
TN-20LEU-19
SP
Leu16(VL-VH)
linker
FMC63(VH-VL)
hinge
CD28 TM
4-1BB
CD3z
TN-20OF-19 (C-CAR039)
SP
OF (VL-VH)
linker
FMC63(VH-VL)
hinge
CD28 TM
4-1BB
CD3z

FIG. 1

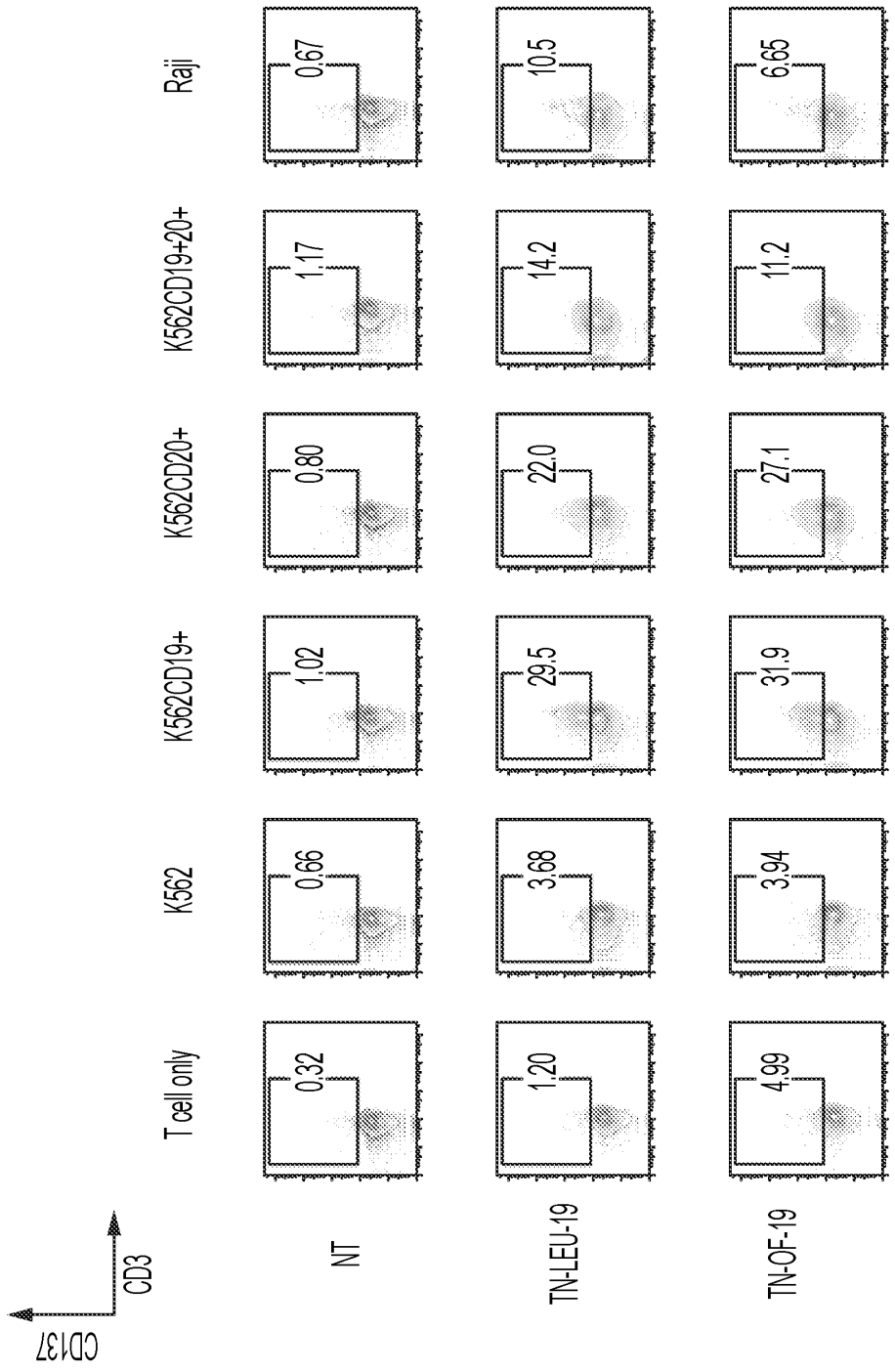

T cell only
K562
K562CD19+
K562CD20+
K562CD19+20+
Raji
NT
TN-LEU-19
TN-OF-19
CD3
CD137
0.32
0.66
1.02
0.80
1.17
0.67
1.20
3.68
29.5
22.0
14.2
10.5
4.99
3.94
31.9
27.1
11.2
6.65

FIG. 2A

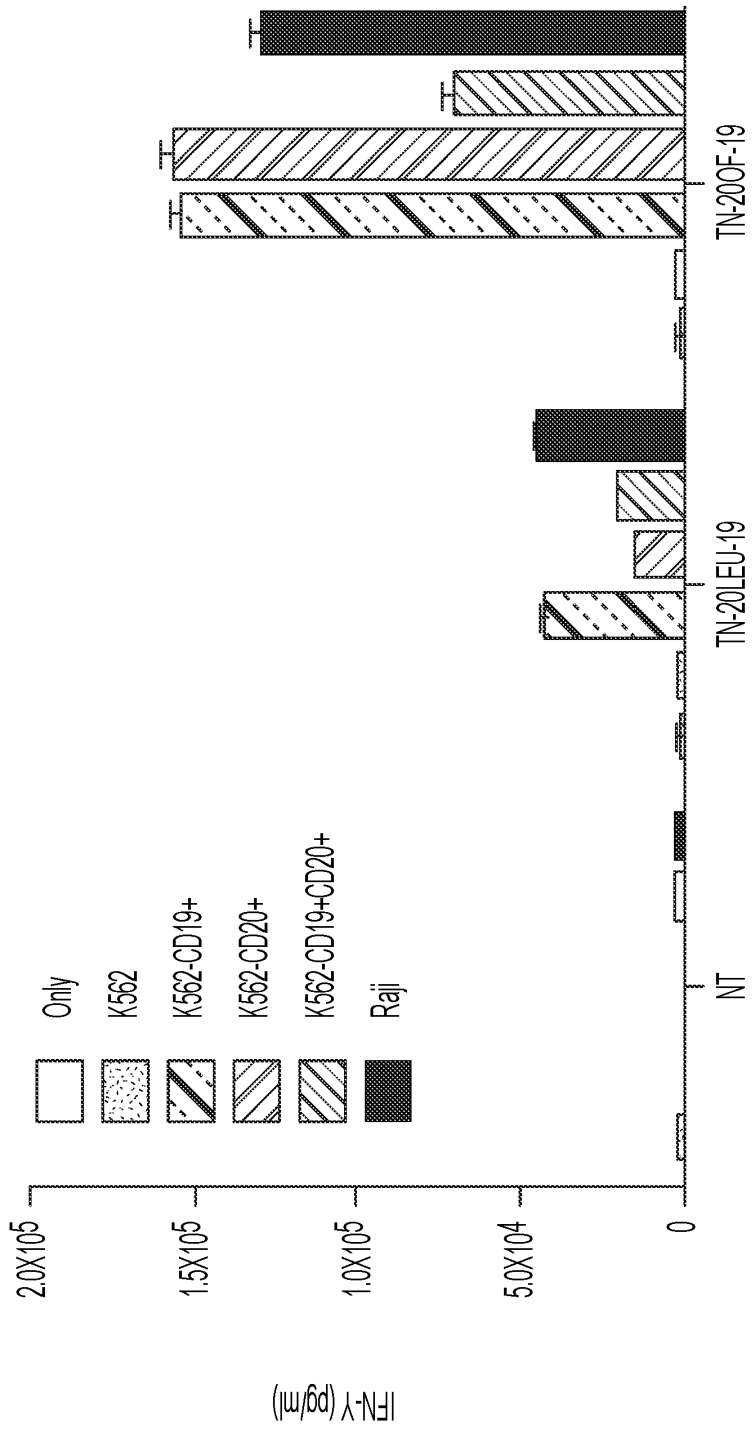

IFN-γ (pg/ml)
2.0X10^5
1.5X10^5
1.0X10^5
5.0X10^4
0
Only
K562
K562-CD19+
K562-CD20+
K562-CD19+CD20+
Raji
NT
TN-20LEU-19
TN-20OF-19

FIG. 2B

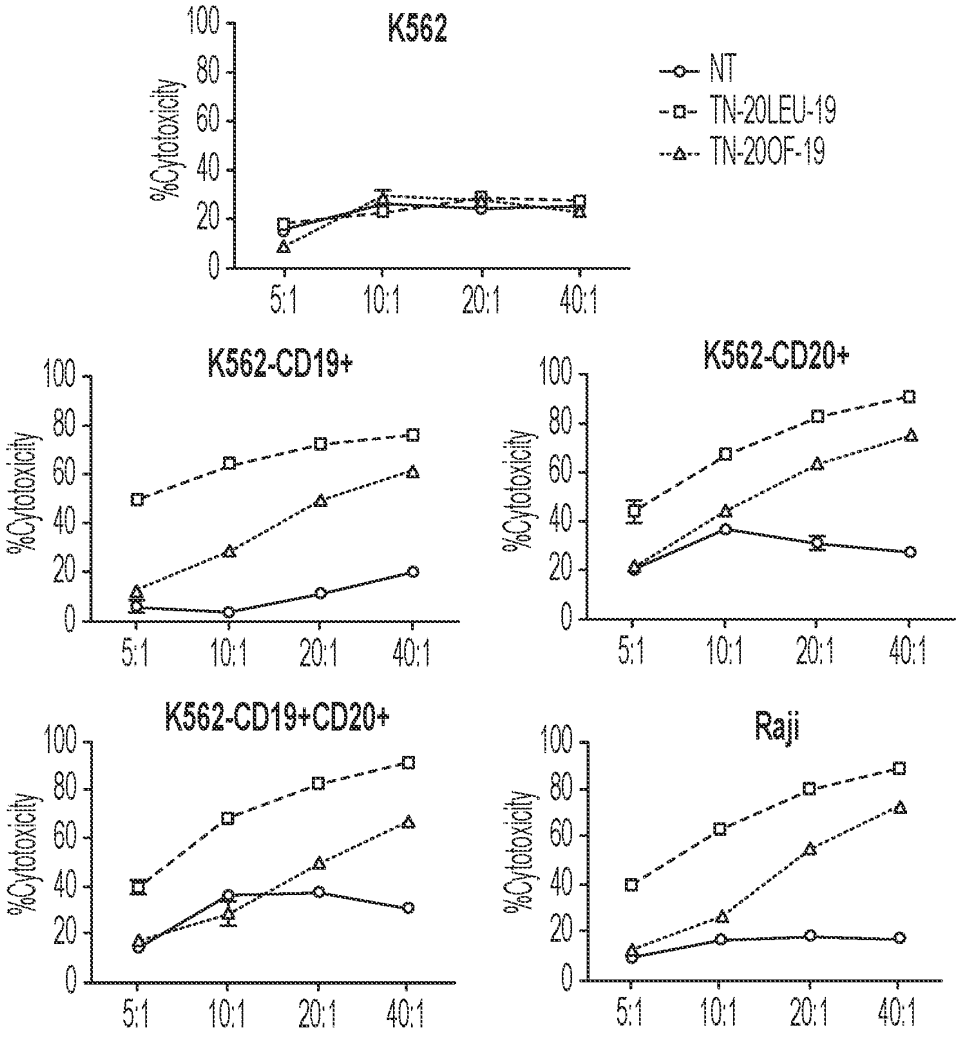

K562
%Cytotoxicity
100
80
60
40
20
0
5:1
10:1
20:1
40:1
NT
TN-20LEU-19
TN-20OF-19
K562-CD19+
K562-CD20+
K562-CD19+CD20+
Raji

