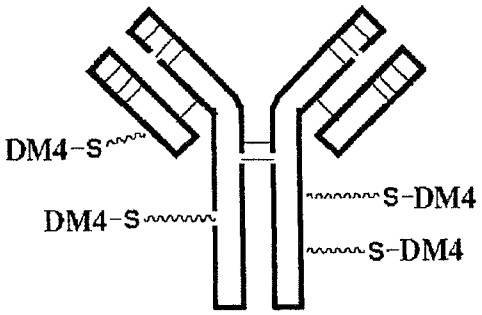
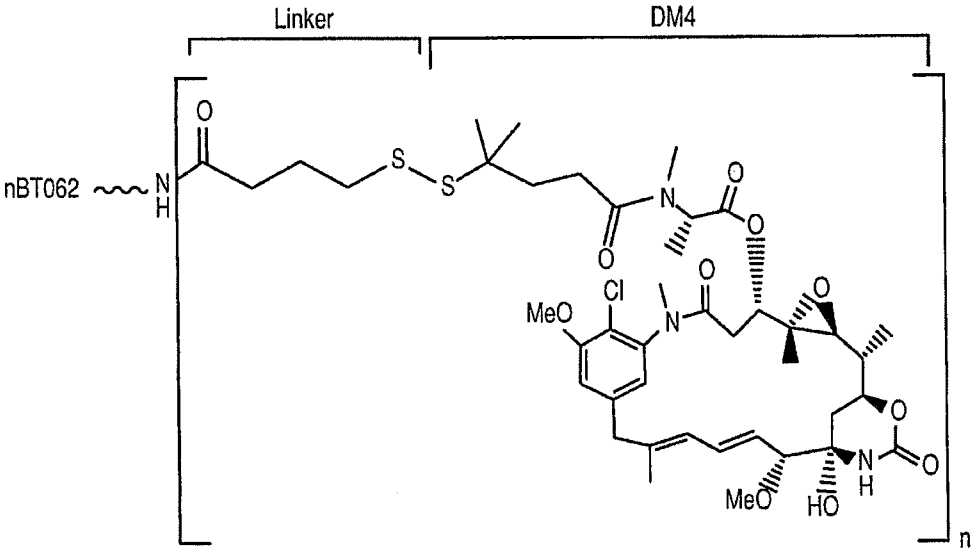
FIG. 1





*n is approximately 3.5 drug linked per antibody molecule

FIG. 2

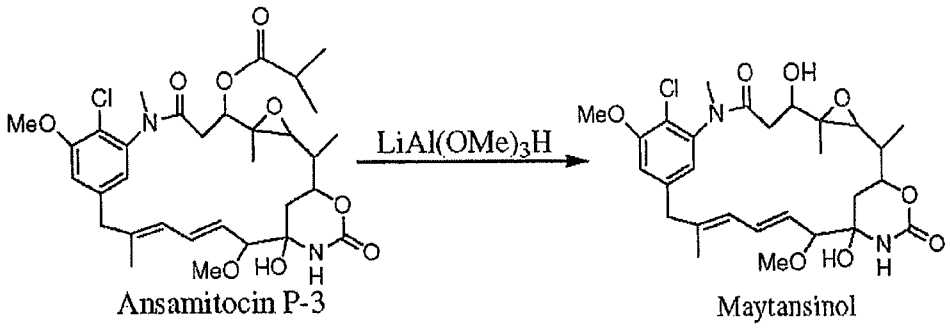
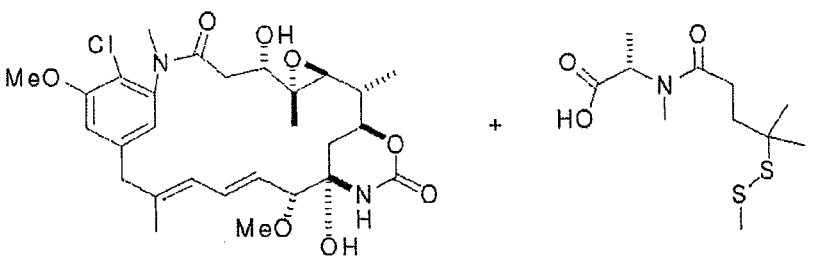
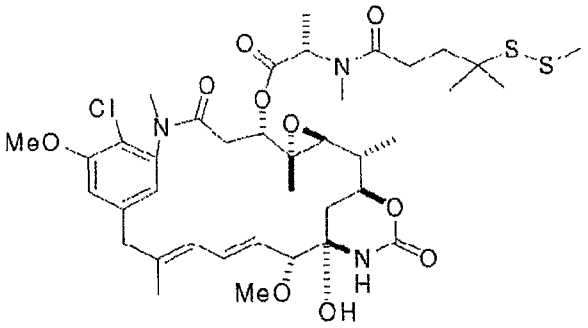


FIG. 3



Maytansinol + DM4 Side Chain

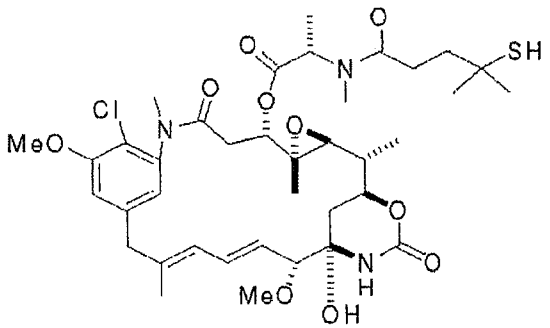
Step I: 1) DCC, $ZnCl_2$, CH_2Cl_2 2) Chromatography



L-DM4-SMe

FIG. 4

Step II: 1) DTT, DME, phosphate buffer 2) Chromatography



L-DM4

DCC: 1,3-dicyclohexylcarbodiimide
DTT: Dithiothreitol
DME: 1,2-Dimethoxyethane

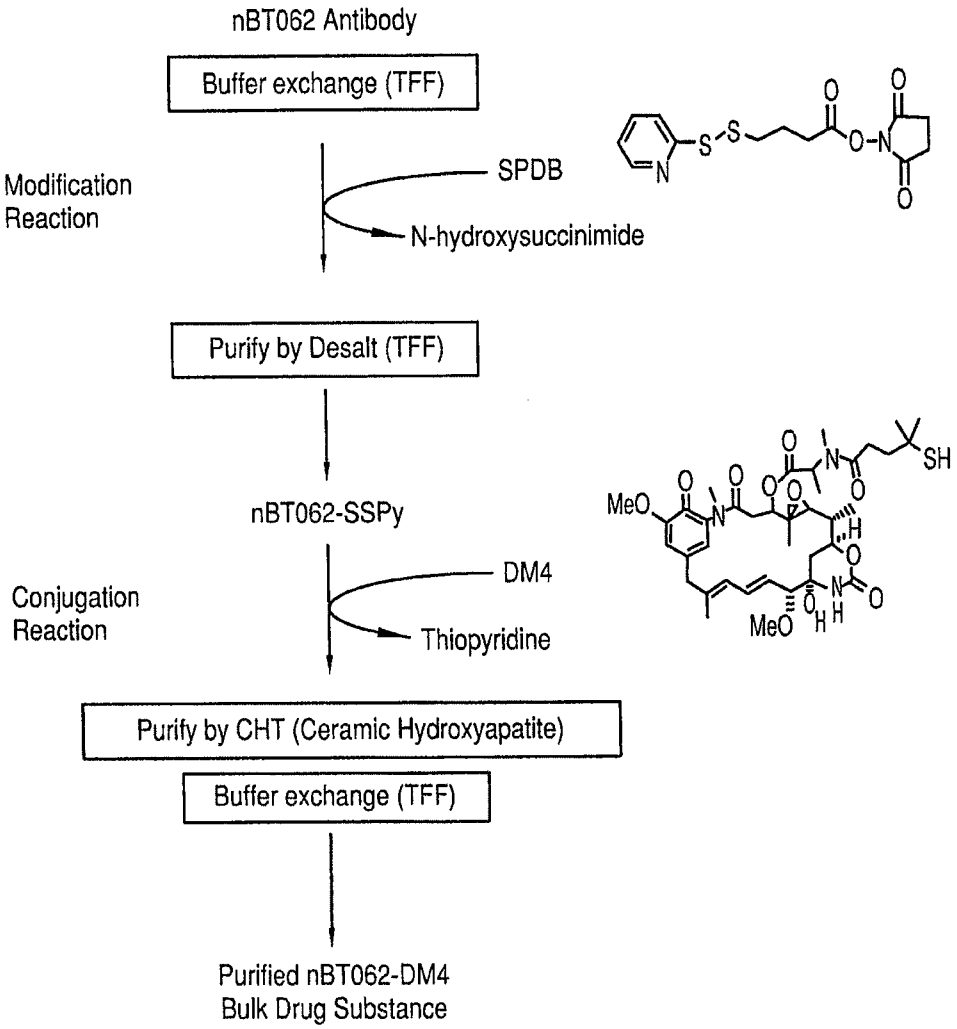

nBT062 Antibody
Buffer exchange (TFF)
Modification Reaction
SPDB
N-hydroxysuccinimide
Purify by Desalt (TFF)
nBT062-SSPy
Conjugation Reaction
DM4
Thiopyridine
Purify by CHT (Ceramic Hydroxyapatite)
Buffer exchange (TFF)
Purified nBT062-DM4
Bulk Drug Substance

FIG. 5

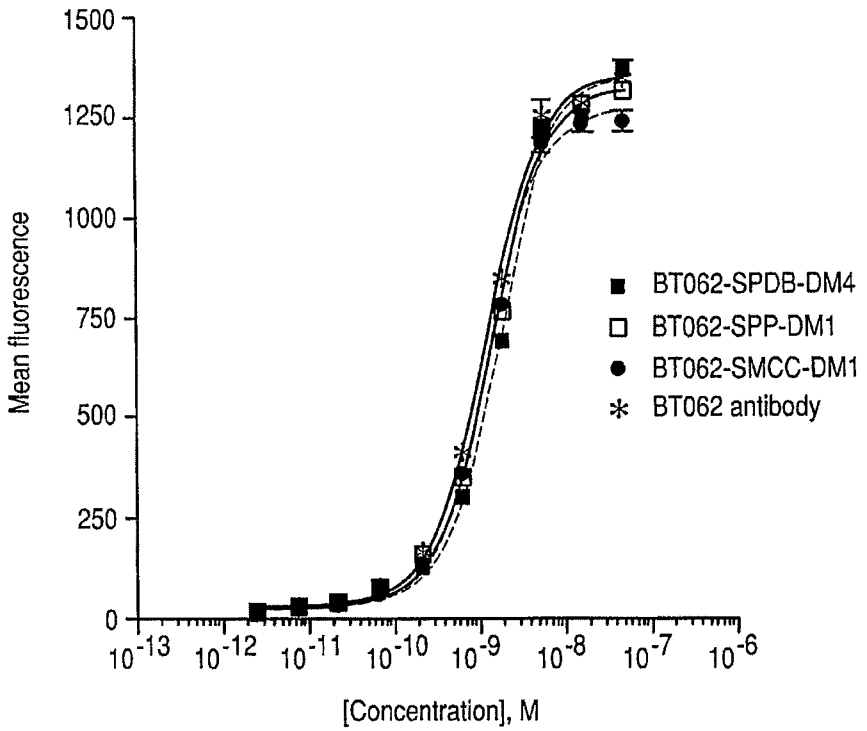

1500
1250
1000
750
500
250
0
Mean fluorescence
10-13
10-12
10-11
10-10
10-9
10-8
10-7
10-6
[Concentration], M
BT062-SPDB-DM4
BT062-SPP-DM1
BT062-SMCC-DM1
BT062 antibody

FIG. 6

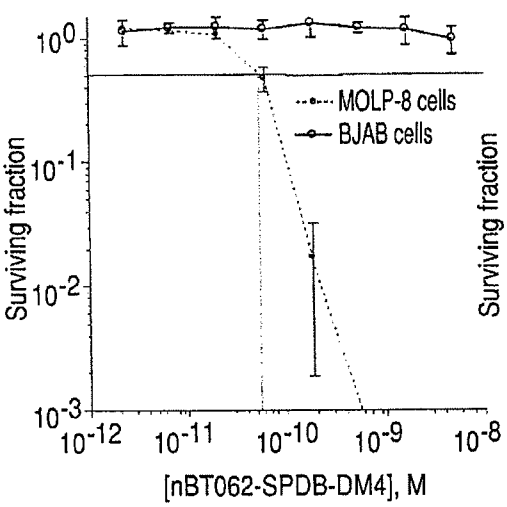


FIG. 7A

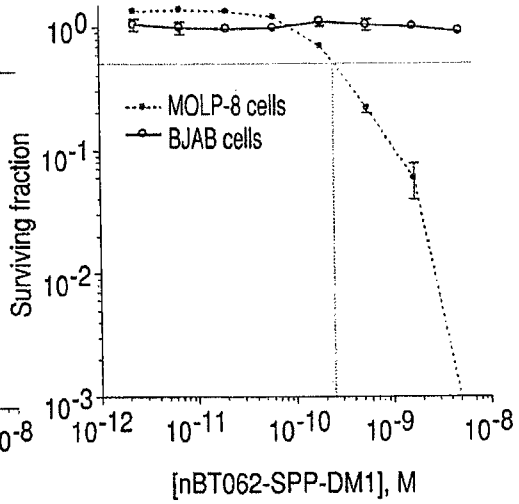


FIG. 7B

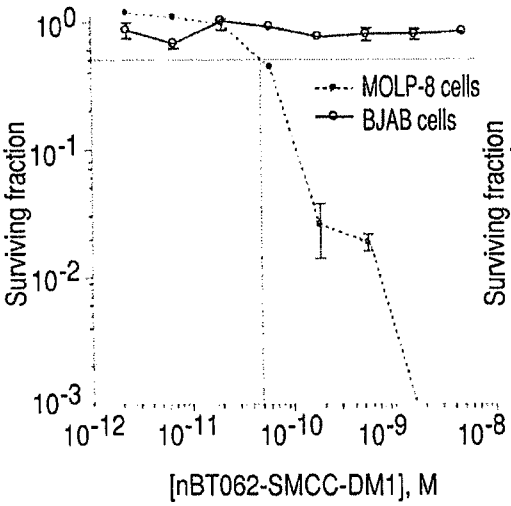


FIG. 7C

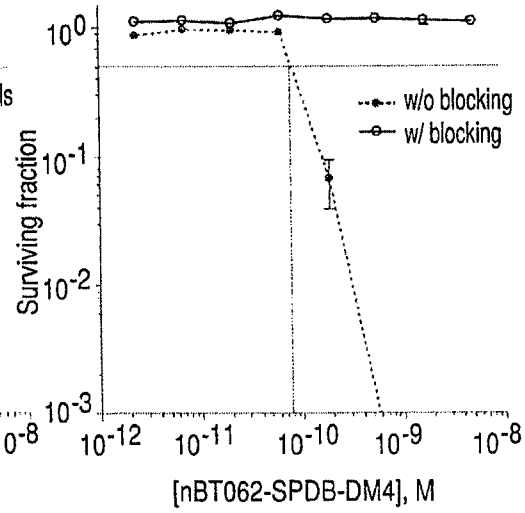


FIG. 7D

FIG. 8

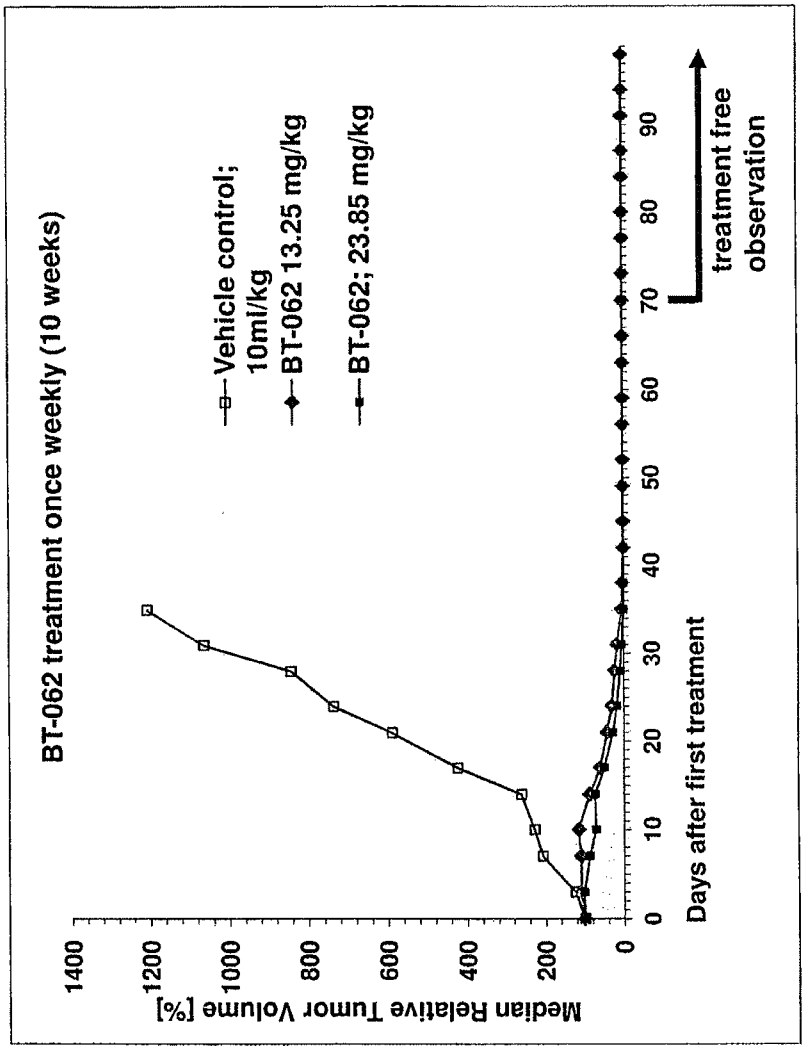

BT-062 treatment once weekly (10 weeks)
Vehicle control; 10ml/kg
BT-062 13.25 mg/kg
BT-062; 23.85 mg/kg
treatment free observation
Median Relative Tumor Volume [%]
Days after first treatment
0
200
400
600
800
1000
1200
1400
0
10
20
30
40
50
60
70
80
90

FIG. 9

Xenograft model: Mammary carcinoma:
Complete remission in all BT-062 treated mice

