In-silico Comparison of MTD Determination in a Phase I Dose-finding Framework

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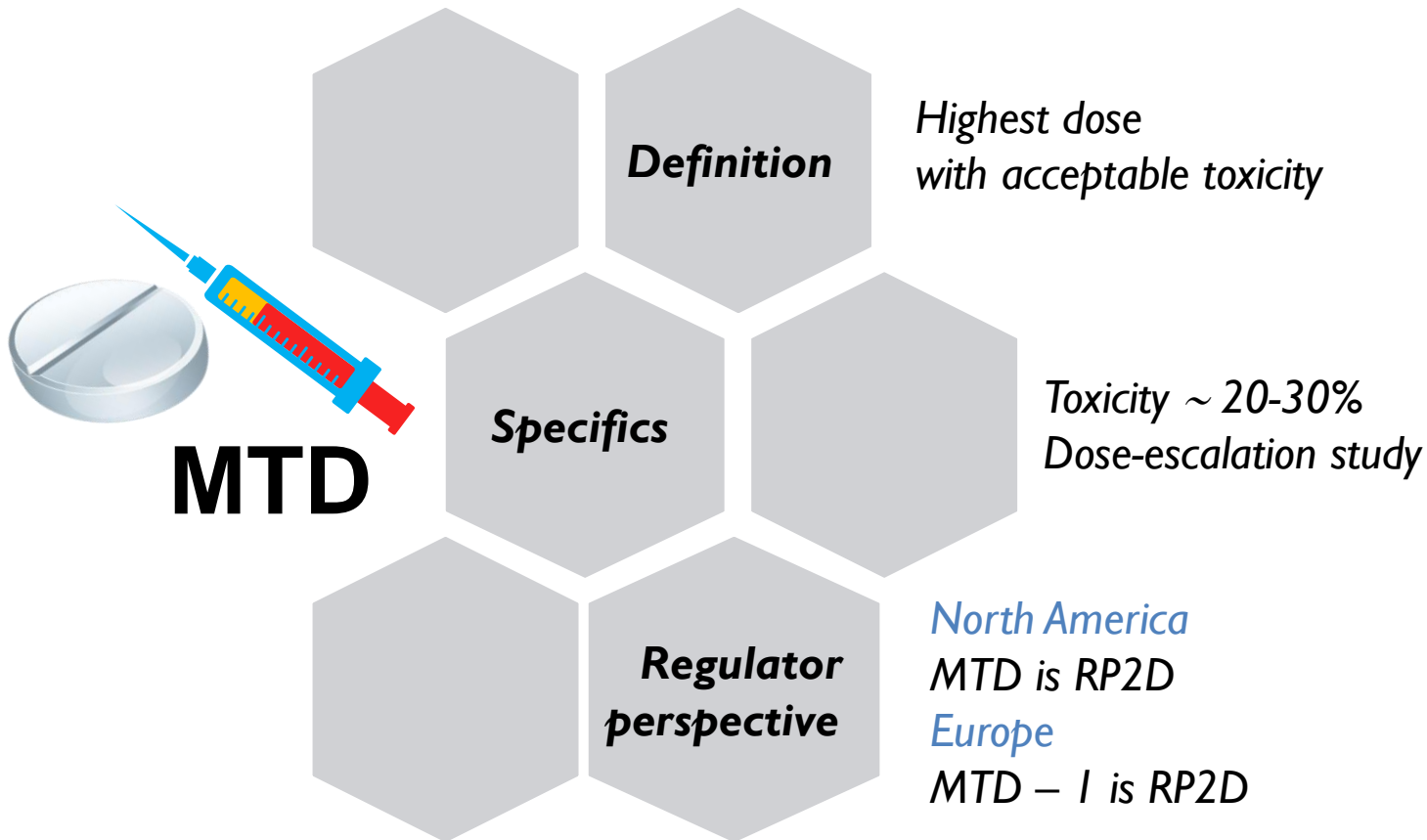[1]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

[2]Clinical Pharmacokinetics & Pharmacometrics department, and

[3]Oncology Business Unit, Institut de Recherches Internationales Servier, Suresnes, France
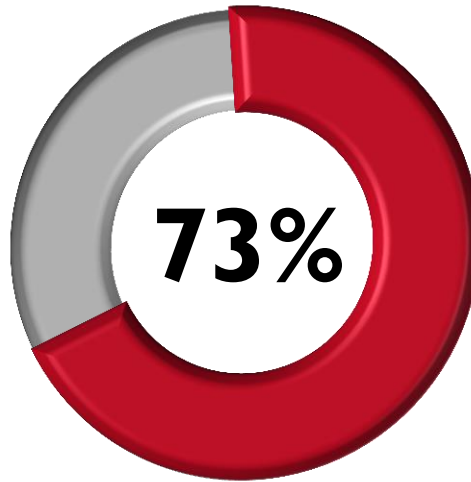
Primary objective: MTD
Maximum Tolerated Dose (MTD) vs. Recommended Phase 2 Dose (RP2D)

MTD

Definition

Highest dose
with acceptable toxicity

Specifics

Toxicity ~ 20-30%
Dose-escalation study

Regulator perspective

North America
MTD is RP2D
Europe
MTD – 1 is RP2D
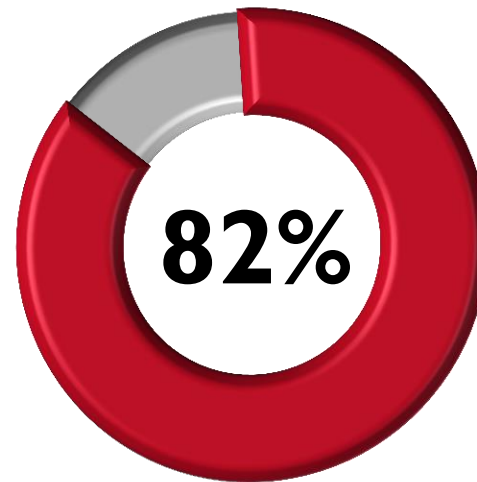
Motivating statistics
for Recommended Phase II Dose (RP2D)

73%

FDA approved oncology drugs having their registered doses within 20% of their RPD2

Motivating statistics
for Recommended Phase II Dose (RP2D)

82%

Among them, exactly as their RPD2

Uniqueness of Oncology phase I trials

- *Huge emphasis of Ethical conduct:*
  - *Vulnerable and rare patients population*
  - *Heterogeneous treatment-resistance*
  - *Most responses occur 80%-120% of MTD**
  - *reduced dose exploration range carried forward*
    i.e. 1 or 2 doses in the vicinity of RP2D in Phase II/III

→ ***The success of future trials is*** ***conditioned*** ***on the estimate of RP2D in phase I oncology trials***

Low success probability

for majority of oncology trials

95%

2014

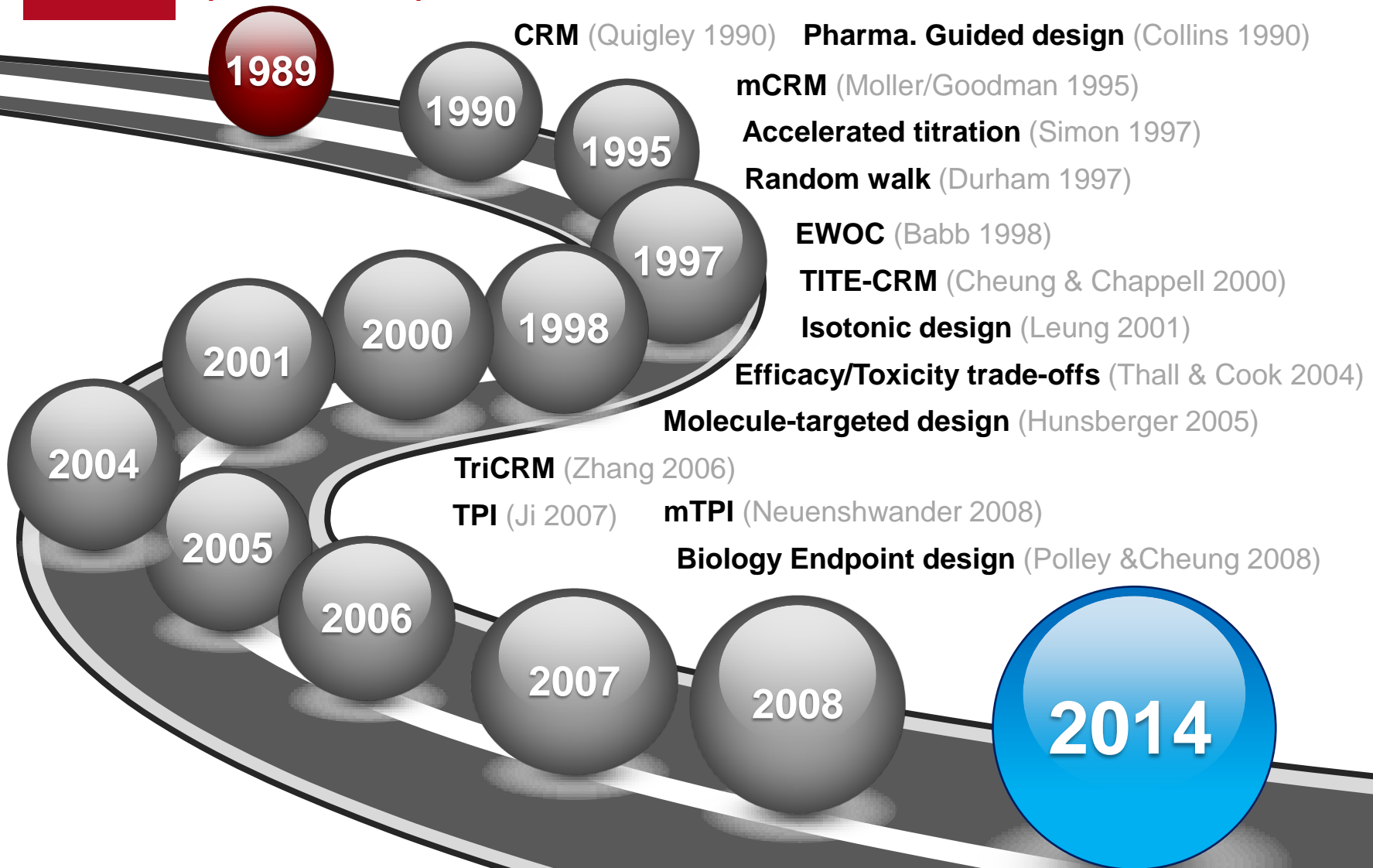*Oncology trials are conducted as* **3+3 designs** *namely "Traditional approach"*

Why do we fancy this method?