FIG. 3A

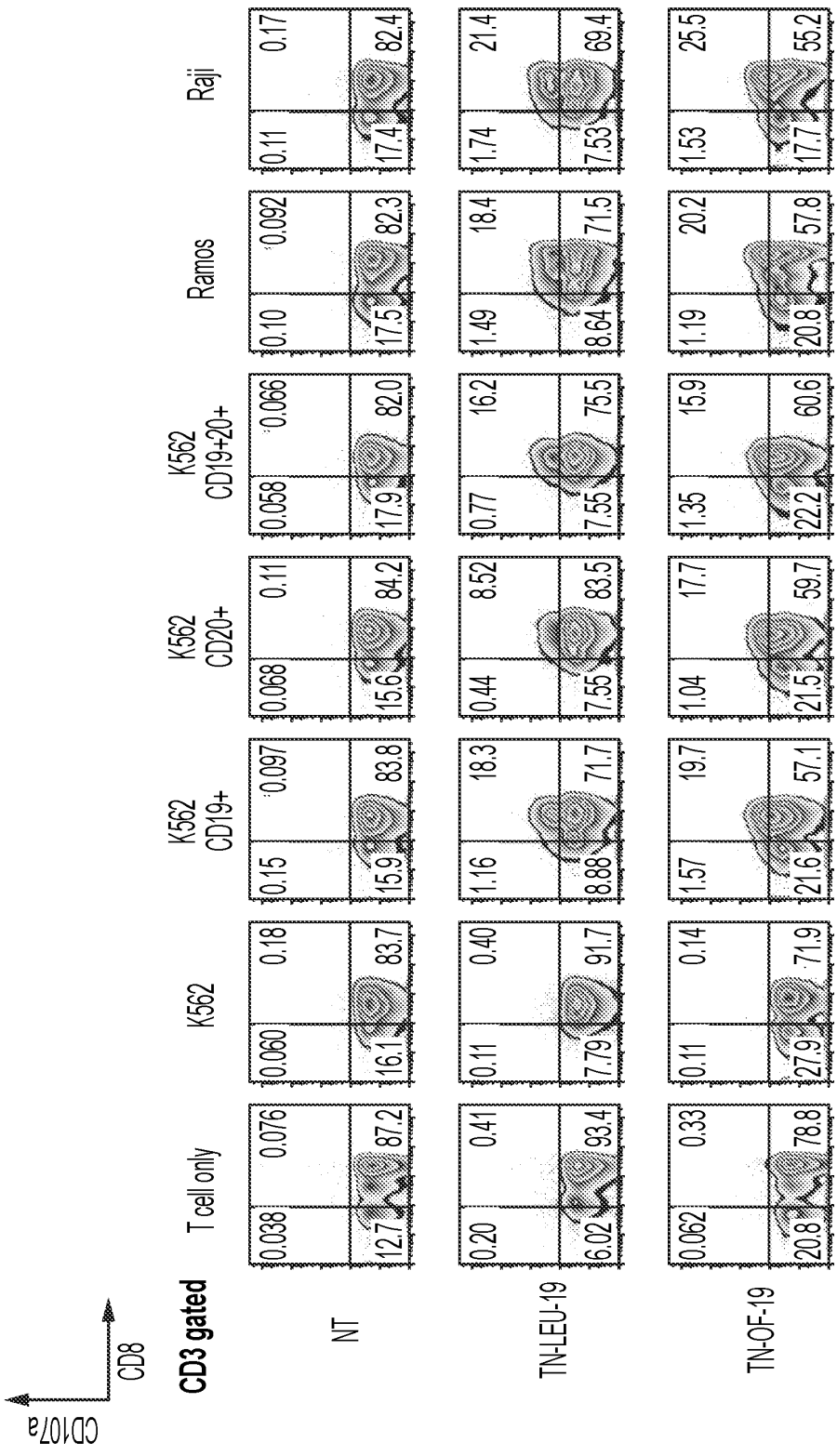

CD107a
CD8
CD3 gated
T cell only
K562
K562 CD19+
K562 CD20+
K562 CD19+20+
Ramos
Raji
NT
TN-LEU-19
TN-OF-19
0.038
0.076
12.7
87.2
0.20
0.41
6.02
93.4
0.062
0.33
20.8
78.8
0.060
0.18
16.1
83.7
0.11
0.40
7.79
91.7
0.11
0.14
27.9
71.9
0.15
0.097
15.9
83.8
1.16
18.3
8.88
71.7
1.57
19.7
21.6
57.1
0.068
0.11
15.6
84.2
0.44
8.52
7.55
83.5
1.04
17.7
21.5
59.7
0.058
0.066
17.9
82.0
0.77
16.2
7.55
75.5
1.35
15.9
22.2
60.6
0.10
0.092
17.5
82.3
1.49
18.4
8.64
71.5
1.19
20.2
20.8
57.8
0.11
0.17
17.4
82.4
1.74
21.4
7.53
69.4
1.53
25.5
17.7
55.2

FIG. 3B

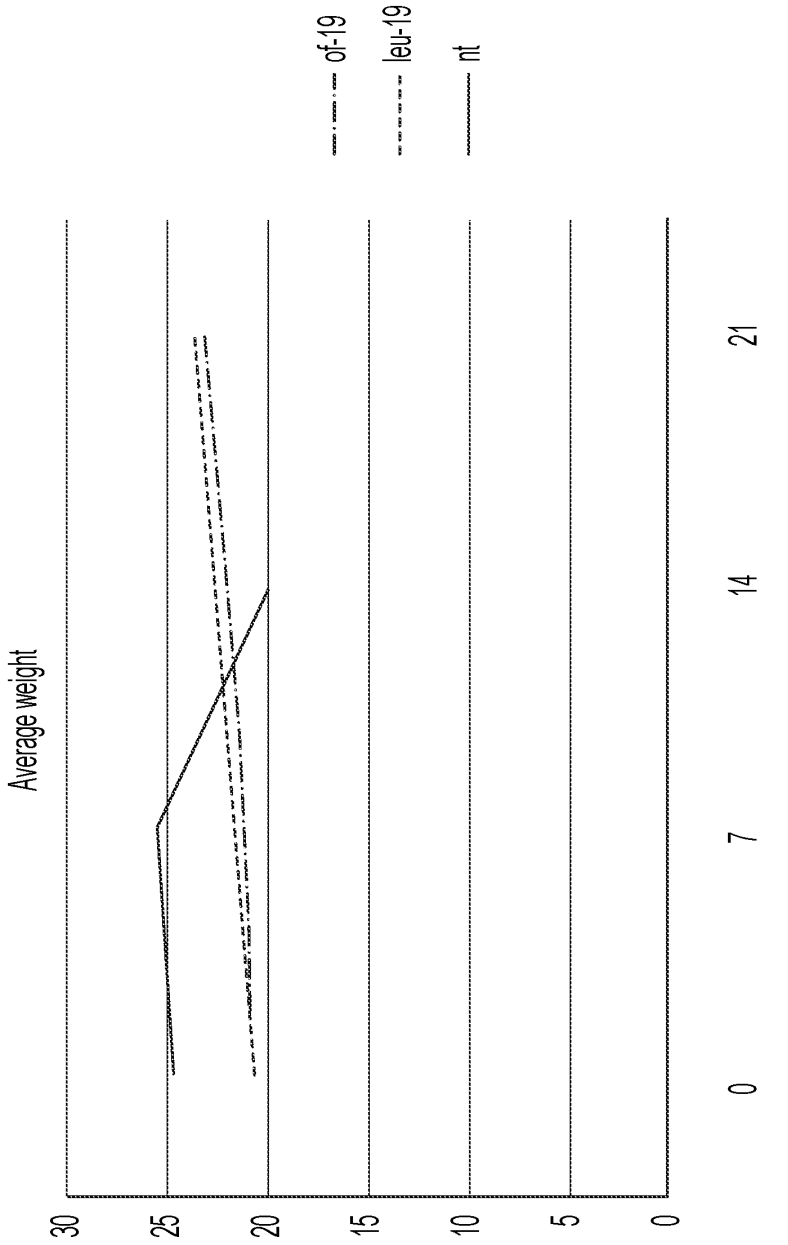


FIG. 4A

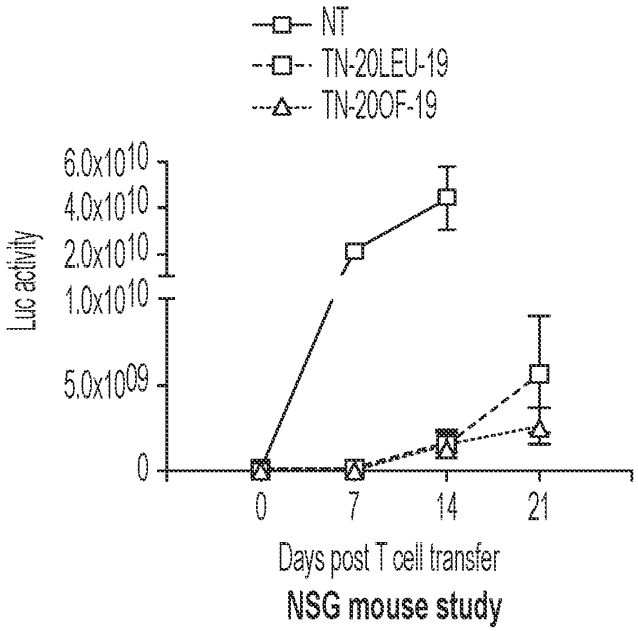

NT
TN-20LEU-19
TN-20OF-19
6.0x10^10
4.0x10^10
2.0x10^10
1.0x10^10
5.0x10^09
0
Luc activity
0
7
14
21
Days post T cell transfer
NSG mouse study

FIG. 4B

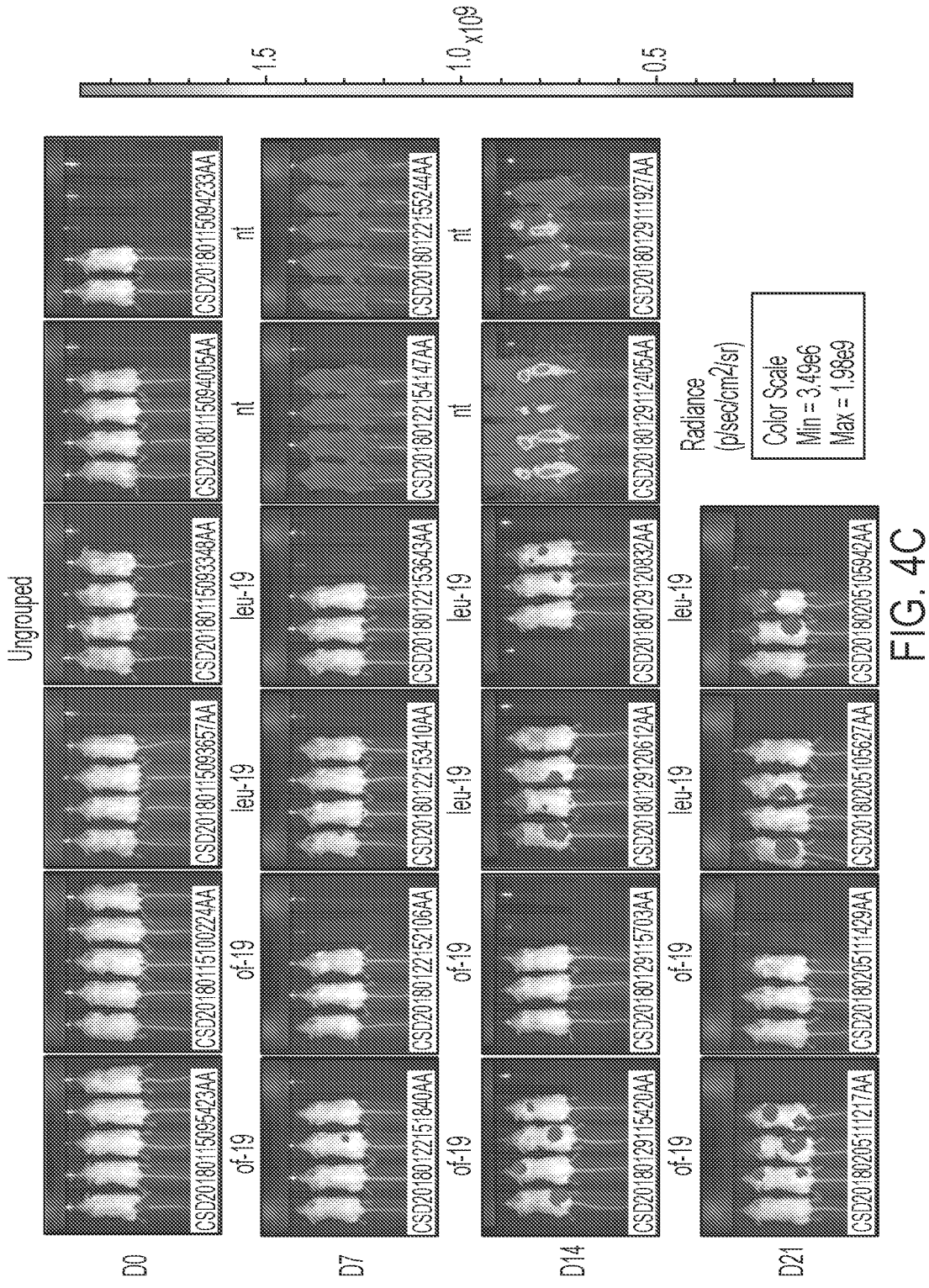

Ungrouped
D0
D7
D14
D21
of-19
leu-19
nt
1.5
1.0 x10^9
0.5
Radiance (p/sec/cm2/sr)
Color Scale
Min = 3.49e6
Max = 1.98e9

FIG. 4C

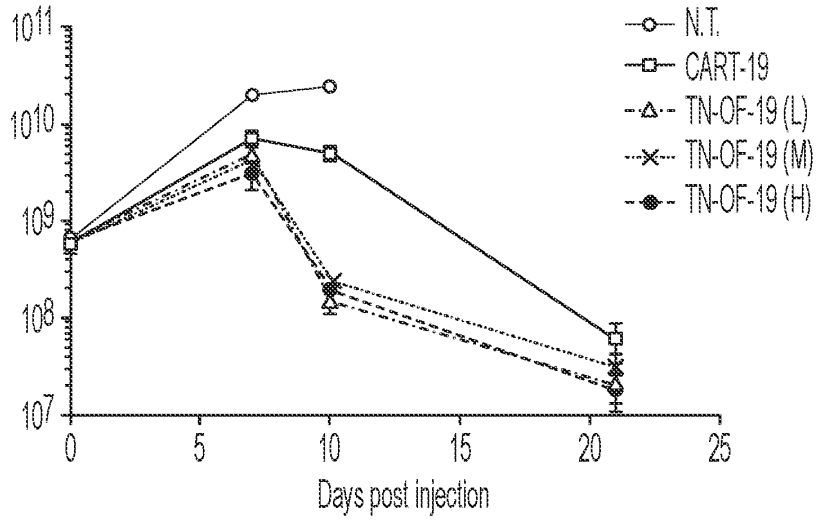

10^{11}
10^{10}
10^{9}
10^{8}
10^{7}
0
5
10
15
20
25
Days post injection
N.T.
CART-19
TN-OF-19 (L)
TN-OF-19 (M)
TN-OF-19 (H)

