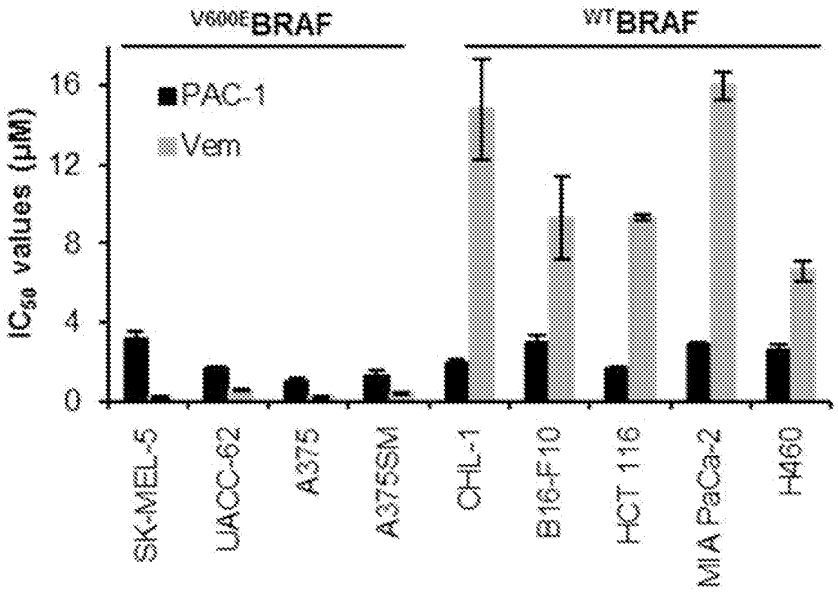

V600EBRAF
WTBRAF
PAC-1
Vem
IC50 values (μM)
16
12
8
4
0
SK-MEL-5
UACC-62
A375
A375SM
CHL-1
B16-F10
HCT 116
MIA PaCa-2
H460

Fig. 1A

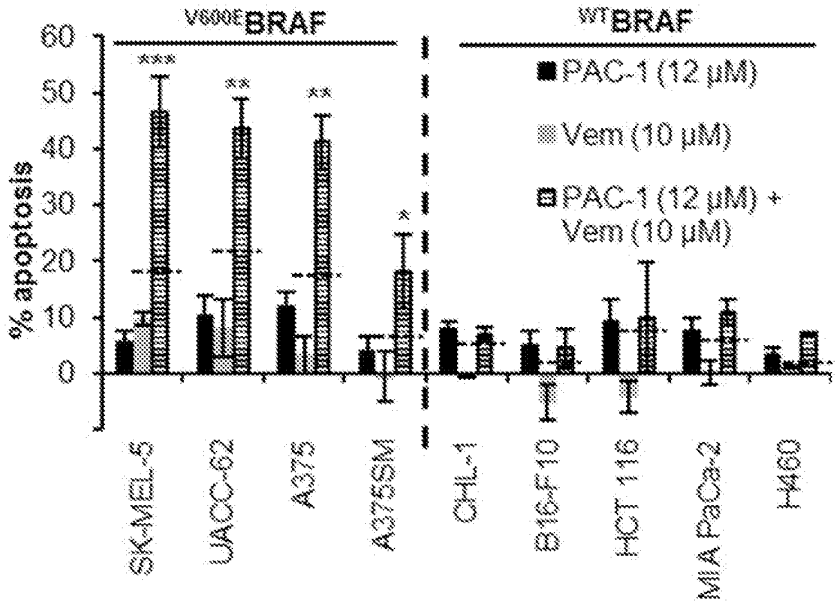

V600EBRAF
WTBRAF
PAC-1 (12 μM)
Vem (10 μM)
PAC-1 (12 μM) + Vem (10 μM)
% apoptosis
60
50
40
30
20
10
0
***
**
**
*
SK-MEL-5
UACC-62
A375
A375SM
CHL-1
B16-F10
HCT 116
MIA PaCa-2
H460

Fig. 1B

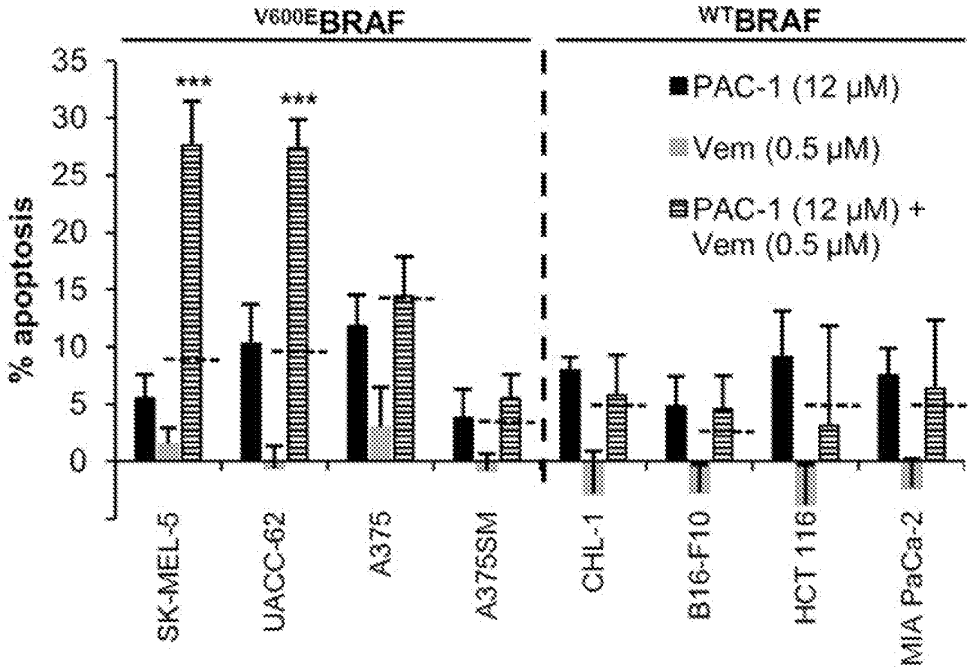

V600EBRAF
WTBRAF
PAC-1 (12 μM)
Vem (0.5 μM)
PAC-1 (12 μM) + Vem (0.5 μM)
% apoptosis
35
30
25
20
15
10
5
0
***
***
SK-MEL-5
UACC-62
A375
A375SM
CHL-1
B16-F10
HCT 116
MIA PaCa-2

Fig. 1C

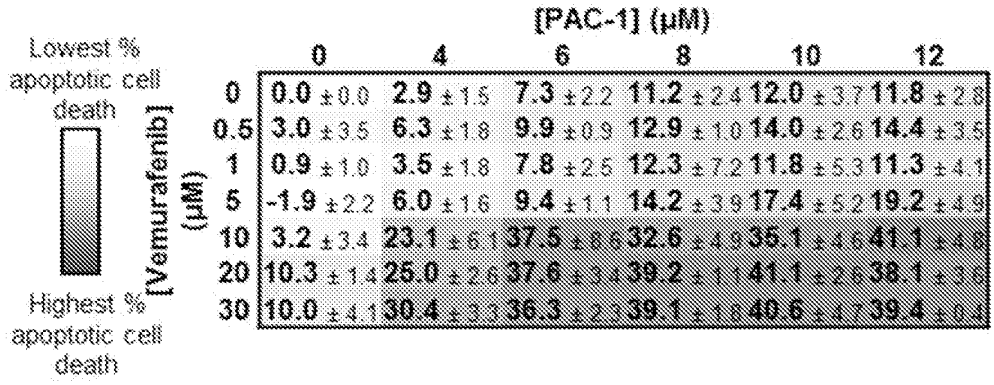

[PAC-1] (μM)
0 4 6 8 10 12
[Vemurafenib] (μM)
0 0.0 ±0.0 2.9 ±1.5 7.3 ±2.2 11.2 ±2.4 12.0 ±3.7 11.8 ±2.8
0.5 3.0 ±3.5 6.3 ±1.8 9.9 ±0.9 12.9 ±1.0 14.0 ±2.6 14.4 ±3.5
1 0.9 ±1.0 3.5 ±1.8 7.8 ±2.5 12.3 ±7.2 11.8 ±5.3 11.3 ±4.1
5 -1.9 ±2.2 6.0 ±1.6 9.4 ±1.1 14.2 ±3.9 17.4 ±5.2 19.2 ±4.9
10 3.2 ±3.4 23.1 ±6.1 37.5 ±8.6 32.6 ±4.9 35.1 ±4.6 41.1 ±4.8
20 10.3 ±1.4 25.0 ±2.6 37.6 ±3.4 39.2 ±1.1 41.1 ±2.6 38.1 ±3.6
30 10.0 ±4.1 30.4 ±3.3 36.3 ±2.3 39.1 ±1.8 40.6 ±4.7 39.4 ±0.4
Lowest % apoptotic cell death
Highest % apoptotic cell death

