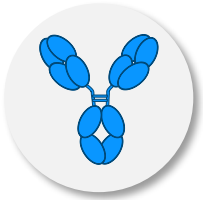
Target-response relationship of bevacizumab may be more relevant than exposure-response: a Target-Mediated Drug Disposition model

Sarah Lobet[1], Morgane Caulet[2], Nicolas Azzopardi[3], Gilles Paintaud[4,5], Thierry Lecomte[1,2], David Ternant[4,5]

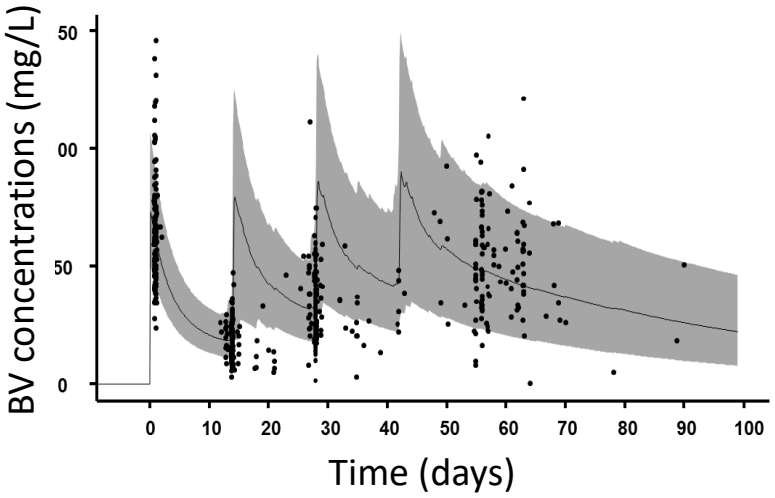
[1]*Tours University, Inserm UMR 1069, Nutrition Croissance et Cancer (N2C), France*
[2]*Tours University Hospital, Department of Gastroenterology and Digestive Oncology, France*
[3]*Tours University, EA7501 GICC, France*
[4]*Tours University Hospital, Department of clinical pharmacology, France*
[5]*Tours University, EA4245 Transplantation, Immunologie, Inflammation (T2i), France*

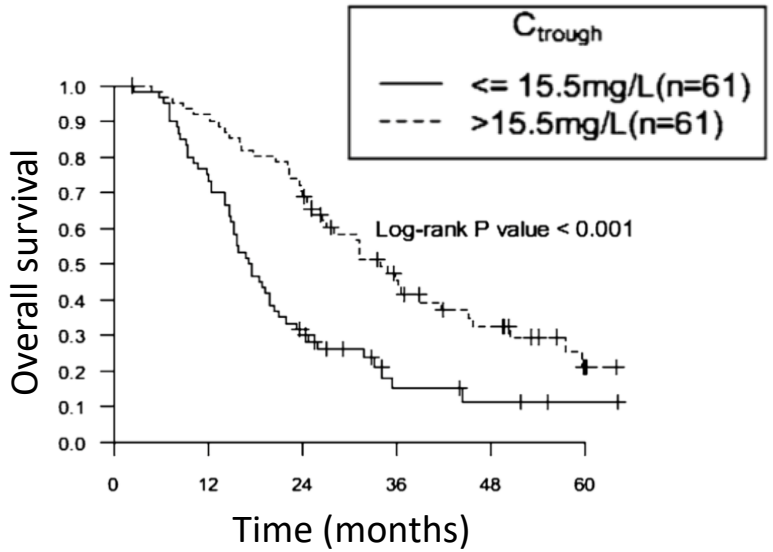
Contact: sarah.lobet@univ-tours.fr

Bevacizumab



- anti-VEGF monoclonal antibody
- first-line treatment in metastatic colorectal cancer





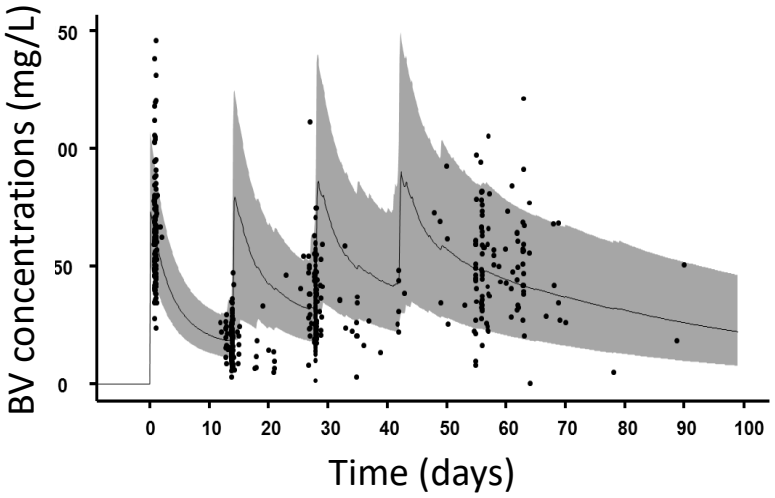
Caulet, 2016

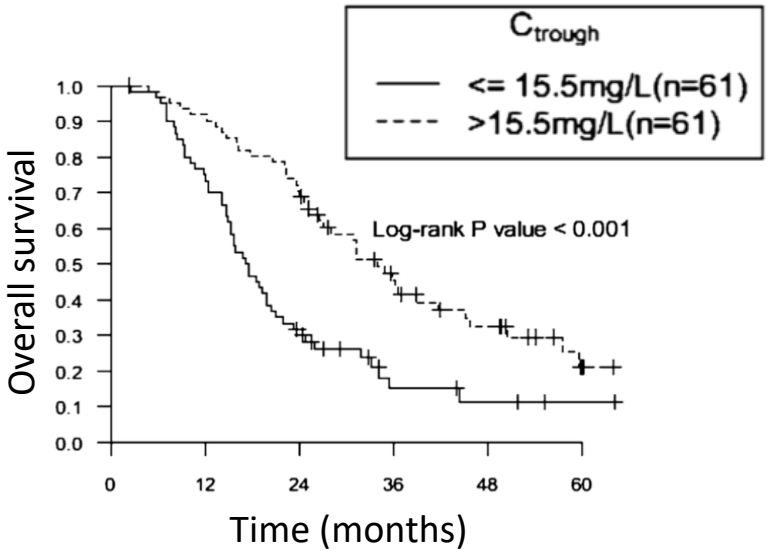
High PK interindividual variability

↗ BV Concentration ⇨ ↗ Survival

VEGF = vascular endothelial growth factor

Bevacizumab exposure-survival relationship questioned

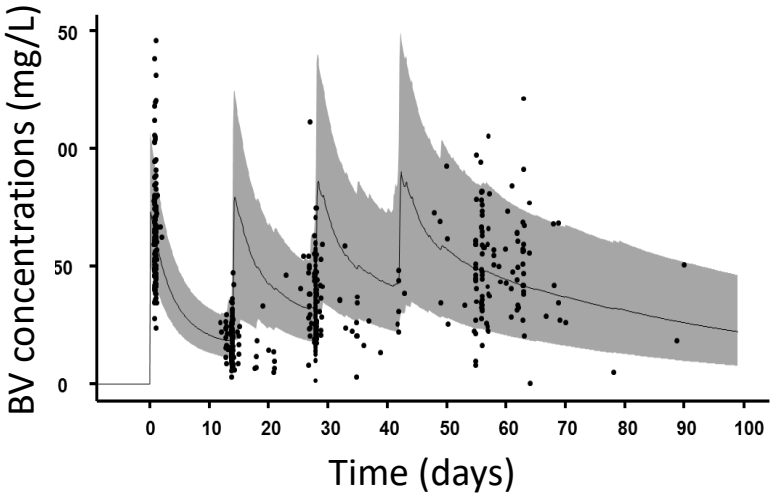




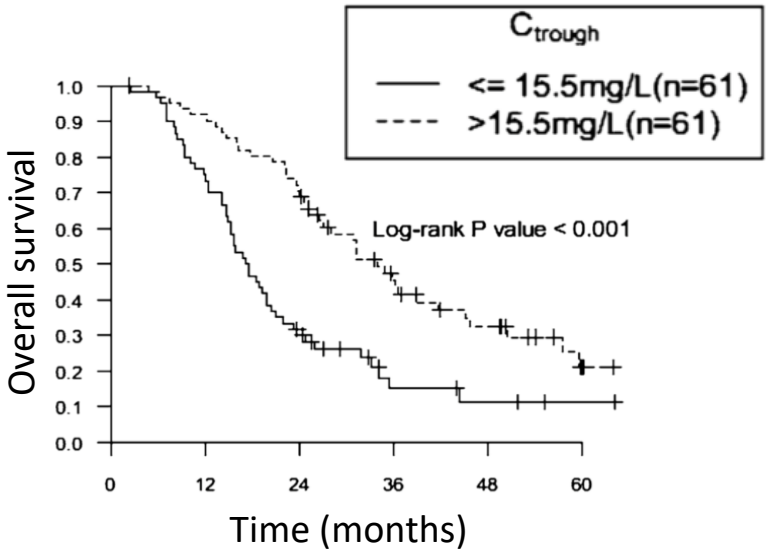
Ref.	Patients	Cancer	Relationship
Lu, 2008	491	Various	✗
Caulet, 2016	130	mCRC	✓
Akbulut, 2018	88	mCRC	✓
Papachristos, 2020	46	mCRC	✓
Peña-Cabia, 2021	28	mCRC	✗

Bevacizumab exposure-survival relationship questioned

Dose → BV concentration → Survival



?



