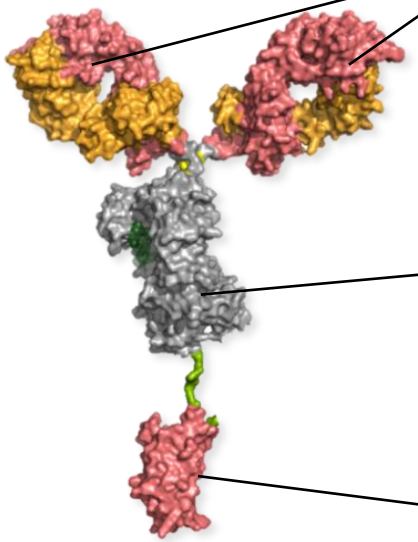
PKPD analysis of soluble CD25 to characterize the concentration–effect relationship observed following the administration of Cergutuzumab Amunaleukin, a targeted immunocytokine for cancer immunotherapy

Hanna E. Silber Baumann[1], Christophe Boetsch[1], Jehad Charo[2], Claire Petry[1], Volker Teichgräber[2], Valerie Cosson[1]

Roche Pharma Research and Early Development, Roche Innovation Center Basel[1] and Zürich[2]

Cergutuzumab Amunaleukin (CEA-IL2v) is a tumor-targeted immune cell growth factor

Engineered Immunoglobulin-cytokine fusion protein



High affinity for tumor antigen (CEA)

Inert Fc part

Modified IL2-variant

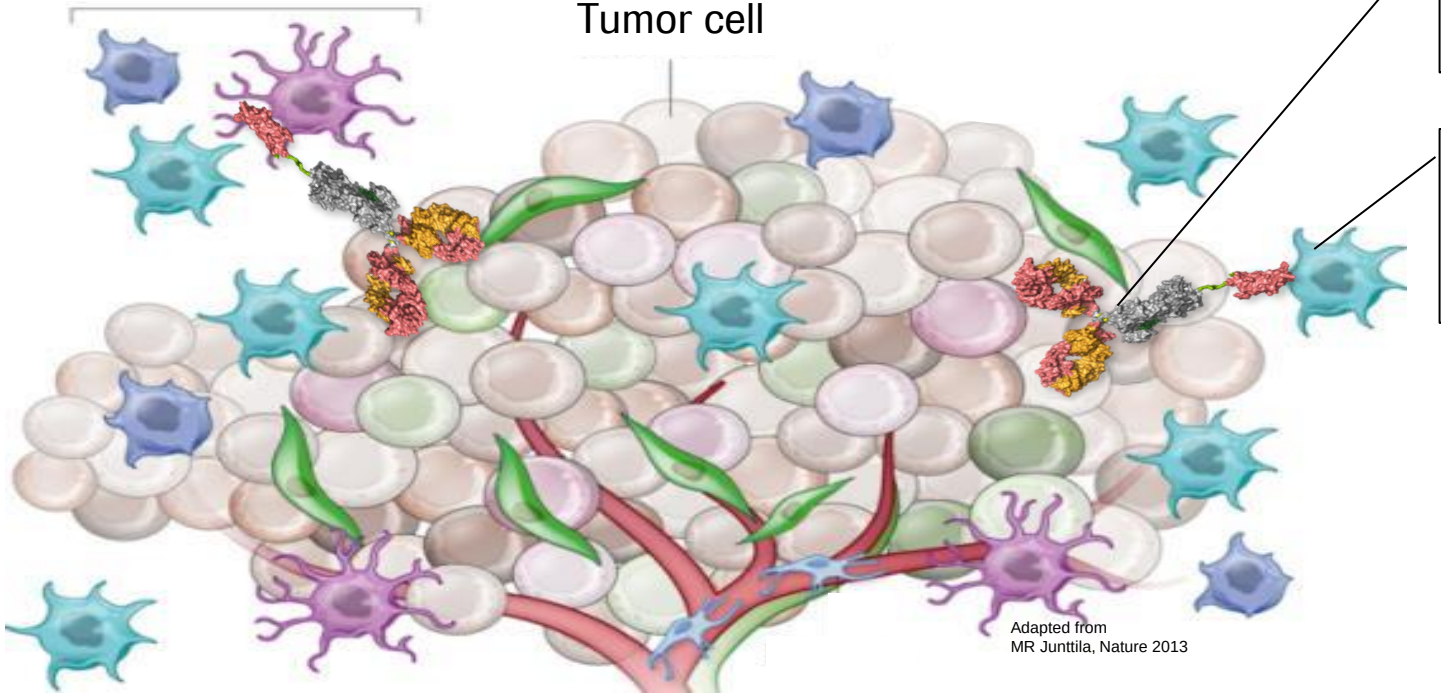
Advantages over wild type IL2:

