USE OF A TMDD MODEL TO SUPPORT DOSE SELECTION: GA101 EXAMPLE

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TARGET MEDIATED DISPOSITION MODEL (TMDD)

GA101: A glycoengineered CD20 antibody

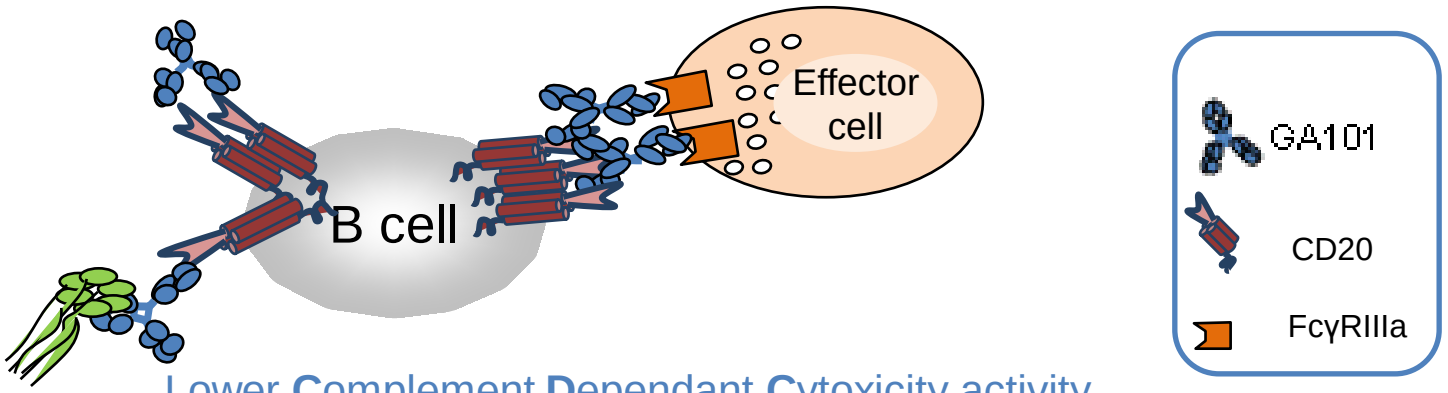
- Rituximab: central therapy- type I antibody
- Preclinical studies: GA101 superior to Rituximab in inhibiting tumour cell growth in lymphoma xenograft model

Increased direct cell death

Type II versus Type I antibody

Enhanced **A**ntibody-**D**ependant **C**ell-mediated **C**ytotoxicity

Glycoengineering for increased affinity to FcγRIIIa



Lower **C**omplement **D**ependant **C**ytoxicity activity

Type II versus Type I antibody

Mössner E, et al. Blood 2010; 115:4393−4402.

Phase I/II database at the time of dose and schedule selection

Two phase I/II monotherapy studies
One phase I combotherapy study

N=160 patients and 4018 concentrations

Population	Doses	Regimen
• Indolent NHL • Aggressive NHL • Relapse patients • CLL (n=34)	• 50-2000 mg • N=3-20/cohort	• q3w, 8 or 6 cycles • qw, 4 cycles