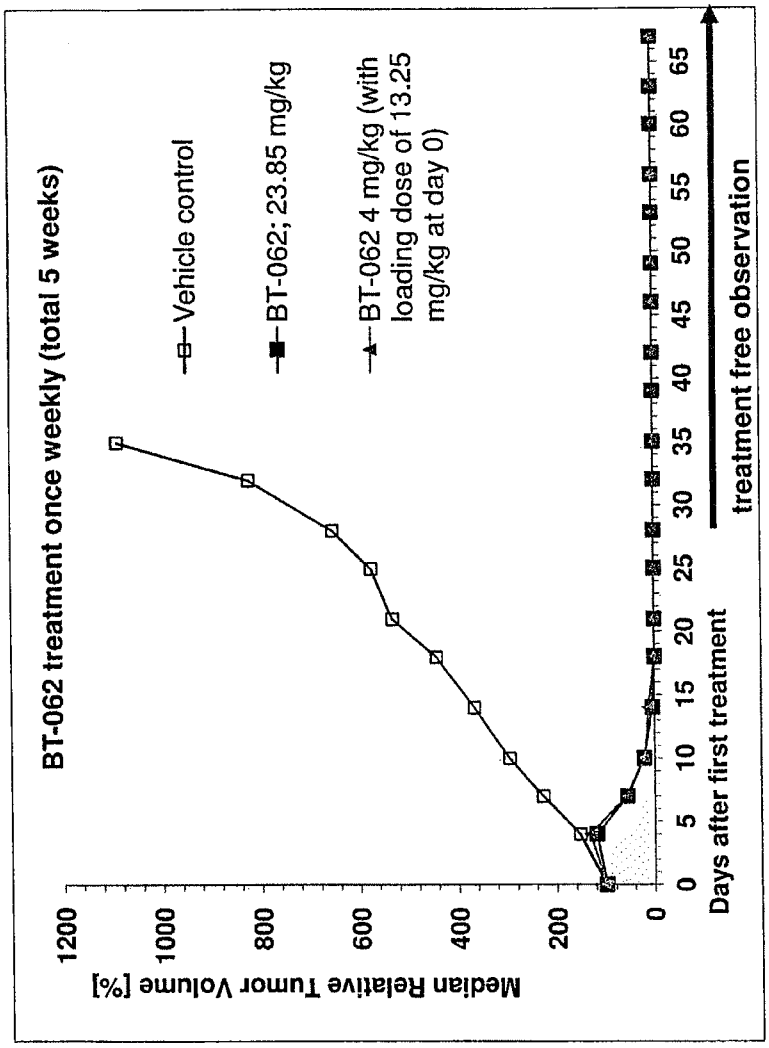
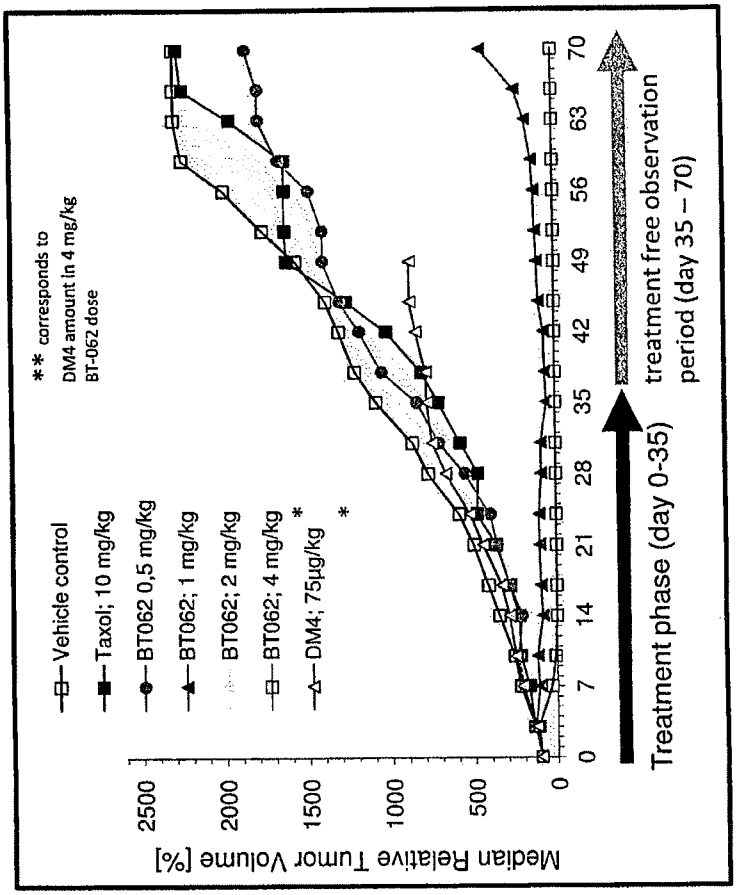


FIG. 10



Treatment:

BT-062 on days: 0, 7,14, 21, 28, 35
Taxol on days 1, 8, 15, 22, 29

Group	Partial remission	Complete remission
PBS	0/7	0/7
Taxol (10 mg/kg)	0/7	1/7
BT-062; 0,5 mg/kg	0/7	0/7
BT-062; 1 mg/kg	2/7	3/7
BT-062; 2 mg/kg	0/7	7/7
BT-062; 4 mg/kg	0/7	7/7
DM4; 75 µg/kg	0/4	0/4

FIG. 11

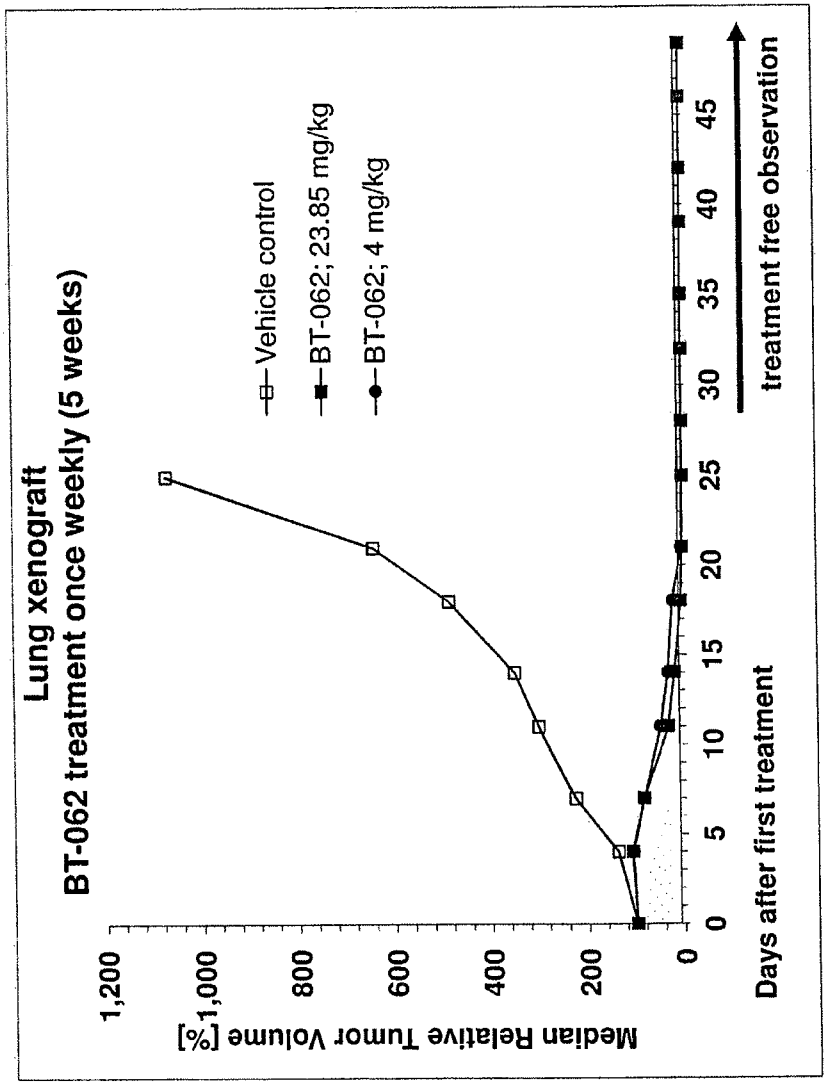

Lung xenograft
BT-062 treatment once weekly (5 weeks)
Vehicle control
BT-062; 23.85 mg/kg
BT-062; 4 mg/kg
Median Relative Tumor Volume [%]
1,200
1,000
800
600
400
200
0
0
5
10
15
20
25
30
35
40
45
Days after first treatment
treatment free observation

FIG. 12

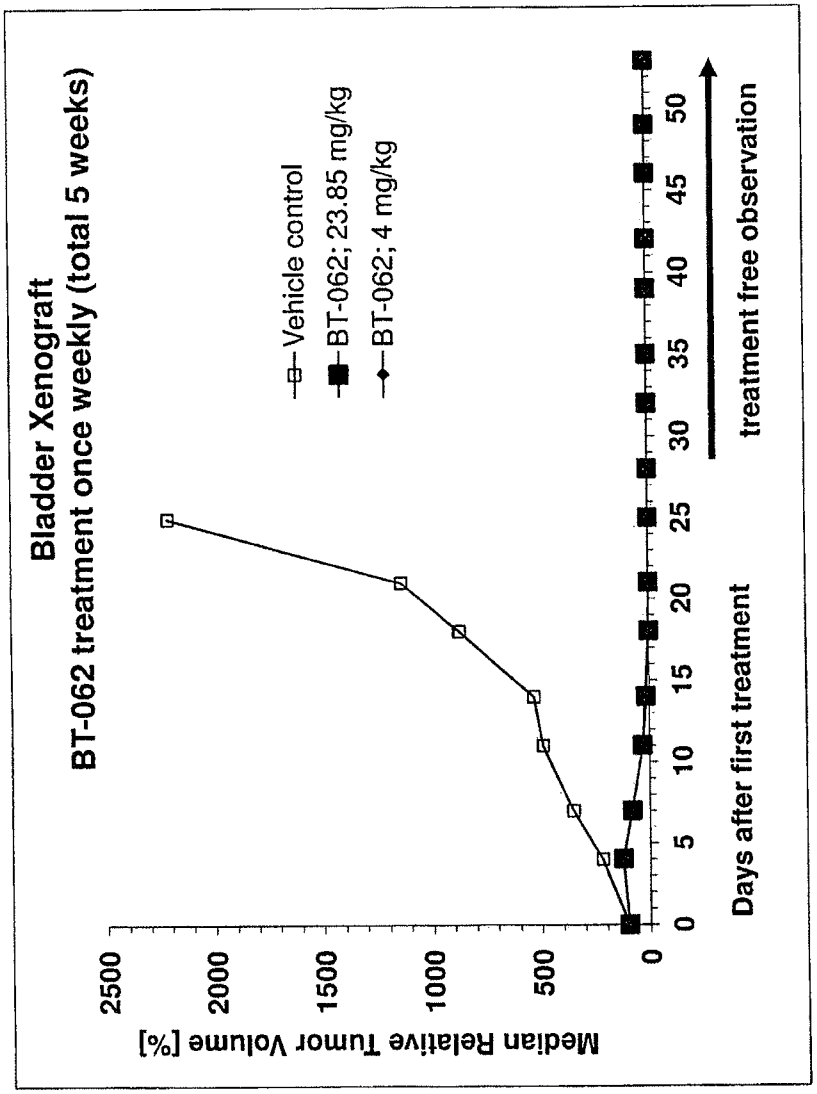
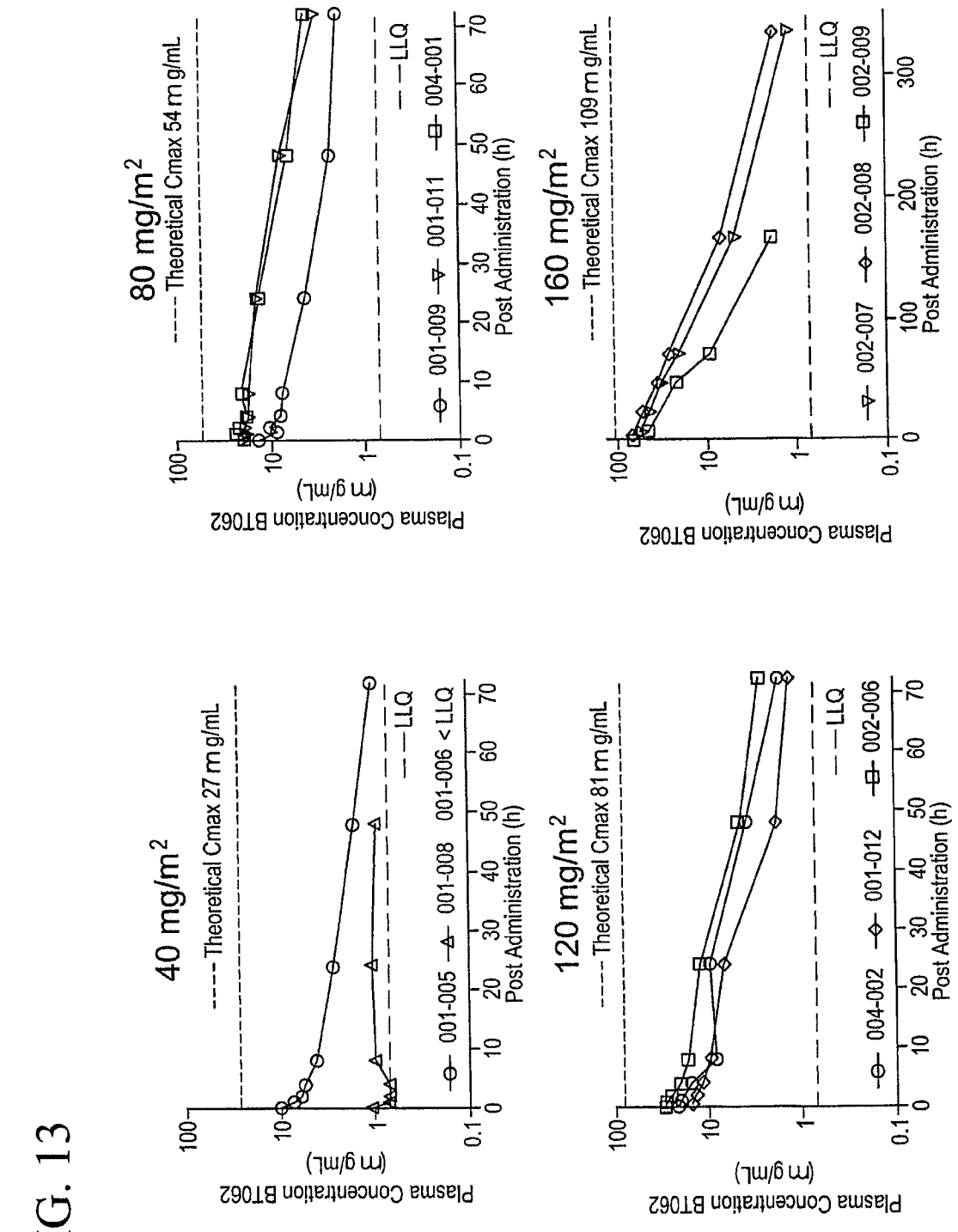

Bladder Xenograft
BT-062 treatment once weekly (total 5 weeks)
Vehicle control
BT-062; 23.85 mg/kg
BT-062; 4 mg/kg
Median Relative Tumor Volume [%]
2500
2000
1500
1000
500
0
0
5
10
15
20
25
30
35
40
45
50
Days after first treatment
treatment free observation

FIG. 13


40 mg/m2
Theoretical Cmax 27 m g/mL
LLQ
001-005
001-008
001-006 < LLQ
Plasma Concentration BT062 (m g/mL)
Post Administration (h)
80 mg/m2
Theoretical Cmax 54 m g/mL
LLQ
001-009
001-011
004-001
Plasma Concentration BT062 (m g/mL)
Post Administration (h)
120 mg/m2
Theoretical Cmax 81 m g/mL
LLQ
004-002
001-012
002-006
Plasma Concentration BT062 (m g/mL)
Post Administration (h)
160 mg/m2
Theoretical Cmax 109 m g/mL
LLQ
002-007
002-008
002-009
Plasma Concentration BT062 (m g/mL)
Post Administration (h)

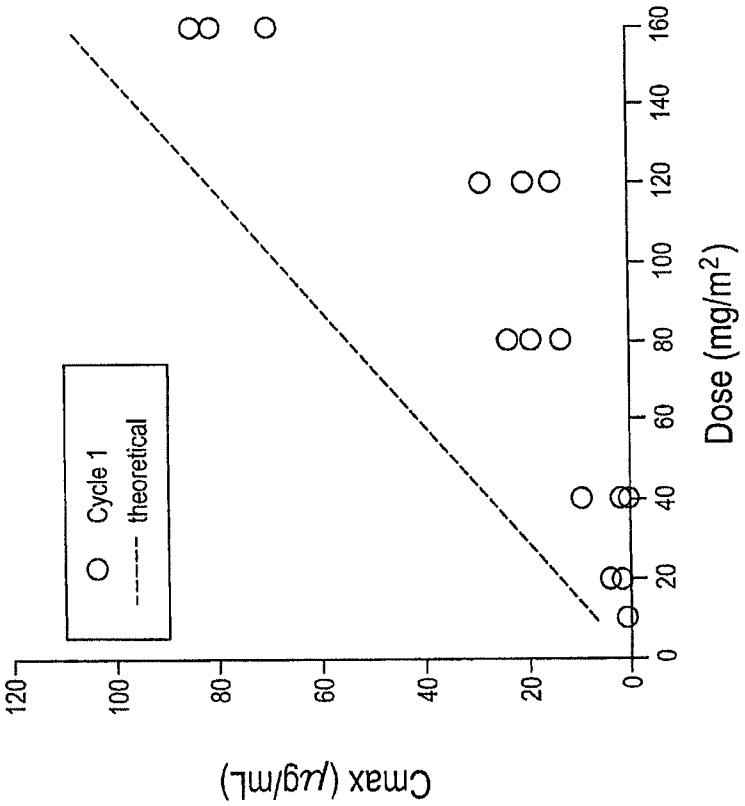

Cmax (µg/mL)
120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
160
Dose (mg/m2)
Cycle 1
theoretical