Several confounding factors

- Tumor burden ↗
- Protein consumption (cachexia)

⇨ CL ↗

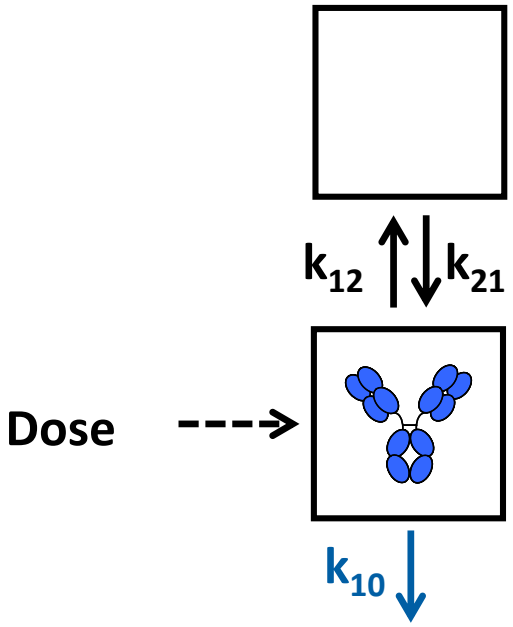
⇨ mAb «consumption»↗

Wangs, 2017; Kawakatsu, 2021; Dai, 2020; Chatelut, 2020

Bevacizumab pharmacokinetics

Endogenous elimination

Target-mediated elimination

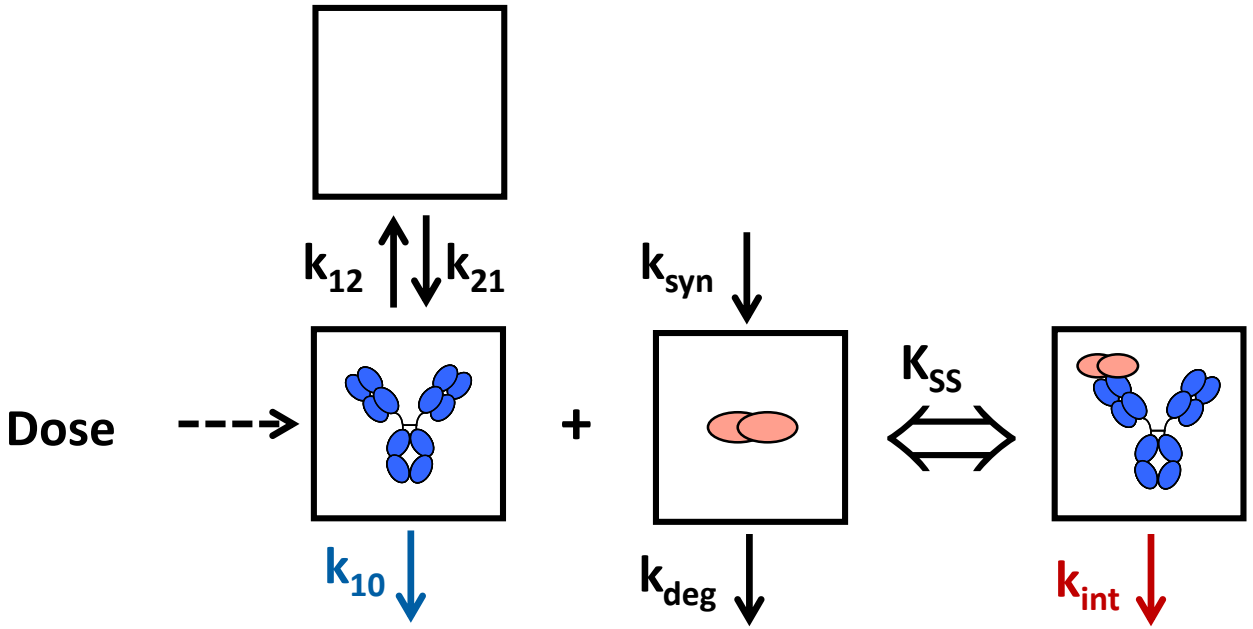


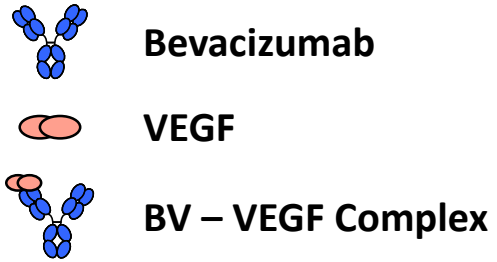
Bevacizumab

Bevacizumab pharmacokinetics

Endogenous elimination

Target-mediated elimination

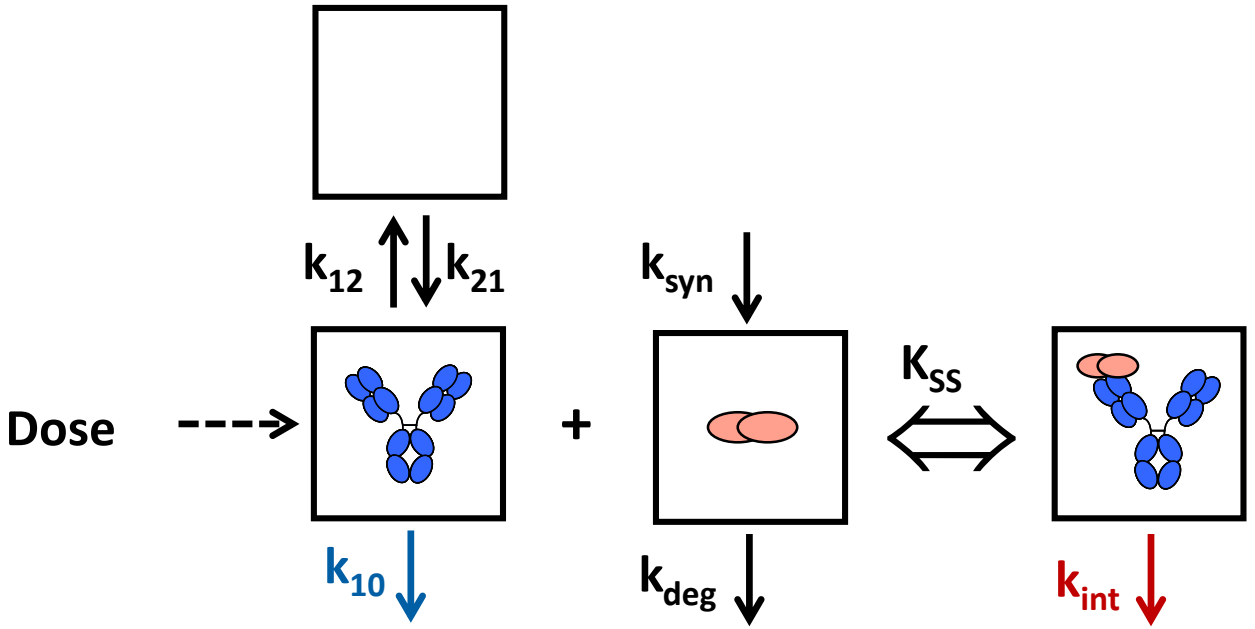


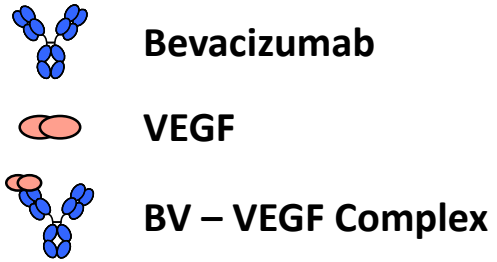


Bevacizumab pharmacokinetics

Endogenous elimination

Target-mediated elimination





↗ **Target-mediated elimination:**

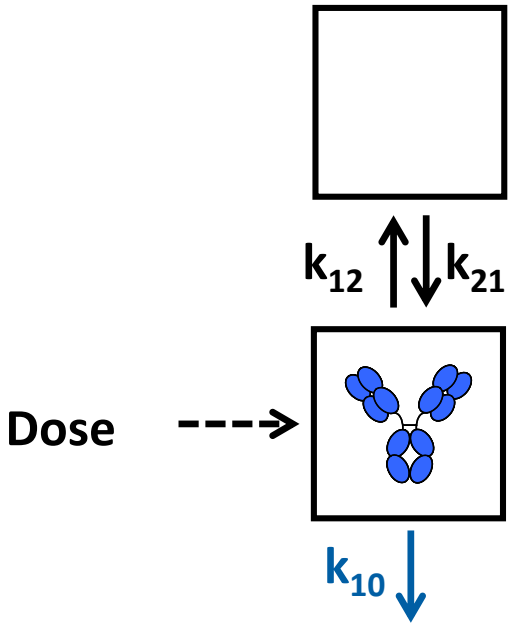
- ↗ target level
- ↘ mAb concentration

⇨ Non-linear elimination

Bevacizumab target-mediated elimination

Endogenous elimination

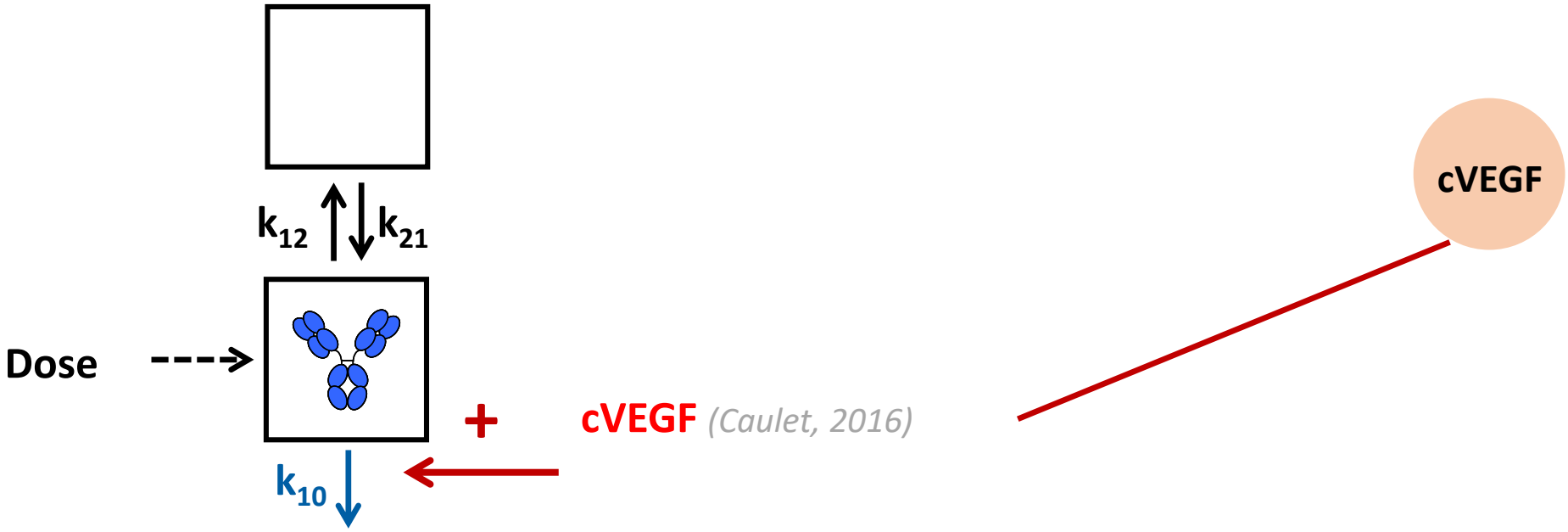
Target-mediated elimination



Bevacizumab target-mediated elimination

Endogenous elimination

Target-mediated elimination



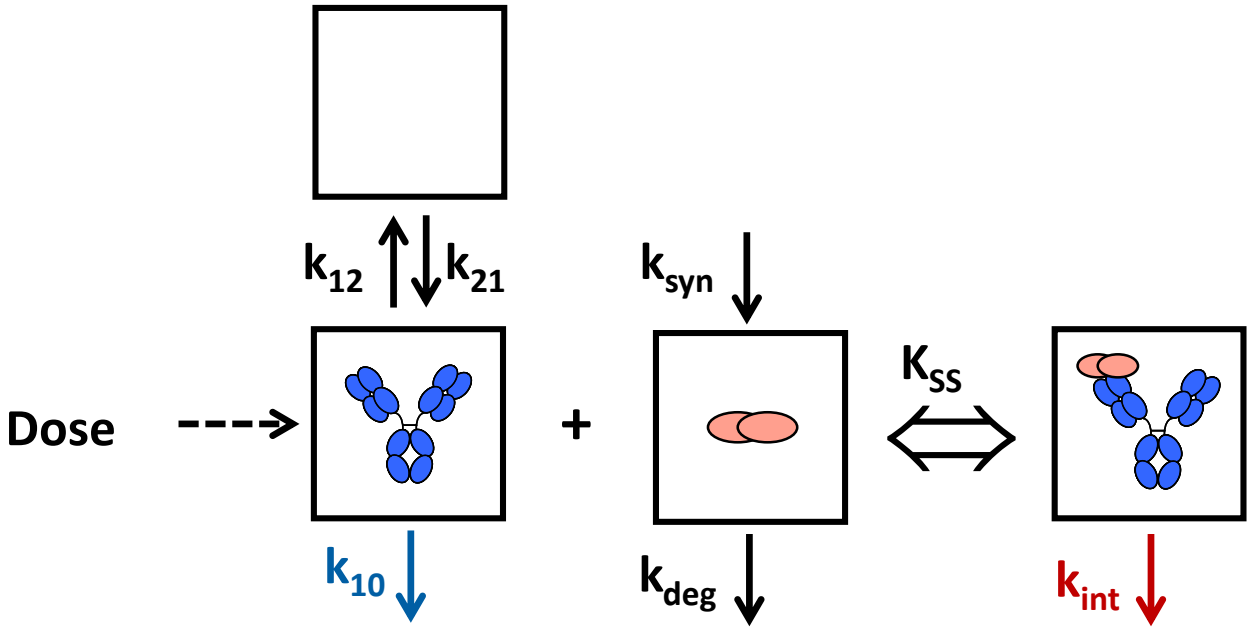
cVEGF = circulating VEGF

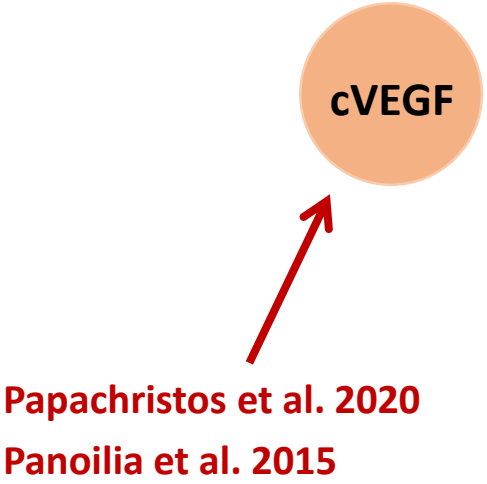
↗ cVEGF ⇨ ↗ k_{10} → Target-mediated elimination

