Designing a seamless P1/P2a open enrollment CRM dose escalation study

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Elias Laurin Meyer

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Trial Background

- Fictitious, but using learnings from actual trials BC has designed
- First-in-human study of novel compound
- Animal data and first PK/PD data exist
- Preparing for IND submission
- Not a small Biotech – not interested in only P1 PoC, but going all the way to registration
- Ideally skip P2 altogether and at the end of this P1/P2a go to a seamless P2/P3

- → Keeping in mind Project Optimus and learning not only about MTD but also about “optimal dose” as soon as possible and seamlessly

General Design Requirements

- DLT observation period 14 days
- TTL of 25%; acceptable limits 15% - 35%
- Have at most three trial participants simultaneously in DLT period at new dose levels or MTD estimate (coming from 3+3)
- Starting dose 100mg, available doses 100mg – 350mg in 25mg steps
  - Aim before P2/P3 is to identify “correct optimal” dose +-25mg
  - Therapeutic effect a priori assumed to start around 175mg
- Efficacy observation period 4 weeks (not final endpoint, based on PK/PD model)
- Maximum sample size to determine MTD of 60 (phase 1)
- Another (up to) 50 trial participants available to determine dose-response (phase 2a)

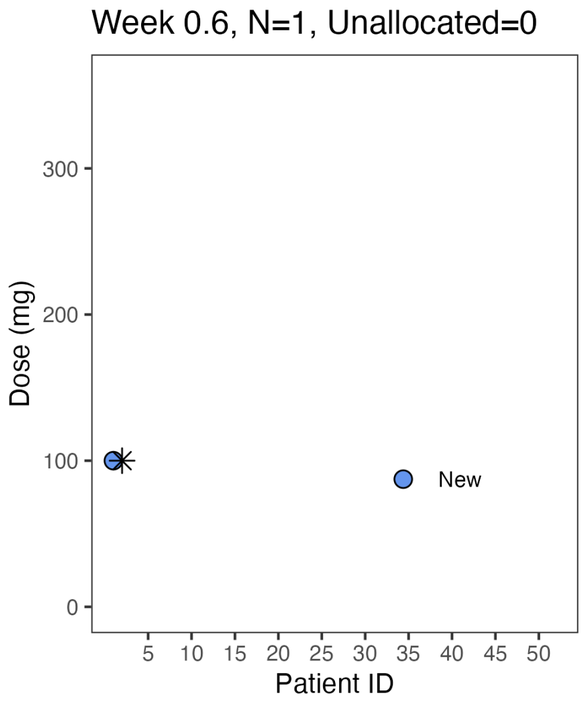
Open enrollment

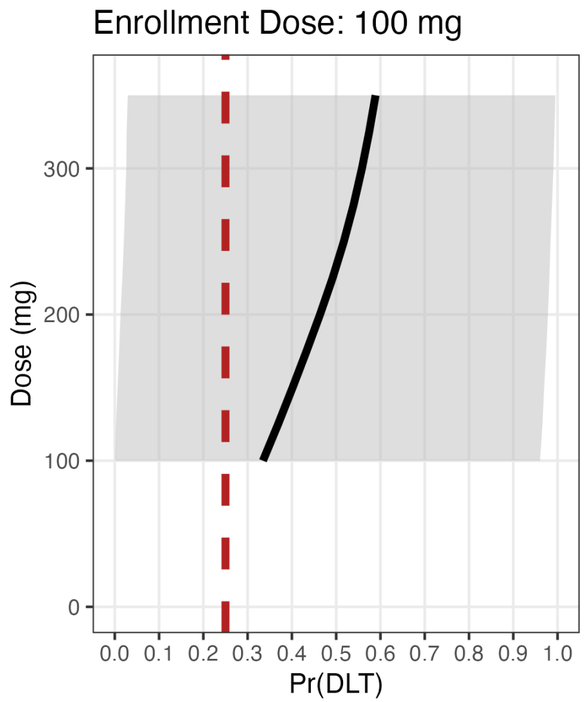
- Cohort enrollment: fixed number of trial participants per dose, trial is paused until results available

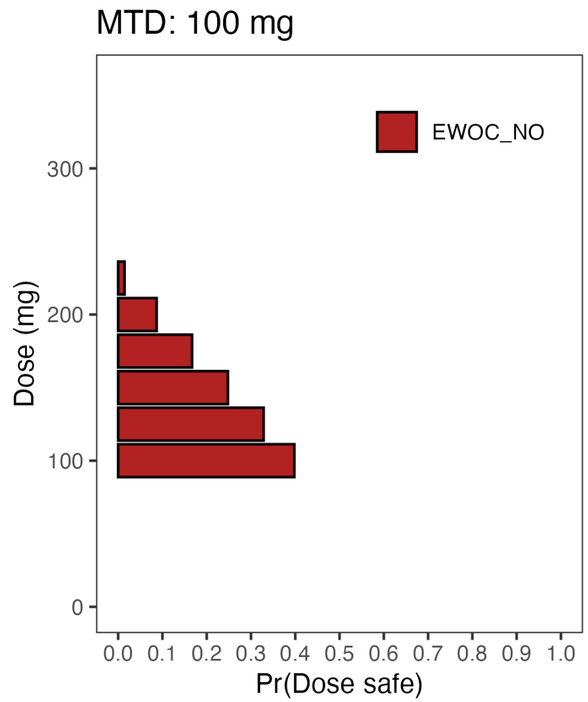
- Open enrollment: Trial participants may be enrolled while the current “cohort” is completing
  - Requires additional rules and risk management, but can offer many advantages

