Surv-CRM-12
A Bayesian Phase I/II Survival CRM for Right-Censored Toxicity Endpoints with Competing Disease Progression

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CHALLENGES FOR DOSE-FINDING TRIALS IN ONCOLOGY

- Delayed effects, including toxicities **(extended observation windows)**

  → Depending on the patient accrual rate, generate **incomplete data**

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- **New definition of the target dose** (instead of the MTD)

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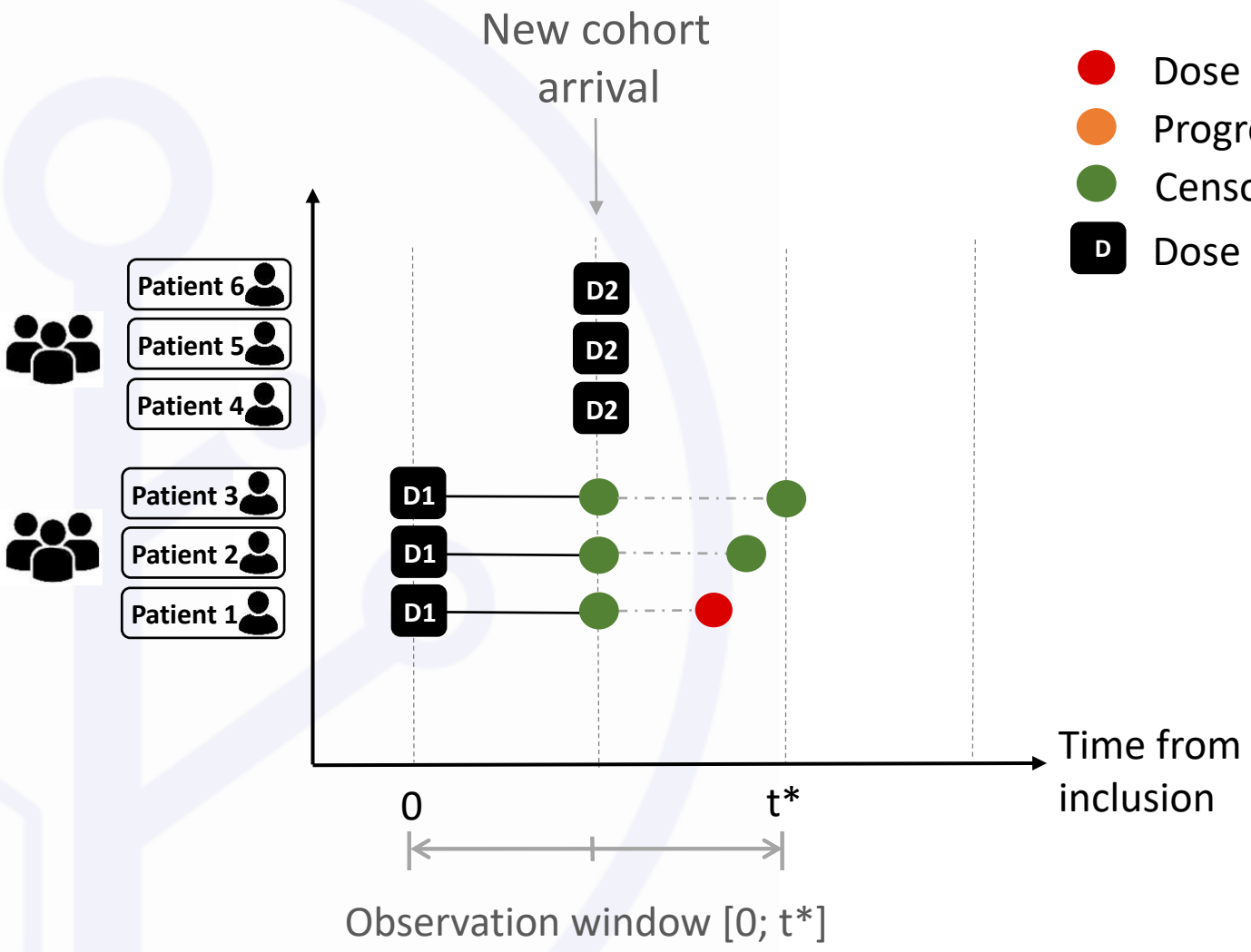
INCOMPLETE DATA



- Dose Limiting Toxicity (DLT)
- Progression
- Censored
- D Dose level

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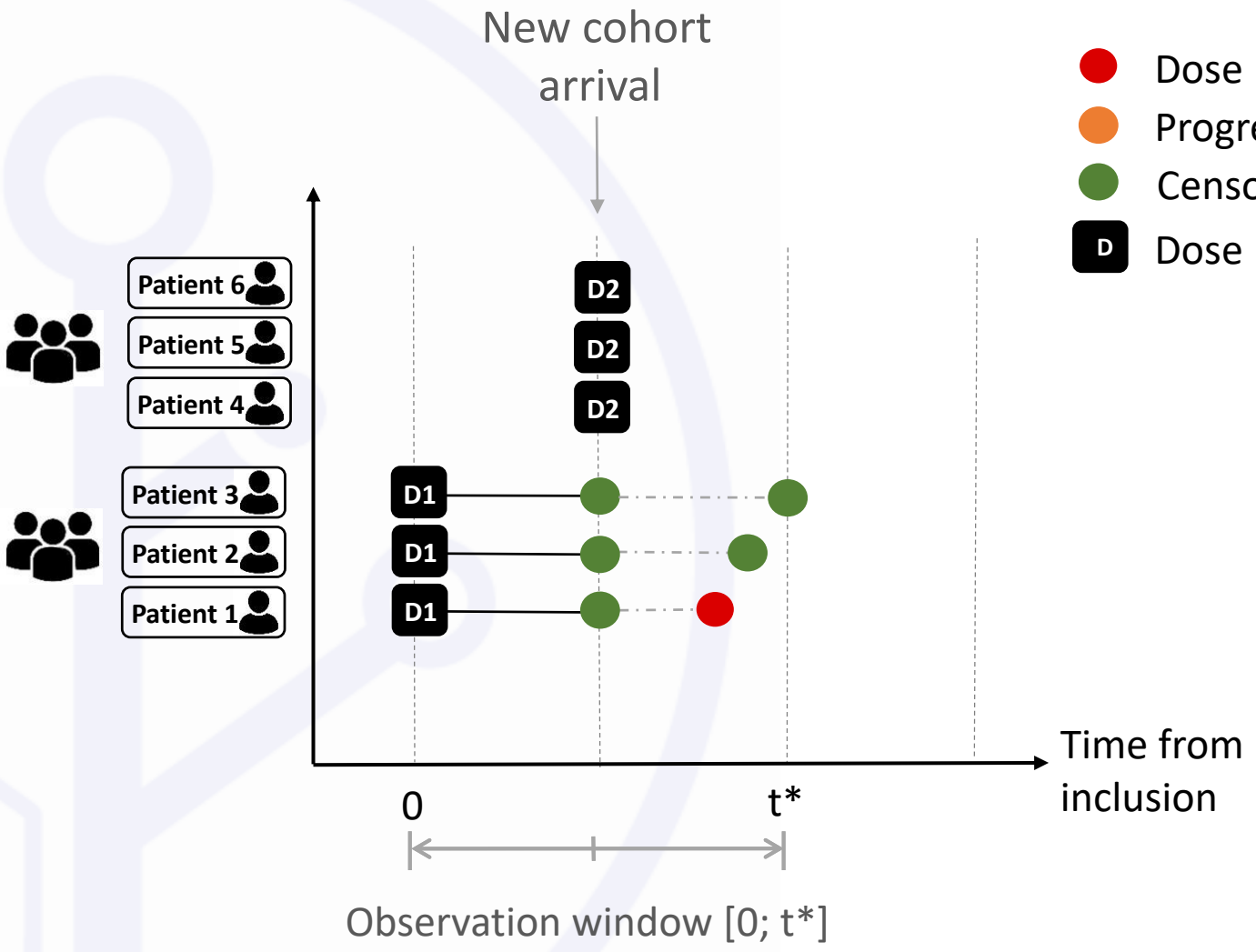

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→ **Administrative censoring**
incomplete observation at the time of dose-assignment