FIG. 14

FIG. 15

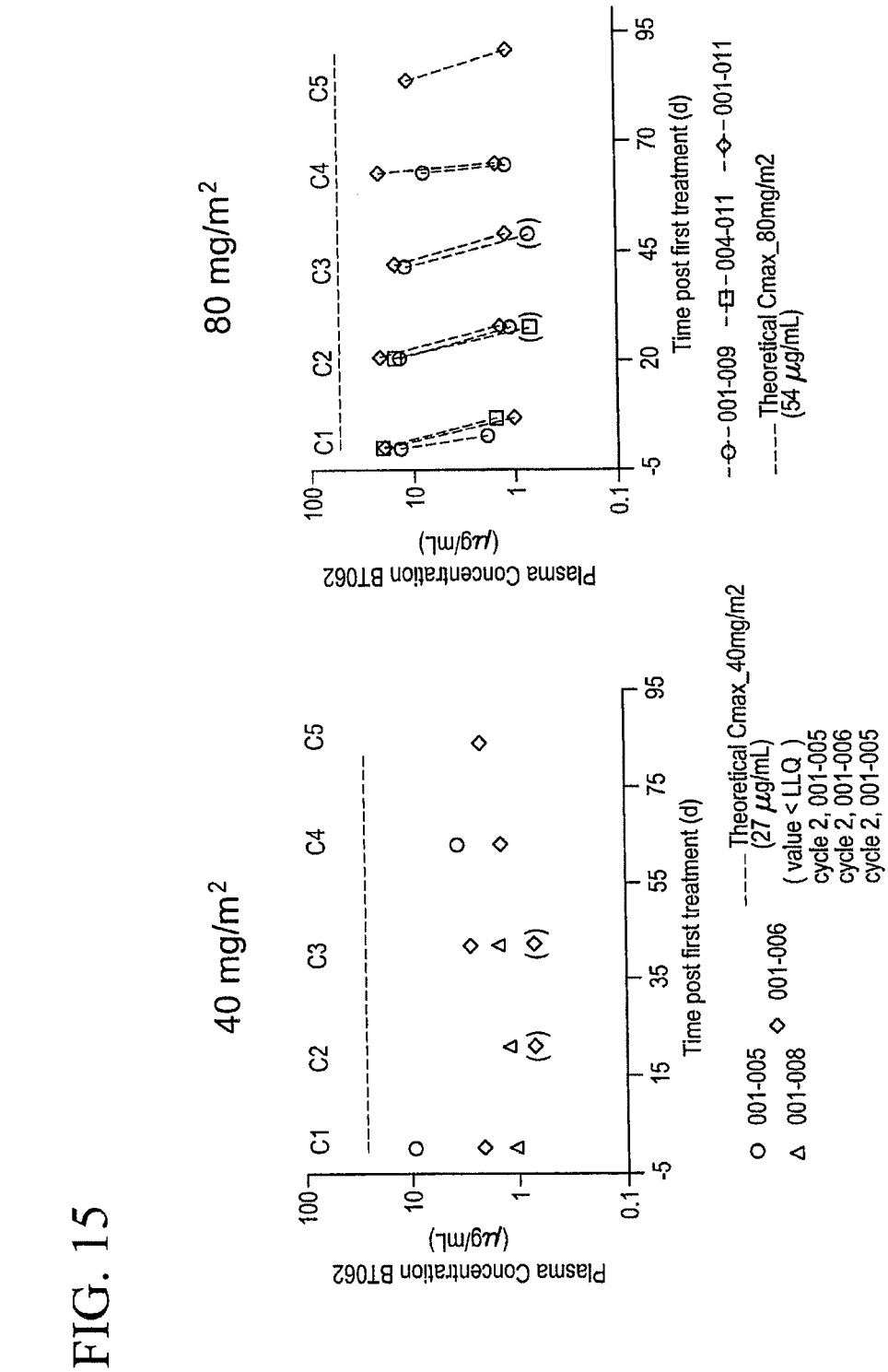

40 mg/m2
80 mg/m2
Plasma Concentration BT062 (µg/mL)
100
10
1
0.1
C1
C2
C3
C4
C5
-5
15
35
55
75
95
20
45
70
Time post first treatment (d)
001-005
001-006
001-008
001-009
004-011
001-011
Theoretical Cmax_40mg/m2 (27 µg/mL)
Theoretical Cmax_80mg/m2 (54 µg/mL)
(value < LLQ)
cycle 2, 001-005
cycle 2, 001-006
cycle 2, 001-005

FIG. 16

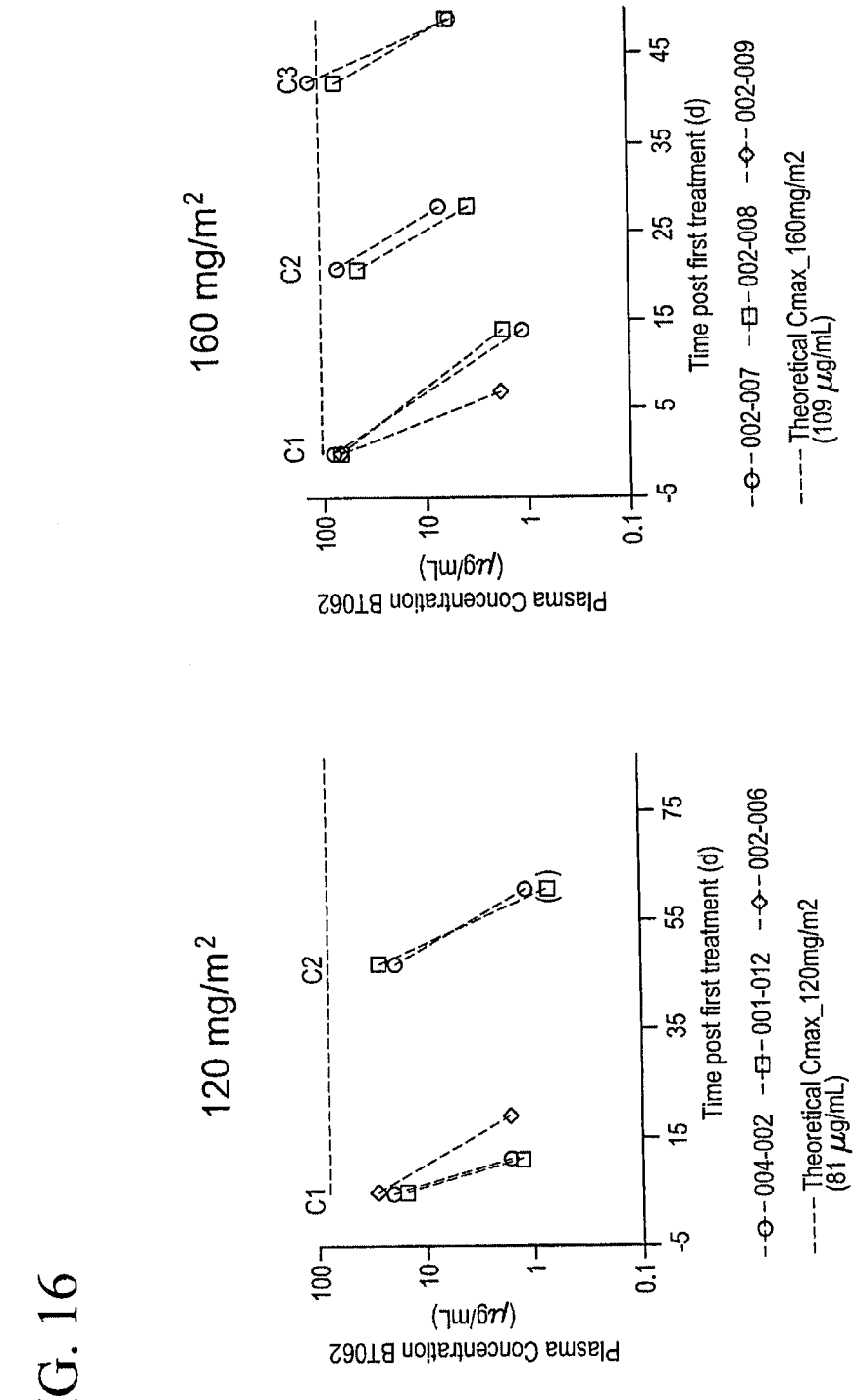
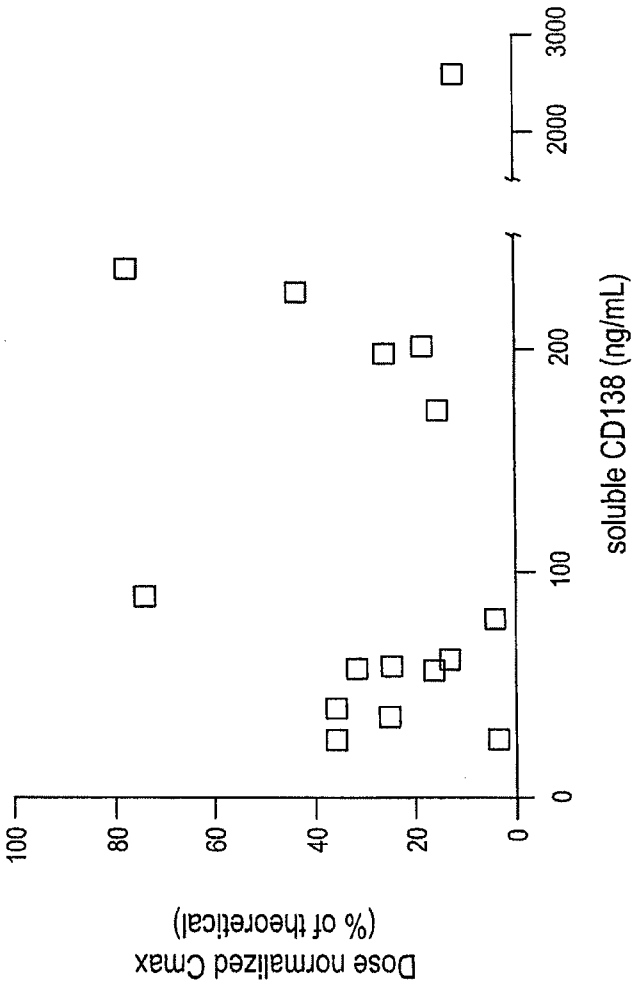

160 mg/m2
C1
C2
C3
100
10
1
0.1
-5
5
15
25
35
45
Plasma Concentration BT062 (µg/mL)
Time post first treatment (d)
002-007
002-008
002-009
Theoretical Cmax_160mg/m2 (109 µg/mL)
120 mg/m2
C1
C2
100
10
1
0.1
-5
15
35
55
75
Plasma Concentration BT062 (µg/mL)
Time post first treatment (d)
004-002
001-012
002-006
Theoretical Cmax_120mg/m2 (81 µg/mL)

FIG. 17


Dose normalized Cmax
(% of theoretical)
0
20
40
60
80
100
0
100
200
soluble CD138 (ng/mL)
2000
3000

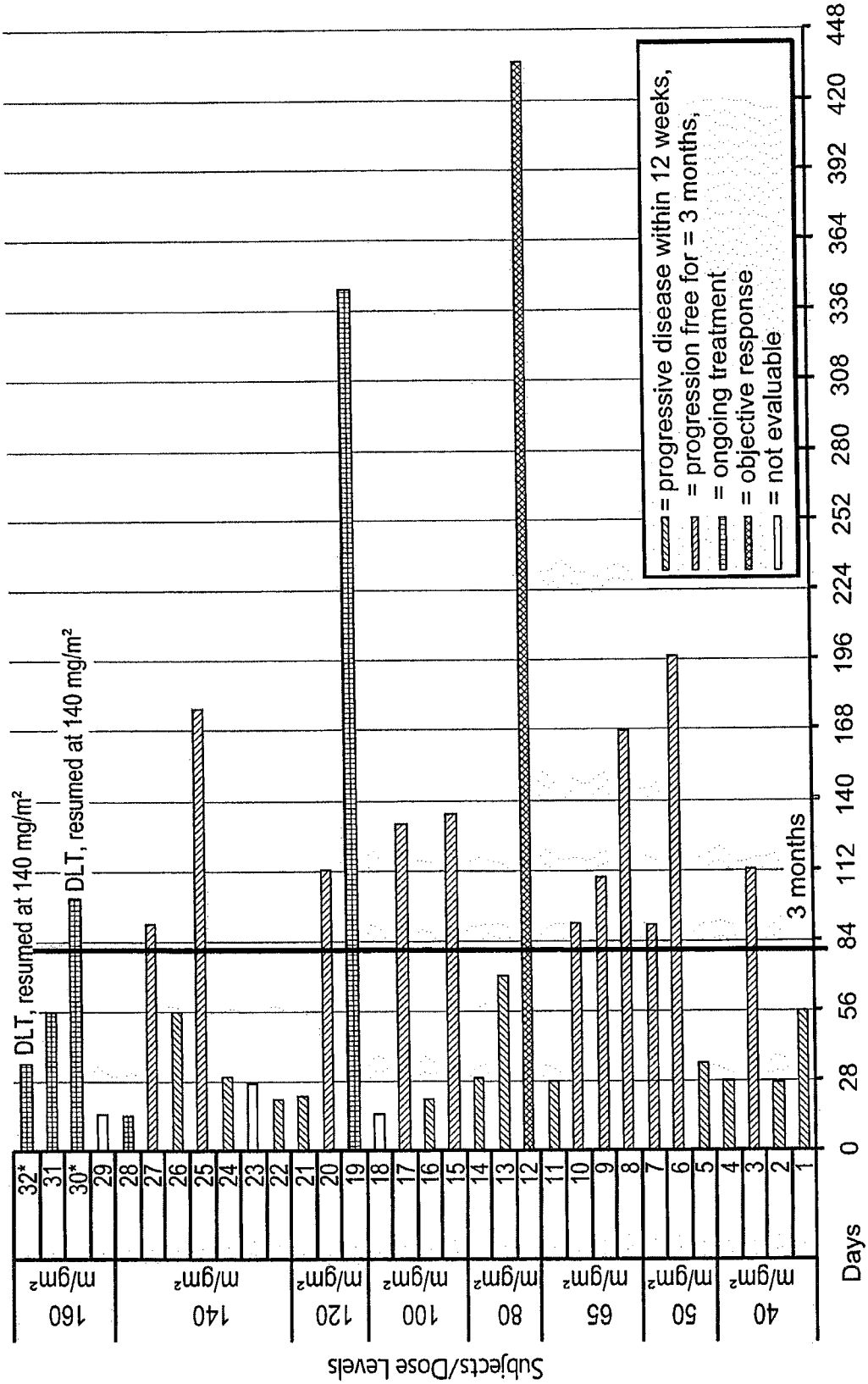


FIG. 18

LEGEND: Patients no. 30 and 32: DLT, resumed at 140mg/m2

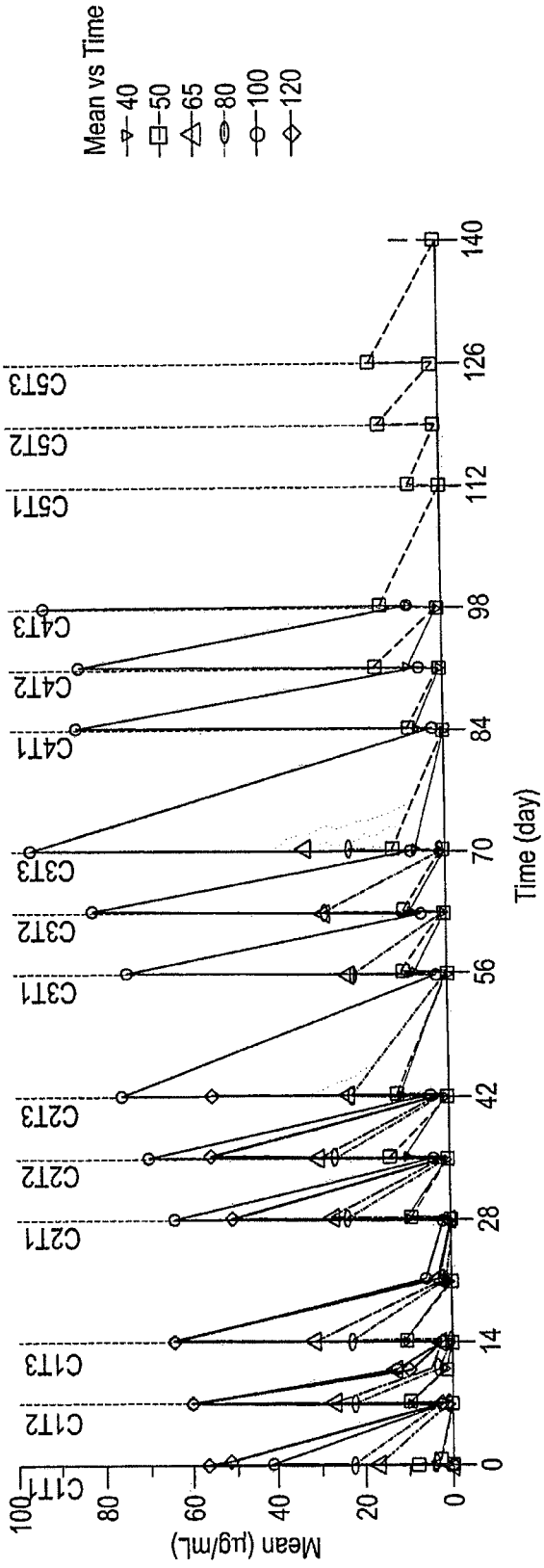

Mean vs Time
40
50
65
80
100
120
Mean (µg/mL)
Time (day)
C11T1
C11T2
C11T3
C21T1
C21T2
C21T3
C31T1
C31T2
C31T3
C41T1
C41T2
C41T3
C51T1
C51T2
C51T3

