Crizotinib

Xalkori®

Mechanism of Action

According to the FDA NDA 202570, "crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS1 (c-ros), and Recepteur d'Origine Nantais (RON). Translocations can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins. Crizotinib demonstrated concentration-dependent inhibition of ALK, ROS1, and c-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed echinoderm microtubule-associated protein-like 4 (EML4)-or nucleophosmin (NPM)-ALK fusion proteins or c-Met.

In vitro, crizotinib induced apoptosis and inhibited proliferation and ALK-mediated signaling in ALCL-derived cell lines (containing NPM-ALK) at clinically achievable exposures. In vivo data obtained in an ALCL-derived mouse model showed complete regression of the tumor at a dose of 100 mg/kg once daily."

Toxicology

According to the FDA NDA 202570:

In a 1-month oral toxicity study of beagles given crizotinib at 0, 1, 6, or 20 mg/kg, effects included emesis and diarrhea in both males and females at > 6 mg/kg, and decreased cellularity of the thymus in males at 20 mg/kg. ECG results showed that QT/QTc intervals before or after dosing on Day 22 were increased compared to pre-study values in 2 dogs (1 male and 1 female) at the 20 mg/kg dose level.

In a 3-month oral toxicity study of beagles given crizotinib at 0, 1, 5, or 25 mg/kg followed by a 2-month recovery period, **target organs** of toxicity included the bone marrow, mesenteric lymph node, jejunum, and stomach. **Hematology** changes included a decrease in RBC parameters (RBC count, hemoglobin, and hematocrit) and increases in white blood cell parameters (WBC count, neutrophils, lymphocytes, monocytes, and eosinophils), platelets, and fibrinogen. Clinical **chemistry** changes included increases in ALT, AST, ALP, and GGT and decreases in albumin and calcium. **Clinical signs** included emesis and water/mucoid feces at ≥ 5 mg/kg. **Electrophysiological** changes included increasedQT interval from pretreatment levels in males treated with 5 and 25 mg/kg and females treated with 25 mg/kg at Weeks 6 and 13. No mortality was observed in this study, and body weights, organ weights, and urinalysis findings were

unremarkable. No treatment-related ophthalmic findings were observed in the 1- and 3-month general toxicology studies.

Hemodynamic and electrophysiological parameters: In isoflurane-anesthetized beagles receiving IV crizotinib (loading infusions over 10 min; maintenance infusions over 25 minutes), there were significant decreases in heart rate and increases in left ventricular end diastolic pressure (LVEDP) at the two highest doses (1.192 and 1.907 mg/kg loading dose, 0.0834 and 0.134 mg/kg/min maintenance dose) compared to vehicle treatment. Additionally, there were significant differences in myocardial contractility (LV+dP/dt) at the highest dose (1.907 mg/kg loading dose, 0.134 mg/kg/min maintenance dose). There were significant increases in PR-interval, QRS-interval, and QT-interval at the two highest doses of PF-02341066 [crizotinib].

FDA Labeled Use

Xalkori® is not labeled for dogs; therefore use of this drug in the dog is off-label.

According to the FDA's Highlight of Prescribing Information (Reference ID 4860921):
Xalkori® is indicated for the treatment of

- patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test.
- pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive.

Selected Canine Publications

:: Preclinical

- Treatment of a canine osteosarcoma cell line (OSA8) with crizotinib (0.25-8 μM) reduced proliferation in a dose dependent manner. Treatment with a combination of gefinitib and crizotinib inhibited cell proliferation in an additive manner (McCleese JK et al.).

- Crizotinib only slightly inhibited viability of COS osteosarcoma cells at concentrations of 100 nM and greater (no effect on Clone-4 cells at concentrations less than 3 μM). The crizotinib IC50 for the COS cells were 340 nM and 357 nM for the untreated and HGF-treated cells, respectively; and no IC50 values were observice for crizotinib in the Clone-4 cells because the drug did not effectively reduce viability in these cells (Marley K et al.).