FIG. 5A

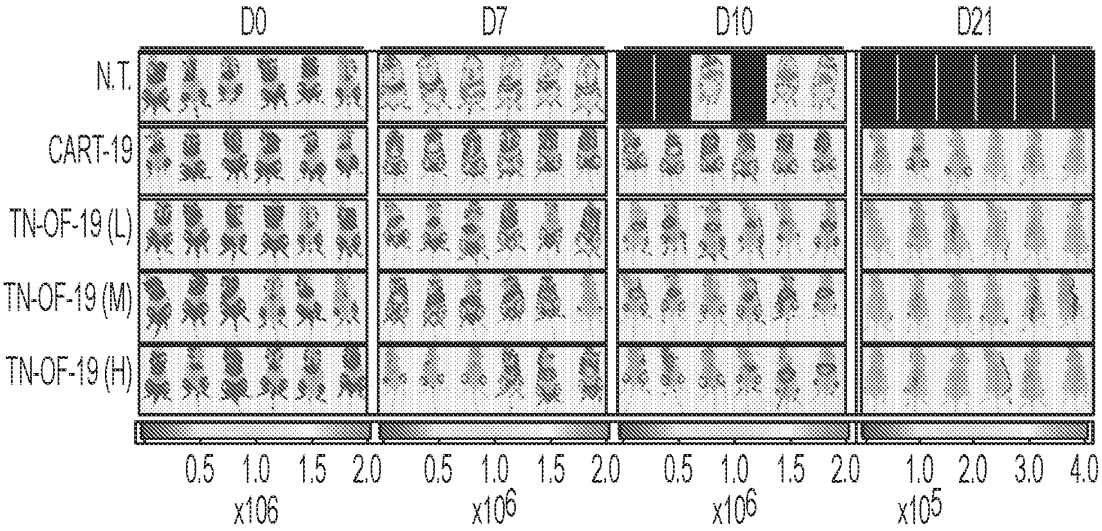

D0
D7
D10
D21
N.T.
CART-19
TN-OF-19 (L)
TN-OF-19 (M)
TN-OF-19 (H)
0.5 1.0 1.5 2.0
x106
0.5 1.0 1.5 2.0
x10^6
0.5 1.0 1.5 2.0
x10^6
1.0 2.0 3.0 4.0
x10^5

FIG. 5B

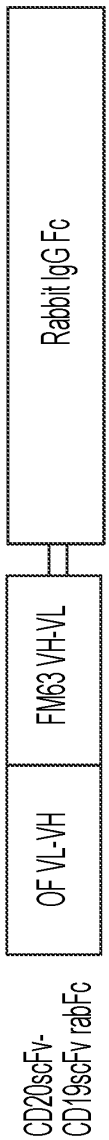


FIG. 6A

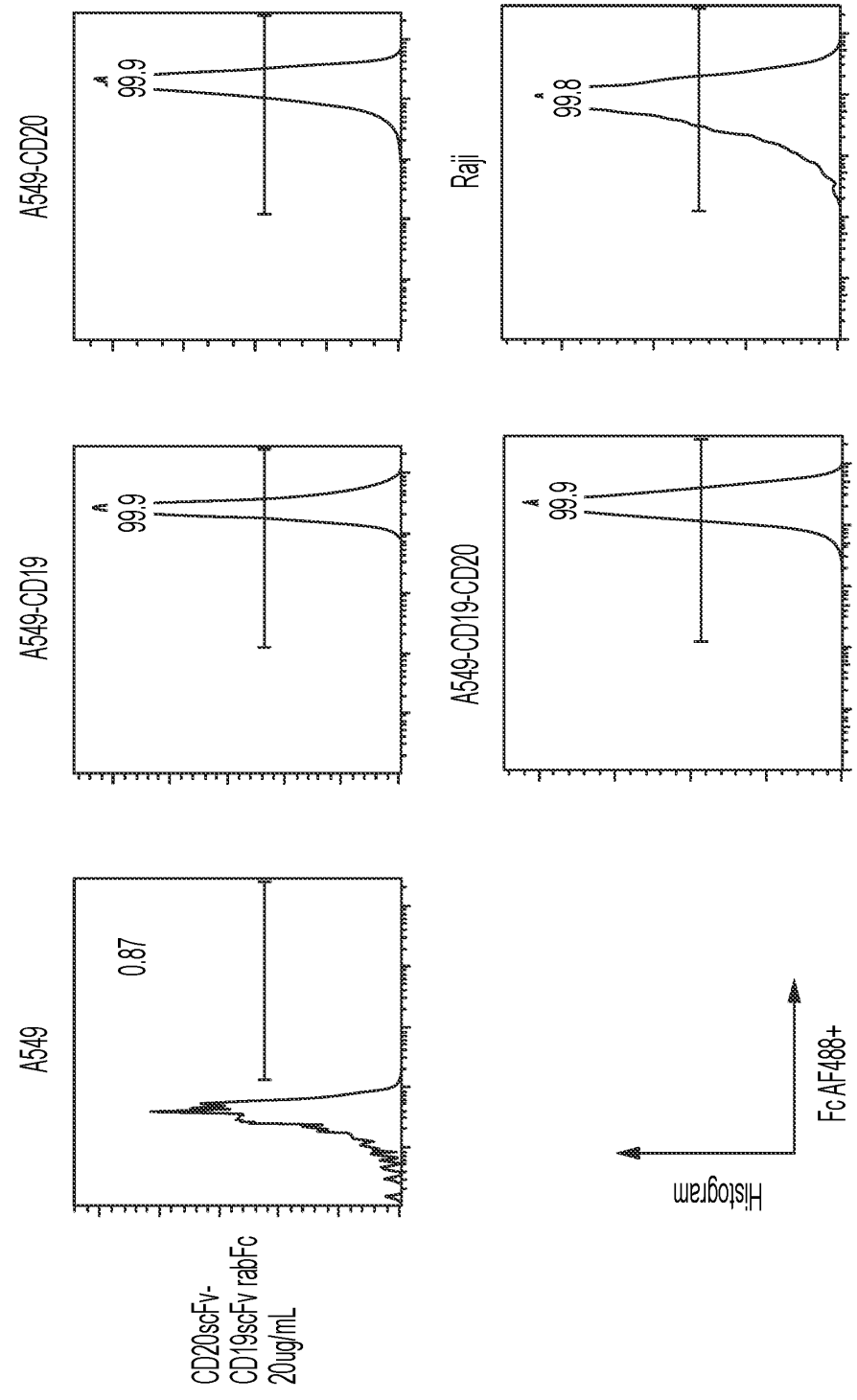

A549
0.87
A549-CD19
99.9
A549-CD20
99.9
A549-CD19-CD20
99.9
Raji
99.8
CD20scFv-CD19scFv rabFc 20ug/mL
Histogram
Fc AF488+

FIG. 6B

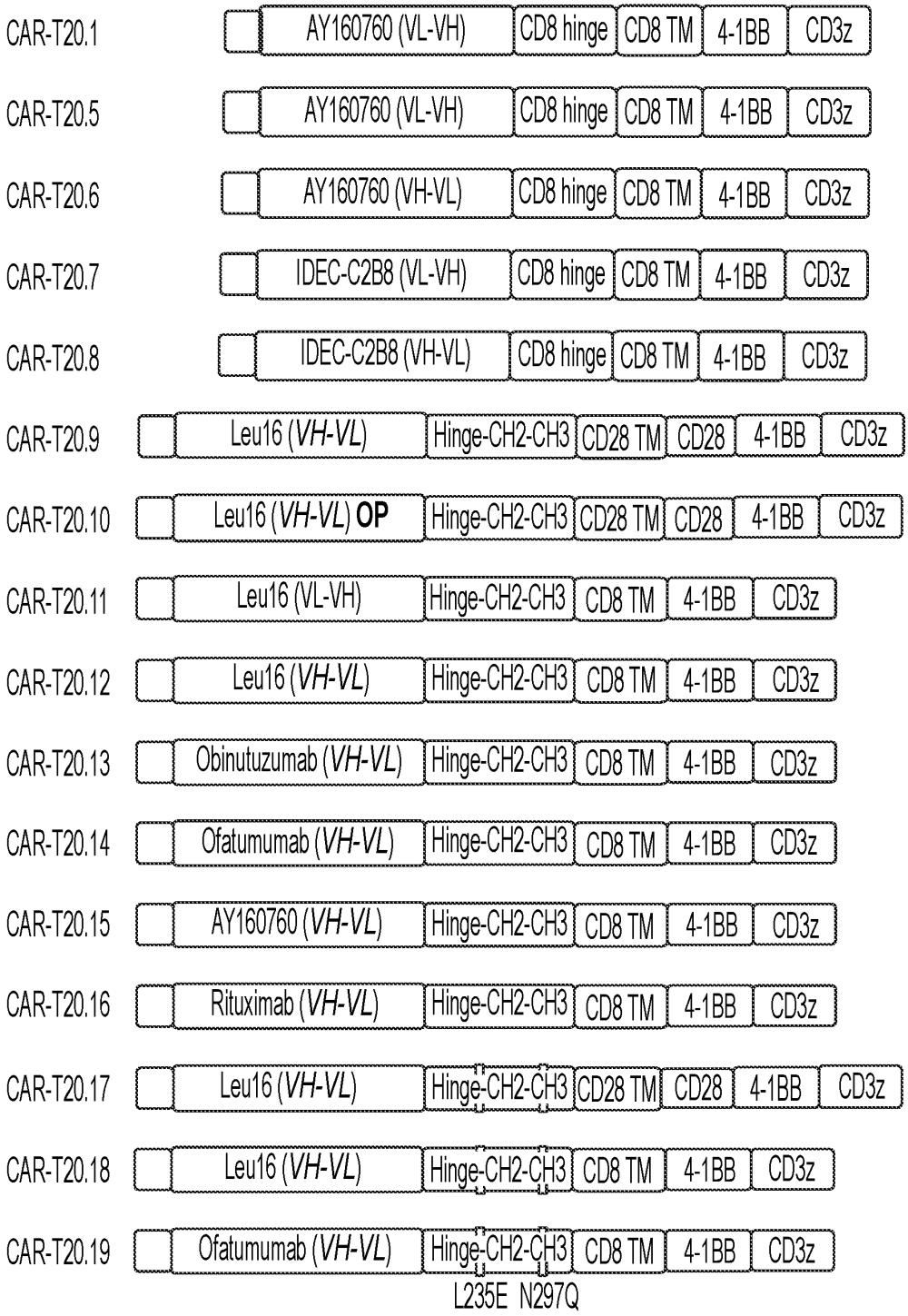

CAR-T20.1
AY160760 (VL-VH)
CD8 hinge
CD8 TM
4-1BB
CD3z
CAR-T20.5
AY160760 (VL-VH)
CD8 hinge
CD8 TM
4-1BB
CD3z
CAR-T20.6
AY160760 (VH-VL)
CD8 hinge
CD8 TM
4-1BB
CD3z
CAR-T20.7
IDEC-C2B8 (VL-VH)
CD8 hinge
CD8 TM
4-1BB
CD3z
CAR-T20.8
IDEC-C2B8 (VH-VL)
CD8 hinge
CD8 TM
4-1BB
CD3z
CAR-T20.9
Leu16 (VH-VL)
Hinge-CH2-CH3
CD28 TM
CD28
4-1BB
CD3z
CAR-T20.10
Leu16 (VH-VL) OP
Hinge-CH2-CH3
CD28 TM
CD28
4-1BB
CD3z
CAR-T20.11
Leu16 (VL-VH)
Hinge-CH2-CH3
CD8 TM
4-1BB
CD3z
CAR-T20.12
Leu16 (VH-VL)
Hinge-CH2-CH3
CD8 TM
4-1BB
CD3z
CAR-T20.13
Obinutuzumab (VH-VL)
Hinge-CH2-CH3
CD8 TM
4-1BB
CD3z
CAR-T20.14
Ofatumumab (VH-VL)
Hinge-CH2-CH3
CD8 TM
4-1BB
CD3z
CAR-T20.15
AY160760 (VH-VL)
Hinge-CH2-CH3
CD8 TM
4-1BB
CD3z
CAR-T20.16
Rituximab (VH-VL)
Hinge-CH2-CH3
CD8 TM
4-1BB
CD3z
CAR-T20.17
Leu16 (VH-VL)
Hinge-CH2-CH3
CD28 TM
CD28
4-1BB
CD3z
CAR-T20.18
Leu16 (VH-VL)
Hinge-CH2-CH3
CD8 TM
4-1BB
CD3z
CAR-T20.19
Ofatumumab (VH-VL)
Hinge-CH2-CH3
CD8 TM
4-1BB
CD3z
L235E N297Q

