Supplementary Material for

Utilizing Minimal Physiologically Based Pharmacokinetic Modeling to Bridge Bevacizumab Pharmacokinetics from Adult to Pediatric Patients

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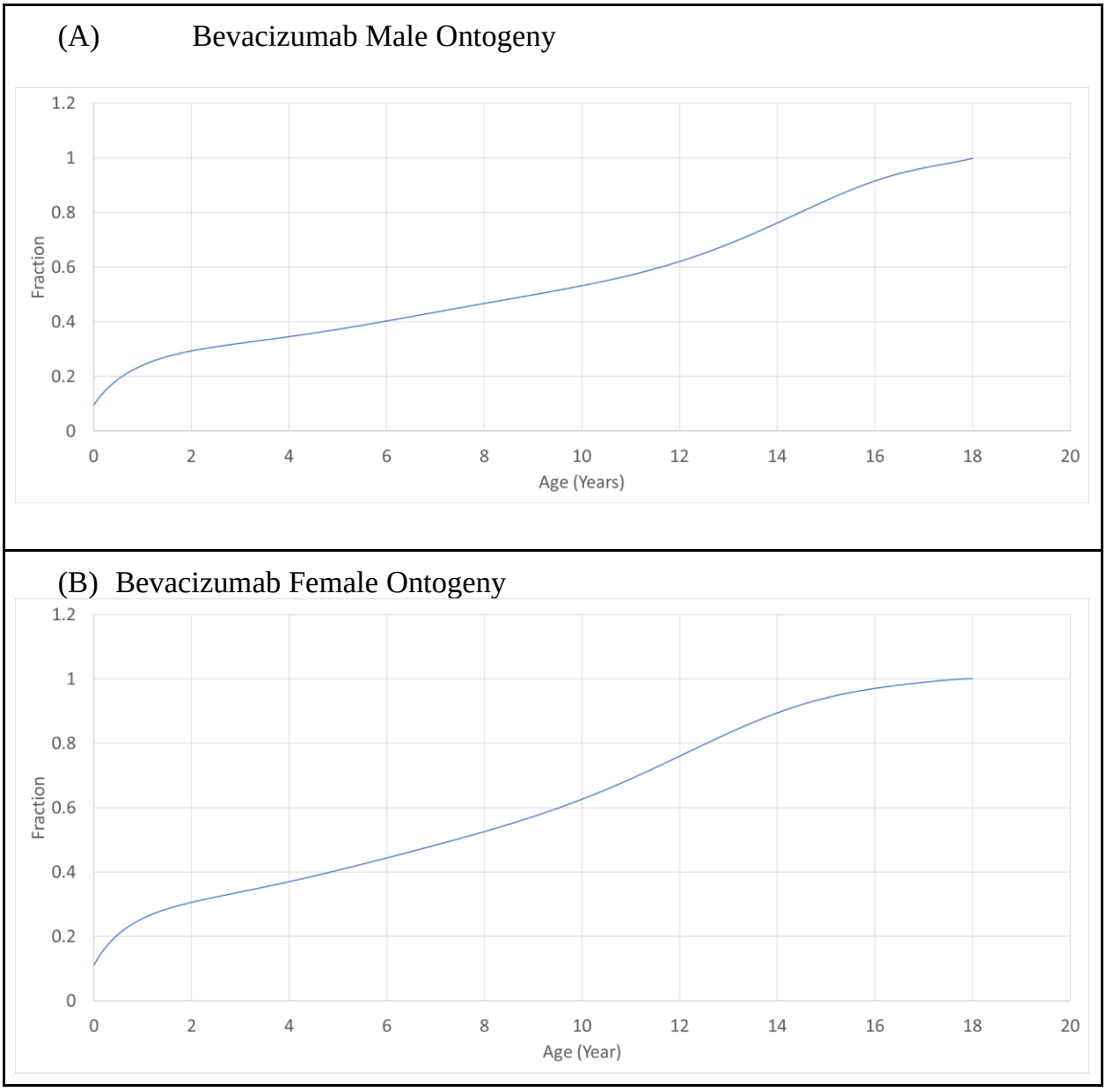
