Supplementary Material for "A Phase I-II Basket Trial Design to Optimize Dose-Schedule Regimes based on Delayed Outcomes'

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S.1 Bayesian data augmentation steps

The steps of the BDA procedure of the proposed model are given as follows:

(1) Imputation step: Impute a missing toxicity or efficacy outcome by sampling from the distributions

$$\begin{aligned} X_i \mid \delta_{X,i}=0, p, q, \beta, D_n^{\text{obs}} &\sim \text{Bernoulli}(\Pr(X_i=1 \mid \delta_{X,i}=0, p, q, \beta, D_n^{\text{obs}})), \\ Y_i \mid \delta_{Y,i}=0, \boldsymbol{\alpha}, \mathbf{w}, \sigma_\eta^2, \tilde{D}_n^{\text{obs}} &\sim \text{Bernoulli}(\Pr(Y_i=1 \mid \delta_{Y,i}=0, \boldsymbol{\alpha}, \mathbf{w}, \sigma_\eta^2, \tilde{D}_n^{\text{obs}})). \end{aligned}$$

We denote the completed data obtained after filling in any missing outcomes in this way by $\tilde{D}_n^{\text{com}}$.

(2) Posterior step:

(i) Sample $\boldsymbol{\theta}$ from $\pi(\boldsymbol{\theta} \mid \boldsymbol{\theta}_0, \tilde{D}_n^{\text{com}})$.

(ii) Sample (p, q, β) from $\pi(p, q, \beta \mid \boldsymbol{\theta}_1, \tilde{D}_n^{\text{com}})$.

(iii) Sample $(\boldsymbol{\alpha}, \mathbf{w})$ from $\pi(\boldsymbol{\alpha}, \mathbf{w} \mid \boldsymbol{\theta}_2, \tilde{D}_n^{\text{com}})$.

S.2 Establishing a prior

The following steps may be followed to determine a prior.

Determining $\boldsymbol{\theta}_0$ in the primary inference model (2.1).

Step 1. Specify the hyperparameters of $(\sigma_\xi^2, \sigma_\eta^2, \Sigma_{u,v})$, which can be arbitrarily reasonable values as the simulation study demonstrates that the proposed model is robust to model misspecification. For example, one can choose $\sigma_\xi^2 \in (0.5, 10)$, $\sigma_\eta^2 \in (0.5, 10)$, the diagonal values of $\Sigma_{u,v}$ from $(0, \min(\sigma_\xi^2, \sigma_\eta^2))$, and the off-diagonal values of $\Sigma_{u,v}$ from $(-0.5, 0.5)$.

Step 2. Given a regime r and subtype b, we solve for the values of ξ_0 and η_0 by matching the respective modes of the prior elicited toxicity probability $\pi_X(b, r)^{\text{e}}$ and efficacy probability $\pi_Y(b, r)^{\text{e}}$, which are obtained from the clinicians. Formally,

$$\xi_0 = \Phi^{-1}\left(1 - \pi_X(b, r)^{\text{e}}, \sigma_\xi^2 + \Sigma_{u,v}(1, 1)\right),$$

where $\Sigma_{u,v}(1,1)$ is the $(1,1)$th element of the covariance matrix $\Sigma_{u,v}$ and $\Phi^{-1}(\cdot)$ is the quantile function of a standard normal distribution. Similarly,

$$\eta_0 = \Phi^{-1}\left(1 - \pi_Y(b,r)^{\mathrm{e}}, \sigma_\xi^2 + \Sigma_{u,v}(2,2)\right).$$

Step 3. Assume preliminary values of the rest of the hyperparameters in $\boldsymbol{\theta}_0$, i.e., ν_ξ^2, ν_η^2, ψ_0 and γ_0. For example, one can set $\nu_\xi^2 = \nu_\eta^2 = 5^2$, $\psi_0 = 0$, and $\gamma_0 = 5$.

Step 4. Given the prespecified $\boldsymbol{\theta}_0$, jointly simulate a sample of $(\pi_X(b,r), \pi_Y(b,r))$ using the primary inference model (2.1).

Step 5. Using the method of moments, fit the simulated prior sample of $\pi_X(b,r)$ values to a Beta$(\alpha_{br}, \beta_{br})$ distribution. That is,

$$\alpha_{br} = \bar{\pi}_X(b,r)\left[\frac{\bar{\pi}_X(b,r)\{1-\bar{\pi}_X(b,r)\}}{s_X(b,r)} - 1\right]$$

and

$$\beta_{br} = \frac{\alpha_{br}(1-\bar{\pi}_X(b,r))}{\bar{\pi}_X(b,r)},$$

where $\bar{\pi}_X(b,r)$ and $s_X^2(b,r)$ are, respectively, the mean and variance of the prior sample of simulated $\pi_X(b,r)$ values. An approximate prior ESS is then given by $\alpha_{br} + \beta_{br}$ for toxicity. An approximate prior ESS is obtained similarly for efficacy.

