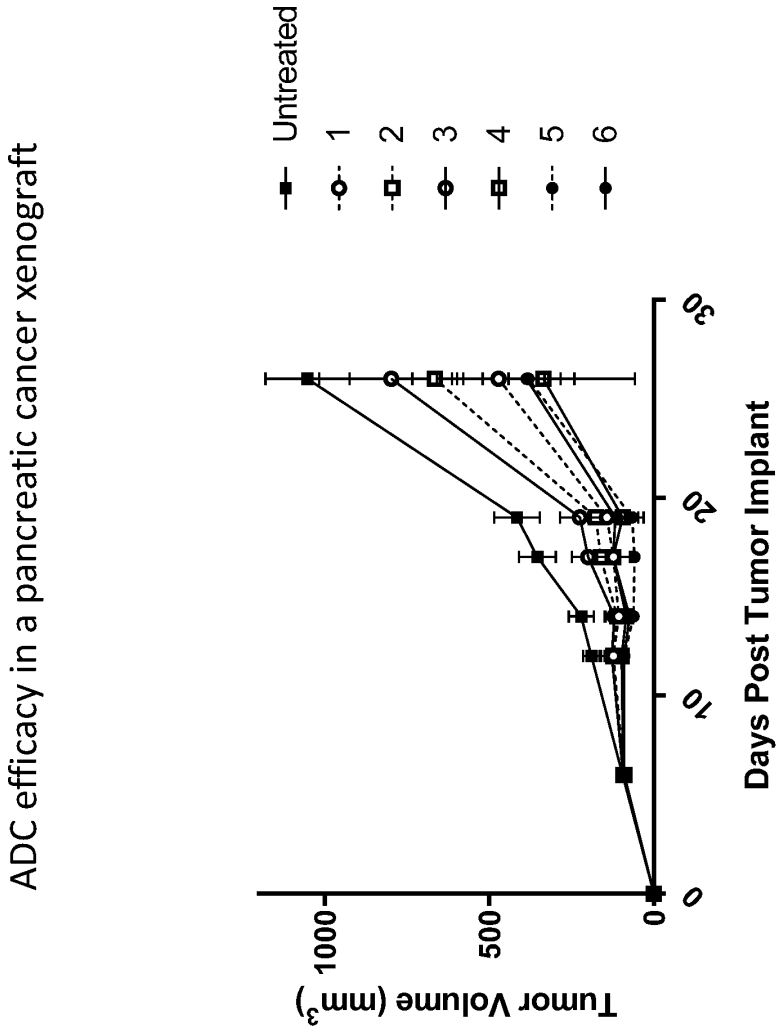

ADC efficacy in a pancreatic cancer xenograft
Untreated
1
2
3
4
5
6
Tumor Volume (mm³)
0
500
1000
0
10
20
30
Days Post Tumor Implant

FIG. 1A

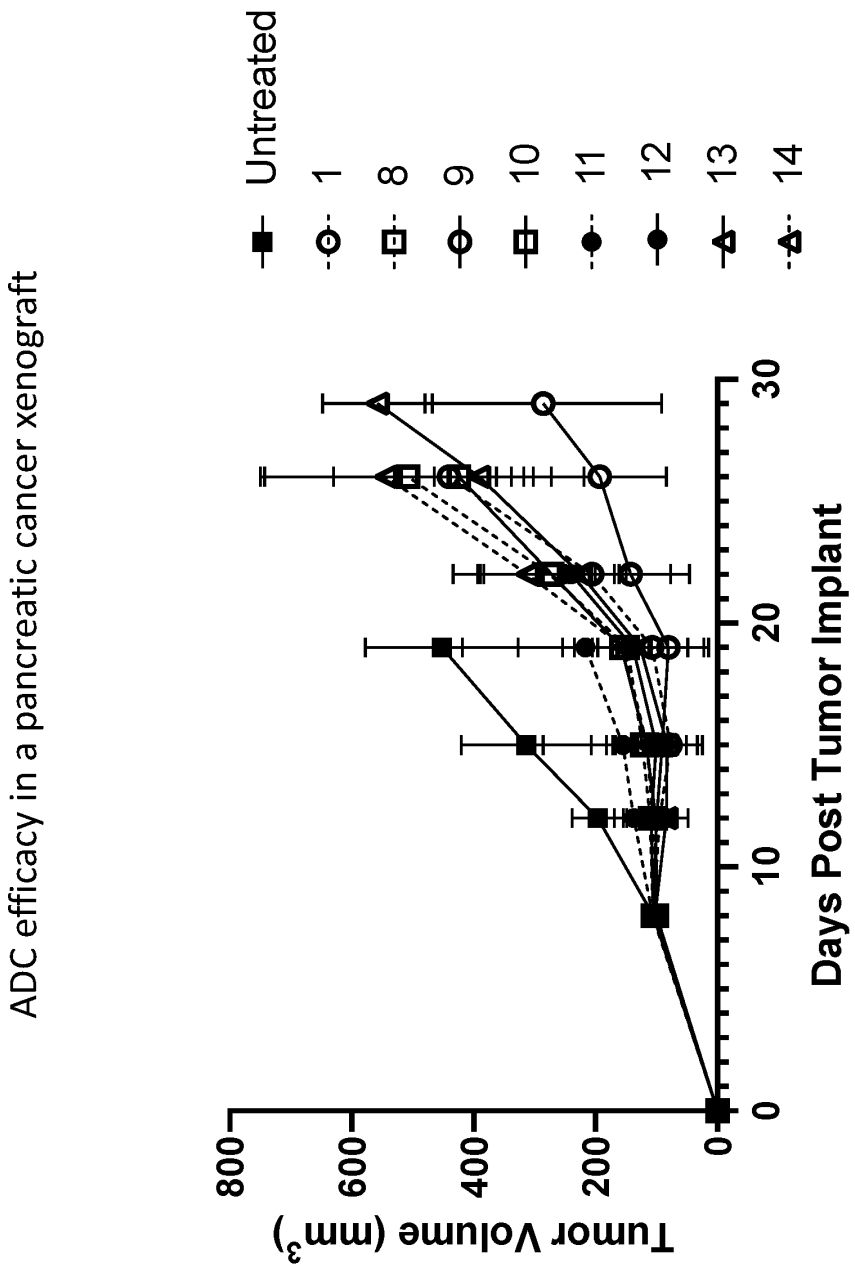

ADC efficacy in a pancreatic cancer xenograft
Untreated
1
8
9
10
11
12
13
14
Tumor Volume (mm3)
800
600
400
200
0
0
10
20
30
Days Post Tumor Implant

FIG. 1B

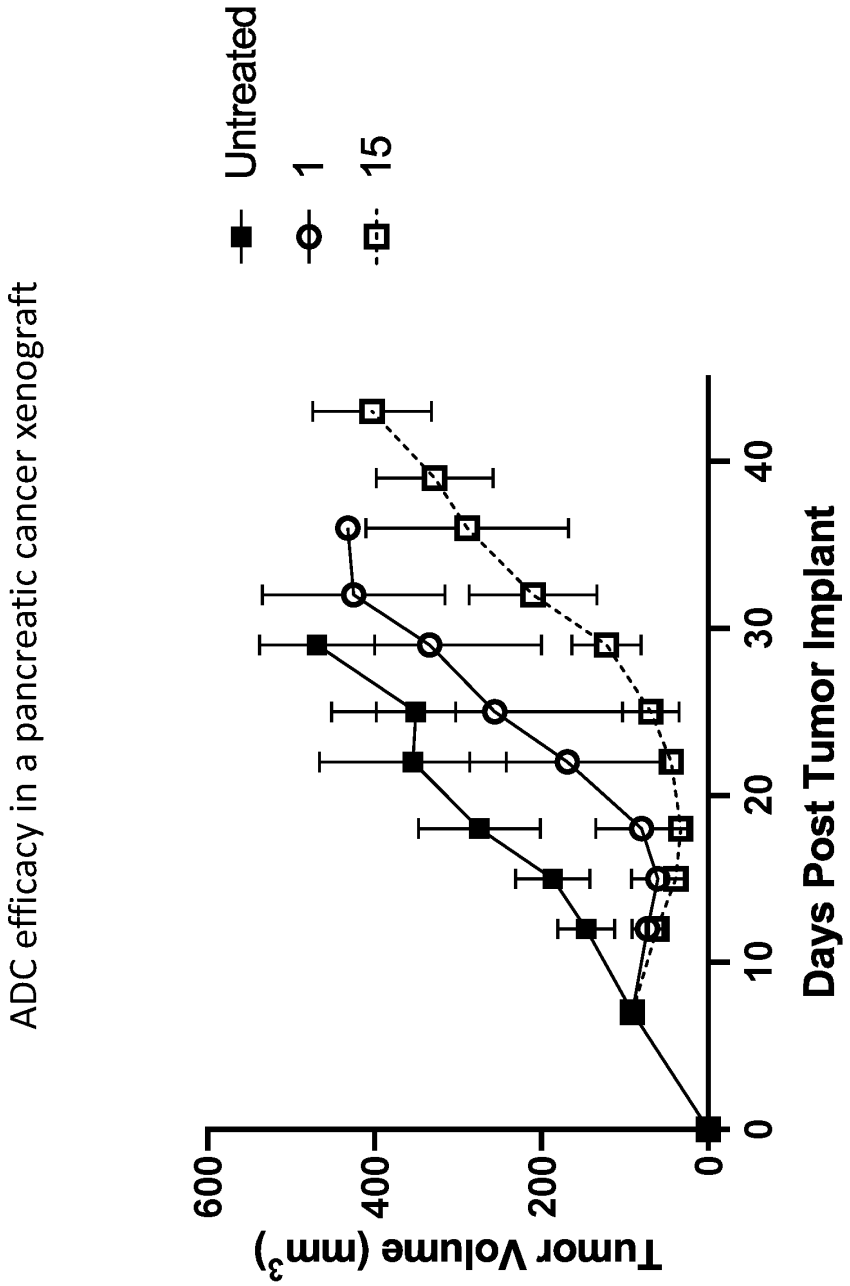

ADC efficacy in a pancreatic cancer xenograft
Untreated
1
15
Tumor Volume (mm³)
600
400
200
0
0
10
20
30
40
Days Post Tumor Implant

FIG. 1C

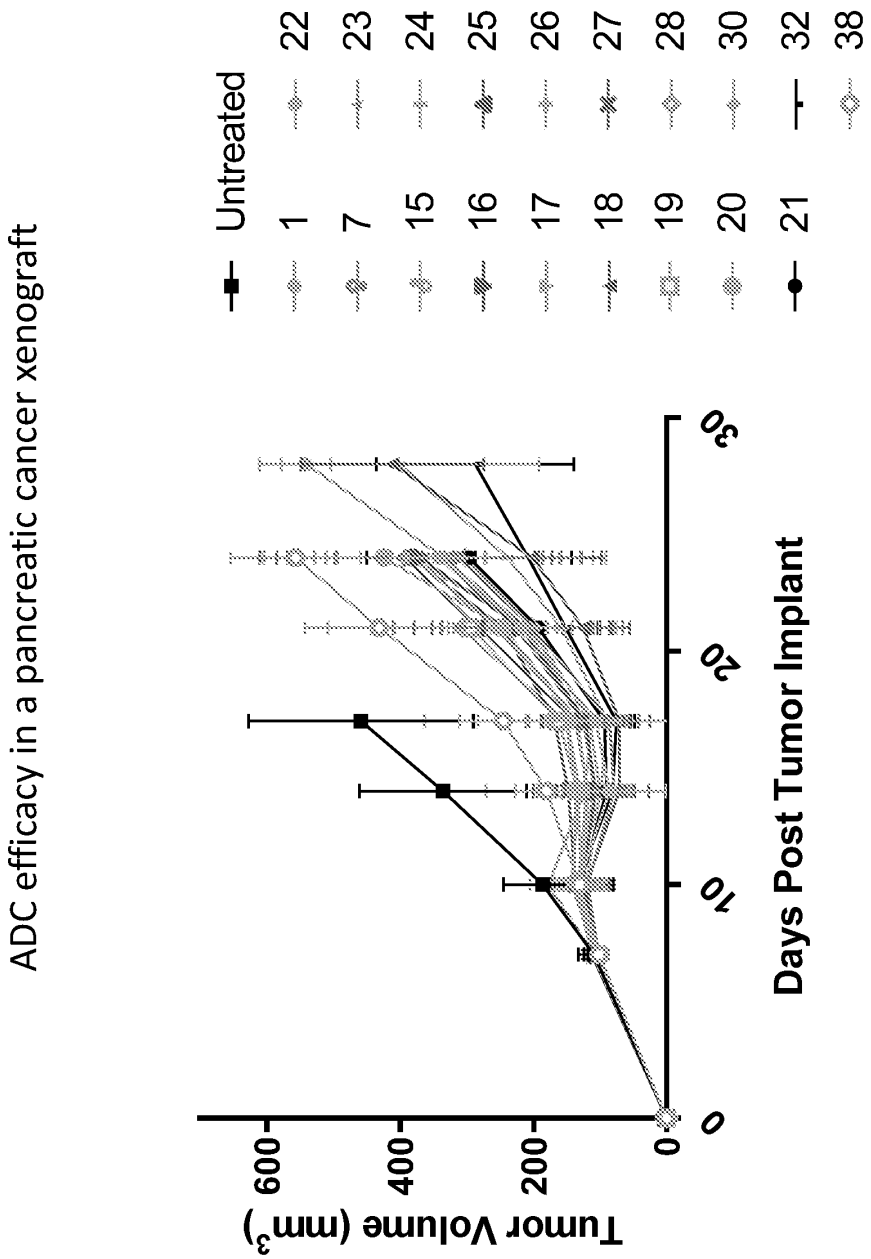

ADC efficacy in a pancreatic cancer xenograft
Untreated
1
7
15
16
17
18
19
20
21
22
23
24
25
26
27
28
30
32
38
Tumor Volume (mm3)
0
200
400
600
0
10
20
30
Days Post Tumor Implant

FIG. 1D

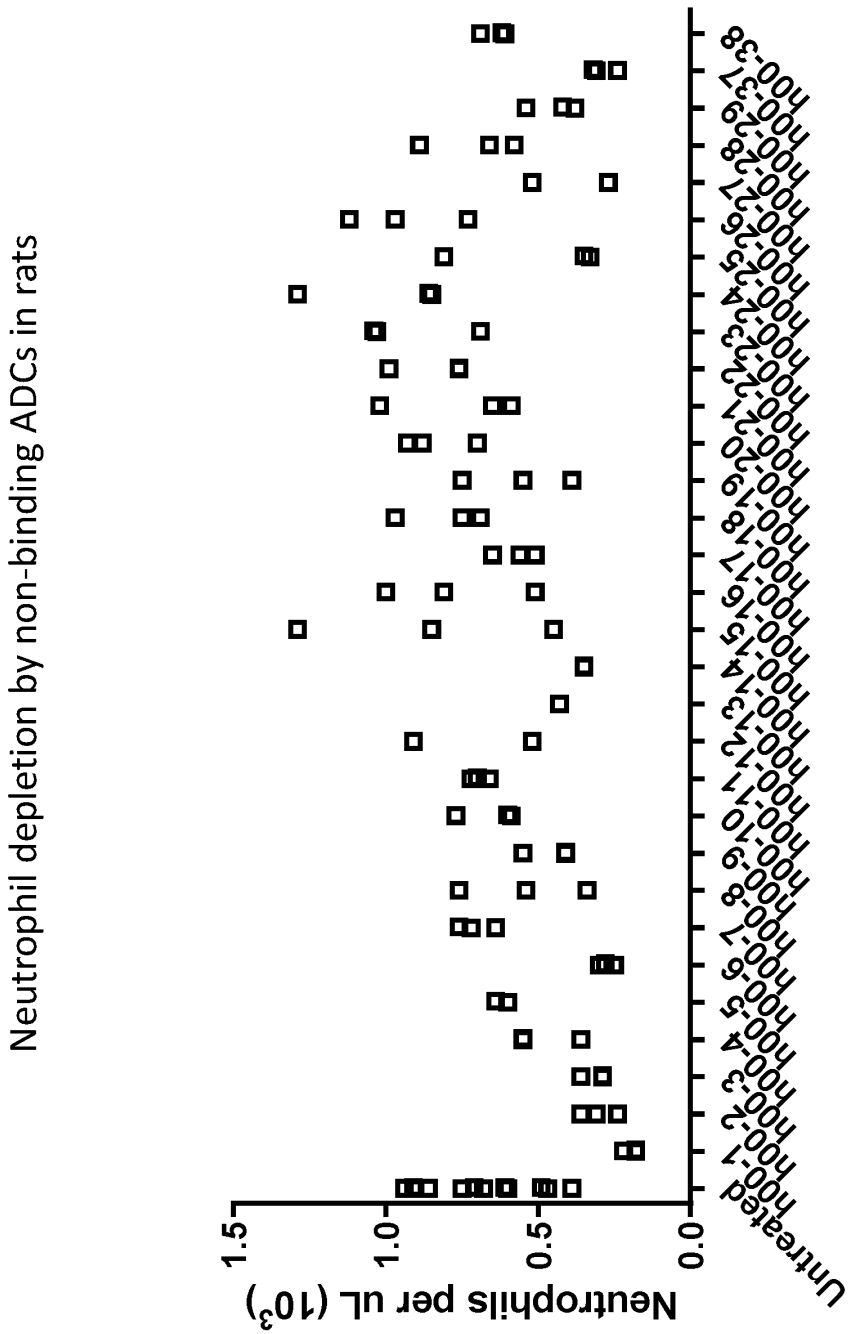
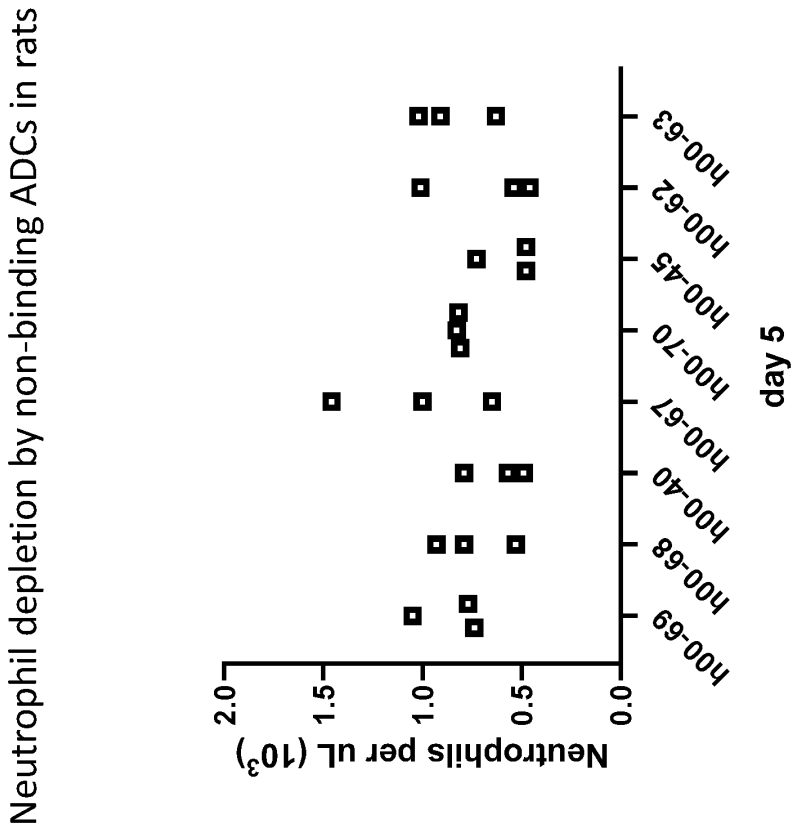

