Special Care Foundation for Companion Animals-
Angel Care Cancer Center
PolyMVA

Protocol PolyMVA/SCFCA/CVS 10-5

PROSPECTIVE DOUBLE BLIND, RANDOMIZED, PLACEBO CONTROLLED STUDY TO DETERMINE THE SAFETY AND EFFICACY OF PolyMVA IN DOGS WITH SPONTANEOUSLY OCCURING, HISTOLOGICALLY CONFIRMED MALIGNANCIES

Protocol Date: February 15, 2010

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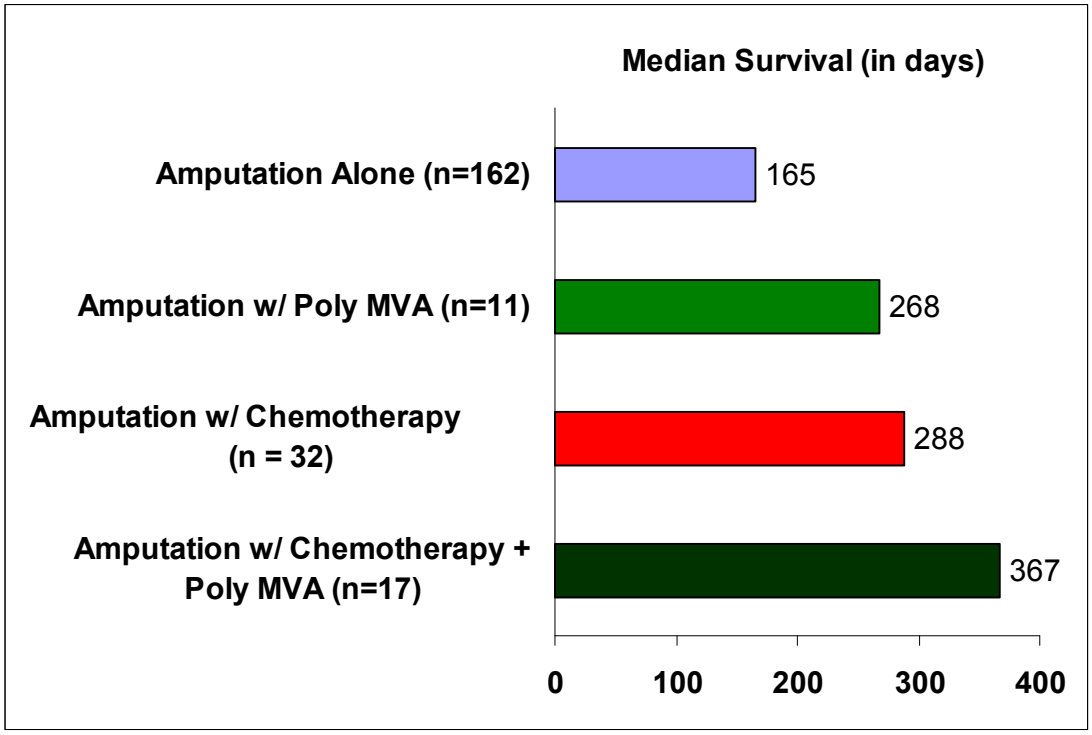
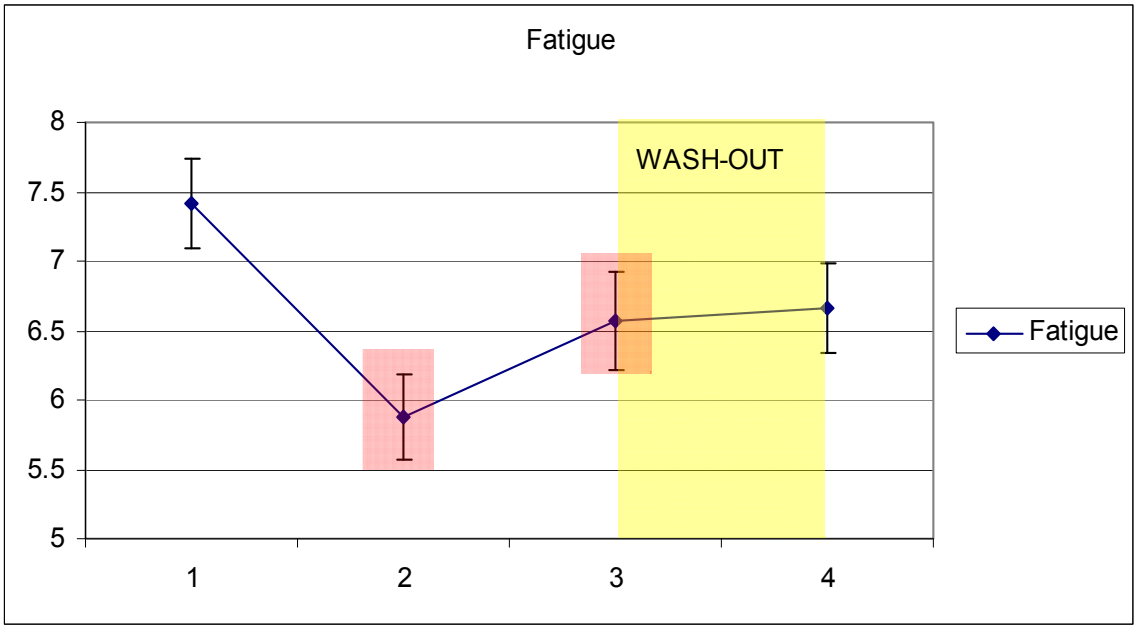
- **Clinical Human and Veterinary Studies**
  - Veterinary – (California Veterinary Specialist – P.I. Dr. Greg Ogilvie) The largest integrative cancer investigation of LAMC supplement was an open-label, veterinary oncology program with over 900 dogs enrolled, since its inception in January 2004. Patients received the LAMC supplement (Poly MVA) as part of their chemotherapy, radiation and/or surgical protocol at a dosage of 1mL/5 lbs. P.O. twice daily (equivalent human dose of approximately 8 tsp.). The LAMC seemed most effective in the cases of solid tumors (i.e. soft tissue sarcoma, hemangiosarcoma, mast cell, transition cell carcinoma, lung, anal sac carcinoma, renal carcinoma, squamous cell carcinoma, fibrosarcoma, melanoma, menigioma, neuroblastoma, mammary adenocarcinoma). Some of the most effective findings were apparent in the osteosarcoma patients. The etiology of osteosarcoma in large dogs is considered identical to the disease progression in humans. While in canines the "standard of care" is limb amputation followed by chemotherapy, in human patients, limb–sparing surgery following tumor excision is performed (Ogilvie and Moore, 2006). In this open labeled study, integrative LAMC support (LAMC + amputation) improved the animals' median survival time 62% (103 days more) compared to surgery alone (n= 11 and 162, respectively). When LAMC was added to the chemotherapeutic regimen (carboplatin + doxorubicin) the dogs exhibited a 27% longer median survival (79 days more) (n= 32 amputation with chemotherapy; n= 17 amputation + chemotherapy + LAMC). Furthermore, there was no significant difference (p=0.30) in median survival time between dogs treated with amputation + LAMC versus those that were treated with amputation + the "standard of care" chemotherapy.(see figure below)



