U-DESPA: a Utility-based Bayesian approach for dosage optimization handling PK, PD safety and efficacy in oncology clinical trials

October 26th, 2023

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On the importance of finding the best dosage…

Conditions the full development

- Too high dosage may bring safety concerns, potentially leading to an efficacious compound not entering into market
- Wrong dosing regimen may decrease the efficacy
- Postmarketing trials to evaluate lower doses

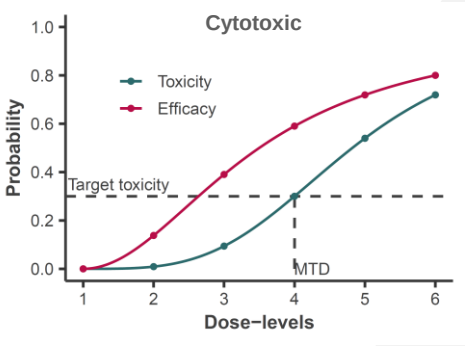
Examples of Drugs Whose Doses or Schedules Were Modified for Safety or Tolerability after Approval.*

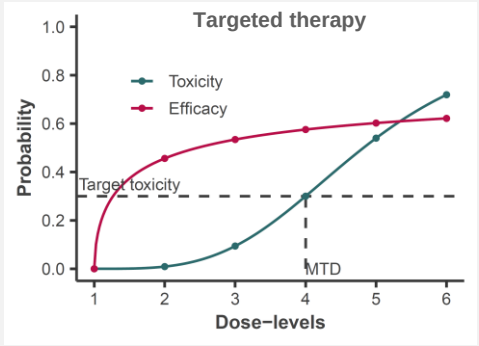
Drug	Initial Dose and Trials	Modified or Added Dose and Trials	Reason for Modified or Added Dose
Small-molecule drugs			
Ceritinib (Zykadia)	750 mg PO daily fasted (ASCEND-1)	450 mg PO daily with food (ASCEND-8)	Reduce gastrointestinal toxic effects
Dasatinib (Sprycel)	70 mg PO twice daily (CA180013, CA180005, CA180006, and CA180015)	100 mg PO daily (CA180034)	Reduce hematologic toxic effects and fluid retention
Niraparib (Zejula)	300 mg PO daily (NOVA)	200 mg PO daily (PRIMA)	Reduce thrombocytopenia in patients with a lower platelet count or lower body weight
Ponatinib (Iclusig)	45 mg PO daily (PACE)	45 mg PO daily, then 15 mg PO daily once ≤1% *BCR-ABL* is achieved (OPTIC)	Reduce vascular occlusive events
Chemotherapy			
Cabazitaxel (Jevtana)	25 mg/m² IV every 3 wk (TROPIC)	20 mg/m² IV every 3 wk (PROSELICA)	Reduce hematologic toxic effects and infections
Antibody–drug conjugates			
Gemtuzumab ozogamicin (Mylotarg)	9 mg/m² IV on days 1 and 15 (Study 201, Study 202, and Study 203)	3 mg/m² IV on days 1, 4, and 7 (Mylofrance-1)	Reduce veno-occlusive disease and treatment-related mortality

* Adapted from the Food and Drug Administration.[3] IV denotes intravenous, and PO by mouth.

The Drug-Dosing Conundrum in Oncology — When Less Is More | NEJM

More is not necessarily better and sometimes less is definitively better…





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Reforming the dose optimization and dose selection paradigm in oncology

Project Optimus

Reforming the dose optimization and dose selection paradigm in oncology

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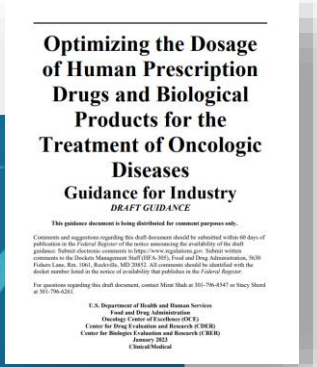


Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

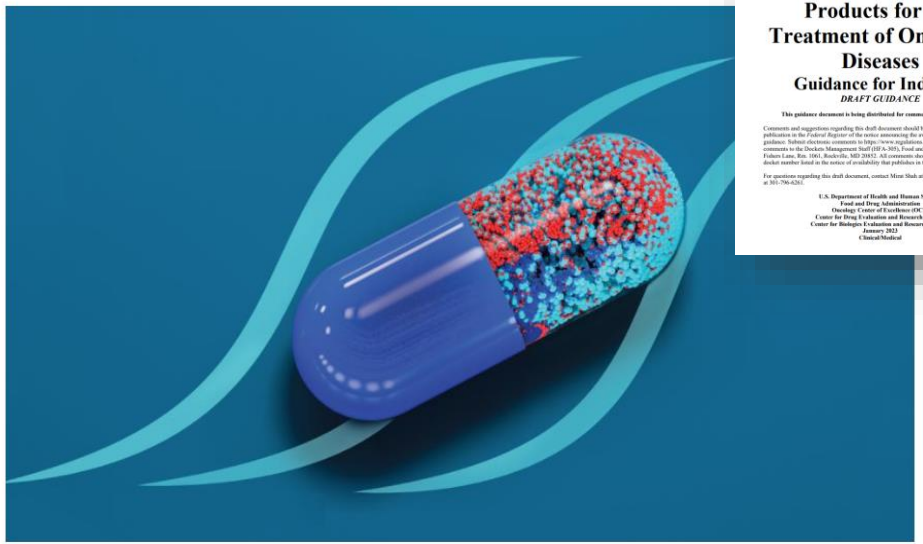
DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Mirat Shah at 301-796-8547 or Stacy Shord at 301-796-0261.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2023
Clinical/Medical



Publications

- Improving Dose-Optimization Processes Used in Oncology Drug Development to Minimize Toxicity and Maximize Benefit to Patients. Fourie Zirkelbach J, Shah M, Vallejo J, Cheng J, Ayyoub A, Liu J, Hudson R, Sridhara R, Ison G, Amiri-Kordestani L, Tang S, Gwise T, Rahman A, Pazdur R, Theoret MR. J Clin Oncol. 2022 Sep 12:JCO2200371.
- How to Get the Dose Right. The ASCO Post. Mirat Shah, Atiqur Rahman, Marc R. Theoret, and Richard Pazdur. May 10, 2022.
- Optimizing Dosing in Oncology Drug Development Q&A. Friends of Cancer Research. April 7, 2022. Shah M, Rahman A, Theoret MR, Pazdur R.
- The Drug-Dosing Conundrum in Oncology - When Less Is More. N Engl J Med. 2021 Oct 14;385(16):1445-1447. doi: 10.1056/NEJMp2109826. Epub 2021 Oct 9. PMID: 34623789.
- Friends of Cancer Research White Paper. Optimizing Dosing in Oncology Drug Development. Friends of Cancer Research Annual Meeting 2021.

FDA Guidance Documents

- Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases (draft guidance, January 2023)
- Population Pharmacokinetics
- Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications
- ICH Topic E4: Dose-Response Information to Support Drug Registration

How should the Optimal dosage (/RP2D) be selected ?

Recommended Phase 2 dosage(s) (RP2D) should not necessary be the Maximum Tolerated Dose (MTD)

Exposure	- drives activity (safety and efficacy) of the compound. - Assessed using a relevant exposure metric (e.g. plasma AUC24)
Target engagement	- Identification of active exposure/dosages - Assessed using PDy marker(s)
Efficacy	- Reach clinical anti tumor activity - Assessed from tumor shrinkage (e.g. sum of target lesions diam)
Safety	- Only safe dosage can be considered - Assessed using safety parameters (e.g. DLT)

Propose a unified approach to support dosage recommendation. Balancing safety, activity and efficacy in taking into account the exposure and its variability

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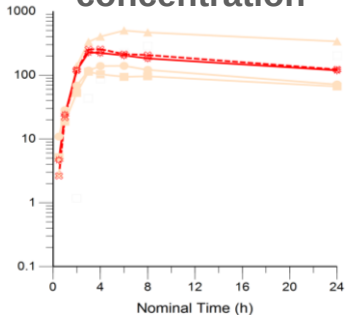
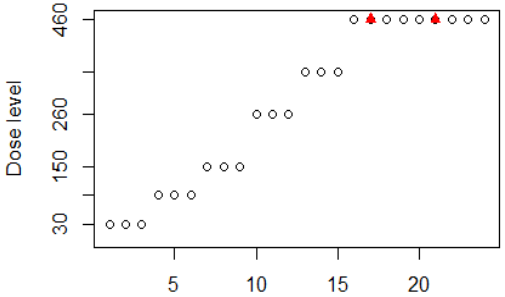
Data (Simulated): Pharmacokinetics, Pharmacodynamics, safety and anti-tumor activity

