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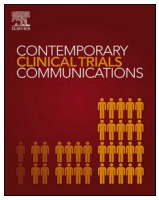

Three steps toward dose optimization for oncology dose finding

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ABSTRACT

Background: Traditional dose selection for oncology registration trials typically employs a one- or two-step single maximum tolerated dose (MTD) approach. However, this approach may not be appropriate for molecularly targeted therapy, which tends to have toxicity profiles that are markedly different than cytotoxic agents. The US Food and Drug Administration launched Project Optimus to reform dose optimization in oncology drug development and has recently released a related guidance for industry.

Methods: We propose a "three steps toward dose optimization" procedure, in response to these initiatives, and discuss the details in dose-optimization designs and analyses. The first step is dose escalation to identify the MTD or maximum administered dose with an efficient hybrid design, which can offer good overdose control and increases the likelihood of the recommended MTD being close to the true MTD. The second step is the selection of appropriate recommended doses for expansion (RDEs), based on all available data, including emerging safety, pharmacokinetics, pharmacodynamics, and other biomarker information. The third step is dose optimization, which uses data from a randomized fractional factorial design with multiple RDEs explored in multiple tumor cohorts during the expansion phase to ensure a feasible dose is selected for registration trials, and that the tumor type most sensitive to the investigative treatment is identified.

Conclusion: We believe using this three-step approach can increase the likelihood of selecting an optimal dose for a registration trial that demonstrates a balanced safety profile while retaining much of the efficacy observed at the MTD.

1. Introduction

Over the past decade, drug development in oncology has evolved and shifted from the use of cytotoxic agents to drugs with novel mechanisms of action (MOAs), such as immunotherapies, targeted therapeutics, T-cell engagers, and others [1,2]. Key differences exist in the MOAs, treatment procedures, and pharmacodynamic (PD) and clinical effects among these therapies, which can markedly influence the dose-optimization process for registration trials. Because cytotoxic treatments are typically administered for a short duration in a fixed number of cycles and have narrow therapeutic indexes with steep dose-response/toxicity relationships, the maximum tolerated dose (MTD) is typically a reasonable dose for the registration study [1,2]. In addition, serious toxicities from cytotoxic therapies are relatively predictable and often occur early in the treatment course. In contrast, the dose-selection process for targeted therapeutics or immunotherapies can be much more complex; if tolerable, these treatments are usually administered until disease progression, which can be many months or years after study initiation [1,2]. In the case of these non-cytotoxic or selectively cytotoxic therapies, serious safety signals may only become apparent at later stages of treatment, and long-term toxicities above grade 2 may not be tolerated due to the chronic nature of these therapies. Moreover, targeted therapies may have wide therapeutic indexes and non-linear dose-response/toxicity relationships. Therefore, the MTD may not be reached during the course of the study and the optimal dose selected for the registration study may differ substantially from the MTD [1,2].

The traditional approach to defining a dose for a registration study typically employs a one- or two-step approach [1,2]. The one-step approach involves conducting a dose-escalation study to determine the MTD of an investigative treatment, which is used as the study dose for comparison with the standard of care in subsequent registration trials. The two-step approach uses a dose-escalation study to determine the MTD, which is used in the expansion phase for different cohorts. Similar to the one-step approach, the MTD of the investigative treatment is then used as the registration study dose compared with the standard of care. In the traditional one- or two-step approach, suboptimal

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Abbreviations

BLRM = Bayesian logistic regression model
DLT = dose-limiting toxicity
FDA = US Food and Drug Administration
HD = high dose
LD = low dose
MAD = maximum administered dose
MOA = mechanism of action
MTD = maximum tolerated dose
mTPI = modified toxicity probability interval
PD = pharmacodynamics
PK = pharmacokinetics
RDE = recommended dose for expansion
RR = response rate
RE = relative efficacy

characterization of the dosing schedule can lead to inappropriate dose selection for the registration trial, potentially leading to increased toxicity without additional efficacy. Severe toxicities may lead to high rates of dose reduction or premature discontinuation, resulting in failure to realize the full therapeutic potential of the investigative treatment. Furthermore, persistent or irreversible toxicities could potentially limit options for subsequent therapies and any benefits they may provide.

The old approach of "more is better" may be applicable for dose selection of chemotherapy; however, this assumption no longer holds true for many of the newer targeted therapies with vastly different MOAs and other features [1,2]. Thus, the current paradigm for dose selection using the one- or two-step approach, developed around cytotoxic chemotherapeutics, may lead to an investigative molecularly targeted therapy entering registration trials without adequately characterized dosing schedules. In response, the Oncology Center of Excellence announced an initiative, Project Optimus, to reform the dose-optimization and dose-selection paradigm in oncology drug development [3–5]. As a result, health authorities, in particular the US Food and Drug Administration (FDA), now mandate rigorous dose-finding and dose-optimization processes before the initiation of pivotal trials for new oncology drugs [6].

