UTILITY-BASED BAYESIAN METHOD FOR DOSE OPTIMIZATION IN ONCOLOGY – U-DESPE

Anaïs Andrillon[1], **Sandrine Micallef**[2],
Moreno Ursino, Pavel Mozgunov, Marie-Karelle Riviere

[1] Department of Statistical Methodology, Saryga
[2] Debiopharm International

PSI 2026 CONFERENCE

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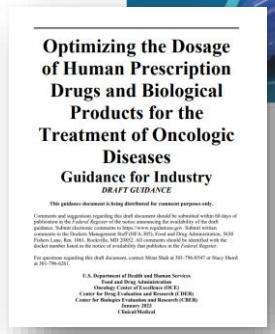
How can we embrace Optimus ?

The example of zedoresertib

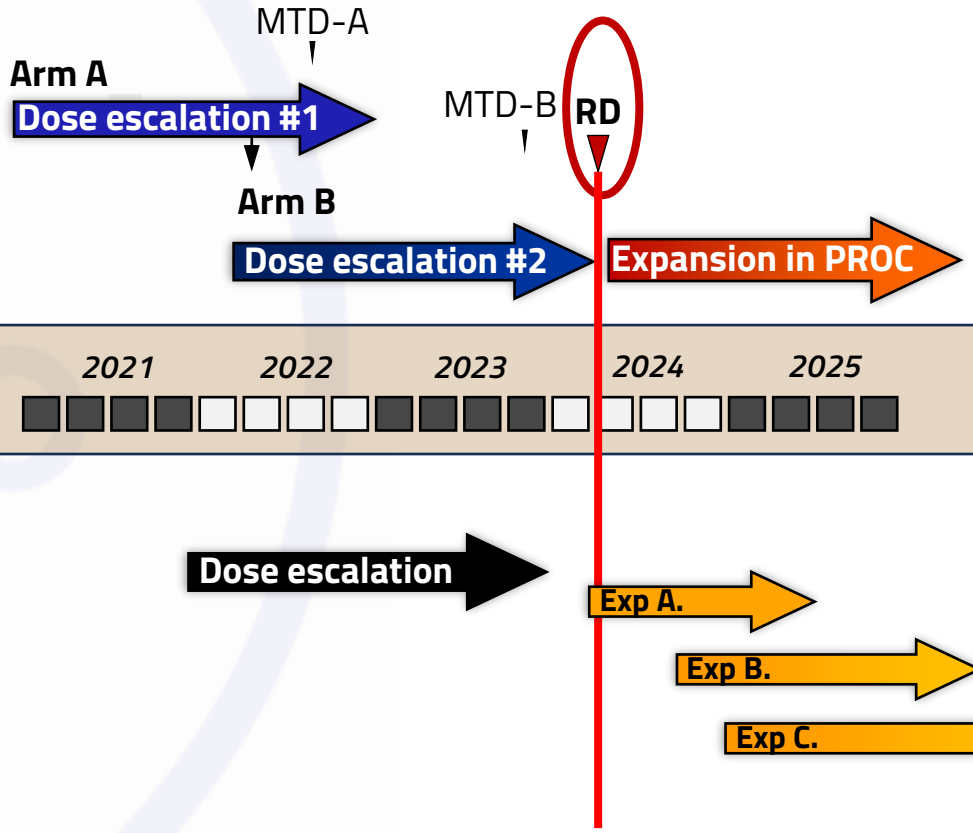

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases
Guidance for Industry
DRAFT GUIDANCE

RD analysis: What's the best dosing regimen for further investigation in PROC* population ?

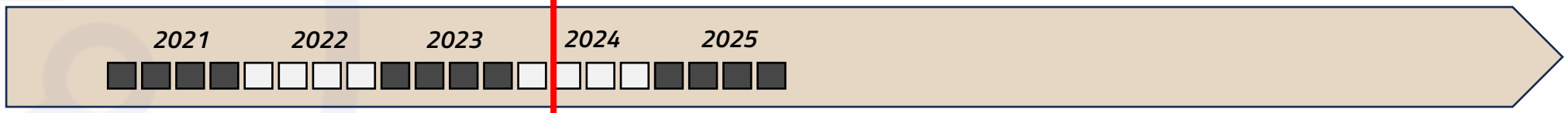
CT-101

Combination with Carboplatin

Solid Tumors (prior platin, incl. PROC)



- Dose Escalation
- Arm A and B explored 2 different dosing schedules:
  - Arm A: 3 days monoT, then 3Days on, every 3wks cy
  - Arm B: 3Days on 4Days off, the first 2 wks of a 3wks cy
- Data collected: DLT, AEs, PK, PD, BOR



CT-102

MonoT

Solid Tumors

- Dosing schedules: Daily
- MTD=260mg
- Data collected: DLT, AEs, PK, PD, BOR

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*PROC: Platinum Resistant Ovarian Cancer ; DLT: Dose Limiting Toxicities ; MTD: Maximum Tolerated Dose. AE: Adverse Event ; PK: Pharmacokinetic ; PD: Pharmacodynamy ; BOR: Best Overall response as per RECIST

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WHY IS THE DOSE TO BE RECOMMENDED FOR EXPANSION IS COMPLEX TO SELECT ? DIFFICULTIES AND OUR SOLUTIONS

CT-101 Escalation

Combination with Carboplatin

Solid Tumors
(prior platin, incl. PROC)

Need to select one administration schedule and one Dose level for PROC patients

Best efficacy in the range of well tolerated dosages

CT-101-Expansion

Combination with Carboplatin

Platinum resistant Ovarian Cancer

Dose escalation

- Arm A and B explored **2 different dosing schedules**
- Data collected:
  - **Safety** (primary): DLT, AEs,
  - **Pharmacology**: PK, PD,
  - **Efficacy**: BOR, ORR

Compare different dose and admin. schedules → **Use Exposure-response**

Handle both Safety, PK, PD and efficacy → **Use benefit risk (Utility) function**

Different regimens → **Use Population PK**

Different populations → **Select (PR)OC patients**

Dose expansion

- Early proof of concept
- Dosage to maximise the benefit???

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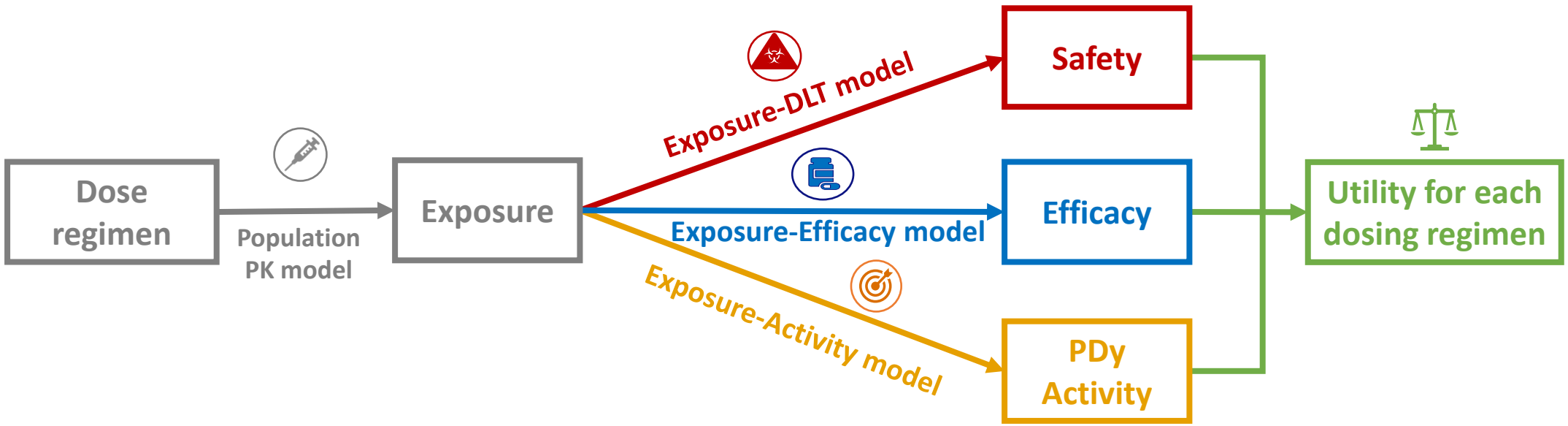
U-DESPE DESIGN

A Bayesian Utility-based methodology for dosing regimen optimization in early-phase oncology trials based on Dose-Exposure, Safety, Pharmacodynamics, Efficacy

→ **Quantitative decisions tool** that optimizes dosing regimen by modeling the **benefit risk balance**