Bevacizumab target-mediated elimination

Endogenous elimination

Target-mediated elimination





Papachristos et al. 2020

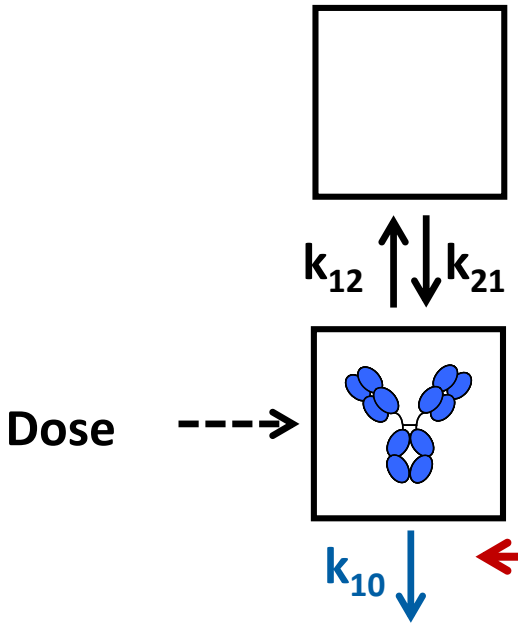
Panoilia et al. 2015

2 publications with TMDD models – measurements of

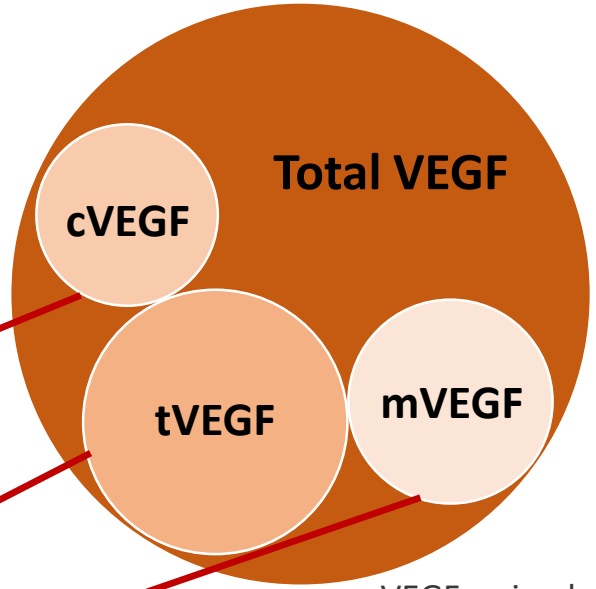
- Bevacizumab concentrations
- cVEGF levels

Bevacizumab target-mediated elimination

Endogenous elimination



Target-mediated elimination



\+ **cVEGF** *(Caulet, 2016)*

Tumor type *(Li, 2013; Han, 2015)*

Baseline CEA *(Caulet, 2016)*

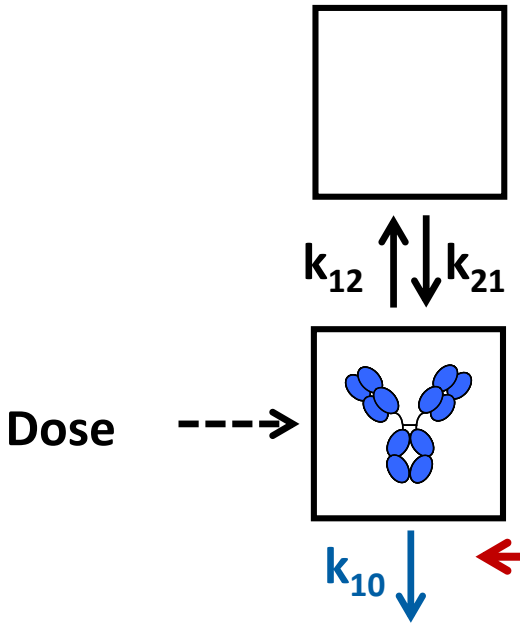
EH metastases *(Caulet, 2016)*

cVEGF = circulating VEGF
tVEGF = tumoral VEGF
mVEGF = metastasis VEGF
CEA = Carcinoembryonic antigen
EH = Extra-hepatic

Bevacizumab target-mediated elimination

Endogenous elimination

Target-mediated elimination



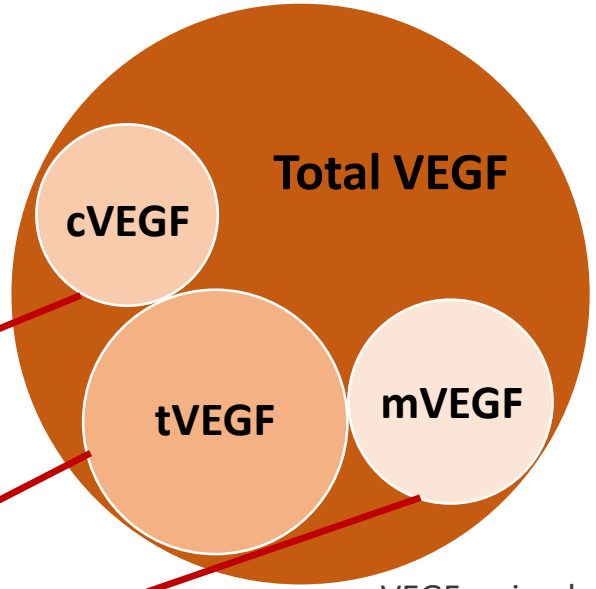
\+

cVEGF *(Caulet, 2016)*

Tumor type *(Li, 2013; Han, 2015)*

Baseline CEA *(Caulet, 2016)*

EH metastases *(Caulet, 2016)*



cVEGF = circulating VEGF
tVEGF = tumoral VEGF
mVEGF = metastasis VEGF
CEA = Carcinoembryonic antigen
EH = Extra-hepatic

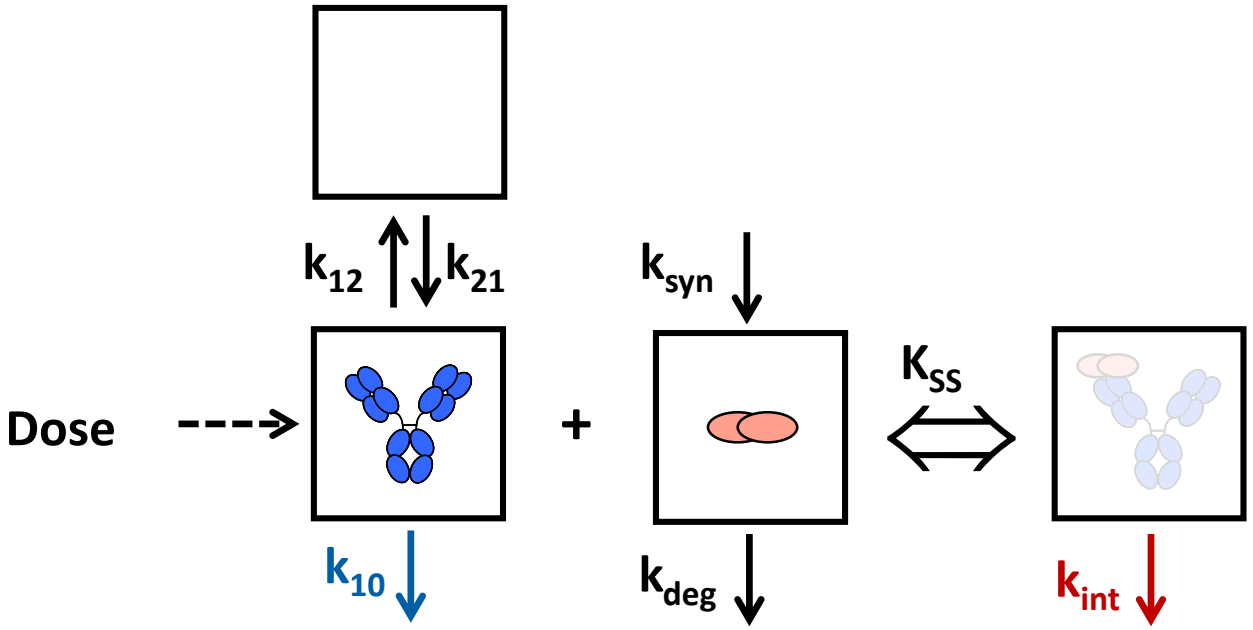
Tumor VEGF > circulating VEGF *(Kut, 2007; Martins, 2011)*

