Figure 1

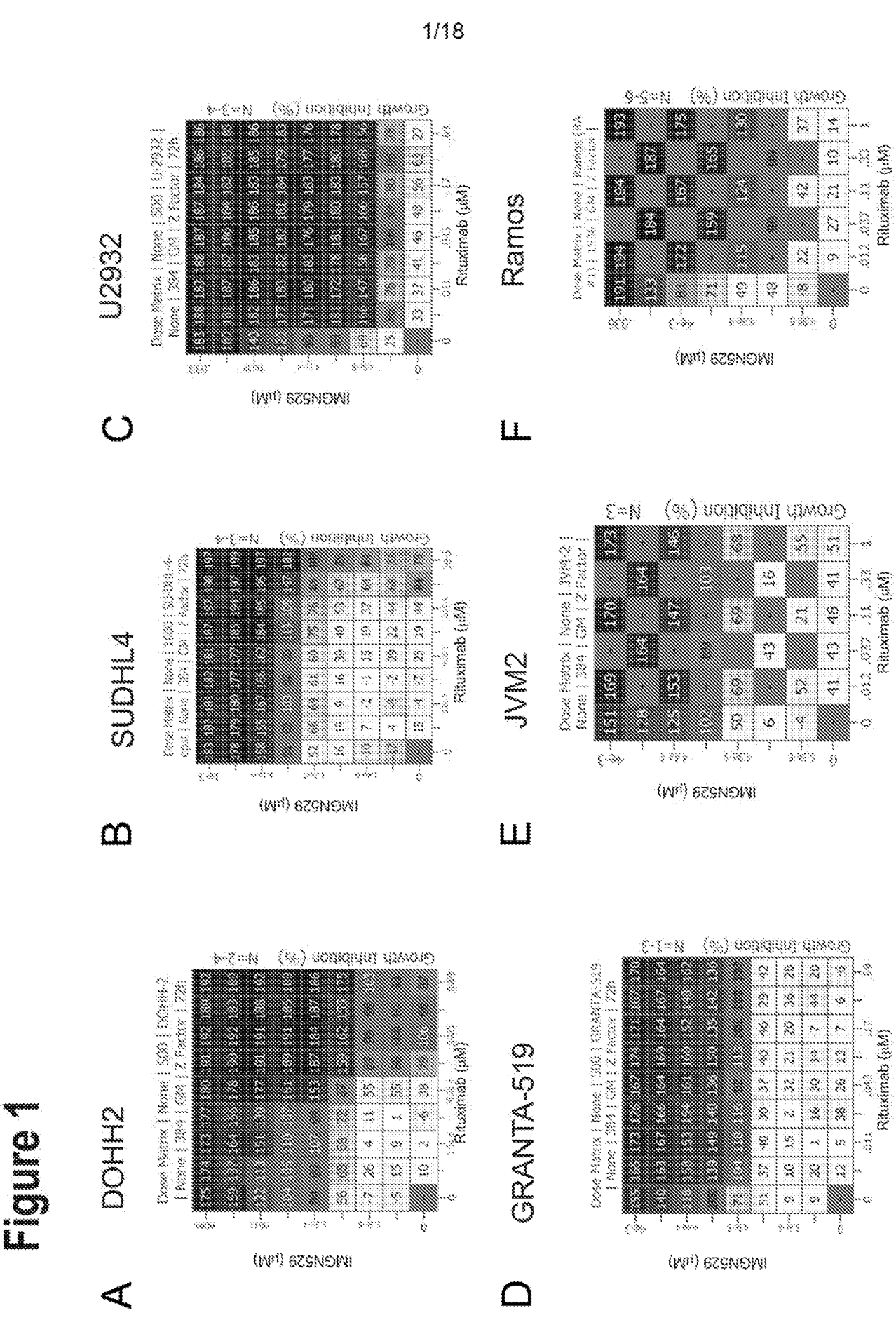

A
DOHH2
B
SUDHL4
C
U2932
D
GRANTA-519
E
JVM2
F
Ramos
IMGN529 (μM)
Rituximab (μM)
Growth Inhibition (%)

Figure 2

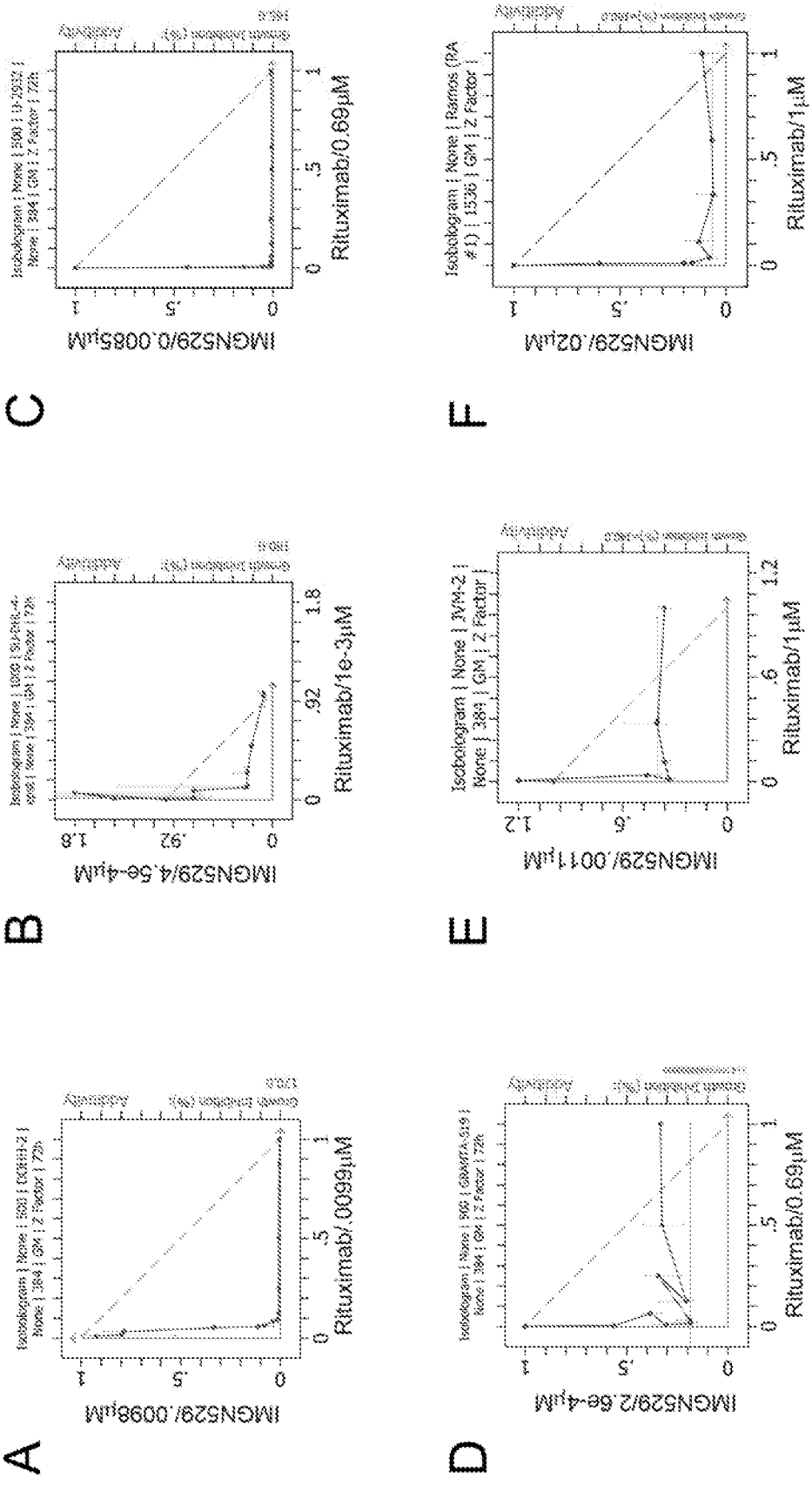

A
IMGN529/.0098μM
Rituximab/.0099μM
B
IMGN529/4.56e-4μM
Rituximab/1e-3μM
C
IMGN529/0.0085μM
Rituximab/0.69μM
D
IMGN529/2.66-4μM
Rituximab/0.69μM
E
IMGN529/.0011μM
Rituximab/1μM
F
IMGN529/.02μM
Rituximab/1μM