Neutrophil depletion by non-binding ADCs in rats
Neutrophils per uL (10^3)
1.5
1.0
0.5
0.0
Untreated
h00-1
h00-2
h00-3
h00-4
h00-5
h00-6
h00-7
h00-8
h00-9
h00-10
h00-11
h00-12
h00-13
h00-14
h00-15
h00-16
h00-17
h00-18
h00-19
h00-20
h00-21
h00-22
h00-23
h00-24
h00-25
h00-26
h00-27
h00-28
h00-29
h00-37
h00-38

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

FIB. 2B

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

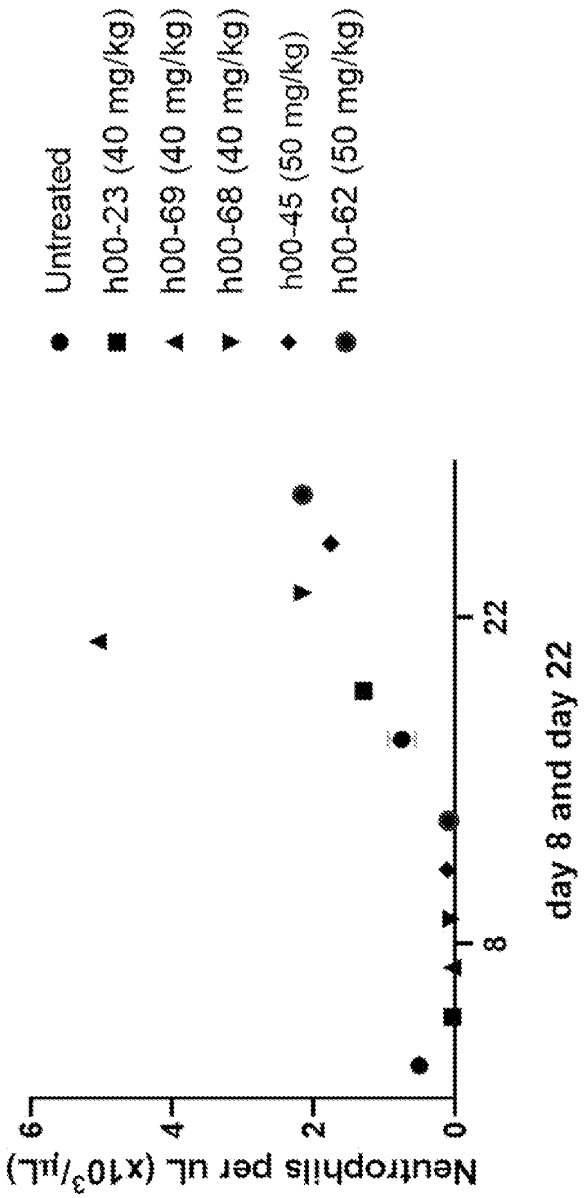


FIG. 2C

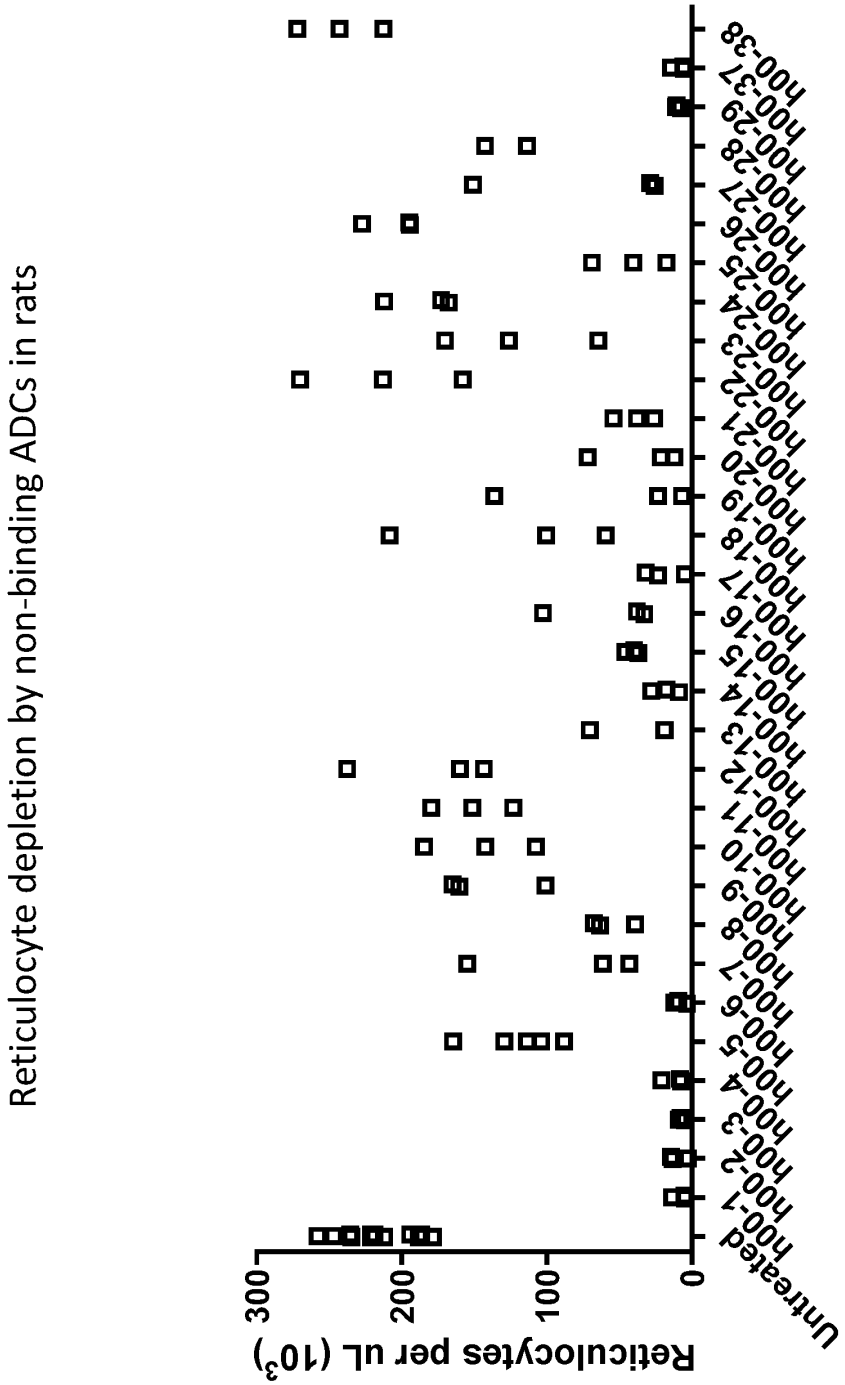

Reticulocyte depletion by non-binding ADCs in rats
Reticulocytes per uL (10^3)
300
200
100
0
Untreated
h00-1
h00-2
h00-3
h00-4
h00-5
h00-6
h00-7
h00-8
h00-9
h00-10
h00-11
h00-12
h00-13
h00-14
h00-15
h00-16
h00-17
h00-18
h00-19
h00-20
h00-21
h00-22
h00-23
h00-24
h00-25
h00-26
h00-27
h00-28
h00-29
h00-37
h00-38

FIG. 3A

Reticulocyte depletion by non-binding ADCs in rats

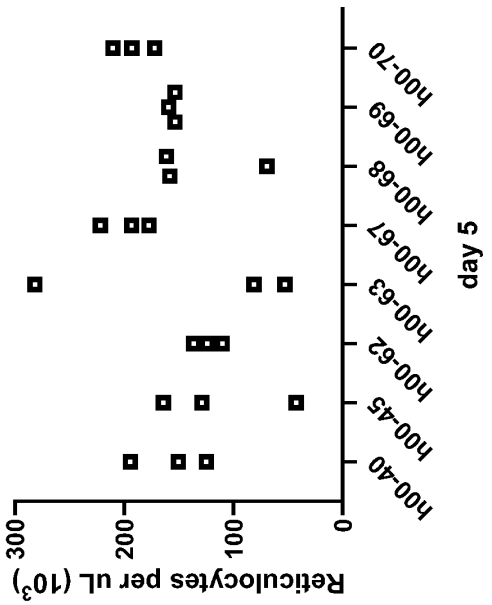


FIG. 3B

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

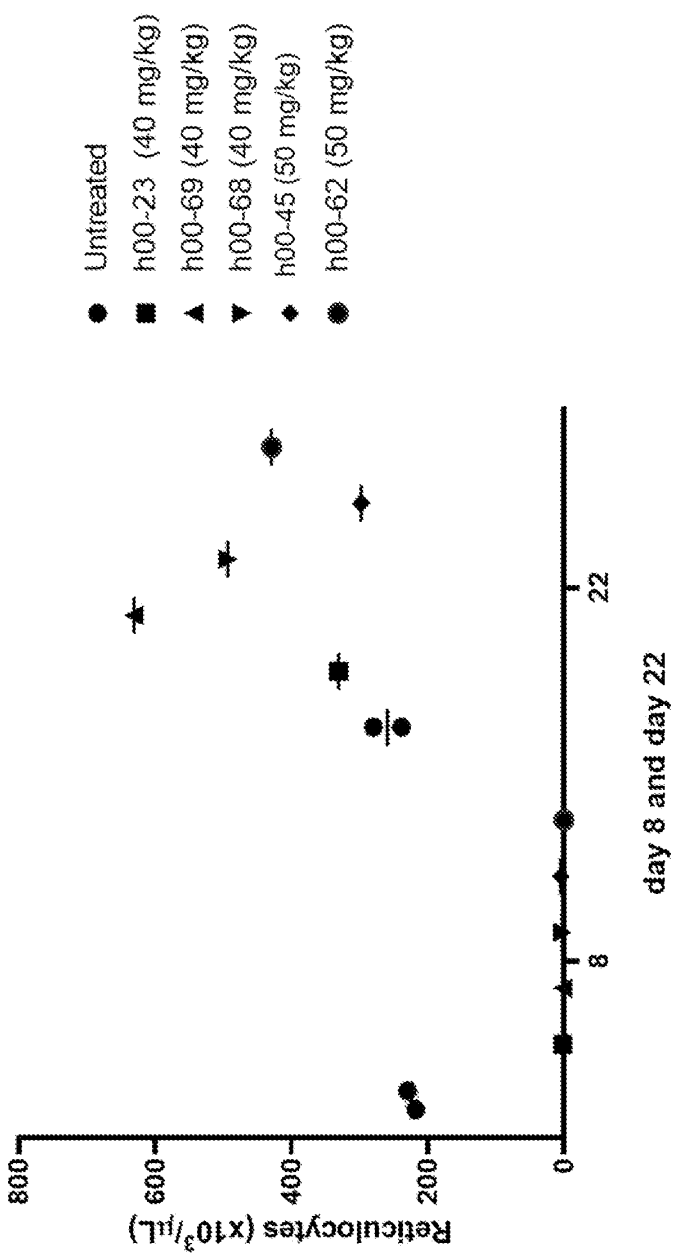


FIG. 3C

Bone marrow toxicity by non-binding ADCs in rats

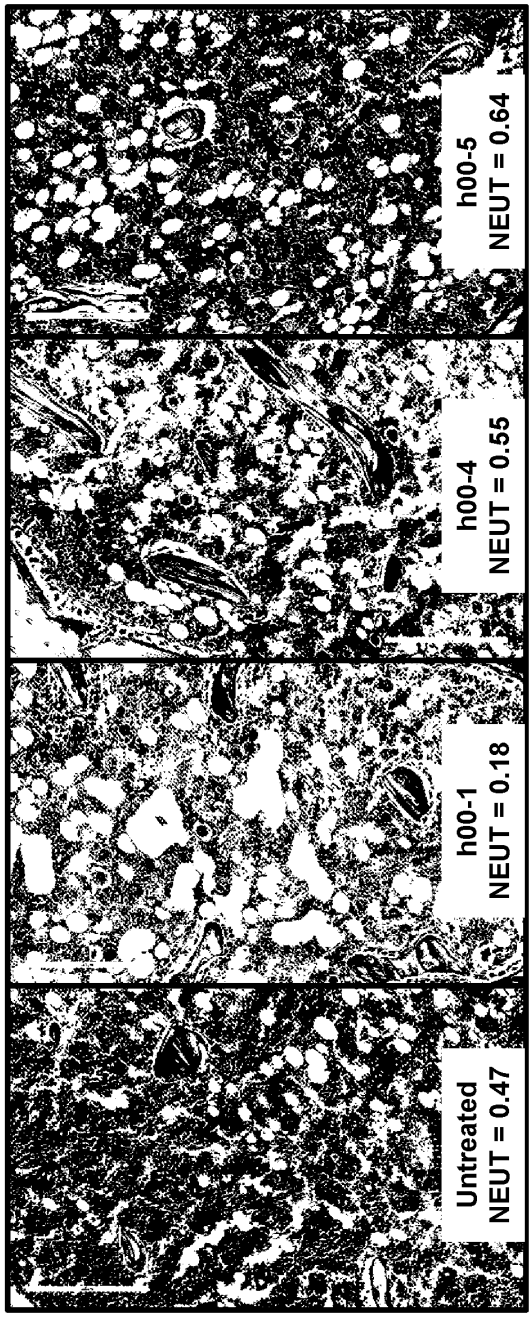


FIG. 4

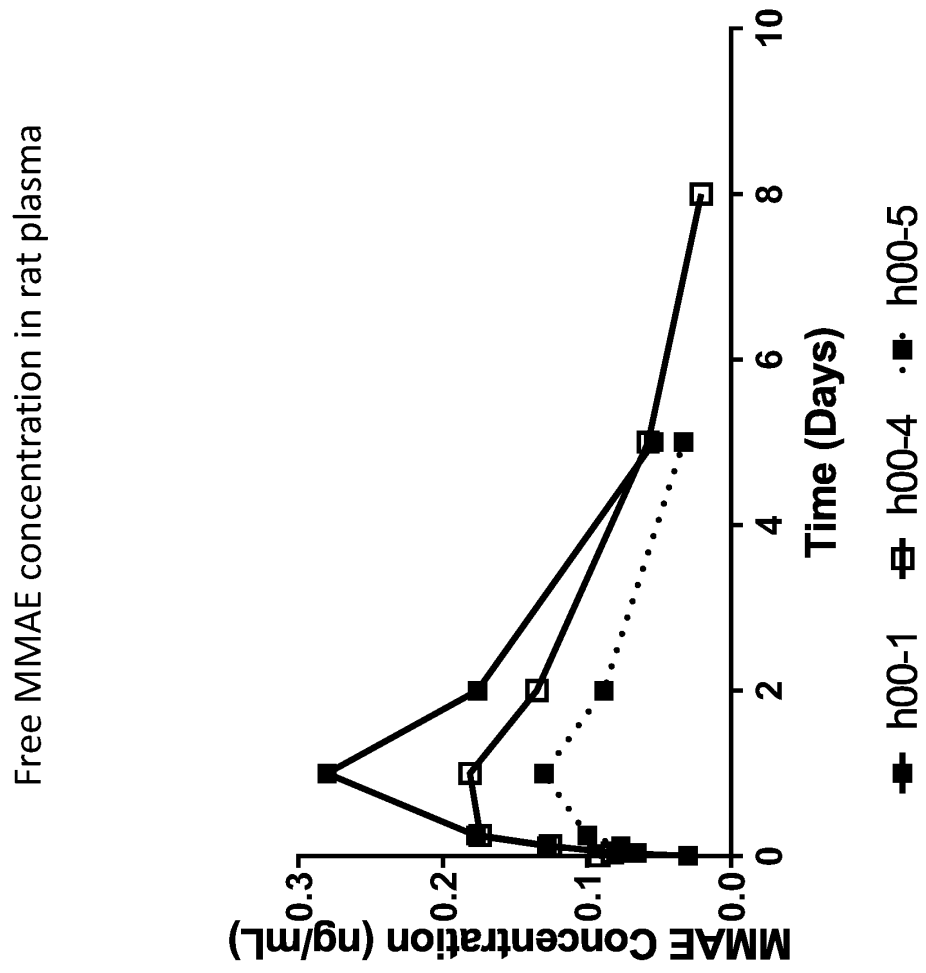

Free MMAE concentration in rat plasma
MMAE Concentration (ng/mL)
0.0
0.1
0.2
0.3
0
2
4
6
8
10
Time (Days)
h00-1
h00-4
h00-5

