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OBJECTIVES

- To test the influence of sorafenib dose rate and plasma exposure on the hazard of tumour progression and of adverse events (AE) in differentiated thyroid cancer (DTC),
- To simulate progression-free survival and the probability of AEs for various sorafenib dose rates and dose reduction schemes,
- To simulate the benefit/risk ratios for various sorafenib dose rates.

INTRODUCTION

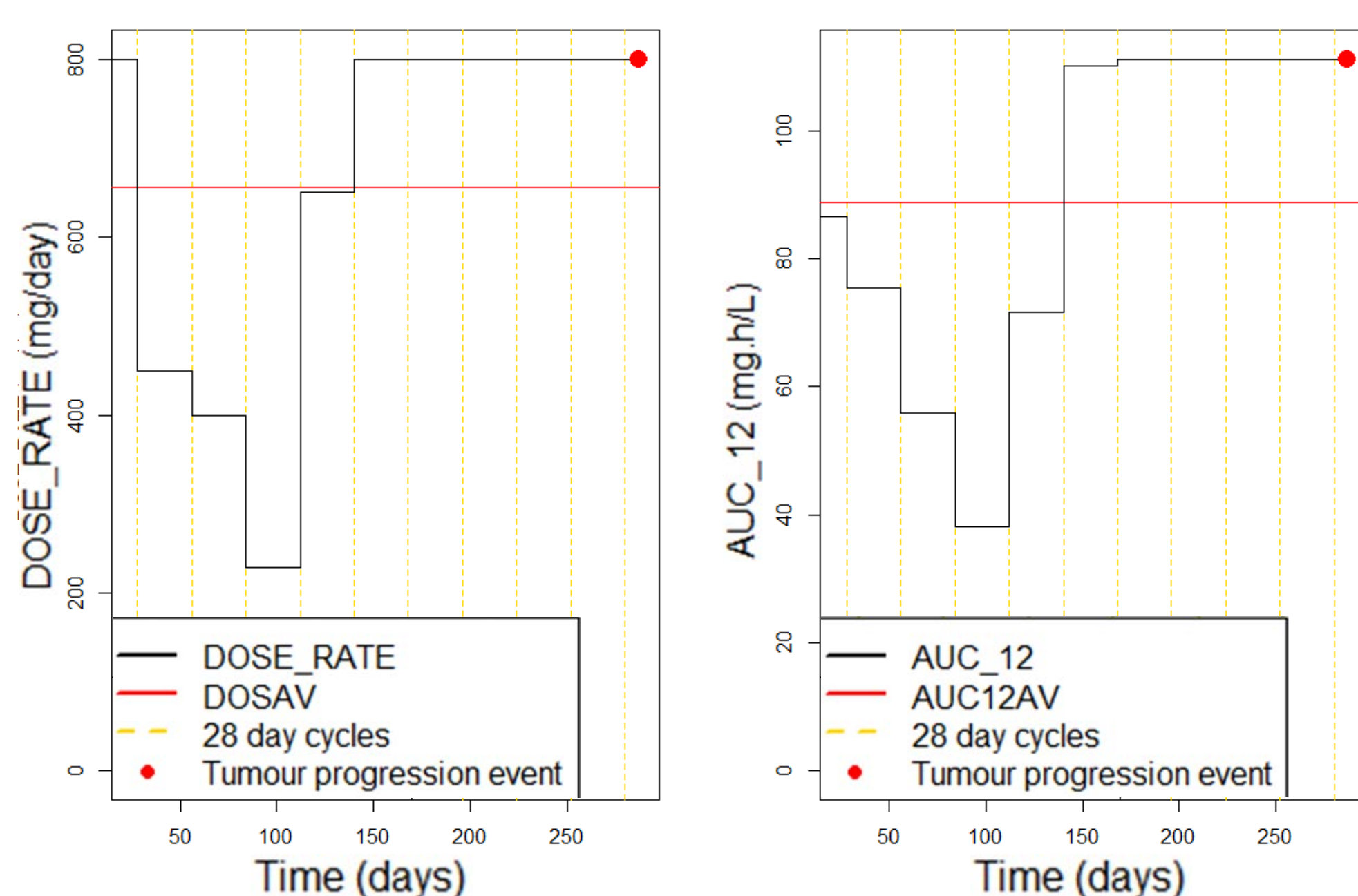
In Study 14295 (DECISION), the Phase III, placebo-controlled, pivotal trial of sorafenib in locally advanced/metastatic RAI-refractory DTC, the average plasma exposure of sorafenib was found to be about twice as high as in other clinical trials [1,2]. In order to explore *in silico* lower starting doses and dose reductions of sorafenib in DTC, parametric hazard models were built. It was expected that actual dose reductions provided a wide enough range of changing sorafenib dose rates and plasma exposures to explore exposure-response relationships.

