

Phase 1 Oncology Trials

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Phase 1 Oncology Trials

- Oncology Phase 1 trials are very different than phase 1 trials in other therapeutic areas
- Historically oncology treatment *cause* adverse events – tied to the mechanism of action
- Cytotoxic drugs, crudely, aim to do damage to the host – just not too much
- Applying these therapies to healthy volunteers would be unethical -
- likely damage with no therapeutic benefit
 - And the AE profile may well be different in a cancer patient than a healthy volunteer
- Never control patients

Phase 1 Oncology Trial Structure

- Define a target toxicity rate (typically based on grade 3 toxicities)
 - Trying to find the **maximum tolerated dose** (highest dose with DLT rate < target rate)
- Start at a very low dose found very likely to not be harmful (animal and tox studies)
- Enroll patients on the highest cleared dose level
- **Modeling** of the level of bad things (dose-limiting toxicities)
- **Escalation** rules
- **De-escalation** rules
- **Stopping** rules

3+3 Design: Simplest, Most Common Design

- Define set of dose levels: 1, 2, 3, 4, 5, 6, 7 (k levels)
- Define the maximum tolerated dose as the maximum dose with a DLT rate $< 33\%$
- **Model:** Enroll 3 patients on a dose!
- **Escalation:** If 0 DLTs, then escalate to next dose
 - If 1 of 3, next cohort at the same dose
 - If 1/6 escalate, if 2/6 this is the MTD, if 3+, dose lower is MTD
 - If 2+ of 3, declare lower dose the MTD
- De-escalation: No de-escalation!
- **Stopping Rule:** 6 at highest dose or reach MTD declaration above

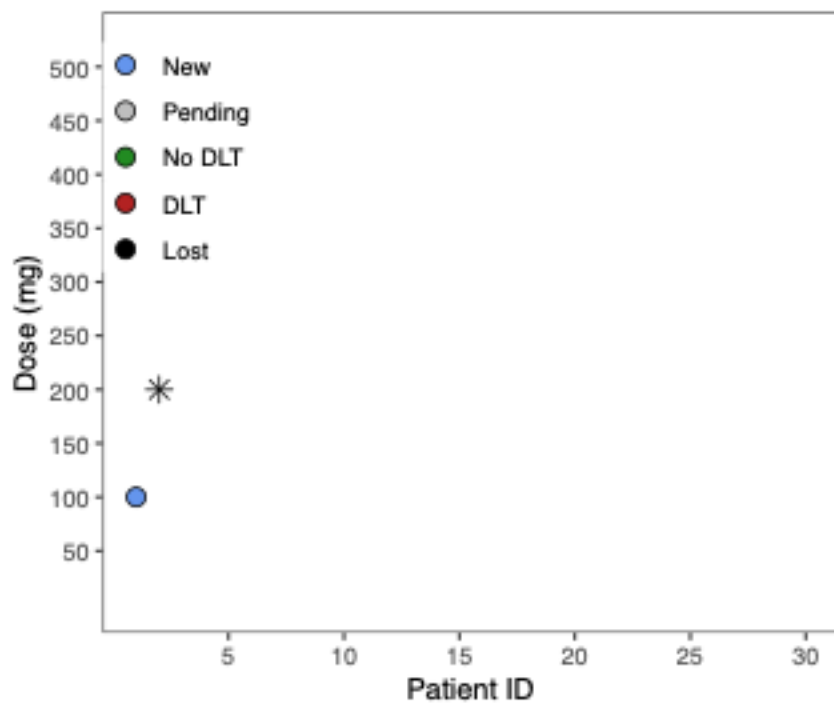
3+3 Notes

- Many tweaks have been created
- Safety Review Committee (SRC) very important role (oversee dose escalations)
- Historically a goal to get out of P1 as fast as possible
 - Typically the next trial is to put 10+ patients on the MTD as an expansion cohort and start to evaluate efficacy
- Can write 3+3 as the design and get a good SRC to right any wrongs
- A growing reflection 3+3 designs work very poorly
- A growing move away from 33% rate and moving forward with the MTD

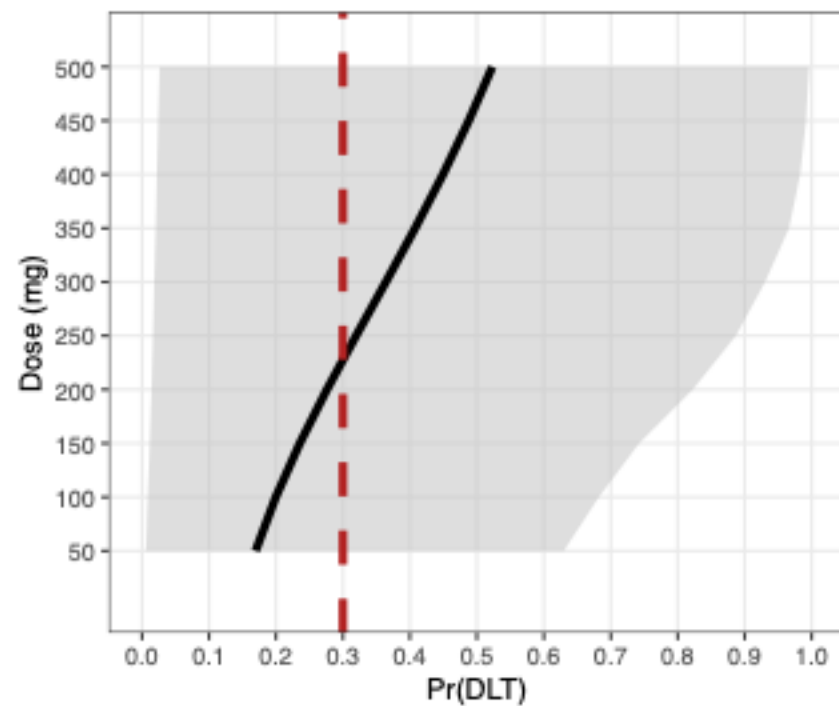
Model-Based Approaches

- Continual Re-assessment method (CRM)
- Start at same dose, with 3 patients
- Use a dose-DLT model
 - Typically a logistic regression model)
 - The estimate of the DLT rate at a dose depends on data from all doses
- Escalate **when 3 at a dose** and the model says dose is safe
 - Escalate to the dose the model says is safe with maximum jump sizes (1.5 or 2 times)
- De-Escalate when model says current dose is “likely unsafe”
- Typically **stopping rule** is some # at current safe dose (6, 8, 10, ...)

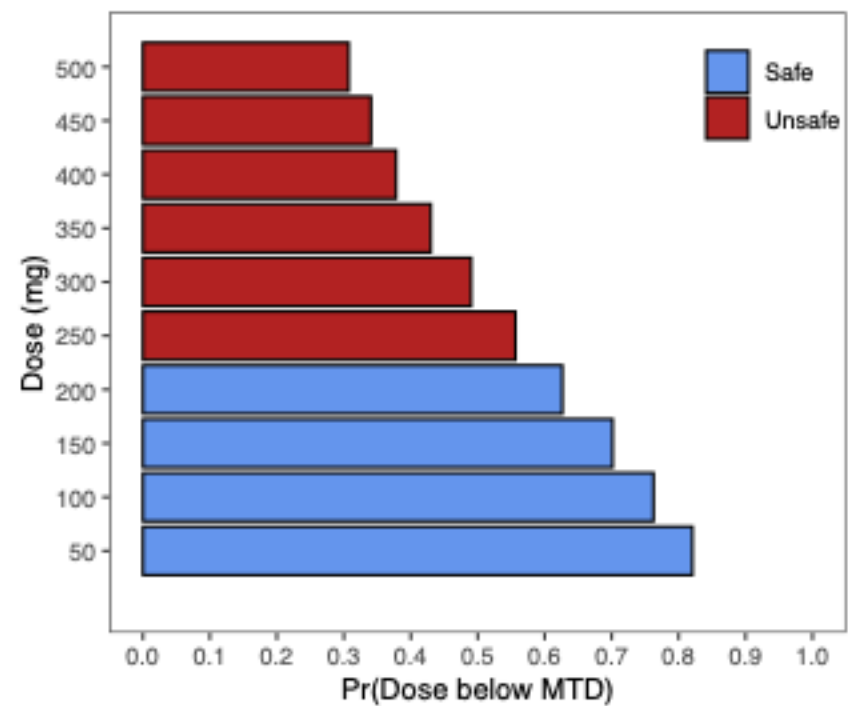
Week 1.8, N=1, Lost=0



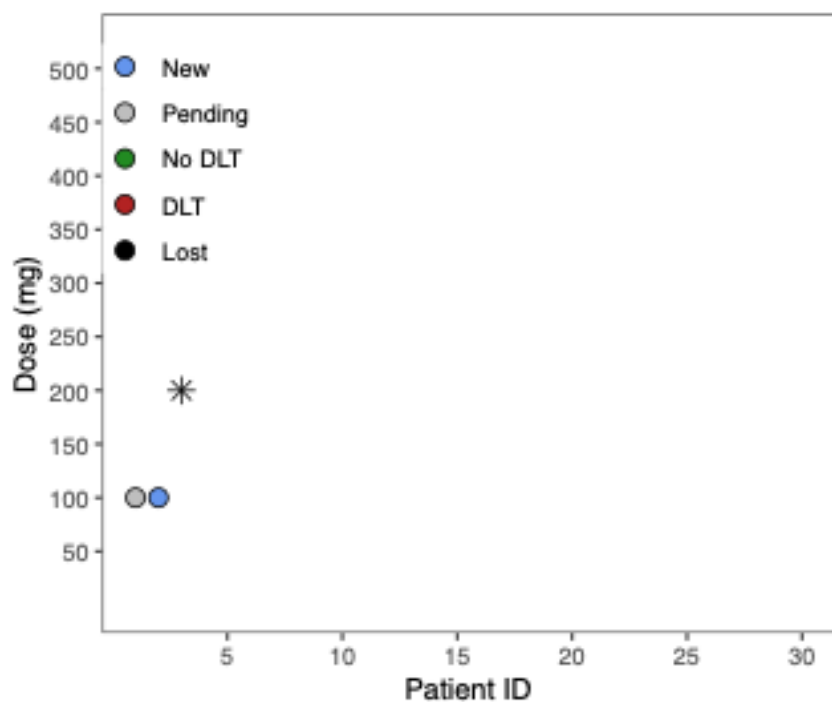
Enrollment Dose: 100 mg



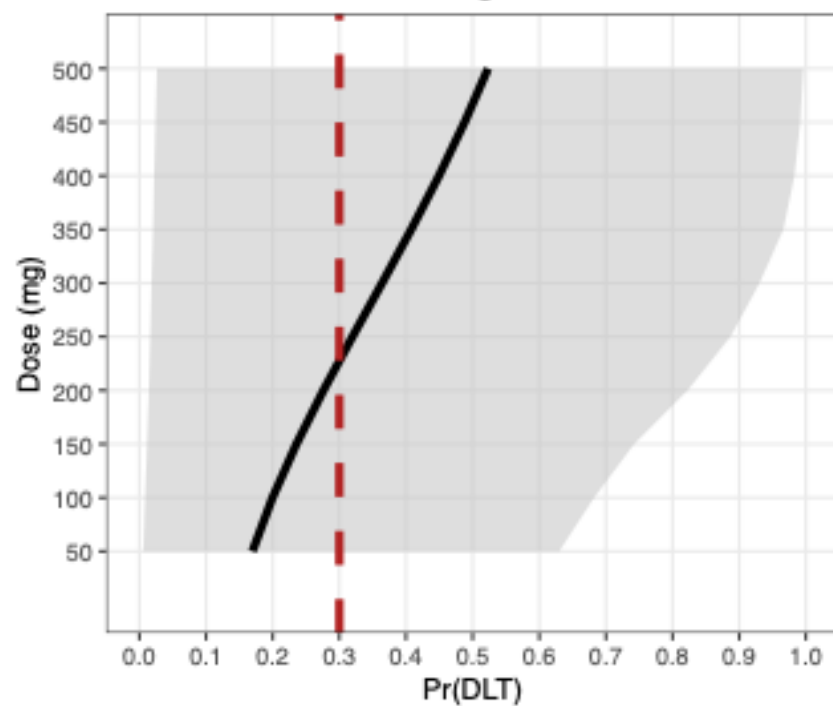
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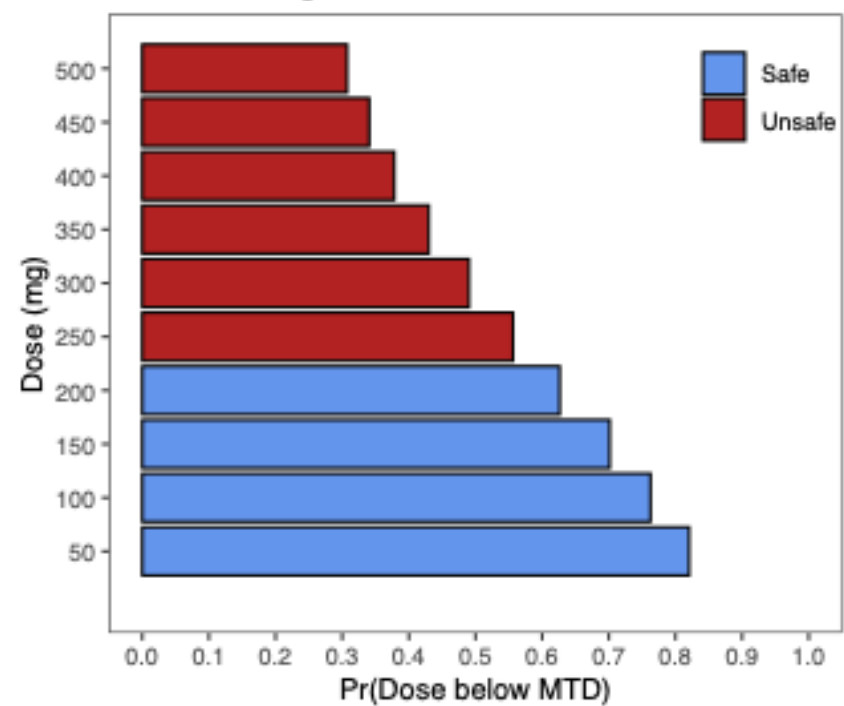
Week 2.7, N=2, Lost=0



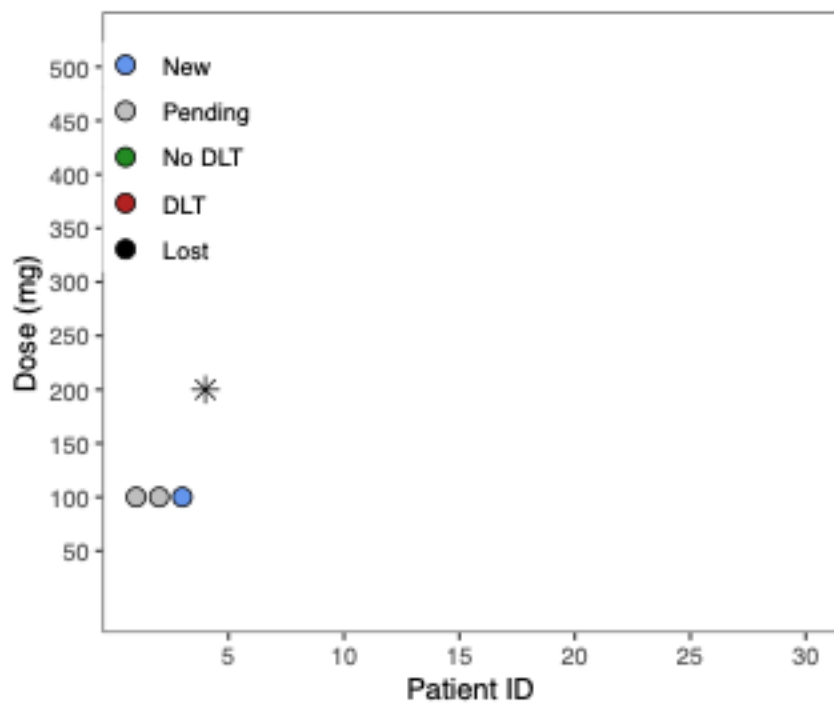
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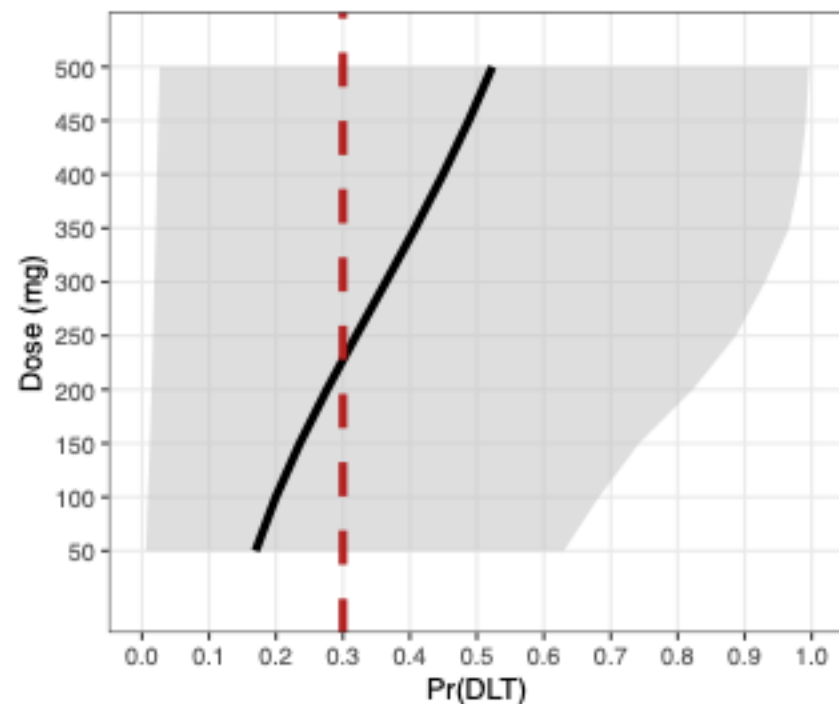
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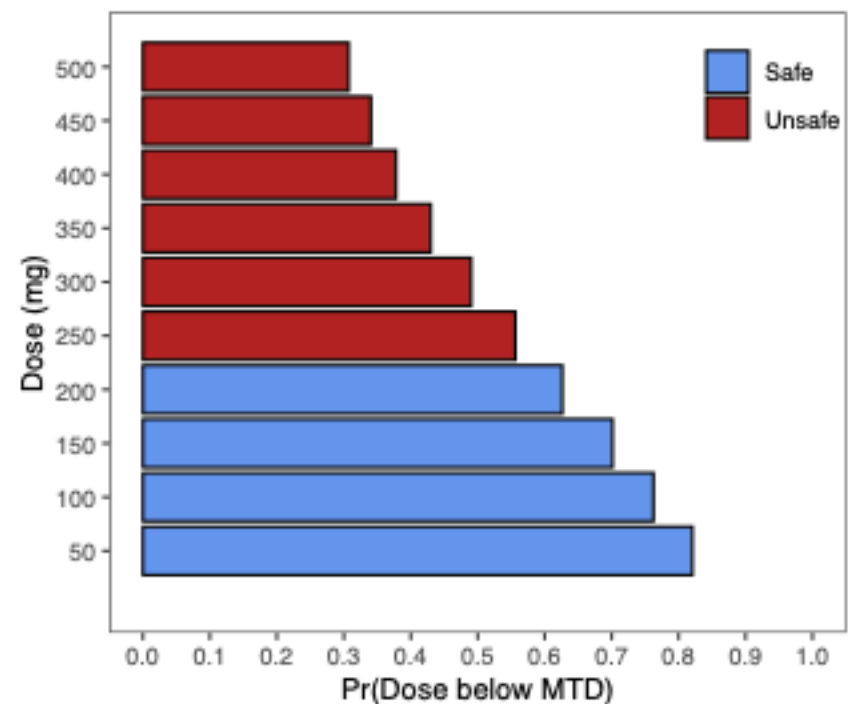
Week 5.1, N=3, Lost=0