FIG. 5A

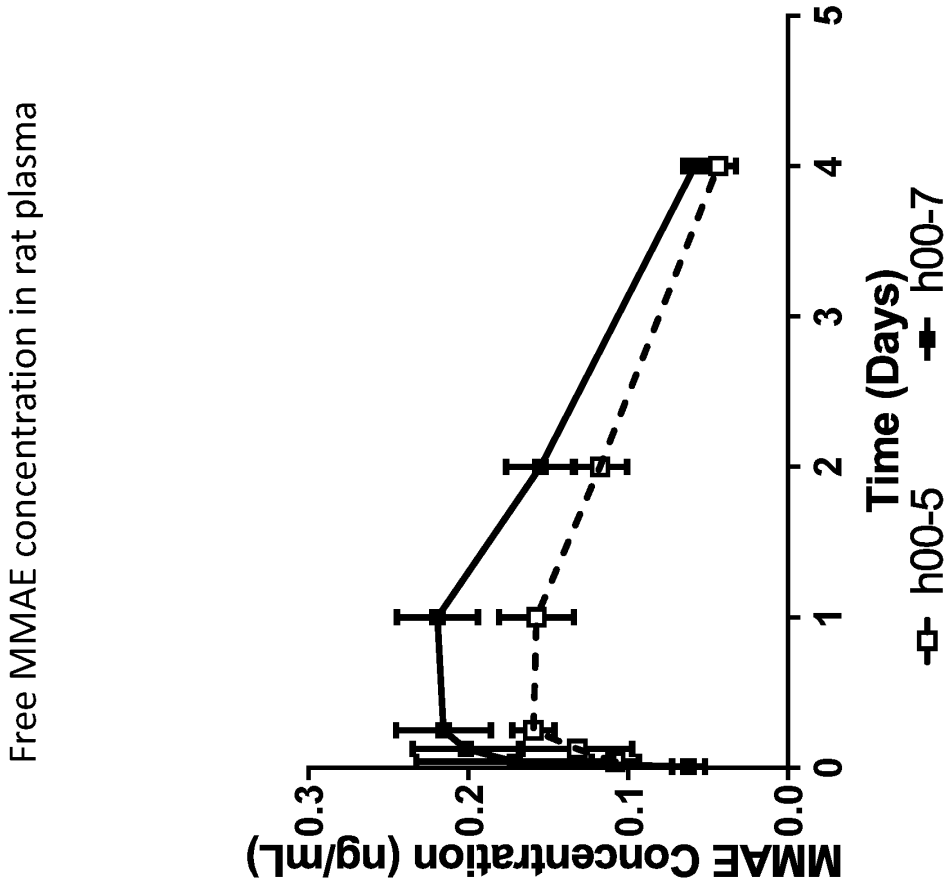

Free MMAE concentration in rat plasma
MMAE Concentration (ng/mL)
0.0
0.1
0.2
0.3
0
1
2
3
4
5
Time (Days)
h00-5
h00-7

FIG. 5B

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

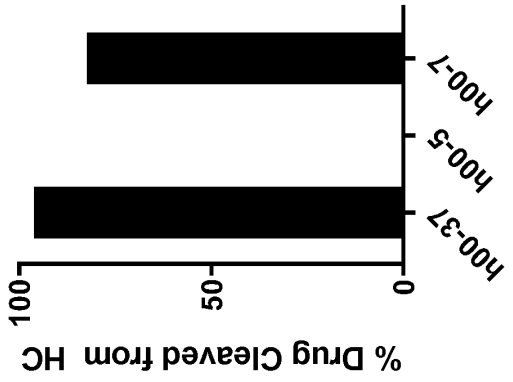


FIG. 6A

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

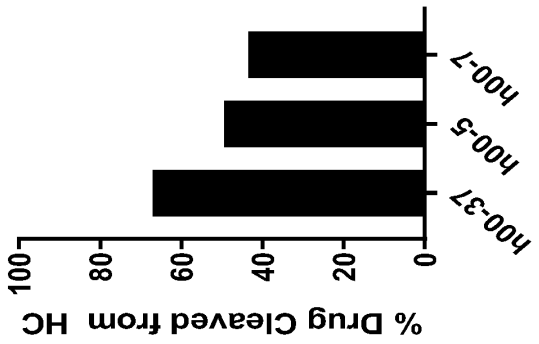


FIG. 6B

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

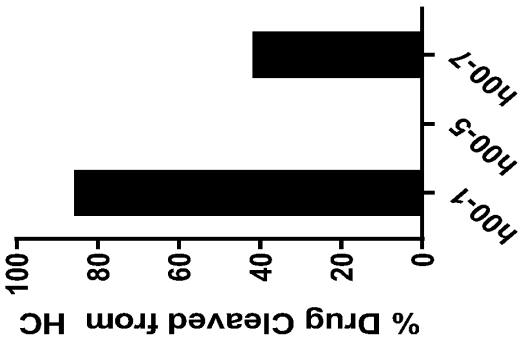


FIG. 6C

Free tumor MMAE from ADC efficacy in a pancreatic cancer xenograft

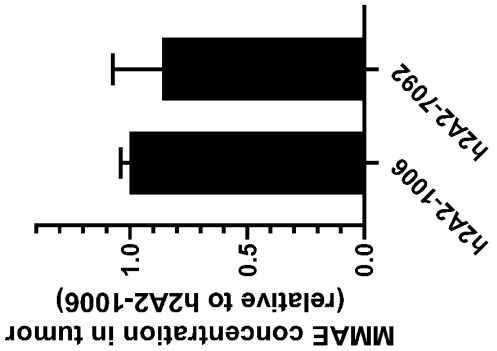


FIG. 6D

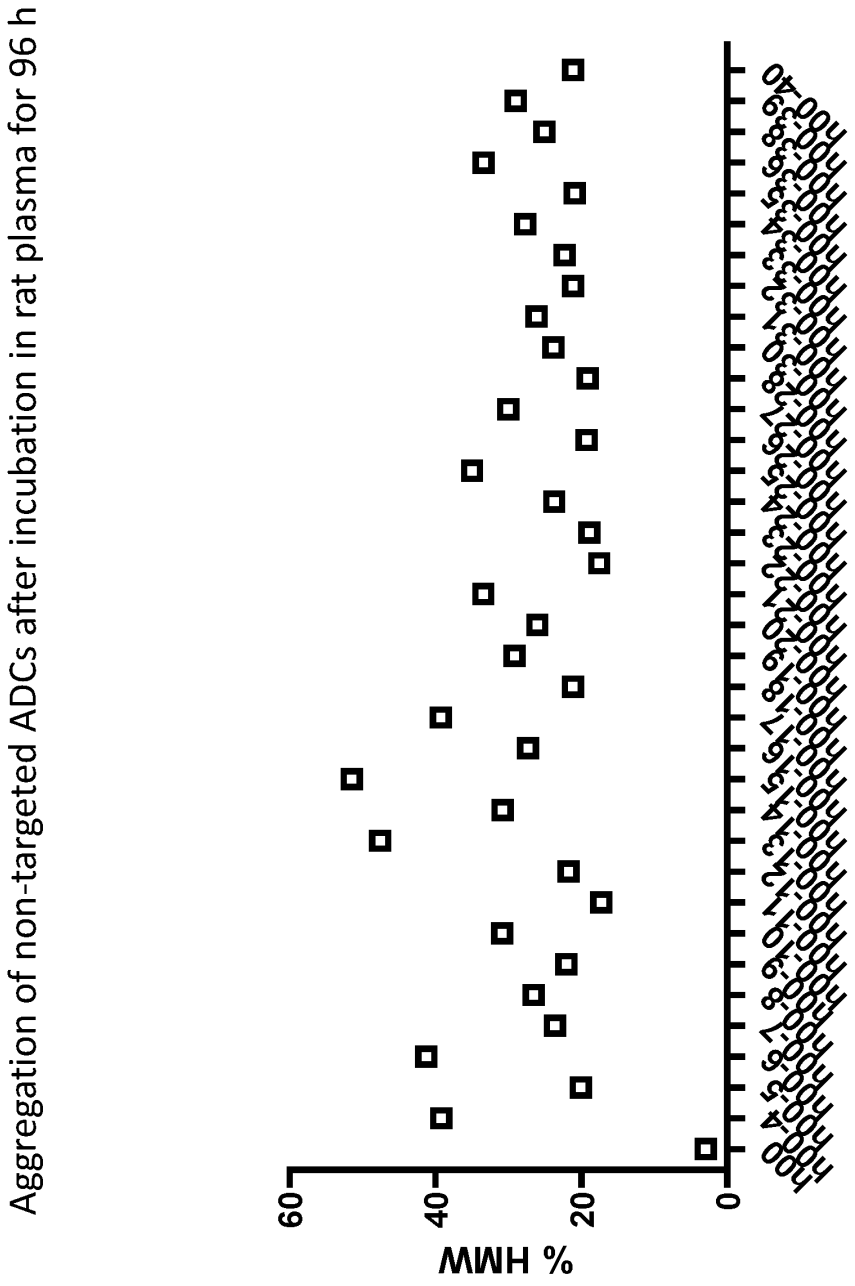

Aggregation of non-targeted ADCs after incubation in rat plasma for 96 h
% HMW
60
40
20
0

FIG. 7A

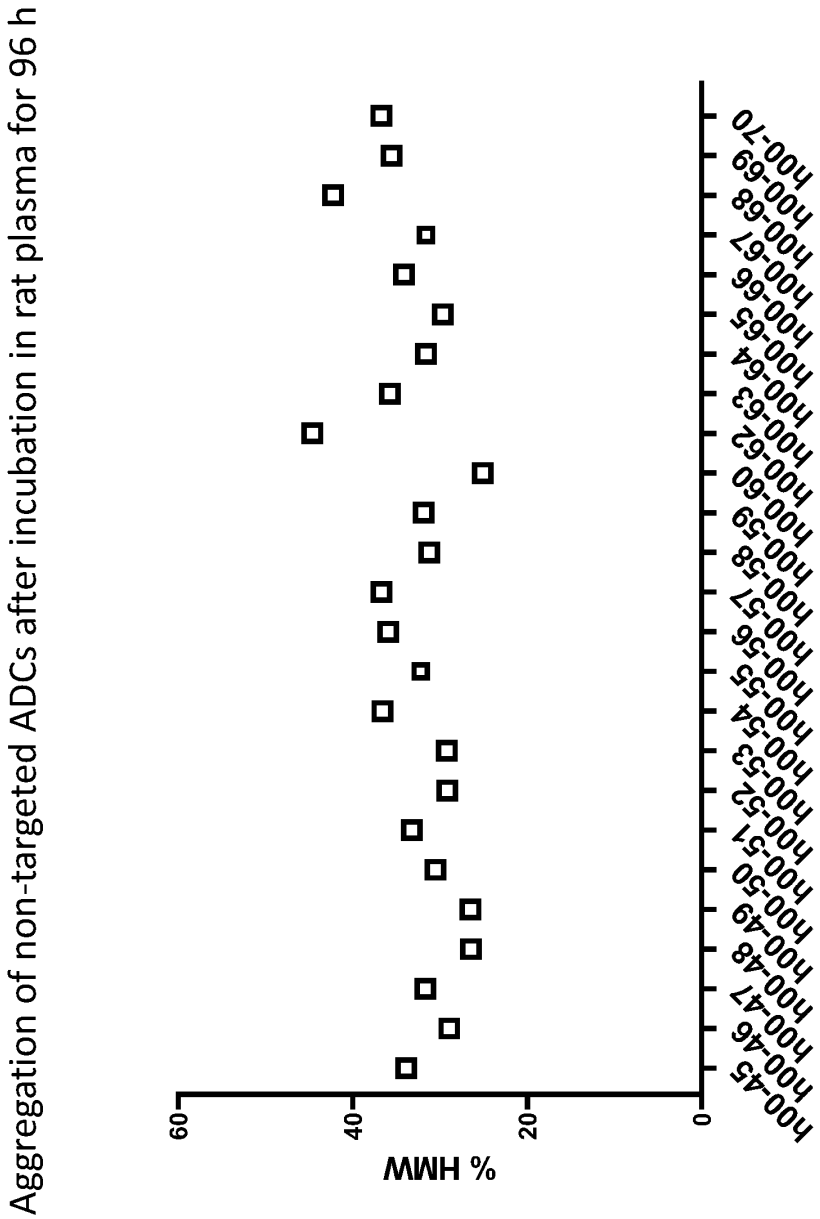

Aggregation of non-targeted ADCs after incubation in rat plasma for 96 h
% HMW
0
20
40
60
h00-45
h00-46
h00-47
h00-48
h00-49
h00-50
h00-51
h00-52
h00-53
h00-54
h00-55
h00-56
h00-57
h00-58
h00-59
h00-60
h00-62
h00-63
h00-64
h00-65
h00-66
h00-67
h00-68
h00-69
h00-70

FIG. 7B

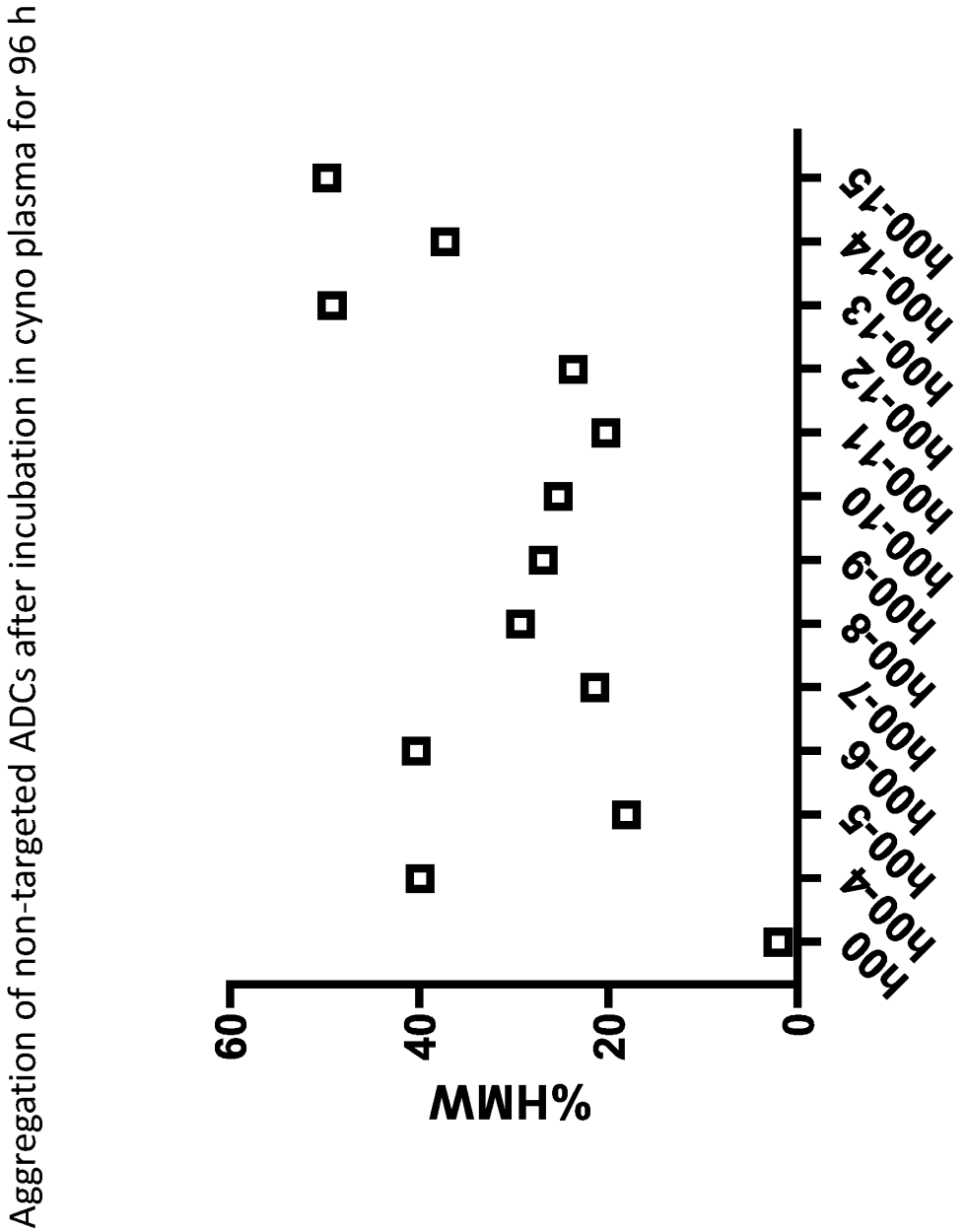

Aggregation of non-targeted ADCs after incubation in cyno plasma for 96 h
%HMW
0
20
40
60
h00
h00-4
h00-5
h00-6
h00-7
h00-8
h00-9
h00-10
h00-11
h00-12
h00-13
h00-14
h00-15

