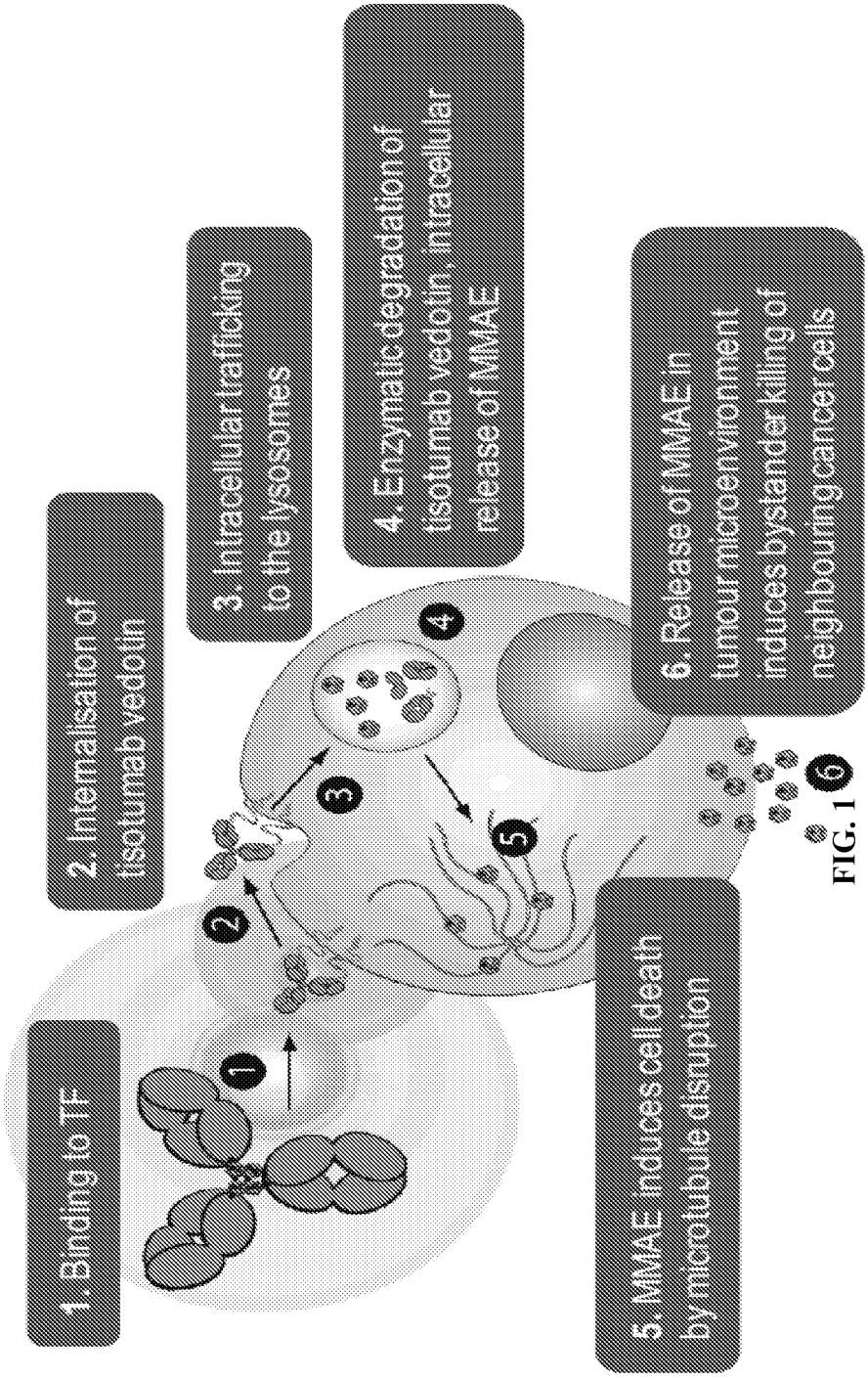

1. Binding to TF
2. Internalisation of isotuzumab vedotin
3. Intracellular trafficking to the lysosomes
4. Enzymatic degradation of isotuzumab vedotin, intracellular release of MMAE
5. MMAE induces cell death by microtubule disruption
6. Release of MMAE in tumour microenvironment induces bystander killing of neighbouring cancer cells