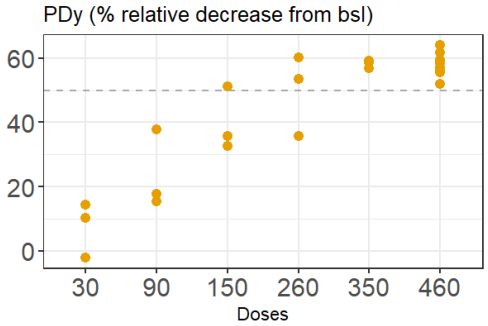
Exposure-concentration



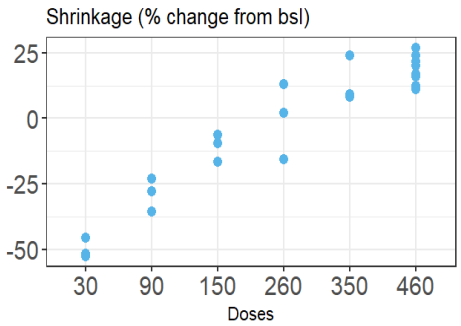
Safety- DLT

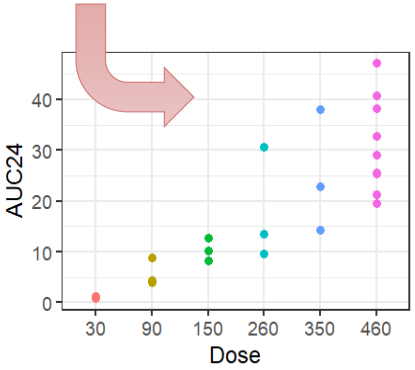


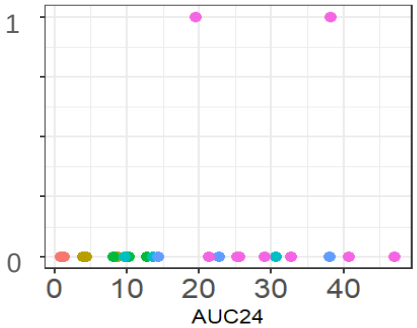
Target engagement - PDy marker

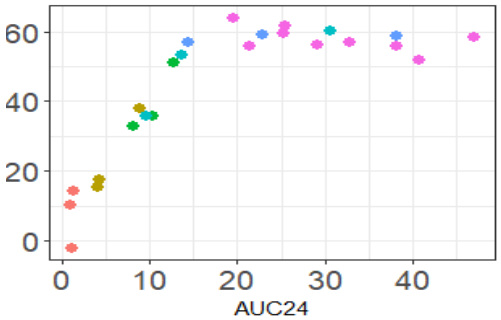


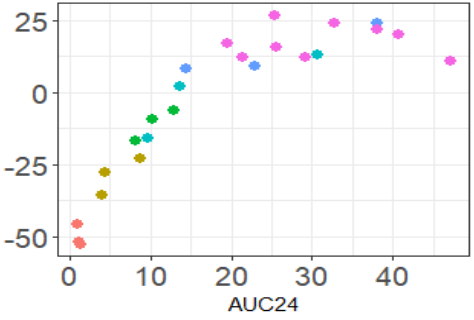
Efficacy- Tumor shrinkage



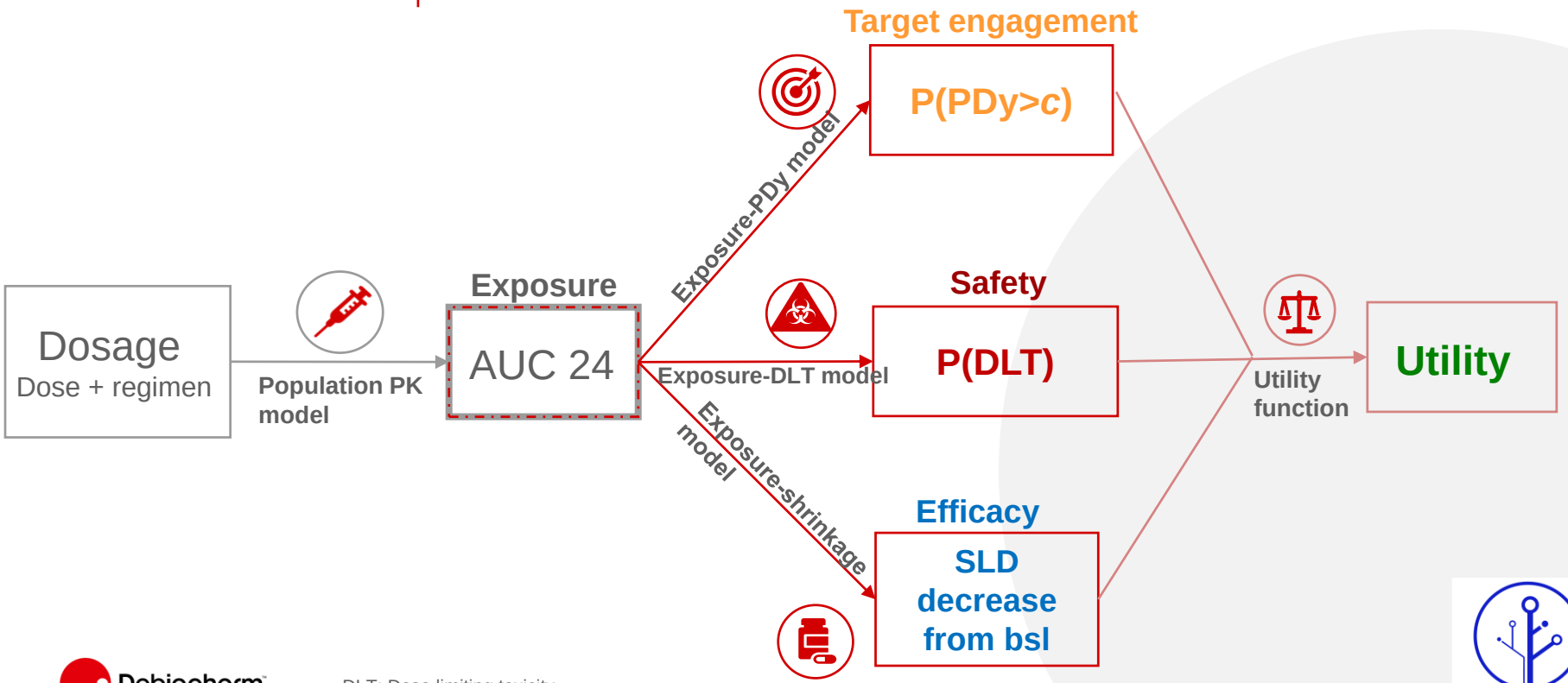








Quantification of the physiological processes and benefit risk balance



DLT: Dose limiting toxicity
SLD: Sum of the longest diameter of tumor target lesions

