Table S1. List of cancer-associated $A_{2A}AR$ mutations investigated in this study.

Mutation	Affected cases per cancer type across the GDC	Cancer type
$A15S^{1.41}$	1/987	Breast invasive carcinoma
$F70L^{ECL1}$	1/533	Uterine Corpus Endometrial Carcinoma
$I92M^{3.40}$	1/1060	Lung adenocarcinoma
$L95F^{3.43}$	1/1060	Lung squamous cell carcinoma
$S132L^{4.53}$	3/533 1/399	Uterine Corpus Endometrial Carcinoma (3 cases) Colon adenocarcinoma (1 case)
$A165V^{ECL2}$	1/399	Colon adenocarcinoma
$I251T^{6.53}$	1/399	Colon adenocarcinoma
$F257L^{6.59}$	1/533	Uterine Corpus Endometrial Carcinoma
$A265S^{ECL3}$	1/987	Breast invasive carcinoma
$A265V^{ECL3}$	1/987	Breast invasive carcinoma
$*A265T^{ECL3}$	1/1060	Lung squamous cell carcinoma
$V275A^{7.40}$	1/533	Uterine Corpus Endometrial Carcinoma
$H278N^{7.43}$	1/399	Colon adenocarcinoma
$*S281L^{7.46}$	1/533 1/79	Uterine Corpus Endometrial Carcinoma (1 case) Rectum adenocarcinoma (1 case)
$P285L^{7.50}$	1/1060	Lung squamous cell carcinoma

Mutations are shown in the numbering of $A_{2A}AR$ amino acid sequence as well as the Ballesteros and Weinstein number in superscript.
* $A_{2A}AR$ Mutations that were also identified as natural variants.

