Vemurafenib

Zelboraf®

Mechanism of Action

According to the FDA NDA 202429, "vemurafenib is a low molecular weight, orally available inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E. Vemurafenib also inhibits other kinases in vitro such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5, and FGR at similar concentrations. Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Vemurafenib has anti-tumor effects in cellular and animal models of melanomas with mutated BRAF V600E."

Toxicology

According to the FDA NDA 202429:
A 39-week dosing study was started but soon aborted.

- Due to the high doses (450 mg/kg twice daily [BID] and 300 mg/kg BID, HD) proving to be intolerable. Two dogs were moribund (450 mg/kg BID) and showed clinical signs of excessive salivation, vomiting, dehydration, and soft or malformed feces, hypoactivity, thin appearance, tremor, and reddened skin. HD dogs lost weight and were hypoxic. Dogs given 150 mg/kg BID (median dose, MD) showed these signs less frequently and with less severity. Twelve dogs were given 50 mg/kg BID (low dose, LD).
- There was a dose-dependent increase in liver function enzymes and decreases in all parameters consistent with significant liver damage. There was also a dose-dependent neutrophilia and profound eosinophilia consistent with an allergic response.
- The two moribund dogs had post-mortem examination; in the liver, there was minimal scattered hepatocellular degeneration, mild-moderate increase in Kupffer cells, and pigment in hepatocytes and Kupffer cells. These changes correlated to the increased ALP, ALT, AST, GGT levels.
- Some dogs in all doses vocalized and struggled during dosing, suggesting pain.

In a 13-week oral gavage study, beagles given 300 mg/kg BID (HD) resulted in 2 early deaths (males) and 1 moribund female given 150 mg/kg BID with early death.

- These dogs had lost weight, appeared thin, refused canned food, vomited, and vocalized during handling suggesting pain. Histomorphological changes in the liver included necrosis, perivascular mixed infiltrates, and Kupffer cell increases, although the damage in the liver was not sufficient to account for the animal's demise. These dogs had been treated with vemurafenib one month earlier; the previous exposure likely contributed to their death.

- Those animals that survived to Day 28 showed signs of vomiting, vocalizing, and weight loss in males. Dogs necropsied on Day 28 showed signs of hepatic damage (increased liver function enzymes, decreased serum protein and microscopic damage). BUN was low. Liver damage as measured by ALT was somewhat worse in females. HD males had a prolonged QT interval.

In a 13-week oral gavage study, dogs given 75 mg/kg BID (LD) resulted in 2 moribund dogs and early euthanasia, and dogs given 150 mg/kg BID (HD) resulted in 2 moribund dogs and early death. Previous exposure to vemurafenib likely contributed to the death of 3 dogs, and 1 dog died of aspiration pneumonia, secondary to vomiting; death was not considered to be drug-related.

- *Clinical signs*: HD dogs had marked increased incidence of interdigital cage sores or reddened skin relative to controls. Several in each group struggled during dosing and some vocalized suggesting pain. The incidence of vomiting was high in both groups for both genders. There were fecal abnormalities in all groups including controls probably associated with excretion of the vehicle. One HD male developed a "wart like growth" in the front left paw.
- *Hematology*: There was progressive neutrophilia with lymphocytosis. Monocytes were elevated and eosinophils were strikingly increased, suggesting allergic reaction, with effects more pronounced in males. Decrease in APTT (activated partial thromboplastin clotting time) while small was consistent across time in both sexes, possibly due to overexpression of a particular factor in the clotting cascade.
- *Chemistry*: Decreases in blood glucose and BUN were small and possibly due to decreased food consumption. Decreases in albumin, and increases in ALT, GGT, and AST are consistent with dose dependent liver damage and diminished liver function.
- *Histopathology*: the most pronounced damage was in the liver, along with thymus atrophy. Animals killed after 4 weeks of recovery showed only minimal damage in the liver indicating progressive recovery.

FDA Labeled Use

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

According to the FDA's Highlights of Prescribing Information (Reference ID 4610371):

- Zelboraf® is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
- Zelboraf® is indicated for the treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation.

Selected Canine Publications

:: Preclinical

Novel canine TCC cell lines were more sensitive to sorafenib compared to vemurafenib in regards to cell viability. By comparing the expression level of phosphorylated BRAF and

phosphorylated ERK1/2 proteins by Western blot analysis after drug treatment, sorafenib inhibited the MAPK pathway more effectively than vemurafenib (Jung et al.).

