

# Analyses of drug combinations using missing data shortens trial periods in phase I/II oncology trials



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## ABSTRACT

In previous phase I/II oncology trials for drug combinations, a number of methods have been studied to determine the dose combination for the next cohort. However, there is a risk that trial durations will be unfeasibly long if methods for evaluating safety and efficacy are based on the best overall response and toxicity during trial design. In this study, we propose an approach to shorten the duration of drug trials in oncology. In this method, the dose combination to be allocated to the next cohort is decided before all data for patients in the current cohort is known and best overall response is determined. The efficacy of drug combinations in patients for whom the best overall response has not been determined is treated as missing data. The missing data mechanism is modeled by nonparametric prior processes. The probabilities of efficacy and toxicity are estimated after applying data augmentation to missing data, and the dose combination to be allocated to the next cohort is decided using these probabilities. Simulation studies from the present study show that this proposed approach would shorten trial durations without the low-performing of the trial design in comparison to existing approaches. Shortening trial durations would enable patients with the targeted disease to receive effective therapy at an earlier stage. This also enables clinical trial sponsors to use fewer patients in drug trials, which would lead to a reduction in the costs associated with clinical development.

## 1. Introduction

The primary objective of phase I trials in oncology is to investigate the safety of dose-dependent therapies and to recommend dosages for subsequent phase II trials. The safety endpoint of each patient is where dose limiting toxicity (DLT) is experienced. The DLT shall hereafter be referred to as “toxicity”. The primary objective of phase II trials in oncology is to assess the therapeutic efficacy of the phase I trial and to select the optimal dose for efficacy. Tumor response is often used as an efficacy endpoint [1]. Tumor response is assessed by the use of Response Evaluation Criteria in Solid Tumors (RECIST) [2]. The efficacy probability is defined as the proportion of patients who had the best overall response, designated as either complete response (CR) or partial response (PR), and could be analyzed for therapeutic efficacy.

In clinical trials, there has been an increasing tendency to combine phase I and phase II trials and implement them as one trial in order to drive drug development and reduce associated costs [3]. To date, a variety of research has been conducted on phase I/II oncology trials for drug combinations [4–8]. However, when applying these methods using the best overall response as the efficacy endpoint and toxicity as

the safety endpoint, trial duration is substantially lengthened.

Generally, treatments using anticancer drugs have an administration period of 3–4 weeks, which are administered in a single cycle (cycle 1), repeated a number of times (cycles 2, 3, 4, etc.). Safety is usually based on toxicity during cycle 1, although this depends on the type of tumor being treated or on the trial drug being administered. On the other hand, the efficacy is determined at each protocol-specified time point as the overall response, which integrates the evaluation of target lesions, non-target lesions, and the presence or absence of new lesions. The best overall response is determined at the point at which the overall response has been established for all time points. Thus, in trial designs that evaluate both safety and efficacy in selecting the appropriate dose combination for the next cohort, it is not possible to determine the dose combination to be allocated to the next cohort until efficacy outcomes have been determined for all time points in the current cohort. As a result, trial durations become unfeasibly long.

To address these issues, Chen et al. [9] proposed a method that treated unobserved data as missing data in phase I/II oncology trials. A phase I/II oncology trial was designed to evaluate the safety and efficacy of BKM120 in patients with advanced solid malignancies. In this

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trial design, where safety is evaluated based on toxicity in cycle 1 and efficacy is evaluated in cycle 2, assignment to the next cohort is conducted at the time when the current cohort has completed cycle 1. Efficacy data is treated as missing data at any instances where efficacy is not experienced by the time that patients are assigned to the next cohort, and missing data is imputed.

In treating cancer, the use of a combination of drugs is thought to provide a greater therapeutic efficacy in comparison to monotherapy. In this study, we expanded upon the method advocated by Chen et al. [9] in phase I/II oncology trials for drug combinations. We estimated the efficacy probability for each dose combination using a hierarchical model to enable the flexible application of this method to a variety of cases. The use of the gamma process model enables the selection of a missing data mechanism to explain the accumulated data. We propose a novel trial design using this method, and demonstrate the operating characteristics of our proposed approach through simulation studies. The proposed trial design would both shorten the duration of clinical trials and respond to the grave need to improve the development of new anticancer drugs.

## 2. Methods

### 2.1. Probability model

#### 2.1.1. Phase I

The model assumes the use of two drugs (A and B), and  $J$  combinations of drug A and drug B. The random value of toxicity for  $i$ th patients with the  $j$ th dose combination ( $i = 1, \dots, n_j; j = 1, 2, \dots, J$ ) is  $Y_T$  ( $Y_T = 1$ : toxicity,  $Y_T = 0$ : no toxicity). A copula-type model [10,11] is applied to toxicity probability  $\pi_j$  for  $j$ th dose combinations.

$$\pi_j = 1 - \left\{ \left(1 - p_j^\alpha\right)^{-\gamma} + \left(1 - q_j^\beta\right)^{-\gamma} - 1 \right\}^{-1/\gamma} \tag{1}$$

where,  $p_j$  and  $q_j$  are the initial guesses of drug A and drug B for  $j$ th dose combination, and  $\alpha, \beta,$  and  $\gamma$  are the model parameters. We conveyed gamma distribution using the location parameter  $a$  and scale parameter  $1/b$  (hereinafter written as  $Ga(a, b)$ ) as the prior distribution for the model parameters [10,11], and the toxicity probability of the  $j$ th dose combination is estimated using the posterior distribution.