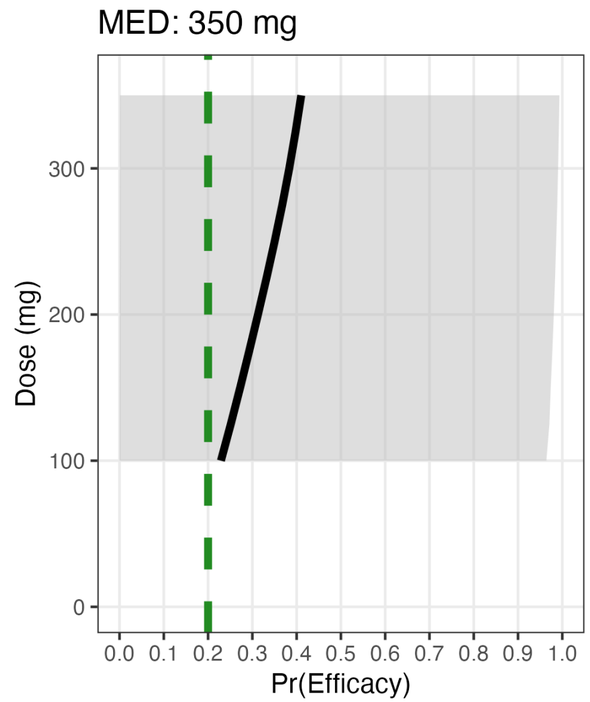
Broglio, Kristine R., et al. "Bayesian dose escalation in oncology with sharing of information between patient populations." Contemporary clinical trials 44 (2015).

Movie of possible trial trajectory

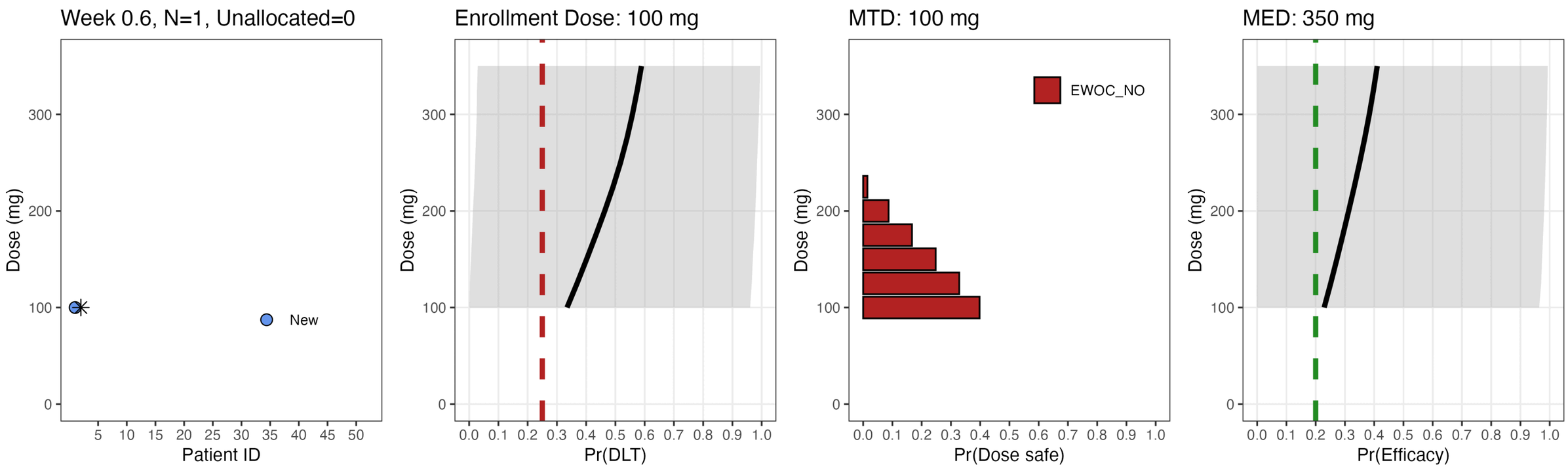








Movie of possible trial trajectory



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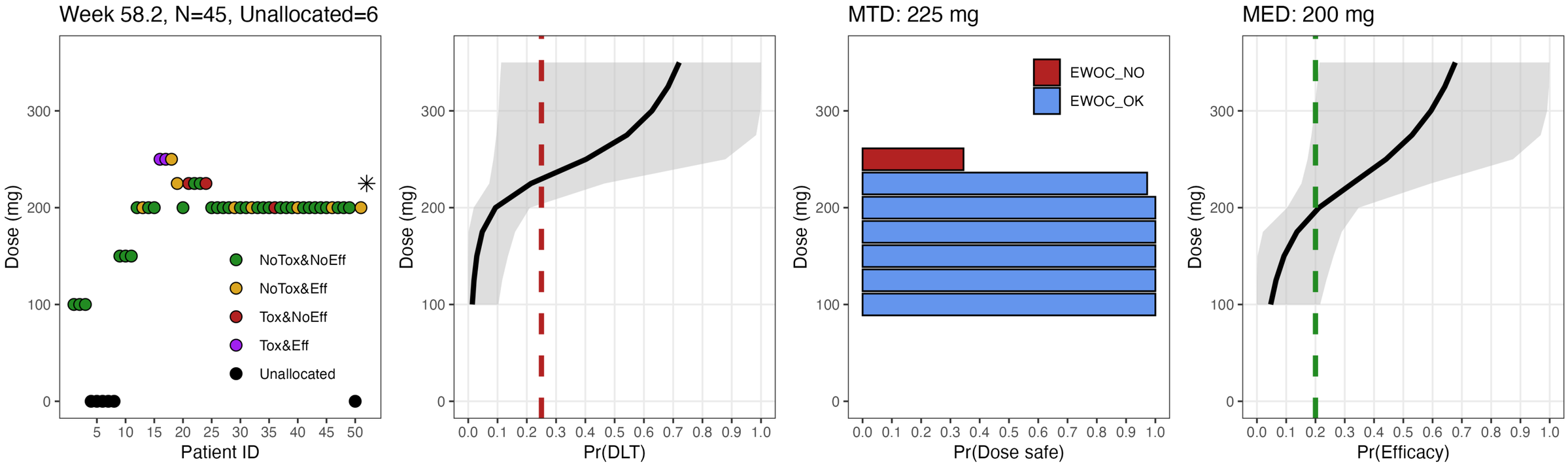
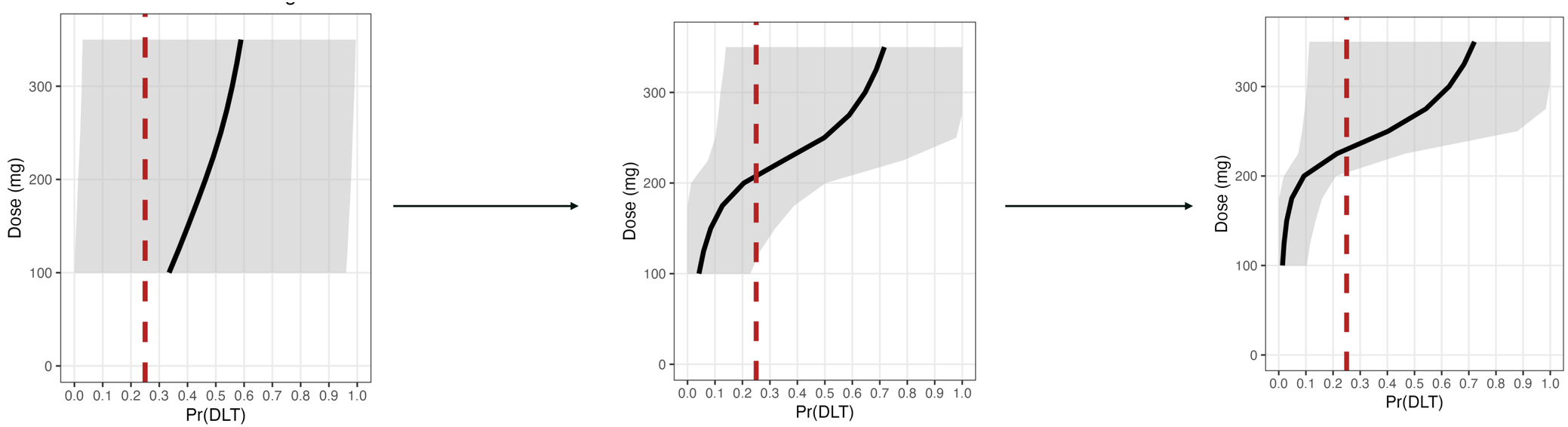


