```
                    10        20        30        40        50
                    |....|....|....|....|....|....|....|....|....|....|....
hLiv-14 HA          QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHWVRQAPGQGLEWMGWIDPENGDTEY
hLiv-14 HB          ..........................IE..............................
hLiv-14 HC          ..........................IE..............................
hLiv-14 HD          ........................F.....................................
hLiv-14 HE          ......................FNIE..................I.............
BR2-14a             ....Q.....LVRS.....L..T...FNIE.......K.R.K.....I.............
CDRs                                        *****                 ***********
                    60        70        80            90        100         110
                    |....|....|....|....|.......|....|....|....|.......|....|...
hLiv-14 HA          APTFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARHDAHYGTWFAYWGQGTLVTVSS
hLiv-14 HB          ................N.....................................................
hLiv-14 HC          ......KA...A.........................................................
hLiv-14 HD          ..................................NV.....................
hLiv-14 HE          ......KA...A....N..................NV.....................
BR2-14a             ......KA...A...SN...LQ..S.T.E.......NV.....................A
CDRs                ******                                ***********

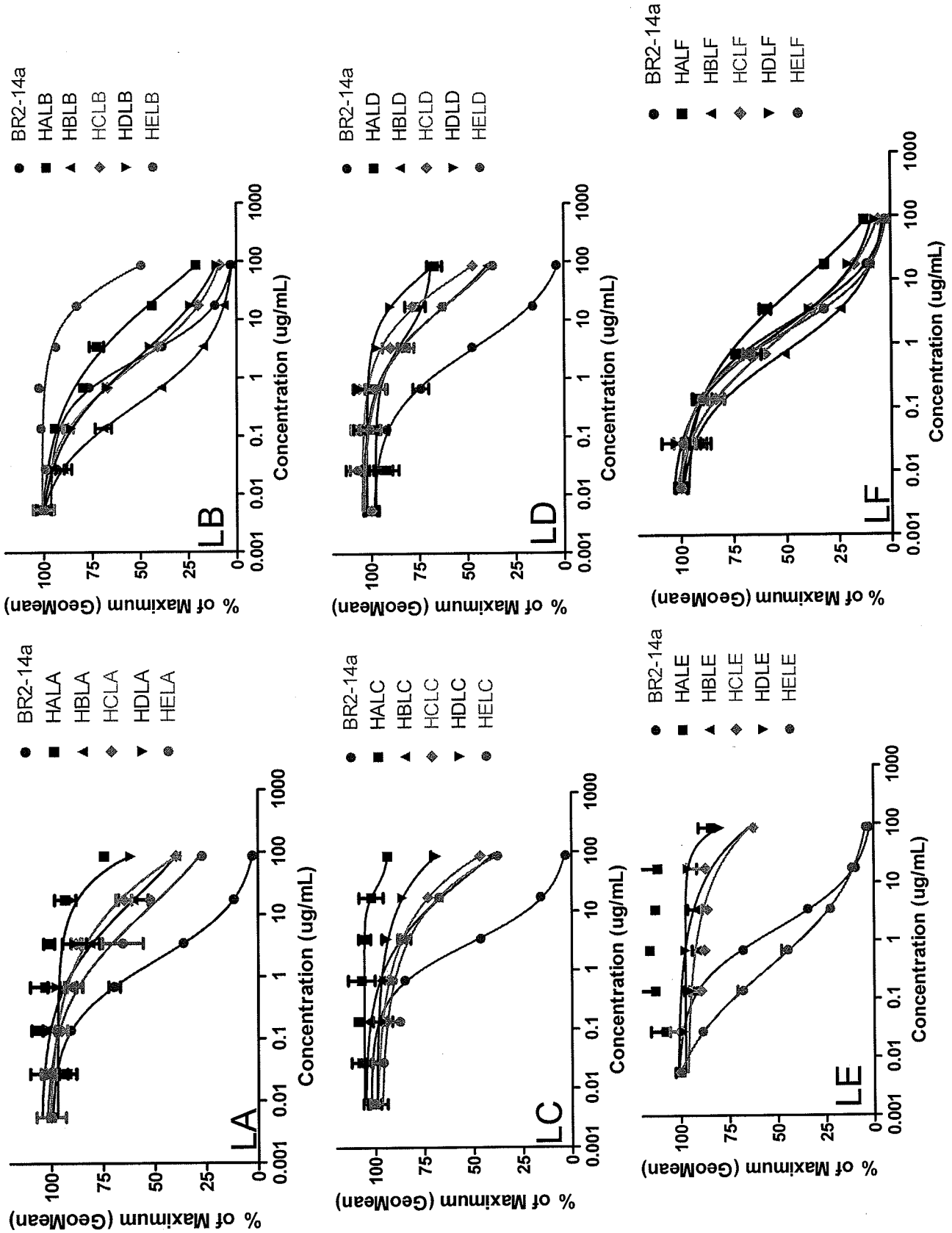
                              10        20                30        40        50
                              |....|....|....|....|.........|....|....|....|....|....|
hLiv-14 LA                    DVVMTQSPLSLPVTLGQPASISCRSSQSIIRNDGNTYLEWFQQRPGQSPRRLIYRVSNRF
hLiv-14 LB                    ........................................Y.....................
hLiv-14 LC                    ........................................L.....................
hLiv-14 LD                    ..............................................K.............
hLiv-14 LE                    ................................................L.........
hLiv-14 LF                    ........................................YL.K.....KL.........
BR2-14a                       ..L...T......S..DQ.....................YL.K.....KL.........
CDRs                                        ****************                ******

                                 60        70        80        90        100
                                 |....|....|....|....|....|....|....|....|....|...
hLiv14 LA                        SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPYTFGGGTKVEIKR
hLiv14 LB                        ..................................................
hLiv14 LC                        ..................................................
hLiv14 LD                        ..................................................
hLiv14 LE                        ..................................................
hLiv14 LF                        ..................................................
BR2-14a                          ........................L.....................L....
CDRs                             *                                 *********
```

FIGURE 1

FIGURE 2

Antigen binding by humanized BR2-14a antibodies



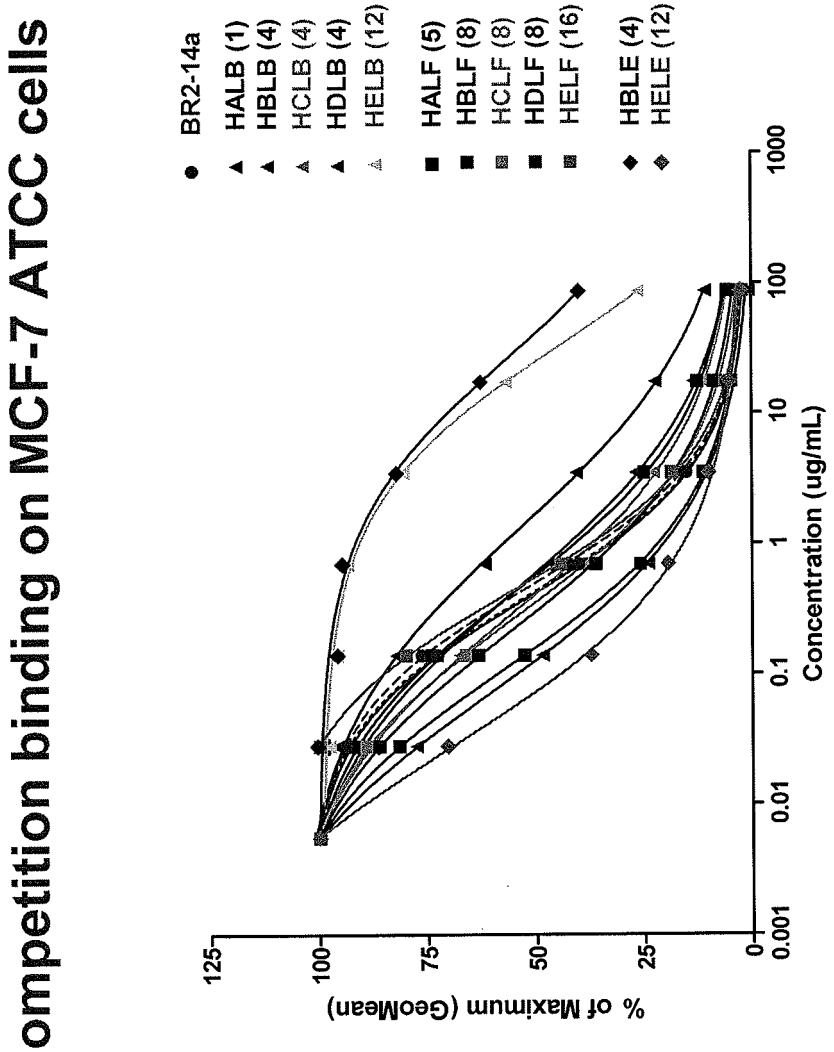
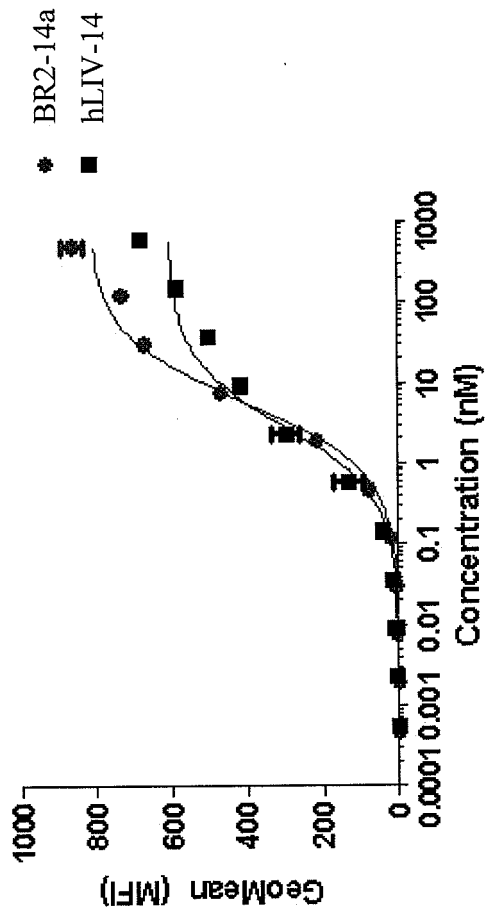
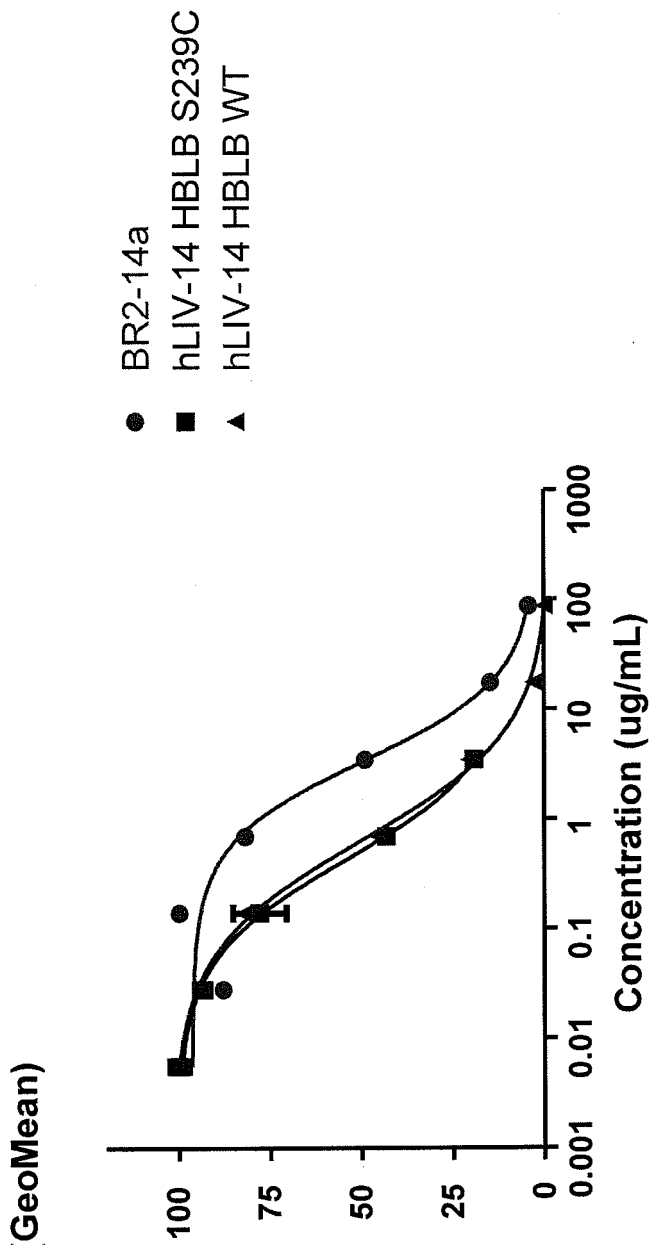