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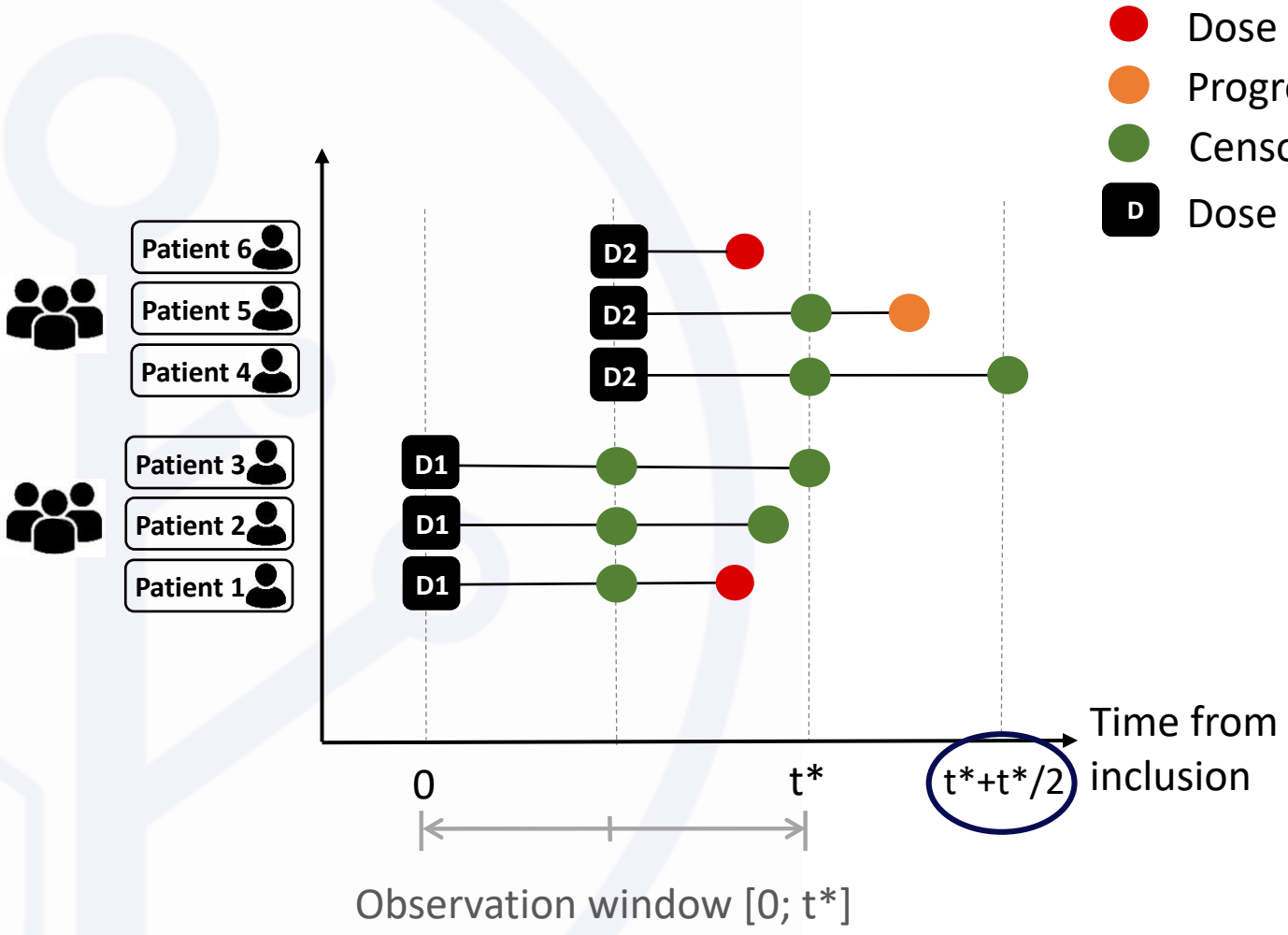

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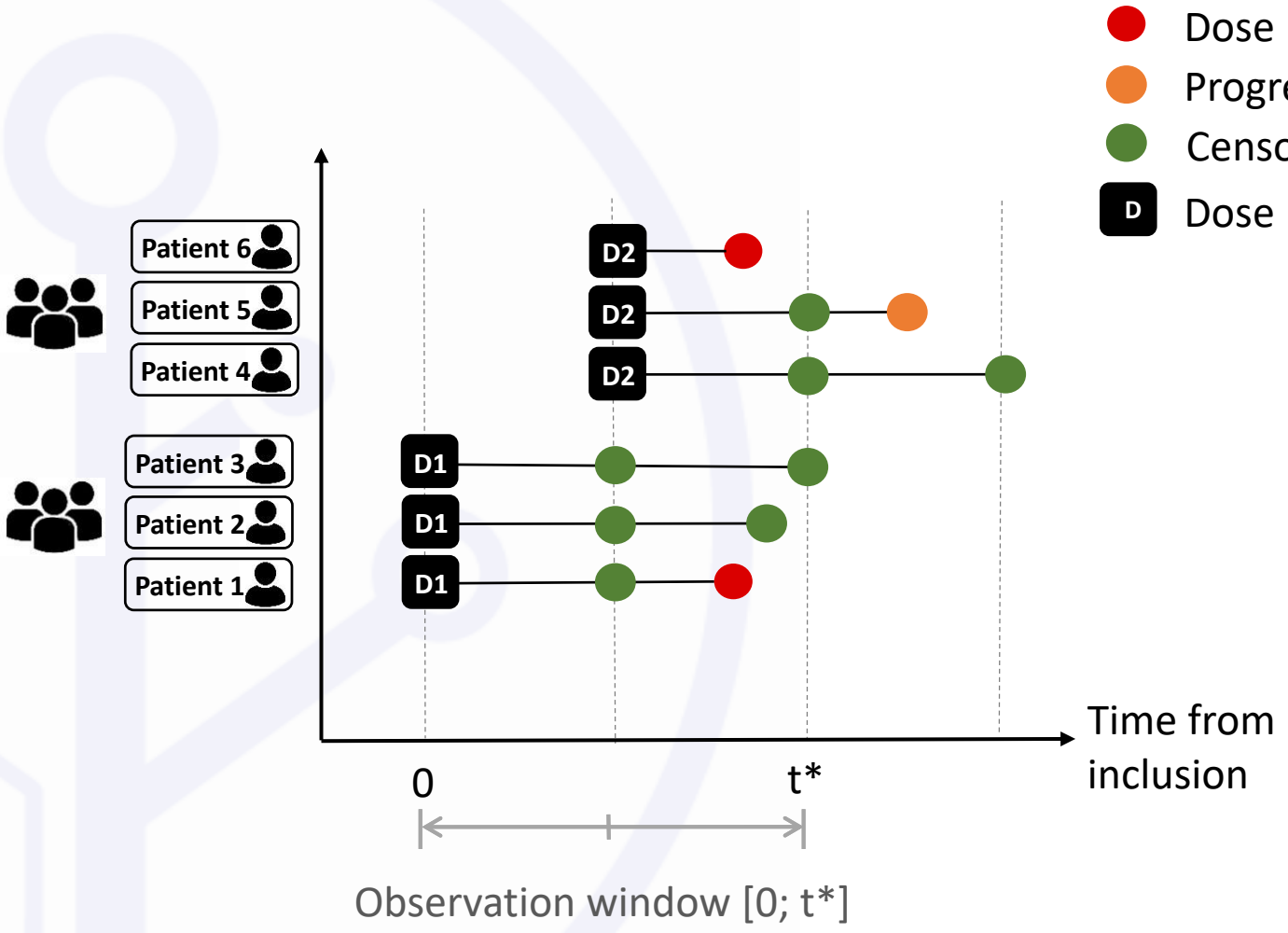

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due to trial discontinuations

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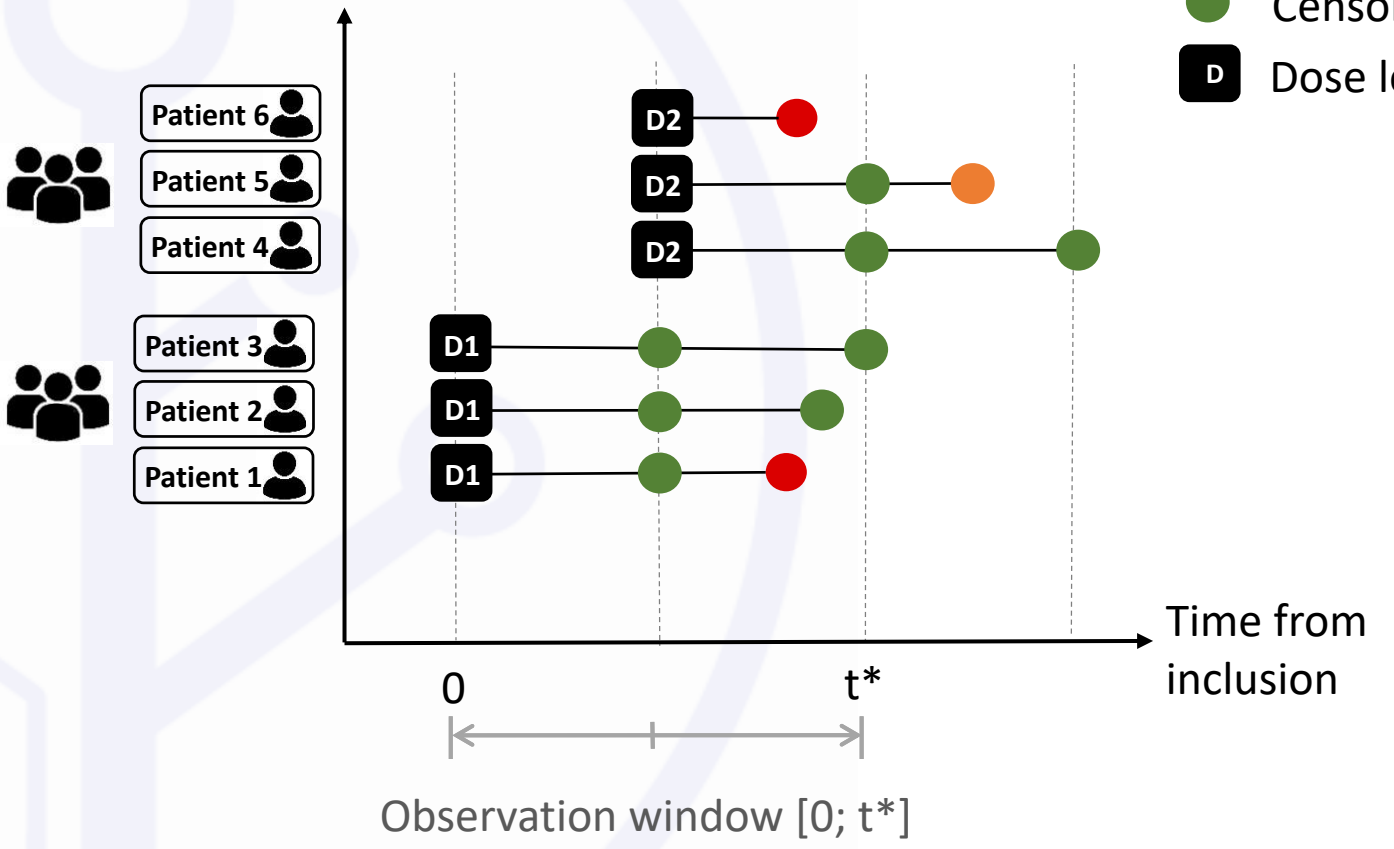