Figure 3

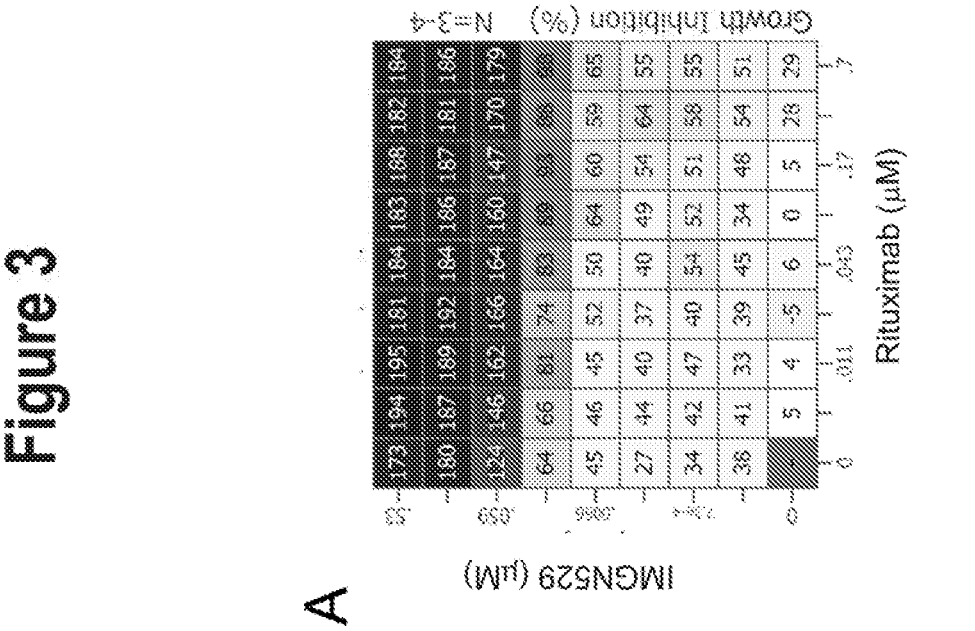

A
IMGN529 (μM)
Rituximab (μM)
Growth Inhibition (%) N=3-4
B
IMGN529/56μM
Rituximab/.7μM
Isobolegram | None | 1000 | OCI-Ly18 | None | 384 | GM | Z Factor | 72h
Growth Inhibition (%)
Additivity
Synergy score = 11.3
Best CI = 0.23

Figure 4

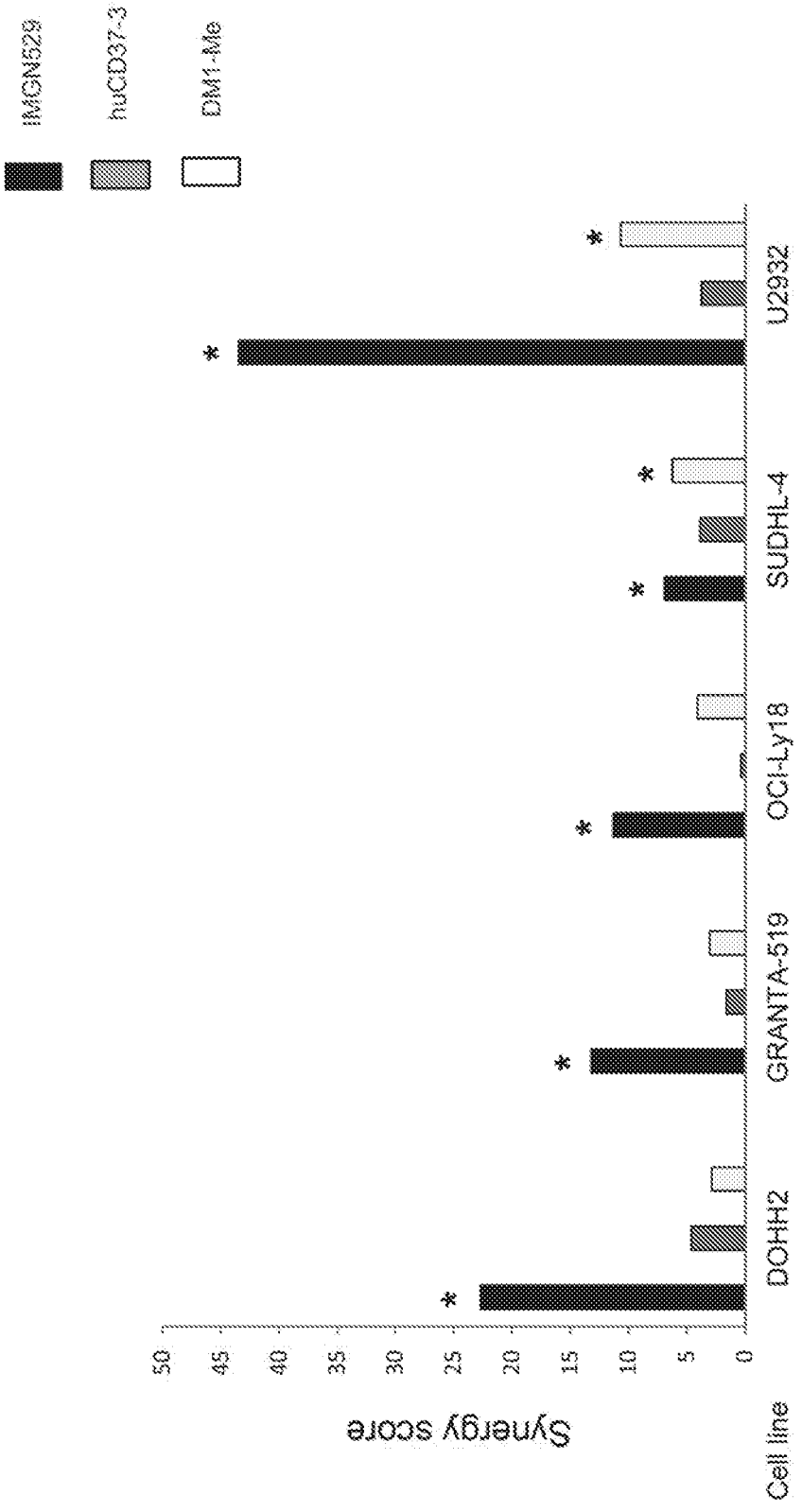

IMGN529
huCD37-3
DM1-Me
Synergy score
0
5
10
15
20
25
30
35
40
45
50
DOHH2
GRANTA-519
OCI-Ly18
SUDHL-4
U2932
Cell line

