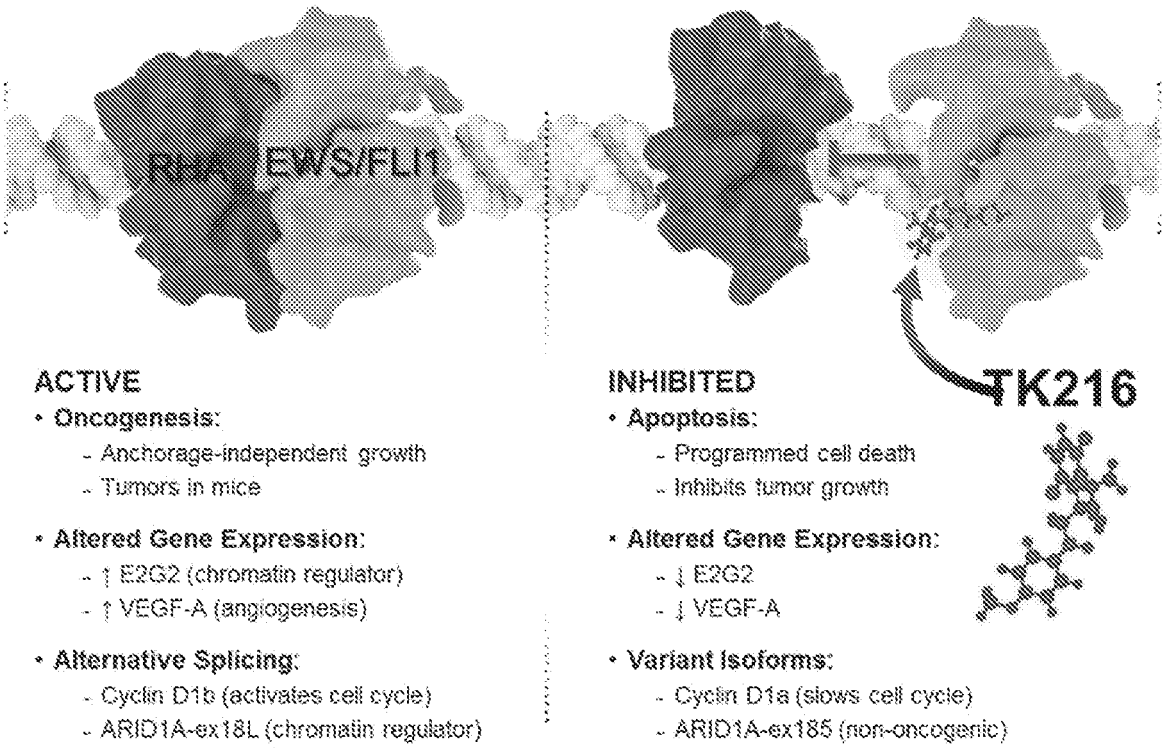

RHA
EWS/FLI1
TK216
ACTIVE
• Oncogenesis:
- Anchorage-independent growth
- Tumors in mice
• Altered Gene Expression:
- ↑ E2G2 (chromatin regulator)
- ↑ VEGF-A (angiogenesis)
• Alternative Splicing:
- Cyclin D1b (activates cell cycle)
- ARID1A-ex18L (chromatin regulator)
INHIBITED
• Apoptosis:
- Programmed cell death
- Inhibits tumor growth
• Altered Gene Expression:
- ↓ E2G2
- ↓ VEGF-A
• Variant Isoforms:
- Cyclin D1a (slows cell cycle)
- ARID1A-ex185 (non-oncogenic)

FIG. 1

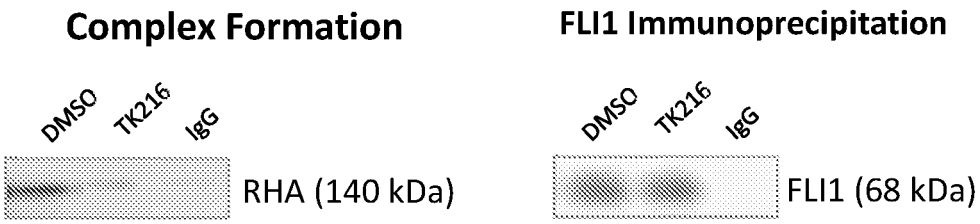

Complex Formation
DMSO
TK216
IgG
RHA (140 kDa)
FLI1 Immunoprecipitation
DMSO
TK216
IgG
FLI1 (68 kDa)

