FIG. 1

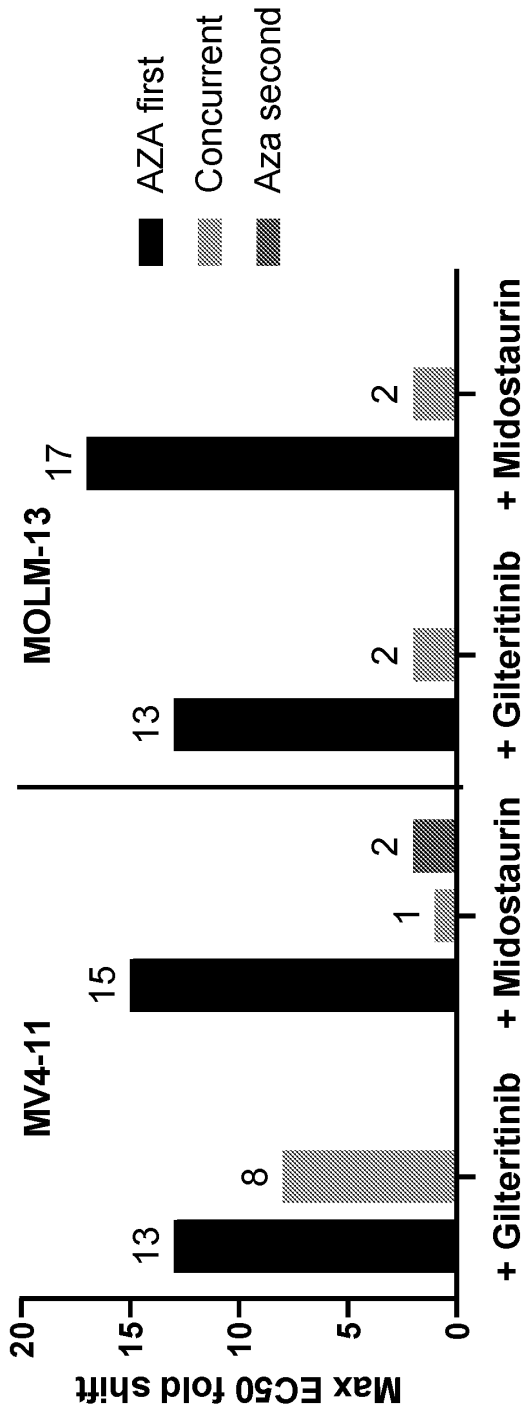

AZA first
Concurrent
Aza second
Max EC50 fold shift
0
5
10
15
20
MV4-11
MOLM-13
13
8
15
1
2
13
2
17
2
+ Gilteritinib
+ Midostaurin
+ Gilteritinib
+ Midostaurin

FIG. 2

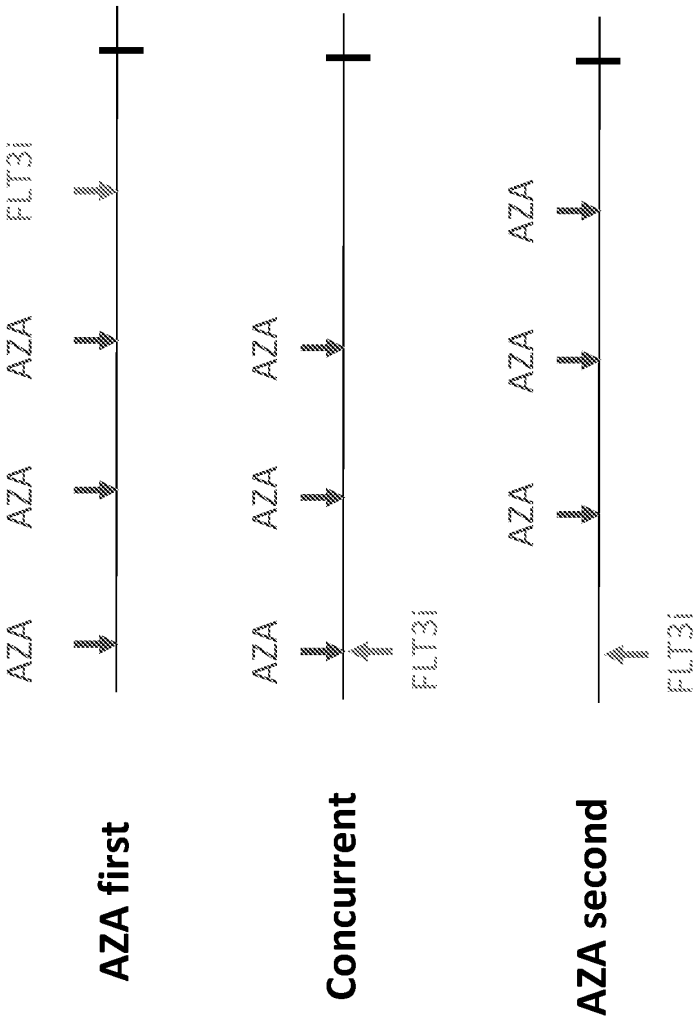

AZA
AZA
AZA
FLT3i
AZA first
AZA
AZA
AZA
FLT3i
Concurrent
AZA
AZA
AZA
FLT3i
AZA second

FIG. 3

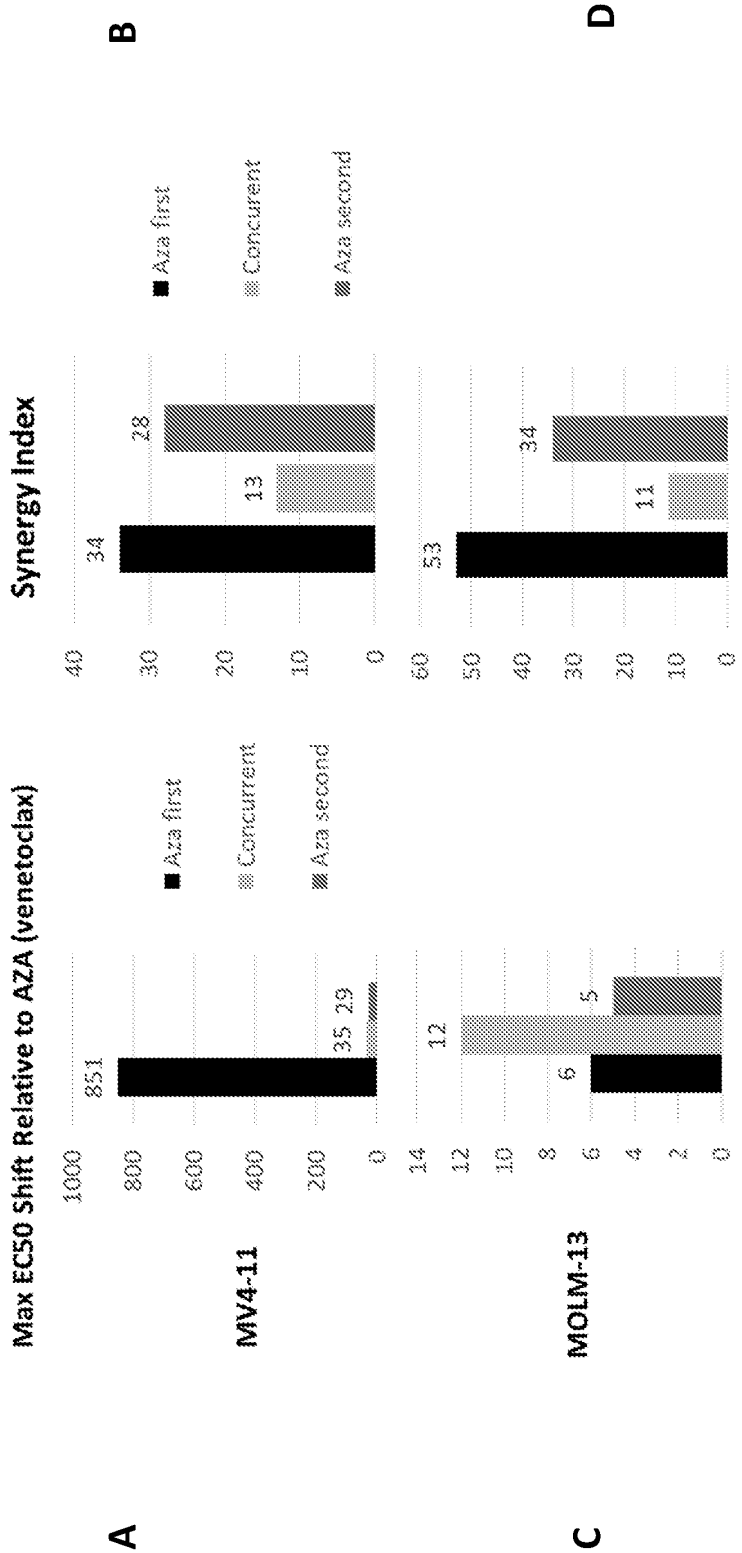

A
Max EC50 Shift Relative to AZA (venetoclax)
MV4-11
Aza first
Concurrent
Aza second
1000
800
600
400
200
0
851
35
29
C
MOLM-13
14
12
10
8
6
4
2
0
12
6
5
B
Synergy Index
40
30
20
10
0
34
13
28
D
60
50
40
30
20
10
0
53
11
34

FIG. 4

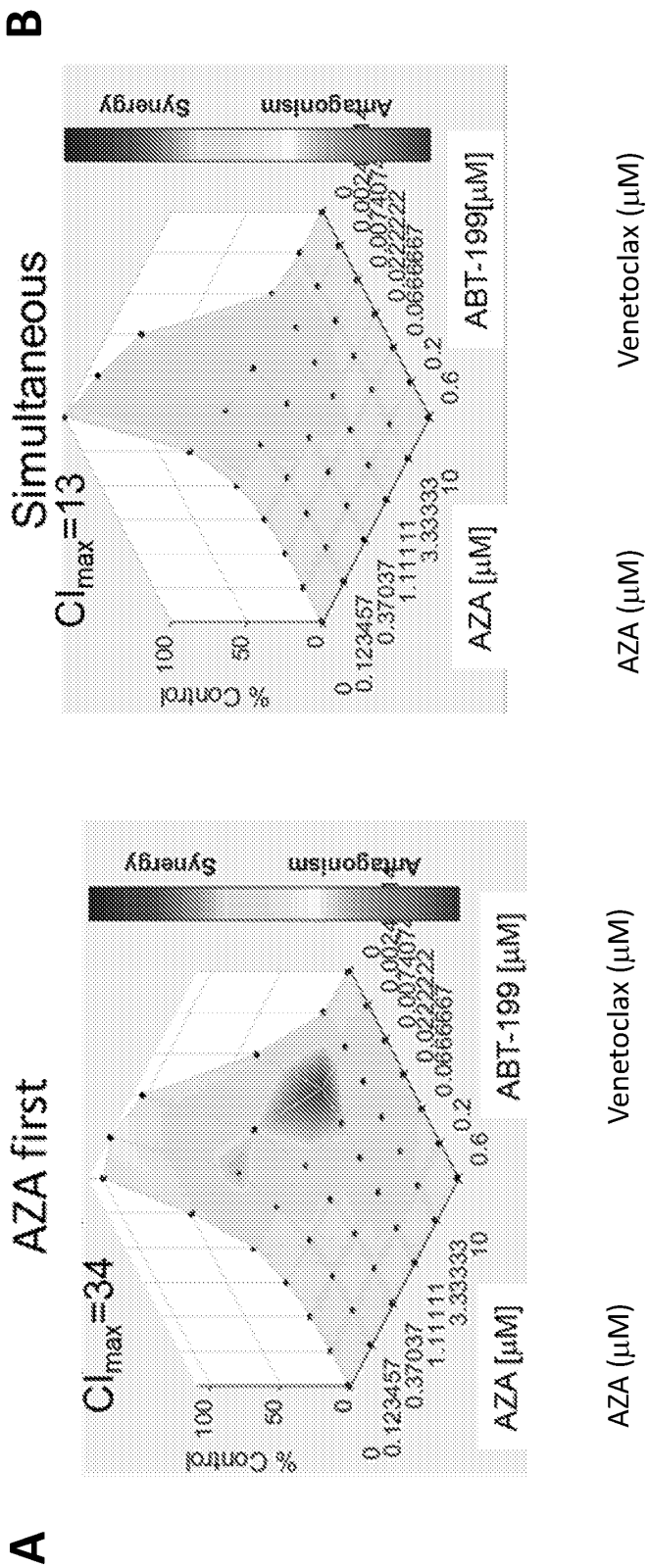

A
AZA first
CI_{max}=34
Synergy
Antagonism
% Control
100
50
0
0
0.123457
0.37037
1.11111
3.33333
10
AZA [μM]
0
0.0022
0.007407
0.022222
0.066667
0.2
0.6
ABT-199 [μM]
AZA (μM)
Venetoclax (μM)
B
Simultaneous
CI_{max}=13
Synergy
Antagonism
% Control
100
50
0
0
0.123457
0.37037
1.11111
3.33333
10
AZA [μM]
0
0.0022
0.007407
0.022222
0.066667
0.2
0.6
ABT-199[μM]
AZA (μM)
Venetoclax (μM)

FIG. 4 (continued)

c

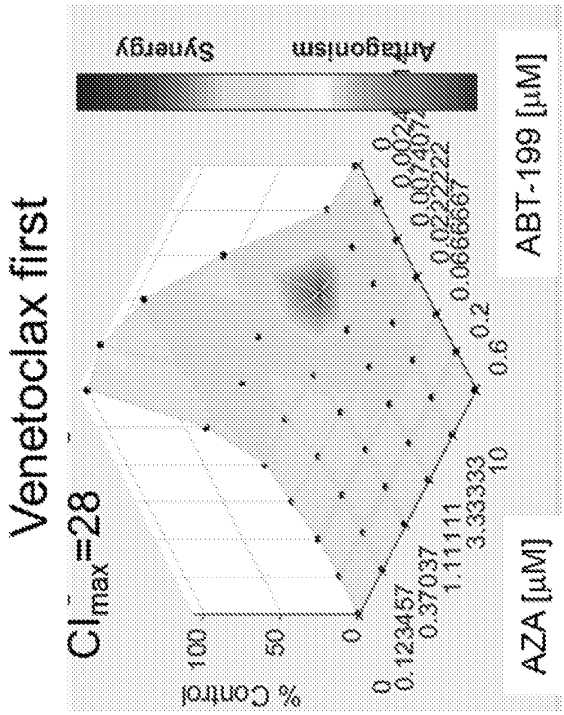


FIG. 5

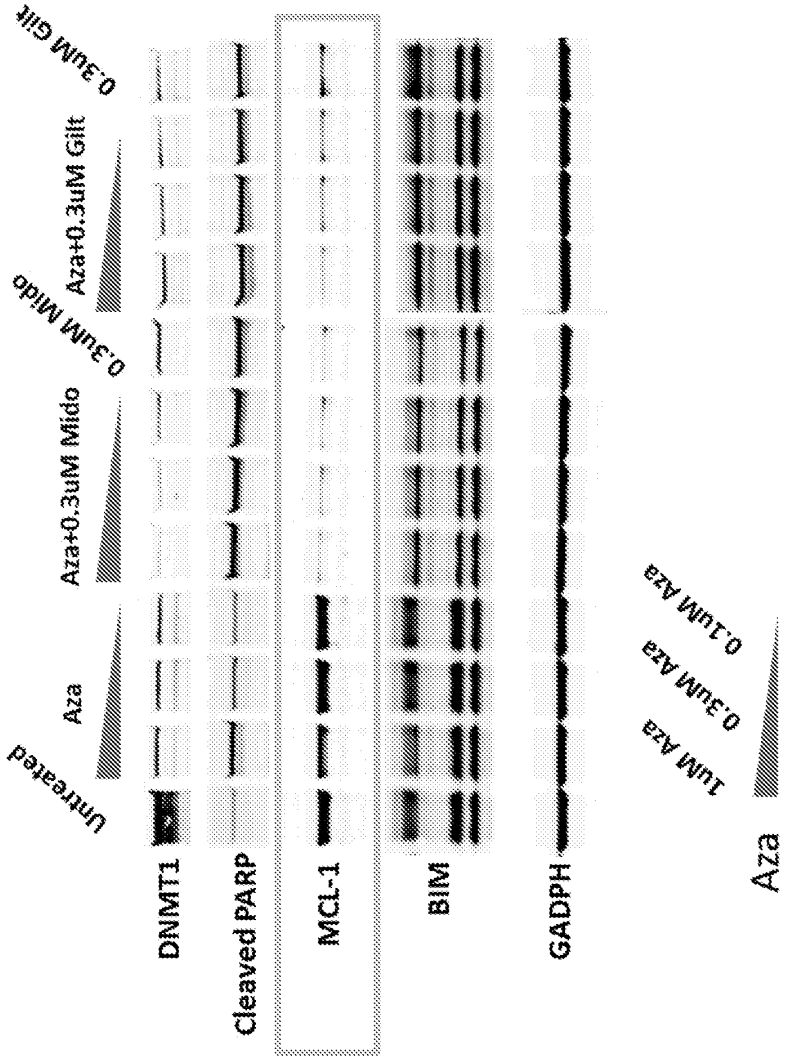

Untreated
Aza
Aza+0.3uM Mido
Aza+0.3uM Gilt
0.3uM Mido
0.3uM Gilt
DNMT1
Cleaved PARP
MCL-1
BIM
GADPH
1uM Aza
0.3uM Aza
0.1uM Aza
Aza

