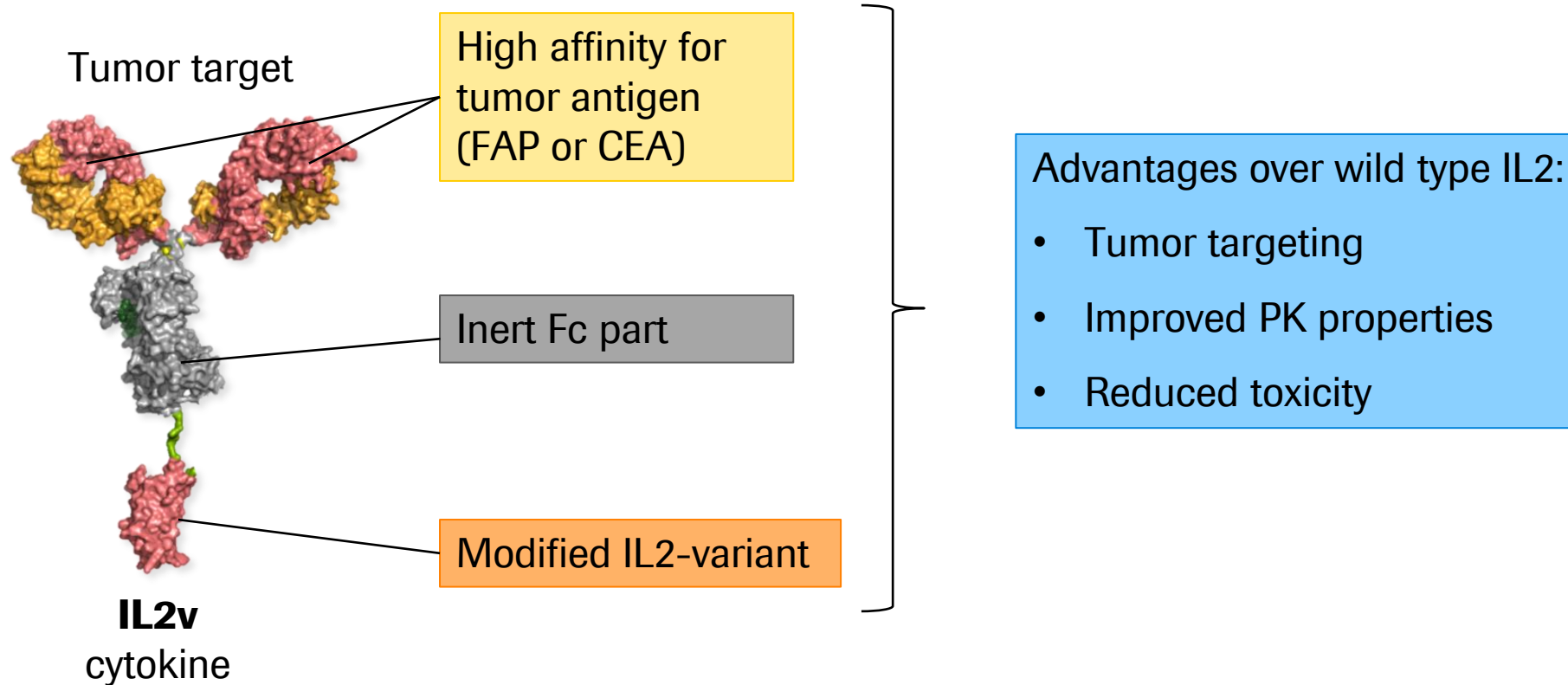

Using pharmacokinetic simulation to guide dose escalation decisions for targeted IL2v immunocytokines

Hanna Silber Baumann¹, Christophe Boetsch¹, Volker Teichgräber², Benjamin Ribba¹, Valerie Cosson¹

Roche Pharma Research and Early Development, Roche Innovation Center Basel¹ and Zürich²

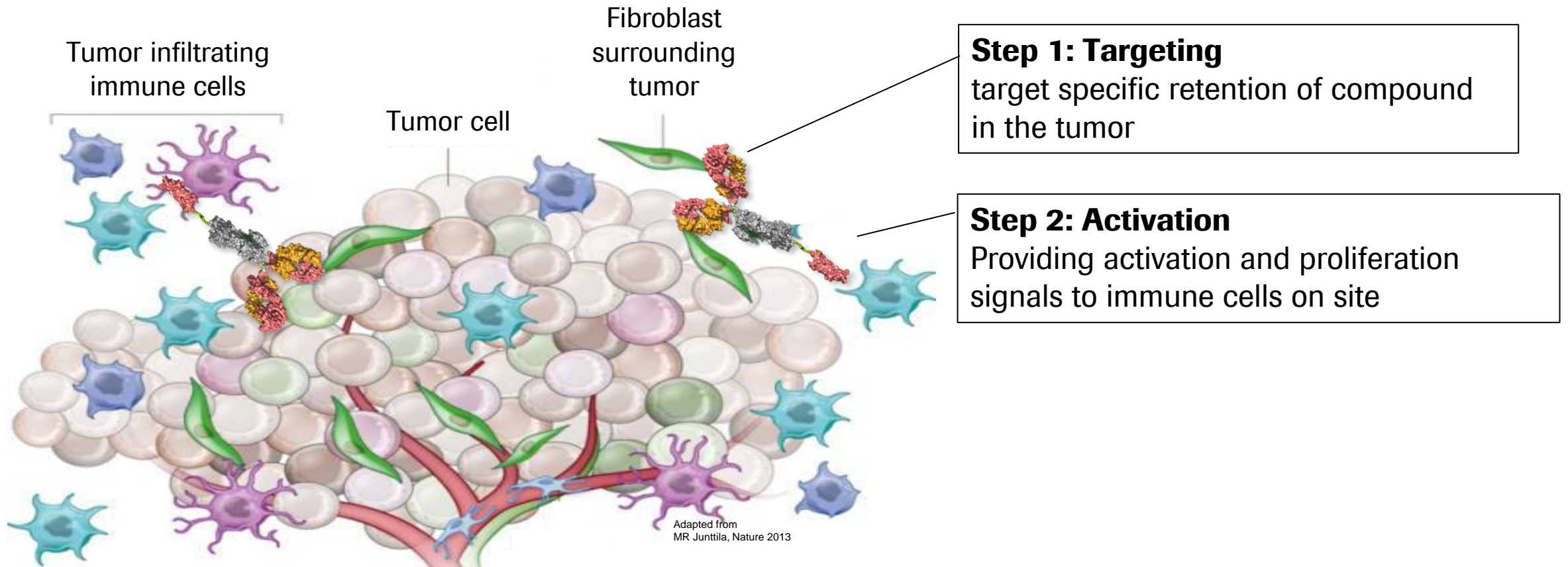
Tumor-targeted immune cell growth factor

