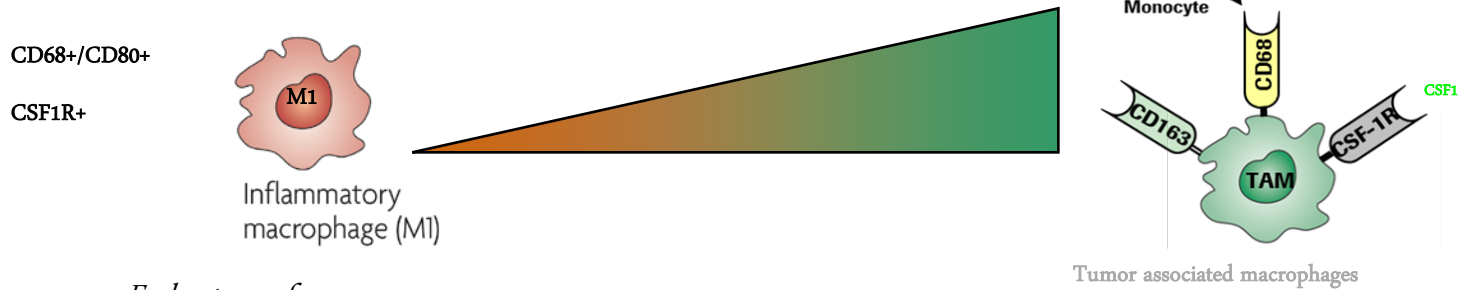# Shifting the MTD paradigm in Oncology

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Roche
pRED
Oncology

MabCSF-1R

Macrophages (MΦ) are Polarized during Tumorigenesis

Tumors recruit MΦ and induce M2-subtype

by secreting CSF-1 and immunosuppressive cytokines

CD68+/CD80+

CSF1R+

M1

Inflammatory
macrophage (M1)

Monocyte

IL-4 or
IL-10

CD68

CD163

CSF-1R

CSF1

TAM

Tumor associated macrophages

Early stage of cancer:

M1-MΦ subtype dominates

- Phagocytosis

- Antigen presenting

- Defense against pathogen

Invasive carcinoma:

M2-MΦ subtype dominates

- Tissue repair

- Tissue remodeling

- Immunoregulation
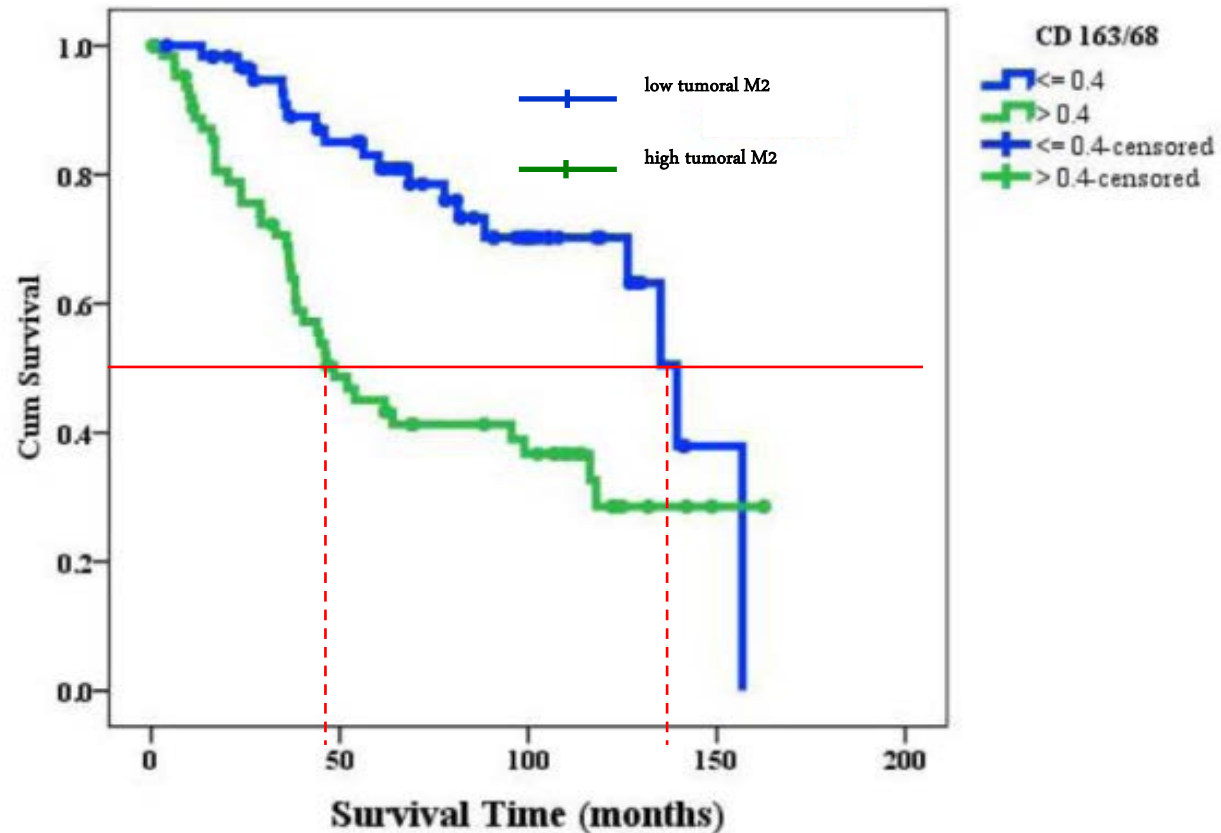
*adapted from Pollard Nat Rev. Immunol. 2009

