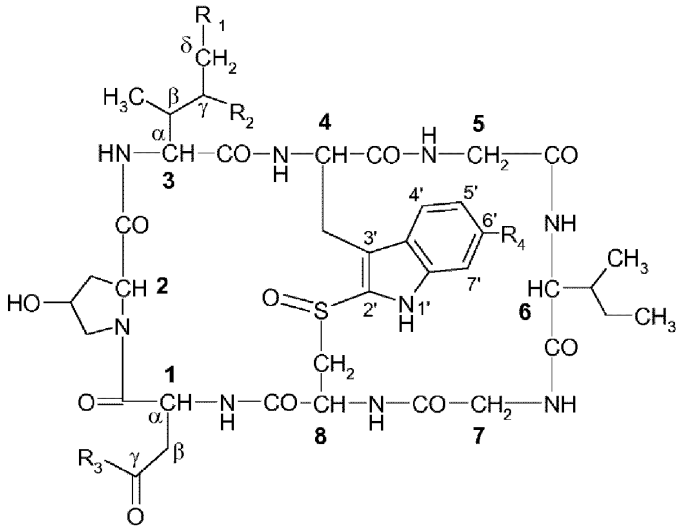
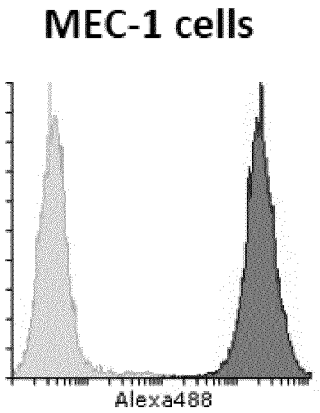


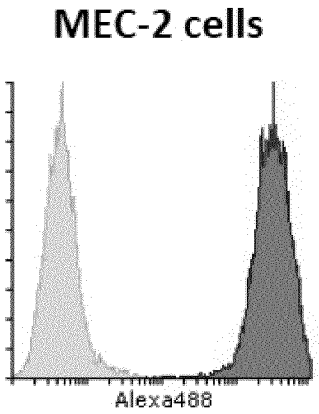
	R_1	R_2	R_3	R_4
α-amanitin	OH	OH	NH_2	OH
β-amanitin	OH	OH	OH	OH
γ-amanitin	H	OH	NH_2	OH
ε-amanitin	H	OH	OH	OH
amanin	OH	OH	OH	H
amaninamide	OH	OH	NH_2	H
amanullin	H	H	NH_2	OH
amanullinic acid	H	H	OH	OH
γ-amanin	H	OH	OH	H
γ-amaninamide	H	OH	NH2	H

FIG. 1

A


MEC-1 cells
Alexa488

B


MEC-2 cells
Alexa488

C

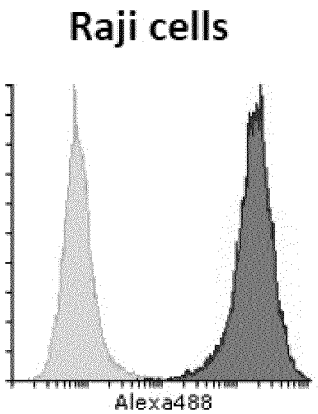

Raji cells
Alexa488

FIG. 2

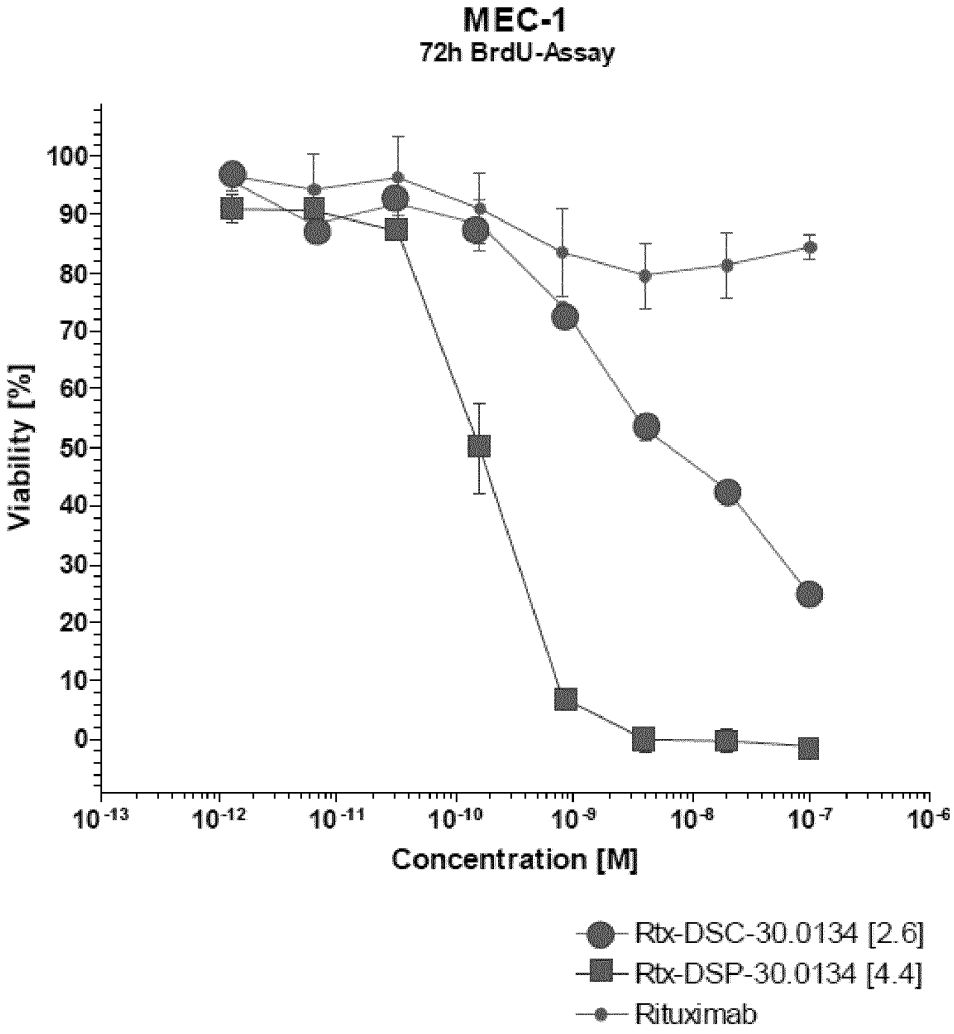

MEC-1
72h BrdU-Assay
Viability [%]
100
90
80
70
60
50
40
30
20
10
0
10-13
10-12
10-11
10-10
10-9
10-8
10-7
10-6
Concentration [M]
Rtx-DSC-30.0134 [2.6]
Rtx-DSP-30.0134 [4.4]
Rituximab

