Dose finding in early-stage development:

BOIN design for Maximum Tolerated Dose (MTD) and Optimal Biological Dose (OBD)

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Dose Escalation in Oncology: Background

- Historically, dose escalation in oncology was based on very simple principle and methods
- Cytotoxic agents are aimed at killing cancer cells and higher doses were automatically considered more effective, provided that the patients can tolerate the dose
- 3+3 design was a golden standard to define Maximum Tolerated Dose (MTD) in the phase I, which was then selected to Phase II conducted in a single-arm study
- 3+3 is based on simple algorithm
  - if the DLT rate is 0/3 after a cohort of 3 patients then the dose is increased
  - If the DLT rate is 1/3, then next cohort of 3 is treated on the same dose level
  - If the DLT rate is 1/6 after the new cohort of 3 patients, then the dose is increased
  - If the 2 DLT (out of 3 or 6 patients) are observed, then MTD is defined as the previous dose level where the DLT rate is below 2/6
- Thus, the dose was increased until over 30% of patients experienced severe toxicity, i.e. Adverse reactions defined as Dose Limiting Toxicities (DLT)

Basics of Bayesian Optimal Interval (BOIN) design

- Original paper in 2015 by Lin and Yuan
- 2021 FDA granted BOIN fit-for-purpose status in phase I dose finding trials
- Essentially, BOIN can be considered as an extension of the traditional 3+3 design with a modified decision rule for the MTD
- BOIN has better operative characteristics* than 3+3 and is simpler than other model-based methods (e.g. CRM), see for example Ruppert, Shoben (2018)
- Decisions of escalating, de-escalating, or staying at the current dose are based on the observed DLT rate after each cohort
- Decisions depend on the target DLT rate, and the predefined design parameters (commonly applied default options available)
- Need to specify:
  - DLT criteria and time frame for observing toxicities (DLT period)
  - Target DLT rate (usually 0.3 or below)
  - Cohort size and number of doses and cohorts (=maximum sample size)

*The design selects the MTD more accurately and doses a larger percentage of patients at the MTD than the 3 + 3 design does, and it has a lower probability of overdosing patients than some other designs

Example (using R BOIN suite)

4.1. Single-agent phase I trial

Consider a single-agent phase I trial with 5 dose levels, in which the objective is to find the MTD with a target DLT rate of 0.3. The maximum sample size is 30 patients, treated in cohort sizes of 3. To design and conduct this trial, we first ran the following commands:

```
R> bound <- get.boundary(target = 0.3, ncohort = 10, cohortsize = 3)
R> summary(bound)
R> plot(bound)
```

This yields the dose escalation and de-escalation boundaries as shown in Table 3, and a flowchart of the trial design similar to Figure 1. The trial started by treating the first cohort of 3 patients at dose level 1 and none of the patients had dose limiting toxicity (DLT).

	Number of patients treated									
	3	6	9	12	15	18	21	24	27	30
Escalate if # of DLT $\leq$	0	1	2	2	3	4	4	5	6	7
De-escalate if # of DLT $\geq$	2	3	4	5	6	7	8	9	10	11
Eliminate if # of DLT $\geq$	3	4	5	7	8	9	10	11	12	14

Table 3: Dose escalation and de-escalation rule for the BOIN design.

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Example (cont)

