Optimal dose selection considering both toxicity and activity data; plateau detection for molecularly targeted agents

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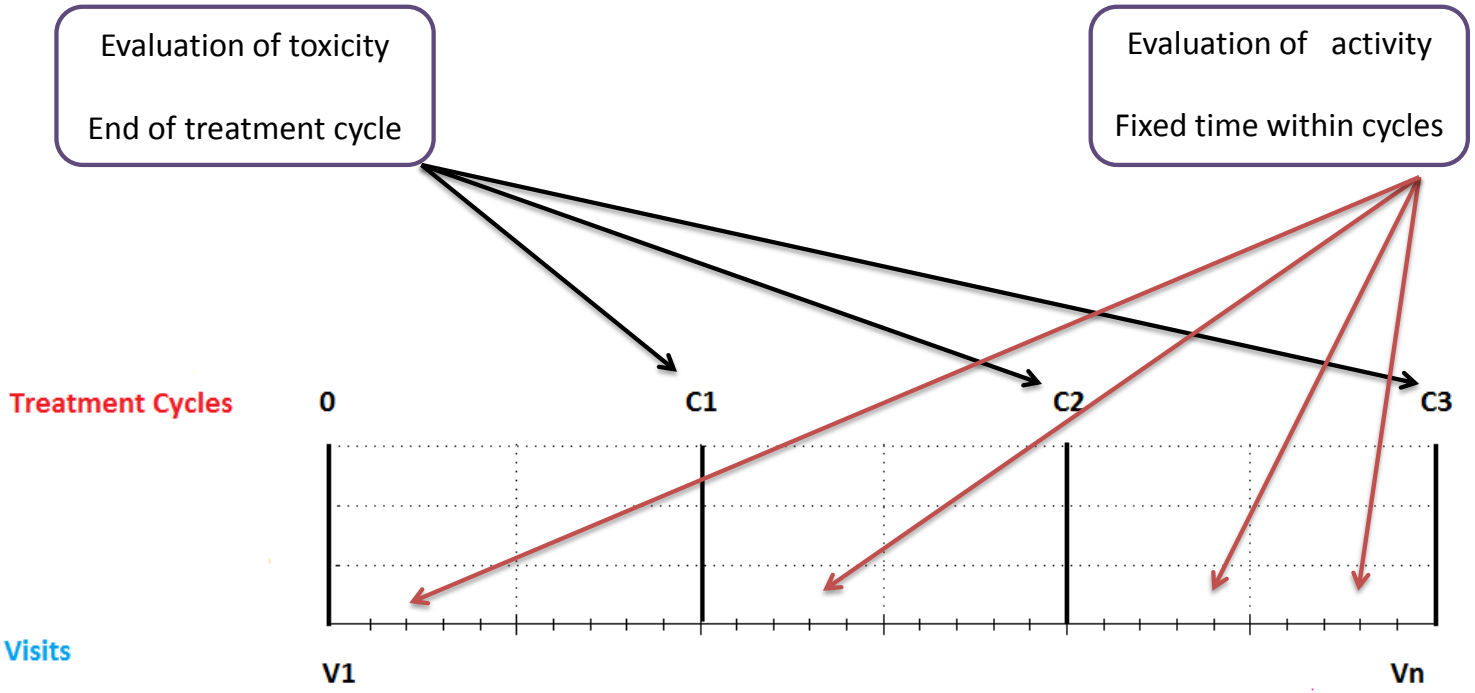
Toxicity and activity endpoints



Drop out:

1) **Dose limiting toxicity**
2) **Lack of activity**
3) **Consent withdrawal**

MTD definition

Evaluation of the MTD, using toxicity data collected during the *first* treatment cycle.

MTD: 20%-33% of dose limiting toxicities (DLTs) in the *first* treatment cycle !!!

Targeted therapies

Targeted therapies:

- different toxicity profiles from cytotoxic agents
- long administration

➤ **Delayed and cumulative toxicities!**

➤ *More than 50% of severe toxicities occurred after cycle 1*[1]

1. Postel-Vinay et al (2014). Towards new methods for the determination of dose limiting toxicities and the assessment of the recommended dose for further studies of molecularly targeted agents - Dose-limiting toxicity and toxicity assessment recommendation group for early trials of targeted therapies, an European Organisation for Research and Treatment of Cancer-led study.

➤ Immunotherapy: median time of first severe toxicity 5-15 weeks (2-5 cycles)[2]

➤ *"Poor prediction of future approved dose levels from phase I and the resulting re-evaluation of the MTD in subsequent phases."*[3,4]

2. Champiat et al (2016). Management of immune checkpoint blockade dysimmune toxicities: A collaborative position paper.
3. Iasonos et al (2012). The impact of non-drug-related toxicities on the estimation of the maximum tolerated dose in phase i trials.
4. Jardim et al (2014). Predictive value of phase i trials for safety in later trials and final approved dose: Analysis of 61 approved cancer drugs.