FIG. 3

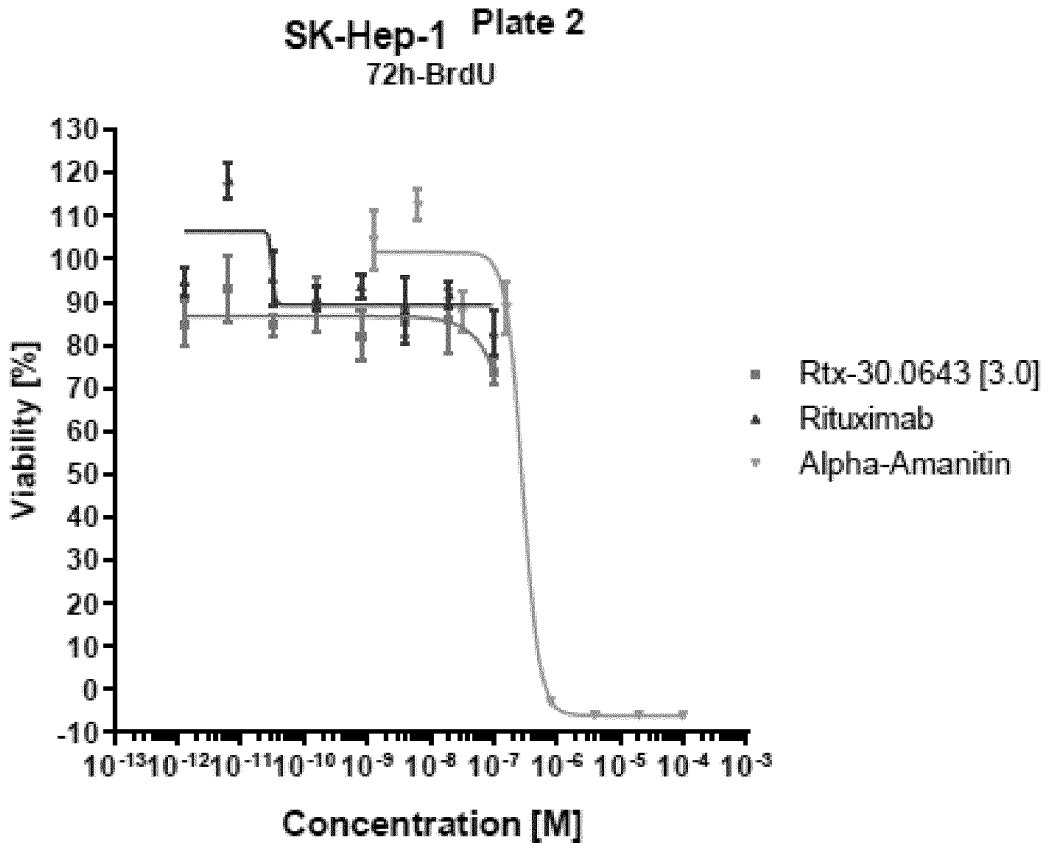
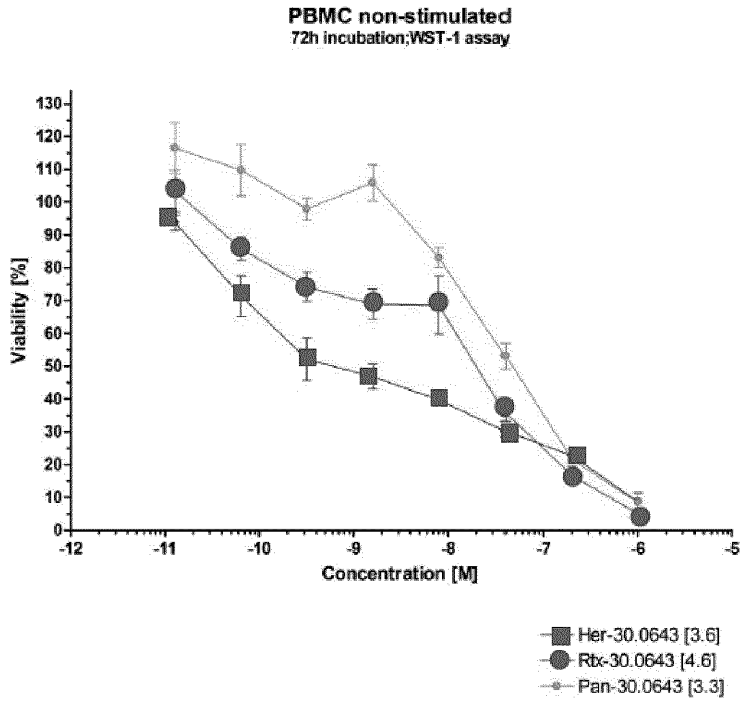

SK-Hep-1 Plate 2
72h-BrdU
Viability [%]
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
10-13 10-12 10-11 10-10 10-9 10-8 10-7 10-6 10-5 10-4 10-3
Concentration [M]
Rtx-30.0643 [3.0]
Rituximab
Alpha-Amanitin

FIG. 4

A


PBMC non-stimulated
72h incubation;WST-1 assay
Viability [%]
Concentration [M]
Her-30.0643 [3.6]
Rtx-30.0643 [4.6]
Pan-30.0643 [3.3]

B

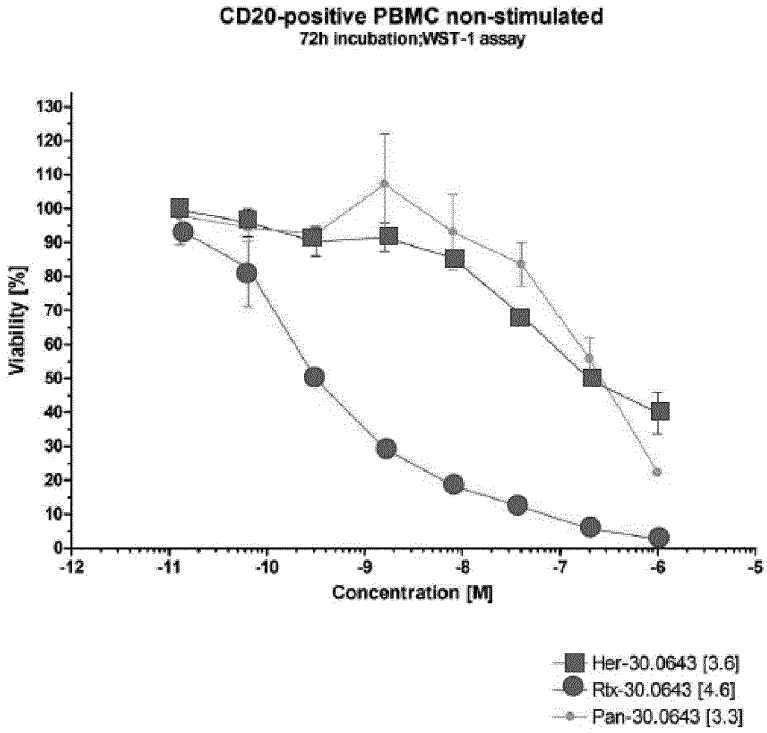

CD20-positive PBMC non-stimulated
72h incubation;WST-1 assay
Viability [%]
Concentration [M]
Her-30.0643 [3.6]
Rtx-30.0643 [4.6]
Pan-30.0643 [3.3]

FIG. 5

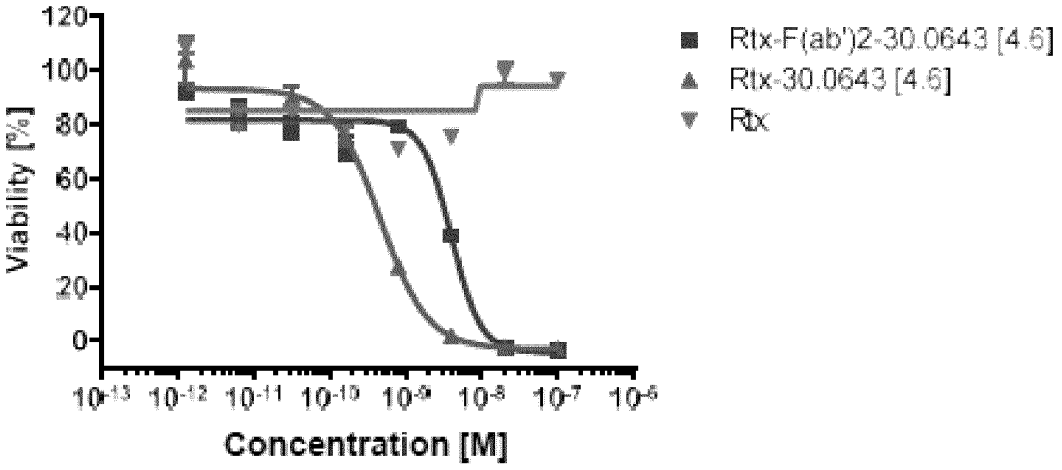

120
100
80
60
40
20
0
Viability [%]
10-13 10-12 10-11 10-10 10-9 10-8 10-7 10-6
Concentration [M]
Rtx-F(ab')2-30.0643 [4.6]
Rtx-30.0643 [4.6]
Rtx

