The Modified Combo i3+3 Design for *Novel-Novel Combination Dose-Finding Trials* in Oncology

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Abstract

We consider a modified Ci3+3 (MCi3+3) design for dual-agent dose-finding trials in which both agents are tested on multiple doses. This usually happens when the agents are novel therapies. The MCi3+3 *design* offers a flexible two- or three-stage process. Initially, it begins with single-agent dose *escalation,* followed by a *model-free* combination dose-finding stage for both agents, and optionally, a model-based third stage. *MCi3+3 aims to maintain a relatively simple framework to facilitate practical application, while also address challenges that are unique to novel-novel combination dose finding.* Through simulations, we demonstrate that the MCi3+3 design adeptly manages various toxicity scenarios. It exhibits operational characteristics on par with other combination designs, while offering an enhanced safety profile.

Keywords: *Combo Design; Model-Free Designs; Phase I; Toxicity; Toxicity Probability Interval.*

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1 Introduction

In the evolving landscape of oncology therapeutics, the introduction of combination therapies, particularly with PD-1 inhibitors like pembrolizumab (Long et al., 2017; Baldini et al., 2022; Berinstein et al., 2019), has marked a significant advancement. These therapies often involve administering a novel drug alongside an established one at a fixed dosage, which has been validated for its efficacy and safety. The main aim is to explore the enhanced efficacy of the new drug in combination with a standard treatment regimen. While such trials offer valuable insights, the approach, due to the fixed dosage of the existing drug, mirrors that of single-agent dose-finding studies, thereby simplifying the trial design.

However, as the field of drug development progresses, there's an emerging need to simultaneously develop and test multiple new drugs, adding complexity to clinical trials. This shift has led to the exploration of dose combinations, presenting challenges in determining the optimal dosing strategies due to the intricate interplay between the drugs, which can significantly impact both their efficacy and toxicity profiles. Although some methods for dual-agent trials exist, they often do not fully address these complexities. Waterfall design (Zhang and Yuan, 2016) aimied to identify the MTD contour by dividing the process into sequential one-dimensional subtrials that leverage previous outcomes to inform subsequent ones. Mander and Sweeting (2015) introduces a nonparametric dual-agent trial design (PIPE) that simplifies incorporating historical data through conjugate Bayesian inference, ensuring monotonicity in dose-escalation decisions and facilitating varied experimentation along the maximum tolerated contour. In addition, there are methodologies such as the BOIN Combo (Lin and Yin, 2017), which adapts the single-agent BOIN design Liu and Yuan (2015) for combination therapies, and the Ci3+3 design (Yuan et al., 2021), an extension of the i3+3 design (Liu et al., 2020)tailored for dual-agent trials.

While existing methodologies have largely advanced the field for combo dose finding, many challenges and improvements remain. For instance, prior information from single-agent dose finding is not formally modeled, and most methods do not provide sufficiently flexible algorithms that allow thorough and quick exploration of the dose combination space. Addressing the pressing needs of dual-agent Phase I trial designs, we introduce the Modified Ci3+3 (MCi3+3) design specifically *developed to tackle the intricacies of dual-agent dose-finding trials. MCi3+3 is a three-stage design with the first two stages based on model-free rules and an optional third stage based on model-based statistical inference. The first stage begins with single-agent dose finding using the i3+3 design (Liu et al., 2020) for each agent in parallel. The trial proceeds to the second stage focusing on exploration of dose combinations (DCs) of the two agents. Importantly, data from the first stage are useful for the second stage in two aspects. First, since a single-agent MTD is expected to be located for each agent from the first stage, data from the first stage helps determine the starting dose combinations (DCs) for the second stage. Second, the data from the first stage is also*

directly used in the second and third stage dose finding decisions. The second stage extends the Ci3+3 design (Yuan et al., 2021) with a more intelligent and safer set of rules allowing thorough and efficient exploration of the two-dimensional DC space. Lastly, an optional third stage utilizing logistic regression models is available, offering refined allocation strategies over rule-based designs when sufficient patient data is present. This model-based stage assesses the posterior probability of dose combinations within a specified Equivalence Interval, guiding the selection of doses for future cohorts. Ultimately, the trial culminates in the selection of MTDCs, drawing from both combination and single-agent phase data.

The third stage option gives investigators flexibility to go further or stop the trial. We will show this flexibility later using numerical examples.

We need to provide a motivating example from Moderna, masking the names of the drug.

This paper is structured as follows: Section 2 introduces the methodology, followed by Section 3 which illustrates a trial sample within the framework of the complex rules. Section 4 displays the outcomes of our simulations. Finally, Section 5 provides reflections and directions for future research.

