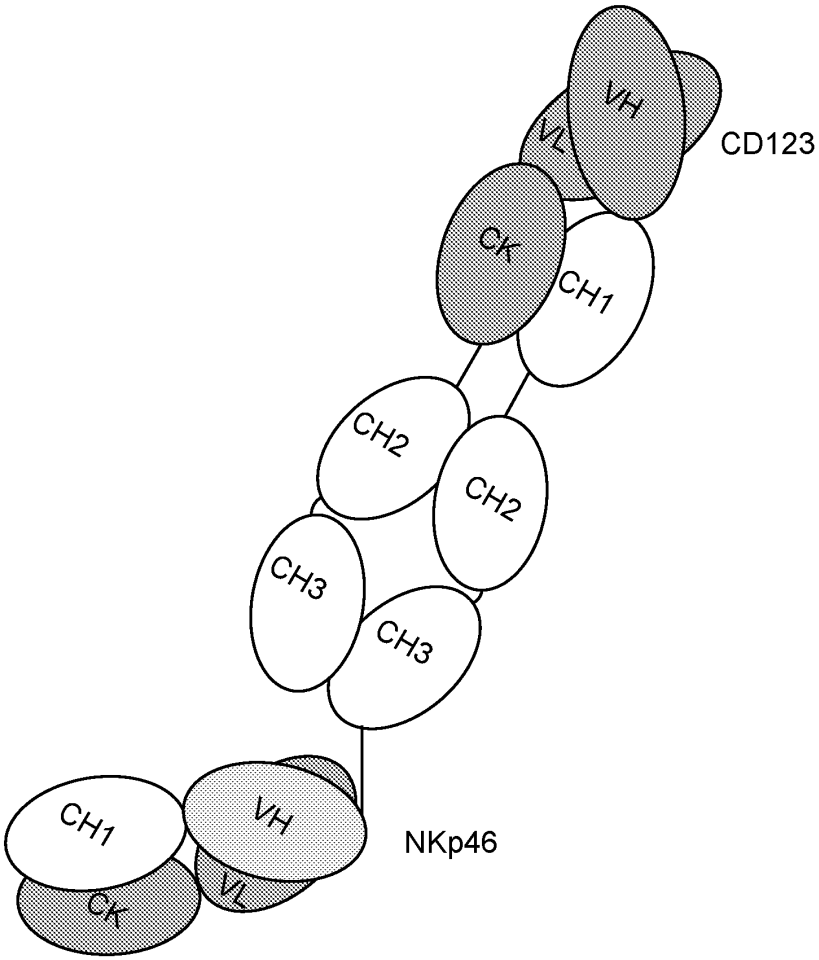
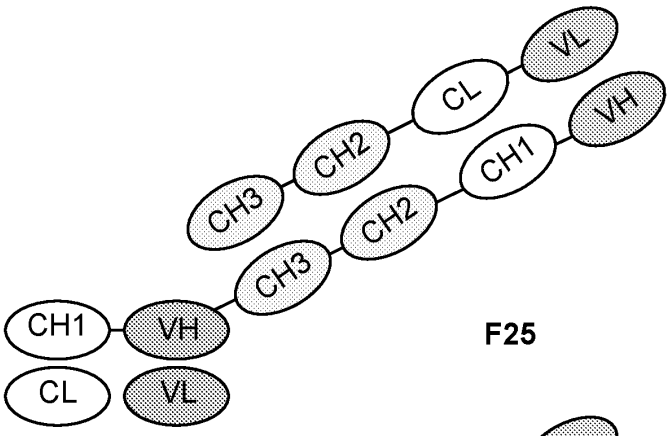
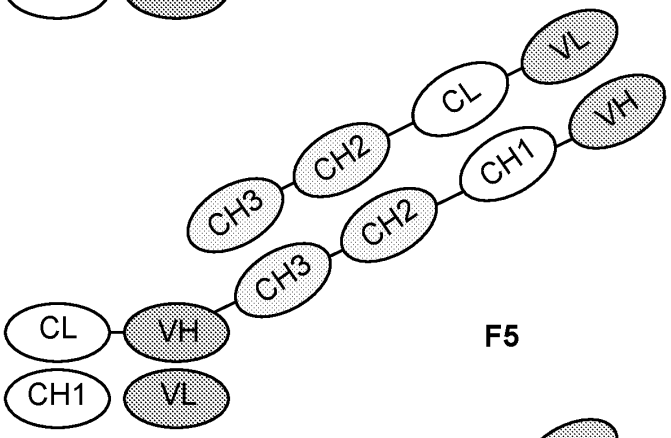


FIG. 1



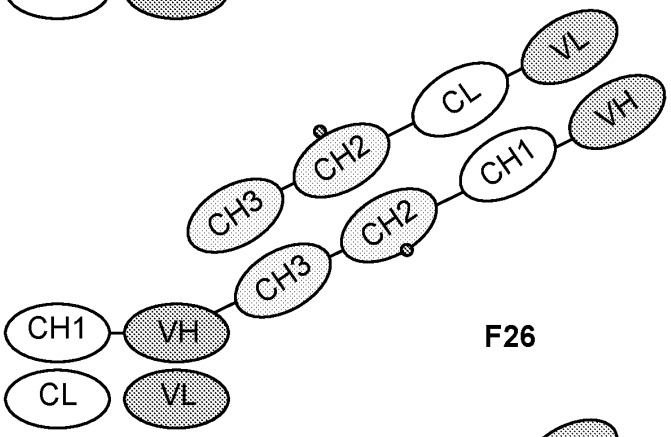
F25

FIG. 2A



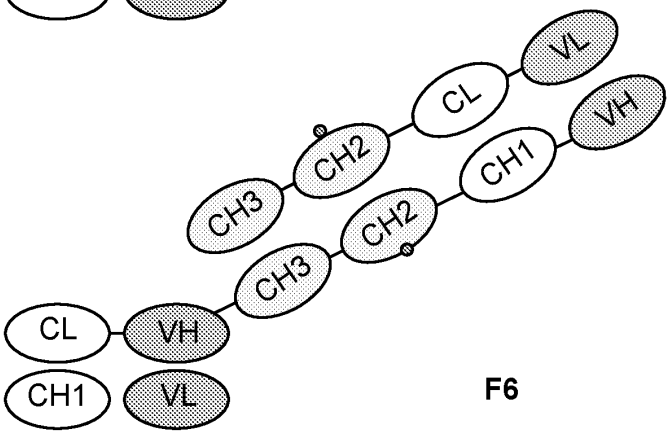
F5

FIG. 2B



F26

FIG. 2C



F6

FIG. 2D

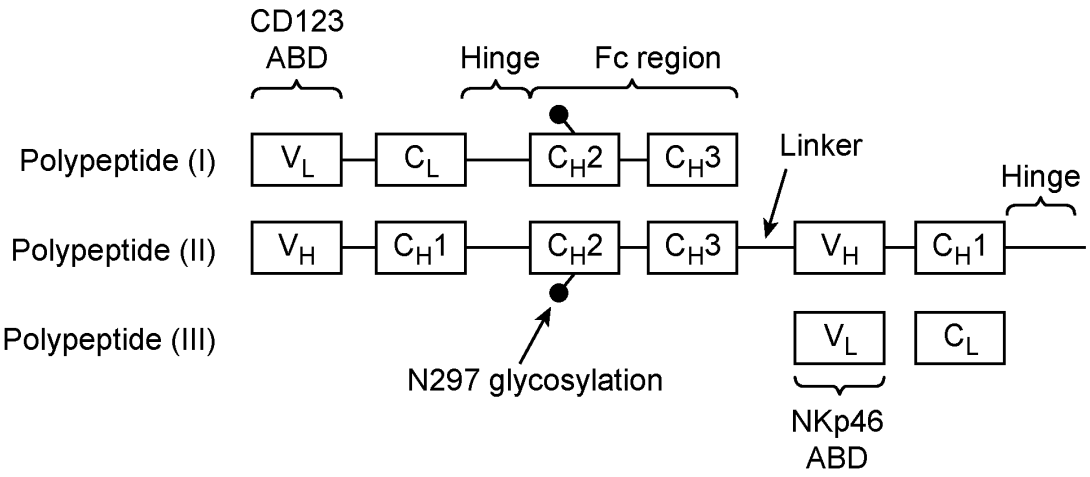

CD123
ABD
Hinge
Fc region
Linker
Hinge
Polypeptide (I)
Polypeptide (II)
Polypeptide (III)
V_L
C_L
C_H2
C_H3
V_H
C_H1
N297 glycosylation
NKp46
ABD

FIG. 2E

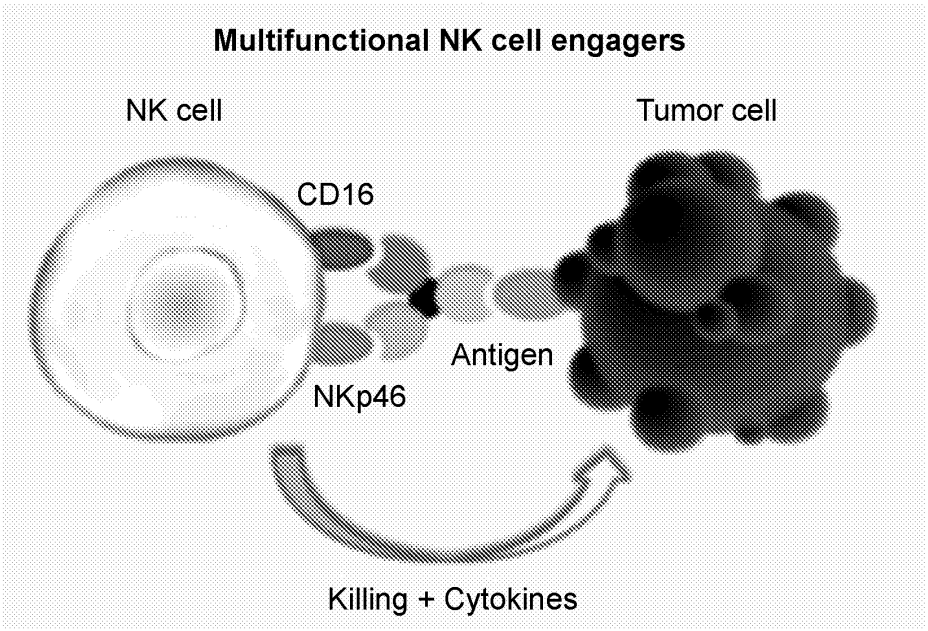

Multifunctional NK cell engagers
NK cell
Tumor cell
CD16
Antigen
NKp46
Killing + Cytokines

FIG. 3

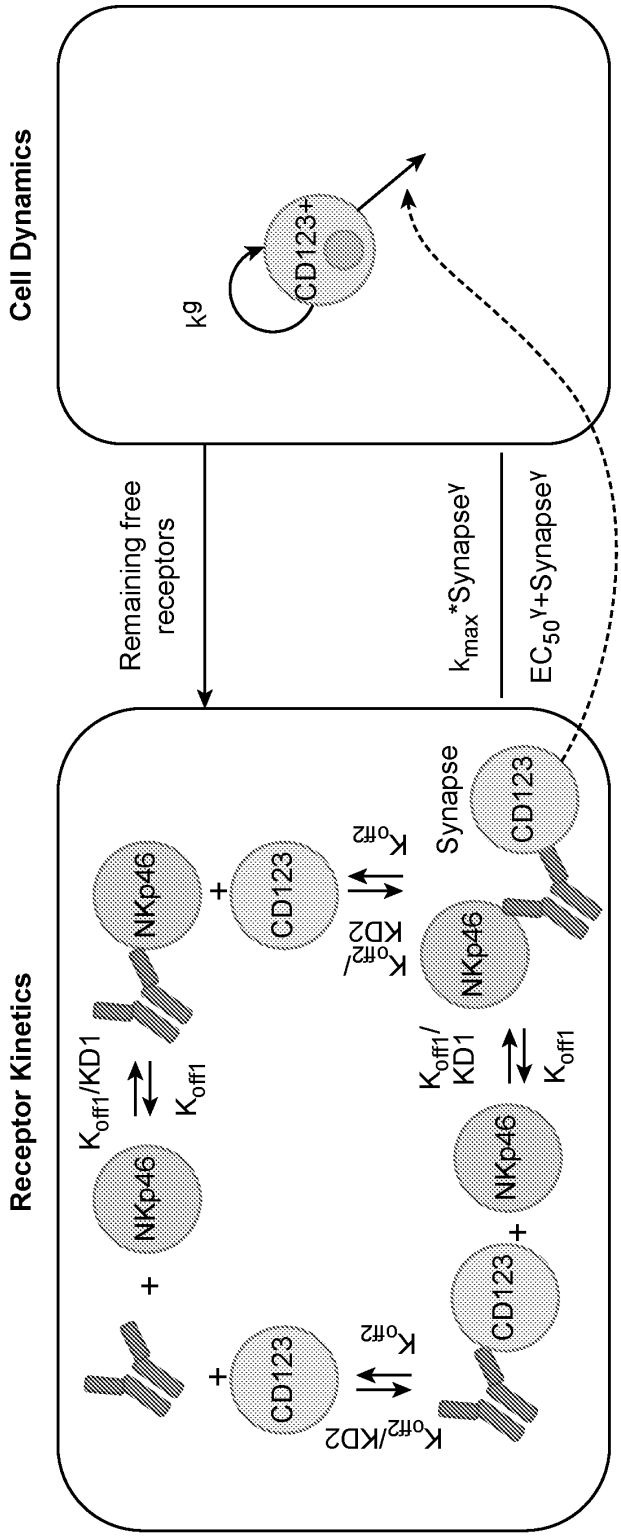

Cell Dynamics
CD123+
k^g
Remaining free receptors
k_{max}*Synapse$^\gamma$
$EC_{50}{}^\gamma$+Synapse$^\gamma$
Receptor Kinetics
Synapse
CD123
NKp46
K_{off2}
K_{off2}/KD2
K_{off1}/KD1
K_{off1}

FIG. 4A

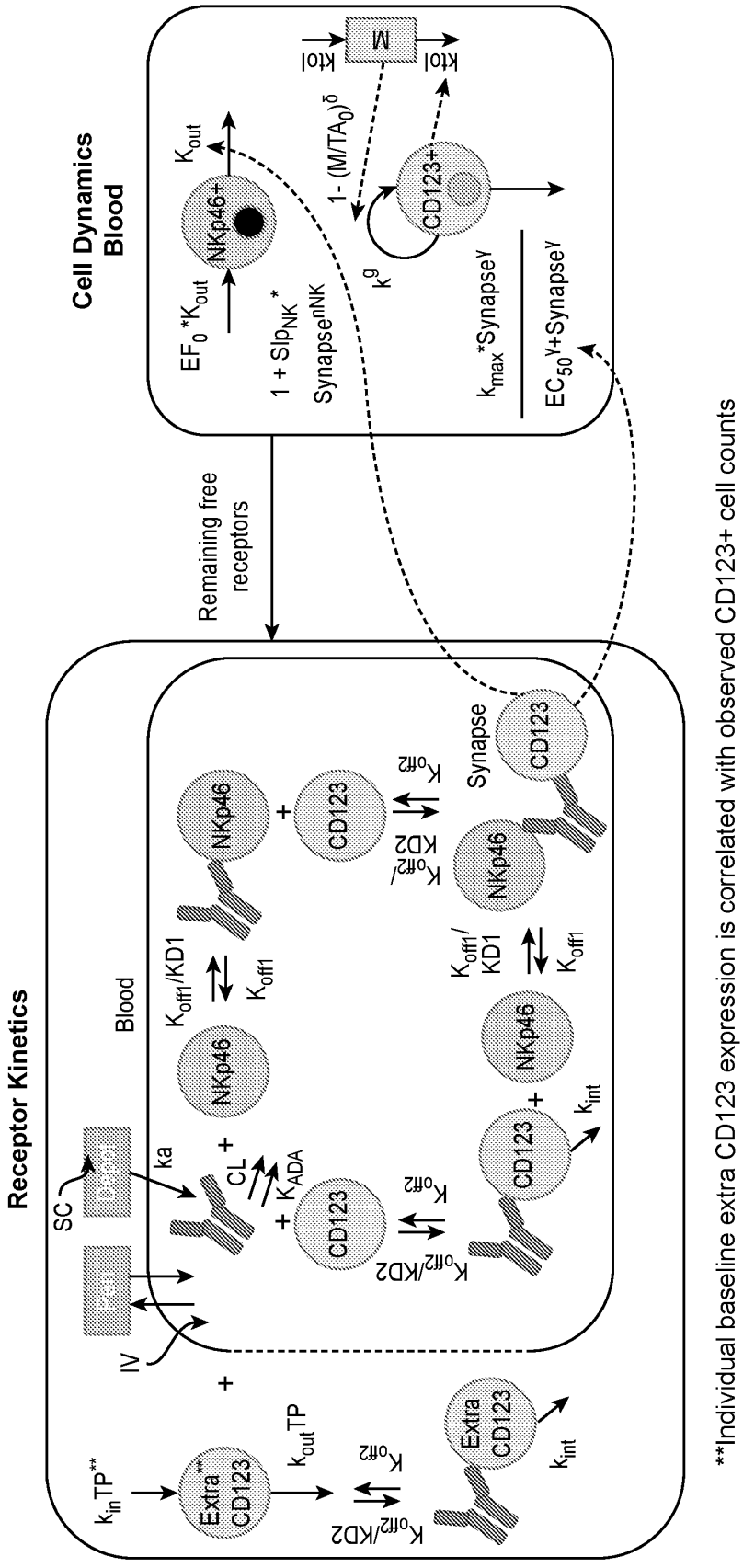

Cell Dynamics
Blood
M
ktol
ktol
K_{out}
NKp46+
EF_0 *K_{out}
1 + Slp_{NK} *
$Synapse^{nNK}$
1- $(M/TA_0)^{\delta}$
k^g
CD123+
k_{max} *$Synapse^{\gamma}$
$EC_{50}{}^{\gamma}$+$Synapse^{\gamma}$
Remaining free receptors
Receptor Kinetics
Blood
SC
IV
ka
CL
K_{ADA}
K_{off1}/KD1
K_{off1}
K_{off2}
K_{off2}/KD2
k_{int}
k_{out}TP
k_{in}TP**
Extra** CD123
Extra CD123
NKp46
CD123
Synapse
**Individual baseline extra CD123 expression is correlated with observed CD123+ cell counts

