A hybrid PKPD agent-based model of the tumour immune interaction: effects of anti-cancer combination therapy

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1 Supplementary

1.1 PD1 antibody

The PD1 antibody treatment module is implemented with a PKPD model from the literature [1] where a system of ODEs is used to calculate the receptor occupancy of pembrolizumab on the PD1 effector cell receptor which will determine the effector cell exhaustion rate.

The monoclonal PD1 antibody is administrated i.v. into the central (blood) compartment as the concentration C_1, where it can be distributed to the peripher compartment as the concentration C_2 and redistributed to the central compartment with rates K_{12}, K_{21}. Elimination from the central compartment can be linear with the rate K or nonlinear with the Michaelis-Menten rate $\frac{V_{max}}{K_M+C_1}$. Inside the central compartment, the antibody can bind to the PD1 receptors in the blood (e.g on immune effector cells) denoted with C_{PD1b} which leads to the bound drug-receptor complex $PD1_b$. Binding and detaching rates are K_{onPD1} and K_{offPD1}. The complex can be degraded with the rate K_{deg}. The tumour plasma flow transports the unbound antibody to the tumour compartment at the rate PLQ. The tumour compartment consists of the vasculature, the endosomal layer and the interstitium. The monoclonal antibody inside the vasculature (C_{vs}) is transported from the tumour vasculature to the interstitium via the neonatal fragment crystallizable-receptor (FcRn) salvage pathway [2]. The antibody will be engulfed and released by the endosomal cell through

pinocytosis with the rate $CLup$. The unbound drug (C_{ub}) binds to the FcRn receptor with the rates K_{onFcRn} and $K_{offFcRn}$. Unlike unbound proteins or unbound antibodies, the FcRn receptor antibody complex will not be degraded by lysosomes with the rate K_{deg} and a fraction of the bound drug (C_b) on the FcRn receptor will be released by the vesicle to either the vascular side as C_{vs} or the interstitial side as C_{is} with the rate $FR * CLup$. Pinocytosis can also transport the antibody from the interstitium (C_{is}) with the rate $CLup$ to the endosomal compartment. In addition, the lymph flow can transfer the drug from the tumour vasculature (C_{vs}) to the interstitium (C_{is}) with the rate $(1 - vref) * L$. The lymph flow can further eliminate the drug from the vascular compartment with the rate L or from the interstitium with the rate $(1 - vref) * L$. Inside the interstitial compartment, the antibody concentration C_{is} binds to the PD1 receptor on immune effector cells ($CPD1_t$) with the rates K_{onPD1} and K_{offPD1}. The bound drug-receptor complex $PD1_t$ can initiate hyperbolic feedback and cause a receptor upregulation ($MPD1_t$) on the immune effector cell. The receptor occupancy of the drug in the tumour compartment is calculated with the relation of antibody-drug complex ($PD1_t$) to the concentration of unoccupied receptors ($CPD1_t$).

Central compartment:

$$V_1 \frac{dC_1}{dt} = -K(C_1 * V_1) - \frac{V_{max}}{K_M + C_1} C_1 - PLQC_1 + PLQC_{vs} - K_{12}C_1V_1 \tag{1}$$

$$+ K_{21}C_2V_2 - K_{onPD1}(C_{PD1_b} - PD1_b) + K_{offPD1}PD1_bV_1 \tag{2}$$

Peripheral compartment:

$$V_2 \frac{dC_2}{dt} = K_{12}C_1V_1 - K_{21}C_2V_2 \tag{3}$$

Vascular space tumour:

$$V_{vs} \frac{dC_{vs}}{dt} = PLQC_1 - (PLQ - L)C_{vs} - (1 - v_{ref})LC_{vs} \tag{4}$$

$$- CL_{up}C_{vs} + CL_{up}FrC_b \tag{5}$$

Endosomal space monoclonal antibody (mAb) unbound to FcRn:

$$\frac{dC_{ub}}{dt} = \frac{CL_{up}}{V_{es}}(C_{vs} + C_{is}) - K_{onFcRn}C_{ub}FcRn + K_{offFcRn}C_b - K_{deg}C_{ub} \tag{6}$$