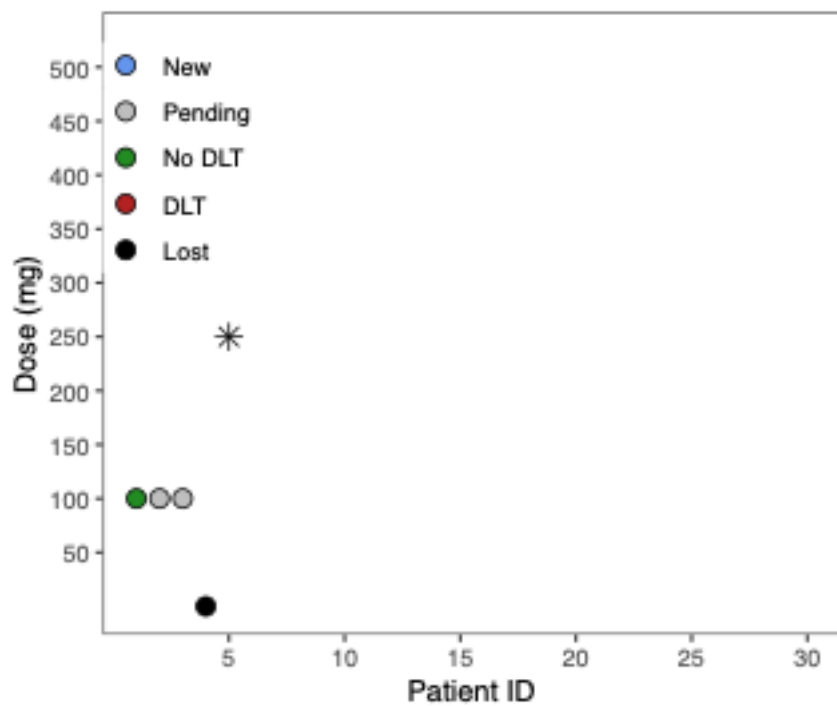
Enrollment Dose: 100 mg



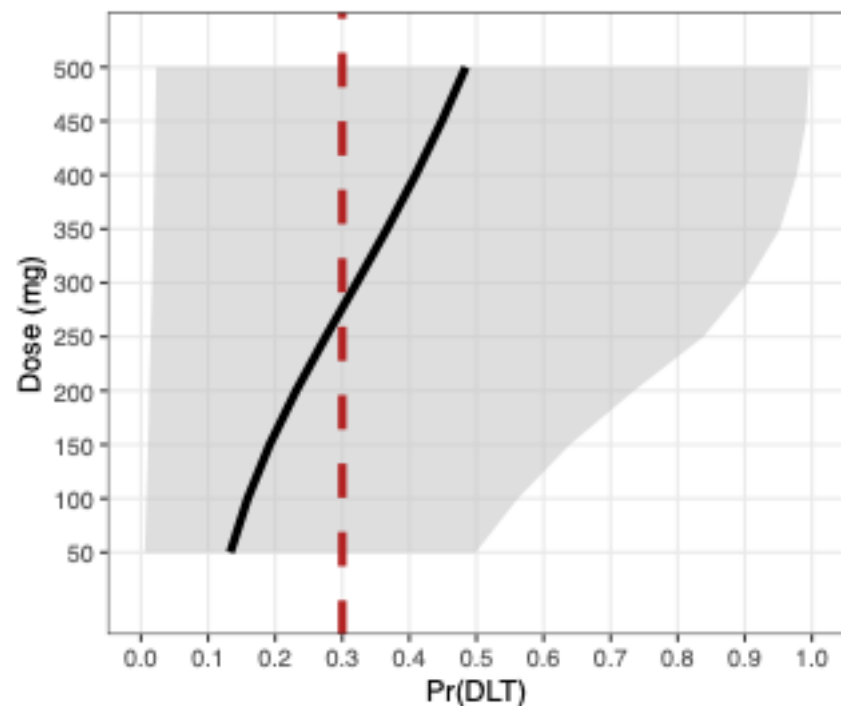
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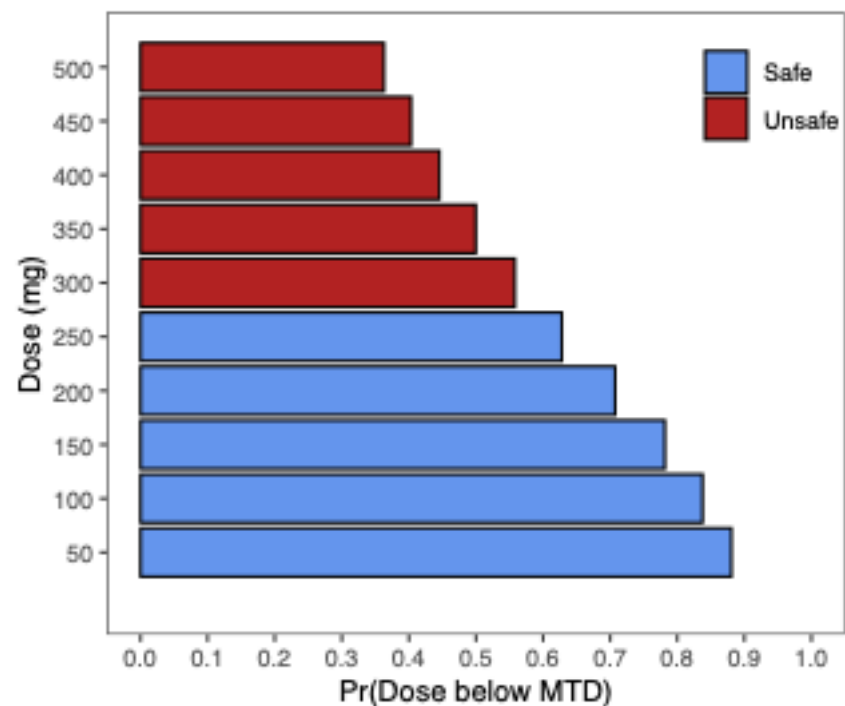
Week 5.9, N=3, Lost=1



