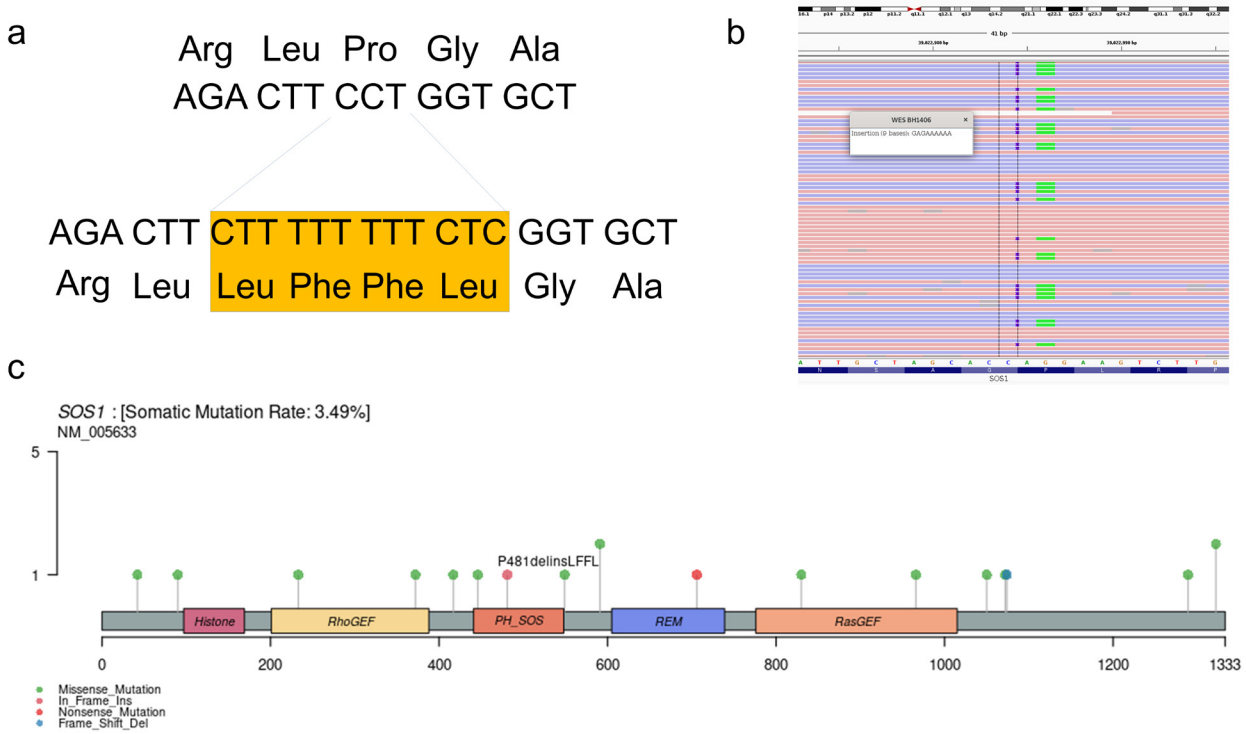

Figure S1 Mutation data. (A) For the activating SOS1 mutation in BH1406, one triplet of the genome was substituted by a four triplet insert of the four amino acids as shown. (B) This picture shows the different DNA sequencing runs and in green the four triplet insert coding the activating SOS1 mutation. (C) Depicts the whole genomic sequence of the SOS1 gene and its different domains. The markers indicate the site of distinct mutations and the nature of the mutations is colour coded.