References: Le Tourneau et al. 2009, Mielke et al. 2014
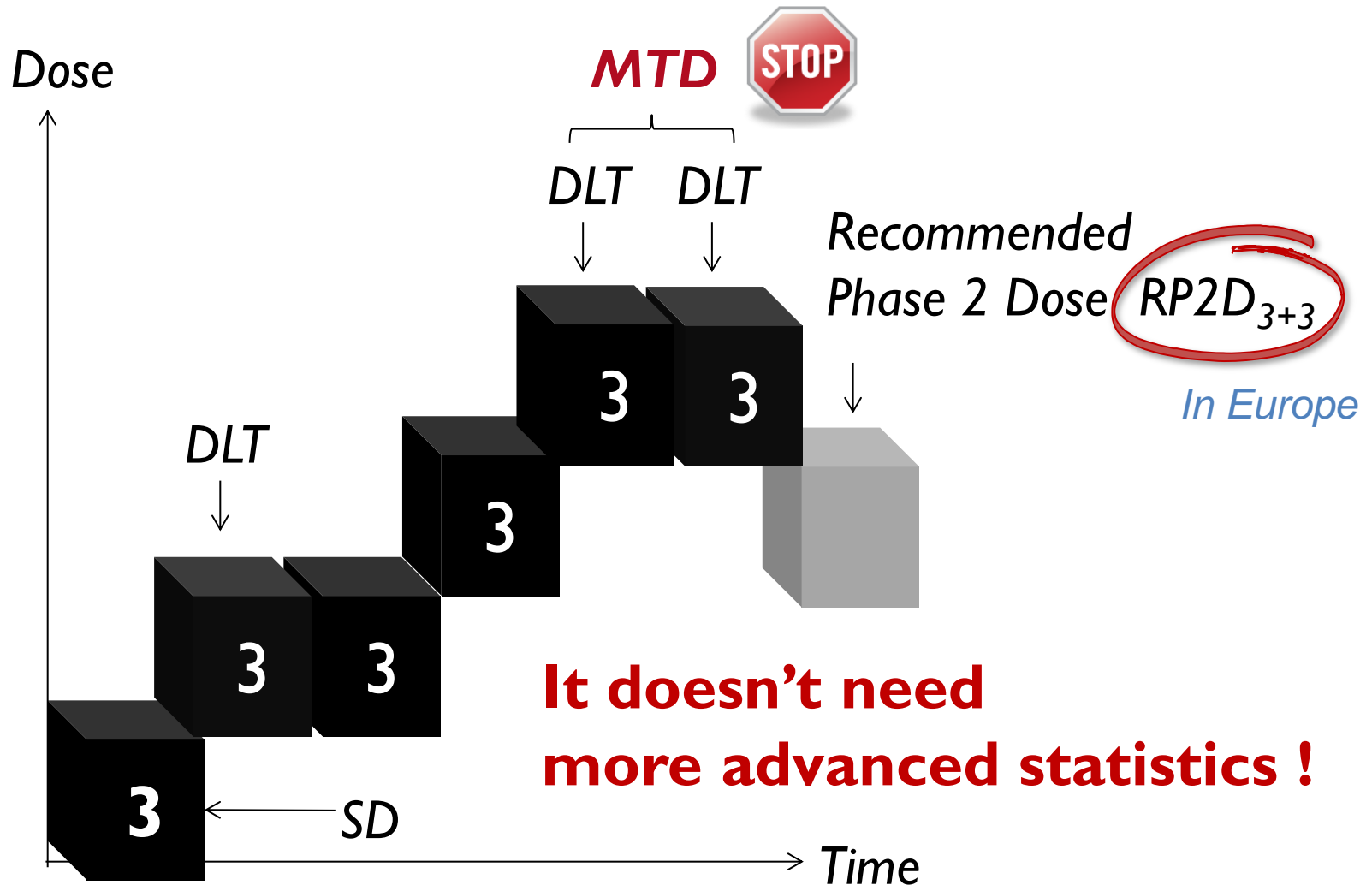
Popularity of 3+3 designs
a historical presence

3+3 design (Storer 1989)

CRM (Quigley 1990)   **Pharma. Guided design** (Collins 1990)

mCRM (Moller/Goodman 1995)

Accelerated titration (Simon 1997)

Random walk (Durham 1997)

EWOC (Babb 1998)

TITE-CRM (Cheung & Chappell 2000)

Isotonic design (Leung 2001)

Efficacy/Toxicity trade-offs (Thall & Cook 2004)

Molecule-targeted design (Hunsberger 2005)

TriCRM (Zhang 2006)

TPI (Ji 2007)   **mTPI** (Neuenshwander 2008)

Biology Endpoint design (Polley &Cheung 2008)

1989
1990
1995
1997
1998
2000
2001
2004
2005
2006
2007
2008
2014

Popularity of 3+3 designs
Easy implementation & monitoring

MTD

DLT   DLT

Recommended
Phase 2 Dose   RP2D$_{3+3}$

DLT

In Europe

**It doesn't need
more advanced statistics !**

Dose

SD

Time

Reference: Storer et al. 1989

Common knowledge
Poor operating characteristics of 3+3 designs

UNETHICAL

Tends to treat a high percentage of patients at doses outside of the therapeutic range.

➡️ **No benefit for patients!**

UNEFFICIENT

Not reliable for selecting the correct maximum tolerated dose

➡️ **Wrong dose carried forward to future trials!**

Use only the current cohort to make next dose assignment decision
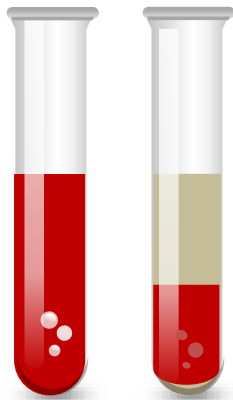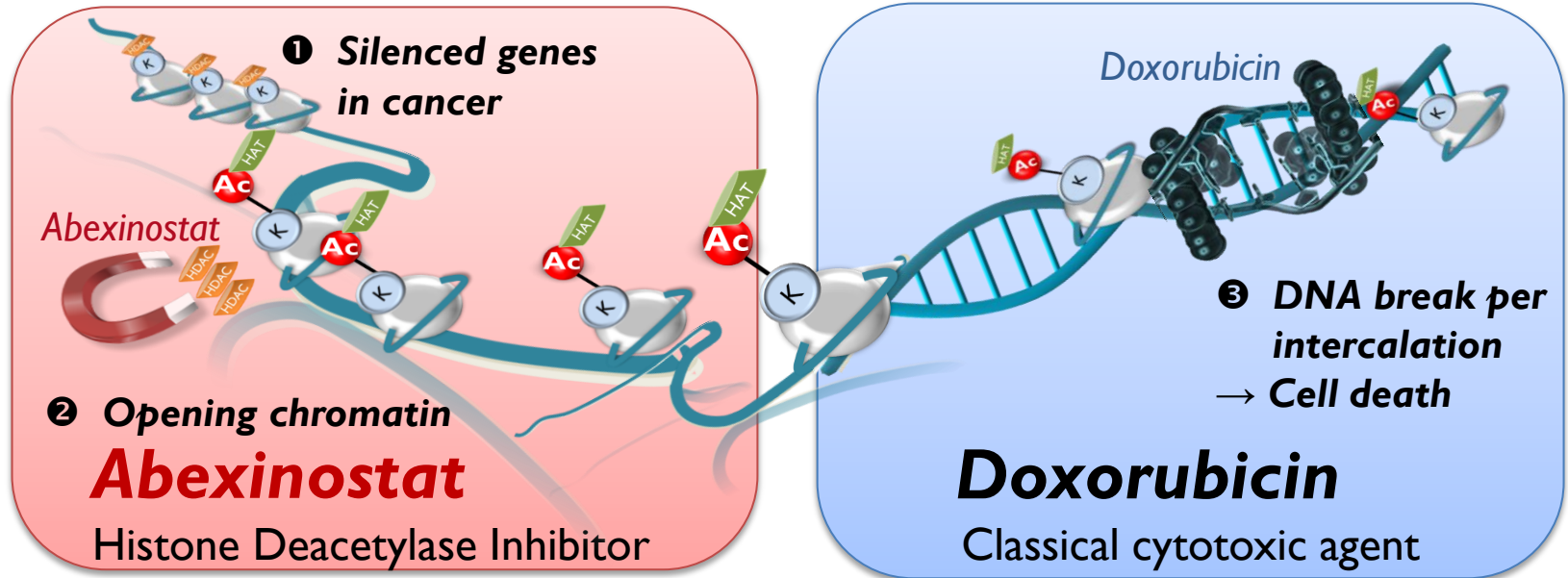
➡️ **Imprecised MTD!**

Aims of this talk

*To demonstrate **the need of a paradigm change***

*To illustrate using a real oncology example how Clinical Trial Simulation (CTS) can help to investigate the **predictivity** of different MTD determination methods **to the true MTD***

