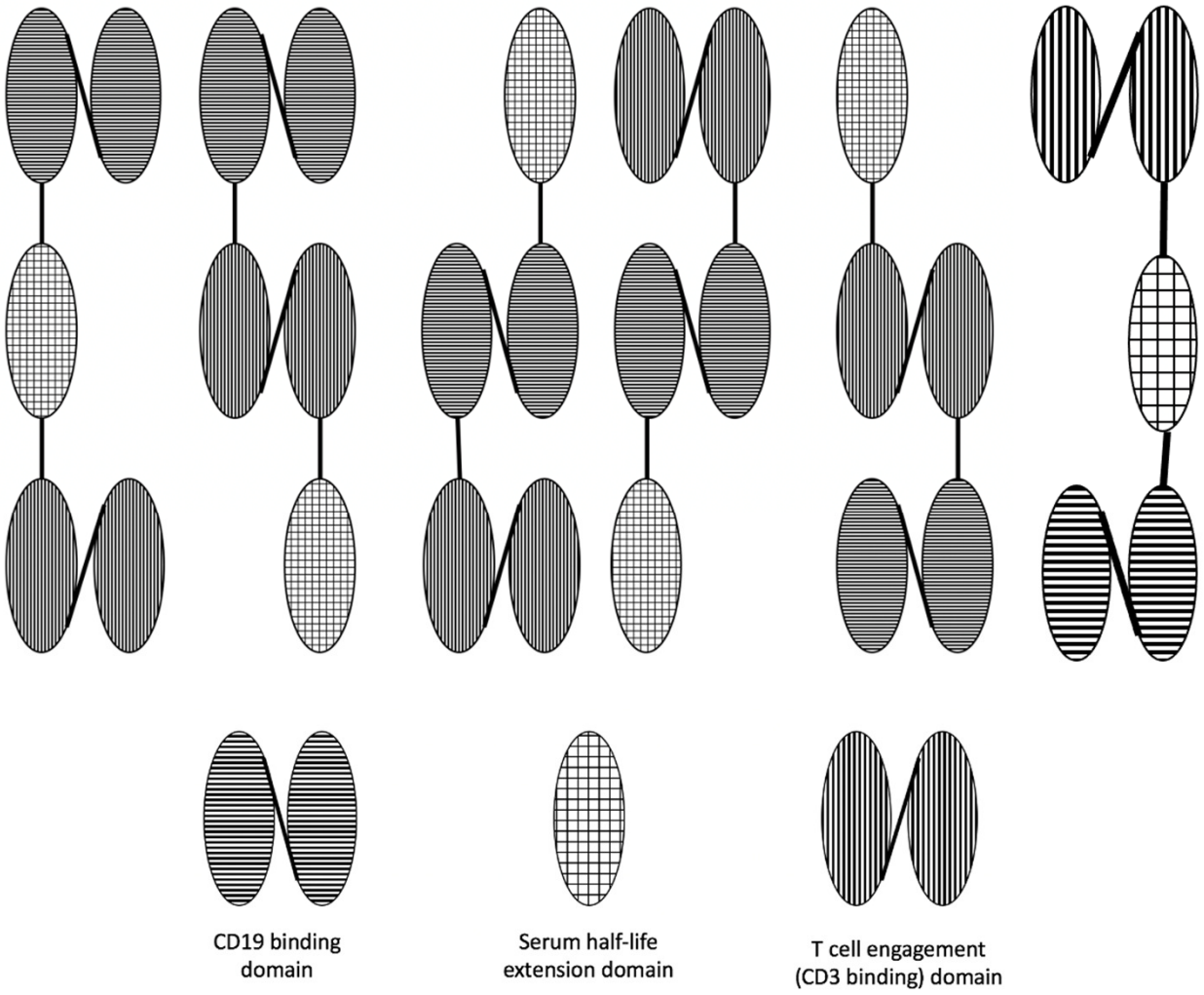

CD19 binding domain
Serum half-life extension domain
T cell engagement (CD3 binding) domain

FIG. 1A

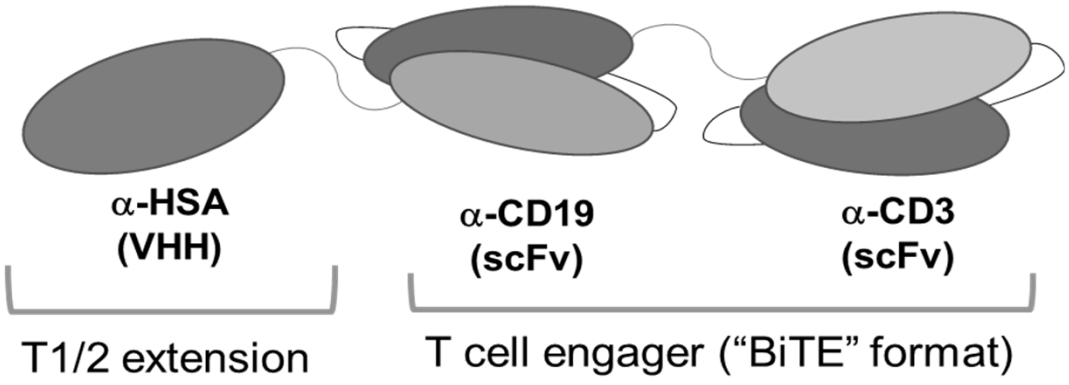

α-HSA (VHH)
α-CD19 (scFv)
α-CD3 (scFv)
T1/2 extension
T cell engager ("BiTE" format)

FIG. 1B

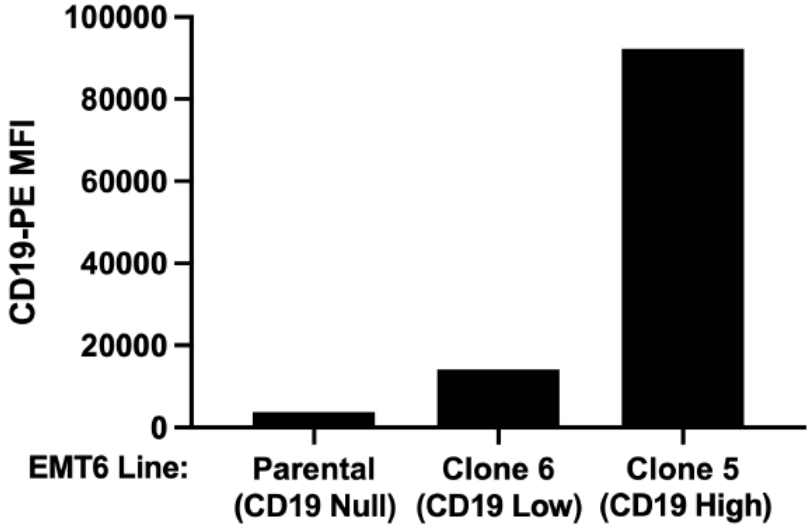

100000
80000
60000
40000
20000
0
CD19-PE MFI
EMT6 Line:
Parental
(CD19 Null)
Clone 6
(CD19 Low)
Clone 5
(CD19 High)

FIG. 2A

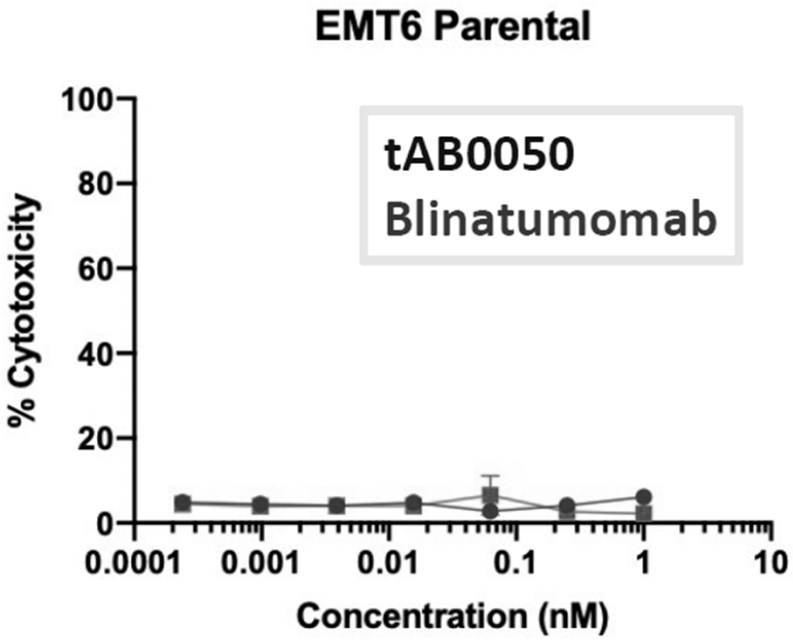

EMT6 Parental
tAB0050
Blinatumomab
% Cytotoxicity
100
80
60
40
20
0
0.0001
0.001
0.01
0.1
1
10
Concentration (nM)

FIG. 2B

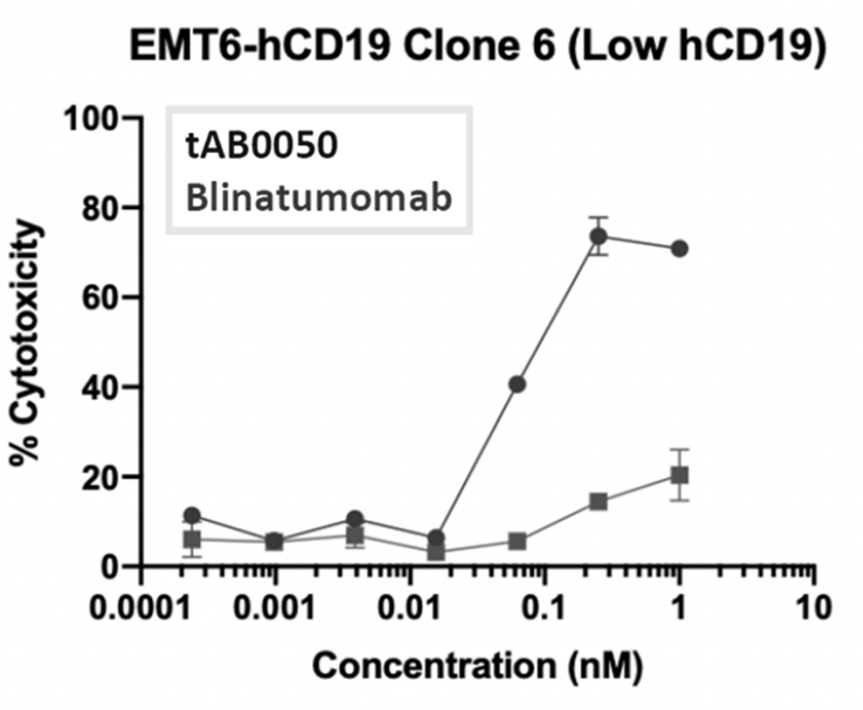

EMT6-hCD19 Clone 6 (Low hCD19)
tAB0050
Blinatumomab
% Cytotoxicity
100
80
60
40
20
0
0.0001
0.001
0.01
0.1
1
10
Concentration (nM)

FIG. 2C

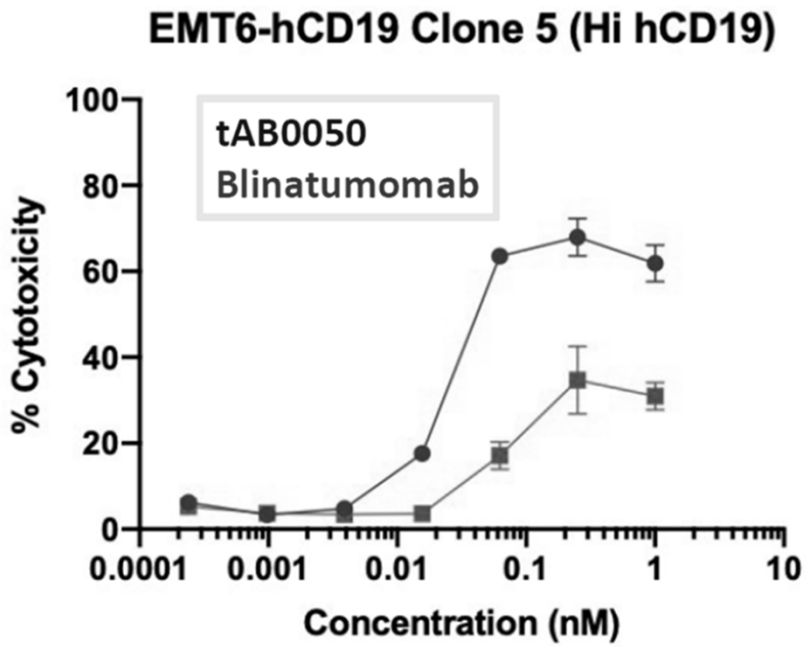

EMT6-hCD19 Clone 5 (Hi hCD19)
tAB0050
Blinatumomab
% Cytotoxicity
100
80
60
40
20
0
0.0001
0.001
0.01
0.1
1
10
Concentration (nM)

FIG. 2D

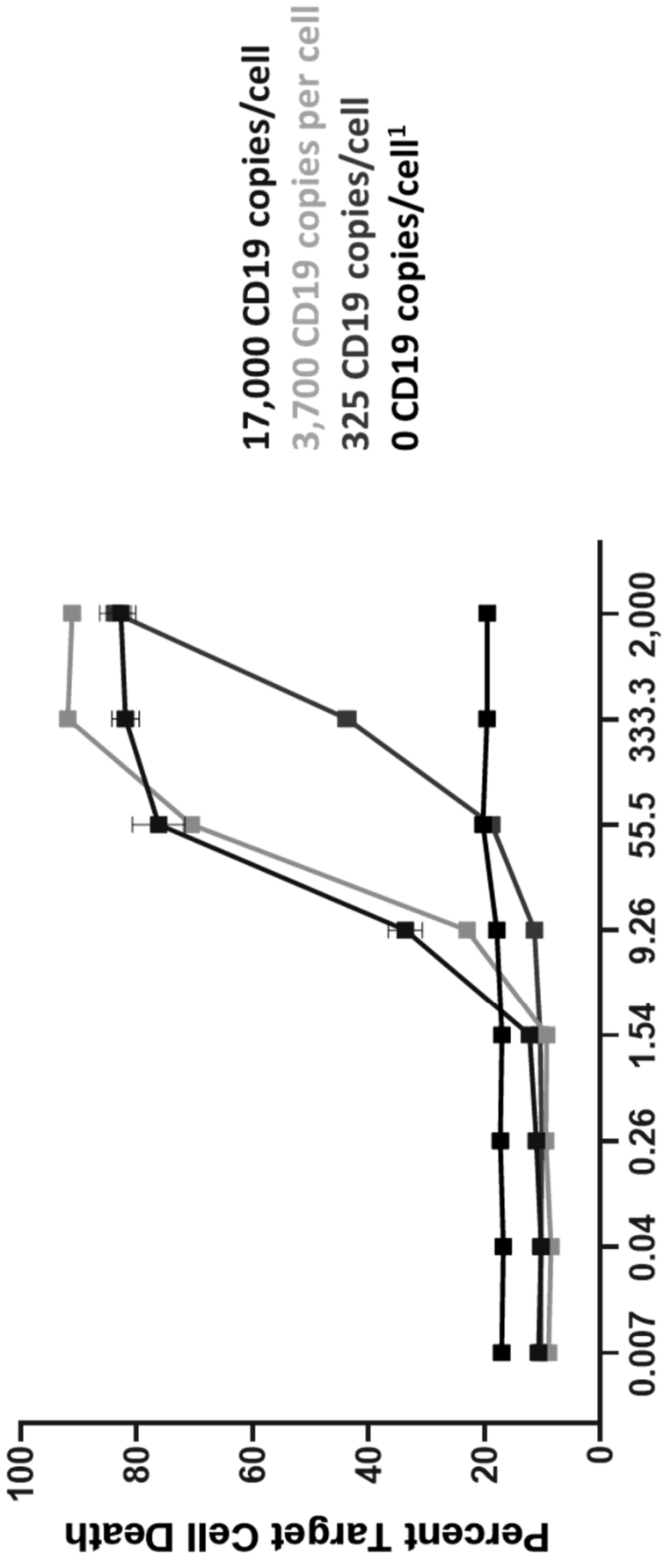

17,000 CD19 copies/cell
3,700 CD19 copies per cell
325 CD19 copies/cell
0 CD19 copies/cell[1]
Percent Target Cell Death
100
80
60
40
20
0
0.007
0.04
0.26
1.54
9.26
55.5
333.3
2,000
Concentration (pM)

FIG. 3A

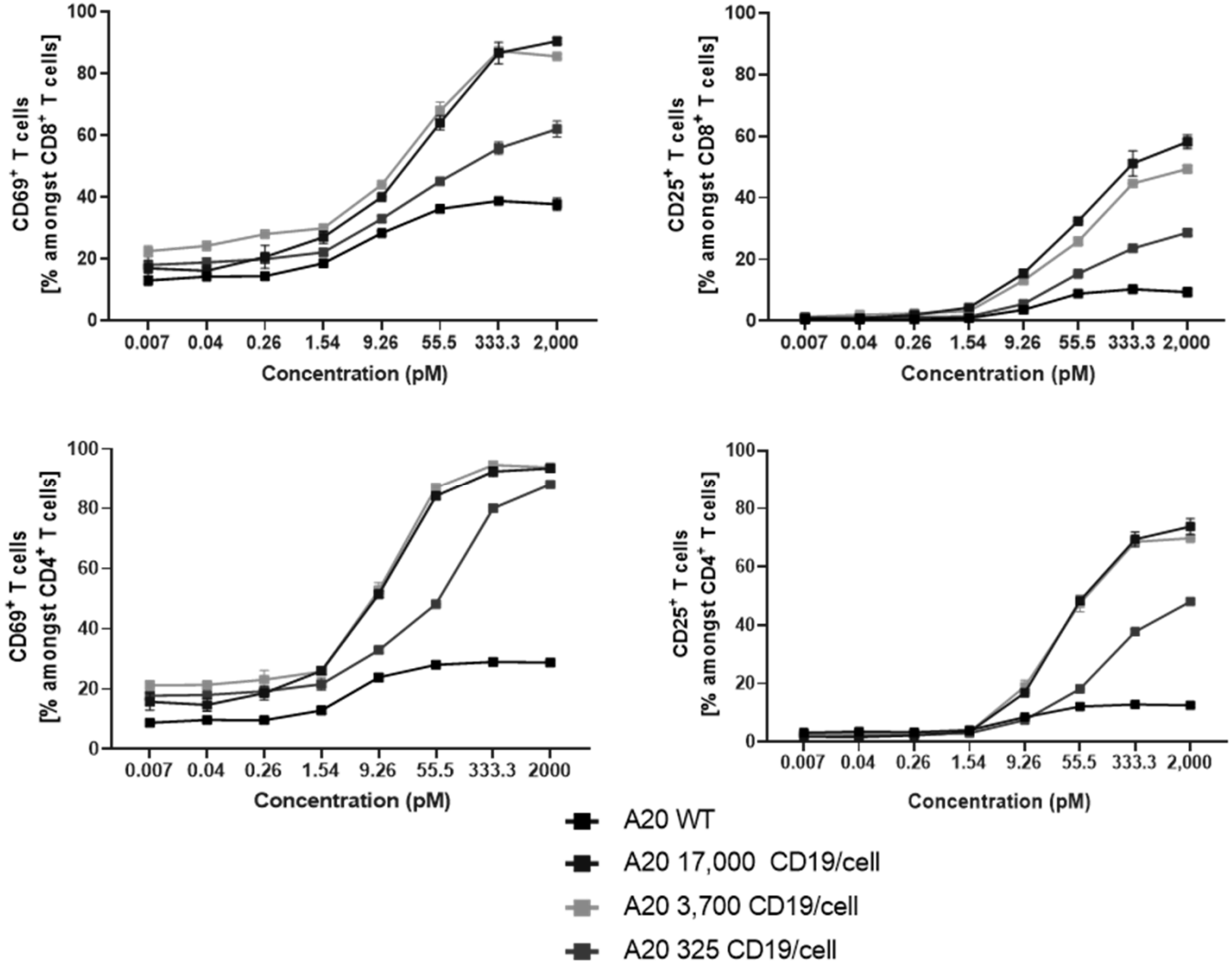

CD69+ T cells [% amongst CD8+ T cells]
CD25+ T cells [% amongst CD8+ T cells]
CD69+ T cells [% amongst CD4+ T cells]
CD25+ T cells [% amongst CD4+ T cells]
0
20
40
60
80
100
0.007 0.04 0.26 1.54 9.26 55.5 333.3 2,000
0.007 0.04 0.26 1.54 9.26 55.5 333.3 2000
Concentration (pM)
A20 WT
A20 17,000 CD19/cell
A20 3,700 CD19/cell
A20 325 CD19/cell