Engineered Immunoglobulin-cytokine fusion protein

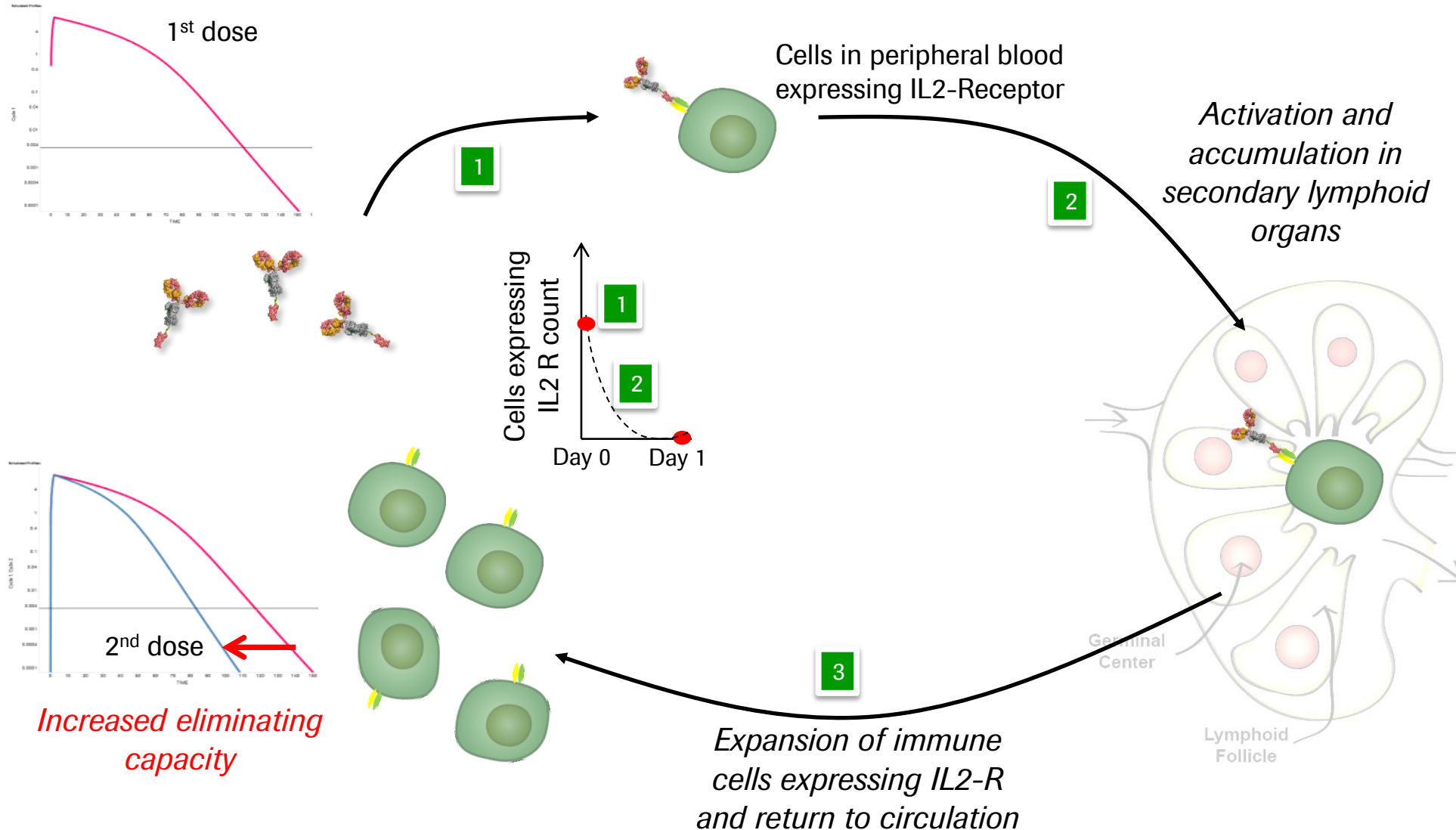


Targeted IL2v Mechanism of Action

Growth factor for Natural Killer cells and Killer T-cells in the tumor

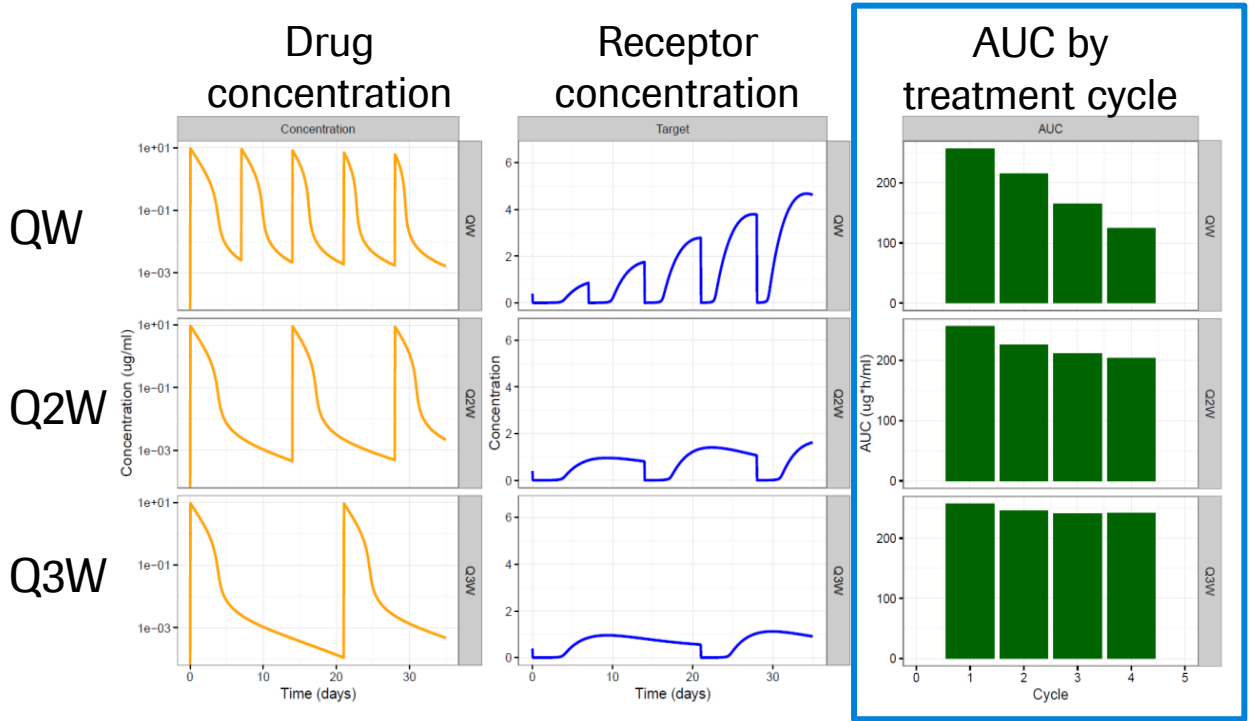
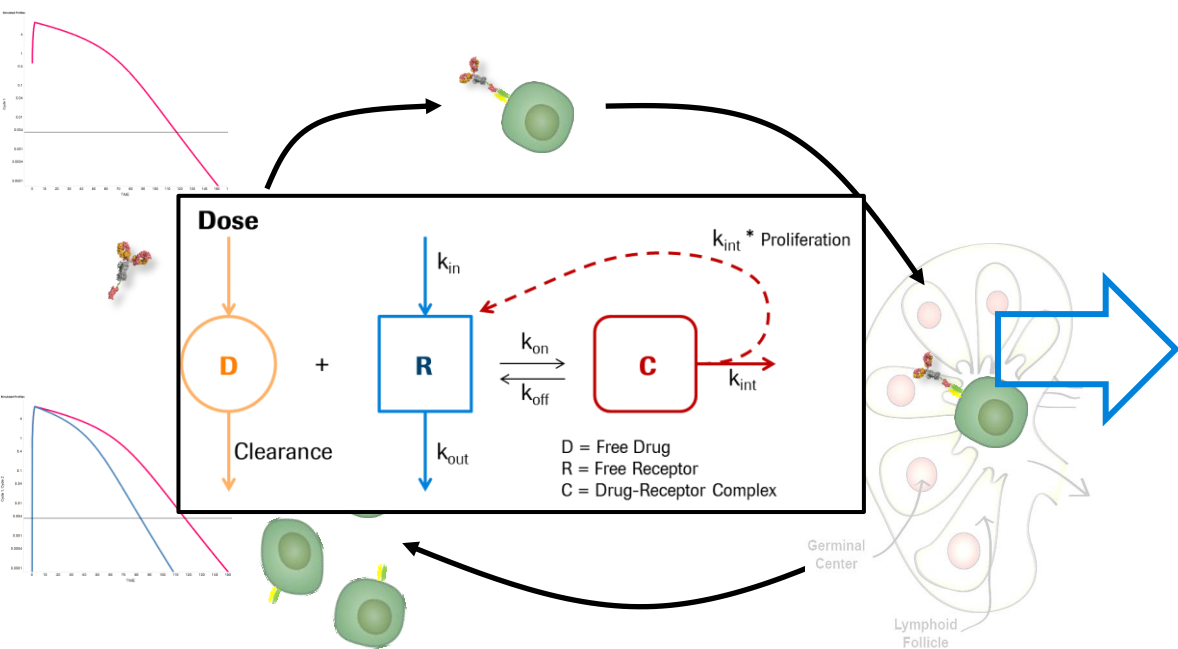


Pharmacokinetic behavior is driven by TMDD and self induced clearance

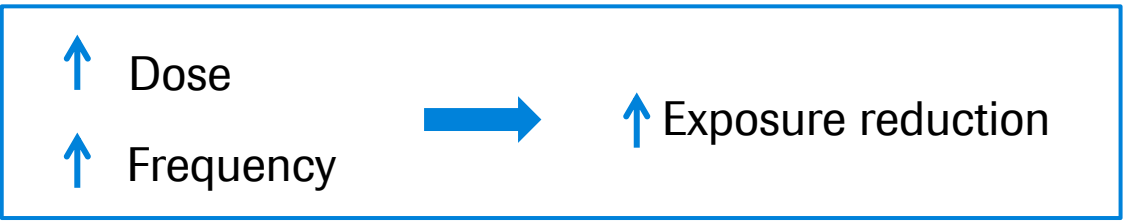


PK properties lead to exposure reduction following multiple dosing

*Extent of exposure reduction is dependent on the **dose** and **frequency** of administration*