FIG. 6

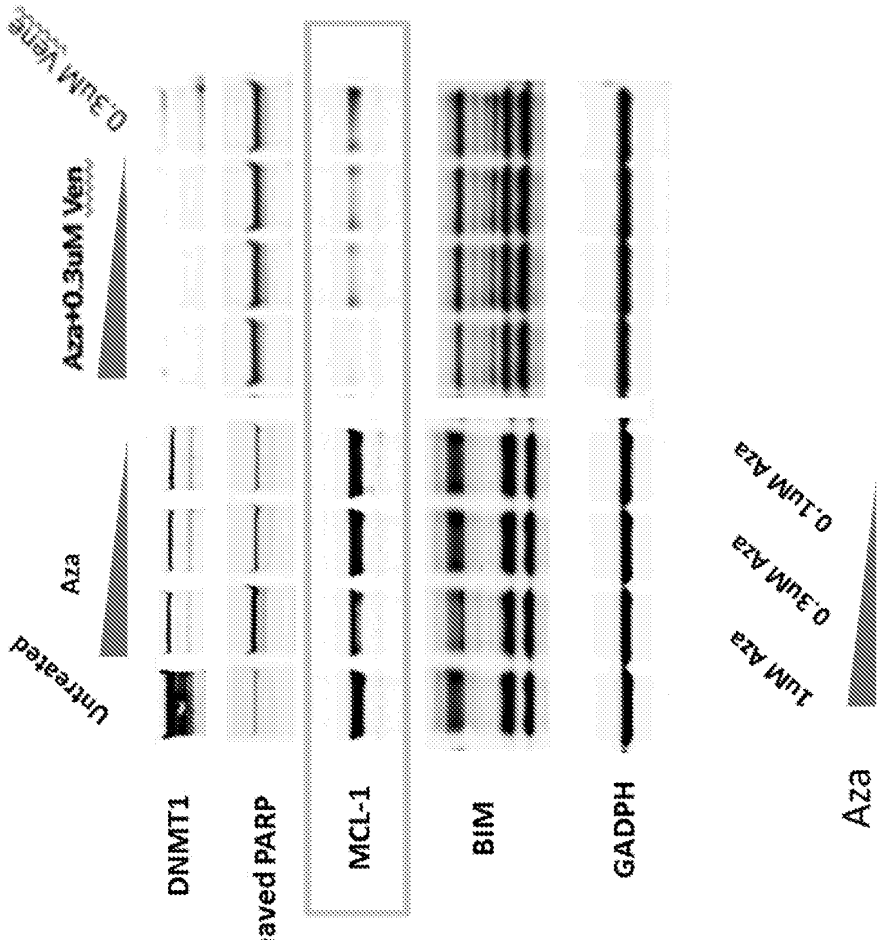

Untreated
Aza
Aza+0.3uM Ven
0.3uM Ven
DNMT1
Cleaved PARP
MCL-1
BIM
GADPH
1uM Aza
0.3uM Aza
0.1uM Aza
Aza

FIG. 7A

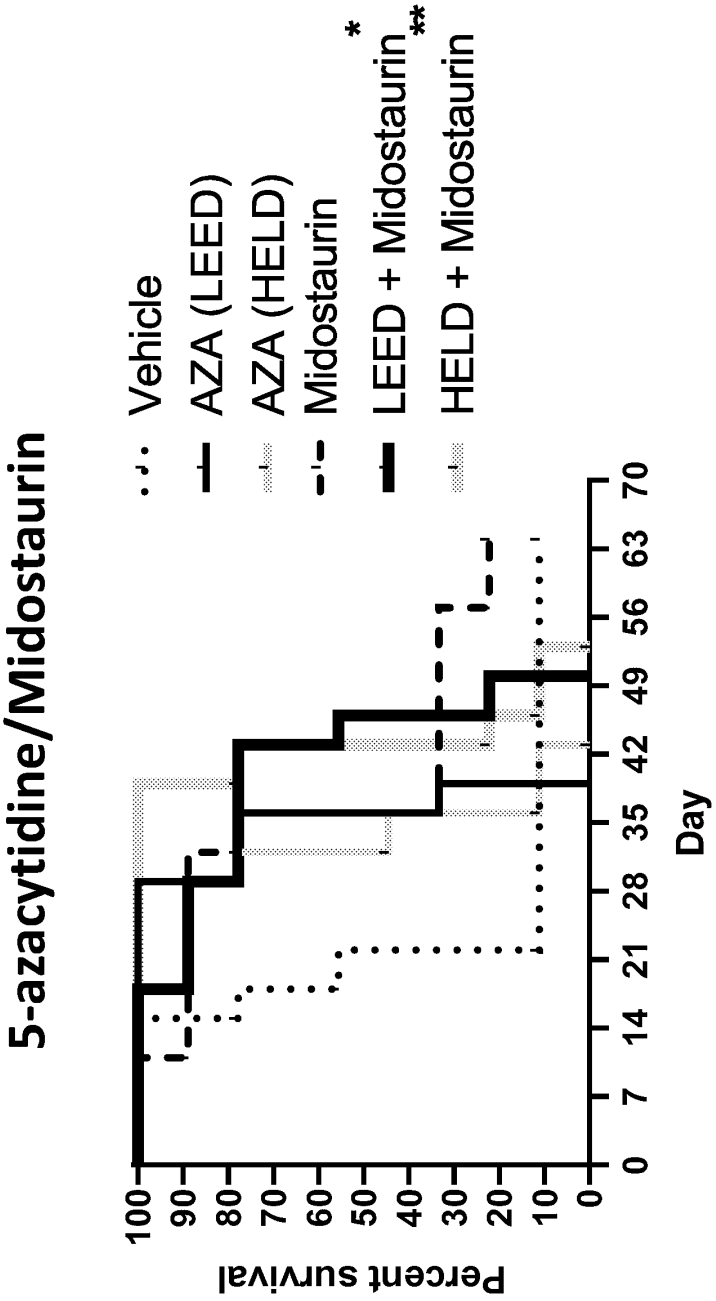

5-azacytidine/Midostaurin
Vehicle
AZA (LEED)
AZA (HELD)
Midostaurin
LEED + Midostaurin*
HELD + Midostaurin**
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
70
Day

FIG. 7B

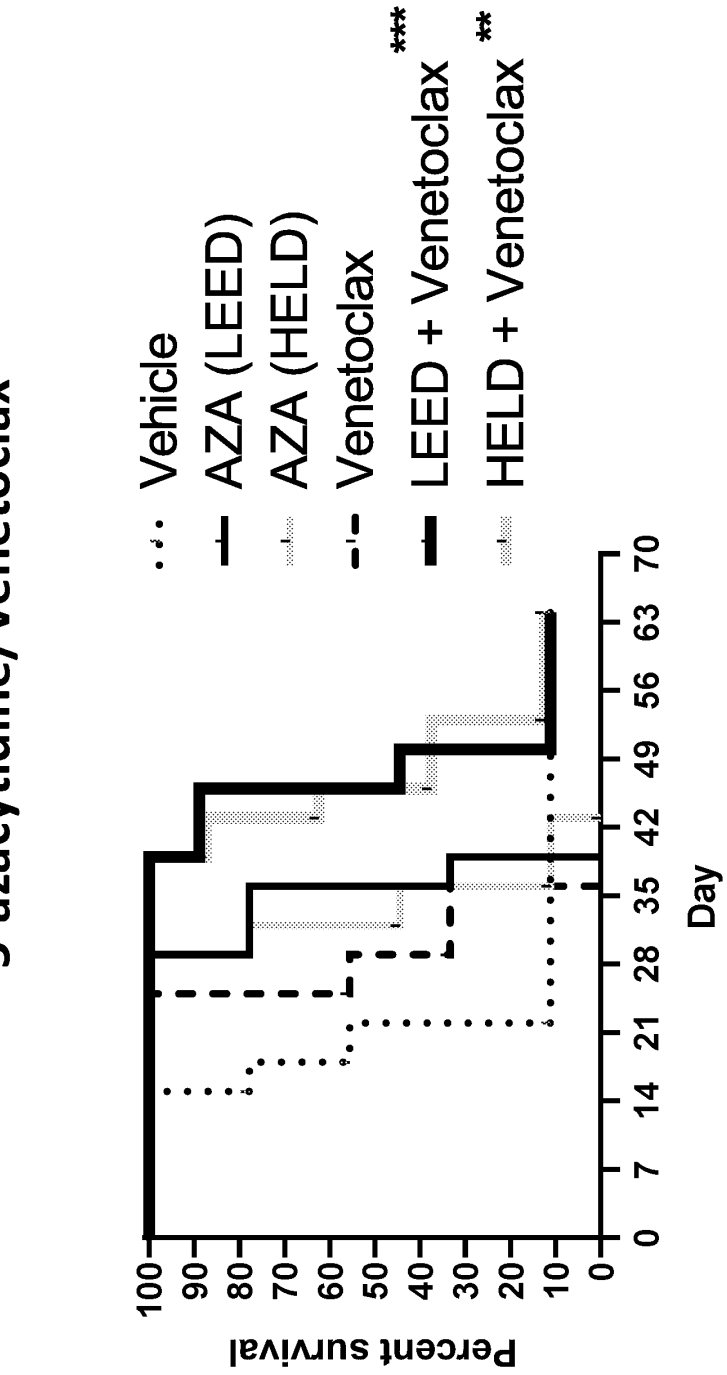

5-azacytidine/Venetoclax
Vehicle
AZA (LEED)
AZA (HELD)
Venetoclax
LEED + Venetoclax
HELD + Venetoclax
***
**
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
70
Day

FIG. 7C

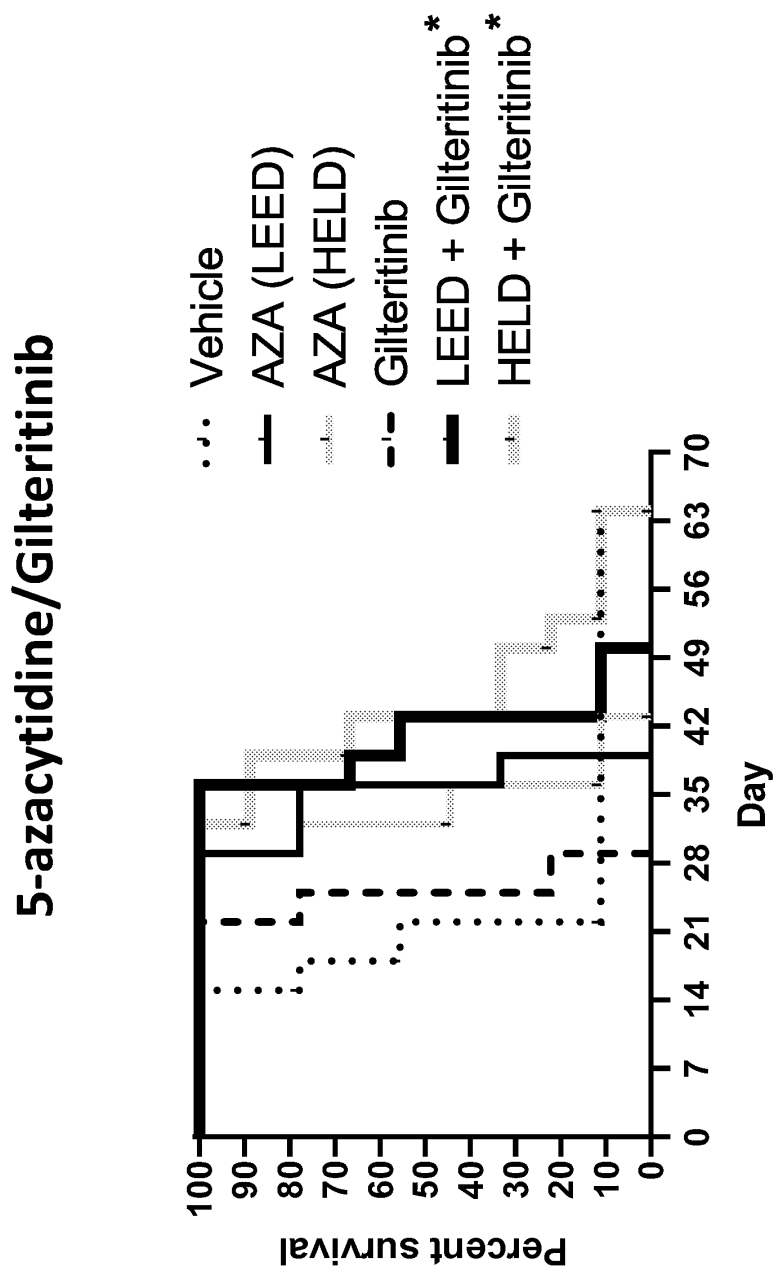

5-azacytidine/Gilteritinib
Vehicle
AZA (LEED)
AZA (HELD)
Gilteritinib
LEED + Gilteritinib*
HELD + Gilteritinib*
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
70
Day

FIG. 8A


AZA
EC50 (μM)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
MOLM-13
KG-1a
MUTZ-8
Nomo-1
OCI-AML2
KASUMI-1
HL-60
HTN-34
MV4-11
HEL
THP-1
KG-1
SIG-M5
OCI-AML3
F36P
ML-2
GDM-1
UT-7
AML-193
KASUMI-3
TF-1
U937
biphasic

FIG. 8B

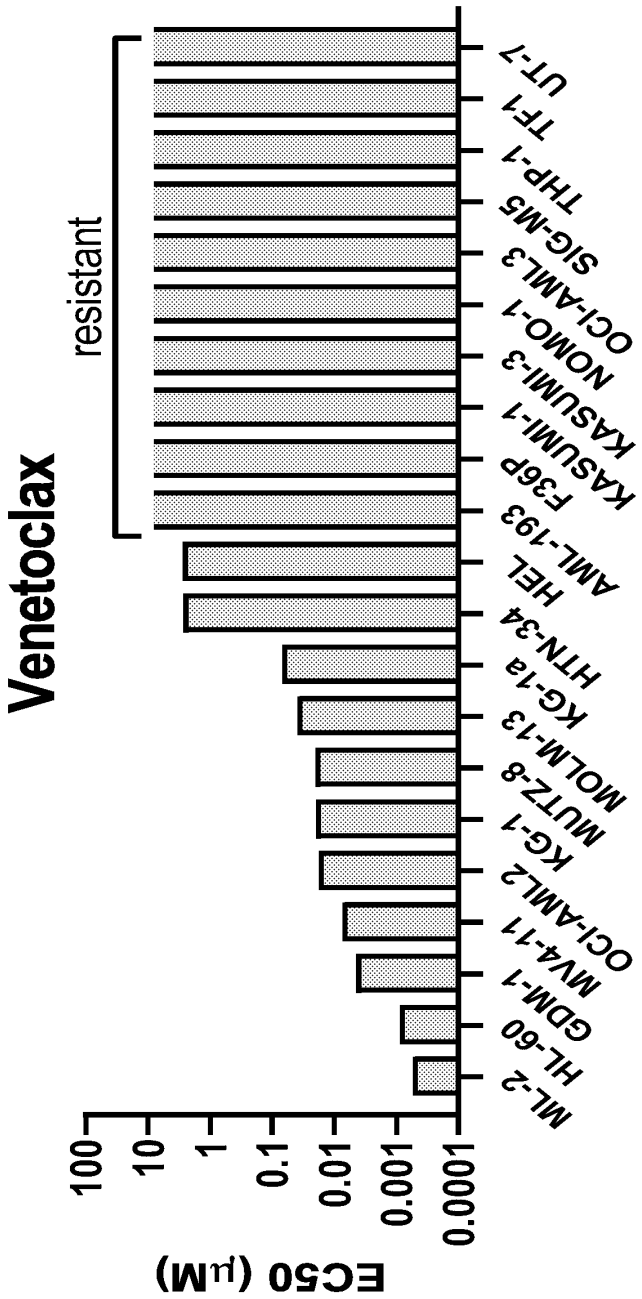

Venetoclax
resistant
EC50 (μM)
100
10
1
0.1
0.01
0.001
0.0001
ML-2
HL-60
GDM-1
MV4-11
OCI-AML2
KG-1
MUTZ-8
MOLM-13
KG-1a
HTN-34
HEL
AML-193
F36P
KASUMI-1
KASUMI-3
NOMO-1
OCI-AML3
SIG-M5
THP-1
TF-1
UT-7

FIG. 8C

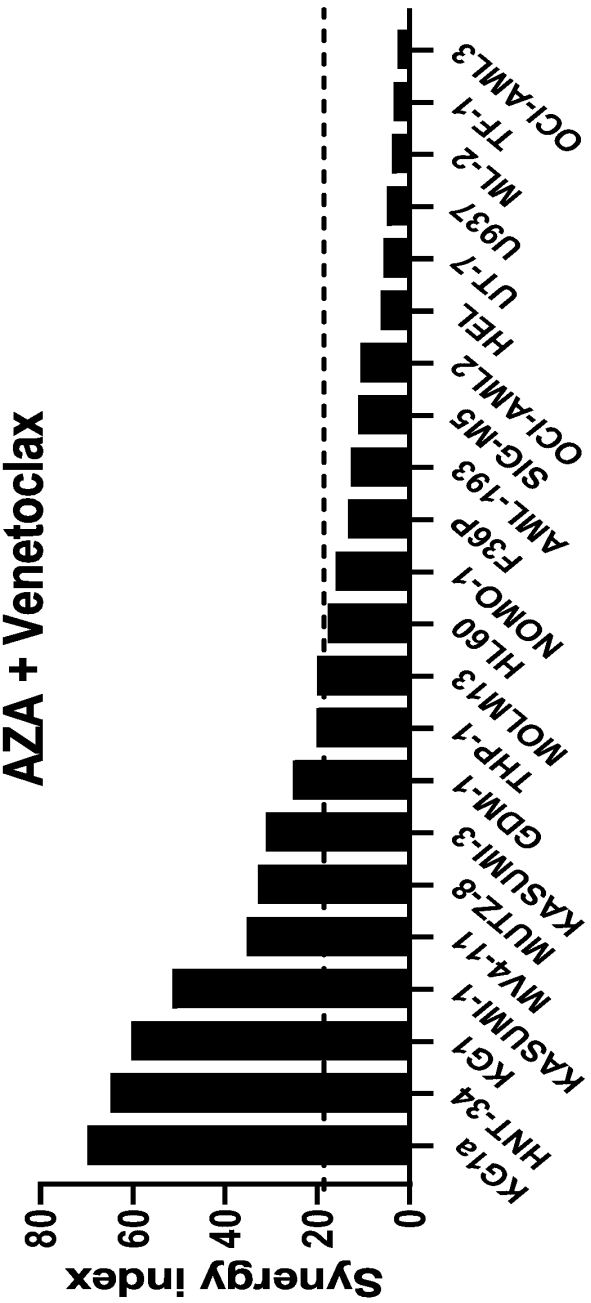

AZA + Venetoclax
Synergy index
0
20
40
60
80
KG1a
HNT-34
KG1
KASUMI-1
MV4-11
MUTZ-8
KASUMI-3
GDM-1
THP-1
MOLM13
HL60
NOMO-1
F36P
AML-193
SIG-M5
OCI-AML2
HEL
UT-7
U937
ML-2
TF-1
OCI-AML3