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CONTINUAL REASSESSMENT METHOD (CRM)
→ **COMPLETE DATA**

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INCOMPLETE DATA

HANDLE ADMINISTRATIVE CENSORING IN PHASE I DESIGNS

- Mostly, weighting the observation with its partial follow-up time (**binary endpoints**)
  → TITE-CRM (Cheung and Chappell 2000), TITE-BOIN (Yuan et al. 2018), TITE-mTPI (Lin and Yuan 2020)

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HANDLE INFORMATIVE CENSORING DUE TO TRIAL DISCONTINUATIONS

1. **Replacement** of non-evaluable patients

2. Practical strategies for managing partial observation
   - **Weighted likelihood**

→ Impacting performance of dose-toxicity centered designs (Biard et al 2020)

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PROPOSAL: BAYESIAN SURVIVAL MODELING FRAMEWORK

SURVIVAL-CONTINUAL REASSESSMENT METHOD (SURV-CRM) [1]

- **Handling fast and continual patient accrual**
- Phase I design
  - Objective: identify the **MTD**

[1] Andrillon et al. *JBS* 2020

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INFORMATIVE SURVIVAL-CONTINUAL REASSESSMENT METHOD (SURV-CRM) [1]

- **Handling fast and continual patient accrual**
- **Early treatment discontinuation**

Phase I design

- Objective: identify the **MTD**

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PROPOSAL: BAYESIAN SURVIVAL MODELING FRAMEWORK

SURVIVAL-CONTINUAL REASSESSMENT METHOD-12 (SURV-CRM-12) [2]

Disease progression

- Reported in approximately 70% of the cases of premature discontinuation from a phase I trial (Olmos et al. 2012)
- **Efficacy information, but requiring treatment discontinuation**

Phase I/II design

- Objective: identify the **Optimal Dose (OD)** based on toxicity and efficacy-related information

[2] Andrillon et al. *Stat Med* 2022

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MOTIVATING EXAMPLE

COMBOLA TRIAL*

- Patients with low-risk myelodysplastic syndrome (MDS)
- Dose finding trial of luspatercept in combination with erythropoietin
- Toxicity observation windows: 42 days
- 5 dose levels

- Phase I/II trial using the **TITE-BOIN-ET design** (Takeda et al. 2020)

- **Progression free survival (PFS) was a secondary endpoint**

**Groupe Francophone des Myélodysplasies (GFM), NCT05181735*

SURVIVAL-CRM-12

- **Toxicity and progressoin endpoints** within the observation window (t∗)
- T, **the time-to-DLT or progression**

→ **Administrative censoring**: during the trial and at the end of the observation window

→ **Informative censoring**: discontinuations due to progression

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- Survival analysis framework with competing risks
- $h_1(.)$, the **cause-specific instantaneous hazard function** for DLT, d scaled dose

$$h_1(\beta_1, d) = \exp(d \exp(\beta_1))$$

- $h_2(.)$, the **cause-specific instantaneous hazard function**, for progression, d scaled dose

$$h_2(\beta_2, d) = \exp(-d \exp(\beta_2))$$

*Benichou & Gail. *Biometrics* 1990

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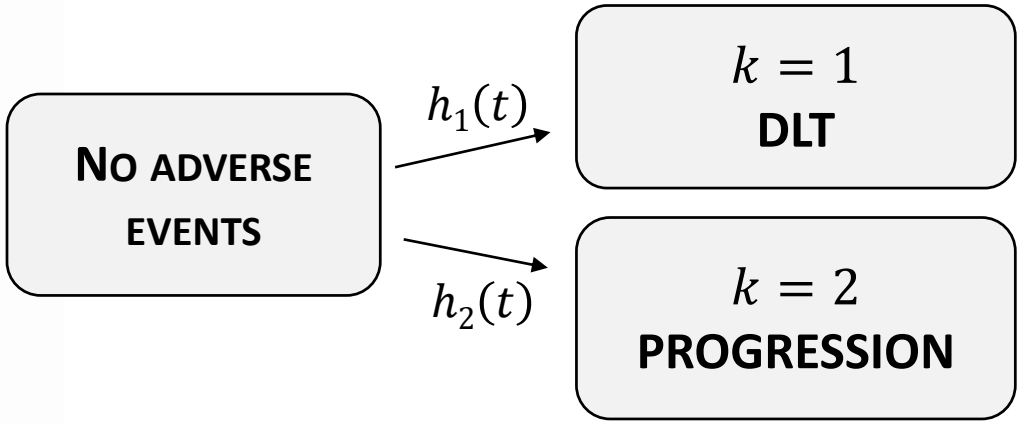
SURVIVAL MODELS FOR COMPETING EVENTS



Observed cumulative incidence for event $k = 1, 2$ at time t^*

$$F_k(t^*, h_1, h_2, d) = \frac{h_k(t^\star, d)}{h_1(t^\star, d) + h_2(t^\star, d)} \left(1 - \exp\left(-\left(H_1(t^\star, d) + H_2(t^\star, d)\right)\right)\right)$$

with $h_k(.)$ the cause-specific hazard function,
and $H_k(.)$ the corresponding cumulative hazards
event $k = 1$ for DLT and $k = 2$ for progression
$[0; t^\star]$: observation window

Putter et al. *Stat Med* 2006

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SURVIVAL-CRM-12

Dose finding objective

The optimal dose : $$d^* = \underset{d \in \mathcal{A}_{ccept}}{arg\,min}\, F_2(t^*, h_1, h_2, d)$$

$F_1(.)$ the cumulative incidence of toxicity and $F_2(.)$ the cumulative incidence of progression

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SURVIVAL-CRM-12

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Dose finding algorithm

$\mathcal{A}_{ccept}$, **the set of *acceptable* doses**, $\mathcal{A} = \{d : d \leq arg\min_{d \in D} |F_1(t^*, h_1, h_2, d) - \pi_{DLT}|\}$

$\mathcal{G}_{ood}$, **the set of *good* doses**, $\mathcal{G} = \{d \in \mathcal{A}: F_2(t^*, h_1, h_2, d) - min\,(F_2(t^*, h_1, h_2, d)) \leq \delta_p\,,\ \delta_p \geq 0\}$

Adaptive randomization

Randomization of the next inclusion at dose $d \in \mathcal{G}$ with probability $R = \frac{1-F_2(t^*,h_1,h_2,d)}{\sum_{d \in \mathcal{G}_{ood}} 1-F_2(t^*,h_1,h_2,d)}$

BAYESIAN INFERENCE

DATA

- C : Right-censored failure time
- Y : Observed outcome
  - Y=1 if DLT, Y=2 if Progression, Y=0 otherwise
- D *:* Allocated doses

PRIOR DISTRIBUTIONS OF $\boldsymbol{\beta_k}$, $\boldsymbol{\phi(\beta_k)}$

Normal distribution with mean 0 and least informative prior variance*

Inference on cause-specific hazard performed separately for toxicity and progression**

Posterior mean of $\boldsymbol{\beta_k}$: $\widehat{\beta_k} = \frac{\int_{-\infty}^{\infty} \beta_k L(B;C,Y,D)\phi(\beta_k)\, d\beta_k}{\int_{-\infty}^{\infty} L(B;C,Y,D)\phi(\beta_k)\, d\beta_k}$, with $L(B;C,\ Y,D)$, the survival likelihood

Estimates of the cumulative incidences of DLT and Progression: $\widehat{F_k}(t^*, h_1, h_2, d)$ for each dose level

Apply the dose-finding objective

* Lee and Cheung. *Stat in Med* 2011; **Benichou & Gail. *Biometrics* 1990

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SIMULATION STUDY: COMPARATORS

- **TITE-BOIN-ET** (Takeda et al. 2020)
  - Handling pending data via a weighted likelihood
  - Obj: the dose maximizing the efficacy probability among the doses lower or equal to the MTD

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  Gray (1988) estimator at t* from all generated complete data

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Incomplete information *(Real clinical trial)*

	Doses				
	D1	D2	D3	D4	D5
Y_1	*	*	0	*	*

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→ **Provide a scenario-specific assessment of the accuracy of dose-finding designs**
(PCS upper bound estimate)