EMA guidelines

"For MTAs, DLTs may occur after multiple cycles of therapy. This is of importance for the RP2D and may require alternative strategies with regard to definition of DLT and MTD."

➤ Recommendations

- Broader DLT definitions with longer DLT observation periods
- Distinction between cycle 1 acute toxicity, prolonged toxicity and late severe toxicity
- Assessment of RP2D based on adverse events reported by treatment cycle

5. European Medicines Agency (2016). Draft Guideline on the evaluation of anticancer medicinal products in man.

DLT-Targett

➢ DLT-Targett database created by E.O.R.T.C

- ❖ 27 phase I NCI studies of MTAs as monotherapy
- ❖ 963 patients
- ❖ cycles of treatment, dose, toxicities (type and grade), etc.

Objective: Evaluate the conditional and cumulative probability of toxicity over 6 treatment cycles at the MTD.

Toxicity over 6 cycles

Table 1: Conditional probability of a grade 3-4 toxicity at the MTD.

cycle_1	cycle_2	cycle_3	cycle_4	cycle_5	cycle_6
0.283	0.185	0.111	0.061	0.031	0.014

Table 2: Cumulative probability of a grade 3-4 toxicity at the MTD.

cycle_1	cycle_2	cycle_3	cycle_4	cycle_5	cycle_6
0.283	0.416	0.481	0.512	0.527	0.534

Challenge with activity of MTAs

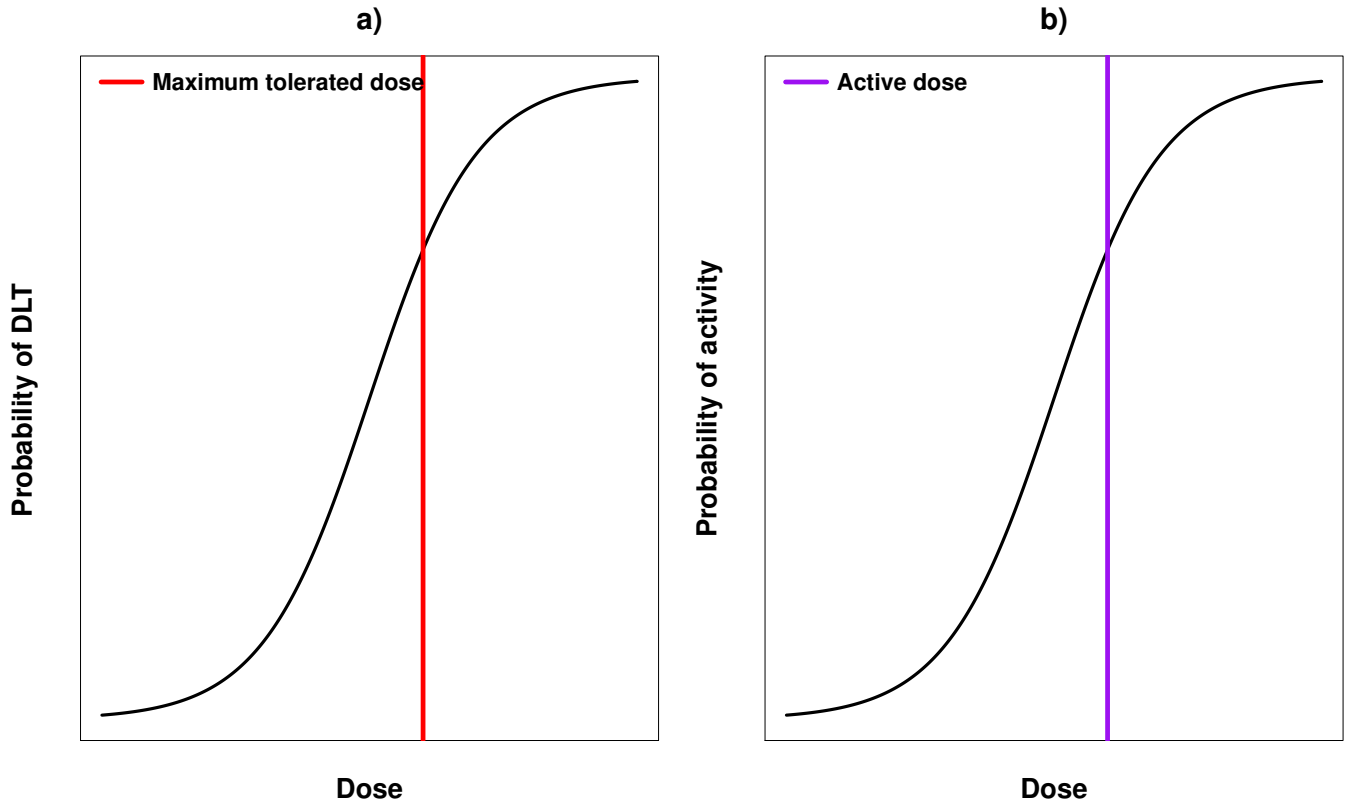


Figure 1: Dose-toxicity and dose-activity relationships for cytotoxic agents.