Endosomal space mAb bound to FcRn:

$$\frac{dC_b}{dt} = -\frac{CL_{up}}{V_{es}}C_{vs} + K_{onFcRn}C_{ub}FcRn - K_{offFcRn}C_b \tag{7}$$

Endosomal FcRn:

$$\frac{dFcRn}{dt} = \frac{CL_{up}}{V_{es}}C_{vs} - K_{onFcRn}C_{ub}FcRn + K_{offFcRn}C_b \tag{8}$$

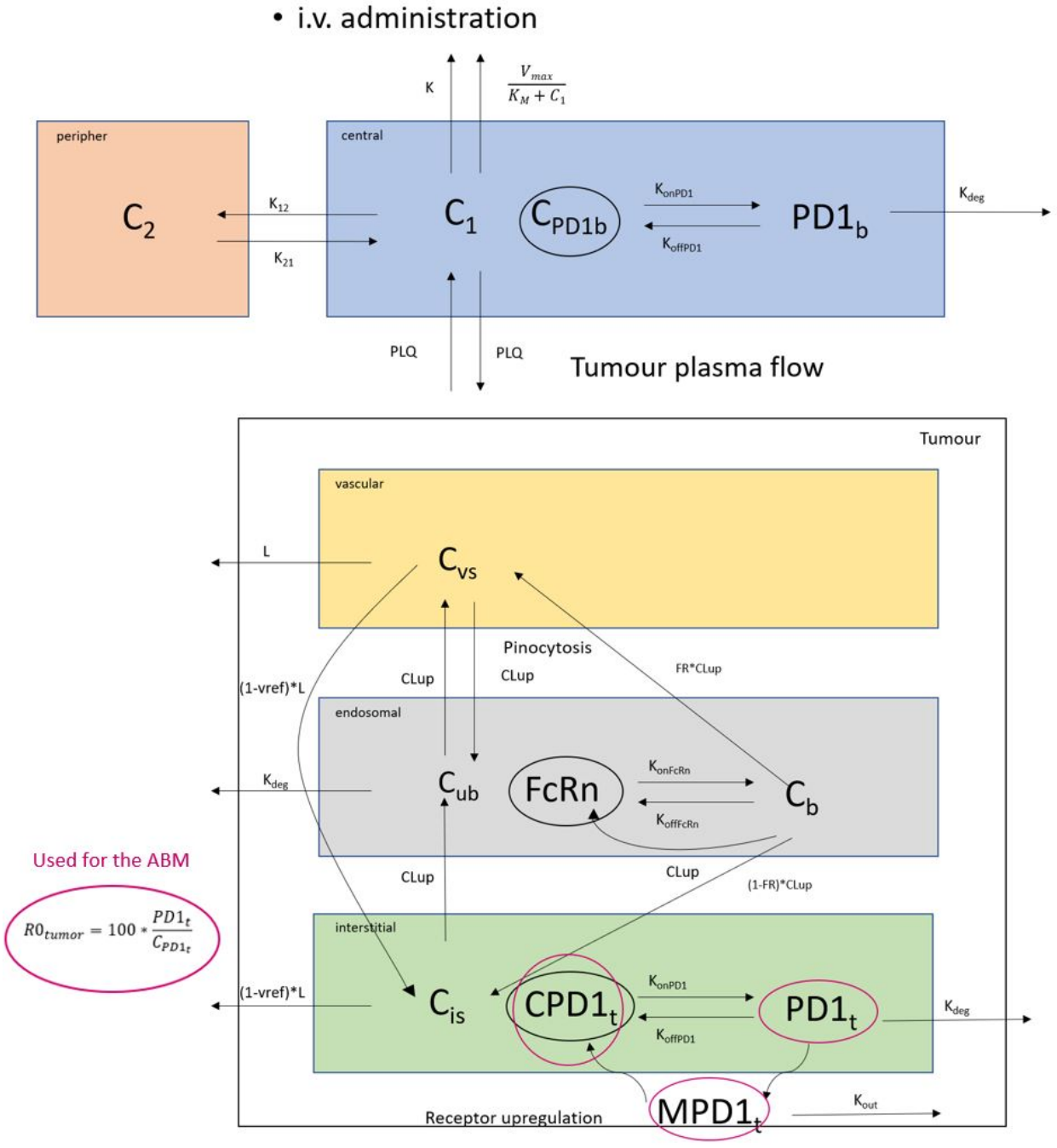

Figure 1: Schematic of the PKPD model for pembrolizumab

Interstitial compartment:

