Clinical evaluation of early phase clinical trials in Oncology

FAHMP

BRUSSELS

15.09.2023

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Early phase (phase I or I/II) clinical trials in Oncology

First evaluation of a new anticancer medicine in humans (more specifically early phase dose-finding trials)

- Monotherapy: first-in-class or not.
- Combinations:
  - investigational medicinal product (IMP) + approved MP;
  - IMP + IMP (novel-novel combinations);
  - IMP + other interventions (e.g. radiotherapy).

Clinical pharmacology trials

Generally used objectives in dose-finding trials

Primary:

- characterise the safety and tolerability;
- define dosage for further development, e.g. recommended phase II dose (RP2D), e.g. based on the maximum tolerated dose (MTD).

Secondary:

- evaluate PK*/PD**;
- evaluate antitumor activity, preliminary efficacy (e.g. response rate);
- others (e.g. biomarkers, biomarker substudies)

***PK aspects to consider:**

- PK sampling scheme, choice of the PK parameters, Cmax and AUC;
- derived from the plasma concentration-time profiles using standard non-compartmental methods.

****PD aspects to consider:**

- proof-of-mechanism (hit the target, PD markers);
- proof-of-activity (effect of hitting the target in the tumour, mechanism-based adverse events).

Study population in oncology dose-finding trials

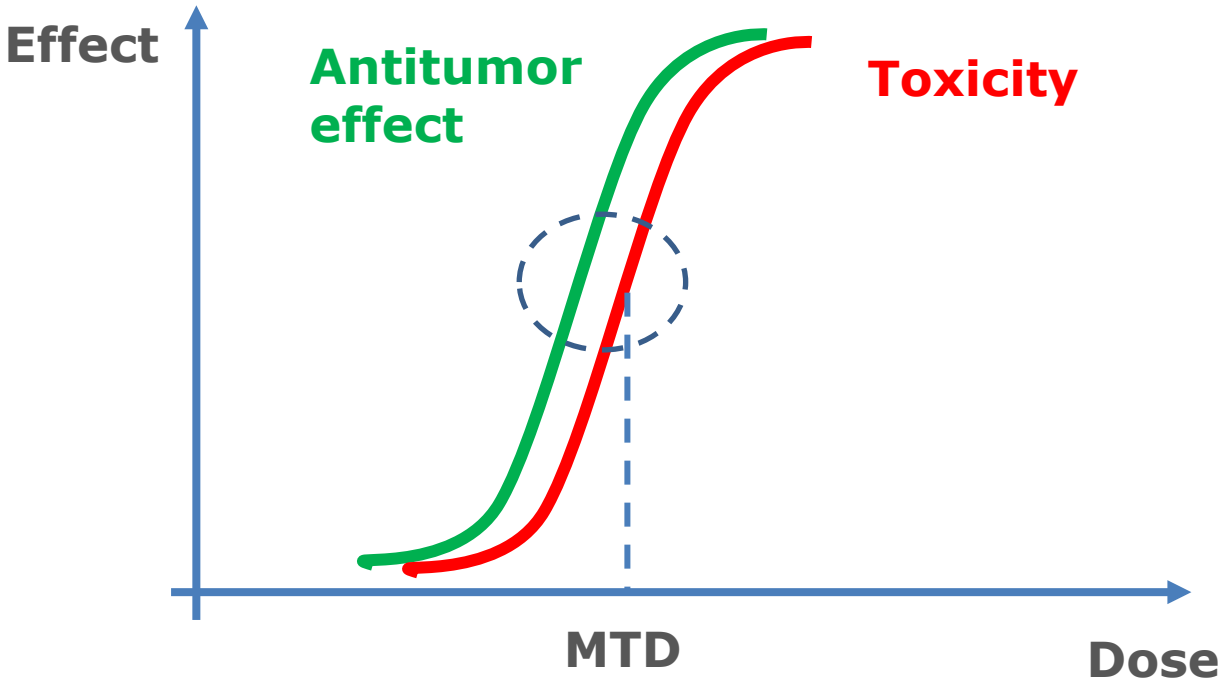
Typical eligibility criteria (examples):

- patients with advanced tumors unresponsive to standard therapies or/no known effective treatment;
- performance status;
- specification on organ function, comorbidities, prior lines.

IMP-specific eligibility criteria may include:

- restriction to certain patient populations (with rationale);
- specific functions informed by preclinical data: eg QTc, LVEF, hypertension … ;
- prohibited medication.