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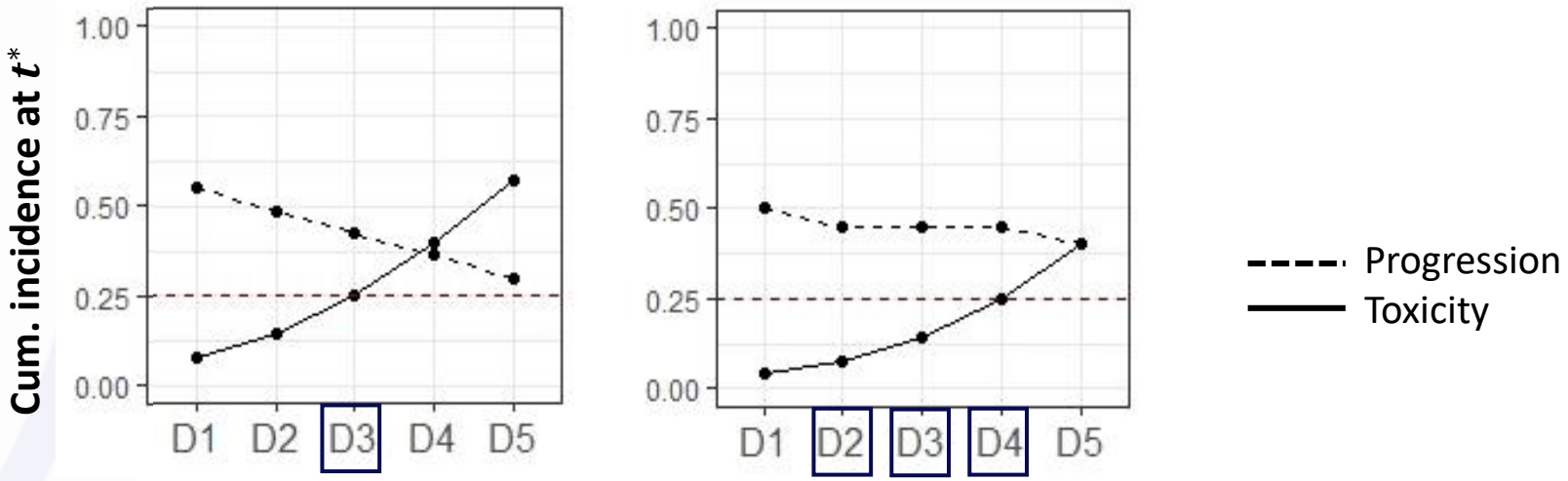
SIMULATION STUDY: SCENARIOS

N = 10,000 trials; **n = 45 patients**; π_{DLT} = 0.25
Accrual rate of 4 patients per obs. window

12 scenarios

- Cytotoxic
- Plateau dose progression relationship



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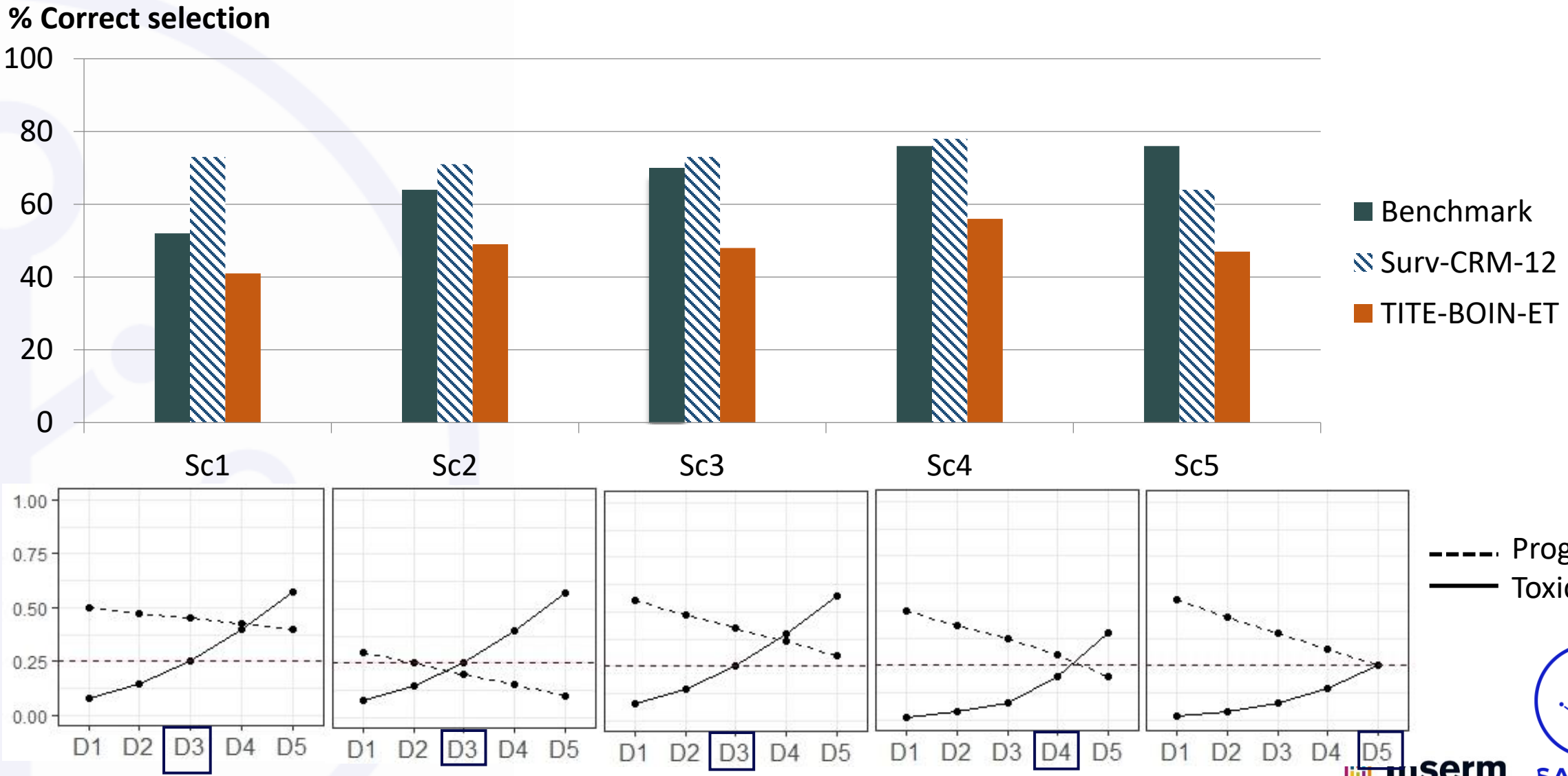
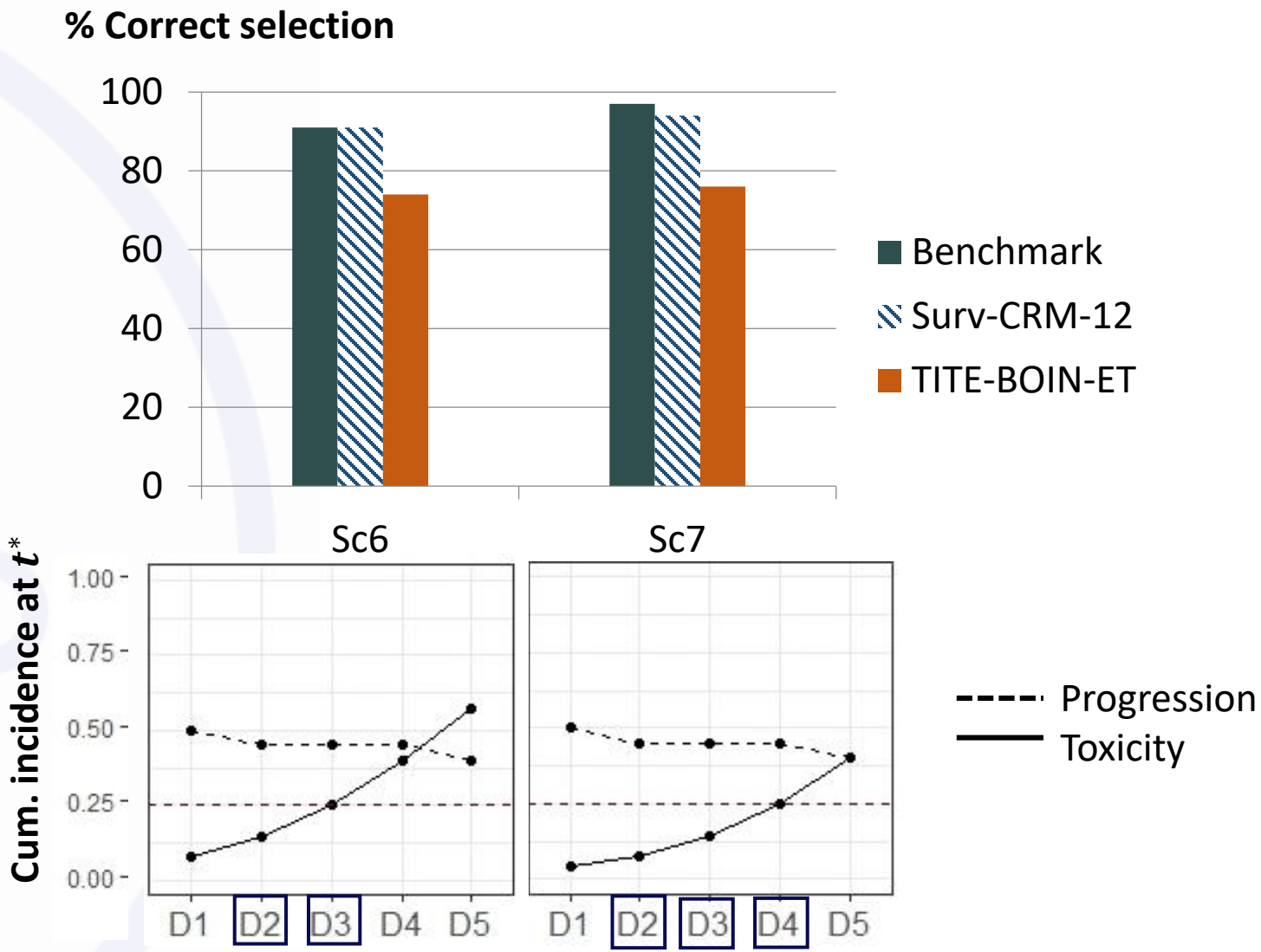
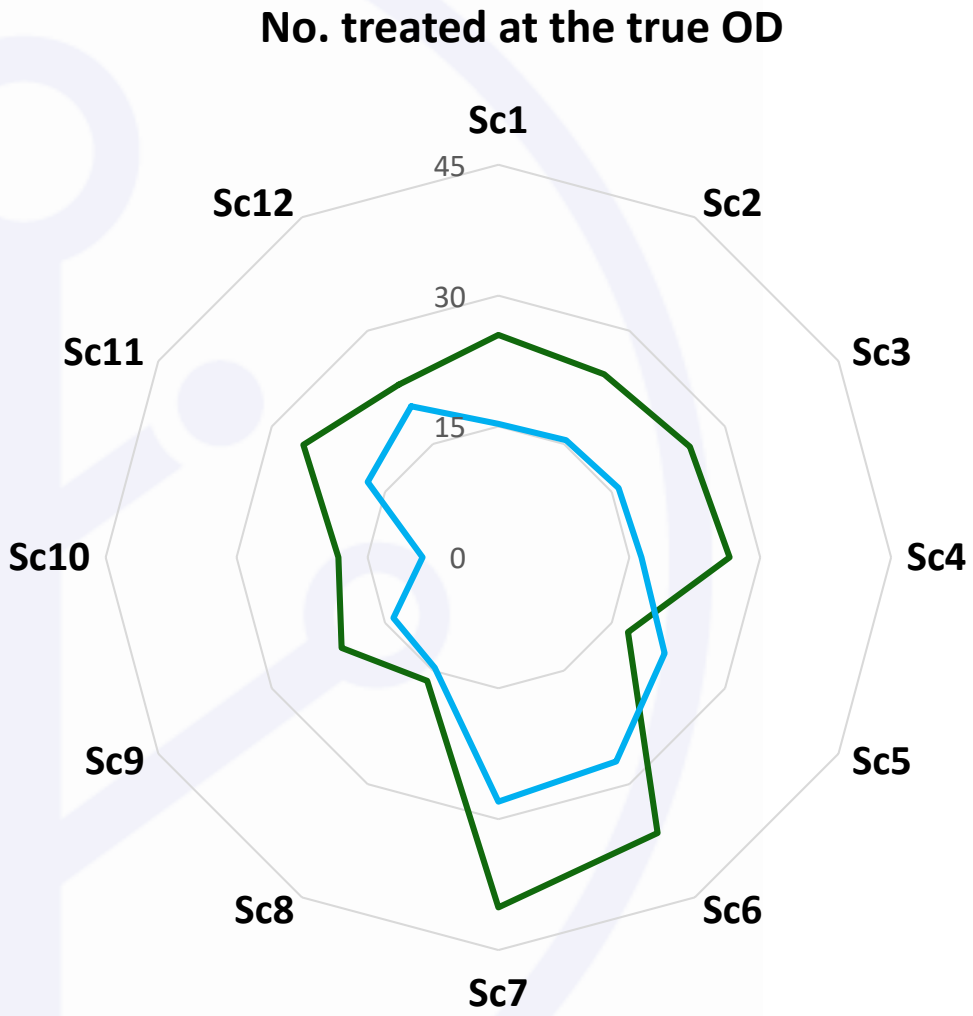
RESULTS: SURV-CRM-12; CYTOTOXIC SCENARIOS