:: Safety/dosing

None currently

:: Efficacy

None currently

Pharmacokinetics

According to the FDA NDA 202570, a single oral dose of crizotinib 10 mg/kg is primarily eliminated in the feces (62.47% and 85.36% of the administered dose in males and females, respectively), with minor excretion in the urine (~2% of administered amount in both males and females).

The average unbound fraction was 0.043 (4.3%) in dog plasma (over concentrations 0.5, 5, and 20 µM).

Pharmacokinetic data excerpted from the FDA NDA 202570:

Table 35: Pharamacokinetic parameters for radioactivity in plasma of male and female dogs after a single administration of [14C] PF-02341066 (10 mg/kg)

Pharmacokinetic parameters	Males	Females
C_{max} (ng eq/g)	938	781
T_{max} (hours)	6	1
$AUC_{(0-t)}$ (ng eq·hours/g)	15900	12000
$AUC_{(0-\infty)}$ (ng eq·hours/g)	17600	13900
$t_{1/2}$ (hours)	14.0	12.4

Toxicokinetic results showed that in general, exposure to crizotinib was similar between male and female dogs. Excerpted from the FDA NDA 202570:

Dose (mg/kg/day)	Study Day	Gender	Cmax (ng/mL)			tmax (h)			AUC(0-24) (ng*h/mL)		
			Mean	SD	n	Mean	SD	n	Mean	SD	n
1	1	Male	40.4	12.9	5	2.6	1.3	5	518	149	5
		Female	44.8	13.1	5	2.0	0.0	5	502	118	5
		Overall	42.6	12.5	10	2.3	0.95	10	510	127	10
	91	Male	78.8	16.6	5	3.0	1.4	5	1220	277	5
		Female	82.6	4.12	5	3.2	1.1	5	1280	119	5
		Overall	80.7	11.6	10	3.1	1.2	10	1250	204	10
5	1	Male	300	250	5	1.2	0.45	5	3930	3220	5
		Female	322	63.1	5	1.4	0.55	5	4150	686	5
		Overall	311	172	10	1.3	0.48	10	4040	2200	10
	91	Male	614	238	5	4.0	2.1	5	10200	3740	5
		Female	475	64.2	5	1.6	1.3	5	7570	1720	5
		Overall	545	180	10	2.8	2.1	10	8900	3080	10
25	1	Male	739	655	5	1.6	1.3	5	9270	7490	5
		Female	889	442	5	1.8	1.3	5	12800	6620	5
		Overall	814	532	10	1.7	1.3	10	11100	6920	10
	91	Male	1440	547	5	4.8	3.0	5	25900	10100	5
		Female	2200	748	5	6.0	2.2	5	43400	13700	5
		Overall	1820	737	10	5.4	2.6	10	34600	14600	10

Overall = Males and Females Combined

Sources

- Best Pet Rx (https://bestpetrx.com/): (as of October 18, 2021) Unavailable.

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of December 3, 2021): Available in dose range of 10 mg to 100 mg capsules:

Dose 10 mg, quantity 30, $495.
Dose 100 mg, quantity 30, $595.

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/items/crizotinib-capsule.html): (as of September 29, 2021) Available in dose range* of 22 mg to 30 mg capsules:
Dose 22 mg capsules, quantity 30, $159.50
Dose 30 mg capsules, quantity 30, $195.75

**This dose range may not appear on your online portal. If so, please call Wedgewood Pharmacy (call center 877.357.6613) to prescribe this drug.*

Anecdotal Information from Veterinary Oncologists

None currently.

References

Xalkori® (Crizotinib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 202570, August 2011.

Marley K et al. Dasatinib modulates invasive and migratory properties of canine osteosarcoma and has therapeutic potential in affected dogs. *Transl Oncol*. 2015 Aug;8(4):231-8. doi: 10.1016/j.tranon.2015.03.006.

McCleese JK et al. Met interacts with EGFR and Ron in canine osteosarcoma. *Vet Comp Oncol.* 2013 June;11(2):124-139. doi:10.1111/j.1476-5829.2011.00309.x.

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