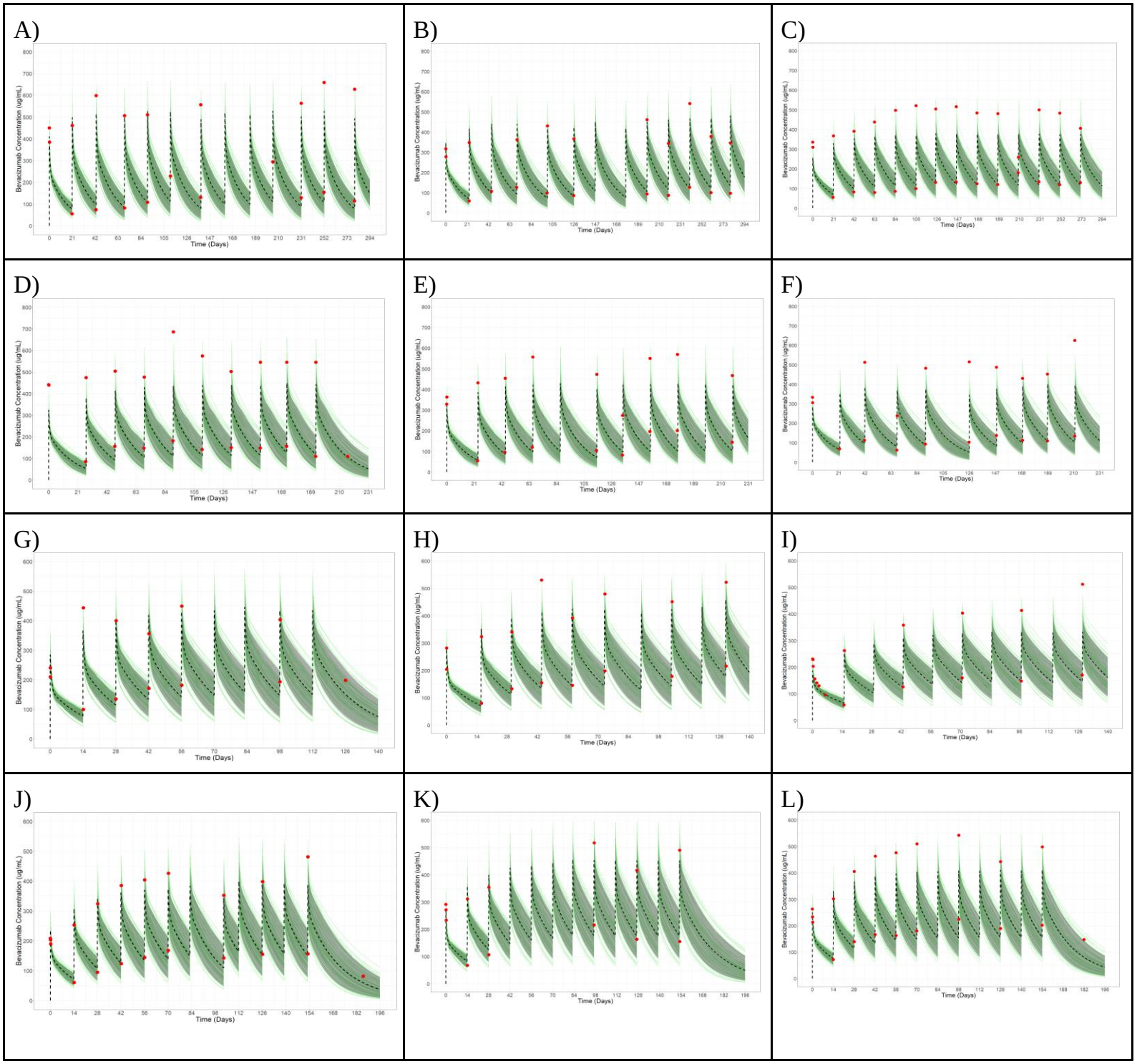
Figure S1
Pediatrics Ontogeny Additional Clearance Scaling Factor



Note: Bevacizumab male (A) and female (B) ontogeny scaling for the fractional additional clearance relative to body weight.