Challenge with activity of MTAs

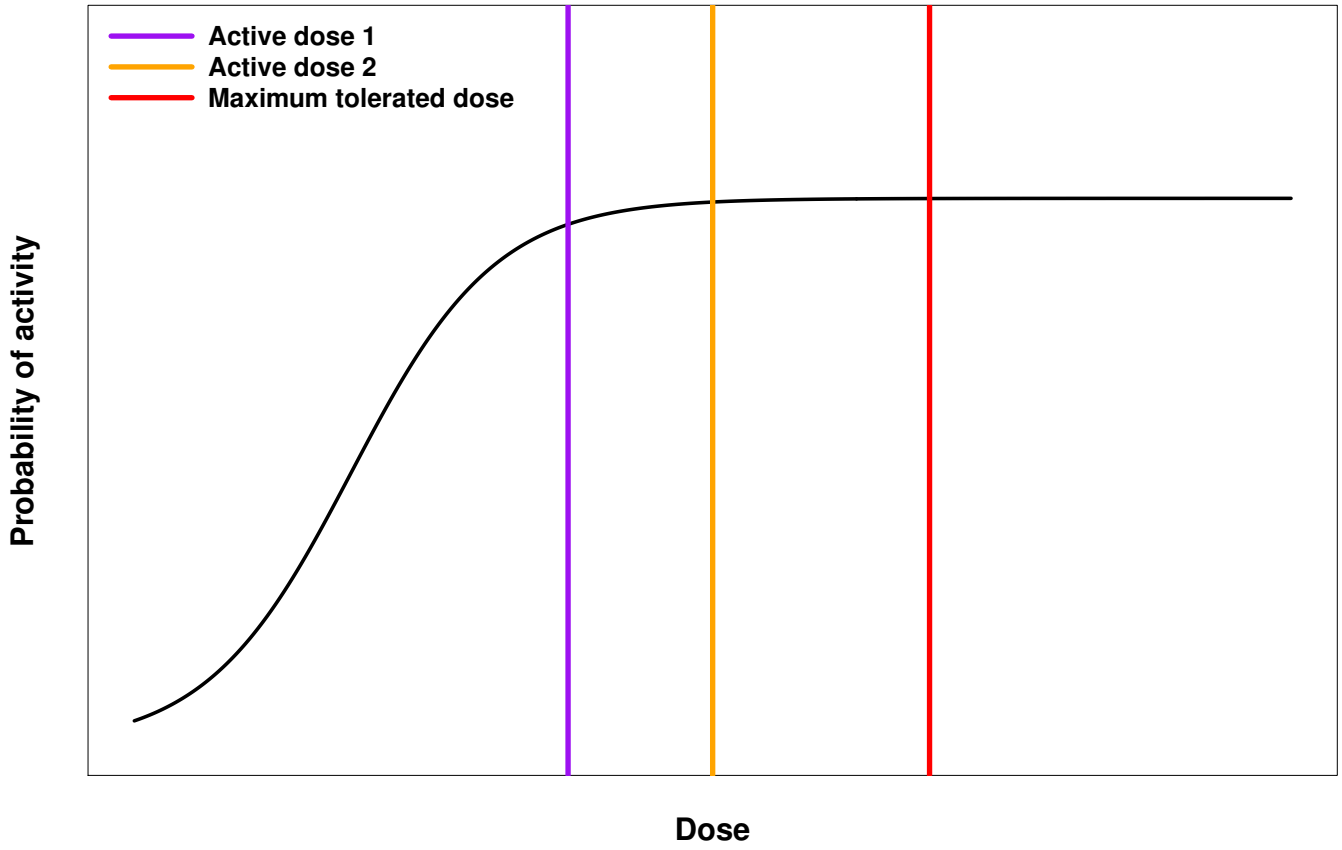


Figure 2: Dose-activity relationship for targeted agents.

Objective: Adaptive design

➢ Propose an adaptive design for phase I/II trials

➢ Define a maximum tolerated dose (MTD) and an optimal dose (OD)

- ❖ MTD: The maximal dose acceptably tolerated cumulatively over all treatment cycles
- ❖ OD: The lowest dose within a range of highly active doses, below or equal to the MTD

➢ Combine data of time to first dose limiting toxicity (DLT) and biomarker activity over several treatment cycles

Joint modeling

➢ Joint modeling of

- discrete time-to-DLT data
- repeated and continuous biomarker measurements
- shared random effect

6. Rizopoulos, D. (2012). Joint models for longitudinal and time-to-event data with applications in R. Chapman and Hall/CRC Biostatistics Series.
7. Barrett, J. et al. (2015). Joint modelling of repeated measurements and time-to-event outcomes: flexible model specification and exact likelihood inference. J R Stat Soc Series B Stat Methodol., 77(1): 131-148.

