

Inhibition of FGFR3-BAIAP2L1 fusion kinase oncogenic potential by CH5183284/Debio 1347, a compound that inhibits FGFR3 kinase activity constitutively activated by BAIAP2L1 BAR domain dimerization.

Nukinori Akiyama¹, Yoshito Nakanishi¹, Toshiyuki Tsukaguchi¹, Yasuko Satoh¹, Yasue Nagata¹, Tsutomu Takahashi², Yukari Nishito¹, Motoki Ashihara¹, Nobuya Ishii¹, Masahiro Aoki¹.

¹Chugai Pharmaceutical Co.,Ltd., Kanagawa, Japan; ²Chugai Research Institute for Medical Science, Inc., Kanagawa, Japan

Advances in next-generation sequencing technologies have made possible to identify more efficiently novel fusion proteins in cancer. Among them, fusion kinases are well known as potent oncogenes and promising therapeutic targets for cancer patients. Recently, several FGFR fusion genes, such as FGFR1-TACC1, FGFR2-CCDC6, FGFR3-TACC3, and FGFR3-BAIAP2L1, have been identified in GBM, bladder cancer, and breast cancer as well as other tumor types. In this study, we focused on the FGFR3-BAIAP2L1 (F3-B) gene fusion and investigated its prevalence in clinical samples, tumorigenic activity, mechanism of constitutive activation, and sensitivity to CH5183284/Debio 1347.

We screened cancer tissue panels by RT-PCR for F3-B mRNA and identified F3-B positive specimens in bladder cancer (4.3%: 2/47) and lung cancer (1.2%: 1/83). All these F3-B fusions were confirmed by cDNA sequencing. To expand this study further, we established an FGFR3 break apart FISH assay. In a larger bladder cancer panel, we found 2 additional positive cases (2.2%: 2/89). To investigate the role of F3-B in tumors, we established Rat-2 transfectants with full length F3-B and assessed tumorigenic activity of these cells in in vitro and in vivo settings. Rat-2/F3-B cells acquired sphere forming activity even without FGF1 in vitro, and efficiently formed tumors when subcutaneously inoculated the cells into nude mice. Consistent with these observations, FGFR3 or BAIAP2L1 siRNA blocked the proliferation of F3-B positive SW780 cells. Interestingly, the selective FGFR inhibitor, CH5183284/Debio 1347, effectively inhibited the in vivo tumor growth of Rat-2/F3-B and SW780 cells, indicating that F3-B oncogenic activity is depending on FGFR kinase activity. To confirm this, we established Rat-2/F3-B- Δ BAR, which lacks dimerization domain of BAIAP2L1 (BAR domain: Bin-Amphiphysin-Rvs). Phosphorylation of FGFR3 in Rat-2/F3-B- Δ BAR cells was lowered as compared to that in Rat-2/F3-B cells. Furthermore, Rat-2/F3-B- Δ BAR cells exhibited lower spheroid formation activity and slower tumor growth compared with Rat-2/F3-B cells. Taking this information together, the constitutive dimerization through BAR domain is essential for F3-B fusion to exert its potent oncogene activity in tumors. These findings underline the oncogenic potential of FGFR3-BAIAP2L1 gene fusion and warrant further clinical evaluation of the therapeutic potential of CH5183284/Debio 1347 in patients harboring this genetic alteration.