FIG. 19A

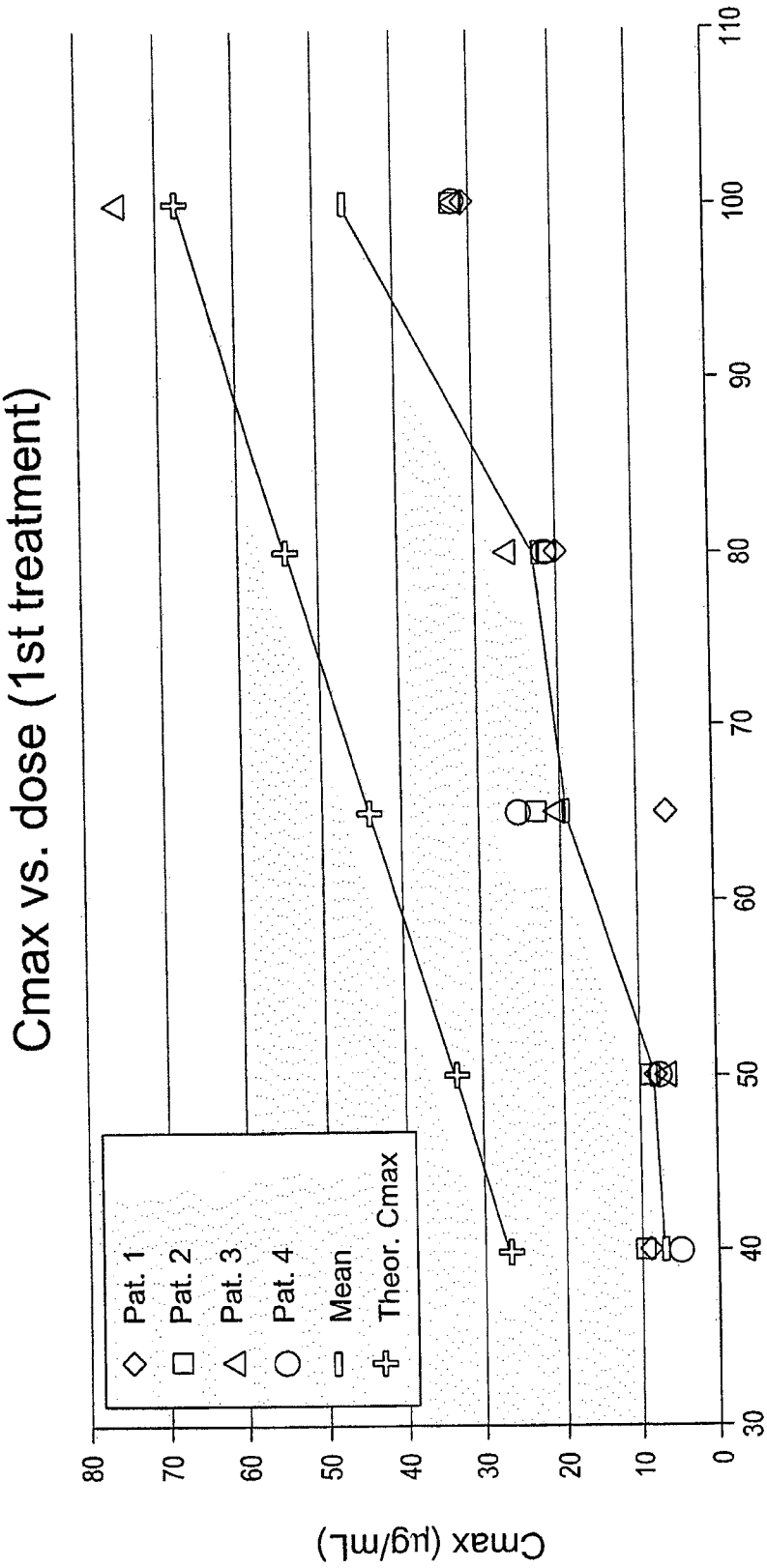

Cmax vs. dose (1st treatment)
Cmax (µg/mL)
Dose (mg/m2)
Pat. 1
Pat. 2
Pat. 3
Pat. 4
Mean
Theor. Cmax
0
10
20
30
40
50
60
70
80
30
40
50
60
70
80
90
100
110

FIG. 19B

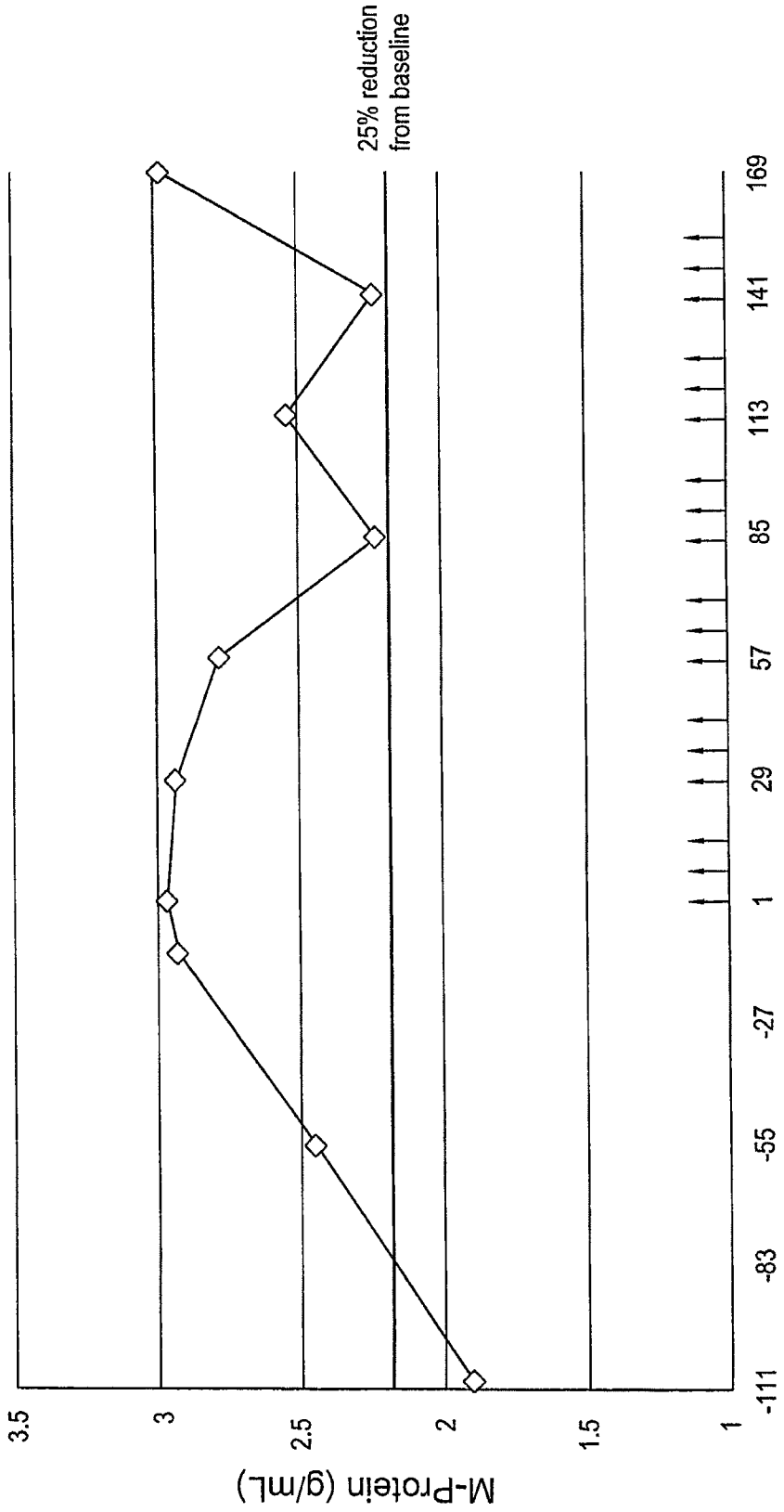

25% reduction
from baseline
M-Protein (g/mL)
3.5
3
2.5
2
1.5
1
-111
-83
-55
-27
1
29
57
85
113
141
169

FIG. 20

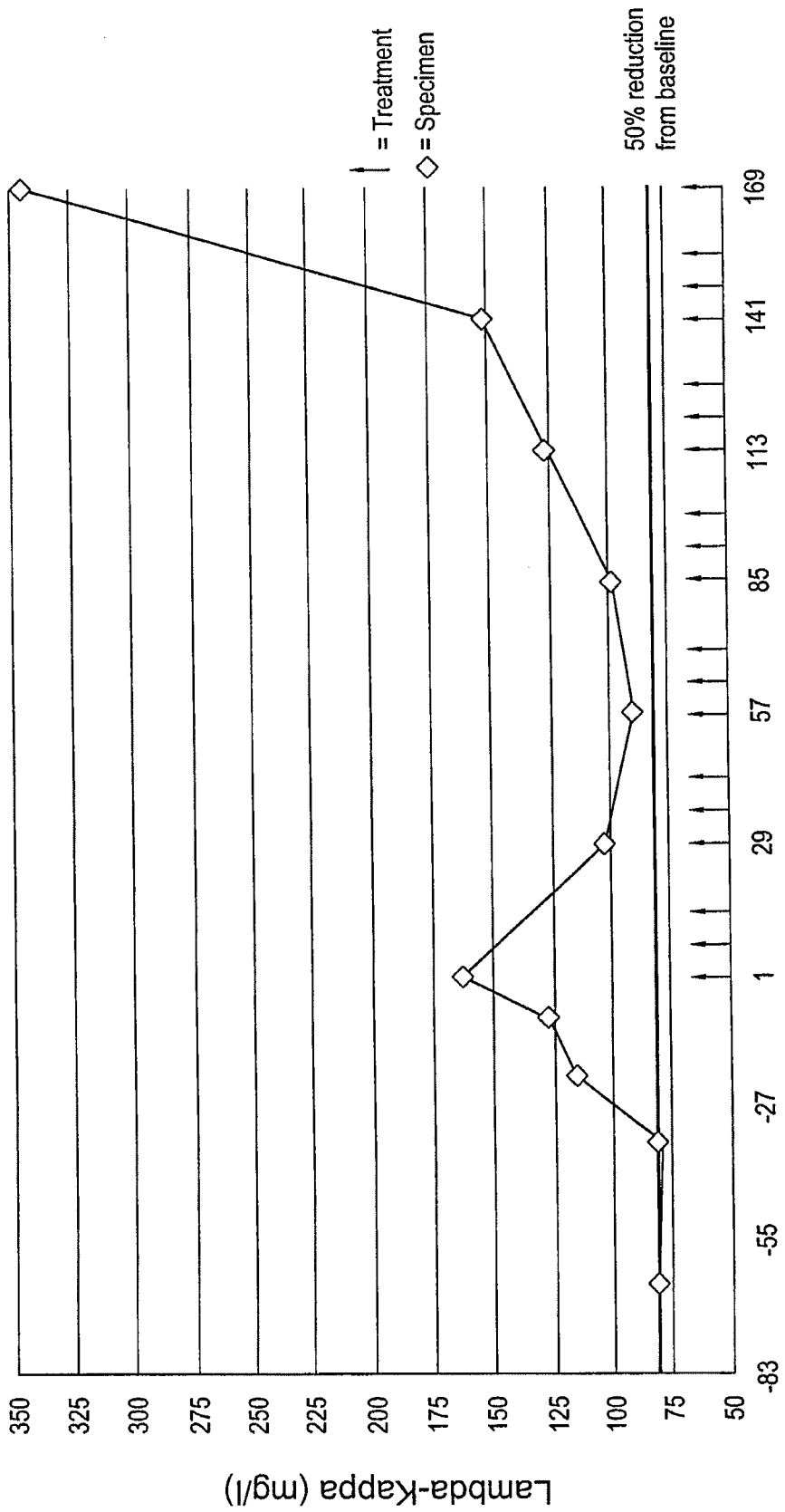

Lambda-Kappa (mg/l)
350
325
300
275
250
225
200
175
150
125
100
75
50
-83
-55
-27
1
29
57
85
113
141
169
= Treatment
= Specimen
50% reduction from baseline

FIG. 21

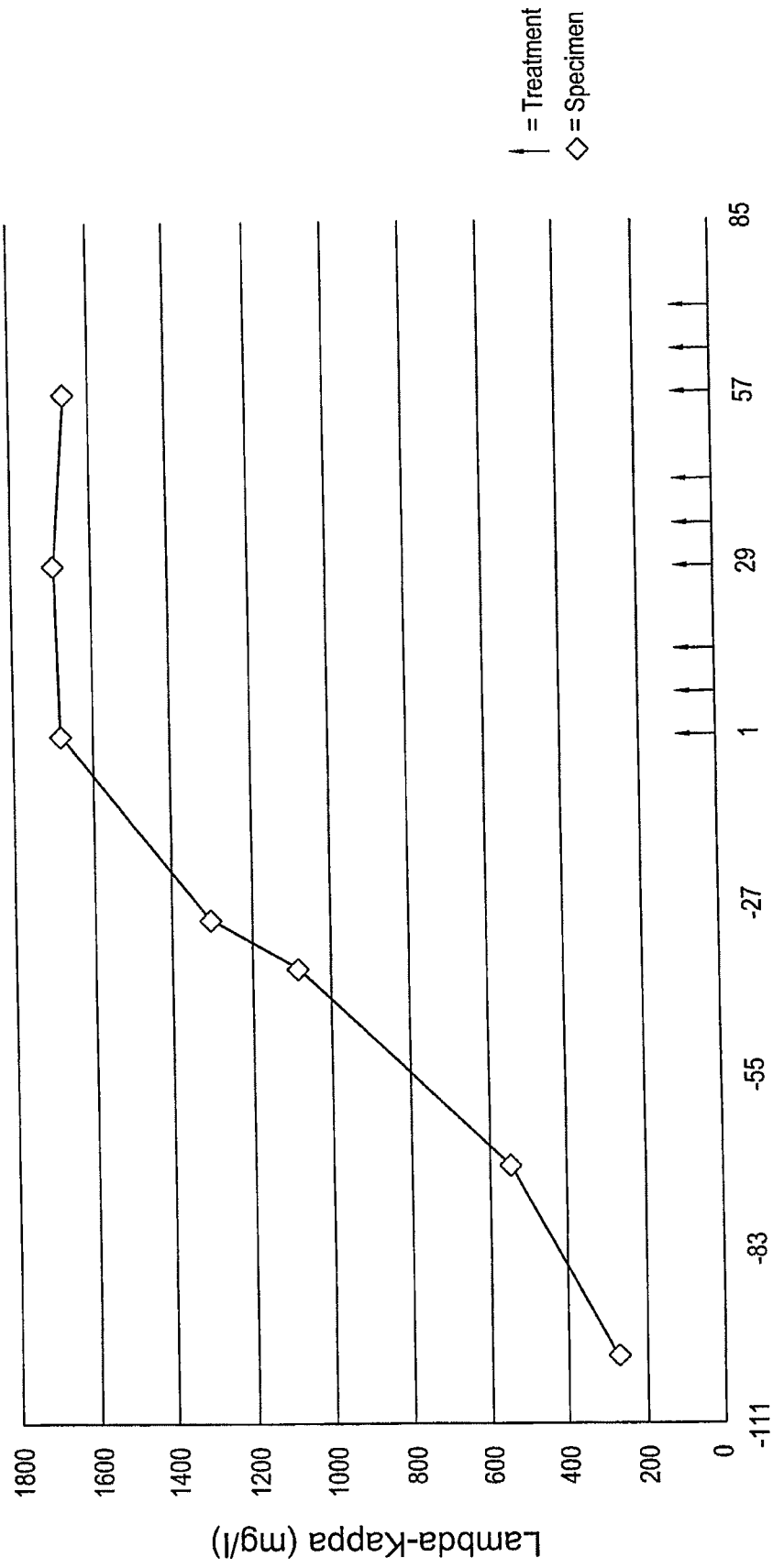

= Treatment
= Specimen
Lambda-Kappa (mg/l)
1800
1600
1400
1200
1000
800
600
400
200
0
-111
-83
-55
-27
1
29
57
85

FIG. 22

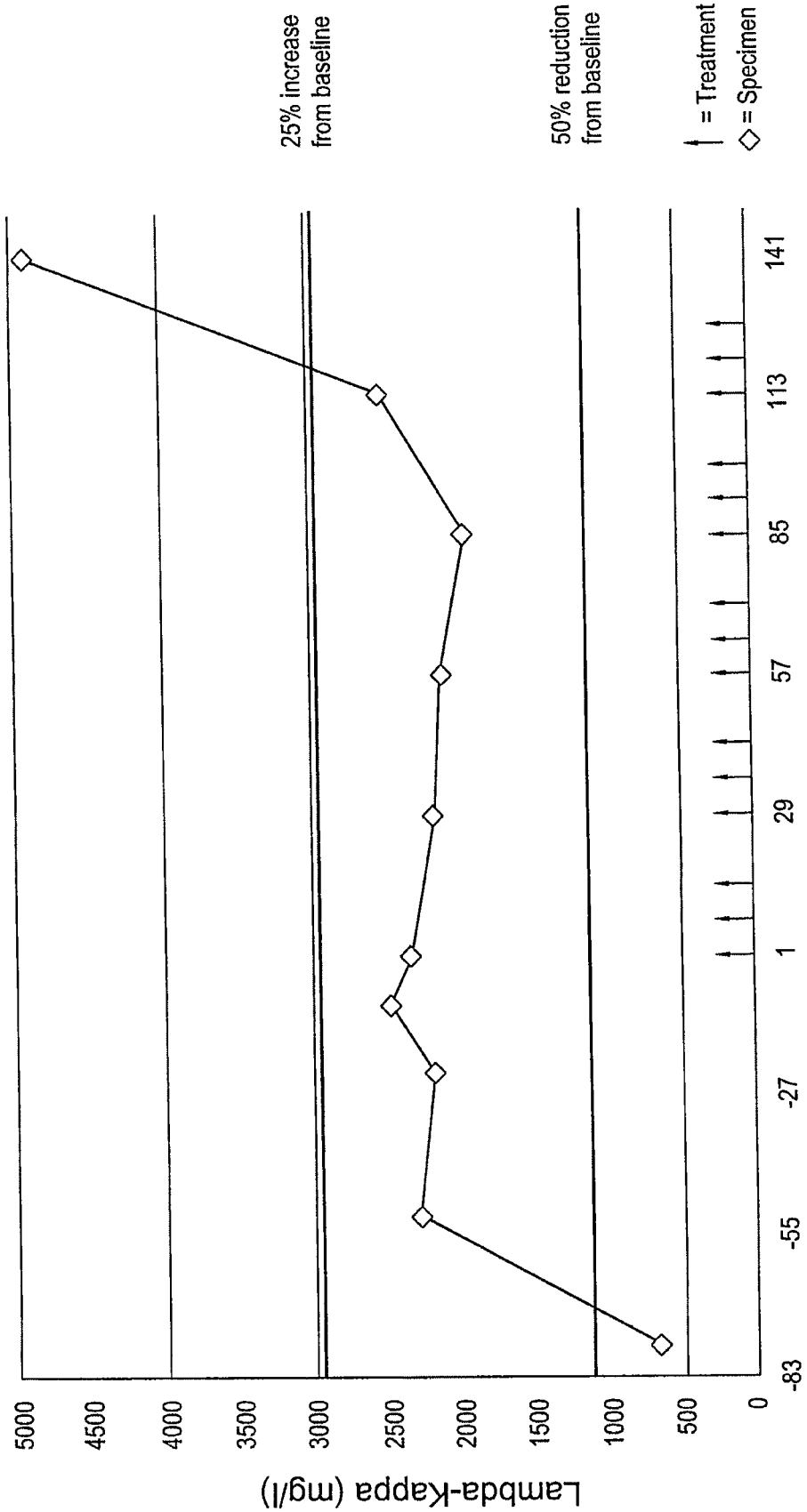

25% increase from baseline
50% reduction from baseline
= Treatment
= Specimen
Lambda-Kappa (mg/l)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-83
-55
-27
1
29
57
85
113
141