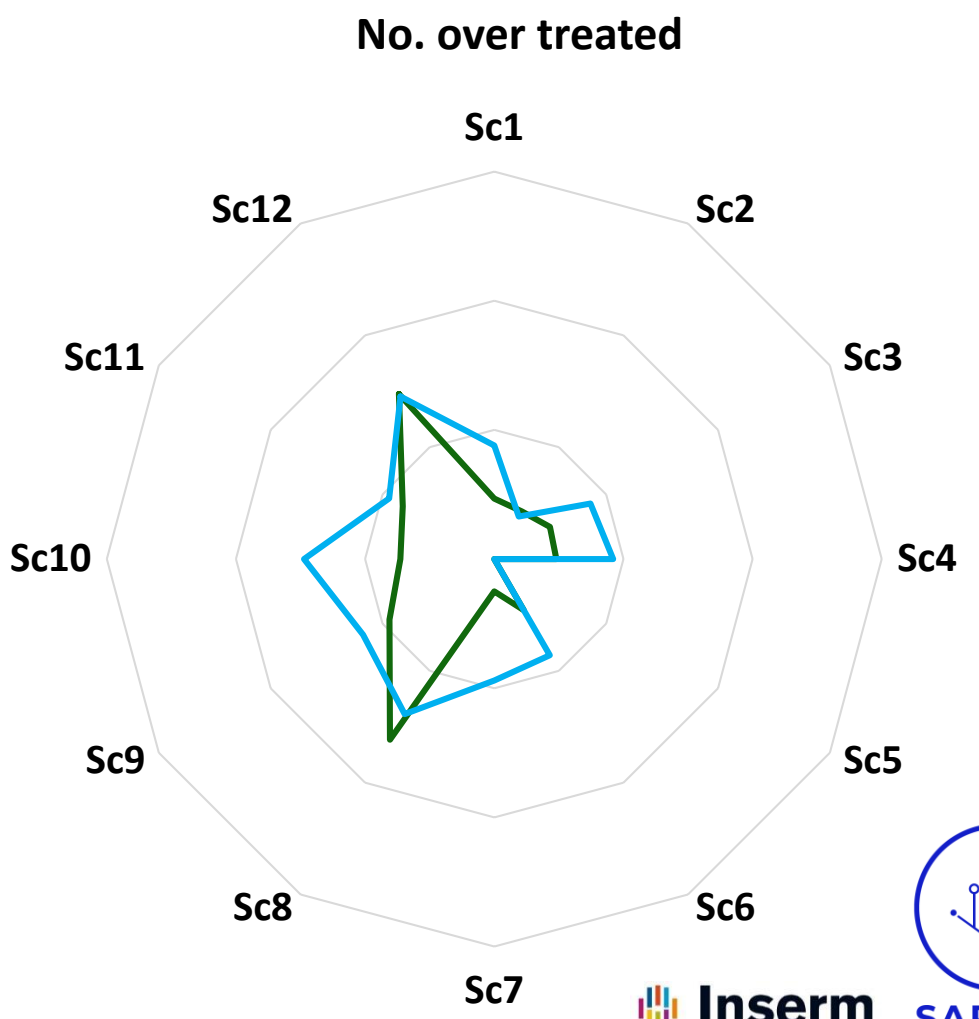


RESULTS: SURV-CRM-12; PLATEAU SCENARIOS



RESULTS: SURV-CRM-12; SAFETY DURING THE TRIAL





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CONCLUDING REMARKS

A FRAMEWORK FOR DOSE-FINDING (PHASE I & PHASE I/II)

WITH RIGHT CENSORED ENDPOINTS AND COMPETING RISKS ISSUES

→ **Surv-CRM-12**

- **Desirable properties** (statistical performance, safety, feasibility)
- **Sensitivity analyses** (patient accrual rate, sample size, variance specification, correlated time to toxicity and progression)

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Utrecht 2023


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BACK-UP

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CRESS Epidemiology Statistics

Bayes Bayesian Biostatistics Utrecht 2023

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SURVIVAL MODELS FOR COMPETING EVENTS

Marginal cause-specific cumulative incidences of event $k = 1, 2$ at time t^* (unobserved)

$$1 - \exp(H_k(t^\star, d))$$

Observed cumulative incidence for event $k = 1, 2$ at time t^*

$$F_k(t^*, h_1, h_2, d) = \frac{h_k(t^\star, d)}{h_1(t^\star, d) + h_2(t^\star, d)} \left(1 - \exp\left(-\left(H_1(t^\star, d) + H_2(t^\star, d)\right)\right)\right)$$

with $h_k(.)$ the cause-specific hazard function,
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event $k = 1$ for DLT and $k = 2$ for treatment discontinuation
$[0; t^\star]$: observation window