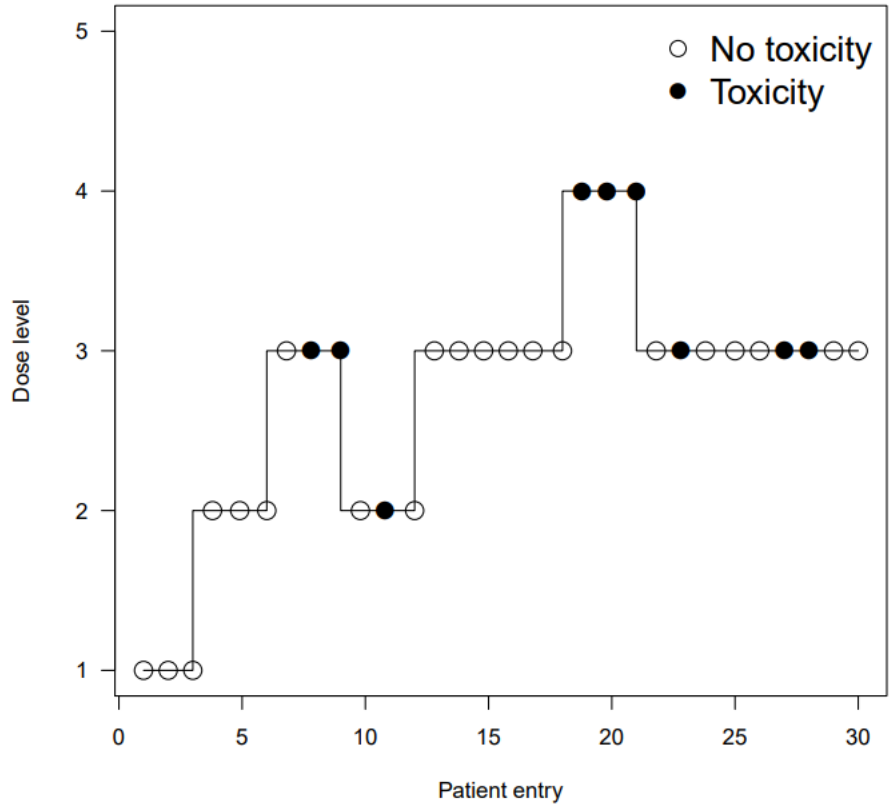

Figure 8: Illustration of the single agent phase I trial using the BOIN design.

	The number of evaluable participants treated at current dose												
Decision	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Escalate if # of DLT <=	0	0	1	1	1	1	2	2	2	2	3	3	3
Stay if # of DLT =	1	1	NA	2	2	2	3	3	3	3-4	4	4-5	4-5
De-escalate if # of DLT >=	2	2	2	3	3	3	4	4	4	5	5	6	6
Eliminate if # of DLT >=	3	3	4	4	5	5	5	6	6	7	7	8	8

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Example results

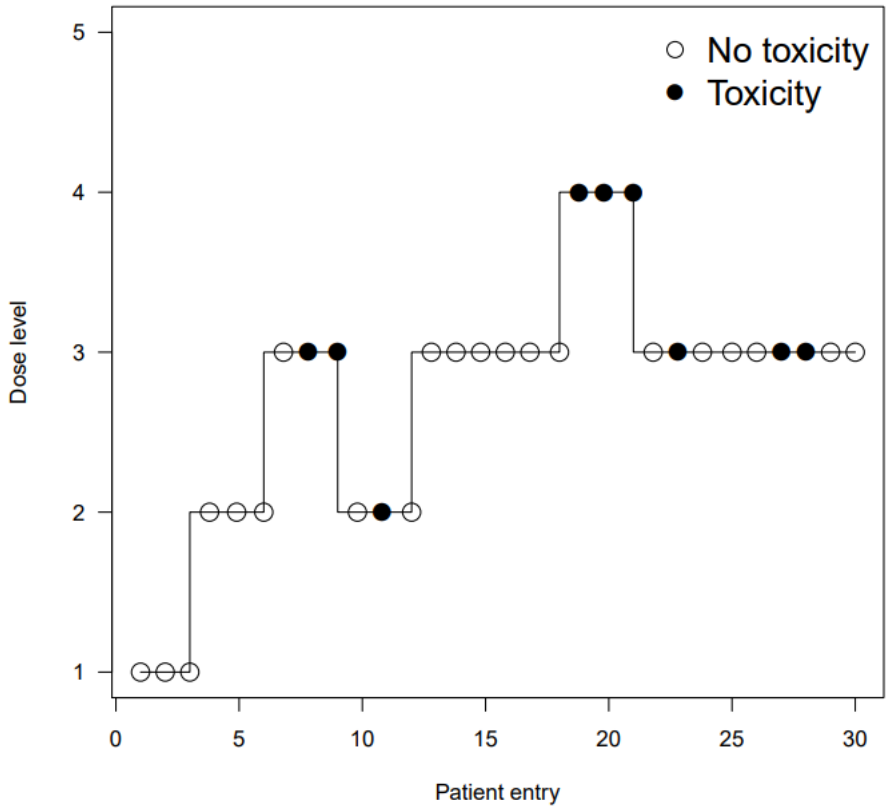

Figure 8: Illustration of the single agent phase I trial using the BOIN design.