- Tumor targeting
- Improved PK properties
- Reduced toxicity

CEA = Carcinoembryonic antigen, IL2=Interleukin 2, cytokine for cell signaling

Targeted IL2v Mechanism of Action

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



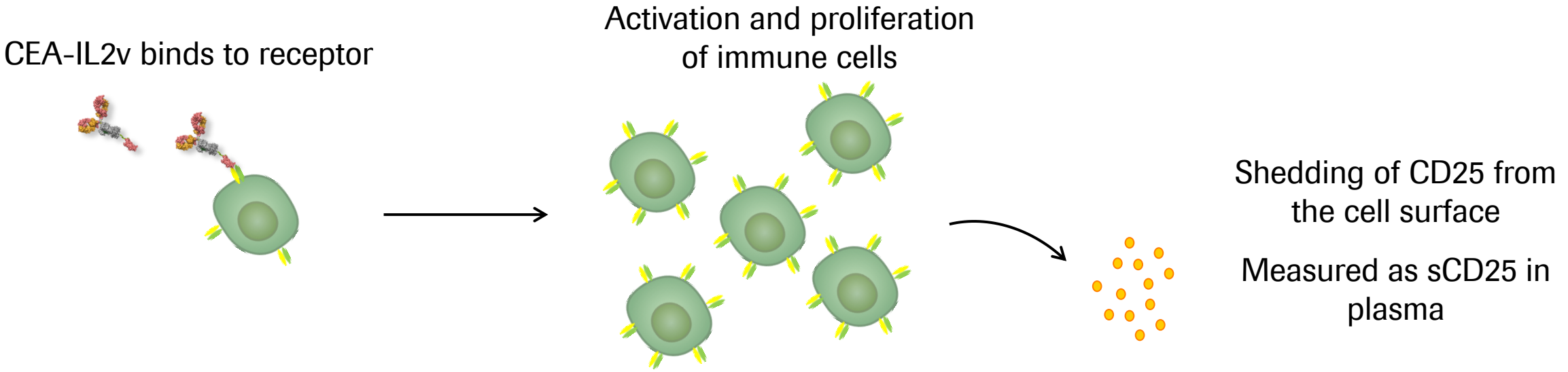
Step 1: Targeting
target specific retention of compound in the tumor

Step 2: Activation
Providing activation and proliferation signals to immune cells on site

Tumor infiltrating immune cells: Natural Killer cells, T-cells, B-cells, Macrophages

IL2v-IL2R interaction leads to immune activation and CD25 release

Amount of sCD25 in plasma is proportional to number of active immune cells

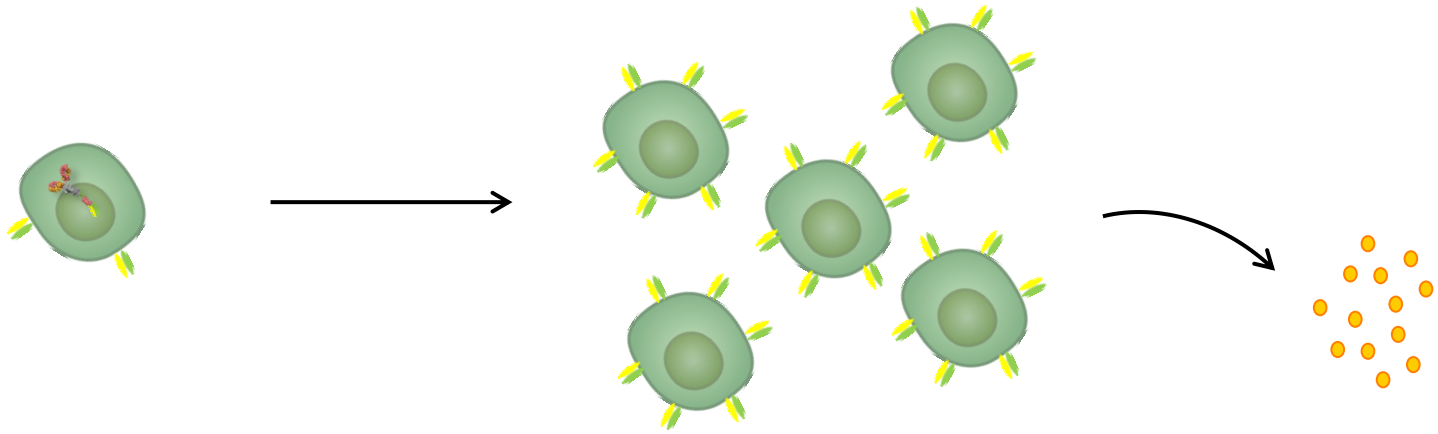


Assumption: sCD25 measured in periphery is a good reflection of immune activation in the tumor

IL2v-IL2R interaction is a pathway for drug elimination

CEA-IL2v binds to receptor

Activation and proliferation of immune cells



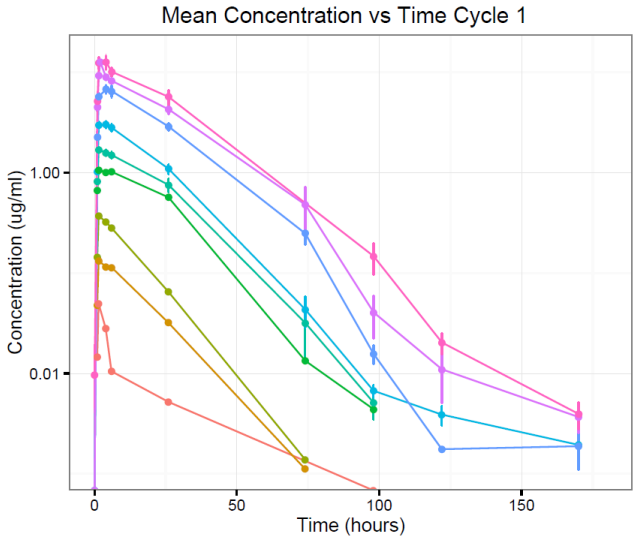
Shedding of CD25 from the cell surface

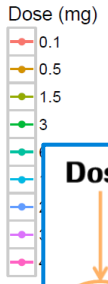
Measured as sCD25 in plasma

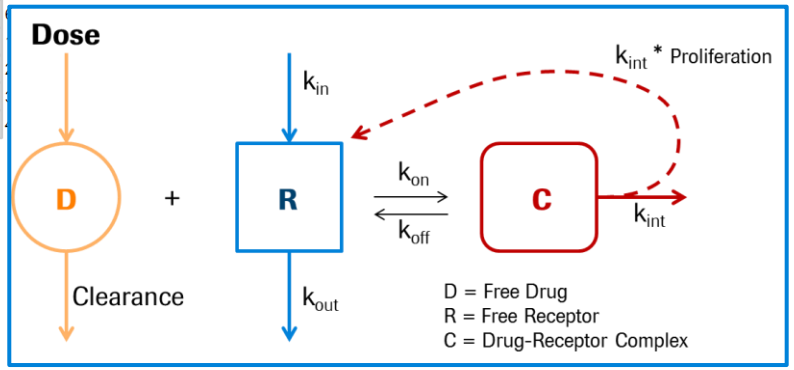
Internalization of drug-receptor complex is a pathway for elimination (TMDD)