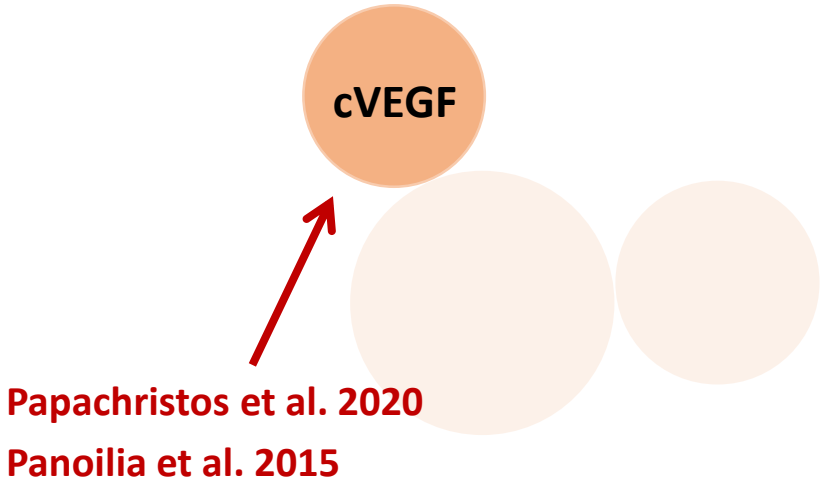
↗ Tumor burden⇨ ↗ k_{10} → Target-mediated elimination

Bevacizumab target-mediated pharmacokinetics

Endogenous elimination

Target-mediated elimination

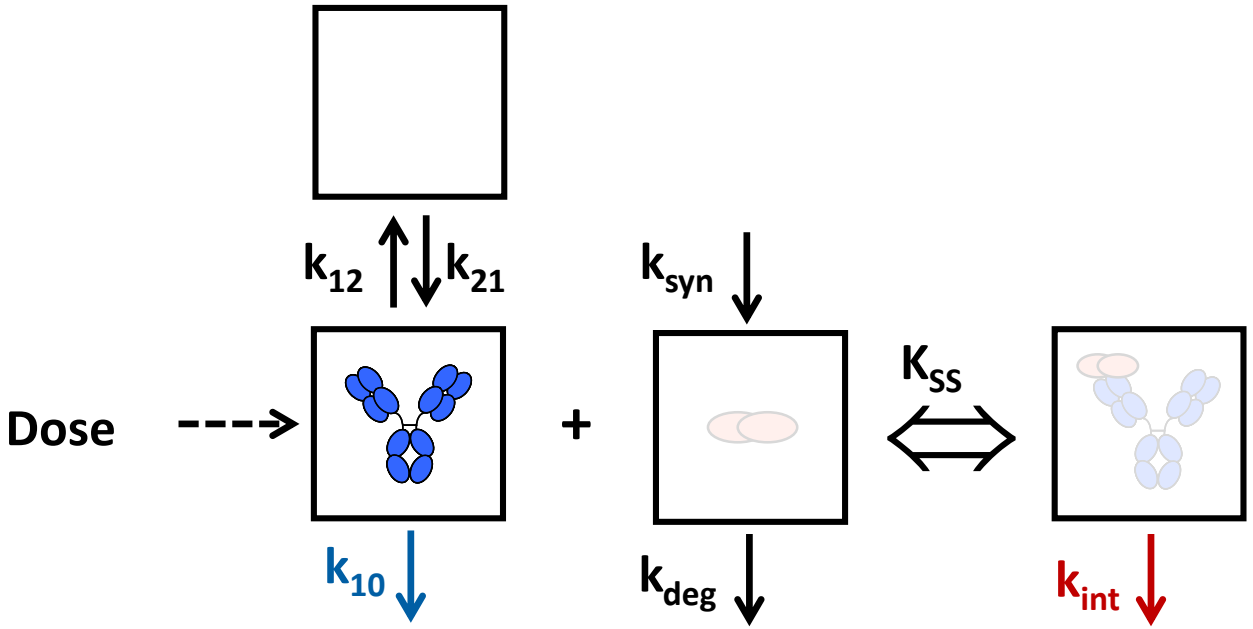


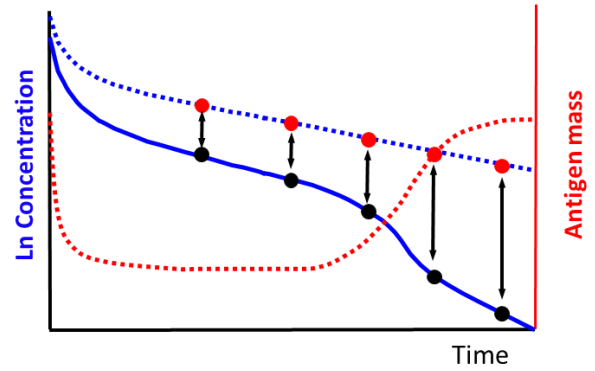


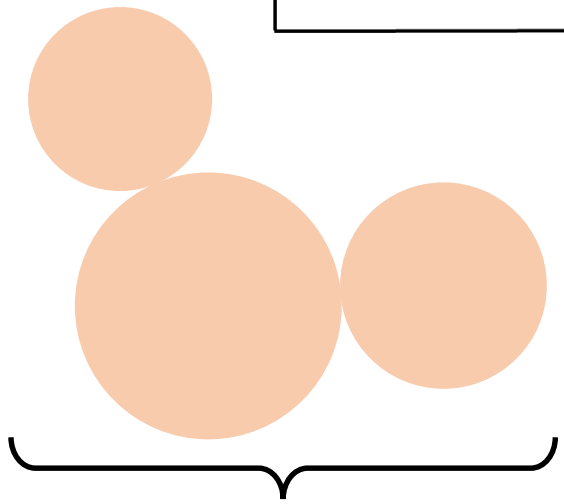
2 publications with TMDD models – measurements of

- Bevacizumab concentrations
- cVEGF levels ⇨ ***only part of target amount levels***

Antigen mass





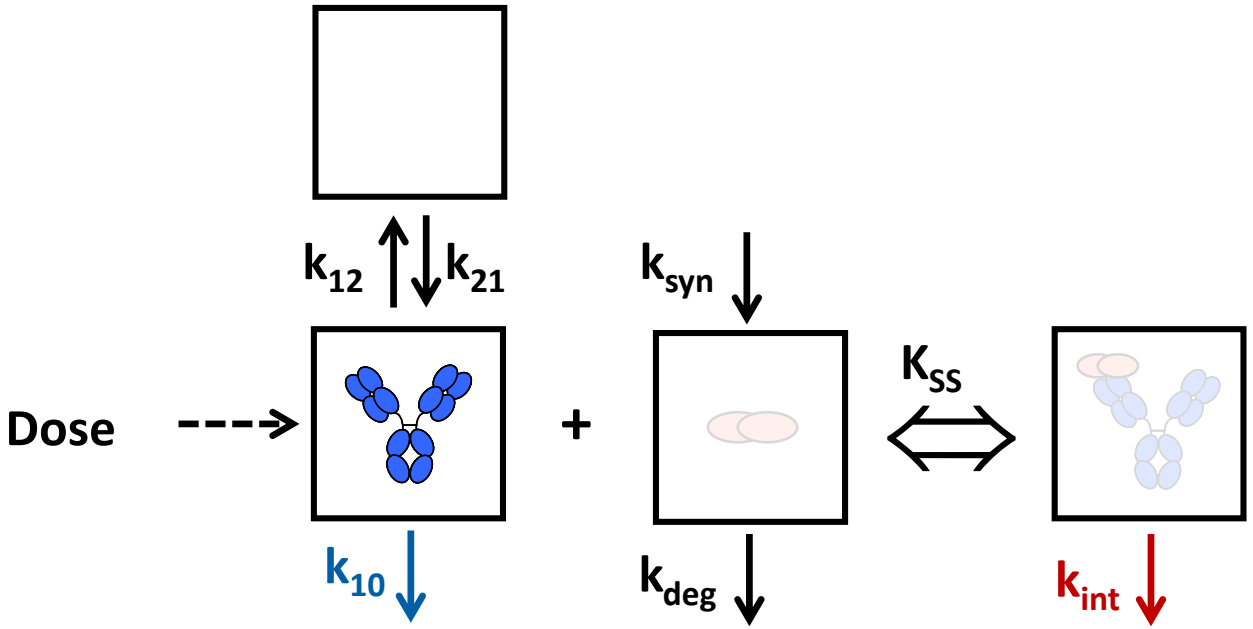


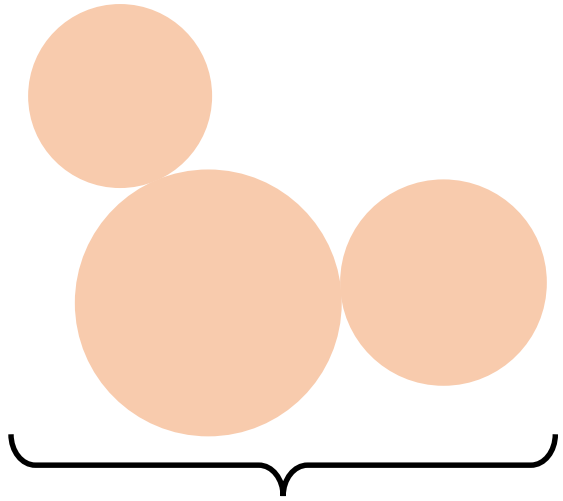
Antigen mass

Antigen mass

- Total target amount bound to bevacizumab
- Estimated with TMDD model (latent)

Objectives





- Question 1: is antigen mass related to cVEGF and tumor burden?
- Question 2: is antigen mass associated with survival?