FIG. 6

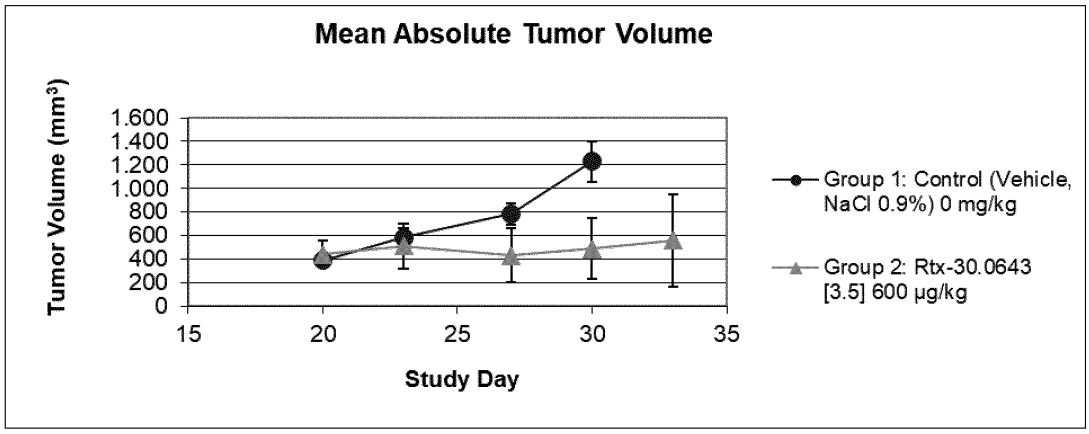

Mean Absolute Tumor Volume
Tumor Volume (mm³)
1.600
1.400
1.200
1.000
800
600
400
200
0
15
20
25
30
35
Study Day
Group 1: Control (Vehicle, NaCl 0.9%) 0 mg/kg
Group 2: Rtx-30.0643 [3.5] 600 µg/kg

FIG. 7

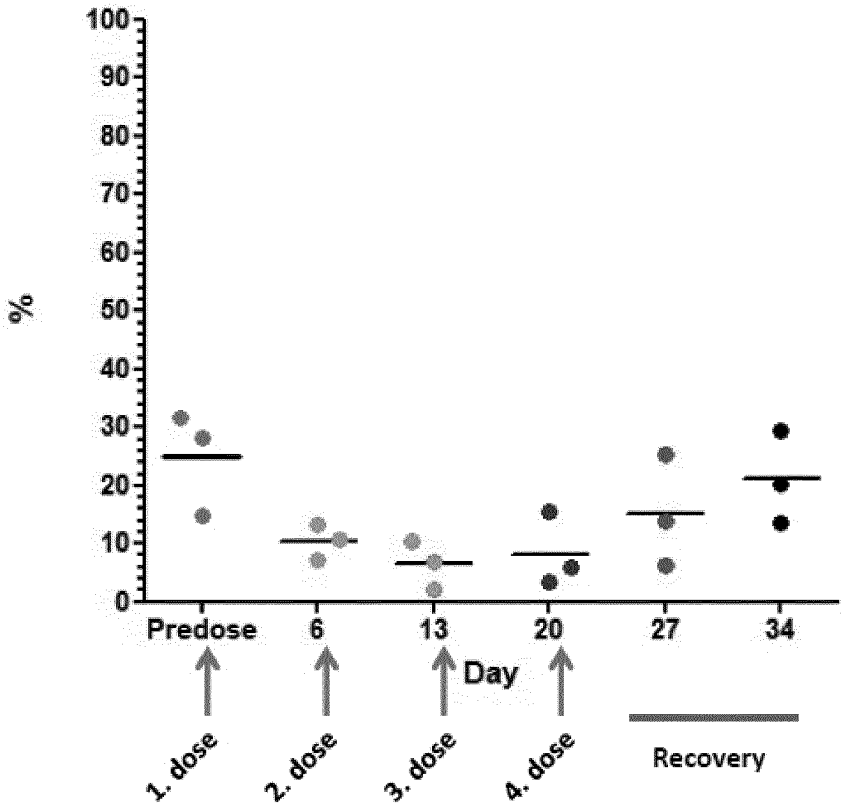

100
90
80
70
60
50
40
30
20
10
0
%
Predose
6
13
20
27
34
Day
1. dose
2. dose
3. dose
4. dose
Recovery

