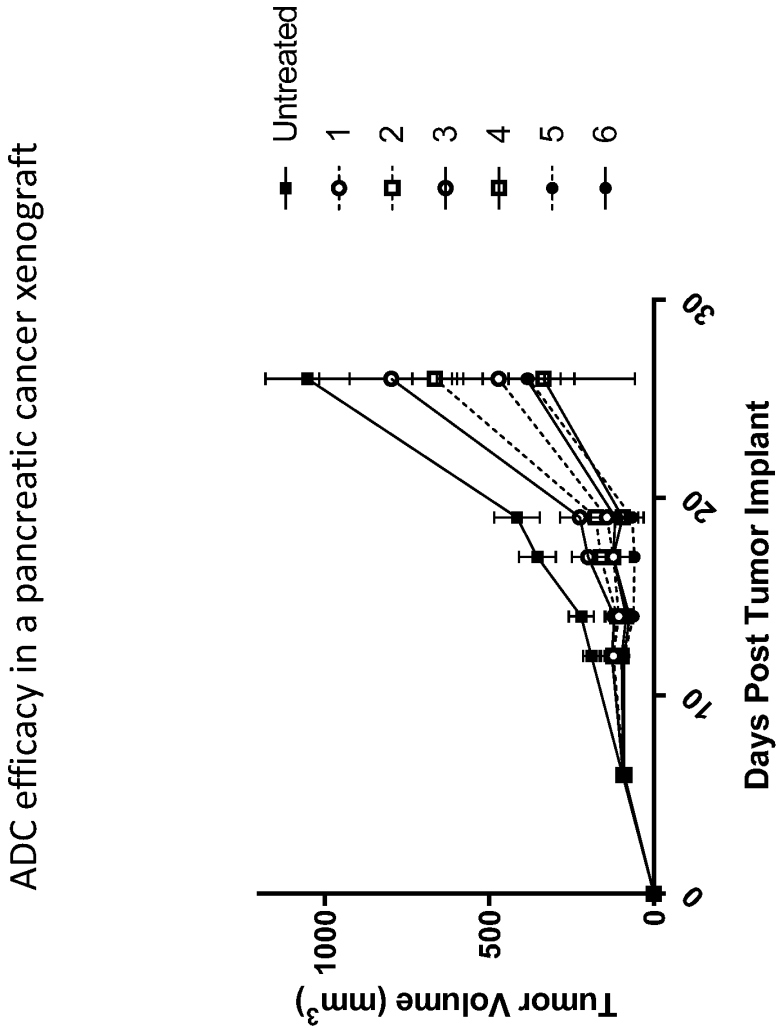

ADC efficacy in a pancreatic cancer xenograft
Untreated
1
2
3
4
5
6
Tumor Volume (mm³)
0
500
1000
0
10
20
30
Days Post Tumor Implant

FIG. 1A

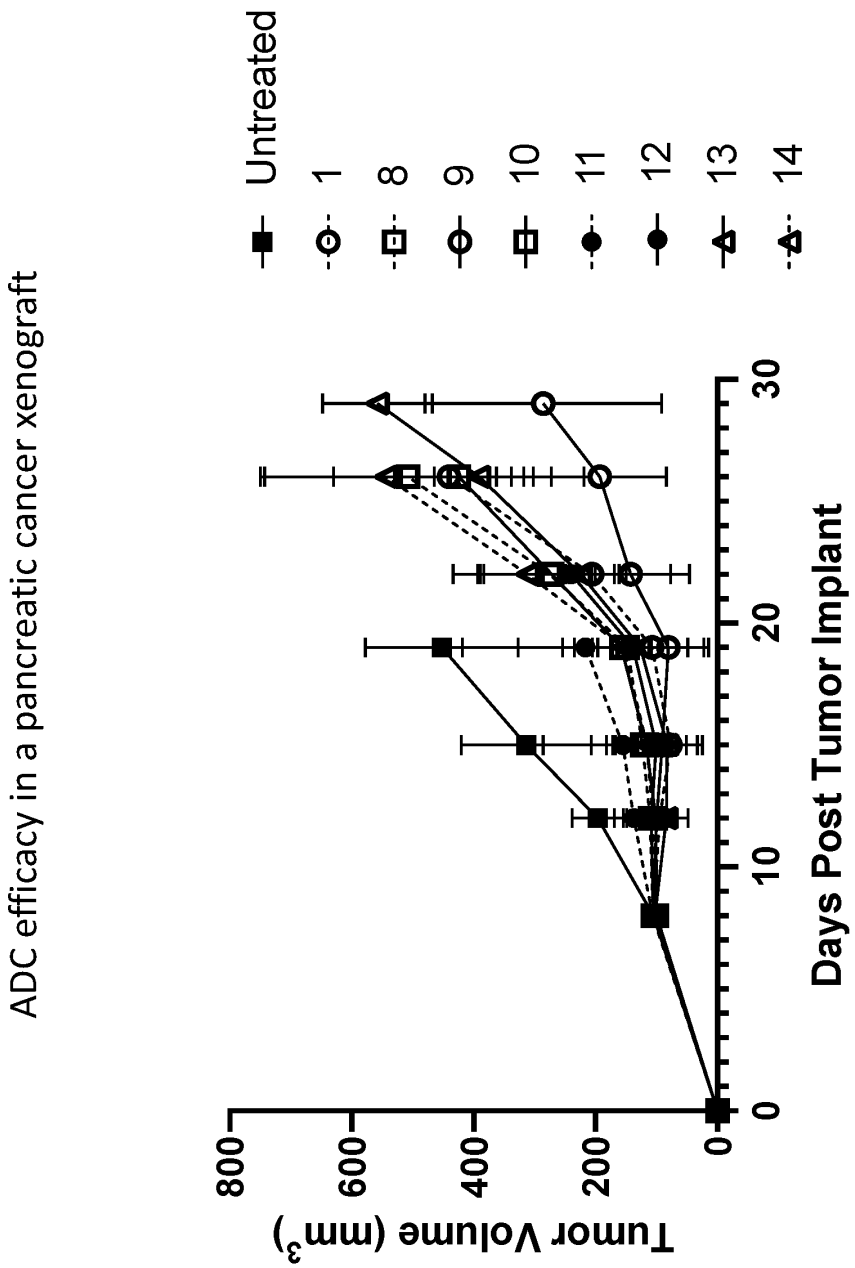

ADC efficacy in a pancreatic cancer xenograft
Untreated
1
8
9
10
11
12
13
14
Tumor Volume (mm3)
0
200
400
600
800
0
10
20
30
Days Post Tumor Implant

FIG. 1B

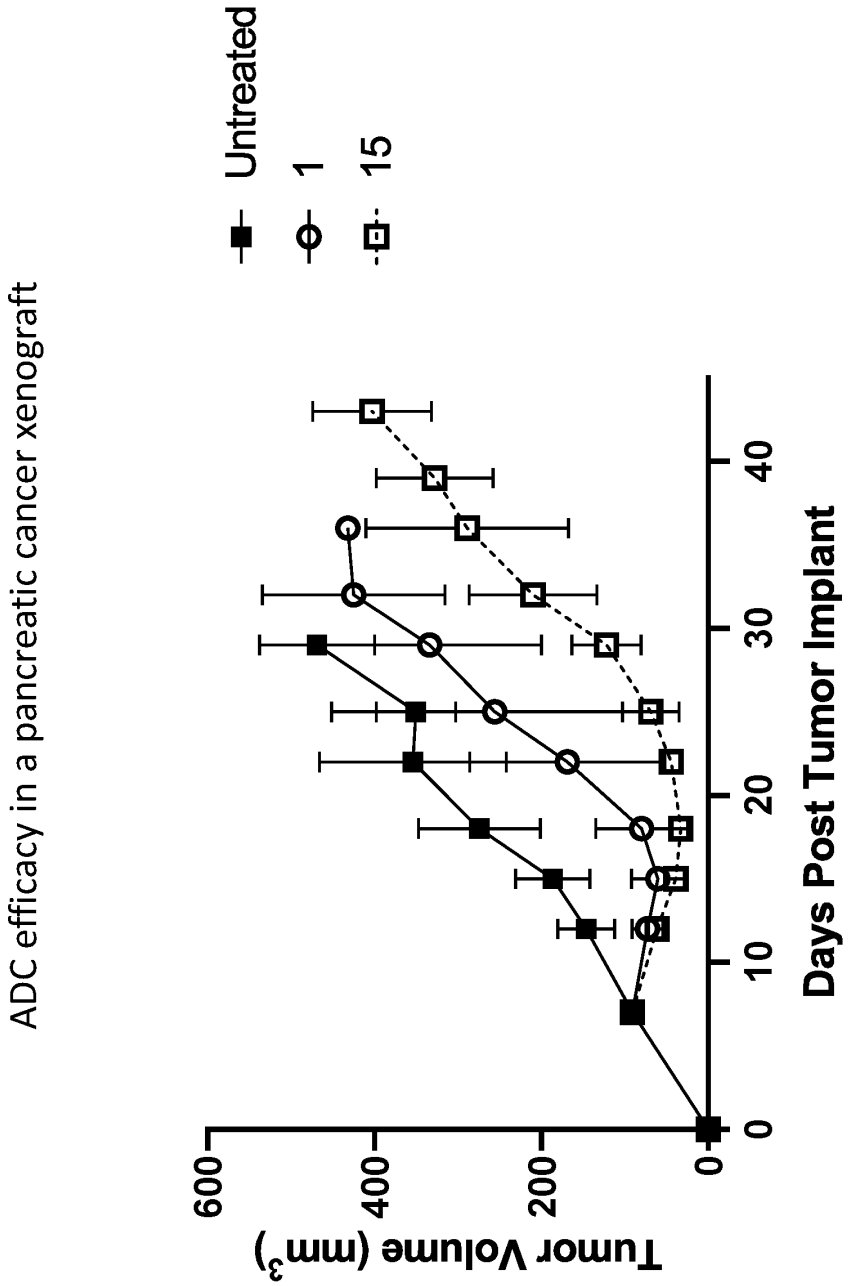

ADC efficacy in a pancreatic cancer xenograft
Untreated
1
15
Tumor Volume (mm³)
600
400
200
0
0
10
20
30
40
Days Post Tumor Implant

FIG. 1C

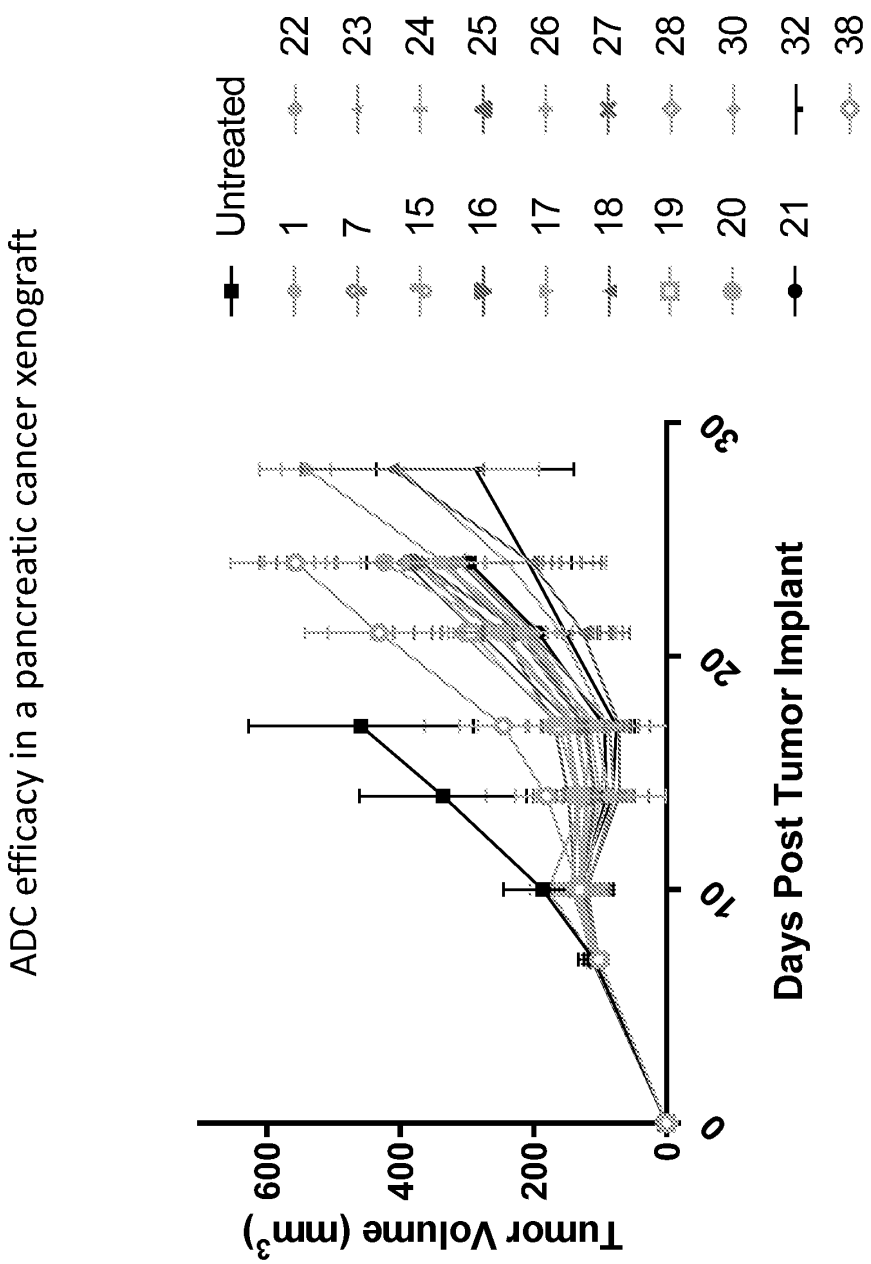

ADC efficacy in a pancreatic cancer xenograft
Untreated
1
7
15
16
17
18
19
20
21
22
23
24
25
26
27
28
30
32
38
Tumor Volume (mm3)
0
200
400
600
0
10
20
30
Days Post Tumor Implant

FIG. 1D

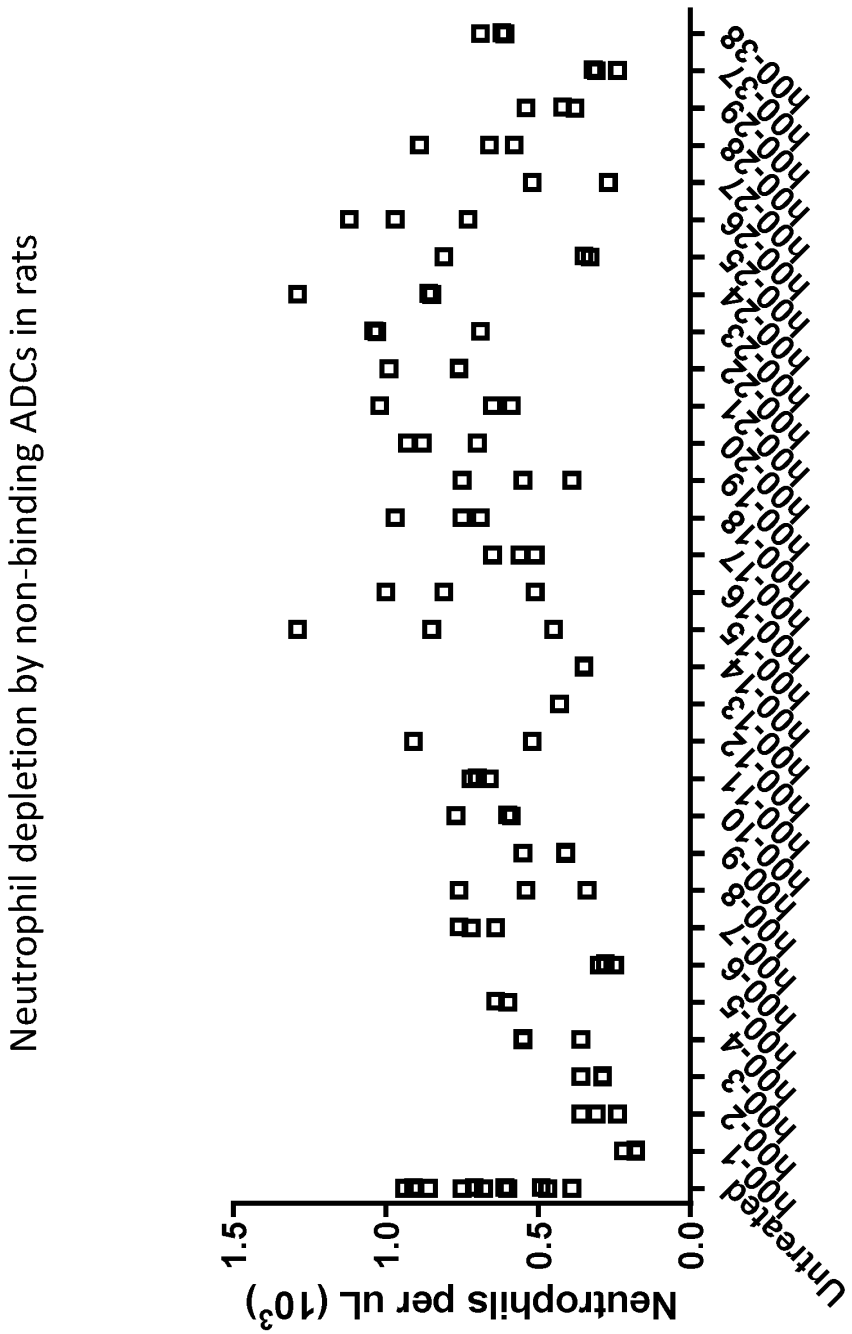

Neutrophil depletion by non-binding ADCs in rats
Neutrophils per uL (10^3)
1.5
1.0
0.5
0.0
Untreated
hOO-1
hOO-2
hOO-3
hOO-4
hOO-5
hOO-6
hOO-7
hOO-8
hOO-9
hOO-10
hOO-11
hOO-12
hOO-13
hOO-14
hOO-15
hOO-16
hOO-17
hOO-18
hOO-19
hOO-20
hOO-21
hOO-22
hOO-23
hOO-24
hOO-25
hOO-26
hOO-27
hOO-28
hOO-29
hOO-37
hOO-38

FIG. 2A

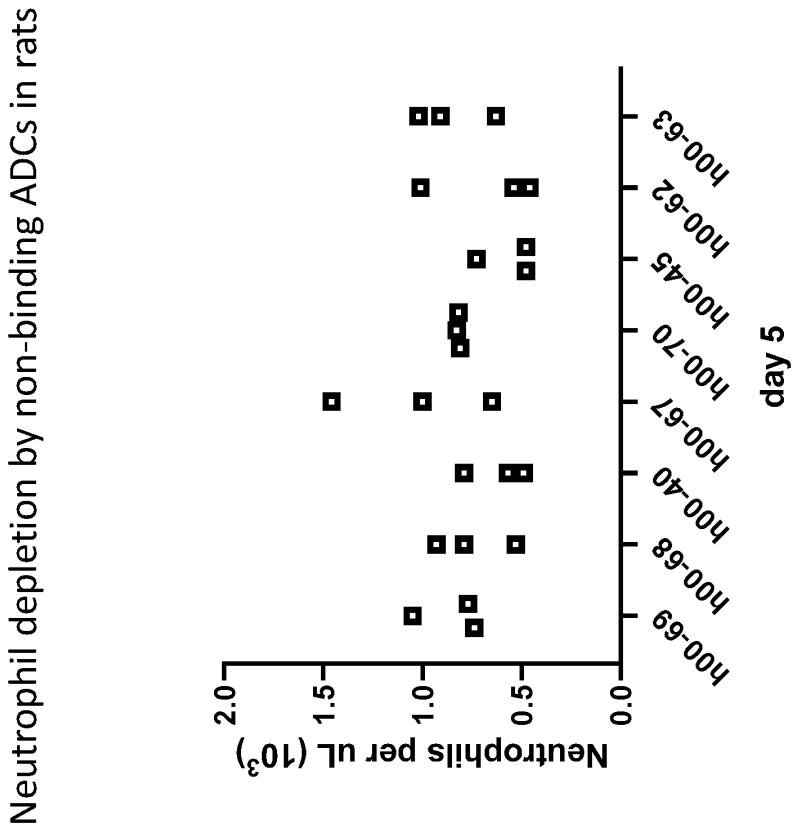

Neutrophil depletion by non-binding ADCs in rats
Neutrophils per uL (10^3)
2.0
1.5
1.0
0.5
0.0
h00-69
h00-68
h00-40
h00-67
h00-70
h00-45
h00-62
h00-63
day 5

FIG. 2B

Neutrophil depletion by non-targeted tripeptide ADCs after administration in rats at highest tolerated dose

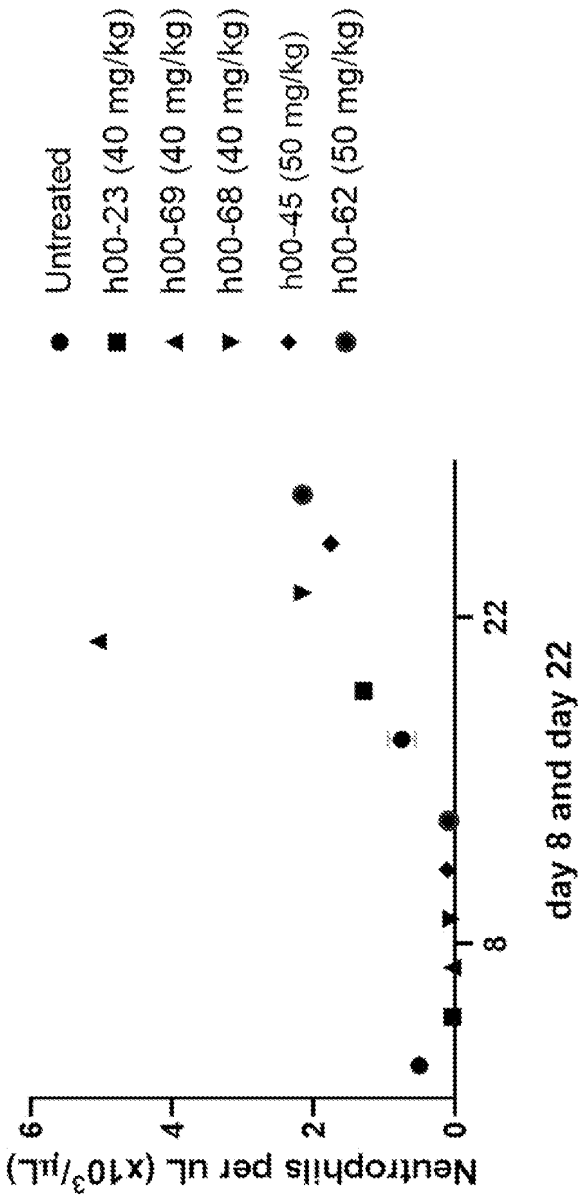


FIG. 2C

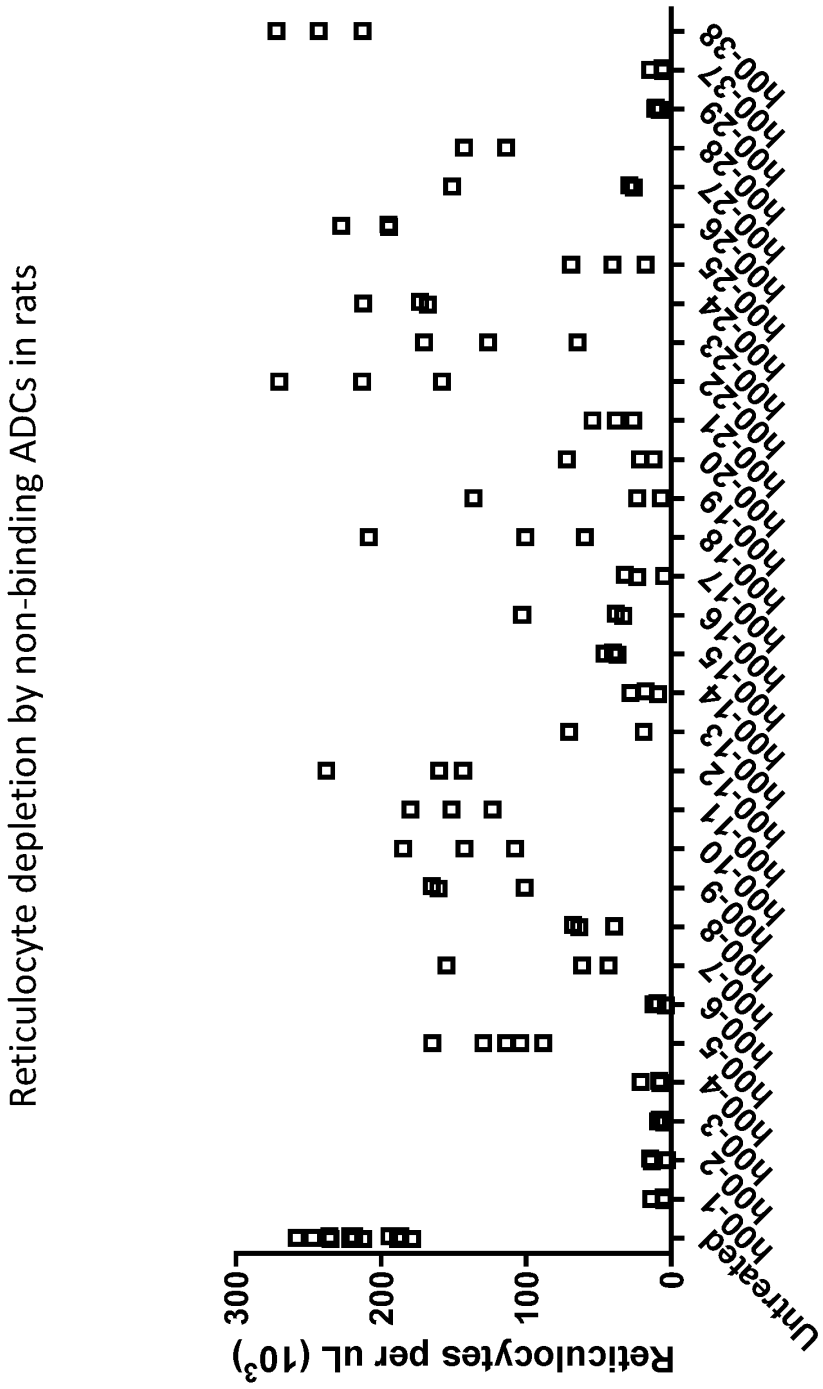

Reticulocyte depletion by non-binding ADCs in rats
Reticulocytes per uL (10^3)
300
200
100
0
Untreated
hOO-1
hOO-2
hOO-3
hOO-4
hOO-5
hOO-6
hOO-7
hOO-8
hOO-9
hOO-10
hOO-11
hOO-12
hOO-13
hOO-14
hOO-15
hOO-16
hOO-17
hOO-18
hOO-19
hOO-20
hOO-21
hOO-22
hOO-23
hOO-24
hOO-25
hOO-26
hOO-27
hOO-28
hOO-29
hOO-37
hOO-38

