Dose Optimization: New Statistical Concepts for Phase 1 and Phase Ib/II Studies

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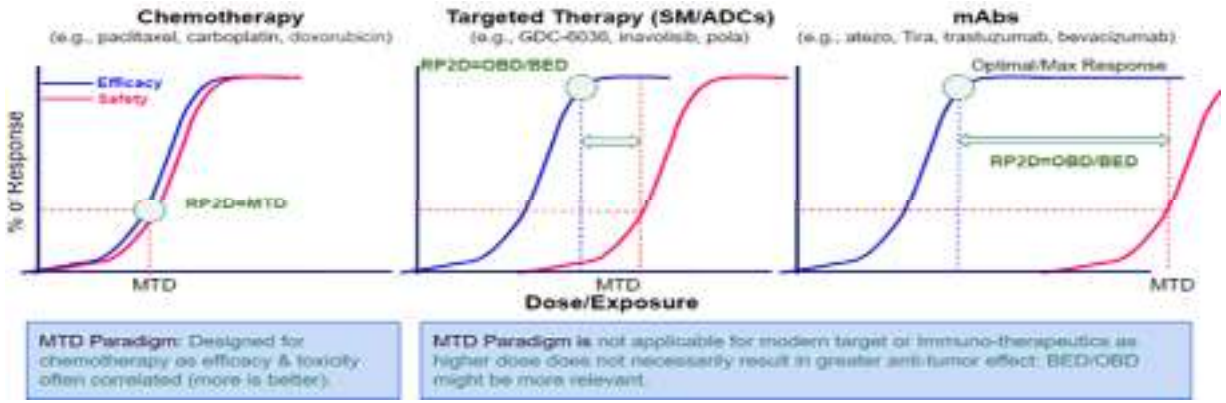
Need for new statistical concepts for phase I/II oncology studies

- Targeted therapies and cancer immuno-therapies change the way how to select the recommended phase II dose



  - Late onset toxicities can arise with targeted or cancer-immuno therapies
  - Maximum tolerated dose (MTD) concept was fine for cytotoxic agents but not necessarily the best option for cancer immuno-therapies
  - T-cell engaging therapies show often immune related safety problems like CRS

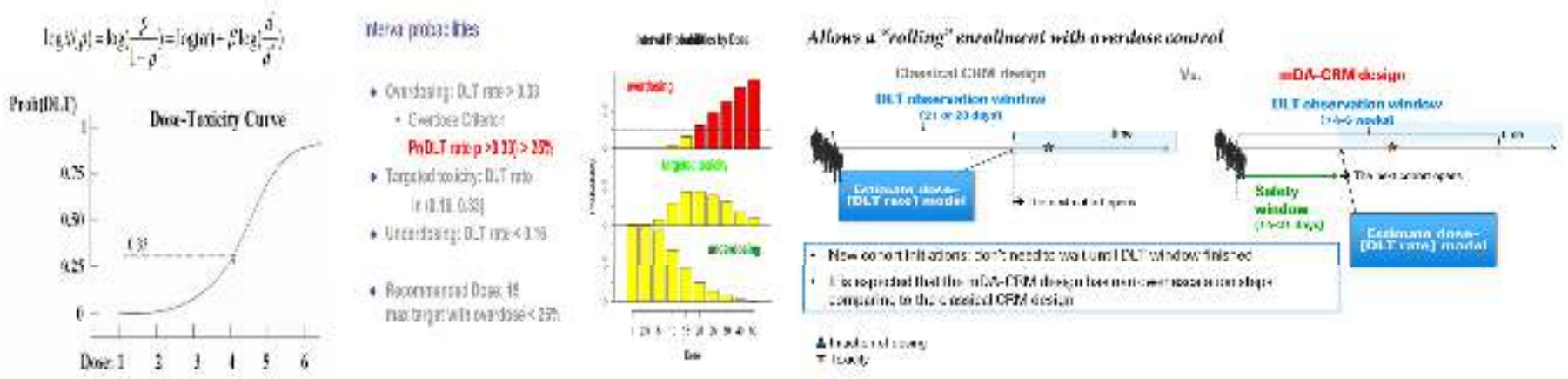
⇒ Need for models respecting DLT's beyond the 1st cycle

