Optimizing Natural Killer Cell Doses for Heterogeneous Cancer Patients Based on Multiple Event Times

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Abstract

A sequentially adaptive Bayesian design is presented for a clinical trial of cord blood derived natural killer cells to treat severe hematologic malignancies. Given six prognostic subgroups defined by disease type and severity, the goal is to optimize cell dose in each subgroup. The trial has five co-primary outcomes, the times to severe toxicity, cytokine release syndrome, disease progression or response, and death. The design

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assumes a multivariate Weibull regression model, with marginals depending on dose, subgroup, and patient frailties that induce association among the event times. Utilities of all possible combinations of the nonfatal outcomes over the first 100 days following cell infusion are elicited, with posterior mean utility used as a criterion to optimize dose. For each subgroup, the design stops accrual to doses having an unacceptably high death rate, and at the end of the trial selects the optimal safe dose. A simulation study is presented to validate the design's safety, ability to identify optimal doses, and robustness, and to compare it to a simplified design that ignores patient heterogeneity.

Keywords: Cellular Therapy; Dose Finding; Natural Killer Cells; Precision Medicine; Phase I-II Clinical Trial.

1 Introduction

This paper describes a sequentially adaptive Bayesian design for an early phase clinical trial of umbilical cord blood derived natural killer (NK) cells as therapy for advanced hematologic diseases. NK cells are lymphocytes that can be used for cancer immunotherapy because they play a critical role in natural immune surveillance and are the body's first line of defense against viruses and newly transformed cancer cells (Rezvani and Rouce, 2015). Patients may have chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), or non-Hodgkin's lymphoma (NHL), with either low or high bulk disease (LBD or HBD), so disease type and bulk determine six prognostic subgroups. The trial's primary goal is to identify an optimal NK cell dose for each subgroup. Rather than monitoring one toxicity as in phase I trials (Cheung, 2011) or bivariate (efficacy, toxicity) as in phase I-II (Yuan *et al.*, 2016), there are five co-primary outcomes. These are the times from cell infusion to death (D), disease progression (P), response (R), severe toxicity (T), and severe cytokine release syndrome (C). Since T and C are most likely to occur soon after cell infusion, they are monitored

for $L_T = L_C = 100$ days, while P, R, and D are monitored for $L_P = L_R = L_D = 365$ days. The time Y_j to event j is independently censored at L_j for each $j \in \{P, R, T, C, D\}$, death informatively censors all other events, and Y_P and Y_R are competing risks. Based on clinical experience, the Y_j's are interdependent, the distribution of $\boldsymbol{Y} = (Y_R, Y_C, Y_P, Y_T, Y_D)$ varies between subgroups, and the adverse event times (Y_C, Y_P, Y_T, Y_D) are positively associated.

Denote NK cell dose by d, subgroup by g, and the probability of death prior to day 100 by $\pi_D(d, g) = \Pr(Y_D \leq 100 \mid d, g)$ for all (g, d) pairs. In the design, if $\pi_D(d, g)$ is unacceptably high compared to an elicited fixed upper limit $\bar{\pi}_D(g)$ for subgroup g, then d is discontinued in g. A conventional safety rule ignoring subgroups would discontinue d for all patients if an interim estimate of $\pi_D(d) = \Pr(Y_D \leq 100 \mid d)$ is unacceptably high. This rule produces a design with high probabilities of making incorrect decisions within subgroups. For example, given historical values $\bar{\pi}_D(1) = 0.10$ and $\bar{\pi}_D(2) = 0.40$ with standard therapy for subgroups $g = 1$ (low risk) and $g = 2$ (high risk), if the interim estimate $\widehat{\pi}_D(d) = 0.25$, obtained by ignoring subgroups, triggers the decision to stop all accrual to dose d, this is likely to be correct for subgroup $g = 1$ but incorrect for $g = 2$.

A major logistical problem in trial conduct is that each patient's outcome is based on five event times monitored up to 365 days. Each outcome is fully evaluated at its occurrence time, or censored by death or administratively at the end of its 100 or 365 day follow up period. To choose a dose adaptively for a new patient, it is likely that some outcomes of previous patients have not been evaluated fully, and it is not feasible to suspend accrual to wait for full evaluation of all previous patients' data. This problem was solved for phase I trials by the time-to-event continual reassessment method (TiTE-CRM) (Cheung and Chappell, 2000). Phase I-II designs based on bivariate (efficacy, toxicity) event times have been proposed by Zhou *et al.* (2006) Thall *et al.* (2013), and Jin *et al.* (2014), among others.

In the NK cell trial, it is assumed that Pr(CLL) = Pr(ALL) = Pr(NHL) = 1/3, and Pr(LBD) = 1/3 and Pr(HBD)= 2/3. Thus, given maximum sample size $N_{\max} = 60$, ap-

proximate expected subgroup sample sizes are (7, 7, 7, 13, 13, 13), and these subsamples are divided further among the NK cell doses. This limits the reliability of subgroup-specific safety monitoring and optimal dose selection. Based on current knowledge about NK cell biology, the six hazard functions may not be monotone in NK cell dose. Finally, given the five event time outcomes, what is meant by "optimal NK cell dose" in each subgroup is not obvious. We present a design that addresses all of these problems.

To provide a basis for dose-finding, we assume a Bayesian multivariate parametric regression model for $\boldsymbol{Y}$, with Weibull marginals having scale parameters that vary with (d, g). A vector of patient frailties is introduced, with one frailty acting multiplicatively on the marginal hazard of each event time. The frailty vector accounts for additional variability not accounted for by subgroup, and also induces dependence between the elements of $\boldsymbol{Y}$. Frailty models have been used widely for multivariate failure time data, including the multivariate log-normal distribution (Ripatti and Palmgren, 2000), competing risks (Gorfine and Hsu, 2011), and semi-competing risks (Lee *et al.*, 2016).

Our design is nominally phase I-II since it includes the desirable event R and adverse events $\{P, T, C, D\}$, and is an example of precision medicine since decisions are subgroup-specific. Reviews of phase I-II designs are given by Zohar and Chevret (2007) and Yuan *et al.* (2016). Our use of posterior mean utility is similar to, for example, the phase I-II designs of Houede *et al.* (2010), and Thall *et al.* (2013), and the randomized trial design of Murray *et al.* (2016). Phase I-II designs accounting for patient heterogeneity have been given by Thall *et al.* (2008), Chen *et al.* (2016), and Guo and Yuan (2017).

Section 2 presents the probability model underlying the design. Section 3 describes utility computation, and Section 4 presents the design. In Section 5, a simulation study is presented to evaluate the design's safety, ability to identify optimal doses, and robustness, and to compare it to a simplified design ignoring patient heterogeneity. We close with a brief discussion in Section 6.

2 Probability Model

2.1 Recording Event Times

For interim sample size $n(t) \leq N_{\max}$ at trial time t, index patients in order of enrollment by $i = 1, \cdots, n(t)$, with trial entry times $0 \leq e_1 \leq e_2 \leq \cdots \leq e_{n(t)}$. For patient i, the trial time of event j for patient i is $e_i + Y_{i,j}$, if it is observed. For $j = P, R$ or D, $Y_{i,j}$ is followed until $e_i + 365$, and $Y_{i,T}$ and $Y_{i,C}$ are followed until $e_i + 100$. Let $Y^o_{i,j}$ denote the time of observation of Y_j or right-censoring, with $\delta_{i,j} = 1$ if $Y^o_{i,j} = Y_{i,j}$ and 0 otherwise. At trial time $t > e_i$, if $Y_{i,D} > t - e_i$ or $Y_{i,D} > 365$, then $Y^o_{i,D}$ is the time of independent right censoring ($\delta_{i,D} = 0$). If $Y_{i,D} < \min(t - e_i, 365)$, then $Y^o_{i,D} = Y_{i,D}$ is the observed time of death ($\delta_{i,D} = 1$). For nonfatal events $j = T, C$, if $Y_{i,j} < \min\{t - e_i, L_j, Y_{i,D}\}$, then $Y^o_{i,j} = Y_{i,j}$ ($\delta_{i,j} = 1$) and otherwise $Y^o_{i,j}$ is the time of right-censoring ($\delta_{i,j} = 0$). If $Y_{i,P} < \min\{t - e_i, L_P, Y_{i,R}, Y_{i,D}\}$, i.e. $Y_{i,P}$ is observed, then $Y^o_{i,P} = Y^o_{i,R} = Y_{i,P}$ and $(\delta_{i,P}, \delta_{i,R}) = (1, 0)$. If $Y_{i,R} < \min\{t - e_i, L_R, Y_{i,P}, Y_{i,D}\}$, then $Y^o_{i,P} = Y^o_{i,R} = Y_{i,R}$ and $(\delta_{i,P}, \delta_{i,R}) = (0,\ 1)$. If neither Y_P nor Y_R occurs, $(\delta_{i,P}, \delta_{i,R}) = (0,\ 0)$. Since P and R are competing risks, $(\delta_{i,P}, \delta_{i,R}) = (1,\ 1)$ is not possible. If censoring is due to the fact that $Y_{i,j} > \min\{t - e_i, L_j\}$ and the patient is alive at trial time t, then censoring is independent. For $j \neq D$, if censoring of $Y_{i,j}$ is due to death, i.e. $Y_{i,D} < Y_{i,j}$, then the censoring is not independent and $Y^o_{i,j} = Y^o_{i,D}$ ($\delta_{i,j} = 0$).

2.2 Sampling and Frailty Models

Index NK cell doses by $d = 1, 2, 3$, and define $Z = 0$ for LBD and $Z = 1$ for HDB. Index $r = 1, 2, 3$, for disease types CLL, ALL, NHL. Denote $\boldsymbol{Z} = (Z, r)$, which replaces the subgroup index g. For $i = 1, \cdots, n(t)$, denote dose by d_i and covariates by $\boldsymbol{Z}_i = (Z_i, r_i)$. Generalizing the description of two semi-competing risks given by Fine *et al.* (2001), here the joint distribution of $\boldsymbol{Y}$ is defined on the set $\mathcal{Y}_D = \{\boldsymbol{y} \subset [0, \infty)^5 : \max(y_P, y_R, y_C, y_T) < y_D\}$, since death censors any nonfatal event but not conversely. On $\mathcal{Y}_D$, Y_R and Y_P have the

usual competing risks structure, with at most one observed. Thus, h_R and h_P are subhazard functions (cause-specific hazards) where $h_j(y)$, $j = R, P$ is interpreted as the hazard of R or P occurring at time y and being j, and $h_R(y) + h_P(y)$ is the hazard of either P or R on $\mathcal{Y}_D$. In the sequel we will abuse conventional terminology by referring to either hazards or subhazards as "hazard functions," and do the same for survivor functions $S_j(y)$.

We assume Weibull marginal event time distributions,

$$Y_{i,j} \mid \alpha_j, \lambda_{i,j} \overset{indep}{\sim} \text{Weibull}(\alpha_j, \exp(\lambda_{i,j})), \quad i = 1, \ldots, n(t) \text{ and } j \in \{P, R, T, C, D\}, \tag{1}$$

with shape parameter $\alpha_j > 0$ and scale $\exp(\lambda_{i,j})$, which has hazard and survival functions $h_j(y \mid \alpha_j, \lambda_{i,j}) = \alpha_j \exp(\lambda_{i,j}) y^{\alpha_j - 1}$ and $S_j(y \mid \alpha_j, \lambda_{i,j}) = \exp\{-\exp(\lambda_{i,j}) y^{\alpha_j}\}$ for $y > 0$. The joint conditional likelihood for all observable outcomes on $\mathcal{Y}_D$ is the product of the individual likelihoods, $p(\boldsymbol{y}_i^o, \boldsymbol{\delta}_i \mid \boldsymbol{\alpha}, \boldsymbol{\lambda}) = \prod_{j \in \{P, \ldots, D\}} \{h_j(y_j^o \mid \alpha_j, \lambda_{i,j})\}^{\delta_j} S_j(y_{i,j}^o \mid \alpha_j, \lambda_{i,j})$ for observed $(\boldsymbol{y}_i^o, \boldsymbol{\delta}_i)$, (Prentice *et al.*, 1978; Kalbfleisch and Prentice, 2011).

Given the form (1) of the marginals, we formulate a joint model to account for effects of dose and subgroup on each Y_{ij}, by including dose-subgroup parameters in each $\lambda_{i,j}$. Let $u_{i,j}$ be a latent frailty associated with patient i for outcome j, with $\boldsymbol{u}_i = (u_{i,P}, \cdots, u_{i,D})$. The relationship between $Y_{i,j}$, d_i, and $\boldsymbol{Z}_i = (Z_i, r_i)$ is based on the regression model

$$\lambda_{i,j}(\boldsymbol{Z}_i, d_i, u_{i,j}) = \beta_j Z_i + \xi_j \psi_{r_i, d_i} + u_{i,j}, \tag{2}$$

with $\xi_D \equiv 1$ to ensure identifiability. Thus, $\psi_{r,d}$ is the effect of d on the death rate for disease type r. Since $\psi_{r,d}$ describes the relationship between r, d, and Y_j for all j, it combines information across outcomes. Larger $\psi_{r,d}$ implies a higher risk of death for patients with disease type r and dose d. If $\xi_j > 0$ ($\xi_j < 0$), this implies a higher (lower) risk for outcome j. The parameter β_j is the additive effect of HBD ($Z = 1$) on $\log(h_j)$, with $\beta_j > 0$ reflecting a higher rate, equivalently smaller $\mathrm{E}(Y_j)$, for HBD versus LBD. The regression model in (2)

reduces the number of parameters, from $6 \times 3 \times 5 = 90$ if $\psi_{Z,r,d,j}$ were used to $5+9+4 = 18$. The model is parsimonious to allow adaptive subgroup specific decision making to be done tractably even with the trial's limited sample size, yet it is still quite flexible to accommodate possible relationships between d, $\boldsymbol{Z}$ and $\boldsymbol{Y}$.

For the patient frailties, we assume $\boldsymbol{u}_i \overset{iid}{\sim} \mathrm{N}_5(\boldsymbol{0}, \Omega)$ with $\Omega \sim$ inverse-Wishart(ν, Ω^0) for fixed $\nu > J-1$ and 5×5 positive definite hyper-parameter matrix Ω^0. We incorporate $\{\boldsymbol{u}_i, i = 1, \cdots, n\}$ into the five hazard functions to account for possible heterogeneity between patients beyond that due to the prognostic subgroups. The correlations among the $u_{i,j}$'s also induce dependence among the outcomes of each patient. Combining (1) and (2), conditional on $u_{i,j}$, the hazard function j for Y_{ij} is

$$h_j(y \mid \alpha_j, \xi_j, \psi_{r_i,d_i}, Z_i, u_{i,j}) = \alpha_j \exp(\beta_j Z_i + \xi_j \psi_{r_i,d_i} + u_{i,j}) y^{\alpha_j - 1}, \quad y > 0,$$

and we assume conditional independence of the elements of $\boldsymbol{Y}_i$ given $\boldsymbol{u}_i$ and $\boldsymbol{\theta}$ on the set on $\mathcal{Y}_D$. Suppressing patient index i, the joint survival function for $\boldsymbol{y} \in \mathcal{Y}_D$ is obtained by averaging over the frailty distribution,

$$\begin{aligned} S(y', y_T, y_C, y_D \mid \boldsymbol{\alpha}, \boldsymbol{\xi}, \psi_{r,d}, Z, \nu, \Omega^0) &= \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \prod_{j \in \{P,R\}} S_j(y' \mid \alpha_j, \xi_j, \psi_{r,d}, u_j) \\ &\quad \times \prod_{j \in \{T,C,D\}} S_j(y_j \mid \alpha_j, \xi_j, \psi_{r,d}, u_j) p(\boldsymbol{u}, \Omega \mid \nu, \Omega^0) d\boldsymbol{u}. \end{aligned}$$

In this model, the hazard functions of all outcomes, including the competing risks P and R, are estimable (Prentice *et al.*, 1978; Kalbfleisch and Prentice, 2011).

2.3 Prior Distributions and Posterior Computation

We specify priors for the model parameters $\boldsymbol{\alpha} = (\alpha_j, j = P, \ldots, D)$, $\boldsymbol{\beta} = (\beta_j, j = P, \ldots, D)$, $\boldsymbol{\xi} = (\xi_j, j = P, R, T, C)$, and $\boldsymbol{\psi} = (\psi_{r,d}, r = 1, \ldots, K, d = 1, \ldots, m)$ as follows. We assume

$\alpha_j \overset{indep}{\sim} \text{Ga}(a_j, b_j)$ where $\text{Ga}(a_j, b_j)$ represents gamma distributions with mean a_j/b_j and variance $a_j/{b_j}^2$, and let $\xi_j \overset{indep}{\sim} \text{N}(\bar{\xi}_j, \omega_j^2)$ for each j, with $\xi_D \equiv 1$. We assume $\psi_{r,d} \overset{indep}{\sim} \text{N}(\bar{\psi}_r, \tau_r^2)$ to allow the diseases CLL, ALL, NHL ($r = 1, 2, 3$) to have different outcome rates. To reflect higher hazards of adverse outcomes for patients with HBD, we assume that their effects follow normal distributions truncated below at 0, thus $p(\beta_j) \propto \exp\{-(\beta_j - \bar{\beta}_j)^2/(2\sigma_j^2)\}$ for $\beta_j > 0$, $j = T, C, D$, where $\bar{\beta}_j$ and σ_j^2 denote fixed hyperparameters for all j. The priors express no information on the directions of the HBD effects on the hazards of the sub-distributions of $Y_{i,P}$ and $Y_{i,R}$, so $\beta_j \sim \text{N}(\bar{\beta}_j, \sigma_j^2)$ for $j = P, R$. We denote $\boldsymbol{\theta} = (\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\xi}, \boldsymbol{\psi}, \Omega)$, and hyperparameter vector $\boldsymbol{\theta}^* = (\boldsymbol{a}, \boldsymbol{b}, \bar{\boldsymbol{\xi}}, \boldsymbol{\omega}^2, \bar{\boldsymbol{\psi}}, \boldsymbol{\tau}^2, \bar{\boldsymbol{\beta}}, \boldsymbol{\sigma}^2, \nu, \Omega^0)$ where $(\boldsymbol{a}, \boldsymbol{b}) = \{(a_j, b_j), j = P, \ldots, D\}$, $(\bar{\boldsymbol{\xi}}, \boldsymbol{\omega}^2) = \{(\bar{\xi}_j, \omega_j^2), j = P, \ldots, C\}$, $(\bar{\boldsymbol{\psi}}, \boldsymbol{\tau}^2) = \{(\bar{\psi}_r, \tau_r^2), r = 1, \ldots, K\}$, $(\bar{\boldsymbol{\beta}}, \boldsymbol{\sigma}^2) = \{(\bar{\beta}_j, \sigma_j^2), j = P, \ldots, D\}$.