Fig. 2A

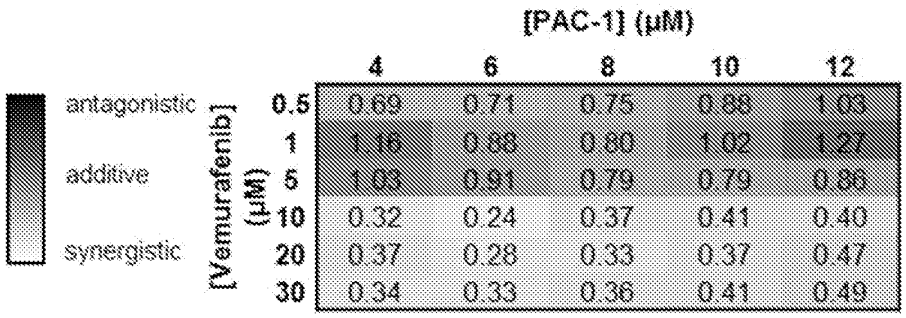

antagonistic
additive
synergistic
[PAC-1] (μM)
4 6 8 10 12
[Vemurafenib] (μM)
0.5 0.69 0.71 0.75 0.88 1.03
1 1.16 0.88 0.80 1.02 1.27
5 1.03 0.91 0.79 0.79 0.86
10 0.32 0.24 0.37 0.41 0.40
20 0.37 0.28 0.33 0.37 0.47
30 0.34 0.33 0.36 0.41 0.49

Fig. 2B

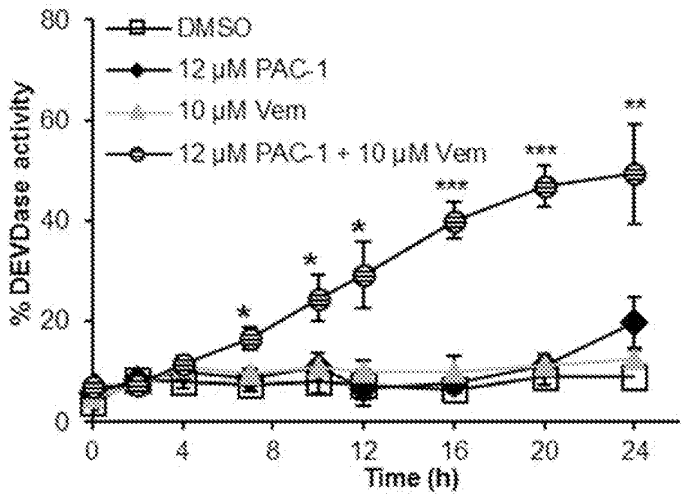

DMSO
12 μM PAC-1
10 μM Vem
12 μM PAC-1 + 10 μM Vem
% DEVDase activity
Time (h)
0
20
40
60
80
0
4
8
12
16
20
24
*
*
*
***
***
**

Fig. 2C

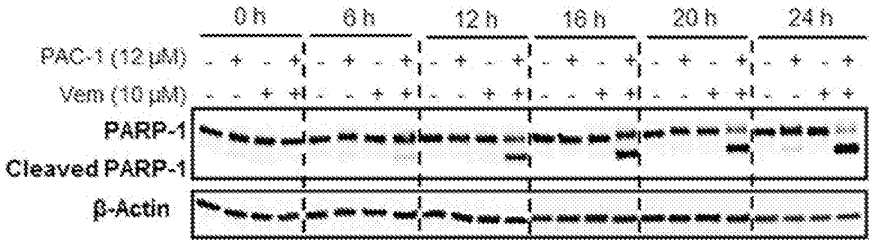

0 h
6 h
12 h
16 h
20 h
24 h
PAC-1 (12 μM)
Vem (10 μM)
PARP-1
Cleaved PARP-1
β-Actin

Fig. 2D

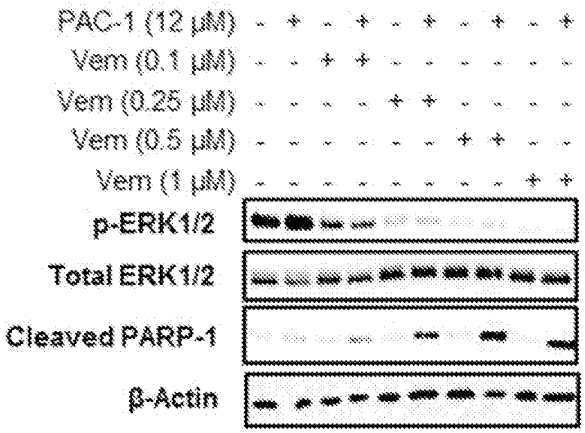

PAC-1 (12 μM)
Vem (0.1 μM)
Vem (0.25 μM)
Vem (0.5 μM)
Vem (1 μM)
p-ERK1/2
Total ERK1/2
Cleaved PARP-1
β-Actin

Fig. 2E

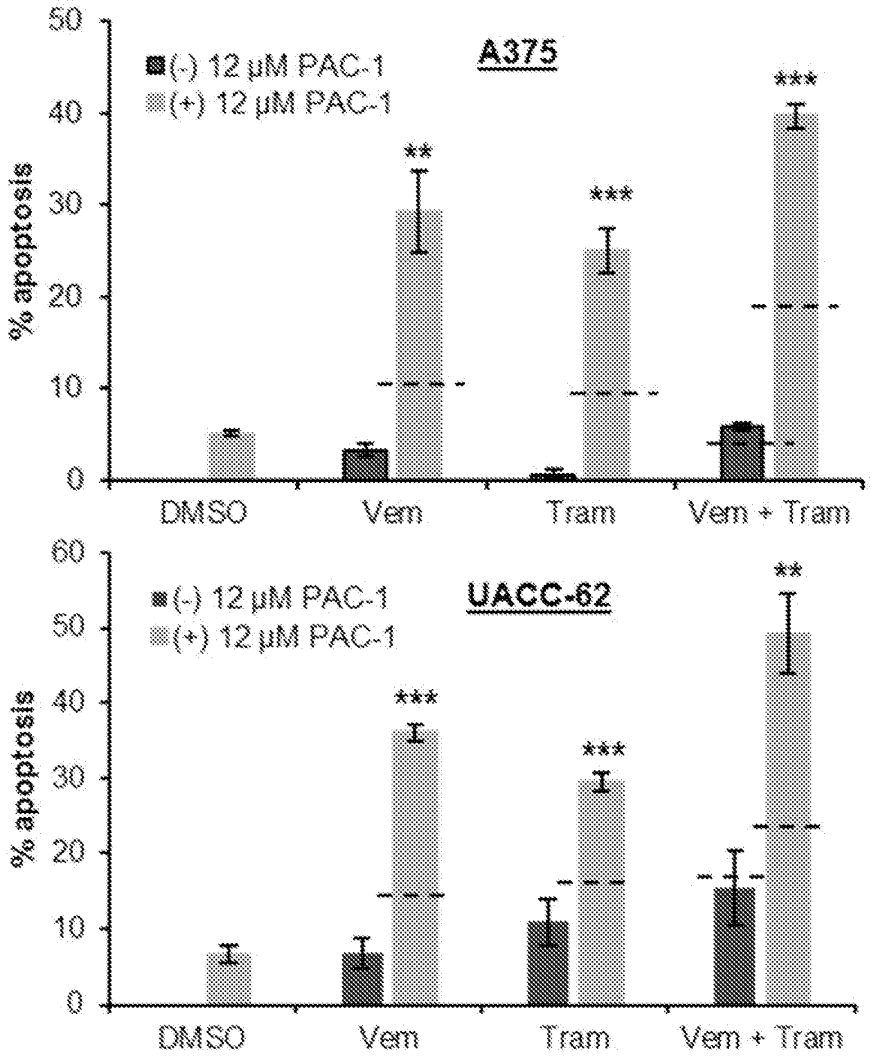

A375
(-) 12 μM PAC-1
(+) 12 μM PAC-1
% apoptosis
50
40
30
20
10
0
**
***
***
DMSO
Vem
Tram
Vem + Tram
UACC-62
(-) 12 μM PAC-1
(+) 12 μM PAC-1
% apoptosis
60
50
40
30
20
10
0
***
***
**
DMSO
Vem
Tram
Vem + Tram

Fig. 3A

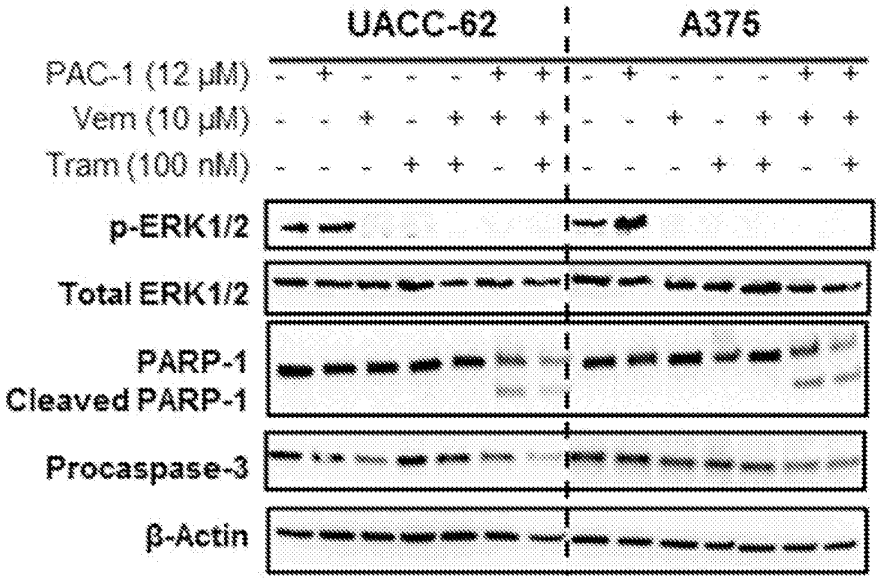

UACC-62
A375
PAC-1 (12 μM)
Vem (10 μM)
Tram (100 nM)
p-ERK1/2
Total ERK1/2
PARP-1
Cleaved PARP-1
Procaspase-3
β-Actin