Step 6. Repeat Steps 3–5 until the prior ESS value is near 1 for each combination of (b,r) by adjusting the values of ν_ξ^2, ν_η^2, ψ_0 and γ_0. For example, if the prior ESS value is greater than 1, one can enlarge the values of ν_ξ^2, ν_η^2 and γ_0.

Determining $\boldsymbol{\theta}_1$ in the imputation PH model (2.3).

Step 1. Specify prior estimates of low-grade toxicity probabilities $\pi_L(b,r)^{\mathrm{e}} = \Pr(L_i = 1 \mid b,r)$, which can be elicited from the clinicians.

Step 2. Assume preliminary values of the hyperparameters in $\boldsymbol{\theta}_1$, i.e., σ_β, α_p, β_p, α_q, β_q. For example, one can take $\sigma_\beta = 10$, $\alpha_p = \beta_p = \alpha_q = \beta_q = 0.1$, which perform well in most settings.

Step 3. Given (b,r), use the priors in (2.3) to simulate a sample of (β,p,q) values based on $\boldsymbol{\theta}_1$ in Step 2. Obtain a sample of $\pi_X(b,r)$ values based on the relationship

$$\pi_X(b,r) = (1-\pi_L(b,r)^{\mathrm{e}})\Pr(U_i \le T_X \mid L=0,p,q,\beta) + \pi_L(b,r)^{\mathrm{e}}\Pr(U_i \le T_X \mid L=1,p,q,\beta),$$

where

$$\Pr(U_i \le T_X \mid L,p,q,\beta) = 1 - \exp(-pT_X^q)^{\exp(\beta L)}, \quad L = 0,\ 1,$$

is the cumulative distribution function of U_i based on the specified PH model. This is the conditional probability of experiencing a DLT, given the indicator L of whether earlier low-grade toxicity occurred.

Step 4. Using the method of moments, fit the prior sample of $\pi_X(b,r)$ values to a Beta(α_{br},β_{br}) distribution, and use this to determine an approximate prior ESS as $\alpha_{br}+\beta_{br}$ for toxicity, as done earlier when determining $\boldsymbol{\theta}_0$.

Step 5. Repeat Steps 3–4 until the prior ESS value is near 1 for each combination of (b,r) by adjusting the values of $\boldsymbol{\theta}_1$.

Determining $\boldsymbol{\theta}_2$ in the imputation bioactivity model (2.4).

Step 1. Specify the hyperparameters of (σ_η^2,α_0), which can be arbitrarily reasonable values as the simulation study demonstrates that the proposed model is robust to model misspecification. For example, one can choose $\sigma_\eta^2\in(0.5,10)$, and $\alpha_0\in(-5,5)$.

Step 2. Specify the hyperparameters of $(\tau_{w_0}^2,\tau_\alpha^2,\alpha_z,\beta_z,v_w^2)$. These hyperparameters are associated with prior variances, so any reasonably large values are suitable. For example, one may set $\tau_{w_0}^2=\tau_\alpha^2=v_w^2=10$, and $\alpha_z=\beta_z=0.1$.

Step 3. Assume preliminary values of the rest of the hyperparameters in $\boldsymbol{\theta}_2$, i.e., $\bar{w}_0$, ψ_0 and γ_0. For example, we take $\bar{w}_0=\psi_0=0$ and $\gamma_0=5$.

Step 4. Based on the above values, simulate a sample of $(\alpha_1,\alpha_2,w_{br})$ values, and use these to obtain a sample of $\pi_Y(b,r)$ values based on the relationship

$$\pi_Y(b,r)=1-\Phi\left(0,\alpha_0+\alpha_1 w_{br}+\alpha_2 w_{br}^2,\sigma_\eta^2\right).$$

Step 5. Using the method of moments, fit the prior sample of $\pi_Y(b,r)$ values to a Beta(α_{br},β_{br}) distribution, and determine the approximate prior ESS as $\alpha_{br}+\beta_{br}$ for efficacy.

Step 6. Repeat Steps 3–5 until the prior ESS value is near 1 for each combination of (b,r) by adjusting the values of $\bar{w}_0$, ψ_0 and γ_0.