Figure S2

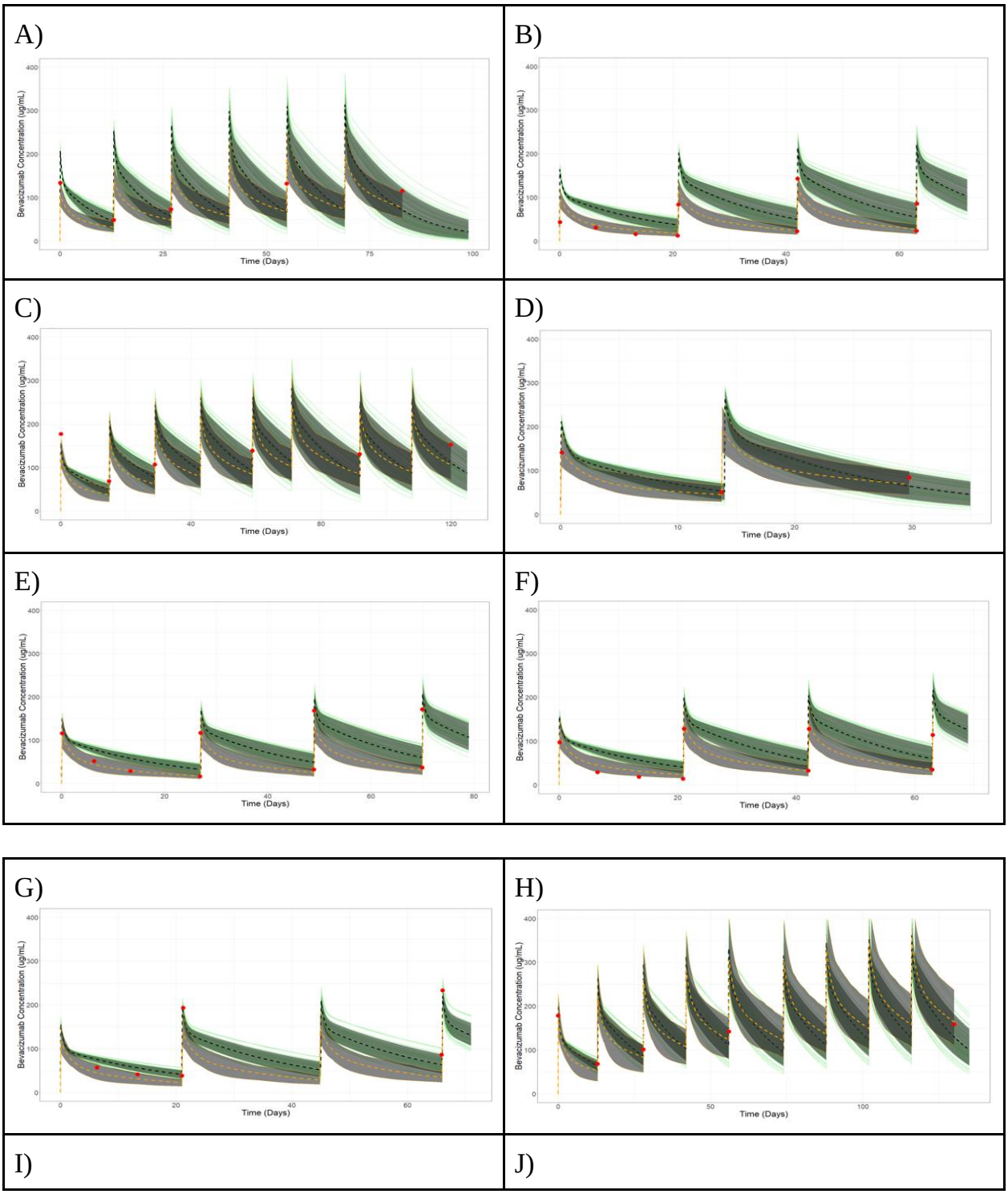
Adult PBPK Bevacizumab 15 mg/kg & 10 mg/kg Time vs. Concentration Plot Simulation Overlay with Clinical Data