the sixth cohort was also treated at dose level 3. Figure 8 shows the dose assignment for all 30 patients. At the end of the trial, the number of patients and the number of DLTs at the 5 doses were `n = c(3, 6, 18, 3, 0)` and `y = c(0, 1, 5, 3, 0)`. To select the MTD, we ran the following commands:

```
R> n <- c(3, 6, 18, 3, 0)
R> y <- c(0, 1, 5, 3, 0)
R> sel.single <- select.mtd(target = 0.3, ntox = y, npts = n)
R> summary(sel.single)

The MTD is dose level  3

Dose    Posterior DLT            95%
Level     Estimate        Credible Interval   Pr(toxicity>0.3|data)
  1         0.02          (0.00,0.20)            0.01
  2         0.17          (0.01,0.53)            0.18
  3         0.28          (0.10,0.50)            0.39
  4         0.98          (0.80,1.00)            1.00
  5         ----          (----,----)            ----
```

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Example for 15 patients and 3 dose levels

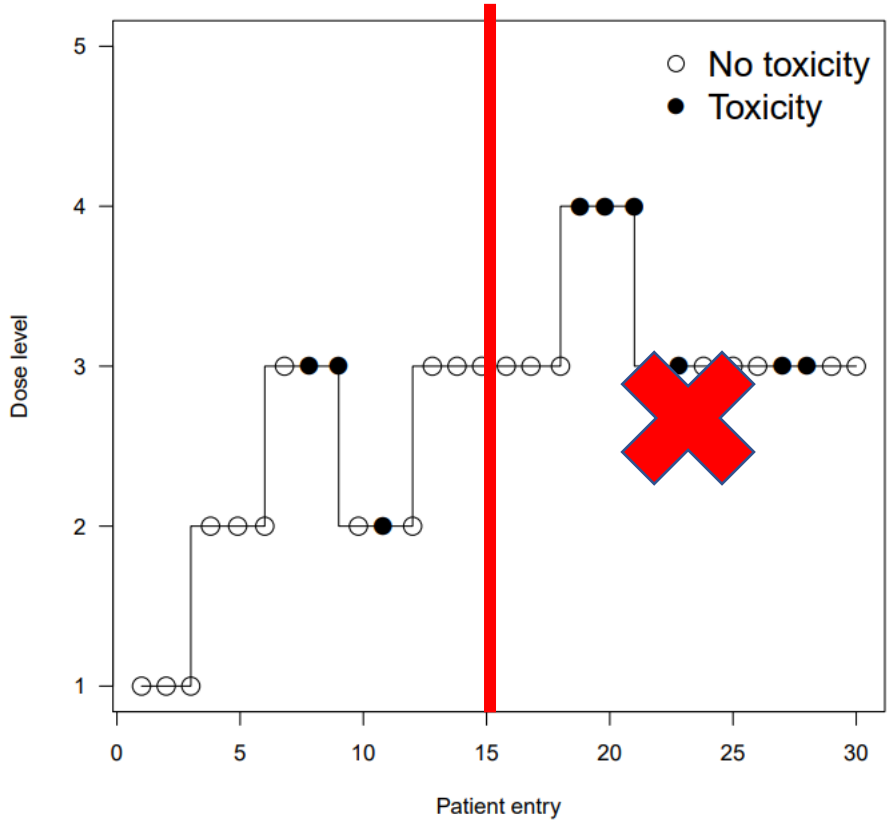

Figure 8: Illustration of the single agent phase I trial using the BOIN design.

```
> n <- c(3, 6, 6)
> y <- c(0, 1, 2)
> sel.single <- select.mtd(target = 0.3, ntox = y, npts = n,
+                          boundMTD=TRUE, extrasafe=TRUE, offset = 0.5)
> summary(sel.single)
The MTD is dose level  3

Dose    Posterior DLT            95%
Level     Estimate         Credible Interval   Pr(toxicity>0.3|data)
  1         0.02            (0.00,0.20)            0.01
  2         0.17            (0.01,0.53)            0.18
  3         0.34            (0.06,0.72)            0.54
```

* For this case, 3+3 design would have excluded the dose level 3 after observing 2 DLTs and stopped after 12 patients selecting dose level 2, but with BOIN it can return to dose level 3 for extra patients and still select this dose

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MTD and OBD

- Issue: although BOIN is outperforming 3+3, it is focused on defining the Maximum Tolerated Dose (MTD)
- Many Immuno-oncological (IO) molecules are rather well tolerated
- The most effective dose is not necessarily the highest tolerated dose
- This Optimal Biologic Dose (OBD) could be among the cleared dose levels
- Dose finding trials are many times conducted on the last treatment line and with fragile/refractory patients which are not optimal for efficacy evaluation

