A New Approach to Predict PFS in Ovarian Cancer Based on Tumor Growth Dynamics

Jiajie Yu Nina Wang Matts Kagedal

Department of Clinical Pharmacology, Genentech Research and Early Development, South San Francisco, USA

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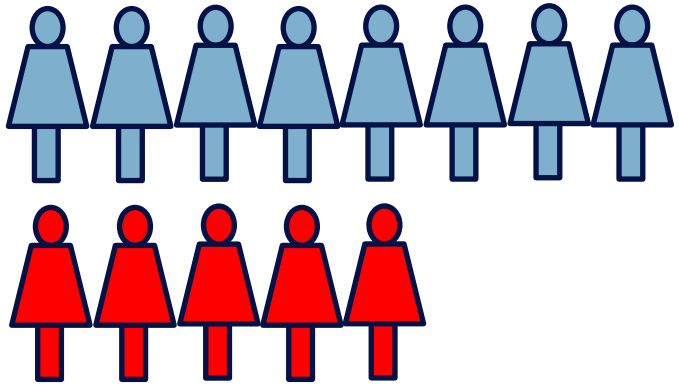
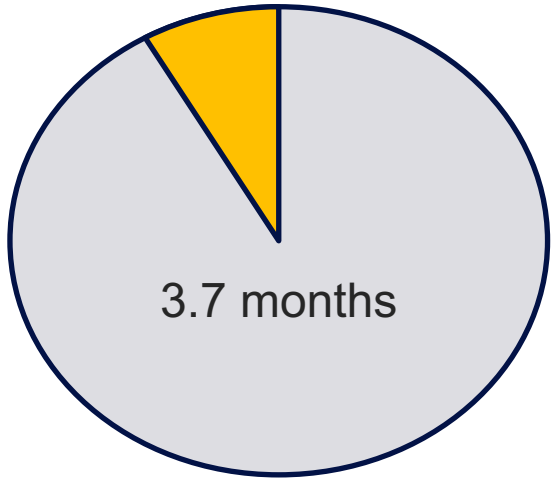
Progression-free survival (PFS) is currently an acceptable clinical endpoint for regulatory decision in ovarian cancer

- There is a high unmet medical need in ovarian cancer



There were 22,240 new cases of ovarian cancer diagnosed and 14,070 ovarian cancer deaths in the US in 2018



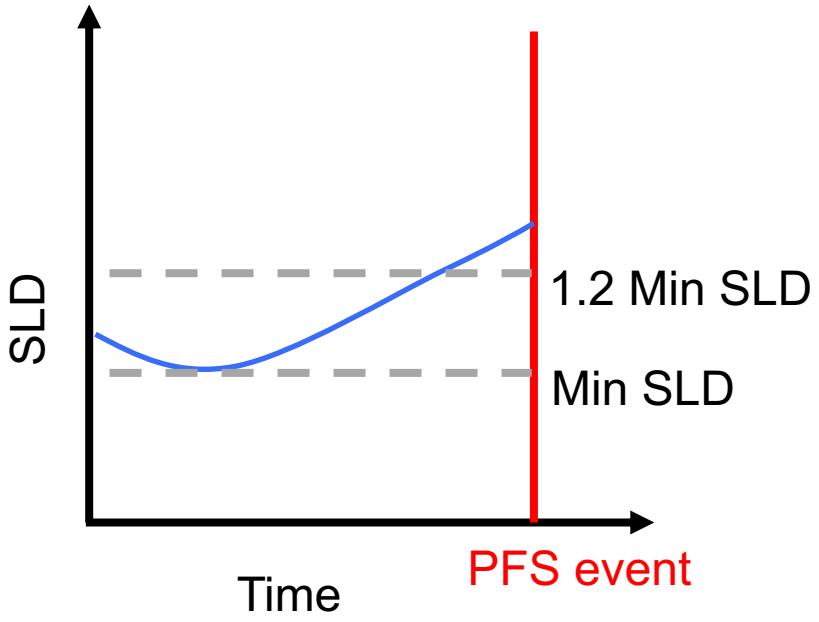
For platinum resistant patients, chemo therapy such as pegylated liposomal doxorubicin demonstrated response rates of 10%-15%.

- Progression-free survival is defined as the time from the first day of study treatment (Cycle 1 Day 1) to disease progression or death within 30 days of the last study drug administration, whichever occurs first.

Monk BJ, Herzog, TJ, Kay SB, et al. Trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer. J Clin Oncol 2010;29:3107-14.
Torre, Lindsey A., et al. "Ovarian cancer statistics, 2018." CA: a cancer journal for clinicians 68.4 (2018): 284-296.
https://seer.cancer.gov/statfacts/html/ovary.html

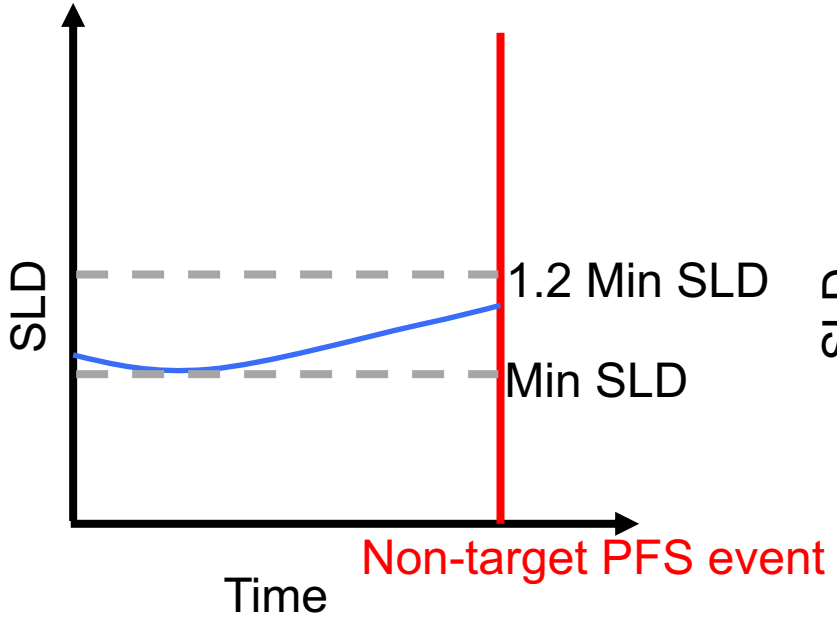
Disease progression can be target lesion related or non-target related

Per RECIST 1.1 guidance and study protocol, Progressive Disease (PD) is defined as,



