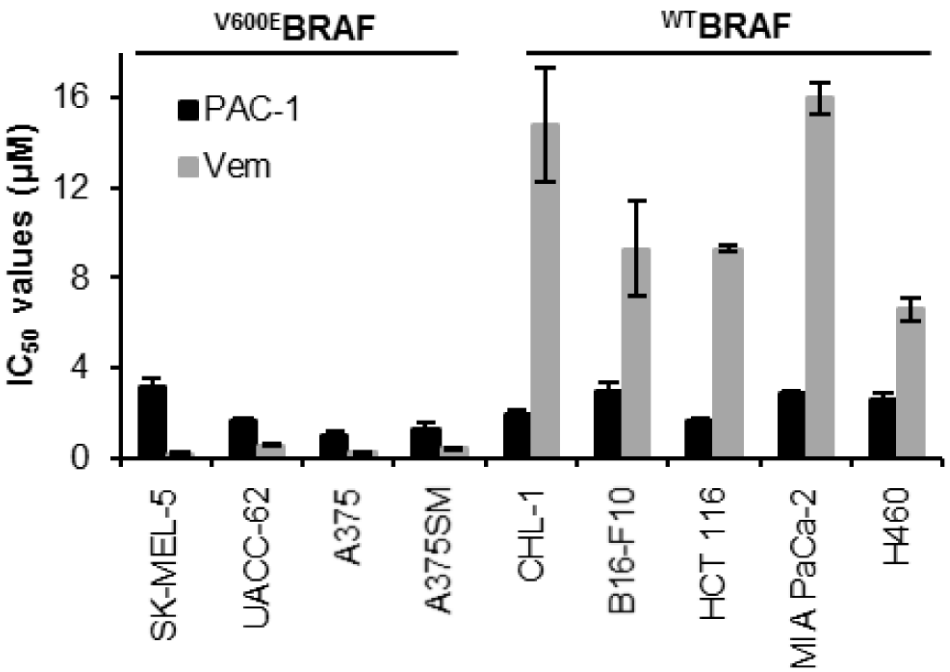

V600EBRAF
WTBRAF
PAC-1
Vem
IC50 values (μM)
16
12
8
4
0
SK-MEL-5
UACC-62
A375
A375SM
CHL-1
B16-F10
HCT 116
MIA PaCa-2
H460

Fig. 1A

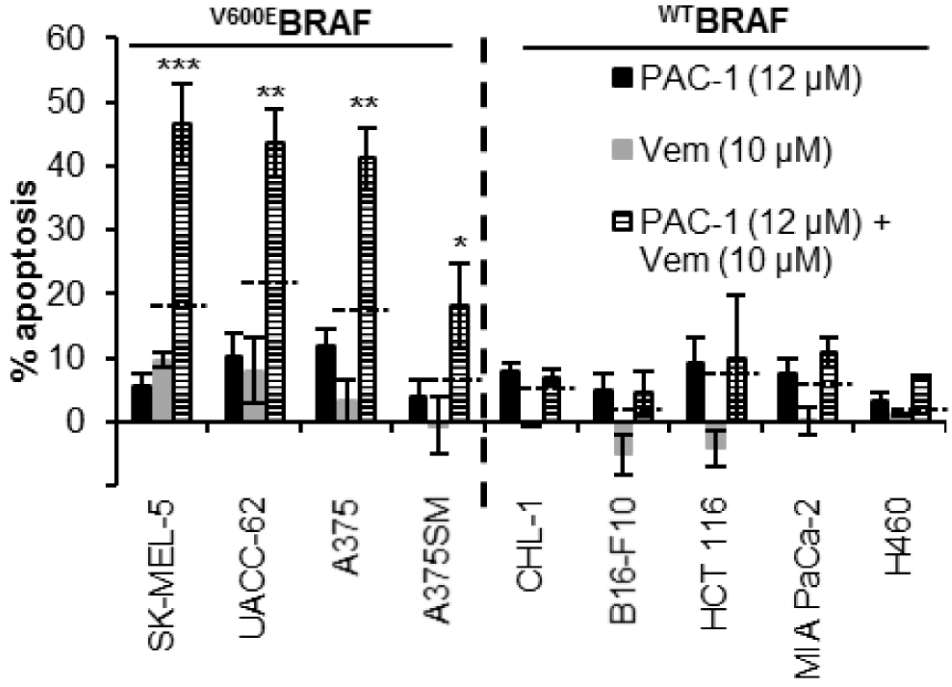

V600EBRAF
WTBRAF
PAC-1 (12 μM)
Vem (10 μM)
PAC-1 (12 μM) + Vem (10 μM)
% apoptosis
60
50
40
30
20
10
0
***
**
**
*
SK-MEL-5
UACC-62
A375
A375SM
CHL-1
B16-F10
HCT 116
MIA PaCa-2
H460

Fig. 1B

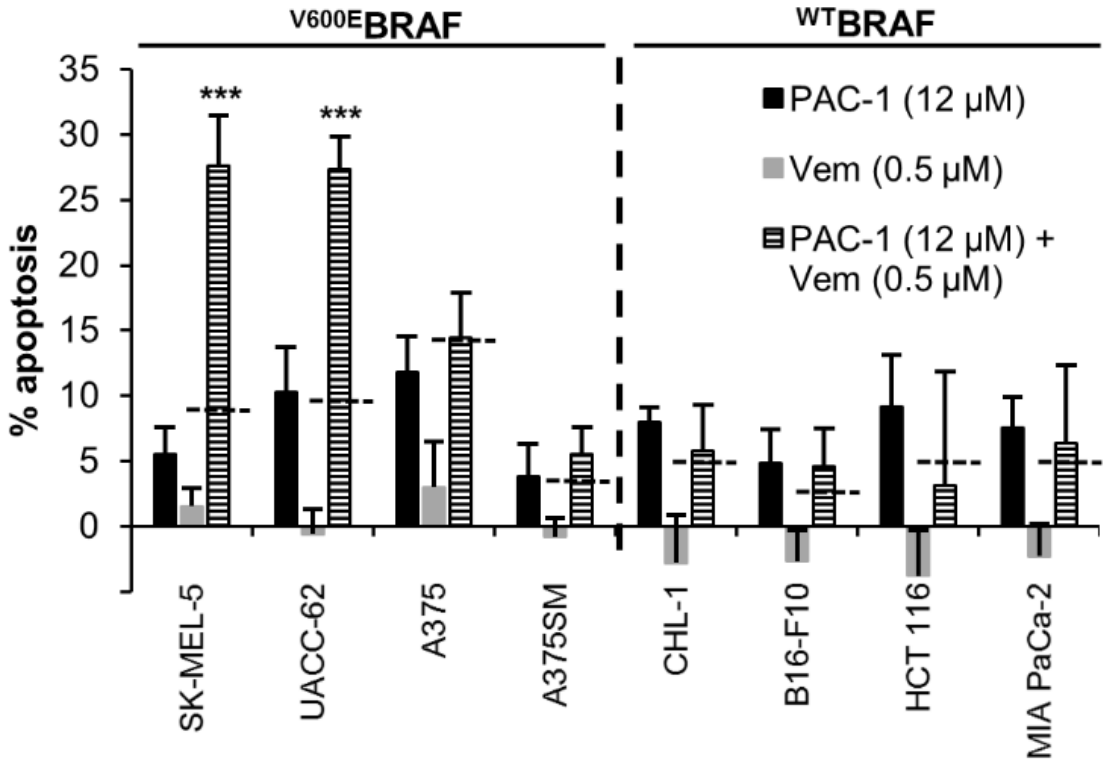

V600EBRAF
WTBRAF
% apoptosis
35
30
25
20
15
10
5
0
***
***
PAC-1 (12 μM)
Vem (0.5 μM)
PAC-1 (12 μM) + Vem (0.5 μM)
SK-MEL-5
UACC-62
A375
A375SM
CHL-1
B16-F10
HCT 116
MIA PaCa-2

Fig. 1C

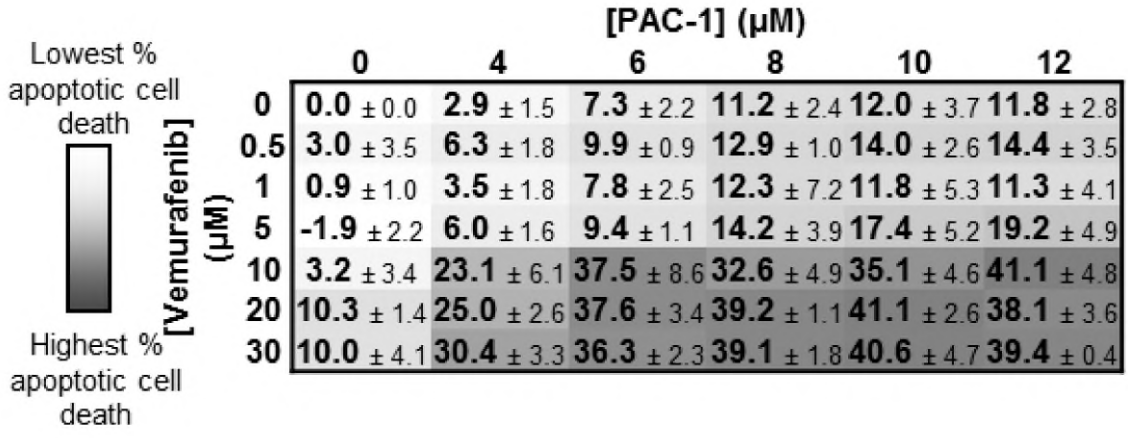
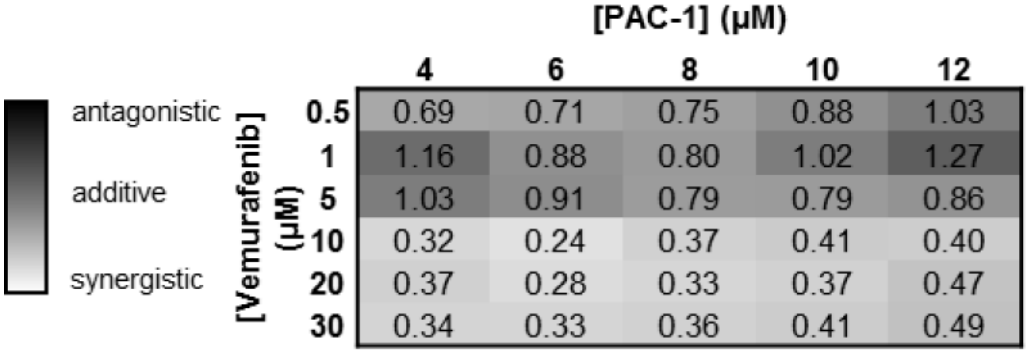