Dose selection principles in oncology (dose-finding paradigm for cytotoxic agents)



DLTs:

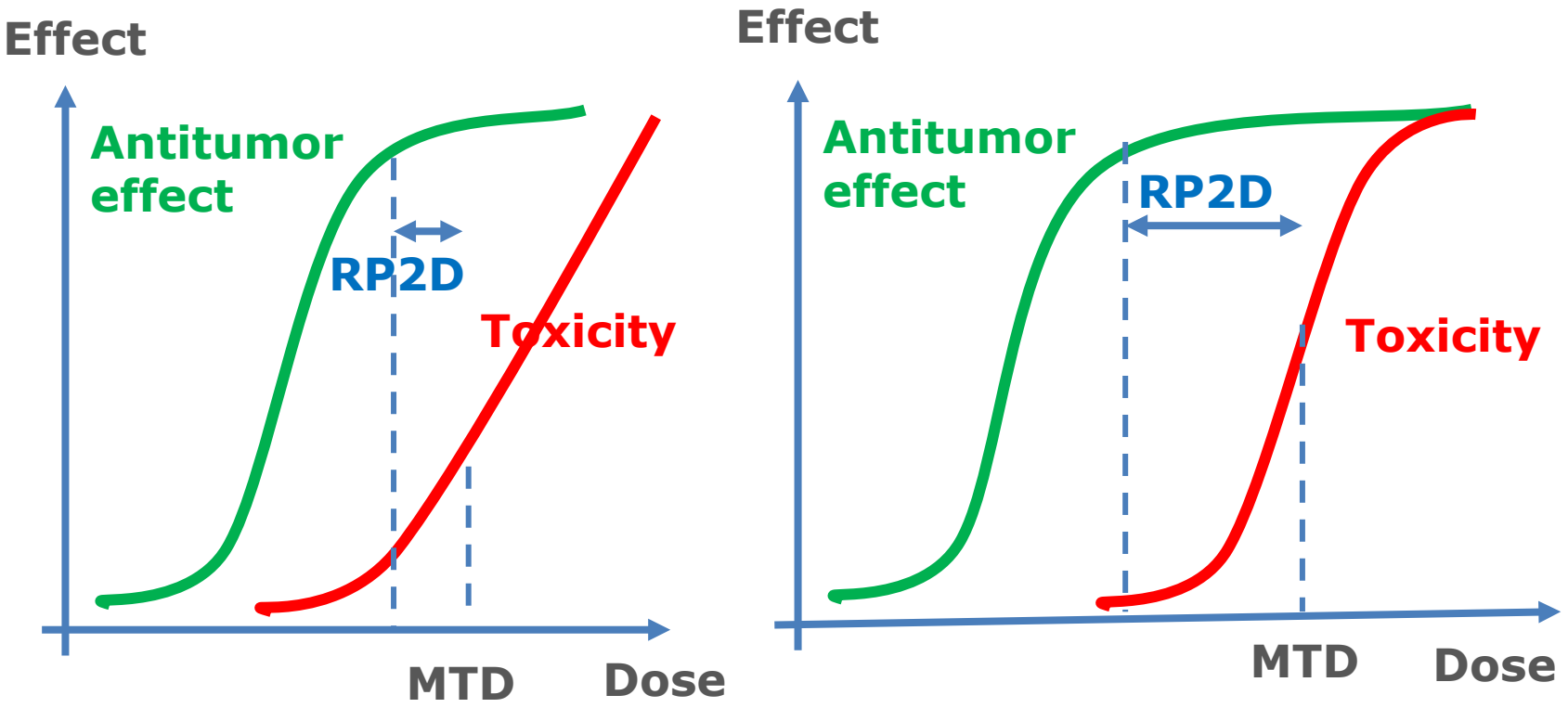
- usually G3-G5;
- during first cycle.

MTD:

- based on incidence of DLTs;
- during first cycle.

DLT: dose-limiting toxicity.
MTD: maximum tolerated dose.