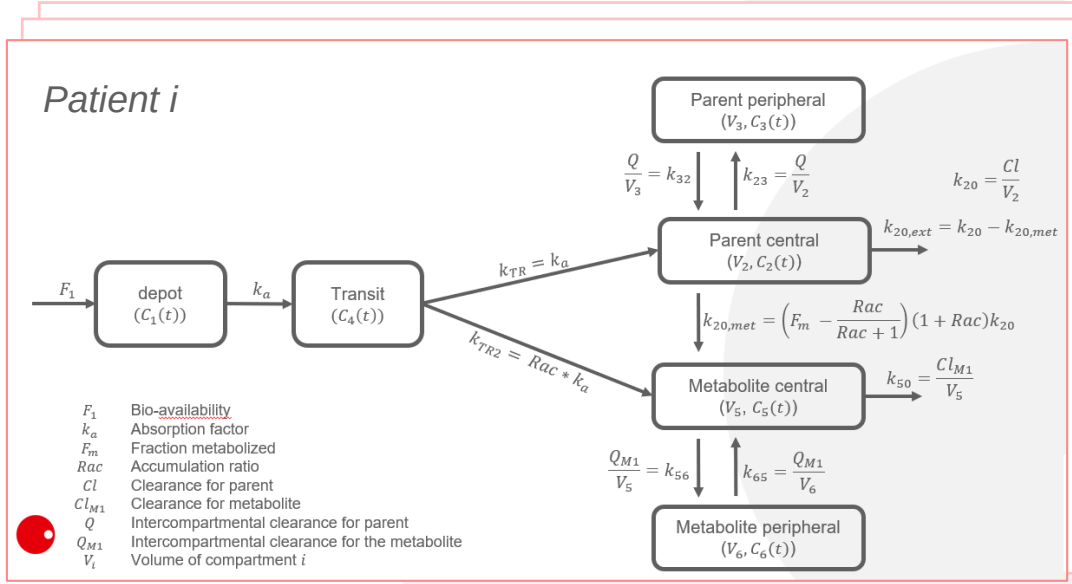
Dose-exposure relationship – Population PK model

- **Nonlinear mixed effects model for drug concentration C from repeated measurements**

$$C_i(t,d) = f(\theta_i, t, d) + h(\theta_i, t, d, \xi)\varepsilon$$

With:

- $i = 1, \dots, N$: patient
- t: time
- d: dose
- C_i: concentration for patient i
- f: structural model (Compartment model defined from a system of differential equations)
- θ_i: patient-specific parameters, $\theta_i = \mu e^{\eta_i}$ **with μ the fixed effects and $\eta_i \sim N(0, \Omega)$ the random effects**
- h: error model