Statistical Model

- Two parameter Bayesian logistic regression model
- Start with reasonably uninformative priors
- Parameters re-estimated after every patient with complete DLT information
- As MTD we choose the dose for which P(DLT) is closest to the target toxicity rate of 0.25



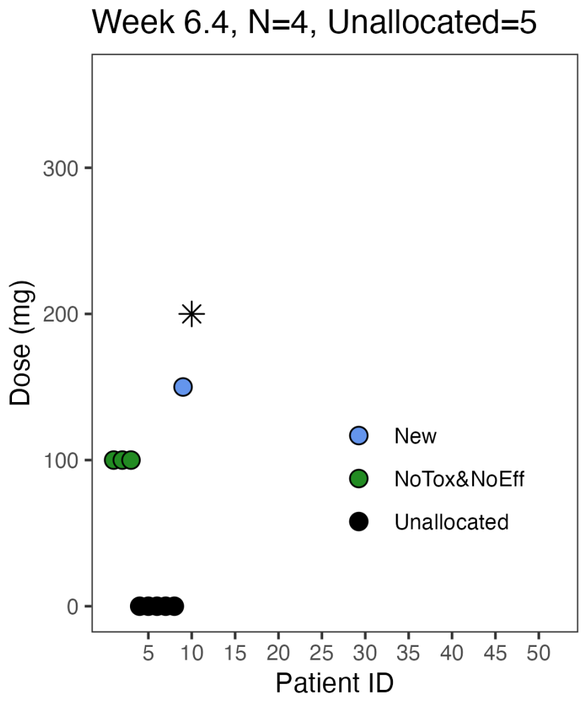
Prior

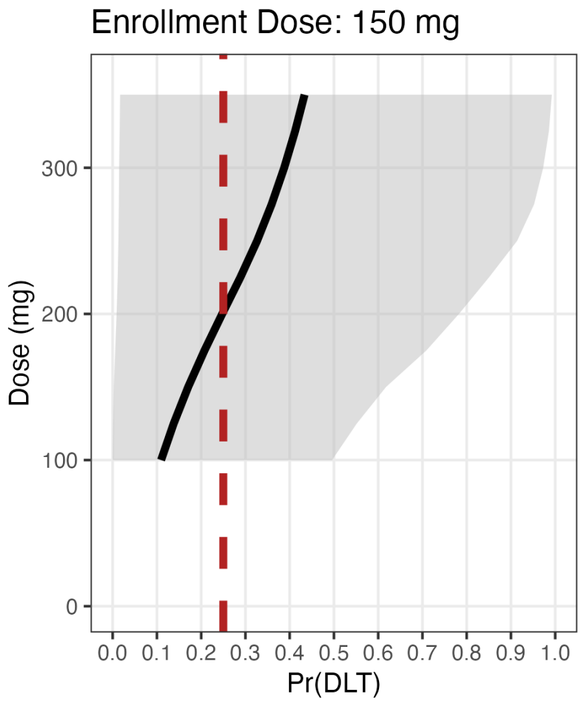
After 15 pts

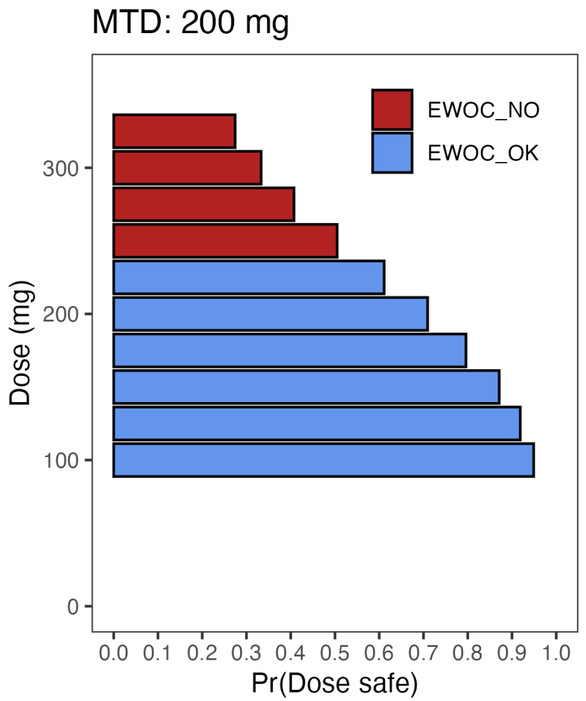
Choosing a final dose

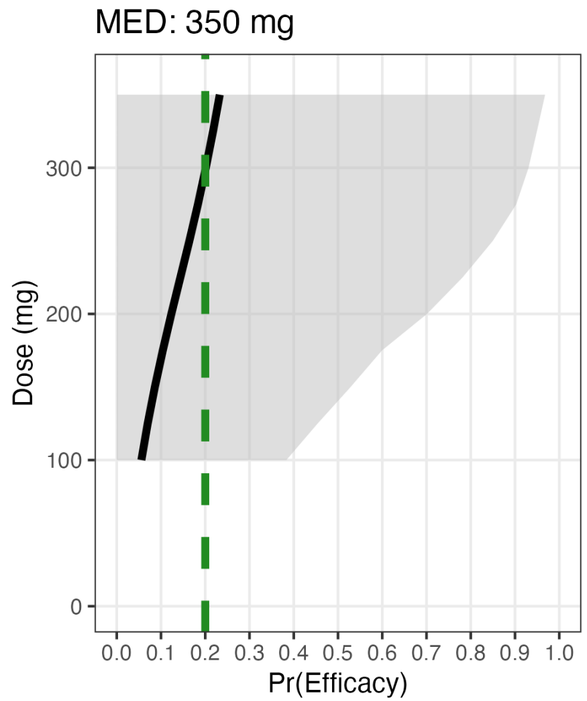
Ad-hoc rules

- Start at the lowest dose
- Skip at most 1 dose levels (i.e. increments of 50mg ok)
- Require DLT data on 3 pts before escalation