FIG. 2

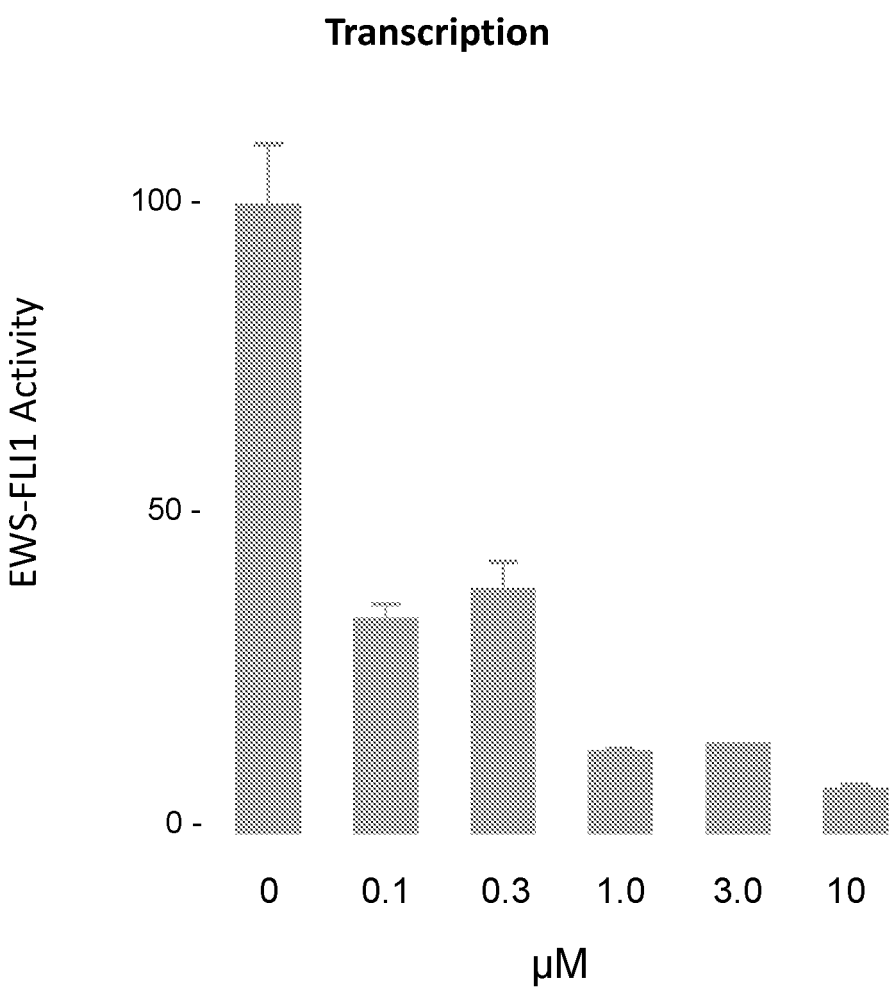


FIG. 3

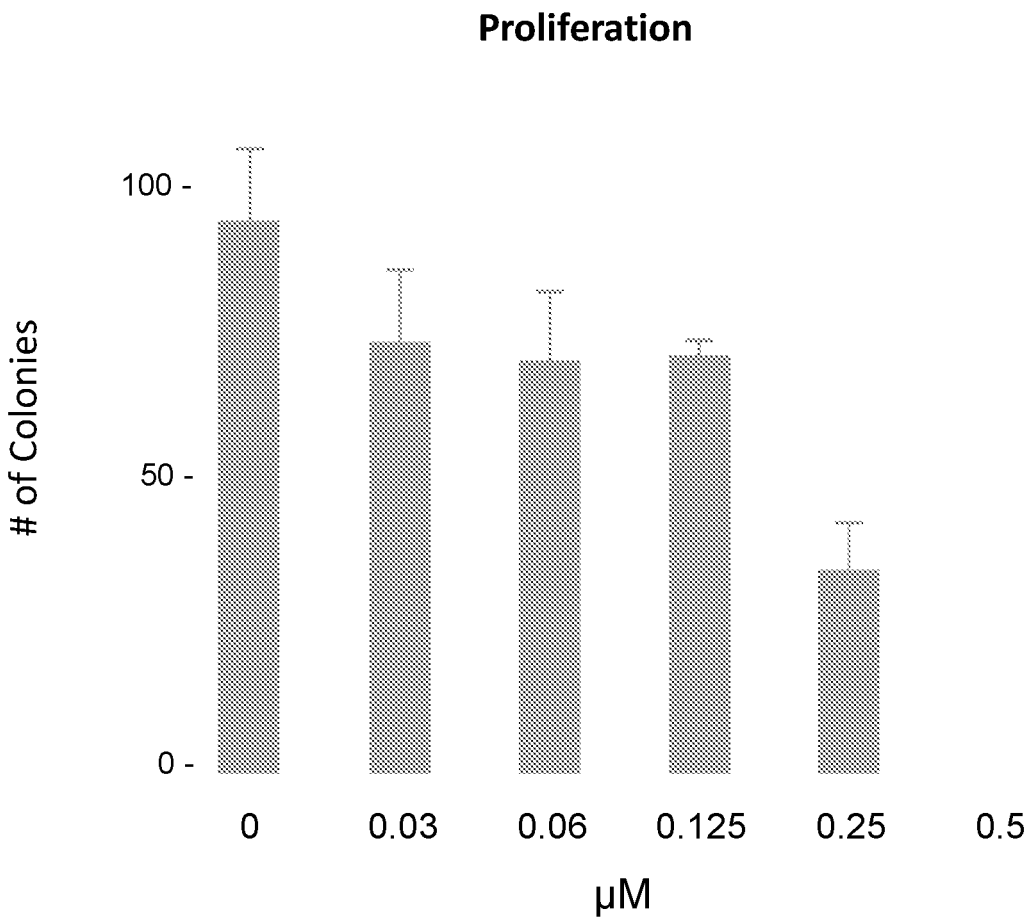


FIG. 4

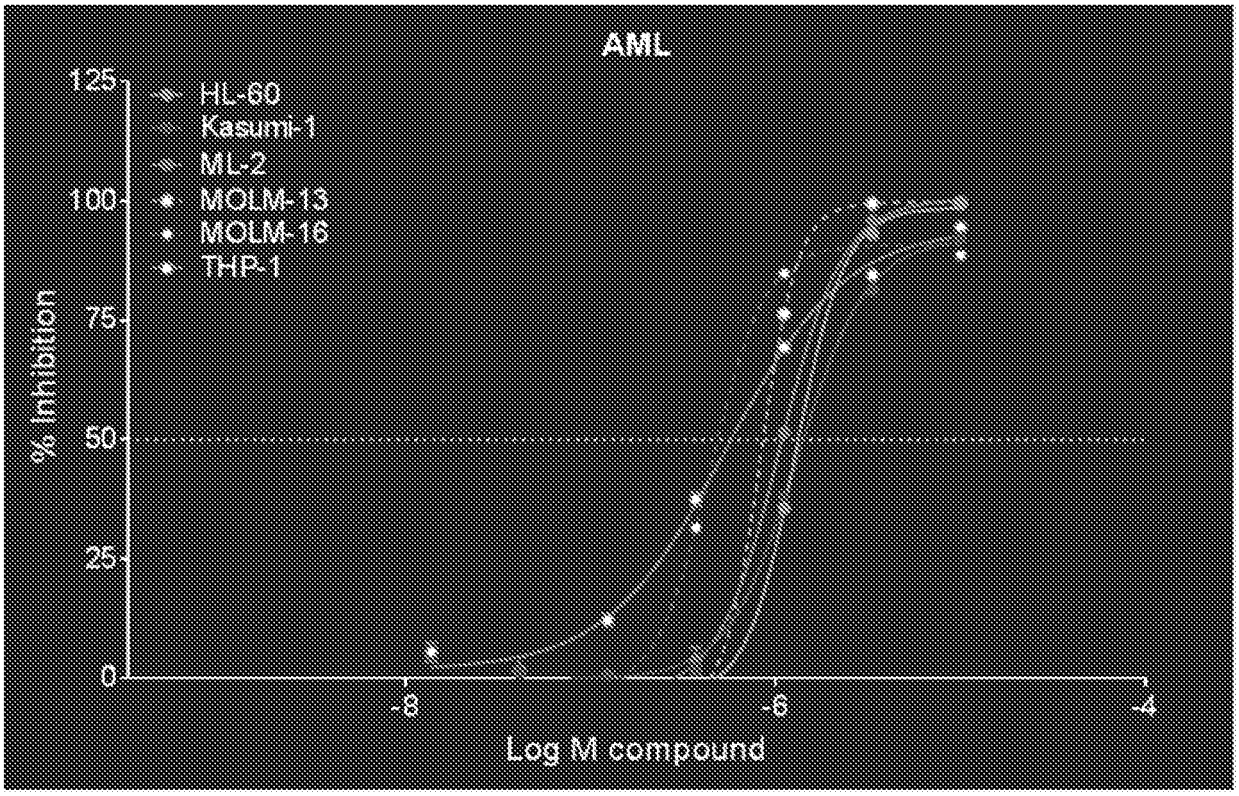

AML
HL-60
Kasumi-1
ML-2
MOLM-13
MOLM-16
THP-1
% Inhibition
125
100
75
50
25
0
-8
-6
-4
Log M compound

