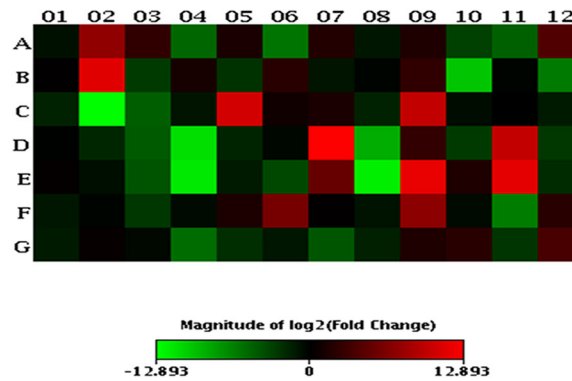


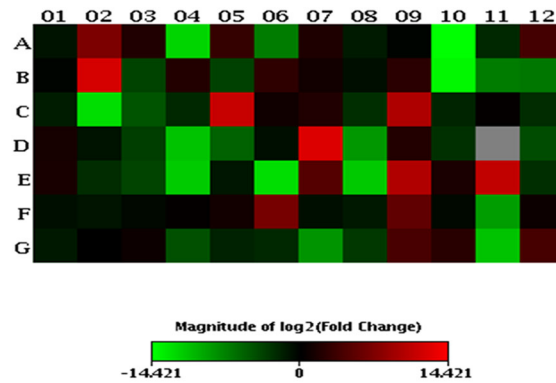
# In pursuit of synergy: An investigation of the PI3K/mTOR/MEK co-targeted inhibition strategy in NSCLC

## SUPPLEMENTARY FIGURES AND TABLE



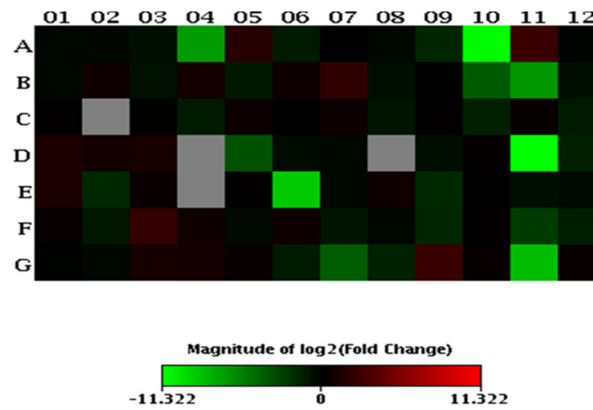
Layout	01	02	03	04	05	06	07	08	09	10	11	12
<b>A</b>	Akt1 <b>-1.74</b> OKAY	Akt1s1 <b>165.10</b> A	Akt2 <b>5.42</b> OKAY	Akt3 <b>-36.56</b> OKAY	Cab39 <b>2.40</b> OKAY	Cab39l <b>-57.08</b> OKAY	Cdc42 <b>3.24</b> OKAY	Chuk <b>-2.15</b> OKAY	Ddit4 <b>2.89</b> OKAY	Ddit4l <b>-9.14</b> OKAY	Deptor <b>-28.38</b> OKAY	Eif4b <b>16.99</b> OKAY
<b>B</b>	Eif4e <b>1.07</b> OKAY	Eif4ebp1 <b>2706.94</b> A	Eif4ebp2 <b>-7.73</b> OKAY	Fkbp1a <b>2.16</b> OKAY	Fkbp8 <b>-5.83</b> OKAY	Gsk3b <b>3.93</b> OKAY	Hif1a <b>-2.02</b> OKAY	Hras1 <b>-1.12</b> OKAY	Hspa4 <b>5.44</b> OKAY	Igf1 <b>-1007.08</b> A	Igfbp3 <b>-1.16</b> OKAY	Ikbkb <b>-73.96</b> OKAY
<b>C</b>	Ilk <b>-3.27</b> OKAY	Ins2 <b>-7215.66</b> A	Insr <b>-26.92</b> OKAY	Irs1 <b>-2.05</b> OKAY	Mapk1 <b>1717.71</b> A	Mapk3 <b>1.80</b> OKAY	Mapkap1 <b>2.41</b> OKAY	Mlst8 <b>-3.21</b> OKAY	Mtor <b>951.67</b> A	Myo1c <b>-1.55</b> OKAY	Pdpc1 <b>1.01</b> OKAY	Pik3c3 <b>-2.46</b> OKAY
<b>D</b>	Pik3ca <b>-1.04</b> OKAY	Pik3cb <b>-3.91</b> OKAY	Pik3cd <b>-23.61</b> OKAY	Pik3cg <b>-2536.82</b> A	Pld1 <b>-3.63</b> OKAY	Pld2 <b>-1.26</b> OKAY	Ppp2ca <b>7606.65</b> A	Ppp2r2b <b>-451.23</b> A	Ppp2r4 <b>5.93</b> OKAY	Prkaa1 <b>-7.40</b> OKAY	Prkaa2 <b>984.27</b> A	Prkab1 <b>-7.10</b> OKAY
<b>E</b>	Prkab2 <b>1.15</b> OKAY	Prkag1 <b>-1.69</b> OKAY	Prkag2 <b>-19.66</b> OKAY	Prkag3 <b>-3564.03</b> A	Prkca <b>-2.56</b> OKAY	Prkcb <b>-12.16</b> OKAY	Prkcg <b>34.90</b> A	Prkce <b>-4565.00</b> A	Pten <b>3634.11</b> A	Rheb <b>2.82</b> OKAY	Rhoa <b>3078.48</b> A	Rictor <b>-4.30</b> OKAY
<b>F</b>	Rps6 <b>-2.10</b> OKAY	Rps6ka1 <b>-1.17</b> OKAY	Rps6ka2 <b>-6.50</b> OKAY	Rps6ka5 <b>-1.39</b> OKAY	Rps6kb1 <b>2.70</b> OKAY	Rps6kb2 <b>63.40</b> A	Rptor <b>1.04</b> OKAY	Rraga <b>-1.94</b> OKAY	Rragb <b>140.59</b> A	Rragc <b>-1.46</b> OKAY	Rragd <b>-77.26</b> OKAY	Sgk1 <b>4.10</b> OKAY
<b>G</b>	Stk11 <b>-2.42</b> OKAY	Stradb <b>1.20</b> OKAY	Telo2 <b>-1.29</b> OKAY	Trp53 <b>-43.42</b> OKAY	Tsc1 <b>-4.86</b> OKAY	Tsc2 <b>-2.15</b> OKAY	Ulk1 <b>-20.97</b> OKAY	Ulk2 <b>-3.06</b> OKAY	Vegfa <b>2.93</b> OKAY	Vegfb <b>4.02</b> OKAY	Vegfc <b>-6.22</b> OKAY	Ywhaq <b>12.32</b> OKAY