FIG. 3B

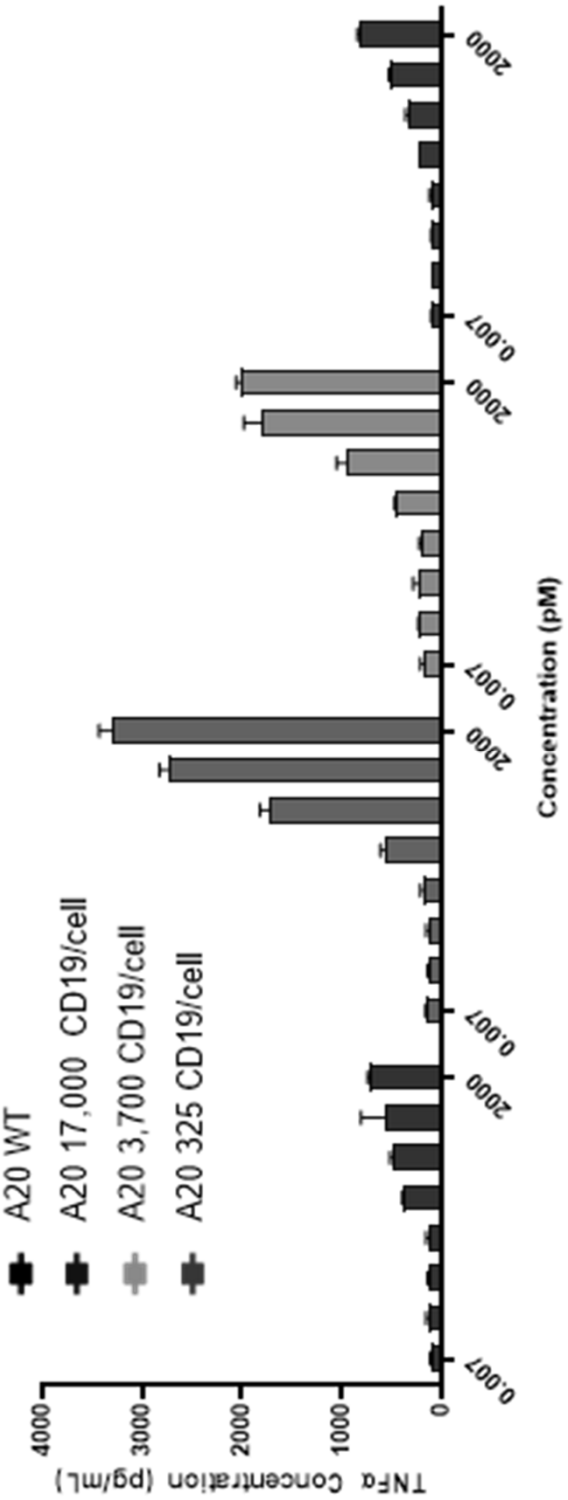

A20 WT
A20 17,000 CD19/cell
A20 3,700 CD19/cell
A20 325 CD19/cell
TNFa Concentration (pg/mL)
4000
3000
2000
1000
0
0.007
2000
Concentration (pM)

FIG. 3C

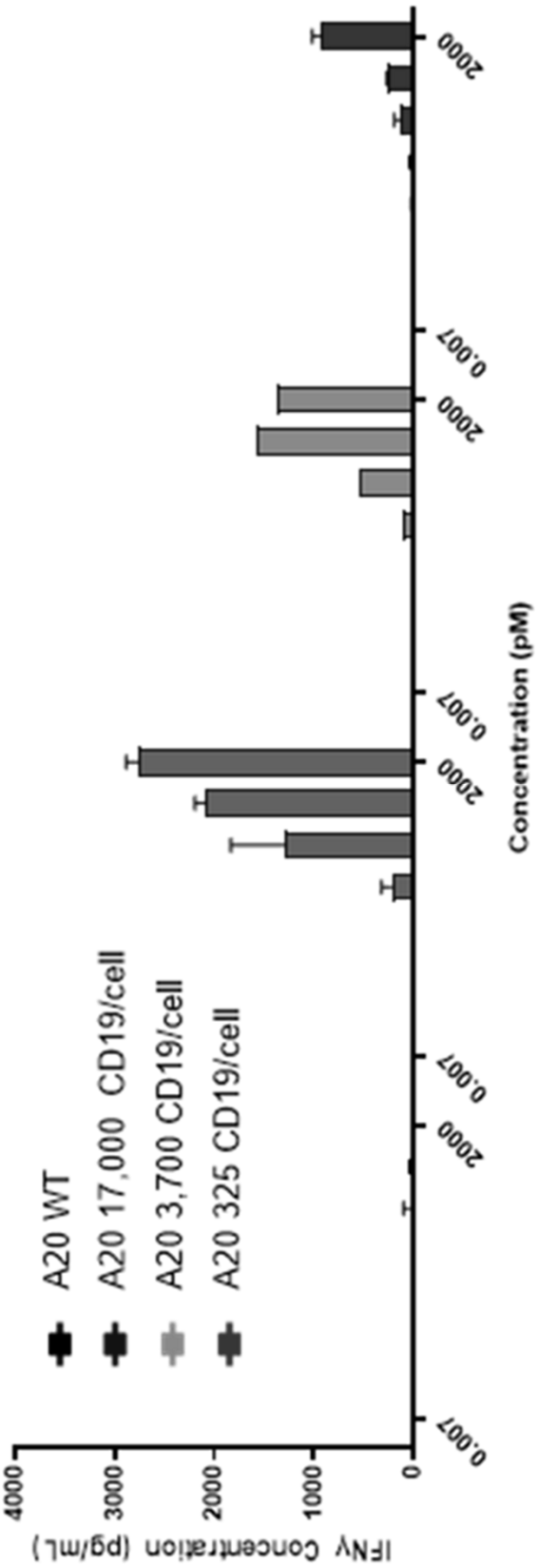

IFNγ Concentration (pg/mL)
4000
3000
2000
1000
0
A20 WT
A20 17,000 CD19/cell
A20 3,700 CD19/cell
A20 325 CD19/cell
0.007
2000
0.007
2000
0.007
2000
0.007
2000
Concentration (pM)

FIG. 3D

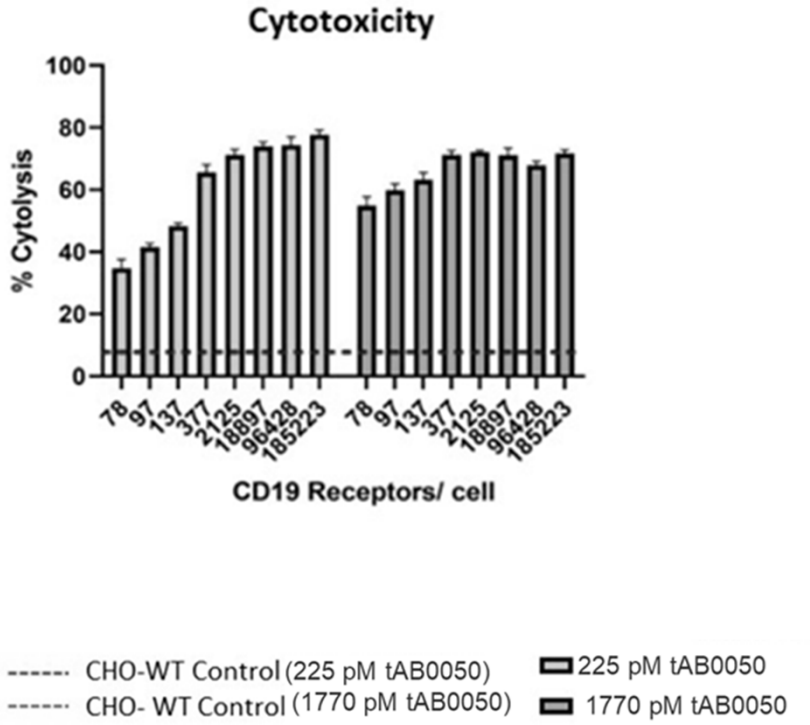

Cytotoxicity
% Cytolysis
100
80
60
40
20
0
78
97
137
377
2125
18897
96428
185223
CD19 Receptors/ cell
CHO-WT Control (225 pM tAB0050)
CHO- WT Control (1770 pM tAB0050)
225 pM tAB0050
1770 pM tAB0050

FIG. 4A

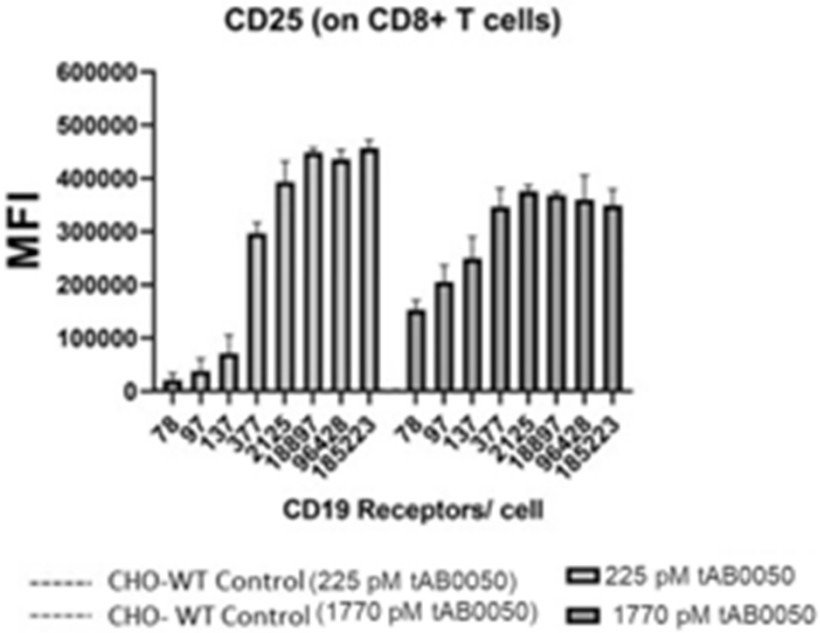

CD25 (on CD8+ T cells)
MFI
600000
500000
400000
300000
200000
100000
0
78
97
137
377
2125
18897
96428
185223
CD19 Receptors/ cell
CHO-WT Control (225 pM tAB0050)
CHO- WT Control (1770 pM tAB0050)
225 pM tAB0050
1770 pM tAB0050

FIG. 4B

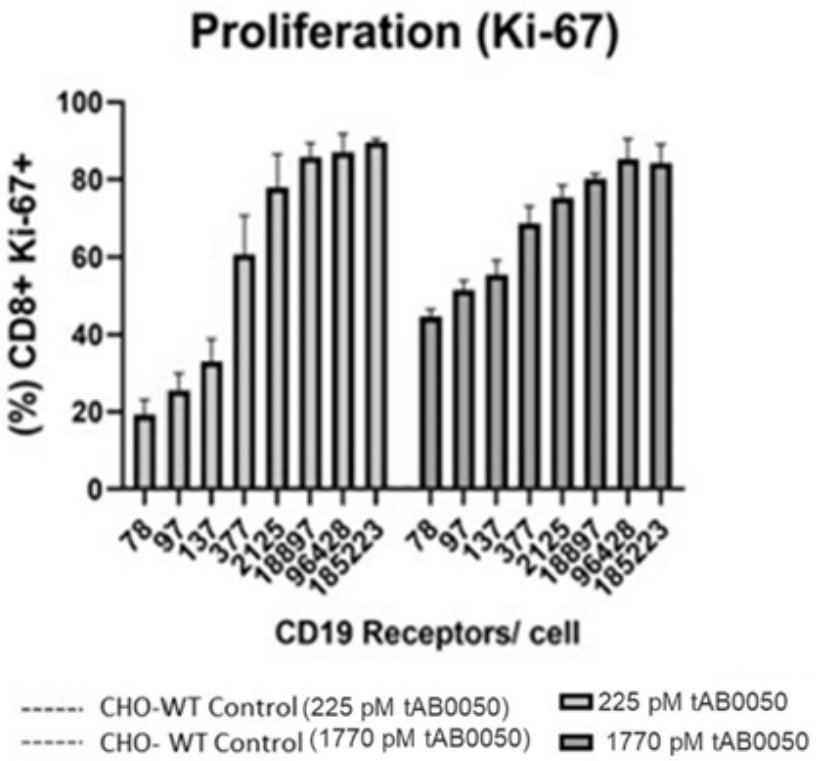

Proliferation (Ki-67)
(%) CD8+ Ki-67+
100
80
60
40
20
0
78
97
137
377
2125
18897
96428
185223
CD19 Receptors/ cell
CHO-WT Control (225 pM tAB0050)
CHO- WT Control (1770 pM tAB0050)
225 pM tAB0050
1770 pM tAB0050

FIG. 4C

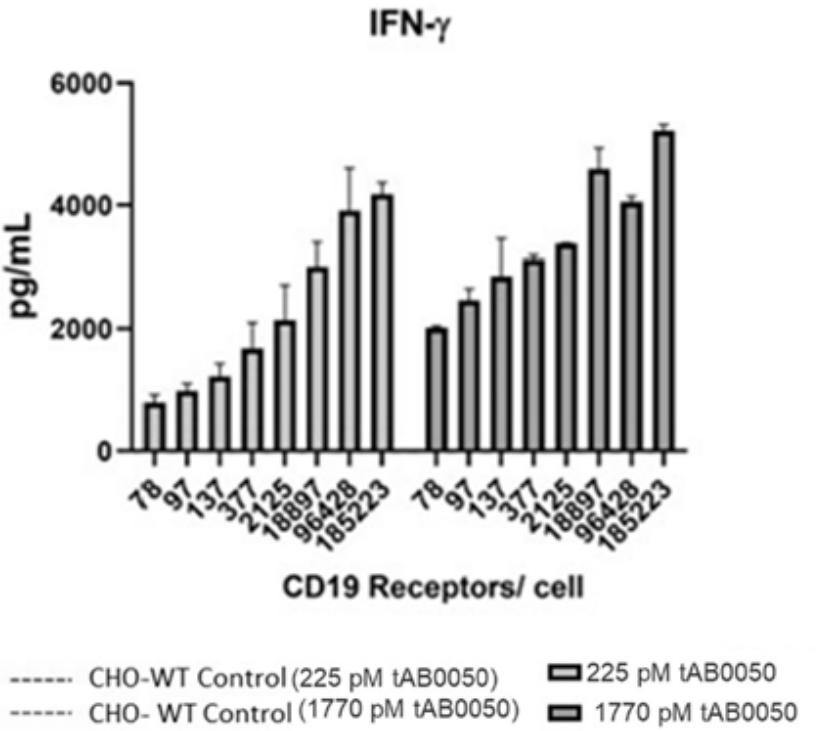

IFN-γ
pg/mL
6000
4000
2000
0
78
97
137
377
2125
18897
96428
185223
CD19 Receptors/ cell
CHO-WT Control (225 pM tAB0050)
CHO- WT Control (1770 pM tAB0050)
225 pM tAB0050
1770 pM tAB0050

FIG. 4D

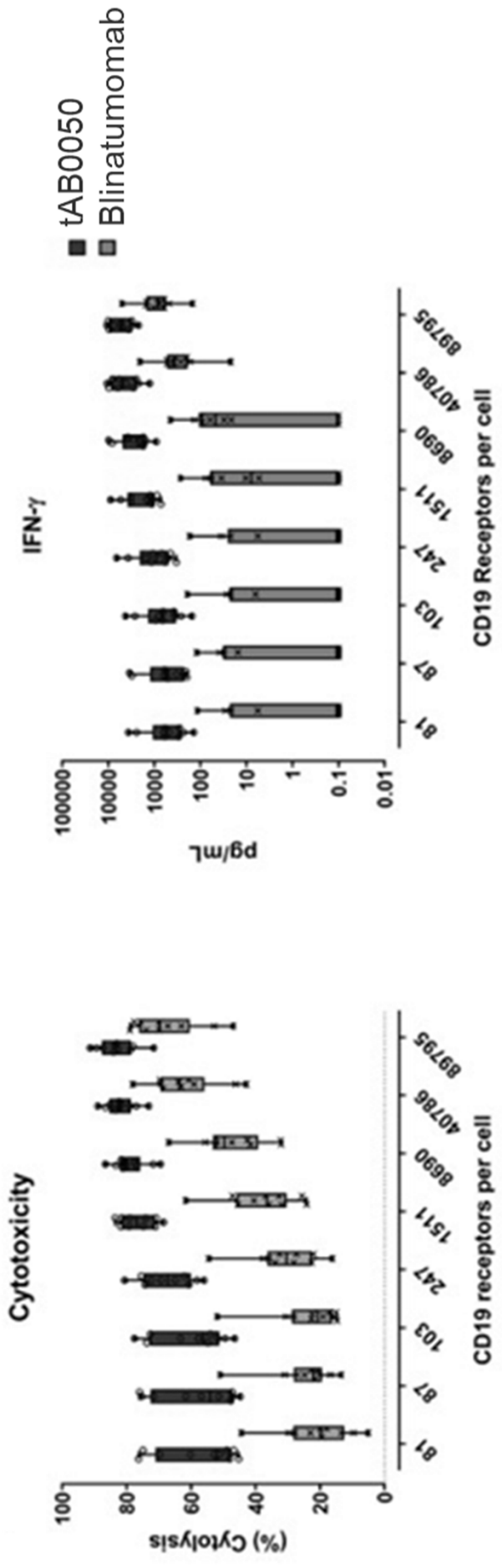

tAB0050
Blinatumomab
IFN-γ
pg/mL
100000
10000
1000
100
10
1
0.1
0.01
81
87
103
247
1511
8690
40786
89795
CD19 Receptors per cell
Cytotoxicity
(%) Cytolysis
100
80
60
40
20
0
81
87
103
247
1511
8690
40786
89795
CD19 receptors per cell

FIG. 4E

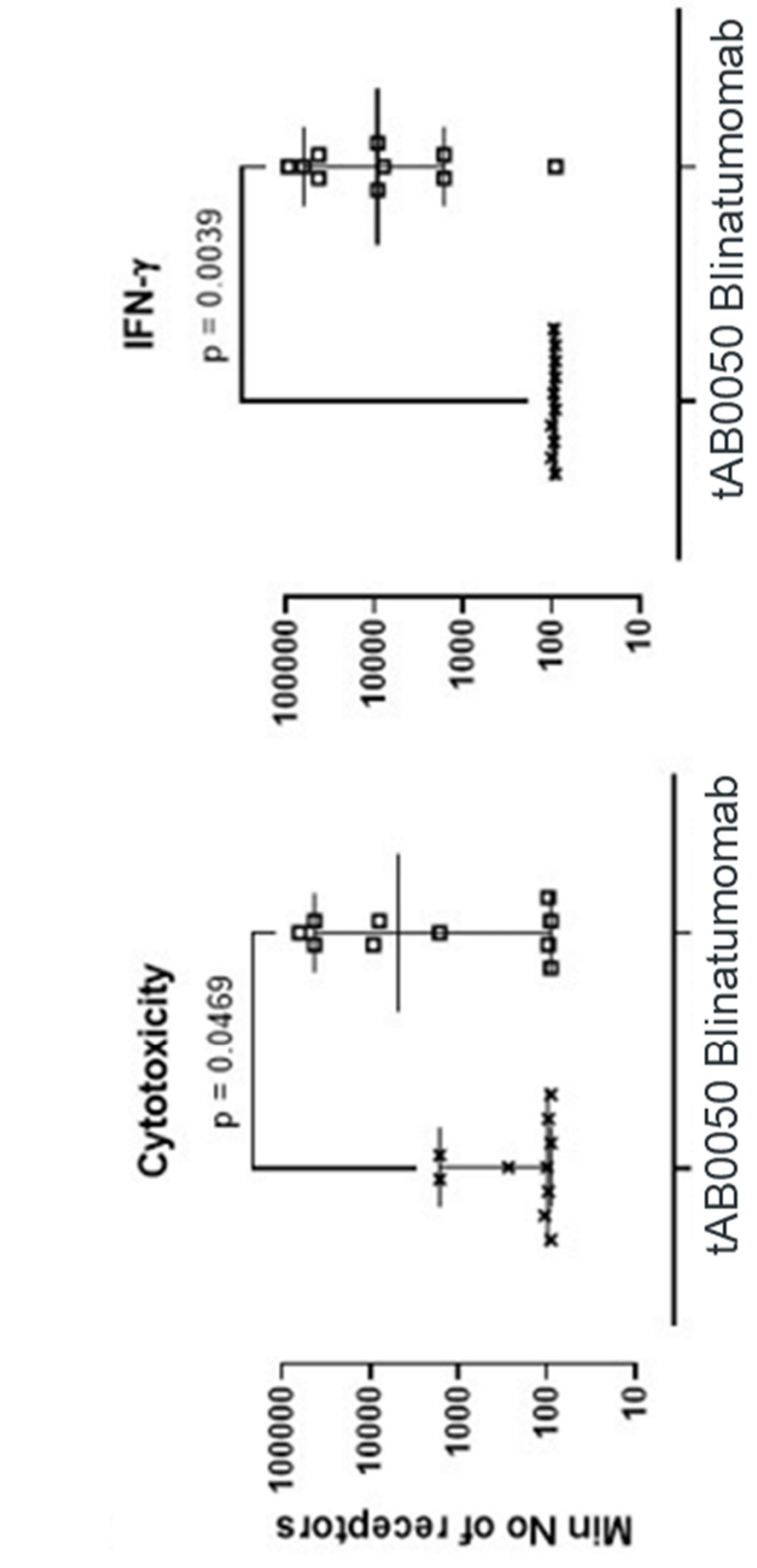
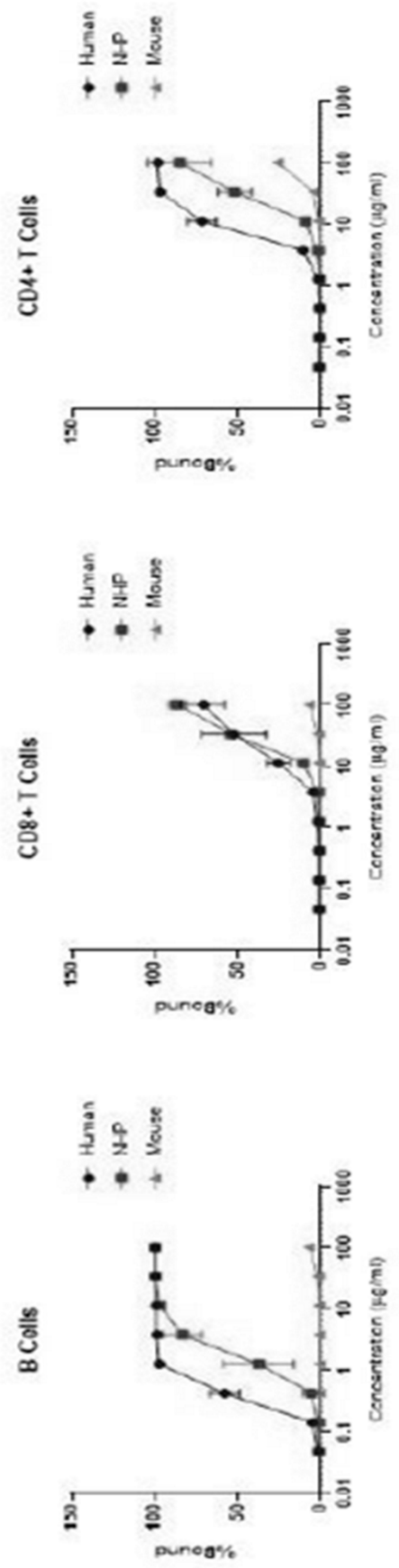