The combination therapy
and its main DLT

❶ *Silenced genes in cancer*

Abexinostat

❷ *Opening chromatin*

Abexinostat
Histone Deacetylase Inhibitor

Doxorubicin

❸ *DNA break per intercalation* → *Cell death*

Doxorubicin
Classical cytotoxic agent

Thrombocytopenia

DLT   as Platelet count < 25×10^9/L
          as **Grade 4 toxicity** (CTCAE v4.0)
          during the 1st cycle ONLY
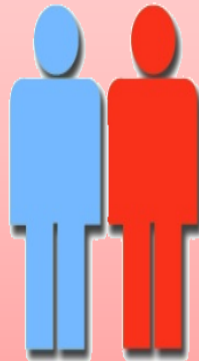
Data and study designs
Two "3+3 design" dose-escalation studies

**Abexinostat
with Free Doxo.
In solid tumors**

X 4 groups

n=4 at **30** mg/m^2
n=3 at **45** mg/m^2
n=9 at **60** mg/m^2
n=8 at **75** mg/m^2

Confirmatory phase
n =12 patients
at 60 mg/m^2

36

**Abexinostat
With Peg. Lypo. Doxo.
In ovarian cancer**

X 4 groups

n=3 at **30** mg/m^2
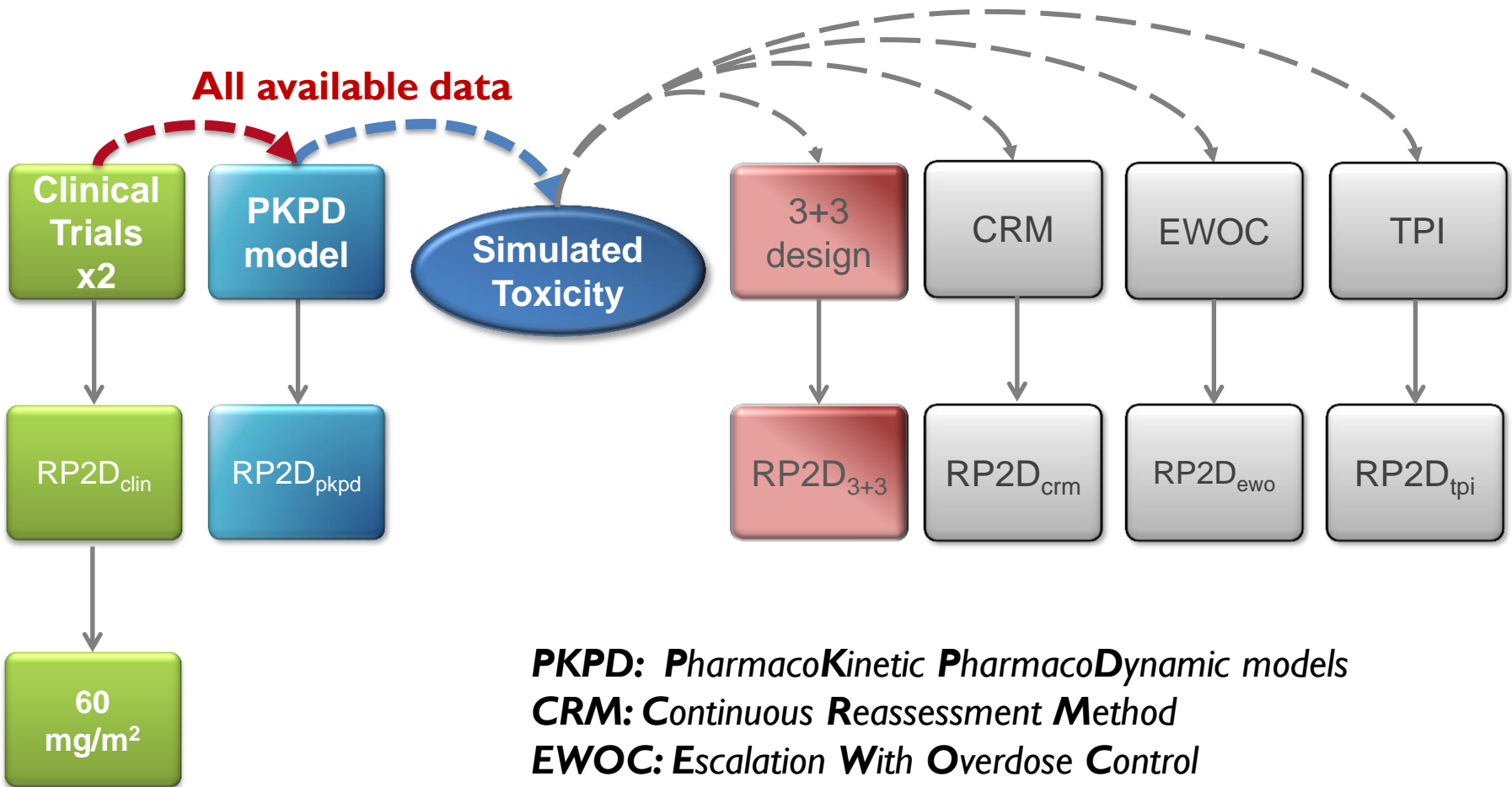n=4 at **45** mg/m^2
n=3 at **60** mg/m^2
n=7 at **75** mg/m^2

17

Clinical RP2D at 60 mg/m^2 was "suspiciously" low
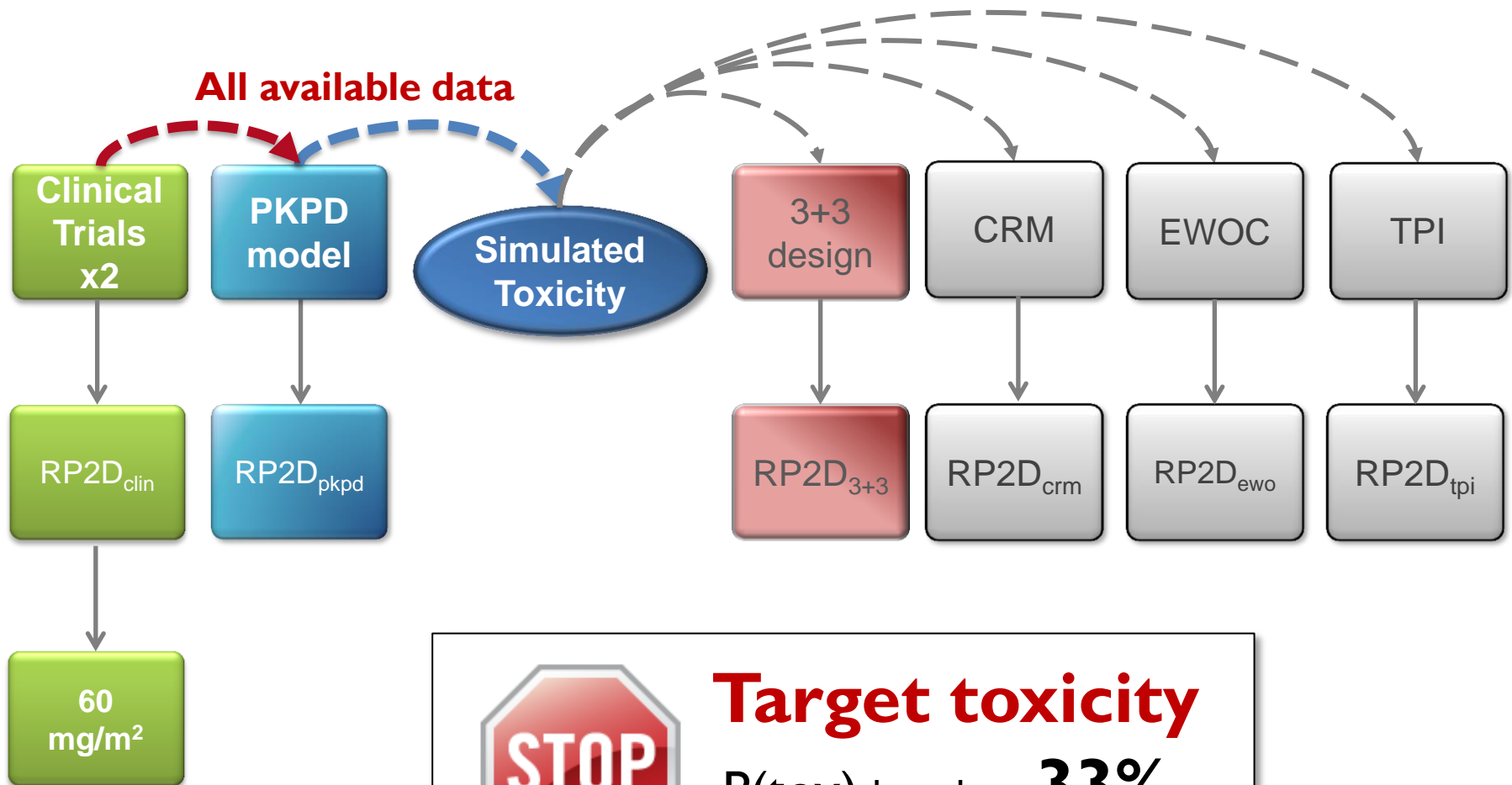
RP2D methodology
Comparison Framework

All available data

Clinical Trials x2 → PKPD model → Simulated Toxicity → 3+3 design, CRM, EWOC, TPI

RP2D$_{clin}$

RP2D$_{pkpd}$

RP2D$_{3+3}$

RP2D$_{crm}$

RP2D$_{ewo}$

RP2D$_{tpi}$

60 mg/m^2

PKPD: **P**harmaco**K**inetic **P**harmaco**D**ynamic models
CRM: **C**ontinuous **R**eassessment **M**ethod
EWOC: **E**scalation **W**ith **O**verdose **C**ontrol
TPI: **T**oxicity **P**robability **I**nterval

