When Population PK modeling helps drive oncology phase I trial: First implementation of Exposure Driven dose Escalation With Overdose Control (ED-EWOC) design

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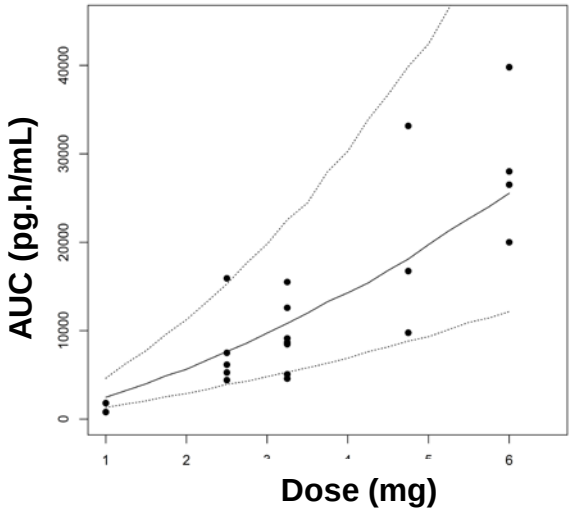
ED-EWOC as a new design for dose finding trials

- ED-EWOC can provide benefit through **exposure quantification** in the **dose escalation** process and in the **dose recommendation**:
  - When PK **variability** is large (and particularly when it can be explained by **covariates)**
  - When PK is **non linear**

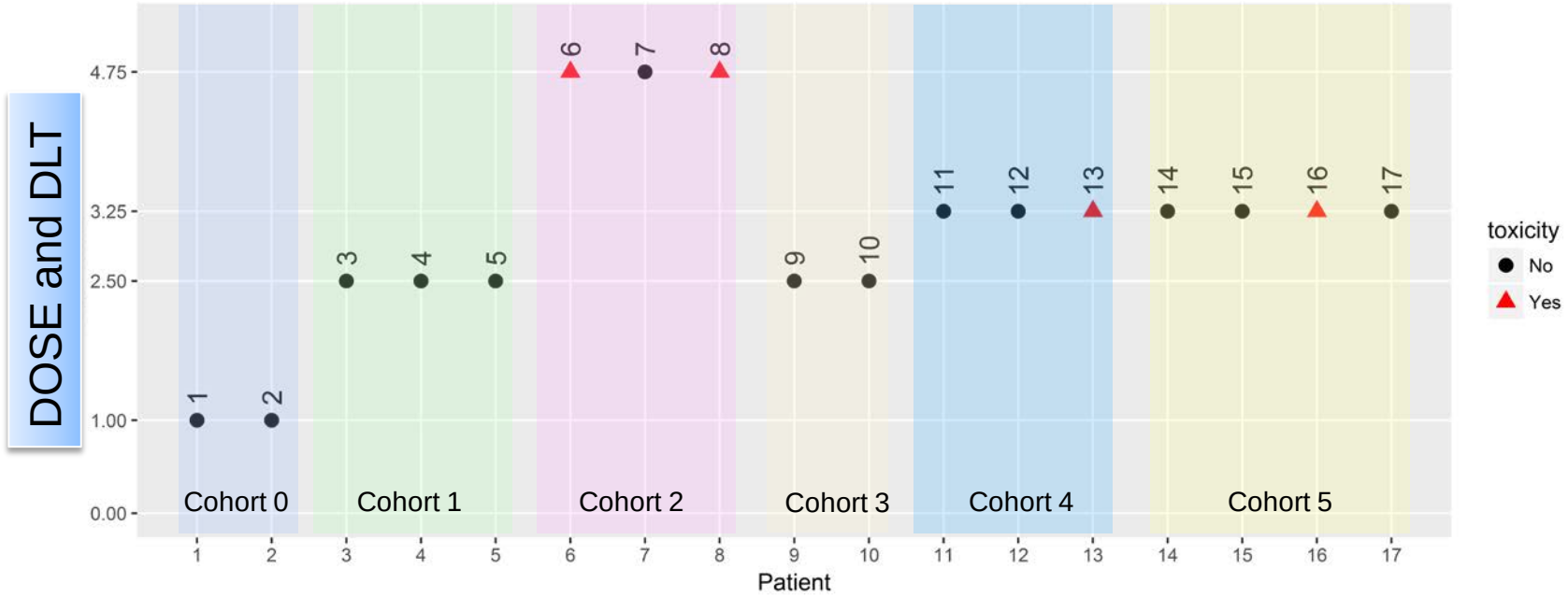
- Methodology explored using simulations of similar CRM-designs[1]

- **Implemented**
  - in a multi center, open label, phase I, dose finding study in patients with late stage cancer
  - Pilot, actual dose escalation in the study was driven by EWOC



[1] Ursino, M., Zohar, S., Lentz, F., Alberti, C., Friede, T., Stallard, N., & Comets, E. (2017). Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations. *Biometrical Journal*.

AUC explains DLT better than dose



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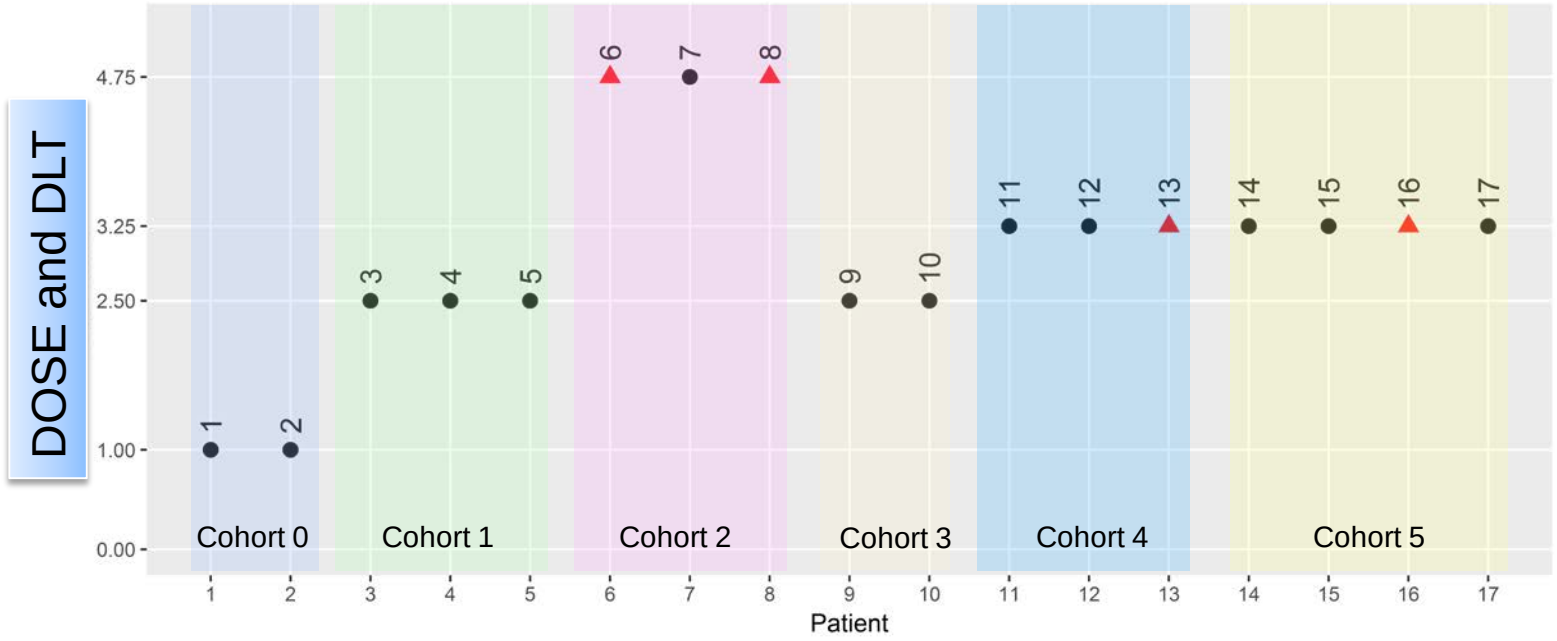