M2 MΦ Correlation with Prognosis

High M2-MΦ infiltration correlates with poor prognosis

- HER2+ Breast cancer [5]

- Ovarian cancer [4]

- Pancreatic cancer [3]

- Glioma [6]

- Hepatocellular carcinoma [7]

Overall survival in breast cancer

1) Ma BMC Cancer 2010, 2) Al-Shibli Histopathology 2009 3) Kurahara J Surg Res 2009

4) Kawamura Pathol Int 2009 5) Nanda SABCS 2009 6) Komohara J Pathol 2008 7) Jia Oncologist 2010

MabCSF-1R: Clinical Ph1/Ph1b study design

Challenging the MTD paradigm in clinical oncology studies

Dose escalation study - *Monotherapy & combination with paclitaxel*

- **100 mg run-in dose, followed by biweekly (Q2W) therapeutic dosing strategy**
  - *100 mg run in to characterise Target Mediated Drug Disposition (TMDD)*
    - *use TMDD to inform on optimal doses.*

Dose escalation

3,000 mg

2,000 mg (4)

1,350 mg (5)

900 mg (3)

600 mg

400 mg

200 mg

100 mg
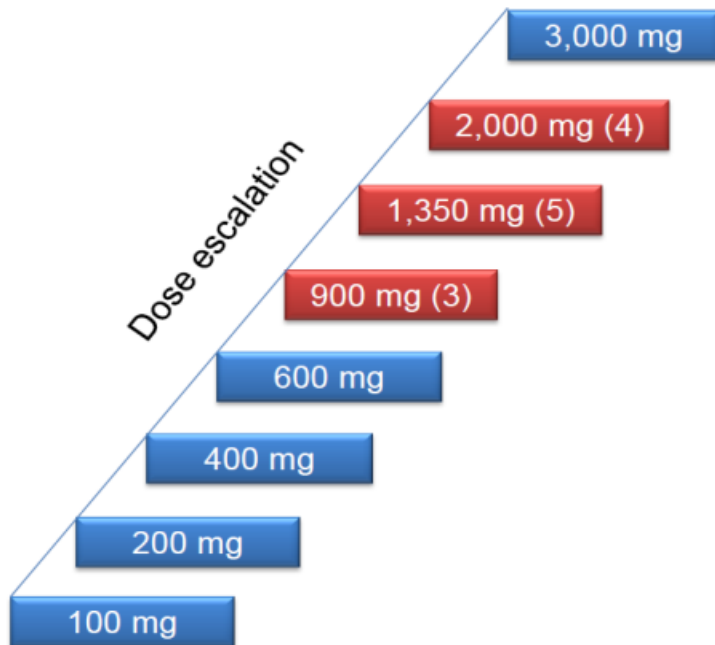
No SAE or Dose limiting toxicities reported

MTD not achieved!

Planned 4500 mg

Is such a high dose necessary?

Could biomarker & exposure data steer us towards an optimal dose?