Cytotoxicity
p = 0.0469
IFN-γ
p = 0.0039
Min No of receptors
100000
10000
1000
100
10
tAB0050 Blinatumomab
tAB0050 Blinatumomab

FIG. 4F

Protein	ka (1/Ms)	kd (1/s)	KD (pM)
CD19	1.90×10^{5}	1.39×10^{-5}	73.8
CD3	8.15×10^{5}	6.43×10^{-3}	7,997
Albumin	7.57×10^{5}	4.50×10^{-4}	596

FIG. 5A



Species	EC_{50} (µg/mL)		
	B cells	CD8+ T cells	CD4+ T cells
Human	0.375 ± 0.046	44.19 ± 50.82	7.93 ± 0.92
Cynomolgus monkey	1.72 ± 0.79	28.66 ± 1.21	28.86 ± 4.31
Mouse	>100	>100	>100

FIG. 5B

Species	Protein	Serum Albumin	ka (1/Ms)	KD (nM)
Human	CD19	-	1.90×10^5	0.0738
		+	ND	ND*
	CD3	-	6.98×10^5	7.18
		+	2.23×10^5	16.79
Cynomolgus	CD19	-	9.26×10^4	19.22
		+	3.08×10^4	44.98
	CD3	-	7.30×10^5	6.04
		+	2.05×10^5	16.45

*The kinetics of CLN-978 were not amenable to the investigation of the effects of albumin on the CLN-978-human CD19 interaction

FIG. 6

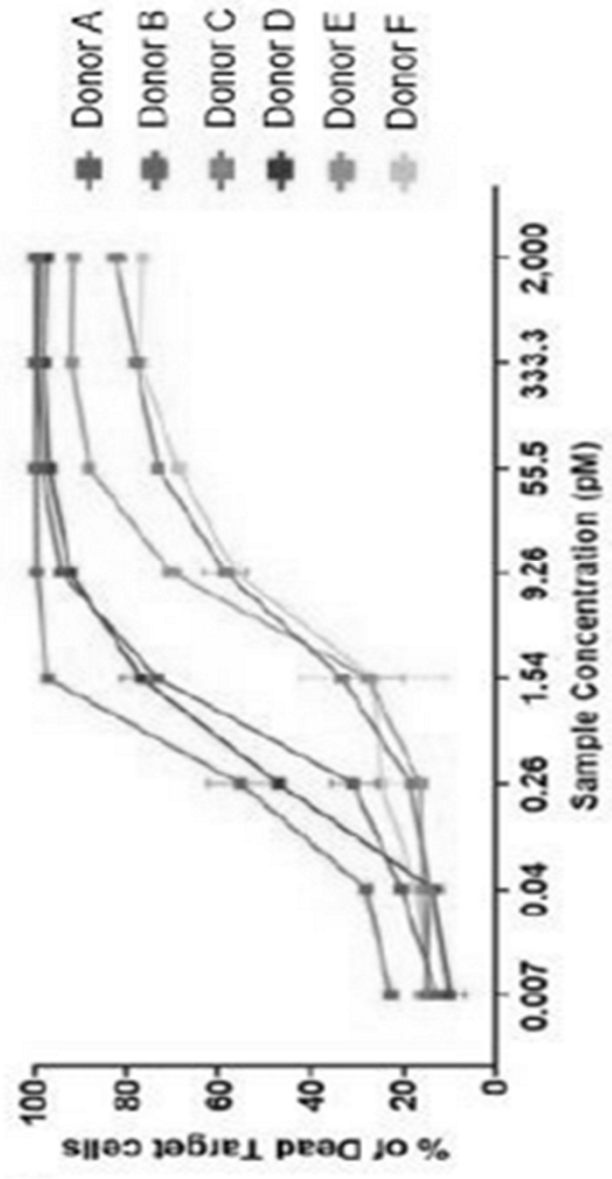

Donor A
Donor B
Donor C
Donor D
Donor E
Donor F
% of Dead Target cells
100
80
60
40
20
0
0.007
0.04
0.26
1.54
9.26
55.5
333.3
2,000
Sample Concentration (pM)

FIG. 7A

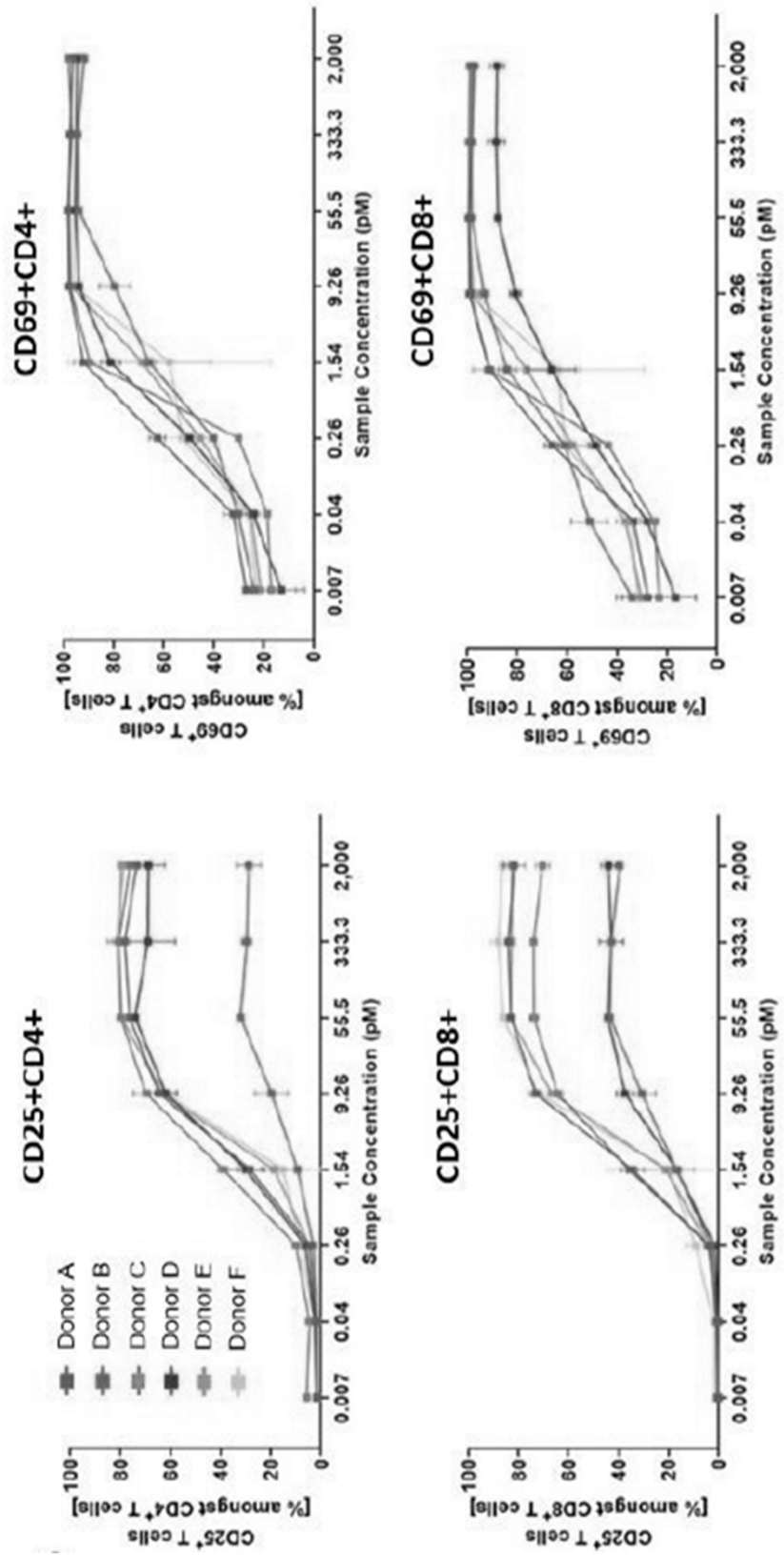

CD69+CD4+
CD69+ T cells [% amongst CD4+ T cells]
Sample Concentration (pM)
0.007 0.04 0.26 1.54 9.26 55.5 333.3 2,000
0 20 40 60 80 100
CD69+CD8+
CD69+ T cells [% amongst CD8+ T cells]
Sample Concentration (pM)
CD25+CD4+
CD25+ T cells [% amongst CD4+ T cells]
Sample Concentration (pM)
Donor A
Donor B
Donor C
Donor D
Donor E
Donor F
CD25+CD8+
CD25+ T cells [% amongst CD8+ T cells]
Sample Concentration (pM)

FIG. 7B

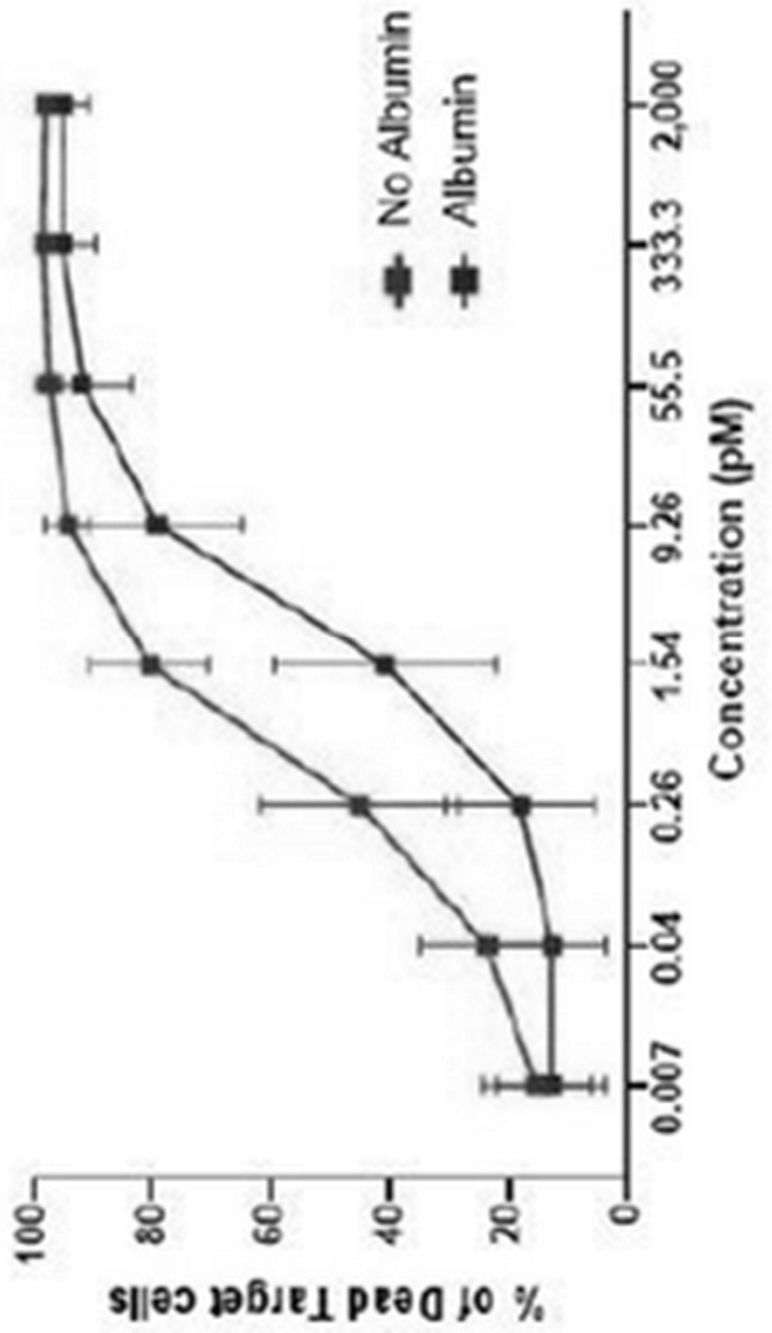

% of Dead Target cells
100
80
60
40
20
0
0.007
0.04
0.26
1.54
9.26
55.5
333.3
2,000
Concentration (pM)
No Albumin
Albumin

FIG. 7C

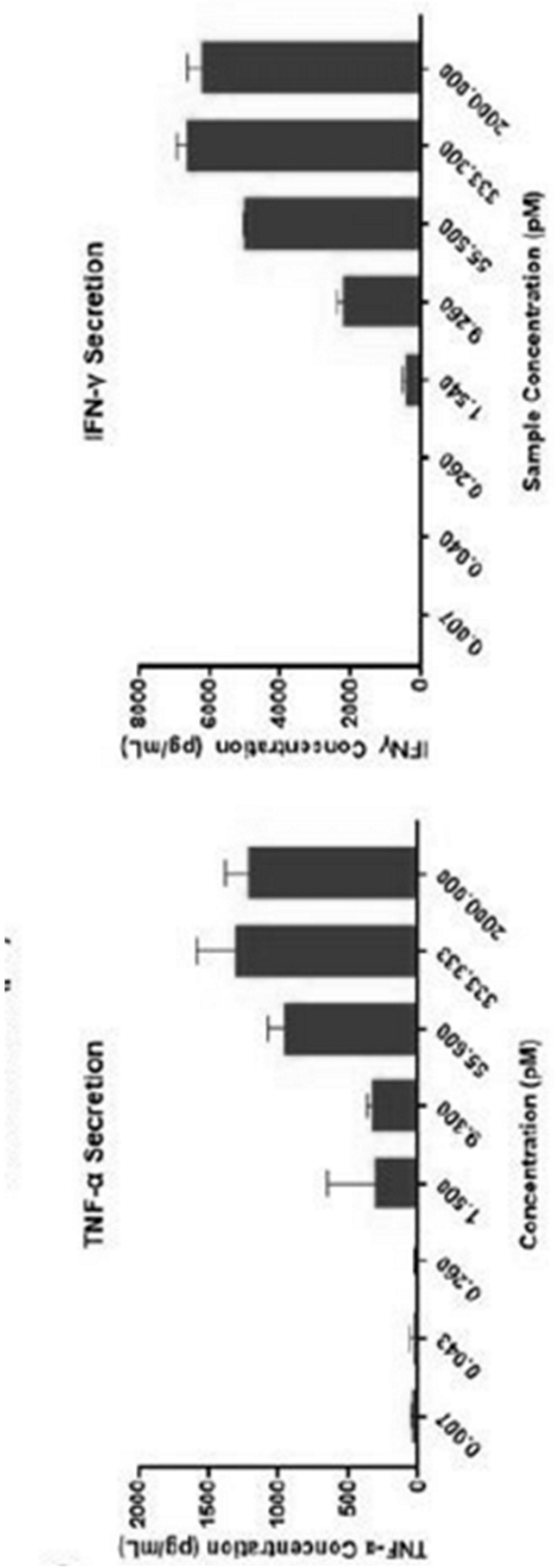

IFN-γ Secretion
IFNγ Concentration (pg/mL)
8000
6000
4000
2000
0
0.007
0.040
0.260
1.540
9.260
55.500
333.300
2000.000
Sample Concentration (pM)
TNF-α Secretion
TNF-α Concentration (pg/mL)
2000
1500
1000
500
0
0.007
0.043
0.260
1.500
9.300
55.600
333.333
2000.000
Concentration (pM)

FIG. 7D

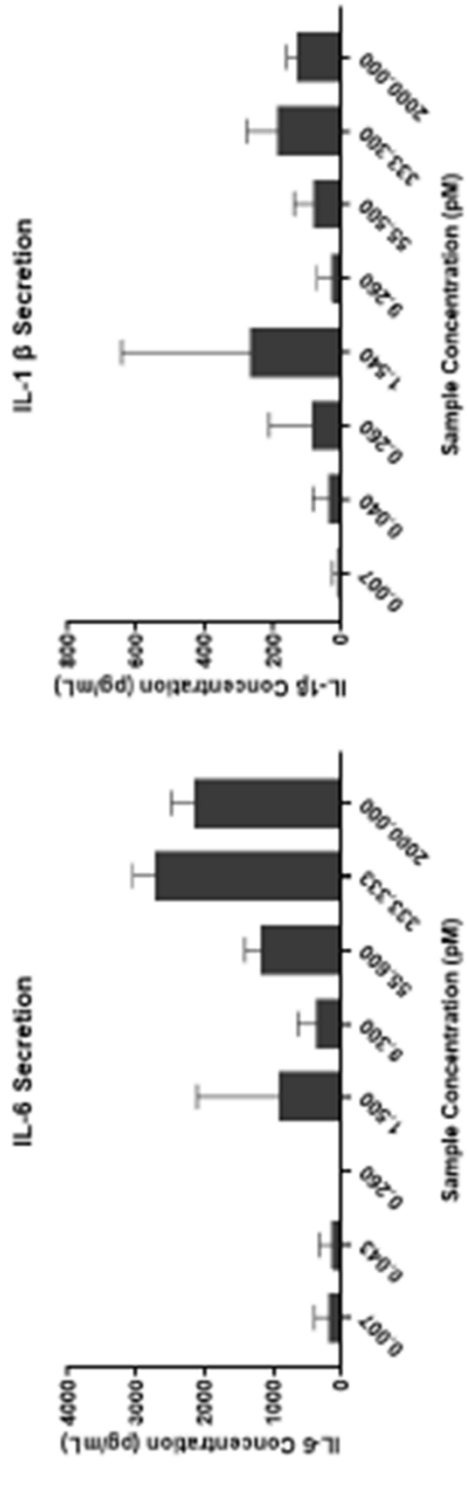

IL-1 β Secretion
IL-1β Concentration (pg/mL)
0
200
400
600
800
0.007
0.040
0.260
1.540
9.260
55.500
333.300
2000.000
Sample Concentration (pM)
IL-6 Secretion
IL-6 Concentration (pg/mL)
0
1000
2000
3000
4000
0.007
0.043
0.260
1.500
9.300
55.600
333.333
2000.000
Sample Concentration (pM)
Data represents mean with ± SD (n=2)

FIG. 7E

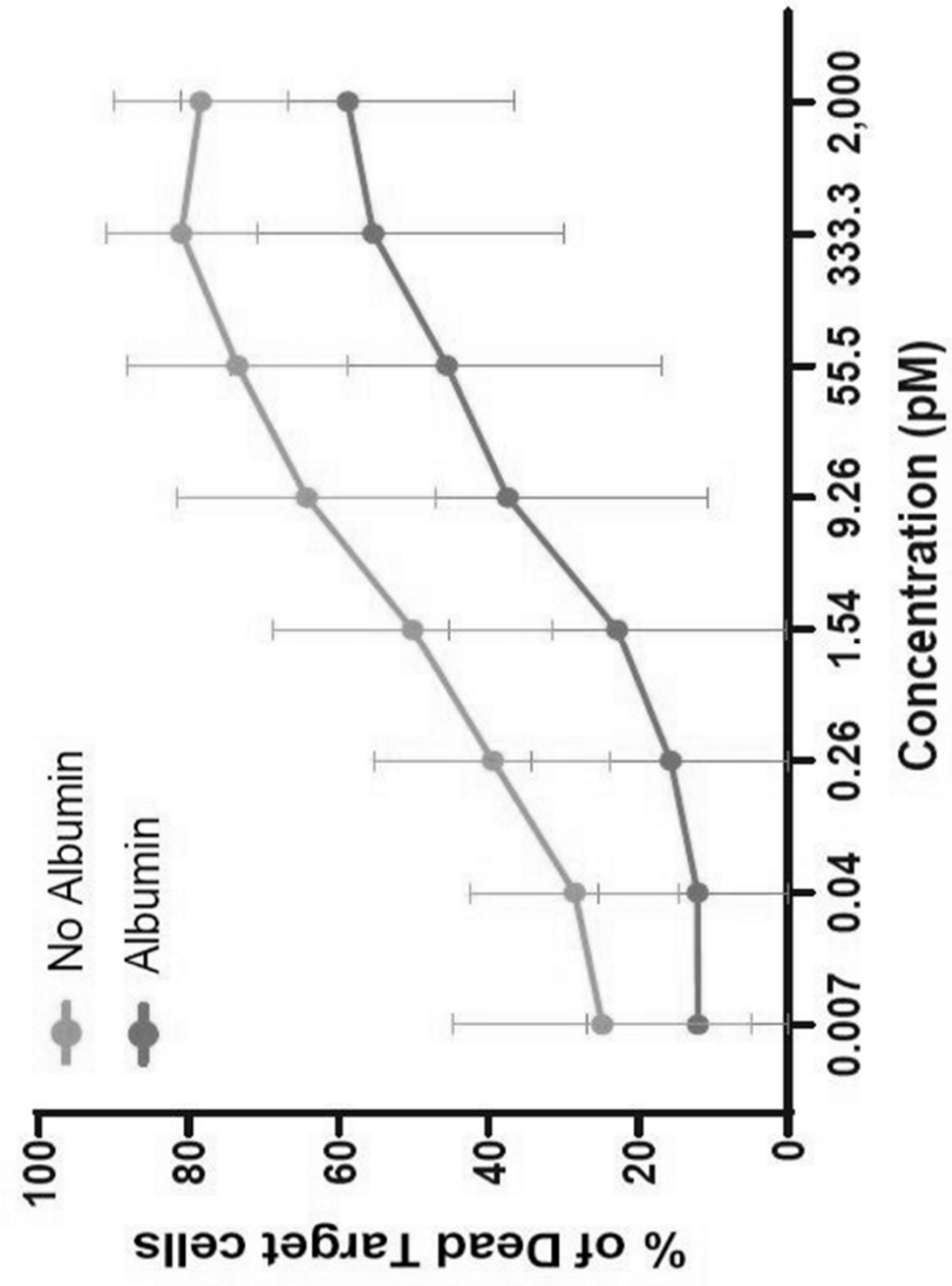
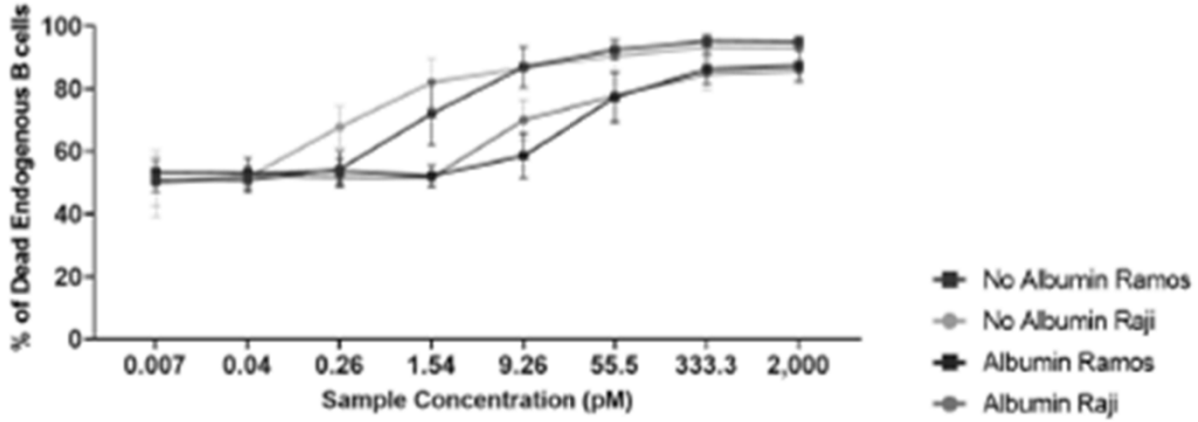

