Data-dependent early completion of dose-finding trials for drug-combination

Masahiro Kojima¹,²

Context summary
I propose a data-dependent early completion of dose-finding trials for drug combinations. Early completion is determined when the dose retainment probability using both the trial data and the number of remaining patients is high. An early completion method in which the dose retainment probability is adjusted by a bivariate isotonic regression is also proposed. Early completion is demonstrated for a virtual trial. The performance of the early completion method is evaluated by simulation studies with 12 scenarios. I have shown that, compared with non-early completion designs, the proposed early completion methods reduce the number of patients treated while maintaining similar performance. The number of patients for determining early completion before a trial start is determined and the program code for calculating the dose retainment probability is provided.

Abstract
Purpose: Model-assisted designs for drug combination trials have been proposed as novel designs with simple and superior performance. However, model-assisted designs have the disadvantage that the sample size must be set in advance, and trials cannot be completed until the number of patients treated reaches the pre-set sample size. Model-assisted designs have a stopping rule that can be used to terminate the trial if the number of patients treated exceeds the predetermined number, there is no statistical basis for the predetermined number. Here, I propose two methods for data-dependent early completion of dose-finding trials for drug combination: (1) an early completion method based on dose retainment probability, and (2) an early completion method in which the dose retainment probability is adjusted by a bivariate isotonic regression.
Methods: Early completion is determined when the dose retainment probability using both trial data and the number of remaining patients is high. Early completion of a virtual trial was demonstrated. The performances of the early completion methods were evaluated by simulation studies with 12 scenarios.
Results: The simulation studies showed that the percentage of early completion was an average of approximately 70%, and the number of patients treated was 25% less than the planned sample size. The percentage of correct maximum tolerated dose combination selection for the early completion methods was similar to that of non-early completion methods with an average difference of approximately 3%.
Conclusion: The performance of the proposed early completion methods was similar to that of the non-early completion methods. Furthermore, the number of patients for determining early completion before the trial starts was determined and a program code for calculating the dose retainment probability was proposed.

Keywords
Model-assisted designs, early completion of drug combination finding trials, Bayesian optimal interval design, keyboard design

¹Biometrics Department, R&D Division, Kyowa Kirin Co., Ltd, Tokyo, Japan
²Research Center for Medical and Health Data Science, The Institute of Statistical Mathematics, Tokyo, Japan

Corresponding author:
Masahiro Kojima, Biometrics Department, R&D Division, Kyowa Kirin Co., Ltd, Otemachi Financial City Grand Cube, 1-9-2 Otemachi, Chiyoda-ku, Tokyo 100-004, Japan.
Email: masahiro.kojima.tk@kyowakirin.com
1 Introduction

A dose-finding trial for drug combinations that aims to identify a maximum tolerated dose (MTD) combination is proposed. MTD is a dose combination for which the dose-limiting toxicity (DLT) rate is closest to the target toxicity level (TTL). To determine the MTD, dose adjustments are repeatedly needed based on the experience of multiple doses. The classical design for the dose adjustments is the 3 + 3 design, which uses a simple algorithm that is easy to operate, but its performance in selection the correct MTD is poor. Hence, designs based on statistical models have been proposed. However, such model-based designs are rarely used in actual clinical trials because they require complex assumptions to be made. Therefore, Bayesian optimal interval (BOIN), Keyboard, modified toxicity probability interval (mTPI), and extended model-assisted designs have been proposed as simple models that perform well in selecting MTDs. Pan et al. (2020) have extended the Keyboard design to the drug-combination dose-finding design. Lin and Yin have suggested the BOIN design for dose finding in the drug-combination trials. Zhang and Yuan have proposed the waterfall design to explore the two-dimensional dose combinations efficiently. The BOIN and Keyboard designs generate dose-assignment decision tables based on simple statistical models before a trial starts, but the sample size must be set in advance, and the trial cannot complete until the number of patients treated reaches the sample size. Although the BOIN and Keyboard designs have a stopping rule that can be used to terminate the trial if the number of patients treated exceeds the predetermined number, there is no statistical basis for the predetermined number. Kojima proposed an early completion method for model-assisted designs but did not discuss the applicability of this method for dose combination trials.