**Supplementary Figure S1: mTOR pathway mRNA up/down-regulation in H460 cells compared to and A549s.** RNA was extracted from H460 and A549 cells. cDNA was synthesized, which was then added to mTOR pathway RT<sup>2</sup> Profiler Arrays. H460 gene expression was compared to A549 gene expression. A heat map was constructed using SABiosciences online software, with fold changes shown below, where ‘A’ refers to genes which amplified late (>30 cycles) in either sample, ‘B’ refers to genes which amplified late (>30 cycles) in both samples, and ‘C’ refers to samples where no expression was detected in either sample. 27 genes were upregulated >2 fold and 39 genes were downregulated >2 fold) in H460 cells compared with A549 cells.



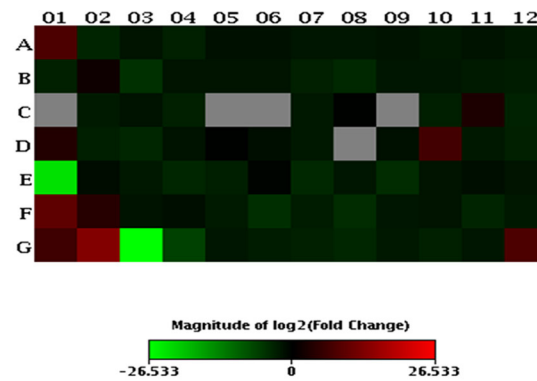
Layout	01	02	03	04	05	06	07	08	09	10	11	12
<b>A</b>	Akt1 -2.03 OKAY	Akt1s1 130.99 A	Akt2 3.48 OKAY	Akt3 -4396.99 A	Cab39 7.96 OKAY	Cab39l -124.22 OKAY	Cdc42 3.22 OKAY	Chuk -2.69 OKAY	Ddit4 -1.13 OKAY	Ddit4l -21929.11 A	Deptor -4.72 OKAY	Eif4b 14.73 OKAY
<b>B</b>	Eif4e -1.21 OKAY	Eif4ebp1 4548.62 A	Eif4ebp2 -12.88 OKAY	Fkbp1a 3.91 OKAY	Fkbp8 -12.14 OKAY	Gsk3b 6.12 OKAY	Hif1a 2.07 OKAY	Hras1 -1.68 OKAY	Hspa4 5.29 OKAY	Igf1 -16289.27 A	Igfbp3 -126.95 OKAY	Ikbkb -111.27 OKAY
<b>C</b>	Ilk -3.11 OKAY	Ins2 -6120.15 A	Insr -27.85 OKAY	Irs1 -4.71 OKAY	Mapk1 2447.82 A	Mapk3 1.82 OKAY	Mapkap1 3.56 OKAY	Mlst8 -5.85 OKAY	Mtor 1015.72 A	Myo1c -4.23 OKAY	Pdpk1 1.21 OKAY	Pik3c3 -5.41 OKAY
<b>D</b>	Pik3ca 2.33 OKAY	Pik3cb -2.07 OKAY	Pik3cd -11.48 OKAY	Pik3cg -2151.67 A	Pld1 -45.77 OKAY	Pld2 -1.77 OKAY	Ppp2ca 5895.18 A	Ppp2r2b -382.72 A	Ppp2r4 3.85 OKAY	Prkaa1 -6.59 OKAY	Prkaa2 -2.60 C	Prkab1 -19.54 OKAY
<b>E</b>	Prkab2 2.58 OKAY	Prkag1 -5.82 OKAY	Prkag2 -14.47 OKAY	Prkag3 -3022.93 A	Prkce -2.36 OKAY	Prkcb -5913.82 A	Prkcg 27.31 A	Prkce -2757.04 A	Pten 1055.37 A	Rheb 2.85 OKAY	Rhoa 2040.93 A	Rictor -5.98 OKAY
<b>F</b>	Rps6 -1.69 OKAY	Rps6ka1 -2.26 OKAY	Rps6ka2 -1.36 OKAY	Rps6ka5 1.18 OKAY	Rps6kb1 1.98 OKAY	Rps6kb2 98.95 A	Rptor -1.79 OKAY	Rraga -2.50 OKAY	Rragb 43.38 A	Rragc -1.37 OKAY	Rragd -500.88 A	Sgk1 1.63 OKAY
<b>G</b>	Stk11 -2.53 OKAY	Stradb -1.04 OKAY	Telo2 1.56 OKAY	Trp53 -23.51 OKAY	Tsc1 -3.91 OKAY	Tsc2 -4.88 OKAY	Ulk1 -358.85 OKAY	Ulk2 -8.76 OKAY	Vegfa 16.27 OKAY	Vegfb 4.89 OKAY	Vegfc -2130.25 A	Ywhaq 15.31 OKAY

**Supplementary Figure S2: mTOR pathway mRNA up/down-regulation in H1975 cells compared to and A549 cells.** RNA was extracted from H1975 and A549 cells. cDNA was synthesized, which was then added to mTOR pathway RT<sup>2</sup> Profiler Arrays. H1975 gene expression was compared to A549 gene expression. A heat map was constructed using SABiosciences online software, with fold changes shown below, where ‘A’ refers to genes which amplified late (>30 cycles) in either sample, ‘B’ refers to genes which amplified late (>30 cycles) in both samples, and ‘C’ refers to samples where no expression was detected in either sample. 26 genes were upregulated >2 fold and 41 genes were downregulated >2 fold in H1975 cells compared with A549 cells.