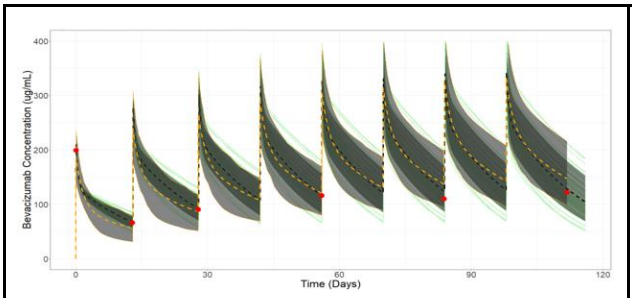


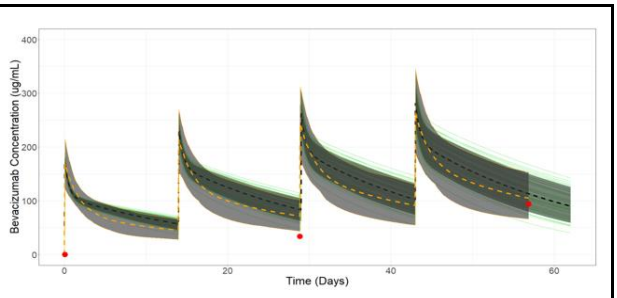
Note: The figure presents data from patients who received two different dosages. For those administered 15 mg/kg, the data includes three female patients: a 72-year-old with a solid tumor (Panel A), a 70-year-old with a solid tumor (Panel B), and a 64-year-old with a solid tumor (Panel C). Additionally, three male patients were included: a 72-year-old with a solid tumor (Panel D), a 65-year-old with a solid tumor (Panel E), and a 53-year-old with a solid tumor (Panel F). For the 10 mg/kg dosage group, the data comprises three female patients: a 53-year-old with breast cancer (Panel G), a 49-year-old with breast cancer (Panel H), and a 41-year-old with breast cancer (Panel I). The male patients in this group include a 71-year-old with a solid tumor (Panel J), a 70-year-old with a solid tumor (Panel K), and an 80-year-old with a solid tumor (Panel L). The red circles represent the observed data obtained from clinical studies. The green lines represent 100 simulated virtual patients, the dashed black line represents the mean data for the simulated virtual patients. The green shaded area represents the 5th to 95th percentiles of the simulation.

Figure S3

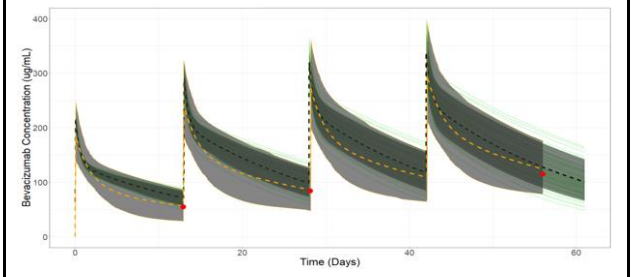
PBPK & PopPK Simulation Overlay with Clinical Data – Age Distribution Ranging from 6 months to 6 Years Old