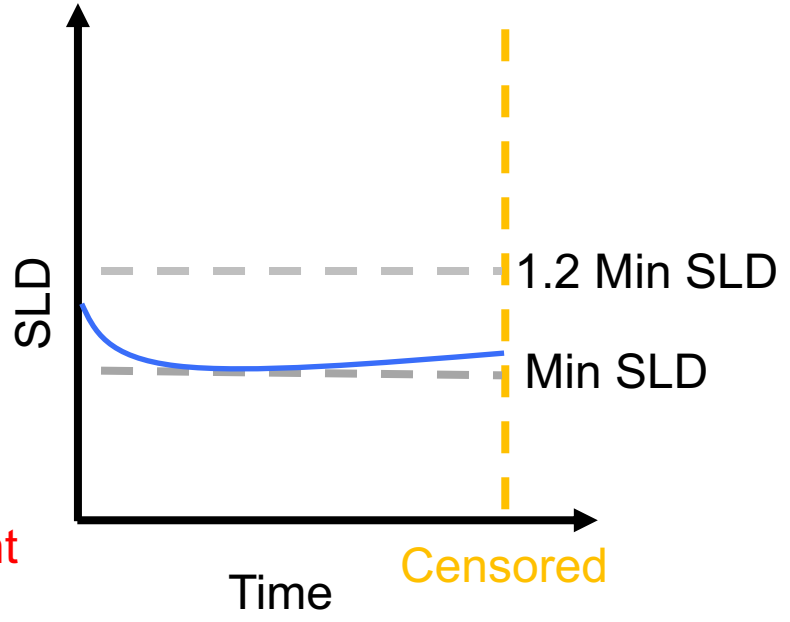
Target lesion progression:

- At least a 20% increase of sum of the longest diameters (SLD) using the minimum SLD observed in study as reference
- Absolute increase is at least 5 mm



Non-target progression :

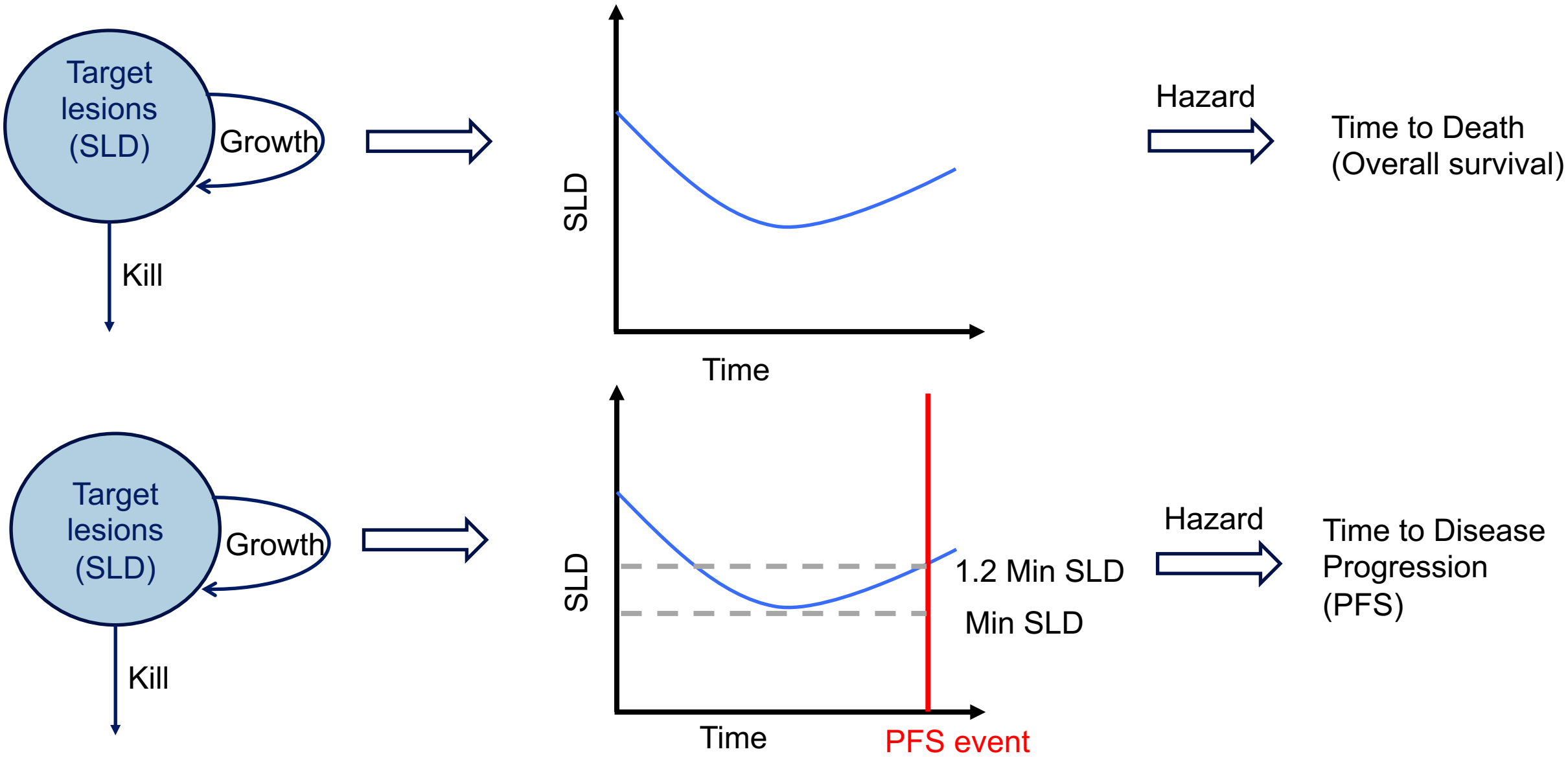
- Growth of Non-target Lesion
- New Lesion
- Symptomatic Deterioration
- Death



Patient drop out

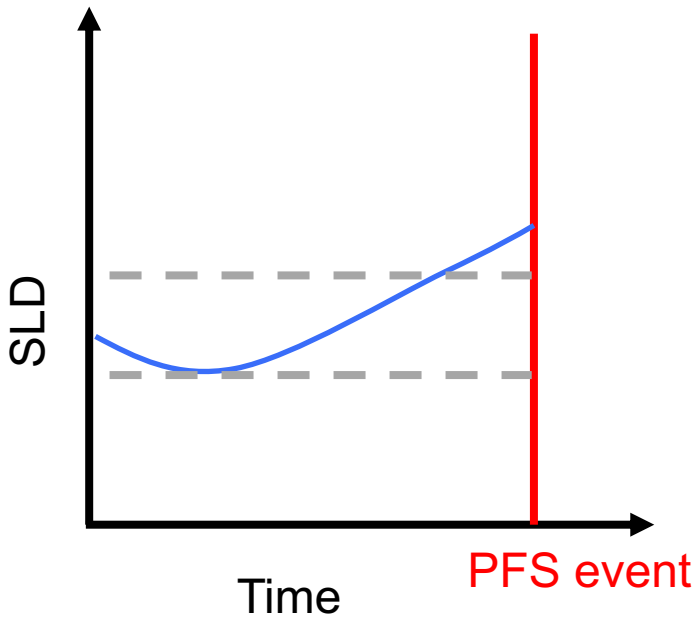
Eisenhauer, Elizabeth A., et al. "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." European journal of cancer 45.2 (2009): 228-247.