- Veterinary – It is important to note that following LAMC complementary support, chemotherapeutic animals' demonstrated improvements in various objective parameters (i.e. weight, anemia, liver and kidney function). In addition to these enhanced clinical parameters, a subjective owner quality of life survey resulted in an 86% improvement following the addition of LAMC supplement adjunctive support.
- Human – (Century Wellness Clinic - P.I. Dr. James Forsythe) An outcome-based study of stage IV cancer patients was conducted 2004-2006. Over 225 stage IV patients were in this observational cohort, with prostate, breast and lung cancer being the best responders. The typical oral dosage used was 40 mL or 8 teaspoons per day. Treatment with Poly MVA or Poly MVA + chemotherapy provided a 6 year Overall Survival rate of 32%, while the average 5 year survival rate is 2.1% in all stage IV cancers, as reported in the Clinical Journal of Oncology.
- Human – (Century Wellness Clinic - P.I. Dr. James Forsythe) The current (2014) outcome-based study is now utilizing genetic chemosensitivity testing, immune therapy, insulin-potentiated therapy, along with IV Poly MVA to enhance his results. The patients are discharged on oral Poly MVA and targeted treatments, with follow-up every 3 months. Thus far, 59% of the patients have reached 40 months in the study.
- Human – (Department of Neurology at Stony Brook University – P.I. Dr. Candice Perkins) A dose-escalation safety study and kinetics profile of the Palladium Lipoic Acid formulation was conducted in preparation for the current glioblastoma program. This was an IRB approved study, which was monitored by a DSMB (Data Safety and Monitoring Board), as well as, being granted an IND from the FDA.
- Human - A Palliative Care Study was conducted by the Indian pharmaceutical company CIPLA. Patients took the LAMC supplement Poly MVA for 24 days, followed by a 12 day clearance period. The following parameters demonstrated statistically significant patient improvement: Cognitive Functioning, Emotional Functioning, Social Functioning, Fatigue, Sleep Disturbances, and Appetite Loss. (see fatigue example below)