The goal of Project Optimus is to move forward with a dose-finding and dose-optimization standard across oncology that emphasizes selection of a dose or doses to maximize not only the efficacy of a drug, but also safety and tolerability. The Project Optimus initiative recommends a balanced benefit-risk ratio in defining the optimal dose early in development [3,7]. Recently, the FDA published a draft guidance for industry on optimizing dosage in the treatment of oncologic diseases [8], ensuring maximal efficacy is retained at optimal dose(s) relative to the MTD, while striving for a better-balanced safety profile. This represents a shift toward identifying an optimal (biological) dose, which considers overall efficacy and tolerability, where the MTD represents the upper limit of the optimal dose range, and away from solely determining the MTD. Fig. 1 illustrates the different relationships between the optimal dose and the MTD/maximum administered dose (MAD) among different drug treatments, where the MTD/MAD needs to be determined and the optimal dose will be identified in the dose optimization procedure. Such optimization requires consideration of complex MOAs, schedule optimization, long-term drug tolerability, and potentially novel PD endpoints. Consequently, thoughtful study designs, exposure information, translational data, and statistical modeling play an increasingly important role. In response to Project Optimus and the FDA draft guidance on dose optimization in oncology drug development, we propose a "three-step toward dose optimization" procedure.

2. Three steps toward dose optimization

Determining the optimal dose of a drug should start with considering the fundamentals of the therapeutic index. In general, the difficulty of developing a drug with a balanced efficacy and safety profile increases as the therapeutic window narrows. Regardless of the therapeutic index, it is important to first identify an upper boundary when searching for the optimal dose (Fig. 1), as this narrows the search range for an optimal dose.

2.1. Step 1: dose escalation in identifying an MTD/MAD

Since the introduction of Project Optimus, there could be a misconception that the MTD of a non-cytotoxic drug is no longer relevant. However, finding an accurate MTD estimate that closely resembles the true MTD with a low likelihood of overdose toxicity remains pertinent. As described, the first step of searching for an optimal dose involves establishing the upper boundary to limit the search range. If the MTD of some targeted therapeutics or immunotherapies cannot be established, the MAD may be used as an alternative for establishing an upper boundary for an optimal dose.

The MTD is often identified during the dose-escalation part of a phase 1 study, with various study designs such as the algorithm-based 3 + 3, model-assisted mTPI (modified toxicity probability interval) and the model-based BLRM (Bayesian logistic regression model). We recommend a recently developed hybrid design [9] for identifying the MTD. This is a hybrid design on two levels; it is a hybrid of a modified mTPI design and a dose-toxicity model, as well as a hybrid of the Bayesian approach for each individual dose level and the frequentist approach for combining available information from all tested doses. The design retains the merits of existing designs while minimizing the

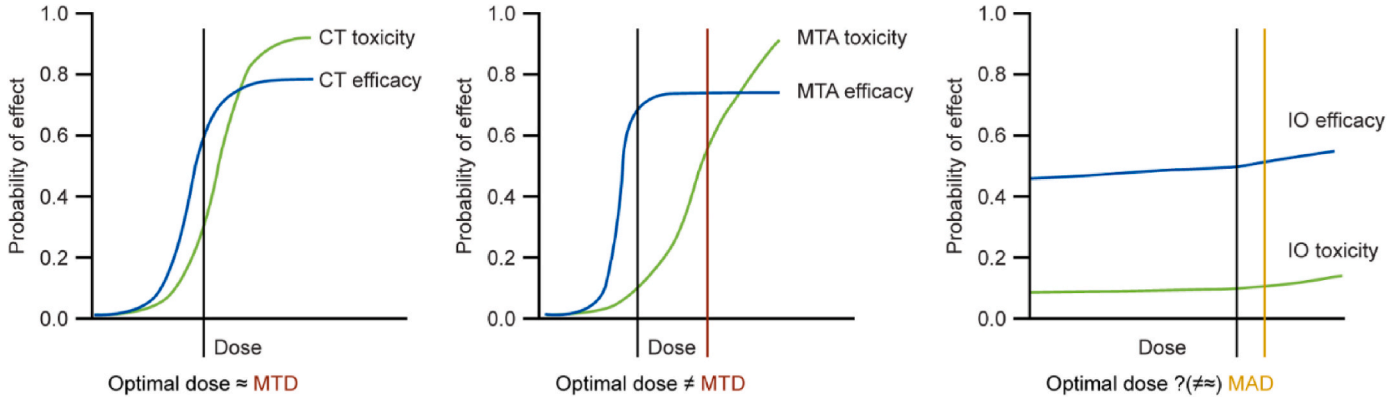

Fig. 1. Relationship between the optimal dose and the MTD/MAD among different drug treatments. Note: CT = cytotoxic therapy; IO = immunotherapy; MAD = maximum administered dose; MTA = molecularly targeted agent; MTD = maximum tolerated dose.

limitations. This hybrid design has demonstrated robust performance with good overdose control, which can minimize the difference in the recommended dose for trial and the true MTD [9]. With the integration of all available dose groups in addition to a modified mTPI, the hybrid design could improve accuracy and efficiency in dose selection. The hybrid design is composed of three stages (Fig. 2).