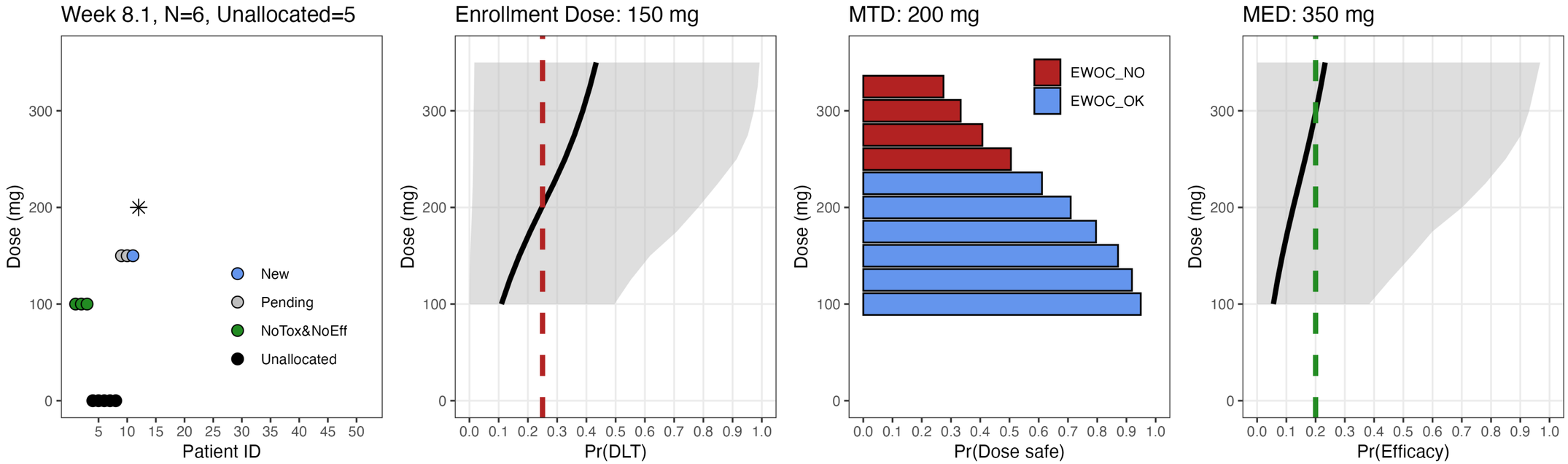






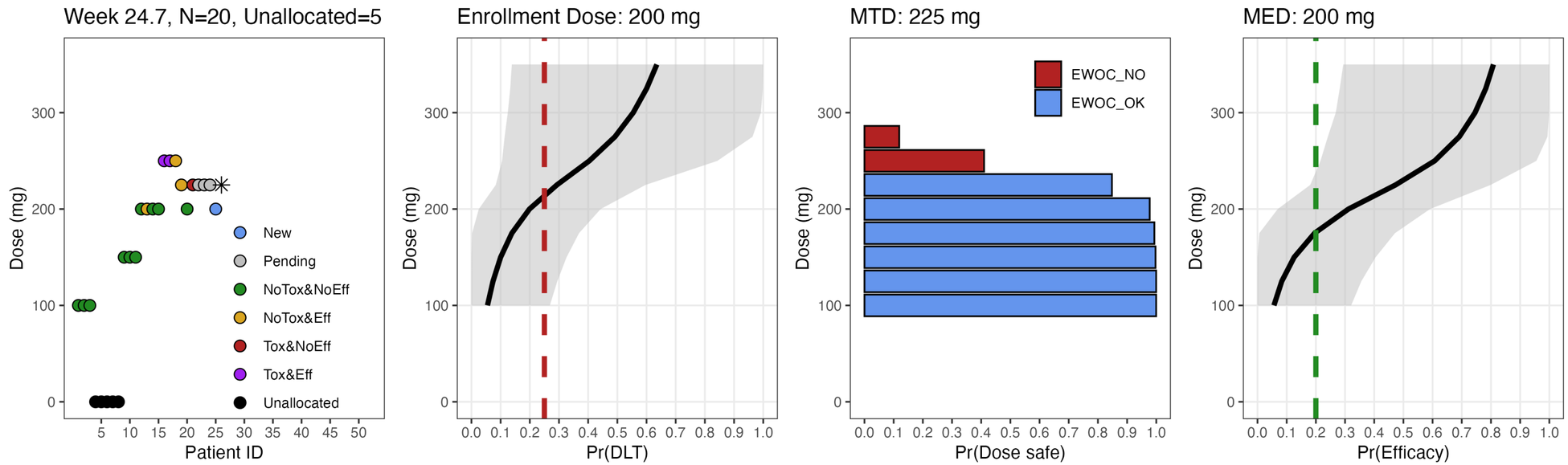
Rules for open enrollment

- Three queue concepts govern how many trial participants without DLT results can be allocated at a given dose:
  - *Uncleared* doses (3)
  - *Cleared* doses at MTD (3)
  - *Cleared* doses below MTD (6)



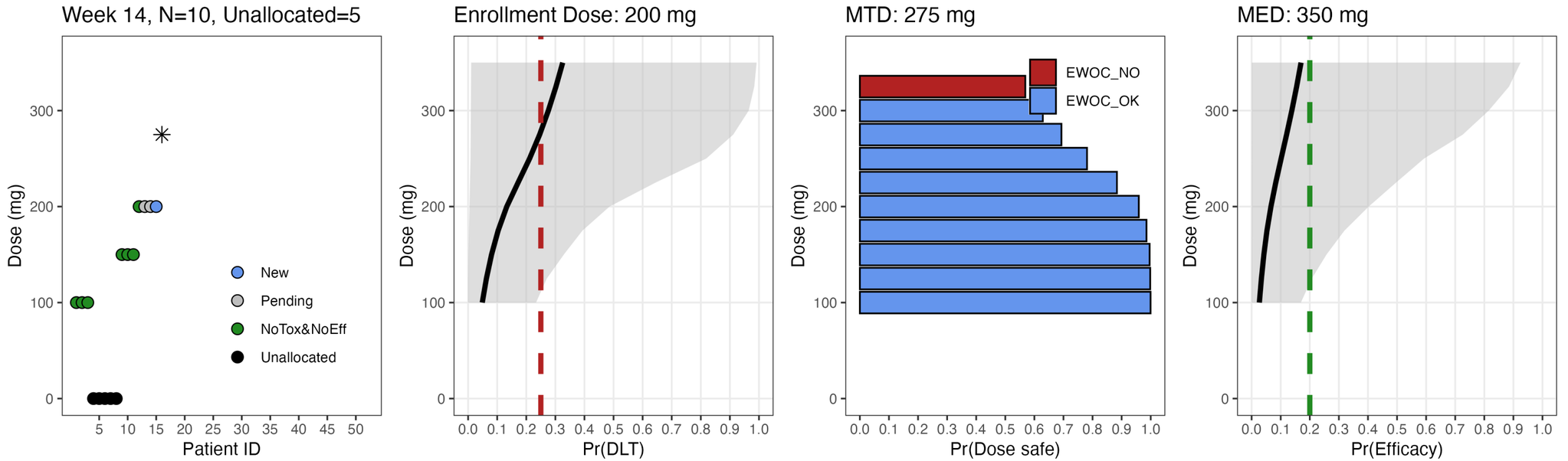
Backfilling

- When the highest dose is unavailable for assignment (according to open enrollment queues), patients are either not assigned, or assigned to lower doses (backfilling)