To establish $\boldsymbol{\theta}^*$, we elicited probabilities of the 12 joint events occurring within follow of 30 days for C and 100 days for each $j \neq C$ (Table 1), chosen by the clinical investigators. Denote $\boldsymbol{L}' = (L'_P, L'_R, L'_T, L'_C, L'_D) = (100, 100, 100, 30, 100)$. We then solved sets of equations under the assumed model to obtain prior means, and calibrated dispersion parameters to reflect vague prior knowledge. Details of prior calibration are given in Supplementary §3.

Given $\boldsymbol{\theta}^*$ and interim data $\mathcal{D}_{n(t)}$ at trial time t, the joint posterior of all parameters $\boldsymbol{\theta}$ and patient specific random effects $\boldsymbol{u} = \{\boldsymbol{u}_i, i = 1, \ldots, n(t)\}$ is

$$\begin{aligned} p(\boldsymbol{\theta}, \boldsymbol{u} \mid \mathcal{D}_{n(t)}, \boldsymbol{\theta}^*) &\propto \prod_{i=1}^{n(t)} p(\boldsymbol{y}_i^o, \boldsymbol{\delta}_i \mid \boldsymbol{\theta}, \boldsymbol{u}_i) p(\boldsymbol{\theta}, \boldsymbol{u} \mid \boldsymbol{\theta}^*) \\ &= \prod_{i=1}^{n(t)} \prod_{j \in \{P, \ldots, D\}} \big(h_j(y_{i,j}^o \mid \alpha_j, \lambda_{i,j})\big)^{\delta_{i,j}(t)} S_j(y_{i,j}^o \mid \alpha_j, \lambda_{i,j}) p(\boldsymbol{\theta}, \boldsymbol{u} \mid \boldsymbol{\theta}^*). \quad (3) \end{aligned}$$

We use Markov chain Monte Carlo (MCMC) simulation to generate posterior samples of $\boldsymbol{\theta}$ and $\boldsymbol{u}$. Details of posterior computation are given in Supplementary §1. A computer program "NKcelldosefinding" for implementing this methodology is available from `https:`

//users.soe.ucsc.edu/~juheelee/.

3 Computing Utilities

Denote $\boldsymbol{\delta}' = (\delta'_P, \delta'_R, \delta'_T, \delta'_C, \delta'_D)$, where $\delta'_j = 1$ if Y_j is observed by L'_j, and 0 otherwise. Since $(\delta'_P, \delta'_R) = (1,1)$ is impossible, there are $3 \times 2^3 = 24$ possible outcomes $\boldsymbol{\delta}' \in \Delta$. Denote by Δ^0 the subset of Δ with $\delta_D = 0$, for patients who survive 100 days. As a practical approach, we elicited utilities on the set $\boldsymbol{\delta}' \in \Delta^0$, rather than for all possible $\boldsymbol{Y}$, by first fixing minimum utility $U(\boldsymbol{\delta}') = 0$ if $\delta'_D = 1$, i.e. if a patient dies before day 100. There are $|\Delta^0| = 12$ possible early event combinations in Δ^0, so computation of the posterior mean utility for each $(d, \boldsymbol{Z})$ only requires evaluation of $\pi(\boldsymbol{\delta}' \mid d, \boldsymbol{Z}, \boldsymbol{\theta})$ for each of the 12 indicator vectors $\boldsymbol{\delta}' \in \Delta^0$. The elicited utilities $U(\boldsymbol{\delta}')$ for all $\boldsymbol{\delta}' \in \Delta^0$ are given in Table 2.

To compute mean utilities, we use the fact that the distribution of $[\boldsymbol{\delta}' \mid d, \boldsymbol{Z}]$ is induced by that of $[\boldsymbol{Y} \mid d, \boldsymbol{Z}]$, for each $(d, \boldsymbol{Z})$. For example,

$$\begin{aligned} \pi((1,0,1,0,0) \mid d, \boldsymbol{Z}, \boldsymbol{\theta}) &= \Pr(Y_P \le L'_p, Y_R > Y_P, Y_T \le L'_T, Y_C > L'_C, Y_D > L'_D \mid d, \boldsymbol{Z}, \boldsymbol{\theta}) \\ &= \int_0^{L'_P} \int_{Y_P}^{\infty} \int_0^{L'_T} \int_{L'_C}^{\infty} \int_{L'_D}^{\infty} \int_{\mathbb{R}^5} p(\boldsymbol{y} \mid d, \boldsymbol{Z}, \boldsymbol{u}, \boldsymbol{\theta}) p(\boldsymbol{u} \mid \boldsymbol{\theta}) d\boldsymbol{u}\, d\boldsymbol{y}. \end{aligned}$$

Given $\boldsymbol{\theta}$, the mean utility of assigning dose d to a patient with covariates $\boldsymbol{Z}$ is

$$\bar{U}(d, \boldsymbol{Z}, \boldsymbol{\theta}) = \sum_{\boldsymbol{\delta}' \in \Delta^0} U(\boldsymbol{\delta}')\ \pi(\boldsymbol{\delta}' \mid d, \boldsymbol{Z}, \boldsymbol{\theta}). \tag{4}$$

To estimate $\bar{U}(d, \boldsymbol{Z}, \boldsymbol{\theta})$, a frequentist approach might plug in an estimator, $\hat{\boldsymbol{\theta}}$, and use $\bar{U}(d, \boldsymbol{Z}, \hat{\boldsymbol{\theta}})$. We exploit the Bayesian structure to compute posterior predictive mean utilities for use as dose selection criteria. Given the final data, $\mathcal{D}_{N_{\max}}$, when all $N_{\max}$ patients have been followed up fully, for a future patient with covariates $\boldsymbol{Z}$, the posterior predictive

mean utility of giving dose d to that patient is

$$u(d, \boldsymbol{Z} \mid \mathcal{D}_{N_{\max}}) = \int_{\boldsymbol{\theta}} \bar{U}(d, \boldsymbol{Z}, \boldsymbol{\theta}) p(\boldsymbol{\theta} \mid \mathcal{D}_{N_{\max}}) d\boldsymbol{\theta}. \tag{5}$$

This is used as an optimality criterion for dose selection at the end of the trial. While utilities are elicited over the early follow up intervals $\boldsymbol{L}'$, all of the follow up information on $(\boldsymbol{Y}_i, \boldsymbol{\delta}_i)$, for $i = 1, \cdots, N_{\max}$ over $\boldsymbol{L}$ is used to compute $u(d, \boldsymbol{Z} \mid \mathcal{D}_{N_{\max}})$, using a posterior MCMC sample of $\boldsymbol{\theta} \sim p(\boldsymbol{\theta} \mid \mathcal{D}_{N_{\max}}, \boldsymbol{\theta}^*)$. Details are given in Supplementary §1.

4 Trial Design

To ensure ethical conduct of the NK cell trial, subgroup-specific safety monitoring rules are used. For each $(d, \boldsymbol{Z})$, we denote $\pi_D(d, \boldsymbol{Z}, \boldsymbol{\theta}) = \Pr(Y_D \leq L'_D \mid d, \boldsymbol{Z}, \boldsymbol{\theta}) = \Pr(\delta'_D = 1 \mid d, \boldsymbol{Z}, \boldsymbol{\theta})$. Let $\bar{\pi}_D(\boldsymbol{Z})$ be an elicited fixed upper limit on $\pi_D(d, \boldsymbol{Z}, \boldsymbol{\theta})$ for subgroup $\boldsymbol{Z}$, and let $p_{D,1}$ be a fixed cut-off probability. At trial time t, if

$$\Pr\{\pi_D(d, \boldsymbol{Z}, \boldsymbol{\theta}) > \bar{\pi}_D(\boldsymbol{Z}) \mid \mathcal{D}_{n(t)}\} \ > \ p_{D,1} \tag{6}$$

then d is considered unsafe for subgroup $\boldsymbol{Z}$, and is no longer administered to patients in that subgroup. Elicited values of $\bar{\pi}_D(\boldsymbol{Z})$ are given in Table 3. To obtain a design with high subgroup-specific probabilities of stopping a truly unsafe dose and selecting the best safe dose for each $\boldsymbol{Z}$, we investigated cut-offs 0.80 and 0.90, and chose $p_{D,1} = 0.80$.

The design is defined in terms of possible actions $\mathcal{A} = \{0, 1, 2, 3\}$, where any $d \geq 1$ is a dose and $d = 0$ is the action to not administer any NK cells. Let $\mathcal{A}(\boldsymbol{Z}, \mathcal{D}_{n(t)})$ be the subset of acceptable actions for a patient with covariates $\boldsymbol{Z}$ at trial time t based on interim data $\mathcal{D}_{n(t)}$. If no doses are safe for $\boldsymbol{Z}$, i.e. $\mathcal{A}(\boldsymbol{Z}, \mathcal{D}_{n(t)}) = \{0\}$, then no patient in subgroup $\boldsymbol{Z}$ is treated. The acceptable dose sets $\mathcal{A}(\boldsymbol{Z}_1, \mathcal{D}_{n(t)})$ and $\mathcal{A}(\boldsymbol{Z}_2, \mathcal{D}_{n(t)})$ may differ for $\boldsymbol{Z}_1 \neq \boldsymbol{Z}_2$ at

time t during the trial, and these sets may change adaptively as data accumulate.

During trial conduct, for each disease type r, patients are randomized among the three doses in order of entry to the trial by randomly permuting the integers $(1, 2, 3)$. Safety monitoring is begun for each disease type r when nine patients have been enrolled in r and at least five of the nine have died or been followed for 100 days. For each disease type r, we define action sets, $\mathcal{A}((0, r), t)$ and $\mathcal{A}((1, r), t)$, for the two disease bulk subgroups. E.g., suppose the initial permuted dose blocks are $(3, 1, 2)$, for $r = 1$, $(3, 2, 1)$ for $r = 2$, and $(2, 1, 3)$ for $r = 3$. Once safety monitoring is begun, unsafe doses are eliminated from each block adaptively. For example, if the design gives doses $(3, 1, 2)$ for a cohort with disease type r, the following two possible cases illustrate details of trial conduct.

1. Suppose the first patient in the cohort has $\boldsymbol{Z} = (0, r)$. We first update $\mathcal{A}((0, r), t)$. If the updated $\mathcal{A}((0, r), t) = \{0\}$, i.e. no dose is safe for this subgroup, we do not give any NK cells to the patient. If $3 \in \mathcal{A}(\boldsymbol{Z}, t)$, the patient is treated at $d = 3$. If not, we move on to a dose in the permutation that has not been used and is safe for $\boldsymbol{Z}$.

2. Suppose $d = 3$ is given to the previous patient in the cohort, and the next patient in the cohort has $\boldsymbol{Z} = (1, r)$. We update $\mathcal{A}(1, r)$ based on the most recent data. If $\mathcal{A}((1, r), t) = \{0\}$, we do not give any NK cells to the patient. If $1 \in \mathcal{A}((1, r), t)$, then we give $d = 1$ to the patient. If not, we proceed to $d = 2$. If $d = 2$ is not safe, then $d = 3$ is the only safe dose for $\boldsymbol{Z} = (1, r)$, since all doses in $(3, 1, 2)$ have been used. A new cohort is started by randomly permuting (1, 2, 3). Suppose this gives $(1, 3, 2)$. Since $d = 1$ must be skipped since it is not safe, $d = 3$ is given to the patient. At this point, only $d = 2$ is left in that block for the next patient with disease type r.

An additional rule imposed by a regulatory agency also is included. The regulator required a safety rule that ignores $\boldsymbol{Z}$ and stops the trial if the probability of death within 30 days at $d = 1$ is too high. To comply with this requirement, we formulated a sim-

plified model for this safety rule only, assuming $\delta_D(30) \mid q_D \sim \text{Ber}(q_D)$, where $q_D(30) = \Pr(Y_D < 100 \mid d = 1)$ for all $\boldsymbol{Z}$, and $q_D \sim \text{Be}(0.4, 0.6)$ *a priori*. If $\Pr(q_D > .40 \mid \mathcal{D}_{n(t)}) > .90$, then this rule stops the trial and concludes that no dose is safe for any patient. Thus, the trial can be stopped either by the regulator's rule or the subgroup-specific safety rules.

To determine a final optimal action for each $\boldsymbol{Z}$ when $N_{\max} = 60$ at $T_{\max}$, we identify $\mathcal{A}(\boldsymbol{Z}, T_{\max})$ using the safety rule in (6). If $\mathcal{A}(\boldsymbol{Z}, T_{\max}) = \{0\}$, then no dose is selected for $\boldsymbol{Z}$, denoted by $d_{\text{sel}}(\boldsymbol{Z}) = 0$. If $\mathcal{A}(\boldsymbol{Z}, T_{\max}) \neq \{0\}$, then the selected optimal dose is

$$d_{\text{sel}}(\boldsymbol{Z}) = \arg \max_{d \in \mathcal{A}(\boldsymbol{Z}, T_{\max})} u(d, \boldsymbol{Z} \mid \mathcal{D}_{N_{\max}}).$$

5 Simulation Study

5.1 Simulation Design

We simulated the NK cell trial under six scenarios to evaluate the design's performance. For Scenario 1, we used the prior occurrence probabilities $\{\pi^{(e)}_{j,Z,r}\}$ elicited from the clinicians in Table 1 to simulate data, with fixed "true" parameter values α_j^{TR} and $\bar{\lambda}^{\text{TR}}_{j,Z,r,d}$ determined by solving the equations

$$\pi^{(e)}_{j,Z,r} = 1 - S(L'_j \mid \alpha_j^{\text{TR}}, \bar{\lambda}^{\text{TR}}_{j,Z,r,d}) = 1 - \exp\{-\exp(\bar{\lambda}^{\text{TR}}_{j,Z,r,d})(L'_j)^{\alpha_j^{\text{TR}}}\} \tag{7}$$

for (j, Z, r). In Scenario 1, we assumed dose has no effect, with the same $\bar{\lambda}^{\text{TR}}_{j,Z,r,d}$ for all d and no regression relationship in (2) for $\bar{\lambda}^{\text{TR}}$. We simulated data from the Weibull distribution,

$$y_{i,j} \mid \alpha_j^{\text{TR}}, \bar{\lambda}^{\text{TR}}_{j,Z_{1i},r_i,d_i}, u^{\text{TR}}_{i,j} \overset{indep}{\sim} \text{Weibull}(\alpha_j^{\text{TR}}, \exp(\bar{\lambda}^{\text{TR}}_{j,Z_{1i},r_i,d_i} + u^{\text{TR}}_{i,j})),$$