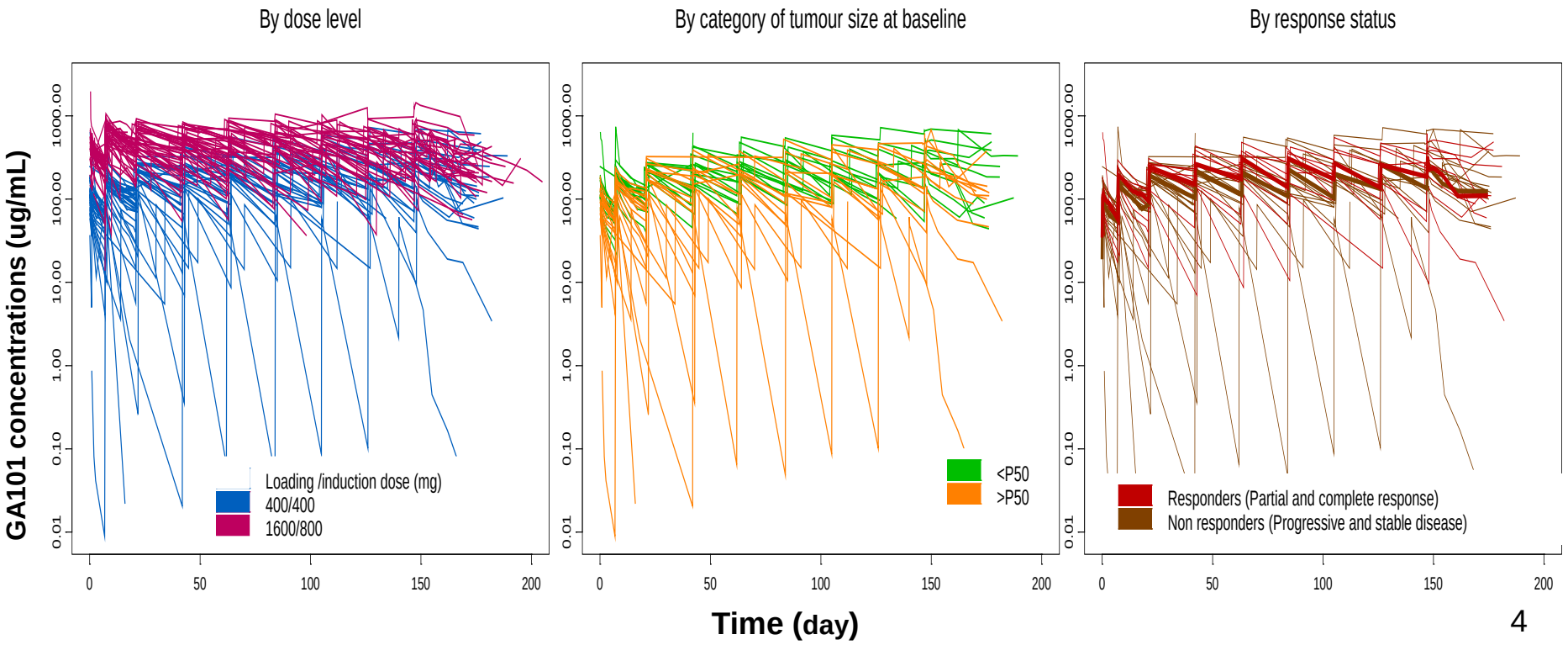
CLL: Chronic Lymphocytic Leukemia , NHL : Non-Hodgkin Lymphoma

PK concentrations contain information on target

- PK variability decreases with increased dose
- PK variability increases with tumour burden at baseline

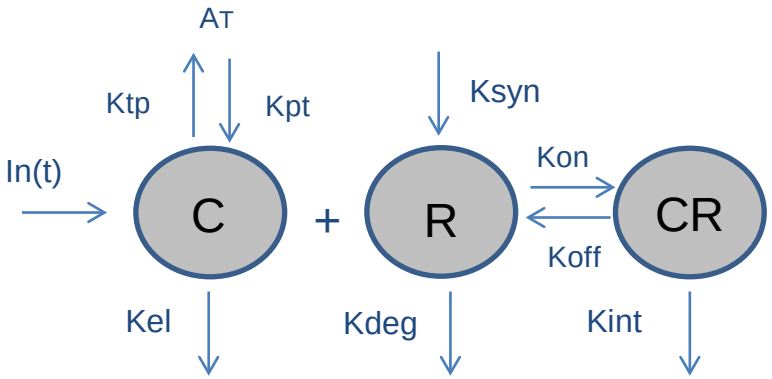
} TMDD?

