

## Supplementary tables

### E-cadherin/ROS1 inhibitor synthetic lethality in breast cancer

Ilijana Bajrami<sup>1,2</sup>, Rebecca Marlow<sup>3</sup>, Marieke van de Ven<sup>4</sup>, Rachel Brough<sup>1,2</sup>, Helen N. Pemberton<sup>1,2</sup>, Jessica Frankum<sup>1,2</sup>, Fei Fei Song<sup>1,2</sup>, Rumana Rafiq<sup>1,2</sup>, Asha Konde<sup>1,2</sup>, Dragomir B. Krastev<sup>1,2</sup>, Malini Menon<sup>1,2</sup>, James Campbell<sup>1,2</sup>, Aditi Gulati<sup>1,2</sup>, Rahul Kumar<sup>1,2</sup>, Stephen J. Pettitt<sup>1,2</sup>, Mark D. Gurden<sup>1</sup>, Marta Llorca Cardenosa<sup>1,5</sup>, Irene Chong<sup>1</sup>, Patrycja Gazinska<sup>3</sup>, Fredrik Wallberg<sup>6</sup>, Elinor J. Sawyer<sup>7</sup>, Lesley-Ann Martin<sup>1</sup>, Mitch Dowsett<sup>1</sup>, Spiros Linardopoulos<sup>1,8</sup>, Rachael Natrajan<sup>1</sup>, Colm J. Ryan<sup>9</sup>, Patrick W.B. Derksen<sup>10</sup>, Jos Jonkers<sup>11</sup>, Andrew N.J. Tutt<sup>1,3</sup>, Alan Ashworth<sup>12\*</sup>, Christopher J. Lord<sup>1,2\*</sup>

**Supplementary Table S1 Small molecule inhibitor profiling in CRISPR-Cas9 generated E-cadherin defective MCF7 model.** Median surviving fraction, median ratio and *p* value for MCF7 A02 and MCF7 Parental cells are shown.

Small molecule inhibitor ID	Median surviving fraction in MCF7 Parental	Median surviving fraction in MCF7 A02	Median MCF7 A02/Median MCF7 Parental ratio	<i>p</i> value
PF-02341066(MET/ALKi)(1000nM)	0.659	0.256	0.389	0.0004
PF-03758309(PAKi)(1000nM)	0.34	0.136	0.399	0.0001
PF-03758309(PAKi)(100nM)	0.472	0.189	0.4	4.0278E-05
PF-03758309(PAKi)(50nM)	0.393	0.168	0.428	2.5432E-05
PF-03758309(PAKi)(5nM)	0.518	0.226	0.436	0.0002032
BEZ-235(PI3K/mTORi)(500nM)	0.333	0.15	0.449	0.0011
BI-2536(PLKi)(100nM)	0.294	0.134	0.457	0.0071
PF-03814735(Aurora)(100nM)	1.078	0.498	0.462	0.0002
gemcitabine.HCl(DNArepinhib)(50nM)	0.287	0.134	0.467	9.5427E-06
PF-02341066(MET/ALKi)(500nM)	0.789	0.372	0.472	0.0002
gemcitabine.HCl(DNArepinhib)(500nM)	0.272	0.129	0.473	0.0022
crizotinib(ALKi)(500nM)	0.769	0.379	0.493	0.0002
crizotinib(ALKi)(1000nM)	0.605	0.298	0.493	0.0032
PF-03758309(PAKi)(10nM)	0.687	0.341	0.496	0.0001
paclitaxel(microtubulepoison)(1000nM)	0.26	0.129	0.496	0.0137
Foretinib(METi,VEGFR2i,KDRi)(500nM)	0.781	0.39	0.499	0.0072
gemcitabine.HCl(DNArepinhib)(100nM)	0.286	0.146	0.511	0.0002
BEZ-235(PI3K/mTORi)(1000nM)	0.28	0.143	0.512	0.0002
Foretinib(METi,VEGFR2i,KDRi)(1000nM)	0.734	0.382	0.521	0.0001
MLN-4924(NEDDi)(100nM)	0.33	0.174	0.528	0.0003
PF-03814735(Aurora)(1000nM)	0.792	0.42	0.53	0.0006
paclitaxel(microtubulepoison)(100nM)	0.334	0.179	0.536	0.0031
sunitinib(VEGFR1-3i,PDGFRi,Kiti,CSF1Ri)(1000nM)	0.558	0.313	0.56	0.0051
YM155(Survivin-suppressant)(10nM)	0.376	0.211	0.561	0.0071
paclitaxel(microtubulepoison)(10nM)	0.379	0.214	0.566	0.0008
YM155(Survivin-suppressant)(5nM)	0.793	0.45	0.568	0.0008
paclitaxel(microtubulepoison)(5nM)	0.449	0.256	0.57	0.0215
(S)+camptothecin(TOPOIpoison)(50nM)	0.366	0.211	0.578	0.0003
PLX-4720(BRAF <sub>i</sub> )(0.5nM)	1.057	0.611	0.578	0.0011
BEZ-235(PI3K/mTORi)(100nM)	1.085	0.629	0.579	0.0021
paclitaxel(microtubulepoison)(50nM)	0.304	0.179	0.59	0.0028
PF-04929113(HSP90i)(50nM)	0.53	0.317	0.597	0.0041
sunitinib(VEGFR1-3i,PDGFRi,Kiti,CSF1Ri)(10nM)	1.109	0.667	0.601	0.0011
lestaurtinib(1mM)(JAK2/FLT3/TrkAi)(200nM)	0.873	0.527	0.604	0.0069
(S)+camptothecin(TOPOIpoison)(100nM)	0.284	0.172	0.606	0.0009
sapacitabine(CNDAC)(1000nM)	0.647	0.401	0.619	0.0035
etoposide(TOPOIi)(1000nM)	0.524	0.335	0.638	0.0016
BMN-673(PARPi)(100nM)	0.713	0.456	0.64	0.0014
PF-04929113(HSP90i)(100nM)	0.261	0.168	0.641	0.0126
BMN-673(PARPi)(500nM)	0.626	0.404	0.645	0.0009
PF-03814735(Aurora)(500nM)	0.989	0.641	0.648	0.0001
MLN-4924(NEDDi)(50nM)	0.418	0.272	0.65	0.0022
Sapacitabine(CNDAC)(500nM)	0.762	0.499	0.656	0.0043
DMX_2320(IKKeinhibitor)(1000nM)	0.975	0.641	0.657	0.0196
sapacitabine(CNDAC)(10nM)	0.887	0.586	0.661	0.0278
etoposide(TOPOIi)(500nM)	0.576	0.382	0.663	0.0006
(S)+camptothecin(TOPOIpoison)(0.5nM)	0.836	0.562	0.672	0.0421
BMN-673(PARPi)(1000nM)	0.62	0.421	0.679	0.002
gemcitabine.HCl(DNArepinhib)(10nM)	0.292	0.206	0.708	0.0232
5-FU(anti-metabolite)(1000nM)	0.894	0.634	0.709	0.0024
doxorubicin.HCl(DNAintercalator)(50nM)	0.351	0.25	0.712	0.001
BMN-673(PARPi)(50nM)	0.703	0.502	0.714	0.0037
methotrexate(10nM)	1.107	0.818	0.739	0.0034
(S)+camptothecin(TOPOIpoison)(10nM)	0.603	0.446	0.74	0.0103
17-AAG(HSP90i)(50nM)	0.364	0.272	0.749	0.0068