2 Methodology

2.1 Notation

Suppose I dose levels of drug A and J levels of drug B are tested. Let (i,0) and (0,j) represent dose i of drug A alone and dose j of drug B alone respectively. Let $x_{ij} = (x_{1i}, x_{2j})$ be the actual dose (i,j) which denotes the combination of dose i of drug A and dose j of drug B, $i = 0, \cdots, I$ and $j = 0, \cdots, J$. For simplicity, we use DCs to refer the Dose Combinations in the trial. We use the binary outcome to demonstrate the toxicity under a dose level. That's to say, under a toxicity probability the patient will have DLT or no DLT during the observation window. Let p_{ij} denotes the toxicity probability of DC (i,j), we assume

$$y_{ij}|n_{ij}, p_{ij} \sim Bin(n_{ij}, p_{ij}).$$

In the MCi3+3 design, we proposed the novel dose eascalation rules based on the basic up and down decisions obtained from the i3+3 design (Liu et al., 2020). Due to the concision of the i3+3 design, only 3 pre-specified parameters and the outcome data are needed, thus it is implemented in both single agent and dual agent dose finding. We utilized the equivalence interval (EI) as $[p_T - \epsilon_1, p_T + \epsilon_2]$ with the target toxicity level p_T to generate decisions. The dose-finding algorithm of the i3+3 design can be summarised in Table 1. Decisions E, S, and D represent escalation to the next higher dose, stay at the current dose, and de-escalation to the next lower dose,

respectively.

Table 1: The decision rules in the i3+3 design. Notation: d represents the current dose being investigated in the trial; n_d and y_d denote the number of patients enrolled and those with DLT at dose d, respectively.

Condition	*Decision*	*Dose for next cohort*
$\frac{y_d}{n_d}$ below EI	Escalation (E)	$d+1$
$\frac{y_d}{n_d}$ inside EI	Stay (S)	d
$\frac{y_d}{n_d}$ above EI and $\frac{y_d-1}{n_d}$ below EI	Stay (S)	d
$\frac{y_d}{n_d}$ above EI and $\frac{y_d-1}{n_d}$ inside EI	De-escalation (D)	$d-1$
$\frac{y_d}{n_d}$ above EI and $\frac{y_d-1}{n_d}$ above EI	De-escalation (D)	$d-1$

Phase I oncology trials enroll patients in cohorts, say a group of three patients per cohort. After a cohort is enrolled and assigned to a dose level for treatment, the patients are followed for three to four weeks to evaluate drug safety and record any DLT outcomes.

2.2 Proposed MCi3+3 design

For the MCi3+3 design, we proposed a three-stage design but offer two kind of choices.

2.2.1 Stage I - Single agent dose finding

The initial stage focuses on single-agent dose finding, wherein each drug is individually assessed to determine the starting dose for subsequent stages utilizing the i3+3 design (Liu et al., 2020). Our goal is to pinpoint a starting dose that is both effective and safe for each drug, marked with decision 'E'. This step is crucial as we anticipate an increased toxicity level during the combination phase and thus aim to initiate with a dose that optimally balances efficacy and safety.The process unfolds through the following steps:

1. Enroll the initial two cohorts at the starting doses for each drug, which are (1,0) and (0,1) respectively.

2. After each cohort completes the DLT evaluation period, use the decisions of the i3+3 design in Table 1 to determine dose escalation (E), de-escalation (D) or staying at the current dose (S), which specifies the dose level for the next cohort of subjects.

3. For either drug, enroll one more cohort of subjects and treat the cohort at the dose based on the decision of the previous dose of the drug.

4. Repeat steps 2-3 until the single-drug dose finding reaches the highest dose or, for the first time, a dose is assigned a decision S or D by i3+3.

5. Enter the second stage and denote the highest doses with decision E of the drugs A and B as (i_0,0) and (0,j_0), respectively.

The starting dose for the second stage is determined by the denoted highest dose. Denote the starting dose set be $\mathcal{B}$, it is derermined as follows:

Algorithm 1 Starting Dose Determination

if $i_0 \geq 1$, $j_0 \geq 1$, $i_0 \neq j_0$ **then**

$\mathcal{B} = \{(i_0, 1), (1, j_0)\}$

else

$\mathcal{B} = \{(1, 1)\}$

end if

return $\mathcal{B}$

2.2.2 Stage II - Rule-Based dose finding

In the second stage, one or more DCs are assigned to cohorts of patients, and decision E, S, or D are generated based on the i3+3 design. However, there could be multiple candidate DCs for each decision. For example, a decision E for DC (i,j) could mean (i+1,j) or (i,j+1), as candidate DCs for the next cohort. Here we borrow and extended some up and down rules in the Ci3+3 design (Yuan et al., 2021). Note that we do not allow simultaneous change of both doses for a single decision. MCi3+3 selects up to two DCs with the highest utility among the candidates. Denote $\sigma = \{(i, j), 0 \leq i \leq I, 0 \leq j \leq J\} \backslash (0, 0)$, i.e., the set of all ($I$+1)*($J$+1) DCs excluding (0,0).