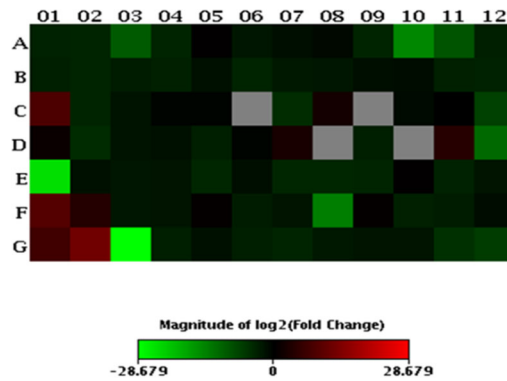
Layout	01	02	03	04	05	06	07	08	09	10	11	12
<b>A</b>	Akt1 <b>-1.17</b> OKAY	Akt1s1 <b>-1.26</b> OKAY	Akt2 <b>-1.56</b> OKAY	Akt3 <b>-120.27</b> A	Cab39 <b>3.31</b> OKAY	Cab39l <b>-2.18</b> OKAY	Cdc42 <b>-1.01</b> OKAY	Chuk <b>-1.25</b> OKAY	Ddit4 <b>-3.26</b> OKAY	Ddit4l <b>-2399.85</b> A	Deptor <b>6.01</b> OKAY	Eif4b <b>-1.15</b> OKAY
<b>B</b>	Eif4e <b>-1.29</b> OKAY	Eif4ebp1 <b>1.68</b> OKAY	Eif4ebp2 <b>-1.67</b> OKAY	Fkbp1a <b>1.81</b> OKAY	Fkbp8 <b>-2.08</b> OKAY	Gsk3b <b>1.56</b> OKAY	Hif1a <b>4.17</b> OKAY	Hras1 <b>-1.51</b> OKAY	Hspa4 <b>-1.03</b> OKAY	Igf1 <b>-16.17</b> B	Igfbp3 <b>-109.24</b> OKAY	Ikbkb <b>-1.50</b> OKAY
<b>C</b>	Ilk <b>1.05</b> OKAY	Ins2 <b>1.18</b> C	Insr <b>-1.03</b> OKAY	Irs1 <b>-2.29</b> OKAY	Mapk1 <b>1.43</b> OKAY	Mapk3 <b>1.01</b> OKAY	Mapkap1 <b>1.48</b> OKAY	Mlst8 <b>-1.83</b> OKAY	Mtor <b>1.07</b> OKAY	Myo1c <b>-2.73</b> OKAY	Pdpk1 <b>1.20</b> OKAY	Pik3c3 <b>-2.20</b> OKAY
<b>D</b>	Pik3ca <b>2.44</b> OKAY	Pik3cb <b>1.89</b> OKAY	Pik3cd <b>2.06</b> OKAY	Pik3cg <b>1.18</b> C	Pld1 <b>-12.61</b> OKAY	Pld2 <b>-1.41</b> OKAY	Ppp2ca <b>-1.29</b> OKAY	Ppp2r2b <b>1.18</b> C	Ppp2r4 <b>-1.54</b> OKAY	Prkaa1 <b>1.12</b> OKAY	Prkaa2 <b>-2560.61</b> A	Prkab1 <b>-2.75</b> OKAY
<b>E</b>	Prkab2 <b>2.24</b> OKAY	Prkag1 <b>-3.45</b> OKAY	Prkag2 <b>1.36</b> OKAY	Prkag3 <b>1.18</b> C	Prkca <b>1.08</b> OKAY	Prkcb <b>-486.53</b> A	Prkcg <b>-1.28</b> OKAY	Prkce <b>1.66</b> B	Pten <b>-3.44</b> OKAY	Rheb <b>1.01</b> OKAY	Rhoa <b>-1.51</b> OKAY	Rictor <b>-1.39</b> OKAY
<b>F</b>	Rps6 <b>1.24</b> OKAY	Rps6ka1 <b>-1.93</b> OKAY	Rps6ka2 <b>4.78</b> OKAY	Rps6ka5 <b>1.64</b> OKAY	Rps6kb1 <b>-1.37</b> OKAY	Rps6kb2 <b>1.56</b> OKAY	Rptor <b>-1.86</b> OKAY	Rraga <b>-1.29</b> OKAY	Rragb <b>-3.24</b> OKAY	Rragc <b>1.07</b> OKAY	Rragd <b>-6.48</b> A	Sgk1 <b>-2.51</b> OKAY
<b>G</b>	Stk11 <b>-1.05</b> OKAY	Stradb <b>-1.25</b> OKAY	Telo2 <b>2.02</b> OKAY	Trp53 <b>1.85</b> OKAY	Tsc1 <b>1.24</b> OKAY	Tsc2 <b>-2.27</b> OKAY	Ulk1 <b>-17.11</b> OKAY	Ulk2 <b>-2.86</b> OKAY	Vegfa <b>5.56</b> OKAY	Vegfb <b>1.22</b> OKAY	Vegfc <b>-342.61</b> A	Ywhaq <b>1.24</b> OKAY

**Supplementary Figure S3: mTOR pathway mRNA up/down-regulation in H1975 cells compared to and H460 cells.** RNA was extracted from H1975 and H460 cells. cDNA was synthesized, which was then added to mTOR pathway RT<sup>2</sup> Profiler Arrays. H1975 gene expression was compared to H460 gene expression. A heat map was constructed using SABiosciences online software, with fold changes shown below, where ‘A’ refers to genes which amplified late (>30 cycles) in either sample, ‘B’ refers to genes which amplified late (>30 cycles) in both samples, and ‘C’ refers to samples where no expression was detected in either sample. 9 genes were upregulated > 2 fold and 23 genes were downregulated in H1975 cells compared with H460 cells.



