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Efficacy + Safety in Phase 1/2 Immunotherapy Oncology Trials: OBD vs. MTD

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ABSTRACT

Traditionally, the purpose of having a Phase I / Phase 2 dose-finding design in cancer clinical studies has been to find the Maximum Tolerated Dose based solely on the toxicity of the study drug. Traditional designs, considering a Dose Limiting Toxicity, implicitly assumes a monotonically increasing relationship between dose and response efficacy. However, for targeted investigative drug products, few toxicity effects may arise prior to the most efficacious dose. This challenges the conventional principle of "*more is better until toxic"* . Instead, the Optimal Biological Dose, which is defined as the lowest dose with the highest rate of efficacy while safe, is a more appropriate endpoint.

This presentation details the use of Bayesian Optimal Interval algorithms in finding the Optimal Biological Dose in Phase 1 or combination Phase 1/2 clinical trials (BOIN12). The BOIN12 clinical trial design (R. Lin, 2020). The BOIN12 design discussed here provides a codified pathway to explore the complete relationship between toxicity and efficacy in an immunotherapeutic oncology study.

The typical set-up of the Bayesian informed prior input is then discussed producing both numerical dose level outputs and graphical displays of the best processes for obtaining the Optimum Biological Dose. Parallel R and SAS® programs used to produce the output will be provided. A brief general overview of the programming will replace a line-by-line discussion.

INTRODUCTION

With the emergence of immunotherapies, such as checkpoint inhibitors and chimeric antigen receptor T-cell therapy, the search for an MTD might not be as necessary as it once was. With these targeted therapies, an MTD might not be attained in the formal course of dosing. Therefore, the objective of dose-finding trials in this setting is to identify the Optimal Biological Dose (OBD) that optimizes patients' risk-benefit trade-off. The OBD is generally defined as the lowest dose providing the highest rate of efficacy while being safely administered (Y. Zang, 2014).

TOXICITY AND EFFICACY IN A PHASE I IMMUNOTHERAPY ONCOLOGY TRIAL

The dose-response curve below shows a dose-response graph (H. Pan, Y. Yuan,2023) from a typical Phase I immunotherapy oncology trial. The Efficacy response (red curve) plateaus before the Toxicity response (blue curve) reaches a maximum acceptable toxicity. There are also two vertical dashed lines that show the OBD and the MTD. The OBD occurs at the greatest positive differential where the Efficacy curve is **superior** to the Toxicity curve. The MTD occurs where the Toxicity curve crosses the Bayesian prediction for Maximum Acceptable Toxicity (which is usually established before the trial begins).

The question arises: "If the efficacy of an investigative product rises and plateaus before any prior-determined maximum acceptable toxicity occurs, why not choose the dose with highest efficacy prior to unacceptable toxicity?"

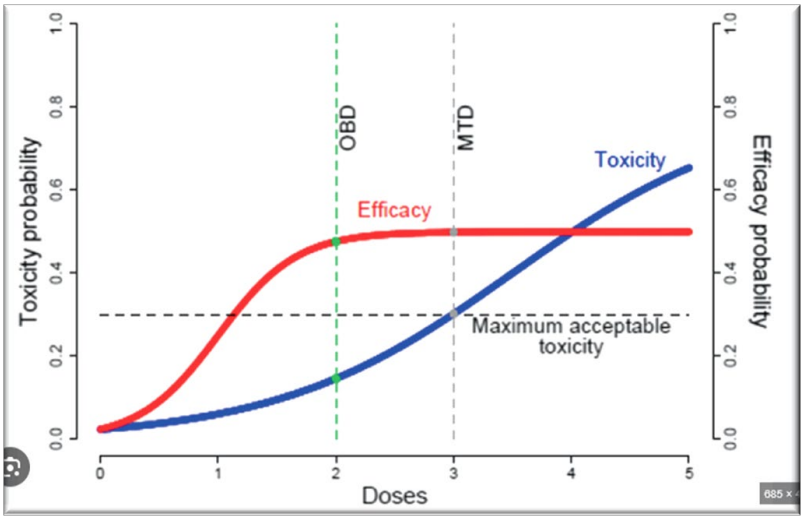

Figure 1. Dose-Response Curves for Efficacy and Toxicity for a Phase 1 Clinical Trial (H. Pan, Y. Yuan,2023).