FIG. 3A

Reticulocyte depletion by non-binding ADCs in rats

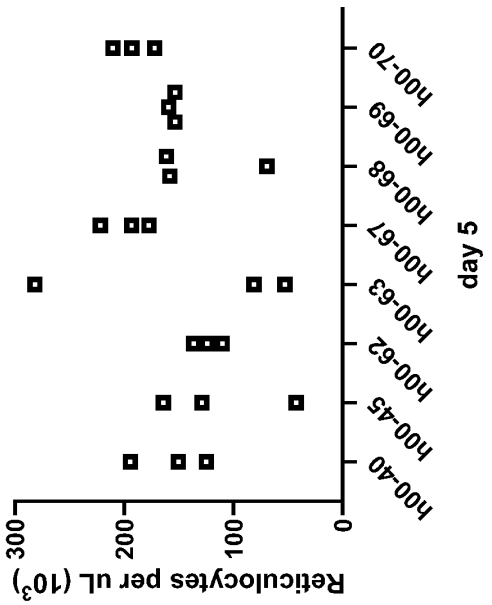


FIG. 3B

Reticulocyte depletion by non-targeted tripeptide ADCs after administration in rats at highest tolerated dose

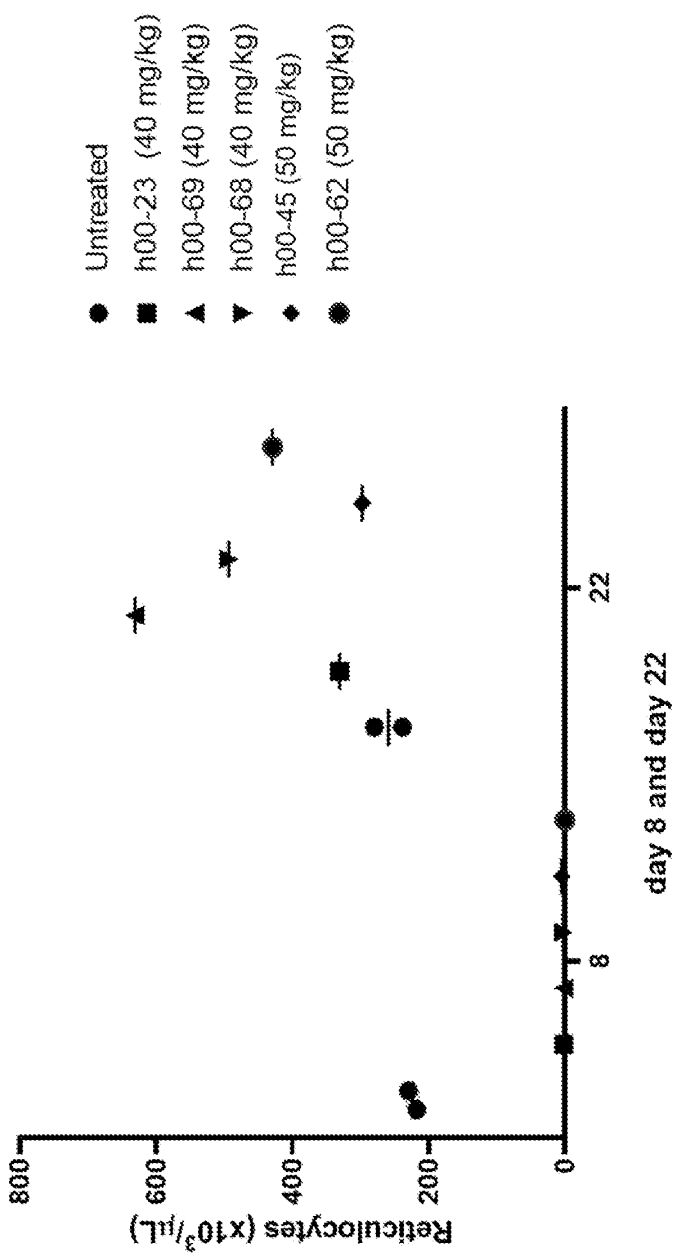


FIG. 3C

Bone marrow toxicity by non-binding ADCs in rats

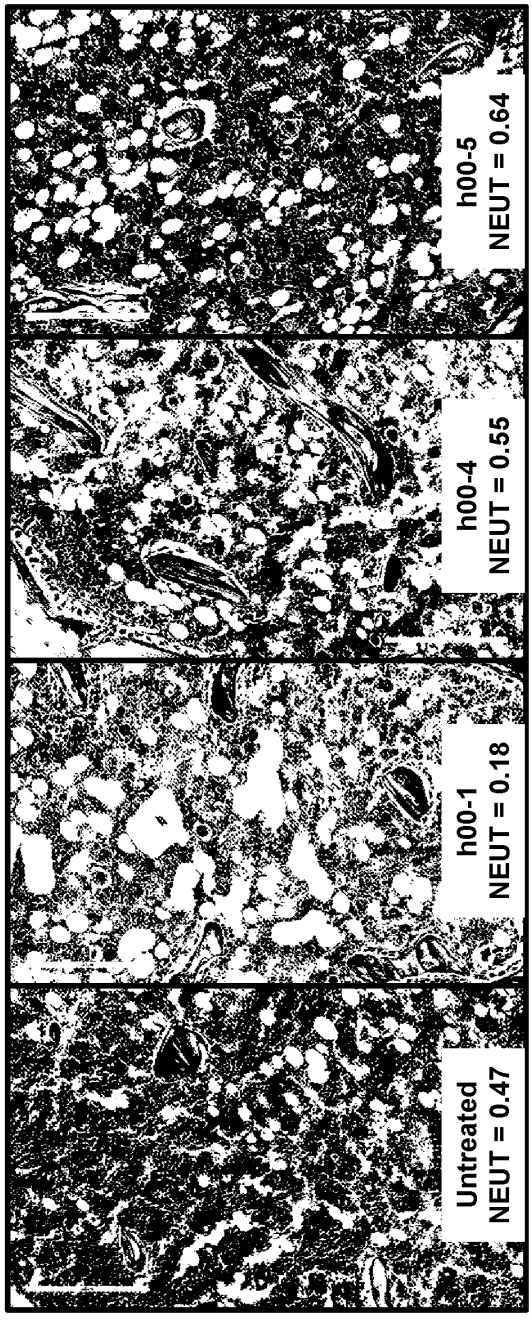


FIG. 4

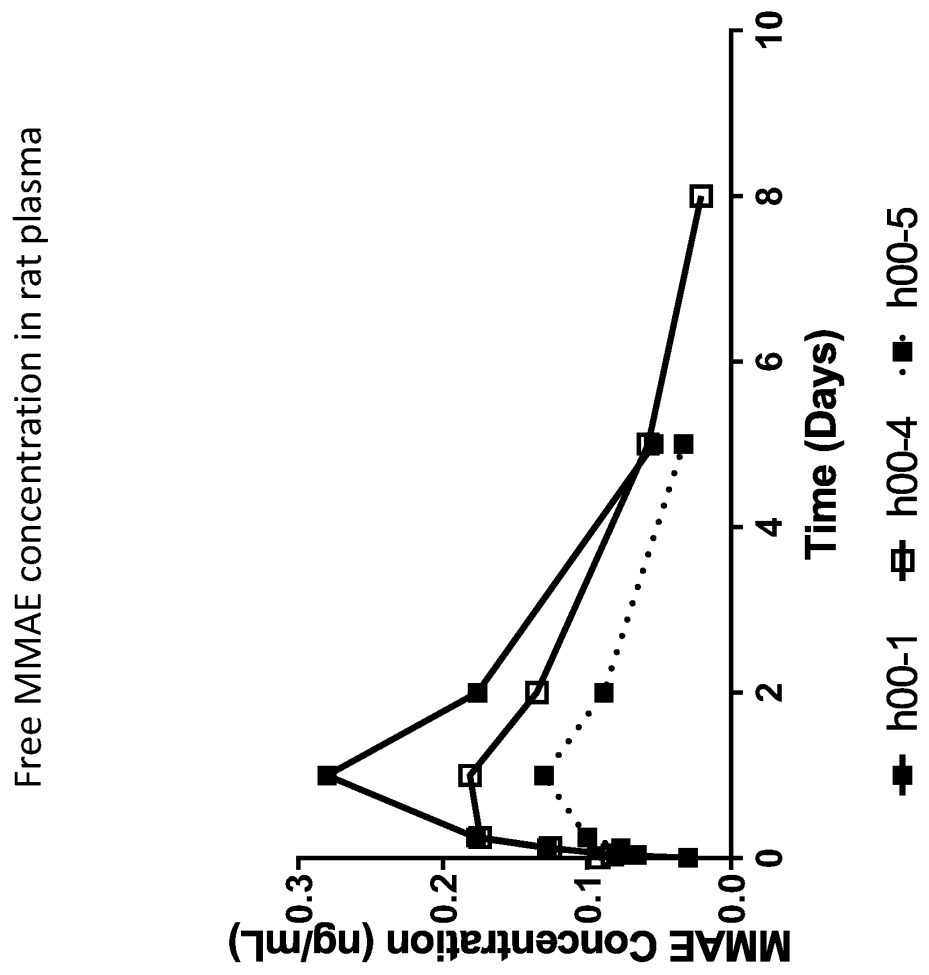

Free MMAE concentration in rat plasma
MMAE Concentration (ng/mL)
0.0
0.1
0.2
0.3
0
2
4
6
8
10
Time (Days)
h00-1
h00-4
h00-5

FIG. 5A

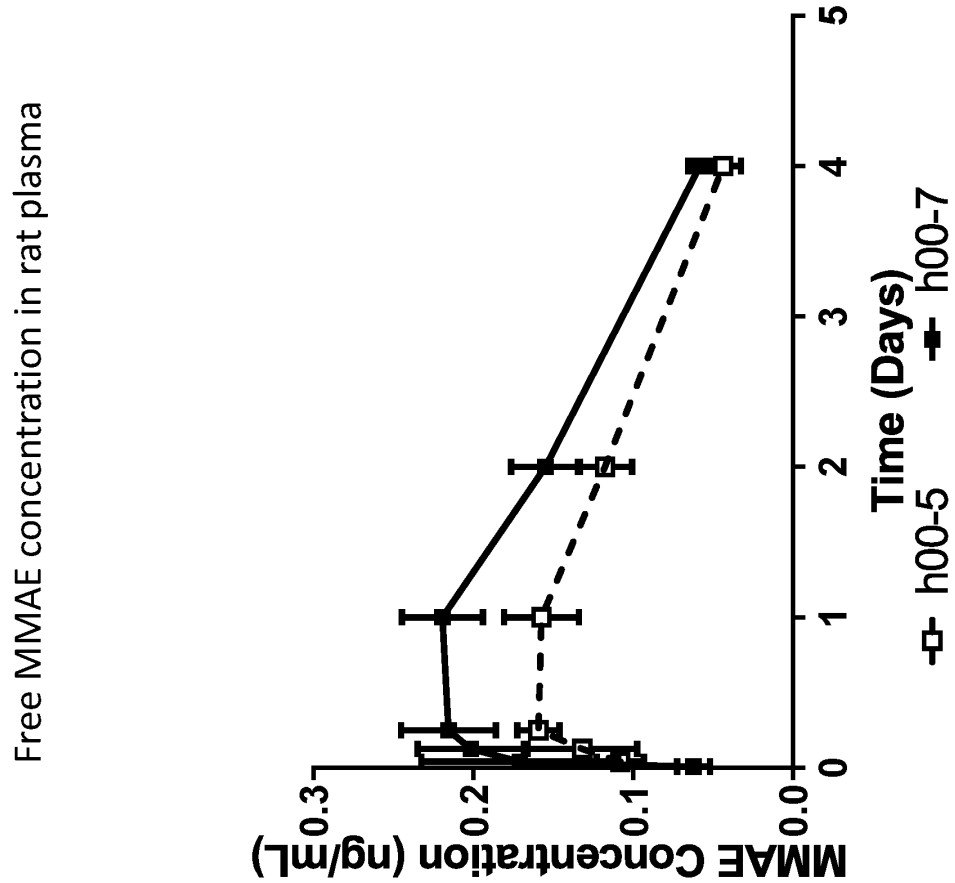

Free MMAE concentration in rat plasma
MMAE Concentration (ng/mL)
0.0
0.1
0.2
0.3
0
1
2
3
4
5
Time (Days)
h00-5
h00-7

FIG. 5B

Percent drug cleaved from heavy chain of non-targeted ADCs in vitro by neutrophil elastase

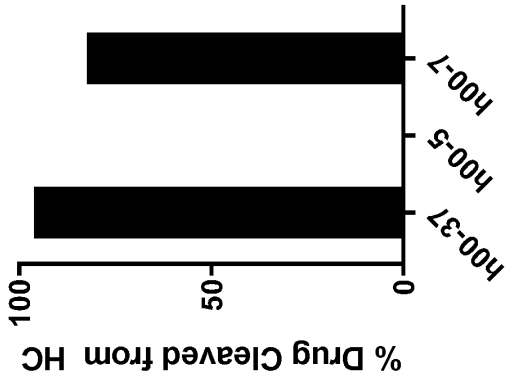


FIG. 6A

Percent drug cleaved from heavy chain of non-targeted ADCs in vitro by Cathepsin B

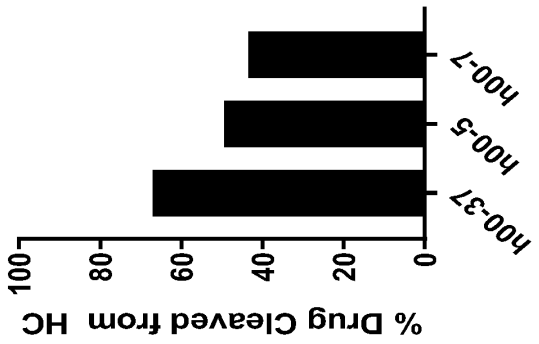


FIG. 6B

Percent drug cleaved from heavy chain of non-targeted ADCs in vitro by Cathepsin B

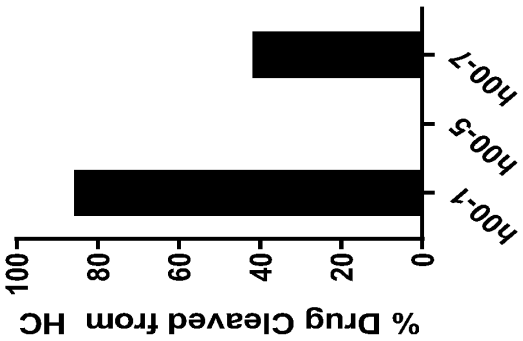


FIG. 6C

Free tumor MMAE from ADC efficacy in a pancreatic cancer xenograft

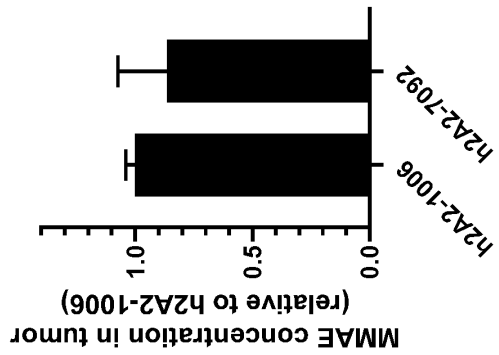


FIG. 6D

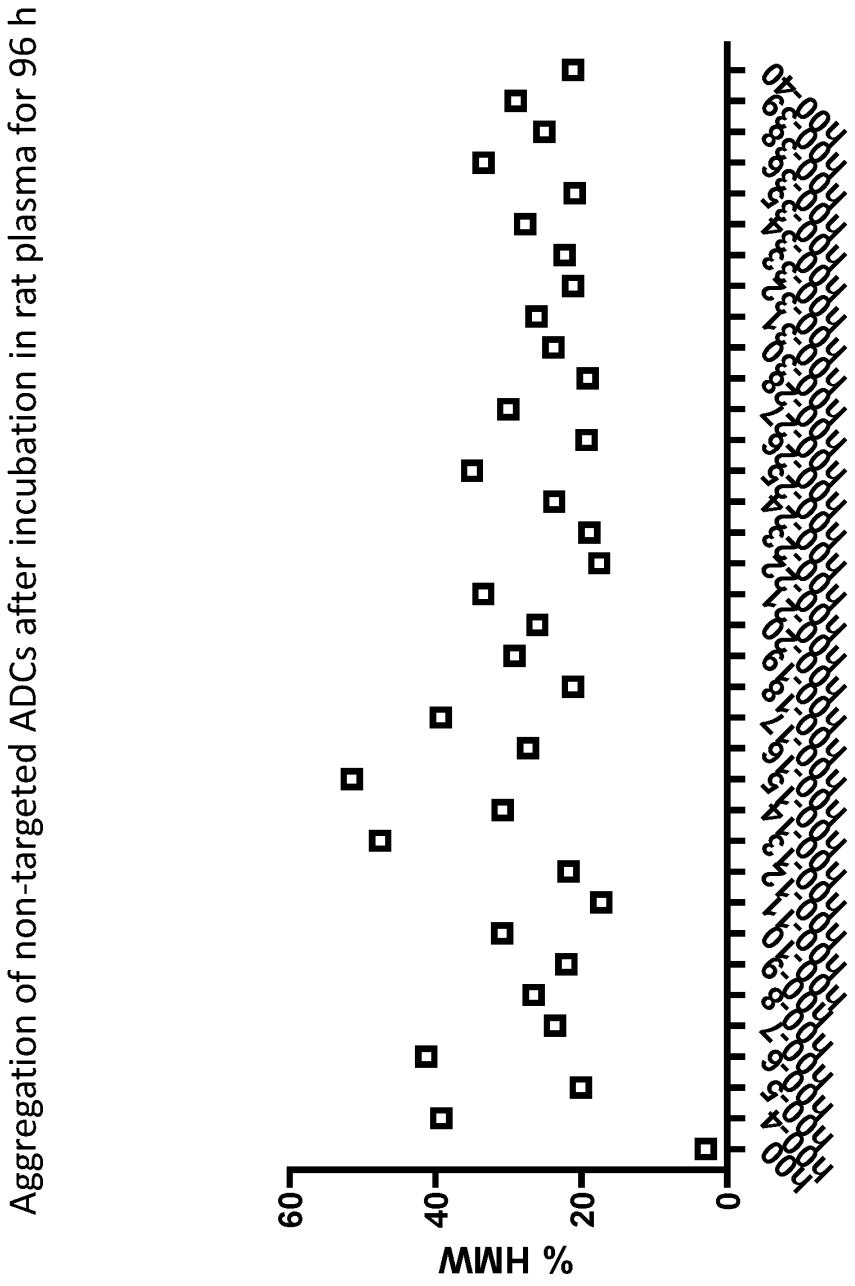

Aggregation of non-targeted ADCs after incubation in rat plasma for 96 h
% HMW
0
20
40
60

FIG. 7A

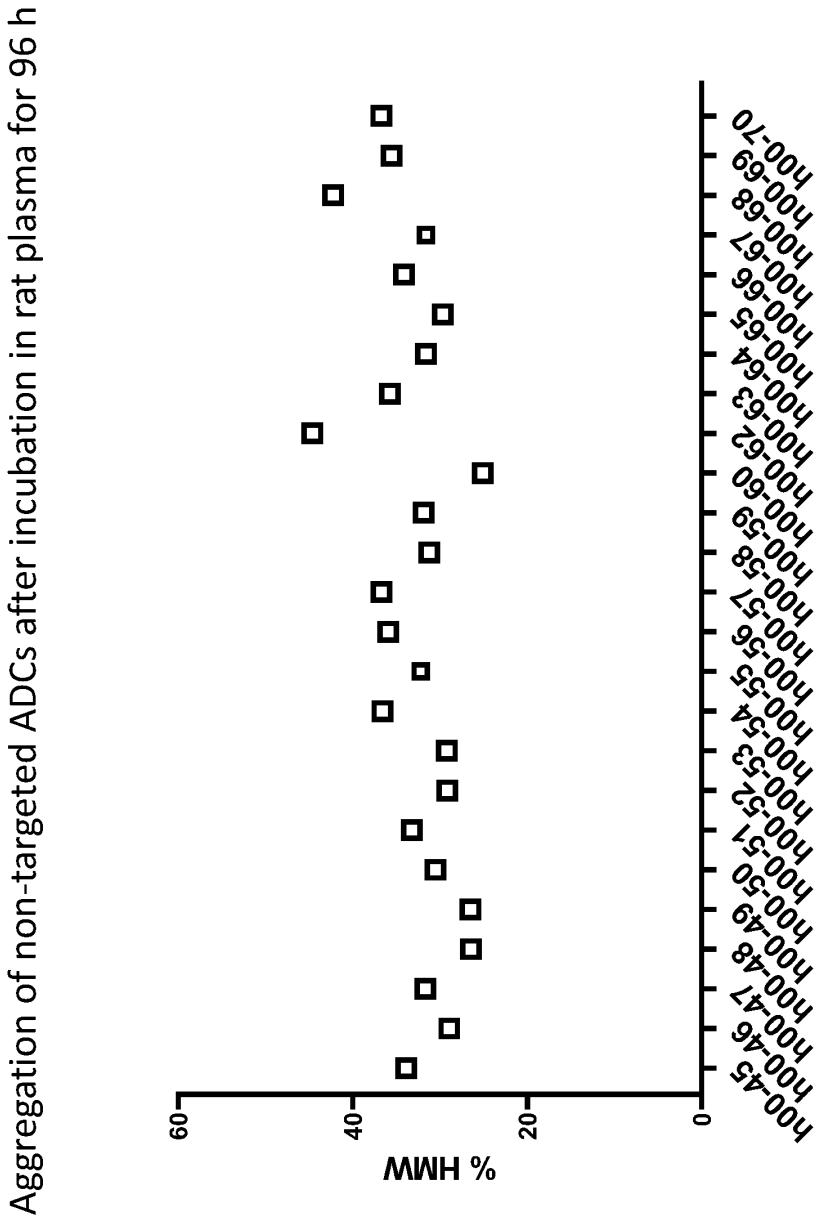

Aggregation of non-targeted ADCs after incubation in rat plasma for 96 h
% HMW
0
20
40
60
h00-45
h00-46
h00-47
h00-48
h00-49
h00-50
h00-51
h00-52
h00-53
h00-54
h00-55
h00-56
h00-57
h00-58
h00-59
h00-60
h00-62
h00-63
h00-64
h00-65
h00-66
h00-67
h00-68
h00-69
h00-70