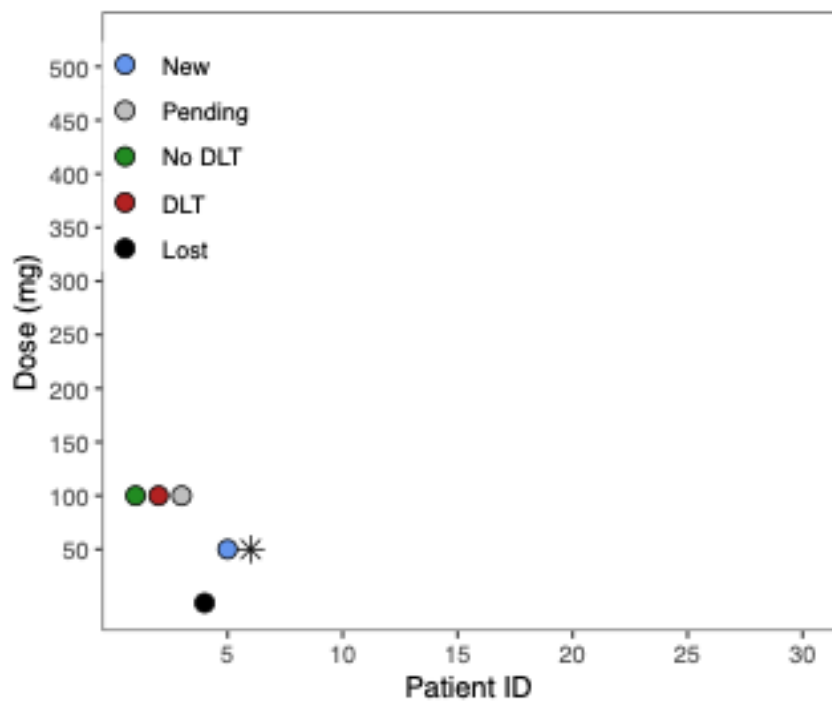
Enrollment Dose: 50 mg



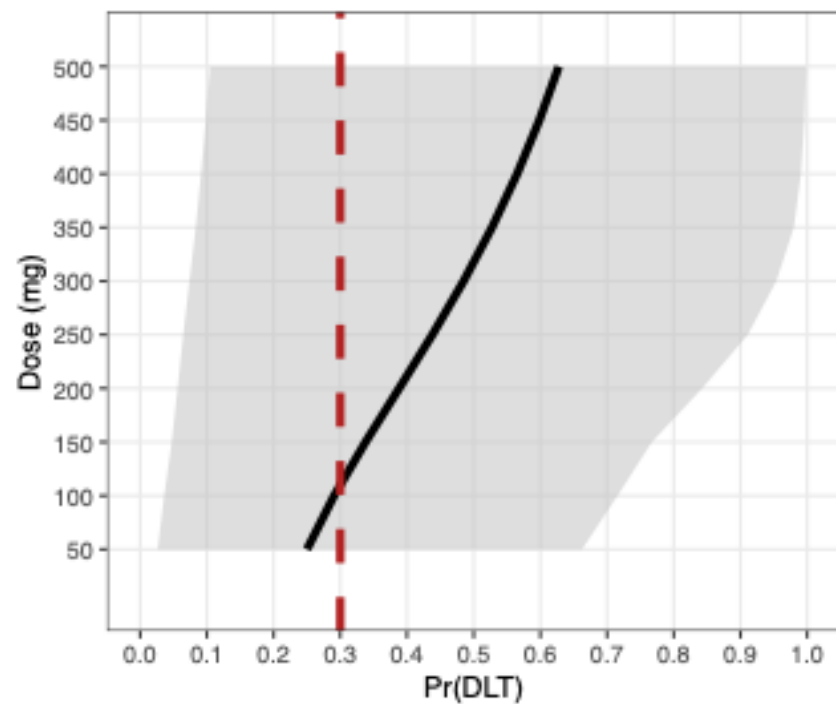
MTD: 250 mg



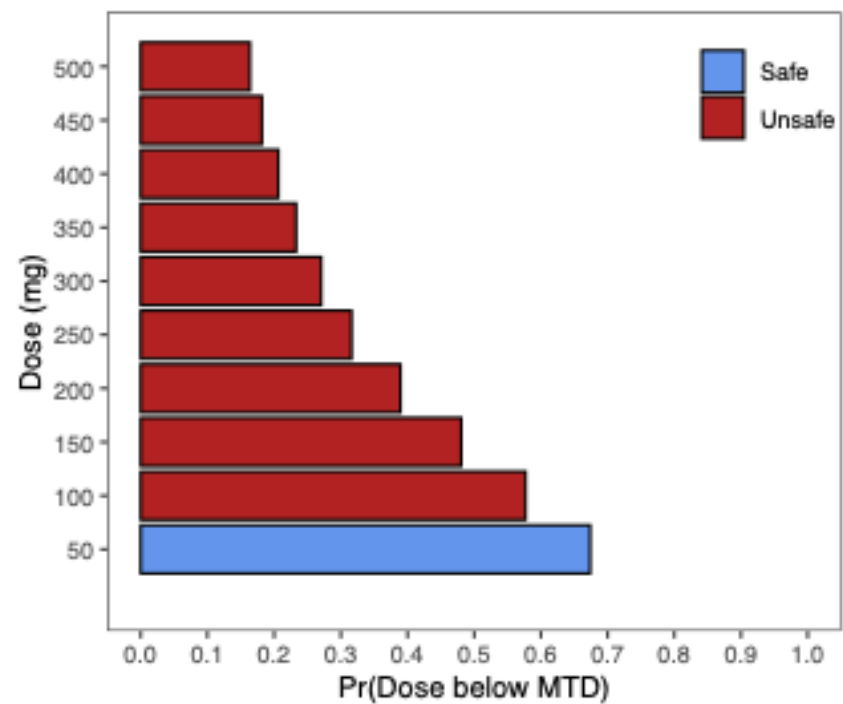
Week 7.8, N=4, Lost=1



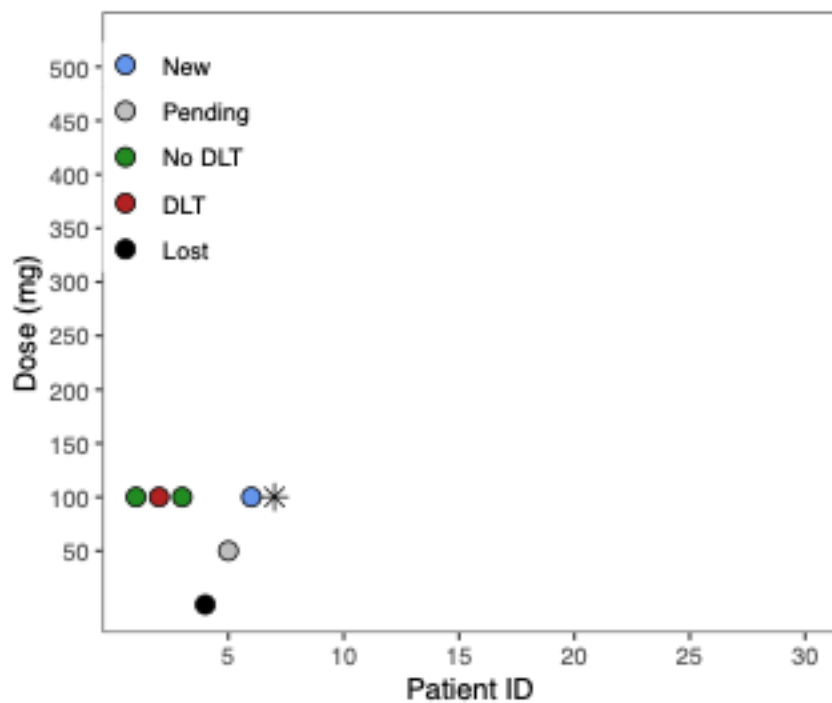
Enrollment Dose: 100 mg



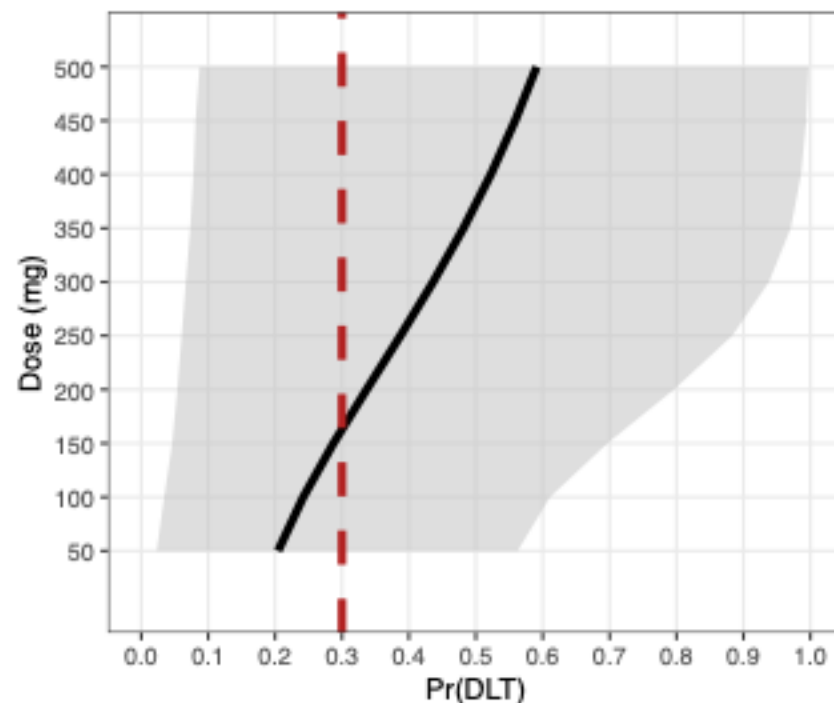
MTD: 50 mg



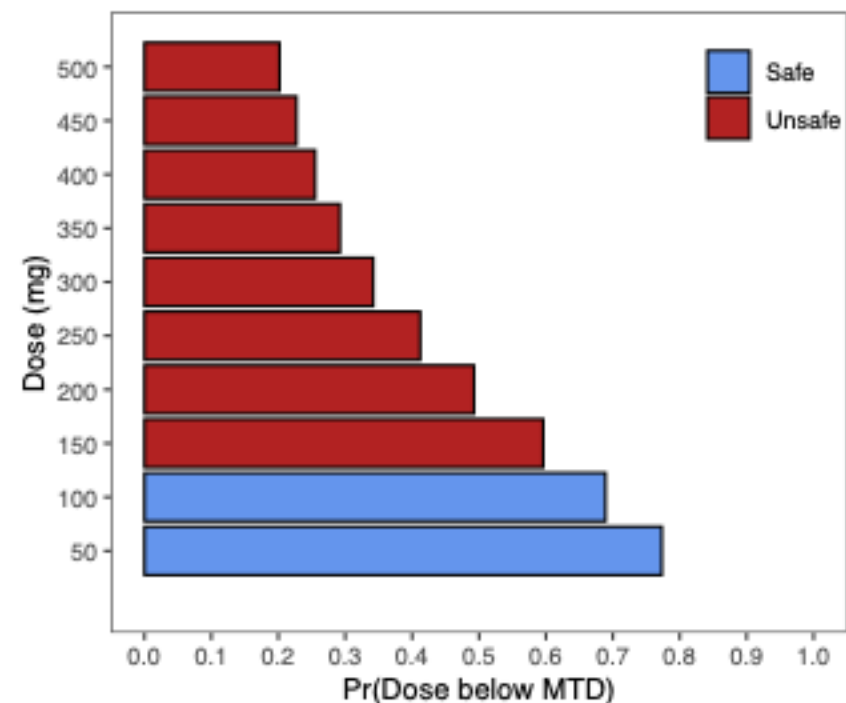
Week 9.8, N=5, Lost=1



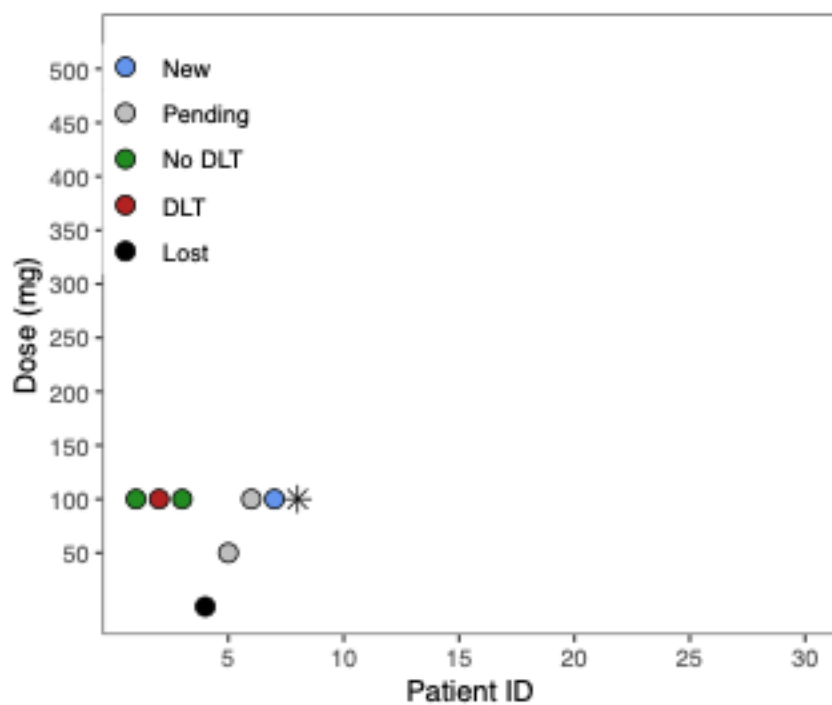
Enrollment Dose: 100 mg



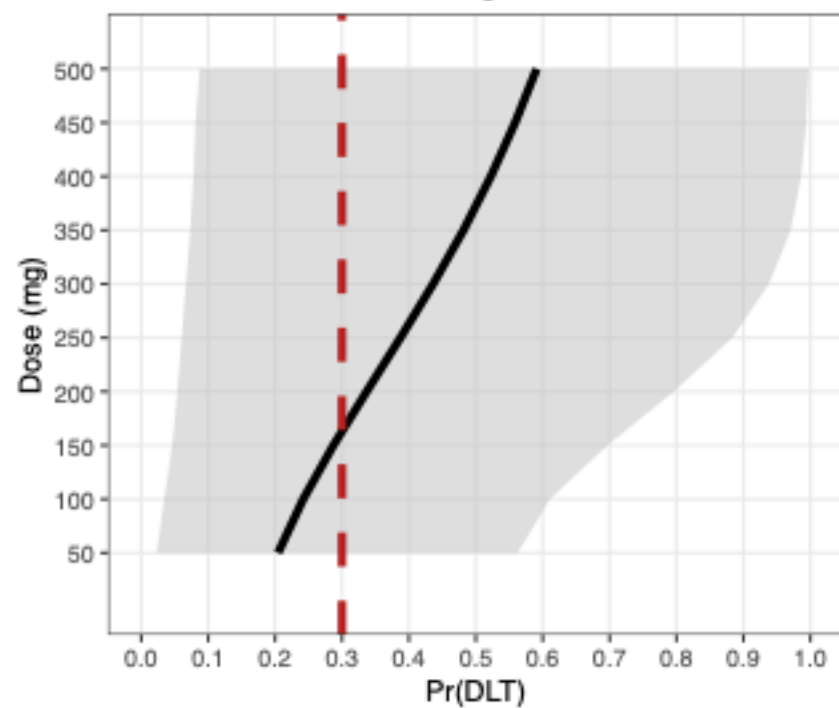
MTD: 100 mg



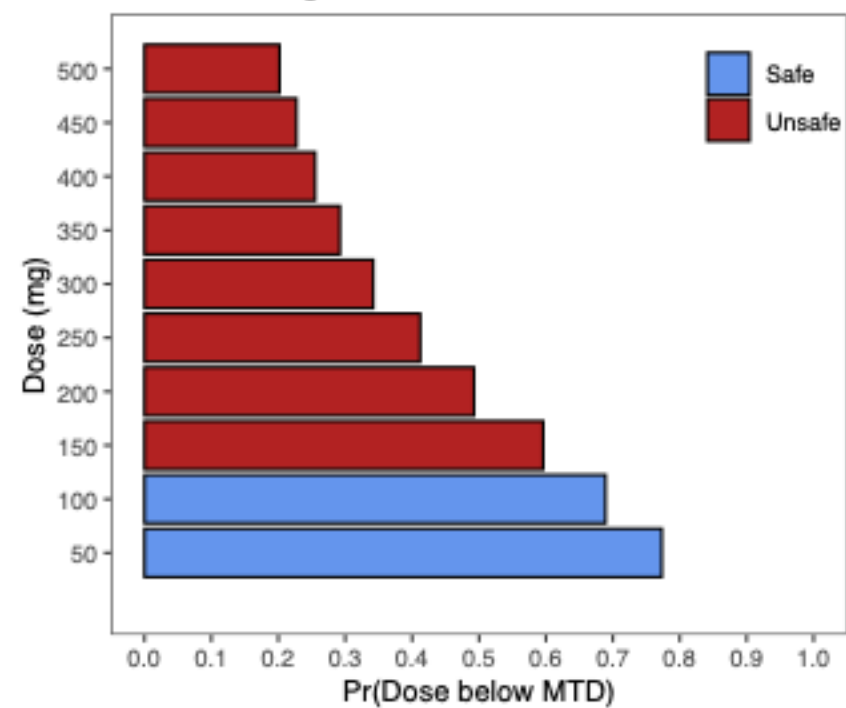
Week 10.7, N=6, Lost=1



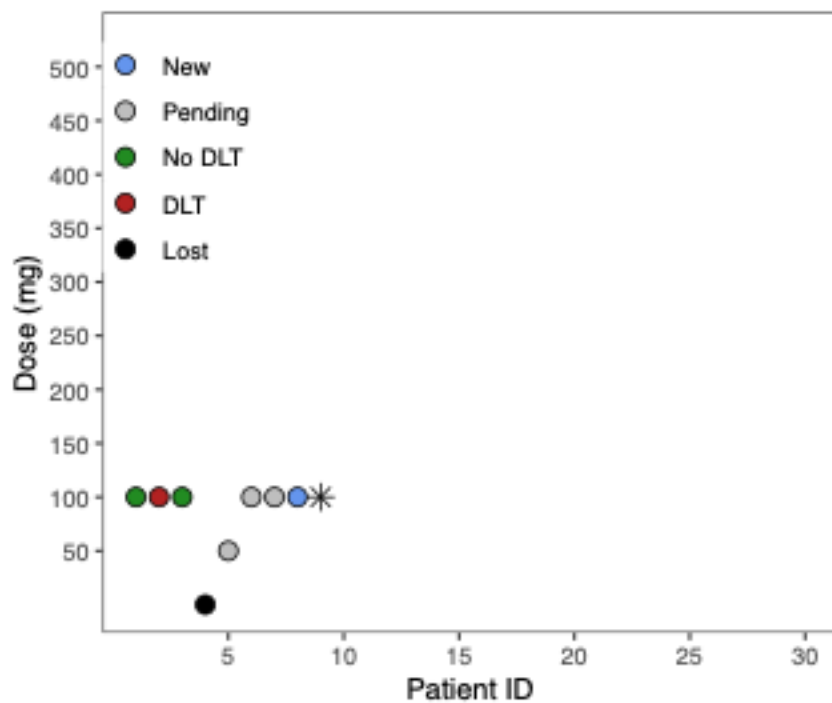
Enrollment Dose: 100 mg



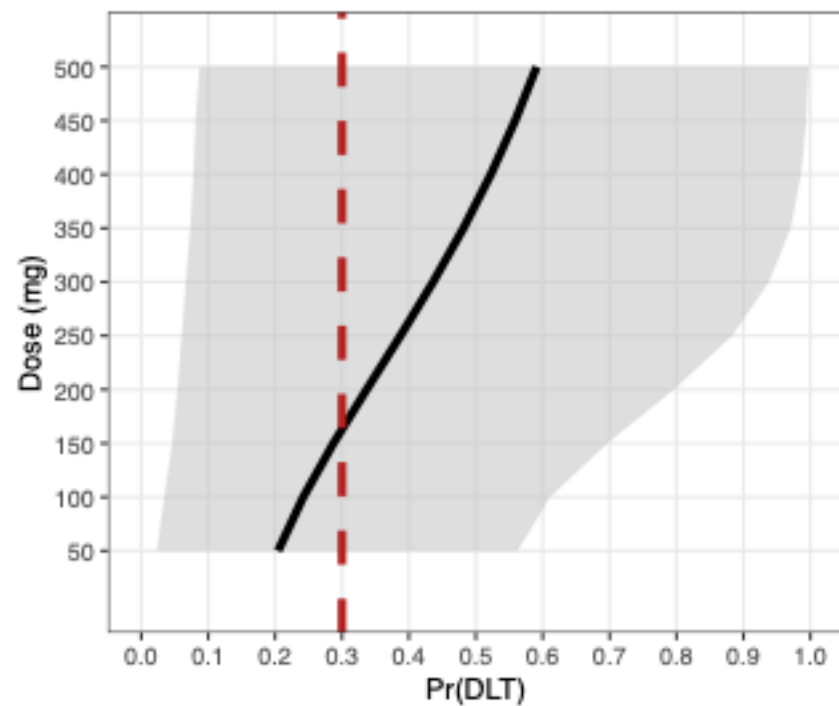
MTD: 100 mg



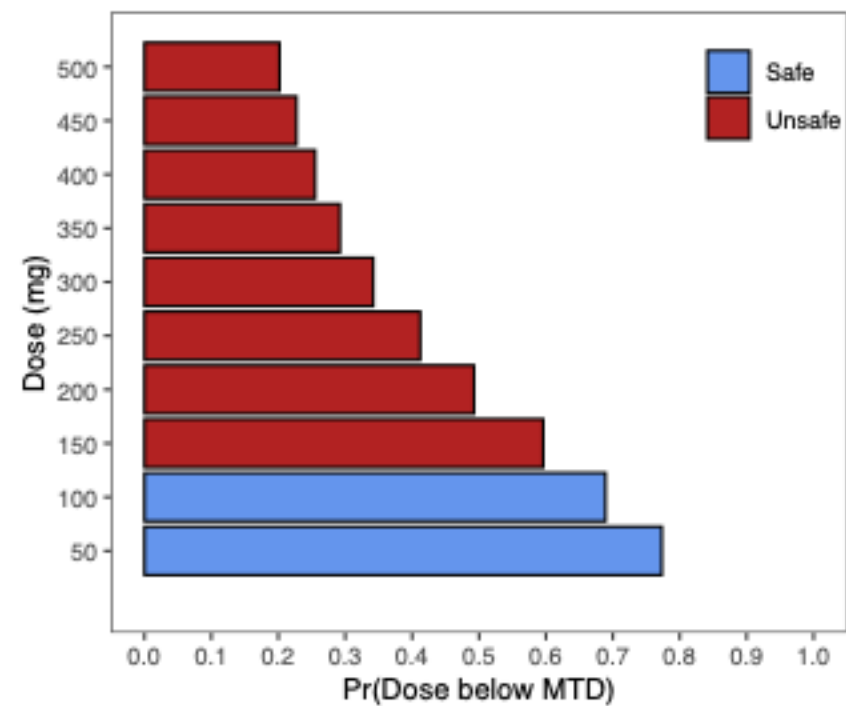
Week 11.8, N=7, Lost=1



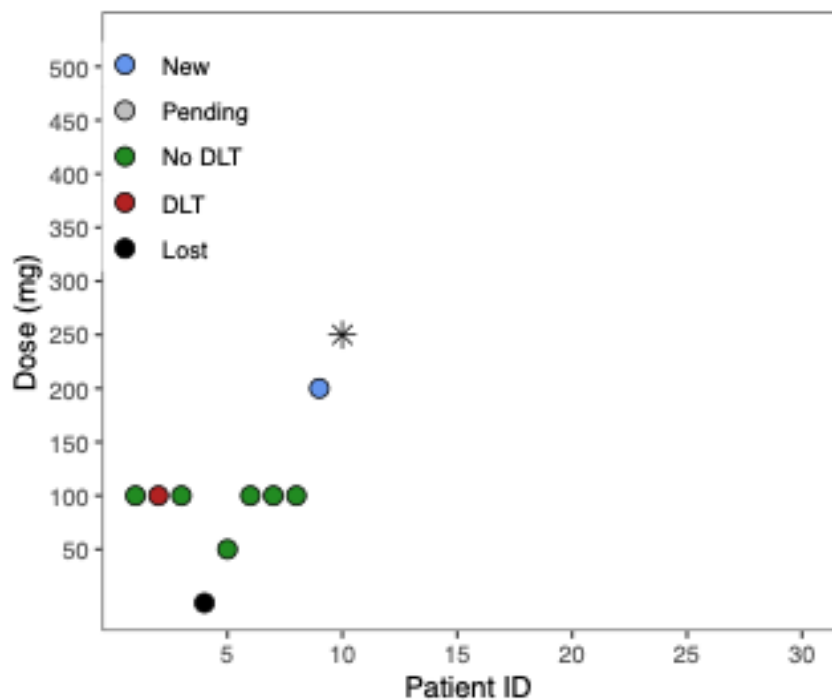