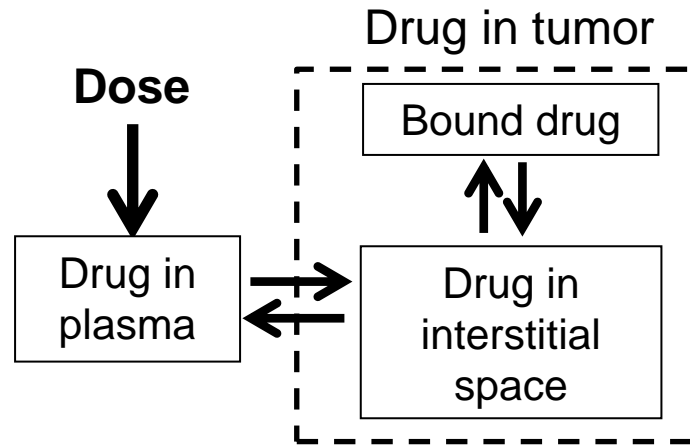
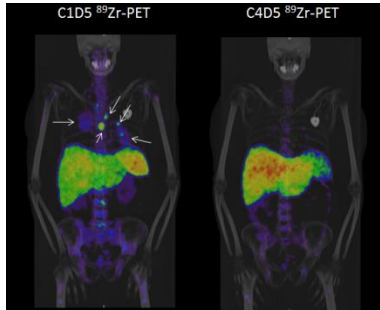


PK model was presented by H.P. Grimm et al @ PAGE 2016

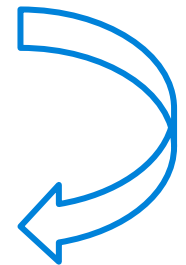


Imaging study demonstrated specific tumor uptake after single dose but was reduced following repeated dosing (Q2W)

Reduction in tumor uptake is likely due to peripheral exposure reduction

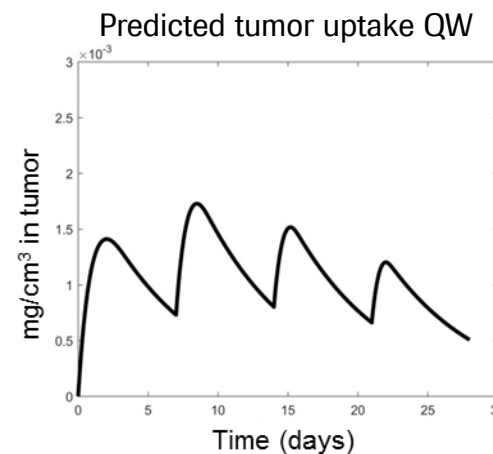
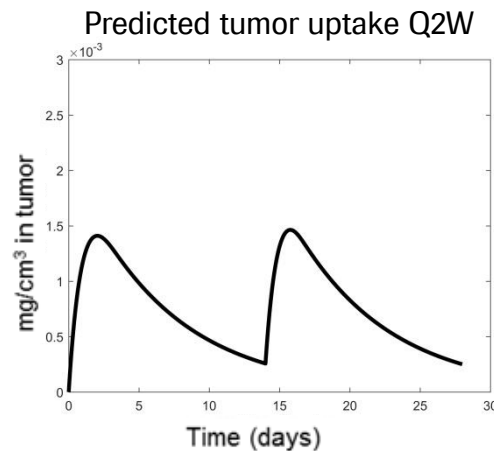