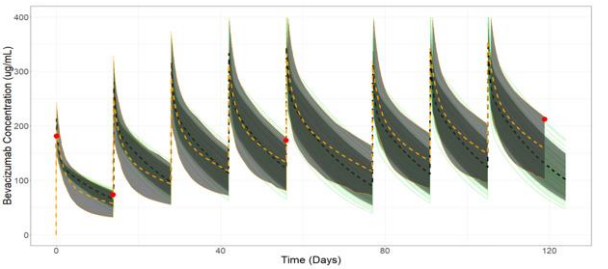

Bevacizumab Concentration (ug/mL)
Time (Days)


Bevacizumab Concentration (ug/mL)
Time (Days)

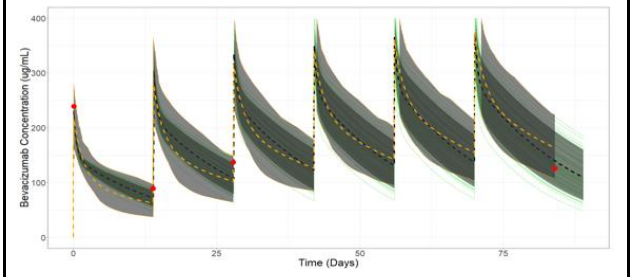
K)


Bevacizumab Concentration (ug/mL)
Time (Days)

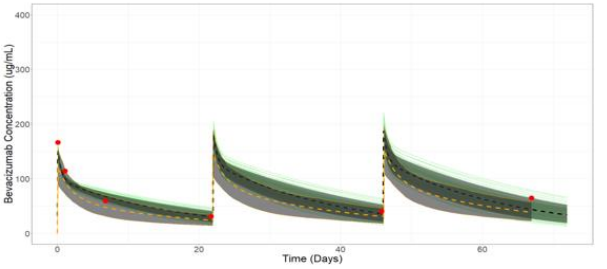
L)


Bevacizumab Concentration (ug/mL)
Time (Days)

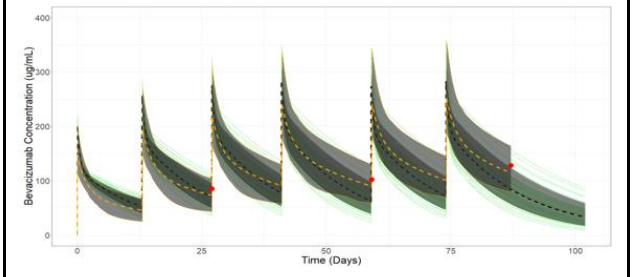
M)


Bevacizumab Concentration (ug/mL)
Time (Days)

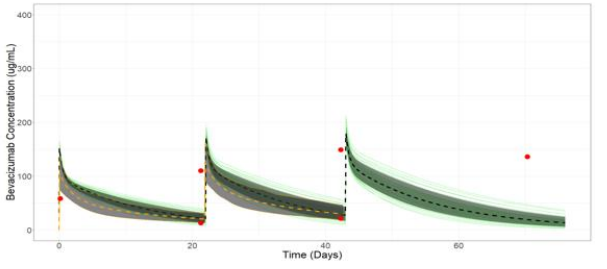
N)


Bevacizumab Concentration (ug/mL)
Time (Days)

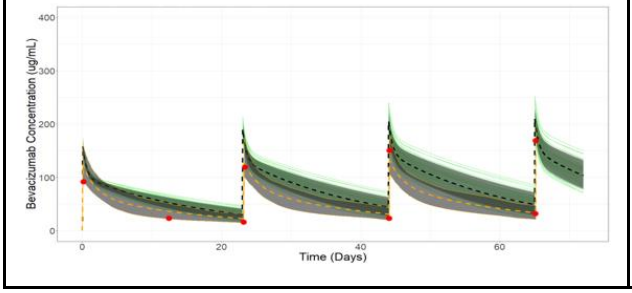
O)


Bevacizumab Concentration (ug/mL)
Time (Days)

