Supplementary note

Objective

We aimed to study if the type of *KRAS* mutation were enriched in any clusters of phosphoprotein changes caused by an individual drug. Because some of the KRAS mutations were more prevalent, we grouped the *KRAS* mutations into G12C, G12D, G12V and miscellaneous.

Methods - Clustering

Before clustering cell lines according to GAPDH-normalised phosphoprotein changes, we removed outliers to limit the effect of very large changes in a small number of phosphoproteins. We performed average linkage hierarchical clustering using the correlation distance metric. The distance between cell lines i and j was defined as

$$\mathrm{dist}(i,j) = 1 - \frac{\langle L_i - \bar{L}_i, L_j - \bar{L}_j \rangle}{\|L_i - \bar{L}_i\|_2 \left\|L_j - \bar{L}_j\right\|_2}$$

where $\langle \cdot,\cdot \rangle$ denotes the inner product, $\|\cdot\|_2$ the standard vector norm, L_i the i-th row of the low-rank matrix L, and $\bar{L}_i$ its mean.

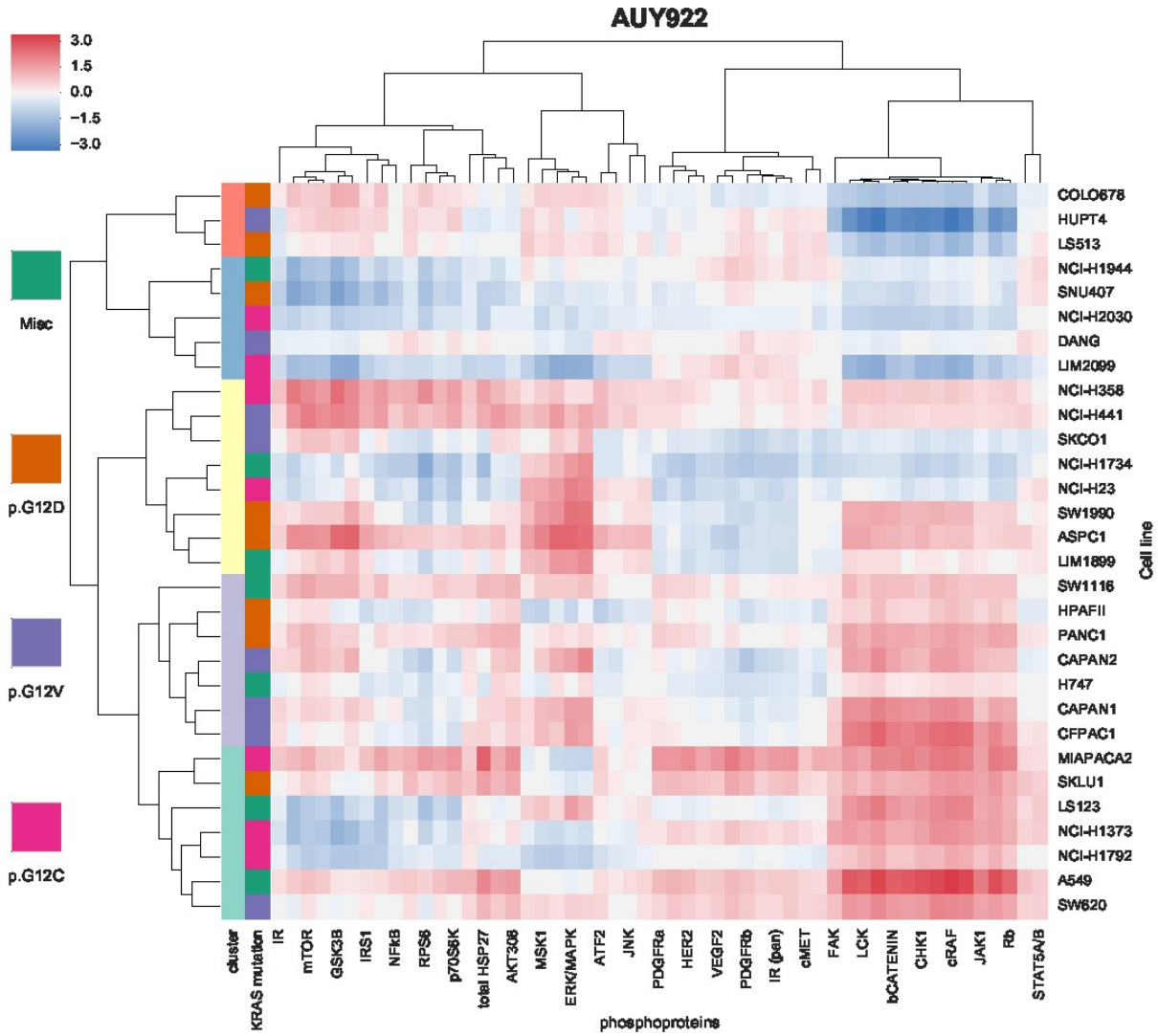
Methods - Enrichment of KRAS mutations in different clusters.

