产品名称：ARRY-380
产品别名：Tucatinib；ONT-380

生物活性：

Description	Tucatinib (Irbinitinib; ARRY-380; ONT-380) is a potent and selective HER2 inhibitor with an IC_{50} of 8 nM.
IC_{50} & Target	HER2
In Vitro	Tucatinib (ONT-380) is a potent, selective, ATP-competitive, orally administered small-molecule inhibitor of HER2. Tucatinib has nanomolar activity against purified HER2 enzyme and is approximately 500-fold selective for HER2 versus EGFR in cell-based assays. Tucatinib selectively inhibits the receptor tyrosine kinase HER2 relative to EGFR. In HER2 overexpressing cell lines, Tucatinib blocks proliferation and the phosphorylation of HER2 and its downstream effector, Akt. By contrast, in the EGFR overexpressing cell lines, it weakly inhibits phosphorylation and proliferation, demonstrating that Tucatinib may have potential to block HER2 signaling without causing the toxicities of EGFR inhibition[1].
In Vivo	In preclinical studies with intracranial tumor models, treatment of mice with Tucatinib (ONT-380) compared with GW572016 or neratinib shows a survival benefit when each drug is dosed at the maximum-tolerated dose[1]. In the Tucatinib (ARRY-380)-treated-group, 75% of the animals are alive on Day 43. Tucatinib and its active metabolite causes a significant reduction in brain pErbB2 (80%)[2]. Tucatinib (ARRY-380) demonstrates significant dose-related tumor growth inhibition (TGI; 50% at 50 mg/kg/d and 96% at 100 mg/kg/d) with numerous partial regressions (>50% reduction from baseline size) at the higher dose level in 9/12 animals. Tucatinib (50 mg/kg/d) in combination with trastuzumab shows a 98% TGI with complete regressions in 9/12 animals and two partial regressions. At dose of 100 mg/kg/d of Tucatinib in combination with trastuzumab, there is 100% TGI and all animals have complete responses[3].

Solvent&Solubility

In Vitro:

DMSO：50 mg/mL (104.05 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0811 mL	10.4054 mL	20.8108 mL
	5 mM	0.4162 mL	2.0811 mL	4.1622 mL
	10 mM	0.2081 mL	1.0405 mL	2.0811 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 (5.20 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.20 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。

	2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (5.20 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.20 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 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (5.20 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.20 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Moulder-Thompson S, et al. Phase 1 Study of ONT-380, a HER2 Inhibitor, in Patients with HER2+ Advanced Solid Tumors, with an Expansion Cohort in HER2+ Metastatic Breast Cancer (MBC). Clin Cancer Res. 2017 Jan 4. pii: clincanres.1496.2016. [2]. Abstract: In: Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research; 2012 Mar 31-Apr 4; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2012;72(8 Suppl):Abstract nr 852. doi:1538-7445.AM2012-852 [3]. P. Lee, et al. In Vivo Activity of ARRY-380, a Potent, Small Molecule Inhibitor of ErbB2 in Combination with RP-56976. Cancer Research

实验参考：

Animal Administration	Mice: For the SKOV-3 tumor studies, female nude mice are inoculated with cells subcutaneously in the flank. Animals received: doses of Tucatinib ranging up to 200 mg/kg/d, PO; and/or Trastuzumab at 20 mg/kg, IP, Q3D or QW; and/or RP-56976 at 10 mg/kg, IV, Q3D; and/or Bevacizumab at 10 mg/kg, IP, Q4D x3. Tumor size is measured at regular intervals and subsets of animals are monitored for up to 90 days to determine tumor-free survival [3]
References	[1]. Moulder-Thompson S, et al. Phase 1 Study of ONT-380, a HER2 Inhibitor, in Patients with HER2+ Advanced Solid Tumors, with an Expansion Cohort in HER2+ Metastatic Breast Cancer (MBC). Clin Cancer Res. 2017 Jan 4. pii: clincanres.1496.2016. [2]. Abstract: In: Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research; 2012 Mar 31-Apr 4; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2012;72(8 Suppl):Abstract nr 852. doi:1538-7445.AM2012-852 [3]. P. Lee, et al. In Vivo Activity of ARRY-380, a Potent, Small Molecule Inhibitor of ErbB2 in Combination with RP-56976. Cancer Research