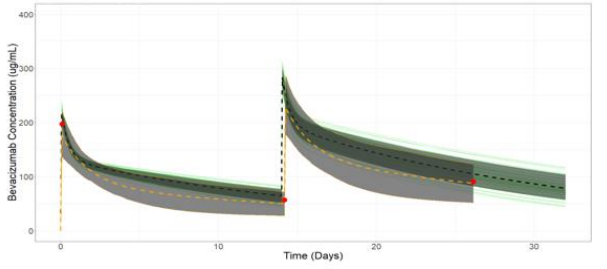
P)


Bevacizumab Concentration (ug/mL)
Time (Days)

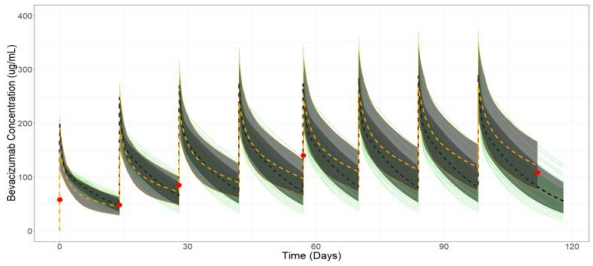
Q)


Bevacizumab Concentration (ug/mL)
Time (Days)

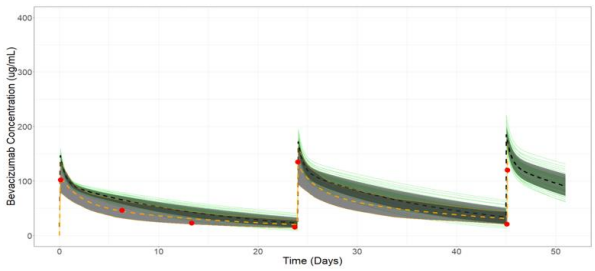
R)


Bevacizumab Concentration (ug/mL)
Time (Days)

S)



T)



Note: Bevacizumab time vs. concentration plots of pediatric aged 6 months to 6 years old. The red circles represent the observed data. The green lines represent 100 PBPK-simulated patients, with the green shaded area showing the 5th to 95th percentiles of the PBPK simulations. The dashed black lines represent the mean data for the PBPK simulated individuals. Similarly, the dashed orange line represents the mean data for the PopPK simulated individuals, and the orange shaded area represents the 5th to 95th percentiles of the PopPK simulations. A) 6-months-old male on 10 mg/kg, B) 1-year-old male on 7.5 mg/kg, C) 2-year-male on 7.5 mg/kg, D) 2-year-old male on 10 mg/kg, E) 2-year-old female on 7.5 mg/kg, F) 2-year-old female on 7.5 mg/kg. G) 3 year old female on 7.5 mg/kg, H) 3.4 year old female on 10 mg/kg, I) 3.7 year old female on 10 mg/kg, J) 5.3 year old female on 8.5 mg/kg, K) 4.2 year old female on 10 mg/kg, L) 4.7 year old female on 10 mg/kg, M) 5.6 year old female on 11 mg/kg, N) 6 year old male on 7.5 mg/kg, O) 4.3 year old male on 9 mg/kg, P) 5 year old male on 7.5 mg/kg, Q) 6 year old male on 7.5 mg/kg, R) 4.6 year old male on 9 mg/kg, S) 5.6 year old male on 10 mg/kg, T) 4 year old male on 7.5 mg/kg.