#### 2.1.2. Phase II

The efficacy probability of the  $j$ th dose combination ( $j = 1, 2, \dots, J$ ),  $p_j$ , is as follows using a Bayesian hierarchical model [12,13]:

$$\begin{aligned} p_j &= \exp(\theta_j) / (1 + \exp(\theta_j)) \\ \theta_j &\sim N(\mu_\theta, \tau_\theta^{-1}) \\ \mu_\theta &\sim N(m_\theta, \sigma_\theta^2), \tau_\theta \sim Ga(\alpha_\theta, \beta_\theta) \end{aligned} \tag{2}$$

where  $\mu_\theta$  has prior mean  $m_\theta$  and variance  $\sigma_\theta^2$ , and  $\tau_\theta$  has prior mean  $\alpha_\theta/\beta_\theta$  and variance  $\alpha_\theta/\beta_\theta^2$ .  $\theta = (\theta_1, \theta_2, \dots, \theta_j)$ ,  $\mathbf{y}$  is the observed data for efficacy,  $f(\boldsymbol{\varphi})$  is the prior distribution for the hyper-parameter  $\boldsymbol{\varphi} = (\mu_\theta, \tau_\theta)$ ,  $f(\boldsymbol{\theta}|\boldsymbol{\varphi})$  is the prior distribution for  $\boldsymbol{\theta}$  given  $\boldsymbol{\varphi}$ , and  $f(\mathbf{y}|\mathbf{p})$  is the conditional probability for  $\mathbf{y}$  given efficacy probability  $\mathbf{p} = (p_1, p_2, \dots, p_j)$ . The posterior distribution for  $\mathbf{p}$  given  $\mathbf{y}$  is given by

$$p(\mathbf{p}|\mathbf{y}) = \frac{\int f(\mathbf{y}|\mathbf{p})f(\mathbf{p}|\boldsymbol{\varphi})f(\boldsymbol{\varphi})d\boldsymbol{\varphi}}{\int \int f(\mathbf{y}|\mathbf{p})f(\mathbf{p}|\boldsymbol{\varphi})f(\boldsymbol{\varphi})d\mathbf{p}d\boldsymbol{\varphi}} \tag{3}$$

The efficacy probability of each dose combinations is estimated using the posterior distribution (3), and the dose combination to be allocated to the next cohort of patients is determined from this model.

We assume that there are patients for whom the best overall response has not been determined at the time when the dose combination is allocated to next cohort. A patient is considered to be a person experiencing efficacy if his/her best overall response is either Complete Response (CR) or Partial Response (PR). If  $i$ th patient has not yet

experienced efficacy and has not yet finished the assessment period, the efficacy outcome for  $i$ th patient ( $Y_i^E$ ) is missing. Let  $t_i$  be denoted as the time to efficacy for  $i$ th patient. If  $i$ th patient has not reached efficacy during the assessment period  $[0, T]$ , we set  $t_i = \infty$ . The missingness indicator  $M_i$  is assigned using the following equation:

$$M_i = \begin{cases} 1 & (t_i > u_i \text{ and } u_i < T) \\ 0 & (\text{otherwise}) \end{cases} \tag{4}$$

where  $u_i$  is the accrual follow-up time for  $i$ th patient. The efficacy outcome for  $i$ th patient is set as:

$$Y_i^E = \begin{cases} \text{missing} & (t_i > u_i \text{ and } u_i < T) \\ 1 & (t_i \leq u_i \leq T) \\ 0 & (t_i > u_i \text{ and } u_i = T) \end{cases} \tag{5}$$

The efficacy outcome is missing ( $M_i = 1$ ) if  $i$ th patient has not yet experienced efficacy ( $t_i > u_i$ ) and has not finished the assessment period ( $u_i < T$ ). The efficacy outcome is observed ( $M_i = 0, Y_i^E = 1$ ) if  $i$ th patient has experienced efficacy ( $t_i \leq u_i \leq T$ ). The efficacy outcome is observed ( $M_i = 0, Y_i^E = 0$ ) if  $i$ th patient has not yet experienced efficacy ( $t_i > u_i$ ) and has completed the entire assessment period ( $u_i = T$ ).

As stated by Yin [3], “Based on the missing data theory, a natural approach to dealing with unobserved outcomes is to impute the missing data so that the standard complete-data method can be applied”. We propose that a data augmentation algorithm [14] in the Bayesian context can be used to handle missing efficacy data to estimate efficacy probability. However, incorporating a missing mechanism is a necessity owing to non-ignorable missing data. Under the missing data mechanism (4), the probability of missingness for  $Y_i^E$  depends on the time to efficacy, thus the missingness for  $Y_i^E$  is non-ignorable. Based on this feature, incorporating the missing mechanism using a piecewise exponential model has been proposed [9,15,16]. In this study, a more flexible method is implemented by modeling the missing mechanism using a gamma process and incorporating a data augmentation algorithm as described below.

We assume the time to efficacy for  $i$ th patient as follows:

$$\omega_i = I(t_i \leq T)$$

$$N_i(t) = I(t_i \leq t, \omega_i = 1)$$

$$Y_i(t) = I(t_i \leq t)$$

where  $I(\cdot)$  is the indicator function that takes a value of 1 when equality holds within the parentheses, and is 0 in all other cases. Let  $D = \{N_i(t), Y_i(t)\}_i$  represent a dataset of  $n$  patients. The posterior distribution for the cumulative hazard function  $\Lambda(t)$  is given by

$$p(\wedge(t) | D) \leq p(D | \wedge(t)) \times p(\wedge(t)), \tag{6}$$

where  $p(\wedge(t))$  is the prior distribution for  $\Lambda(t)$ , and  $p(D|\wedge(t))$  is the likelihood for the given data  $D$ . The cumulative hazard function, representing death or disease progression, is often used in oncology trials. In the present study, the cumulative hazard function representing efficacy is used. The likelihood is

$$p(D|\wedge(t)) = \prod_i \left[ \prod_{t>0} I_i(t) dN_i(t) \right] e^{-I_i(t)dt}, \tag{7}$$

where  $dN_i(t)$  is the increment of  $N_i$  over the smallness interval  $dt$ , and  $I_i(t)$  is the increment of intensity function over the smallness interval  $dt$ . We write  $I_i(t)dt = Y_i(t)d\Lambda(t)$ , where  $d\Lambda(t)$  is the increment of hazard function  $\Lambda(t)$  over the smallness interval  $dt$  [17].

