Anti-Tumor Activity of ASTX029, a Dual-Mechanism Inhibitor of ERK1/2, in Preclinical AML Models

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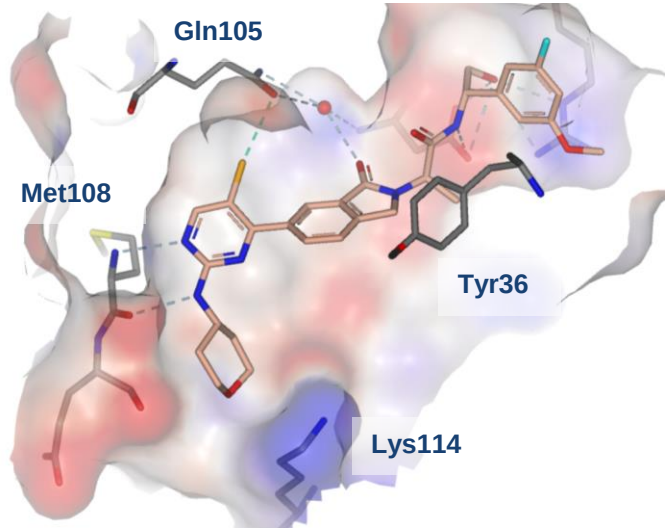
Disclosures

- **All authors are current employees of Astex Pharmaceuticals**

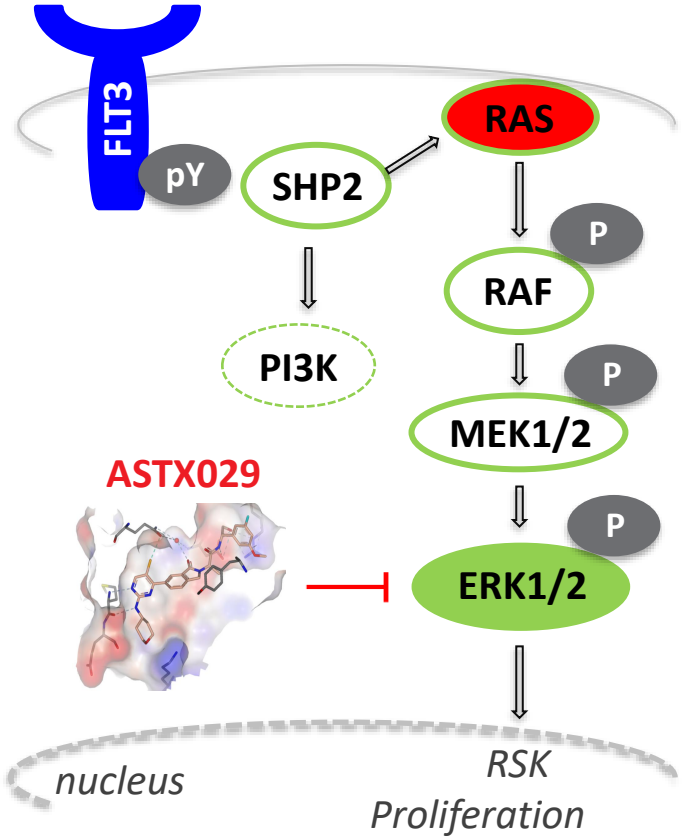
ASTX029, a Novel Dual-Mechanism ERK1/2 Inhibitor Discovered Using Fragment-Based Drug Discovery (FBDD)

