FIG. 1

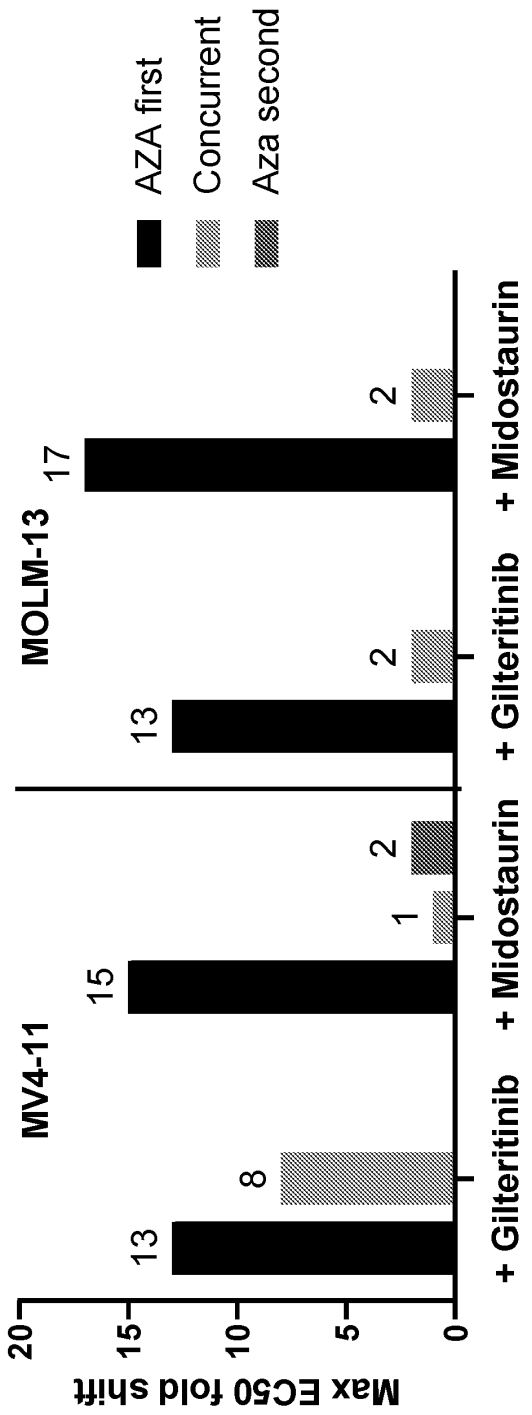

AZA first
Concurrent
Aza second
Max EC50 fold shift
0
5
10
15
20
MV4-11
MOLM-13
13
8
15
1
2
13
2
17
2
+ Gilteritinib
+ Midostaurin
+ Gilteritinib
+ Midostaurin

FIG. 2

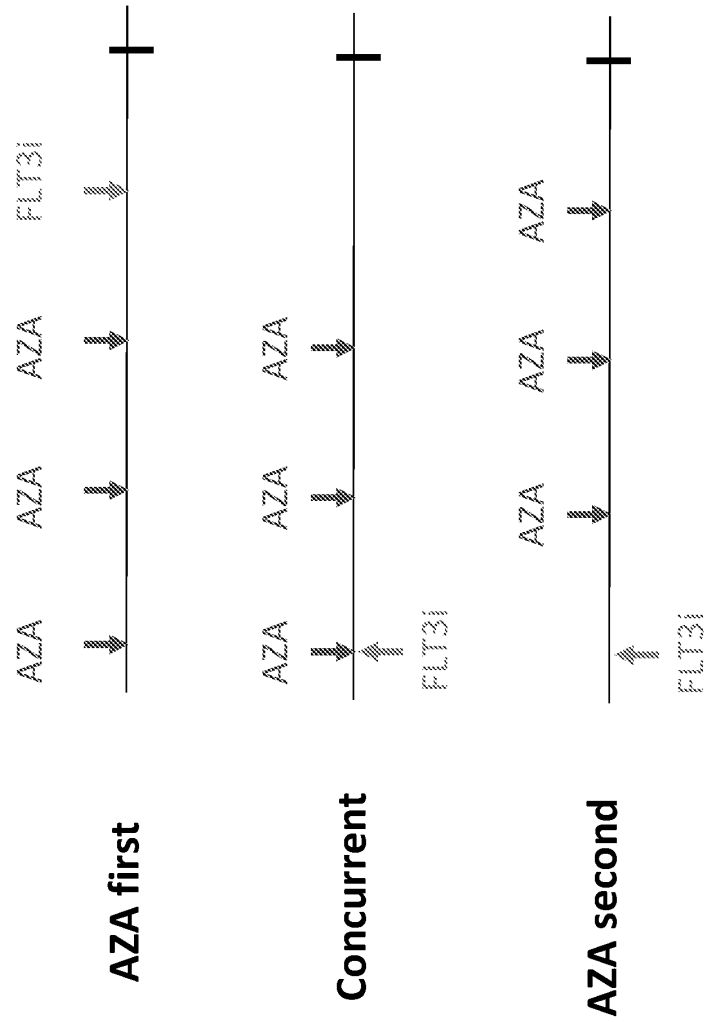

AZA
AZA
AZA
FLT3i
AZA first
AZA
AZA
AZA
FLT3i
Concurrent
AZA
AZA
AZA
FLT3i
AZA second

FIG. 3

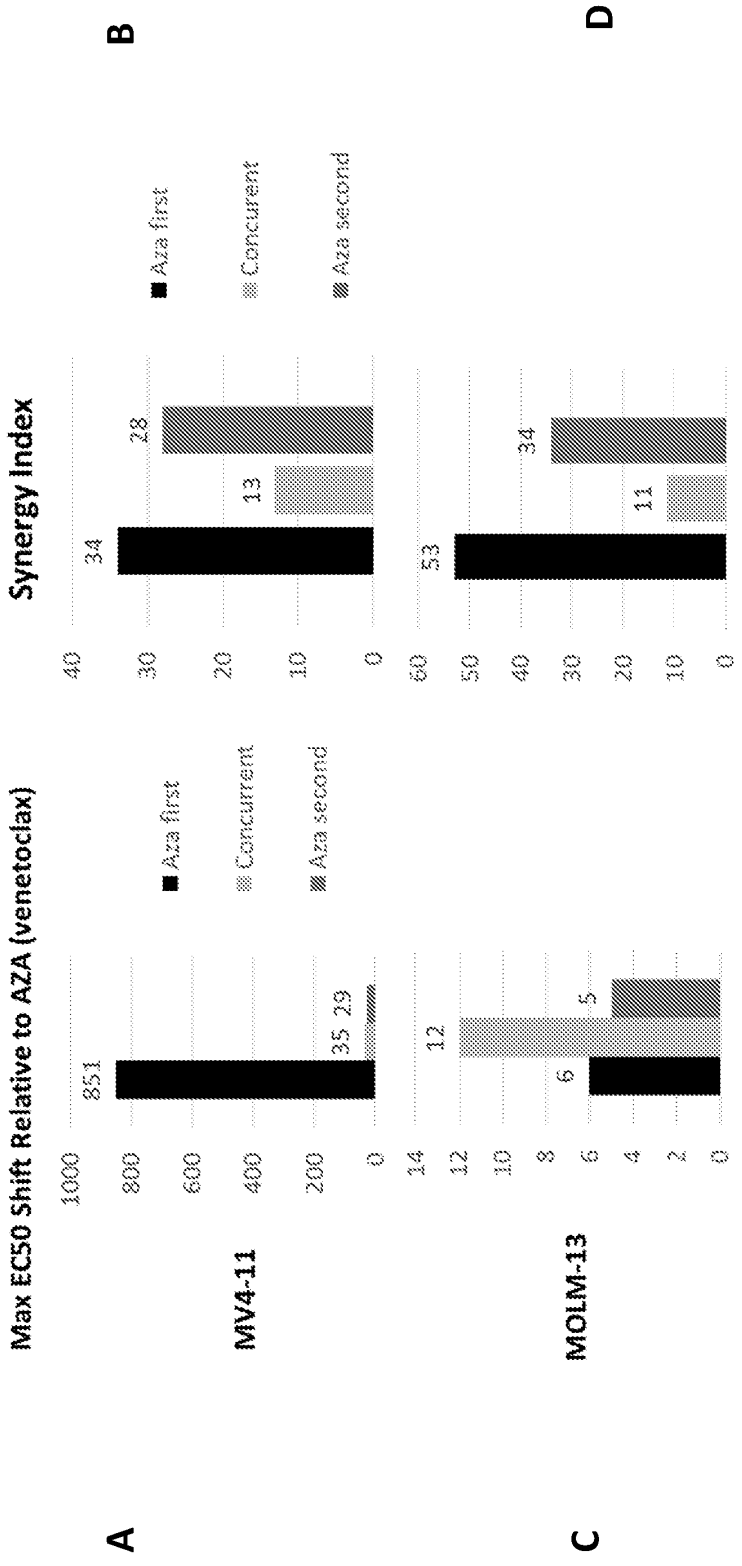

A
B
C
D
Max EC50 Shift Relative to AZA (venetoclax)
Synergy Index
MV4-11
MOLM-13
Aza first
Concurrent
Aza second
851
35
29
6
12
5
53
34
11
28
13
34
1000
800
600
400
200
0
14
12
10
8
6
4
2
0
60
50
40
30
20
10
0
40
30
20
10
0

FIG. 4

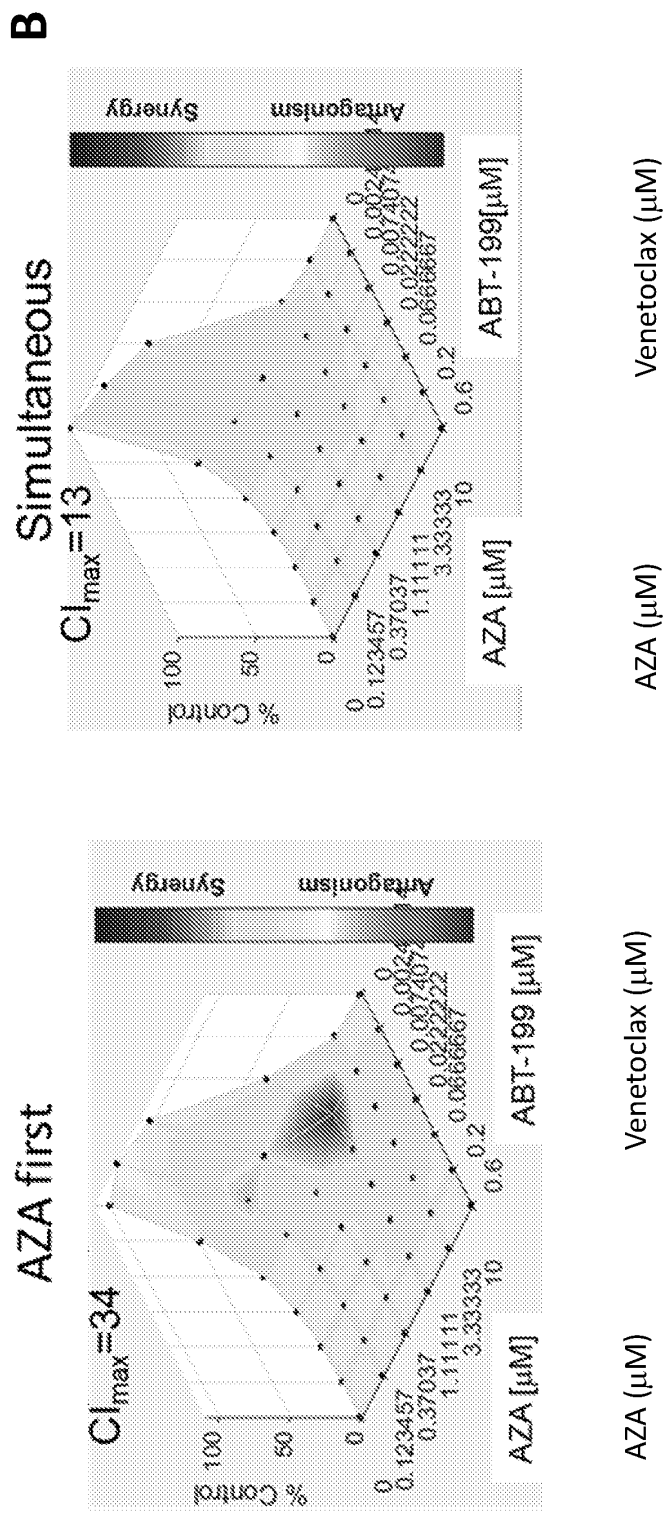

A
AZA first
Synergy
Antagonism
% Control
100
50
0
CImax=34
AZA [μM]
ABT-199 [μM]
Venetoclax (μM)
AZA (μM)
B
Simultaneous
CImax=13
ABT-199[μM]
Venetoclax (μM)
AZA (μM)

FIG. 4 (continued)

c

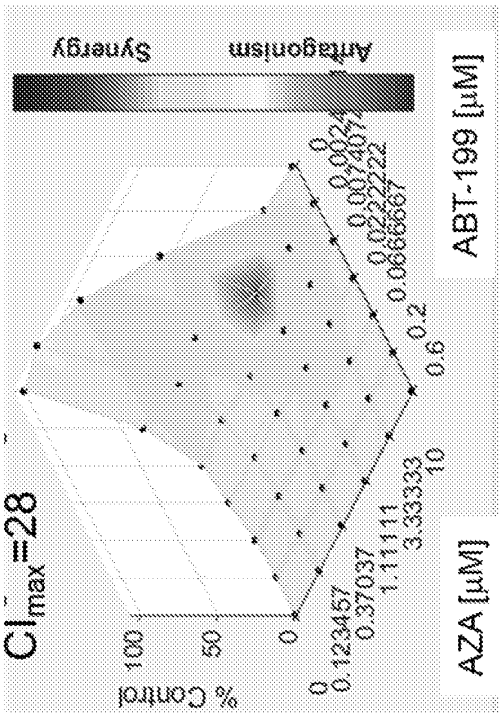


FIG. 5

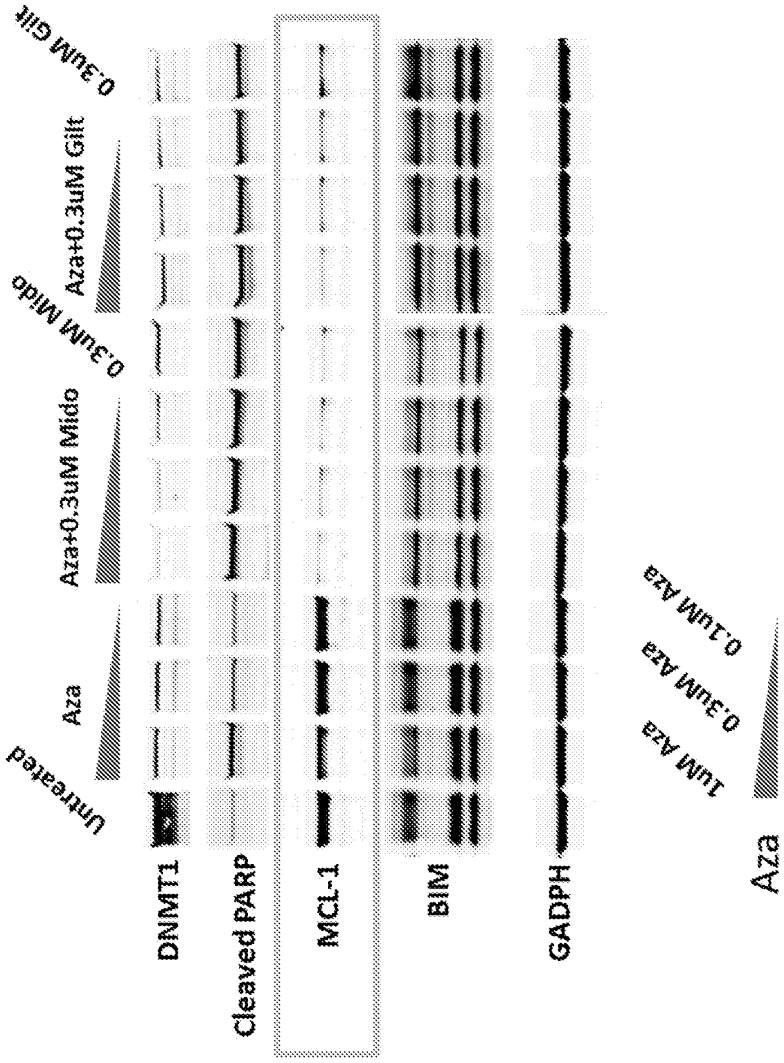

Untreated
Aza
Aza+0.3uM Mido
0.3uM Mido
Aza+0.3uM Gilt
0.3uM Gilt
DNMT1
Cleaved PARP
MCL-1
BIM
GADPH
1uM Aza
0.3uM Aza
0.1uM Aza
Aza

FIG. 6

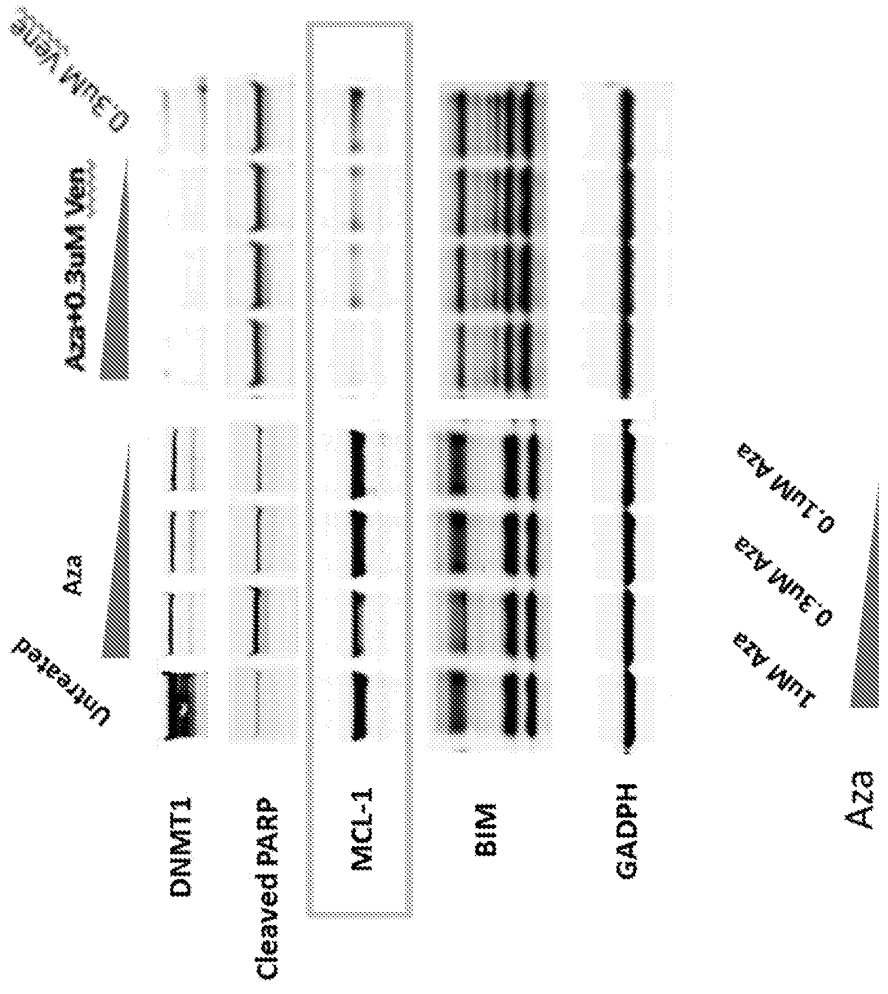

Untreated
Aza
Aza+0.3uM Ven
0.3uM Ven
DNMT1
Cleaved PARP
MCL-1
BIM
GADPH
1uM Aza
0.3uM Aza
0.1uM Aza
Aza

