

## The added value of Bayesian interim analysis in randomized phase II and phase III clinical trials in hemato-oncology

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## LETTER TO THE EDITOR

### The added value of Bayesian interim analysis in randomized phase II and phase III clinical trials in hemato-oncology

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#### Author contributions

A.J.T.S., N.v.d.M., J.V., J.C. contributed to the conceptualization and writing - original draft. A.J.T.S. and N.v.d.M. participated in formal analysis. J.V. have accessed and verified the data. A.J.T.S., N.v.d.M., J.V., E.v.W., and J.C. contributed to data interpretation, revising the manuscript, and approving this manuscript for submission. All other authors provided study materials or enrolled patients, were involved in the collection and assembly of clinical data, contributed to writing - review and editing, and approved the manuscript for submission.

### **Disclosures**

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### **Data sharing statement**

The data that support the findings of this study are available from HOVON but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of HOVON.

### **Clinical trial information**

This study included data of the HOVON95/EMN02 trial, the HOVON87/NMSG18 trial and the HOVON103/SAKK30/10 trial. The HOVON95/EMN02 trial is registered at the EU Clinical Trials Register (EudraCT 2009-017903-28) and ClinicalTrials.gov (NCT01208766). The HOVON87/NMSG18 trial is registered at [www.trialregister.nl](http://www.trialregister.nl) as NTR1630 (EudraCT number 2007-004007-34). The HOVON103/SAKK30/10 trial is registered at [www.trialregister.nl](http://www.trialregister.nl) as NL5748 (NTR5902).

Prospective phase III randomized controlled trials (RCTs) are the gold standard for evaluating the benefit-risk ratio of new therapies.<sup>1,2</sup> RCTs frequently include interim analyses, primarily to ensure patient safety and monitor treatment efficacy.<sup>3</sup> These interim analyses may potentially result in early trial termination or modification if there is evidence of harm, overwhelming efficacy, or futility. The time between initiation and obtaining final results of RCTs is generally very long, which delays access to new therapies for patients. Conventional frequentist statistical approaches apply conservative stopping rules at interim analyses and require long-term follow-up. Bayesian statistical methods may address these challenges and may potentially reduce the time of RCTs and the exposure of patients to ineffective or harmful treatment regimens, as recently suggested.<sup>4-7</sup> However, the use of Bayesian interim analyses in phase II/III hemato-oncology trials, particularly in varying situations involving superiority, no superiority and inferiority has not been well explored. Therefore, the current study applied Bayesian interim analysis to three phase II/III randomized controlled trials to evaluate the added value of Bayesian statistical models next to conventional interim designs.

Clinical and outcome data from three randomized trials were used, including the phase III HOVON95/EMN02 trial and the phase III HOVON87/NMSG18 trial for patients with multiple myeloma (MM) and the phase II HOVON103/SAKK30/10 trial for patients with AML, which were previously reported.<sup>8-10</sup> The study designs are summarized in Supplemental Figure 1. The trials were approved by the institutional review boards of each participating site, as previously reported.<sup>8-10</sup> Three interim analyses were retrospectively mimicked based on actual data after the inclusion of 50%, 75% and 100% of the total included patients in all three trials for early benefit-risk assessment. This corresponded to three simulated interim analyses after the inclusion of 599, 898, and 1197 patients in the HOVON95/EMN02 trial, after the inclusion of 319, 478, and 637 patients in the HOVON87/NMSG18 trial and after the inclusion of 51, 77 and 102 patients in the HOVON103/SAKK30/10 trial (Fig. 1A, 2A, 3A).

The primary endpoint in the HOVON95/EMN02 trial was progression-free survival (PFS) and the anticipated median PFS improvement in the experimental arm corresponded to a target HR of 0.78.<sup>8</sup> The primary endpoint in the HOVON87/NMSG18 trial was PFS with a projected median PFS improvement of eight months for the experimental arm corresponding to a target HR of 0.714.<sup>9</sup> The primary endpoint in the HOVON103/SAKK30/10 trial was complete response (CR) and the anticipated difference in CR rates between the two treatment arms was set at 20%.<sup>10</sup> The HOVON95/EMN02 trial showed superiority for PFS in the experimental arm, whereas in the HOVON87/NMSG18 trial no superiority for PFS was observed, and CR rates were lower with the experimental arm in the HOVON103/SAKK30/10 trial.