FIG. 9A

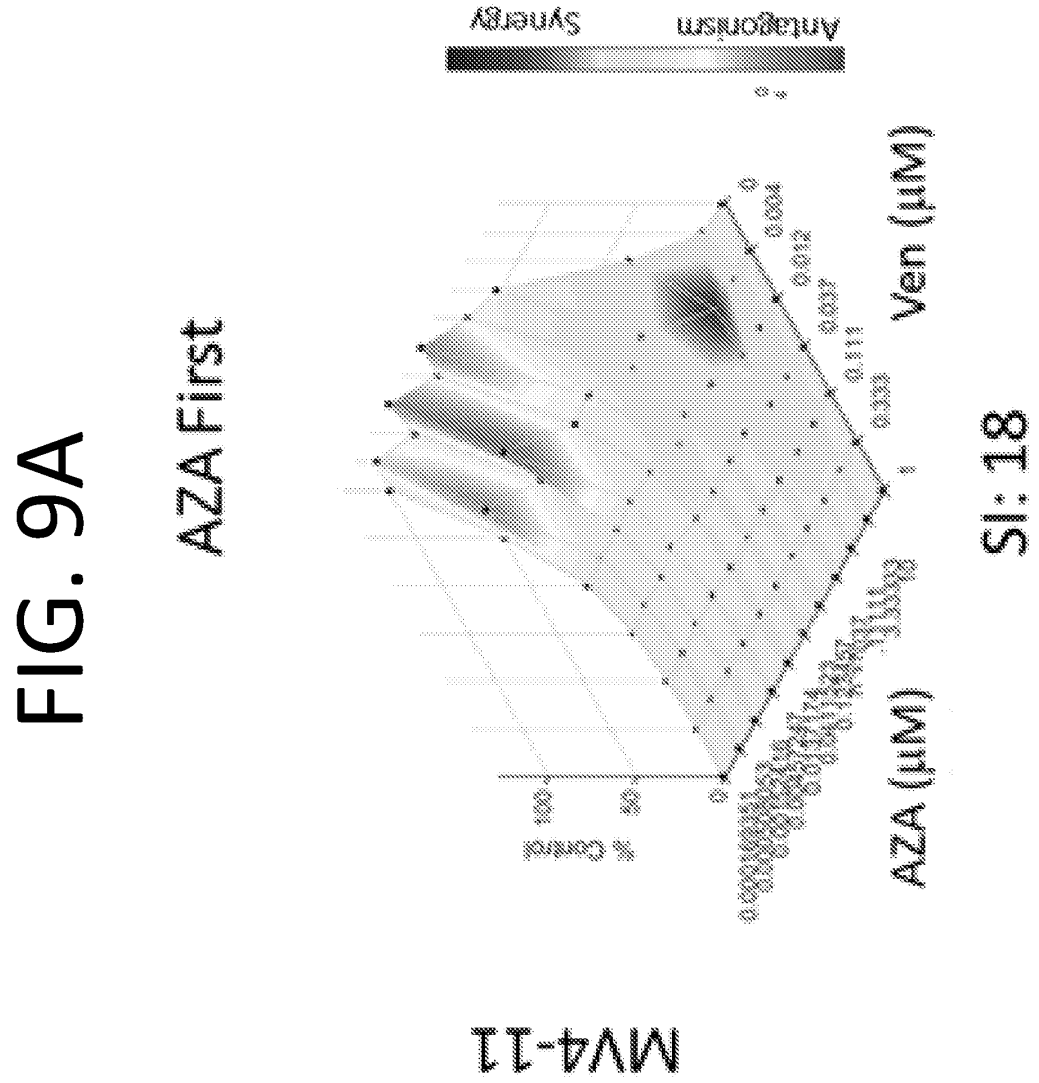


FIG. 9B

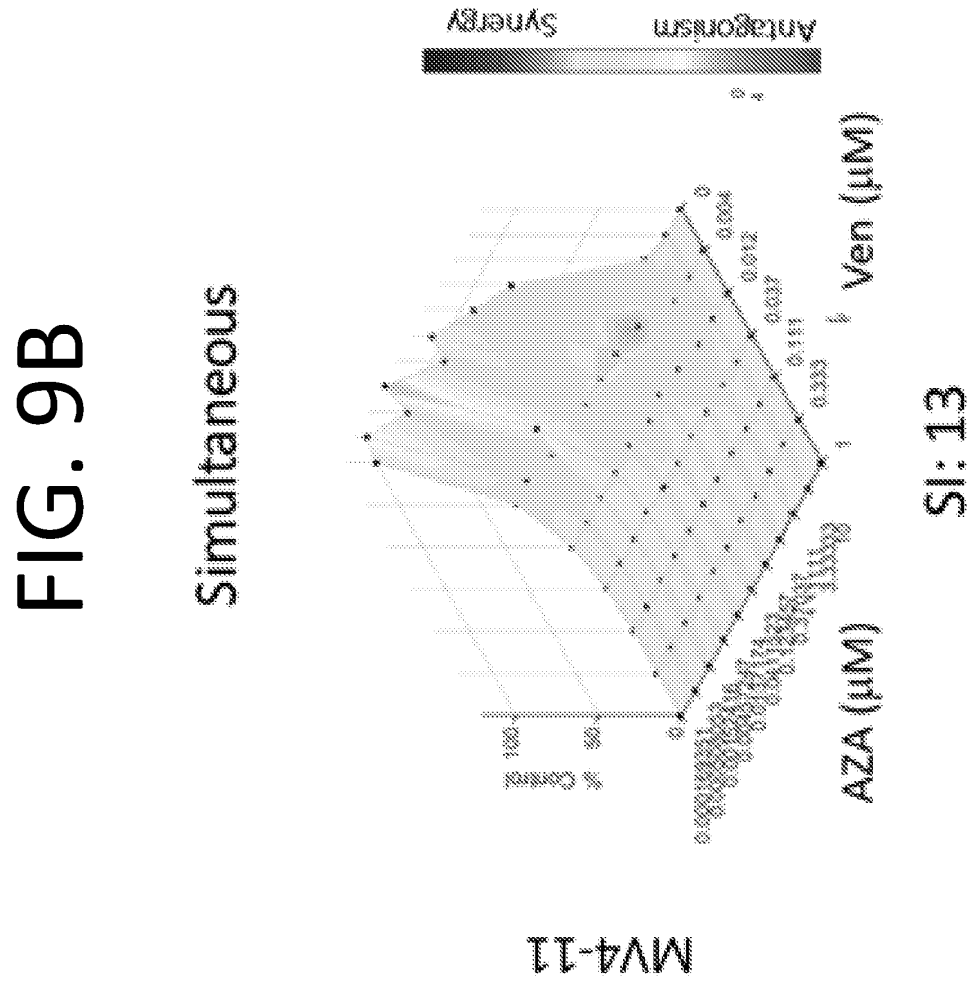

MV4-11
Simultaneous
Synergy
Antagonism
Ven (μM)
AZA (μM)
% Cells
SI: 13

FIG. 9C

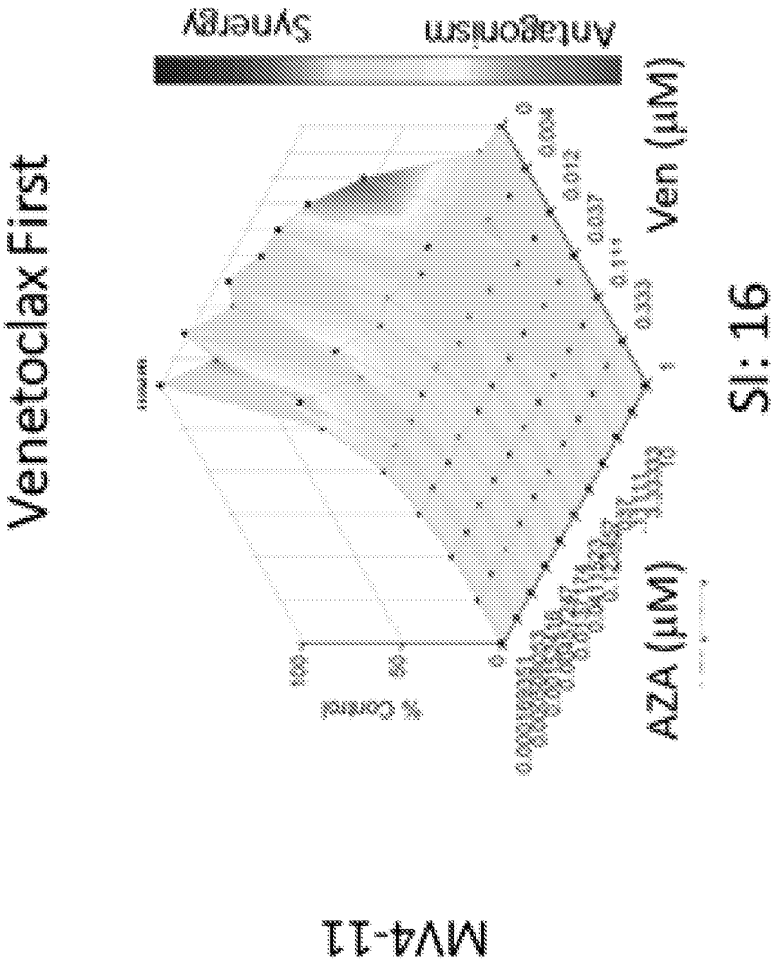

Venetoclax First
Synergy
Antagonism
Ven (μM)
AZA (μM)
% Cereal
SI: 16
MV4-11

FIG. 9D

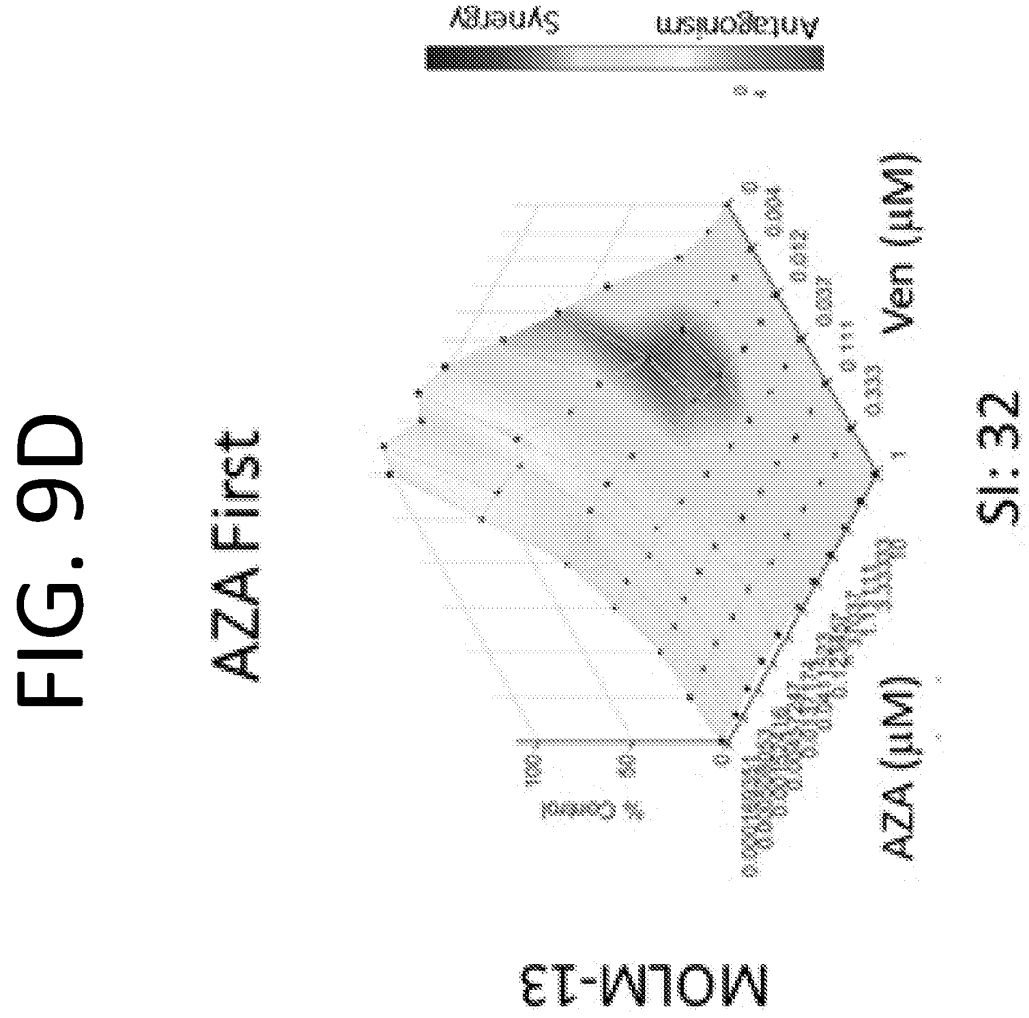


FIG. 9E

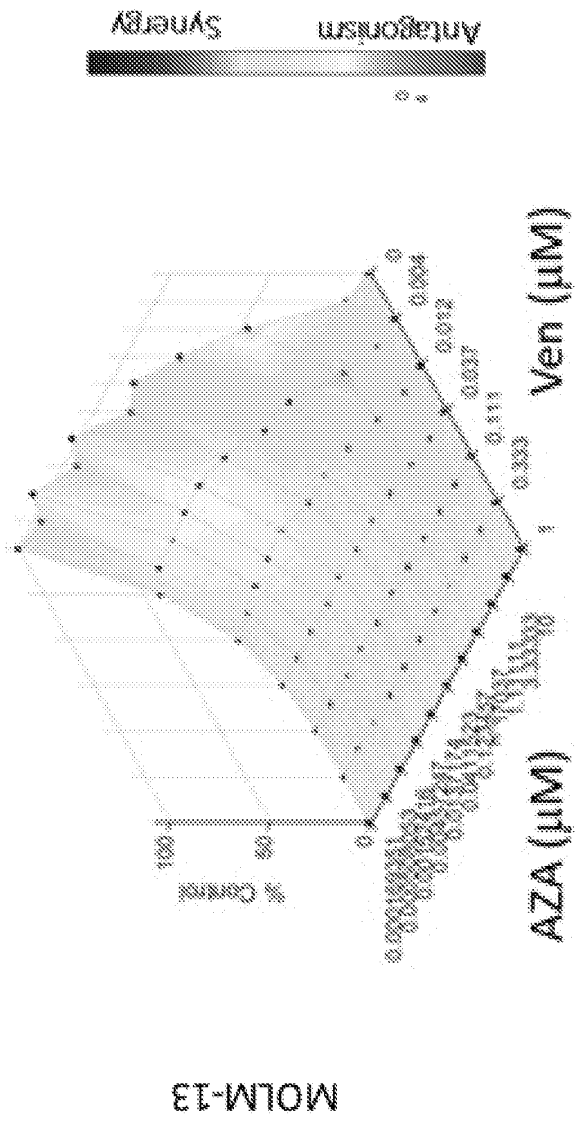

Simultaneous
Antagonism
Synergy
Ven (μM)
AZA (μM)
% Cells
SI: 10
MOLM-13

FIG. 9F

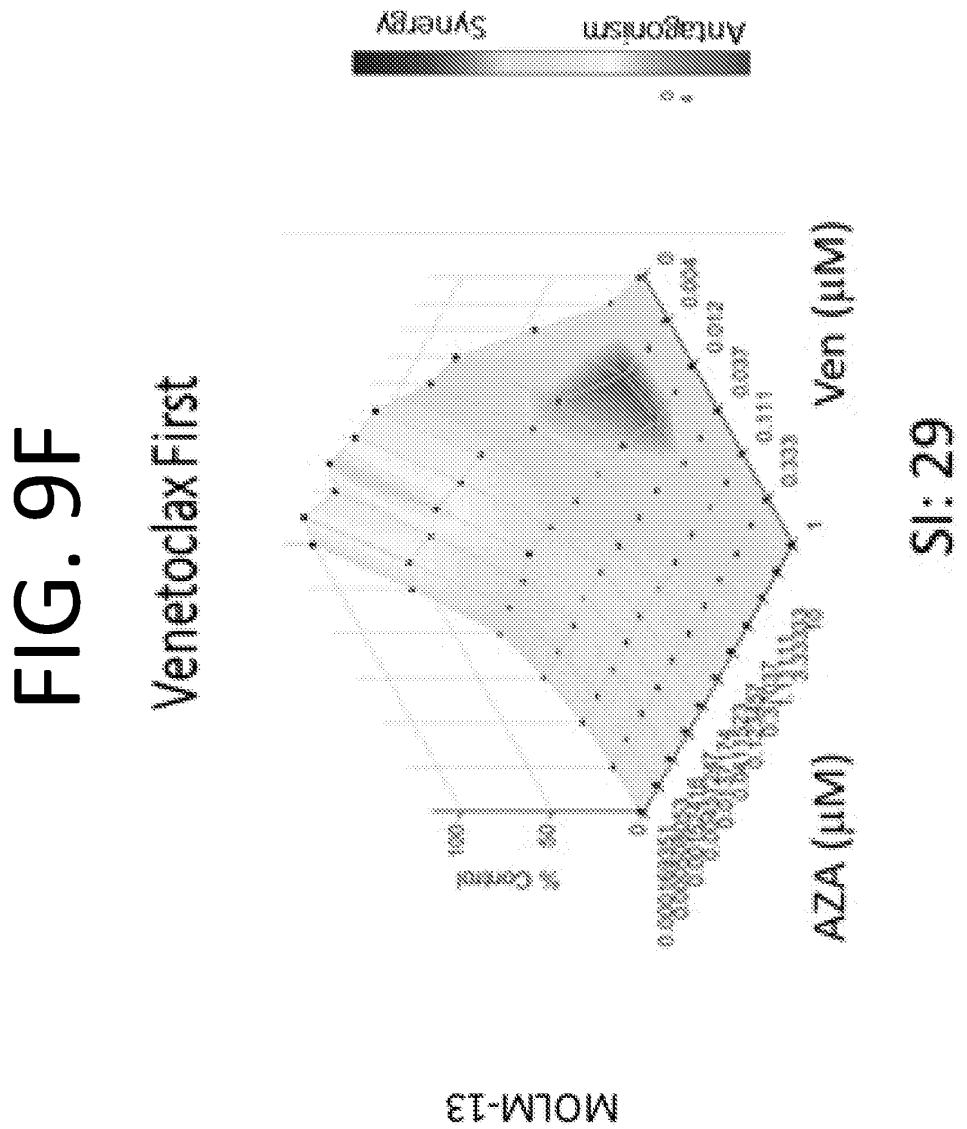

Venetoclax First
MOLM-13
Antagonism
Synergy
% Cell
100
0
Ven (μM)
0
0.004
0.012
0.037
0.111
0.333
1
AZA (μM)
SI: 29