Enrollment Dose: 200 mg



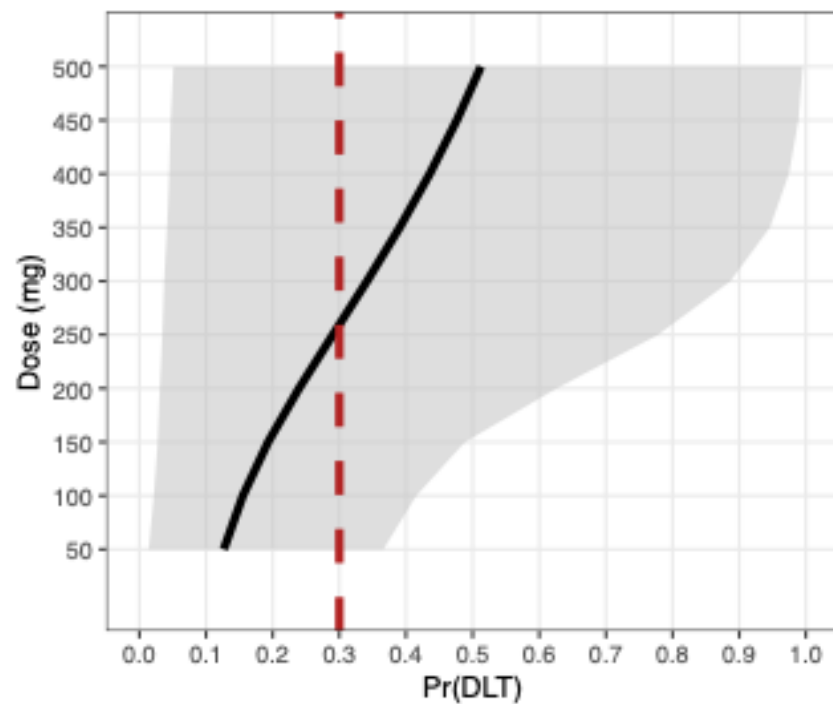
MTD: 100 mg



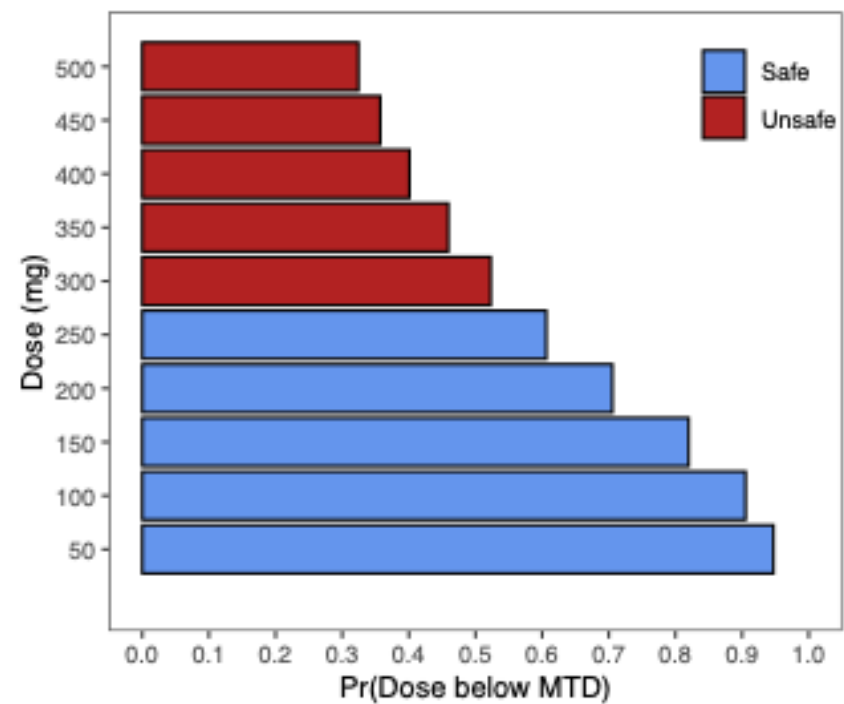
Week 16, N=8, Lost=1



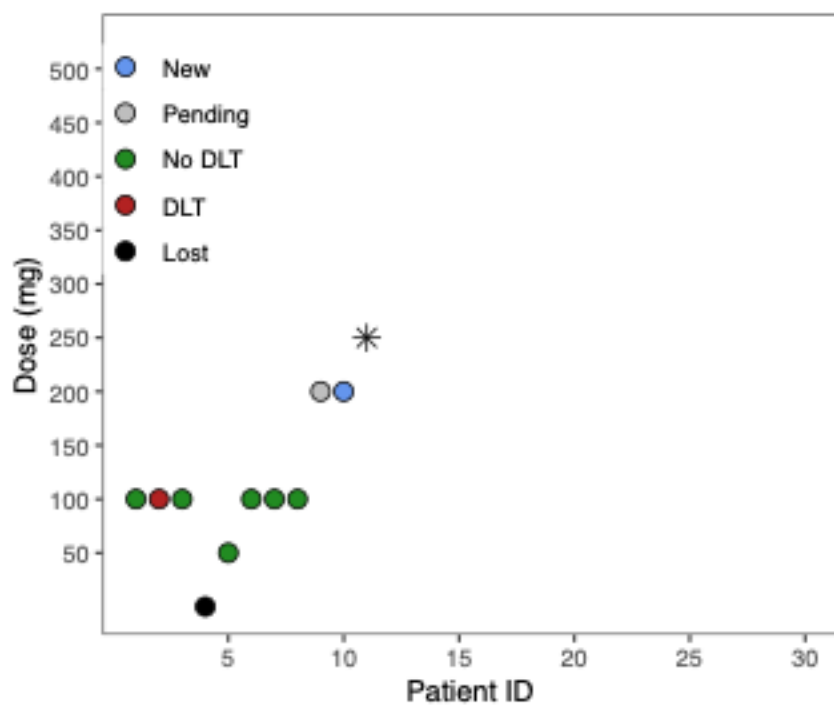
Enrollment Dose: 200 mg



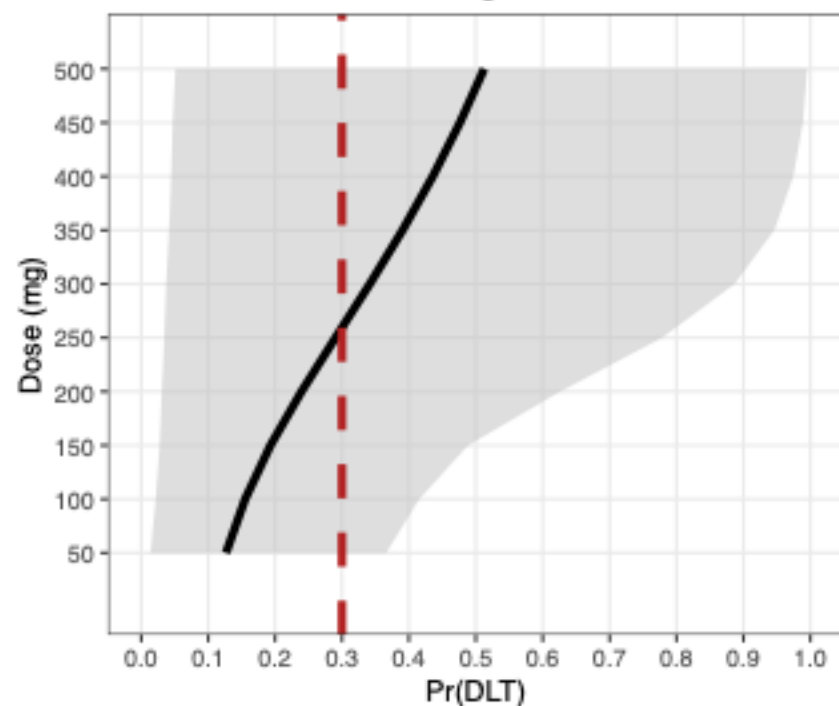
MTD: 250 mg



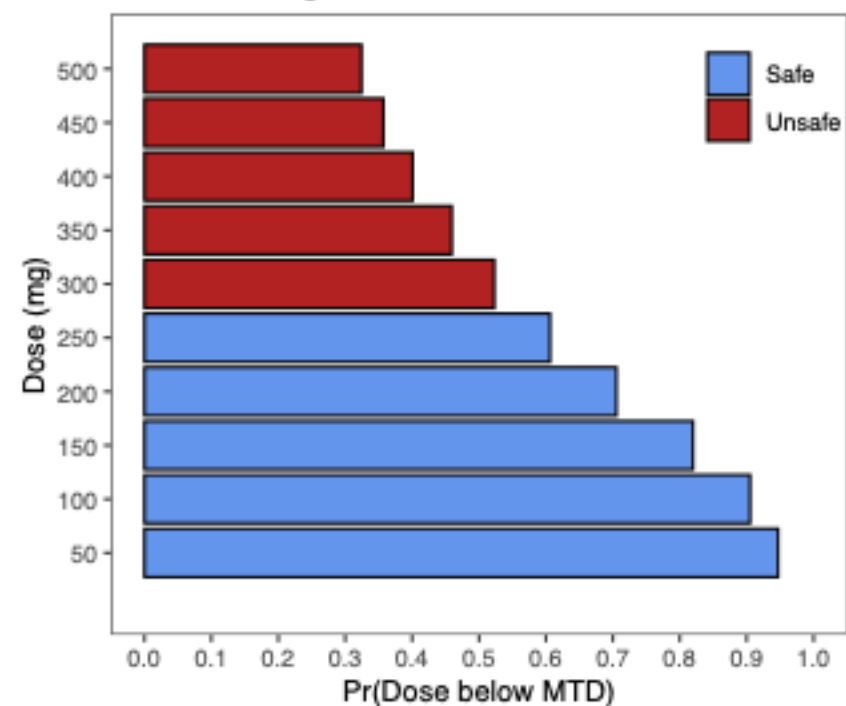
Week 16.2, N=9, Lost=1



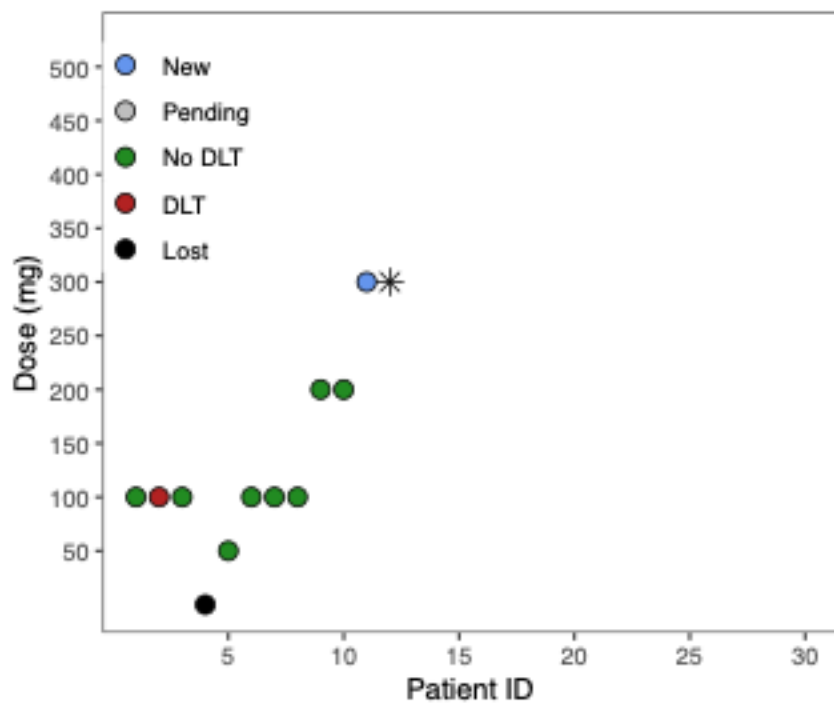
Enrollment Dose: 300 mg



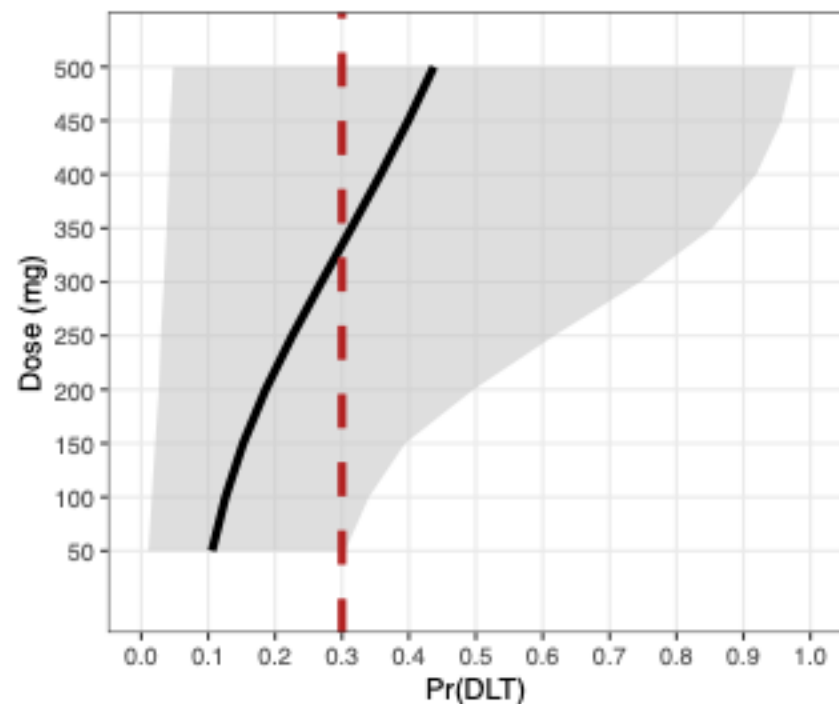
MTD: 250 mg



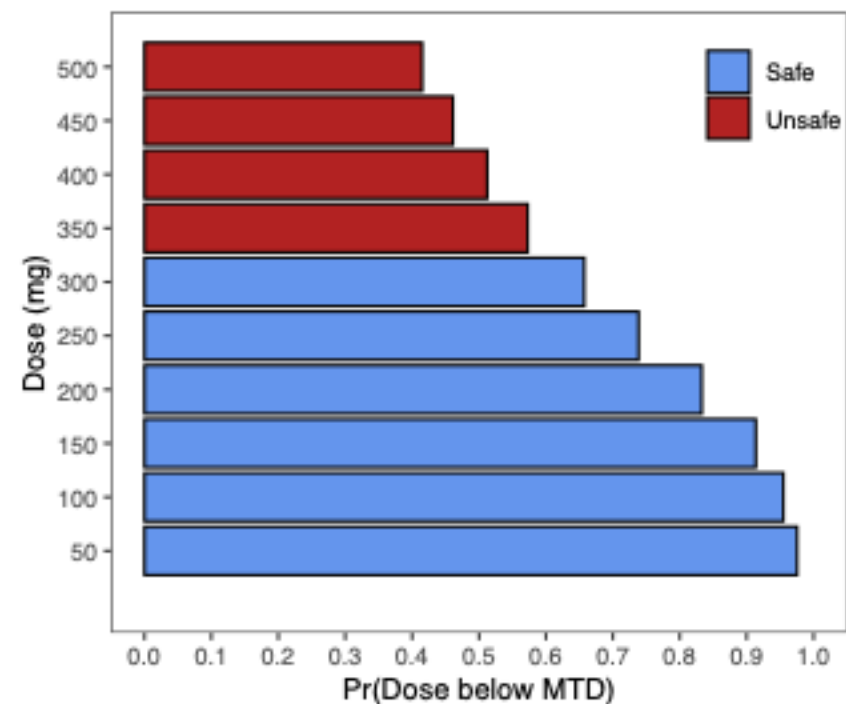
Week 20.3, N=10, Lost=1



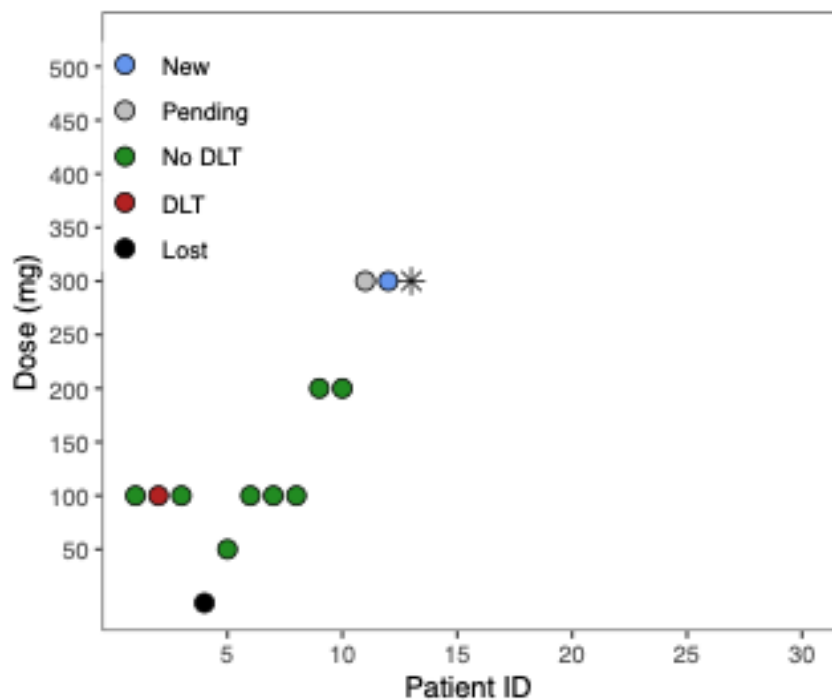
Enrollment Dose: 300 mg



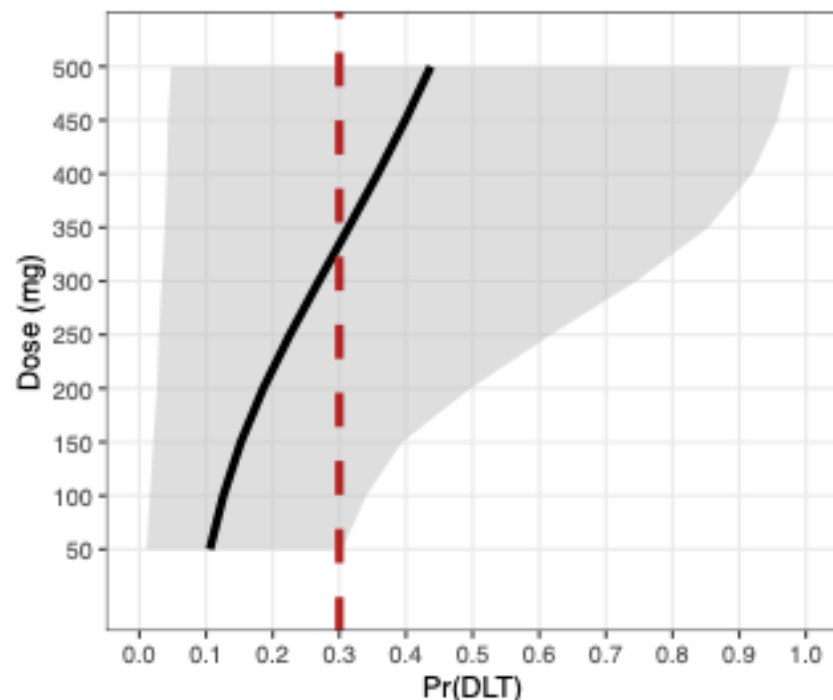
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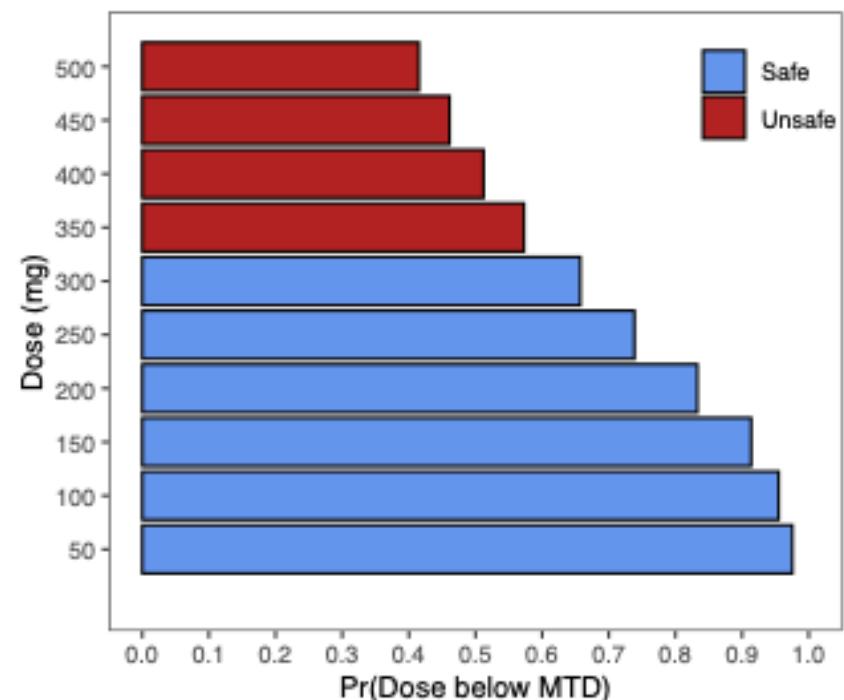
Week 21.1, N=11, Lost=1