Model selection

c ⇨ treatment cycle
d ⇨ dose
k ⇨ max number of cycles

t ⇨ time of visit
l ⇨ dose level
pl ⇨ plateau start

Probit model - Toxicity

$$P(S_i = s | S_i > s-1, U_i) = 1 - \Phi\left\{a_0 + a_1 c_{i(s-1)} + a_c d_i + \gamma U_i\right\}, \quad c \in \{1, 2, ..., k+1\},$$

where i is the index for the patient level and $U_i \sim N(0, \sigma_1^2)$ is the shared random effect.

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Linear mixed effects model - Activity

$$y_{ij(l)} = \beta_0 + \beta_1 t_{ij}^2 + \beta_2 t_{ij}(d_{i(l)} 1(l < pl) + d_{i(pl)} 1(l \geq pl)) + u_i t_{ij} + r_{ij}, \quad j = 1, \ldots, n$$

where $R_{ij} \sim MVN(0, \sigma_2^2 I)$ mutually independent errors and n total number of visits.

Biomarker-dose relationship

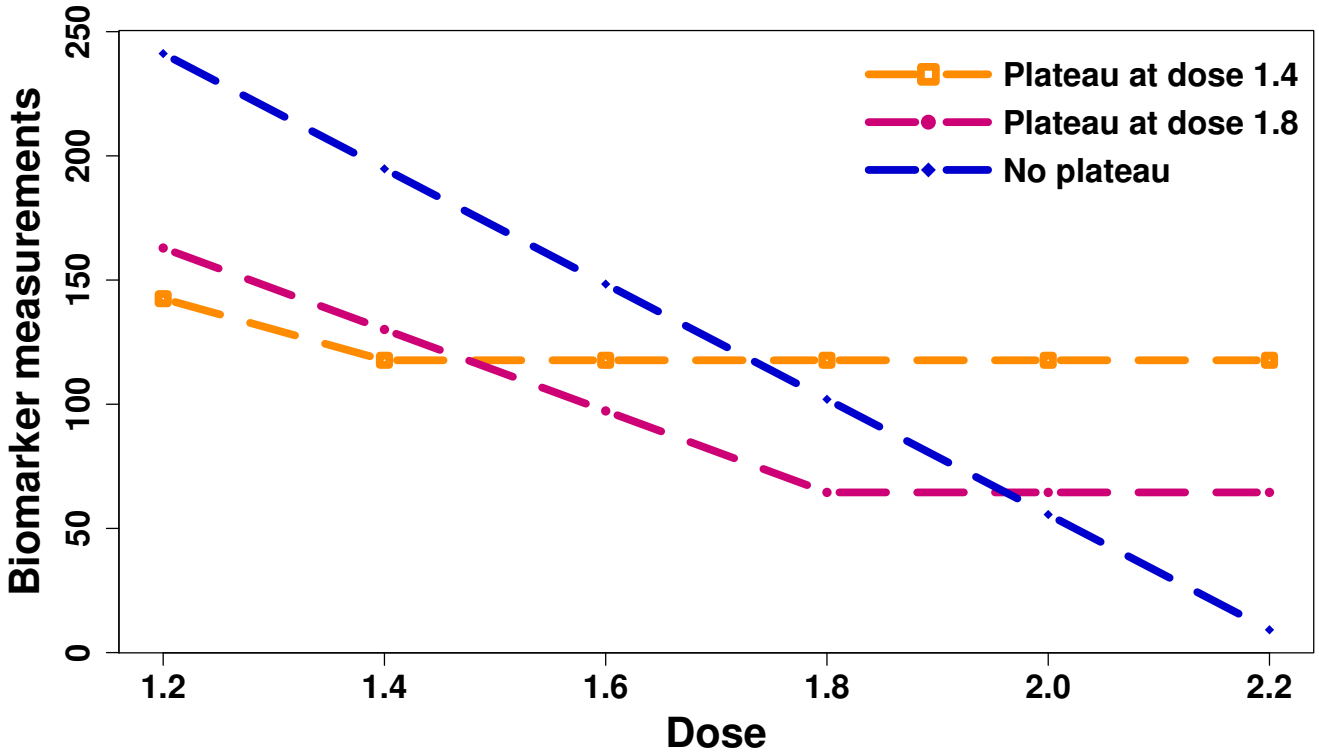

Figure 3: Dose-biomarker trajectories, illustrating plateau and strictly linear relationships.