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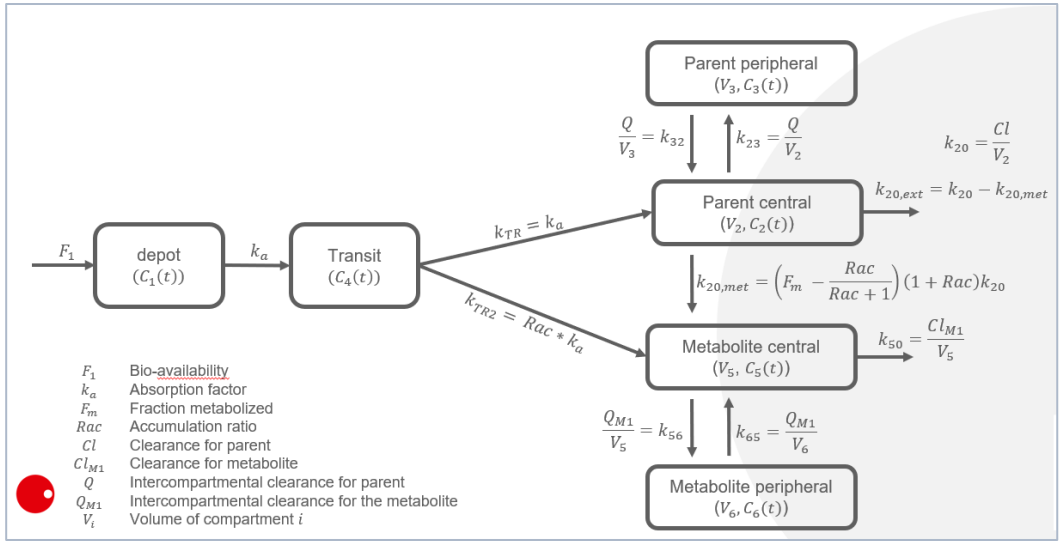
MODELS

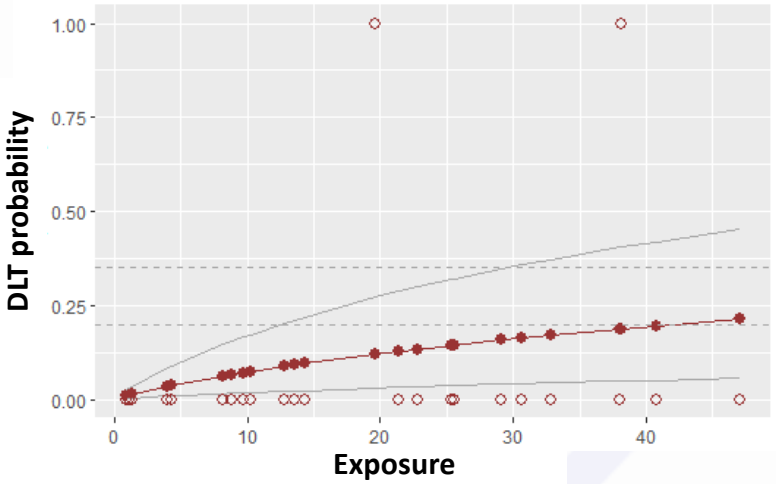
Dose-exposure relationship – Population PK model

→ Handling the **variability and uncertainty in the PK mechanism** into the dose finding process

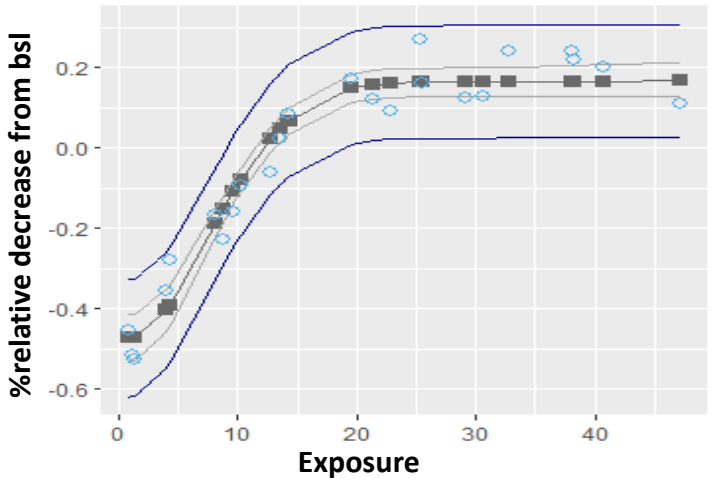


Exposure-Endpoints: Bayesian modeling

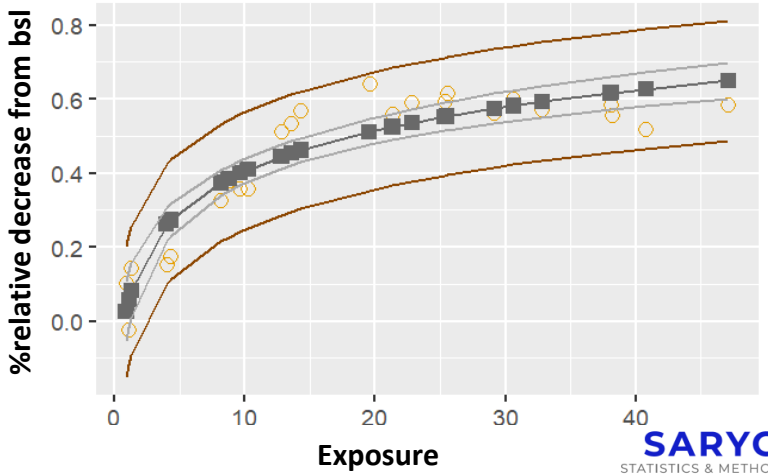
Safety: exposure- DLT model
→ Bayesian Logistic Regression



Efficacy: Exposure- Tumor shrinkage
→ piecewise monotone cubic splines



Activity: Exposure- PDy marker
→ log linear model



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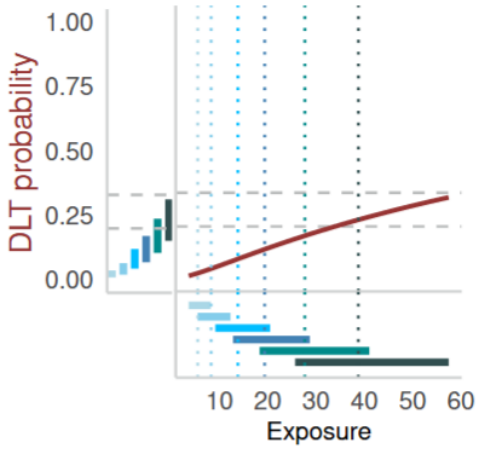
UTILITY AS A FUNCTION OF ENDPOINT ESTIMATES

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

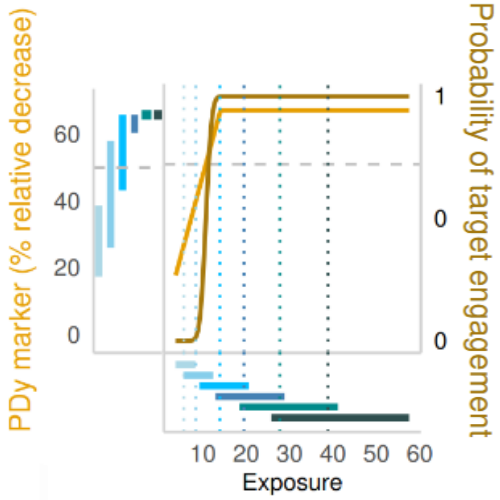
Safety

p_k , probability of DLT at dosing regimen k



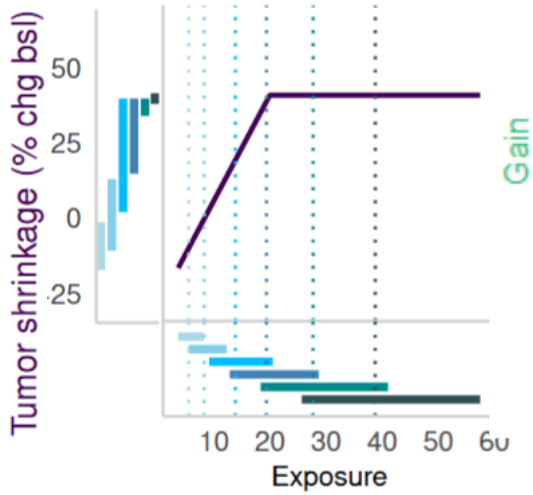
Activity

q_k , probability that the relative decrease of PDy exceeds a threshold c



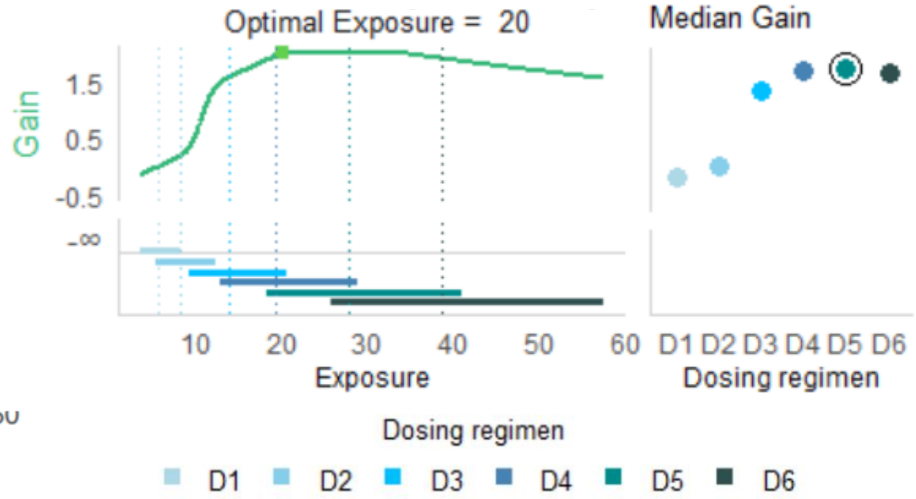
Efficacy

s_k , tumor shrinkage



Utility

for $\alpha_1 = -4, \alpha_2 = 1, \alpha_3 = 2,$
$\delta_{min} = 0.20, \delta_{max} = 0.33$



