Discovery of ETS-001, a Highly Potent Allosteric SHP2 Inhibitor to Treat RTK/RAS-driven Cancers

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Introduction

- The non-receptor tyrosine phosphatase SHP2, encodes by PTPN11, functions as a conduit node downstream of multiple receptor tyrosine kinases (RTKs), and is required for full activation of the MAPK pathway. Preclinical evidence suggest that suppression of SHP2 activity leads to inhibition of MAPK signaling and cell growth in a wide spectrum of cancers, especially those driven by RTK alterations and RAS pathway mutations (e.g., KRAS\(^{G12C}\), BRAF\(^{V600E}\), etc).
- ETS-001 is a highly potent, selective and orally bioavailable small-molecule allosteric inhibitor of SHP2. It is effective in various human cancer models bearing oncogenic alterations in the RTK/RAS pathway.
- Besides, as the effectiveness of RAS pathway inhibitors is ultimately limited by rapid emergence of resistance via multiple mechanisms, including bypass activation of alternative RTKs, SHP2 inhibitor has the potential to overcome the resistance as combinational strategy associated with various RAS pathway-targeted therapies. Here we show that ETS-001 exhibited strong synergistic effect with EGFR-TKI (gefitinib), KRAS\(^{G12D}\) (AMG510), MEK1 (Trametinib), and CDK4/6 (ribociclib) in appropriate cancer models in vitro and in vivo.

Excellent Anti-Proliferative Activity across Cancer Cells Bearing Oncogenic Alterations in RTK/RAS Pathway

- ETS-001 potently inhibits the proliferation of cancer cells with RAS-dependence or genetic mutations of KRAS\(^{G12C}\), BRAF\(^{V600E}\) and NF1\(^{LOF}\). (Fig. A, B, C).
- Potent anti-proliferative activity in somatostatin-resistant BaX73 cells harboring the on-target resistance mutation C78T5S.
- Strong in vivo anti-tumor activity in somatostatin-resistant EGFR-mutant NSCLC bearing MEK-targeted amplification.

Potential Anti-Tumor Activity in RTK-Amplified Esophageal Cancer

- RTKs amplification/overexpression occur with high incidence in ESCOC and EAC.
- ETS-001 exhibits potent anti-proliferative activity in esophageal cancer cell lines and PDTOs, with profound combinational effect with EGFR TKIs.
- ETS-001 demonstrates strong in vivo anti-tumor activity with good correlation with PK/PD profiles in the ETS-001 treated esophageal cancer xenograft.

References

1. Wong et al., Nat Med. 2018 24(7):968

ETS-001 Profile Highlights

- Extremely potent against SHP2-dependent cancer cell lines and PDTOs (RTK-driven, class 3-BSAP mutants, KRAS\(^{G12C}\), NF1 loss, etc).
- Excellent anti-proliferative and combinational activity against preclinical species.
- Good biodistribution and wide safety margin.
- Robust efficacy in multiple preclinical models.
- Multiple potent combo opportunities to overcome resistance (RTK-TKIs, KRAS, MEK, CDK4/6, etc).
- ND-enabling study completed

ETS-001 Overcomes Multiple Mechanisms Underlying Gaiomeritinib Resistance

- In vitro anti-proliferative synergistic effect of ETS-001 and somatostatin, consistent with sustained pERK suppression.

Strong Single Agent and Combinational Benefits in KRAS\(^{G12C}\) and BRAF\(^{V600E}\) In Vivo Models

- ETS-001 exhibits potent anti-proliferative activity in gastric cancer PDTOs.

Potential Anti-Proliferative Activity in Gastric Cancer

- ETS-001 strongly suppresses phosphate activity of the full-length SHP2 with sub-nM activity, but not that of the truncated phosphate domain (PTP).
- Highly selective across phosphate panel (all IC\(_{50}\) > 10,000 nM) kinase panel (all IC\(_{50}\) > 1,000 nM) screen.

ETS-001 is a Potent and Selective Allosteric Inhibitor of SHP2

- KRAS\(^{G12C}\) and KRAS\(^{G12D}\) PDX.
- ETS-001 exhibits profound combinational effect with KRAS\(^{G12C}\) in KRAS\(^{G12C}\) bearing tumors.
- KRAS amplifications without coding mutations were mostly identified in esophageal adenocarcinomas (17%) and the chromosomal instability (CIN) variant of gastric cancer (13%).
- ETS-001 exhibits strong synergistic effect with MEK7 in KRAS amplified GC cells, attenuating MEK-driven AKT reactivation.

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