Applying the Overall Survival modeling methodology to PFS can be considered



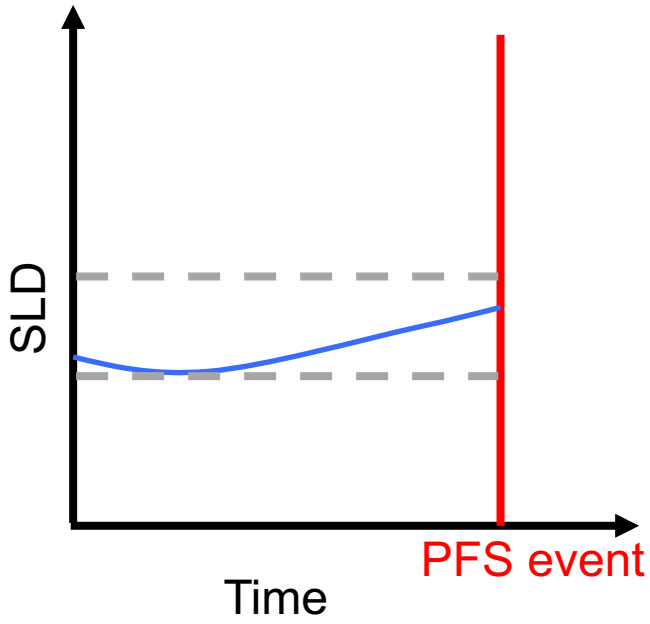
Proposed modelling approach
- Separate model for target and non-target progression

Target lesion progression



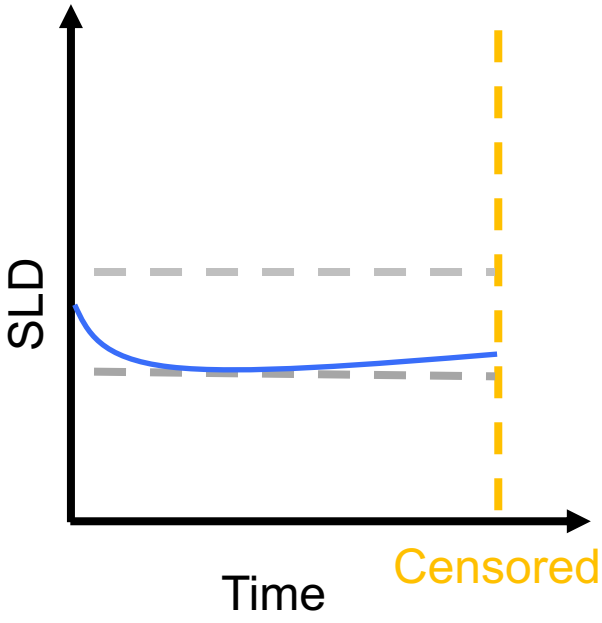
Modeled based on longitudinal tumor size data

Non-target progression



Hazard = f(SLD Dynamics)

Drop Out



Hazard= f(Time)

jointly to predict PFS

Eisenhauer, Elizabeth A., et al. "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." European journal of cancer 45.2 (2009): 228-247.

A pooled dataset was assembled from multiple studies conducted in Genentech among platinum-resistant ovarian cancer patients

- The dataset was pooled from 3 phase I studies and 1 phase 2 studies, total 230 patients were included.
- Patients received one of following four single agent treatments:
  - Anti-MUC16 ADC (n=43)
  - Anti-MUC16 TDC (n=65)
  - Anti-NaPi2b ADC (n=76)
  - Pegylated Liposomal Doxorubicin (n=46)
- Wide ranges of doses were tested in phase I studies.
- Tumor assessments were conducted every 6 weeks or every 8 weeks.

Target lesion tumor growth dynamic was modeled based on longitudinal sum of longest diameters (SLD) data

- The Claret model was used to model tumor dynamics (SLD).
- Drug effect, linear with dose, was added on tumor size shrinkage parameter (KS).
- M3 method was used to handle BLOQ data (<5mm per RECIST[2]).

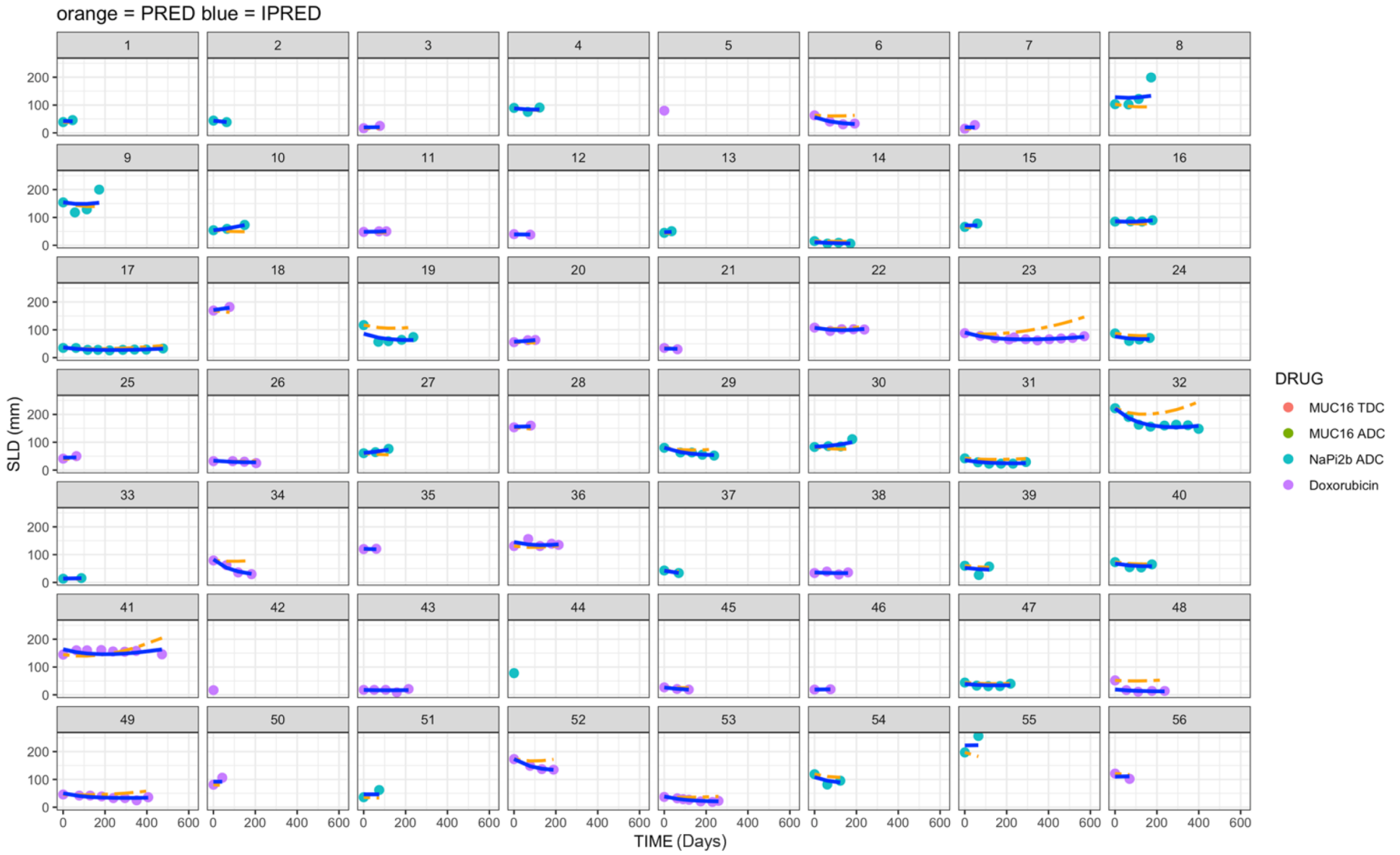
$$\frac{dSLD}{dt} = kg \times SLD - ks \times SLD$$