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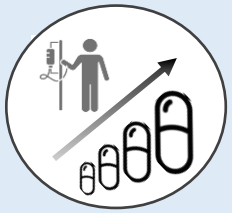
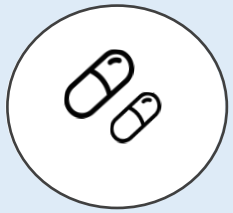
SIMULATIONS - SCENARIO 1: « OPTIMAL DOSE IS LOWER THAN MTD»

Dose escalation
(BLRM)

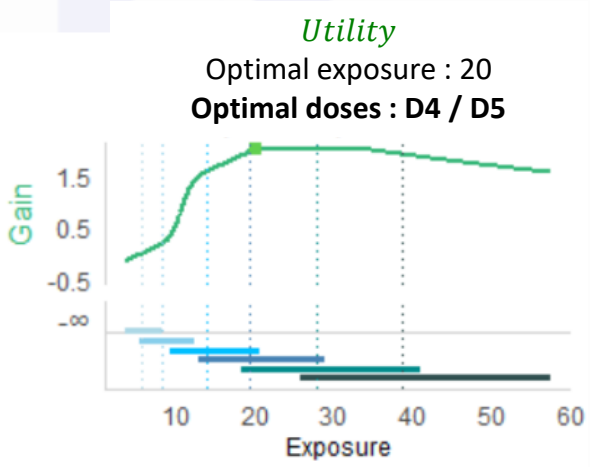


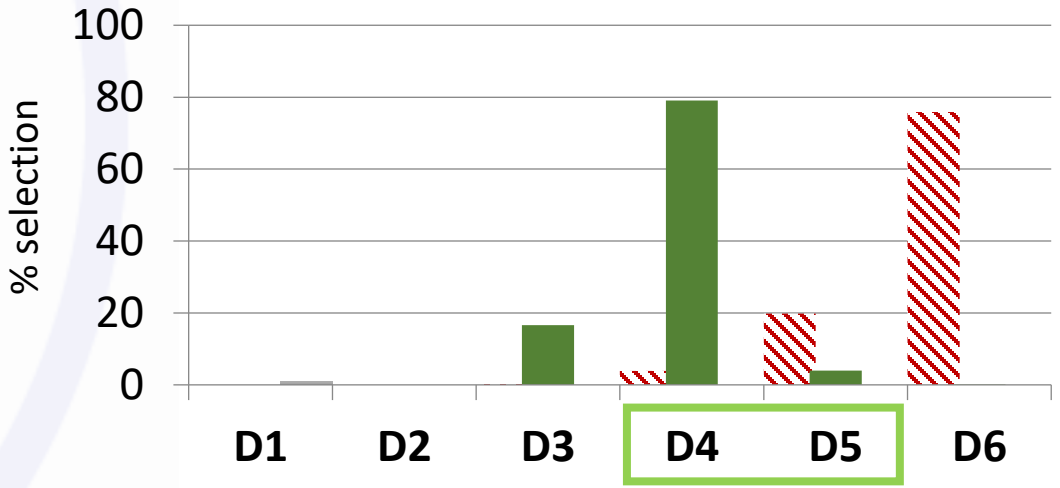
N=42 patients

Dose recommendation
(U-DESPE)



42 patients in total





BLRM
(MTD)

U-DESPE
(Maximum Gain Dose -1%)

Average patient allocation (BLRM)	3.0	3.3	3.6	5.4	8.1	18.3

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SIMULATIONS - SCENARIO 1: « OPTIMAL DOSE IS LOWER THAN MTD»

Dose escalation
(BLRM)

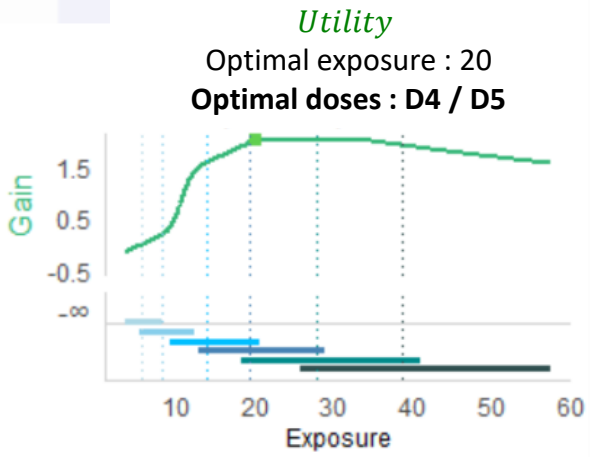
N=24 patients

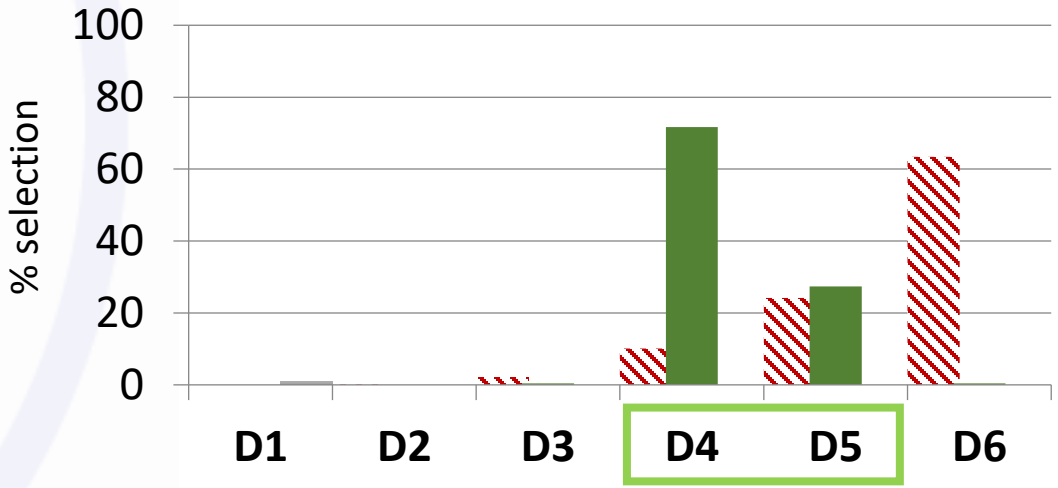
Dose optimization
Adaptive allocation
according to Pr(being the MGD-1%)
(U-DESPE)

N=18 patients

Dose recommendation
(U-DESPE)

42 patients in total





BLRM
(MTD)

U-DESPE
(Maximum Gain Dose -1%)