PET data was incorporated into a model for tumor uptake



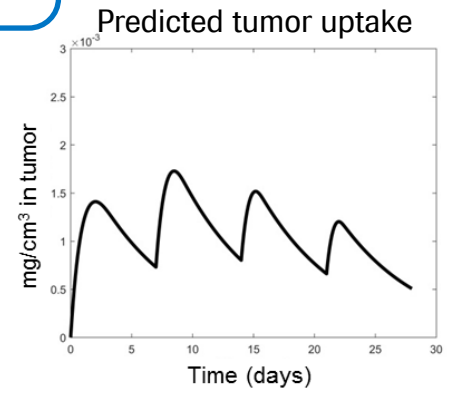
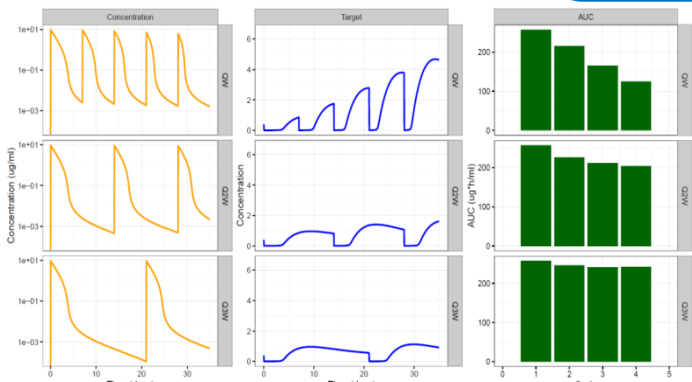
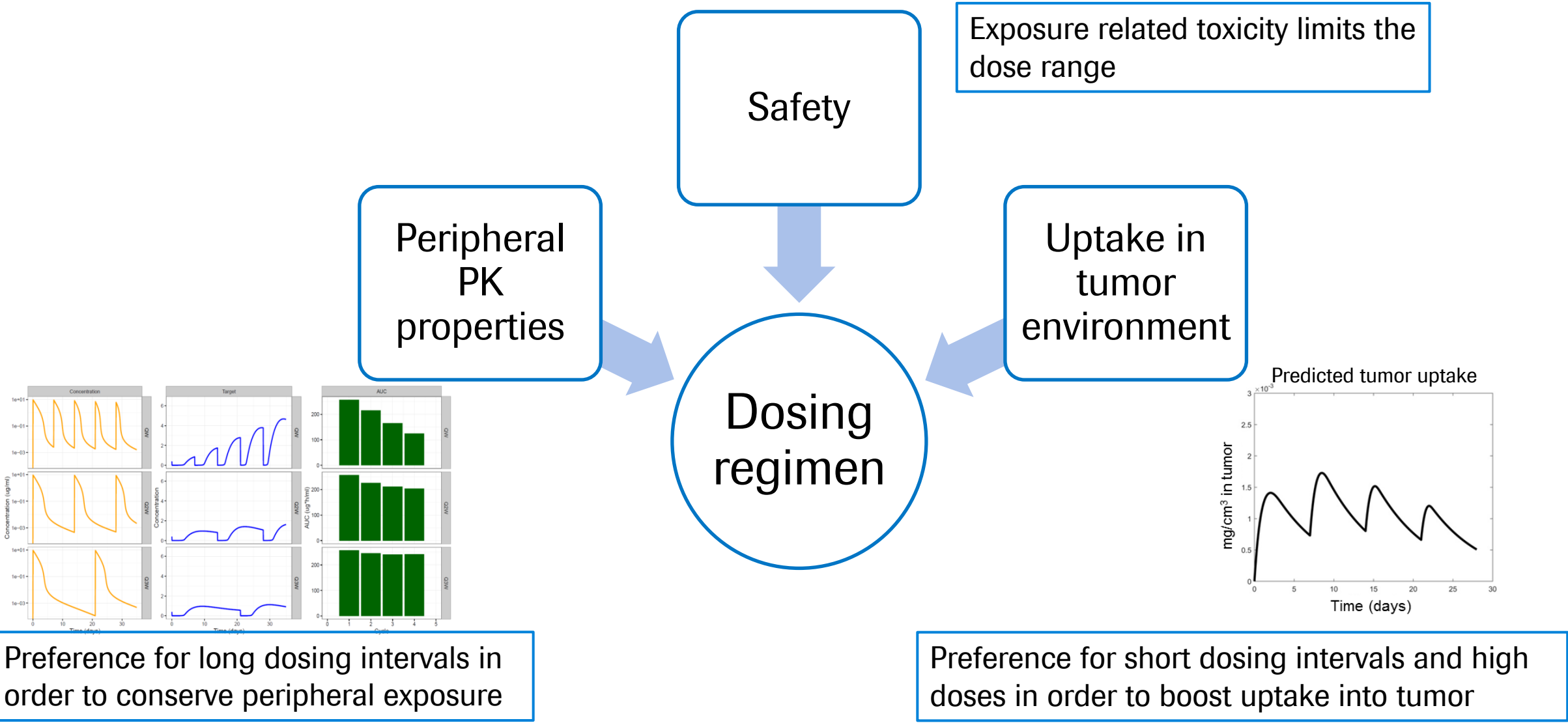
PET imaging study with radiolabeled CEA-IL2v

Amount of drug in the tumor lesion was measured longitudinally



Model predictions indicated that more frequent dosing improves tumor uptake also when the peripheral exposure is reduced as a result

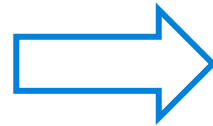
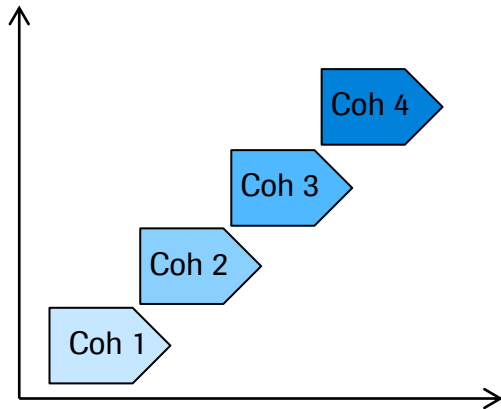
Three main factors need to be considered when choosing the dosing regimen



PK simulation was performed to investigate the possibility of dose up-titration

Maintained exposure over multiple cycles expected to benefit tumor uptake

Fixed dose QW regimen
Escalation supported by CRM



Additional options investigated through simulation:

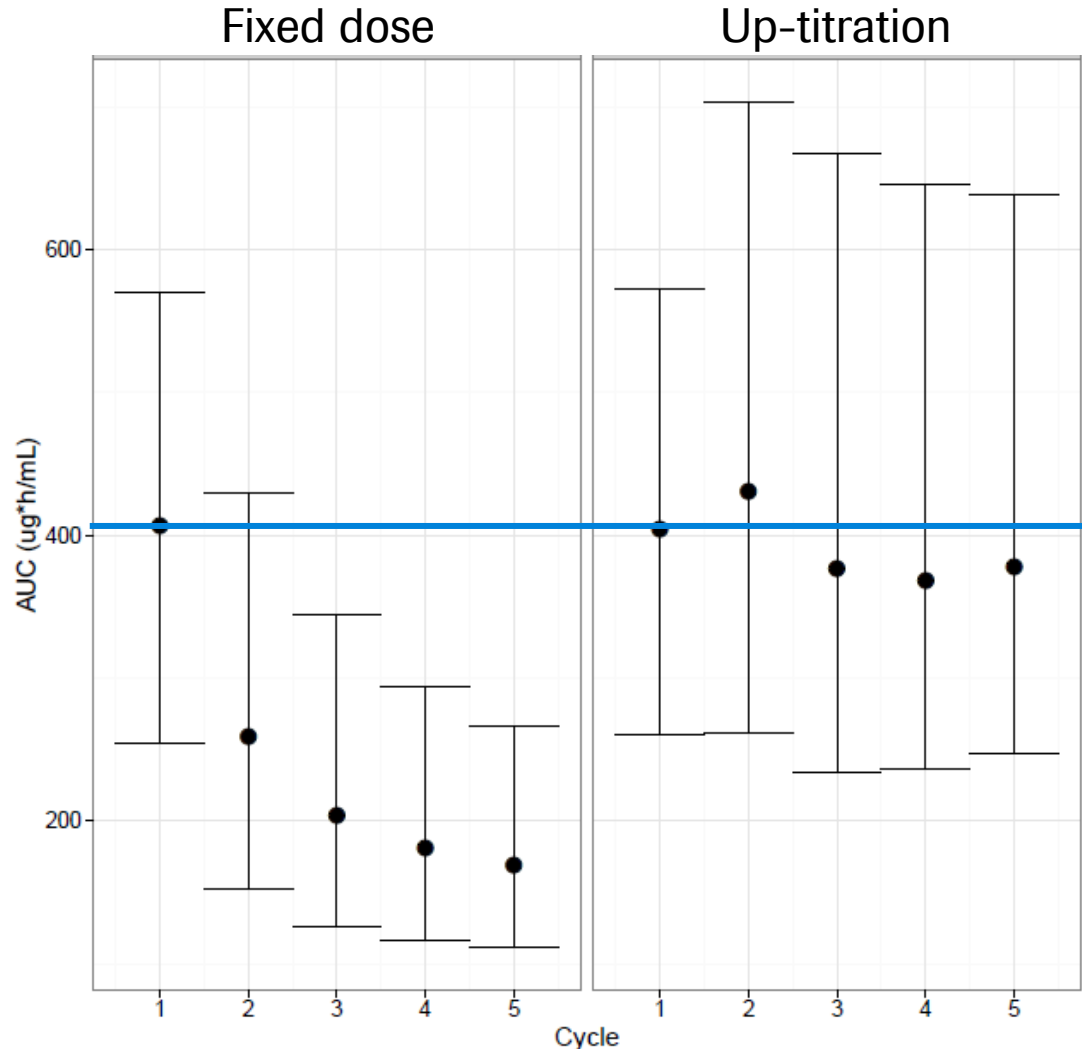
- Dose up-titration on one or more occasions
- Administration frequency – QW, Q2W
- Mixed schedules of different frequency

