Fig.1

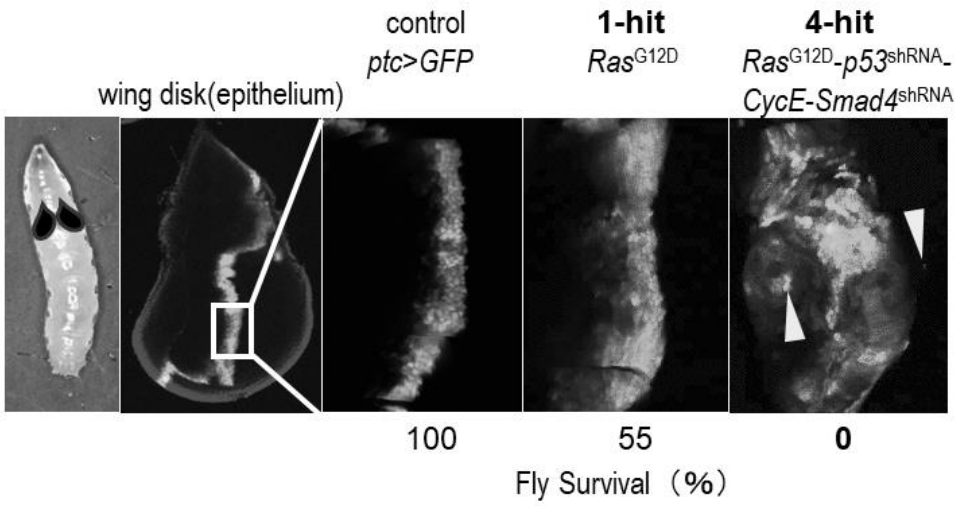

control
ptc>GFP
1-hit
RasG12D
4-hit
RasG12D-p53shRNA-
CycE-Smad4shRNA
wing disk(epithelium)
100
55
0
Fly Survival (%)

Fig.2

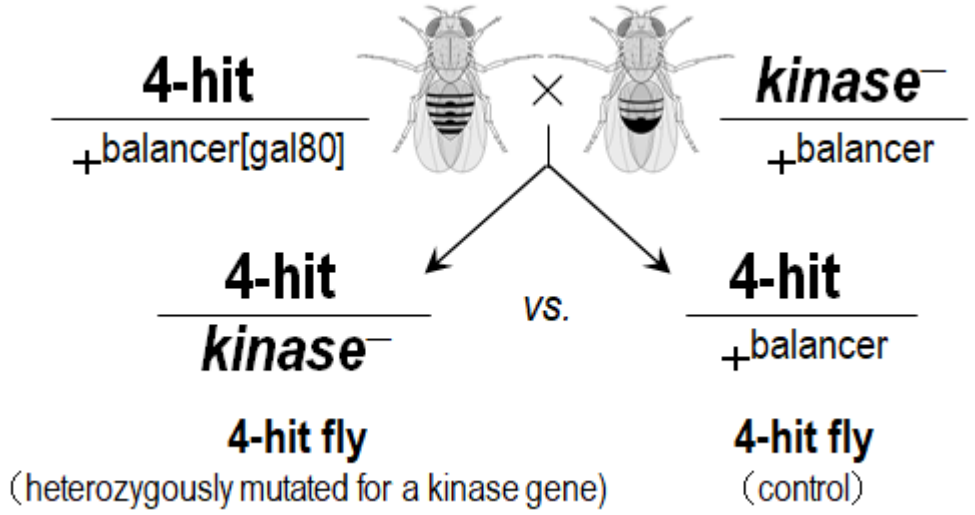

4-hit
+balancer[gal80]
kinase−
+balancer
4-hit
kinase−
vs.
4-hit
+balancer
4-hit fly
(heterozygously mutated for a kinase gene)
4-hit fly
(control)