where $\boldsymbol{u}_i^{\text{TR}} \overset{iid}{\sim} \text{N}_5(\boldsymbol{0}, \Omega^{\text{TR}})$, with $\Omega_{j,j}^{\text{TR}} = 0.001$, $\Omega_{j,R}^{\text{TR}} = -0.5 \times 0.001$, $j \neq R$ and $\Omega_{j,j'}^{\text{TR}} = 0.5 \times 0.001$, $j \neq j'$, $j, j' \neq R$. For Scenarios 2–6, we assumed the same Ω^{TR} and specified $\boldsymbol{\alpha}^{\text{TR}}$ and true marginal probability of death by $L'_D = 100$ for LBD ($Z = 0$), disease type r and dose d, $\pi_{D,0,r,d}^{\text{TR}} = \Pr(Y_D \leq L'_D \mid d, Z = 0, r)$. The survival function in (7) with α_D^{TR} and $\pi_{D,0,r,d}^{\text{TR}}$ gives $\bar{\lambda}_{D,0,r,d}^{\text{TR}}$. For subgroups with $Z = 1$ and the other outcomes, we specified $\bar{\xi}_j^{\text{TR}}$ and simulated $\xi_{j,r,d}^{\text{TR}} \overset{indep}{\sim} \text{N}(\bar{\xi}_j^{\text{TR}}, 0.01^2)$ for all combinations of (j, r, d) with $\xi_{D,r,d}^{\text{TR}} = 1$. Similarly, we specified $\bar{\beta}_j^{\text{TR}}$ and simulated $\beta_{j,r,d}^{\text{TR}} \overset{indep}{\sim} \text{N}(\bar{\beta}_j^{\text{TR}}, 0.01^2)$, $j = P, R$, and $\log(\beta_{j,r,d}^{\text{TR}}) \overset{indep}{\sim} \text{N}(\log(\bar{\beta}_j^{\text{TR}}), 0.05^2)$, $j = T, C, D$, to ensure that $\beta_{j,r,d}^{\text{TR}} > 0$ for adverse outcomes. We set $\bar{\lambda}_{j,Z,r,d}^{\text{TR}} = \beta_{j,r,d}^{\text{TR}} Z + \xi_{j,r,d}^{\text{TR}} \psi_{D,r,d}^{\text{TR}}$ and $\lambda_{i,j}^{\text{TR}} = \bar{\lambda}_{j,Z_i,r_i,d_i}^{\text{TR}} + u_{i,j}^{\text{TR}}$. We generated event time $Y_{i,j}$ for a patient with $\boldsymbol{Z}_i$ from Weibull$(\alpha_j^{\text{TR}}, \lambda_{i,j}^{\text{TR}})$. Under the model assumed for the simulation truth, β^{TR} and ξ^{TR} are indexed by j, r and d. This more complex model includes the design's assumed Weibull model as a special case by letting $\beta_{j,r,d}^{\text{TR}} = \beta_j$ and $\xi_{j,r,d}^{\text{TR}} = \xi_j$ for all (r, d). The assumed true probabilities of death, $\pi_{D,Z,r,d}^{\text{TR}}$ for each (Z, r, d), are shown on the first lines of the simulation scenario boxes in Table 3, with the probabilities exceeding the subgroup-specific upper limits $\bar{\pi}_D(\boldsymbol{Z})$ marked in grey. The second lines give the true expected utilities $\bar{U}^{\text{TR}}$ for each $(\boldsymbol{Z}, d)$, and the maximum utility for each $\boldsymbol{Z}$ is underlined. For example, all doses are safe for all $\boldsymbol{Z}$ under Scenario 1, while all doses unsafe for all $\boldsymbol{Z}$ under Scenario 3. Under Scenario 1, all doses are equally good, while under Scenarios 2, 4, 5, and 6, the optimal safe doses vary with $\boldsymbol{Z}$ and using patient subgroup information is critical. Under Scenario 4, doses 2 and 1 are optimal for patients with $Z = 0$ and $Z = 1$, respectively, regardless of r. Under Scenario 5, the optimal doses vary with disease type r but not with disease bulk Z. Under Scenario 6, the true mean utilities vary with (d, Z, r), and the set of acceptable doses varies with $\boldsymbol{Z}$. Values of $\boldsymbol{\alpha}^{\text{TR}}$, $\bar{\boldsymbol{\beta}}^{\text{TR}}$, $\bar{\boldsymbol{\xi}}^{\text{TR}}$ assumed for the scenarios are given in Supplementary Table 2. A total of $M = 1000$ trials were simulated under each scenario.

We examined the design's robustness by simulating the $Y_{i,j}$'s from a log-logistic distribution. To obtain fair comparisons, in each scenario, given $\pi_{j,Z,r,d}^{\text{TR}}$ values under the Weibull

distribution we solved for true parameter values under the log-logistic distribution by matching the $\pi^{\text{TR}}_{j,Z,r,d}$'s, so the marginal probabilities of occurrence during follow-up were identical for the two models, and truly unsafe doses remained unsafe regardless of the assumed true model used to simulate the data. In contrast, the rates of occurrence over time under the two models necessarily differed, which caused the mean utilities to change, due to P and R being competing risks and the semi-competing risks structure between D and the other outcomes on $\mathcal{Y}_D$. The true mean utilities under the log-logistic are given in Supplementary Table 6. Most differences in true mean utilities are minor, although in some cases there are non-trivial differences. For example, under the Weibull distribution $d = 1$ clearly is optimal for $Z = 1$ in Scenario 4, but under the log-logistic distribution differences between expected utilities for the three doses are much smaller. Details of the simulation design are given in Supplementary §3.

As a comparator, we considered a simplified version of the design that does not use covariates or make subgroup-specific inferences. For this design, we assumed a simpler model ignoring $\boldsymbol{Z}$ but still accounting for the five event times and their competing risks and semi-competing risks relationships. This model assumes each $Y_{i,j} \mid \alpha'_j, \lambda'_{i,j} \overset{indep}{\sim} \text{Weibull}(\alpha'_j, \exp(\lambda'_{i,j}))$, where $\lambda'_{i,j} = \xi'_j \psi'_{d_i} + u'_{i,j}$ with $\xi'_D = 1$ and $\boldsymbol{u}'_i \overset{iid}{\sim} \text{N}_5(\boldsymbol{0}, \Omega)$. Similar to the full model, for the simpler model we assumed a gamma prior for α'_j, normal priors for ξ'_j and ψ'_d and an inverse Wishart prior for Ω. Under the simpler design, we defined $\mathcal{A}(t)$ as a function of t only, so if a dose was declared unsafe this pertained to all patients. A similar randomization with blocks of size $m = 3$ was used for allocating patients to doses in $\mathcal{A}(t)$, and a dose d was declared unsafe if $\Pr(\pi'_D(d, \boldsymbol{\theta}') > .25 \mid \mathcal{D}_{n(t)}) > .80$, where $\pi'_D(d, \boldsymbol{\theta}')$ is the probability of death by L'_D with d and $\boldsymbol{\theta}' = (\boldsymbol{\alpha}', \boldsymbol{\psi}', \boldsymbol{\xi}')$. Fixed prior hyperparameters under the simpler model were specified, by using the elicited probabilities in Table 1, but ignoring any effects of $\boldsymbol{Z}$. Posterior mean utility, for each d but ignoring $\boldsymbol{Z}$, was used as a criterion to choose an optimal dose for any future patient.

We evaluated the designs using two criteria, the probabilities of identifying doses with truly excessive probabilities of death and of selecting the true optimal safe dose for each $\boldsymbol{Z}$. For each simulated trial $\ell = 1, \ldots, M$, and each $\boldsymbol{Z}$, each design selects a dose $d_{\text{sel},\ell}(\boldsymbol{Z})$, with $d_{\text{sel},\ell}(\boldsymbol{Z}) \equiv d_{\text{sel},\ell}$ for all $\boldsymbol{Z}$ under the simpler design. We let $\kappa_{1,\ell}(d, \boldsymbol{Z}) = 1$ if dose d is identified as unsafe for a patient with $\boldsymbol{Z}$ in simulated trial ℓ, or 0 if not. We let $\kappa_{2,\ell} = 1$ if trial ℓ is not terminated by the regulator's safety rule, and 0 otherwise. For $\mathrm{I}(\cdot)$ the indicator function, we summarized simulation results using the empirical proportions among trials not stopped by the regulator's safety rule, given for each d and $\boldsymbol{Z}$ by

$$\Pr(\text{Stop} \mid d, \boldsymbol{Z}) = \frac{\sum_{\ell=1}^{M} \kappa_{2,\ell}\kappa_{1,\ell}(d, \boldsymbol{Z})}{\sum_{\ell=1}^{M} \kappa_{2,\ell}} \quad \text{and} \quad \Pr(\text{Select} \mid d, \boldsymbol{Z}) = \frac{\sum_{\ell=1}^{M} \kappa_{2,\ell}\mathrm{I}(d = d_{\text{sel},\ell}(\boldsymbol{Z}))}{\sum_{\ell=1}^{M} \kappa_{2,\ell}}.$$

5.2 Simulation Results

Simulation results are summarized in Table 3, including the simulation truth to facilitate evaluation, with $\Pr(\text{Stop} \mid d, \boldsymbol{Z})$ and $\Pr(\text{Select} \mid d, \boldsymbol{Z})$ shown in the third and fourth lines for each $\boldsymbol{Z}$. Overall, the design reliably identifies unsafe doses and selects optimal doses for each subgroup, based on $N_{\max} = 60$. Large $\Pr(\text{Stop} \mid d, \boldsymbol{Z})$ is achieved for $\boldsymbol{Z}$ and d with large π_D^{TR}. When π_D^{TR} is clearly greater than $\bar{\pi}_D(\boldsymbol{Z})$, $\Pr(\text{Stop} \mid d, \boldsymbol{Z})$ is particularly high, such as in the cases with $r = 1$ in Scenario 3. Cases where $\pi_{D,Z,r}^{\text{TR}}$ is slightly greater than $\bar{\pi}_D(\boldsymbol{Z})$ tend not to achieve high $\Pr(\text{Stop} \mid d, \boldsymbol{Z})$, in part due to the small sub-sample size per subgroup. The design makes more accurate decisions for $Z = 1$ compared to $Z = 0$, due to the prevalences $\Pr(Z = 1) = 2/3$ and $\Pr(Z = 0) = 1/3$. For example, in Scenario 3, π_D^{TR} exceeds $\bar{\pi}_D$ by approximately the same difference for $\boldsymbol{Z} = (0, 1)$ and $\boldsymbol{Z} = (1, 1)$, but Pr(Stop) is much larger for $\boldsymbol{Z} = (1, 1)$ due to there being more data on HBD patients ($Z = 1$). Truly optimal safe doses have large $\Pr(\text{Select} \mid d, \boldsymbol{Z})$, shown on the fourth lines for each $\boldsymbol{Z}$ in the table. In Scenario 1, doses have the same true expected utilities for each $\boldsymbol{Z}$, and doses are selected with almost equal probabilities for all (Z, r). When there are clearly optimal doses,

as in Scenario 2, the design has large Pr(Select | $d, \boldsymbol{Z}$) for those doses. When two doses have similar expected utilities, such as cases with $Z = 0$ in Scenario 6, the design selects both doses with large Pr(Select | $d, \boldsymbol{Z}$). When no dose is safe, as in Scenario 3, Pr(Select | $d, \boldsymbol{Z}$) is small for all d. Scenario 6 is complex in that the pattern of the true utilities varies with both Z and r. The design captures this pattern well and makes correct decisions with high probabilities.

The proportions of patients treated in trials for each dose and subgroup are summarized in Supplementary Table 5, showing the design reliably identifies unsafe doses for each subgroup and assigns fewer patients to doses declared unsafe. If all doses are identified as safe for a subgroup, patients in the subgroup will be assigned to a dose at random, as in Scenario 1. Proportions of trials terminated by the regulator's safety rule are summarized in Supplementary Table 7. The regulator's safety rule rarely terminates the trial, even for Scenario 3 where π_D^{TR} exceeds $\bar{q}_D$ for all $\boldsymbol{Z}$. This is because, under Scenario 3, a trial is terminated earlier by the subgroup-specific safety rule since all doses are unsafe for all subgroups. When $d = 1$ is unsafe, it is likely that the subgroup-specific safety rule identifies this and stops further allocation of patients to $d = 1$, so no more deaths occur at $d = 1$. This helps to prevent the regulator's safety rule from incorrectly terminating the entire trial when only $d = 1$ is unsafe, thus continuing accrual for safe doses and improving evaluation of outcomes for those doses.

Stopping and dose selection probabilities under the simpler design that ignores $\boldsymbol{Z}$ are compared to those under the design with subgroup specific decisions in Figure 1 and summarized in Supplementary Tables 3 and 4. Panels (a) and (b) of the figure give histograms of the differences, Pr(Stop | $d, \boldsymbol{Z}$) − Pr(Stop | d), for truly safe doses and unsafe doses, respectively, for all $(d, \boldsymbol{Z})$ and all scenarios. Panel (a) shows that the design accounting for $\boldsymbol{Z}$ often has much smaller Pr(Stop | $d, \boldsymbol{Z}$) for truly safe doses (thus negative differences). This advantage is substantial in cases like Scenario 2, where the true safety of a dose varies greatly

across subgroups, and most doses are unsafe. The histogram in (b) shows that the simpler design often stops truly unsafe doses with higher probability (thus negative differences). This is mainly due to Scenario 3 where all doses are unsafe for all subgroups. However, when a dose is unsafe only for some subgroups, as in Scenarios 4 and 5, the design accounting for $\boldsymbol{Z}$ greatly increases the probability of correctly stopping truly unsafe doses, shown by the large cluster above 0.40. Panel (c) gives the histogram of differences in empirical proportions $\Pr(\text{select} \mid d, \boldsymbol{Z}) - \Pr(\text{select} \mid d)$, for truly optimal doses for all $(d, \boldsymbol{Z})$ across Scenarios 2-6. The design accounting for $\boldsymbol{Z}$ is much more likely to select truly optimal doses (thus many more positive differences). Doses assigned to patients under the simpler design are summarized in Supplementary Table 5. The table shows that when unsafe doses vary between subgroups, as in Scenario 2, more patients are treated at unsafe doses under the simpler design. A detailed discussion is given in Supplementary §4.

Results of the robustness study are summarized in Supplementary Table 6. When data are simulated from the log-logistic distribution, some correct stopping and selection probabilities are decreased under Scenarios 3 and 4 in the LBD subgroups, since $\Pr(\text{LBD}) = 1/3$. In the other cases, differences in the patterns of the hazard functions over time affect the design's performance only slightly. Thus, the design appears to be robust.

To examine how much the design's performance is improved by a larger sample size, we re-ran the simulations using $N_{\max} = 120$. Supplementary Tables 5 and 8 illustrate the results for $N_{\max} = 120$ under all scenarios, showing that subgroup-specific dose assignments are improved (Table 5) and probabilities of correctly stopping unsafe doses and selecting optimal doses are greatly increased for many combinations of $(d, \boldsymbol{Z})$ (Table 8). For example, in Scenario 6, for patients with NHL, $\Pr(\text{Stop} \mid d, \boldsymbol{Z})$ values increase from 0.51 to 0.67 (LBD) and from 0.91 to 0.99 (HBD) for $d = 3$. For subgroups with HBD, the truly optimal doses are selected with higher rates for $N_{\max} = 120$. It thus appears that a larger $N_{\max}$ is highly desirable for designs making subgroup-specific decisions.

We also investigated how the performance of the proposed design changes with shorter follow up, by reducing follow up from $\boldsymbol{L} = (365, 365, 100, 100, 365)$ to $\boldsymbol{L}' = (100, 100, 100, 30, 100)$. The results are summarized in Supplementary Table 9. The design's performance greatly deteriorates with shorter follow up, on average, for both $\Pr(\text{Stop} \mid d, \boldsymbol{Z})$ and $\Pr(\text{Select} \mid d, \boldsymbol{Z})$. For example, the probability that dose 1 is correctly identified as unsafe decreases from 0.76 to 0.53 for (CLL, LBD) in Scenario 6. Thus, incorporating data from patients monitored for a longer period greatly enhances the design's performance.

6 Discussion

We have presented a clinical trial design that does subgroup-specific safety monitoring and dose selection for a clinical trial of NK cells as therapy for severe hematologic diseases. Decisions are based on five time-to-event outcomes by formulating a utility-based dose optimization criterion. Our simulations show that the design performs well under a wide variety of dose-subgroup-outcome scenarios, and that accounting for patient heterogeneity in this setting is very important, since failure to do so is likely to produce a design with extremely large incorrect decision probabilities in many subgroups. The results in Supplementary Table 8 strongly suggest that trials that make subgroup-specific decisions should have larger sample sizes than conventional trials. A general conclusion is that phase I-II designs should do precision medicine and have larger sample sizes than used conventionally.

To apply this methodology if some outcome hazards are known to increase with dose, a monotonicity assumption would be needed, and the block randomization would be replaced by a sequentially adaptive within-subgroup dose assignment procedure. The trial would be more difficult to conduct, since the resulting imbalance in dose-subgroup sample sizes would reduce reliability. If the prevalence for one or more subgroups is very low, the proposed design may not be feasible due to unacceptably small sample sizes for those subgroups.

Thus, it may be more appropriate to exclude rare subgroups.

Our use of five outcomes shows large variability in the elicited utilities of the 12 possible nonfatal elementary events in Table 2. If R were considered to be efficacy and toxicity were defined as any of the four adverse events, this would combine adverse events with utilities ranging from 0 to 70. Thus, our more refined utility structure appears warranted.

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Supplementary Materials

Supplementary materials are available under the Paper Information link at the journal website.

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Disease Bulk	Disease Type	Progression	Response	Severe Toxicity	Death
Low Bulk	CLL ($r = 1$)	0.05	0.20	0.25	0.02
Disease	ALL ($r = 2$)	0.15	0.50	0.25	0.10
($Z = 0$)	NHL ($r = 3$)	0.10	0.35	0.25	0.05
High Bulk	CLL ($r = 1$)	0.20	0.35	0.25	0.10
Disease	ALL ($r = 2$)	0.40	0.60	0.40	0.20
($Z = 1$)	NHL ($r = 3$)	0.40	0.40	0.25	0.15

Table 1: Elicited probabilities $\pi^{(e)}_{j,Z,r}$ provided by the clinicians. The probabilities are used to establish values for fixed prior hyperparameters, $\bar{\psi}$, $\bar{\beta}$, $\bar{\xi}$ and a.

