**FIGURE LEGENDS**

**Figure 1. Swimmer plot by dose level (evaluable analysis set).** The swimmer plot shows responses and durations of response in evaluable patients.

Abbreviations: T, trastuzumab; P, pertuzumab; A, anti-HER2 ADC; S, small molecular anti-HER2 TKI

**Figure 2. Pharmacokinetic profile of KN026 in patients with metastatic HER2-positive breast cancer.** (A) KN026 concentration-time profile after single dose. (B) KN026 concentration-time profile after multiple doses. Each line represents the mean (error bars reflect standard deviation of the mean [SD]) KN026 plasma concentration.

20 μg/mL: target trough concentration derived from pre-clinical translational models. Lower limit of quantification (LLOQ) of the bioassay is 0.0625 μg/mL.

**Figure 3. Waterfall plot and spider plot by dose level (evaluable analysis set).** Tumor responses of all evaluable patients in this study. (A) Maximal (%) reduction of tumor size from baseline per RECIST v1.1 for patients with at least one post treatment radiographic evaluation. The length of the bar represents maximal decrease or minimal increase in target lesion(s). (B) Percentage change of individual tumor burden over time from baseline assessed per RECIST v1.1. Tumor response was assessed before treatment, once every 6 weeks during first 12 months and every 12 weeks thereafter until progressive disease, starting a new anti-tumor therapy or withdrawal of informed consent.

Abbreviations: LD, length diameter

**Figure 4. *HER2/CDK12* co-amplification as a potential biomarker for KN026.** (A) Differential clinical responses of KN026 treatment between patients with and without *HER2/CDK12* co-amplification. The BOR was used to define Response (PR) and Nonresponse (SD and PD) groups. *P*-value, Fisher’s exact test (B) The frequency distribution of *HER2/CDK12* co-amplification across 33 cancer types using TCGA cohorts (+: thresholded calls as 1; ++: thresholded calls as 2). TCGA cancer type acronyms are listed below. (C) The frequency distribution of *HER2/CDK12* co-amplification across the PAM50 subtypes of breast cancer (Her2: HER2-enriched subtype; LumA: luminal A subtype; LumB: luminal B subtype; Basal: basal-like subtype; Norm: normal-like subtype; +: thresholded calls as 1; ++: thresholded calls as 2). (D) A volcano plot showing genes differentially expressed in the tumor with and without *HER2/CDK12* co-amplification. The genes with FDR < 0.1 and fold change > 2 are shown in red. (E) Pathways inhibited in the *HER2/CDK12* co-amplification group based on mRNA expression (up) and RPPA-based protein expression data (bottom) identified by GSEA. (F) Immune cell abundance difference between tumors with and without *HER2/CDK12* co-amplification groups. (E bottom panel and G) *P* values: Wilcoxon rank sum test. The middle line in the box is the median, the bottom and top of the box are the first and third quartiles, and the whisker extended to 1.5× interquartile range of the lower and the upper quartiles, respectively. (G) Decreased immune activity in the *HER2/CDK12* co-amplification group. (H) Progression-free survival in patients with and without *HER2/CDK12* co‑amplification. Median longer PFS was observed in patients with HER2 and CDK12 co‑‑amplification (8.2 vs 2.7 months, Log-rank test, *P* = 0.04).

Abbreviations: (A) BOR, best overall response; PD, progressive disease; PR, partial response; SD, stable disease. (B and C) ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma. STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, Uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma. (D, E, F, G, and H) FDR, false discovery rate; NS, non-significant; PFS, progression-free survival.

**Figure S1.** (A) **Visual predictive checks of observed and model-predicted KN026 concentrations.** 20 mg/kg Q2W schedule and 30 mg/kg Q3W schedule. Simulations showed that both 20 mg/kg Q2W and 30 mg/kg Q3W schedules achieved more than 20 μg/mL target threshold derived from preclinical studies in more than 90% of simulated population. (B) **Patient screening and post-treatment cycle 4 CT scans.** (a,c,e) Pre-treatment and (b,d,f) post-treatment scans from a patient with relapsed breast cancer who had a partial response. The patient was previously treated with adjuvant chemotherapy and radiotherapy, first-line docetaxel/trastuzumab/pertuzumab and second-line capecitabine/lapatinib. There was a significant reduction in tumor size in treatment cycle 4 of third-line KN026 (30 mg/kg q3w). Left lung (a,b), anterior mediastinal lymph nodes (c,d) and right axillary lymph nodes (e,f) were included in the target lesions. Left pleural effusion (c,d) was the non-target lesion. The median PFS for the patients was 6.77 months.

Abbreviations: CT, computerized tomography; PFS, progression-free survival

**Figure S2.** PTEN shows a significant mutation bias in CDK12 non-amplification group from HER2+ breast cancer. Patients with loss-of-function mutations in PTEN are shown in red, otherwise in grey.

**Figure S3.** **Tissue (A) and peripheral blood ctDNA (B) mutation profile of 22 patients.** The bars located at the bottom of the oncoprint denote different groups of best response. Each column represents a patient and each row represents a gene. Values on the left represent the mutation rate of each gene. Values on the right indicate the genes. Top plot represents the overall number of mutations a patient carried. Different colors denote different types of mutation.