Dose selection principles in oncology (evolving paradigm for non-cytotoxic agents)



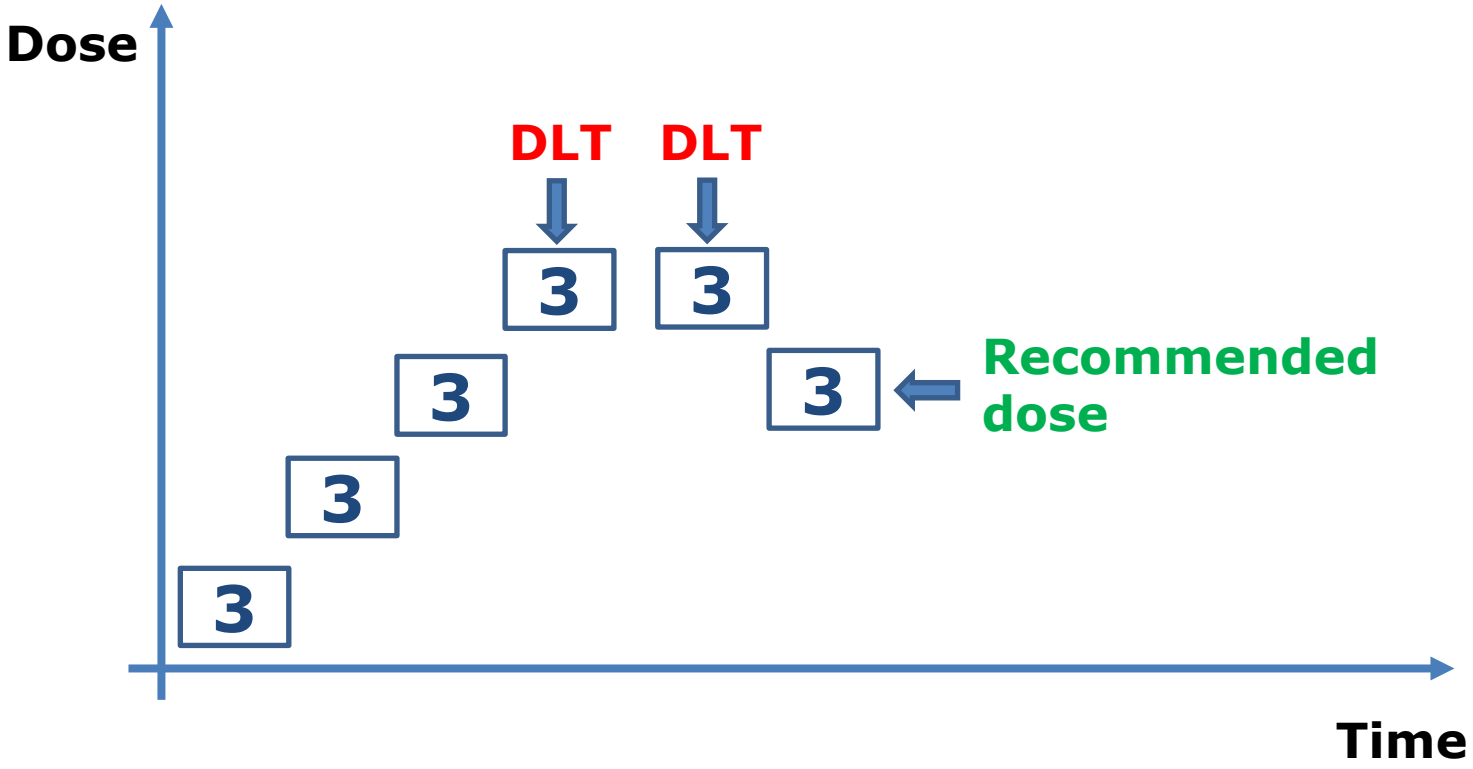
DLT: dose-limiting toxicity.
MTD: maximum tolerated dose.
RP2D: recommended phase 2 dose.

Various dose-finding designs in oncology

- Dose (de-)escalation and dose expansion parts.
- IMP-specific dose-limiting toxicities.
- Designs considering toxicity alone, toxicity and activity, totality of data.
- Different statistical operating characteristics (statistical properties of the design).