« STIC AVASTIN » study

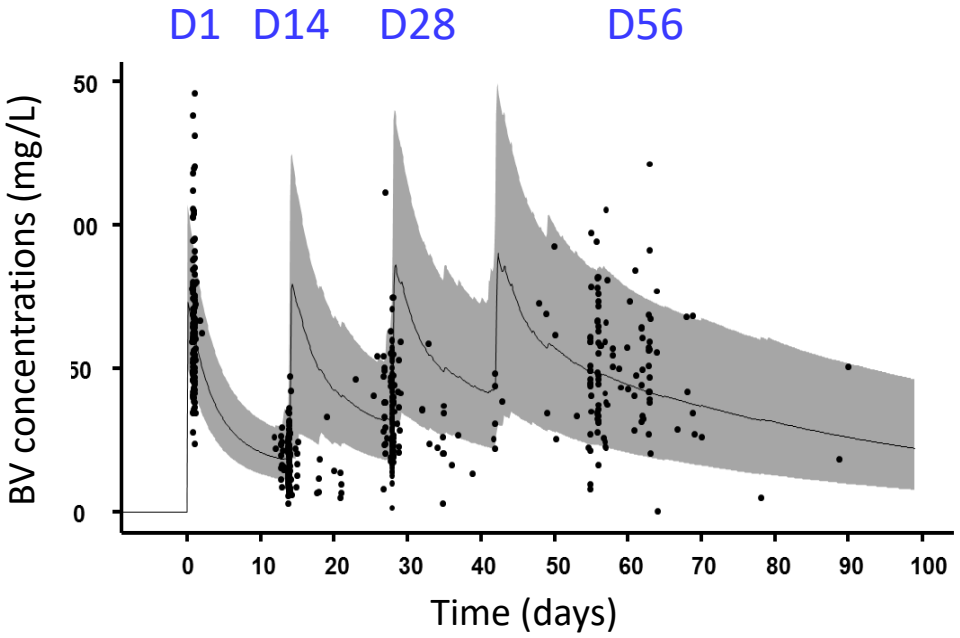
Non-comparative Phase II multicenter study (*NCT00489697):* *PIs : Profs. T Lecomte, G Paintaud*

137 mCRC patients with liver metastasis

First-line treatment

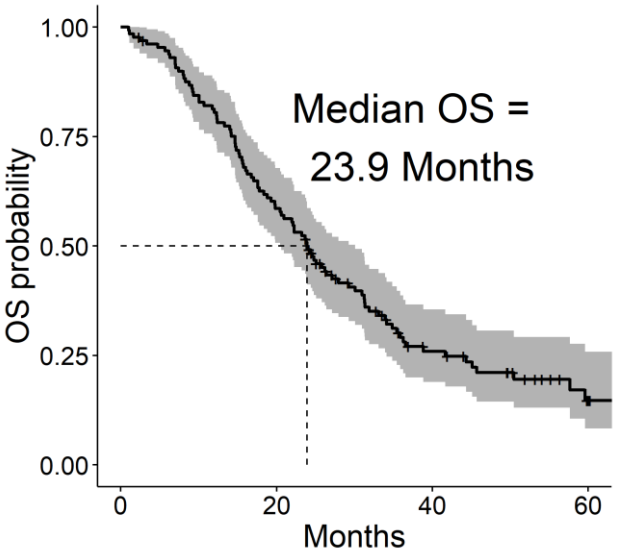
Bevacizumab + CHEMO
4 cycles 5 mg/kg Q2W

BV concentrations (N=130; n=486)

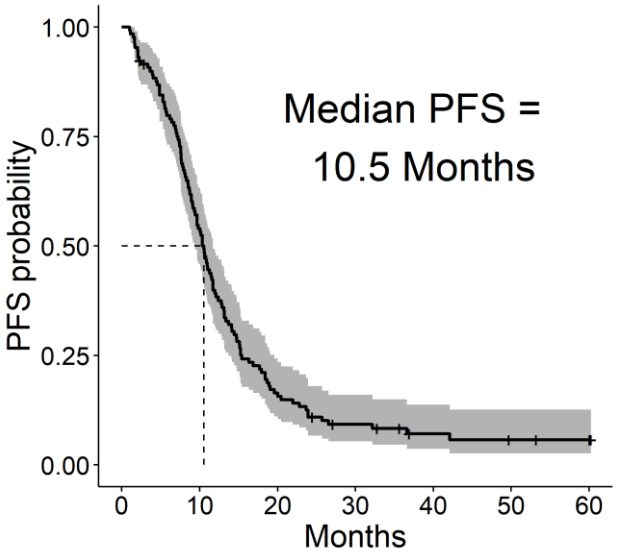


Survival (N=130)

OS



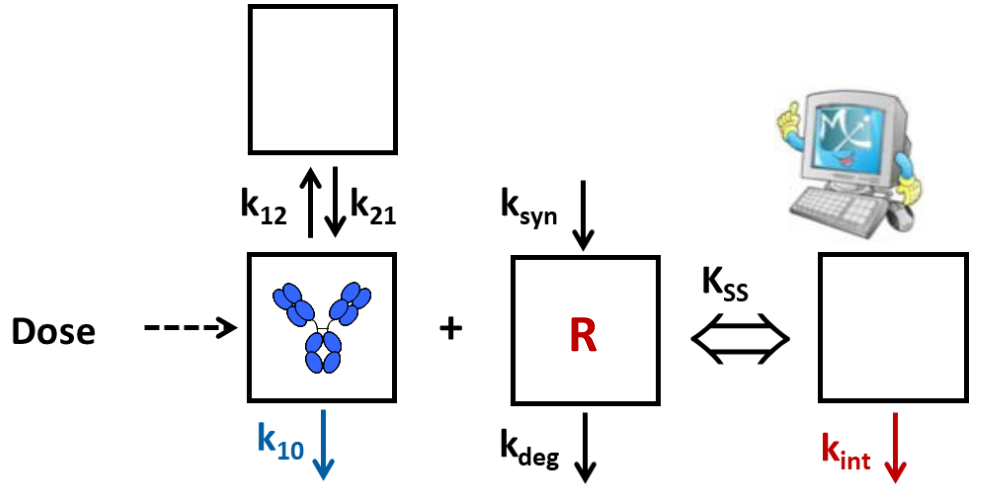
PFS



Target-mediated pharmacokinetics

Parameters	Estimates (RSE %)		$\omega_{\%}$ (RSE %)		P*
V_1, L	4.1	(3.8)	32	(10)	
HT on V_1	3.6	(20)			4.1×10^{-7}
CL, L/day	0.16	(7.8)	30	(18)	
HT on CL	4.0	(26)			6.5×10^{-5}
V_2, L	4.7	(6.8)	-	-	
Q, L/day	1.0	(0.28)	-	-	
R_0, nM	8.4	(14)	29	(19)	
cVEGF on R_0	0.34	(40)			1.2×10^{-2}
CEA on R_0	0.072	(37)			6.6×10^{-3}
mEH on R_0	0.20	(50)			4.7×10^{-2}
k_{int}, day^{-1}	0.56	(5.8)	-	-	
k_{deg}, day^{-1}	0.96	(0.57)	-	-	
K_{SS}, nM	12	(24)	-	-	
σ_{prop}, %	21	(4,3)			

*based on Wald test



TMDD model, QSS approximation

$$\frac{dC_T}{dt} = In(t) - \frac{CL}{V_1}.C - \frac{Q}{V_1}.C + \frac{Q}{V_2}.C_P - k_{int}.(C_T - C)$$

$$\frac{dC_P}{dt} = \frac{Q}{V_1}.C - \frac{Q}{V_2}.C_P$$

$$\frac{dR_T}{dt} = k_{syn} - k_{deg}.(R_T - C_T + C) - k_{int}.(C_T - C)$$

$$C = \frac{1}{2}\left[(C_T - R_T - K_{SS}) + \sqrt{(C_T - R_T - K_{SS})^2 - 4.K_{SS}.C_T}\right]$$

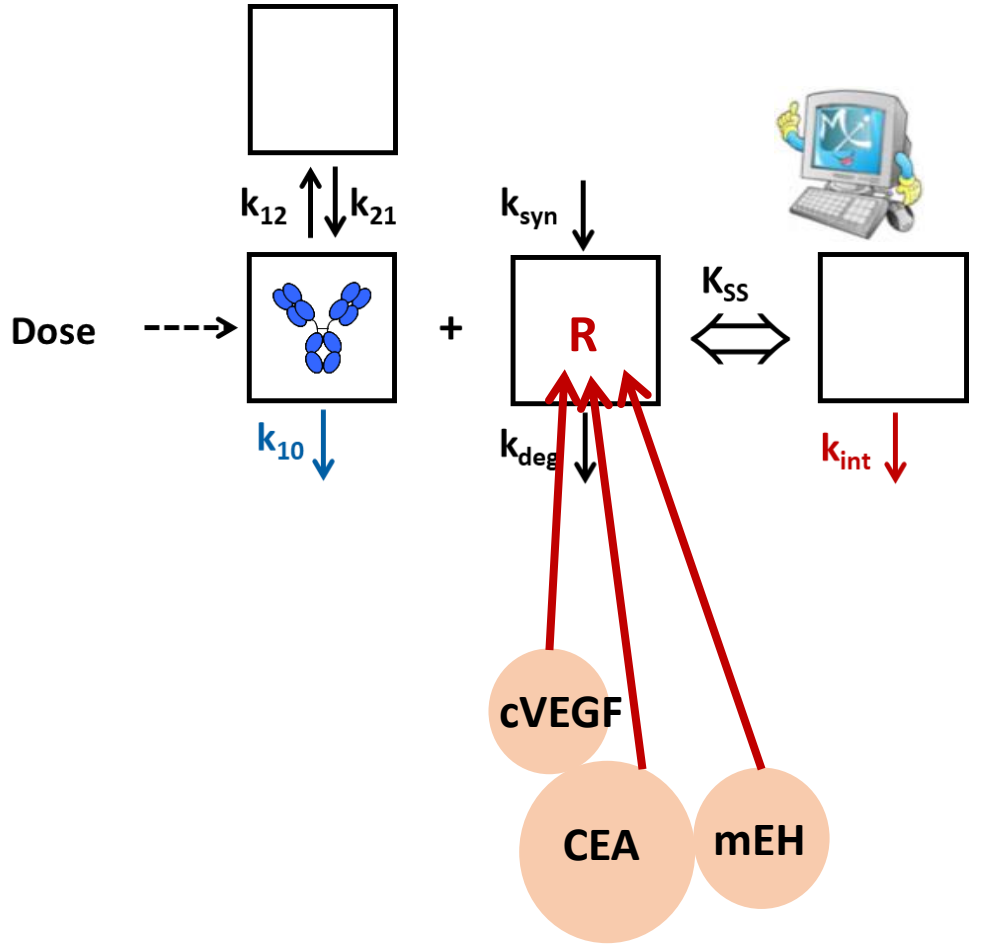
R_0 = initial target amount

$$R_0 = \frac{k_{syn}}{k_{deg}}$$

Target-mediated pharmacokinetics and covariates

Parameters	Estimates (RSE %)		$\omega_{\%}$ (RSE %)		P*
V_1, L	4.1	(3.8)	32	(10)	
HT on V_1	3.6	(20)			4.1×10^{-7}
CL, L/day	0.16	(7.8)	30	(18)	
HT on CL	4.0	(26)			6.5×10^{-5}
V_2, L	4.7	(6.8)	-	-	
Q, L/day	1.0	(0.28)	-	-	
R_0, nM	8.4	(14)	29	(19)	
cVEGF on R_0	0.34	(40)			1.2×10^{-2}
CEA on R_0	0.072	(37)			6.6×10^{-3}
mEH on R_0	0.20	(50)			4.7×10^{-2}
k_{int}, day^{-1}	0.56	(5.8)	-	-	
k_{deg}, day^{-1}	0.96	(0.57)	-	-	
K_{SS}, nM	12	(24)	-	-	
σ_{prop}, %	21	(4,3)			