FIG. 7A

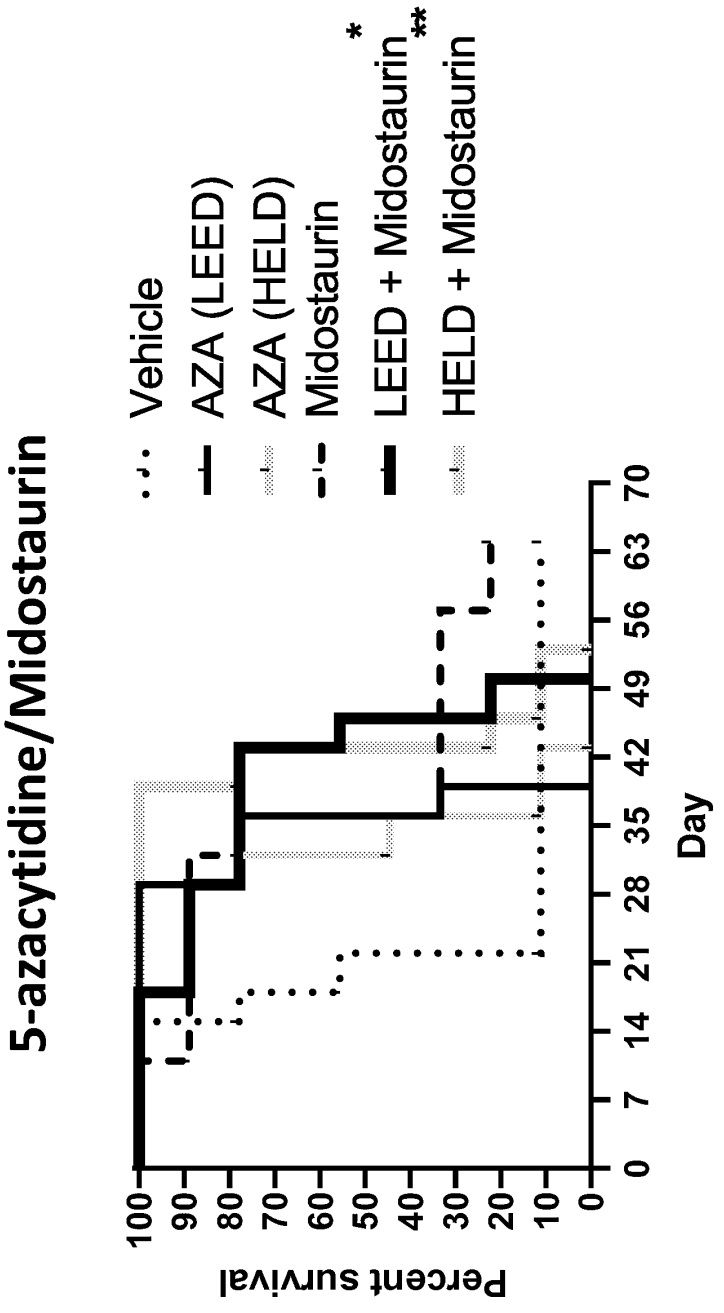

5-azacytidine/Midostaurin
Vehicle
AZA (LEED)
AZA (HELD)
Midostaurin
LEED + Midostaurin
HELD + Midostaurin
*
**
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
70
Day

FIG. 7B

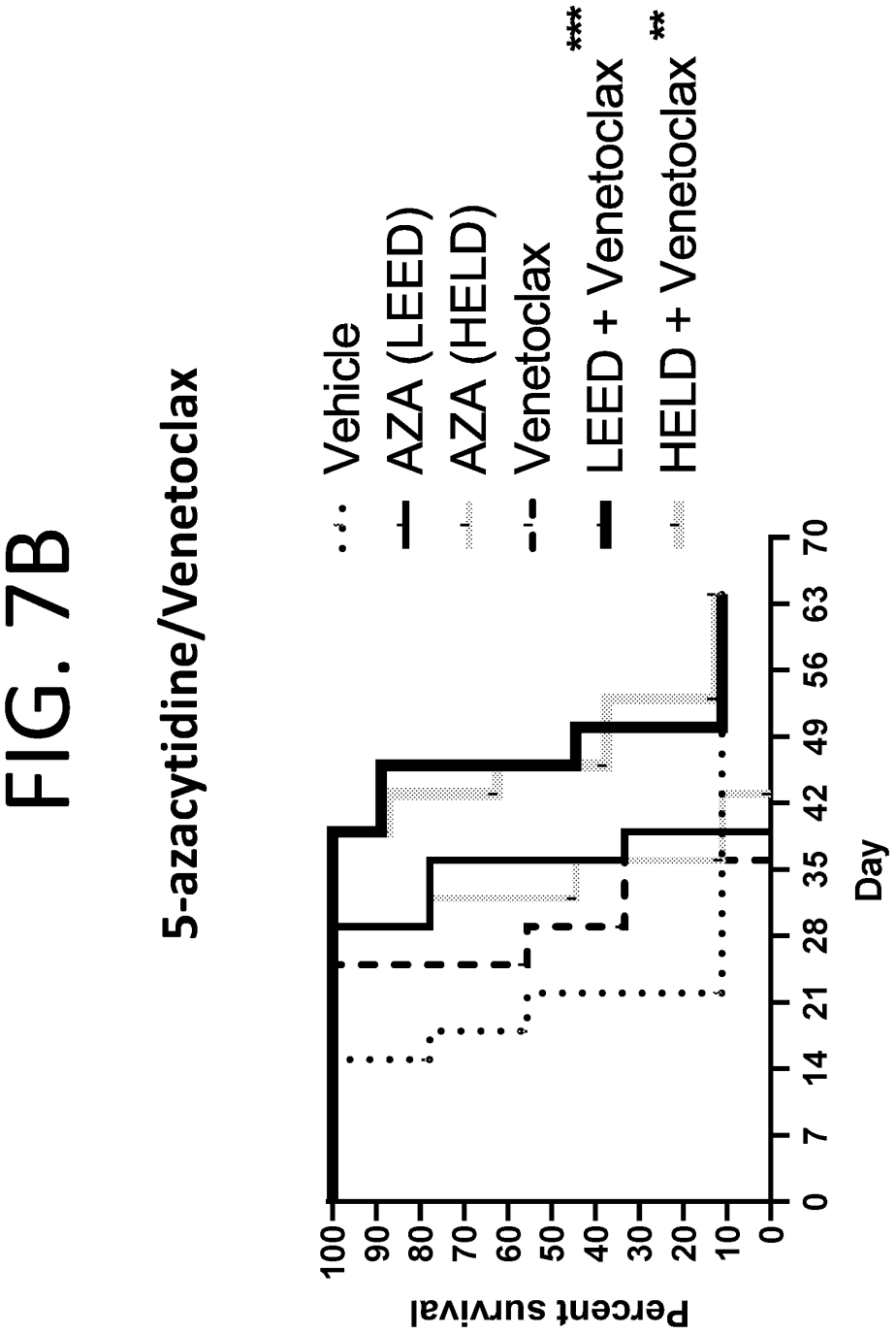

5-azacytidine/Venetoclax
Vehicle
AZA (LEED)
AZA (HELD)
Venetoclax
LEED + Venetoclax
HELD + Venetoclax
***
**
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
70
Day

FIG. 7C

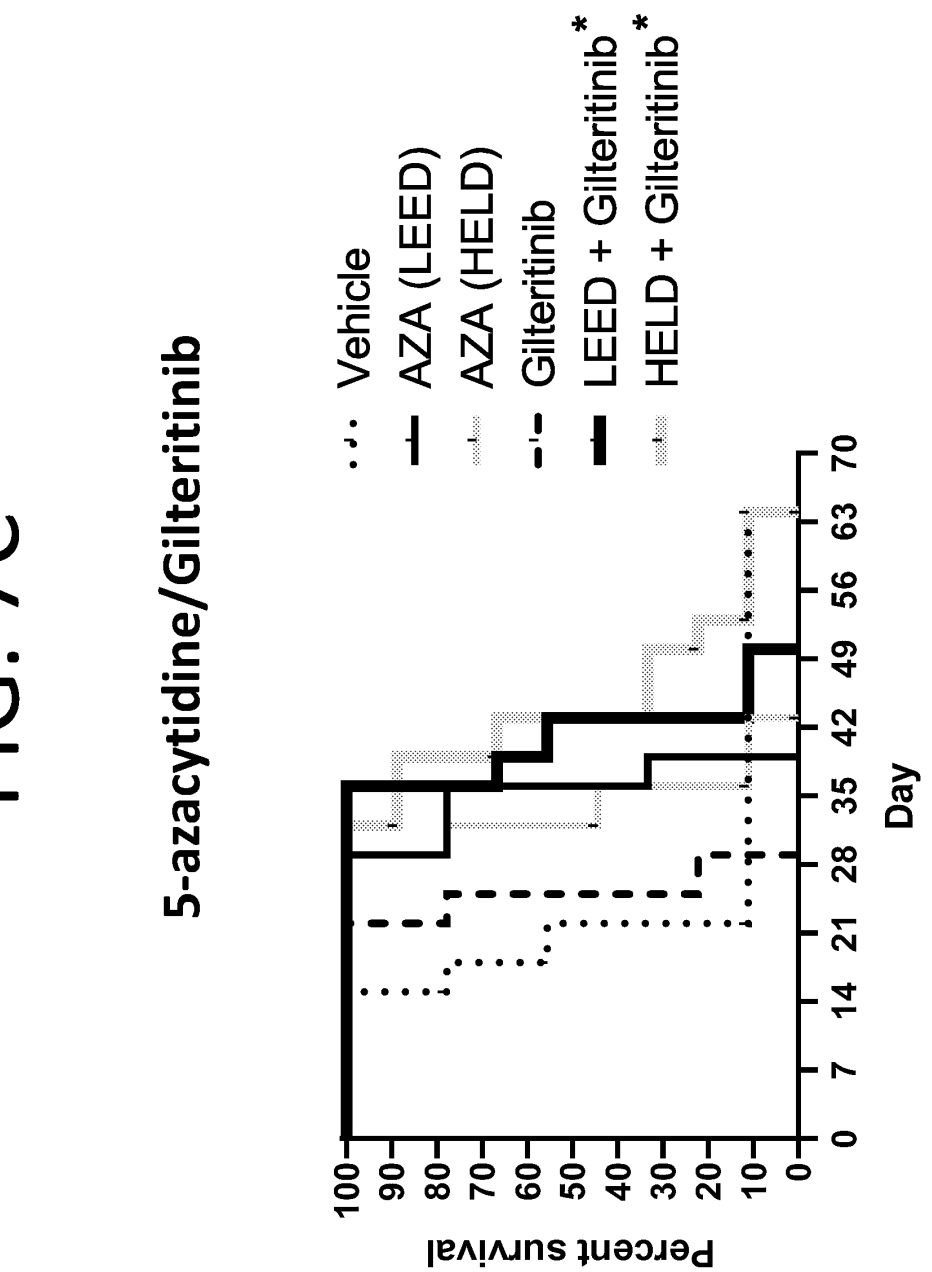

5-azacytidine/Gilteritinib
Vehicle
AZA (LEED)
AZA (HELD)
Gilteritinib
LEED + Gilteritinib*
HELD + Gilteritinib*
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
70
Day

FIG. 8A

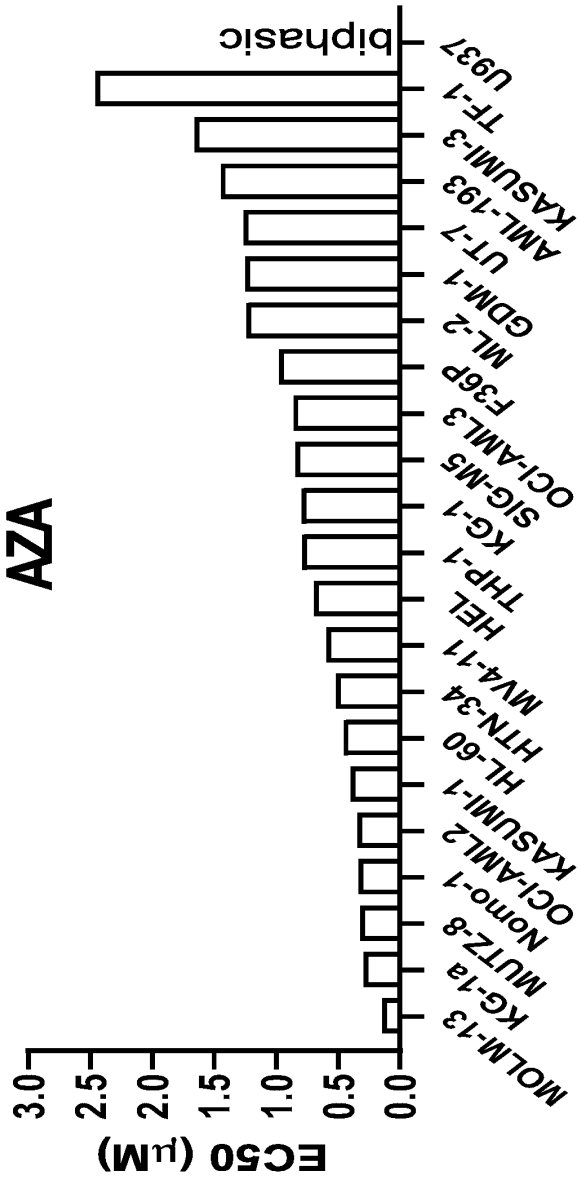

AZA
EC50 (μM)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
MOLM-13
KG-1a
MUTZ-8
Nomo-1
OCI-AML2
KASUMI-1
HL-60
HTN-34
MV4-11
HEL
THP-1
KG-1
SIG-M5
OCI-AML3
F36P
ML-2
GDM-1
UT-7
AML-193
KASUMI-3
TF-1
U937
biphasic

FIG. 8B

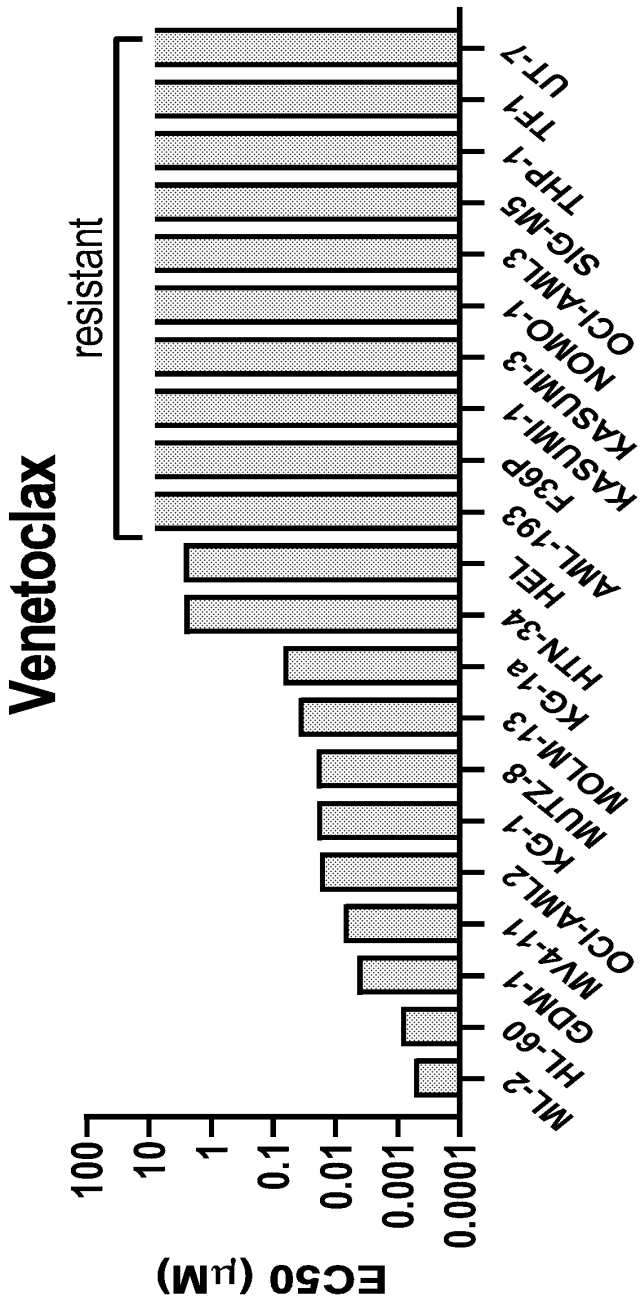

Venetoclax
resistant
EC50 (μM)
100
10
1
0.1
0.01
0.001
0.0001
ML-2
HL-60
GDM-1
MV4-11
OCI-AML2
KG-1
MUTZ-8
MOLM-13
KG-1a
HTN-34
HEL
AML-193
F36P
KASUMI-1
KASUMI-3
NOMO-1
OCI-AML3
SIG-M5
THP-1
TF-1
UT-7

FIG. 8C

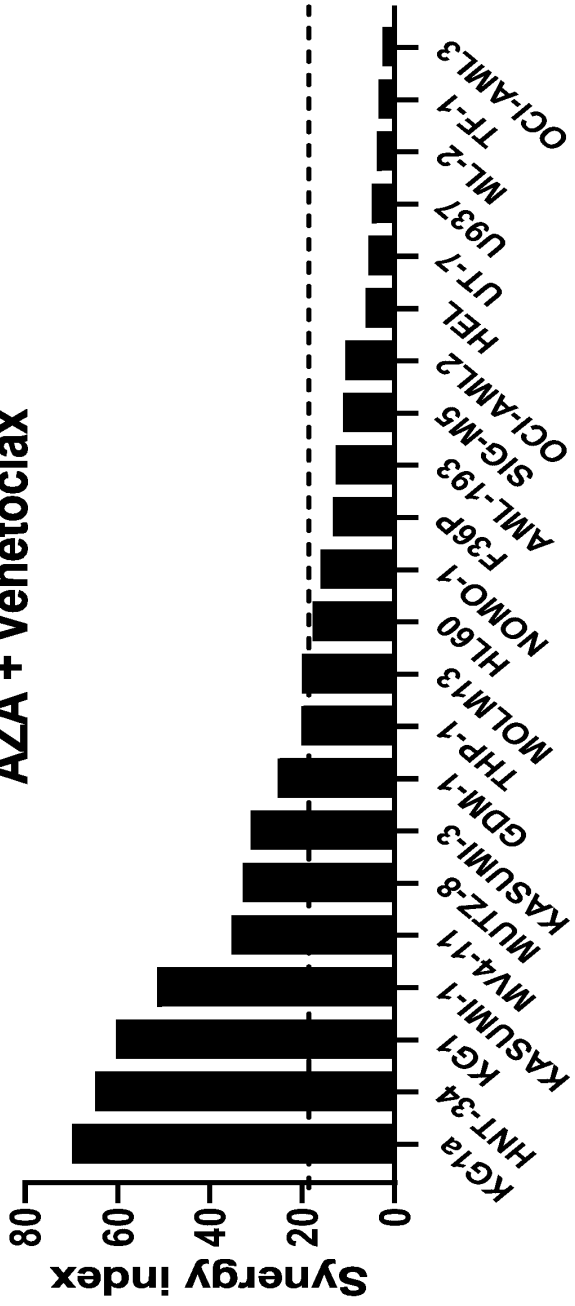

AZA + Venetoclax
Synergy index
0
20
40
60
80
KG1a
HNT-34
KG1
KASUMI-1
MV4-11
MUTZ-8
KASUMI-3
GDM-1
THP-1
MOLM13
HL60
NOMO-1
F36P
AML-193
SIG-M5
OCI-AML2
HEL
UT-7
U937
ML-2
TF-1
OCI-AML3

FIG. 9A

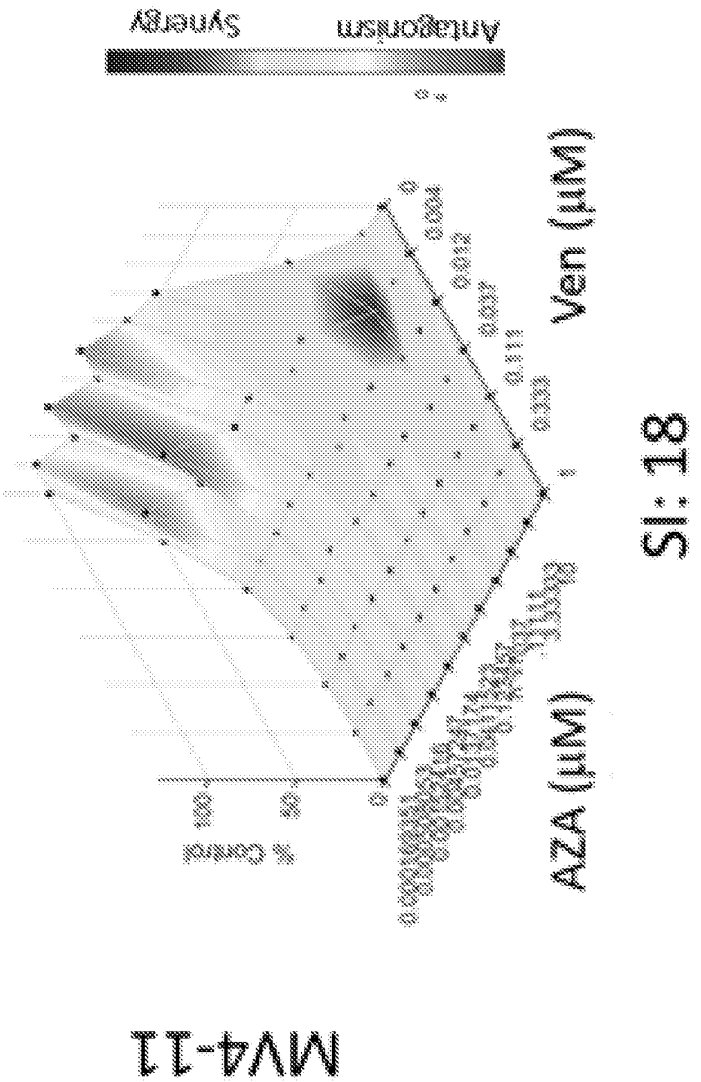

MV4-11
AZA First
Synergy
Antagonism
% control
100
50
0
AZA (μM)
Ven (μM)
0
0.004
0.012
0.037
0.111
0.333
1
3
SI: 18