RP2D methodology
Comparison Framework

All available data

Clinical Trials x2 → PKPD model → Simulated Toxicity → 3+3 design | CRM | EWOC | TPI

RP2D$_{clin}$ | RP2D$_{pkpd}$ | RP2D$_{3+3}$ | RP2D$_{crm}$ | RP2D$_{ewo}$ | RP2D$_{tpi}$

60 mg/m^2

STOP

Target toxicity
P(tox) less than **33%**

RP2D methodology
Comparison Framework

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RP2D$_{clin}$ RP2D$_{pkpd}$

RP2D$_{3+3}$ RP2D$_{crm}$ RP2D$_{ewo}$ RP2D$_{tpi}$

SAFE

% patients with DLT

EFFICIENT

RP2D Trajectory

ETHICAL

Over or under dosing

Thrombocytopenia model

Thrombocytopenia model
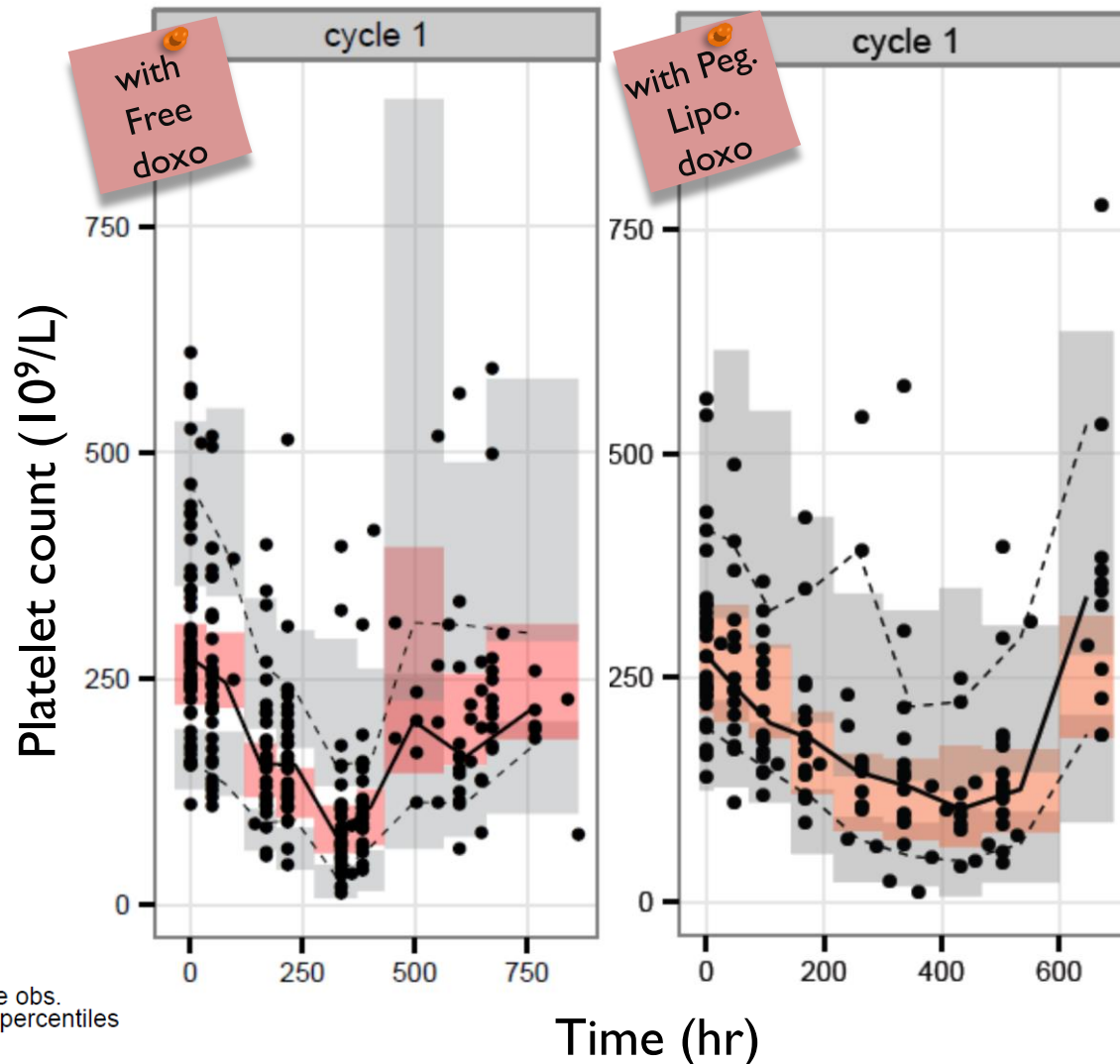

Abexinostat

Pegylated Liposomal Doxorubicin

Depot

Periph. — Central — Periph.

CL_A

Central Lypos.D

Cl_{LyposD}

Released compt.

Free doxorubicin $K_{released}$

Periph. — Parent Central — Periph.

CL_{freeD}

$E_{drug} = EFF_S + EFF_D$

$K_{prol} = K_{tr}$

Proliferating Precursor Pool

$Feedback = (\textbf{Base}/Platelets)^\gamma$

Thrombocytopenic toxicity

Prediction

K_{tr}

Transit 1 — K_{tr} → Transit 2 — K_{tr} → Transit 3 — K_{tr} → **Circulating Platelets**

$Mean\ Transit\ Time\ (\textbf{MTT}) = 4/K_{tr}$

$K_{elim} = K_{tr}$
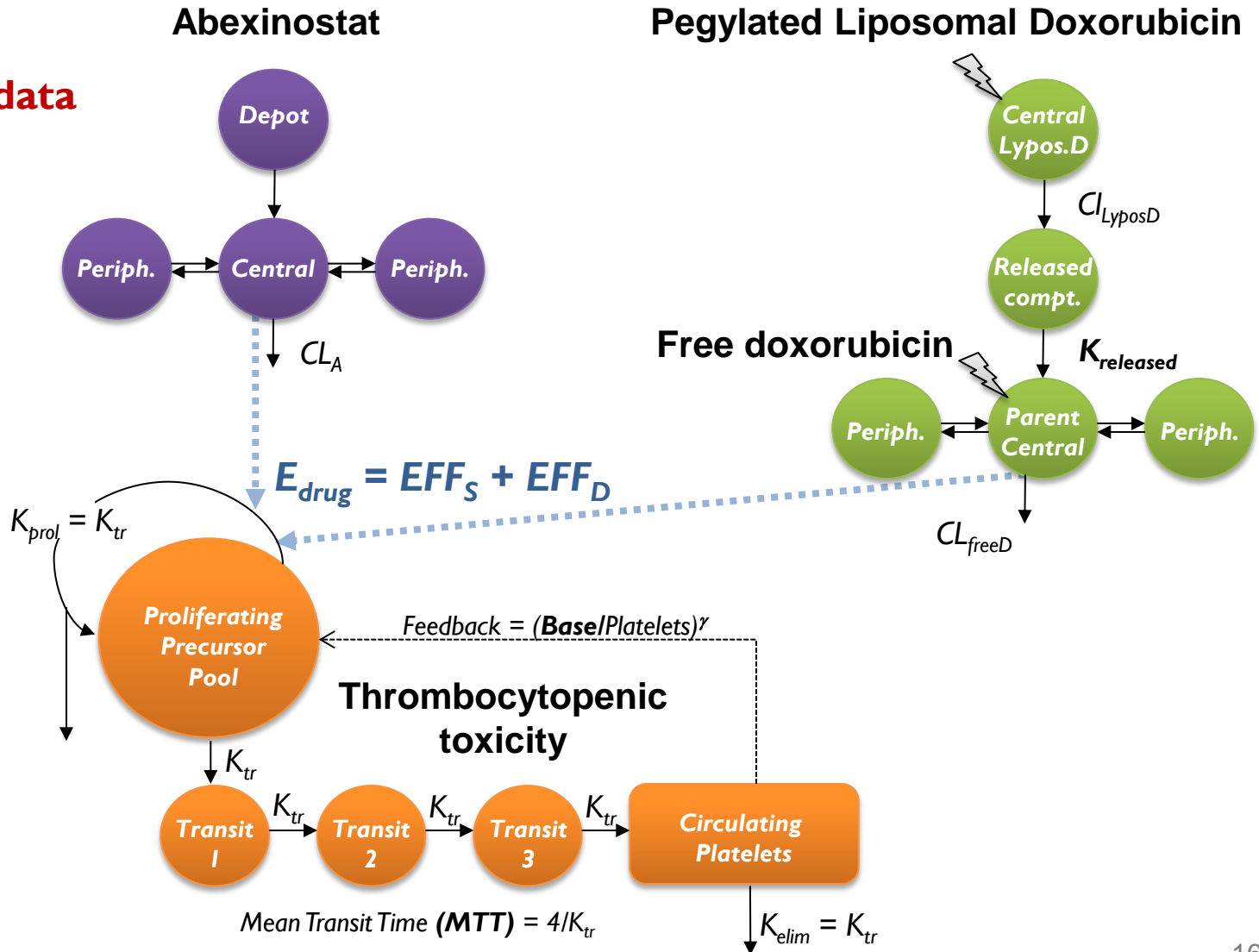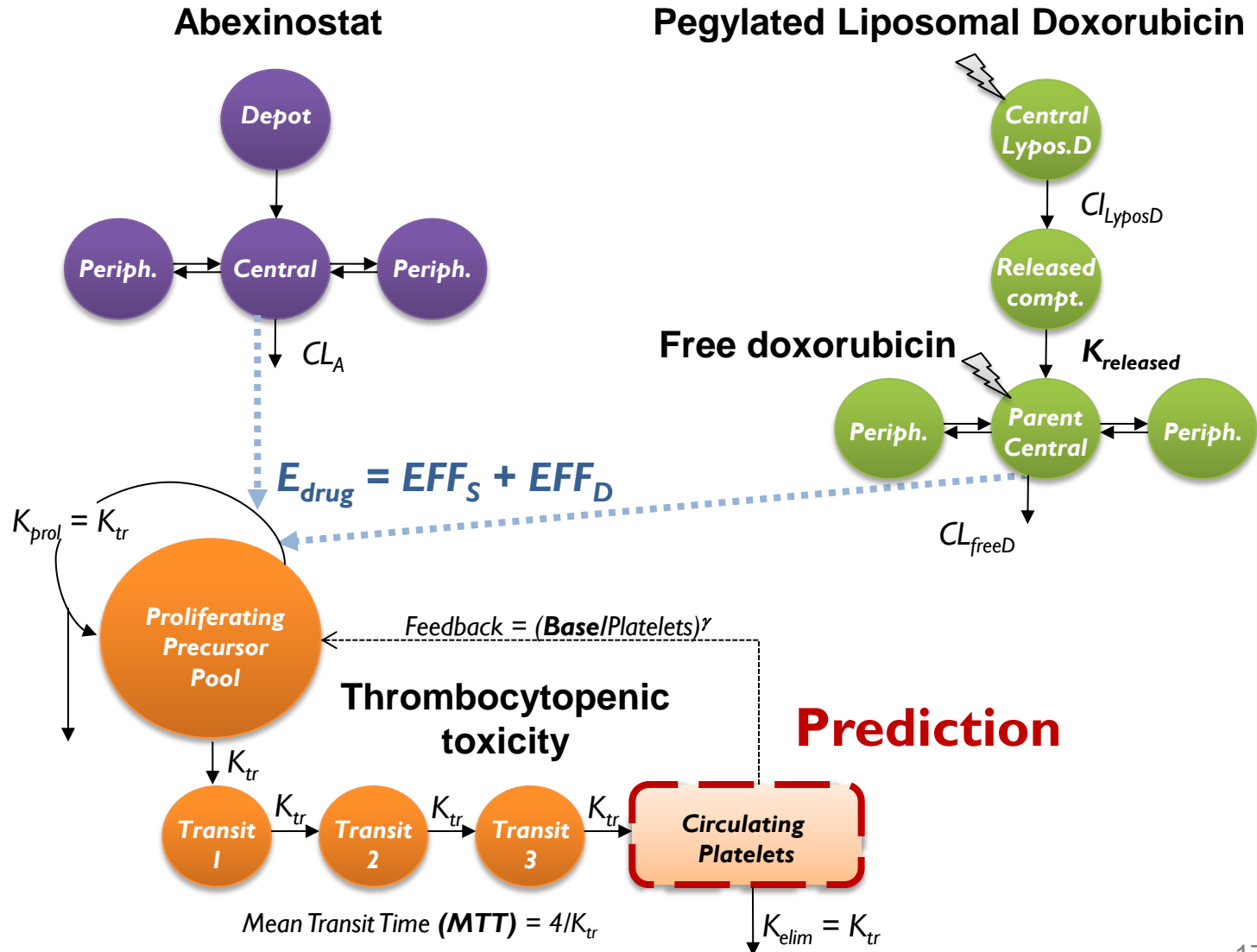
Diagnostics
Prediction-corrected Visual Predicted Check plots