To assess whether clusters are enriched for certain *KRAS* mutations, we first cut the hierarchical clustering into 5 flat clusters followed by testing the null hypothesis that

KRAS mutations are randomly distributed among clusters using a permutation test. For a given clustering and *KRAS* mutation, we defined the test statistic as the percentage of cell lines of the specified *KRAS* mutation in each cluster, we refer to this value as support. Its distribution under the null can be computed by randomly permuting the tissue type label. When testing for multiple tissue types and clusters, we corrected p-values to control the false-discovery rate using the Benjamini Hockberg method.

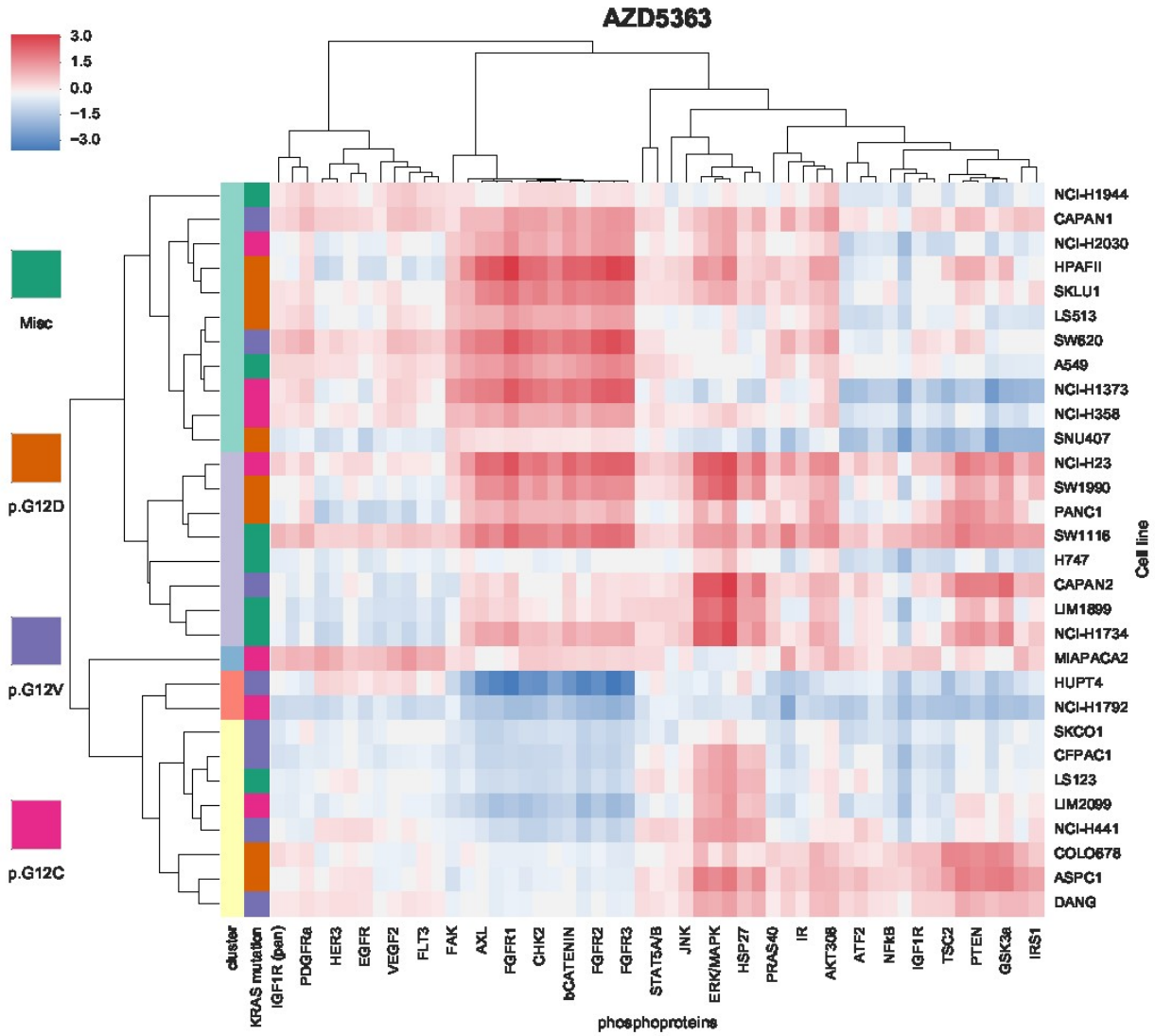
Results

We have presented the data per drug as a heat map and a table. The heat map shows clustering of into 5 clusters in the 1st column. The second column indicates the distribution of the type of *KRAS* mutation and the color codes have been annotated on the figure e.g. G12C, G12V etc. The table following each figure for an individual drug has the color coding of the 5 flat clusters (column 1 of the heat map), the type of mutation, the support, the *P* value and the *P* value adjusted for multiple testing, Benjamini Hochberg (BH).