Executive Summary of Study

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We hypothesize that PolyMVA will improve quality of life, enhance cellular energetics and reduce oxidative damage with clinically acceptable toxicity when used to treat dogs with histologically confirmed cancer, a condition of extreme oxidative and metabolic stress. Client owned dogs with spontaneously occurring, histologically confirmed malignancies will be entered into this double blind, randomized, placebo controlled (3:1) clinical trial. Ten dogs will be entered into each group to be evaluated one to another as well as to compare changes from baseline (pretreatment values). Dogs in this study will come from the patient population from Angel Care Cancer Center and its network of allied collaborators. Once entered, the patients will follow the randomized protocol criteria to determine if there is a response to therapy as determined by clinical, biochemical, hematologic and metabolic testing. It is anticipated that there will be a best in class response to therapy noted by enhanced cellular energetics, reduced oxidative metabolism, reduced urinary isoprostanes and improved quality of life indices.

Study Schedule for Each Patient

	Weeks			
Test	**0**	**3**	**6**	**9**
Physical Exam	X	X	X	X
CBC, Biochem UA	X			X
Urinary Isoprostanes	X	X	X	X
Oxidative Metabolism	X	X	X	X
Energy Profile	X	X	X	X
Quality of Life Survey	X	X	X	X
VCOG Toxicity	X	X	X	X

Gregory K. Ogilvie

Dr. Ogilvie is Director of the **Angel Care Cancer Center** at California Veterinary Specialists, President of the Special Care Foundation for Companion Animal,s and is on the University of California Veterinary Medical Center-San Diego's Clinical Advisory Board. At the Angel Care Cancer Center, he cares for patients and their families and teach interns, residents, and veterinary students within an active cancer research program. Prior to his move to Southern California, Greg was a full tenured Professor, Internist, Dept. Head of Medical Oncology and Director of the Medical Oncology Research Laboratory, Animal Cancer Center at Colorado State University from 1987 until 2003. During this 16 year period at CSU, Greg also spent one year on sabbatical teaching, developing new, innovative cancer therapies at the medical school and the Laboratoire Nutrition, Croisance et Cancer at the Université François Rabelais in Tours France. Dr. Ogilvie lectures to thousands of veterinary students, physicians, graduate veterinarians and scientists each year.

Dr. Ogilvie received his DVM from Colorado State University and was in private practice in Connecticut before completing a residency at Tufts University/Angell Memorial Animal Hospital. From there he joined the faculty as a Professor at the University of Illinois before moving on to his professorship in Colorado. Dr. Ogilvie is Board Certified in both the specialties of Internal Medicine and Oncology by the American College of Veterinary Internal Medicine and Oncology, and is a Diplomate of the European College of Veterinary Internal Medicine-Companion Animals, Specialty of Oncology.