  - No backfill below 175mg (that's where we expect to see therapeutic effects a priori)
  - At most one level below current escalation dose
  - No backfill if number of pts on dose would exceed 9
  - Maximum 5 pts allocated via backfill to a dose



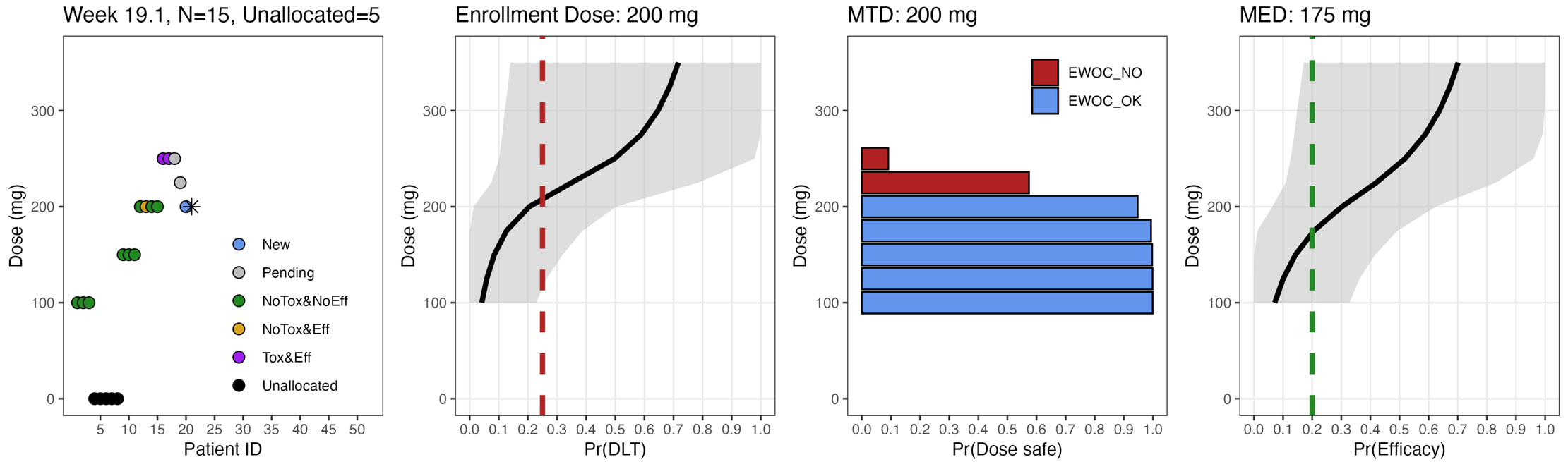
Frontfilling

- Backfilling to front dose (assign more patients to current escalation dose)
  - Follows backfill rules (e.g. not below 175mg)