1. The starting dose set is $\mathcal{B}$ determined from stage I.

2. MCi3+3 allows multiple DCs to be tested at each step, resulting in multiple current DCs. Assume (i,j) is one of the current DCs. Let $\mathbf{n}$ denote the number of enrolled patients and $\mathbf{x}$ the number of patients with DLTs at all DCs. Calculate the dosing decision E, S, or D for DC(i,j) based on the i3+3 design in Table 1. Let Ω denote the candidate DCs for the next cohorts, which is defined as follows.

    a. If the decision of DC (i,j) is E, DCs (i+1,j) and (i,j+1) are added to Ω.

    b. Else if the decision of DC (i,j) is S,

- If (i+1,j-1) and (i-1,j+1) have been tested and their decisions are E or S, DCs (i,j),(i+1,j-1),(i-1,j+1),(i+2,j-2) and (i-2,j+2) are added to Ω if (i+2,j-2) and (i-2,j+2) are untested.
- Else, DCs (i,j), (i+1,j-1), and (i-1,j+1) are added to Ω.

c. Else if the decision of DC (i,j) is D, DCs (i-1,j) and (i,j-1) are added to Ω.

d. We call DC (i,j) is higher than ($i^{'}$,$j^{'}$) if

- i>$i^{'}$ and j>$j^{'}$,
- or i>$i^{'}$ and $j = j^{'}$,
- $i = i^{'}$ and j>$j^{'}$.

e. We define DC (i,j) is lower than ($i^{'}$,$j^{'}$) if

- i<$i^{'}$ and j<$j^{'}$,
- or i<$i^{'}$ and $j = j^{'}$,
- $i = i^{'}$ and j<$j^{'}$.

f. Denote the current available trial data ($\mathbf{n}$,$\mathbf{x}$) at all the tried DCs. Compute the dosing decisions on all the tried DCs based on the i3+3 design (Table 1).

- If the decision of any tried DC is D, all the DCs higher than the DC, defined as $\sigma_D(\mathbf{n}, \mathbf{x})$, should be removed from Ω.
- Else if the decision of any tried DC is E, all the DCs lower than the DC, defined as $\sigma_E(\mathbf{n}, \mathbf{x})$, should be removed from Ω.
- Else if the decision of any tried DC is DU, this DC and all the DCs higher than this DC should be removed from Ω and eliminated from the study.
- The set of remaining DCs $(\sigma - \sigma_D) \cap (\sigma - \sigma_E)$ are considered admissible.

g. Doses of a single agent will be removed from Ω.(Optional)

3. Denote the current DCs as $\{A_1, \cdots, A_K\}$. Denote Ω the final set of candidate DCs from Step 2 above.

- If Ω is not empty, then check if any current DC A_k is in Ω. If an A_k is in Ω but its decision is not 'Stay', remove A_k from Ω.
- If Ω is empty, let Ω equal $(\sigma - \sigma_D) \cap (\sigma - \sigma_E)$, the set of admissible DCs.

4. Select the two DCs with the highest utilities from Ω and treat the next cohorts at the two DCs. We also proposed a little calculation method to handle ties, which is demonstrate later.

– The utility of DC (i,j) is defined as $U_{ij} = \Pr\{p_{ij} \in \text{EI} | (y_{ij}, n_{ij})\}$ with $Beta(0.05,0.05)$ as the prior.

– If there are more than two DCs with the same highest utility, select two randomly.

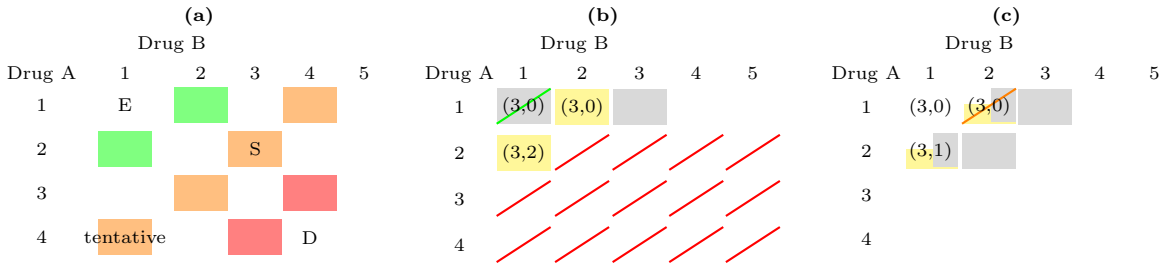
When the posterior probability of one dose falling into EI is bigger than the threshold η (let's say 0.4), we will enter stage III. The posterior probability is calculated using the following logistic model:

$$\text{logit}(p_{ij}) = \beta_0 + (\beta_1 x_{1i} + \beta_2 x_{2j} + \beta_3 x_{1i} x_{2j}) I(x_{1i} \leq x_{1max}) I(x_{2j} \leq x_{2max}) + (\beta_4 x_{1i} + \beta_5 x_{2j} + \beta_6 x_{1i} x_{2j})(1 - I(x_{1i} \leq x_{1max}) I(x_{2j} \leq x_{2max}))$$

where x_{1j} denotes the dose level of drug A and x_{1max} the maximum dose level with enrolled patients of drug A; x_{2j} denotes the dose level of drug B and x_{2max} the maximum dose level with enrolled patients of drug B, here $x_{1i} \in \{1, \cdots, I\}$ and $x_{2j} \in \{1, \cdots, J\}$. The priors for β_1 to β_3 are set as log-normal distributions, characterized by a mean of -2 and a large variance. We utilize a normal prior with a mean of -4 for β_0 to indicate the toxicity level when no doses are administered. Additionally, for β_4 to β_6, we assign a mean of -2 with a normal prior, catering to scenarios where the doses have not been previously tried.

To enhance understanding of the aforementioned rule, Figure 1 has been crafted. Figure 1 (a) delineates the candidate development process as outlined in steps 2.a to 2.c. Figure 1 (b) elucidates the rule applicable to step 2.f, while Figure 1 (c) visually interprets the rule for step 3.