% of Dead Target cells
100
80
60
40
20
0
No Albumin
Albumin
0.007
0.04
0.26
1.54
9.26
55.5
333.3
2,000
Concentration (pM)

FIG. 8A

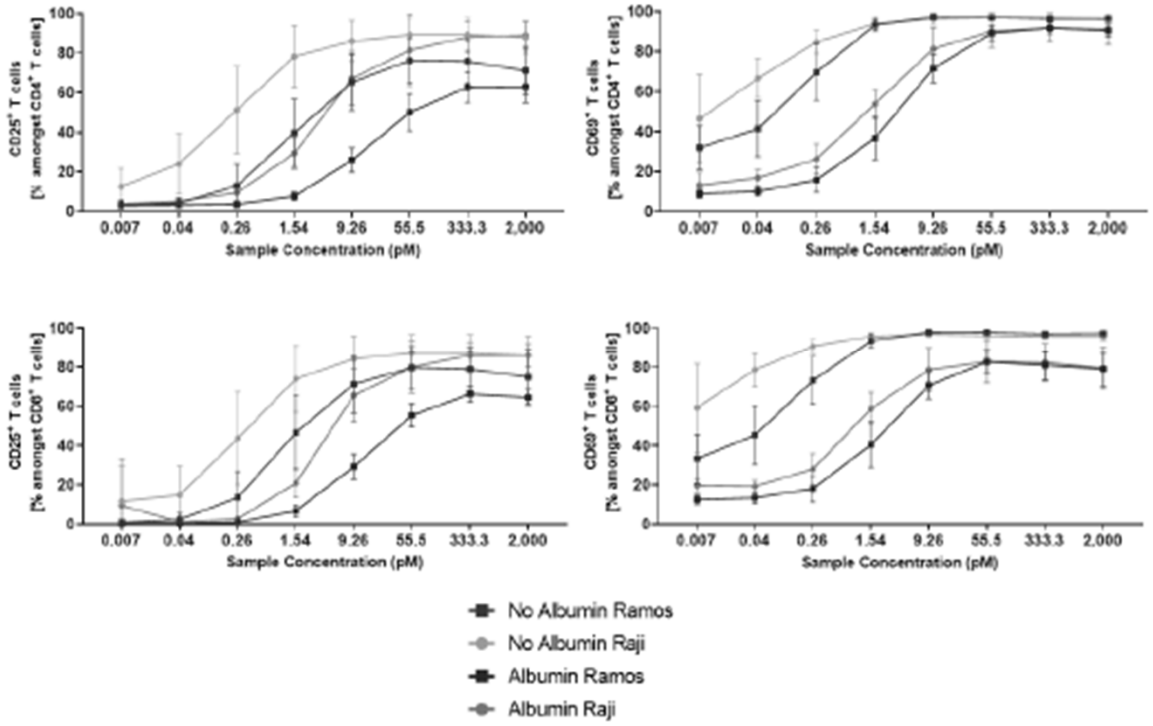


Data represents mean with ± SD (n=10 for Ramos assessments, n=8 for Raji assessments)

Albumin Treatment	Target Cell	EC_{50} (pM)	SEM
Y	Ramos	29.97	5.01
	Raji	9.30	2.06
N	Ramos	1.73	0.27
	Raji	0.34[a]	0.11

[a] Software was capable of calculating a best-fit value, however, was unable to calculate a complete confidence interval, therefore, the determined EC_{50} should be interpreted with caution.

FIG. 8B



Data represents mean with ± SD (n=10 for Ramos assessments, n=8 for Raji assessments)

Albumin treatment	Target Cell Line	CD4+CD25+		CD4+CD69+		CD8+CD25+		CD8+CD69+	
		EC_{50} (pM)	SEM	EC_{50} (pM)	SEM	EC_{50} (pM)	SEM	EC_{50} (pM)	SEM
Y	Ramos	15.76	1.97	3.03	0.26	11.62	0.88	2.12	0.25
	Raji	3.38	0.55	1.43	0.21	4.10	0.73	1.02	0.17
N	Ramos	1.48	0.29	0.19	0.26	1.10	0.21	0.15	0.03
	Raji	0.23	0.07	0.03	0.03	0.33	0.10	0.02	0.03

FIG. 8C

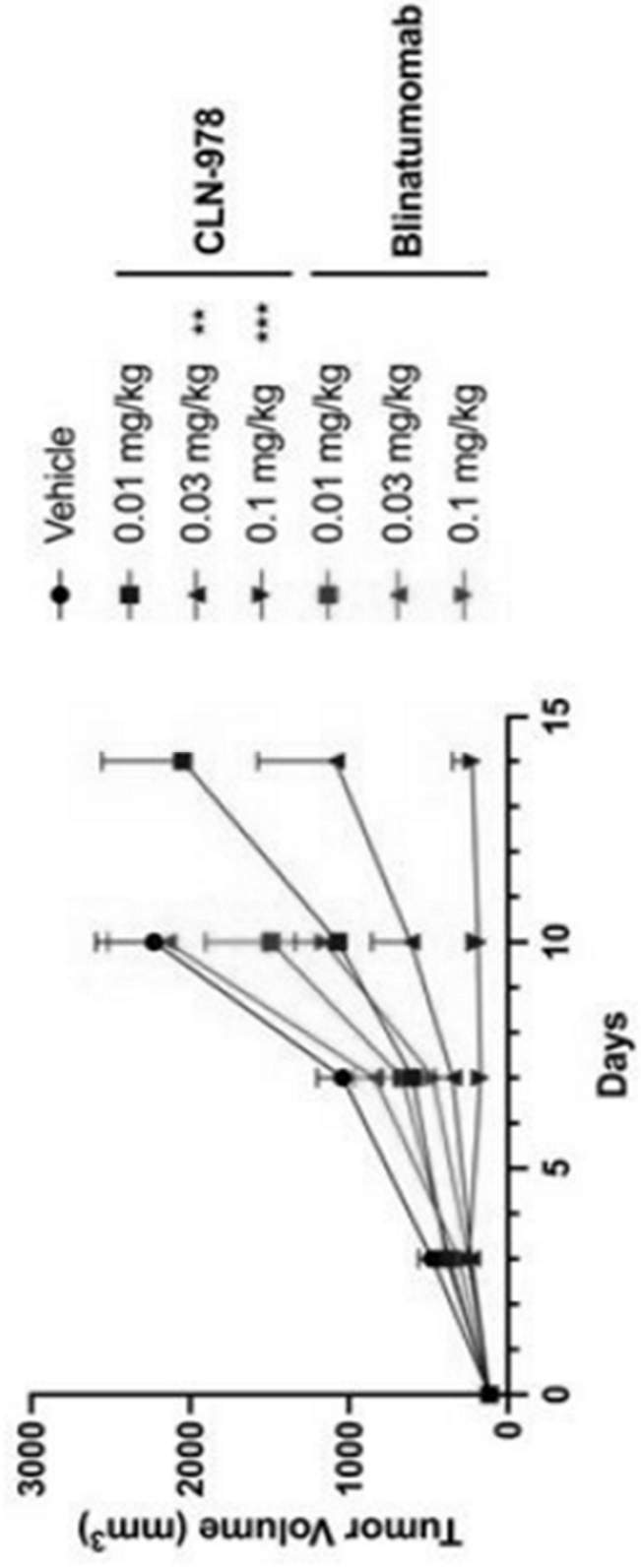

Tumor Volume (mm³)
3000
2000
1000
0
0
5
10
15
Days
Vehicle
0.01 mg/kg
0.03 mg/kg **
0.1 mg/kg ***
CLN-978
0.01 mg/kg
0.03 mg/kg
0.1 mg/kg
Blinatumomab

FIG. 9A

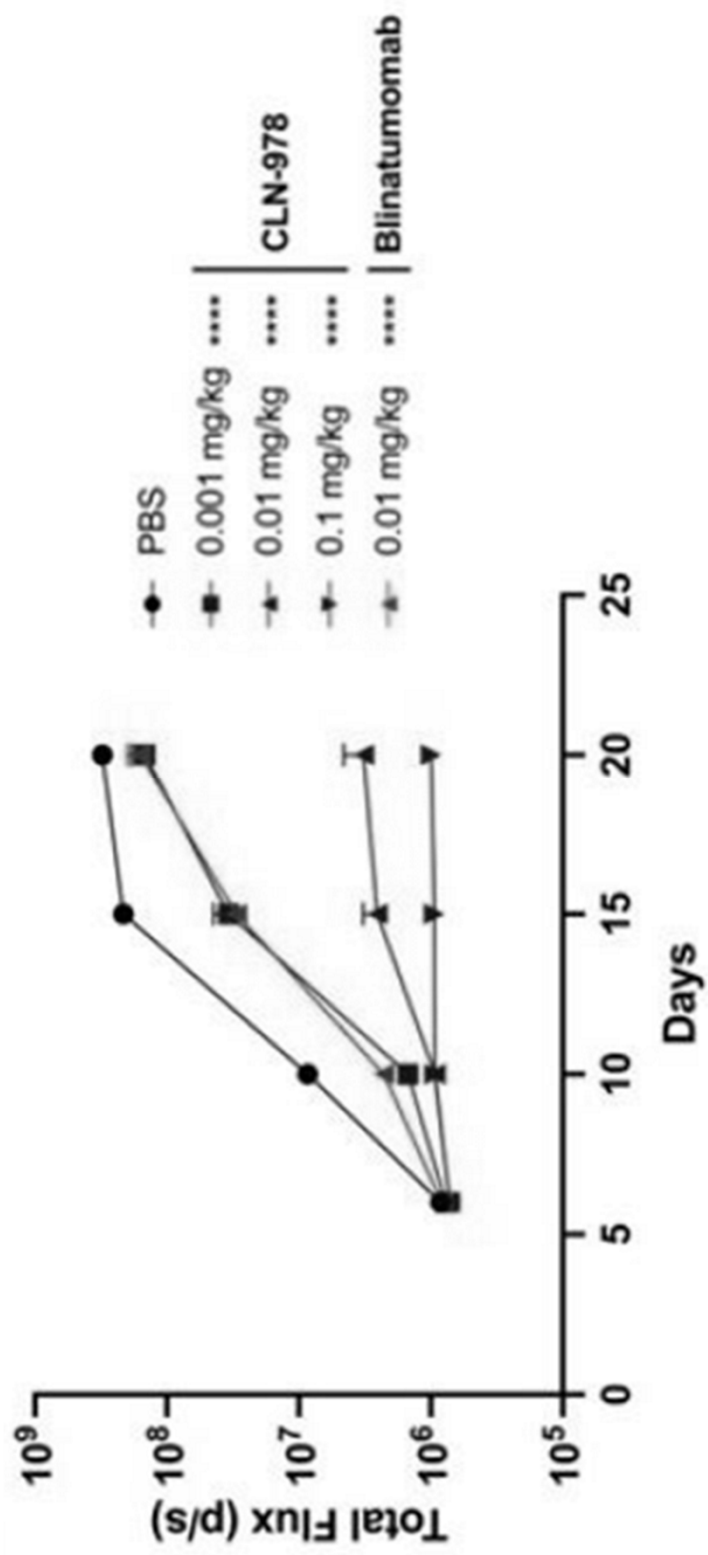

Total Flux (p/s)
10^9
10^8
10^7
10^6
10^5
0
5
10
15
20
25
Days
PBS
0.001 mg/kg
0.01 mg/kg
0.1 mg/kg
0.01 mg/kg
CLN-978
Blinatumomab

FIG. 9B

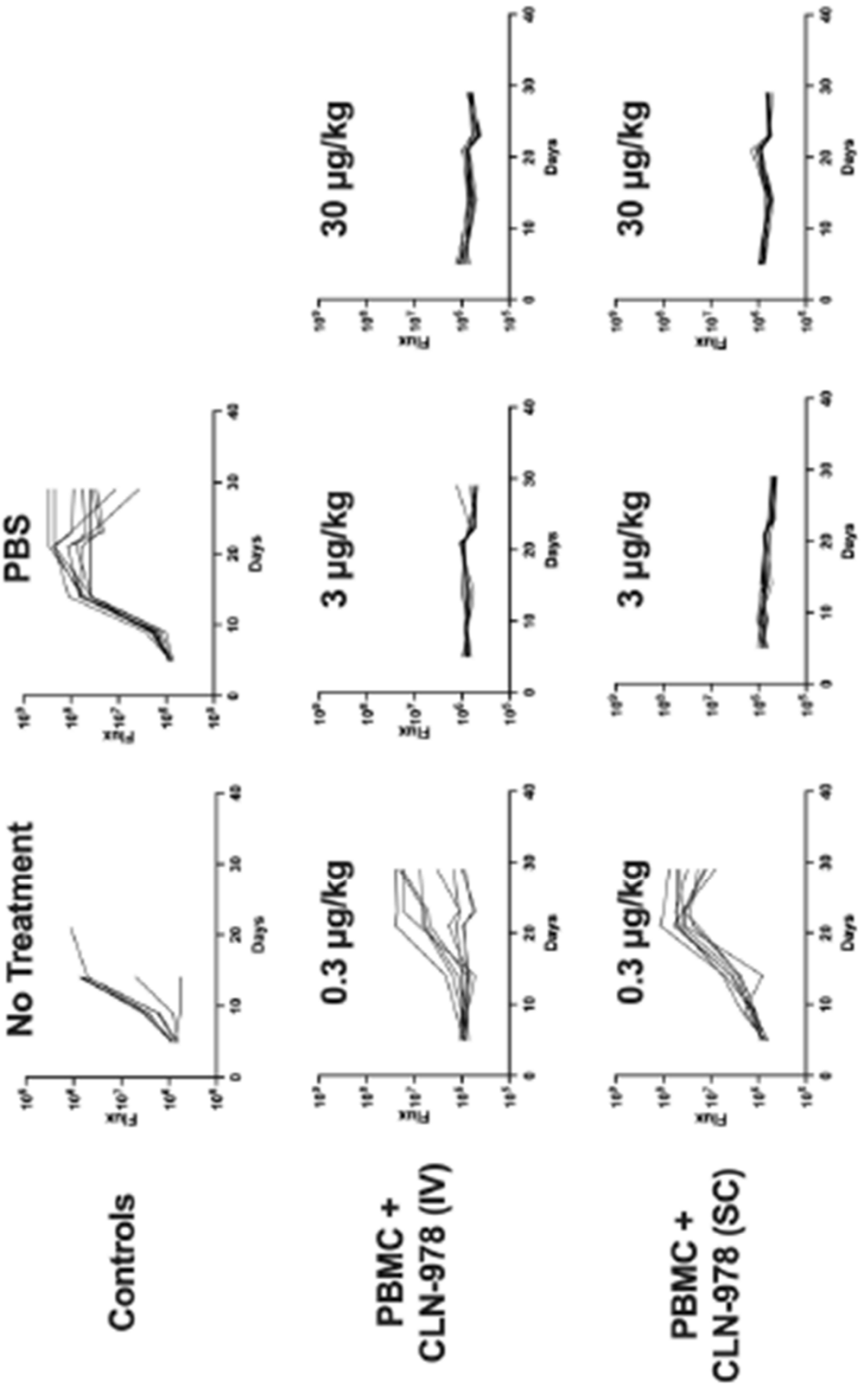

Controls
No Treatment
PBS
PBMC + CLN-978 (IV)
0.3 µg/kg
3 µg/kg
30 µg/kg
PBMC + CLN-978 (SC)
0.3 µg/kg
3 µg/kg
30 µg/kg
Flux
Days

FIG. 9C

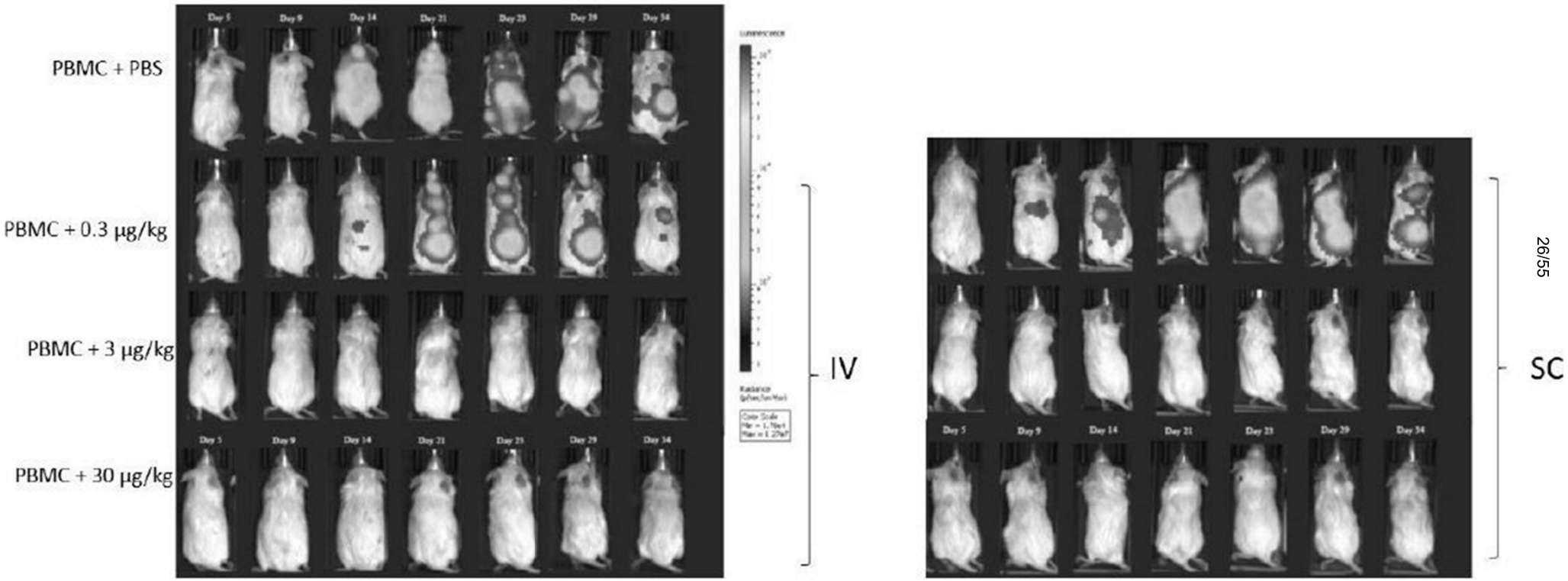
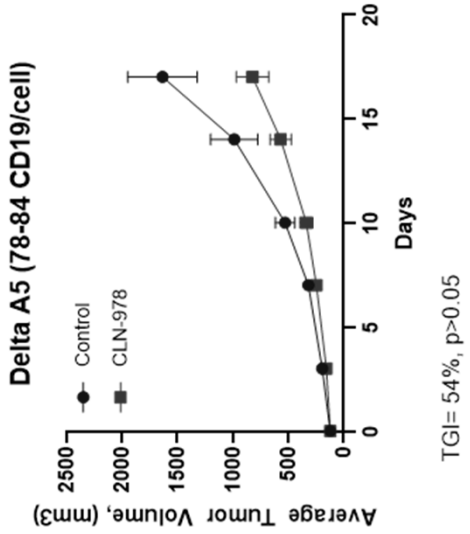
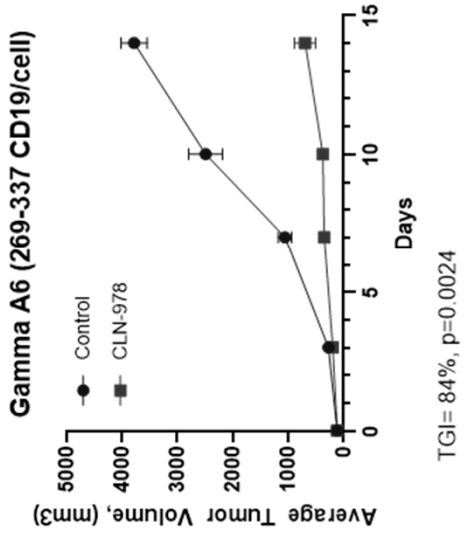

PBMC + PBS
PBMC + 0.3 µg/kg
PBMC + 3 µg/kg
PBMC + 30 µg/kg
Day 5
Day 9
Day 14
Day 21
Day 25
Day 29
Day 34
IV
SC

