## ABSTRACT

**Background:** The 90-kDa heat shock protein (HSP90) is a chaperone protein expressed at high levels in cancer cells and is involved in the folding or stabilization of several client proteins, including epidermal growth factor receptor (EGFR). Ganetespib is a second-generation HSP90 inhibitor with a potent antitumor effect against various cancers.

**Materials and Methods:** We examined the antitumor effect of ganetespib in *EGFR*-mutant non-small cell lung cancer (NSCLC) cells and experimentally established EGFR-tyrosine kinase inhibitor (TKI)-resistant cells harboring various resistant mechanisms, including *EGFR* T790M mutation, *MET* amplification, and epithelial–mesenchymal transition.

**Results:** Ganetespib showed a potent antitumor effect at low concentrations, suppressing EGFR-related downstream pathway molecules and inducing apoptosis in all examined EGFR-TKI-resistant cells *in vitro*. Ganetespib also inhibited *in vivo* tumor growth in resistant cells harboring *EGFR* T790M.

**Conclusion:** Ganetespib might be a promising therapeutic option for the treatment of patients with EGFR-TKI-resistant NSCLC.