FIG. 9B

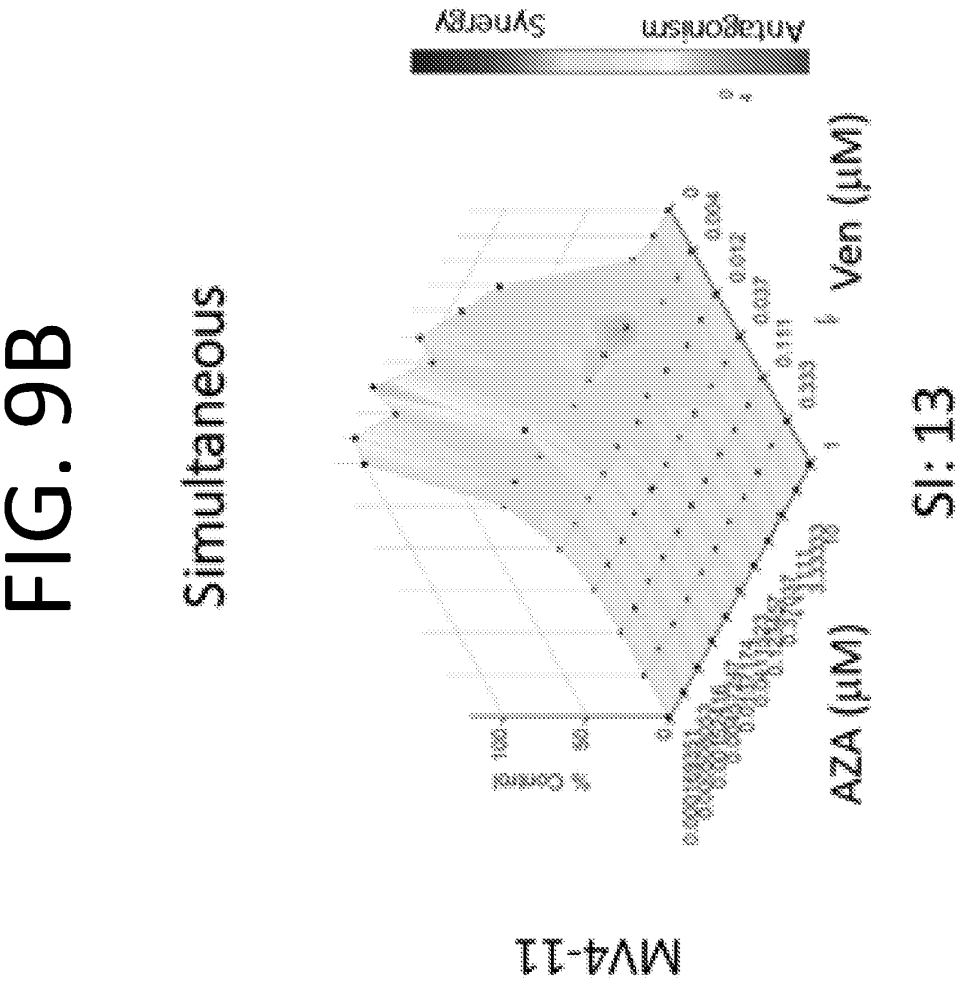

Simultaneous
Antagonism
Synergy
Ven (μM)
AZA (μM)
% Cells
MV4-11
SI: 13

FIG. 9C

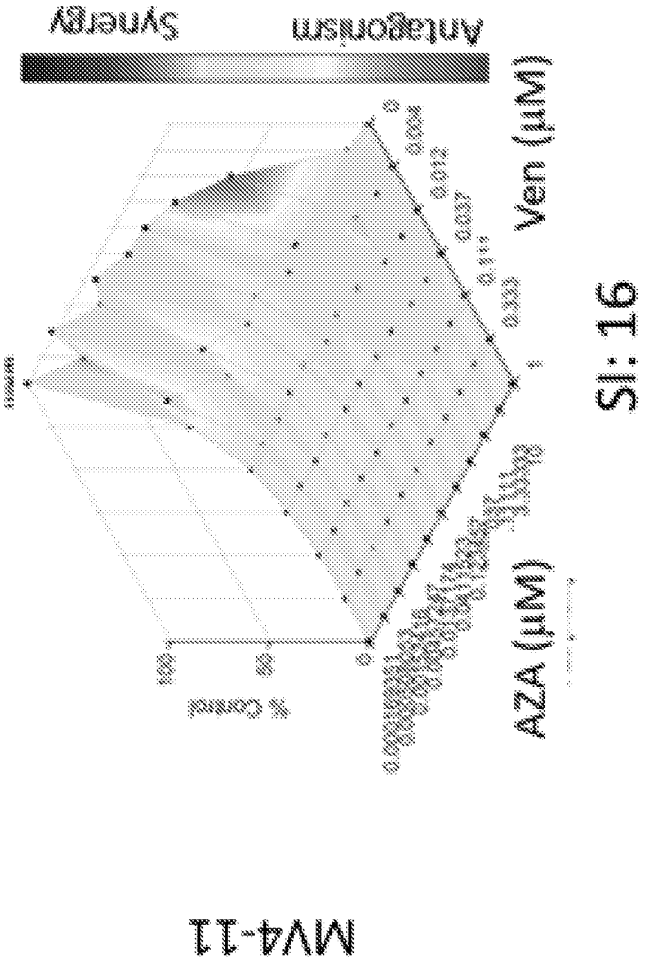

MV4-11
Venetoclax First
Antagonism
Synergy
Ven (μM)
AZA (μM)
% Control
SI: 16

FIG. 9D

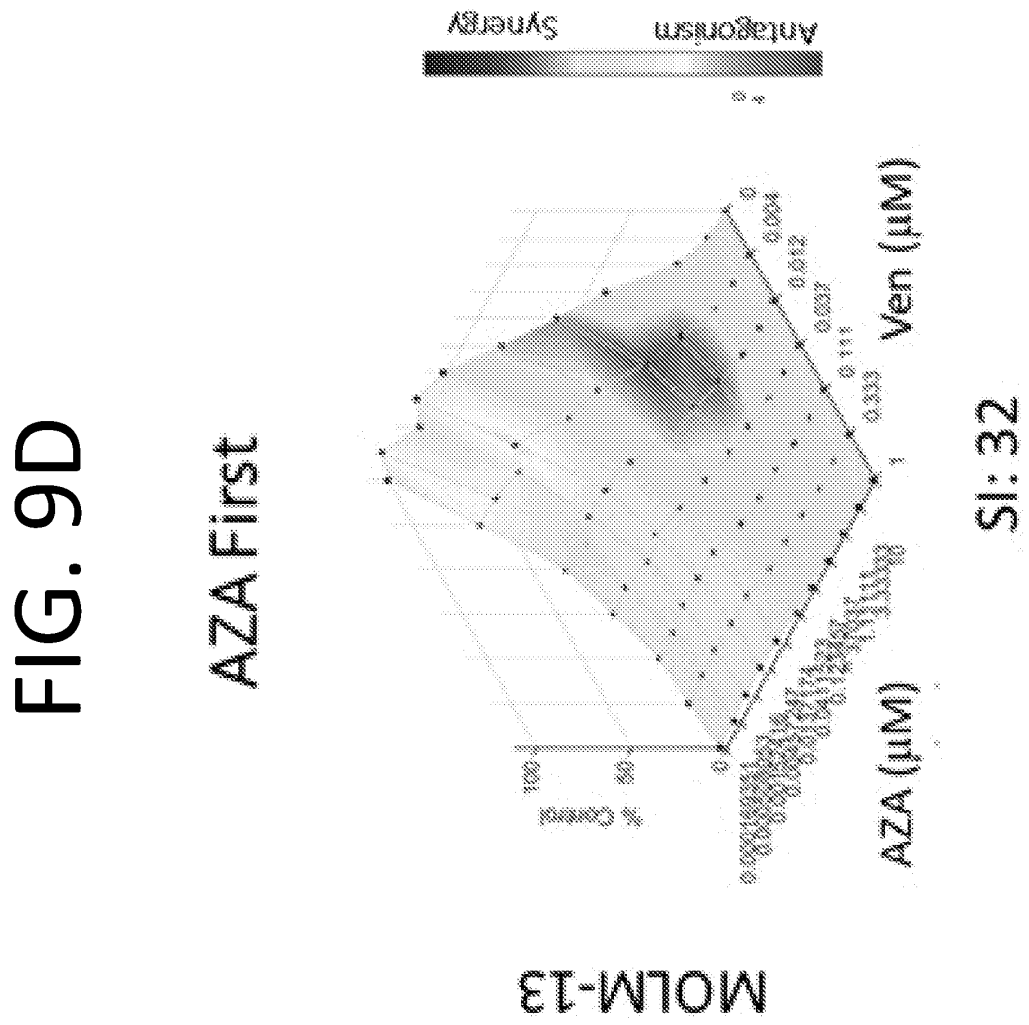

AZA First
MOLM-13
Antagonism
Synergy
Ven (μM)
AZA (μM)
% Cntrl
SI: 32

FIG. 9E

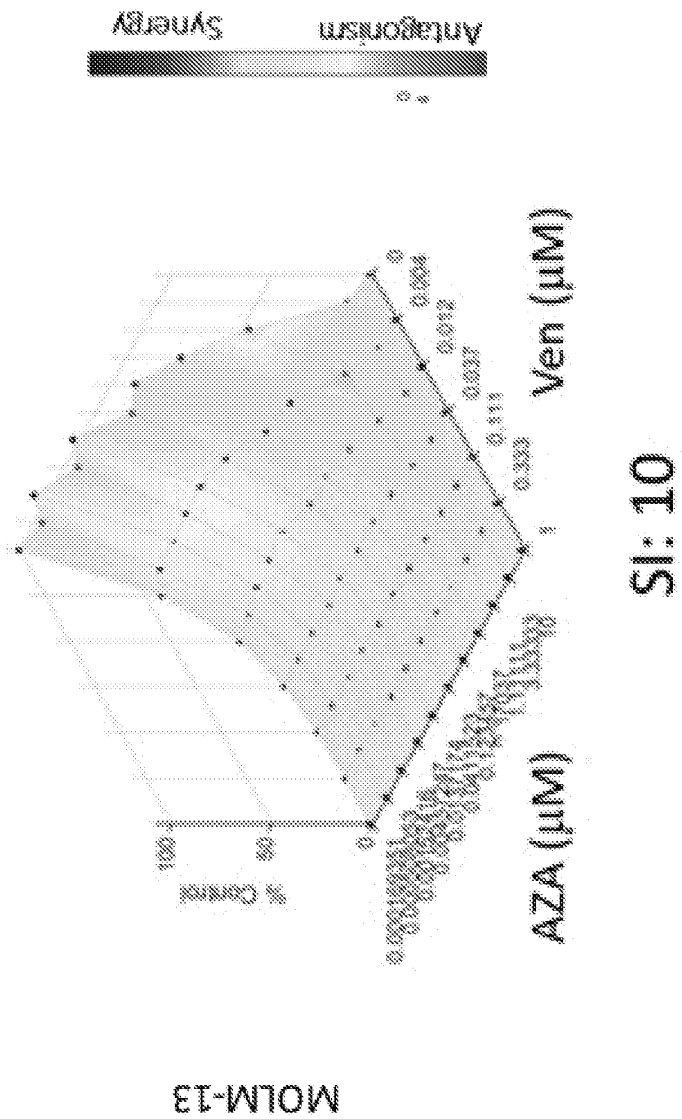

Antagonism
Synergy
Simultaneous
Ven (μM)
AZA (μM)
% Cells
SI: 10
MOLM-13

FIG. 9F

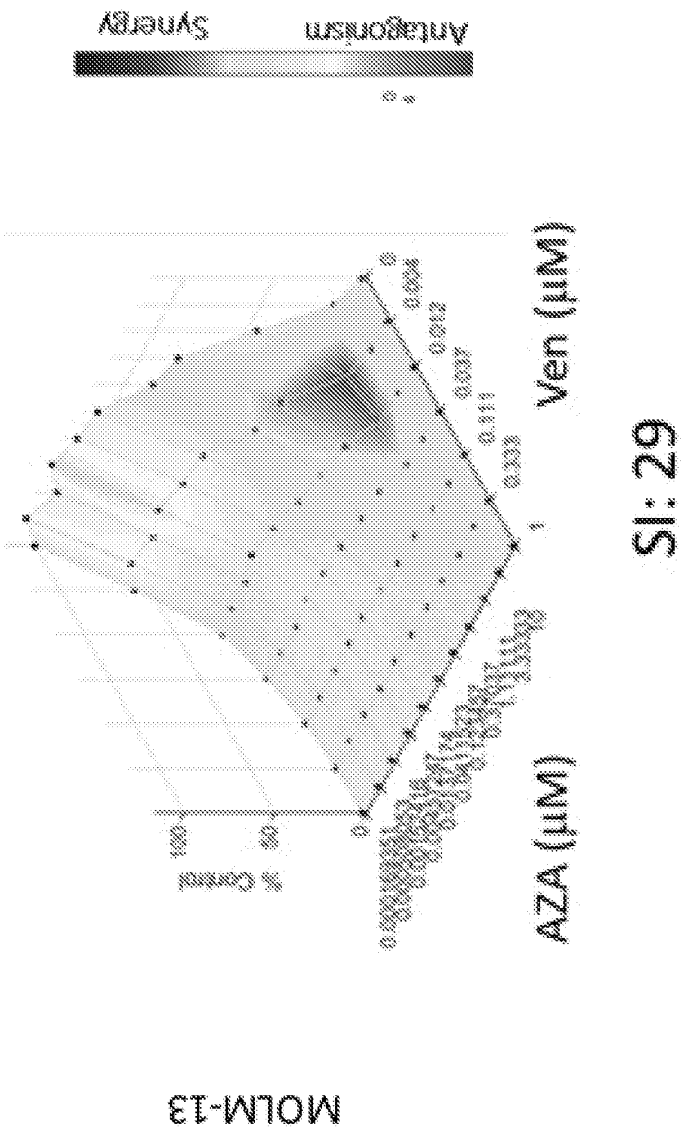

Venetoclax First
Antagonism
Synergy
Ven (μM)
AZA (μM)
% Cell
SI: 29
MOLM-13

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

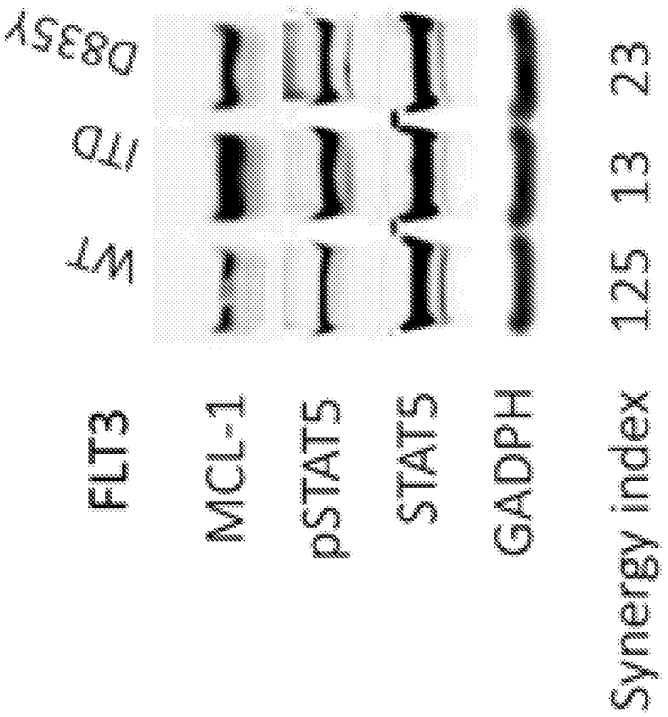

FLT3
MCL-1
pSTAT5
STAT5
GADPH
Synergy index
WT
ITD
D835Y
125
13
23

FIG. 10C

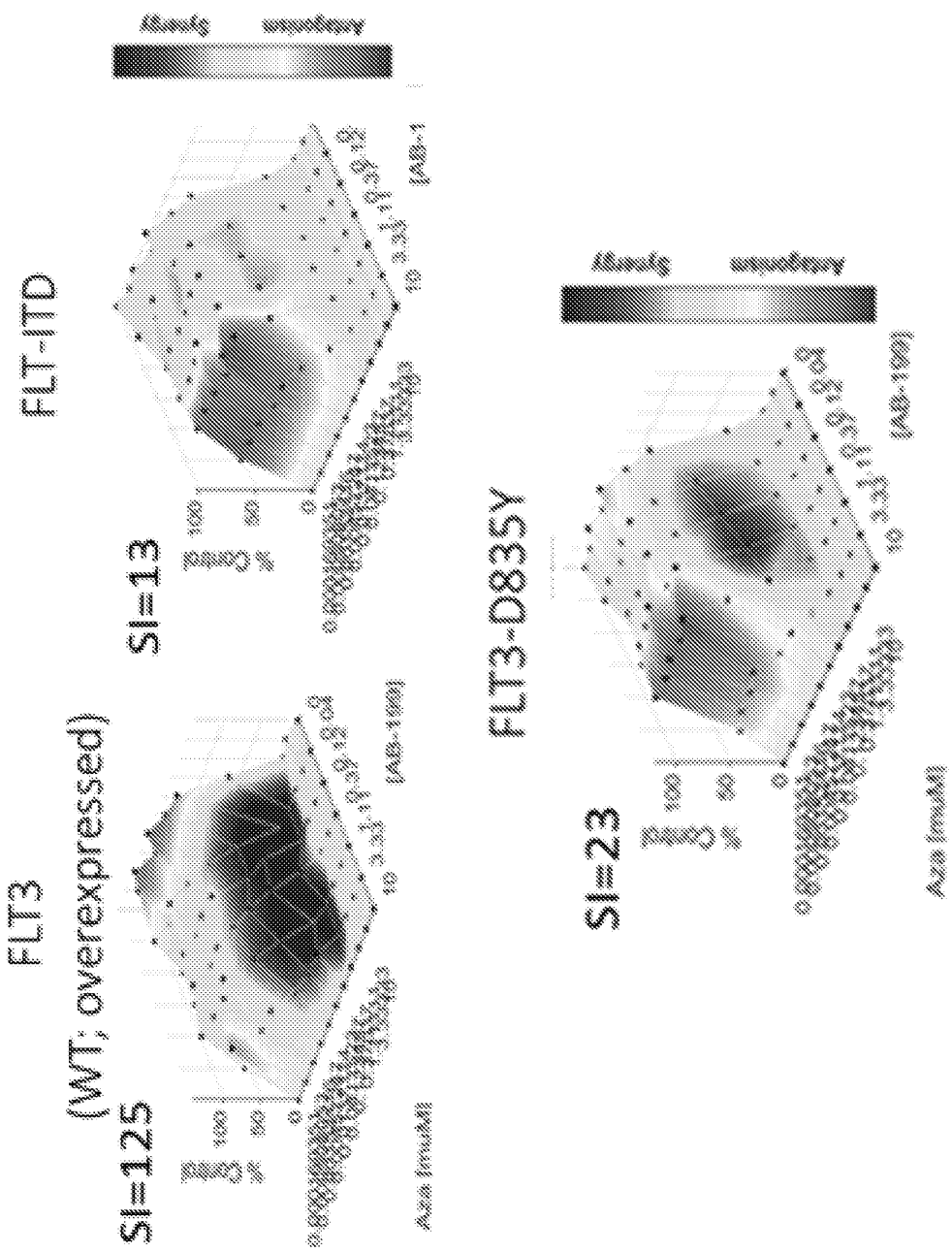

FLT3
(WT; overexpressed)
SI=125
FLT-ITD
SI=13
FLT3-D835Y
SI=23
Effect
Selectivity
Axis 1 (nM)
Axis 2 (nM)
Axis 3 (nM)
Cell %