Figure 5

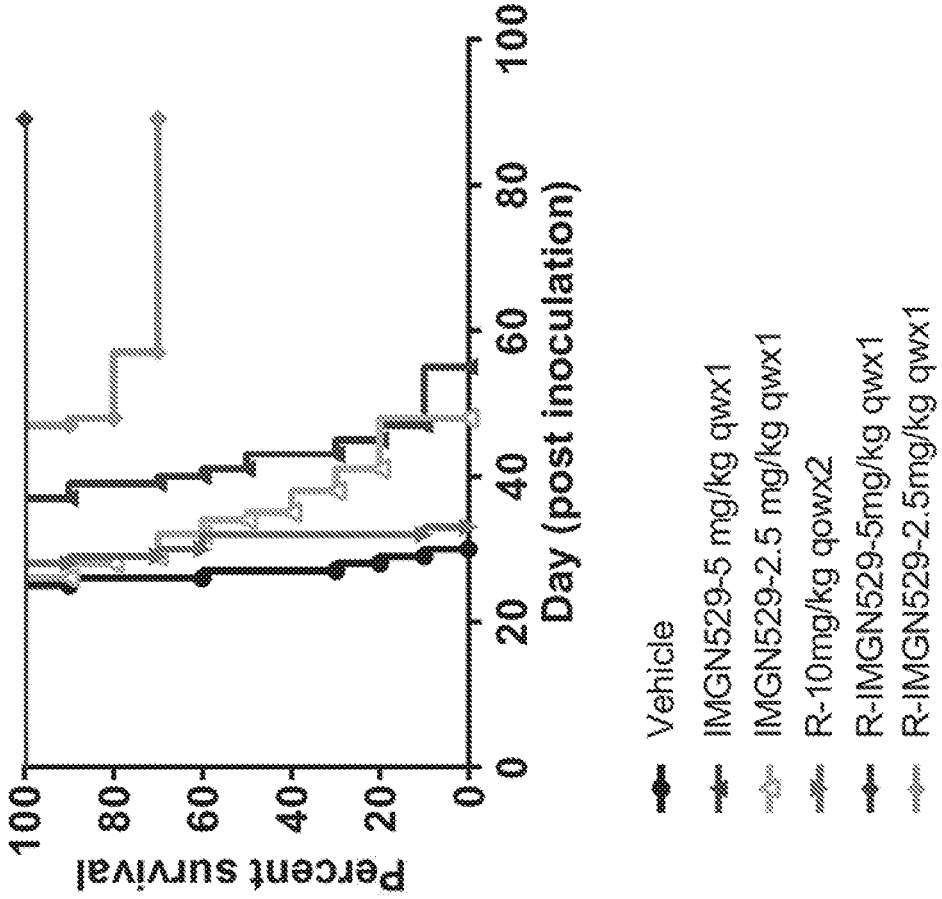
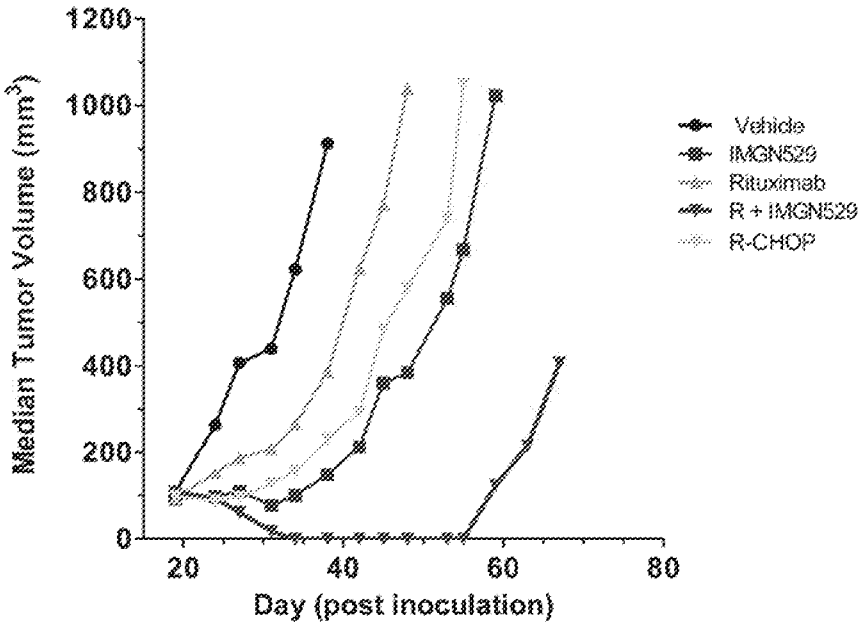
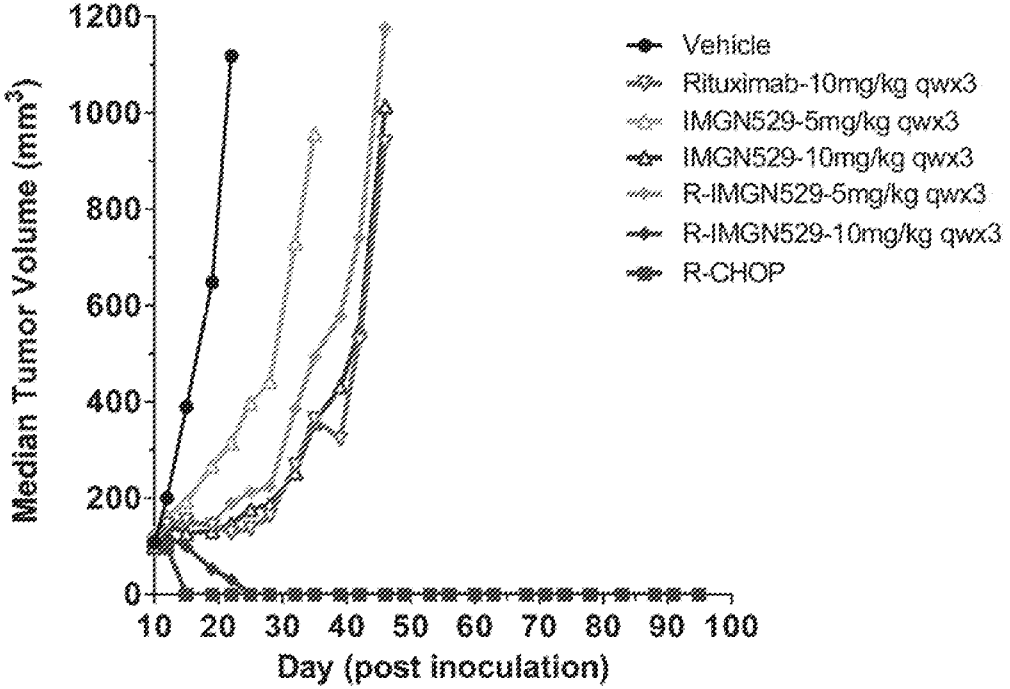

Percent survival
100
80
60
40
20
0
0
20
40
60
80
100
Day (post inoculation)
Vehicle
IMGN529-5 mg/kg qwx1
IMGN529-2.5 mg/kg qwx1
R-10mg/kg qowx2
R-IMGN529-5mg/kg qwx1
R-IMGN529-2.5mg/kg qwx1