**Supplementary Table S2 Summary table of drug screen AUC, AUC ratios and *p* values for MCF7 A02 and MCF7 Parental isogenic cells**

<b>Small molecule inhibitor ID</b>	<b>MCF7 A02 median AUC</b>	<b>MCF7 Parental median AUC</b>	<b>MCF7 A02 AUC/MCF7 Parental AUC ratio</b>	<b><i>p</i> value</b>
PF-03758309(PAKi)	135.3	311.4	0.43	0.0000056
gemcitabine.HCl(DNArepinhib)	146.3	273.9	0.53	0.0000535
paclitaxel(microtubulepoison)	154.5	266.4	0.58	0.0012748
BEZ-235(PI3K/mTORi)	327.3	551.9	0.59	0.0006430
PF-03814735(Aurora)	577.6	961.8	0.60	0.0000959
MLN-4924(NEDDi)	156.4	238.9	0.65	0.0026734
BMN-673(PARPi)	431.4	656.6	0.66	0.0002943
Camptothecin(TOPOIpoison)	83.83	127.4	0.66	0.0000090
Foretinib(METi,VEGFR2i,KDRi)	591	879.5	0.67	0.0073153
Everolimus(mTORi)	911	1353	0.67	0.0000939
PF-04691502(PI3K/mTORi)	228.6	336.7	0.68	0.0071079
PF-02341066(MET/ALKi)	577.4	831.6	0.69	0.0004426
Crizotinib(ALKi)	625.2	879.1	0.71	0.0000970
Flavopiridol(CDKi)	149	204.2	0.73	0.0194037
Doxorubicin(DNAintercalator)	100.4	136.9	0.73	0.0029741
PF-04929113(HSP90i)	146.1	196	0.75	0.0013952
17-AAG(HSP90i)	124.6	167.1	0.75	0.0116781
PF-332991(CDK4/6i)	1070	1430	0.75	0.0015142
RO-3306(CDK1i)	1027	1279	0.80	0.0301231
Sapacitabine(CNDAC)	686.4	842.9	0.81	0.0180510
Etoposide(TOPOIi)	702.7	854	0.82	0.0018328
MK2206(AKTi)	1131	1349	0.84	0.0118299
YM155(Survivin-suppressant)	31.61	37.58	0.84	0.0042925
GSK2194069A(FASi)	2113	2505	0.84	0.0210857
Methotrexate	676.6	767.1	0.88	0.0180580
Sorafenib(inhibitsRAF,PDGF,VEGF1&2)	1114	1026	1.09	0.0492614
Salinomycin(microtubulepoison)	1305	730.3	1.79	0.0001269

**Supplementary Table S3 RNAi screen in CRISPR-Cas9 generated E-cadherin defective model.** The difference in Z-score data of median of E-cadherin defective and median of wt. groups are shown.