FIG. 7

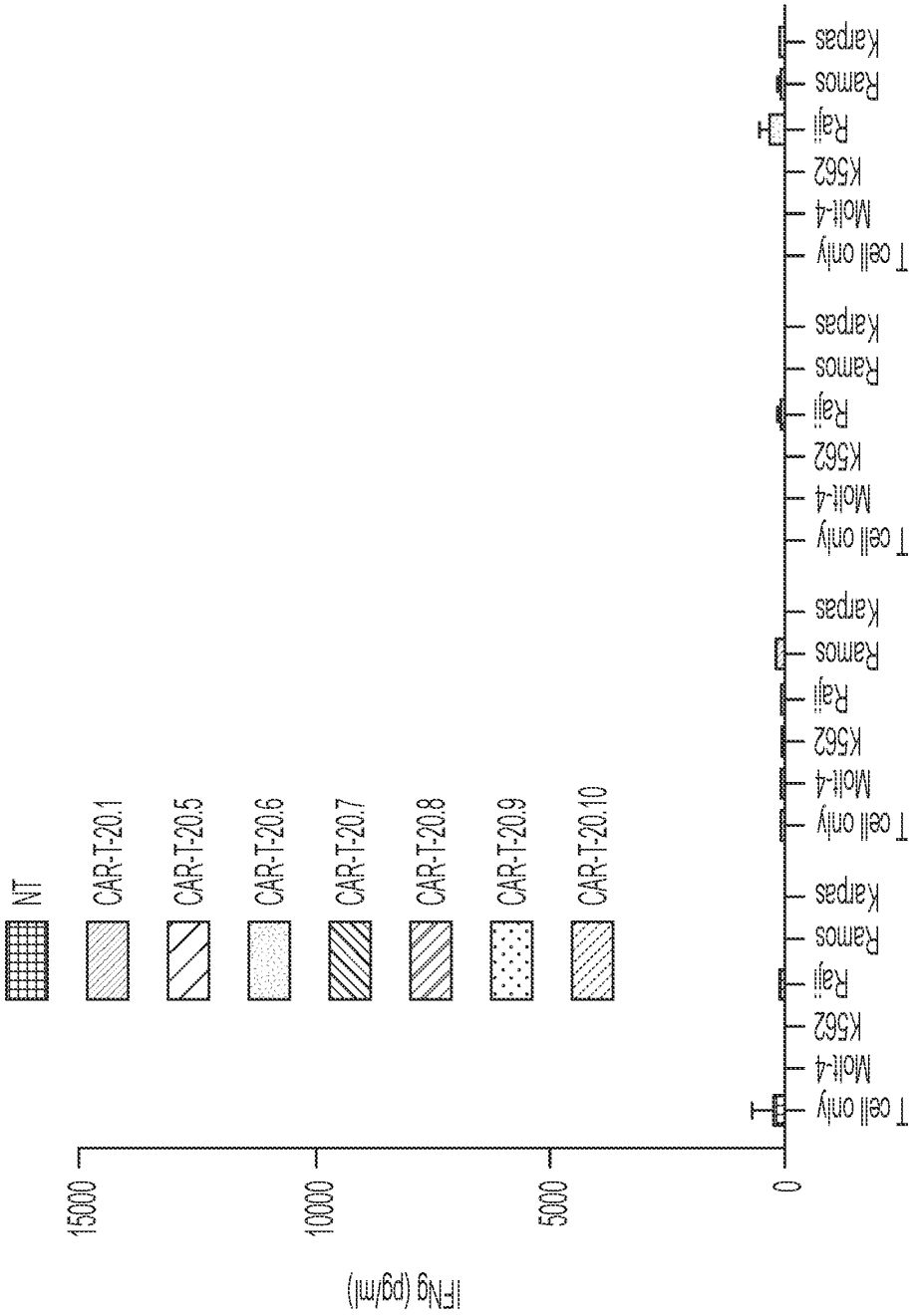

IFNg (pg/ml)
15000
10000
5000
0
NT
CAR-T-20.1
CAR-T-20.5
CAR-T-20.6
CAR-T-20.7
CAR-T-20.8
CAR-T-20.9
CAR-T-20.10
T cell only
Molt-4
K562
Raji
Ramos
Karpas

FIG. 8A

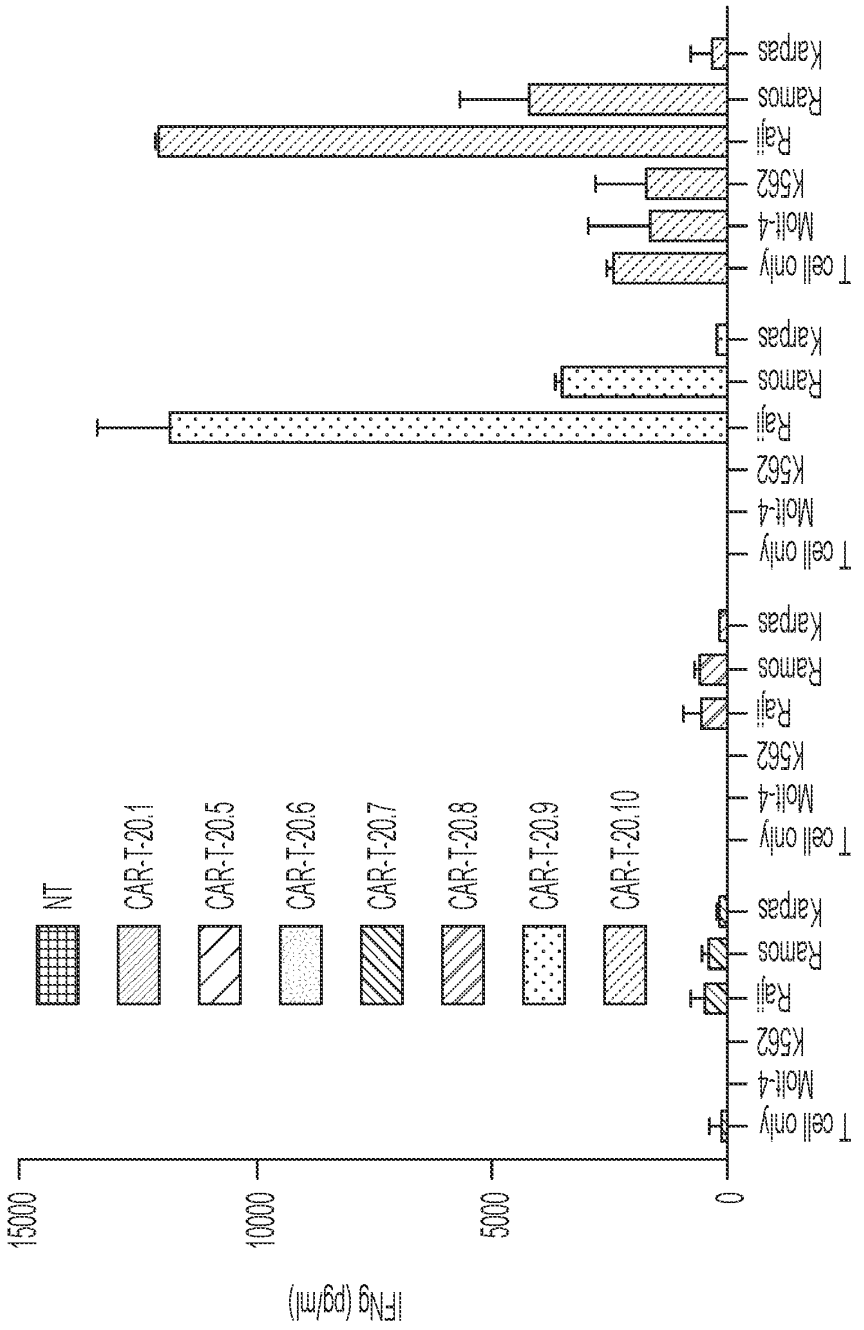


FIG. 8A CONTINUED

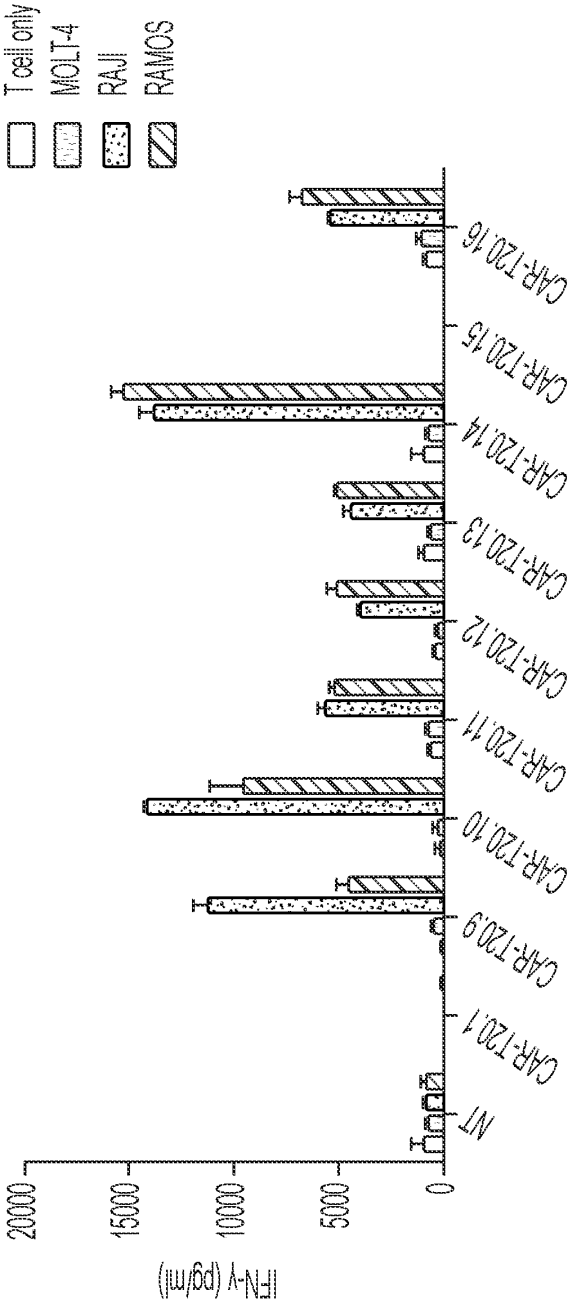

T cell only
MOLT-4
RAJI
RAMOS
IFN-γ (pg/ml)
20000
15000
10000
5000
0
NT
CAR-T20.1
CAR-T20.9
CAR-T20.10
CAR-T20.11
CAR-T20.12
CAR-T20.13
CAR-T20.14
CAR-T20.15
CAR-T20.16

FIG. 8B

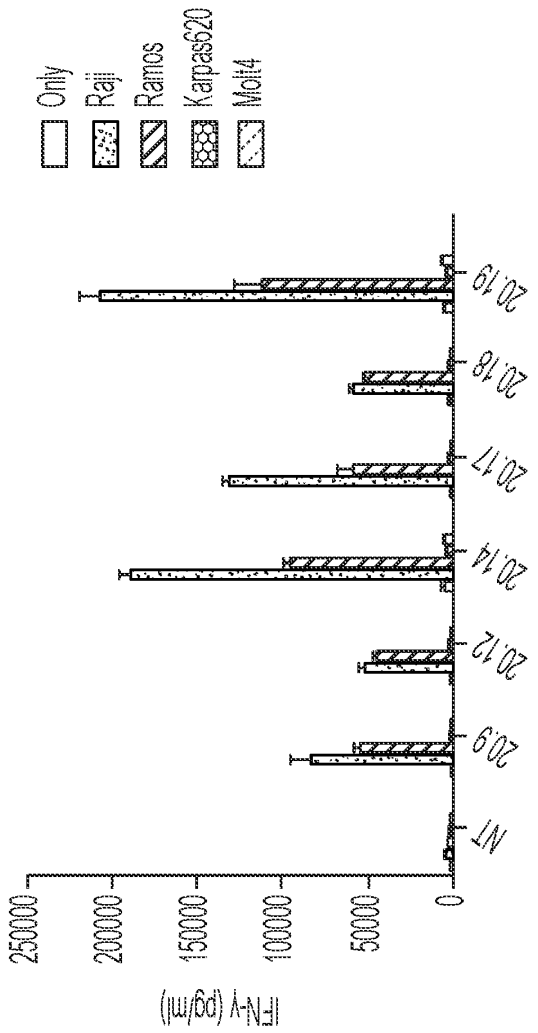

Only
Raji
Ramos
Karpas620
Molt4
IFN-γ (pg/ml)
250000
200000
150000
100000
50000
0
NT
20.9
20.12
20.14
20.17
20.18
20.19