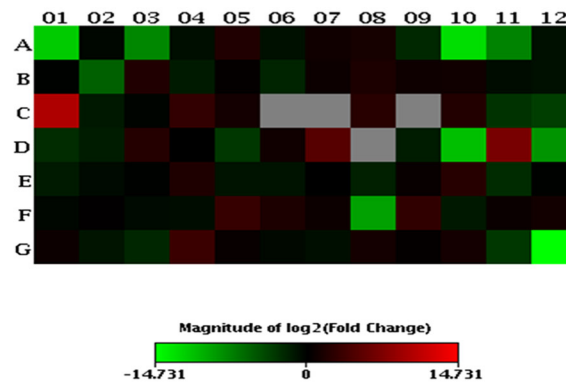
Layout	01	02	03	04	05	06	07	08	09	10	11	12
<b>A</b>	ABCB1 250.43 A	ABCC1 -13.71 OKAY	ABCC2 -4.42 OKAY	ABCC3 -9.53 OKAY	ABCC5 -3.29 OKAY	ABCG2 -2.99 OKAY	AHR -5.12 OKAY	AP1S1 -4.66 OKAY	APC -3.62 OKAY	AR -5.42 OKAY	ARNT -3.60 OKAY	ATM -5.40 OKAY
<b>B</b>	BAX -9.59 OKAY	BCL2 2.71 OKAY	BCL2L1 -30.74 OKAY	BLMH -4.37 OKAY	BRCA1 -4.45 OKAY	BRCA2 -4.22 OKAY	CCND1 -9.59 OKAY	CCNE1 -16.98 OKAY	CDK2 -4.75 OKAY	CDK4 -4.72 OKAY	CDKN1A -6.90 OKAY	CDKN1B -7.24 OKAY
<b>C</b>	CDKN2A -3.15 C	CDKN2D -6.79 OKAY	CLPTM1L -3.49 OKAY	CYP1A1 -10.40 A	CYP1A2 -3.15 C	CYP2B6 -3.15 C	CYP2C19 -5.38 B	CYP2C8 -1.08 B	CYP2C9 -3.15 C	CYP2D6 -8.62 OKAY	CYP2E1 7.26 A	CYP3A4 -11.60 B
<b>D</b>	CYP3A5 12.36 A	DHFR -8.97 OKAY	EGFR -16.57 OKAY	ELK1 -3.58 OKAY	EPHX1 -1.22 OKAY	ERBB2 -2.86 OKAY	ERBB3 -5.27 A	ERBB4 -3.15 C	ERCC3 -3.19 OKAY	ESR1 122.26 A	ESR2 -5.98 B	FGF2 -9.46 OKAY
<b>E</b>	FOS -12345286.65 OKAY	GSK3A -2.50 OKAY	GSTP1 -5.48 OKAY	HIF1A -15.68 OKAY	IGF1R -8.90 OKAY	IGF2R -1.36 OKAY	MET -18.83 OKAY	MSH2 -5.18 OKAY	MVP -23.78 OKAY	MYC -4.01 OKAY	NAT2 -2.76 A	NFKB1 -4.47 OKAY
<b>F</b>	NFKB2 865.93 A	NFKBIB 14.96 A	NFKBIE -3.90 OKAY	PPARA -2.87 OKAY	PPARD -6.74 OKAY	PPARG -26.55 OKAY	RARA -7.80 OKAY	RARB -25.22 OKAY	RARG -5.08 OKAY	RB1 -4.49 OKAY	RELB -12.72 OKAY	RXRA -5.26 OKAY
<b>G</b>	RXRB 89.25 A	SOD1 14609.22 A	SULT1E1 -97118311.28 A	TNFRSF11A -102.30 A	TOP1 -4.56 OKAY	TOP2A -7.87 OKAY	TOP2B -10.02 OKAY	TP53 -14.59 OKAY	TPMT -5.55 OKAY	UGCG -10.74 OKAY	XPA -5.20 OKAY	XPC 245.80 OKAY

**Supplementary Figure S4: Cancer drug resistance mRNA up/down-regulation in H460 cells compared to A549 cells.** RNA was extracted from H460 and A549 cells. cDNA was synthesized, which was then added to cancer drug resistance RT<sup>2</sup> Profiler Arrays. H460 gene expression was compared to A549 gene expression. A heat map was constructed using SABiosciences online software, with fold changes shown below, where ‘A’ refers to genes which amplified late (>30 cycles) in either sample, ‘B’ refers to genes which amplified late (>30 cycles) in both samples, and ‘C’ refers to samples where no expression was detected in either sample. 9 genes were upregulated > 2 fold and 65 genes were downregulated > 2 fold in H460 cells compared with A549 cells.



