Product Data Sheet

Product Name: Toceranib
Cat. No.: GC10719

Chemical Properties

Cas. No.	356068-94-5		
Chemical Name	5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-N-(2-pyrrolidin-1-ylethyl)-1H-pyrrole-3-carboxamide		
SMILES	CC1=C(NC(=C1C(=O)NCCN2CCCC2)C)C=C3C4=C(C=CC(=C4)F)NC3=O		
Formula	$C_{22}H_{25}FN_4O_2$	M.Wt	396.46
Solubility	DMF: 0.25 mg/ml,DMSO: 0.5 mg/ml	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	Toceranib		

Protocol

Cell experiment:

The c-kit mutant canine C2 mastocytoma cell line, derived from a spontaneously occurring cutaneous mast cell tumors (MCTs), is used as the parental cell line. Cells are propagated in RPMI 1640 supplemented with 2 mM L-glutamine, 10% FBS, 100 g/mL Streptomycin, and 100 U/mL Penicillin in a 37°C incubator under a humidified atmosphere of 5% CO2. Toceranib-resistant C2 cells are selected by growing C2 cells in concentrations of Toceranib ranging from 0.02 uM to 0.3 uM and increasing in 0.025-0.05 uM increments. Three independent, Toceranib -resistant sublines are established over a period of 7 months[2].

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

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Animal experiment:	Dogs[3]Fifteen client-owned dogs with advanced tumors are used. Dogs receive Toceranib at 2.75 mg/kg once every other day. After 2 weeks, oral cyclophosphamide (CYC) is added at 15 mg/m2 daily. Numbers of Treg and lymphocyte subsets are measured in blood by flow cytometry during the 8-week study period. Serum concentrations of IFN-γ are measured by ELISA.

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References:

[1]. London CA, et al. Phase I dose-escalating study of SU11654, a small molecule receptor tyrosine kinase inhibitor, in dogs with spontaneous malignancies. Clin Cancer Res. 2003 Jul;9(7):2755-68.
[2]. Halsey CH, et al. Development of an in vitro model of acquired resistance to toceranib phosphate (Palladia) in canine mast cell tumor. BMC Vet Res. 2014 May 6;10:105.
[3]. Mitchell L, et al. Clinical and immunomodulatory effects of toceranib combined with low-dose cyclophosphamide in dogs with cancer. J Vet Intern Med. 2012 Mar-Apr;26(2):355-62.

Background

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Background

Toceranib is an inhibitor which blocks various tyrosine kinases expressed on the cell surface. Receptor tyrosine kinases (RTKs) are excellent candidates for molecular targeted therapy, because they play key roles in controlling cell proliferation and survival and are frequently dysregulated in a variety of malignancies.

In vitro: Toceranib inhibited KIT phosphorylation and cell proliferation in a dose-dependent manner in the treatment-naïve, parental C2 line (IC50 < 10 nM). In addition, chronic TOC exposure resulted in c-kit mRNA and KIT protein overexpression in the TOC-resistant sublines [1].

In vivo: Fourteen dogs with advanced mast cell tumors (MCTs) were enrolled in a prevoius study, among which 11 dogs were evaluable for KIT target modulation. Of these, eight MCTs showed reduced levels of phosphorylated KIT relative to total KIT after treatment with Toceranib, compared with pretreatment biopsies. All four evaluable MCTs expressing ITD mutant c-kit showed modulation of KIT phosphorylation, as did four of seven tumors expressing non-ITD c-kit. [2].

Clinical trials: Currenlty no clinical data are available.

References:
[1] Halsey CH, Gustafson DL, Rose BJ, Wolf-Ringwall A, Burnett RC, Duval DL, Avery AC, Thamm DH. Development of an in vitro model of acquired resistance to toceranib phosphate (Palladia®) in canine mast cell tumor. BMC Vet Res. 2014;10:105. doi: 10.1186/1746-6148-10-105.
[2] Pryer NK, Lee LB, Zadovaskaya R, Yu X, Sukbuntherng J, Cherrington JM, London CA. Proof of target for SU11654: inhibition of KIT phosphorylation in canine mast cell tumors. Clin Cancer Res. 2003;9(15):5729-34.

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