Preclinical activity of NVL-655 in ALK-driven cancer models beyond non-small cell lung cancer

Anupong Tangpeerachai1, Ludovic Bigot2, Luc Friboulet2, and Henry E. Pelisek1

**Addressing a Medical Need**

**ALK MECHANISMS OF ONCOGENESIS**

- ALK fusions have been identified in rare cases of cholangiocarcinomas.
- M899V is an STRN ALK G1202R xerograft model derived from an ALK-positive cholangiocarcinoma and NKX2.1-negative.
- NVL-655 is efficacious in the M899 STRN ALK G1202R patient-derived xenograft model, inducing deep regression at both doses tested (0.3-3.7 μg/kg).

**ALK MODELS BEYOND NON-SMALL CELL LUNG CANCER**

- ALK-driven cancer models beyond non-small cell lung cancer, including ALK alternative transcription initiation (ATI4), or post-translational stages.

**NEUROBLASTOMA**

- F1174L, F1174S, and R1275Q are among the most common activating ALK mutations in neuroblastoma.
- TL1151 is identified.
- NVL-655 exhibits potent activity (IC50 = 2 nM) against the human anaplastic large-cell lymphoma cell line Kelly.

**CHOLANGIOCARCINOMA**

- Anaplastic thyroid cancer (~11%)
- L1198F & G1201E

**SOFT-TISSUE SARCOMA**

- Soft-tissue sarcomas encompass many types of cancers arising from soft tissues, and some soft-tissue sarcomas have been shown to re-express ALK re-arrangements.
- Aska-S is a human cancer cell line established from synovial sarcoma, a type of soft-tissue sarcoma, and is driven by ALK partial deletion around exons 2-3.
- NVL-655 exhibits activity (IC50 = 7 μM) against Aska-S.

**Comparative selectivity analysis**

- NVL-655 shows strong activity in diverse preclinical models of ALK-driven cancers: cholangiocarcinoma, neuroblastoma, lymphoma, and soft-tissue sarcoma.
- Among all inhibitors tested, NVL-655 shows the broadest activity for diverse ALK oncogenes including non-small cell lung cancers, and partial deletion of internal tandem duplication.
- NVL-655 shows larger ALK vs TRKB selectivity windows than lorlatinib and TPX-0131.
- Preclinical activity against diverse ALK oncogenes (fusions, mutations, and partial deletions) may explain the broad selectivity for ALK-driven cancers.

**Conclusions**

- NVL-655 was designed to selectively inhibit ALK while sparing TRKB, showing 91- to 970-fold selectivity for ALK (with or without resistance mutations) over TRKB.
- By comparison, lorlatinib shows a 9-fold selectivity window for ALK over TRKB, and TPX-0131 shows a 1-fold selectivity window.

**Financial Disclosures:** Nuvalent Inc. holds intellectual property on NVL-655. All authors have submitted financial disclosures to AACR. For disclosures, please see AACR’s Author Submission System (http://www AACR.org).

*Correspondence: atangpeerachai@nuvalent.com*