GeneID	Median Z score Parental	Median Z score A02	Difference in Z score	Students t-test
PMS1	-0.37868745	-8.98291435	-8.6042269	0.000157058
KIT	-0.51398672	-8.83138319	-8.31739647	3.23471E-06
CHIC2	-0.24934777	-7.56700148	-7.31765371	0.000491343
FBXO11	-0.47643587	-7.75906429	-7.28262842	5.75639E-05
PRKAR2B	-0.22223177	-7.3524416	-7.13020984	0.00377432
DCLRE1A	-1.15851394	-7.98333021	-6.82481627	0.000612272
KMT2C	-1.15948954	-7.97654051	-6.81705097	1.74845E-05
CSNK1A1	-1.24075613	-7.72050314	-6.47974701	0.000216709
H3F3A	1.227762649	-5.0679676	-6.29573025	0.005129908
INSRR	-1.48048109	-7.77183138	-6.29135029	0.00020486
PIM1	0.384101613	-5.87138389	-6.25548551	0.000381328
FLJ21816	-1.43658773	-7.64235611	-6.20576838	0.000201037
EBF1	0.776518801	-5.34505678	-6.12157558	0.015351369
UBR5	-1.28318069	-7.35090876	-6.06772807	9.81113E-05
CRK7	-0.48822231	-6.35016686	-5.86194455	0.001680351
CCDC6	-1.42492956	-7.06507291	-5.64014335	0.000156725
HUNK	-1.4630816	-7.04536056	-5.58227896	0.000488868
DGDUOK	0.650828892	-4.85190435	-5.50273324	0.000314777
CDC2	-0.72278912	-6.21507314	-5.49228402	0.00022434
ATRIP	0.362360903	-5.12005718	-5.48293608	0.000538097
WRN	-0.98830613	-6.47105232	-5.4827462	0.001924952
CTNNB1	-0.63465189	-6.03550606	-5.40085417	0.005050959
KMT2D	-1.33572548	-6.72874917	-5.39302369	0.000396323
RUNX1	-0.82421605	-6.1880993	-5.36388325	0.000805091
AAK1	-0.33184708	-5.69220545	-5.36035836	0.000973975
PRKCN	0.570660407	-4.75171683	-5.32237724	0.009811467
GATA1	-0.98775391	-6.28738778	-5.29963387	0.001862397
SBK1	-0.73078421	-5.9563222	-5.22553799	0.001572046
MAP2K7	-0.8058538	-5.97229345	-5.16643965	0.000376876
PFKFB4	-0.54289259	-5.57442057	-5.03152797	0.020316338
ARID1A	-0.60278036	-5.58206205	-4.97928169	0.005199919
MSH3	-0.76262113	-5.67603399	-4.91341286	0.001794646
TRIM24	-0.47812214	-5.38892315	-4.910801	0.000382544
STK38L	-0.67035213	-5.49776299	-4.82741086	0.004361046
DDX5	-1.35122612	-6.12012632	-4.7689002	0.000141545
PRDM16	0.78940912	-3.97140585	-4.76081497	0.019166968
RP88KA2	-1.25391289	-5.98601505	-4.73210216	0.000796379
TGFBR1	0.409488382	-4.30637608	-4.71586447	0.011352904
EPHA4	-0.9245529	-5.60847235	-4.68391945	0.002335804
RPA3	-1.38333275	-6.04486487	-4.66153212	8.77224E-05
TRIP11	0.005157012	-4.63756233	-4.64271934	0.024706798
PFKP	-0.67442115	-5.21603922	-4.54161807	0.045371638
ADP-GK	-0.97323477	-5.48985303	-4.51661827	0.001854579
POT1	-1.36896822	-5.88109006	-4.51212183	0.000146199
NEK4	-0.08598567	-4.57934673	-4.49336106	0.033345167
GTF2H4	-0.27520057	-4.72076013	-4.44555957	0.002583076
ADCK4	0.333301162	-4.03184327	-4.36514444	0.017771881
GTF2H1	-0.6274943	-4.90083955	-4.27334525	0.011279748
PLK1	-1.01026031	-5.20775162	-4.19749131	0.001593987
PTEN	0.42616659	-3.70382457	-4.12999116	0.001203126
AK5	-1.173301	-5.28589924	-4.11259824	0.010069824
ATF1	0.083926536	-4.00854044	-4.09246697	0.000411106
ZBTB16	0.215516313	-3.82420709	-4.03972341	0.015400172
GRK4	-1.34929841	-5.35582664	-4.00652822	0.000498204
PLK3	-1.29844066	-5.25143729	-3.95299664	0.004324462
FYN	-1.31220116	-5.2442765	-3.93207534	0.002023798
ROS1	-0.49442849	-4.34423518	-3.84980669	0.030213832
POLM	-0.44870629	-4.29010774	-3.84140145	0.000297354
FANCI	-0.8100982	-4.63999479	-3.82989659	0.053240715
DAXX	0.821090414	-2.99236049	-3.8134509	0.000897737
PRKAG3	-1.360728	-5.1598619	-3.7991339	0.000970212
FEV	-1.17576063	-4.96998464	-3.79422401	0.00116181
SSX2	-1.02529557	-4.81330784	-3.78801227	0.007729931
CLK3	-0.58729081	-4.34366846	-3.75637765	0.009591982
PRKCB1	-1.50048056	-5.25292696	-3.7524464	0.000158787
FES	-0.39210366	-4.1442883	-3.75218464	0.008493374
MSH4	-0.30542159	-4.04339584	-3.73797426	0.013932418

  

GeneID	Median Z score Parental	Median Z score A02	Difference in Z score	Students t-test
NPM1	-1.11536265	-4.70782033	-3.59245769	0.045643175
PDCD1LG2	-1.42689663	-5.00114015	-3.57424351	0.012844291
PLAG1	-1.36229198	-4.88575082	-3.52345884	0.00019456
FANCG	-0.52069173	-4.00109819	-3.48040646	0.000432207
HOXC11	1.125960451	-2.28970679	-3.41566725	0.000106356
DDIT3	-1.04256821	-4.32625127	-3.28368306	0.017071472
CDK12	-0.1036177	-3.37288538	-3.26926767	0.038503948
FANCB	-0.38206882	-3.61986303	-3.23779421	0.040548552
MERTK	-0.81953587	-3.87690355	-3.05736768	0.01453234
RECQL	-0.41383062	-3.42166959	-3.00783897	0.005132054
CREB3L2	-1.13816631	-4.1443255	-3.00615918	0.002602646
KDM6A	-0.63013955	-3.63298606	-3.00284651	0.002069589
CLTC	-1.30341603	-4.22631583	-2.92289979	0.000861809
NUTM1	0.424446202	-2.27999367	-2.70443987	0.011105984
GALK1	-0.46920544	-3.14914839	-2.67994295	0.004391752
CDC2L1	-0.87741537	-3.52404619	-2.64663082	0.002308364
CPNIE3	-0.50139866	-3.10907394	-2.60767528	0.044875919
CRTC3	0.362399679	-2.15444816	-2.51688384	0.009290478
MITF	0.34934652	-2.13805273	-2.48739925	0.008902537
TREX2	-1.23565199	-3.67032532	-2.43467332	0.004135544
SMARCE1	-0.40796467	-2.82778089	-2.41981622	0.043945748
PAK4	-1.50379621	-3.89188488	-2.38808866	0.004456848
POLH	-1.07087282	-3.39267782	-2.32180499	1.08771E-05
MYLK2	-0.95124097	-3.26527182	-2.31403085	8.27814E-05
C10ORF89	-1.14154789	-3.41840933	-2.27686144	0.034933998
SETD2	-1.08157534	-3.35432983	-2.27275449	0.000327971
LMTK3	-1.25882889	-3.5221478	-2.26331891	0.000174692
DCK	-0.87783821	-3.14074738	-2.26290917	0.005743764
FLT4	0.113209615	-2.1488326	-2.26204222	0.049605366
C8F1R	-1.25867281	-3.49019105	-2.23151824	0.026100848
PCNA	-0.95920804	-3.16452046	-2.20531242	0.023688738
USP6	-0.59633921	-2.76106527	-2.16472607	0.019816483
PNU1L1	-0.90801383	-3.06208253	-2.15406687	0.048633502
TOPBP1	-1.44774262	-3.5871968	-2.13945418	0.008390008
ARAF1	0.047569234	-2.0269218	-2.07449103	0.036405259
MN1	-0.41296756	-2.4427168	-2.02974923	0.001726923
PIK3C2A	-1.46227691	-3.48384269	-2.02156578	0.00665146