FIG. 5

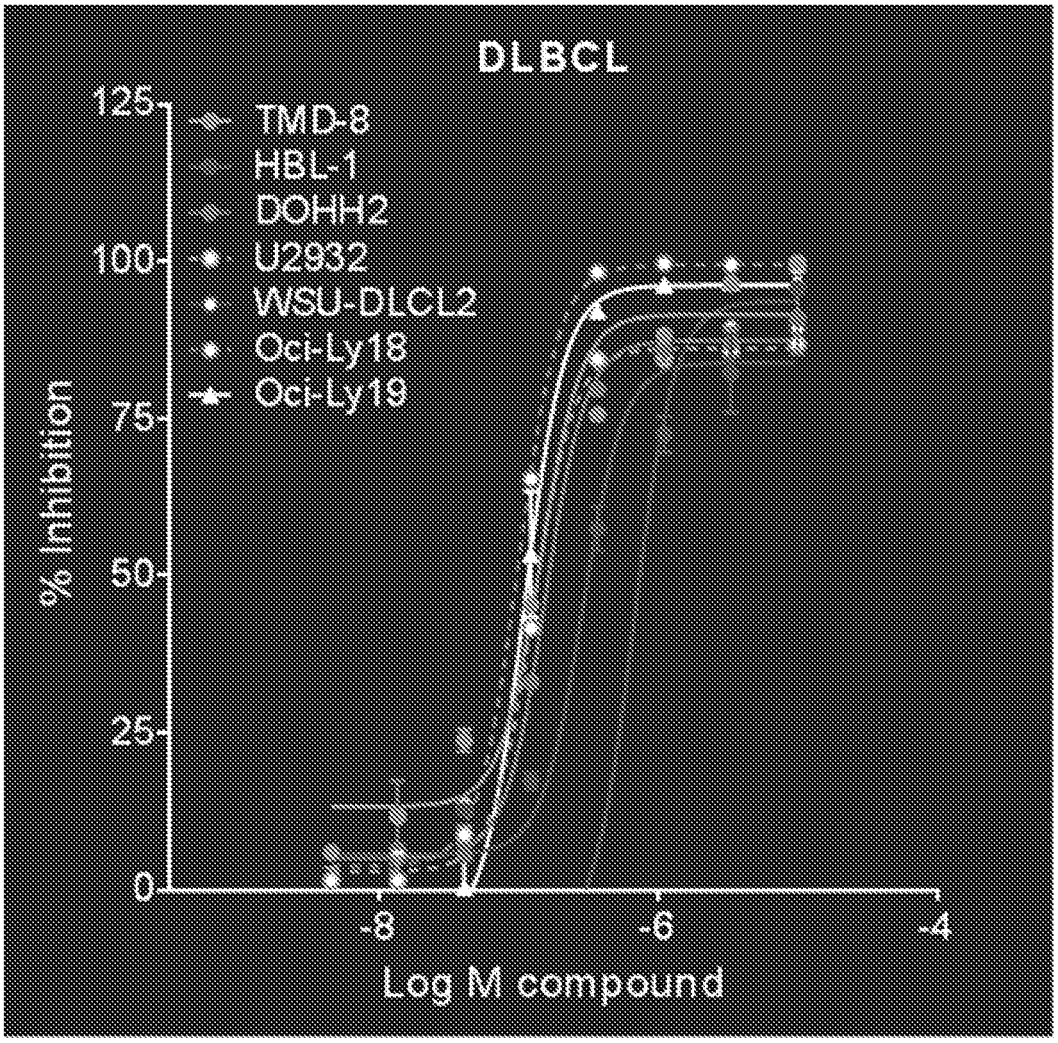

DLBCL
125
100
75
50
25
0
% Inhibition
TMD-8
HBL-1
DOHH2
U2932
WSU-DLCL2
Oci-Ly18
Oci-Ly19
-8
-6
-4
Log M compound

FIG. 6

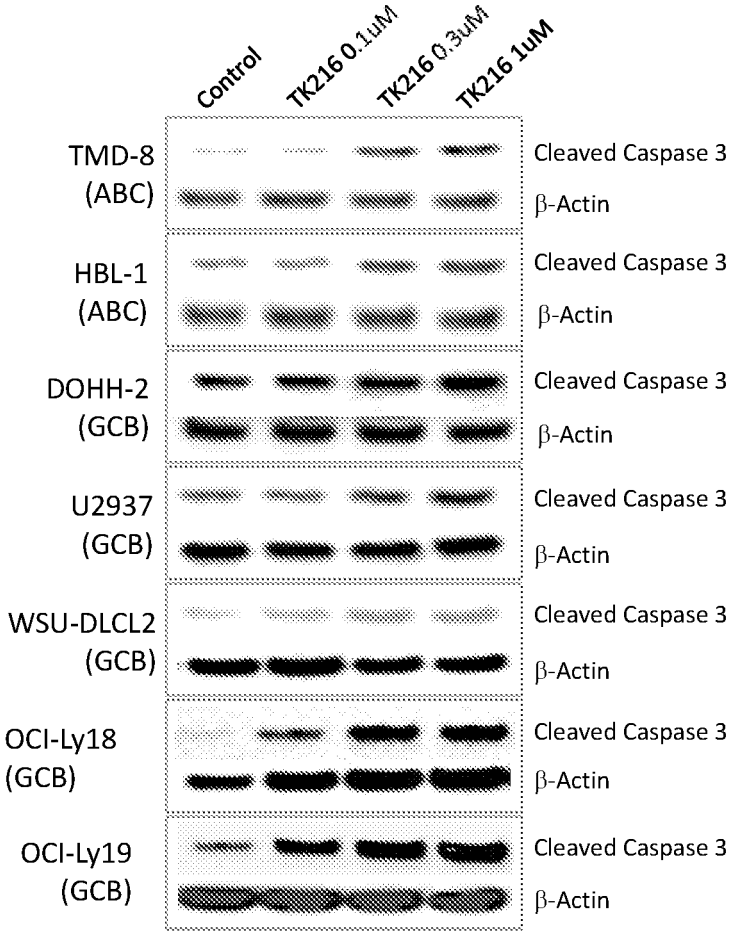

Control
TK216 0.1uM
TK216 0.3uM
TK216 1uM
TMD-8 (ABC)
HBL-1 (ABC)
DOHH-2 (GCB)
U2937 (GCB)
WSU-DLCL2 (GCB)
OCI-Ly18 (GCB)
OCI-Ly19 (GCB)
Cleaved Caspase 3
β-Actin

FIG. 7

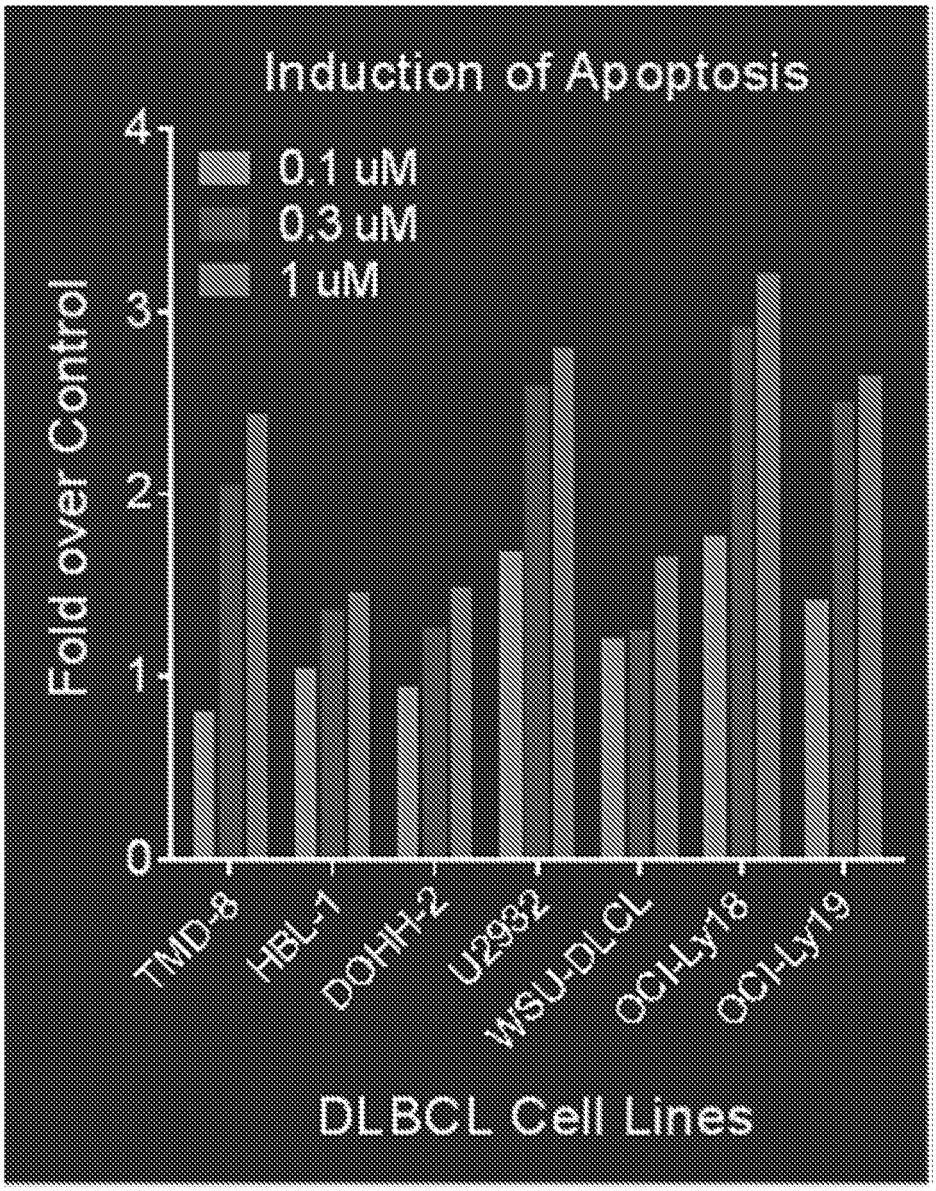

Induction of Apoptosis
0.1 uM
0.3 uM
1 uM
Fold over Control
0
1
2
3
4
TMD-8
HBL-1
DOHH-2
U2932
WSU-DLCL
OCI-Ly18
OCI-Ly19
DLBCL Cell Lines

