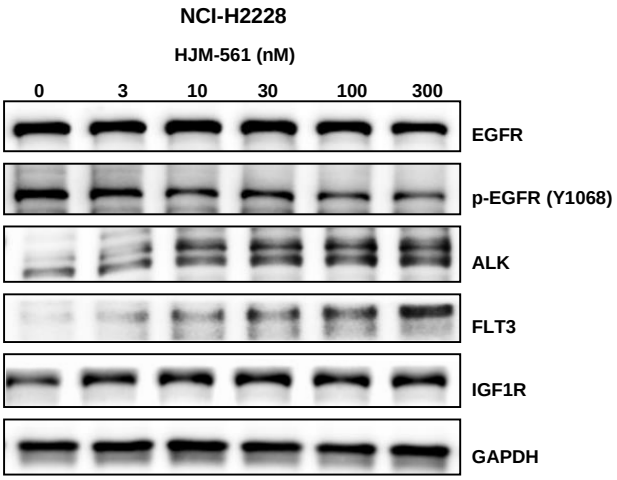
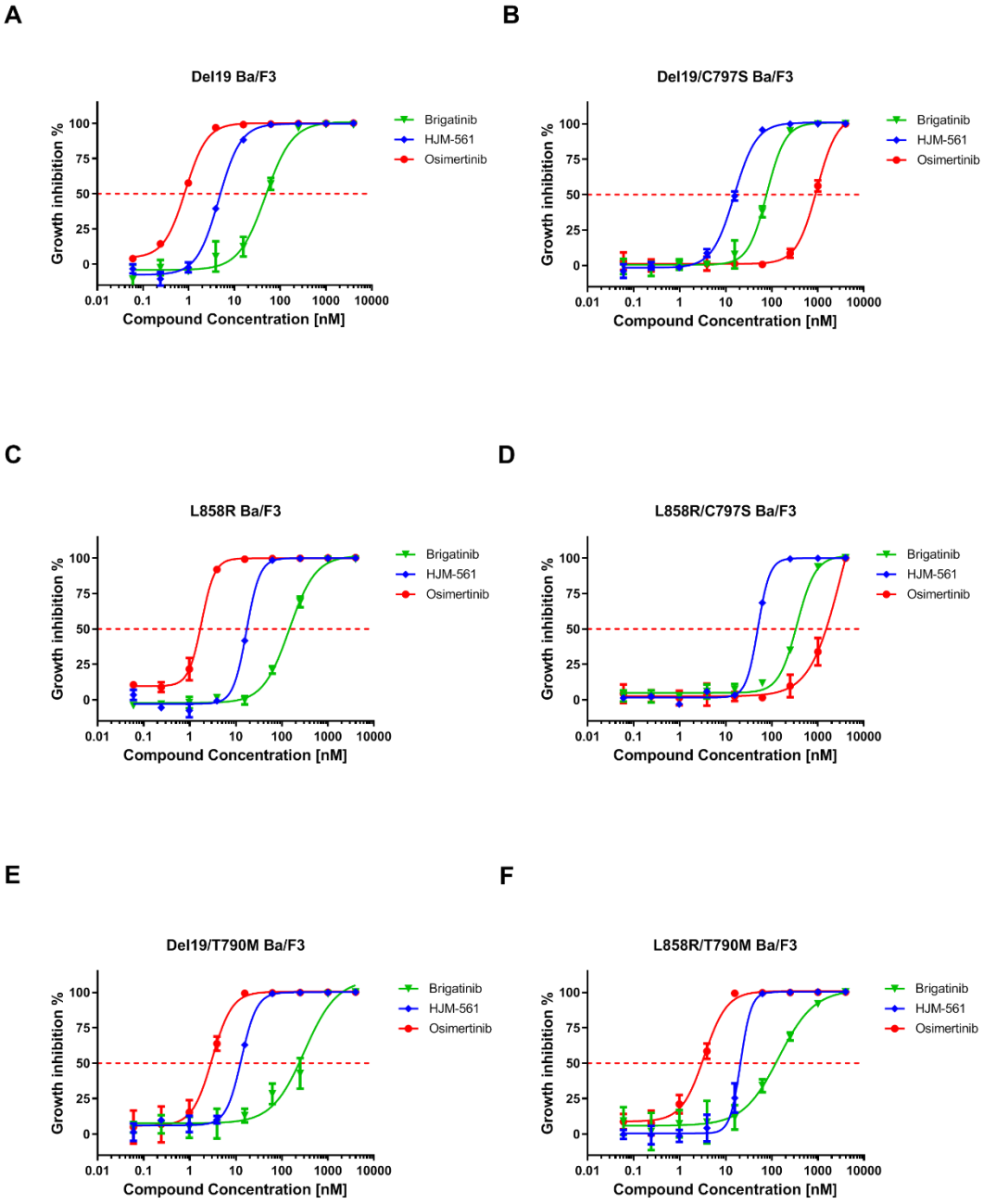
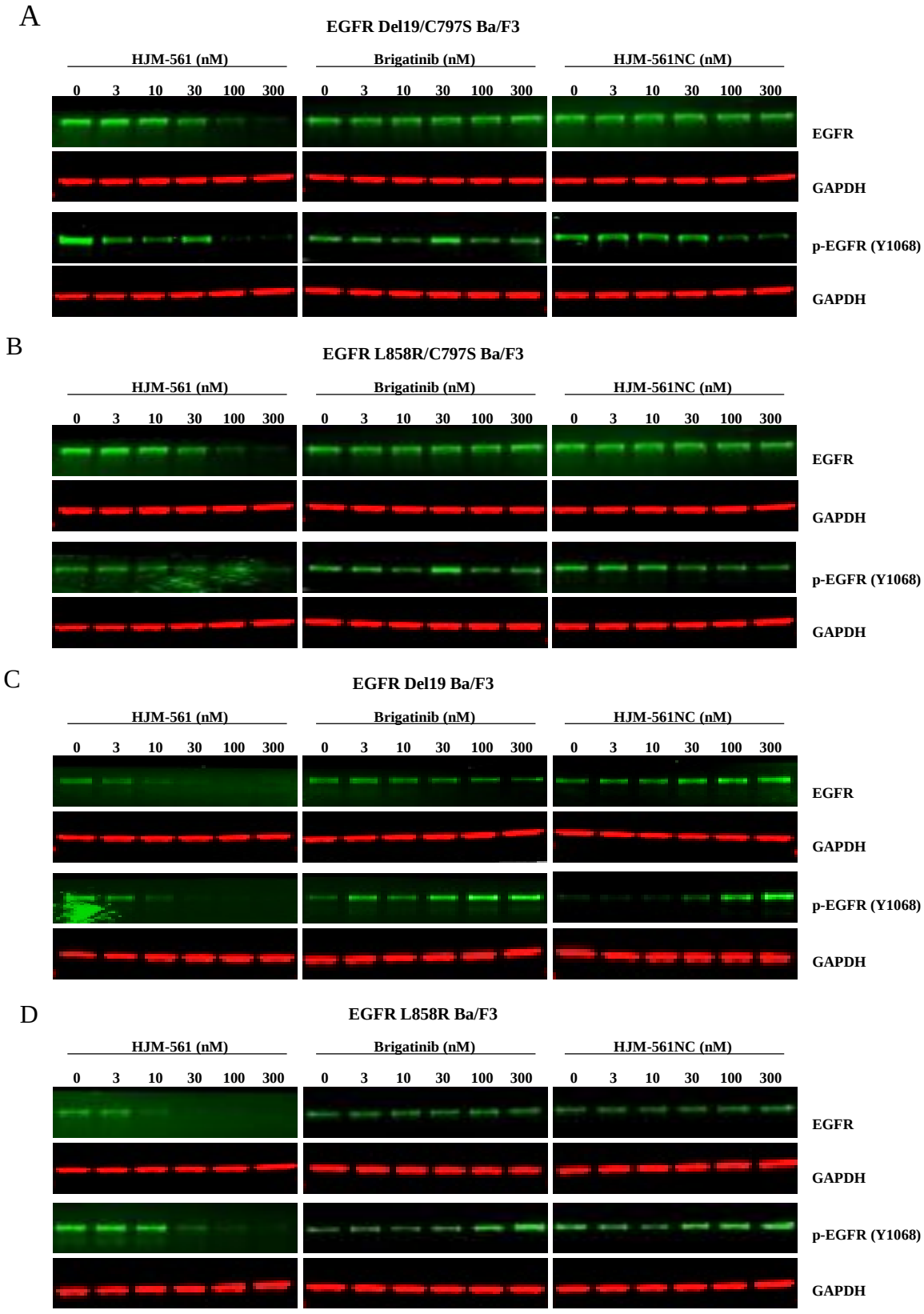
Supplemental Figure S1. Western blot of EGFR, p-EGFR, ALK, FLT3 and IGF1R in NCI-H2228 cells treated with HJM-561 for 24h.