FIG. 9D


Delta A5 (78-84 CD19/cell)
Control
CLN-978
Average Tumor Volume, (mm3)
2500
2000
1500
1000
500
0
0
5
10
15
20
Days
TGI= 54%, p>0.05


Gamma A6 (269-337 CD19/cell)
Control
CLN-978
Average Tumor Volume, (mm3)
5000
4000
3000
2000
1000
0
0
5
10
15
Days
TGI= 84%, p=0.0024

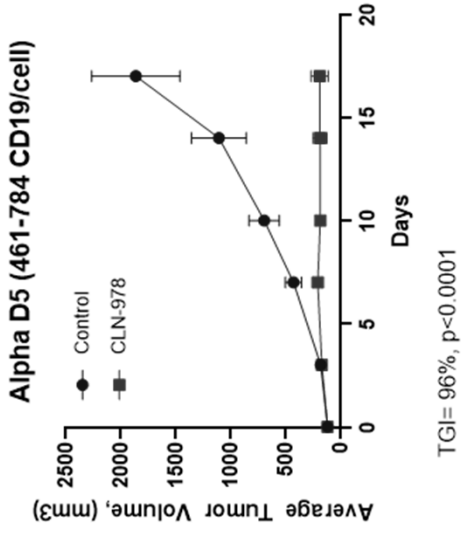

Alpha D5 (461-784 CD19/cell)
Control
CLN-978
Average Tumor Volume, (mm3)
2500
2000
1500
1000
500
0
0
5
10
15
20
Days
TGI= 96%, p<0.0001

FIG. 9E

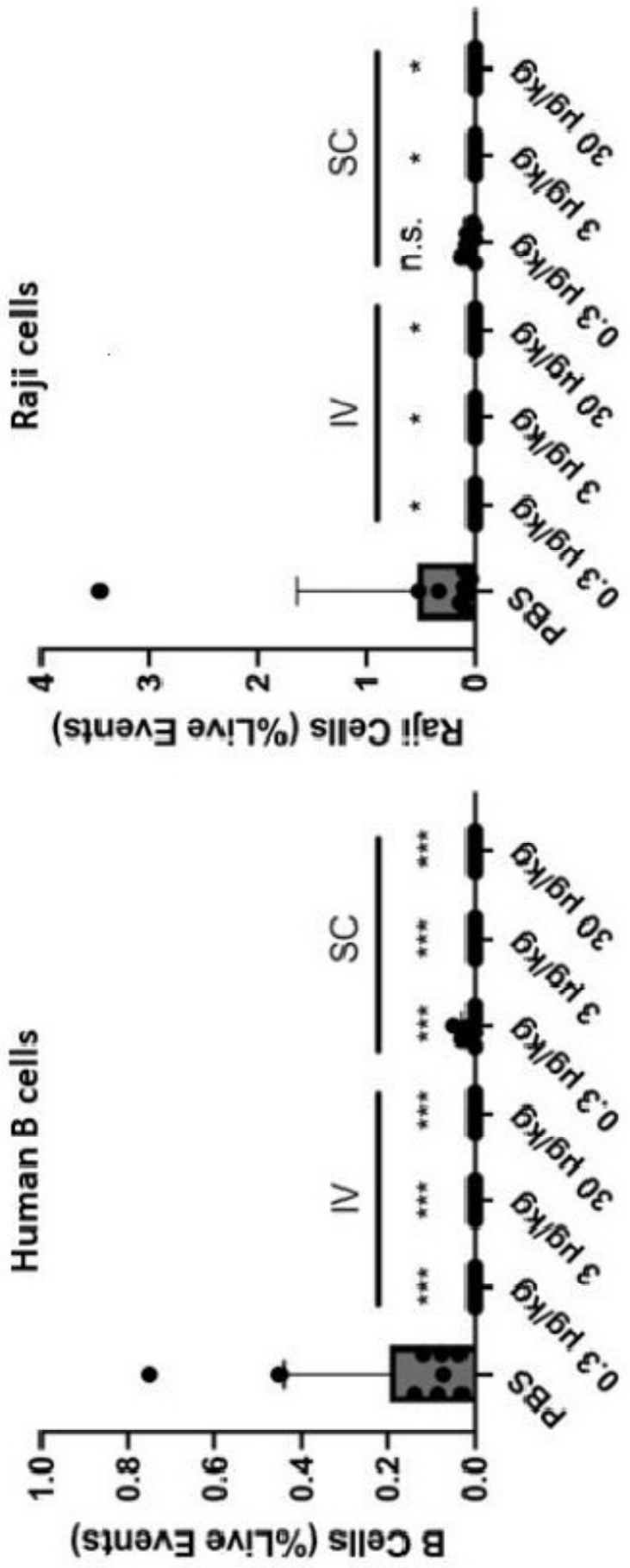

Human B cells
B Cells (%Live Events)
1.0
0.8
0.6
0.4
0.2
0.0
IV
SC
***
***
***
***
***
***
PBS
0.3 µg/kg
3 µg/kg
30 µg/kg
0.3 µg/kg
3 µg/kg
30 µg/kg
Raji cells
Raji Cells (%Live Events)
4
3
2
1
0
IV
SC
*
*
*
*
n.s.
*
*
PBS
0.3 µg/kg
3 µg/kg
30 µg/kg
0.3 µg/kg
3 µg/kg
30 µg/kg

FIG. 10A

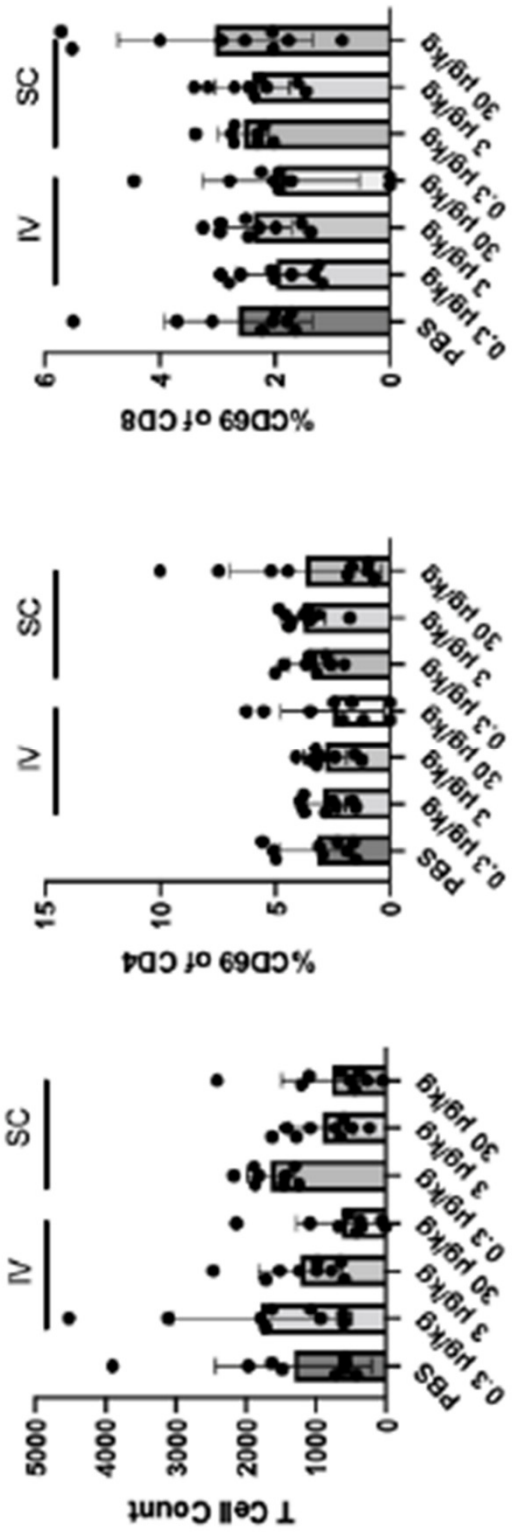

T Cell Count
5000
4000
3000
2000
1000
0
IV
SC
PBS
0.3 µg/kg
3 µg/kg
30 µg/kg
0.3 µg/kg
3 µg/kg
30 µg/kg
%CD69 of CD4
15
10
5
0
%CD69 of CD8
6
4
2
0

FIG. 10B

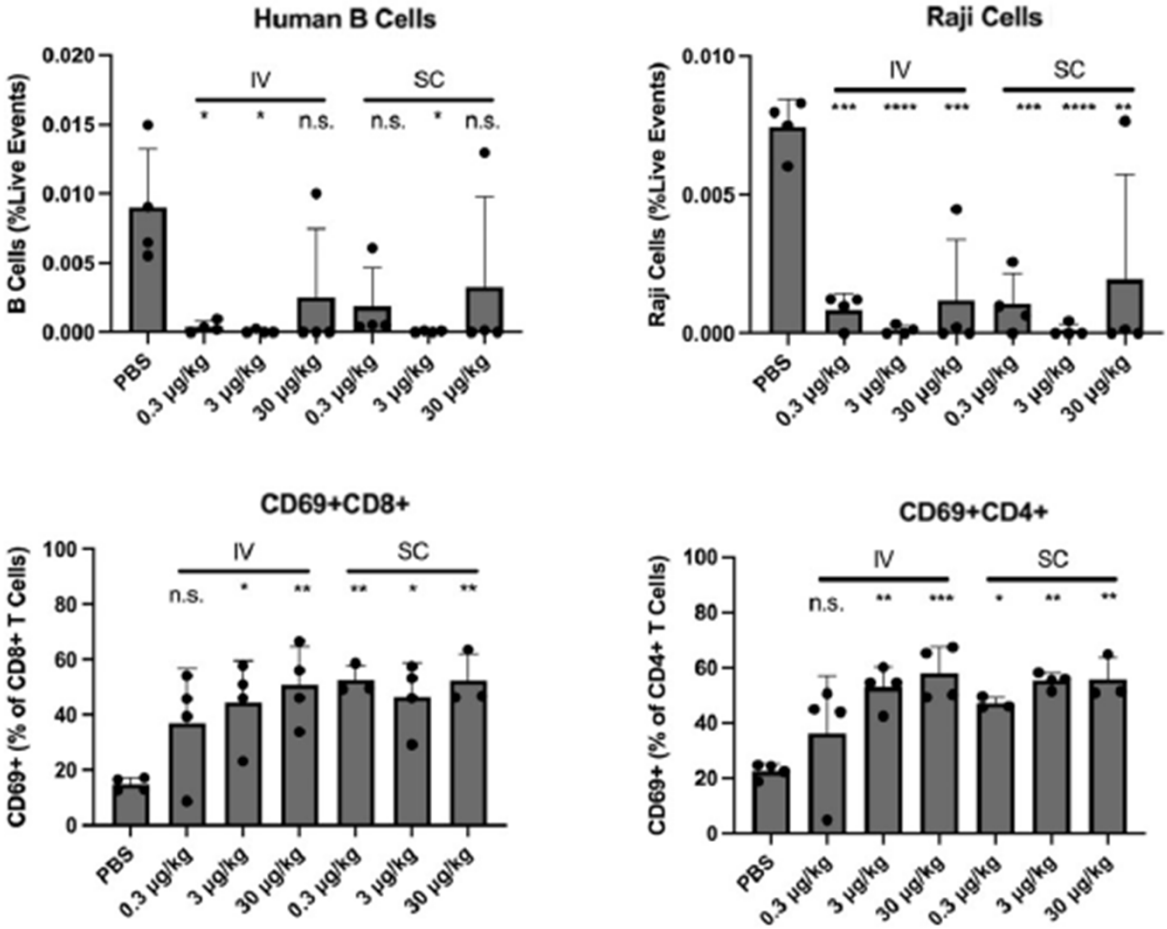

Human B Cells
B Cells (%Live Events)
0.020
0.015
0.010
0.005
0.000
IV
SC
*
*
n.s.
n.s.
*
n.s.
PBS
0.3 µg/kg
3 µg/kg
30 µg/kg
0.3 µg/kg
3 µg/kg
30 µg/kg
Raji Cells
Raji Cells (%Live Events)
0.010
0.005
0.000
IV
SC
***
****
***
***
****
**
PBS
0.3 µg/kg
3 µg/kg
30 µg/kg
0.3 µg/kg
3 µg/kg
30 µg/kg
CD69+CD8+
CD69+ (% of CD8+ T Cells)
100
80
60
40
20
0
IV
SC
n.s.
*
**
**
*
**
PBS
0.3 µg/kg
3 µg/kg
30 µg/kg
0.3 µg/kg
3 µg/kg
30 µg/kg
CD69+CD4+
CD69+ (% of CD4+ T Cells)
100
80
60
40
20
0
IV
SC
n.s.
**
***
*
**
**
PBS
0.3 µg/kg
3 µg/kg
30 µg/kg
0.3 µg/kg
3 µg/kg
30 µg/kg

FIG. 10C

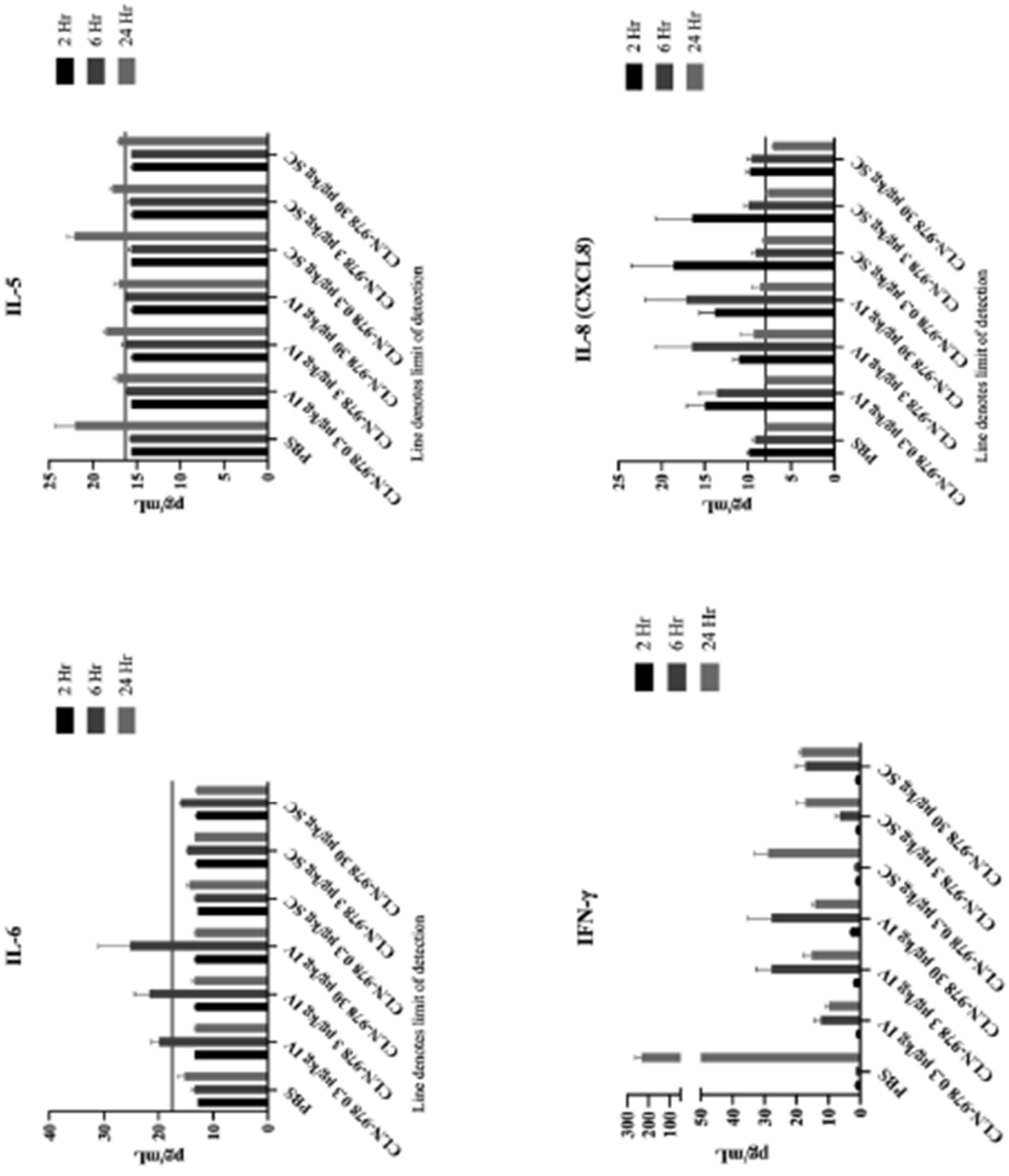

IL-5
IL-8 (CXCL8)
IL-6
IFN-γ
2 Hr
6 Hr
24 Hr
pg/mL
Line denotes limit of detection
PBS
CLN-978 0.3 mg/kg IV
CLN-978 3 mg/kg IV
CLN-978 30 mg/kg IV
CLN-978 0.3 mg/kg SC
CLN-978 3 mg/kg SC
CLN-978 30 mg/kg SC

FIG. 11A

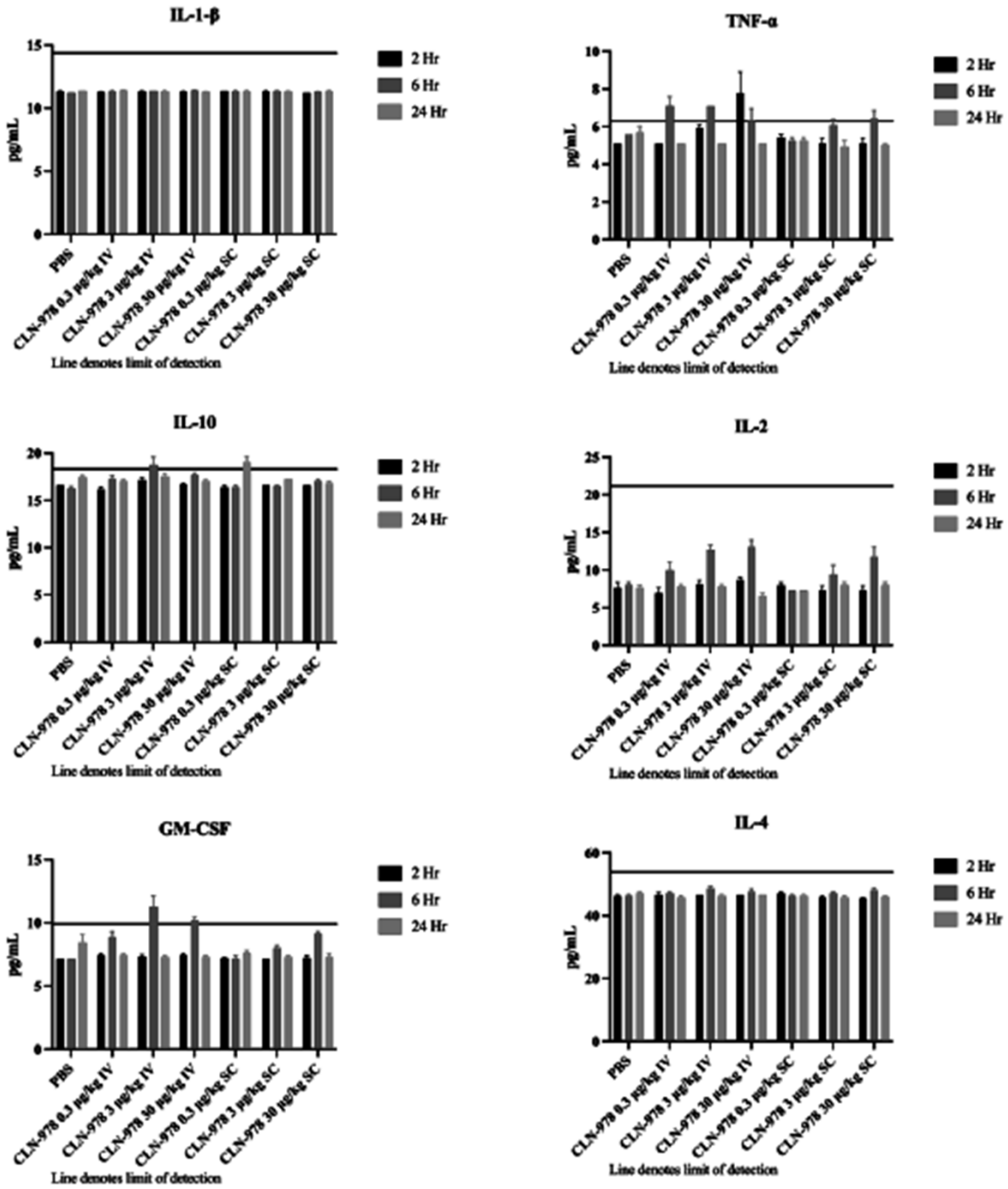

IL-1-β
TNF-α
IL-10
IL-2
GM-CSF
IL-4
pg/mL
2 Hr
6 Hr
24 Hr
PBS
CLN-978 0.3 μg/kg IV
CLN-978 3 μg/kg IV
CLN-978 30 μg/kg IV
CLN-978 0.3 μg/kg SC
CLN-978 3 μg/kg SC
CLN-978 30 μg/kg SC
Line denotes limit of detection