Figure 6



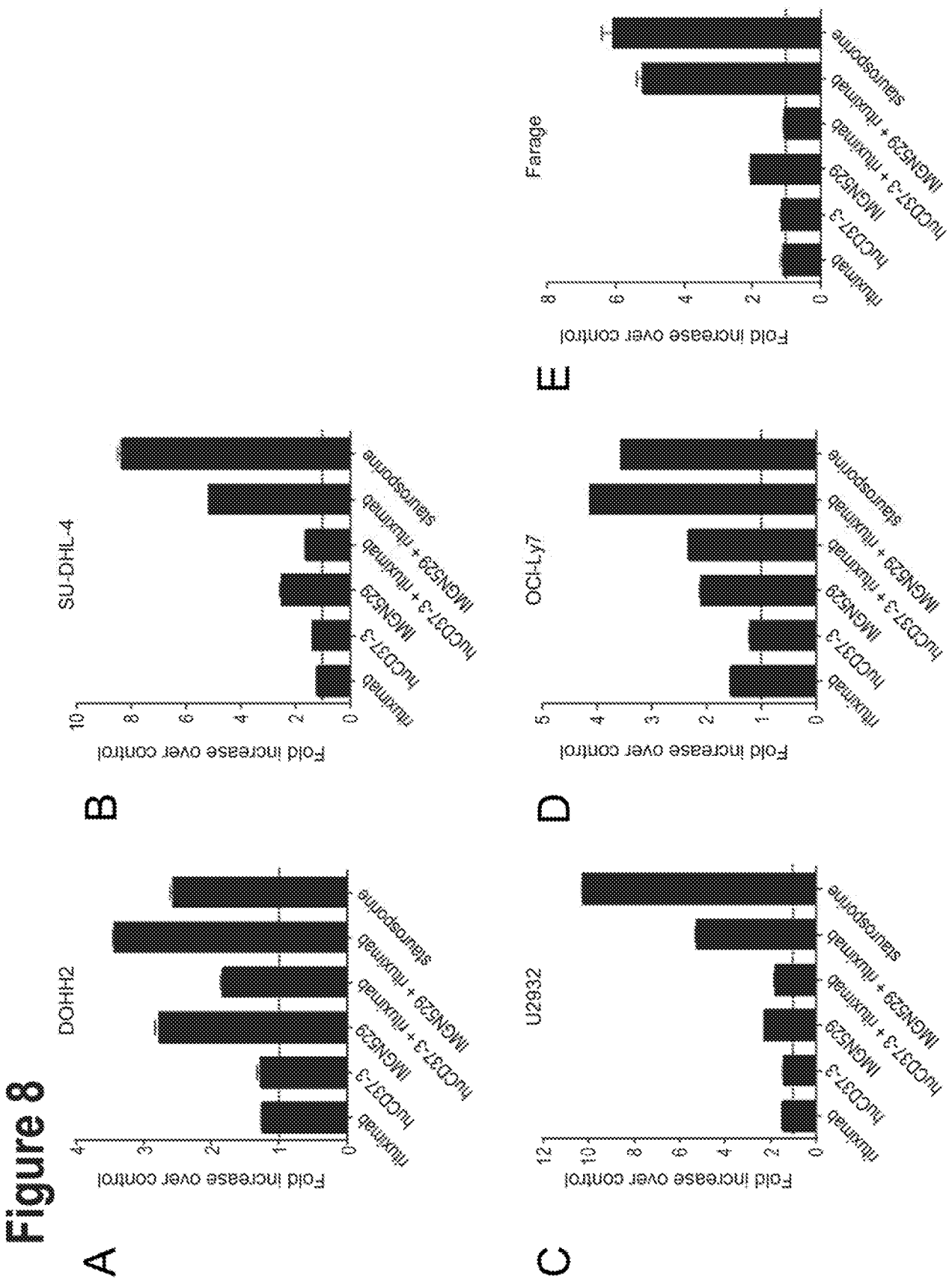
Treatment	Dose	T/C (%)	CR	TFS	% BWL (Nadir)	Result
IMGN529	10 mg/kg 1X	16	1/8	0/8	2.5 (Day 27)	Active
Rituximab	10 mg/kg 1X	42	2/8	2/8	1.4 (Day 24)	Active
IMGN529 + Rituximab	10 mg/kg 10 mg/kg	0	5/8	4/8	2.0 (Day 27)	Highly Active
R-CHOP	Rituximab 10 mg/kg 1X Cyclophosphamide 30 mg/kg 1X Doxorubicin 2.5 mg/kg 1X Vincristine 0.375 mg/kg 1X Prednisone 0.15 mg/kg qdx5	25	2/8	1/8	7.5 (Day 24)	Active

Figure 7



Treatment	Dose	T/C (%)	PR	CR	TFS	T/C Result	LCK	LCK Activity	% BWL (Nadir)
Rituximab	10 mg/kg qwx3	13	2/8	2/8	2/8	Active	1.69	++	3 (Day 15)
IMGN529	5 mg/kg qwx3	30	0/8	0/8	0/8	Active	1.14	+	5 (Day 15)
IMGN529	10 mg/kg qwx3	14	1/8	1/8	1/8	Active	1.76	++	5 (Day 15)
IMGN529 + Rituximab	5 mg/kg qwx3 10 mg/kg qwx3	18	1/8	1/8	0/8	Active	1.69	++	5 (Day 15)
IMGN529 + Rituximab	10 mg/kg qwx3 10 mg/kg qwx3	4	7/8	7/8	7/8	Highly Active	2.13	+++	3 (Day 12)
R-CHOP	Rituximab 10 mg/kg X Cyclophosphamide 30 mg/kg X Doxorubicin 2.5 mg/kg 1X Vincristine 0.375 mg/kg 1X Prednisone 0.15 mg/kg qdx5	0	8/8	8/8	5/8	Highly Active	3.01	++++	5 (Day 15)

Figure 8


A
DOHH2
Fold increase over control
rituximab
huCD37-3
IMGN529
huCD37-3 + rituximab
IMGN529 + rituximab
staurosporine
B
SU-DHL-4
Fold increase over control
C
U2932
Fold increase over control
D
OCI-Ly7
Fold increase over control
E
Farage
Fold increase over control

