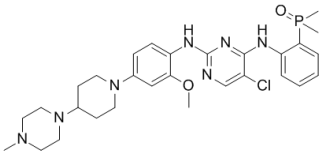
Data Sheet

Product Name:	Brigatinib
Cat. No.:	CS-4278
CAS No.:	1197953-54-0
Molecular Formula:	$C_{29}H_{39}ClN_7O_2P$
Molecular Weight:	584.09
Target:	ALK
Pathway:	Protein Tyrosine Kinase/RTK
Solubility:	DMSO : 2 mg/mL (3.42 mM; Need ultrasonic); Ethanol : 10 mg/mL (17.12 mM; Need ultrasonic and warming)



BIOLOGICAL ACTIVITY:

Brigatinib is a highly potent and selective **ALK** inhibitor, with **IC_{50}** of 0.6 nM.
IC50 & Target: IC50: 0.6 nM (ALK)[1]
In Vitro: Brigatinib potently inhibits the in vitro kinase activity of ALK (IC_{50}, 0.6 nM) and all five mutant variants tested, including G1202R (IC_{50}, 0.6-6.6 nM). Brigatinib demonstrates a high degree of selectivity, only inhibiting 11 additional native or mutant kinases with IC_{50} <10 nM. These include ROS1, FLT3, and mutant variants of FLT3 (D835Y) and EGFR (L858R; IC_{50}, 1.5-2.1 nM). Brigatinib exhibits more modest activity against EGFR with a T790M resistance mutation (L858R/T790M), native EGFR, IGF1R, and INSR (IC_{50}, 29-160 nM) and does not inhibit MET (IC_{50} >1000 nM). In cellular assays, brigatinib inhibits ALK and ROS1 with IC_{50}s of 14 and 18 nM, respectively. Brigatinib inhibits FLT3 and IGF-1R with about 11-fold lower potency (IC_{50}, 148-158 nM) and inhibits mutant variants of FLT3 and EGFR with 15- to 35-fold lower potency (IC_{50}, 211-489 nM). Brigatinib inhibits cell growth with GI_{50} values ranging from 503 to 2,387 nM in three ALK-negative ALCL and NSCLC cell lines[1]. Brigatinib inhibits ALK activity and abrogates proliferation of ALK addicted neuroblastoma cell lines, with IC_{50} of 75.27 ± 8.89 nM. Brigatinib inhibits both the ALK-I1171N and the ALK-G1269A mutant receptors at 10 and 4 nM levels, respectively[3].
In Vivo: Brigatinib (10, 25, or 50 mg/kg once daily, p.o.) leads to a dose-dependent inhibition of tumor growth in ALK^+ Karpas-299 (ALCL) and H2228 (NSCLC) xenograft mouse models. Brigatinib markedly enhances survival of mice bearing ALK^+ brain tumors compared with crizotinib[1]. Brigatinib (10, 25, 50 mg/kg, p.o.) results in dose-dependent antitumor activity, with tumor regressions in a mouse model of NSCLC[2].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]In vitro HotSpot^{SM} kinase profiling of 289 kinases is performed. The assay is conducted in the presence of 10 μM [^{33}P]-ATP, using brigatinib concentrations ranging from 0.05 nM to 1 μM. **Cell Assay:** [3]Cells are seeded at 15,000 per well with serial dilutions of the indicated inhibitors. After 72 hours cell viability is assessed by resazurin. IC_{50} values are calculated with GraphPad Prism 6.0 by fitting data to a log (inhibitor concentration) vs. normalized response (variable slope) equation. Each experiment is performed in duplicate and repeated at least three times. **Animal Administration:** [2]Mice: (1) Eight- to 10-week-old female SCID/beige mice are injected intravenously with 5×10^6 H3122 cells per mouse and are randomly selected into treatment groups (n=10) when the average tumor size reaches appr 300 mm^3 (day zero). Treatments are administered orally for up to 21 consecutive days at a 10 mL/kg dose volume. Subcutaneous tumors are measured two or three times weekly. Tumor volume (in mm^3) is calculated using the formula $(L\times W^2)/2$. When a tumor reaches 10% of the body weight of the host, the animal is euthanized via CO_2 asphyxiation. (2) Eight- to 10-week old female SCID/beige mice are injected subcutaneously with 2.5×10^6 Karpas-299 cells per mouse and are randomly selected into treatment groups (n=10) when the average tumor size reached appr 180 mm^3 (day zero). Treatments are administered orally for

14 consecutive days at a 10 mL/kg dose volume. Tumor volume is measured and calculated as described for the H3122 model.

References:

[1]. Zhang S, et al. The Potent ALK Inhibitor Brigatinib (AP26113) Overcomes Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in Preclinical Models. Clin Cancer Res. 2016 Nov 15;22(22):5527-5538

[2]. Huang WS, et al. Discovery of Brigatinib (AP26113), a Phosphine Oxide-Containing, Potent, Orally Active Inhibitor of Anaplastic Lymphoma Kinase. J Med Chem. 2016 May 26;59(10):4948-64.

[3]. Siaw JT, et al. Brigatinib, an anaplastic lymphoma kinase inhibitor, abrogates activity and growth in ALK-positive neuroblastoma cells, Drosophila and mice. Oncotarget. 2016 May 17;7(20):29011-22

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