Competition binding on MCF-7 ATCC cells
BR2-14a
HALB (1)
HBLB (4)
HCLB (4)
HDLB (4)
HELB (12)
HALF (5)
HBLF (8)
HCLF (8)
HDLF (8)
HELF (16)
HBLE (4)
HELE (12)
% of Maximum (GeoMean)
125
100
75
50
25
0
0.001
0.01
0.1
1
10
100
1000
Concentration (ug/mL)

FIGURE 3

FIGURE 4



	BR2-14a	hLIV-14
Kd (nM)	5.8	2.9
Kd (ug/mL)	0.8	0.4

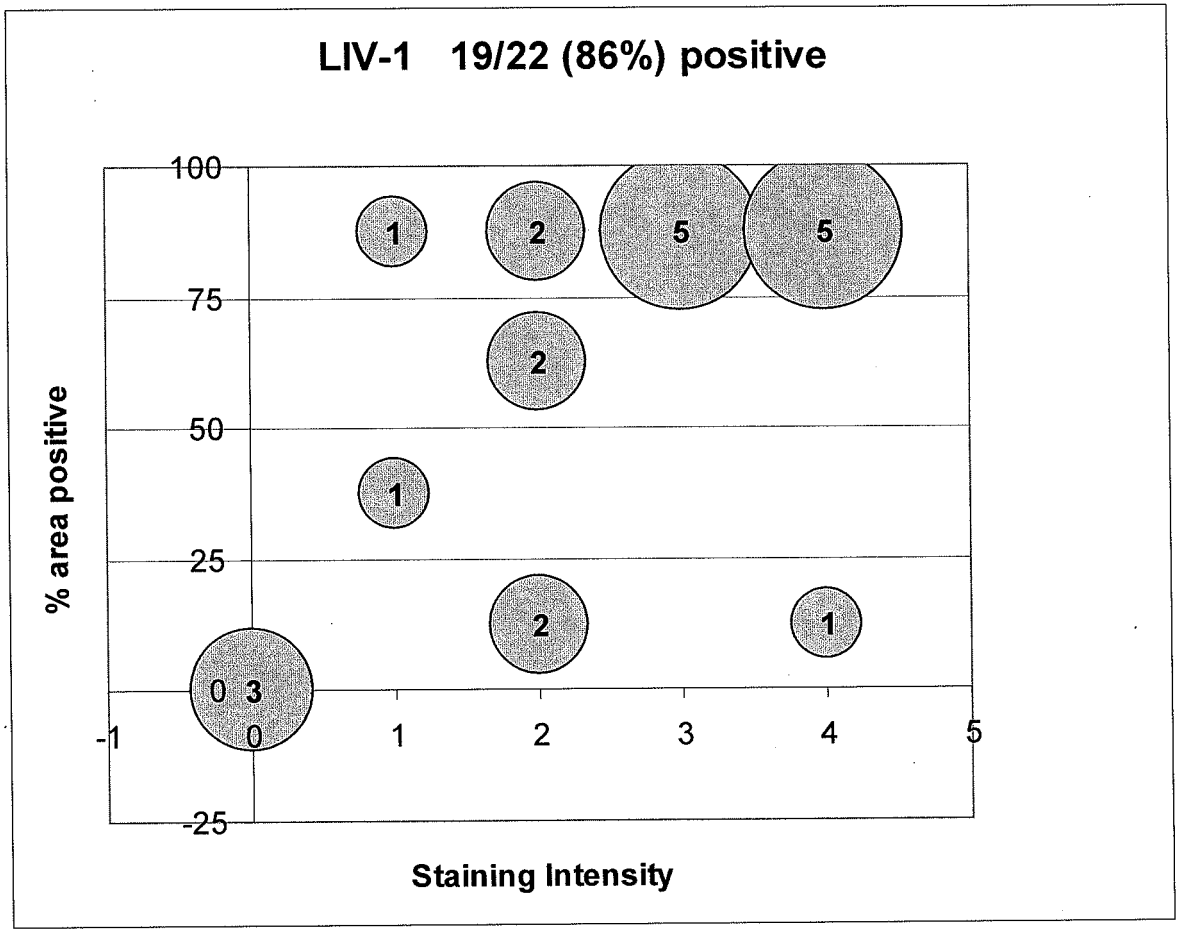


	BR2-14a	hLIV-14 HBLB S239C	hLIV-14 HBLB WT
EC50	3.421	0.4195	0.6416

FIGURE 5

FIGURE 6

High LIV-1 Expression in Post-Hormone Treated Breast Cancers



- Samples of primary and metastatic lesions from patients previously treated with hormonal therapy, including tamoxifen and aromatase inhibitors
- Tissue samples from 5 commercial sources

LIV-1 Expression in Hormone Refractory Metastatic Prostate Cancer (Sorted By Site)

	LIV-1	
	#	%
Total Number of Samples+ (intensity 1-4+)	36/50	72
Bone Mets	15/25	60
Soft Tissue Mets	21/25	82