MabCSF-1R: Clinical Ph1 study design

- Data existed from a number of investigational biomarkers:

  - Skin surrogate macrophages (pre-treatment and C2D1)

    - CSF1R +ve

    - CD163+ve

  - Circulating 'activated' monocytes (pre-cursor to macrophages)

    - Time course

  - Tumour Associated Macrophages (TAM)

    - Paired biopsy data

      - Pre-treatment

      - After 2 cycles of treatment (C3D1)

  - Pharmacokinetics

    - Time course

Pharmacokinetics

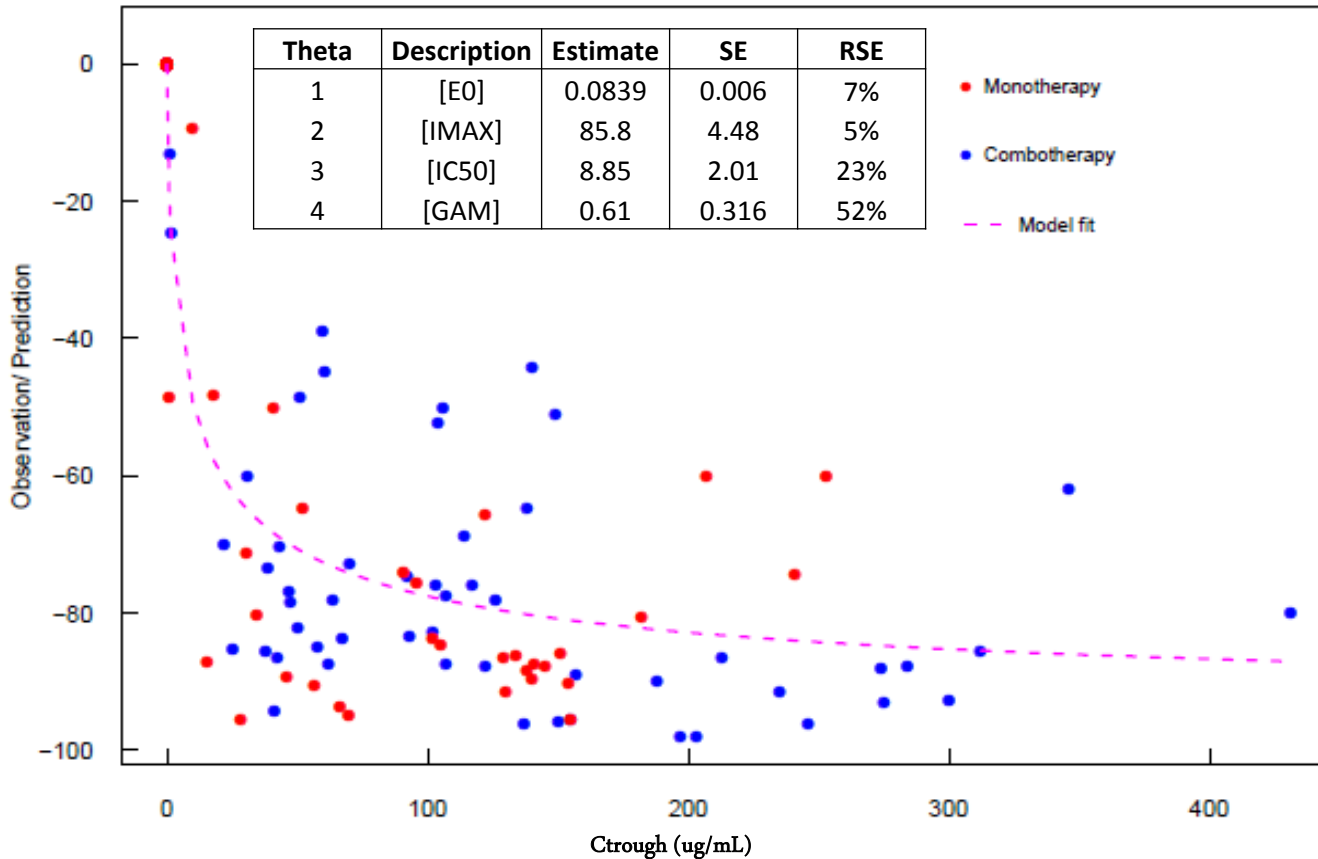- 2 compartment PK model with saturable and non-saturable elimination (TMDD)