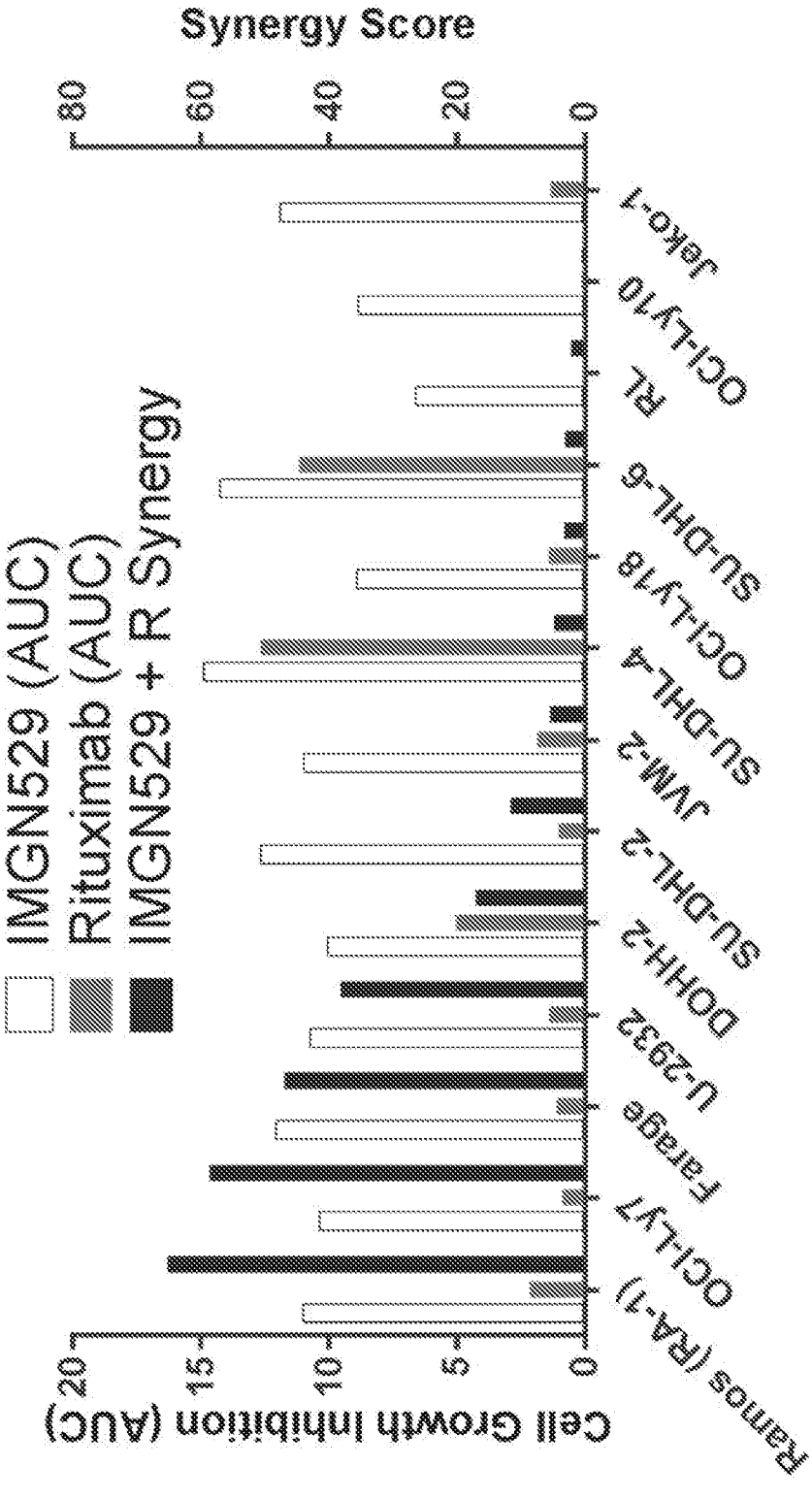

Synergy Score
80
60
40
20
0
IMGN529 (AUC)
Rituximab (AUC)
IMGN529 + R Synergy
cell Growth Inhibition (AUC)
20
15
10
5
0
Ramos (RA-1)
OCI-LY7
Farage
U-2932
DOHH-2
SU-DHL-2
JVM-2
SU-DHL-4
OCI-LY18
SU-DHL-6
RL
OCI-LY10
Jeko-1

Figure 9

Figure 10

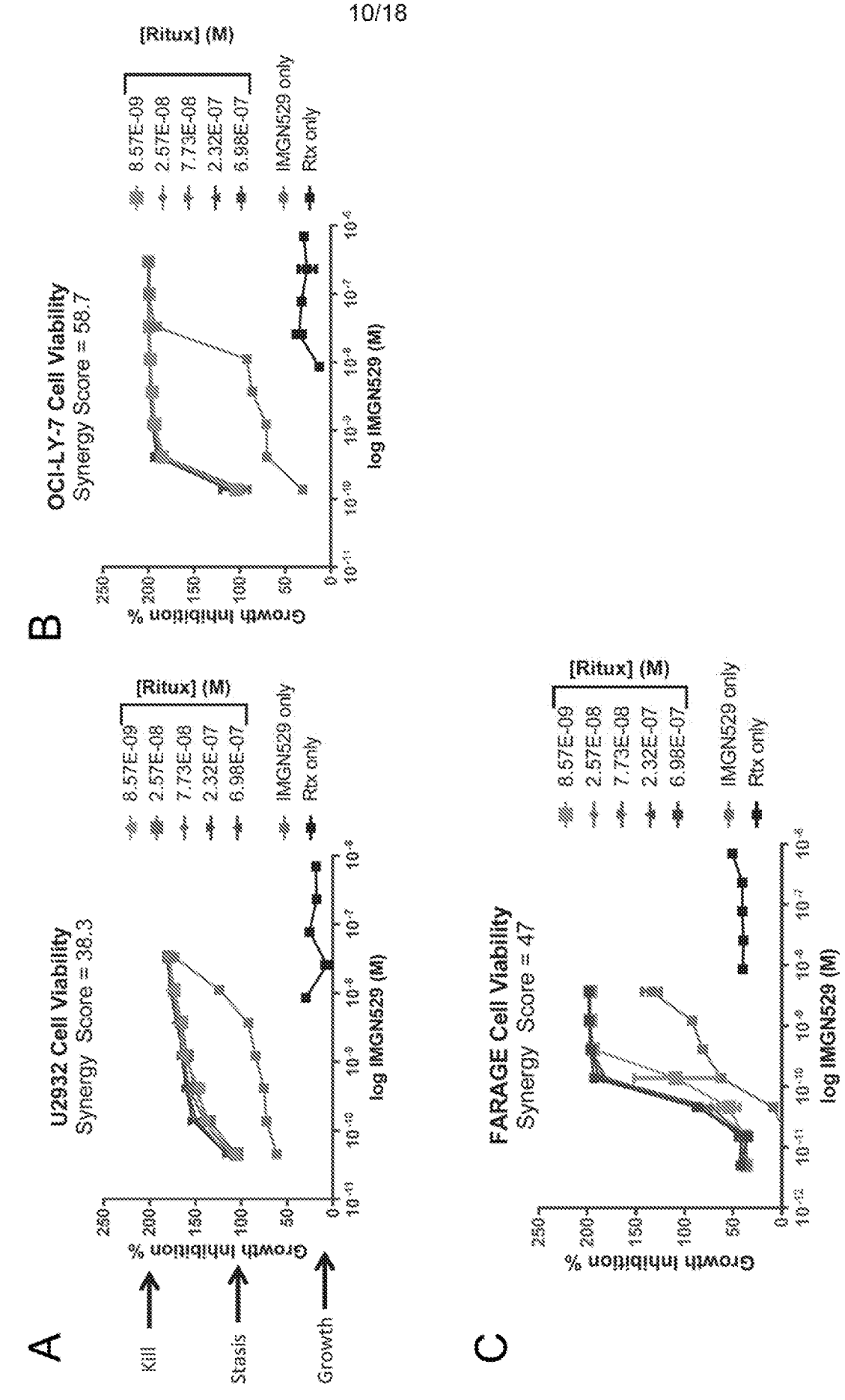
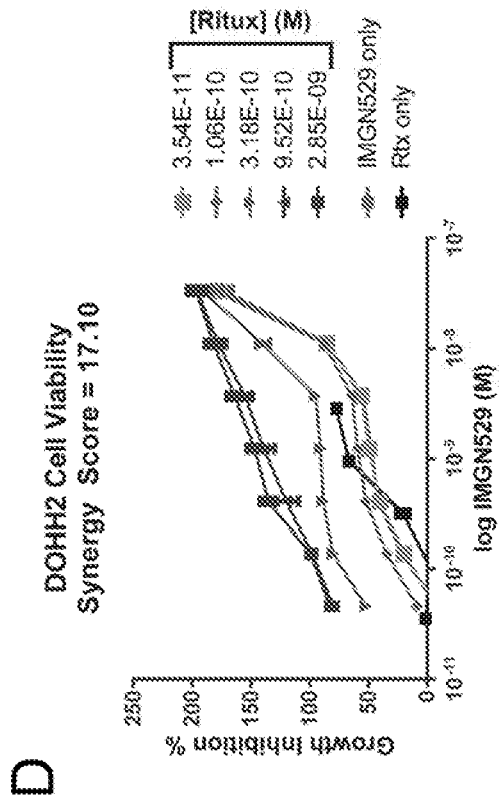

A
U2932 Cell Viability
Synergy Score = 38.3
Growth Inhibition %
log IMGN529 (M)
[Ritux] (M)
8.57E-09
2.57E-08
7.73E-08
2.32E-07
6.98E-07
IMGN529 only
Rtx only
Kill
Stasis
Growth
B
OCI-LY-7 Cell Viability
Synergy Score = 58.7
C
FARAGE Cell Viability
Synergy Score = 47

Figure 10


D
DOHH2 Cell Viability
Synergy Score = 17.10
Growth Inhibition %
log IMGN529 (M)
[Ritux] (M)
3.54E-11
1.06E-10
3.18E-10
9.52E-10
2.85E-09
IMGN529 only
Rtx only

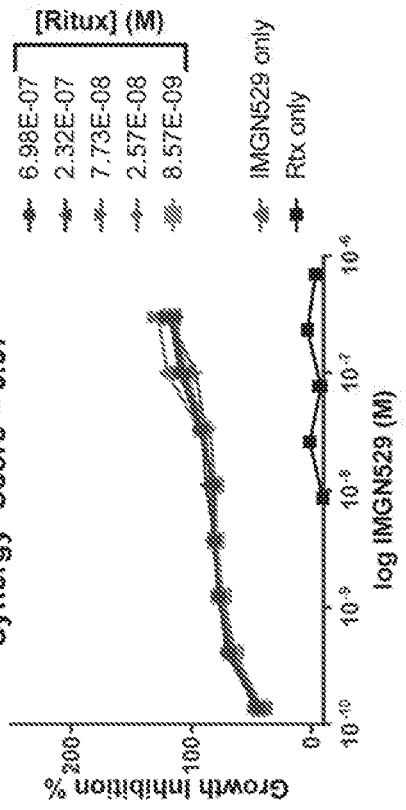

E
OCI-LY-10 Cell Viability
Synergy Score = 0.57
Growth Inhibition %
log IMGN529 (M)
[Ritux] (M)
6.98E-07
2.32E-07
7.73E-08
2.57E-08
8.57E-09
IMGN529 only
Rtx only