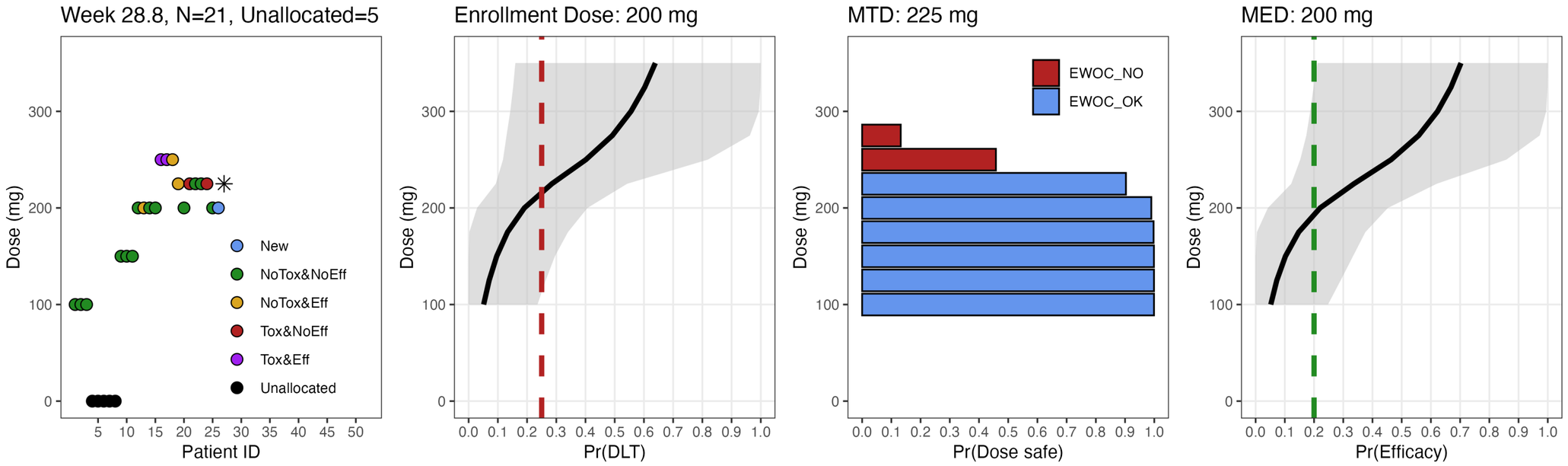
EWOC – Escalation With Overdose Control

- Temporarily exclude doses from allocation that have too high probability of “unacceptable” toxicity
- Pr(Toxicity > 0.35) < 0.5 AND Pr(Toxicity > 0.5) < 0.2



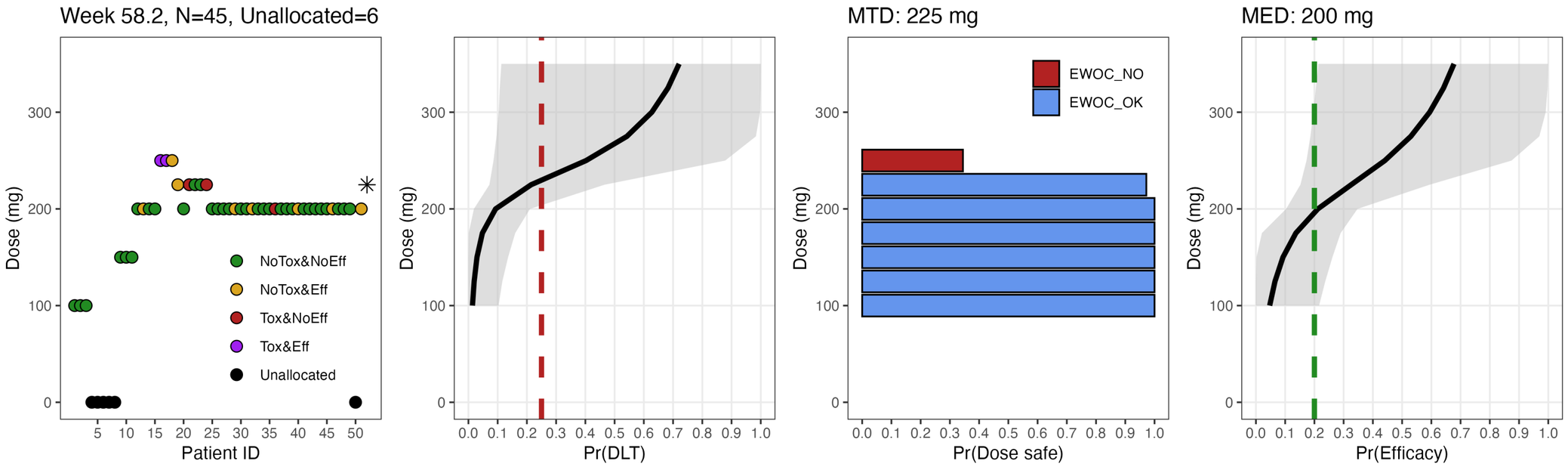
Early stopping rules (Phase I)

- In general, maximum sample size is 60
- If there are 9 DLT completers on the (model estimated) MTD or ±25mg, stop the trial
- Stop only if probability of being near (±25mg) true MTD greater than threshold (here 60%)
- In practice, the DMC/SRC or sponsor may overrule and continue assignment of patients



Early stopping rules (Phase I/IIa)

- In general, maximum sample size is 110
- Stop if there are 25 DLT completers on the model estimated MED (minimum efficacious dose)
- Stop only if probability of being true MED greater than threshold (here 50%)