Figure 1: *(a) Green, orange, and red boxes correspond to candidate combos for decisions E, S, and D, respectively. (b) DCs (1,2) and (2,1) are the current DCs. All the DCs with a cross (red or green) are not allowed due to being too conservative or risky; only DC (1,3) is allowed for further testing. (c) DCs (1,2) and (2,1) are the current DCs. DCs (1,3) and (2,2) are candidates for further testing, but DC (1,2) is not allowed since its data indicate the combo is too conservative.*



2.2.3 Stage III - Model-Based combination dose finding

In stage III , we will use a logistic model to calculate the posterior probability of each dose in EI, the logistic regression model is as follows:

$$\text{logit}(p_{ij}) = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2j} + \beta_3 x_{1i} x_{2j}$$

Denote the dose with the highest posterior probability in EI as a candidate. Here the notations and priors used for the parameters are the same as mentioned in stage II. Define the set of all the doses enrolled patients and the doses higher than the enrolled doses with level 1 as set σ_3. We call DC (i,j) is higher than $(i^{'},j^{'})$ with level 1 if:

- $i = i^{'} + 1$ and $j = j^{'}$,
- or $i = i^{'}$ and $j = j^{'} + 1$

If the candidate is in σ_3, then enroll a cohort of patients at the candidate dose. Else if the candidate is not in σ_3, then calculate the admissible set defined in stage II :

- If the admissible set is not empty, then pick one dose with the highest utility and enroll one cohort patients at that dose.
- Else if the admissible set is empty, stop the trial.

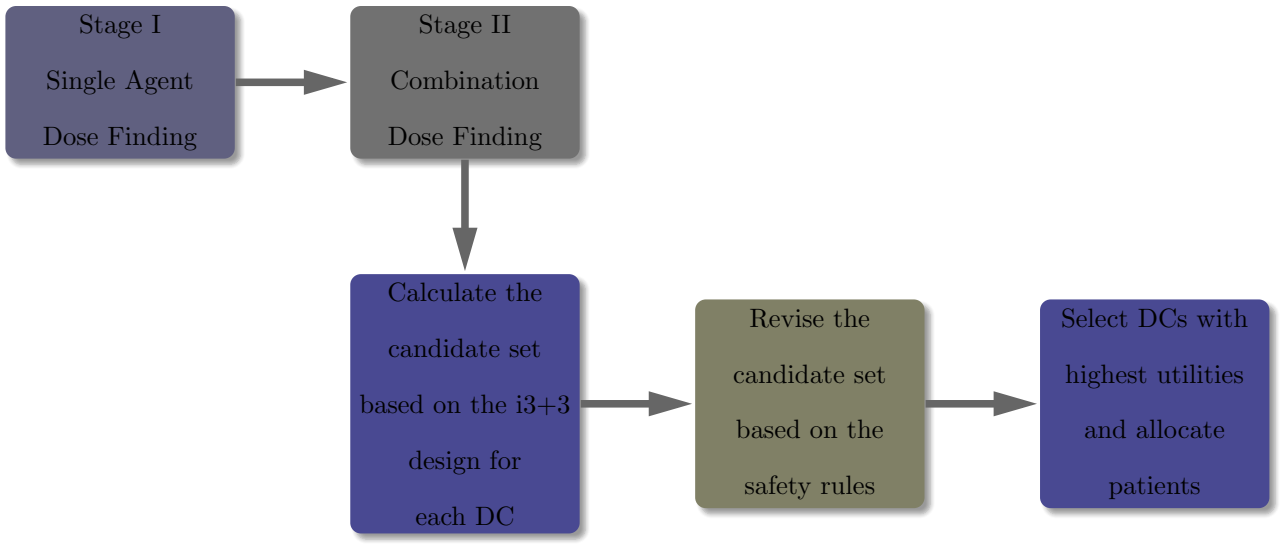


Figure 2: Flowchart illustrating the dose finding process.

2.2.4 Modification for utility calculation

In order to select the more effective dose through utility, we made some minor changes to the basic equation $U_{ij} = \Pr\{p_{ij} \in \text{EI}|(y_{ij}, n_{ij})\}$. First, we define $\widetilde{p}_{ij} = \frac{y_{ij}}{n_{ij}}$ and $\delta = (x_{1i} + x_{2j}) * \epsilon$, where ϵ is a minor value such as 1e-6 and compute the utility as follows:

Algorithm 2 Utility Calculation

if $n_{ij} \neq 0$, $\widetilde{p}_{ij} \leq p_T$ **then**

$U_{ij}^{'} = U_{ij} + \delta$

else if $n_{ij} \neq 0$, $\widetilde{p}_{ij} > p_T$ **then**

$U_{ij}^{'} = U_{ij} - \delta$

else

$U_{ij}^{'} = U_{ij}$

end if

return $U_{ij}^{'}$

Through the small modification of equation, we pull the dosages into consideration based on the estimation $\widetilde{p}_{ij}$. If two DCs (i_1,j_1) and (i_2,j_2) both have enrolled patients and both satisfy the condition that $\widetilde{p}_{i_1 j_1} \leq p_T$ and $\widetilde{p}_{i_2 j_2} \leq p_T$, then the higher DC will get a higher utility as δ is calculated using the dose level. That is to say, if the estimated toxicity is lower than the target toxicity, then with the same U_{ij}, the algorithm will guide the decisions to the higher doses. Similarly, if $\widetilde{p}_{ij}$ of two different DCs are same but higher than the p_T, then the algorithm will tend to go to the lower doses by subtracting δ from U_{ij}. However, if no patients are enrolled, then the modifications will not implement.

