SUPPLEMENTAL TABLE 1. Parameters in the RIT and in the Model

Parameter	Value	Sources
V	140 mL	*(Guyton and Hall, 2000; Silverberg et al., 2001)*
CL_{CSF}	20 mL/h	
$t_{1/2\text{-}I}$ of iodine 131	193 h	*(Kramer et al., 2007)*
$Dose_A$	2 mg	*(Kramer et al., 1997 ; Heiner et al., 1987)*
Molecular weight of anti-GD_2 (3F8)	150kD	
C_{I0}	370 MBq/mg	
k_{AR}	3×10^{3}-3×10^{5} $M^{-1}s^{-1}$	*(Xu and Cheung, 2007)*
k_{-AR}	3×10^{-5}-3×10^{-3} s^{-1}	
K_d	10^{-6}-10^{-10} M	
N_R	10^{5}-10^{7} antigens/cell	
S	≥1800 cm^2	*(Blasberg et al., 1977; Barta and Dazzan, 2003)*

C_{I0}	Initial specific activity of isotope (kBq/g)
CL_{CSF}	CSF bulk flow rate (mL/h)
$Dose_A$	Antibody dosage injected to the CSF space
k_{AR}	Association rate coefficient of antibody-tumor antigen binding (1/Ms)
k_{-AR}	Dissociation rate coefficient of antibody-tumor antigen unbinding (1/s)
K_d	Equilibrium dissociation constant (apparent affinity) (M)
k_I	Decay constant of isotope (1/s)
N_R	Number of antigens on the surface of individual tumor cell
S	Inner surface area of CSF space (m^2)
$t_{1/2\text{-}I}$	Half-life of the isotope (s)
V	CSF volume (mL)

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SUPPLEMENTAL TABLE 2. Estimation for Tumor Antigen Concentrations at the Surface of CSF Compartment

Antigen concentration C_{R0}* (antigens/ml)	**Fraction of CSF surface covered with one layer of tumor cells f (%)**	**Number of antigens at the surface of a single tumor cell N_R (antigens/cell)**
5.73×10^{11}	0.003	10^7
	0.03	10^6
	0.3	10^5
5.73×10^{12}	0.03	10^7
	0.3	10^6
	3	10^5
5.73×10^{13}	0.3	10^7
	3	10^6
	30	10^5
5.73×10^{14}	3	10^7
	30	10^6

* $C_{R0}=f \times C_{SC} \times N_R$. Here tumor cell density at the surface of CSF space $C_{SC}=\frac{1}{\frac{4}{3}\pi\left(\frac{D_T}{2}\right)^3}$, assume tumor cell diameter D_T=10 μm.

SUPPLEMENAL TABLE 3. Comparison of measured data and model predictions

Patient 1			Patient 2			Patient 3		
$Dose_A$= 2.30 mg protein C_{R0}= 5.73x10^{13} antigens/mL CL_{CSF}=20 mL/h, n=1,V=140 mL			$Dose_A$= 4.52 mg protein C_{R0}= 5.73x10^{14} antigens/mL CL_{CSF}=20 mL/h, n=1,V=140 mL			$Dose_A$= 2.86 mg protein C_{R0}= 5.73x10^{14} antigens/mL CL_{CSF}=17 mL/h, n=14,V=140 mL		
Time (min)	Experiment (kBq/g)	Model (kBq/g)	Time (min)	Experiment (kBq/g)	Model (kBq/g)	Time (min)	Experiment (kBq/g)	Model (kBq/g)
5	2748.95	2854.45	5	5859.86	5749.27	5	1919.20	2300.39
10	2722.83	2816.20	10	5813.70	5665.96	10	1807.42	1894.69
30	2621.78	2691.11	60	5372.24	5223.72	30	1560.02	1571.60
60	2477.076	2519.13	120	4887.15	4744.91	60	1431.62	1478.19
120	2211.49	2207.63	240	4046.26	3915.65	120	1339.92	1333.94
1590	146.21	92.85	1440	638.45	605.99	240	1209.61	1096.93
			2880	80.37	102.20	1440	437.75	291.89
						2880	129.28	122.97

Patient 4			Patient 5			Patient 6		
$Dose_A$= 2.82 mg protein C_{R0}= 5.73x10^{14} antigens/mL CL_{CSF}=13 mL/h, n=7,V=140 mL			$Dose_A$= 2.14 mg protein, C_{R0}= 5.73x10^{14} antigens/mL CL_{CSF}=17 mL/h, n=7, V=140 mL			$Dose_A$= 2.30 mg protein C_{R0}= 5.73x10^{14} antigens/mL CL_{CSF}=40 mL/h, n=6, V=140 mL		
Time (min)	Experiment (kBq/g)	Model (kBq/g)	Time (min)	Experiment (kBq/g)	Model (kBq/g)	Time (min)	Experiment (kBq/g)	Model (kBq/g)
5	2173.60	1440.19	5	12615.15	3355.44	5	2361.31	1899.20
15	671.03	771.66	10	4125.15	3228.03	15	1754.15	1281.24