FIG. 11

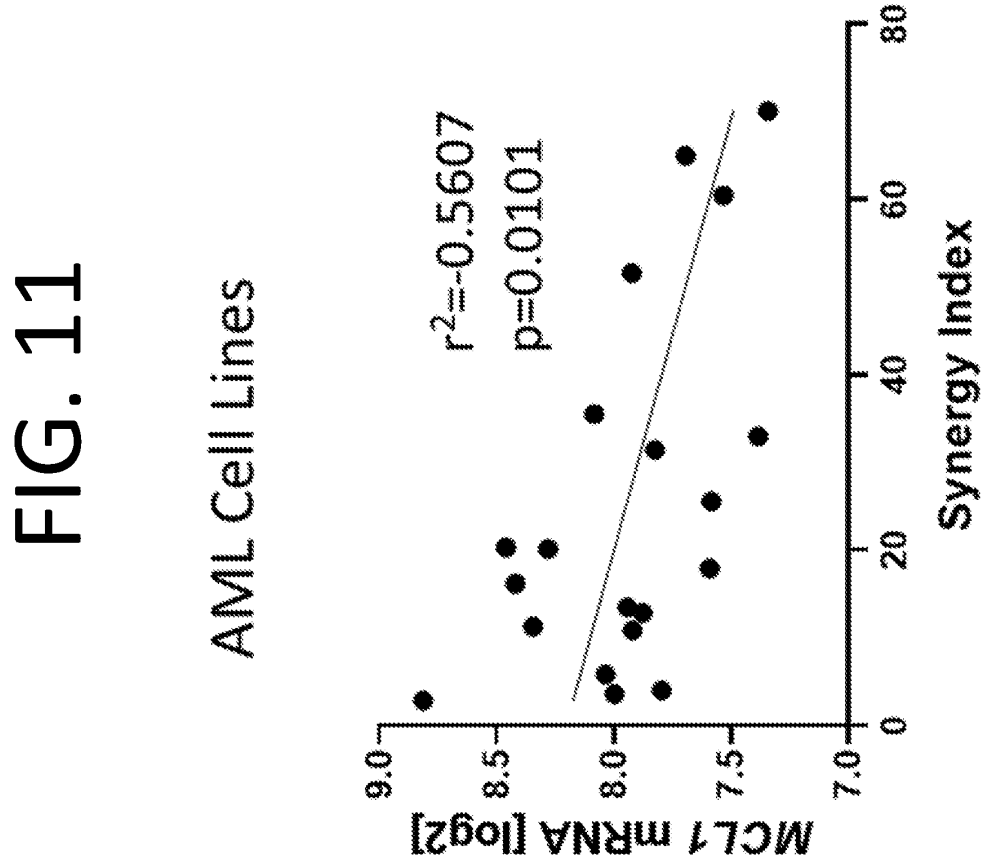

AML Cell Lines
r2=-0.5607
p=0.0101
MCL1 mRNA [log2]
9.0
8.5
8.0
7.5
7.0
0
20
40
60
80
Synergy Index

FIG. 12

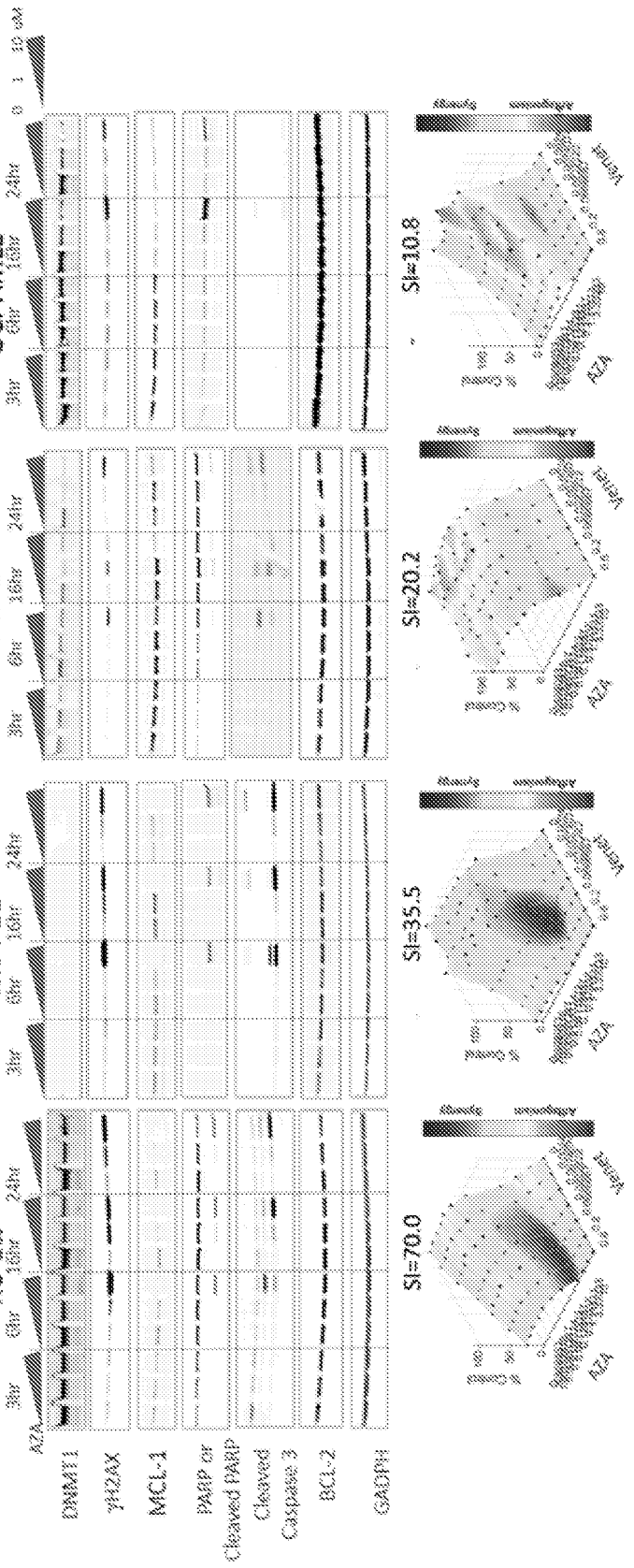

A
B
C
D
KG-1α
MV4-11
THP-1
OCI-AML2
3hr
6hr
16hr
24hr
AZA
0
1
10 uM
DNMT1
γH2AX
MCL-1
PARP or Cleaved PARP
Cleaved Caspase 3
BCL-2
GADPH
E
F
G
H
SI=70.0
SI=35.5
SI=20.2
SI=10.8
Vehicle
AZA

FIG. 13

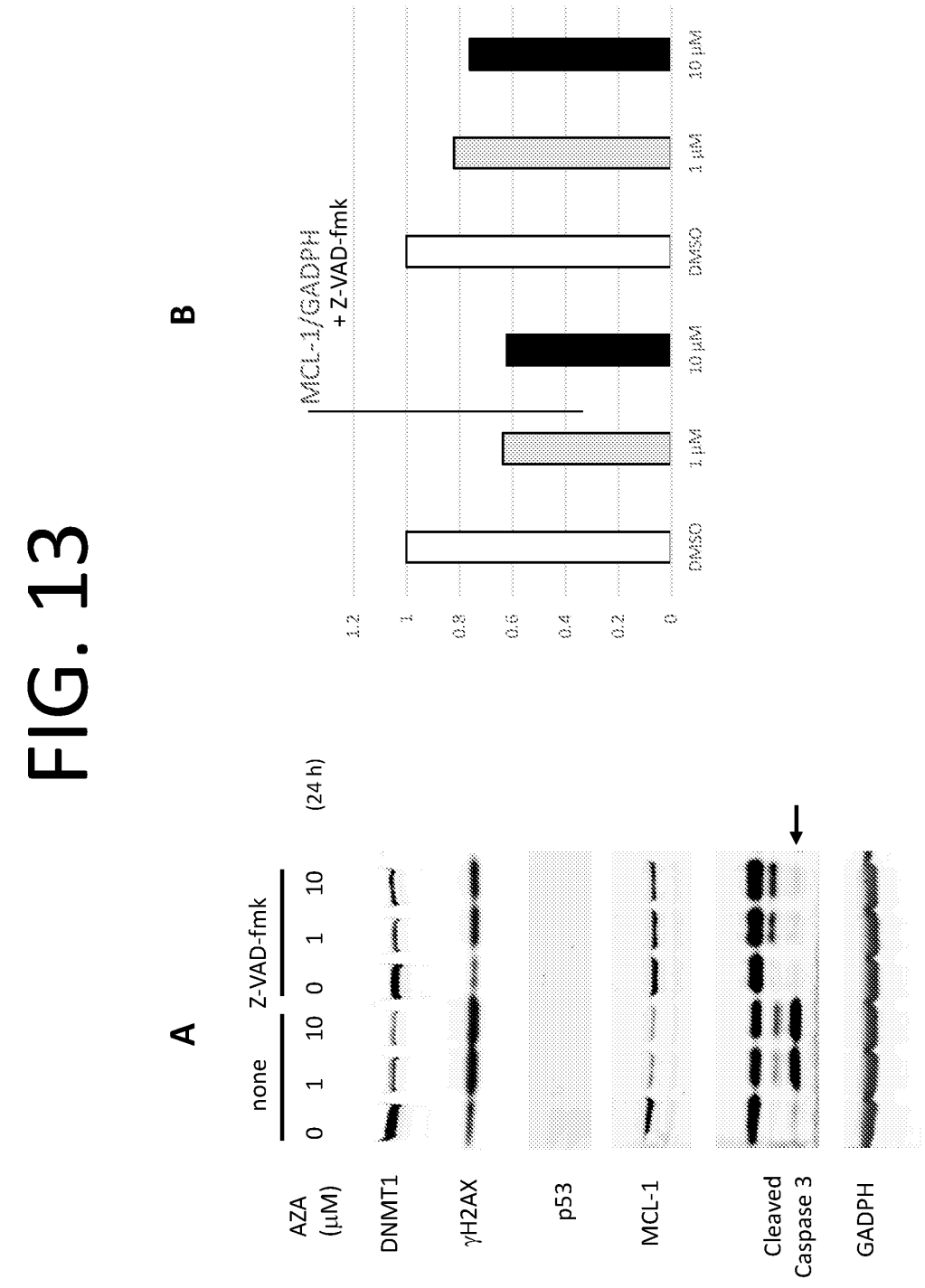

A
AZA (μM)
none
Z-VAD-fmk
0
1
10
0
1
10
(24 h)
DNMT1
γH2AX
p53
MCL-1
Cleaved Caspase 3
GADPH
B
MCL-1/GADPH + Z-VAD-fmk
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
1 μM
10 μM
DMSO
1 μM
10 μM

FIG. 14

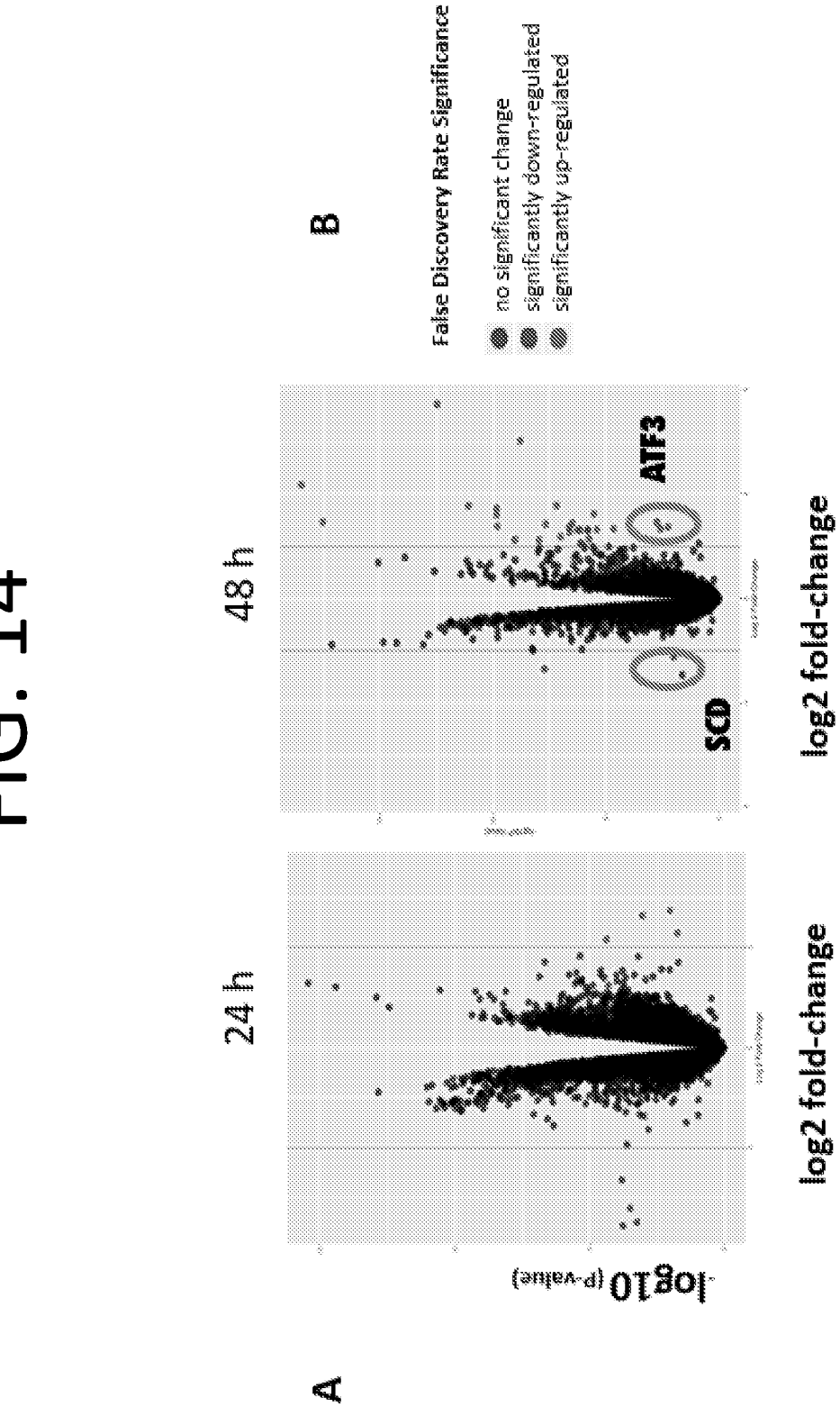

A
B
24 h
48 h
-log10 (p-value)
log2 fold-change
log2 fold-change
False Discovery Rate Significance
no significant change
significantly down-regulated
significantly up-regulated
ATF3
SCD

FIG. 14

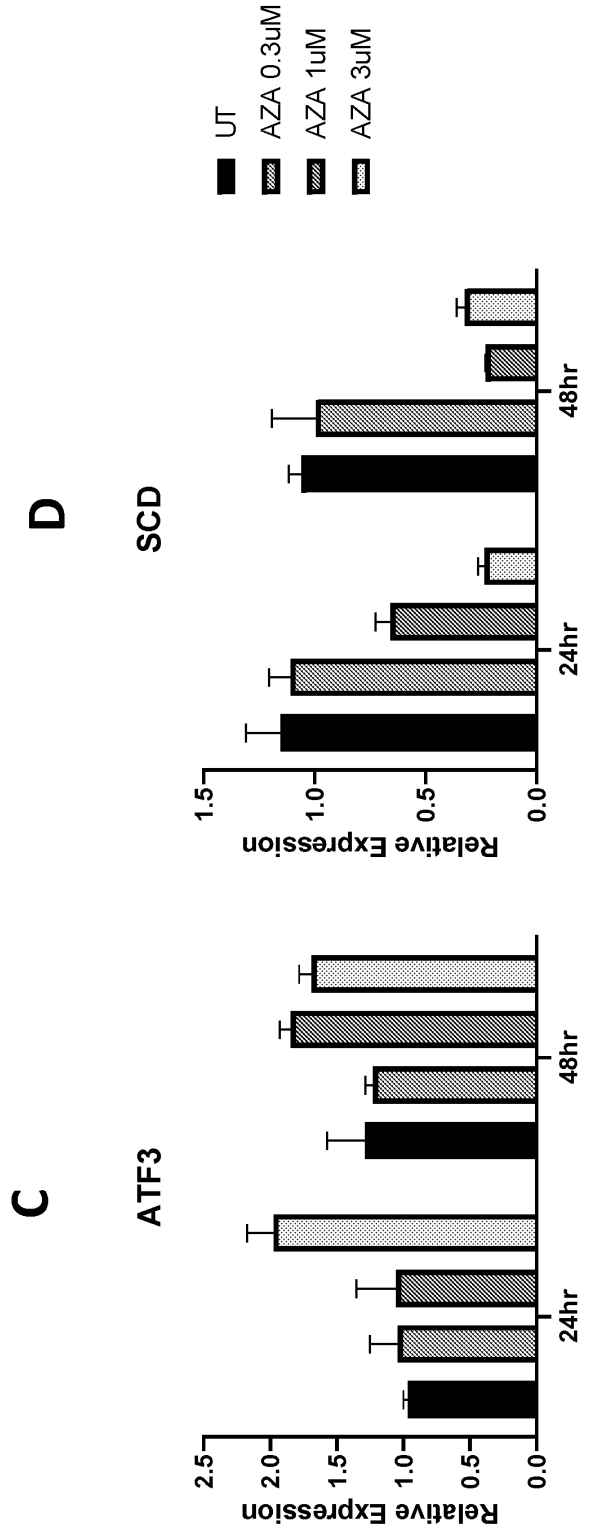

C
ATF3
Relative Expression
2.5
2.0
1.5
1.0
0.5
0.0
24hr
48hr
D
SCD
Relative Expression
1.5
1.0
0.5
0.0
24hr
48hr
UT
AZA 0.3uM
AZA 1uM
AZA 3uM

FIG. 15A

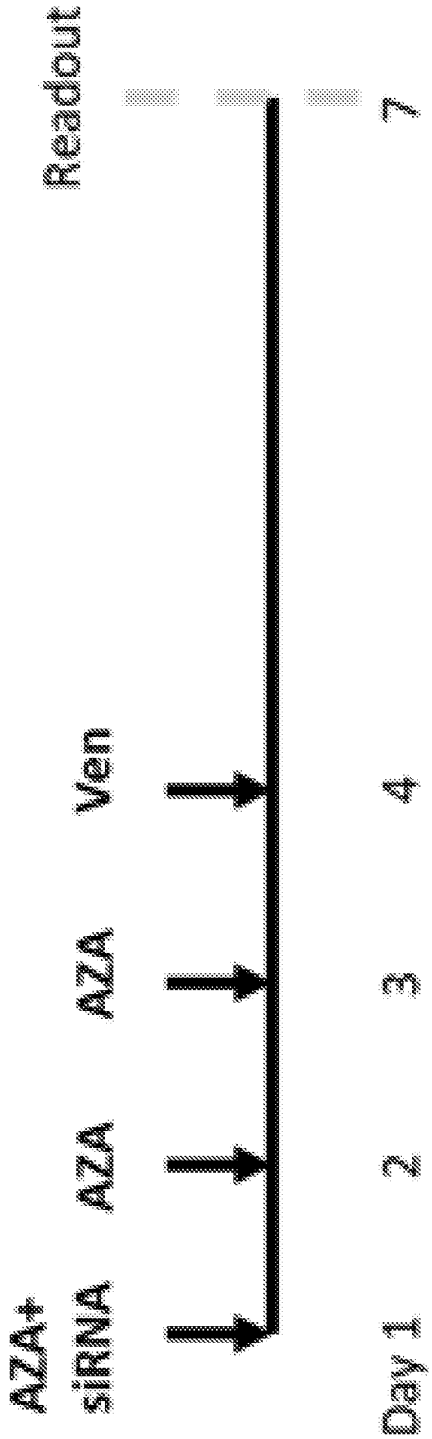


FIG. 15

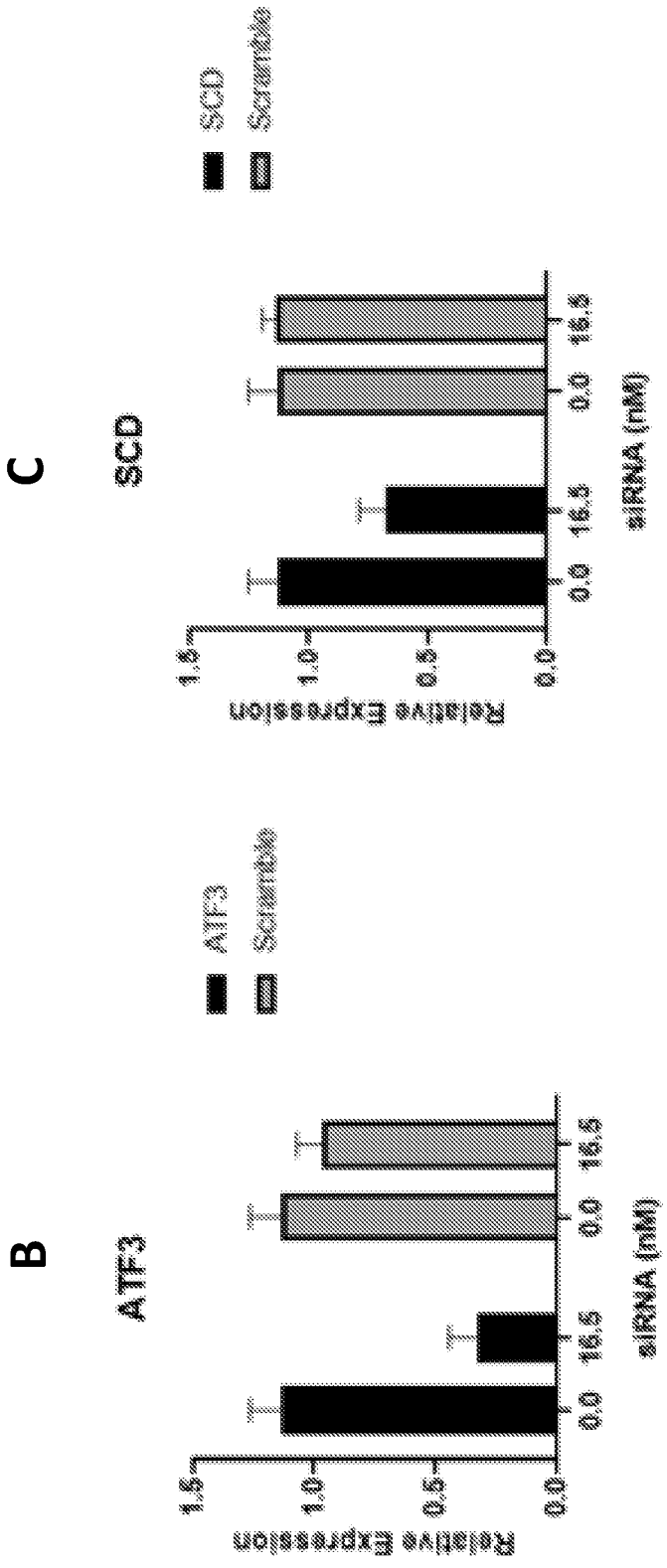

B
ATF3
ATF3
Scramble
Relative Expression
1.5
1.0
0.5
0.0
0.0
16.5
0.0
16.5
siRNA (nM)
C
SCD
SCD
Scramble
Relative Expression
1.5
1.0
0.5
0.0
0.0
16.5
0.0
16.5
siRNA (nM)

