NST-628 is a potent, fully brain-penetrant, RAS MAPK pathway molecular glue inhibitor with efficacy in CNS tumor models

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Abstract

Alterations in the RAS/MAPK/ERK signaling cascade are common across multiple solid tumor types and are often driving forces for CNS and BRAF-driven cancers. Apart from approved mutation-selective inhibitors for BRAF V600 and the RAF/MEK inhibitors, other classes of RAS and BRAF inhibitors are currently under clinical development, and there is a need for inhibitors with superior efficacy, improved brain penetration, and resistance to existing BRAF/MAPK inhibitors. Currently approved inhibitors of the RAS/MAPK pathway also have limited central nervous system (CNS) exposure and are of significant interest as a treatment modality for solid tumors in the brain. The clinical model used for selecting inhibitors using the CNS tumor models, which included both xenograft and transgenic animal models, showed high CNS penetrability of NST-628. NST-628 inhibits the growth of both NRAS- and KRAS-driven cell lines and xenograft models. NST-628 has CNS penetrability, with a p2/p3 > 1.5, that is far higher than that of trametinib or cobimetinib (p2/p3 < 1.1, respectively). The predicted effective plasma levels of NST-628 (150 μM) are not only brain penetrable but also high enough to completely inhibit the target pathway (ERK) in mouse brain tissue, as measured by phospho-ERK, in an in vitro bioluminescent SK-MEL-2 neuroblastoma assay model (IC50 386 ± 100 nM). NST-628 leads to tumor regressions with a 100% response rate against multiple solid tumors in both primary and metastatic CNS tumors, including Wuxi Pharmaron MEK mutant primary and metastatic CNS tumors, in the United States (FDA) and the United Kingdom, respectively. NST-628 is highly brain penetrant compared to trametinib or VS 6766. NST-628 reduces the growth of NRAS/MAPK mutant patient intracranial tumors, including Wuxi Pharmaron MEK mutant primary and metastatic CNS tumors, in the United States (FDA) and the United Kingdom, respectively. NST-628 is also a potent inhibitor of RAS/MEK/ERK signaling in primary and metastatic CNS tumors, including Wuxi Pharmaron MEK mutant primary and metastatic CNS tumors, in the United States (FDA) and the United Kingdom, respectively.

Conclusions/Acknowledgements

NST-628 is not only a highly brain penetrant and efficacious CNS tumor model, but it also has high therapeutic potential for the treatment of NRAS-driven intracranial tumors. NST-628 demonstrates superior CNS PK/PD, with a half-life of 150 μM and CNS penetration of > 80% for the target pathway (ERK) in mouse brain tissue. NST-628 is an orally bioavailable potent inhibitor of RAF, MEK, and ERK, with a predicted half-life of 150 μM and CNS penetration of > 80% for the target pathway (ERK) in mouse brain tissue. NST-628 demonstrates superior CNS PK/PD, with a half-life of 150 μM and CNS penetration of > 80% for the target pathway (ERK) in mouse brain tissue. NST-628 is highly brain penetrant compared to trametinib or VS 6766, leading to greater inhibition of MAPK signaling in the brain.

NST-628 reduces the growth of NRAS/MAPK mutant intracranial tumors, including Wuxi Pharmaron MEK mutant primary and metastatic CNS tumors, in the United States (FDA) and the United Kingdom, respectively. NST-628 addresses an area of unmet patient need.

NST-628 inhibits the RAS MAPK pathway and growth of NF1-mutant brain tumors in mice

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B)

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