Fig. 3B

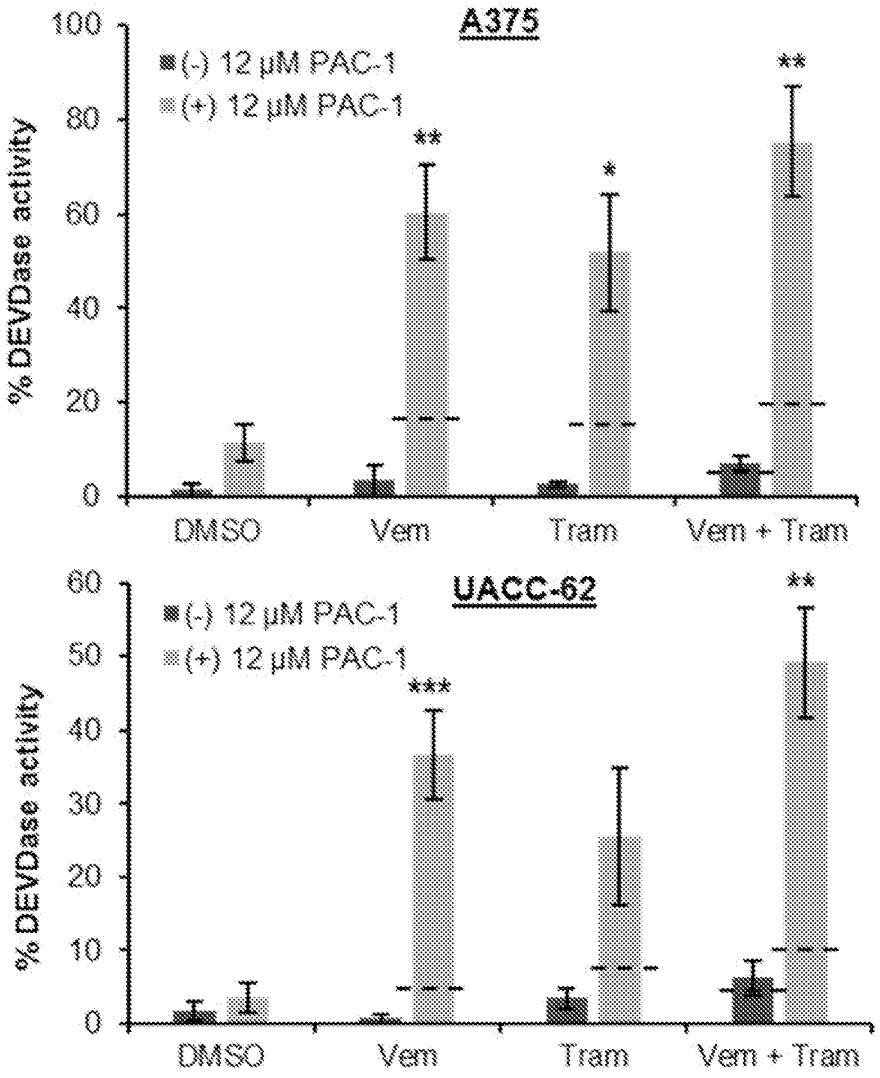

A375
(-) 12 μM PAC-1
(+) 12 μM PAC-1
% DEVDase activity
100
80
60
40
20
0
**
*
**
DMSO
Vem
Tram
Vem + Tram
UACC-62
(-) 12 μM PAC-1
(+) 12 μM PAC-1
% DEVDase activity
60
50
40
30
20
10
0
***
**
DMSO
Vem
Tram
Vem + Tram

Fig. 3C

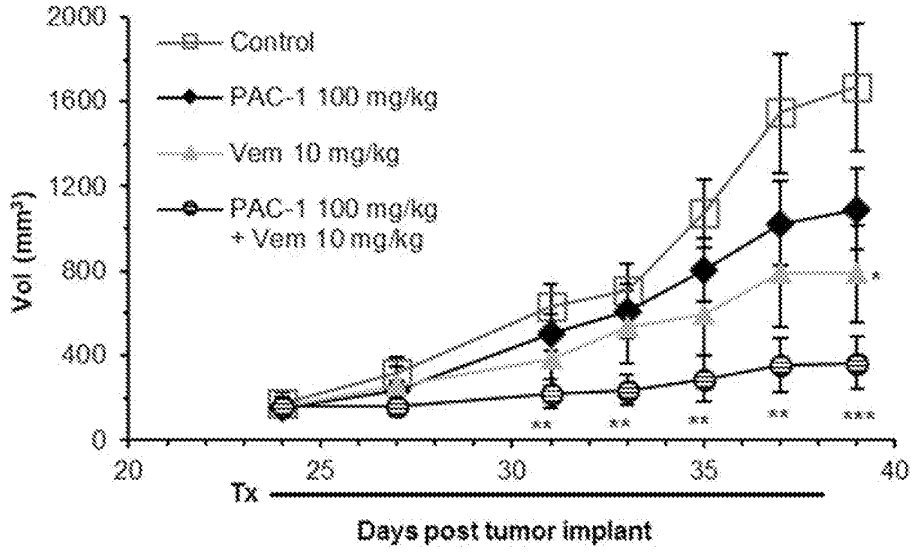

2000
1600
1200
800
400
0
Vol (mm³)
Control
PAC-1 100 mg/kg
Vem 10 mg/kg
PAC-1 100 mg/kg
+ Vem 10 mg/kg
**
**
**
**
***
*
20
25
30
35
40
Tx
Days post tumor implant

Fig. 4A

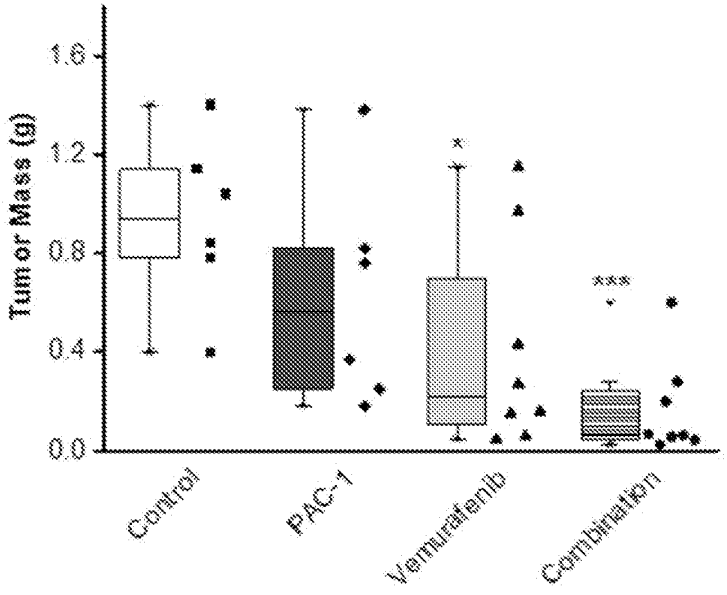

1.6
1.2
0.8
0.4
0.0
Tumor Mass (g)
***
Control
PAC-1
Vemurafenib
Combination

Fig. 4B

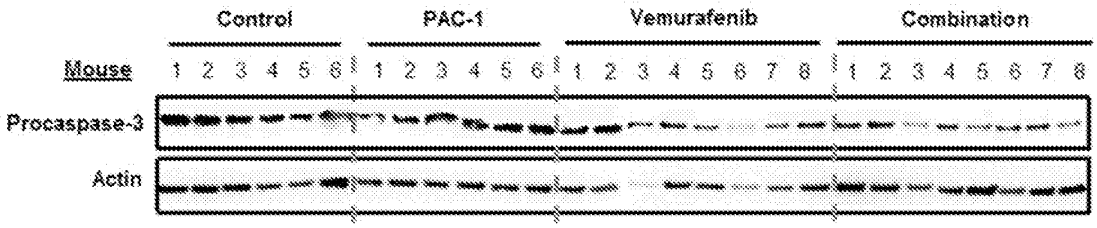

Control
PAC-1
Vemurafenib
Combination
Mouse
1 2 3 4 5 6
1 2 3 4 5 6
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8
Procaspase-3
Actin