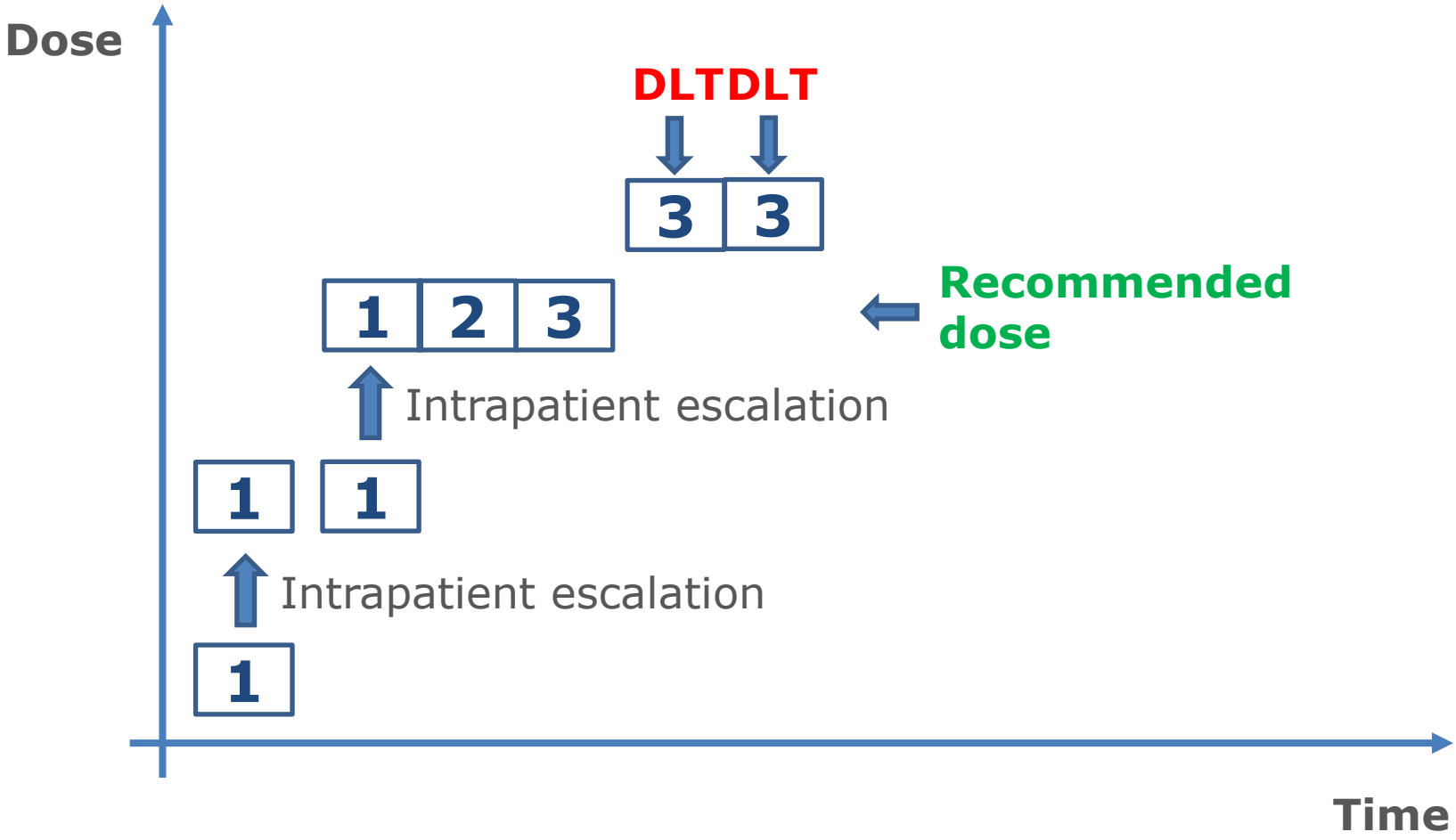
Traditional 3+3 design
(rule/algorithm-based, all the rules pre-specified).

Traditional 3+3 design



DLT: dose-limiting toxicity.

Accelerated titration design



DLT: dose-limiting toxicity

MTD-based traditional approach to select R2PD

Based on assumptions

- Monotonicity in increased toxicity and efficacy with increased dose (the higher the dose, the greater the likelihood of toxicity/efficacy; dose-related acute toxicity is regarded as a surrogate for efficacy, the highest safe dose considered as most likely efficacious).
- This dose-effect assumption is primarily for cytotoxic agents and may not apply to molecularly targeted agents.

Does not account for antitumor activity.