2.2.5 Safety Rule

Following the i3+3 design (Liu et al., 2020), apart from E, S and D, DU is also defined by calculating the posterior probability $Pr\{p_{ij} > p_T \mid \mathcal{H}\} > \eta$, where $\mathcal{H} = \{(y_{ij}, n_{ij}), i = 1, \cdots, I, j = 1, \cdots, J\}$ and the threshold η is close to 1, say 0.95. This probability is calculated based on the prior $Beta(\alpha_0, \beta_0), \alpha_0 = \beta_0 = 0.05$ for p_{ij} through the whole design whenever a new outcome is available. If the condition is met and $n_{ij} \geq 3$, then the current and all higher doses will be excluded from the trial. If the lowest dose is eliminated from the trial, then stop the trial.

2.2.6 MTDC Selection

At the end of the study, if the study stops early due to the safety rule, no selection. Otherwise, an isotonic regression(*Only DCs from combo stage are considered) is constructed to estimate the toxicity probabilities of DCs. After removing the DCs with the decision DU and their higher doses and the DCs without patients, the DC with the closest estimation to the target toxicity rate is selected as the MTDC, i.e.,

$$\arg\max_{(i,j)} |\hat{p}_{ij} - p_T| \tag{1}$$

Additionally, we offer the flexibility to select multiple Maximum Tolerable Dose Combinations (MTDCs). In the combination phase, it is conceivable that various doses may fall within the Equivalence Interval (EI), we will illustrate that kind of scenarios in the simulation section. Therefore, if the option for multiple MTDCs is employed, we will consider those doses with posterior toxicity values falling within the EIs as MTDCs.

3 Trial Sample

Building on the intricate rules outlined in Section 2.2, we construct a trial sample (Table 3)to elucidate their application. The scenario of true toxicity corresponds to scenario 3 in Table 2, with a target toxicity probability (p_T) set at 0.3 and an Equivalence Interval (EI) defined between 0.25 and 0.35. To effectively illustrate the trial process, we establish a sample size of 48 for the combination phase. Following Cohort 11, in the absence of viable candidates, we revisit the previously defined admissible set to identify potential candidates. The trial concludes after the enrollment of Cohorts 16 and 17, leading to the selection of the MTDC.

4 Simulation

In the simulation section, we conduct a comparative analysis of the MCi3+3 and Ci3+3 designs to assess their operational characteristics. Building upon scenarios derived from the Ci3+3 design, which is tailored exclusively for combination phase dose findings, we adapt and extend it to single-agent toxicity scenarios. To this end, we introduce seven scenarios featuring multiple Maximum Tolerated Dose Combinations (MTDCs), providing a comprehensive comparison between the two designs. The true toxicity are shown in Table 2.

Here we are trying to compare our method with Ci3+3 design. As we are allocating patients for single agent and dual agent. So we set the overall sample size as 96 and p_T =0.3. As Ci3+3 is designed for combo phase, in order to a fair comparison, we set the average sample size from MCi3+3 combo phase 74 as the overall sample size for Ci3+3 design.

Table 2: True Toxicity

Scenario 1

	Drug B					
Drug A	0	1	2	3	4	5
0		0.02	0.04	0.06	0.08	0.09
1	0.02	0.04	0.08	0.12	0.16	0.18
2	0.05	0.10	0.14	0.18	0.22	**0.26**
3	0.08	0.16	0.20	0.24	**0.28**	**0.30**
4	0.11	0.22	**0.26**	**0.30**	**0.34**	0.36

Scenario 2

	Drug B					
Drug A	0	1	2	3	4	5
0		0.04	0.09	0.14	0.145	0.15
1	0.04	0.08	0.18	**0.28**	**0.29**	**0.3**
2	0.045	0.09	0.19	**0.29**	**0.3**	**0.32**
3	0.05	0.1	0.2	**0.3**	**0.31**	**0.35**
4	0.055	0.11	0.21	**0.31**	0.41	0.51

Scenario 3

	Drug B					
Drug A	0	1	2	3	4	5
0		0.02	0.045	0.075	0.15	0.165
1	0.02	0.04	0.09	0.15	**0.3**	**0.33**
2	0.04	0.08	0.12	**0.3**	0.45	0.5
3	0.055	0.11	**0.3**	0.45	0.51	0.55
4	0.15	**0.3**	0.46	0.5	0.55	0.6

Scenario 4

	Drug B					
Drug A	0	1	2	3	4	5
0		0.025	0.045	0.06	0.08	0.15
1	0.025	0.05	0.09	0.12	0.16	**0.3**
2	0.08	0.16	**0.3**	0.45	0.49	0.52
3	0.15	**0.3**	0.46	0.48	0.5	0.53
4	0.23	0.46	0.48	0.5	0.52	0.54