Outcome measures:

- Comparison of AUC and Cmax to target values

PK model developed based on available PK data – fixed dosing

Maintained exposure over several cycles with QW dosing can only be attained by continuous up-titration

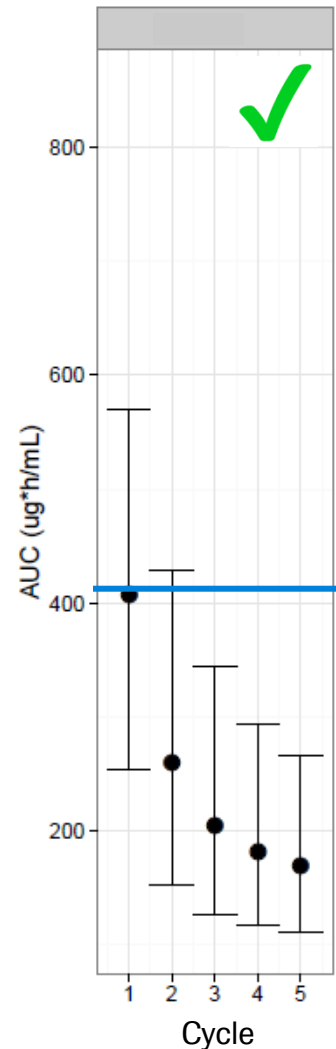


- Multiple dose up-titration considered not feasible from study management perspective
 - Limitation at 1 or possibly 2 dose up-titrations
- Safety concerns limited the doses clinicians were willing to administer

Target exposure correspond to the exposure of a well tolerated dose on cycle 1 – indicated by the blue line

Schedules with 1 dose up-titration on the 2nd or 3rd dose in a QW schedule were implemented in clinic