- GA101 concentrations apparently higher in responder patients

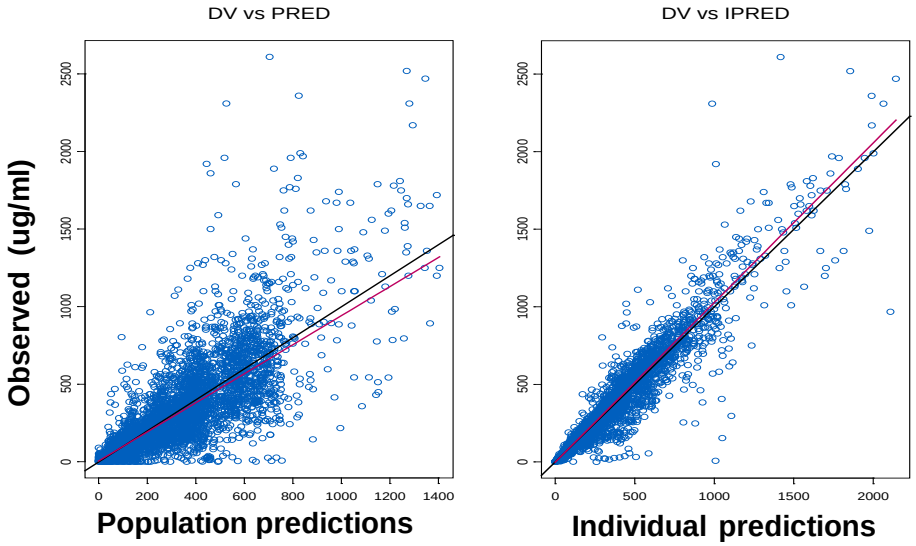


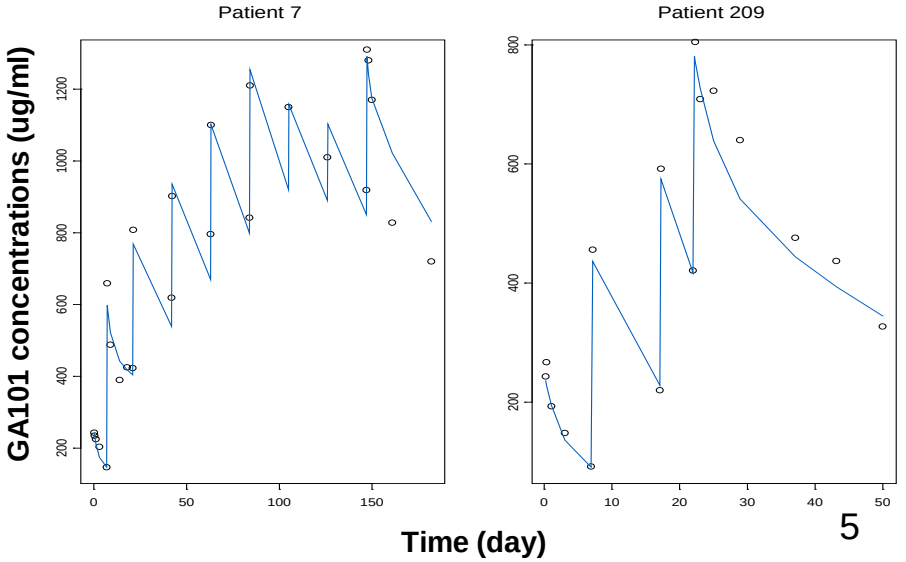
Target-mediated disposition model: A quantification of the relationship between drug exposure and target binding

General model (Mager, JPP 2001)



- Only PK data are available
- An approximation of the model with assumption of quasi steady-state was used (Gibiansky, JPKPD 2008, Ma Pharm res 2012)