FIG. 7B

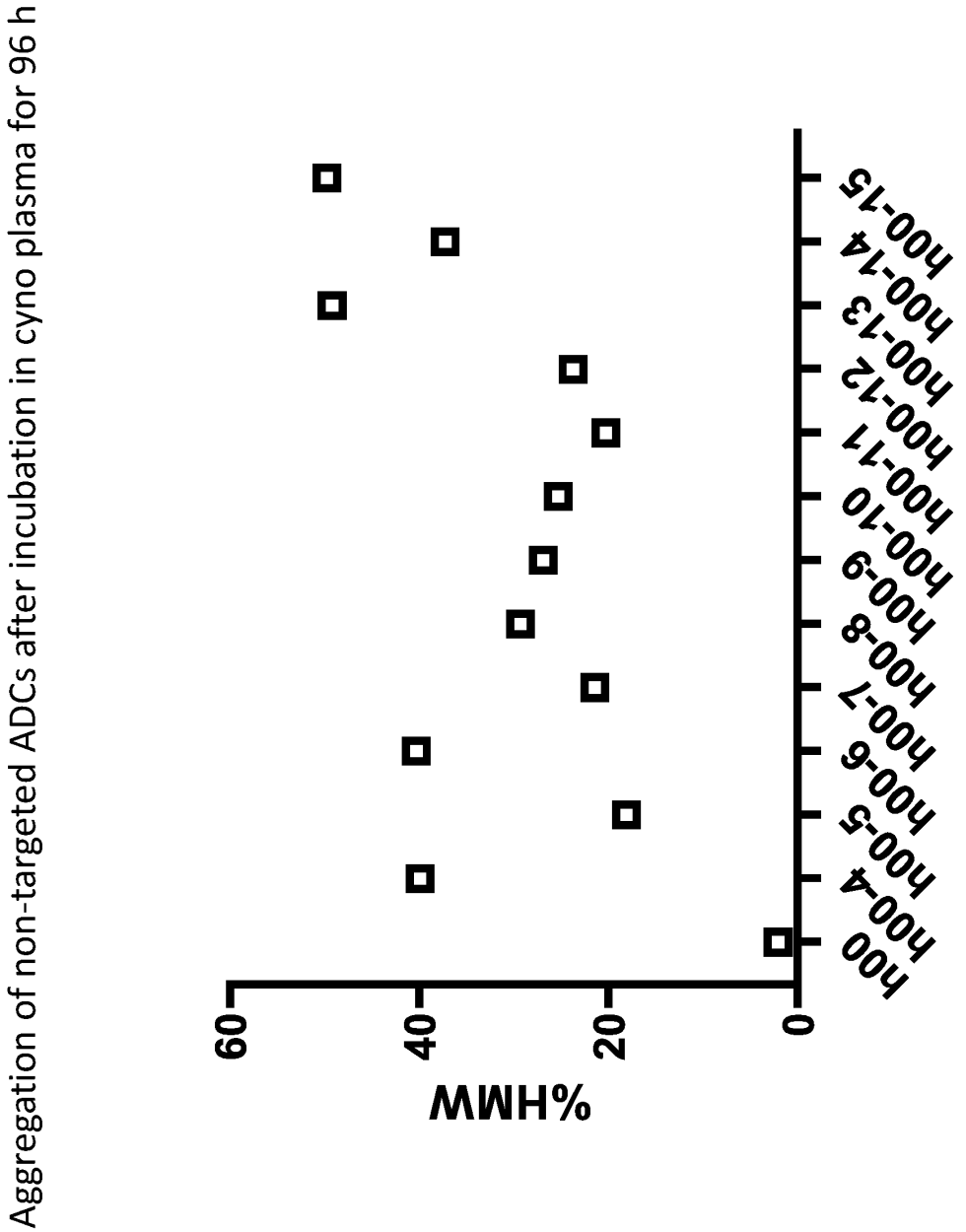

Aggregation of non-targeted ADCs after incubation in cyno plasma for 96 h
%HMW
0
20
40
60
hr
hr-4
hr-5
hr-6
hr-7
hr-8
hr-9
hr-10
hr-11
hr-12
hr-13
hr-14
hr-15

FIG. 8

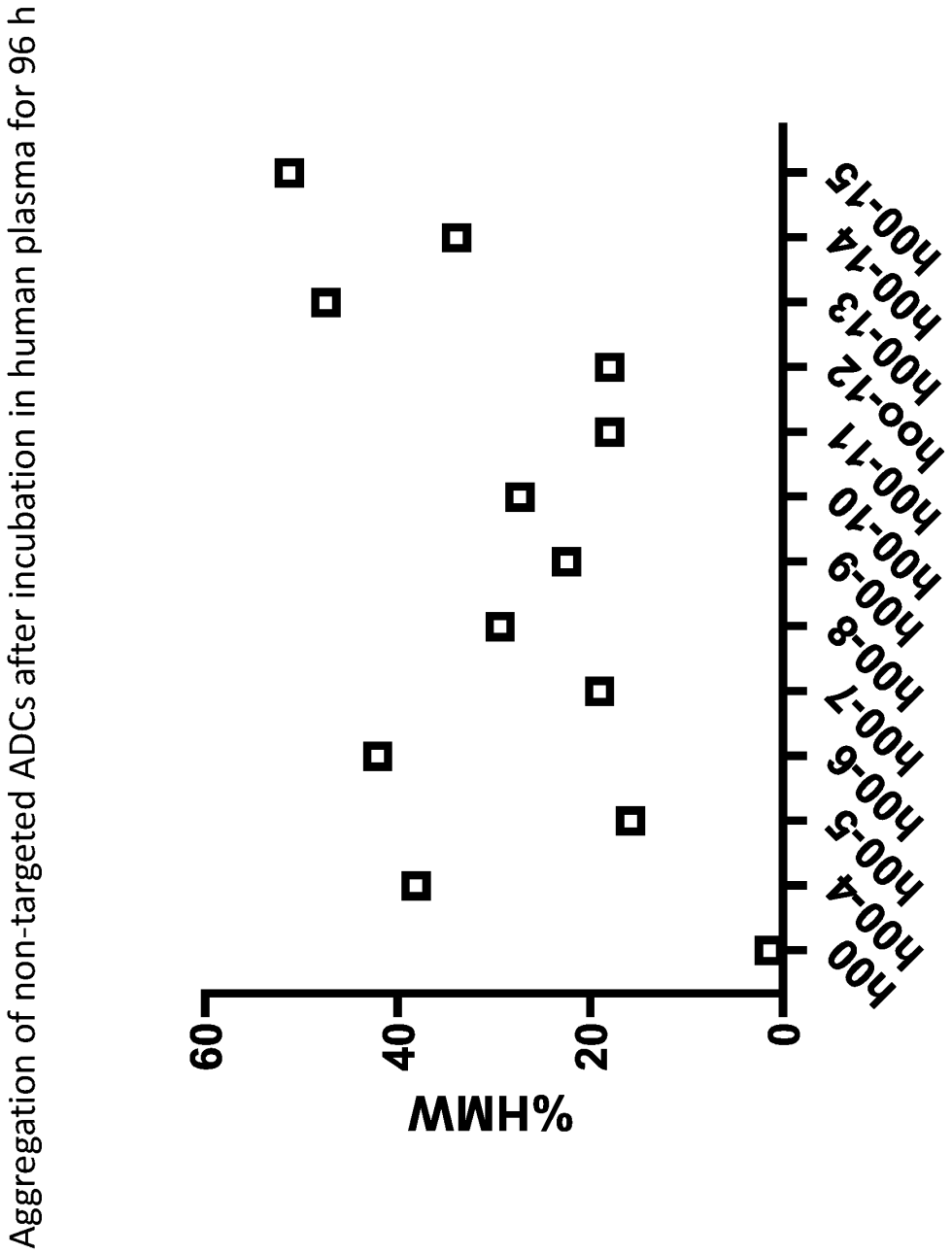

Aggregation of non-targeted ADCs after incubation in human plasma for 96 h
MWH%
60
40
20
0
h00
h00-4
h00-5
h00-6
h00-7
h00-8
h00-9
h00-10
h00-11
h00-12
h00-13
h00-14
h00-15

FIG. 9

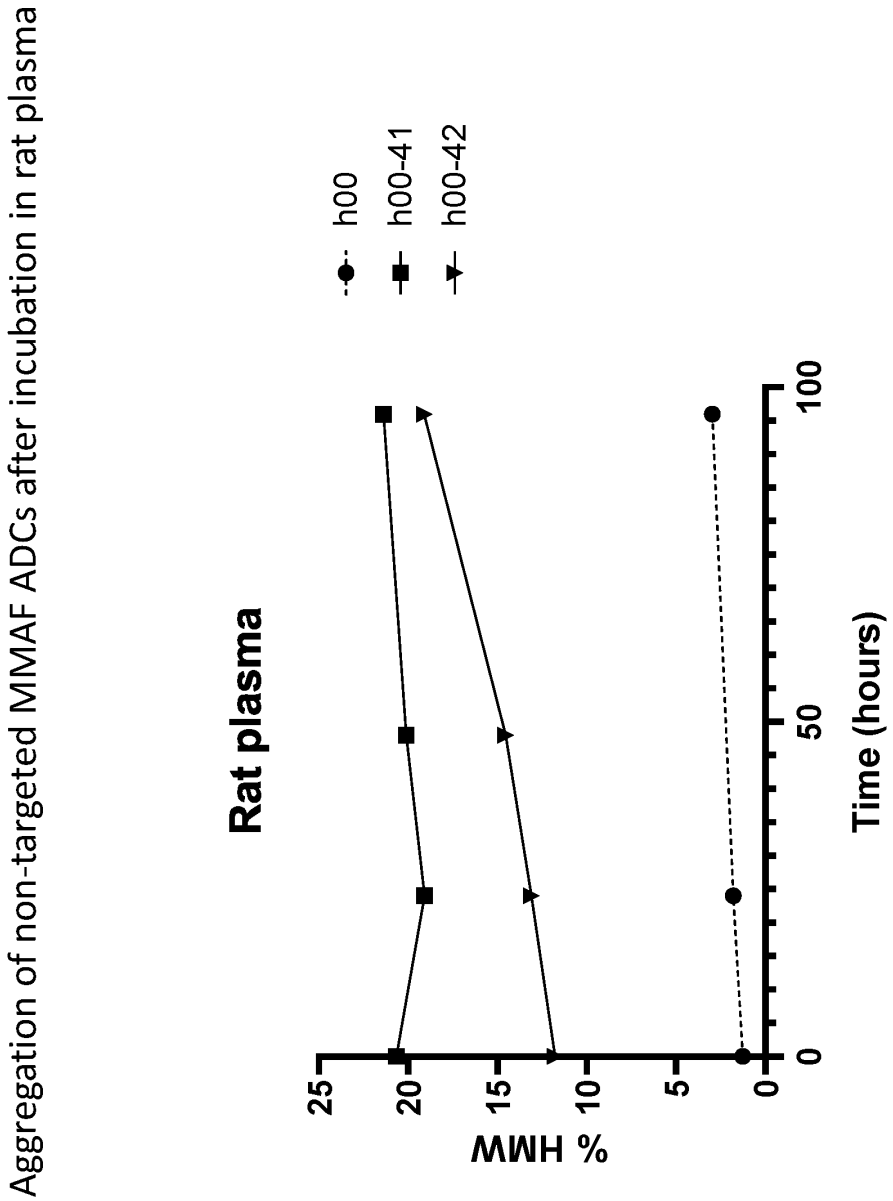

Aggregation of non-targeted MMAF ADCs after incubation in rat plasma
h00
h00-41
h00-42
Rat plasma
MWH %
25
20
15
10
5
0
0
50
100
Time (hours)

FIG. 10

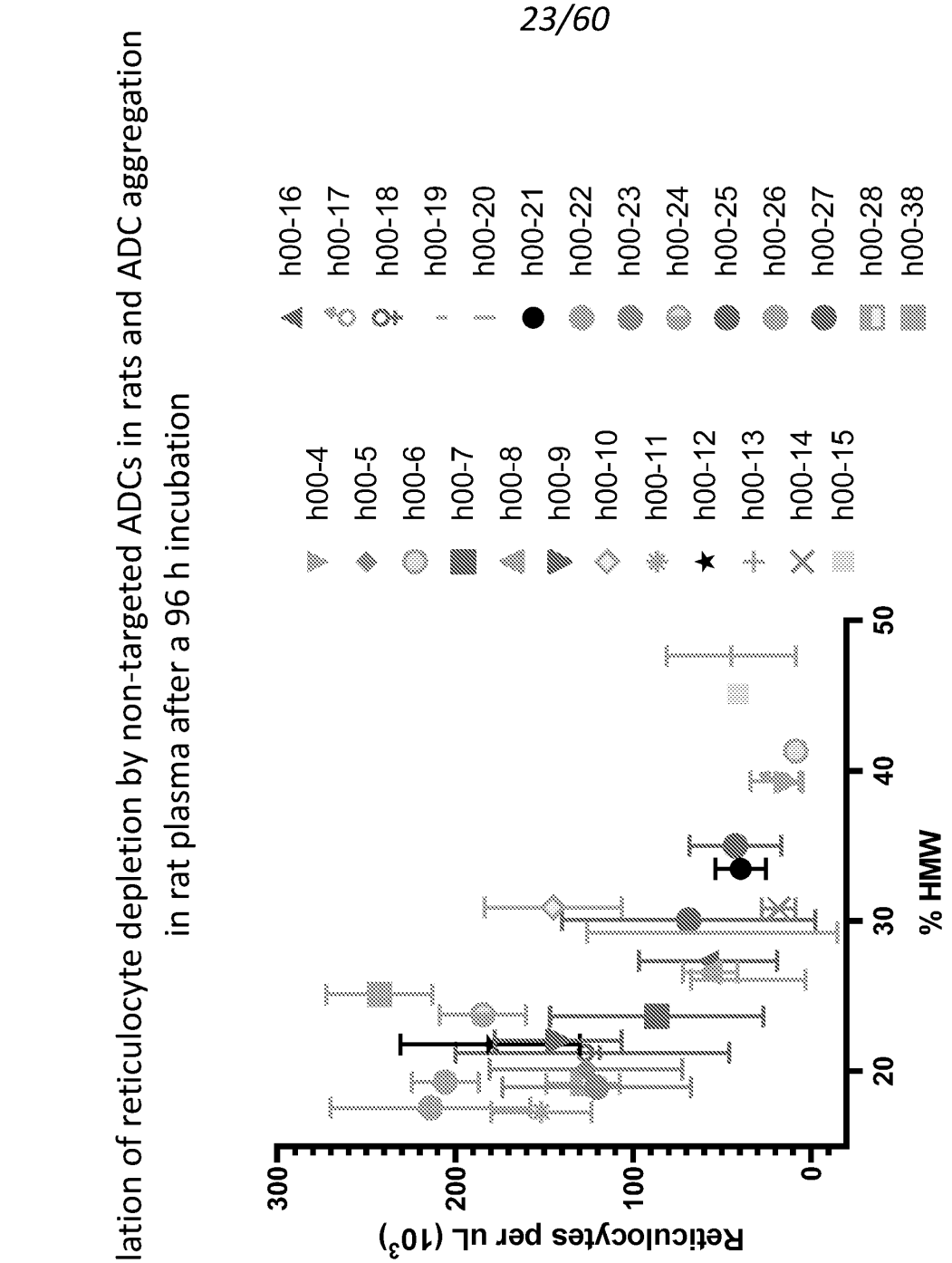

Relation of reticulocyte depletion by non-targeted ADCs in rats and ADC aggregation in rat plasma after a 96 h incubation
Reticulocytes per uL (10^3)
300
200
100
0
20
30
40
50
% HMW
h00-4
h00-5
h00-6
h00-7
h00-8
h00-9
h00-10
h00-11
h00-12
h00-13
h00-14
h00-15
h00-16
h00-17
h00-18
h00-19
h00-20
h00-21
h00-22
h00-23
h00-24
h00-25
h00-26
h00-27
h00-28
h00-38

FIG. 11

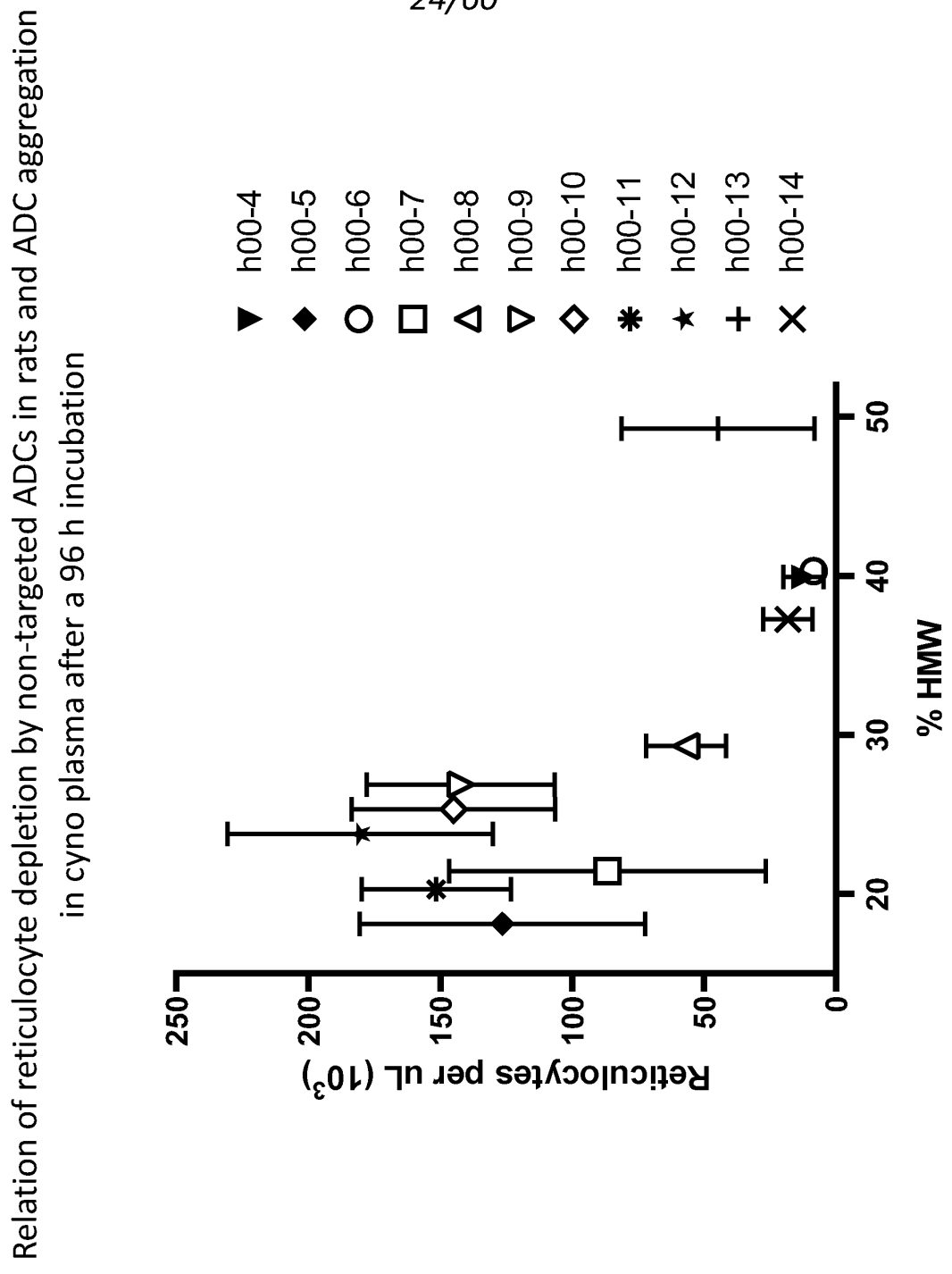

Relation of reticulocyte depletion by non-targeted ADCs in rats and ADC aggregation in cyno plasma after a 96 h incubation
h00-4
h00-5
h00-6
h00-7
h00-8
h00-9
h00-10
h00-11
h00-12
h00-13
h00-14
Reticulocytes per uL (10^3)
250
200
150
100
50
0
20
30
40
50
% HMW

FIG. 12

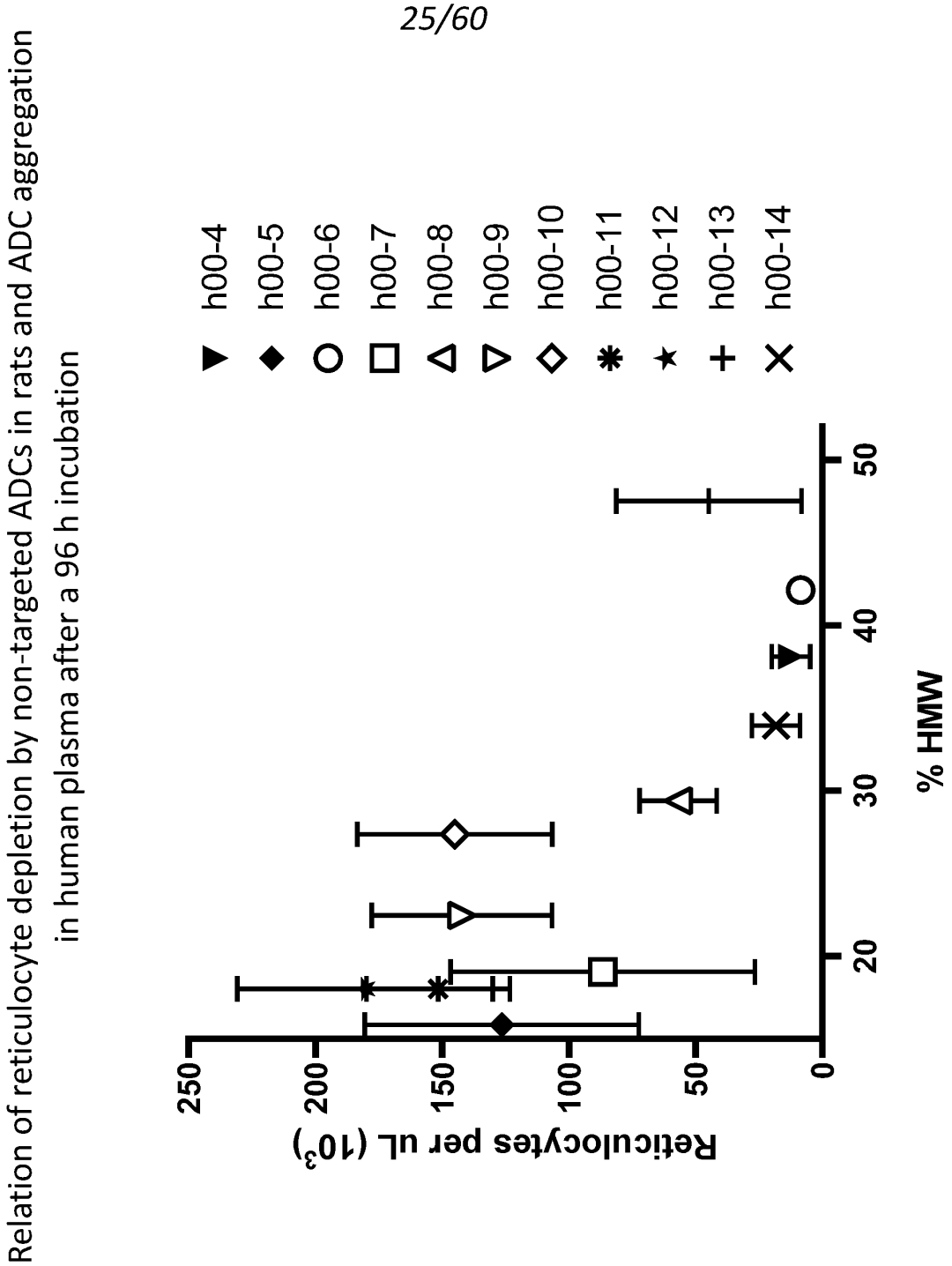

Relation of reticulocyte depletion by non-targeted ADCs in rats and ADC aggregation in human plasma after a 96 h incubation
h00-4
h00-5
h00-6
h00-7
h00-8
h00-9
h00-10
h00-11
h00-12
h00-13
h00-14
Reticulocytes per uL (10^3)
250
200
150
100
50
0
20
30
40
50
% HMW