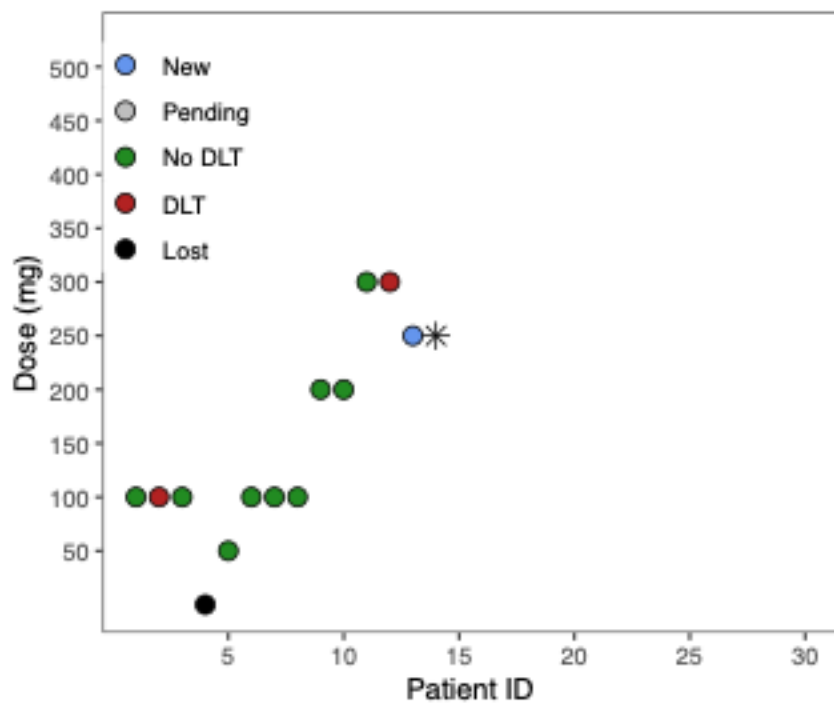
Enrollment Dose: 250 mg



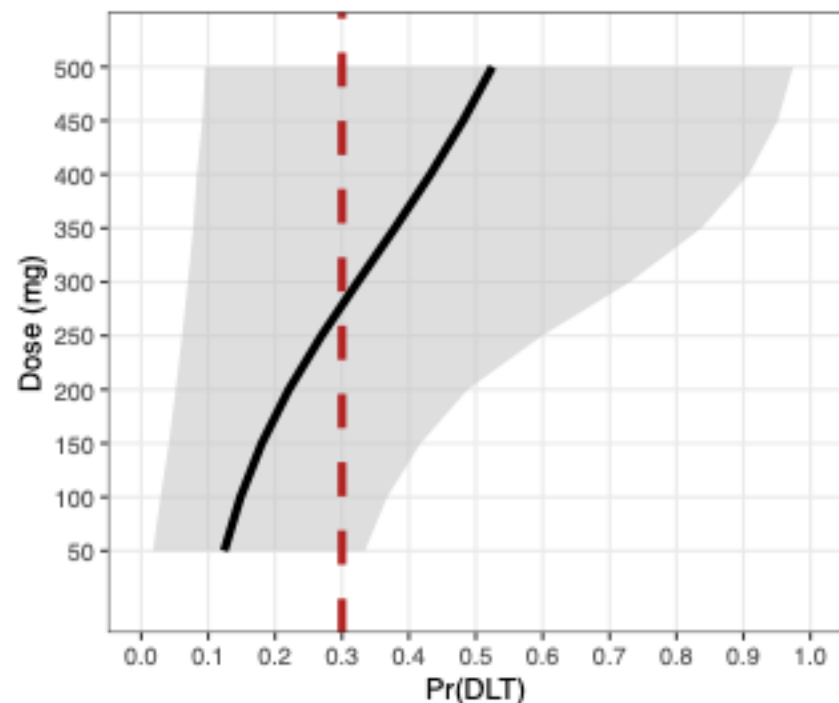
MTD: 300 mg



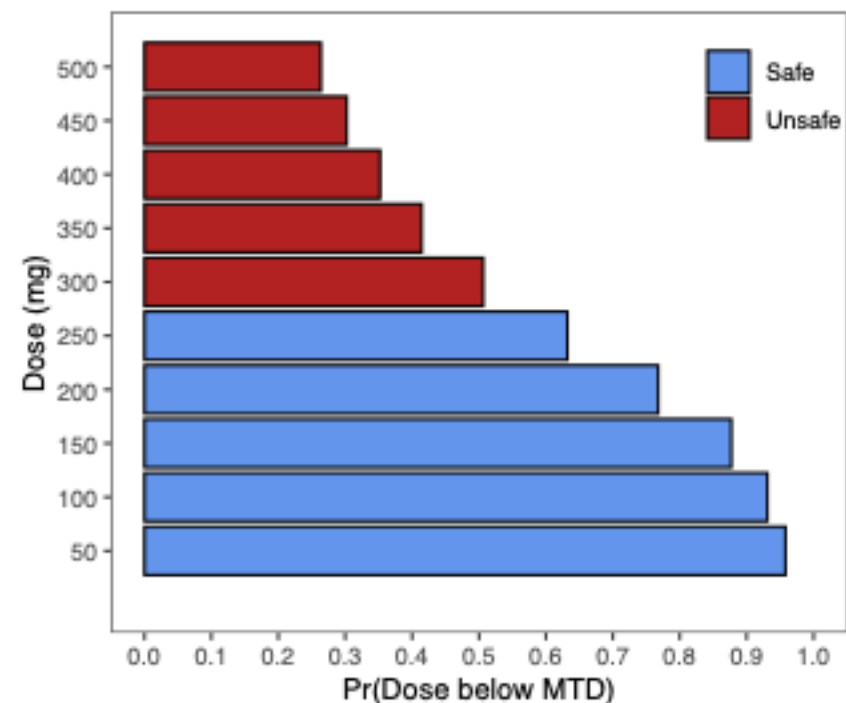
Week 25.3, N=12, Lost=1



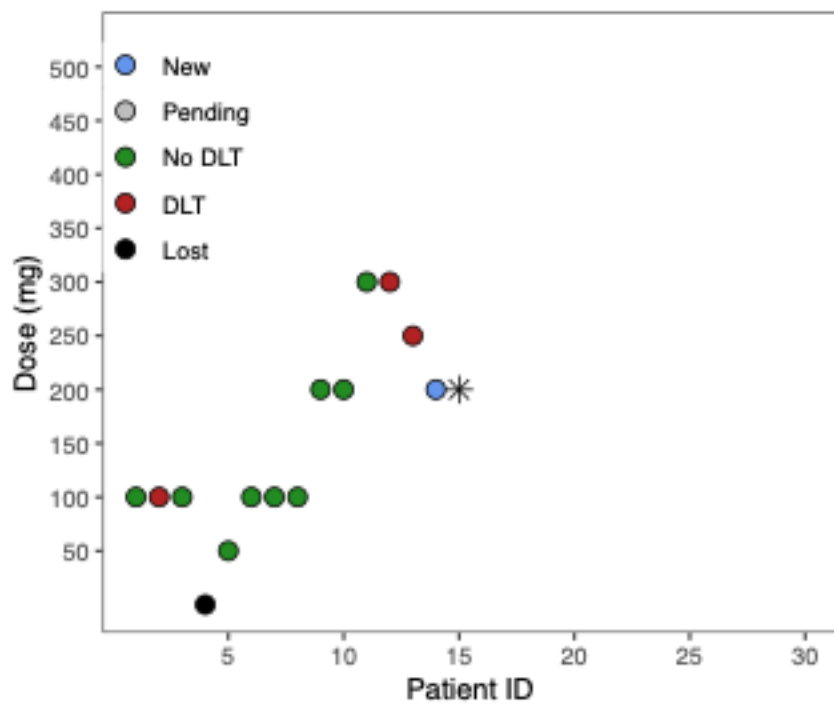
Enrollment Dose: 200 mg



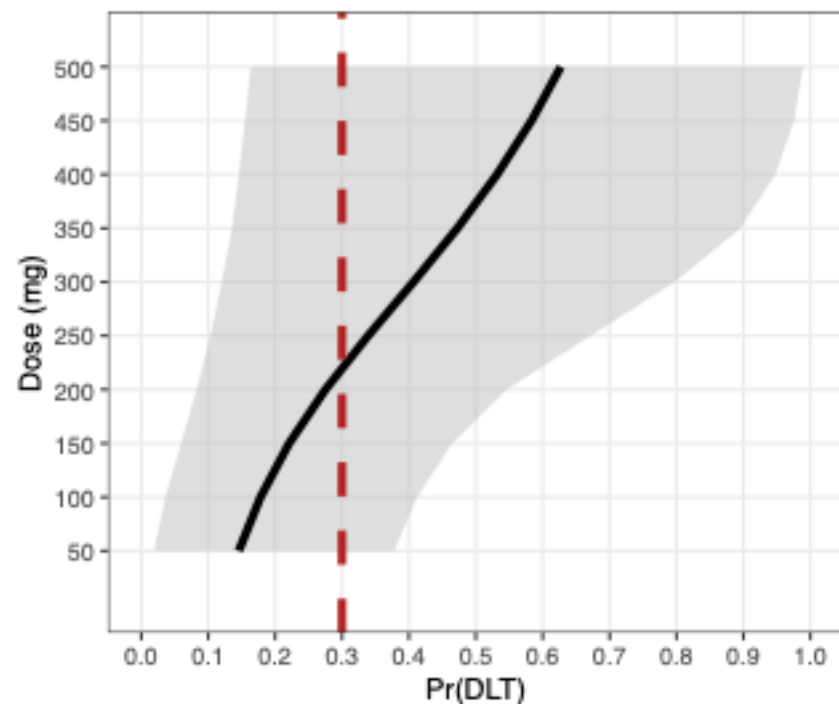
MTD: 250 mg



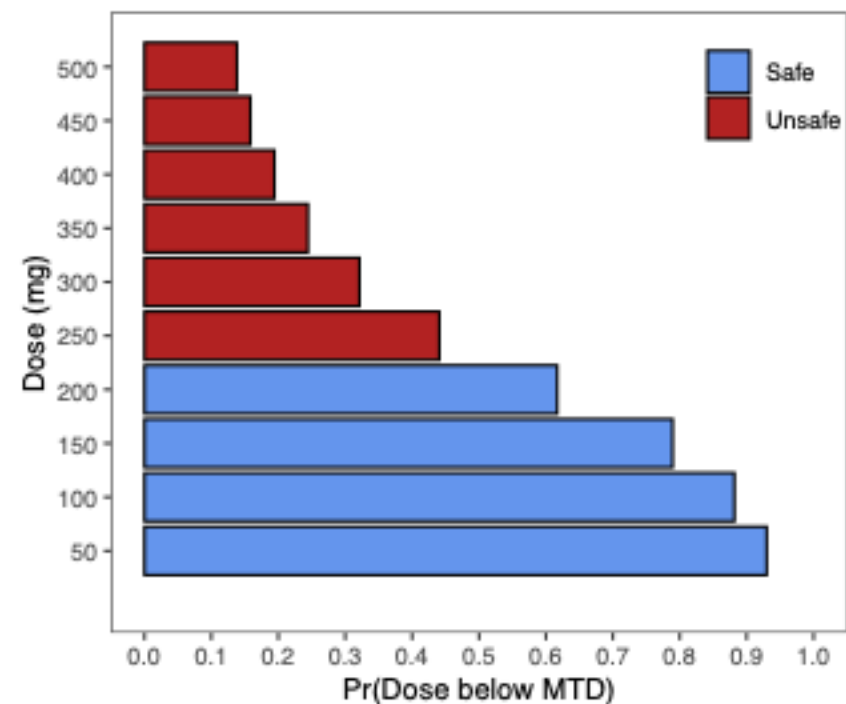
Week 29.4, N=13, Lost=1



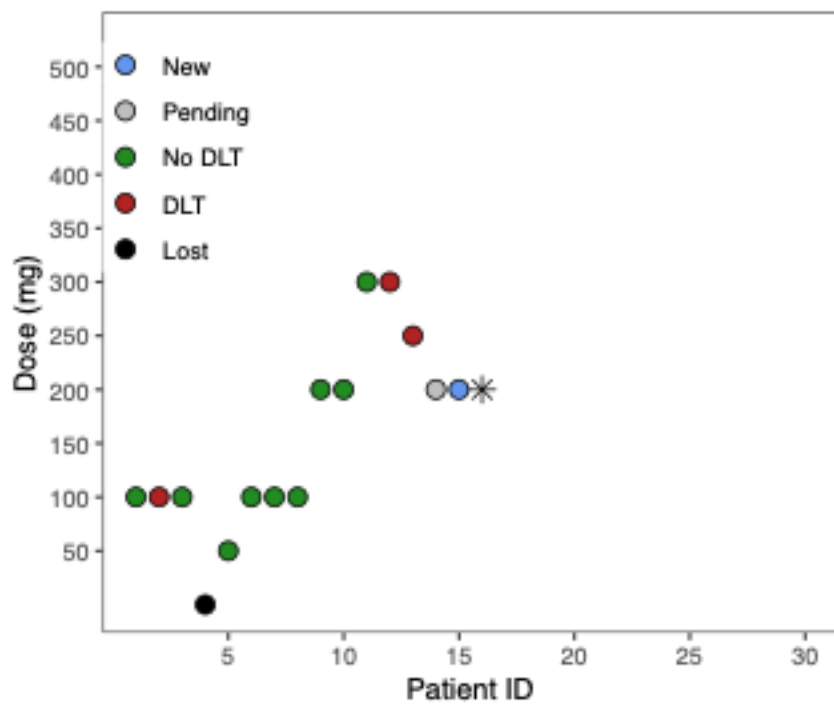
Enrollment Dose: 200 mg



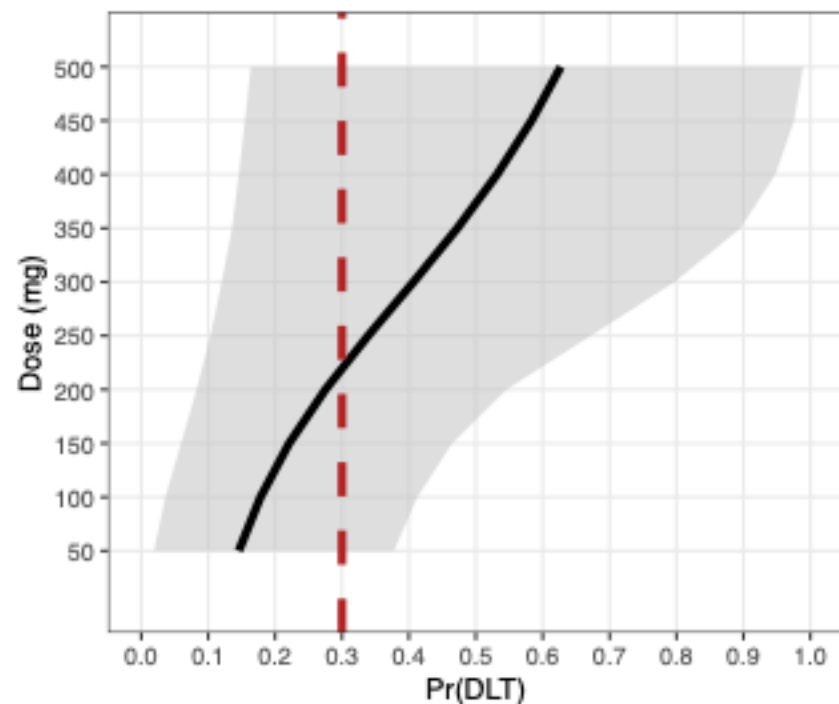
MTD: 200 mg



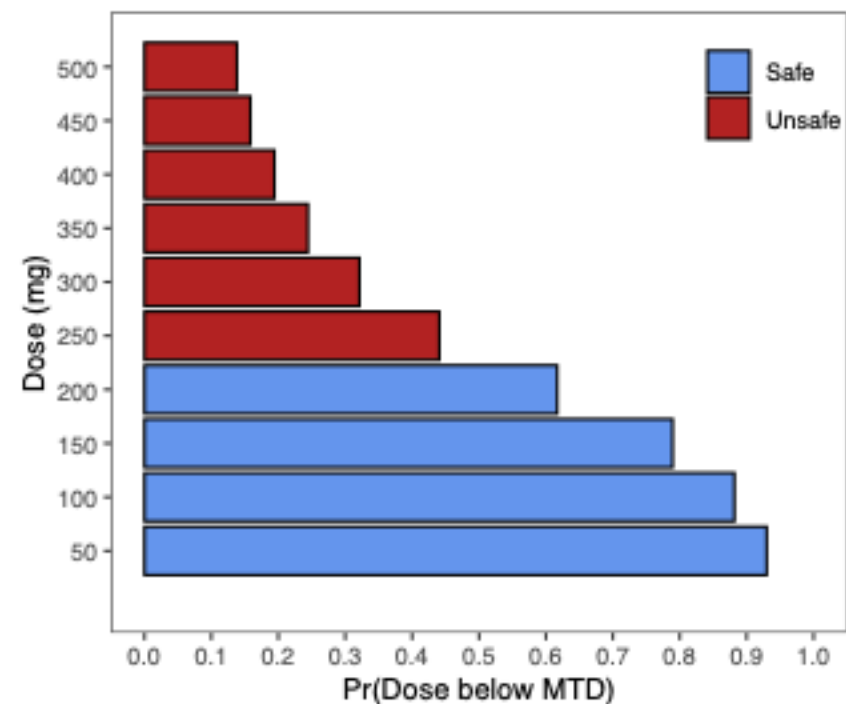
Week 32.2, N=14, Lost=1



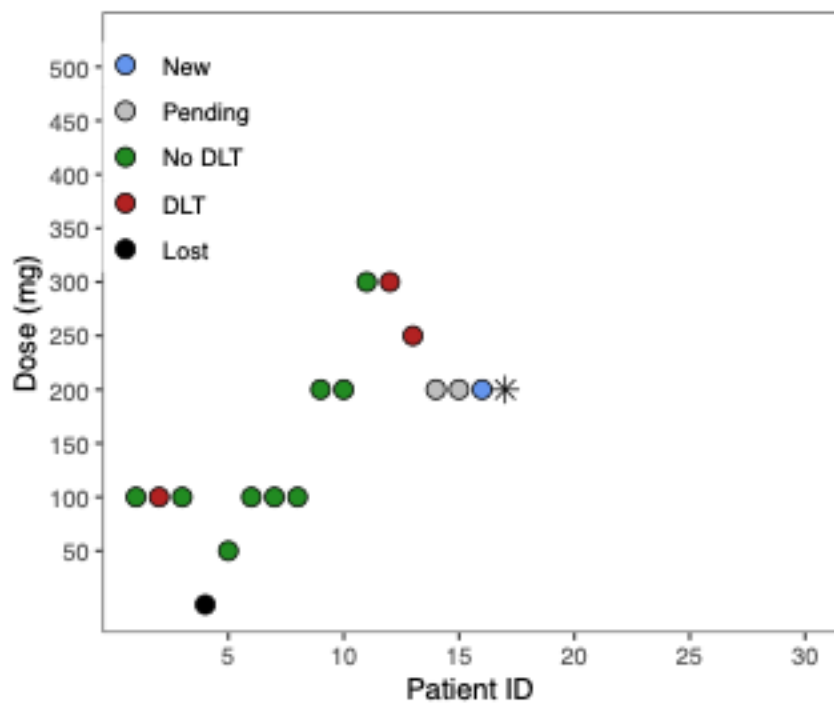
Enrollment Dose: 200 mg



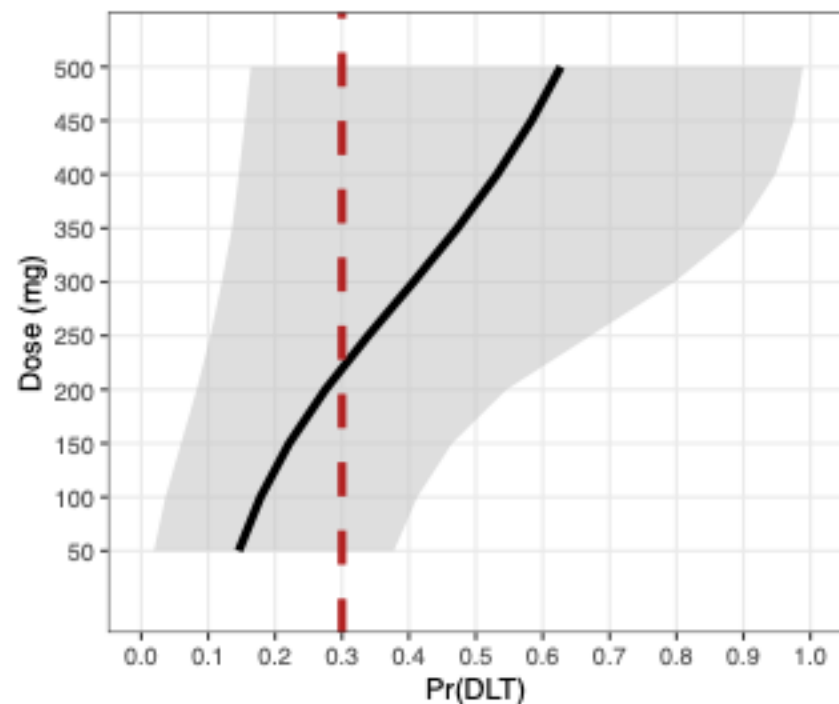
MTD: 200 mg



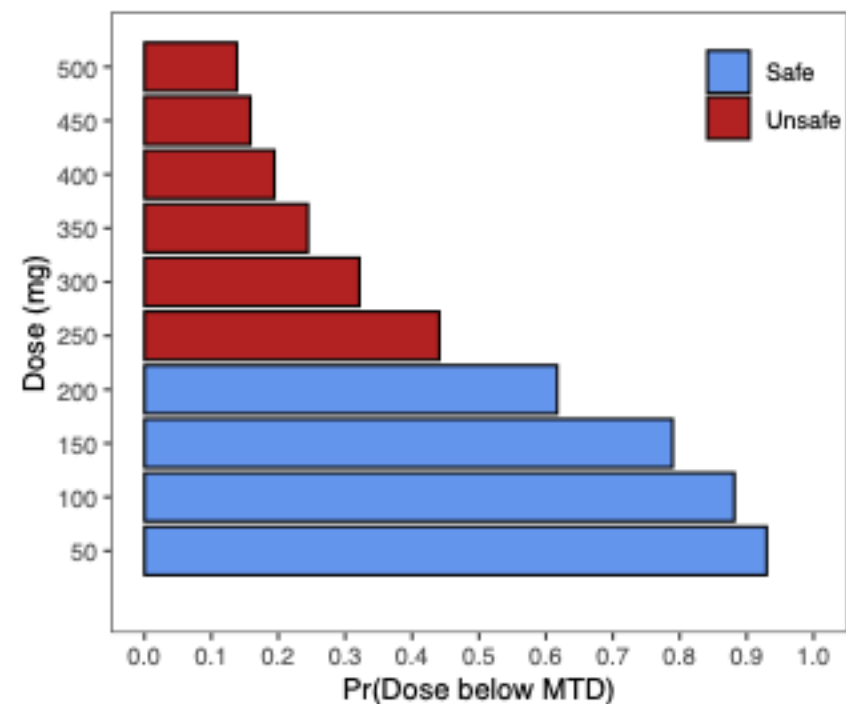
Week 33.1, N=15, Lost=1



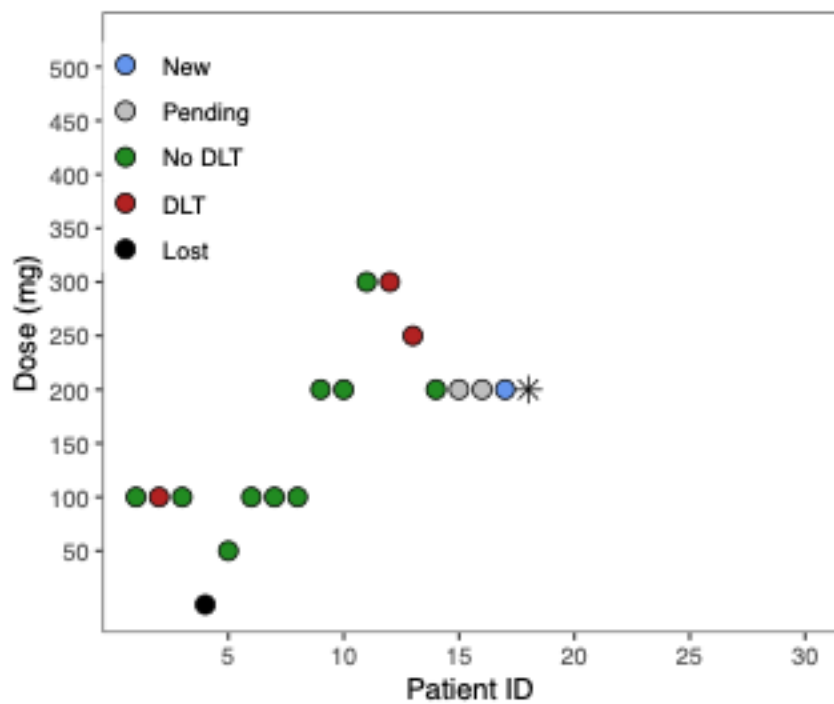
Enrollment Dose: 200 mg



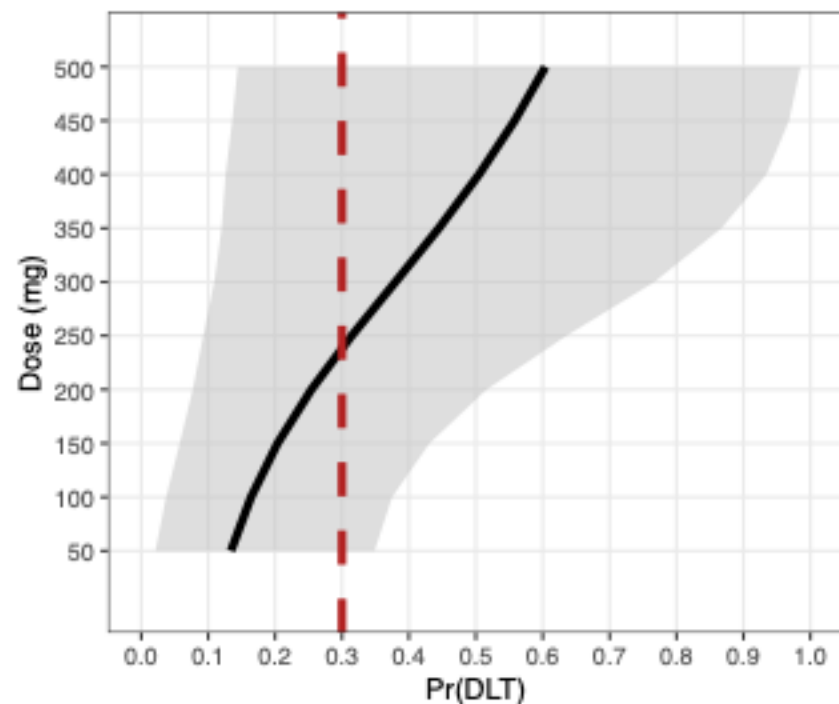
MTD: 200 mg



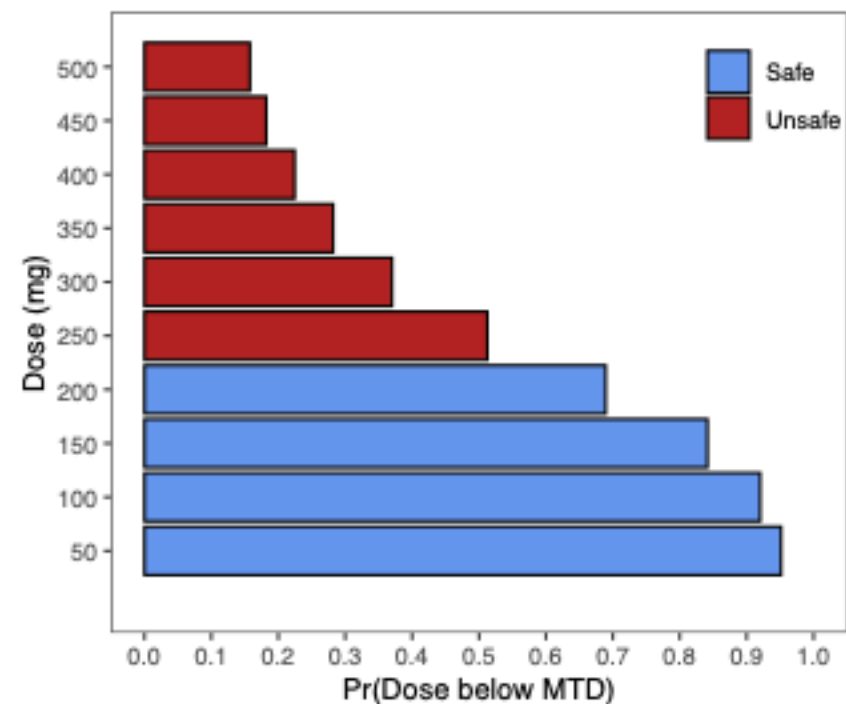
Week 33.8, N=16, Lost=1



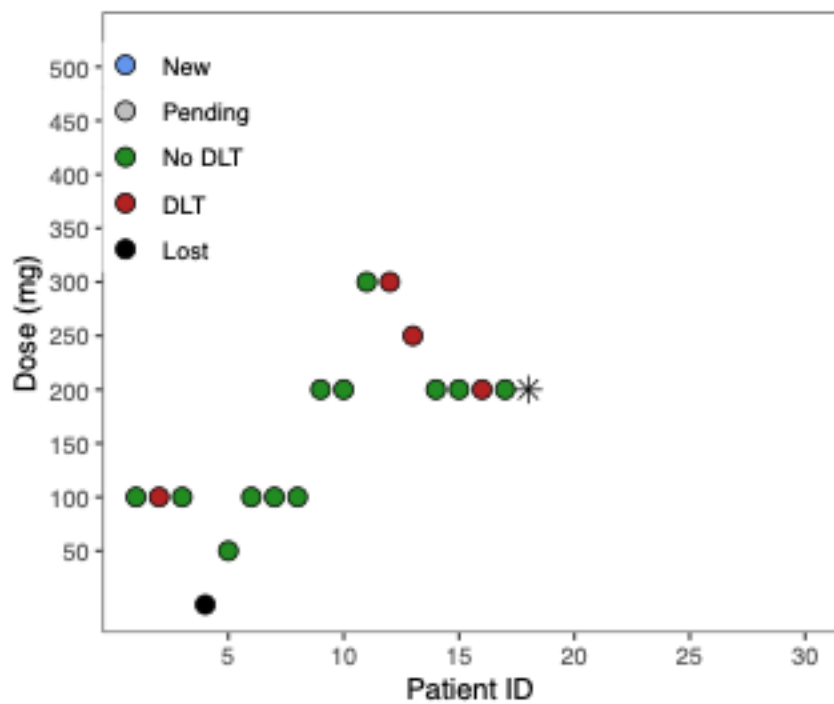
Enrollment Dose: 200 mg



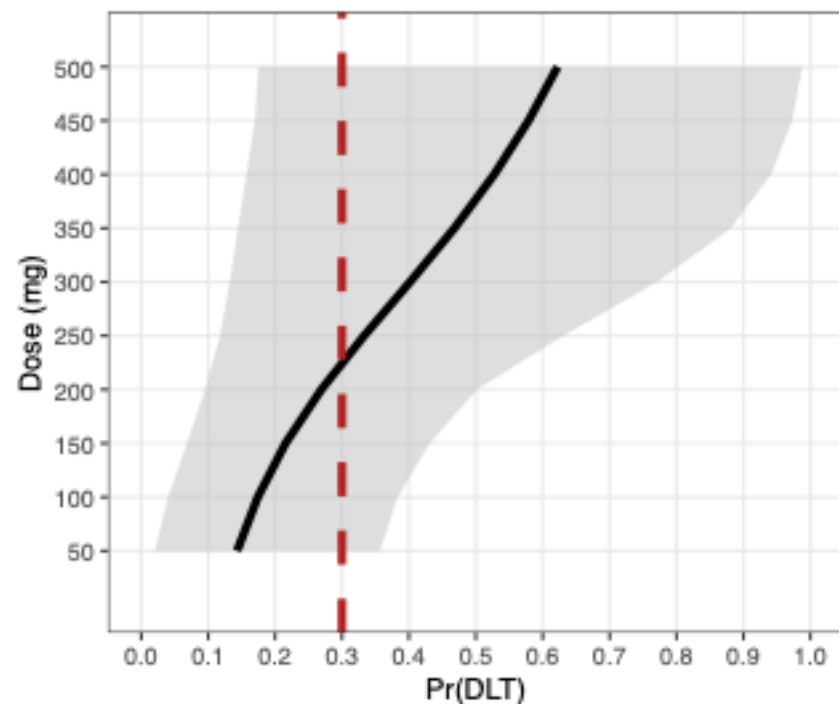
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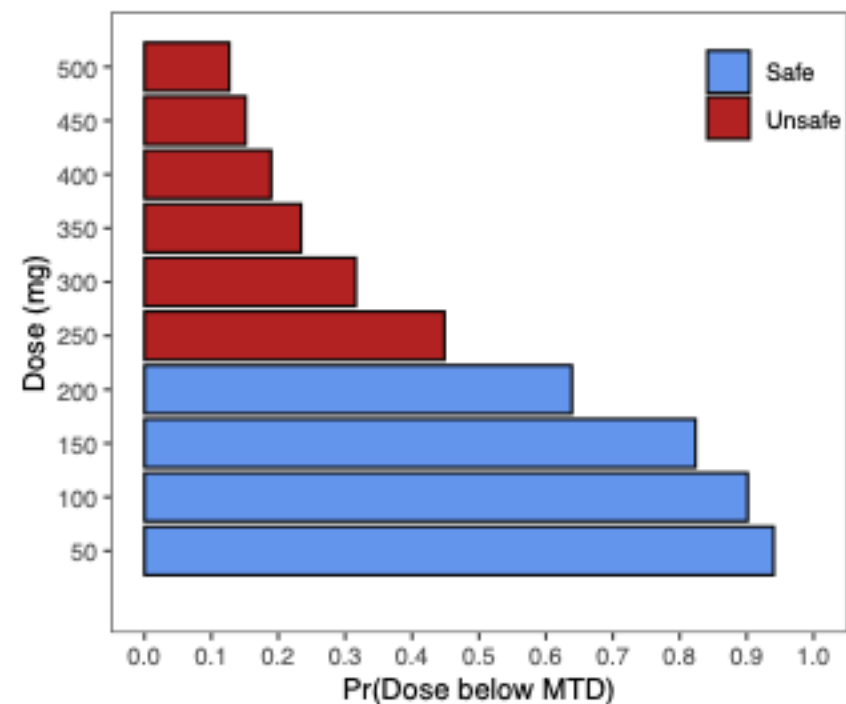