In this paper, two methods for data-dependent early completion of dose-finding trials for drug combination are proposed: (1) an early completion method based on dose retention probability, and (2) an early completion method in which a dose retention probability is adjusted by a bivariate isotonic regression. Early completion is determined when the beta-binomial probability for dose retention using both trial data and the number of remaining patients is high. Early completion for a virtual trial was demonstrated, and the performance of the early completion method was evaluated by simulation studies with 12 scenarios.

2 Methods

2.1 Modeling dose combination trials

A drug combination trial was modeled as follows: sample size of $N$, $J$ dose levels of drug A and $K$ dose levels of drug B; current combined dose level $(j, k)$ of $d_{jk}$; the total number of patients treated at $d_{jk}$ is $n_{jk}$; the total number of DLTs at current dose $d_{jk}$ is $m_{jk}$; observed DLT rate at current dose is $\hat{p}_{jk} = m_{jk} / n_{jk}$; the number of remaining patients is $l$; the TTL is $\phi$; and a prior distribution of each dose-combination is Beta(1,1).

The Bayesian optimal interval (BOIN) design model generates a dose-assignment decision table and compares $\hat{p}_{jk}$ and a proper dosing interval $I_{pro,BOIN} = (\lambda_\phi, \lambda_{\phi} + \phi)$ for the DLT rate around the TTL $\phi$. $\lambda_\phi$ is the maximum value at which a dose escalation is determined, and $\lambda_{\phi}$ is the minimum value at which a dose de-escalation is determined. The boundaries of the proper dosing interval are calculated by minimizing the incorrect decisions of dose adjustment. For example, when $\phi = 0.3$, $I_{pro,BOIN} = (0.236, 0.358)$. The Keyboard design conducts a dose assignment compared an interval probability of a proper dosing interval $I_{pro,Key} = (\phi - 0.05, \phi + 0.05)$ called a target key and other interval probabilities. In this paper, when there is no need to distinguish $I_{pro,BOIN}$ and $I_{pro,Key}$, $I_{pro}$ is used.

For drug combination trials, if the dose for the next cohort is the same as the current dose, the dose adjustment is simple. However, one of the problems with combination trials is that there are many ways to determine dose escalation and de-escalation. For safety reasons in real-life settings, it is not possible to try all combinations, therefore strategic dose selection is necessary to identify the MTD in a limited sample size. An example of a dose-assignment design is shown in Figure 1. Pan et al. proposed algorithms to escalate or de-escalate the doses of two drugs simultaneously, but here the focus is on a method to increase or decrease only one dose of the two drugs.

2.2 Dose escalation/de-escalation algorithm used in the dose combination trial

When the dose combination for the next cohort is determined as an escalation after $d_{jk}$ is administered, the dose combination is escalated to the one that has the highest interval posterior probability of the interval $I_{pro}$ for either $d_{j,k+1}$ or $d_{j+1,k}$. If the candidate combination for dose escalation has never been administered, the interval probability will be calculated using the prior distribution. If the interval probabilities are equal, the drug combination is chosen randomly.
When the dose combination for the next cohort is determined as a de-escalation after \( d_{j,k} \) is administered, the dose combination is de-escalated to the one that has the highest interval posterior probability of the interval \( I_{pro} \) for either \( d_{j-1,k} \) or \( d_{j,k-1} \). If the candidate combination for dose escalation has never been administered, the interval probability is calculated using the prior distribution. If the interval probabilities are equal, the drug combination is chosen randomly.

If the administered drug combination is too toxic \( (P(j_{i,k} > \phi) > 0.95) \), administration of the current dose combination and all higher dose combinations in the trial is stopped. After completion of the trial, the MTD is selected as the dose combination for which the observed toxicity rate is closest to the TTL. Because of the small sample size in the dose-finding trial, the observed toxicity rates are adjusted by bivariate isotonic regression\(^{40}\) to give a monotonic increase for the toxicity rates, and then the MTD is selected. When there are multiple-dose combinations that are close to the TTL, if the observed toxicity rates of the multiple dose combinations are all below the TTL, the highest dose combination is selected as the MTD. If the observed toxicity rates of the multiple dose combinations are all over the TTL, the lowest dose combination is selected as the MTD. The BOIN and Keyboard designs require that the sample size is set in advance, and the trial cannot be completed until the number of patients treated reaches the sample size. Although these designs have a stopping rule to terminate the trial if the number of patients treated exceeds the predetermined number, there is no statistical basis for the maximum number of patients treated to be used for the stopping rule.