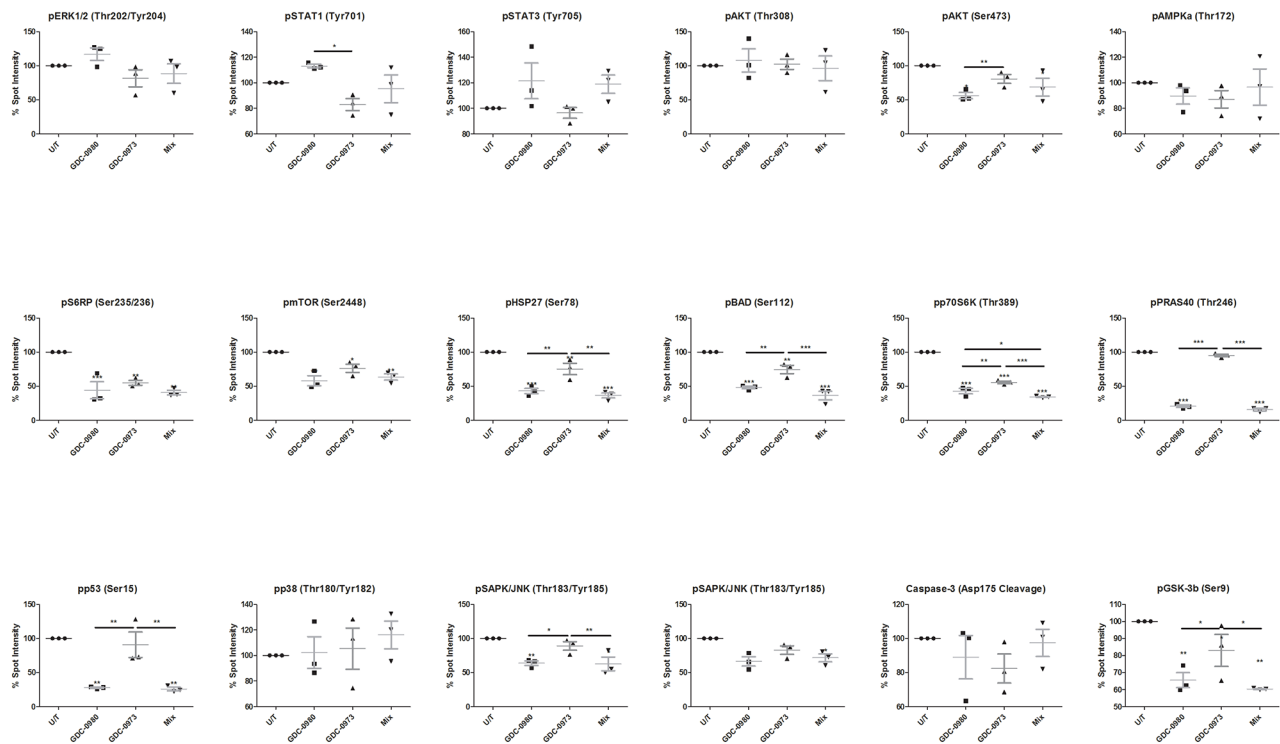
Layout	01	02	03	04	05	06	07	08	09	10	11	12
<b>A</b>	ABCB1 -14.11	ABCC1 -17.49	ABCC2 -1049.74	ABCC3 -16.09	ABCC5 1.10	ABCG2 -5.77	AHR -2.80	AP1S1 -1.88	APC -17.80	AR -39194.01	ARNT -712.26	ATM -10.01
	B	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	A	A	OKAY
<b>B</b>	BAX -10.73	BCL2 -16.90	BCL2L1 -8.68	BLMH -12.84	BRCA1 -3.70	BRCA2 -17.38	CCND1 -6.07	CCNE1 -5.32	CDK2 -2.81	CDK4 -2.58	CDKN1A -11.61	CDKN1B -13.50
	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY
<b>C</b>	CDKN2A 362.66	CDKN2D -17.64	CLPTM1L -4.16	CYP1A1 -1.39	CYP1A2 -1.47	CYP2B6 -18.17	CYP2C19 -31.04	CYP2C8 4.75	CYP2C9 -18.17	CYP2D6 -2.14	CYP2E1 -1.05	CYP3A4 -137.74
	A	OKAY	OKAY	OKAY	B	C	B	A	C	OKAY	A	B
<b>D</b>	CYP3A5 2.07	DHFR -27.37	EGFR -4.05	ELK1 -3.57	EPHX1 -11.00	ERBB2 -1.46	ERBB3 6.17	ERBB4 -18.17	ERCC3 -9.76	ESR1 -18.17	ESR2 19.92	FGF2 -3952.55
	A	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	C	OKAY	OKAY	A	OKAY
<b>E</b>	FOS -35994733.47	GSK3A -3.63	GSTP1 -5.96	HIF1A -4.55	IGF1R -18.37	IGF2R -2.88	MET -19.18	MSH2 -19.16	MVP -17.41	MYC 1.10	NAT2 -15.00	NFKB1 -4.68
	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	A	OKAY
<b>F</b>	NFKB2 683.36	NFKBIB 15.74	NFKBIE -5.80	PPARA -4.74	PPARD 1.28	PPARG -8.63	RARA -4.72	RARB -17159.69	RARG 1.33	RB1 -12.08	RELB -8.24	RXRA -2.58
	A	A	OKAY	OKAY	OKAY	OKAY	OKAY	A	OKAY	OKAY	OKAY	OKAY
<b>G</b>	RXRB 145.52	SOD1 6595.14	SULT1E1 -429817058.38	TNFRSF11A -9.64	TOP1 -3.38	TOP2A -10.49	TOP2B -17.45	TP53 -6.75	TPMT -4.68	UGCG -4.66	XPA -45.43	XPC -110.60
	A	A	A	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY	OKAY

**Supplementary Figure S5: Cancer drug resistance mRNA up/down-regulation in H1975 cells compared to A549 cells.** RNA was extracted from H1975 and A549 cells. cDNA was synthesized, which was then added to cancer drug resistance RT<sup>2</sup> Profiler Arrays. H1975 gene expression was compared to A549 gene expression. A heat map was constructed using SABiosciences online software, with fold changes shown below, where ‘A’ refers to genes which amplified late (>30 cycles) in either sample, ‘B’ refers to genes which amplified late (>30 cycles) in both samples, and ‘C’ refers to samples where no expression was detected in either sample. 9 genes were upregulated > 2 fold and 60 genes were downregulated > 2 fold in H1975 cells compared with A549 cells.