METHODS

Study 14295 provided 401 and 413 patients for the analysis of centrally assessed tumour progression and for AEs, respectively (12 patients could not be included in the tumour assessment due to early drop-out). Sorafenib dosage for each patient was represented as the average dose rate leading up to an event (DOSAV) and time-varying dose rate recalculated for each 28 day cycle (DOSERATE). An existing population PK model [3] was used to estimate AUC from simulated PK profiles for each patient leading to the average exposure (AUC12AV) and the time-varying exposure (AUC12). **Figure 1** displays dose and exposure variables for a typical patient.

The times until the first occurrence of tumour progression (TP) or specified AEs were analysed with time-to-event (TTE) models. The influence of exposure variables on the hazard was explored by maximal likelihood estimation. The selected TTE models were used in simulations of the probabilities of AEs and TP for constant sorafenib dosing regimens ranging from 400 to 800 mg/day and for dose reduction schemes.

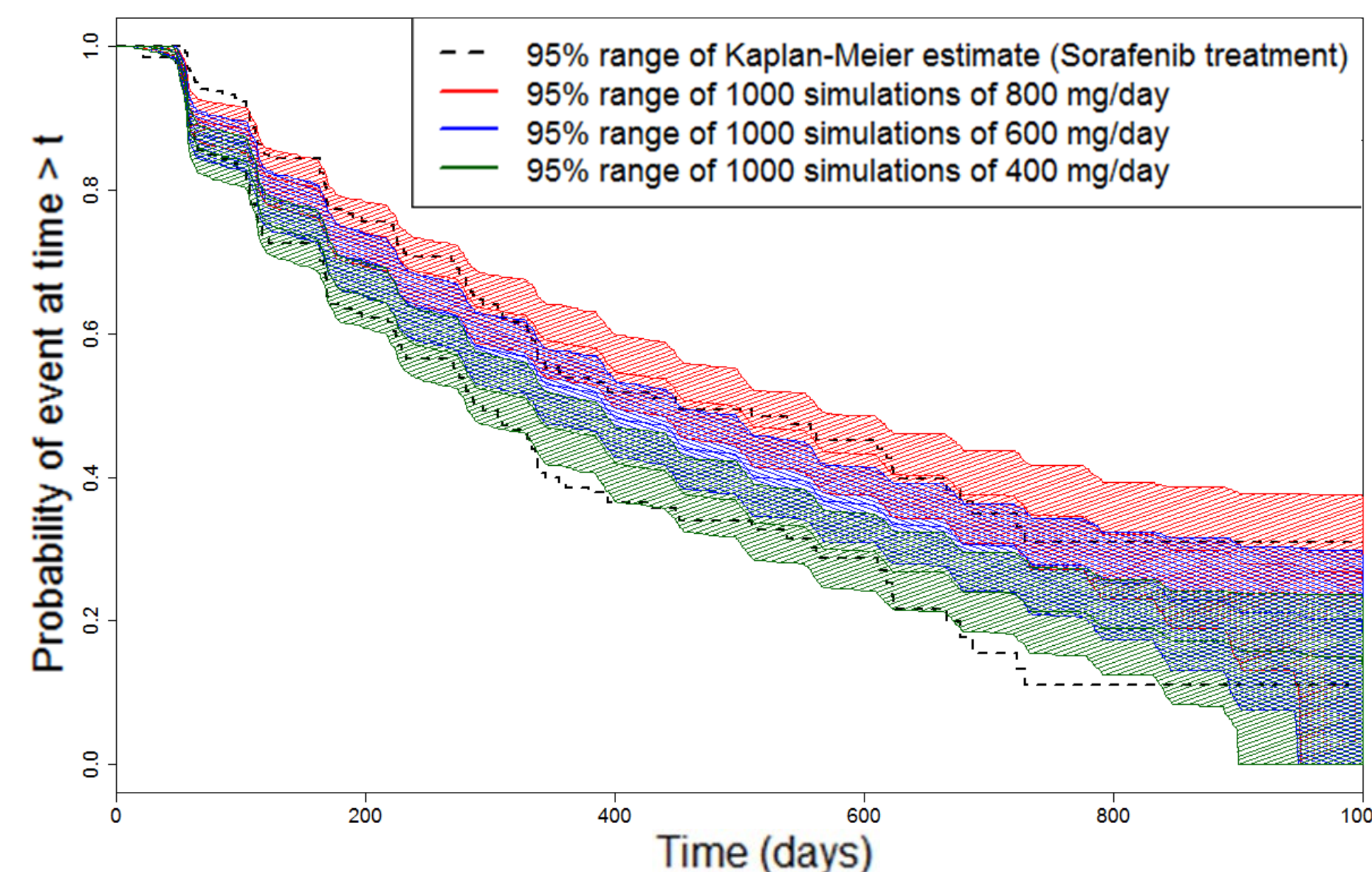
Figure 1. Example of sorafenib exposure and dose rate in an individual patient