[PAC-1] (μM)
0
4
6
8
10
12
Lowest % apoptotic cell death
Highest % apoptotic cell death
[Vemurafenib] (μM)
0 | 0.0 ± 0.0 | 2.9 ± 1.5 | 7.3 ± 2.2 | 11.2 ± 2.4 | 12.0 ± 3.7 | 11.8 ± 2.8
0.5 | 3.0 ± 3.5 | 6.3 ± 1.8 | 9.9 ± 0.9 | 12.9 ± 1.0 | 14.0 ± 2.6 | 14.4 ± 3.5
1 | 0.9 ± 1.0 | 3.5 ± 1.8 | 7.8 ± 2.5 | 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

Fig. 2A



[Vemurafenib] (μM) \ [PAC-1] (μM)	4	6	8	10	12
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

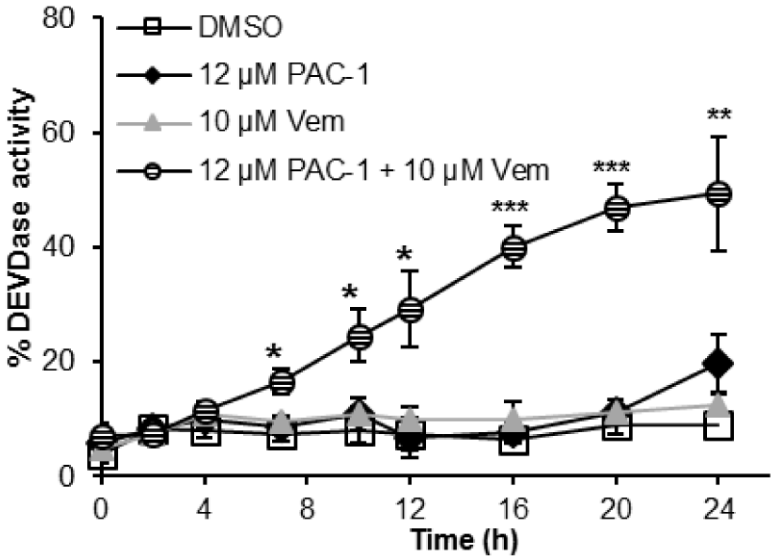


Fig. 2C

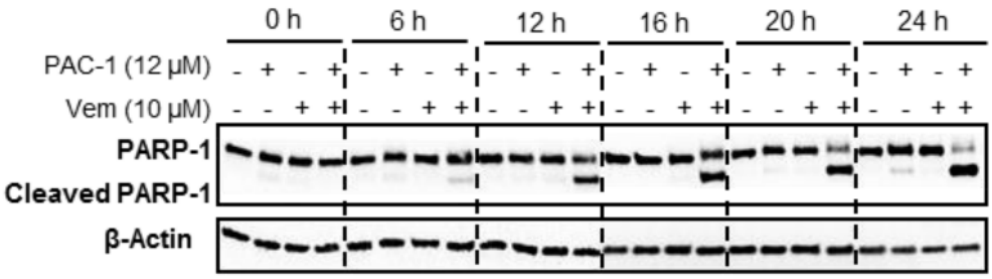

0 h
6 h
12 h
16 h
20 h
24 h
PAC-1 (12 μM)
Vem (10 μM)
PARP-1
Cleaved PARP-1
β-Actin

Fig. 2D

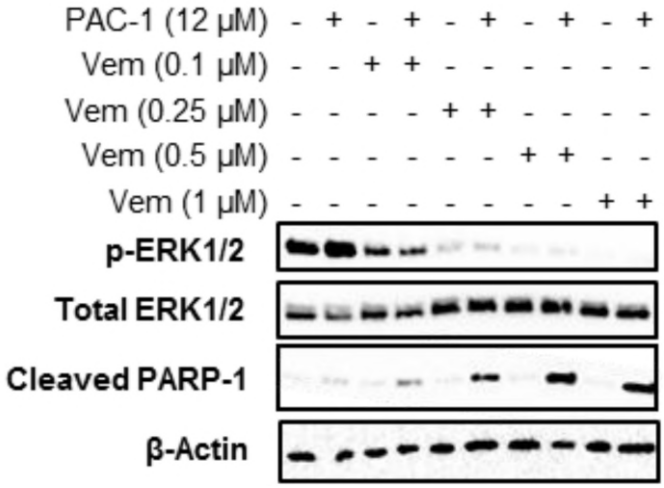

PAC-1 (12 μM)
Vem (0.1 μM)
Vem (0.25 μM)
Vem (0.5 μM)
Vem (1 μM)
p-ERK1/2
Total ERK1/2
Cleaved PARP-1
β-Actin

Fig. 2E

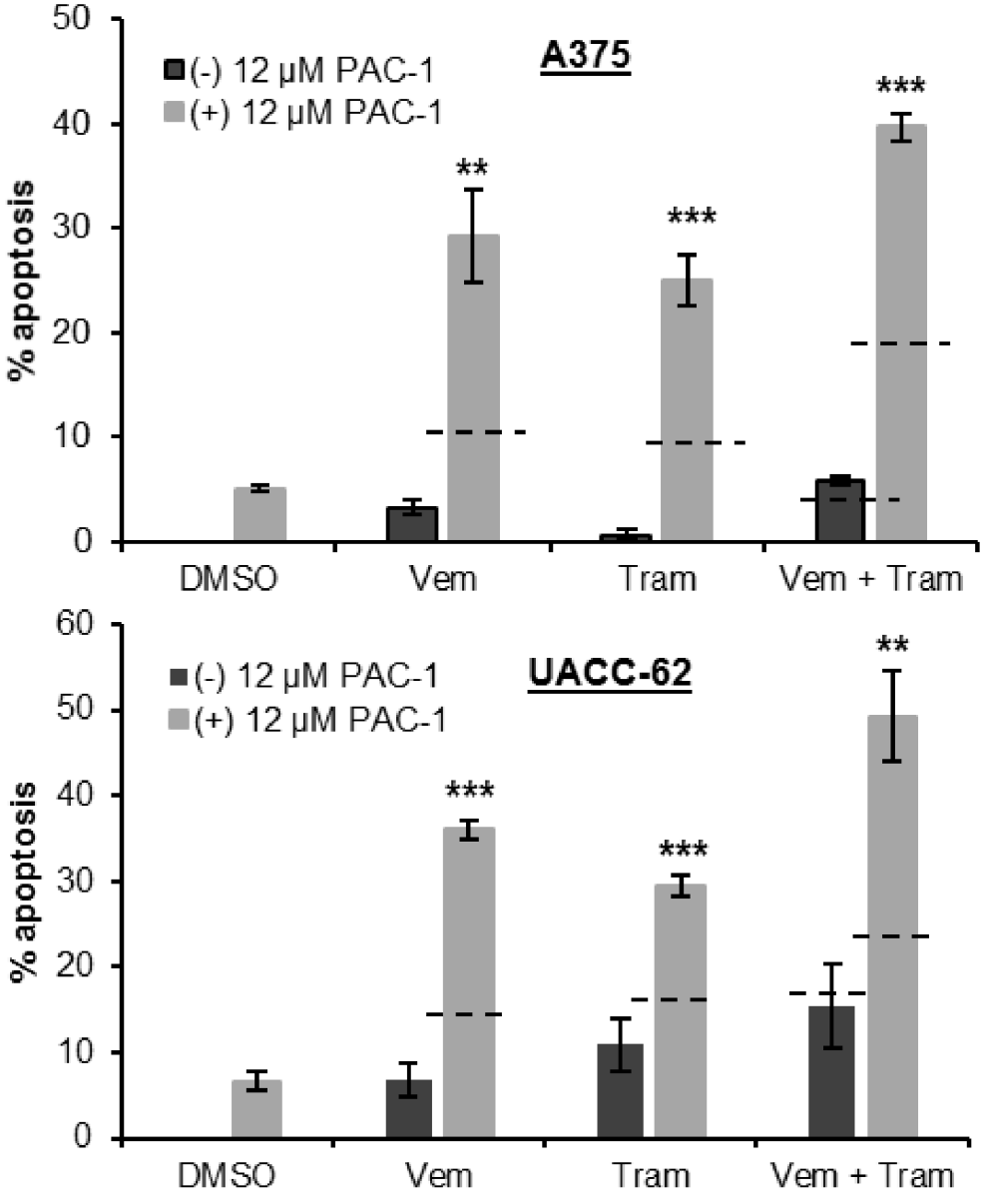

A375
(-) 12 µM PAC-1
(+) 12 µM PAC-1
% apoptosis
50
40
30
20
10
0
**
***
***
DMSO
Vem
Tram
Vem + Tram
UACC-62
(-) 12 µM PAC-1
(+) 12 µM PAC-1
% apoptosis
60
50
40
30
20
10
0
***
***
**
DMSO
Vem
Tram
Vem + Tram

Fig. 3A

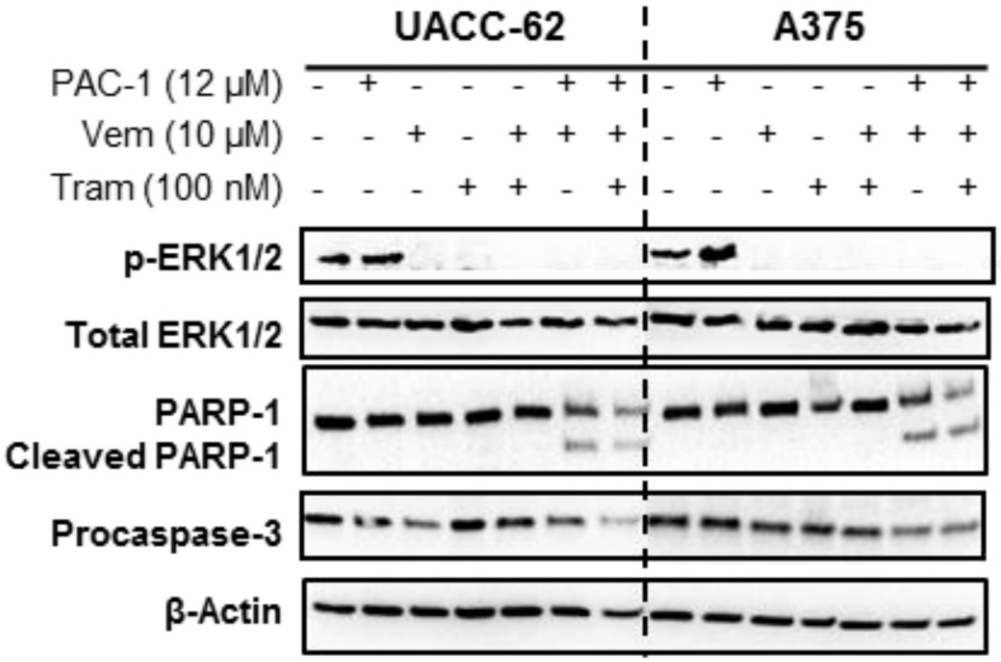

UACC-62
A375
PAC-1 (12 μM) - + - - - + + - + - - - + +
Vem (10 μM) - - + - + + + - - + - + + +
Tram (100 nM) - - - + + - + - - - + + - +
p-ERK1/2
Total ERK1/2
PARP-1
Cleaved PARP-1
Procaspase-3
β-Actin

