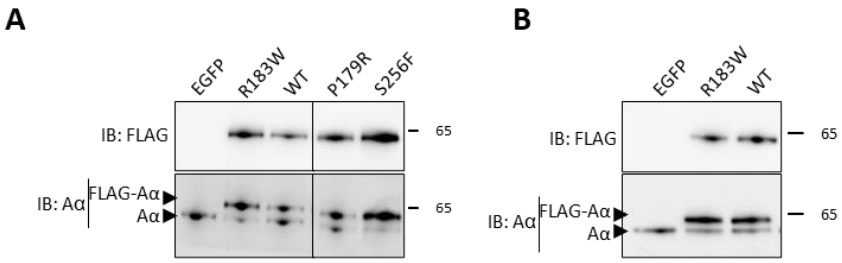
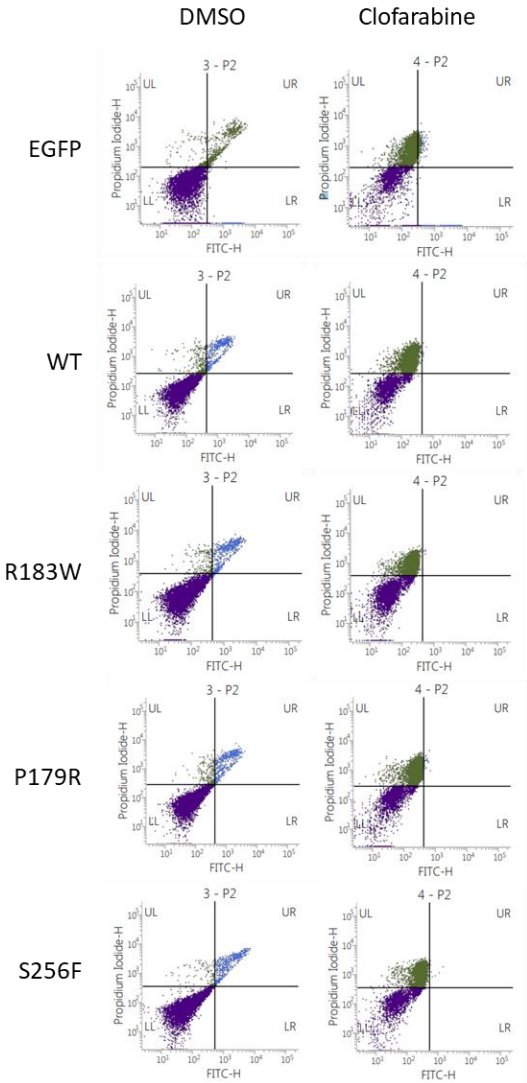
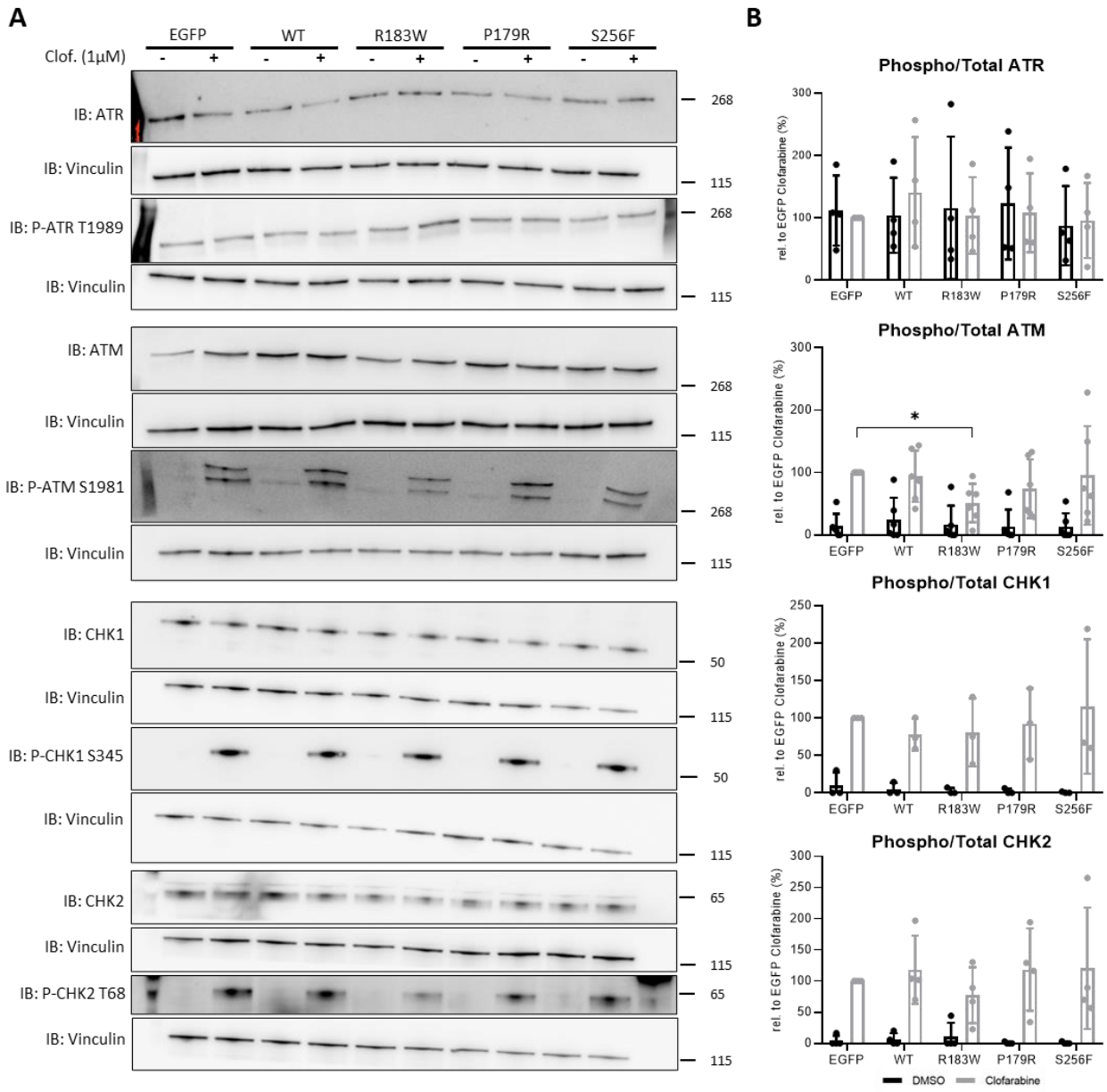