FIG. 4B

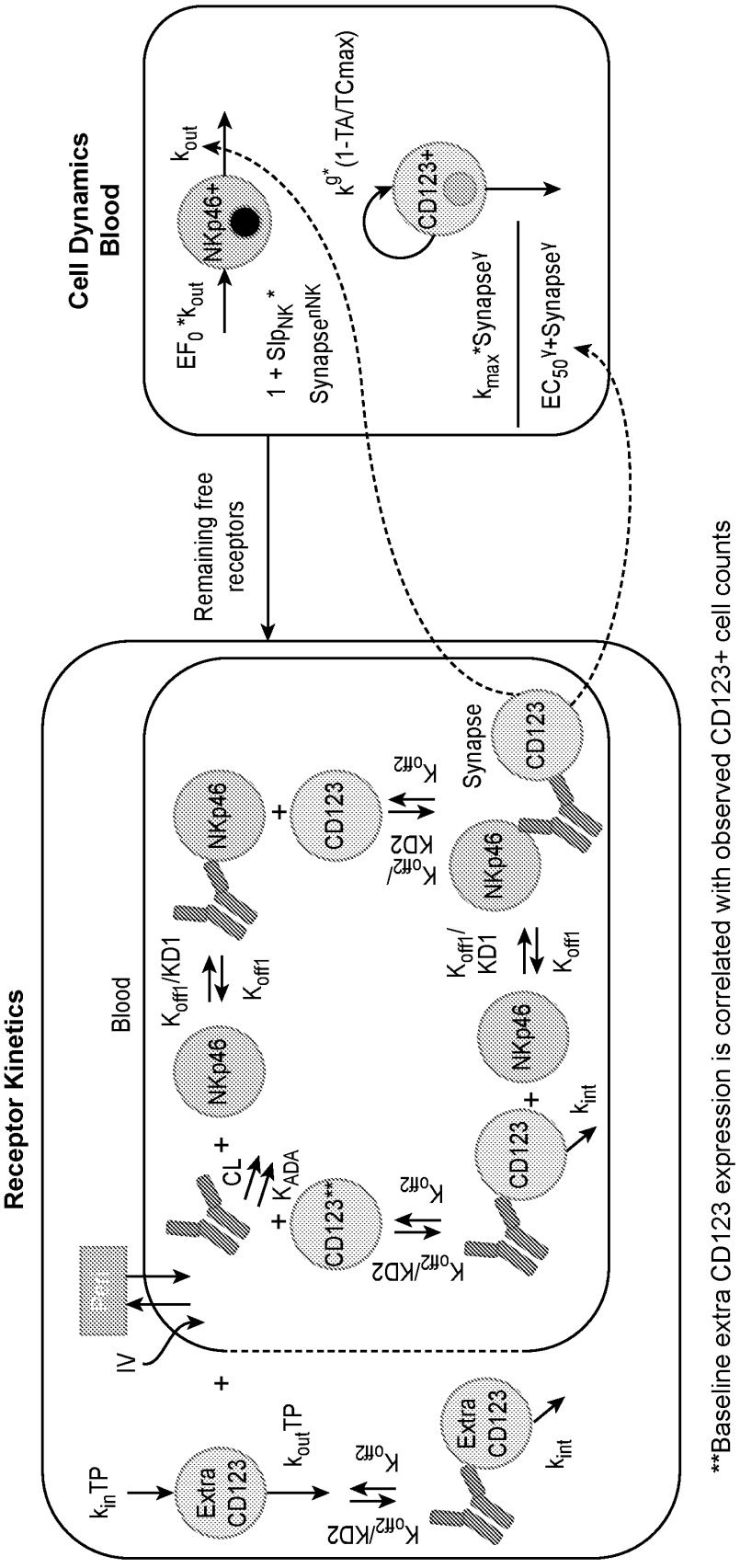

Cell Dynamics
Blood
NKp46+
k_{out}
EF_0 *k_{out}
1 + Slp_{NK} *
$Synapse^{nNK}$
k^{g*} (1-TA/TCmax)
CD123+
k_{max}*$Synapse^{\gamma}$
$EC_{50}{}^{\gamma}$+$Synapse^{\gamma}$
Remaining free receptors
Receptor Kinetics
Blood
Extra CD123
k_{in}TP
k_{out}TP
K_{off2}/KD2
K_{off2}
k_{int}
IV
BAT
CL
K_{ADA}
CD123**
NKp46
K_{off1}/KD1
K_{off1}
Synapse
K_{off2}/KD2
**Baseline extra CD123 expression is correlated with observed CD123+ cell counts

FIG. 4C

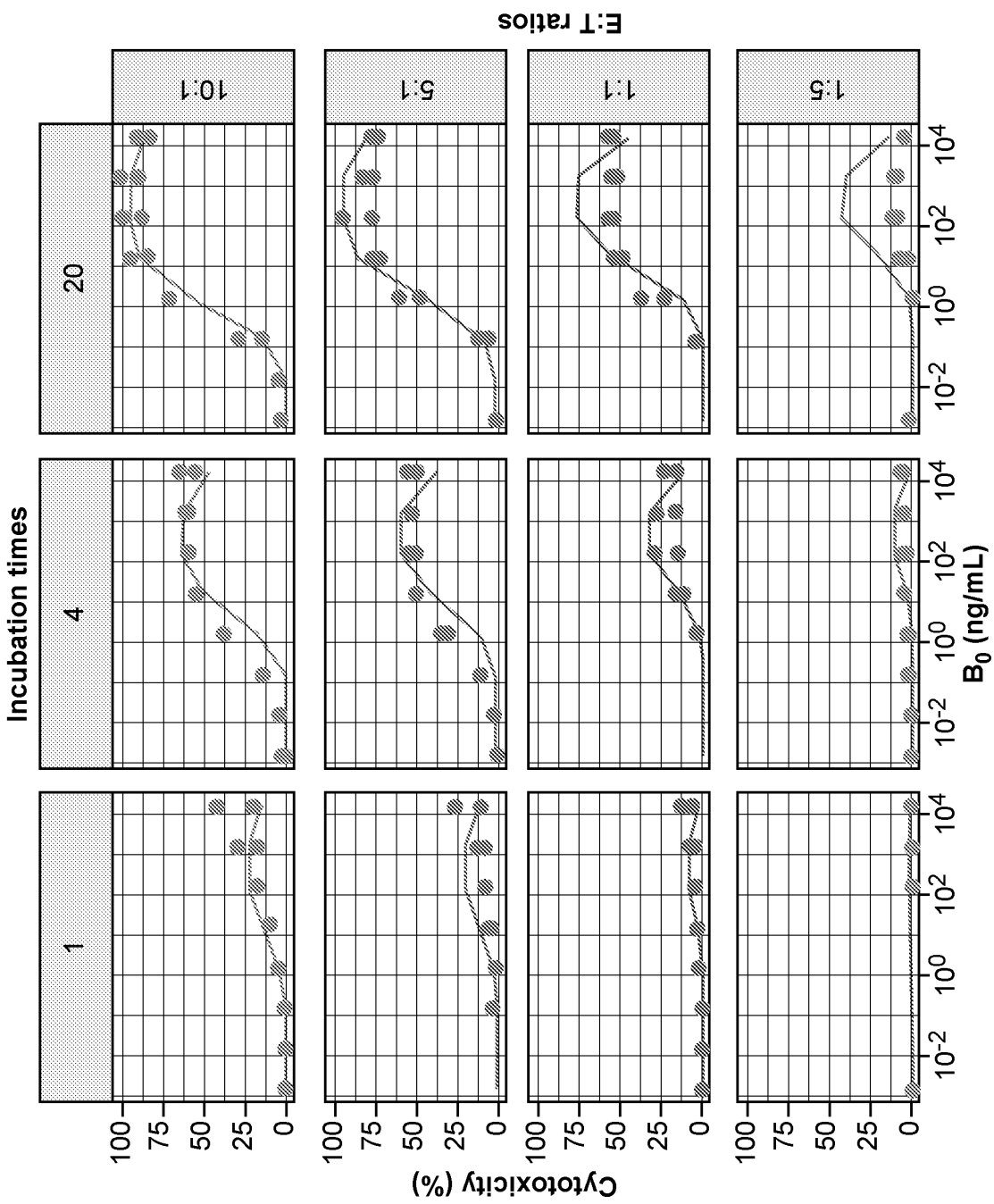

Incubation times
1
4
20
E:T ratios
10:1
5:1
1:1
1:5
Cytotoxicity (%)
0
25
50
75
100
10^{-2}
10^{0}
10^{2}
10^{4}
B_0 (ng/mL)

FIG. 5

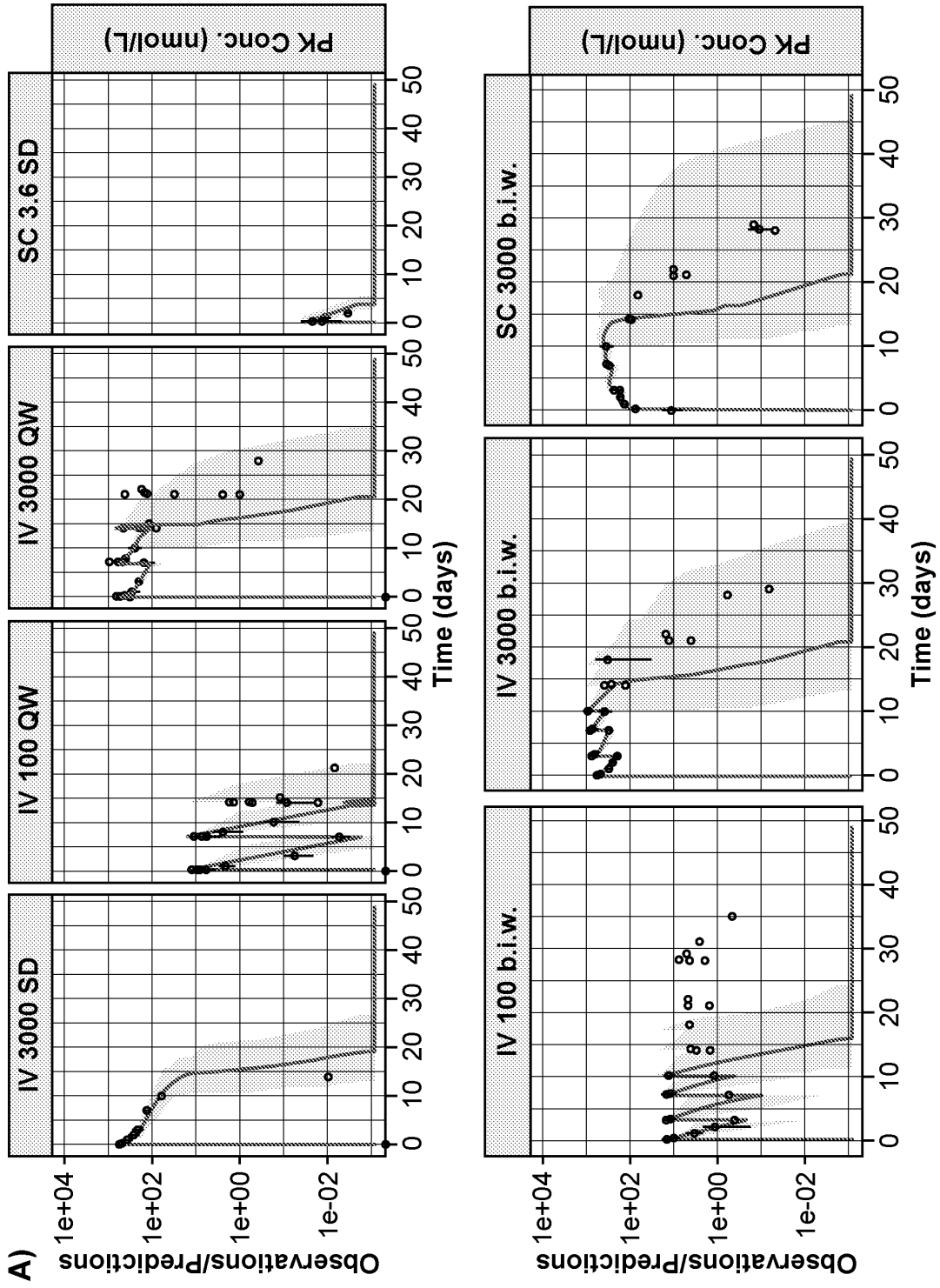

A)
Observations/Predictions
1e+04
1e+02
1e+00
1e-02
IV 3000 SD
IV 100 QW
IV 3000 QW
SC 3.6 SD
IV 100 b.i.w.
IV 3000 b.i.w.
SC 3000 b.i.w.
PK Conc. (nmol/L)
0 10 20 30 40 50
Time (days)

FIG. 6A

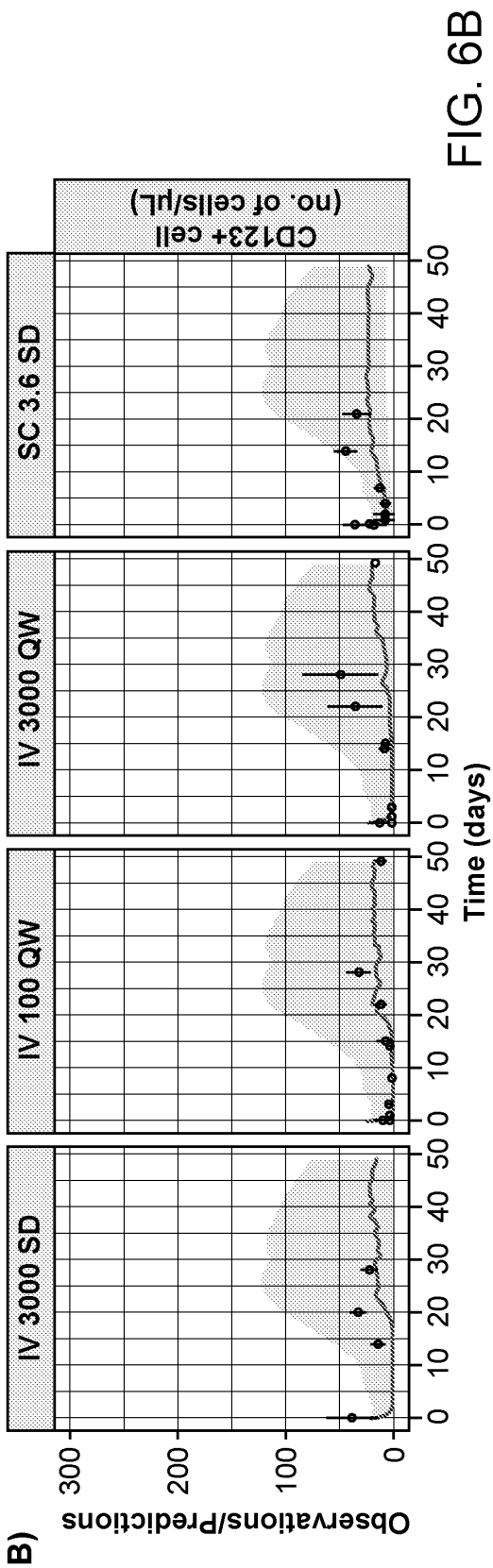

B)
Observations/Predictions
0
100
200
300
IV 3000 SD
IV 100 QW
IV 3000 QW
SC 3.6 SD
CD123+ cell
(no. of cells/µL)
0 10 20 30 40 50
Time (days)

FIG. 6B

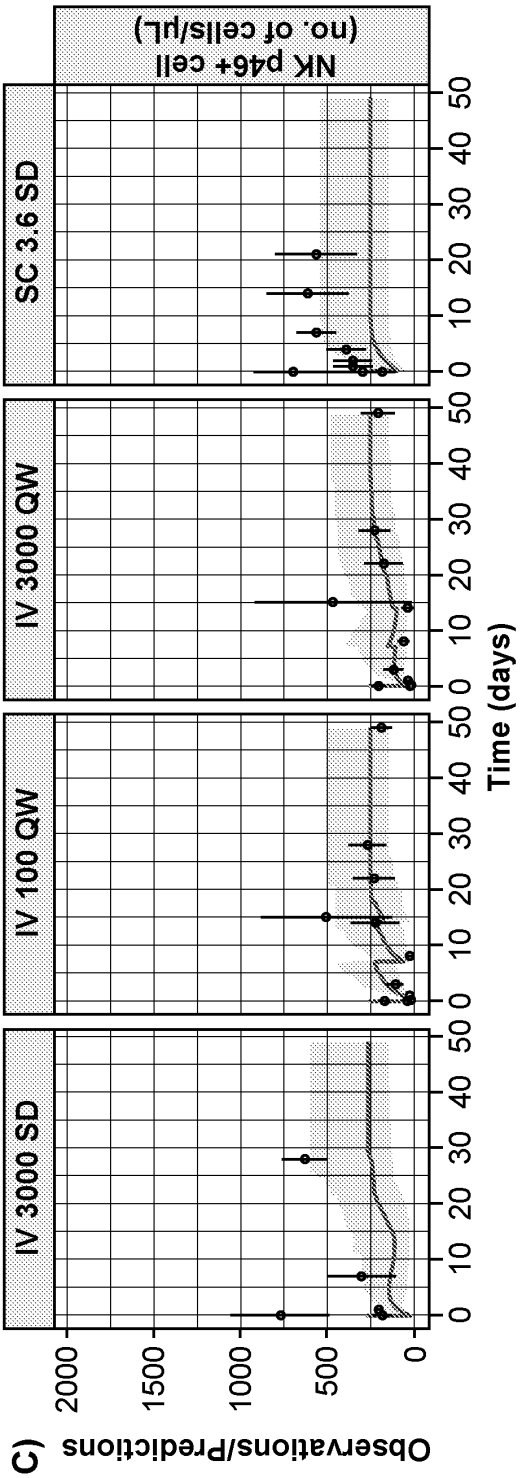

C)
Observations/Predictions
0
500
1000
1500
2000
IV 3000 SD
IV 100 QW
IV 3000 QW
SC 3.6 SD
NK p46+ cell
(no. of cells/µL)
0 10 20 30 40 50
Time (days)

FIG. 6C

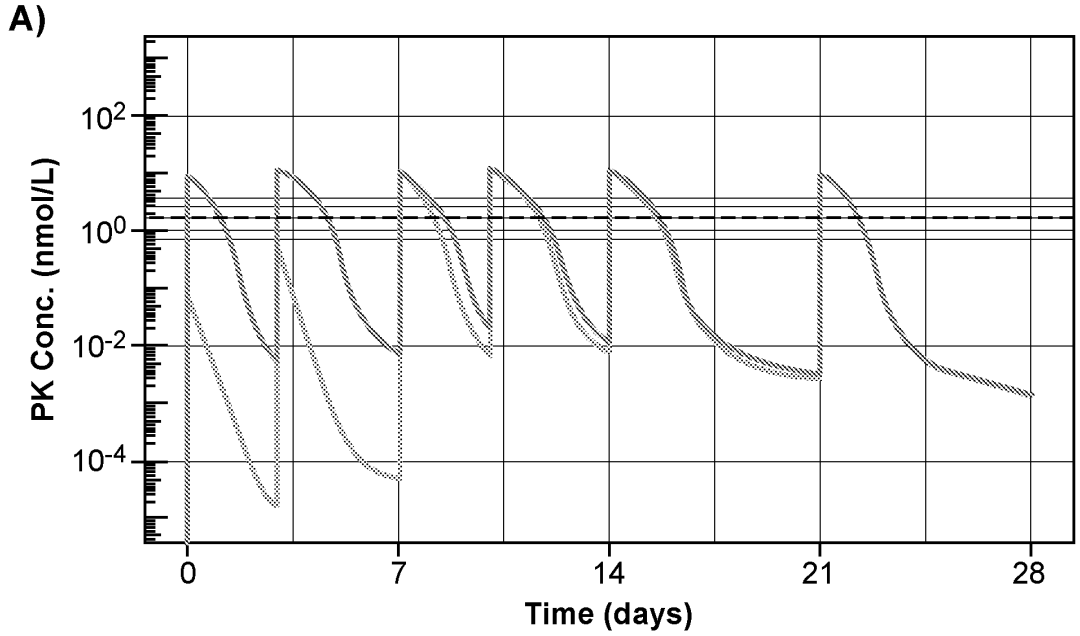

A)
PK Conc. (nmol/L)
10^2
10^0
10^{-2}
10^{-4}
0
7
14
21
28
Time (days)