S.3 Data generating mechanism

For the simulations, the trial data for the toxicity and efficacy outcomes (x_i,y_i), $i=1,\ldots,n$ are generated using the hierarchical model (2.1). The time-to-event outcomes t_i, $i=1,\ldots,n$ are generated based on the Cox PH model (2.3). The bioactivity outcomes z_{ik}, $i=1,\ldots,n$ are generated from the model (2.4). In particular, we set $\sigma_\xi^{2.\text{true}}=\sigma_\eta^{2.\text{true}}=0.5^2$, and $\Sigma_{u,v}^{\text{true}}(1,1)=\Sigma_{u,v}^{\text{true}}(2,2)=0.3^2$ and $\Sigma_{u,v}^{\text{true}}(1,2)=\Sigma_{u,v}^{\text{true}}(2,1)=-0.2\times 0.3^2$, where $\Sigma_{u,v}^{\text{true}}(i,j)$ denotes the (i,j)th entry of the covariance matrix $\Sigma_{u,v}^{\text{true}}$. The true values of $(\tilde{\xi}_{b,r}^{\text{true}},\tilde{\eta}_{b,r}^{\text{true}})$ are then given by $\tilde{\xi}_{b,r}^{\text{true}}=\Phi^{-1}\left(\pi_X(b,r),0,\Sigma_{\xi,\eta}^{\text{true}}(1,1)\right)$ and $\tilde{\eta}_{b,r}^{\text{true}}=\Phi^{-1}\left(\pi_Y(b,r),0,\Sigma_{\xi,\eta}^{\text{true}}(2,2)\right)$, where $\Phi^{-1}(\cdot,0,\sigma^2)$ denotes the quantile distribution of a normal random variable with mean 0 and variance σ^2. To simulate the time-to-toxicity data, we require that $S(T_X\mid L_i,b,r)=1-\pi_X(b,r)$ and assume that $S_0=S(T_X\mid L_i=0)=0.99$ and $S_1=S(T_X\mid L_i=1)=0.40$. We also assume that the baseline survival S_0 is a Weibull random variable with the cumulative hazard function as qT^p and take $S(T_X/2\mid L_i=0)=1-(1-S_0)/2$. Then we have $\beta^{\text{true}}=\log(\log S_1/\log S_0)$,

$p^{\text{true}} = \log(\log(S_0)/\log(1-(1-S_0)/2))/\log(2)$ and $q^{\text{true}} = -\log(S_0)/T_X^{p^{\text{true}}}$. We obtain the latent variables for $1-S_0$ and $1-S_1$, as $\xi_{S_0}^{\text{true}} = \Phi\left(1-S_0, 0, \Sigma_{\xi,\eta}^{\text{true}}(1,1)\right)$ and $\xi_{S_1}^{\text{true}} = \Phi\left(1-S_1, 0, \Sigma_{\xi,\eta}^{\text{true}}(1,1)\right)$. The lower-grade toxicity probability is given by $\pi_L(b,r) = \Pr(L_i = 1 \mid b, r) = (1 - S_0 - \pi_X(b,r))/(S_1 - S_0)$. To generate the bioactivity data, we take $\alpha_0^{\text{true}} = 0.5$, $\alpha_1^{\text{true}} = -1$ and $\alpha_2^{\text{true}} = 0$. The latent variable $w_{b,r}^{\text{true}}$ then can be obtained by solving the equation $\tilde{\eta}_{b,r}^{\text{true}} = \alpha_0^{\text{true}} + \alpha_1^{\text{true}} w_{b,r}^{\text{true}}$. In addition, we set $w_0^{\text{true}} = 3$ and $\sigma_z^{2.\text{true}} = 1$.

The data (X, Y, L, T, Z) for a patient with subtype b and treatment regime $r = (d, s)$ can be simulated based on the following steps.

Step 1. Generate patient-level random effects $(u, v) \sim \text{BN}(\mathbf{0}_2, \Sigma_{u,v}^{\text{true}})$.

Step 2. Generate the toxicity data sequentially following steps 2.1–2.3.

Step 2.1. Generate the lower-grade toxicity $L \sim \text{Bernoulli}(\pi_L(b,r))$.

Step 2.2. Generate the toxicity outcome $X \sim \text{Bernoulli}(\pi_X)$, where $\pi_X = \text{I}(L = 0)\Phi(\xi_{S_0}^{\text{true}} + u, 0, \sigma_\xi^{2.\text{true}}) + \text{I}(L = 1)\Phi(\xi_{S_1}^{\text{true}} + u, 0, \sigma_\xi^{2.\text{true}})$.

Step 2.3. Generate the time-to-toxicity data T from the truncated Cox PH model with the support given by $\text{I}(X = 0)(T_X, \infty) + \text{I}(X = 1)(0, T_X)$.

Step 3. Generate the efficacy data sequentially following steps 3.1–3.2.

Step 3.1. Generate the efficacy outcome $Y \sim \text{Bernoulli}(\Phi(\tilde{\eta}_{b,r}^{\text{true}}, 0, \eta^{2.\text{true}}))$.

Step 3.2. Generate the bioactivity outcome $Z \mid t \sim \text{N}(w_0^{\text{true}} + w_{b,r}^{\text{true}} t, \sigma_z^{2.\text{true}})$.