Scenario 5

	Drug B					
Drug A	0	1	2	3	4	5
0		0.02	0.04	0.06	0.1	0.12
1	0.02	0.04	0.08	0.12	0.2	0.24
2	0.05	0.1	0.14	0.18	0.22	**0.26**
3	0.08	0.16	0.2	0.24	**0.3**	**0.34**
4	0.09	0.18	**0.26**	**0.3**	**0.34**	0.36

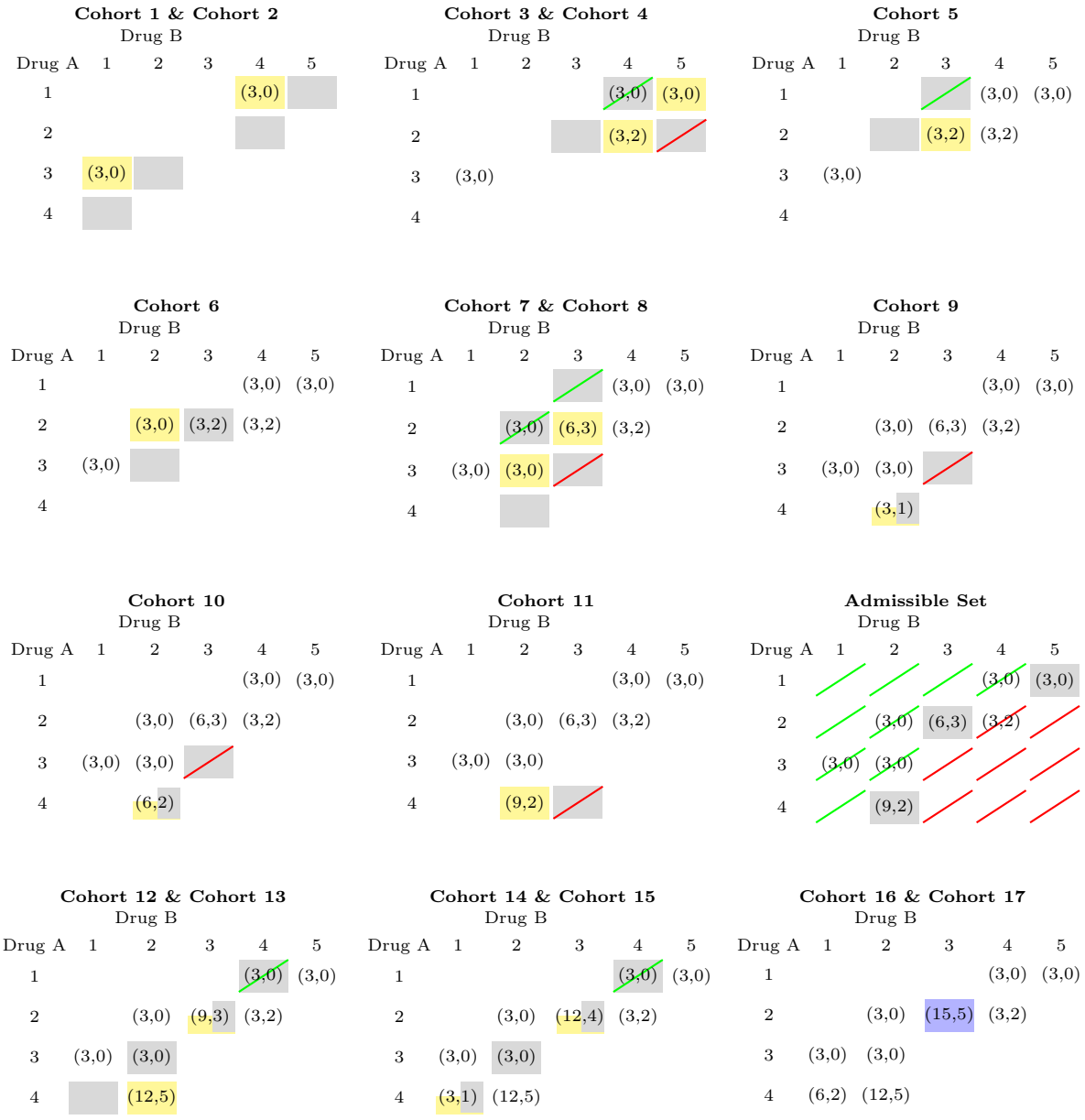
Scenario 6

	Drug B					
Drug A	0	1	2	3	4	5
0		0.02	0.065	0.125	0.165	0.195
1	0.02	0.04	0.13	**0.25**	**0.33**	0.39
2	0.04	0.08	0.15	**0.3**	0.45	0.5
3	0.055	0.11	0.21	0.45	0.51	0.55
4	0.1	0.2	**0.3**	0.5	0.55	0.65

Scenario 7

	Drug B					
Drug A	0	1	2	3	4	5
0		0.02	0.03	0.05	0.06	0.08
1	0.02	0.04	0.06	0.1	0.12	0.16
2	0.04	0.08	0.15	0.2	0.24	**0.25**
3	0.055	0.11	0.2	0.22	**0.26**	**0.3**
4	0.07	0.14	0.21	**0.29**	0.36	0.38

Figure 3: Trial Sample: *Yellow boxes are the current DCs; grey candidate DCs for further testing, and boxes with green or red crosses are not allowed for testing. Up to 2 combos are allowed for testing at each step.* The final Maximum Tolerated Dose Combination (MTDC) is determined to be (2,3).