		(δ'_P, δ'_R)		
δ'_C	δ'_T	(1,0)	(0,0)	(0,1)
0	0	20	50	90
	1	10	30	70

		(δ'_P, δ'_R)		
δ'_C	δ'_T	(1,0)	(0,0)	(0,1)
1	0	10	30	70
	1	5	20	50

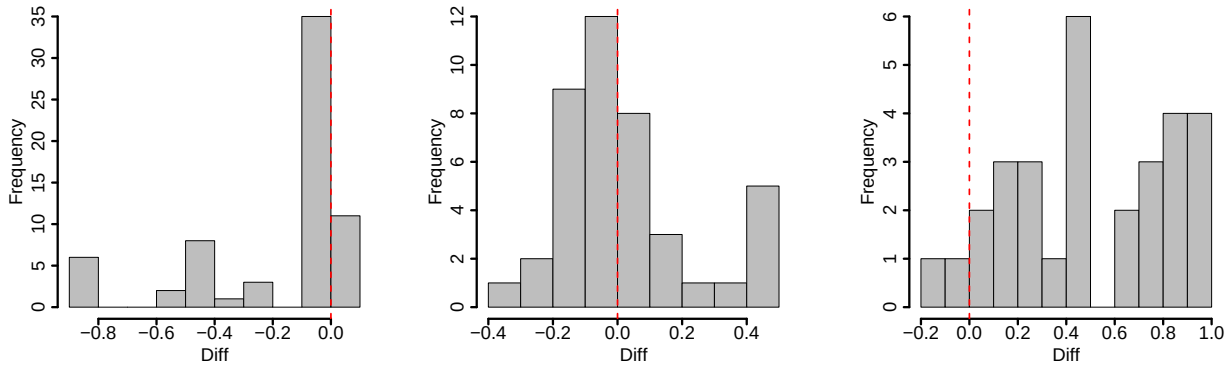
Table 2: Elicited utilities of all possible combinations of discrete outcomes for patients who survive 100 days, $U(\boldsymbol{\delta}')$ for $\boldsymbol{\delta}'$ with $\delta'_D = 0$. For any $\boldsymbol{\delta}'$ with $\delta'_D = 1$, $U(\boldsymbol{\delta}') = 0$. The set Δ of all possible values does not include any $\boldsymbol{\delta}'$ with $(\delta'_P, \delta'_R) = 1(1, 1)$, since P and R are competing risks.

		Bulk ($\rightarrow$)	LBD ($Z=0$)				HBD ($Z=1$)			
	Types ($\downarrow$)	Dose ($\rightarrow$)	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$
Scenario 1	CLL	π_D^{TR}	0.02	0.02	0.02	*0.15*	0.10	0.10	0.10	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	<u>46.32</u>	<u>46.32</u>	<u>46.32</u>		<u>44.04</u>	<u>44.04</u>	<u>44.04</u>	
		Pr(Stop)	0.00	0.00	0.00		0.00	0.00	0.00	
		Pr(Select)	0.33	0.37	0.30		0.33	0.34	0.33	
	ALL	π_D^{TR}	0.10	0.10	0.10	*0.20*	0.25	0.25	0.25	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	<u>50.52</u>	<u>50.52</u>	<u>50.52</u>		<u>37.97</u>	<u>37.97</u>	<u>37.97</u>	
		Pr(Stop)	0.00	0.01	0.00		0.03	0.03	0.02	
		Pr(Select)	0.33	0.35	0.32		0.32	0.36	0.33	
	NHL	π_D^{TR}	0.05	0.05	0.05	*0.20*	0.15	0.15	0.15	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	<u>49.18</u>	<u>49.18</u>	<u>49.18</u>		<u>38.35</u>	<u>38.35</u>	<u>38.35</u>	
		Pr(Stop)	0.00	0.00	0.00		0.00	0.00	0.00	
		Pr(Select)	0.33	0.34	0.33		0.35	0.31	0.34	
Scenario 2	CLL	π_D^{TR}	0.02	0.45	0.60	*0.15*	0.04	0.70	0.84	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	<u>42.34</u>	22.86	16.00		<u>39.73</u>	9.49	4.63	
		Pr(Stop)	0.00	0.89	0.97		0.00	0.98	1.00	
		Pr(Select)	1.00	0.00	0.00		1.00	0.00	0.00	
	ALL	π_D^{TR}	0.40	0.60	0.05	*0.20*	0.64	0.84	0.10	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	23.81	15.82	<u>40.41</u>		10.99	4.62	<u>36.02</u>	
		Pr(Stop)	0.67	0.92	0.00		0.81	0.98	0.00	
		Pr(Select)	0.00	0.00	1.00		0.00	0.00	1.00	
	NHL	π_D^{TR}	0.65	0.05	0.35	*0.20*	0.88	0.10	0.58	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	14.03	<u>40.47</u>	26.31		3.46	<u>36.08</u>	13.26	
		Pr(Stop)	0.95	0.00	0.55		1.00	0.00	0.68	
		Pr(Select)	0.00	1.00	0.00		0.00	1.00	0.00	
Scenario 3	CLL	π_D^{TR}	0.42	0.38	0.37	*0.15*	0.66	0.62	0.60	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	40.33	44.40	<u>44.55</u>		20.71	24.52	<u>24.81</u>	
		Pr(Stop)	0.88	0.85	0.82		0.96	0.95	0.94	
		Pr(Select)	0.07	0.11	0.13		0.03	0.05	0.05	
	ALL	π_D^{TR}	0.52	0.58	0.65	*0.20*	0.77	0.83	0.88	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	<u>33.99</u>	29.43	24.52		<u>14.34</u>	11.01	7.57	
		Pr(Stop)	0.93	0.96	0.98		0.99	0.99	1.00	
		Pr(Select)	0.06	0.03	0.01		0.01	0.01	0.00	
	NHL	π_D^{TR}	0.40	0.42	0.45	*0.20*	0.64	0.67	0.70	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	<u>42.49</u>	40.21	38.79		<u>22.61</u>	20.32	18.95	
		Pr(Stop)	0.73	0.77	0.84		0.85	0.87	0.94	
		Pr(Select)	0.19	0.16	0.07		0.12	0.11	0.04	

Table 3: **Simulation Truth and Results**. π_D^{TR} = true probability of death within 100 days for each combination of disease type (r), dose level (d), disease bulk (Z), with $\bar{\pi}(\boldsymbol{Z})$ = the fixed safety threshold. Unsafe doses are given in grey. $\bar{U}^{\text{TR}}$ = true expected utility for each (r, d, Z). Optimal doses are underlined.

		Bulk ($\rightarrow$)	LBD ($Z=0$)				HBD ($Z=1$)			
	Types ($\downarrow$)	Dose ($\rightarrow$)	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$
Scenario 4	CLL	π_D^{TR}	0.01	0.10	0.25	*0.15*	0.01	0.11	0.27	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	48.99	58.91	45.84		38.03	24.74	14.45	
		Pr(Stop)	0.00	0.00	0.26		0.00	0.00	0.13	
		Pr(Select)	0.04	0.95	0.01		1.00	0.00	0.00	
	ALL	π_D^{TR}	0.01	0.09	0.27	*0.20*	0.01	0.10	0.29	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	48.82	58.66	43.95		37.54	26.47	14.55	
		Pr(Stop)	0.00	0.00	0.14		0.00	0.00	0.05	
		Pr(Select)	0.02	0.98	0.00		1.00	0.00	0.00	
	NHL	π_D^{TR}	0.01	0.08	0.30	*0.20*	0.01	0.09	0.33	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	48.87	58.22	40.45		40.28	26.92	11.70	
		Pr(Stop)	0.00	0.00	0.29		0.00	0.00	0.12	
		Pr(Select)	0.01	0.99	0.00		1.00	0.00	0.00	
Scenario 5	CLL	π_D^{TR}	0.01	0.09	0.30	*0.15*	0.01	0.12	0.38	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	44.30	33.82	22.05		41.40	27.18	14.33	
		Pr(Stop)	0.00	0.00	0.48		0.00	0.00	0.44	
		Pr(Select)	1.00	0.00	0.00		1.00	0.00	0.00	
	ALL	π_D^{TR}	0.12	0.03	0.18	*0.20*	0.16	0.04	0.23	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	30.68	40.15	27.96		23.62	35.88	20.52	
		Pr(Stop)	0.00	0.00	0.02		0.00	0.00	0.01	
		Pr(Select)	0.00	1.00	0.00		0.00	0.99	0.00	
	NHL	π_D^{TR}	0.10	0.15	0.01	*0.20*	0.13	0.20	0.01	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	32.73	28.73	44.09		26.24	21.60	41.22	
		Pr(Stop)	0.00	0.01	0.00		0.00	0.00	0.00	
		Pr(Select)	0.00	0.00	1.00		0.00	0.00	1.00	
Scenario 6	CLL	π_D^{TR}	0.35	0.03	0.13	*0.15*	0.75	0.10	0.37	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	41.74	59.80	57.69		14.53	55.48	40.90	
		Pr(Stop)	0.76	0.00	0.09		0.99	0.00	0.34	
		Pr(Select)	0.00	0.56	0.44		0.00	0.99	0.01	
	ALL	π_D^{TR}	0.08	0.45	0.02	*0.20*	0.24	0.86	0.06	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	57.75	34.95	57.83		47.19	7.81	55.07	
		Pr(Stop)	0.00	0.82	0.00		0.02	0.99	0.00	
		Pr(Select)	0.80	0.00	0.20		0.04	0.00	0.96	
	NHL	π_D^{TR}	0.05	0.10	0.30	*0.20*	0.16	0.29	0.70	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	59.50	57.18	46.28		52.57	44.10	18.84	
		Pr(Stop)	0.00	0.01	0.51		0.00	0.03	0.91	
		Pr(Select)	0.53	0.47	0.01		0.89	0.11	0.00	

Table 3 (continued): **Simulation Truth and Results.** π_D^{TR} = true probability of death within 100 days for each combination of disease type (r), dose level (d), disease bulk (Z), with $\bar{\pi}(\boldsymbol{Z})$ = the fixed safety threshold. Unsafe doses are given in grey. $\bar{U}^{\text{TR}}$ = true expected utility for each (r, d, Z). Optimal doses are underlined.



(a) $\Pr(\text{Stop} \mid d, \boldsymbol{Z}) - \Pr(\text{Stop} \mid d)$ for truly safe doses

(b) $\Pr(\text{Stop} \mid d, \boldsymbol{Z}) - \Pr(\text{Stop} \mid d)$ for truly unsafe doses

(c) $\Pr(\text{Select} \mid d, \boldsymbol{Z}) - \Pr(\text{Select} \mid d)$ for truly optimal doses

Figure 1: Comparison to the simpler design ignoring subgroups ($\boldsymbol{Z}$): Panels (a) and (b) give histograms of differences in empirical proportions $\Pr(\text{Stop} \mid d, \boldsymbol{Z}) - \Pr(\text{Stop} \mid d)$ for truly safe doses and unsafe doses, respectively, for all $(d, \boldsymbol{Z})$ and all scenarios. Panel (c) gives the histogram of differences in empirical proportions of correctly selecting a truly optimal dose, $\Pr(\text{Select} \mid d, \boldsymbol{Z}) - \Pr(\text{Select} \mid d)$ for all $\boldsymbol{Z}$ and all scenarios.

Supplementary Materials: Optimizing Natural Killer Cell Doses for Heterogeneous Cancer Patients Based on Multiple Event Times

1 Posterior Computation

Recall that we denote the random parameter vector $\boldsymbol{\theta} = (\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\xi}, \boldsymbol{\psi}, \Omega)$ and the fixed hyperparameter vector $\boldsymbol{\theta}^* = (\boldsymbol{a}, \boldsymbol{b}, \bar{\boldsymbol{\xi}}, \boldsymbol{\omega}^2, \bar{\boldsymbol{\psi}}, \boldsymbol{\tau}^2, \bar{\boldsymbol{\beta}}, \boldsymbol{\sigma}^2, \nu, \Omega^0)$. We use the Markov chain Monte Carlo (MCMC) simulation to draw a sample of $\boldsymbol{\theta}$ values and patient random effects $\boldsymbol{u}$ from the following posterior distribution.

$$\begin{aligned} p(\boldsymbol{\theta}, \boldsymbol{u} \mid \mathcal{D}_{n(t)}) &\propto \prod_{i=1}^{n(t)} p(\boldsymbol{y}_i^o, \boldsymbol{\delta}_i \mid \boldsymbol{\theta}, \boldsymbol{u}_i) p(\boldsymbol{\theta}, \boldsymbol{u}) \\ &= \prod_{i=1}^{n(t)} \prod_{j \in \{P, \ldots, D\}} \left(h_j(y_{i,j}^o \mid \alpha_j, \lambda_{i,j})\right)^{\delta_{i,j}(t)} S_j(y_{i,j}^o \mid \alpha_j, \lambda_{i,j}) p(\boldsymbol{\theta}, \boldsymbol{u}), \end{aligned}$$

where $\mathcal{D}_{n(t)}$ denotes data of $n(t)$ patients at trial time t, $\{\boldsymbol{Z}_i, \boldsymbol{y}_i^o, \boldsymbol{\delta}_i\}_{i=1}^{n(t)}$. Recall that patient i has covariate $\boldsymbol{Z}_i = (Z_i, r_i)$ and treatment at dose d_i. The parameters are estimated by iteratively drawing samples from the full conditional distributions given the data and the other parameters. Recall that $\lambda_{i,j} = \beta_j Z_i + \xi_j \psi_{r_i, d_i} + u_{i,j}$.

1. Full conditional of β_j

Let $\boldsymbol{\theta}_{-\beta_j}$ denote the vector of all random parameters, excluding β_j. For $j \in \{P, R, T, C, D\}$,

$$\begin{aligned} p(\beta_j \mid \mathcal{D}_{n(t)}, \boldsymbol{u}, \boldsymbol{\theta}_{-\beta_j}) &\propto \prod_{i=1}^{n(t)} \{f(y_{i,j}^o(t) \mid \boldsymbol{\theta}, \boldsymbol{u}_i, d_i, \boldsymbol{Z}_i)\}^{\delta_{i,j}(t)} \{S(y_{i,j}^o(t) \mid \boldsymbol{\theta}, \boldsymbol{u}_i, d_i, \boldsymbol{Z}_i)\}^{1-\delta_{i,j}(t)} \\ &\quad \times p(\beta_j \mid \bar{\beta}_j, \sigma_j^2) \\ &\propto \exp\left[\sum_{i=1}^{n(t)} \left\{\delta_{i,j}(t)\lambda_{i,j} - \exp(\lambda_{i,j})(y_{i,j}^o(t))^{\alpha_j}\right\}\right] \exp\left\{-\frac{(\beta_j - \bar{\beta}_j)^2}{2\sigma_j^2}\right\}. \end{aligned}$$

Let $\boldsymbol{\theta}_{-\psi_{r,d}}$ denote the vector of all random parameters, excluding $\psi_{r,d}$. For $r = 1, \ldots, K$ and $d = 1, \ldots, m$,

$$\begin{aligned} p(\psi_{r,d} \mid \mathcal{D}_{n(t)}, \boldsymbol{u}, \boldsymbol{\theta}_{-\psi_{r,d}}) &\propto \prod_{i=1 \mid d_i=d, r_i=r}^{n(t)} \prod_j \{f(y_{i,j}^o(t) \mid \boldsymbol{\theta}, \boldsymbol{u}_i, d_i, \boldsymbol{Z}_i)\}^{\delta_{i,j}(t)} \{S(y_{i,j}^o(t) \mid \boldsymbol{\theta}, \boldsymbol{u}_i, d_i, \boldsymbol{Z}_i)\}^{1-\delta_{i,j}(t)} \\ &\quad \times p(\psi_{r,d} \mid \bar{\psi}, \tau^2) \\ &\propto \exp\left[\sum_{i=1 \mid d_i=d, r_i=r}^{n(t)} \prod_j \left\{\delta_{i,j}(t)\lambda_{i,j} - \exp(\lambda_{i,j})(y_{i,j}^o(t))^{\alpha_j}\right\}\right] \times \exp\left\{-\frac{(\psi_{r,d} - \bar{\psi})^2}{2\tau^2}\right\}, \end{aligned}$$

.

2. Full conditional of ξ_j

   Let $\boldsymbol{\theta}_{-\xi_j}$ denote a vector of all random parameters, excluding ξ_j. For $j \in \{P, R, T, C\}$,

$$\begin{aligned} p(\xi_j \mid \mathcal{D}_{n(t)}, \boldsymbol{u}, \boldsymbol{\theta}_{-\xi_j}) &\propto \prod_{i=1}^{n(t)} \{f(y_{i,j}^o(t) \mid \boldsymbol{\theta}, \boldsymbol{u}_i, d_i, \boldsymbol{Z}_i)\}^{\delta_{i,j}(t)} \{S(y_{i,j}^o(t) \mid \boldsymbol{\theta}, \boldsymbol{u}_i, d_i, \boldsymbol{Z}_i)\}^{1-\delta_{i,j}(t)} \\ &\quad \times p(\xi_j \mid \bar{\xi}_j, w_j^2) \\ &\propto \exp\left[\sum_{i=1}^{n(t)} \left\{\delta_{i,j}(t)\lambda_{i,j} - \exp(\lambda_{i,j})(y_{i,j}^o(t))^{\alpha_j}\right\}\right] \times \exp\left\{-\frac{(\xi_j - \bar{\xi}_j)^2}{2w_j^2}\right\}, \end{aligned}$$

   .