S.4 Design configuration

To implement the proposed design in the simulation study, we set $\overline{\pi}_X = 0.15$ and $\underline{\pi}_Y = 0.20$ as the design parameters that control treatment regime admissibility. Given these values, the cutoff probabilities were tuned based on extensive preliminary simulations, which motivated $c_X = c_Y = 0.95$. The utility function we consider for the MM trial is given as $U(0,1) = 100, U(0,0) = 60, U(1,1) = 40, U(1,0) = 0$. This utility reflects the viewpoint that protecting patient safety is considered slightly more important than achieving a treatment response. We set $\kappa = 0.15$, so on average, 9 patients are assigned to each schedule for each subtype in stage 1 in order to obtain enough toxicity data to identify any overly toxic regimes in stage 1. Following the approach described earlier for deriving a prior, we set the hyperparameters for BTD_{12} to be $\sigma_\xi^2 = \sigma_\eta^2 = 2^2$, $\nu_\xi^2 = \nu_\eta^2 = 5^2$, $\xi_0 = -6$, $\eta_0 = -1$, $\psi_0 = 0$, $\gamma_0 = 5$, and set the diagonal values of $\Sigma_{u,v}$ to be 1 and the off-diagonal values to be -0.5. This specification of the hyperparameters $\boldsymbol{\theta}_0$ gives approximate ESS values ranging from 0.25 to 2 for the priors of interest. We also used the ESS approach to determine the hyperparameters $\boldsymbol{\theta}_1$ and $\boldsymbol{\theta}_2$ in the PH model (2.3) and the bioactivity model (2.4). We took $\boldsymbol{\theta}_1 = (\sigma_\beta, \alpha_p, \beta_p, \alpha_q, \beta_q) = (10, 0.1, 0.1, 0.1, 0.1)$, which leads to noninformative priors for the PH model. For $\boldsymbol{\theta}_2$ in the bioactivity model, we fixed $\sigma_\eta^2 = 2^2, \alpha_0 = 1, \tau_{w_0}^2 = \tau_\alpha^2 = 10, \alpha_z = \beta_z = 0.1, \bar{w}_0 = 0, \nu_w^2 = 10, \psi_0 = 0$ and $\gamma_0 = 5$.

S.5 Simulation scenarios and results

Table S1 provides the marginal probabilities of toxicity and efficacy, $(\pi_X(b,r), \pi_Y(b,r))$, for the 12 scenarios considered in Section 4. The expected utility $\mathrm{E}(U(X,Y) \mid b,r)$ of each subtype-specific dose–schedule regime is given in Table S2, where the optimal treatment regimes for each subtype are in boldface. Table S3 summarizes the within-subtype regime selection percentages, based on the proposed designs, across 1000 simulated trials for each of the 12 scenarios given in Table S1. Table S4 summarizes the number of patients allocated to each regime based on the proposed design.

S.6 Additional simulations

As suggested by an Associate Editor, we conducted an additional simulation study to examine the performance of the proposed design in a setting where the treatment effects are very similar for some subtypes and very different for the other subtypes. To do this, we modified scenarios 1, 3, 9, and 11 in Table S1 by changing the marginal toxicity and efficacy probabilities of the dose–schedule regimes for subtype 3, so that subtypes 1 and 2 have homogeneous treatment effects while subtype 3 has different treatment effects for subtypes 1 and 2. The four additional simulation scenarios are given in Table S5. We compared the operating characteristics of BTD_{12} with those of the naive design, which is based on the subtype homogeneity assumption, and the ITD_{12} design, which is based on the subtype heterogeneity assumption. The simulation results in Table S6 show that the proposed BTD_{12} design still reliably strikes a balance between the no-information-borrowing design ITD_{12}) and the fully-information-borrowing naive design in these cases.

Table S1: True marginal toxicity and efficacy probabilities $(\pi_X(b,r), \pi_Y(b,r))$ under the 12 simulation scenarios. The scenarios given in boxes correspond to the heterogenous cases.