Putter et al. *Stat Med* 2006

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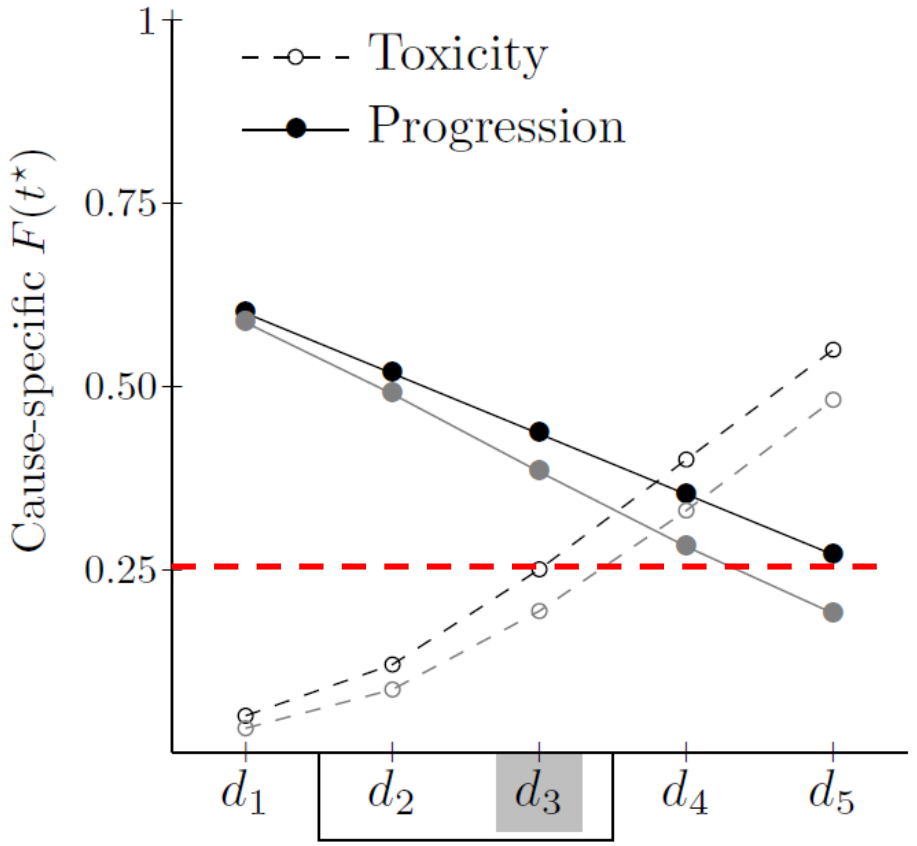
OBJECTIVE

- Black lines (solid and dashed) : Cause-specific marginal cumulative incidences of event at t*
- Gray lines (solid and dashed): Observed cumulative incidences of events at t*



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SURV-CRM-12: DATA GENERATION

- **Competing risks data generation** (Beyersmann et al. 2009)
  - Cause-specific risks back computed from scenarios cumulative incidence at t*
  - Time to any event sampled from exponential distribution with rate (h1+h2)
  - Event case determined by a random drawn from a Bernouilli (h1/h1+h2) for toxicity
  - Administrative censoring applied at t*

- **Dose skeletons calibration:** indifference intervals (Lee and Cheung 2009)

- **Least informative prior variance for β_1 and β_2** (Lee and Cheung 2011)

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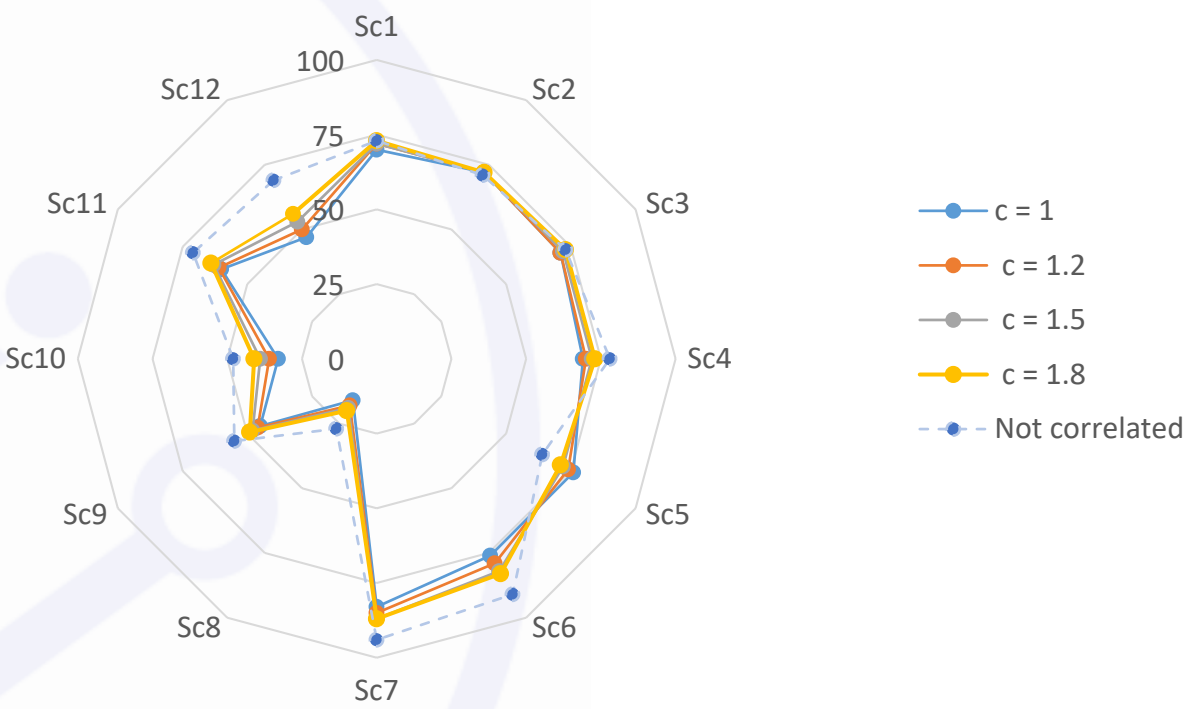
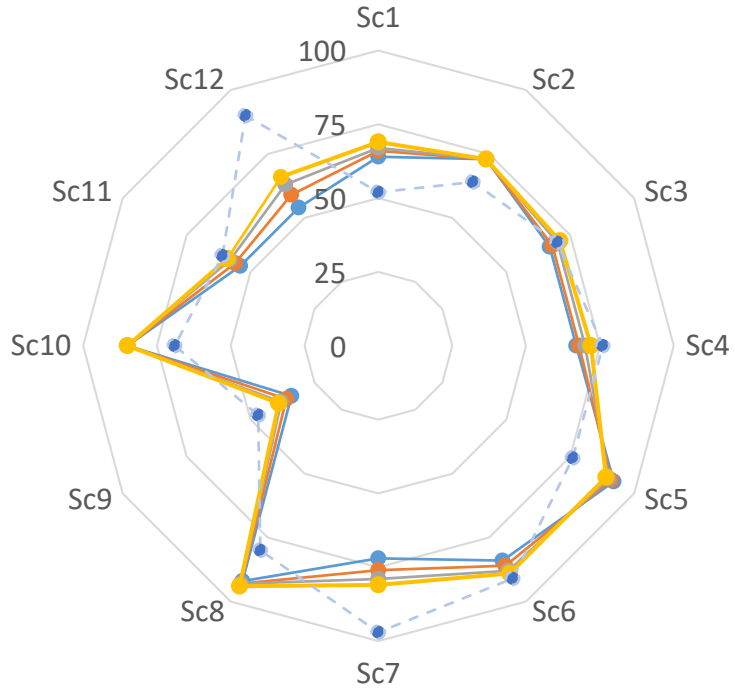
RESULTS: SURV-CRM-12; SENSITIVITY ANALYSES

% Correct selection Surv-CRM-12



% Correct selection Benchmark



Clayton model for data generation

When $c \to 0$ the correlation approaches 1 and, when $c \to \infty$ the correlation converges to 0

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PHASE I/II DESIGNS FOR LATE-ONSET COMPETING RISK OUTCOMES

Competing Risk-CRM (Biard et al. 2021)

- Survival framework, targeting **theoretical marginal incidence of events**

Obj: a dose or a set of doses associated with the **minimum progression marginal risk within an admissible set**

Bayesian data augmentation design (Zhang et al. 2021)

- Late-onset competing risks outcome modeled by the **cause-specific hazard rate**
- Piecewise exponential model
- Pending data during the trial are treated as **missing data**

Obj: the dose yielding the **highest posterior mean utility within an admissible set**

COMPETING RISKS CRM DESIGNS

- **CR-CRM**
  - Likelihood estimation
  - 3 stage design
  - Target unobserved cause specific incidences
  - Non monotone dose progression relationship

- **Surv-CRM-12:**
  - Bayesian
  - One-stage design
  - Target observed cumulative incidence of events
  - Monotonicity assumption

DOSE SKELETONS

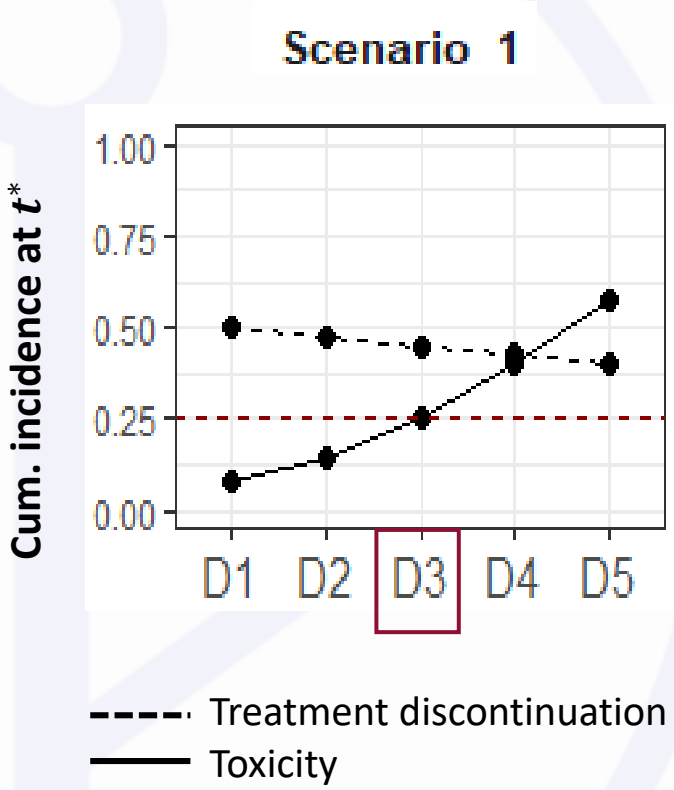
- Surv-CRM {0.069, 0.151, 0.250, 0.346, 0.426}.