Observed and model predicted concentrations
following repeated IV administration [Q2W]
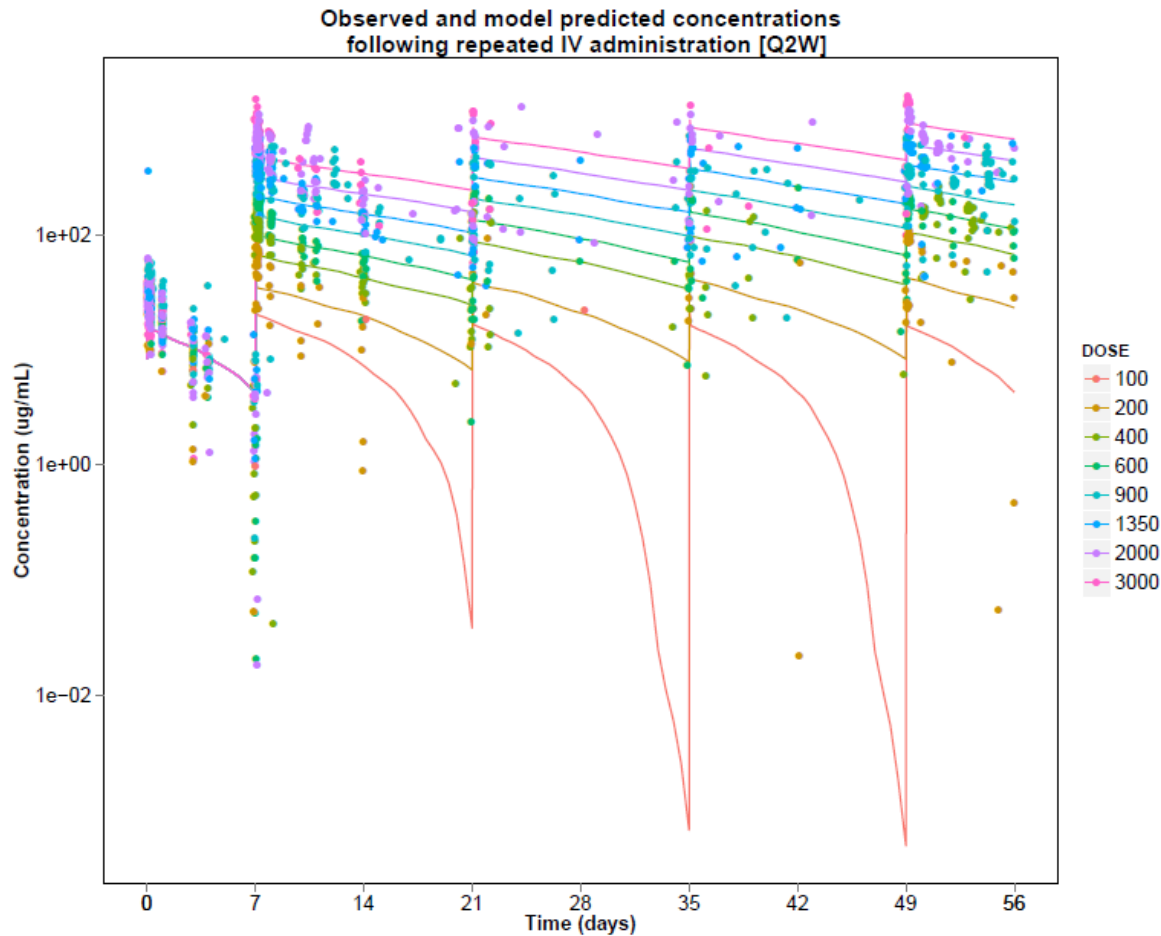
- Clear non-linearity during 100 mg run-in

- Above 900 mg Q2W, concentrations high enough to saturate TMDD
  - Linear PK

Parameter	Estimate	SE	RSE
[CL] (L/h)	0.0105	0.0006	6%
[VM] ((ug/mL)/h)	0.340	0.0241	7%
[KM] (ug/mL)	0.461	0.178	39%

Dose (mg)	t1/2 (h)
100	37
200	122
400	155
600	148
900	189
1350	193
2000	187
3000	190

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Skin surrogate macrophages

Change from baseline CD163+ macrophages with exposure in Mono and Combotherapy

Theta	Description	Estimate	SE	RSE
1	[E0]	0.0839	0.006	7%
2	[IMAX]	85.8	4.48	5%
3	[IC50]	8.85	2.01	23%
4	[GAM]	0.61	0.316	52%

- Monotherapy
- Combotherapy
- - - Model fit

y-axis: Observation/ Prediction — 0, -20, -40, -60, -80, -100

x-axis: Ctrough (ug/mL) — 0, 100, 200, 300, 400

- Exploration of reduction in skin macrophages (C2D1) v pre-dose drug level (Ctrough)

