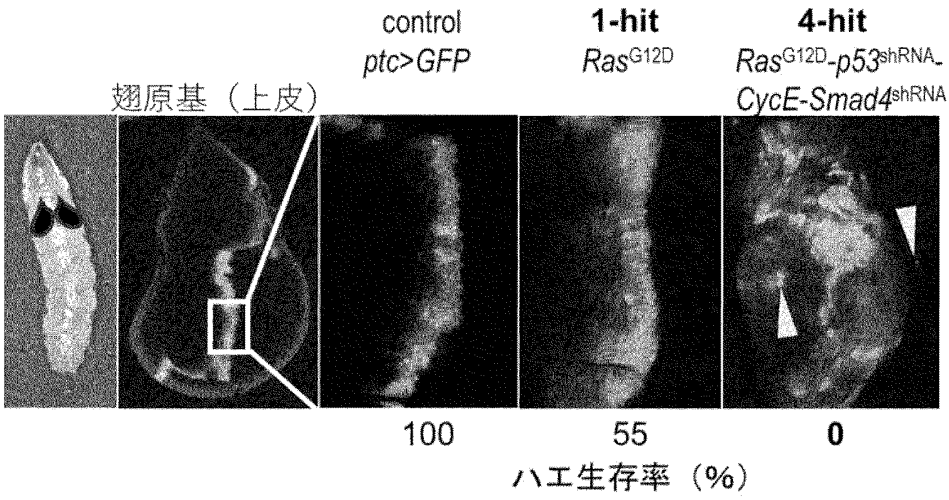
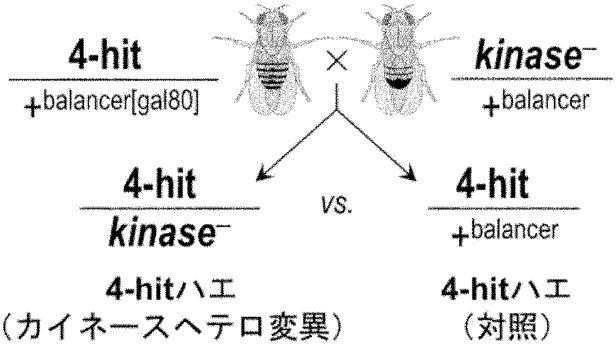
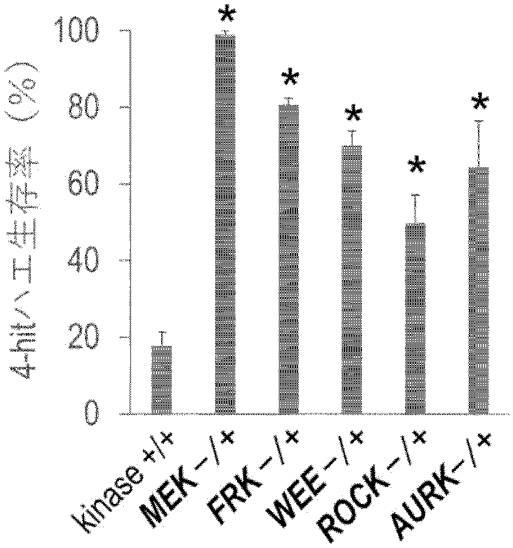
[図1]


control
ptc>GFP
1-hit
RasG12D
4-hit
RasG12D-p53shRNA-
CycE-Smad4shRNA
翅原基（上皮）
100
55
0
ハエ生存率（%）

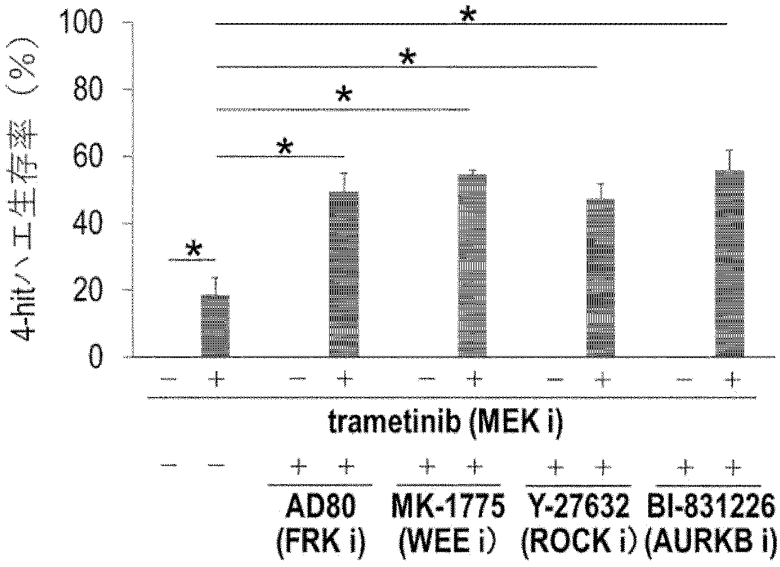
[図2]