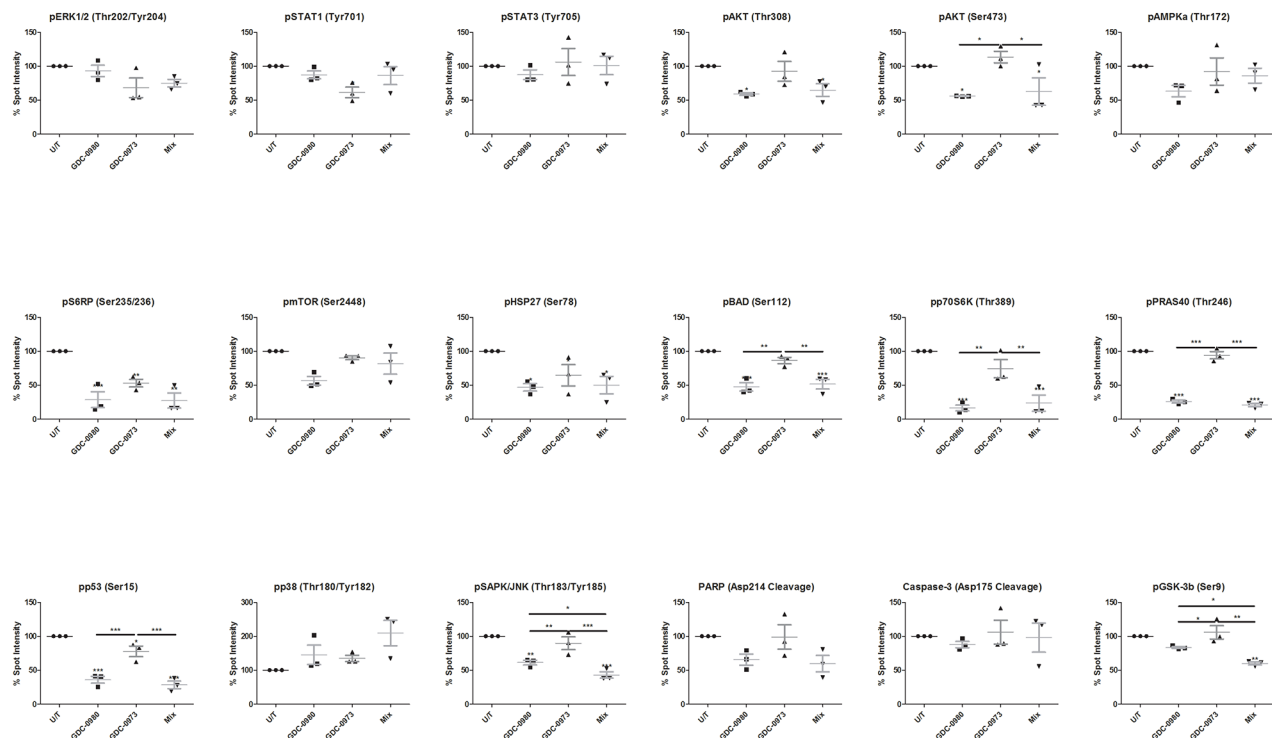


Layout	01	02	03	04	05	06	07	08	09	10	11	12
<b>A</b>	ABCB1	ABCC1	ABCC2	ABCC3	ABCC5	ABCG2	AHR	AP1S1	APC	AR	ARNT	ATM
	-3532.55 A	-1.28 OKAY	-237.48 OKAY	-1.69 OKAY	3.63 OKAY	-1.93 OKAY	1.83 OKAY	2.47 OKAY	-4.92 OKAY	-7231.58 A	-197.97 A	-1.85 OKAY
<b>B</b>	BAX	BCL2	BCL2L1	BLMH	BRCA1	BRCA2	CCND1	CCNE1	CDK2	CDK4	CDKN1A	CDKN1B
	-1.12 OKAY	-45.81 OKAY	3.54 OKAY	-2.94 OKAY	1.20 OKAY	-4.12 OKAY	1.58 OKAY	3.19 OKAY	1.69 OKAY	1.83 OKAY	-1.68 OKAY	-1.86 OKAY
<b>C</b>	CDKN2A	CDKN2D	CLPTM1L	CYP1A1	CYP1A2	CYP2B6	CYP2C19	CYP2C8	CYP2C9	CYP2D6	CYP2E1	CYP3A4
	1141.35 A	-2.60 OKAY	-1.19 OKAY	7.49 A	2.14 B	-5.77 C	-5.77 C	5.13 A	-5.77 C	4.03 OKAY	-7.59 OKAY	-11.87 B
<b>D</b>	CYP3A5	DHFR	EGFR	ELK1	EPHX1	ERBB2	ERBB3	ERBB4	ERCC3	ESR1	ESR2	FGF2
	-5.97 OKAY	-3.05 OKAY	4.09 OKAY	1.00 OKAY	-9.00 OKAY	1.96 OKAY	32.54 A	-5.77 C	-3.06 OKAY	-2221.47 A	119.11 A	-417.78 OKAY
<b>E</b>	FOS	GSK3A	GSTP1	HIF1A	IGF1R	IGF2R	MET	MSH2	MVP	MYC	NAT2	NFKB1
	-2.92 OKAY	-1.45 OKAY	-1.09 OKAY	3.44 OKAY	-2.06 OKAY	-2.12 OKAY	-1.02 OKAY	-3.70 OKAY	1.37 OKAY	4.42 OKAY	-5.44 OKAY	-1.05 OKAY
<b>F</b>	NFKB2	NFKBIB	NFKBIE	PPARA	PPARD	PPARG	RARA	RARB	RARG	RB1	RELB	RXRA
	-1.27 OKAY	1.05 OKAY	-1.49 OKAY	-1.65 OKAY	8.64 OKAY	3.08 OKAY	1.65 OKAY	-680.38 A	6.73 OKAY	-2.69 OKAY	1.54 OKAY	2.04 OKAY
<b>G</b>	RXRB	SOD1	SULT1E1	TNFRSF11A	TOP1	TOP2A	TOP2B	TP53	TPMT	UGCG	XPA	XPC
	1.63 OKAY	-2.22 OKAY	-4.43 B	10.62 A	1.35 OKAY	-1.33 OKAY	-1.74 OKAY	2.16 OKAY	1.19 OKAY	2.31 OKAY	-8.74 OKAY	-27186.46 OKAY