Fig. 4C

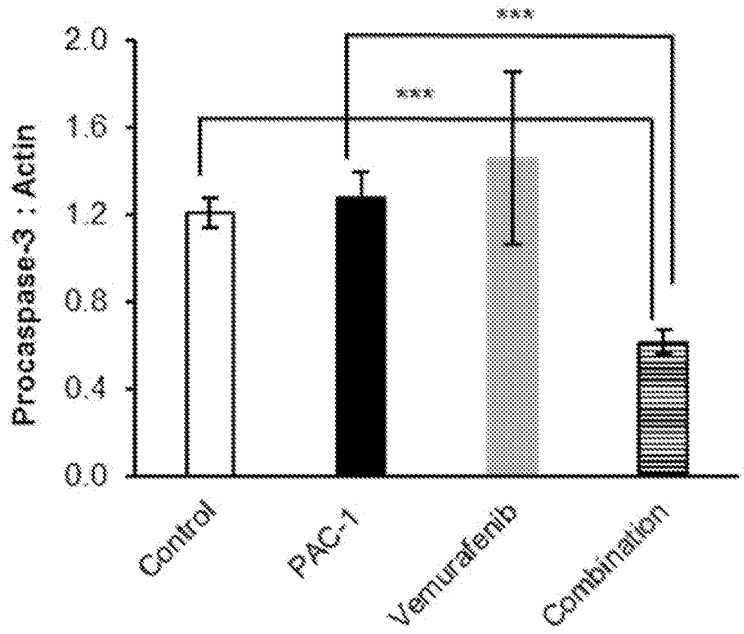

***
***
2.0
1.6
1.2
0.8
0.4
0.0
Procaspase-3 : Actin
Control
PAC-1
Vemurafenib
Combination

Fig. 4D

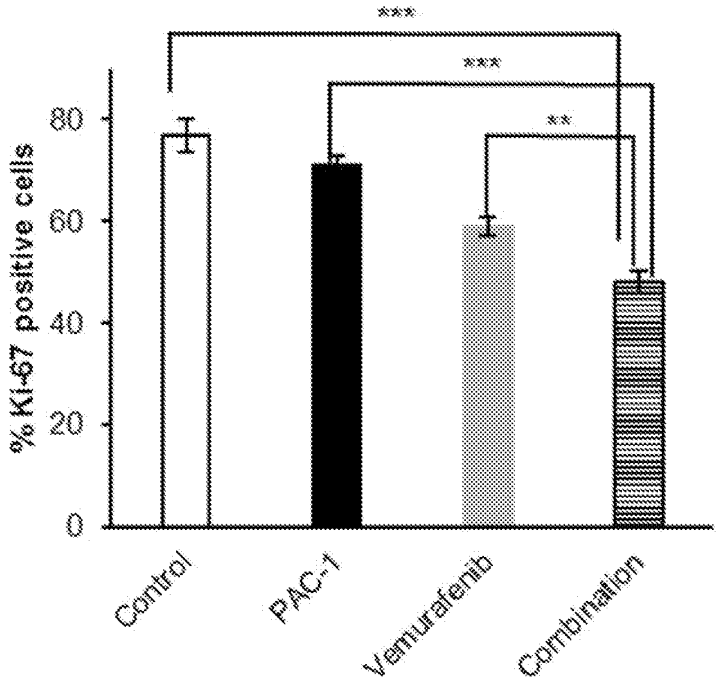
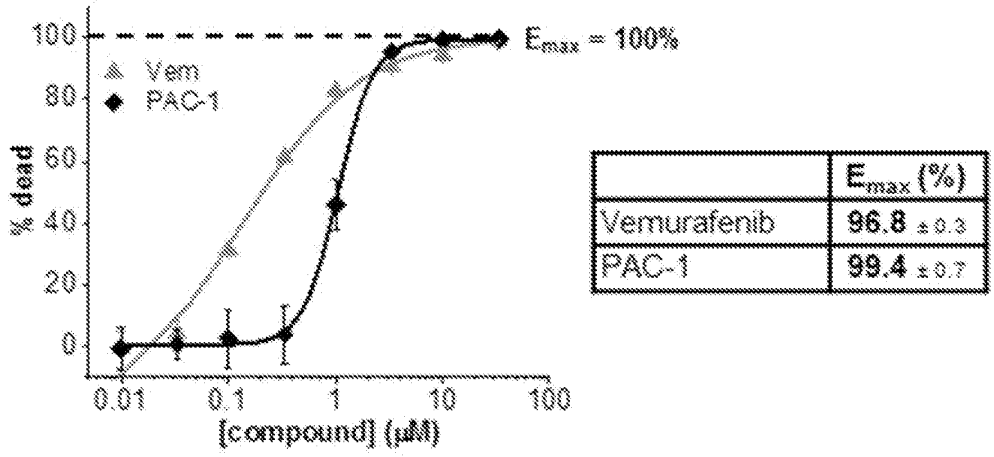


Fig. 4E



	E_{max} (%)
Vemurafenib	**96.8** ± 0.3
PAC-1	**99.4** ± 0.7

Fig. 5A

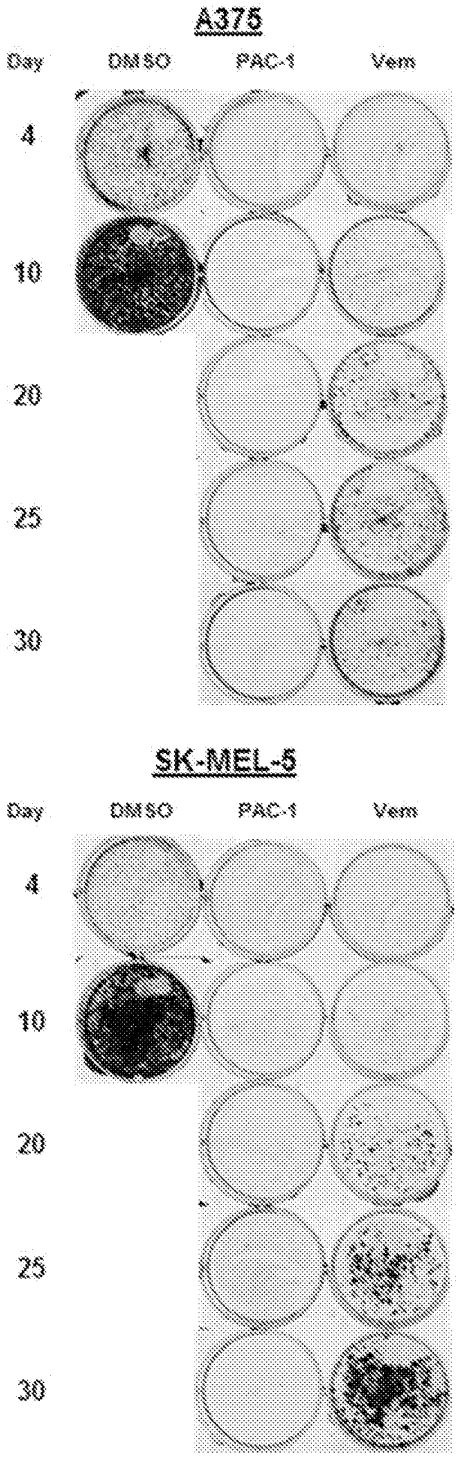

A375
Day
DMSO
PAC-1
Vem
4
10
20
25
30
SK-MEL-5
Day
DMSO
PAC-1
Vem
4
10
20
25
30

Fig. 5B

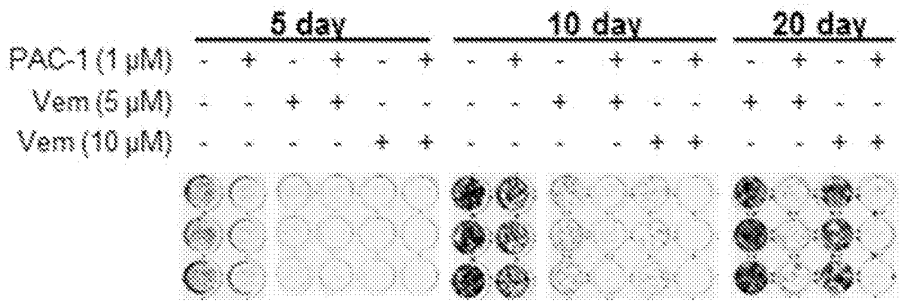

5 day
10 day
20 day
PAC-1 (1 μM) - + - + - + - + - + - + - + - +
Vem (5 μM) - - + + - - - - + + - - + + - -
Vem (10 μM) - - - - + + - - - - + + - - + +

Fig. 5C

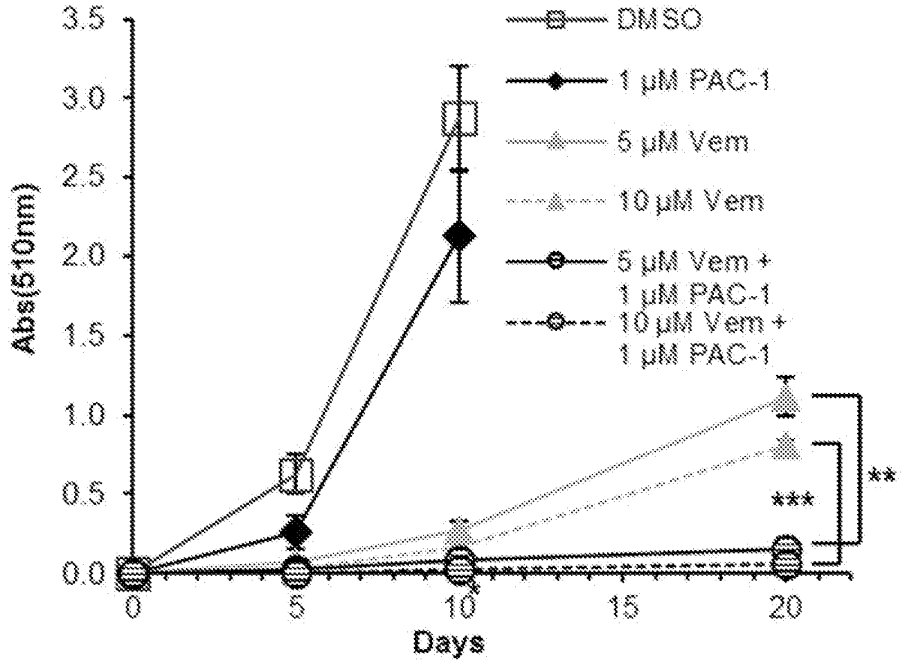
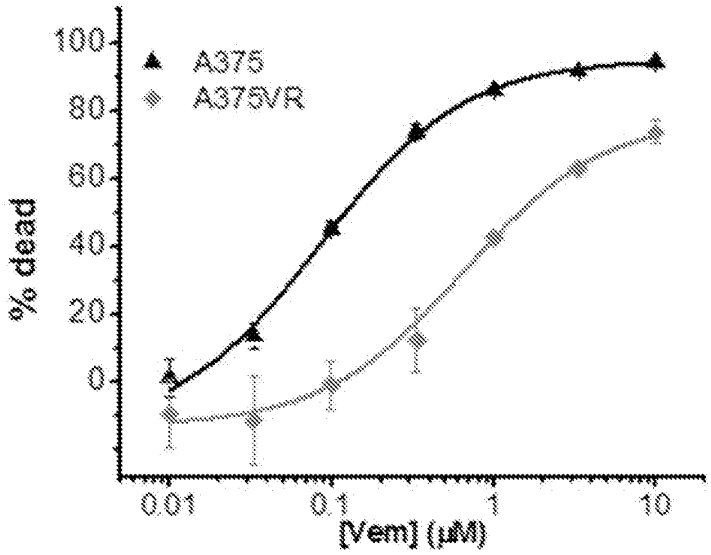