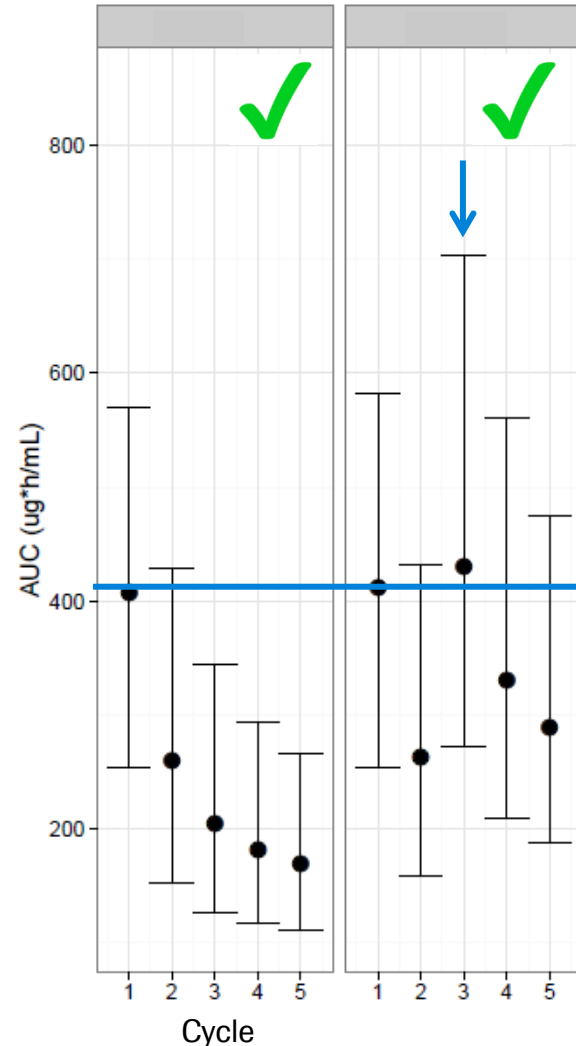
Decision was guided by PK simulation



Graphs show simulated data

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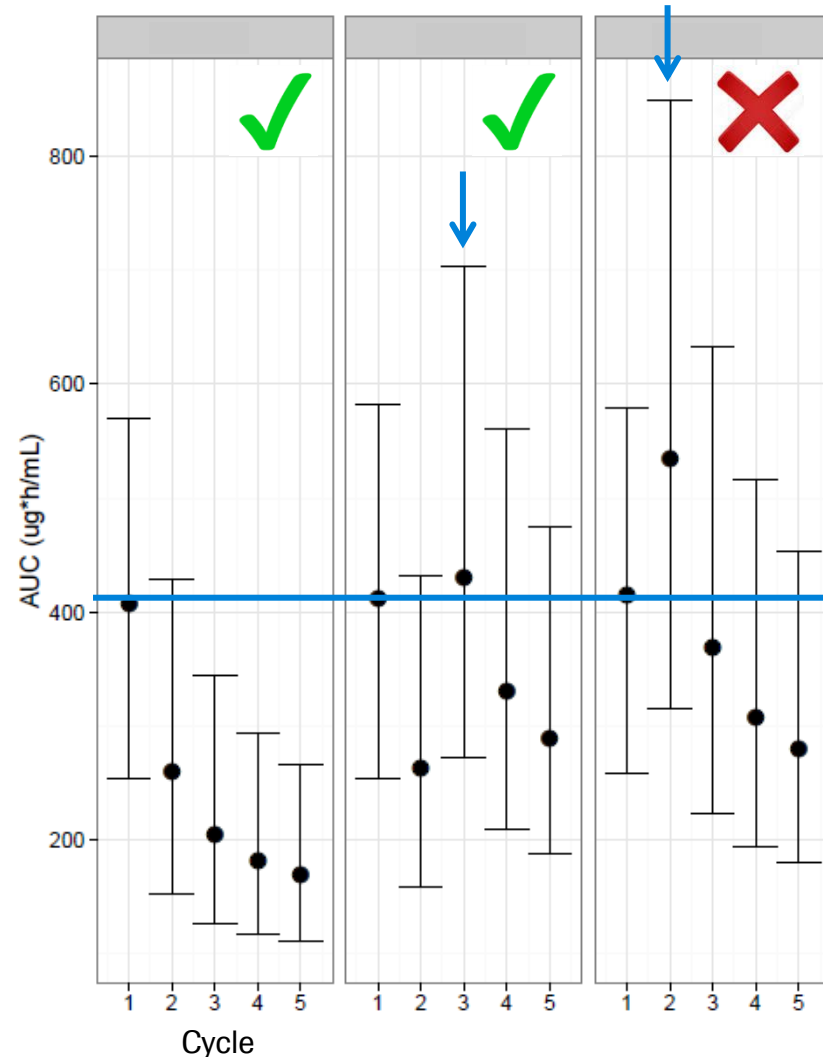
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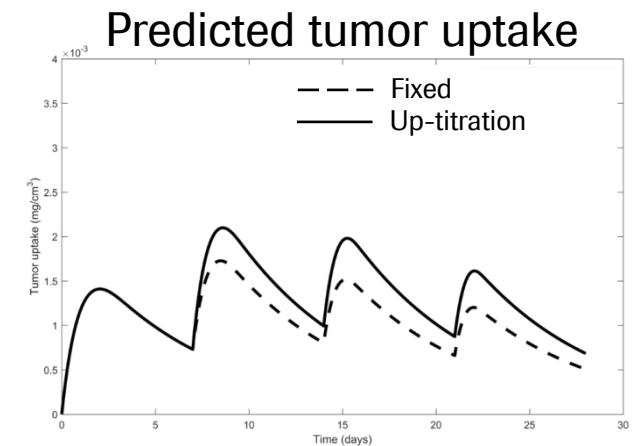
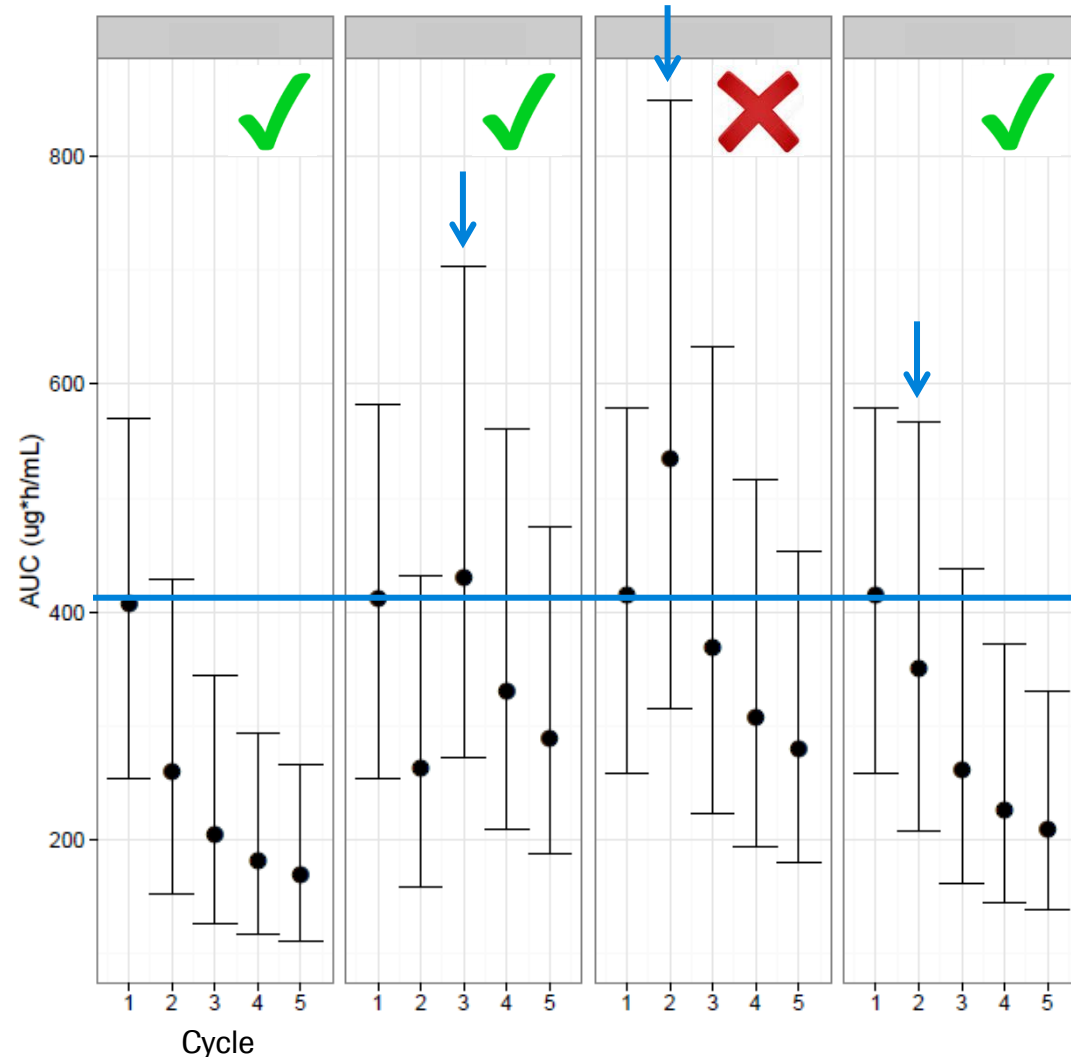
Decision was guided by PK simulation