FIG. 7A

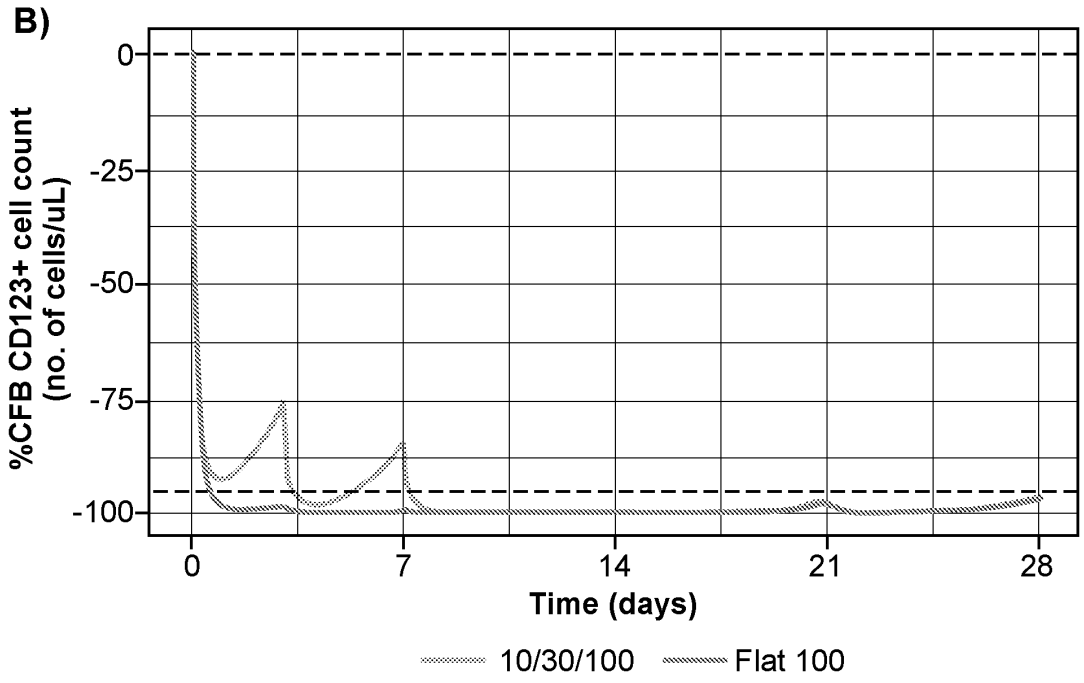

B)
%CFB CD123+ cell count (no. of cells/uL)
0
-25
-50
-75
-100
0
7
14
21
28
Time (days)
10/30/100
Flat 100

FIG. 7B

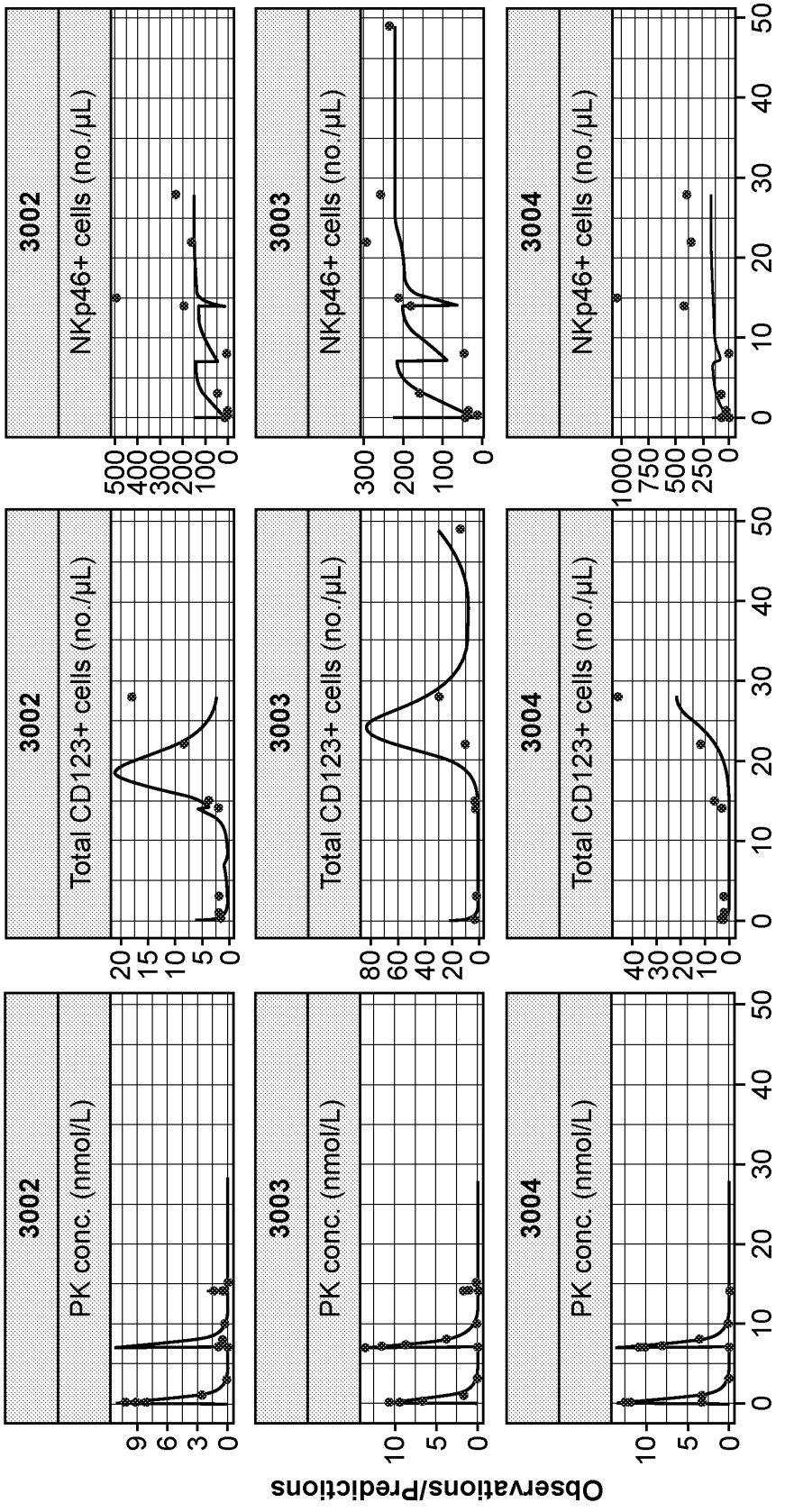

3002
PK conc. (nmol/L)
3003
PK conc. (nmol/L)
3004
PK conc. (nmol/L)
3002
Total CD123+ cells (no./µL)
3003
Total CD123+ cells (no./µL)
3004
Total CD123+ cells (no./µL)
3002
NKp46+ cells (no./µL)
3003
NKp46+ cells (no./µL)
3004
NKp46+ cells (no./µL)
Observations/Predictions
Time (days)

FIG. 8

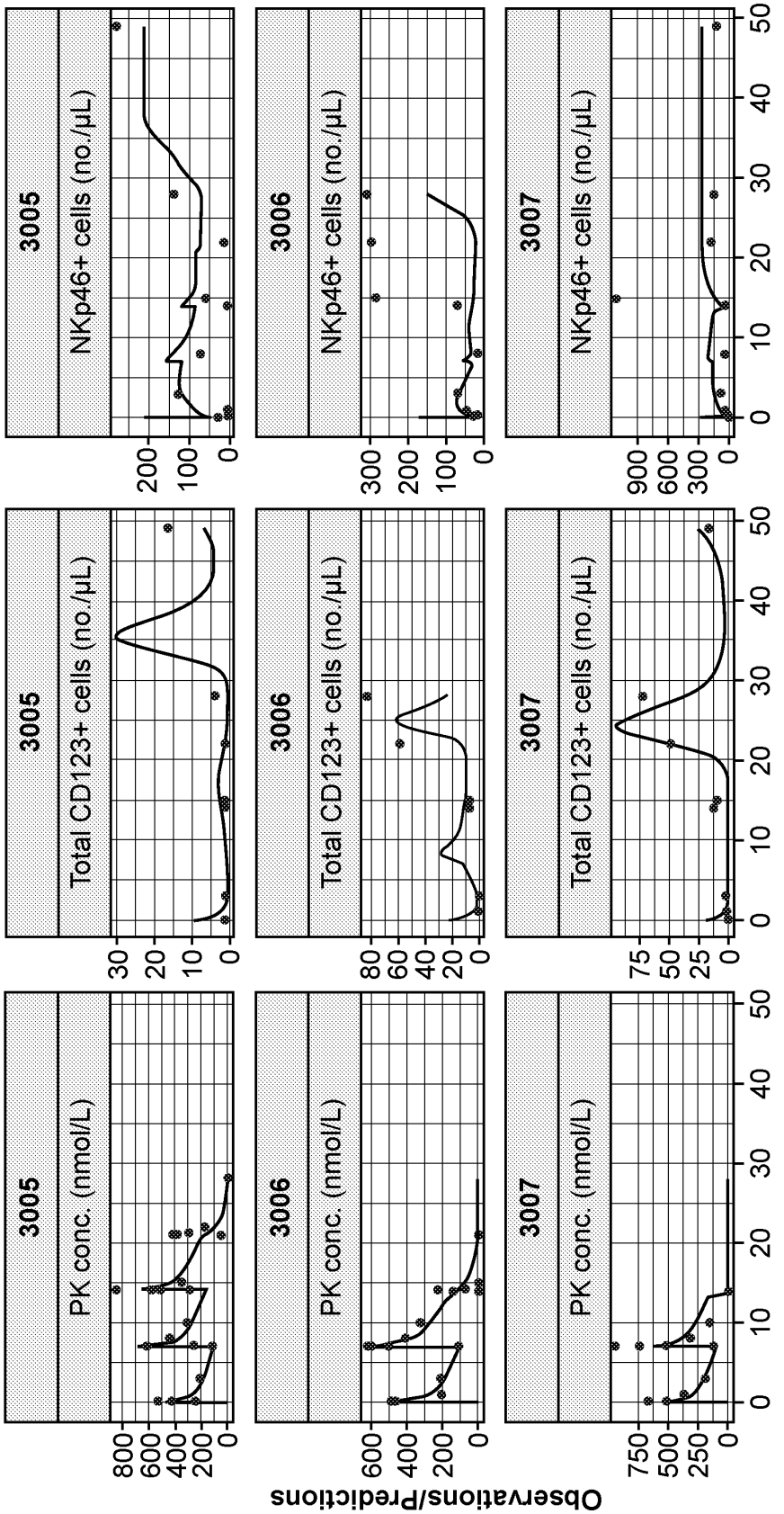

3005
PK conc. (nmol/L)
3006
PK conc. (nmol/L)
3007
PK conc. (nmol/L)
3005
Total CD123+ cells (no./µL)
3006
Total CD123+ cells (no./µL)
3007
Total CD123+ cells (no./µL)
3005
NKp46+ cells (no./µL)
3006
NKp46+ cells (no./µL)
3007
NKp46+ cells (no./µL)
Observations/Predictions
Time (days)

FIG. 8 (Cont.)

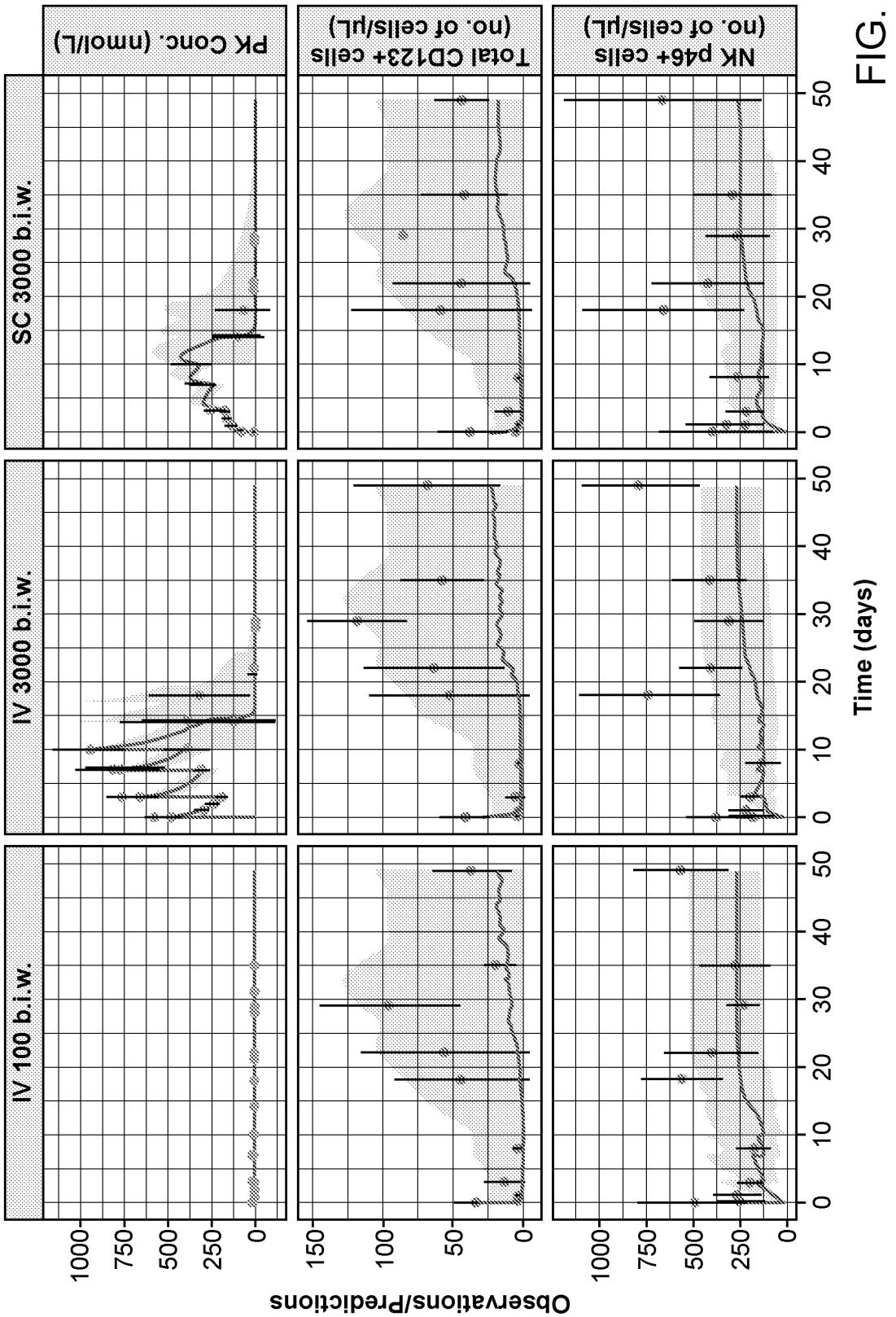

IV 100 b.i.w.
IV 3000 b.i.w.
SC 3000 b.i.w.
PK Conc. (nmol/L)
Total CD123+ cells (no. of cells/µL)
NK p46+ cells (no. of cells/µL)
Observations/Predictions
Time (days)