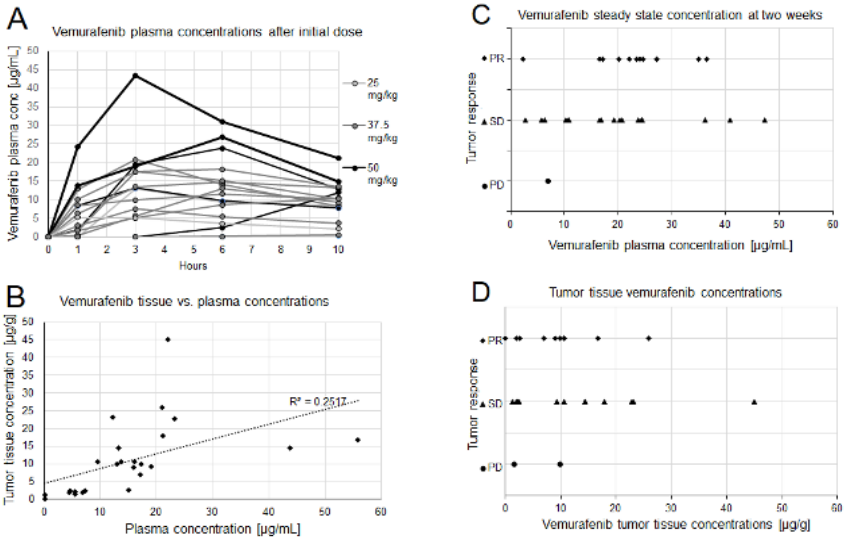
Safety/dosing and Efficacy

In a phase I/II trial of vemurafenib in dogs with naturally occurring BRAF_mutated urothelial carcinoma (Rossman et al.):

- Pet dogs with naturally occurring invasive urothelial carcinoma harboring the $BRAF^{V595E}$ mutation.
- Maximum tolerated dose (MTD) was 37.5 mg/kg PO BID
- At MTD, partial remission in 9/24 dogs (38%), and median progression free interval 181 days (range 53-608 days)
- Vemurafenib-related survival (vemurafenib start to death): 272 days (males 314 days, females 187 days)
- Overall survival (diagnosis to death): 354 days
- Dose-limiting toxicity (DLT): gastrointestinal (anorexia)
- Unusual adverse effect (known pharmacodynamic effect in humans receiving vemurafenib): formation of new cutaneous squamous cell carcinoma and squamous papillomas in 18% of dogs
- Increase in patterns of T lymphocyte infiltration during the first month of vemurafenib; immune failure accompanying cancer progression.

Pharmacokinetics

There was considerable variation noted between dogs. There were inconsistencies with drug digestion, with the finding of intact pills in the feces by 2 owners. Neither tissue nor plasma concentrations correlated with toxicity or antitumor activity (Rossman et al.):



According to the FDA NDA 202429:
In beagles given 75 mg/kg (LD) or 150 mg/kg (HD) TWICE daily orally (via gavage) for 13 weeks with a 4-week interim sacrifice and 4-week recovery phase, the apparent T_{max} was usually 9-11 hours (long). The C_{max} and AUC are approximately proportional to the dose (higher dose = higher C_{max}). With the HD, C_{max} in males was higher than it was in females on days 28 and 92, and AUC was also somewhat higher in males on day 29, both consistent with increased toxicity observed in males during the first month.

Table 17: PK Parameters from 13 Week Dog Study—Female

Female	Dose mg/kg	Day	T_{max}	C_{max} (ng/mL)	C_{max} (µM)	$AUC_{(0-24h)}$ ng*hr/mL	$AUC_{(0-24h)}$ µM*hr
G2	150	1	9	20600	42	282000	576
G2	150	29	11	27600	56.3	396000	808
G2	150	92	9	22400	45.7	250000	510
G3	300	1	11	42300	86.3	571000	1170
G3	300	29	3	31600	64.5	423000	863
G3	300	92	9	25900	52.9	360000	735

Table 16: PK Parameters from 13 Week Dog Study—Male

Male	Dose mg/kg/day	Day	T_{max} (hours)	C_{max} (ng/mL)	C_{max} (µM)	$AUC_{(0-24h)}$ ng*hr/mL	$AUC_{(0-24h)}$ µM*hr
G2	150	1	9	25400	51.8	345000	704
G2	150	29	9	28100	57.4	414000	845
G2	150	92	9	23100	47.1	289000	590
G3	300	1	11	43500	88.8	590000	1200
G3	300	29	6	36100	73.7	478000	976
G3	300	92	9	34900	71.2	384000	784

Sources

- Best Pet Rx (https://bestpetrx.com/contact-us/): (as of December 3, 2021): Unavailable

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of December 3, 2021) Unavailable

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/veterinary-practices/): (as of September 7, 2021) Unavailable

Anecdotal Information from Veterinary Oncologists

None currently

References

Jung et al. Establishment of canine transitional cell carcinoma cell lines harboring BRAF V595E mutation as a therapeutic target. *Int J Mol Sci*. 2021 Aug 25;22(17):9151. doi:10.3390/ijms22179151.

Rossman et al. Phase I/II trial of vemurafenib in dogs with naturally occurring, BRAF-mutated urothelial carcinoma. *Mol Cancer Ther*. 2021 Nov;20(11):2177-2188. doi: 10.1158/1535-7163.MCT-20-0893.

Zelboraf® (Vemurafenib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 202429, August 2011.

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