FIG. 23

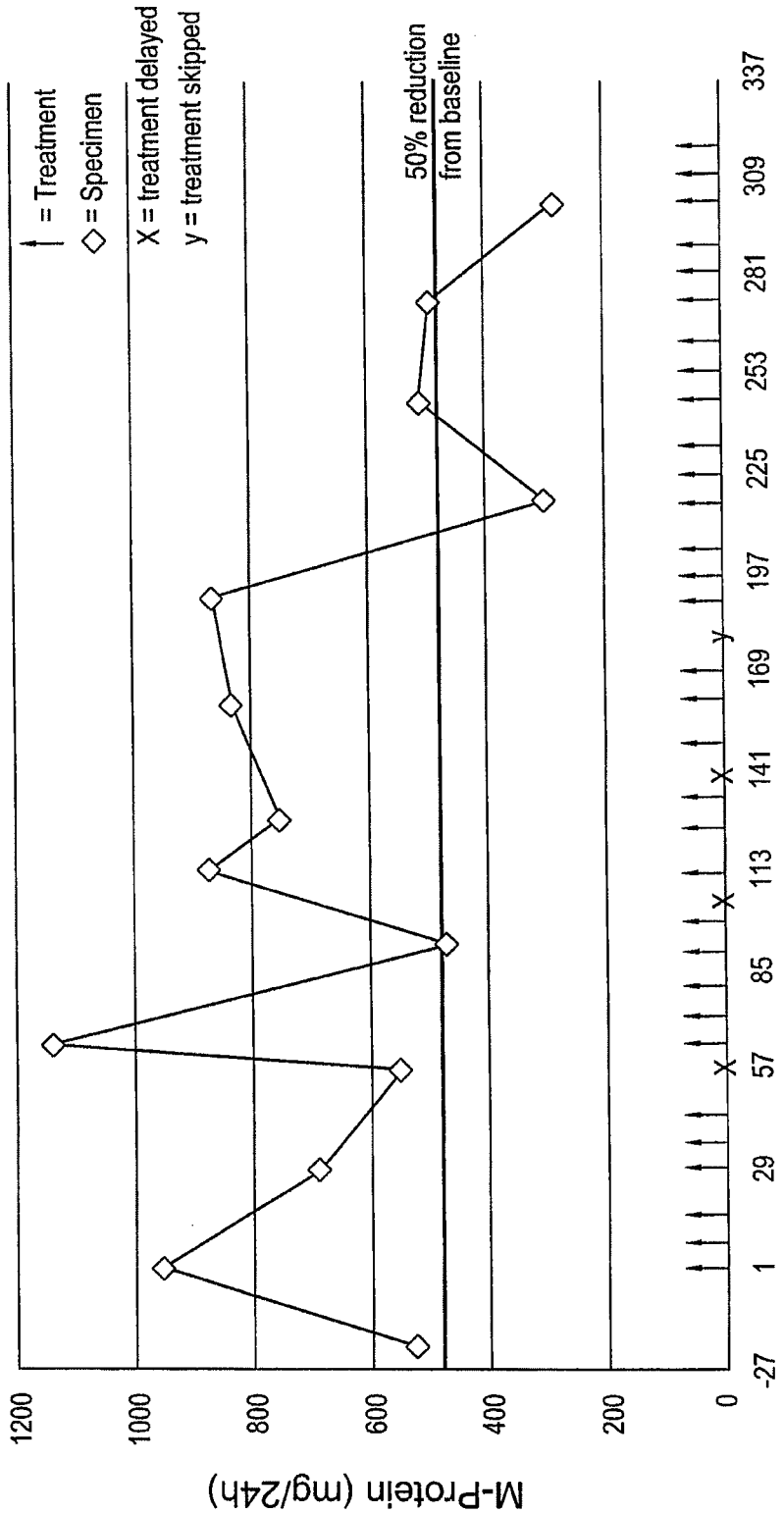

M-Protein (mg/24h)
1200
1000
800
600
400
200
0
-27
1
29
57
85
113
141
169
197
225
253
281
309
337
X
X
X
y
= Treatment
= Specimen
X = treatment delayed
y = treatment skipped
50% reduction
from baseline

FIG. 24

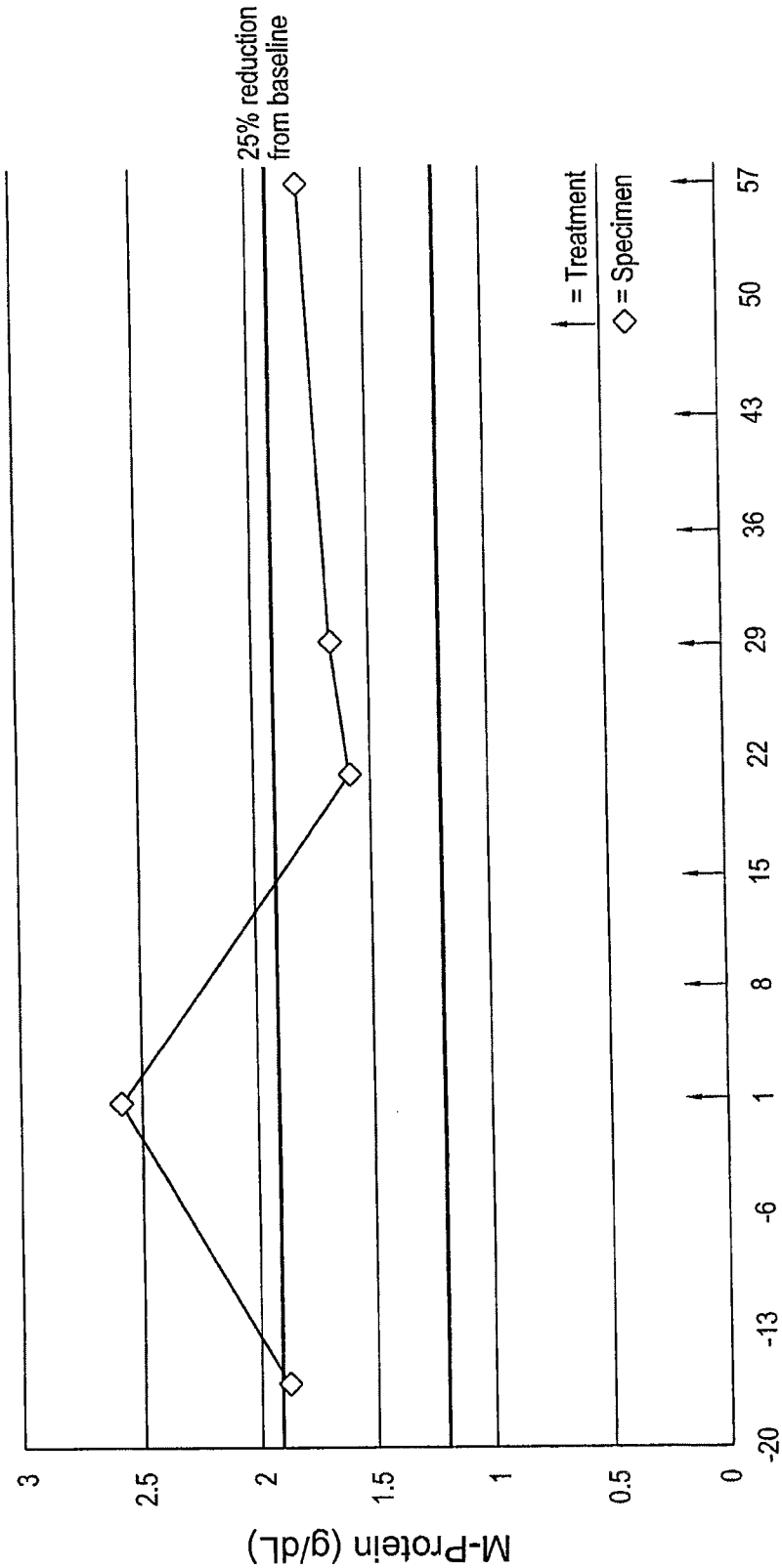

25% reduction from baseline
= Treatment
◇ = Specimen
M-Protein (g/dL)
3
2.5
2
1.5
1
0.5
0
-20
-13
-6
1
8
15
22
29
36
43
50
57

FIG. 25

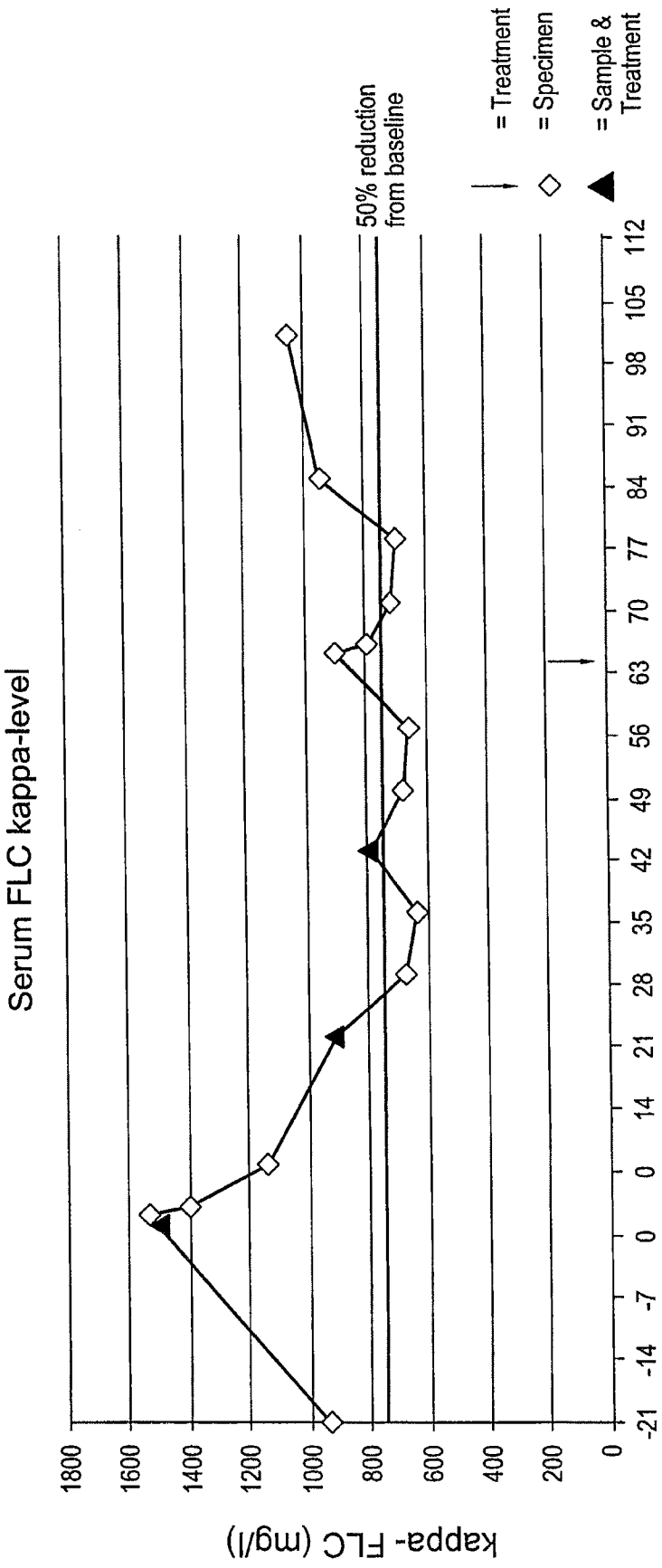

Serum FLC kappa-level
kappa- FLC (mg/l)
1800
1600
1400
1200
1000
800
600
400
200
0
-21
-14
-7
0
0
14
21
28
35
42
49
56
63
70
77
84
91
98
105
112
Days
50% reduction from baseline
= Treatment
= Specimen
= Sample & Treatment

FIG. 26

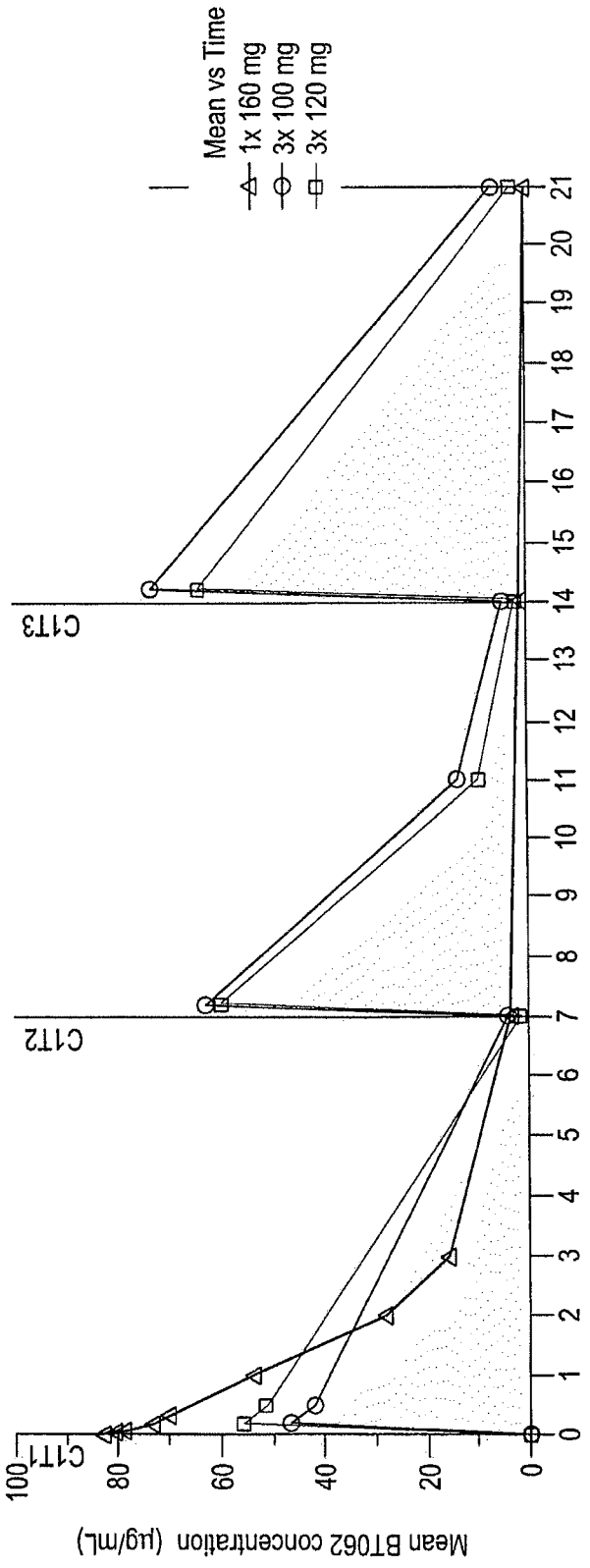

Mean vs Time
1x 160 mg
3x 100 mg
3x 120 mg
C1T1
C1T2
C1T3
Mean BT062 concentration (µg/mL)
Time (days)
0
20
40
60
80
100
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

FIG. 27

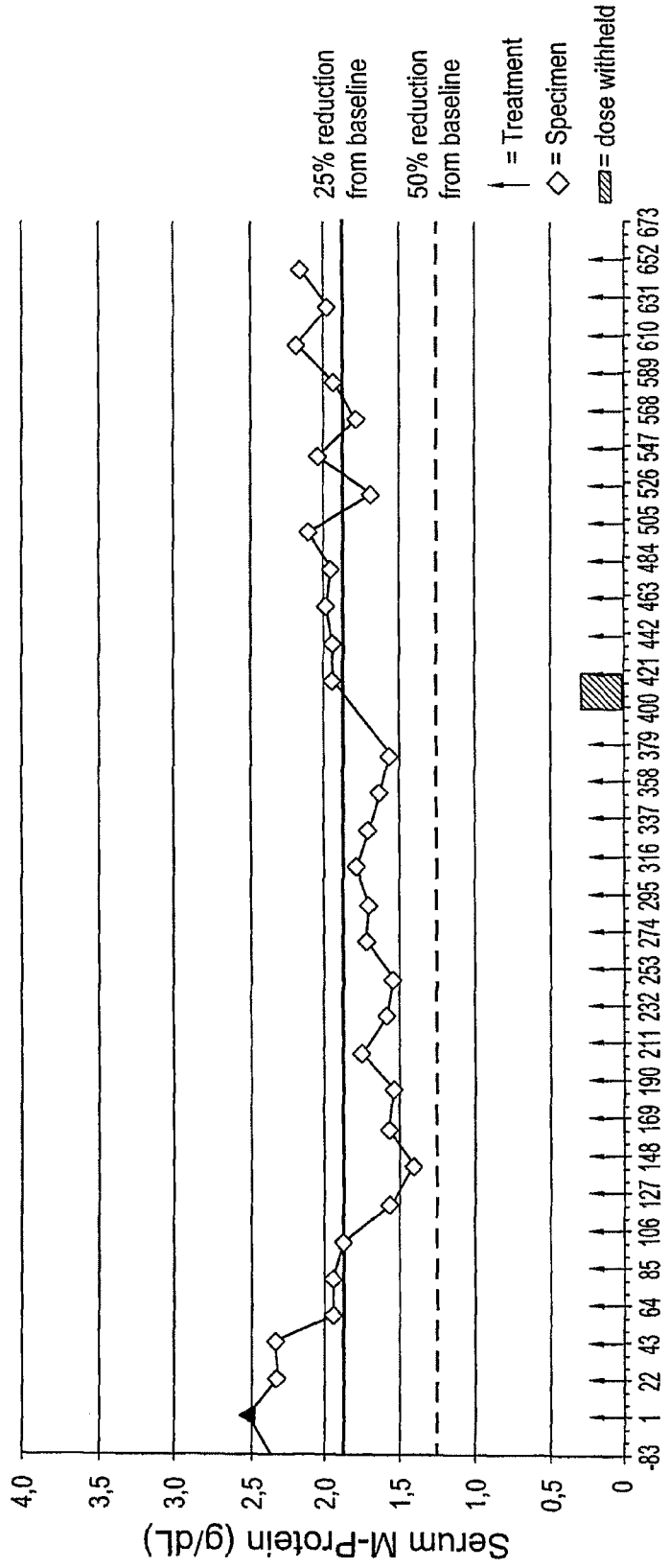

Serum M-Protein (g/dL)
4,0
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0
-83 1 22 43 64 85 106 127 148 169 190 211 232 253 274 295 316 337 358 379 400 421 442 463 484 505 526 547 568 589 610 631 652 673
Days
25% reduction from baseline
50% reduction from baseline
= Treatment
◇ = Specimen
= dose withheld