Fig. 3B

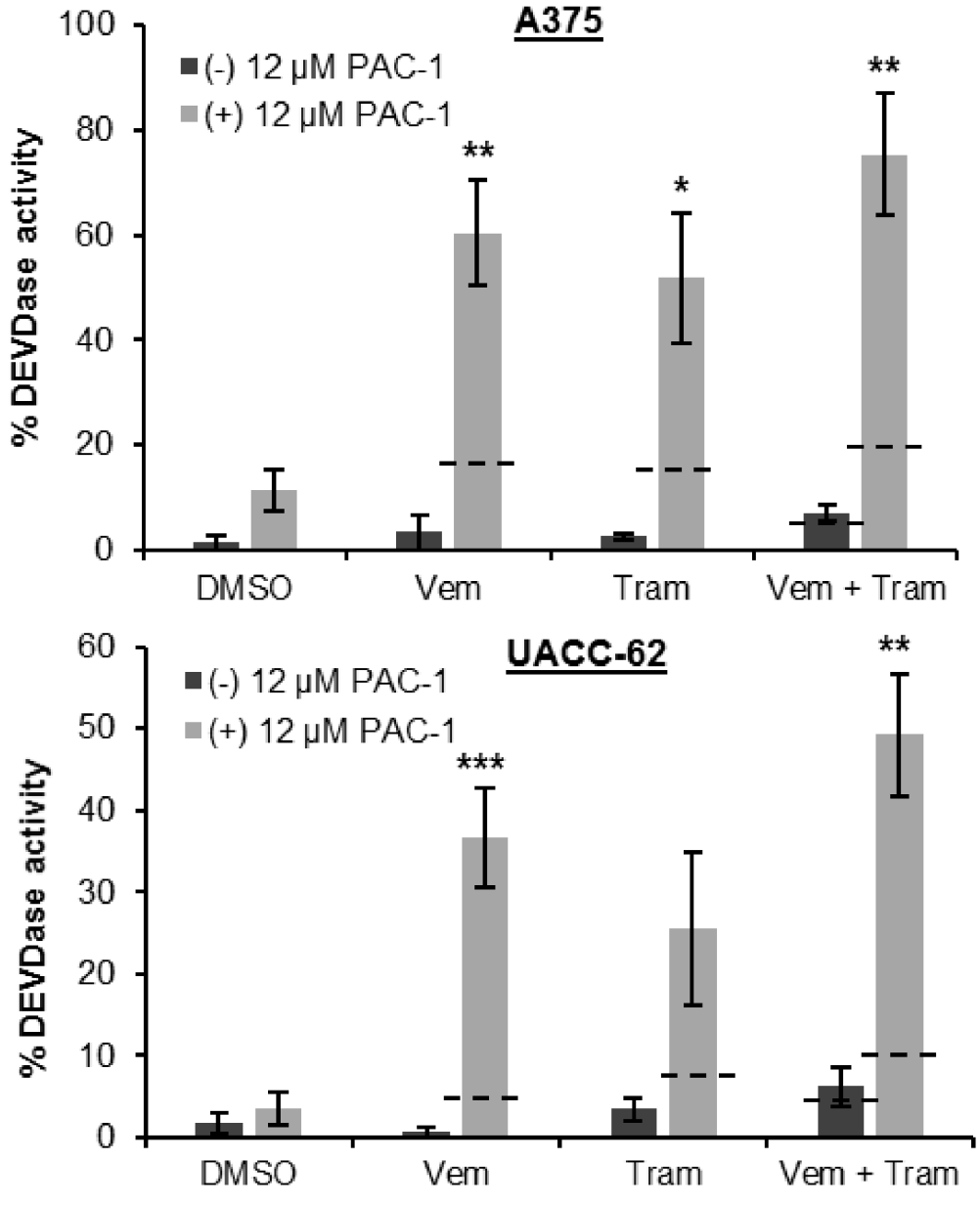

A375
(-) 12 μM PAC-1
(+) 12 μM PAC-1
% DEVDase activity
100
80
60
40
20
0
**
*
**
DMSO
Vem
Tram
Vem + Tram
UACC-62
(-) 12 μM PAC-1
(+) 12 μM PAC-1
% DEVDase activity
60
50
40
30
20
10
0
***
**
DMSO
Vem
Tram
Vem + Tram

Fig. 3C

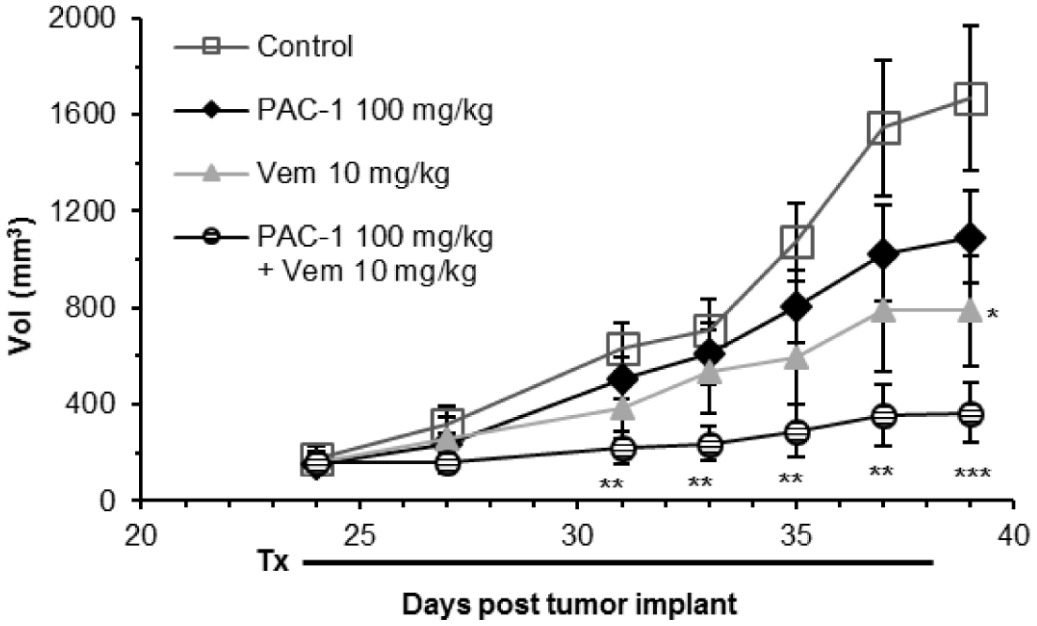

2000
1600
1200
800
400
0
Vol (mm³)
Control
PAC-1 100 mg/kg
Vem 10 mg/kg
PAC-1 100 mg/kg
+ Vem 10 mg/kg
**
**
**
**
***
*
20
25
30
35
40
Tx
Days post tumor implant

Fig. 4A

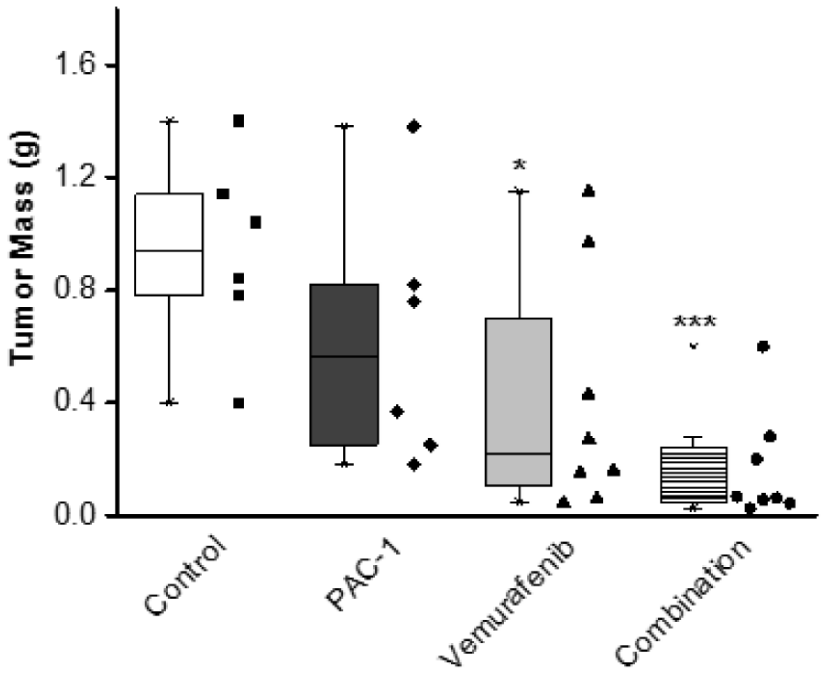

1.6
1.2
0.8
0.4
0.0
Tumor Mass (g)
*
***
Control
PAC-1
Vemurafenib
Combination

Fig. 4B

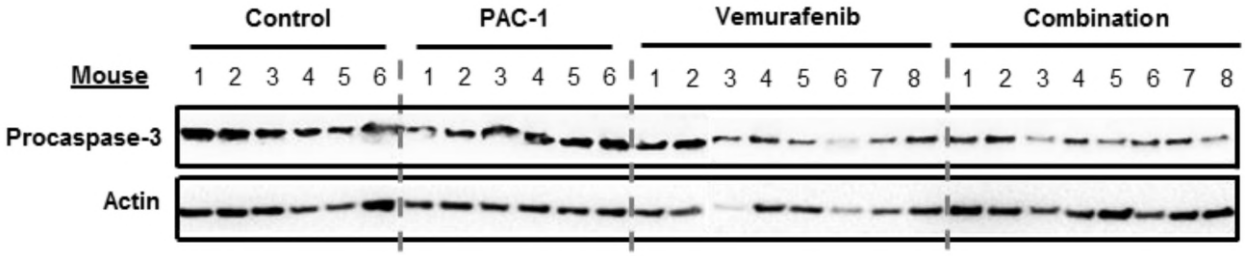

Control
PAC-1
Vemurafenib
Combination
Mouse
1 2 3 4 5 6
1 2 3 4 5 6
1 2 3 4 5 6 7 8
1 2 3 4 5 6 7 8
Procaspase-3
Actin