FIG. 10A

BaF3 cells expressing various FLT3 (EC50, nM)

	BaF-FLT3(WT)	BaF-FLT3-ITD	BaF-FLT3(D835Y)
AZA	189	598	456
Gilteritinib	4	1.8	1.8
Midostaurin	23	5.5	5.4
Quizartinib	3	0.008	9.5
Venetoclax	>10000	>10000	4332

FIG. 10B

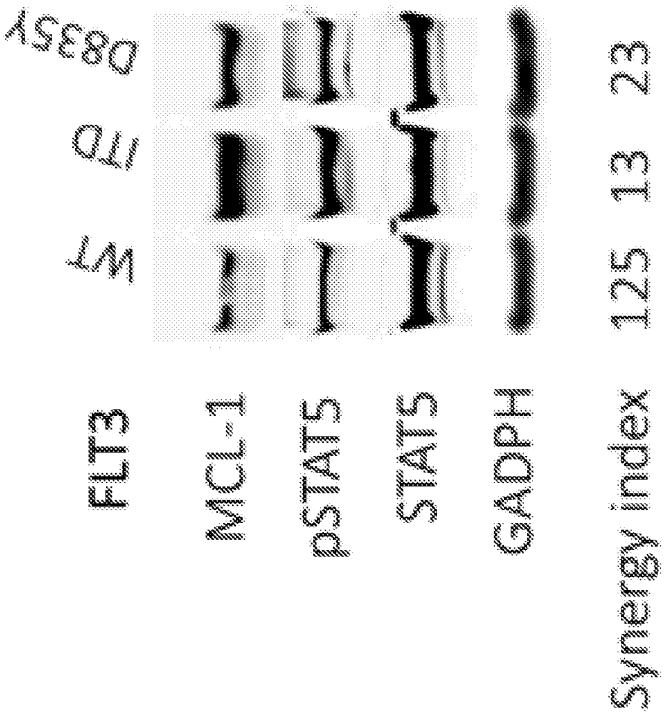

FLT3
WT
ITD
D835Y
MCL-1
pSTAT5
STAT5
GADPH
Synergy index
125
13
23

FIG. 10C

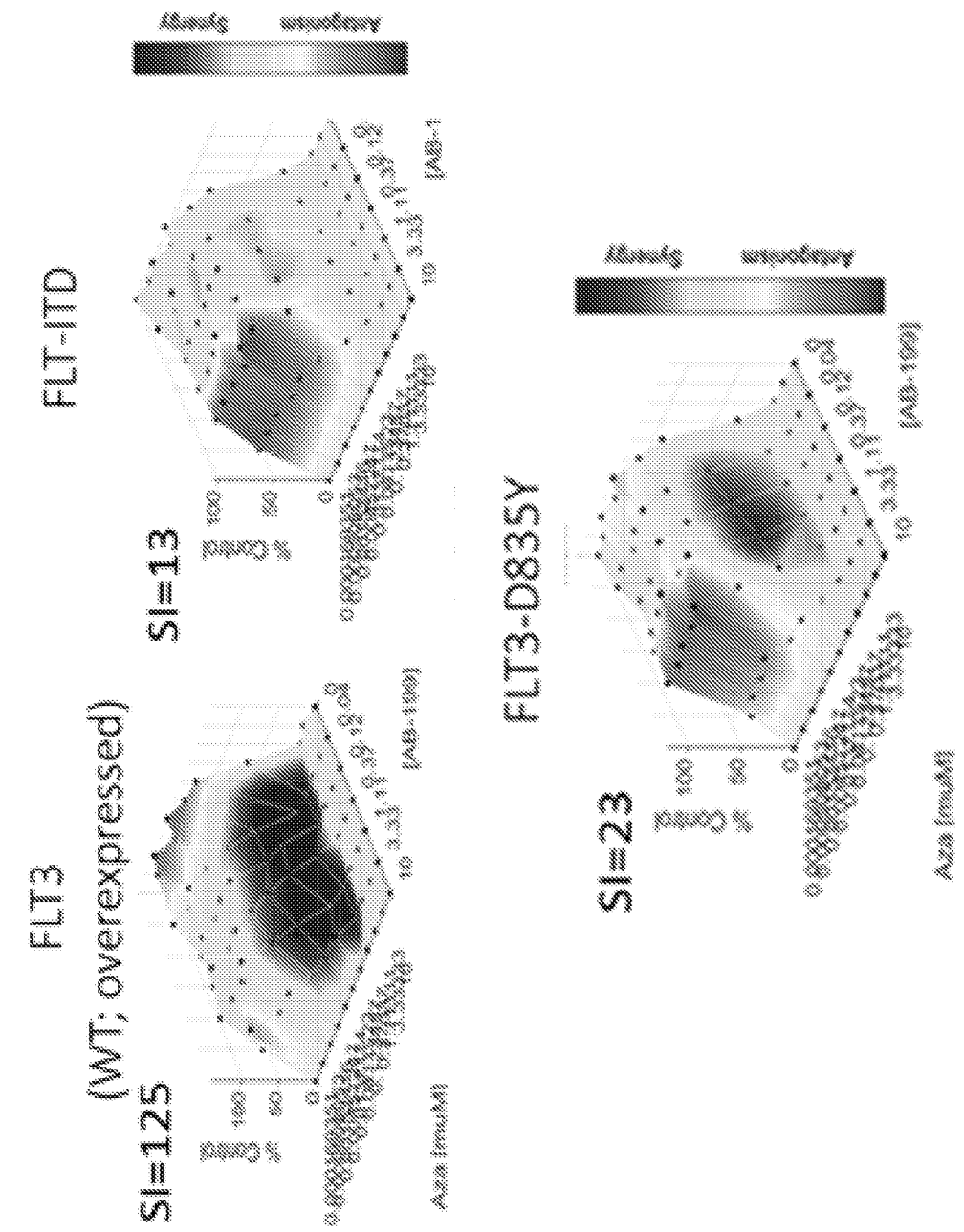

FLT3
(WT; overexpressed)
SI=125
FLT-ITD
SI=13
FLT3-D835Y
SI=23
Azacitidine (mM)
[AB-100]
[AB-1]
Viability
Apoptosis

FIG. 11

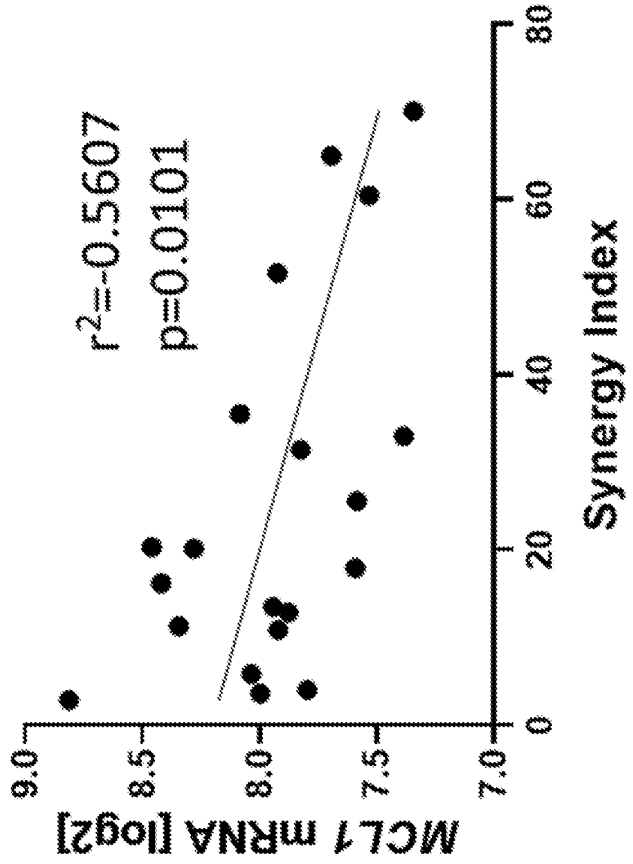

AML Cell Lines
r^2=-0.5607
p=0.0101
MCL1 mRNA [log2]
9.0
8.5
8.0
7.5
7.0
0
20
40
60
80
Synergy Index

FIG. 12

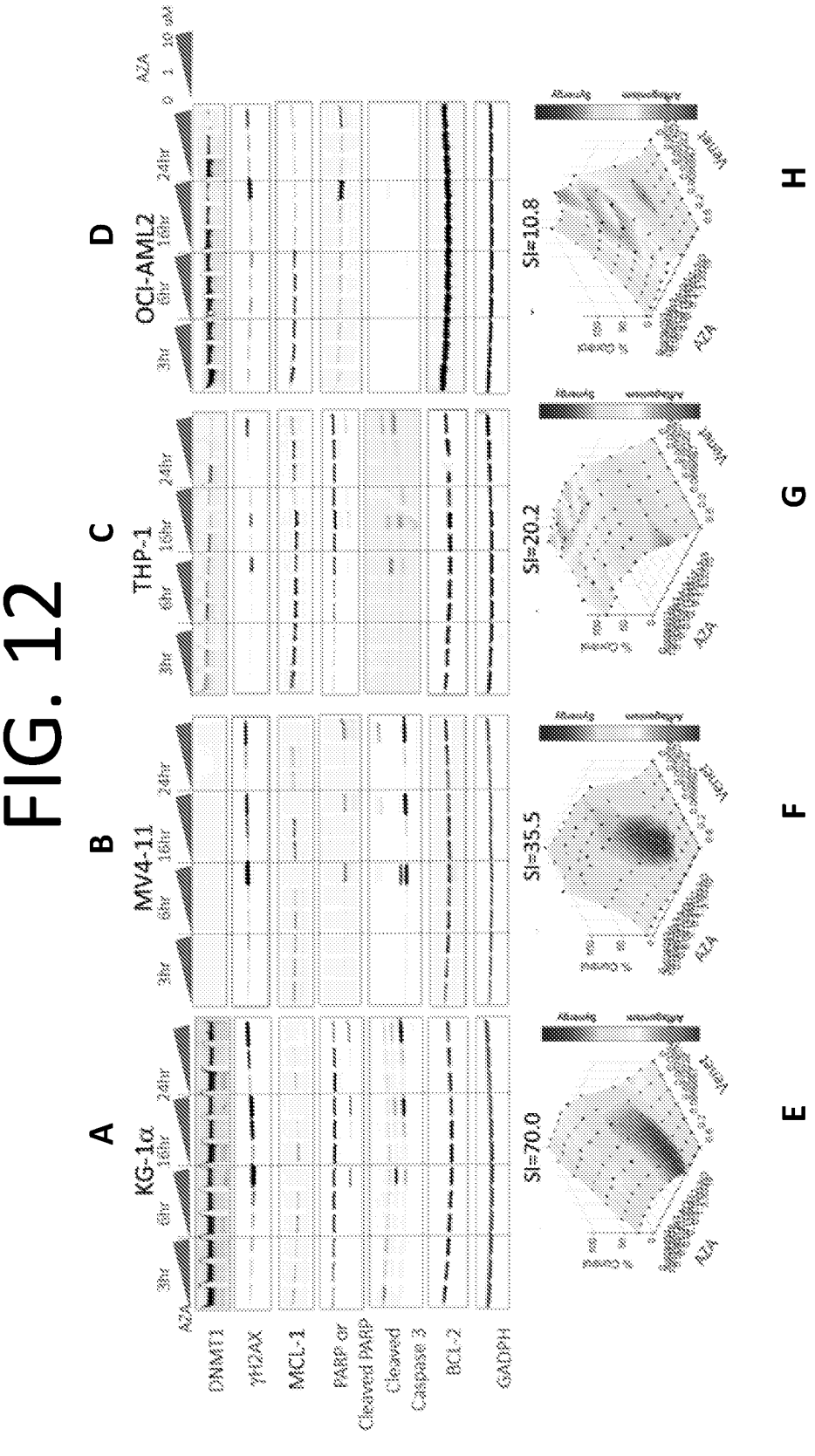

A
B
C
D
KG-1α
MV4-11
THP-1
OCI-AML2
AZA
3hr
6hr
16hr
24hr
0
1
10 nM
DNMT1
γH2AX
MCL-1
PARP or Cleaved PARP
Cleaved Caspase 3
BCL-2
GADPH
E
F
G
H
SI=70.0
SI=35.5
SI=20.2
SI=10.8
Vehicle
AZA
Viable
Dead

FIG. 13

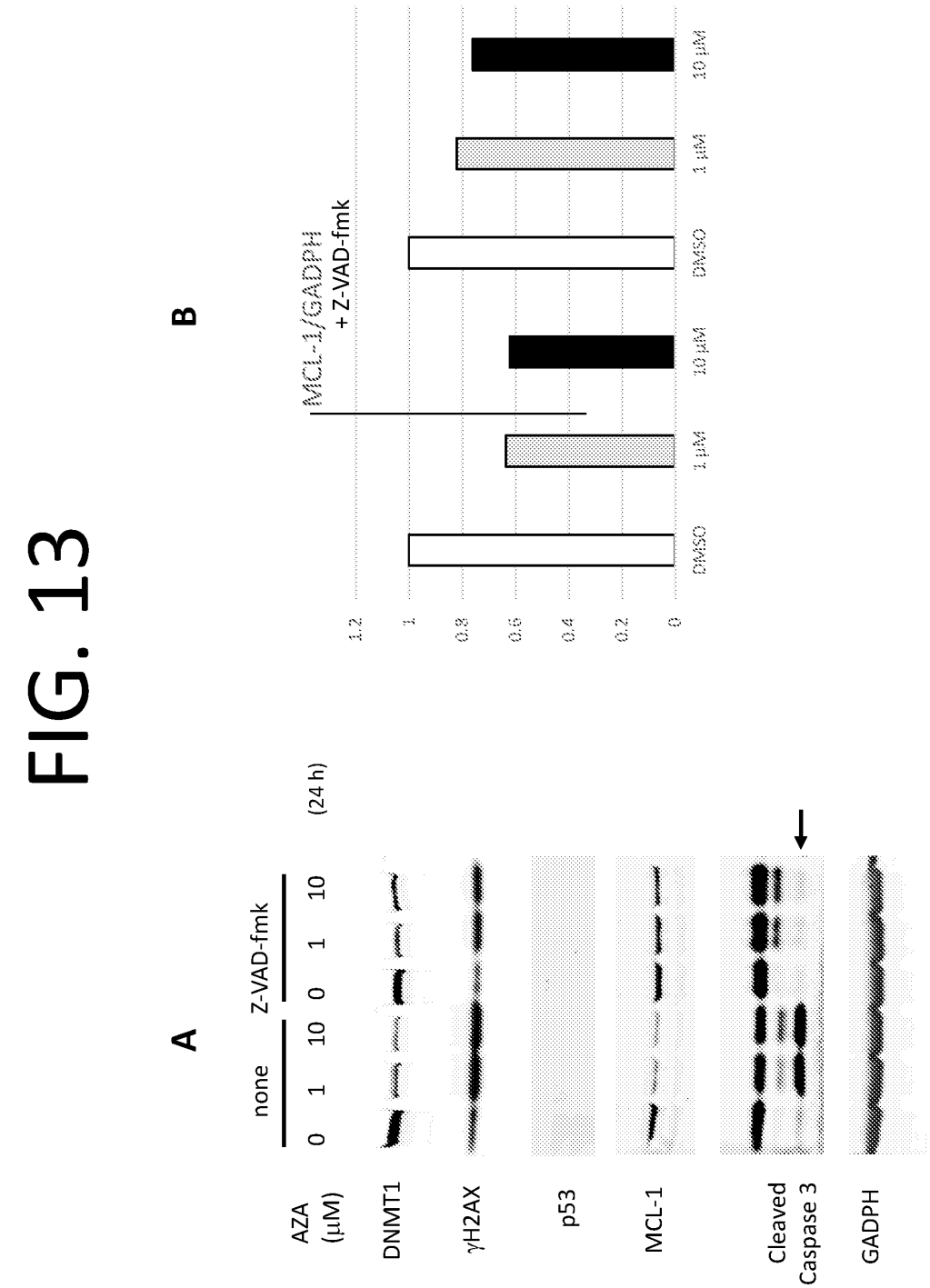

A
AZA (μM)
none
Z-VAD-fmk
0
1
10
0
1
10
(24 h)
DNMT1
γH2AX
p53
MCL-1
Cleaved Caspase 3
GADPH
B
MCL-1/GADPH + Z-VAD-fmk
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
1 μM
10 μM
DMSO
1 μM
10 μM