Bayesian inference allows for the evaluation of the probability that a treatment provides a benefit exceeding various clinically meaningful thresholds. In contrast to traditional frequentist approaches, which rely on null hypothesis significance testing and p-values, Bayesian inference distributes probability across a spectrum of parameter values—such as a treatment effect—updating these as new data emerge, designated as the posterior probability. Bayesian posterior probability distributions of the treatment difference were calculated for the primary endpoints of the trial: PFS (HOVON95/EMN02 trial; HOVON87/NMSG18 trial) and CR (HOVON103/SAKK30/10 trial), respectively. The probability distributions were summarized to provide estimates of the probability distribution median and 95% Bayesian credible intervals (95% CrI) of the hazard ratio, whereas frequencies were calculated using the highest density interval method. Non-informative priors were used for the interim analyses as no prior data was available. Four Markov Monte Carlo chains were run with 50,000 iterations and chain convergence was evaluated by quantile plots and Gelman–Rubin diagnostics. PFS was evaluated using a Bayesian Cox proportional hazards survival model. The probabilities of HR were estimated based on the assumed effect size for PFS. CR, adverse events (AE) grade 3-5 and death within 100 days after the start of treatment (early death) were evaluated using a

Bayesian beta-binomial model. The probability of any benefit (treatment difference >0%) in CR, AE or early death was estimated for the experimental treatment arm compared with the control treatment arm. Bayesian statistical methods were retrospectively applied and the results were aligned with a conventional group sequential design at the same interim time points to offer additional context. Therefore, no stopping boundaries were applied nor applicable. Analyses were performed in R (version 4.2.2.) using the software of JAGS version 4.3.0 in the package “rjags” and the “brms” package and using EAST statistical software (version 6).<sup>11,12</sup> The R-script of all the main analyses are published online (<https://github.com/niekvandermaas/Analysis-of-The-Added-Value-of-Bayesian-Interim-Analysis>).

In the HOVON95/EMN02 trial, Bayesian interim analyses showed that the probability of a HR below 0.78 (target HR<0.78) for the HSCT arm compared with the VMP arm was 76.2% at interim analysis 1, 77.1% at interim analysis 2 and 93.7% at interim analysis 3 (Figure 1B). Collectively, Bayesian analysis provided early signs of efficacy upon all three successive interim analyses. Nevertheless, the conventional group sequential design showed that the HR of PFS crossed the efficacy boundary only at the third interim analysis (Supplemental Fig. 2A). Grade 3-5 AEs excluding hematological AEs were more frequently observed in the HSCT arm compared with the VMP arm with a treatment difference of 8-10% across the three interim analyses (Figure 1C).

In the HOVON87/NMSG18 trial, Bayesian interim analyses showed low posterior probabilities of the target benefit (target HR<0.714) for the MPR-R arm compared with the MPT-T arm being 76.2% at interim analysis 1, 37.7% at interim analysis 2 and 9.1% at interim analysis 3 (Fig. 2). Collectively, from the second interim analysis onward, the likelihood of achieving the targeted relative benefit corresponding to at least an 8-month increase in median PFS became highly unlikely, and even elusive at the last interim analysis. However, the conventional group

sequential design did not show signs of futility given that the HR of PFS did not cross the futility boundary at interim analyses 1, 2 and 3, respectively (Supplemental Fig. 2). AE grade 3-5 were more frequently observed in the MPR-R arm compared with the MPT-T arm with a treatment difference of ~7% across interim analyses (Fig. 2C).

In the HOVON103/SAKK30/10 trial, both Bayesian interim analyses and conventional interim methods consistently indicated futility. The probability of a higher CR rate in the selinexor treatment arm compared with the control treatment arm was 2.9% at interim analysis 1, 0.5% at interim analysis 2 and 0.8% at interim analysis 3 (Fig. 3B). Similarly, the conventional group sequential design showed that the treatment difference of CR crossed the futility boundary at all three interim analyses (Supplemental Fig. 2). Additionally, death within 100 days was more frequently observed in the selinexor treatment arm compared with the control treatment arm at all three interim analyses (Fig. 3C).

In summary, this study showed that Bayesian interim analyses provided early and informative insight into the efficacy and harm of treatments, which compared favorably with the conventional group sequential design in 2 out of 3 trials (HOVON95/EMN02 trial and HOVON87/NMSG18 trial). It aligns with previous findings from a Bayesian interim analysis study of the HOVON132 AML trial by van der Maas et al., in which an early lack of efficacy in all four simulated interim analyses was detected, while the frequentist group sequential design only showed futility at the third interim time point.<sup>4</sup>

The paucity of events early in the trial conduct may pose a challenge in early interim analyses as conducted in our study. This is especially a challenge in MM, where novel agents have substantially improved survival outcomes and delayed disease progression, resulting in prolonged time-to-event times. In contrast to MM, AML is still characterized by a more rapid

disease progression and time-to-event times in AML trials are shorter compared with other hemato-oncological diseases. This shorter timeline enhances the potential of Bayesian interim analyses and might enable a more rapid data and safety monitoring board (DSMB) advice, in order to limit patient exposure to ineffective or harmful treatments. On the other hand, short timelines necessitate careful consideration and in the case of overwhelming efficacy, early termination of a trial is not always feasible and depends on the strength of evidence and the time to develop adverse events. Incorporating external control data from historical MM or AML trials as a Bayesian prior in our model may further enhance the utility of Bayesian analyses, which data were not available for the trial settings used in this analysis.<sup>5,13,14</sup> Successful implementation of Bayesian interim monitoring will, however, depend on timely data delivery, robust data infrastructure, and defining standardized, prespecified Bayesian decision thresholds to ensure consistency across trials.