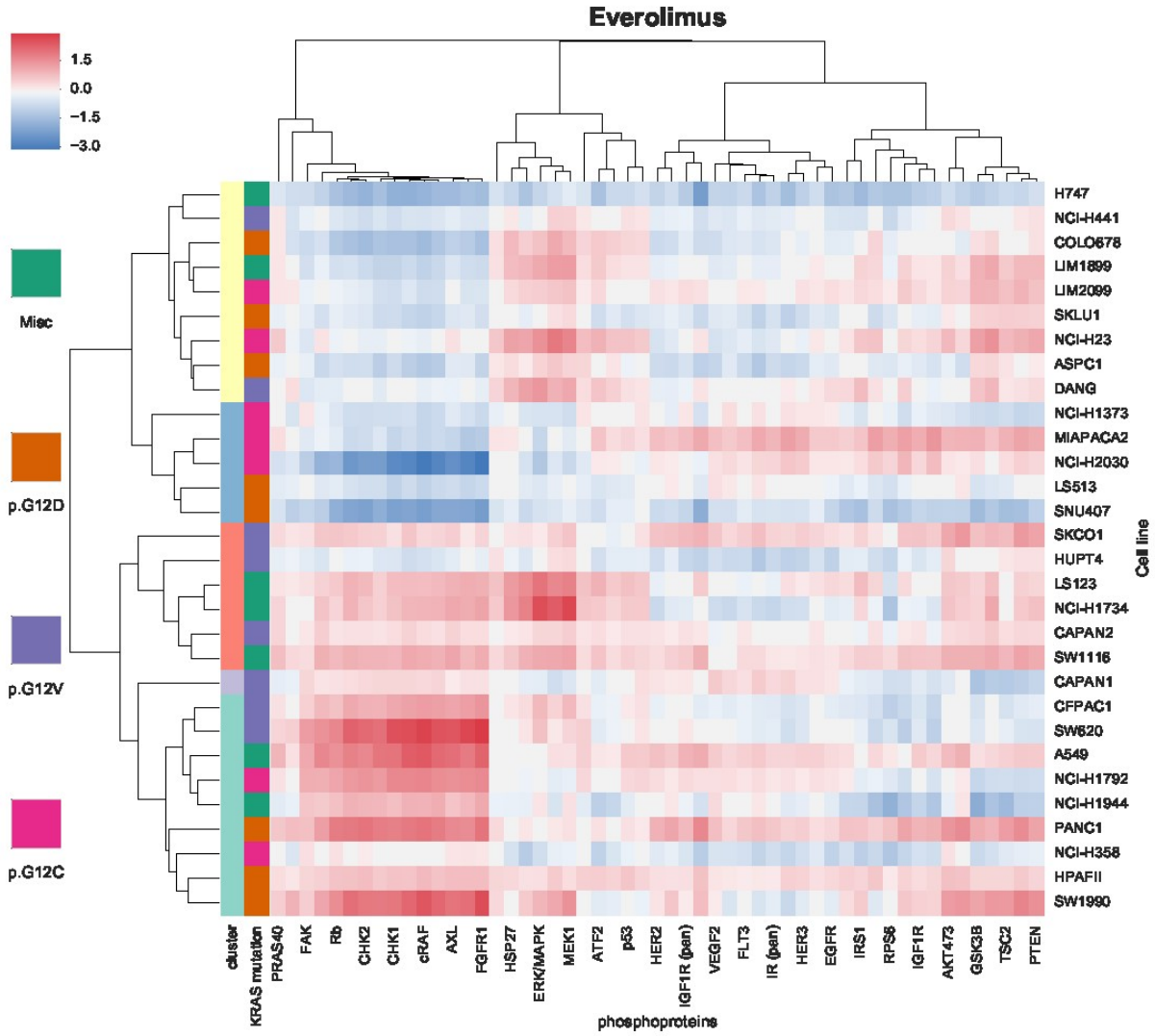
AUY922

cluster		support	p-value	p-adjusted (BH)
0	p.G12C	0.428571429	0.169	1
0	Misc	0.285714286	0.511	1
0	p.G12V	0.125	0.933	1
0	p.G12D	0.125	0.923	1
1	p.G12V	0.25	0.683	1
1	p.G12D	0.25	0.715	1
1	p.G12C	0.285714286	0.642	1
1	Misc	0.285714286	0.624	1
2	p.G12V	0.375	0.264	1
2	p.G12D	0.25	0.607	1
2	Misc	0.285714286	0.568	1
2	p.G12C	0	1	1
3	p.G12D	0.25	0.159	1
3	p.G12V	0.125	0.618	1
3	p.G12C	0	1	1
3	Misc	0	1	1
4	p.G12C	0.285714286	0.335	1
4	p.G12V	0.125	0.81	1
4	p.G12D	0.125	0.802	1
4	Misc	0.142857143	0.766	1