FIG. 9

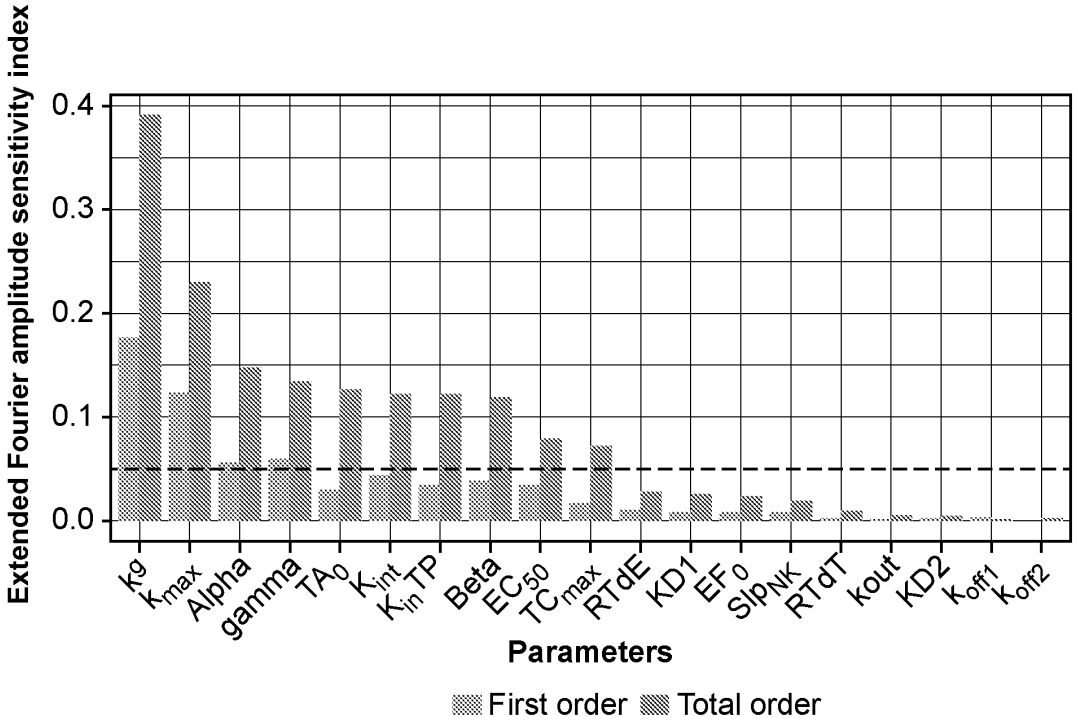


FIG. 10A

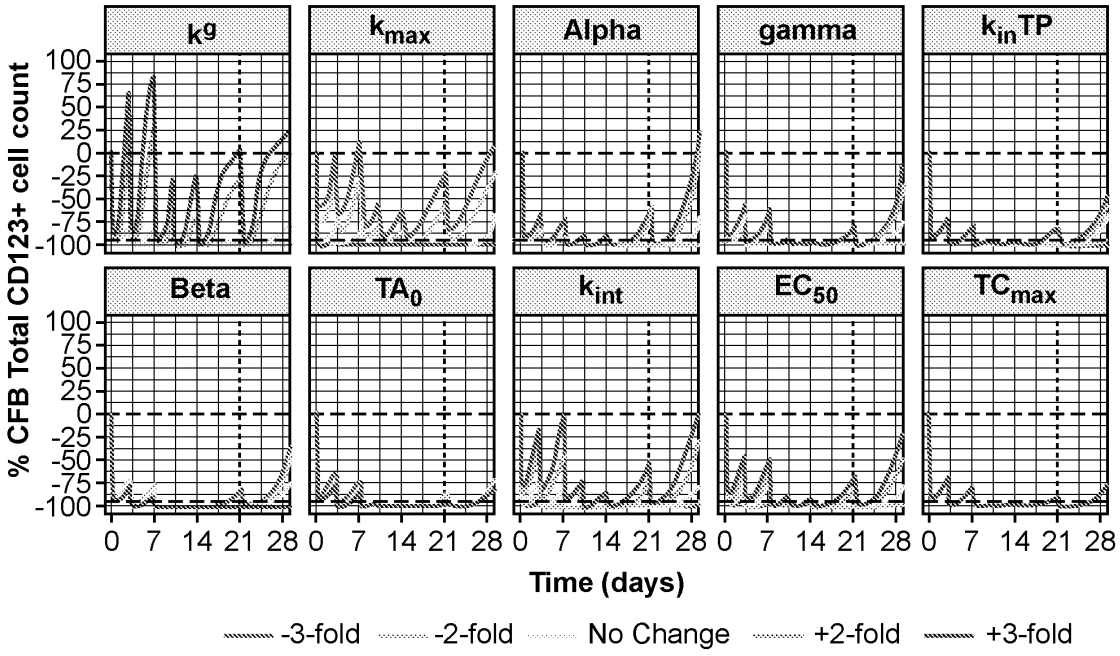
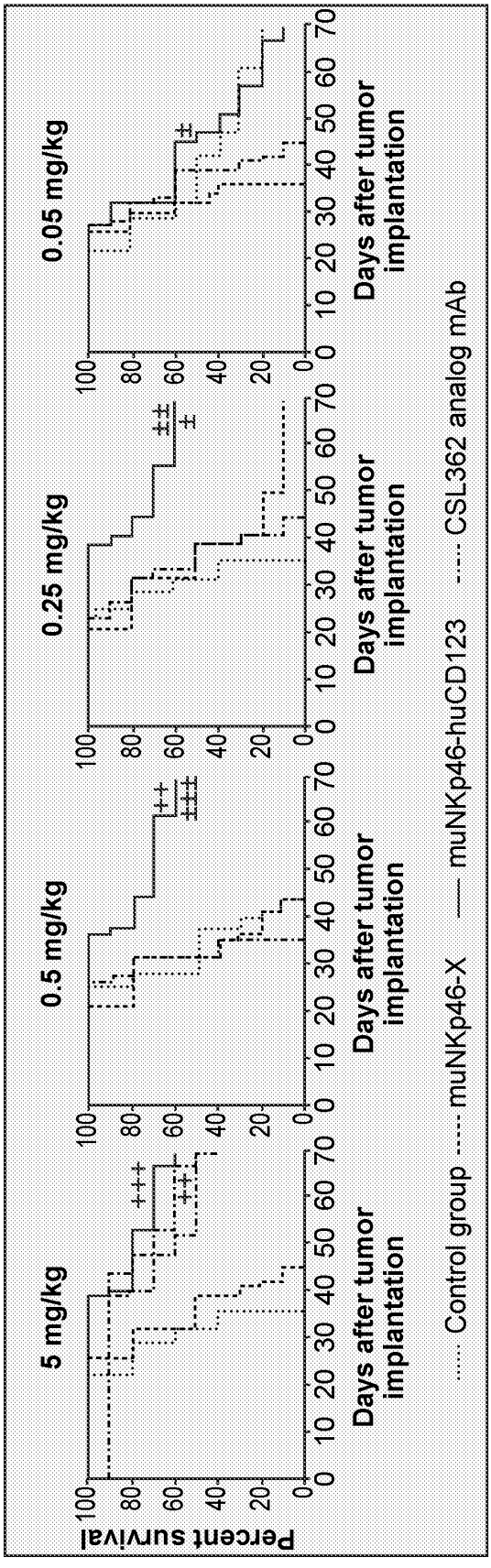


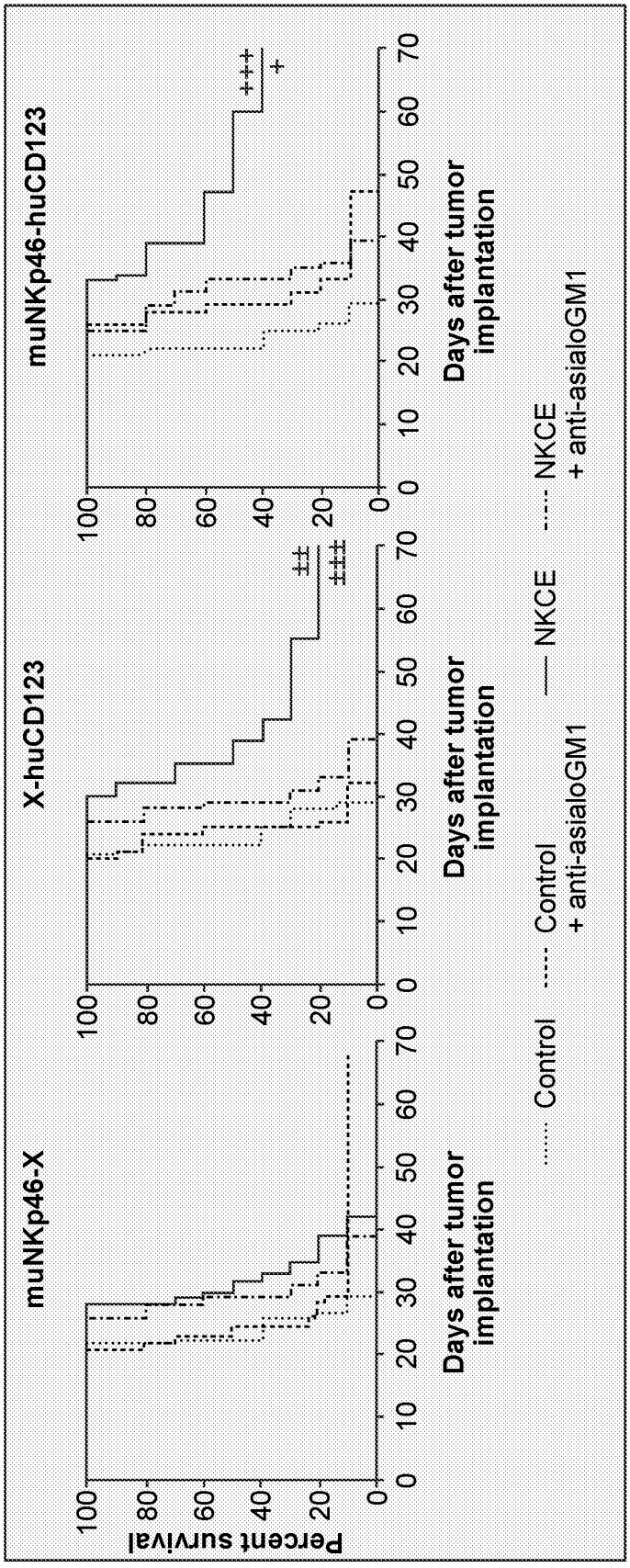
FIG. 10B



MOLM-13 cells injected IV at Day 0 -single administration on day 1 by IP route. n = 5 to 10 mice/group; $^{+++}$: p <0.001 versus control group $^{++}$: p <0.01 versus control group;$^{+}$: p <0.05 versus control group; ###. p <0.001 versus CSL362 analog mAb; #. p<0.05 versus CSL362 analog mAb

Abbreviations: IP: Intraperitoneal; IV: intravenous; mAb: Monoclonal antibody; SCID: Severe-combined-immunodeficient

FIG. 11



MOLM-13 cells injected IV at Day 0 -single administration on day 1 by IP route. n = 10 mice / group; NK depletion induced by 2 IP administrations of anti-asialo GM1 at Day 1 and Day 5; $^{+++}$: p <0.001 versus control group; $^{++}$: p < 0.01 versus control group; ###: p <0.001 versus same treatment + NK depletion; #: p < 0.05 versus same treatment + NK depletion

Abbreviations: IP: Intraperitoneal; IV: intravenous; SCID: Severe-combined-immunodeficient

FIG. 12

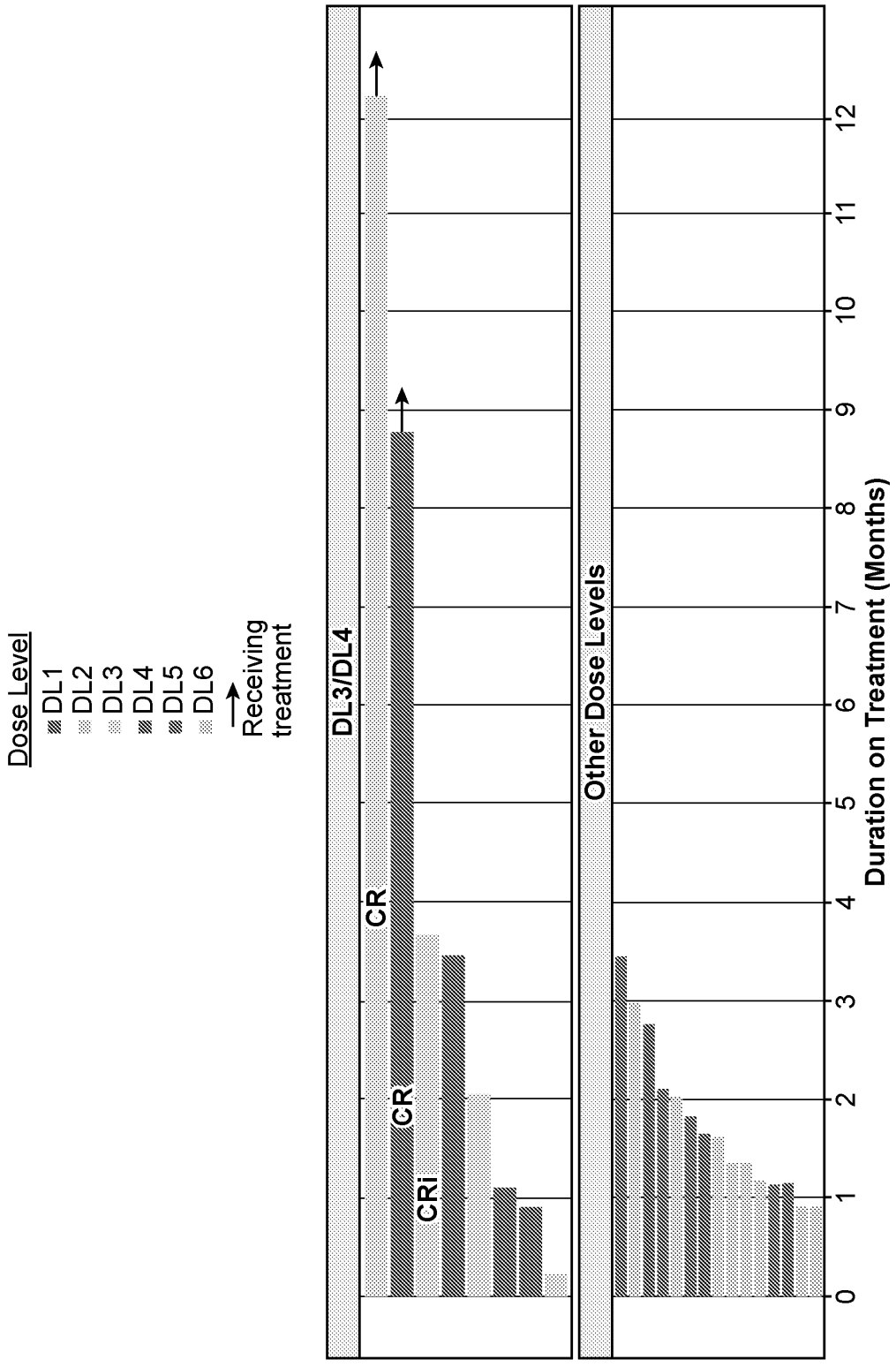

Dose Level
DL1
DL2
DL3
DL4
DL5
DL6
Receiving treatment
DL3/DL4
CR
CR
CRi
Other Dose Levels
0
1
2
3
4
5
6
7
8
9
10
11
12
Duration on Treatment (Months)

FIG. 13A

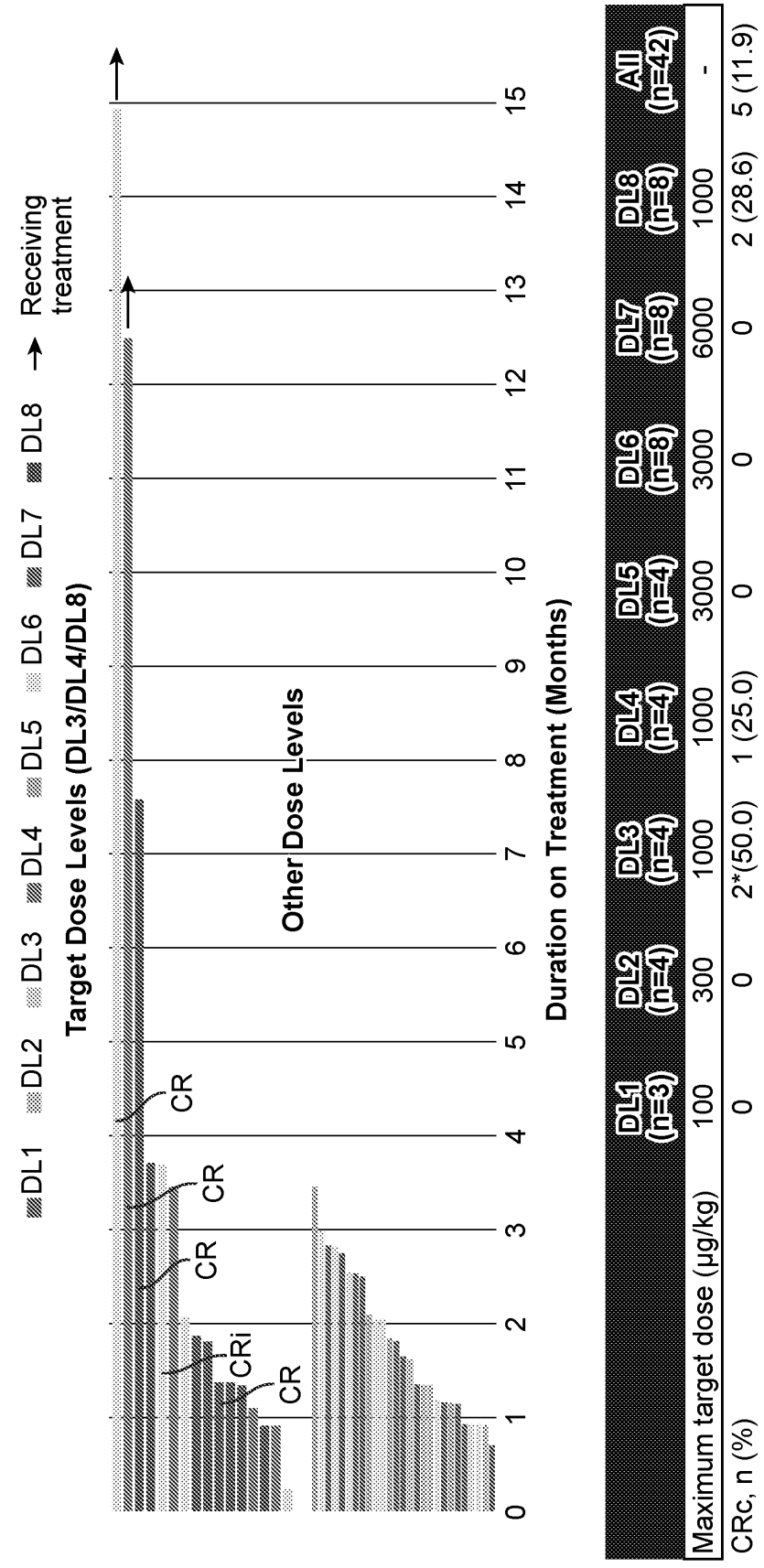

DL1
DL2
DL3
DL4
DL5
DL6
DL7
DL8
Receiving treatment
Target Dose Levels (DL3/DL4/DL8)
CR
CR
CR
CRi
CR
Other Dose Levels
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Duration on Treatment (Months)
DL1 (n=3)
DL2 (n=4)
DL3 (n=4)
DL4 (n=4)
DL5 (n=4)
DL6 (n=8)
DL7 (n=8)
DL8 (n=8)
All (n=42)
Maximum target dose (µg/kg) 100 300 1000 1000 3000 3000 6000 1000 -
CRc, n (%) 0 0 2*(50.0) 1 (25.0) 0 0 0 2 (28.6) 5 (11.9)

FIG. 13B

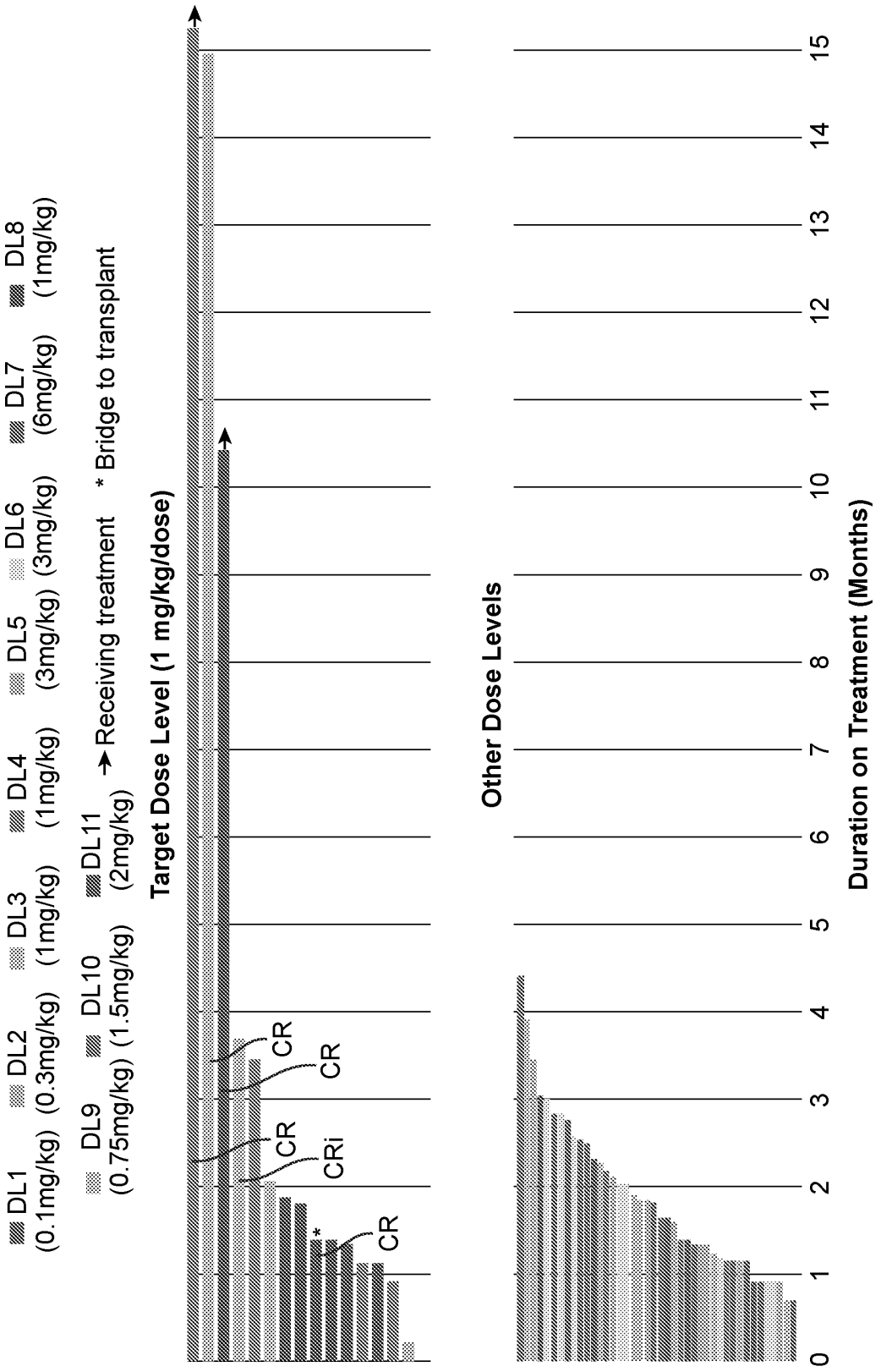

DL1 (0.1mg/kg)
DL2 (0.3mg/kg)
DL3 (1mg/kg)
DL4 (1mg/kg)
DL5 (3mg/kg)
DL6 (3mg/kg)
DL7 (6mg/kg)
DL8 (1mg/kg)
DL9 (0.75mg/kg)
DL10 (1.5mg/kg)
DL11 (2mg/kg)
→ Receiving treatment
* Bridge to transplant
Target Dose Level (1 mg/kg/dose)
CR
CR
CR
CRi
*
CR
Other Dose Levels
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Duration on Treatment (Months)