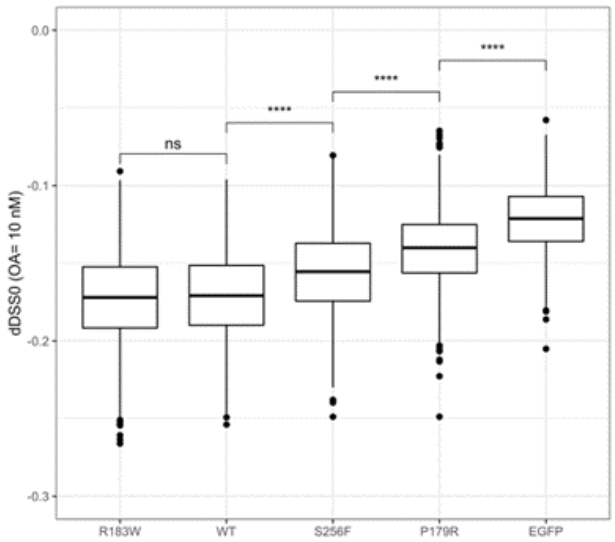
Supplementary figure S1: Ectopic expression of FLAG-tagged EGFP, WT Aα or mutant Aα (p.P179R, p.R183W and p.S256F) in ARK-4 and ARK-1 cells. (A) Representative immunoblots (IB) of ARK-4 cells expressing FLAG-tagged EGFP, WT Aα or mutant Aα. The upper band in the Aα immunoblot represents the FLAG-tagged Aα while the lower band represents the endogenous Aα, as indicated with the arrowheads. **(B)** Representative immunoblots of ARK-1 cells expressing FLAG-tagged EGFP, WT Aα or p.R183W Aα. The upper band in the Aα immunoblot represents the FLAG-tagged Aα while the lower band represents the endogenous Aα, as indicated with the arrowheads.