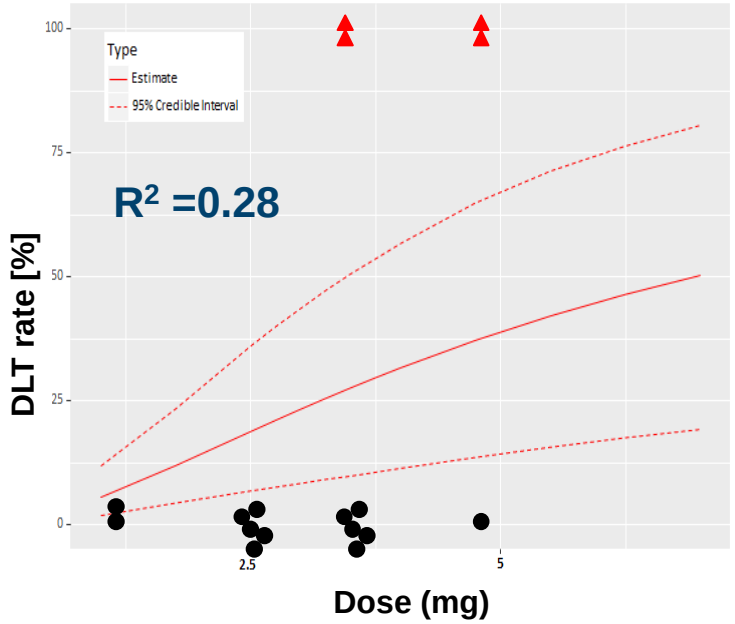

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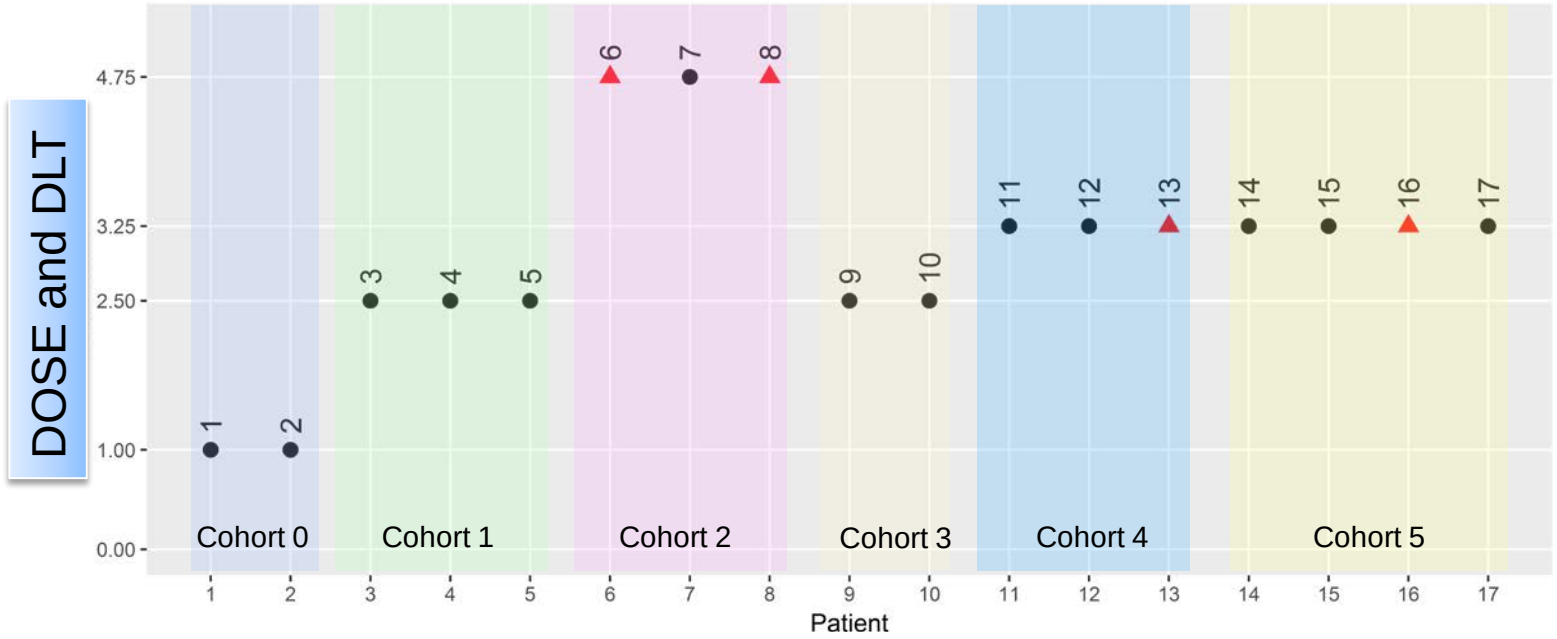