FIG. 13C

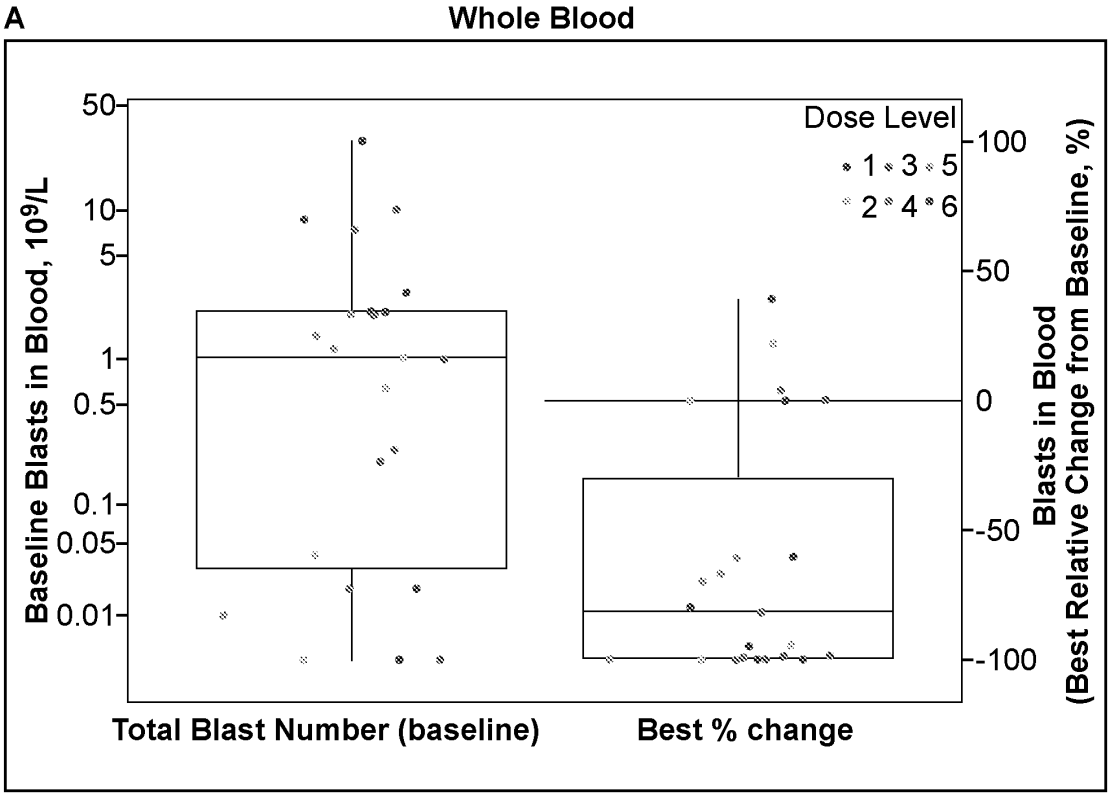


FIG. 14A

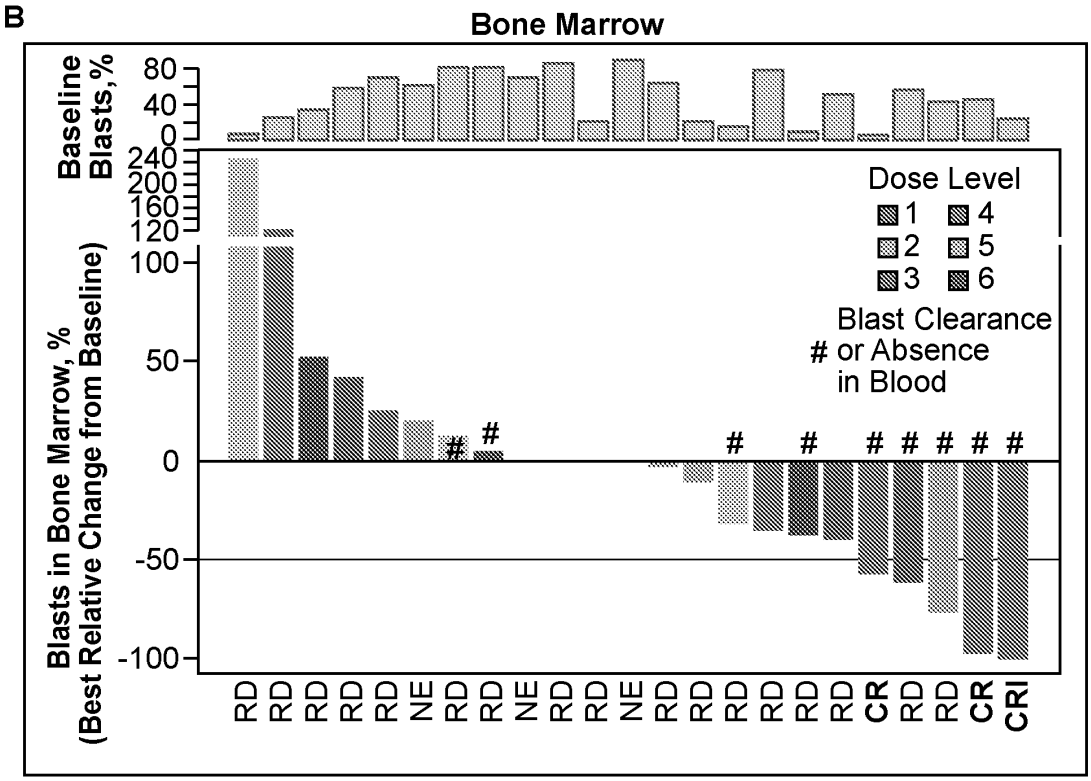


FIG. 14B

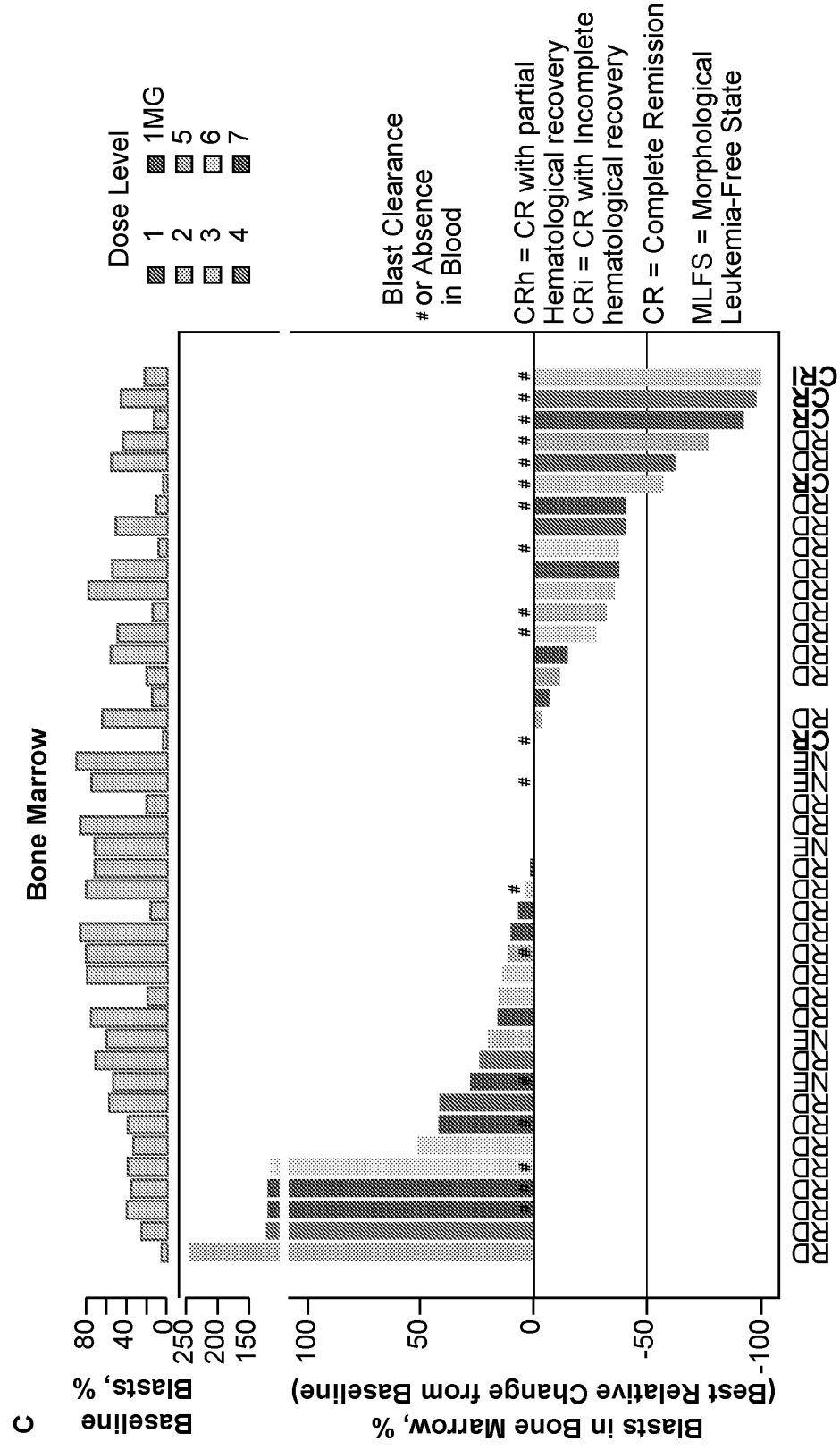

C
Baseline Blasts, %
Bone Marrow
Blasts in Bone Marrow, %
(Best Relative Change from Baseline)
Dose Level
1 1MG
2 5
3 6
4 7
Blast Clearance
or Absence
in Blood
CRh = CR with partial
Hematological recovery
CRi = CR with Incomplete
hematological recovery
CR = Complete Remission
MLFS = Morphological
Leukemia-Free State

FIG. 14C

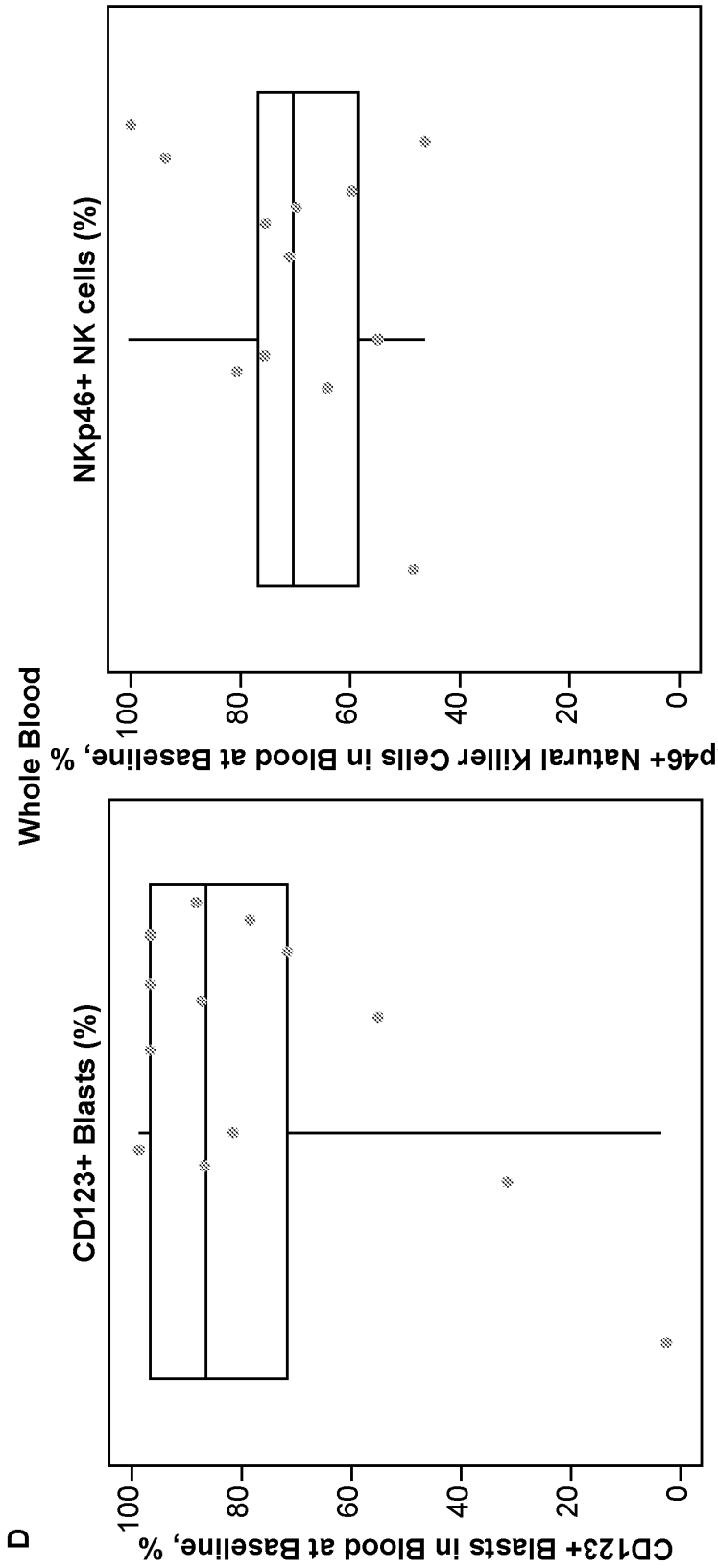

D
Whole Blood
CD123+ Blasts in Blood at Baseline, %
CD123+ Blasts (%)
NKp46+ Natural Killer Cells in Blood at Baseline, %
NKp46+ NK cells (%)
0
20
40
60
80
100

FIG. 14D

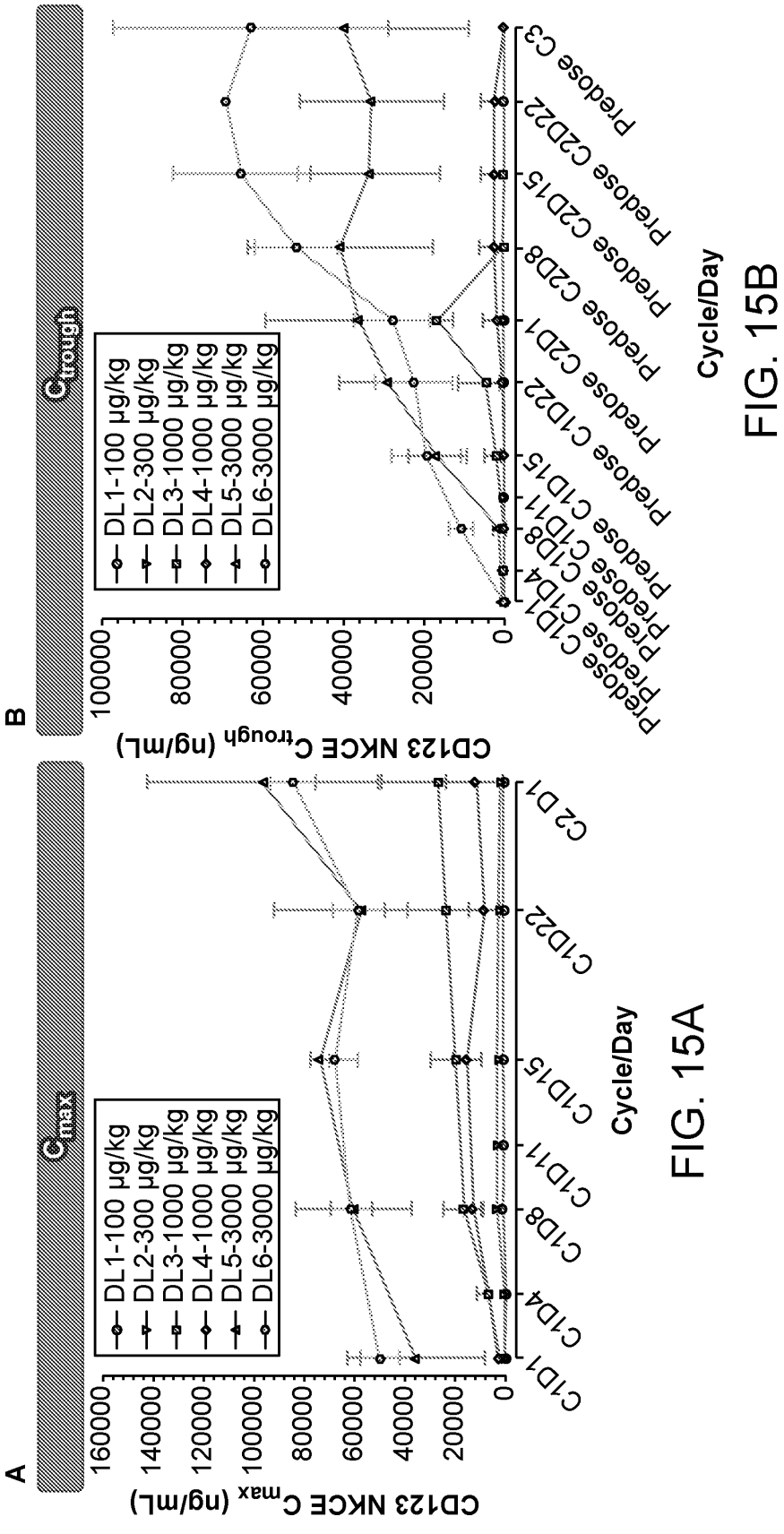
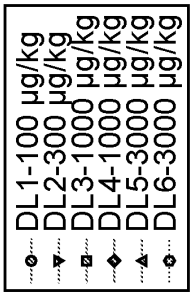