3. Full conditional of α_j

Let $\boldsymbol{\theta}_{-\alpha_j}$ denote a vector of all random parameters, excluding α_j. For $j \in \{P, R, T, C, D\}$,

$$\begin{aligned} p(\alpha_j \mid \mathcal{D}_{n(t)}, \boldsymbol{u}, \boldsymbol{\theta}_{-\alpha_j}) &\propto \prod_{i=1}^{n(t)} \{f(y^o_{i,j}(t) \mid \boldsymbol{\theta}, \boldsymbol{u}_i, d_i, \boldsymbol{Z}_i)\}^{\delta_{i,j}(t)} \{S(y^o_{i,j}(t) \mid \boldsymbol{\theta}, \boldsymbol{u}_i, d_i, \boldsymbol{Z}_i)\}^{1-\delta_{i,j}(t)} \\ &\quad \times p(\alpha_j \mid a_j, b_j) \\ &\propto \alpha_j^{\sum_i \delta_{i,j}(t)} \exp\left[\sum_{i=1}^{n(t)} \left\{\delta_{i,j}(t)(\alpha_j - 1)\log(y^o_{i,j}(t)) - \exp(\lambda_{i,j})(y^o_{i,j}(t))^{\alpha_j}\right\}\right] \\ &\quad \times \alpha_j^{a_j - 1} \exp(-b_j \alpha_j), \end{aligned}$$

.

4. Full conditional of $\boldsymbol{u}_i$

   For $i = 1, \ldots, n(t)$,

$$\begin{aligned} p(\boldsymbol{u}_i \mid \mathcal{D}_{n(t)}, \boldsymbol{\theta}) &\propto \prod_{j \in \{P,R,T,C,D\}} \{f(y^o_{i,j}(t) \mid \boldsymbol{\theta}, \boldsymbol{u}_i, d_i, \boldsymbol{Z}_i)\}^{\delta_{i,j}(t)} \{S(y^o_{i,j}(t) \mid \boldsymbol{\theta}, \boldsymbol{u}_i, d_i, \boldsymbol{Z}_i)\}^{1-\delta_{i,j}(t)} \\ &\quad \times p(\boldsymbol{u}_i \mid \Omega) \\ &\propto \exp\left[\sum_{j \in \{P,R,T,C,D\}} \left\{\delta_{i,j}(t)\lambda_{i,D}(t) - \exp(\lambda_{i,j})(y^o_{i,j}(t))^{\alpha_j}\right\}\right] \\ &\quad \times \exp\left\{-\frac{1}{2}\boldsymbol{u}_i' \Omega^{-1} \boldsymbol{u}_i\right\}, \end{aligned}$$

.

5. Full conditional of Ω

$$\begin{aligned} p(\Omega \mid \mathcal{D}_{n(t)}, \boldsymbol{\theta}) &\propto \prod_{i=1}^{n(t)} p(\boldsymbol{u}_i \mid \Omega) p(\Omega \mid \nu, \Omega^0) \\ &\propto \prod_{i=1}^{n(t)} |\Omega|^{-1/2} \exp\left(-\frac{1}{2}\boldsymbol{u}_i' \Omega^{-1} \boldsymbol{u}_i\right) |\Omega|^{\frac{\nu+J+1}{2}} \exp\left\{-\frac{1}{2} tr(\Omega^0 \Omega^{-1})\right\}. \end{aligned}$$

Thus, the full conditional distribution is $\Omega \sim$ inverse-Wishart$(\nu + n(t), \Omega^0 + \sum_{i=1}^{n(t)} \boldsymbol{u}_i \boldsymbol{u}_i')$.

We generate a posterior sample of $\boldsymbol{\theta}$ values through posterior MCMC simulation and use it to evaluate quantities needed for decisions in the trial, such as criteria for selecting an optimal

dose and declaring a dose unsafe. For selecting an optimal dose, we proceed as follows: We generate a Mote Carlo sample according to $\boldsymbol{\theta} \sim p(\boldsymbol{\theta} \mid \mathcal{D}_{N_{\max}}, \boldsymbol{\theta}^*)$, where $\mathcal{D}_{N_{\max}}$ is the final data from the trial and $\boldsymbol{\theta}^*$ fixed hyperparameters, and evaluate the posterior predictive mean utility of dose d for each $\boldsymbol{Z}$ $u(d, \boldsymbol{Z} \mid \mathcal{D}_{N_{\max}})$ in (5) of the main text using the sample. It may appear that numerical computation of $u(d, \boldsymbol{Z} \mid \mathcal{D}_{N_{\max}})$ is prohibitively difficult, since it is defined in terms of $\bar{U}(d, \boldsymbol{Z}, \boldsymbol{\theta})$ in (4) of the main text, which requires evaluation of a 10-dimensional integral to obtain each $\pi(\boldsymbol{\delta} \mid d, \boldsymbol{Z}, \boldsymbol{\theta})$. Once the posterior sample has been obtained, however, computation of $u(d, \boldsymbol{Z} \mid \mathcal{D}_{N_{\max}})$ for each d and $\boldsymbol{Z}$ is straightforward, using the following algorithm. Denote the posterior sample from the MCMC simulation by $\{\boldsymbol{\theta}^{(q)}$, $q = 1, \ldots, Q\}$. For each d and $\boldsymbol{Z}$, the computation proceeds as follows:

1. For each $q = 1, \ldots, Q$ and $m = 1, \ldots, M$
   (a) Simulate $\boldsymbol{u}^{(q,m)}$ from $p(\boldsymbol{u} \mid \boldsymbol{\theta}^{(q)})$.
   (b) Simulate $\boldsymbol{y}^{(q,m)}$ from $p(\boldsymbol{y} \mid d, \boldsymbol{Z}, \boldsymbol{u}^{(q,m)}, \boldsymbol{\theta}^{(q)})$.
   (c) Determine $\boldsymbol{\delta}^{(q,m)}$ from $\boldsymbol{y}^{(q,m)}$ and evaluate $U(\boldsymbol{\delta}^{(q,m)})$.
2. Use sample the mean $\frac{1}{QM} \sum_{q=1}^{Q} \sum_{m=1}^{M} U(\boldsymbol{\delta}^{(q,m)})$ to estimate $u(d, \boldsymbol{Z} \mid \mathcal{D}_{N_{\max}})$.

The values $Q = 5000$ and $M = 5$ are used for our simulation study in §5 of the main text.

2 Computing Prior Hyperparameters

Recall that $\boldsymbol{\theta}$ and $\boldsymbol{\theta}^*$ denote random model parameters and fixed hyper-parameters, respectively, where $\boldsymbol{\theta} = (\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\xi}, \boldsymbol{\psi}, \Omega)$ and $\boldsymbol{\theta}^* = (\boldsymbol{a}, \boldsymbol{b}, \bar{\boldsymbol{\xi}}, \boldsymbol{\omega}^2, \bar{\boldsymbol{\psi}}, \boldsymbol{\tau}^2, \bar{\boldsymbol{\beta}}, \boldsymbol{\sigma}^2, \nu, \Omega^0)$. To establish numerical values of the prior hyperparameters $\boldsymbol{\theta}^*$, we first use probabilities elicited from the clinicians to determine location parameters, and then calibrate dispersion parameters to obtain suitable prior uncertainty so that the data will dominate adaptive decisions. Recall

that we use the early follow up times $\boldsymbol{L}' = (100, 100, 100, 30, 100)$ for hyperparameter specification. Denote $\pi_{j,Z,r}(\boldsymbol{\theta}) = \Pr(Y_j \leq L'_j \mid Z, r, \boldsymbol{\theta})$, for each (j, Z, r). Elicited prior means of these probabilities for the NK cell trial, which we denote by $\pi^{(e)}_{j,Z,r}$, are given in Table 1 of the main text. To obtain additional prior information about patterns of the hazards h_T and h_C over these early time periods, we also elicited $\Pr^{(e)}(Y_T \leq 20 \mid Y_T \leq 100) = 0.65$, $\Pr^{(e)}(Y_C \leq 30) = 0.25$, and $\Pr^{(e)}(7 \leq Y_C \leq 14 \mid Y_C \leq 30) = 0.90$, which are average values in that they do not vary with $\boldsymbol{Z} = (Z, r)$. We use the information in the elicited values by first replacing α_j and $\lambda_{i,j}$ in $S_j(y \mid \alpha_j, \lambda_{i,j})$ with the prior means $\bar{\alpha}_j$ and $\bar{\lambda}_{j,Z,r} = \bar{\beta}_j Z + \bar{\xi}_j \bar{\psi}_r$, respectively, to obtain the approximate survival probabilities

$$\tilde{S}_j(y \mid \bar{\alpha}_j, \bar{\beta}_j, \bar{\xi}_j, \bar{\psi}_r, Z) = \exp\{-\exp(\bar{\beta}_j Z + \bar{\xi}_j \bar{\psi}_r) y^{\bar{\alpha}_j}\}. \tag{1}$$

In this approximation, we set $u_{i,j} = 0$, ignore i and d, and replace α_j, β_j, ξ_j and $\psi_{r,d}$ with their respective prior means $\bar{\alpha}_j$, $\bar{\beta}_j$, $\bar{\xi}_j$ and $\bar{\psi}_r$. To solve for numerical values of the prior means, we treated elicited values as outcome variables and prior means as parameters in a set of nonlinear regression equations of the form

$$\begin{aligned} \pi^{(e)}_{j,Z,r} &= 1 - \tilde{S}_j(L'_j \mid \bar{\alpha}_j, \bar{\beta}_j, \bar{\xi}_j, \bar{\psi}_r, Z) \\ &= 1 - \exp\{-\exp(\bar{\beta}_j Z + \bar{\xi}_j \bar{\psi}_r)(L'_j)^{\bar{\alpha}_j}\}, \end{aligned} \tag{2}$$

for each (j, Z, r). Similar equations were formed using the elicited prior conditional probabilities for Y_T and Y_C, given above. This is an application of the general approach for establishing prior mean hyperparameters described by Yuan *et al.* (2016), Section 3.3.1.

To solve for the means $\{\bar{\alpha}_j, j = P, R, D, T, C\}$, we note that these are shape parameters, since α_j determines the time varying pattern of the hazard h_j of Y_j under the Weibull distribution. Since the elicited values $\pi^{(e)}_{j,Z,r}$ for $j = P, R, D$ given in Table 1 of the main

text are probabilities of occurrence in the interval (0, 100], they provide no prior information about change in the hazards h_P, h_R, or h_D over time. Thus, we fix $\bar{\alpha}_P = \bar{\alpha}_R = \bar{\alpha}_D = 1$. In contrast, the elicited conditional probabilities given above provide prior information about how h_T and h_C change over time, and thus allow us to solve (2) for $\bar{\alpha}_T$ and $\bar{\alpha}_C$. Details are as follows;

- $\bar{\alpha}_T$: The elicited probability $\Pr^{(e)}(Y_T \leq 20 \mid Y_T \leq 100) = 0.65$ does not condition on (Z, r) different from $\pi^{(e)}_{T,Z,r}$ in the table. We take the weighted average of $\pi^{(e)}_{T,Z,r}$ across (Z, r) assuming that patients have one of the three disease types with equal probability and either of LBD and HBD with probabilities 1/3 and 2/3 and find $\Pr^{(e)}(Y_T \leq 100) = 0.283$. We use (4) of the main text, drop covariate index (Z, r) and obtain the following equation;

$$\tilde{S}_T(y \mid \bar{\alpha}_T, \bar{\lambda}_T) = \exp\left\{-\exp(\bar{\lambda}_T) y^{\bar{\alpha}_T}\right\}. \tag{3}$$

  Plugging the elicited probabilities $\Pr^{(e)}(Y_T \leq 20 \mid Y_T \leq 100) = 0.65$ and $\Pr^{(e)}(Y_T \leq 100) = 0.283$ into (3) yields the nonlinear equations

$$\begin{aligned} \exp\left\{-\exp(\bar{\lambda}_T) 100^{\bar{\alpha}_T}\right\} &= 1 - 0.283, \\ \exp\left\{-\exp(\bar{\lambda}_T) 20^{\bar{\alpha}_T}\right\} &= 1 - (0.283 \times 0.65). \end{aligned}$$

  Solving the equations for $\bar{\alpha}_T$ yields $\bar{\alpha}_T = 0.306$.

- $\bar{\alpha}_C$: The elicited prior probabilities for outcome C are $\Pr^{(e)}(Y_C \leq 30) = 0.25$ and $\Pr^{(e)}(7 \leq Y_C \leq 14 \mid Y_C \leq 30) = 0.90$. We first approximate the marginal probability

$\Pr^{(e)}(Y_C \leq 14)$ as follows:

$$\begin{aligned}
\overset{(e)}{\Pr}(Y_C < 14) &= \overset{(e)}{\Pr}(Y_C \leq 14 \mid Y_C \leq 30)\overset{(e)}{\Pr}(Y_C \leq 30) \\
&= \{\overset{(e)}{\Pr}(7 \leq Y_C \leq 14 \mid Y_C \leq 30) + \overset{(e)}{\Pr}(Y_C < 7 \mid Y_C \leq 30)\}(Y_C \leq 30) \\
&= \{0.9 + \underbrace{0.1 \times 6/22}_{=A}\} \times 0.25 = 0.232.
\end{aligned}$$

The term A is from the approximation $\Pr^{(e)}(Y_C < 7 \mid Y_C \leq 30) \approx 0.1 \times 6/22$ under the assumption that the probability of occurring outcome C is equal for days less than 7 (6 days) or between 15 and 30 inclusive (16 days). Similar to $\bar{\alpha}_T$, we solve the following equations,

$$\begin{aligned}
\exp\left\{-\exp(\bar{\lambda}_C)30^{\bar{\alpha}_C}\right\} &= 1 - 0.25, \\
\exp\left\{-\exp(\bar{\lambda}_C)7^{\bar{\alpha}_C}\right\} &= 1 - 0.232.
\end{aligned}$$

Solving the equations yields $\bar{\alpha}_C = 0.114$.

Recall that $\alpha_j \overset{indep}{\sim} \text{Ga}(a_j, b_j)$. To express vague prior information, we fix $b_j = 0.1$ for all j and let $a_j = \bar{\alpha}_j b_j$. We next use the elicited probabilities in Table 1 of the main text and elicit $\bar{\beta}_j$, $\bar{\xi}_j$ with $\bar{\xi}_D = 1$ and $\bar{\psi}_r$. By using $\pi^{(e)}_{j,Z,r}$ and rearranging (1), we obtain

$$\bar{\beta}_j Z + \bar{\xi}_j \bar{\psi}_r = \log\left\{-\frac{\log(1 - \pi^{(e)}_{j,Z,r})}{(L'_j)^{\bar{\alpha}_j}}\right\}. \tag{4}$$

We next determine numerical values of prior means, $\bar{\beta}_j$, $\bar{\xi}_j$, $\bar{\psi}_r$.

- $\bar{\psi}_r$: Under the assumed model, we set $\xi_D = 1$ and $\bar{\psi}_r$ quantifies the effect of disease type r on death for a patient with low bulk disease $Z = 0$. We plug in the corresponding elicited probabilities, $\pi^{(e)}_{D,0,r}$, $r = 1, 2, 3$ from Table 1 of the main text for (2); with

$Z = 0$ and $\bar{\xi}_D = 1$,

$$\begin{aligned}
\bar{\psi}_1 &= \log\left\{-\frac{\log(1-0.02)}{100^{\bar{\alpha}_D}}\right\}, \\
\bar{\psi}_2 &= \log\left\{-\frac{\log(1-0.10)}{100^{\bar{\alpha}_D}}\right\}, \\
\bar{\psi}_3 &= \log\left\{-\frac{\log(1-0.05)}{100^{\bar{\alpha}_D}}\right\},
\end{aligned}$$

which yields -8.507, -6.856, and -7.575 for disease types $r = 1, 2, 3$, respectively, with the elicited $\bar{\alpha}_D = 1$.

- $\bar{\xi}_j$, $j \neq D$: Under the assumed model ξ_j is the parameter that modifies the effect of disease type r on death to quantify the effect on outcome j. For example, consider $j = P$ and use $\pi^{(e)}_{P,0,r}$. We obtain the following equations using (4), with $Z = 0$ and $j = P$:

$$\begin{aligned}
\bar{\xi}_P\bar{\psi}_1 &= \log\left\{-\frac{\log(1-0.05)}{100^{\bar{\alpha}_P}}\right\}, \\
\bar{\xi}_P\bar{\psi}_2 &= \log\left\{-\frac{\log(1-0.15)}{100^{\bar{\alpha}_P}}\right\}, \\
\bar{\xi}_P\bar{\psi}_3 &= \log\left\{-\frac{\log(1-0.10)}{100^{\bar{\alpha}_P}}\right\}.
\end{aligned}$$

Using the values of $\bar{\psi}_r$, $r = 1, 2, 3$ above, we find $\bar{\xi}_P$ for the equations, which gives 0.890, 0.937, and 0.905 for disease types $r = 1, 2, 3$, respectively. These three values are different since the elicited probabilities do not necessarily satisfy the model assumption, $\bar{\lambda}_{j,Z,r} = \bar{\beta}_j Z + \bar{\xi}_j\bar{\psi}_r$. We have the value across the disease types, $\bar{\xi}_P = 0.911$. We solve for $\bar{\xi}_j$ for the remaining outcomes R, T and C similarly. The elicited values are $\bar{\xi}_j = 0.721$, 0.771, 0.214 for outcomes $j = R$, T and C, respectively.