In conclusion, the current study supports a broader use of Bayesian analysis in early interim analyses in phase III randomized controlled trials in hemato-oncology. While the overall study design may remain consistent with conventional RCT practices, Bayesian analyses show added value for interim analyses that may inform DSMB members for their meetings in addition to conventional interim analyses. Bayesian interim analysis may allow for identifying a clinically relevant treatment difference and/or clinically relevant toxicities at early interim timepoints. By providing informative, additional insights during a trial, this approach holds promise for optimizing methodologies in future prospective comparative studies, ultimately enhancing trial efficiency and decision-making.



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**Figure 1. Study design and Bayesian analysis of the HOVON95/EMN02 trial comparing HSCT and VMP in PFS and adverse events**

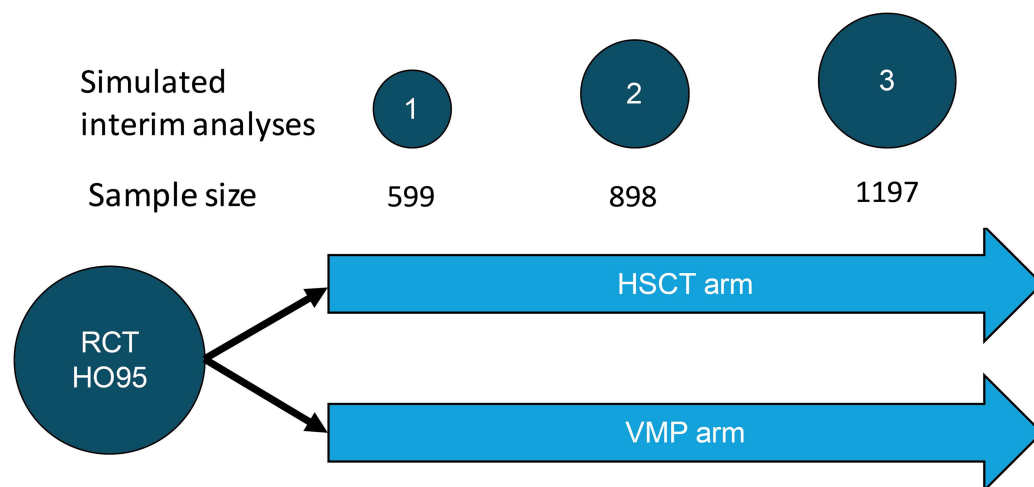
Study design flow diagram of the HOVON95/EMN02 trial (A) with the estimation of the probability for the assumed treatment effect ( $HR \leq 0.78$ ) by Bayesian analysis of PFS comparing HSCT versus VMP (control arm) (B) and comparison of HSCT versus VMP by Bayesian analysis of adverse events (C). Abbreviations: AE: adverse events; HR: hazard ratio; HSCT: hematopoietic stem cell transplantation; PFS: progression-free survival; RCT: randomized controlled trial; VMP: bortezomib, melphalan, prednisone; \*excluding hematological adverse events.

**Figure 2. Study design and Bayesian analysis of the HOVON87/NMSG18 trial comparing MPR-R and MPT-T in PFS and adverse events**

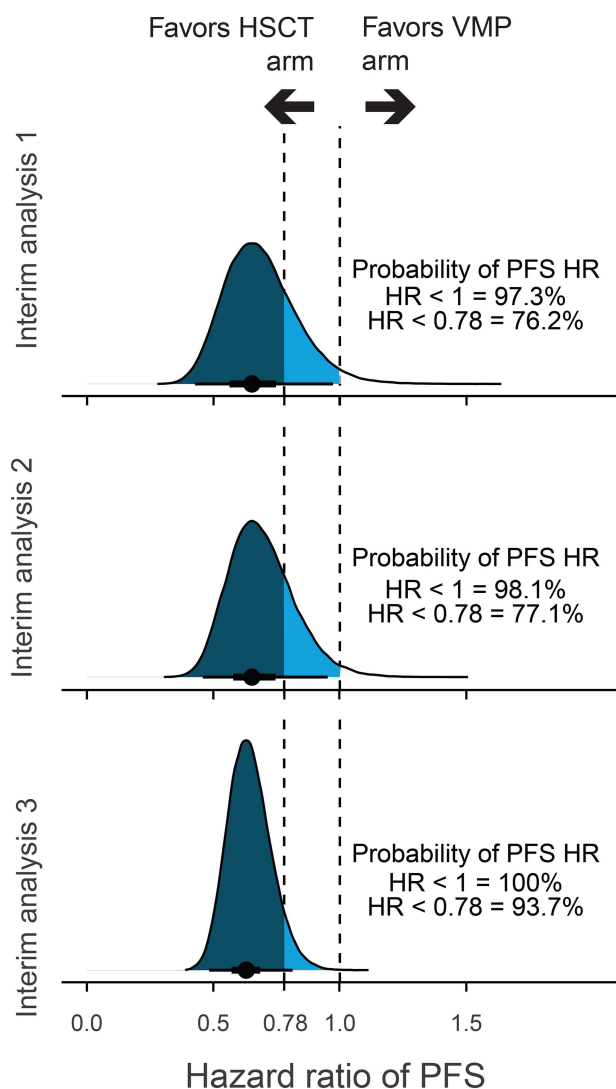
Study design flow diagram of the HOVON87/NMSG18 trial (A) with the estimation of the probability for the assumed treatment effect ( $HR \leq 0.714$ ) by Bayesian analysis of PFS comparing MPR-R treatment versus control (MPT-T) (B) and comparison of MPR-R versus control by Bayesian analysis of adverse events (C). Abbreviations: AE: adverse events; HR: hazard ratio; MPR-R: melphalan, prednisone, and lenalidomide; MPT-T: melphalan, prednisone, and thalidomide; PFS: progression-free survival; RCT: randomized controlled trial; \*including hematological adverse events.