based on Wald test



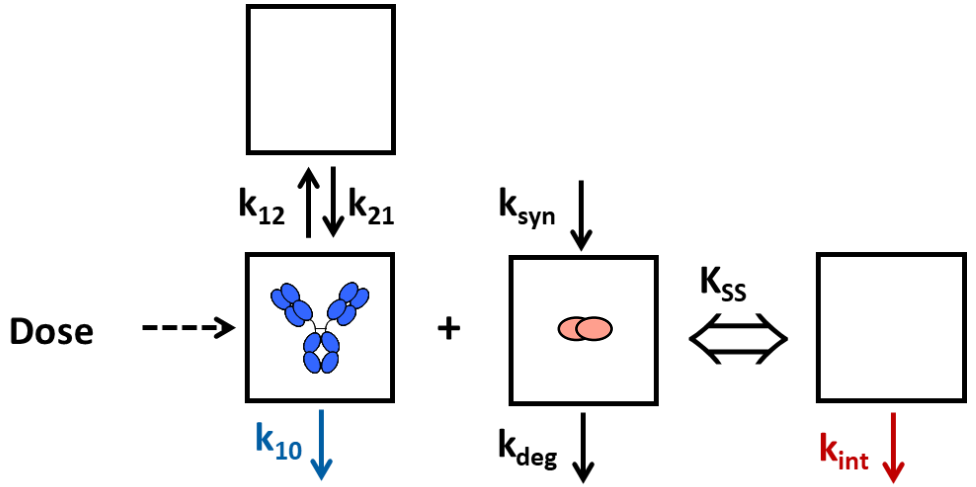
R_0 = initial target amount

$$R_0 = \frac{k_{syn}}{k_{deg}}$$

Target-mediated pharmacokinetics

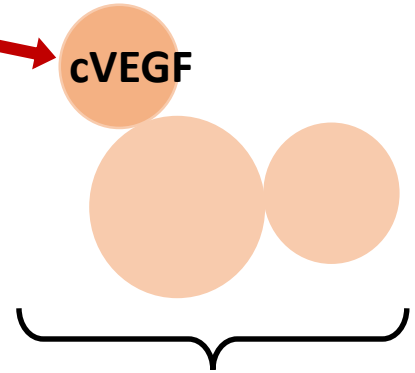
			Panoilia, 2015		Papachristos, 2020	
Parameters	**Estimates**	**ω%**	**Estimates**	**ω%**	**Estimates**	**ω%**
V_1, L	4.1	32	3.2	22	5.8	17
HT on V_1	3.6					
CL, L/day	0.16	30	0.18	20	0.34	31
HT on CL	4.0					
V_2, L	4.7	-	3.1	-	3.2	56
Q, L/day	1.0	-	1.4	-	0.14	20
R_0, nM	**8.4**	29	**0.0053**	33	**0.014**	24
cVEGF on R_0	0.34					
CEA on R_0	0.072					
mEH on R_0	0.20					
k_{int}, day^{-1}	0.56	-	0.056*	-	0.059*	-
k_{deg}, day^{-1}	0.96	-	0.401	-	0.12	-
K_{SS}, nM	12	-	267	-	135	-
$\sigma_{prop,\ BV}$, %	21		28		25	
$\sigma_{prop,\ VEGF}$, %			32		29	

*fixed to k_{10} value



Papachristos, 2020

Panoilia, 2015



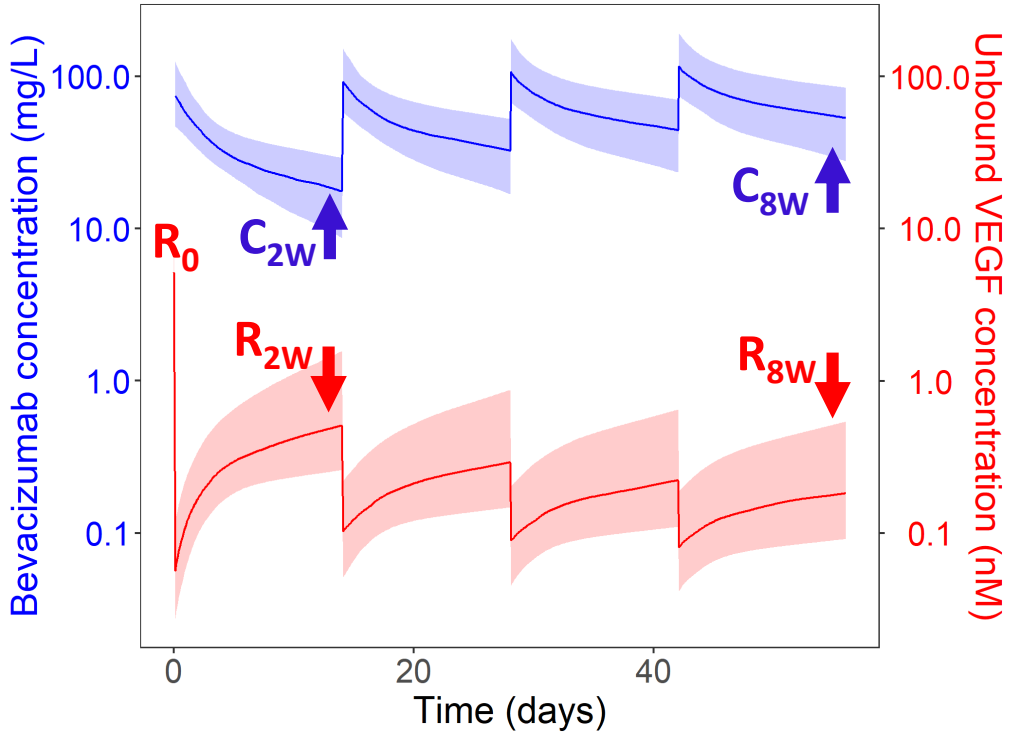
Our study

R_0 = initial target amount

$$R_0 = \frac{k_{syn}}{k_{deg}}$$

Latent target – response relationship

Bevacizumab, mCRC, 5 mg/kg Q2W

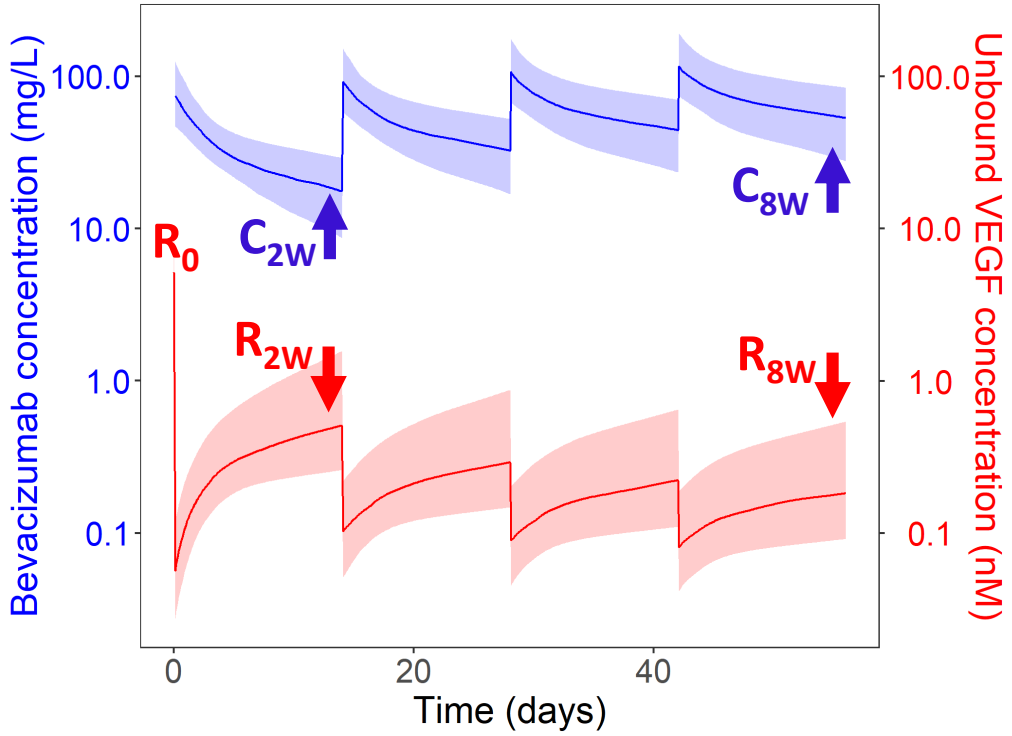


R_0 = initial target amount

$$R_0 = \frac{k_{syn}}{k_{deg}}$$

Latent target – response relationship

Bevacizumab, mCRC, 5 mg/kg Q2W



Cox Analysis (n = 130)

	Progression free survival			Overall survival		
	HR	95% CI	*P*	HR	95% CI	*P*
R_{2W}	1.8	1.2-2.6	0.0022	2.3	1.5-3.5	9.2×10^{-5}
R_0	1.8	1.2-2.6	0.0028	2.1	1.4-3.1	5.6×10^{-4}
R_{8W}	1.7	1.2-2.5	0.005	2.1	1.4-3.2	0.0007
C_{2W}	0.70	0.49-1.0	0.06	0.57	0.37-0.85	0.0068
C_{8W}	0.75	0.51-1.1	0.13	0.68	0.45-1.0	0.073