Week 37.8, N=16, Lost=1



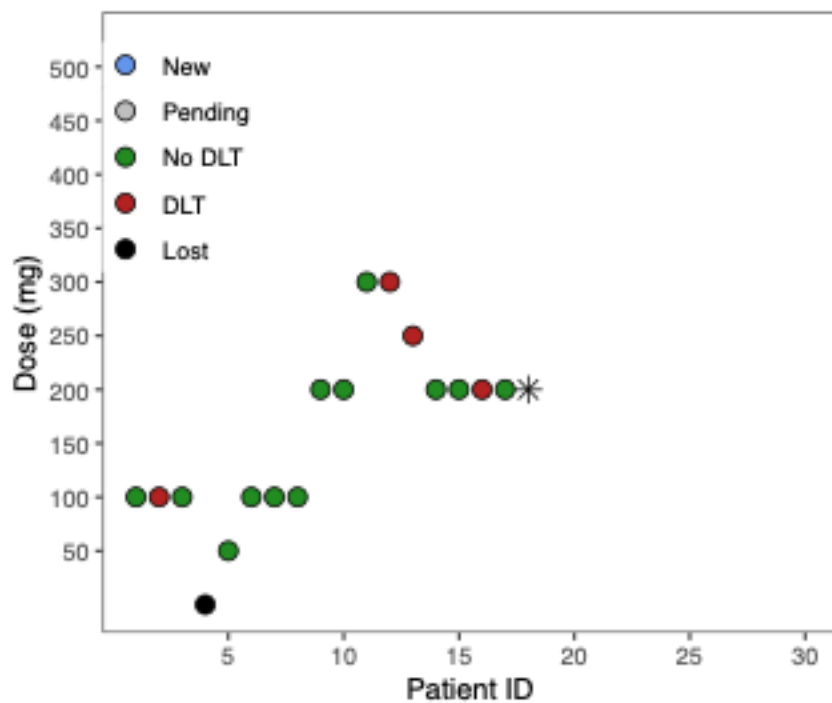
Enrollment Dose: 200 mg



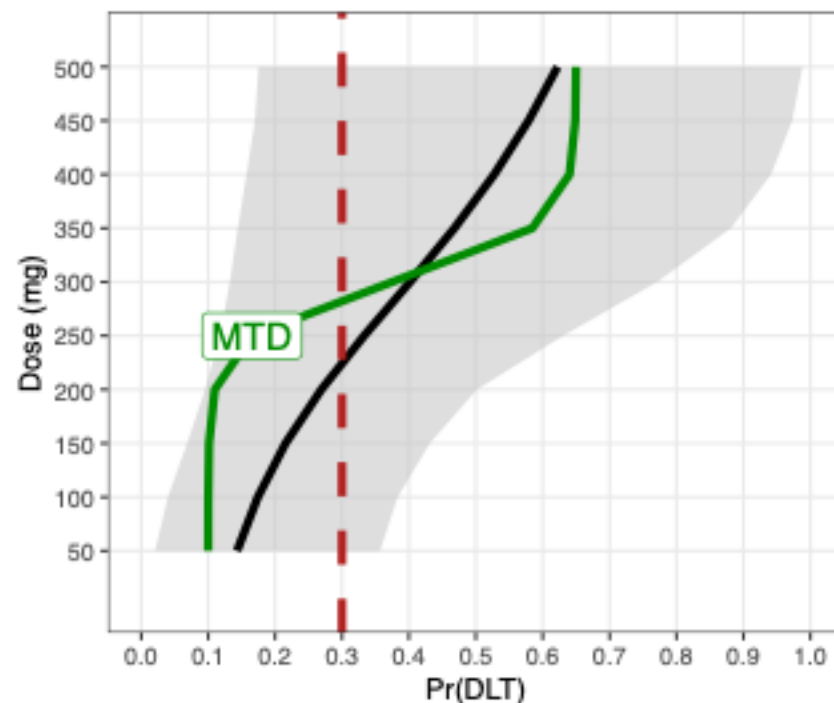
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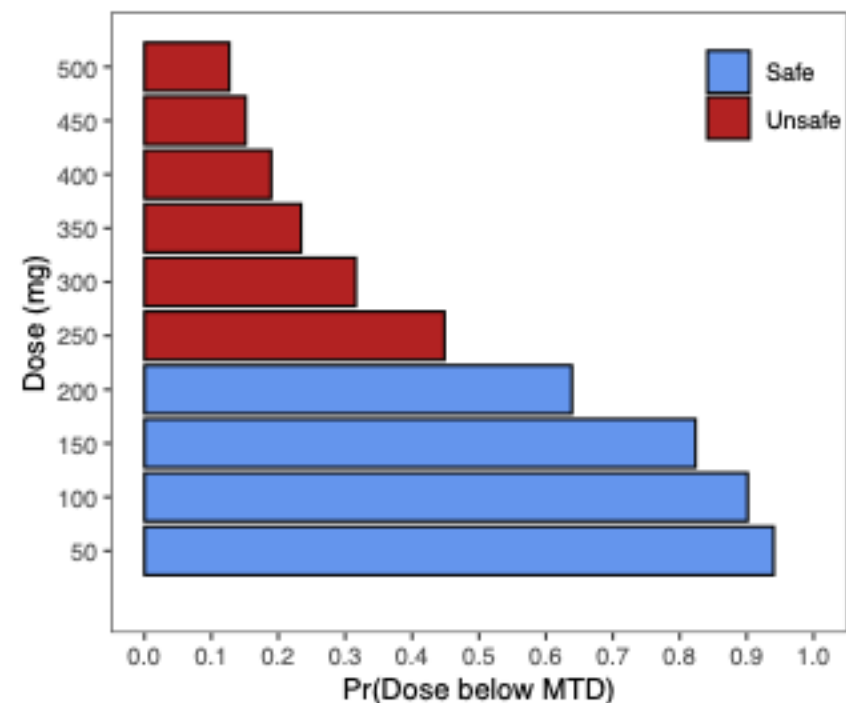
Week 37.8, N=16, Lost=1

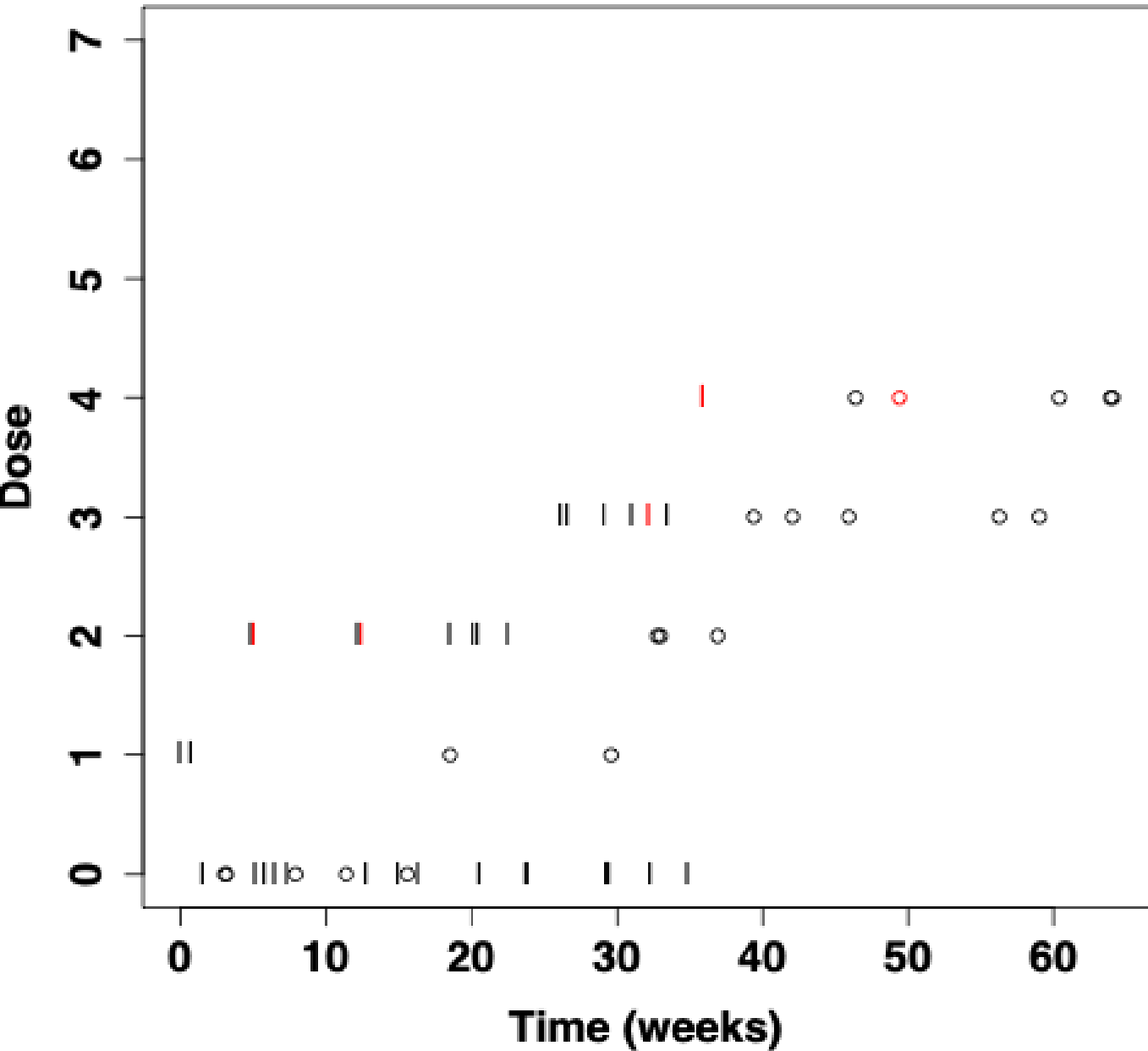


Enrollment Dose: 200 mg



MTD: 200 mg





- Lines are adults (ALL)
- Circles are pediatric patients
- Modeled together to allow peds to accelerate escalation

Broglia KR, Sandalic L, Albertson T, Berry SM (2015) Bayesian Dose Escalation in Oncology with Sharing of Information Between Patient Populations. *Contemporary Clinical Trials*, 44, 56-63, doi: 10.1016/j.cct.2015.07.003.

Evolution...

- A pushback on the “complexity” of the designs using model-based approaches
- A desire for the ease of ‘rule-based’ tables!
- Development of mTPI/BOIN designs
- BOIN: Bayesian Optimal INterval Designs

BOIN

- Define a **target toxicity rate** p_T
- Define a **target interval** around p_T , the “Equivalence Interval” EI $[p_T - \varepsilon_1, p_T + \varepsilon_2]$, $[p_l, p_u]$
- Calculate the “optimal” boundaries that minimize incorrect (E, S, D) decisions.
