27O-ISMS15 **Discovery of a Novel Inhibitor (ASP8273) of EGFR T790M Mutation**

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EGFR tyrosine kinase inhibitors (TKIs) have showed significant efficacy in NSCLC patients with activating EGFR mutants (e.g. L858R). However, acquired drug resistance occurred in most patients, the representative cause of which is mutation of the gatekeeper T790 residue (T790M). Therefore, we have pursued a potent EGFR TKI which demonstrates anti-tumor efficacy in L858R/T790M double mutant cancer.

1
EGFR L858R/T790M: 1.3nM
H1975 cell growth: 25nM

2 (ASP8273)
EGFR L858R/T790M: 0.41nM
H1975 cell growth: 26nM

Compound **1** was derived from high throughput screening hit series as a result of introduction of irreversible warhead structure. Further chemical modification of hydrophobic amino phenol moiety led us to discover **2** (**ASP8273)** as a novel, irreversible inhibitor, which demonstrates high potency to the T790M resistance mutations with improved aqueous solubility.

2 demonstrated potent anti-tumor efficacy in *in vivo* xenograft mice model with NCI-H1975 cell line which internally expressed EGFR L858R/T790M mutation, which strongly supported selection of **2** as a clinical candidate. In this poster, we will discuss the detail of structure-activity relationships of compounds with novel pharmacophore, pyrazine 2-carboxamide.