⇒ Novel dosing strategies like stepup-dosing were established to mitigate the CRS risk

⇒ Dose selection for phase III must be based on efficacy and safety

Model based dose-escalation designs for late-onset toxcities

- Classical CRM based on DLT's during the first cycle only) (see: Neuenschwander, Branson und Gsponer, 2008)
- Modified CRM's for late onset toxicities (Tite-CRM/ rolling CRM,Tite-Boin) allow prolonged DLT periods while escalating early) (e.g: Zhu u. a., 2021)

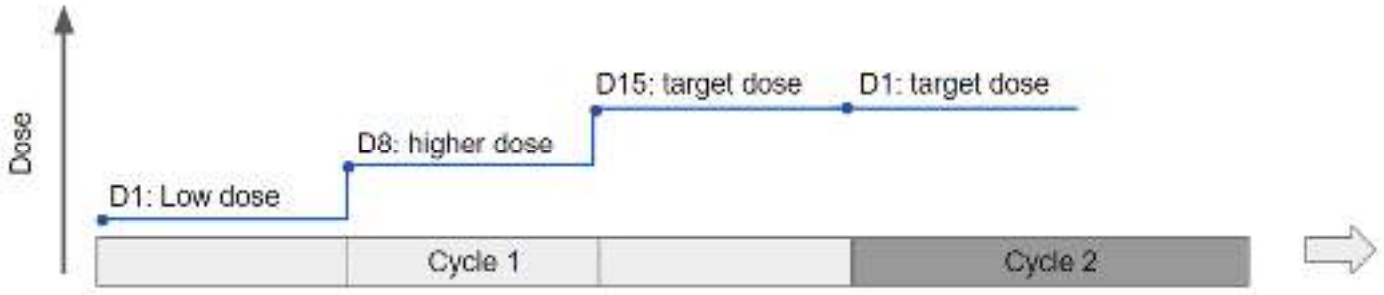


- DLT probability at the end of the DLT period will be predicted given the partially observed patients data
- In the absence of a DLT, the model weights each entered patient by the proportion of the full observation period that he/she has been observed

Cytokine Release Syndrom and Step-up Dosing

- Cytokine release syndrome (CRS) is a systemic inflammatory response that can be triggered by certain drugs, e.g. also by T-cell engaging Therapies (bi-specifics, CART cells,..) (see: Shimabukuro-Vornhagen u. a., 2018)
- CRS represents one of the most frequent serious adverse effects of these therapies

Step-up dosing has demonstrated an effect of de-sensitization



Challenge:
How to design a dose-escalation trial to determine the right dose-levels for C1D1, C1D8 and C1D15 in relation to safety (3+3, CRM, etc. do no longer work)

Proposed strategy: Model assisted dose escalation while allowing modifications of the dose sequences

- Start with a pre-defined number of dose sequences with increasing safety risks and C1D1 ≤ C1D8 ≤ C1D15
- Decide to escalate/de-escalate or stay at the current dose level using e.g. BOIN design rules

Cohort	C1D1	C1D8	C1D15
1	0.006	0.018	0.018
2	0.006	0.018	0.09
3	0.03	0.09	0.27
4	0.09	0.27	0.8
5	0.27	0.8	2.4
6	0.8	2.4	7.2

	The number of participants treated at the current sequence					
Action	3	4	5	6	9	12
Next dose sequence if # of participants who experienced DLT ≤	0	0	1	1	2	2
Previous dose sequence if # of participants who experienced DLT ≥	2	2	2	3	4	5
Eliminate if # of participants who experienced DLTs ≥	3	3	4	4	5	7

- In case of de-escalation/elimination:
  Modified sequences with reduced C1D1, C1D8 or C1D15 dose levels can be introduced informed by modelling approaches for the current and higher dose sequences

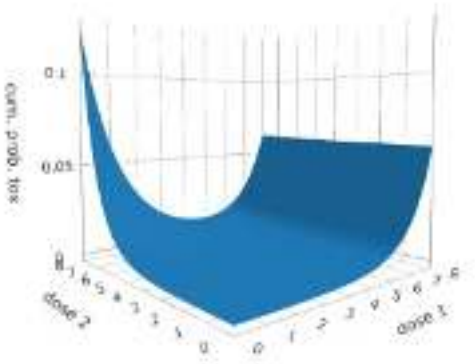
Potential statistical model: Recurrent event survival model