**Supplementary Table S4** Gene ontology analysis of a list of 104 genes identified as E-cadherin synthetic lethal targets using EnrichR analysis.

Name	P-value	Adjusted p-value	Z-score	Combined score	Genes involved
RNA polymerase II carboxy-terminal domain kinase activity	3.48E-13	1.60E-10	-3.19	91.47	PLK3, AAK1, HUNK, CSNK1A1, NEK4, PAK4, CPNE3, PIM1, CLK3, RPS6KA2, SBK1, STK38L, TGFB1, GTF2H1, GTF2H4, CDK12
protein serine/threonine kinase activity	5.29E-13	1.60E-10	-3.21	90.66	PLK3, AAK1, HUNK, CSNK1A1, NEK4, PAK4, CPNE3, PIM1, CLK3, RPS6KA2, SBK1, STK38L, GTF2H1, GTF2H4, CDK12, EPHA4
myosin light chain kinase activity	4.24E-11	8.52E-09	-3.16	75.5	PLK3, AAK1, HUNK, CSNK1A1, NEK4, PAK4, CPNE3, PIM1, CLK3, RPS6KA2, SBK1, STK38L, TGFB1, MYLK2
calmodulin-dependent protein kinase activity	5.87E-11	8.85E-09	-3.11	73.37	PLK3, AAK1, HUNK, CSNK1A1, NEK4, PAK4, CPNE3, PIM1, CLK3, RPS6KA2, SBK1, STK38L, TGFB1, GTF2H1, GTF2H4, CDK12
cyclin-dependent protein serine/threonine kinase activity	8.44E-11	1.02E-08	-3.12	72.41	
cyclic nucleotide-dependent protein kinase activity	4.11E-10	1.35E-08	-3.06	66.21	
transmembrane receptor protein serine/threonine kinase activity	4.29E-10	1.35E-08	-3.06	65.99	
GTP-dependent protein kinase activity	4.11E-10	1.35E-08	-3.05	65.96	PLK3, AAK1, HUNK, CSNK1A1, NEK4, PAK4, CPNE3, PIM1, CLK3, RPS6KA2, SBK1, STK38L, TGFB1
Rho-dependent protein serine/threonine kinase activity	4.11E-10	1.35E-08	-3.04	65.81	PLK3, AAK1, HUNK, CSNK1A1, NEK4, PAK4, CPNE3, PIM1, CLK3, RPS6KA2, SBK1, STK38L, TGFB1
ribosomal protein S6 kinase activity	4.11E-10	1.35E-08	-3.04	65.72	
protein kinase C activity	4.49E-10	1.35E-08	-3.05	65.71	
histone threonine kinase activity	4.29E-10	1.35E-08	-3.04	65.63	
3-phosphoinositide-dependent protein kinase activity	4.11E-10	1.35E-08	-3.04	65.62	
eukaryotic translation initiation factor 2alpha kinase activity	4.29E-10	1.35E-08	-3.04	65.59	
DNA-dependent protein kinase activity	4.49E-10	1.35E-08	-3.04	65.49	
G-protein coupled receptor kinase activity	4.29E-10	1.35E-08	-3.03	65.43	
histone serine kinase activity	4.69E-10	1.35E-08	-3.05	65.42	
Fas-activated serine/threonine kinase activity	4.11E-10	1.35E-08	-3.03	65.4	
calcium-dependent protein serine/threonine kinase activity	4.29E-10	1.35E-08	-3.03	65.39	
AMP-activated protein kinase activity	4.69E-10	1.35E-08	-3.04	65.37	

**Supplementary Table S5** A summary of mutations, mRNA expression, copy number alterations and western blot analysis in a panel of 34 breast cell line models.