DMSO
1 μM PAC-1
5 μM Vem
10 μM Vem
5 μM Vem + 1 μM PAC-1
10 μM Vem + 1 μM PAC-1
Abs(510nm)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
Days
**
***

Fig. 5D



	A375	A375VR
5-day Vem IC_{50} (μM)	**0.13** ± 0.01	**1.5** ± 0.1
E_{max} Vem (%)	**93** ± 1.2	**79** ± 6.3

Fig. 6A

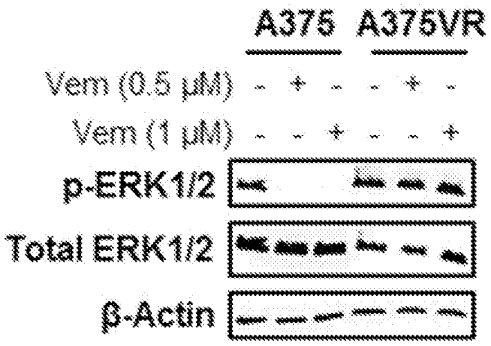
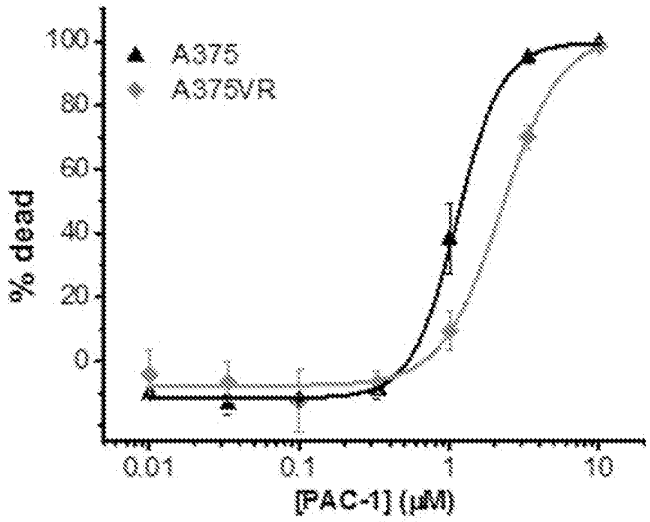


Fig. 6B



	A375	A375VR
5-day PAC-1 IC_{50} (μM)	**1.2** ± 0.1	**2.4** ± 0.3
E_{max} PAC-1 (%)	**99** ± 0.1	**100** ± 1.4

Fig. 6C

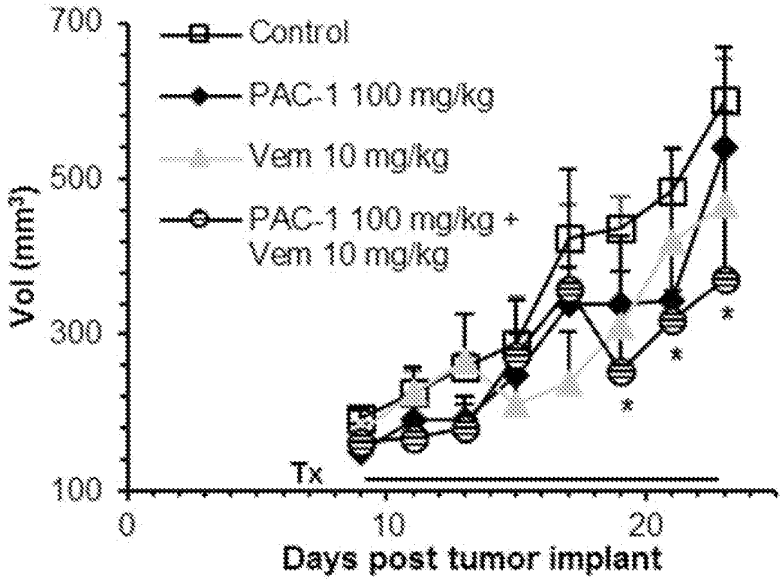
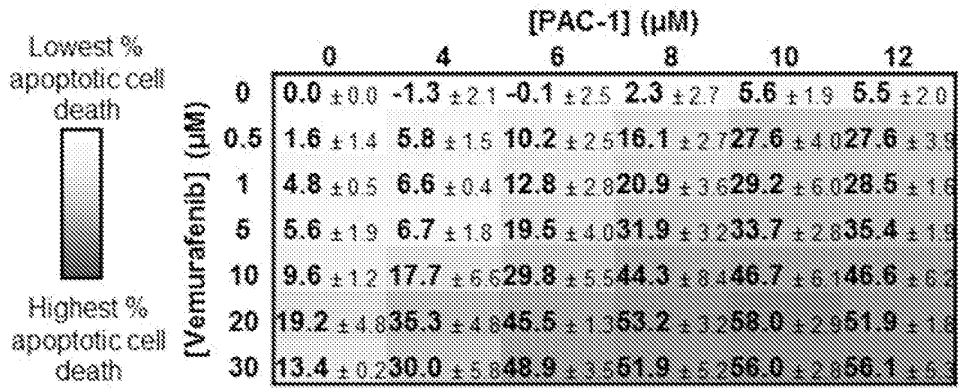
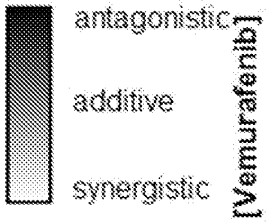


Fig. 6D



[Vemurafenib] (μM) \ [PAC-1] (μM)	0	4	6	8	10	12
0	0.0 ± 0.0	-1.3 ± 2.1	-0.1 ± 2.5	2.3 ± 2.7	5.6 ± 1.9	5.5 ± 2.0
0.5	1.6 ± 1.4	5.8 ± 1.5	10.2 ± 2.5	16.1 ± 2.7	27.6 ± 4.0	27.6 ± 3.9
1	4.8 ± 0.5	6.6 ± 0.4	12.8 ± 2.8	20.9 ± 3.6	29.2 ± 6.0	28.5 ± 1.6
5	5.6 ± 1.9	6.7 ± 1.8	19.5 ± 4.0	31.9 ± 3.2	33.7 ± 2.8	35.4 ± 1.9
10	9.6 ± 1.2	17.7 ± 6.6	29.8 ± 5.5	44.3 ± 8.4	46.7 ± 6.1	46.6 ± 6.2
20	19.2 ± 4.8	35.3 ± 4.8	45.5 ± 1.3	63.2 ± 3.2	58.0 ± 2.9	51.9 ± 1.6
30	13.4 ± 0.2	30.0 ± 5.8	48.9 ± 3.6	51.9 ± 6.2	56.0 ± 2.6	56.1 ± 5.3

Fig. 7A



[Vemurafenib] (μM) \ [PAC-1] (μM)	4	6	8	10	12
0.5	0.45	0.41	0.45	0.36	0.43
1	0.50	0.37	0.48	0.35	0.43
5	1.23	0.49	0.43	0.33	0.38
10	0.38	0.34	0.32	0.26	0.31
20	0.18	0.21	0.23	0.21	0.28
30	0.27	0.16	0.22	0.22	0.26

Fig. 7B

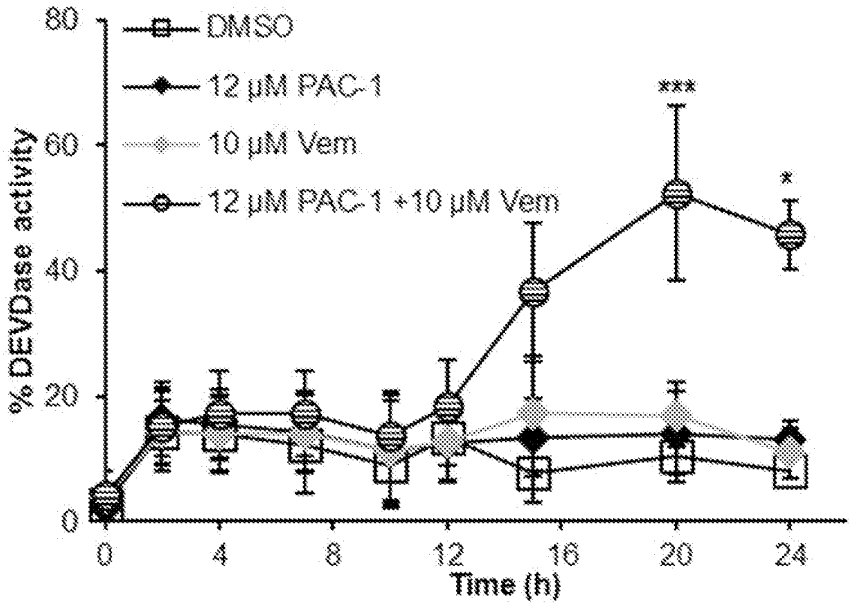

DMSO
12 μM PAC-1
10 μM Vem
12 μM PAC-1 +10 μM Vem
% DEVDase activity
Time (h)
0
20
40
60
80
0
4
8
12
16
20
24
***
*