We assign gamma process  $GP(c\Lambda^*(t), c)$  as the prior process for the cumulative hazard function  $\Lambda(t)$ , where  $c > 0$  and  $\Lambda^*(t)$  is a left continuous function on  $[0, \infty)$  with  $\Lambda^*(0) = 0$ . Based on the definition for gamma process [18], an increment of  $\Lambda(t)$  at time interval  $[t, t + dt]$ ,  $d\Lambda(t)$ , follows an independent and identical  $Ga(c d\Lambda^*(t), c)$ , where  $d\Lambda^*(t)$

is the increment of  $\Lambda^*(t)$  over the smallness interval  $dt$ . The posterior for  $\Lambda(t)$  is a gamma process. The increment of  $\Lambda(t)$  over the smallness interval  $dt$  is an independent and identical gamma distribution  $Ga(c d\Lambda^*(t) + N_+(t), c + R_+(t))$  [19], where  $N_+(t)$  is the sum of  $N_i(t)$  over  $i$ , and  $R_+(t)$  is the sum of  $Y_i(t)$  over  $i$ . In this study, let  $d\Lambda^*(t) = rdt$ , where  $r > 0$  is an efficacy expression rate [17]. Suppose that the time to efficacy for patients is  $0 = \tau_0 < \tau_1 < \tau_2 < \dots < \tau_K < \tau_{K+1} = T$ , and assume a cumulative hazard function. The prior for  $\Lambda(t)$  is the independent increments gamma process using

$$\Lambda(\tau_k) - \Lambda(\tau_{k-1}) \sim Ga(cr(\tau_k - \tau_{k-1}), c) \quad (k = 1, 2, \dots, K),$$

and the posterior for  $\Lambda(t)$  is the other independent increments gamma process using

$$\Lambda(\tau_k) - \Lambda(\tau_{k-1}) \sim Ga(cr(\tau_k - \tau_{k-1}) + N_+(\tau_k), c + R_+(\tau_k)) \quad (k = 1, 2, \dots, K).$$

For the estimation of efficacy, let  $\mathbf{y}_{\text{ful}}$  be all the observation data (hereinafter referred to as the “full data”), the  $\mathbf{y}_{\text{obs}}$  observed data, and  $\mathbf{y}_{\text{mis}}$  the missing data. In the presence of missing data, we denote  $\mathbf{y}_{\text{ful}}$  as  $(\mathbf{y}_{\text{obs}}, \mathbf{y}_{\text{mis}})$ . At the  $r$ th iteration process of data augmentation [14], given the posterior distribution of  $\mathbf{p}$ , based on the data including missing data  $p^{(r)}(\mathbf{p} | \mathbf{y}_{\text{obs}})$ :

- Imputation step; I step

The plausible values of  $\mathbf{y}_{\text{mis}}$  are obtained using the observed data  $\mathbf{y}_{\text{obs}}$  and the estimated parameters. That is:

- 1)  $\mathbf{p}^{(r)}$  is drawn from  $p^{(r)}(\mathbf{p} | \mathbf{y}_{\text{obs}})$ .
  - 2)  $\mathbf{y}_{\text{mis}}$  is generated from  $f(\mathbf{y}_{\text{mis}} | \mathbf{y}_{\text{obs}}, \mathbf{p}^{(r)})$ .
- Posterior step; P step

The model parameters are estimated from the posterior distribution (3) using  $\mathbf{y} = (\mathbf{y}_{\text{obs}}, \mathbf{y}_{\text{mis}})$ , where  $\mathbf{y}_{\text{mis}}$  are obtained in 2) of the I step.

Steps I and P are repeated until the Markov Chain convergences. At the  $r$ th iteration process in I, step 2), given observed data  $\mathbf{y}_{\text{obs}}$  and parameter  $\mathbf{p}^{(r)}$ , the plausible values of  $\mathbf{y}_{\text{mis}}$  are obtained by drawing samples from the Bernoulli distribution with a success probability of

$$\frac{p_{j(i)}^{(r)} \Pr(t_i > u_i | y_i^E = 1)}{1 - p_{j(i)}^{(r)} + p_{j(i)}^{(r)} \Pr(t_i > u_i | y_i^E = 1)}, \tag{8}$$

where  $p_{j(i)}^{(r)}$  is the efficacy probability of the dose combination assigned to the  $i$ th patient in (2). Because (8) includes the unknown probability  $\Pr(t_i > u_i | y_i^E = 1)$ , it is necessary to model  $t_i$  to impute the missing data. In the previous studies, a piecewise exponential model was used [9,15,16]. Under the gamma model, the probability of success (8) is given by

$$\frac{p_{j(i)}^{(r)} \exp\left(-\sum_{k:\tau_k < u_i} d\Lambda(\tau_k)\right)}{1 - p_{j(i)}^{(r)} + p_{j(i)}^{(r)} \exp\left(-\sum_{k:\tau_k < u_i} d\Lambda(\tau_k)\right)}, \tag{9}$$

where  $d\Lambda(t)$  follows the independent and identical gamma distribution  $Ga(c\Lambda^*(t) + N_+(t), c + R_+(t))$ . Thus, the plausible values of  $\mathbf{y}_{\text{mis}}$  are obtained by drawing samples from the Bernoulli distribution with a success probability of (9).

The toxicity probability is estimated using the posterior distribution in the same way as in phase I (Section 2.1.1).

## 2.2. Trial design

### 2.2.1. Phase I

The trial progressed in accordance with the following algorithm proposed by Yin and Yuan [10,11]. According to this method,  $l$  doses were set for drug A with dose levels starting at 1 as the lowest value, followed by dose level 2, and finally dose level  $l$ ; and  $m$  doses were set for drug B with dose levels starting at 1 as the lowest value, followed by

dose level 2, and finally dose level  $m$ . Supposing that  $\phi_T$  is the target toxicity probability,  $c_e$  is the fixed probability threshold for dose escalation, and  $c_d$  is the fixed probability threshold for dose de-escalation. The algorithm is as follows:

Step 1: For the first cohort, the lowest dose combination  $(A_1, B_1)$  is administered.

Step 2: The probability model is updated using accumulated patient data, and the toxicity probability is estimated. Let  $\pi_T$  denote the toxicity probability of the current dose combination  $(A_i, B_m)$ .

- If  $\Pr(\pi_T < \phi_T) > c_e$ , the dose combination is escalated to the next combination for which the toxicity probability is higher than  $\pi_T$  and closest to  $\phi_T$ . If the current dose combination is the highest dose combination, the current dose combination is used to treat the next cohort.
- If  $\Pr(\pi_T < \phi_T) < c_d$ , the dose combination is de-escalated to the next combination for which the toxicity probability is lower than  $\pi_T$  and closest to  $\phi_T$ . If the current dose combination is the lowest dose combination, the trial is terminated.
- Otherwise, the current dose combination is used to treat the next cohort.