Stage 1: The mTPI design is modified to control overdose toxicity more efficiently by an additional constraint using the posterior probability of the dose-limiting toxicity (DLT) rate in the overdosing interval (δ_2, 1) being less than a value γ (e.g., <0.75).
Stage 2: This stage uses a dose-toxicity model by pooling observed safety information from all previous doses to estimate the DLT rate for the current dose level and to predict the DLT rate for the next dose level in the provisional dose list.
Stage 3: Dose-escalation decisions from stages 1 and 2 are pooled to make a conservative dose-escalation decision to further control overdose toxicity.

Image adapted from "A hybrid design for dose-finding oncology clinical trials", by Liao, JJZ, Zhou F, Zhou H, Petruzzelli L, Hou K, Asatiani E., Int J Cancer 2022; 151(9):1602–1610, is licensed under *CC BY 4.0*.

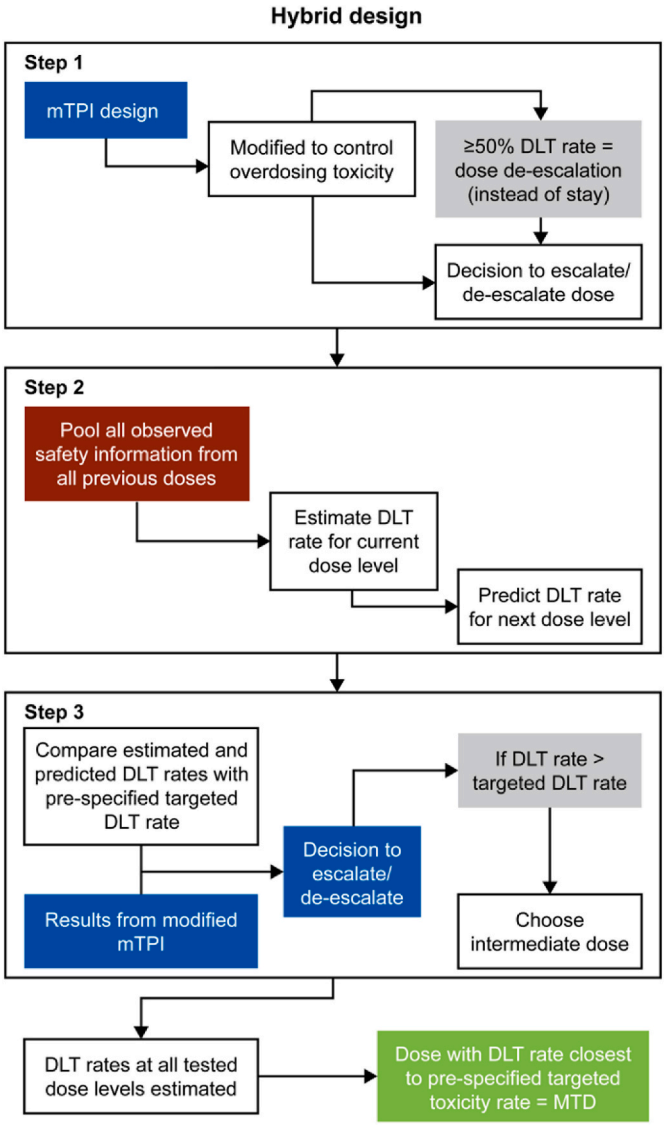

Fig. 2. Hybrid design for dose escalation. Note: DLT = dose-limiting toxicity; MTD = maximum tolerated dose; mTPI = modified toxicity probability interval.

Details of this hybrid design and an example of its application have been reported [9]. To use this in practice, an R-package "HybridDesign" [10] and an R-shiny tool (*https://fzh223.shinyapps.io/HybridModel/*) have been developed. These tools are freely available to guide clinicians at every step of the dose-finding process using the hybrid design.

As emphasized in Liao et al., a dose-escalation procedure can be continued to search for an MTD with a tolerated toxicity limit. If the MTD is not reached or does not exist, but the MAD has satisfactory efficacy, the dose-escalation process may be stopped [9]. In such cases, an upper boundary may be established using either the MTD or MAD for efficient search of the optimal dose. To better characterize the exposure-response before progressing to identifying the dose levels for further evaluations, the backfill cohorts at certain dose levels in the dose-escalation study could be explored with more patients in selected populations to gain additional information on pharmacokinetics (PK) and PD.

2.2. Step 2: dose selection to identify recommended doses for expansion (RDEs)

After the MTD or MAD with satisfactory efficacy has been identified, multiple different dose levels may be selected for the dose-response assessment for efficacy and toxicity. Before determining the RDEs, the dose/exposure and efficacy/toxicity-response relationships should be well characterized. This provides a preliminary understanding of dose- and exposure-response relationships for activity, safety, and tolerability [8]. As such, all available data should be evaluated; this includes non-clinical and clinical data, with emerging clinical safety, PK, PD, and other biomarker information.