Biomarker-time relationship

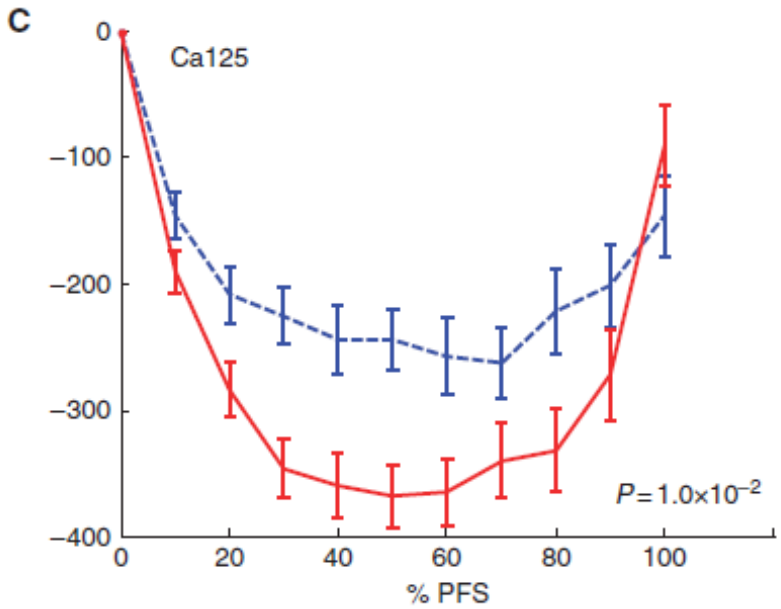

Figure 4: CA 125 trajectory plotted against the percentage of progression free survival. Red line refers to the experimental arm and blue line refers to the standard arm. Figure from a randomized clinical trial.

8. Zhou, C. et al. (2016). Systematic analysis of circulating soluble angiogenesis-associated proteins in ICON7 identifies Tie2 as a biomarker of vascular progression on bevacizumab. British Journal of Cancer, 115: 228-235.

Dose selection

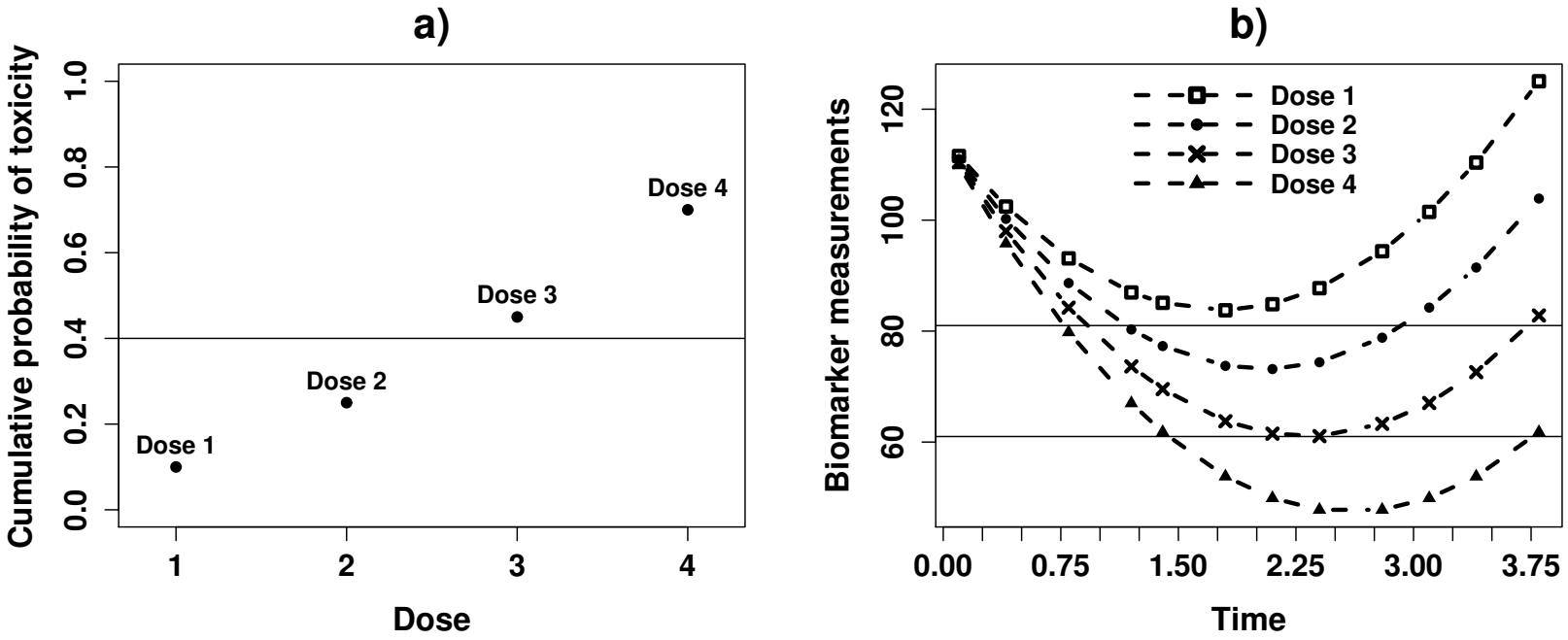

Figure 5: a): Cumulative probability of toxicity over 4 cycles at each dose level. The horizontal line represents the target. b) Biomarker trajectory over time.