4-hit
+balancer[gal80]
×
kinase⁻
+balancer
4-hit
kinase⁻
vs.
4-hit
+balancer
4-hitハエ
（カイネースヘテロ変異）
4-hitハエ
（対照）

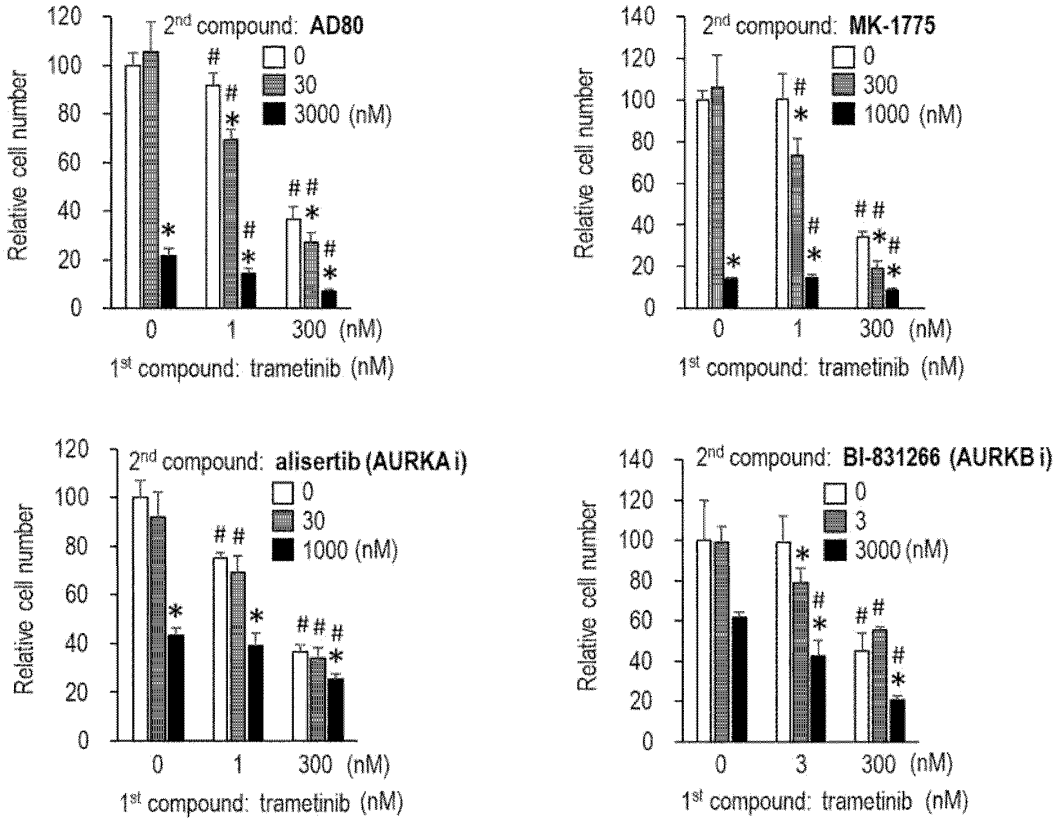
[図3]


4-hitハエ生存率（%）
100
80
60
40
20
0
*
kinase+/+
MEK−/+
FRK−/+
WEE−/+
ROCK−/+
AURK−/+

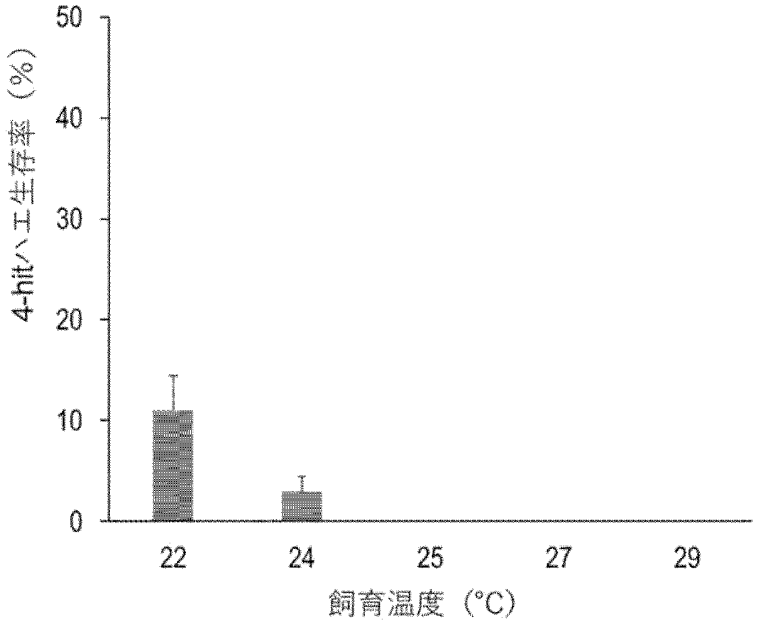
[図4]