FIGURE 7

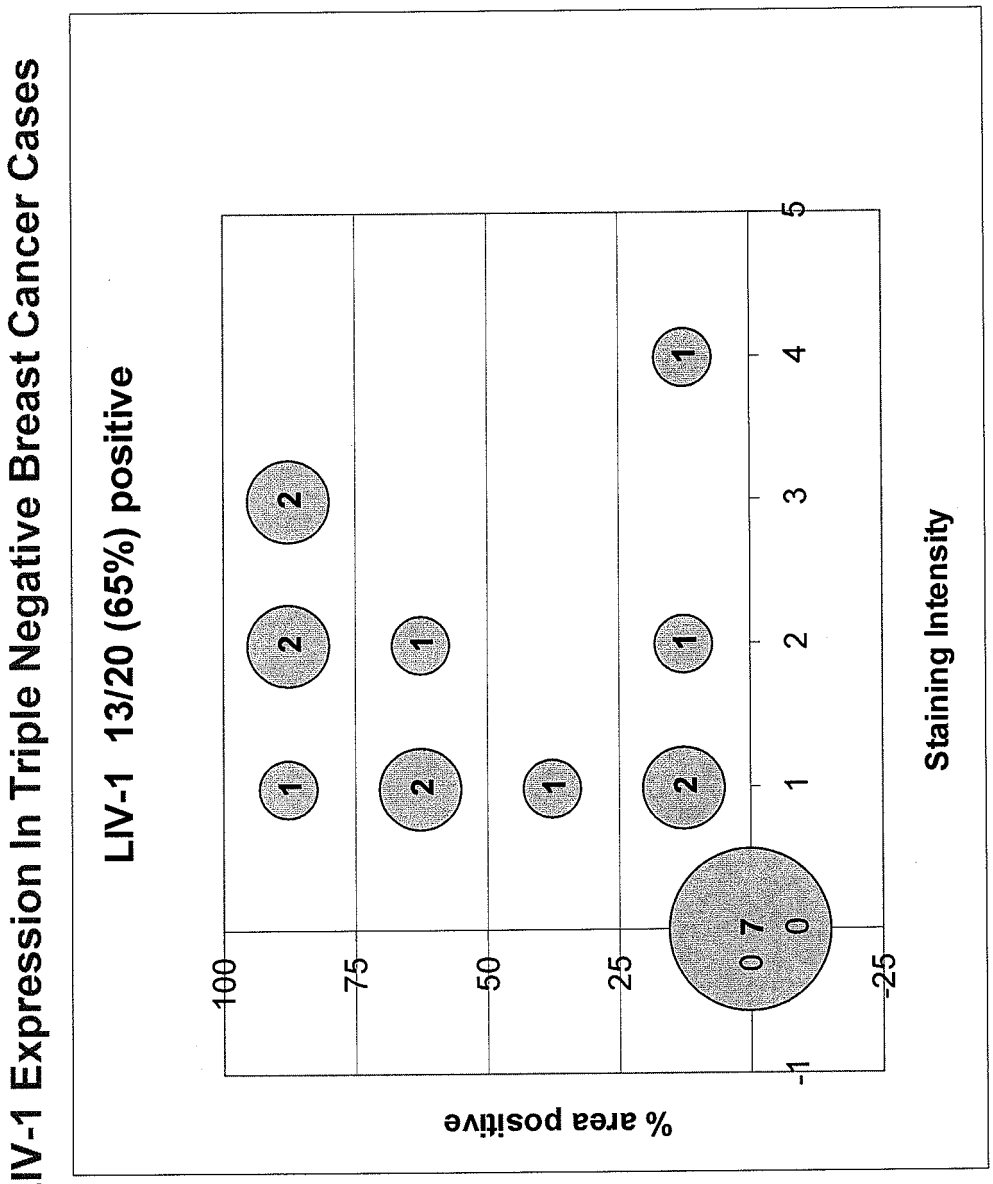
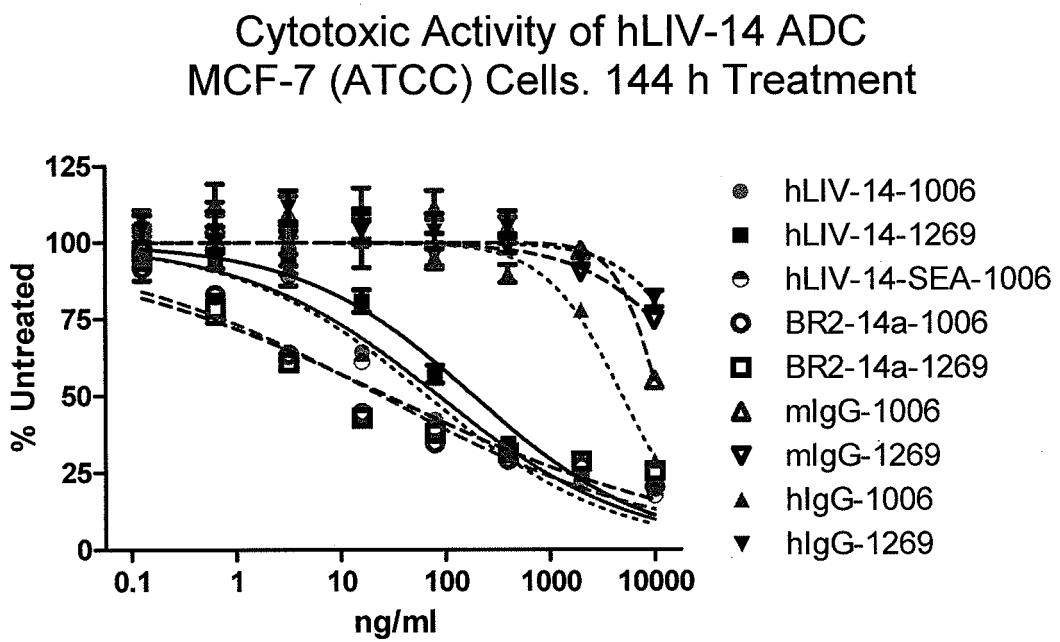
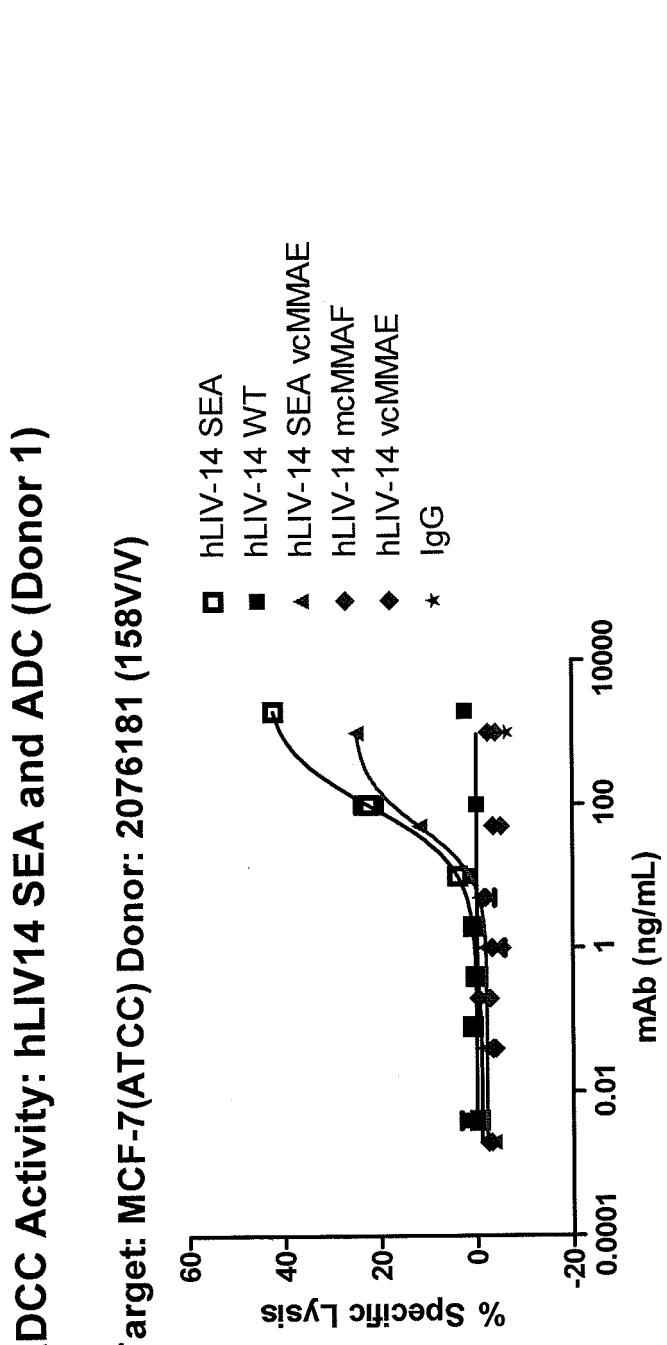

LIV-1 Expression In Triple Negative Breast Cancer Cases
LIV-1 13/20 (65%) positive
% area positive
100
75
50
25
-25
-1
0 7 0
1
2
3
4
5
Staining Intensity

FIGURE 8



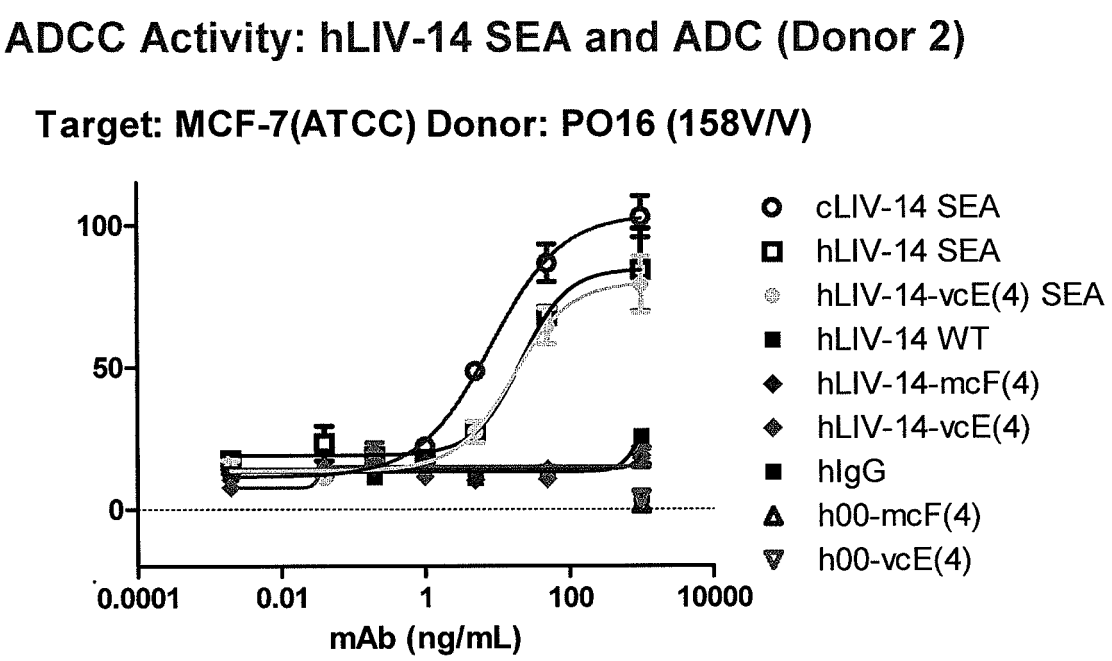
	hLIV-14-1006	hLIV-14-SEA-1006	BR2-14a-1-1006	hIgG-1006	mIgG-1006	hLIV-14-1269	BR2-14a-1269	hIgG-1269	mIgG-1269
IC50 ng/ml	91	91	20	>10 000	4786	195	20	>10 000	>10 000

FIGURE 9



	IC50 (ng/mL)	Max Lysis
hLIV-14 SEA	97.1	44%
hLIV-14 SEA vcMMAE	49.9	26%

FIGURE 10



	IC50 (ng/mL)	Max Lysis
hLIV-14 SEA	21.8	85%
hLIV-14 SEA vcMMAE	17.0	80%

FIGURE 11

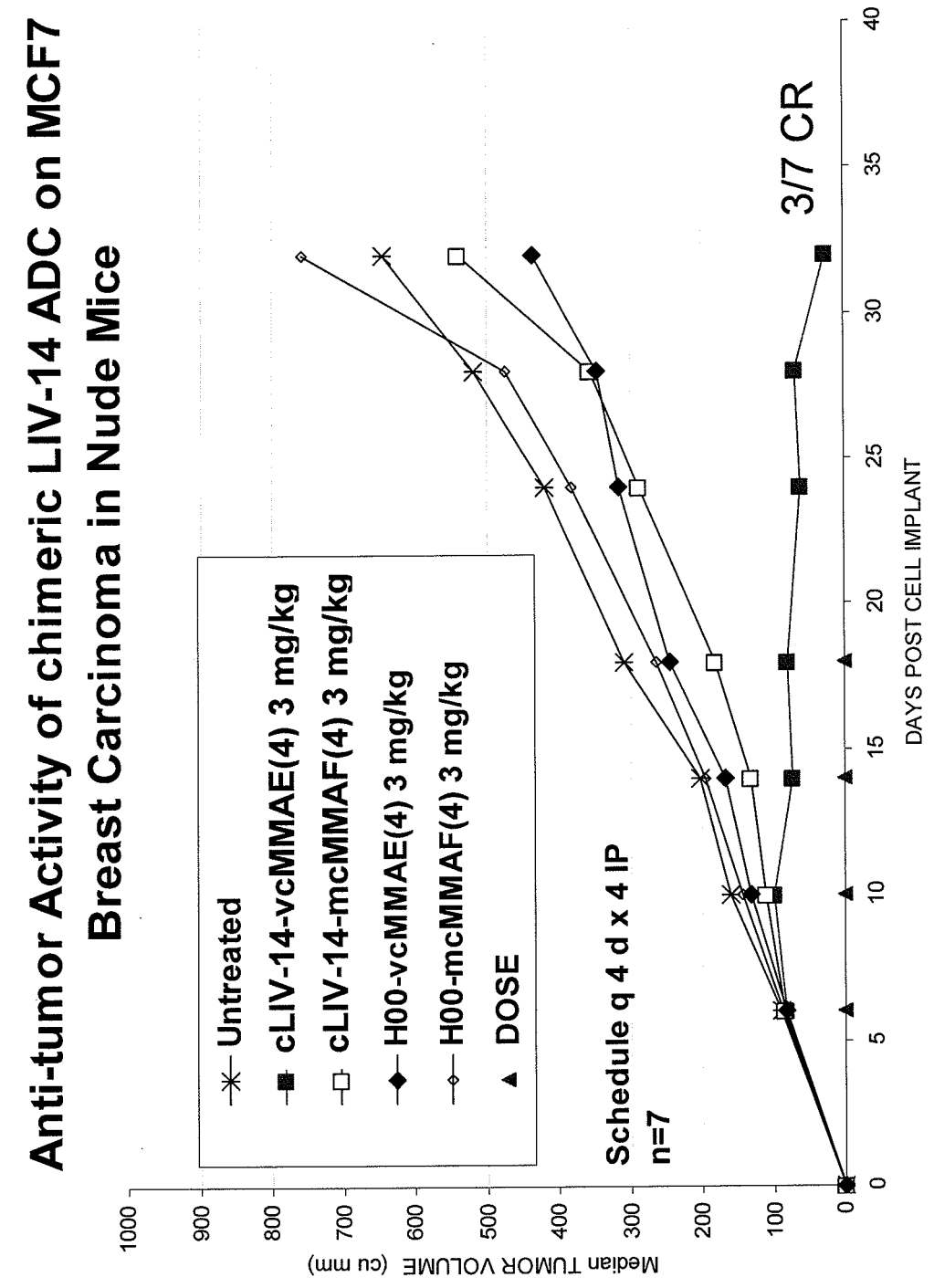

Anti-tumor Activity of chimeric LIV-14 ADC on MCF7 Breast Carcinoma in Nude Mice
Untreated
cLIV-14-vcMMAE(4) 3 mg/kg
cLIV-14-mcMMAF(4) 3 mg/kg
H00-vcMMAE(4) 3 mg/kg
H00-mcMMAF(4) 3 mg/kg
DOSE
Schedule q 4 d x 4 IP
n=7
3/7 CR
Median TUMOR VOLUME (cu mm)
DAYS POST CELL IMPLANT
0
100
200
300
400
500
600
700
800
900
1000
0
5
10
15
20
25
30
35
40