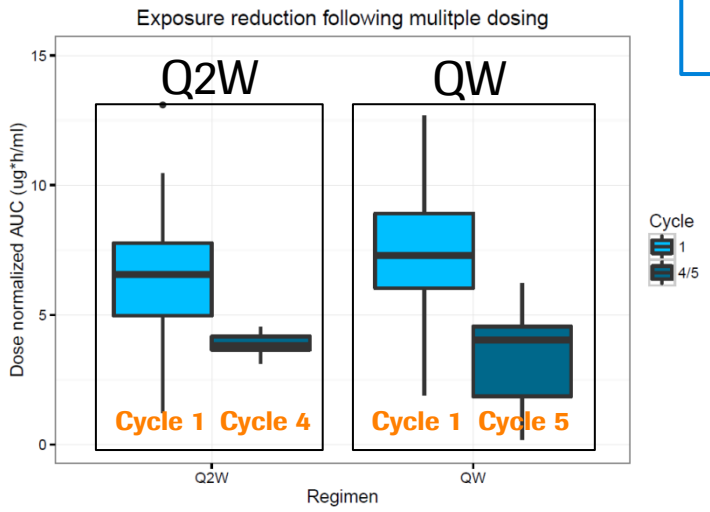
Increased cell count lead to increased elimination capacity at next drug administration

Pharmacokinetic behavior is driven by TMDD and self induced clearance which lead to exposure reduction following multiple dosing





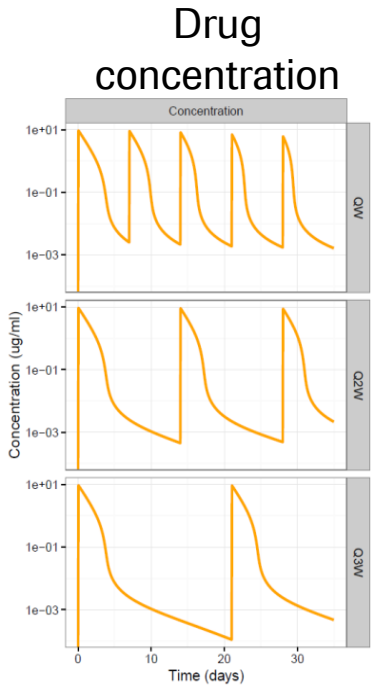


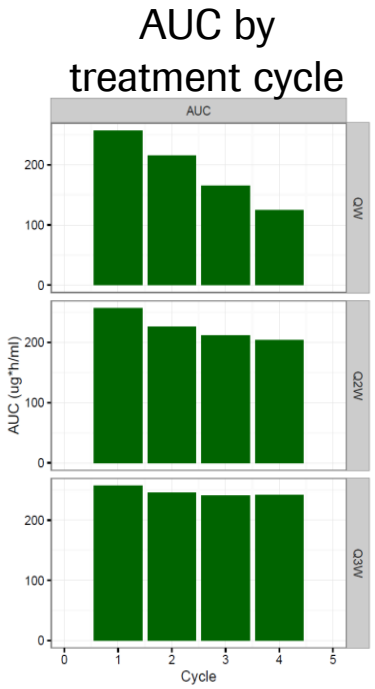


QW

Q2W

Q3W





↑ Dose

↑ Frequency

→ ↑ Exposure reduction

PK work was presented by H.P. Grimm et al @ PAGE 2016 and by H.E. Silber Baumann et al @ PAGE 2017

Team challenge and motivation for analysis

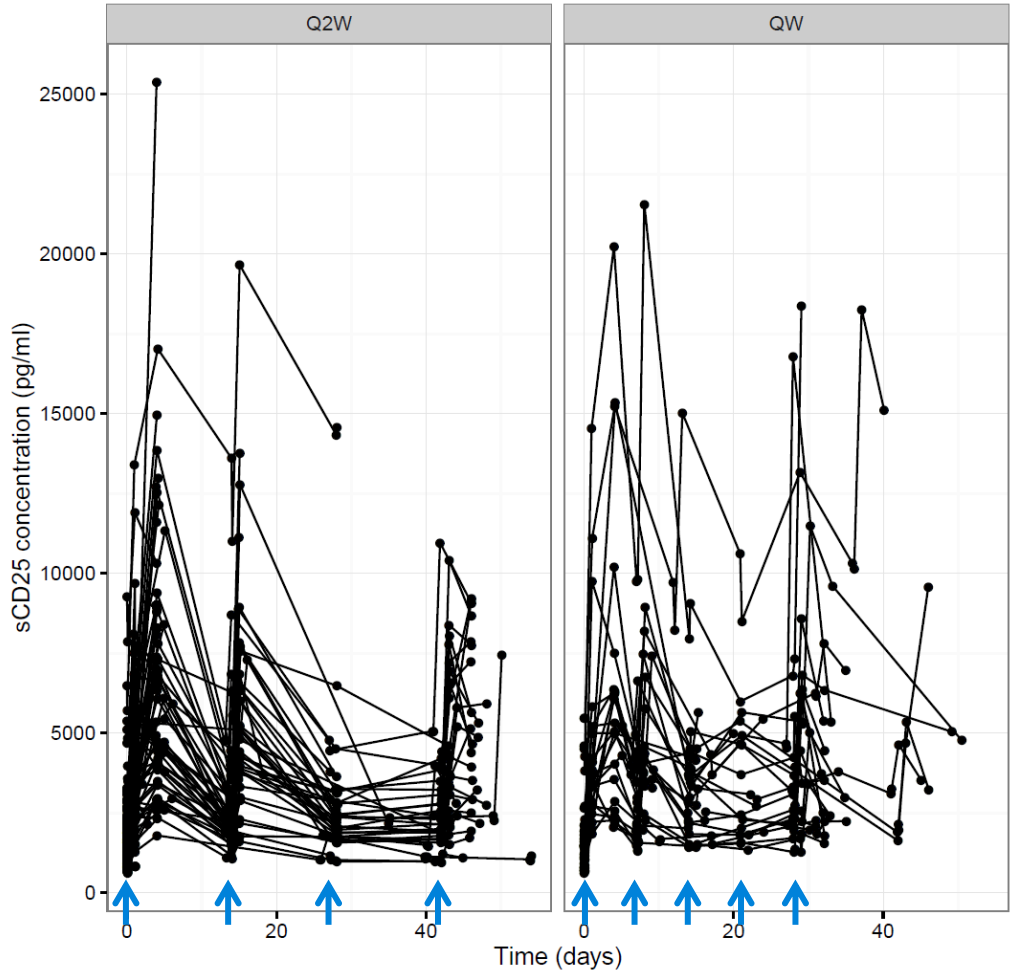
- Objective
  - To quantify the concentration-effect relationship of CEA-IL2v on sCD25
  - To support optimization of the dosing regimen of CEA-IL2v by investigating the impact of alternative dosing regimens on sCD25 through simulations