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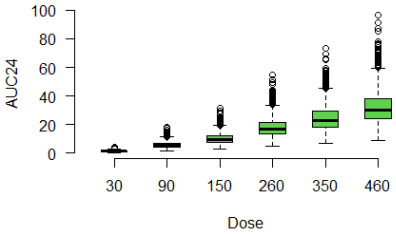
Models and Bayesian calibration

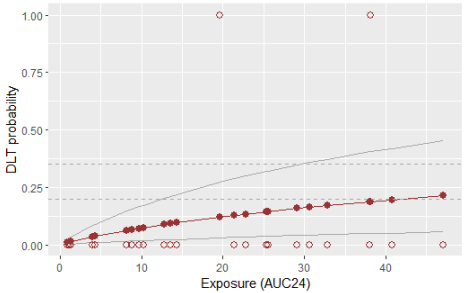
Dose - Exposure



$$C_i(t,d) = f(\theta_i,t,d) + g(\theta_i,t,d,\xi)\varepsilon$$

- $i = 1,\dots,N$: patient
- AUC_i: AUC of patient i
- AUC_{ref}: reference AUC

Safety: Exposure-DLT rate, p_i

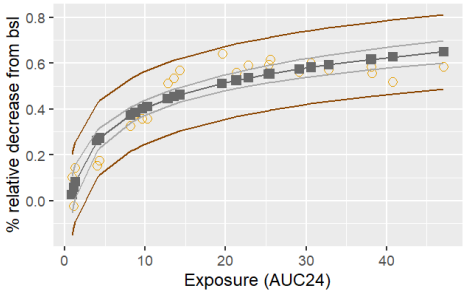


$$logit(p_i) = \phi_1 + e^{\phi_2}.\log\left(\frac{AUC_i}{AUC_{ref}}\right)$$

Prior: $\phi = (\phi_1,\phi_2) \sim BVN(\mu_\phi,\Sigma_\phi)$

- p_i: DLT probability for AUC of patient i

Target engagement: Exposure- PDy marker, q_i , r_i,



$$r_i = \beta_1 + \beta_2.\log\left(\frac{AUC_i}{AUC_{ref}}\right) + \varepsilon_i$$

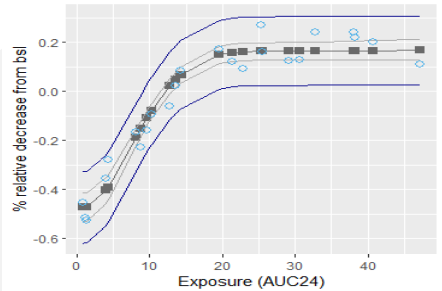
$$q_i = P(r_i \geq c)$$

Priors: $\beta = (\beta_1,\beta_2) \sim BVN(\mu_\beta,\Sigma_\beta)$

$\frac{1}{\sigma_r^2} \sim \Gamma(0.1,0.1)$

- r_i: relative pCDC2 reduction from baseline of AUC of patient i
- q_i: probability that relative pCDC2 reduction is greater than a threshold c
- ε_i: errors, $\varepsilon_i \sim N(0,{\sigma_r}^2)$

Efficacy: Exposure-Tumor shrinkage, s_i



$$s_i = a_0 + \sum_{k=1}^{4} a_i * B_{k,i}\left(\frac{AUC_i}{AUC_{ref}}\right) + \varepsilon_i$$

Prior: $a_0 \sim N(0,100)$, $a_i \sim \Gamma(0.01,0.01)$, $\frac{1}{\sigma_s^2} \sim \Gamma(0.01,0.01)$

- s_i: relative decrease from baseline vs AUC for patient i
- ε_i: errors, $\varepsilon_i \sim N(0,{\sigma_s}^2)$
- $a_i \in \mathbb{R}$: spline coefficients
- $B_{k,i}\left(\frac{AUC_i}{AUC_{ref}}\right)$ k'th member of a family of B-splines functions

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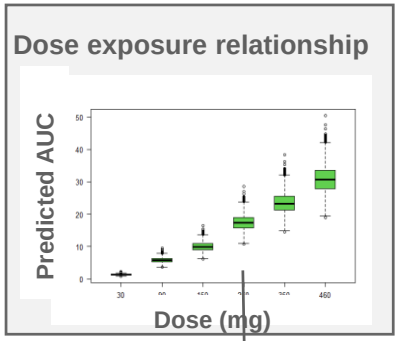
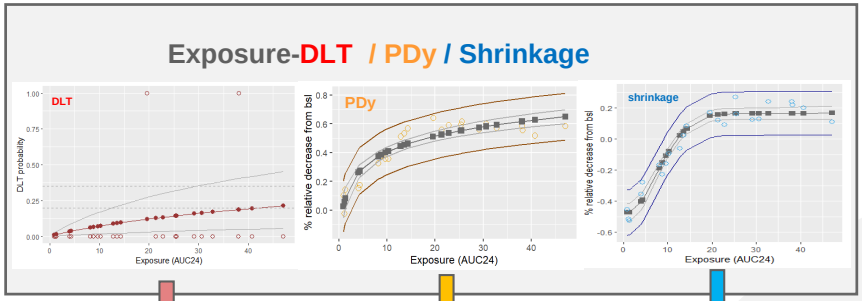
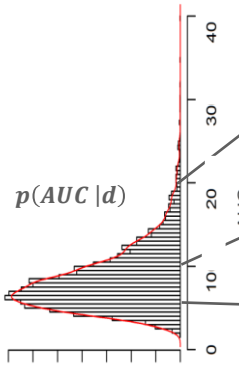