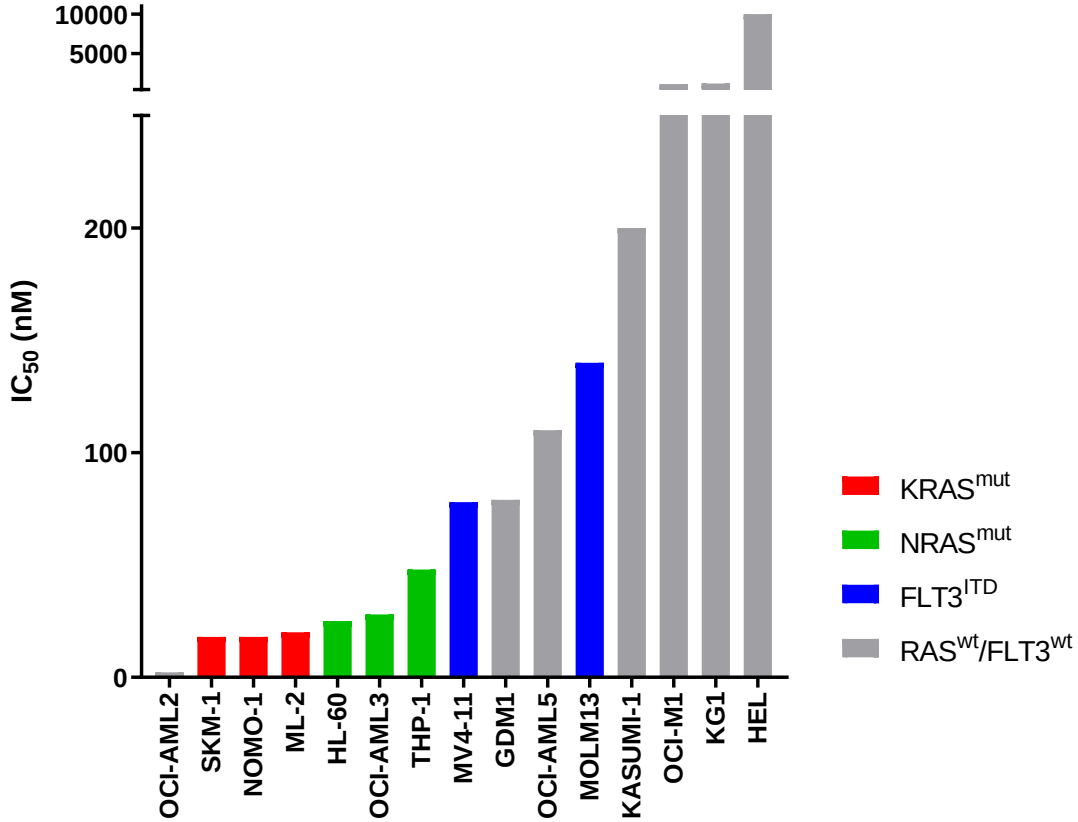
- We have recently reported* the discovery of ASTX029, a novel, potent and selective inhibitor of ERK1/2 with a dual-mechanism of action
- The compound was discovered using FBDD and binds to the active site in an extended conformation, exploiting a pocket created by an unusual movement of the P-loop Tyr36 residue
- ASTX029 inhibits both the kinase activity of ERK and its phosphorylation by MEK1/2 and is a potent inhibitor of cell growth in MAPK-activated tumor models*
- We identified through a broad cell panel screen that FLT3- and RAS-mutant AML cell lines were also sensitive to ASTX029



* Data presented at EORTC-NCI-AACR 2020 Virtual Meeting, Munck *et al.*, poster no. 187 – available to download from www.astx.com

ASTX029 Has Growth Inhibitory Activity in MAPK-activated AML Cell Lines In Vitro



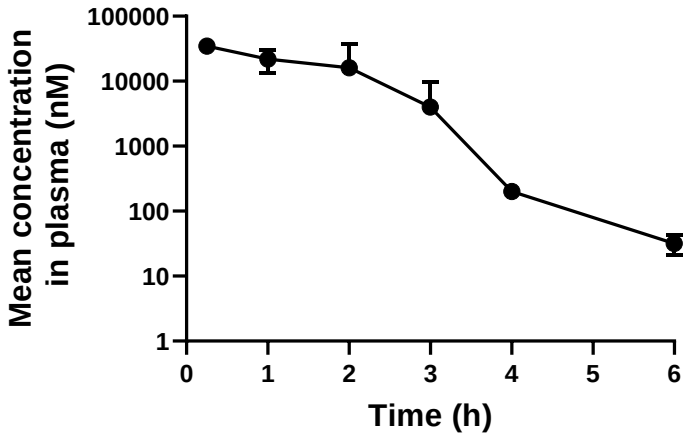


ASTX029 showed potent growth inhibitory activity in 8 AML cell lines bearing activating mutations in KRAS, NRAS or FLT3

– Average IC_{50} value for MAPK-activated cell lines was 47 nM compared to 1800 nM for the other 7 cell lines

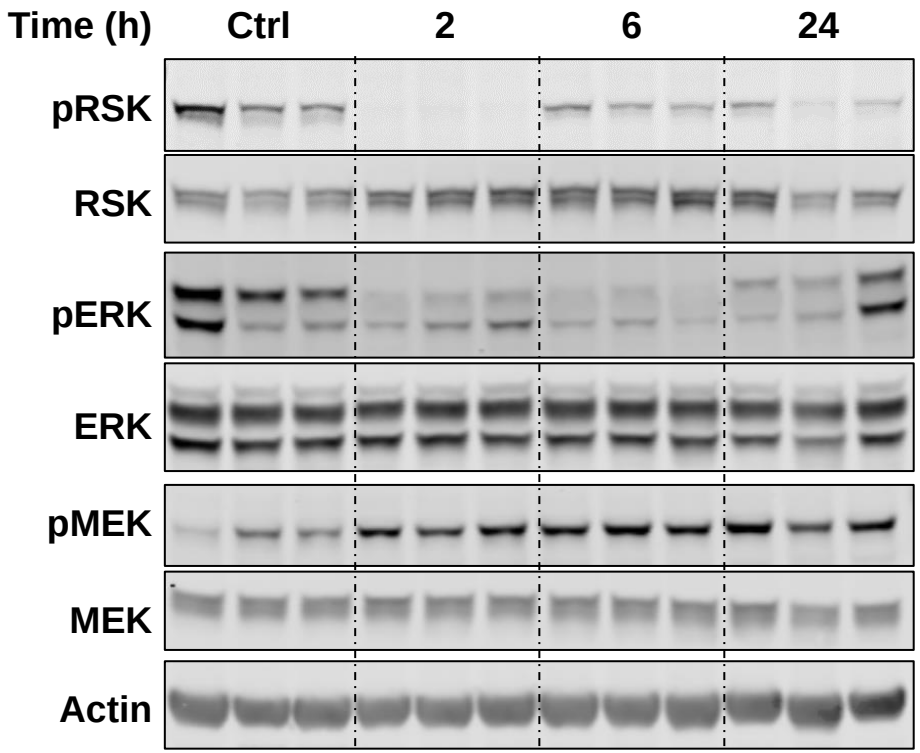
ASTX029 Exhibits Good Exposure Following Oral Administration