A BAYESIAN METHOD FOR OPTIMIZING THE EFFICACY- TOXICITY RELATIONSHIP IN IMMUNOTHERAPEUTIC ONCOLOGY STUDIES: BOIN12.

There are many methods for balancing the efficacy versus toxicity relationship in clinical studies. In the present discussion, the BOIN12 design will focus on the binomial distribution of the two endpoints of Toxicity and Efficacy. This design introduces a Utility Function that captures the Bayesian Prior Probability Distributions for efficacy and toxicity with information about the study design. The Utility Function produces weights for the probabilities to all possible toxicity-efficacy outcomes and selects the dose that optimizes the trade-off.

The Utility Function quantifies the toxicity-efficacy interplay, as shown by the following 2×2 utility table (Table 1), which displays each possible toxicity and efficacy outcome. BOIN12 requires the utility (i.e. desirability) of the (No Toxicity, Efficacy), (No Toxicity, No Efficacy), (Toxicity, Efficacy), and (Toxicity, No Efficacy).

The general utility table:

General Utility Table		
Toxicity	**Efficacy**	
	Yes	*No*
No	u_1	u_2
Yes	u_3	u_4

Table 1. The Utility 2 X 2 Table for All Possible Binomial Combinations of Efficacy and Toxicity. (R. Lin, 2020).

It is noted that other processes that have 3 or greater endpoints that relate to toxicity and efficacy can be used to build Utility Functions. Other Utility Functions (not presented here) have discussions on combining PK parameters (PK-BOIN12) (H. Sun, 2024), RECIST category endpoints (R. Lin, 2020), late-onset Toxicity (Z. Yanhong, 2024), and combined drug trials (M. Lu, 2024).

EXAMPLE STUDY USING BOIN12: BAYESIAN OPTIMAL INTERVAL PHASE I/II TRIAL DESIGN

To best demonstrate the BOIN12 method, this presentation will pose a simulated Phase I/II clinical study of an immunotherapeutic oncology drug with 5 dose levels. The focus will be only upon the utility and probability of the previously discussed four possible outcomes when pairing efficacy and toxicity of the investigative product.

The Utility Function assigns weighted values that reflect the clinical desirability of each possible toxicity and efficacy outcome. The BOIN12 procedure uses the utility (i.e. desirability) of the (No Toxicity, Efficacy), (No Toxicity, No Efficacy), (Toxicity, Efficacy), and (Toxicity, No Efficacy).

Ideally, the study would assign the most desirable outcome, No Toxicity and Complete Efficacy, a "weighted" utility score of u_1 = 100, and the least desirable outcome, Toxicity with No Efficacy, a utility score of u_4 = 0. The values of u_2 and u_3 for the other two Toxicity-Efficacy categories are assigned in favor of efficacy such that (Efficacy and Toxicity) = u_3 = 60. The category of No Efficacy and No Toxicity would equal u_2 =40. Specifying $u_3 > u_2$ means that the efficacy is weighted more importantly (more desirable) than the toxicity; and vice versa. Note that $u_3 + u_2$ =100 to match the sum of $u_1 + u_4$.

Utility Table		
Toxicity	**Efficacy**	
	Yes	*No*
No	u_1 = 100	u_2 = 40
Yes	u_3 = 60	u_4 = 0

Table 2. The Utility 2 X 2 Table for the present simulated study.

BOIN12 requires a Prior Informed Bayesian probability for each dose level, d, by $p_1(d)$,$p_2(d)$, $p_3(d)$, and $p_4(d)$, respectively, d = 1, … , 5 (since this example has 5 dose levels. The marginal efficacy and marginal toxicity probabilities are given by $p_E(d) = p_1(d) + p_3(d)$ and $p_T(d) = p_3(d) + p_4(d)$, respectively. These probabilities are termed "marginal" because their probability of occurrence is considered as independent of other events.