Average patient allocation (BLRM + U-DESPE)	3.1	3.6	5.0	14.8	8.5	6.9

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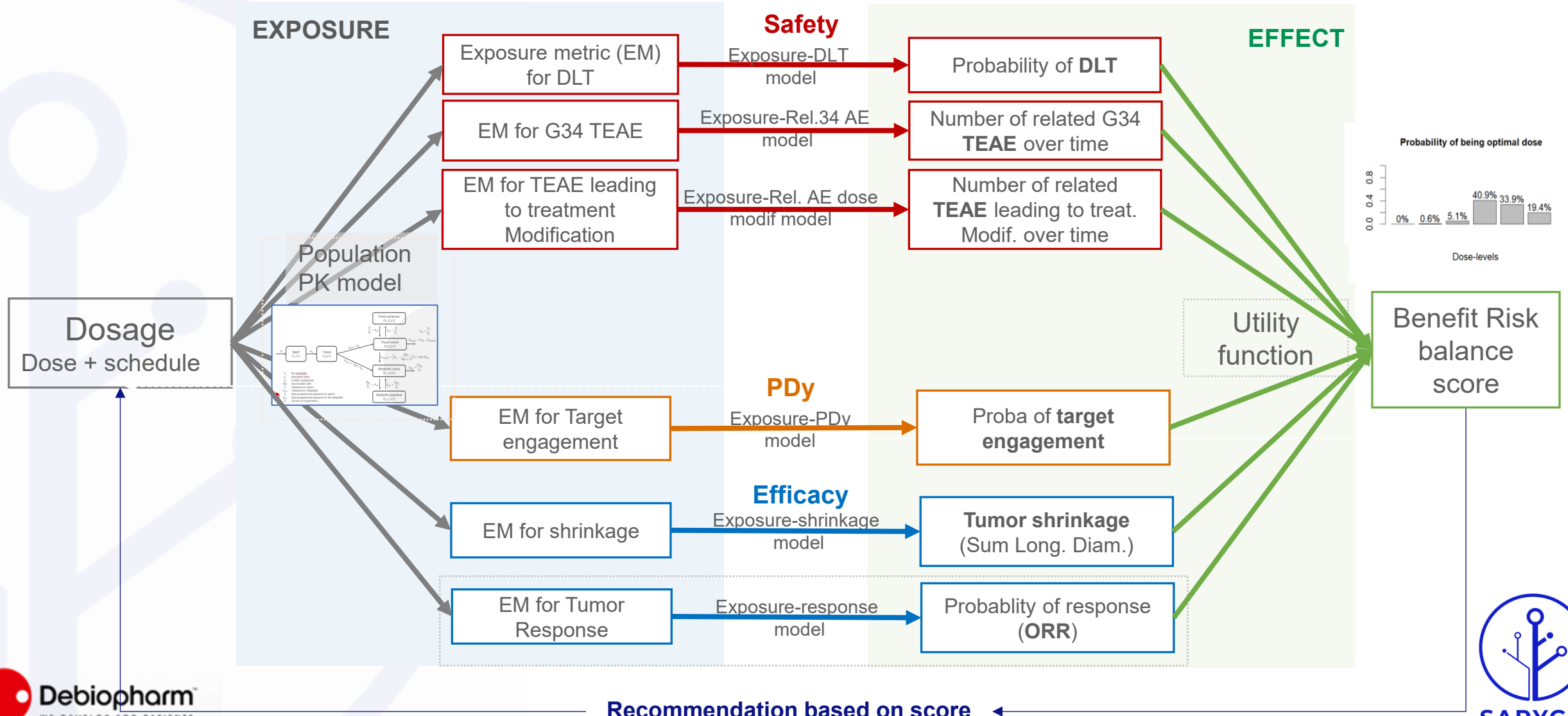
How did U-DESPE support the Zedoresertib.101 dosage selection in PROC ?



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BENEFIT RISK BALANCE: UTILITY FUNCTION FOR ZEDORESERTIB.101 DOSAGE SELECTION

$$U(.) = \begin{cases} -\infty & \text{if } \Pr(p_j \geq \delta) \geq 0.25 \\ \alpha_1.s_k + \alpha_2.r_k + \alpha_{3,1}.\lambda_{k,1} + \alpha_{3,2}.\lambda_{k,2} + \alpha_4.q_k & \text{otherwise} \end{cases}$$

Elicitation

« How much are you consenting to increase the TEAE rate to gain 5% in ORR? »

- Loss (Negative utility):
  - pk is the probability of experiencing a DLT $(\delta = 40\%)$
  - $\lambda_{k,1}$ is the number of related Gr3-4 TEAE over one cycle (21d)
  - $\lambda_{k,2}$ is the number of related TEAE leading to dose modification over one cycle (21d)
- Gain (Positive utility):
  - s_k is the tumor shrinkage (relative change from baseline in SLD)
  - q_k is the probability of target engagement, i.e. Pr(pCDC2 change from baseline < -20%)
  - r_k is the probability of an Objective response

k, index for dosing regimen

Utility function Parameter	weight (endpoint importance)	Comments
α_1	1	Gain associated with a mean increase of 1% in tumor shrinkage (1% SLD of target lesion decrease)
α_2	3	Gain associated with an increase of 1% of probability of objective response
$\alpha_{3,1}$	2	Loss associated with an increase of 1 Gr 3 4 TEAE per unit time (per cycle)
$\alpha_{3,2}$	4	Loss associated with an increase of 1 TEAE leading to dose modification per unit time (per cycle)
α_4	5	Gain associated with an increase of 1% in population reaching the 20% decrease in pCDC2

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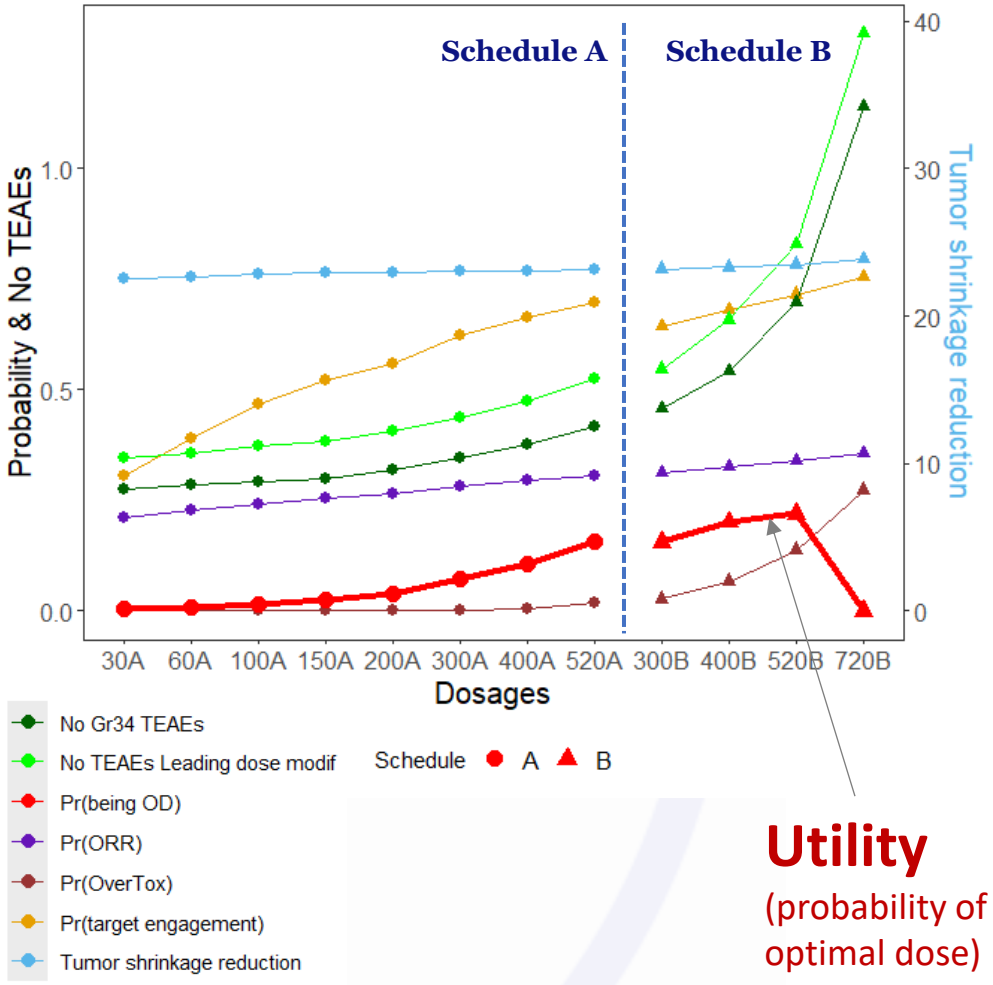
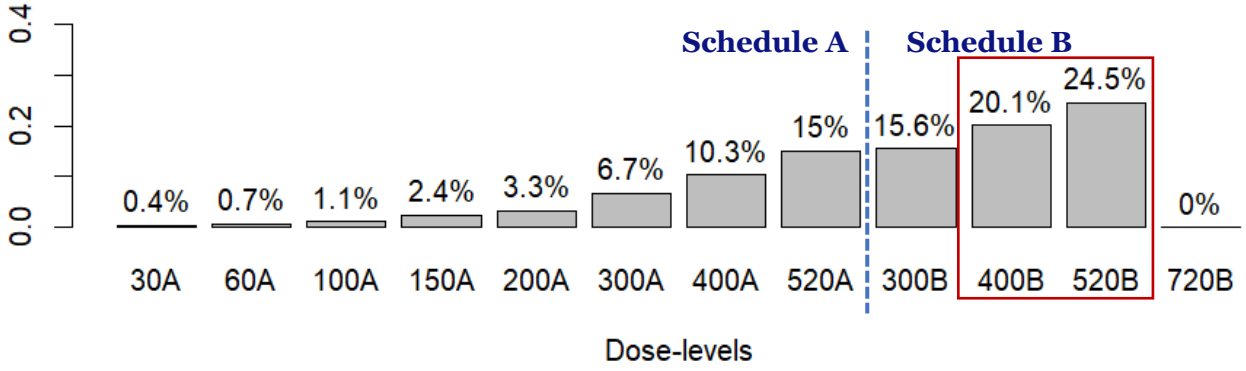
RECOMMENDATION: ESTIMATED PROBABILITY FOR EACH DOSING REGIMEN BEING THE OPTIMAL