$$ks = ks_0 \times e^{-Gamma \times t} \times DOSE_{adj}$$

$$DOSE_{adj} = DOSE * POT_{drug}$$

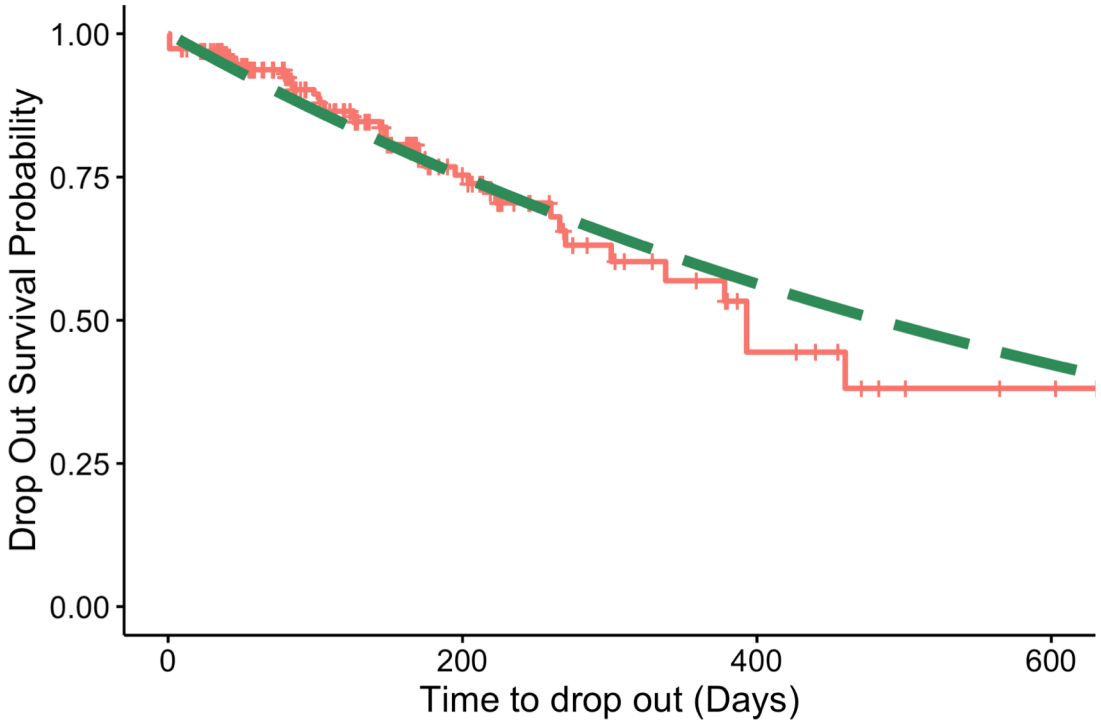
Claret, Laurent, et al. "Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics." Clinical Oncology (2006).
Eisenhaer, Elizabeth A., et al. "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." European journal of cancer 45.2 (2009): 228-247.
Food and Drug Administration. "Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers." Center for Drug Evaluation and Research (CDER) (2005): 7.

Model could capture individual SLD data



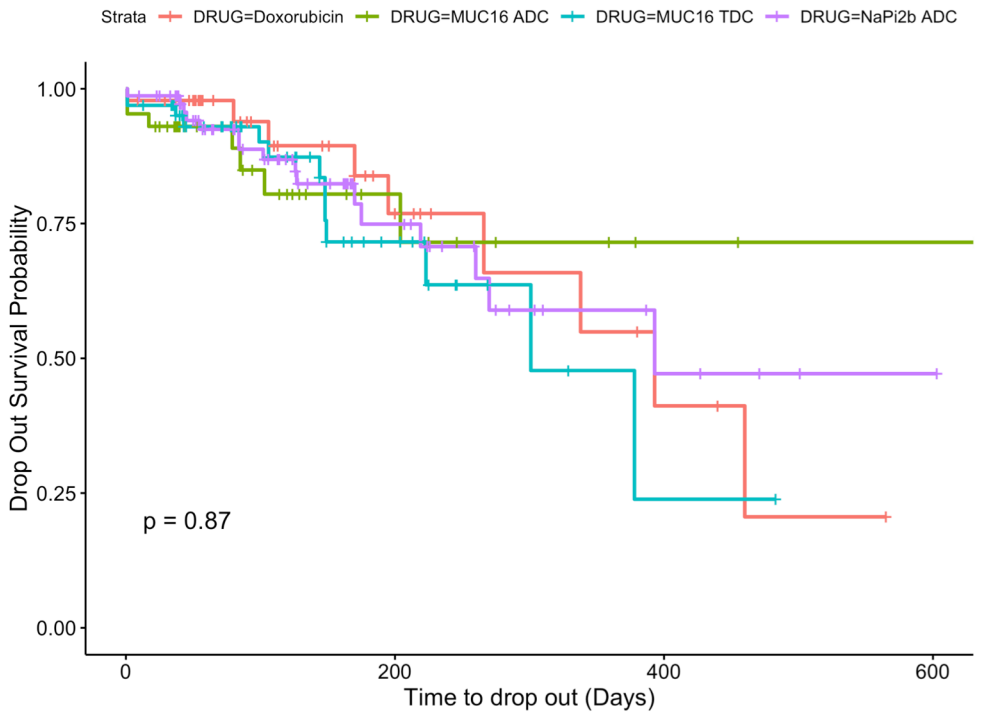
A dataset for dropout TTE analysis was created and patient dropout was modeled in R