Across various scenarios, the Probability of Correct Selection (PCS) for the two-stage MCi3+3 is comparable to, or exceeds, that of the Ci3+3 design, which is demonstrated in Figure 4. This distinction is particularly notable in scenario 3, where the true MTDC forms a diagonal line from the lower left to the upper right. The three-stage MCi3+3 design also demonstrates performance on par with Ci3+3.

The advantage of MCi3+3 becomes more evident in patient allocation, benefiting significantly from its capacity

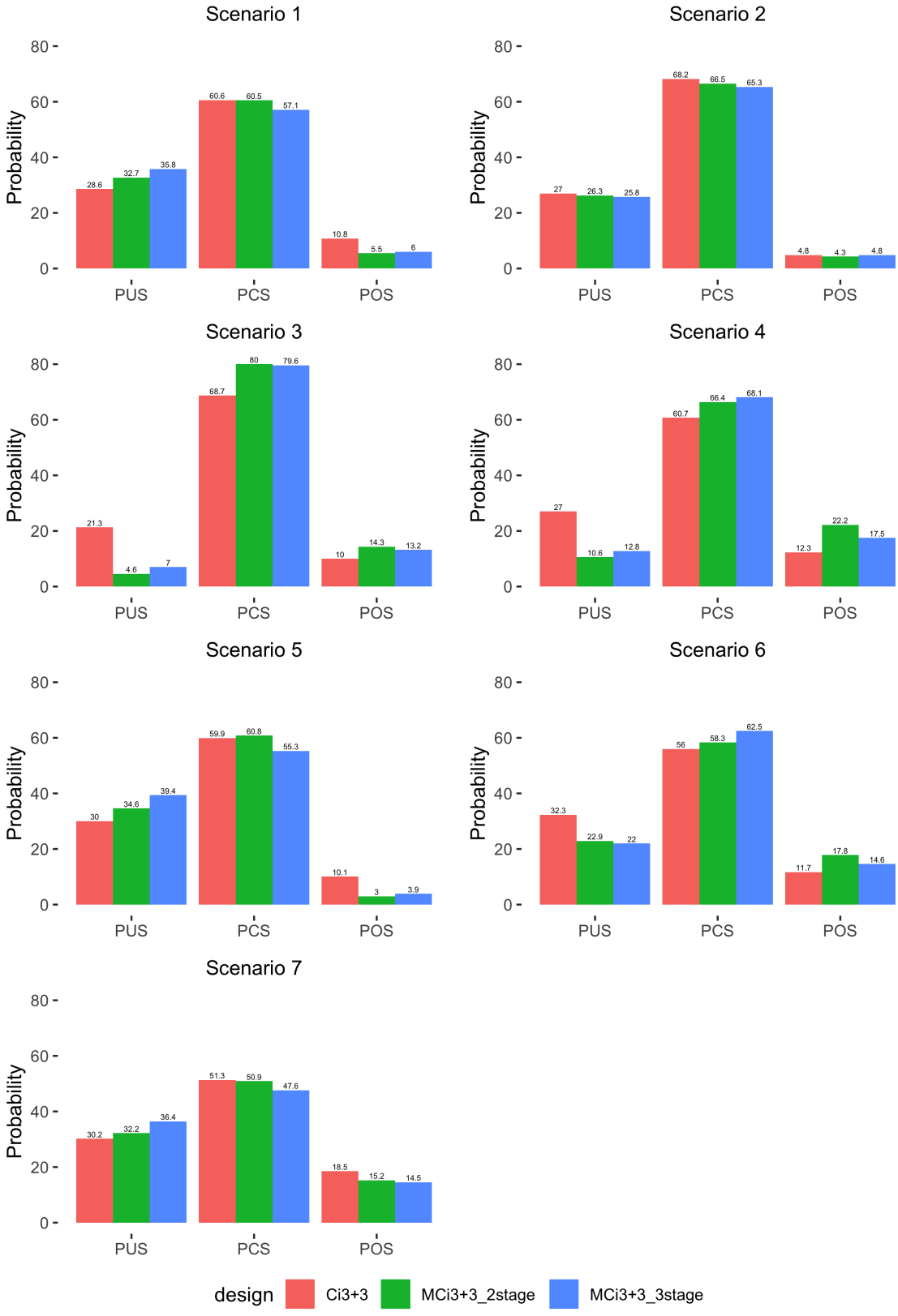


Figure 4: MTD Selection of the Designs.

for parallel allocations. Considering that the overall patient enrollment varies between the two designs, we focus on comparing the probability of allocation for the combination phase. As illustrated in Figure 5, the MCi3+3 design consistently demonstrates a higher or comparable Probability of Correct Allocation (PCA) compared to the Ci3+3 design, with the exception of scenario 7. Furthermore, across all scenarios, the MCi3+3 design consistently exhibits a lower Probability of Overdose Allocation (POA) than the Ci3+3 design, indicating a safer allocation strategy.