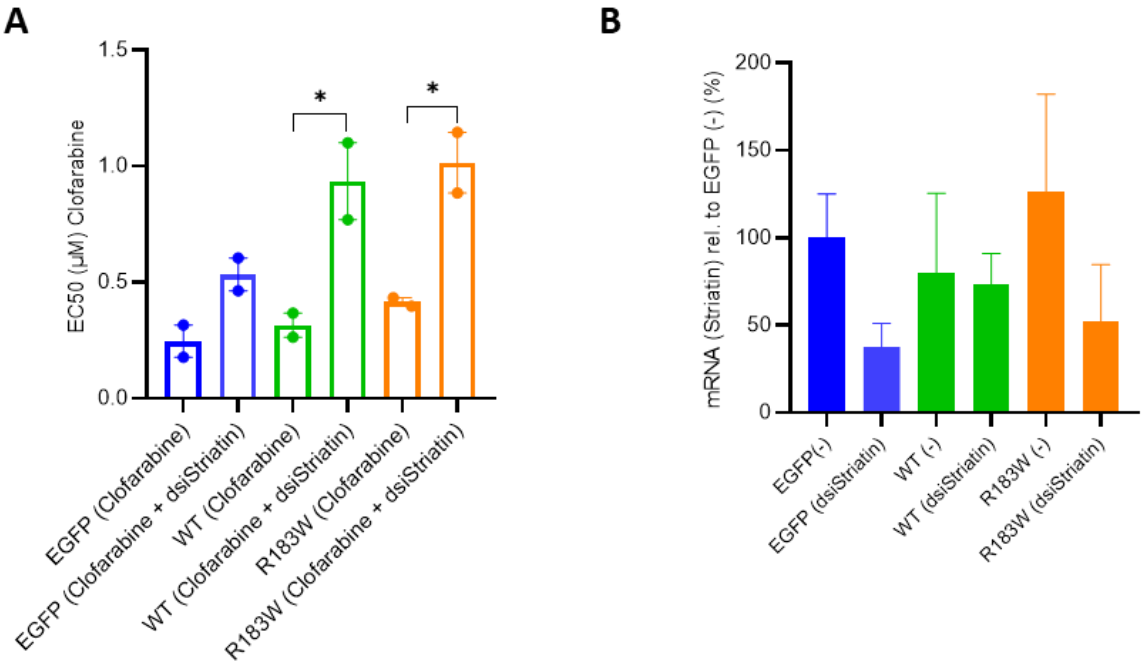
Supplementary figure S2: p.R183W mutant Aα expressing USC cells undergo less apoptotic cell death after clofarabine treatment. Representative Annexin V (FITC conjugated)/Propidium Iodide (PI) flow cytometry plots for ARK-4 cells expressing EGFP, mutant Aα (p.P179R, p.R183W and p.S256F) or WT Aα, after treatment with 250nM clofarabine for 72 hours.



Supplementary figure S3: p.R183W Aα expressing USC cells show reduced ATM signaling activation after treatment with clofarabine for 3 hours. (A) Representative immunoblots (IB) for checkpoint signaling kinases ATR/ATM and CHK1/2 after treatment with 1µM clofarabine or DMSO for 3 hours. Vinculin was used as loading control. **(B)** Quantification of immunoblots in (A) relative to clofarabine-treated EGFP cells. Data are represented as mean ± SD, n≥3. *P* values were determined by One-Way ANOVA compared to clofarabine-treated EGFP cells with Dunnett's correction for multiple comparisons, **p*<0.05.



Supplementary figure S4: p.R183W Aα expressing ARK-4 cells have the highest reduction in dDSS0 after combination treatment of clofarabine with okadaic acid (OA). The differential drug sensitivity score (dDSS0) is calculated by subtracting the control DSS0 (OA = 0nM) from the DSS0 (OA = 10nM). DSS0 is calculated as AUC (Area under the curve)$_{\text{min~max compound concentration}}$ − BOTTOM$_{(\text{max compound concentration} - 0)}$. The boxplots represent the interquartile range of dDSS0 from 1000 Monte Carlo simulations. The Wilcoxon test is used to examine the statistical difference in dDSS0 between cell lines. ****p<0.0001, ns=not significant.



Supplementary figure S5: Knockdown of Striatin increases resistance of the ARK-4 cells to clofarabine. (A) EC_{50} (µM) values from 72 hours clofarabine treatment with or without knockdown (KD) of Striatin via dicer-substrate small-interferingRNA (dsiRNA) as measured by MTT assay. Data are represented as mean ± SEM, n=2. **(B)** mRNA levels as measured by qRT-PCR, confirming knockdown of striatin in EGFP and p.R183W Aα expressing ARK-4 cells at time of MTT assay (A).

Supplementary Table S1: Antibody list

Antibody	Company	Product number
Cleaved PARP (Asp214) (D64E10) XP ®	Cell Signaling	5625S
Cleaved caspase-3 (Asp175)	Cell Signaling	9661S
Total ATR	Cell Signaling	2790S
Phospho (T1989) ATR	Cell Signaling	2853S
Total ATM	Cell Signaling	2873S
Phospho (S1981) ATM	Cell Signaling	13050S
Total CHK1	Cell Signaling	2360S
Phospho (S345) CHK1	Cell Signaling	2348S
Total CHK2	Cell Signaling	6334S
Phospho (T68) CHK2	Cell Signaling	2197S
Total dCK	Cell Signaling	10478S
Phospho (Ser74) dCK	Cell Signaling	40371S
Vinculin	Sigma	V9131
B56δ	Abcam	Ab188323
Aα (C5.3D10)	Generous gift of Prof. S. Dilworth	/
FLAG	Sigma	F1804
Anti-mouse (secondary antibody)	Dako	P0260
Anti-rabbit (secondary antibody)	Cell Signaling	7074S