**Figure 3. Study design and Bayesian analysis of the HOVON103/SAKK30/10 trial comparing the selinexor treatment arm versus the control treatment arm in CR and early deaths**

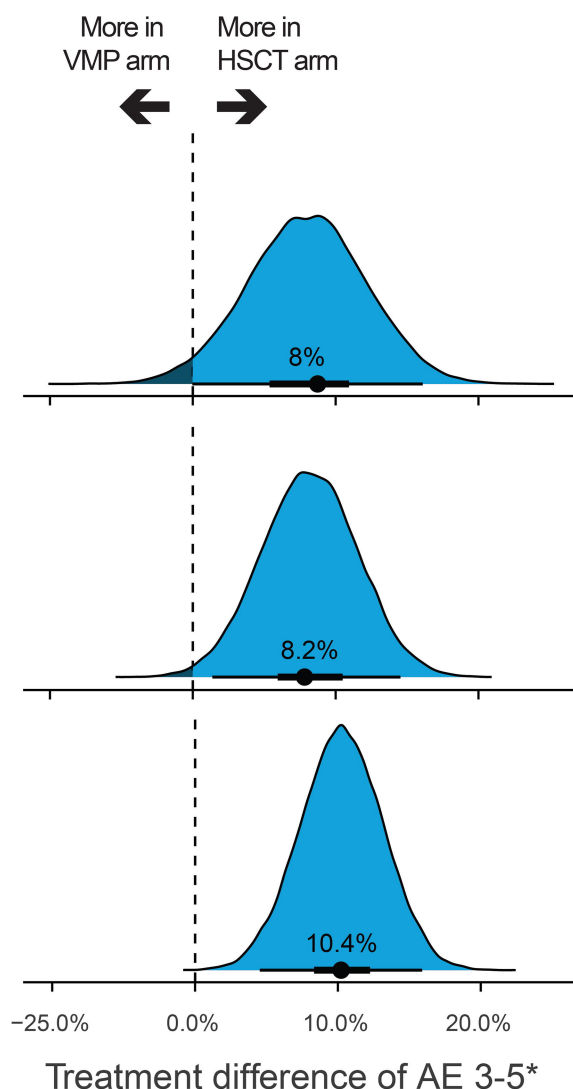
Study design flow diagram of the HOVON103/SAKK30/10 trial (A) with the estimation of the probability for the assumed treatment effect (treatment difference  $>0$ ) by Bayesian analysis of CR comparing the selinexor treatment arm versus the control treatment arm (B) and comparison of the selinexor treatment arm versus control treatment arm by Bayesian analysis of early death (C). Abbreviations: CR: complete remission; RCT: randomized controlled trial.

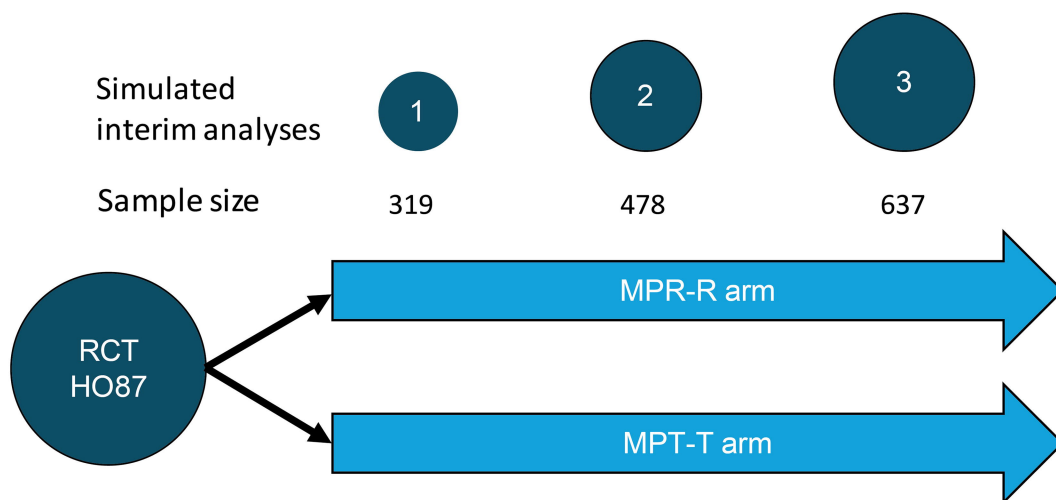
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### Bayesian analysis of Progression-free survival