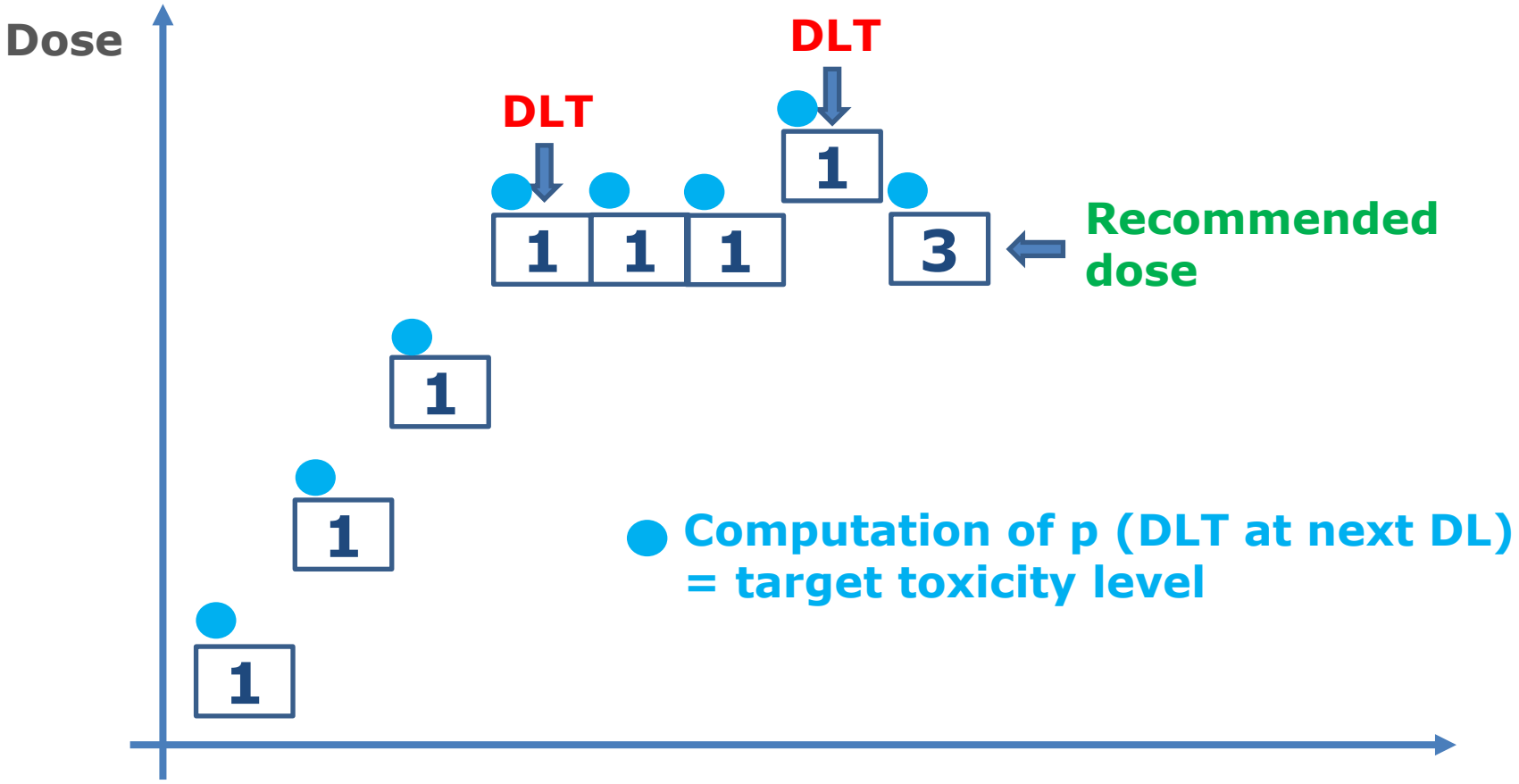
Does not account for late toxicities.

Various dose-finding designs in oncology

Traditional 3+3 design
(rule/algorithm-based, all the rules pre-specified).

Model-based designs
(use statistical models to determine decision for the next dose).
e.g. CRM (continual reassessment method),
EWOC (escalation with overdose control).