Zedoresertib.101 study

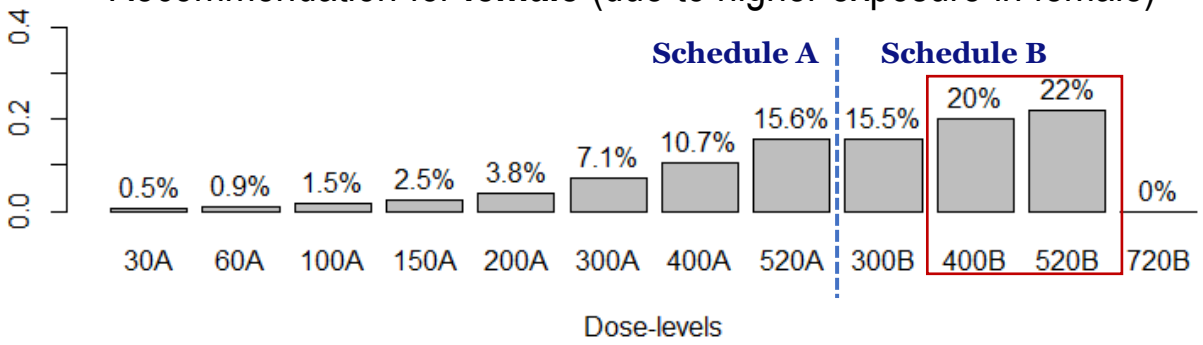


Utility
(probability of optimal dose)

Recommendation for **overall population** (male and female)



Recommendation for **female** (due to higher exposure in female)



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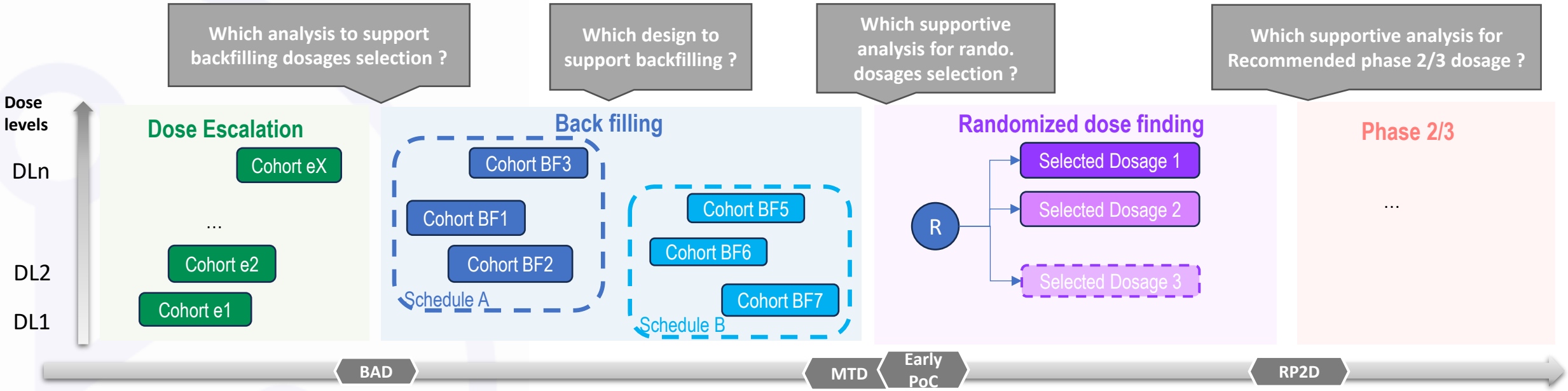
U-DESPE FOR AN OPTIMUS COMPLIANT EARLY DEVELOPMENT

CAPITALIZING ON EVERY DATA POINT AVAILABLE TO OPTIMIZE THE DOSE DECISION MAKING



U-DESPE identifies:
- Well tolerated exposure/dosages
- Biologically active dosages

U-DESPE enables:
- Benefit risk balance assessment of active exposure / dosages in the target population
- Compare different administration schedules

U-DESPE selects:
- dosing regimens according to their benefit risk balance assessment

U-DESPE provides:
- Quantitative rational for optimzed dosage

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Andrillon Micallef, et al. U-DESPE: a Bayesian Utility-based methodology for dosing regimen optimization in early-phase oncology trials based on Dose-Exposure, Safety, Pharmacodynamics, Efficacy
https://arxiv.org/abs/2511.17376

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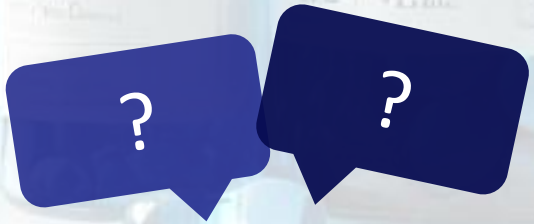

ANY QUESTIONS ?

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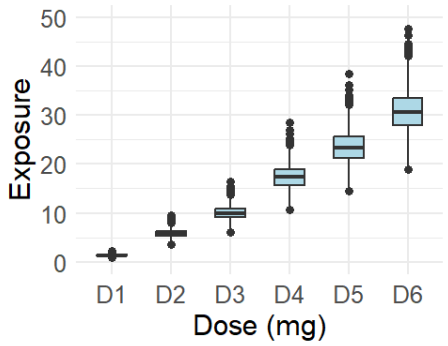
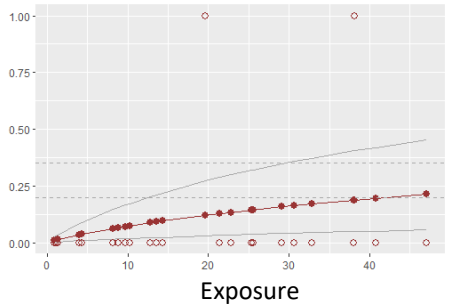
UNCERTAINTY PROPAGATION

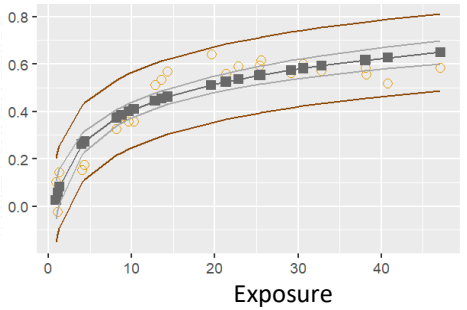
Dose exposure relationship



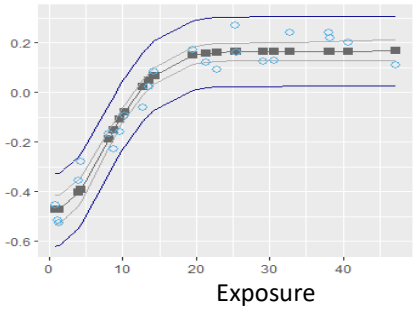
Exposure- DLT



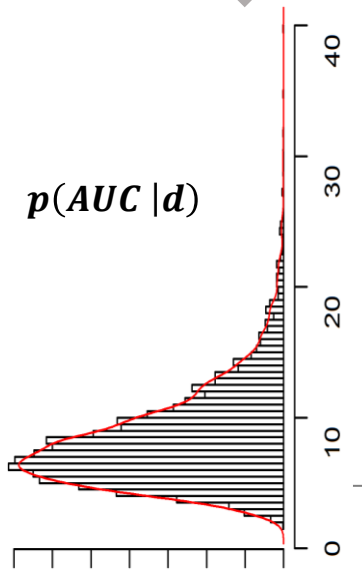
Exposure- PDy



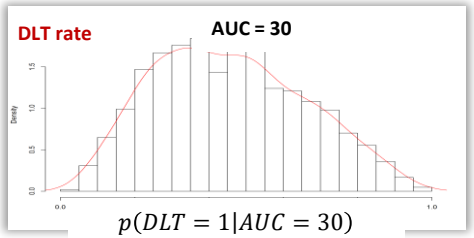
Exposure- Efficacy



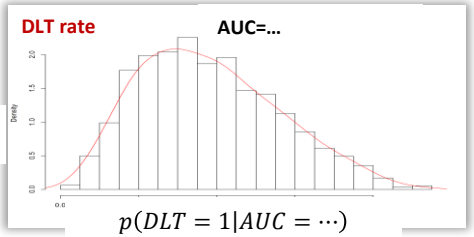
For each dose $\boldsymbol{d}$



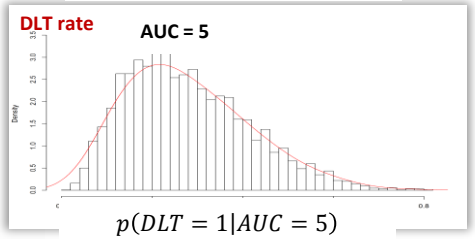
$p(AUC = 30|d)$



$p(AUC = \cdots|d)$



$p(AUC = 5|d)$



$$\boldsymbol{p(d)} = p(AUC = 30|\boldsymbol{d}).p(\boldsymbol{DLT}|AUC = 30) + p(AUC = \cdots|\boldsymbol{d}).p(\boldsymbol{DLT}|AUC = \cdots) + p(AUC = 5|\boldsymbol{d}).p(\boldsymbol{DLT}|AUC = 5) + \ldots$$