### 2.3 Early completion method

I propose methods for data-dependent early completion of dose-finding trials for drug combinations. Early completion is determined when the beta-binomial probability for dose retainment using both the trial data and the number of remaining patients is high. The BOIN and Keyboard designs summarize the number of patients treated for whom dose retainment is determined in dose-assignment decision tables, and the dose retainment probability uses this number. I assume that \( \mathcal{R} \) represents the set size of the number of patients for dose retainment for \( n_{j,k} + l \), then for example, \( \mathcal{R} \) includes three and four patients when the number of patients is 12 patients for the BOIN design. The dose retainment probability is calculated as

\[
\text{Dose retainment probability} = \sum_{r \in \mathcal{R}} \text{BetaBinom}(r - m_{j,k}; l, m_{j,k} + 1, n_{j,k} - m_{j,k} + 1)
\]

where \( \text{BetaBinom} \) is the beta-binomial probability function that \( r - m_{j,k} \) DLTs occur in the remaining \( l \) patients when there are \( m_{j,k} \) DLTs for \( n_{j,k} \) patients. The trial is completed early when the dose retainment probability is over a threshold. Kojima\(^{29}\) recommended a threshold of 0.4 because the dose retainment interval for the DLT rate for the BOIN

![Figure 1. Example of a dose-assignment design. From dose combination \(d_{1,1}\), there are two candidate combinations for dose escalation, \(d_{1,2}\) and \(d_{2,1}\). The dose is escalated to \(d_{1,1}\) (the solid blue line) because its dose-limiting toxicity (DLT) rate is closer to the target toxicity level (TTL). Subsequent dose escalations are selected in the same manner. If a dose de-escalation is determined after the administration of \(d_{3,2}\), the dose combination can be de-escalated to \(d_{3,1}\) or \(d_{2,2}\), depending on which of them a DLT rate closer to the TTL. Solid lines indicate that the drug was administered; dotted lines indicate that the drug was a candidate for dose escalation/de-escalation; blue indicates dose escalation; red indicates dose de-escalation.](image)
design is a maximum of 0.4. Because the MTD is selected by using the toxicity rate adjusted by bivariate isotonic regression, the early completion method using the toxicity rate adjusted by the bivariate isotonic regression is also considered. If the current dose combination is the maximum dose combination, \( R \) includes the number of patients for which a dose escalation is determined. Because \( R \) includes not only the number of patients for dose retainment but also the number for dose escalation, the dose retainment probability (equation (1)) is divided by 2. The maximum dose combination is the maximum dose of two drugs, and if the planned maximum doses are changed by the stopping rule, the maximum doses are also changed. The minimum dose is calculated in the same way. Dose retainment probability, which is calculated by replacing \( m_{j,k} \) in the equation (equation (1)) with \( n_{j,k} \times \text{adjusted toxicity rate} \), is also proposed.

The early completion of a virtual dose-finding trial is demonstrated. Hereafter, the normal dose retainment probability is abbreviated as DRP and the dose retainment probability based on the bivariate isotonic regression is abbreviated as DRP-I.

### 2.4 Virtual dose-finding trial

A virtual dose-finding trial was set up with the three dose levels of drug A and the three dose levels of drug B, sample size 30, cohort size 3, TTL 30%, and threshold for early completion of 0.4. The results of 24 patients treated are shown in Table 1, and dose adjustments for up to 24 patients are shown in Supplemental Example S1. The current dose combination was \( d_{2,2} \) and the safety evaluation was completed. The \( R \) for 15 patients (nine treated and six untreated) for the BOIN design was \( \{4, 5\} \). Because the \( R \) for the BOIN and Keyboard designs is the same, early completion was considered without distinguishing between them.

The DRP is calculated as

\[
\text{BetaBinom}(4 - 3; 6, 3 + 1, 9 - 3 + 1) + \text{BetaBinom}(5 - 3; 6, 3 + 1, 9 - 3 + 1) = 0.493
\]

Because the DRP is over the threshold of 0.4, this trial halts early.