RESULTS

A Weibull hazard function for TP with AUC12AV as covariate (DOSERATE and DOSAV were also significant) correctly described the interval censored data. Simulations of various dosing schedules (**Figure 2**) illustrate the benefit of the highest dose rate (800 mg/day).

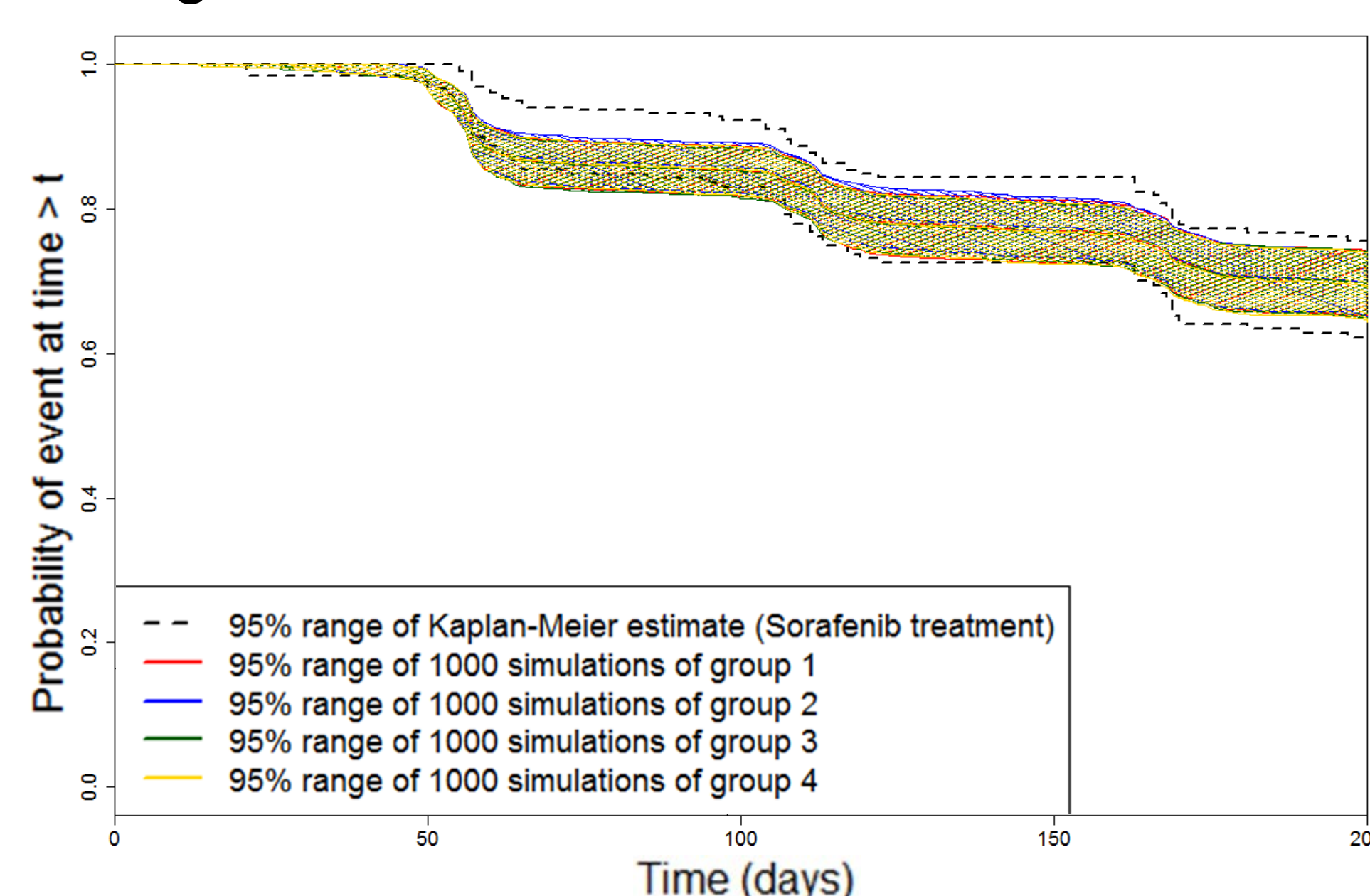
Figure 2. Simulated TP based on different starting doses