Step 3: Once the maximum sample size  $n_1$  in phase I has been reached, the  $j$ th dose combinations that satisfy  $\Pr(\pi_j < \phi_T) > c_a$  are determined to be admissible dose combinations, and used as the dose combination in phase II.  $c_a$  is the fixed probability threshold for dose admissibility.

When conducting a trial, the design parameters  $\phi_T$ ,  $c_e$ ,  $c_d$ , and  $c_a$  must be specified before starting the trial.  $\phi_T$  is provided by the clinical physician.  $c_e$ ,  $c_d$ , and  $c_a$  can be calibrated through simulation studies such that the trial has desirable operating characteristics.

### 2.2.2. Phase II

In phase II, trials progress in accordance with the following rules targeting dose combinations that were determined to be admissible at the end of the phase I.

Step 1: For the first cohort, the dose combination with a toxicity probability closest to  $\phi_T$  is administered.

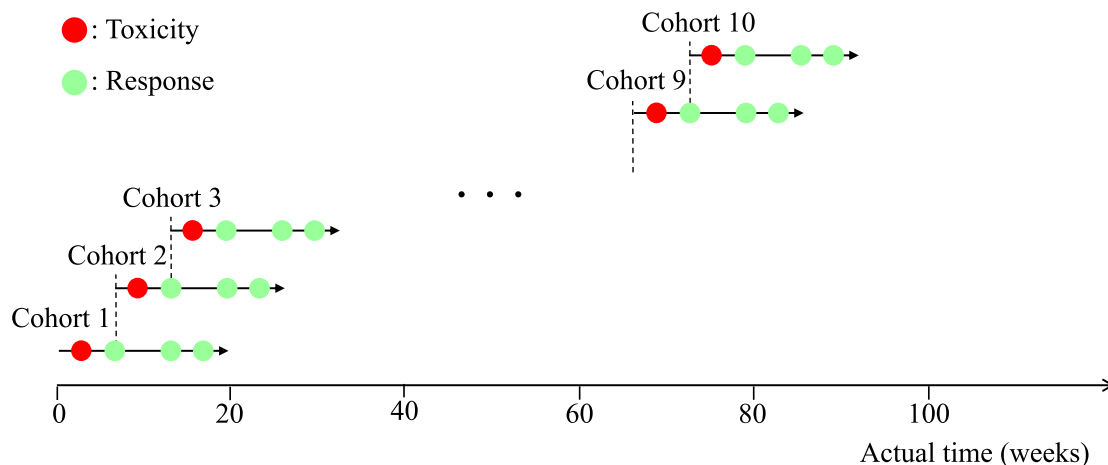
Step 2: The toxicity probability and efficacy probability of each dose combination are estimated using the accumulated data.

Step 3: The dose combination to be allocated to the next cohort is decided in accordance with the Bayesian moving-reference adaptive randomization (hereinafter referred to as “MAR”) [6] using the efficacy probability.

Step 4: If dose combinations satisfy either  $\Pr(\pi_T < \phi_T) < c_a$  or  $\Pr(\pi_E < \phi_E) < c_f$  for toxicity probability ( $\pi_T$ ) and efficacy probability ( $\pi_E$ ), the dose combinations are determined to be not admissible for the toxicity or fertility (hereinafter referred to as “unacceptable dose combinations”). No patient assignments are made for dose combinations determined to be not admissible.  $\phi_E$  is the expected efficacy probability lower limit and  $c_f$  is the fixed probability for trial fertility.

Step 5: Once the maximum sample size  $n_2$  in phase II has been reached, the acceptable dose combination with the highest efficacy probability is selected as the optimal dose combination.

The most important feature of the method proposed in this study (hereinafter referred to as the “proposed approach”) is that the dose combination allocated to the next cohort is decided before all the data for each patient are known in the current cohort in phase II. Fig. 1 illustrates trial progression in phase II using the proposed approach. As a comparison, Fig. 2 shows that the existing method, where the dose combination allocated to the next cohort is decided after all the data for each patient is known in the current cohort in phase II (hereinafter referred to as the “completed-data approach”). The horizontal axis in both figures is the actual time from the start of the trial (weeks), on which the time point of safety and efficacy in each cohort are plotted. In Figs. 1 and 2, a cycle is defined as a 4-week period. The trial is



**Fig. 1.** Patient enrollment, toxicity, and response in phase II using the proposed approach. Using the proposed approach, the dose combination allocated to the next cohort is decided before all the data for each patient is known in the current cohort in Phase II. A cycle is defined as a 4-week period. The trial is conducted with the safety based on toxicity at cycle 1, and the efficacy based on the overall response at cycles 2, 4, and 5.

conducted with the safety based on toxicity at cycle 1, and the efficacy based on the overall response at cycle 2 (4–8 weeks from the start of the treatment), cycle 4 (12–16 weeks from the start of the treatment), and cycle 5 (16–20 weeks from the start of the treatment).

Fig. 1 depicts the trial design, where the dose combination allocated to the next cohort is decided at the end of cycle 2 for the current cohort. The dose combination allocated to cohort 2 is decided at the end of cycle 2 for cohort 1. The best overall response for cohort 1 is not yet determined at the time when the dose combination allocated to the cohort 2 is decided. Thus, the efficacy data for the cohort 1 is treated as missing data. The efficacy probability for each dose combination is estimated, and the dose combination to be allocated to the cohort 2 is decided. In this way, the efficacy data for the cohort, for which the best overall response is not yet determined, is treated as missing data when the dose combination allocated to the next cohort is decided. The efficacy probability for each dose combination is estimated after imputation for the missing data using data augmentation, and the dose combination allocated to the next cohort is decided.