Cell line ID	Histology	ccle protein mutations	ccle cDNA mutations	ccle expression data	ccle CN data	COSMIC prot mut	COSMIC CDS mut	Sanger expression norm	sanger copy number	Western (1=defective, 0=wt)	Call used for analysis
BT20	BREAST	p.I451I	AMP, c1353T>C	10.70444	1.072			1650.961	5	0	0
BT474	BREAST			10.77893	0.0683					0	0
CAMA1	BREAST	p.G571_splice	c.1712_splice	7.893037	0.1527	p.?	c.1712-1G>A	257	2	0	0
DU4475	BREAST			7.708805	0.04			376.9675	4	0	0
HCC1143	BREAST			9.936666	-0.1906			905	3	0	0
HCC1954	BREAST			10.09732	0.4385			1622.896	6	0	0
HCC202	BREAST			9.009011	0.1866					0	0
HCC38	BREAST			8.384195	0.0624			1027.918	4	0	0
HCC70	BREAST			9.823594	0.603			1284.946	6	0	0
HMT3552	BREAST									0	0
JIMT1	BREAST			10.27569	-0.2986					0	0
MCF12A	BREAST									0	0
MCF7	BREAST			9.998439	0.0797			1413.805	3	0	0
MDAMB468	BREAST			8.032266	-0.3456			405.8228	2	0	0
SUM149	BREAST									0	0
SUM52	BREAST									0	0
T47D	BREAST			9.600242	0.0838			1474.012	3	0	0
VP229	BREAST									0	0
ZR751	BREAST			8.592579	0.9041					0	0
MCF10A	BREAST									0	0
MFM223	BREAST							1060	2		0
CAL51	BREAST			7.276337	-0.0055			996.4421	2	0	0
BT549	BREAST			4.587023	0.0331			18.20013	2	1	1
CAL120	BREAST			7.52427	-0.0577			69.7	3	1	1
HS578T	BREAST			4.442452	-0.3383			1.92	2	1	1
MDAMB134	BREAST	p.L230_P277del	c.688_832del	6.35283	-0.9568					1	1
MDAMB157	BREAST			4.102815	-0.1466			12.1	4	1	1
MDAMB231	BREAST			4.229351	-0.3833			14.50108	2	1	1
MDAMB436	BREAST			4.367926	-0.5437					1	1
MDAMB453	BREAST	p.W638*	c.1913G>A Homozygous deletion	6.867313	-0.4483	p.W638*	c.1913G>A	79.1	3	1	1
SKBR3	BREAST			4.490762	-5.279					1	1
SUM159	BREAST									1	1
SUM44	BREAST	p.F423fs*8	c.1269delT							1	1
ZR7530	BREAST	p.E243*	c.727G>T	5.859798	-0.7924	p.E243*	c.727G>T	54.3	2	1	1

**Supplementary Table S6 Synthetic lethality in E-cadherin defective breast tumour cell line models.** The difference in Z-score data of median of E-cadherin defective and median of wt. groups are shown.

**grpA = E-cadherin defective**  
**grpB = E-cadherin wild type**

target	med.grpA	med.grpB	med.grpA- med.grpB	min.grpA	min.grpB	mptest.p
CDC42BPA	-2.64178	-0.57188	-2.06990	-5.37019	-5.52563	0.002
PLK4	-2.21741	-1.17528	-1.04213	-6.17464	-5.27888	0.025
MAPKAPK3	-2.07782	-1.04596	-1.03186	-3.64434	-3.02670	0.003
GSK3A	-1.47758	-0.53077	-0.94681	-6.62653	-2.90063	0.026
ROS1	-0.93360	0.00883	-0.94242	-3.35439	-1.85628	0.04
ROCK2	-0.26440	0.58160	-0.84599	-0.70468	-0.78533	0.001
PSKH2	-0.80327	0.01788	-0.82095	-2.50469	-1.55815	0.016
RELA	-1.72711	-0.92667	-0.80044	-3.06619	-3.10870	0.051
STK16	-0.49386	0.28049	-0.77436	-1.27060	-2.34356	0.019
STK33	-0.39610	0.33121	-0.72731	-2.64870	-1.48138	0.034
EPHB3	-0.84407	-0.12037	-0.72370	-2.01908	-2.13862	0.003
PRKCA	-1.15198	-0.43134	-0.72064	-1.87986	-4.19953	0.013
DUSP21	0.04199	0.73586	-0.69388	-1.05426	-0.30027	0.009
HRI	-0.27956	0.39963	-0.67918	-1.45645	-1.25856	0.04
AAK1	-0.67495	-0.01526	-0.65970	-2.49785	-0.87453	0.008
STK23	-0.37167	0.28025	-0.65192	-0.65074	-1.72014	0.052
HIPK2	-0.09839	0.54787	-0.64626	-2.99720	-1.25732	0.028
TEC	0.14326	0.78498	-0.64172	-1.34624	0.05313	0.027
PIK3R2	-0.49107	0.12405	-0.61512	-2.67861	-0.53011	0.008
MAP3K7IP1	0.10123	0.70366	-0.60243	-0.55046	-0.71759	0.043
SNF1LK	0.05268	0.65430	-0.60162	-1.45619	-0.51718	0.037
ACVR2	0.05574	0.64468	-0.58893	-1.76541	-1.16943	0.047
TAO1	-0.18255	0.38160	-0.56415	-1.51591	-0.76176	0.017
PRKAG2	0.21464	0.75624	-0.54160	-0.89369	-0.54274	0.038
YES1	-0.33304	0.19853	-0.53157	-1.62334	-1.21128	0.032
CDKN2B	0.39549	0.92686	-0.53136	-0.68004	0.12244	0.008
ZAK	0.16561	0.68305	-0.51744	-0.80647	-1.00769	0.003
IRAK4	0.10837	0.58922	-0.48085	-1.02341	-0.99621	0.047
CAMK1G	0.32019	0.78996	-0.46977	-0.80620	-0.36789	0.035
DYRK1A	-0.24752	0.19443	-0.44195	-1.10156	-2.35672	0.026
CHEK2	0.23970	0.63783	-0.39812	-0.97307	-1.14818	0.009

**Supplementary Table S7 Synthetic lethality in E-cadherin defective mixed histology tumour cell line models.** The difference in Z-score data of median of E-cadherin defective and median of wt. groups are shown.