FIGURE 12

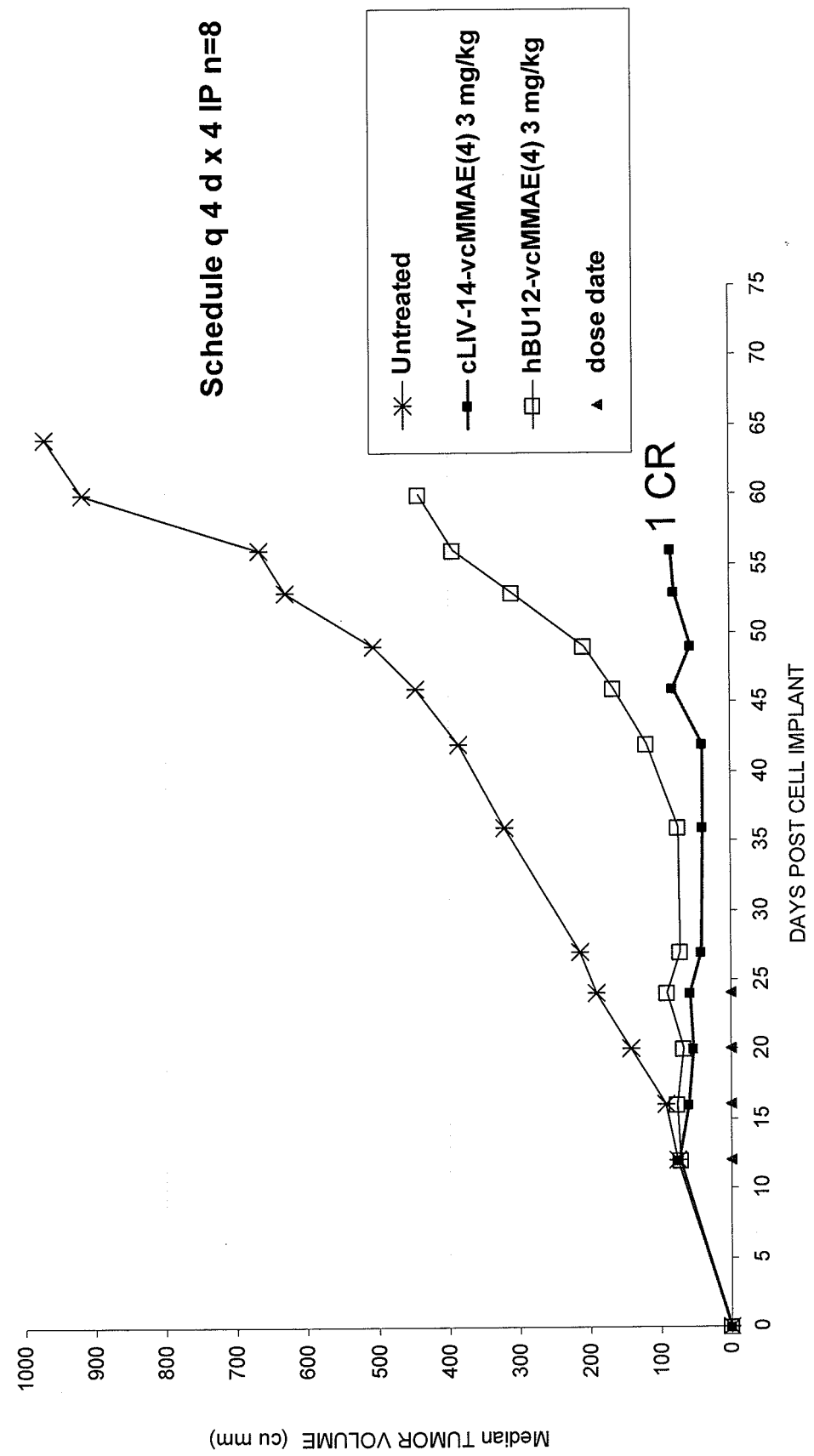

Anti-tumor Activity of chimeric LIV-14-vcMMAE on PC3 (ATCC) Prostate Carcinoma in Male Nude Mice
Schedule q 4 d x 4 IP n=8
Untreated
cLIV-14-vcMMAE(4) 3 mg/kg
hBU12-vcMMAE(4) 3 mg/kg
dose date
1 CR
Median TUMOR VOLUME (cu mm)
DAYS POST CELL IMPLANT
0
100
200
300
400
500
600
700
800
900
1000
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75

FIGURE 13

FIGURE 14

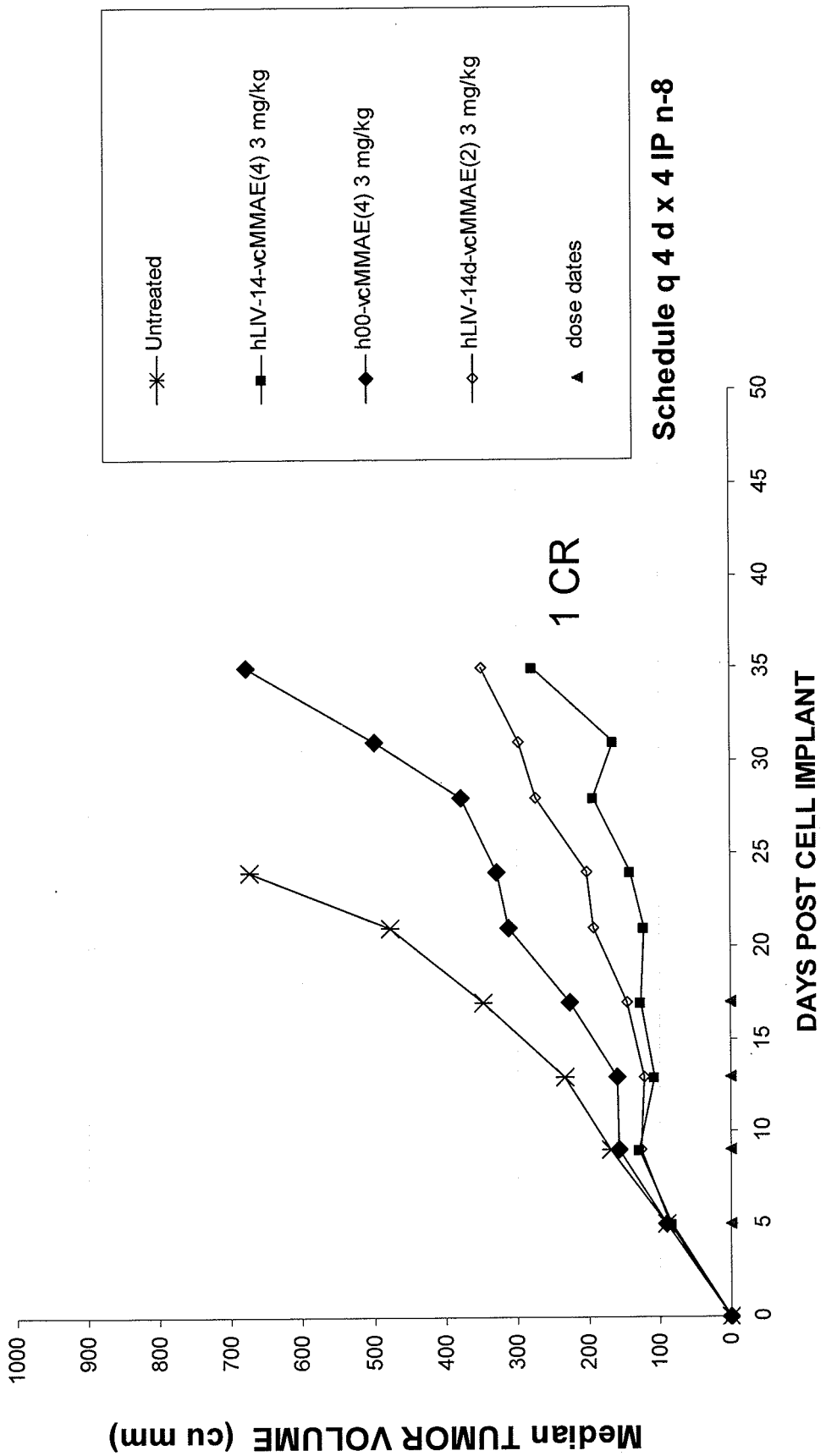
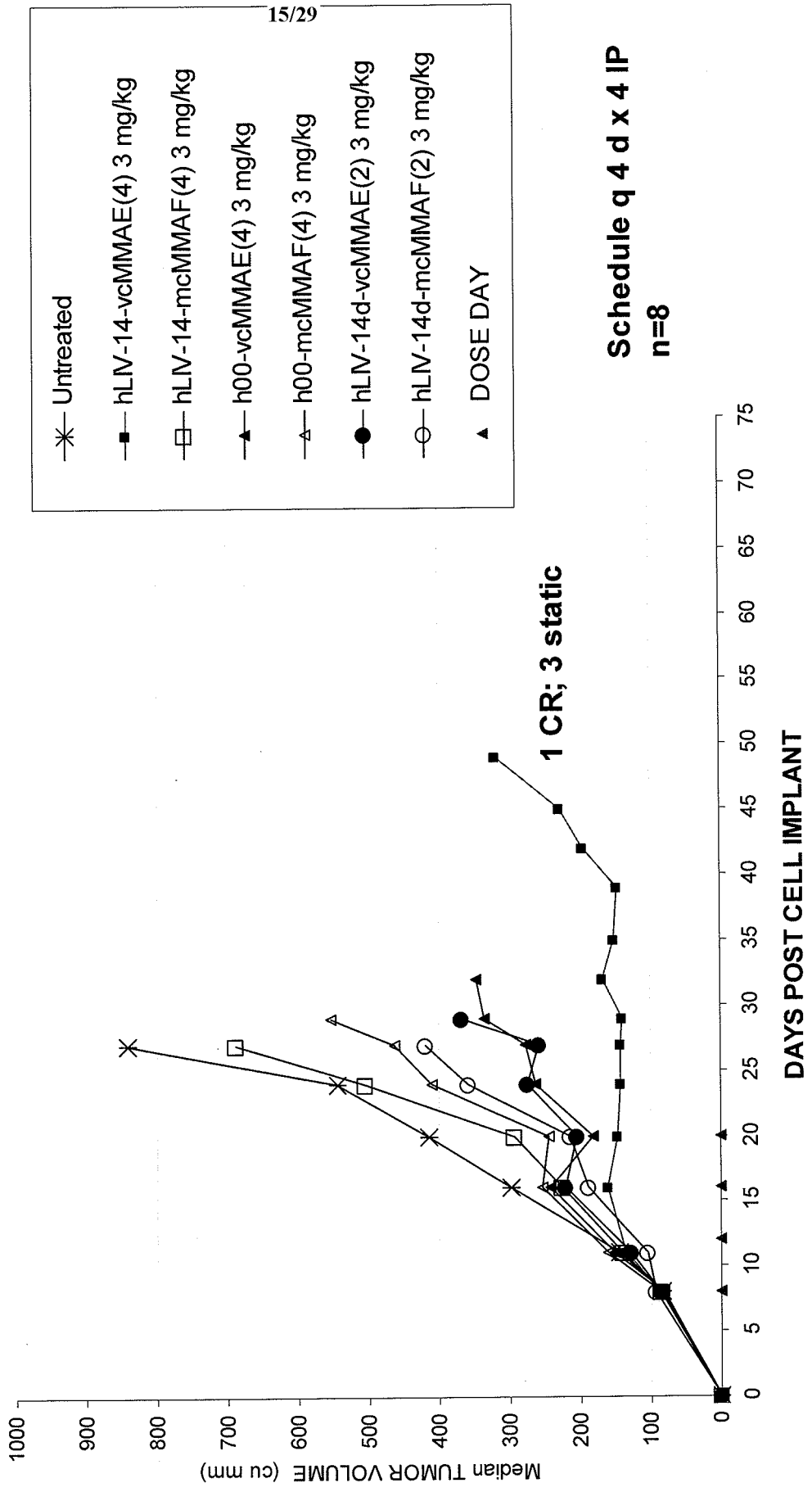