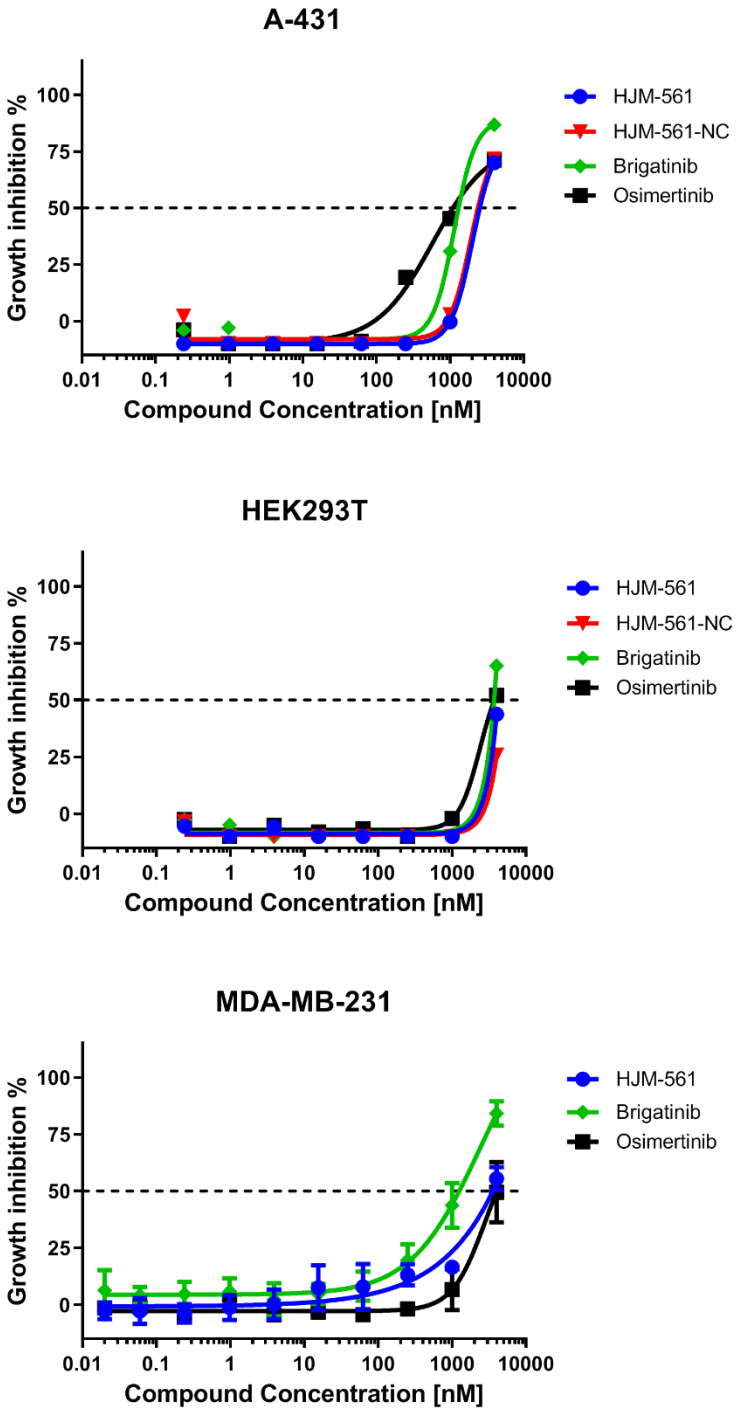
Supplemental Figure S2. Inhibitory activity of HJM-561, brigatinib and osimertinib in Ba/F3 cell expressing single or double mutant EGFR. (A) Del19 EGFR, (B) Del19/C797S, (C) L858R, (D) L858R/C797S, (E) Del19/T790M, (F) L858R/T790M.