- Challenge for understanding concentration-effect relationship
  - Non-linear PK
  - Heterogeneous data

⇨ Population PKPD analysis provides a powerful methodology to analyze the full set of data while accounting for the actual dosing history and non-linearity in PK

sCD25 concentration-time data was collected from an EIH dose escalation trial in mixed population of solid tumors

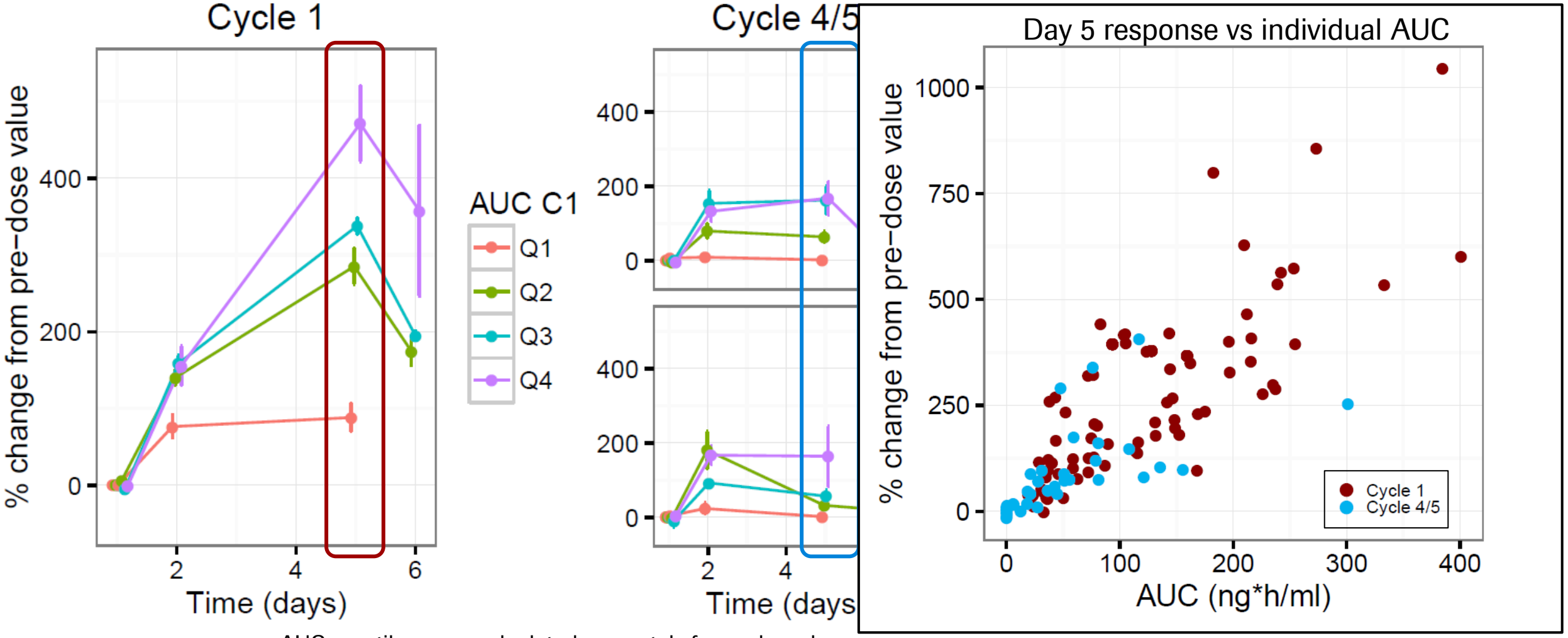
sCD25 was measured up to 4 or 5 treatment cycles



- 106 patients
- Mixed regimens
  - weekly (QW) or bi-weekly (Q2W)
  - Intra-patient up-titration
- Doses 6-40 mg

An exposure-response relationship could be identified over multiple treatment cycles