grpA = E-cadherin defective		grpB = E-cadherin wild type				
target	med.grpA	med.grpB	med.grpA-med.grpB	min.grpA	min.grpB	mpitest.p
TGFBFR2	-1.243274	0.138601	-1.381875	-2.997574	-2.562569	0
KSR1	-1.679058	-0.418926	-1.260132	-5.513046	-4.779142	0
STK39	-2.452338	-1.247593	-1.204745	-6.440513	-5.665470	0.007
PI4KA	-0.926708	0.164015	-1.090723	-2.970935	-2.165499	0
PTK7	-2.165658	-1.119660	-1.045998	-8.527493	-6.414201	0.034
GALK2	-1.325077	-0.406614	-0.918463	-6.318603	-3.502433	0.047
ERN1	-1.118289	-0.220308	-0.897981	-5.740674	-3.347093	0.039
DGCR14	-0.730032	0.094997	-0.825029	-4.693139	-2.202150	0.004
DGKI	-0.058328	0.750789	-0.809117	-4.511130	-1.777454	0
PDGFRA	-0.502712	0.305059	-0.807771	-2.788124	-1.922740	0.001
ADRBK1	-0.971987	-0.170078	-0.801909	-2.185112	-3.181181	0.015
PDK4	-0.660132	0.135210	-0.795342	-3.948641	-2.708407	0.008
TEX14	-0.742206	0.046444	-0.788650	-3.555046	-2.051626	0.026
NEK8	-1.920802	-1.156006	-0.764796	-4.725576	-5.894615	0.047
C8NK2B	-1.480697	-0.724058	-0.756639	-4.335044	-3.696255	0.002
HIFK2	-0.237391	0.502075	-0.739466	-2.205681	-1.609760	0.002
DGKQ	-1.654679	-0.943299	-0.711380	-11.845917	-5.255620	0.012
ACVR2B	-0.631440	0.075280	-0.706720	-3.556247	-2.754110	0.02
RELA	-2.065871	-1.381996	-0.683875	-5.379719	-3.322088	0.025
TESK1	-0.694235	-0.052710	-0.641525	-3.121612	-1.827845	0.004
STK33	-0.926057	-0.285008	-0.641049	-4.497377	-1.866116	0
RP86KA5	-0.857149	-0.232182	-0.624967	-2.728001	-2.498135	0.042
DYRK1B	0.056933	0.675336	-0.618404	-1.190798	-1.486860	0.003
MARK3	-1.465187	-0.851111	-0.614076	-7.416331	-3.089232	0.008
TSSK3	-1.078410	-0.474033	-0.604377	-3.631533	-2.452670	0.007
PRKDC	-0.883021	-0.279376	-0.603645	-4.243728	-2.543423	0.013
MAP2K1	-0.150412	0.451418	-0.601830	-2.007355	-1.758468	0.008
PAP8S2	-0.116934	0.482086	-0.599020	-2.160100	-1.224303	0.011
SYK	-1.216762	-0.621014	-0.595747	-5.717837	-3.609074	0.018
DMPK	-0.846393	-0.303005	-0.543388	-2.510067	-2.156521	0.03
PIK3R5	-0.692260	-0.149402	-0.542858	-3.593491	-2.271940	0.05
PFKFB4	-0.431352	0.101159	-0.532512	-2.910369	-2.006308	0.029
ABL2	-0.291865	0.222316	-0.514181	-3.027379	-2.202006	0.032
PRKCH	-1.231438	-0.734734	-0.496704	-7.005438	-4.782421	0.01
ROB1	-0.865455	-0.369936	-0.495519	-4.880350	-1.922964	0.018
INSR	-0.841129	-0.359606	-0.481523	-5.000156	-2.754405	0.017
SGK4S4	0.000530	0.462871	-0.462341	-1.779279	-2.218415	0.047
RP86KL1	-1.100377	-0.641046	-0.459330	-5.578052	-4.386062	0.023
RNASEL	0.001219	0.446264	-0.445044	-1.725733	-0.762448	0.038
SPHK1	-0.662750	-0.229248	-0.433501	-2.856694	-3.705312	0.024
CDKL2	-0.553056	-0.149727	-0.403329	-3.325781	-2.094427	0.023
IKBKAP	0.228990	0.631039	-0.402049	-1.438710	-1.067847	0.047
CDK5	-0.193360	0.205544	-0.398904	-2.385988	-1.410798	0.031
PANK2	-0.075430	0.320886	-0.396316	-2.204769	-0.351271	0.015
ATR	-0.824295	-0.434661	-0.389635	-3.210269	-2.610254	0.054
CKS1B	0.140897	0.524611	-0.383714	-1.652039	-1.220660	0.018
ITPKC	0.154354	0.521787	-0.367433	-1.623605	-0.680141	0.034
EIF2AK3	0.543862	0.321654	0.222208	-1.818900	-2.604610	0.024
RIPK3	0.430480	0.186146	0.244334	-0.895032	-1.853933	0.053
PAK5	0.569676	0.260049	0.309627	-0.763488	-2.366362	0.029
MAST1	-0.149406	-0.475622	0.326215	-2.242699	-3.619800	0.017
MAK	0.177387	-0.152060	0.329447	-0.873301	-2.391710	0.04
BMX	0.734513	0.402102	0.332411	-1.213764	-1.243430	0.044
GK2	0.584713	0.251732	0.332980	-0.651581	-1.316440	0.046
MLTK	0.847545	0.489719	0.357826	-1.490000	-1.173233	0.019
CAMKK1	0.873687	0.514153	0.359534	-0.218984	-6.484650	0.05
FXN	0.824474	0.460452	0.364022	-0.107796	-1.000000	0.041
STK10	0.225717	-0.140088	0.365806	-1.385076	-2.225885	0.023
DLG2	0.899179	0.526510	0.372669	-0.990287	-1.250076	0.031
RYK	0.841602	0.445273	0.396329	-0.961652	-0.922224	0.011
CHKB	0.708232	0.309908	0.398324	-0.826940	-1.492716	0.011
TLK2	0.641715	0.242506	0.399208	-0.463055	-1.942379	0.046
XRCC6BP1	0.408797	-0.012229	0.421026	-1.716343	-1.373838	0.038
ITPKB	0.010137	-0.418758	0.428895	-0.967109	-2.516106	0.029
COMMD3	-0.423298	-0.872774	0.449476	-3.024309	-4.354284	0.038
GRK1	0.636621	0.172336	0.464285	-1.054254	-1.010654	0.01
CAMK2G	0.520000	0.029266	0.490734	-2.765941	-6.807591	0.001
PIK3CD	0.445943	-0.047794	0.493736	-2.420122	-2.552814	0.004
PI4K2A	0.613821	0.112399	0.501422	-1.113786	-2.302300	0.012
CDKL5	0.488426	-0.020762	0.509188	-2.401872	-5.030140	0.029
RFK	0.562565	0.051000	0.511565	-11.218788	-3.239306	0.012
PAK3	-0.079431	-0.591682	0.512251	-2.787965	-1.583351	0.037
BLK	0.744972	0.229039	0.515934	-1.095004	-1.667110	0.019
XYLB	0.485913	-0.049250	0.535163	-0.814253	-1.881183	0.01
MAP4K2	-0.122674	-0.686796	0.564122	-6.431871	-3.729617	0.019
SCYL3	-0.212622	-0.792468	0.579846	-1.852586	-3.104754	0.005
PRKCD	0.020193	-0.569268	0.589461	-1.982389	-3.635411	0.026
PRKCE	0.175195	-0.429886	0.605081	-2.068204	-2.601848	0.02
FLT1	0.541576	-0.065291	0.606867	-0.687280	-1.980176	0.012
PIK3CA	0.632857	0.009453	0.623404	-2.095434	-3.346469	0.041
PRKACB	0.416099	-0.283455	0.698555	-0.786927	-4.714100	0
NRBP1	-0.154554	-0.867996	0.713442	-6.646961	-3.689409	0.014
MAP3K2	0.997364	0.235848	0.761516	-9.240182	-4.313790	0