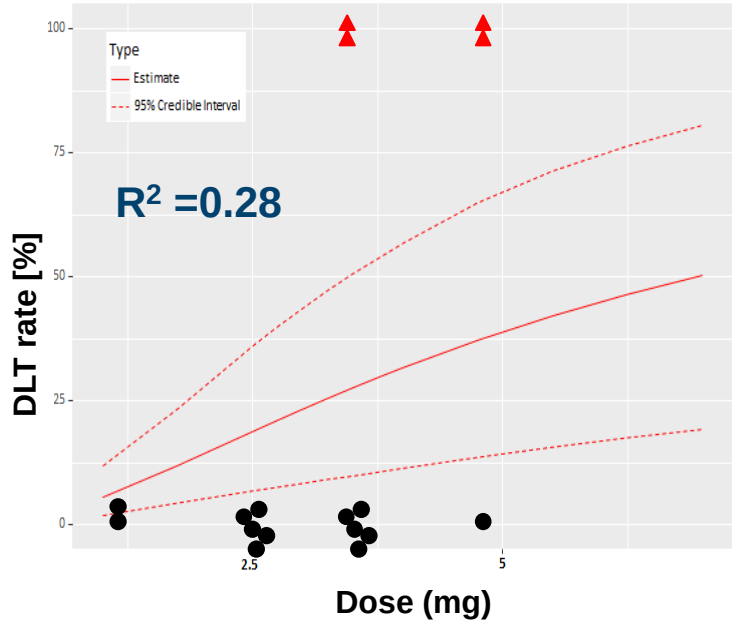
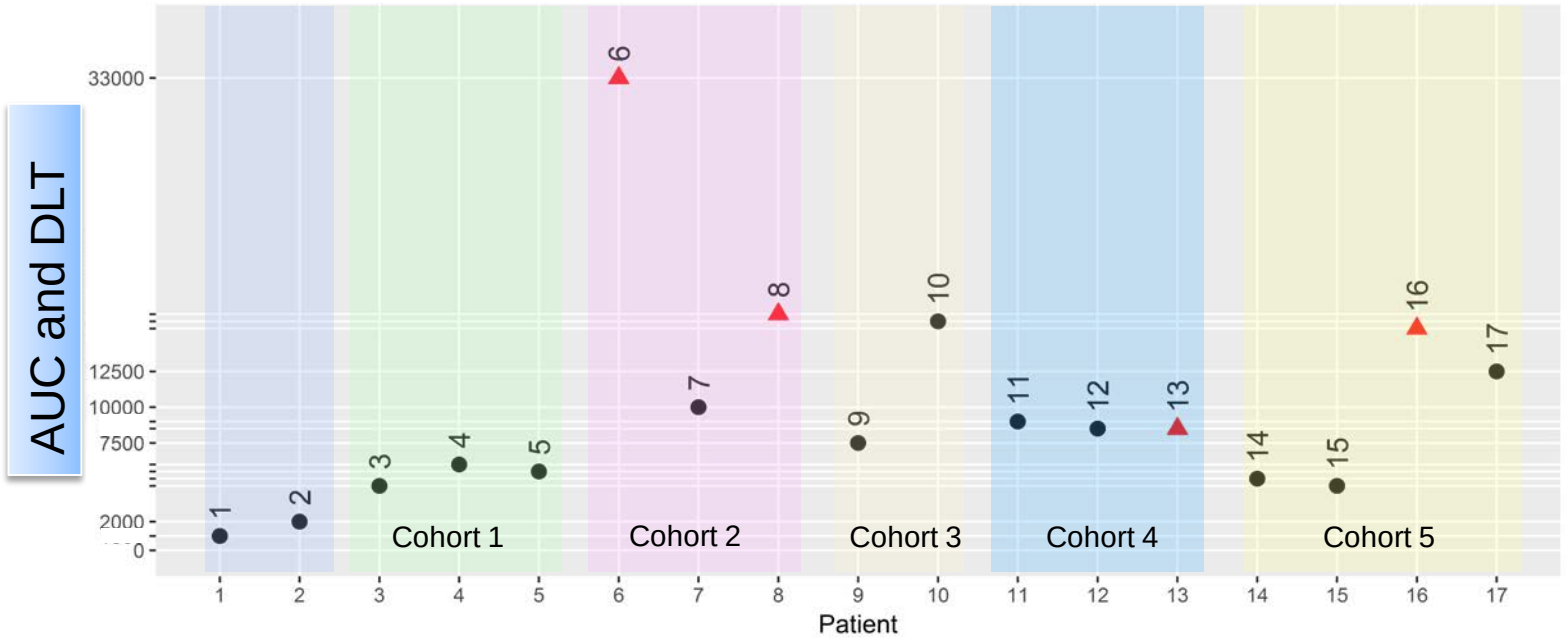
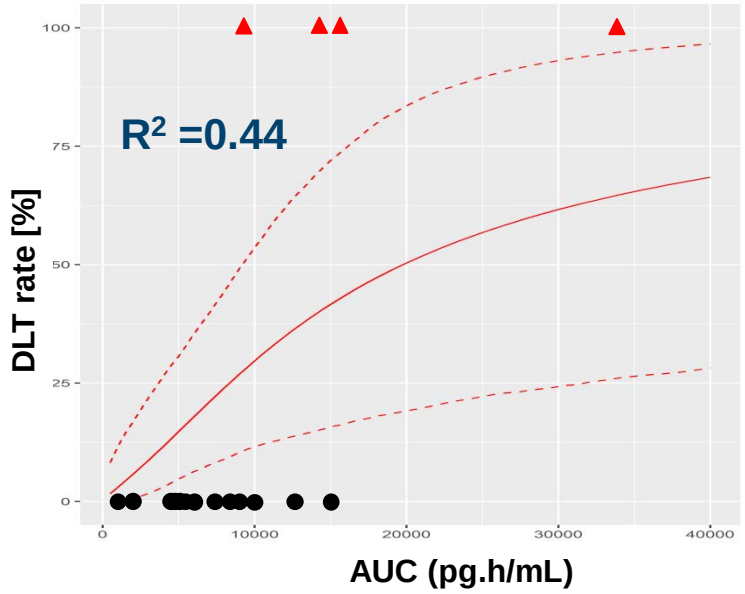
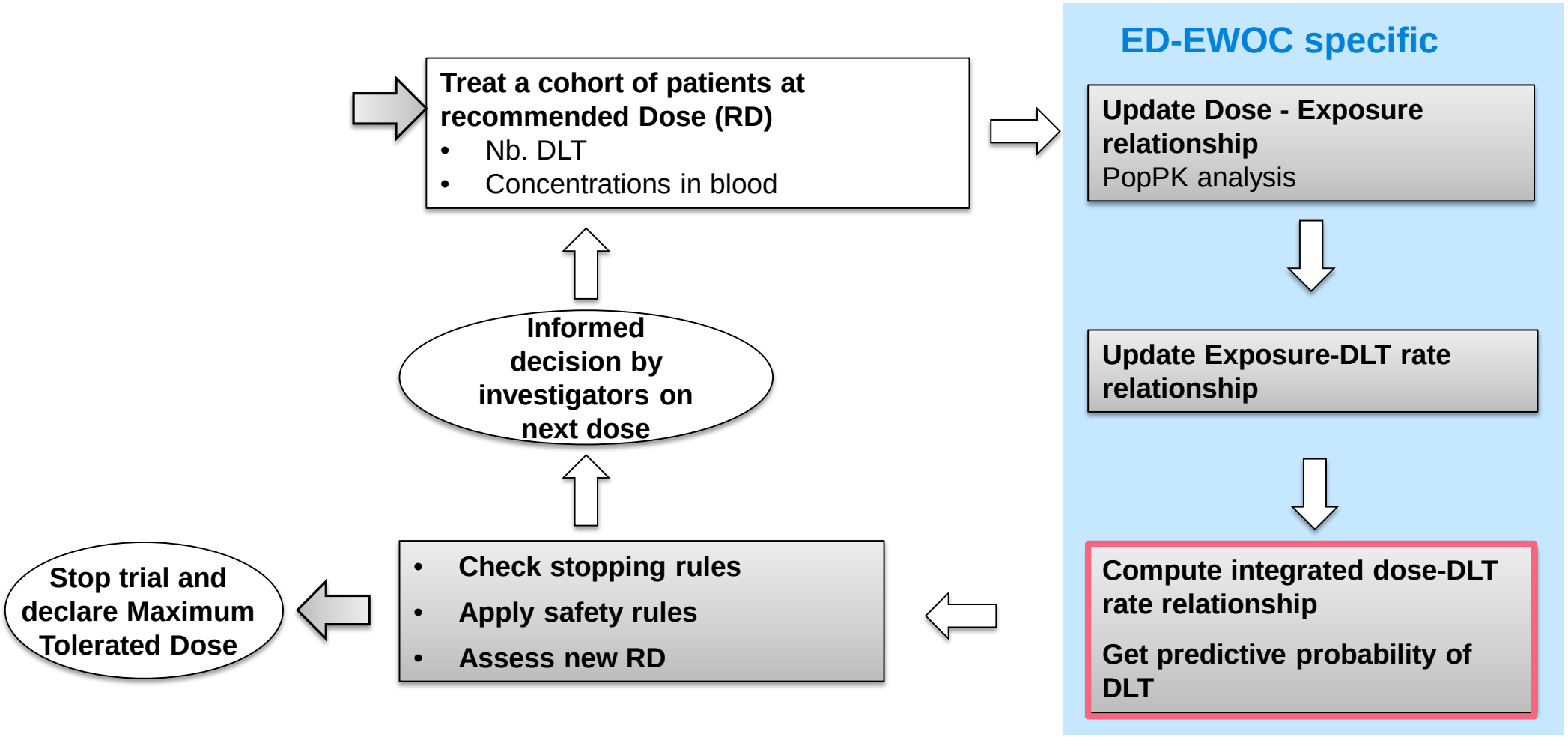