FIG. 14

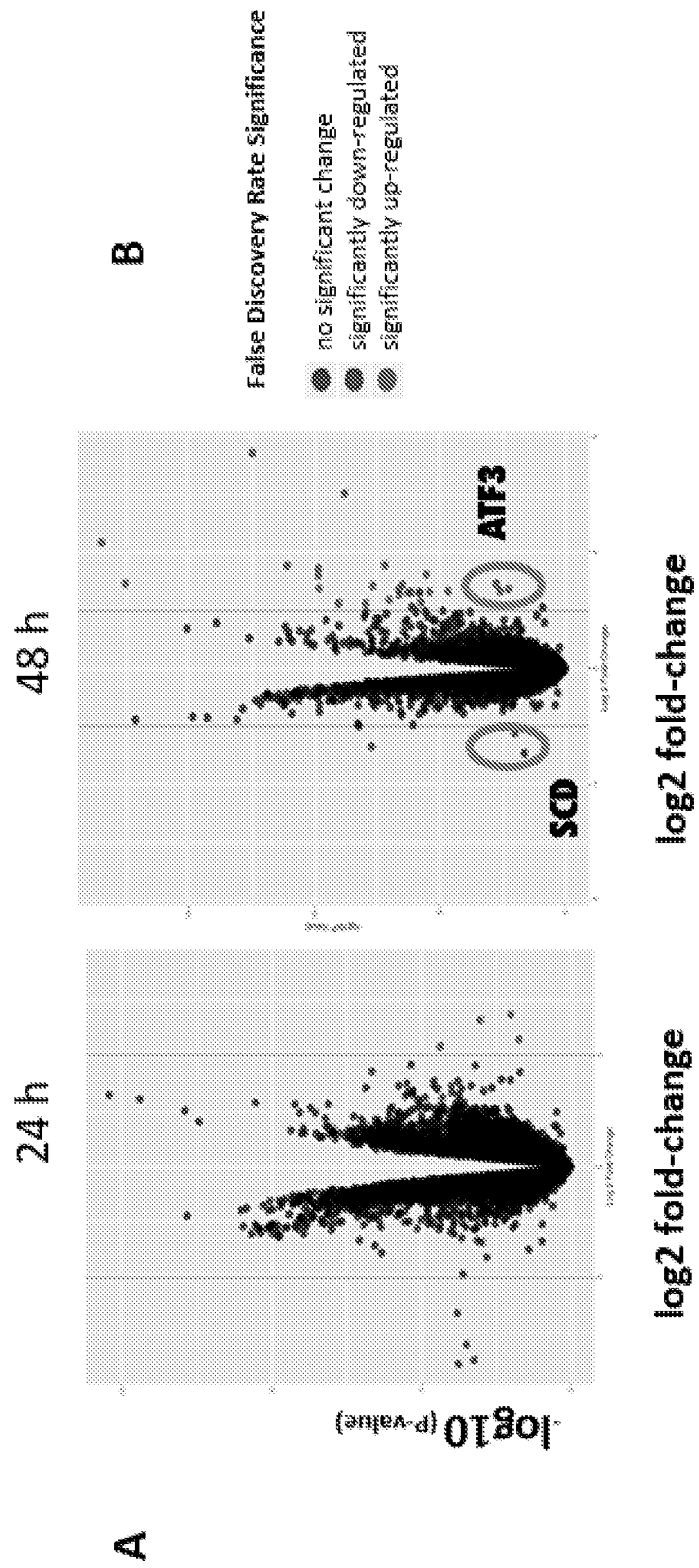

A
B
24 h
48 h
-log10 (p-value)
log2 fold-change
log2 fold-change
False Discovery Rate Significance
no significant change
significantly down-regulated
significantly up-regulated
ATF3
SCD

FIG. 14

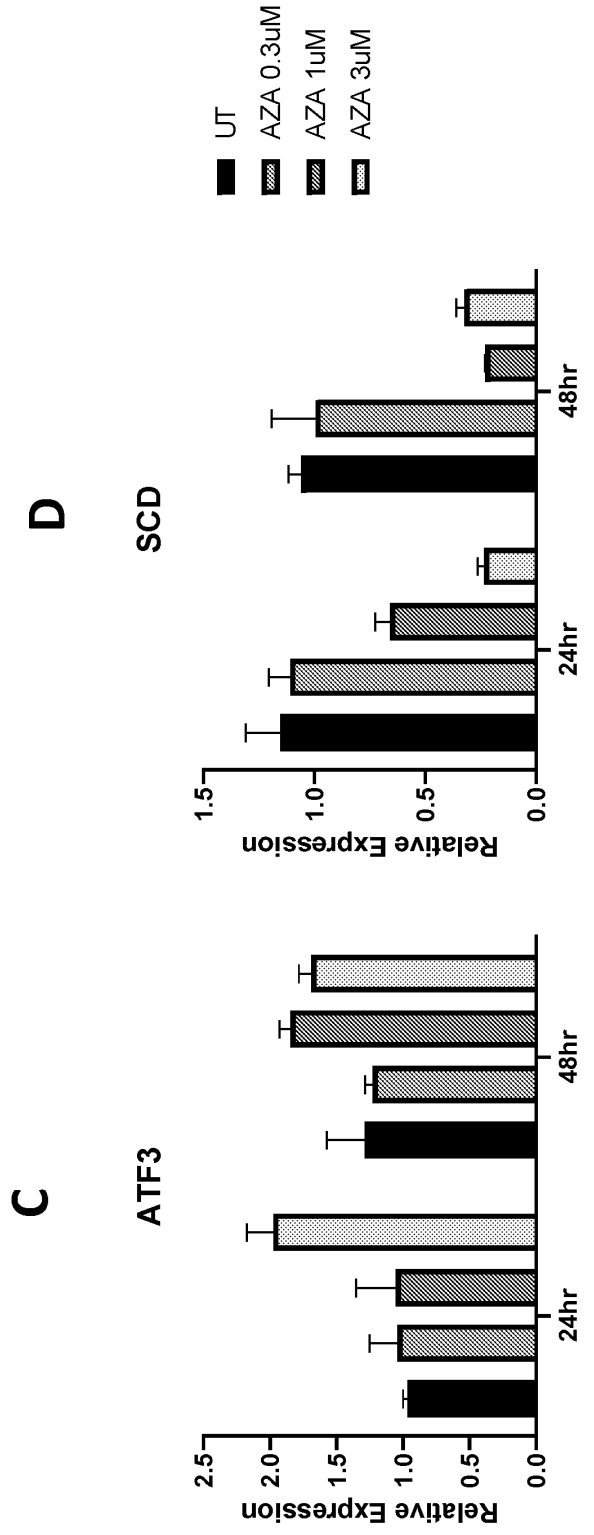

C
ATF3
Relative Expression
2.5
2.0
1.5
1.0
0.5
0.0
24hr
48hr
D
SCD
Relative Expression
1.5
1.0
0.5
0.0
24hr
48hr
UT
AZA 0.3uM
AZA 1uM
AZA 3uM

FIG. 15A

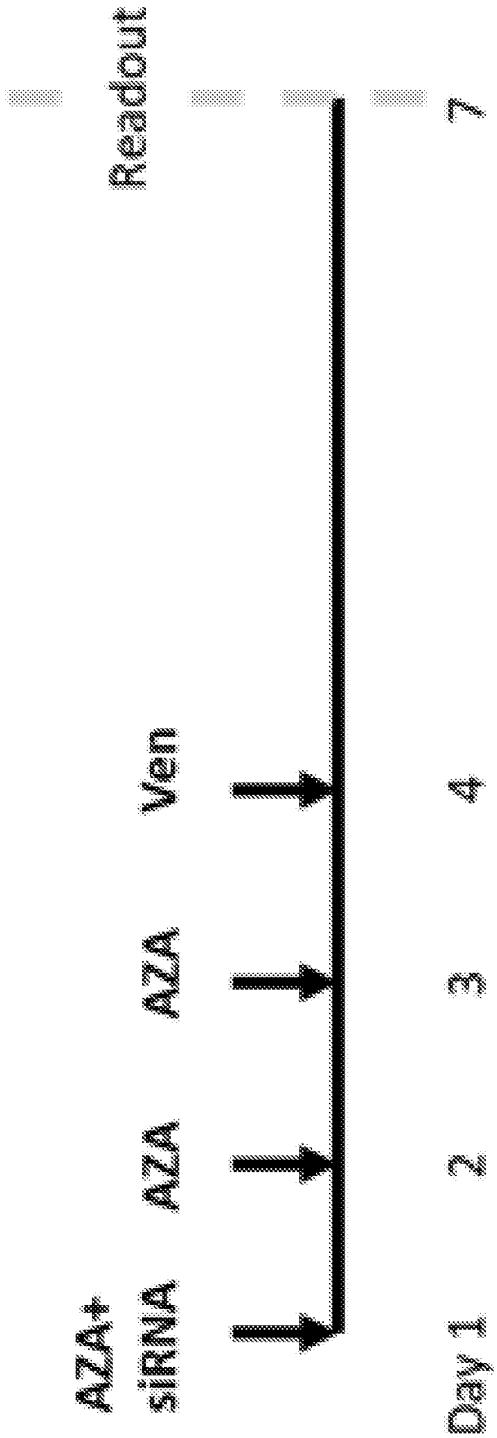


FIG. 15

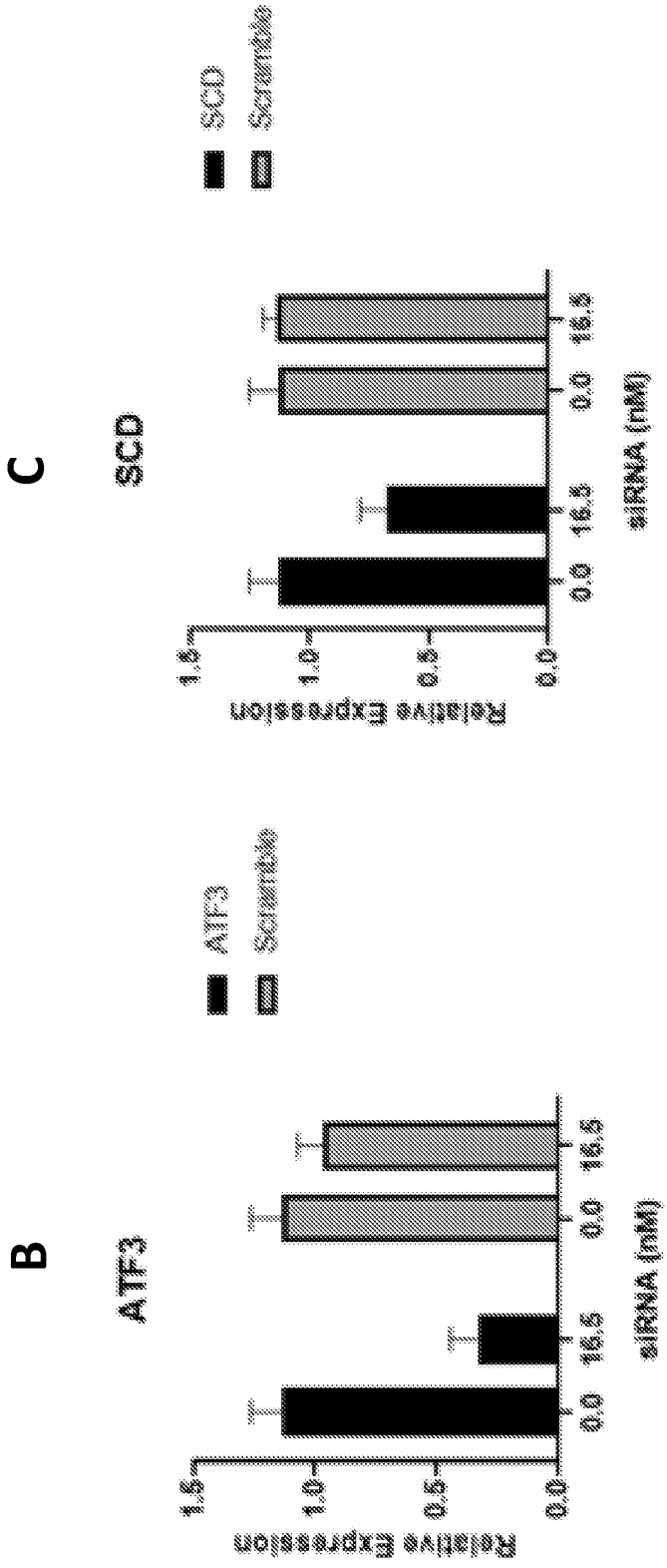

B
ATF3
ATF3
Scramble
Relative Expression
1.5
1.0
0.5
0.0
0.0
16.5
0.0
16.5
siRNA (nM)
C
SCD
SCD
Scramble
Relative Expression
1.5
1.0
0.5
0.0
0.0
16.5
0.0
16.5
siRNA (nM)

FIG. 15

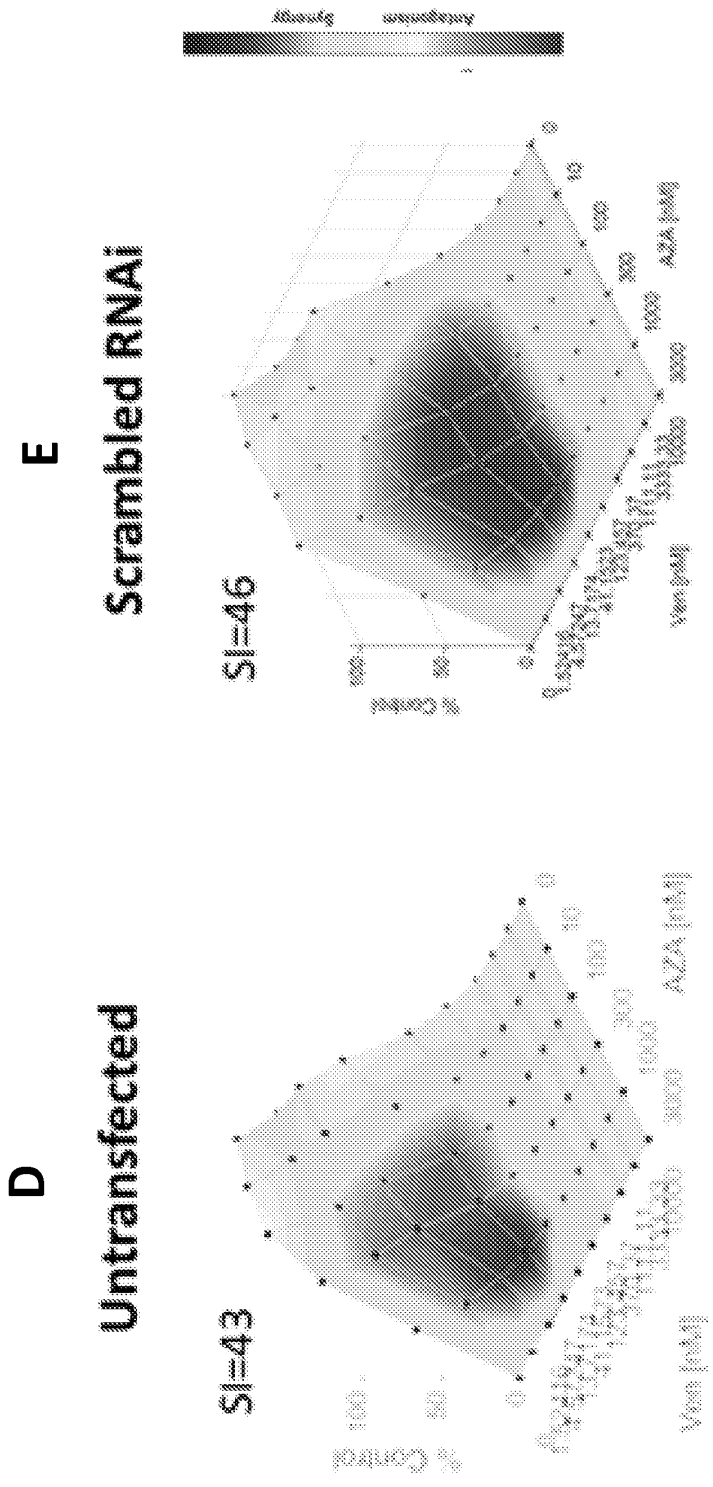

D
Untransfected
SI=43
% Control
Vin [nM]
AZA [nM]
E
Scrambled RNAi
SI=46
% Cell
Ven [nM]
AZA [nM]