- iSurv-CRM, best guess prior. Polley (2011),
  - Toxicity: {0.05, 0.10, 0.25, 0.35, 0.50}
  - Trial discontinuation: {0.50, 0.45, 0.40, 0.35, 0.35}

- TITE-CRM: {0.043; 0.124; 0.250; 0.398; 0.542}. Lee and Cheung (2009)

- **Surv-CRM-12**
  - Toxicity: {0.055, **0.130, 0.250, 0.406**, 0.571}
  - Progression {0.666, 0.541, 0.400, 0.266, 0.158}.

RESULTS: ISURV-CRM



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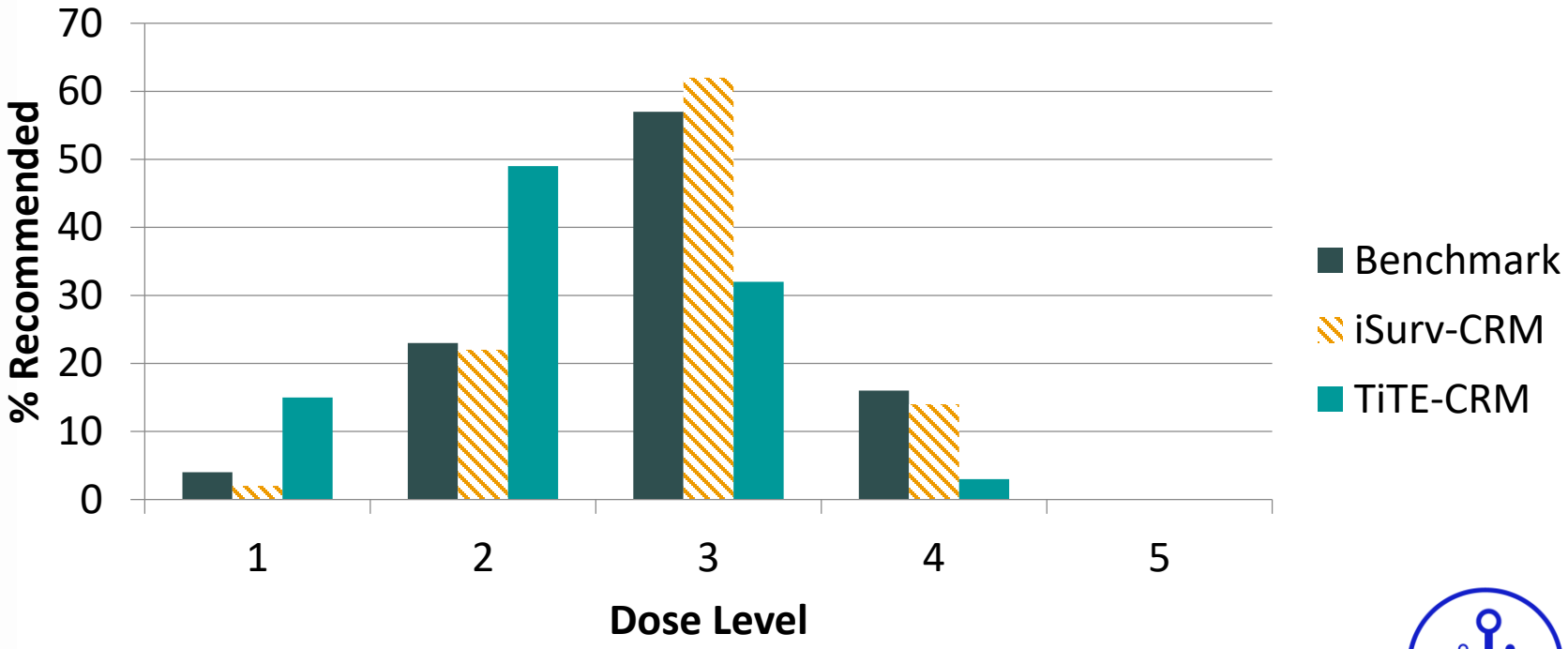
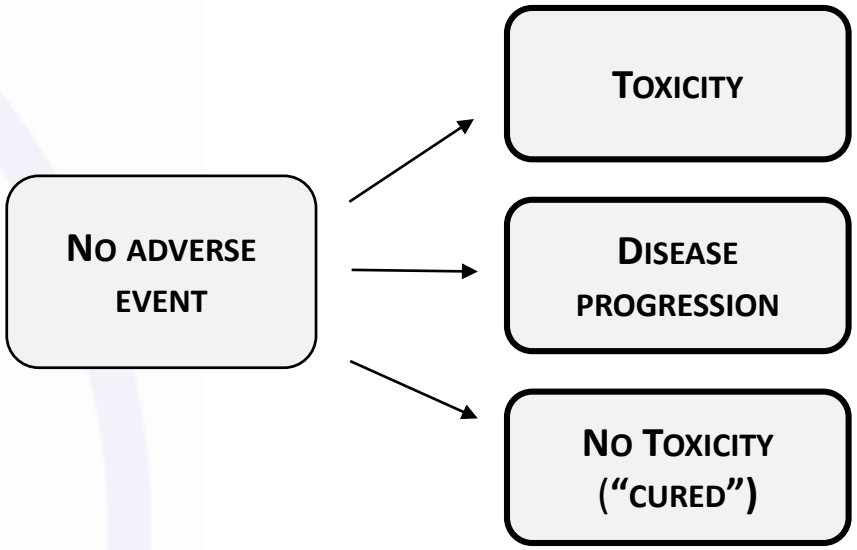
Accrual rate of 4 patients per obs. window



PATIENTS WHO EXPERIENCED NEITHER DISEASE PROGRESSION NOR DLT AT T* → *ADMINISTRATIVE CENSORING?*



- Patients who experienced neither disease progression nor DLT at t* → *informative censoring*

→ **Trinomial response outcomes** (Zhang et al. 2021)

→ **Cure rate models:** a fraction of subjects in the population will never experience the event of interest (Berkson and Gage, 2006)

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HANDLING ADMINISTRATIVE CENSORING

1. **Weight the observations**
2. **Time-to-event endpoint**
3. **Missing data methodology**

	Model-based	Model-assisted
Phase I	TITE-CRM (Cheung and Chappell 2000)	TITE-mTPI (Lin and Yuan 2020)
Phase I/II	Seamless phase I/II TITE-CRM (Yan et al. 2019), Robust Bayesian EffTox design (Liu and Johnson 2016) Phase I/II MTA (Riviere et al. 2016)	TITE-BOIN-ET (Takeda et al. 2020)
Phase I	fCRM (Yin et al. 2013)	
Phase I/II	Survival joint model (Yuan and Yin, 2009), Survival EffTox (Koopmeiners and Modiano 2014)	
Phase I	EM-CRM (Yuan and Yin 2011), DA-CRM (Liu et al. 2013)	TITE-BOIN (Yuan et al. 2018)
Phase I/II	LO-EffTox (Jin et al. 2014)	TITE-BOIN-12 (Zhou et al. 2022)

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SURVIVAL-CRM

- **Toxicity endpoint**: DLT within the observation window (t∗)
- T, **the time-to-DLT**

→ **Administrative censoring**: during the trial and at the end of the observation window
  - Independent from the time-to-DLT

- Survival analysis framework
  - **Instantaneous hazard of toxicity** for DLT, d scaled dose: $h(\beta, d) = exp(d\, exp(\beta))$
  - Cumulative hazard, $\mathrm{H}(\beta, d)$
  - **Cumulative incidence of DLT** at the end of the observation window, t*

$$F(d, t^*, h) = 1 - \exp(-h(\beta, d)t^*)$$

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SURVIVAL-CRM

- CRM dose finding-algorithm

Identify the MTD, d^*, the dose with the probability of toxicity at time t^*closest to a pre-specified target π_{DLT} (e.g., 0.25), among the set D of candidate dose levels

$$\boldsymbol{d^* = arg\min_{d \in D} |F(d, t^*, h) - \pi_{DLT}|}$$

- With $\boldsymbol{F(d, t^*, h)}$, the **cumulative incidence of toxicity** at time t^*