MTD and OBD

- In oncology the efficacy is measured by response criteria using different endpoint definitions based on the disease and line of treatment
- The dichotomous endpoint would allow similar modeling for efficacy than what is applied to toxicity
- However, the responses are many times heterogeneous within the dichotomy (complete or partial, varied duration, complicated response definitions, long duration of SD)
- 3 patients is too little for any efficacy purpose and for PK/PD evaluation which is of utmost importance with the targeted IO agents, also 6 patients leaves a lot of uncertainty
- There are several novel methods for combined model-based methods evaluating efficacy and toxicity simultaneously (also BOIN12) but with efficacy evaluation including the PK/PD, more flexibility could be beneficial

BOIN with backfilling (BOIN-BF)

- However, there are possibilities within the basic BOIN framework to improve the performance with the evaluation of OBD and the shape of dose-response curve
- In the lack of DLTs, BOIN allocates most of the patients to the highest dose level which is not necessarily optimal for OBD selection purposes
- Accounting for this, you can specify early stopping rule for BOIN, for example stopping the escalation if 12 subjects are allocated to same dose
- Another technique is to use backfilling during the dose escalation (Zhao et al 2024)
  - Allocating more subjects to cleared dose levels than BOIN is guiding, provided that there has been some responding patients in the dose levels where backfilling is applied
  - https://pubmed.ncbi.nlm.nih.gov/38048044/
- This way, you could have ~10 patients at the end of Ph1 for every dose level that has shown some anti-cancer activity
- This allows better characterization of PK/PD including receptor occupancy (are you reaching your target cells in blood and in tumor)

BOIN with flexible cohort size

- By default, BOIN design decisions are based on the DLT evaluable patients
- Replacements are not needed as it has decision rules for each case
- However, for the new dose levels, there can be a rule for a minimum number of evaluable patients
- Accelerated titration allows escalation even with 1 patient at sub-therapeutic dose levels
- Recent article (Park et al 2021) has also explored that deviation in the planned cohort size does not affect the performance of BOIN (or CRM) notably
  - https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776531
- Instead of fixed cohort size you can specify a cohort size of 3-5 for example
- This increases the flexibility in the study conduct as investigators could include 1 or 2 additional patients in the current dose level, if there are patients lined up for enrollment

Summary of BOIN designs

- Basic BOIN is an extension to 3+3 design with improved operational characteristics and decision rules for each situation
- BOIN allows also backfilling of cohorts (BOIN-BF) and utilizing flexible cohort sizes
- There are also several other extensions to BOIN for consideration, combining efficacy-modeling and time-to-event approaches (TITE models accounting for longer toxicity observation periods)
- These are summarized in a review article (Ananthakrishnan et al 2022)
  - https://pubmed.ncbi.nlm.nih.gov/35812822/

Summary of dose finding in early stage

- Dose escalation, dose exploration and dose optimization are different items
- Questions you need to answer:
- First question: which doses are safe?
  - **dose escalation** with BOIN
- Second question: which doses are active in treating the disease?
  - **dose exploration** utilizing efficacy-toxicity modeling or BOIN with backfilling/flexible cohort sizes
- Third question: which 2 or more doses should be explored in the phase II?
  - Multidimensional approach considering safety, efficacy, PK/PD, target cells/mode of action
- This is the objective of phase I: to confirm safe doses and explore effective doses to be further investigated in phase II (=**dose optimization** using randomization)

Summary of dose finding in early stage

- In reality, phases I and II are mixed and combined during the drug development in oncology, as well as phases II and III, still often in the ph3 the question of correct dose is out in the air
- Statistician is facing several questions for the suitable, efficient and optimal designs and sample size for phase I trial and combined phase I/II trial
- Despite decades of existence of targeted immuno-oncological agents, clinicians (and statisticians!) are still puzzled about the dose finding principles and methods
- BOIN design is answering the same question than 3+3 design which is set up for cytotoxic agents with linear efficacy-response and finding Maximum Tolerated Dose (MTD)
- The questions about efficacy and PK/PD variables need separate methodological considerations
- MTD is not necessarily the OBD
- BOIN framework has flexibility to cover these aspects in addition to examination of tolerability
- BOIN is simple and accepted by authorities, still it requires careful defining of rules and parameters to ensure the interpretation and operational aspects within the study group
- ***Everything can not be answered in phase I***

References

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