- Model of hazard of event after each dose as a function of the dose
- Accounts for multiple doses and events per patients
- Toxicity after C1D8 depends on both, the C1D1 and C1D8 doses
- Small number of parameters
- several possible parametrizations were explored
- one example on the right

- Example with 1 step
- At higher doses for dose 1 toxicity for dose 2 goes down (tolerance effect)

$$
\begin{aligned}
h(t) &= \frac{g_1(d_1)I(t \leq 7)}{7} + \frac{g_2(d_1, d_2)I(7 < t \leq 21)}{14} \\
H(t) &= \int_0^t h(t)dt \\
S(t) &= \exp(-H(t))
\end{aligned}
$$

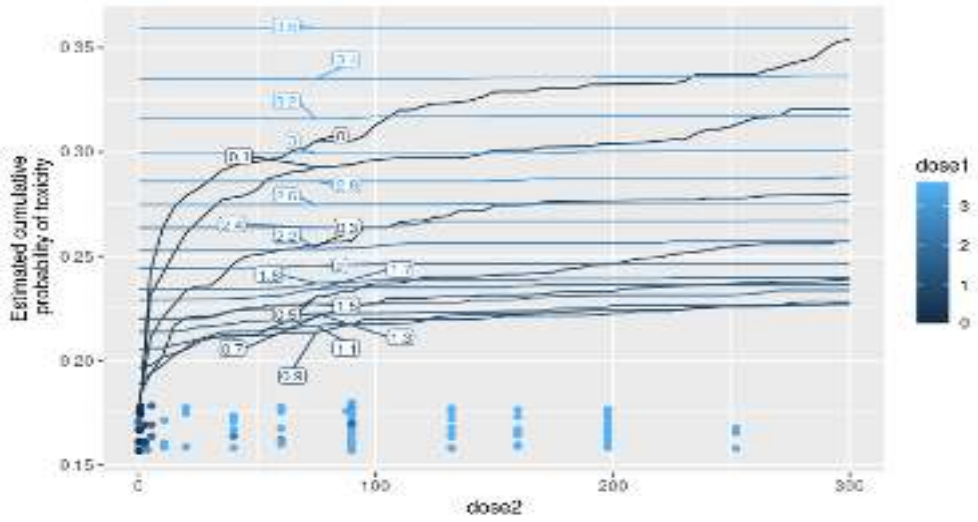
$$
\begin{aligned}
g_1(d_1) &= \exp(\alpha_{01} + \exp(\beta_{01})d_1) \text{ and} \\
g_2(d_1, d_2) &= \exp(\alpha_{02} + \exp(\beta_{02} + \beta_1 d_1)d_2).
\end{aligned}
$$



Example data fitted recurrent event model to real data

- At low dose 1 (dark lines) ⇒ Cumulative probability increases as function of dose 2
- At high dose 1 (light blue) ⇒ Cumulative probability is flat as function of dose 2

  When dose 1 is sufficiently high ⇒ dose 2 does not influence cumulative probability of CRS



At the end of dose escalation

Range of possible sequences (set of C1D1, C1D8, C1D15 doses) provided by the dose-CRS models

⇒ Safety criteria not enough to select recommended phase II dose (RP2D)

Selection of the recommended phase Ib/II dose(s)

- In case the de-sensitization works, the C1D15 could be escalated to unnecessary high dose-levels (e.g. bell shaped dose response, plateau)
- For the appropriate selection of the C1D15 dose, additional PD endpoints must be taken into account
  - General safety
  - Target inhibition, receptor occupancy
  - PD Biomarker
  - Model based approaches like PD dose/exposure response models, tumor kinetic modelling
  - back-fill of several dose levels below MTD
- Modeling efforts and added data help to provide a data driven rationale for the proposed recommended phase Ib/II dose(s)

FDA Project Optimus to reform the dose optimization and dose selection paradigm in oncology drug development