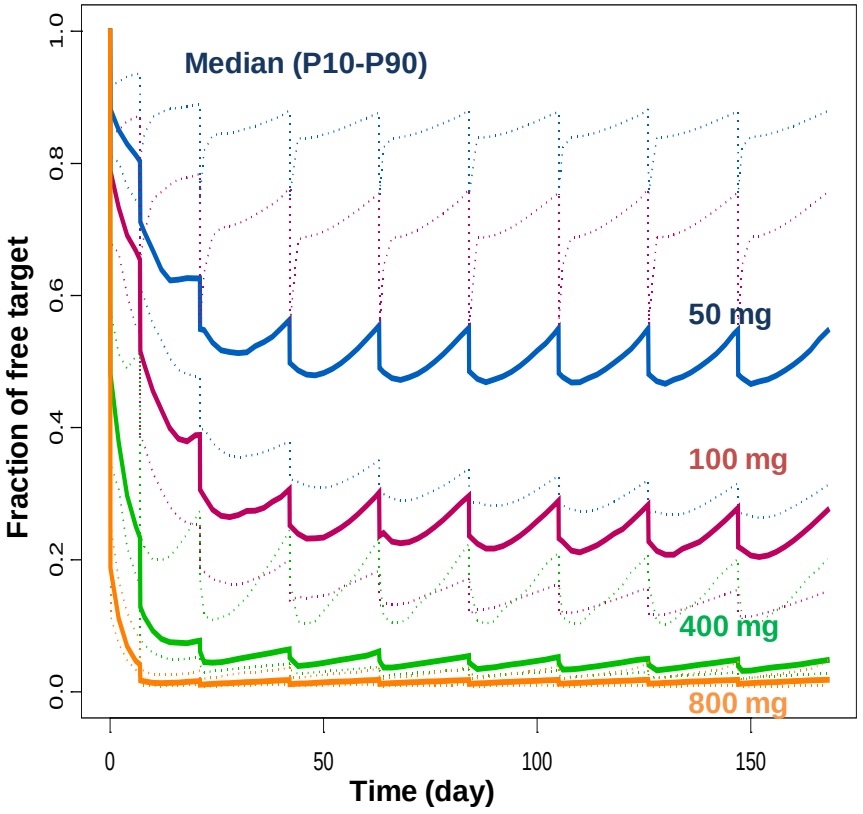




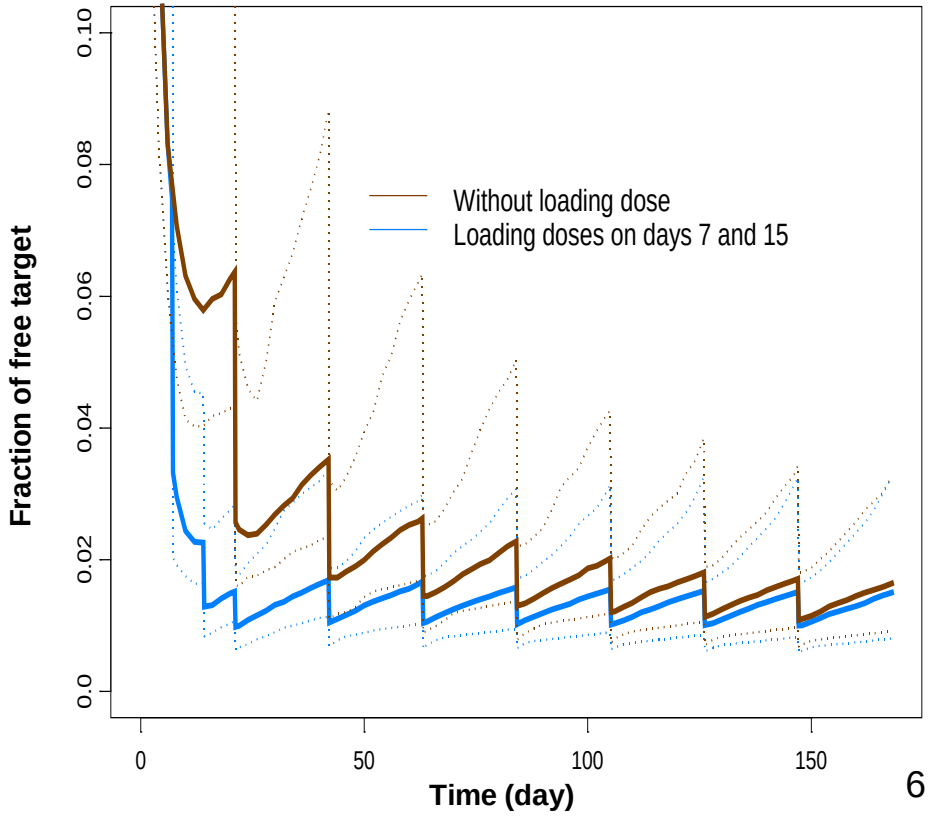
Target-mediated disposition model predictions

- Based on theoretical results, the PK model quantifies the decrease in free target related to drug exposure