He is co- author with Dr. Antony Moore of three books, Managing the Veterinary Cancer Patient (Veterinary Learning Systems, 1995, in English, French and Japanese), Feline Oncology: Compassionate Care for Cats with Cancer (Veterinary Learning Systems, 2001 in English and Japanese) and the book, Managing the Canine Cancer Patient: A Practical Guide to Compassionate Care (Veterinary Learning Systems, 2006 in English, Spanish and Japanese). He has written over 200 scientific articles and chapters, as well as over 120 scientific abstracts and posters. He has been awarded two international patents, over 10 million dollars in research grants and endowments as a principal or co-investigator, and is the recipient of many awards including: the Arnold O. Beckman Research Award, the Beecham Research Award, the Purina Small Animal Research Award, the Scheidy Memorial Research Award and the AVMA/American Kennel Club Award.

Dr. Ogilvie has lectured in scores of countries to many thousands of students, veterinarians, physicians and scientists in Africa, Australia, New Zealand, Asia, Europe, the Middle East, South America, and North America by sharing his love of the practice of veterinary medicine and oncology. Dr. Ogilvie's teaching skills have also been frequently recognized.

He is the recipient of the Outstanding Teachers Award; two Norden Distinguished Teacher Awards; the MSD Agvet Award for Creativity in Teaching; the SCAVMA Award for "Dedication to Students and the Profession" and was named Outstanding Companion Animal Speaker for 1999 at the North American Annual Veterinary Conference.

Greg has also been recognized with: the American Veterinary Medical Association's "Veterinarian of the Year-1995"; the American Animal Hospital Association's "Veterinarian of the Year-1996"; the Colorado Veterinary Medical Association Outstanding Faculty Award-1996; and the 1999 SHARE Human Animal Bond Companion Animal Award. Greg was awarded the World Small Animal Veterinary Association Hills Award for Excellence in Veterinary Healthcare for the year 2001.

When not caring for pets and people, Greg is a certified ski instructor and enjoys camping, scuba and long distance cycling. He has volunteered for 15 years as a counselor at the Sky High Hope Camp for children with cancer , and is on the Board of Directors for **Angel on a Leash** to benefit children with cancer. His greatest joys are his daughter, Torrie and his wife, Karla.

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Table of Contents

PolyMVA Study

1 Title:

A prospective, double blind, randomized, placebo controlled study of the safety and efficacy of PolyMVA in dogs with spontaneously occurring, histologically confirmed, measurable malignancies.

2 Protocol/Study No.: PolyMVA/SCFCA/CVS 10-5

2.1 Scope of Protocol:

Prospective Clinical Study, Phase II. Double blind, randomized, placebo controlled.

2.2 Study Status:

Pilot Study

2.3 Study Classification:

Clinical Study (Sponsor/Monitor)

2.4 Standards Applied:

The study will be conducted in accordance with CFR 21, 511, (b) and CVM Guidelines for Conduct of Clinical Investigations: (October, 1992).

3 Protocol Approval Signatures:

3.1 Study Sponsor:

_____ Date:_____

PolyMVA

Principal Investigator:

_____ Date:_____

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2120 Faraday Ave, Carlsbad Research Center, Carlsbad CA 92008

3.2 Study Monitor/Study Director:

_____ Date:_____

Lee VanHorn, RVT

3.3 Statistics Consultant:

_____ Date:_____

Mark Enns
Department of Statistics
Colorado State University
Ft. Collins CO 80523

4 Sponsor:

Name: *PolyMVA*

4.1 Mailing Address:

5 Personnel:

5.1 Author of the Protocol:

Name: Gregory K. Ogilvie
Association: Special Care Foundation for Companion Animals, Angel Care Cancer Center

5.2 Investigator/Testing Facilities:

NAME	HOSPITAL/CLINIC	PHONE #	FAX #
Greg Ogilvie	Angel Care Cancer Center California Veterinary	Hospital 760-431-2283	431-431-1084
Coiurney Zwaylen	Southern California Veterinary Referal Center		
Andrew Vaugn	Las Vegas Veterinary Referal Center		

5.3 Laboratory Diagnostics:

Site Specific

5.4 Quality Assurance Unit:

Name: Candi Miller

5.5 Archivist:

Name: **PolyMVA**

6 Objective:

The objective of the study is to test the hypothesis that PolyMVA will improve quality of life, enhance cellular energetics and reduce oxidative damage with clinically acceptable toxicity when used to treat dogs with histologically confirmed cancer, a condition of extreme oxidative and metabolic stress. In this study, **40** client owned dogs with spontaneously occurring, histologically confirmed malignancies will be entered into this double blind, randomized, placebo controlled (3:1) clinical trial. Once entered, the patients will follow the randomized protocol criteria to determine if there is a response to therapy via clinical, biochemical, hematologic and metabolic testing. It is anticipated that there will be a best in class response to therapy noted by enhanced cellular energetics, reduced oxidative metabolism, reduced urinary isoprostanes and improved quality of life indices.