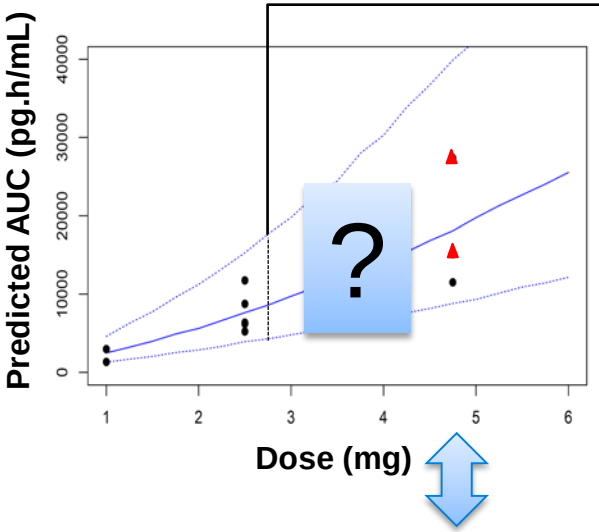




Exposure driven EWOC is an iterative adaptive process



From Cohort 3 (2.5mg) to Cohort 4 (2.75mg) : dose recommendation with ED-EWOC



Cohort	PT Id	DOSE	AUCi	DLT
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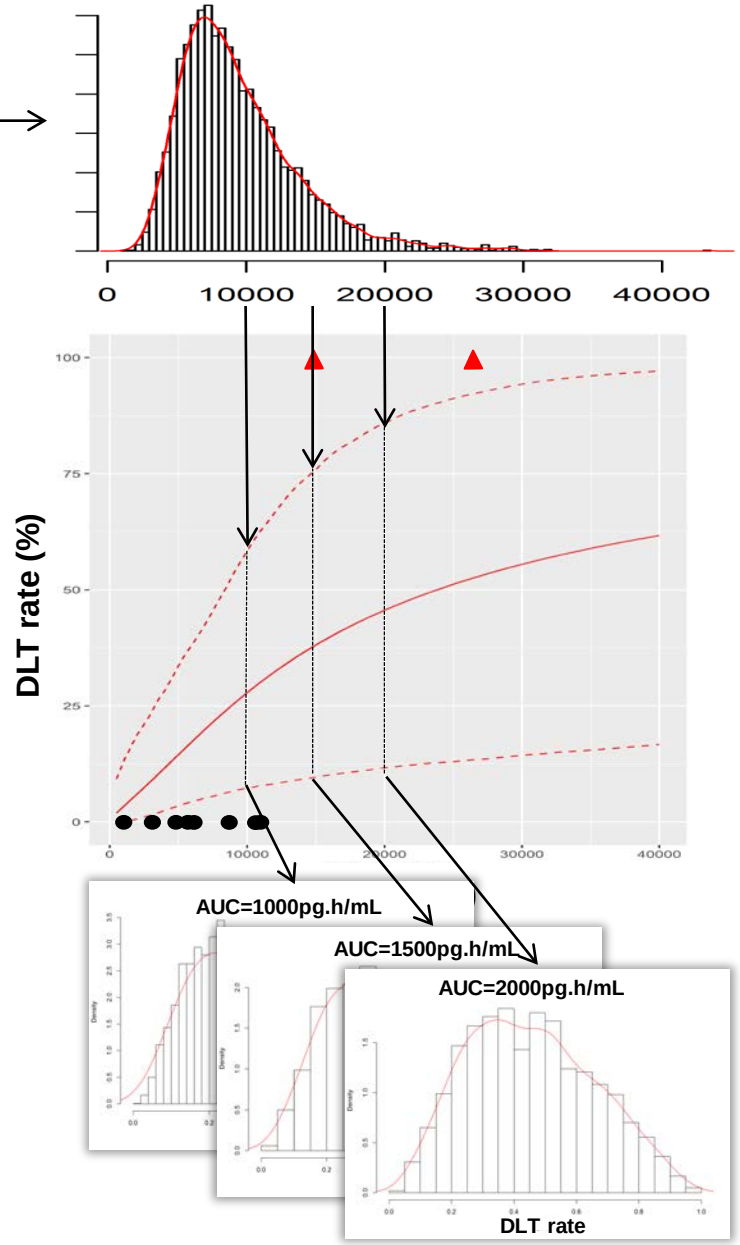
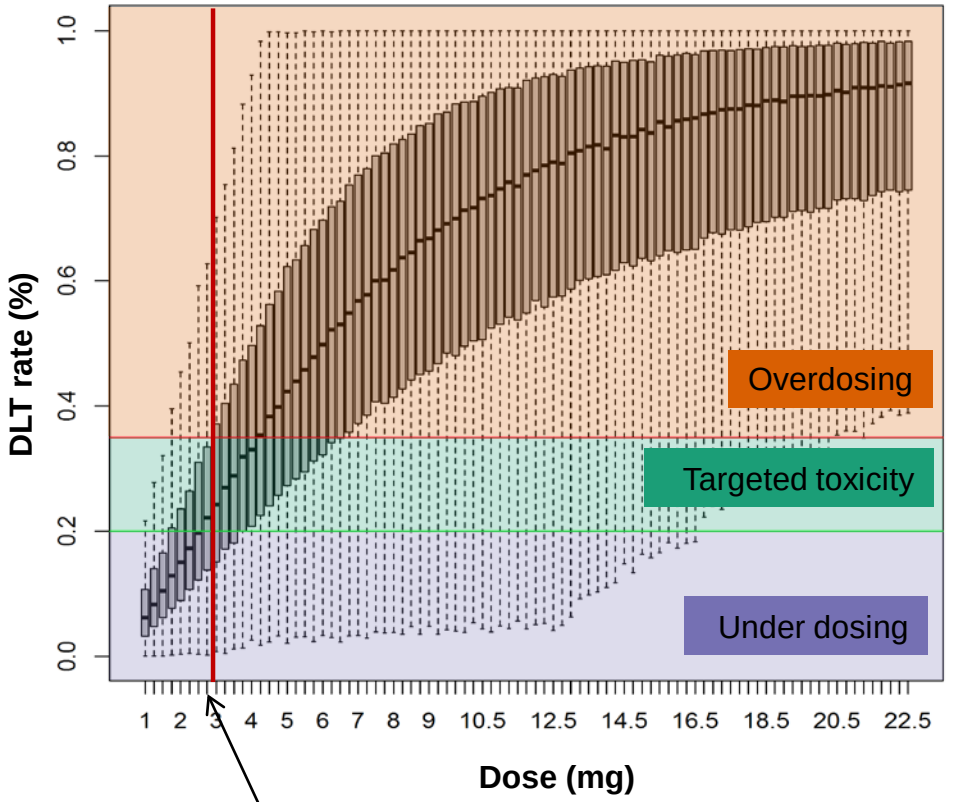
0	2	1	2968	0
1	3	2.5	5236	0
1	4	2.5		NA
1	5	2.5	6203	0
1	6	2.5	6365	0
2	7	4.75	27350	1
2	8	4.75	15171	1
2	9	4.75	11496	0
3	10	2.5	8751	0
3	11	2.5	11758	0



