

Supplementary Figure Legends

Supplementary Figure 1. Identification of CDK7 as a druggable kinase in ESCC cells

Heatmap showing the sensitivity of TE7, TE5, KYSE30 and KYSE180 cells to a panel of 7 different CDK inhibitors.

Supplementary Figure 2. Cell-cycle analysis of TE7 and KYSE510 cells treated with THZ1

TE7 and KYSE510 cells were treated with indicated concentrations of THZ1 for either 24 or 48 hr and analyzed by flow cytometry by staining with propidium iodide (PI) .

Supplementary Figure 3. THZ1 treatment did not cause loss of weight of NSG mice

During 24 days of THZ1 treatment (twice daily, 10 mg/kg), no significant loss of weight was observed in the mice (Mean \pm SD of 12 mice).

Supplementary Figure 4. H3K27ac ChIP-seq profiles of representative SE-associated genes in TE7 and KYSE510 cells

Supplementary Figure 5. mRNA expression levels of TP63 and SOX2 in various types of cancer cells

(A) Left, mRNA expression of TP63 was the highest in ESCC and head and neck squamous cancers among various types of cancer cell lines. Right, TP63 expression was higher in ESCC than EA cell lines (** $P < .01$). (B) SOX2 expression was the highest in ESCC and ranked 3rd in head and neck squamous cancers. SOX2

expression was higher in ESCC than EA, albeit it did not achieve statistical significance (n.s.d). Data were retrieved from CCLE project.

Supplementary Figure 6. SE-associated candidate oncogenes were required for the proliferation in both TE7 and KYSE510 cells

Proliferation rate (MTT assay) of TE7 and KYSE510 cells was measured upon knockdown of the candidate genes by siRNAs (* $P < .05$, ** $P < .01$, *** $P < .001$, compared with Scramble group).

Supplementary Figure 7. Identification of PAK4 as a SE-associated drug target in ESCC

(A) Dose-response curves of ESCC cell lines (high PAK4 expression) to treatment with KPT9274 (PAK4 inhibitor). Data are represented as mean \pm SD of three replicates. (B) Proliferation assay (MTT) shows effects of KPT9274 treatment on ESCC cell lines at indicated time points. Bars represent mean \pm SD (*** $P < .001$). (C) Photographs and (D) Tumor weights of KYSE510 xenografts from both vehicle and KPT9274 (150 mg/kg, twice daily, 5 days/week, orally) treatment groups at the endpoint of experiment (28 days) (**** $P < .0001$). (E) H&E and IHC staining of tumor tissue sections. Cell proliferation and apoptosis was examined by Ki67 and CC9 staining, respectively. Original magnification, X 400. (F) No significant difference in the weight of mice between vehicle and KPT9274 groups was observed during the 28 days of treatment.

Supplementary Figure 8. mRNA expression levels of DNAJB1 in various types of cancer cell lines

mRNA expression of DNAJB1 was the highest in ESCC and head/neck squamous cancers among various types of cancer cell lines. Data were retrieved from CCLE project.