$$\boldsymbol{q(d)} = p(AUC = 30|\boldsymbol{d}).p(\boldsymbol{PDy}|AUC = 30) + p(AUC = \cdots|\boldsymbol{d}).p(\boldsymbol{PDy}|AUC = \cdots) + p(AUC = 5|\boldsymbol{d}).p(\boldsymbol{PDy}|AUC = 5) + \ldots$$

$$\boldsymbol{s(d)} = p(AUC = 30|\boldsymbol{d}).p(\boldsymbol{s}|AUC = 30) + p(AUC = \cdots|\boldsymbol{d}).p(\boldsymbol{s}|AUC = \cdots) + p(AUC = 5|\boldsymbol{d}).p(\boldsymbol{s}|AUC = 5) + \ldots$$

$$G(\boldsymbol{p(d)}, \boldsymbol{q(d)}, \boldsymbol{s(d)})$$

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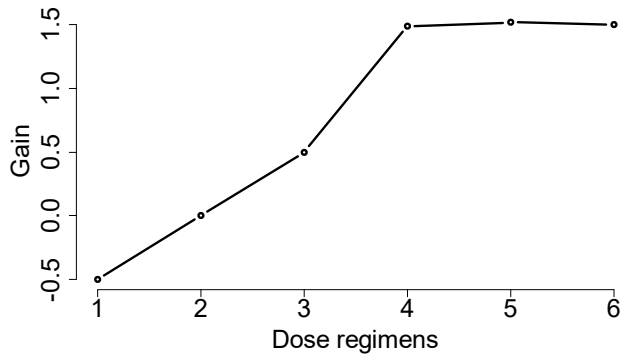
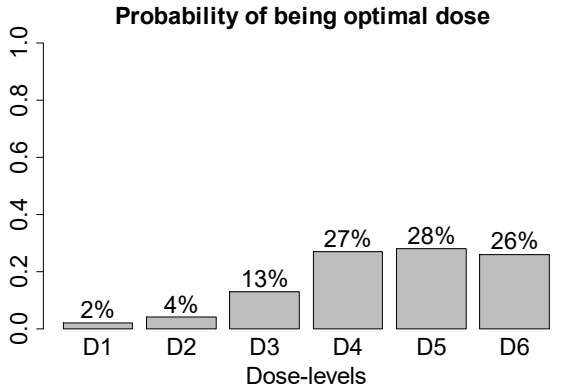
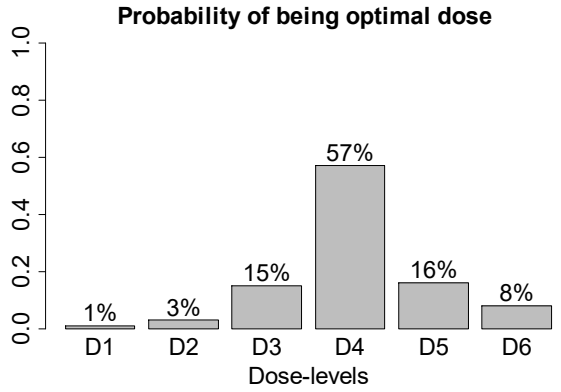
FINAL DOSE RECOMMENDATION







- **Maximum Gain Dosing regimen (MGD):** dose with the maximize gain value

- **Relative decrease from maximize gain**

MGD-1%: lowest dose with a gain decrease from maximum gain lower than 1%

Probability of being the MGD: proportion across MCMC samples where dosing regimen is the MGD

→ Account for **uncertainty around gain estimation**

- **Optimal dose regimen (OD):** dose with highest probability of being the MGD

- **OD-1%:** dose with highest probability of being the MGD-1%

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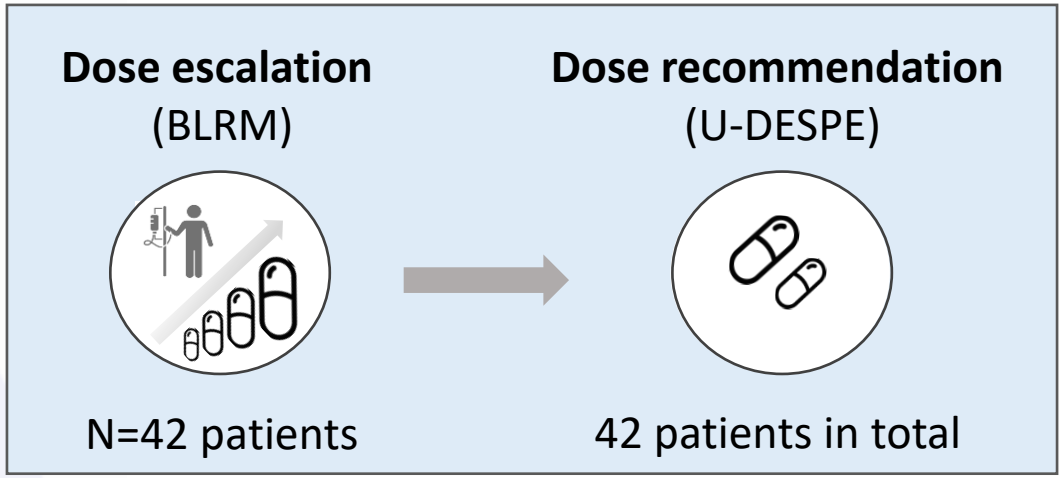
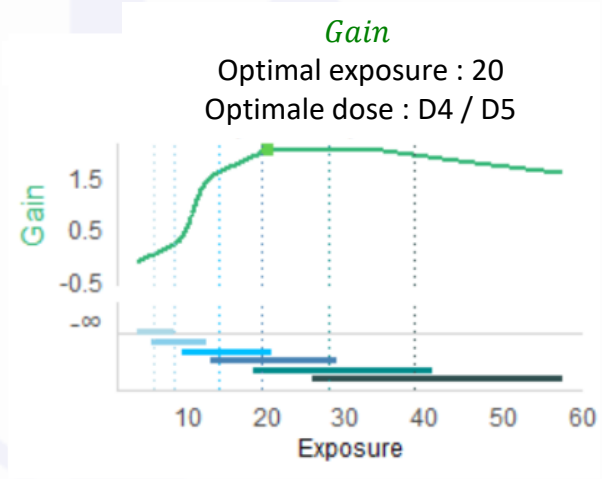
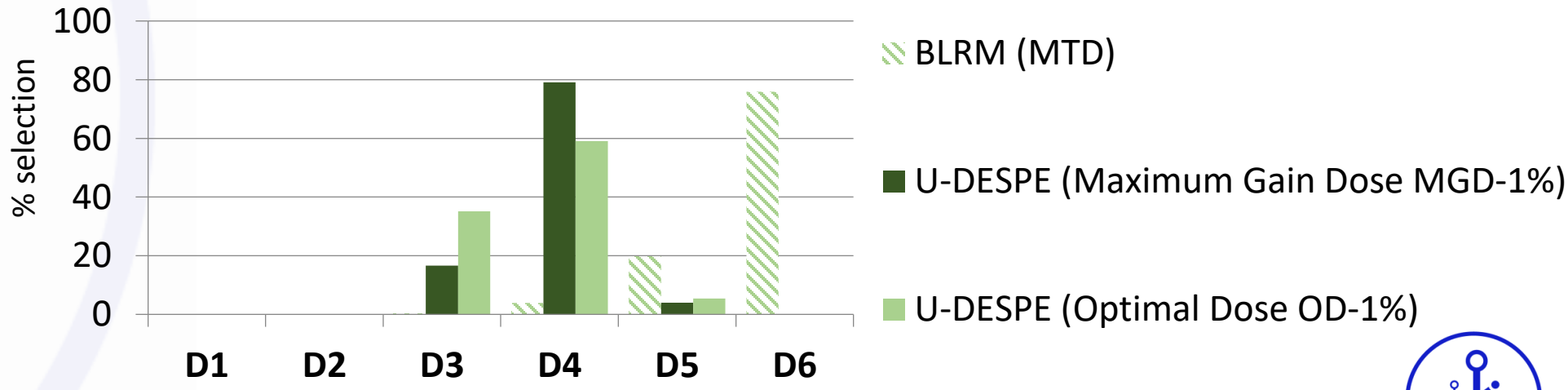
SIMULATIONS - SCENARIO 1: « OPTIMAL DOSE IS LOWER THAN MTD»