**Supplementary Figure S6: Cancer drug resistance mRNA up/down-regulation in H1975 cells compared to H460 cells.** RNA was extracted from H1975 and H460 cells. cDNA was synthesized, which was then added to cancer drug resistance RT<sup>2</sup> Profiler Arrays. H1975 gene expression was compared to H460 gene expression. A heat map was constructed using SABiosciences online software, with fold changes shown below, where ‘A’ refers to genes which amplified late (>30 cycles) in either sample, ‘B’ refers to genes which amplified late (>30 cycles) in both samples, and ‘C’ refers to samples where no expression was detected in either sample. 20 genes were upregulated >2 fold and 26 genes were downregulated in H1975 cells compared with H460 cells.

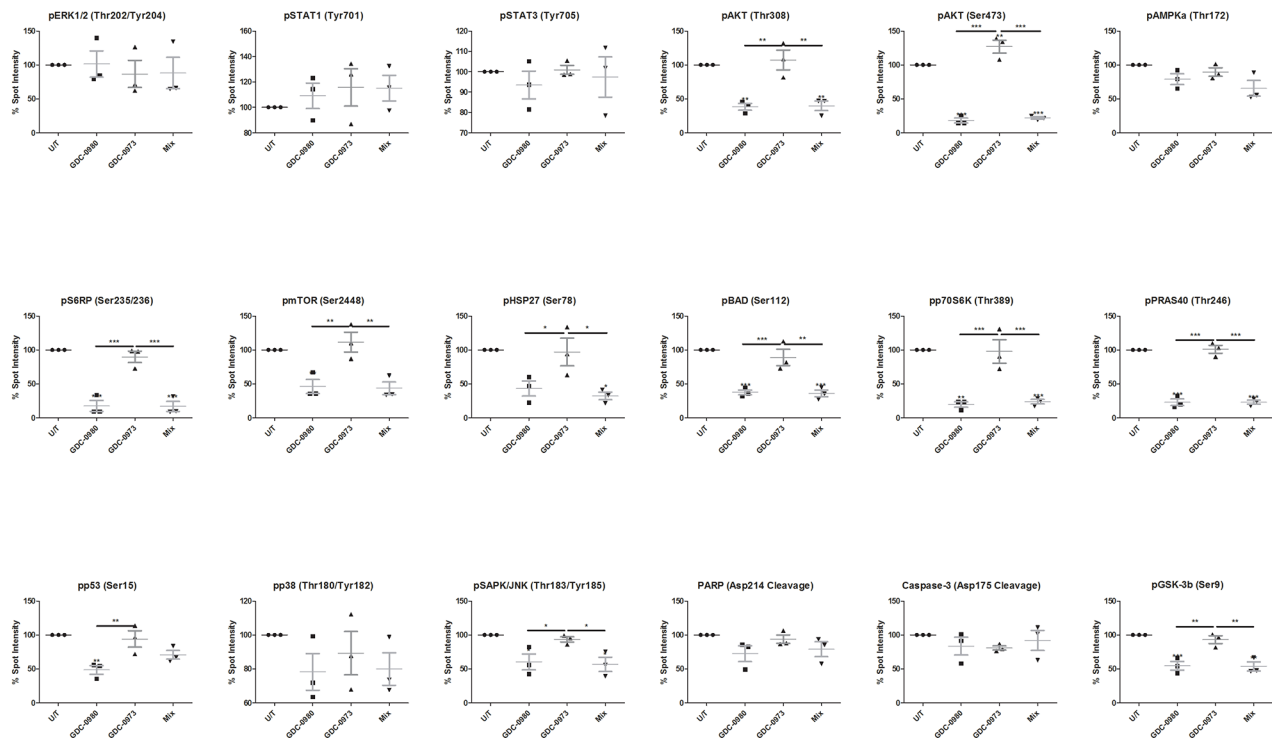


**Supplementary Figure S7: Effect of GDC-0980 and/or GDC-0973 treatment on phosphoprotein expression in H460 cells.** Protein was isolated from H460 cells untreated (4hrs) and treated with GDC-0980 (1 $\mu$ M, 4hrs), GDC-0973 (1 $\mu$ M, 4hrs) and a 1:1 mix of the 2 drugs using Cell Signalling lysis buffer. Phosphoprotein expression was explored using PathScan arrays (duplicate spots, n=3). Spot intensity was quantified through ImageJ software and data were expressed as relative mean  $\pm$  SEM.