FIG. 28

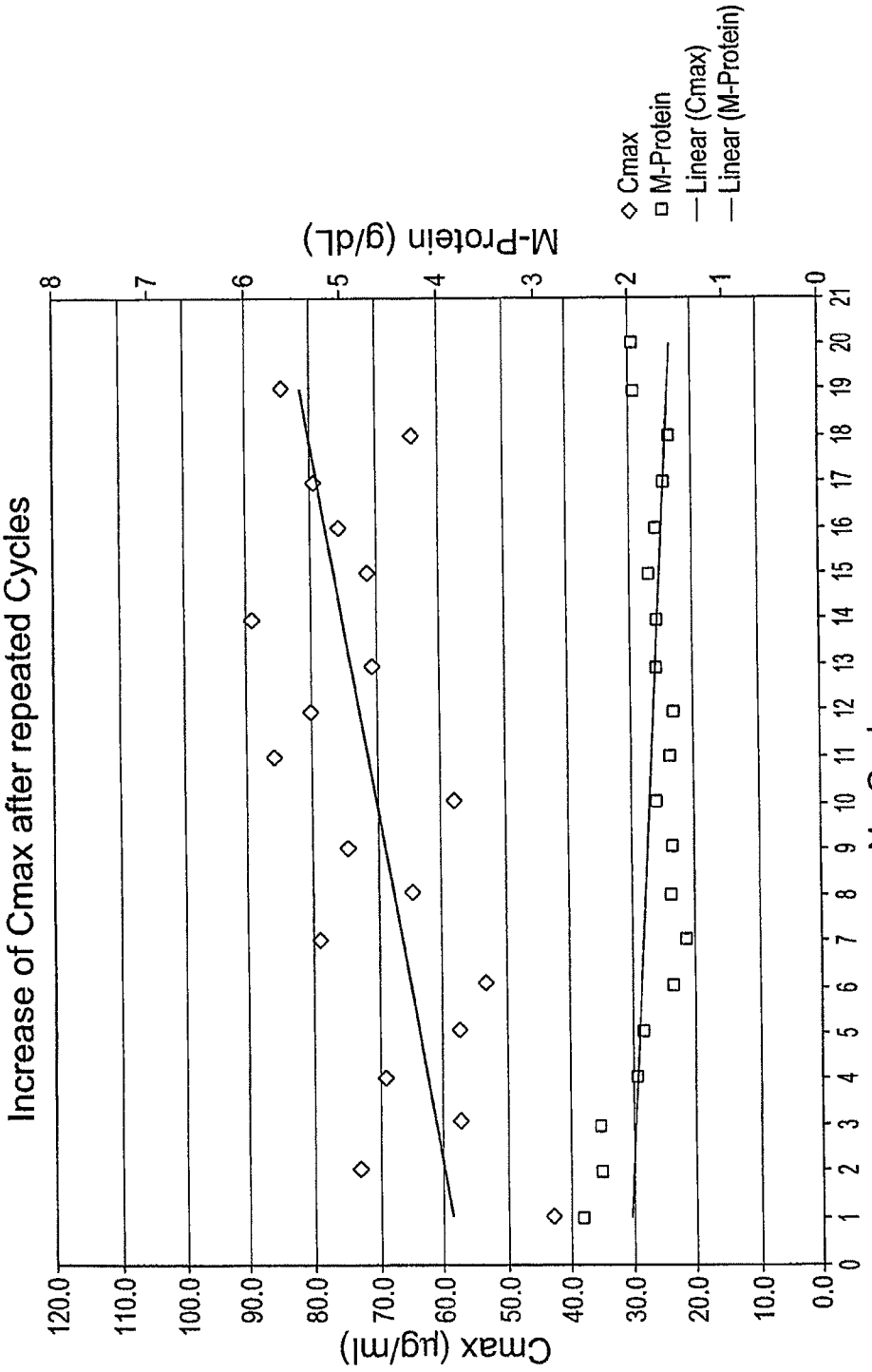

Increase of Cmax after repeated Cycles
Cmax (µg/ml)
M-Protein (g/dL)
Nr. Cycle
Cmax
M-Protein
Linear (Cmax)
Linear (M-Protein)
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
8
7
6
5
4
3
2
1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

FIG. 29

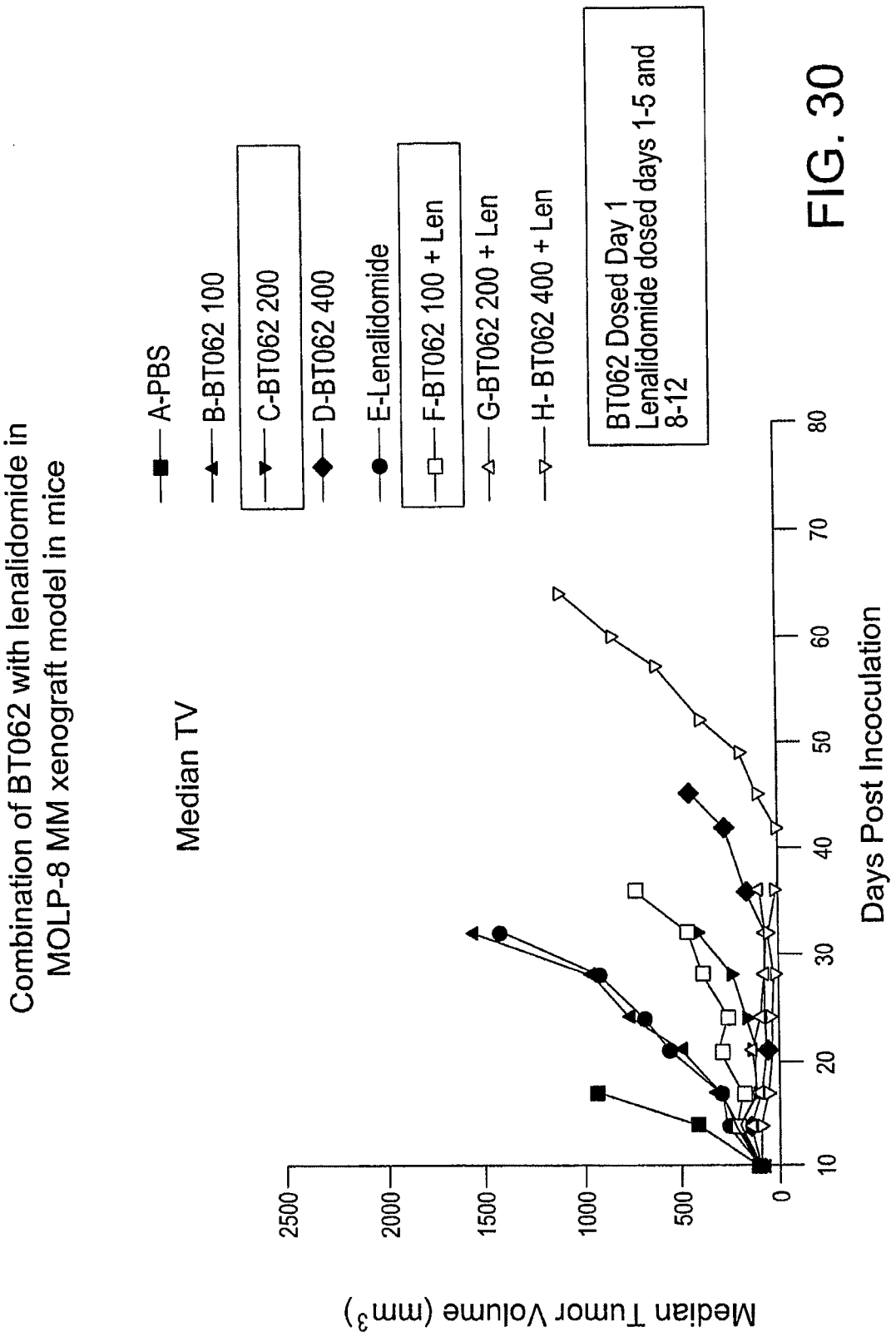

Combination of BT062 with lenalidomide in MOLP-8 MM xenograft model in mice
Median TV
A-PBS
B-BT062 100
C-BT062 200
D-BT062 400
E-Lenalidomide
F-BT062 100 + Len
G-BT062 200 + Len
H- BT062 400 + Len
BT062 Dosed Day 1
Lenalidomide dosed days 1-5 and 8-12
Median Tumor Volume (mm3)
Days Post Incoculation
0
500
1000
1500
2000
2500
10
20
30
40
50
60
70
80

FIG. 30

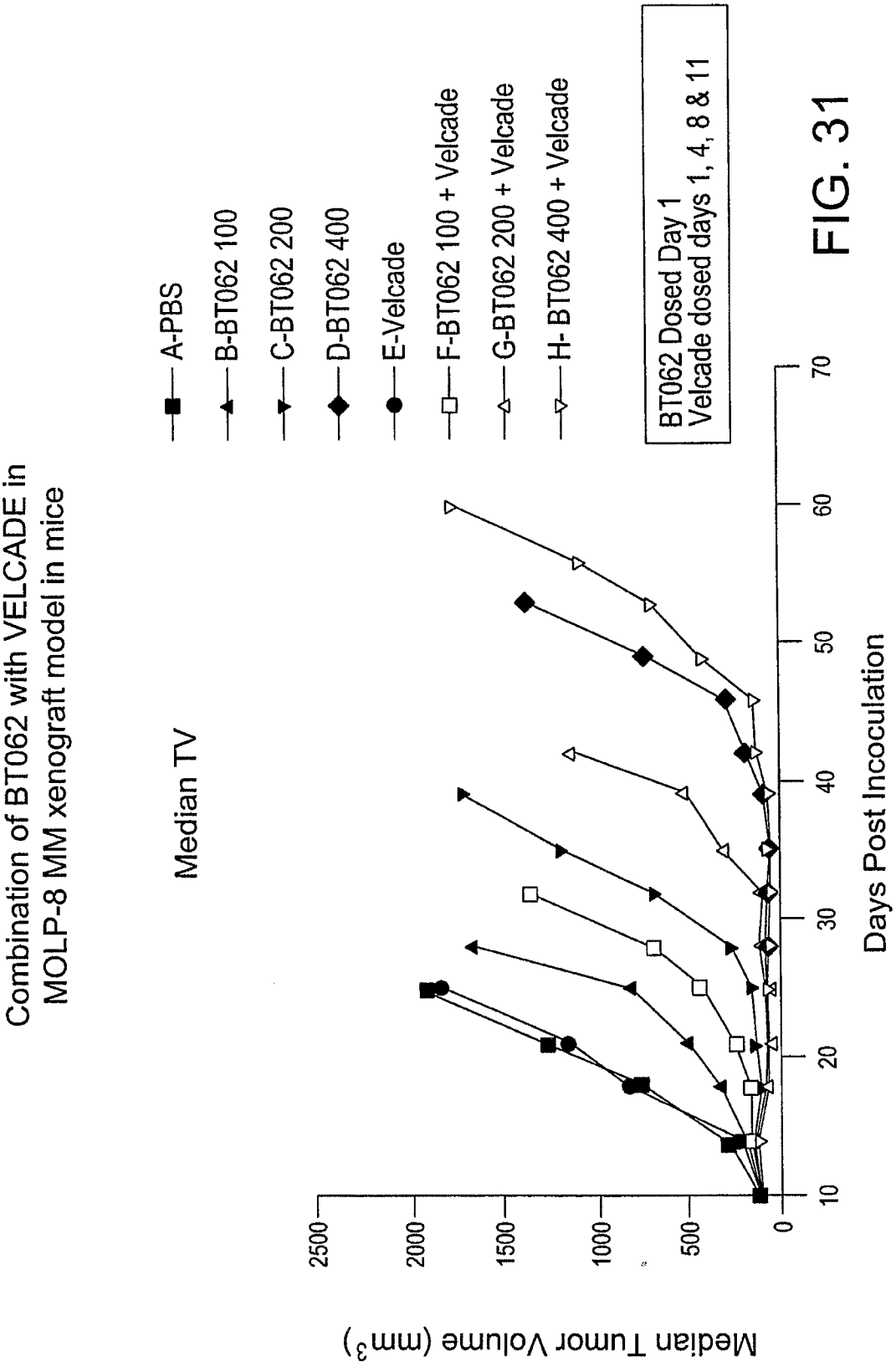

Combination of BT062 with VELCADE in MOLP-8 MM xenograft model in mice
Median TV
A-PBS
B-BT062 100
C-BT062 200
D-BT062 400
E-Velcade
F-BT062 100 + Velcade
G-BT062 200 + Velcade
H- BT062 400 + Velcade
BT062 Dosed Day 1
Velcade dosed days 1, 4, 8 & 11
Median Tumor Volume (mm3)
2500
2000
1500
1000
500
0
10
20
30
40
50
60
70
Days Post Incoculation

FIG. 31

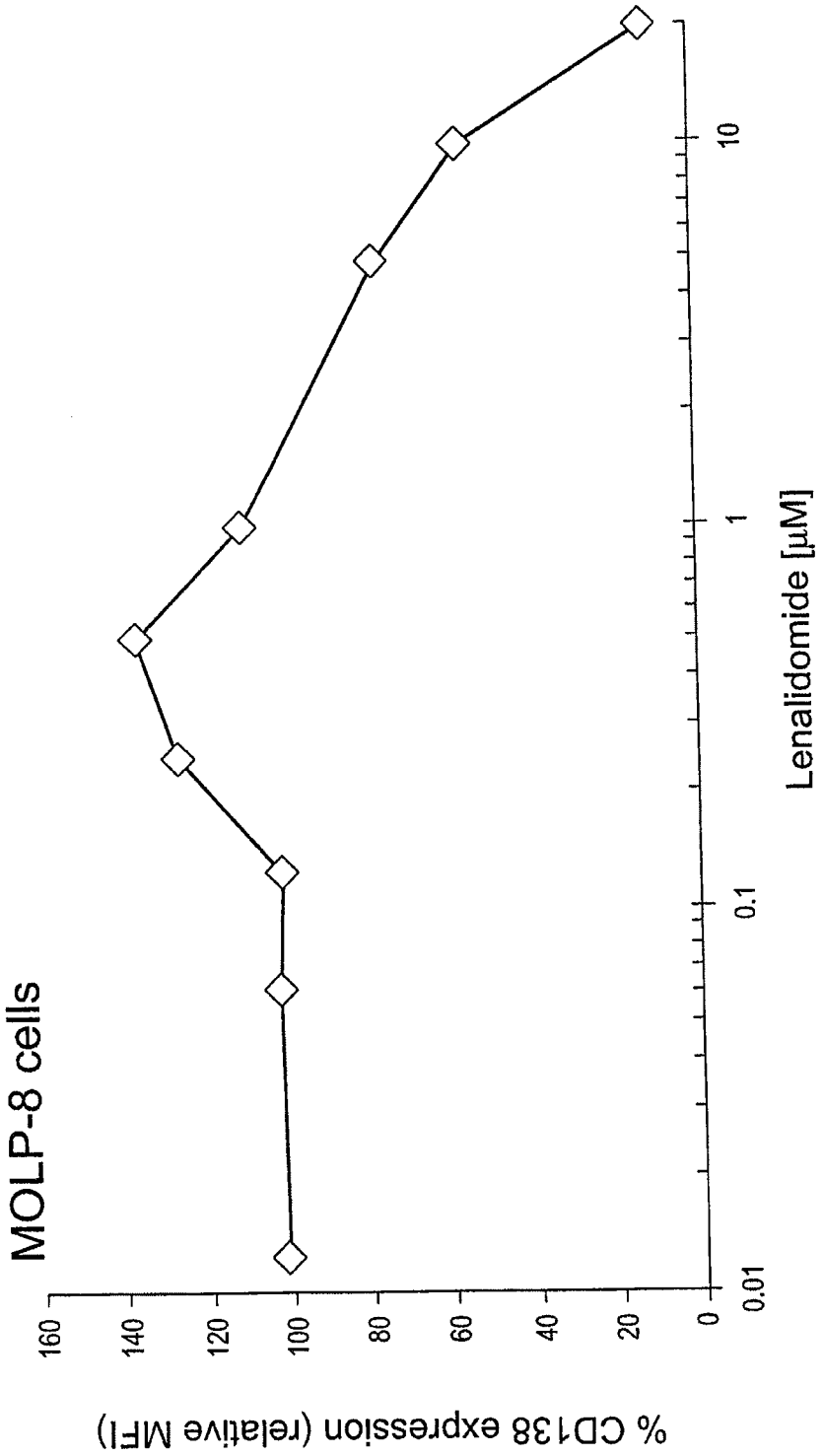

MOLP-8 cells
% CD138 expression (relative MFI)
160
140
120
100
80
60
40
20
0
0.01
0.1
1
10
Lenalidomide [µM]