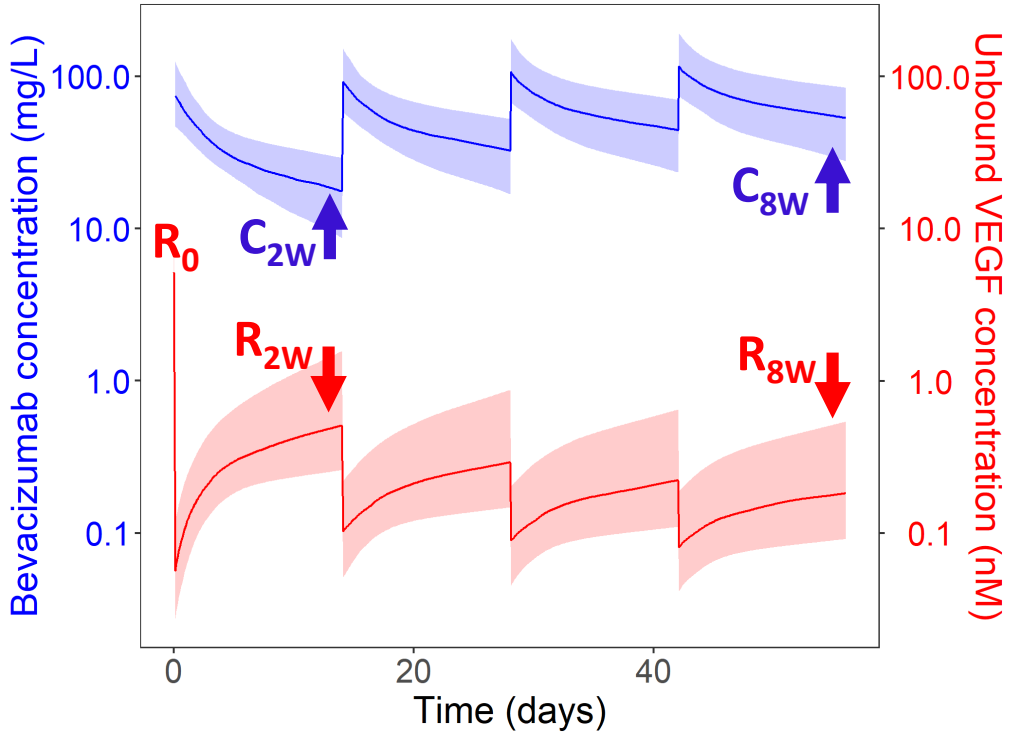
**all parameters were dichotomized around the median value*

PFS and OS are most strongly associated with

- Target involvement (R_{2W})
- Baseline antigen mass (R0)

Latent target – response relationship

Bevacizumab, mCRC, 5 mg/kg Q2W



Cox Analysis (n = 130)

	Progression free survival			Overall survival		
	HR	95% CI	*P*	HR	95% CI	*P*
R_{2W}	1.8	1.2-2.6	0.0022	2.3	1.5-3.5	9.2×10^{-5}
R_0	1.8	1.2-2.6	0.0028	2.1	1.4-3.1	5.6×10^{-4}
R_{8W}	1.7	1.2-2.5	0.005	2.1	1.4-3.2	0.0007
C_{2W}	0.70	0.49-1.0	0.06	0.57	0.37-0.85	0.0068
C_{8W}	0.75	0.51-1.1	0.13	0.68	0.45-1.0	0.073

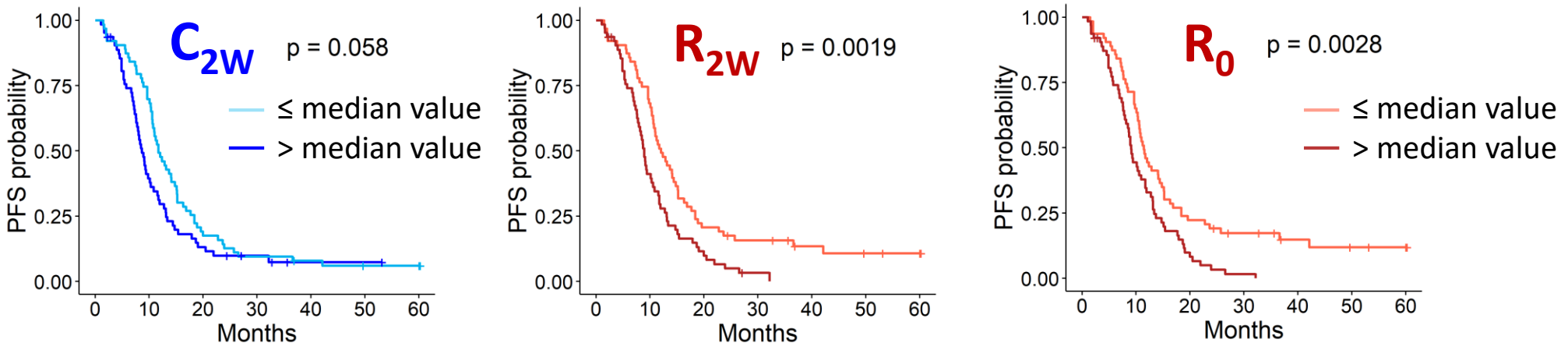
**all parameters were dichotomized around the median value*

PFS and OS are most strongly associated with

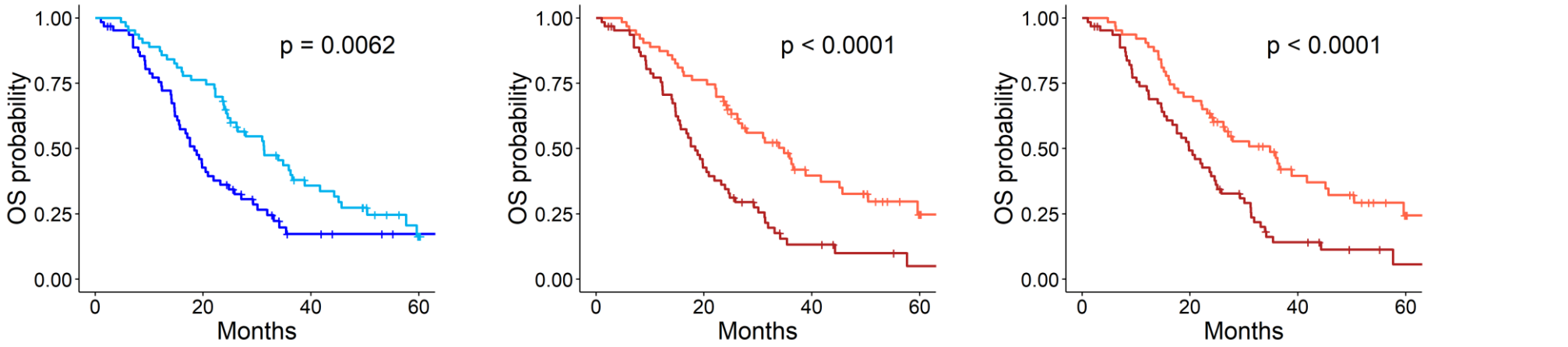
- Target involvement (R_{2W})
- Baseline antigen mass (R0)

Latent target – response relationship

PFS



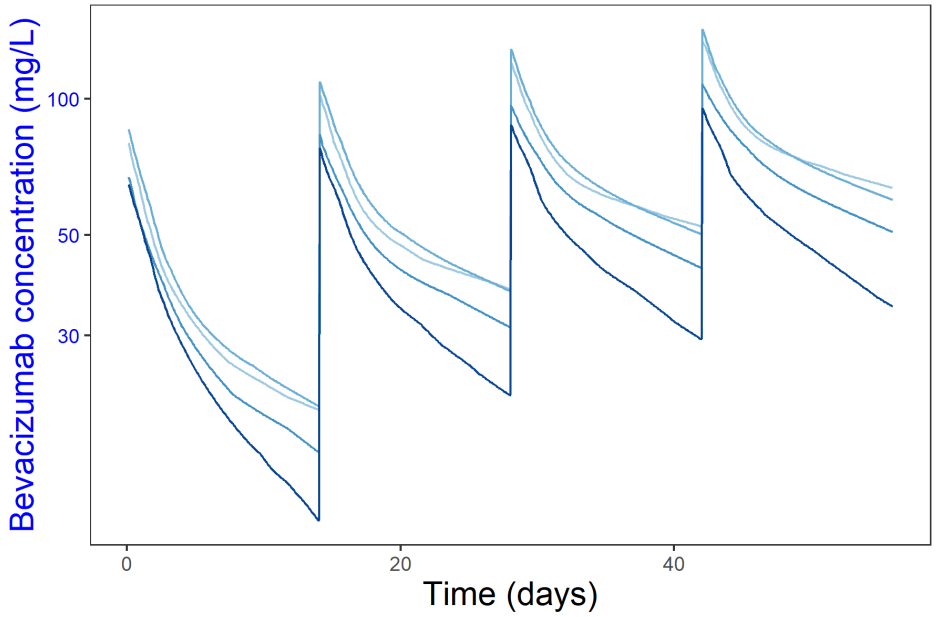
OS

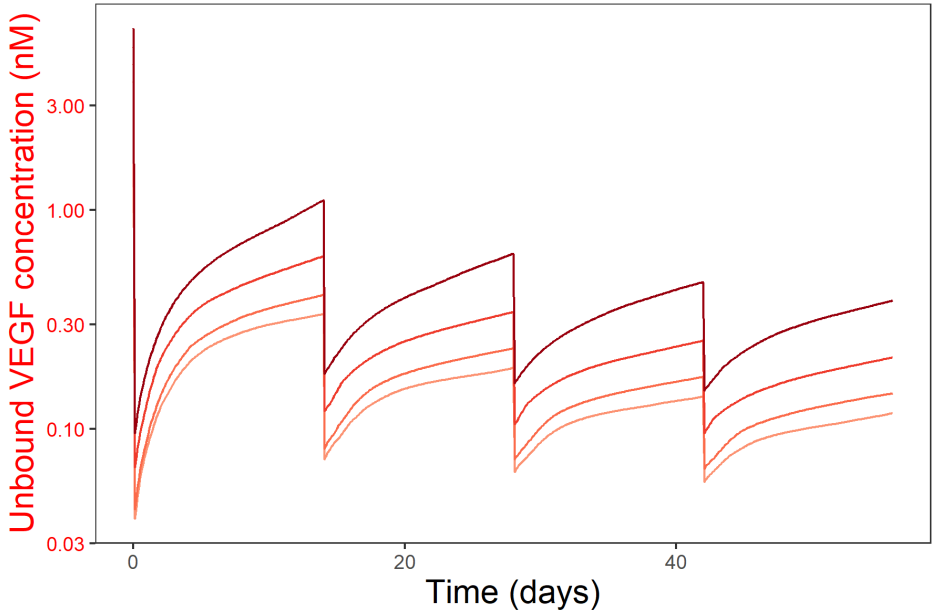


Short PFS and OS are associated with

- Low C_{2W} ⇨ High BV « consumption » *(as found by Caulet, 2016)*
- High R_{2W} ⇨ Low target involvement ?
- High R_0 ⇨ High target expression