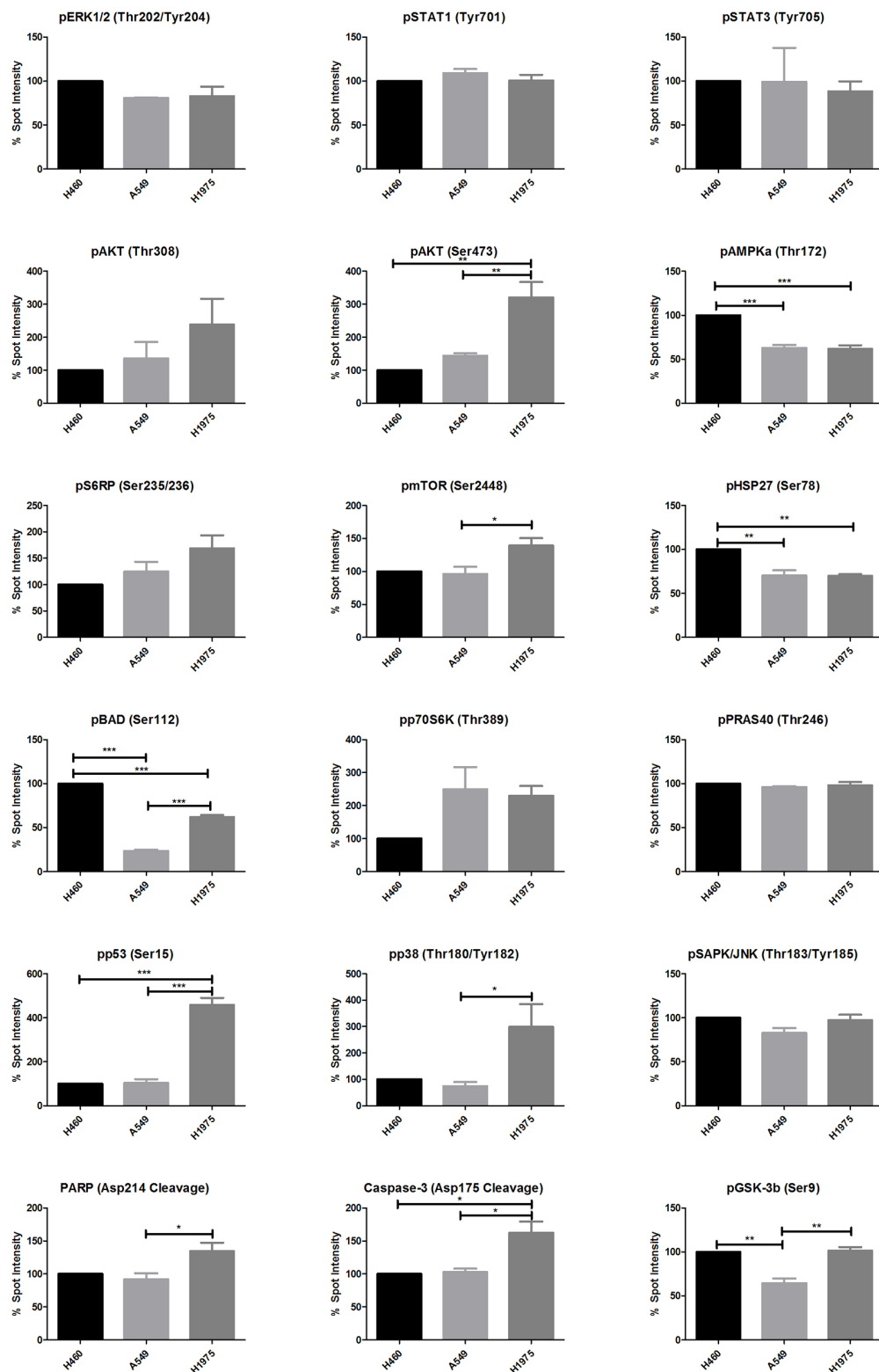


**Supplementary Figure S8: Effect of GDC-0980 and/or GDC-0973 treatment on phosphoprotein expression in A549 cells.** Protein was isolated from A549 cells untreated (4hrs) and treated with GDC-0980 (1 $\mu$ M, 4hrs), GDC-0973 (1 $\mu$ M, 4hrs) and a 1:1 mix of the 2 drugs using Cell Signalling lysis buffer. Phosphoprotein expression was explored using PathScan arrays (duplicate spots, n=3). Spot intensity was quantified through ImageJ software and data were expressed as relative mean  $\pm$  SEM.





**Supplementary Figure S9: Effect of GDC-0980 and/or GDC-0973 treatment on phosphoprotein expression in H1975 cells.** Protein was isolated from H1975 cells untreated (4hrs) and treated with GDC-0980 (1 μM, 4hrs), GDC-0973 (1 μM, 4hrs) and a 1:1 mix of the 2 drugs using Cell Signalling lysis buffer. Phosphoprotein expression was explored using PathScan arrays (duplicate spots, n=3). Spot intensity was quantified through ImageJ software and data were expressed as relative mean ± SEM.



**Supplementary Figure S10: Baseline phosphoprotein expression in H460, A549 and H1975 cells.** Protein was isolated from H460, A549 and H1975 cells (untreated) using Cell Signalling lysis buffer. Phosphoprotein expression was explored using PathScan arrays (duplicate spots, n=3). Spot intensity was quantified through ImageJ software and data were expressed as relative mean  $\pm$  SEM. \*/\*\*/\*\*: p<0.05/0.01/0.001 respectively, from one way ANOVA with Tukey test.

**Supplementary Table S1: Fluidigm gene panel 13-gene. 175 Irish NSCLC tumour samples were profiled by Fluidigm Technology, using an allele-specific test covering 13 genes (150 mutations).**

**See Supplementary File 1**