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Table S1 Summary of all gene variants detected in the SOS1 gene so far. The variants are characterized by a unique ensemble number (Transcript), the type of change in DNA (DNA change), the type of change in proteins (Protein change), and the Variant allele frequency (VAF). Links to VarSome are included for all genes (Varsome annotation). The gene variants are further classified by the ACMG classification

Gene name	Transcript	DNA change	Protein change	VAF	Varsome annotation	ACMG classification
TENT5C	ENST00000369448.4	c.895G>A	p.Glu299Lys	31.20%	http://varsome.com/variant/hg38/chr1-117623763-G-A	Benign
PDE4DIP	ENST00000695795.1	c.6163C>A	p.Gln2055Lys	37.70%	http://varsome.com/variant/hg38/chr1-149021033-C-A	Benign
NTRK1	ENST00000497019.7	c.818C>T	p.Pro273Leu	31.30%	http://varsome.com/variant/hg38/chr1-156873895-C-T	Likely benign
FCGR2B	ENST00000358671.10	c.214del	p.Arg72GlyfsTer55	33.50%	http://varsome.com/variant/hg38/chr1-161671470-GC-G	Likely pathogenic
DNMT3A	ENST00000321117.10	c.760G>A	p.Ala254Thr	32.70%	http://varsome.com/variant/hg38/chr2-25248132-C-T	Uncertain significance
AFF3	ENST00000672756.2	c.1781C>T	p.Thr594Ile	65.40%	http://varsome.com/variant/hg38/chr2-99593880-G-A	Likely benign
PTPN13	ENST00000411767.7	c.2767C>G	p.Arg923Gly	67.60%	http://varsome.com/variant/hg38/chr4-86750586-C-G	Uncertain significance
FBXW7	ENST00000703554.1	c.511G>A	p.Val171Ile	33.30%	http://varsome.com/variant/hg38/chr4-152382357-C-T	Benign
PDGFRB	ENST00000261799.9	c.1033C>T	p.Pro345Ser	99.70%	http://varsome.com/variant/hg38/chr5-150132844-G-A	Benign
SND1	ENST00000354725.8	c.200A>C	p.Gln67Pro	49.20%	http://varsome.com/variant/hg38/chr7-127686734-A-C	Benign
KMT2C	ENST00000262189.11	c.3955G>C	p.Asp1319His	46.90%	http://varsome.com/variant/hg38/chr7-152205112-C-G	Benign
PDCD1LG2	ENST00000397747.5	c.235C>G	p.Gln79Glu	99.60%	http://varsome.com/variant/hg38/chr9-5534924-C-G	Benign
WNK2	ENST00000427277.7	c.4064C>T	p.Ser1355Leu	62.40%	http://varsome.com/variant/hg38/chr9-93288818-C-T	Benign
LARP4B	ENST00000316157.8	c.1158T>A	p.Asn386Lys	44.30%	http://varsome.com/variant/hg38/chr10-825838-A-T	Uncertain significance
FAT3	ENST00000525166.6	c.1006A>T	p.Ser336Cys	99.80%	http://varsome.com/variant/hg38/chr11-92353118-A-T	Likely benign
FAT3	ENST00000525166.6	c.1550T>C	p.Leu517Ser	99.80%	http://varsome.com/variant/hg38/chr11-92353662-T-C	Benign