FIG. 13

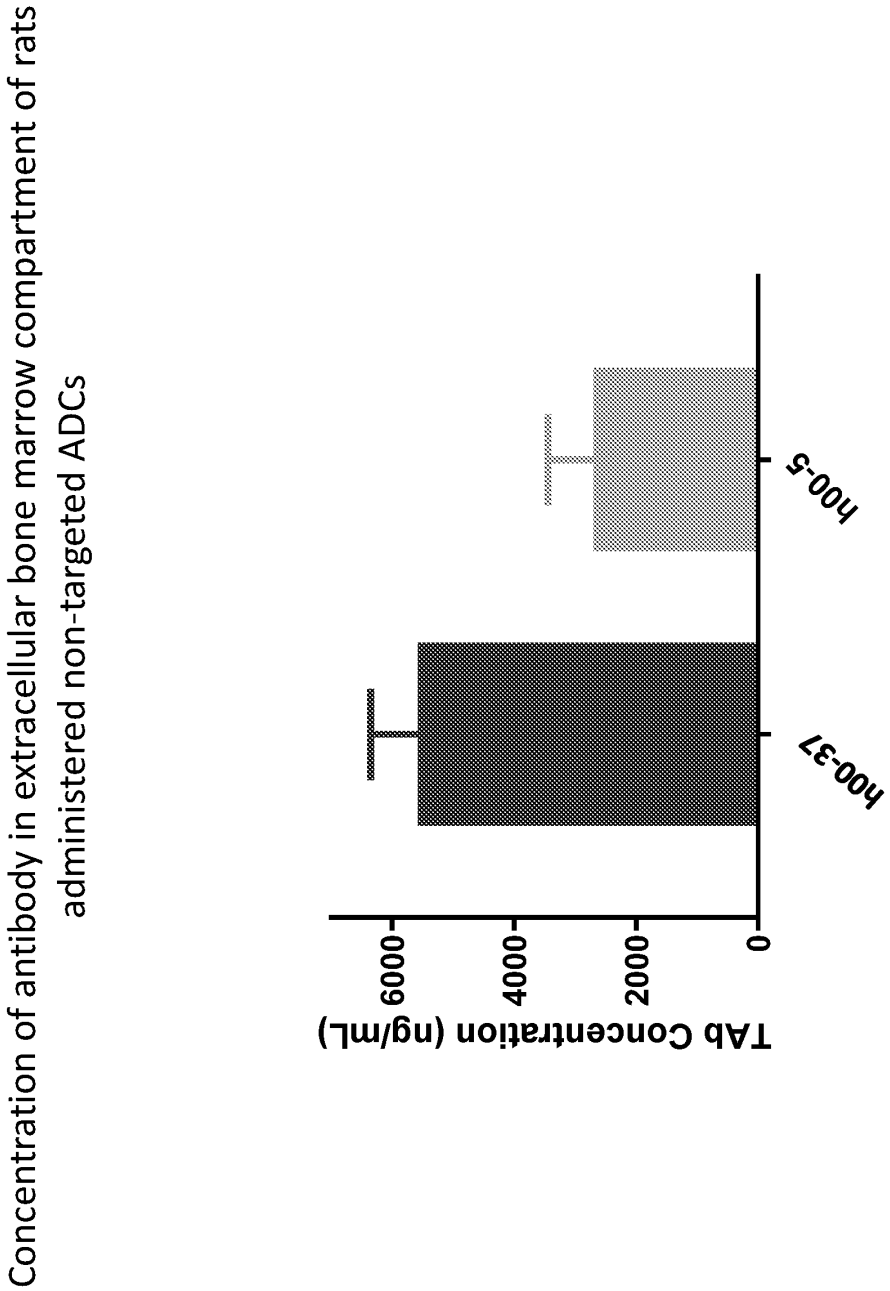

Concentration of antibody in extracellular bone marrow compartment of rats administered non-targeted ADCs
TAb Concentration (ng/mL)
0
2000
4000
6000
h00-37
h00-5

FIG. 14

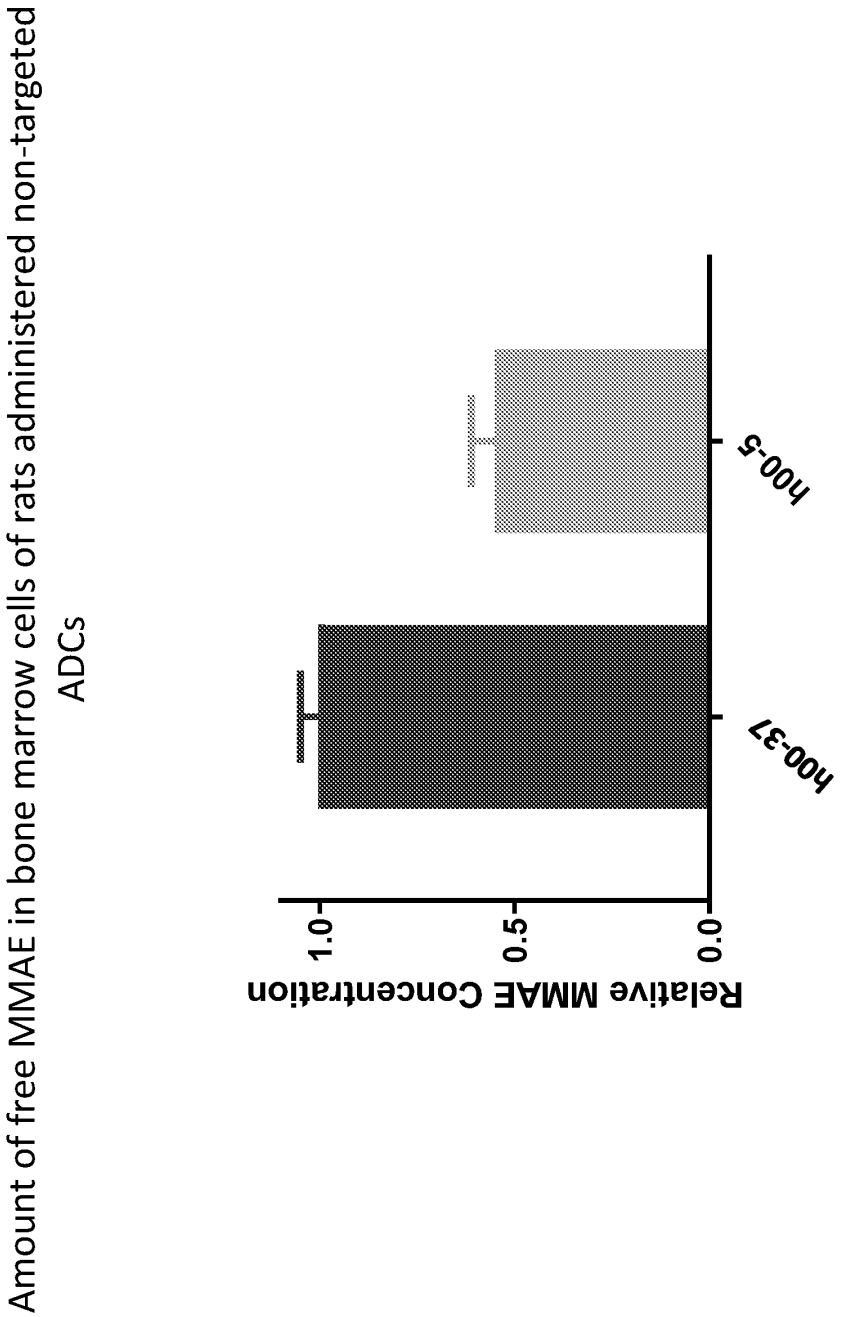

Amount of free MMAE in bone marrow cells of rats administered non-targeted ADCs
Relative MMAE Concentration
0.0
0.5
1.0
h00-37
h00-5

FIG. 15

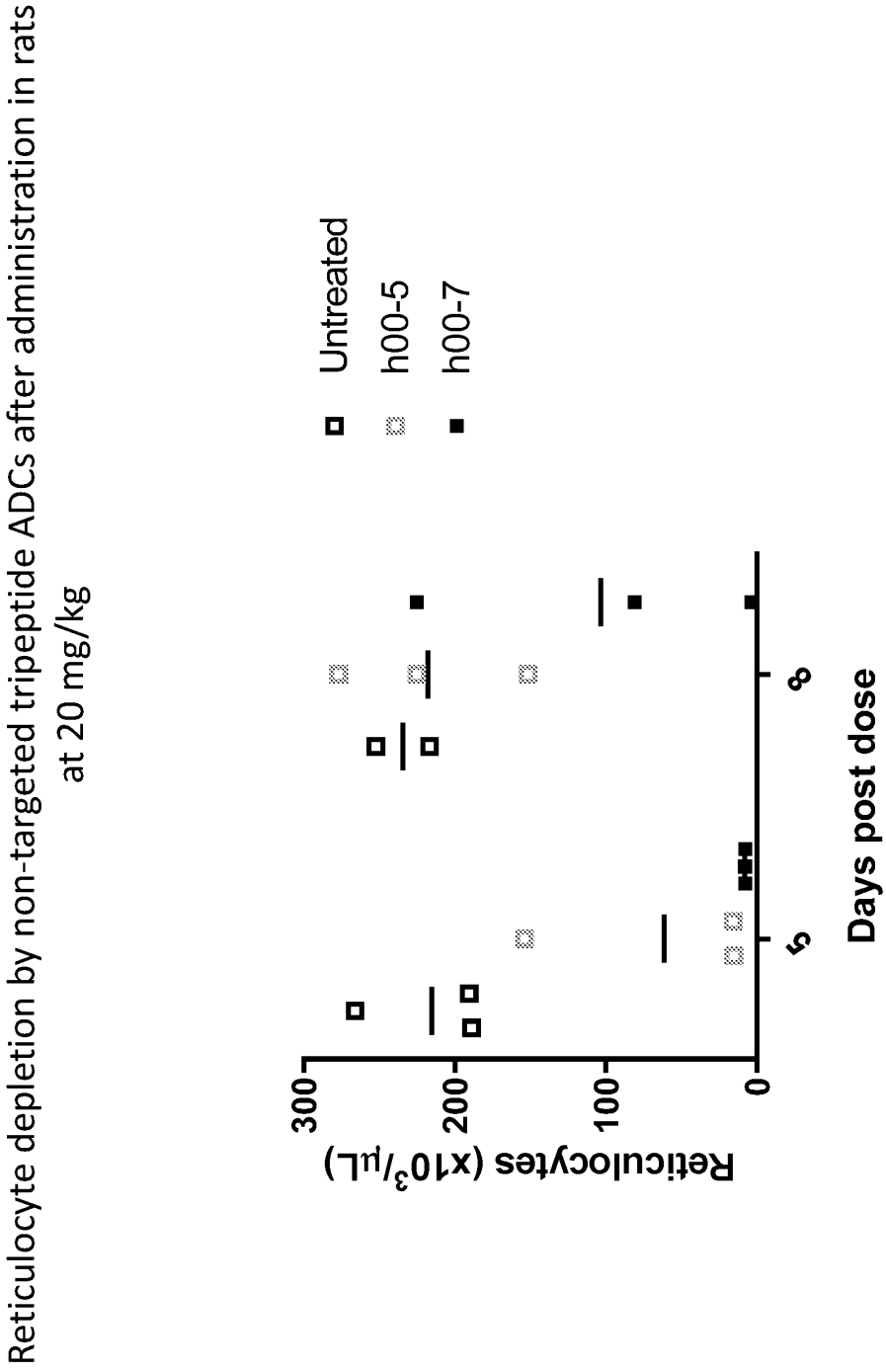

Reticulocyte depletion by non-targeted tripeptide ADCs after administration in rats at 20 mg/kg
Untreated
h00-5
h00-7
Reticulocytes (x10³/μL)
300
200
100
0
5
9
Days post dose

FIG. 16

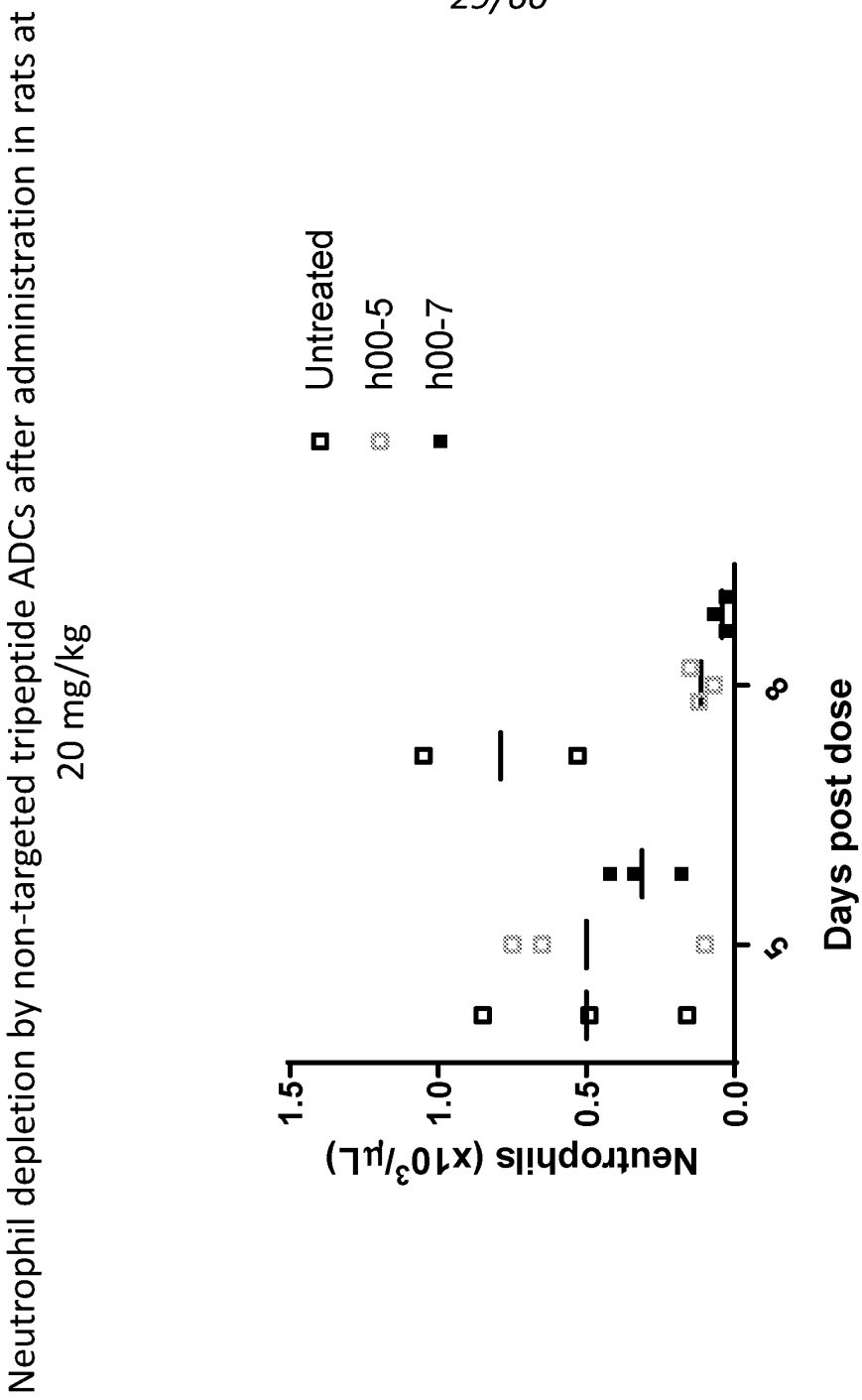

Neutrophil depletion by non-targeted tripeptide ADCs after administration in rats at 20 mg/kg
Untreated
h00-5
h00-7
Neutrophils (x10³/μL)
1.5
1.0
0.5
0.0
5
8
Days post dose

FIG. 17

Histology of bone by non-targeted tripeptide ADCs after administration in rats at 20 mg/kg

		h00-5							h00-7							
	Day post dose	5	5	5	8	8	8	8	5	5	5	5	8	8	8	8
TISSUE	**Animal #**	1	2	3	4	5	6		7	8	9	10	11	12		
BONE MARROW, FEMUR Depletion		3	3	3	1	2	-		4	4	4	3	2	1		
BONE MARROW, STERNUM Depletion		3	3	3	-	2	NE		4	4	4	3	2	-		

FIG. 18

Correlation between cLogP of the linkers and the aggregation of the corresponding h00 conjugate in rat plasma after a 96 h incubation (expressed as % HMW = %high molecular weight species)

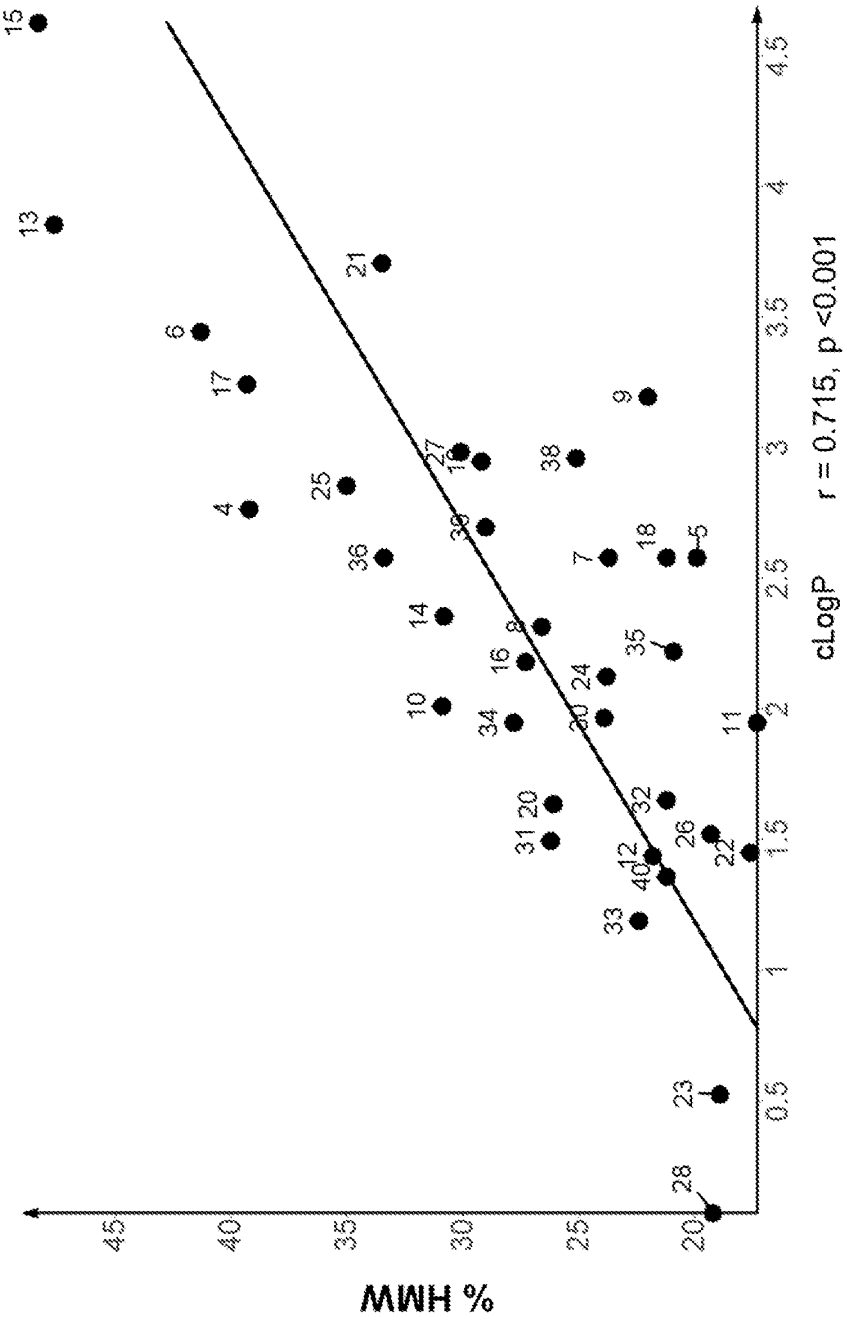


FIG. 19

Correlation between reticulocyte depletion caused by non-targeted ADCs in rats and ADC aggregation in rat plasma after a 96 h incubation (expressed as % HMW = %high molecular weight species)

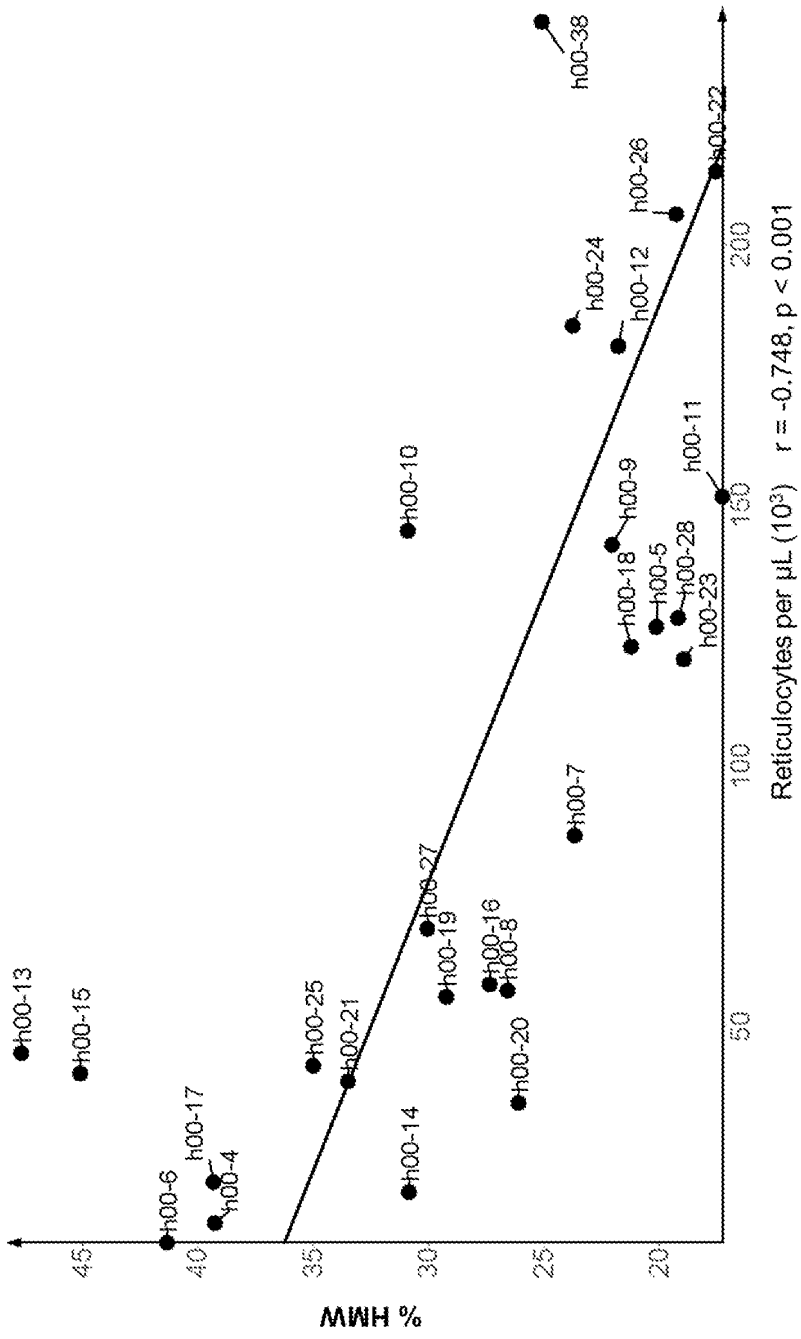


FIG. 20

Correlation between reticulocyte depletion caused by non-targeted ADCs in rats and ADC aggregation in human plasma after a 96 h incubation (expressed as % HMW = %high molecular weight species)