AFT model	AIC
exponential	681
weibull	683
loglogistic	687
lognormal	701
logistic	718

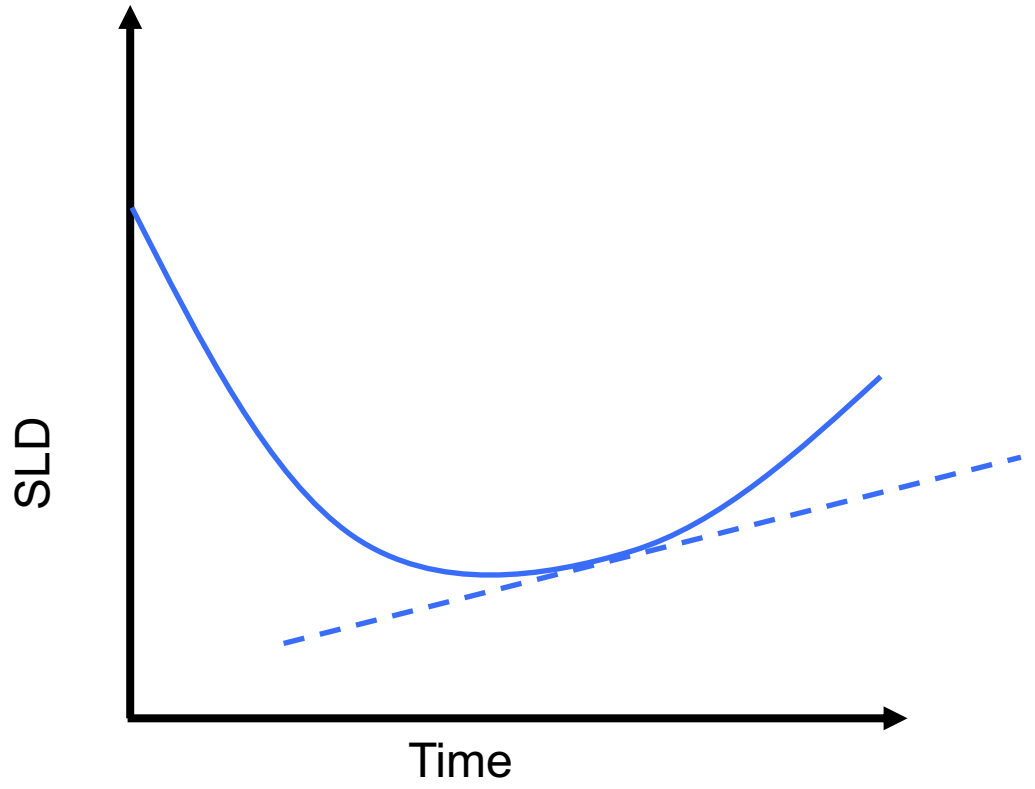


Exponential model fit overlaid with K-M plot for dropout

No statistically significant difference was observed between study treatments.



The hazard for Non-target progression was linked to target lesion tumor growth dynamics