Activity of Humanized LIV-14 ADC on MCF7 (NCI) Breast Carcinoma Tumors in Nude Mice
Untreated
hLIV-14-vcMMAE(4) 3 mg/kg
h00-vcMMAE(4) 3 mg/kg
hLIV-14d-vcMMAE(2) 3 mg/kg
dose dates
Schedule q 4 d x 4 IP n-8
1 CR
Median TUMOR VOLUME (cu mm)
DAYS POST CELL IMPLANT
0
100
200
300
400
500
600
700
800
900
1000
0
5
10
15
20
25
30
35
40
45
50

FIGURE 15


Activity of Humanized LIV-14 ADC On PC3 (DSMZ) Prostate Carcinoma Tumors in Nude Female Mice
Untreated
hLIV-14-vcMMAE(4) 3 mg/kg
hLIV-14-mcMMAF(4) 3 mg/kg
h00-vcMMAE(4) 3 mg/kg
h00-mcMMAF(4) 3 mg/kg
hLIV-14d-vcMMAE(2) 3 mg/kg
hLIV-14d-mcMMAF(2) 3 mg/kg
DOSE DAY
Schedule q 4 d x 4 IP
n=8
1 CR; 3 static
Median TUMOR VOLUME (cu mm)
DAYS POST CELL IMPLANT
0
100
200
300
400
500
600
700
800
900
1000
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75

```
                    10        20        30        40        50
                    ....|....|....|....|....|....|....|....|....|....|....
hLiv22 HA   QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHWVRQAPGQGLEWMGWIDPENGDTEY
hLiv22 HB   ..........................IE..............................
hLiv22 HC   ....................................................
hLiv22 HD   ..........................F.....................................
hLiv22 HE   ..........................F.IE.................I.....
hLiv22 HF   ..........................L.IE..............................
hLiv22 HG   ..........................L.IE..............................
mLiv22 H    E...Q.....LVRS.....L..T...LNIE.......K.R.E.....I.....
CDRs                                  *****              ***********

                    60        70        80          90        100         110
                    |....|....|....|....|.......|....|....|....|.......|....|...
hLiv22 HA   GPKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARHNAHYGTWFAYWGQGTLVTVSS
hLiv22 HB   ................N.....................................................
hLiv22 HC   ......KA...A.....................................................
hLiv22 HD   ..................................TV.....................
hLiv22 HE   ......KA...A....N.................TV.....................
hLiv22 HF   ..................................V......................
hLiv22 HG   ................N.................V......................
mLiv22 H    ......KA...A...SN...LQ..S.T.G.......TV.....................A
CDRs        ******                              ***********
```

hLiv22 HA
hLiv22 HB
hLiv22 HC
hLiv22 HD
hLiv22 HE
hLiv22 HF
hLiv22 HG
hLiv22 H

FIGURE 16A

```
                  10        20        30        40        50
             ....|....|....|....|....|.........|....|....|....|....|....|
hLiv22 LA    DVVMTQSPLSLPVTLGQPASISCRSSQSLLHSSGNTYLEWFQQRPGQSPRRLIYKISTRF
hLiv22 LB    ...........................................Y.....................
hLiv22 LC    ...........................................L.....................
hLiv22 LD    ..................................................K...........
hLiv22 LE    ..................................................L...........
hLiv22 LF    ...........................................YL.......KL..........
hLiv22 LG    ...........................................y.........p..........
mLiv22 L     ..L...T......S..DQ.........................YL.......KP..........
CDRs                            ****************                  ******

                  60        70        80        90        100
             ....|....|....|....|....|....|....|....|....|....|...
hLiv22 LA    SGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPYTFGGGTKVEIKR
hLiv22 LB    ..................................................................
hLiv22 LC    ..................................................................
hLiv22 LD    ..................................................................
hLiv22 LE    ..................................................................
hLiv22 LF    ..................................................................
hLiv22 LG    ..................................................................
mLiv22 L     ............................L.L.................L.....
CDRs         *                             *********
```

FIGURE 16B

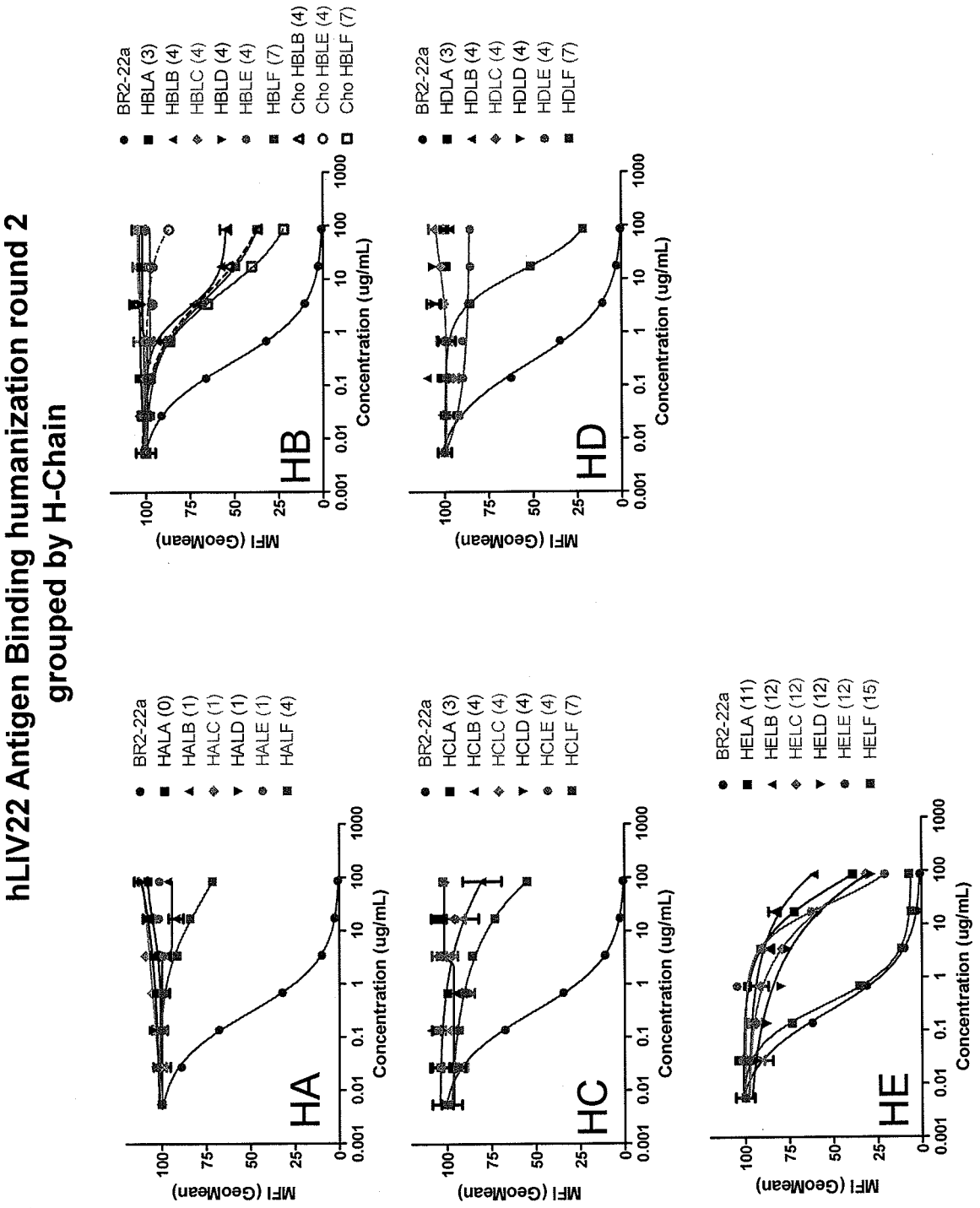

hLIV22 Antigen Binding humanization round 2 grouped by H-Chain
HA
HB
HC
HD
HE
MFI (GeoMean)
Concentration (ug/mL)
BR2-22a
HALA (0)
HALB (1)
HALC (1)
HALD (1)
HALE (1)
HALF (4)
HBLA (3)
HBLB (4)
HBLC (4)
HBLD (4)
HBLE (4)
HBLF (7)
Cho HBLB (4)
Cho HBLE (4)
Cho HBLF (7)
HCLA (3)
HCLB (4)
HCLC (4)
HCLD (4)
HCLE (4)
HCLF (7)
HDLA (3)
HDLB (4)
HDLC (4)
HDLD (4)
HDLE (4)
HDLF (7)
HELA (11)
HELB (12)
HELC (12)
HELD (12)
HELE (12)
HELF (15)

FIGURE 17

LIV22 Back Mutations (round2)