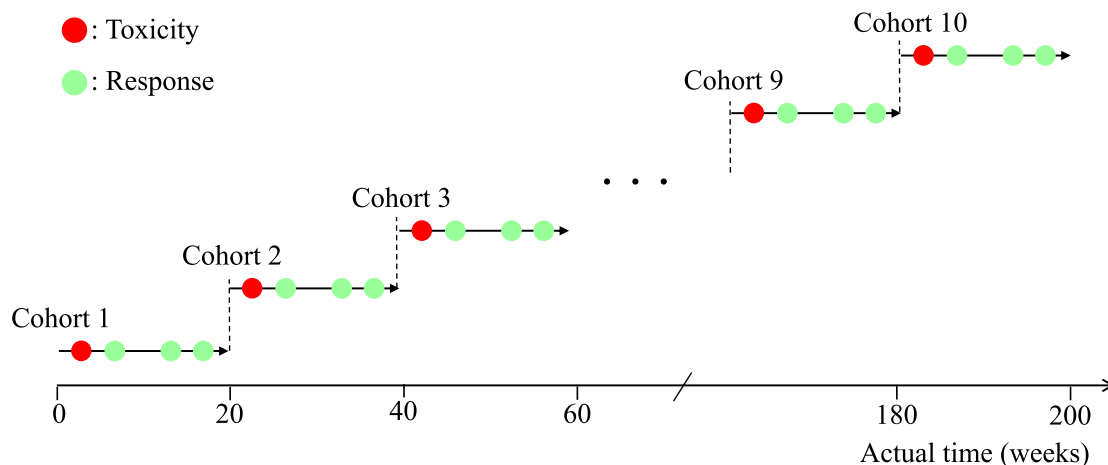
These approaches require that  $\phi_E$  and  $c_f$  are set before starting the trial.  $\phi_E$  is specified by the clinical physician, while  $c_f$  can be calibrated through simulation studies such that the trial has desirable operating characteristics.

### 3. Simulation studies

#### 3.1. Simulation settings

The performance of the proposed approach was examined using simulation studies. In the simulation studies, we conducted phase I/II trials for drug combinations, where a cycle is defined as a 4-week period with a maximum of 5 cycles. The assessment of safety is conducted based on the toxicity in cycle 1. The assessment of efficacy was conducted based on the overall responses in cycles 2, 4, and 5. The trial design for the proposed approach is as described below.

In phase I, treatment for the next cohort commences when the assessment of safety is conducted in cycle 1 for the current cohort. The



**Fig. 2.** Patient enrollment, toxicity, and response in phase II using the completed-data approach. Using the completed-data approach, the dose combination allocated to the next cohort is decided after all the data for each patient is known in the current cohort in Phase II. A cycle is defined as a 4-week period. The trial is conducted with the safety based on toxicity at cycle 1, and the efficacy based on the overall response at cycles 2, 4, and 5.

toxicity probability for each dose combination is estimated with a copula-type model (1) using the toxicity in cycle 1. The drug combination in the next cohort is determined in accordance with the algorithm shown in 3.1. Once the trial is completed up to the maximum sample size in phase I, the admissible dose combination is identified, and phase II is subsequently started. Therefore, if phase I is conducted with a maximum sample size of  $n_1 = 20$ , and a cohort size of 1, the trial duration of phase I would be 96 weeks, providing that the trial is not discontinued early. In phase II, the dose combination allocated to the next cohort is decided after the assessment at cycle 2 for the current cohort. When the dose combination allocated to the next cohort is decided, the efficacy data for any cases where the assessment at cycle 5 has not been completed and the best overall response has not been determined, will be treated as missing data. The efficacy probability of each dose combination is estimated using full data with the imputation for missing data using the method shown in Section 2.1.2. The dose combination allocated to the next cohort is determined in accordance with MAR [6], using the estimated efficacy probability. This is repeated until the maximum sample size in phase II is reached. No patient assignments were made for any dose combinations determined to be not admissible. If, for example, phase II is conducted with a maximum sample size of  $n_2 = 30$ , and a cohort size of 3, the trial duration of phase II would be 92 weeks (providing the trial is not discontinued early) as a result of starting treatment with the next cohort after cycle 2 of the current cohort.

We compared the proposed approach with the following two approaches. One approach is the completed-data approach, in which the dose combination allocated to the next cohort is decided after all the data for each patient is known in the current cohort. In the second approach, the dose combination allocated to the next cohort is decided while excluding patients who have not finished the assessment period (hereinafter referred to as the “completer-only approach”).

The trial design for the completed-data approach is described as follows. Phase I progresses in a similar way to the proposed approach. As with the proposed approach, phase II begins by targeting the dose combination determined to be admissible in phase I. Once the current cohort has completed up to cycle 5 of the treatment, the best overall response for the current cohort is determined, and then the efficacy probability for each dose combination is estimated based on (3), using the efficacy data accumulated. No patient assignments are made for any dose combinations that are determined to be not admissible, as is the case when using the proposed approach. If, for example, phase II is conducted with a maximum sample size of  $n_2 = 30$ , and a cohort size of 3, the trial duration of phase II would be 200 weeks (providing the trial is not discontinued early).

The trial design for the completer-only approach is described as follows. Phase I progresses in a similar way to the proposed approach. As with the proposed approach, phase II begins by targeting the dose combination determined to be admissible in phase I. In phase II, the dose combination allocated to the next cohort is decided after the assessment at cycle 2 for the current cohort. When the dose combination allocated to the next cohort is decided, the efficacy data for any cases where the assessment at cycle 5 has not been completed, and the best overall response has not been determined, will be excluded from the analysis. No patient assignments are made for any dose combinations that are determined to be not admissible, as is the case when using the proposed approach. If, for example, phase II is conducted with a maximum sample size of  $n_2 = 30$ , and a cohort size of 3, the trial duration of phase II would be 92 weeks (providing the trial is not discontinued early).

We conducted simulation studies based on the 8 scenarios shown in Table 1, to compare the operating features of all three approaches. The true efficacy and toxicity probabilities for each scenario were set by referencing existing research [7,8], and were not set based on a specific model.