FIG. 15

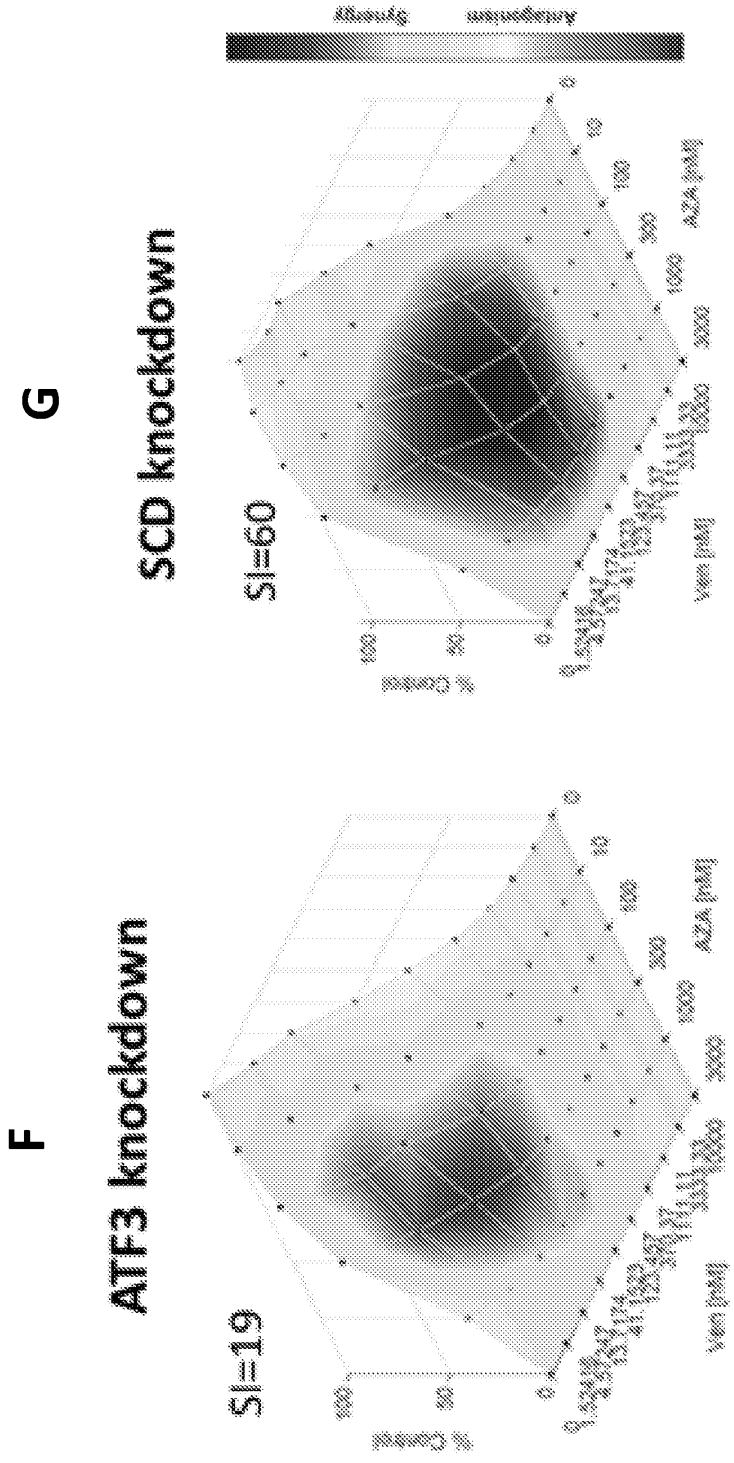

F
ATF3 knockdown
SI=19
% Cmax
Ven [nM]
AZA [nM]
G
SCD knockdown
SI=60
% Cmax
Ven [nM]
AZA [nM]
Synergy
Antagonism

FIG. 16A

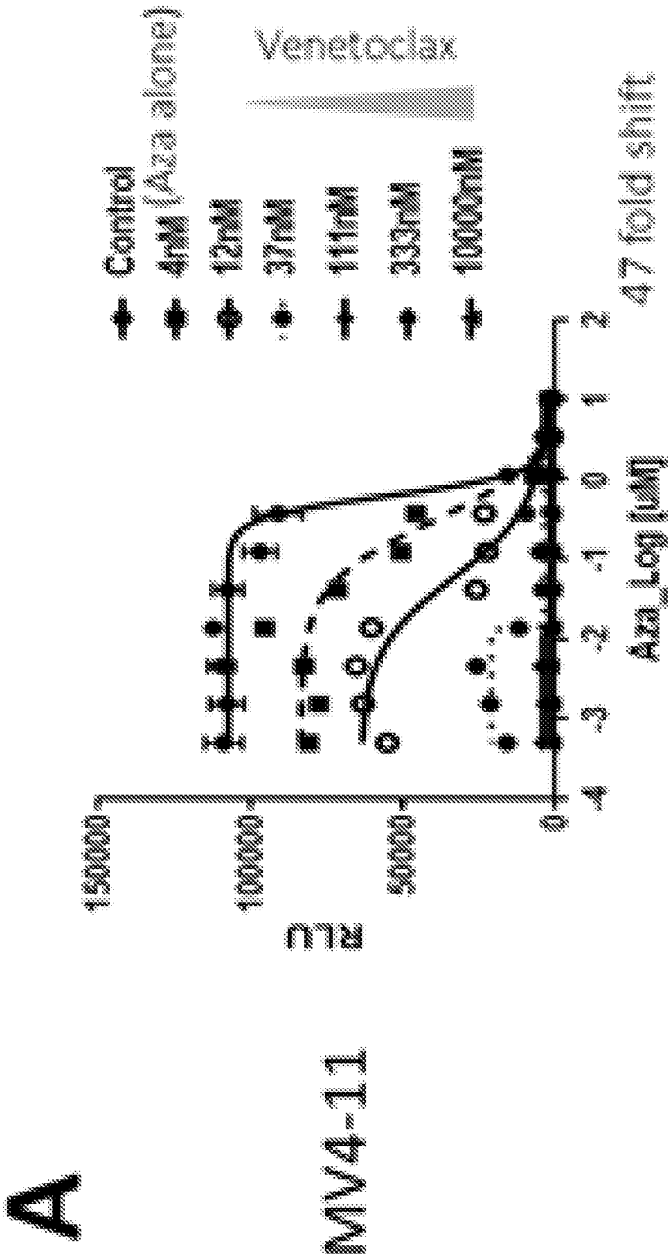

A
MV4-11
RLU
150000
100000
50000
0
-4
-3
-2
-1
0
1
2
Aza_Log [uM]
47 fold shift
Venetoclax
Control
4nM (Aza alone)
12nM
37nM
111nM
333nM
1000nM

Fig. 16B

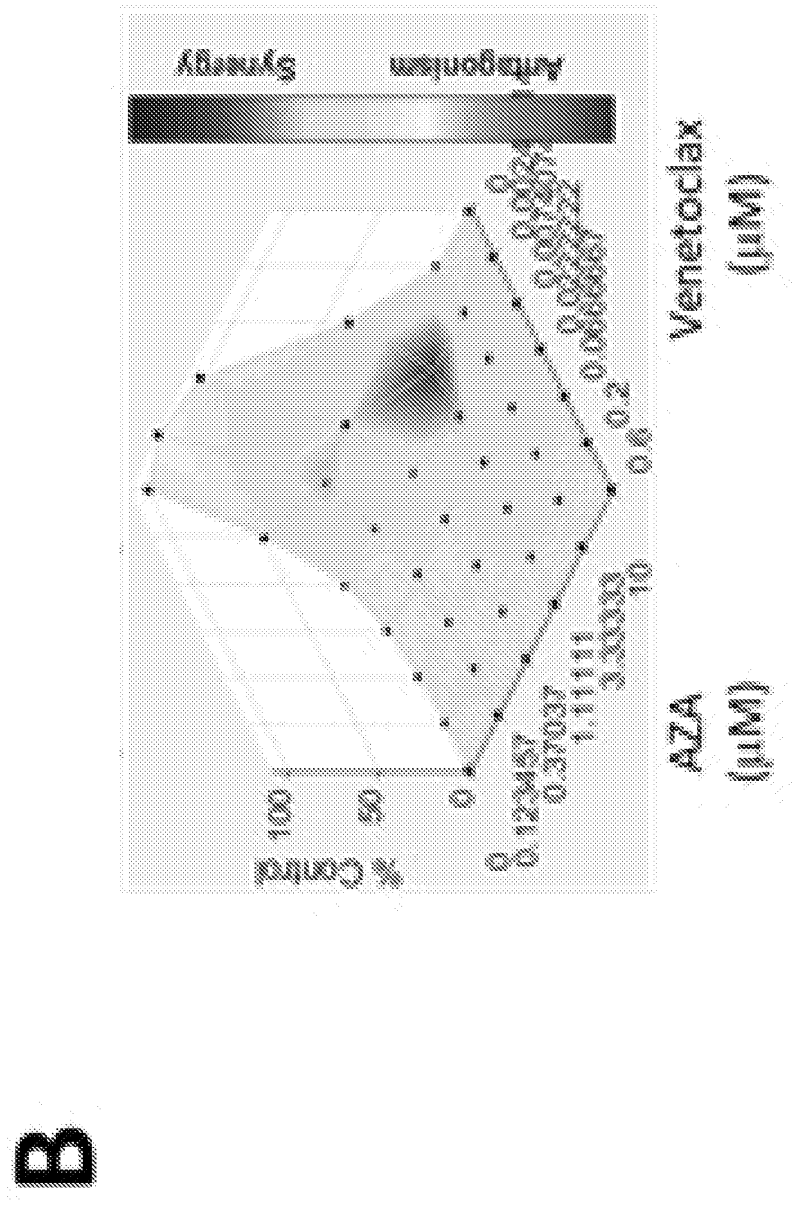

B
Synergy
Antagonism
% Cntrl
100
50
0
0.123457
0.37037
1.11111
3.33333
10
AZA
(μM)
0.2
0.6
Venetoclax
(μM)

FIG. 16C

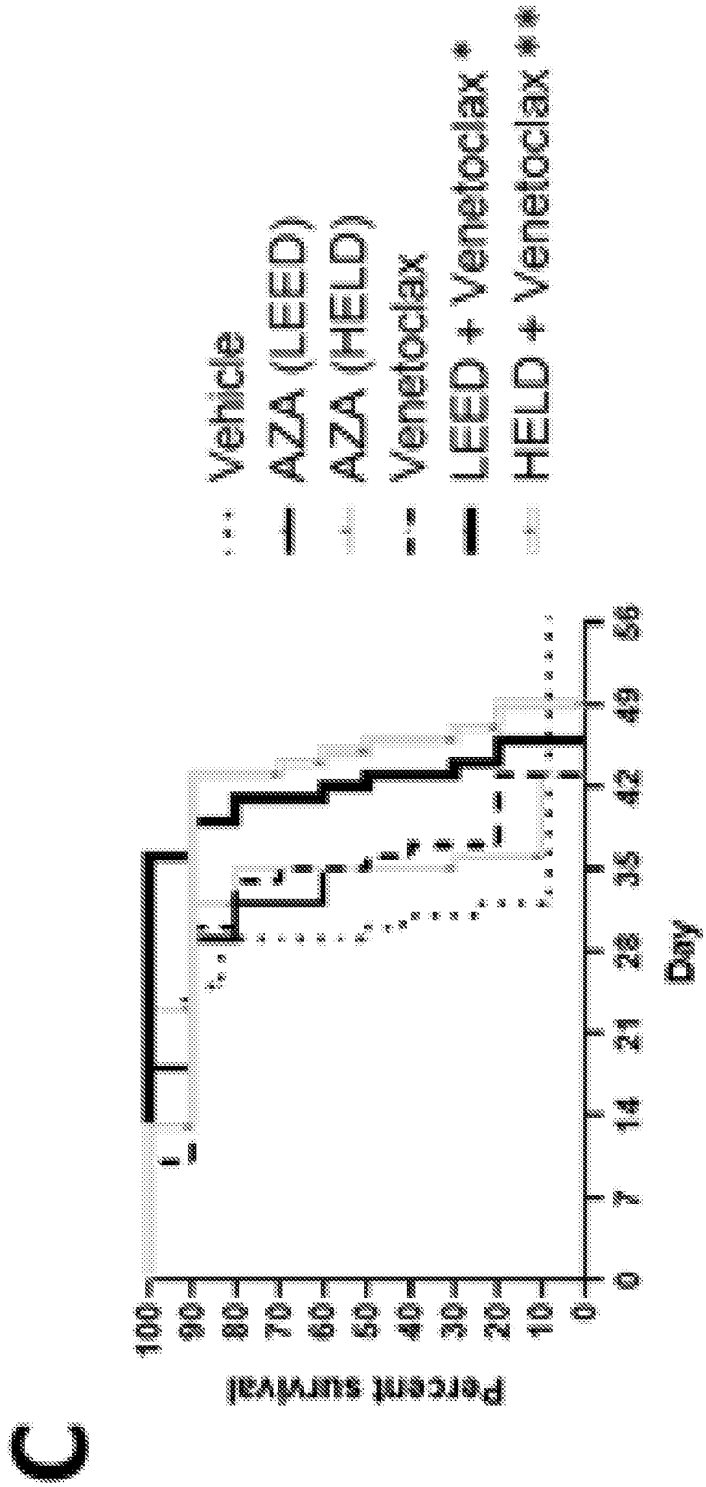

C
Percent survival
Day
0
7
14
21
28
35
42
49
56
100
90
80
70
60
50
40
30
20
10
0
Vehicle
AZA (LEED)
AZA (HELD)
Venetoclax
LEED + Venetoclax *
HELD + Venetoclax **

FIG. 16D

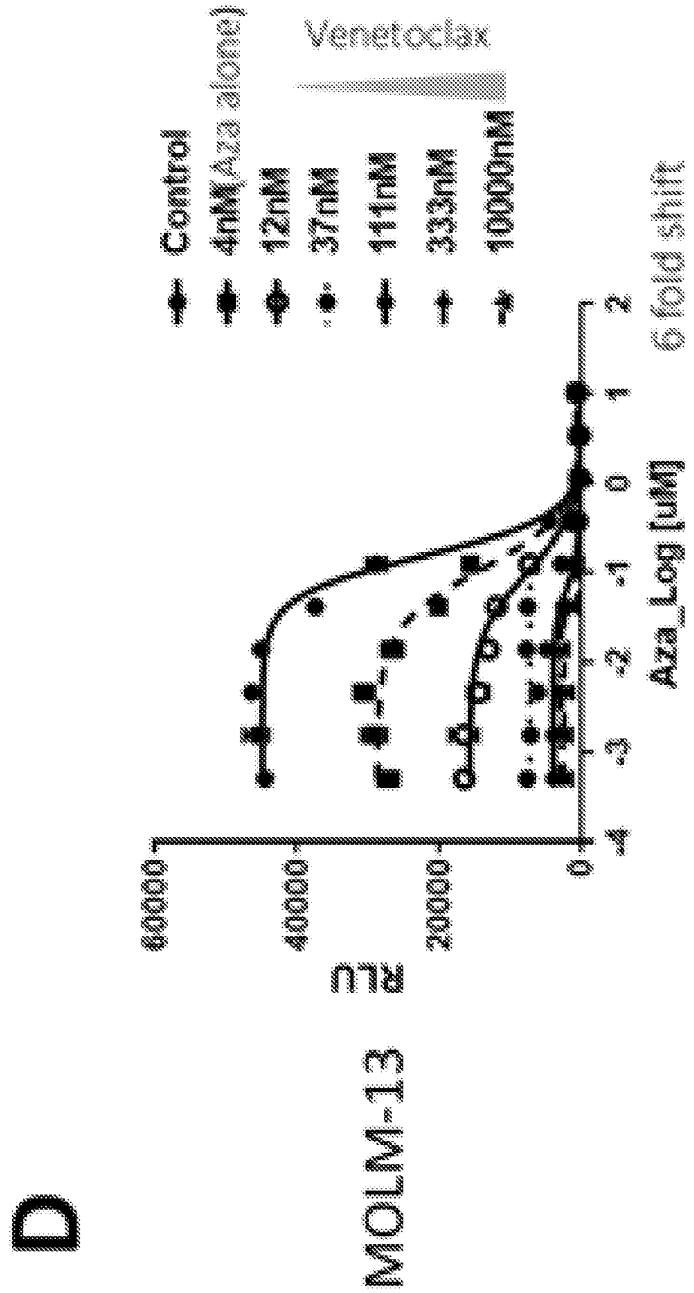

D
MOLM-13
RLU
60000
40000
20000
0
-4
-3
-2
-1
0
1
2
Aza_Log [uM]
6 fold shift
Control
4nM(Aza alone)
Venetoclax
12nM
37nM
111nM
333nM
1000nM

FIG. 16E

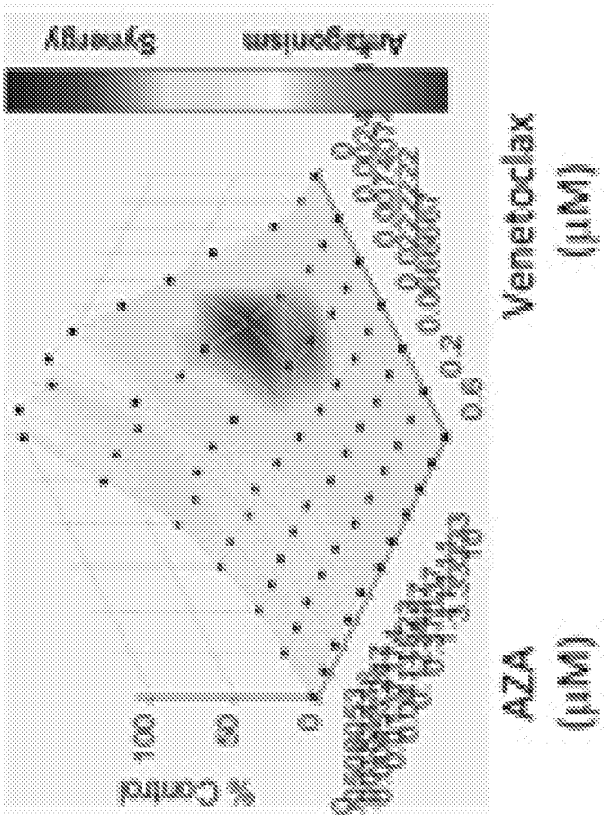

Synergy
Antagonism
% Control
100
50
0
0.2
0.6
Venetoclax (μM)
AZA (μM)