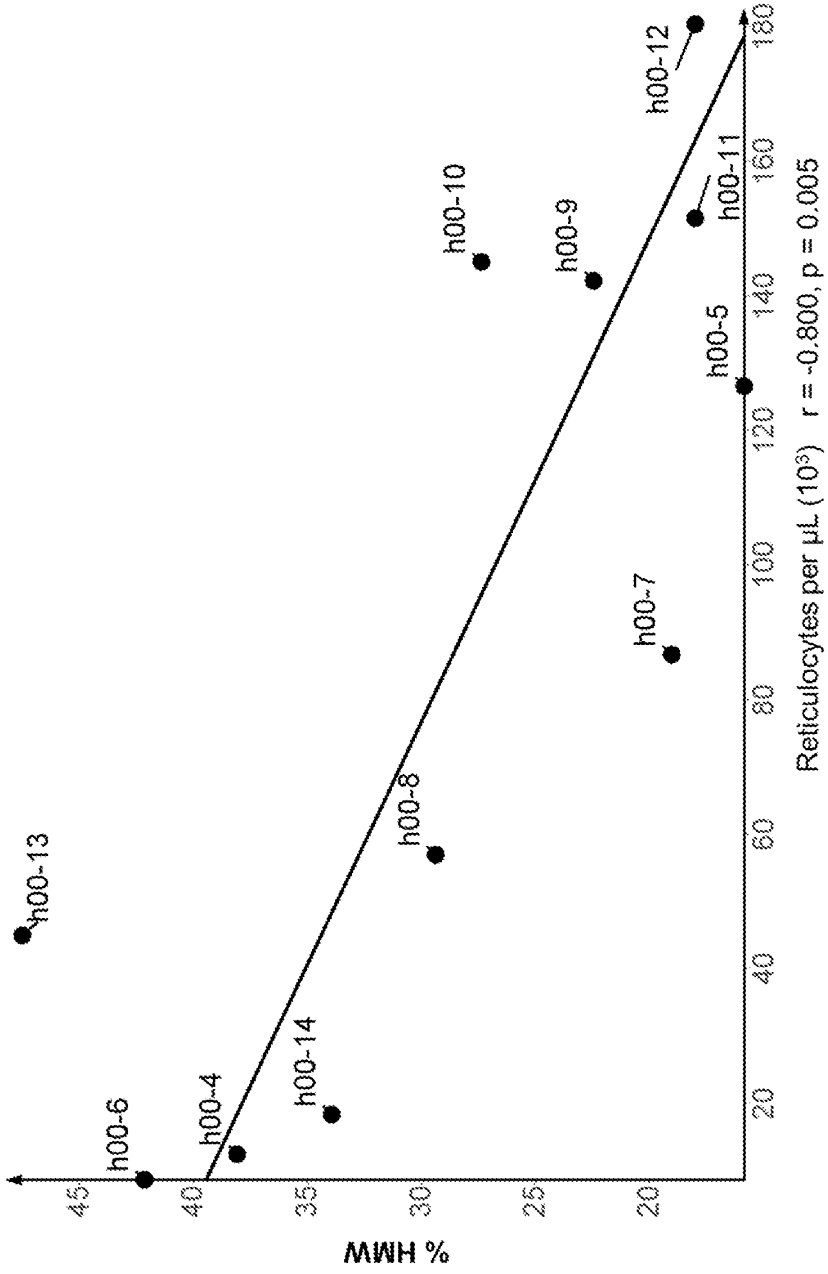


FIG. 21

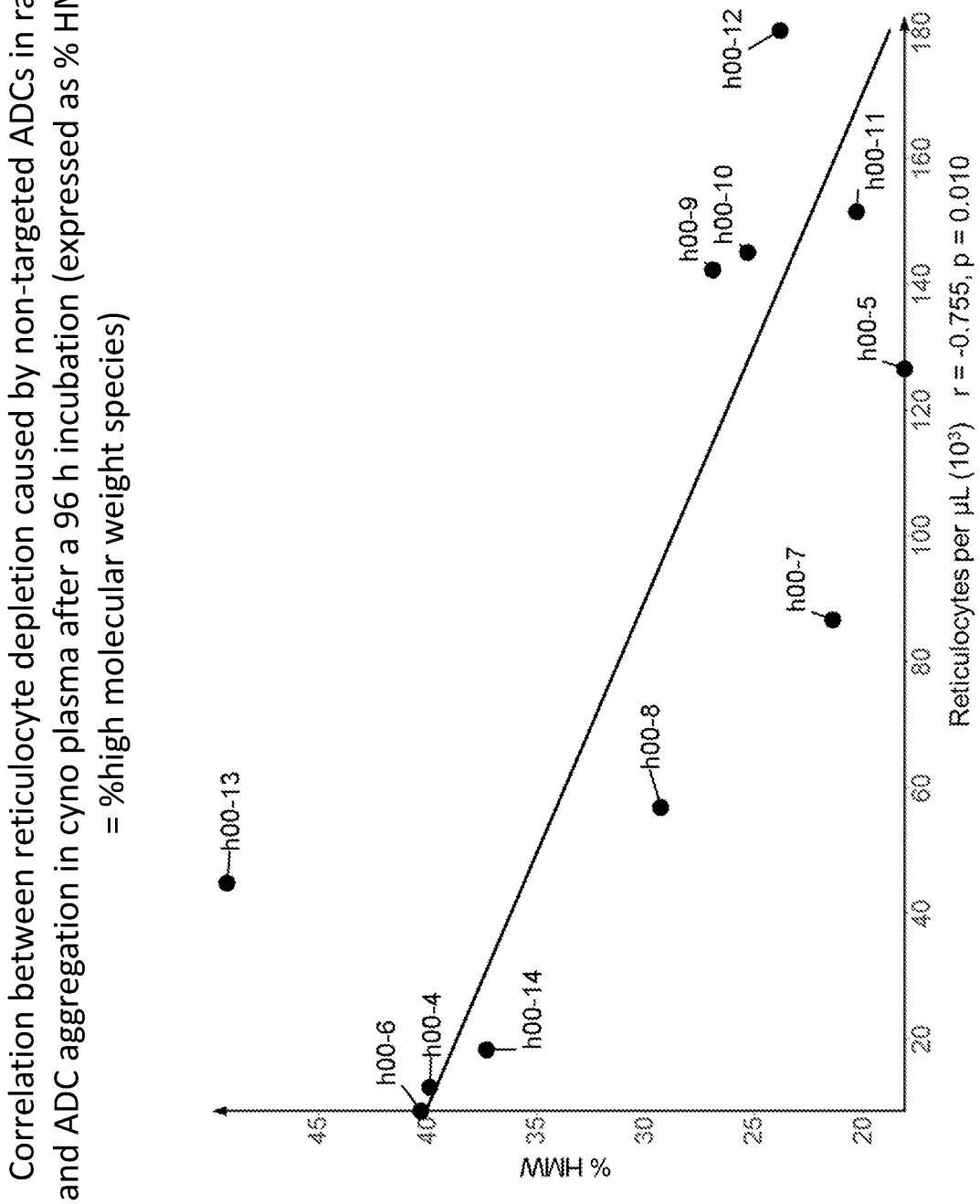

Correlation between reticulocyte depletion caused by non-targeted ADCs in rats and ADC aggregation in cyno plasma after a 96 h incubation (expressed as % HMW = %high molecular weight species)
h00-13
h00-6
h00-4
h00-14
h00-8
h00-7
h00-9
h00-10
h00-12
h00-11
h00-5
% HMW
45
40
35
30
25
20
Reticulocytes per µL (10³) r = -0.755, p = 0.010
20
40
60
80
100
120
140
160
180

FIG. 22

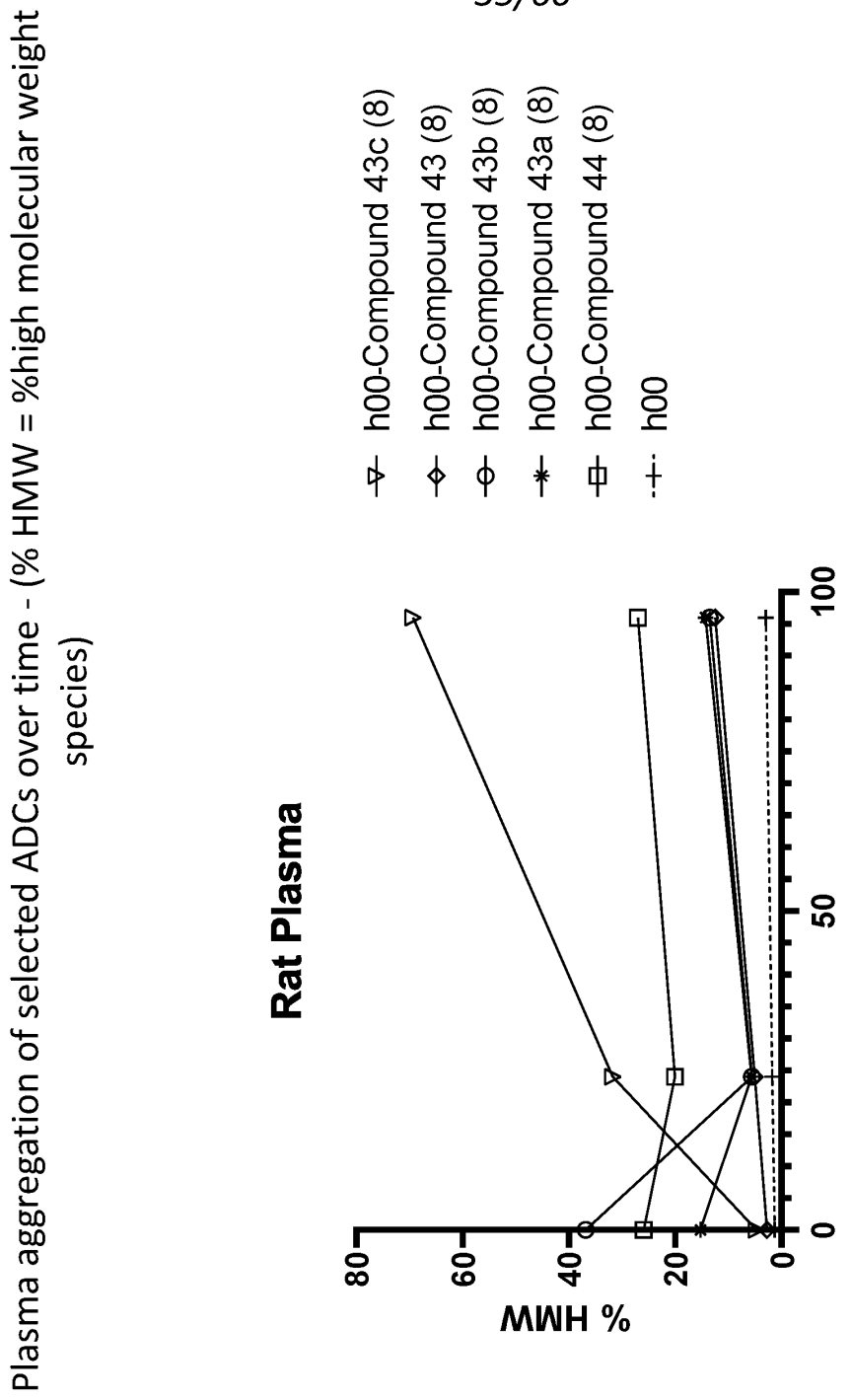

Plasma aggregation of selected ADCs over time - (% HMW = %high molecular weight species)
h00-Compound 43c (8)
h00-Compound 43 (8)
h00-Compound 43b (8)
h00-Compound 43a (8)
h00-Compound 44 (8)
h00
Rat Plasma
% HMW
0
20
40
60
80
0
50
100

FIG. 23

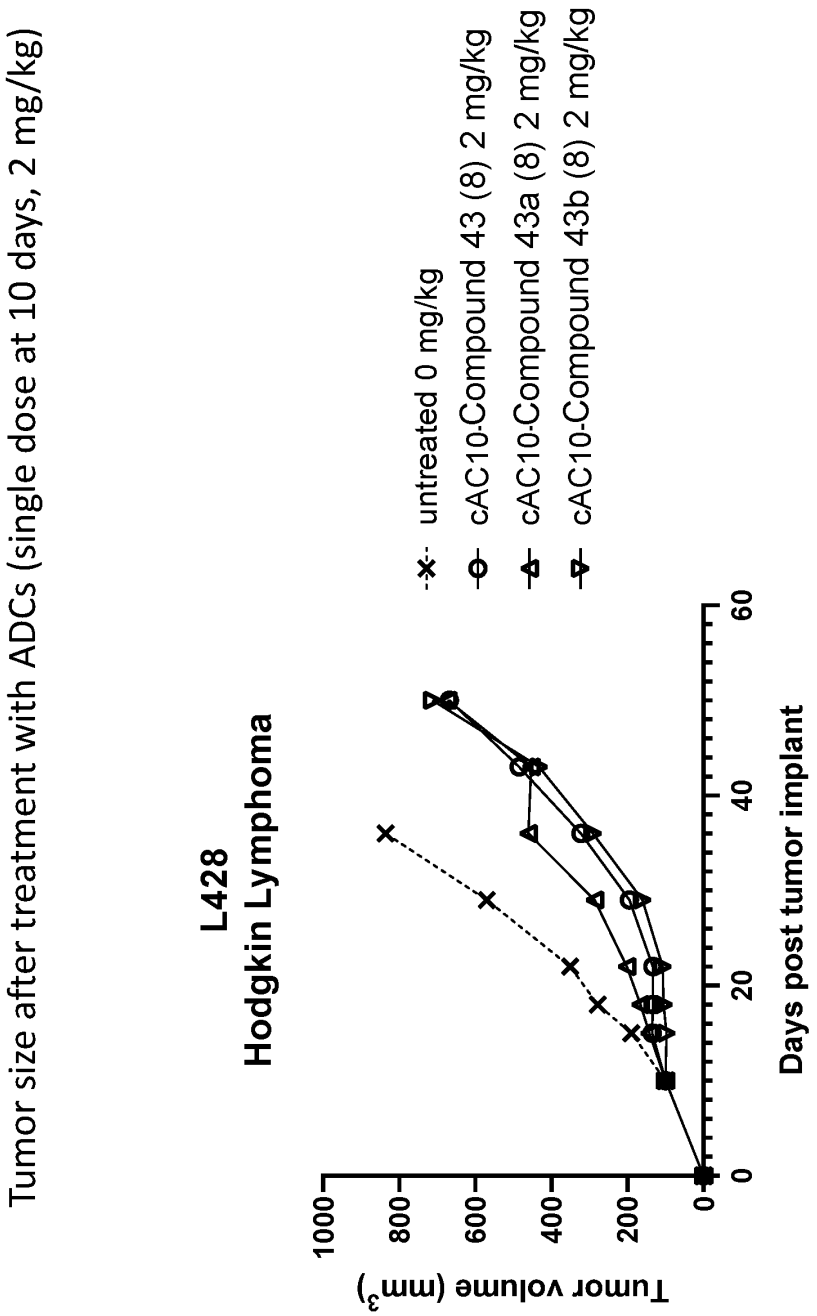

Tumor size after treatment with ADCs (single dose at 10 days, 2 mg/kg)
L428
Hodgkin Lymphoma
untreated 0 mg/kg
cAC10-Compound 43 (8) 2 mg/kg
cAC10-Compound 43a (8) 2 mg/kg
cAC10-Compound 43b (8) 2 mg/kg
Tumor volume (mm3)
1000
800
600
400
200
0
0
20
40
60
Days post tumor implant

FIG. 24A

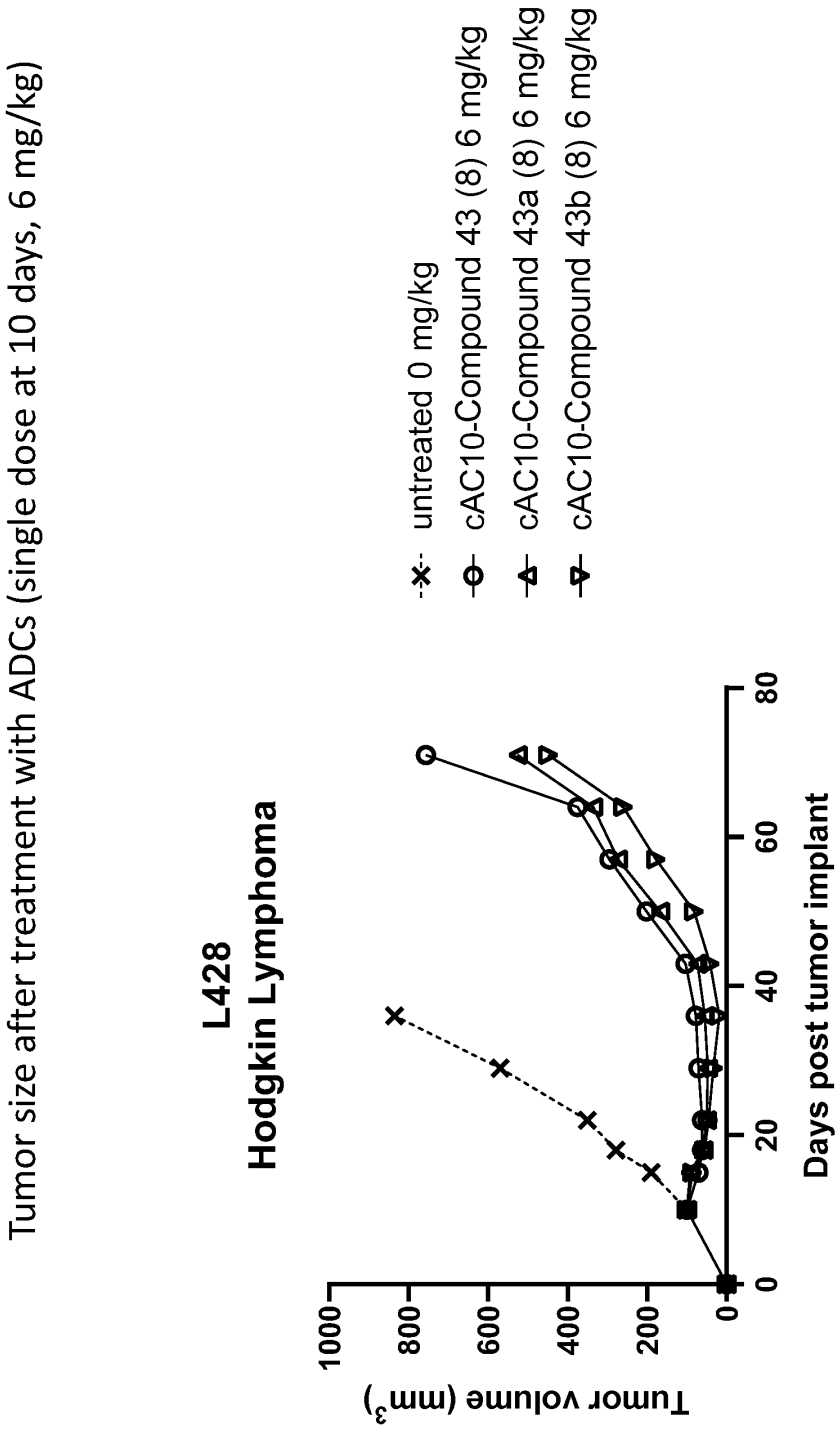

Tumor size after treatment with ADCs (single dose at 10 days, 6 mg/kg)
L428
Hodgkin Lymphoma
untreated 0 mg/kg
cAC10-Compound 43 (8) 6 mg/kg
cAC10-Compound 43a (8) 6 mg/kg
cAC10-Compound 43b (8) 6 mg/kg
Tumor volume (mm3)
0
200
400
600
800
1000
0
20
40
60
80
Days post tumor implant

FIG. 24B

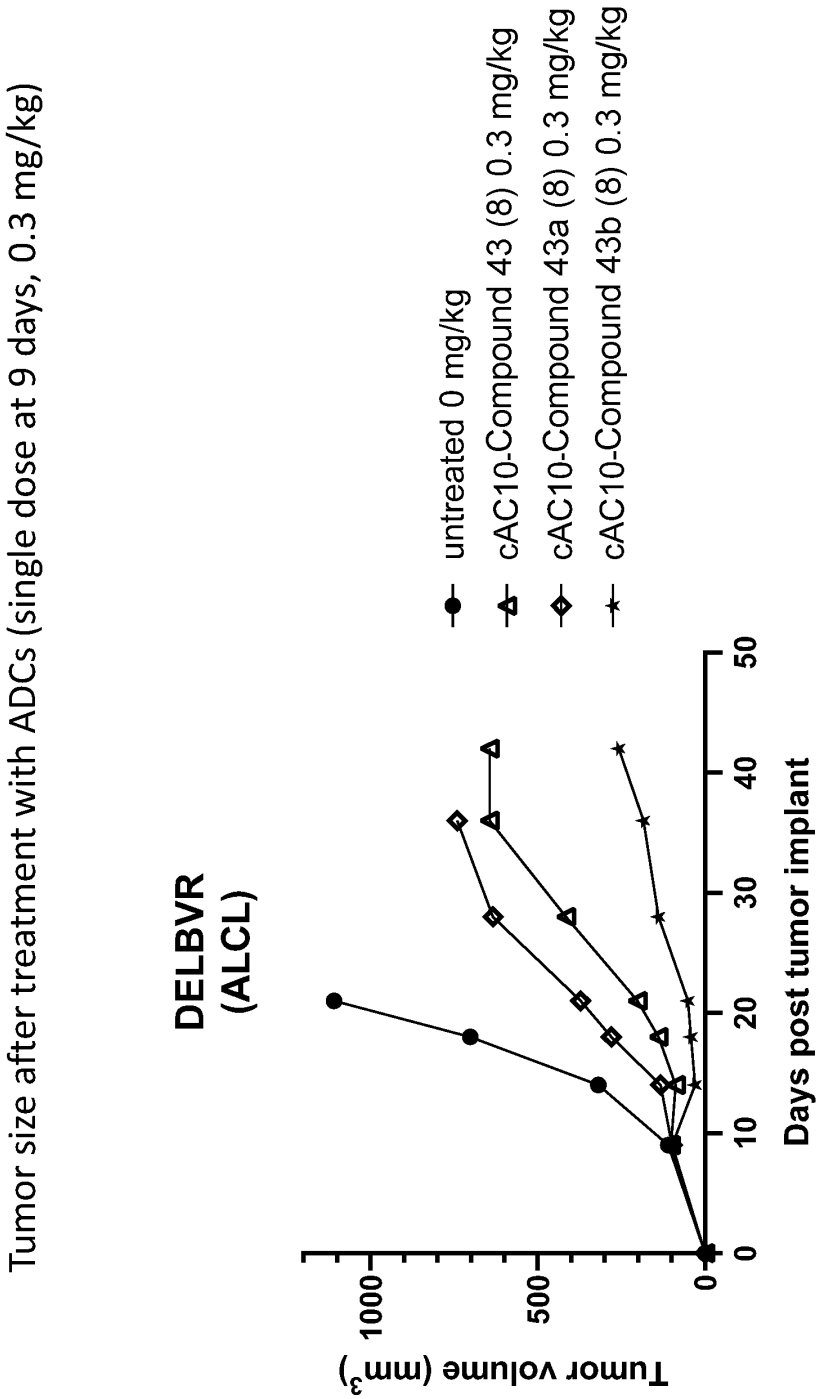

Tumor size after treatment with ADCs (single dose at 9 days, 0.3 mg/kg)
DELBVR
(ALCL)
untreated 0 mg/kg
cAC10-Compound 43 (8) 0.3 mg/kg
cAC10-Compound 43a (8) 0.3 mg/kg
cAC10-Compound 43b (8) 0.3 mg/kg
Tumor volume (mm3)
0
500
1000
0
10
20
30
40
50
Days post tumor implant