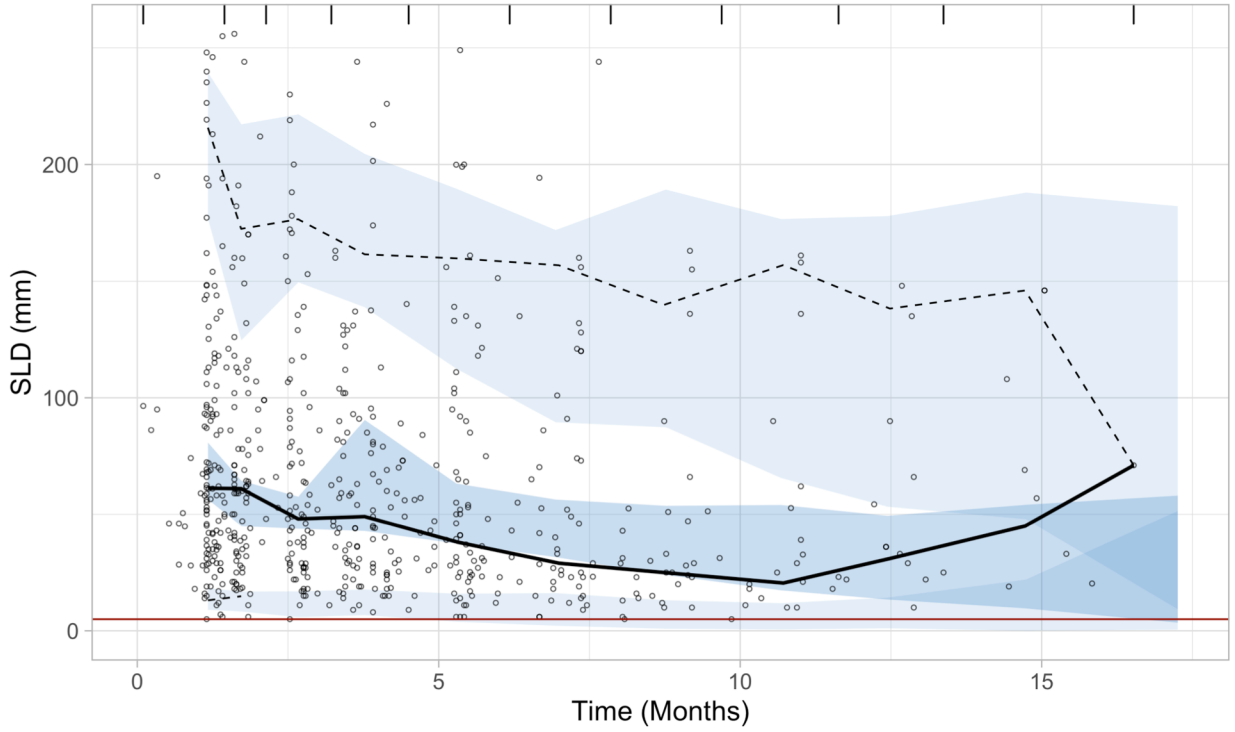


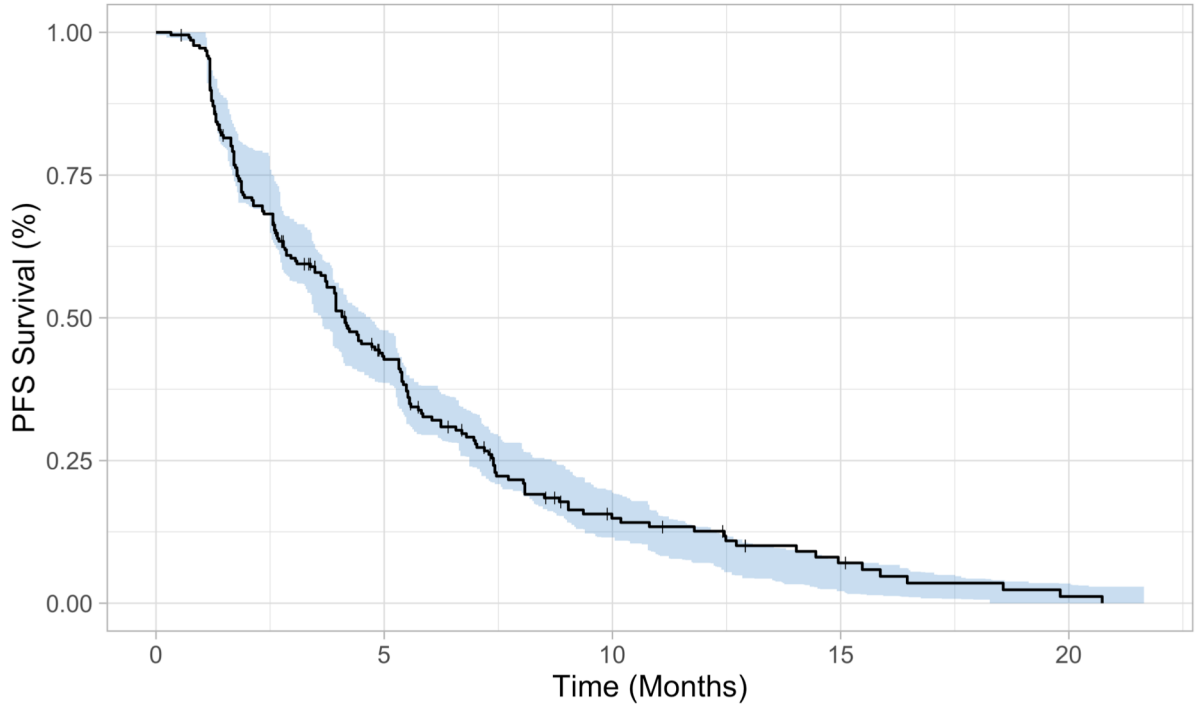
Models and covariates tested:
Constant hazard
SLD ratio to baseline ($\frac{SLD}{Baseline\ SLD}$)
Relative SLD change ($\frac{dSLD}{dt * SLD}$)
Baseline Albumin
Baseline ECOG
Baseline Total Protein

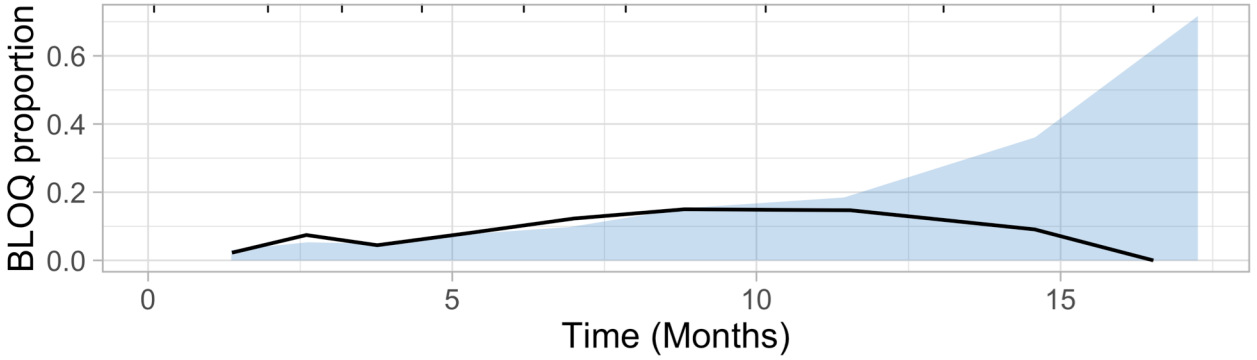
⇒ Non-target progression

- A linear model linking the slope of the SLD over time ($\frac{dSLD}{dt}$) to the hazard for non-target lesion progression was selected as the most appropriate model.

The model could capture both SLD and PFS data verified by VPCs - Across all treatments