FIG. 16F

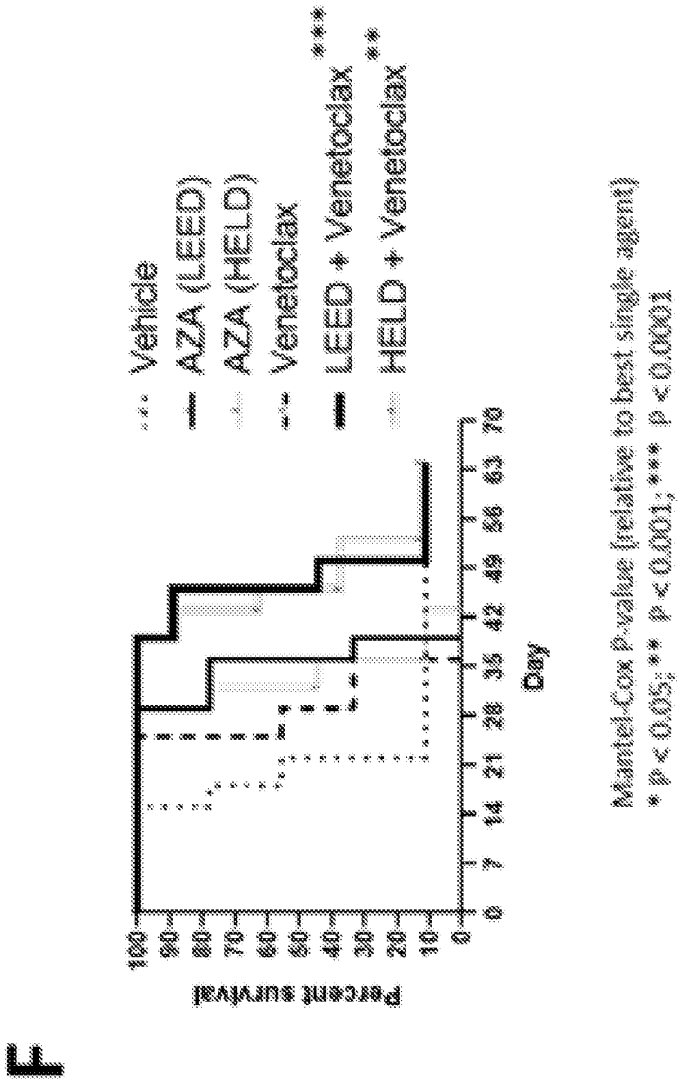

Vehicle
AZA (LEED)
AZA (HELD)
Venetoclax
LEED + Venetoclax***
HELD + Venetoclax**
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
70
Day
Mantel-Cox p-value (relative to best single agent)
* p < 0.05; ** p < 0.001; *** p < 0.0001

FIG. 17A

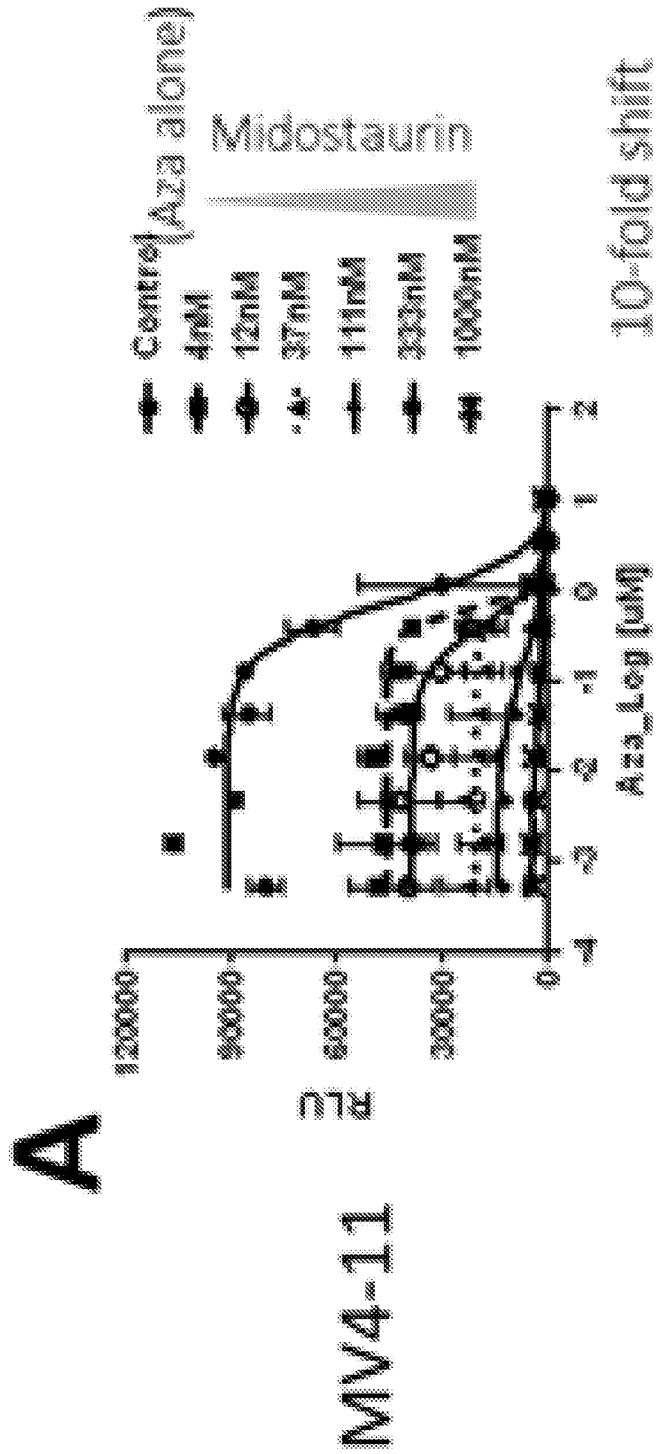

A
MV4-11
RLU
120000
90000
60000
30000
0
-4
-3
-2
-1
0
1
2
Aza_Log [uM]
Midostaurin
Control (Aza alone)
4nM
12nM
37nM
111nM
333nM
1000nM
10-fold shift

FIG. 17B

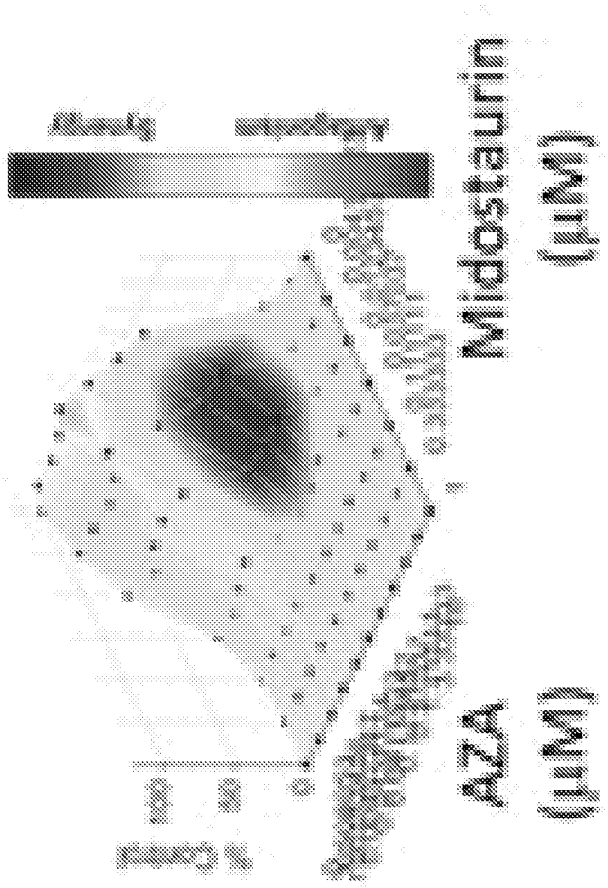


FIG. 17

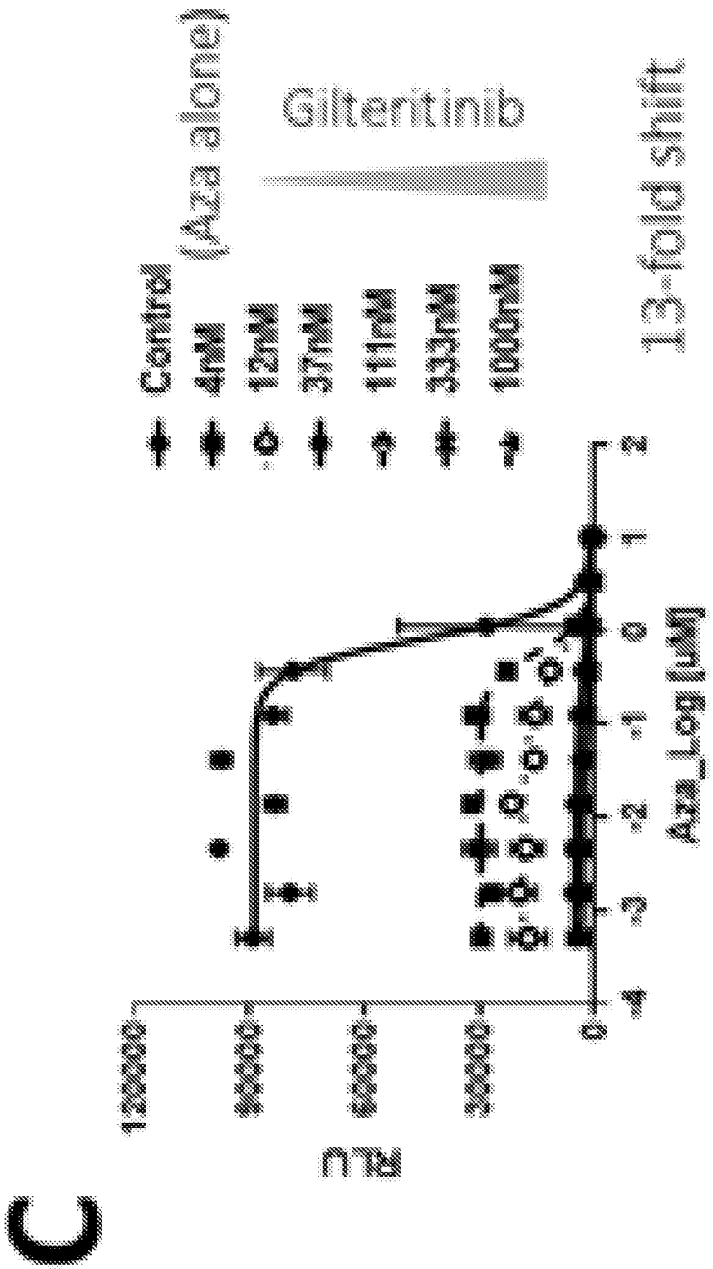

C
RLU
120000
90000
60000
30000
0
-4
-3
-2
-1
0
1
2
Azn_Log [uM]
Control
(Azn alone)
4nM
12nM
37nM
111nM
333nM
1000nM
Gilteritinib
13-fold shift

Fig. 17D

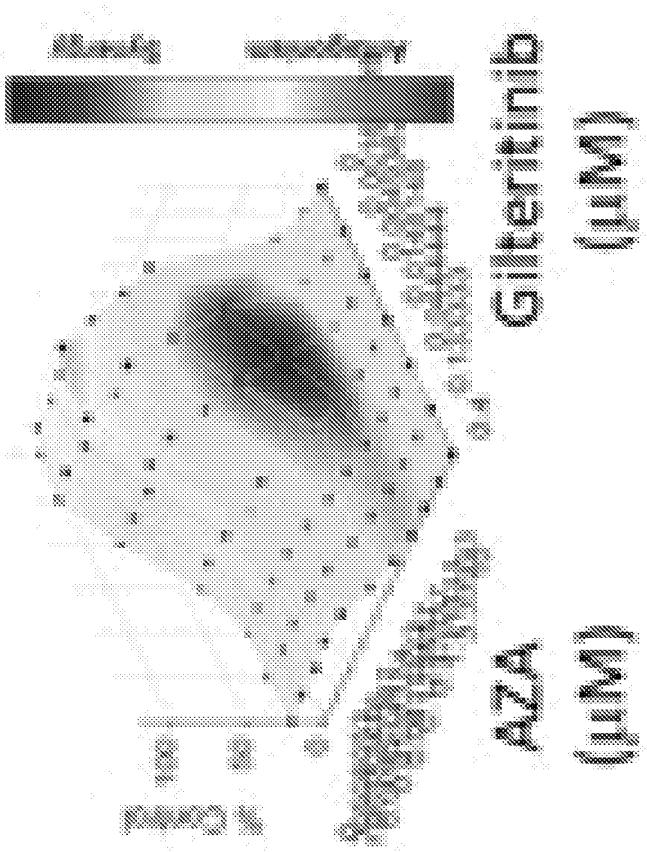


FIG. 17E

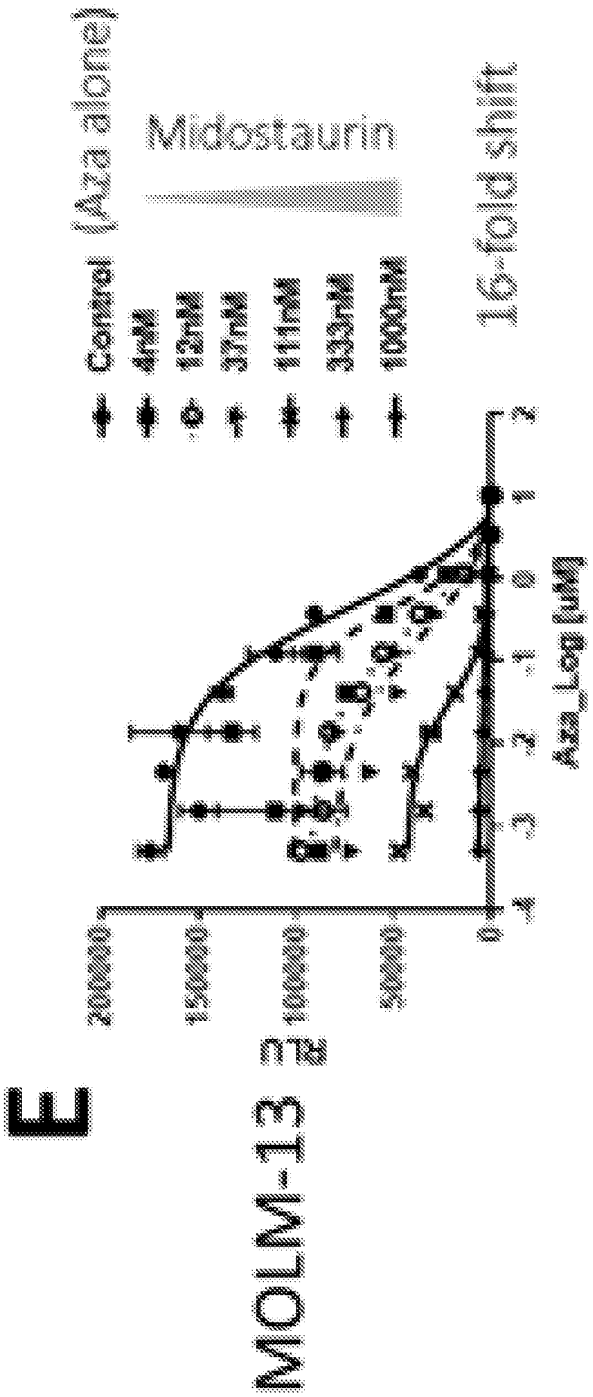

E
MOLM-13
RLU
200000
150000
100000
50000
0
-4
-3
-2
-1
0
1
2
Aza_Log [uM]
16-fold shift
Midostaurin
Control (Aza alone)
4nM
12nM
37nM
111nM
333nM
1000nM

FIG. 17F

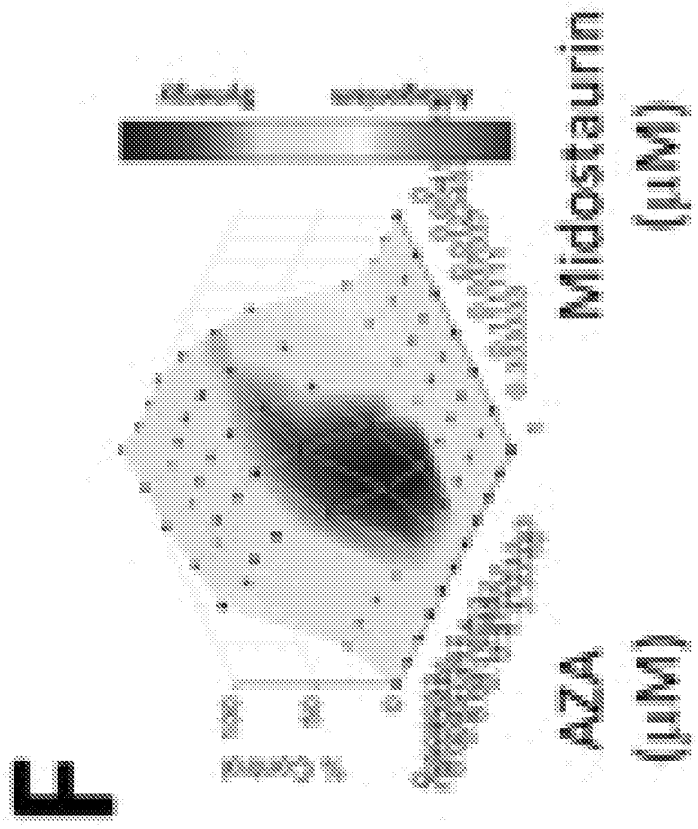


FIG. 17G

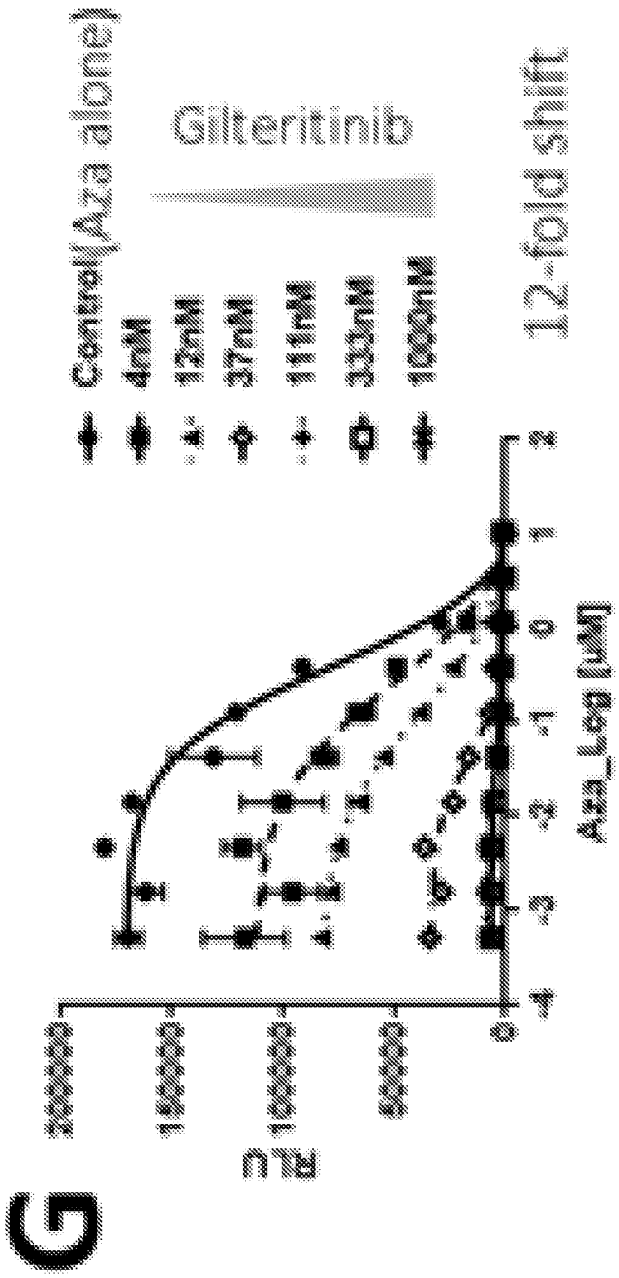

G
Control(Aza alone)
Gilteritinib
4nM
12nM
37nM
111nM
333nM
1000nM
12-fold shift
RLU
Aza_Log [uM]