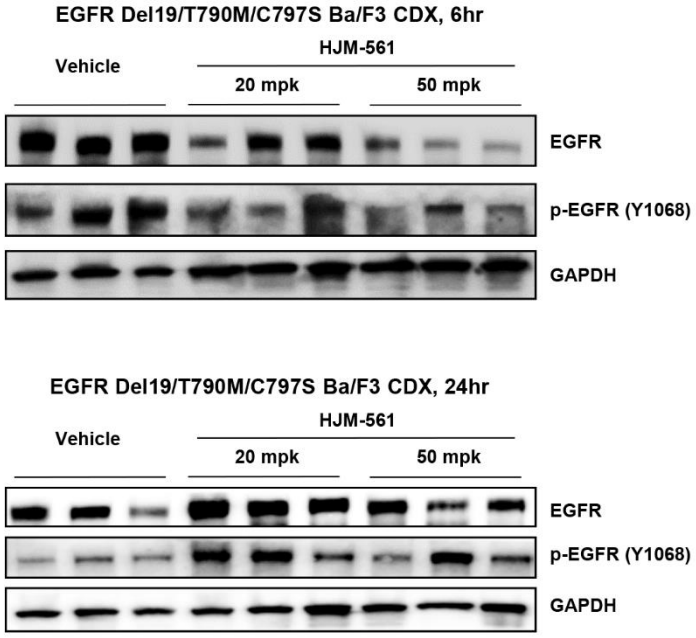
Supplemental Figure S3. HJM-561 induced EGFR degradation and inhibited EGFR signaling in a dose-dependent manner in Ba/F3 cell expressing single or double mutant EGFR. (A) Del19/C797S, (B) L858R/C797S, (C) Del19, (D) L858R.