FIG. 8

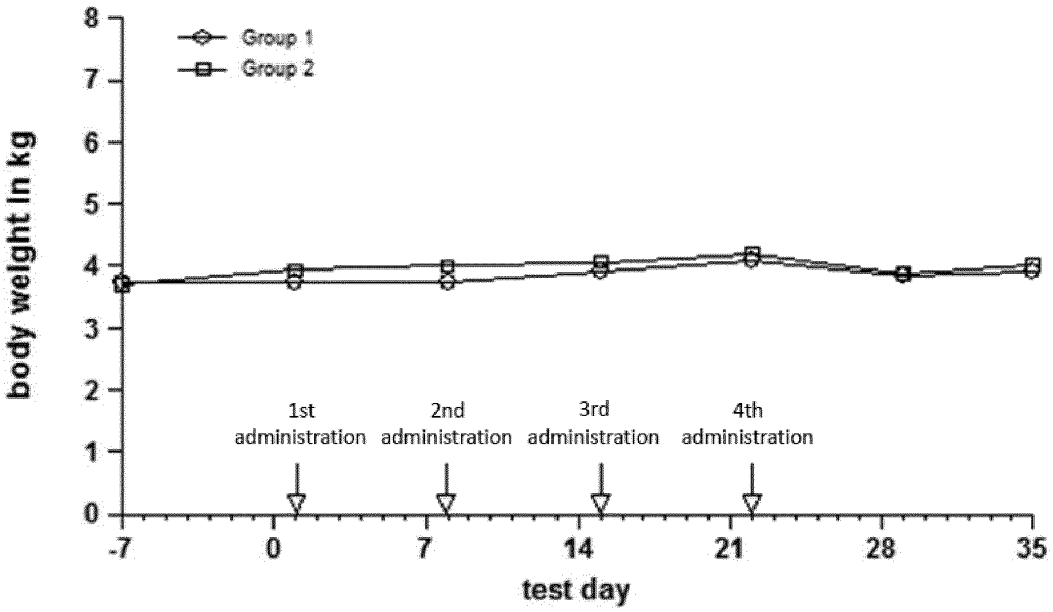
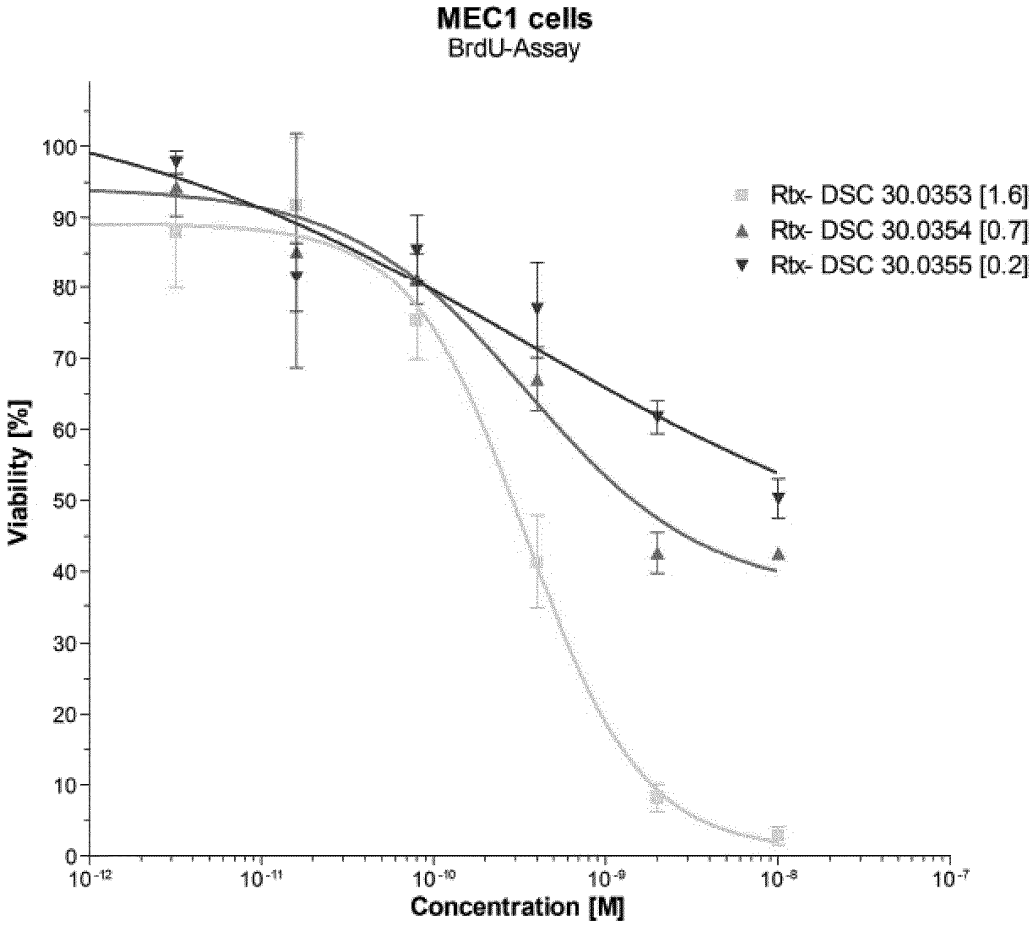

Group 1
Group 2
body weight in kg
8
7
6
5
4
3
2
1
0
1st administration
2nd administration
3rd administration
4th administration
-7
0
7
14
21
28
35
test day

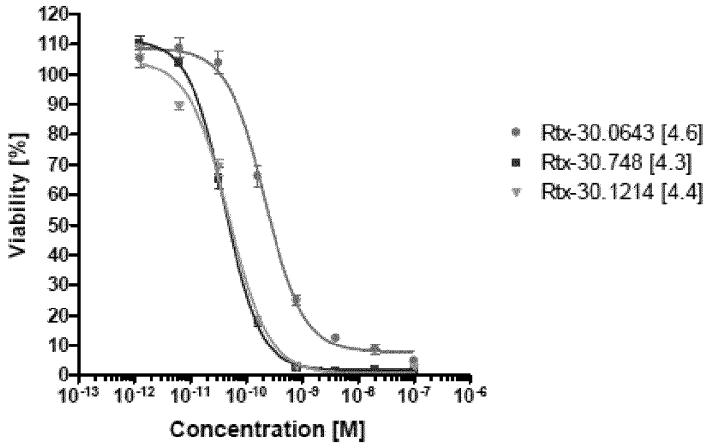
FIG. 9



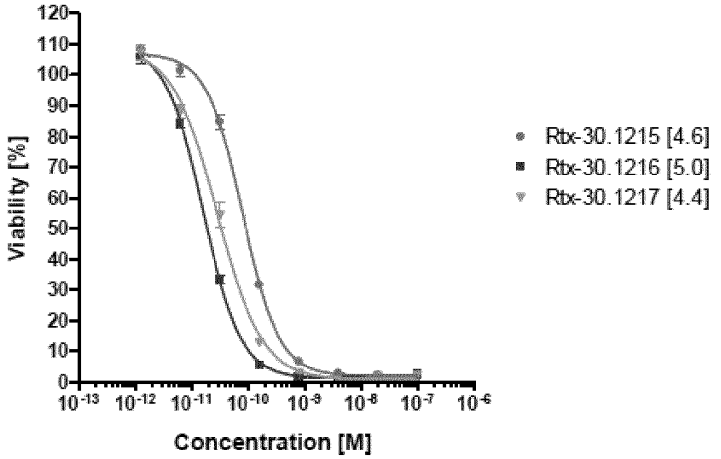
	Rtx- DSC 30.0353	Rtx- DSC 30.0354	Rtx- DSC 30.0355
EC50	3.370e-010	3.430e-010	9.782e-006

FIG. 10

A


Viability [%]
Concentration [M]
Rtx-30.0643 [4.6]
Rtx-30.748 [4.3]
Rtx-30.1214 [4.4]

B


Viability [%]
Concentration [M]
Rtx-30.1215 [4.6]
Rtx-30.1216 [5.0]
Rtx-30.1217 [4.4]

C

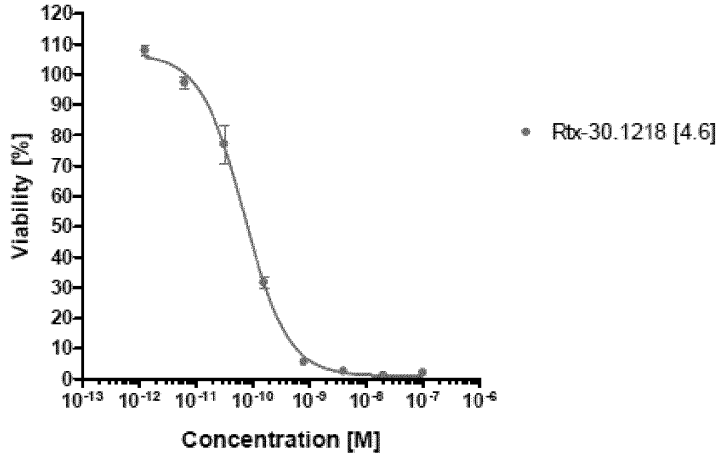
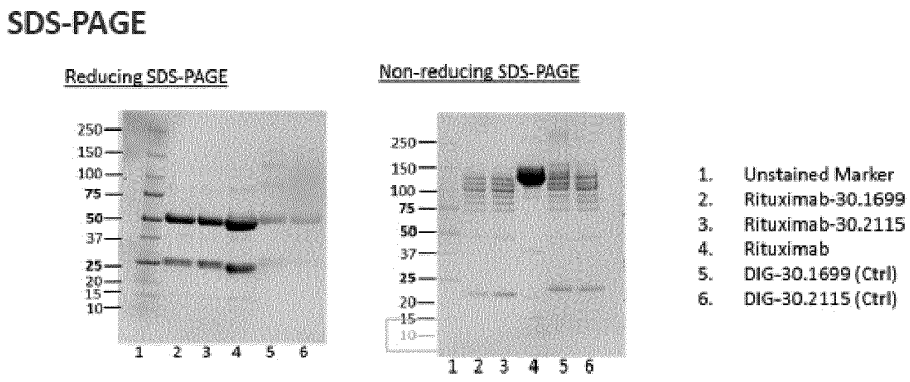