Average patient allocation (BLRM + U-DESPE)	3.0	3.3	3.6	5.4	8.1	18.3

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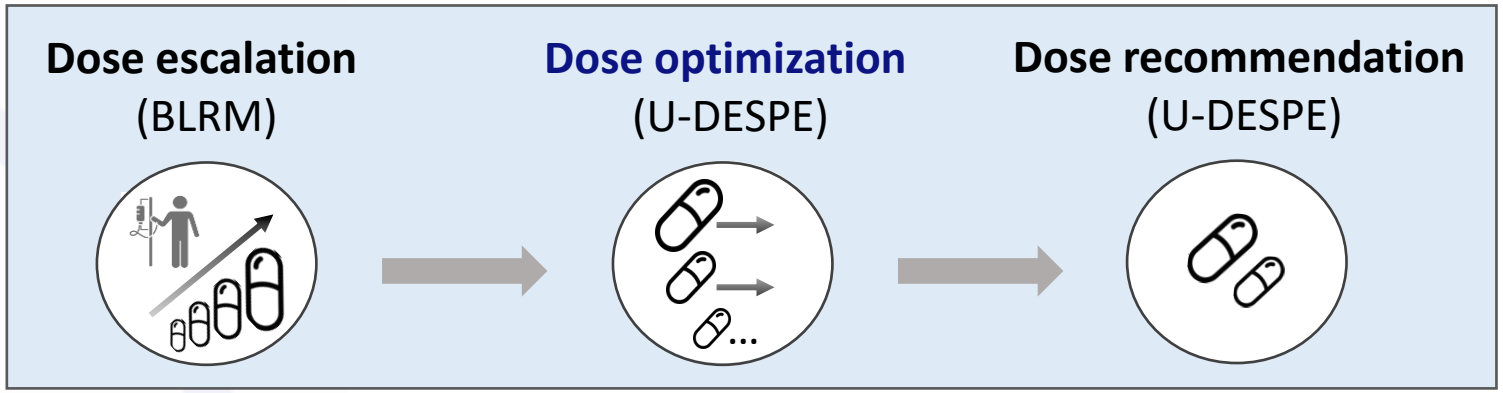
DOSE OPTIMIZATION AFTER DOSE-ESCALATION



DOSE OPTIMIZATION

- **Adaptive allocation:** allocate in parallel to dose j $\lfloor n \times u'_j \rfloor$ patients with $j = \{1, \dots, MTD\}$ and u'_j the probabilities of being the MGD-1% at the end of the escalation phase (renormalized probabilities)

→ Models are updated only twice: at the end of the escalation phase and at the end of the dose optimization phase

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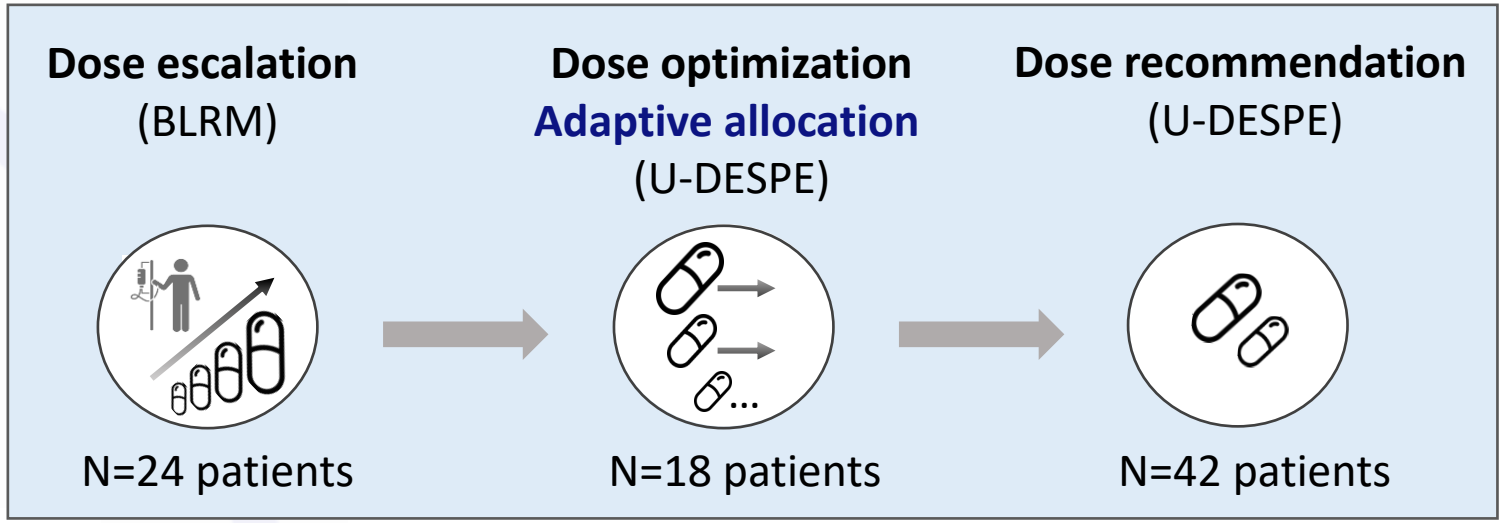
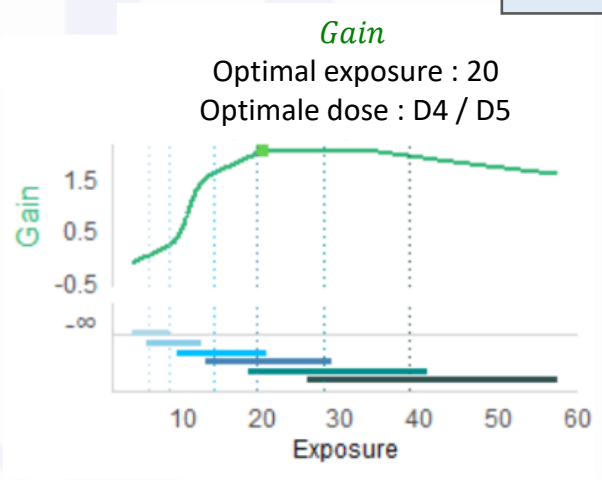
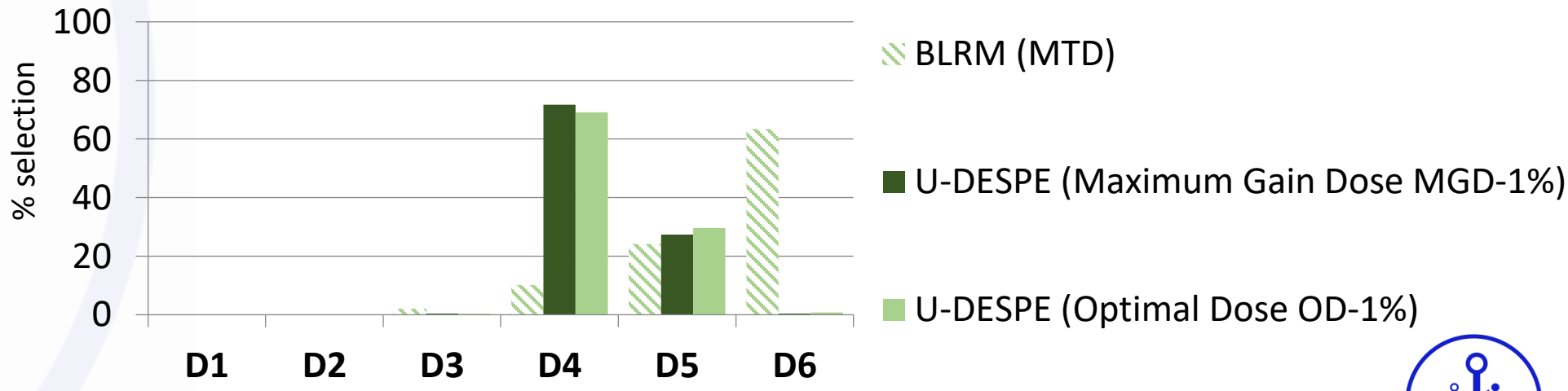
SIMULATIONS - SCENARIO 1: « OPTIMAL DOSE IS LOWER THAN MTD»







Average patient allocation (BLRM)	3.1	3.6	5.0	14.8	8.5	6.9

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GAIN FUNCTION PARAMETERS

$$G(.) = \begin{cases} -\infty & \text{if } \Pr(p_k \geq \delta) \geq 0.25 \\ \alpha_1 . s_k + \alpha_2 . r_k + \alpha_{3,1} . \lambda_{k,1} + \alpha_{3,2} . \lambda_{k,2} + \alpha_4 . q_k & \text{otherwise} \end{cases}$$

- Loss (Negative utility)
  - pk Pr(experiencing a DLT)
  - $\lambda_{k,1}$ No related Gr3-4 TEAE
  - $\lambda_{k,2}$ No related TEAE leading to dose modification
- Gain (Positive utility)
  - s_k Tumor shrinkage
  - q_k Pr(target engagement)
  - r_k Pr(Objective response)

Gain function Parameter	Rank	Weight (*)	Comments
δ	-	-	Probability of DLT corresponding to the Overdosing limit
α_1	#1	-	Gain associated with a mean increase of 1% in tumor shrinkage (1% SLD of target lesion decrease)
α_2	#3	-	Gain associated with an increase of 1% of probability of objective response
$\alpha_{3,1}$	#2	25%	Loss associated with an increase of 1 Gr 3 4 TEAE per unit time (per cycle)
$\alpha_{3,2}$	#4	15%	Loss associated with an increase of 1 TEAE leading to dose modification per unit time (per cycle)
α_4	#5	-	Gain associated with an increase of 1% in population reaching the 20% decrease in pCDC2

(*) The parameters associated to the TEAEs will be calibrated together, we need a weight associated to each TEAE

Of note for the 101, we applied the following weight ratio $\left(\frac{\alpha_{3,1}}{\alpha_{3,2}} = \frac{0.25}{0.15}\right)$*, i.e. a weight of 25% for the Gr3-4 TEAE and 15% for TEAE leading to dose modification*

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ELICITATION OF GAIN VALUE PARAMETERS – HOW DOES THAT WORK ?