FIG. 1

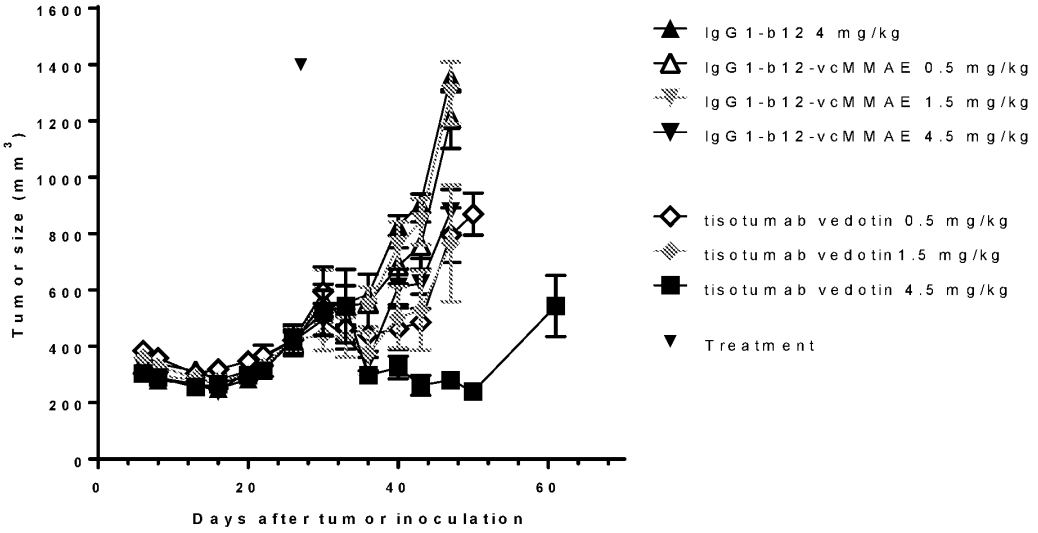
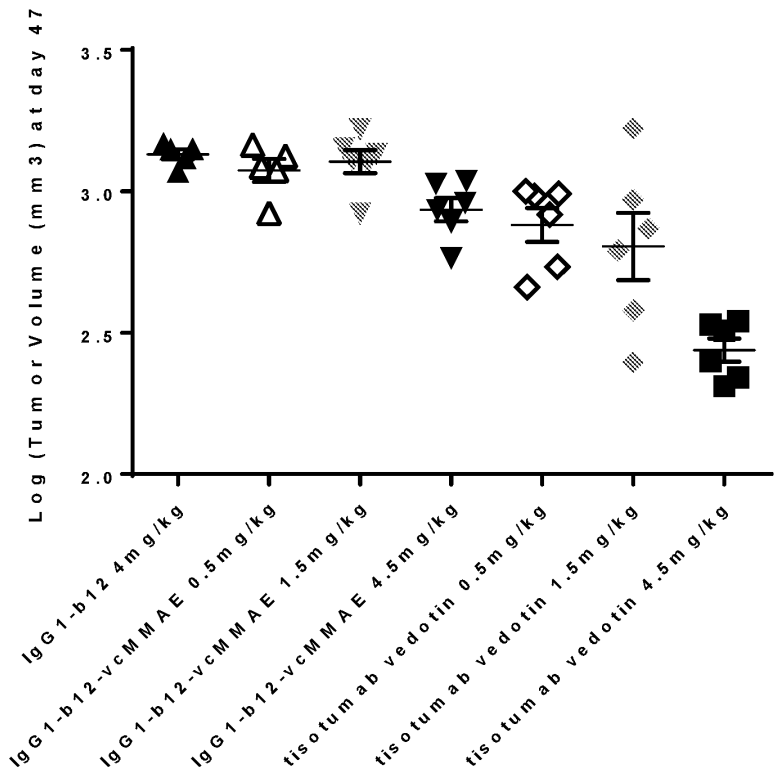

1600
1400
1200
1000
800
600
400
200
0
Tumor size (mm3)
0
20
40
60
Days after tumor inoculation
IgG1-b12 4 mg/kg
IgG1-b12-vcMMAE 0.5 mg/kg
IgG1-b12-vcMMAE 1.5 mg/kg
IgG1-b12-vcMMAE 4.5 mg/kg
tisotumab vedotin 0.5 mg/kg
tisotumab vedotin1.5 mg/kg
tisotumab vedotin 4.5 mg/kg
Treatment

