Background Epidermal growth factor receptor (EGFR) is a key factor in cellular proliferation, differentiation, and survival, which has been considered as a main target in the treatment of malignancies. Although treatment with EGFR-targeted therapy and chemotherapy improved outcomes for EGFR overexpressing cancer, its clinical application is limited due to drug resistance. Therefore, there is an urgent unmet medical need for new therapies that can overcome drug resistance, particularly for EGFR overexpressing cancer. Combination with immunotherapy would be one of the new treatment options to resolve drug resistance. 4-1BB (CD137) is a key costimulatory receptor expressed on activated T cells and natural killer (NK) cells, which is a promising therapeutic target in cancer. A novel YH32364 (ABL104) has been generated to overcome the challenges with EGFR-drug resistance via tumor-directed 4-1BB agonism and EGFR signal blocking.

Methods YH32364 is EGFR/4-1BB-bispecific antibody with an engineered IgG1 isotype. Its activity was determined using cell-based 4-1BB bioassay and co-culture assay with human peripheral blood mononuclear cells (hPBMC). In vivo antitumor efficacy of YH32364 and the infiltrated-immune cells into tumor were assessed in h4-1BB knock-in (KI) mice models. Three-week repeated dose toxicity study of YH32364 for dose range finding (DRF) was conducted in cynomolgus monkeys at the dose of 30 and 100 mg/kg.

Results YH32364 binds to EGFR and 4-1BB with high affinity. YH32364 not only blocked EGFR signaling of tumor cells, but also activated T cells as indicated by IFN-γ secretion, leading to tumor cell lysis in co-culture assay using hPBMC and EGFR-expressing tumor cells. YH32364 exhibited superior efficacy on tumor regression and anti-tumor immunity in MC38/hEGFR-bearing h4-1BB KI mouse models, compared to the equimolar dosing of cetuximab. In 3-week toxicity study in monkey, there were no YH32364-related toxicological findings including skin toxicity, mortality, body weight, hematol- ogy, clinical chemistry etc., indicating a favorable safety profile.

Conclusions YH32364 exhibited potent in vitro and in vivo efficacy and it was well tolerated and safe potentially due to tumor-localized T cell activation. These results suggest that YH32364 could be a promising therapeutic for EGFR-overexpressing cancer patients, especially with EGFR drug resistance.