FIG. 32A

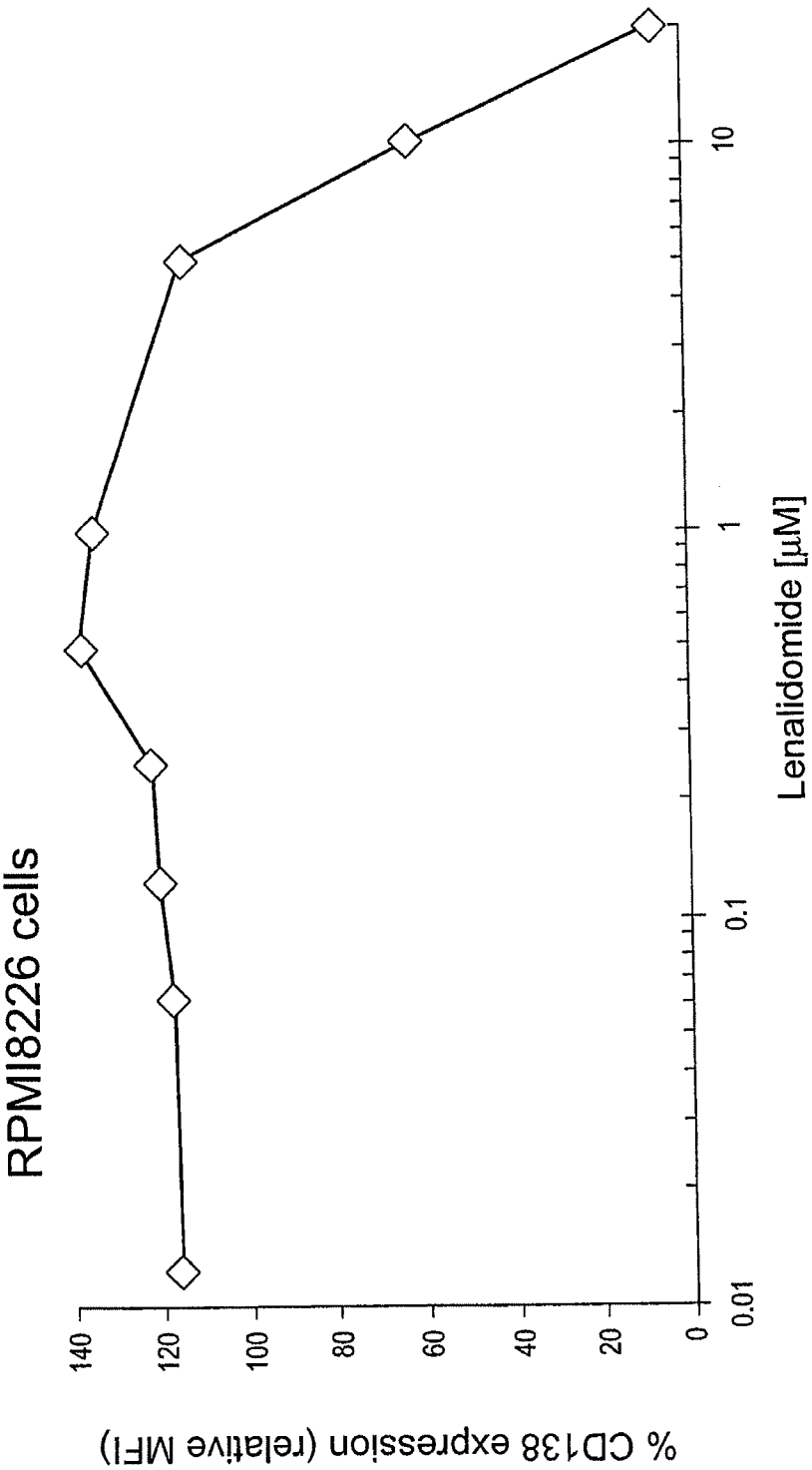

RPMI8226 cells
% CD138 expression (relative MFI)
140
120
100
80
60
40
20
0
0.01
0.1
1
10
Lenalidomide [µM]

FIG. 32B

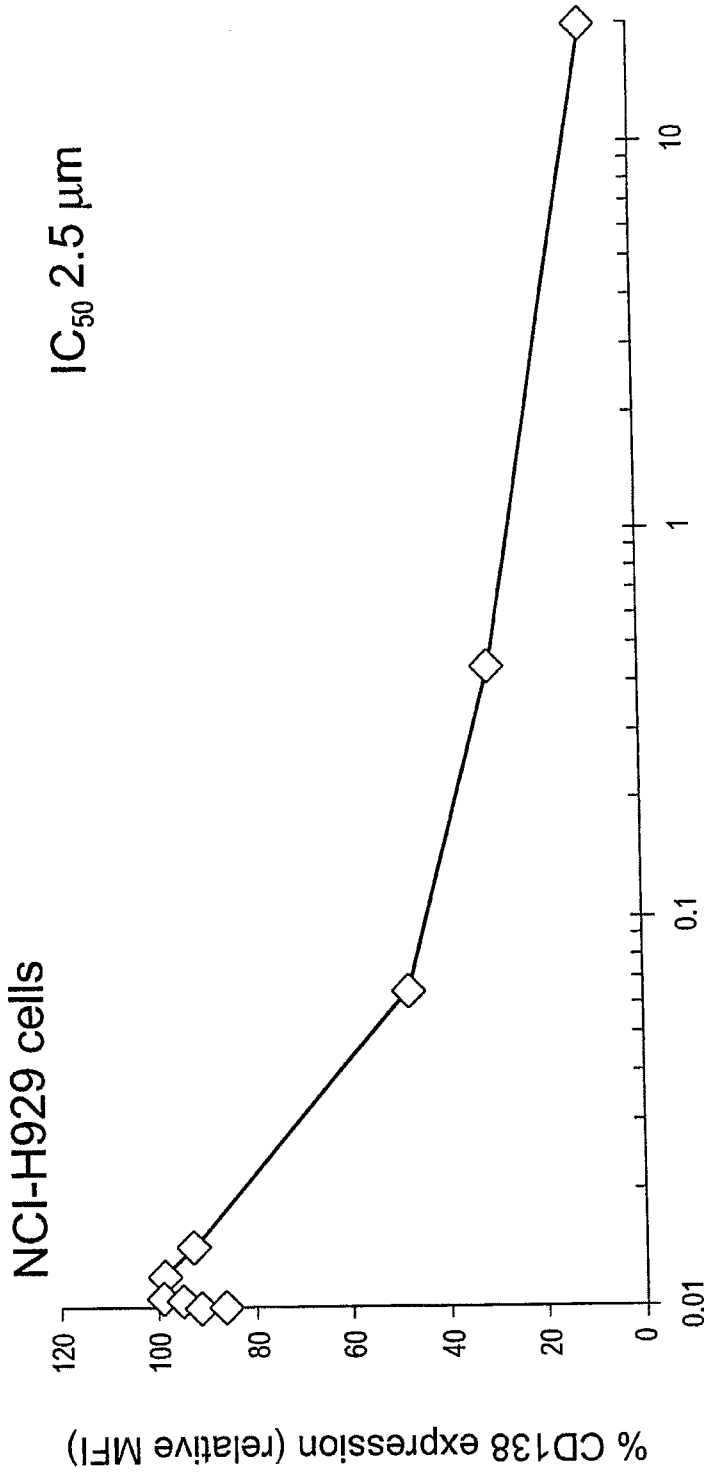

NCI-H929 cells
IC_{50} 2.5 µm
% CD138 expression (relative MFI)
120
100
80
60
40
20
0
0.01
0.1
1
10
Lenalidomide [µM]

FIG. 32C

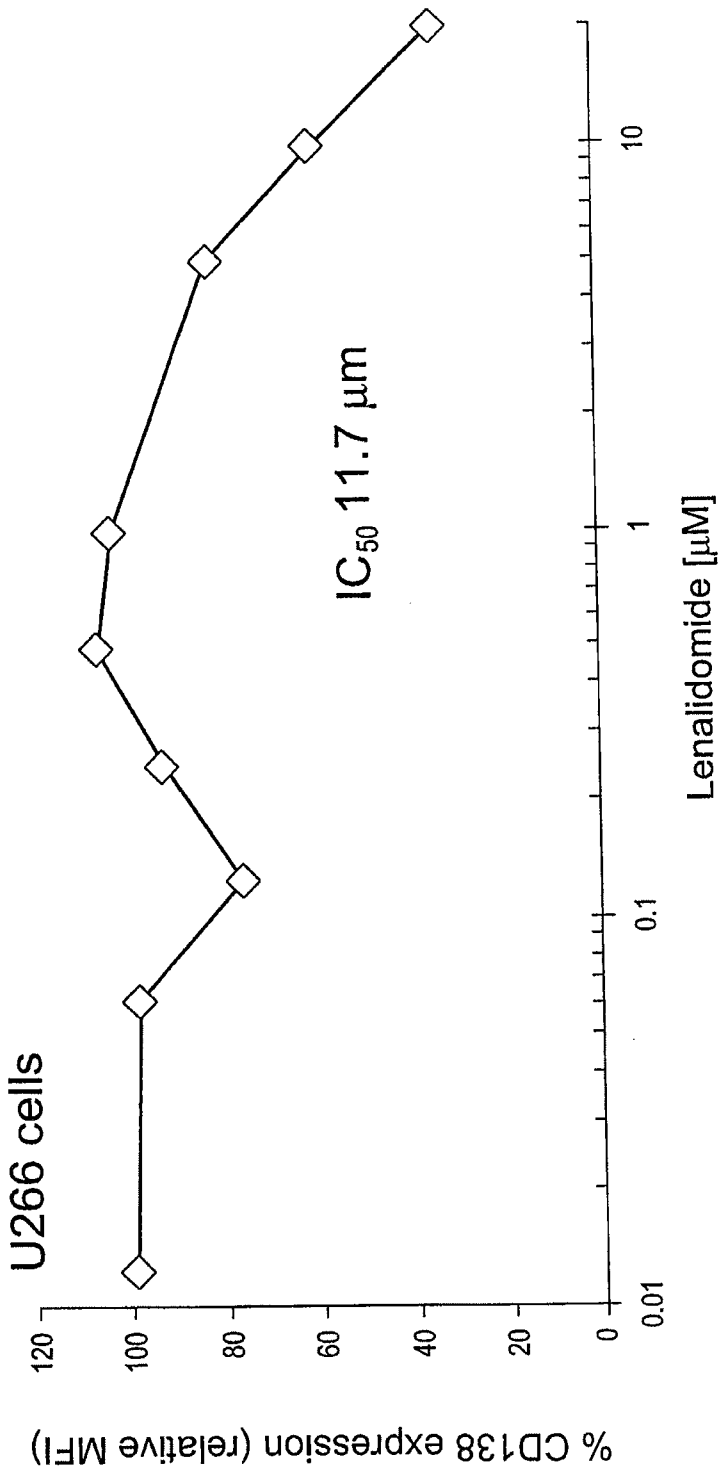

U266 cells
IC_{50} 11.7 µm
% CD138 expression (relative MFI)
120
100
80
60
40
20
0
0.01
0.1
1
10
Lenalidomide [µM]

FIG. 32D

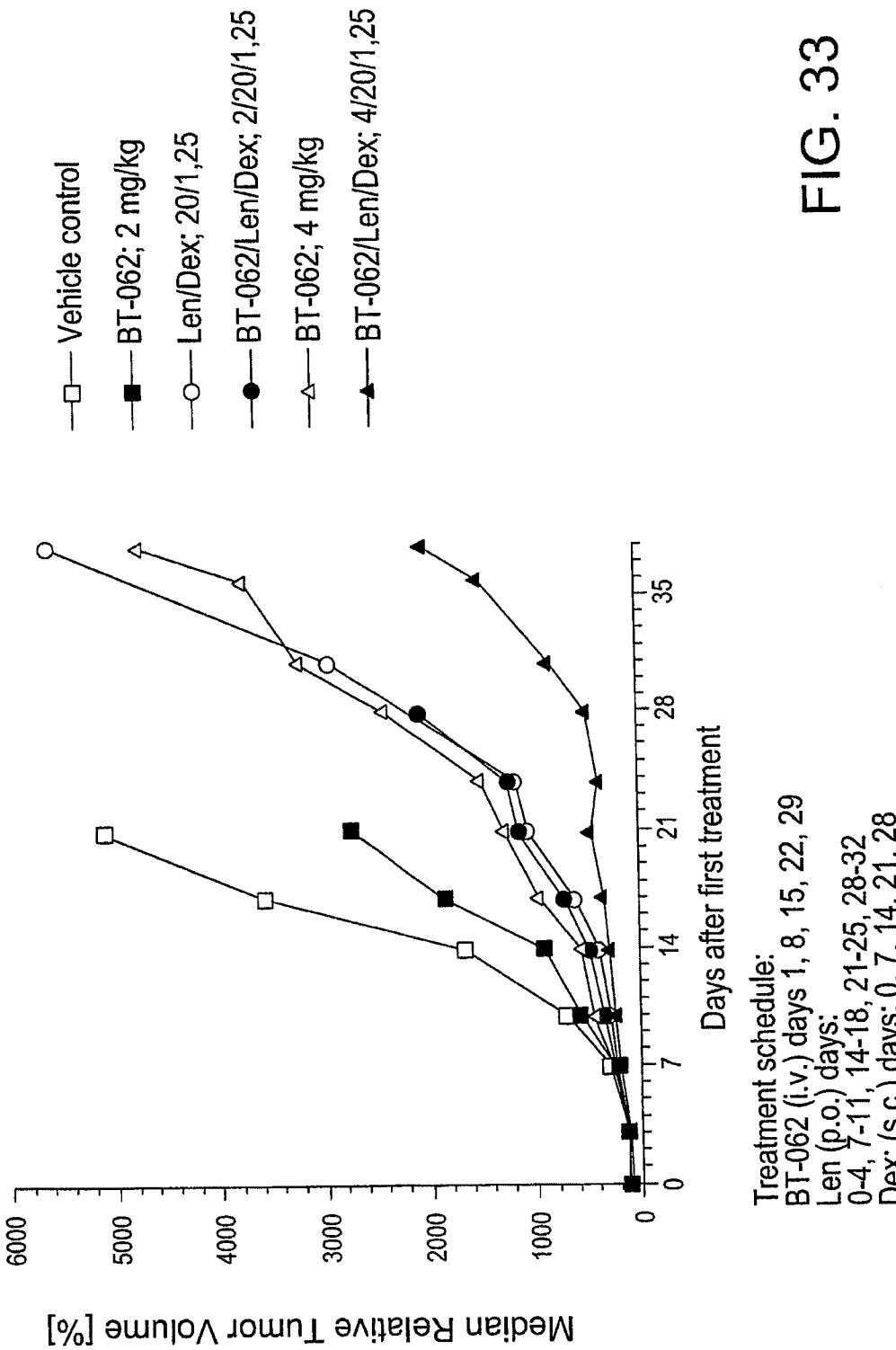

Vehicle control
BT-062; 2 mg/kg
Len/Dex; 20/1,25
BT-062/Len/Dex; 2/20/1,25
BT-062; 4 mg/kg
BT-062/Len/Dex; 4/20/1,25
Median Relative Tumor Volume [%]
6000
5000
4000
3000
2000
1000
0
0
7
14
21
28
35
Days after first treatment
Treatment schedule:
BT-062 (i.v.) days 1, 8, 15, 22, 29
Len (p.o.) days:
0-4, 7-11, 14-18, 21-25, 28-32
Dex: (s.c.) days: 0, 7, 14, 21, 28

FIG. 33

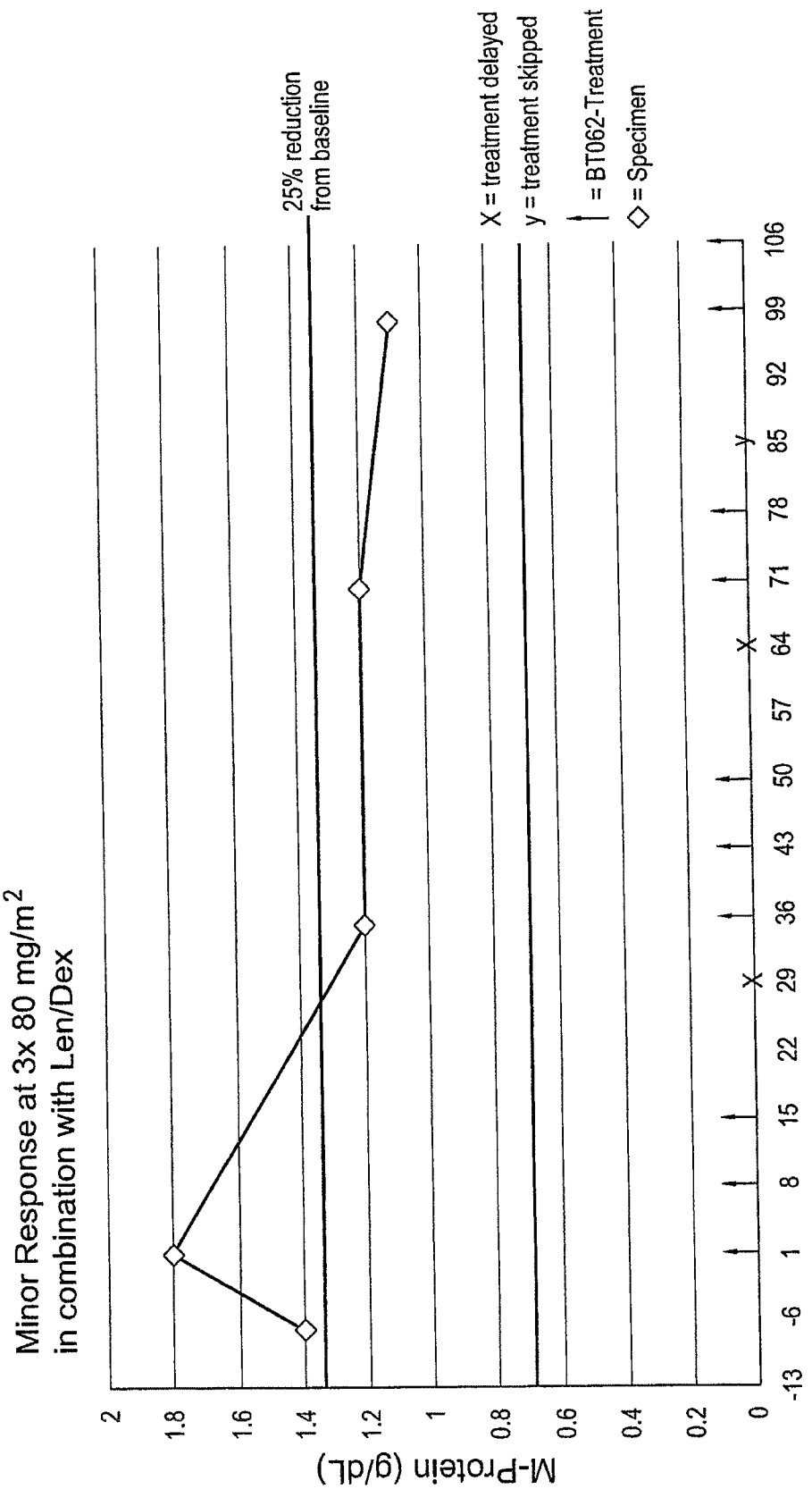

Minor Response at 3x 80 mg/m2
in combination with Len/Dex
M-Protein (g/dL)
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-13
-6
1
8
15
22
29
36
43
50
57
64
71
78
85
92
99
106
25% reduction
from baseline
X = treatment delayed
y = treatment skipped
= BT062-Treatment
◇ = Specimen