FIG. 2A



day 47	IgG1-b12 4mg/kg	IgG1-b12-MMAE 0.5mg/kg	IgG1-b12-MMAE 1.5mg/kg	IgG1-b12-MMAE 4.5mg/kg		tisotumab vedotin 0.5mg/kg	tisotumab vedotin 1.5mg/kg	tisotumab vedotin 4.5mg/kg
IgG1-b12 4mg/kg							*	***
IgG1-b12-MMAE 0.5mg/kg								***
IgG1-b12-MMAE 1.5mg/kg							*	***
IgG1-b12-MMAE 4.5mg/kg								***
tisotumab vedotin 0.5mg/kg								***
tisotumab vedotin 1.5mg/kg	*		*					**
tisotumab vedotin 4.5mg/kg	***	***	***	***		***	**	

FIG. 2B

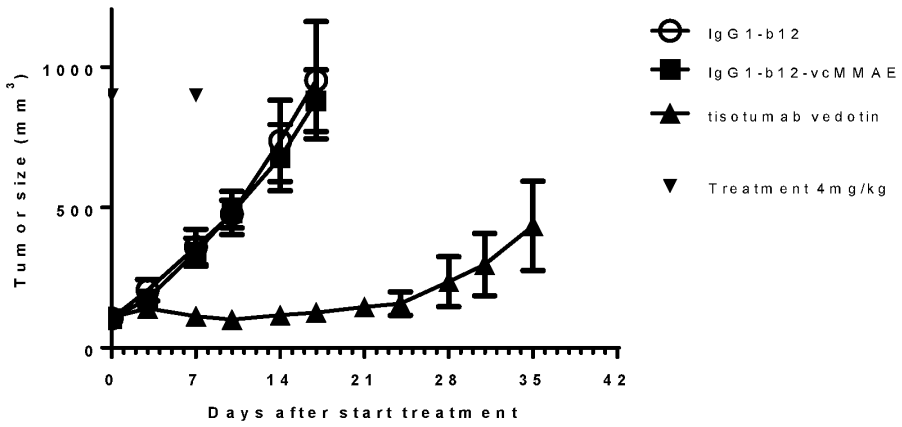

Tumor size (mm3)
1000
500
0
0
7
14
21
28
35
42
Days after start treatment
IgG1-b12
IgG1-b12-vcMMAE
tisotumab vedotin
Treatment 4mg/kg

FIG. 3

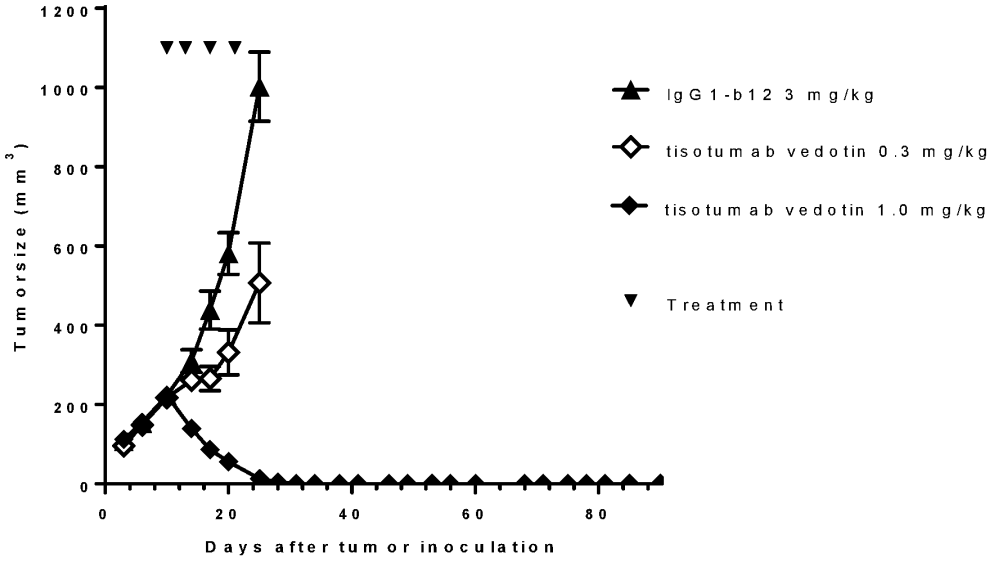
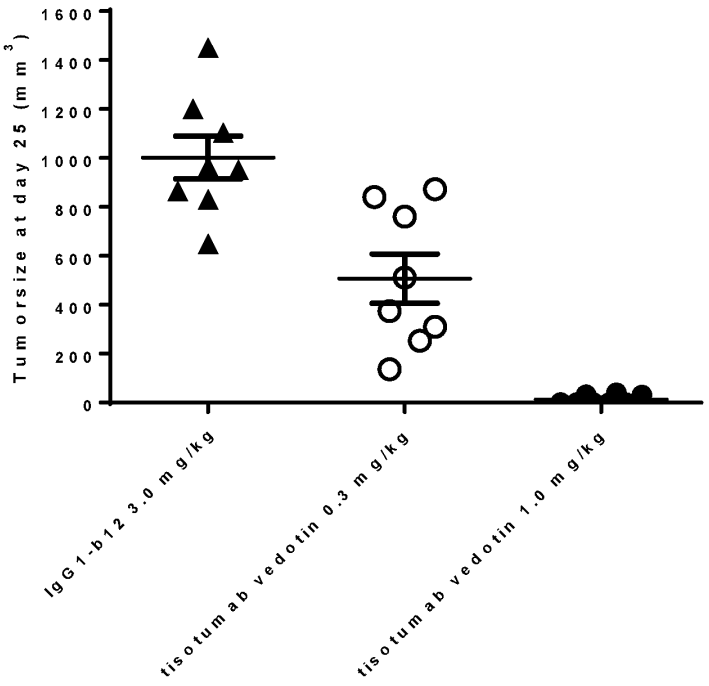

