AUBURN UNIVERSITY

ATTN:1/28/2016

COLLEGE OF VETERINARY MEDICINE

DEPARTMENT OF CLINICAL SCIENCES

CLIENT INFORMED CONSENT FORM

Title: D16CA- 519: Evaluation of Orally Administered mTOR inhibitor Rapamycin in Dogs in the Adjuvant Setting with Osteosarcoma

1. **Why is the study being performed?**

Osteosarcoma is the most common bone tumor in dogs. Amputation and chemotherapy significantly improves median survival times for dogs with this tumor type, from around 4-6 months to around 10-12 months. However, most dogs are not cured, and die due to the spread of their disease (metastasis) within 1-2 years. Better treatment options to treat cancer spread are needed to improve survival time for these patients.

Rapamycin (sirolimus) is a drug that works through the blockade of mTOR, a cellular pathway that is associated with tumor spread. Preliminary studies have been performed in cell lines, in mice, and in dogs that demonstrate anti-tumor activity. Previous studies have also established a safe dose in healthy dogs and dogs with cancer. The addition of this drug to standard amputation followed by carboplatin chemotherapy is hoped to delay or prevent tumor spread, thus improving patient survival.

2. **Which animals / patients can participate in the study?**

Dogs weighing > 25kg that have been diagnosed with osteosarcoma through biopsy or cytology of a bone lesion may participate. No previous treatment is allowed. The disease must be in a site that can be surgically removed through amputation, and there can be no evidence of metastasis based on physical exam, thoracic radiographs, and abdominal ultrasound. Dogs must be otherwise clinically healthy as assessed by examination and bloodwork.

3. **Why might my animal NOT be able to participate in the study?**

Dogs < 25 kg in size, dogs without measurable disease, and dogs that have received any prior therapy for osteosarcoma may not participate. No concurrent medications deemed incongruent with this study, including other purported anti-tumor therapies such as herbal supplements, etc. are permitted. Any significant illness, which includes but is not limited to kidney or liver failure, history of congestive heart failure or clinical bleeding disorder, or any significant bloodwork abnormalities including but not limited to creatinine > 3.0, bilirubin > 2.0, or elevated bile acids, HCT < 25%, and platelets < 150,000 will disqualify a patient from the study.

4. **What will be happening to my animal if we participate in the study?**

All dogs receive the current recommended therapy for osteosarcoma (standard of care: SOC), consisting of amputation followed by 4 doses of carboplatin chemotherapy, given 3 weeks apart, initiated within 10-14 days of surgery. Your dog will then be randomly assigned to enter the study group that receives SOC alone, or the group that has the addition of the drug rapamycin (Rapa). All dogs in both groups will return every two months for monitoring for disease progression, including chest radiographs.

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Rapamycin is an oral drug, given at home, daily on Monday, Tuesday, Wednesday, and Thursday of each week, with no drug administered on Fridays, Saturdays, or Sundays for a total of four months. Additional visits for the Rapa group of dogs includes 5 overnight stays (two the first month, then 3 additional monthly visits) for the purposes of a 24 hour blood collection to determine the levels of the drug in your dog's body. In order to minimize the number of times your dog's vein must be punctured for blood collection, a central venous catheter will be placed, under minor sedation.

								Rapamycin Dogs			**All dogs**
	Qualification (- 10 days)	Week 1	Week 3	Week 6	Week 9	Week 12	Week 15*	Day 11 post-rapamycin initiation	Day 25 post-rapamycin initiation	Monthly x 3 months	Every 2 months until tumor progression
Patient eligibility screening (not covered by study)	X										
Physical exam		X	X	X	X	X	X	X	X	X	X
Amputation		X									
Chest films		X			X		X			X (2nd & 4th visit)	X
Bloodwork (CBC,chemistry) and urinalysis			X	X	X	X	X		X	X	
Carboplatin chemotherapy			X	X	X	X					
Study blood sample (serum, whole blood, PBMCs			X						X	X	
Pharmacokinetics – 7 samples (requires overnight stay)								X	X	X	

*Rapamycin must start within 7 days of Day 15 recheck

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5. **Are there any benefits from the study for my animal?**

Your dog will receive standard therapy at a discounted cost (see details in #11). The usual initial costs of managing a patient with osteosarcoma with amputation and carboplatin are around $4000-5000. Four months of rapamycin and monitoring would be an additional $2000-3000. Monitoring after the completion of treatment is usually around $200 per visit. The addition of rapamycin might improve survival time over the expected median of 10-12 months with amputation and carboplatin chemotherapy.

6. **Are there any risks or discomforts for my animal?**

There are no additional risks in receiving surgery and carboplatin chemotherapy by enrolling in the study. Risks of bleeding and infection are present with any surgery; anesthesia risks are present, which can very rarely include death. Carboplatin can cause nausea or a decreased white blood cell or platelet count, which may put your pet at risk for infection or bleeding, and, very rarely, death from these adverse effects.

Rapamycin has been studied previously in dogs, and a tolerated dose has been established. However, because it is a chemotherapy agent, there are potential side effects, including death. The most common side effects seen with this drug in previous studies include a drop in the white blood cell count (increases infection risk), nausea, loss of appetite, and diarrhea. These side effects are similar to that seen with other chemotherapy drugs and are usually manageable with treatment when immediately reported. Even with standard treatment, the tumor may spread.

Minor risks associated with the placement of a catheter and the drawing of blood or urine include bleeding or bruising at the site. Sedation for central catheter placement may result in some sleepiness, but no long-term adverse effects are anticipated. The catheter will be removed prior to your dog returning home.