Fig. 4C

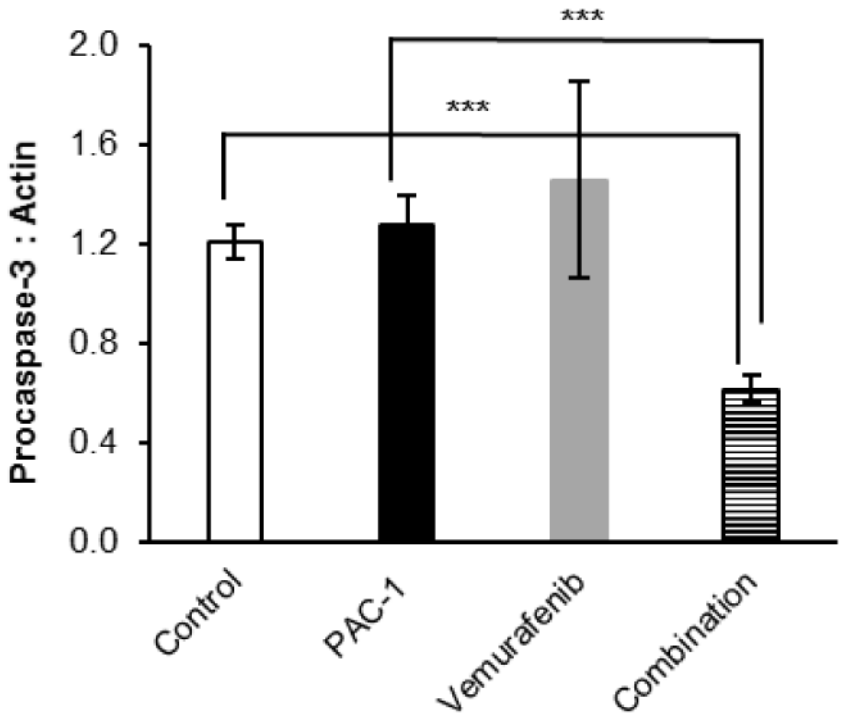

***
***
2.0
1.6
1.2
0.8
0.4
0.0
Procaspase-3 : Actin
Control
PAC-1
Vemurafenib
Combination

Fig. 4D

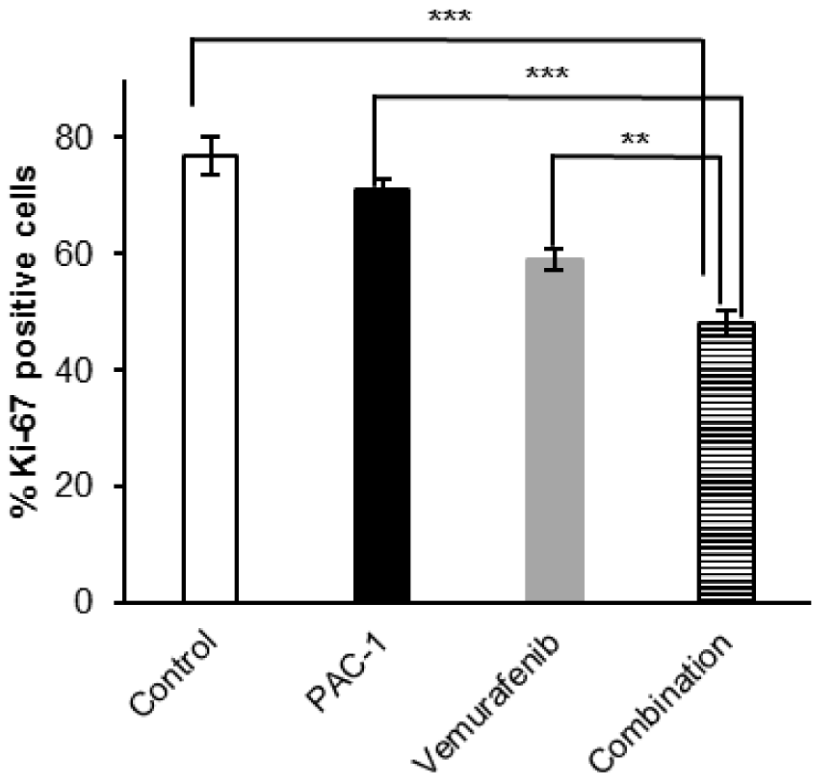
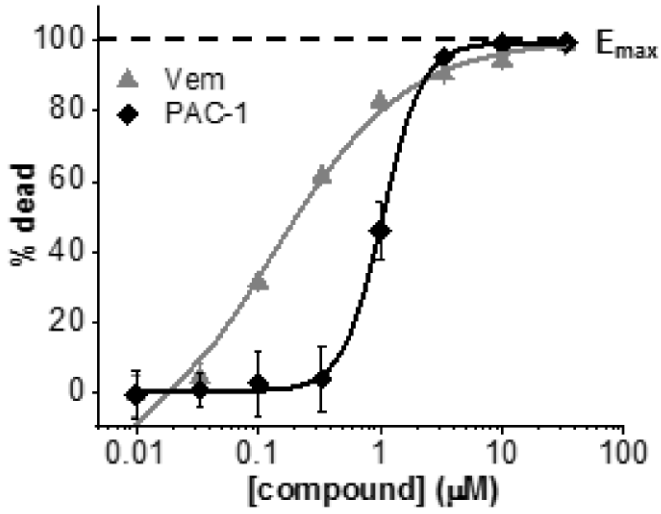


Fig. 4E



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

Fig. 5A

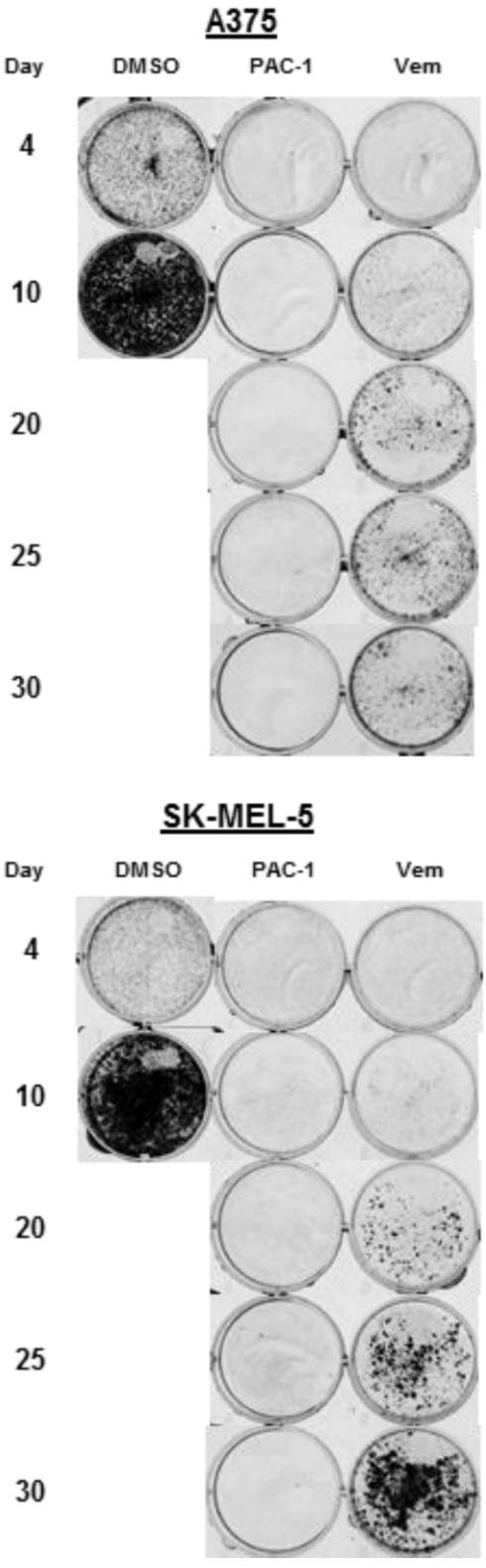

A375
Day
DMSO
PAC-1
Vem
4
10
20
25
30
SK-MEL-5
Day
DMSO
PAC-1
Vem
4
10
20
25
30

Fig. 5B

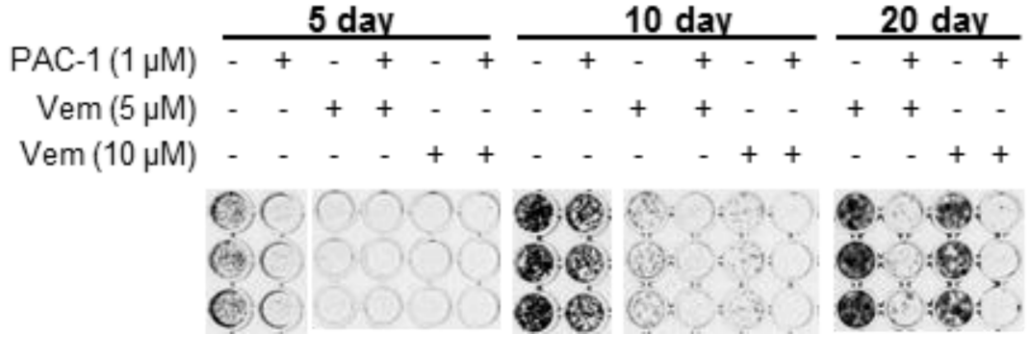

5 day
10 day
20 day
PAC-1 (1 μM) - + - + - + - + - + - + - + - + - +
Vem (5 μM) - - + + - - - - + + - - + + - -
Vem (10 μM) - - - - + + - - - - + + - - + +