Tumorsize (mm3)
1200
1000
800
600
400
200
0
0
20
40
60
80
Days after tumor inoculation
IgG1-b12 3 mg/kg
tisotumab vedotin 0.3 mg/kg
tisotumab vedotin 1.0 mg/kg
Treatment

FIG. 4A



day 25	IgG1-b12	tisotumab vedotin 0.3 mg/kg	tisotumab vedotin 1.0 mg/kg
IgG1-b12		***	***
tisotumab vedotin 0.3 mg/kg	***		***
tisotumab vedotinC 1.0 mg/kg	***	***	

FIG. 4B

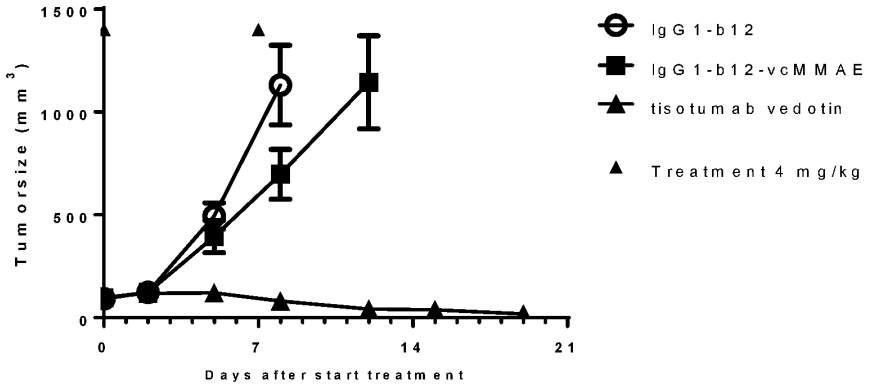

1500
1000
500
0
Tumorsize (mm3)
0
7
14
21
Days after start treatment
IgG1-b12
IgG1-b12-vcMMAE
tisotumab vedotin
Treatment 4 mg/kg