In a general dose-exposure-response relationship, there are two layers of variabilities. Given the same dose, the patients' exposure can be different and given the same exposure, patients' response (efficacy or safety) can be different. Thus, to identify the doses with acceptable responses (efficacy/safety), two calibration stages are needed for deriving the dose for specified desired responses. The first stage is to derive the desired exposure from the specified responses (Fig. 3A), where many modeling techniques can be applied. Some of the example model techniques, such as the exposure model, PK/PD model, PK/safety model, PK/efficacy model, or biomarker/efficacy correlation, could be used to identify the exposure range. Note the safety/efficacy data could be categorical or continuous outcomes and Fig. 3B only displays the principal using the categorical data format. At the second calibration stage, exposure information derived from the first stage is used to define the RDEs (Fig. 3B), which should be dose levels no greater than the MTD/MAD, and no less than the pharmacologically active dose.

As depicted in Fig. 1, the relationship between the optimal dose and the MTD/MAD differs with different drugs. The potential uncertainty of the response curve and variability at different dose levels can render identifying the optimal dose challenging. As such, the selections of RDEs for comparison with the MTD/MAD should build upon the shape of dose response (efficacy/toxicity) and variability. Therefore, multiple doses should be selected and recommended for expansion (phase 2) [8] to fully explore all potential clinical benefits of the drug, which may not be limited to prolonged survival but may also include improved quality of life. The goal for evaluating multiple RDEs is to decrease uncertainty by identifying an optimal dosage(s) [8]; the probability of selecting the appropriate optimal dose(s) increases with the number of RDEs being evaluated.

Araujo et al. suggested that at least two, but preferably three, RDEs be selected for evaluation: one for the minimum reproducibly active dose, another for an effective dose close to the MTD, and one for an intermediate dose [11]. This suggestion is supported by the fact that at least three doses are required to accurately ascertain non-linearity of the dose-response curve. Moreover, the greater the degree of non-linearity,

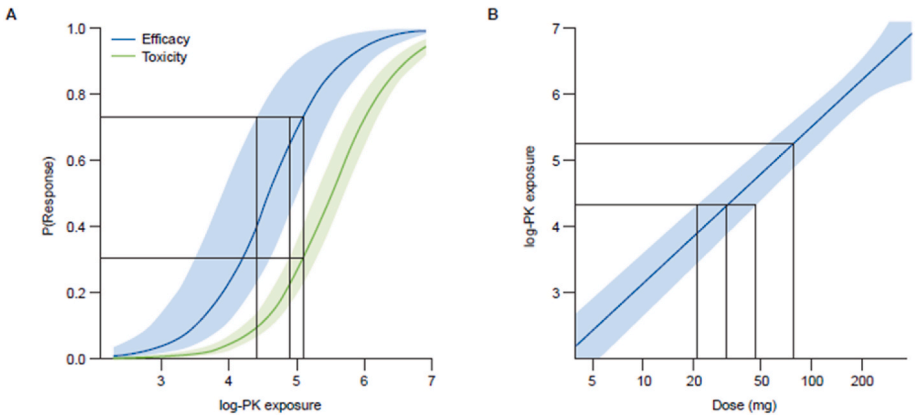

Fig. 3. Two calibration stages in deriving the RDEs: **A)** Identify the exposure range where the efficacy could be a selected biomarker (efficacy and toxicity curves with 95 % CI) and **B)** identify the doses (dose exposure with 95 % CI). Note: CI = confidence interval; PK = pharmacokinetics; P(Response) = probability of response; RDE = recommended dose for expansion.

the more RDEs are needed to better capture the non-linearity. In respect to selecting the optimal dose(s), three or more RDEs should be identified and a subset of these identified RDEs compared because of the potential non-linearity of the dose response and the variability at each dose level. The choice and number of RDEs selected for comparison should strike a balance between scientific rationale and clinical and practical considerations.

2.3. Step 3: dose optimization

Following the selection of multiple RDEs in step 2, a dose-optimization procedure is conducted in a randomized, parallel, dose-response trial by applying the selected RDEs [8]. At this early stage, more information is needed on tumor sensitivity, including that in different tumor types and diseases/populations. In 2022, the FDA issued guidance recommending the use of multiple expansion cohort trials to expedite oncology drug development [12]. A unique feature of multiple expansion cohort trials is the two-dimensional dependency structure across doses and indications, which collects evidence on whether a drug may be effective across a range of diseases/populations and it can identify treatment-sensitive diseases/populations [12]. Thus, the efficacy and safety of different RDEs are evaluated in different cohorts and an optimal dose is selected based on a balanced benefit-risk ratio through a randomized design. The design should be fit-for-purpose and could be a randomized multidose and/or multistage design, with options to discontinue inadequate dose arms to limit patient exposure to sub-optimal doses that are either inefficacious or unsafe [8].