Scenario	Cancer subtype	1			2			3		
	Schedule/dose	1	2	3	1	2	3	1	2	3
1	1	(.03,.10)	(.05,.20)	(.15,.60)	(.03,.10)	(.05,.20)	(.15,.60)	(.03,.10)	(.05,.20)	(.15,.60)
	2	(.05,.50)	(.15,.40)	(.30,.40)	(.05,.50)	(.15,.40)	(.30,.40)	(.05,.50)	(.15,.40)	(.30,.40)
	3	(.13,.35)	(.45,.40)	(.60,.45)	(.13,.35)	(.45,.40)	(.60,.45)	(.13,.35)	(.45,.40)	(.60,.45)
2	1	(.03,.10)	(.05,.20)	(.15,.60)	(.03,.10)	(.05,.50)	(.15,.40)	(.03,.40)	(.05,.10)	(.15,.40)
	2	(.05,.50)	(.15,.40)	(.30,.40)	(.05,.20)	(.15,.60)	(.30,.40)	(.05,.30)	(.15,.30)	(.30,.40)
	3	(.13,.35)	(.45,.40)	(.60,.45)	(.13,.35)	(.45,.40)	(.60,.45)	(.13,.60)	(.45,.40)	(.60,.45)
3	1	(.05,.10)	(.15,.40)	(.40,.10)	(.05,.10)	(.15,.40)	(.40,.10)	(.05,.10)	(.15,.40)	(.40,.10)
	2	(.05,.40)	(.18,.20)	(.40,.10)	(.05,.40)	(.18,.20)	(.40,.10)	(.05,.40)	(.18,.20)	(.40,.10)
	3	(.03,.15)	(.08,.23)	(.15,.45)	(.03,.15)	(.08,.23)	(.15,.45)	(.03,.15)	(.08,.23)	(.15,.45)
4	1	(.05,.10)	(.15,.40)	(.40,.10)	(.05,.40)	(.15,.30)	(.40,.10)	(.05,.10)	(.15,.20)	(.40,.30)
	2	(.05,.40)	(.18,.20)	(.40,.10)	(.05,.10)	(.18,.20)	(.40,.10)	(.05,.40)	(.18,.40)	(.40,.40)
	3	(.03,.15)	(.08,.23)	(.15,.45)	(.03,.15)	(.08,.33)	(.15,.35)	(.03,.45)	(.08,.30)	(.15,.30)
5	1	(.03,.10)	(.05,.30)	(.10,.60)	(.03,.10)	(.05,.30)	(.10,.60)	(.03,.10)	(.05,.30)	(.10,.60)
	2	(.07,.30)	(.15,.40)	(.30,.50)	(.07,.30)	(.15,.40)	(.30,.50)	(.07,.30)	(.15,.40)	(.30,.50)
	3	(.05,.25)	(.10,.34)	(.15,.25)	(.05,.25)	(.10,.34)	(.15,.25)	(.05,.25)	(.10,.34)	(.15,.25)
6	1	(.03,.10)	(.05,.30)	(.10,.60)	(.03,.10)	(.05,.30)	(.10,.30)	(.03,.10)	(.05,.30)	(.10,.40)
	2	(.07,.30)	(.15,.40)	(.30,.50)	(.07,.20)	(.15,.65)	(.30,.40)	(.07,.30)	(.15,.40)	(.30,.30)
	3	(.05,.25)	(.10,.34)	(.15,.25)	(.05,.25)	(.10,.30)	(.15,.25)	(.05,.60)	(.10,.40)	(.15,.30)
7	1	(.05,.10)	(.12,.25)	(.20,.33)	(.05,.10)	(.12,.25)	(.20,.33)	(.05,.10)	(.12,.25)	(.20,.33)
	2	(.07,.05)	(.13,.45)	(.25,.30)	(.07,.05)	(.13,.45)	(.25,.30)	(.07,.05)	(.13,.45)	(.25,.30)
	3	(.02,.23)	(.05,.15)	(.08,.10)	(.02,.23)	(.05,.15)	(.08,.10)	(.02,.23)	(.05,.15)	(.08,.10)
8	1	(.05,.10)	(.12,.25)	(.20,.33)	(.05,.35)	(.12,.35)	(.20,.35)	(.05,.01)	(.12,.05)	(.20,.40)
	2	(.07,.05)	(.13,.45)	(.25,.30)	(.07,.35)	(.13,.35)	(.25,.35)	(.07,.01)	(.13,.05)	(.25,.40)
	3	(.02,.23)	(.05,.15)	(.08,.10)	(.02,.35)	(.05,.35)	(.08,.35)	(.02,.01)	(.05,.05)	(.08,.40)
9	1	(.10,.30)	(.27,.40)	(.55,.50)	(.10,.30)	(.27,.40)	(.55,.50)	(.10,.30)	(.27,.40)	(.55,.50)
	2	(.25,.25)	(.30,.30)	(.40,.40)	(.25,.25)	(.30,.30)	(.40,.40)	(.25,.25)	(.30,.30)	(.40,.40)
	3	(.08,.15)	(.12,.35)	(.25,.35)	(.08,.15)	(.12,.35)	(.25,.35)	(.08,.15)	(.12,.35)	(.25,.35)
10	1	(.10,.30)	(.27,.40)	(.55,.50)	(.10,.20)	(.27,.30)	(.55,.40)	(.10,.25)	(.27,.25)	(.55,.25)
	2	(.25,.25)	(.30,.30)	(.40,.40)	(.25,.25)	(.30,.30)	(.40,.40)	(.25,.33)	(.30,.33)	(.40,.33)
	3	(.08,.15)	(.12,.35)	(.25,.35)	(.08,.35)	(.12,.35)	(.25,.35)	(.08,.08)	(.12,.08)	(.25,.08)
11	1	(.05,.05)	(.07,.07)	(.09,.09)	(.05,.05)	(.07,.07)	(.09,.09)	(.05,.05)	(.07,.07)	(.09,.09)
	2	(.08,.10)	(.13,.35)	(.30,.40)	(.08,.10)	(.13,.35)	(.30,.40)	(.08,.10)	(.13,.35)	(.30,.40)
	3	(.11,.30)	(.13,.20)	(.20,.10)	(.11,.30)	(.13,.20)	(.20,.10)	(.11,.30)	(.13,.20)	(.20,.10)
12	1	(.05,.05)	(.07,.07)	(.09,.09)	(.05,.01)	(.07,.02)	(.09,.03)	(.05,.03)	(.07,.05)	(.09,.10)
	2	(.08,.10)	(.13,.35)	(.30,.40)	(.08,.18)	(.13,.45)	(.30,.50)	(.08,.05)	(.13,.30)	(.30,.35)
	3	(.11,.30)	(.13,.20)	(.20,.10)	(.11,.35)	(.13,.18)	(.20,.10)	(.11,.20)	(.13,.10)	(.20,.03)

Table S2: Expected utilities $\mathrm{E}(U(X,Y) \mid b, r)$ under the 12 simulation scenarios in Table S1. The scenarios given in boxes correspond to the heterogenous cases. The optimal treatment regime utilities are in boldface.