FIG. 15A

FIG. 15B



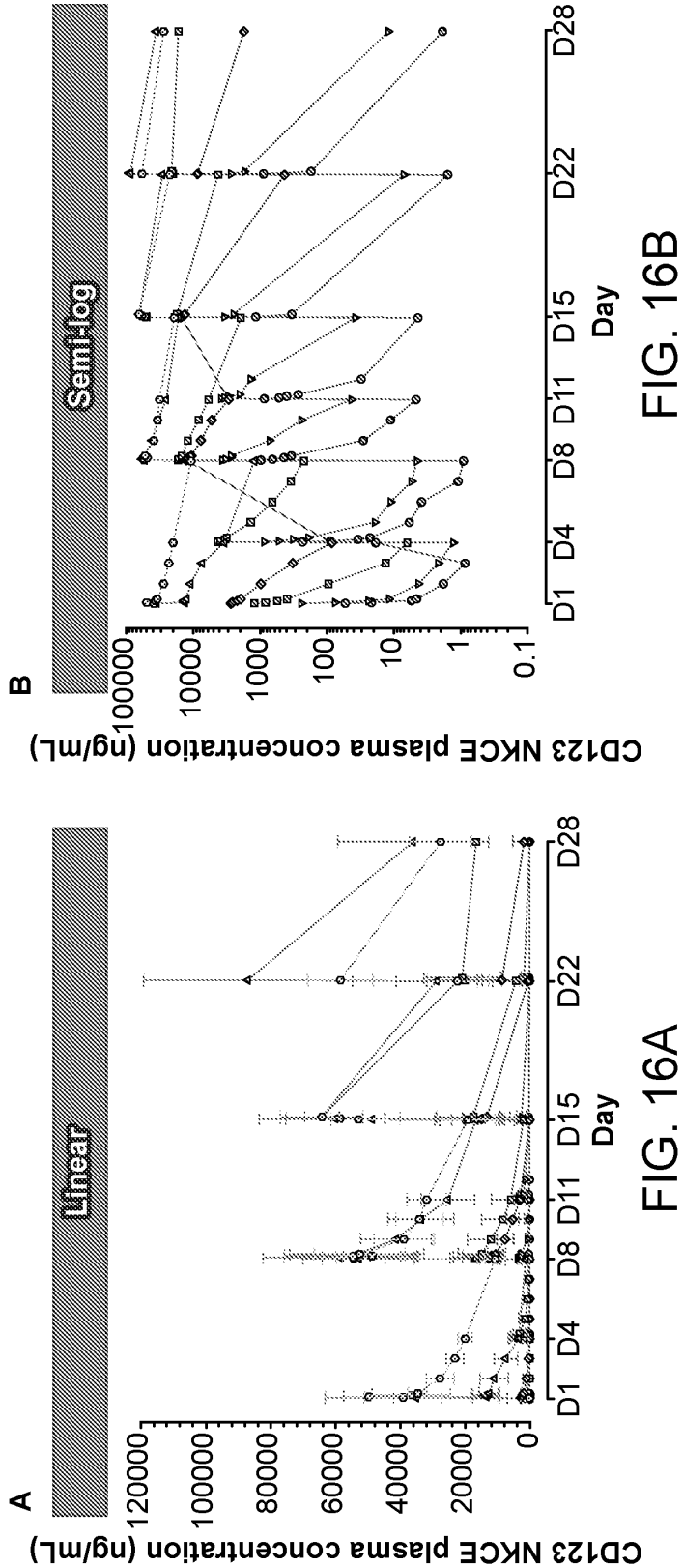


FIG. 16A

FIG. 16B

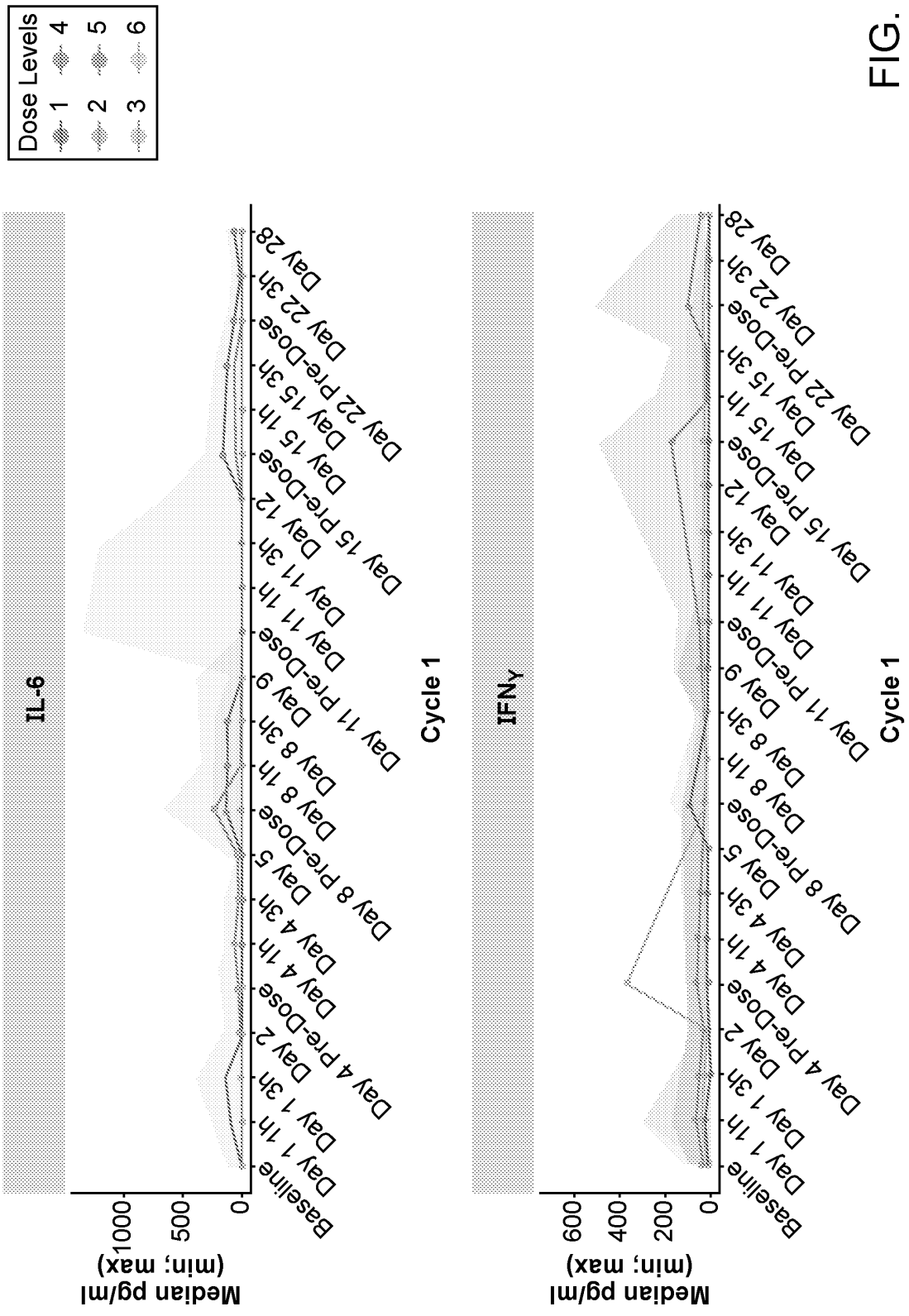

Dose Levels
1
2
3
4
5
6
IL-6
Median pg/ml (min; max)
0
500
1000
Baseline
Day 1 1h
Day 1 3h
Day 2
Day 4 Pre-Dose
Day 4 1h
Day 4 3h
Day 5
Day 8 Pre-Dose
Day 8 1h
Day 8 3h
Day 9
Day 11 Pre-Dose
Day 11 1h
Day 11 3h
Day 12
Day 15 Pre-Dose
Day 15 1h
Day 15 3h
Day 22 Pre-Dose
Day 22 3h
Day 28
Cycle 1
IFNγ
Median pg/ml (min; max)
0
200
400
600
Baseline
Day 1 1h
Day 1 3h
Day 2
Day 4 Pre-Dose
Day 4 1h
Day 4 3h
Day 5
Day 8 Pre-Dose
Day 8 1h
Day 8 3h
Day 9
Day 11 Pre-Dose
Day 11 1h
Day 11 3h
Day 12
Day 15 Pre-Dose
Day 15 1h
Day 15 3h
Day 22 Pre-Dose
Day 22 3h
Day 28
Cycle 1

FIG. 17

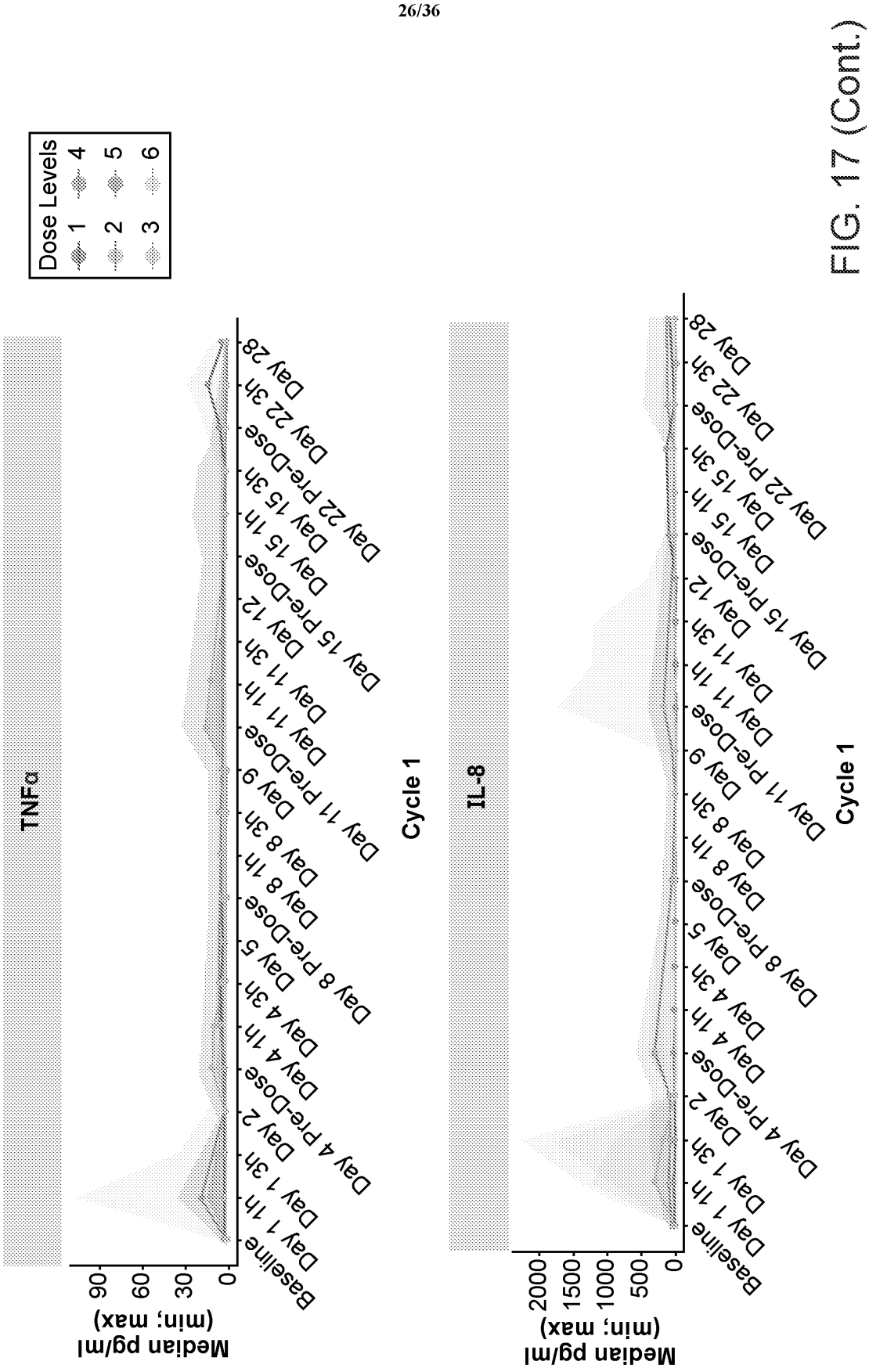

TNFα
Dose Levels
1
2
3
4
5
6
Median pg/ml (min; max)
0
30
60
90
Baseline
Day 1 1h
Day 1 3h
Day 2
Day 4 Pre-Dose
Day 4 1h
Day 4 3h
Day 5
Day 8 Pre-Dose
Day 8 1h
Day 8 3h
Day 9
Day 11 Pre-Dose
Day 11 1h
Day 11 3h
Day 12
Day 15 Pre-Dose
Day 15 1h
Day 15 3h
Day 22 Pre-Dose
Day 22 3h
Day 28
Cycle 1
IL-8
Median pg/ml (min; max)
0
500
1000
1500
2000
Baseline
Day 1 1h
Day 1 3h
Day 2
Day 4 Pre-Dose
Day 4 1h
Day 4 3h
Day 5
Day 8 Pre-Dose
Day 8 1h
Day 8 3h
Day 9
Day 11 Pre-Dose
Day 11 1h
Day 11 3h
Day 12
Day 15 Pre-Dose
Day 15 1h
Day 15 3h
Day 22 Pre-Dose
Day 22 3h
Day 28
Cycle 1

FIG. 17 (Cont.)

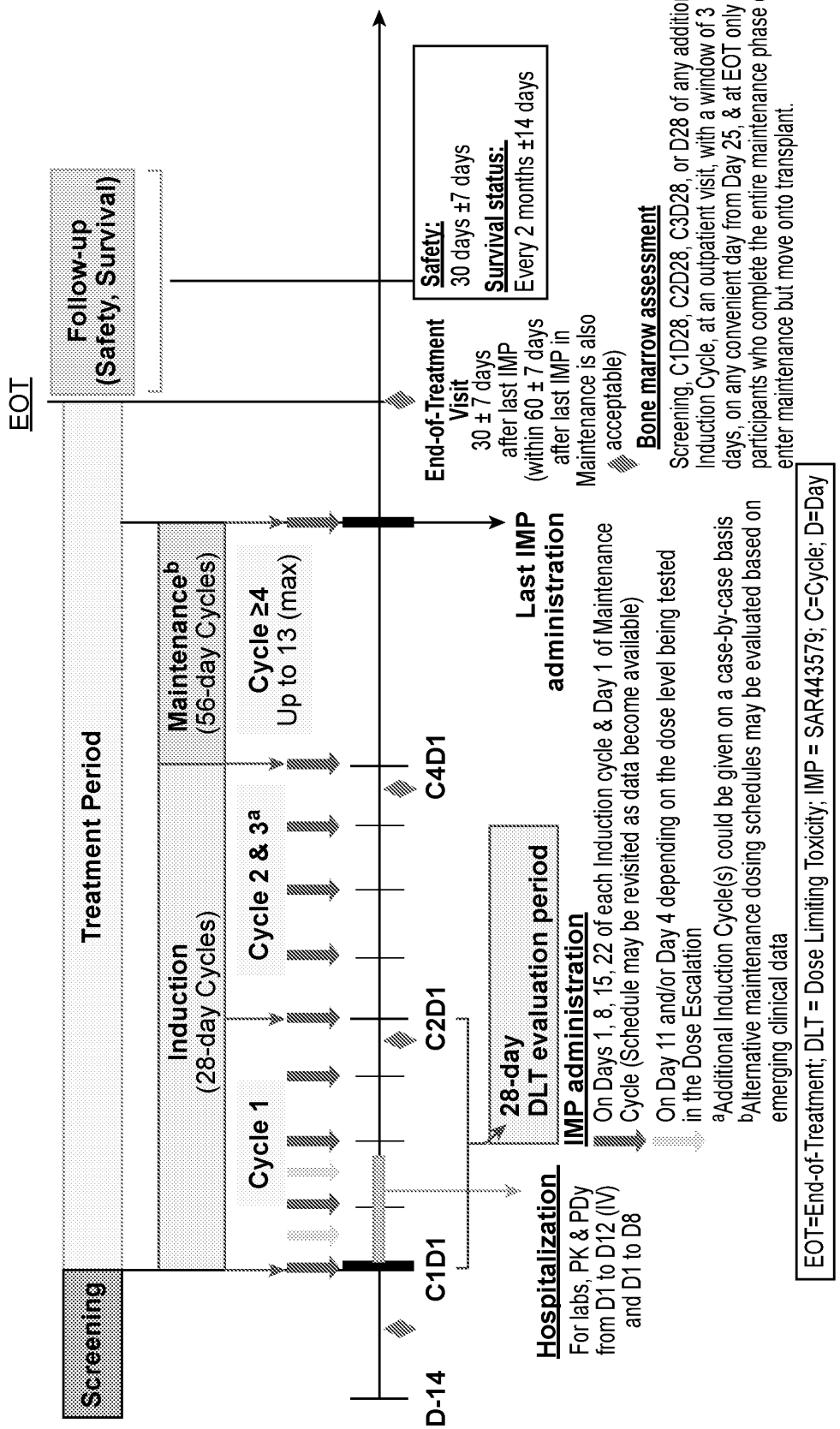

Screening
Treatment Period
Induction
(28-day Cycles)
Cycle 1
Cycle 2 & 3a
Maintenanceb
(56-day Cycles)
Cycle ≥4
Up to 13 (max)
Follow-up
(Safety, Survival)
EOT
D-14
C1D1
C2D1
C4D1
28-day
DLT evaluation period
Last IMP
administration
End-of-Treatment
Visit
30 ± 7 days
after last IMP
(within 60 ± 7 days
after last IMP in
Maintenance is also
acceptable)
Safety:
30 days ±7 days
Survival status:
Every 2 months ±14 days
Hospitalization
For labs, PK & PDy
from D1 to D12 (IV)
and D1 to D8
IMP administration
On Days 1, 8, 15, 22 of each Induction cycle & Day 1 of Maintenance
Cycle (Schedule may be revisited as data become available)
On Day 11 and/or Day 4 depending on the dose level being tested
in the Dose Escalation
aAdditional Induction Cycle(s) could be given on a case-by-case basis
bAlternative maintenance dosing schedules may be evaluated based on
emerging clinical data
Bone marrow assessment
Screening, C1D28, C2D28, C3D28, or D28 of any additional
Induction Cycle, at an outpatient visit, with a window of 3
days, on any convenient day from Day 25, & at EOT only for
participants who complete the entire maintenance phase or
enter maintenance but move onto transplant.
EOT=End-of-Treatment; DLT = Dose Limiting Toxicity; IMP = SAR443579; C=Cycle; D=Day