$$V_{is}\frac{dC_{is}}{dt} = (1-vref)LC_{vs} - (1-vref)LC_{is} - CL_{up}C_{is} \tag{9}$$

$$+ CL_{up}(1-FR)C_b - K_{onPD1}C_{is}V_{is}(C_{PD1_t} - PD1_t) + K_{offPD1}PD1_tV_{is} \tag{10}$$

Drug receptor binding in the tumour:

$$\frac{dPD1_t}{dt} = K_{onPD1}C_{is}(C_{PD1_t} - PD1_t) - K_{offPD1}PD1_t - K_{degPD1}PD1_t \tag{11}$$

Drug receptor binding in blood:

$$\frac{dPD1_b}{dt} = K_{onPD1}C_1(C_{PD1_b} - PD1_b) - K_{offPD1}PD1_b - K_{degPD1}PD1_b \tag{12}$$

Tumour PD-1 receptor upregulation and elimination (amount):

$$\frac{dMPD1_t}{dt} = k_{in}\left(1 + E_{maxtp}\frac{PD1_t}{EC_{50tp} + PD1_t}\right) - k_{out}M_{PD1t} \tag{13}$$

Receptor occupancy:

$$R0_{tumour} = 100 * \frac{PD1_t}{C_{PD1_t}} \tag{14}$$

1.2 Radiotherapy

In the radiotherapy module, the survival probability of each cell is simulated with a modified linear square model and oxygen modification factor (OMF) according to Powathil et al [3].

$$OMF = \frac{OER(pO_2)}{OER_m} = \frac{1}{OER_m}\frac{OER_m pO_2(x) + K_m}{pO_2(x) + K_m} \tag{15}$$

$pO_2(x)$ describes the oxygen concentration at position x. The ratio of the radiation doses needed for the same cell kill under anoxic and oxic conditions is OER. $OER_m = 3$ is the maximum ratio. $K_m = 3mm$ Hg is defined as the pO_2 at half the increase from 1 to OER_m.

The modified linear square model is used to calculate the survival probability of each cell:

$$S(d) = exp[\gamma(-\alpha OMF * d - \beta(OMF * d)^2)] \tag{16}$$

S(d) describes the survival probability of a cell which has a certain oxygen modification factor due to its position and receives a radiation dose d. α and β are sensitivity parameters. The sensitivity parameters γ reflect the different susceptibility of each cell kind and cancer cell cycle

phase.

$$\gamma = \begin{cases} 1 & \text{for cancer cells in S-G2-M phase [3]} \\ 0.5 & \text{for cancer cells in the G1 phase [3]} \\ 0.25 & \text{for cancer cells in the G0 phase [3]} \\ 1 & \text{for immune effector cells [assumed]} \\ 0.6 & \text{for immune suppressor cells [assumed]} \end{cases} \tag{17}$$

The sensitivity parameter γ ranges from 0 to 1. The S, G2, and M phases are the most radiosensitive phases with $\gamma = 1$, while the resting phase G0 is the least affected phase by radiation with $\gamma = 0.25$. The G1 phase has a γ value of 0.5. Immune effector cells are more radiosensitive than immune suppressor cells [4]. Hence, it is assumed that γ is 1 for effector cells and 0.6 for suppressor cells.

Considering that damage caused by low-dose radiation (less than 5 Gy), can be repaired within hours, a modified linear square model is used [3].

$$S^*(d) = \begin{cases} S & d > 5 \\ S + (1 - S) \times 0.5 & d \leq 5 \end{cases} \tag{18}$$

The cell cycle delay in the G1 and G2 phase after radiation is drawn from a uniform distribution between 1-9h [3]. A cell survives if a random number drawn from a uniform distribution between 0-1 is smaller than the modified survival probability $S^*(d)$ and dies otherwise. Immune cell infiltration is modelled deterministically according to Alfonso et al [5] and depends on the number of radiotherapy doses N_{RT}, time of irradiation t_j, number of cancer cells killed by the irradiation K_{Tj}, a stimulation decay c, and immune cell recruitment factors δ_E for immune effector cells and δ_S for suppressor cells.