The table below (Table 3) shows the Probability of Efficacy and the Probability of Toxicity over all five doses in our hypothetical study:

Scenario	$(p_T(d), p_E(d))$ at dose level				
	1	2	3	4	5
This Example	(0.08, 0.10)	(0.10, 0.20)	(0.15, 0.70)	(0.32, 0.70)	(0.40, 0.75)

Table 3. The probability of toxicity, p_T , and the probability of efficacy, p_E , for this example study.

The interior of the basic probability table (shaded light gray) gives the values $p_1(d)$, $p_2(d)$, $p_3(d)$ and $p_4(d)$. The margins contain $p_E(d) = p_1(d) + p_3(d)$ and $p_T(d) = p_3(d) + p_4(d)$. Note that $p_1(d) + p_2(d) + p_3(d)$

+$p_4(d)$ = 0.595 + 0.255 + 0.105 + 0.045 = 1.0 (a complete probability distribution). When the marginal probability of Toxicity, p_T = 0.15, then the probability of No Toxicity then equals 1 - p_T = 0.85. Likewise, the marginal probability of Efficacy, p_E , is 0.70 and the probability of No Efficacy equals 1 - p_E = 0.30. The table below shows the probabilities ONLY for dose level 3:

Probability Table Based on Dose Level 3			
Toxicity	**Efficacy**		
	Yes	*No*	*Marginal*
No	p_1 = 0.595	p_2 = 0.255	1 - $p_T(d)$ = 0.85
Yes	p_3 = 0.105	p_4 = 0.045	$p_T(d)$ = 0.15 = $p_3(d)$ + $p_4(d)$
Marginal	$p_E(d)$ = 0.7 = $p_1(d)$ + $p_3(d)$	1 - $p_E(d)$ = 0.3	Total Probability = 1.0

Table 4. The case and marginal probabilities of dose level 3 for this simulated study.

The following table is a summary of marginal probabilities for dose level 3 (d_3):

Outcome	Symbol Set	Probability
Toxicity	$p_T(d_3)$	0.15
Efficacy	$p_E(d_3)$	0.70
No Toxicity	1 - $p_T(d_3)$	0.85
No Efficacy	1 - $p_E(d_3)$	0.3

Table 5. Summary of marginal probabilities of dose level 3 for this simulated study.

The designation, d_3, in the stepwise calculations that follow indicates that the focus is on dose-level three. These calculations must be done for all other dose levels as well. The symbols, u_n, identify the weighted utility coefficient for each category. The probabilities, p_n, correspond to the related utility categories. As before, $p_T(d_3)$ = probability of toxicity at dose-level 3 and $p_E(d_3)$ = probability of efficacy at dose-level 3.

The summary of the calculation is as follows:

Activity	Calculations
The utility function for dose level 3	$u(d_3) = u_1p_1(d_3) + u_2p_2(d_3) + u_3p_3(d_3) + u_4p_4(d_3)$
Substituting weighted coefficients	$u(d_3) = 100p_1(d_3) + 40p_2(d_3) + 60p_3(d_3) + 0p_4(d_3)$
Replacing categorical probabilities with marginal probability equivalents	$u(d_3)$ = 100((1-$p_T(d_3)$)($p_E(d_3)$) + 40((1-$p_T(d_3)$)(1- $p_E(d_3)$) + 60($p_T(d_3)$, $p_E(d_3)$) + 0(($p_T(d_3)$)(1- $p_E(d_3)$))
Numerical substitutions and completed product-sum numerical result	$u(d_3)$ = 100(.85)(.70)+ 40(.85)(.3)+ 60(.15)(.7) + 0(.15)(.3)
	$u(d_3)$ = 100(.595)+ 40(.255)+ 60(.105) + 0(.045)
	$u(d_3)$ = 59.5 + 10.2 + 6.3 + 0 = **76**

Table 6. Summary of the calculations needed to find the numerical Utility at dose-level 3.