Model-based RP2D$_{PKPD}$
120 mg/m²

RP2D$_{3+3}$ distribution

Reference: Storer et al. 1989
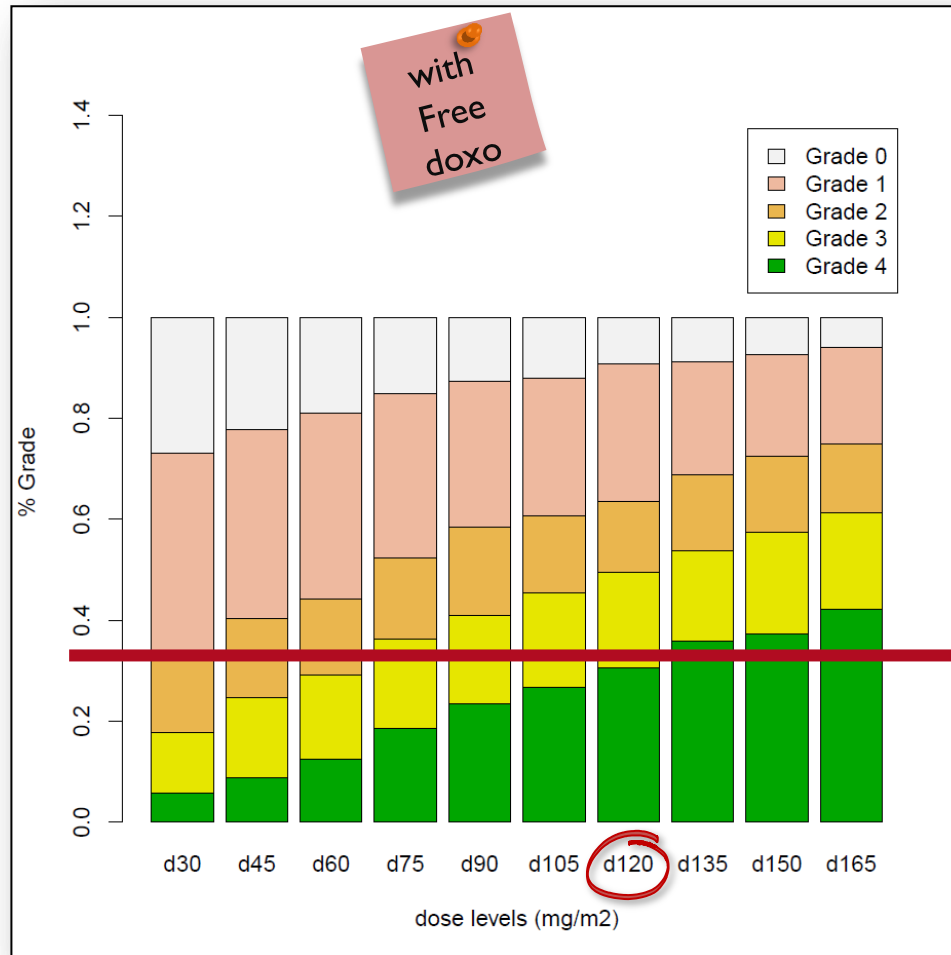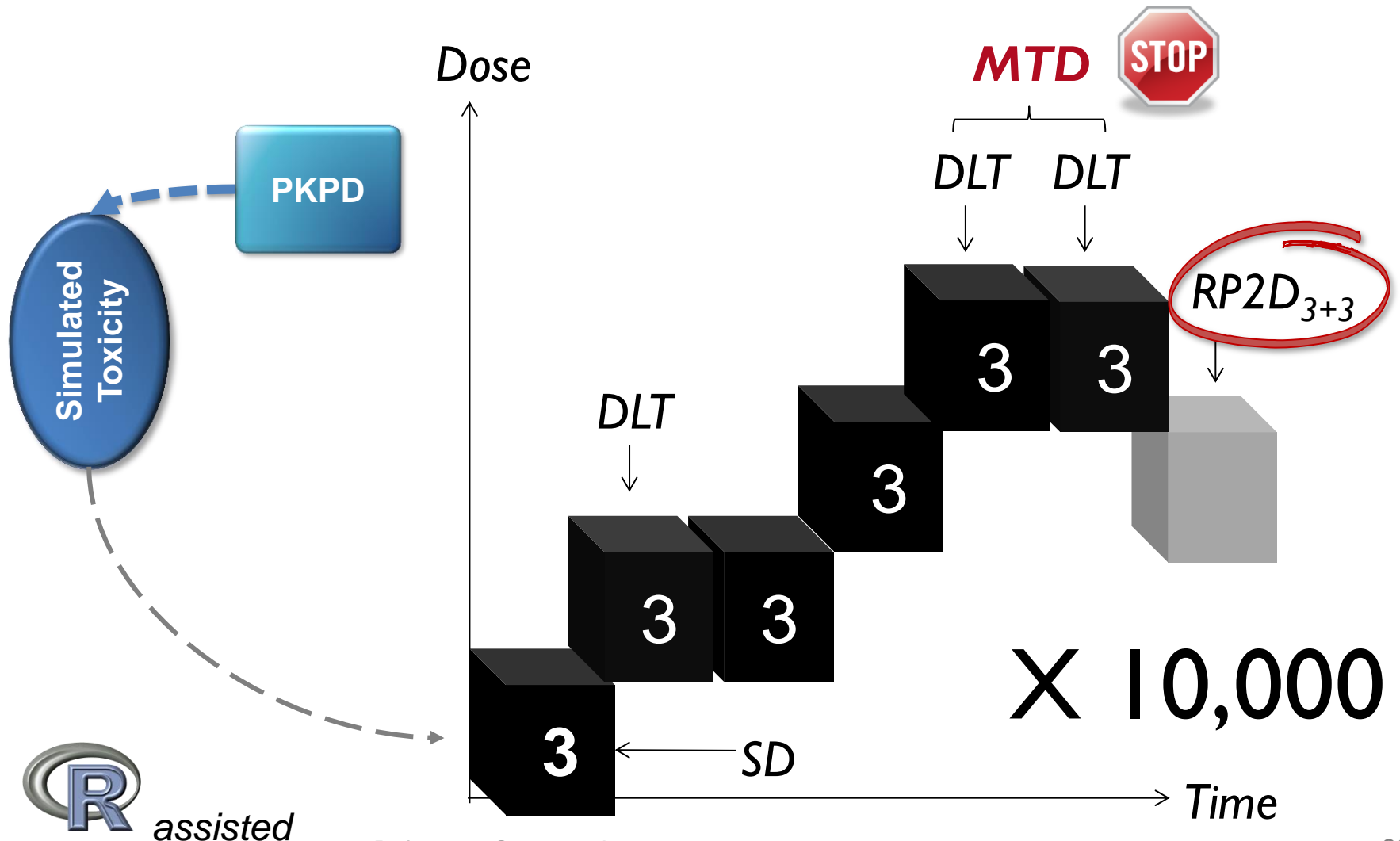
RP2D$_{crm}$,RP2D$_{ewo}$,RP2D$_{tpi}$
starting setup