FIG. 5

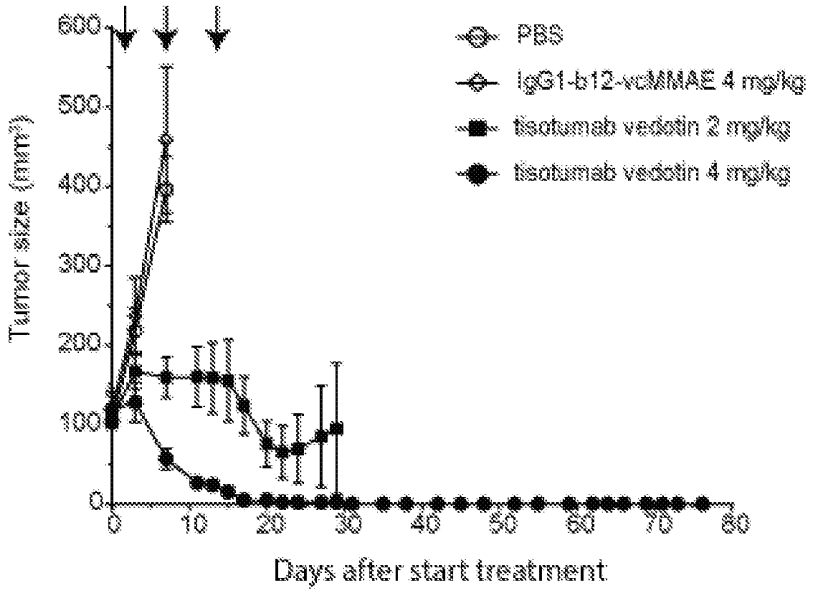

600
500
400
300
200
100
0
Tumor size (mm3)
0
10
20
30
40
50
60
70
80
Days after start treatment
PBS
IgG1-b12-vcMMAE 4 mg/kg
tisotumab vedotin 2 mg/kg
tisotumab vedotin 4 mg/kg

FIG. 6

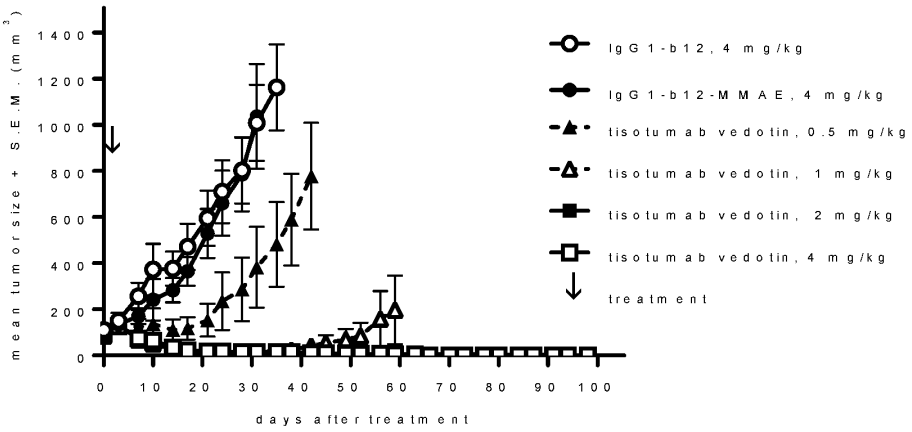

mean tumor size + S.E.M. (mm3)
1400
1200
1000
800
600
400
200
0
0 10 20 30 40 50 60 70 80 90 100
days after treatment
IgG1-b12, 4 mg/kg
IgG1-b12-MMAE, 4 mg/kg
tisotumab vedotin, 0.5 mg/kg
tisotumab vedotin, 1 mg/kg
tisotumab vedotin, 2 mg/kg
tisotumab vedotin, 4 mg/kg
treatment

FIG. 7

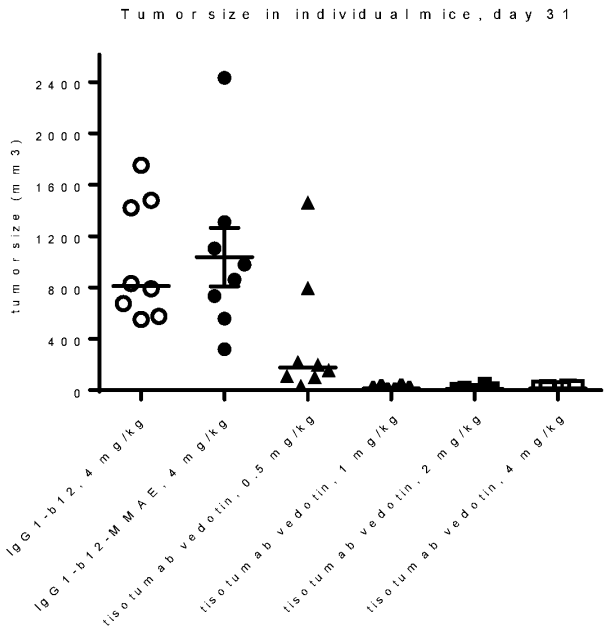

Tumor size in individual mice, day 31
tumor size (mm3)
2400
2000
1600
1200
800
400
0
IgG1-b12, 4 mg/kg
IgG1-b12-MMAE, 4 mg/kg
tisotumab vedotin, 0.5 mg/kg
tisotumab vedotin, 1 mg/kg
tisotumab vedotin, 2 mg/kg
tisotumab vedotin, 4 mg/kg