FIG. 34

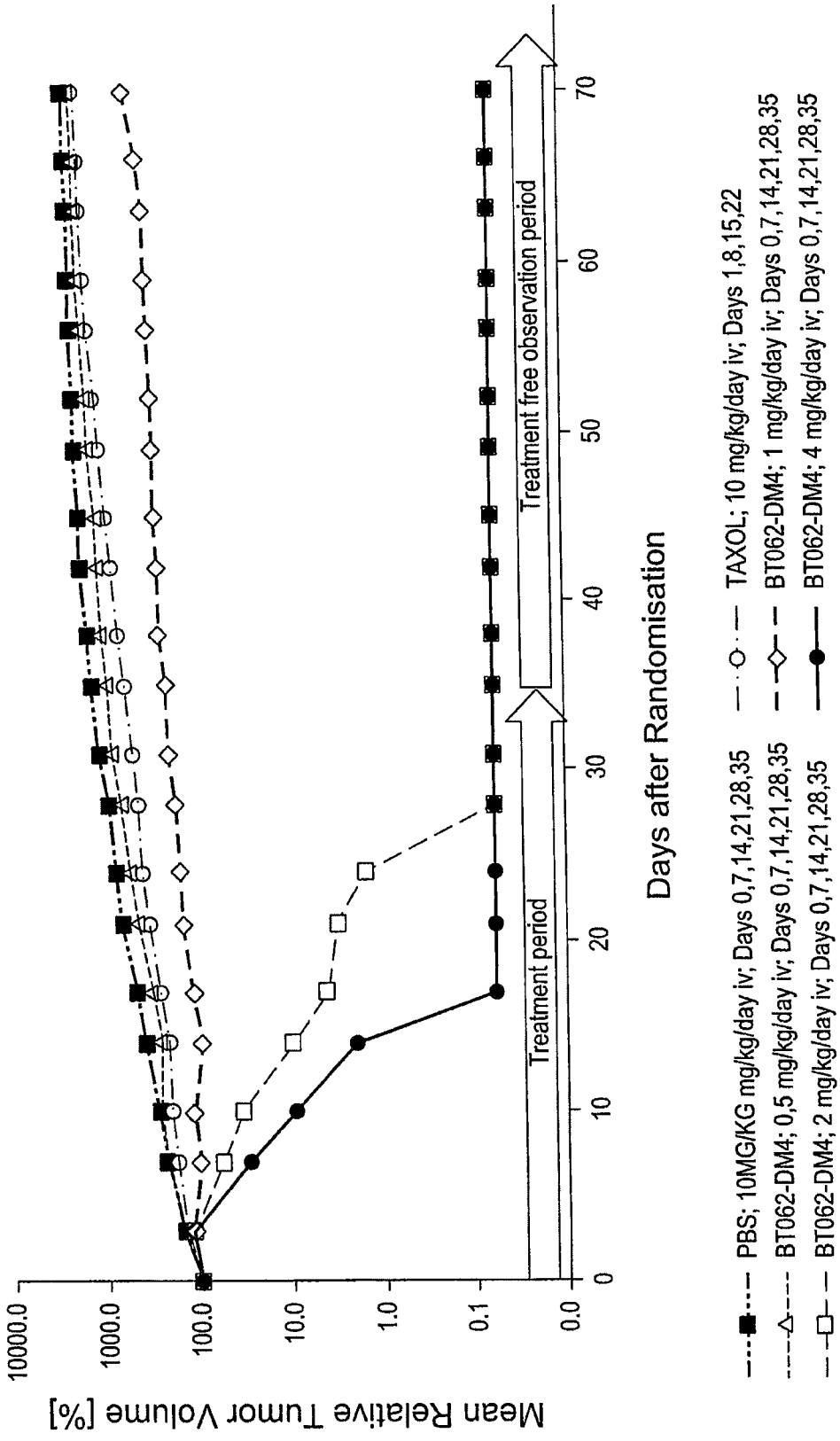

Mean Relative Tumor Volume [%]
10000.0
1000.0
100.0
10.0
1.0
0.1
0.0
0
10
20
30
40
50
60
70
Days after Randomisation
Treatment period
Treatment free observation period
PBS; 10MG/KG mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 0,5 mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 2 mg/kg/day iv; Days 0,7,14,21,28,35
TAXOL; 10 mg/kg/day iv; Days 1,8,15,22
BT062-DM4; 1 mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 4 mg/kg/day iv; Days 0,7,14,21,28,35

FIG. 35

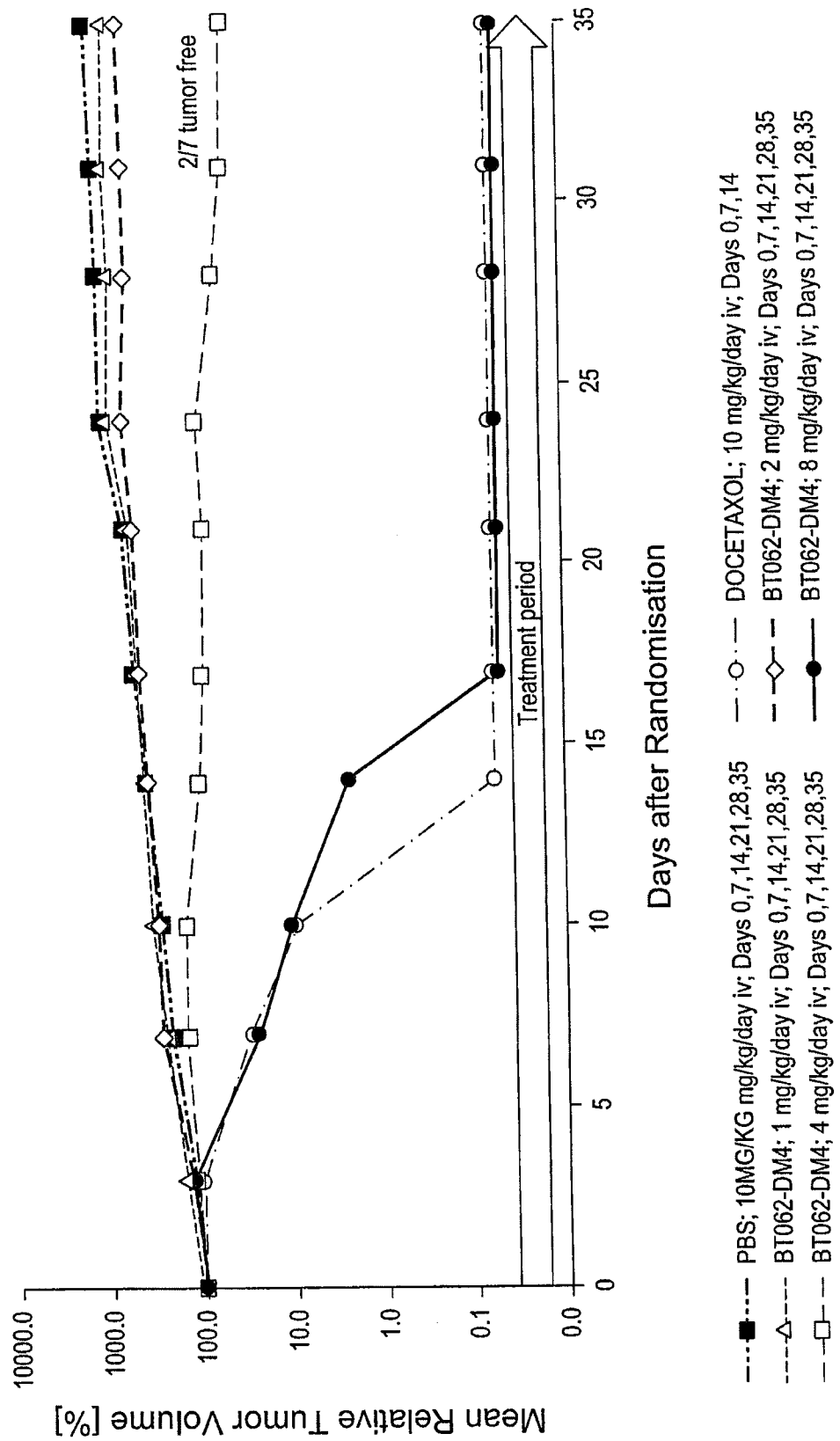

Mean Relative Tumor Volume [%]
10000.0
1000.0
100.0
10.0
1.0
0.1
0.0
0
5
10
15
20
25
30
35
Days after Randomisation
2/7 tumor free
Treatment period
PBS; 10MG/KG mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 1 mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 4 mg/kg/day iv; Days 0,7,14,21,28,35
DOCETAXOL; 10 mg/kg/day iv; Days 0,7,14
BT062-DM4; 2 mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 8 mg/kg/day iv; Days 0,7,14,21,28,35

FIG. 36

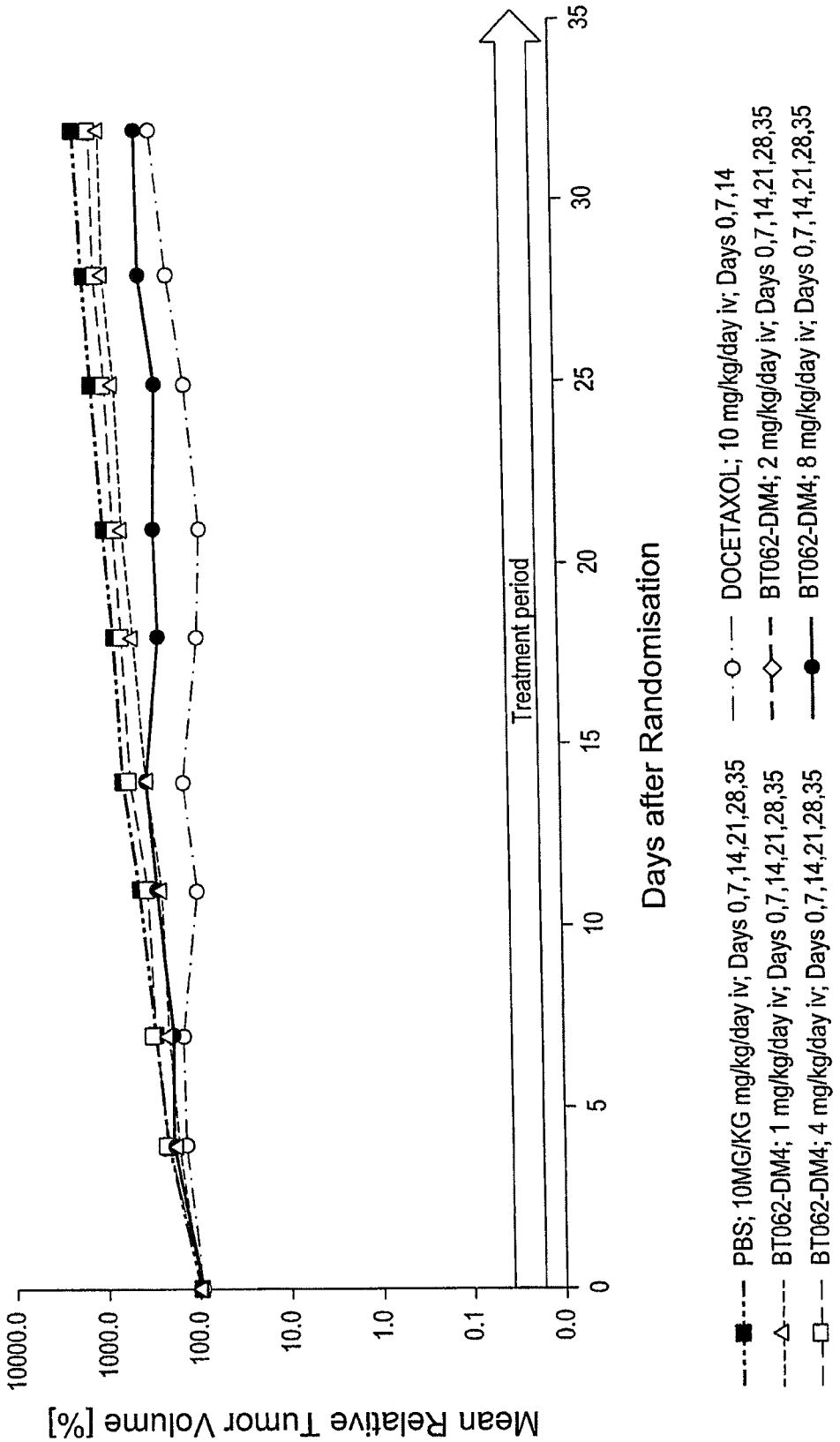

Mean Relative Tumor Volume [%]
10000.0
1000.0
100.0
10.0
1.0
0.1
0.0
0
5
10
15
20
25
30
35
Days after Randomisation
Treatment period
PBS; 10MG/KG mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 1 mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 4 mg/kg/day iv; Days 0,7,14,21,28,35
DOCETAXOL; 10 mg/kg/day iv; Days 0,7,14
BT062-DM4; 2 mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 8 mg/kg/day iv; Days 0,7,14,21,28,35

FIG. 37

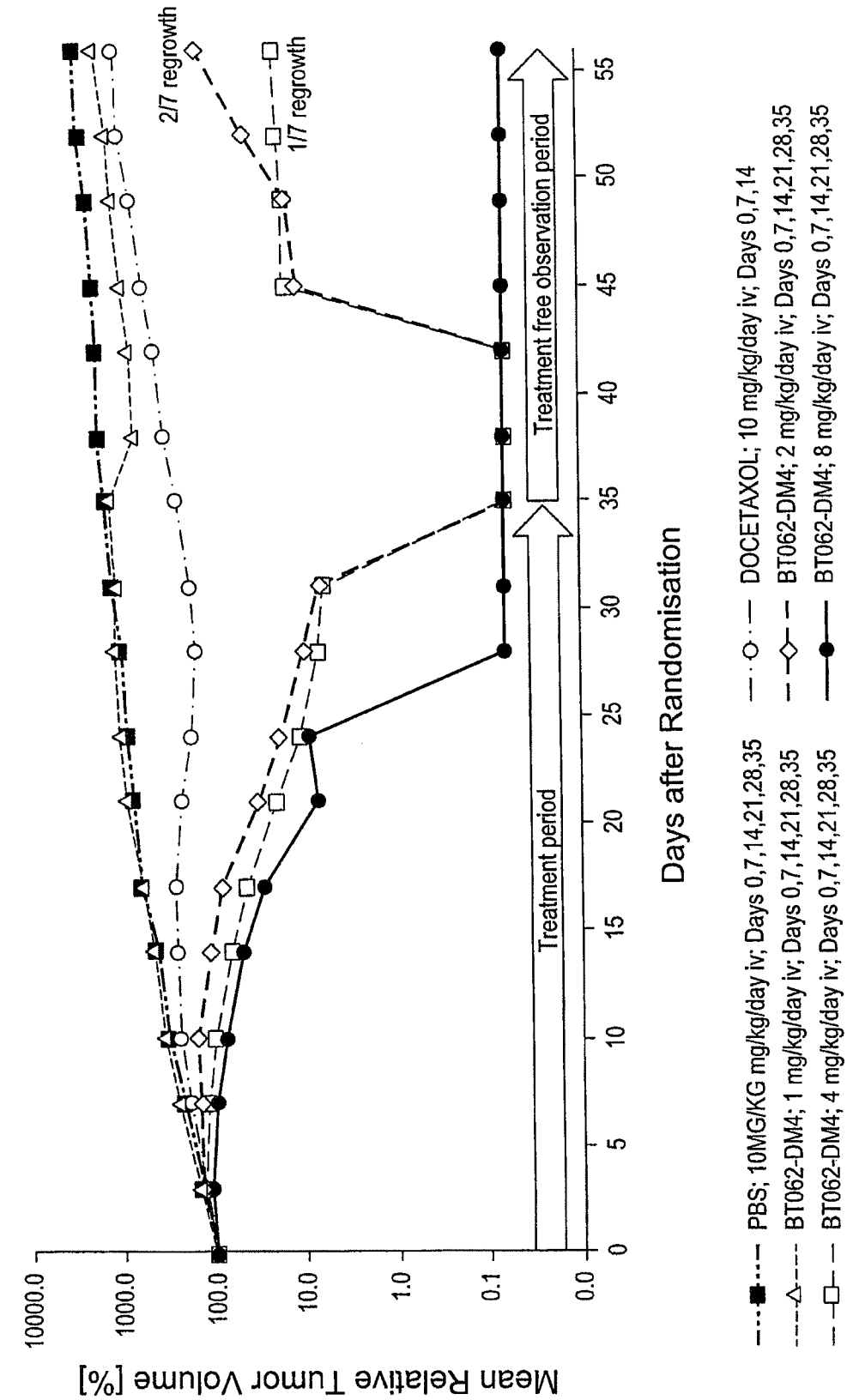

Mean Relative Tumor Volume [%]
10000.0
1000.0
100.0
10.0
1.0
0.1
0.0
0
5
10
15
20
25
30
35
40
45
50
55
Days after Randomisation
2/7 regrowth
1/7 regrowth
Treatment period
Treatment free observation period
PBS; 10MG/KG mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 1 mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 4 mg/kg/day iv; Days 0,7,14,21,28,35
DOCETAXOL; 10 mg/kg/day iv; Days 0,7,14
BT062-DM4; 2 mg/kg/day iv; Days 0,7,14,21,28,35
BT062-DM4; 8 mg/kg/day iv; Days 0,7,14,21,28,35

FIG. 38