FIG. 8C

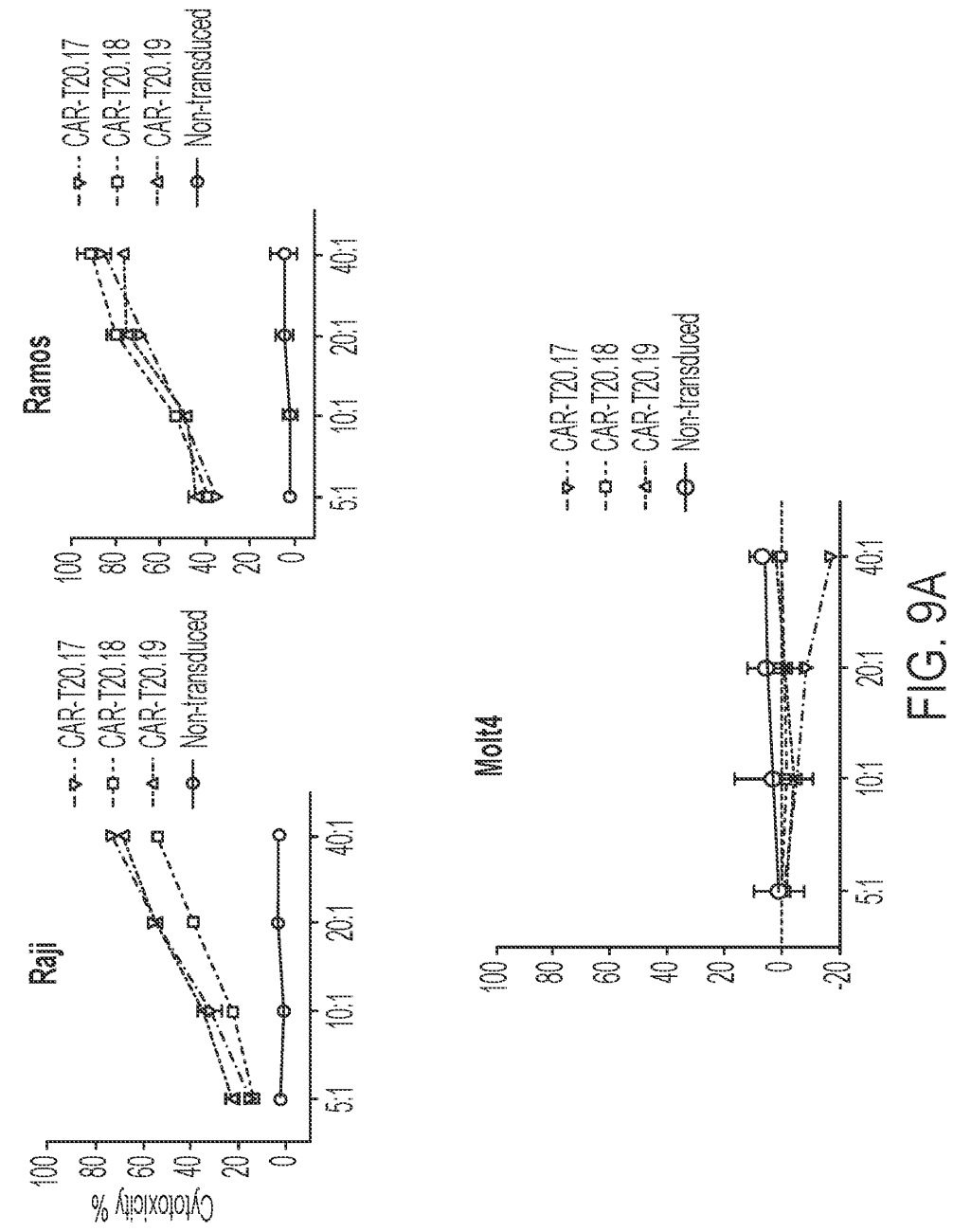

Raji
Ramos
Molt4
Cytotoxicity %
CAR-T20.17
CAR-T20.18
CAR-T20.19
Non-transduced
100
80
60
40
20
0
-20
5:1
10:1
20:1
40:1

FIG. 9A

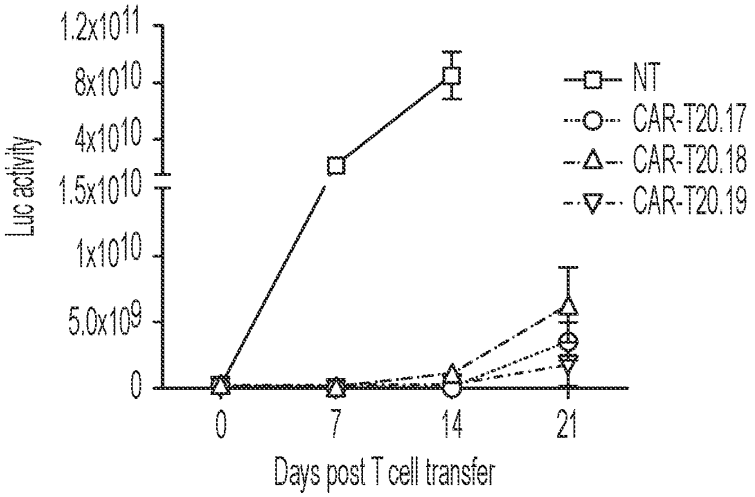

1.2x10^11
8x10^10
4x10^10
1.5x10^10
1x10^10
5.0x10^9
0
Luc activity
0
7
14
21
Days post T cell transfer
NT
CAR-T20.17
CAR-T20.18
CAR-T20.19

FIG. 9B

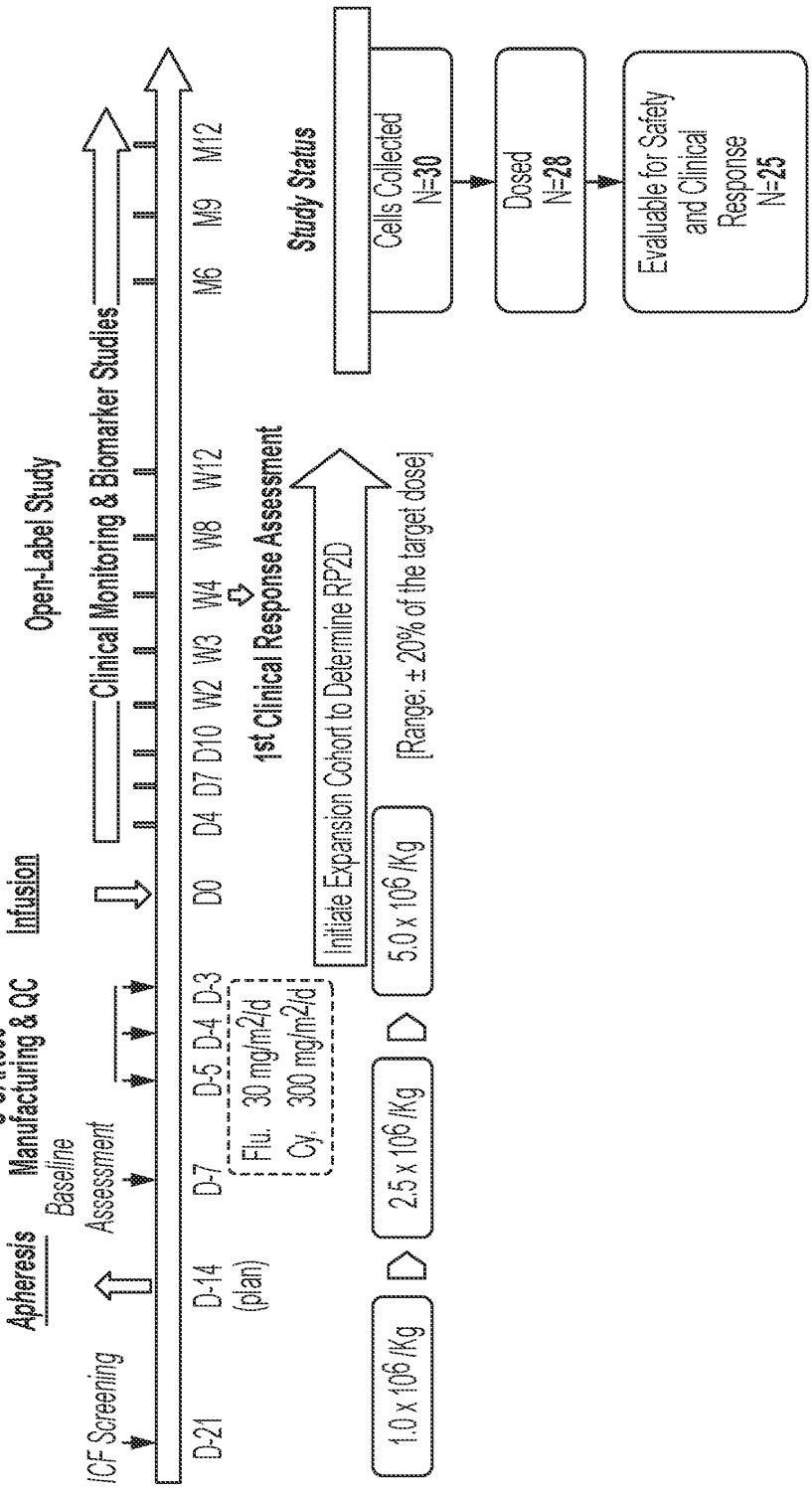

Open-Label Study
C-CAR039
Apheresis
Manufacturing & QC
Infusion
Baseline
Assessment
ICF Screening
Clinical Monitoring & Biomarker Studies
D-21
D-14
(plan)
D-7
D-5 D-4 D-3
D0
D4 D7 D10
W2 W3 W4
W8 W12
M6 M9 M12
Flu. 30 mg/m2/d
Cy. 300 mg/m2/d
1st Clinical Response Assessment
Initiate Expansion Cohort to Determine RP2D
1.0 x 10^6 /Kg
2.5 x 10^6 /Kg
5.0 x 10^6 /Kg
[Range: ± 20% of the target dose]
Study Status
Cells Collected N=30
Dosed N=28
Evaluable for Safety and Clinical Response N=25

FIG. 10

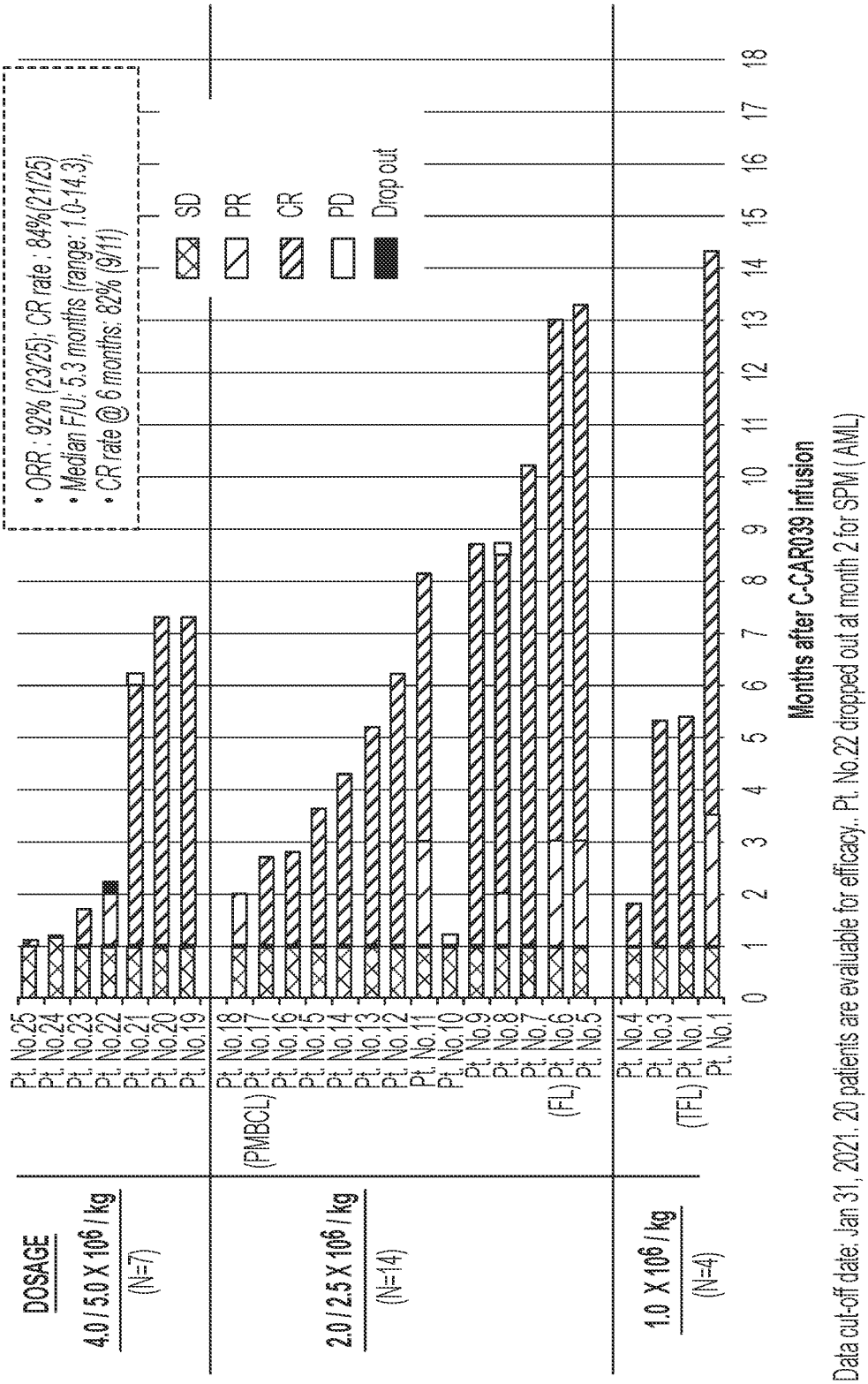

• ORR : 92% (23/25); CR rate : 84%(21/25)
• Median F/U: 5.3 months (range: 1.0-14.3),
• CR rate @ 6 months: 82% (9/11)
SD
PR
CR
PD
Drop out
DOSAGE
4.0 / 5.0 X 10^6 / kg
(N=7)
2.0 / 2.5 X 10^6 / kg
(N=14)
1.0 X 10^6 / kg
(N=4)
Pt. No.25
Pt. No.24
Pt. No.23
Pt. No.22
Pt. No.21
Pt. No.20
Pt. No.19
Pt. No.18 (PMBCL)
Pt. No.17
Pt. No.16
Pt. No.15
Pt. No.14
Pt. No.13
Pt. No.12
Pt. No.11
Pt. No.10
Pt. No.9
Pt. No.8
Pt. No.7
Pt. No.6 (FL)
Pt. No.5
Pt. No.4
Pt. No.3
Pt. No.1 (TFL)
Pt. No.1
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Months after C-CAR039 infusion
Data cut-off date: Jan 31, 2021. 20 patients are evaluable for efficacy. Pt. No.22 dropped out at month 2 for SPM (AML)