Viability [%]
Concentration [M]
Rtx-30.1218 [4.6]

FIG. 11

A


SDS-PAGE
Reducing SDS-PAGE
Non-reducing SDS-PAGE
250
150
100
75
50
37
25
20
15
10
1 2 3 4 5 6
1. Unstained Marker
2. Rituximab-30.1699
3. Rituximab-30.2115
4. Rituximab
5. DIG-30.1699 (Ctrl)
6. DIG-30.2115 (Ctrl)

B

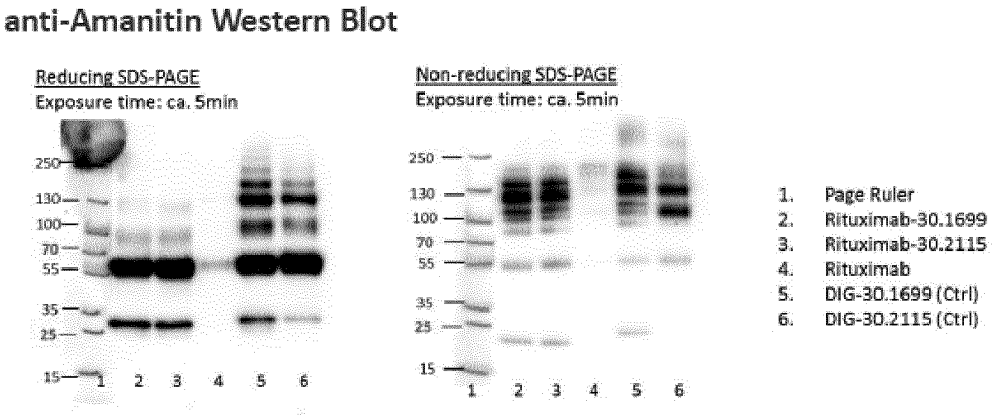

anti-Amanitin Western Blot
Reducing SDS-PAGE
Exposure time: ca. 5min
Non-reducing SDS-PAGE
Exposure time: ca. 5min
250
130
100
70
55
35
25
15
1 2 3 4 5 6
1. Page Ruler
2. Rituximab-30.1699
3. Rituximab-30.2115
4. Rituximab
5. DIG-30.1699 (Ctrl)
6. DIG-30.2115 (Ctrl)

FIG. 12

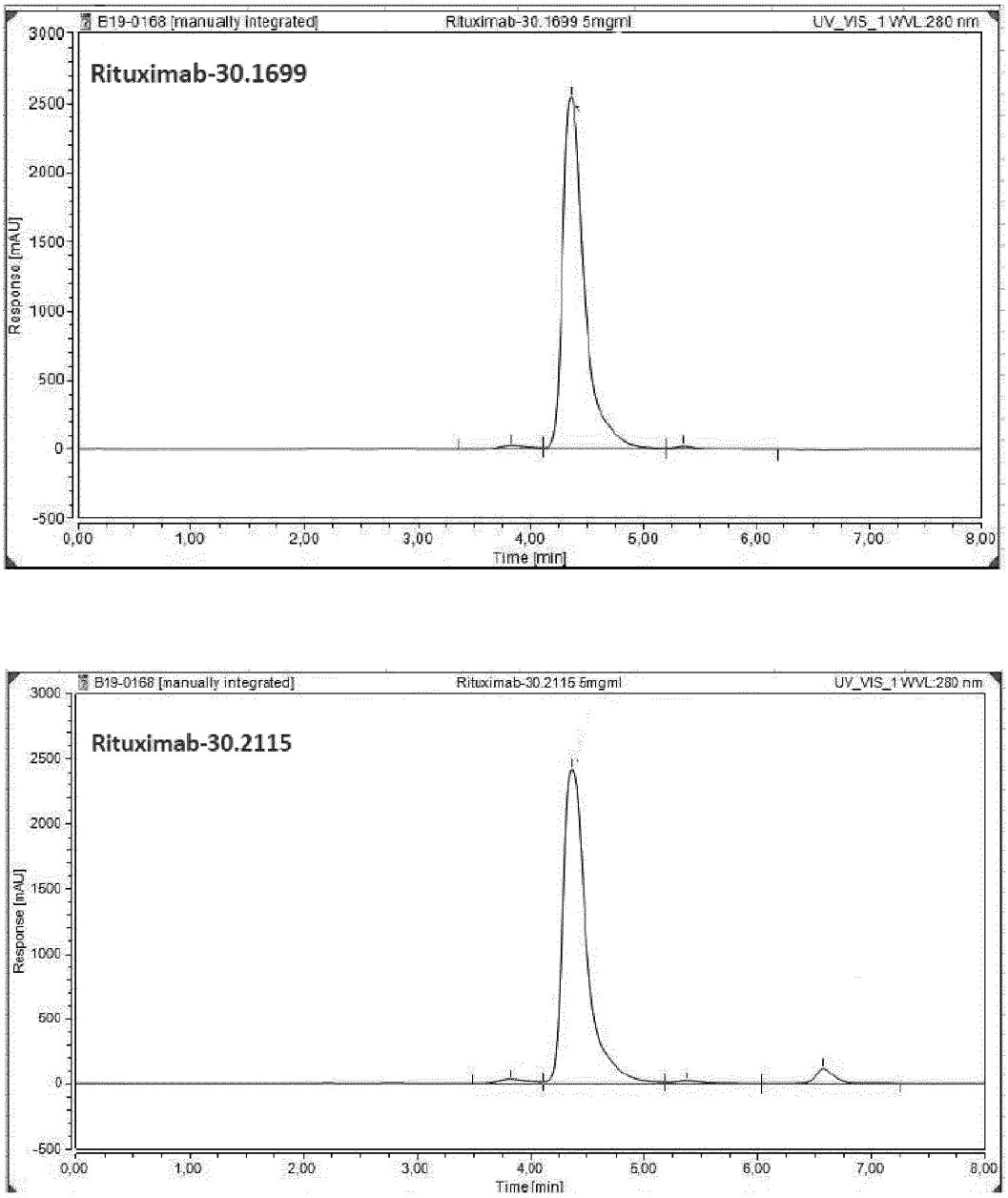
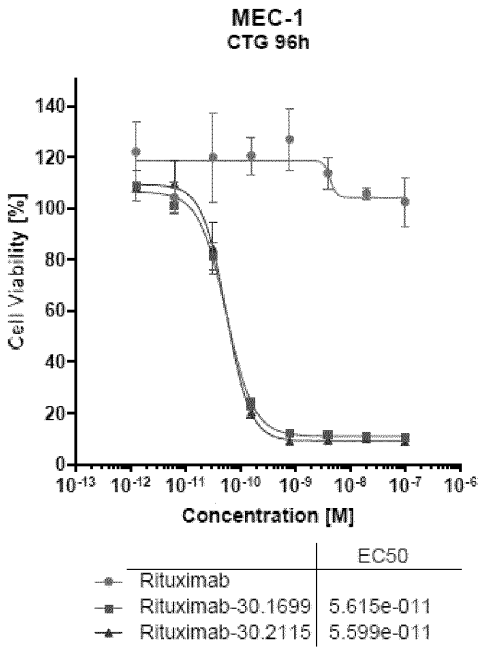