7. **Unforeseen adverse events**

A dose that is deemed reasonably safe has been determined previously in dogs. However, as with any chemotherapy drug, unforeseen events can occur, including illness or death.

8. **Are there other treatment options other than participating in the study?**

Osteosarcoma in dogs may be treated with surgery, radiation, chemotherapy, or some combination, depending on the location, grade (aggressiveness) of the tumor, presence of tumor spread (metastasis), overall general health of the patient, and a client's expectations. All potential treatment options, including this study, will be presented. You may decline treatment, or choose a different treatment regimen for your pet. Declining participation will not negatively affect any further care your pet receives at our hospital.

9. **Owner responsibilities**

Owners are required to return their dog to the Auburn oncology service for all scheduled rechecks and bring empty pill vials and a completed owner assessment form to each visit. Owners are responsible for administering the rapamycin with safety precautions as instructed at home, maintaining a diary of their dog's activities, and recording confirmation of

drug administration. Dogs must be fasted (no food, water is okay) 4 hours before rapamycin administration and 1 hour after administration. Owners are responsible for reporting any concerns regarding their dog's condition promptly, and returning to the Auburn oncology service prior to a scheduled recheck at the instruction of an oncology clinician. If your pet dies during treatment, a necropsy (autopsy) will need to be performed as soon as possible to determine the cause of death. Your pet's body may be returned to you, at your request.

10. **Participant dismissal**

A patient may be removed from the study at the owner's request at any time. Lack of compliance with the scheduled monitoring and treatment will result in dismissal from the study. If your dog has significant side effects (determined by you or the clinician) associated with treatment that cannot be controlled with routine supportive care, or the tumor spreads, your dog will be dismissed from the study and other treatment options will be presented. Dismissal may occur if any other anti-tumor treatment (including NSAIDs or steroids, supplements, etc.) is initiated, so all new medications should be discussed with the study clinician prior to initiating treatment. If your pet is dismissed as a result of removal by your request, lack of compliance with scheduled treatment and monitoring, or initiation of other treatments without prior approval, there will be no further financial compensation from that point.

11. **Financial obligations of all parties**

The study sponsor will pay for $1000 to be applied towards amputation (the usual cost of amputation is $2500-3000). The sponsor will completely cover the protocol-related costs of all continued follow-up visits, including carboplatin chemotherapy (usually $300/dose), rapamycin (usually $200 per week), and monitoring ($200/visit). Additionally, any costs related to management of adverse events will be covered up to $500 (costs above this amount are unlikely). Additional costs associated with amputation and patient care are the client's responsibility.

12. **Access to study information**

Information from this study will not be distributed to you as an individual but may be available through scientific publications.

13. **Confidentiality**

Information, case materials, photos and generic patient information gathered in this study may be used for scientific presentations and publications. Confidentiality of personal information (client and animal) will be maintained to the extent of the law.

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14. **Contact persons regarding this study**
Participants may contact any of these individuals with questions about this study.

Annette N. Smith, DVM, MS, DACVIM (Oncology & Small Animal IM)	334-844-4690 smith30@auburn.edu
Stephanie Schleis, DVM, DACVIM (Oncology)	334-844-4690 ses0034@auburn.edu
Brad Matz, DVM, DACVS, Fellow, Surgical Oncology	334-844-4690 bmm0007@auburn.edu
Jennifer Spooner, LVT	334-844-4690 jsh0014@auburn.edu

15. **Hospital review contact person**
Participants with concerns about any research study at the AU College of Veterinary Medicine may also contact:
Doug Allen, DVM, MS, DACVS. Director, Veterinary Teaching Hospital. College of Veterinary Medicine, Auburn University. (334) 844-4690.
Frank F. "Skip" Bartol, PhD. Associate Dean of Research and Graduate Studies. College of Veterinary Medicine; Auburn University. (334) 844-3700.

16. **Owner acknowledgements:**
As legal owner of (or agent for) this animal, I understand and acknowledge the following:
   a. **I am agreeing to participate in a research study at the AU College of Veterinary Medicine.**
   b. **I am free to withdraw my consent and to discontinue participation in the study at any time.**
   c. **The decision for my animal to participate in this study is mine alone and *participation is voluntary.***
   d. **The decision to withdraw from the study or to disregard the recommendations of the veterinarians involved in the study, relieves the investigators of current and future obligations (both medical and financial) to the pet and/or owner covered by this study.**
   e. **Non-study treatment protocols have been discussed and I understand the relative benefits of those treatments.**
   f. **I am responsible for decisions and financial obligations related to treatment(s) sought or required for my animal at AU-VTH or at any other veterinary facility that are NOT specified in this document. This would include treatment for disease progression or for medical complications - related or unrelated to the study.**
   g. **If I withdraw my animal from the study, I may be responsible for medical, diagnostic and treatment costs incurred even if these were originally covered by the study.**
   h. **Any decision to discontinue participation in this study, whether to pursue other therapies or to have my animal euthanized, does not entitle me to any financial reimbursement for costs incurred during participation.**
   i. **I have discussed the procedures / benefits and risks of study participation and had the chance to have my questions about the study answered.**

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_____ _____

Owner signature Date

17. **Investigator assurances**
    a. I have explained the study details and answered questions to the best of my ability.
    b. If the animal is a patient in the Auburn University Veterinary Teaching Hospital, I have discussed enrolling the patient into this study with the senior faculty member responsible for this patient's care.

_____ _____

Primary Investigator Date

_____ _____

Witness Date

This study has been reviewed and approved by the Clinical Research Review Committee of the College of Veterinary Medicine (CRRC) and the Auburn University Institutional Animal Care and Use Committee (IACUC). (Effective date – Feb 2010)