FIG. 15

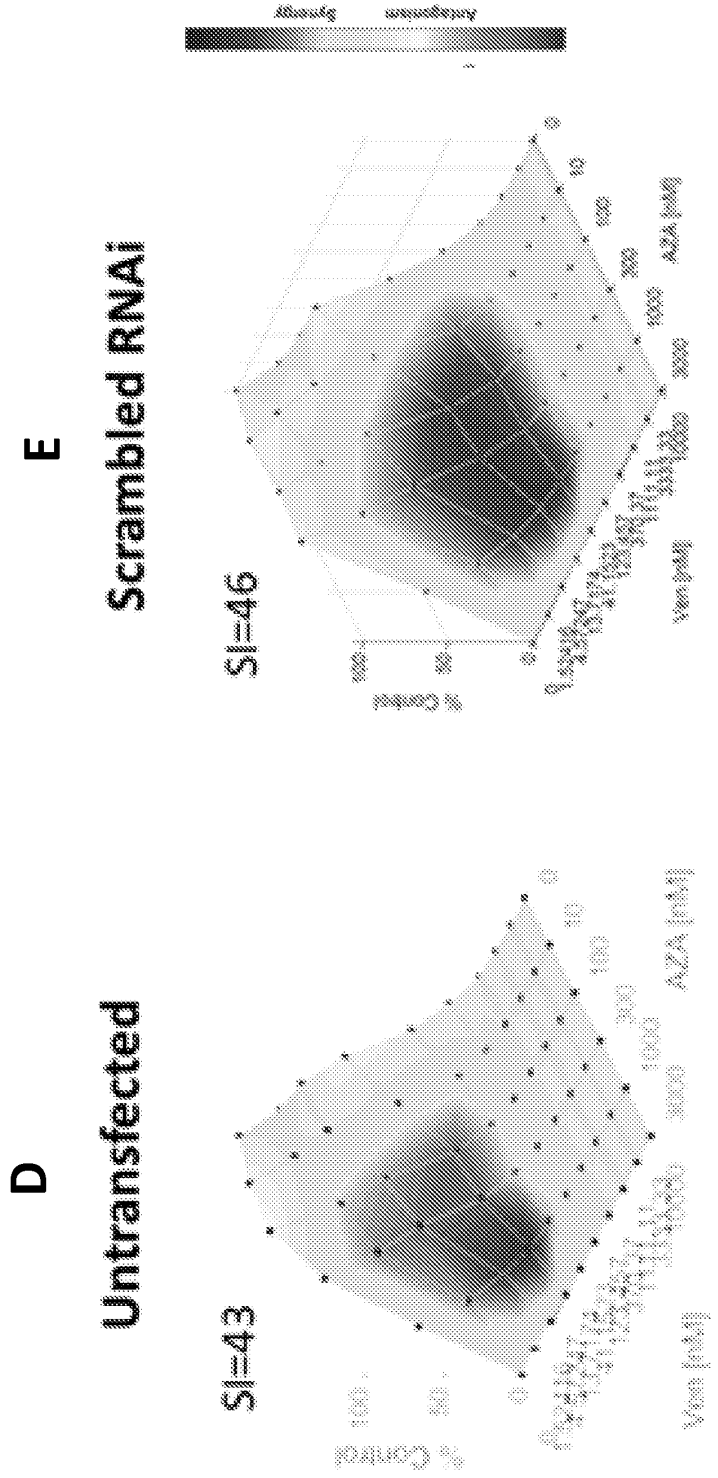

D
Untransfected
SI=43
% Control
AZA [nM]
Vcm [nM]
E
Scrambled RNAi
SI=46
% Control
AZA [nM]
Vcm [nM]

FIG. 15

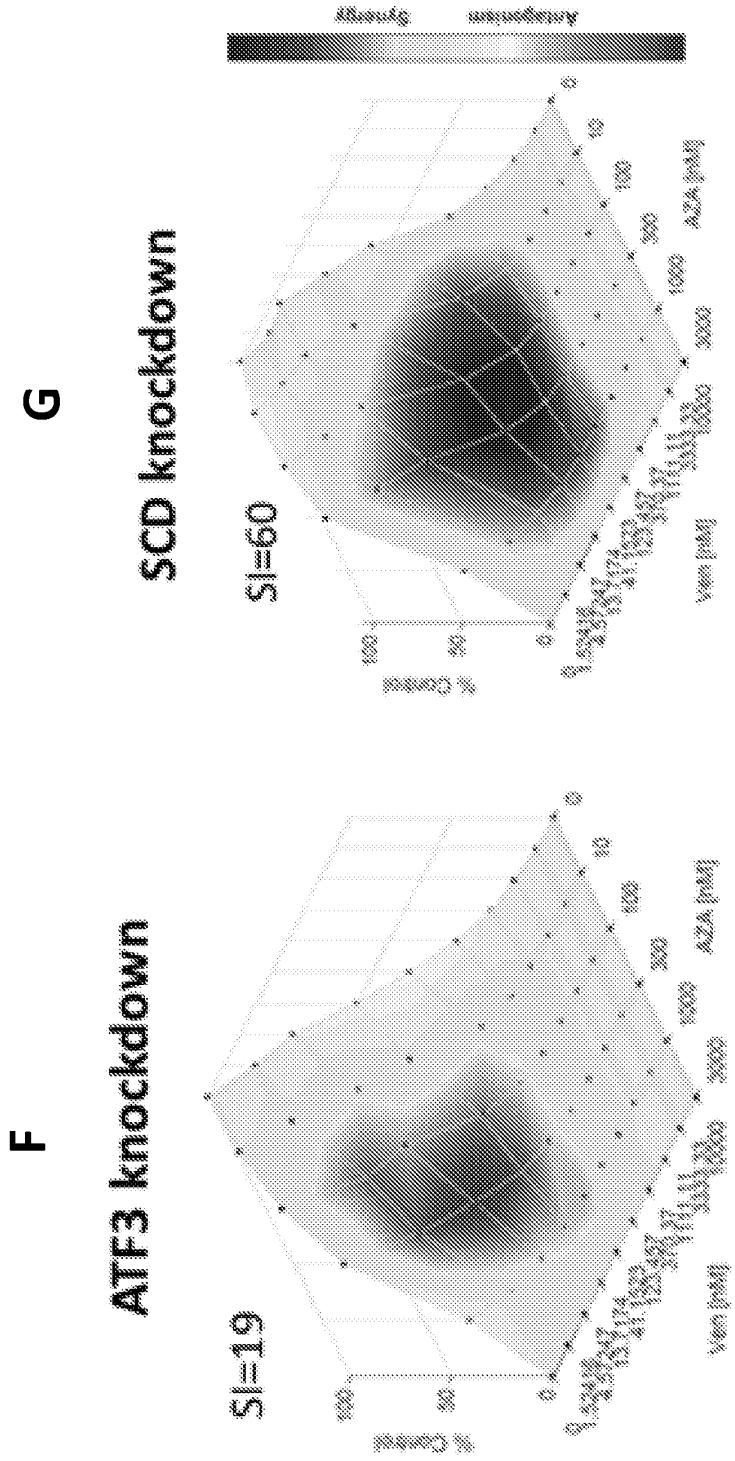

F
ATF3 knockdown
SI=19
% Cells
Ven [nM]
AZA [nM]
G
SCD knockdown
SI=60
% Cells
Ven [nM]
AZA [nM]
Antagonism
Synergy

FIG. 16A

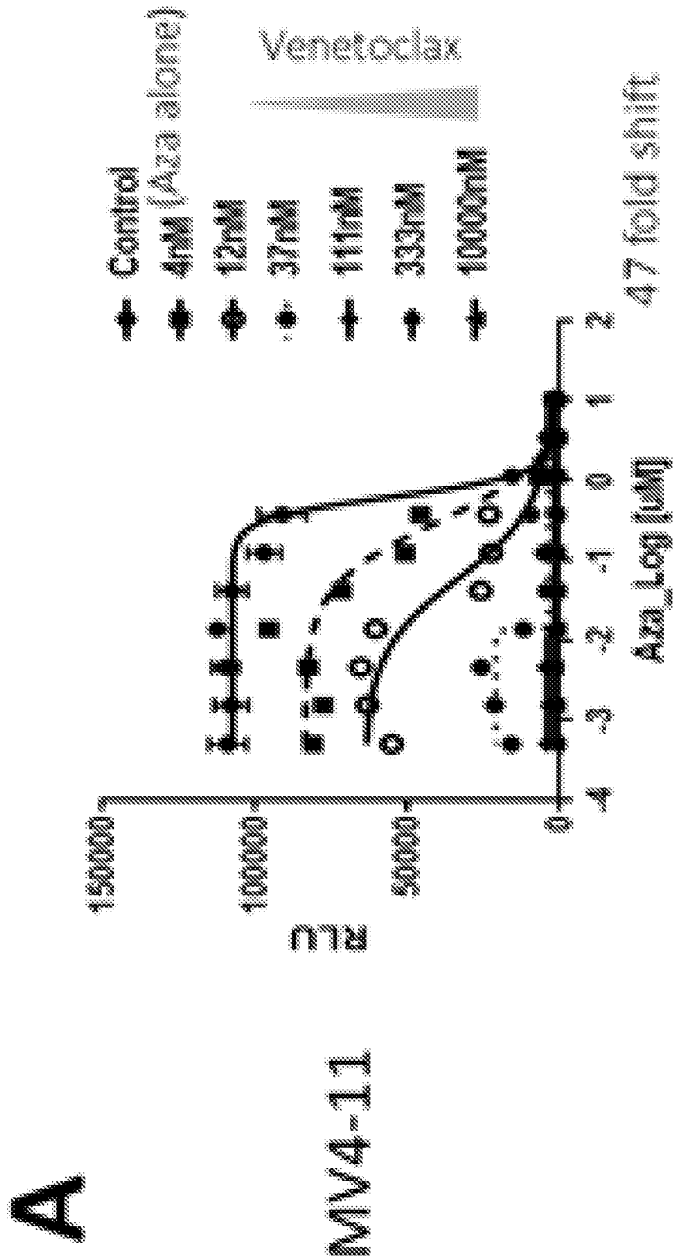

A
MV4-11
RLU
150000
100000
50000
0
-4
-3
-2
-1
0
1
2
Aza_Log [uM]
47 fold shift
Venetoclax
Control
4nM (Aza alone)
12nM
37nM
111nM
333nM
1000nM

Fig. 16B

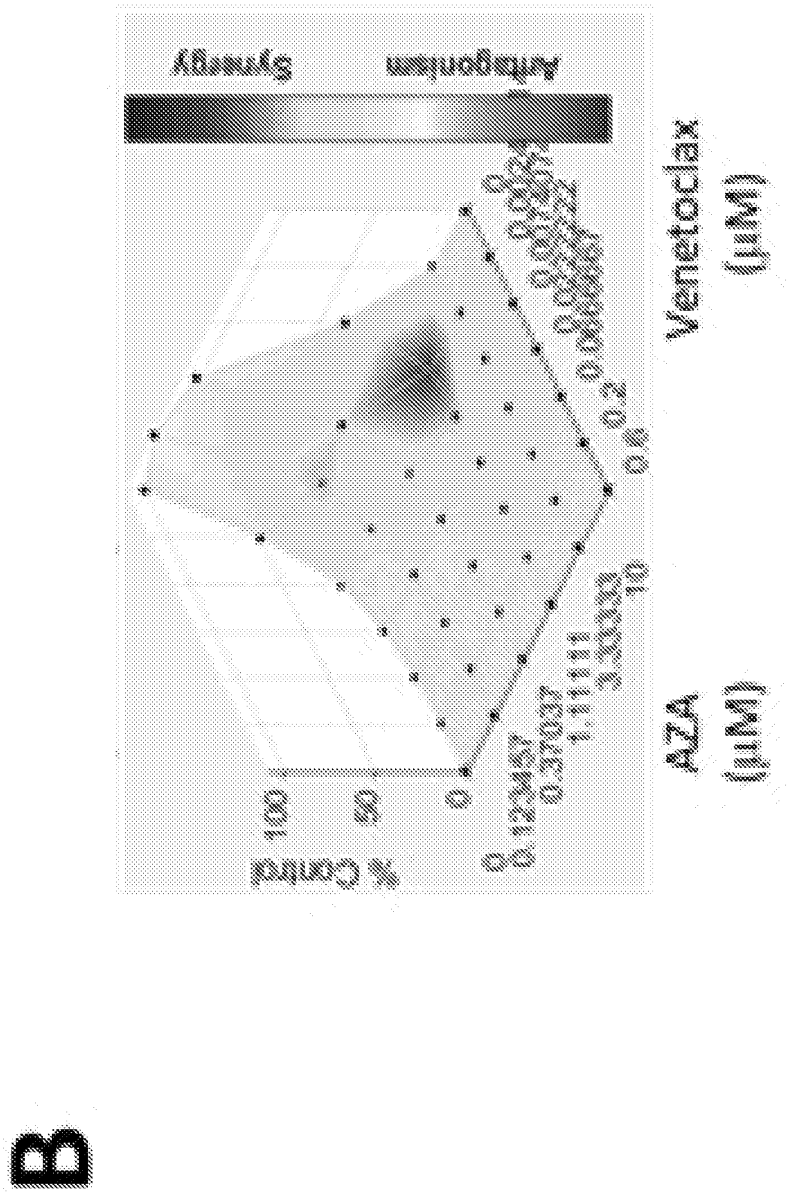

B
% Cells
100
50
0
Synergy
Antagonism
Vemetodax (μM)
AZA (μM)
0
0.123457
0.37037
1.111111
3.333333
10
0.2
0.6
0.0222
0.0667
0.2

FIG. 16C

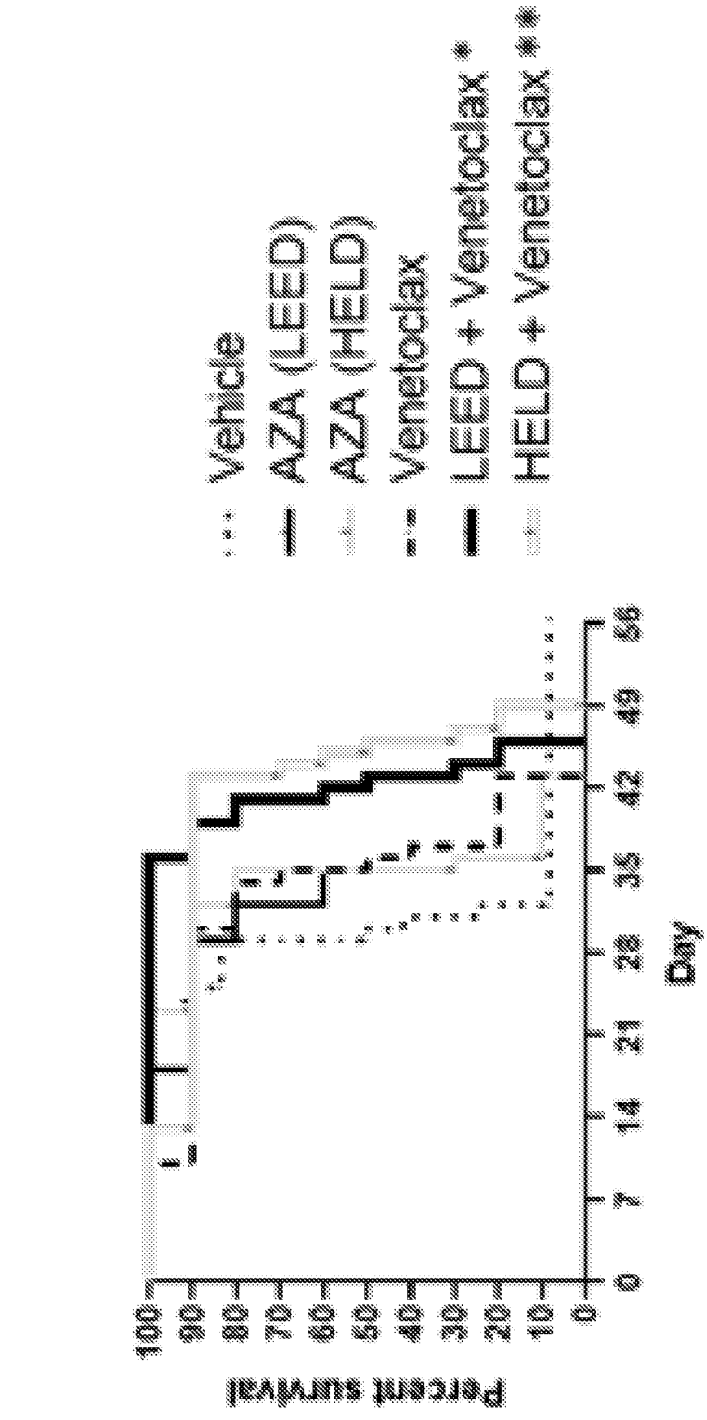

C
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
Day
Vehicle
AZA (LEED)
AZA (HELD)
Venetoclax
LEED + Venetoclax *
HELD + Venetoclax **

FIG. 16D

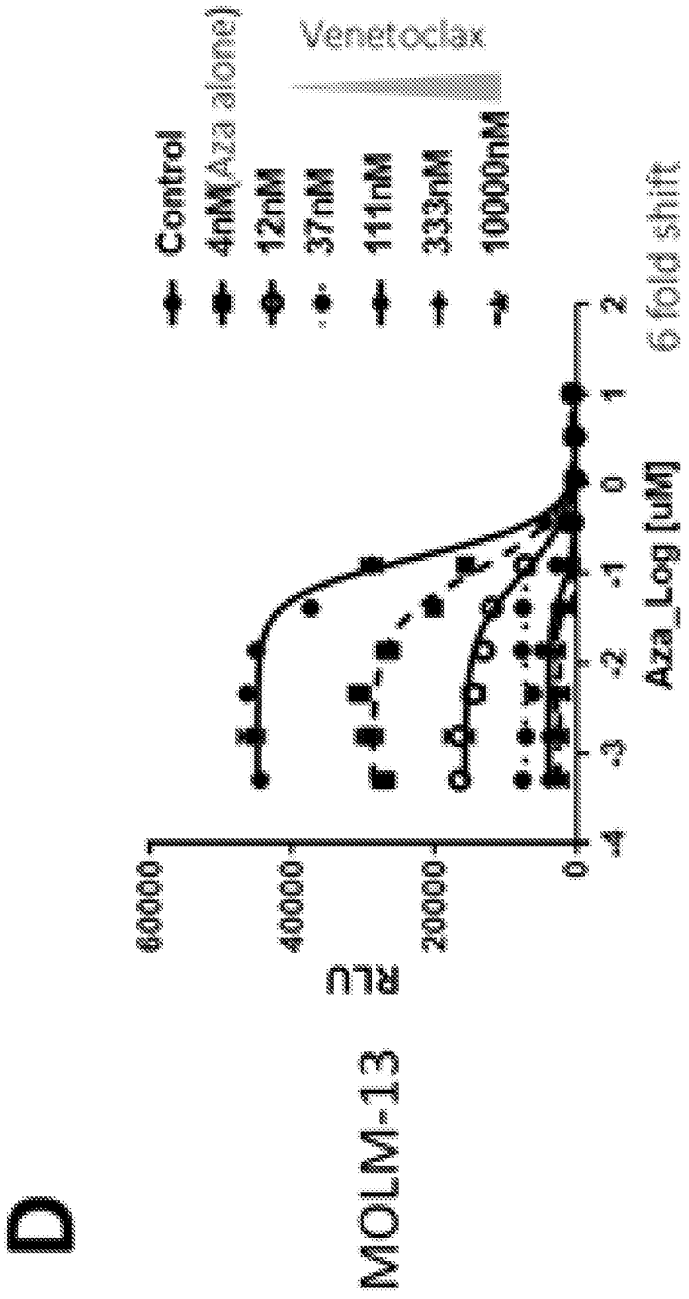

D
MOLM-13
RLU
60000
40000
20000
0
-4
-3
-2
-1
0
1
2
Aza_Log [uM]
6 fold shift
Control
4nM (Aza alone)
12nM
37nM
111nM
333nM
10000nM
Venetoclax