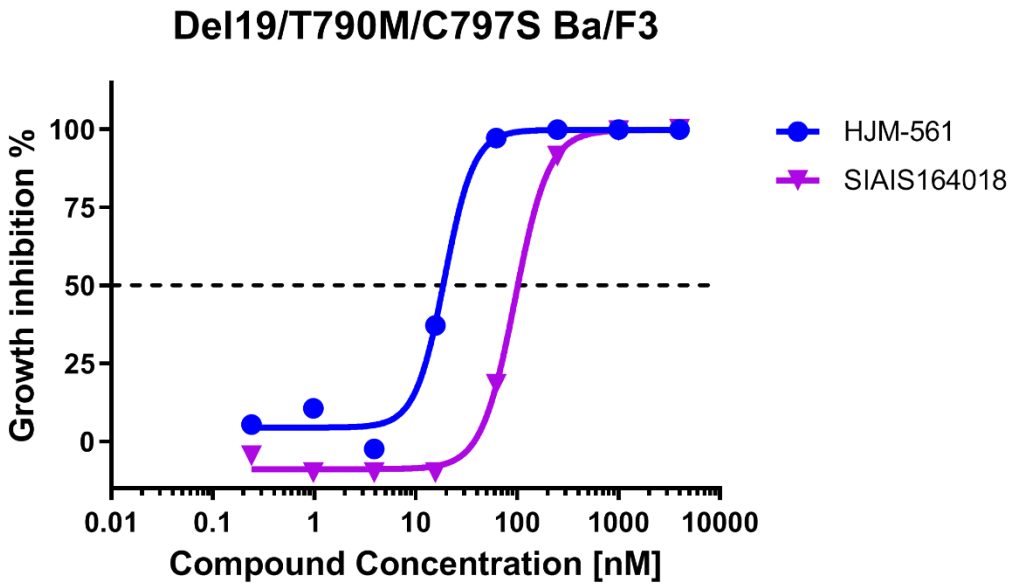
Supplemental Figure S4. HJM-561 did not affect the viability of A431, HEK293T and MDA-MB-231 cells.

