Discovery and synthesis of covalent HER2 selective inhibitors for the treatment of HER2 Exon 20 insertion driven tumors

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Oncogenic mutations in human epidermal growth factor receptor 2 (HER2) occur in 2-3% of patients with non-small cell lung cancer. Many known inhibitors of HER2 are limited by adverse events resulting from inhibition of EGFR wild type. We therefore initiated a drug discovery program aiming at finding novel HER2 selective inhibitors sparing EGFR wild type activity.
Here, we report the synthesis, medicinal chemistry optimization, and pharmacological characterization of novel selective HER2 exon 20 mutation inhibitors. The presentation will focus on structure-based design efforts which resulted in new, orally bioavailable inhibitors that show excellent potency on HER2, including hard-to-hit mutations. The synthetic routes for the preparation of these novel inhibitors will also be discussed.

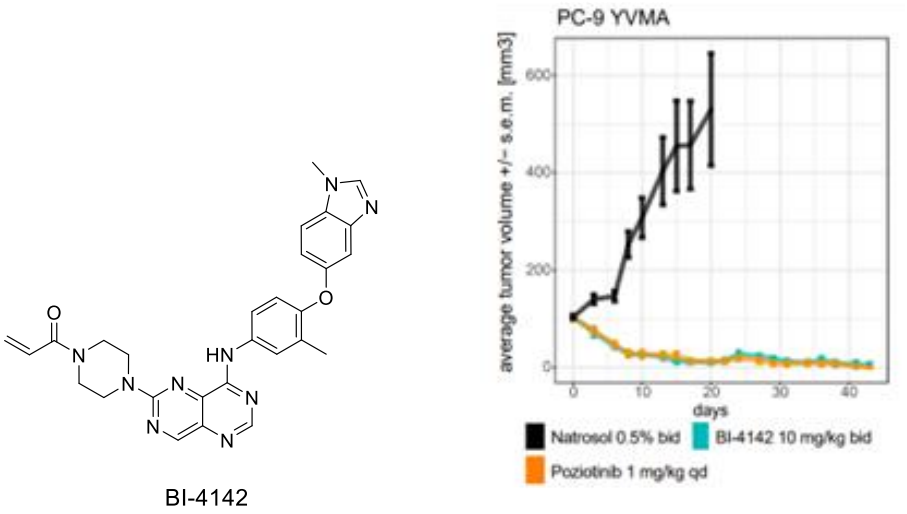

Figure 1. left panel, chemical structure of BI-4142,
right panel, xenotransplantation experiment using PC-9 HER2^{YVMA} cells with compounds and doses indicated. Natrosol, n = 10 animals; BI-4142, n = 8 animals; and poziotinib, n = 8 animals.

Upon treatment with the inhibitors, cancer cell survival and proliferation were reduced, which translated into tumor regressions in preclinical xenotransplantation models of HER2 exon 20 mutant driven cancers [1]. Our results suggest that HER2 exon 20 insertions can be effectively treated by a potent and highly selective HER2 inhibitor that spares EGFR wild type. These findings show the successful optimization of a covalent inhibitor and warrant clinical testing of covalent HER2 selective, EGFR wild type sparing inhibitors in HER2 mutant NSCLC patients.

References

[1] B. Wilding, R. Neumueller, F. Solca et al, *Nature Cancer* **2022**, *3*, 821-836.