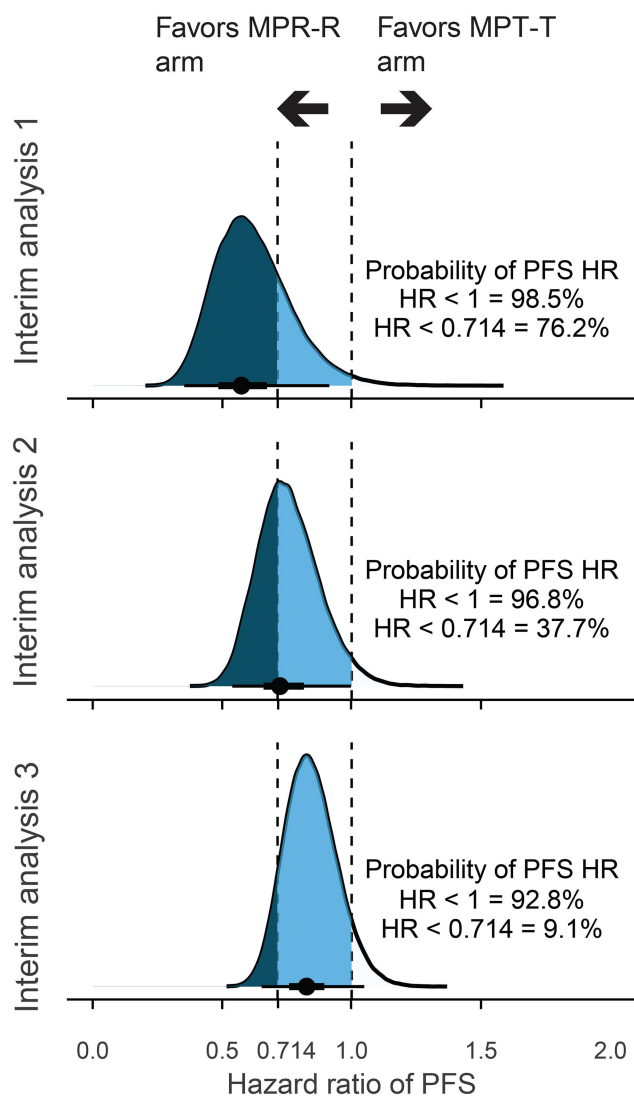
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### Bayesian analysis of adverse events