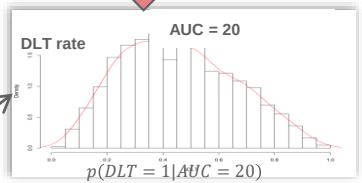
For each dose d

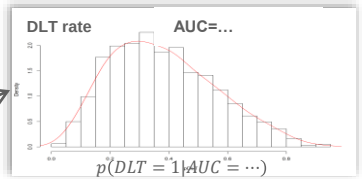


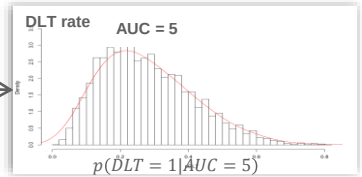
$p(AUC = 20|d)$

$p(AUC = \cdots|d)$

$p(AUC = 5|d)$







$$p(d) = p(AUC = 20|d).p(\boldsymbol{DLT}|AUC = 20) + p(AUC = \cdots|d).p(\boldsymbol{DLT}|AUC = \cdots) + p(AUC = 5|d).p(\boldsymbol{DLT}|AUC = 5) + \dots$$

$$q(d) = p(AUC = 20|d).p(PDy|AUC = 20) + p(AUC = \cdots|d).p(PDy|AUC = \cdots) + p(AUC = 5|d).p(\boldsymbol{PDy}|AUC = 5) + \dots$$

$$s(d) = p(AUC = 20|d).p(\boldsymbol{s}|AUC = 20) + p(AUC = \cdots|d).p(\boldsymbol{s}|AUC = \cdots) + p(AUC = 5|d).p(\boldsymbol{s}|AUC = 5) + \dots$$

$$G(p, q, s)$$

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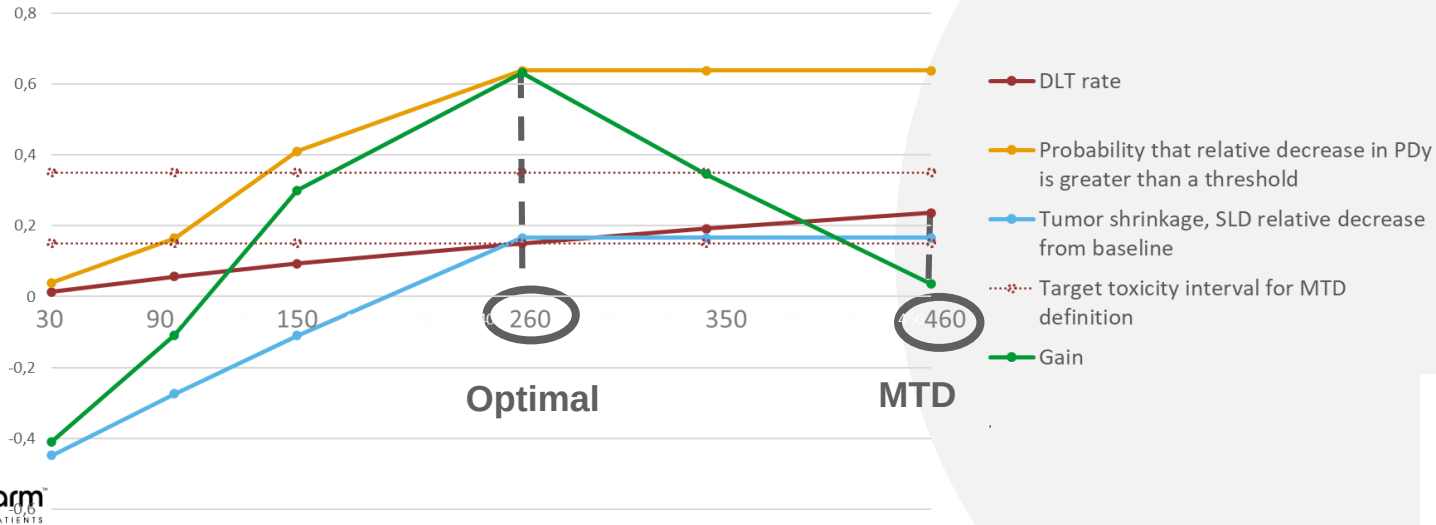
Utility as a function of endpoint estimates

