Supplemental Material to
Dose Optimization for Cancer Treatments with Considerations for Late-onset Toxicities

by Lucie Biard, Anaïs Andrillon, Rebecca B Silva and Shing M Lee

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Table S1: Simulations results for the idelalisib example: percent of recommendations of each dose level (D1 to D5) estimated over 10000 simulated trials, with a 4-week or 16-week observation window for toxicity, a total sample size of 30 patients, an accrual rate of 2 patients per month.

Hazard		D1	D2	D3	D4	D5	Duration
16-week obs. window (8 patients per obs.window)							
Constant	True Probability of Toxicity	0.10	**0.25**	0.45	0.60	0.75	
	% recommended by TITE-CRM	19	**66**	15	0	0	76 weeks
	% recommended by TITE-BOIN	15	**71**	13	1	0	100 weeks
4 week obs. window (2 patients per obs.window)							
Decreasing	True Probability of Toxicity	0.077	**0.196**	0.364	0.501	0.650	
	% recommended by TITE-CRM	5	**55**	37	3	0	64 weeks
	% recommended by TITE-BOIN	6	**61**	30	3	0	62 weeks
Decreasing	True Probability of Toxicity	0.056	0.147	**0.281**	0.396	0.534	
	% recommended by TITE-CRM	1	28	**52**	17	1	64 weeks
	% recommended by TITE-BOIN	1	37	**47**	13	1	62 weeks
Constant	True Probability of Toxicity	0.026	0.069	0.139	0.205	**0.293**	
	% recommended by TITE-CRM	0	1	14	42	**43**	64 weeks
	% recommended by TITE-BOIN	0	4	22	38	**36**	62 weeks

Table S2: Dose-finding designs for late-onset toxicities incorporating toxicity and efficacy.

Authors	Dose-finding objective	Recommends >1 dose	Preliminary toxicity-centered stage
Binary outcomes			
Jin et al. (2014)[1]	MDD: dose maximizing a desirability function summarizing the toxicity/efficacy trade-off	No	No
Liu & Johnson (2016)[2]	MDD: dose with the highest utility function	No	No
Rivière et al. (2018)[3]	OD: lowest safe dose which maximizes efficacy	No	Ruled-based start-up stage until the first toxicity is observed
Yan et al. (2019)[4]	OD: dose with the highest efficacy among safe doses	Possibly	No
Takeda et al. (2020)[5]	OD: dose lower or equal to the MTD which maximizes efficacy	No	No
Zhang & Zang (2021)[6]	MDD: dose with the highest utility function	No	Yes
Zhou et al. (2022)[7]	MDD: dose with the highest utility among doses equal or lower to the MTD	No	No
Time to event outcomes			
Yuan & Yin (2009)[8]	OD: dose with the higher AUSC value while satisfying acceptable toxicity requirement	No	No
Koopmeiners & Modiano (2014)[9]	MDD: dose maximizing a desirability function summarizing the toxicity/efficacy trade-off	No	No
Altzerinakou & Paoletti (2019)[10]	OD: lowest dose, within a range of highly active doses, below or equal to the MTD	No	Ruled-based start-up stage followed by a Time-to-DLT CRM
Biard et al. (2021)[11]	OD: dose with acceptable toxicity risk and minimum progression risk in terms of marginal rates of events	Possibly	Ruled-based start-up stage until the first toxicity is observed
Zhang et al. (2021)[12]	MDD: dose with the highest utility among an admissible set in terms of toxicity	Possibly	Yes
Andrillon et al. (2022)[13]	OD: dose equal or lower to the MTD with the minimum progression cumulative incidence	No	No

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Table S3: Dose-finding designs for late-onset toxicities incorporating toxicity and efficacy: statistical considerations.

Authors	Non-monotone dose-efficacy relationship	Method for pending data	Smallest sample size explored	Available software
Binary outcomes				
Jin et al. (2014)[1]	Yes	Data augmentation process	N=48	None listed
Liu & Johnson (2016)[2]	No	Weighting scheme	N=48	None listed
Riviere et al. (2018)[3]	Yes	Weighting scheme	N=36	R package `dfmta`
Yan et al. (2019)[4]	Yes	Weighting scheme	N=35	None listed
Takeda et al. (2020)[5]	Yes	Weighting scheme	N=36	SAS code upon request
Zhang & Zang (2021)[6]	Yes	Weighting scheme	N=60	R code available on GitHub CWL
Zhou et al. (2022)[7]	Yes	Weighting scheme, Imputation or Data augmentation process	N=36	R shiny app trialdesign.org
Right-censored outcomes				
Yuan & Yin (2009)[8]	No	Cure rate survival model	N=48	None listed
Koopmeiners & Modiano (2014)[9]	Yes	Cure rate survival model	N=30	None listed
Altzerinakou & Paoletti (2019)[10]	Yes	Probit time-to-DLT model	N=15	None listed
Biard et al. (2021)[11]	Yes	Exponential survival model	N=50	R code upon request
Zhang et al. (2021)[12]	No	Data augmentation process	N=60	R code as supplementary material
Andrillon et al. (2022)[13]	No	Exponential survival model	N=45	R code upon request

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