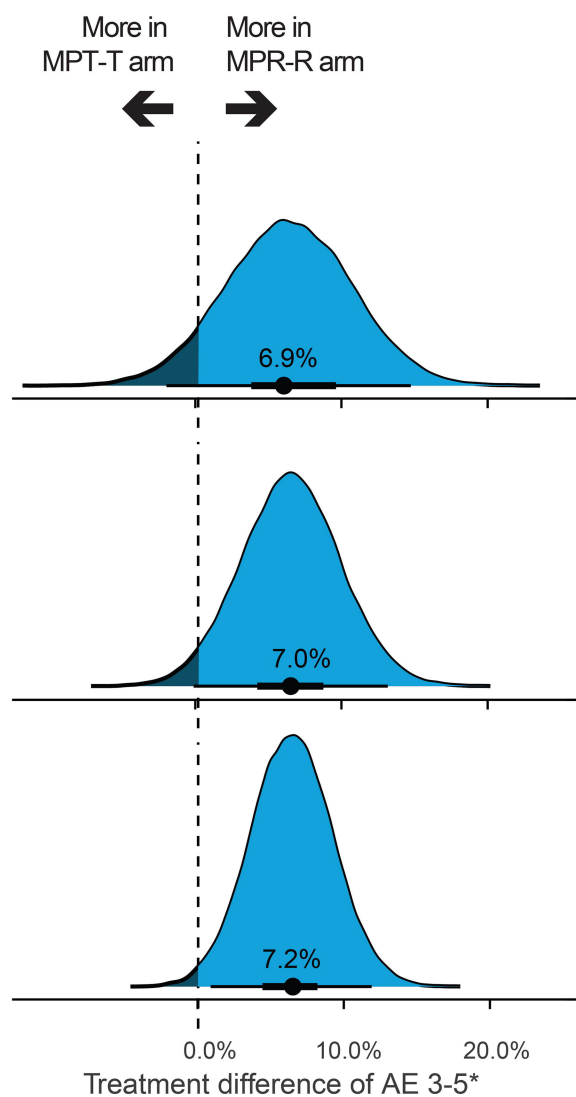


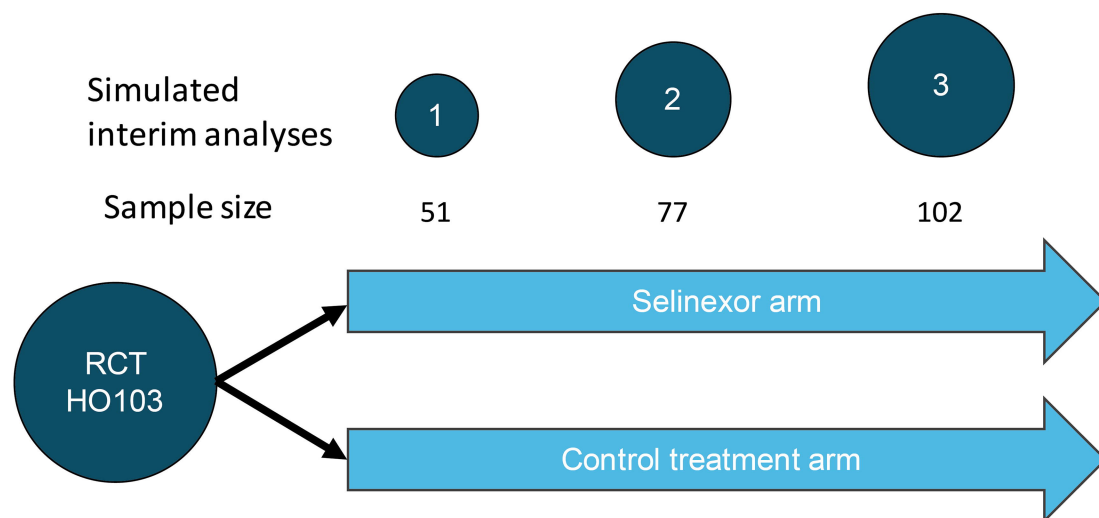
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### Bayesian analysis of Progression-free survival

**C**

### Bayesian analysis of adverse events

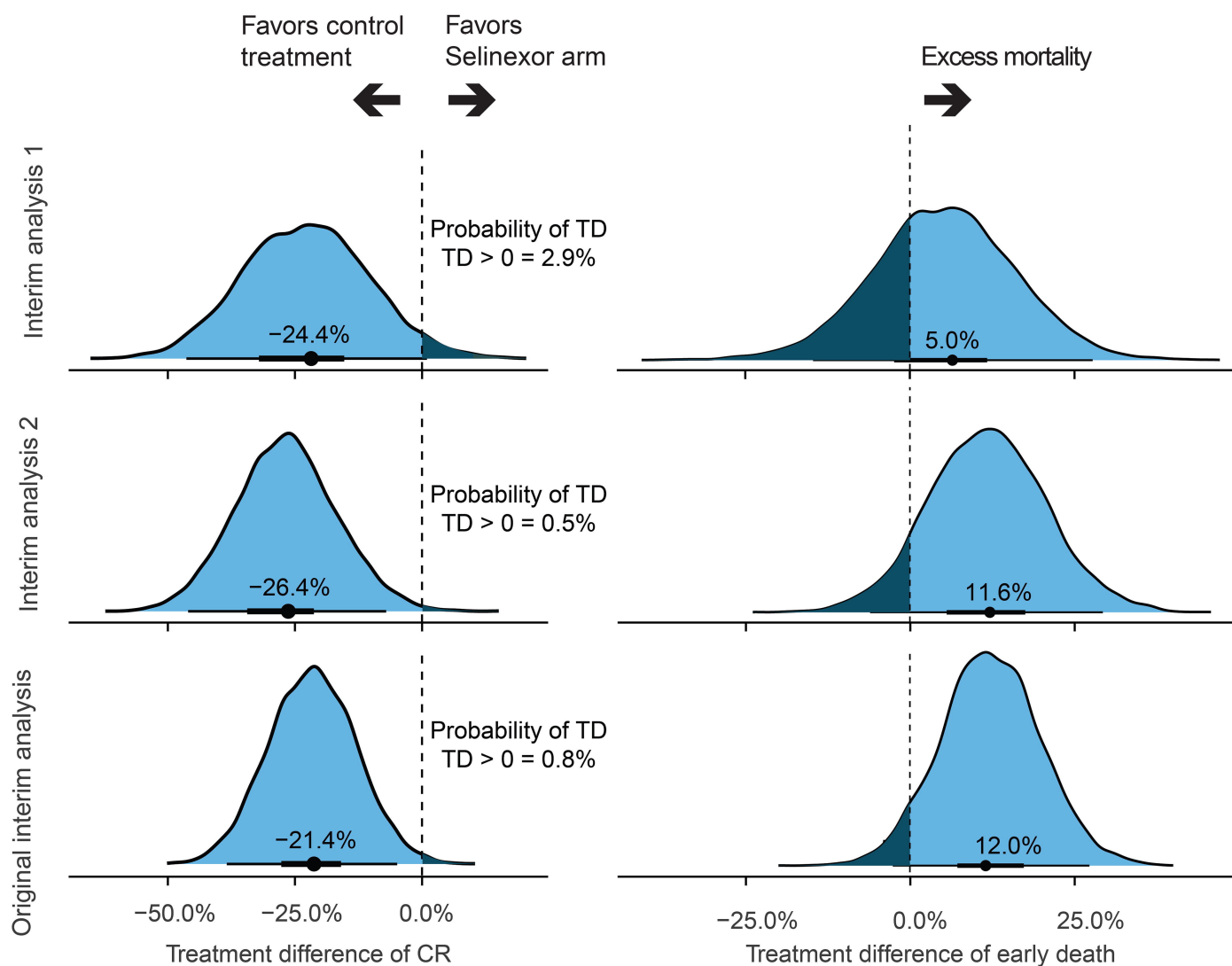


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### Bayesian analysis of treatment difference