Figure 11

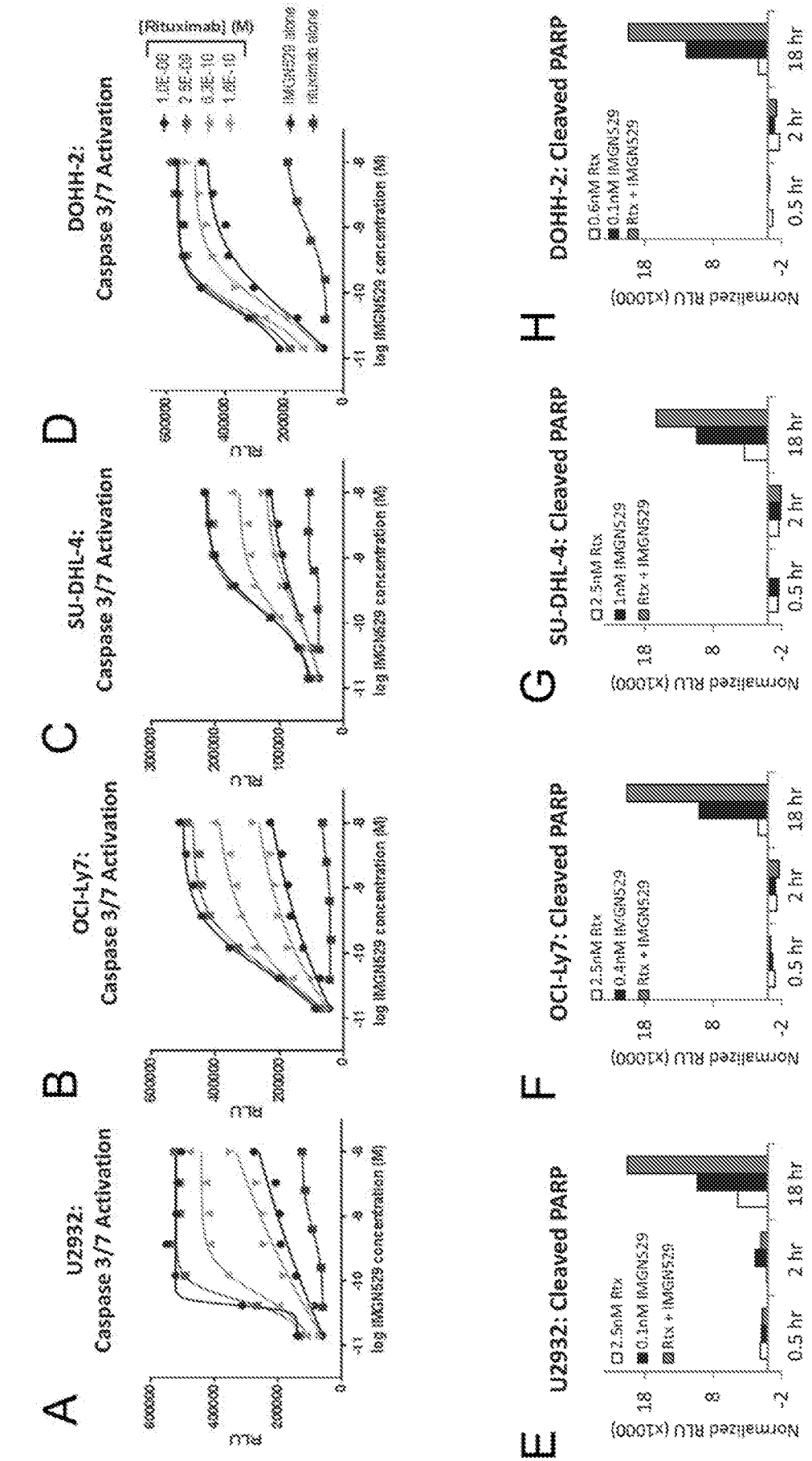
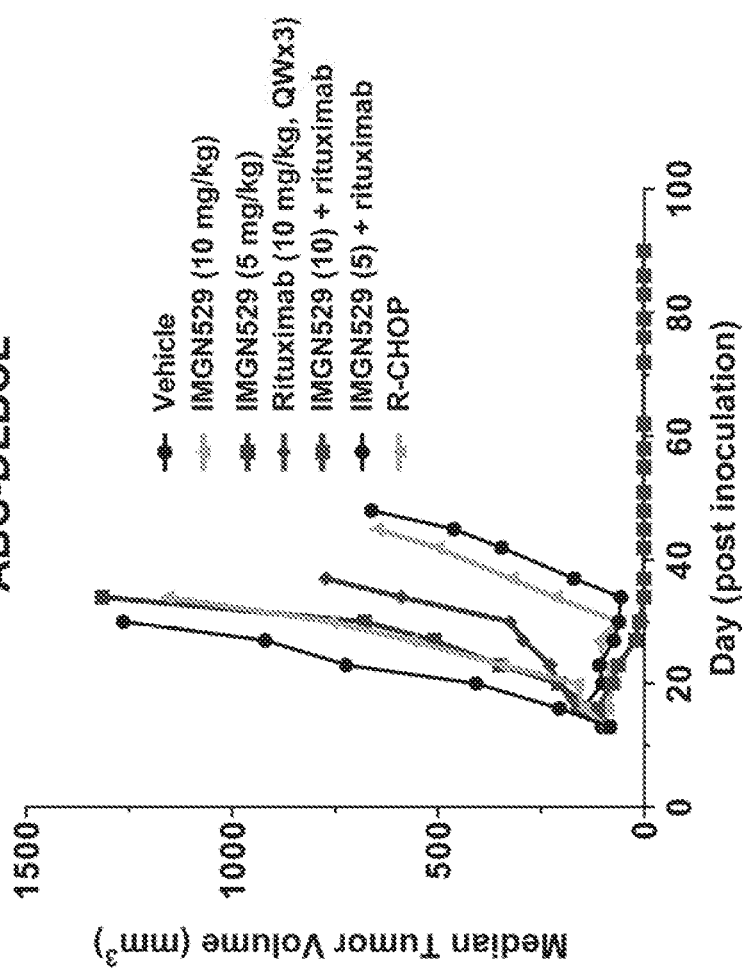

A
U2932:
Caspase 3/7 Activation
B
OCI-Ly7:
Caspase 3/7 Activation
C
SU-DHL-4:
Caspase 3/7 Activation
D
DOHH-2:
Caspase 3/7 Activation
RLU
log IMGN529 concentration (M)
(Rituximab) (M)
1.0E-08
2.5E-09
6.3E-10
1.6E-10
IMGN529 alone
rituximab alone
E
U2932: Cleaved PARP
F
OCI-Ly7: Cleaved PARP
G
SU-DHL-4: Cleaved PARP
H
DOHH-2: Cleaved PARP
Normalized RLU (x1000)
2.5nM Rtx
0.4nM IMGN529
0.1nM IMGN529
Rtx + IMGN529
0.5 hr
2 hr
18 hr