ATM	ENST00000675843.1	c.6860G>C	p.Gly2287Ala	41.20%	http://varsome.com/variant/hg38/chr11-108326110-G-C	Likely benign
ETNK1	ENST00000672951.1	c.17_30del	p.Pro6ArgfsTer140	59.80%	http://varsome.com/variant/hg38/chr12-22625177-GCCCGCGGTCCAGCT-G	Uncertain significance
PPFIBP1	ENST00000228425.11	c.1235C>G	p.Pro412Arg	29.70%	http://varsome.com/variant/hg38/chr12-27671519-C-G	Benign
ARID2	ENST00000334344.11	c.2758C>T	p.Gln920Ter	99.80%	http://varsome.com/variant/hg38/chr12-45850881-C-T	Pathogenic
NACA	ENST00000549855.5	c.-192C>T		30.60%	http://varsome.com/variant/hg38/chr12-56725452-G-A	Benign
NCOR2	ENST00000405201.6	c.5509_5517dup	p.Ser1837_Gly1839dup	99.70%	http://varsome.com/variant/hg38/chr12-124340175-C-CGCCGCTGCT	Benign
NCOR2	ENST00000405201.6	c.1529_1531dup	p.Gln510dup	66%	http://varsome.com/variant/hg38/chr12-124402512-G-GGCT	Benign
NBEA	ENST00000689568.1	n.213-7T>G,		98.70%	http://varsome.com/variant/hg38/chr13-35474943-T-G	Benign
BLM	ENST00000355112.8	c.2119C>T	p.Pro707Ser	30.50%	http://varsome.com/variant/hg38/chr15-90765340-C-T	Benign
POLR2A	ENST00000674977.2	c.5511_5512del	p.His1837GlnfsTer76	99.80%	http://varsome.com/variant/hg38/chr17-7513774-CCA-C	Benign
TP53	ENST00000269305.9	c.832C>T	p.Pro278Ser	99.80%	http://varsome.com/variant/hg38/chr17-7673788-G-A	Pathogenic
STK11	ENST00000326873.12	c.646_658del	p.Pro217ArgfsTer66	99.70%	http://varsome.com/variant/hg38/chr19-1220627-GCTCCCCGGCTTTC-G	Likely pathogenic
CD209	ENST00000315599.12	c.995G>T	p.Gly332Val	99.70%	http://varsome.com/variant/hg38/chr19-7744125-C-A	Likely benign
KEAP1	ENST00000171111.10	c.523del	p.Leu175TrpfsTer55	99.90%	http://varsome.com/variant/hg38/chr19-10499510-AG-A	Uncertain significance
ZNF429	ENST00000358491.9	c.1168A>G	p.Ile390Val	99.30%	http://varsome.com/variant/hg38/chr19-21537221-A-G	Benign
CEP89	ENST00000305768.10	c.1661T>C	p.Leu554Ser	99.60%	http://varsome.com/variant/hg38/chr19-32901317-A-G	Benign
SIRPA	ENST00000358771.5	c.394_395inv	p.Val132Thr	32.40%	http://varsome.com/variant/hg38/chr20-1915413-GT-AC	Likely benign
ASXL1	ENST00000375687.10	c.3973C>T	p.Leu1325Phe	48.70%	http://varsome.com/variant/hg38/chr20-32436685-C-T	Benign
BCR	ENST00000305877.13	c.3275_3278dup	p.Val1094ArgfsTer17	26%	http://varsome.com/variant/hg38/chr22-23311788-T-TCCGG	Likely pathogenic
BCR	ENST00000305877.13	c.3316G>A	p.Asp1106Asn	20.90%	http://varsome.com/variant/hg38/chr22-23311830-G-A	Likely benign
FAM47C	ENST00000358047.5	c.1888C>A	p.Leu630Ile	93.40%	http://varsome.com/variant/hg38/chrX-37010298-C-A	Benign