  - AUC and Cav were also used as independent variable

- Estimated IC90 is ~320 ug /mL

  - Lowest dose which affords cover is 900 mg Q2W

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Circulating activated monocytes

Activated monocyte levels following IV administration of MabCSF1R [Q2W]
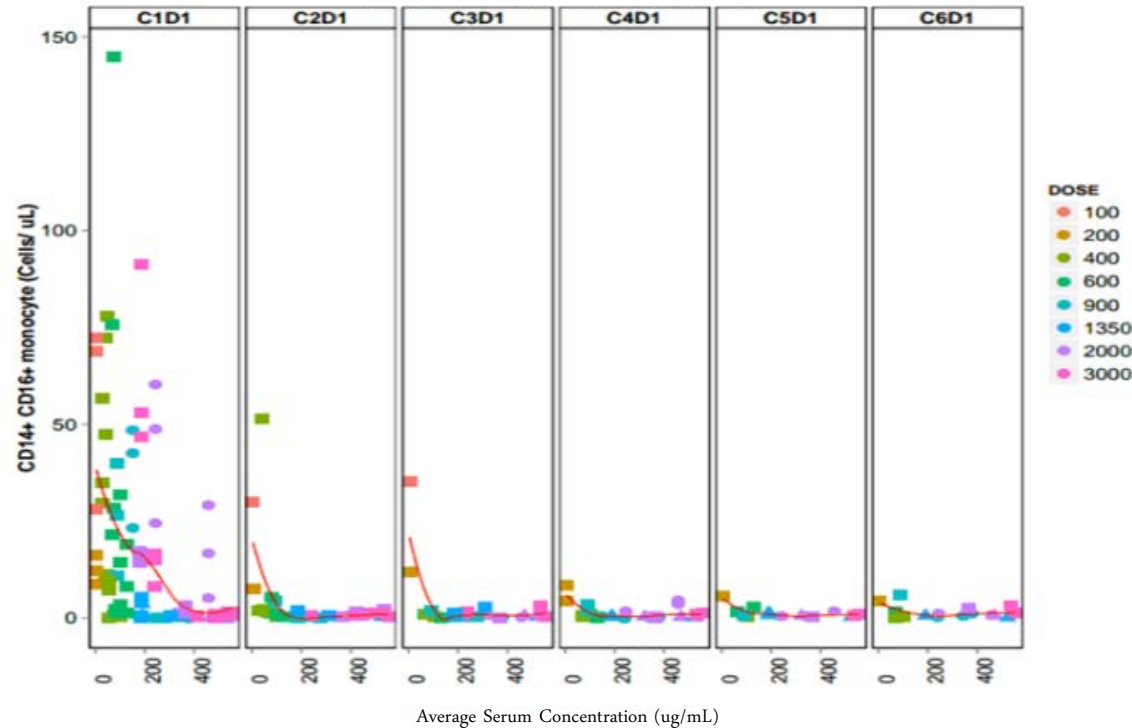
- Marked reduction in activated monocytes with increasing average concentration, Ctrough or AUC.

- Depleted at beginning of the second cycle

  – No recovery at doses > 200mg

- Plateau appear to be reached at doses $\geq$ 400 mg Q2W

- Explored relationship of reduction in monocytes with concentration, exposure and dose

Biomarker efficacy linked to PK

- What level of saturation of TMDD component optimal for efficacy?

