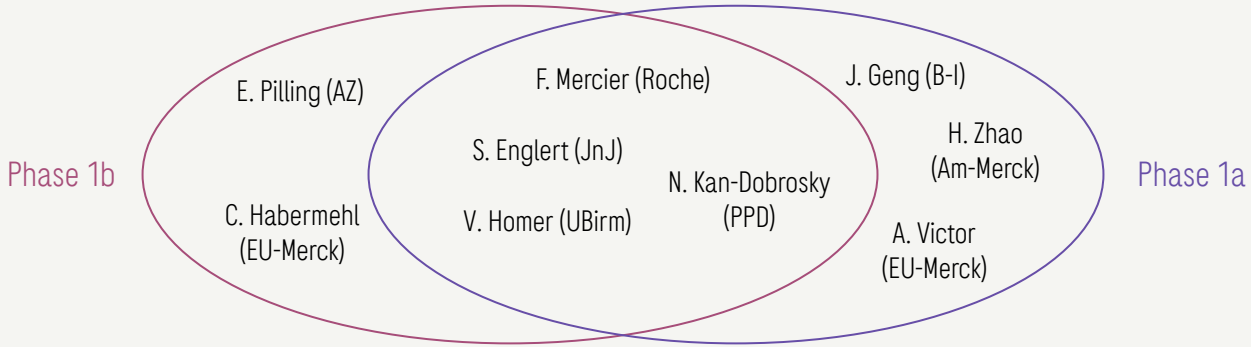
Estimand thinking in oncology Phase 1a dose escalation clinical trials

Francois Mercier (Roche-Genentech)

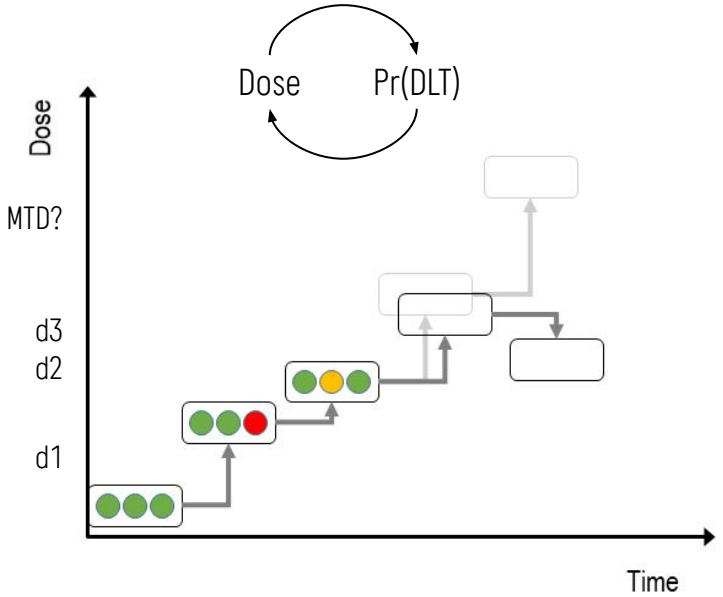
Acknowledgement

Members of the **E**arly **D**evelopment **E**stimand **N**exus,
a task force the oncoestimand WG



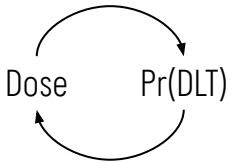
Oncology Phase 1a dose escalation studies are adaptive and iterative

- Escalate until maximum tolerated dose (MTD) is reached.
- Toxicity is evaluated by a binary endpoint: Presence of Dose-Limiting Toxicity (DLT) during the DLT assessment period (e.g. 21 days)



What is the clinical question?

- To determine the dose for the next cohort?
- To estimate the Pr(DLT) at the end of the current cohort?
- To estimate the MTD at the end of dose-escalation?
- To estimate the MTD2 across multiple dose-escalation/finding studies (e.g. pooling Phase 1a and Phase 1b data about DLT)?
- To establish the RDE (Recommended Dose for Expansion) at the end of dose-escalation?
- All of the above?