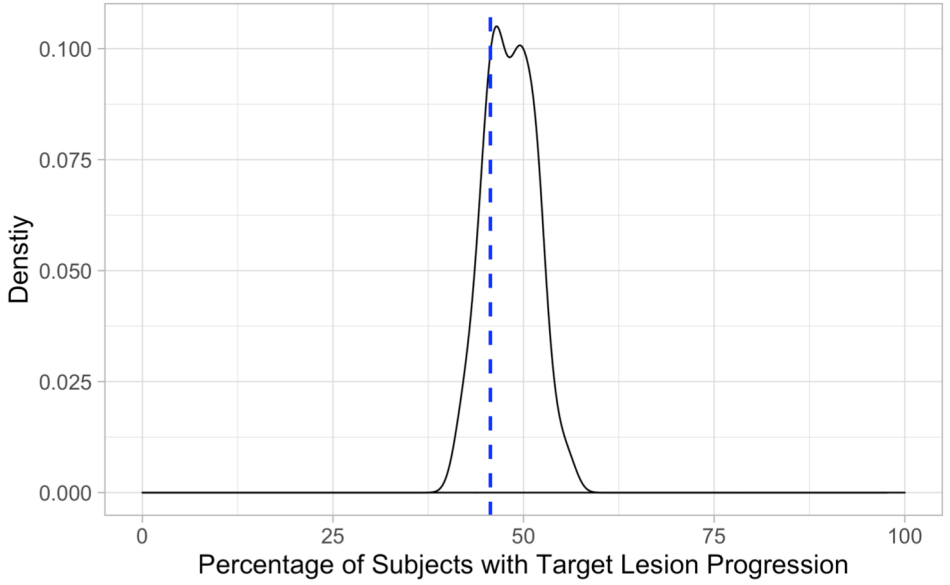


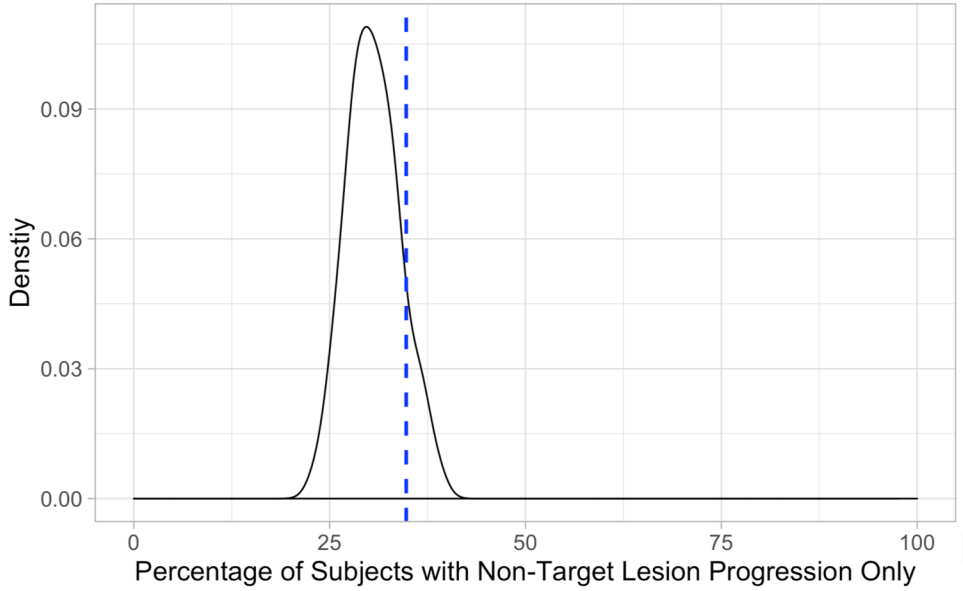


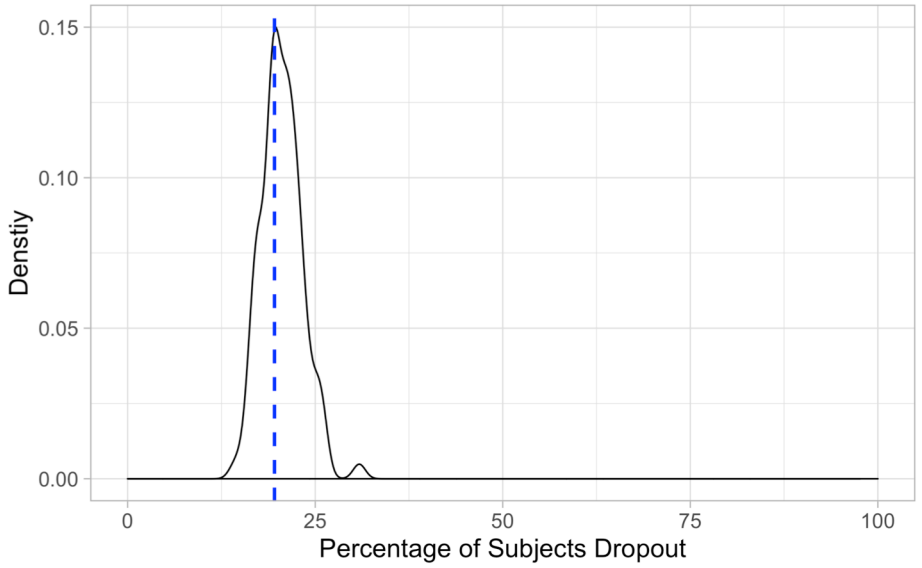
Sim =100 times Shades = 95% CI

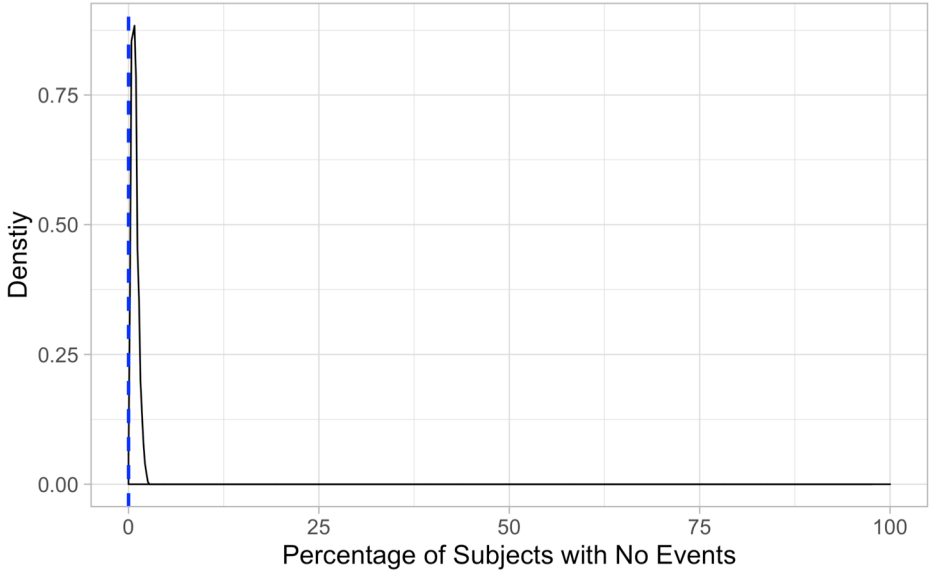
BLOQ around 10% - consistent with the clinical finding