FIG. 11

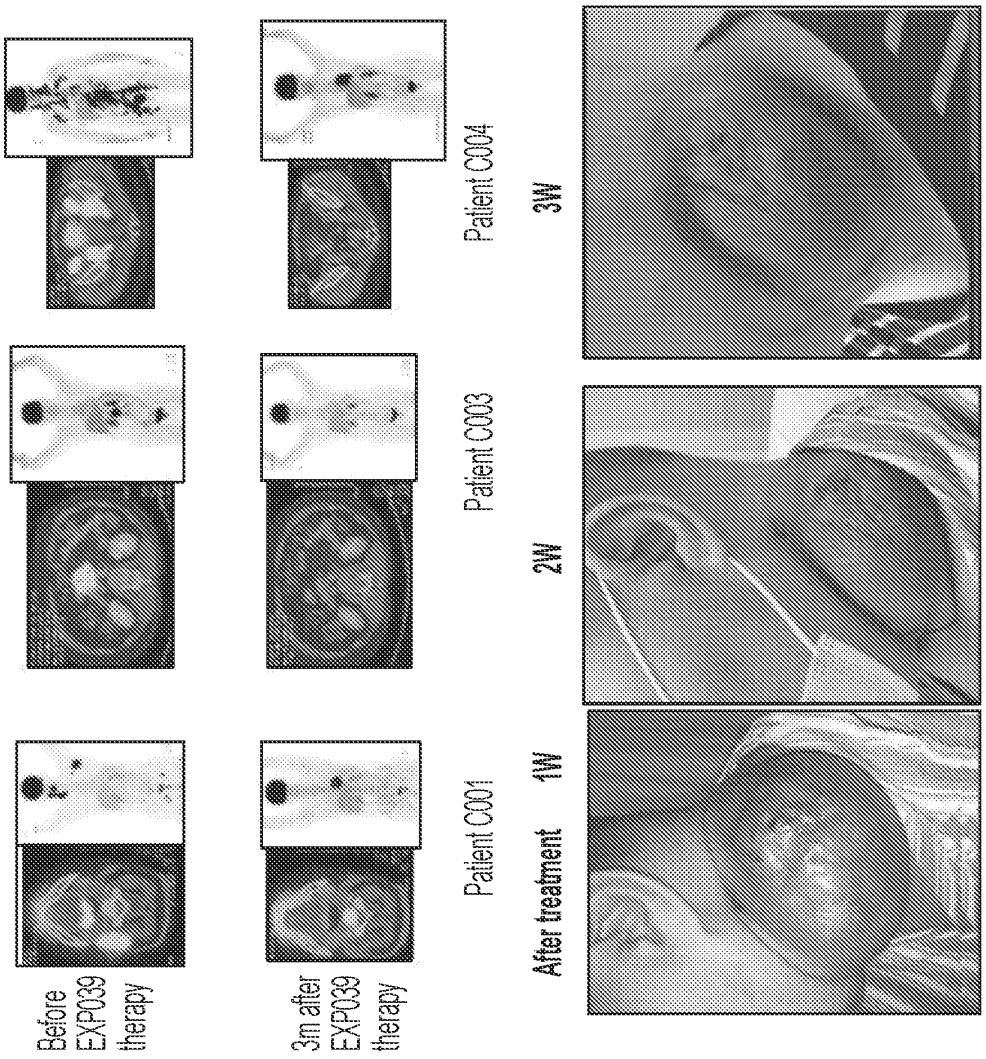

Before EXP039 therapy
3m after EXP039 therapy
Patient C001
Patient C003
Patient C004
After treatment
1W
2W
3W

FIG. 12

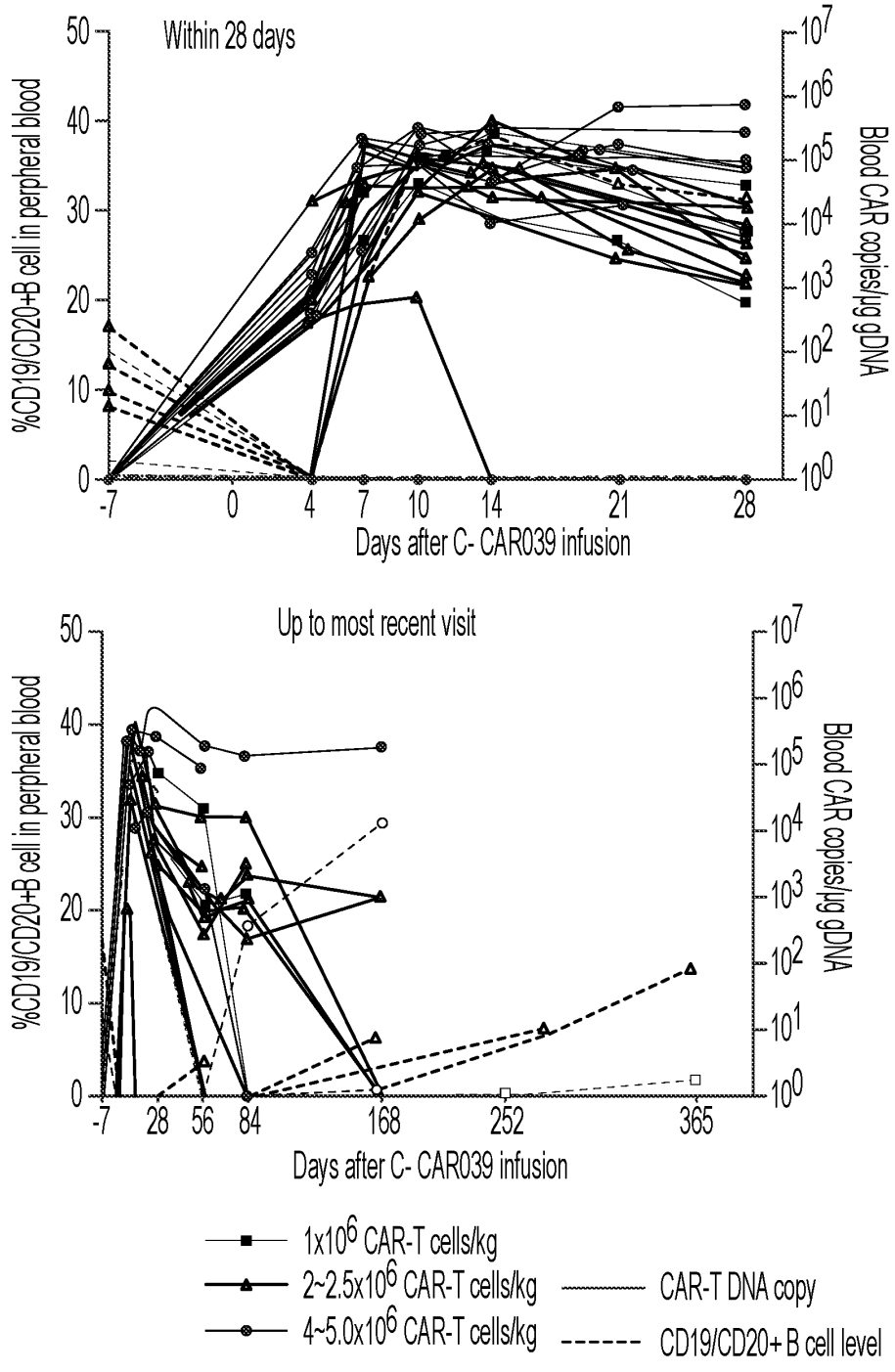

Within 28 days
%CD19/CD20+B cell in perpheral blood
Blood CAR copies/μg gDNA
Days after C- CAR039 infusion
Up to most recent visit
%CD19/CD20+B cell in perpheral blood
Blood CAR copies/μg gDNA
Days after C- CAR039 infusion
1x10^6 CAR-T cells/kg
2~2.5x10^6 CAR-T cells/kg
4~5.0x10^6 CAR-T cells/kg
CAR-T DNA copy
CD19/CD20+ B cell level

FIG. 13

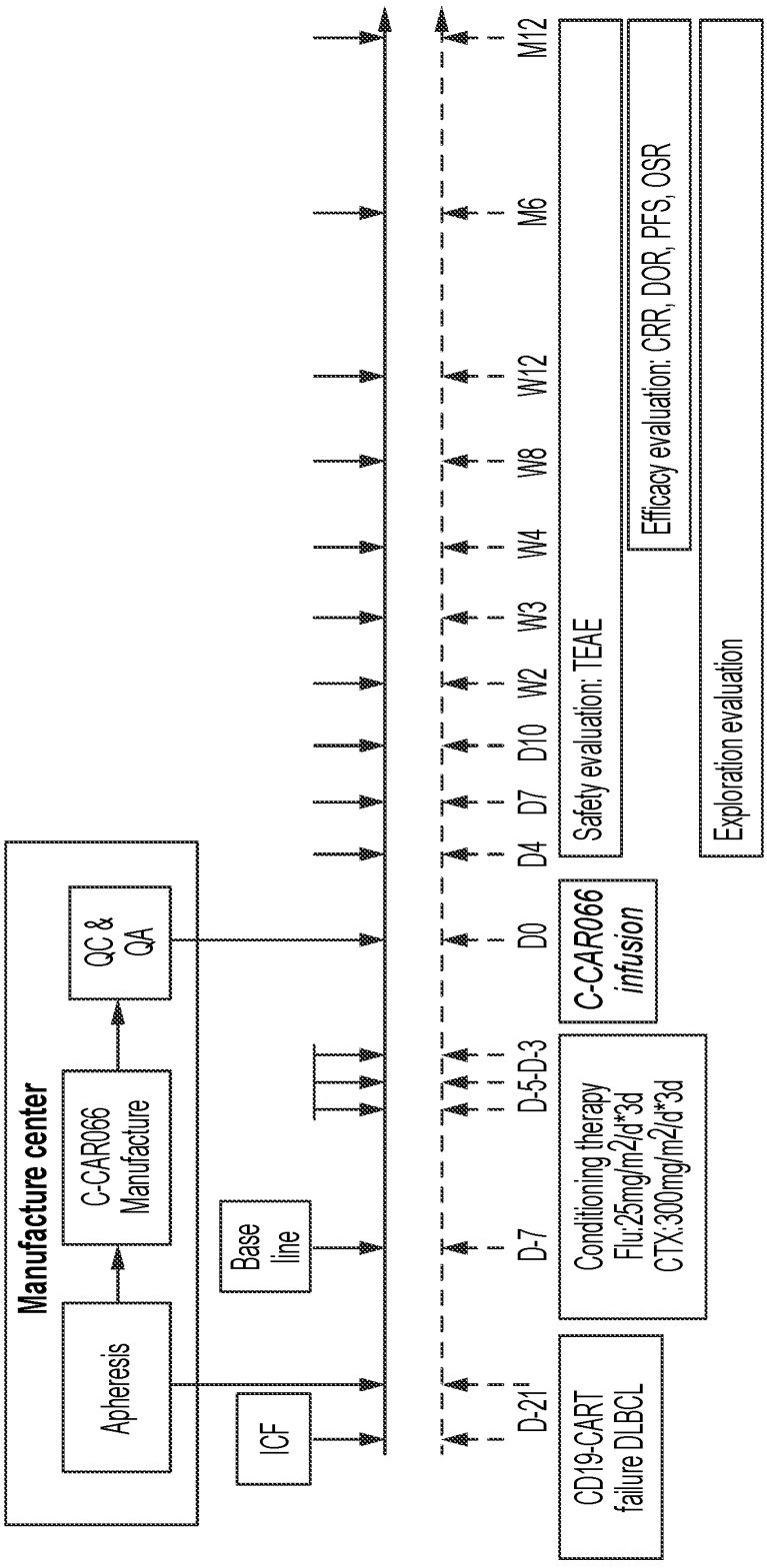

Manufacture center
Apheresis
C-CAR066 Manufacture
QC & QA
ICF
Base line
CD19-CART failure DLBCL
Conditioning therapy Flu:25mg/m2/d*3d CTX:300mg/m2/d*3d
C-CAR066 infusion
Safety evaluation: TEAE
Efficacy evaluation: CRR, DOR, PFS, OSR
Exploration evaluation
D-21
D-7
D-5-D-3
D0
D4
D7
D10
W2
W3
W4
W8
W12
M6
M12