FIG. 16E

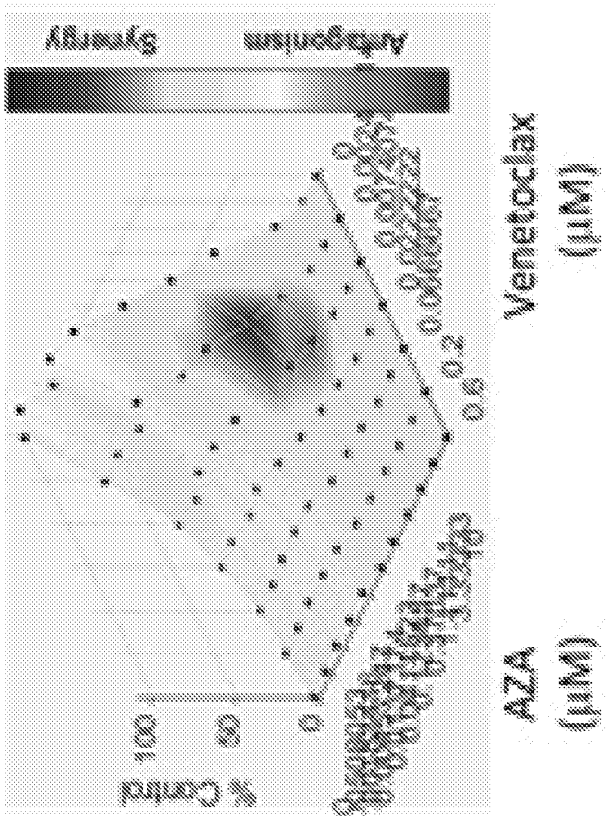


FIG. 16F

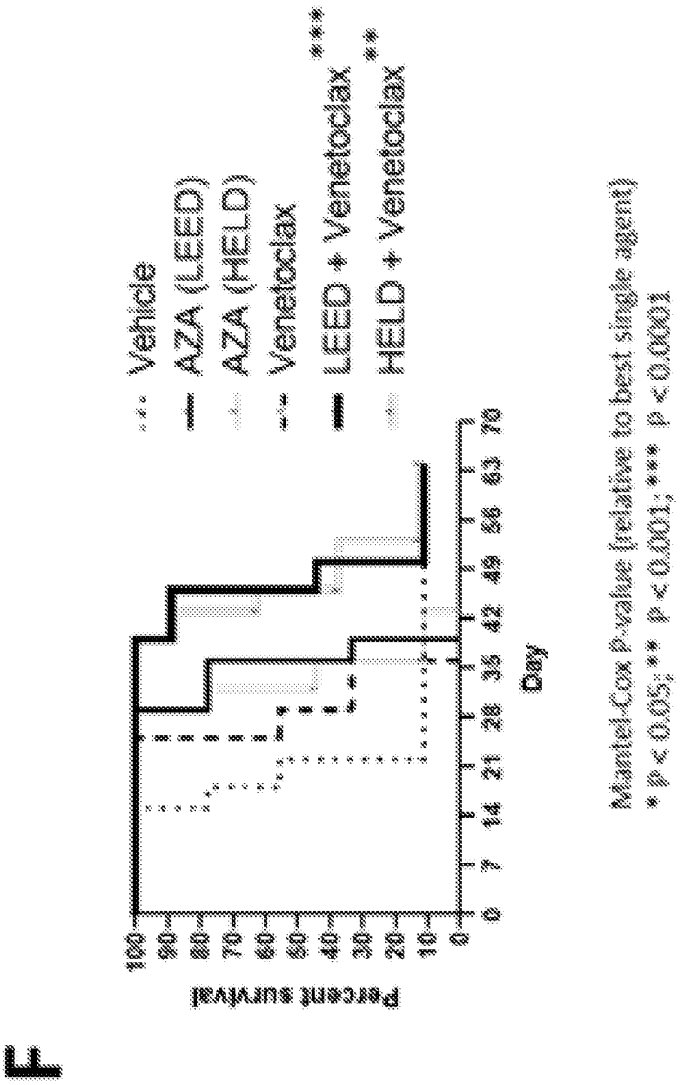

F
Vehicle
AZA (LEED)
AZA (HELD)
Venetoclax
LEED + Venetoclax***
HELD + Venetoclax**
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
70
Day
Mantel-Cox p-value [relative to best single agent]
* p < 0.05; ** p < 0.001; *** p < 0.0001

FIG. 17A

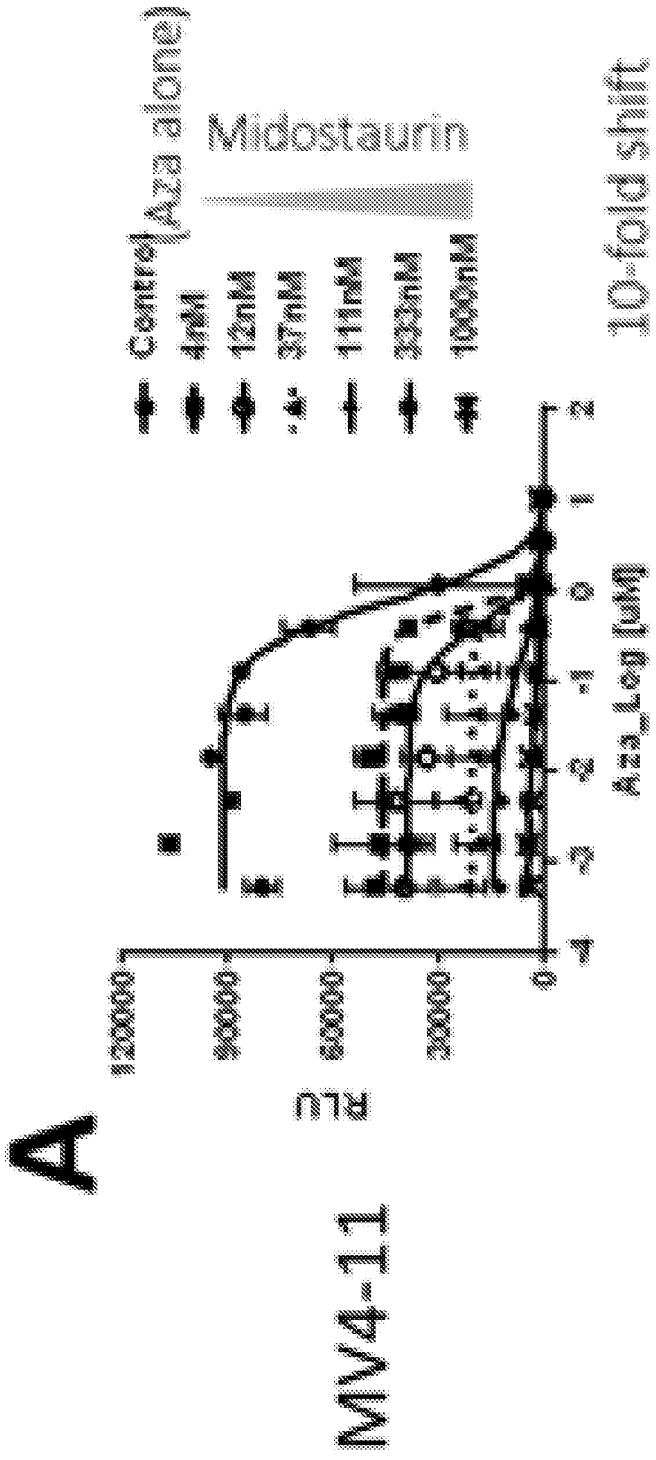

A
MV4-11
RLU
120000
90000
60000
30000
0
-4
-3
-2
-1
0
1
2
Aza_Log [uM]
10-fold shift
Midostaurin
Control (Aza alone)
4nM
12nM
37nM
111nM
333nM
1000nM

FIG. 17B

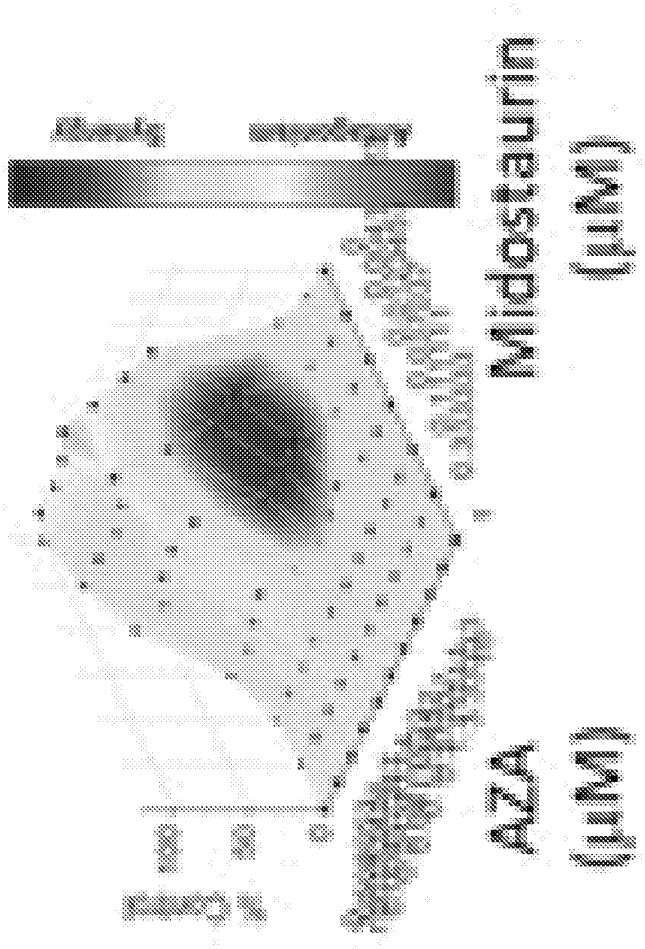


FIG. 17

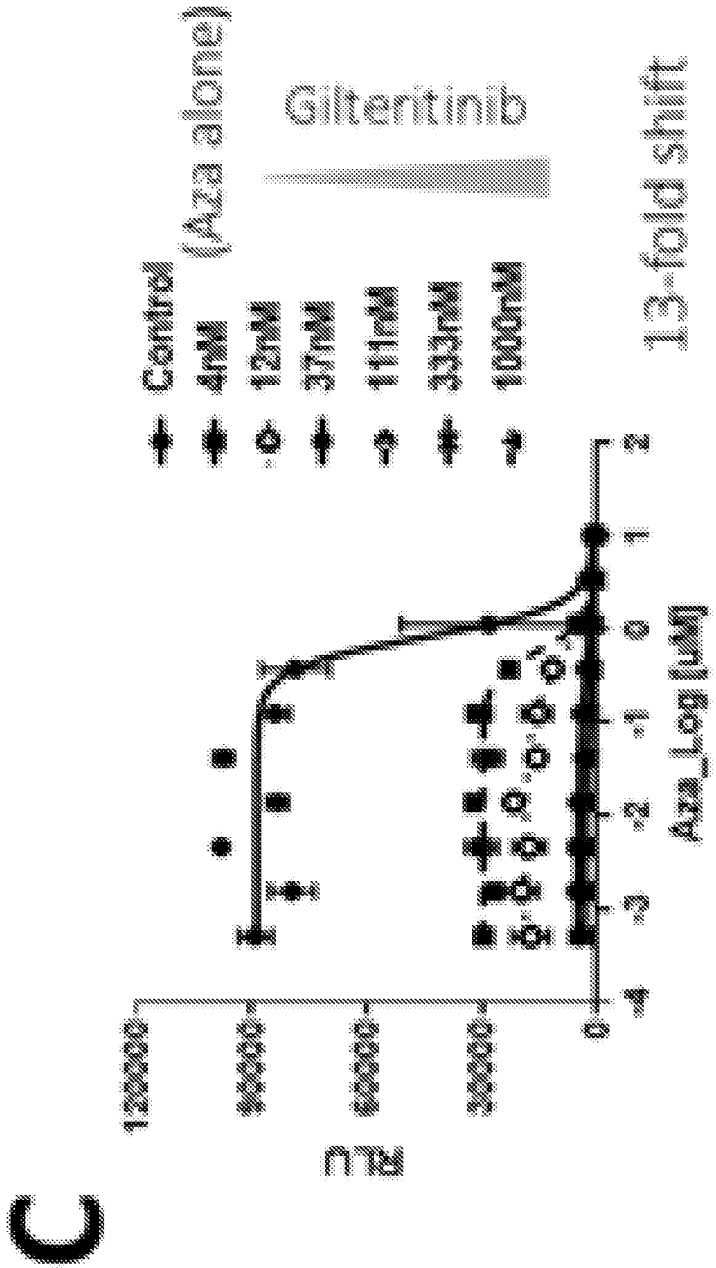

C
RLU
122000
92000
62000
32000
0
-4
-3
-2
-1
0
1
2
Aza_Log [uM]
13-fold shift
Gilteritinib
(Aza alone)
Control
4nM
12nM
37nM
111nM
333nM
1000nM

Fig. 17D

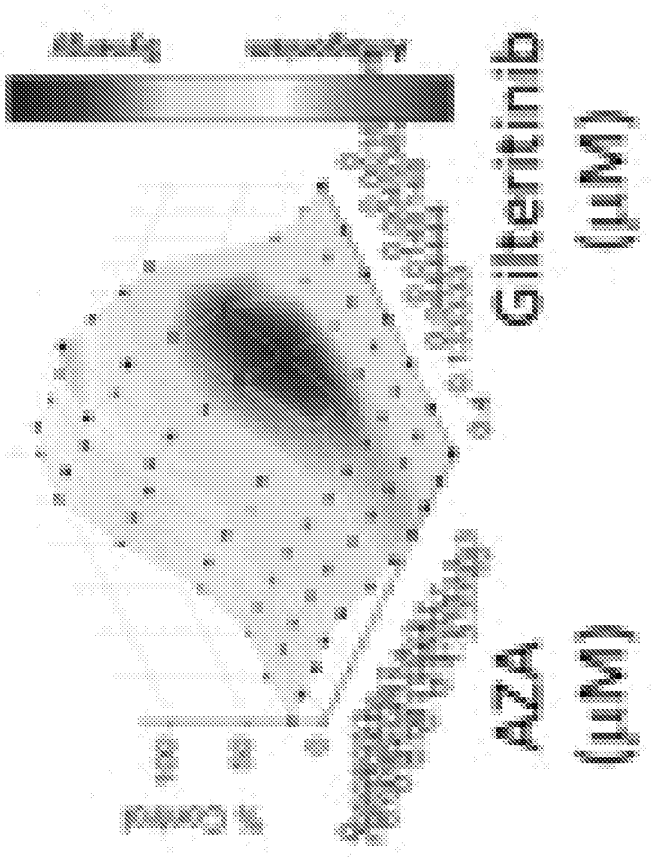


FIG. 17E

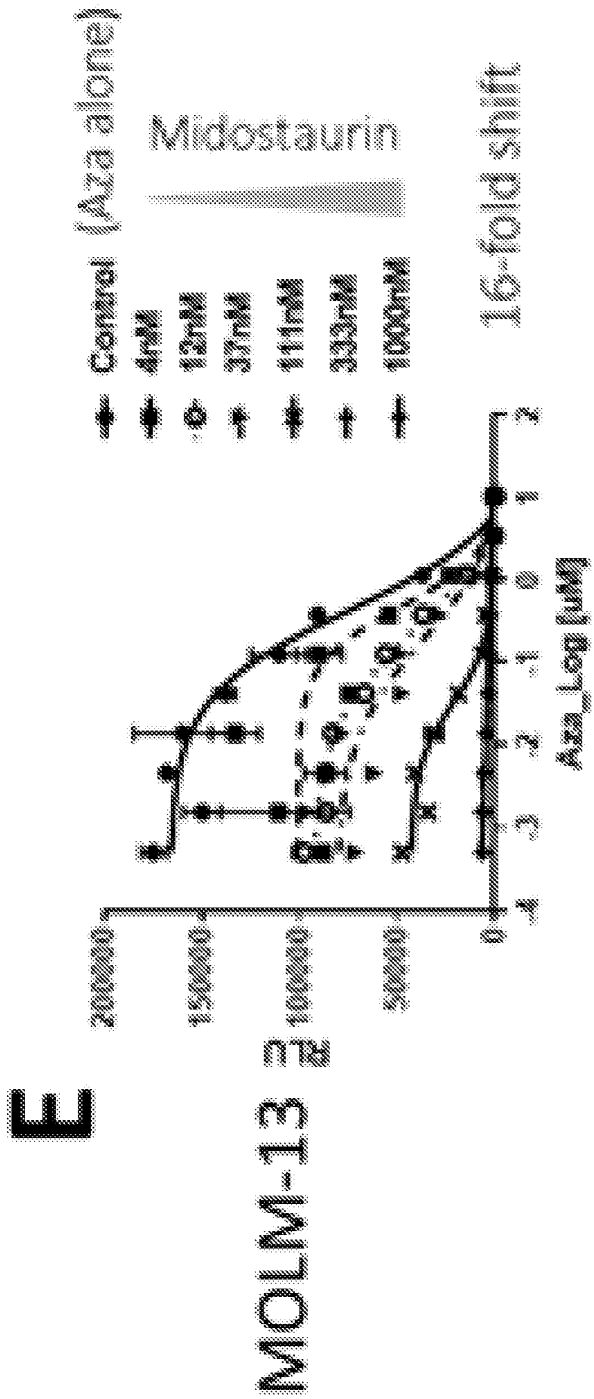

E
MOLM-13
CTG
Midostaurin
Control (Aza alone)
4nM
12nM
37nM
111nM
333nM
1000nM
16-fold shift
Aza_Log [uM]

FIG. 17F

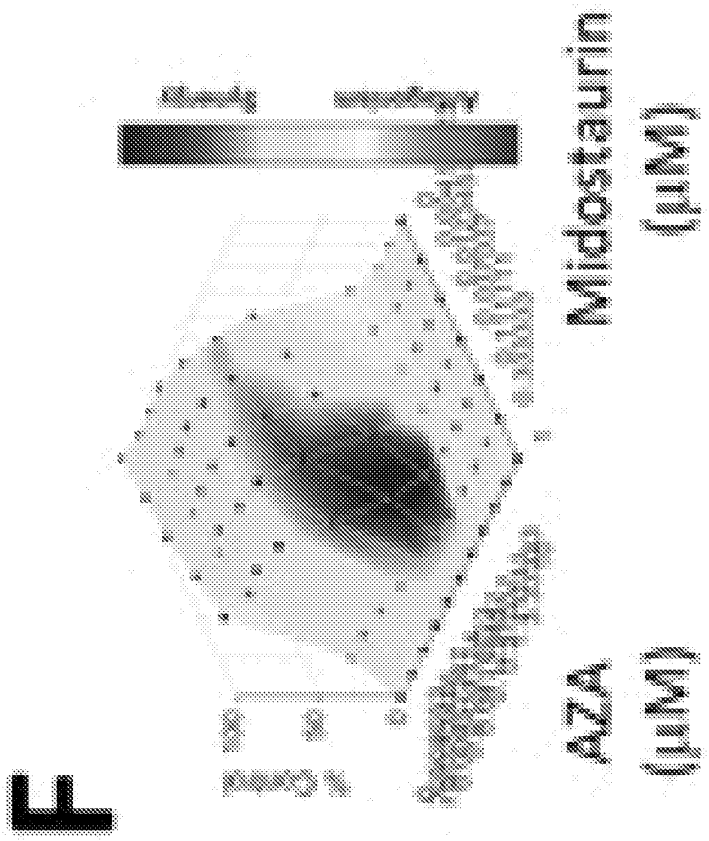


FIG. 17G

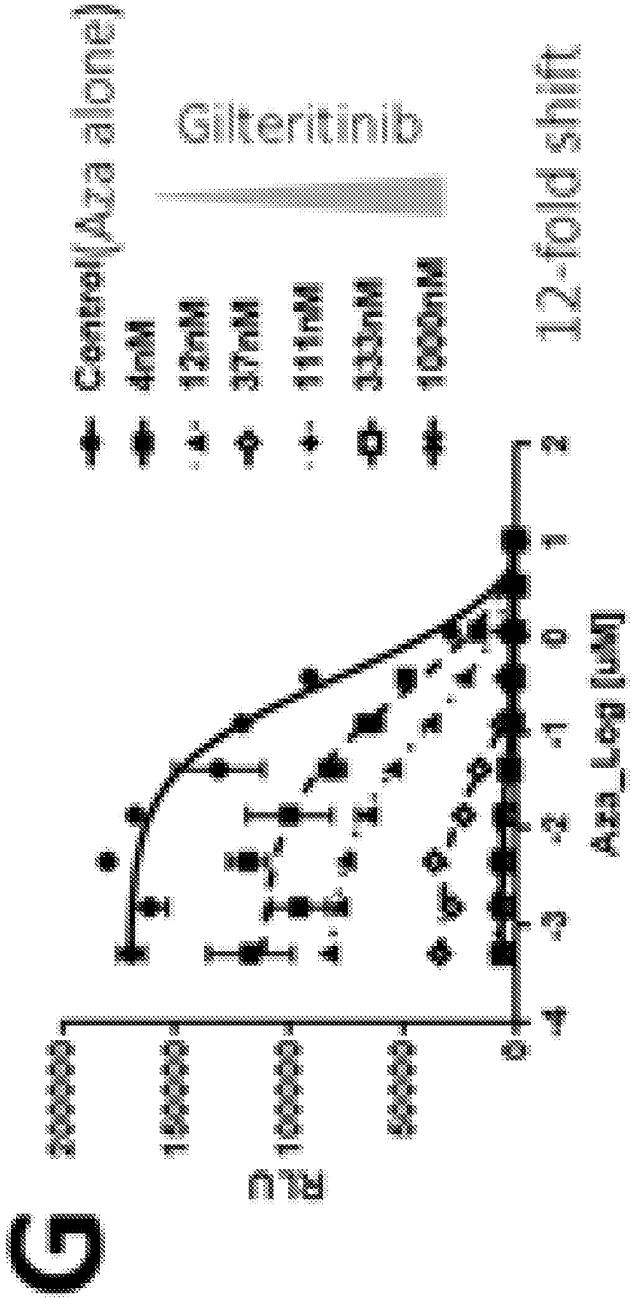

G
RLU
Aza_Log [uM]
12-fold shift
Gilteritinib
Control(Aza alone)
4nM
12nM
37nM
111nM
333nM
1000nM