FIG. 18A

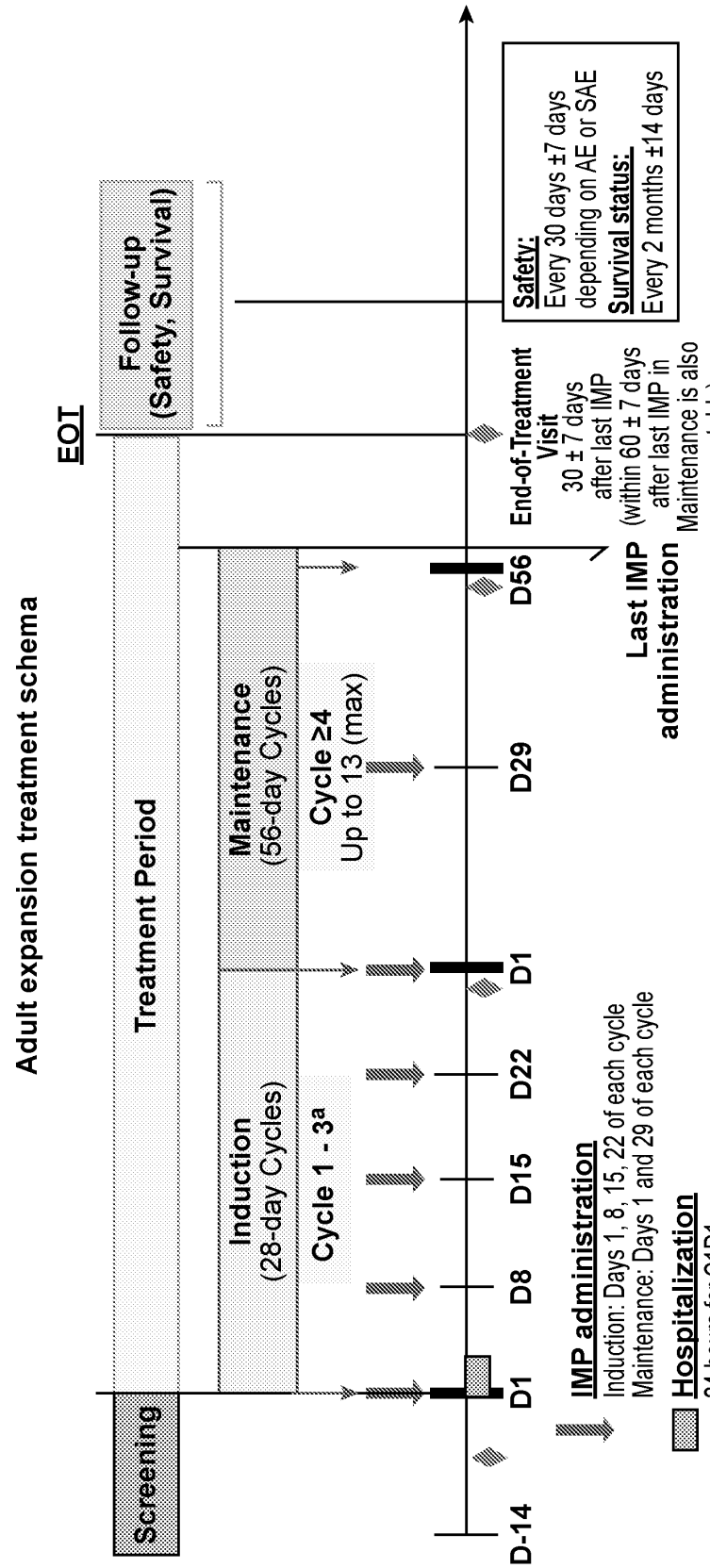

Adult expansion treatment schema
Screening
Treatment Period
Induction
(28-day Cycles)
Cycle 1 - 3a
Maintenance
(56-day Cycles)
Cycle ≥4
Up to 13 (max)
Follow-up
(Safety, Survival)
EOT
D-14
D1
D8
D15
D22
D1
D29
D56
Last IMP administration
End-of-Treatment Visit
30 ± 7 days after last IMP
(within 60 ± 7 days after last IMP in Maintenance is also acceptable)
Safety:
Every 30 days ±7 days depending on AE or SAE
Survival status:
Every 2 months ±14 days
IMP administration
Induction: Days 1, 8, 15, 22 of each cycle
Maintenance: Days 1 and 29 of each cycle
Hospitalization
24 hours for C1D1
Bone marrow assessment
Screening, D28 of each induction cycle, D56 of initial maintenance cycle and then every other maintenance cycle. EOT only for participants who complete the entire maintenance phase (13 cycles) or move onto transplant.
*Additional Induction Cycle(s) could be given on a case-by-case basis
AE = Adverse event; D=Day; EOT = End-of-Treatment; IMP = SAR443579; SAE = Serious adverse event

FIG. 18B

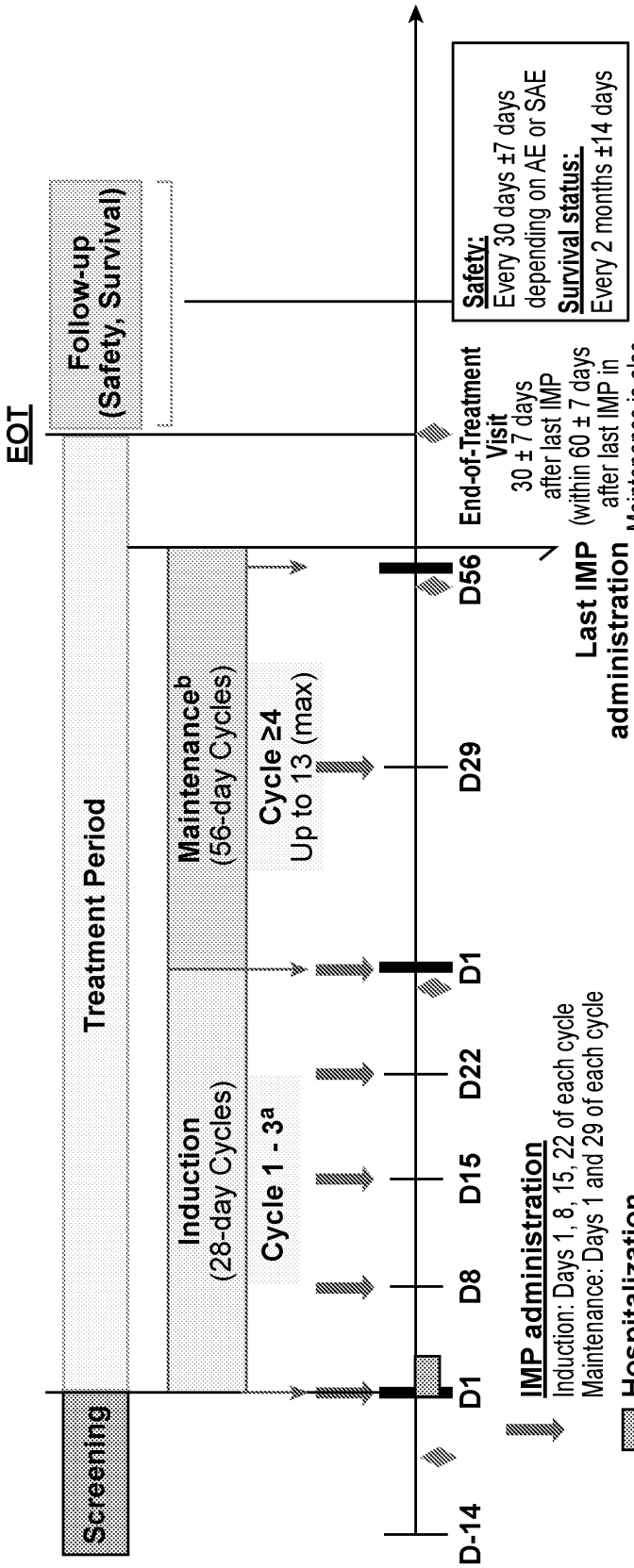
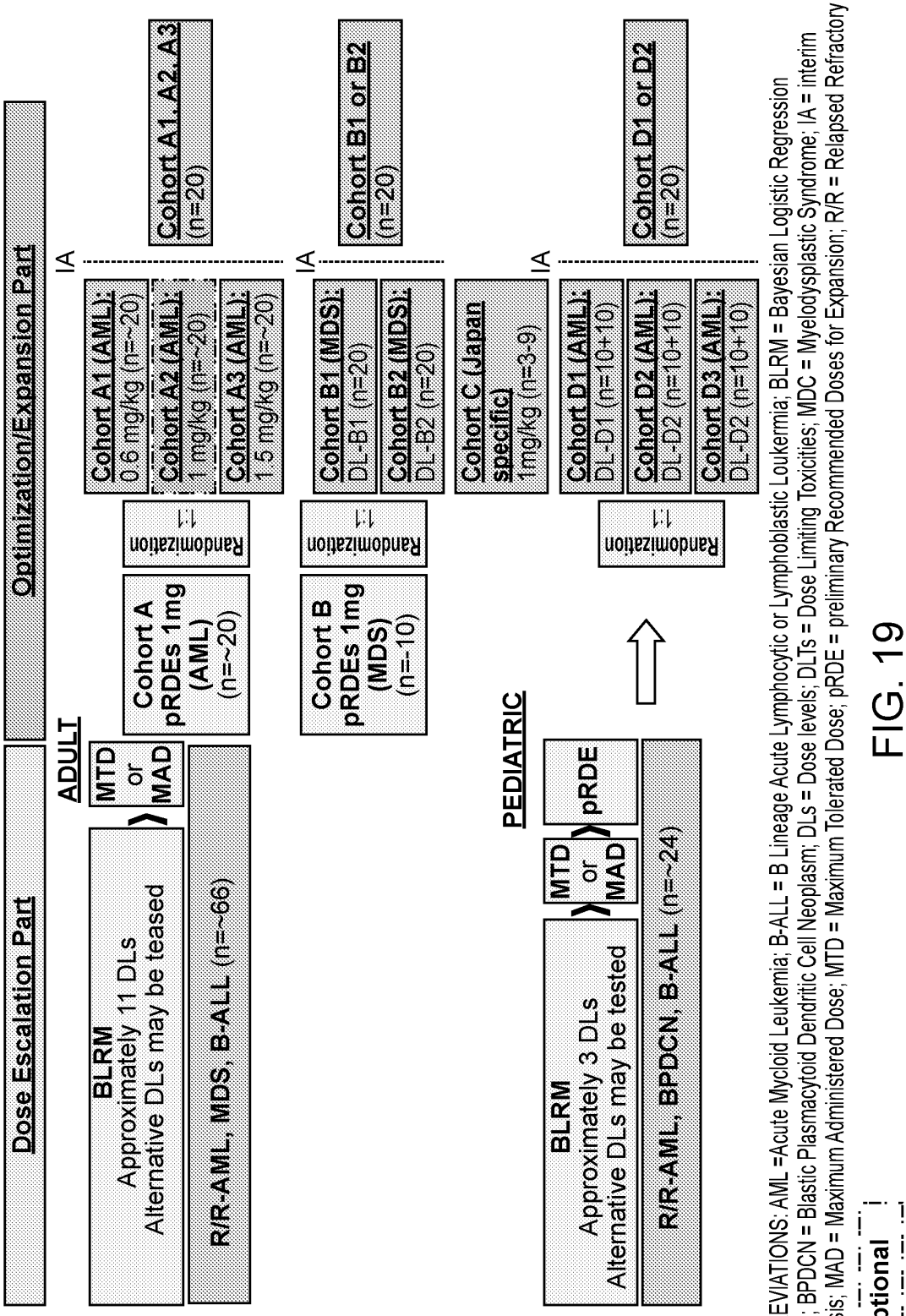

EOT
Follow-up (Safety, Survival)
Treatment Period
Induction (28-day Cycles)
Maintenance[b] (56-day Cycles)
Cycle 1 - 3[a]
Cycle ≥4 Up to 13 (max)
Screening
D-14
D1
D8
D15
D22
D1
D29
D56
Last IMP administration
End-of-Treatment Visit 30 ± 7 days after last IMP (within 60 ± 7 days after last IMP in Maintenance is also acceptable)
Safety: Every 30 days ±7 days depending on AE or SAE
Survival status: Every 2 months ±14 days
IMP administration
Induction: Days 1, 8, 15, 22 of each cycle
Maintenance: Days 1 and 29 of each cycle
Hospitalization
48 hours for C1D1 and C1D8
Bone marrow assessment
Screening, D28 of each induction cycle, D56 of initial maintenance cycle and then every other maintenance cycle. EOT only for participants who complete the entire maintenance phase (13 cycles) or move onto transplant.
[a]Additional Induction Cycle(s) could be given on a case-by-case basis
[b]Alternative maintenance dosing schedules may be evaluated based on emerging clinical data
AE = Adverse event; D=Day; EOT = End-of-Treatment; IMP = SAR443579; SAE = Serious adverse event

FIG. 18C



ABBREVIATIONS: AML =Acute Mycloid Leukemia; B-ALL = B Lineage Acute Lymphocytic or Lymphoblastic Loukermia; BLRM = Bayesian Logistic Regression Model; BPDCN = Blastic Plasmacytoid Dendritic Cell Neoplasm; DLs = Dose levels; DLTs = Dose Limiting Toxicities; MDC = Myelodysplastic Syndrome; IA = interim analysis; MAD = Maximum Administered Dose; MTD = Maximum Tolerated Dose; pRDE = preliminary Recommended Doses for Expansion; R/R = Relapsed Refractory

FIG. 19

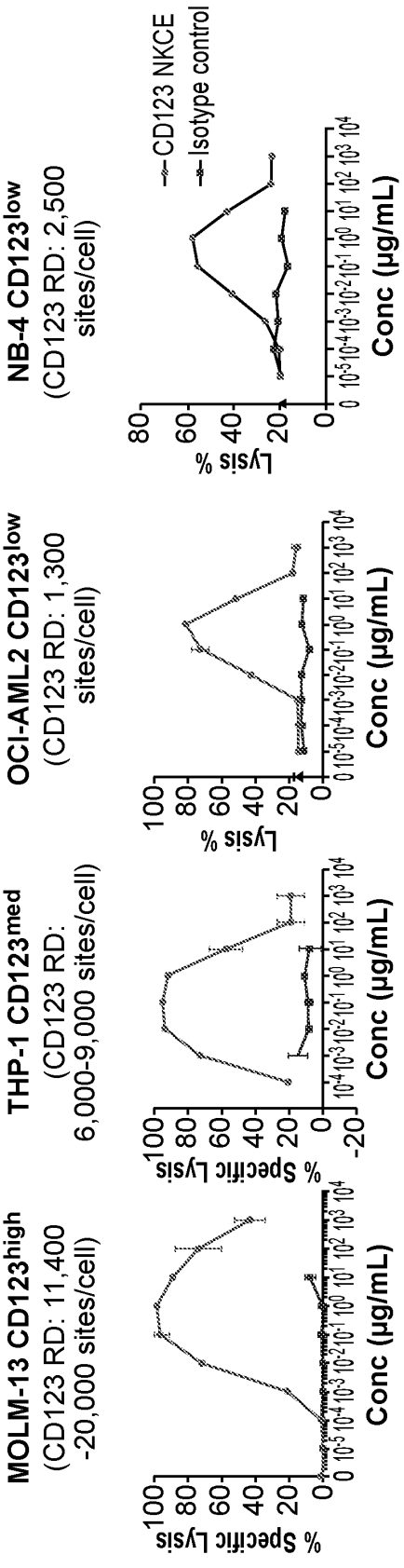

MOLM-13 CD123high
(CD123 RD: 11,400
-20,000 sites/cell)
THP-1 CD123med
(CD123 RD:
6,000-9,000 sites/cell)
OCI-AML2 CD123low
(CD123 RD: 1,300
sites/cell)
NB-4 CD123low
(CD123 RD: 2,500
sites/cell)
% Specific Lysis
Lysis %
Conc (µg/mL)
CD123 NKCE
Isotype control

FIG. 20

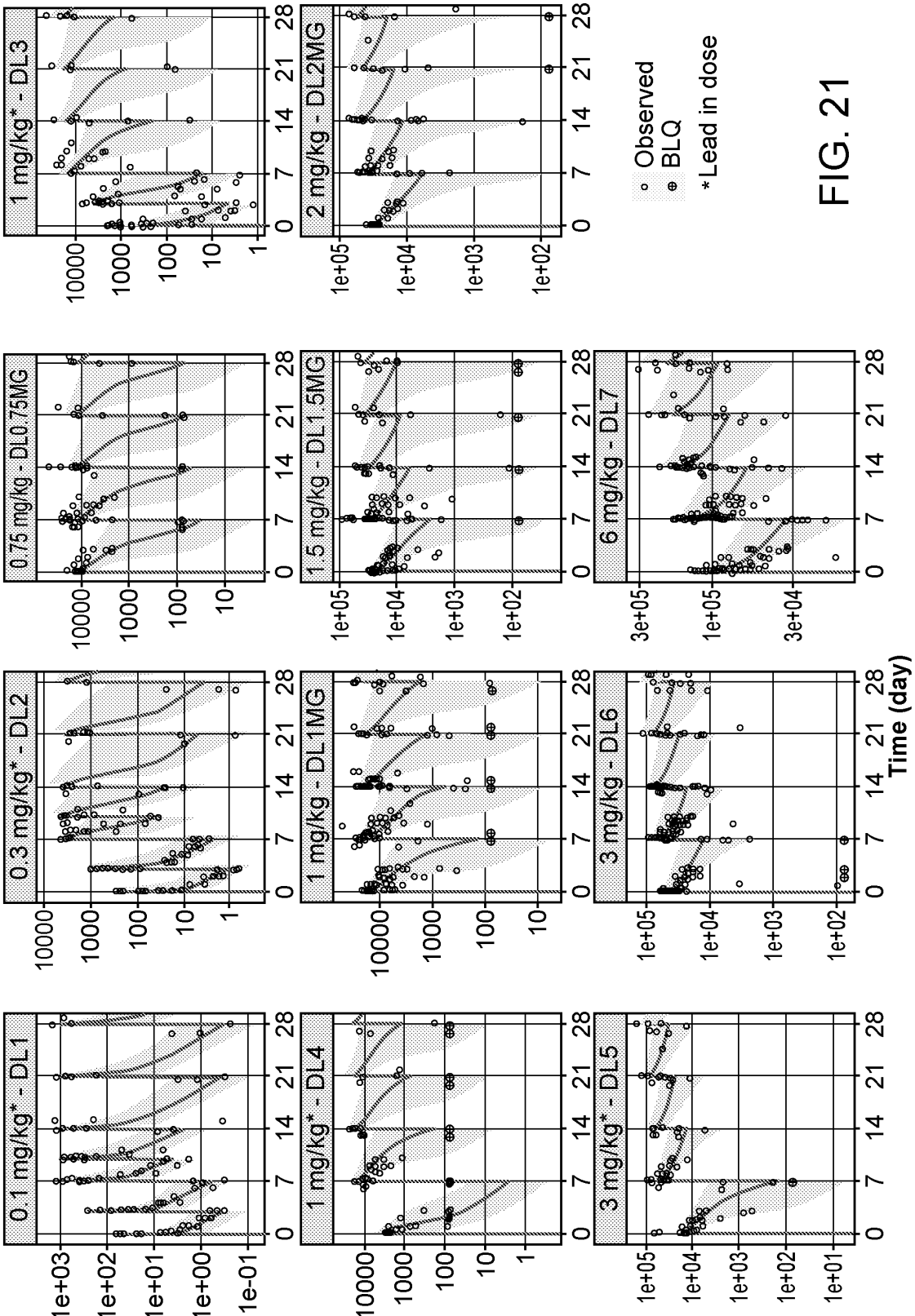

0.1 mg/kg* - DL1
0.3 mg/kg* - DL2
0.75 mg/kg - DL0.75MG
1 mg/kg* - DL3
1 mg/kg* - DL4
1 mg/kg - DL1MG
1.5 mg/kg - DL1.5MG
2 mg/kg - DL2MG
3 mg/kg* - DL5
3 mg/kg - DL6
6 mg/kg - DL7
SAR443579 concentration (ng/mL)
Time (day)
Observed
BLQ
*Lead in dose