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INFORMATIVE SURVIVAL-CRM

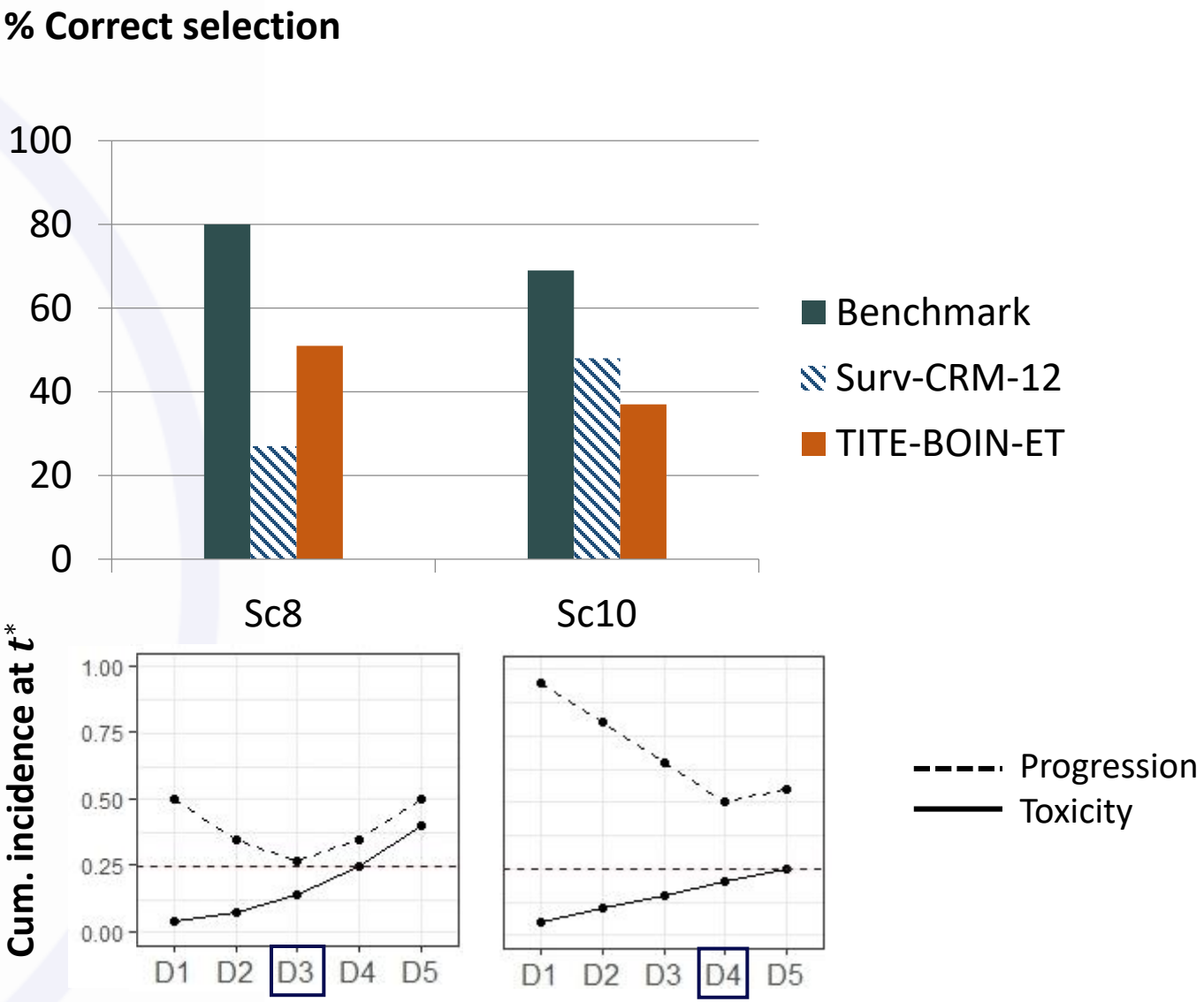
- CRM dose finding-algorithm

Identify the MTD, d^*, the dose with the probability of toxicity at time t^*closest to a pre-specified target π_{DLT} (e.g., 0.25), among the set D of candidate dose levels

$$\boldsymbol{d^* = arg\min_{d \in D} |F_1(t^*, h_1, h_2, d) - \pi_{DLT}|}$$

- With $F_1(.)$, the **observed cumulative incidence for toxicity** at time t^*

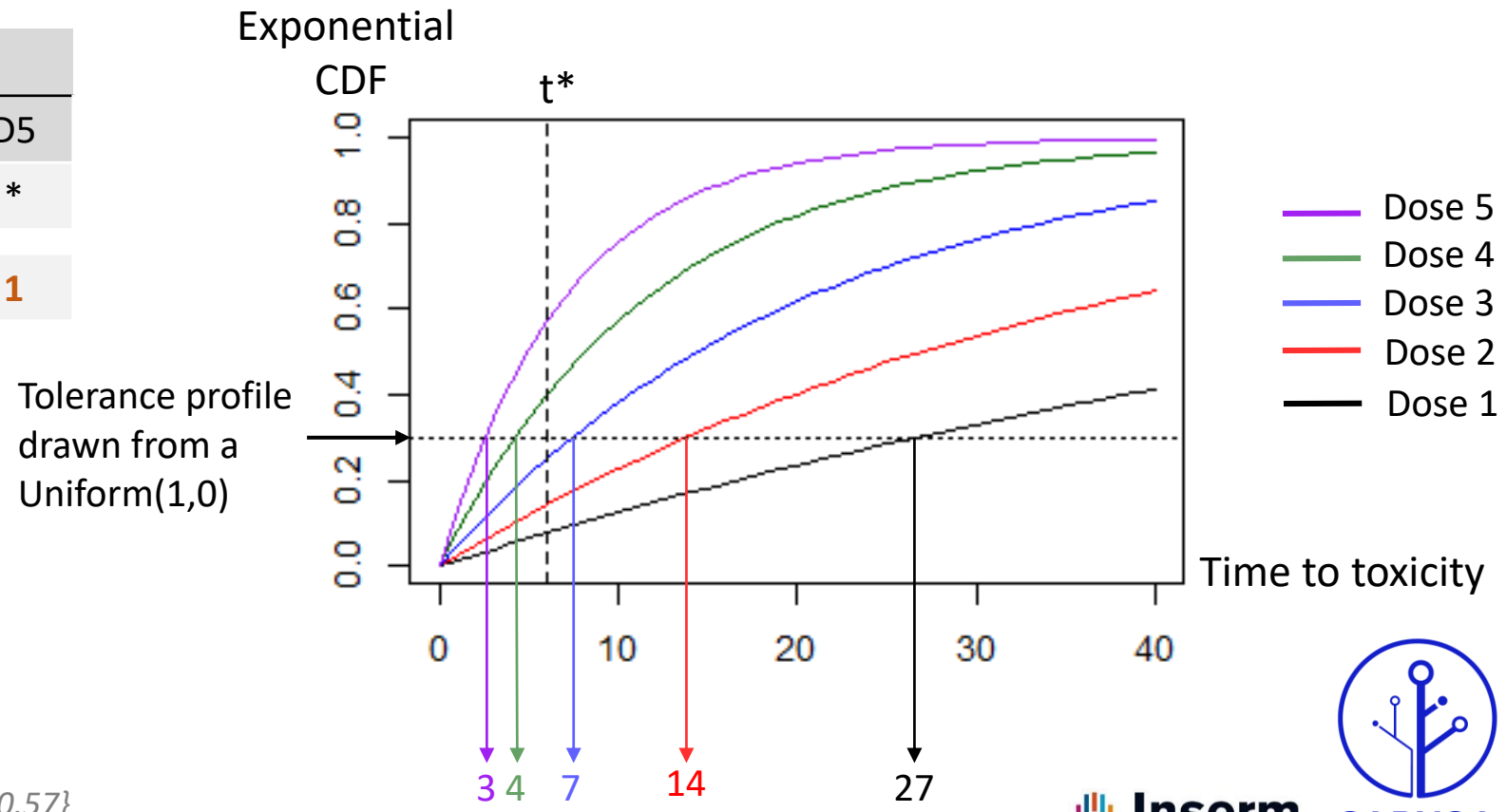
RESULTS: SURV-CRM-12; U-SHAPE SCENARIOS



SIMULATION STUDY: COMPARATORS

Nonparametric Benchmark (O'Quigley et al. 2002, Cheung 2014, Mozgunov et al. 2020)

		Doses				
		D1	D2	D3	D4	D5
(Real clinical trial)	Y_1	**0**	**0**	0	*	*
(Simulations)	Y_1	**0**	**0**	0	**1**	**1**



True Toxicity probability by dose : {0.08, 0.14, 0.25, 0.40, 0.57}

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DISCUSSION AND PERSPECTIVES

Surv-CRM-12 Optimal Dose definition: $\boldsymbol{d^* = arg \min_{d \in \mathcal{A}} F_2(t^*, h_1, h_2, d)}$

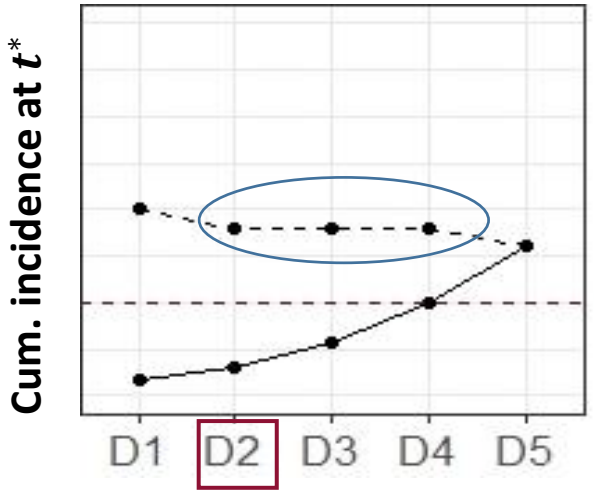
- **'Optimus' FDA project recommendations**

→ **OD**: **lowest** safe dose that achieves the highest efficacy

- **Extension of the efficacy working model to strictly non-monotone relationship**

Cause-specific instantaneous hazard function, for progression

$$h_2(\beta_2, d) = \exp(\beta_{02} + \exp(\beta_{12})\, d + \exp(\beta_{22})\, d^2)$$



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DISCUSSION AND PERSPECTIVES

Intention To Treat (ITT) approach

- Treatment decision at the time of the patient's inclusion in the trial

- **Repeated treatment administration over several cycles**
  - Estimation of the MTD associated to some cumulative risk of DLT over a predefined number of treatment cycles (Altzerinakou, 2019, Ursino, 2021)

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