In scenario 1, the efficacy probability increases with increasing

dosage levels, and the maximum dose combination (dose combination  $(A_4, B_4)$ ) is determined to be the optimal dose combination. In scenario 2, the efficacy probability increases with increasing dosage levels, as seen in scenario 1; however, the optimal dose combination here is  $(A_3, B_4)$ . In scenario 3, the efficacy probability plateaus at the high dose level combinations  $(A_4, B_3)$  and  $(A_4, B_4)$ . In scenario 4, the efficacy probability increases with increasing dosage levels for drug A, but the efficacy probability decreases after exceeding a fixed level with drug B. In scenario 5, the efficacy probability increases initially for drugs A and B, whereas the efficacy probability decreases when a fixed level is exceeded for drugs A and B. In scenario 6, the efficacy probability decreases with increasing dosage levels of drug A, and the efficacy probability decreases after exceeding a fixed level with drug B. In scenario 7, the efficacy probability increases with increasing dosage levels, and there are some dose combinations that cannot be admissible in terms of safety. The dose combinations  $(A_3, B_2)$  and  $(A_4, B_1)$  are the optimal drug combinations. In scenario 8, the efficacy probability is lower than the expected efficacy probability in all other dose combination scenarios; in this case, it would be preferable to discontinue the trial early.

In the simulation studies, we simulated the time to efficacy from a truncated Weibull distribution. In trials where conformation is required, the best overall response is determined to be CR or PR only when the criteria are met at the subsequent time point [2]. In this circumstance, the time to efficacy is measured as the time measurement criterion necessary for each response to be met. Therefore, when evaluating efficacy in cycles 2, 4, and 5, the time to efficacy ranges to cycle 4 (16 weeks). In the simulation studies, we assigned the parameters of the truncated Weibull distribution  $G(t)$  with a supporting range  $t \in [0, 16]$  to ensure that the cumulative distribution function of the time to efficacy at cycle 4 would be equal to the true efficacy probability. We simulated three different types of hazards: decreasing hazard of efficacy, constant hazard of efficacy, and increasing hazard of efficacy. The initial guesses of toxicity probability were 0.07, 0.15, 0.22, and 0.30 for drug A, while the initial guesses of toxicity probability were 0.12, 0.18, 0.24, and 0.30 for drug B. The target toxicity probability was set as  $\phi_T = 0.35$ , the fixed probability threshold for dose escalation was set as  $c_e = 0.85$ , the fixed probability threshold for dose de-escalation was set as  $c_d = 0.45$ , and the fixed probability threshold for dose admissibility was set as  $c_a = 0.45$ . The expected efficacy lower limit was set as  $\phi_E = 0.20$ , and the fixed probability for trial futility was set as  $c_f = 0.10$ . In the copula-type model (1), we used  $Ga(0.5, 0.5)$  as the prior distribution for  $\alpha, \beta$ , and  $Ga(0.1, 0.1)$  as the prior distribution for  $\gamma$ . We took 5000 posterior samples of the model parameters after 2000 burn-in iterations for the toxicity probability inference. In the hierarchical model (2), we used  $N(0, 10)$  as the prior distribution for  $\tau_\theta$ . We took 10,000 posterior samples of the model parameters after 2000 burn-in iterations for the efficacy probability inference. We used independent  $Ga(0.0001, 0.001)$  as the prior distribution for increments in  $\lambda(t)$  over the small time interval  $dt$ . We conducted 1000 simulations for each condition.

### 3.2. Simulation results

The simulation results are summarized in Table 2. We defined a dose combination with a toxicity probability that is equal to or less than the target toxicity probability and the highest efficacy probability as an “optimal dose combination”. We defined a dose combination with a toxicity probability that is equal to or less than the target toxicity probability and an efficacy probability that is equal to or higher than 0.40 as a “target dose combination”. Table 2 shows the selection percentages of the optimal dose combinations, the selection percentages of the target dose combinations, the percentage of discontinued trials, the numbers of patients enrolled, and the trial duration (weeks) of phase II.

In all scenarios, the selection percentages of the optimal dose combinations and the selection percentages of the target dose



**Table 1**  
True probabilities of efficacy and toxicity for each dose combination in each scenario.

Scenario	Drug B	True efficacy probabilities				True toxicity probabilities			
		Drug A				Drug A			
		1	2	3	4	1	2	3	4
1	4	0.22	0.28	0.35	<b>0.60</b>	0.12	0.15	0.16	<b>0.23</b>
	3	0.20	0.25	0.32	<b>0.45</b>	0.10	0.12	0.15	<b>0.19</b>
	2	0.18	0.22	0.28	<b>0.40</b>	0.07	0.11	0.14	<b>0.17</b>
2	1	0.16	0.18	0.25	0.35	0.05	0.10	0.12	0.14
	4	0.18	0.35	<b>0.60</b>	<b>0.40</b>	0.16	0.18	<b>0.20</b>	<b>0.30</b>
	3	0.12	0.25	<b>0.40</b>	0.35	0.14	0.16	<b>0.18</b>	0.20
3	2	0.10	0.20	0.35	0.30	0.12	0.14	0.16	0.18
	1	0.05	0.15	0.20	0.25	0.10	0.12	0.14	0.16
	4	0.20	0.30	<b>0.40</b>	<b>0.55</b>	0.20	0.24	<b>0.26</b>	<b>0.33</b>
4	3	0.18	0.25	0.36	<b>0.55</b>	0.16	0.20	0.24	<b>0.28</b>
	2	0.12	0.20	0.30	<b>0.40</b>	0.12	0.18	0.22	<b>0.26</b>
	1	0.10	0.15	0.25	0.35	0.10	0.14	0.20	0.24
5	4	0.15	0.20	0.25	0.30	0.18	0.22	0.24	0.28
	3	0.20	0.30	<b>0.40</b>	<b>0.60</b>	0.15	0.18	<b>0.21</b>	<b>0.25</b>
	2	0.15	0.20	0.30	0.35	0.11	0.16	0.18	0.22
6	1	0.10	0.15	0.20	0.25	0.10	0.12	0.15	0.20
	4	0.20	0.32	0.30	0.26	0.16	0.21	0.30	0.35
	3	0.15	0.30	0.36	0.30	0.13	0.17	0.24	0.32
7	2	0.12	0.25	<b>0.40</b>	0.35	0.09	0.13	<b>0.20</b>	0.26
	1	0.10	0.20	<b>0.50</b>	<b>0.40</b>	0.06	0.11	<b>0.15</b>	<b>0.24</b>
	4	<b>0.40</b>	0.30	0.25	0.20	<b>0.15</b>	0.18	0.22	0.26
8	3	<b>0.60</b>	<b>0.40</b>	0.35	0.32	<b>0.14</b>	<b>0.15</b>	0.19	0.23
	2	<b>0.40</b>	0.35	0.30	0.25	<b>0.10</b>	0.12	0.17	0.21
	1	0.30	0.28	0.25	0.20	0.08	0.10	0.14	0.18
9	4	0.20	0.33	0.55	0.60	0.28	0.35	0.40	0.45
	3	0.18	0.28	0.48	0.55	0.24	0.30	0.35	0.40
	2	0.16	0.24	<b>0.45</b>	0.50	0.16	0.24	0.32	0.36
10	1	0.15	0.20	<b>0.40</b>	<b>0.45</b>	0.12	0.18	0.24	0.33
	4	0.10	0.10	0.10	0.10	0.27	0.33	0.36	0.40
	3	0.10	0.10	0.10	0.10	0.24	0.28	0.32	0.35
11	2	0.10	0.10	0.10	0.10	0.21	0.22	0.27	0.33
	1	0.10	0.10	0.10	0.10	0.18	0.20	0.24	0.28