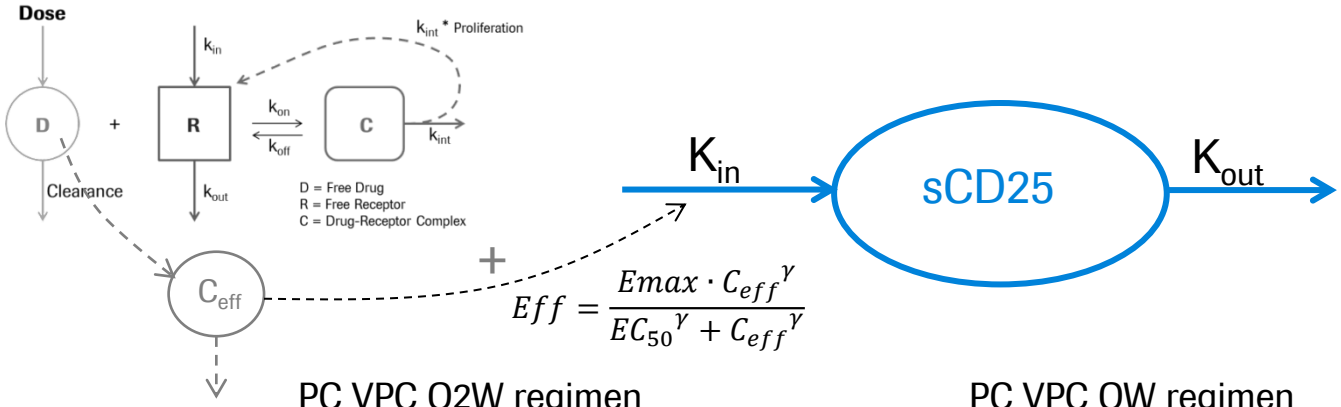
Smaller effect was observed at later cycles, likely due to reduced exposure

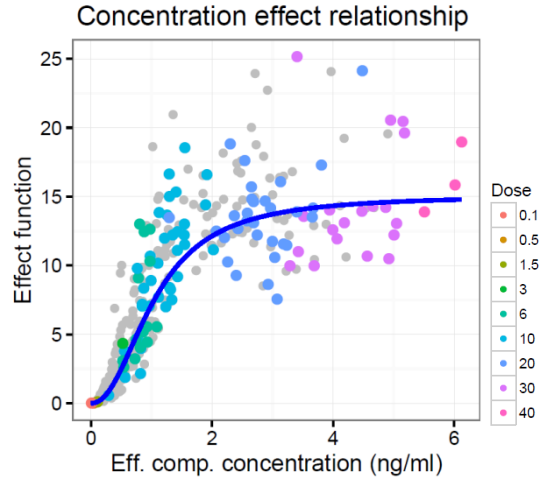


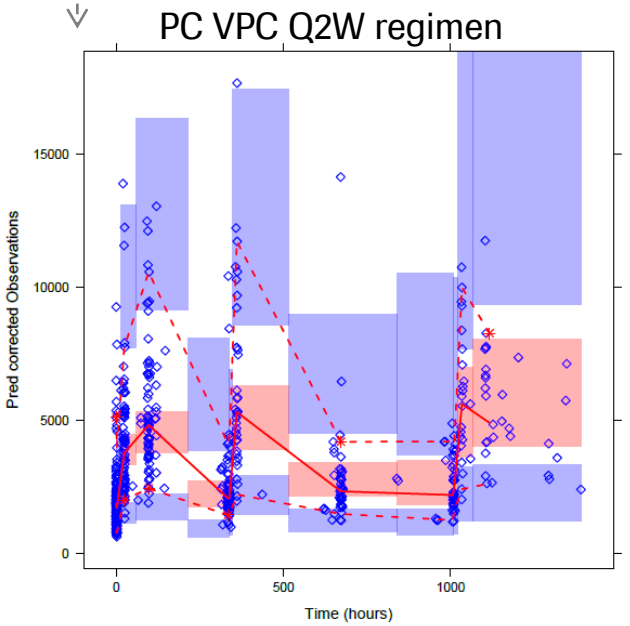
AUC quartiles were calculated separately for each cycle

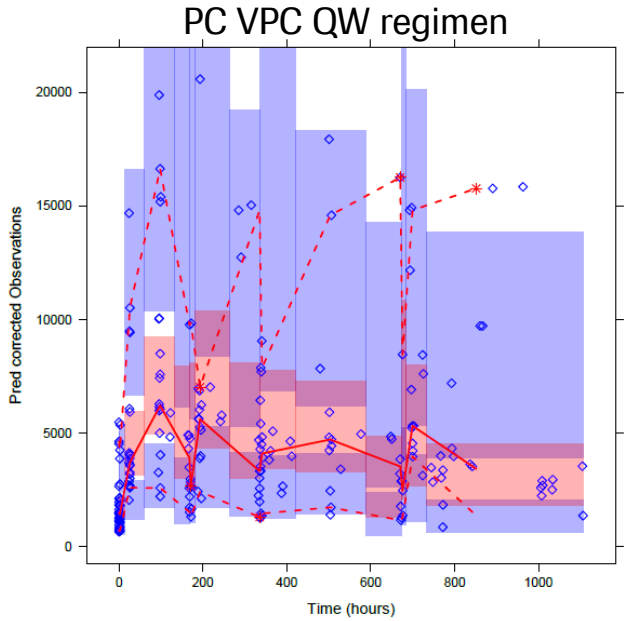
An indirect response model with a drug effect on sCD25 production was used to describe the PKPD relationship

The PKPD relationship remain constant, confirming that the drop in effect after multiple dose is driven by the drop in exposure