Model simulation is in line with observed data in PFS event triggers





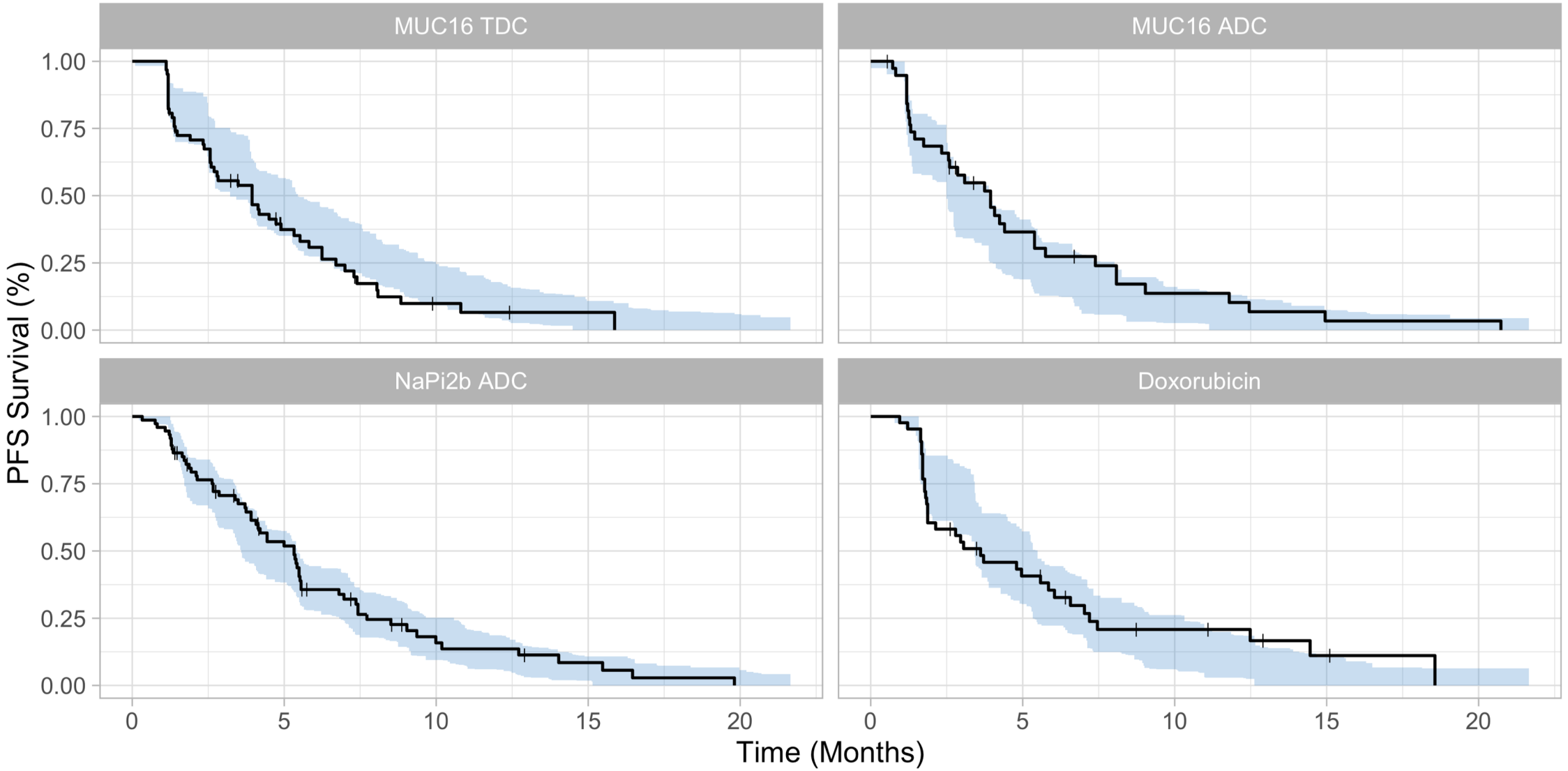




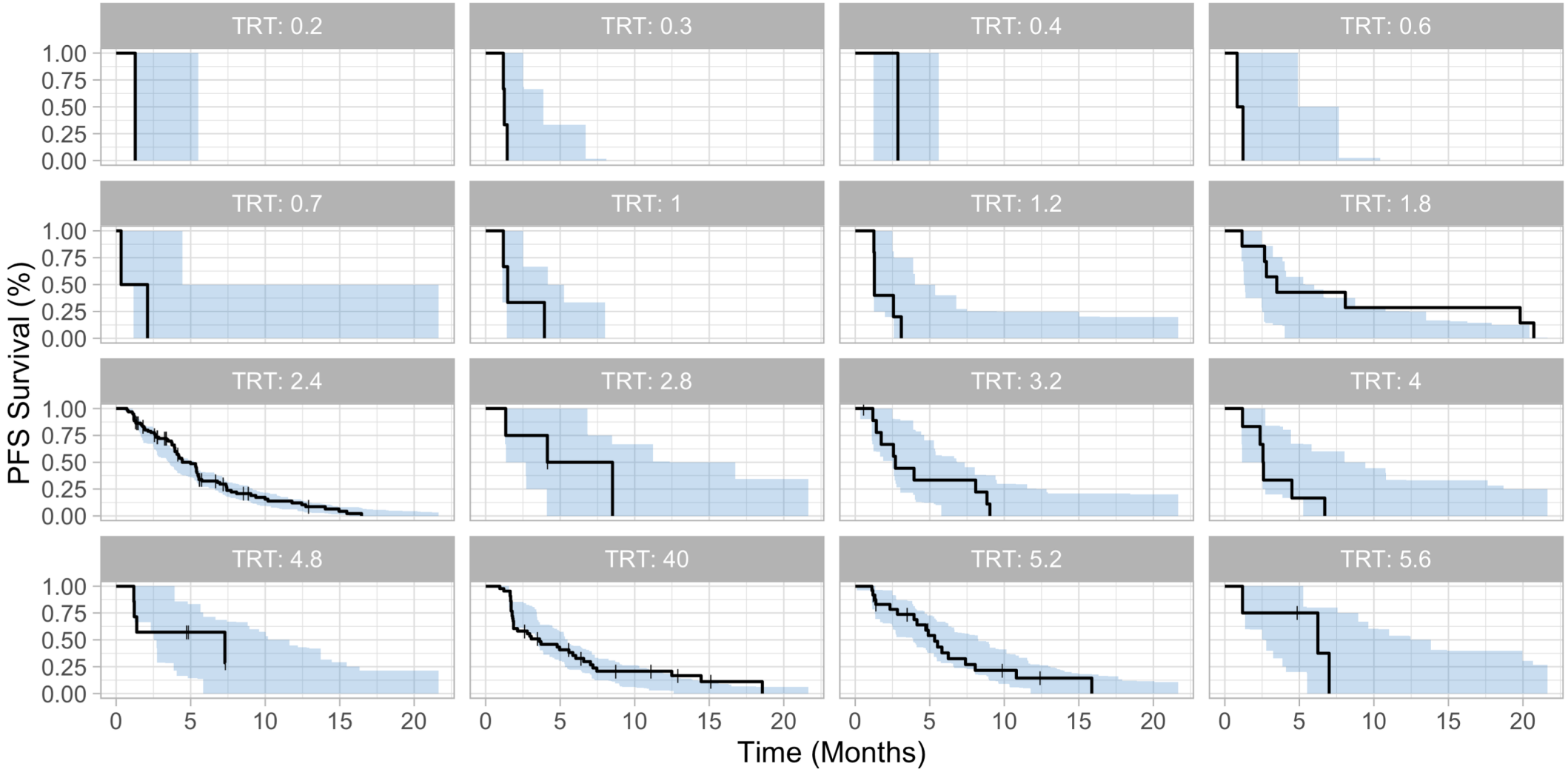
Dash line – observed value
Grey bar – model simulation

Sim = 100 times

Model could generally capture the PFS across different treatments



VPC suggests that model could capture dose response across different treatments



Summary

- A new method was developed to model and predict PFS using longitudinal tumor size data.
  - Progression due to target lesion – continuous endpoint
  - Progression due to non target event – time to event analysis
  - Patient drop out - time to event analysis

  } PFS

- To correctly model PFS, the target lesion progression criteria, BLOQ data and censoring need to be appropriately addressed.

- Besides standard NONMEM Goodness-of-fit plots, VPCs and other diagnostic plots are critical for the model evaluation.

- The model can potentially be used to predict PFS for future clinical studies in platinum-resistant ovarian cancer patients.

Acknowledgements

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Muc16 ADC study team and patients
NaPi2b ADC study team and patients
Muc16 TDC study team and patients