	L36	L37	L45	L46	# back mutations
LA	F	Q	R	R	0
LB	Y	Q	R	R	1
LC	F	L	R	R	1
LD	F	Q	K	R	1
LE	F	Q	R	P	1
LF	Y	L	K	P	4

	H27	H28	H29	H30	H48	H66	H67	H71	H76	H93	H94	# back mutations
HA	Y	T	F	T	M	R	V	R	S	A	R	0
HB	Y	T	I	(E)	M	R	V	R	N	A	R	3
HC	Y	T	F	T	M	K	A	A	S	A	R	3
HD	L	T	F	T	M	R	V	R	S	T	V	3
HE	L	N	I	(E)	I	K	A	A	N	T	V	11

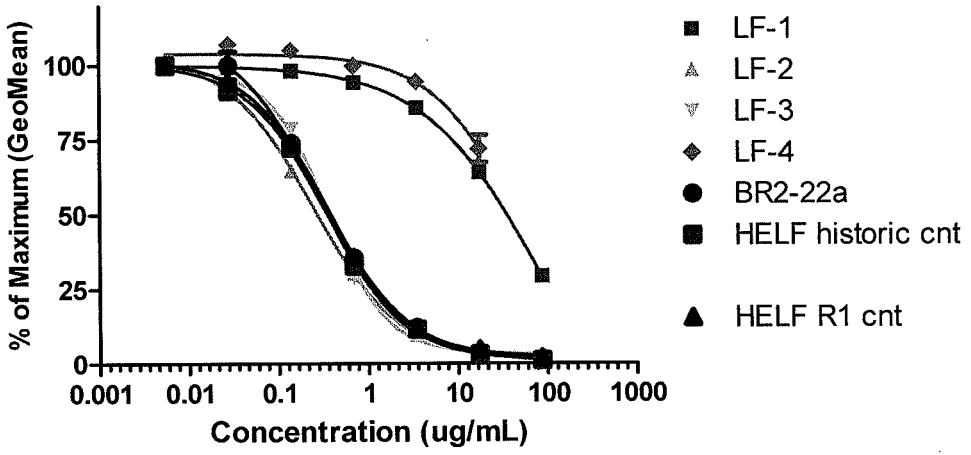
Additional LIV22 Mutations (round3)

	L36	L37	L45	L46	# back mutations
LF	Y	L	K	P	4
LF-1	F	L	K	P	3
LF-2	Y	Q	K	P	3
LF-3	Y	L	R	P	3
LF-4	Y	L	K	R	3

	H27	H28	H29	H30	H48	H66	H67	H71	H76	H93	H94	# back mutations
HE	L	N	I	(E)	I	K	A	A	N	T	V	11
HE-1	Y	N	I	(E)	I	K	A	A	N	T	V	10
HE-2	L	T	I	(E)	I	K	A	A	N	T	V	10
HE-3	L	N	F	(E)	I	K	A	A	N	T	V	10
HE-4	L	N	I	T	I	K	A	A	N	T	V	10
HE-5	L	N	I	(E)	M	K	A	A	N	T	V	10
HE-6	L	N	I	(E)	I	R	A	A	N	T	V	10
HE-7	L	N	I	(E)	I	K	V	A	N	T	V	10
HE-8	L	N	I	(E)	I	K	A	R	N	T	V	10
HE-9	L	N	I	(E)	I	K	A	A	S	T	V	10
HE10	L	N	I	(E)	I	K	A	A	N	A	V	10
HE11	L	N	I	(E)	I	K	A	A	N	T	R	10

FIGURE 18

hLIV22 Competition Binding: LF (round3)



Additional LIV22 Back Mutations: LF

	L36	L37	L45	L46	# back mutations
LF	Y	L	K	P	**4**
LF-1	F	L	K	P	**3**
LF-2	Y	Q	K	P	**3**
LF-3	Y	L	R	P	**3**
LF-4	Y	L	K	R	**3**

residues to maintain antigen binding:

Y36 (Tyrosine) & P46 (Proline)

FIGURE 19

hLIV22 Competition Binding: HE (round3)

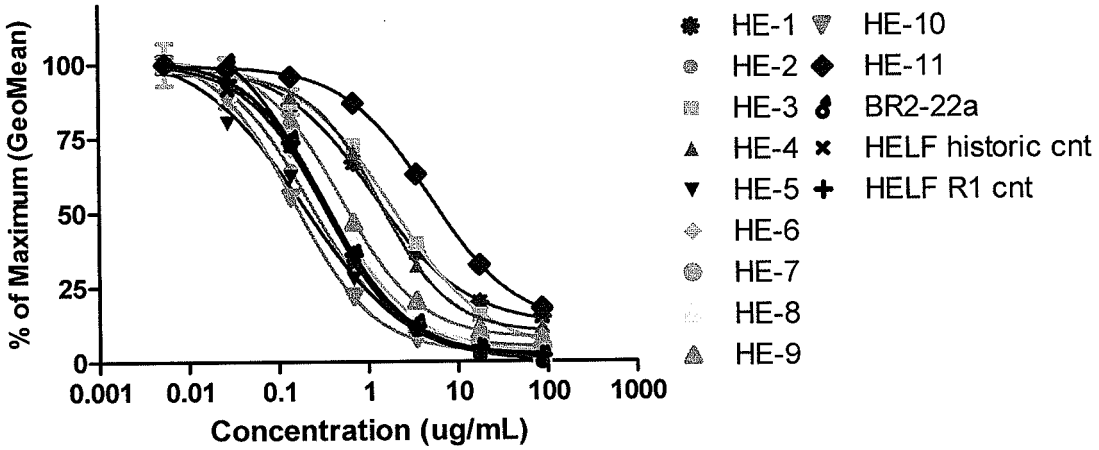


FIGURE 20

Additional hLIV22 Back Mutations: HE

	H27	H28	H29	H30	H48	H66	H67	H71	H76	H93	H94	# back mutations
HE	L	N	I	E	I	K	A	A	N	T	V	11
HE-1	Y	N	I	E	I	K	A	A	N	T	V	10
HE-2	L	T	I	E	I	K	A	A	N	T	V	10
HE-3	L	N	F	E	I	K	A	A	N	T	V	10
HE-4	L	N	I	T	I	K	A	A	N	T	V	10
HE-5	L	N	I	E	M	K	A	A	N	T	V	10
HE-6	L	N	I	E	I	R	A	A	N	T	V	10
HE-7	L	N	I	E	I	K	V	A	N	T	V	10
HE-8	L	N	I	E	I	K	A	R	N	T	V	10
HE-9	L	N	I	E	I	K	A	A	S	T	V	10
HE-10	L	N	I	E	I	K	A	A	N	A	V	10
HE-11	L	N	I	E	I	K	A	A	N	T	R	10

residues to maintain antigen binding:

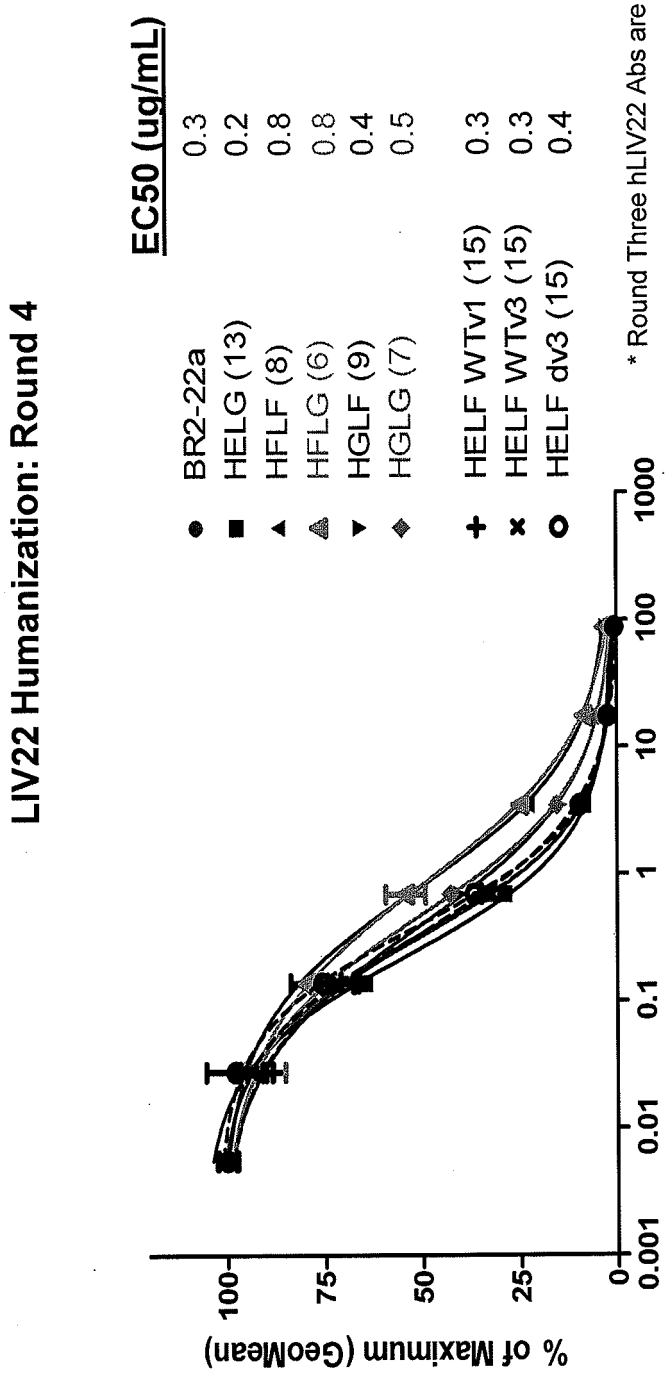
L27 (Leucine)

I29 (Isoleucine)

E30 (Glutamic Acid)

N76 (Asparagine)

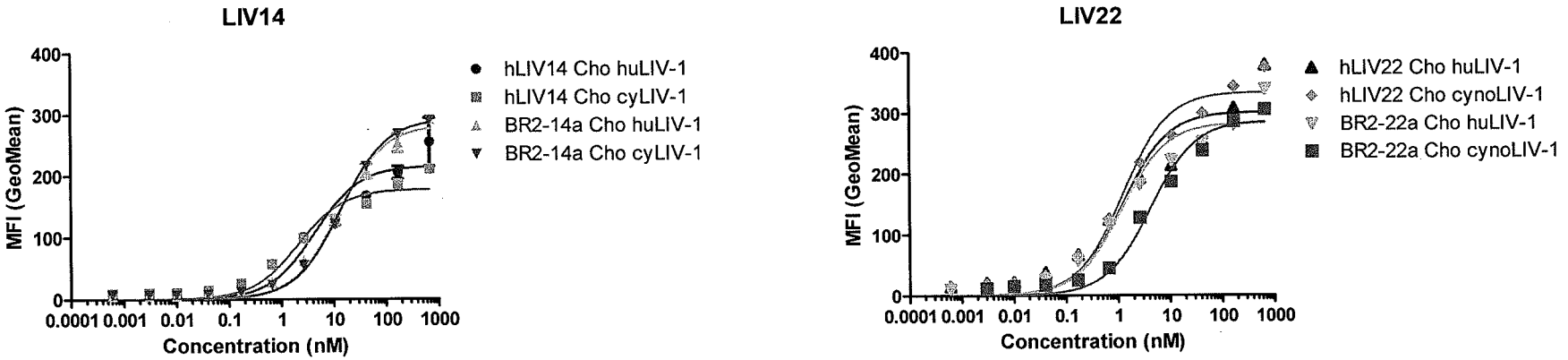
V94 (Valine)