Motivating example

➢ Phase 1b multicenter trial in patients with platinum resistant epithelial ovarian carcinoma (EOC)

❖ Primary endpoint:

- Determine MTD
- Determine OD ⇛ RP2D

➢ Response and disease progression measured by tumor volume and **CA 125** measurements

Scenario

Objective: Evaluate the correct selection of the MTD and OD, through different sets of scenarios and extensive simulations.

- 60 patients
- 6 dose levels
- 6 treatment cycles and max 3 biomarker measurements per cycle
- drop out based on DLTs, lack of activity or consent withdrawal (8%)
- intermittent missing responses (7%)
- target toxicity level 40% after 6 cycles
- max mean clinical difference between 2 doses 20 units

Simulation results

Table 3: Percentage of dose selection at the end of the trial ($\boldsymbol{P_{\%}}$) and mean number of patients assigned to each dose level ($\boldsymbol{\bar{N}_{pat}}$). The optimal dose is in bold, the MTD in red and the beginning of the plateau is underlined.

Scenario		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	None Selected
1	$(Y_{(l),min}, p_l)$	(92, 0.02)	(68, 0.07)	**(40, 0.20)**	(40, **0.43**)	(40, 0.68)	(40, 0.88)	
	$P_{\%}$	0.0	0.8	99.2	0.0	0.0	0.0	0.0
	$\bar{N}_{pat}$	2.1	2.8	34.7	11.3	7.7	1.4	
2	$(Y_{(l),min}, p_l)$	(140, 0.00)	(118, 0.00)	(92, 0.03)	(64, 0.12)	**(32, 0.38)**	(32, 0.75)	
	$P_{\%}$	0.1	0.0	0.0	0.7	99.2	0.0	0.0
	$\bar{N}_{pat}$	2.0	2.0	2.2	5.8	42.7	5.2	
3	$(Y_{(l),min}, p_l)$	**(78, 0.07)**	(74, 0.19)	(69, **0.39**)	(63, 0.64)	(57, 0.84)	(50, 0.96)	
	$P_{\%}$	99.7	0.3	0.0	0.0	0.0	0.0	0.0
	$\bar{N}_{pat}$	31.8	6.0	11.0	9.1	2.0	0.1	
4	$(Y_{(l),min}, p_l)$	(96, 0.02)	**(88, 0.07)**	(80, 0.20)	(71, **0.43**)	(71, 0.68)	(71, 0.88)	
	$P_{\%}$	13.6	86.3	0.1	0.0	0.0	0.0	0.0
	$\bar{N}_{pat}$	6.4	26.9	6.3	11.2	7.8	1.4	
5	$(Y_{(l),min}, p_l)$	(78, 0.71)	(74, 0.88)	(69, 0.97)	(63, 0.99)	(57, 0.99)	(50, 0.99)	
	$P_{\%}$	18.1	0.0	0.0	0.0	0.0	0.0	81.9
	$\bar{N}_{pat}$	17.5	1.1	0.0	0.0	0.0	0.0	

Conclusions

➢ Identification of the OD

- High percentage of correct OD selection ($> 86\%$)
- Dose selection within a safe yet efficient range of doses (0% OD selection above the MTD)

➢ Additional simulations for:

- larger variance and smaller sample size
- random effects from different distributions
- increasing hazard for each successive cycle
- data generation from different models
  - both random intercept and random slope
  - different biomarker trajectories

Discussion

✓

- Inclusion of continuous and repeated biomarker measurements
- Inclusion of multiple treatment cycles
- Cumulative definition of the MTD and the OD

✗

- Lack of comparability with the existing designs
- Joint modeling restricted to shared random effects

Thank you !

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Bias and coverage

Table 4: Shown are the percentage of bias and the coverage of the joint model parameters over five different sample sizes: $N = 20$, $N = 25$, $N = 30$, $N = 40$, and $N = 60$.

Parameter	Bias					Coverage				
	N=20	N=25	N=30	N=40	N=60	N=20	N=25	N=30	N=40	N=60
Longitudinal										
β_0	−0.36	−0.16	−0.10	−0.13	−0.02	0.93	0.95	0.95	0.95	0.94
β_1	0.02	0.00	0.00	−0.01	−0.01	0.93	0.94	0.93	0.94	0.95
β_2	−0.13	0.20	0.02	0.02	−0.08	0.91	0.91	0.92	0.93	0.94
β_3	4.00	5.40	−0.25	−0.13	2.30	0.92	0.91	0.93	0.93	0.93
σ_1	−8.20	−8.30	−7.30	−5.90	−6.20	0.99	0.99	0.99	0.99	0.98
σ_2	−3.40	−2.50	−2.10	−1.40	−0.88	0.97	0.97	0.97	0.96	0.96
Survival										
δ_0	0.23	−0.19	0.15	−0.12	0.09	0.97	0.95	0.95	0.95	0.95
δ_1	13.50	8.80	7.50	6.01	3.10	0.97	0.97	0.96	0.96	0.95
γ	40.62	−25.37	12.29	10.96	−2.70	0.99	0.99	0.99	0.99	0.97