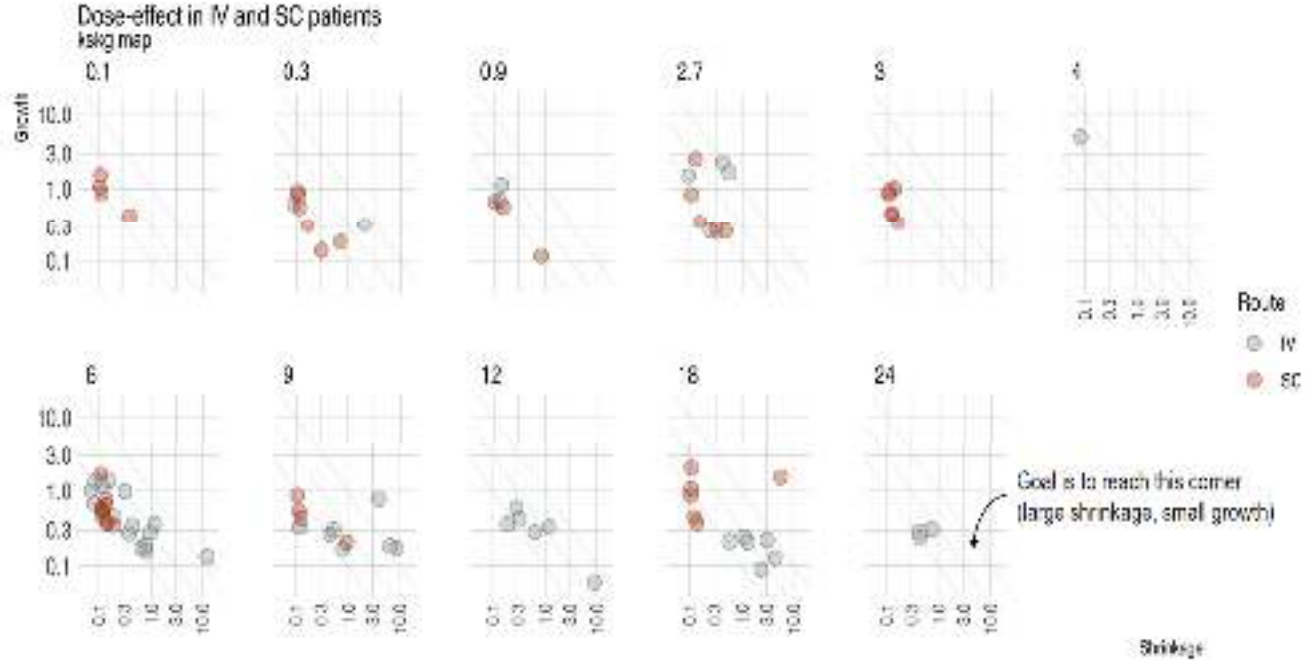
- FDA Guidance for Industry: Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases
  - Multiple dosages should be compared in a clinical trial(s) designed to assess activity, safety, and tolerability to decrease uncertainty with identifying an optimal dosage(s) in a marketing application
  - A recommended trial design to compare these dosages is a randomized, parallel dose-response trial
  - The trial should be sized to allow for sufficient assessment of activity, safety and tolerability for each dosage. The trial does not need to be powered to demonstrate statistical superiority of a dosage or statistical non-inferiority among the dosages

⇒ Either randomized expansion cohorts or randomized phase II with a sample-size per arm larger than in dose escalation will be required

⇒ Possibility to use these cohorts to estimate differences not only based on early endpoints but to predict differences in late endpoints (OS or PFS)