CRM, EWOC, TPI use <u>Bayesian theory</u>

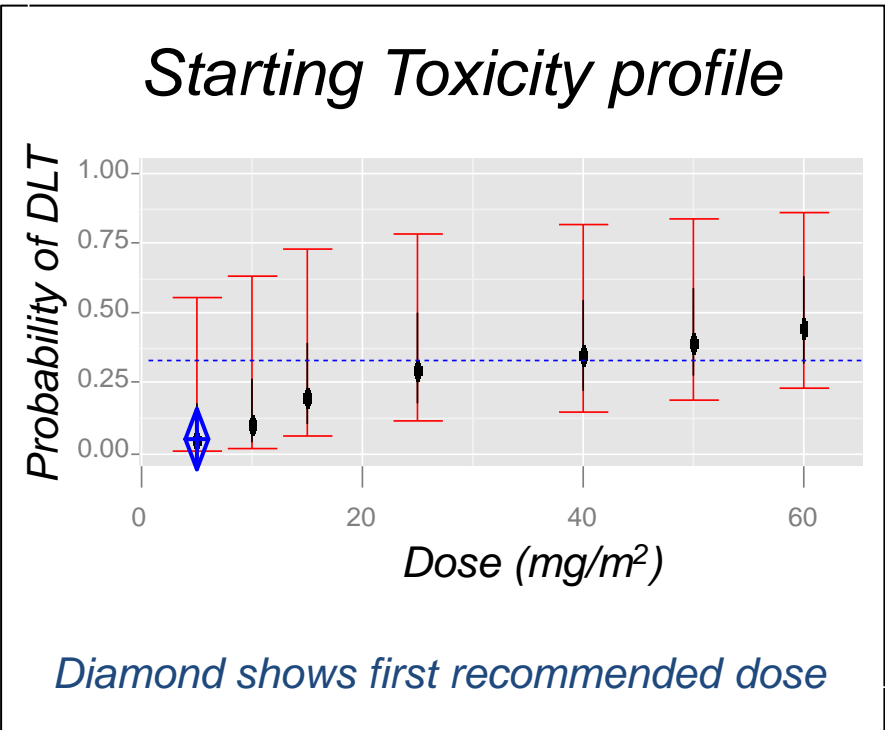**Before Trial**

Prior Information

Prior DLT risk per dose

Toxicity Model Assumption

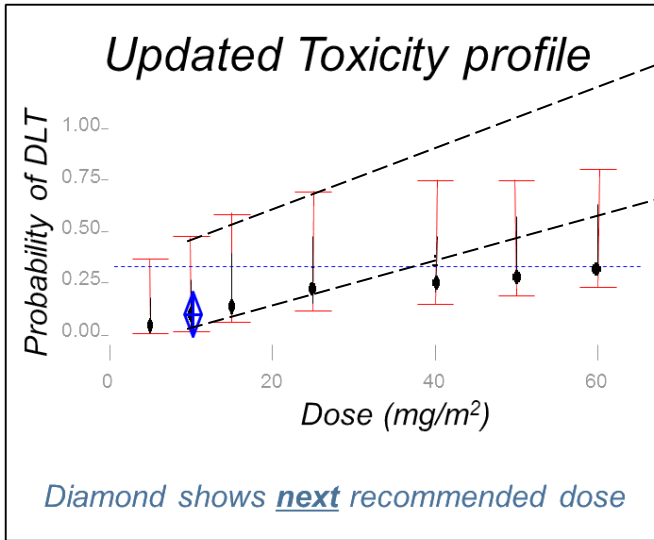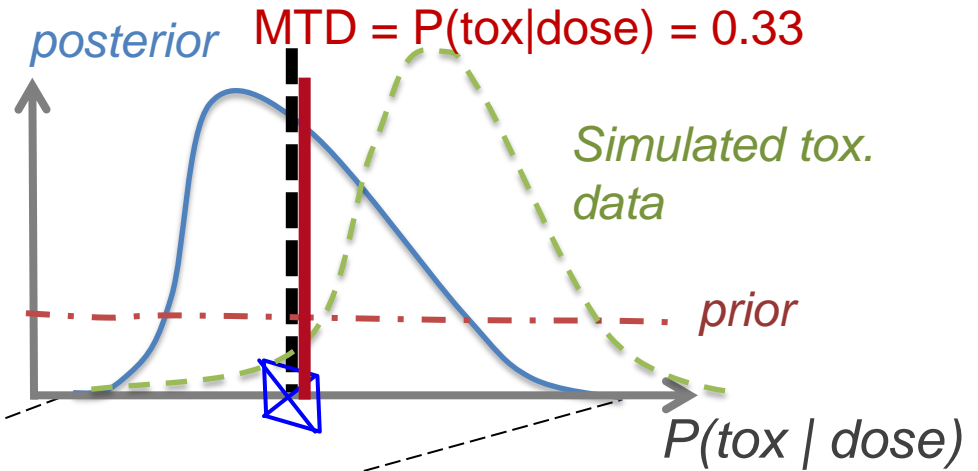| Prior parameter distribution *Uniform* | Power function $P_j = (\hat{x}_j)^\beta$ |

Starting Toxicity profile

Probability of DLT
- 1.00
- 0.75
- 0.50
- 0.25
- 0.00

Dose (mg/m²)
- 0
- 20
- 40
- 60

Diamond shows first recommended dose

Bcrm assisted

Reference: Quigley et al. 1990, Moller et al. & Goodman et al. 1995

CRM designs

posterior   MTD = P(tox|dose) = 0.33

Simulated tox. data

prior

P(tox | dose)

During Trial

Updated Toxicity profile

Diamond shows **_next_** recommended dose

CRM: Point-estimate of the posterior distribution

Reference: Quigley et al. 1990, Moller et al. & Goodman et al. 1995

EWOC designs

- Introducing an **overdose control**: expected proportion of patients treated at doses above MTD is equal to a specified value **α, the feasibility bound**.

- Using a two-parameter logistic model

MTD = P(tox|dose) = 0.33

α = 25% patients treated above MTD

P(tox | dose)
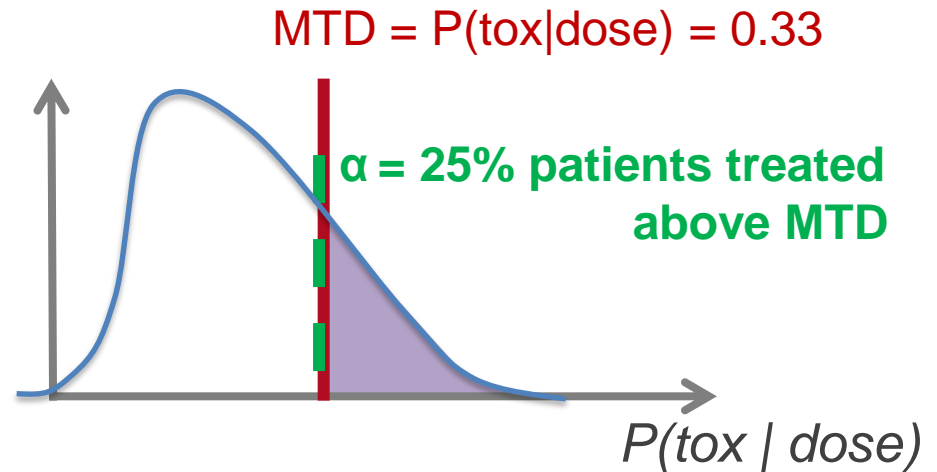
EWOC: 75th quantile of the posterior distribution

Bcrm, OpenBUGS (BRugs) assisted

Reference: Babb et al. 1998

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- Introducing Toxicity Probability intervals

- Introducing corresponding penalty loss function
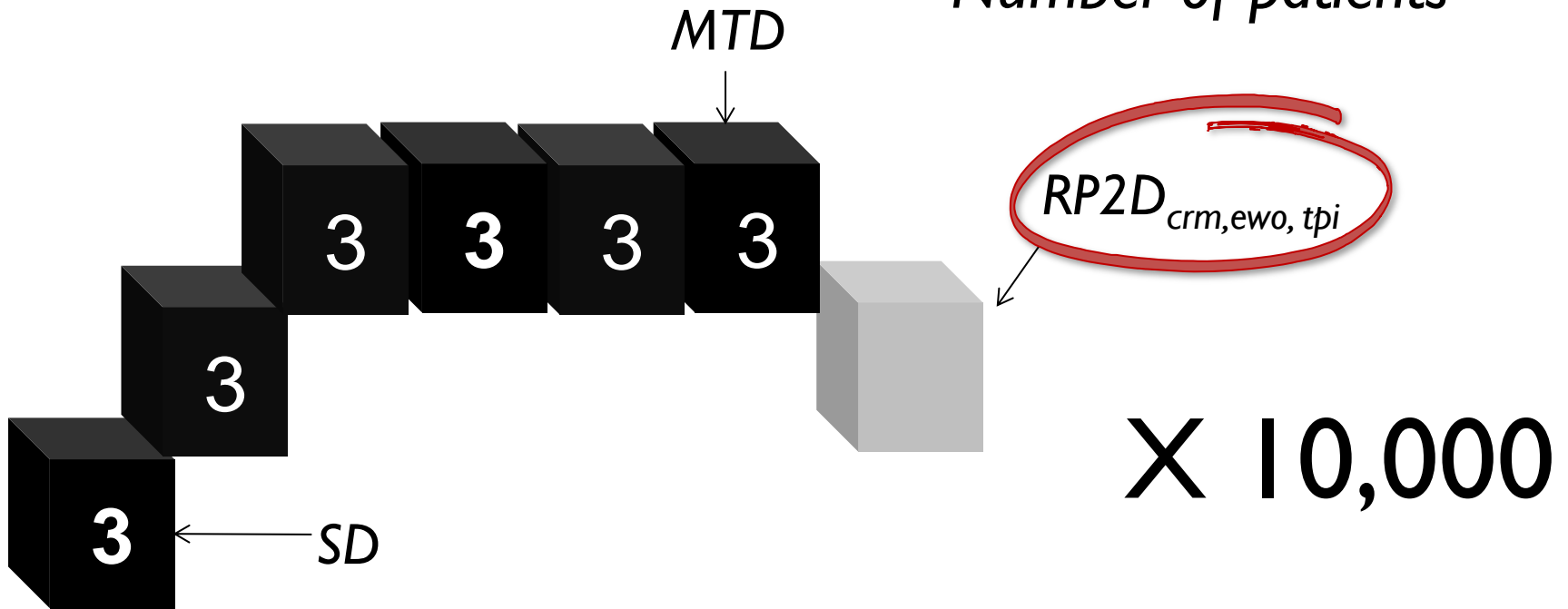
- Using a two-parameter logistic model