75 mg/kg ASTX029 PO



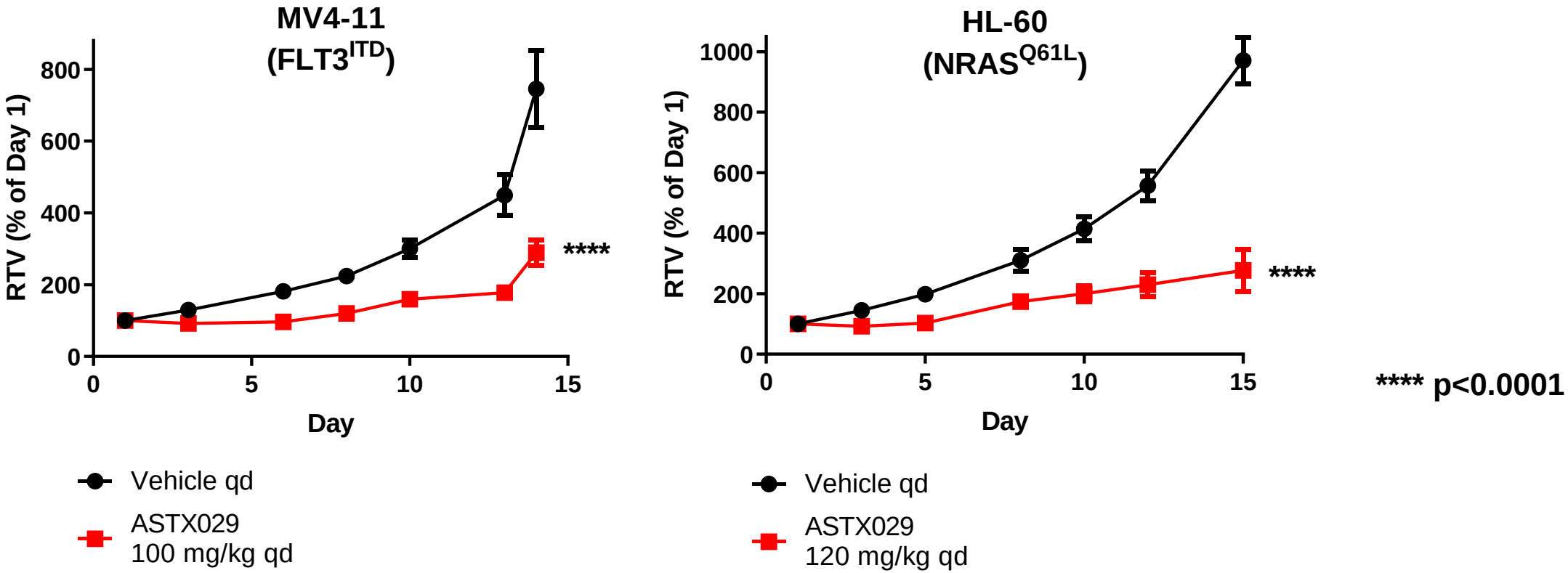
	ASTX029 (75 mg/kg)
$T_{½}$ (h)	0.53
T_{max} (h)	0.25
C_{max} (nM)	35000
AUC (h*nM)	57000

MV4-11 ($FLT3^{ITD}$) xenograft tumors



- **Single, oral dose of 75 mg/kg ASTX029 administered to mice**
- **Target engagement observed in vivo**
  - Reduction in pRSK observed on treatment with ASTX029
  - Despite increase in pMEK, pERK levels reduced on treatment with ASTX029
  - Reduction of both pRSK and pERK confirms dual-mechanism of action

ASTX029 Inhibits Tumor Growth in Subcutaneous AML Xenograft Models In Vivo



- **ASTX029 demonstrates anti-tumor activity in subcutaneous xenograft models of AML**
  - Activity observed in mutant FLT3- and RAS-driven models

Summary and conclusions

- ASTX029 inhibits growth of FLT3- and RAS-mutant AML models
- ASTX029 is a dual-mechanism inhibitor which reduces levels of pRSK and pERK in vivo
- The compound was well tolerated in a once-daily dosing schedule, leading to anti-tumor activity in subcutaneous xenograft models
- The data provide a rationale for testing of ASTX029 in AML, potentially in combination with other agents
- Clinical development of ASTX029 is ongoing in a Ph1/2 trial in advanced solid tumors (NCT03520075)

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