grade ≥3 or grade ≥4 neutropenia between monotherapy and combination therapy regimens in the IM/EM group, the IM group, and the EM group, respectively. There were no statistically significant haematological toxicity differences between monotherapy versus combination therapy in the IM and EM groups.

Table 1A
Treatment outcomes of irinotecan monotherapy versus combination therapy in UGT1A1 IM/EM with normal dose.

	Monotherapy ± targeted agent (N = 68)	Combination therapy (N = 251)	P value
Grade ≥3 neutropenia	10 (15%)	43 (17%)	0.63
Grade ≥4 neutropenia	7 (10%)	21 (8%)	0.62

Table 1B
Treatment outcomes of irinotecan monotherapy versus combination therapy in UGT1A1 IM with normal dose.

	Monotherapy ± targeted agent (N = 33)	Combination therapy (N = 125)	P value
Grade ≥3 neutropenia	8 (24%)	27 (22%)	0.75
Grade ≥4 neutropenia	7 (21%)	12 (10%)	0.08

Table 1C
Treatment outcomes of irinotecan monotherapy versus combination therapy in UGT1A1 EM with normal dose.

	Monotherapy ± targeted agent (N = 35)	Combination therapy (N = 126)	P value
Grade ≥3 neutropenia	2 (5.7%)	16 (12%)	0.36
Grade ≥4 neutropenia	0 (0.0%)	9 (7.1%)	0.21

Data are provided as N (%).
Abbreviations: UGT1A1 IM= UGT1A1 intermediate metaboliser, UGT1A1 EM = UGT1A1 extensive metaboliser.

Third, they stated that given the fact that the incidence of neutropenia was higher in UGT1A1 IM versus EM patients in the overall patient population, the dose of irinotecan in UGT1A1 IMs should also be appropriately reduced. Of note, this specific observation in our study may act as a further confirmation of previously described data; it is generally known that there is a difference in irinotecan-induced toxicity incidences between UGT1A1 IMs an EMs [2–6]. However, the question is whether IMs should be dosed lower or whether EMs should be dosed higher. Namely, one must notice that the incidence of neutropenia was indeed higher in IMs compared to EMs; however, treatment was generally well tolerated, and in an additional analysis, the median dose intensity after all cycles was comparable in IMs versus EMs (93% [IQR: 81–100%] versus 96% [IQR: 83–100%]). Moreover, several genotype-guided dose-finding studies have been conducted, and the aggregated conclusion of these dose-finding studies in UGT1A1 IM and EM patients was that the maximum tolerated dose was higher than 100% [7]. In addition, the IM phenotype is the major group among White populations. The initial standard irinotecan dose derived in earlier phase I studies was, therefore, mainly driven by the IM phenotype. Therefore, *a priori* lowering the dose in IMs, in our opinion, would be inappropriate and might even lead to underdosing.

Fourth, Kong *et al.* suggested that in future research, it would be more meaningful if the authors include clinical efficacy indicators, including clinical response and survival data. We completely agree that these are important parameters to be assessed following genotype-guided dosing. However, to properly analyse clinical efficacy parameters, large and homogeneously treated patient populations are required, with preferably hundreds of UGT1A1 PM patients. Therefore, as surrogate marker, we conducted a pharmacokinetic analysis that showed therapeutic drug exposure is reached following a 30% dose reduction in UGT1A1 PMs.

Fifth, Kong *et al.* stated that the observation period of this study was only 12 weeks, and they posed that a longer follow-up might give a more pronounced difference in toxicity and costs between the different groups and might strengthen the advantages of genotype-guided dosing even more. This, however, seems unlikely, since most of the toxicity was seen in the first cycles. Moreover, almost all treatment cycles were covered with our observation period of 12 weeks, as the median number of treatment cycles was 6 (IQR 4–8) with most patients being treated on a two-weekly

treatment regimen. In addition, a longer follow-up may also introduce confounding because the patients' cancer is more likely to progress, and progression symptoms may resemble treatment-related toxicity. In our analysis, we used a decision tree model for our cost analysis, which is typically suited for short-term outcomes. Indeed, to assess long-term effects, a Markov model could be used as such as e.g. described by Butzke *et al.* Within this Markov model analysis, a time horizon of five years was modelled, and the results showed that *UGT1A1* testing before the start of therapy increases the quality of life and reduces costs, in line with the results of our study [8].

In conclusion, further effort should be made to incorporate pre-therapeutic *UGT1A1* genotyping in clinical treatment guidelines, as well as on the assessment of further efficacy outcomes of genotype-guided dosing. Routine clinical testing enables safer therapy for the individual patient and is cost-effective from a healthcare payer perspective. Therefore, in the Netherlands, pre-therapeutic *UGT1A1* screening has become common practice since our data were available. In addition, additional safety and efficacy data are herewith acquired that allows for further improvement of irinotecan treatment in each individual patient.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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