Table S1
Summary of Studies and Observed Clinical Data

Adult Studies

Study	Indication	Phase	No. of Patients (M/F)	No. of PK Samples	Age Range (year)	Weight Range (kg)
AVF0737g	Solid tumors	I	25 (8/17)	554	21-70	48.50-108.00
AVF0757g	NSCLC	II	66 (35/31)	1230	34-80	40.00-152.00
AVF0775g	HRPC	II	15 (M)	257	62-83	65.90-139.10
AVF0776g	Breast cancer	II	74 (F)	937	31-78	40.45-133.00
AVF0780g	CRC	II	67 (32/35)	1233	25-85	42.00-129.10
AVF2107g	CRC	III	236 (141/95)	733	27-88	44.00-195.00
AVF2119g	Breast cancer	III	38 (F)	151	31-75	46.70-108.90
BO17706	Pancreatic cancer	III	80 (45/35)	242	20-81	39.50-106.80
JO18157	CRC	I	18 (8/10)	422	45-72	36.50-83.00
JO19901	Breast cancer	II	69 (F)	718	34-70	38.00-88.80
JO19907	NSCLC	II	59 (35/24)	553	35-72	36.40-95.60
BP20689	Solid tumors	I	39 (16/23)	720	37-73	42.50-83.50

Pediatric Studies

Study	Indication	Phase	No. of Patients (M/F)	No. of PK Samples	Age Group	Weight (kg)
AVF2771s (NCT00085111)	Solid tumors	I	6 (4/2)	61	6-12yo: 2 12-18yo: 4	23-68
AVF3842s (NCT00381797)	Gliomas	II	71 (36/35)	307	< 2yo: 3 2-6yo: 16 6-12yo: 32 12-18yo: 20	5.94-104.6
AVF4117s (NCT00667342)	Osteosarcoma	II	25 (15/10)	686	6-12yo: 13 12-18yo: 12	22.10-109.60
BO20924 (NCT00643565)	RMS/NRSTS	II	39 (22/17)	298	< 2yo: 4 2-6yo: 6 6-12yo: 11 12-18yo: 18	11.60-76.70

NSCLC: Non-Small Cell Lung Cancer, *HRPC*: Hormone Refractory Prostate Cancer *CRC*: Metastatic Colorectal Cancer, *RMS*: Rhabdomyosarcoma, *NRSTS:* Non-Rhabdomyosarcoma Soft Tissue Sarcoma

Table S2
Bevacizumab Single Dose Adult Patient Demographics

Dose	Male	Female
15 mg/kg	● Number of patients: 54 ● Ages: 18 – 73 years old ● Average Height: 168 cm ● Average Weight: 67 kg	● Number of patients: 75 ● Ages: 19 – 80 years old ● Average Height: 160 cm ● Average Weight: 62 kg
10 mg/kg	● Number of patients: 41 ● Ages: 44 – 85 years old ● Average Height: 175 cm ● Average Weight: 79 kg	● Number of patients: 135 ● Ages: 24 – 82 years old ● Average Height: 160 cm ● Average Weight: 62 kg
5 mg/kg	● Number of patients: 169 ● Ages: 29 – 88 years old ● Average Height: 177 cm ● Average Weight: 82 kg	● Number of patients: 131 ● Ages: 18 – 79 years old ● Average Height: 161 cm ● Average Weight: 64 kg

Table S3
Adult PBPK Bevacizumab 10 mg/kg every two weeks Simulation

Sex	Age [n]	Average	Single Dose (C1)			Multiple Dose (C9)		
			AUC_{tau} (mg.hr/L)	C_{max} (mg/L)	C_{min} (mg/L)	AUC_{tau} (mg.hr/L)	C_{max} (mg/L)	C_{min} (mg/L)
Female	≥ 18 [100]	Geo Mean	36231.10	262.33	77.25	70269.00	404.62	134.96
		Median	36765.82	261.61	77.70	71900.28	410.35	140.59
		5th – 95th Percentile	29706.09 – 42330.66	209.07 – 332.56	55.99 – 97.53	67168.72 – 73512.39	393.02 – 416.57	126.42 – 144.08
Male	≥ 18 [100]	Geo Mean	32220.16	212.68	69.66	63469.58	341.77	123.13
		Median	32411.56	208.63	69.02	63249.36	341.00	126.66
		5th – 95th Percentile	27196.03 – 36512.43	183.49 – 253.73	50.18 – 87.80	60661.75 – 66407.37	332.56 – 351.25	115.38 – 131.40