Fig. 7C

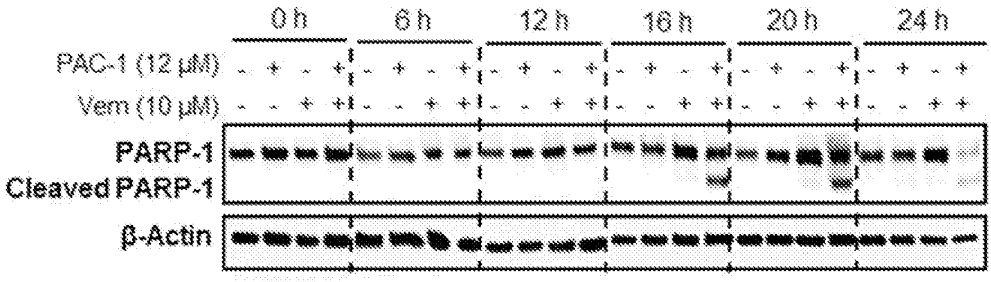

0 h
6 h
12 h
16 h
20 h
24 h
PAC-1 (12 μM)
Vem (10 μM)
PARP-1
Cleaved PARP-1
β-Actin

Fig. 7D

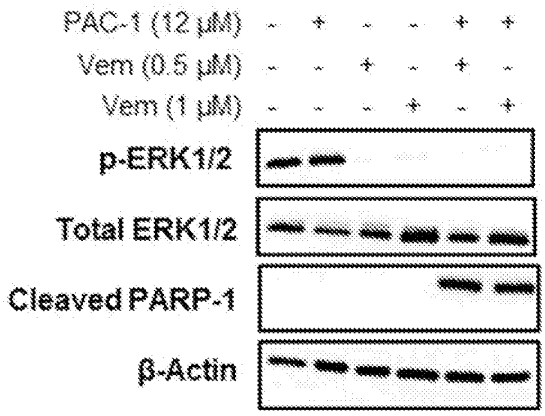

PAC-1 (12 μM) - + - - + +
Vem (0.5 μM) - - + - + -
Vem (1 μM) - - - + - +
p-ERK1/2
Total ERK1/2
Cleaved PARP-1
β-Actin

Fig. 7E

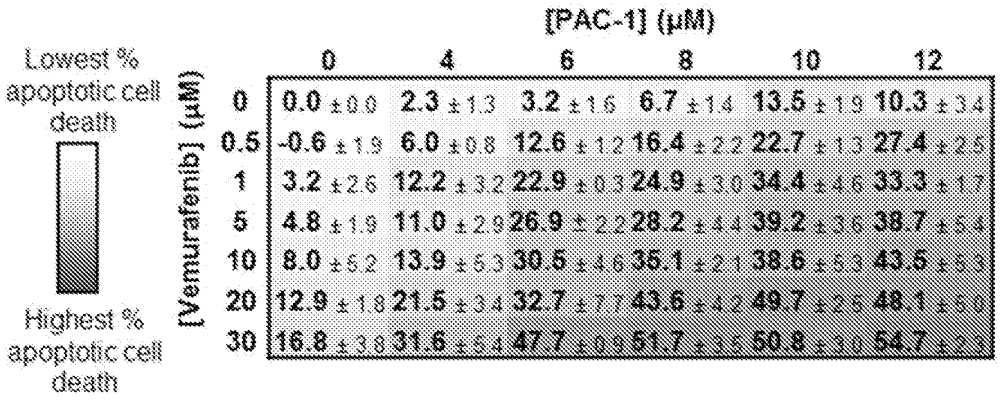

[PAC-1] (μM)
0 4 6 8 10 12
[Vemurafenib] (μM)
0 0.0 ± 0.0 2.3 ± 1.3 3.2 ± 1.6 6.7 ± 1.4 13.5 ± 1.9 10.3 ± 3.4
0.5 -0.6 ± 1.9 6.0 ± 0.8 12.6 ± 1.2 16.4 ± 2.2 22.7 ± 1.3 27.4 ± 2.5
1 3.2 ± 2.6 12.2 ± 3.2 22.9 ± 0.3 24.9 ± 3.0 34.4 ± 4.6 33.3 ± 1.7
5 4.8 ± 1.9 11.0 ± 2.9 26.9 ± 2.2 28.2 ± 4.4 39.2 ± 3.6 38.7 ± 5.4
10 8.0 ± 5.2 13.9 ± 5.3 30.5 ± 4.6 35.1 ± 2.1 38.6 ± 5.3 43.5 ± 5.3
20 12.9 ± 1.8 21.5 ± 3.4 32.7 ± 7.7 43.6 ± 4.2 49.7 ± 2.5 48.1 ± 5.0
30 16.8 ± 3.8 31.6 ± 5.4 47.7 ± 0.9 51.7 ± 3.5 50.8 ± 3.0 54.7 ± 2.3
Lowest % apoptotic cell death
Highest % apoptotic cell death

Fig. 8A

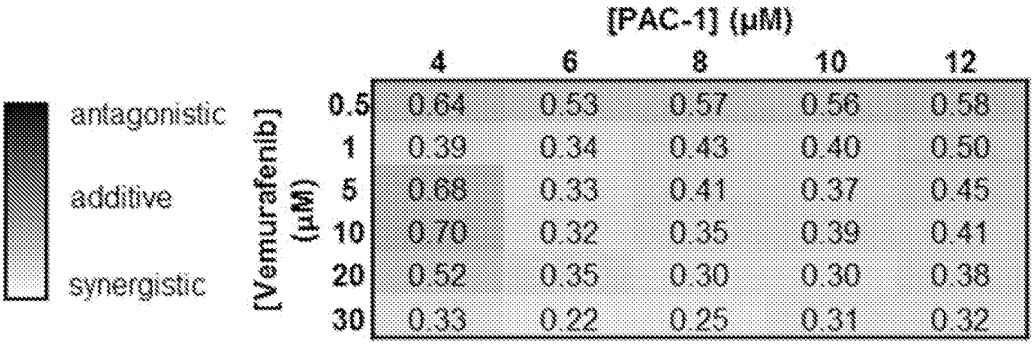

antagonistic
additive
synergistic
[Vemurafenib] (μM)
[PAC-1] (μM)
4 6 8 10 12
0.5 0.64 0.53 0.57 0.56 0.58
1 0.39 0.34 0.43 0.40 0.50
5 0.68 0.33 0.41 0.37 0.45
10 0.70 0.32 0.35 0.39 0.41
20 0.52 0.35 0.30 0.30 0.38
30 0.33 0.22 0.25 0.31 0.32

Fig. 8B

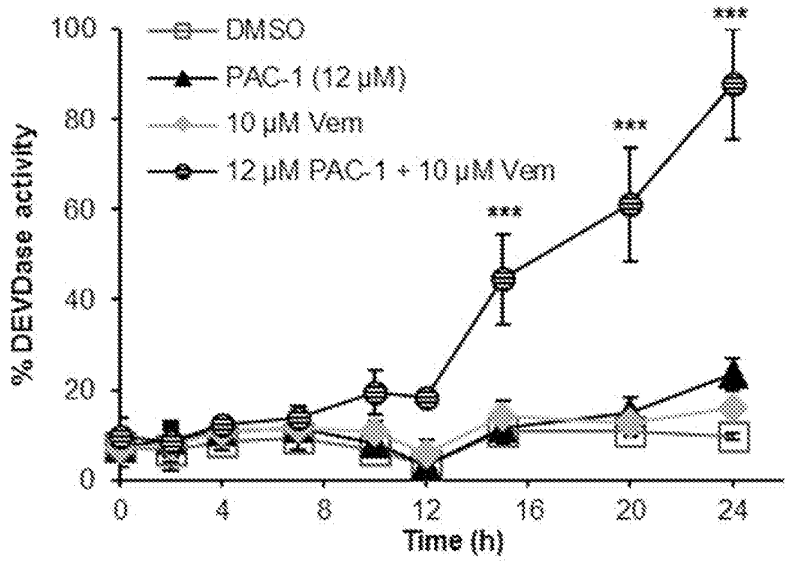

DMSO
PAC-1 (12 μM)
10 μM Vem
12 μM PAC-1 + 10 μM Vem
% DEVDase activity
Time (h)
0 20 40 60 80 100
0 4 8 12 16 20 24
***
***
***