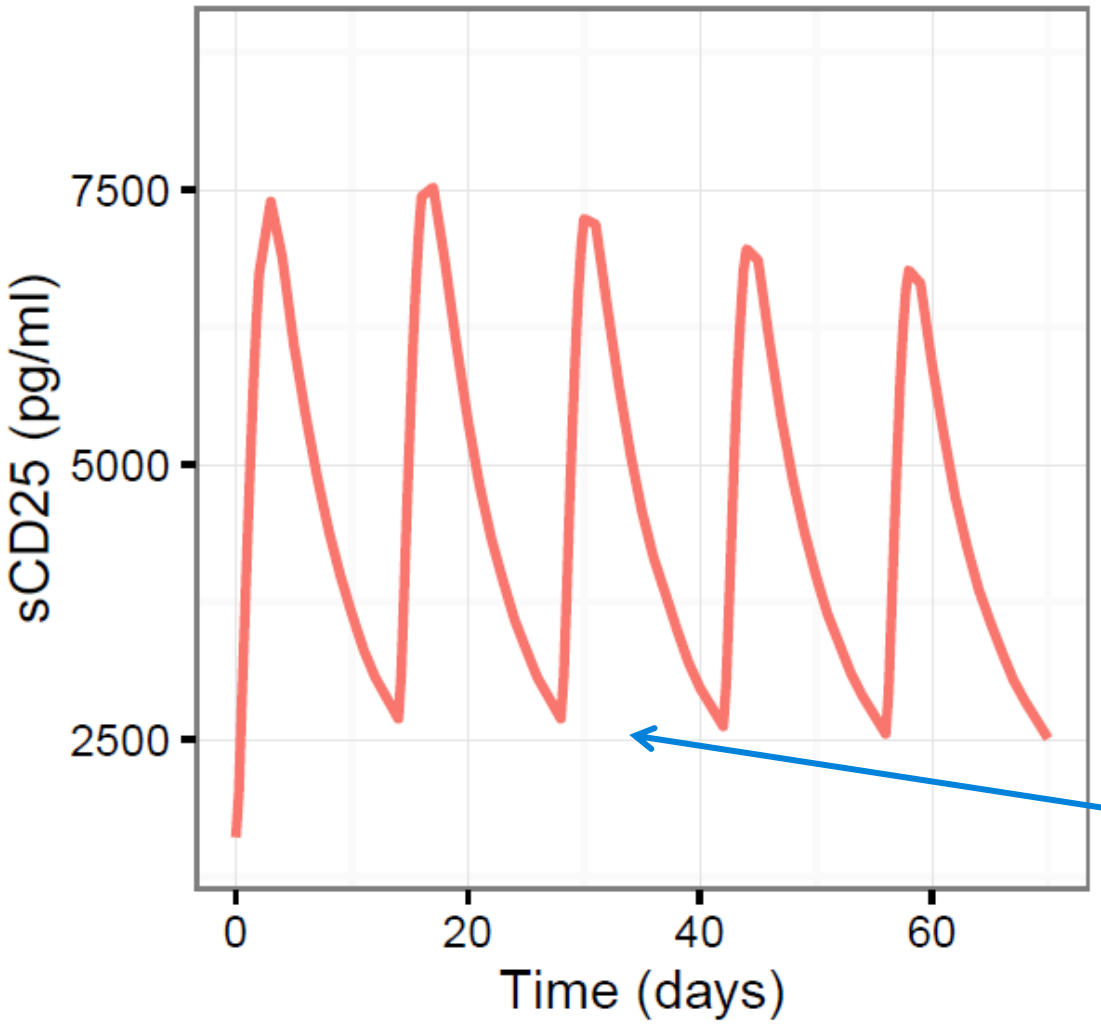




Parameter	Population value (RSE%)	IIV % (RSE%)
CD25 Baseline (pg/ml)	1720 (5)	49 (14)
Kout (/h)	0.0067 (5)	33 (22)
Emax (-)	15.1 (5)	27 (50)
EC50 (ng/ml)	1.05 (6)	32 (50)
Ke (/h)	0.09 (7)	60 (20)
γ (-)	2.2 (4)	-
CD25bl on Emax (-)	-0.42 (24)	-
Proportional error (%)	17 (3)	-

Administration frequency and non-linear PK affects sCD25 profiles

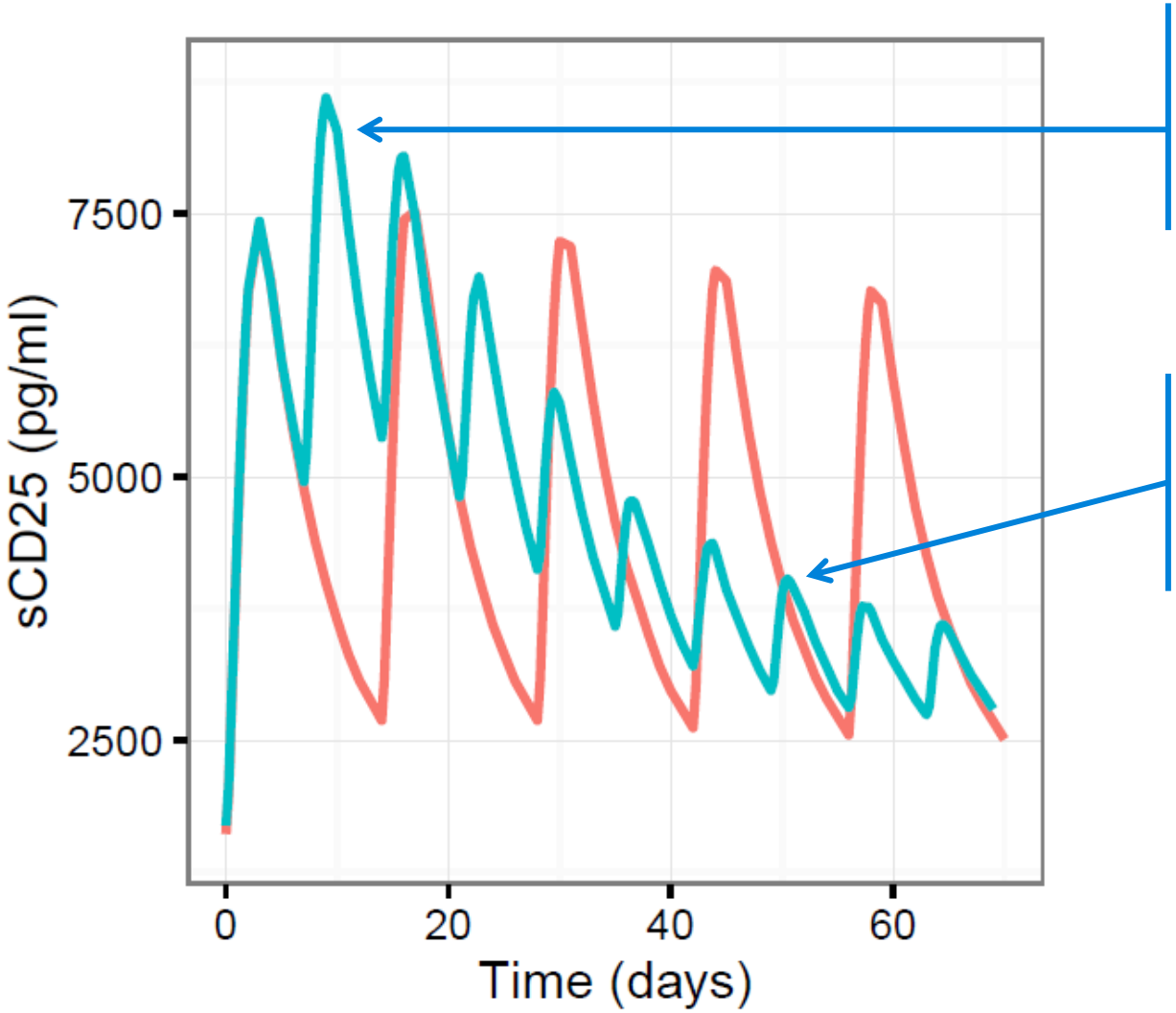
The PKPD relationship is the same for the QW and Q2W regimens