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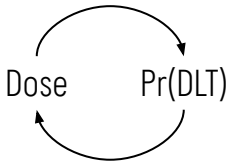
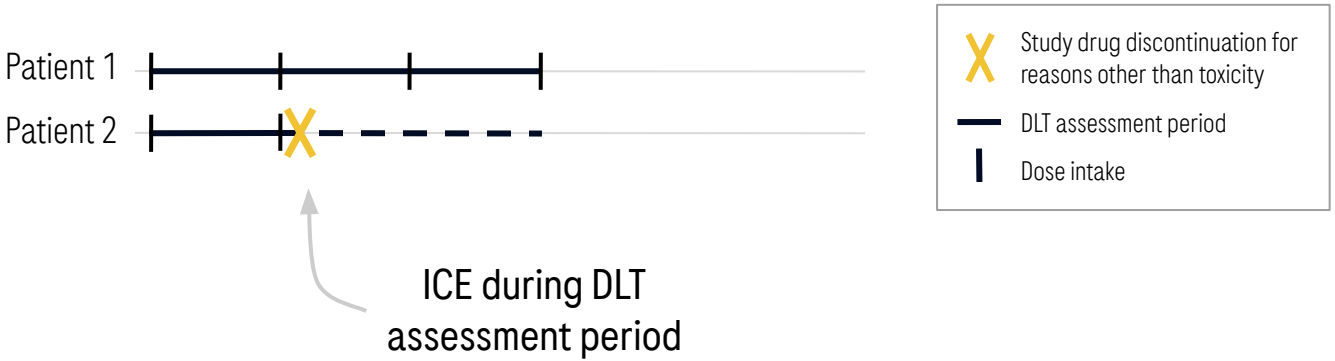


Estimand attributes

Attribute	Definition	Comment
Target population	Patients presumed to be sensitive to the expected MoA of the investigational drug	
Treatment	Intervention: dose strength, route, frequency, etc.	Actual initiation of treatment, at the actual dose.
Endpoint	Presence/absence of DLT over a given assessment period (e.g. 21 days)	DLT is an AE at least possibly related to the investigational treatment. Nuances in DLT definition are many (assessment period duration, grades, type of AEs, etc.) → Recommendation: add every possible detail.
Pop-level summary	Pr(DLT)	'Absolute' (≠ relative) effect size (in abs. of control) Necessary to contextualize the estimated effect size.

Impact of ICE on DLT assessment

Example of Treatment discontinuation for reasons other than toxicity



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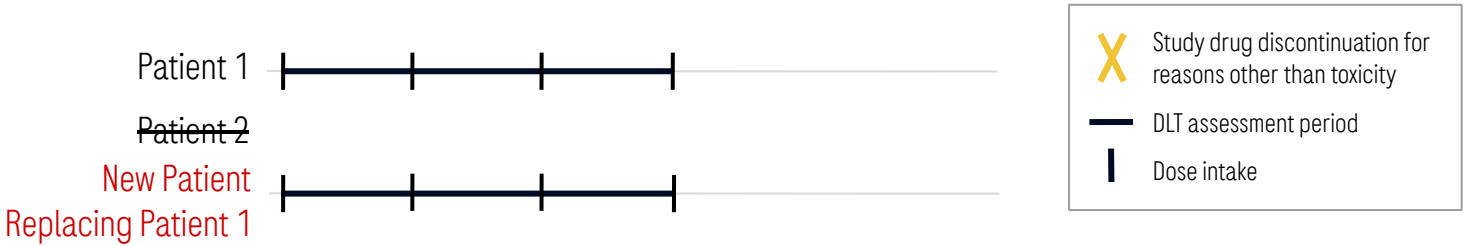
The **convention** in oncology Phase 1a DE studies is to (discard and) **replace** the patient experiencing the ICE.