WAS	ENST00000376701.5	c.995T>C	p.Val332Ala	99.60%	http://varsome.com/variant/hg38/chrX-48688723-T-C	Benign
ATRX	ENST00000373344.11	c.2785G>C	p.Glu929Gln	99.60%	http://varsome.com/variant/hg38/chrX-77682471-C-G	Benign
IRS4	ENST00000372129.4	c.1232_1233delinsAT	p.Arg411His	99.60%	http://varsome.com/variant/hg38/chrX-108735112-TC-AT	Uncertain significance
FLNA	ENST00000369850.10	c.1882G>A	p.Asp628Asn	99.80%	http://varsome.com/variant/hg38/chrX-154364666-C-T	Likely benign

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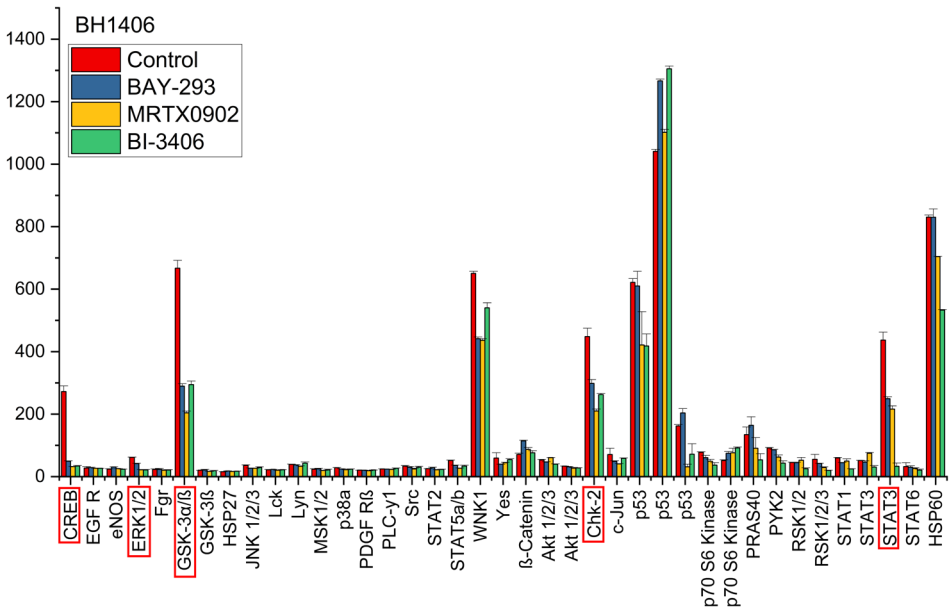

Figure S2 Comparison of the relative phosphorylation of proteins in BH1406 and BH1406 treated with 0.5 μM BAY-293, 0.5 μM MRTX0902 and 0.2 μM BI-3406. Proteins in red brackets were chosen for figure 4 in the manuscript. Data represent mean values ± SD. Abbreviations in the figure are as follows: cAMP-response Element Binding protein (CREB), Epidermal Growth Factor Receptor (EGF R), Nitric Oxide Synthase 3 (eNOS), Extracellular signal-Regulated Kinases 1/2 (ERK 1/2), FGR Proto-Oncogene, Src Family Tyrosine Kinase (Fgr), Glycogen Synthase Kinase 3 Alpha/ Beta (GSK-3a/β), Glycogen Synthase Kinase 3 Beta (GSK-3β), Heat Shock Protein Family B (Small) Member 1 (HSP27), Mitogen-Activated Protein Kinase 8/9/10 (JNK 1/2/3), LCK Proto-Oncogene Src Family Tyrosine Kinase (Lck), LYN Proto-Oncogene Src Family Tyrosine Kinase (Lyn), Ribosomal Protein S6 Kinase A4/A5 (MSK1/2), Mitogen-Activated Protein Kinase 14 (p38a), Platelet Derived Growth Factor Subunit B (PDGF Rβ), Phospholipase C Gamma 1 (PLC-γ1), SRC Proto-Oncogene Non-Receptor Tyrosine Kinas (Src), Signal Transducer And Activator Of Transcription 2 (STAT2), Signal Transducer And Activator Of Transcription 5A/B (STAT5a/b) WNK Lysine Deficient Protein Kinase 1 (WNK1), YES Proto-Oncogene 1 (Yes), AKT Serine/Threonine Kinase 1, 2 and 3 (AKT 1/2/3-T308,S473), Checkpoint Kinase 2 (Chk-2), (c-Jun), (p53), Ribosomal Protein S6 Kinase B1 (p70 S6 Kinase-T389, T421/S424), AKT1 Substrate 1 (PRAS40), Protein Tyrosine Kinase 2 Beta (PYK2), Ribosomal Protein S6 Kinase A1, A2 (RSK1/2), Ribosomal Protein S6 Kinase A1, A2, A3 (RSK1/2/3), Signal Transducer And Activator Of Transcription 1 (STAT 1), Signal Transducer And Activator Of Transcription 3 (STAT3 Y705) and Signal Transducer And Activator Of Transcription 3 (STAT3 S727), Signal Transducer And Activator Of Transcription 6 (STAT6) and Heat Shock Protein Family D Member 1 (HSP60).