4-hit ハ工生存率（%）
100
80
60
40
20
0
trametinib (MEK i)
AD80 (FRK i)
MK-1775 (WEE i)
Y-27632 (ROCK i)
BI-831226 (AURKB i)

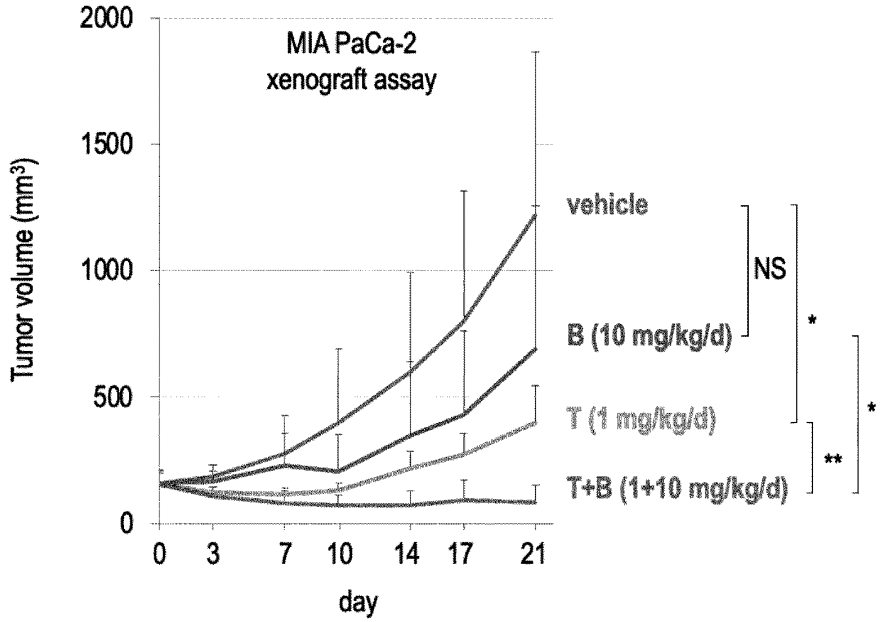
[図5]


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

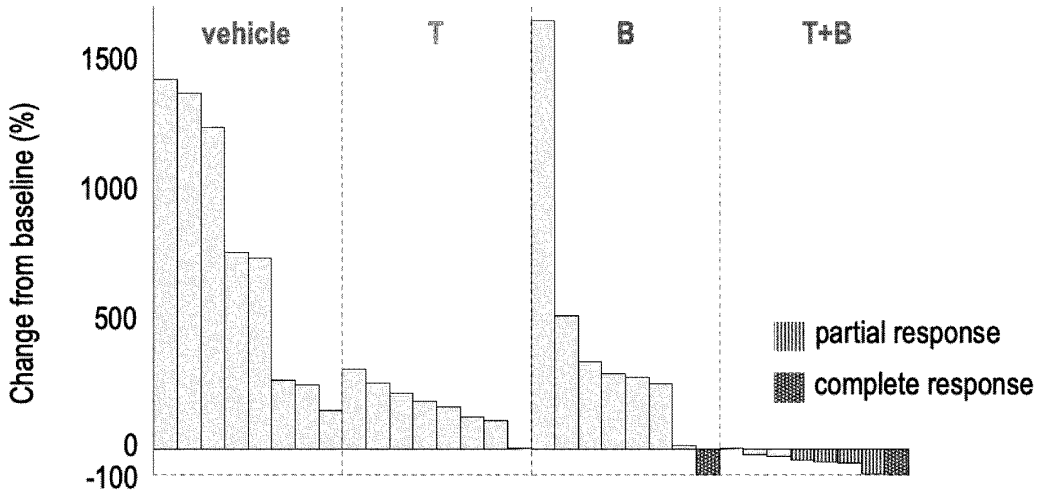
[図6]


4-hitハエ生存率（%）
50
40
30
20
10
0
22
24
25
27
29
飼育温度（°C）

[図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
*
**
*

[図7B]


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