One such design involves randomizing patients in each cohort to all the selected RDEs. This full factorial design commonly used in trials [13] requires large numbers of patients with multiple different selected RDEs, which may impose a significant resource burden on trial sponsors. To achieve dose optimization using a smaller number of patients and within shorter timelines, we propose a randomized fractional factorial design, as illustrated in Fig. 4A. Patients in each cohort are randomized to two RDEs, one of which is common to every cohort in the study; in addition to further characterizing the exposure-response relationship, this information can be used to identify the tumor types most sensitive to the investigative treatment for a registration trial.

Fig. 4B illustrates the outcomes of a hypothetical fractional factorial design with five cohorts and two RDEs within each cohort, where six different doses (HD, LD1, LD2, LD3, LD4, LD5) are compared. This fractional factorial design offers reductions of sample sizes when compared with the full factorial design. For example, if there are 20 patients enrolled for each RDE in each cohort, the commonly used full factorial design would require a total sample size of approximately 600 patients (5 × 6 × 20), but a fractional factorial design only requires

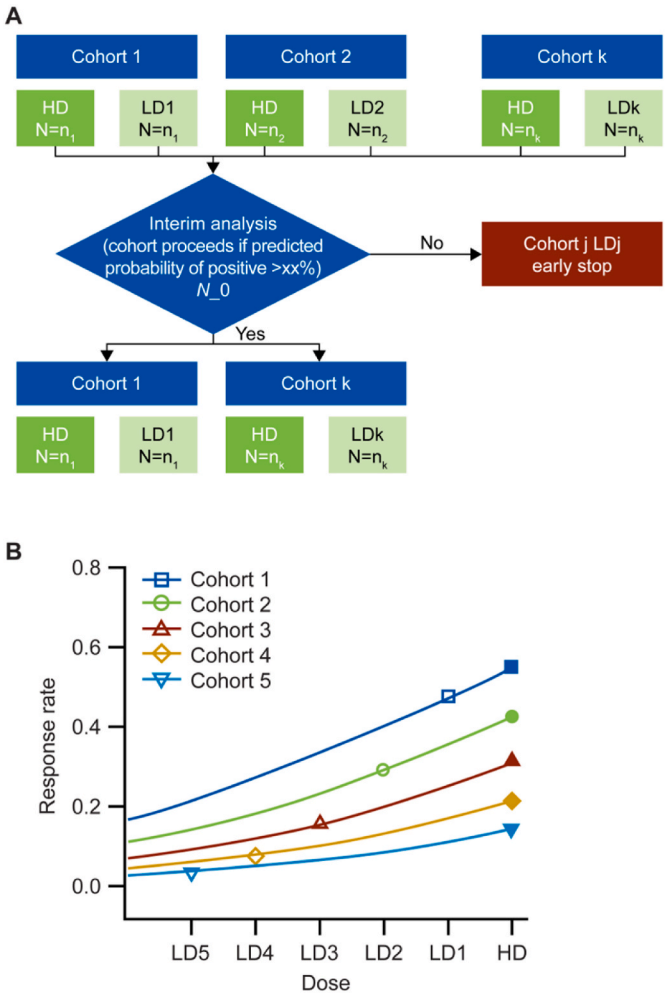

Fig. 4. A) The randomized fractional factorial design for dose optimization. **B)** Dose-optimization design with five cohorts and different lower RDEs. Note: HD = high dose; LD = low dose; RDE = recommended dose for expansion.

around 200 patients (5 × 2 × 20). If this fractional factorial design is used for k cohorts, a total of k + 1 different doses could be investigated in a randomized fashion for a higher chance of finding the optimal dose (s) with less uncertainty. Note that some of the low doses (LDs) could be the same and the full factorial design could be considered as a special

case of the fractional factorial design, with 100% as the fraction.

With k+1 RDEs identified for dose optimization, a fractional factorial design in Fig. 4A is preferred over the full factorial design. This fractional factorial design offers the following several advantages over a full factorial design: 1) the proposed design could efficiently investigate as many as k + 1 dose levels for k different tumors and tumor sensitivity identified in a randomized fashion, reducing the uncertainty of optimal dose identification with less patients and cost; 2) exposure to inefficacious/toxic doses is well controlled in the staged design or continuous monitoring in an adaptive fashion and thus is limited to a few patients; and 3) decision-making uses aggregated information from different cohorts; 4) a common high dose (HD) is used to directly compare the efficacy and safety across different cohorts and a sensitive tumor cohort which gives a better response could be identified. The fractional factorial design can be used for the expansion phase or standalone phase 2 studies. The sample size could be calculated with the desired efficacy in mind; as stated in the FDA dose-optimization guidance, the chosen sample size is not necessarily powered for a certain hypothesis, but rather for estimating the response rate (RR) with high precision [8]. The sample size for each dose level in a selected cohort could be chosen, for example, using a Simon's two stage approach along with certain estimation precision requirement. With an adequate sample size for each RDE studied, the general dose-response profile for the investigational treatment can be estimated efficiently.