Fig. 5C

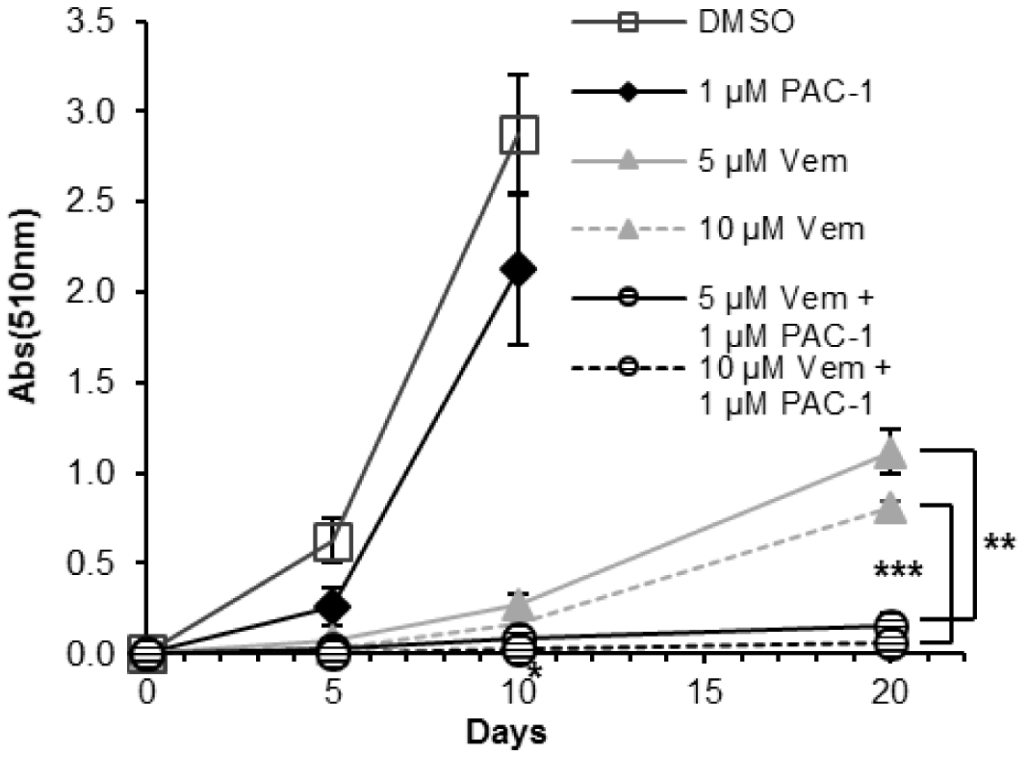
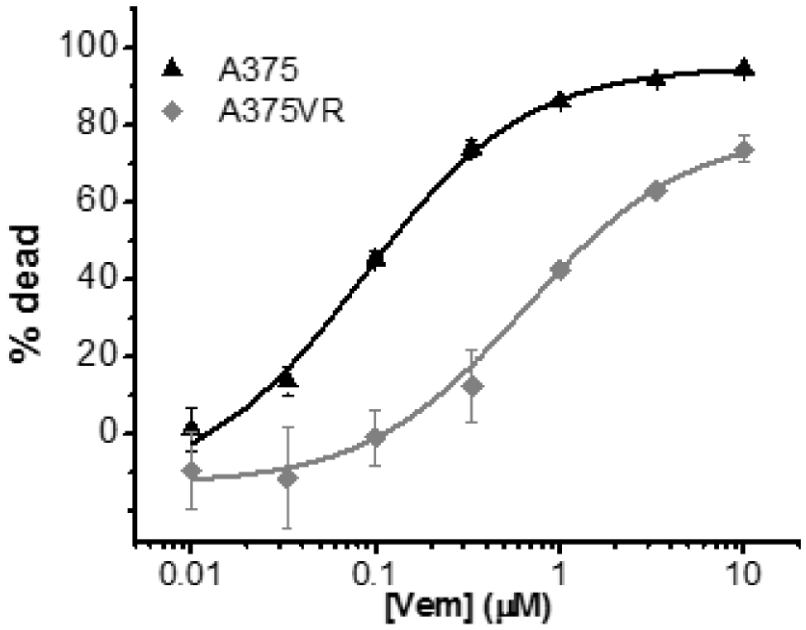

DMSO
1 μM PAC-1
5 μM Vem
10 μM Vem
5 μM Vem + 1 μM PAC-1
10 μM Vem + 1 μM PAC-1
Abs(510nm)
Days
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
*
**
***

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

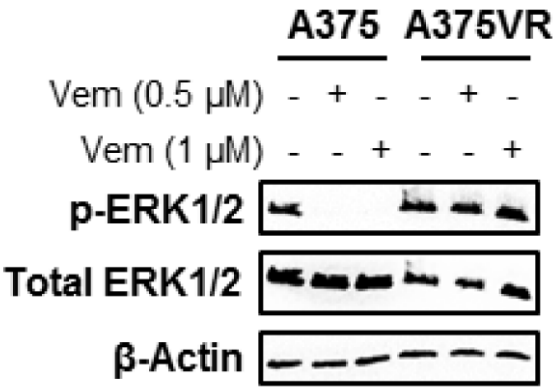
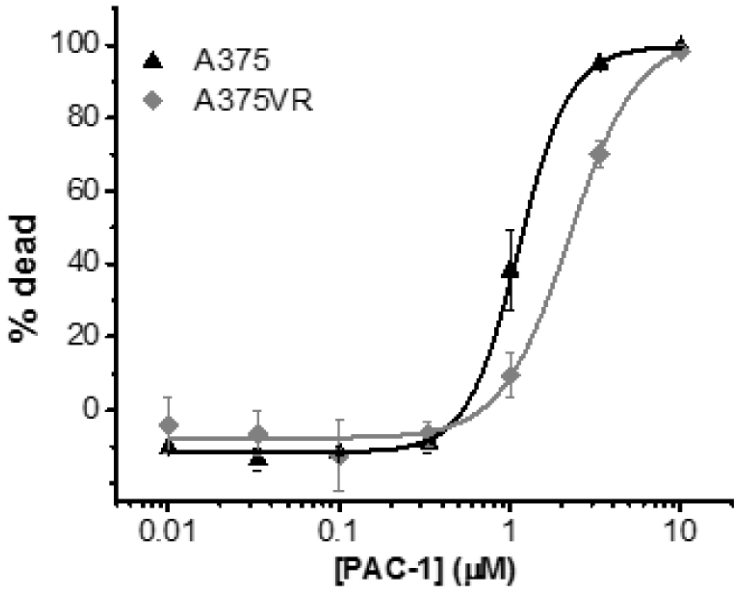


Fig. 6B



	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

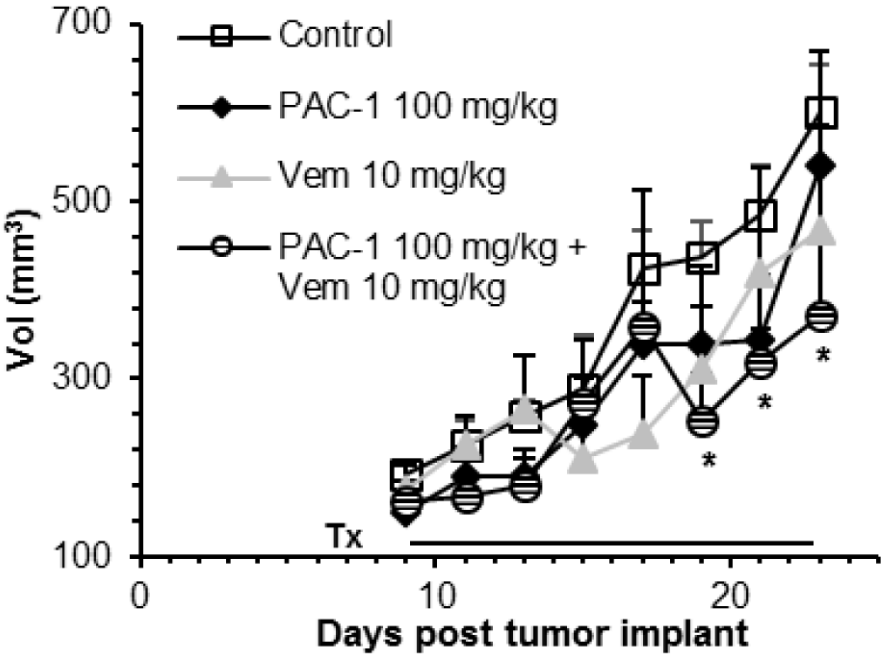
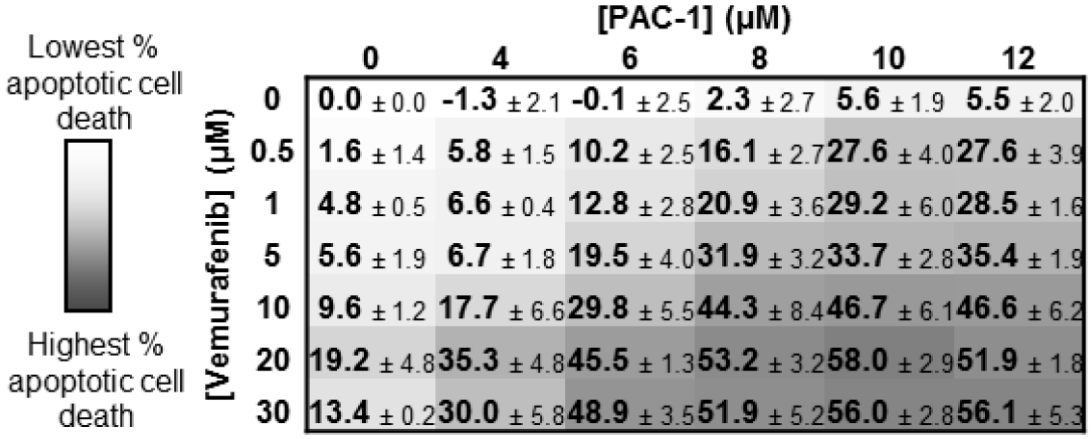


Fig. 6D



[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	53.2 ± 3.2	58.0 ± 2.9	51.9 ± 1.8
30	13.4 ± 0.2	30.0 ± 5.8	48.9 ± 3.5	51.9 ± 5.2	56.0 ± 2.8	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