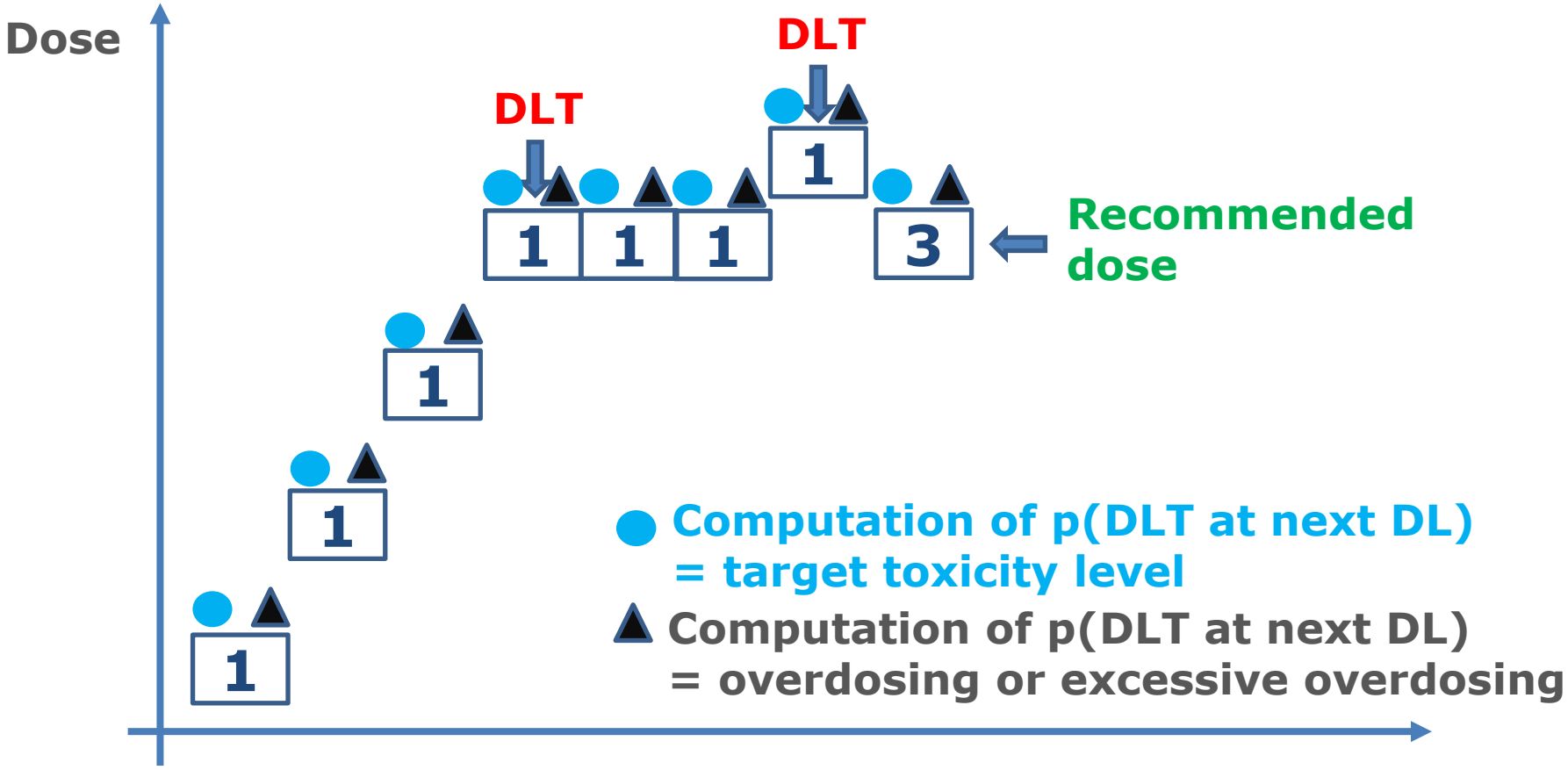
Continual reassessment method (model-based)



DLT: dose-limiting toxicity.

pDLT: probability of dose-limiting toxicity.

Escalation with overdose control (model based)



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Various dose-finding designs in oncology

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Model-assisted designs (mixture of the previous designs, dose escalation/de-escalation rules determined using a statistical model before conducting the trial).
e.g. mTPI (modified toxicity parameter interval) and BOIN (Bayesian optimal interval).

Conclusions for dose-finding trials goals

Ensure favourable benefit-risk:

- for patients in the trial (starting dose, stopping rules, minimise exposure to subtherapeutic doses and overexposure);
- for further development (maximise the efficacy, minimise the toxicity);
- aiming at optimal dosage to the extent possible, totality of data.

Ensure/discuss optimal operating characteristics:

- probability of correctly identifying MTD, probability of treating patients at doses above the MTD, sample size justification;
- efficiency of the development in terms of resources and increasing probability of success in later development.

Justify the choice of the design at the CTA submission.

Thank you for your attention!

Questions?

Contact

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