Fig.3

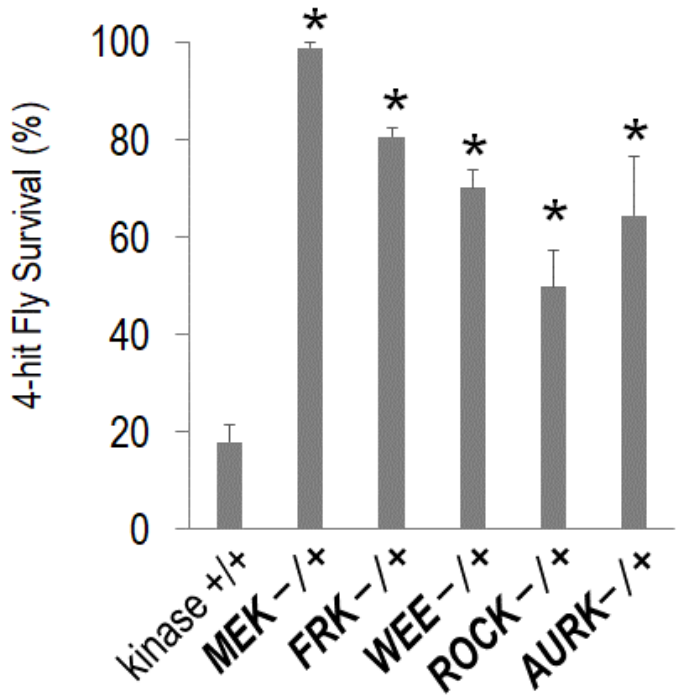

4-hit Fly Survival (%)
100
80
60
40
20
0
*
kinase +/+
MEK −/×
FRK −/×
WEE −/×
ROCK −/×
AURK −/×

Fig.4

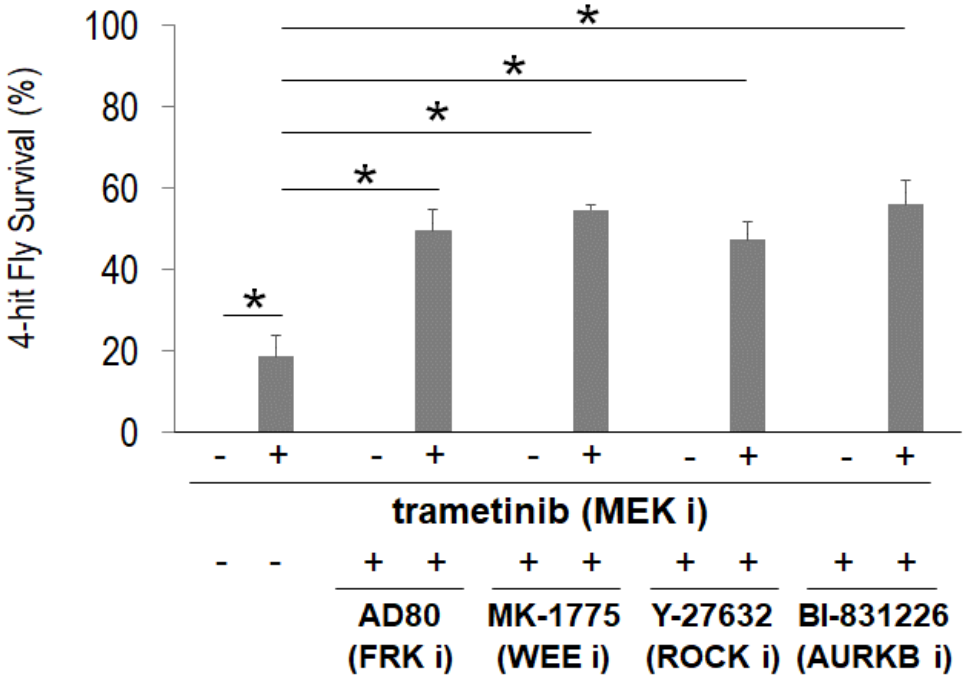

4-hit Fly Survival (%)
100
80
60
40
20
0
*
- + - + - + - + - +
trametinib (MEK i)
- - + + + + + + + +
AD80 (FRK i)
MK-1775 (WEE i)
Y-27632 (ROCK i)
BI-831226 (AURKB i)