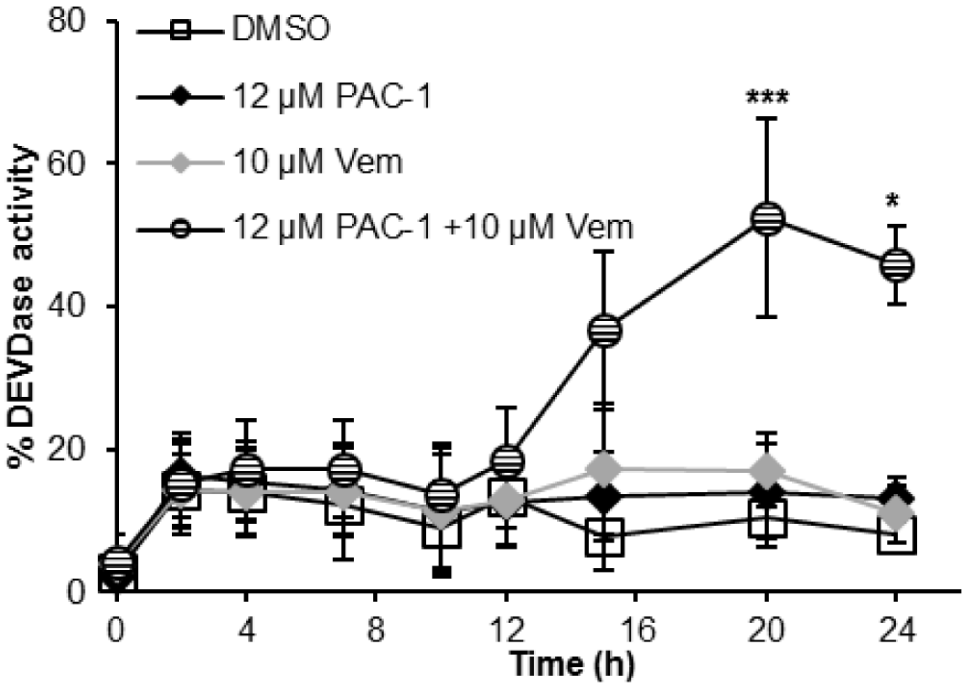

80
60
40
20
0
% DEVDase activity
DMSO
12 μM PAC-1
10 μM Vem
12 μM PAC-1 +10 μM Vem
***
*
0
4
8
12
16
20
24
Time (h)

Fig. 7C

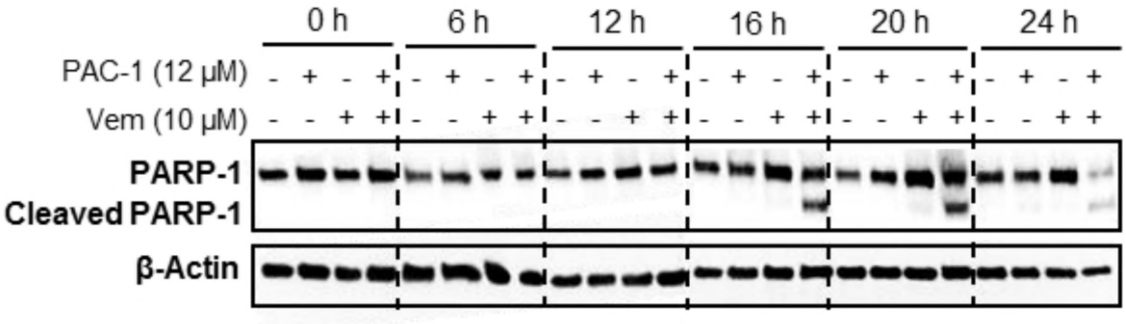

0 h
6 h
12 h
16 h
20 h
24 h
PAC-1 (12 μM)
Vem (10 μM)
PARP-1
Cleaved PARP-1
β-Actin

Fig. 7D

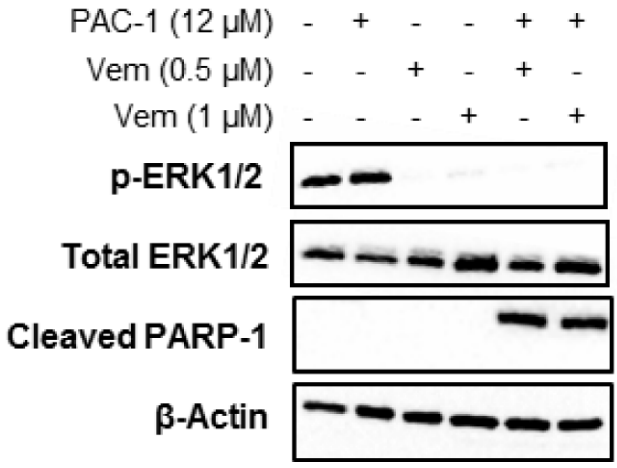


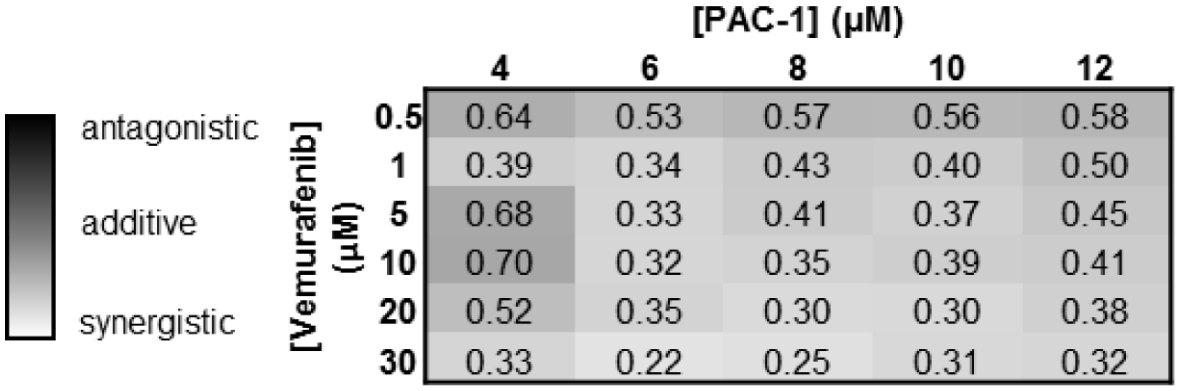
Fig. 7E

Lowest % apoptotic cell death

Highest % apoptotic cell death

[Vemurafenib] (μM) \ [PAC-1] (μM)	0	4	6	8	10	12
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

Fig. 8A



[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

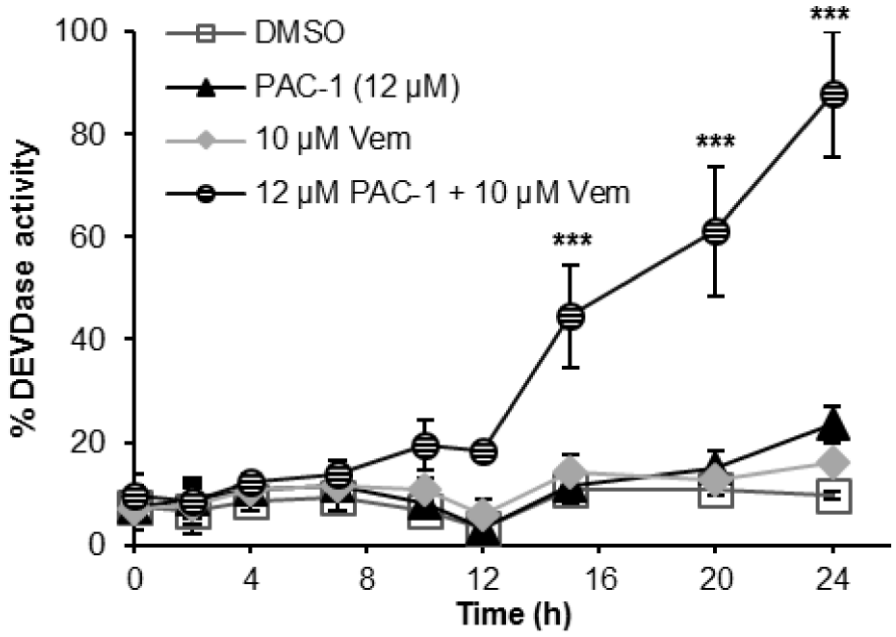


Fig. 8C

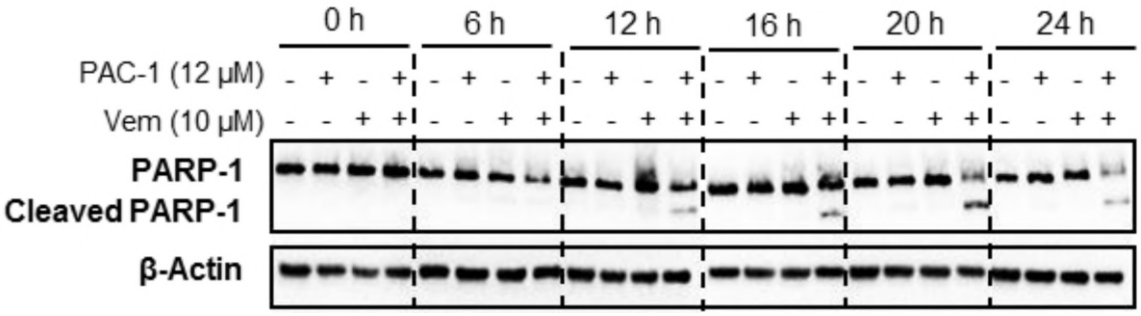

0 h
6 h
12 h
16 h
20 h
24 h
PAC-1 (12 μM)
Vem (10 μM)
PARP-1
Cleaved PARP-1
β-Actin

Fig. 8D

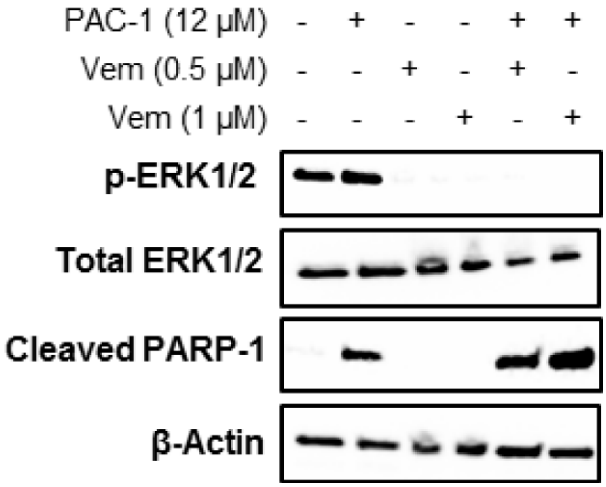

PAC-1 (12 μM)
Vem (0.5 μM)
Vem (1 μM)
p-ERK1/2
Total ERK1/2
Cleaved PARP-1
β-Actin