5 Discussion

Existing Phase I designs for dual-agent trials do not support parallel allocation and may underutilize historical single-phase data. In response, we introduce the MCi3+3 design, a versatile framework accommodating a two or three-stage approach. It commences with single-agent dose finding to determine the starting dose for the combination phase. The subsequent stage employs a rule-based design that facilitates parallel allocation, and, should the trial advance to the third stage, a model-based approach is adopted to steer patient allocation. Upon trial completion, data from both the single-agent and combination phases are integrated to identify the Maximum Tolerated Dose Combination (MTDC).

In our proposed MCi3+3 design, while the single-agent dose-finding stage is designed for parallel patient enrollment, this is not a strict requirement. This means that the trial can commence at different time points. Historical data can still be utilized, as the data from the single-agent phase are crucial for determining the starting dose of the second stage and for modeling in the third stage. Additionally, while we maintain a consistent target toxicity level across both the single-agent and combination phases, this parameter can be adjusted to enhance flexibility in the trial design. Furthermore, although the starting doses for the second stage are typically derived from the first stage, they can also be specified by practitioners. This decision might be based on prior knowledge of the drug's toxicity profile or lower doses, such as (1,1), if required by regulatory authorities.

In the MCi3+3 design, the primary decision-making is guided by the i3+3 design. However, other rule-based Phase I designs like mTPI, mTPI-2, and the traditional 3+3 can also be considered. This flexibility allows for a more tailored approach to dose determination, accommodating various clinical and regulatory considerations.

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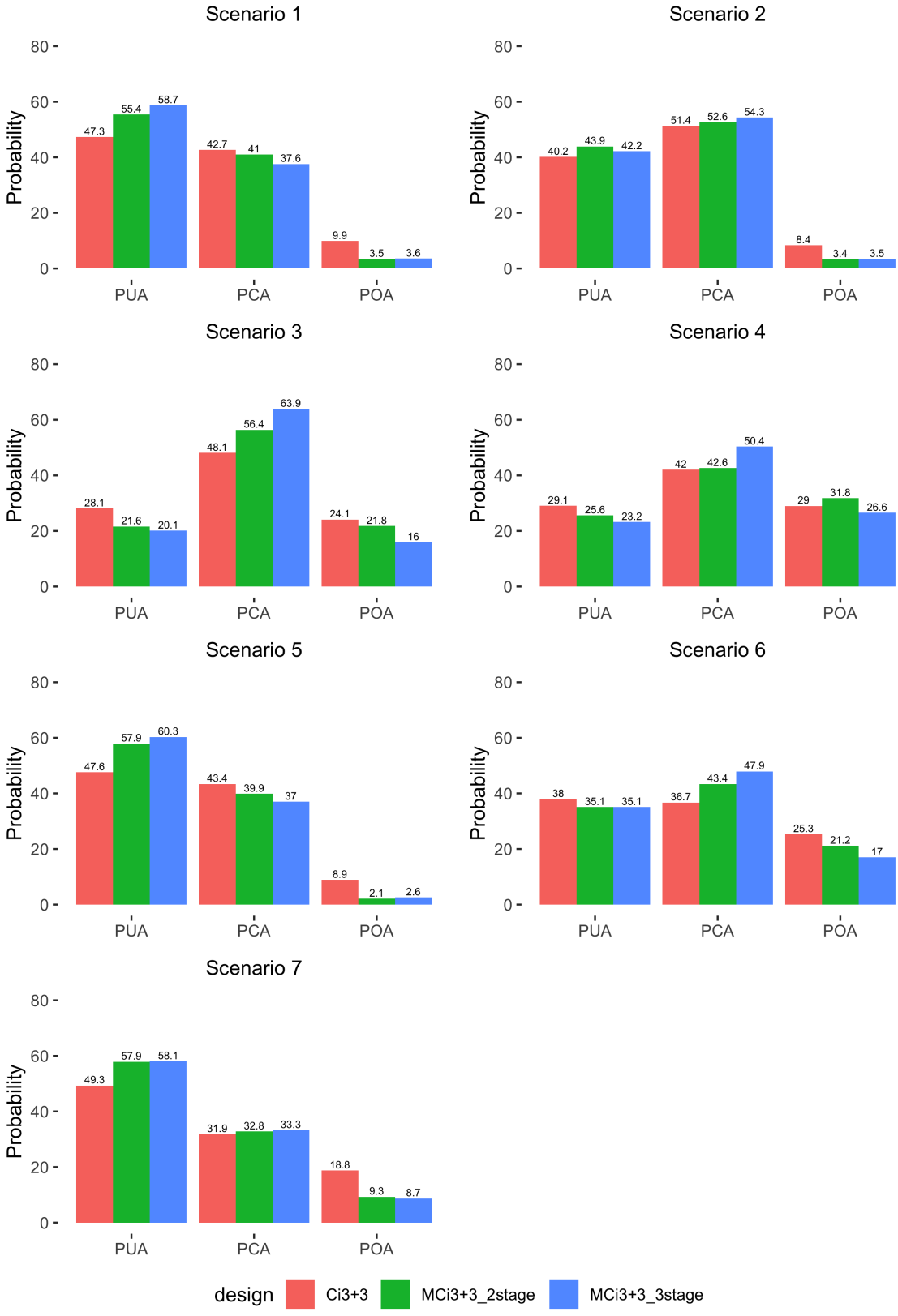

Figure 5: Patient Allocation of the Designs.

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