Fig.5

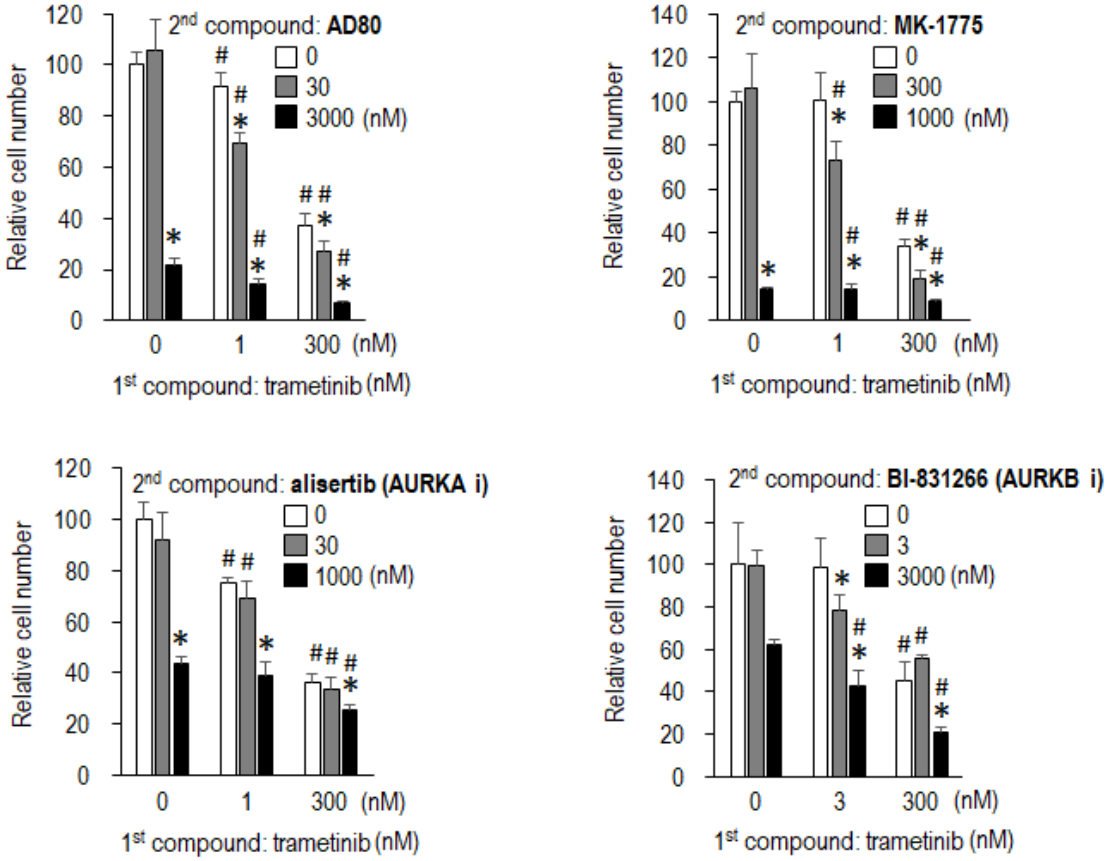

2nd compound: AD80
0
30
3000 (nM)
Relative cell number
1st compound: trametinib (nM)
2nd compound: MK-1775
0
300
1000 (nM)
Relative cell number
1st compound: trametinib (nM)
2nd compound: alisertib (AURKA i)
0
30
1000 (nM)
Relative cell number
1st compound: trametinib (nM)
2nd compound: BI-831266 (AURKB i)
0
3
3000 (nM)
Relative cell number
1st compound: trametinib (nM)

Fig.6

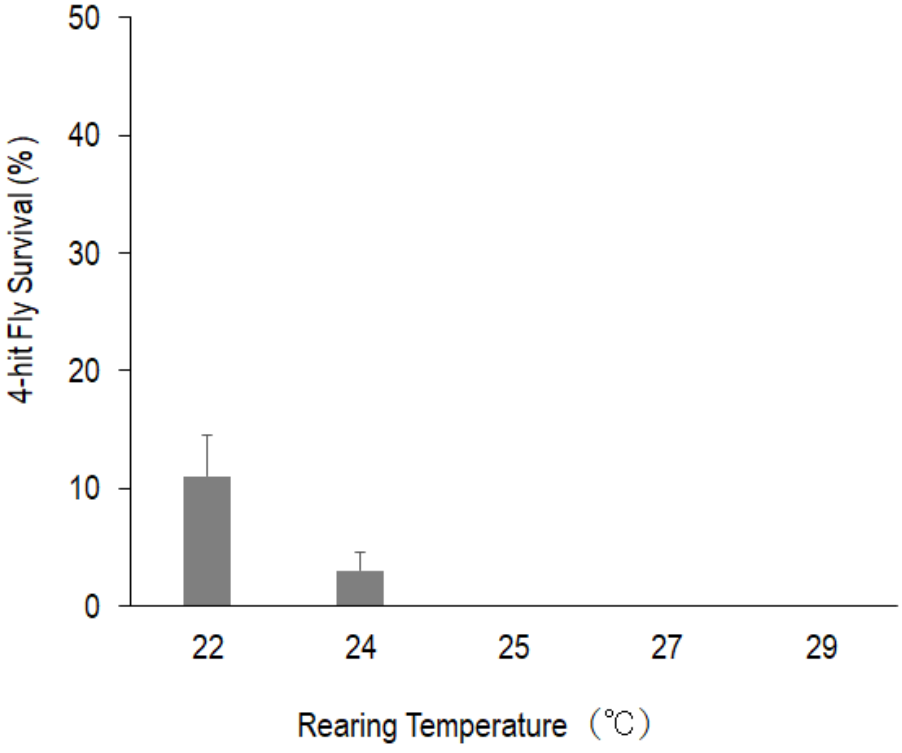

4-hit Fly Survival (%)
Rearing Temperature (℃)