FIG. 8

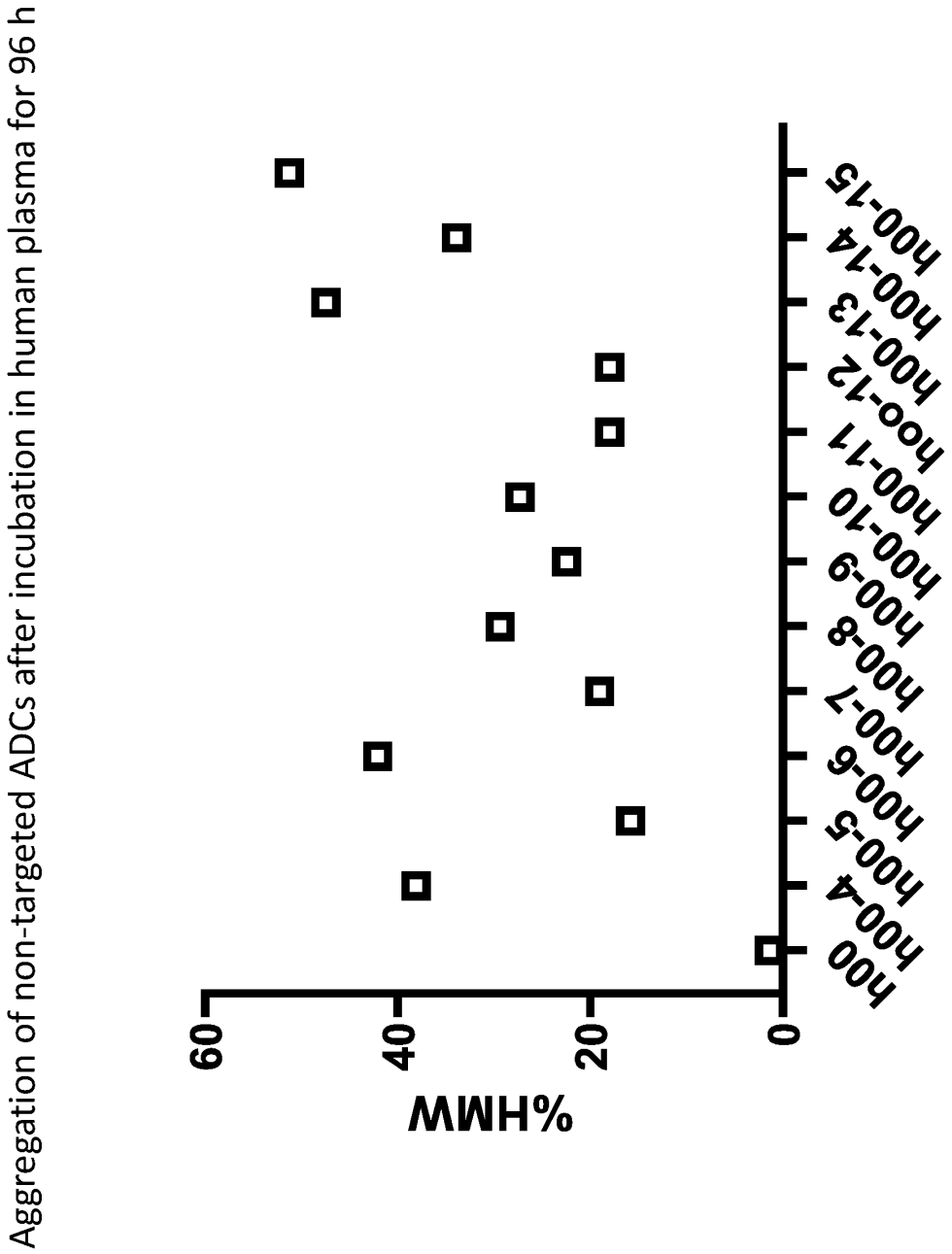

Aggregation of non-targeted ADCs after incubation in human plasma for 96 h
MWH%
60
40
20
0
h00
h00-4
h00-5
h00-6
h00-7
h00-8
h00-9
h00-10
h00-11
h00-12
h00-13
h00-14
h00-15

FIG. 9

Aggregation of non-targeted MMAF ADCs after incubation in rat plasma

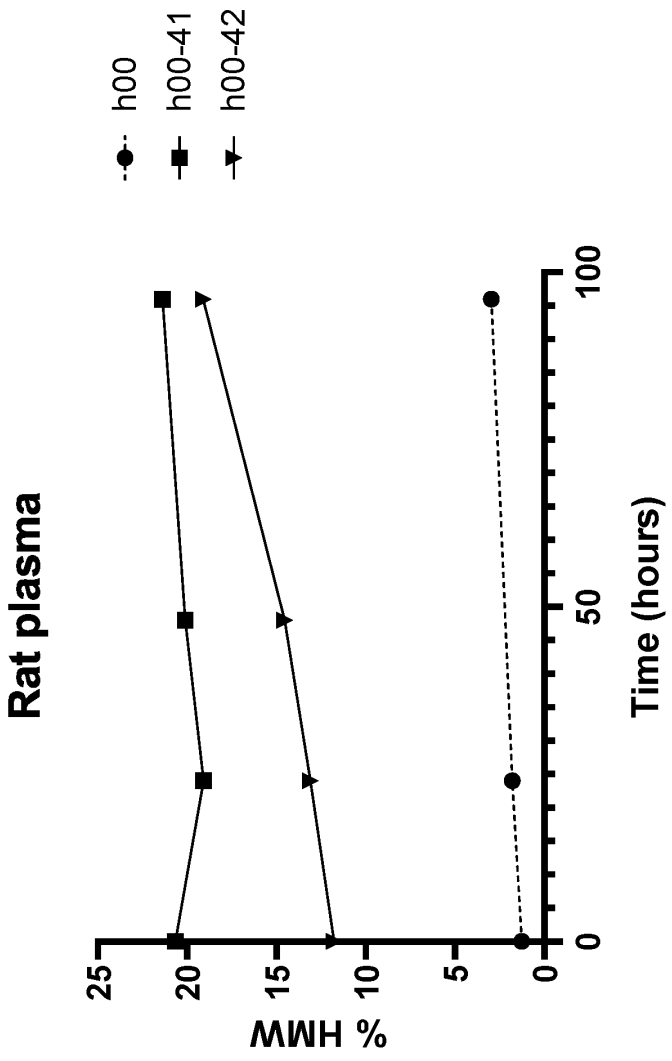


FIG. 10

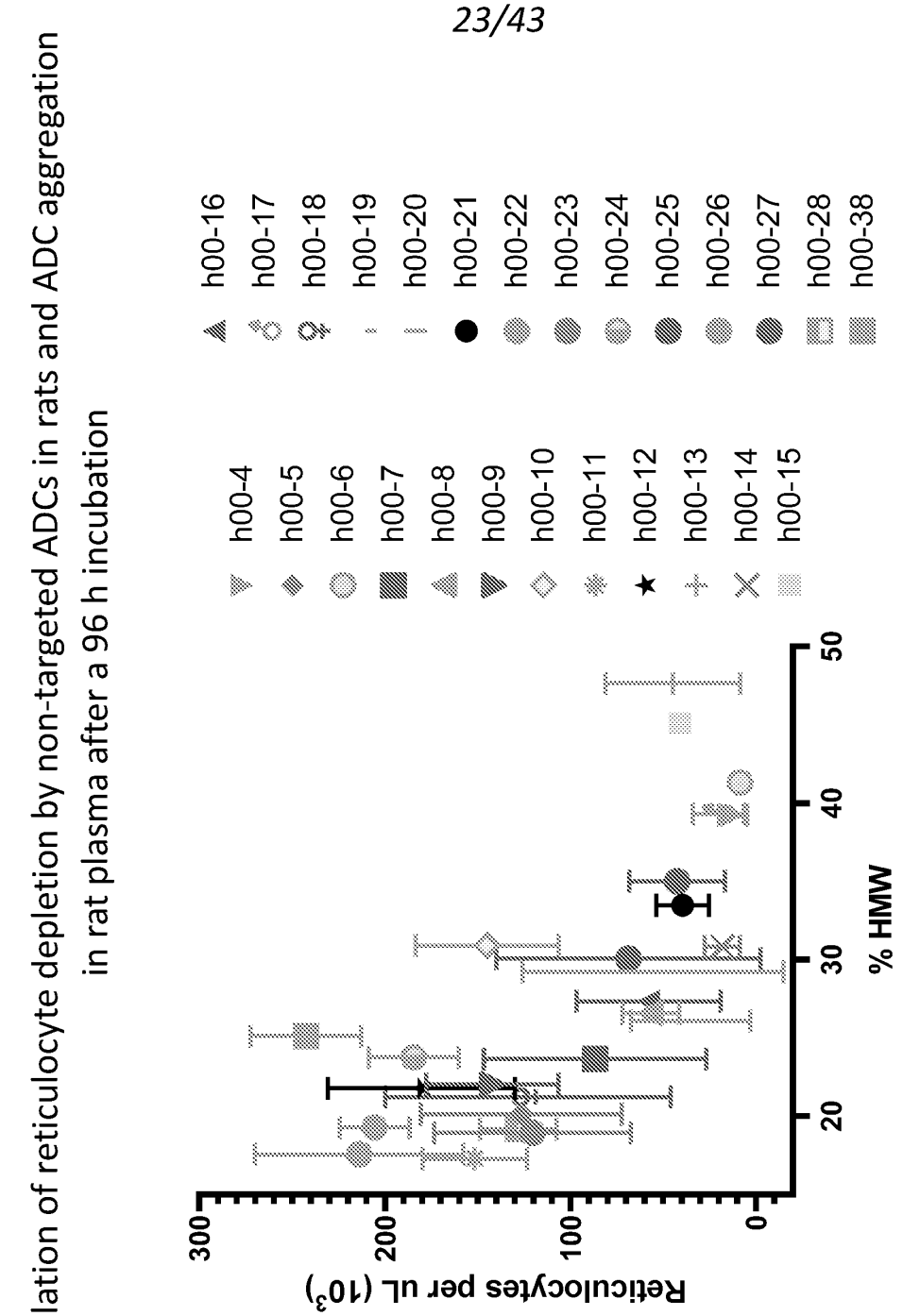

Relation of reticulocyte depletion by non-targeted ADCs in rats and ADC aggregation in rat plasma after a 96 h incubation
h00-4
h00-5
h00-6
h00-7
h00-8
h00-9
h00-10
h00-11
h00-12
h00-13
h00-14
h00-15
h00-16
h00-17
h00-18
h00-19
h00-20
h00-21
h00-22
h00-23
h00-24
h00-25
h00-26
h00-27
h00-28
h00-38
Reticulocytes per uL (10³)
300
200
100
0
20
30
40
50
% HMW

FIG. 11

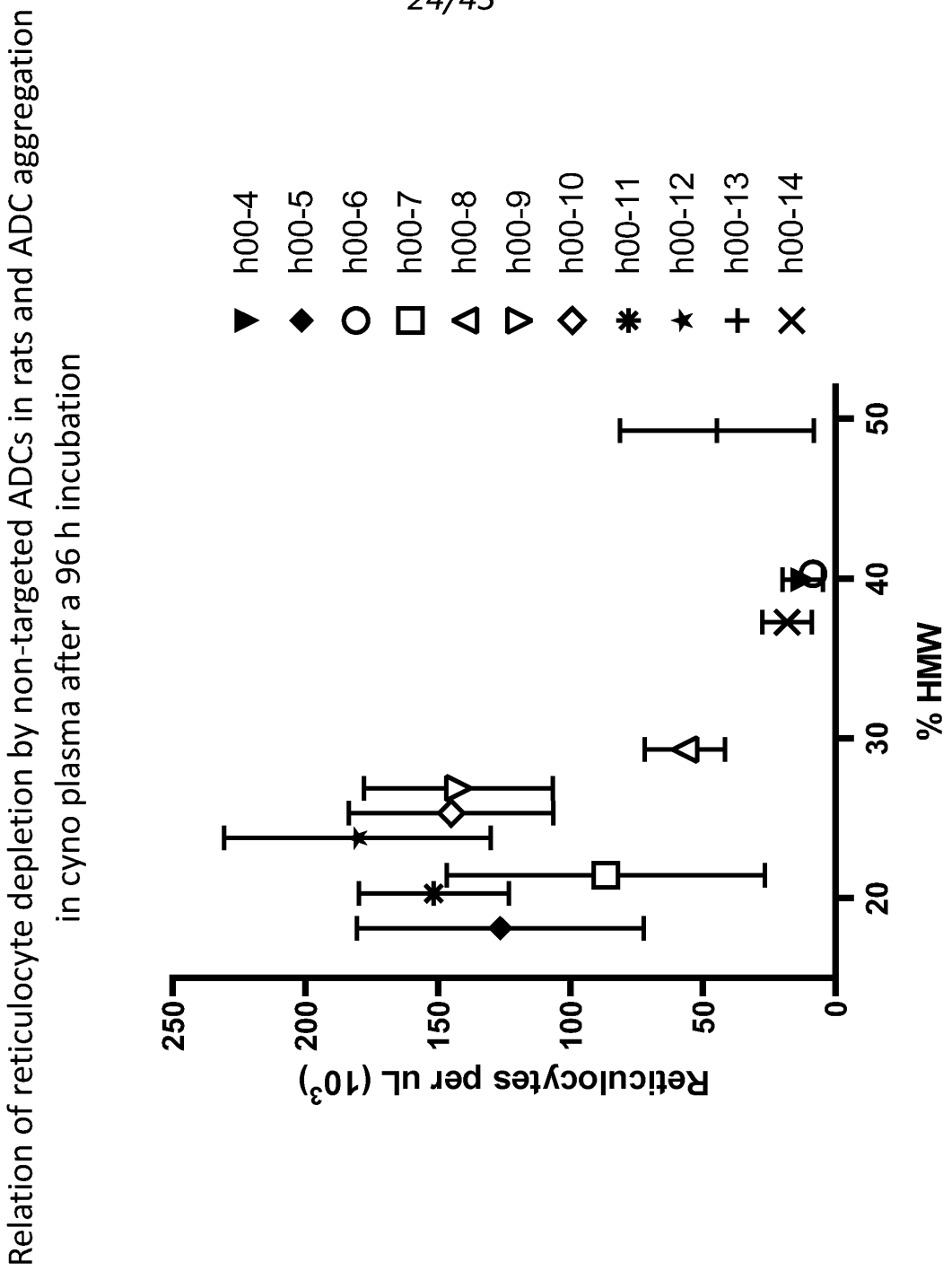

Relation of reticulocyte depletion by non-targeted ADCs in rats and ADC aggregation in cyno plasma after a 96 h incubation
h00-4
h00-5
h00-6
h00-7
h00-8
h00-9
h00-10
h00-11
h00-12
h00-13
h00-14
Reticulocytes per uL (10^3)
250
200
150
100
50
0
20
30
40
50
% HMW