CSF1R+ Macrophage levels following IV administration

% Target Saturation

NB: different x-axes
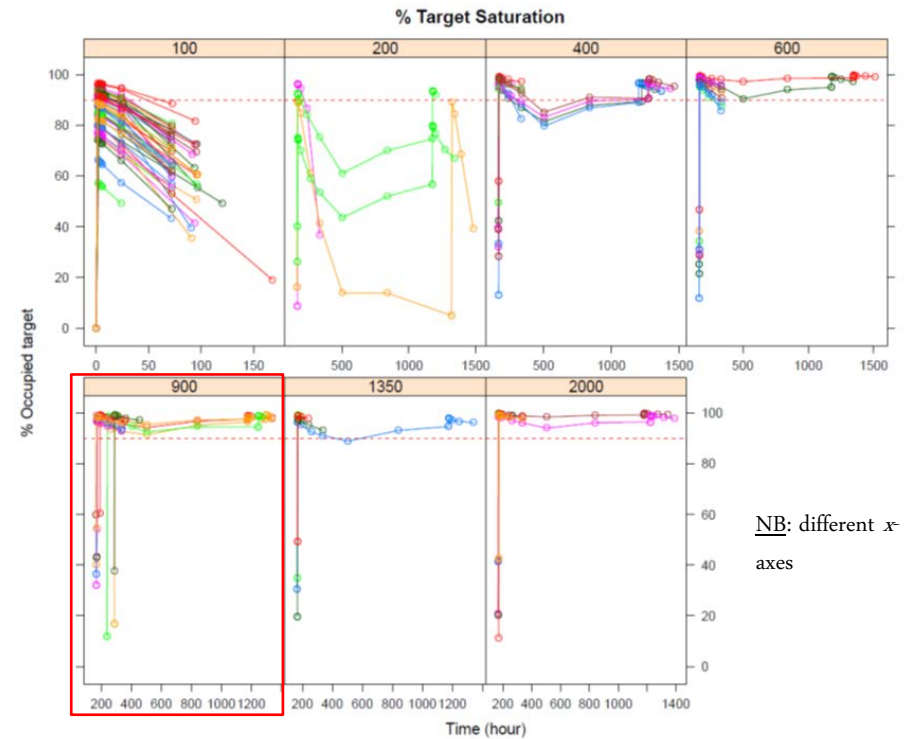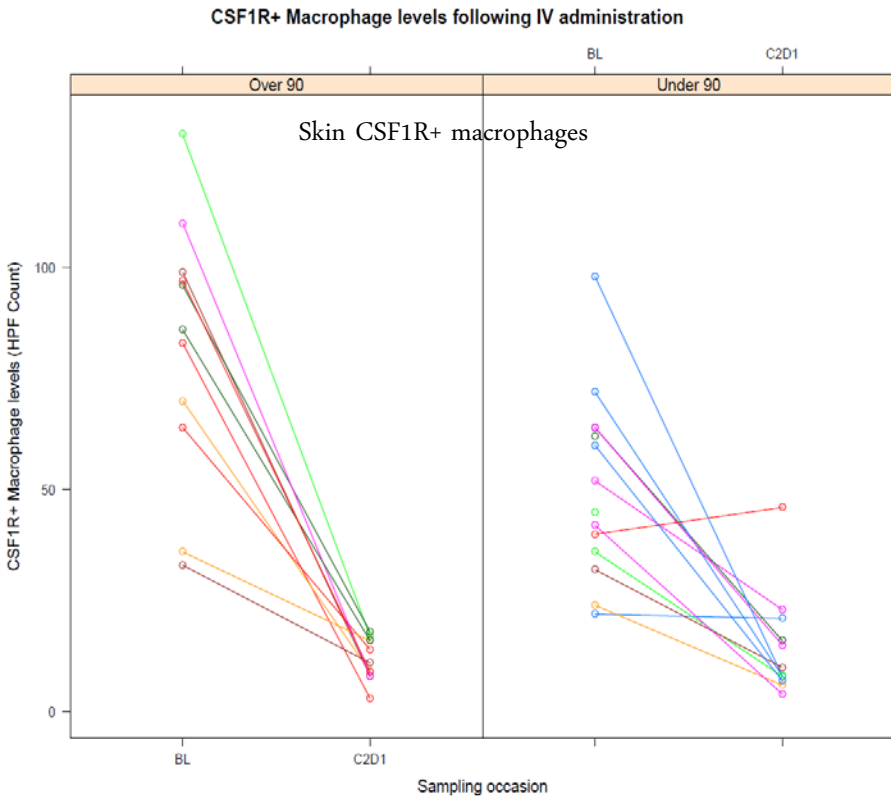
- Over 90% saturation, the reduction in macrophages and activated monocytes is close to maximal – no further decrease with >95% saturation

- A dose of ~900 mg Q2W is needed to ensure adequate saturation levels throughout dose cycle