$$G(p_k, q_k, s_k; \alpha_1, \alpha_2, \delta, \psi) = \begin{cases} -\infty & \text{if } p_k \geq \delta \\ \alpha_1 . s_k + \alpha_2 . q_k + \alpha_3 . (p_k - \delta_{min}) & \text{if } \delta_{min} \leq p_k < \delta \\ \alpha_1 . s_k + \alpha_2 . q_k & otherwise\ (p_k \leq \delta_{min}) \end{cases}$$

For $\alpha_1 = 1,\ \alpha_2 = 1,\ \delta = 0.35,\ \delta_{min} = 0.15,\ \alpha_3 = -7$



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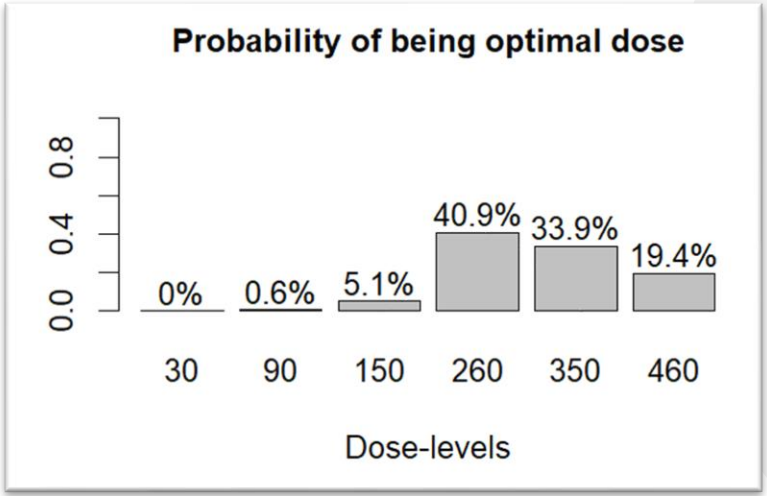
Dose recommendation: *The dose with the highest probability to maximize the gain*

For each MCMC sample, the Optimal Dose is defined as:

- **The lowest dose**
- **among the doses having the highest gain (less than 1% of the maximum gain)**

The recommended dose is the one with the highest probability of being the optimal dose



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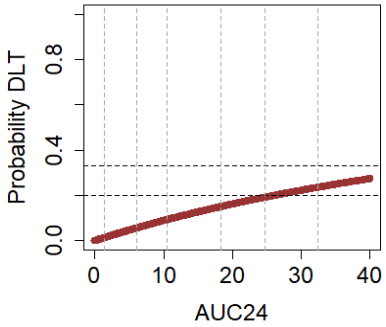
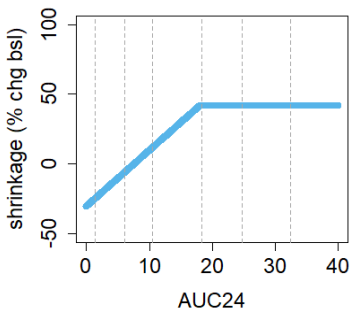
Design's performance: Simulations

- **Scenario 1** « targeted therapy: optimal dose is lower than MTD». 1000 simulated trials