Integrated Dose-AUC-DLT rate



Recommended dose: **2.75mg**

Recommended AUC: 8500pg.h/mL

Learnings and conclusion

Key results

- The process for dose escalation recommendation from ED-EWOC was smooth, (well specified responsibilities)
- ED-EWOC is implementable from an operational perspective, (1 additional week required for data analysis and for running design)

	EWOC	ED-EWOC
Advantage / Benefit	• Quite simple implementation • Software available (CRMPack)	• Quantitate the impact of PK variability on clinical endpoint • Characterization of PK and PD related uncertainty • Leverage prior knowledge on PK, PD • In line with the recent EMA Guideline recommendations[2]
Requirements	• Define priors on dose-DLT rate	• Define priors on dose-exposure DLT rate • population PK model developed at time of protocol set up • Team agility, PK bioanalysis and data availability

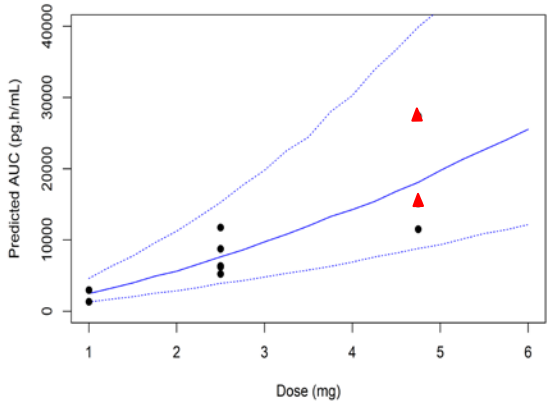
Next steps

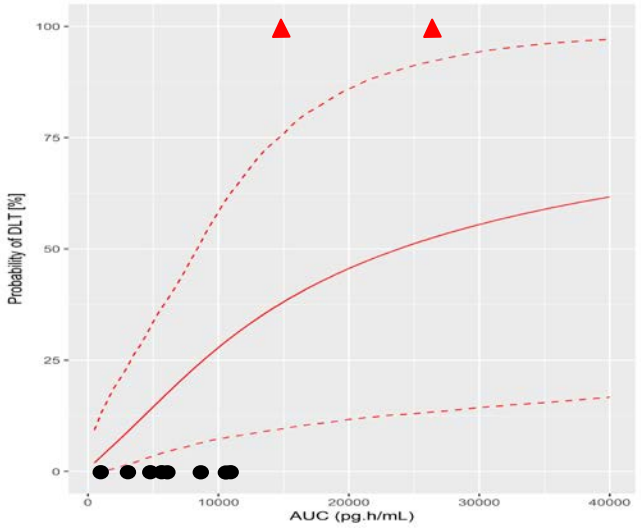
- Quantify the gains of ED-EWOC as compared to EWOC:
  - non-linear PK, large PK variability
- Expand ED-EWOC methodology to PD biomarker to find safe pharmacology active doses
- New application to any other type of dose finding trials