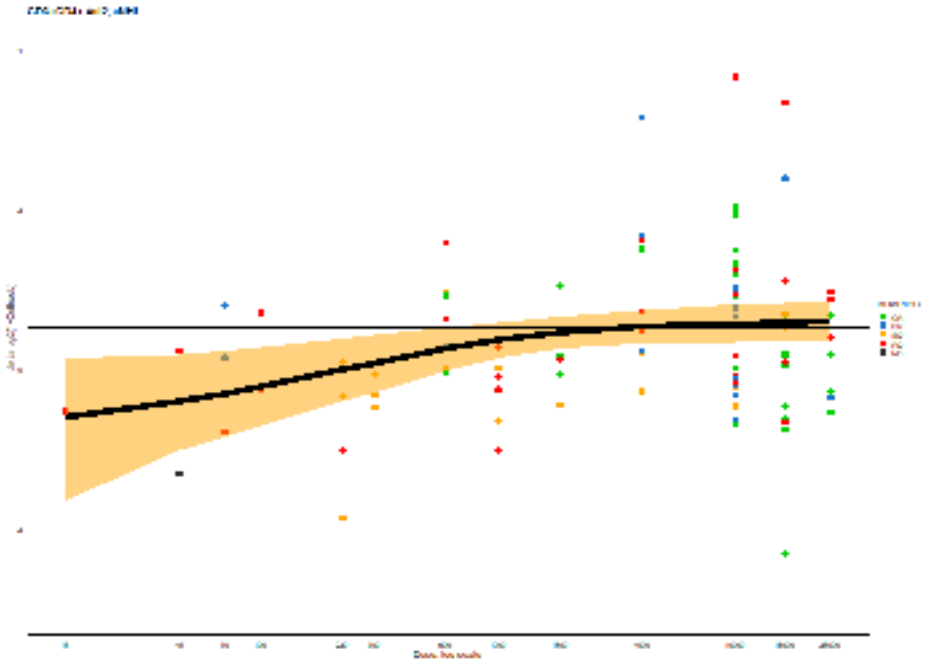
Example1: Supporting the dose selection with TK-modelling

- For efficacious drugs, we hope to observe an increase in tumor shrinkage and a reduction in tumor growth with increasing dose
- A mixed-effects tumor-growth model like
  $SLD_{ij} = Bas_i \cdot (exp(KG_i \cdot t_{ij} + exp(-KS_{ij} \cdot t_{ij}) - 1) + \epsilon_{ij})$ (see: Stein u. a., 2008)
- estimated patient level shrinkage (x-axis) and re-growth (y-axis) parameter plotted by dose-level should show a trend moving to the right lower corner



Example2: Supporting the dose selection with biomarker analyses

- Depending on the mode of action, biomarker like increase activated T-cells can support the right dose selection
- If there is a plateau in the observed response rate across a larger dose range, a fitted e-max model to analyse the biomarker (or exposure)-response can help to support the right dose-selection below the MTD (e.g. based on the ED90)



Innovative statistical concept examples for phase Ib/II (1)

Prediction of OS through tumor growth kinetic via joint longitudinal time to event modelling

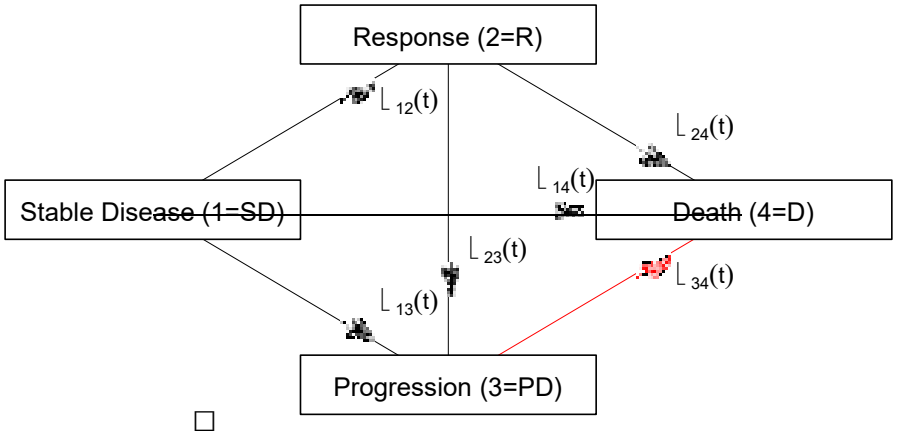
- the longitudinal sub-model is the tumor growth kinetic model
  $SLD_{ij} = Bas_i \cdot (exp(KG_i \cdot t_{ij} + exp(-KS_{ij} \cdot t_{ij}) - 1) + \epsilon_{ij})$
- the time-to-event model is $h_i(t|SLD_{it}, w_i) = h_0(t) \cdot exp(\gamma \cdot w_i + \alpha \cdot KG_i)$
  (w_i are baseline covariates)
- the model will be trained on historical data
- baseline hazards as well as γ and α will be kept (population parameters borrowed from historical data)
- in new expansion cohorts, tumor growth kinetic parameters will be estimated for each patient

$\Rightarrow$ using the estimated tumor-kinetic parameters by patient from the expansion cohort in the trained model allows prediction differences between the expansion cohorts in time-to-event endpoints (PFS, OS)