FIG. 8

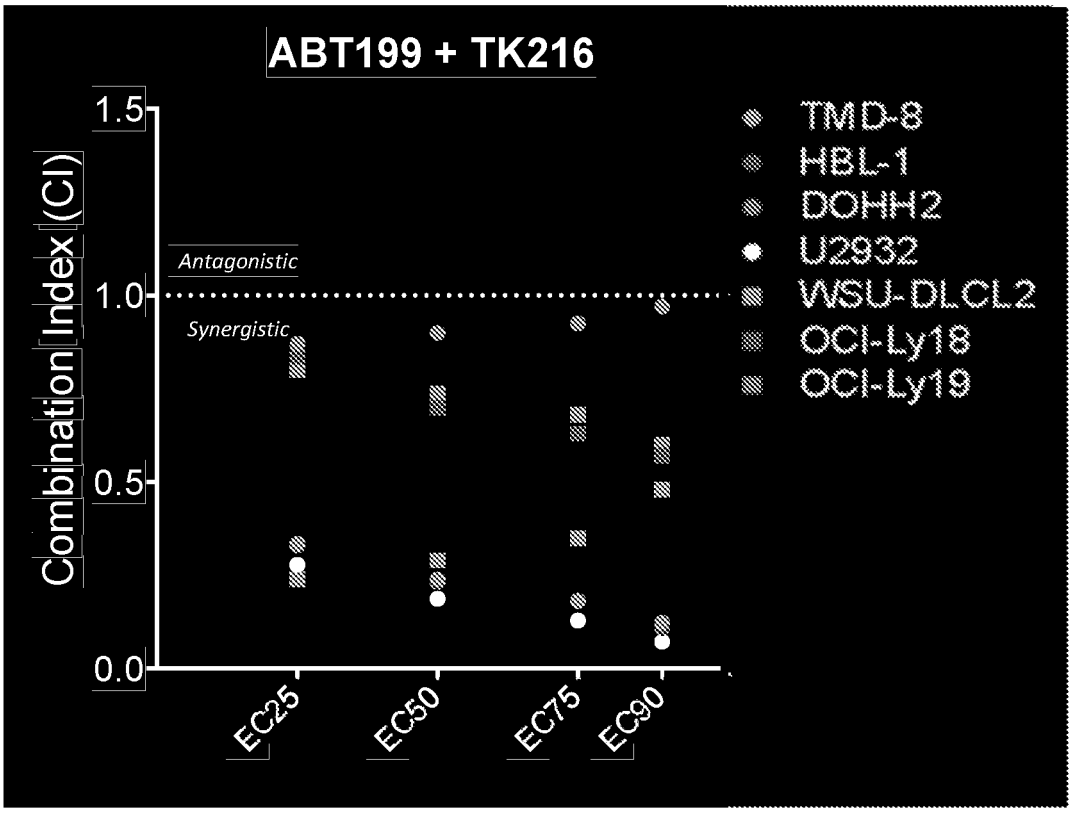

ABT199 + TK216
Combination Index (CI)
1.5
1.0
0.5
0.0
Antagonistic
Synergistic
EC25
EC50
EC75
EC90
TMD-8
HBL-1
DOHH2
U2932
WSU-DLCL2
OCI-Ly18
OCI-Ly19

FIG. 9

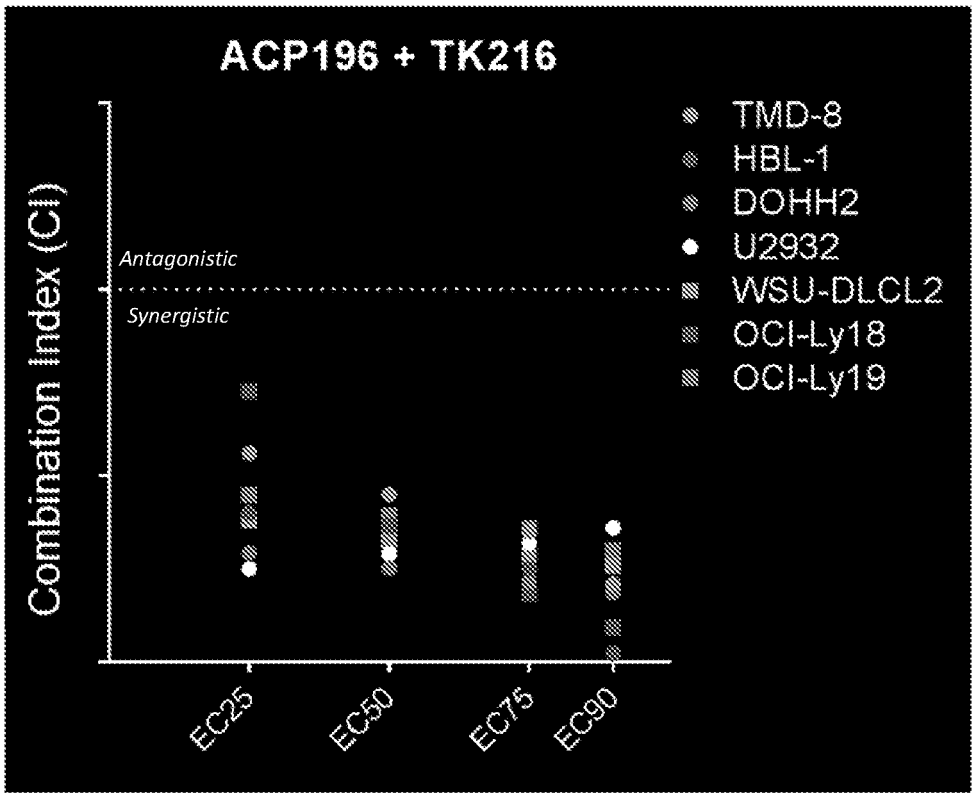

ACP196 + TK216
Combination Index (CI)
Antagonistic
Synergistic
TMD-8
HBL-1
DOHH2
U2932
WSU-DLCL2
OCI-Ly18
OCI-Ly19
EC25
EC50
EC75
EC90