FIG. 17H

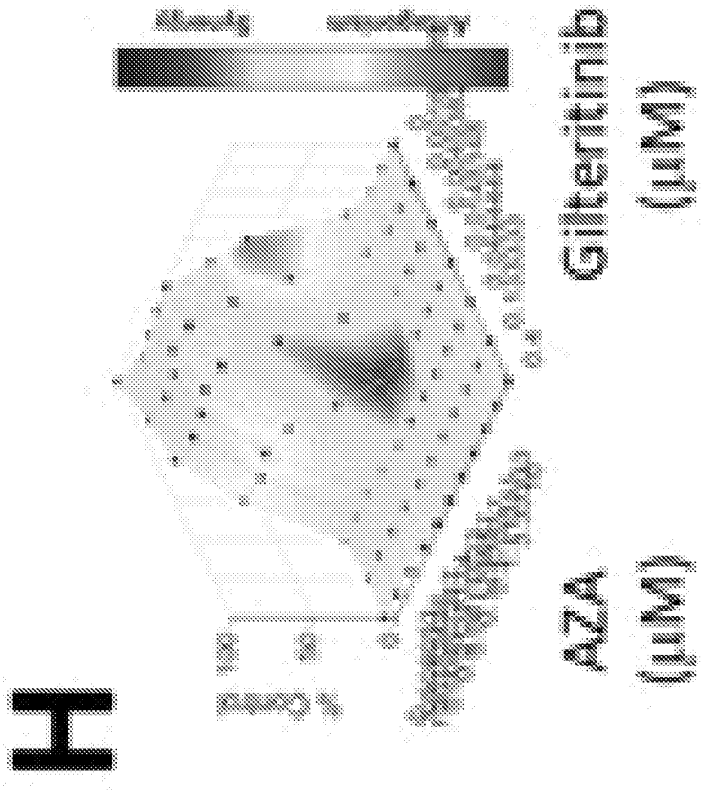


FIG. 17I

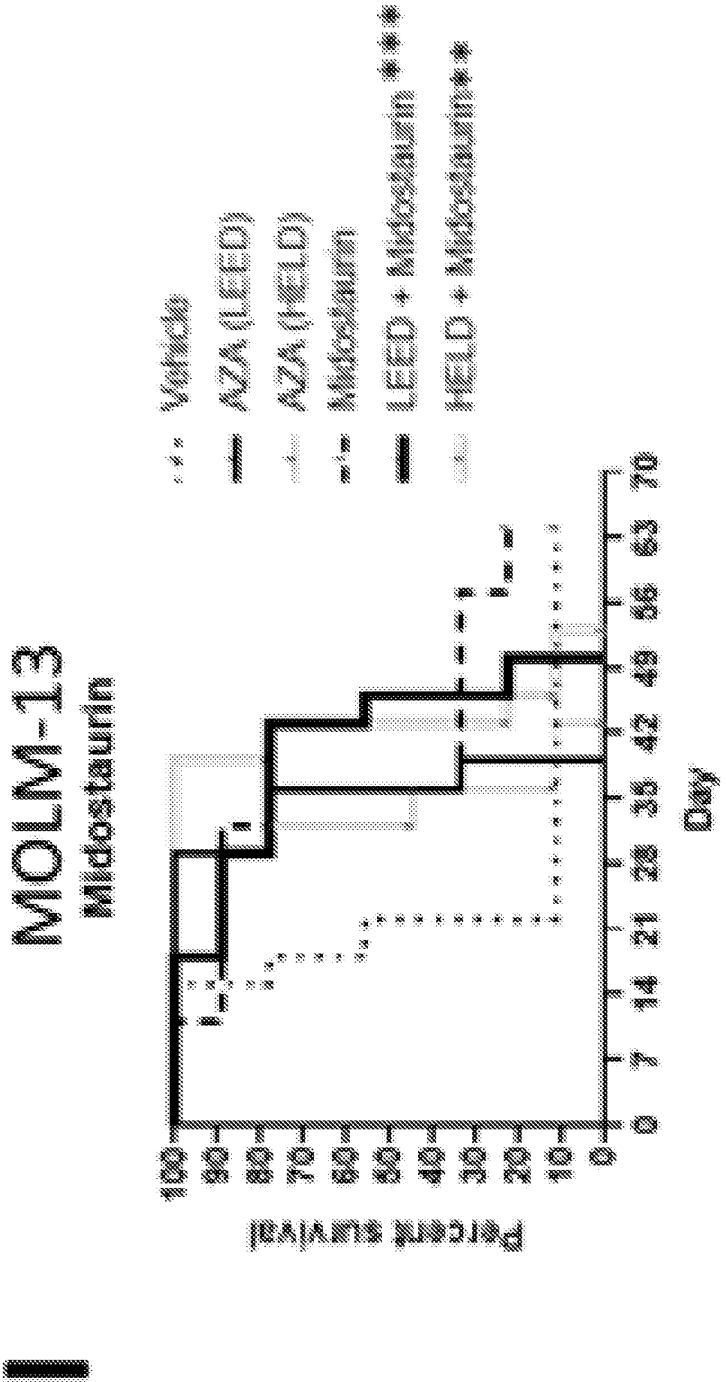

MOLM-13
Midostaurin
Vehicle
AZA (LEED)
AZA (HELD)
Midostaurin
LEED + Midostaurin***
HELD + Midostaurin***
Percent survival
Day
0
7
14
21
28
35
42
49
56
63
70
100
90
80
70
60
50
40
30
20
10
0

FIG. 17J

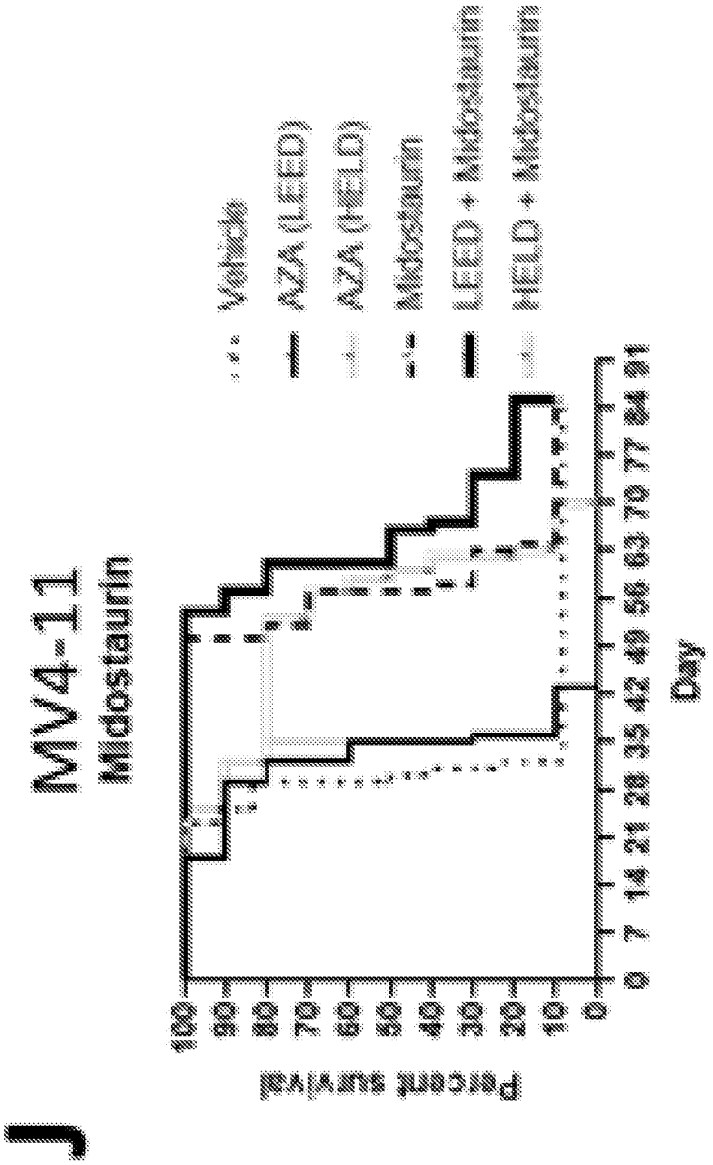

J
MV4-11
Midostaurin
Percent survival
Day
Vehicle
AZA (LEED)
AZA (HELD)
Midostaurin
LEED + Midostaurin
HELD + Midostaurin

FIG. 17K

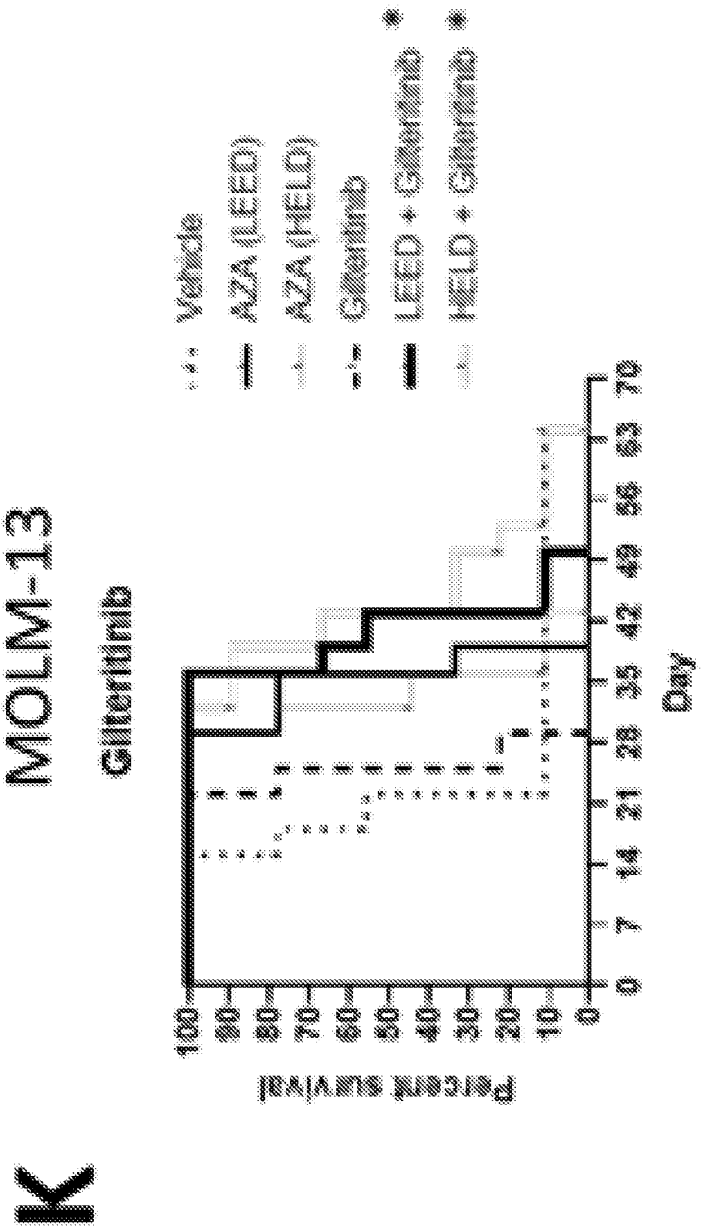

K
MOLM-13
Gilteritinib
Vehicle
AZA (LEED)
AZA (HELD)
Gilteritinib
LEED + Gilteritinib
HELD + Gilteritinib
*
*
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
7
14
21
28
35
42
49
56
63
70
Day

FIG. 18A

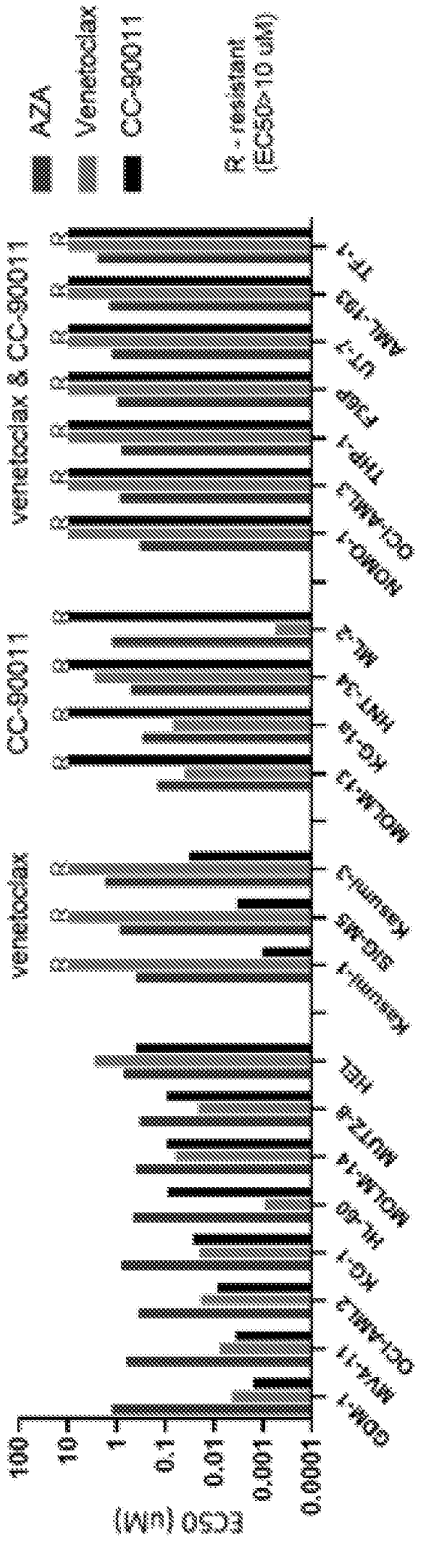

AZA
Venetoclax
CC-90011
R - resistant
(EC50>10 uM)
Resistant to venetoclax & CC-90011
Resistant to CC-90011
Resistant to venetoclax
ECS0 (uM)
100
10
1
0.1
0.01
0.001
0.0001
GDM-1
MV4-11
OCI-AML2
KG-1
ML-60
MOLM-14
MUTZ-8
HEL
Kasumi-1
SIG-M5
Kasumi-3
MOLM-13
KG-1a
MNT-3d
ML-2
NOMO-1
OCI-AML3
THP-1
F36P
UT-7
AML-193
TF-1

FIG. 18B

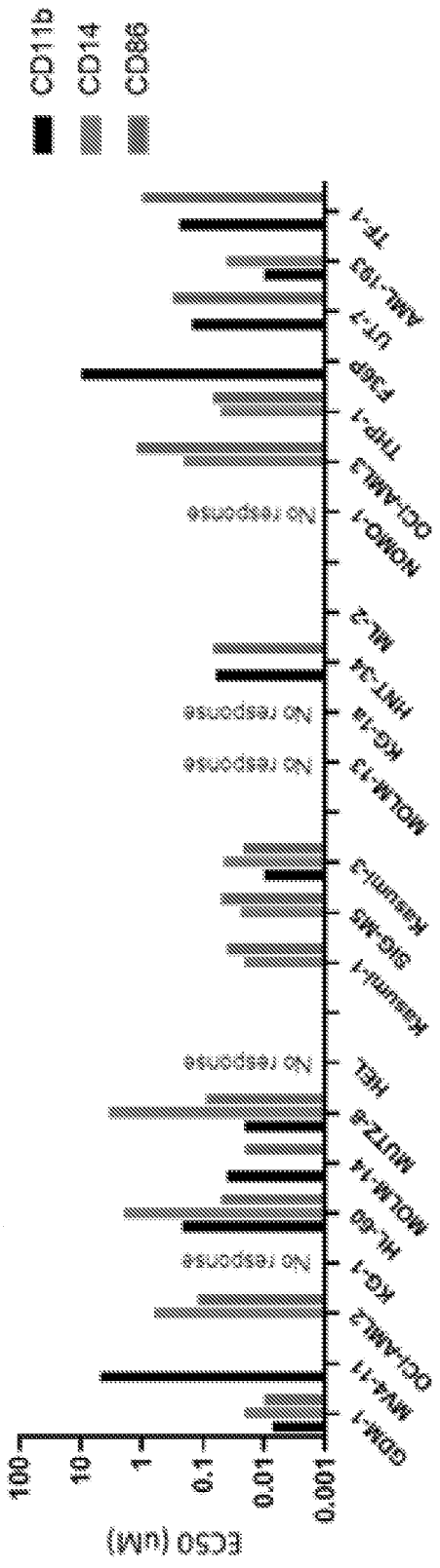

CD11b
CD14
CD86
EC50 (uM)
100
10
1
0.1
0.01
0.001
No response
GDM-1
MV4-11
OCI-AML2
KG-1
HL-60
MOLM-14
MUTZ-8
HEL
Kasumi-1
SIG-M5
Kasumi-3
MOLM-13
KG-1a
HNT-34
ML-2
NOMO-1
OCI-AML3
THP-1
P39P
U7-7
AML-193
TF-1

FIG. 18C

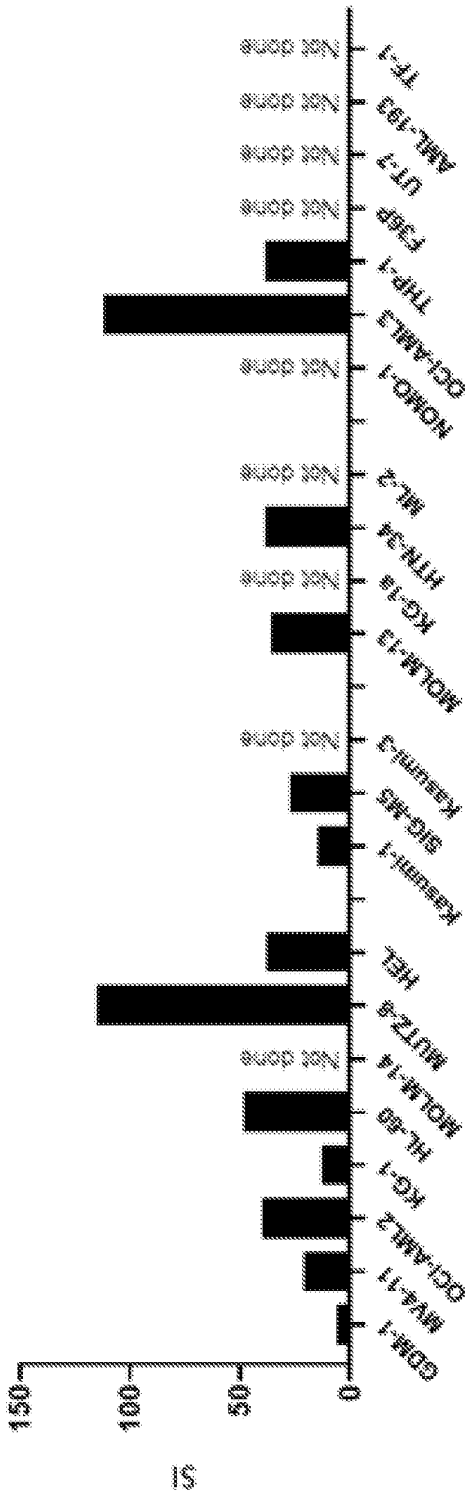

SI
150
100
50
0
GDM-1
MV4-11
OCI-AML2
KG-1
HL-60
MOLM-14
MUTZ-8
HEL
Kasumi-1
SIG-M5
Kasumi-3
MOLM-13
KG-1a
HTN-34
ML-2
MONO-1
OCI-AML3
THP-1
F36P
U7-1
AML-193
TF-1
No data