	# Back mutations	EC50 (ug/mL)
HGLG	7	0.5
HGLF	9	0.4
HFLG	6	0.8
HFLF	8	0.8

FIGURE 21

Saturation Binding
AF-647



Apparent Kd (nM) of BR2-14a, BR2-22a, hLIV14 and hLIV14 for human and cyno LIV-1

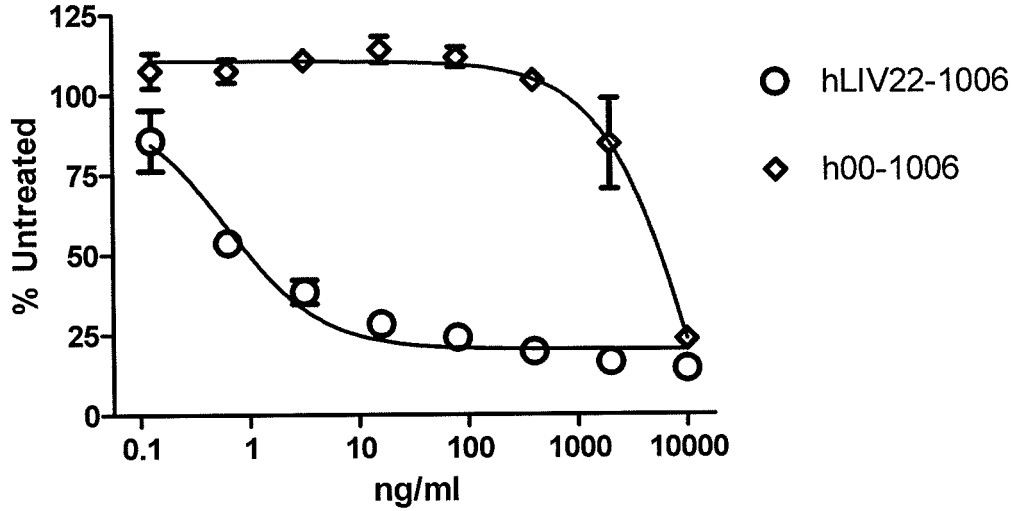
antigen	BR-14a	hLIV14	BR-22a	hLIV22
Human LIV1	12.5	4.3	1.2	1.2
Cyno LIV1	14.0	2.1	4.2	1.3

Negative control: m2H12

FIGURE 22

Cytotoxic Activity of hLIV22-vcMMAE

MCF-7 (ATCC) cells. 144 hour treatment

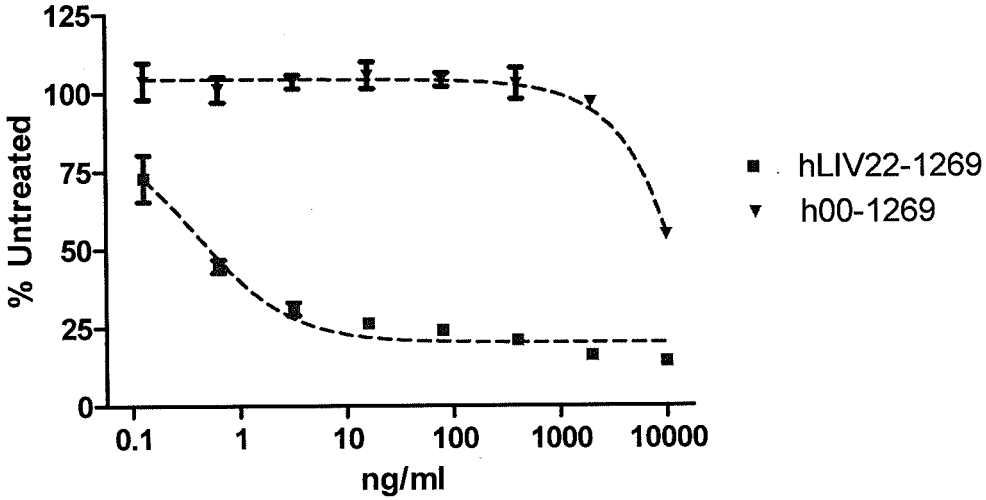


EC50 table. Average from 2 experiments

	EC50 (ng/ml)
hLIV22 -1006	0.9
h00 -1006	4981

FIGURE 23

Cytotoxic Activity of hLIV22-mcMMAF
MCF-7 (ATCC) cells. 144 hour treatment



EC50 table. Average from 2 experiments

-1269 ADC	EC50 (ng/ml)
hLIV22	0.7
h00	>10000

FIGURE 24

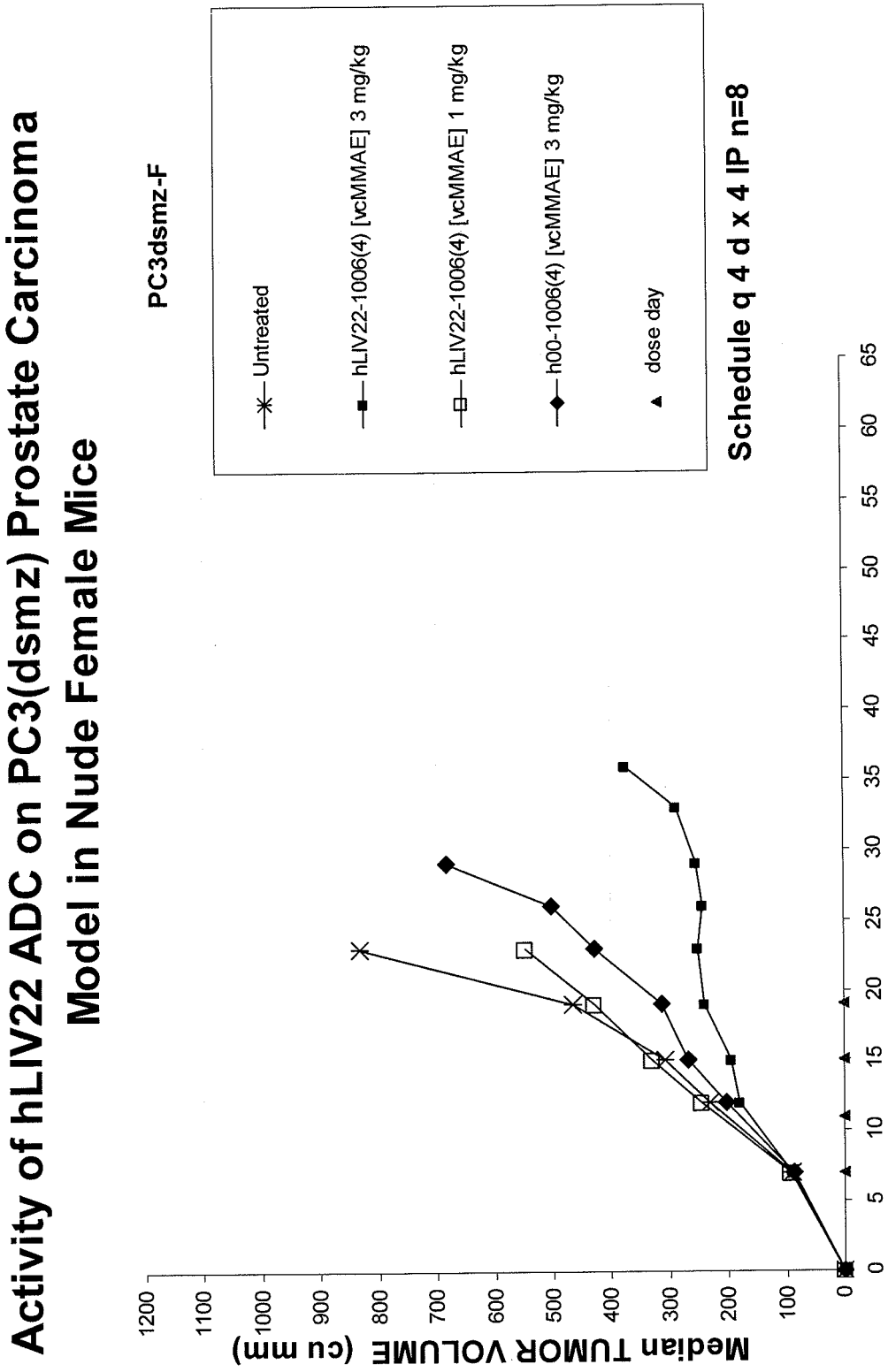

Activity of hLIV22 ADC on PC3(dsmz) Prostate Carcinoma Model in Nude Female Mice
PC3dsmz-F
Schedule q 4 d x 4 IP n=8
Untreated
hLIV22-1006(4) [vcMMAE] 3 mg/kg
hLIV22-1006(4) [vcMMAE] 1 mg/kg
h00-1006(4) [vcMMAE] 3 mg/kg
dose day
Median TUMOR VOLUME (cu mm)
DAYS POST CELL IMPLANT
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
0
5
10
15
20
25
30
35
40
45
50
55
60
65