FIG. 10

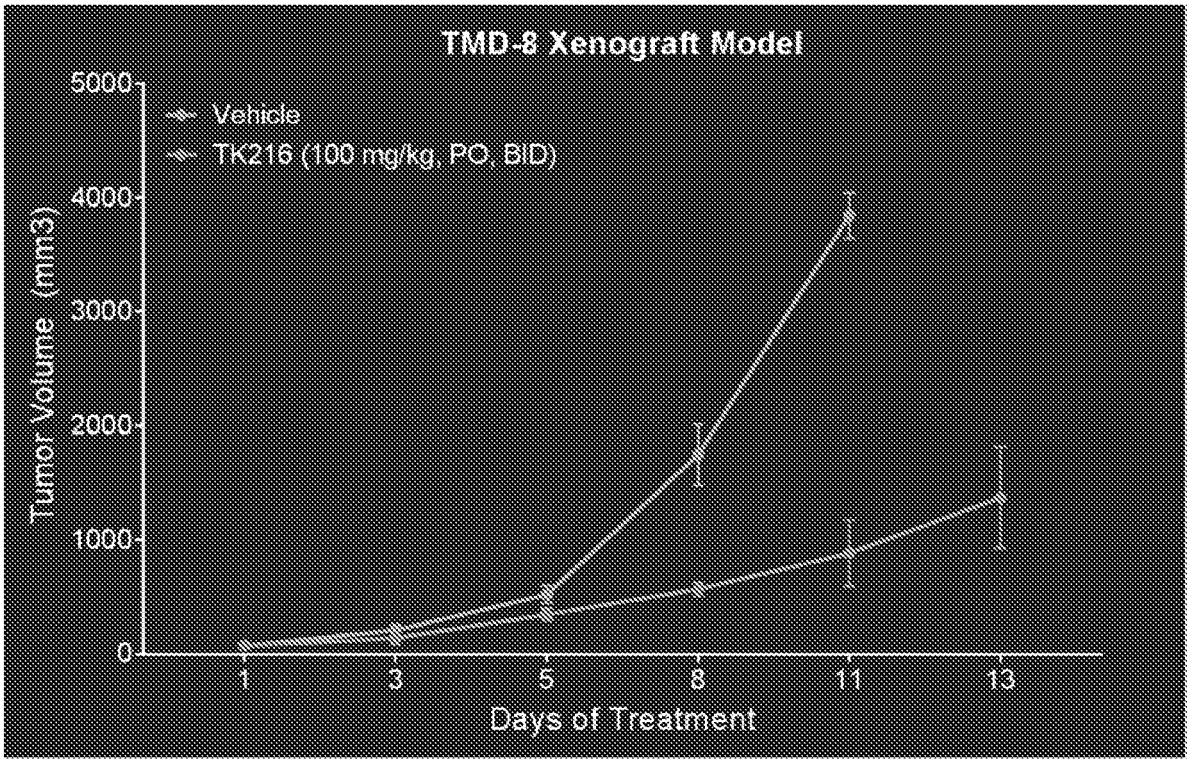

TMD-8 Xenograft Model
Vehicle
TK216 (100 mg/kg, PO, BID)
Tumor Volume (mm3)
5000
4000
3000
2000
1000
0
1
3
5
8
11
13
Days of Treatment

FIG. 11

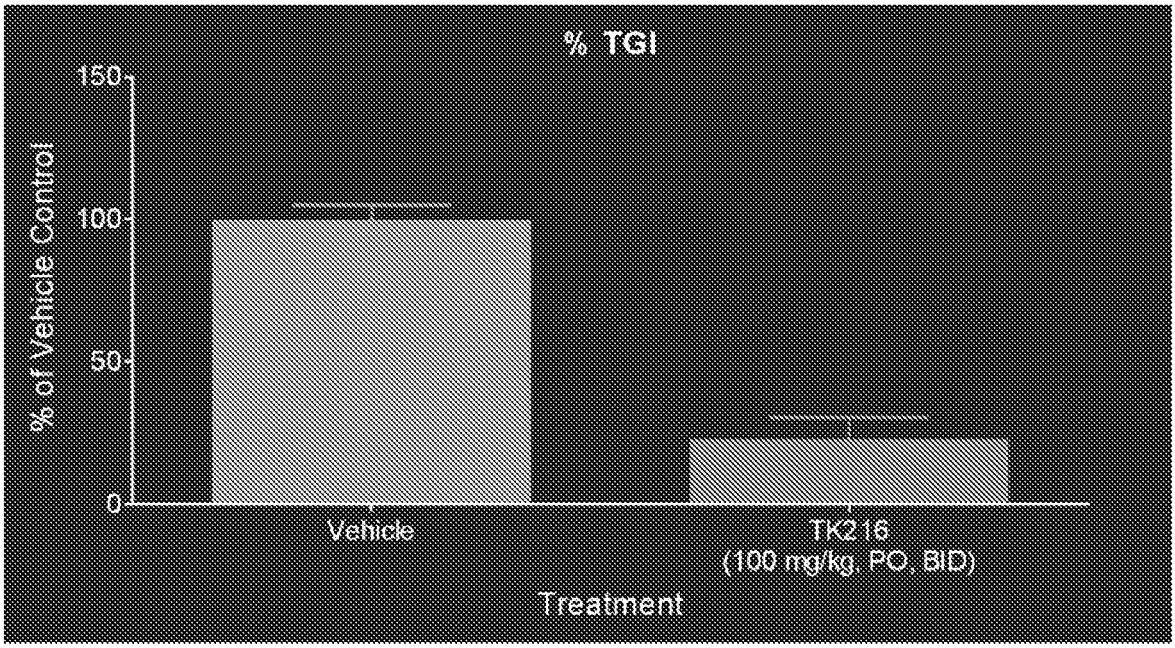

% TGI
150
100
50
0
% of Vehicle Control
Vehicle
TK216
(100 mg/kg, PO, BID)
Treatment