Figure 12



Treatment group	T/C	PR	CR
Vehicle	-	-	-
IMGN529 (10 mg/kg)	62%	0/8	0/8
IMGN529 (5 mg/kg)	55%	0/8	0/8
Rituximab (10 mg/kg, QWx3)	32%	1/8	0/8
IMGN529 (10 mg/kg) + rituximab	2%	7/8	6/8
IMGN529 (5 mg/kg) + rituximab	8%	4/8	4/8
R-CHOP	12%	4/8	2/8

Figure 13

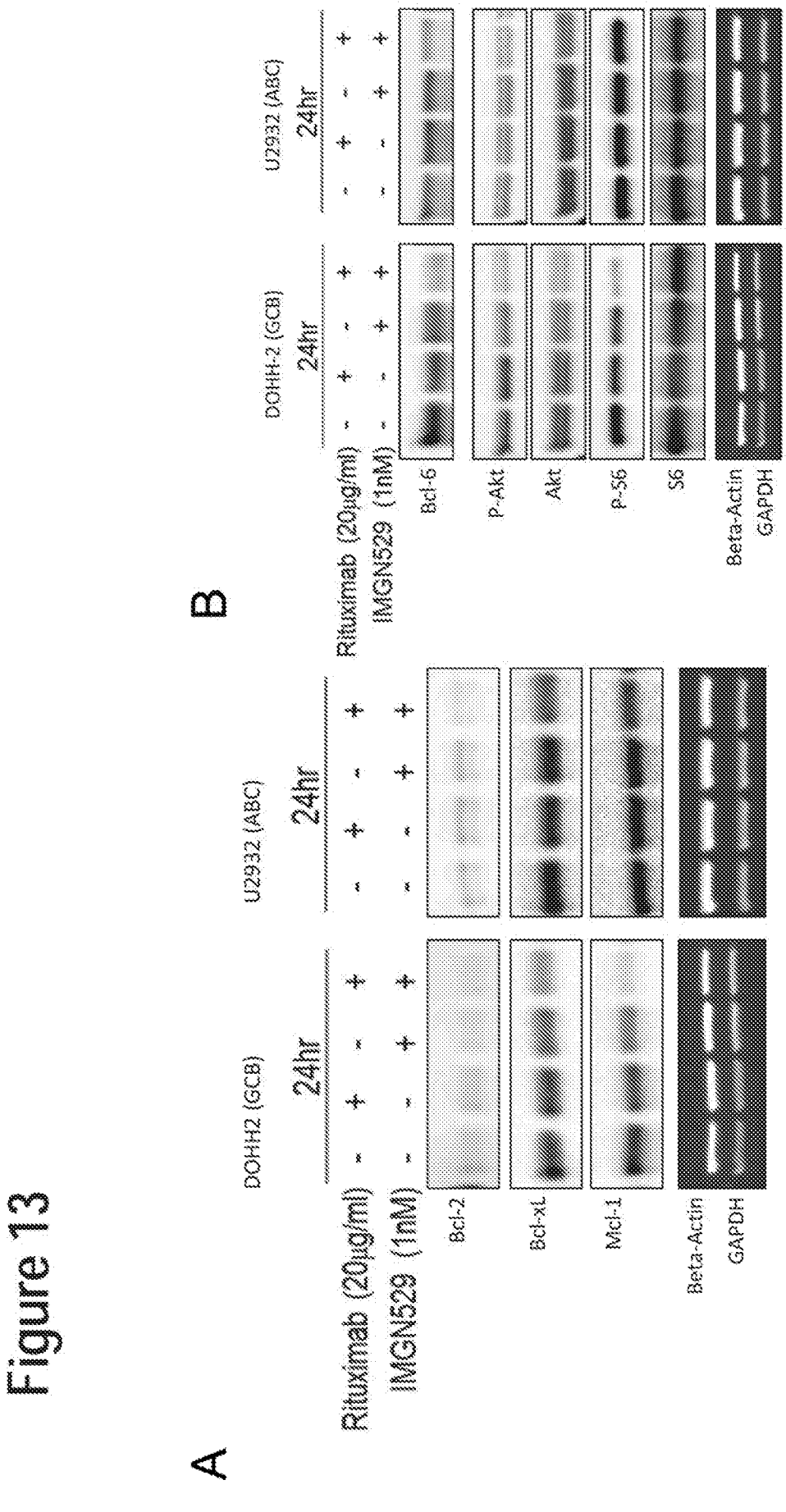
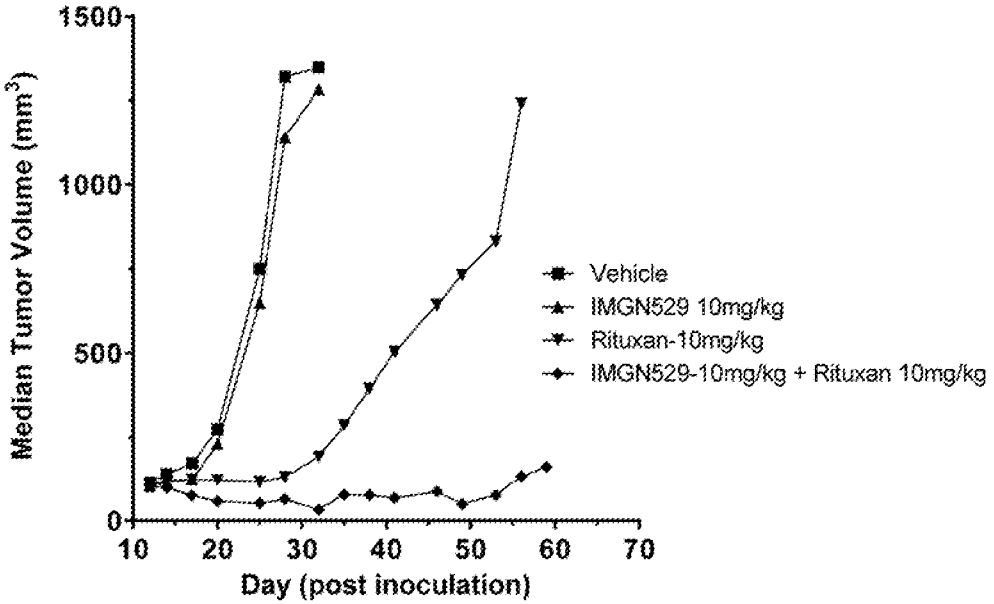

A
DOHH2 (GCB)
U2932 (ABC)
24hr
Rituximab (20μg/ml) - + - + - + - +
IMGN529 (1nM) - - + + - - + +
Bcl-2
Bcl-xL
Mcl-1
Beta-Actin
GAPDH
B
DOHH-2 (GCB)
U2932 (ABC)
24hr
Rituximab (20μg/ml) - + - + - + - +
IMGN529 (1nM) - - + + - - + +
Bcl-6
P-Akt
Akt
P-S6
S6
Beta-Actin
GAPDH

Figure 14



Group	Agent	Dosage/ injection (mg/kg)	Route	Dose schedule	Total dose (mg/kg)	Tx day	Mean BWL (nadir)	Time to reach 1000mm^3 (days)	% T/C	T-C	LCK	Regressions		TFS	Results
												Partial	Complete		
A	PBS	(0.2ml)	IV	single	-	-	-	26	-	-	-	-	-	-	-
B	IMGN529	10	IV	single	10	12	1% (D14)	27	88%	1	0.07	0/8	0/8	0/8	Inactive
C	Ritxuan	10	IV	single	10	12	-	50	12%	24	1.72	3/8	0/8	0/8	Active
D	IMGN529	10	IV	single	10	12	1% (D14)	44	0.1	18	1.3	6/8	2/8	1/8	Highly Active
	Ritxuan	10	IV	single	10	12									