Once the calculations for all dose levels are complete, Table 7 can be completed with the Utility value at each of the five dose levels. Note that each of the results for the Utility Function are multiplied by 0.01 for overlay placement with the efficacy and toxicity probabilities on the upcoming graphs.

(u_1, u_2, u_3, u_4)	(100, 40, 60, 0)				
Dose Level	1	2	3	4	5
Utility Function Result at Dose	42.8	48	**76**	69.2	69
Numerical Value Used in Graph	0.428	0.48	**0.76**	0.692	0. 69

Table 7. Utility Function outputs at each dose level.

R AND SAS® CODE FOR SELECTING OBD AND DISPLAYING RESULTS.

R PROGRAM FOR CALCULATING OPTIMAL BIOLOGICAL DOSE (OBD).

Ruitao Lin (2020) has developed an R Shiny app that is found in the **escalation** R library package. The model that selects the Optimal Biological dose is **get_boin12.** The following R program displays the code that is needed based upon the hypothetical dosing scenario presented here. In the model, the code pronounces the **num_doses** = 5 (as demonstrated in the present example). Notational equivalents of **phi_t** = p_T, **phi_e** = p_E, u_2 and u_3 are assigned as in the scenario. A fictional set of five dosing outcomes are also entered into the model. In this case: N = neither Efficacy nor Toxicity is noted, E = noted Efficacy, and T = noted Toxicity. The numerical digit preceding each letter triad is the dose level.

```
library(escalation)

# Examples in Lin et al.
model <- get_boin12(num_doses = 5, phi_t = 0.15, phi_e = 0.70,
                    u2 = 40, u3 = 60, n_star = 6)
fit <- model %>% fit('1NNN 2NNE 3NEE 3EEE 4TNT')
fit %>% recommended_dose()
fit %>% continue()
fit %>% is_randomising()
fit %>% dose_admissible()
fit %>% prob_administer()
```

Display 2: R input code for the present dosing scenario.

The following output shows (in red font) that the OBD is dose-level 3, that a TRUE Boolean value is related to admissible dose 3, and that the calculated probability favors dose 3 at 0.4.

```
> library(escalation)
>
> # Examples in Lin et al.
> model <- get_boin12(num_doses = 5, phi_t = 0.15, phi_e = 0.70,
+                     u2 = 40, u3 = 60, n_star = 6)
> fit <- model %>% fit('1NNN 2NNE 3NEE 3EEE 4TNT')
> fit %>% recommended_dose()
[1] 3
> fit %>% continue()
[1] TRUE
> fit %>% is_randomising()
[1] FALSE
> fit %>% dose_admissible()
[1] FALSE FALSE  TRUE FALSE  TRUE
> fit %>% prob_administer()
  1   2   3   4   5
0.2 0.2 0.4 0.2 0.0
```

Output 1. R-Code for Finding Dose using Techniques of BOIN12

The graphical displays of the three curves and their relative positions are both interesting and useful. The following code and graphical displays show both SAS® and R programming with the resulting figures.

R AND SAS® PROGRAMS FOR GRAPHICAL DISPLAY OF UTILITY, TOXICITY AND

EFFICACY FUNCTION CURVES.