Target – response relationship

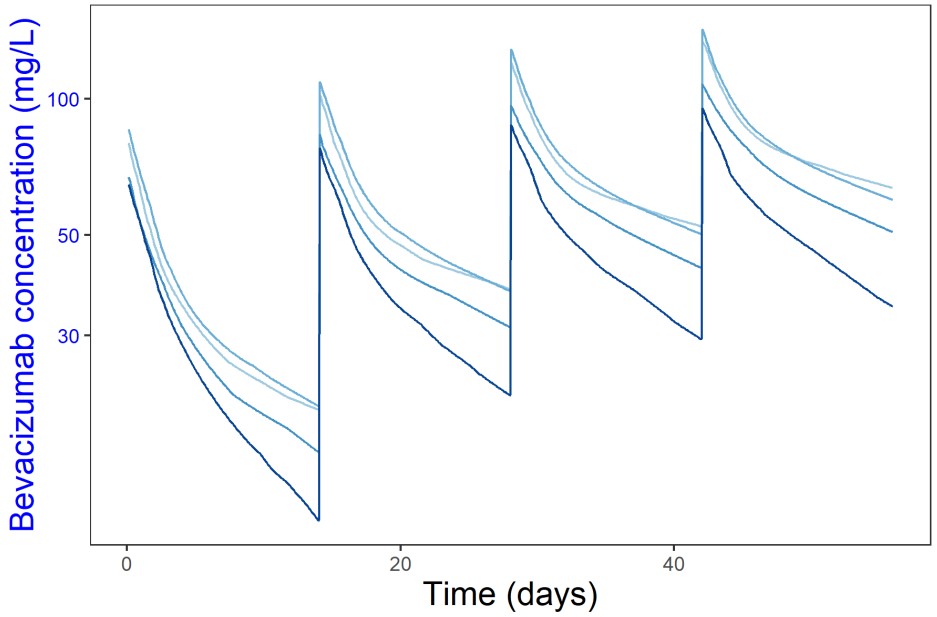


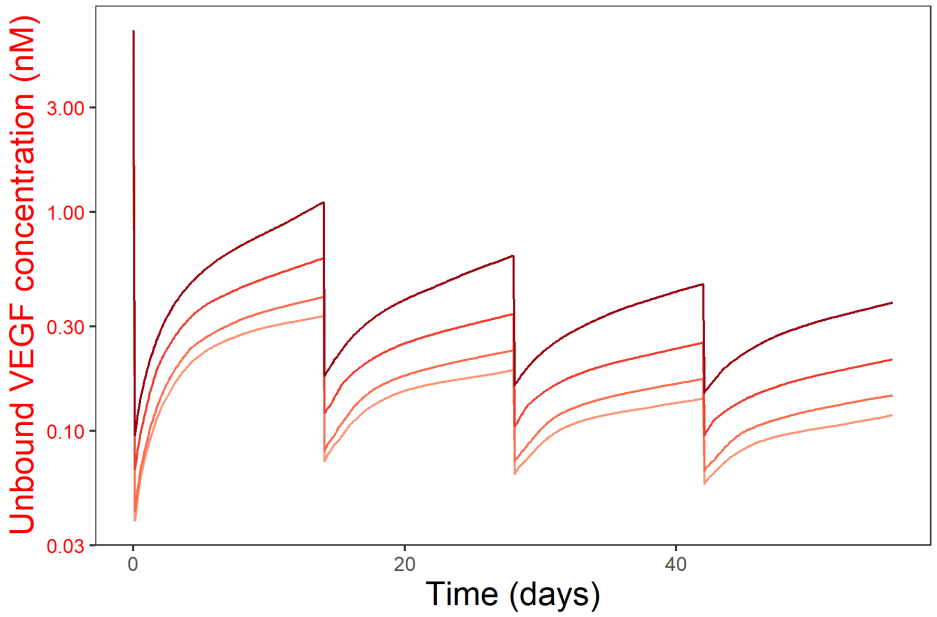


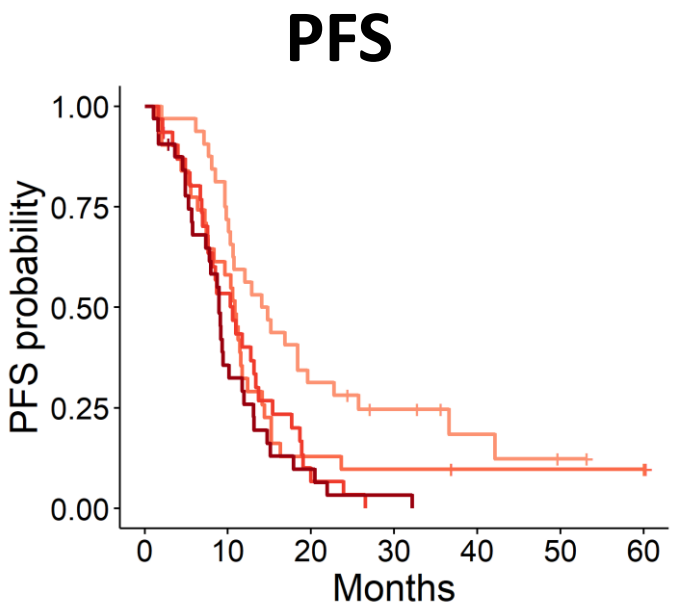
[BV] [VEGF]

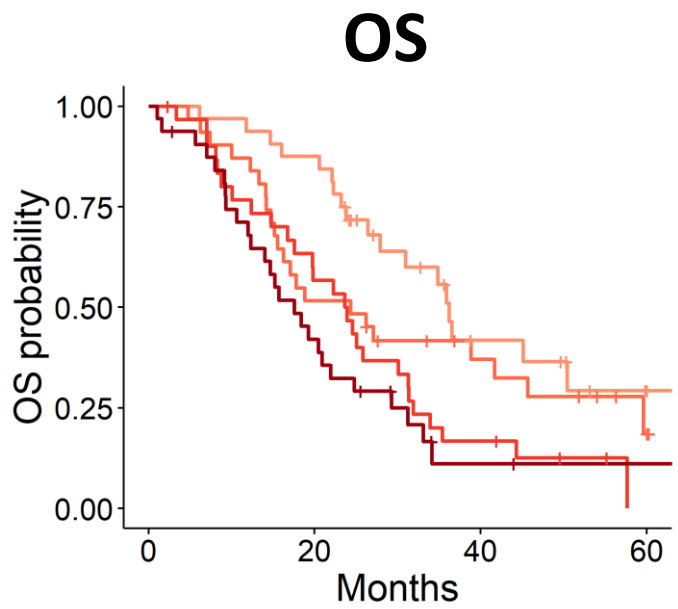
- [0-25th] perc
- [25-50th] perc
- [50-75th] perc
- [75-100th] perc

Target – response relationship







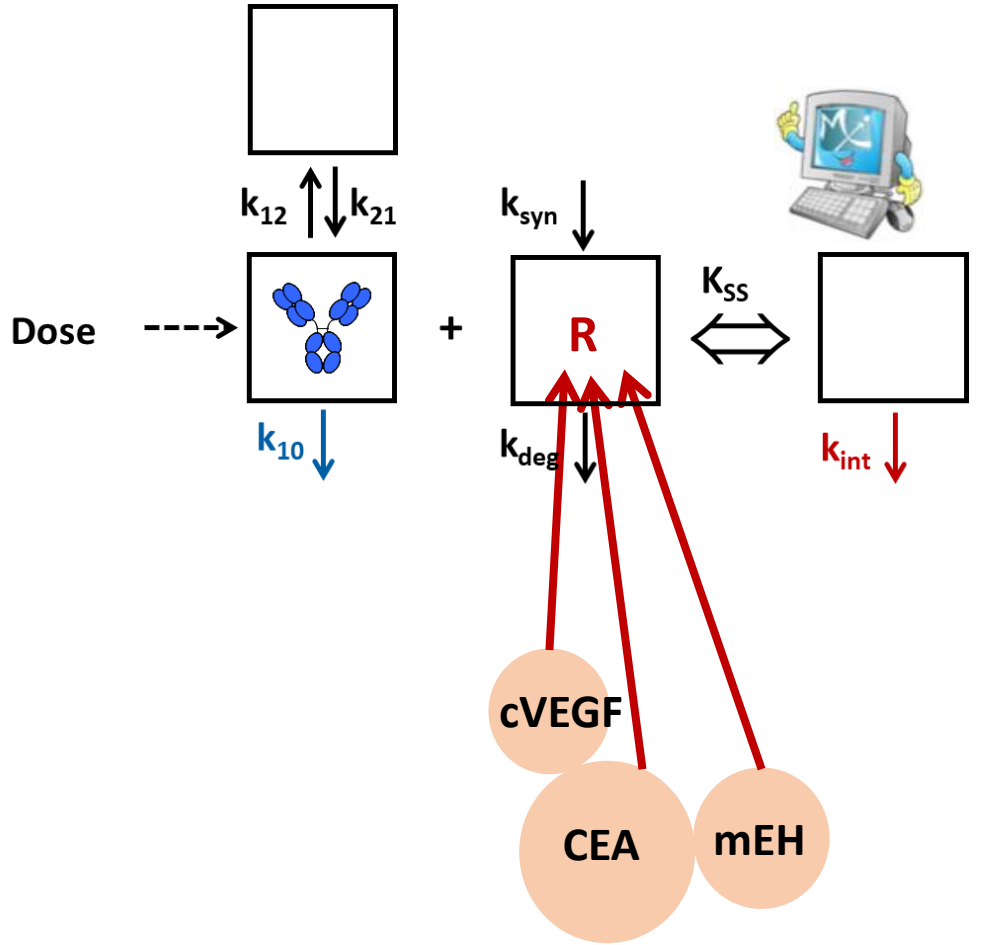


$R_{0\ cat}$	Median PFS	Median OS
[0-25th] perc	14.4	36.3
[25-50th] perc	10.9	24.4
[50-75th] perc	10.6	23.8
[75-100th] perc	8.9	17.6

Conclusion – perspectives

Latent antigen mass estimated using TMDD modeling

- Using unbound BV concentrations
- Accounts for total target amount bound to BV



Latent antigen mass computed associated with

- Tumor burden and cVEGF
- Progression-free survival and overall survival

  ⇨ Relevant predictor of bevacizumab efficacy ?

Further work needed

⇨ Refine relationships of both target involvement and sarcopenia/cachexia with clinical efficacy

⇨ Demonstrate benefit of dosing intensification in patient with poor target involvement

Acknowledgments

Inserm UMR 1069 - Équipe N2C

Dr. Christophe Vandier (PI)

Prof. Thierry Lecomte

Dr. Stéphane Servais

Dr. William Raoul

EA 4245 - Équipe T2I

Dr. Sébastien Roger (PI)

Prof. Gilles Paintaud

Dr. David Ternant

Prof. Theodora Bejan-Angoulvant

Dr. Céline Desvignes

CHRU Tours

Dr. Morgane Caulet

Anne-Claire Duveau

Caroline Guerineau

CNRS 7001 - GICC - Equipe PATCH

Dr. Nicolas Azzopardi

Thanks for your attention