With a Q2W regimen, a new steady-state is reached within a few treatment cycles

Administration frequency and non-linear PK affects sCD25 profiles

The PKPD relationship is the same for the QW and Q2W regimens

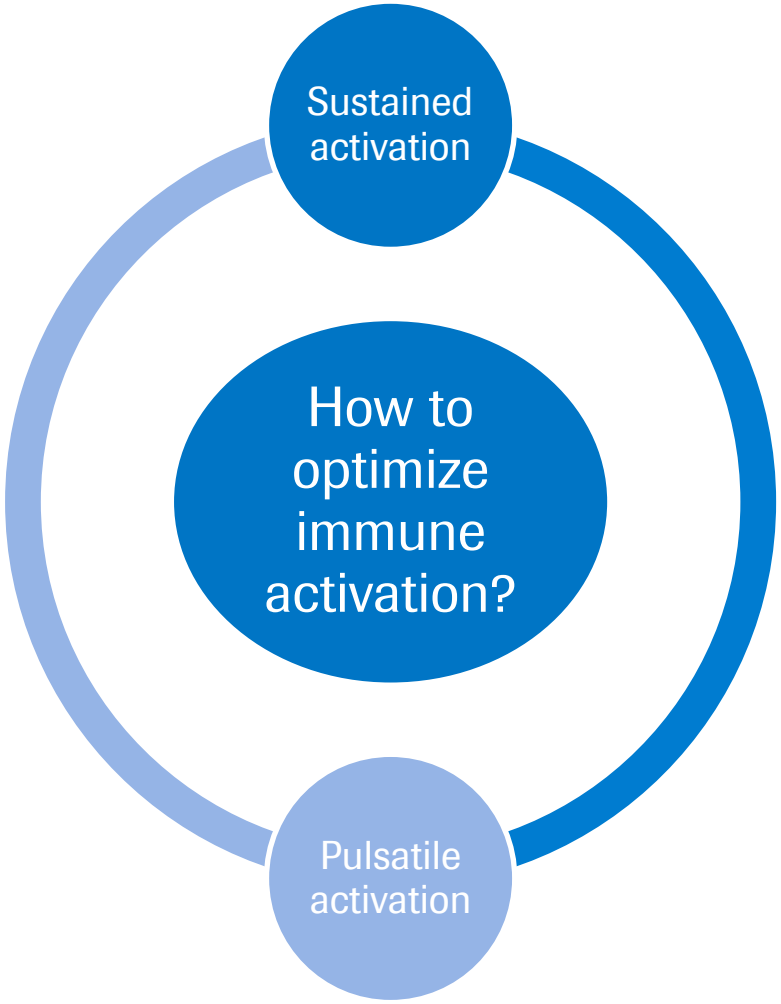


QW regimen initially leads to higher accumulation

Non-linear PK results in lower plasma concentrations and smaller effect as a result

Different dosing strategies to optimize immune activation

Induction/maintenance (QW -> Q2W) v.s. Q3W



Sustained activation – frequent dosing (QW -> Q2W)

+ Initial strong activation

+ Predicted increased accumulation within the tumor micro-environment

- Cannot be maintained without multiple dose up-titration due to non-linear PK

- Must reduce dosing frequency due to tolerability

Pulsatile activation – less frequent dosing (Q3W)