Fig. 8E

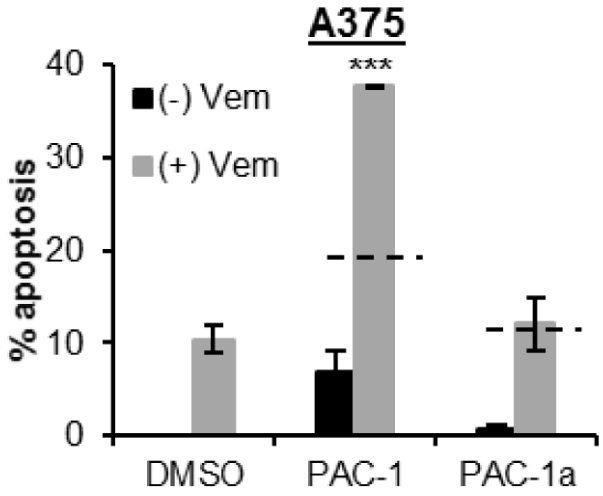

A375
***
(-) Vem
(+) Vem
% apoptosis
40
30
20
10
0
DMSO
PAC-1
PAC-1a

Fig. 9A

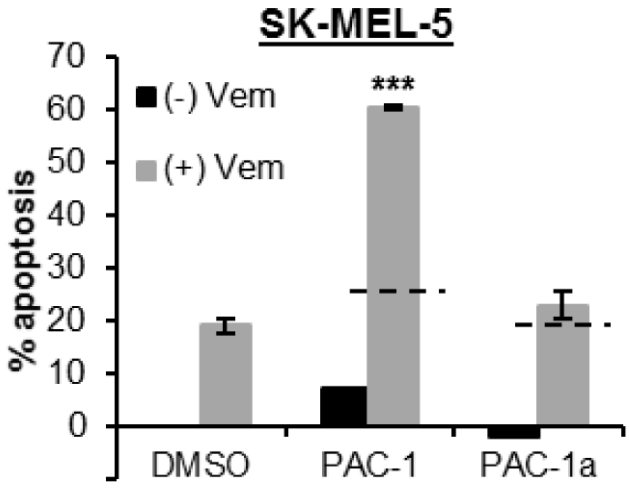

SK-MEL-5
***
(-) Vem
(+) Vem
% apoptosis
70
60
50
40
30
20
10
0
DMSO
PAC-1
PAC-1a

Fig. 9B

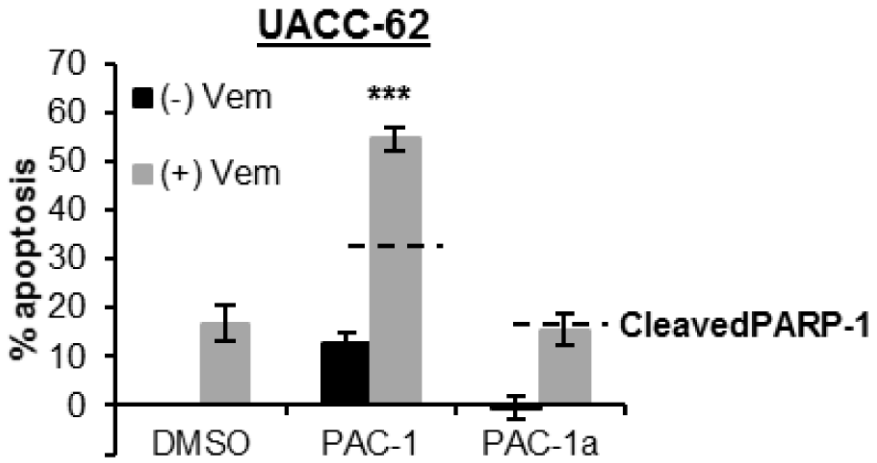

UACC-62
70
60
50
40
30
20
10
0
% apoptosis
(-) Vem
(+) Vem
***
CleavedPARP-1
DMSO
PAC-1
PAC-1a

Fig. 9C

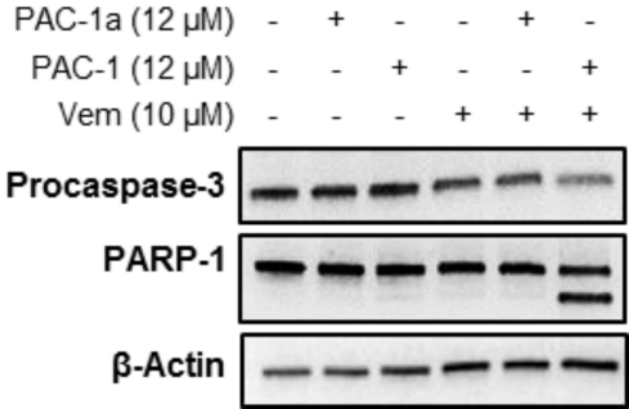

PAC-1a (12 μM) - + - - + -
PAC-1 (12 μM) - - + - - +
Vem (10 μM) - - - + + +
Procaspase-3
PARP-1
β-Actin

Fig. 9D

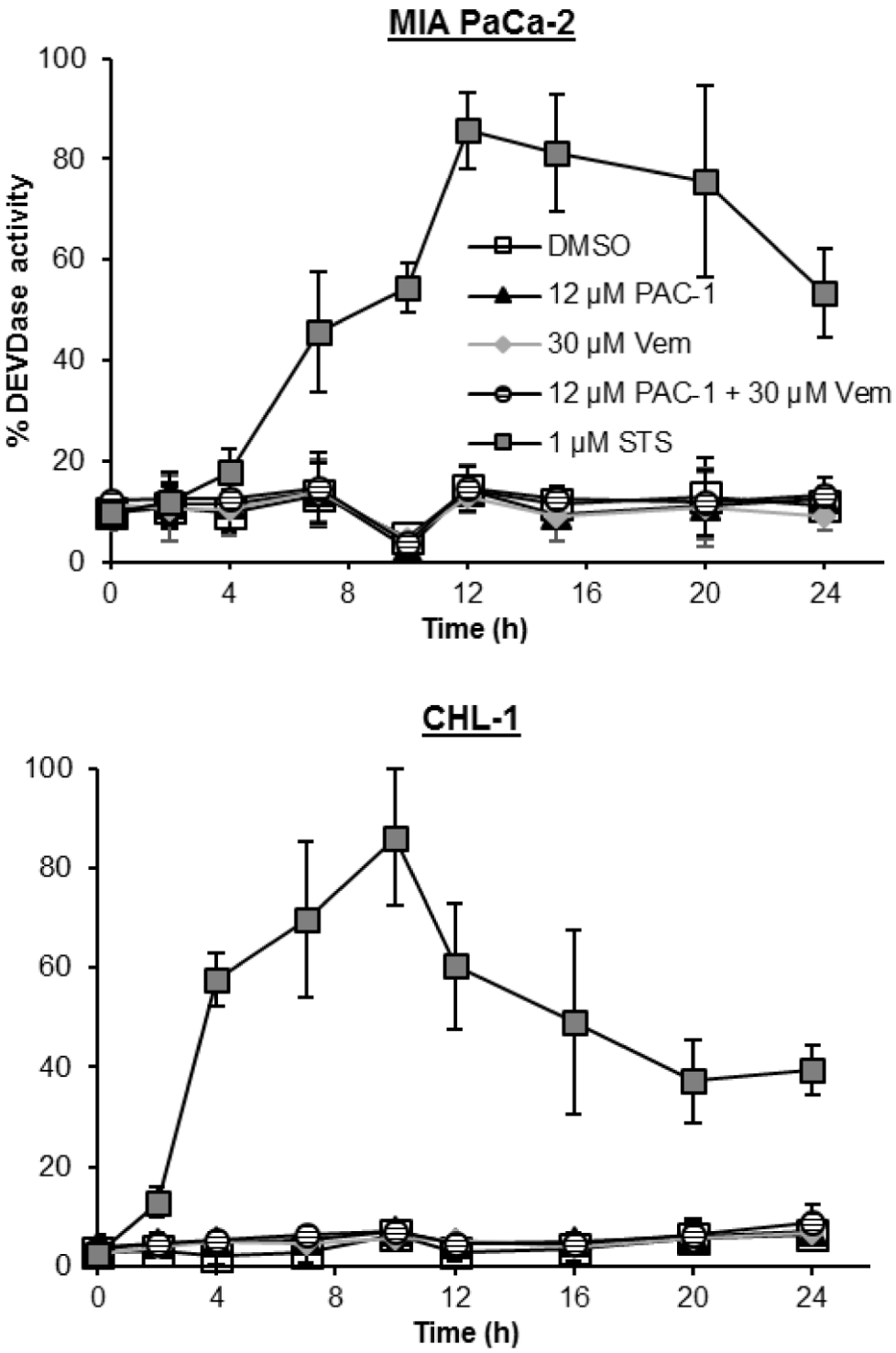

MIA PaCa-2
% DEVDase activity
Time (h)
DMSO
12 μM PAC-1
30 μM Vem
12 μM PAC-1 + 30 μM Vem
1 μM STS
CHL-1
Time (h)