Immune cell infiltration:

$$E_i = \sum_{j=1}^{N_{RT}} K_{Tj}(\delta_E e^{-c(t_i - t_j)}) \tag{19}$$

$$S_i = \sum_{j=1}^{N_{RT}} K_{Tj}(\delta_S e^{-c(t_i - t_j)}) \tag{20}$$

1.3 Chemotherapy

For the chemotherapy module, we simulated treatment with docetaxel with a K/PD model from Frances et al [6].

$$\frac{dD}{dt} = -k_d D + u_D(t)D(0) \tag{21}$$

where D describes the docetaxel amount, k_D the 'biological constant' to control the dose history profiles, $u_D(t)$ the dosing schedule, and D(0) the initial dose. To take into consideration that the drug distribution differs throughout the 3D lattice, the drug concentration is scaled based on the predicted oxygen gradient. To take emerging resistance into account, the kill rate $f_D(t)$ depends on the time t, the amount of drug in the system $D(t)$, the efficacy rate p_D, and the resistance parameter r_D.

$$f_D(t) = p_D e^{(-r_D t)} D(t) \tag{22}$$

The chemotherapy will affect immune cells and cancer cells in the G2 and M phases. The death probability is calculated by the kill rate $f_D(t)$ divided by the maximum kill rate. A random number is drawn from a uniform distribution, if it is smaller than the survival probability, the cell with die and survive otherwise.

1.4 DNA damage response inhibitor

The DNA damage response inhibitor treatment module is based on a PKPD model from Terranova et al [7].

$$\frac{dCEN}{dt} = -(q + cl) * \frac{CEN}{v1} + q * \frac{PER}{v2} \tag{23}$$

$$\frac{dPER}{dt} = q * (\frac{CEN}{v1} - \frac{PER}{v2}) \tag{24}$$

where CEN is the drug amount in mg/m^2 given i.v. in the central compartment. From there the drug amount can be distributed and redistributed to the periphere compartment with the rate q where it will be the drug amount PER. The drug is cleared from the body with the rate cl. $v1$ is the volume of the central compartment and $v2$ is the volume of the periphere compartment. To take into account that the drug that reaches the cancer cells depends on the location, the drug amount predicted by the PK ODE model is scaled based on the predicted oxygen gradient. The drug effect $E(\bar{x}, t)$ at time t and at a certain location $\bar{x}$ is modelled by using the Emax model

$$E(\bar{x}, t) = Emax \frac{CEN(\bar{x}, t)^h}{EC_{50}^h + CEN(\bar{x}, t)^h} \tag{25}$$

where $Emax$ denotes the maximal drug effect. Emax is 1 when the repair inhibition is complete. EC_{50} is the drug concentration that archives half of the maximal drug effect ($0.5 * E_{max}$) and h is the Hill coefficient.

The drug only affects cancer cells in the S phase. A random number is drawn and compared with survival probability $E(\bar{x}, t)$. If that number is bigger than $E(\bar{x}, t)$, the cell dies.