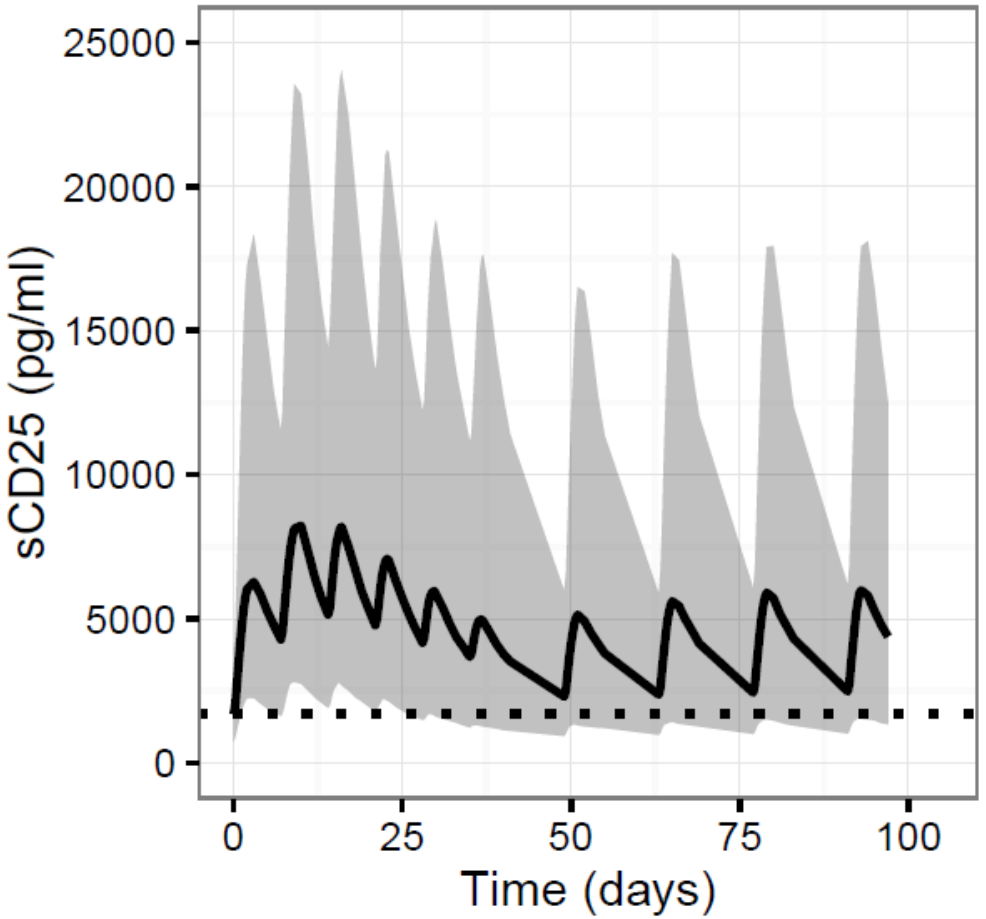
+ Repeated activation with maintained magnitude, small impact of non-linear PK

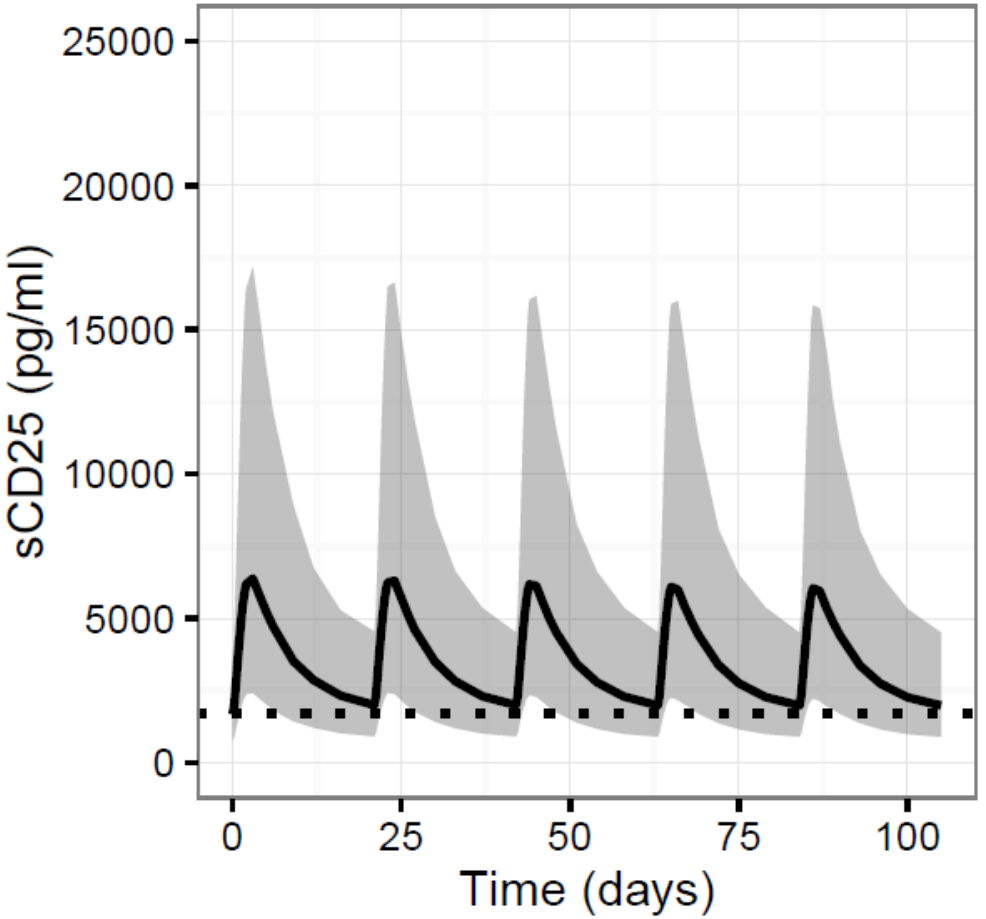
+ Convenient

- Predicted limited accumulation within tumor micro-environment

The simulations indicate a clear difference in the impact of the schedule on IL-2R engagement

Not clear if this translates into differential efficacy





Conclusions

- An indirect response model was found to describe the observed concentration-time profile of sCD25 well
  - CEA-IL2v PK with a delay (effect compartment) was used to provide a drug effect on sCD25 production
- Reduced response with time was found to be due to non-linear PK and was more pronounced with a weekly regimen compared to bi-weekly regimen
- Simulations of alternative regimens were performed to investigate an induction-maintenance regimen and a 3-weekly regimen as alternatives that may be tolerable to patients while providing meaningful immune activation

Acknowledgment

- Nicolas Frey
- Alexander Phipps
- Richard Peck
- Lucy Hutchinson
- Benjamin Ribba
- Daniel Dejardin
- Stefan Evers
- Hans Peter Grimm

Thank you for listening!

Doing now what patients need next