7 Introduction:

7.1 Product Profile:

POLY-MVA Safety

The formulation has undergone extensive toxicology study (Calvert Laboratories, Inc; Pharmakon USA, Inc.). The toxicology was conducted both intravenously and orally with PdLA. Mice were administered doses of 5,000 mg/kg (a typical human dose is 20 mg/kg). No deaths or signs of organ damage occurred in the test animals. It was concluded that the LD50 of PdLA exceeds 5,000 mg/kg. The same independent lab conducted the Ames test and no mutagenic effects were observed.

While platinum and palladium share many chemical properties, it appears that platinum coordination complexes are carcinogenic and genotoxic. There is no evidence of any mutagenic property for palladium(Bunger et al. 1996). In a study examining human lymphocytes, platinum demonstrated significant genotoxicity, likely mediated by oxidative damage, compared to palladium (Migliore et al. 2002). Furthermore, palladium demonstrated no genotoxicity in mammalian or bacterial cells when tested using the cytokinesis-block micronucleus test (MNT) or SOS chromotest, respectively (Gebel et al. 1997).

Human Safety:

1. A university phase I (SAFETY) study of PdLA was completed. 13 research subjects received study compound (POLY-MVA 10 mL/day) for varying time periods. There were no reported SAEs (Severe Adverse Events) attributed to the product. Nine subjects experienced an AE (Adverse Event) during the study which was considered potentially related to the study compound, while five subjects had AEs which were either possibly or probably related to the study compound. The events which were possibly or probably related to the study compound included: fatigue after cessation of compound, diarrhea, worsening leg cramps, headache, increased urination, light-headedness, difficulty sleeping, increased excitement.
2. Current: Stony Brook University -DESSTINI trial (Dose Escalation Safety Study In Normal Individuals taking Poly MVA) - Phase I safety studies, under an Investigational New Drug (IND) application issued by the FDA. This is a 3 tier (2 tsp, 4 tsp, and 8tsp) dose escalation safety study, being monitored by a DSMB (Data Safety and Monitoring Board) and IRB (Institutional Review Board). They are also monitoring kinetics. Tiers I and II have been cleared for safety, with no SAEs reported and minor AEs (e.g. adversion to taste, initial nausea, lack of energy after cessation of product). This supplement is intended for eventual use as adjunctive support for those undergoing chemotherapy and radiation treatment for brain cancer.

Bunger, J, Stork, J, Stalder, K. (1996) Cyto- and genotoxic effects of coordination complexes of platinum, palladium and rhodium in vitro. *Int. Arch. Occup. Environ. Health*; 69(1):33-38.

Gebel, T., Lantzsch, H., Plessow, K., Dunkelberg, H. (1997) Genotoxicity of platinum and palladium compounds in human and bacterial cells. *Mutat. Res.* 389(2-3):183-190.

Migliore, L., Frenzilli,G., Nesti, C., Fortaner, S., Sabbioni, E. (2002) Cytogenetic and oxidative damage induced in human lymphocytes by platinum, rhodium and palladium compounds. *Mutagenesis*; 17(5):411-417.

Safe dosage:

PolyMVA has completed extensive subjective dose determination studies to treat people however little data exists in the dog. In one study conducted by Dr. Gregory Ogilvie et al, 134 dogs with cancer were given PolyMVA and assessed for toxicity. None was found. Furthermore, another study was done to assess the safety and efficacy of PolyMVA for the treatment of dogs with lymphoma concurrently treated with the CHOP protocol and compared to untreated controls. No toxicity was found. Taken together, these data suggest that PolyMVA is safe at 0.5 mls/kg BID.