Any dose reduction scheme after two cycles of 800 mg/day sorafenib had little influence on the simulated TP events (**Figure 3**).

- Scheme 1:** 2 cycles on 800 mg/day, then reduction to 600 mg/day.
- Scheme 2:** 2 cycles on 800 mg/day, then reduction to 400 mg/day.
- Scheme 3:** 2 cycles on 800 mg/day, then reduction to 600 mg/day for 2 cycles followed by 800 mg/day.
- Scheme 4:** 2 cycles on 800 mg/day, then reduction to 400 mg/day for 2 cycles followed by 800 mg/day.

Figure 3. Influence of dose reduction on TP



Parametric hazard models described the first occurrence of AEs (**Table 1**). A constant plus Gompertz hazard function with DOSAV as covariate fitted GR3 events best. **Figure 4** shows the qualification of the survival model for GR3 events. The other 4 AE models were fitted similarly well. Simulations of GR3 events under various dosing schedules are shown in **Figure 5**.

Any dose reduction scheme after two cycles of 800 mg/day sorafenib had little influence on the simulated GR3 events (not shown).

Table 1. Modelled adverse events

Adverse Events	Incidence
First event of hand-foot skin reaction Grade 3 (HFS)	11.4%
First event of hypertension Grade ≥3 (HYP)	5.8%
First event of diarrhoea Grade ≥2 (DIA)	14.3%
First event of any AE Grade 4 or higher (GR4)	11.4%
First event of any AE Grade 3 or higher (GR3)	62.7%