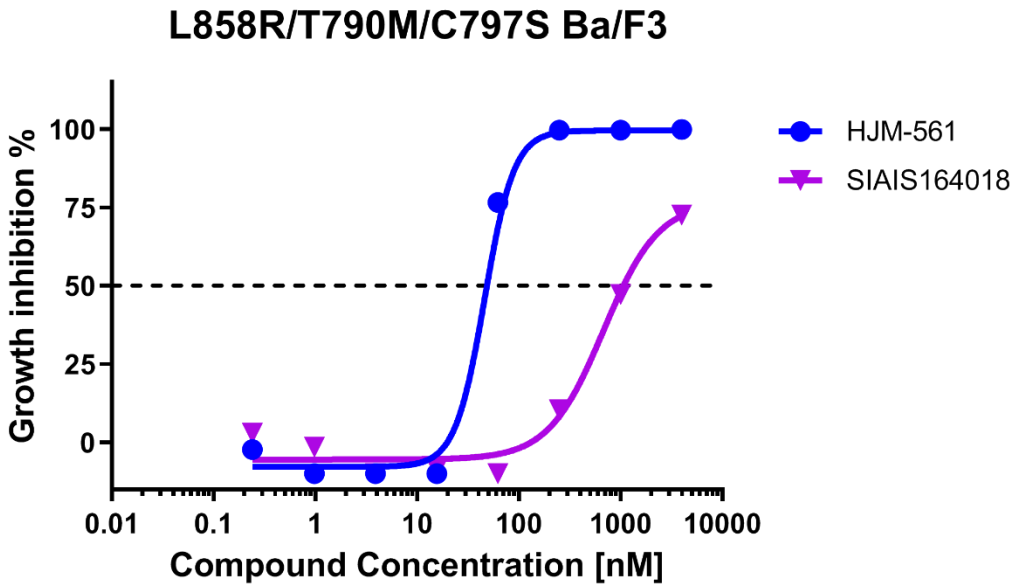


Supplemental Figure S5. Pharmacodynamic analysis of HJM-561 in EGFR Del19/T790M/C797S Ba/F3 CDX model. Tumor samples were taken 6 hours and 24 hours after a single dose of HJM-561 at indicated doses. EGFR, p-EGFR and GAPDH were determined by Western blot in tumor lysates.



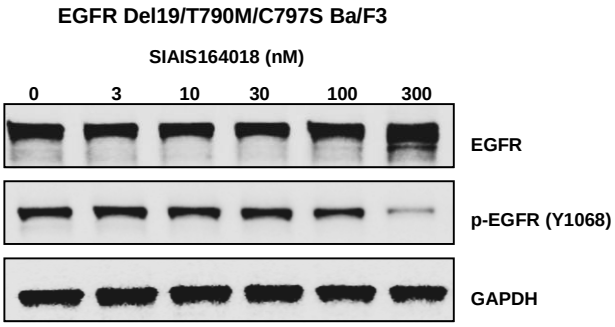
Supplemental Figure S6. Cell proliferation assay of HJM-561 and SIAIS164018 in Ba/F3 cells expressing EGFR Del19/T790M/C797S and L858R/T790M/C797S triple mutants. SIAIS164018 was synthesized according to the paper (J. Med. Chem. 2021, 64, 9152−9165).



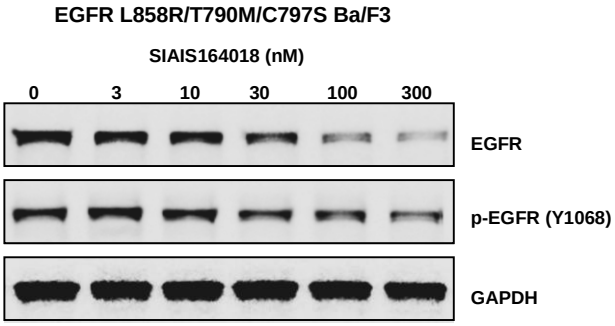


Supplemental Figure S7. Western blot of total EGFR, p-EGFR and GAPDH in Ba/F3 cells expressing EGFR triple mutants treated with SIAIS164018 for 24h (A and B). SIAIS164018 is very weak in degrading EGFR triple mutants compared with HJM-561 which is shown in Figure 1B of the manuscript. SIAIS164018 degrades ALK in SR cells (C).

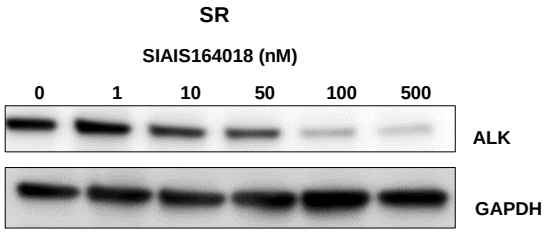
A



B



C



Supplemental Figure S8. HJM-561 induced degradation of EGFR mutants in PC-9 (Del19) and H1975 (L858R/T790M) lung cancer cells.