Fig. 10A

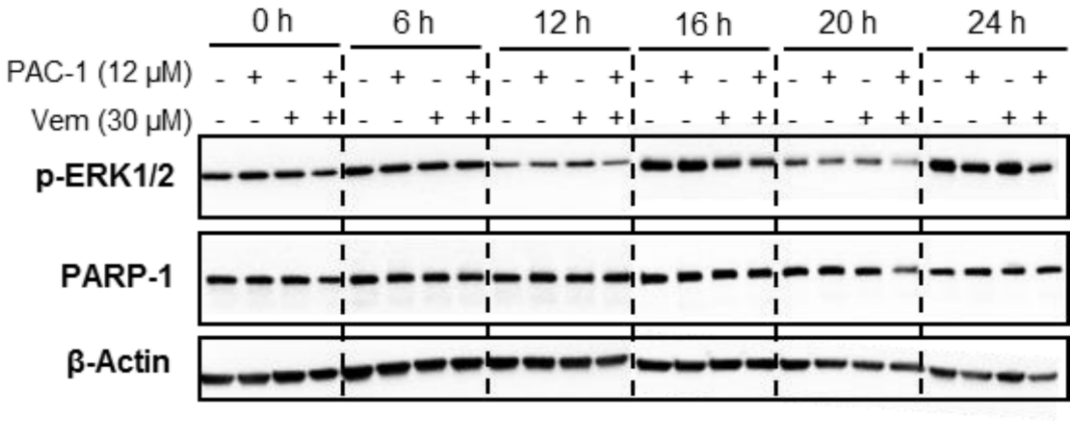


Fig. 10B

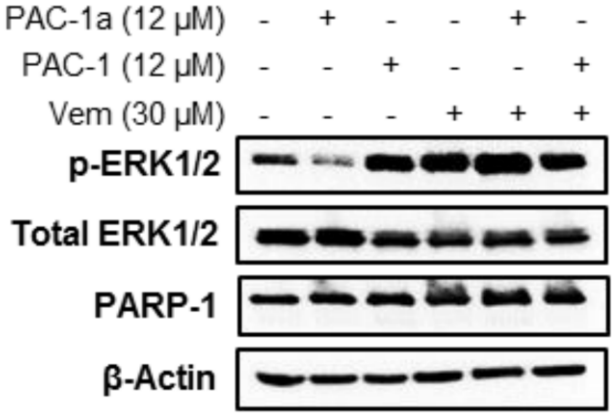


Fig. 10C

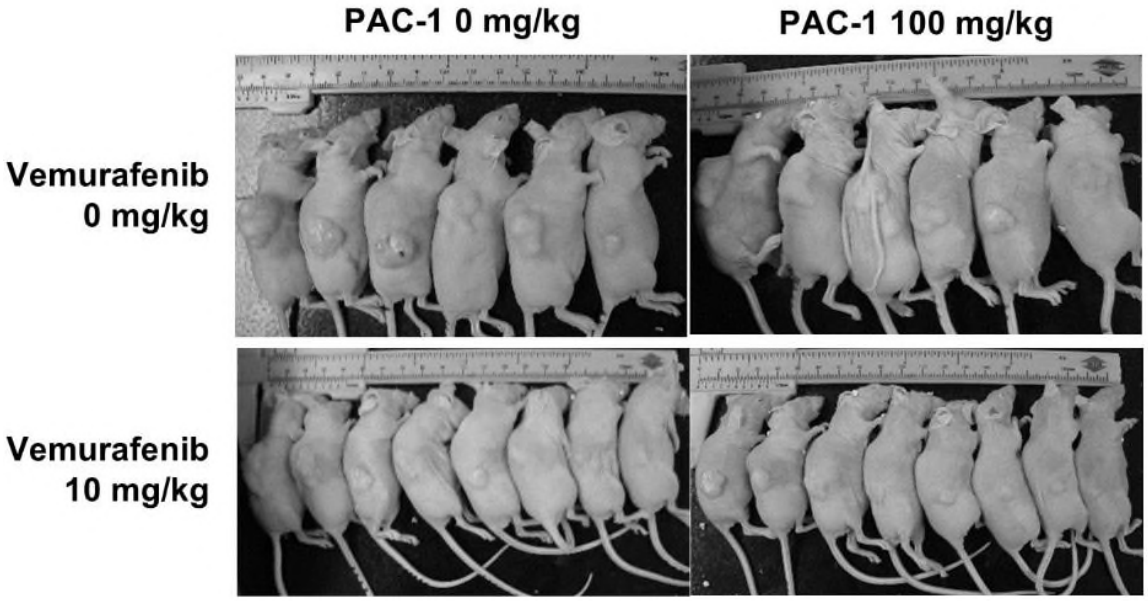

PAC-1 0 mg/kg
PAC-1 100 mg/kg
Vemurafenib
0 mg/kg
Vemurafenib
10 mg/kg

Fig. 11

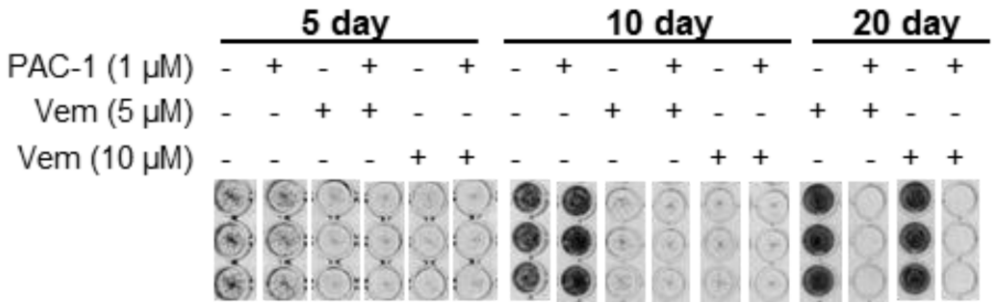


Fig. 12A

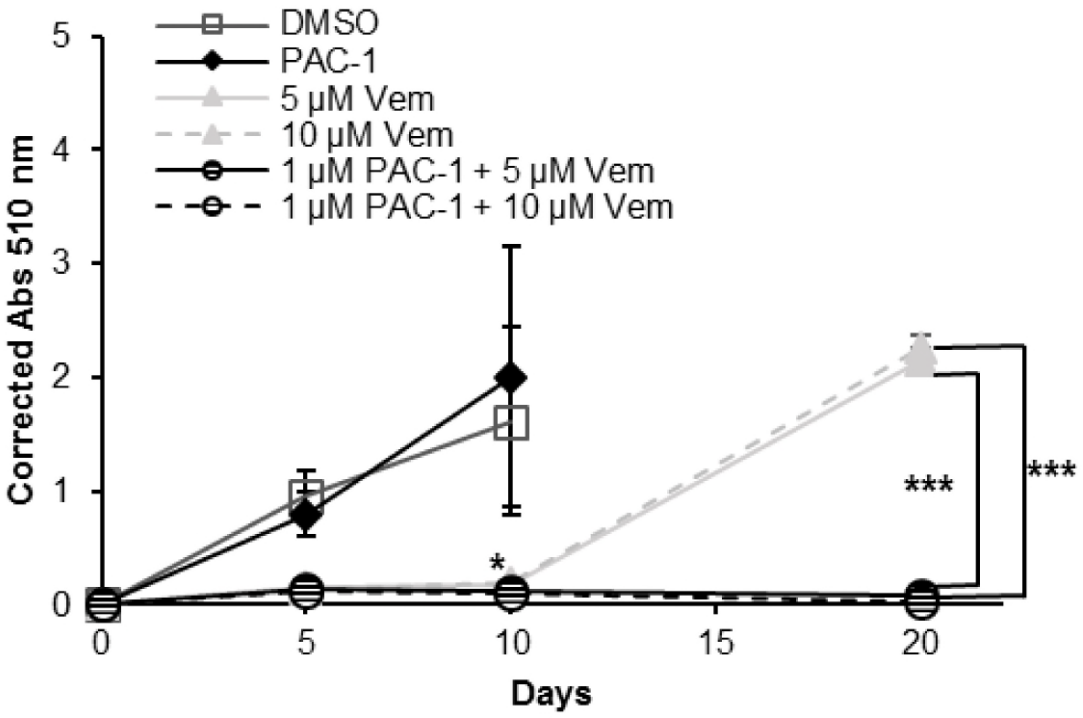


Fig. 12B

Lowest % apoptotic cell death

Highest % apoptotic cell death

[Vemurafenib] (μM)	[PAC-1] (μM) 0	4	6	8	10	12
0	0.0 ± 0.0	1.8 ± 1.1	4.6 ± 1.9	5.5 ± 1.2	9.8 ± 3.3	9.9 ± 0.8
0.5	-0.1 ± 1.1	4.2 ± 2.0	13.3 ± 1.0	9.9 ± 1.2	12.3 ± 3.1	12.9 ± 0.6
1	1.6 ± 0.9	10.7 ± 2.5	15.1 ± 0.8	12.2 ± 0.7	23.4 ± 3.2	18.2 ± 1.1
1.5	1.9 ± 1.5	10.5 ± 1.9	23.8 ± 5.0	16.5 ± 3.7	20.4 ± 1.3	19.7 ± 2.1

Fig. 13A

[Vemurafenib] (μM)	[PAC-1] (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

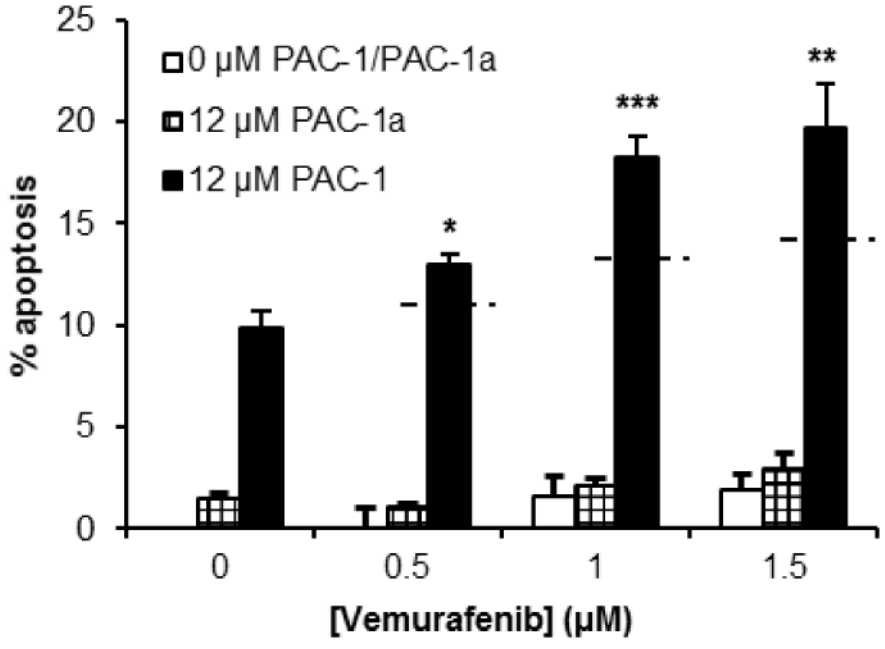


Fig. 13C