\*Optimal dose combination: a dose combination with the highest efficacy probability with the toxicity probability  $\leq 0.35$ ; target dose combination: a dose combination with the toxicity probability  $\leq 0.35$  and the efficacy probability  $\geq 0.40$ . The dose combination in boldface and underline represents the optimal dose combination for each scenario/dose combination, when identified. The dose combination in boldface represents the target dose combination for each scenario/dose combination, when identified.

combinations using the proposed approach were the same as, or slightly lower than those of the completed-data approach. The percentage of discontinued trials using the proposed approach was equivalent to or greater than that of the completed-data approach. The trial duration was shorter with the proposed approach than with the completed-data approach.

A comparison of the completer-only approach with the proposed approach revealed that the selection percentages of the optimal dose combinations and the selection percentages of target dose combinations were either similar to or lower than those of the completer-only approach. For the trial duration, excluding the scenario in which is preferable to discontinue the trial early, the completer-only approach and the proposed approach were similar. In the scenario in which is preferable to discontinue the trial early, the trial duration of the completer-only approach was longer than that of the proposed approach, and the percentage of discontinued trials in the completer-only approach was lower than that of the proposed approach.

#### 4. Discussion

In the proposed approach, the follow-up period for all patients enrolled in the trial is not considered complete at the point where the dose combination allocated to the next cohort is decided. In the completed-data approach, the dose combination allocated to the next cohort is only decided once the follow-up period is completed for all the patients enrolled. Thus, in the completed-data approach, the efficacy of a given treatment is evaluated to the fullest extent possible. It is worth noting

that much more information on which to base the dose combination allocated to the next cohort is available using the completed-data approach in comparison to the proposed approach. Therefore, there is a concern that the proposed approach underperforms the completed-data approach in the selection percentages of the optimal and target dose combinations. However, the results of the simulations in the present study suggest that the selection percentages for the optimal and target dose combinations using the proposed approach are similar to the selection percentages of the completed-data approach, and that the shortened trial duration of the proposed approach is sufficient to offset the decreases in the selection percentages of dose combinations.

In both the proposed approach and completer-only approach, the dose combination assigned to patients in the next cohort was decided after the assessment at cycle 2 in the current cohort. However, in the completer-only approach, information on the patients currently undergoing treatment was excluded from the analysis when determining the dose combination assigned to patients in the next cohort. The simulation results showed that in some scenarios, the selection percentages for the optimal dose combination and the target dose combination were lower in the completer-only approach than in the proposed approach. Moreover, in the scenario with early trial discontinuation, the trial duration was longer in the completer-only approach than in the proposed approach.

Shortening the trial duration and moving to the next phase of drug development at an earlier time means that it may be possible for patients with the target disease to receive promising treatment at an earlier stage. For the sponsors of clinical trials, this would prevent the

**Table 2**  
Summary of the simulation studies for the eight scenarios of the efficacy probabilities and the toxicity probabilities of dose combinations.

Method	Scenario							
	1	2	3	4	5	6	7	8
	Selection percentage of optimal dose combinations							
Proposed <sup>*1</sup>	52.3	21.4	29.3	34.9	31.2	17.6	17.2	n/a
Proposed <sup>*2</sup>	50.9	20.3	28.3	35.2	30.6	17.8	17.7	n/a
Proposed <sup>*3</sup>	51.3	20.7	27.7	33.5	32.1	16.8	17.5	n/a
Completer-only	50.8	15.9	30.0	30.3	30.7	13.6	16.1	n/a
Completed-data	51.7	19.9	28.3	34.3	30.7	19.7	17.6	n/a
	Selection percentage of target dose combinations							
Proposed <sup>*1</sup>	72.1	44.7	42.1	43.9	54.1	37.1	32.4	n/a
Proposed <sup>*2</sup>	70.1	43.9	41.9	42.9	52.2	36.8	33.3	n/a
Proposed <sup>*3</sup>	70.9	43.8	40.7	42.7	53.8	36.6	32.8	n/a
Completer-only	70.2	38.9	42.2	37.7	51.5	31.7	32.6	n/a
Completed-data	71.2	44.3	41.9	42.3	52.5	40.1	35.6	n/a
	Percentage of discontinued trials							
Proposed <sup>*1</sup>	0.9	8.8	6.8	6.4	2.1	1.6	7.0	50.3
Proposed <sup>*2</sup>	0.9	9.2	7.7	6.9	2.4	1.6	7.4	53.8
Proposed <sup>*3</sup>	0.9	9.4	7.6	7.5	2.2	2.1	7.7	53.9
Completer-only	0.5	6.5	4.3	4.6	1.6	1.5	4.2	38.3
Completed-data	0.3	5.5	5.3	4.6	1.5	1.4	5.3	47.8
	Number of patients enrolled							
Proposed <sup>*1</sup>	49.55	45.60	46.60	46.80	48.95	49.20	46.50	24.85
Proposed <sup>*2</sup>	49.55	45.40	46.15	46.55	48.80	49.20	46.30	23.10
Proposed <sup>*3</sup>	49.55	45.30	46.20	46.25	48.90	48.95	46.15	23.05
Completer-only	49.75	46.75	47.85	47.70	49.20	49.25	47.90	31.35
Completed-data	49.85	47.25	47.35	47.70	49.25	49.30	47.35	26.10
	Trial duration (weeks) of phase II							
Proposed <sup>*1</sup>	91.4	86.6	88.2	88.2	90.7	91.0	88.0	65.5
Proposed <sup>*2</sup>	91.4	86.4	87.6	87.9	90.6	91.0	88.0	64.3
Proposed <sup>*3</sup>	91.4	86.3	87.7	87.8	90.7	90.9	87.9	64.2
Completer-only	91.7	88.1	89.6	89.6	91.2	91.2	89.5	74.3
Completed-data	199.5	192.0	193.3	193.5	197.9	197.7	192.9	138.3

