ONCEPT™

*The first DNA-based canine cancer vaccine, now **fully licensed** by the USDA.*

Proven to extend survival time in dogs treated for oral melanoma.*[1]

*Product indications: vaccine aids in extending survival times of dogs with stage II or stage III oral melanoma and for which local disease control has been achieved.

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ONCEPT™. *Fully licensed. Proven to extend survival time.**

Since 2007, thousands of dogs[2] have been treated with a therapeutic vaccine following surgical removal of primary canine oral melanoma (COM) tumors, under a conditional license. Meanwhile, additional clinical trials of the vaccine's efficacy have been conducted and are reported here.

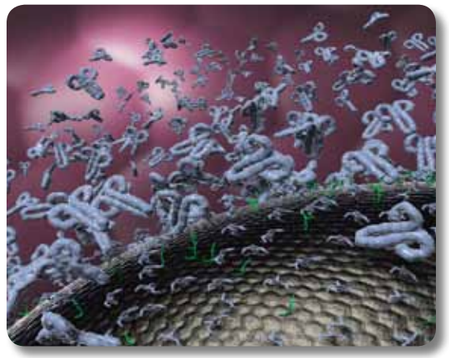
Now this innovative vaccine is fully licensed by the USDA and is available to board-certified oncology specialists as ONCEPT™ Canine Melanoma Vaccine, DNA.

The technology behind ONCEPT. How it works.

ONCEPT is the first DNA-based vaccine to aid in extending survival time in dogs treated for COM.[1]

The challenge with many cancers is that the host does not recognize the tumor as foreign, so the immune system is not elicited to defend the body against the tumor-producing cells. ONCEPT is produced with xenogeneic plasmid DNA containing canine DNA for human tyrosinase (huTyr). This results in the production of a human antigen that is homologous to canine tyrosinase (cTyr), but recognized as foreign.[3]

In contrast to normal cutaneous melanocytes, tyrosinase is over-expressed on malignant cells.[4] Therefore, the immune response appears to be tumor-specific.[4]

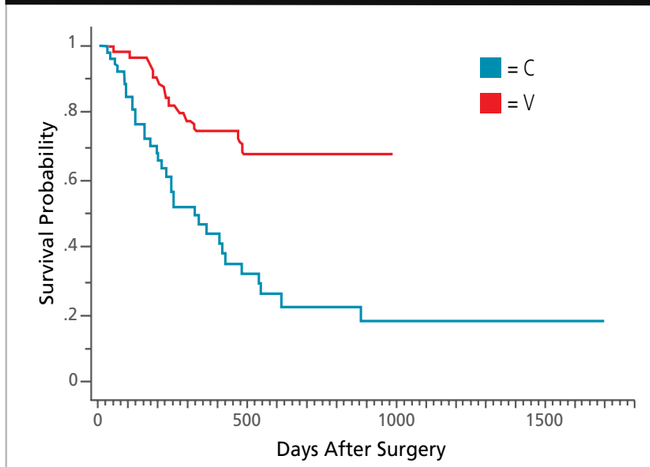


Melanoma tumors express an unusually large quantity of tyrosinase (shown in gray-blue on the cell surface) — far more than that produced by normal melanocytes. The immune system of a dog vaccinated with ONCEPT mounts a tyrosinase specific response to reject the tumor-producing cells.

ONCEPT significantly prolongs survival time.[1]

- Traditionally, dogs with WHO stage II or stage III oral melanoma have reported survival times of less than five to six months when treated with surgery alone.[3]
- In a study, 58 dogs with stage II or stage III COM were treated by vaccination with ONCEPT following local disease control achieved through surgery.[1]
- At a follow-up for survival data six months after the conclusion of the study, less than 50% of treated dogs have died of disease related to canine oral melanoma.[1]
- Quartile estimates of survival time for vaccinates (25% mortality [95% confidence intervals]) was 464 days.