FIG. 8

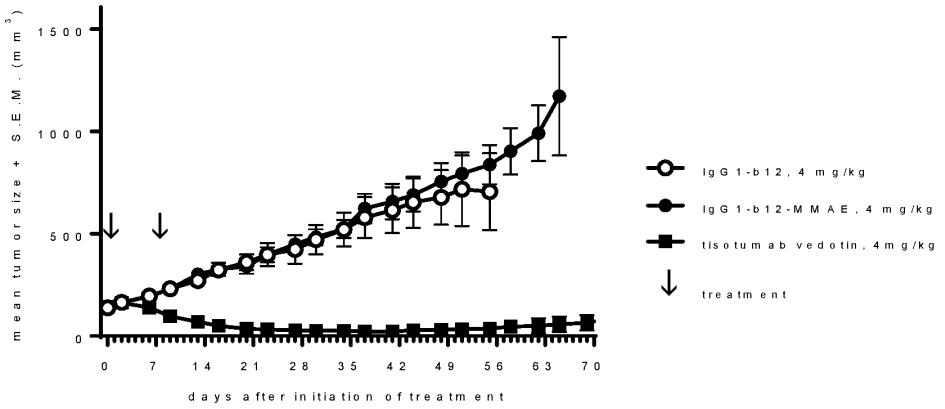

mean tumor size + S.E.M. (mm3)
1500
1000
500
0
0 7 14 21 28 35 42 49 56 63 70
days after initiation of treatment
IgG1-b12, 4 mg/kg
IgG1-b12-MMAE, 4 mg/kg
tisotumab vedotin, 4 mg/kg
treatment

FIG. 9

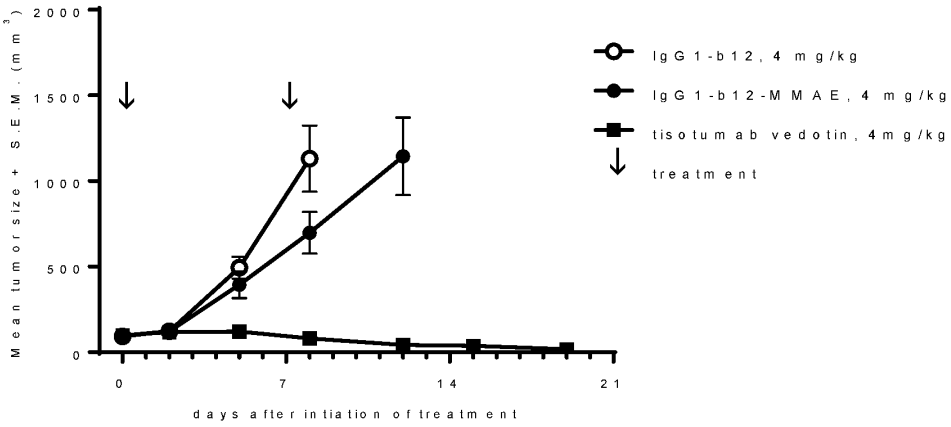

Mean tumor size + S.E.M. (mm3)
2000
1500
1000
500
0
0 7 14 21
days after initiation of treatment
IgG1-b12, 4 mg/kg
IgG1-b12-MMAE, 4 mg/kg
tisotumab vedotin, 4 mg/kg
treatment