Elicitation of gain value parameters is sequential and respects the order of clinical importance of the endpoints

1. Physician sets the ranking of endpoints by clinical importance :The first parameter of clinical interest is the tumor shrinkage, then secondly the TEAEs
2. We fix the coefficient the shrinkage parameter to 1 as this is the most important criteria
3. We elicit together the parameters for the TEAEs. For that, we consider
   - Dose A associated with, for example, 50% of tumor reduction and 1 TEAE, and
   - Dose B associated with 60% of tumor reduction and **X** TEAEs
   - **The physician has to chose which configuration of Dose B gives the same utility value than Dose A** → **X** is selected such that the clinician considers Dose A and Dose B equally good (in terms of the utility)
4. For the selected value of **X**, we then back calculate the parameters for TEAEs ($\boldsymbol{\alpha_{3,1}}$ and $\boldsymbol{\alpha_{3,2}}$), applying the weight ratio $\left(\frac{\alpha_{3,1}}{\alpha_{3,2}} = \frac{w_{3,1}}{w_{3,2}}\right)$
5. We elicit parameter for ORR similarly
6. We elicit parameter for PDy similarly

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ELICITATION OF GAIN VALUE PARAMETERS

$$G(.) = \begin{cases} -\infty & \text{if } \Pr(p_k \geq \delta) \geq 0.25 \\ \alpha_1 . s_k + \alpha_2 . r_k + \alpha_{3,1} . \lambda_{k,1} + \alpha_{3,2} . \lambda_{k,2} + \alpha_4 . q_k & \text{otherwise} \end{cases}$$

Elicitation of $\alpha_{3,1}$ and $\alpha_{3,2}$ values (parameters associated to TEAEs)

- $\lambda_{k,1}$ is the adjusted number of related Gr3-4 TEAE over one cycle (21d) → **weight 25%**
- $\lambda_{k,2}$ is the adjusted number of related TEAE leading to dose modification over one cycle (21d) → **weight 15%**

Which configuration of Dose B should give the same gain value as Dose A ?

To increase the ORR of 10%, up to how much do you consent to increase the number of TEAE?

			Average No TEAE per cycle				
	Pr(DLT)	ORR	Gr 3 4	Leading to dose modif	% tumor reduction	Pr(ORR)	Pr target engagement
Dose A	-	**30%**	**0.2**		-	-	-
Dose B-1	-	**40%**	**0.3**		-	-	-

			Average No TEAE per cycle				
	Pr(DLT)	ORR	Gr 3 4	Leading to dose modif	% tumor reduction	Pr(ORR)	Pr target engagement
Dose A	-	**50%**	**0.2**		-	-	-
Dose B-1	-	**60%**	**0.3**		-	-	-

Note: when calculating the values of $\alpha_{3,1}$ and $\alpha_{3,2}$ keep $\frac{\alpha_{3,1}}{\alpha_{3,2}} = \frac{0.25}{0.15}$

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ELICITATION OF GAIN VALUE PARAMETERS

$$G(.) = \begin{cases} -\infty & \text{if } \Pr(p_k \geq \delta) \geq 0.25 \\ \alpha_1 . s_k + \alpha_2 . q_k + \alpha_{3,1} . \lambda_{k,1} + \alpha_{3,2} . \lambda_{k,2} + \alpha_4 . r_k + \alpha_5 . c_k + \alpha_6 . t_k & \text{otherwise} \end{cases}$$

Elicitation of α_1 (parameters associated to tumor shrinkage)

- s_k is the tumor shrinkage (change from baseline in SLD)

Which configuration of Dose B should give the same gain value as Dose A ?

To increase percentage of tumor reduction, up to how much do you consent to increase the average number of adverse event?

			Average No TEAE per cycle					
	Pr(DLT)	Pr(PFS > 16 weeks)	Gr 3 4	Leading to dose modif	% tumor reduction	Pr(ORR)	Pr target engagement	QTc change from bsl
Dose A	-	-	**0.2**	**0.2**	**40%**	-	-	-
Dose B-1	-	-	0.4	0.35	**50%**	-	-	-

			Average No TEAE per cycle					
	Pr(DLT)	Pr(PFS > 16 weeks)	Gr 3 4	Leading to dose modif	% tumor reduction	Pr(ORR)	Pr target engagement	QTc change from bsl
Dose A	-	-	**0.5**	**0.5**	**40%**	-	-	-
Dose B-1	-	-	0.6	0.6	**50%**	-	-	-

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ENDPOINTS AND DATA CONSIDERED FOR THE EXPOSURE-EFFECT ANALYSES

Debio0123.101 study

Endpoints (EFFECT)	Data	Data set	PK-metric used for the analysis (EXPOSURE)
DLT	CT101 arm A & B	DLT evaluable	**AUC21 C1** for arm A & B
TEAE	CT101 arm A & B	Safety set	**AUC21 C1** for arm A & B
pCDC2	**CT101 arm A & CT102 (monotherapy)**	pCDC2 evaluable (according to pCDC2 flag)	**AUC24h** before sampling • For arm A: AUC C1 D3 • ~~For arm B: AUC C1 D10~~ • For 102 study, AUC24 at SS: AUC C2 D1
Tumor shinkage	CT101 arm A & B	**Ovarian population only**	AUC21 C1 for arm A & B
ORR	CT101 arm A & B	Efficacy set / Ovarian population	AUC21 C1 for arm A & B

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BENEFIT RISK BALANCE: UTILITY FUNCTION FOR DEBIO0123.101 STUDY

$$G(.) = \begin{cases} -\infty & \text{if } \Pr(p_j \geq \delta) \geq 0.25 \\ \alpha_{1,1}.\lambda_{j,1} + \alpha_{1,2}.\lambda_{j,2} + \alpha_2.s_j + \alpha_3.q_j + \alpha_4.r_j & \text{otherwise} \end{cases}$$

	Utility function parameter	Weight in the Utility function	Rank	Comments
$\lambda_{j,1}$: adjusted number of related Gr3-4 TEAE over one cycle (21d)	$\alpha_{1,1}$	**25%**	#2	**Loss** associated with an increase of 1 Gr 3 4 TEAE per unit time (per cycle)
$\lambda_{j,2}$: adjusted number of related TEAE leading to dose modification over one cycle (21d)	$\alpha_{1,2}$	**15%**	#4	**Loss** associated with an increase of 1 TEAE leading to dose modification per unit time (per cycle)
q_j: probability of target engagement, i.e. Pr(pCDC2 change from baseline < -20%)	α_3	**10%**	#5	**Gain** associated with an increase of 1% in population reaching the 20% decrease in pCDC2
s_j: tumor shrinkage (change from baseline in SLD)	α_2	**30%**	#1	**Gain** associated with a mean increase of 1% in tumor shrinkage (1% SLD of target lesion decrease)
r_j: probability of an Objective response	α_4	**20%**	#3	**Gain** associated with an increase of 1% of probability of objective response

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U-DESPE - A QUANTITATIVE TOOL TO SUPPORT DOSE OPTIMIZATION

- Any relevant endpoints entering in the dose optimization decision can be considered (*e.g.* safety: Gr3-4 related AE, Cardiotoxicity etc.) → capitalizing on every data point available to optimize the dose decision making
- Allows to compare not only doses but also dose regimen (dose + schedule + duration of treatment)
- Approach in line with Optimus guidance
- **U-DESPE built to be used all along the clinical development**
  - Within Phase 1a/b trial: at the end of the dose escalation, after backfilling for dose randomization, for the RP2D selection
  - To justify Optimized dosage used for pivotal phase (HA interactions)
  - To justify dosage and further development in specific population at a post approval stage
- *U-DESPE: a Bayesian Utility-based methodology for dosing regimen optimization in early-phase oncology trials based on Dose-Exposure, Safety, Pharmacodynamics, Efficacy* https://arxiv.org/abs/2511.17376

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