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7.2 Study Overview:

Client owned dogs with spontaneously occurring, histologically confirmed malignancies will be entered into this double blind, randomized, placebo controlled (3:1) clinical trial. Ten dogs will be entered in each group. Dogs in this study will come from the patient population from Angel Care Cancer Center and its network of allied collaborators. Canine patients with various cancers will be entered into the study if they meet the entrance criteria. Once entered, the patients will follow the randomized study scenarios to determine if there is a response to therapy. It is anticipated that there will be a best in class response to therapy noted by enhanced cellular energetics, reduced oxidative metabolism, reduced urinary isoprostanes and improved quality of life indices.

7.2.1 Dogs with various cancers

Fourty Dogs with histologically confirmed cancer will be given the oral PolyMVA or placebo daily at 0.5mls/kg/q12 hrs and evaluated every three weeks for 9 weeks until the end of the treatment period, or until the tumor has increased in size by 50% (progressive disease), or until the patient's death. Clinical data, blood and urine will be obtained to assess quality of life, energy profiles, oxidative state and general health at each period.

Approximate Study Duration: 6 months

8 Test and Control Articles:

8.1 Test Article:

Trade name: **PolyMVA**

8.1.1 Dosage:

PolyMVA is being formulated by PolyMVA to be administered at the HNTD of 0.5mls/kg/q12 hrs.

8.1.2 Formulation of PolyMVA :

Final: See Certificate of Analysis (to be provided)

8.1.3 Source of raw material (mfg. site):

PolyMVA

8.1.4 Lot/Serial No.: TBD

8.1.5 Expiration date: TBD

8.1.6 Packaging: TBD

8.1.7 Container labeling:

Labeling will be with clinical supplies in accordance with a prospective study but are not specifically required by local, state or national regulations at this stage of study.

8.1.8 Storage requirements:

PolyMVA should be stored at room temperature +/- 5C: 15-25 degrees C.

9 Study Schedule:

9.1 Proposed Date(s) of Study Initiation:

Feb 15th, 2010 – But it will be depending of shipment constraints

9.2 Proposed Date(s) of Study End (In-life):

This will be determined by interim findings of both clinical relevance and statistical significance as defined later in Section 13.5.

10 Study Design:

10.1 Treatment Groups (to be labeled in code as this is a double blind, randomized, placebo controlled study):

10.1.1 Group 1: PolyMVA (3/4 patients)

10.1.2 Group II: PLACEBO (1/4 patients)

Experimental Design:

This is a prospective, randomized, double blind, randomized, placebo controlled (4:1) clinical trial to determine if PolyMva has any efficacy against the most

common tumor types in the dog. At the time of the first evaluation, the eligible dogs will be staged on day one, then rechecked every three weeks until the end of the study (9 weeks), whereupon they will be reassessed metabolically and clinically. The dogs that are qualified will begin oral daily treatment with the PolyMVA according to the study guidelines. The 40 selected patients will be treated daily 0.5 mls/kg PO BID PolyMVA or a PLACEBO after the client has signed an informed consent. The patients will be rechecked every 21 days following the schedule described in Section 13. The study will end for each patient at day 63, or when that patient returns with progressive or metastatic disease, or dies, or the study is stopped because of UNacceptable significance or quality of life was determined.

10.2 Blocking Factor(s):

The patients will be stratified as follows: Various cancer patients will be stratified by the presence or absence of measurable tumor.

10.3 Eligibility Procedures:

A patient's potential eligibility should be evident by the first treatment visit. Data demonstrating potential eligibility collected at the first treatment visit should be recorded by the protocol officer (RVT Lee VanHorn) shortly after collection and before the first chemotherapy treatment.

At the first treatment visit the patient will both be treated, as well as given a final assessment of eligibility. Should eligibility be confirmed by the clinician, the patient should undergo a complete staging assessment and the client should receive a supply of the PolyMVA or placebo for maintenance until the final staging visit 63 days later. Should the patient not be found to be eligible then participation in this study is considered to be ended.