FIG. 10

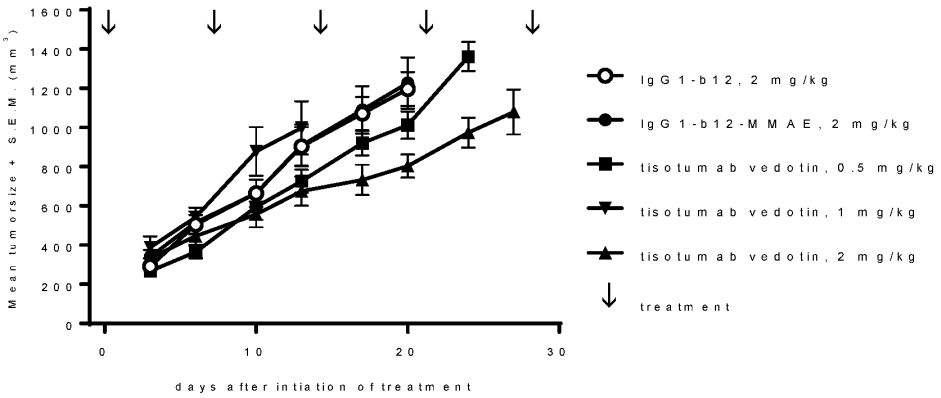

Mean tumor size + S.E.M. (mm3)
1600
1400
1200
1000
800
600
400
200
0
0
10
20
30
days after intiation of treatment
IgG1-b12, 2 mg/kg
IgG1-b12-MMAE, 2 mg/kg
tisotumab vedotin, 0.5 mg/kg
tisotumab vedotin, 1 mg/kg
tisotumab vedotin, 2 mg/kg
treatment

FIG. 11

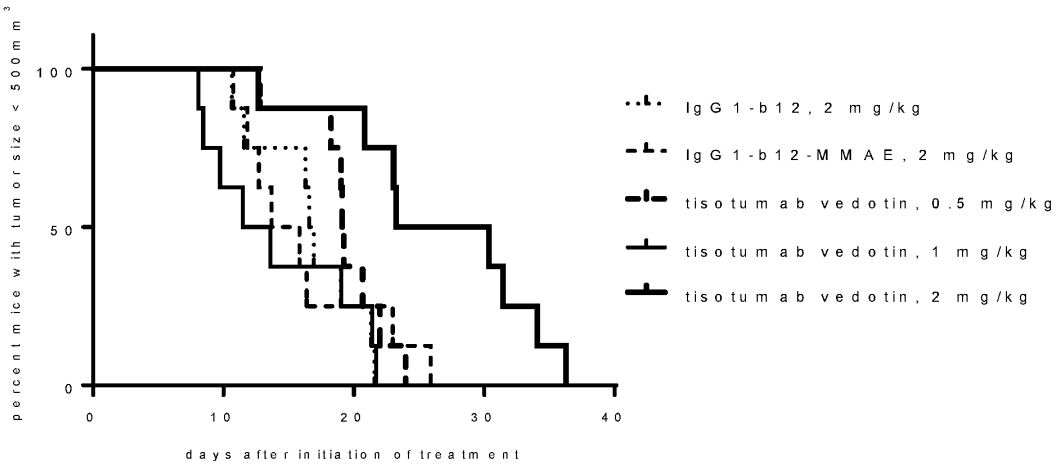

percent mice with tumor size < 500mm3
100
50
0
0
10
20
30
40
days after intiation of treatment
IgG1-b12, 2 mg/kg
IgG1-b12-MMAE, 2 mg/kg
tisotumab vedotin, 0.5 mg/kg
tisotumab vedotin, 1 mg/kg
tisotumab vedotin, 2 mg/kg