Scenario	Cancer subtype	1			2			3		
	Schedule/dose	1	2	3	1	2	3	1	2	3
1	1	62.2	65	**75**	62.2	65	**75**	62.2	65	**75**
	2	**77**	67	58	**77**	67	58	**77**	67	58
	3	66.2	49	42	66.2	49	42	66.2	49	42
2	1	62.2	65	**75**	62.2	**77**	67	**74.2**	61	67
	2	**77**	67	58	65	**75**	58	69	63	58
	3	66.2	49	42	66.2	49	42	**76.2**	49	42
3	1	61	67	40	61	67	40	61	67	40
	2	**73**	57.2	40	**73**	57.2	40	**73**	57.2	40
	3	64.2	64.4	**69**	64.2	64.4	**69**	64.2	64.4	**69**
4	1	61	67	40	**73**	63	40	61	59	48
	2	**73**	57.2	40	61	57.2	40	**73**	65.2	52
	3	64.2	64.4	**69**	64.2	**68.4**	65	**76.2**	67.2	63
5	1	62.2	69	**78**	62.2	69	**78**	62.2	69	**78**
	2	67.8	67	62	67.8	67	62	67.8	67	62
	3	67	67.6	61	67	67.6	61	67	67.6	61
6	1	62.2	69	**78**	62.2	69	66	62.2	69	70
	2	67.8	67	62	63.8	**77**	58	67.8	67	54
	3	67	67.6	61	67	66	61	**81**	70	63
7	1	61	62.8	61.2	61	62.8	61.2	61	62.8	61.2
	2	57.8	**70.2**	57	57.8	**70.2**	57	57.8	**70.2**	57
	3	**68**	63	59.2	**68**	63	59.2	**68**	63	59.2
8	1	61	62.8	61.2	**71**	**66.8**	62	57.4	54.8	64
	2	57.8	**70.2**	57	**69.8**	**66.2**	59	56.2	54.2	61
	3	**68**	63	59.2	**72.8**	**71**	**69.2**	59.2	59	**71.2**
9	1	**66**	59.8	47	**66**	59.8	47	**66**	59.8	47
	2	55	54	52	55	54	52	55	54	52
	3	61.2	**66.8**	59	61.2	**66.8**	59	61.2	**66.8**	59
10	1	**66**	59.8	47	62	55.8	43	**64**	53.8	37
	2	55	54	52	55	54	52	58.2	55.2	49.2
	3	61.2	**66.8**	59	**69.2**	**66.8**	59	58.4	56	48.2
11	1	59	58.6	58.2	59	58.6	58.2	59	58.6	58.2
	2	59.2	**66.2**	58	59.2	**66.2**	58	59.2	**66.2**	58
	3	**65.4**	60.2	52	**65.4**	60.2	52	**65.4**	60.2	52
12	1	59	58.6	58.2	57.4	56.6	55.8	58.2	57.8	58.6
	2	59.2	**66.2**	58	62.4	**70.2**	62	57.2	**64.2**	56
	3	**65.4**	60.2	52	**67.4**	59.4	52	**61.4**	56.2	49.2

The subgroup-specific optimal treatment regimes are defined as those have expected utilities no less than $u_b^{\max} - 5$, where $u_b^{\max}$ denotes the largest expected utility for all 9 regimes in subtype b.

Table S3: Dose–schedule regime selection percentages based on the proposed method under the 12 simulation scenarios in Table S1. Scenarios given in boxes correspond to the heterogenous cases. Selection percentages of optimal treatment regimes are in boldface.