The observed DLT rates adjusted by the bivariate isotonic regression are

\[
\begin{pmatrix}
0.000 & 0.000 & 0.000 \\
0.167 & 0.335 & 0.664 \\
0.000 & 0.664 & 0.000
\end{pmatrix}
\]

and the dose corresponding to each element is

\[
\begin{pmatrix}
d_{1,1} & d_{1,2} & d_{1,3} \\
d_{2,1} & d_{2,2} & d_{2,3} \\
d_{3,1} & d_{3,2} & d_{3,3}
\end{pmatrix}
\]

The adjusted \( m_{2,2} \) is 3.015 (= adjusted DLT rate of \( 0.335 \times n_{2,2} \) of 9) and the DRP-I is 0.491 (= \( \text{BetaBinom}(4 - 3.015; 6, 3.015 + 1, 9 - 3.015 + 1) + \text{BetaBinom}(5 - 3.015; 6, 3.015 + 1, 9 - 3.015 + 1) \)), which is over the threshold of 0.4. Hence, this trial halts early. The early completion method halted this trial without dosing six patients. Six fewer patients can mean a seven-month reduction in the trial duration, if, for example, the safety evaluation period is one month and the enrollment of patients takes one month. The sample R program code used to calculate the dose retainment probabilities is provided in Supplemental Example S2.

### Table 1. A number of patients treated for dose retainment (target toxicity level = 0.3).

| Design | Number of patients treated at current dose combination* |
|--------|----------------------------------------------------------|
|        | 3  | 6  | 9  | 12 | 15 | 18 |
| Keyboard | 1  | 2  | 3  | 4-5| 4-5| 5-6|
| BOIN    | 1  | 2  | 3  | 3-4| 4-5| 5-6|

*If the current dose combination is the maximum dose combination, the dose combination is retained even if it is below the number of patients treated. If the current dose combination is the minimum dose combination, the dose combination is retained even if it is over the number of patients treated. BOIN: Bayesian optimal interval design; Key: Keyboard design.
2.5 Simulation study

Simulation settings. The performances of the early completion methods were evaluated by Monte Carlo simulations. Six designs were prepared, namely BOIN, BOIN using the early completion method based on DRP (BOIN-EC), BOIN using the early completion method based on DRP-I (BOIN-ECI), Keyboard (Key), Keyboard using the early completion method based on DRP (Key-EC), Keyboard using the early completion method based on DRP-I (Key-ECI). Two dose matrices sizes (3 × 4 and 5 × 6) were assumed for each design, making a total of 12 scenarios. The 12 scenarios were based on those considered by Lin and Yin. Two detailed true DLT rates for each scenario are provided in Supplemental Table S1. The sample sizes were 45 and 90 for the 3 × 4 drug combinations and 5 × 6 drug combinations, respectively; cohort size was 3; TTL was 30%; and the threshold for early completion was 0.4. Sensitivity analyses were performed by changing the sample sizes to 36 and 75 for 3 × 4 and for 5 × 6, respectively, the TTL to 20%, and the threshold for early completion set to 0.35 and 0.45. The simulation study was conducted in R.

Evaluation criteria. The following criteria were used to evaluate the performance of each method: (1) percentage for correct MTD selection; (2) percentage for dose selection lower than the correct MTD; (3) percentage for dose selection higher than the correct MTD; (4) average number of patients treated; (5) percentage change of patients treated from planned sample size; and (6) percentage for early completion.

3 Results

3.1 Percentage for the correct MTDs selection (PCMS)

The PCMS results for the 12 scenarios are shown in Figure 2. The changes in PCMSs of BOIN-EC from those of BOIN averaged −3.9%, with a minimum of −0.9% for scenario 6 and a maximum of −9.9% for scenario 9. The changes in PCMSs of BOIN-ECI from those of BOIN averaged −4.6%, with a maximum increase of 4.0% for scenario 6 and a maximum decrease of −8.6% for scenario 10. The changes in PCMSs of Key-EC from those of Key averaged −2.3%, with a maximum increase of 0.8% for scenario 1 and a maximum decrease of −4.8% for scenario 2. The changes in PCMSs of Key-ECI from those of Key averaged −1.7%, with a maximum increase of 1.4% for scenario 6 and a maximum decrease of −3.8% for scenario 9. The percentage changes in Key-EC were smaller than those of BOIN-EC.

3.2 Percentage for dose selection lower than the correct MTD

The percentage changes between the early completion and non-early completion designs were calculated as the result of the early completion design—the result for the non-early completion design. For BOIN-EC and BOIN-ECI, the average changes were 3.5% and 7.0%, respectively. For Key-EC and Key-ECI, the average changes were 1.2% and 2.2%, respectively. The change was the smallest for Key-EC.