FIG. 14

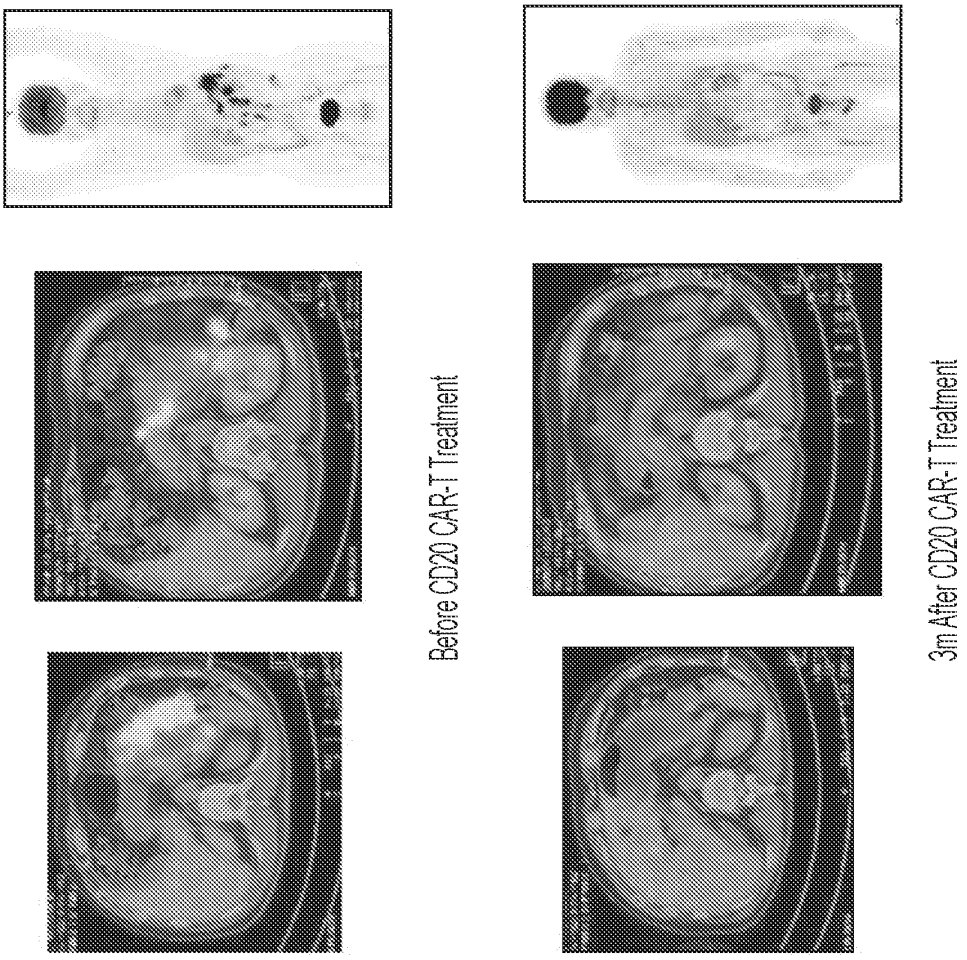


FIG. 15

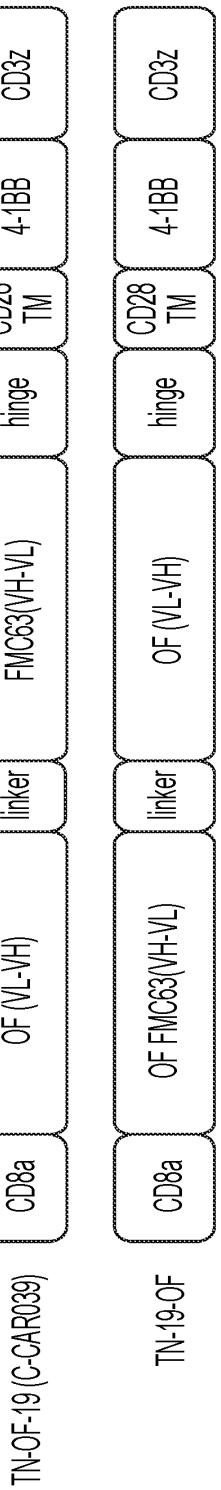

TN-OF-19 (C-CAR039)
CD8a
OF (VL-VH)
linker
FMC63(VH-VL)
hinge
CD28 TM
4-1BB
CD3z
TN-19-OF
CD8a
OF FMC63(VH-VL)
linker
OF (VL-VH)
hinge
CD28 TM
4-1BB
CD3z

FIG. 16A

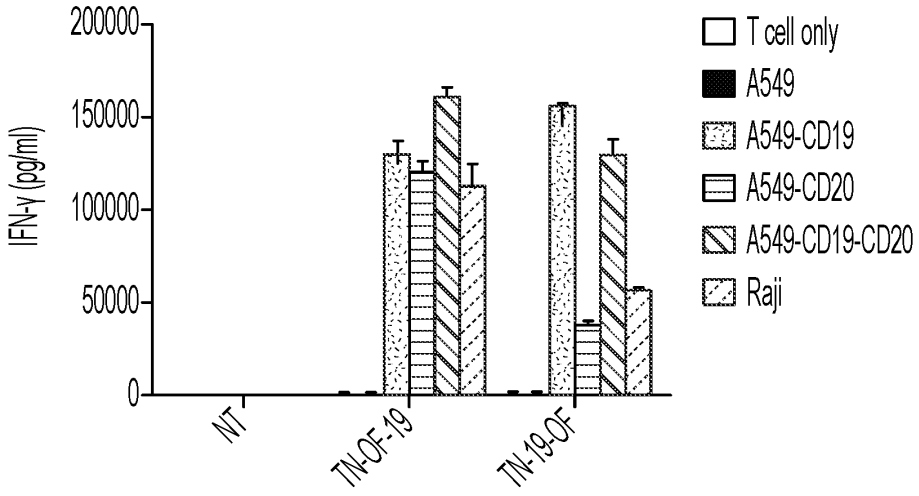

200000
150000
100000
50000
0
IFN-γ (pg/ml)
NT
TN-OF-19
TN-19-OF
T cell only
A549
A549-CD19
A549-CD20
A549-CD19-CD20
Raji

FIG. 16B

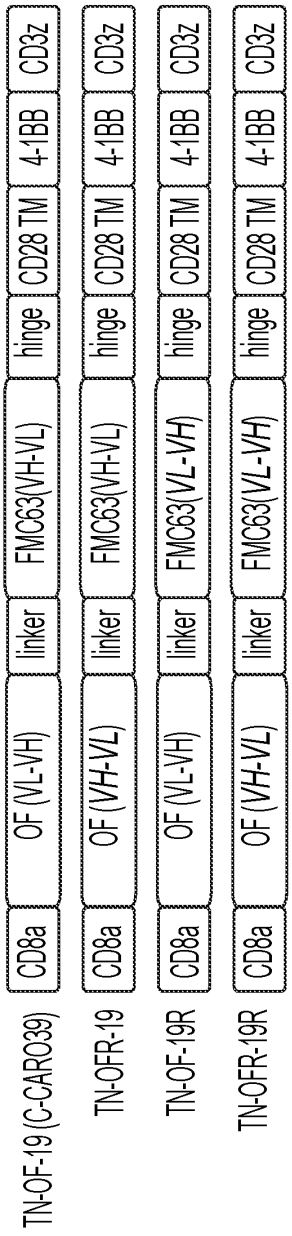

TN-OF-19 (C-CARO39)
CD8a
OF (VL-VH)
linker
FMC63(VH-VL)
hinge
CD28 TM
4-1BB
CD3z
TN-OFR-19
CD8a
OF (VH-VL)
linker
FMC63(VH-VL)
hinge
CD28 TM
4-1BB
CD3z
TN-OF-19R
CD8a
OF (VL-VH)
linker
FMC63(VL-VH)
hinge
CD28 TM
4-1BB
CD3z
TN-OFR-19R
CD8a
OF (VH-VL)
linker
FMC63(VL-VH)
hinge
CD28 TM
4-1BB
CD3z

FIG. 16C

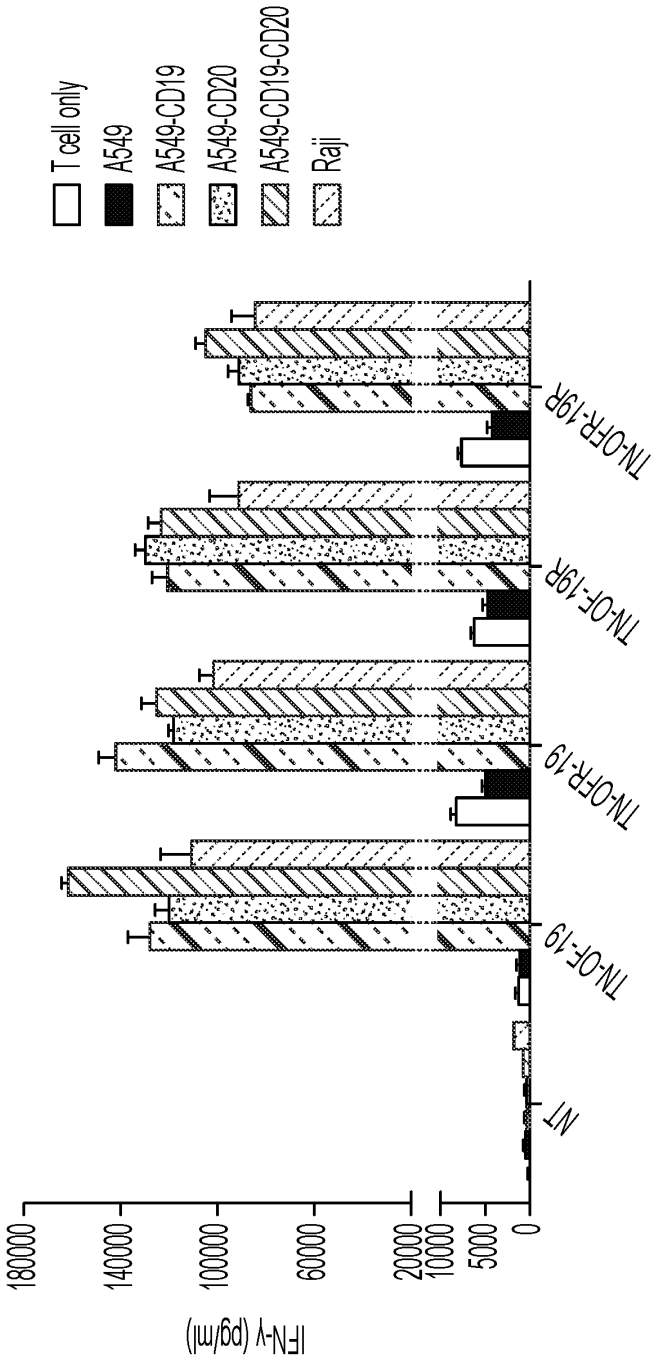

T cell only
A549
A549-CD19
A549-CD20
A549-CD19-CD20
Raji
IFN-γ (pg/ml)
180000
140000
100000
60000
20000
10000
5000
0
NT
TN-OF-19
TN-OFR-19
TN-OF-19R
TN-OFR-19R

FIG. 16D

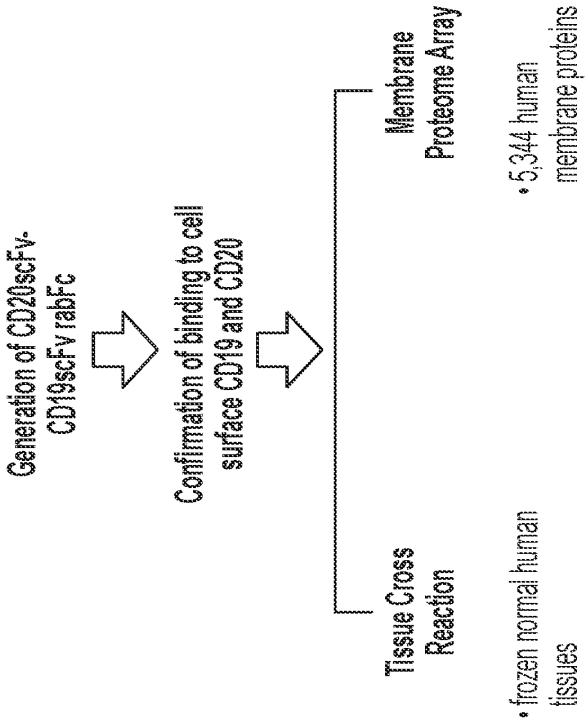

Generation of CD20scFv-CD19scFv rabFc
Confirmation of binding to cell surface CD19 and CD20
Tissue Cross Reaction
• frozen normal human tissues
• derived from three different individual donors
Membrane Proteome Array
• 5,344 human membrane proteins
Validation by co-culture primary cells or antigen over-expressing cells with CAR-T cells