- $\bar{\beta}_j$, $j = P, \ldots, D$: Consider $j = D$. For each r with $Z = 1$,

$$\begin{aligned}
\bar{\beta}_D 1 + \bar{\psi}_1 &= \log\left\{-\frac{\log(1-0.10)}{100^{\bar{\alpha}_D}}\right\}, \\
\bar{\beta}_D 1 + \bar{\psi}_2 &= \log\left\{-\frac{\log(1-0.20)}{100^{\bar{\alpha}_D}}\right\}, \\
\bar{\beta}_D 1 + \bar{\psi}_3 &= \log\left\{-\frac{\log(1-0.15)}{100^{\bar{\alpha}_D}}\right\}.
\end{aligned}$$

  By plugging in $\bar{\alpha}_D = 1$ and $\bar{\psi}_r$ from the above, we have $\bar{\beta}_D = 1.651$, 1.00 and 1.153 for $r = 1$, 2 and 3, respectively. Since the elicited probabilities may not satisfy the model assumption, the solutions $\bar{\beta}_D$ are different for disease types r. We take the value of $\bar{\beta}_D$ averaged across r, which gives the value $\bar{\beta}_D = 1.270$. For the remaining outcomes $j = P, R, T$ and C, we similarly find $\bar{\beta}_j$. The elicited $\bar{\beta}_j$ are 1.398, 0.369, 0.191 and 0.000 for $j = P, R, T$ and C, respectively.

The resulting numerical values of $\boldsymbol{a}$, $\boldsymbol{b}$, $\bar{\boldsymbol{\psi}}$, $\bar{\boldsymbol{\beta}}$, and $\bar{\boldsymbol{\xi}}$ are given in Table 1.

To reflect vague prior information about dose-specific effects for each (Z, r), the dispersion hyperparameters were set to $\sigma_j^2 = \tau_r^2 = \omega_j = 100$. Similarly, we express vague prior information on the time-varying pattern of the hazard function by letting $b_j = 0.1$ and $a_j = \bar{\alpha}_j b_j$ for $\alpha_j \sim \mathrm{Ga}(a_j, b_j)$. The resulting numerical values of $\boldsymbol{a}$, $\boldsymbol{b}$, $\bar{\boldsymbol{\xi}}$, $\bar{\boldsymbol{\psi}}$ and $\bar{\boldsymbol{\beta}}$ are given in Table 1 of the Supplementary Materials. In addition, we specify ν and Ω^0 for the prior distribution of the covariance matrix Ω of $\boldsymbol{u}_i$. We let $\Omega^0_{j,j} = 0.05$, $\Omega^0_{j,j'} = 0.025$ for $j' \neq j$ and $(j, j') \neq (j, R)$, and $\Omega^0_{j,R} = -0.025$ for $j \neq R$. This specification of Ω^0 a priori implies the negative relationship between Y_R and the other four outcomes, and the positive relationships between the four adverse outcomes. We let $\nu = 6$ to express weak prior information about Ω. The specified Ω^0 was calibrated through a preliminary simulation study and implies a priori correlation 0.5 or -0.5. In the preliminary study, we compared posterior predictive probabilities of outcomes occurring during the follow-up intervals with the corresponding empirical

probabilities based on simulated data, and found that their differences are reasonably small.

3 Simulation Design

3.1 Simulation Set-up

We assume six different simulation scenarios to examine the performance of the proposed design. Scenario 1 assumes the elicited probabilities to simulate data (explained below in detail). We construct the other five scenarios as follows:

1. We specify the true marginal probabilities of death within the short follow-up $L'_D = 100$ days for $Z = 0$ (LBD) for all (r, d), denoted by $\pi^{\mathrm{TR}}_{D,Z,r,d}$ with $Z = 0$. Also, specify α^{TR}_j for all j. Using α^{TR}_D and $\pi^{\mathrm{TR}}_{D,Z,r,d}$, we solve the equation

$$\pi^{\mathrm{TR}}_{D,0,r,d} = 1 - \exp\left\{-\exp(\psi^{\mathrm{TR}}_{r,d})(L'_D)^{\alpha^{\mathrm{TR}}_D}\right\} \tag{5}$$

   for $\psi^{\mathrm{TR}}_{r,d}$.

2. We specify $\bar{\xi}^{\mathrm{TR}}_j$, $j \neq D$ and $\bar{\beta}^{\mathrm{TR}}_j$ for all j. We simulate $\xi^{\mathrm{TR}}_{j,r,d} \overset{indep}{\sim} \mathrm{N}(\bar{\xi}^{\mathrm{TR}}_j, 0.01)$, $j \neq D$ and set $\xi^{\mathrm{TR}}_{D,r,d} = 1$ for all (r, d). We simulate $\beta^{\mathrm{TR}}_{j,r,d} \overset{indep}{\sim} \mathrm{N}(\bar{\beta}^{\mathrm{TR}}_j, 0.05)$, $j = P, R$. To reflect information that HBD ($Z_1 = 1$) increases the probability of adverse outcomes, we use $\log(\beta^{\mathrm{TR}}_{j,r,d}) \overset{indep}{\sim} \mathrm{N}(\log(\bar{\beta}^{\mathrm{TR}}_j), 0.05)$, $j = T, C, D$. We let

$$\bar{\lambda}^{\mathrm{TR}}_{j,Z,r,d} = \beta^{\mathrm{TR}}_{j,r,d} Z + \xi^{\mathrm{TR}}_{j,r,d} \psi^{\mathrm{TR}}_{r,d}. \tag{6}$$

3. We assume $\Omega^{\mathrm{TR}}_{j,j} = 0.001$, $\Omega^{\mathrm{TR}}_{j,R} = -0.5 \times 0.001$, $j \neq R$ and $\Omega^{\mathrm{TR}}_{j,j'} = 0.5 \times 0.001$, $j \neq j'$, $j, j' \neq R$ and the same Ω^{TR} is used for all scenarios, and simulate $\boldsymbol{u}^{\mathrm{TR}} \overset{iid}{\sim} \mathrm{N}(\mathbf{0}, \Omega^{\mathrm{TR}})$. Finally, we simulate y_j with $\boldsymbol{Z}$ and d from the Weibull distribution with shape parameter

α_j^{TR} and scale parameter $\exp\left(\bar{\lambda}_{j,Z,r,d}^{\text{TR}} + u_j^{\text{TR}}\right)$, that is,

$$y_j \mid \alpha_j^{\text{TR}}, \psi_{j,Z,r,d}^{\text{TR}}, u_j^{\text{TR}} \overset{indep}{\sim} \text{Weibull}(\alpha_j^{\text{TR}}, \exp(\bar{\lambda}_{j,Z,r,d}^{\text{TR}} + u_j^{\text{TR}})). \tag{7}$$

The proposed design assumes Y_j follows a Weibull distribution with shape parameter α_j and scale parameter $\lambda_j = \beta_j Z + \xi_j \psi_{r,d} + u_j$ for patient with $\boldsymbol{Z}$ and d. By allowing $\xi_{j,r,d}^{\text{TR}}$ and $\beta_{j,r,d}^{\text{TR}}$ in (6) indexed by r and d as well as j, the regression relationship between outcomes, covariates, and doses assumed in (2) of the main text no longer holds for the simulation truth. Compared to the proposed model, the simulation truth is more general and includes the proposed model as a special case. The specified true probabilities of death within the follow-up (L_D) are listed in Table 3 of the main text for Scenarios 2-6. The values of α_j^{TR}, $\bar{\xi}_j^{\text{TR}}$ and $\bar{\beta}_j^{\text{TR}}$ are listed in Table 2. With all simulated $\bar{\lambda}_{j,Z,r,d}^{\text{TR}}$ and Ω^{TR} , probabilities of occurrence of outcome Y_j within the follow-up for patients with $\boldsymbol{Z}$, d and $\bar{\lambda}_{j,Z_1,r,d}^{\text{TR}}$ can be easily found.

For Scenario 1, we test the proposed design using the probabilities provided by clinicians (Table 1 of the main text). The clinicians have no information on dose effects and we assume that $\bar{\lambda}_{j,Z,r,d}^{\text{TR}}$ is the same for all d, but only differs by $\boldsymbol{Z}$, resulting in no difference in $\bar{U}^{\text{TR}}$. Specifically, we let $\pi_{j,Z,r,d}^{\text{TR}}$ equal the corresponding probabilities in the table for all d. Using the additional information described in the main text, we find α_j^{TR} as given in Table 2. We use (5) and find $\bar{\lambda}_{j,Z,r,d}^{\text{TR}}$ for all j, Z, r and d. Use the same Ω^{TR} specified above, and simulate Y_j from (7).

3.2 Simulation Set-up for Robustness

We examine robustness of the proposed design by simulating $Y_{i,j}$ from a log-logistic distribution, which is different from the Weibull distribution assumed for the design. We use the same true marginal probabilities $\pi_{j,Z,r,d}^{\text{TR}}$ specified in Section 3.1 for the Weibull model. Although the probabilities that outcomes occur during the follow-up period are the same

under the two distributions, the rates of occurrences become different according to the hazard functions of the distributions, and the true expected utilities of outcomes evaluated for a fully followed patient may differ due to the competing and semi-competing risks properties. For example, the log-logistic distribution allows a non-monotonic hazard function, such as a $\cap$-shaped function that is not possible under the Weibull distribution. Specifically, the models in (5) and (7) are changed to reflect the different distributions for Y_j as follows. For the log-logistic distribution we let $\alpha_j^{LL,\text{TR}} = \alpha_j^{\text{TR}}$ and find $\bar{\lambda}_{j,Z_1,r,d}^{LL,\text{TR}}$ using the survival function for the log-logistic model,

$$\frac{1}{1+\exp(\bar{\lambda}_{j,Z_1,r,d}^{LL,\text{TR}})L_j^{\alpha_j^{LL,\text{TR}}}} = 1 - \pi_{j,Z_1,r,d}^{\text{TR}}.$$

We simulate $\boldsymbol{u}_i^{\text{TR}} \overset{iid}{\sim} \text{N}_5(\mathbf{0}, \Omega^{\text{TR}})$ and $y_j \mid \alpha_j^{\text{TR}}, \bar{\lambda}_{j,Z_1,r,d}^{\text{TR}}, u_j \overset{indep}{\sim} \text{Log-logsitic}(\alpha_j^{\text{TR}}, \exp(\bar{\lambda}_{j,Z_1,r,d}^{\text{TR}} + u_j))$ for a patient with $\boldsymbol{Z}$ and d.

4 Additional Simulation Results

Tables 3 and 4 give stopping and dose selection probabilities under the simpler model that ignores $\boldsymbol{Z}$, respectively. For easy comparison, the results under the proposed design that utilizes $\boldsymbol{Z}$ are also included in the tables. Note that π_D^{TR} and $\bar{U}^{\text{TR}}$ are listed in Table 3 of the main text. The design with $\boldsymbol{Z}$ outperforms the simpler design when optimal doses or unsafe doses vary substantially across subgroups. For example, under Scenario 6, the stopping probabilities in the (LBD, CLL) subgroup are far too large for $d = 2$ and $d = 3$ under the simpler design, which both have high true mean utilities $\bar{U}^{\text{TR}} = 59.80$ and 57.69, and the selection probabilities 0.24 and 0.34 are far smaller than the corresponding values 0.56 and 0.44 obtained by the design with subgroup-specific decisions. In the (HBD, NHL) subgroup, the incorrect stopping probabilities 0.50 and 0.50 are far too large for the safe doses $d = 1$

and $d = 2$, compared to the values 0.00 and 0.03 obtained by the subgroup-specific design. The full design correctly selects the best dose $d = 1$ in that subgroup, which has $\bar{U}^{\text{TR}} = 52.57$ compared to 44.10 for $d = 2$ and 18.84 for $d = 3$, with probability 0.89 compared to 0.23 with the simpler design. Other comparisons give similarly large differences, leading to the general conclusion that failure to account for heterogeneity may lead to decisions having extremely large false positive and false negative rates.

Table 5 summarizes the proportions of patients treated in a trial, by dose, for each subgroup. The proposed design with sample sizes $N = 60$ and $N = 120$ and the design ignoring patient subgroups are compared. Under the design accounting for patient subgroups, fewer patients are treated at unsafe doses, and as the sample size increases, the design more accurately identifies unsafe doses. For example, in Scenario 2 where unsafe doses are different for different subtypes, patients are more likely to be assigned to safe doses under the proposed design that uses patient subgroups, and the proportions of patients treated at safe doses increase for $N = 120$. In the case where all doses are truly unsafe and no treatment is optimal for all subgroups, the design assigns fewer patients to any dose.

We simulated $\boldsymbol{Y}$ from the log-logistic distribution to examine robustness of the proposed design that assumes a Weibull distribution. The results are summarized in Table 6. From comparison to the results in Table 3 of the main text, the proposed model works reasonably well under the true log-logistic model, in terms of identification of unsafe doses and optimal doses, even when the true model is different from the assumed Weibull model. The performance of the proposed design slightly deteriorates for some scenarios. For example, under Scenario 4 in Table 6, Pr(Stop) only slightly changes compared to those in Table 3 of the main text. However, dose 1 tends to have larger Pr(Select) for patients with $Z = 0$ in Scenario 4. For the subgroups with $Z = 0$, $d = 1$ is safe but has smaller true expected utilities than $d = 2$.

In addition to the subgroup-specific safety rule, the proposed design includes the regula-

tor's safety rule described in Section 4 of the main text. Recall that the regulator's safety rule monitors the probability of death at the lowest dose and does not account for patient's covariates and other doses. The proportions of trials terminated by the regulator's safety rule are summarized in Table 7. As noted in the main text, the regulator's safety rule rarely stops trials even when all doses are truly unsafe. The probabilities with $N_{\max} = 60$ and with $N_{\max} = 120$ in Columns 1 and 3 of the table, respectively, are identical, which implies that trials were not terminated by the regulator's safety rule after $n = 60$. For the last two columns, the log-logistic distribution is used to simulate data but the Weibull is used for the design. Compared to the probabilities under the Weibull distribution, it tends to have slightly fewer terminations when the model is misspecified.

For increased maximum sample size $N_{\max} = 120$, the results are summarized in Tables 5 and 8. Compared to the results in Table 3 of the main text, the sample size increase from 60 to 120 improves design performance substantially. Especially when unsafe doses and/or optimal doses are not clear in a scenario, as in Scenario 4, the amount of improvement is substantial. This implies that when a trial is complicated due to covariates, sample size plays an important role to achieve correct selection decisions. With a larger sample size, the probabilities of subgroup-specific safety decisions are greatly improved, as shown in Table 5. For example, in Scenario 2 the proportions of patients treated at doses 1, 2 and 3 are 0.49, 0.27 and 0.21 for (CLL, LBD) with $N = 60$, since doses 2 and 3 are unsafe. The corresponding proportions are 0.68, 0.17 and 0.12 for $N = 120$. This shows that, as a trial proceeds, the design is more likely to correctly identify doses 2 and 3 as unsafe and stop assigning patients to those doses.

References

Yuan, Y., Nguyen, H. Q., and Thall, P. F. (2016). *Bayesian Designs for Phase I–II Clinical Trials*. Chapman & Hall/CRC: New York.

Hyperparameter	
$\bar{\psi}_r$	-8.51, -6.86, -7.58 for $r = 1, 2, 3$
$\bar{\beta}_j$	1.40, 0.37, 0.19, 0.00, 1.27 for $j = P, R, T, C, D$
$\bar{\xi}_j$	0.91, 0.72, 0.77, 0.21 for $j = P, R, T, C$
a_j	0.10, 0.10, 0.03, 0.01, 0.10 with fixed $b_j = 0.1$ for $j = P, R, T, C, D$

Table 1: [Prior Elicitation] Elicited hyperparameter values.

Scenarios	True Parameter	P	R	T	C	D
Scenario 1	α_j^{TR}	1.000	1.000	0.306	0.114	1.000
Scenario 2	α_j^{TR}	0.700	0.700	0.300	0.200	0.700
	$\bar{\xi}_j^{\mathrm{TR}}$	1.000	1.000	0.600	0.250	
	$\bar{\beta}_j^{\mathrm{TR}}$	0.500	-0.300	0.001	0.250	0.700
Scenario 3	α_j^{TR}	0.700	1.300	0.300	0.200	1.000
	$\bar{\xi}_j^{\mathrm{TR}}$	1.000	1.000	0.600	0.250	
	$\bar{\beta}_j^{\mathrm{TR}}$	0.500	-0.300	0.001	0.250	0.700
Scenario 4	α_j^{TR}	0.500	1.400	0.200	1.500	1.000
	$\bar{\xi}_j^{\mathrm{TR}}$	0.600	0.800	0.100	1.000	
	$\bar{\beta}_j^{\mathrm{TR}}$	2.500	0.800	3.000	2.000	0.100
Scenario 5	α_j^{TR}	0.500	0.800	0.700	1.500	1.000
	$\bar{\xi}_j^{\mathrm{TR}}$	0.600	0.900	0.500	1.000	
	$\bar{\beta}_j^{\mathrm{TR}}$	0.500	-0.200	0.400	0.600	0.300
Scenario 6	α_j^{TR}	0.800	1.000	1.500	0.800	1.200
	$\bar{\xi}_j^{\mathrm{TR}}$	0.700	0.600	1.500	0.500	
	$\bar{\beta}_j^{\mathrm{TR}}$	-0.200	0.200	1.500	0.800	1.200

Table 2: [Simulation Set-up] Values of α_j^{TR}, $\bar{\xi}_j^{\mathrm{TR}}$ and $\bar{\beta}_j^{\mathrm{TR}}$ used for simulation scenarios are listed.