Figure 2. Changes in the percentages for correct maximum tolerated dose (MTD) selection were determined using different designs. BOIN: Bayesian optimal interval design; Key: Keyboard design; EC: early completion based on normal dose retainment probability; ECI: early completion based on dose retainment probability using bivariate isotonic regression.
3.3 Percentage for dose selection higher than the correct MTD

The percentage changes between the early completion and non-early completion designs were calculated as the result of the early completion designs—the result for the non-early completion design. For BOIN-EC and BOIN-ECI, the average changes were 0.7% and −2.0%, respectively. For Key-EC and Key-ECI, the average changes were 1.2% and −0.3%, respectively. The change was the smallest for BOIN-EC.

3.4 Average number of patients treated/percentage change of patients treated from a planned sample size

For the $3 \times 4$ drug combinations with a sample size of 45, the percentage changes of patients treated from the planned sample size an average of −24.6% and −25.1% (reduced by approximately 11 patients) using BOIN-EC and BOIN-ECI, and an average of −20.6% and −17.4% (reduced by approximately nine patients) using Key-EC and Key-ECI. For the $5 \times 6$ drug combinations with a sample size of 90, the percentage changes of patients treated from the planned sample size were an average of −31.6% and −29.8% (reduced by approximately 27 patients) using BOIN-EC and BOIN-ECI, and an average of −21.2% and −20.1% (reduced by approximately 19 patients) using Key-EC and Key-ECI. Overall, all the average percentage changes were similar.

3.5 Percentage for early completion

For the $3 \times 4$ drug combinations, the percentages for early completion were an average of 69.6% and 64.2% for BOIN-EC and BOIN-ECI, and an average of 64.7% to 57.1% for Key-EC and Key-ECI. For the $5 \times 6$ drug combinations, the percentages for early completion were an average of 85.5% and 82.0% for BOIN-EC and BOIN-ECI, and an average of 75.2% and 71.0% for Key-EC and Key-ECI. Overall, BOIN-EC and Key-EC had higher percentages of early completion than BOIN-ECI and KEY-ECI (Figure 3).

4 Discussion

In this study, four early completion methods (BOIN-EC, BOIN-ECI, Key-EC, and Key-ECI) for dose-finding trials for drug combination were proposed and evaluated. Early completion is determined when the beta-binomial probability for dose retainment using both the trial data and the number of remaining patients is high.

Early completion for the virtual trial with $3 \times 3$ drug combinations and a sample size of 36 was demonstrated. By completing the trial early, six of the 36 patients were retained. Six fewer patients can mean a seven-month reduction in the trial duration, if, for example, the safety evaluation period is one month and the enrollment of patients takes one month.

![Figure 3](image.png)

Figure 3. Changes in the percentages for early completion using different designs. BOIN: Bayesian optimal interval design; Key: Keyboard design; EC: early completion based on normal dose retainment probability; ECI: early completion based on dose retainment probability using bivariate isotonic regression.
For the simulation study, the percentages for the correct MTDs selection (PCMSs) in all the early completion designs were almost similar as compared to non-early completion designs. For the BOIN-EC and BOIN-ECI designs, when there were many dose combinations and either maximum dose had a correct MTD, the performance was lower. For the Key-EC and Key-ECI designs, the changes in PMCSs were smaller than those for the Keyboard design. Because the BOIN design needs a higher number of patients to determine dose-retainment than the Keyboard design when the number of patients treated was higher, we considered that the BOIN design continued to retain doses that were not correct MTD, resulting in poorer performance compared to the Keyboard design. The results of the sensitivity analyses with changed planned sample size or TTL showed similar trends.

When the early completion designs were compared with designs that use the stopping rule available on the Integrated Platform for Designing Clinical Trials (trialdesign.org), the overall PCMSs of the designs with the stopping rule were lower than those obtained using the proposed early completion designs, and the PCMSs were reduced by approximately 10% compared with the non-early completion designs in scenarios 9 to 11 as shown in Supplemental Table S7. I recommend that the number of remaining patients should be considered for determining early completion. Early completion was at an average of approximately 70% of the set sample size, meaning the number of patients treated was reduced by approximately about 20%−30%.