FIG. 19

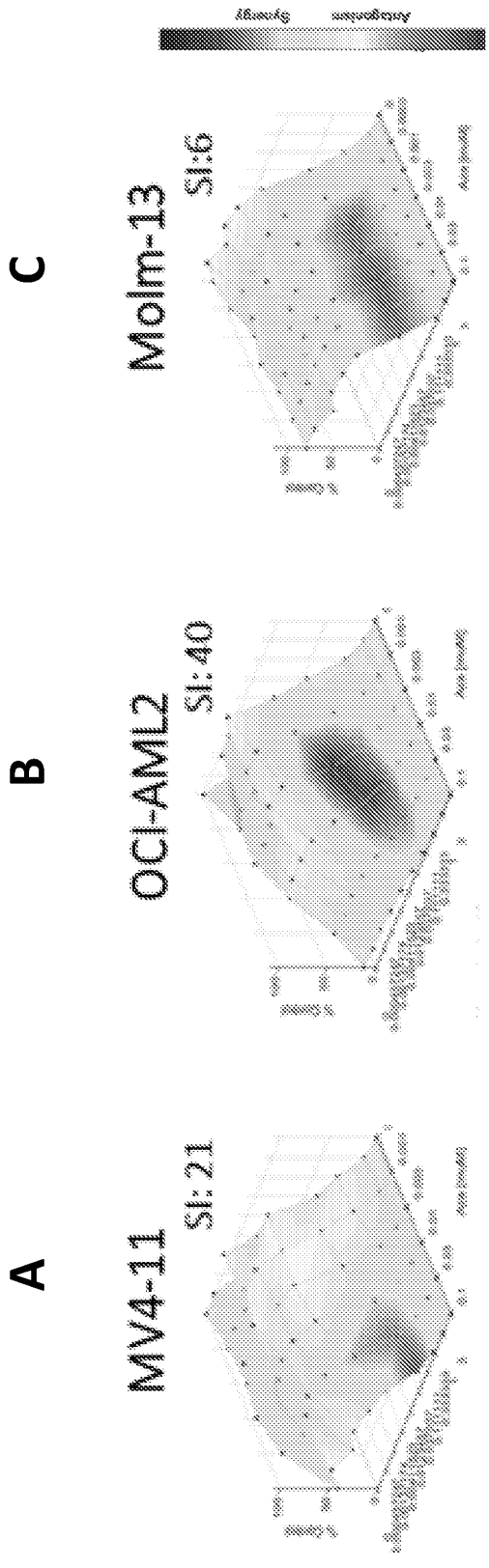


FIG. 19

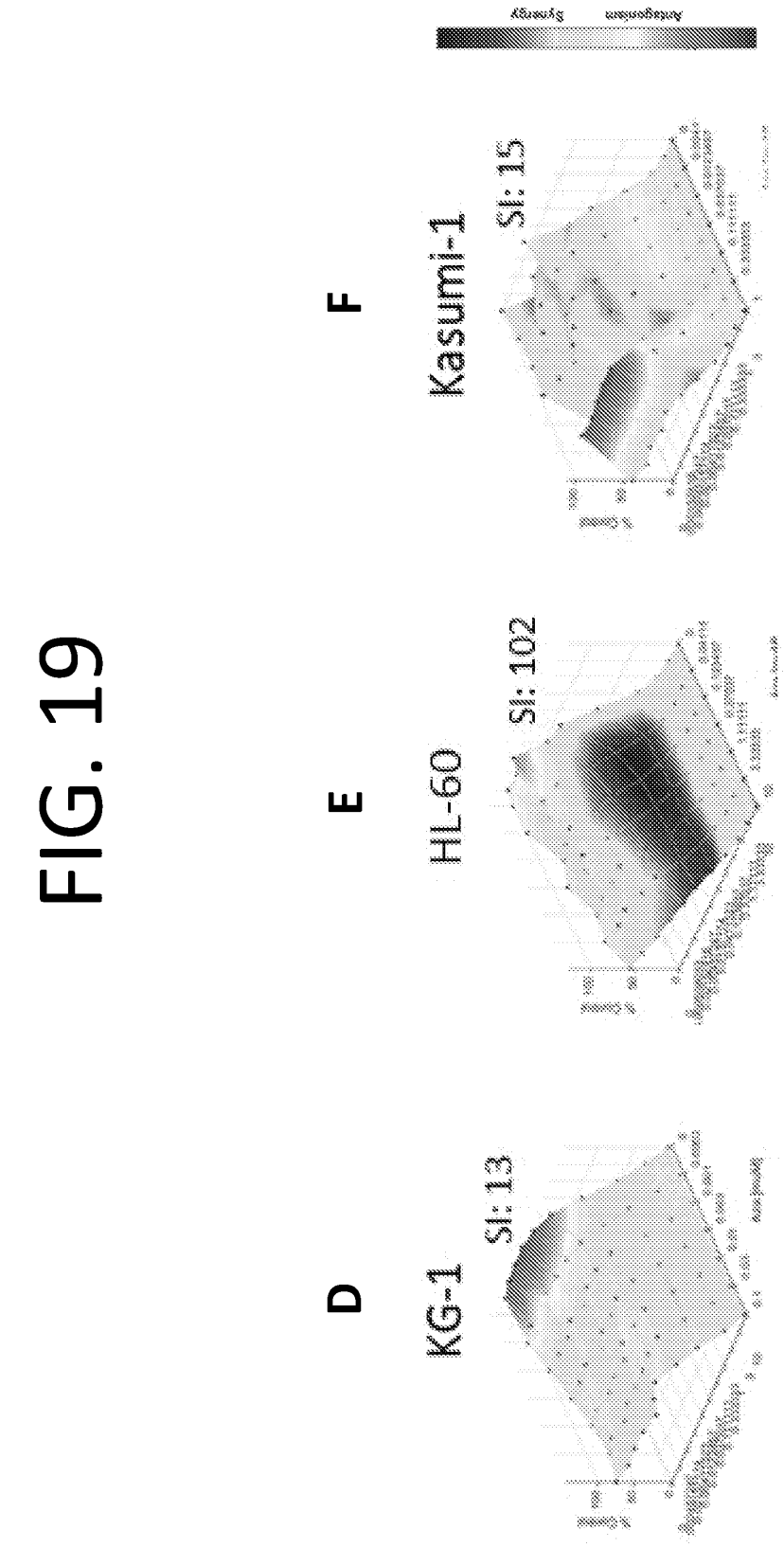


FIG. 19

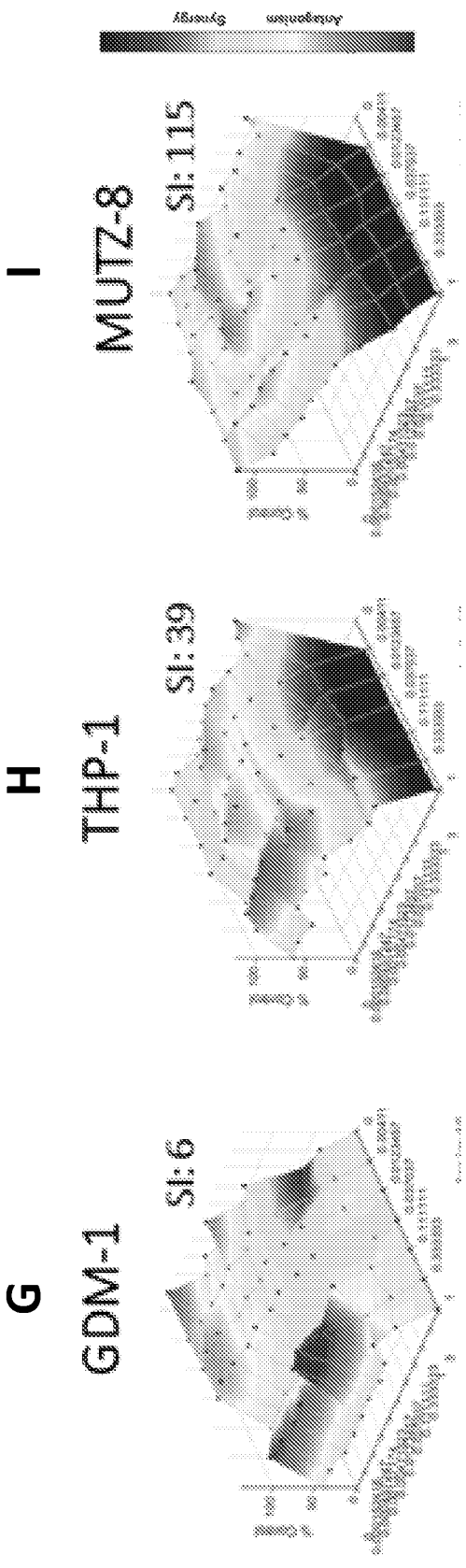


FIG. 19

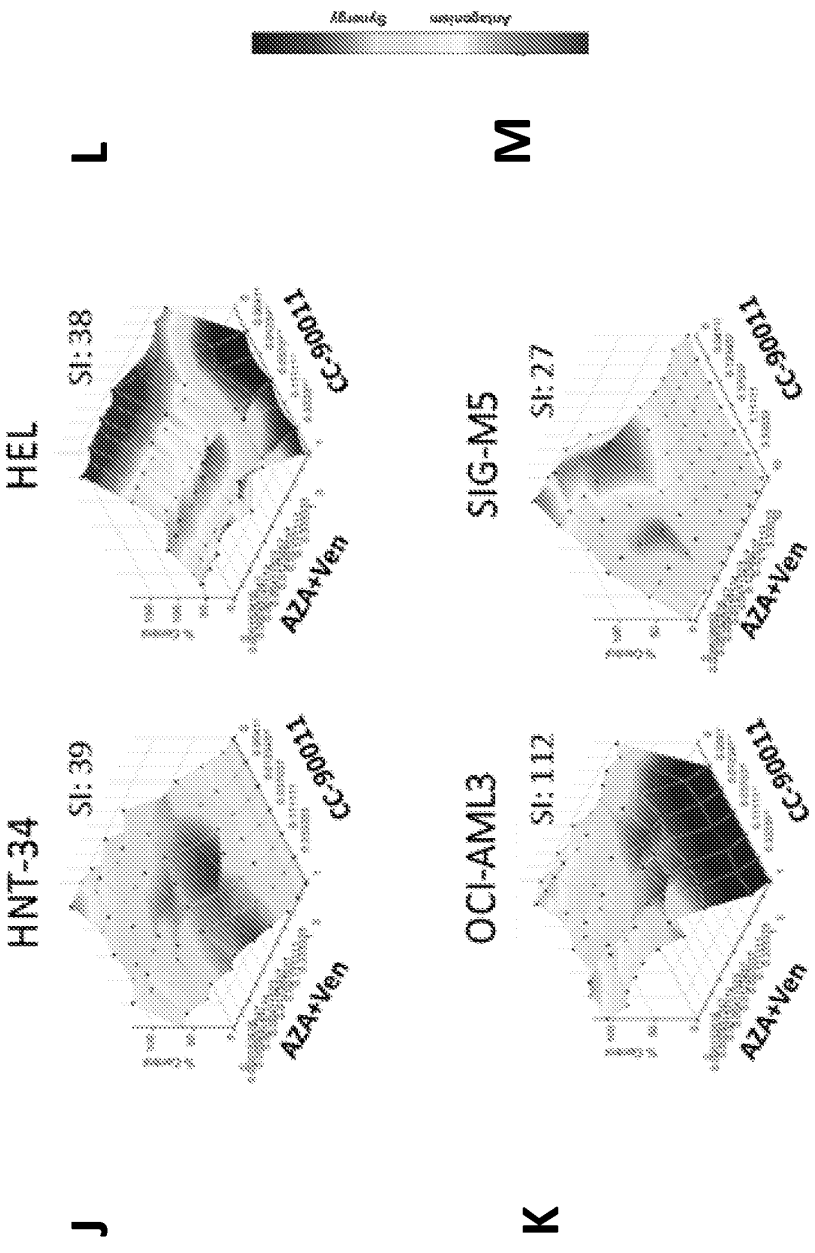

HNT-34
SI: 39
CC-90011
AZA+Ven
J
HEL
SI: 38
CC-90011
AZA+Ven
L
Antagonistic
Synergy
SIG-M5
SI: 27
CC-90011
AZA+Ven
M
OCI-AML3
SI: 112
CC-90011
AZA+Ven
K

FIG. 20

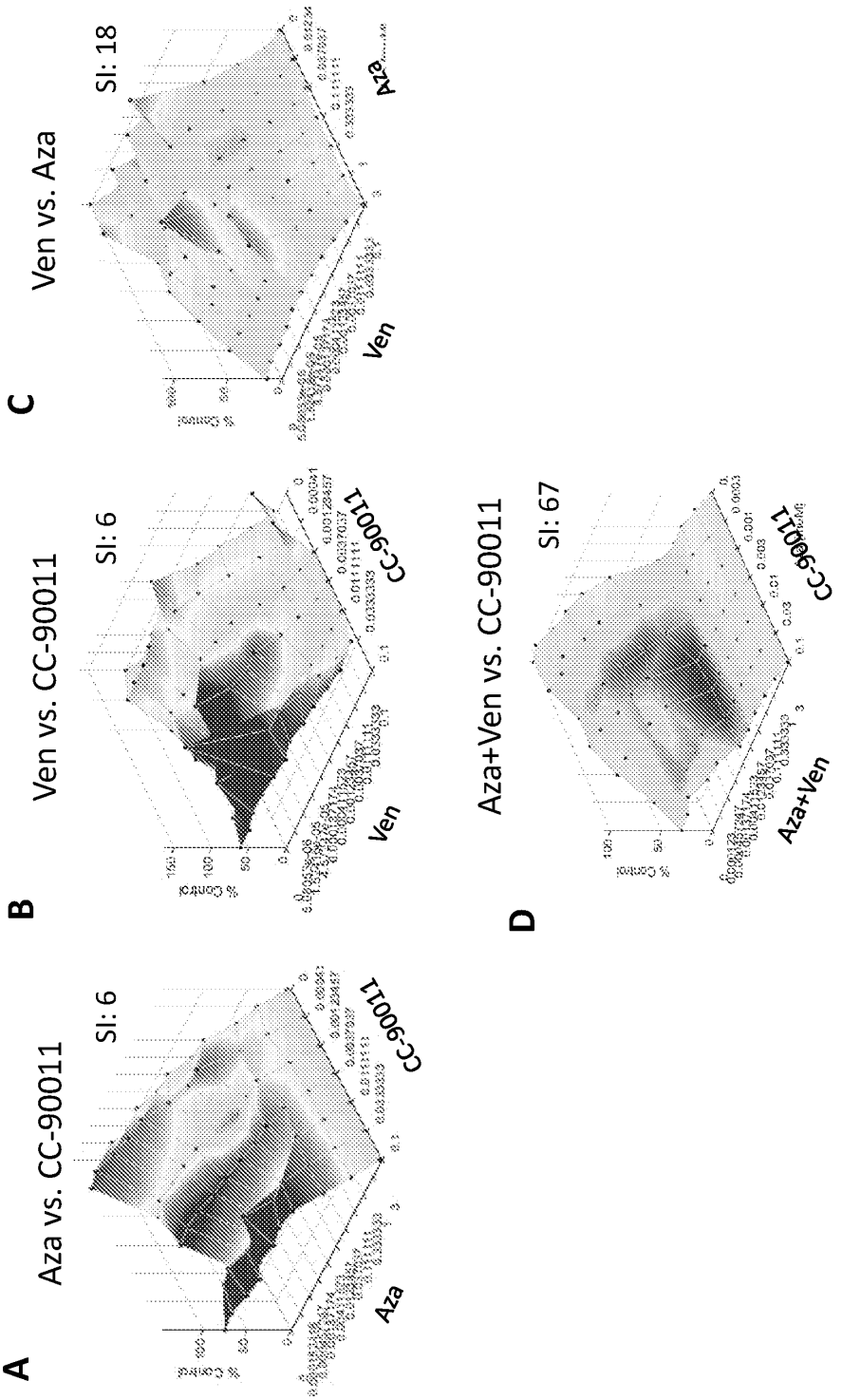
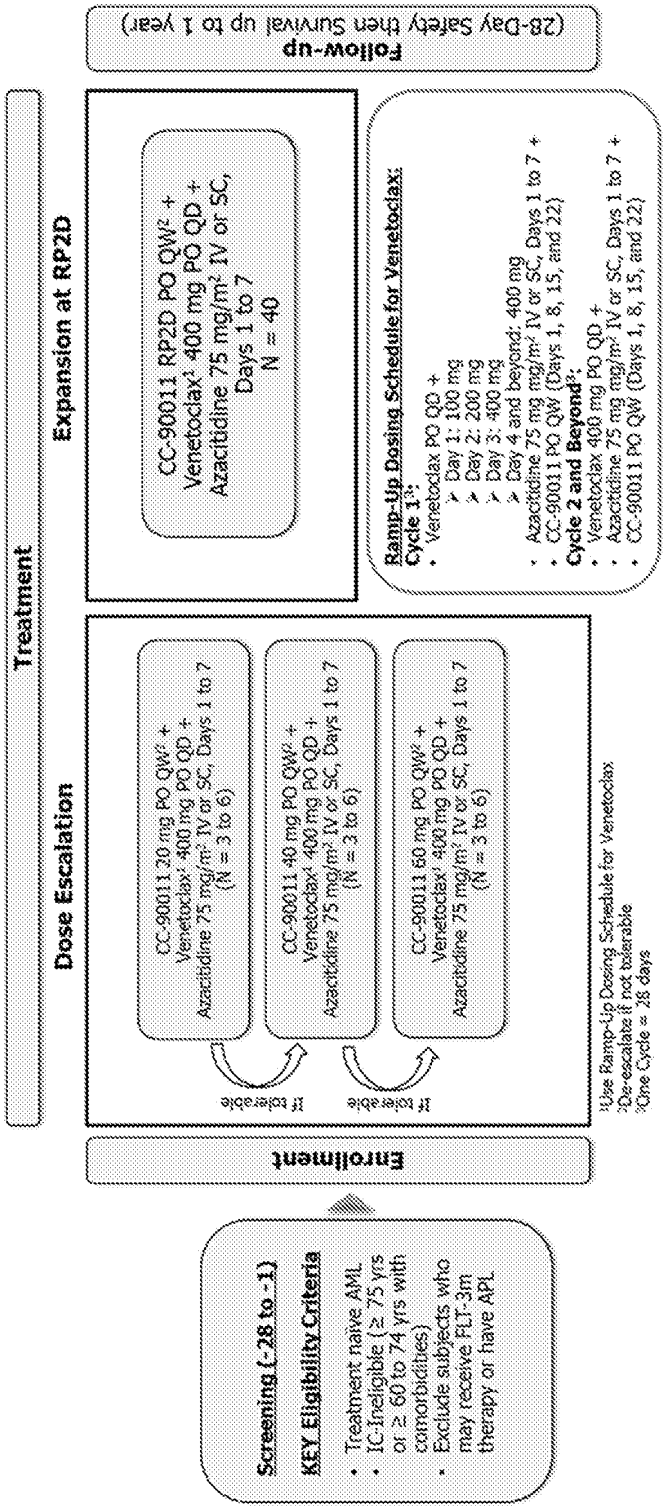

A
Aza vs. CC-90011
SI: 6
% Control
150
100
50
0
Aza
CC-90011
B
Ven vs. CC-90011
SI: 6
% Control
150
100
50
0
Ven
CC-90011
C
Ven vs. Aza
SI: 18
% Control
150
100
50
0
Ven
Aza
D
Aza+Ven vs. CC-90011
SI: 67
% Control
150
100
50
0
Aza+Ven
CC-90011

FIG. 21


Screening (-28 to -1)
KEY Eligibility Criteria
Treatment naive AML
IC-Ineligible (≥ 75 yrs or ≥ 60 to 74 yrs with comorbidities)
Exclude subjects who may receive FLT-3m therapy or have APL
Enrollment
Treatment
Dose Escalation
CC-90011 20 mg PO QW[2] + Venetoclax[1] 400 mg PO QD + Azacitidine 75 mg/m² IV or SC, Days 1 to 7 (N = 3 to 6)
CC-90011 40 mg PO QW[2] + Venetoclax[1] 400 mg PO QD + Azacitidine 75 mg/m² IV or SC, Days 1 to 7 (N = 3 to 6)
CC-90011 60 mg PO QW[2] + Venetoclax[1] 400 mg PO QD + Azacitidine 75 mg/m² IV or SC, Days 1 to 7 (N = 3 to 6)
If tolerable
If tolerable
Expansion at RP2D
CC-90011 RP2D PO QW[2] + Venetoclax[1] 400 mg PO QD + Azacitidine 75 mg/m² IV or SC, Days 1 to 7 N = 40
Ramp-Up Dosing Schedule for Venetoclax[1]:
Cycle 1[3]:
Venetoclax PO QD +
Day 1: 100 mg
Day 2: 200 mg
Day 3: 400 mg
Day 4 and beyond: 400 mg
Azacitidine 75 mg mg/m² IV or SC, Days 1 to 7 +
CC-90011 PO QW (Days 1, 8, 15, and 22)
Cycle 2 and Beyond[3]:
Venetoclax 400 mg PO QD +
Azacitidine 75 mg mg/m² IV or SC, Days 1 to 7 +
CC-90011 PO QW (Days 1, 8, 15, and 22)
Follow-up
(28-Day Safety then Survival up to 1 year)
[1]Use Ramp-Up Dosing Schedule for Venetoclax
[2]De-escalate if not tolerable
[3]One Cycle = 28 days