Design

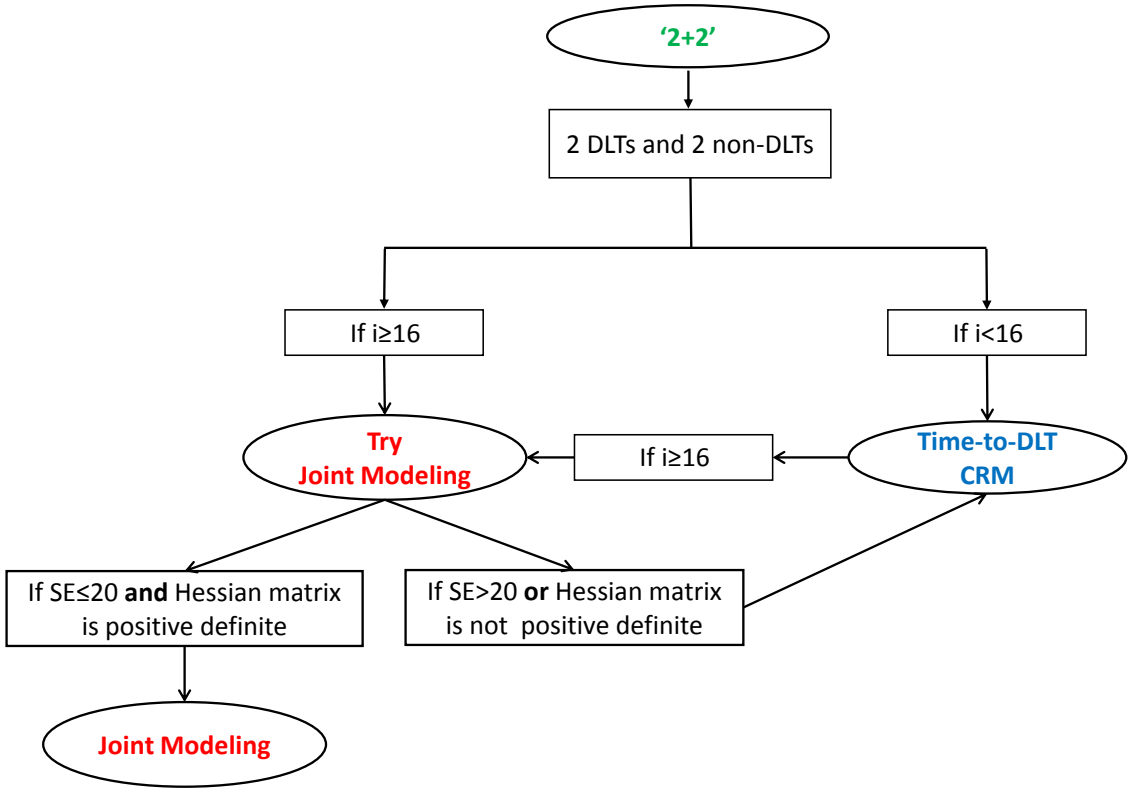

Figure 6: Representation of the study design. Abbreviations: DLTs, Dose Limiting Toxicities; SE, Standard Error; CRM, Continual Reassessment Method.

Sensitivity analysis I

Table 5: Percentage of dose selection at the end of the trial ($\boldsymbol{P_{\%}}$) and mean number of patients assigned to each dose level ($\boldsymbol{\bar{N}_{pat}}$), under the scenarios of Table 3, with different standard deviations, sample size, and random effects' distributions.

Conditions	Scenario		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	None Selected
$\sigma_1 = 2$ and $\sigma_2 = 5$									
N=40	1	$P_{\%}$	0.1	2.3	97.5	0.1	0.0	0.0	0.0
		$\bar{N}_{pat}$	2.1	3.3	20.6	7.9	5.3	1.0	
	2	$P_{\%}$	0.0	0.0	0.0	4.2	95.8	0.0	0.0
		$\bar{N}_{pat}$	2.0	2.0	2.2	5.3	23.6	4.9	
	3	$P_{\%}$	98.6	0.8	0.1	0.1	0.0	0.0	0.4
		$\bar{N}_{pat}$	18.6	5.2	8.3	6.2	1.6	0.1	
	4	$P_{\%}$	17.3	79.0	3.6	0.1	0.0	0.0	0.0
		$\bar{N}_{pat}$	5.1	15.0	5.8	8.0	5.2	0.9	
$U \sim \Gamma(2,2)$ for linear model									
$U \sim N(0,1)$ for probit model									
N=40	1	$P_{\%}$	0.0	0.1	99.9	0.0	0.0	0.0	0.0
$\sigma_1 = 2$ and $\sigma_2 = 3$		$\bar{N}_{pat}$	2.1	2.5	21.1	8.2	5.1	1.0	
	2	$P_{\%}$	0.0	0.0	0.0	5.8	94.2	0.0	0.0
		$\bar{N}_{pat}$	2.0	2.0	2.2	5.3	23.5	5.0	
	3	$P_{\%}$	97.0	1.8	1.1	0.0	0.0	0.0	0.1
		$\bar{N}_{pat}$	18.7	5.3	8.2	6.2	1.5	0.1	
	4	$P_{\%}$	16.8	82.5	0.6	0.1	0.0	0.0	0.0
		$\bar{N}_{pat}$	5.1	15.5	5.4	8.0	5.1	1.0	