30	613.20	664.87	20	3008.86	3124.91	30	823.47	1021.83
60	608.06	641.95	35	2916.28	3025.75	60	534.29	833.28
90	603.34	626.68	60	2789.34	2879.84	120	423.95	621.90
120	598.65	612.04	120	2506.81	2540.88	240	319.99	389.73
300	571.29	535.15	360	1635.31	1560.73	510	154.92	197.05
1440	424.79	278.50	720	861.63	774.08	1620	12.53	52.22
2880	292.16	154.71	1080	453.99	409.73	3000	6.06	19.39
			1440	239.21	236.01			

Patient 7			**Patient 8**			**Patient 9**		
$Dose_A$= 0.22 mg protein, C_{R0}= 5.73x10^{14} antigens/mL, CL_{CSF}=17 mL/h, n=1, V=140 mL			$Dose_A$= 4.44 mg protein, C_{R0}= 5.73x10^{14} antigens/mL CL_{CSF}=30 mL/h, n=11,V=140 mL			$Dose_A$= 3.94 mg protein, C_{R0}= 5.73x10^{14} antigens/mL, CL_{CSF}=25 mL/h, n=13, V=100 mL		
Time (min)	Experiment (kBq/g)	Model (kBq/g)	Time (min)	Experiment (kBq/g)	Model (kBq/g)	Time (min)	Experiment (kBq/g)	Model (kBq/g)
5	612.01	265.54	5	5098.42	2152.96	5	6247.40	1454.54
15	612.01	221.93	15	4206.85	2012.72	15	2951.15	507.24
30	461.08	185.46	30	2284.32	1875.37	30	1024.30	399.00
60	156.55	154.60	60	1221.43	1629.44	60	416.85	381.92
120	152.60	134.72	120	514.06	1235.01	240	136.50	321.91
210	110.51	118.81	480	73.91	314.28	1020	32.55	190.92
1290	11.42	33.39	1140	12.62	111.10	1500	16.78	151.12

1680	5.72	75.07
3000	2.72	42.44

Patient 10		
$Dose_A$= 4.36 mg protein, C_{R0}= 5.73x10^{14} antigens/mL, CL_{CSF}=20 mL/h, n=1,V=100 mL		
Time (min)	Experiment (kBq/g)	Model (kBq/g)
10	9016.88	8134.78
23	8555.96	7745.39
40	7990.21	7266.44
65	7228.61	6615.61
125	5696.79	5282.76
285	3074.21	2907.14
1445	114.88	101.71

* n is the number of tumor cell layers (defined in Eq. A5). Other parameters are the same as in Fig. 2 of the main text.

Appendix

In the CSF space, we considered,

(A) Binding/dissociation between antibodies and antigens

A free antibody A binding to an antigen R on the surface of tumor cells satisfies,

$$A+R \underset{k_{-AR}}{\overset{k_{AR}}{\rightleftarrows}} AR \qquad (A1)$$

where AR is the bound antibody to antigen, k_{AR} is the association rate constant and k_{-AR} the dissociate rate constant, respectively. Mass balance for the free, bound antibodies and antigens gives,

$$\frac{dC_{AR}}{dt} = k_{AR}C_A C_R - k_{-AR}C_{AR} \qquad (A2)$$

$$\frac{dC_A}{dt} = k_{-AR}C_{AR} - k_{AR}C_A C_R \qquad (A3)$$

$$\frac{dC_R}{dt} = k_{-AR}C_{AR} - k_{AR}C_A C_R \qquad (A4)$$

where C_A, C_{AR} and C_R are the concentrations of the free antibody A, bound antibody or antigen AR, and the tumor antigen R, correspondingly.

Tumor cells with diameter D_T are assumed to exist at the surface of the CSF compartment with surface area S and the binding of antibodies to tumor antigens only occurs at the surface. If the CSF bulk flow can wash away the unbound antibodies at rate CL_{CSF}, for an antibody infusion rate of INF_A, mass conservation for free antibodies gives,

$$\frac{dC_A}{dt} = \frac{1}{V} INF_A - \frac{CL_{CSF}}{V} C_A + \frac{nSDT}{V}(k_{-AR}C_{AR} - k_{AR}C_A C_R) \qquad (A5)$$

where V is the CSF volume. The tumor occupied volume nSD_T (n is the number of tumor cell layers) at the surface of the CSF space is much less than V. The first term on the right hand side of Eq. A5 represents the increase rate of the free antibody by infusion (INF_A = 0 under single bolus and split dosing administrations), the second term is the clearance rate of the free antibody by the CSF bulk flow, and the third term indicates the changing rate of the free antibody due to binding/dissociation to/from tumor antigens at the surface of the CSF space.