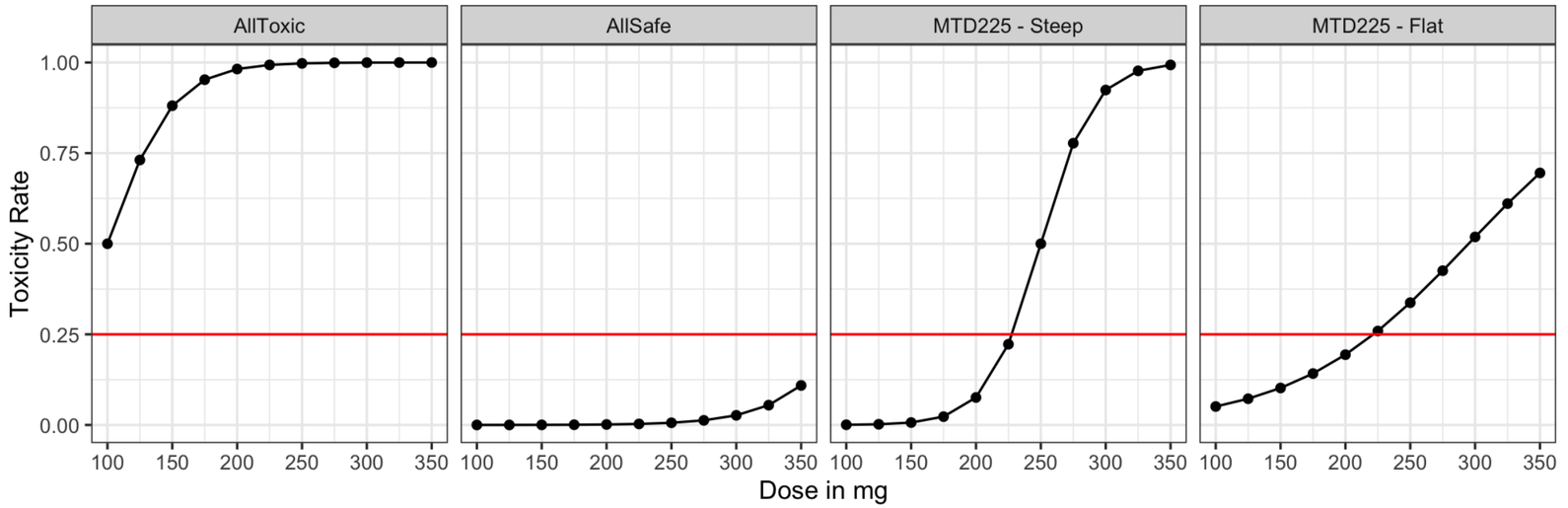
(Some) Things to look out for

- Is the CRM allocating, estimating and stopping “sensibly”:
  - Suggesting escalation after 3/3 DLTs? Suggesting not to escalate after 0/6 DLTs?
    Might have to tweak prior or include pseudo subjects or look at EWOC rules.
  - Assigning patients 31-60 to the same dose with no change in estimated MTD?
    Might have to tweak stopping rules.
  - Fast recruitment and either many lost subjects or too many backfilled subjects?
    Might have to tweak backfill rules.
  - Assigning too many patients to previously untested doses?
    Might have to tweak open enrollment queue lengths.
  - Jumping back and forth between 225mg and 250mg for too long?
    Might have to tweak stopping rules and consider ±25mg as “near”
  - …

Operating Characteristics

- All results based on 10k Simulations rounded to nearest percent
- Investigated four different dose-toxicity relationships
- Investigated three different dose-efficacy relationships
- Efficacy assumed to be available also after 2 weeks (as opposed to 4 weeks)
- Simulations run using pre-release FACTS 7.2.0

Selected MTD – 3+3/BOIN/mTPI2 vs. CRM P1



Sample Size / Percentage of correct pick	3+3	i3+3	mTPI-2	BOIN	CRM	Correct Pick
All Toxic	5 / 80%	8 / 53%	8 / 53%	8 / 53%	5 / 91%	No Dose
All Safe	34 / 87%	40 / 98%	40 / 98%	42 / 98%	29 / 100%	Highest Dose
MTD225 S (250mg)	23 / 93% 8%	28 / 98% 15%	28 / 99% 14%	32 / 97% 7%	24 / 99% 5%	225mg +/- 25mg
MTD225 F (250mg)	20 / 47% 9%	24 / 49% 9%	24 / 50% 9%	29 / 48% 7%	33 / 73% 14%	225mg +/- 25mg

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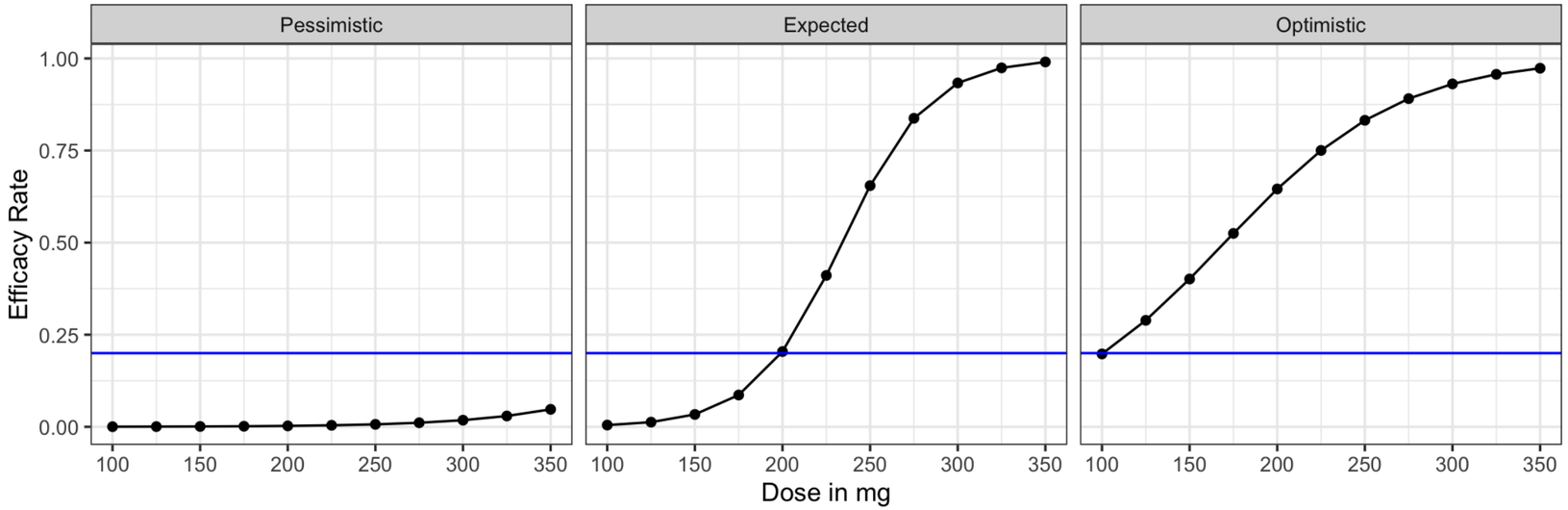
Selected MED – CRM P1/2a