[2] EMA: Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. July 2017

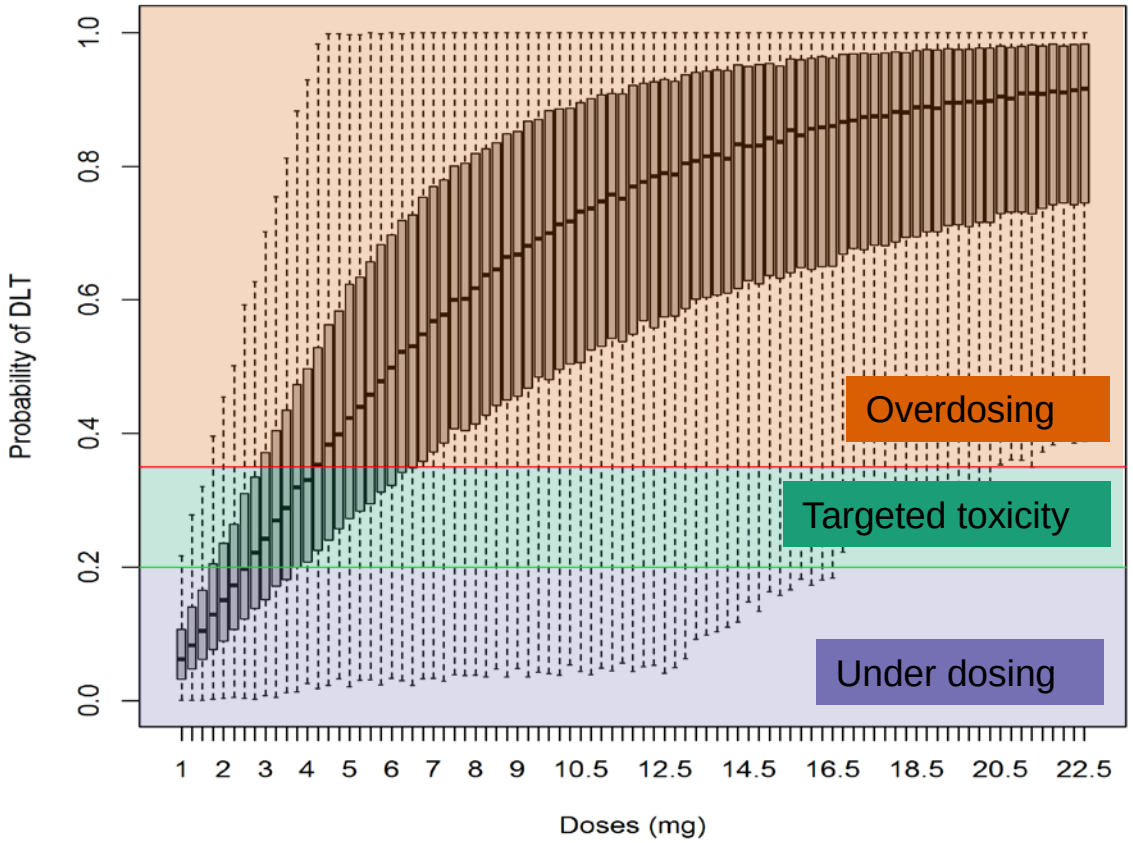
Doing now what patients need next

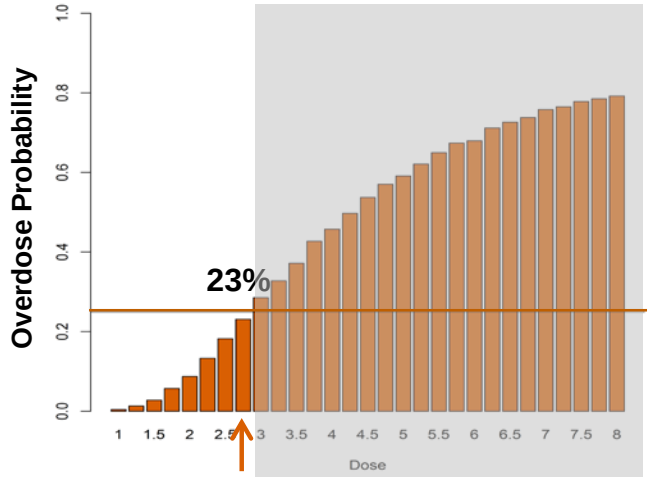
From Cohort 3 (2.5mg) to Cohort 4 (2.75mg) : dose recommendation with ED-EWOC

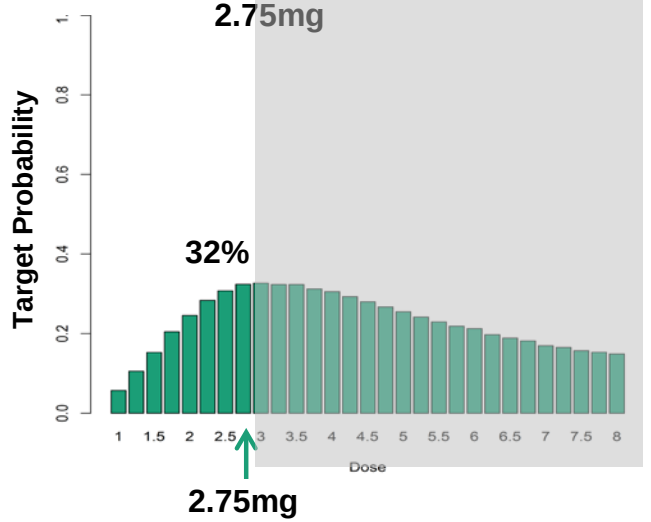




Integrated Dose DLT rate

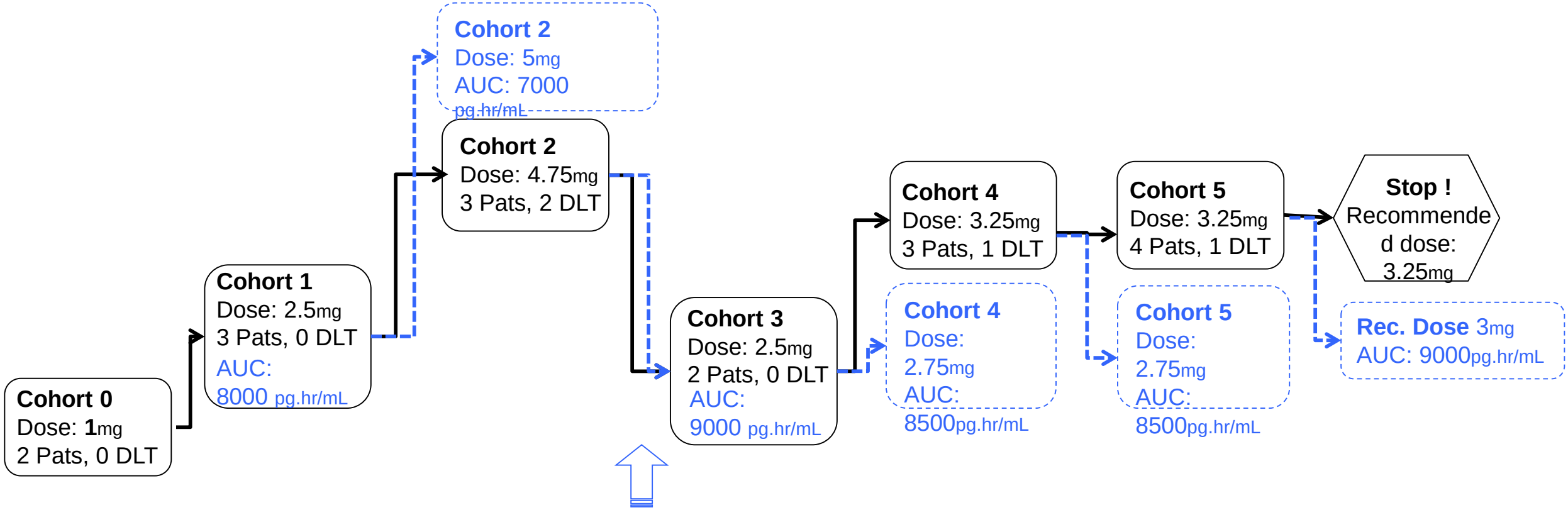






Recommended dose: **2.75mg** as next recommended dose

EWOC dose escalation on a monotherapy study vs. ED-EWOC dose recommendation: An overview