FIG. 12

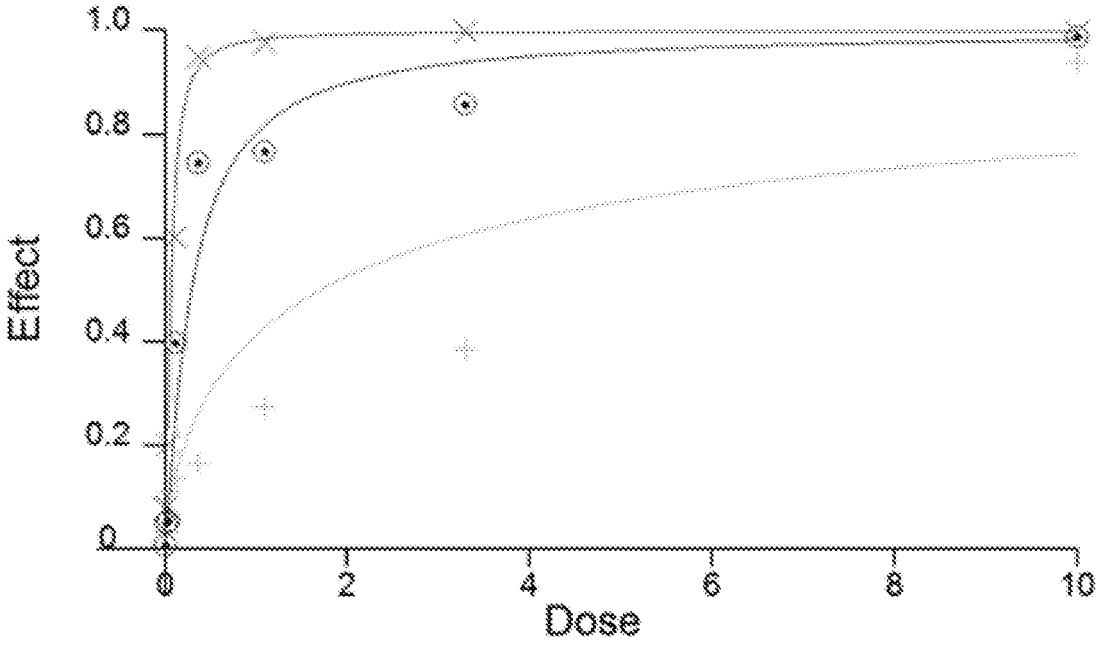


FIG. 13

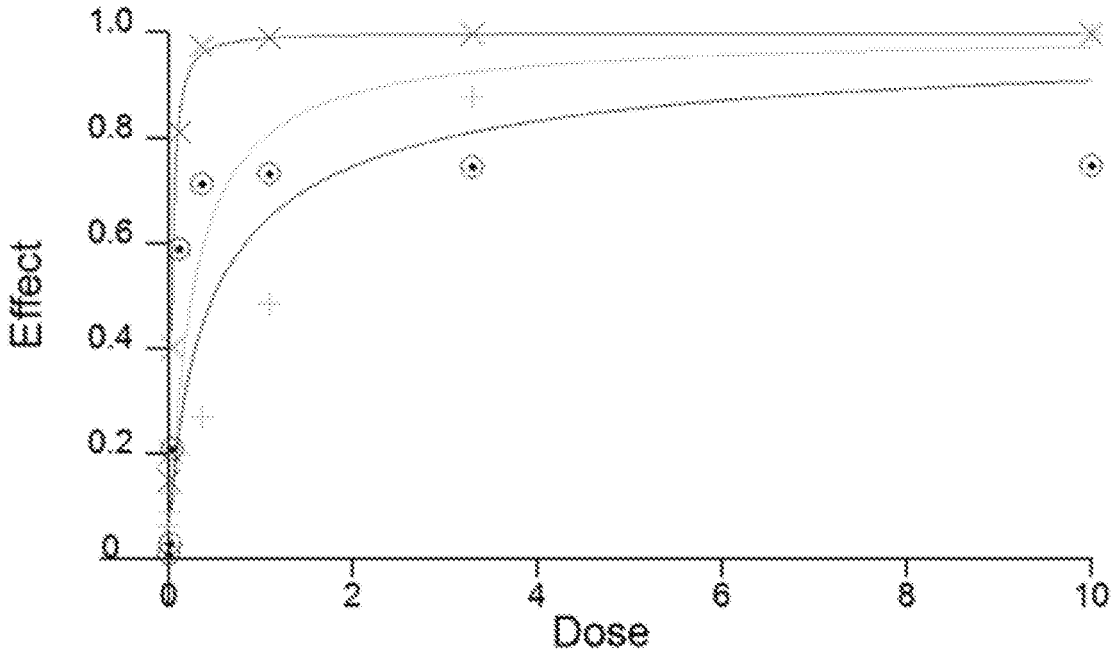


FIG. 14

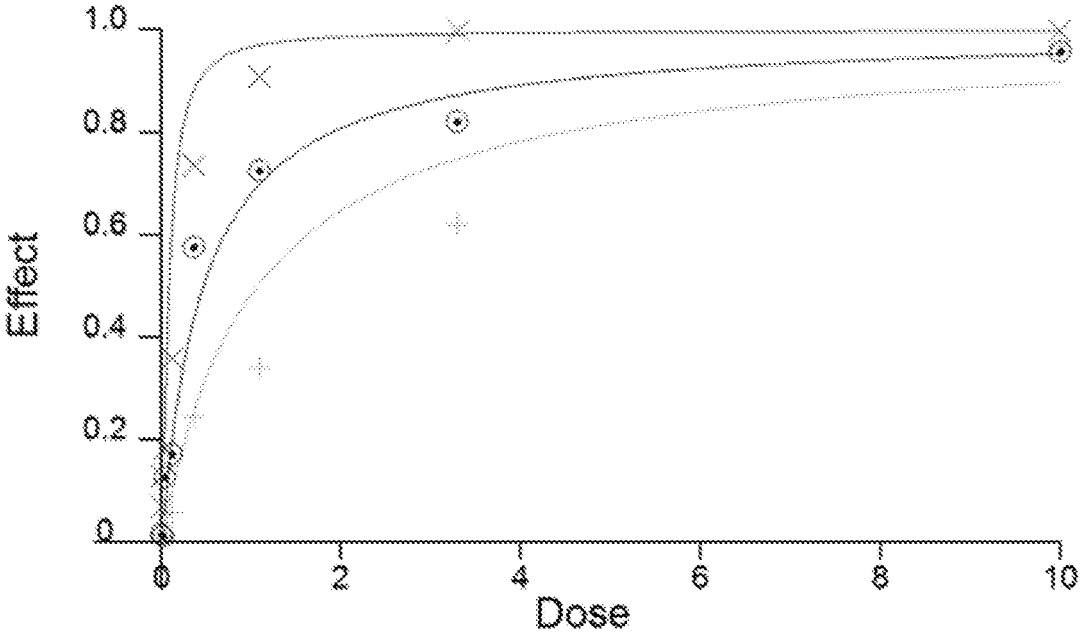


FIG. 15

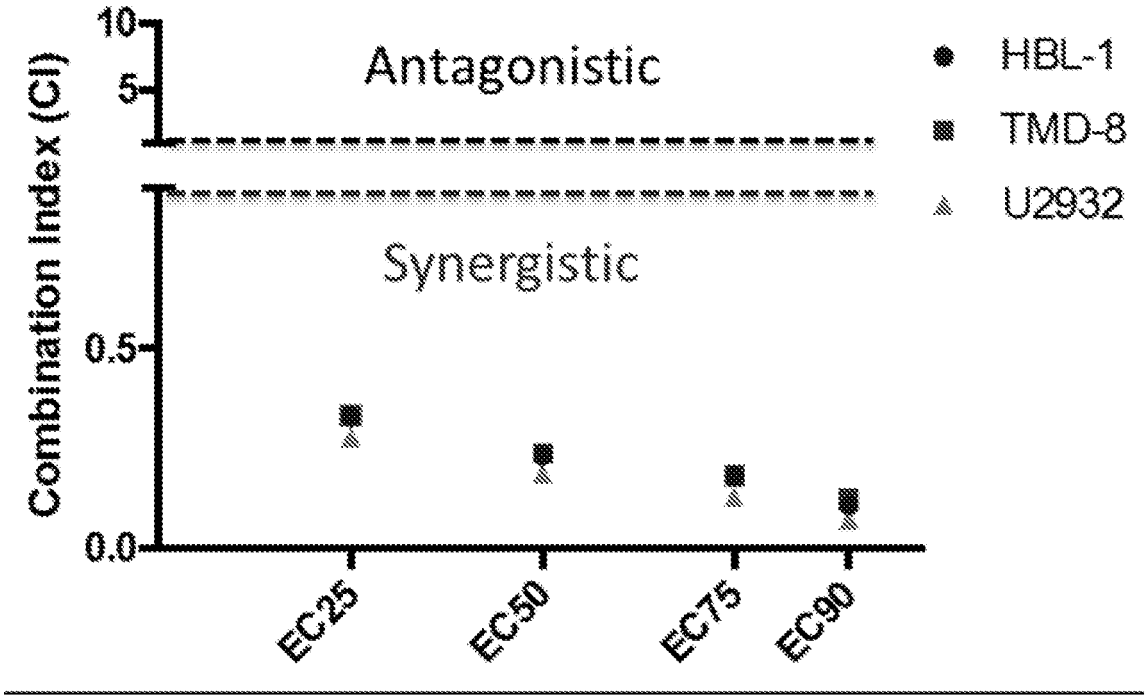

Combination Index (CI)
10
5
0.5
0.0
Antagonistic
Synergistic
HBL-1
TMD-8
U2932
EC25
EC50
EC75
EC90

FIG. 16

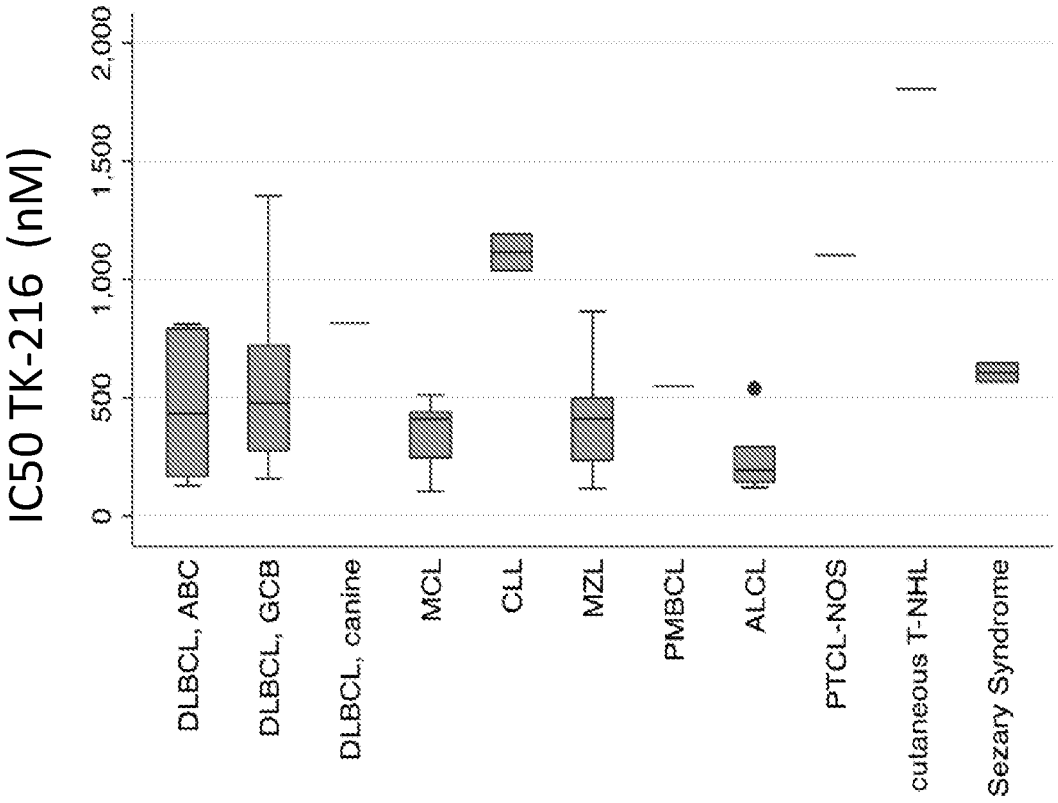

IC50 TK-216 (nM)
0
500
1,000
1,500
2,000
DLBCL, ABC
DLBCL, GCB
DLBCL, canine
MCL
CLL
MZL
PMBCL
ALCL
PTCL-NOS
cutaneous T-NHL
Sezary Syndrome