FIG. 12

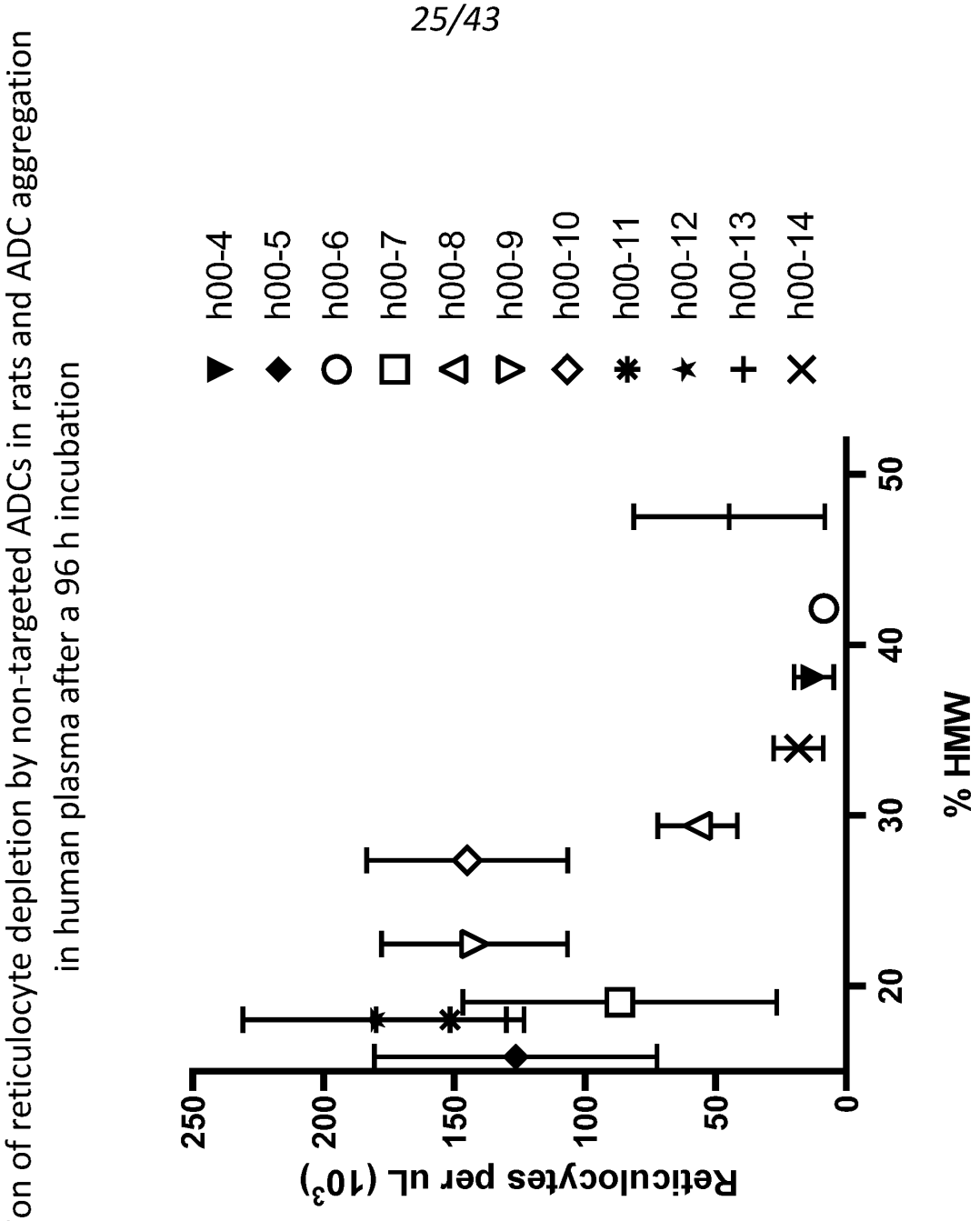

Relation of reticulocyte depletion by non-targeted ADCs in rats and ADC aggregation in human plasma after a 96 h incubation
h00-4
h00-5
h00-6
h00-7
h00-8
h00-9
h00-10
h00-11
h00-12
h00-13
h00-14
Reticulocytes per uL (10³)
250
200
150
100
50
0
20
30
40
50
% HMW

FIG. 13

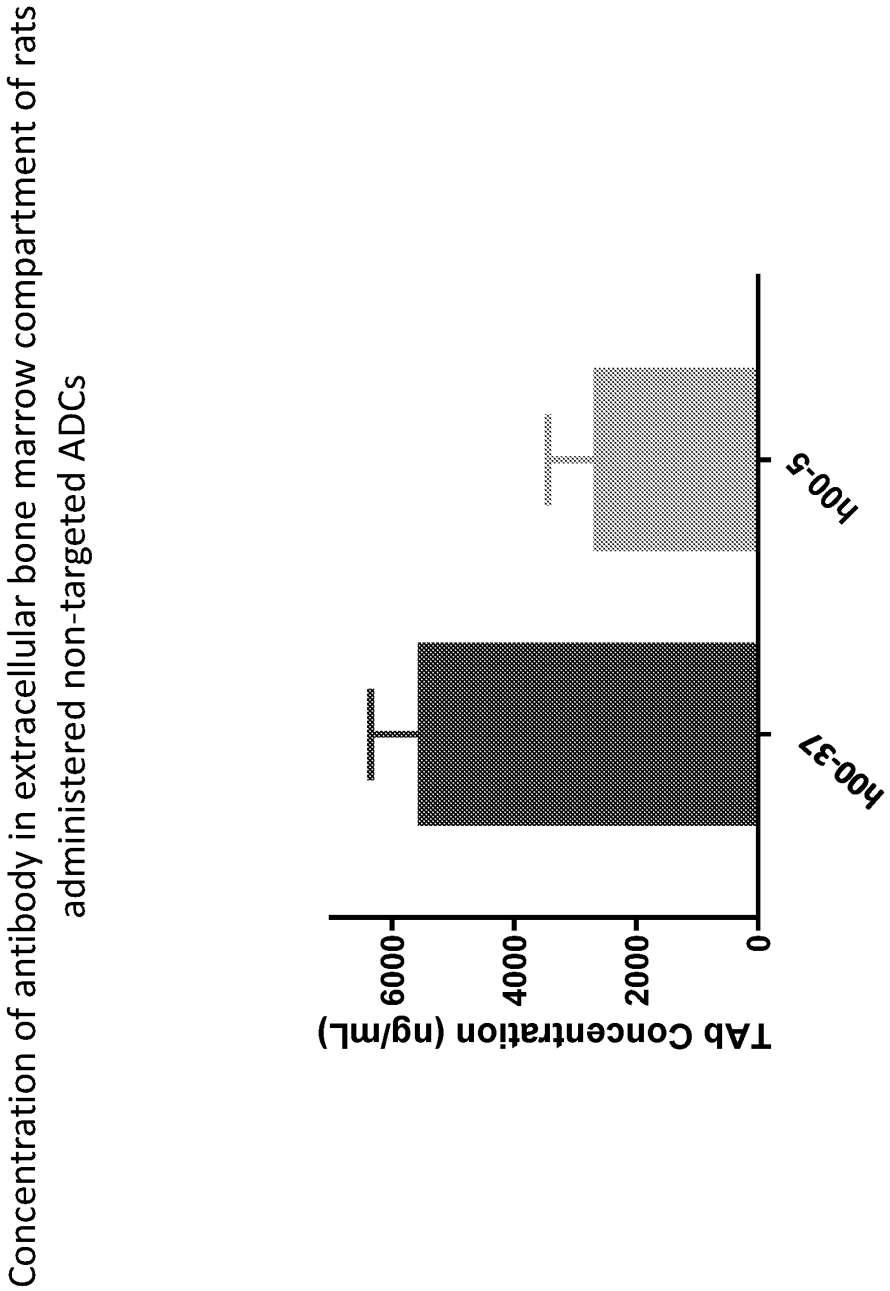

Concentration of antibody in extracellular bone marrow compartment of rats administered non-targeted ADCs
TAb Concentration (ng/mL)
0
2000
4000
6000
h00-37
h00-5

FIG. 14

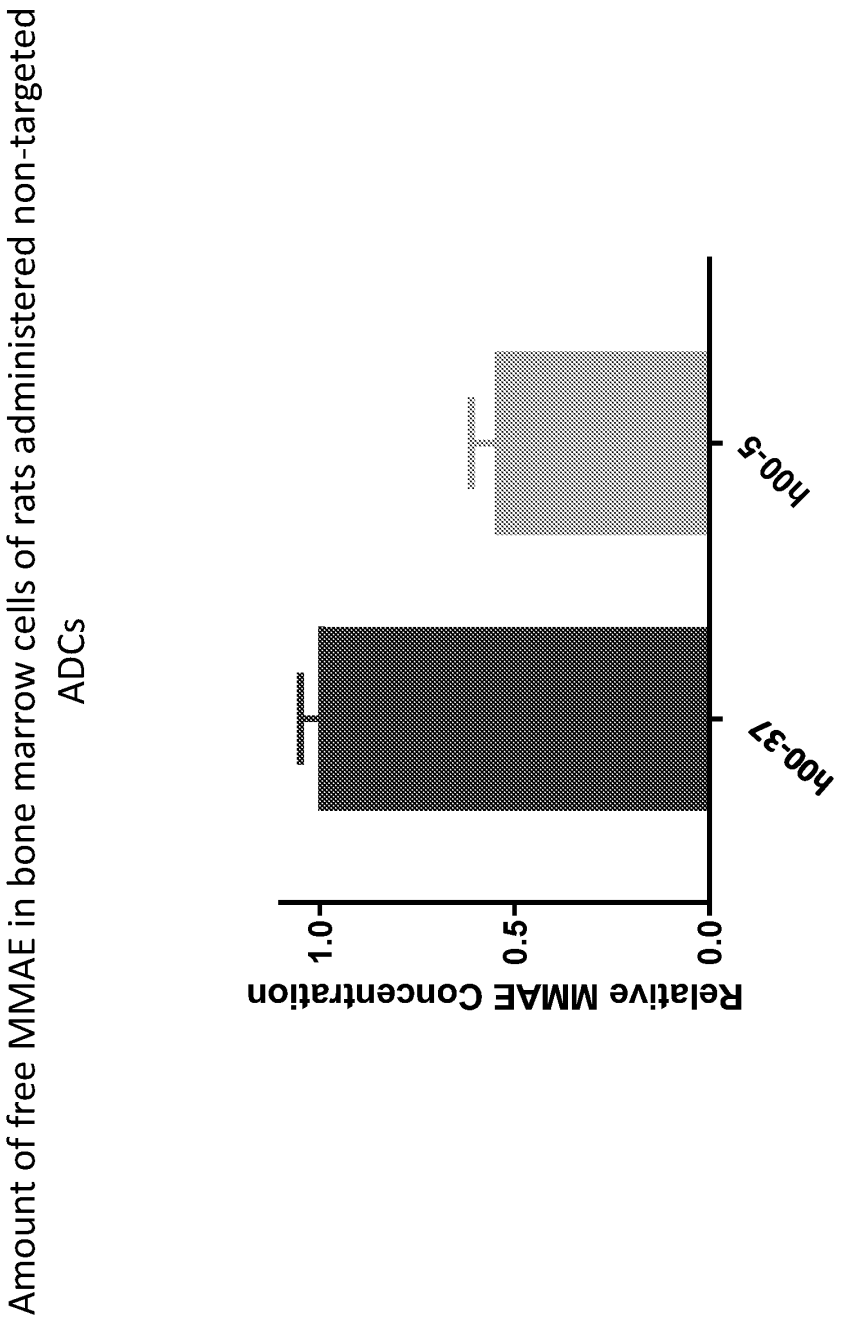

Amount of free MMAE in bone marrow cells of rats administered non-targeted ADCs
Relative MMAE Concentration
0.0
0.5
1.0
h00-37
h00-5

FIG. 15

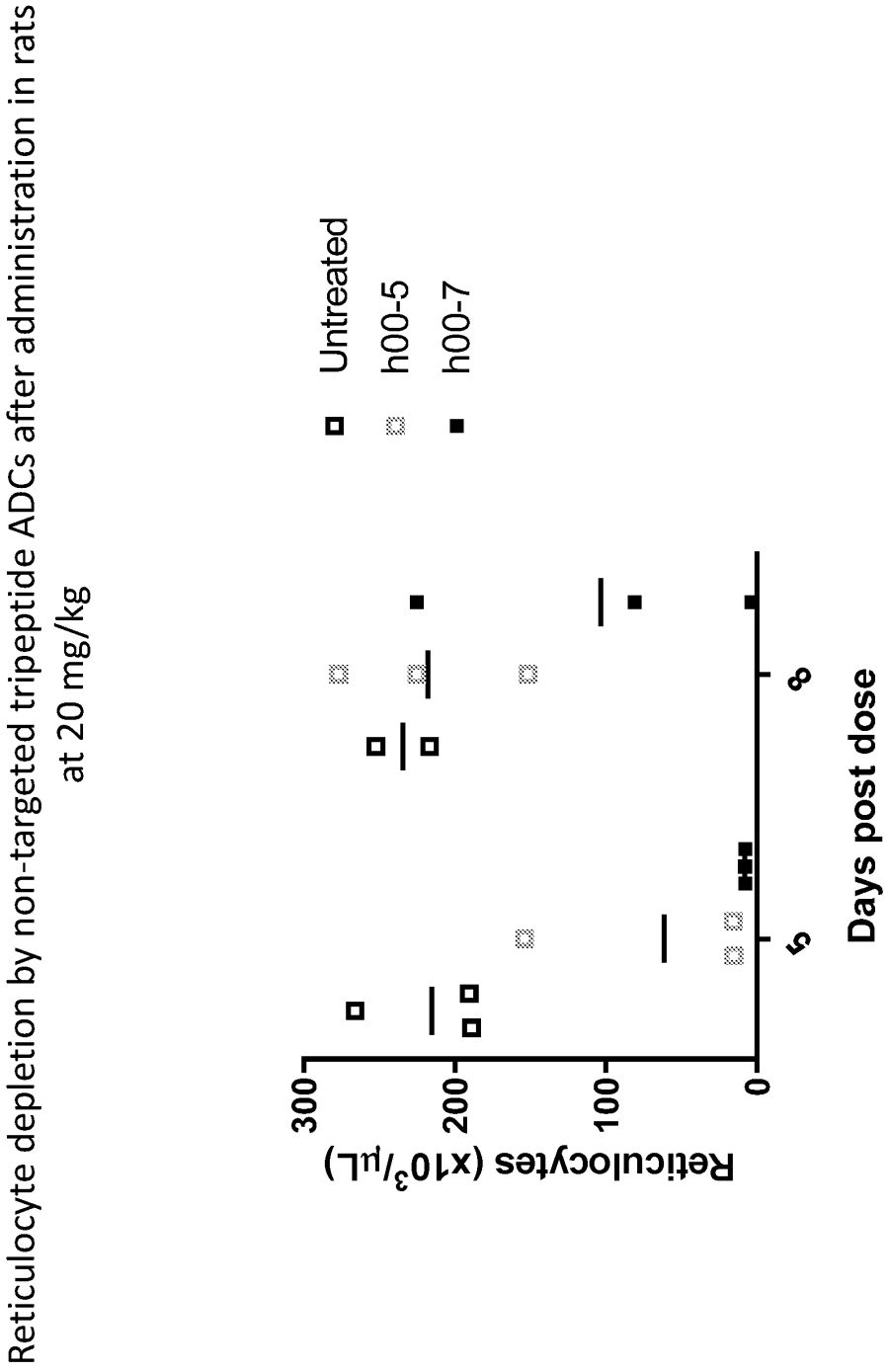

Reticulocyte depletion by non-targeted tripeptide ADCs after administration in rats at 20 mg/kg
Untreated
h00-5
h00-7
Reticulocytes (x10³/μL)
300
200
100
0
5
9
Days post dose

FIG. 16

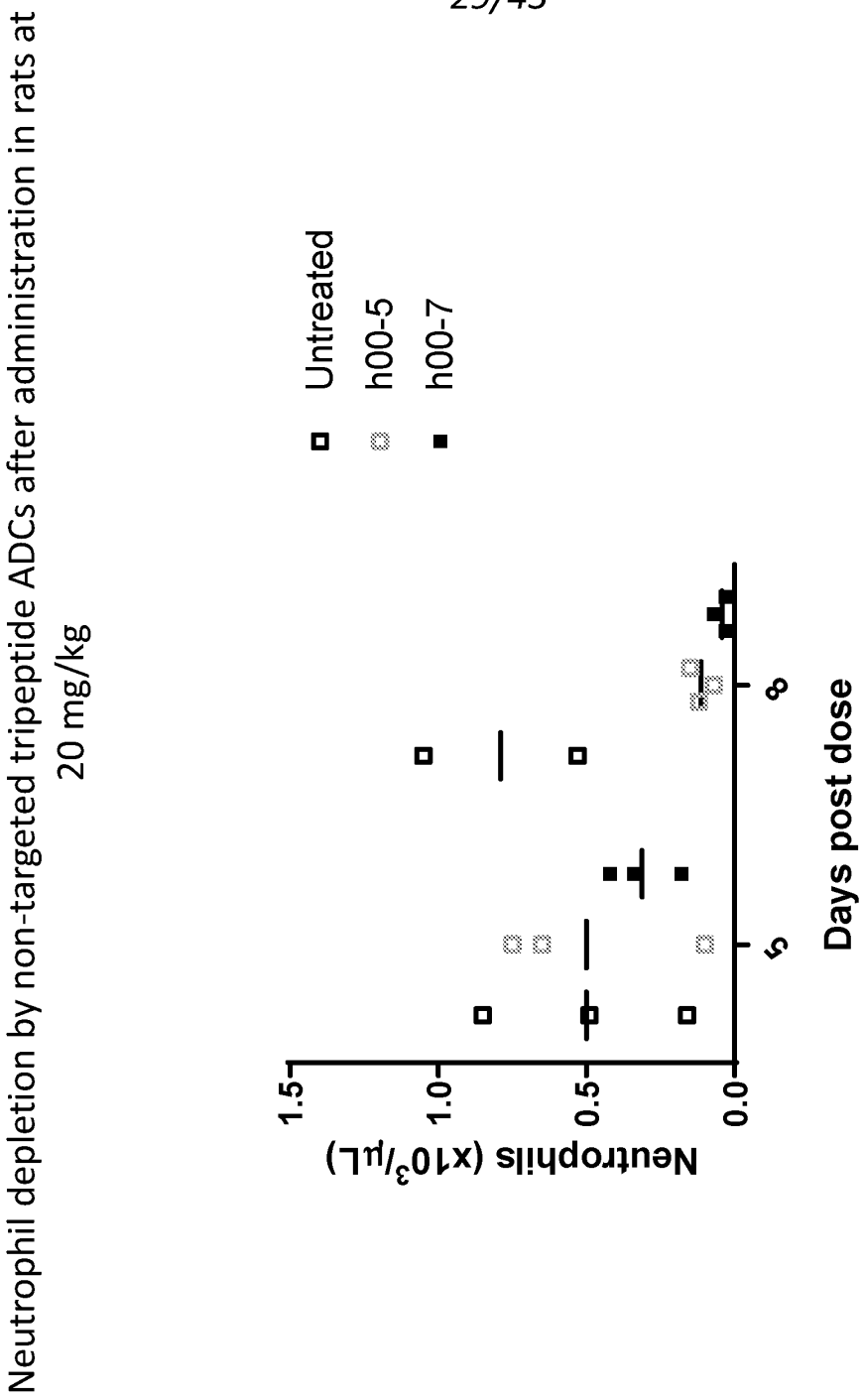

Neutrophil depletion by non-targeted tripeptide ADCs after administration in rats at 20 mg/kg
Untreated
h00-5
h00-7
Neutrophils (x10³/μL)
1.5
1.0
0.5
0.0
5
8
Days post dose