- $\lambda_l = \log\left(\frac{1-p_l}{1-p_T}\right) / \log\left(\frac{p_T(1-p)}{p_l(1-p_T)}\right)$,
- $\lambda_u = \log\left(\frac{1-p_T}{1-p_u}\right) / \log\left(\frac{p_u(1-p_T)}{p_T(1-p_u)}\right)$
- If x is the number of **observed toxicities at dose d** , and n the total number of observations, then
 - If $x/n < \lambda_l$ then **escalated** to the next dose.
 - Else if $\lambda_l < x/n < \lambda_u$ then **stay** at this dose.
 - Else if $x/n > \lambda_u$ then **de-escalate**
- If at the highest dose, stay instead of escalate, if at the lowest dose, stay instead of de-escalate.
- If $Pr(p_d > p_T) > 0.95^*$ **mark dose as unacceptable and de-escalate** (stop trial if at lowest dose). (* in FACTS this is user settable)
- MTD selection **after isotonic regression** as per mTPI (except simply uses observed probabilities)

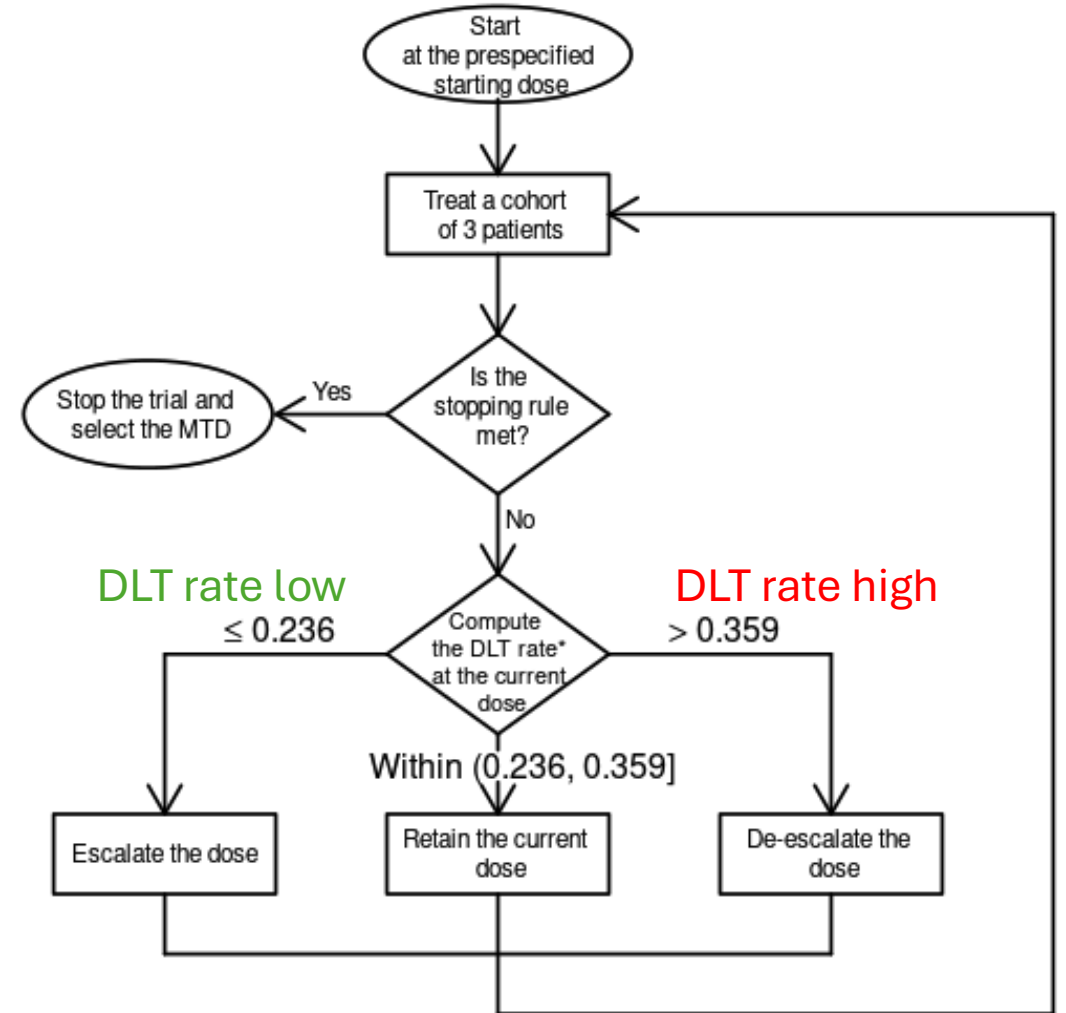
Example BOIN

- 5 dose levels
- Maximum sample size of 18
- Cohorts of size 3
- Accelerated titration for first two dose levels
- Target DLT rate of 30%
 - Escalate if DLT rate below 0.236
 - De-escalate if DLT rate above 0.359