Fig. 8C

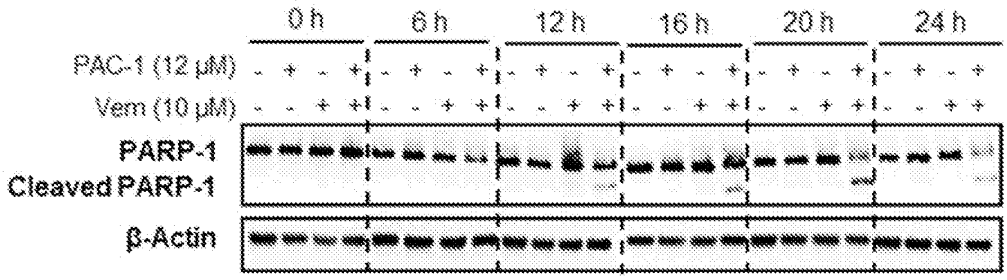

0 h
6 h
12 h
16 h
20 h
24 h
PAC-1 (12 μM)
Vem (10 μM)
PARP-1
Cleaved PARP-1
β-Actin

Fig. 8D

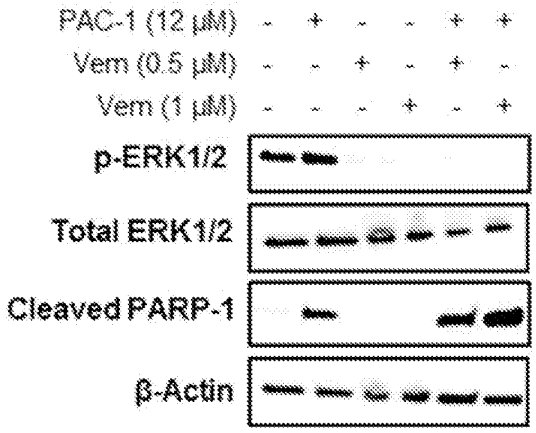

PAC-1 (12 μM)
Vem (0.5 μM)
Vem (1 μM)
p-ERK1/2
Total ERK1/2
Cleaved PARP-1
β-Actin

Fig. 8E

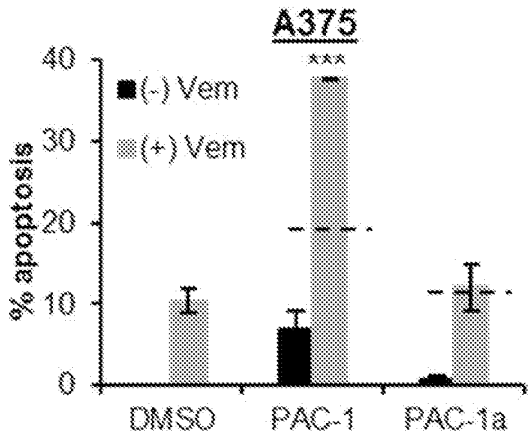

A375
***
(-) Vem
(+) Vem
% apoptosis
40
30
20
10
0
DMSO
PAC-1
PAC-1a

Fig. 9A

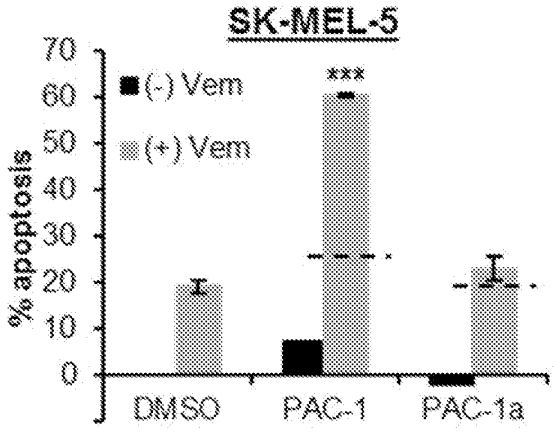

SK-MEL-5
***
(-) Vem
(+) Vem
% apoptosis
70
60
50
40
30
20
10
0
DMSO
PAC-1
PAC-1a

Fig. 9B

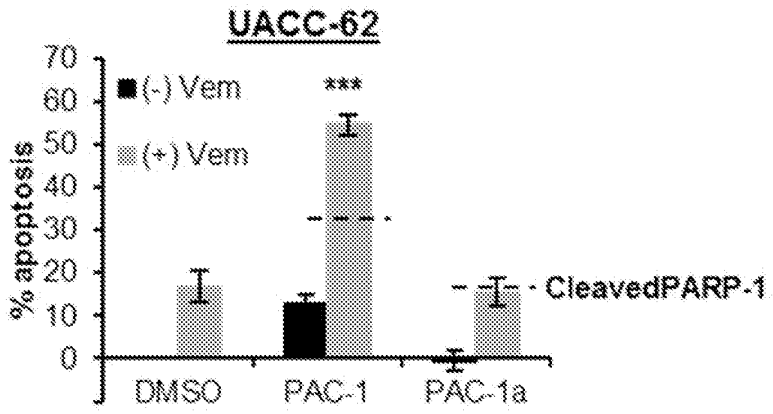

UACC-62
% apoptosis
70
60
50
40
30
20
10
0
(-) Vem
(+) Vem
***
CleavedPARP-1
DMSO
PAC-1
PAC-1a

Fig. 9C

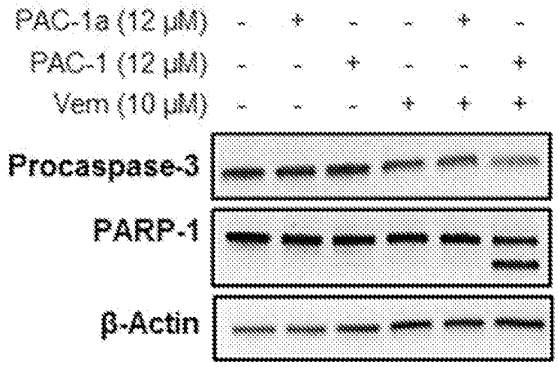

PAC-1a (12 μM) - + - - + -
PAC-1 (12 μM) - - + - - +
Vem (10 μM) - - - + + +
Procaspase-3
PARP-1
β-Actin

Fig. 9D

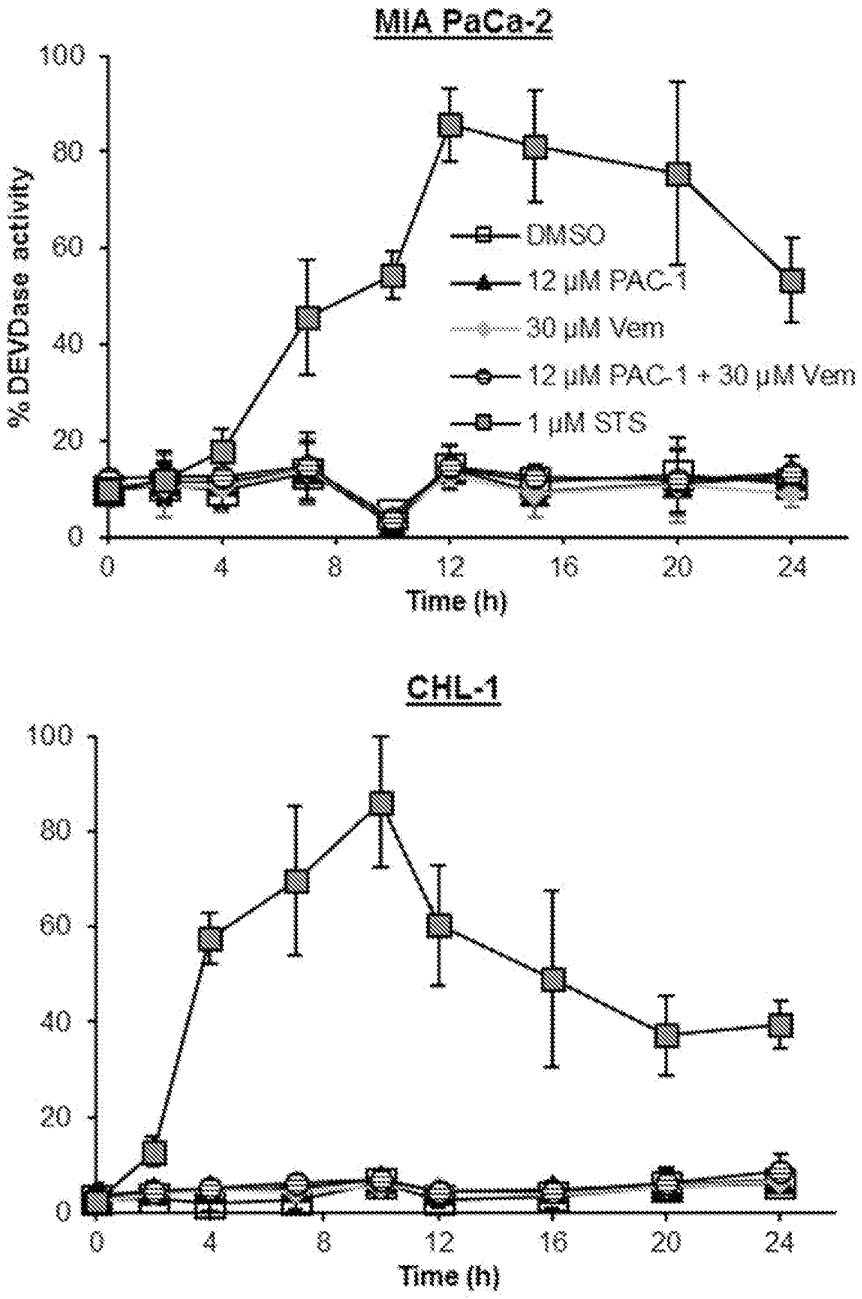

MIA PaCa-2
% DEVDase activity
100
80
60
40
20
0
0
4
8
12
16
20
24
Time (h)
DMSO
12 μM PAC-1
30 μM Vem
12 μM PAC-1 + 30 μM Vem
1 μM STS
CHL-1
100
80
60
40
20
0
0
4
8
12
16
20
24
Time (h)