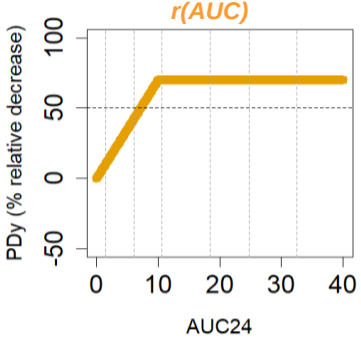
Safety, *p(AUC)*



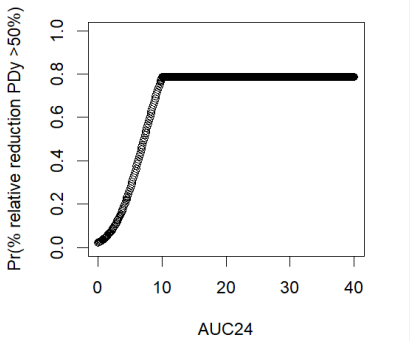
Anti-tumor activity, *s(AUC)*



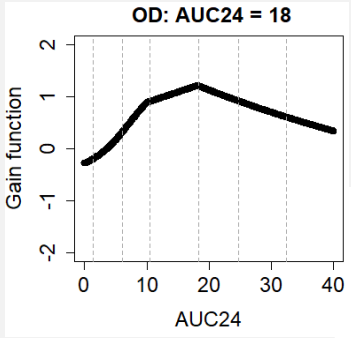
Pharmacodynamy PDy, *r(AUC)*



Target engagement, *q(AUC)*



	D1=30	D2=90	D3=150	D4=260	D5=350	D6=460
% selected as MTD	0	0.9	7.5	16.3	17.8	**57.4**
% recom Opt. Dose U-DESPA	0.8	0.2	23.1	**63.9**	10.8	1.1
Median gain (MCMC)	-0.24	0.02	1.19	1.30	1.13	0.86
Mean % being OD	1.68	7.19	28.32	44.01	15.24	3.45
Mean number of patients	39.9					

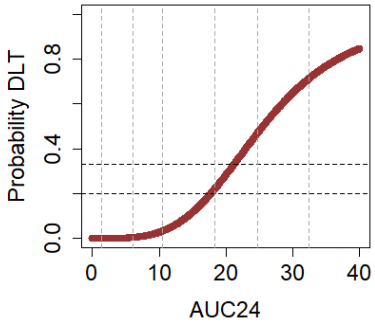


(1) MTD: Maximum Tolerated Dose
(2) OD: Optimal Dose

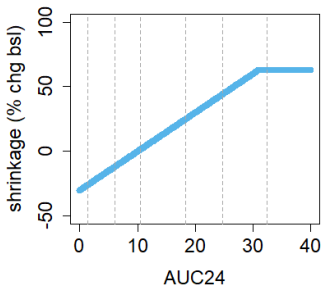
Design's performance: Simulations

- **Scenario 2** « optimal dose close to the MTD ». 1000 simulated trials

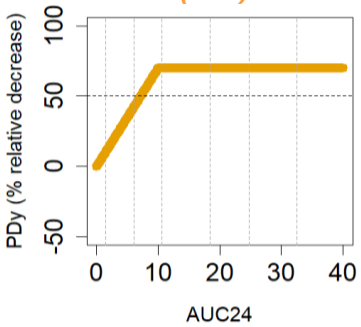
Safety, *p(AUC)*



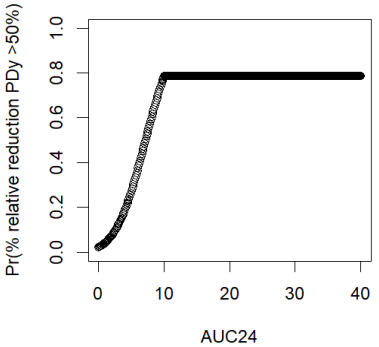
Anti-tumor activity, *s(AUC)*



Pharmacodynamy PDy, *r(AUC)*

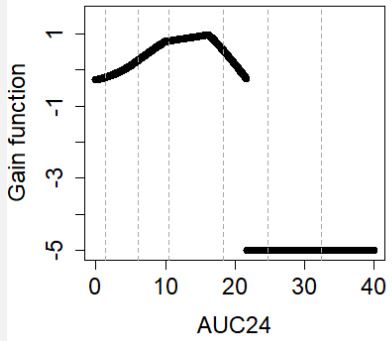


Target engagement, *q(AUC)*



	D1=30	D2=90	D3=150	D4=260	D5=350	D6=460
% selected as MTD	0	0	11.2	**70.6**	17.4	0.8
% recom Opt. Dose U-DESPA	0	0	**47.8**	**38.7**	13.3	0.2
Median gain (MCMC)	-0.236	-0.083	0.774	0.644	-5	-5
Mean % being OD	1.62	17.26	39.54	34.1	7.24	0.24
Mean number of patients	39.26					

OD: AUC24 = 16.1



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SARYGA
STATISTICS & METHODOLOGY

U-DESPA: a new tool to support RP2D selection and optimal dosage

New approach to support dosage selection for phase 2 and optimal dosage

- Relying on different endpoints relevant for dosage selection
- Allows to compare not only doses but also dosages (dose and dosing regimen)
- Approach in line with Optimus guidance

Discussion

- Limited number of patients in dose escalation trial: remaining uncertainty in the estimates…
  - identification of 2 or 3 candidate dosages for further assessment (e.g. in a later randomized portion)
  - Use of relevant data outside of the study to inform models (e.g. PK data from other trials with the same compound)
- Many « parameters » to calibrate (Gain elicitation/function, exposure-response models,…)

Next steps

- Extended simulations under different scenarios
- Robustness to different sample sizes
- Implementation in a real study for RP2D selection

Thank you !

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