FIG. 25A

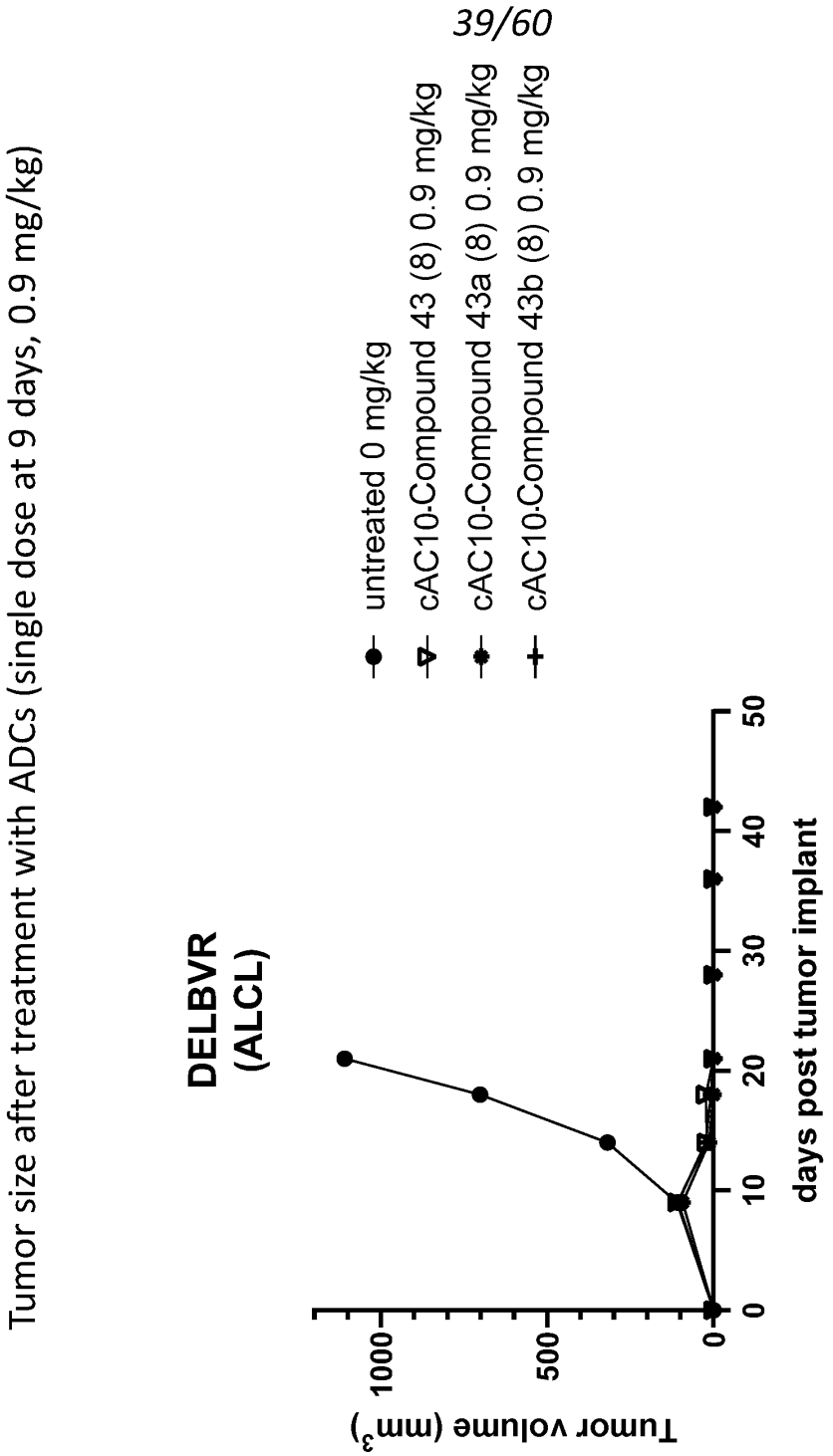

Tumor size after treatment with ADCs (single dose at 9 days, 0.9 mg/kg)
DELBVR
(ALCL)
untreated 0 mg/kg
cAC10-Compound 43 (8) 0.9 mg/kg
cAC10-Compound 43a (8) 0.9 mg/kg
cAC10-Compound 43b (8) 0.9 mg/kg
Tumor volume (mm3)
0
500
1000
0
10
20
30
40
50
days post tumor implant

FIG. 25B

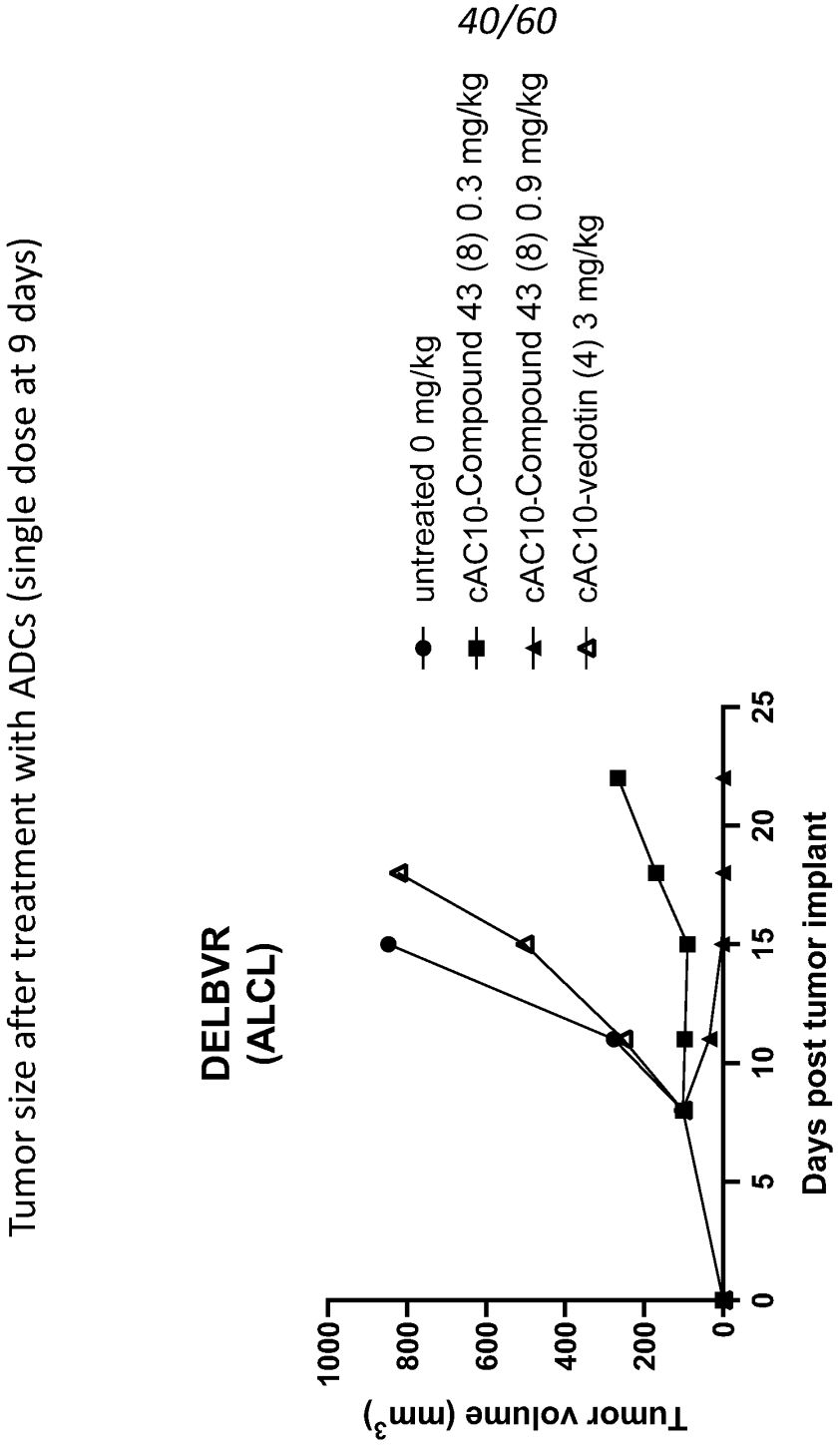

Tumor size after treatment with ADCs (single dose at 9 days)
DELBVR
(ALCL)
untreated 0 mg/kg
cAC10-Compound 43 (8) 0.3 mg/kg
cAC10-Compound 43 (8) 0.9 mg/kg
cAC10-vedotin (4) 3 mg/kg
Tumor volume (mm3)
1000
800
600
400
200
0
0
5
10
15
20
25
Days post tumor implant

FIG. 25C

Survival after treatment with ADCs (single dose at 5 days)

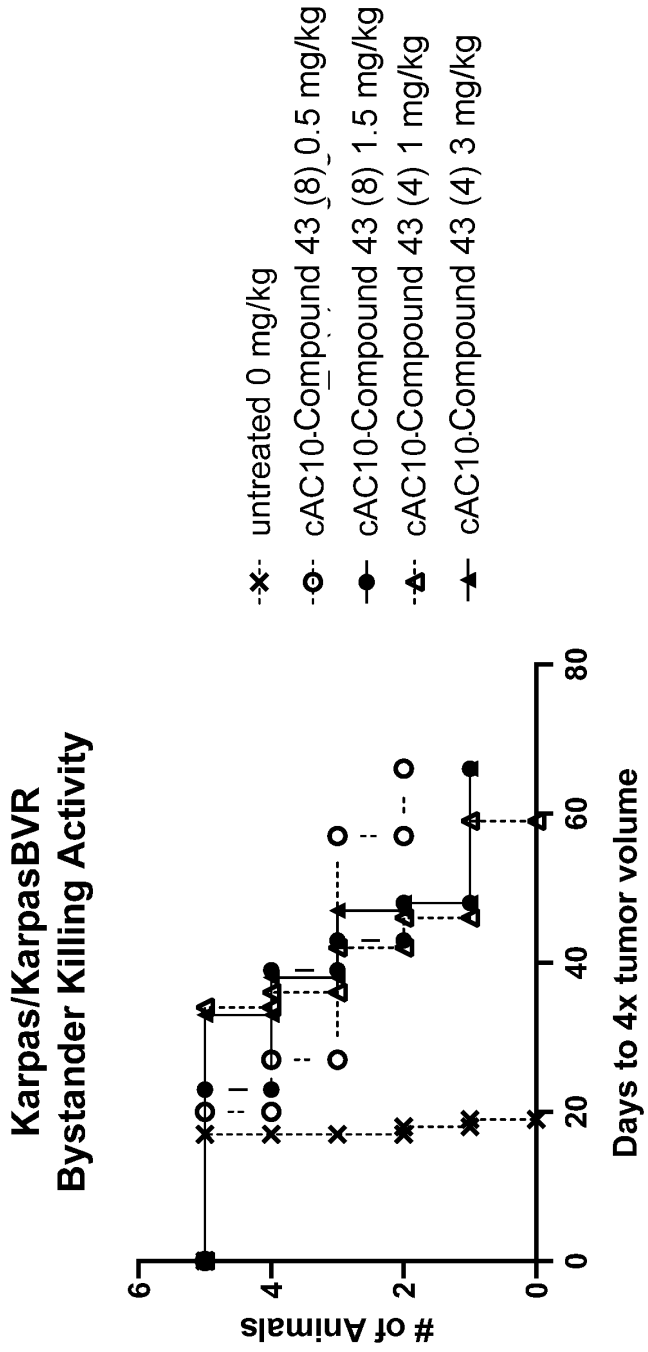


FIG. 26

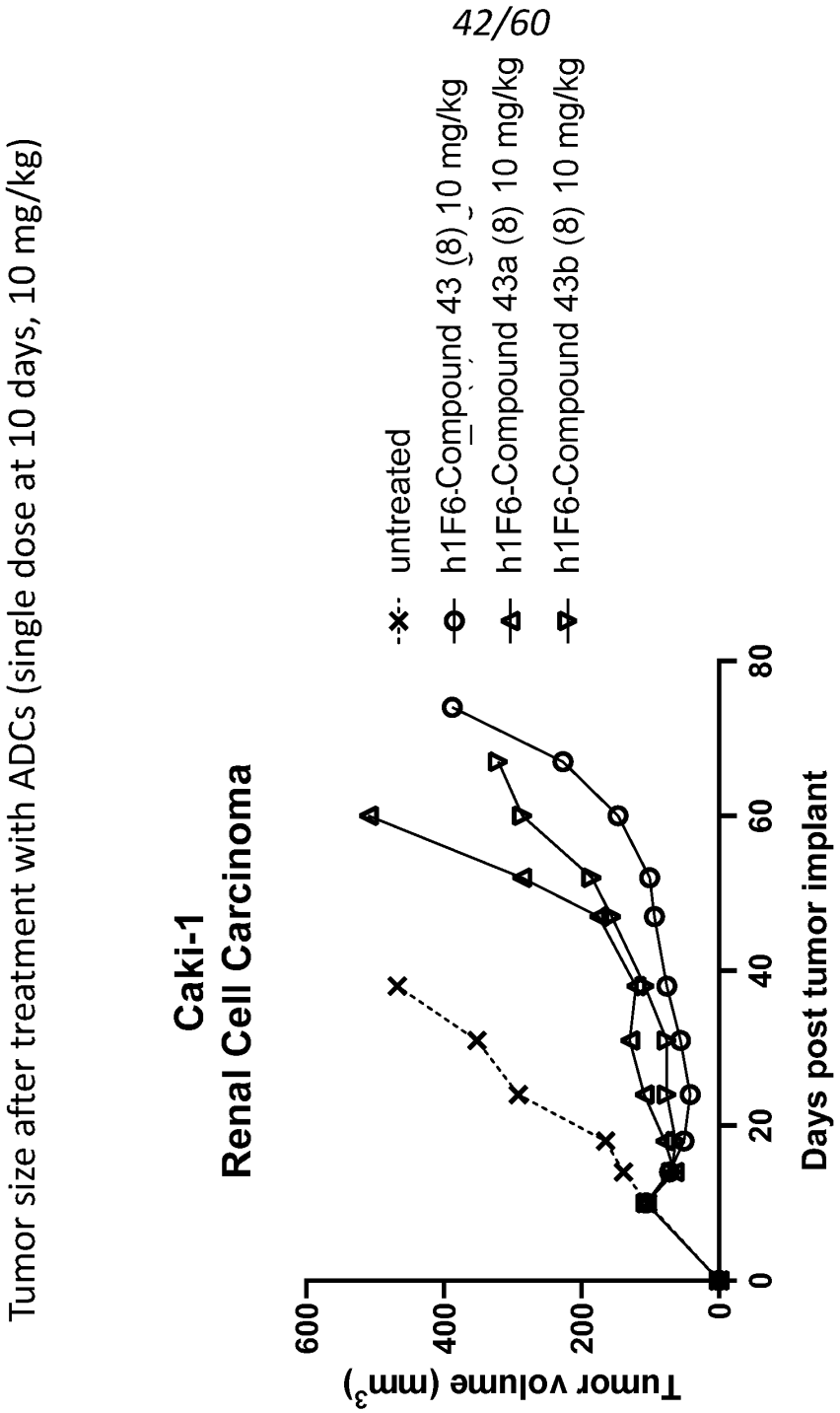

Tumor size after treatment with ADCs (single dose at 10 days, 10 mg/kg)
Caki-1
Renal Cell Carcinoma
untreated
h1F6-Compound 43 (8) 10 mg/kg
h1F6-Compound 43a (8) 10 mg/kg
h1F6-Compound 43b (8) 10 mg/kg
Tumor volume (mm3)
0
200
400
600
0
20
40
60
80
Days post tumor implant

FIG. 27A

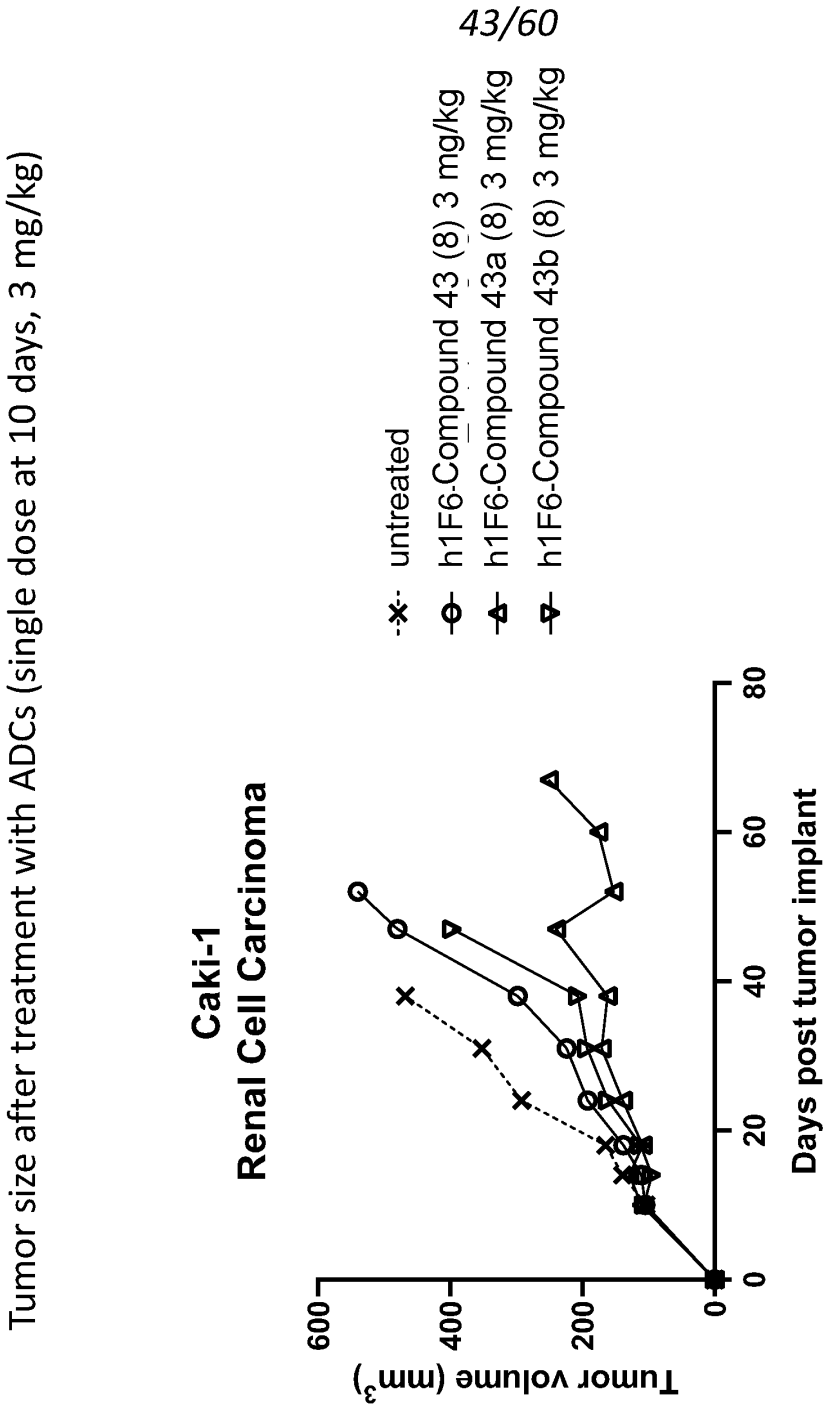

Tumor size after treatment with ADCs (single dose at 10 days, 3 mg/kg)
Caki-1
Renal Cell Carcinoma
untreated
h1F6-Compound 43 (8) 3 mg/kg
h1F6-Compound 43a (8) 3 mg/kg
h1F6-Compound 43b (8) 3 mg/kg
Tumor volume (mm3)
0
200
400
600
0
20
40
60
80
Days post tumor implant

FIG. 27B

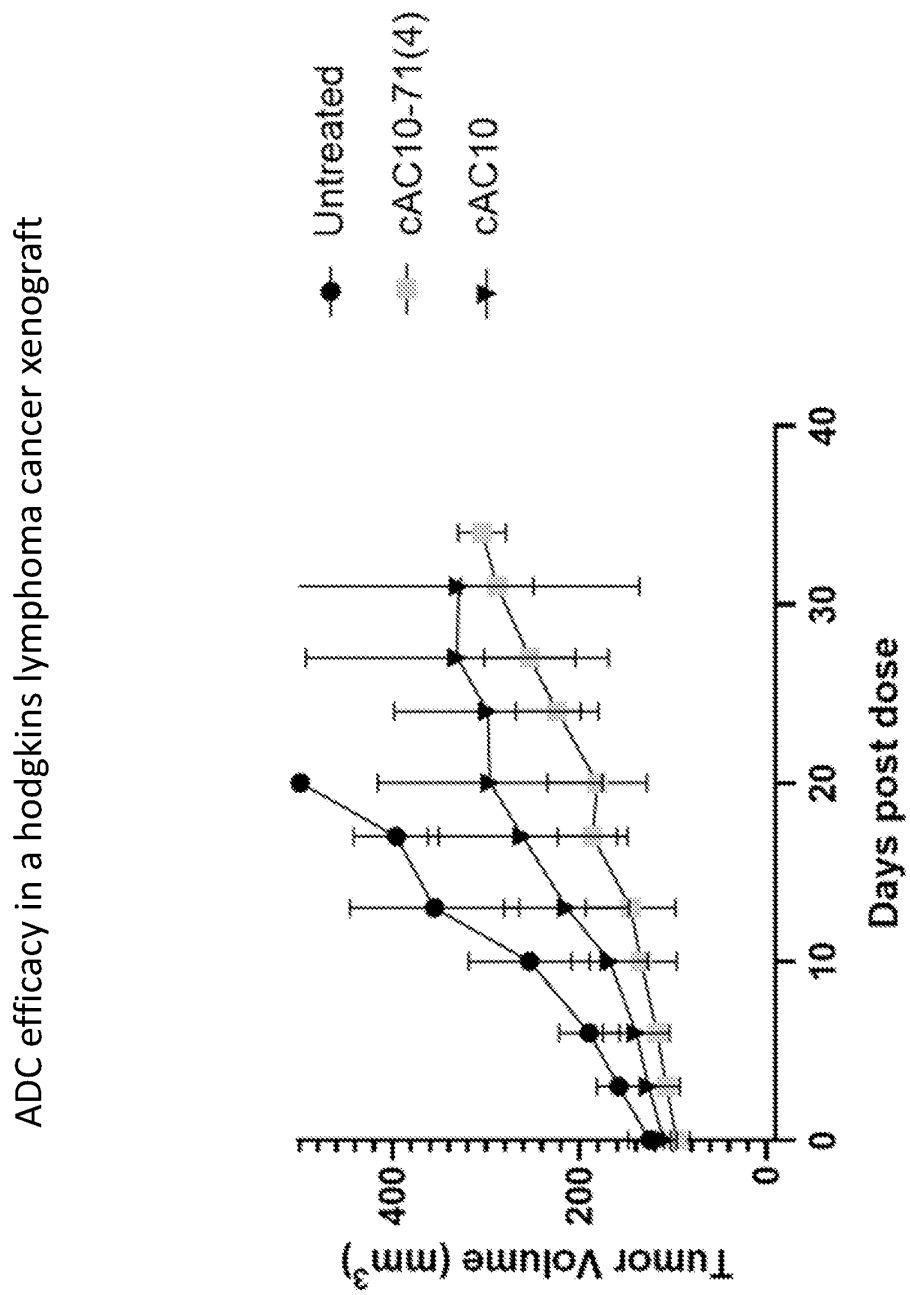

ADC efficacy in a hodgkins lymphoma cancer xenograft
Untreated
cAC10-71(4)
cAC10
Tumor Volume (mm³)
0
200
400
0
10
20
30
40
Days post dose