Fig. 10A

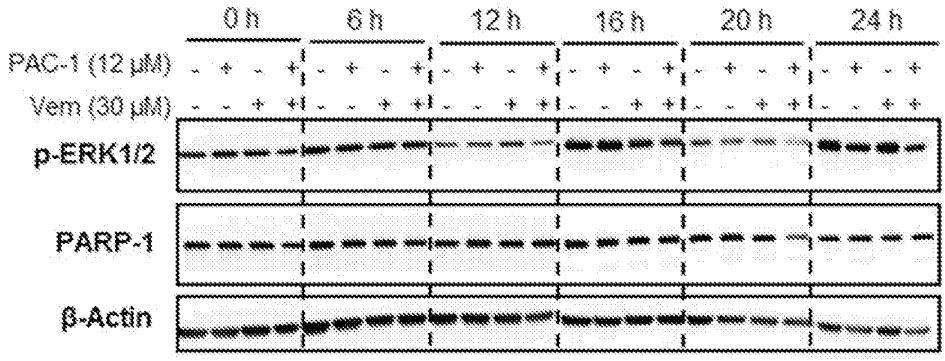


Fig. 10B

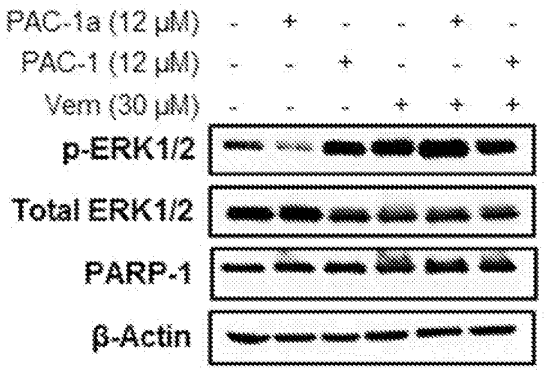


Fig. 10C

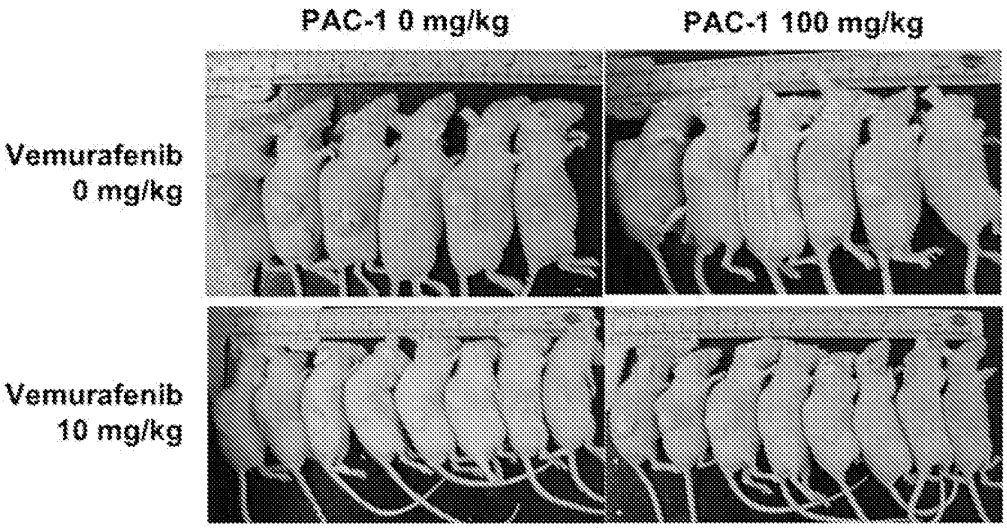

PAC-1 0 mg/kg
PAC-1 100 mg/kg
Vemurafenib
0 mg/kg
Vemurafenib
10 mg/kg

Fig. 11

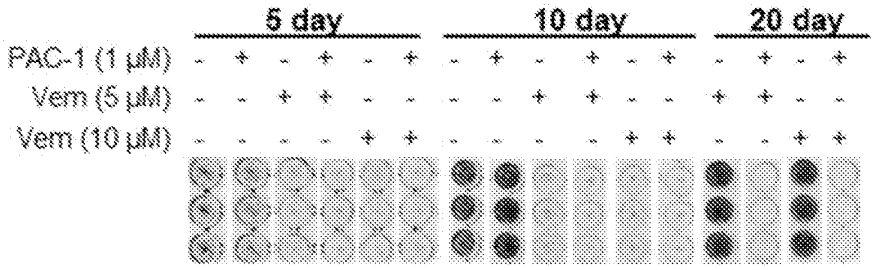


Fig. 12A

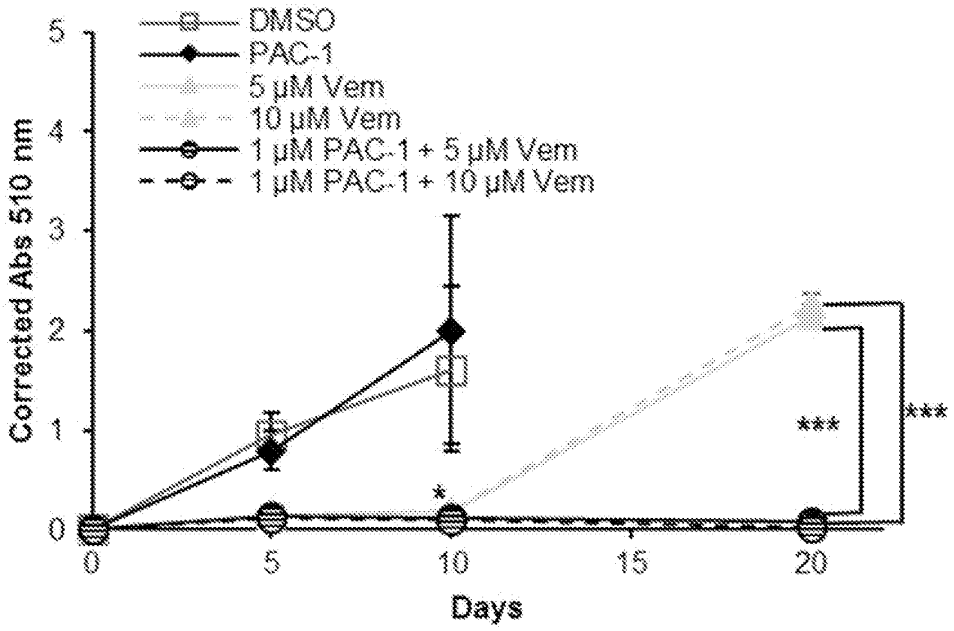


Fig. 12B

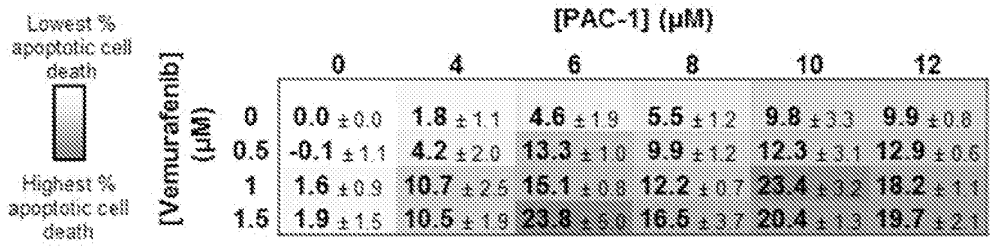


Fig. 13A

[PAC-1] (μM)

[Vemurafenib] (μM)	4	6	8	10	12
0.5	2.5	8.8	4.5	2.6	3.1
1	7.4	9.0	5.2	12.2	6.9
1.5	6.8	17.4	9.2	8.9	8.1

Fig. 13B

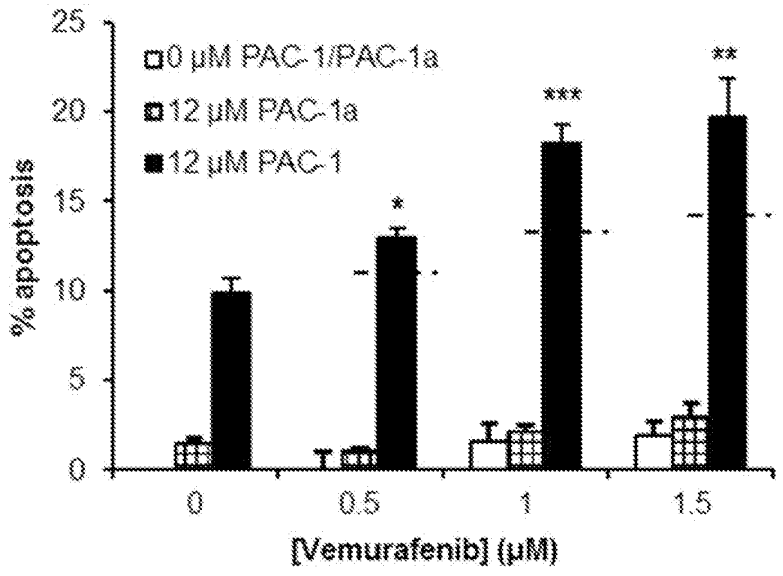


Fig. 13C