Dose-effect relationship



Faster target saturation with loading dose strategy

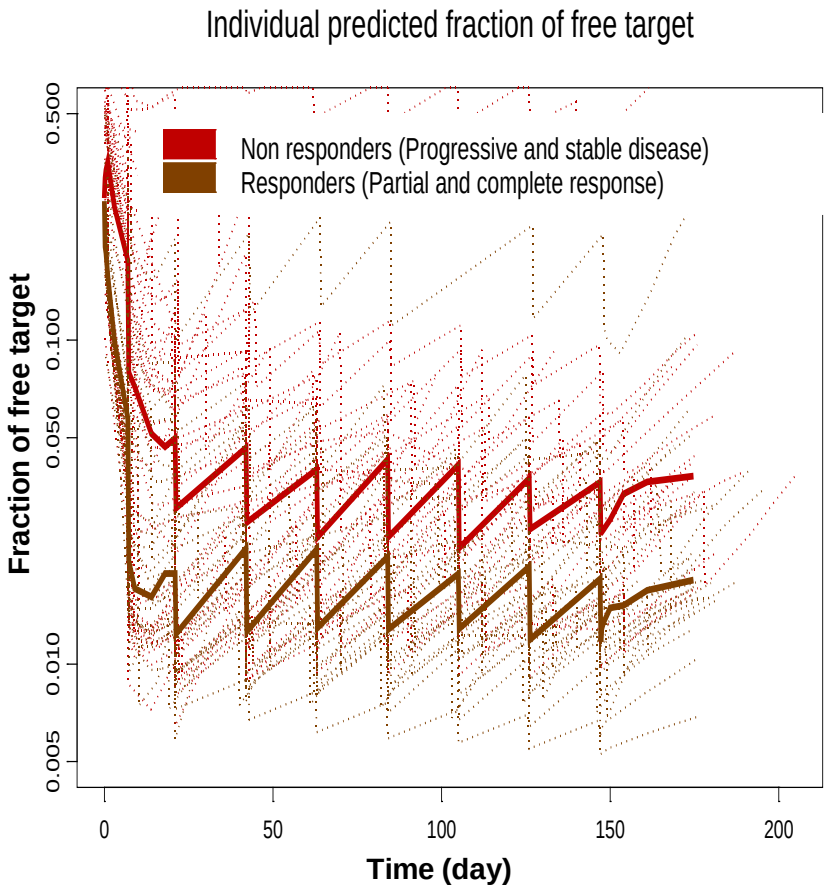


Dose selection based on free target fraction

The free target fraction is lower in responders

Responders	Median	P5-P95
Free target fraction at steady-state	0.02	0.01-0.05
C_{trough} (steady-state)	550 µg/mL	244-1298

- Aim: Fraction of free target below 0.05

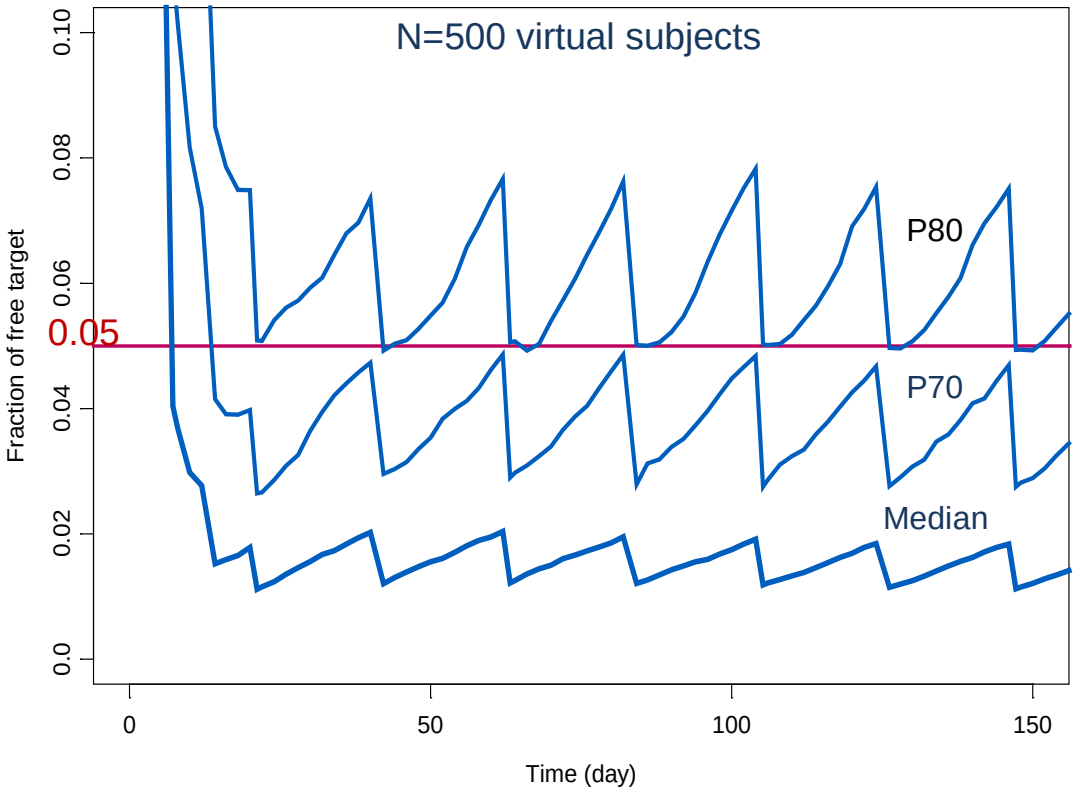


- The targeted concentrations derived from the model are consistent with the xenograft model predictions (300-600 ug/mL)

