

A novel c-Kit inhibitor (AB1010) shows therapeutic potential in dog mast cell tumors

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AB1010 is an orally available small molecule that inhibits the juxtamembrane (JM) mutations of c-Kit with a 10-9M IC50. These mutations are associated with the development of DMCT.

An open-labeled Phase II study was performed to determine the therapeutic potential of AB1010. Dogs having measurable cutaneous grade 2 or 3 tumors, with or without metastasis, were evaluated. Thirteen dogs were enrolled with 9 dogs having sufficient treatment duration to evaluate for responsiveness to AB1010. Complete response was observed in 2 of 9 dogs, partial response in 2 of 9 dogs, stable response in 2 of 9 dogs, with 3 dogs having progressive disease. A partial response of the metastatic disease was observed in 2 of 3 dogs. Measurable responses were noted as early as day 7 of the study period. One of the 2 complete responders maintained remission for at least 182 days. The drug was well tolerated and grade 1 neutropenia was occasionally observed without consequences.

A randomized, double blinded, placebo-controlled, Phase III study is on going to confirm the clinical efficacy of AB1010. Main criteria for inclusion are: (1) non-resectable tumors or recurrent tumors following surgery (2) histopathologic grade 2 or 3 (3) no internal metastasis or lymph node involvement. To date, 170 dogs have been recruited. Complete results will be available in 2007. Genotyping of 40 tumors has been accomplished. Results show c-Kit expression in 100% of the tumors with less than 50% expressing the JM mutations. Furthermore preliminary clinical data strongly suggest that WT-c-Kit expressing tumors are also sensitive to AB1010. Taken together, our data indicate that other oncogenic mechanisms must be involved in the formation of DMCT, some of which appear to be sensitive to AB1010.