B19-0168 [manually integrated]
Rituximab-30.1699 5mgml
UV_VIS_1 WVL:280 nm
Rituximab-30.1699
Response [mAU]
Time [min]
B19-0168 [manually integrated]
Rituximab-30.2115 5mgml
UV_VIS_1 WVL:280 nm
Rituximab-30.2115
Response [mAU]
Time [min]

FIG. 13

A


MEC-1
CTG 96h
Cell Viability [%]
Concentration [M]
EC50
Rituximab
Rituximab-30.1699 5.615e-011
Rituximab-30.2115 5.599e-011

B

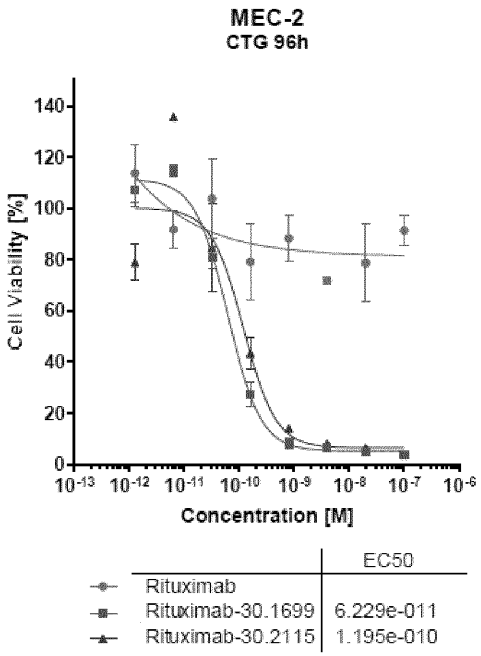
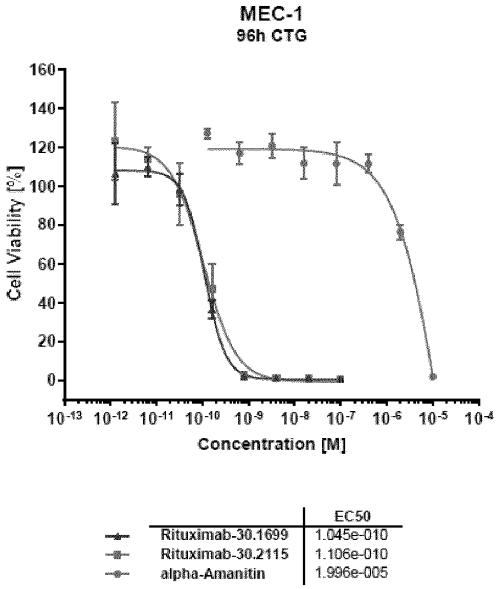
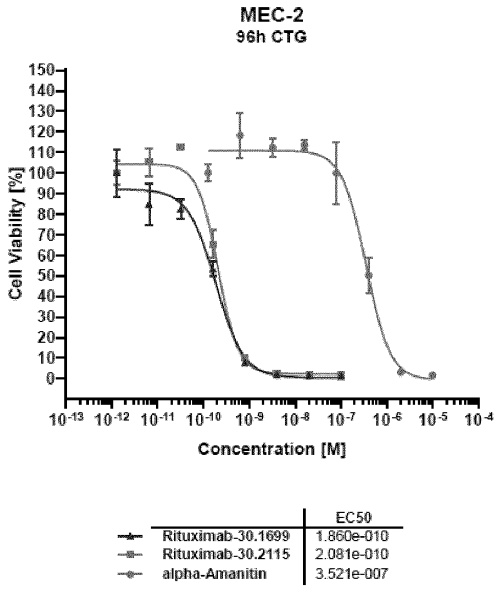

MEC-2
CTG 96h
Cell Viability [%]
Concentration [M]
EC50
Rituximab
Rituximab-30.1699 6.229e-011
Rituximab-30.2115 1.195e-010

FIG. 14

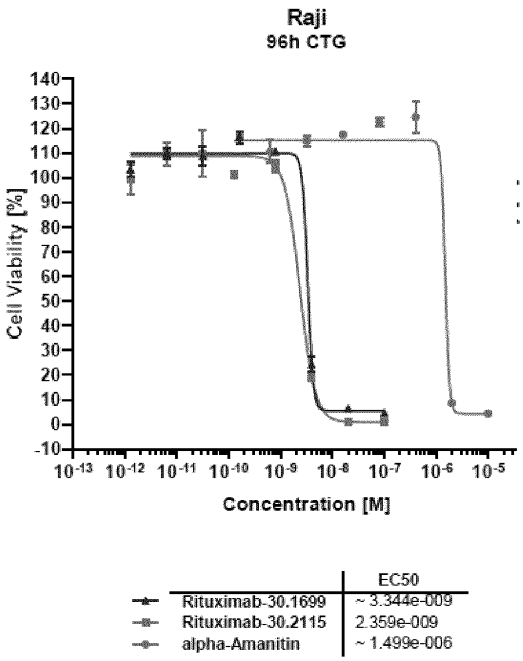
A


MEC-1
96h CTG
Cell Viability [%]
Concentration [M]
EC50
Rituximab-30.1699 1.045e-010
Rituximab-30.2115 1.106e-010
alpha-Amanitin 1.996e-005

B


MEC-2
96h CTG
Cell Viability [%]
Concentration [M]
EC50
Rituximab-30.1699 1.860e-010
Rituximab-30.2115 2.081e-010
alpha-Amanitin 3.521e-007

C


Raji
96h CTG
Cell Viability [%]
Concentration [M]
EC50
Rituximab-30.1699 ~ 3.344e-009
Rituximab-30.2115 2.359e-009
alpha-Amanitin ~ 1.499e-006

D

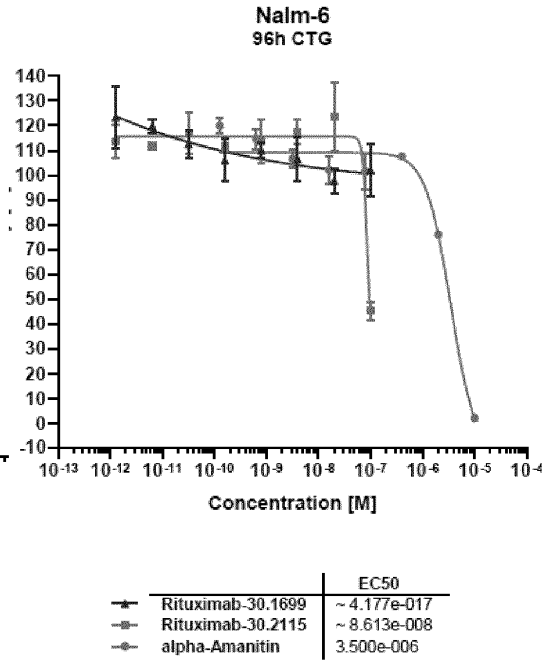

Nalm-6
96h CTG
Concentration [M]
EC50
Rituximab-30.1699 ~ 4.177e-017
Rituximab-30.2115 ~ 8.613e-008
alpha-Amanitin 3.500e-006