Scenario	Cancer subtype	1			2			3		
	Schedule/dose	1	2	3	1	2	3	1	2	3
1	1	0.0	0.5	**32.5**	0.0	0.5	**34.8**	0.1	0.3	**35.6**
	2	**59.2**	4.3	0.3	**58.8**	3.3	0.4	**57.2**	3.8	0.3
	3	3.0	0.2	0.0	2.0	0.2	0.0	2.7	0.0	0.0
2	1	0.5	3.4	**29.2**	1.4	**37.4**	8.2	**24.7**	0.7	7.4
	2	**50.9**	7.6	0.5	5.9	**39.4**	0.4	10.8	3.7	0.4
	3	7.8	0.0	0.1	7.3	0.0	0.0	5**2.3**	0.0	0.0
3	1	0.4	14.3	0.0	0.2	15.1	0.0	0.1	14.5	0.0
	2	**63.8**	0.2	0.1	**64.3**	0.3	0.1	**62.8**	0.4	0.0
	3	1.1	3.4	**16.6**	1.0	3.8	**15.1**	1.4	3.9	**16.8**
4	1	1.2	14.2	0.1	**50.6**	6.5	0.0	0.4	1.0	0.0
	2	**55.7**	1.5	0.0	4.7	1.4	0.0	**36.5**	4.1	0.2
	3	6.7	6.1	**14.5**	7.6	**19.9**	9.3	**47.9**	7.2	2.7
5	1	0.2	5.5	**73.4**	0.3	6.8	**73.9**	0.4	6.1	**73.6**
	2	5.5	4.7	1.9	4.6	4.5	0.8	4.9	3.8	1.6
	3	3.1	5.5	0.2	3.6	5.0	0.5	3.7	5.4	0.5
6	1	0.9	10.2	**47.8**	0.1	11.8	6.7	0.1	3.9	7.5
	2	7.9	13.9	1.8	2.8	**61.3**	0.6	3.5	4.5	0.2
	3	9.7	7.3	0.5	9.9	5.8	1.0	**73.2**	6.3	0.8
7	1	1.1	6.3	3.1	0.6	6.5	4.1	0.8	8.1	3.4
	2	0.3	**63.4**	1.0	0.3	**62.9**	0.7	0.2	**63.3**	1.0
	3	**22.3**	2.4	0.1	**22.0**	2.6	0.3	**20.7**	2.3	0.2
8	1	2.8	6.3	6.6	**16.3**	7.5	2.2	2.4	2.1	17.0
	2	1.4	**44.0**	2.9	**14.6**	7.2	1.5	1.6	1.7	10.9
	3	**28.3**	5.1	2.6	**27.2**	**14.8**	**8.7**	5.3	5.8	5**3.2**
9	1	**38.1**	8.0	0.0	**36.1**	7.1	0.3	**38.4**	8.1	0.2
	2	2.3	1.2	0.2	2.7	0.9	0.1	2.3	0.8	0.4
	3	7.2	**37.8**	5.2	8.9	**38.1**	5.8	7.8	**37.9**	4.1
10	1	**36.9**	7.9	0.2	11.6	1.9	0.0	**51.2**	5.1	0.0
	2	4.4	0.9	0.3	3.0	0.8	0.1	18.6	2.7	0.2
	3	13.3	**32.2**	3.9	**54.3**	**25.0**	3.3	15.2	6.8	0.2
11	1	1.7	1.0	0.5	0.9	0.5	0.6	1.2	2.2	0.8
	2	4.1	**38.4**	3.6	2.6	**38.0**	4.4	2.7	**37.2**	4.1
	3	**46.7**	3.9	0.0	**49.6**	3.2	0.1	**48.1**	3.6	0.0
12	1	0.4	1.1	0.7	0.0	0.2	0.0	0.5	1.3	2.6
	2	3.7	**37.1**	5.7	5.7	**47.0**	6.2	4.2	**43.8**	5.9
	3	**47.7**	3.4	0.2	**39.6**	1.3	0.0	**40.1**	1.6	0.0

Table S4: Number of patients allocated to each dose–schedule regime based on the proposed method under the 12 simulation scenarios in Table S1. The scenarios given in boxes correspond to the heterogenous cases. Sample sizes of optimal treatment regimes are in boldface.