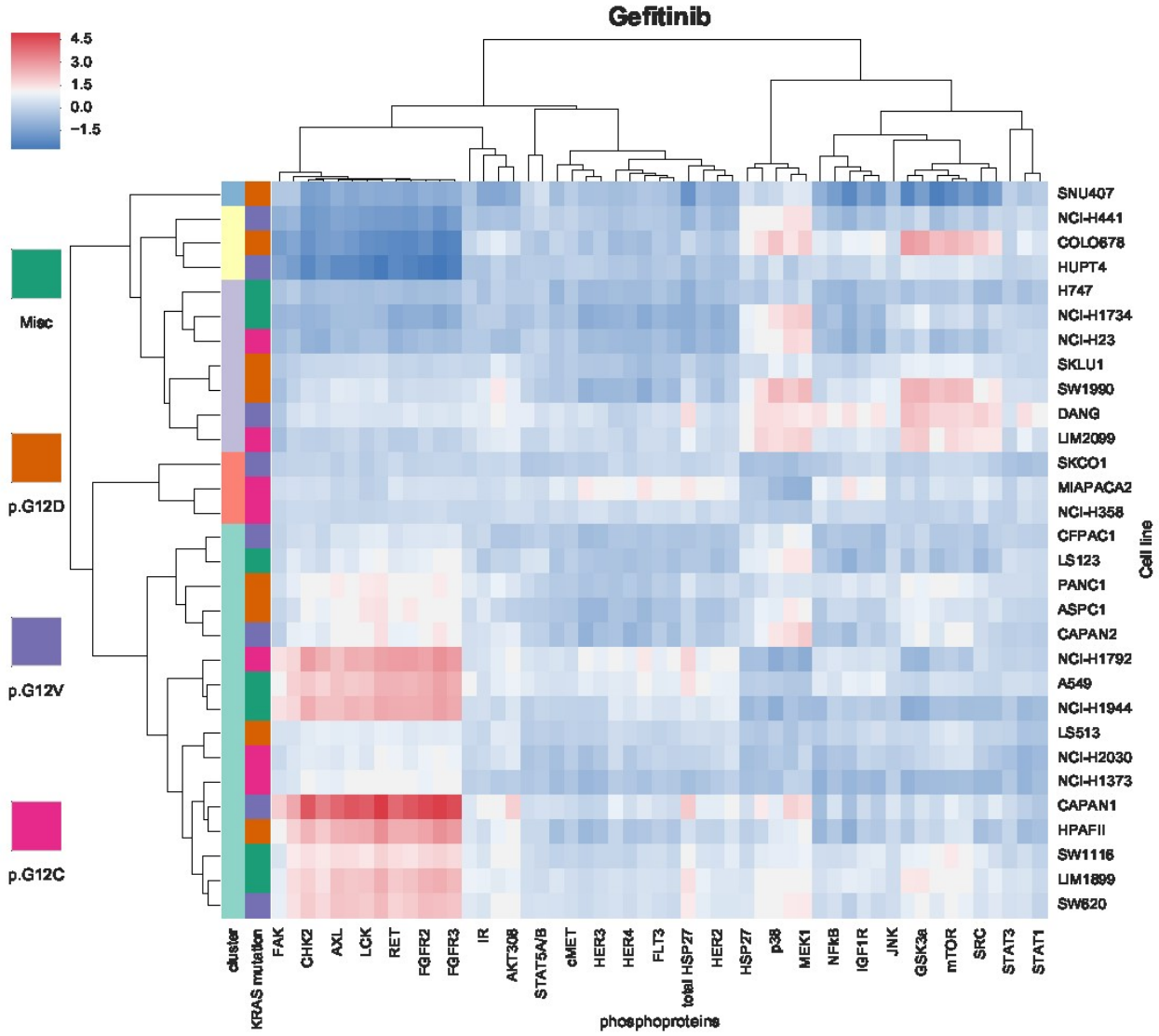
AZD5363

cluster		support	p-value	p-adjusted (BH)
0	p.G12D	0.5	0.312	1
0	p.G12C	0.42857143	0.527	1
0	p.G12V	0.25	0.877	1
0	Misc	0.28571429	0.828	1
1	p.G12V	0.5	0.124	1
1	p.G12D	0.25	0.708	1
1	p.G12C	0.14285714	0.927	1
1	Misc	0.14285714	0.916	1
2	Misc	0.57142857	0.058	1
2	p.G12D	0.25	0.716	1
2	p.G12V	0.125	0.938	1
2	p.G12C	0.14285714	0.911	1
3	p.G12V	0.125	0.489	1
3	p.G12C	0.14285714	0.389	1
3	p.G12D	0	1	1
3	Misc	0	1	1
4	p.G12C	0.14285714	0.233	1
4	p.G12V	0	1	1
4	p.G12D	0	1	1
4	Misc	0	1	1