FIG. 17

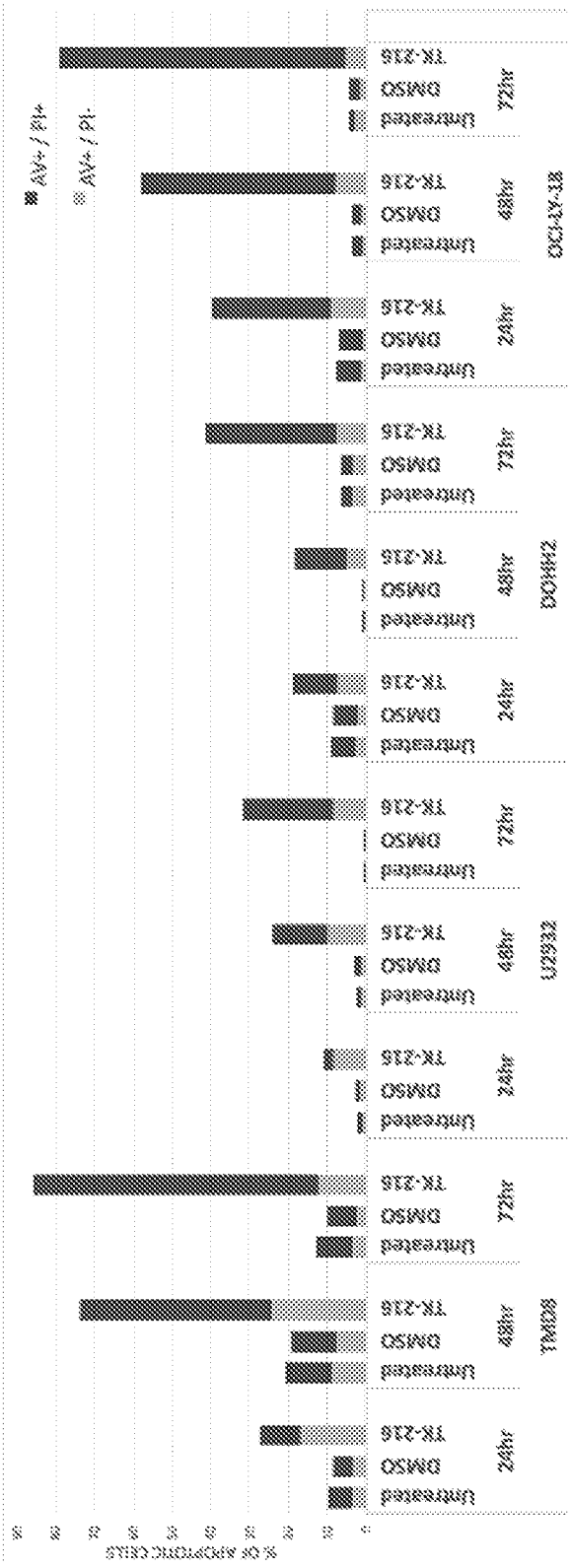

AV+ / PI+
AV+ / PI-
% OF APOPTOTIC CELLS
OCI-AY-3B
DOHH2
U2932
YMD8
72hr
48hr
24hr
untreated
DMSO
TK-216

FIG. 18A

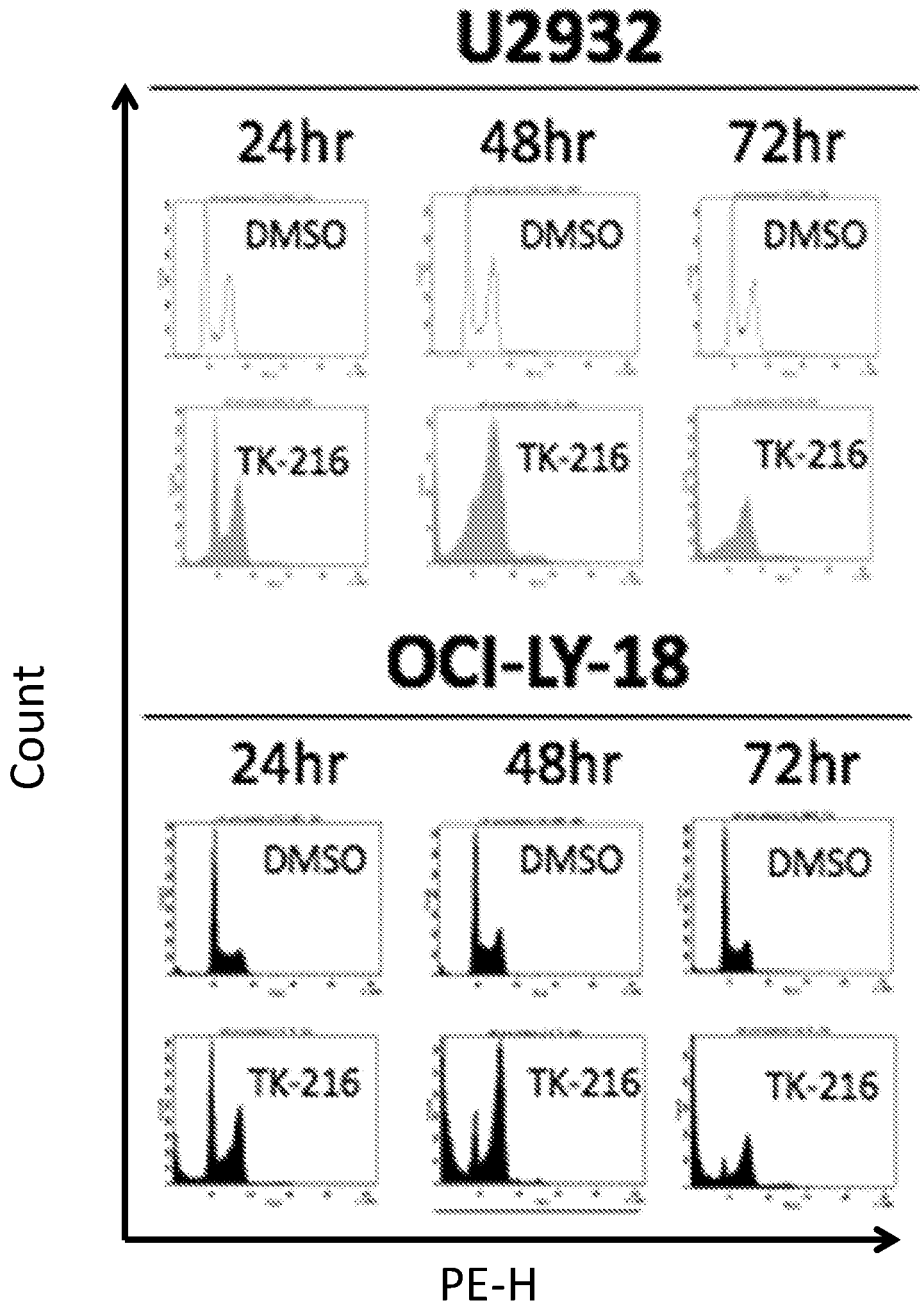

U2932
24hr
48hr
72hr
DMSO
DMSO
DMSO
TK-216
TK-216
TK-216
OCI-LY-18
24hr
48hr
72hr
DMSO
DMSO
DMSO
TK-216
TK-216
TK-216
Count
PE-H