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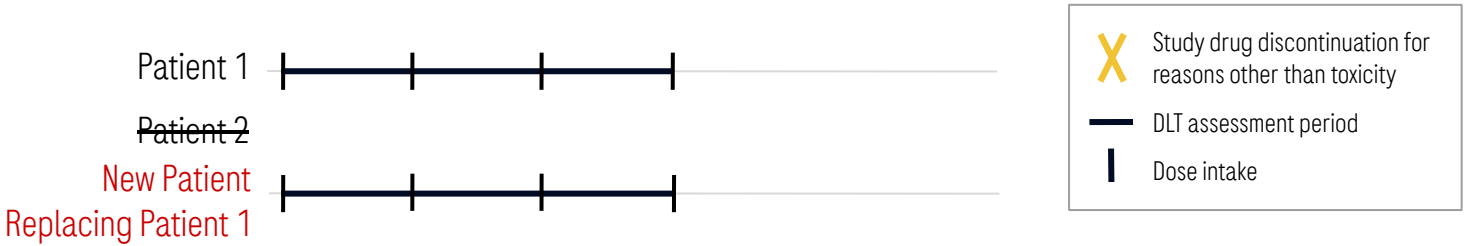

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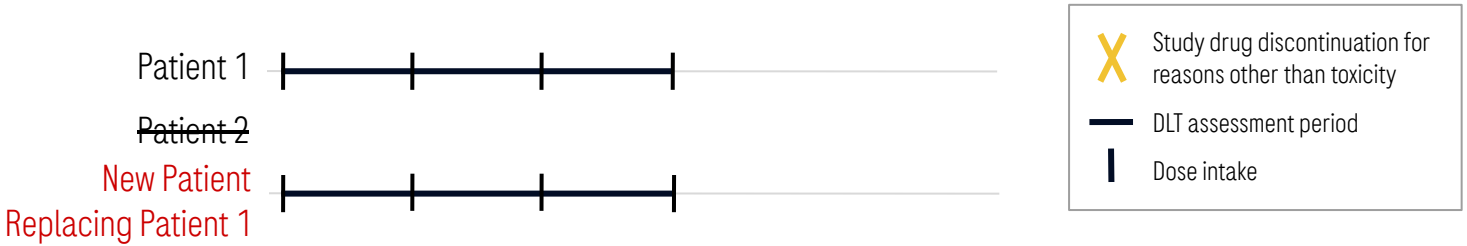

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→ Conflicts with the intended target population

Alternative clinical questions and ICE handling strategies

Example of Treatment discontinuation for reasons other than toxicity

Strategy	Clinical question	Estimator
Treatment policy	What is the Pr(DLT) irrespective of the participant discontinuing treatment? [Not clinically relevant]	-
Composite	What is the Pr(DLT or discontinuation for non-toxicity reasons)? [Not clinical relevant]	-
Hypothetical	What would be the probability of DLT, had treatment discontinuation not occurred? [Fair question]	Possible, e.g. using TITE-BOIN or DA-CRM
While on-treatment	What is the probability of DLT, before treatment discontinuation occurs? [Fair question]	Possible, e.g. using TITE-CRM or TITE-EWOC
Principal stratum	What would be the probability of DLT, in the strata of participants who would not experience discontinuation for non-toxicity reasons? [Fair question]	Difficult

More details, more examples here

Mercier *et al.* (2023+) Estimands in oncology early clinical development: Assessing the impact of intercurrent events on the dose-toxicity relationship *(under review)*

Also covers the case of dose modification as another type of ICE.

Take home messages

- Adopting the ‘estimand thinking’ in early clinical development gives a chance to question the adequation between [study objective] ⇔ [estimand] ⇔ [estimator]

- ICH-E9 (R1) addendum offers:
  - A framework and a language to structure the definition of the estimand in oncology DE trials,
  - A chance to anticipate potential sources of bias due to ICEs

- General practice to replace the patients with ICEs should be challenged if it does not support the intended clinical question

Thank you for your attention

francois.mercier@roche.com

Doing now what patients need next