**Supplementary Table S8 Individual area under the curve (AUC) and surviving fraction 50 (SF<sub>50</sub>) values of foretinib or crizotinib in 12 breast tumour cell lines.**

Cell line name	E-cadherin Defective/WT	IC50		AUC	
		foretinib $\mu$ M	crizotinib $\mu$ M	foretinib	crizotinib
SKBR3	Defective	0.013833975	0.016801266	1.088	1.3
SUM44	Defective	0.042514101	0.032861168	1.112	1.162
CAL120	Defective	0.228411249	0.95616975	1.574	2.101
BT549	Defective	0.251779867	0.995070841	1.492	1.939
MDAMB157	Defective	0.828827209	2.943459062	2.08	2.532
MDAMB231	Defective	0.918108483	1.623166235	2.15	2.411
MFM223	WT	0.742138585	2.353282147	1.941	2.432
T47D	WT	1.010231718	1.010231718	2.04	2.04
SUM149	WT	1.103171415	3.184439483	2.674	2.563
MCF7	WT	2.309787358	2.369119678	2.794	2.848
MCF12A	WT	2.461943036	3.460987255	2.678	2.904
MCF10A	WT	2.682402839	3.772671576	2.673	2.981

Supplementary Table S9 ROS1 genomic alterations in breast tumour cell lines.

Cell line name	E-cadherin status	ROS1 fusions data by Klijn et al 2015	CCLE/COSMIC ROS1 amplifications/deletions	COSMIC ROS1 mutations	CCLE ROS1 mutations
BT20_BREAST	E-cadherin wild type	not detected	AMP	not detected	p.D618E
BT474_BREAST	E-cadherin wild type	not detected	not detected	p.V1916L	p.V1916L
BT549_BREAST	E-cadherin defective	not detected	not detected	not detected	not detected
CAL120_BREAST	E-cadherin defective	not detected	not detected	not detected	not detected
CAL51_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
CAMA1_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
DU4475_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
HCC1143_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
HCC1954_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
HCC202_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
HCC38_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
HCC70_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
HMT3552_BREAST	E-cadherin wild type	not assessed	not detected	not detected	not detected
HS578T_BREAST	E-cadherin defective	not detected	not detected	not detected	not detected
JIMT1_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
MCF10A_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
MCF12A_BREAST	E-cadherin wild type	not assessed	not detected	not detected	not detected
MCF7_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
MDAMB134VI_BREAST	E-cadherin defective	not detected	not detected	not detected	not detected
MDAMB157_BREAST	E-cadherin defective	not detected	not detected	not detected	not detected
MDAMB231_BREAST	E-cadherin defective	not detected	not detected	not detected	not detected
MDAMB436_BREAST	E-cadherin defective	not detected	not detected	not detected	not detected
MDAMB453_BREAST	E-cadherin defective	not detected	not detected	p.V1971V	not detected
MDAMB468_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
MFM223_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
SKBR3_BREAST	E-cadherin defective	not detected	not detected	not detected	not detected
SUM 149_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
SUM 159_BREAST	E-cadherin defective	not detected	not detected	not detected	not detected
SUM44_BREAST	E-cadherin defective	not assessed	not detected	not detected	not detected
SUM S2_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
T47D_BREAST	E-cadherin wild type	not detected	not detected	not detected	not detected
VP229_BREAST	E-cadherin wild type	not assessed	not detected	not detected	not detected
ZR751_BREAST	E-cadherin wild type	not detected	HOMDEL	not detected	not detected
ZR7530_BREAST	E-cadherin defective	not detected	not detected	not detected	p.K2099N
HCC78	Control cell line harbouring a ROS1 fusion	SLC34A2-ROS1			