Phase III trial: A dose of 1000 mg achieves high target saturation

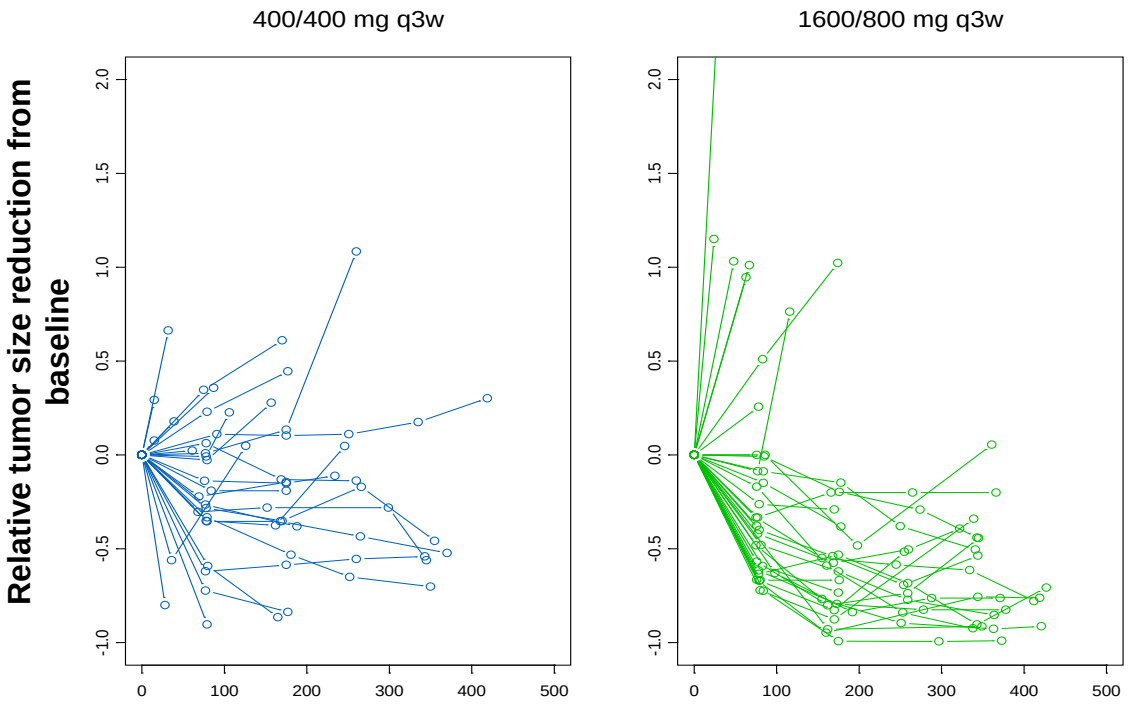
- A dose of 1000 mg q3w with two loading doses on days 7 and 15 results in high target saturation i.e. below 0.05 from day 15 onwards

- 70% of the patients below 5% and 80% below 8%
- Allow outpatient administration



Continuing story: After TMDD..

- **Tumor size:** Greater reduction at high dose under monotherapy
- End of treatment response: High (1600/800 mg) vs. low dose (400/400 mg) responders
  - Heavily pre-treated indolent NHL: 55 % vs 17 %
  - Heavily pre-treated aggressive NHL: 32 % vs 24 %



Conclusion:

Use of TMDD model allowed to predict unobserved target suppression and support dose selection that is currently tested in Phase III

Strengths

- £ Target-mediated disposition model used to elicit target information from concentrations
- £ Particularly useful in early development when clinical efficacy data are limited

Limitation

- £ No observed data yet for model validation

Acknowledgments

Project team:

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PD endpoint : Feasibility assessment

Pharmacodynamics: B-cells
Rapid, strong and sustained depletion-
No clear dose/effect relationship