Pop PK model update

- two compartment model
- zero order absorption
- linear clearance

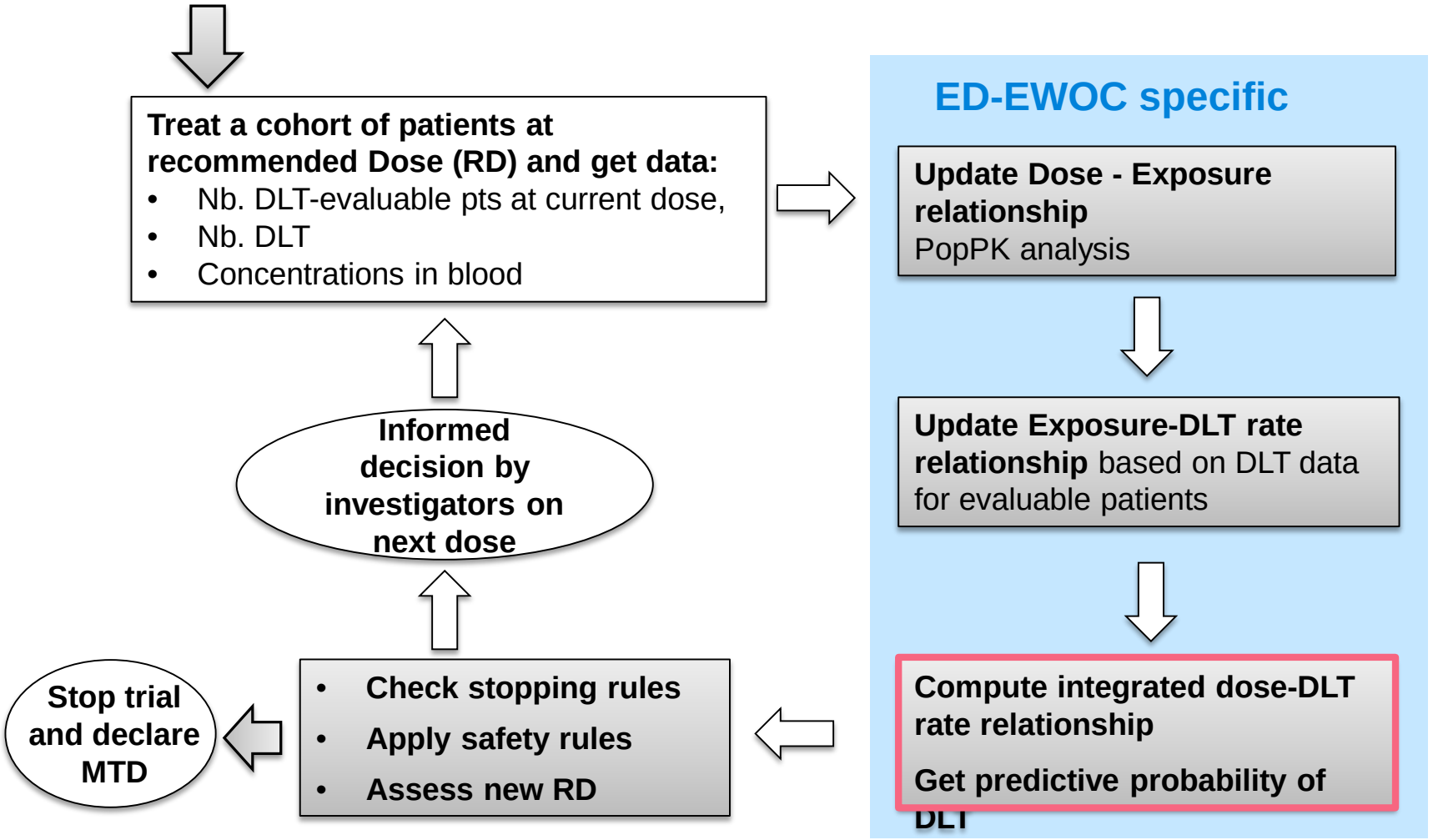
- two compartment model
- 1st-order absorption
- non-linear clearance

Fit

Fit

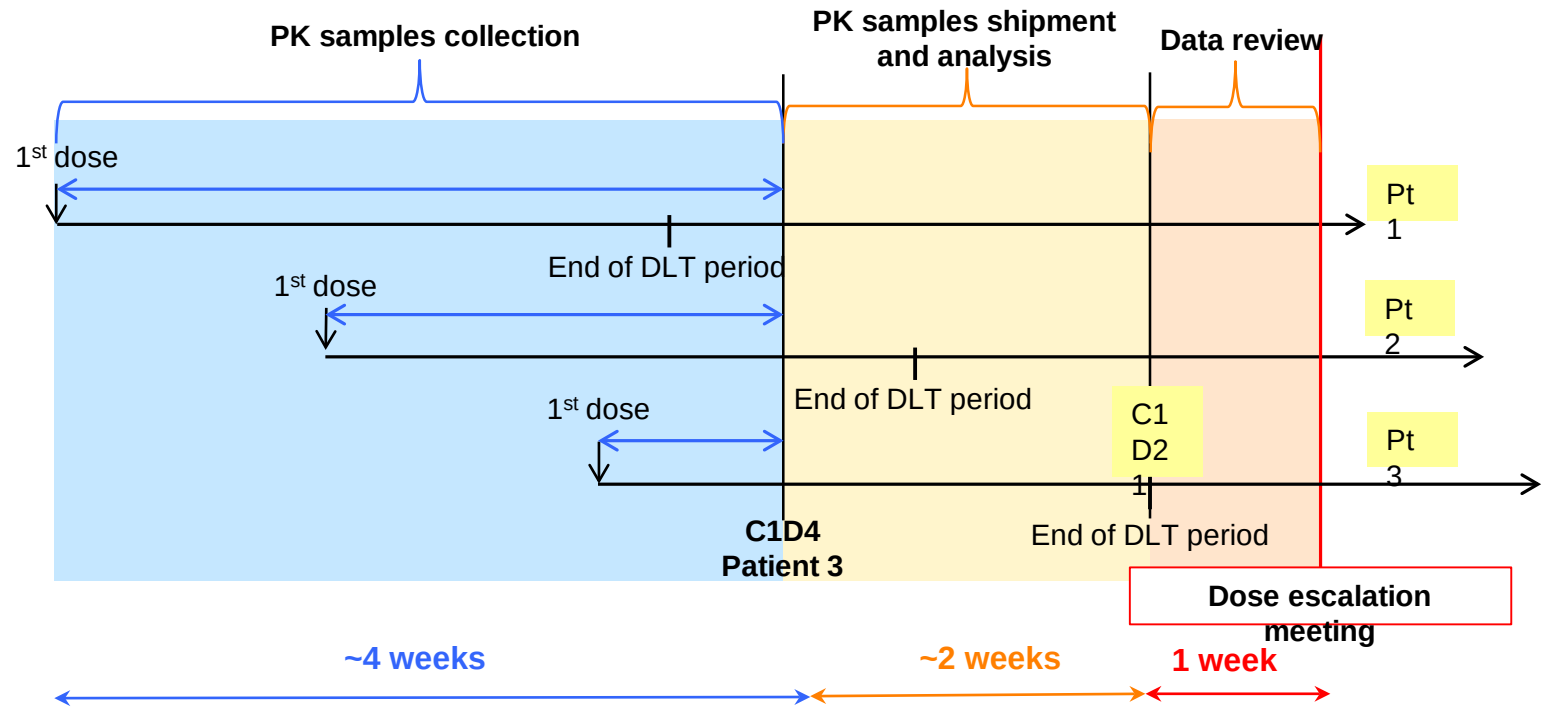
Fit

Exposure driven EWOC is an iterative adaptive process



Operational considerations
Data collection and analysis flow

- The amount of information available varies between patients, due to time required for PK analysis and data review



- PK data from previous cohorts inform the pop PK model as dose escalation proceeds