11 Study Procedures:

11.1 General Overview (Appendix 1, Flow Chart):

Dogs with previously diagnosed, histologically confirmed tumors (n=40) will be entered into this double blind, randomized, placebo controlled (4:1) study to insure a uniform patient population. Clients must live within 300 kilometers or a 3.5 hour commuting distance of the study center. Dogs will be excluded from this study if they have any underlying metabolic or organic disease other than their cancer or have been treated with chemotherapy or radiotherapy 14 days prior to presentation. When an animal is considered as a possible candidate for the study, the client should be advised in general terms of the potential for enrollment. Discretion is advised as to the extent of specific information divulged to facilitate reasonable consideration by the client. Staging may occur with concurrence by the client. When eligibility is determined, the clients will receive complete oral and

written information concerning the study and asked to sign a consent form. All patients will be staged according to the World Health Organization staging scheme prior to, at the end of, or when the disease progresses. Clients must agree to have blood and urine samples obtained before, during (q3 weeks) and at the end of the therap, as well as at the time of illness, death or recurrence and thus the necessity to exit the study for hematologic, biochemical and histopathologic determination.

The purpose of the study is to assess changes in quality of life, cellular energetics, metabolism and oxidative status, as well as NON response to therapy. However, all animals with various cancers will be routinely evaluated for response to therapy using the following parameters to assess progression free survival (PFS):

- A <u>complete remission</u> is defined as the disappearance of all clinically detectable disease.
- A <u>partial remission</u> is defined as an unequivocal decrease of at least 50%, but not 100% ,of the sum of the products of the perpendicular diameters of all measurable tumors, and lack of appearance of new neoplastic lesions, or uncontrolled hypercalcemia.
- <u>Stable disease</u> is defined as those patients that have not yet achieved a partial remission (unequivocal decrease of at least 50%, but not 100% ,of the sum of the products of the perpendicular diameters of all measurable tumors, and lack of appearance of new neoplastic lesions, or uncontrolled hypercalcemia.) or progressive disease (unequivocal increase of at least 50% in the sum of the products of the perpendicular diameters of all measurable tumors, or the appearance of new neoplastic lesions, or uncontrolled hypercalcemia).
- <u>Progressive disease</u> is defined as an unequivocal increase of at least 50% in the sum of the products of the perpendicular diameters of all measurable tumors, or the appearance of new neoplastic lesions, or uncontrolled hypercalcemia.

11.2 Dogs With Various cancers:

11.2.1 Case Selection Criteria:

"Initial Visit" form to be completed (Appendix 2).

11.2.1.1 All dogs with various cancers will be assessed at the beginning of the study and then every 3 weeks until the 63rd day with the following diagnostic tests:

- Complete Blood Count, Biochemical Profile, Urinalysis
- Complete History and Physical Examination
- Quality of life Assessment
- Oxidative Damage
  - Prior to and every 21 days during the 63 day study blood and urine will be evaluated for cellular energy profiles and oxidative damage. Small aliquots of whole blood will be

placed into cryovials[e] containing either no additive or 10% 1-methyl-2-vinylpyridinium trifluoromethanesulfonate scavenger for subsequent erythrocyte reduced and oxidized glutathione (GSH:GSSG) analysis. These samples will be immediately flash frozen in liquid nitrogen and stored at -70°C. Erythrocyte GSH:GSSG concentration will be performed using a commercially available test kit. The remaining whole blood samples without additive will be allowed to clot and then centrifuged at 2000 g for 15 minutes. Serum will then decanted and frozen at -70°C until analysis. Serum C-reactive protein (CRP) will be measured by spectrophotometry. Urine will be collected by voluntary void or cystocentesis and stored at -70°C. Urine 8-epi-prostaglandin $F_{2\alpha}$ ($iPF_{2\alpha}$-III) by commercial ELISA.

- Urine will be obtained every three weeks until the end of the study and frozen at -70C for subsequent energy profile analysis at Genova Diagnostics to determine if PolyMVA improves quality of life from the energy profile perspective.

    - **ANALYTE LIST:**
    - Adipic Acid
    - a-Ketoglutaric Acid
    - b-OH-b-Methylglutaric Acid
    - Cis-Aconitic Acid
    - Citric Acid
    - Fumaric Acid
    - Isocitric Acid
    - Lactic Acid
    - Malic Acid
    - Pyruvic Acid
    - Suberic Acid
    - Succinic Acid
    - Creatinine (Nutritional)
    - B-Hydroxybutyric Acid
    - Cis-Aconitic Acid
    - Citric acid

11.2.2 Exclusion Criteria:

11.2.2.1 Any concurrent disease state that would require additional therapy which could interfere with the assessment of the PolyMVA or that would, in the clinician's opinion, prevent the dog from living 90 days.