Fig.7A

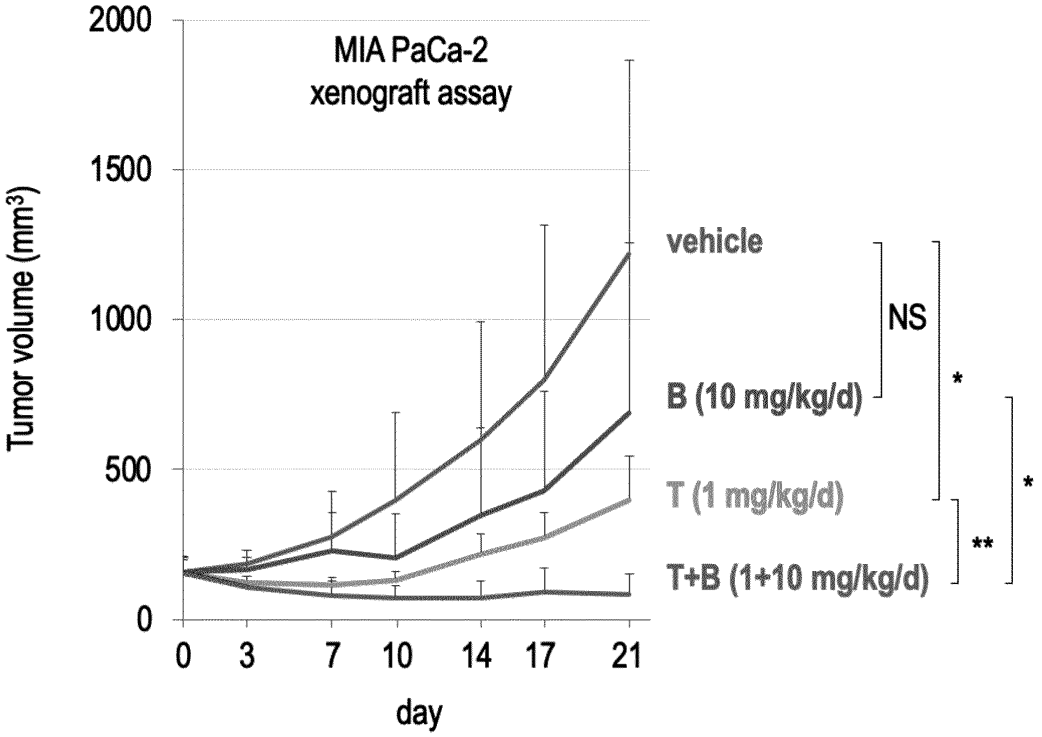
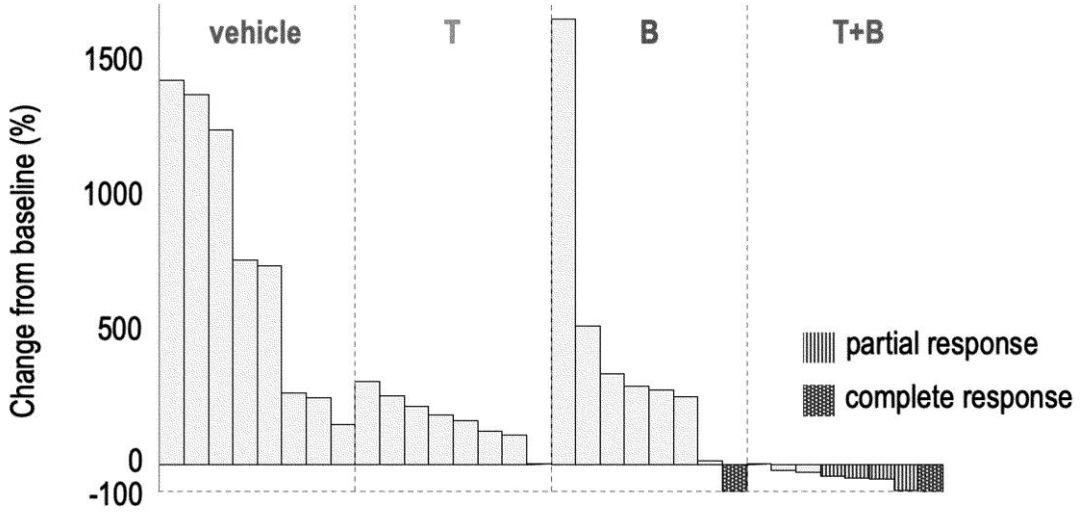

MIA PaCa-2
xenograft assay
Tumor volume (mm³)
2000
1500
1000
500
0
0
3
7
10
14
17
21
day
vehicle
B (10 mg/kg/d)
T (1 mg/kg/d)
T+B (1+10 mg/kg/d)
NS
*
**
*

Fig.7B


vehicle
T
B
T+B
Change from baseline (%)
1500
1000
500
0
-100
partial response
complete response