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	5	5	5	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

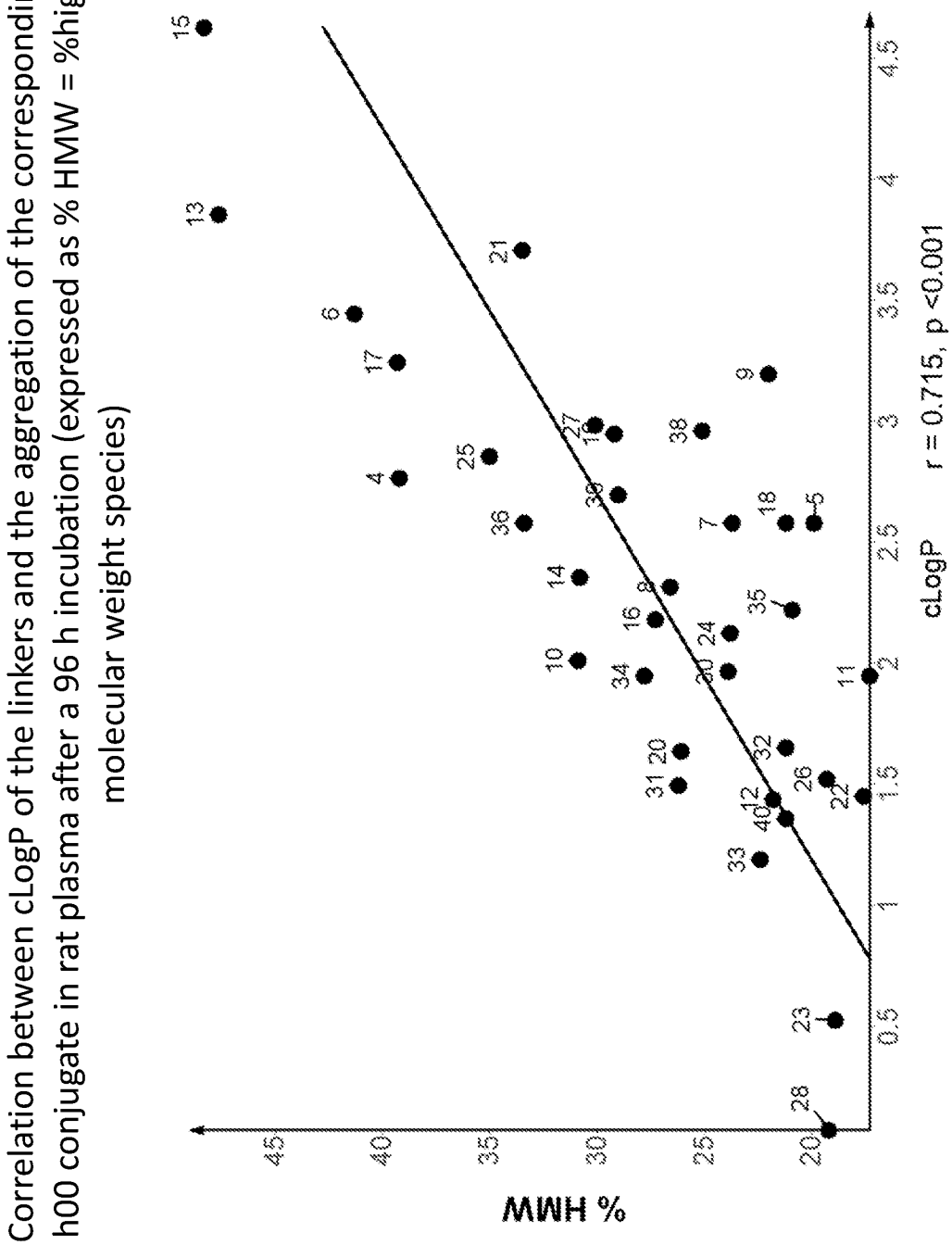

Correlation between cLogP of the linkers and the aggregation of the corresponding h00 conjugate in rat plasma after a 96 h incubation (expressed as % HMW = %high molecular weight species)
MWH %
cLogP
r = 0.715, p <0.001

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)

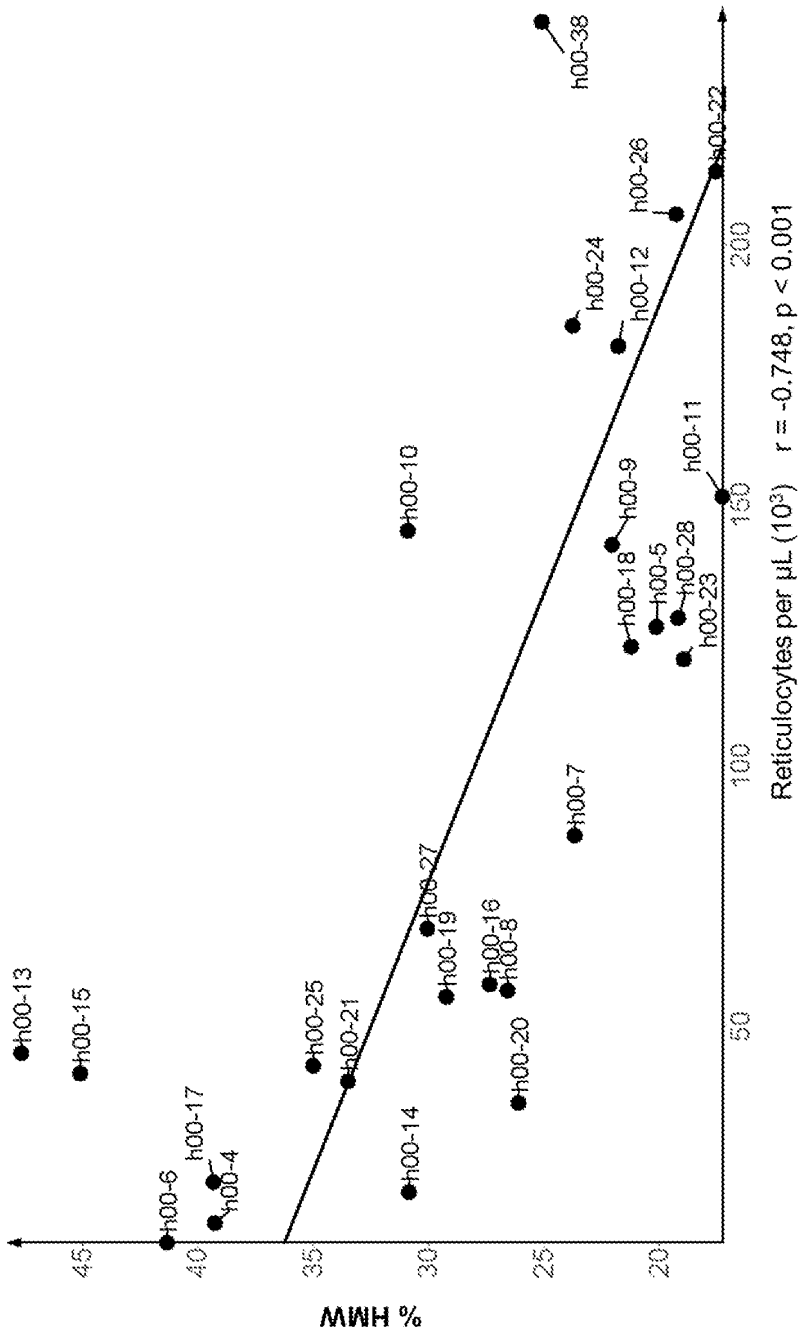


FIG. 20

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)

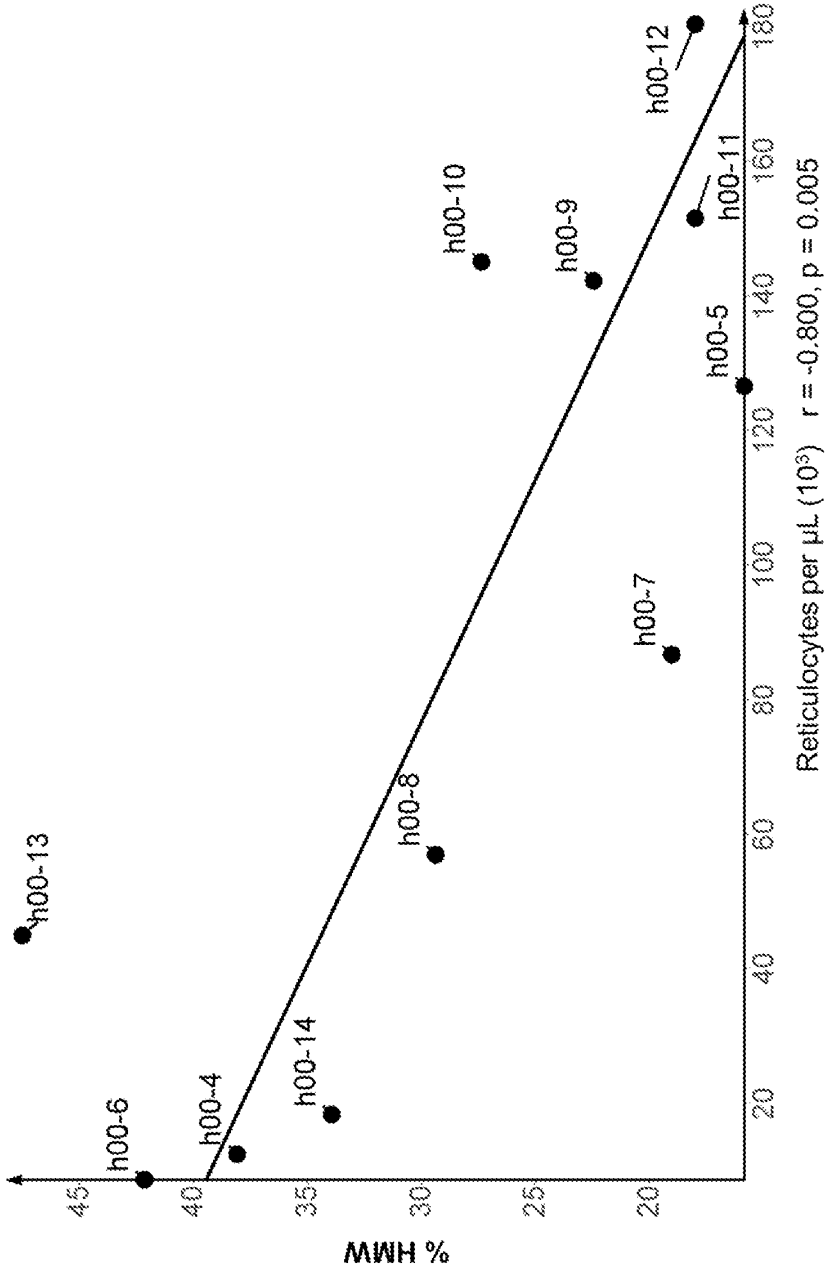


FIG. 21

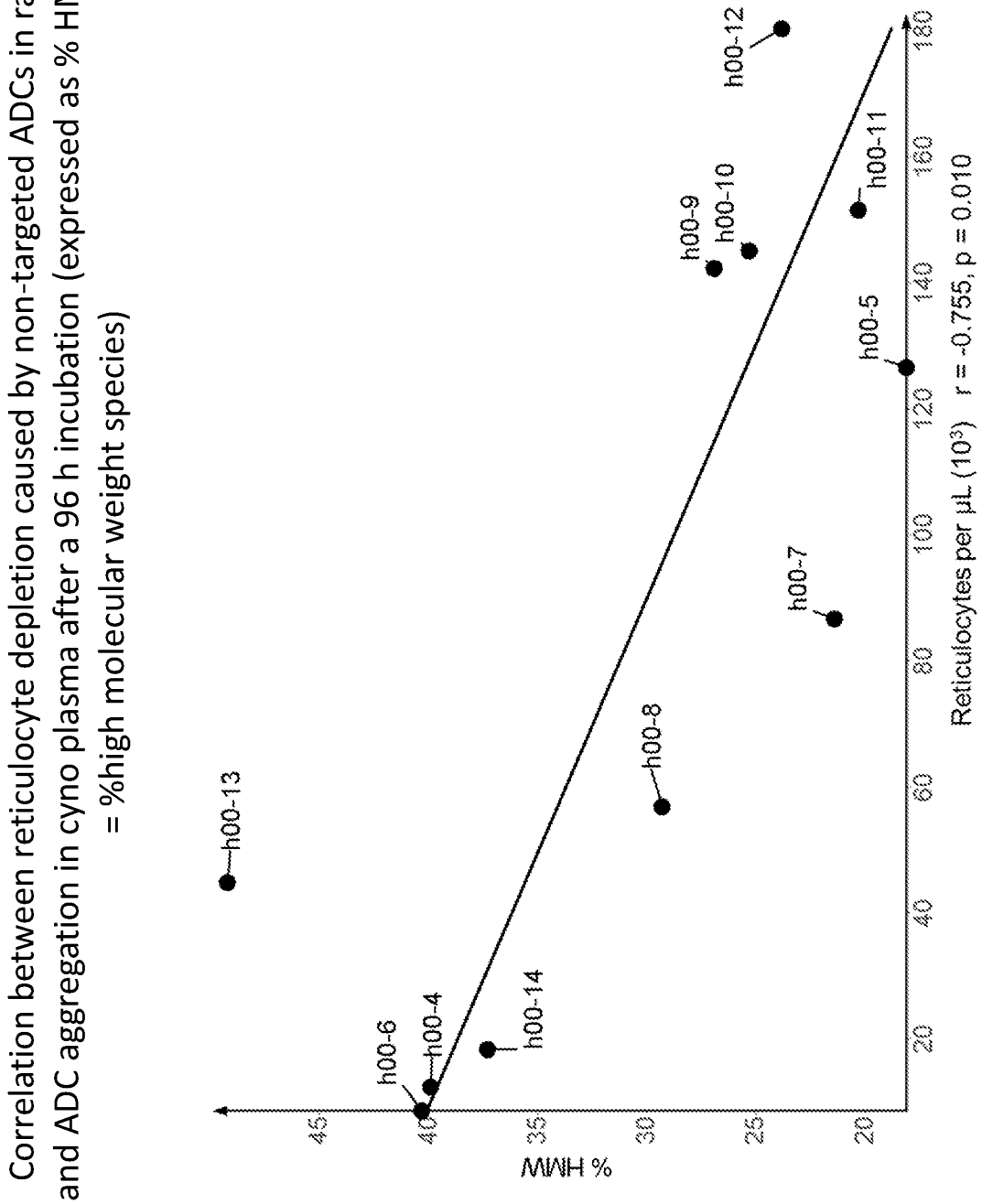

Correlation between reticulocyte depletion caused by non-targeted ADCs in rats and ADC aggregation in cyno plasma after a 96 h incubation (expressed as % HMW = %high molecular weight species)
h00-13
h00-6
h00-4
h00-14
h00-8
h00-7
h00-9
h00-10
h00-12
h00-11
h00-5
%HMW
45
40
35
30
25
20
Reticulocytes per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