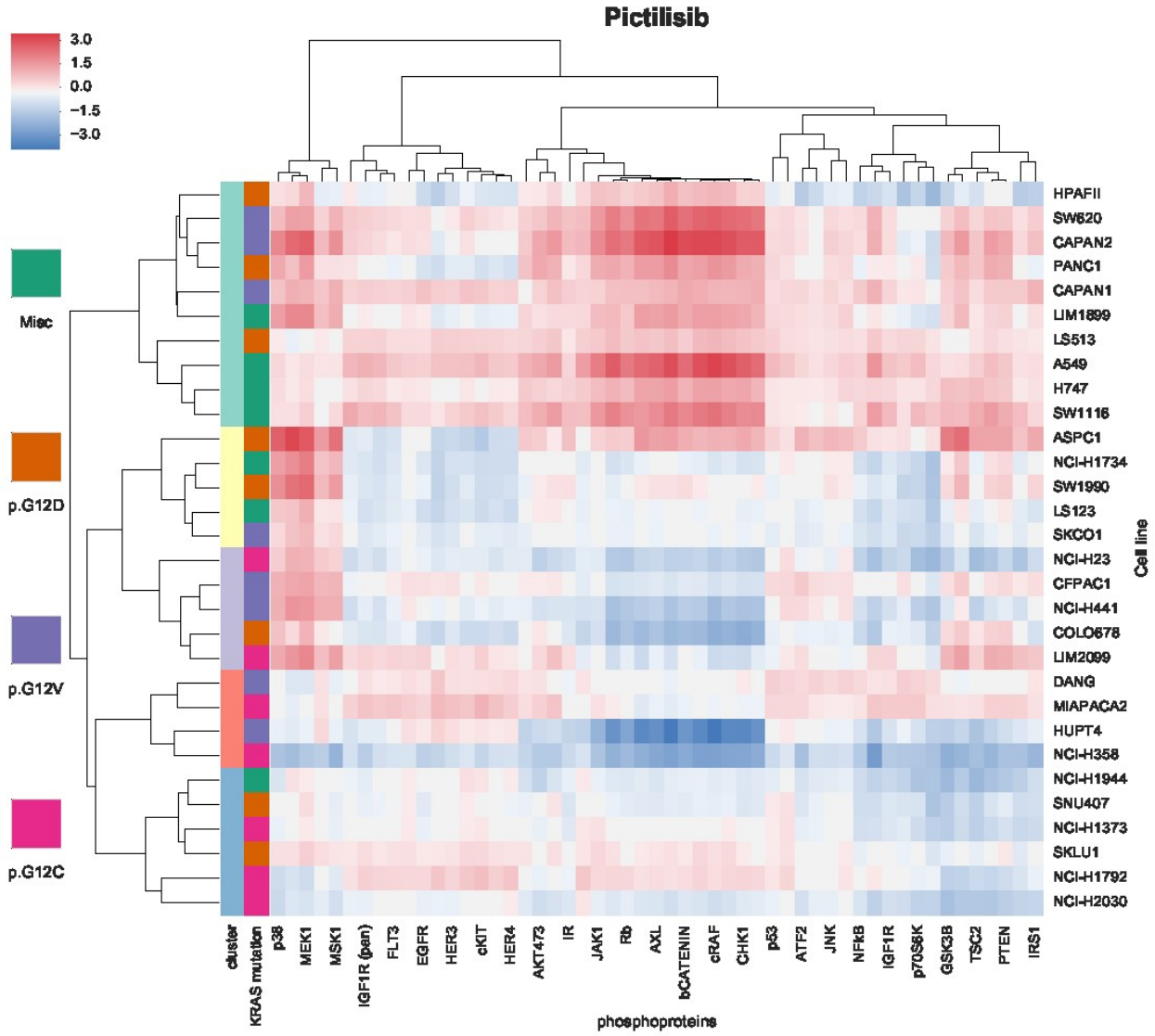
Everolimus

cluster		support	p-value	p-adjusted (BH)
0	p.G12D	0.375	0.453	1
0	p.G12V	0.25	0.787	1
0	p.G12C	0.28571429	0.69	1
0	Misc	0.28571429	0.69	1
1	p.G12D	0.375	0.448	1
1	p.G12V	0.25	0.773	1
1	p.G12C	0.28571429	0.687	1
1	Misc	0.28571429	0.691	1
2	p.G12V	0.125	0.243	1
2	p.G12D	0	1	1
2	p.G12C	0	1	1
2	Misc	0	1	1
3	p.G12V	0.375	0.175	1
3	Misc	0.42857143	0.122	1
3	p.G12D	0	1	1
3	p.G12C	0	1	1
4	p.G12C	0.42857143	0.069	1
4	p.G12D	0.25	0.409	1
4	p.G12V	0	1	1
4	Misc	0	1	1