R-Programming:

```
library(ggplot2)

df <- data.frame(dose=c(1, 2, 3, 4,5),
                 tox=c(0.08, 0.10, 0.15, 0.32,0.4),
                 eff=c(0.1, 0.2, 0.7, 0.7, 0.75),
                 util=c(0.428,0.48,0.76,0.692,0.69))

ggplot() +

  geom_line(data=df,mapping=aes(x=dose,y = tox), color = "gold",linewidth = 1) +
  geom_point(data=df,mapping=aes(x=dose,y = tox), color = "gold",size=3) +
  annotate("text", x = 4 , y = .25, label = "Toxicity Curve")+
  geom_line(data=df,mapping=aes(x=dose,y = eff), color = "red",linewidth = 1) +
  geom_point(data=df,mapping=aes(x=dose,y = eff), color = "red",size=3) +
  annotate("text", x = 3 , y = .52, label = "Efficacy Curve")+
  geom_line(data=df,mapping=aes(x=dose,y = util), color = "darkblue",linewidth = 1)+
  geom_point(data=df,mapping=aes(x=dose,y = util), color = "darkblue",size=3)+
  annotate("text", x = 2, y = .55, label = "Utility Curve")+
  annotate("text", x = 3, y = .75,color="orange",
                   size=13 , label = "*")+
  annotate("text", x = 3.5, y = .78,size = 4,label = "Optimal Biological Dose")+
  geom_hline(yintercept=0.32,linetype=2)+
  annotate("text", x = 3, y = .35, label = "Toxicity Lower Limit")+
  labs(x = "Dose Level",y = "Probability",Title = "BOIN12 Optimum Biological Dose")+
  scale_y_continuous(sec.axis = sec_axis(
    trans = ~ . *100,
    name = "Utility Coefficient X 100 "))+
  theme(
   axis.title.y = element_text(color = "red", size=13),
   axis.title.y.right = element_text(color = "darkblue", size=13)
   )
```

Display 3. R-Code for Finding Utility, Efficacy and Toxicity Curves for Dose – Response Display

The figure below is the result of the previous R code. The toxicity lower limit is equivalent to the maximum acceptable toxicity of the investigative product.

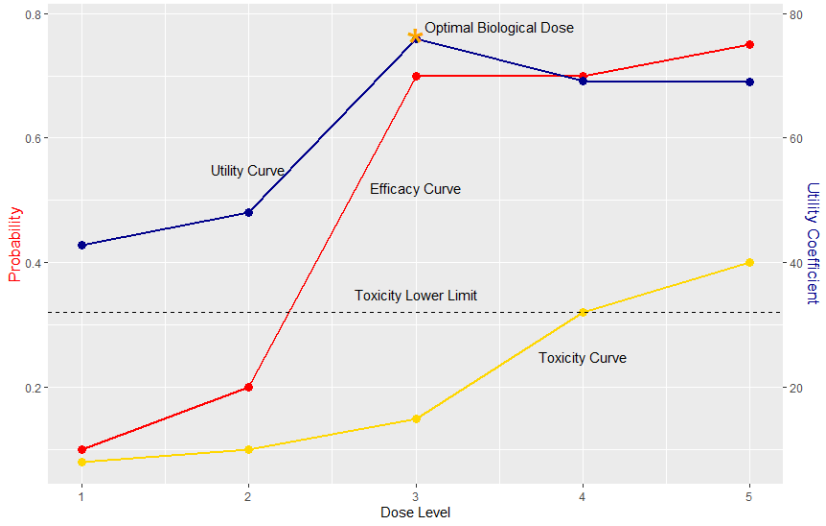

Figure 2. Dose-Response Curves for Utility, Efficacy and Toxicity for a Phase 1 Clinical Trial

SAS® Programming Code for this presentation:

The following SAS® programming code produces a very similar figure to that produced by R code.

```
data df;
    input dose toxicity efficacy utility ;
    datalines;
1 0.08 0.10 0.428
2 0.10 0.20 0.48
3 0.15 0.70 0.76
4 0.32 0.70 0.692
5 0.40 0.75 0.69
;
run;

data df2;
set df;
length text text2 $30;
IF dose = 3 and utility = 0.76 THEN text='Optimal Biological Dose';
IF dose = 3 and utility = 0.76 THEN text2='*';
run ;


proc sgplot data=df2 sganno=anno;
    series x=dose y=toxicity / lineattrs=(color=gold thickness=2);
    scatter x=dose y=toxicity / markerattrs=(symbol=circlefilled color=gold size=8);
    series x=dose y=efficacy / lineattrs=(color=red thickness=2);
    scatter x=dose y=efficacy / markerattrs=(symbol=circlefilled color=red size=8);
    series x=dose y=utility / lineattrs=(color=darkblue thickness=2);
    scatter x=dose y=utility / markerattrs=(symbol=circlefilled color=darkblue size=8);
    TEXT Y=utility X=dose TEXT=text/Position = top TEXTATTRS = (SIZE=11 COLOR='orange');
    TEXT Y=utility X=dose TEXT=text2/Position = center TEXTATTRS = (SIZE=18 COLOR='orange');
    refline 0.32 / axis=y label='Toxicity Lower Limit' lineattrs=(thickness=3 color=black pattern=dash);

    xaxis label="Dose Level";
    yaxis label="Probability";
    yaxis2 label="Utility Coefficient" values=(0 to 1 by 0.1)
           labelattrs=(color=darkblue)
           offsetmin=0.1;

    title "BOIN12 Optimum Biological Dose";
```