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### Bayesian analysis of adverse events

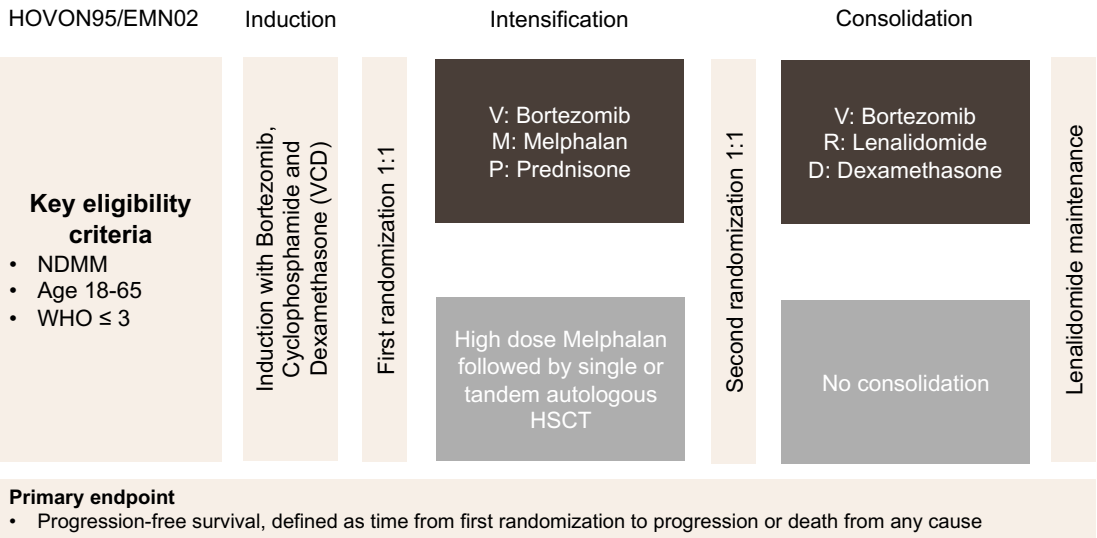


## **SUPPLEMENTARY MATERIALS**

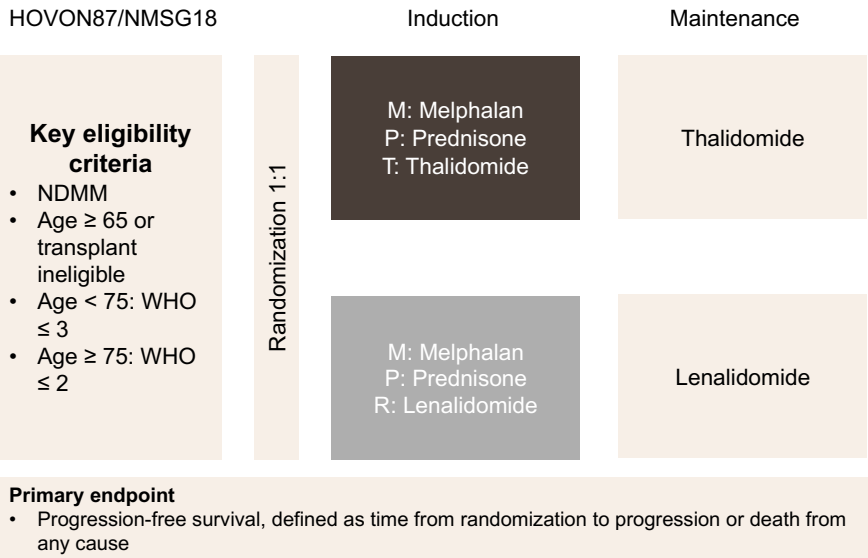
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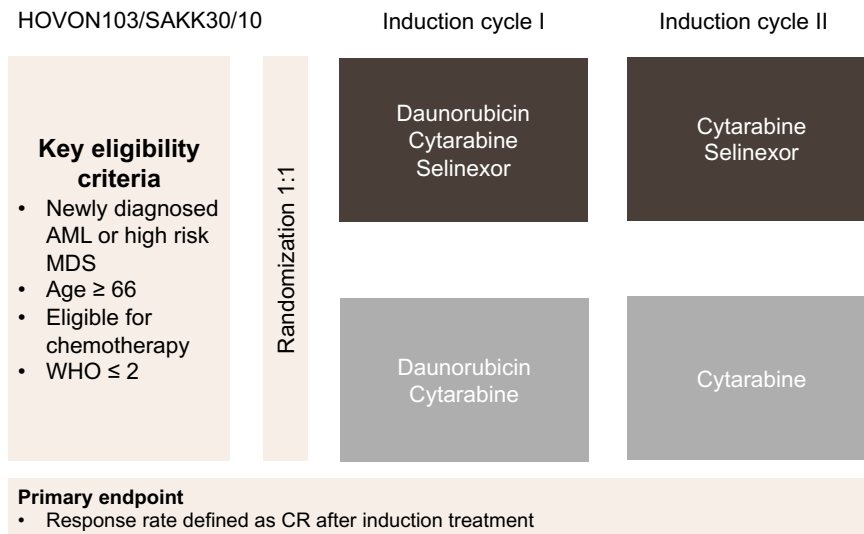