With the efficacy and toxicity information from the randomized study, possible k + 1 doses can be compared, where k is the number of cohorts. If there are no toxicity/tolerability concerns over the HD, it could be selected as the dose for full assessment of efficacy and efficacy in the registration study of the investigational treatment. Otherwise, one of the LDs with a balanced benefit-risk profile could be chosen: a dose at which efficacy is comparable with that of the HD, but with a more tolerable safety profile.

To demonstrate how the aggregated data of both efficacy and safety from the k cohorts could be used in determining the optimal dose, one can build a statistical model for inference. Let $L_i(\theta|D_i)$ be the likelihood from the ith cohort, i = 1, …, k, where θ are the parameters from the response model, such as the logistic model, and D_i are the observed data from ith cohort. Thus, the likelihood function $L_0(\theta|D_1,\cdots,D_k)$ with all k cohorts from this randomized fractional factorial design can be obtained:

$$L_0(\theta|D_1,\cdots,D_k)\propto L_1(\theta|D_1)L_2(\theta|D_2)^{\alpha 2}\cdots L_k(\theta|D_k)^{\alpha k} \quad (1)$$

Where $0 \le \alpha j \le 1$ (j = 2, …, k) is a power parameter to discount the contribution from the jth cohort, $L_1(\theta|D_1)$ is the most sensitive tumor cohort with the highest RR at the HD. When $\alpha j = 0$, it means the jth tumor cohort has no contribution to the most sensitive tumor evaluation. When $\alpha j = 1$, it indicates the jth tumor cohort has the full contribution, i.e., has the same response pattern as the most sensitive tumor. With the response data, these power parameters αj can be set as the ratio of the RR from the jth tumor cohort to that of the most sensitive tumor (cohort 1). This setting is reasonable by calibrating and bringing all the tumor cohorts to the same level to make an inference. Note that model (1) has the same format as the Bayesian power model [14,15], borrowing information from different cohorts.

To assess the efficiency of this statistical inference with the aggregated data, results from a simulation study can be used to demonstrate the performance of the selected optimal dose against the MTD/MAD, and the efficiency of the fractional factorial design against the full factorial design, when the total number of patients is held constant. The goal of the simulation is first, to correctly identify the most sensitive tumor cohort with the highest RR at the HD, and second, to identify a dose that preserves the highest possible efficacy relative to that observed at the MTD/MAD.

To achieve the goals, it is desirable to first estimate the dose response for the most sensitive tumor cohort. Then, based on the inferred statistical model, the intersection of the 90 %, say, lower confidence bound from the fitted value at the MTD/MAD and the fitted dose-response curve is selected as the optimal dose, which is likely to retain most of the efficacy of the MTD/MAD. Because the power parameters αj (j = 2, …, k) are typically unknown in model (1), the estimates using the observed response ratio of the jth tumor to the most sensitive tumor (i.e., the highest tumor response at the MTD/MAD) are used in the statistical inference.

In the example simulation, a logistic dose response is assumed with MTD as 500 mg which is the HD for all five cohorts. Cohorts 1–5 range from the most sensitive tumor type to the least sensitive tumor type at the MTD, i.e., cohort 1 has the highest tumor response at the MTD. The assumed RR at the MTD ranges from 14.2% (Cohort 5 in Fig. 4B) to 55.0% (Cohort 1 in Fig. 4B). A lower dose arrangement for each of schemes1–4 in the fractional factorial design is shown in the 1st half of Table 1. It is also assumed that there are 30 patients for each RDE in each cohort. Thus, the total number of patients is 300 (30 × 2 × 5). To demonstrate the efficiency of the fractional factorial design, a full factorial design with the same number of 300 patients is constructed as scheme 5, with an equal number of patients in all six RDEs for each cohort. Thus, the number of patients in each RDE/cohort is 10 and the total number is the same as 300 (10 × 6 × 5).

The RR at each RDE for each tumor cohort was simulated according to the response curves for the five different cohorts (Fig. 4B). Three confidence levels (80/90/95%) were adopted to select different optimal doses, among which higher confidence level should result in wider confidence band at the MTD and lower estimated optimal dose. This simulation was repeated 10,000 times for each scenario. The 2nd half of Table 1 summarizes the operating characteristics of the chosen optimal dose in terms of estimated optimal dose and the relative efficacy of the estimated dose to the MTD. P(select) is the probability of correctly selecting the most sensitive tumor cohort (i.e., cohort 1). RE (%) is the relative efficacy (RE) of the estimated dose to the HD in cohort 1 and is defined as $100 \times f_1(\widehat{D})/f_1(MTD)$, where $f_1(x)$ is the dose-response function and $\widehat{D}$ is the chosen optimal dose. The percentage of finding a dose whose relative efficacy is lower than 70% is presented as %(RE < 0.7), which reflects the risk of severely underestimate the dose and overly compromise efficacy. As shown in Table 1, when the total number of patients is held constant, the probability of correctly selecting the most sensitive tumor cohort using the full factorial design in Scheme 5 is lower than using the fractional factorial designs (schemes1–4). This is due to the smaller number of patients allocated equally to each RDE, with a larger variability in the full factorial design when compared with fractional factorial designs. Upon comparing the estimated dose from different design schemes, Scheme 2 has the best performance in terms of standard deviation for both estimate and RE of the estimated dose, followed by Scheme 3. Meanwhile, Scheme 2 may also lead to a better choice of LD for each cohort when compared with other schemes. When assigning different LDs to each cohort, it is preferrable to assign the highest LD RDE to the tumor cohort that has the highest hypothetical sensitivity to the study treatment, for better RE of the selected optimal dose.