FIGURE 25

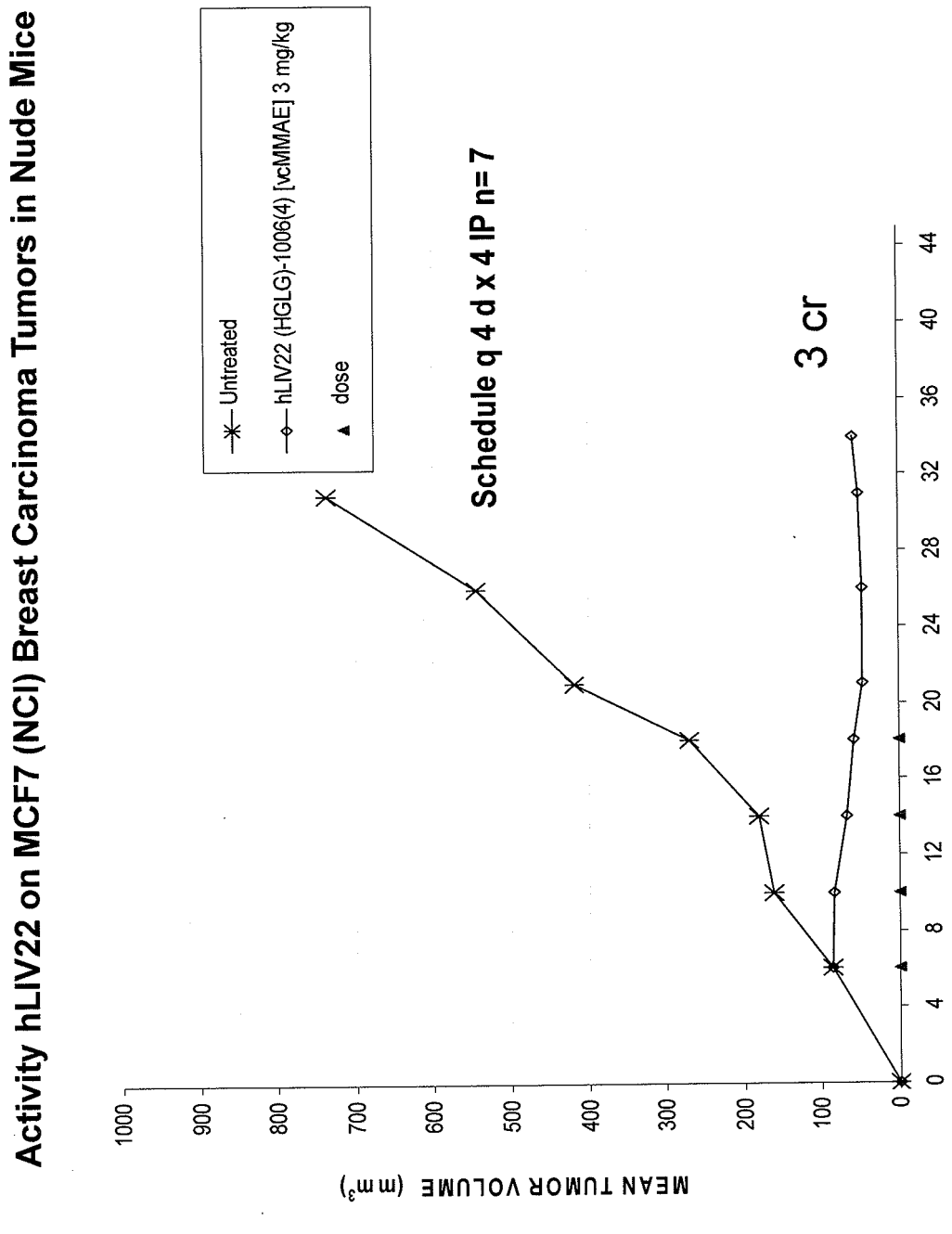

Activity hLIV22 on MCF7 (NCI) Breast Carcinoma Tumors in Nude Mice
Untreated
hLIV22 (HGLG)-1006(4) [vcMMAE] 3 mg/kg
dose
Schedule q 4 d x 4 IP n= 7
3 cr
MEAN TUMOR VOLUME (mm³)
DAYS POST TUMOR IMPLANT
0
100
200
300
400
500
600
700
800
900
1000
0
4
8
12
16
20
24
28
32
36
40
44
Study terminated due to estrogen toxicity

FIGURE 26

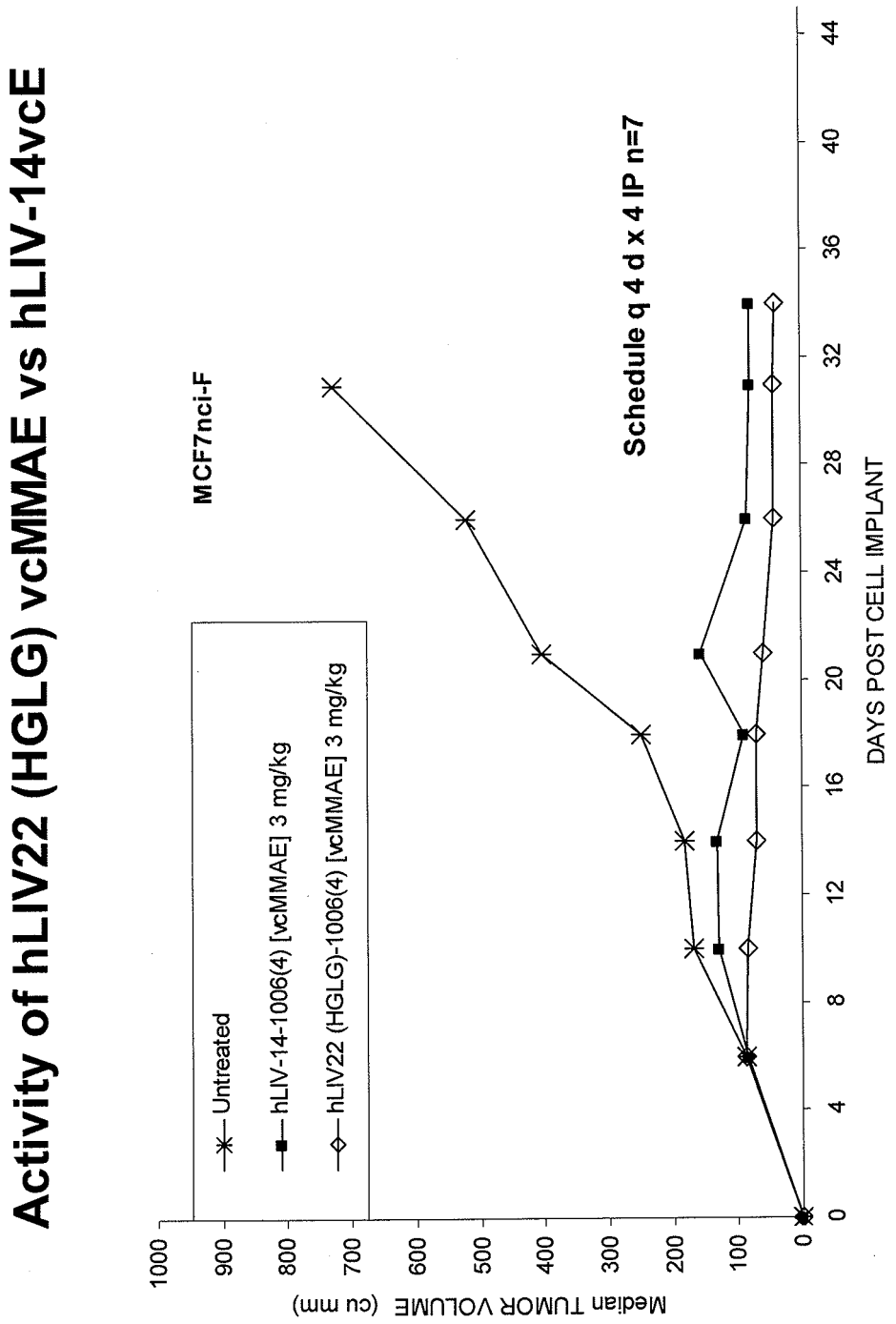

Activity of hLIV22 (HGLG) vcMMAE vs hLIV-14vcE
MCF7nci-F
Schedule q 4 d x 4 IP n=7
Untreated
hLIV-14-1006(4) [vcMMAE] 3 mg/kg
hLIV22 (HGLG)-1006(4) [vcMMAE] 3 mg/kg
Median TUMOR VOLUME (cu mm)
DAYS POST CELL IMPLANT
0
100
200
300
400
500
600
700
800
900
1000
0
4
8
12
16
20
24
28
32
36
40
44

FIGURE 27

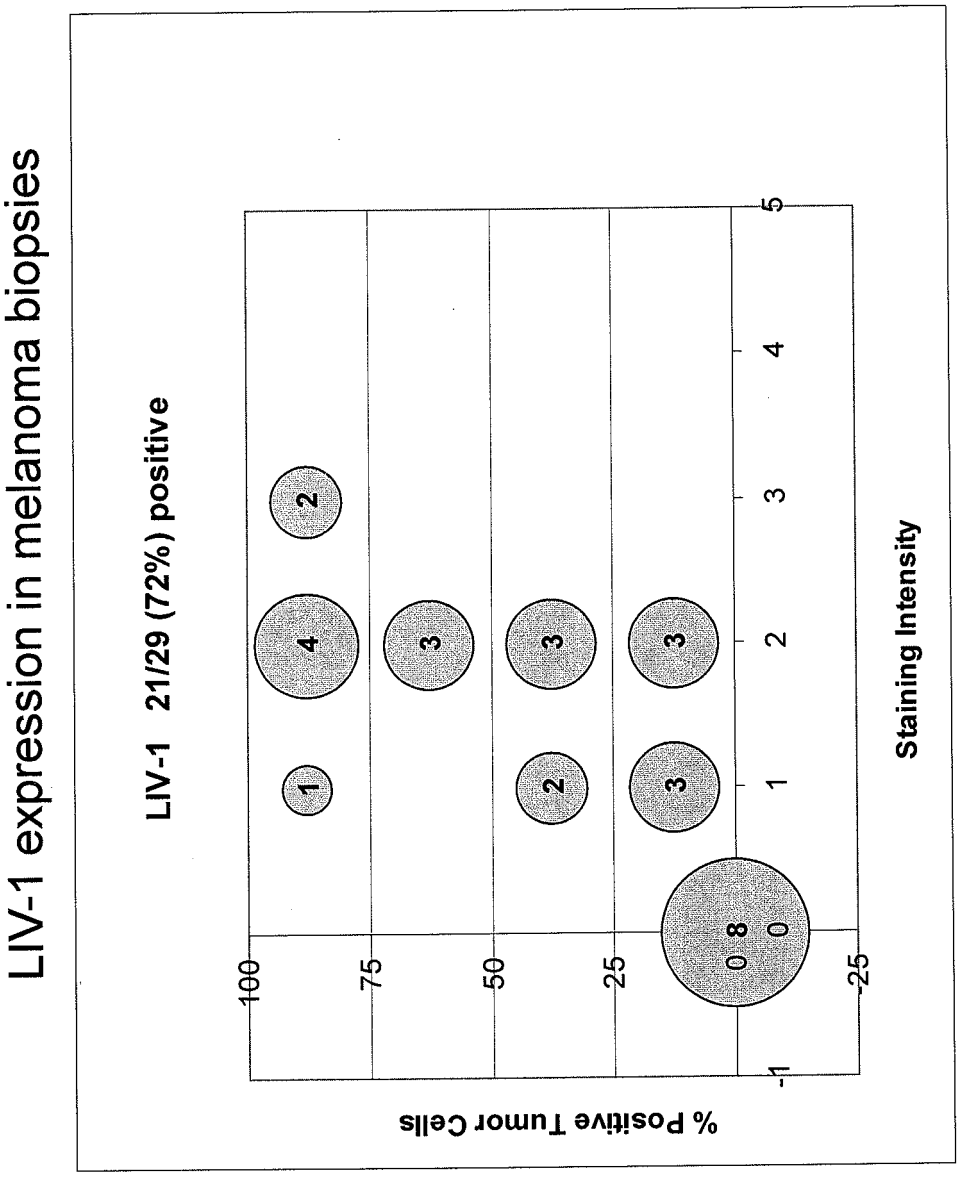

LIV-1 expression in melanoma biopsies
LIV-1 21/29 (72%) positive
% Positive Tumor Cells
100
75
50
25
0
-25
-1
1
2
3
4
5
Staining Intensity
1
4
2
3
3
2
3
3
0
8
0

FIGURE 28