产品名称：Amuvatinib(MP-470)
产品别名：Amuvatinib；MP470; HPK 56

生物活性：

Description	Amuvatinib (MP470) is an orally bioavailable multi-targeted tyrosine kinase inhibitor with potent activity against mutant c-Kit, PDGFRα, Flt3, c-Met and c-Ret. Amuvatinib (MP470) is also a DNA repair suppressor through suppression of DNA repair protein RAD51, thereby disrupting DNA damage repair[1][2][3]. Antineoplastic activity[4].					
IC_{50} & Target	$PDGFR\alpha^{V561D}$	$PDGFR\alpha^{D842V}$	$c\text{-}Kit^{D816H}$	$c\text{-}Kit^{V560G}$	$c\text{-}Kit^{V654A}$	$c\text{-}Kit^{D816V}$
	40 nM (IC_{50})	81 nM (IC_{50})	10 nM (IC_{50})	34 nM (IC_{50})	127 nM (IC_{50})	950 nM (IC_{50})

In Vitro

Amuvatinib (MP470) inhibits c-Kit (D816V), c-Kit (D816H), c-Kit (V560G), c-Kit (V654A), PDGFRα (D842V), and PDGFRα (V561D) with IC50s of 950 nM, 10 nM, 34 nM, 127 nM, 81 nM, and 40 nM, respectively[4].

Amuvatinib (MP470), a novel receptor tyrosine kinase (RTK) inhibitor has shown growth inhibitory activity against a variety of cancer cell lines. Amuvatinib (0.1-10 μM, 4 days incubation) is effective on LNCaP and PC-3 cells with IC50s of ~4 μM and 8 μM, respectively. When Erlotinib (10 μM) is combined with varying doses of Amuvatinib, the IC50 of Amuvatinib decreases to 2 μM on LNCaP cells[5].

Akt activity (as measured by phosphorylation on Ser473) is significantly reduced by 10 μM Amuvatinib (treated for 30 hours) alone but is not reduced by Erlotinib or Imatinib Mesylate (IM). Moreover, Amuvatinib plus Erlotinib completely abolished Akt phosphorylation in LNCaP cells with an unchanged total protein level of Akt[5].

Cell Viability Assay[2]

Cell Line:	Prostate cancer cell lines (LNCaP, PC-3 and DU-145)
Concentration:	0.1-10 μM
Incubation Time:	4 days
Result:	The IC_{50} for LNCaP and PC-3 was ~4 μM and 8 μM, respectively. Had only a modest effect on the viability of DU-145 cells.

Western Blot Analysis[2]

Cell Line:	LNCaP cells
Concentration:	2,5,10 μM
Incubation Time:	30 hours
Result:	Akt activity (as measured by phosphorylation on Ser473) was significantly reduced at 10 μM.

In Vivo

Four LNCaP xenograft arms each with 12 mice are dosed intraperitoneally with DMSO (control) or Erlotinib 80 mg/kg or Amuvatinib (MP470) 50 mg/kg or Erlotinib 80 mg/kg plus Amuvatinib 50 mg/kg daily for 2 weeks and then observed for a further 11 days. Individual therapy with Amuvatinib or Erlotinib shows modest tumor growth inhibition (TGI), while Amuvatinib plus Erlotinib has a marked effect on TGI (45-65%). However, due to the high doses of Amuvatinib used, only five or one mouse remained alive in the combination arm at the end of treatment or at the end of the study, respectively. Therefore the Amuvatinib dose is reduced to 10 mg/kg or 20 mg/kg for the combination treatment. TGI in the group receiving 10 mg/kg Amuvatinib+80 mg/kg Erlotinib is not significantly different from the control group. However, mice receiving 20 mg/kg Amuvatinib+80 mg/kg Erlotinib have a significant TGI compared to the control group (p=0.01)[5].

Animal Model:	Forty eight 6-7 week-old SCID male mice with LNCaP xenograft model[2]

	Dosage:	10 mg/kg and 20 mg/kg, 50 mg/kg
	Administration:	Administered i.p. daily from days 1 to 24
	Result:	Individual therapy showed modest tumor growth inhibition (TGI), while combination had a marked effect on TGI (45-65%).

Solvent&Solubility

In Vitro:

DMSO : 50 mg/mL (**111.73 mM;** Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	**1 mg**	**5 mg**	**10 mg**
	1 mM	2.2346 mL	11.1729 mL	22.3459 mL
	5 mM	0.4469 mL	2.2346 mL	4.4692 mL
	10 mM	0.2235 mL	1.1173 mL	2.2346 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (5.59 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.59 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

References

[1]. Choy G, et al. Safety, tolerability, and pharmacokinetics of amuvatinib from three phase 1 clinical studies in healthy volunteers. Cancer Chemother Pharmacol. 2012 Jul;70(1):183-90.

[2]. Tibes R, et al. A phase I, first-in-human dose-escalation study of amuvatinib, a multi-targeted tyrosine kinase inhibitor, in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2013 Feb;71(2):463-71.

[3]. Baxter PA, et al. Plasma and cerebrospinal fluid pharmacokinetics of MP470 in non-human primates. Cancer Chemother Pharmacol. 2011 Apr;67(4):809-12.

[4]. David J. Bearss, et al. Pharmaceutical formulations comprising salts of a protein kinase inhibitor and methods of using same. US20080226747A1.

[5]. Qi W, et al. MP470, a novel receptor tyrosine kinase inhibitor, in combination with Erlotinib inhibits the HER family/PI3K/Akt pathway and tumor growth in prostate cancer. BMC Cancer. 2009 May 11;9:142.