FIG. 28

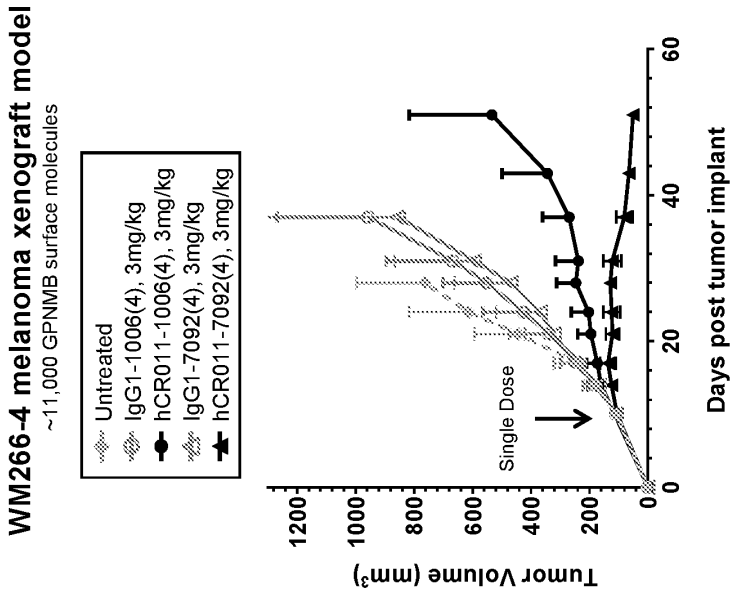

WM266-4 melanoma xenograft model
~11,000 GPNMB surface molecules
Untreated
IgG1-1006(4), 3mg/kg
hCR011-1006(4), 3mg/kg
IgG1-7092(4), 3mg/kg
hCR011-7092(4), 3mg/kg
Single Dose
Tumor Volume (mm3)
0
200
400
600
800
1000
1200
0
20
40
60
Days post tumor implant

FIGURE 29

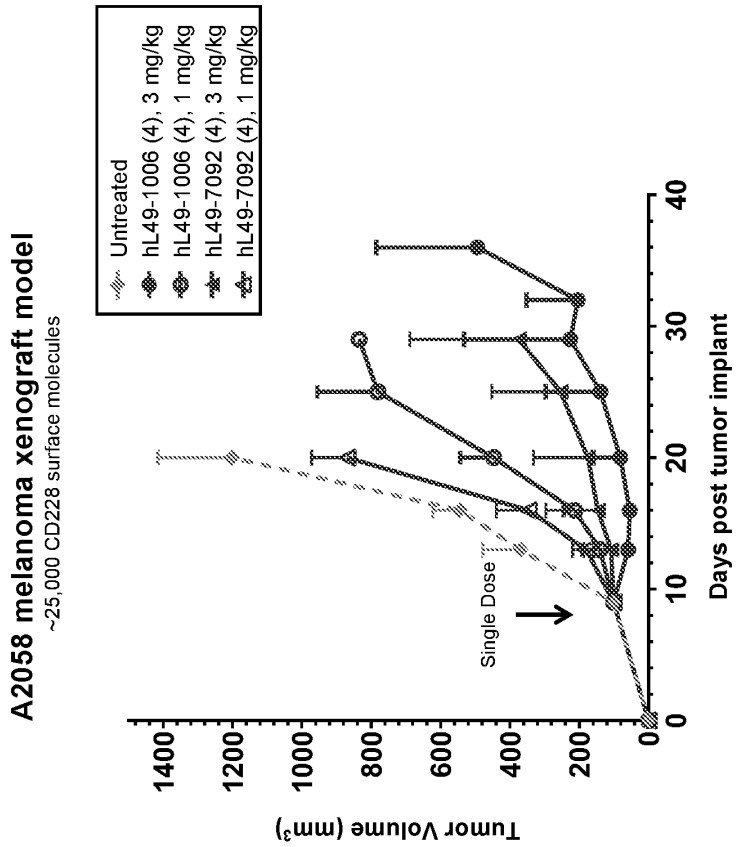

A2058 melanoma xenograft model
~25,000 CD228 surface molecules
Untreated
hL49-1006 (4), 3 mg/kg
hL49-1006 (4), 1 mg/kg
hL49-7092 (4), 3 mg/kg
hL49-7092 (4), 1 mg/kg
Single Dose
Tumor Volume (mm³)
Days post tumor implant
0
200
400
600
800
1000
1200
1400
0
10
20
30
40

FIG. 30

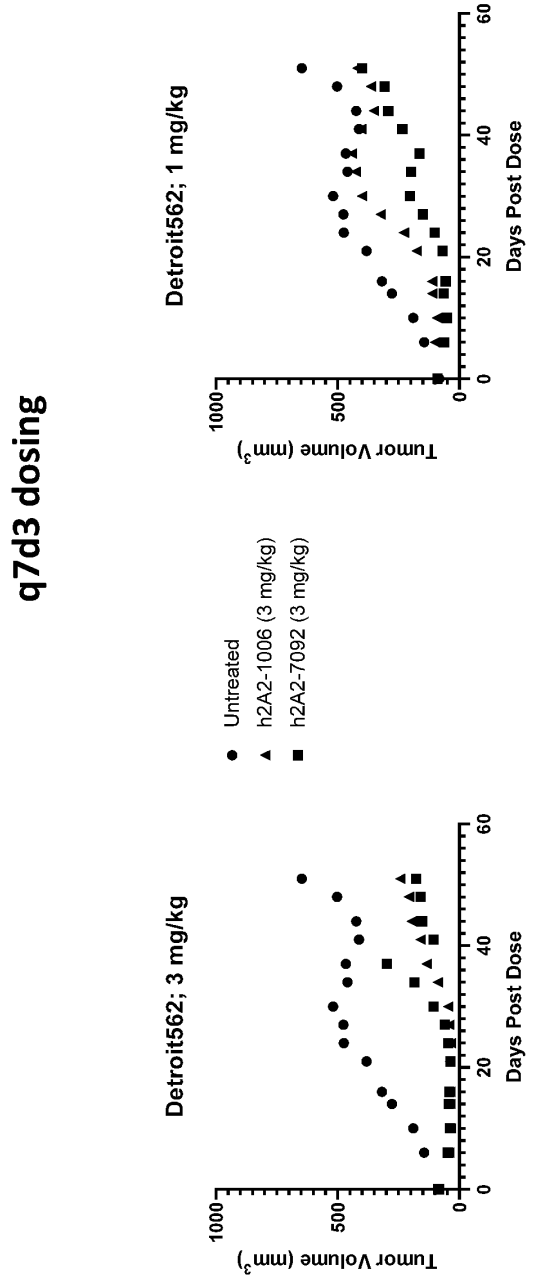

q7d3 dosing
Detroit562; 3 mg/kg
Detroit562; 1 mg/kg
Untreated
h2A2-1006 (3 mg/kg)
h2A2-7092 (3 mg/kg)
h2A2-1006 (1mg/kg)
h2A2-7092 (1 mg/kg)
Tumor Volume (mm3)
Days Post Dose
0
500
1000
0
20
40
60

FIGURE 31

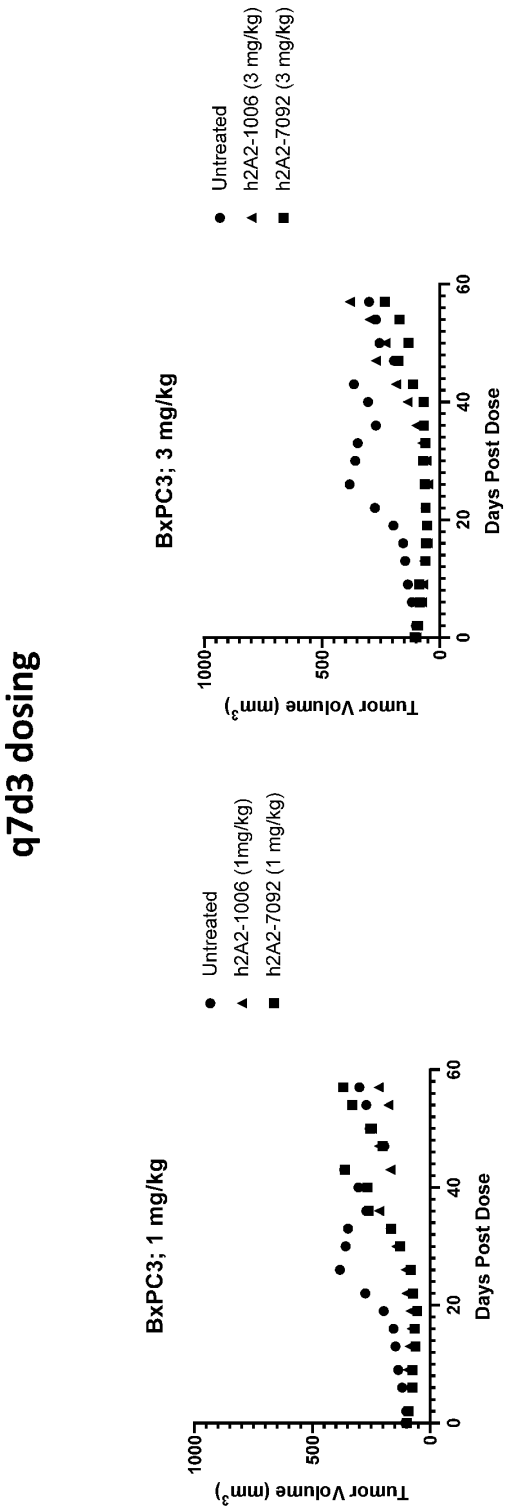

q7d3 dosing
BxPC3; 1 mg/kg
BxPC3; 3 mg/kg
Untreated
h2A2-1006 (1mg/kg)
h2A2-7092 (1 mg/kg)
h2A2-1006 (3 mg/kg)
h2A2-7092 (3 mg/kg)
Tumor Volume (mm3)
Days Post Dose
0
500
1000
0
20
40
60

FIGURE 32

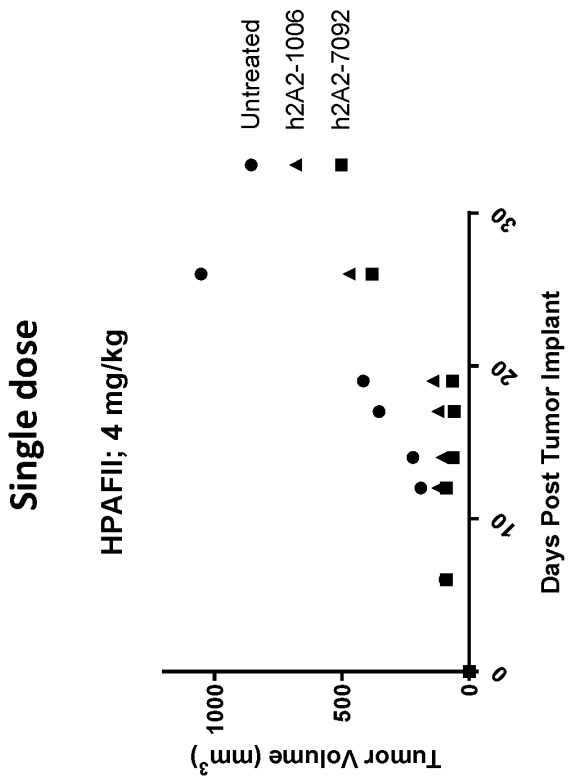

Single dose
HPAFII; 4 mg/kg
Untreated
h2A2-1006
h2A2-7092
Tumor Volume (mm3)
1000
500
0
0
10
20
30
Days Post Tumor Implant

FIGURE 33

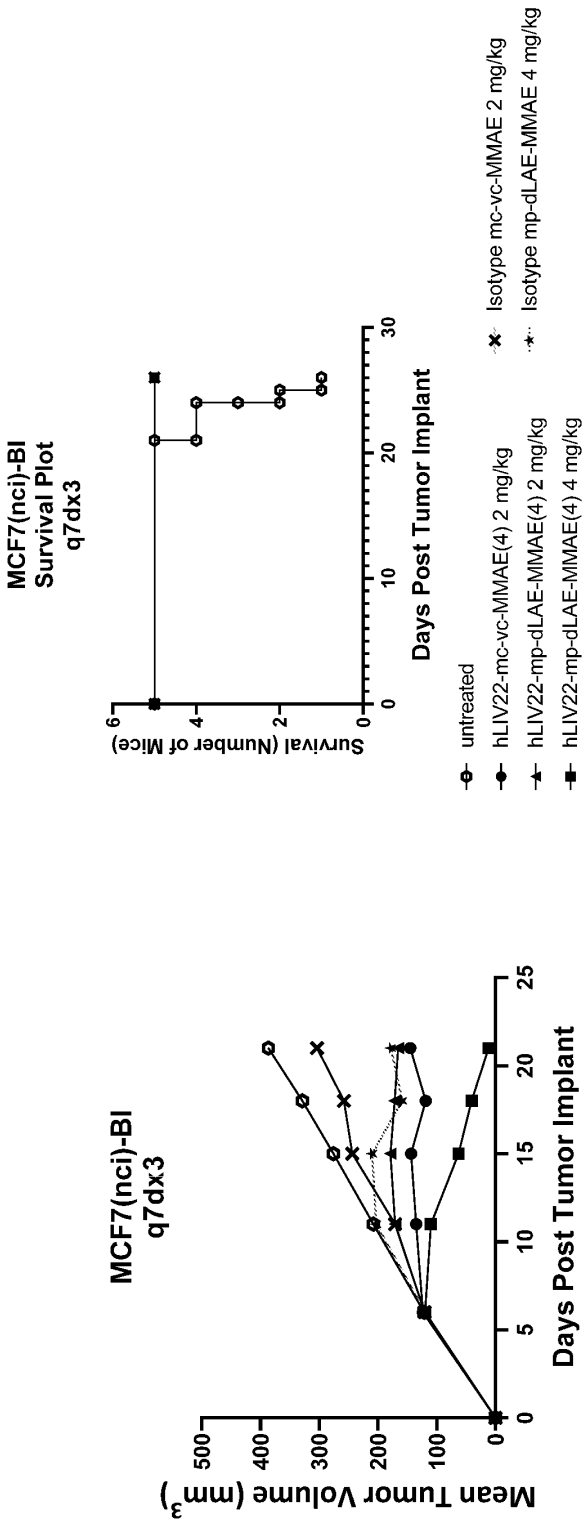

MCF7(nci)-BI
q7dx3
Mean Tumor Volume (mm3)
Days Post Tumor Implant
A
MCF7(nci)-BI
Survival Plot
q7dx3
Survival (Number of Mice)
Days Post Tumor Implant
untreated
hLIV22-mc-vc-MMAE(4) 2 mg/kg
hLIV22-mp-dLAE-MMAE(4) 2 mg/kg
hLIV22-mp-dLAE-MMAE(4) 4 mg/kg
Isotype mc-vc-MMAE 2 mg/kg
Isotype mp-dLAE-MMAE 4 mg/kg
B

FIGURE 34

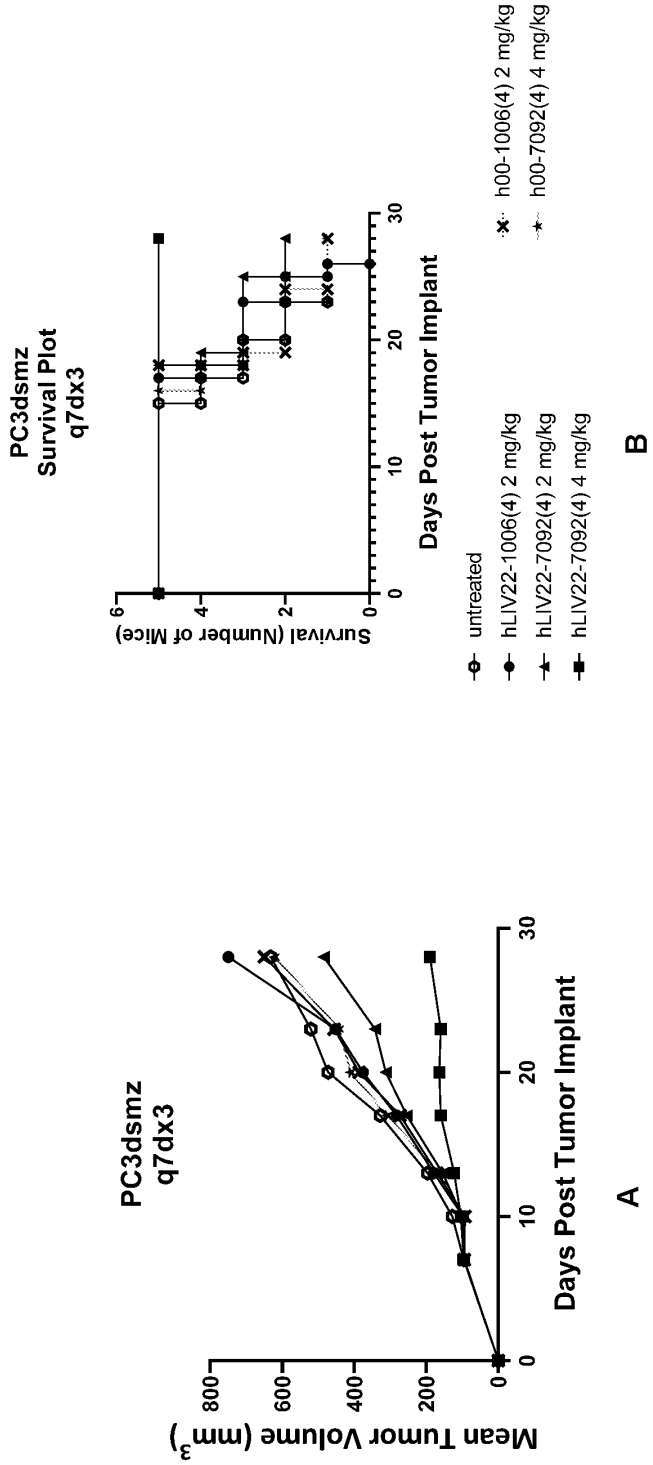
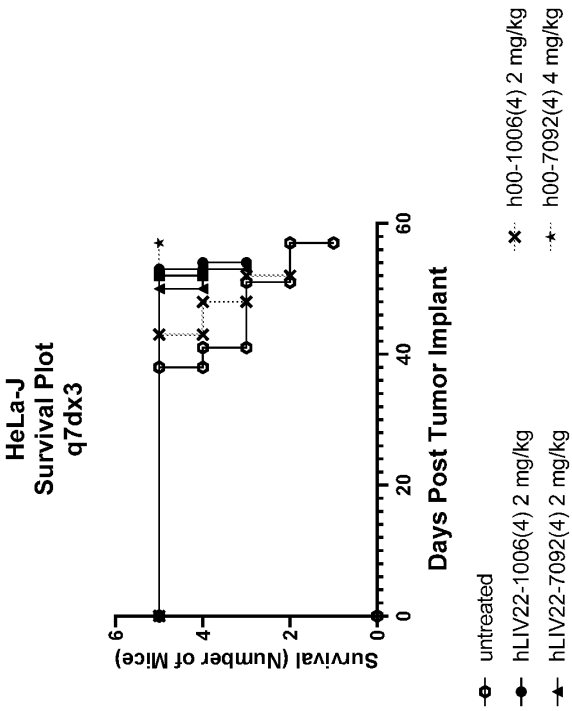

PC3dsmz
q7dx3
Mean Tumor Volume (mm3)
0
200
400
600
800
0
10
20
30
Days Post Tumor Implant
A
PC3dsmz
Survival Plot
q7dx3
Survival (Number of Mice)
0
2
4
6
0
10
20
30
Days Post Tumor Implant
untreated
hLIV22-1006(4) 2 mg/kg
hLIV22-7092(4) 2 mg/kg
hLIV22-7092(4) 4 mg/kg
h00-1006(4) 2 mg/kg
h00-7092(4) 4 mg/kg
B

FIGURE 35


HeLa-J
Survival Plot
q7dx3
Survival (Number of Mice)
0
2
4
6
0
20
40
60
Days Post Tumor Implant
untreated
hLIV22-1006(4) 2 mg/kg
hLIV22-7092(4) 2 mg/kg
hLIV22-7092(4) 4 mg/kg
h00-1006(4) 2 mg/kg
h00-7092(4) 4 mg/kg
B

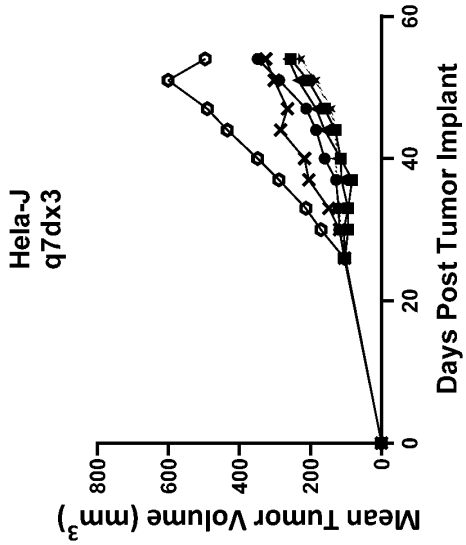

Hela-J
q7dx3
Mean Tumor Volume (mm3)
0
200
400
600
800
0
20
40
60
Days Post Tumor Implant
A

FIGURE 36

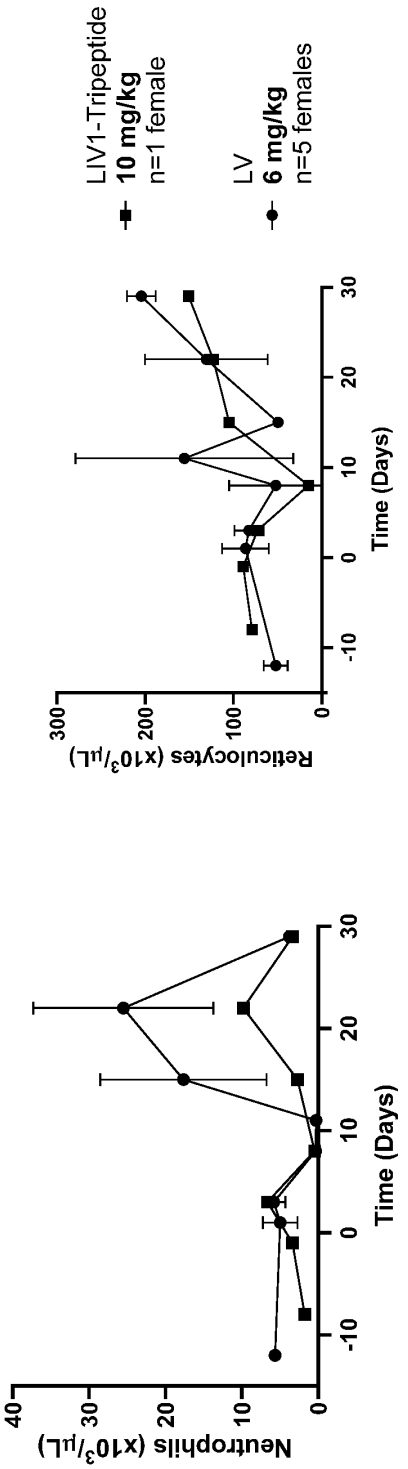

LIV1-Tripeptide
10 mg/kg
n=1 female
LV
6 mg/kg
n=5 females
Reticulocytes (x10³/μL)
Neutrophils (x10³/μL)
Time (Days)
Time (Days)