Figure 4. Qualification of GR3 model

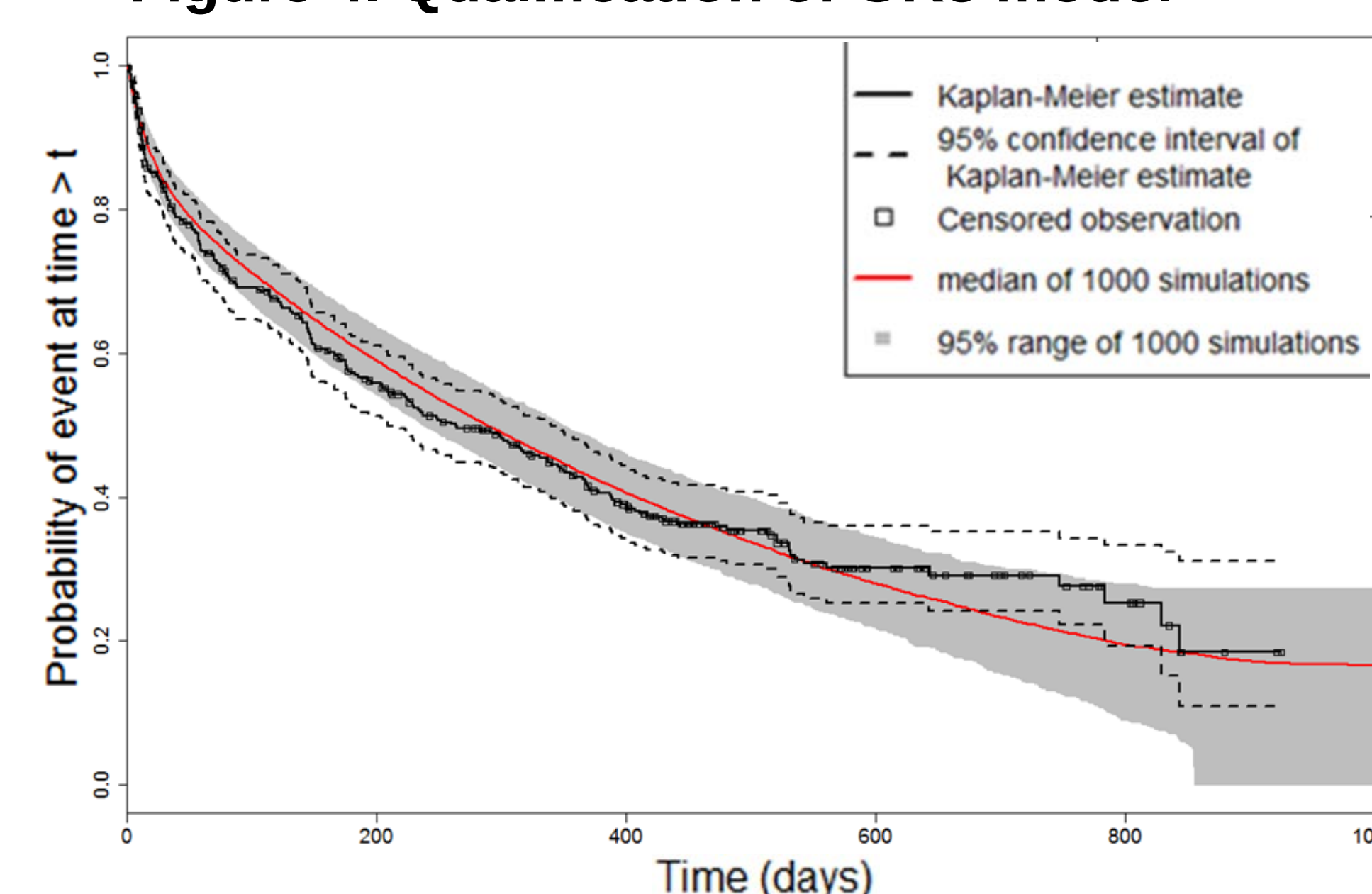


Figure 5. Simulated and observed GR3s based on different starting doses

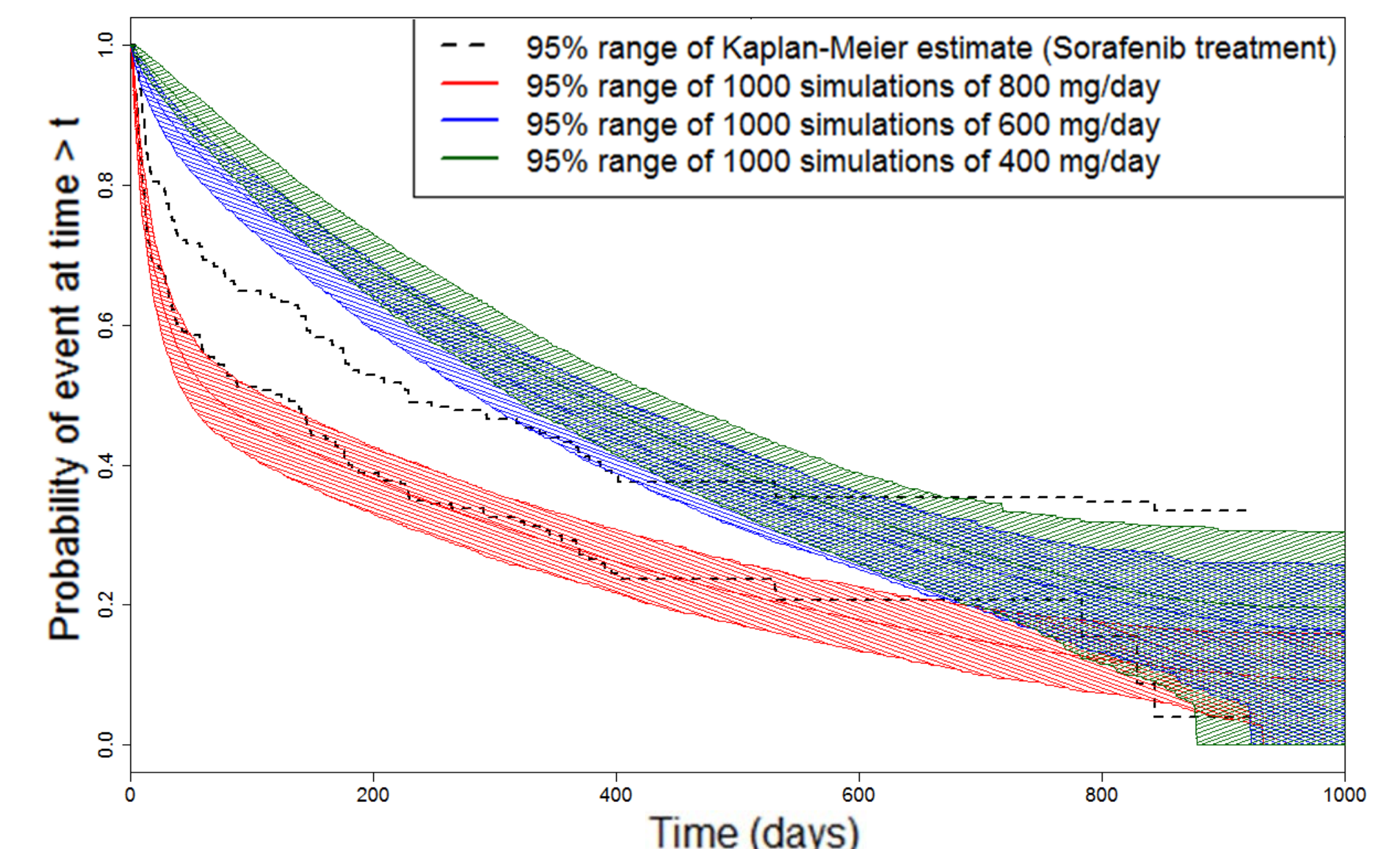


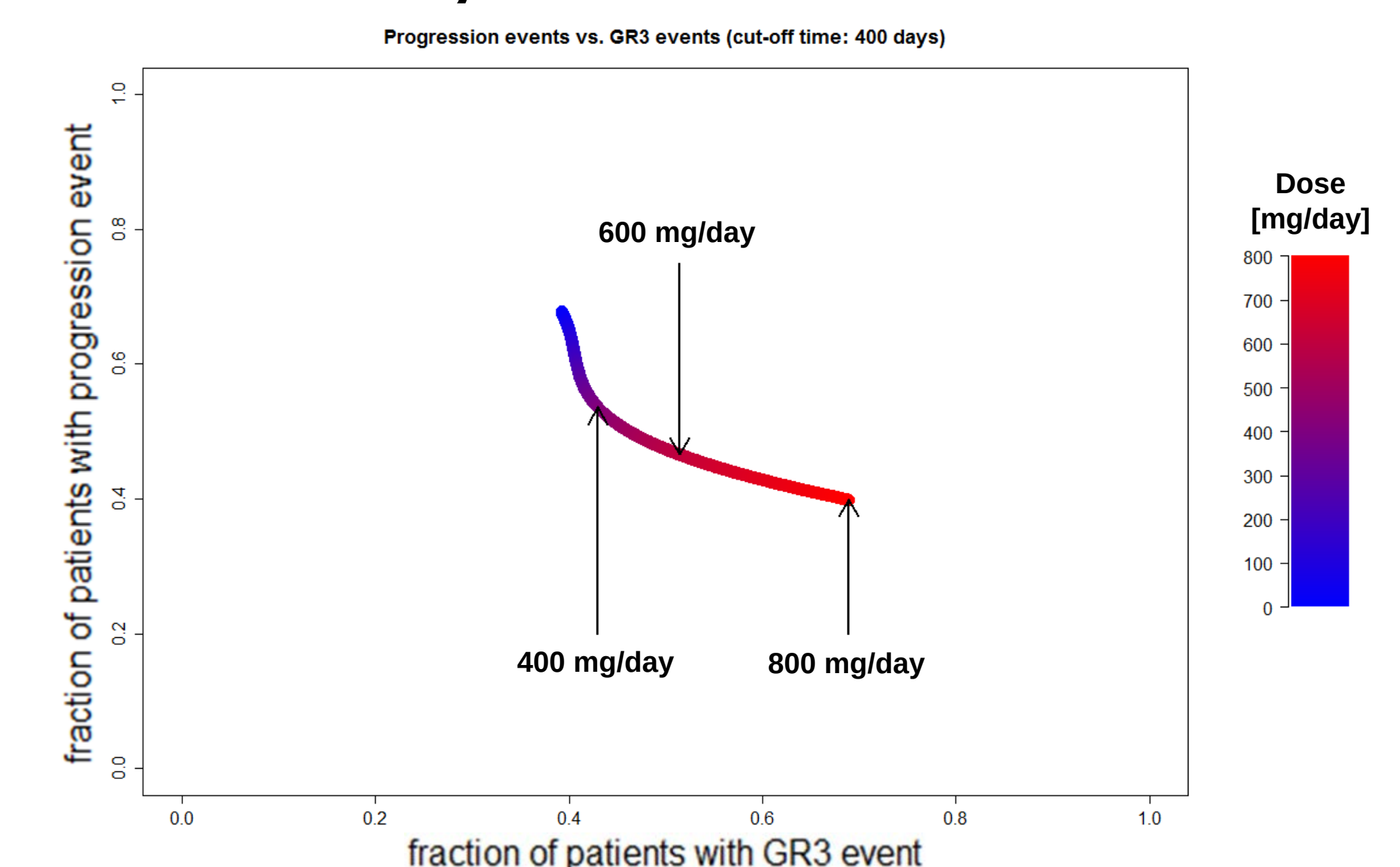
Table 2. Exposure influences on AEs

Adverse Event	Exposure or dose rate influence ¹
HFS	DOSAV, DOSERATE
HYP	AUC12AV
DIA	DOSERATE, DOSAV
GR4	none
GR3	DOSAV, DOSERATE

¹ the strongest significant influence is listed first

The fraction of patients with GR3 and TP events during 400 days of treatment represented the benefit/risk ratio. **Figure 6** shows a continuous improvement for dosing schedules between 100 and 800 mg/day.

Figure 6. Phase plot for GR3 and TP events after 400 days of treatment



CONCLUSIONS

- The highest simulated dose rate of sorafenib (400 mg BID) had the best benefit/risk ratio according to TTE models built for DTC patients.
- All simulations emphasised the importance of high exposure early in treatment.
- All dose reduction schemes starting with two cycles of 800 mg/day (400 mg BID) had similar benefit and risk.
- There is no difference in outcomes (AEs and TP) when the initial dose reduction steps go from 800 to 600 mg/day or directly to 400 mg/day.

REFERENCES

- Sorafenib Pharmacokinetics in Subjects with Thyroid Cancer and Inter-Tumor Type Comparison. Bayer internal report PH-37268, 13-05-2013.
- A Double-Blind, Randomized Phase III Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo in Locally Advanced/Metastatic Radioactive Iodine (RAI)-Refractory Differentiated Thyroid Cancer (DTC). Bayer Clinical Study Report 14295-A57578.
- Population Pharmacokinetic Analysis of sorafenib Plasma Concentrations in Phase II through Phase IV Monotherapy Studies, Bayer internal report number R-8977, 24-09-2013.