

## Chemotherapy for Gingival Squamous Cell Carcinoma?

Unfortunately, gingival squamous cell carcinoma is quite common in geriatric cats. While it tends to have a low metastatic potential, it still is one nasty diagnosis for a few reasons.

Cats are rather stoic and uncommunicative and oral masses are hidden from view in the mouth. Gingival squamous cell carcinoma tends to be invasive, growing from the gingiva down (or up) into the jaw bones. Therefore, by the time a diagnosis is made, the tumor is often quite large and has invaded deep into the facial structures. The small scale of a cat's mouth makes achieving 1 centimeter surgical margins in all planes very challenging. Therefore, surgical cure is often unachievable.

To date, we have not really had much to offer in the way of hope or adjunctive therapy – not for lack of trying. There have been a number of attempts to find some chemo or immunotherapy to improve quality of life and survival times. I recently became aware of an off-label use for a receptor tyrosine kinase (RTK) inhibitor by Pfizer under the name Palladia which has been showing some promise. Here are some bits of information sent to me by Dr. Clotilde Francis of Pfizer.

Technical information: PALLADIA is a antineoplastic agent belonging to the receptor tyrosine kinase (RTK) inhibitor class of drugs. PALLADIA is an oral receptor tyrosine kinase (RTK) inhibitor that blocks the activity of multiple receptors on cancer cells and blood vessels. The active ingredient in PALLADIA is toceranib. It is approved for use in dogs with recurrent non-resectable, cutaneous mast cell tumors (Patnaik grade II or III) with or without regional lymph node involvement.

**What role do receptor tyrosine kinases play in cancer?** Kinases are enzymes that catalyze the transfer of phosphate groups from ATP. Receptor tyrosine kinases (RTKs) are tyrosine kinases on the cell surface that are activated through binding of growth factors. Receptor tyrosine kinases play a role in signaling pathways that govern

normal cellular processes such as proliferation, migration, metabolism, and differentiation. Examples of RTKs include: platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), stem cell factor receptor (Kit). In normal cells, RTK activity is tightly controlled. In some cancerous conditions, abnormalities such as mutations can lead to abnormal activation of RTKs resulting in increased cellular proliferation and growth, prevention of apoptosis (cellular death) as well as increased angiogenesis and metastasis. The result of RTK dysfunction is phosphorylation of the kinase in the absence of an appropriate signal and constitutive signaling and abnormal promotion of cell growth and survival. These conditions promote tumor development, growth and progression.

**How does PALLADIA work?** Toceranib phosphate is a small molecule that has both direct antitumor and antiangiogenic activity. In non-clinical pharmacology studies, toceranib selectively inhibited the tyrosine kinase activity of several members of the split kinase receptor tyrosine kinase (RTK) family, some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Toceranib inhibited the activity of Flk-1/KDR tyrosine kinase (vascular endothelial growth factor receptor, VEGFR2), platelet-derived growth factor receptor (PDGFR), and stem cell factor receptor (Kit) in both biochemical and cellular assays. Toceranib has been shown to exert an antiproliferative effect on endothelial cells *in vitro*. Toceranib treatment can induce cell cycle arrest and subsequent apoptosis in tumor cell lines expressing activating mutations in the split kinase RTK, c-Kit. Canine mast cell tumor growth is frequently driven by activating mutations in c-Kit.

You will note that SCC is not mentioned in that information and nor are cats. That is because Palladia is not cleared for use in cats or in the treatment of SCC. Therefore its use in cats as part of the treatment of SCC is 'off-label' and so Pfizer cannot provide 'on-the-record'

information about such use. However, oncologists are aware of the drug and often use drugs off-label after obtaining informed owner consent.

I will not be using this drug myself. As Clotilde pointed out in her email to me “Because cancer cases are very complex (and time-consuming) to manage, we recommend that cancer patients be referred to a specialist as soon as the attending veterinarian suspects that they could benefit from innovative cancer therapy options.” and in these cases, the specialist I would be calling on is a board-certified veterinary oncologist. This is their shtick, and I am happy to let them do what they do best.