Overall, the performances of the proposed early completion methods were similar to that of the non-early completion designs, except for the early completion BOIN designs when there were many dose combinations and either maximum dose had a correct MTD. However, the performances of the proposed early-completion Keyboard designs were similar to that of the non-early-completion Keyboard design. Among the two early completion methods, ECI was slightly better than EC; however, I recommend using EC because it is easier to implement. The proposed early completion methods can be applied to dose-finding trials with more than two drugs in the same way. Decision tables showing the number of patients for determining early completion before the trial starts are shown in Tables 2 and 3. Such tables can also be applied to a single drug and more than two drug dose-finding trials. A sample program code of early completion is provided in Supplemental Example S2.

Acknowledgements

The author is grateful to the editor, associate editor, and referee for their valuable comments and helpful suggestion. The author thanks Professor Masahiko Gosho and Associate Professor Hisashi Noma for their encouragement and helpful suggestions.

Author's contributions

M Kojima: Conception and design; development of methodology; acquisition of data (e.g. provided animals, acquired and managed patients, provided facilities, etc.): analysis and interpretation of data (e.g. statistical analysis, biostatistics, computational analysis);
writing, review, and revision of the manuscript; administrative, technical, and material support (i.e. reporting and organizing data, constructing databases); and study supervision.

**Declaration of conflicting interests**
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**
The author(s) received no financial support for the research, authorship, and/or publication of this article.