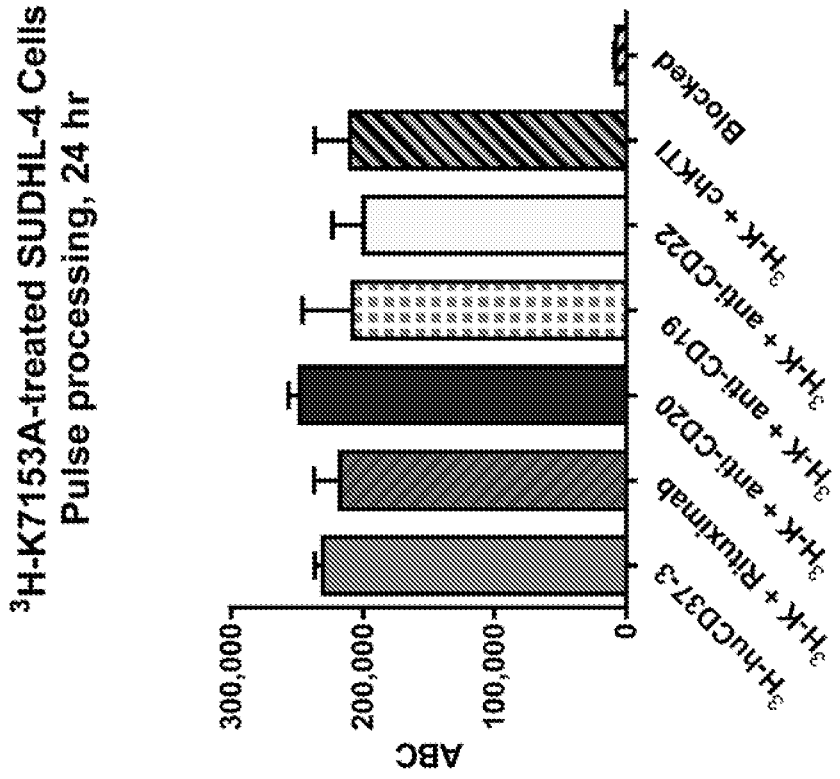

^{3}H-K7153A-treated SUDHL-4 Cells
Pulse processing, 24 hr
ABC
300,000
200,000
100,000
0
^{3}H-huCD37-3
^{3}H-K + Rituximab
^{3}H-K + anti-CD20
^{3}H-K + anti-CD19
^{3}H-K + anti-CD22
^{3}H-K + chKTI
Blocked

Figure 15

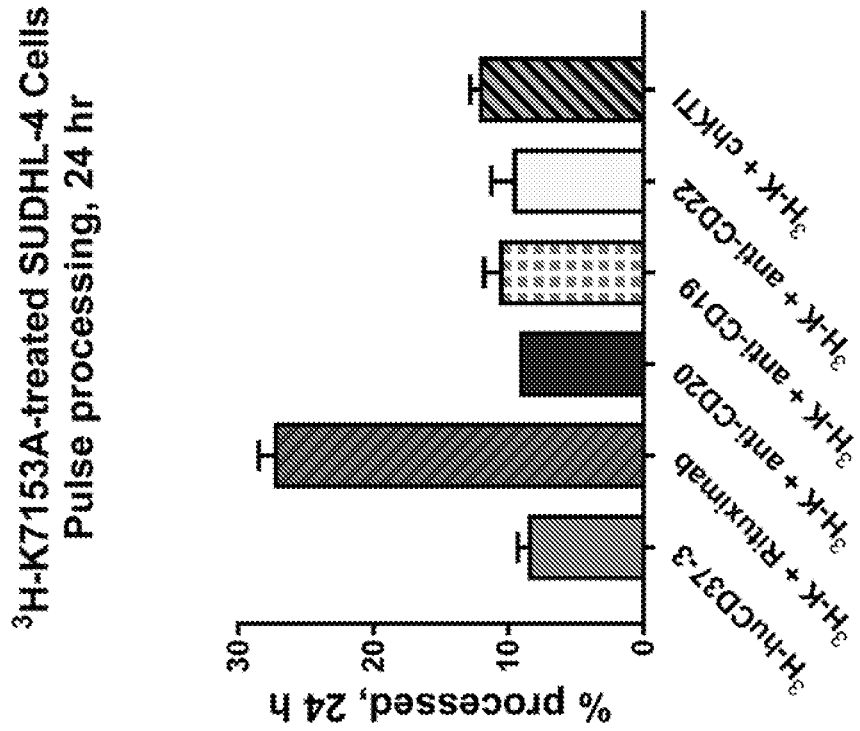
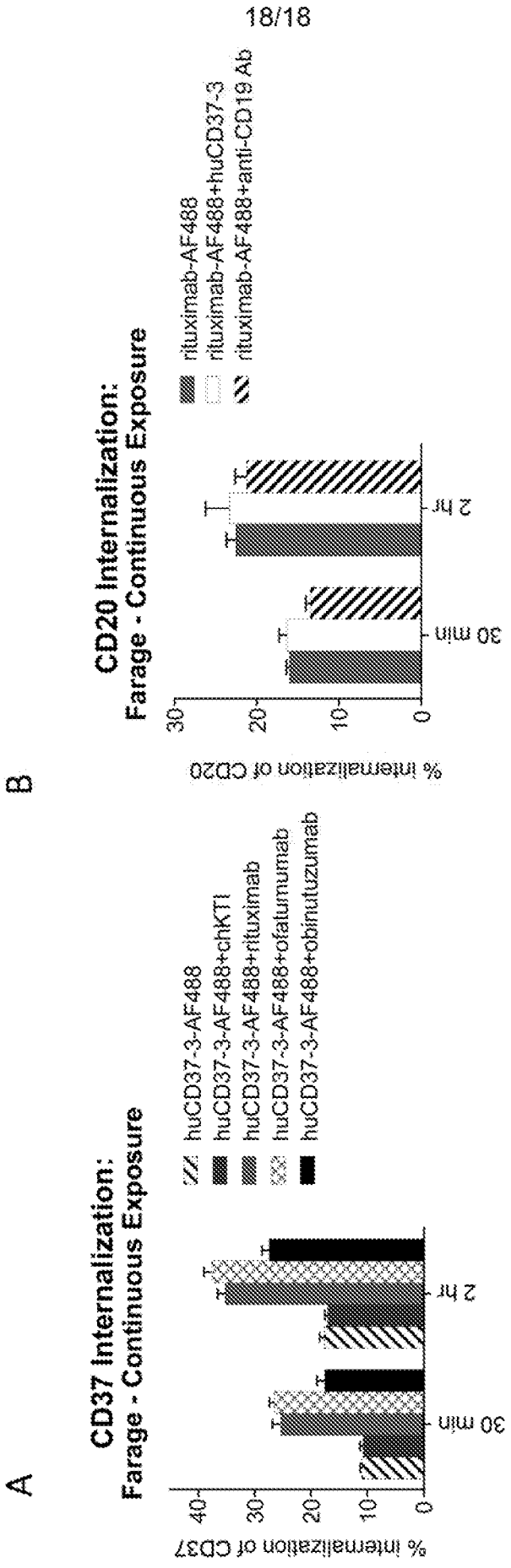

^{3}H-K7153A-treated SUDHL-4 Cells
Pulse processing, 24 hr
% processed, 24 h
0
10
20
30
^{3}H-huCD37-3
^{3}H-K + Rituximab
^{3}H-K + anti-CD20
^{3}H-K + anti-CD19
^{3}H-K + anti-CD22
^{3}H-K + chKT1

Figure 16

Figure 17


A
CD37 Internalization:
Farage - Continuous Exposure
% internalization of CD37
0
10
20
30
40
30 min
2 hr
huCD37-3-AF488
huCD37-3-AF488+chKTI
huCD37-3-AF488+rituximab
huCD37-3-AF488+ofatumumab
huCD37-3-AF488+obinutuzumab
B
CD20 Internalization:
Farage - Continuous Exposure
% internalization of CD20
0
10
20
30
30 min
2 hr
rituximab-AF488
rituximab-AF488+huCD37-3
rituximab-AF488+anti-CD19 Ab