Inhibition of RTK pathways in cancer triggers an adaptive response that promotes therapeutic resistance. Because the adaptive response is multifaceted, the optimal approach to blunting it remains undetermined. TNF upregulation is a biologically significant response to EGFR inhibition in NSCLC. Gong et al. compared a specific TNF inhibitor (etanercept) to thalidomide and prednisone, two drugs that block TNF and also other inflammatory pathways. Prednisone is significantly more effective in suppressing EGFR inhibition-induced inflammatory signals. Remarkably, prednisone induces a shutdown of bypass RTK signaling and inhibits key resistance signals such as STAT3, YAP and TNF-NF-κB. Combined with EGFR inhibition, prednisone is significantly superior to etanercept or thalidomide in durably suppressing tumor growth in multiple mouse models, indicating that a broad suppression of adaptive signals is more effective than blocking a single component. They identify prednisone as a drug that can effectively inhibit adaptive resistance with acceptable toxicity in NSCLC and other cancers [1)]

1)
Gong K, Guo G, Beckley NA, Yang X, Zhang Y, Gerber DE, Minna JD, Burma S, Zhao D, Akbay EA, Habib AA. Comprehensive targeting of resistance to inhibition of RTK signaling pathways by using glucocorticoids. Nat Commun. 2021 Dec 1;12(1):7014. doi: 10.1038/s41467-021-27276-7. PMID: 34853306.