FIG. 17H

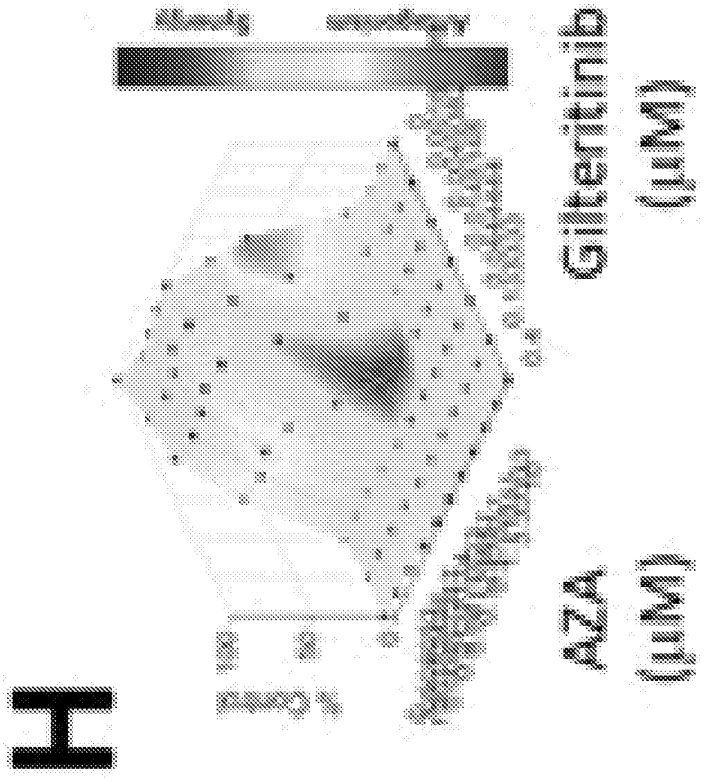


FIG. 17I

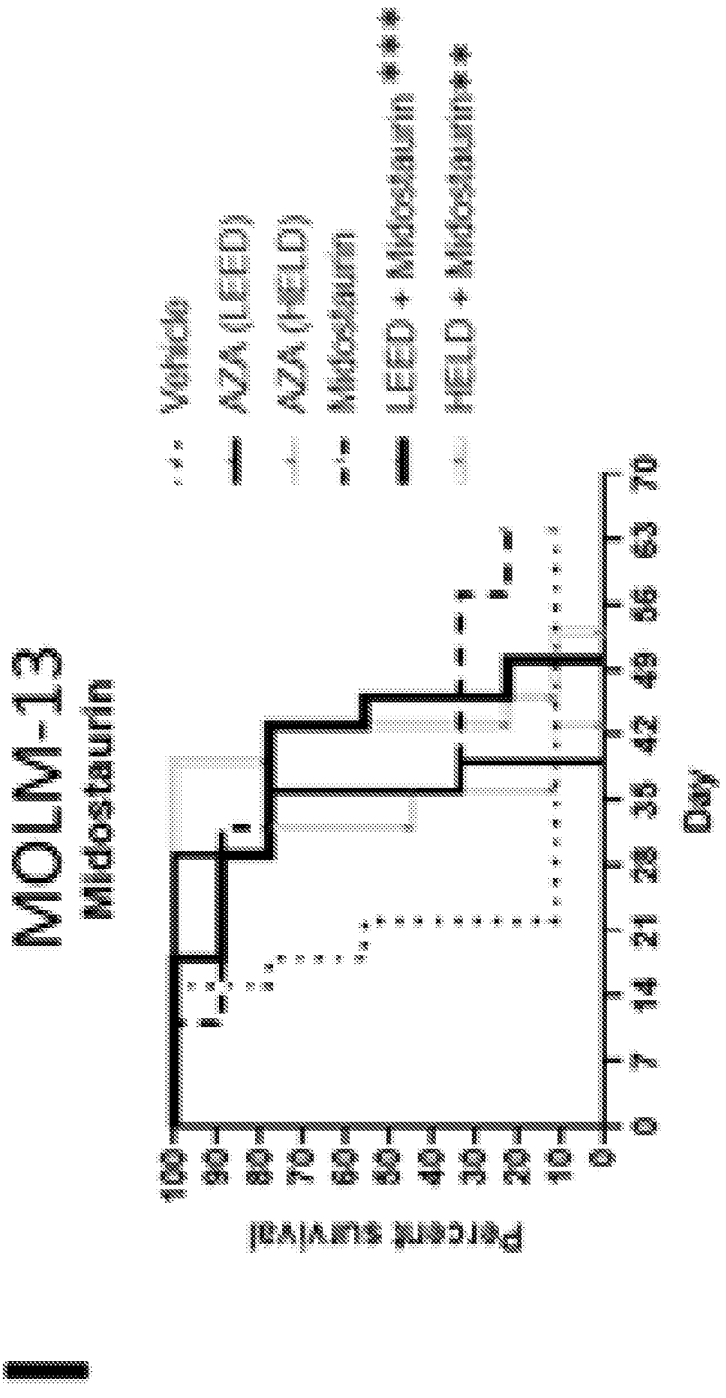

MOLM-13
Midostaurin
Vehicle
AZA (LEED)
AZA (HELD)
Midostaurin
LEED + Midostaurin***
HELD + Midostaurin***
Percent survival
Day
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
70

FIG. 17J

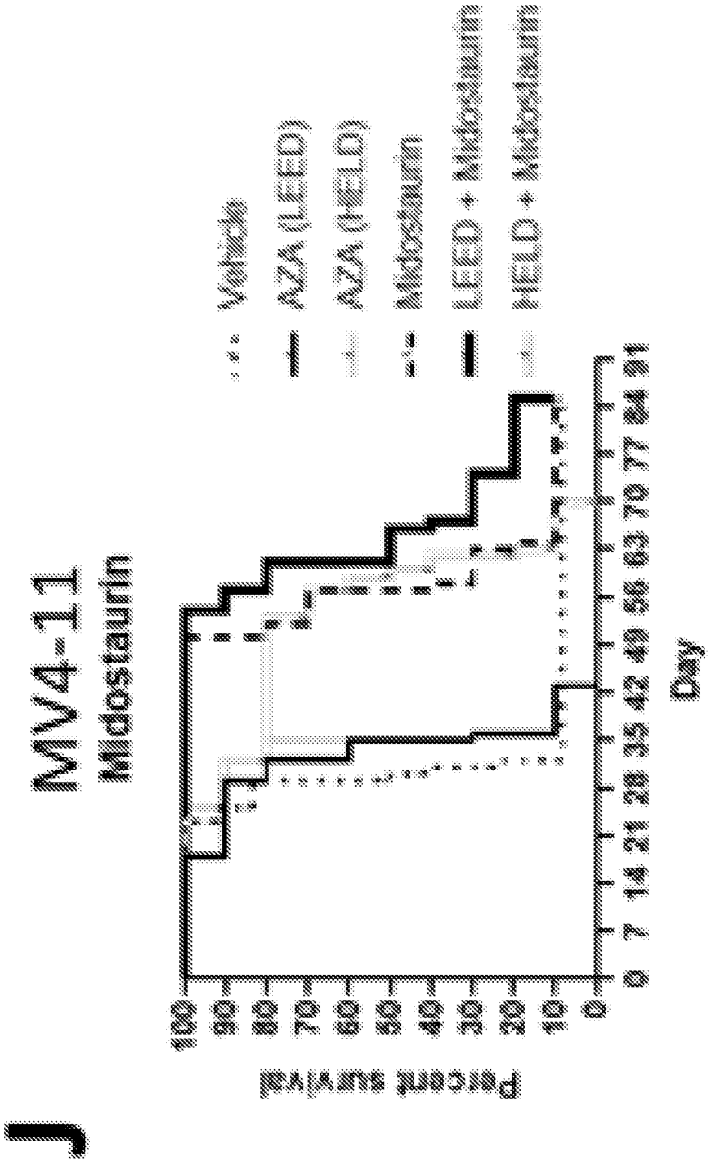

J
MV4-11
Midostaurin
Percent survival
Day
0
7
14
21
28
35
42
49
56
63
70
77
84
91
100
90
80
70
60
50
40
30
20
10
0
Vehicle
AZA (LEED)
AZA (HELD)
Midostaurin
LEED + Midostaurin
HELD + Midostaurin

FIG. 17K

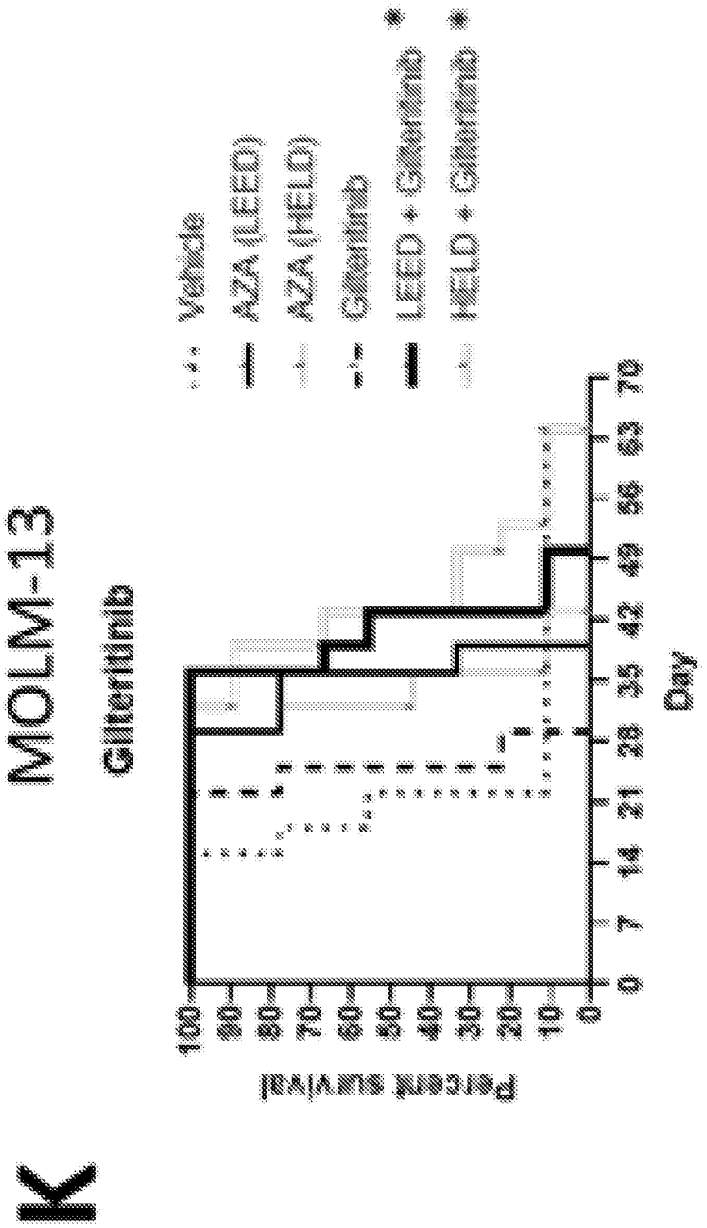
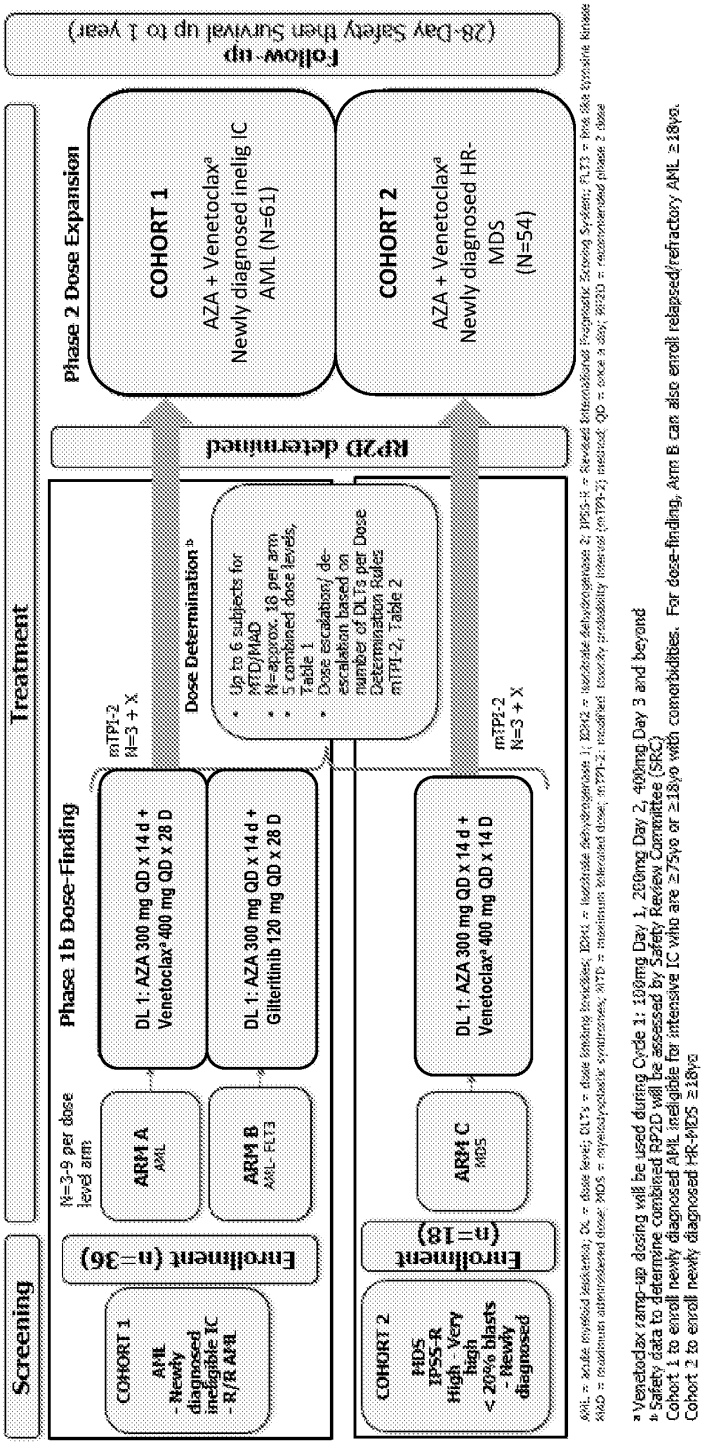

K
MOLM-13
Gilteritinib
Vehicle
AZA (LEED)
AZA (HELD)
Gilteritinib
LEED + Gilteritinib
HELD + Gilteritinib
*
*
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
70
Day

FIG. 18



AML = acute myeloid leukemia; DL = dose level; DLTs = dose limiting toxicities; IDH1 = isocitrate dehydrogenase 1; IDH2 = isocitrate dehydrogenase 2; IPSS-R = Revised International Prognostic Scoring System; FLT3 = fms like tyrosine kinase 3; MAD = maximum administered dose; MDS = myelodysplastic syndromes; MTD = maximum tolerated dose; mTPI-2: modified toxicity probability interval-2(mTPI-2); mtd/qd: QD = once a day; R/R = recommended phase 2 dose

[a] Venetoclax ramp-up dosing will be used during Cycle 1: 100mg Day 1, 200mg Day 2, 400mg Day 3 and beyond
[b] Safety data to determine combined RP2D will be assessed by Safety Review Committee (SRC)
Cohort 1 to enroll newly diagnosed AML ineligible for intensive IC who are ≥75yo or ≥18yo with comorbidities. For dose-finding, Arm B can also enroll relapsed/refractory AML ≥18yo.
Cohort 2 to enroll newly diagnosed HR-MDS ≥18yo