Tumor associated macrophages

Macrophage area coverage following IV administration [Q2W]
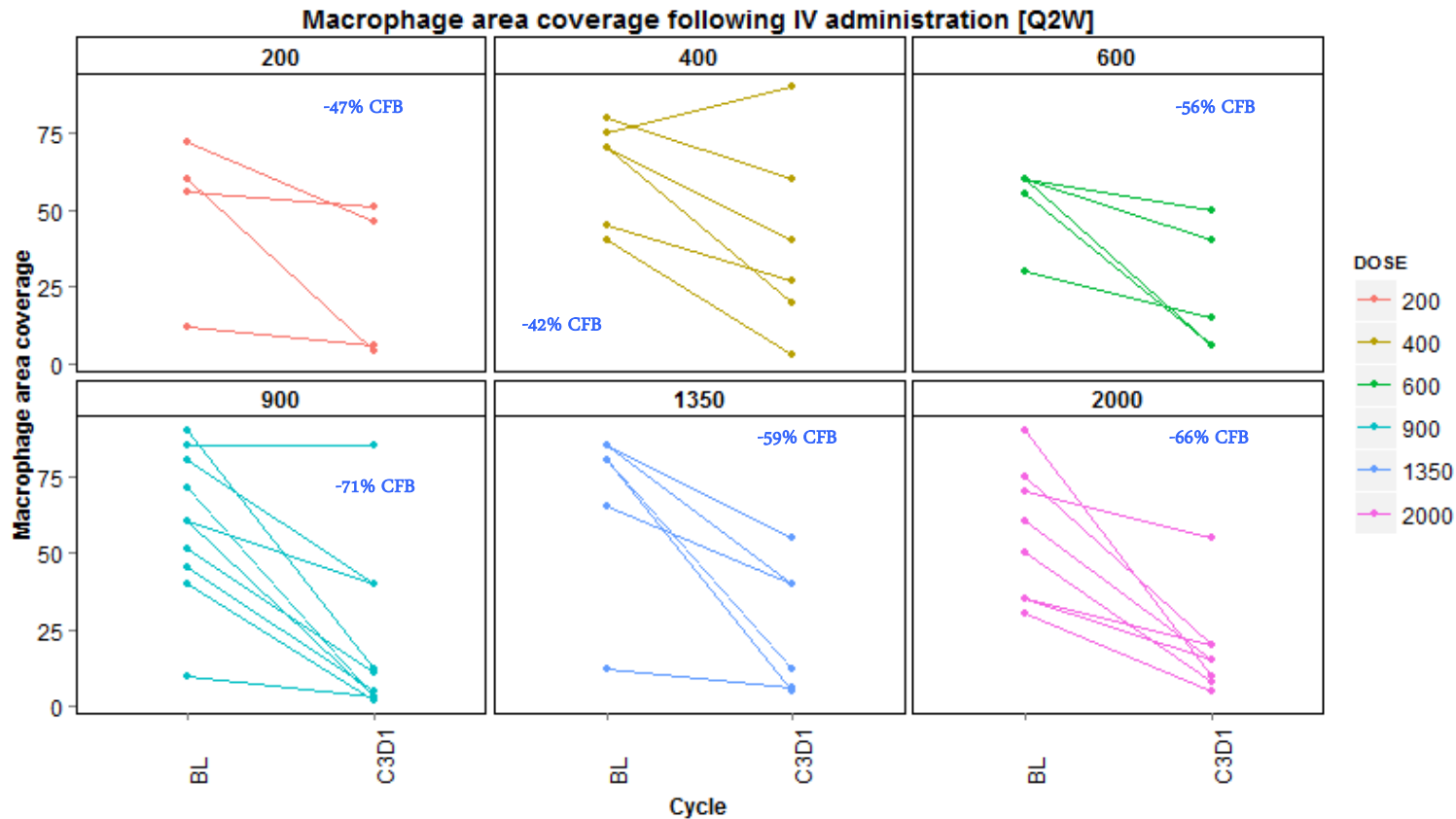
- Overall, 38/40 patients (95%) showed a decrease in levels of TAM between pre-treatment and C3D1

  – Mean -56% CFB (range +20 - -96%)

- No apparent relationship to dose, or to saturation of TMDD.

  – Timing of C3D1 sample.

MabCSF-1R: summary

- We employed a combination of modeling & simulation and pharmacology to show that the optimal dose of MabCSF-1R for efficacy was 3- to 4.5-fold lower than the proposed MTD.

- This was based upon:

  - Reduction in surrogate skin macrophage markers

  - Reduction in circulating activated monocytes

  - Reduction in tumour associated M2 macrophages

  - Saturation of target mediated drug disposition

  - All suggest maximal effect is observed with doses of $\geq$900 mg Q2W

- As a result, a dose of 1000 mg Q2W is now employed in the clinic

- This demonstrates a move away from the MTD paradigm in favour of a PKPD based approach to dose selection.
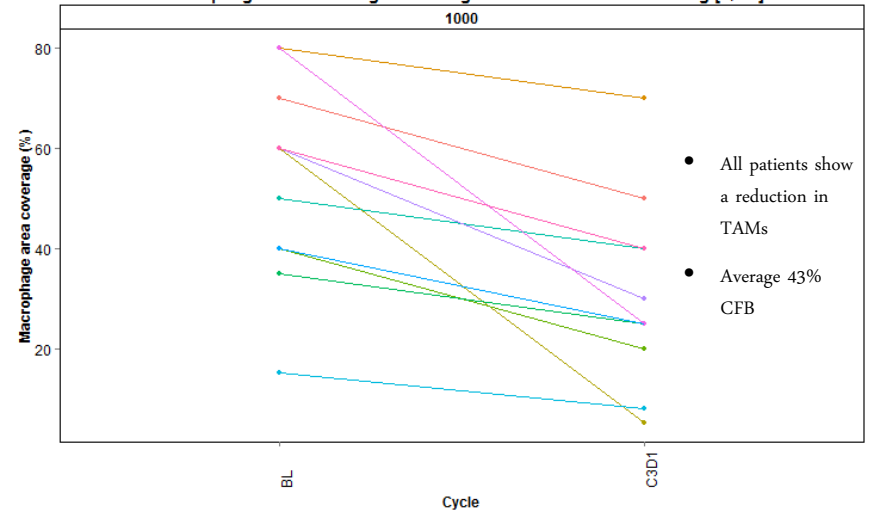
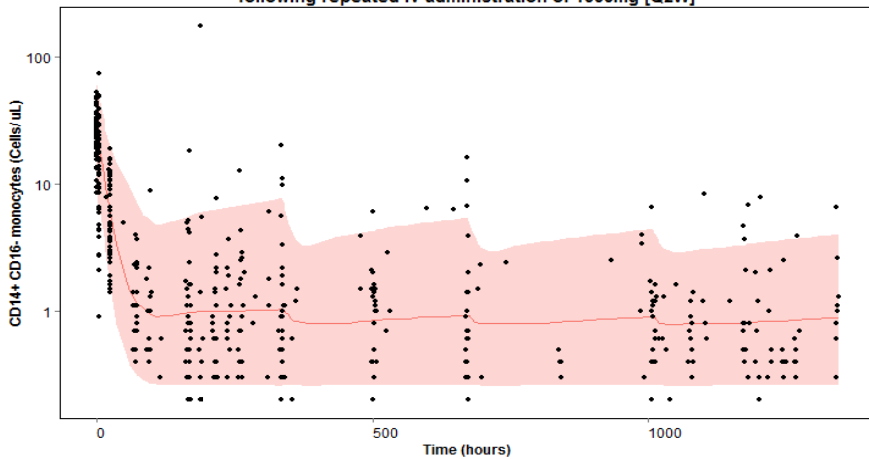# Was it successful?

- Did the 1000 mg Q2W dose work?

Observed and predicted concentrations of following repeated IV administration [Q2W]
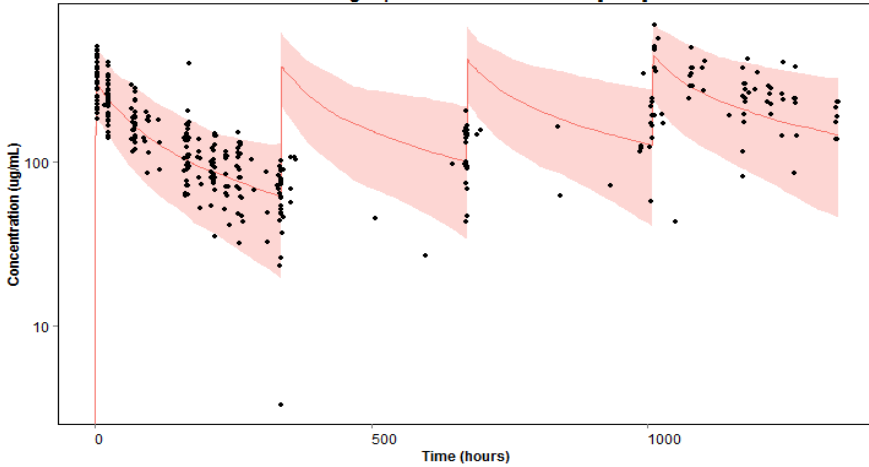
Macrophage area coverage following IV administration of 1000 mg [Q2W]

- All patients show a reduction in TAMs
- Average 43% CFB

Observed and predicted levels of CD14+ CD16- monocytes following repeated IV administration of 1000mg [Q2W]

Acknowledgements

Doing now what patients need next