Sensitivity analysis II

Table 6: Sensitivity analyses of 1000 replicates and a sample size of 60. Percentage of dose selection at the end of the trial ($P_{\%}$) and mean number of patients assigned to each dose level ($\bar{N}_{pat}$). Toxicity data was generated assuming increasing hazard at each successive treatment cycle. The optimal dose is in bold, the MTD in red and the beginning of the plateau is underlined.

Scenario		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	None Selected
1	$(Y_{(l),min}, p_l)$	(88, 0.01)	**(59, 0.03)**	(59, 0.11)	(59, **0.31**)	(59, 0.61)	(59, 0.87)	
	$P_{\%}$	0.0	100.0	0.0	0.0	0.0	0.0	0.0
	$\bar{N}_{pat}$	2.2	34.8	3.0	3.0	3.0	14.0	
2	$(Y_{(l),min}, p_l)$	(201, 0.00)	(176, 0.00)	(147, 0.00)	(114, 0.03)	(77, 0.14)	**(38, 0.42)**	
	$P_{\%}$	0.0	0.0	0.0	0.0	6.5	93.5	0.0
	$\bar{N}_{pat}$	2.0	2.0	2.1	2.4	7.9	43.6	

Biomarker-time relationship

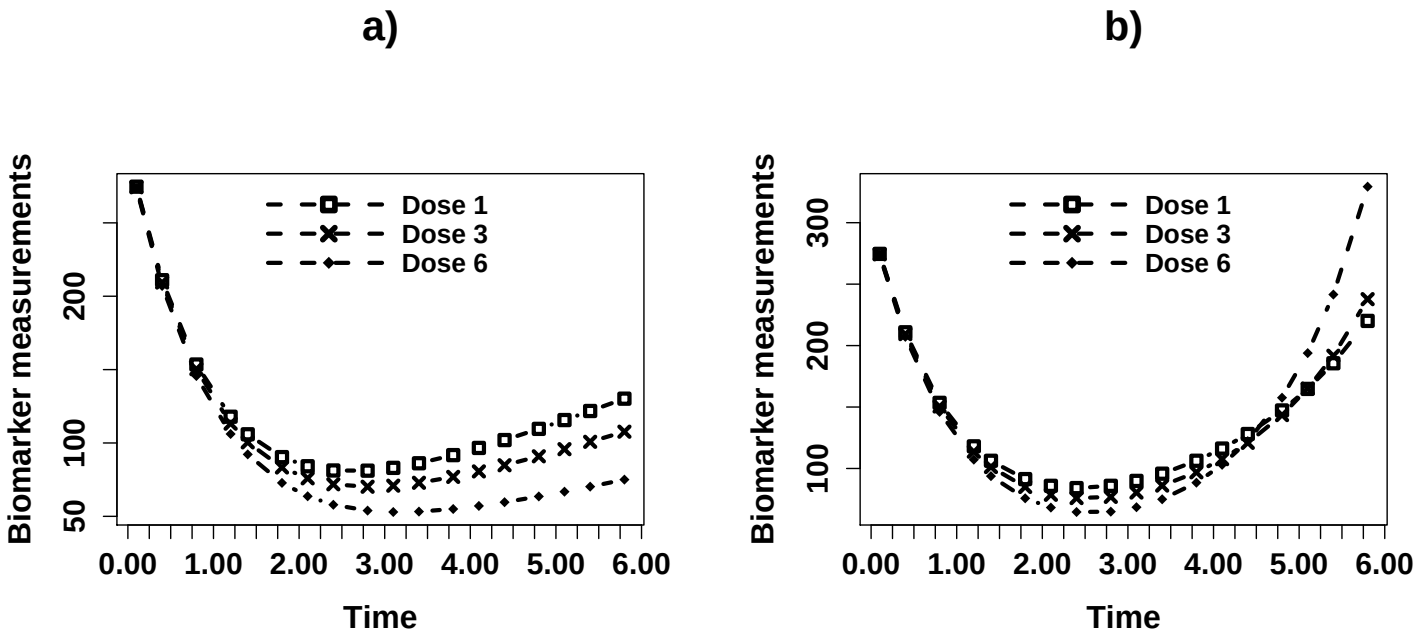

Figure 7: Non-linear biomarker trajectories