Scenario	Dose	Design with Subgroup						No
		(L, C)	(L, A)	(L, N)	(H, C)	(H, A)	(H, N)	Subgroup
Scenario 1	$d = 1$	0.00	0.00	0.00	0.00	0.03	0.00	0.00
	$d = 2$	0.00	0.01	0.00	0.00	0.03	0.00	0.01
	$d = 3$	0.00	0.00	0.00	0.00	0.02	0.00	0.01
Scenario 2	$d = 1$	0.00	0.67	0.95	0.00	0.81	1.00	0.82
	$d = 2$	0.89	0.92	0.00	0.98	0.98	0.00	0.90
	$d = 3$	0.97	0.00	0.55	1.00	0.00	0.68	0.87
Scenario 3	$d = 1$	0.88	0.93	0.73	0.96	0.99	0.85	0.98
	$d = 2$	0.85	0.96	0.77	0.95	0.99	0.87	0.98
	$d = 3$	0.82	0.98	0.84	0.94	1.00	0.94	0.98
Scenario 4	$d = 1$	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	$d = 2$	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	$d = 3$	0.26	0.14	0.29	0.13	0.05	0.12	0.33
Scenario 5	$d = 1$	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	$d = 2$	0.00	0.00	0.01	0.00	0.00	0.00	0.00
	$d = 3$	0.48	0.02	0.00	0.44	0.01	0.00	0.03
Scenario 6	$d = 1$	0.76	0.00	0.00	0.99	0.02	0.00	0.50
	$d = 2$	0.00	0.82	0.01	0.00	0.99	0.03	0.50
	$d = 3$	0.09	0.00	0.51	0.34	0.00	0.91	0.43

Table 3: **Simulation Results of the Design Ignoring Subgroups for Unsafe Dose Identification**. The probabilities that a dose is identified as unsafe are shown under the proposed design with subgroups **(Left)** and the simpler model without subgroups **(Right)**. Unsafe doses in the truth are given in grey. The first letters L and H in each subgroup stand for disease bulks, Low and High, respectively. The second letters C, A and N in each subgroup stand for disease types, CLL, ALL and NHL, respectively.

Scenario	Dose	Design with Subgroup						No Subgroup
		(L, C)	(L, A)	(L, N)	(H, C)	(H, A)	(H, N)	
Scenario 1	$d = 1$	0.33	0.33	0.33	0.33	0.32	0.35	0.34
	$d = 2$	0.37	0.35	0.34	0.34	0.36	0.31	0.34
	$d = 3$	0.30	0.32	0.33	0.33	0.33	0.34	0.33
Scenario 2	$d = 1$	**1.00**	0.00	0.00	**1.00**	0.00	0.00	0.15
	$d = 2$	0.00	0.00	**1.00**	0.00	0.00	**1.00**	0.08
	$d = 3$	0.00	**1.00**	0.00	0.00	**1.00**	0.00	0.10
Scenario 3	$d = 1$	0.07	**0.06**	**0.19**	0.03	**0.01**	**0.12**	0.02
	$d = 2$	0.11	0.03	0.16	0.05	0.01	0.11	0.02
	$d = 3$	**0.13**	0.01	0.07	**0.05**	0.00	0.04	0.02
Scenario 4	$d = 1$	0.04	0.02	0.01	**1.00**	**1.00**	**1.00**	0.51
	$d = 2$	**0.95**	**0.98**	**0.99**	0.00	0.00	0.00	0.49
	$d = 3$	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Scenario 5	$d = 1$	**1.00**	0.00	0.00	**1.00**	0.00	0.00	0.70
	$d = 2$	0.00	**1.00**	0.00	0.00	**0.99**	0.00	0.24
	$d = 3$	0.00	0.00	**1.00**	0.00	0.00	**1.00**	0.06
Scenario 6	$d = 1$	0.00	0.80	**0.53**	0.00	0.04	**0.89**	0.23
	$d = 2$	**0.56**	0.00	0.47	**0.99**	0.00	0.11	0.24
	$d = 3$	0.44	**0.20**	0.01	0.01	**0.96**	0.00	0.34

Table 4: **Simulation Results of the Design Ignoring Subgroups for Dose Selection**. The probabilities that a dose is selected as an optimal dose are shown under the proposed design with subgroups **(Left)** and the simpler model without subgroups **(Right)**. True optimal doses are underlined and in bold. The first letters L and H in each subgroup stand for disease bulks, Low and High, respectively. The second letters C, A and N in each subgroup stand for disease types, CLL, ALL and NHL, respectively.

		Bulk ($\rightarrow$)	LBD ($Z=0$)				HBD ($Z=1$)			
	Types ($\downarrow$)	Dose ($\rightarrow$)	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$
Scenario 1	CLL	π_D^{TR}	0.02	0.02	0.02	*0.15*	0.10	0.10	0.10	*0.30*
	($r=1$)	$N=60$	0.33	0.33	0.34		0.33	0.34	0.33	
		$N=120$	0.33	0.33	0.34		0.33	0.33	0.33	
		No $\boldsymbol{Z}$	0.34	0.33	0.33		0.33	0.34	0.33	
	ALL	π_D^{TR}	0.10	0.10	0.10	*0.20*	0.25	0.25	0.25	*0.40*
	($r=2$)	$N=60$	0.33	0.34	0.33		0.33	0.33	0.33	
		$N=120$	0.34	0.33	0.33		0.33	0.33	0.34	
		No $\boldsymbol{Z}$	0.34	0.33	0.33		0.33	0.33	0.33	
	NHL	π_D^{TR}	0.05	0.05	0.05	*0.20*	0.15	0.15	0.15	*0.40*
	($r=3$)	$N=60$	0.33	0.34	0.33		0.33	0.33	0.33	
		$N=120$	0.33	0.33	0.33		0.33	0.33	0.33	
		No $\boldsymbol{Z}$	0.34	0.32	0.34		0.33	0.34	0.33	
Scenario 2	CLL	π_D^{TR}	0.02	0.45	0.60	*0.15*	0.04	0.70	0.84	*0.30*
	($r=1$)	$N=60$	0.53	0.25	0.19		0.65	0.18	0.15	
		$N=120$	0.72	0.15	0.10		0.81	0.10	0.08	
		No $\boldsymbol{Z}$	0.15	0.14	0.14		0.13	0.11	0.13	
	ALL	π_D^{TR}	0.40	0.60	0.05	*0.20*	0.64	0.84	0.10	*0.40*
	($r=2$)	$N=60$	0.30	0.21	0.44		0.23	0.16	0.55	
		$N=120$	0.23	0.11	0.61		0.14	0.08	0.71	
		No $\boldsymbol{Z}$	0.15	0.12	0.16		0.13	0.11	0.13	
	NHL	π_D^{TR}	0.65	0.05	0.35	*0.20*	0.88	0.10	0.58	*0.40*
	($r=3$)	$N=60$	0.19	0.42	0.30		0.15	0.48	0.24	
		$N=120$	0.10	0.55	0.26		0.08	0.62	0.18	
		No $\boldsymbol{Z}$	0.16	0.13	0.16		0.14	0.13	0.14	
Scenario 3	CLL	π_D^{TR}	0.42	0.38	0.37	*0.15*	0.66	0.62	0.60	*0.30*
	($r=1$)	$N=60$	0.20	0.20	0.22		0.21	0.23	0.25	
		$N=120$	0.09	0.10	0.11		0.13	0.15	0.16	
		No $\boldsymbol{Z}$	0.08	0.08	0.07		0.07	0.07	0.07	
	ALL	π_D^{TR}	0.52	0.58	0.65	*0.20*	0.77	0.83	0.88	*0.40*
	($r=2$)	$N=60$	0.25	0.23	0.20		0.26	0.24	0.22	
		$N=120$	0.18	0.15	0.13		0.18	0.16	0.15	
		No $\boldsymbol{Z}$	0.09	0.08	0.09		0.07	0.07	0.07	
	NHL	π_D^{TR}	0.40	0.42	0.45	*0.20*	0.64	0.67	0.70	*0.40*
	($r=3$)	$N=60$	0.21	0.20	0.16		0.22	0.20	0.17	
		$N=120$	0.10	0.09	0.07		0.12	0.11	0.08	
		No $\boldsymbol{Z}$	0.08	0.08	0.08		0.07	0.07	0.07	

Table 5: **Simulation Results - Proportions of Assigned Doses (1)**. The proportions of doses assigned to patients in a trial are illustrated for the proposed design with $N=60$ and $N=120$ and the simpler design that ignores patient subgroups (no $\boldsymbol{Z}$). It is more desirable that fewer patients are treated at unsafe doses.

		Bulk ($\rightarrow$)	LBD ($Z=0$)				HBD ($Z=1$)			
	Types ($\downarrow$)	Dose ($\rightarrow$)	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$
Scenario 4	CLL	π_D^{TR}	0.01	0.10	0.25	*0.15*	0.01	0.11	0.27	*0.30*
	($r=1$)	$N=60$	0.34	0.33	0.33		0.34	0.35	0.31	
		$N=120$	0.36	0.35	0.28		0.34	0.35	0.31	
		No $\boldsymbol{Z}$	0.37	0.35	0.28		0.36	0.36	0.28	
	ALL	π_D^{TR}	0.01	0.09	0.27	*0.20*	0.01	0.10	0.29	*0.40*
	($r=2$)	$N=60$	0.34	0.34	0.32		0.34	0.34	0.33	
		$N=120$	0.35	0.35	0.30		0.34	0.34	0.33	
		No $\boldsymbol{Z}$	0.36	0.36	0.28		0.36	0.36	0.28	
	NHL	π_D^{TR}	0.01	0.08	0.30	*0.20*	0.01	0.09	0.33	*0.40*
	($r=3$)	$N=60$	0.34	0.35	0.31		0.34	0.34	0.32	
		$N=120$	0.37	0.37	0.26		0.34	0.34	0.32	
		No $\boldsymbol{Z}$	0.36	0.34	0.29		0.36	0.36	0.28	
Scenario 5	CLL	π_D^{TR}	0.01	0.09	0.30	*0.15*	0.01	0.12	0.38	*0.30*
	($r=1$)	$N=60$	0.34	0.35	0.31		0.36	0.36	0.27	
		$N=120$	0.38	0.37	0.24		0.38	0.38	0.23	
		No $\boldsymbol{Z}$	0.35	0.33	0.32		0.34	0.34	0.32	
	ALL	π_D^{TR}	0.12	0.03	0.18	*0.20*	0.16	0.04	0.23	*0.40*
	($r=2$)	$N=60$	0.33	0.34	0.33		0.34	0.33	0.33	
		$N=120$	0.33	0.34	0.33		0.33	0.33	0.33	
		No $\boldsymbol{Z}$	0.34	0.34	0.32		0.33	0.34	0.33	
	NHL	π_D^{TR}	0.10	0.15	0.01	*0.20*	0.13	0.20	0.01	*0.40*
	($r=3$)	$N=60$	0.32	0.34	0.33		0.34	0.33	0.33	
		$N=120$	0.33	0.34	0.33		0.33	0.33	0.33	
		No $\boldsymbol{Z}$	0.34	0.33	0.33		0.34	0.34	0.32	
Scenario 6	CLL	π_D^{TR}	0.35	0.03	0.13	*0.15*	0.75	0.10	0.37	*0.30*
	($r=1$)	$N=60$	0.26	0.35	0.38		0.17	0.48	0.35	
		$N=120$	0.18	0.38	0.43		0.09	0.58	0.34	
		No $\boldsymbol{Z}$	0.29	0.28	0.30		0.27	0.25	0.29	
	ALL	π_D^{TR}	0.08	0.45	0.02	*0.20*	0.24	0.86	0.06	*0.40*
	($r=2$)	$N=60$	0.38	0.26	0.36		0.41	0.17	0.43	
		$N=120$	0.42	0.17	0.41		0.45	0.08	0.47	
		No $\boldsymbol{Z}$	0.29	0.26	0.30		0.29	0.27	0.29	
	NHL	π_D^{TR}	0.05	0.10	0.30	*0.20*	0.16	0.29	0.70	*0.40*
	($r=3$)	$N=60$	0.33	0.35	0.31		0.41	0.39	0.20	
		$N=120$	0.36	0.36	0.28		0.45	0.43	0.11	
		No $\boldsymbol{Z}$	0.30	0.26	0.31		0.28	0.26	0.29	

Table 5 (continued): **Simulation Results - Proportions of Assigned Doses (2)**. The proportions of doses assigned to patients in a trial are illustrated for the proposed design with $N=60$ and $N=120$ and the simpler design that ignores patient subgroups (no $\boldsymbol{Z}$). It is more desirable that fewer patients are treated at unsafe doses.

		Bulk ($\rightarrow$)	LBD ($Z=0$)				HBD ($Z=1$)			
	Types ($\downarrow$)	Dose ($\rightarrow$)	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$
Scenario 1	CLL	π_D^{TR}	0.02	0.02	0.02	*0.15*	0.10	0.10	0.10	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	46.23	46.23	46.23		43.91	43.91	43.91	
		Pr(Stop)	0.00	0.00	0.00		0.00	0.00	0.00	
		Pr(Select)	0.32	0.34	0.34		0.34	0.31	0.35	
	ALL	π_D^{TR}	0.10	0.10	0.10	*0.20*	0.25	0.25	0.25	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	50.85	50.85	50.85		38.20	38.20	38.20	
		Pr(Stop)	0.01	0.00	0.00		0.04	0.02	0.03	
		Pr(Select)	0.32	0.35	0.33		0.33	0.33	0.34	
	NHL	π_D^{TR}	0.05	0.05	0.05	*0.20*	0.15	0.15	0.15	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	49.29	49.29	49.29		38.19	38.19	38.19	
		Pr(Stop)	0.00	0.00	0.00		0.00	0.00	0.00	
		Pr(Select)	0.32	0.35	0.33		0.33	0.33	0.34	
Scenario 2	CLL	π_D^{TR}	0.02	0.45	0.60	*0.15*	0.04	0.70	0.84	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	42.49	22.40	15.88		39.89	8.88	4.48	
		Pr(Stop)	0.00	0.81	0.94		0.00	0.95	0.99	
		Pr(Select)	1.00	0.00	0.00		1.00	0.00	0.00	
	ALL	π_D^{TR}	0.40	0.60	0.05	*0.20*	0.64	0.84	0.10	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	23.81	15.98	40.46		10.42	4.16	35.74	
		Pr(Stop)	0.56	0.89	0.00		0.75	0.97	0.00	
		Pr(Select)	0.00	0.00	1.00		0.00	0.00	1.00	
	NHL	π_D^{TR}	0.65	0.05	0.35	*0.20*	0.88	0.10	0.58	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	14.44	40.36	26.02		3.14	35.96	13.38	
		Pr(Stop)	0.93	0.00	0.44		0.99	0.00	0.62	
		Pr(Select)	0.00	1.00	0.00		0.00	1.00	0.00	
Scenario 3	CLL	π_D^{TR}	0.42	0.38	0.37	*0.15*	0.66	0.62	0.60	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	40.03	44.32	44.64		21.51	24.41	25.37	
		Pr(Stop)	0.77	0.73	0.69		0.91	0.87	0.83	
		Pr(Select)	0.12	0.16	0.20		0.07	0.09	0.14	
	ALL	π_D^{TR}	0.52	0.58	0.65	*0.20*	0.77	0.83	0.88	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	34.19	30.44	25.59		14.69	11.00	8.09	
		Pr(Stop)	0.87	0.91	0.96		0.94	0.98	1.00	
		Pr(Select)	0.12	0.06	0.02		0.06	0.01	0.00	
	NHL	π_D^{TR}	0.40	0.42	0.45	*0.20*	0.64	0.67	0.70	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	43.51	42.20	39.20		22.57	21.09	19.31	
		Pr(Stop)	0.56	0.61	0.74		0.66	0.73	0.86	
		Pr(Select)	0.31	0.23	0.11		0.26	0.19	0.07	

Table 6: **Simulation Results - Robustness**. Log-logistic distributions are assumed to simulate data and the Weibull distribution is assumed for the design. The true marginal probabilities of outcomes occurring within their follow-up remain the same.