FIGURE 37

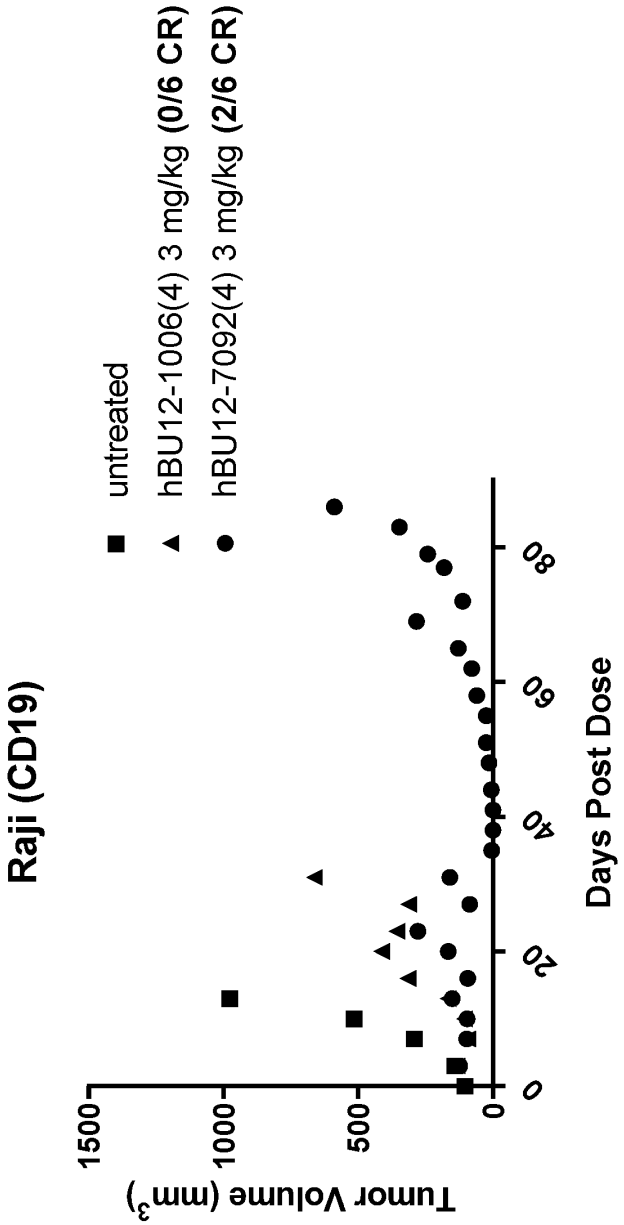

Raji (CD19)
untreated
hBU12-1006(4) 3 mg/kg (0/6 CR)
hBU12-7092(4) 3 mg/kg (2/6 CR)
Tumor Volume (mm3)
1500
1000
500
0
0
20
40
60
80
Days Post Dose

FIGURE 38

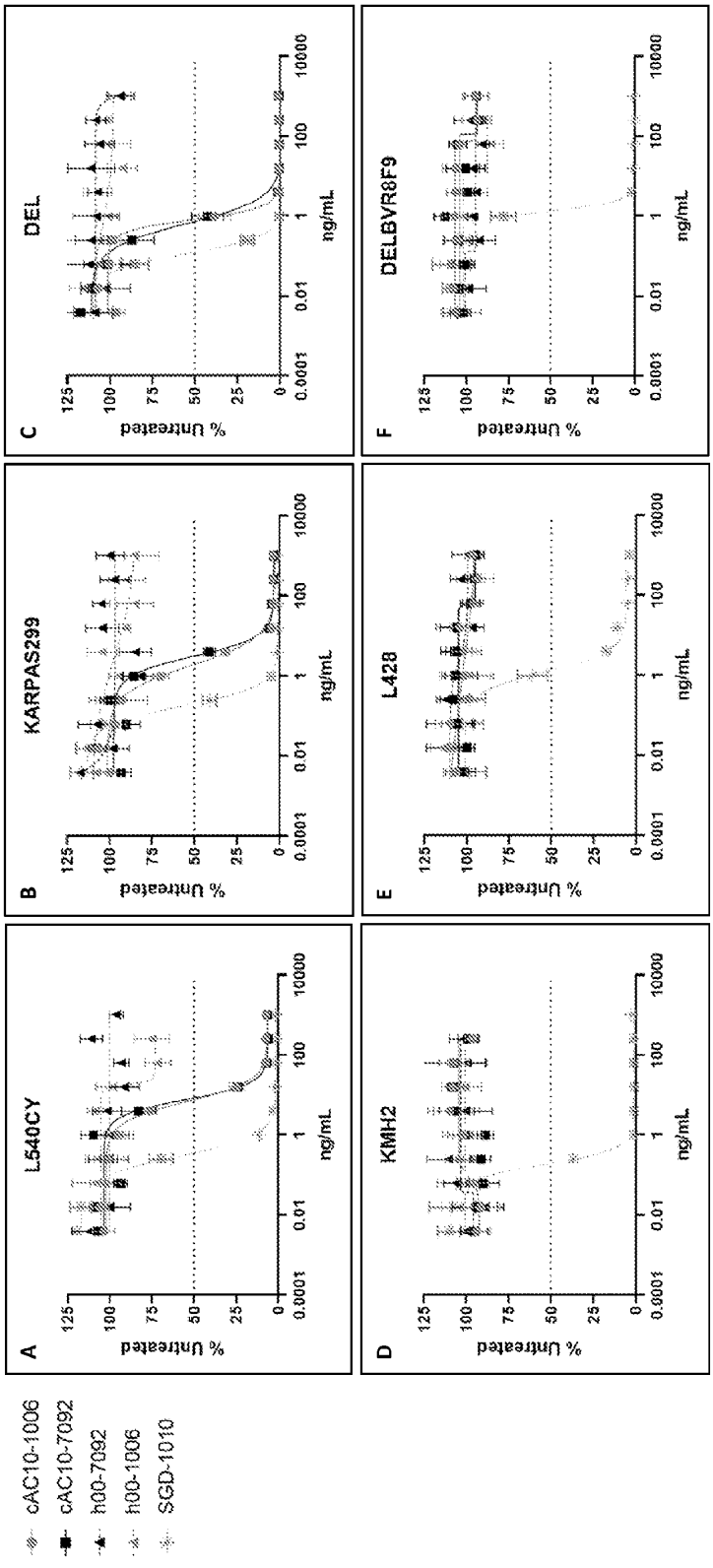

cAC10-1006
cAC10-7092
h00-7092
h00-1006
SGD-1010
A
L540CY
B
KARPAS299
C
DEL
D
KMH2
E
L428
F
DELBVR8F9
% Untreated
ng/mL
0
25
50
75
100
125
0.0001
0.01
1
100
10000

Figure 39

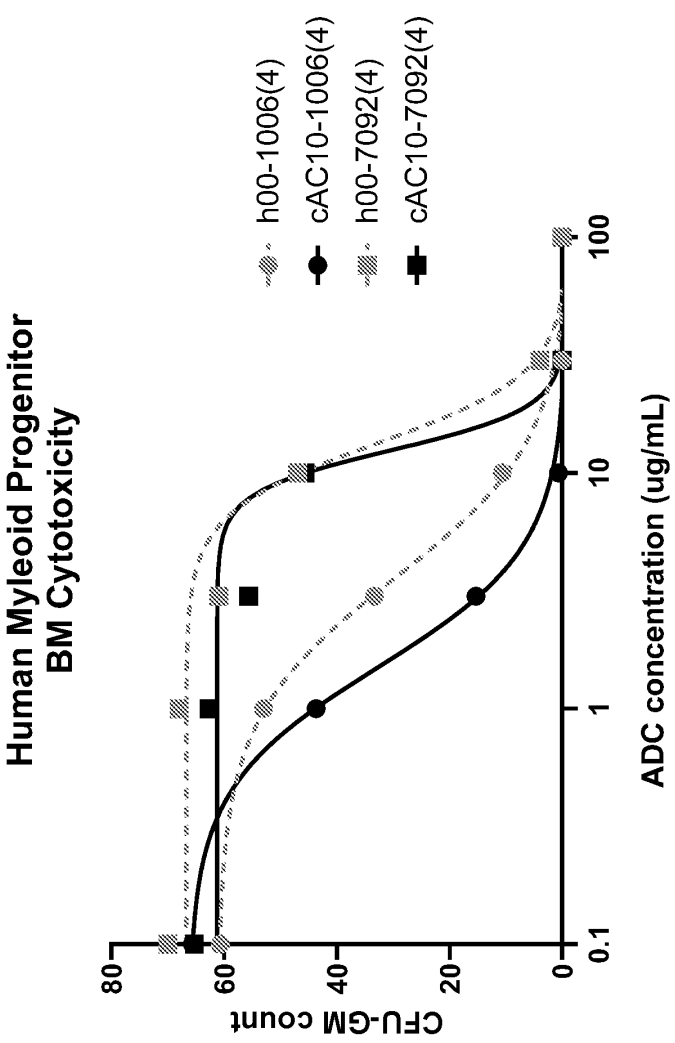

Human Myleoid Progenitor
BM Cytotoxicity
h00-1006(4)
cAC10-1006(4)
h00-7092(4)
cAC10-7092(4)
CFU-GM count
0
20
40
60
80
0.1
1
10
100
ADC concentration (ug/mL)

Figure 40

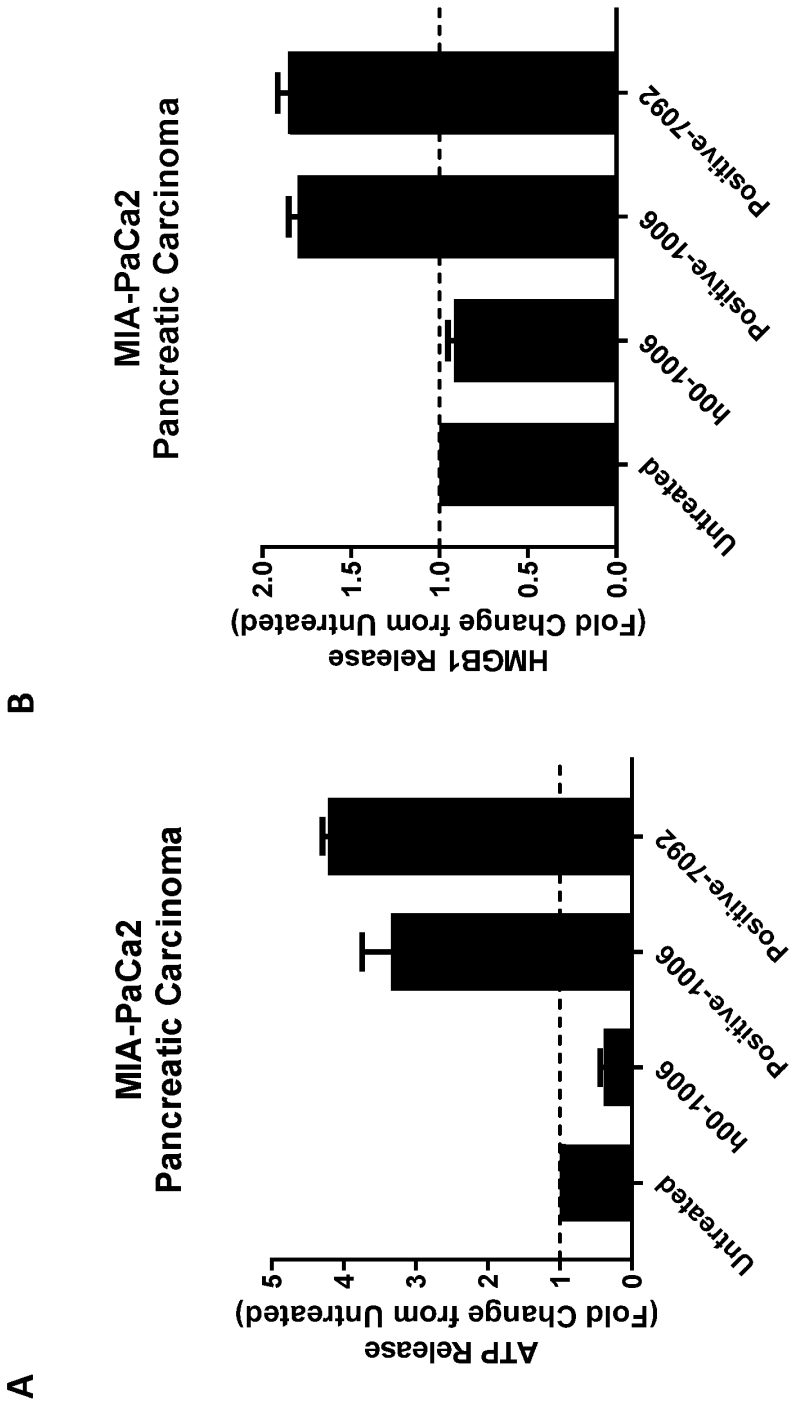

A
MIA-PaCa2
Pancreatic Carcinoma
ATP Release
(Fold Change from Untreated)
0
1
2
3
4
5
Untreated
h00-1006
Positive-1006
Positive-7092
B
MIA-PaCa2
Pancreatic Carcinoma
HMGB1 Release
(Fold Change from Untreated)
0.0
0.5
1.0
1.5
2.0
Untreated
h00-1006
Positive-1006
Positive-7092

Figure 41

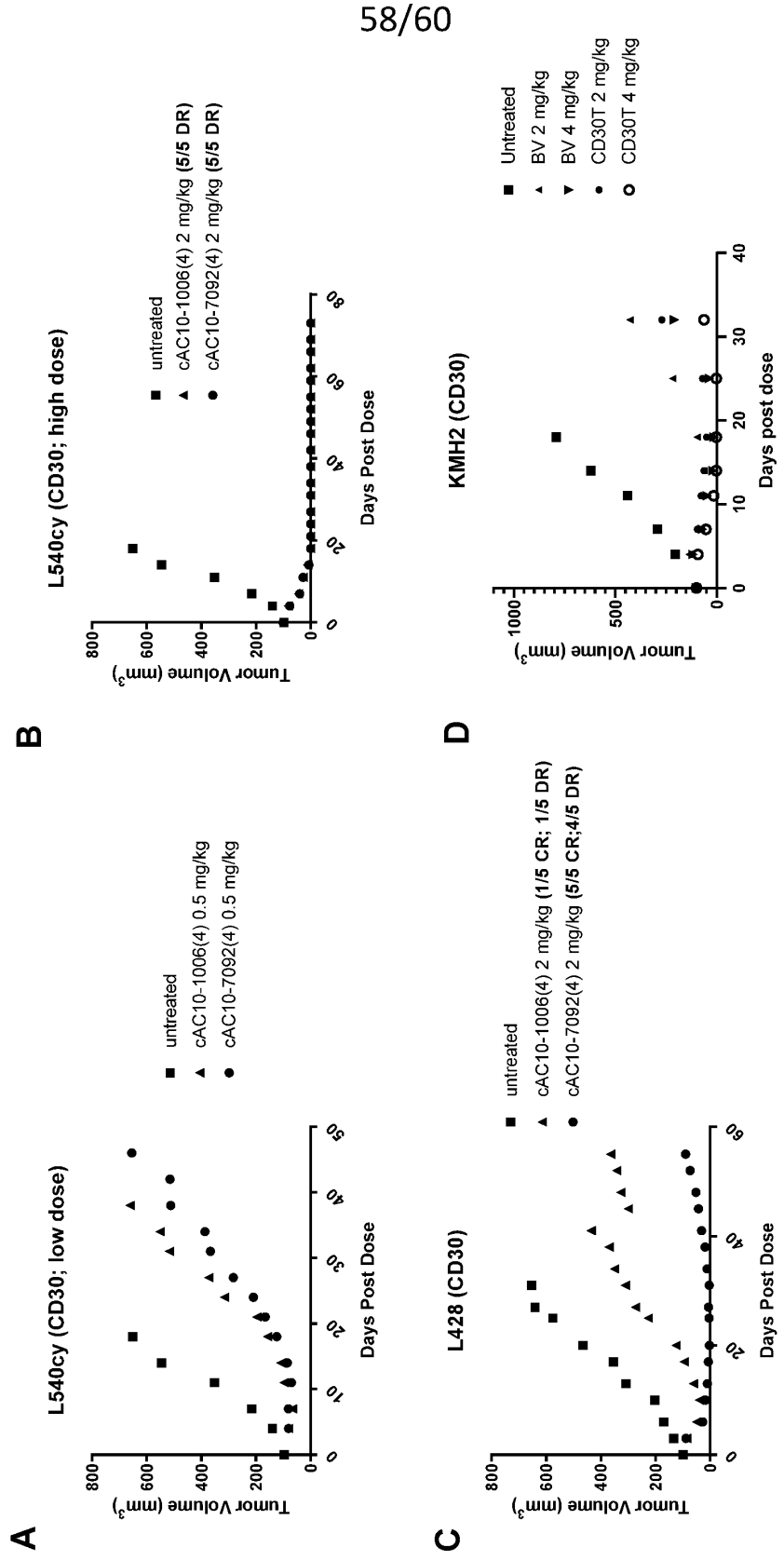
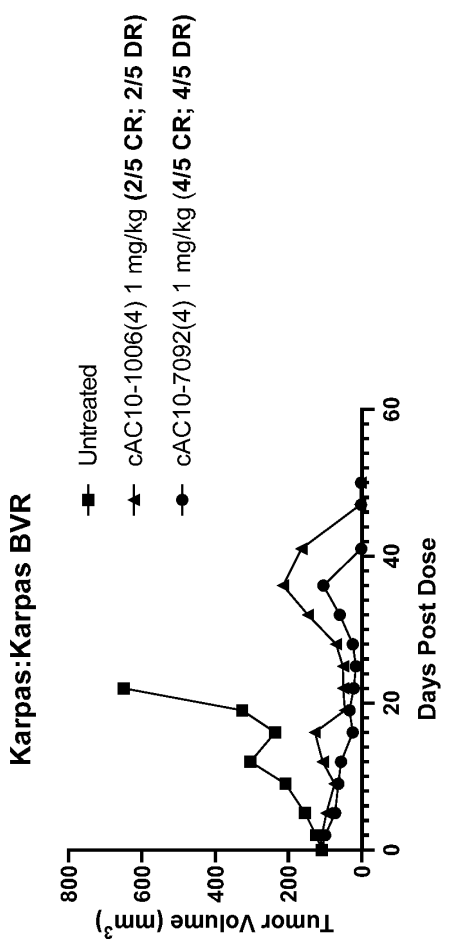

A
L540cy (CD30; low dose)
Tumor Volume (mm3)
Days Post Dose
untreated
cAC10-1006(4) 0.5 mg/kg
cAC10-7092(4) 0.5 mg/kg
B
L540cy (CD30; high dose)
Tumor Volume (mm3)
Days Post Dose
untreated
cAC10-1006(4) 2 mg/kg (5/5 DR)
cAC10-7092(4) 2 mg/kg (5/5 DR)
C
L428 (CD30)
Tumor Volume (mm3)
Days Post Dose
untreated
cAC10-1006(4) 2 mg/kg (1/5 CR; 1/5 DR)
cAC10-7092(4) 2 mg/kg (5/5 CR;4/5 DR)
D
KMH2 (CD30)
Tumor Volume (mm3)
Days post dose
Untreated
BV 2 mg/kg
BV 4 mg/kg
CD30T 2 mg/kg
CD30T 4 mg/kg

FIGURE 42


Karpas:Karpas BVR
Untreated
cAC10-1006(4) 1 mg/kg (2/5 CR; 2/5 DR)
cAC10-7092(4) 1 mg/kg (4/5 CR; 4/5 DR)
Tumor Volume (mm3)
800
600
400
200
0
0
20
40
60
Days Post Dose

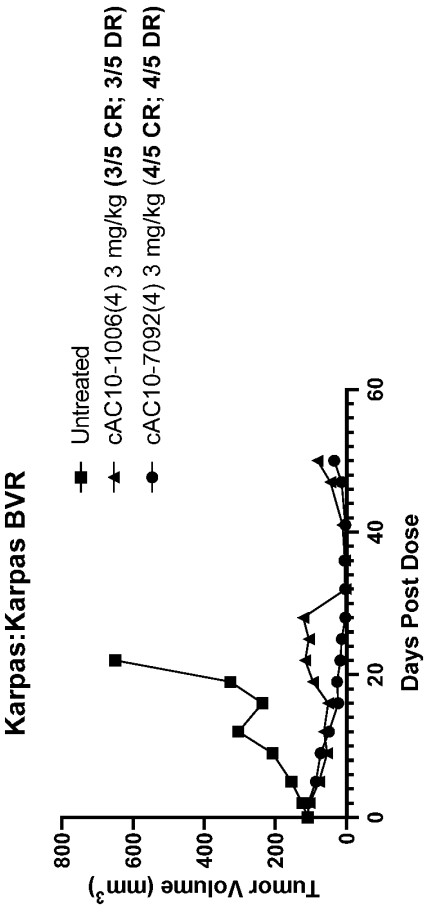

Karpas:Karpas BVR
Untreated
cAC10-1006(4) 3 mg/kg (3/5 CR; 3/5 DR)
cAC10-7092(4) 3 mg/kg (4/5 CR; 4/5 DR)
Tumor Volume (mm3)
800
600
400
200
0
0
20
40
60
Days Post Dose

FIGURE 43

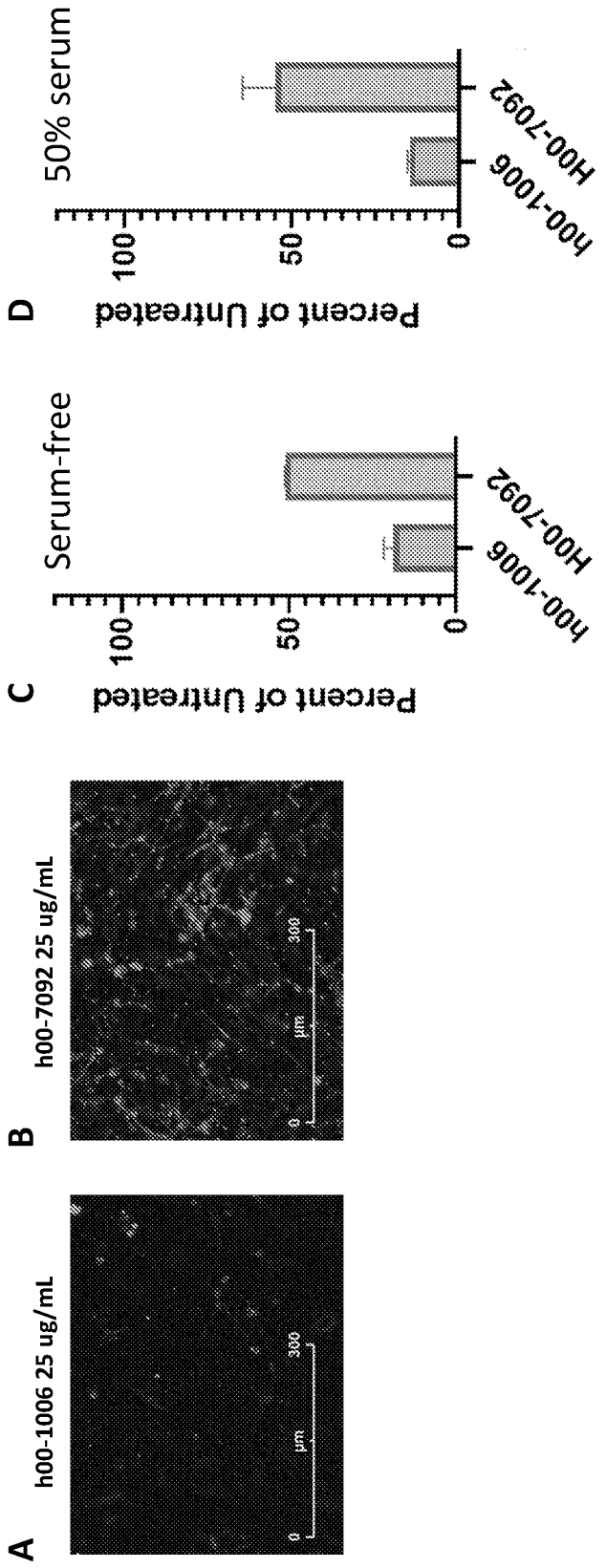

A
h00-1006 25 ug/mL
300
μm
0
B
h00-7092 25 ug/mL
300
μm
0
C
Serum-free
Percent of Untreated
100
50
0
h00-1006
H00-7092
D
50% serum
Percent of Untreated
100
50
0
h00-1006
H00-7092

Figure 44