MED: Total Sample Size / Percentage of correct pick / Extra N compared to P1	**Pessimistic**	**Expected**	**Optimistic**
All Toxic	6 / 31% / 1	6 / 2% / 1	6 / 57% / 1
All Safe	45 / 100% / 16	63 / 100% / 34	60 / 98% / 31
MTD225 - Steep	27 / 100% / 3	62 / 96% / 38	54 / 99% / 30
MTD225 - Flat	38 / 98% / 5	60 / 87% / 27	68 / 98% / 35
Truth	Pick None	Pick 175-225 mg	Pick 100-125mg

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Final thoughts

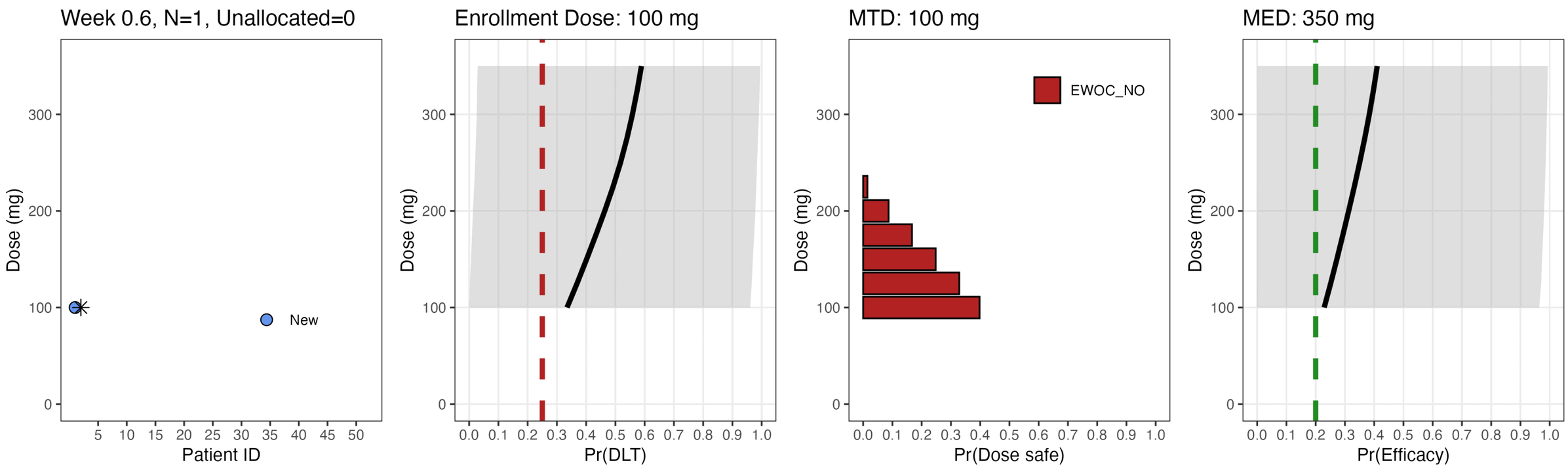
- If an optimal dose had to be chosen based on only CRM, suggest MED, if MED <= MTD, otherwise none
- Incorporating PK/PD data allows for informed decision on “optimal” dose to take into P2/P3
- Statistical and knowledge creation advantages come at increased operational complexity – need to be prepared for ”real-time” updates

- **What else could we explore?**
  - Tweak dose standardizations, prior, pseudo-subjects to further improve OCs
  - Consider small cohort run-in / accelerated titration
  - Investigate more scenarios of varying dose-toxicity relationships
  - Investigate effect of recruitment rate and possibly tweak backfill

- Questions? Reach out to me at elias@berryconsultants.com

Backup

Movie of possible trial trajectory



Basics of Continual Reassessment Method[1]

- Model based dose escalation method
  (as opposed to rule based dose escalation method)
- Uses all available data to estimate dose-toxicity relationship
- Different parametric models possible
  (hyperbolic tangent, one/two parameter logistic regression, …)
- Arriving trial participants assigned to current estimate of MTD

[1] O'Quigley, John, and Larry Z. Shen. "Continual reassessment method: a likelihood approach." Biometrics (1996).

Various possible adaptations of CRM[2]

- Ad-hoc rules:
  - Don’t skip dose levels in escalation / Skip at most X (1) dose levels
  - Start at the lowest dose
- Open enrollment
- Backfilling/Frontfilling
- Early stopping rules
- Target toxicity intervals
- Escalation with overdose control (EWOC)
- Switch between MTD/MED hunt if new emerging data suggests necessity
- …

[2] Neuenschwander, Beat, Michael Branson, and Thomas Gsponer. "Critical aspects of the Bayesian approach to phase I cancer trials." Statistics in medicine 27.13 (2008).

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Individual Simulations

- Before explaining all the design choices, let's see a possible trajectory of the trial
- Time is simulated, showing effect of open enrollment
- Explanation of the movie