The initial conditions for Eqs. A2, A4 and A5 are,

$$t = 0,\ C_A(0) = C_{A0},\ C_{AR}(0) = 0,\ C_R(0) = C_{R0} \qquad \text{(A6)}$$

where $C_{A0} = \frac{Dose_A}{V}$ is the initial concentration of antibodies when single bolus with dosage $Dose_A$ is injected. For continuous infusion, $C_{A0} = 0$, while for split dosing, $C_A(t^*) = \frac{1}{n_s}\frac{Dose_A}{V}$, n_s is the number of dosing, t*= i × interval time between dosing (i = 0, 1, 2, …n_s-1). The 4th order Runge-Kutta method (any numerical method book such as the one listed in the end) was used to solve Eqs. A2, A4 and A5 with initial conditions in Eq. A6. The convergence criterion was 10^{-10} in the relative magnitude of residuals for $C_A(t)$, $C_{AR}(t)$, and $C_A(t)$.

(B) Decay of isotope

The decay of radioactive isotope satisfies,

$$I \xrightarrow{k_I} I' + \alpha \qquad \text{(A7)}$$

where I′ is the decayed isotope. k_I is the decay constant of isotope ($k_I = \ln 2 / t_{1/2-I}$), $t_{1/2-I}$ is the half-life of the isotope. The decay rate of isotope is,

$$\frac{dC_I}{dt} = -k_I C_I \qquad \text{(A8)}$$

Initial condition for Eq. A8 is,

$$t = 0, C_I(0) = C_{I0} \quad \text{(A9)}$$

where C_I is the specific activity of an isotope, C_{I0} is the initial specific activity of an isotope. The solution of Eq. A8 with the initial condition Eq. A9 is,

$$C_I(t) = C_{I0}\exp(-k_I t) \quad \text{(A10)}$$

Finally, the radioactivity on free and bound antibodies C_{IA}, C_{IAR} in the CSF are,

$$C_{IA} = 3.7\times10^7 \cdot C_A \cdot MW \cdot C_I / \rho_{CSF} \ \ (kBq/g) \quad \text{(A11)}$$

$$C_{IAR} = 3.7\times10^7 \cdot C_{AR} \cdot MW \cdot C_I / \rho_T \ \ (kBq/g) \quad \text{(A12)}$$

where C_A and C_{AR} are the concentrations of the free and bound antibodies obtained from Eqs. A2-A5. They are in the unit of M, and C_I obtained from Eq. A10 is in the unit of mCi/mg. ρ_{CSF} is the density of CSF, ρ_T the density of tumor tissue, and MW is the molecular weight of the antibody.

From Eqs.A2-A6, we can see that time-changing concentrations $C_A(t)$, $C_{AR}(t)$, and $C_R(t)$ depend on association/dissociation rate constants k_{AR} and k_{-AR}, or the affinity of the antibody to the antigen $K_d = \frac{k_{-AR}}{k_{AR}}$, the CSF volume (V), the CSF bulk flow rate (CL_{CSF}), the tumor occupied volume (SD_T), the tumor antigen concentration (C_{R0}), the amount (dosage) of the antibody administered (*Dose*$_A$), antibody administration schedules (single bolus: $C_{A0} = \frac{Dose_A}{V}$; continuous infusion: INF_A; split dosing: $C_A(t^*) = \frac{1}{n_s}\frac{Dose_A}{V}$).

From Eqs. A8-A12, we can see that in addition to these kinetic and transport parameters, the radioisotope-labeled free antibody concentration $C_{IA}(t)$ and the bound antibody concentration $C_{IAR}(t)$ depend on the specific activity of isotope (C_{I0}), and the isotope half-life ($t_{1/2\text{-}I}$) as well.

After solving for the $C_{IA}(t)$ and $C_{IAR}(t)$, the area under the C_{IA} vs. time curve $AUC(C_{IA})$ and the area under the C_{IAR} vs. time curve $AUC(C_{IAR})$ can be calculated by the following integrations:

$$AUC(C_{IA}) = \int_0^{\infty} C_{IA}(t)dt \text{ and } AUC(C_{IAR}) = \int_0^{\infty} C_{IAR}(t)dt$$

Because the integrands $C_{IA}(t)$ and $C_{IAR}(t)$ depend on the above described kinetic and transport parameters, $AUC(C_{IA})$ and $AUC(C_{IAR})$ also depend on these parameters. By choosing the optimal values for these parameters in the RIT, we can maximize $AUC(C_{IAR})$ and minimize $AUC(C_{IA})$.

Reference for the Runge-Kutta method:

Chapra SC and Canale RP. Numerical Methods for Engineers. Third Edition, WCB/McGraw-Hill, Boston, 1998.