3. Summary

We propose a "three-step toward dose optimization" procedure (Fig. 5) in response to the FDA's Project Optimus, which aligns with the recently published FDA guidance for industry on dose optimization for drug development in oncology [8]. The proposed three-step procedure is: 1) a dose-escalation part to identify MTD or MAD using an efficient hybrid design; 2) identification and exploration of multiple RDEs using all available data (such as pre-clinical data; emerging clinical safety/efficacy, PK, PD, and other biomarker information; and the exposure-response model and efficacy/toxicity-response model for the dose-expansion phase); and 3) dose optimization using data from a

Table 1
Lower RDEs used for each cohort for different simulation settings and the operating characteristics of the chosen optimal dose from the simulations.

	Dose level (mg)								
	Cohort 1		Cohort 2		Cohort 3		Cohort 4		Cohort 5
Scheme1	250		300		350		400		450
Scheme2	450		400		350		300		250
Scheme3	450		300		250		350		400
Scheme4	250		400		450		350		300
Scheme5	250		300		350		400		450
Scheme	P(select)	CL	Estimated dose (mg)			RE of estimated dose (%)			
			Mean	Median	SD	Mean	Median	SD	% (RE < 0.7)
1	0.85	80 %	443.9	454.5	41.1	85.0	87.6	10.0	4.5
		90 %	426.7	442.5	52.8	80.6	84.4	12.7	8.9
		95 %	409.6	432	62.9	76.3	81.5	14.9	15.2
2		80 %	474.3	475	6.0	93.0	93.2	1.6	0.0
		90 %	467.4	468.5	9.7	91.1	91.4	2.5	0.1
		95 %	460.6	463	17.5	89.3	89.9	4.3	0.5
3		80 %	469.8	471	8.0	91.8	92.1	2.2	0.0
		90 %	461.5	463.5	12.6	89.6	90.1	3.3	0.2
		95 %	453.8	457	18.9	87.5	88.3	4.7	0.6
4		80 %	448.8	458.5	40.0	86.3	88.7	9.7	3.6
		90 %	431.9	447.5	52.8	82.0	85.7	12.7	7.6
		95 %	413.5	437.5	65.6	77.4	83.0	15.6	13.9
5	0.73	80 %	450.5	455.5	25.4	86.6	87.9	6.3	1.2
		90 %	438.4	446	34.3	83.4	85.3	8.3	2.7
		95 %	427.1	438	43.3	80.5	83.1	10.3	5.1

Note: CL = confidence level for the lower confidence bound to derive the estimated optimal dose; P(select) = probability of correctly selecting the most sensitive tumor cohort; RDE = recommended dose for expansion; RE = relative efficacy; SD = standard deviation.