Figure 1. Increased Survival Times in Dogs Treated with ONCEPT[1]



Survival probability comparison between historical stage-matched controls and vaccinates receiving four biweekly doses of ONCEPT, followed by "booster" injections at six-month intervals. Local disease control was achieved for both vaccinates and controls.

- There was a significant group difference ($p<0.0001$) with the vaccinates showing better survival times.[1]
- There was no statistically significant association in response between stage II and stage III canine melanoma ($p=0.58$).[1]
- There was no significant difference in survival between dogs with post-surgical histological reports of clean margins compared with narrow or dirty margins surrounding the excised tumor.[1]

THE CHALLENGE OF CANINE MALIGNANT MELANOMA (CMM) AND COM.

- Canine malignant melanoma (CMM) is the most commonly occurring oral tumor in dogs.[3]
- Spontaneous canine oral melanoma (COM) is a highly metastatic cancer that is resistant to chemotherapy and can serve as a model for cancer immunotherapy.[5]
- Canine melanoma readily metastasizes to the lymph nodes, liver, lungs and kidneys.[6]
- Traditional treatment for CMM is surgery and/or radiation therapy.[7]
- Survival time for dogs with advanced stages of COM treated with surgery alone:

WHO stage II disease —
approximately 150 to 180 days[8]

WHO stage III disease —
approximately 60 to 90 days[8]

- Overall response rates to chemotherapy are low, with little evidence that treatment improves survival time.[6,7]
- The main challenge in developing effective immunotherapy in dogs with CMM has been to selectively activate an immune response that can recognize and target specific antigens on melanoma cells.[6]
- Tyrosinase is a suitable target for CMM immunotherapy because of its tissue-specific expression.[6]

ONCEPT is a breakthrough for prolonging survival time in dogs with COM.*

ONCEPT has demonstrated it is a safe, effective adjunct therapy that can significantly prolong survival times in dogs with stage II or III COM for which local disease control has been achieved by traditional means.[1]

To support ONCEPT, Merial will increase awareness of COM among veterinarians so they can have an informed discussion with their clients about the options for oral malignant melanoma and include referrals to specialists practicing veterinary oncology.

ONCEPT is an oncological concept whose time has come.

For additional questions about ONCEPT, please contact Merial Technical Solutions at 1-888-MERIAL-1, option 3.

ONCEPT™

Four single-dose vials for initial series of biweekly vaccination. Booster doses recommended at six-month intervals.[9]

Available only to veterinary specialists.

*Product indications: vaccine aids in extending survival times of dogs with stage II or stage III oral melanoma and for which local disease control has been achieved.

[1]Data on file at Merial. Study 05-171. 2009.
[2]Data on file at Merial. Canine oral melanoma field database.
[3]Bergman PJ, Wolchok JD. Of mice and men (and dogs): development of a xenogeneic DNA vaccine for canine oral malignant melanoma. *Cancer Therapy* 2008;6:817-826.
[4]Wang S, Bartido S, Yang G, et al. A role for a melanosome transport signal in accessing the MHC Class II presentation pathway and in eliciting CD4+ T cell responses. *J Immunology* 1999;163:5820-5826.
[5]MacEwen EG, Kurzman ID. Adjuvant therapy for melanoma in dogs: Results of randomized clinical trials using surgery, liposome-encapsulated muramyl tripeptide, and granulocyte macrophage colony-stimulating factor. *Clinical Cancer Research* 1989;5:4249-4258.
[6]Liao JCF, et al. Vaccination with human tyrosinase DNA induces antibody responses in dogs with advanced melanoma. *Cancer Immunity* 2006;6:8-17.
[7]Bergman PJ, et al. Development of a xenogeneic DNA vaccine program for canine malignant melanoma at the Animal Medical Center. *Vaccine* 2006;24:4582-4585.
[8]Bergman PJ, et al. Long-Term Survival of Dogs with Advanced Malignant Melanoma after DNA Vaccination with Xenogeneic Human Tyrosinase: A Phase I Trial. *Clinical Cancer Research* 2003;9:1284-1290.
[9]ONCEPT product label.

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