FIG. 11B

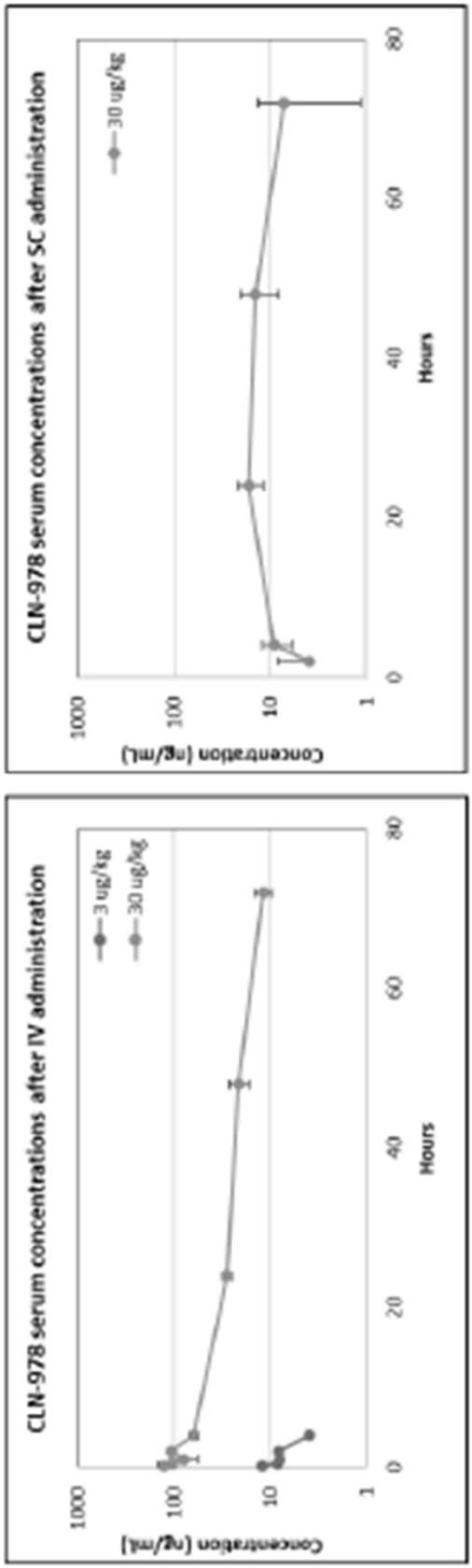
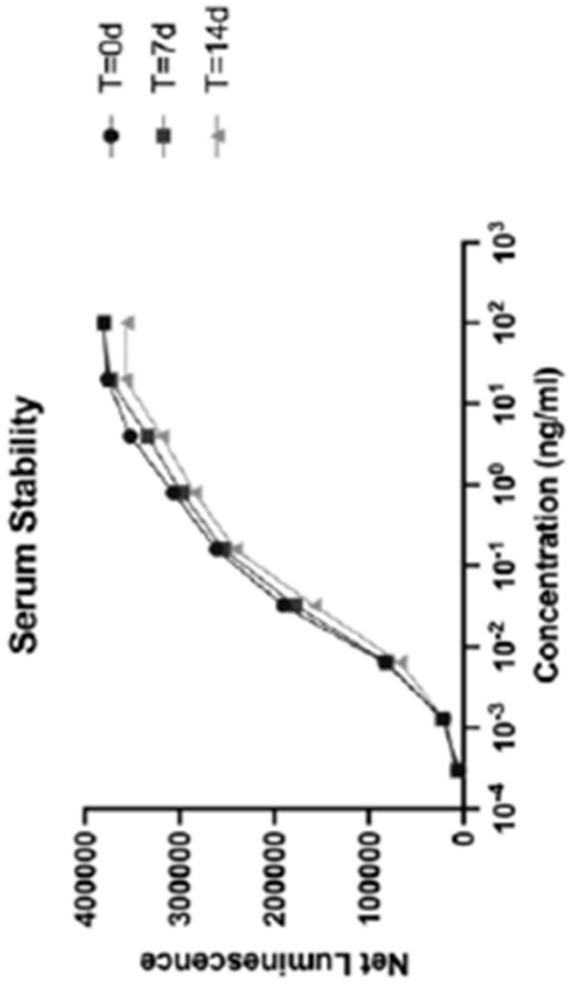

CLN-978 serum concentrations after IV administration
3 ug/kg
30 ug/kg
Concentration (ng/mL)
1000
100
10
1
0
20
40
60
80
Hours
CLN-978 serum concentrations after SC administration
30 ug/kg
Concentration (ng/mL)
1000
100
10
1
0
20
40
60
80
Hours

FIG. 12A

Analyte	Dose (µg/kg)	Route of Administration	C_{max} (ng/mL)	T_{max} (hr)	T_{last} (hr)
CLN-978	3	IV	11.9	0.25	4[a]
CLN-978	30	IV	126.4	0.25	72
CLN-978	30	SC	16.7	24	72

[a] Note, two of four samples at 4 hours post dose were BQL (6.95 ng/mL).

FIG. 12B



Samples	T=0d	T=7d	T=14d
EC_{50}	0.038 ng/mL	0.046 ng/mL	0.052 ng/mL

FIG. 13

Group No.	Test Material	Dose Level (mg/kg)	Dose Volume[a] (mL/kg)	Dose Concentration (mg/mL)	Route of Administration	No.[b] of Females
1	CLN-978	0.1	1	0.1	IV[c]	2
2		1	1	1	IV	2
3		0.1	0.5	0.2	SC[d]	2
4		1	0.5	2[e]	SC	2

[a] Based on the most recent body weight measurement.
[b] No. = Number
[c] IV = Intravenous injection
[d] SC = Subcutaneous injection
[e] Rounded dose concentration as per Certificate of Testing

FIG. 14A

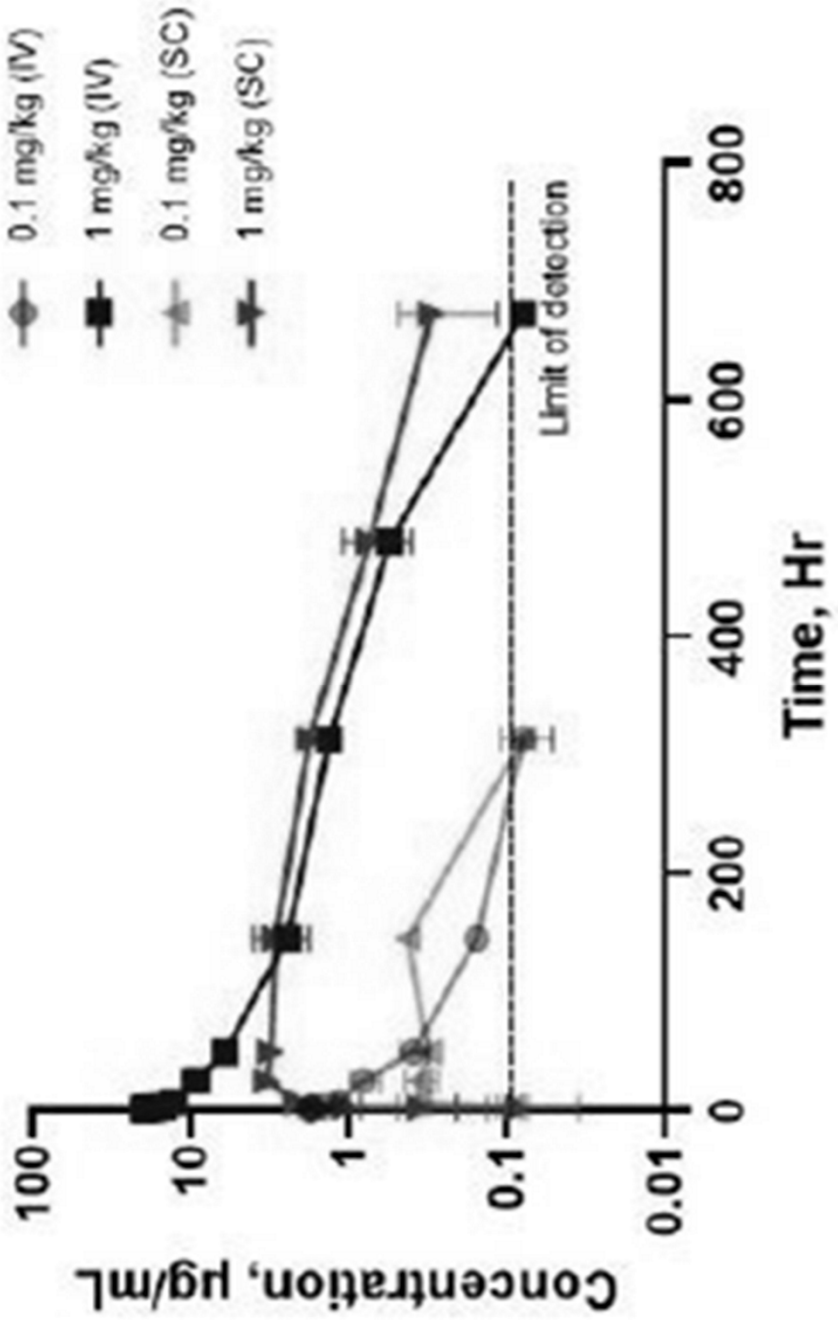

0.1 mg/kg (IV)
1 mg/kg (IV)
0.1 mg/kg (SC)
1 mg/kg (SC)
Limit of detection
Concentration, µg/mL
100
10
1
0.1
0.01
0
200
400
600
800
Time, Hr

FIG. 14B

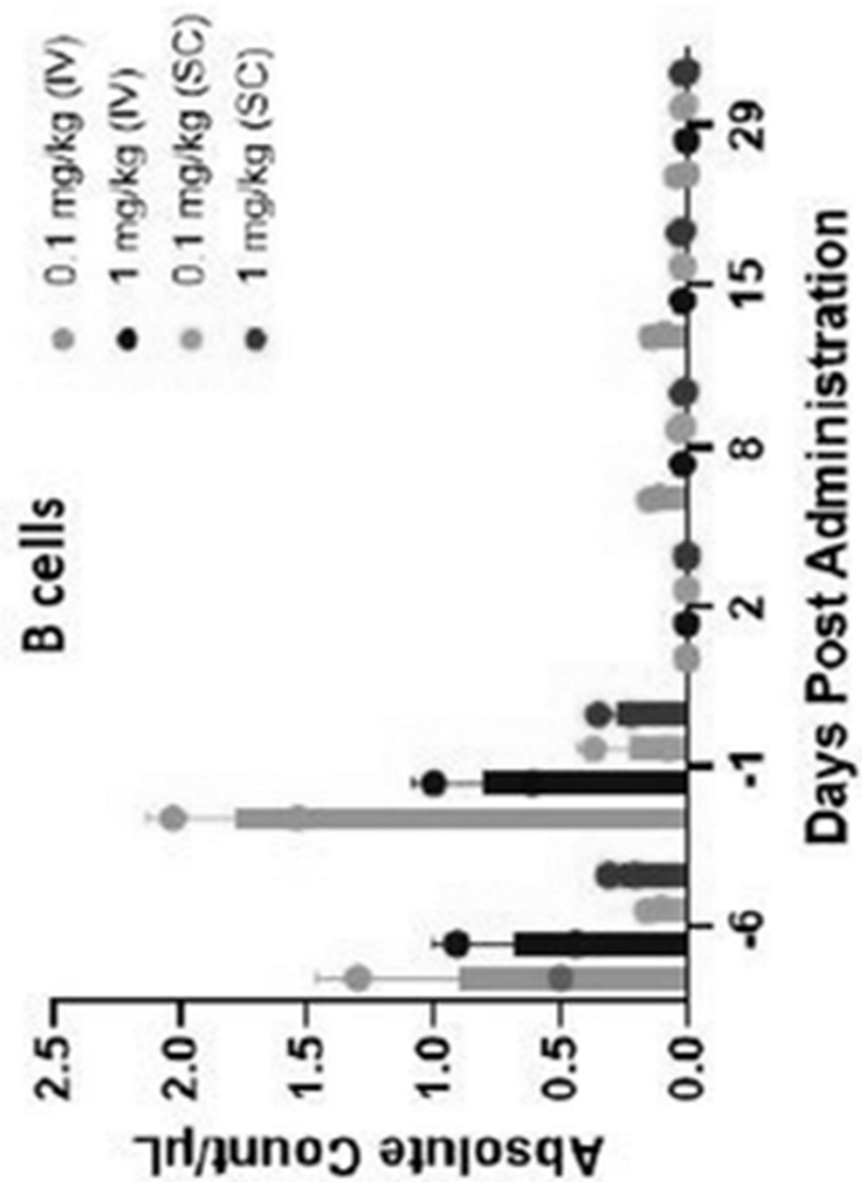

B cells
0.1 mg/kg (IV)
1 mg/kg (IV)
0.1 mg/kg (SC)
1 mg/kg (SC)
Absolute Count/µL
2.5
2.0
1.5
1.0
0.5
0.0
-6
-1
2
8
15
29
Days Post Administration

FIG. 14C

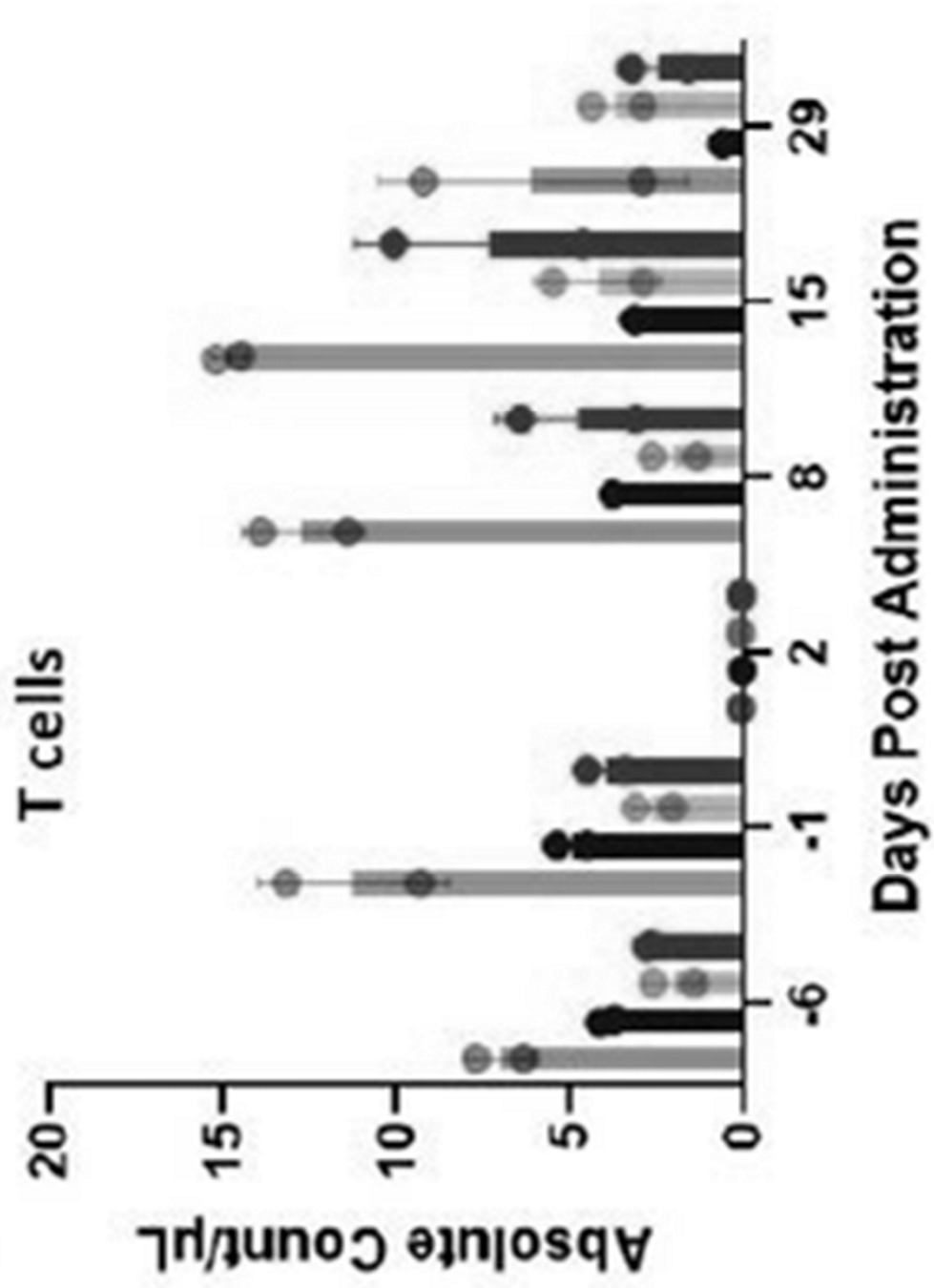

T cells
Absolute Count/μL
20
15
10
5
0
-6
-1
2
8
15
29
Days Post Administration

FIG. 14D

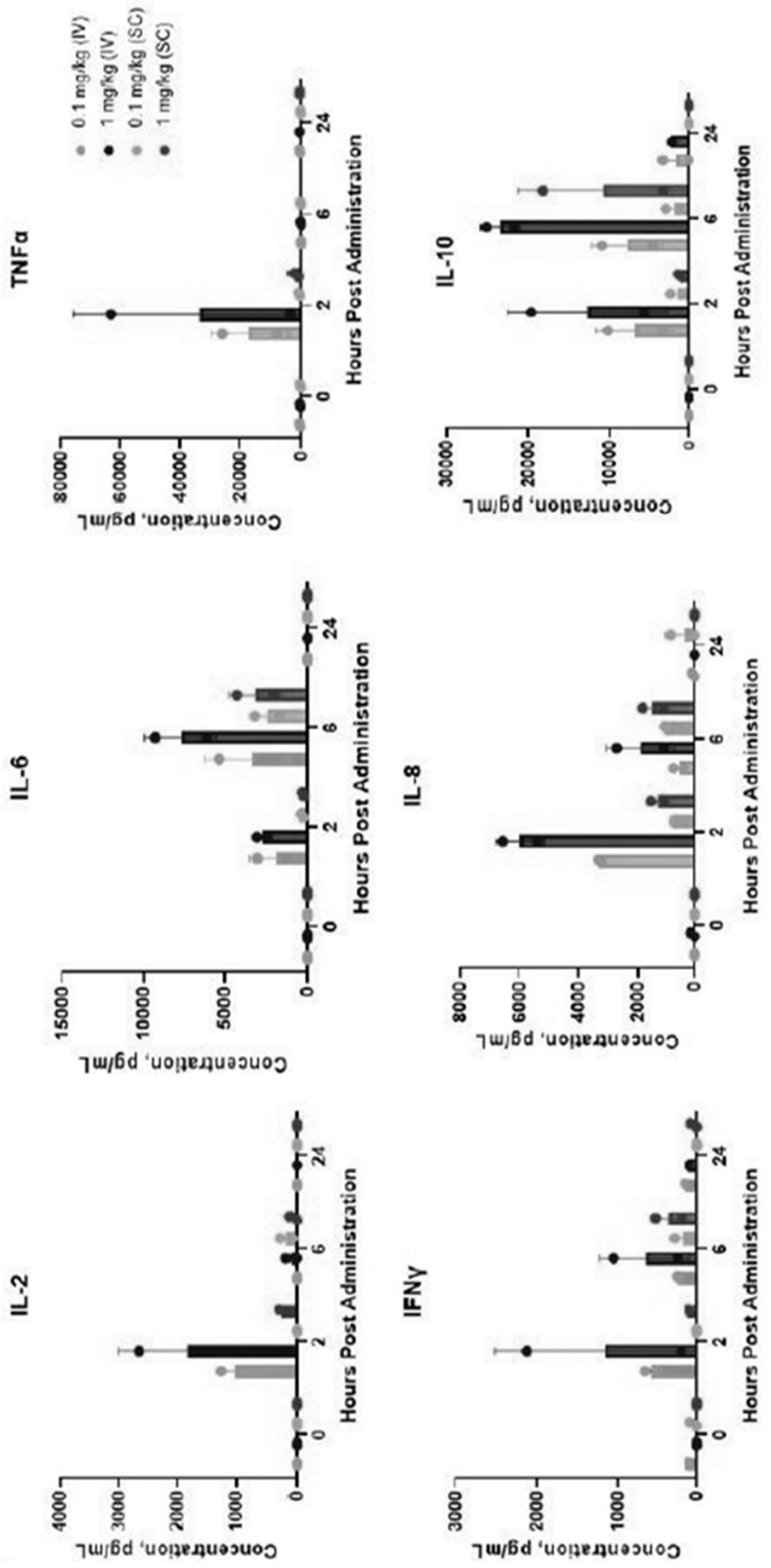

TNFα
IL-6
IL-10
IL-2
IL-8
IFNγ
0.1 mg/kg (IV)
1 mg/kg (IV)
0.1 mg/kg (SC)
1 mg/kg (SC)
Concentration, pg/mL
Hours Post Administration