\*n/a: not applicable.

\*1: constant hazard of efficacy, \*2: when decreasing hazard of efficacy, \*3: when increasing hazard of efficacy.

enrollment of more patients into a trial than is necessary, thereby resulting in a reduction in the cost associated with the clinical trial.

In practice, the completer-only approach is commonly used. As with the proposed approach, the trial duration of the completer-only approach can be shorter than that of the completed-data approach. However, because only the data for patients who finished the assessment period are analyzed, some information is lost, resulting in a lower estimation efficiency. An alternative approach for shortening trial duration would be to use the data for patients for whom the best overall response has been determined at the time point where the assignment to the next cohort is conducted, without the imputation for the missing data. However, if efficacy probability is estimated using the data for patients for whom the best overall response has been determined at the time point where the assignment to the next cohort is conducted without the imputation for the missing data, a selection bias may occur. There is a high risk that the efficacy data for patients with low therapeutic effects would be missing in comparison to the efficacy data for patients with high therapeutic effects. Thus, the proportion of data at the dose combinations with high therapeutic effects used for analysis would be larger by using only the observed data, without imputation for the missing data. Thus, a bias would occur in the analysis by ignoring the missing data mechanism. The proposed approach used in the present study is a method of analysis that considers the missing data mechanism, by reducing possible biases.

The missing data mechanism (5) is missing not at random (MNAR), where the probability of missingness for the efficacy data depends on the efficacy data that should have been obtained when the follow-up period was completed. In the presence of missing data, valid statistical inferences cannot be provided unless using an approach that takes into account the missing data mechanism. Here, we consider that the missing data is a special case of MNAR, where the missing data mechanism is defined by (5) [15]. Chen et al. [9] specified a piecewise

exponential model for the time to efficacy, followed by Liu et al. [16] to model the missing data mechanism. The method followed by Chen et al. [9] requires a finite number of time intervals. In the proposed approach, we use a gamma process for the cumulative hazard function of the time to efficacy to model the missing data mechanism. Although the proposed approach has an infinite number of time intervals, only a finite number of time intervals can be used to explain the obtained data, which enables estimations of the posterior distribution from the obtained data.

In phase I/II oncology trials for drug combinations, it may be possible to assign patients to a more desirable dose combination based on both toxicity and efficacy from the start of the trial. However, in the initial stages of the trial, during which information regarding combination therapy is limited, the accuracy of the estimates is low, which may adversely affect the performance of the trial design. Therefore, in this study, the trial was divided into two parts. In the initial part (phase I), toxicity was assessed, while in the subsequent part (phase II), patients were assigned admissible dose combinations with high efficacies. Thus, the main purpose of phase I is to identify admissible dose combinations based on toxicity probability. In phase II, the purpose is to identify promising dose combinations by assessing efficacy. In simulation studies, the maximum sample sizes in phase I and phase II were 20 and 30, respectively. Extensive discussion and simulation based on practical considerations will be necessary to determine the maximum sample size to increase the probability of selecting a dose combination with a good treatment response from the admissible dose combinations.

The probability models for toxicity and efficacy are set separately. Thus, the relationship between toxicity and efficacy is not reflected in the probability model. Additionally, patient toxicity outcomes are used only for determining the admissibility of each dose combination, and are not used for allocation in phase II. As patients desire both a suppression of toxicity and an improvement in symptoms, it is essential to

have a joint probability distribution of toxicity and efficacy to take the relationship between toxicity and efficacy into consideration, as well as to investigate methods for discovering more clinically suitable dose combinations from the perspective of both efficacy and toxicity.

In the present study, binary data (experience/no-experience) were used as endpoints of toxicity and efficacy. However, this data ignored the information regarding when patients experience toxicity or efficacy. Yuan and Yin [20] proposed a method for modeling toxicity and efficacy as time-to-event endpoints. At the time of selecting the dose assigned to the next cohort, the unobserved data is censored, and the Clayton copula is used to construct a joint density function of survival time regarding toxicity and efficacy. The framework of the proposed approach can be extended to time-to-event endpoints. At the time of selecting the dose combination to be assigned to the next cohort, the data for patients for whom the best overall response has not been determined is treated as missing data, and a missing mechanism may be incorporated in the model, where the gamma process can be used as a prior process for the baseline hazard function.

To analyze the missing data, we used a gamma process for the cumulative hazard function, as it has been recommended that the cumulative hazard function be modeled using a gamma process for grouped data [18]. The model proposed in this study can specify the posterior distribution for the cumulative hazard function, which has the advantage of being computationally simple to implement. However, one of the disadvantages of using the gamma process is that the cumulative hazard function is a discrete function with probability 1 [21]. To overcome this disadvantage, an approach using stochastic processes other than the gamma process should also be considered.

In this study, we proposed a method for shortening the trial duration for phase I/II oncology trials for drug combinations. The dose combination allocated to the next cohort is decided using an analysis that considers a missing data mechanism. The simulation studies show that the proposed approach can shorten the trial duration, while suppressing the performance deterioration of the trial design, in comparison to the existing approaches. However, it is worth noting that the conditions of the simulations conducted in this study are limited, and similar findings may not always be obtained. Validation of the proposed approach, using the application of the proposed approach to an actual clinical trial, is a topic for future investigation.

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