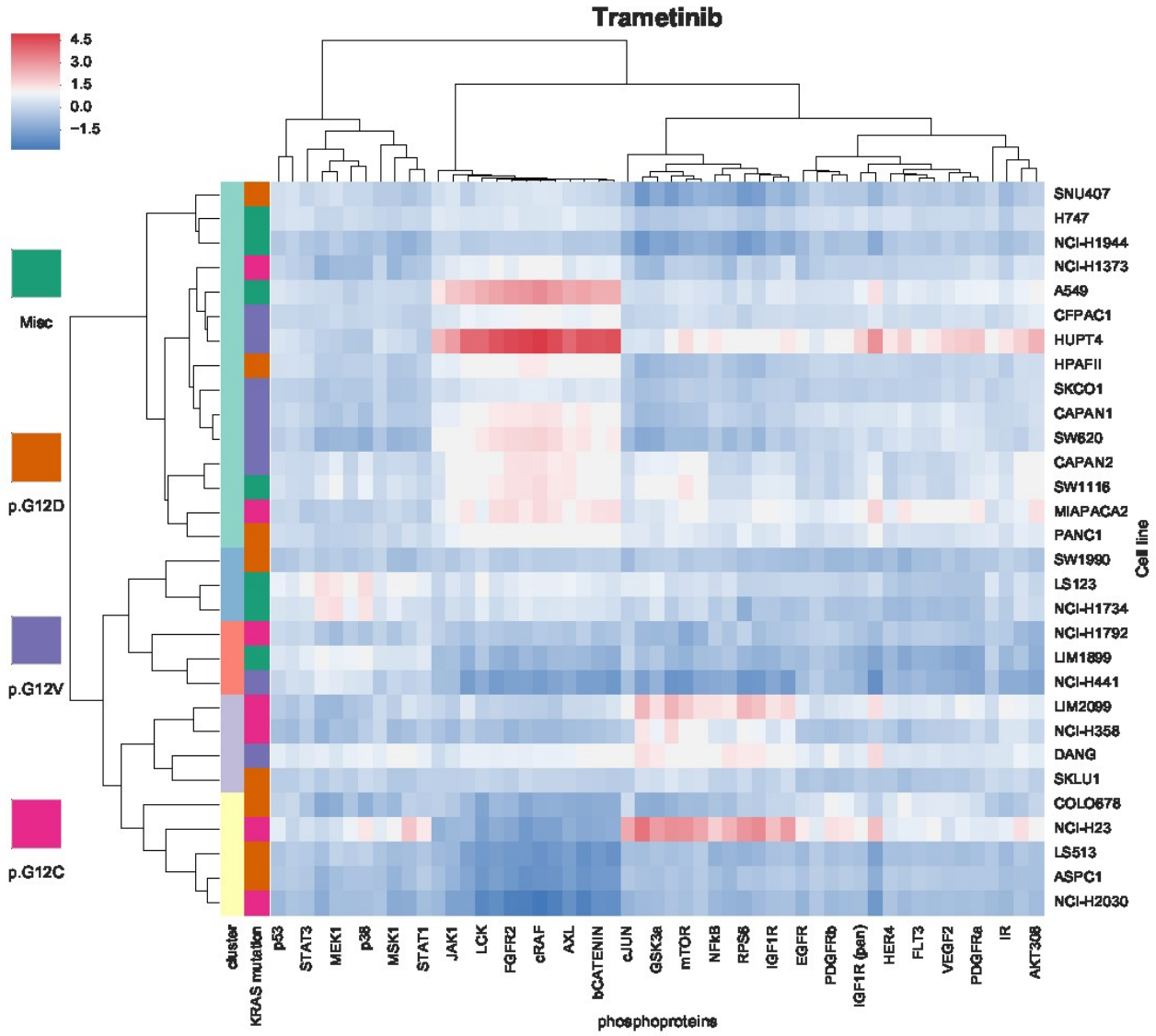
Gefitinib

cluster		support	p-value	p-adjusted (BH)
0	Misc	0.71428571	0.244	1
0	p.G12V	0.5	0.748	1
0	p.G12D	0.5	0.711	1
0	p.G12C	0.42857143	0.849	1
1	p.G12V	0.25	0.174	1
1	p.G12D	0.125	0.619	1
1	p.G12C	0	1	1
1	Misc	0	1	1
2	p.G12D	0.25	0.627	1
2	p.G12C	0.28571429	0.542	1
2	Misc	0.28571429	0.551	1
2	p.G12V	0.125	0.897	1
3	p.G12C	0.28571429	0.133	1
3	p.G12V	0.125	0.61	1
3	p.G12D	0	1	1
3	Misc	0	1	1
4	p.G12D	0.125	0.263	1
4	p.G12V	0	1	1
4	p.G12C	0	1	1
4	Misc	0	1	1