Display 4. SAS®-Code for Display of Utility, Efficacy and Toxicity Curves for Dose – Response Display.

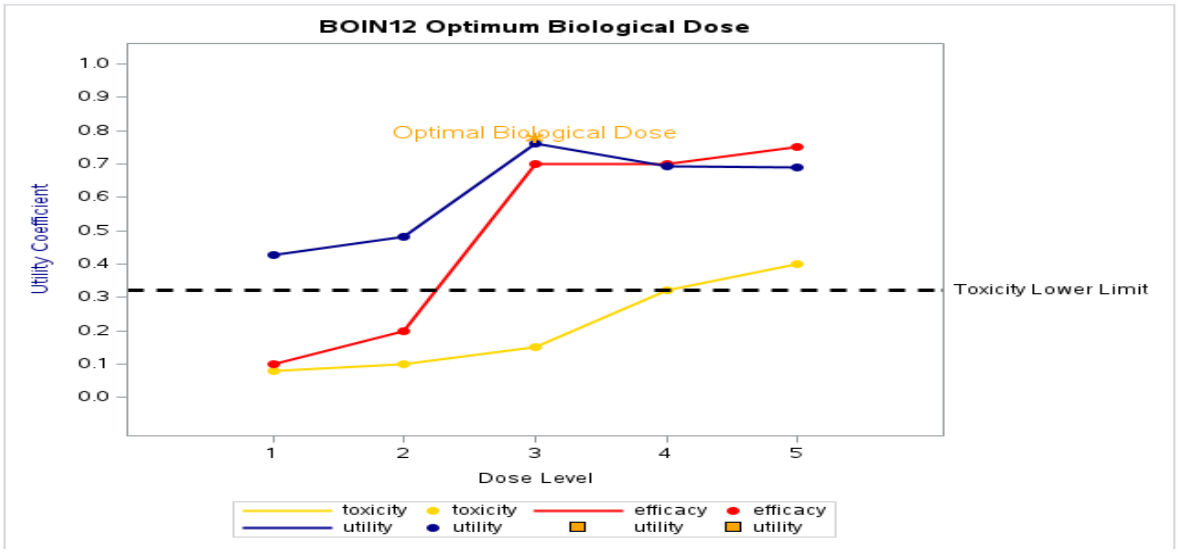

Figure 3. Dose-Response Curves for Utility, Efficacy and Toxicity for a Phase 1 Clinical Trial (Produced by Previous SAS Code)

CONCLUSION

In immunotherapeutic oncology studies, the search for the Maximum Tolerated Dose (MTD) has given way to the primary focus on the Optimal Biological Dose. Statistical researchers have modified the basic Bayesian Optimal Interval (BOIN) approach with several other processes that seek to examine the Efficacy – Toxicity relationship. This presentation focused on one of the processes, the BOIN12 method, in detail and followed the process through a simulated set of study with given Bayesian Priors and possible outcomes.

With oncology studies producing demonstrable efficacy at earlier study Phases, the hope is that statistical analysis incorporating early efficacy evaluations (with minimal weighting for toxicity) will deliver reliable drugs with more clinical study efficiencies.

REFERENCES

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CONTACT INFORMATION

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