These are all placeholder values that
can be customized

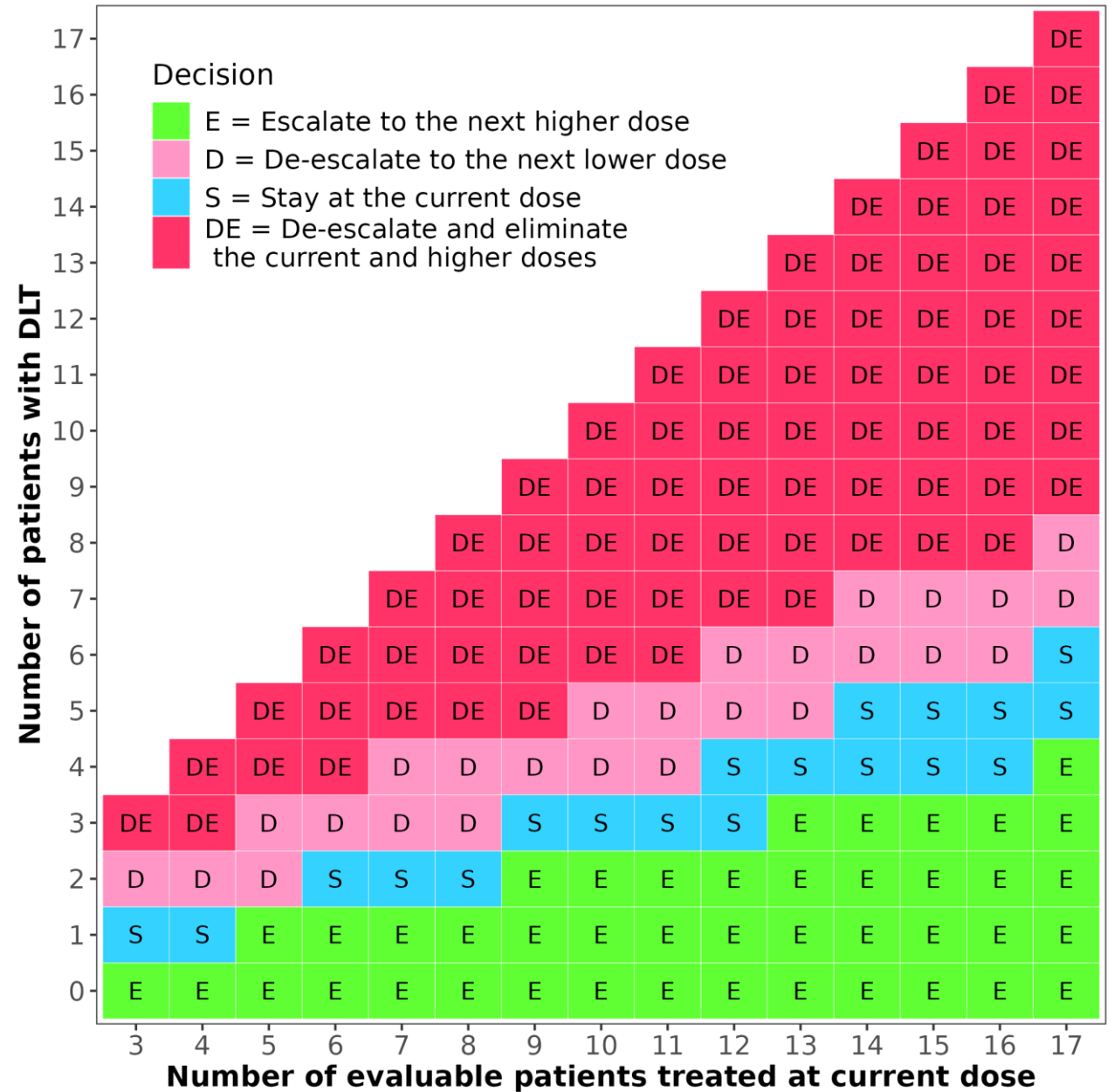
Bayesian Optimal Interval Design (BOIN)

- Simple to implement, similar to 3+3, but more flexible and better ability to identify MTD
- **Escalate**, **stay**, or **de-escalate** dose levels based on the observed DLT rate on the current dose
- Can incorporate accelerated titration design (ATD)



(Figure from [BOIN Shiny app](#))

Decision Table

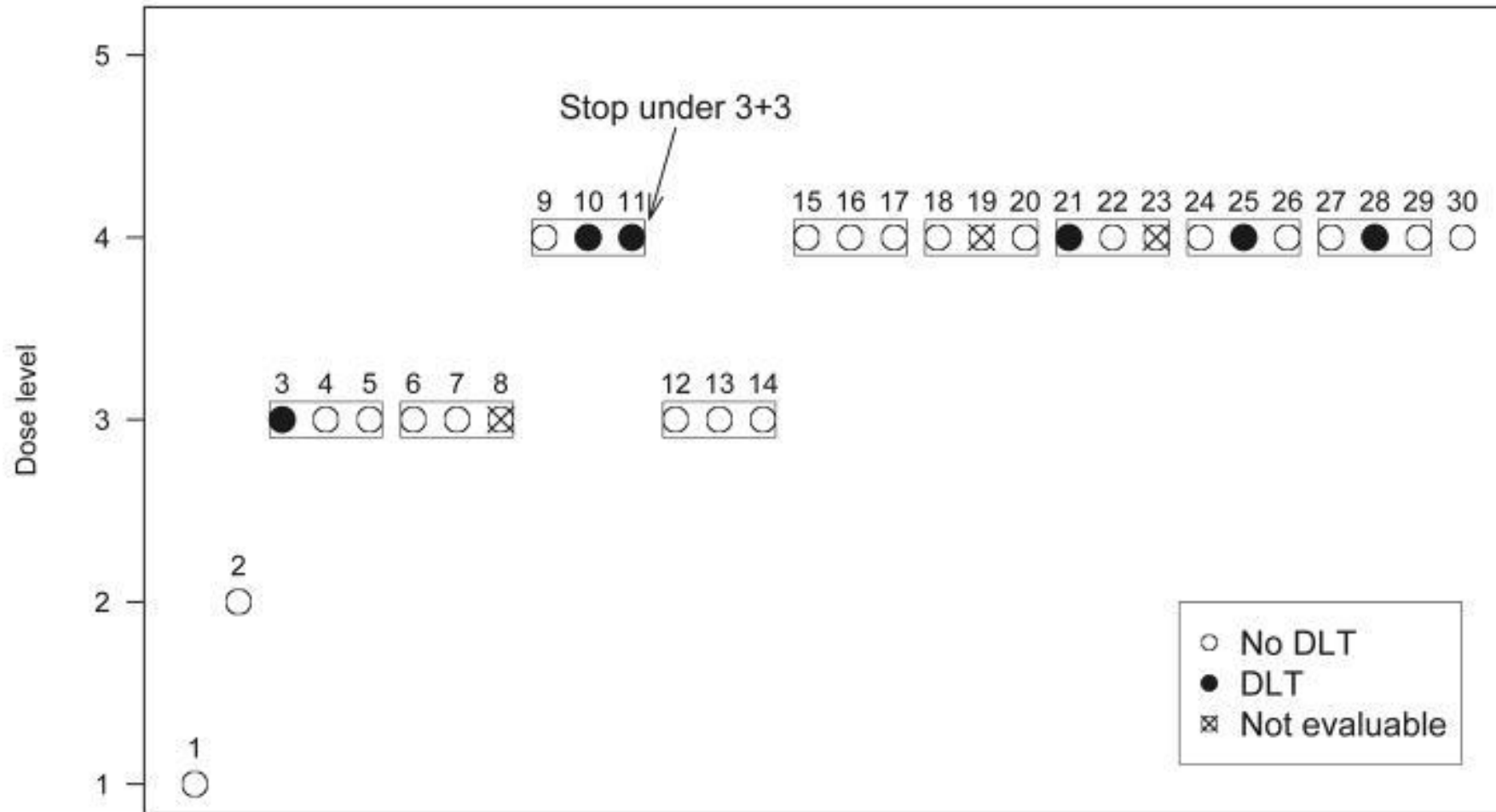


(Figure from [BOIN Shiny app](#))

Selection of the MTD at end of trial

- 3+3 MTD selection rule chooses dose one level below dose that yields 2 or more DLTs (ignoring data on other doses)
- BOIN uses data on all doses and isotonic regression to estimate the MTD

Example Trial



BOIN:

Dose 4 selected as MTD
Estimated DLT Rate (CI) of
29.4% (10%, 56%)

3+3:

Dose 3 selected as MTD
Estimated DLT Rate (CI) of
20% (0.5%, 72%)

Example Simulation Study: The methods:

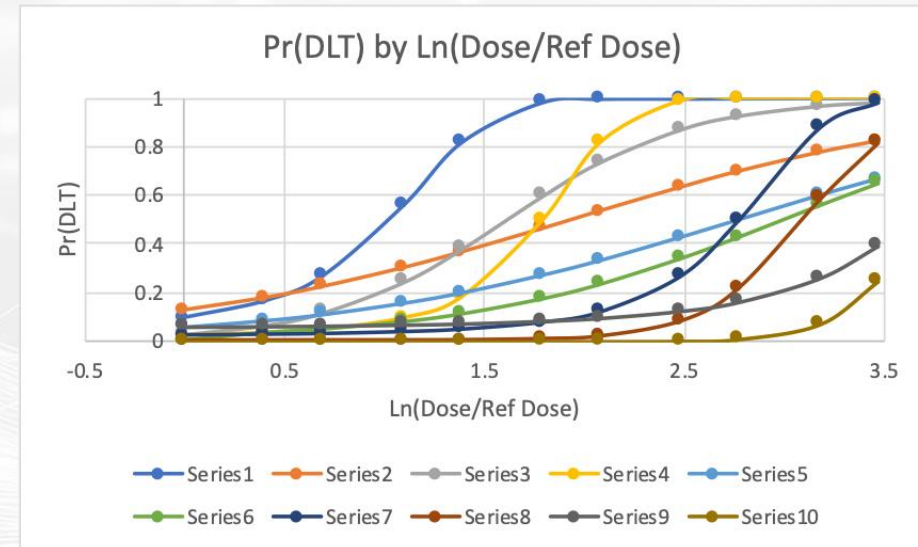
- BLRM / N-CRM / CRM – the CRM as extended by Beat Neuenschwander
 - Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. *Stat Med*. 2008 Jun 15;27(13):2420-39. doi: 10.1002/sim.3230. PMID: 18344187.
- BOIN
 - Yuan Y, Hess KR, Hilsenbeck SG, Gilbert MR. Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials. *Clin Cancer Res*. 2016 Sep 1;22(17):4291-301. doi: 10.1158/1078-0432.CCR-16-0592. Epub 2016 Jul 12. PMID: 27407096; PMCID: PMC5047439.
- I3+3
 - Liu M, Wang SJ, Ji Y. The i3+3 design for phase I clinical trials. *J Biopharm Stat*. 2020 Mar;30(2):294-304. doi: 10.1080/10543406.2019.1636811. Epub 2019 Jul 15. PMID: 31304864.
- mTPI
 - Ji Y, Wang SJ. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. *J Clin Oncol*. 2013 May 10;31(14):1785-91. doi: 10.1200/JCO.2012.45.7903. Epub 2013 Apr 8. PMID: 23569307; PMCID: PMC3641699.
- mTPI2
 - Guo W, Wang SJ, Yang S, Lynn H, Ji Y. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. *Contemp Clin Trials*. 2017 Jul;58:23-33. doi: 10.1016/j.cct.2017.04.006. Epub 2017 Apr 27. PMID: 28458054.

Example Design to simulate

- 6 doses: 25mg, 50mg, 100mg, 200mg, 400mg, 800mg
- 11 doses: 25mg, 37.5mg, 50mg, 75mg, 100mg, 150mg, 200mg, 300mg, 400mg, 600mg, 800mg
- Target: target DLT of 0.225, interval of 0.15-0.3
- 10 scenarios:
 - MTD at 37.5mg, 50mg, ... , 800mg – at each dose except 25mg.
 - Mixing steep and shallow gradients, created using FACTS 4 different parametric models (for response generation) – only 1 matches the BLRM model for analysis
- All designs use cohorts of 3, with a max sample size of 45 (15 cohorts).

BERRY

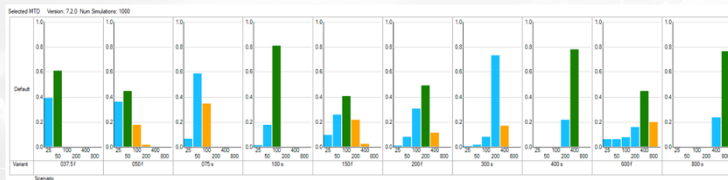
Scenarios



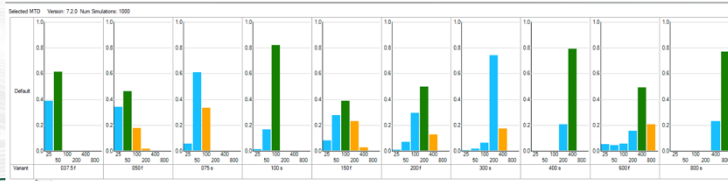
BERRY

Results i3+3, BOIN

i3+3

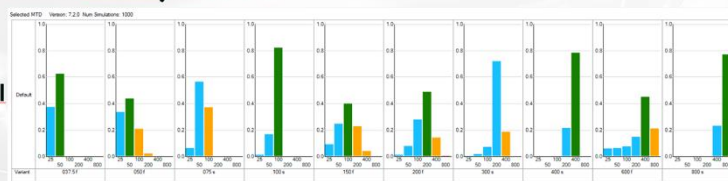


BOIN

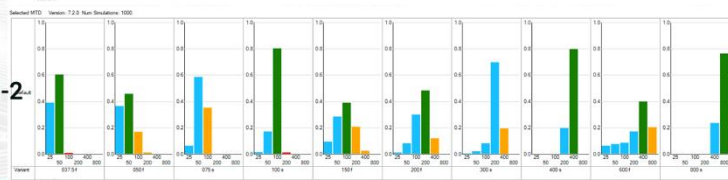


Results mTPI, mTPI-2

mTPI

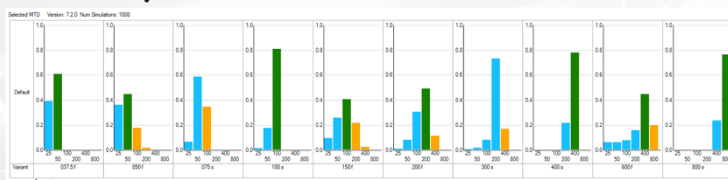


mTPI-2

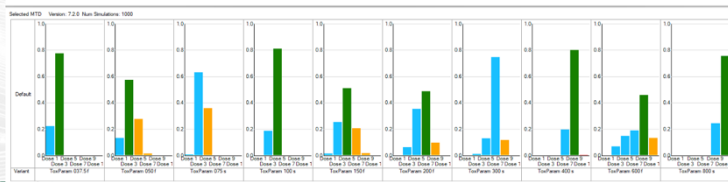


Results i3+3, CRM

i3+3



CRM



Summary

- i3+3, BOIN, mTPI & mTPI-2 results very similar (almost indistinguishable). Note that in the BOIN paper the distinct advantage of BOIN over mTPI is seen when the target toxicity is 0.15 or 0.2.
- The CRM (NCRM) has as distinct advantage in the scenarios where the MTD is at the lower doses, in particular: 037.5f, 050f, 150f.
- To try to get a clearer view we will look at the numeric results:
 - Number of subjects enrolled
 - Ppn of subjects experiencing toxicity
 - Ppn of times a dose with a true toxicity in the range [0.15, 0.3] is selected as MTD.
 - Loss score where score is:
 - 0 for selecting dose in the target range.
 - Ppn of times selected * 200 * (DLT rate – upper bound of target range) if above range.
 - Ppn of times selected * 100 * (lower bound of target range – DLT rate) if below range.

Phase 1 Oncology

- Lots of Methods!
- Given **Project Optimus** lots of focus on backfilling and inclusion of efficacy
- Continuous enrollment (backfilling, frontfilling)
- Modeling to incorporate different schedules, combinations, populations, grade 2 toxicities
- Huge incentive to create prospective adaptive design that prevents continual “protocol amendments”
- Continued research to new methods – remain reasonably “unique” in the drug development space given focus on “desired level of DLT rates”