FIG. 18B

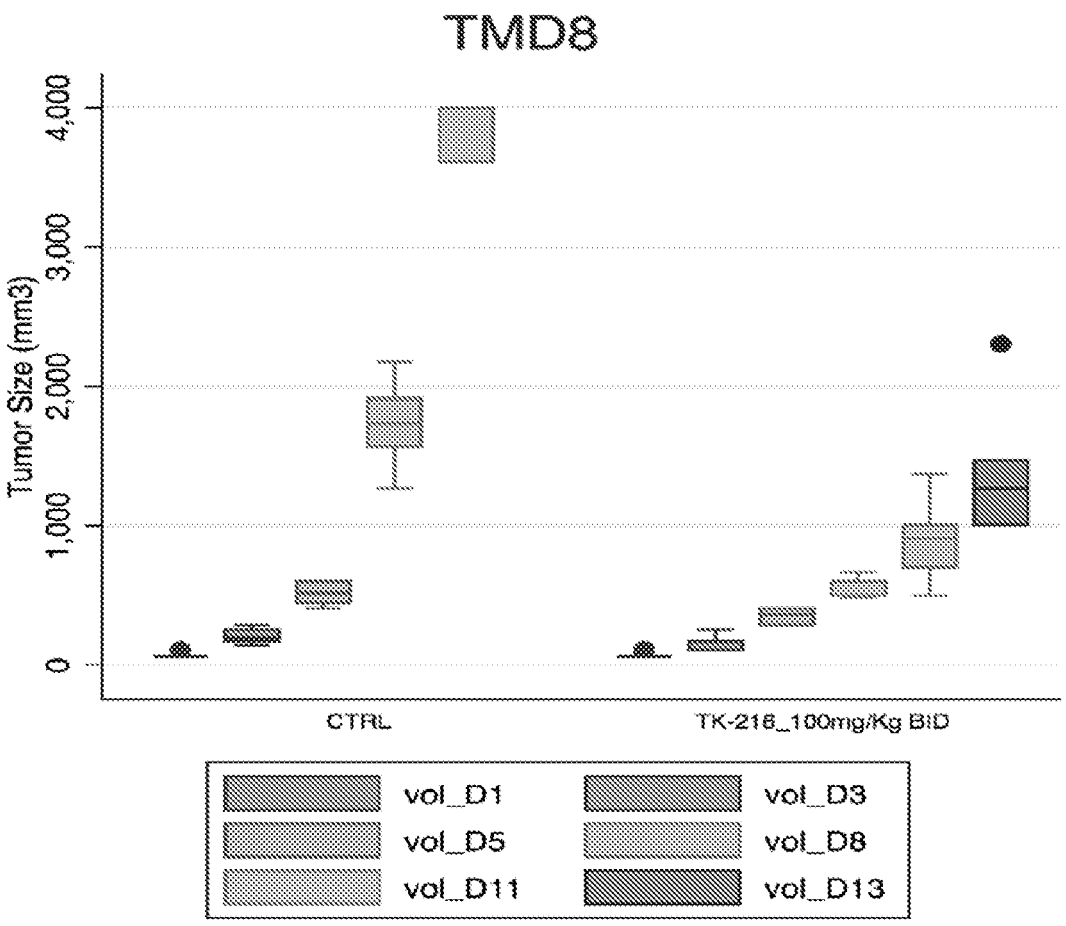

TMD8
Tumor Size (mm3)
0
1,000
2,000
3,000
4,000
CTRL
TK-216_100mg/Kg BID
vol_D1
vol_D3
vol_D5
vol_D8
vol_D11
vol_D13

FIG. 19

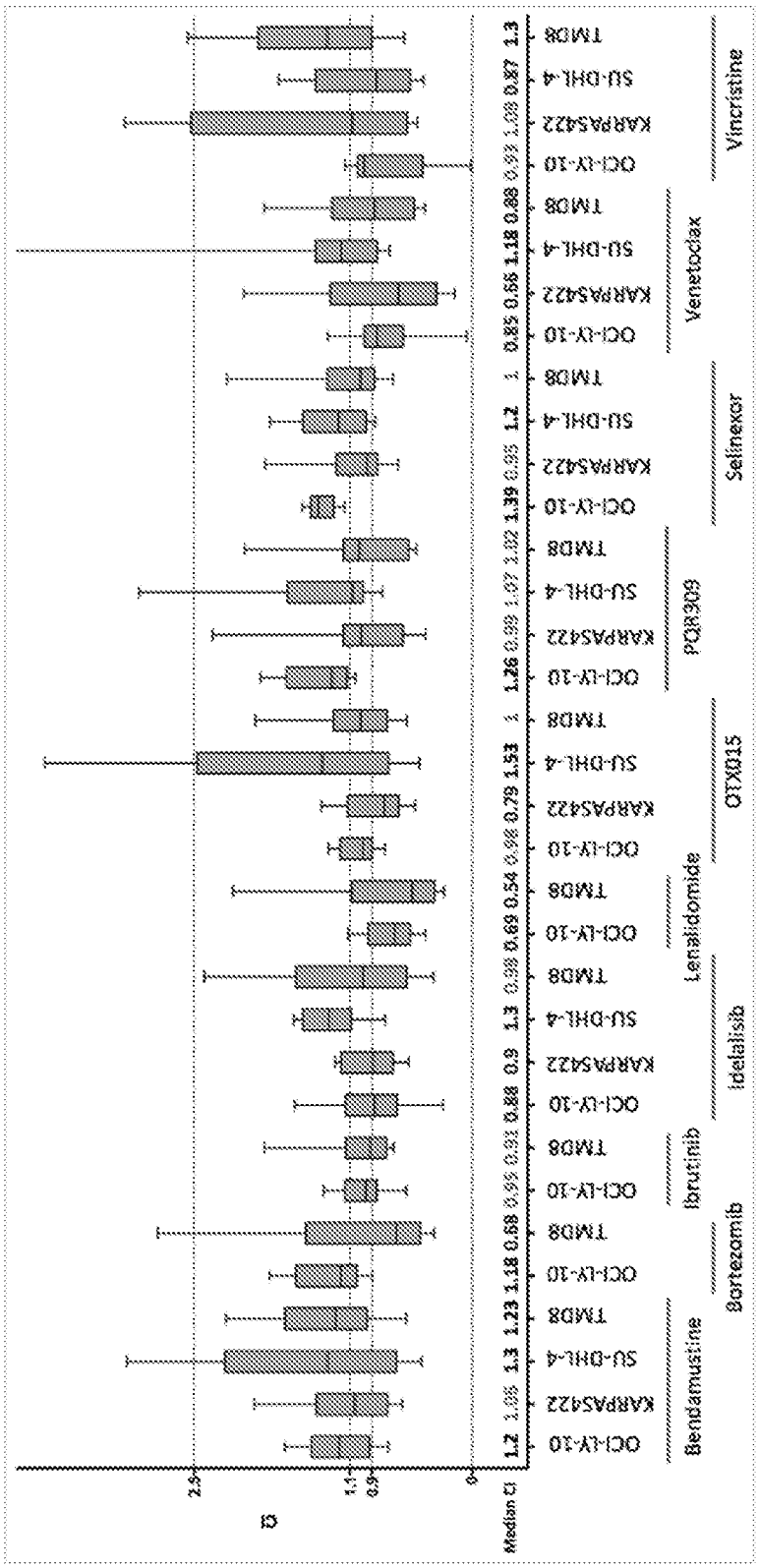

Bendamustine
Bortezomib
Ibrutinib
Idelalisib
Lenalidomide
OTX015
PCI32909
Selinexor
Venetoclax
Vincristine
Median CI
2.9
1.1
0.9
0
IC

FIG. 20