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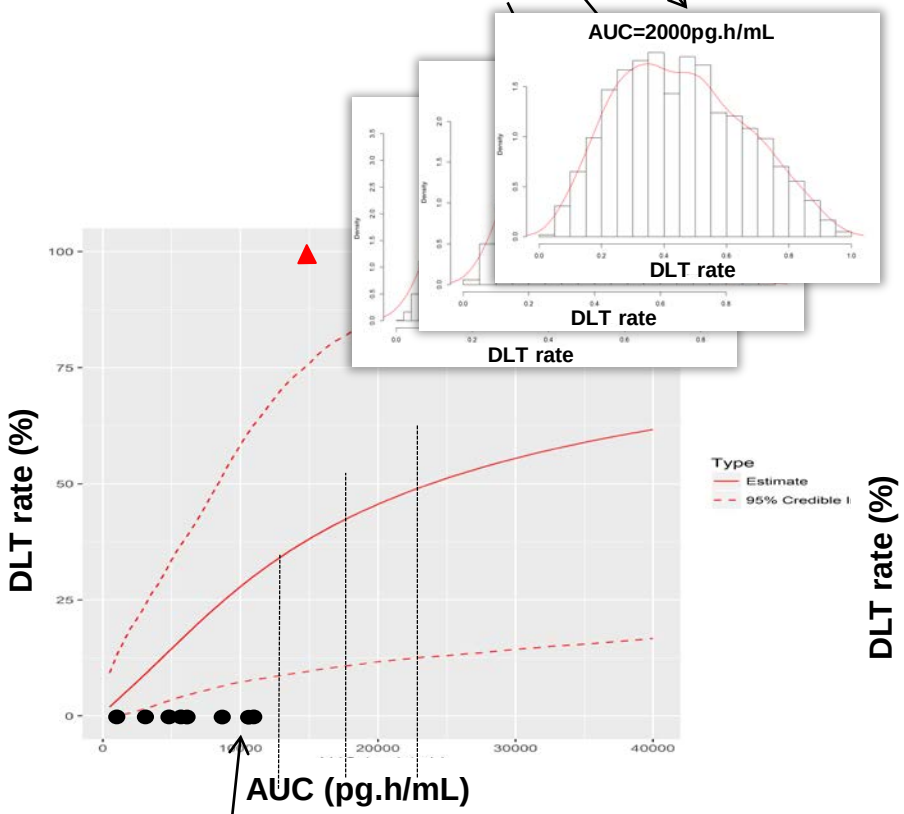

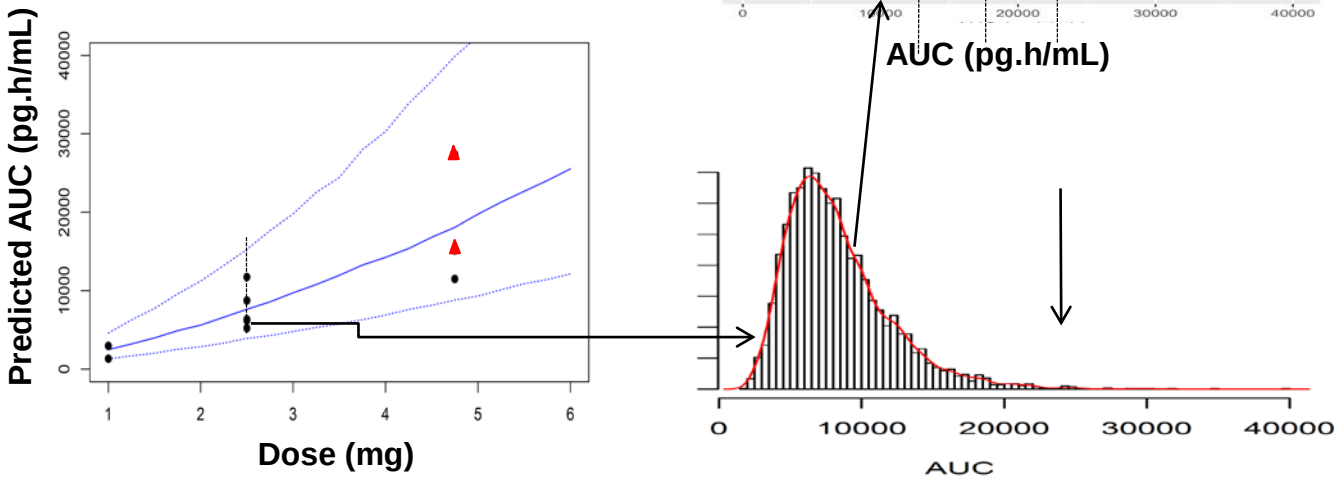

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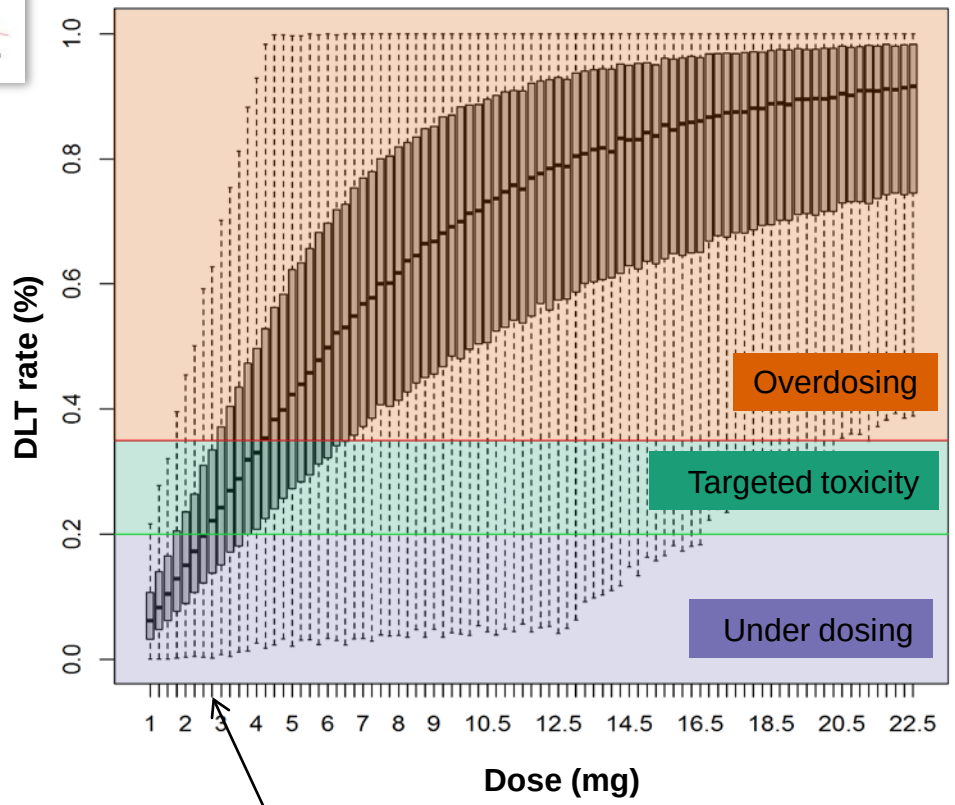

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