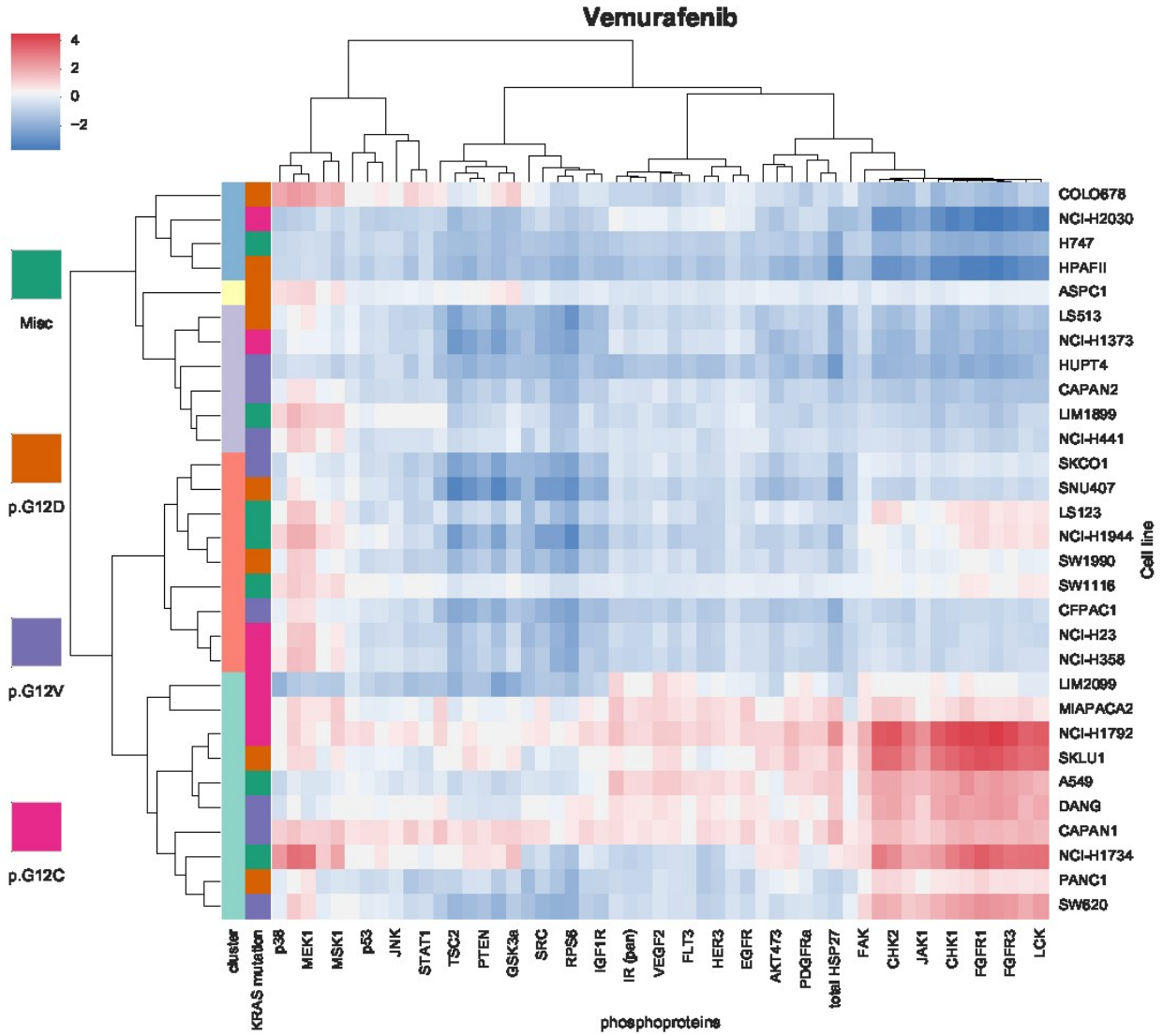
Pictilisib

cluster		support	p-value	p-adjusted (BH)
0	Misc	0.57142857	0.141	0.963636364
0	p.G12V	0.375	0.53	0.963636364
0	p.G12D	0.375	0.53	0.963636364
0	p.G12C	0	1	1
1	p.G12D	0.25	0.426	0.963636364
1	Misc	0.28571429	0.333	0.963636364
1	p.G12V	0.125	0.788	1
1	p.G12C	0	1	1
2	p.G12V	0.25	0.425	0.963636364
2	p.G12C	0.28571429	0.322	0.963636364
2	p.G12D	0.125	0.785	1
2	Misc	0	1	1
3	p.G12V	0.25	0.278	0.963636364
3	p.G12C	0.28571429	0.215	0.963636364
3	p.G12D	0	1	1
3	Misc	0	1	1
4	p.G12C	0.42857143	0.122	0.963636364
4	p.G12D	0.25	0.498	0.963636364
4	Misc	0.14285714	0.822	1
4	p.G12V	0	1	1



Trametinib

cluster		support	p-value	p-adjusted (BH)
0	p.G12V	0.75	0.115	0.78
0	Misc	0.57142857	0.489	1
0	p.G12D	0.375	0.895	1
0	p.G12C	0.28571429	0.956	1
1	p.G12D	0.375	0.1	0.78
1	p.G12C	0.28571429	0.327	1
1	p.G12V	0	1	1
1	Misc	0	1	1
2	p.G12C	0.28571429	0.23	1
2	p.G12V	0.125	0.724	1