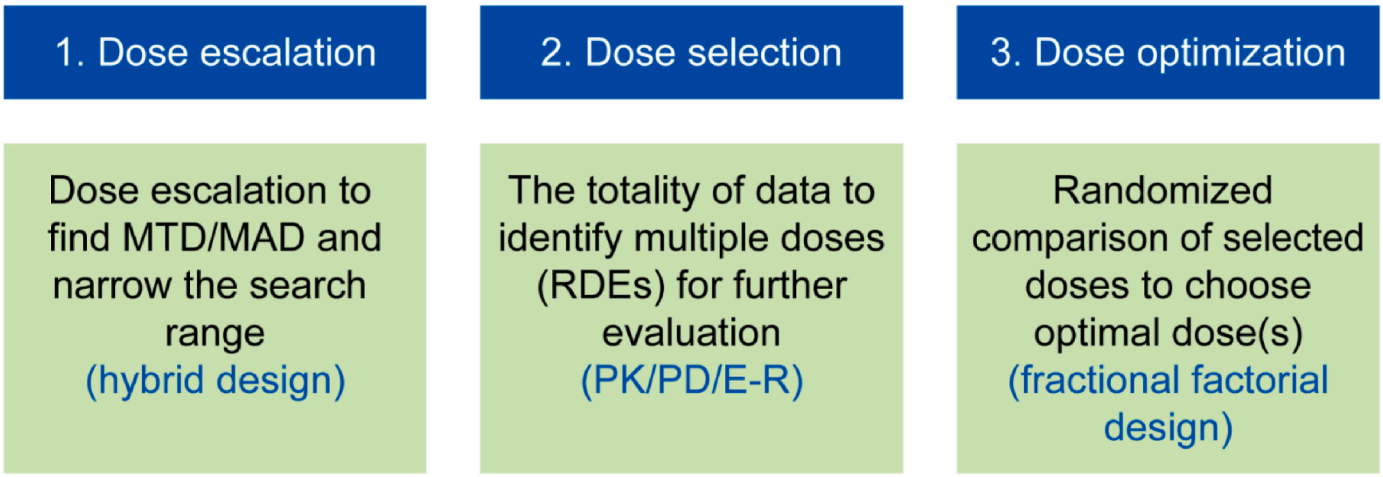

Fig. 5. A summary of the three-step approach leading to dose optimization. Note: E-R = exposure-response; PD = pharmacodynamics; PK = pharmacokinetics; MAD = maximum administered dose; MTD = maximum tolerated dose; RDE = recommended dose for expansion.

randomized fractional factorial design with multiple RDEs explored in the expansion phase or a phase 2 study, to ensure that a feasible optimal dose is selected for registration trials.

We presented the theoretical basis and performed a simulation to demonstrate how the efficient hybrid design in dose-finding studies offers control of overdose toxicities and can lead to an effective recommended MTD that is close to the true MTD. The step 2 uses the totality of data and can efficiently select RDEs with clinical and practical consideration to further generate clinical data in step 3. The randomized fractional factorial design for the dose optimization would enable efficient identification of drug-sensitive tumor types and optimal dose, whereas the use of an adaptive design may help limit patients' exposure to suboptimal or toxic dose(s). As such, this three-step procedure is likely to select a recommended dose that has a favorable safety profile, while retaining most of the observed efficacy at the MTD/MAD. Of note, we recommend identifying at least three RDEs for comparisons in the third step, to reduce the uncertainty of optimal dose selection for drugs that may have non-linear dose-response profiles. We also provided simulation data to support our recommendation for allocating a higher LD RDE to the patient cohort with the tumor type that has the highest hypothetical sensitivity to the investigative treatment for potentially better efficacy outcomes.

The design for dose optimization (Fig. 4A) could have several stages, and it could be continuously monitored using the Bayesian predicted probability of success, e.g., until certain futility criteria are met, such as achieving the desired precision for response estimate, or the maximization of the allocated budget. Once the safety and efficacy information of the investigative treatment becomes available from a well-characterized, randomized, multidose study, the sponsor can select an optimal dose and initiate discussion about the design of a registration study with health agencies. This three-step approach can be viewed as a seamless phase 1/2 study design for finding the optimal dose of investigative oncology drugs; if the treatment is a combination, then a formal phase 2 study for the contribution of components could be carried out.

Recently, Guo and Yuan [16] proposed a two-stage DROID approach for dose optimization using a full factorial design with selected doses. They combined both efficacy and safety assessment in the early part of dose-escalation step, where the dose-escalation (i.e., the first step in our 3-step approach) is typically safety focused and only a very few patients in each dose level and the efficiency to evaluate both efficacy and safety can be weakened. However, some of the methods in the first stage of DROID and other methods mentioned in their paper such as the U-BOIN design [17], BOIN12 and BOIN-ET could be used in our 2nd step (dose-selection). Yang et al. [18] proposed a phase 2 MERIT design using a full factorial randomized multiple-dose trial for dose optimization. Similarly, the methods in the second stage of MERIT could be used in our 2nd step (dose-selection).

The DROID and MERIT use both efficacy and safety information adaptively selecting certain RDEs to generate more data in a full factorial fashion. The step 2 in the proposed approach using the totality of data may select the same RDEs as DROID/MERIT. However, the proposed fractional factorial design can generate different data comparing to a full factorial design with the advantages described in the paper and the simulation conducted in the paper. When there is only one RDE selected in the step 2 in current paper, our design will be reduced to the SHOTGUN [19].

As pointed out by a reviewer, the optimal approach to identifying an optimal dose may in fact be some combination of pre-approval dose optimization and post-approval dose optimization. However, the post-approval dose optimization could be more costly than the pre-approval dose optimization. The proposed three-step approach is for the pre-approval dose optimization. The final decision leading to the choice of optimal dose(s) should be based on both statistical and practical considerations, which is particularly the case for selecting RDEs in the step 2. It is a complex procedure which involves a holistic assessment of various factors beyond statistical considerations using a totality of data.

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The study sponsor was involved in the design of the study, data collection, analysis and interpretation of data, and the development and decision to submit this manuscript for publication.

Data statement

The datasets generated and/or analyzed during the current study are available upon reasonable request from the corresponding author (email: jliao@incyte.com).

CRediT authorship contribution statement

Jason J.Z. Liao: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Ekaterine Asatiani:** Writing – review & editing, Writing – original draft, Methodology. **Qingyang Liu:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Kevin Hou:** Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

This study was funded by Incyte Corporation, Wilmington, DE, USA. Jason J.Z. Liao, Ekaterine Asatiani, Qingyang Liu, and Kevin Hou are employees of and own stock in Incyte Corporation.

Data availability

No data was used for the research described in the article.

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