Parameter	**Value**	**Units**	**Source**
Reaction rates (Gillespie algorithm)			
Cancer cell division rate	0.01	1/h	assumed
Cancer cell mutation rate	0.01	1/h	assumed
Cancer cell kill rate	0.01	1/h	assumed
Cancer cell death rate	0.01	1/h	assumed
Suppressor cell moving rate	0.01	1/h	assumed
Suppressor cell division rate	0.01	1/h	assumed
Suppressor cell infiltration rate	0.01	1/h	assumed
Effector cell exhaustion rate	0.01	1/h	assumed
Effector cell moving rate	0.01	1/h	assumed
Effector cell division rate	0.01	1/h	assumed
Effector cell infiltration rate	0.01	1/h	assumed
Cell attributes			
Cancer cells			
Initial number	100		assumed
Time to division	24	h	assumed
Suppressor cells			
Initial number	1		assumed
Time to division	8	h	assumed
Division count	8		assumed
Lifespan	3*24	h	assumed
Effector cells			
Initial number	1		assumed
Time to division	8	h	[8]
Division count	8		[8]
Lifespan	3*24	h	[8]
Oxygen PDE			
Diffusion coefficient D	1	$\mu m^2/d$	assumed
Division range	100-50	%	assumed
Quiescence range	50-30	%	assumed
Death range	30-0	%	assumed
Oxygen consumption rate for dividing cancer cells ko	0.001	$\%/d$	assumed
Factor for oxygen consumption of quiescent cells qc	0.01		assumed
PD1 antibody treatment			
Molecular weight	149000	g/mol	[9]
V1	2877/1000	l	[9]
V2	2854/1000	l	[9]
W0=V_tot	170/1000000	l	[9]
V_max	114/(MW)*1e3	nmol/h	[9]
V_es	0.005*V_tot	l	[9]
V_is	0.55*V_tot	l	[9]
K_M	0.078/(MW)*1e6	nmol/l	[9]
PLQ	12.7*V_vs	l/h/l	[9]
L	0.002*PLQ*V_vs	l/h/l	[9]
Q	384/(1000*24)	l/h	[9]

K_12	Q/V_1	1/h	[9]
K_21	Q/V_2	1/h	[9]
K_off_PD1	0.144	1/h	[9]
Kon_PD1_iv	2880e6/1e9	1/M/h	[9]
K_IVIV	1		[9]
K_on_PD1= Kon_PD1_iv/K_IVIV		1/nM/h	[9]
CL	167/(1000*24)	l/h	[9]
K	CL/V_1	1/h	[9]
N_Tcell	1000	number of T cells per μl blood	[9]
T_multi	4.3	initial ratio target concentration in tumour vs blood	[9]
V_blood	1400	μl	[9]
N_PD1_TC	10000	number of PD1 receptor per T cell	[9]
N_PD1_b	N_PD1_TC * N_Tcell * V_blood	number of PD1 in blood	[9]
M_PD1_b	N_PD1_b/AV*1e9	PD1 amount in nmoles in blood	[9]
C_PD1b	M_PD1_b/V_1	nmol/l	[9]
C_PD1t	T_multi*C_PD1b	nmol/l	[9]
vref	0.842		[9]
vref_is	0.2		[9]
CL_up	0.0366*V_es	l/h/l	[9]
FR	0.715		[9]
K_on_FcRn	792e6/(1e9)	1/nM/h	[9]
K_off_FcRn	23.9	1/h	[9]
K_deg	42.9	1/h	[9]
K_deg_PD1	0.00249	1/h	[9]
BW (human)	80	kg	[9]
Dose	2	mg/kg	[9]
Initial conditions			
C_1_0	D[nmol]/V_1	nmol/l	[9]
C_2_0	0	nmol/l	[9]
C_vs_0	0	nmol/l	[9]
C_ub_0	0	nmol/l	[9]
C_b_0	0	nmol/l	[9]
FcRn_0	49.8*1000	nmol/l	[9]
C_is_0	0	nmol/l	[9]
PD1_t_0	0	nmol/l	[9]

PD1_b_0	0	nmol/l	[9]
R0t_0	0	%	[9]
M_PD1_t_0	C_PD1b*T_multi*V_is_in	nmol	[9]
EMAXTP	94.7	%	[9]
EC50TP	1.46	nM	[9]
kout	K_deg_PD1	1/h	[9]
kin	M_PD1_t_0 * kout	nmol/h	[9]
Radiotherapy			
OER_m	3		[3]
Km	3		[3]
d	2.5	Gy	[3]
α	0.3		[3]
β	0.3		[3]
Immune cell infiltration			
δ_E	0.05	1/h	[5]
δ_S	0.01	1/h	[5]
c	0.05	1/h	[5]
Chemotherapy			
k_d	0.0285	1/week	assumed
$D(0)$	0.132	g	[6]
p_D	0.047714		assumed
r_D	0.01251		assumed
DNA damage response inhibitor			
q	295	l/h	[7]
cl	65	l/h	[7]
v1	118	l	[7]
v2	1030	l	[7]
Emax	1		assumed
h	1		assumed
EC50	100.84	mg	assumed

Table 1: Model parameters of the tumour immune interaction hybrid PKPD agent based model