Innovative statistical concept examples for phase Ib/II (2)

Prediction of OS via multistate models

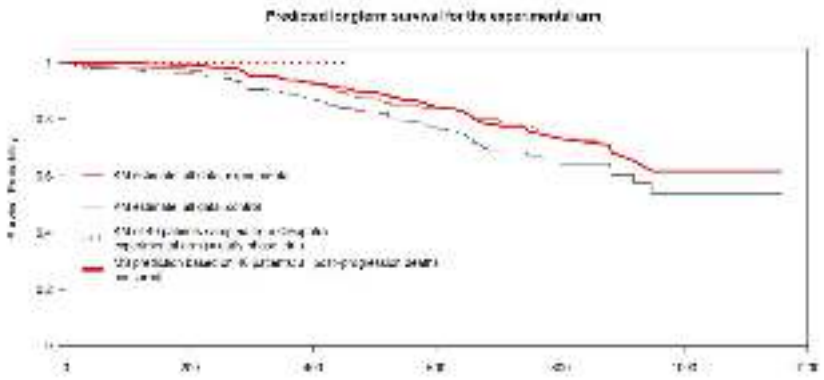
- A multistate model consists of states and transitions between them that reflect the assumed disease mechanism
- Most transitions are observed in early development
- Idea is to train a multistate model using historical control data
  - borrow the baseline long-term transition hazards from the control
  - estimate differences in the transition hazards between the expansion cohorts and historical control with plausible assumptions for unobserved transitions (see: Beyer u. a., 2020)

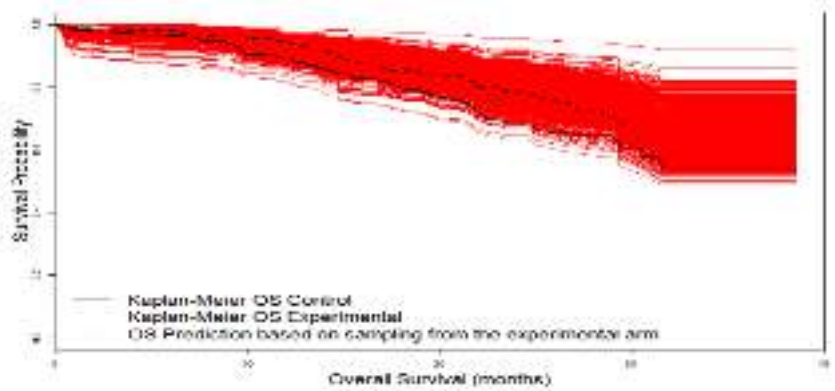


- multistate estimates result in cumulative transition hazards for each transition and transition probabilities
- the transition probabilities respect all transitions over all interim states over time
- 1 - the transition probability from the origin (SD) to death results in the usual KM-curve for survival:

$$S_{OS}(t) = 1 - P_{SD\to D}(0,t) + P_{SD\to PD\to D}(0,t) + P_{SD\to R\to D}(0,t) + P_{SD\to R\to PD\to D}(0,t)$$

Illustration for a multistate prediction
(40 patiens sampled from the experimental arm)





⇒ Differences in selected expansion cohorts with limited sample sizes can be estimated not only based on early endpoints

⇒ Estimated differences in long-term endpoints (OS,PFS) are based on predictions leveraging historical control data

Summary

- Selecting the right dose in cancer immunotherapy is a challenge
- Concepts for late onset DLT's must potentially be considered
- Immune related safety events like CRS requires new concepts like step-up dosing or dose-fractionation
- Also the paradigm that higher doses show better efficacy is no longer valid (bell-shaped or dose-response curves with a long plateau are possible)
- The RP2D must be based on a integrated assessment of safety, pharmacology and PD endpoints
- In spite of sophisticated modelling and statistical methods, back fill cohorts and a phase Ib/II program randomizing to more than 1 dose level might be required
  - The selection of the dose levels for the phase Ib/II expansion must be carefully considered
  - Although the sample size for expansion cohorts will be limited, they open the door estimating differences in late endpoints like PFS or OS based on appropriate prediction models

Acknowledgements

- Jiawen Zhu
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Late onset toxicities
TK-modeling and joint models

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