**ORCID iD**
Masahiro Kojima https://orcid.org/0000-0003-0867-7692

**Supplemental material**
Supplemental material for this article is available online.

**References**
1. Simon R, Rubinstein L, Arbuck SG, et al. Accelerated titration designs for phase I clinical trials in oncology. *J Natl Cancer Inst* 1997; 89: 1138–1147.
2. O’Quigley J, Pepe M and Fisher L. Continual reassessment method: a practical design for phase I clinical trials in cancer. *Biometrics* 1990; 46: 33–48.
3. Thall PF, Millikan RE, Muller P, et al. Dose-finding with two agents in phase I oncology trials. *Biometrics* 2003; 59: 487–496.
4. Conaway MR and Dunbar S. Peddada SD: designs for single- or multiple-agent phase I trials. *Biometrics* 2004; 60: 661–669.
5. Ivanova A and Wang KA. A non-parametric approach to the design and analysis of two-dimensional dose-finding trials. *Stat Med* 2004; 23: 1861–1870.
6. Huang X, Biswas S, Oki Y, et al. A parallel phase I/II clinical trial design for combination therapies. *Biometrics* 2007; 63: 429–436.
7. Fan SK, Venook AP and Lu Y. Design issues in dose-finding phase I trials for combinations of two agents. *J Biopharm Stat* 2009; 19: 509–523.
8. Yin G and Yuan Y. Bayesian dose finding in oncology for drug combinations by copula regression. *J R Stat Soc Ser C Appl Stat* 2009; 58: 211–224.
9. Wages NA, Conway MR and O’Quigley J. Dose-finding design for multi-drug combinations. *Clin Trials* 2011; 8: 380–389.
10. Lee BL and Fan SK. A two-dimensional search algorithm for dose-finding trials of two agents. *J Biopharm Stat* 2012; 22: 802–818.
11. Harrington JA, Wheeler GM, Sweeting MJ, et al. Adaptive designs for dual-agent phase I dose-escalation studies. *Nat Rev Clin Oncol* 2013; 10: 277–288.
12. Hirakawa A, Hamada C and Matsui S. A dose-finding approach based on shrunken predictive probability for combinations of two agents in phase I trials. *Stat Med* 2013; 32: 4515–4525.
13. Liu S and Ning J. A Bayesian dose-finding design for drug combination trials with delayed toxicities. *Bayesian Anal* 2013; 8: 703–722.
14. Lam KC, Lin R and Yin G. Non-parametric overdose control for dose finding in drug combination trials. *J R Stat Soc Ser C Appl Stat* 2019; 68: 1111–1130.
15. Razaei SZ, Cook-Wines G and Tighiouart M. A nonparametric Bayesian method for dose finding in drug combinations cancer trials. *Stat Med* 2022; 41: 1059–1080.
16. Riviere KM, Le Touremeau C, Paoletti X, et al. Designs of drug-combination phase I trials in oncology: a systematic review of the literature. *Ann Oncol* 2015; 26: 669–674.
17. Ji Y, Liu P, Li Y, et al. A modified toxicity probability interval method for dose-finding trials. *Clinical Trials* 2010; 7: 653–663.
18. Guo W, Wang SJ, Yang S, et al. A Bayesian interval dose-finding design addressing Ockham’s razor: mTPI-2. *Contemp Clin Trials* 2017; 58: 23–33.
19. Liu S and Yuan Y. Bayesian optimal interval designs for phase I clinical trials. *J R Stat Soc Ser C Appl Stat* 2015; 64: 507–523.
20. Yuan Y, Lee JJ and Hilsenbeck GS. Model-assisted designs for early-phase clinical trials: simplicity meets superiority. *JCO Precis Oncol* 2019; 3: 1–12.
21. Yan F, Mandrekar JS and Yuan Y. Keyboard: a novel Bayesian toxicity probability interval design for phase I clinical trials. *Clin Cancer Res* 2017; 23: 3994–4003.
22. Lin R and Yin G. Bayesian optimal interval design for dose finding in drug-combination trials. *Stat Methods Med Res* 2017; 26: 2155–2167.
23. Pan H, Lin R, Zhou Y, et al. Keyboard design for phase I drug-combination trials. *Contemp Clin Trials* 2020; 92: 105972.
24. Zhang L and Yuan Y. A practical Bayesian design to identify the maximum tolerated dose contour for drug combination trials. *Stat Med* 2016; 35: 4924–4936.
25. Takeda K, Taguri M and Morita S. BOIN-ET: Bayesian optimal interval design for dose finding based on both efficacy and toxicity outcomes. Pharm Stat 2018; 17: 383–395.
26. Yuan Y, Lin R, Li D, et al. Time-to-event Bayesian optimal interval design to accelerate phase I trials. Clin Cancer Res 2018; 24: 4921–4930.
27. Mu R, Yuan Y, Xu J, et al. gBOIN: a unified model-assisted phase I trial design accounting for toxicity grades, and binary or continuous end points. J R Stat Soc Ser C Appl Stat 2019; 68: 289–308.
28. Zhou Y, Lee JJ and Yuan Y. A utility-based Bayesian optimal interval (U-BOIN) phase I/II design to identify the optimal biological dose for targeted and immune therapies. Stat Med 2019; 38: S5299–S5316.
29. Lin R and Yuan Y: time-to-event model-assisted designs for dose-finding trials with delayed toxicity. Biostatistics 2020; 21: 807–824.
30. Lin R, Zhou Y, Yan F, et al. BOIN12: Bayesian optimal interval phase I/II trial design for utility-based dose finding in immuno-therapy and targeted therapies. JCO Precis Oncol 2020; 4: 1393–1402.
31. Takeda K, Morita S and Taguri M. TITE-BOIN-ET: time-to-event Bayesian optimal interval design to accelerate dose-finding based on both efficacy and toxicity outcomes. Pharm Stat 2020; 19: 335–349.
32. Zhou Y, Lin R, Lee JJ, et al. TITE-BOIN12: a Bayesian phase I/II trial design to find the optimal biological dose with late-onset toxicity and efficacy. Stat Med 2022; 41: 1918–1931.
33. Takeda K, Xia Q, Liu S, et al. TITE-gBOIN: time-to-event Bayesian optimal interval design to accelerate dose-finding accounting for toxicity grades. Pharm Stat 2022; 21: 496–506.
34. Takeda K, Morita S and Taguri M. gBOIN-ET: the generalized Bayesian optimal interval design for optimal dose-finding accounting for ordinal graded efficacy and toxicity in early clinical trials. Biom J 2022; 64: 1178–1191.
35. Kojima M. Early completion of phase I cancer clinical trials with Bayesian optimal interval design. Stat Med 2021; 40: 3215–3226.
36. Kojima M. Early completion of model-assisted designs for dose-finding trials. JCO Precis Oncol 2021; 5: 1449–1457.
37. Kojima M. Adaptive design for identifying maximum tolerated dose early to accelerate dose-finding trial. BMC Med Res Methodol 2022; 22: 97.
38. Kojima M: Early completion based on multiple dosages to accelerate maximum tolerated dose-finding. arXiv preprint arXiv: 2110.00563, 2021
39. Kojima M: Application of multi-armed bandits to model-assisted designs for dose-finding clinical trials. arXiv preprint arXiv: 2201.05268, 2022
40. Lin R, Yin G and Shi H. Bayesian adaptive model selection design for optimal biological dose finding in phase I/II clinical trials. Biostatistics 2021: kxab028.