FIG. 17A

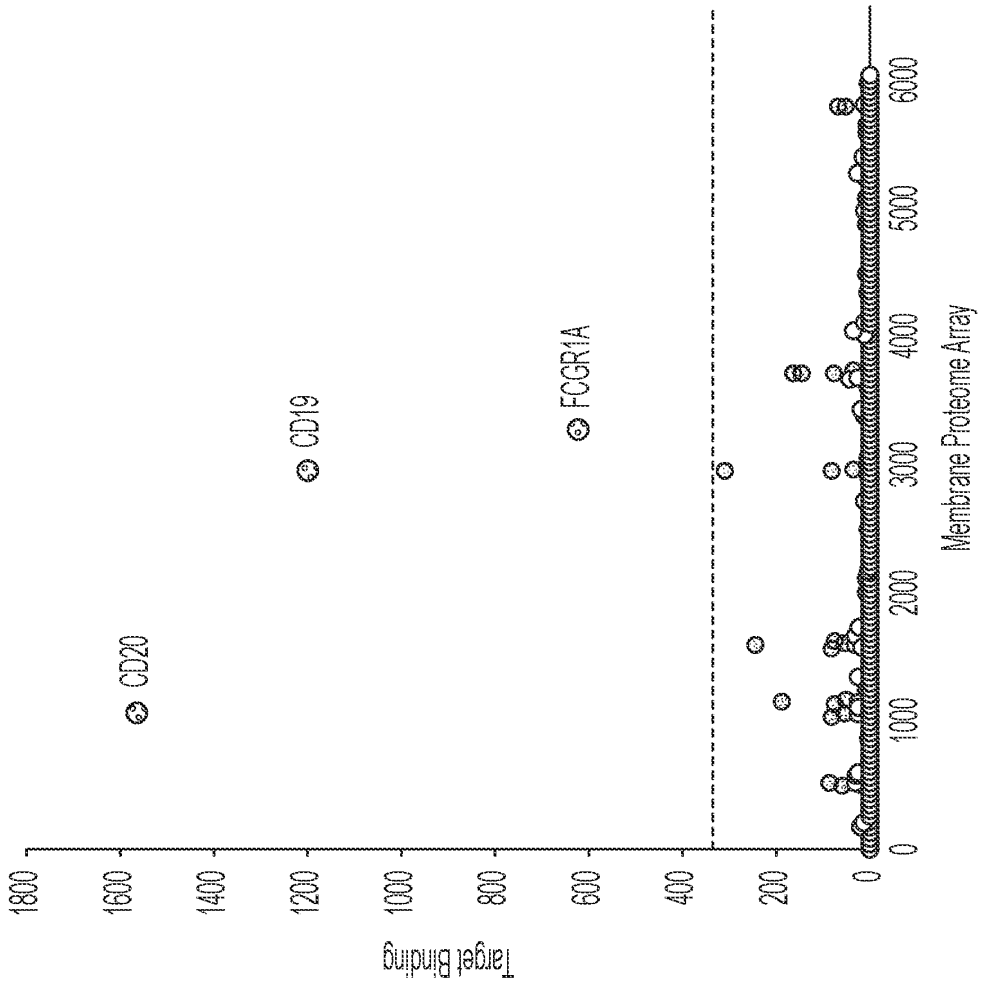
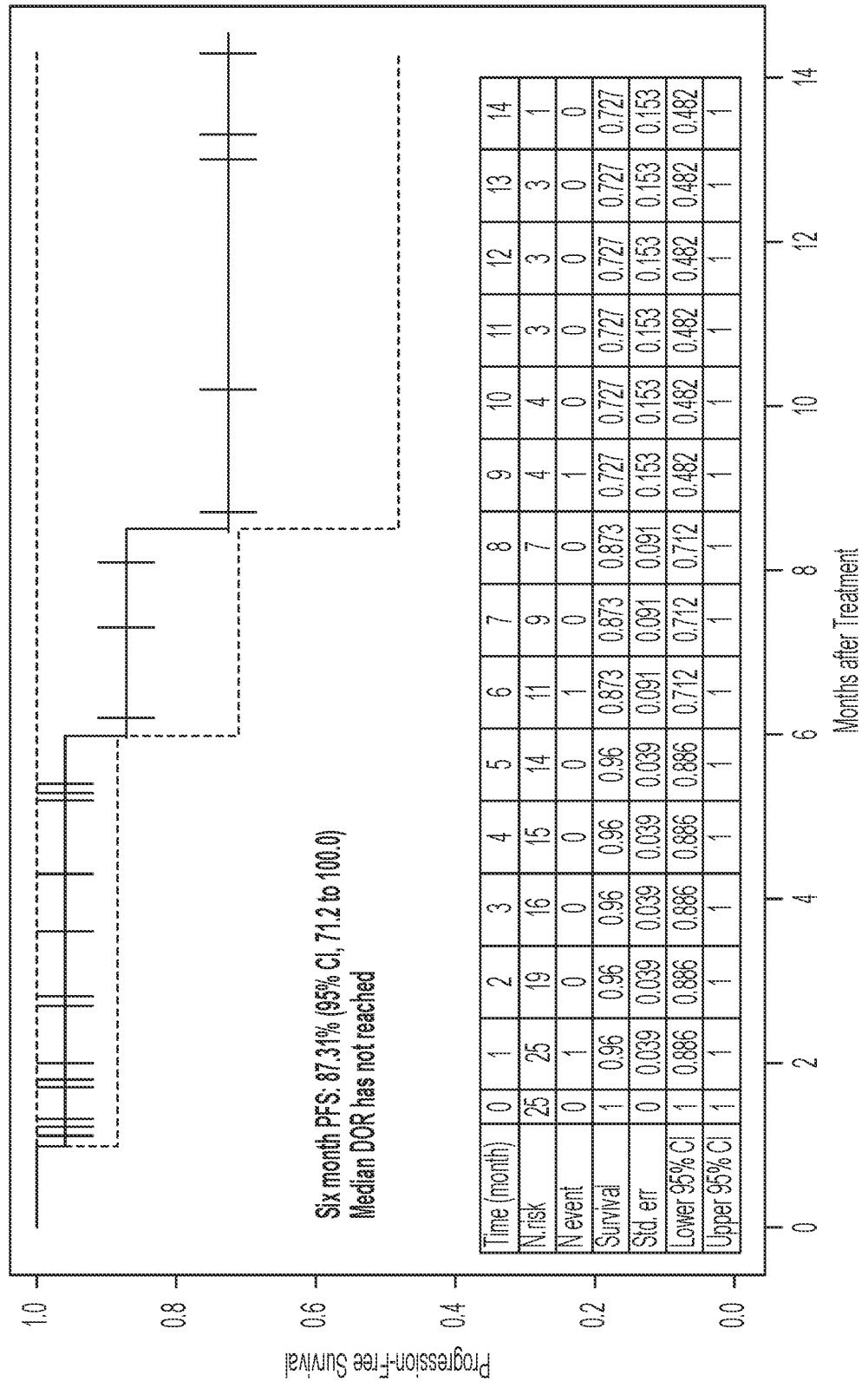

CD20
CD19
FCGR1A
Target Binding
Membrane Proteome Array
0
200
400
600
800
1000
1200
1400
1600
1800
0
1000
2000
3000
4000
5000
6000

FIG. 17B



Time (month)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N.risk	25	25	19	16	15	14	11	9	7	4	4	3	3	3	1
N.event	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0
Survival	1	0.96	0.96	0.96	0.96	0.96	0.873	0.873	0.873	0.727	0.727	0.727	0.727	0.727	0.727
Std. err	0	0.039	0.039	0.039	0.039	0.039	0.091	0.091	0.091	0.153	0.153	0.153	0.153	0.153	0.153
Lower 95% CI	1	0.886	0.886	0.886	0.886	0.886	0.712	0.712	0.712	0.482	0.482	0.482	0.482	0.482	0.482
Upper 95% CI	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

FIG. 18

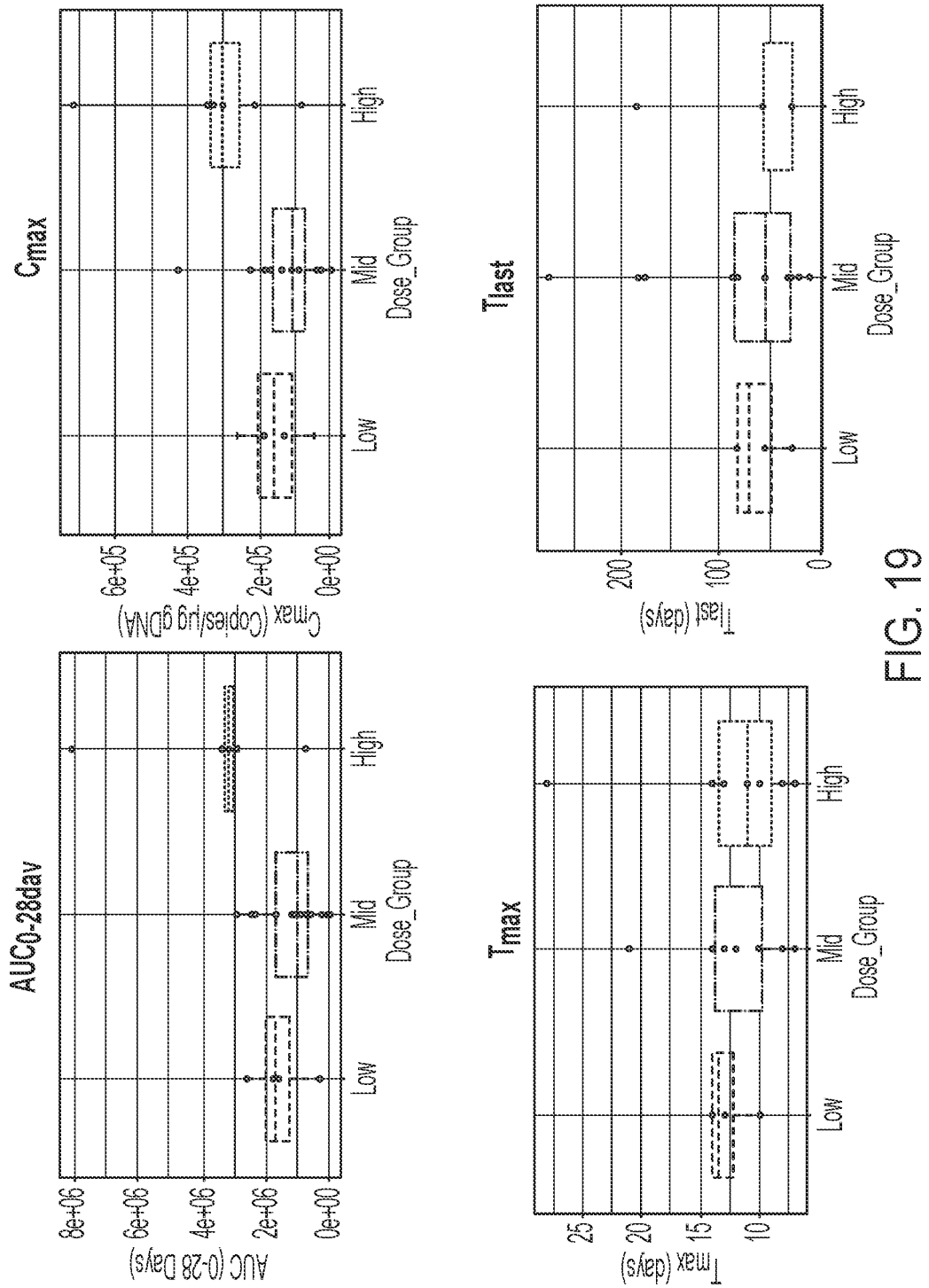

Cmax
Cmax (Copies/µg gDNA)
6e+05
4e+05
2e+05
0e+00
Low
Mid
High
Dose_Group
Tlast
Tlast (days)
200
100
0
Low
Mid
High
Dose_Group
AUC0-28dav
AUC (0-28 Days)
8e+06
6e+06
4e+06
2e+06
0e+00
Low
Mid
High
Dose_Group
Tmax
Tmax (days)
25
20
15
10
Low
Mid
High
Dose_Group

FIG. 19

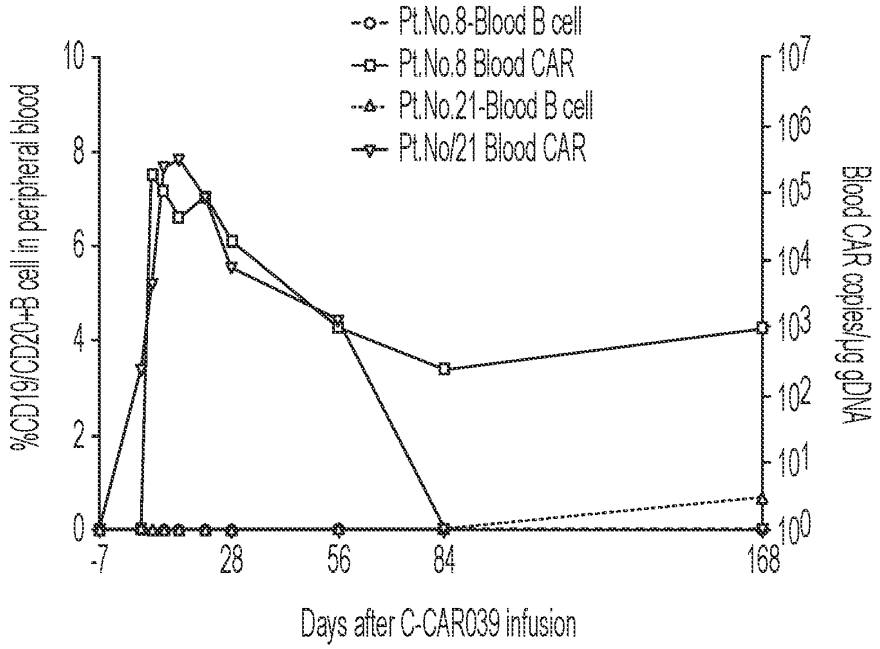

Pt.No.8-Blood B cell
Pt.No.8 Blood CAR
Pt.No.21-Blood B cell
Pt.No/21 Blood CAR
%CD19/CD20+B cell in peripheral blood
Blood CAR copies/μg cDNA
Days after C-CAR039 infusion
0
2
4
6
8
10
-7
28
56
84
168
10^0
10^1
10^2
10^3
10^4
10^5
10^6
10^7

FIG. 20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/22779

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 35/17, A61K 39/395, A61K 47/64 (2021.01)

CPC - A61K 35/17, A61P 35/00, A61P 35/02, A61P 7/00, C07K 14/7051

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ZAH et al. T Cells Expressing CD19/CD20 Bispecific Chimeric Antigen Receptors Prevent Antigen Escape by Malignant B Cells. Cancer Immunology Research. 8 April 2016, Vol. 4, No. 6, pg 498-508; especially abstract; pg 499, col 1, para 2; pg 500, col 1, para 2; Figure 1	1-16
Y	US 2017/0355767 A1 (GENMAB A/S) 14 December 2017 (14.12.2017); especially abstract; para [0021]; Table 1; SEQ ID NOs: 28, 37	1-16
A	GenBank Accession No. AMZ04821, bi-specific chimeric antigen receptor 20-19 Short, partial [synthetic construct]. 24 April 2016 [online]. [Retrieved on 22 July 2021]. Retrieved from the internet: <URL: https://www.ncbi.nlm.nih.gov/protein/AMZ04821> Entire document	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2021 (15.07.2021)	AUG 09 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300