2	p.G12D	0.125	0.731	1
2	Misc	0	1	1
3	p.G12V	0.125	0.639	1
3	p.G12C	0.14285714	0.575	1
3	Misc	0.14285714	0.547	1
3	p.G12D	0	1	1
4	Misc	0.28571429	0.117	0.78
4	p.G12D	0.125	0.634	1
4	p.G12V	0	1	1
4	p.G12C	0	1	1



Vemurafenib

cluster		support	p-value	p-adjusted (BH)
0	p.G12V	0.375	0.54	1
0	p.G12C	0.42857143	0.426	1
0	p.G12D	0.25	0.843	1
0	Misc	0.28571429	0.767	1
1	p.G12D	0.125	0.271	1
1	p.G12V	0	1	1
1	p.G12C	0	1	1
1	Misc	0	1	1
2	p.G12V	0.375	0.19	1
2	p.G12D	0.125	0.873	1
2	p.G12C	0.14285714	0.82	1
2	Misc	0.14285714	0.804	1
3	Misc	0.42857143	0.35	1
3	p.G12V	0.25	0.777	1
3	p.G12D	0.25	0.8	1
3	p.G12C	0.28571429	0.702	1
4	p.G12D	0.25	0.275	1
4	p.G12C	0.14285714	0.67	1
4	Misc	0.14285714	0.674	1
4	p.G12V	0	1	1

Interpretation

KRAS mutations were randomly distributed across the phosphoprotein clusters caused by individual drugs as none of *P* values adjusted for multiple testing were below 0.05 and were thus not significant.