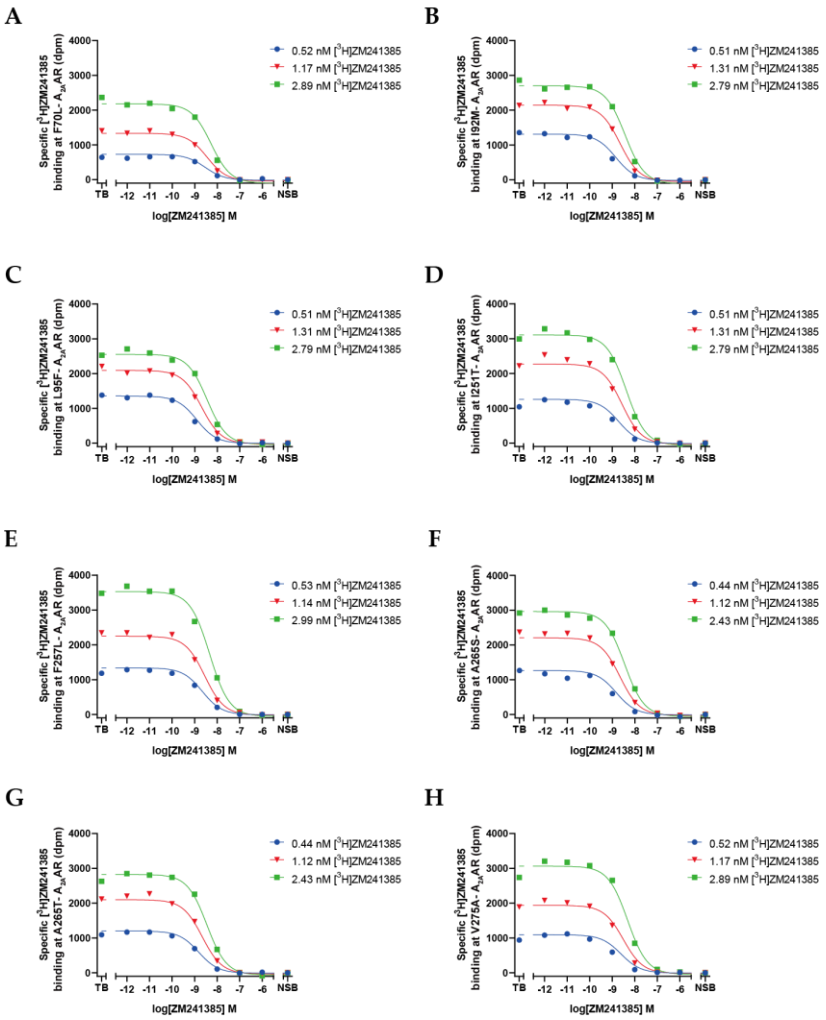

Figure S1. Homologous displacement of three concentrations of [^{3}H]ZM241385 by increasing concentrations of ZM241385 at mutant A_{2A}ARs. Different concentrations of membranes were used dependent on receptor expression levels: (A) F70L-A_{2A}AR (4.5 µg); (B) I92M-A_{2A}AR (4 µg); (C) L95F-A_{2A}AR (3 µg); (D) I251T-A_{2A}AR (3 µg); (E) F257L-A_{2A}AR (1.5 µg); (F) A265S-A_{2A}AR (1.5 µg); (G) A265T-A_{2A}AR (1 µg); (H) V275A-A_{2A}AR (2 µg). Representative curves from one experiment performed in duplicate.

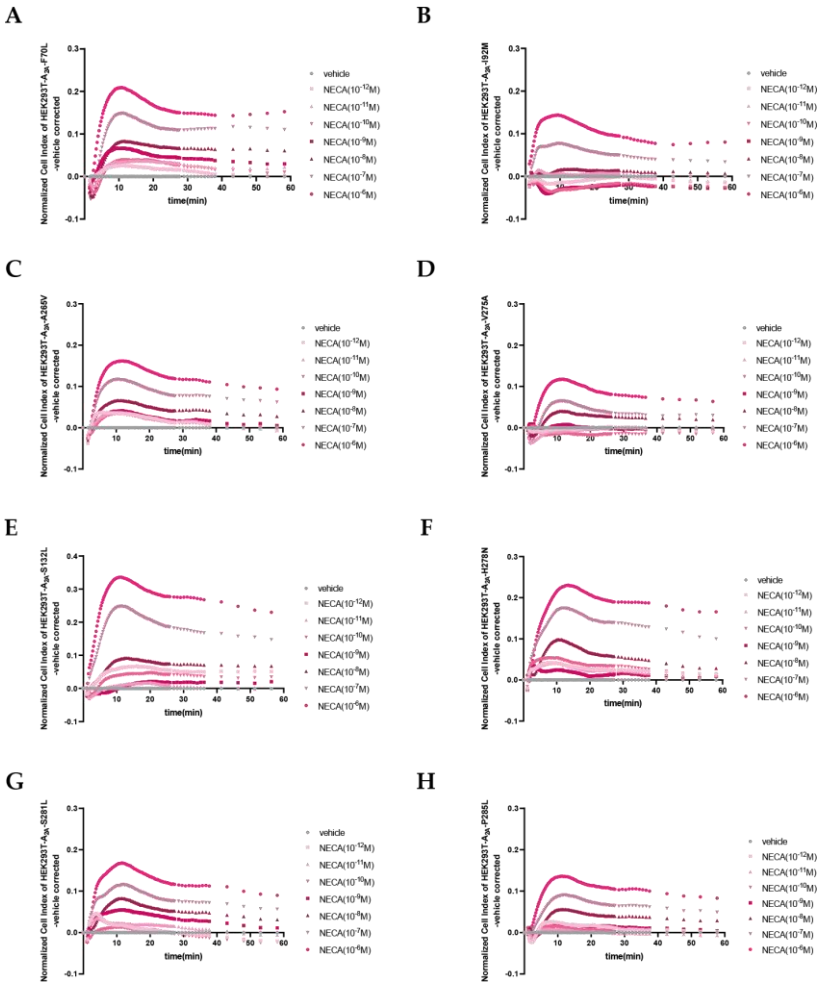

Figure S2. Representative graph of vehicle-normalized cell index after stimulation with different concentrations of NECA at the mutant A_{2A}ARs in a label-free impedance based cell morphology assay. (A) F70L-A_{2A}AR; (B) I92M-A_{2A}AR; (C) A265V-A_{2A}AR; (D) V275A-A_{2A}AR; (E) S132L-A_{2A}AR; (F) H278N-A_{2A}AR; (G) S281L-A_{2A}AR; (H) P285L-A_{2A}AR.