FIG. 22

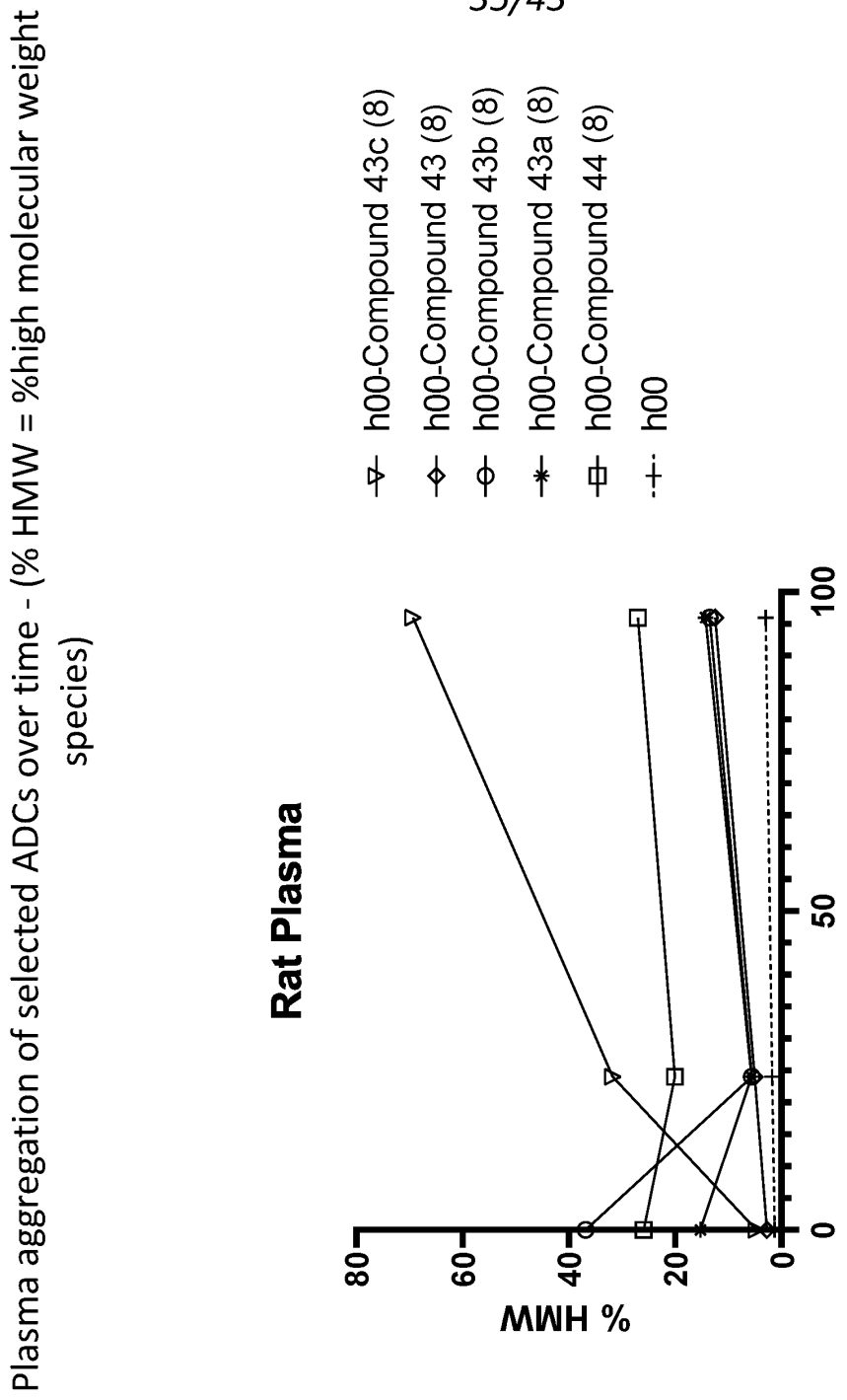

Plasma aggregation of selected ADCs over time - (% HMW = %high molecular weight species)
Rat Plasma
% HMW
0
20
40
60
80
0
50
100
h00-Compound 43c (8)
h00-Compound 43 (8)
h00-Compound 43b (8)
h00-Compound 43a (8)
h00-Compound 44 (8)
h00

FIG. 23

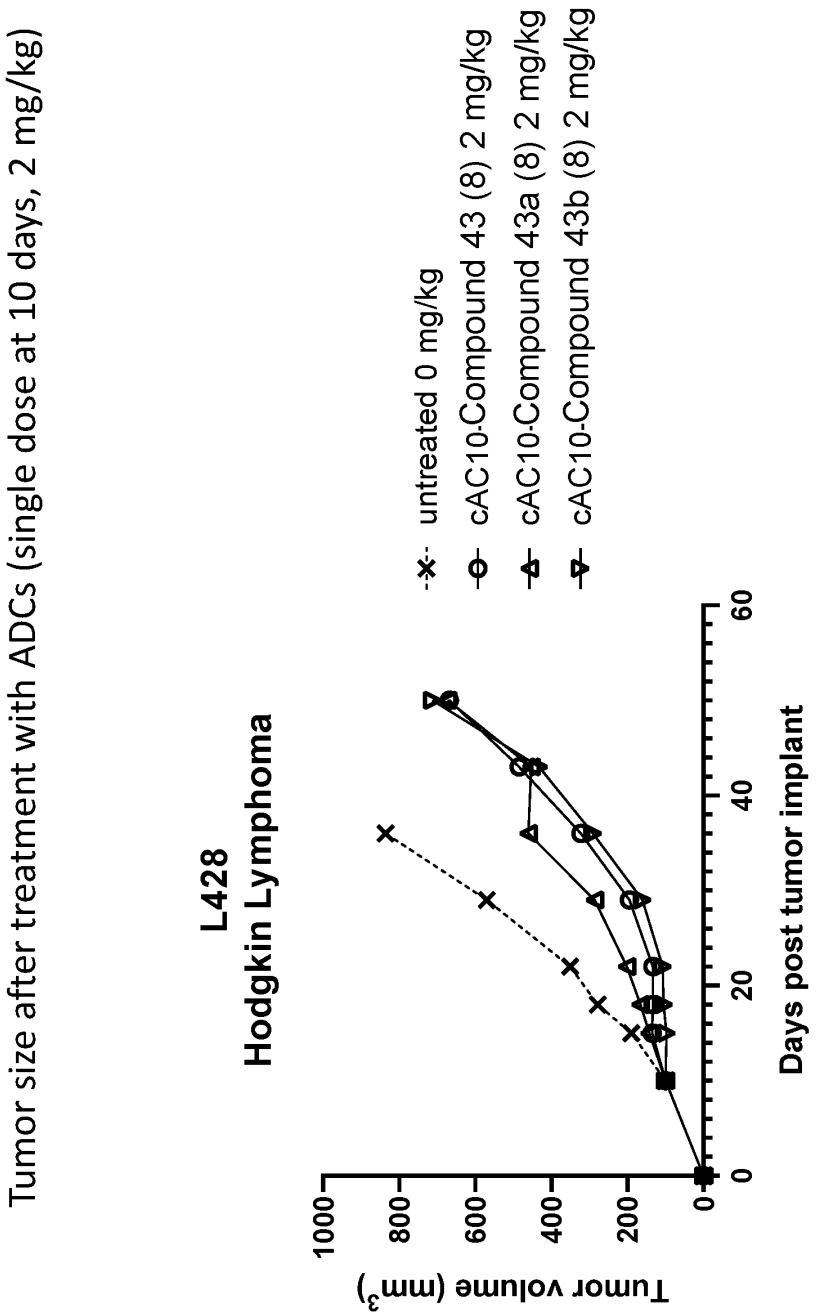

Tumor size after treatment with ADCs (single dose at 10 days, 2 mg/kg)
L428
Hodgkin Lymphoma
untreated 0 mg/kg
cAC10-Compound 43 (8) 2 mg/kg
cAC10-Compound 43a (8) 2 mg/kg
cAC10-Compound 43b (8) 2 mg/kg
Tumor volume (mm3)
1000
800
600
400
200
0
0
20
40
60
Days post tumor implant

FIG. 24A

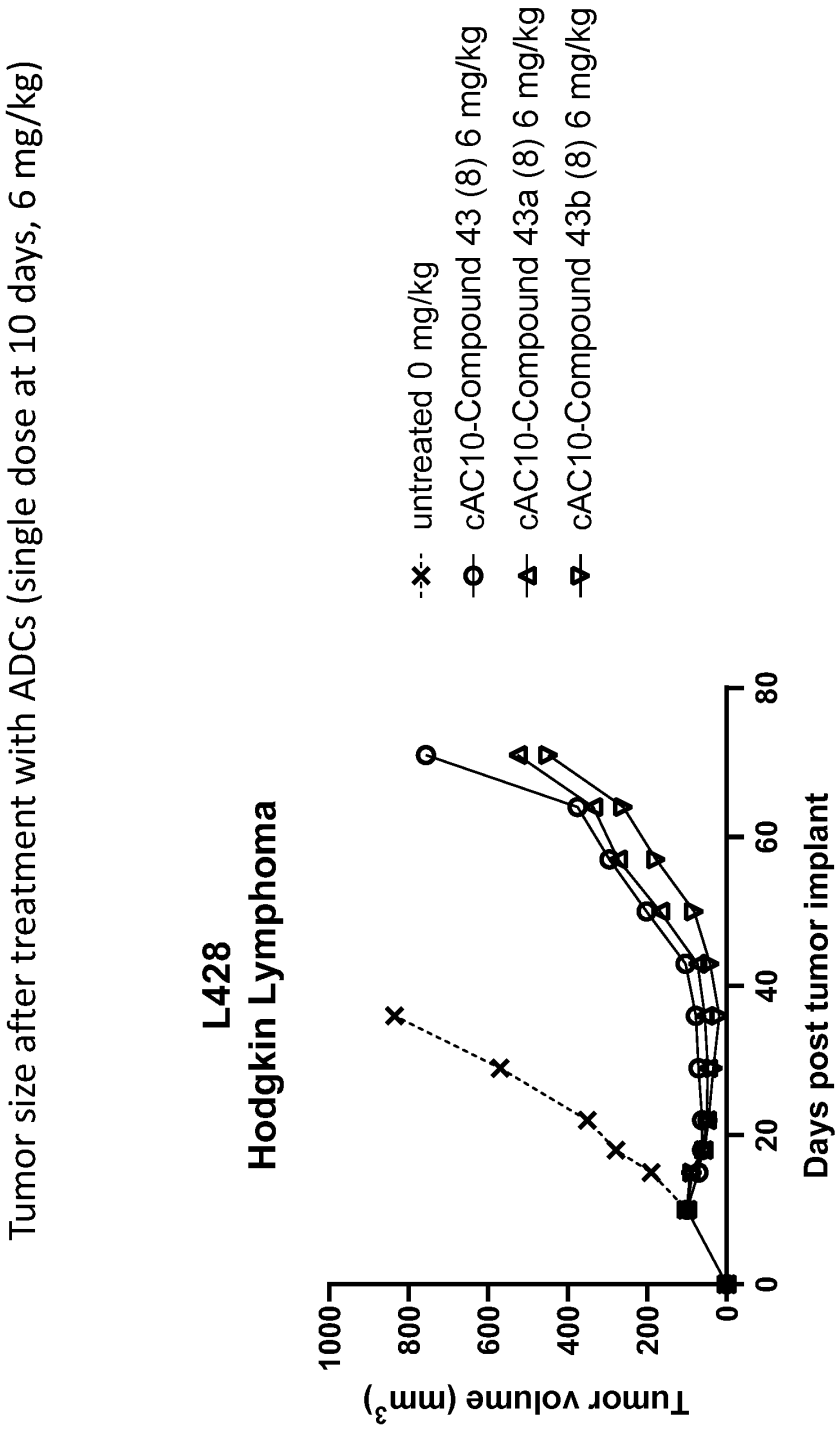

Tumor size after treatment with ADCs (single dose at 10 days, 6 mg/kg)
L428
Hodgkin Lymphoma
untreated 0 mg/kg
cAC10-Compound 43 (8) 6 mg/kg
cAC10-Compound 43a (8) 6 mg/kg
cAC10-Compound 43b (8) 6 mg/kg
Tumor volume (mm3)
0
200
400
600
800
1000
0
20
40
60
80
Days post tumor implant

FIG. 24B

Tumor size after treatment with ADCs (single dose at 9 days, 0.3 mg/kg)

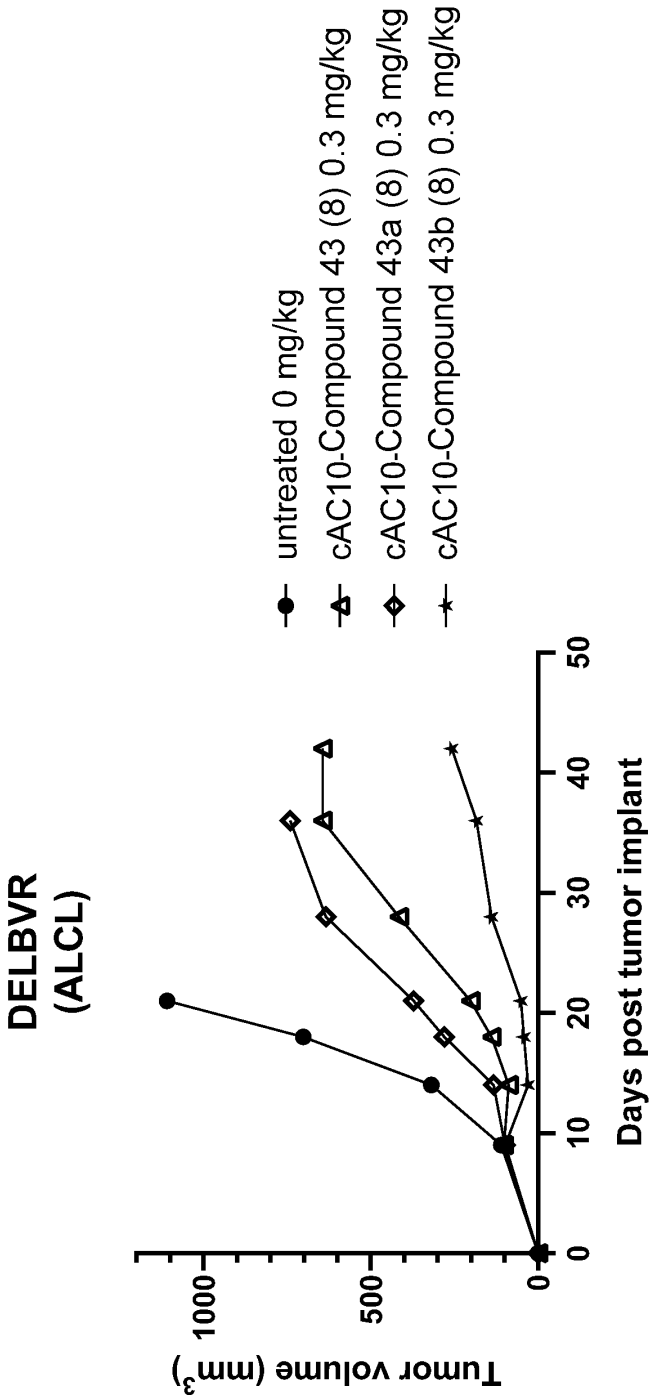


FIG. 25A

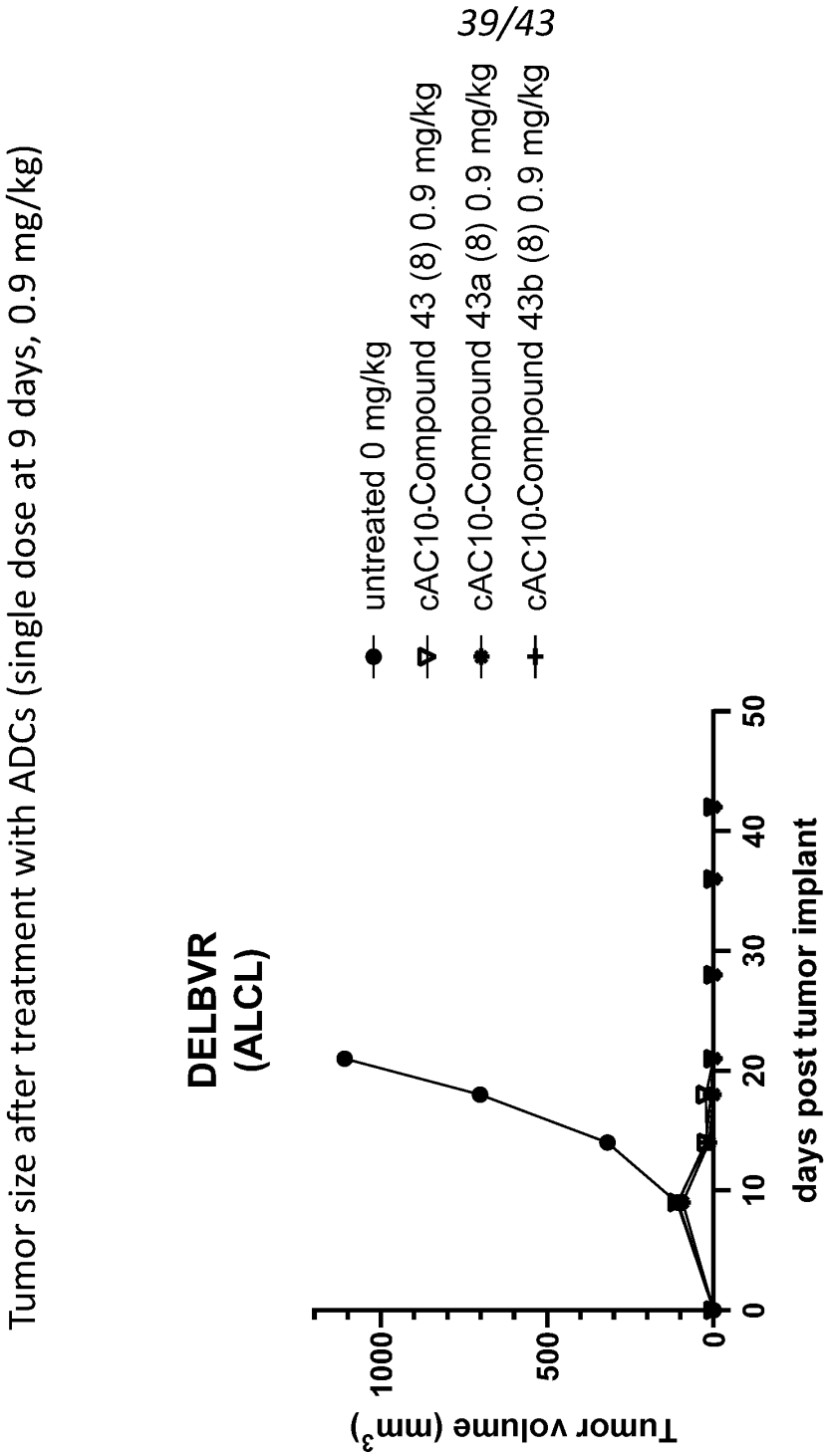

Tumor size after treatment with ADCs (single dose at 9 days, 0.9 mg/kg)
DELBVR
(ALCL)
untreated 0 mg/kg
cAC10-Compound 43 (8) 0.9 mg/kg
cAC10-Compound 43a (8) 0.9 mg/kg
cAC10-Compound 43b (8) 0.9 mg/kg
Tumor volume (mm3)
0
500
1000
0
10
20
30
40
50
days post tumor implant