Graphs show simulated data

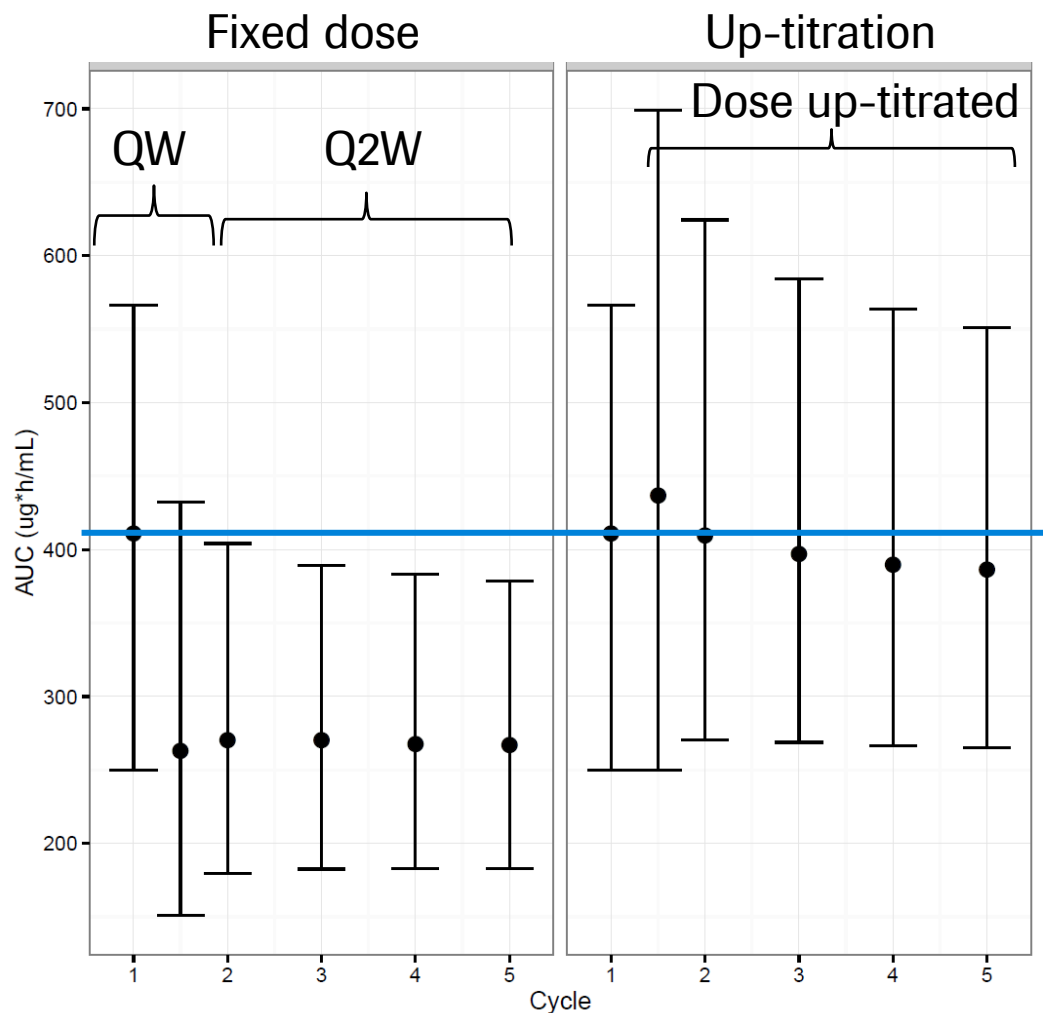
Schedules with 1 dose up-titration on the 2nd or 3rd dose in a QW schedule were implemented in clinic

Decision was guided by PK simulation



Graphs show simulated data

Maintained exposure can be achieved with one dose up-titration when QW regimen is followed by a less intense regimen (Q2W)



- Maintain the benefit of initial frequent dosing
- Peripheral exposure maintained within 10% of target
- Version of this schedule is implemented in an ongoing trial

Conclusions

- Complex PK behaviour together with a narrow safety window demanded the need for non-standard dosing schedules
- Up-titration schedules were implemented based on PK simulations when the standard procedure for dose escalation was not appropriate
- Dose up-titration is believed to facilitate tumor uptake of the evaluated immunocytokines compared with fixed dose regimens and is being implemented in on-going trials

Acknowledgment

- Claire Petry
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- Nicolas Frey
- Alexander Phipps
- Richard Peck

Thank you for listening!

Doing now what patients need next