Underdosing

MTD = P(tox|dose) = 0.33

Target interval

Overdosing

P(tox | dose)
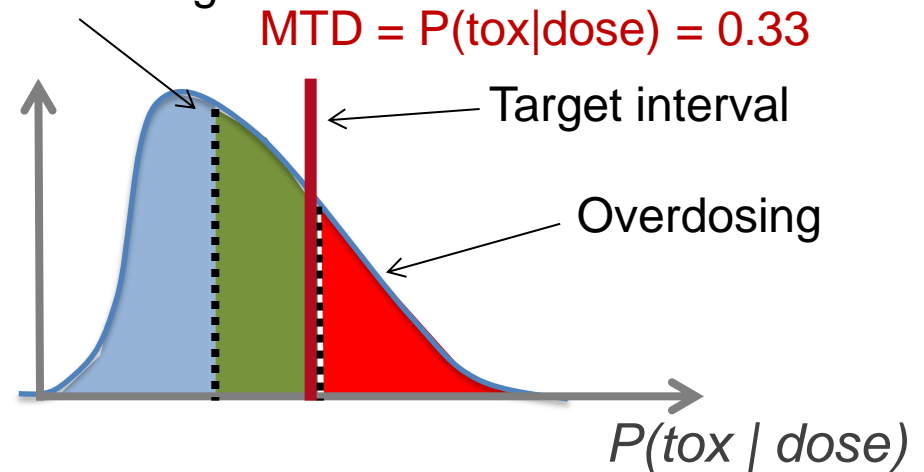
TPI: posterior distribution that maximizes probability in *target interval* with less than x % patients treated above MTD

Bcrm, OpenBUGS (BRugs) assisted

Reference: Ji et al. 2007, Neuenschwander et al. 2008

Reference: Quigley et al. 1990, Moller et al. & Goodman et al. 1995

Results

RP2D distributions – Clinical RP2D at 60 mg/m^2
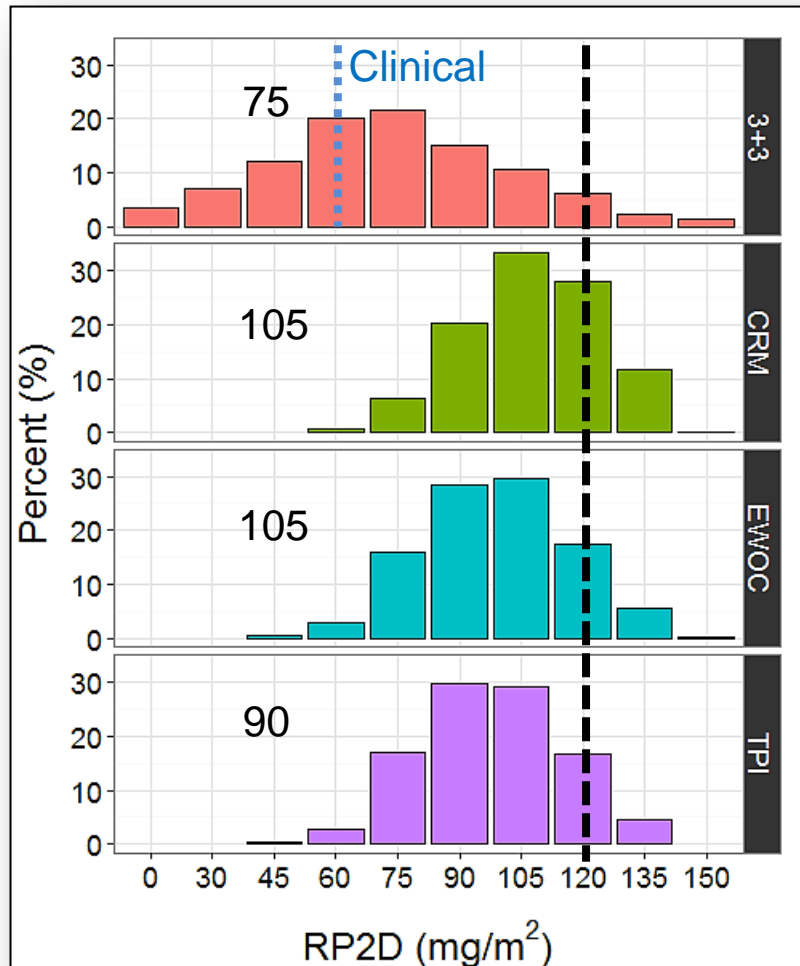
with Free doxo	Number dose level difference
3+3 design	**-3**
CRM	-1
EWOC	-1
TPI	-2
Clinical	**-4**

CRM: Continuous **R**eassessment **M**ethod
EWOC: Escalation **W**ith **O**verdose **C**ontrol
TPI: Toxicity **P**robability **I**nterval