FIG. 14E

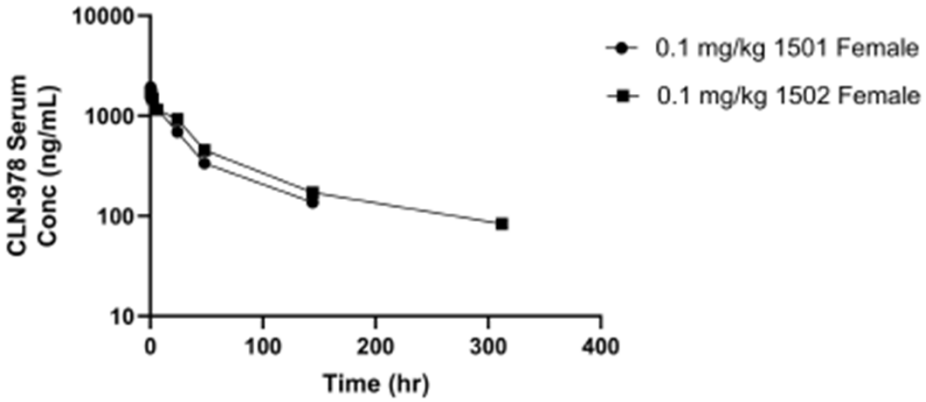


FIG. 15A

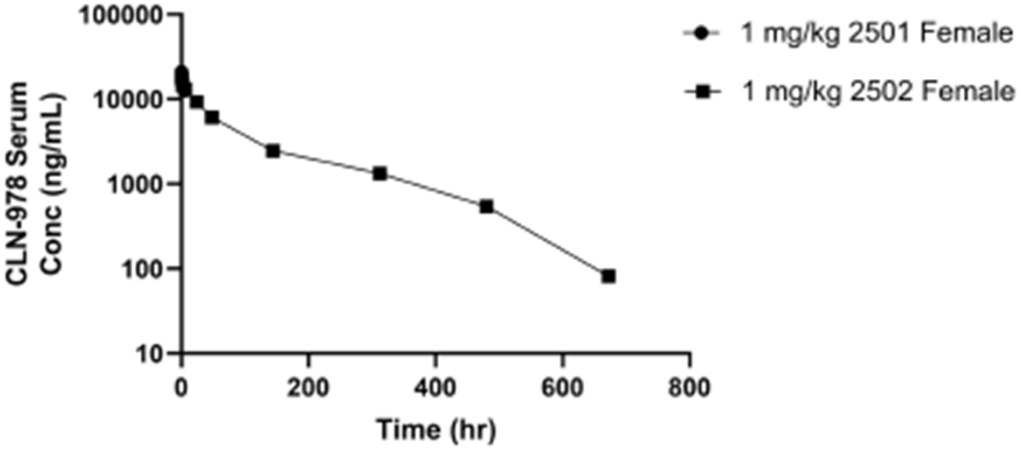


FIG. 15B

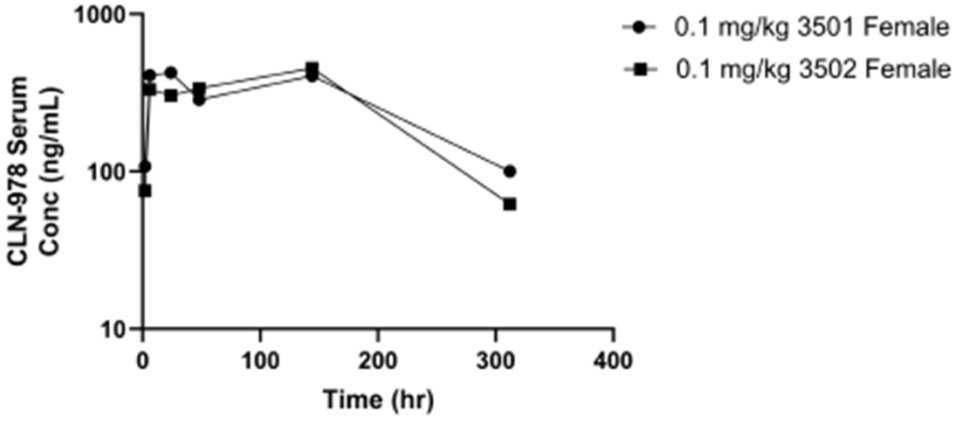


FIG. 15C

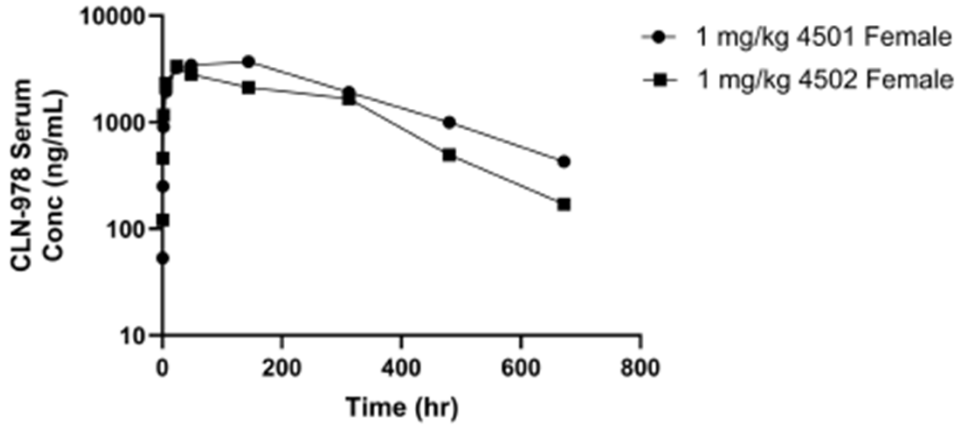


FIG. 15D

Group	Treatment	Dose (ng/kg)	Subject	C_{max} (ng/mL)	C_0 (ng/mL)	T_{max} (hr)	T_{last} (hr)	$T_{1/2}$ (hr)	AUC_{last} (hr*ng/mL)	AUC_{inf} (hr*ng/mL)	Cl (mL/hr/kg)	V_{ss} (mL/kg)
1	IV	100000	1501	1920	2080	0.250	144	43.8	60500	69100	1.45	86.6
			1502	1710	1730	0.250	312	113	95100	109000	0.920	116
			Mean	**1820**	**1900**	**0.250**	**228**	**78.2**	**77800**	**88900**	**1.18**	**101**
			SD	**152**	**247**	**0.00**	**119**	**48.6**	**24500**	**28000**	**0.373**	**21.0**
			CV%	**8.36**	**12.9**	**0.00**	**52.1**	**62.2**	**31.5**	**31.5**	**31.5**	**20.7**
2	IV	1000000	2501	21200	22300	0.250	6.00	ND[a]	93600	ND[a]	ND[a]	ND[a]
			2502	18800	19800	0.250	672	98.3	1420000	1430000	0.697	98.0
			Mean	**20000**	**21000**	**0.250**	**339**	**98.3**	**758000**	**1430000**	**0.697**	**98.0**
			SD	**1730**	**1710**	**0.00**	**471**	**NA**	**939000**	**NA**	**NA**	**NA**
			CV%	**8.64**	**8.14**	**0.00**	**139**	**NA**	**124**	**NA**	**NA**	**NA**

[a] no parameters could be calculated, because the following criteria were not met in order to accept a λz estimate and to report λz, $t_{1/2}$, or AUC_{inf},: (1) three or more points in the terminal phase (C_{max} could not be included); (2) adjusted R^2 (goodness of fit statistic for the terminal phase adjusted for number of points used) > 0.85; (3) $\%AUC_{extrap}$ (the percentage of AUC_{inf} that is due to extrapolation from C_{last} to infinity) <20%; and (4) $t_{1/2}$ less than one-half the time interval over which λz was estimated

AUC_{inf}: area under the concentration versus time curve from time zero to infinity; AUC_{last}: area under the concentration versus time curve from time zero to the time of the last measurable concentration; C_{max}: maximum concentration; t_{last}: time of the last measurable concentration; T_{max}: time of occurrence of maximum concentration; $t_{1/2}$: the apparent terminal half-life; V_{ss}: the steady state volume of distribution; NA: not applicable; ND: could not be determined

FIG. 16A

Group	Treatment	Dose (ng/kg)	Subject	C_{max} (ng/mL)	T_{max} (hr)	T_{last} (hr)	$T_{1/2}$ (hr)	AUC_{last} (hr*ng/mL)	AUC_{inf} (hr*ng/mL)
3	SC	100000	3501	424	24.0	312	ND[a]	92700	ND[a]
			3502	453	144	312	ND[a]	95600	ND[a]
			Mean	**439**	**84.0**	**312**	**NA**	**94100**	**NA**
			SD	**21.0**	**84.9**	**0.00**	**NA**	**2020**	**NA**
			CV%	**4.79**	**101**	**0.00**	**NA**	**2.14**	**NA**
4	SC	1000000	4501	3710	144	672	167	1330000	1430000
			4502	3360	24.0	672	110	933000	960000
			Mean	**3540**	**84.0**	**672**	**138**	**1130000**	**1200000**
			SD	**241**	**84.9**	**0.00**	**40.3**	**279000**	**333000**
			CV%	**6.82**	**101**	**0.00**	**29.1**	**24.7**	**27.8**

[a] no parameters could be calculated, because the following criteria were not met in order to accept a λz estimate and to report λz, $t_{1/2}$, or AUC_{inf},: (1) three or more points in the terminal phase (C_{max} could not be included); (2) adjusted R^2 (goodness of fit statistic for the terminal phase adjusted for number of points used) > 0.85; (3) $\%AUC_{extrap}$ (the percentage of AUC_{inf} that is due to extrapolation from C_{last} to infinity) <20%; and (4) $t_{1/2}$ less than one-half the time interval over which λz was estimated.

AUC_{inf}: area under the concentration versus time curve from time zero to infinity; AUC_{last}: area under the concentration versus time curve from time zero to the time of the last measurable concentration; C_{max}: maximum concentration; t_{last}: time of the last measurable concentration; T_{max}: time of occurrence of maximum concentration; $t_{1/2}$: the apparent terminal half-life; V_{ss}: the steady state volume of distribution; NA: not applicable; ND: could not be determined

FIG. 16B

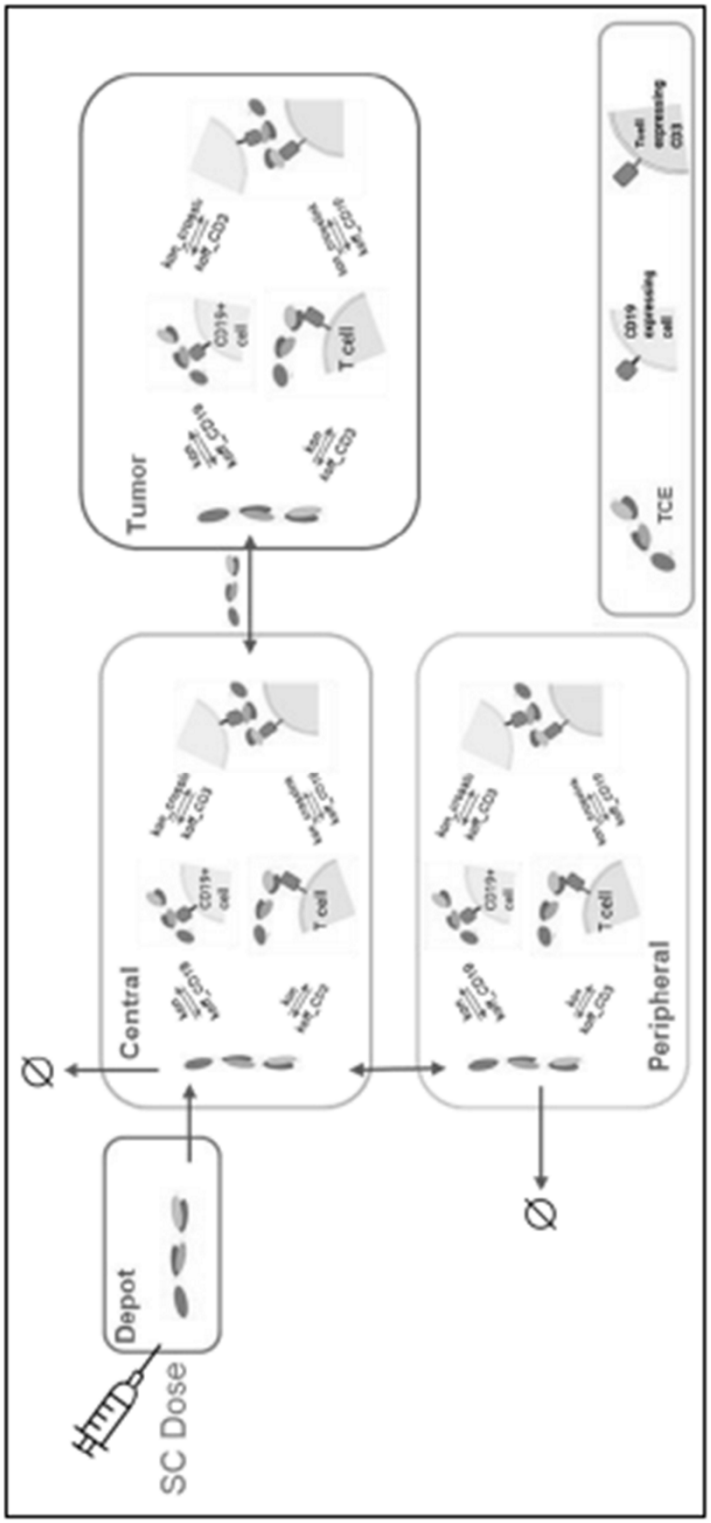


FIG. 17

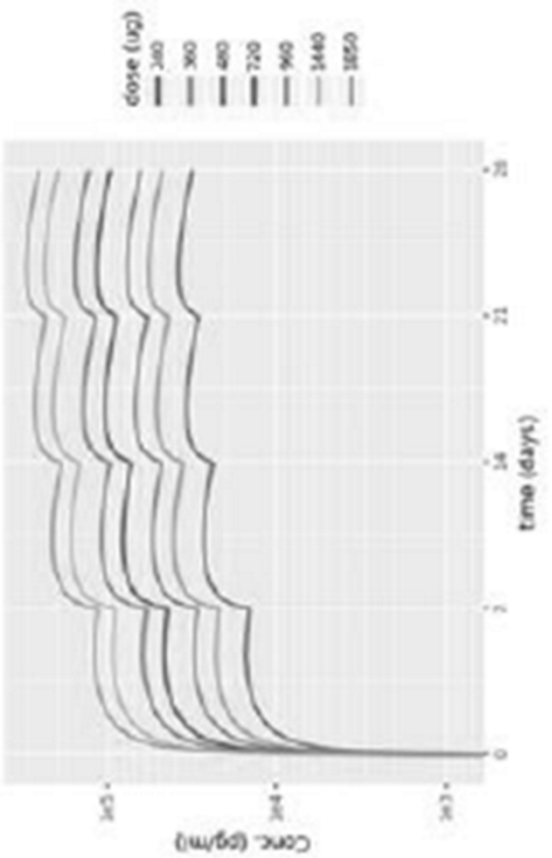


FIG. 18B

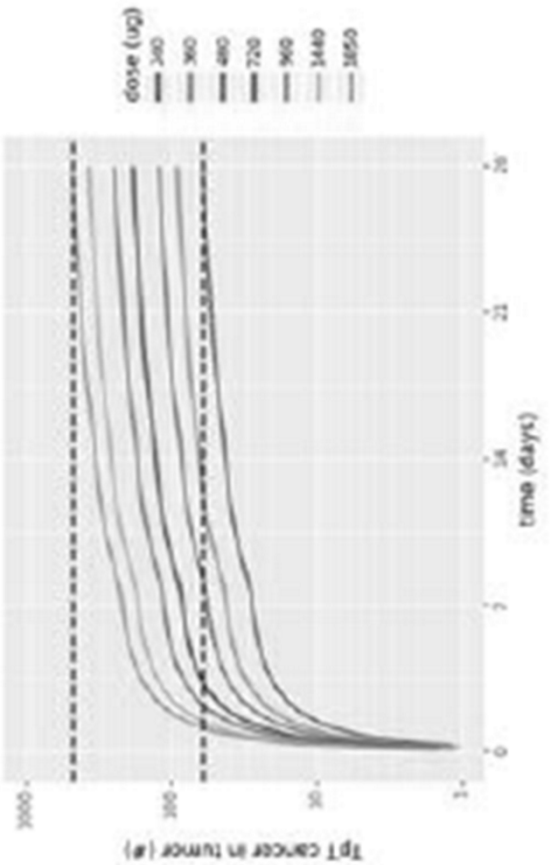
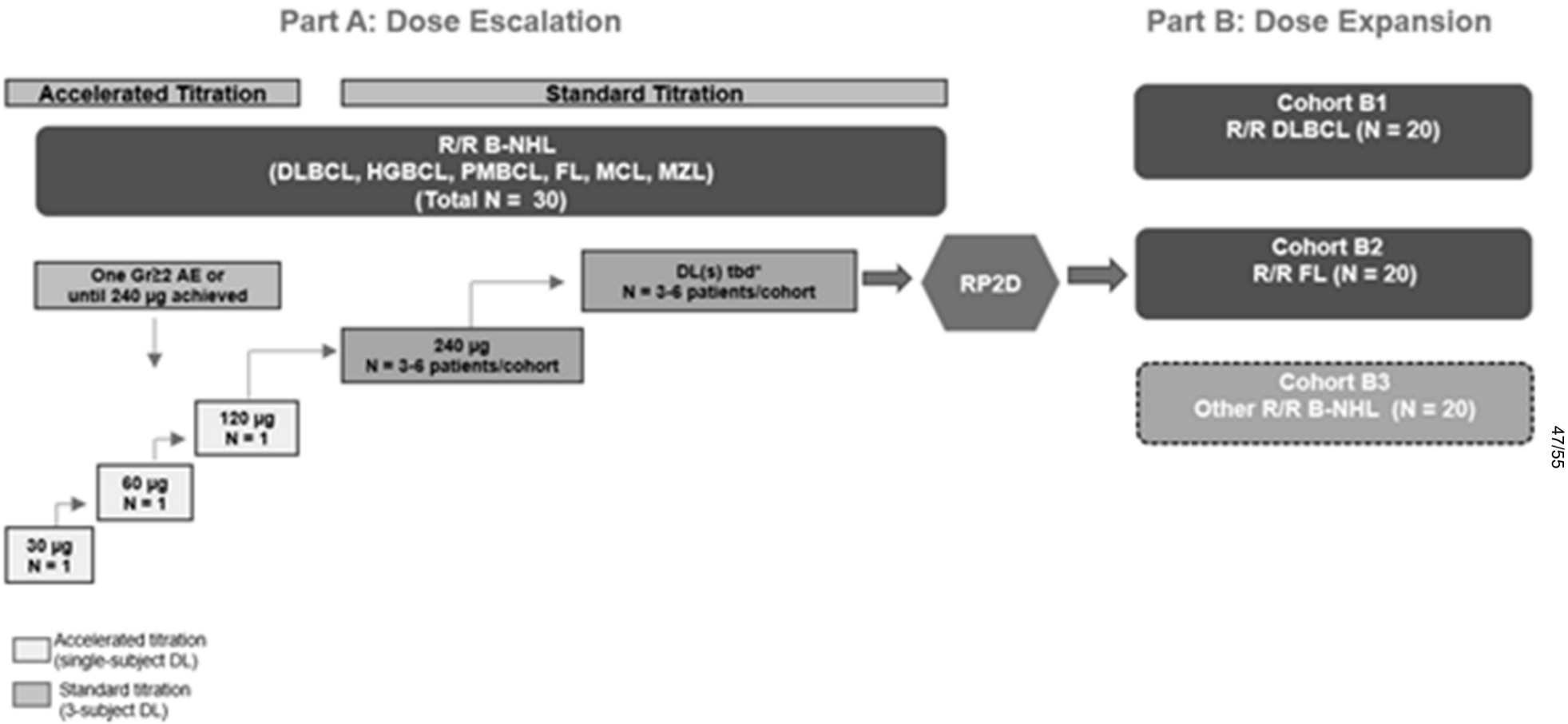


FIG. 18A



AE = adverse event; B-NHL = B-cell non-Hodgkin lymphoma subtypes; DL = dose level; DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; GR = Grade; HGBCL = high-grade B-cell lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; RP2D = recommended phase 2 dose; R/R = relapsed/refractory; tbd = to be determined.; µg = microgram.