FIG. 15

E

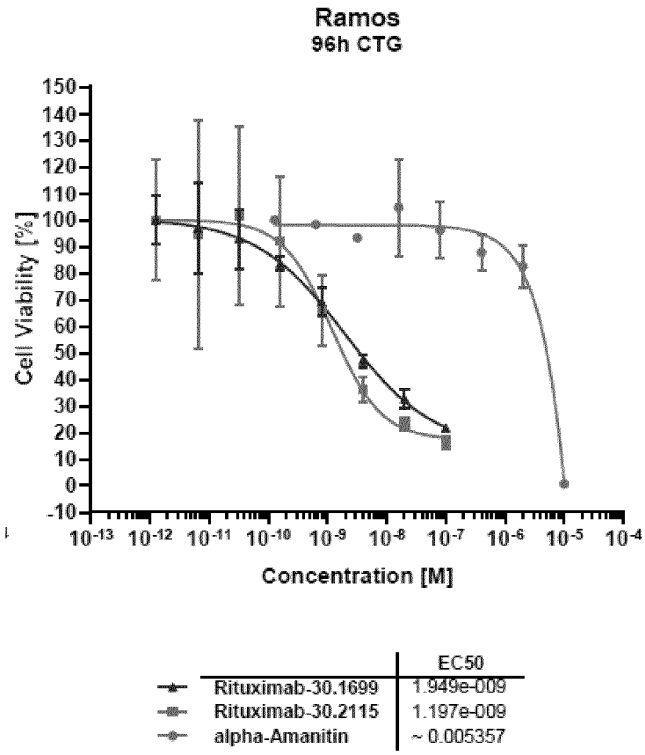

Ramos
96h CTG
Cell Viability [%]
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
10-13 10-12 10-11 10-10 10-9 10-8 10-7 10-6 10-5 10-4
Concentration [M]
EC50
Rituximab-30.1699 1.949e-009
Rituximab-30.2115 1.197e-009
alpha-Amanitin ~ 0.005357

FIG. 15

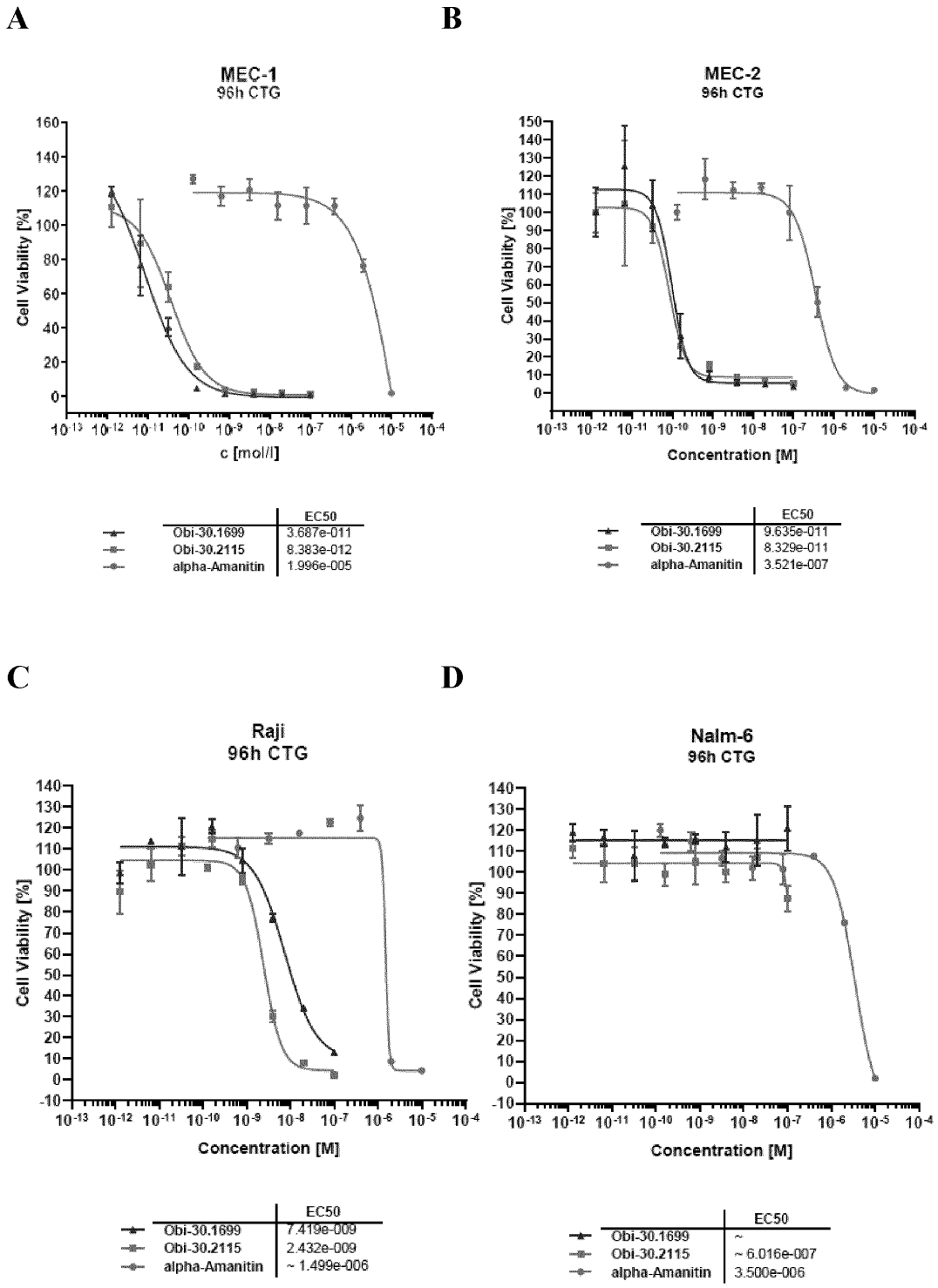
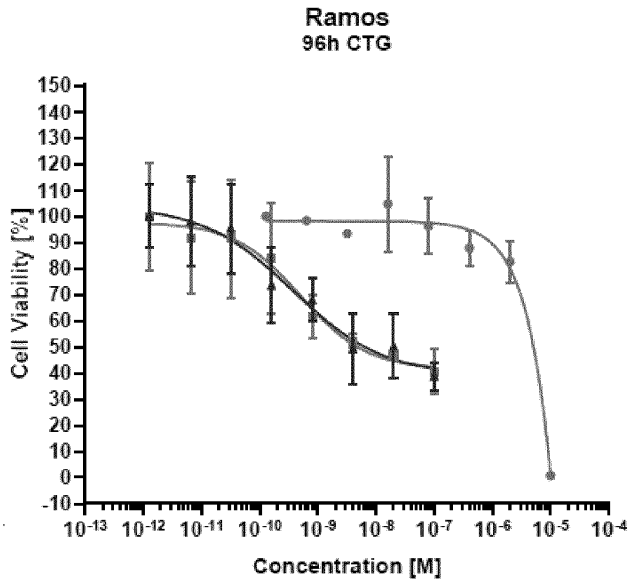

A
MEC-1
96h CTG
Cell Viability [%]
c [mol/l]
EC50
Obi-30.1699 3.687e-011
Obi-30.2115 8.383e-012
alpha-Amanitin 1.996e-005
B
MEC-2
96h CTG
Cell Viability [%]
Concentration [M]
EC50
Obi-30.1699 9.635e-011
Obi-30.2115 8.329e-011
alpha-Amanitin 3.521e-007
C
Raji
96h CTG
Cell Viability [%]
Concentration [M]
EC50
Obi-30.1699 7.419e-009
Obi-30.2115 2.432e-009
alpha-Amanitin ~ 1.499e-006
D
Nalm-6
96h CTG
Cell Viability [%]
Concentration [M]
EC50
Obi-30.1699 ~
Obi-30.2115 ~ 6.016e-007
alpha-Amanitin 3.500e-006