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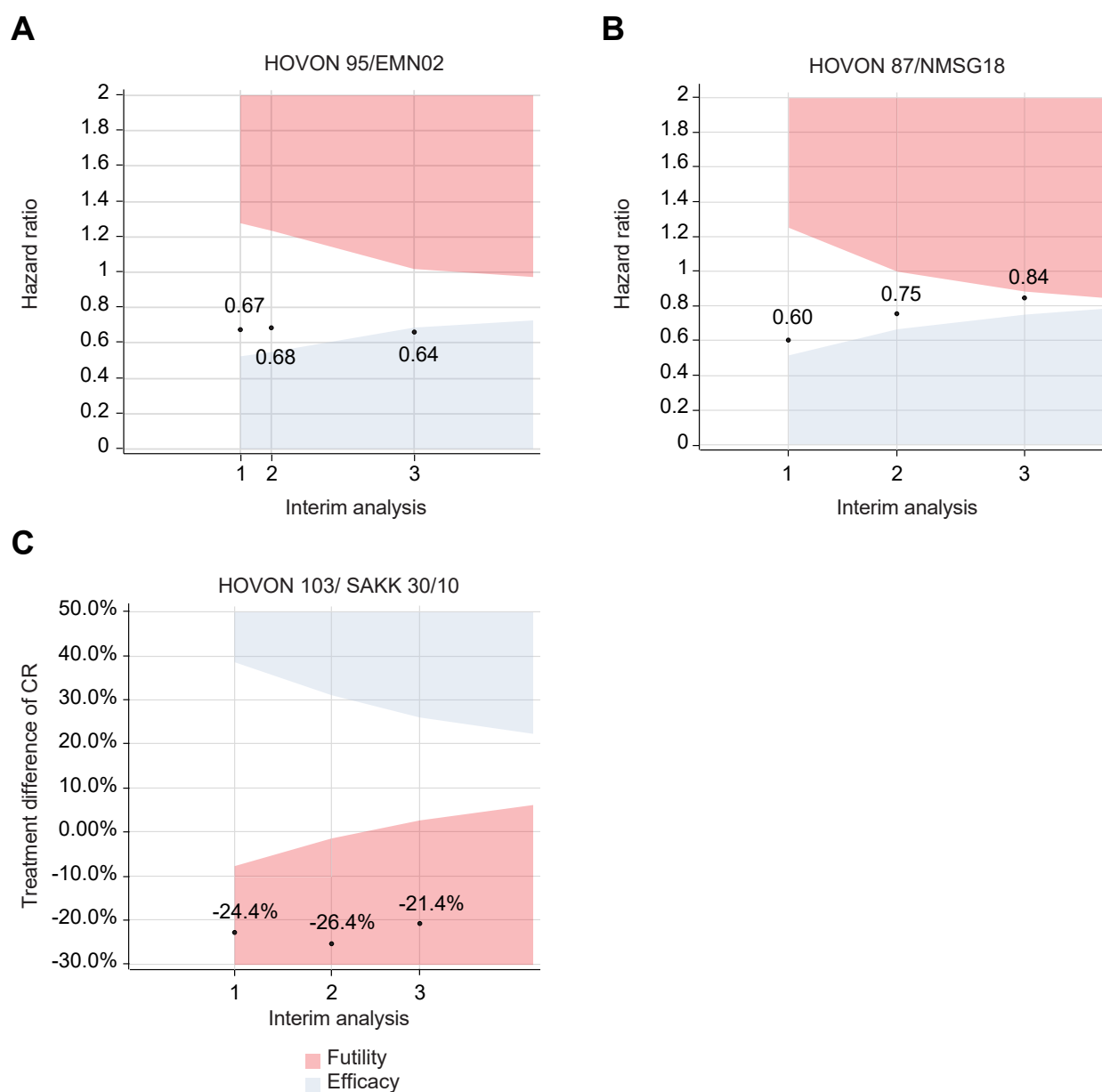


**C**



**Figure S1A-C. Original study design flow diagrams of the HOVON95/EMN02, HOVON87/NMSG18 and HOVON103/SAKK30/10 trials**

Abbreviations: AML: acute myeloid leukemia; CR: complete remission; HSCT: hematopoietic stem cell transplantation; MDS: myelodysplastic syndrome; NDMM: newly diagnosed multiple myeloma; WHO: World Health Organization.



**Figure S2A-C. Conventional group sequential design with non-binding two-sided hazard ratio bounds for stopping for efficacy or futility at each interim analysis of the HOVON95/EMN02, HOVON87/NMSG18 and HOVON103/SAKK30/10 trials**

Abbreviations: CR: complete remission.