FIG. 21

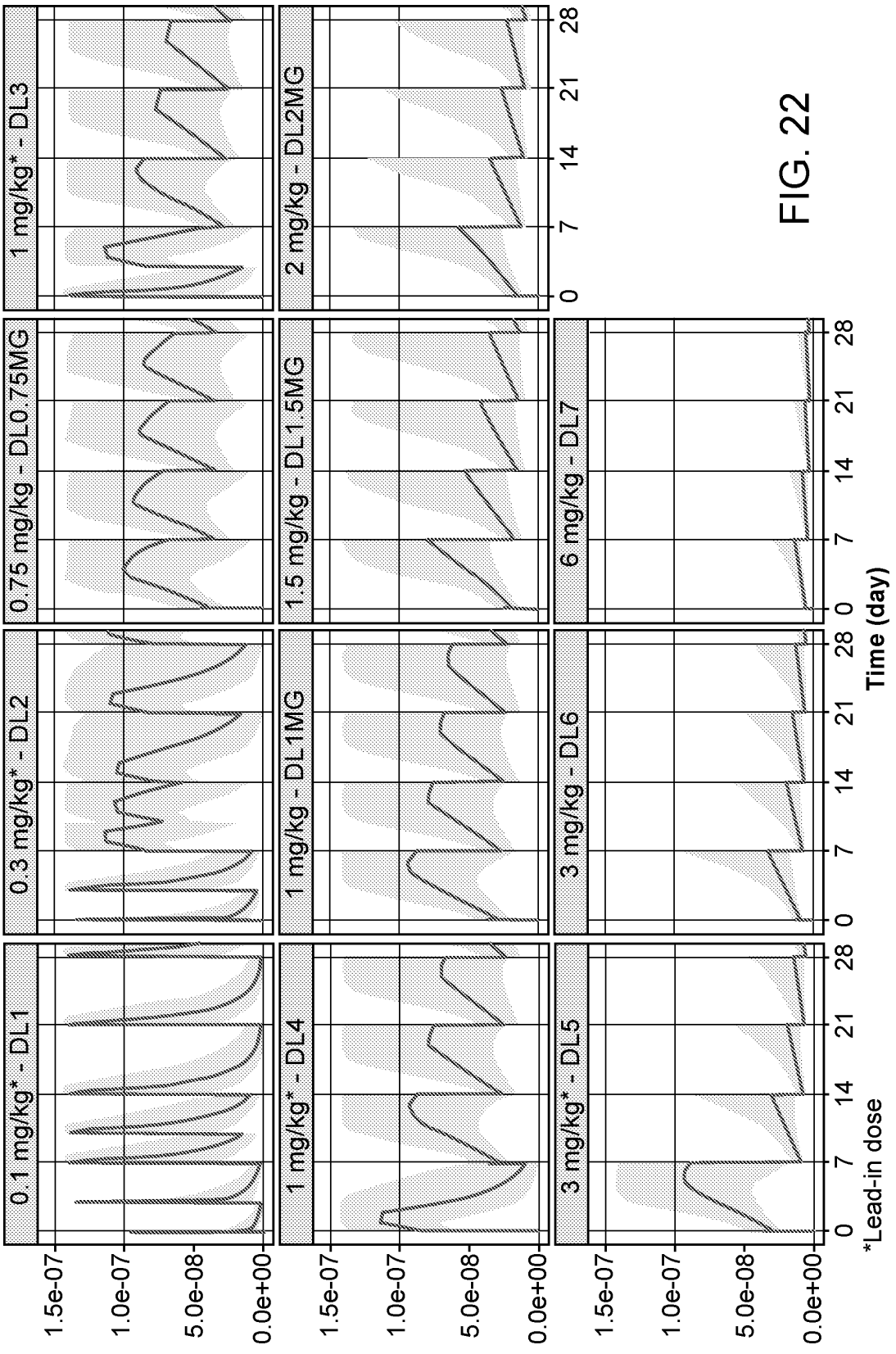

0.1 mg/kg* - DL1
0.3 mg/kg* - DL2
0.75 mg/kg - DL0.75MG
1 mg/kg* - DL3
1 mg/kg* - DL4
1 mg/kg - DL1MG
1.5 mg/kg - DL1.5MG
2 mg/kg - DL2MG
3 mg/kg* - DL5
3 mg/kg - DL6
6 mg/kg - DL7
Synapse concentration (nM)
1.5e-07
1.0e-07
5.0e-08
0.0e+00
0
7
14
21
28
Time (day)
*Lead-in dose

FIG. 22

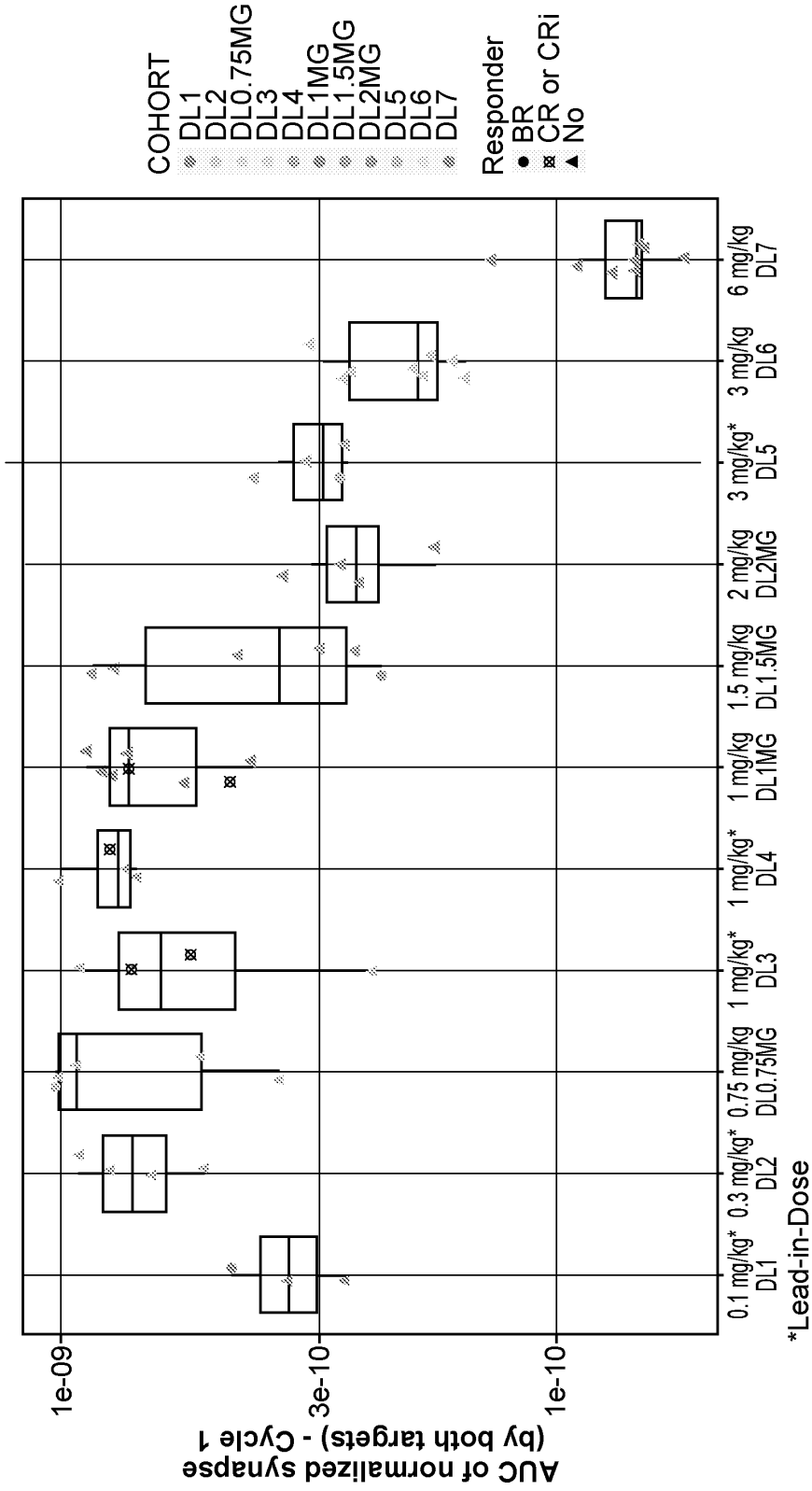

COHORT
DL1
DL2
DL0.75MG
DL3
DL4
DL1MG
DL1.5MG
DL2MG
DL5
DL6
DL7
Responder
BR
CR or CRi
No
AUC of normalized synapse
(by both targets) - Cycle 1
1e-09
3e-10
1e-10
0.1 mg/kg* DL1
0.3 mg/kg* DL2
0.75 mg/kg DL0.75MG
1 mg/kg* DL3
1 mg/kg* DL4
1 mg/kg DL1MG
1.5 mg/kg DL1.5MG
2 mg/kg DL2MG
3 mg/kg* DL5
3 mg/kg DL6
6 mg/kg DL7
*Lead-in-Dose

FIG. 23

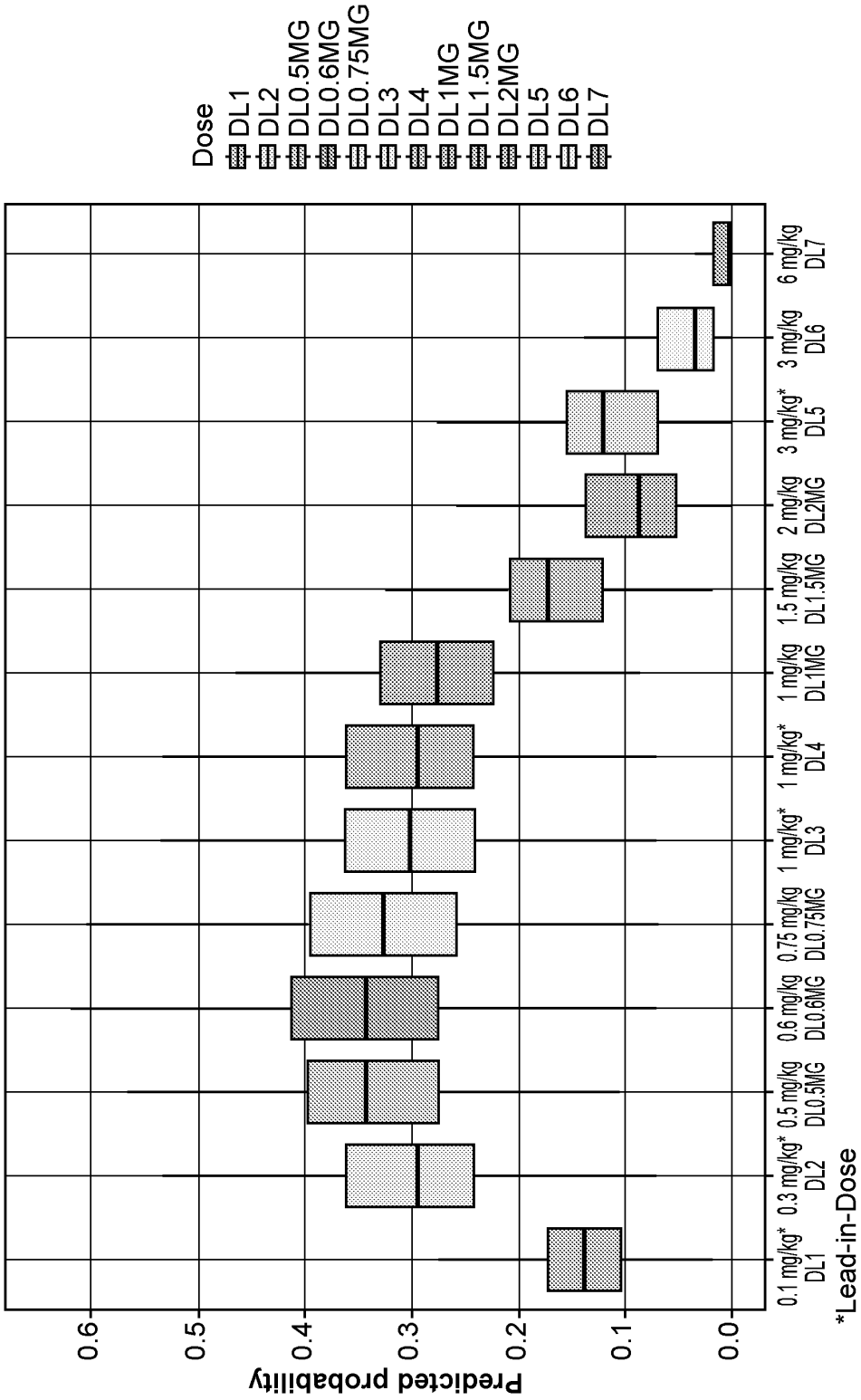

Dose
DL1
DL2
DL0.5MG
DL0.6MG
DL0.75MG
DL3
DL4
DL1MG
DL1.5MG
DL2MG
DL5
DL6
DL7
Predicted probability
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.1 mg/kg* DL1
0.3 mg/kg* DL2
0.5 mg/kg DL0.5MG
0.6 mg/kg DL0.6MG
0.75 mg/kg DL0.75MG
1 mg/kg* DL3
1 mg/kg* DL4
1 mg/kg DL1MG
1.5 mg/kg DL1.5MG
2 mg/kg DL2MG
3 mg/kg* DL5
3 mg/kg DL6
6 mg/kg DL7
*Lead-in-Dose

FIG. 24

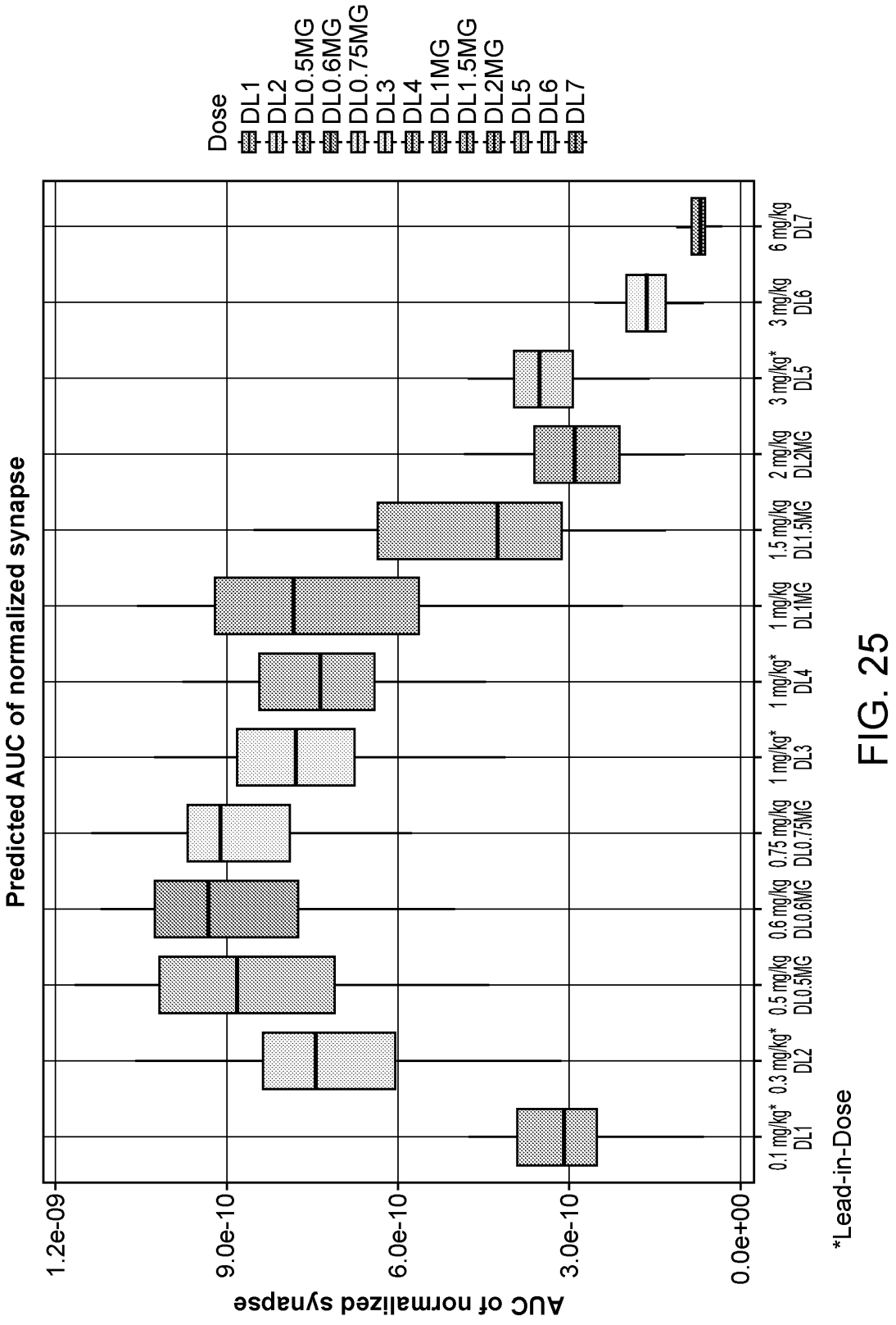

Predicted AUC of normalized synapse
AUC of normalized synapse
1.2e-09
9.0e-10
6.0e-10
3.0e-10
0.0e+00
Dose
DL1
DL2
DL0.5MG
DL0.6MG
DL0.75MG
DL3
DL4
DL1MG
DL1.5MG
DL2MG
DL5
DL6
DL7
0.1 mg/kg* DL1
0.3 mg/kg* DL2
0.5 mg/kg DL0.5MG
0.6 mg/kg DL0.6MG
0.75 mg/kg DL0.75MG
1 mg/kg* DL3
1 mg/kg* DL4
1 mg/kg DL1MG
1.5 mg/kg DL1.5MG
2 mg/kg DL2MG
3 mg/kg* DL5
3 mg/kg DL6
6 mg/kg DL7
*Lead-in-Dose

FIG. 25