FIG. 25B

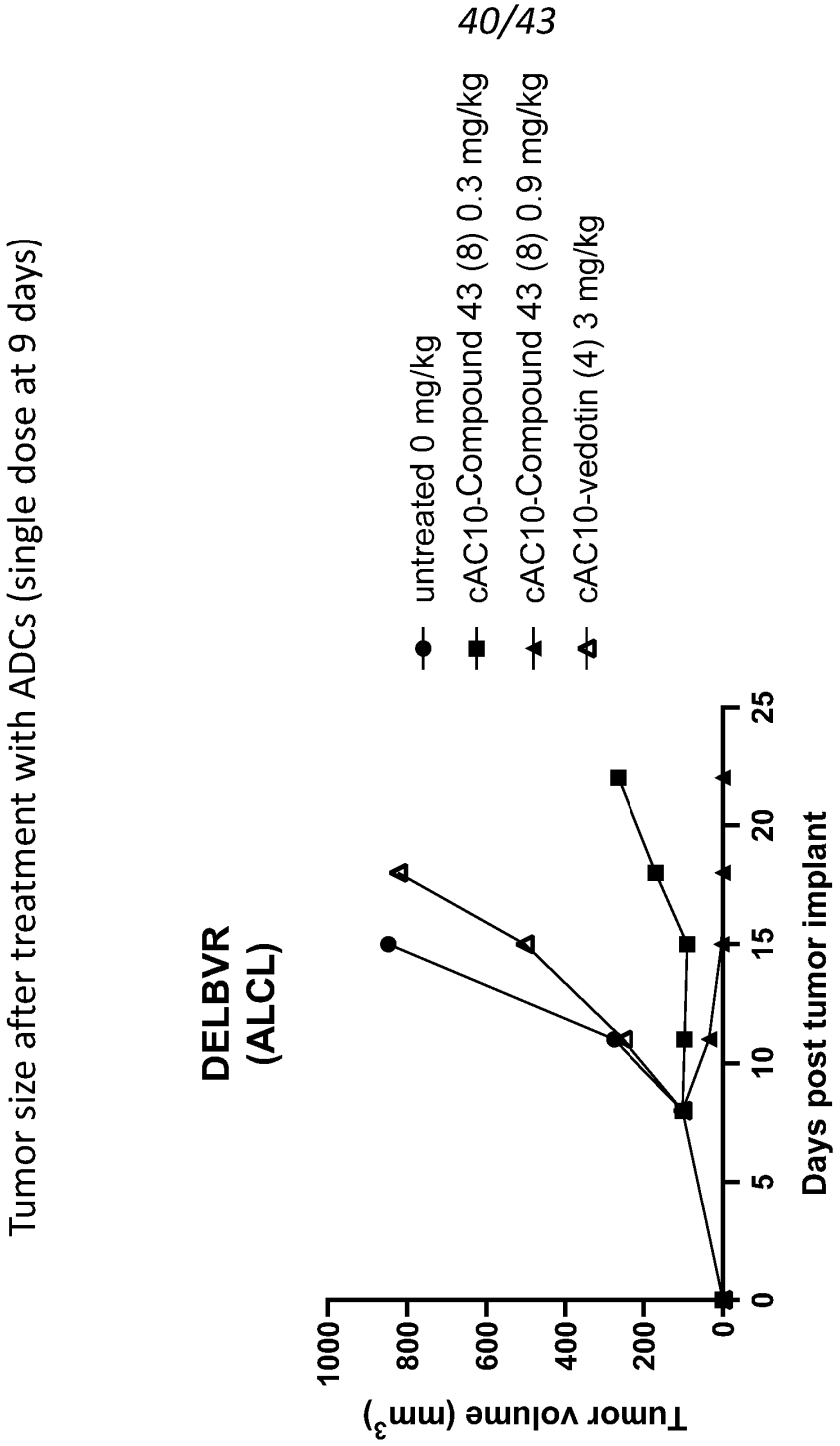

Tumor size after treatment with ADCs (single dose at 9 days)
DELBVR
(ALCL)
untreated 0 mg/kg
cAC10-Compound 43 (8) 0.3 mg/kg
cAC10-Compound 43 (8) 0.9 mg/kg
cAC10-vedotin (4) 3 mg/kg
Tumor volume (mm3)
1000
800
600
400
200
0
0
5
10
15
20
25
Days post tumor implant

FIG. 25C

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

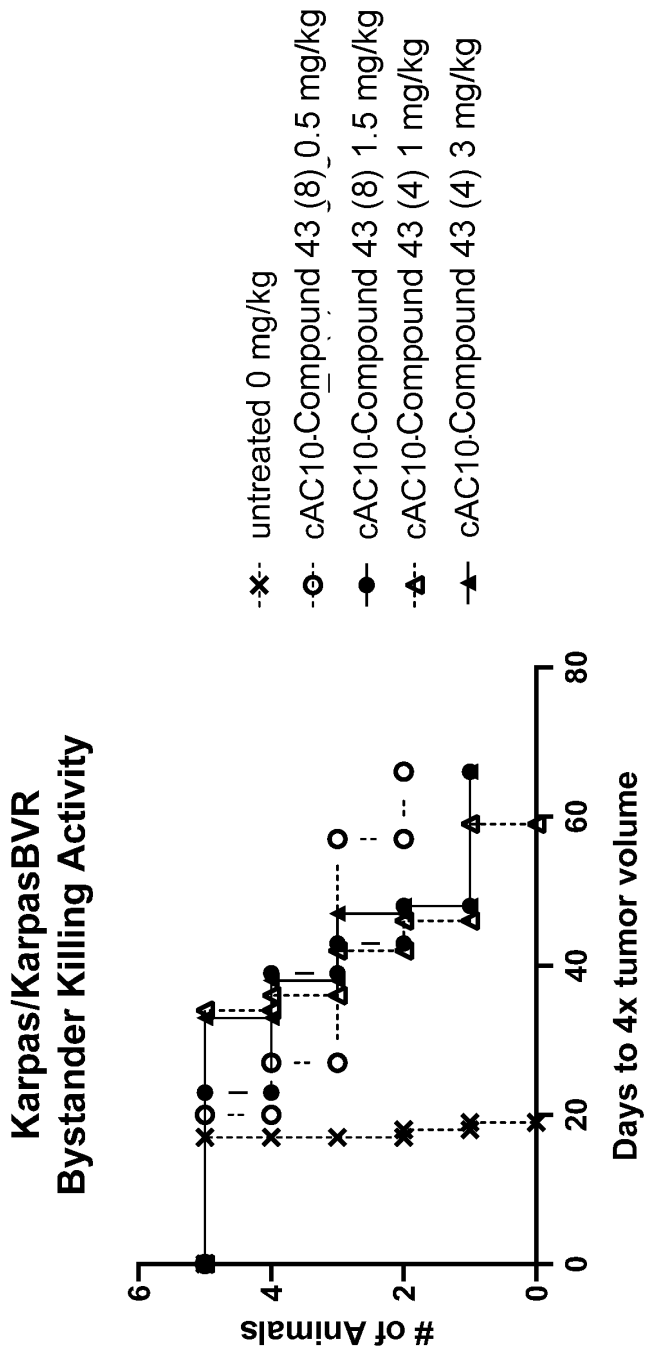


FIG. 26

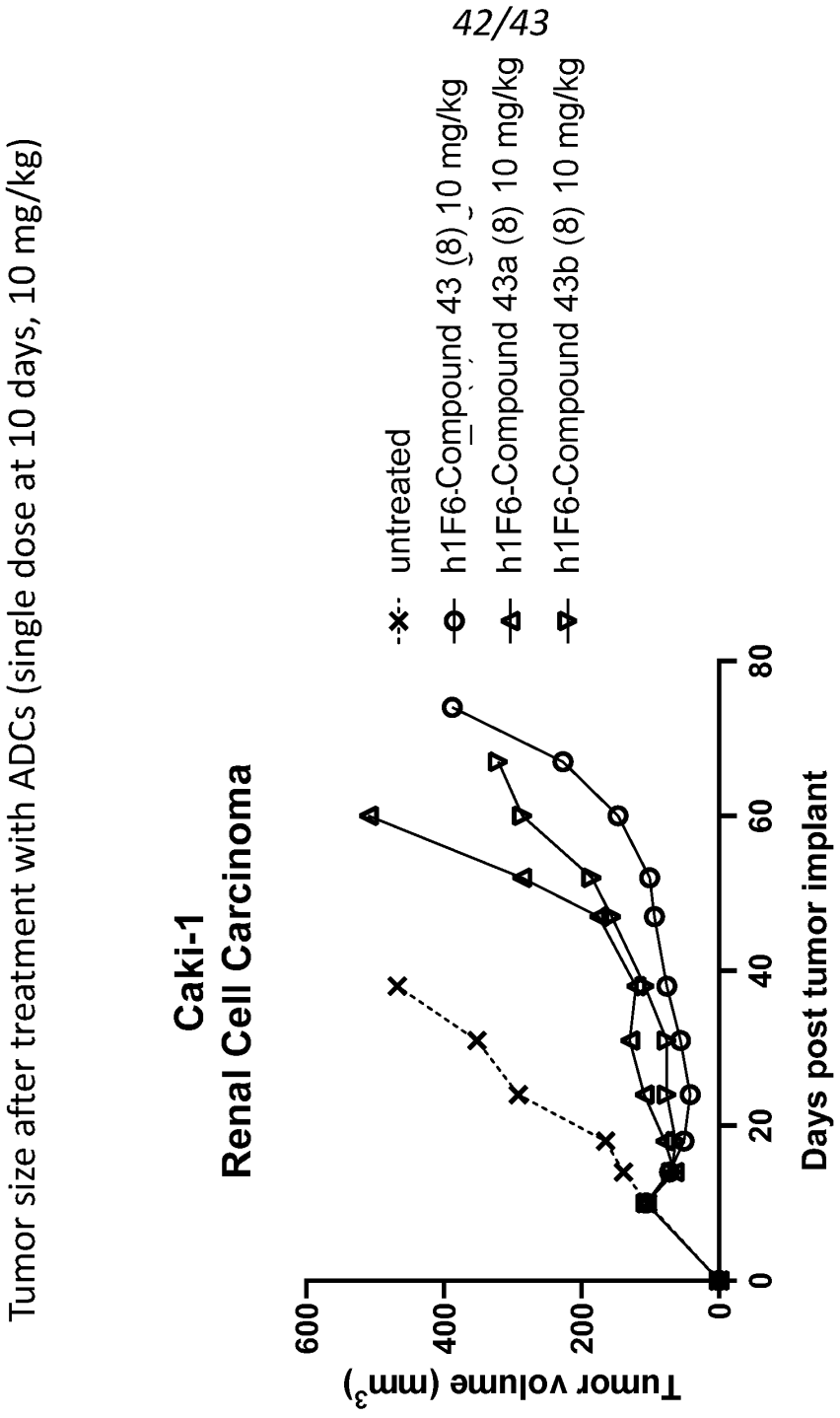

Tumor size after treatment with ADCs (single dose at 10 days, 10 mg/kg)
Caki-1
Renal Cell Carcinoma
untreated
h1F6-Compound 43 (8) 10 mg/kg
h1F6-Compound 43a (8) 10 mg/kg
h1F6-Compound 43b (8) 10 mg/kg
Tumor volume (mm3)
0
200
400
600
0
20
40
60
80
Days post tumor implant

FIG. 27A

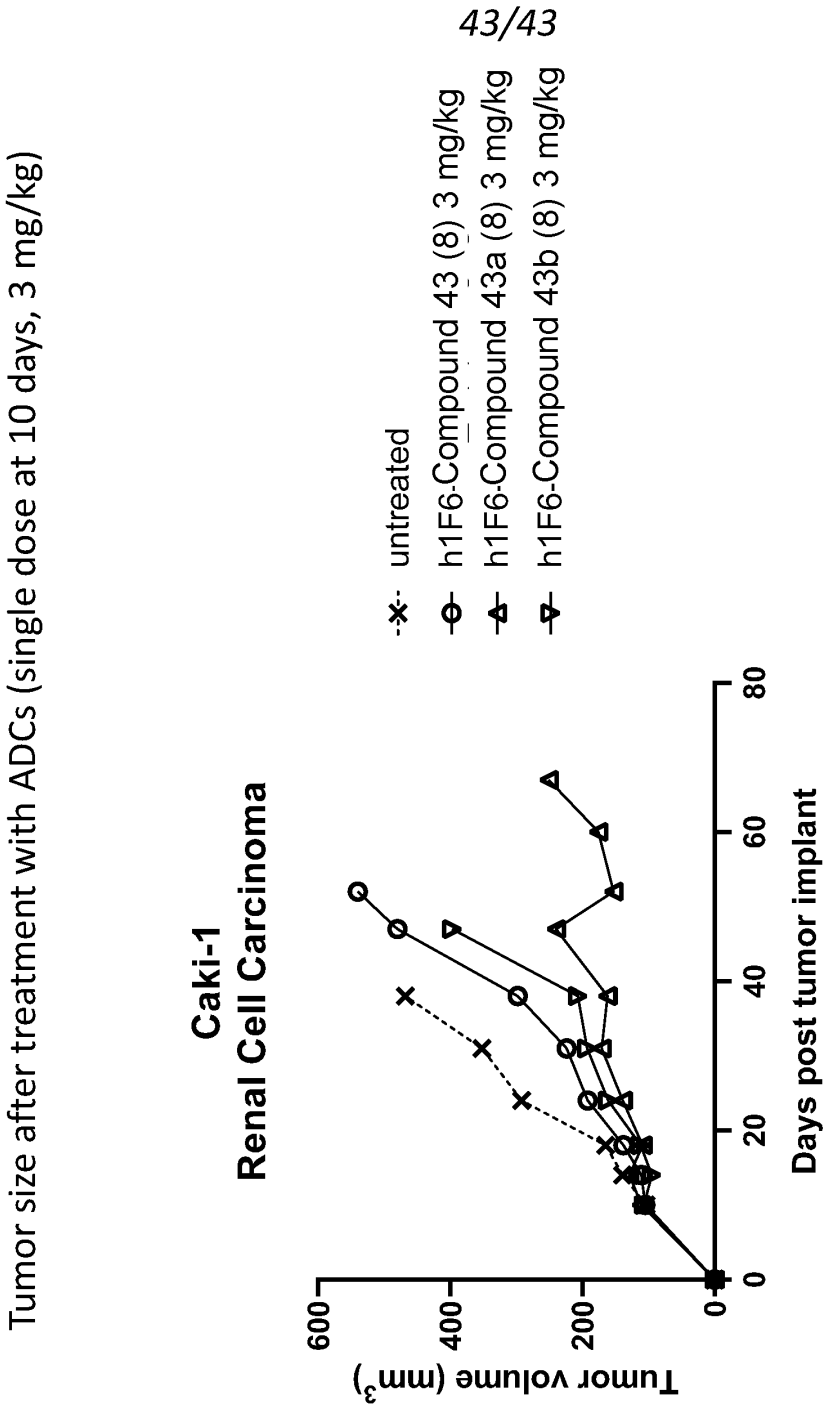

Tumor size after treatment with ADCs (single dose at 10 days, 3 mg/kg)
Caki-1
Renal Cell Carcinoma
untreated
h1F6-Compound 43 (8) 3 mg/kg
h1F6-Compound 43a (8) 3 mg/kg
h1F6-Compound 43b (8) 3 mg/kg
Tumor volume (mm3)
0
200
400
600
0
20
40
60
80
Days post tumor implant

FIG. 27B