		Bulk ($\rightarrow$)	LBD ($Z=0$)				HBD ($Z=1$)			
	Types ($\downarrow$)	Dose ($\rightarrow$)	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$
Scenario 4	CLL	π_D^{TR}	0.01	0.10	0.25	*0.15*	0.01	0.11	0.27	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	48.65	60.71	49.24		37.79	32.70	28.95	
		Pr(Stop)	0.00	0.00	0.58		0.00	0.00	0.36	
		Pr(Select)	0.61	0.39	0.00		1.00	0.00	0.00	
	ALL	π_D^{TR}	0.01	0.09	0.27	*0.20*	0.01	0.10	0.29	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	49.04	59.35	47.58		37.67	32.31	31.00	
		Pr(Stop)	0.00	0.00	0.54		0.00	0.00	0.29	
		Pr(Select)	0.54	0.46	0.00		1.00	0.00	0.00	
	NHL	π_D^{TR}	0.01	0.08	0.30	*0.20*	0.01	0.09	0.33	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	48.92	58.83	44.54		40.53	30.89	28.73	
		Pr(Stop)	0.00	0.00	0.74		0.00	0.00	0.54	
		Pr(Select)	0.46	0.54	0.00		1.00	0.00	0.00	
Scenario 5	CLL	π_D^{TR}	0.01	0.09	0.30	*0.15*	0.01	0.12	0.38	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	44.02	34.12	21.74		41.61	27.04	14.12	
		Pr(Stop)	0.00	0.00	0.44		0.00	0.00	0.40	
		Pr(Select)	0.99	0.01	0.00		1.00	0.00	0.00	
	ALL	π_D^{TR}	0.12	0.03	0.18	*0.20*	0.16	0.04	0.23	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	30.67	40.07	28.05		23.24	35.70	20.14	
		Pr(Stop)	0.00	0.00	0.02		0.00	0.00	0.02	
		Pr(Select)	0.01	0.99	0.00		0.01	0.99	0.00	
	NHL	π_D^{TR}	0.10	0.15	0.01	*0.20*	0.13	0.20	0.01	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	32.81	28.83	44.29		26.24	21.60	41.02	
		Pr(Stop)	0.00	0.01	0.00		0.00	0.01	0.00	
		Pr(Select)	0.00	0.00	1.00		0.00	0.00	1.00	
Scenario 6	CLL	π_D^{TR}	0.35	0.03	0.13	*0.15*	0.75	0.10	0.37	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	42.63	59.91	58.41		15.66	55.39	41.60	
		Pr(Stop)	0.74	0.00	0.09		0.97	0.00	0.31	
		Pr(Select)	0.00	0.74	0.26		0.00	0.98	0.02	
	ALL	π_D^{TR}	0.08	0.45	0.02	*0.20*	0.24	0.86	0.06	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	58.39	36.62	57.72		47.53	8.12	54.71	
		Pr(Stop)	0.00	0.83	0.00		0.02	0.98	0.00	
		Pr(Select)	0.59	0.00	0.41		0.05	0.00	0.95	
	NHL	π_D^{TR}	0.05	0.10	0.30	*0.20*	0.16	0.29	0.70	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	59.74	57.00	48.00		53.30	44.20	19.60	
		Pr(Stop)	0.00	0.02	0.51		0.00	0.04	0.86	
		Pr(Select)	0.64	0.36	0.00		0.86	0.14	0.00	

Table 6 (continued): **Simulation Results - Robustness**. Log-logistic distributions are assumed to simulate data and the Weibull distribution is assumed for the design. The true marginal probabilities of outcomes occurring within their follow-up remain the same.

Truth	Weibull			Log-logistic	Log-normal
Design	Proposed	No Covariate	Proposed with $N_{\max} = 120$	Proposed	Proposed
Scenario 1	0.002	0.000	0.002	0.002	0.000
Scenario 2	0.076	0.029	0.076	0.136	0.060
Scenario 3	0.058	0.015	0.058	0.168	0.043
Scenario 4	0.000	0.000	0.000	0.000	0.000
Scenario 5	0.002	0.000	0.002	0.002	0.000
Scenario 6	0.003	0.000	0.003	0.005	0.002

Table 7: Pr(A trial is termiated by the regulator's safety rule) under simulation scenarios. Three different distributions, Weibull, Log-logistic and Log-normal distributions are used to simulate data as indicated in the first row. Three designs, the proposed design ("Proposed"), the design without covariate ("No Covariate") and the proposed design with $N_{\max} = 120$ ("Proposed with $N_{\max} = 120$) are used. All designs assume the Weibull distribution.

		Bulk ($\rightarrow$)	LBD ($Z=0$)				HBD ($Z=1$)			
	Types ($\downarrow$)	Dose ($\rightarrow$)	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$
Scenario 1	CLL	π_D^{TR}	0.02	0.02	0.02	*0.15*	0.10	0.10	0.10	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	46.32	46.32	46.32		44.04	44.04	44.04	
		Pr(Stop)	0.00	0.00	0.00		0.00	0.00	0.00	
		Pr(Select)	0.34	0.35	0.32		0.32	0.34	0.34	
	ALL	π_D^{TR}	0.10	0.10	0.10	*0.20*	0.25	0.25	0.25	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	50.52	50.52	50.52		37.97	37.97	37.97	
		Pr(Stop)	0.00	0.00	0.00		0.02	0.02	0.01	
		Pr(Select)	0.32	0.35	0.33		0.32	0.34	0.34	
	NHL	π_D^{TR}	0.05	0.05	0.05	*0.20*	0.15	0.15	0.15	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	49.18	49.18	49.18		38.35	38.35	38.35	
		Pr(Stop)	0.00	0.00	0.00		0.00	0.00	0.00	
		Pr(Select)	0.31	0.35	0.34		0.33	0.33	0.34	
Scenario 2	CLL	π_D^{TR}	0.02	0.45	0.60	*0.15*	0.04	0.70	0.84	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	42.34	22.86	16.00		39.73	9.49	4.63	
		Pr(Stop)	0.00	0.98	0.99		0.00	1.00	1.00	
		Pr(Select)	1.00	0.00	0.00		1.00	0.00	0.00	
	ALL	π_D^{TR}	0.40	0.60	0.05	*0.20*	0.64	0.84	0.10	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	23.81	15.82	40.41		10.99	4.62	36.02	
		Pr(Stop)	0.86	0.99	0.00		0.95	1.00	0.00	
		Pr(Select)	0.00	0.00	1.00		0.00	0.00	1.00	
	NHL	π_D^{TR}	0.65	0.05	0.35	*0.20*	0.88	0.10	0.58	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	14.03	40.47	26.31		3.46	36.08	13.26	
		Pr(Stop)	0.99	0.00	0.80		1.00	0.00	0.87	
		Pr(Select)	0.00	1.00	0.00		0.00	1.00	0.00	
Scenario 3	CLL	π_D^{TR}	0.42	0.38	0.37	*0.15*	0.66	0.62	0.60	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	40.33	44.40	44.55		20.71	24.52	24.81	
		Pr(Stop)	0.96	0.94	0.93		0.99	0.98	0.98	
		Pr(Select)	0.03	0.04	0.06		0.01	0.02	0.02	
	ALL	π_D^{TR}	0.52	0.58	0.65	*0.20*	0.77	0.83	0.88	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	33.99	29.43	24.52		14.34	11.01	7.57	
		Pr(Stop)	0.98	0.98	1.00		0.99	1.00	1.00	
		Pr(Select)	0.02	0.01	0.00		0.01	0.00	0.00	
	NHL	π_D^{TR}	0.40	0.42	0.45	*0.20*	0.64	0.67	0.70	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	42.49	40.21	38.79		22.61	20.32	18.95	
		Pr(Stop)	0.88	0.90	0.95		0.94	0.96	0.98	
		Pr(Select)	0.10	0.08	0.04		0.05	0.04	0.02	

Table 8: **Simulation Truth and Results with** $N_{\max} = 120$. The maximum number of patients in a trial is increased from 60 to 120. The simulation results under the proposed design are summarized in Pr(Stop) and Pr(Select). For easy evaluation, the simulation truth is included.

		Bulk ($\rightarrow$)	LBD ($Z=0$)				HBD ($Z=1$)			
	Types ($\downarrow$)	Dose ($\rightarrow$)	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$
Scenario 4	CLL	π_D^{TR}	0.01	0.10	0.25	*0.15*	0.01	0.11	0.27	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	48.99	58.91	45.84		38.03	24.74	14.45	
		Pr(Stop)	0.00	0.00	0.48		0.00	0.00	0.12	
		Pr(Select)	0.01	0.99	0.00		1.00	0.00	0.00	
	ALL	π_D^{TR}	0.01	0.09	0.27	*0.20*	0.01	0.10	0.29	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	48.82	58.66	43.95		37.54	26.47	14.55	
		Pr(Stop)	0.00	0.00	0.28		0.00	0.00	0.04	
		Pr(Select)	0.00	1.00	0.00		1.00	0.00	0.00	
	NHL	π_D^{TR}	0.01	0.08	0.30	*0.20*	0.01	0.09	0.33	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	48.87	58.22	40.45		40.28	26.92	11.70	
		Pr(Stop)	0.00	0.00	0.53		0.00	0.00	0.12	
		Pr(Select)	0.00	1.00	0.00		1.00	0.00	0.00	
Scenario 5	CLL	π_D^{TR}	0.01	0.09	0.30	*0.15*	0.01	0.12	0.38	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	44.30	33.82	22.05		41.40	27.18	14.33	
		Pr(Stop)	0.00	0.00	0.78		0.00	0.00	0.56	
		Pr(Select)	1.00	0.00	0.00		1.00	0.00	0.00	
	ALL	π_D^{TR}	0.12	0.03	0.18	*0.20*	0.16	0.04	0.23	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	30.68	40.15	27.96		23.62	35.88	20.52	
		Pr(Stop)	0.00	0.00	0.02		0.00	0.00	0.01	
		Pr(Select)	0.00	1.00	0.00		0.00	1.00	0.00	
	NHL	π_D^{TR}	0.10	0.15	0.01	*0.20*	0.13	0.20	0.01	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	32.73	28.73	44.09		26.24	21.60	41.22	
		Pr(Stop)	0.00	0.00	0.00		0.00	0.00	0.00	
		Pr(Select)	0.00	0.00	1.00		0.00	0.00	1.00	
Scenario 6	CLL	π_D^{TR}	0.35	0.03	0.13	*0.15*	0.75	0.10	0.37	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	41.74	59.80	57.69		14.53	55.48	40.90	
		Pr(Stop)	0.92	0.00	0.10		1.00	0.00	0.44	
		Pr(Select)	0.00	0.62	0.38		0.00	1.00	0.00	
	ALL	π_D^{TR}	0.08	0.45	0.02	*0.20*	0.24	0.86	0.06	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	57.75	34.95	57.83		47.19	7.81	55.07	
		Pr(Stop)	0.00	0.93	0.00		0.01	1.00	0.00	
		Pr(Select)	0.86	0.00	0.14		0.00	0.00	1.00	
	NHL	π_D^{TR}	0.05	0.10	0.30	*0.20*	0.16	0.29	0.70	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	59.50	57.18	46.28		52.57	44.10	18.84	
		Pr(Stop)	0.00	0.01	0.67		0.00	0.02	0.99	
		Pr(Select)	0.56	0.44	0.00		0.98	0.02	0.00	

Table 8 (continued): **Simulation Truth and Results with** $N_{\max} = 120$. The maximum number of patients in a trial is increased from 60 to 120. The simulation results under the proposed design are summarized in Pr(Stop) and Pr(Select). For easy evaluation, the simulation truth is included.

		Bulk ($\rightarrow$)	LBD ($Z=0$)				HBD ($Z=1$)			
	Types ($\downarrow$)	Dose ($\rightarrow$)	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$
Scenario 1	CLL	π_D^{TR}	0.02	0.02	0.02	*0.15*	0.10	0.10	0.10	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	46.32	46.32	46.32		44.04	44.04	44.04	
		Pr(Stop)	0.00	0.00	0.00		0.00	0.00	0.00	
		Pr(Select)	0.33	0.36	0.32		0.34	0.32	0.33	
	ALL	π_D^{TR}	0.10	0.10	0.10	*0.20*	0.25	0.25	0.25	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	50.52	50.52	50.52		37.97	37.97	37.97	
		Pr(Stop)	0.01	0.00	0.01		0.03	0.04	0.04	
		Pr(Select)	0.33	0.29	0.38		0.32	0.34	0.34	
	NHL	π_D^{TR}	0.05	0.05	0.05	*0.20*	0.15	0.15	0.15	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	49.18	49.18	49.18		38.35	38.35	38.35	
		Pr(Stop)	0.00	0.00	0.00		0.00	0.01	0.01	
		Pr(Select)	0.35	0.32	0.33		0.33	0.35	0.32	
Scenario 2	CLL	π_D^{TR}	0.02	0.45	0.60	*0.15*	0.04	0.70	0.84	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	42.34	22.86	16.00		39.73	9.49	4.63	
		Pr(Stop)	0.00	0.79	0.93		0.00	0.97	0.99	
		Pr(Select)	1.00	0.00	0.00		1.00	0.00	0.00	
	ALL	π_D^{TR}	0.40	0.60	0.05	*0.20*	0.64	0.84	0.10	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	23.81	15.82	40.41		10.99	4.62	36.02	
		Pr(Stop)	0.54	0.86	0.00		0.78	0.98	0.00	
		Pr(Select)	0.01	0.00	0.99		0.00	0.00	1.00	
	NHL	π_D^{TR}	0.65	0.05	0.35	*0.20*	0.88	0.10	0.58	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	14.03	40.47	26.31		3.46	36.08	13.26	
		Pr(Stop)	0.89	0.00	0.48		0.99	0.00	0.68	
		Pr(Select)	0.00	0.99	0.01		0.00	1.00	0.00	
Scenario 3	CLL	π_D^{TR}	0.42	0.38	0.37	*0.15*	0.66	0.62	0.60	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	40.33	44.40	44.55		20.71	24.52	24.81	
		Pr(Stop)	0.77	0.73	0.71		0.94	0.94	0.91	
		Pr(Select)	0.11	0.16	0.18		0.04	0.05	0.08	
	ALL	π_D^{TR}	0.52	0.58	0.65	*0.20*	0.77	0.83	0.88	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	33.99	29.43	24.52		14.34	11.01	7.57	
		Pr(Stop)	0.85	0.89	0.92		0.98	0.99	0.99	
		Pr(Select)	0.11	0.06	0.04		0.02	0.01	0.01	
	NHL	π_D^{TR}	0.40	0.42	0.45	*0.20*	0.64	0.67	0.70	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	42.49	40.21	38.79		22.61	20.32	18.95	
		Pr(Stop)	0.61	0.63	0.75		0.81	0.82	0.91	
		Pr(Select)	0.26	0.21	0.09		0.15	0.14	0.05	

Table 9: **Simulation Truth and Results with Different Follow Up Period**. The follow up period for monitoring patients are reduced from $\boldsymbol{L} = (365, 365, 100, 100, 365)$ to $(100, 100, 100, 30, 100)$. The simulation results under the proposed design are summarized in Pr(Stop) and Pr(Select). For easy evaluation, the simulation truth is included.

		Bulk ($\rightarrow$)	LBD ($Z=0$)				HBD ($Z=1$)			
	Types ($\downarrow$)	Dose ($\rightarrow$)	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$	$d=1$	$d=2$	$d=3$	$\bar{\pi}_D$
Scenario 4	CLL	π_D^{TR}	0.01	0.10	0.25	*0.15*	0.01	0.11	0.27	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	48.99	58.91	45.84		38.03	24.74	14.45	
		Pr(Stop)	0.00	0.00	0.12		0.00	0.00	0.15	
		Pr(Select)	0.04	0.92	0.04		0.99	0.01	0.00	
	ALL	π_D^{TR}	0.01	0.09	0.27	*0.20*	0.01	0.10	0.29	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	48.82	58.66	43.95		37.54	26.47	14.55	
		Pr(Stop)	0.00	0.00	0.08		0.00	0.00	0.10	
		Pr(Select)	0.03	0.94	0.03		0.99	0.01	0.00	
	NHL	π_D^{TR}	0.01	0.08	0.30	*0.20*	0.01	0.09	0.33	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	48.87	58.22	40.45		40.28	26.92	11.70	
		Pr(Stop)	0.00	0.00	0.17		0.00	0.00	0.19	
		Pr(Select)	0.03	0.96	0.01		0.99	0.01	0.00	
Scenario 5	CLL	π_D^{TR}	0.01	0.09	0.30	*0.15*	0.01	0.12	0.38	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	44.30	33.82	22.05		41.40	27.18	14.33	
		Pr(Stop)	0.00	0.01	0.22		0.00	0.01	0.39	
		Pr(Select)	0.98	0.02	0.00		0.98	0.02	0.00	
	ALL	π_D^{TR}	0.12	0.03	0.18	*0.20*	0.16	0.04	0.23	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	30.68	40.15	27.96		23.62	35.88	20.52	
		Pr(Stop)	0.00	0.00	0.02		0.01	0.00	0.03	
		Pr(Select)	0.03	0.96	0.01		0.03	0.96	0.00	
	NHL	π_D^{TR}	0.10	0.15	0.01	*0.20*	0.13	0.20	0.01	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	32.73	28.73	44.09		26.24	21.60	41.22	
		Pr(Stop)	0.00	0.01	0.00		0.01	0.01	0.00	
		Pr(Select)	0.02	0.01	0.98		0.02	0.00	0.98	
Scenario 6	CLL	π_D^{TR}	0.35	0.03	0.13	*0.15*	0.75	0.10	0.37	*0.30*
	($r=1$)	$\bar{U}^{\text{TR}}$	41.74	59.80	57.69		14.53	55.48	40.90	
		Pr(Stop)	0.53	0.00	0.07		0.96	0.00	0.27	
		Pr(Select)	0.02	0.53	0.45		0.00	0.95	0.05	
	ALL	π_D^{TR}	0.08	0.45	0.02	*0.20*	0.24	0.86	0.06	*0.40*
	($r=2$)	$\bar{U}^{\text{TR}}$	57.75	34.95	57.83		47.19	7.81	55.07	
		Pr(Stop)	0.01	0.57	0.00		0.03	0.97	0.00	
		Pr(Select)	0.66	0.01	0.32		0.12	0.00	0.88	
	NHL	π_D^{TR}	0.05	0.10	0.30	*0.20*	0.16	0.29	0.70	*0.40*
	($r=3$)	$\bar{U}^{\text{TR}}$	59.50	57.18	46.28		52.57	44.10	18.84	
		Pr(Stop)	0.00	0.01	0.34		0.00	0.03	0.82	
		Pr(Select)	0.53	0.45	0.03		0.79	0.21	0.00	

Table 9 (continued): **Simulation Truth and Results with Different Follow Up Period** The follow up period for monitoring patients are reduced from $\boldsymbol{L} = (365, 365, 100, 100, 365)$ to $(100, 100, 100, 30, 100)$. The simulation results under the proposed design are summarized in Pr(Stop) and Pr(Select). For easy evaluation, the simulation truth is included.