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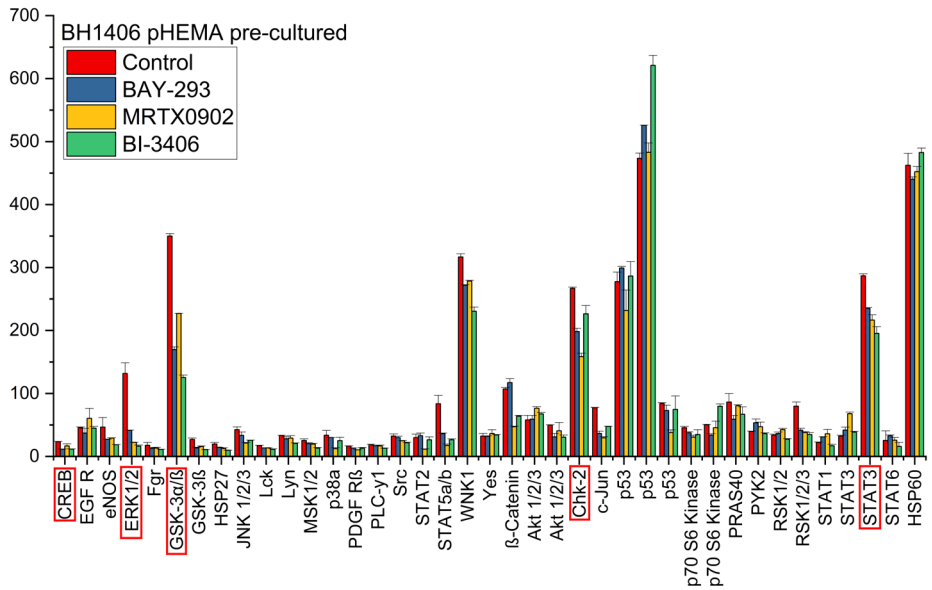

Figure S3 Comparison of the relative phosphorylation of proteins in pHEMA pre-cultured BH1406 and treatment with 0.5 µM BAY-293, 0.5 µM MRTX0902 and 0.2 µM BI-3406. Proteins in red brackets were chosen for figure 4 in the manuscript. Data represent mean values ± SD. Abbreviations in the figure are as follows: cAMP-response Element Binding protein (CREB), Epidermal Growth Factor Receptor (EGF R), Nitric Oxide Synthase 3 (eNOS), Extracellular signal-Regulated Kinases 1/2 (ERK 1/2), FGR Proto-Oncogene, Src Family Tyrosine Kinase (Fgr), Glycogen Synthase Kinase 3 Alpha/ Beta (GSK-3a/β), Glycogen Synthase Kinase 3 Beta (GSK-3β), Heat Shock Protein Family B (Small) Member 1 (HSP27), Mitogen-Activated Protein Kinase 8/9/10 (JNK 1/2/3), LCK Proto-Oncogene Src Family Tyrosine Kinase (Lck), LYN Proto-Oncogene Src Family Tyrosine Kinase (Lyn), Ribosomal Protein S6 Kinase A4/A5 (MSK1/2), Mitogen-Activated Protein Kinase 14 (p38a), Platelet Derived Growth Factor Subunit B (PDGF Rβ), Phospholipase C Gamma 1 (PLC-γ1), SRC Proto-Oncogene Non-Receptor Tyrosine Kinas (Src), Signal Transducer And Activator Of Transcription 2 (STAT2), Signal Transducer And Activator Of Transcription 5A/B (STAT5a/b) WNK Lysine Deficient Protein Kinase 1 (WNK1), YES Proto-Oncogene 1 (Yes), AKT Serine/Threonine Kinase 1, 2 and 3 (AKT 1/2/3-T308,S473), Checkpoint Kinase 2 (Chk-2), (c-Jun), (p53), Ribosomal Protein S6 Kinase B1 (p70 S6 Kinase-T389, T421/S424), AKT1 Substrate 1 (PRAS40), Protein Tyrosine Kinase 2 Beta (PYK2), Ribosomal Protein S6 Kinase A1, A2 (RSK1/2), Ribosomal Protein S6 Kinase A1, A2, A3 (RSK1/2/3), Signal Transducer And Activator Of Transcription 1 (STAT 1), Signal Transducer And Activator Of Transcription 3 (STAT3 Y705) and Signal Transducer And Activator Of Transcription 3 (STAT3 S727), Signal Transducer And Activator Of Transcription 6 (STAT6) and Heat Shock Protein Family D Member 1 (HSP60).

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