Dose escalation trajectory

- Median
- Min & Max
- Lower & Upper Q
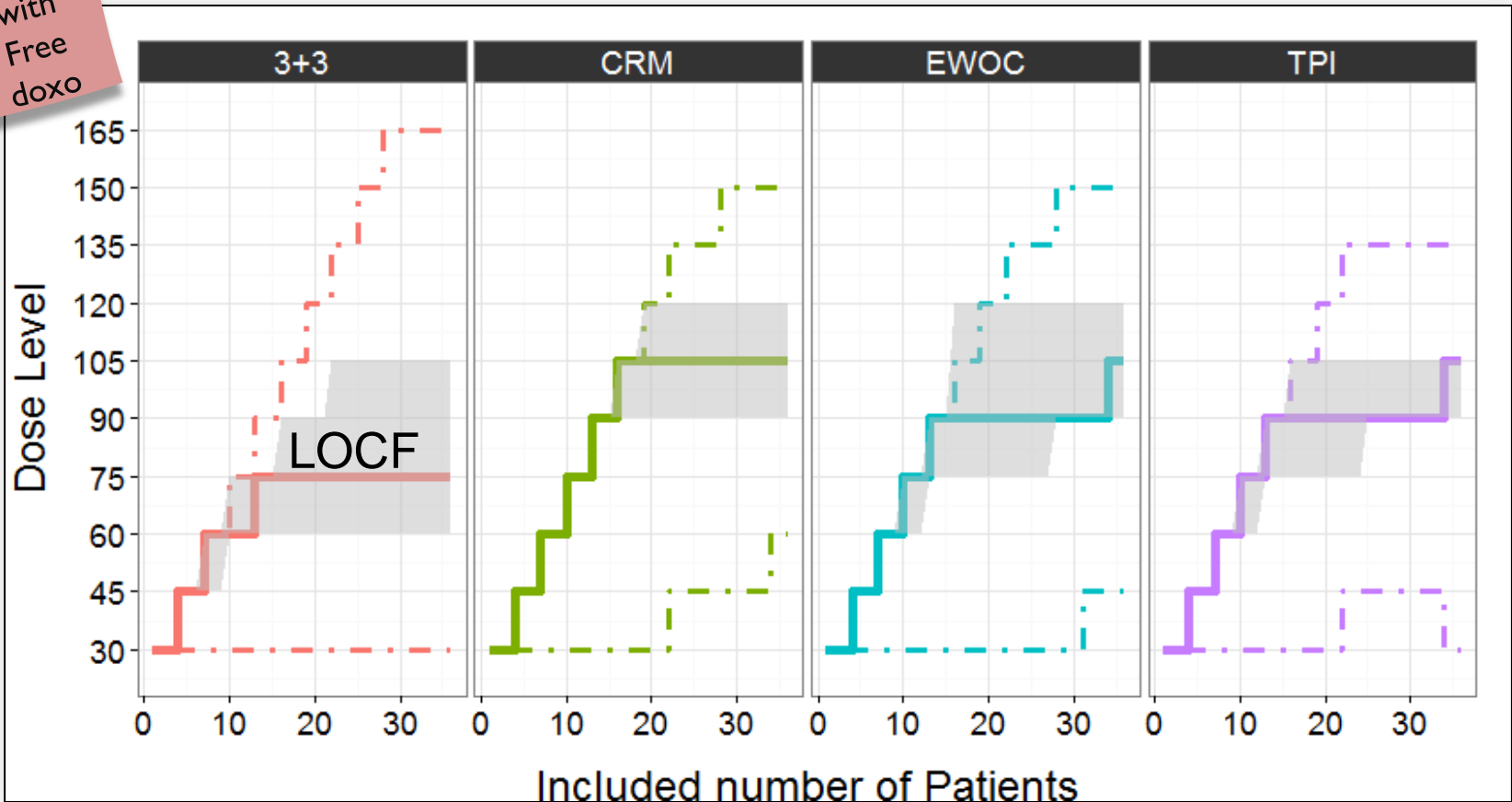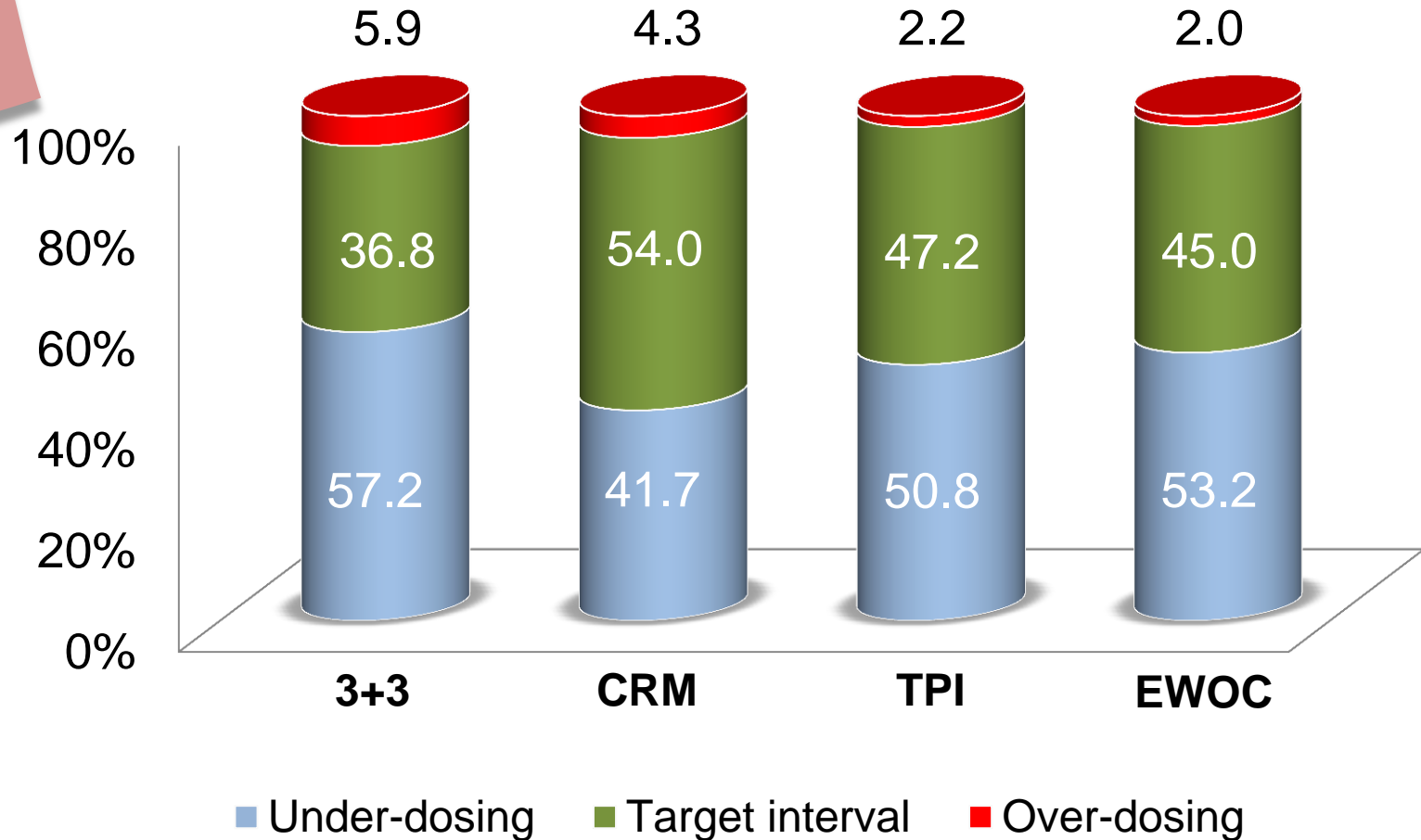

with Free doxo

Results

Comparison of %patients at P(tox) = [0.17-0.33]

Results
% patients with DLT distribution

with Free doxo
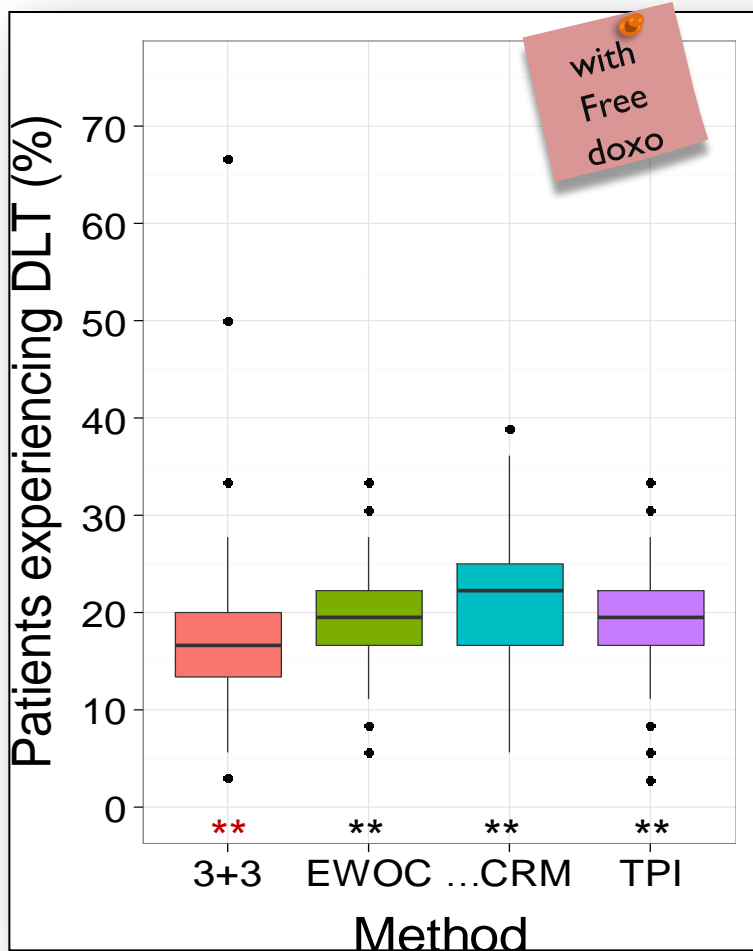
Less DLTs with
3+3 trials

CRM: *Continuous Reassessment Method*
EWOC: *Escalation With Overdose Control*
TPI: *Toxicity Probability Interval*

** significant using Mann-Whitney U Test

Take-home messages

➢ Differences between Bayesian methodologies not as important as the **need to reconsider "3+3 design"**

➢ Using all data available, the **PKPD model-based analysis** at end of Phase I as a valuable tool to re-evaluate RP2D if discrepancy found from 3+3 designs

➢ **Benefits** of Bayesian methods **But** statistically
         complex → Simulations are vital !
         non-intuitive → Better communication
                    More team work

Concluding remarks

… Like a domino effect

*The importance of getting it **right** from the beginning!*
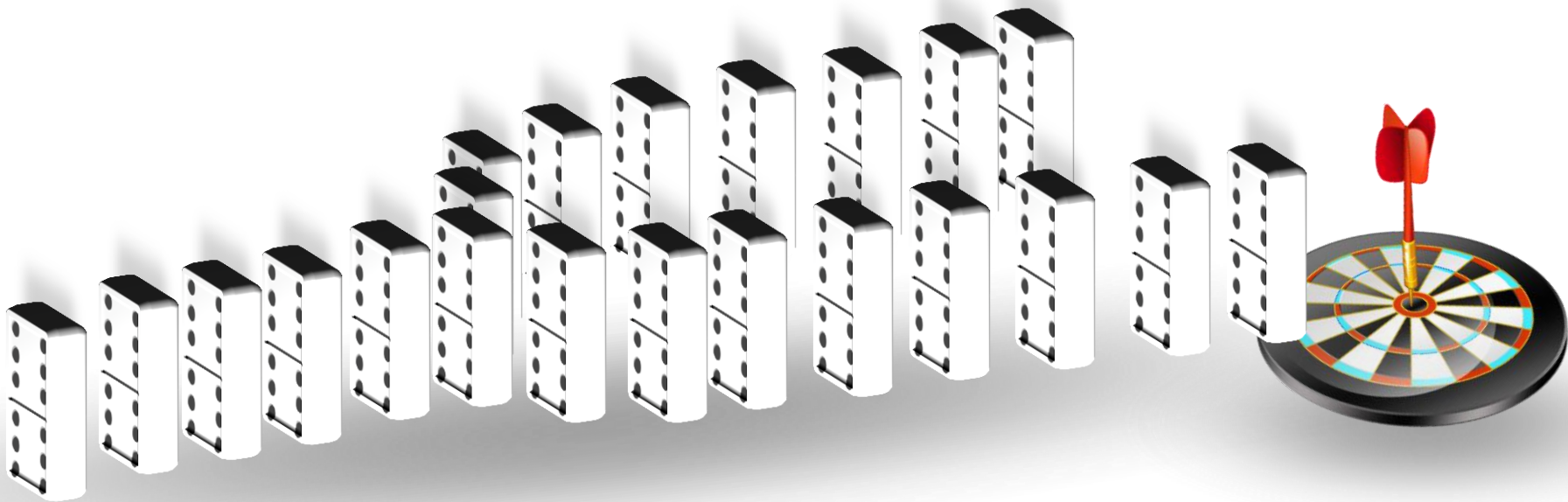
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Thank You for your attention!