FIG. 12

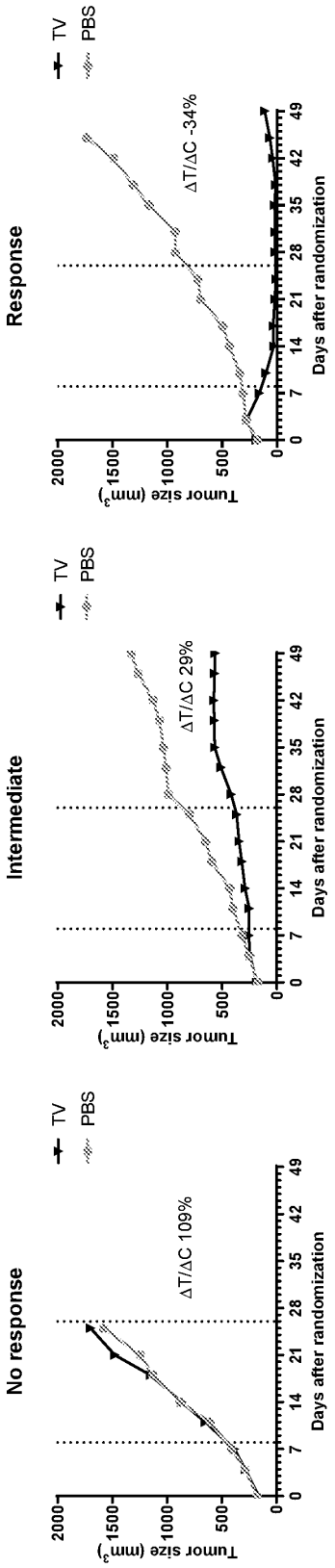

No response
Intermediate
Response
TV
PBS
ΔT/ΔC 109%
ΔT/ΔC 29%
ΔT/ΔC -34%
Tumor size (mm³)
2000
1500
1000
500
0
0
7
14
21
28
35
42
49
Days after randomization

FIG. 13

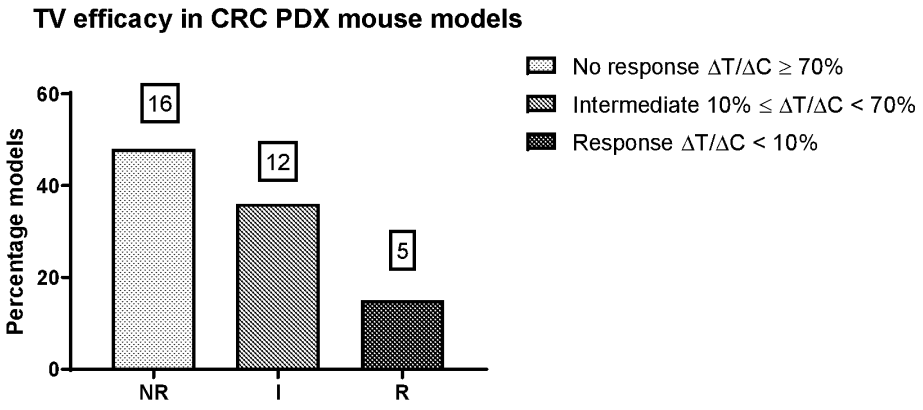

TV efficacy in CRC PDX mouse models
No response ΔT/ΔC ≥ 70%
Intermediate 10% ≤ ΔT/ΔC < 70%
Response ΔT/ΔC < 10%
Percentage models
60
40
20
0
16
12
5
NR
I
R

FIG. 14

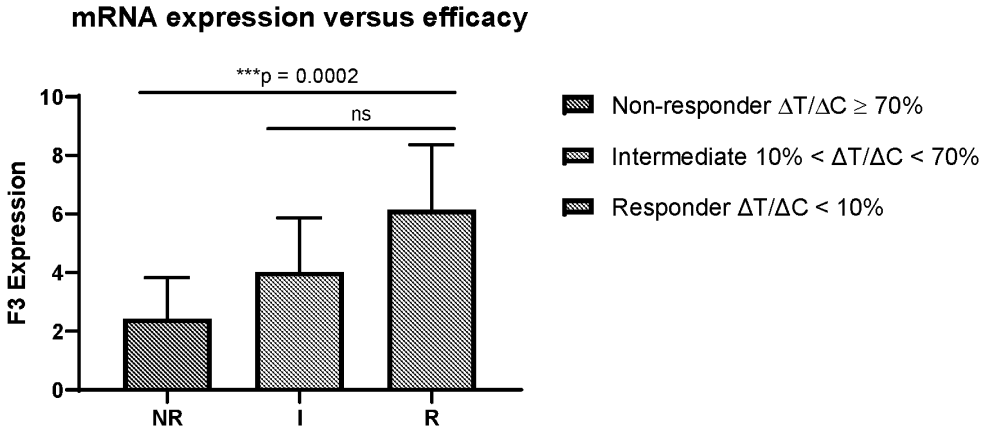

mRNA expression versus efficacy
***p = 0.0002
ns
Non-responder ΔT/ΔC ≥ 70%
Intermediate 10% < ΔT/ΔC < 70%
Responder ΔT/ΔC < 10%
F3 Expression
10
8
6
4
2
0
NR
I
R

FIG. 15