Scenario	Cancer subtype	1			2			3		
	Schedule/dose	1	2	3	1	2	3	1	2	3
1	1	3.3	3.6	**14.4**	3.3	3.5	**14.5**	3.3	3.5	**14.6**
	2	**19.1**	4.7	1.7	**18.7**	4.8	1.7	**18.9**	4.8	1.7
	3	9.6	3.0	0.7	9.7	3.1	0.7	9.6	3.0	0.7
2	1	4.4	4.7	**11.3**	4.2	**11.3**	5.9	**10.1**	3.5	6.0
	2	**15.5**	6.4	1.9	7.0	**13.7**	2.0	10.2	5.8	2.5
	3	12.3	2.9	0.6	12.5	2.9	0.7	19.3	2.2	0.5
3	1	4.9	11.2	1.2	4.8	11.2	1.2	4.8	11.2	1.3
	2	**19.2**	3.0	1.0	**19.0**	3.0	1.1	**19.1**	2.9	1.1
	3	5.4	5.5	**8.6**	5.7	5.6	**8.5**	5.4	5.7	**8.6**
4	1	6.7	9.2	1.3	**15.5**	5.8	1.2	7.0	5.3	1.9
	2	**17.2**	3.7	1.2	9.7	4.7	1.4	**14.8**	5.2	1.4
	3	7.5	6.1	**7.2**	7.6	**8.7**	5.4	**14.9**	5.9	3.8
5	1	3.0	5.0	**18.0**	3.1	5.2	**17.8**	3.1	5.0	**18.0**
	2	7.9	6.6	3.3	7.8	6.9	3.2	7.8	6.8	3.1
	3	6.9	7.0	2.5	6.8	7.0	2.4	7.0	6.9	2.4
6	1	3.4	6.4	**12.8**	3.7	7.7	6.1	3.4	6.4	6.8
	2	7.9	8.8	2.7	5.7	17.2	1.9	7.5	8.0	2.0
	3	9.1	6.5	2.5	9.1	6.2	2.5	**19.0**	5.2	1.8
7	1	5.2	7.5	4.7	5.2	7.3	4.8	5.2	7.5	4.8
	2	3.4	**17.6**	2.5	3.4	**17.7**	2.6	3.3	**17.8**	2.7
	3	**11.8**	4.9	2.6	**11.8**	4.8	2.5	**11.6**	4.9	2.4
8	1	6.3	6.8	5.2	**9.5**	6.1	3.8	6.4	4.5	7.9
	2	4.6	**13.4**	3.5	**9.2**	6.8	3.2	5.9	5.2	6.6
	3	**10.8**	5.7	3.8	**9.6**	**6.9**	**5.1**	6.6	4.7	12.3
9	1	**14.2**	6.7	1.3	**14.0**	6.7	1.4	**14.3**	6.6	1.3
	2	9.2	4.5	1.4	9.2	4.5	1.5	9.0	4.5	1.5
	3	7.1	**11.7**	4.0	7.3	**11.5**	4.0	7.2	**11.7**	4.0
10	1	**13.7**	6.3	1.2	11.8	5.3	1.2	**15.8**	5.0	1.2
	2	10.4	4.5	1.4	9.6	4.6	1.4	12.9	4.9	1.3
	3	8.7	**10.5**	3.4	**14.5**	**8.8**	2.9	10.4	6.1	2.5
11	1	5.1	5.1	4.0	5.2	5.1	4.0	5.3	5.1	4.1
	2	5.6	**13.2**	4.1	5.5	**12.9**	4.2	5.6	**13.1**	4.1
	3	**16.5**	4.7	1.7	**16.7**	4.7	1.6	**16.5**	4.6	1.7
12	1	4.4	4.8	4.0	4.0	4.2	3.6	4.5	4.9	4.6
	2	6.1	**13.1**	4.7	6.5	**14.8**	4.7	6.0	**13.5**	4.7
	3	**16.8**	4.6	1.6	**16.8**	4.0	1.6	**16.2**	4.1	1.6

Table S5: Additional four scenarios by changing the true marginal toxicity and efficacy probabilities $(\pi_X(b,r), \pi_Y(b,r))$ under scenarios 1, 3, 9 and 11 in Table S1 for cancer subtype 3.

Scenario	Cancer subtype 3	$(\pi_X(b,r), \pi_Y(b,r))$			$\mathrm{E}(U(X,Y) \mid b,r)$		
	Schedule/dose	1	2	3	1	2	3
$1'$	1	(.03, .05)	(.05 .10)	(.15, .20)	60.2	61.0	59.0
	2	(.05, .15)	(.15, .25)	(.30, .40)	63.0	61.0	58.0
	3	(.13, .60)	(.45, .40)	(.60, .45)	**76.2**	49.0	42.0
$3'$	1	(.05, .10)	(.15, .45)	(.40, .30)	61.0	**69.0**	48.0
	2	(.05, .05)	(.18, .10)	(.40, .20)	59.0	53.2	44.0
	3	(.03, .10)	(.08, .15)	(.15, .30)	62.2	61.2	63.0
$9'$	1	(.10, .05)	(.27, .05)	(.55, .05)	56.0	45.8	29.0
	2	(.25, .15)	(.30, .15)	(.40, .15)	51.0	48.0	42.0
	3	(.08, .40)	(.12, .20)	(.25, .49)	**71.2**	60.8	49.0
$11'$	1	(.05, .45)	(.07, .10)	(.09, .05)	**75.0**	59.8	56.6
	2	(.08, .05)	(.13, .05)	(.30, .05)	57.2	54.2	44.0
	3	(.11, .10)	(.13, .10)	(.20, .03)	57.4	56.2	49.2

The subgroup-specific optimal treatment regimes are defined as those have expected utilities $\mathrm{E}(U(X,Y) \mid b,r)$ no less than $u_b^{\max} - 5$, where $u_b^{\max}$ denotes the largest expected utility for all 9 regimes in subtype b.

Table S6: Simulation results based on the additional four scenarios in Table S5.

Cancer subtype	Selection percentage of optimal treatment regimes								
	1			2			3		
Scenario	BTD_{12}	Naive	ITD_{12}	BTD_{12}	Naive	ITD_{12}	BTD_{12}	Naive	ITD_{12}
$1'$	87.7	70.5	73.4	87.9	70.5	73.4	84.8	24.8	80.2
$3'$	70.5	53.0	62.5	70.4	53.0	62.5	62.8	40.6	53.0
$9'$	60.9	51.5	53.4	60.9	51.5	53.4	83.0	43.9	71.2
$11'$	81.5	56.8	67.8	78.0	56.8	67.8	85.1	36.0	91.5