FIG. 19

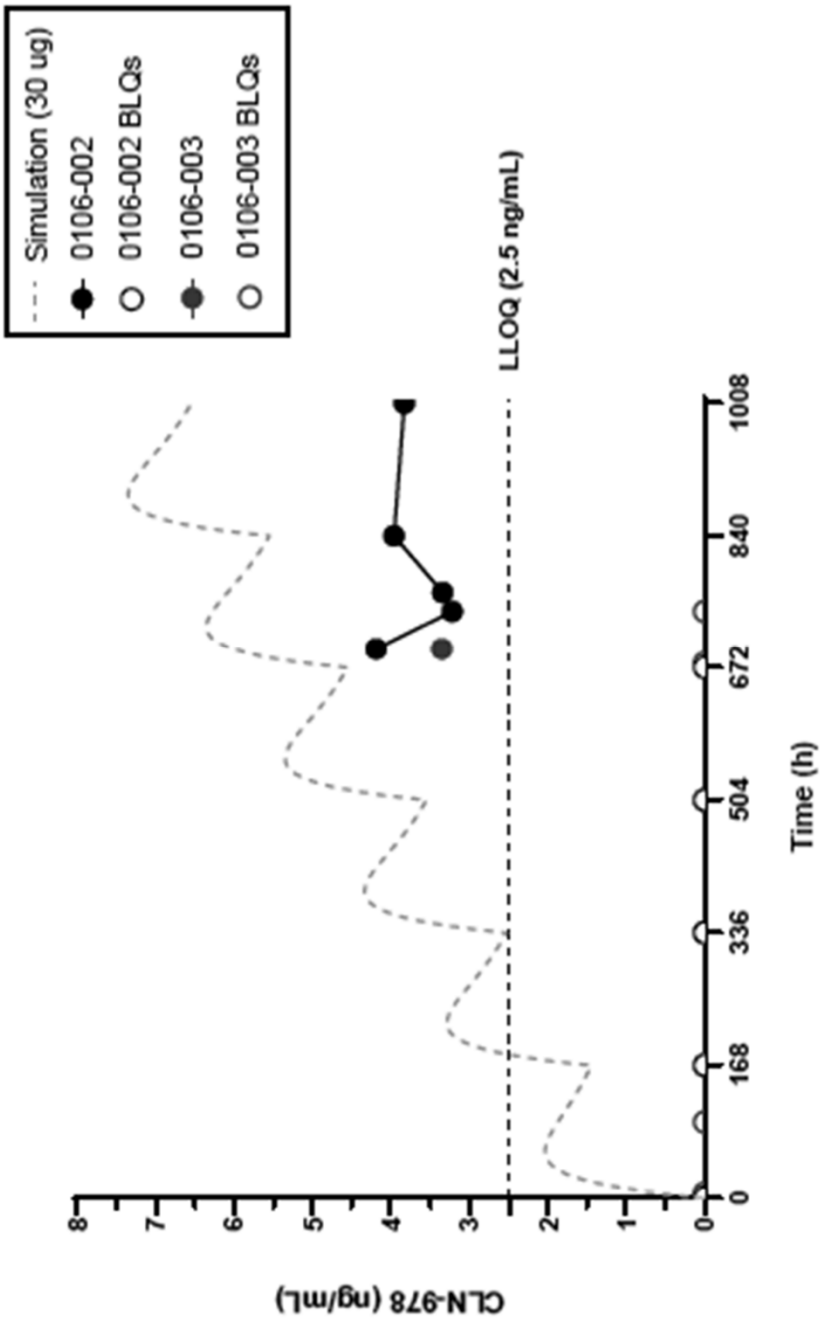

Simulation (30 ug)
0106-002
0106-002 BLQs
0106-003
0106-003 BLQs
LLOQ (2.5 ng/mL)
CLN-978 (ng/mL)
Time (h)
0
1
2
3
4
5
6
7
8
0
168
336
504
672
840
1008

FIG. 20

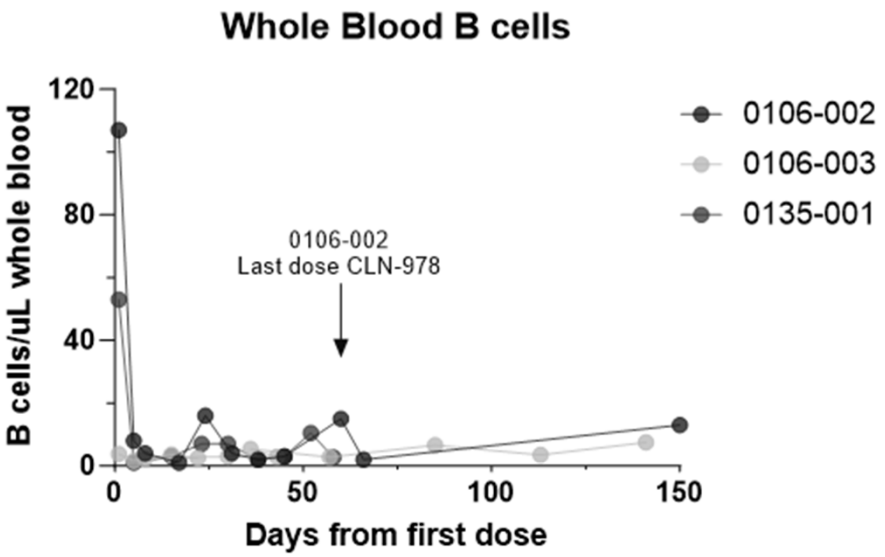


FIG. 21A

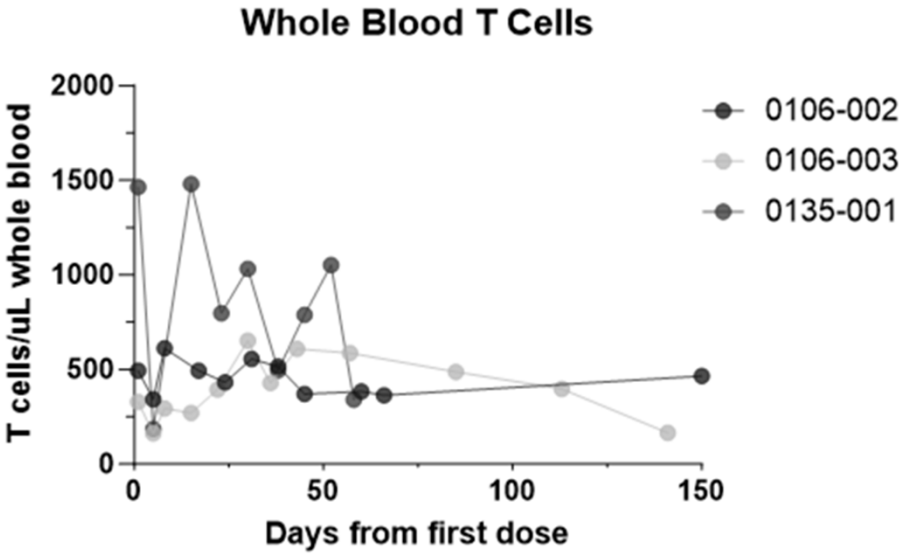


FIG. 21B

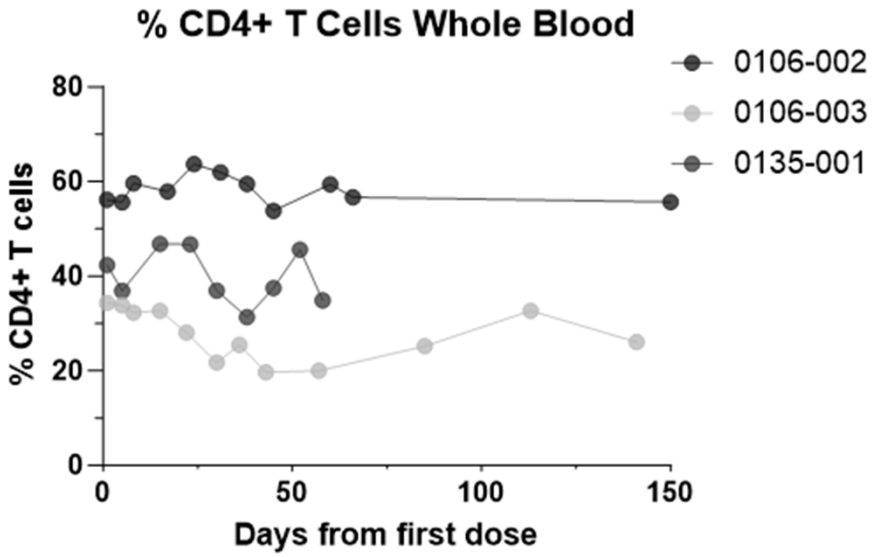


FIG. 21C

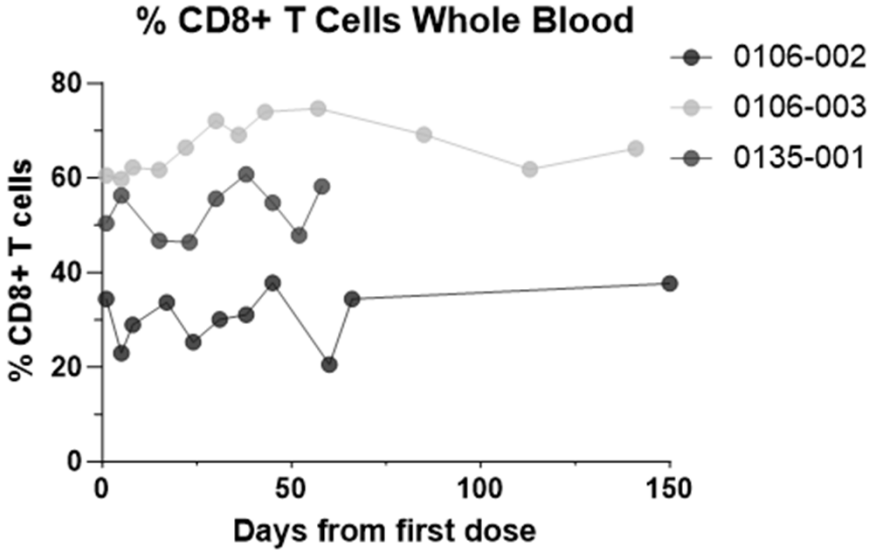


FIG. 21D

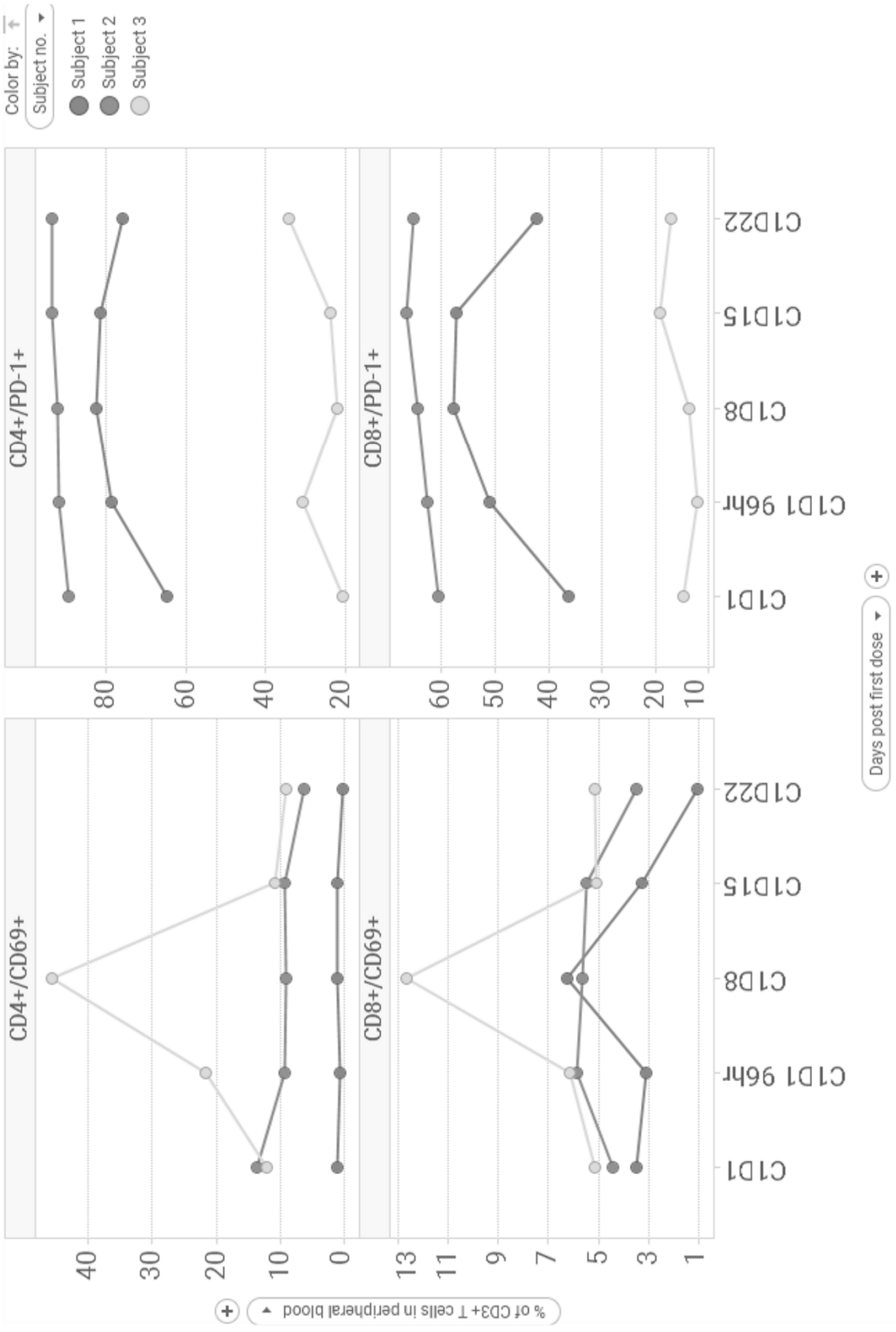

Color by:
Subject no.
Subject 1
Subject 2
Subject 3
CD4+/CD69+
CD8+/CD69+
CD4+/PD-1+
CD8+/PD-1+
% of CD3+ T cells in peripheral blood
Days post first dose
C1D1
C1D1 96hr
C1D8
C1D15
C1D22

FIG. 21E

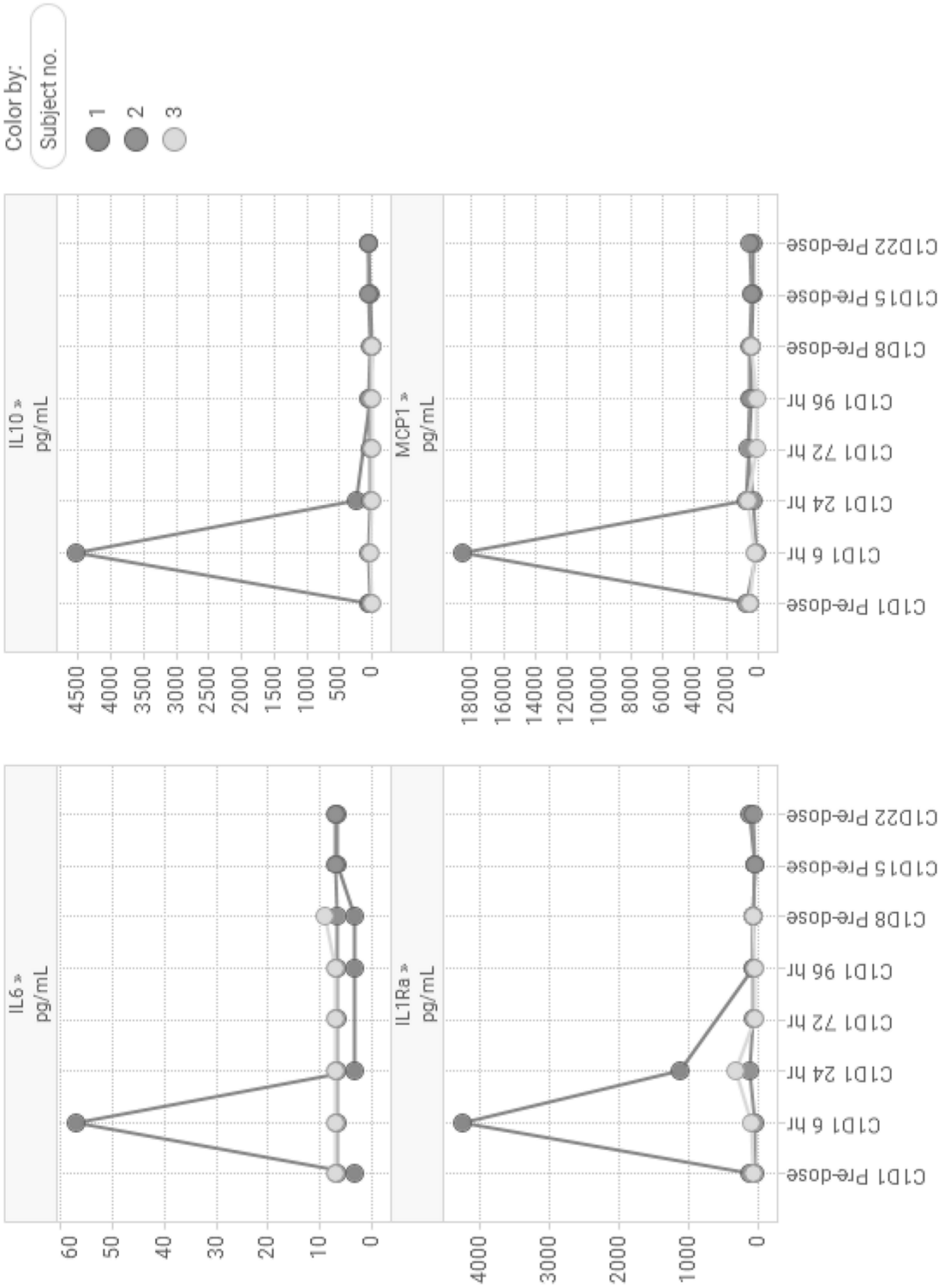

Color by:
Subject no.
1
2
3
IL10 »
pg/mL
MCP1 »
pg/mL
IL6 »
pg/mL
IL1Ra »
pg/mL
C1D1 Pre-dose
C1D1 6 hr
C1D1 24 hr
C1D1 72 hr
C1D1 96 hr
C1D8 Pre-dose
C1D15 Pre-dose
C1D22 Pre-dose
Visit

FIG. 21F

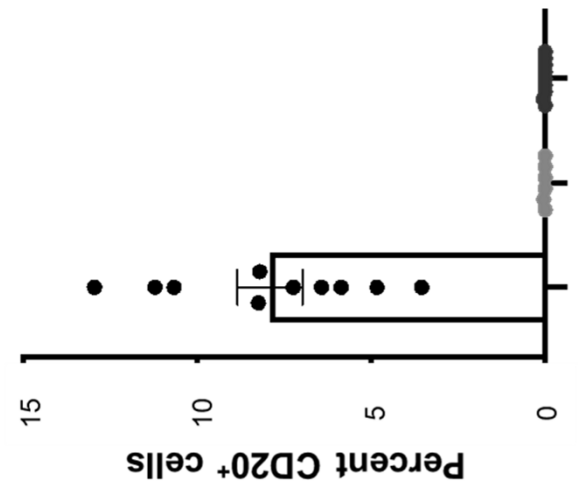


FIG. 22A

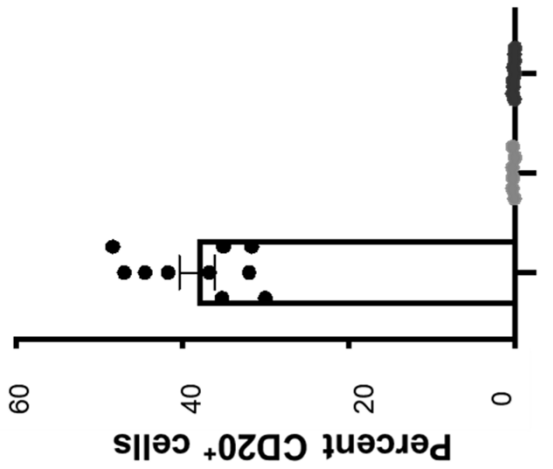


FIG. 22B

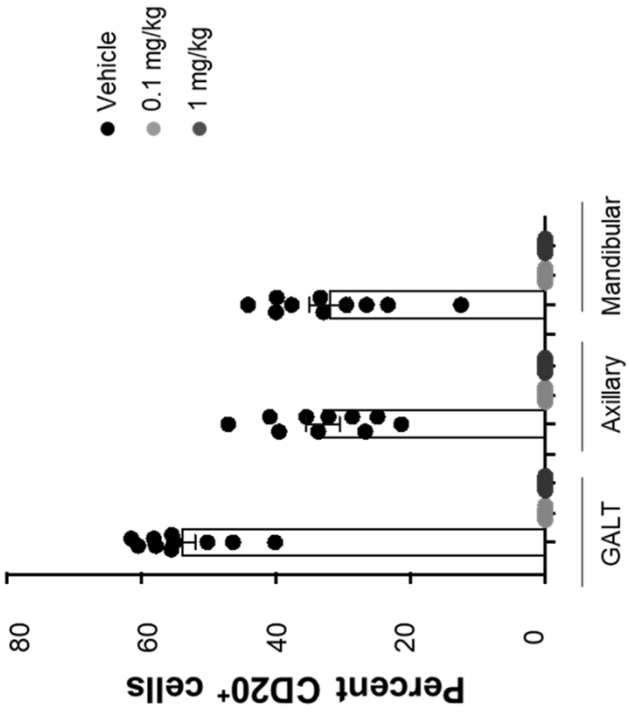


FIG. 22C

Disease Characteristics and Efficacy Observations					Treatment Emergent Adverse Events			
ID	Diagnosis	Prior Lines	Duration of CLN-978 Treatment	Best Response*	Worst Grade Non-Hematological	Worst Grade Hematological	Worst Grade CRS	Worst Grade ICANS
1	DLBCL	3	9 doses (off treatment)	PD	Gr 1 fatigue, nausea, headache	Gr 4 lymphopenia†	Gr 1 (fever)	None
2	Follicular	3	24 doses (ongoing)	SD	Gr 1 hypocalcemia, hypomagnesemia	Gr 4 lymphopenia	Gr 1 (fever)	None
3	Mantle	3	7 doses (off treatment)	PR	Gr 3 vascular access complication (DVT)**	Gr 3 lymphopenia	None	None

- **All patients treated at starting dose: 30 ug SC QW**
- **2 of 3 patients demonstrated objective clinical benefit**

- Class toxicity: max Gr 1 CRS, no ICANS
- Other adverse events: low-grade, manageable, mechanistically based (e.g. lymphopenia), or unrelated

FIG. 23

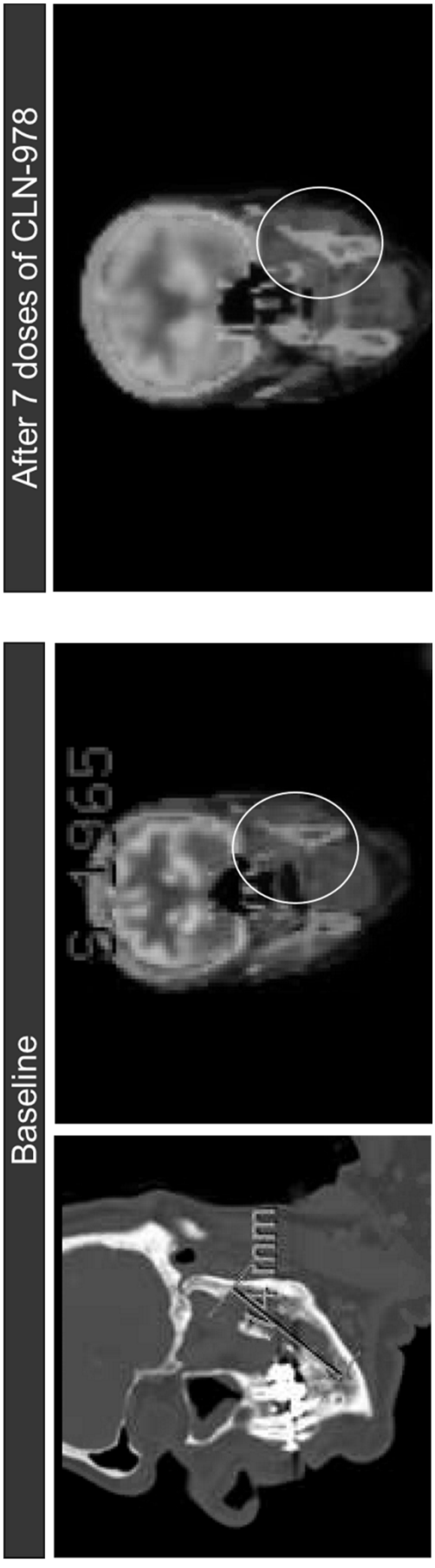


FIG. 24