**Supplementary Table S10 Small molecule inhibitor library.** List of 80 compounds and their molecular targets.

Drugs	Target	Company	Clinical Stage
4-OH-TAMOXIFEN	ER	Off patent generic drug	Licensed
5-FU	DNA	Off patent generic drug	Licensed
6-THIOGUANINE	DNA	GSK	Licensed
ABIRATERONE	CYP17A1	J and J	Licensed
BIBW2992	EGFR/ERBB2	Boehringer Ingelheim	Licensed
BLEOMYCINSULFATE	DNA	BMS	Licensed
CABOZANTINIB	cMET,VEGFR	Exelixis	Licensed
CAMPTOTHECIN	TOPOIpolson	Off patent generic drug	Licensed
CARBOPLATIN	DNA	BMS	Licensed
CELECOXIB	COX2	Pfizer	Licensed
DASATINIB	SRC	BMS	Licensed
DECITABINE	DNA	Janssen-Cilag	Licensed
DOXORUBICIN.HCL	DNA	Off patent generic drug	Licensed
ERLOTINIB	EGFR	Genentech	Licensed
ETOPOSIDE	Topoisomerase	Off patent generic drug	Licensed
EVEROLIMUS	mTOR	Novartis	Licensed
GDC-0449	Hedgehog	Genentech	Licensed
GEFITINIB	EGFR	AZ	Licensed
GEMCITABINE.HCL	DNA	Eli Lilly	Licensed
IMATINIBMESYLATE	ABL	Novartis	Licensed
MDV-3100	AR	Medivation	Licensed
METHOTREXATE	DHFR	Off patent generic drug	Licensed
nilotinib	ABL	Novartis	Licensed
olaparib	PARP1/2	AZ	Licensed
paclitaxel	Microtubules	Off patent generic drug	Licensed
PLX-4720	BRAF	Plexicon	Licensed
sorafenib	VEGF, PDGFR	Bayer	Licensed
sunitinib	RTKs	Pfizer	Licensed
temozolomide	DNA	Schering	Licensed
vinorelbine	Microtubules	Off patent generic drug	Licensed
voronostat	HDACs	Merck	Licensed
MK-1175	WEE1	Merck	Phase 1
MLN-4924	NAE	Millenium	Phase 1
Nutlin3	p53	Roche	Phase 1
PF-00477736	CHEK1	Pfizer	Phase 1
PF-03758309	PAK4	Pfizer	Phase 1
PF-04929113	HSP	Pfizer	Phase 1
SAR-20106	CHKs	ICR	Phase 1
BI-2536	PLK1	Boehringer Ingelheim	Phase 2
17-AAG	HSP90	BMS	Phase 2
2-METHOXYESTRADIOL	ER	Entremed	Phase 2
ABT-737	BCL2	Abbott	Phase 2
AZ4547	FGFRs	AZ	Phase 2
BEZ-235	mTOR/PI3K	Novartis	Phase 2
BMN-673	PARP1/2	Blomarin	Phase 2
BMS-911543	JAK2	BMS	Phase 2
CANERTINIB	panERBB	Pfizer	Phase 2
FLAVOPIRIDOL	CDKs	Sanofi	Phase 2
FORETINIB	cMET, VEGFR	Exelixis/GSK	Phase 2
LESTAURTINIB	JAK	Cephalon	Phase 2
MK0752	Gamma Secretase	Merck	Phase 2
MK2206	AKT	Merck	Phase 2
PF-00299804	EGFR	Pfizer	Phase 2
PF-03814735	AURK	Pfizer	Phase 2
AG-14699	PARP1/2	Pfizer/Clovis	Phase 3
CRIZOTINIB	ALK,ROS1	Pfizer	Phase 3
LAPATINIB	ERBB	GSK	Phase 3
LENVATINIB	VEGF	Elsal	Phase 3
OSI-906	IGF1R	OSI	Phase 3
PD-0332991	CDK4/6	Pfizer	Phase 3
PF-02341066	MET/ALK	Pfizer	Phase 3
PF-04691502	PI3K	Pfizer	Phase 3
PF-332991	CDK4/6	Pfizer	Phase 3
Sapacitabine	DNA	Medivation	Phase 3
ICR_1783	Tankyrase	ICR	Pre-clinical
ICR_1913	Tankyrase	ICR	Pre-clinical
GSK-2334470A	PDK1	GSK	Pre-clinical
GSK1904529A	IGF1R	GSK	Pre-clinical
GSK2194069A	FASN	GSK	Pre-clinical
KU0057788	DNAPKCs	AZ	Pre-clinical
KU60019	ATM	AZ	Pre-clinical
M8C2358705A	DNA-PKl	Merck	Pre-clinical
PD-184352	MEK	Pfizer	Pre-clinical
PD173074	FGFRs	Pfizer	Pre-clinical
resveratrol	SIRT6	Off patent	Pre-clinical
RO-3306	CDKs	Off patent	Pre-clinical
salinomycin	n/k	Off patent	Pre-clinical
Sotrastaurin/AEB071	PKC	Novartis	Pre-clinical
XAV-939	Tankyrase	Novartis	Pre-clinical
YM155	Survivin	positive control for screen	Pre-clinical

**Supplementary Table S11 Summary of antibodies used in this study.** This table lists the antibodies used, supplier and antibody dilution.

<b>Antibody</b>	<b>Supplier</b>	<b>Product Number</b>	<b>Dilution</b>
E-cadherin	Cell signalling	3195	1/1000
ACTIN	Santa Cruz	sc-1616	1/1000
EZRIN	Cell signalling	3145	1/1000
$\alpha$ Tubulin	Santa Cruz	sc-5286	1/1000
Phalloidin	ThermoFisher Scientific	A12379	1/500
MRCK $\alpha$	GeneTex	GTX102598	1/1000
pH2AX	Millipore	05-636	1/1000
MKLP1	Santa Cruz	SC-857	1/200
Catenin $\delta$ -1 Antibody	Cell signalling	4989	1/1000
Phospho-Catenin $\delta$ -1 (Tyr228)	Cell signalling	2911	1/1000
Phospho-Catenin $\delta$ -1 (Ser320)	Cell signalling	8016	1/1000
PARP1	Santa Cruz	sc-8007	1/200
p21	Cell signalling	2947	1/1000
anti-FLAG	Sigma-Aldrich	F3165	1/1000
ROS1	Cell signalling	3287	1/1000
anti-p120	BD Biosciences	610134	1/500
MET	Cell signalling	8198	1/1000
ALK	Cell signalling	3633	1/1000
Akt	Cell signalling	9272	1/1000
Phospho-Akt (Ser473)	Cell signalling	4080	1/1000
Phospho-p44/42 MAPK	Cell signalling	4370	1/1000
p44/42 MAPK	Cell signalling	4895	1/1000
Phospho-ROS1 (Tyr2274)	Cell signalling	3078	1/1000