FIG. 16

E



	EC50
Obi-30.1699	3.722e-010
Obi-30.2115	5.022e-010
alpha-Amanitin	~ 0.005357

FIG. 16

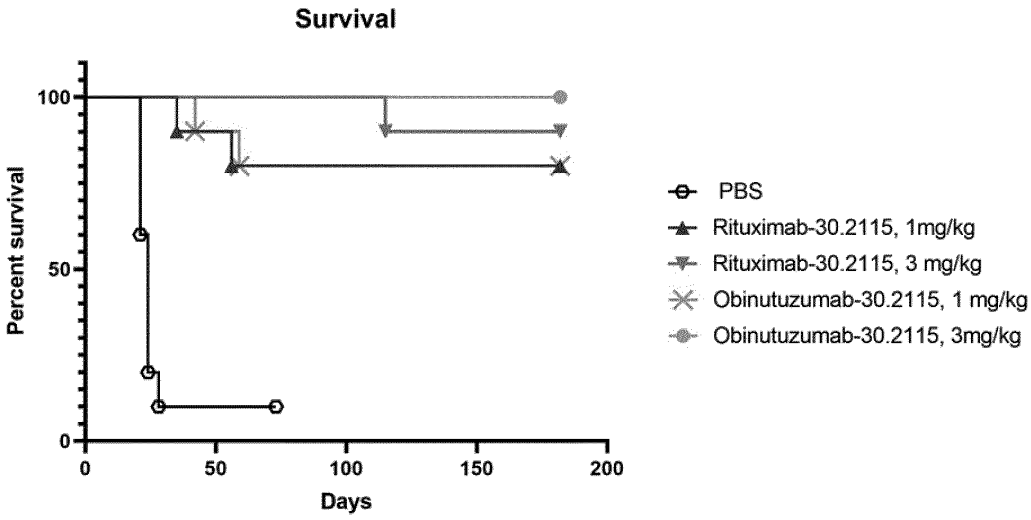

Survival
Percent survival
100
50
0
0
50
100
150
200
Days
PBS
Rituximab-30.2115, 1mg/kg
Rituximab-30.2115, 3 mg/kg
Obinutuzumab-30.2115, 1 mg/kg
Obinutuzumab-30.2115, 3mg/kg

FIG. 17

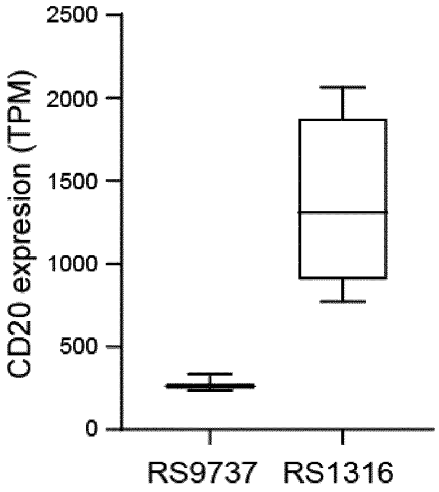
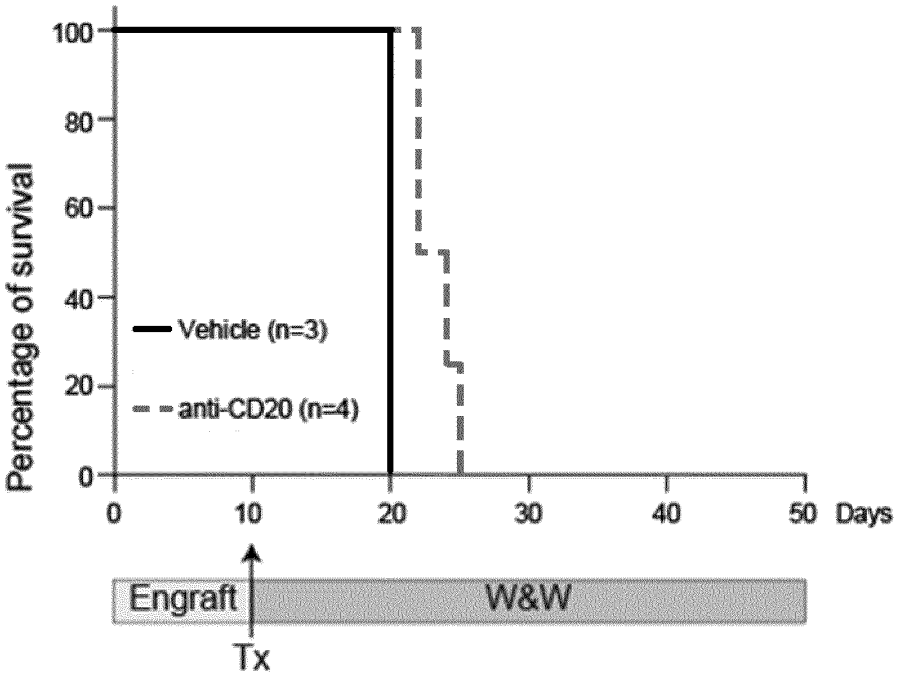


FIG. 18

A


100
80
60
40
20
0
Percentage of survival
Vehicle (n=3)
anti-CD20 (n=4)
0
10
20
30
40
50
Days
Engraft
W&W
Tx

B

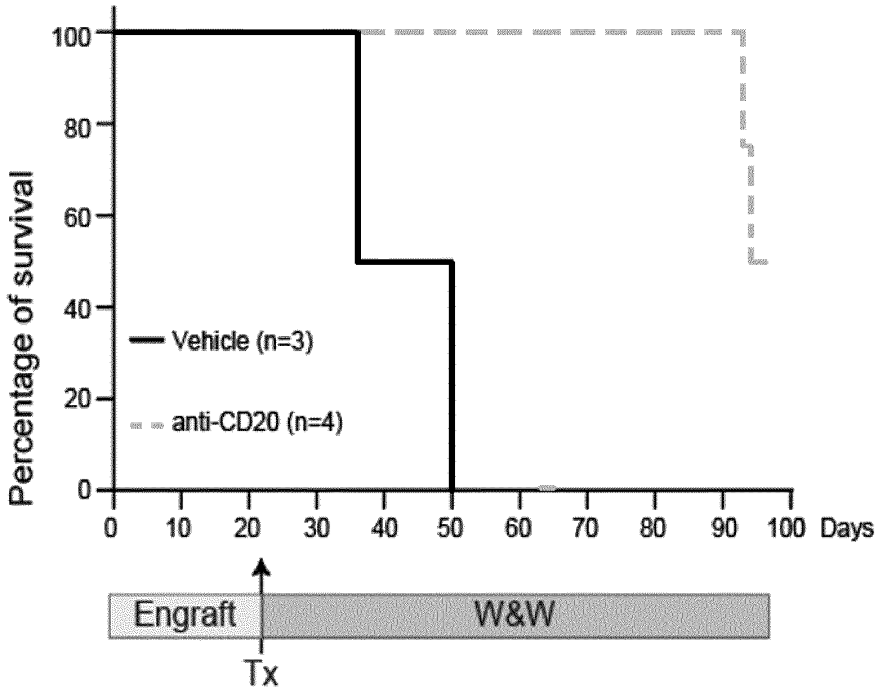

100
80
60
40
20
0
Percentage of survival
Vehicle (n=3)
anti-CD20 (n=4)
0
10
20
30
40
50
60
70
80
90
100
Days
Engraft
W&W
Tx

FIG. 19