11.2.2.2 Having received any chemotherapeutic agents or radiotherapy 30 days prior to entering this study.

11.2.2.3 Having received glucocorticoids or immunosuppresive drugs within 30 days prior to entering this study.

11.2.2.4 Having failed all other available therapies

11.2.3 Inclusion Criteria:

11.2.3.1 Measurable or non measurable, histologically confirmed malignancies and in otherwise, general good health.

11.2.3.2 Clients' consent

11.2.4 Description:

11.2.4.1 Species: Canine, any breed

11.2.4.2 Age: Adult

11.2.4.3 Sex: Either sex to include spayed and neutered dogs

11.2.5 Number of animals in study/number of animals per location:

Twenty dogs per group (80 dogs total) will be included in the randomized (3:1) into the double blind, randomized, placebo controlled study.

11.2.6 Treatment:

"Staging Visit" form to be completed for each visit (Appendix 3) , and if and when an animal is excluded for any reason, the final disposition form (Appendix 4).

Dogs will be entered into the double blind, randomized, placebo controlled (3:1) study and then treated with the medication daily starting at the time the study began for each animal. Pre-treatment evaluation will include a complete physical examination, biochemical profile and a complete blood count. The study could be discontinued at any time in case of non acceptable disease deterioration (up to client or investigator's assessment). When the dogs return for their q21 day visits, they will be re-evaluated for disease status, cellular energetics, oxidative damage and quality of life evaluations. The dogs will be treated with the PolyMVA orally twice daily.

Patient Follow Up: The patient will be evaluated every three weeks for 63 days.
"Staging Visit" form to be completed for each visit (Appendix 3).

11.2.7 Study schedule Treatment

The PolyMVA or the PLACEBO will begin the day the patient is included into the study. The PolyMVA or PLACEBO will be given orally twice daily to 40 patients. Toxicity will be evaluated similarly to other drugs and treatments. The patients will be evaluated every 3 weeks for 63 days using at least the following tests or parameters: routine history and physical examination, complete blood count, biochemical profile, urinalysis as well as tests for oxidative damage and energy profiles. Performance status will be determined by the modified Karnofsky's scoring system (See Appendix 3, Staging Visit In addition, toxicity will be quantitated using a scheme that is modified from the Veterinary Cooperative Oncology Group system (See Appendix 3). These evaluation schemes are essential to quantify subjective and objective evidence of the animal's "Quality of Life." All data obtained from the VCOG and modified Karnofsky's Performance Status scoring will be tabulated for subsequent analysis. Conclusion of an Animal on Study "Final Disposition" form to be completed (Appendix 4).

11.3 Description of Testing Facility/Animal Management:

11.3.1 Testing Facilities:

11.3.1.1 Angel Care Cancer Center

The state of the art facility is located within a larger veterinary complex where common use resources are shared (e.g., cage, treatment/exam, receptionist MRI, CT, nuclear medicine, ultrasound, critical care, chemotherapy, surgery, radiology, radiation therapy, cyberknife, cardiology, etc areas). The Angel Care Cancer Center is strictly a referral practice receiving patients referred for oncology diagnosis and/or therapy and are located in San Diego County in the State of California USA. Diagrams of each facility are on file with the Sponsor.

11.4 Diet:

11.4.1 Feed type/composition:

Each dog will be fed standard diets. If the patient loses weight on that diet, the diet will be increased in 10% increments at each recheck, until weight stabalizes and is regained.

11.5 Client Consent:

Each client will sign a consent form (Appendix 5) after the animal is confirmed to be eligible. The animal is then considered to be on study and a patient notebook started. Clients must agree to report any adverse effects that will be validated by the veterinary health care team (Appendix 6) and any and all concurrent therapies will be recorded (Appendix 7).

11.6 Patient Testing (Clinical Pathology and Urinalyses):

All testing and procedures will be conducted per usual protocol associated with normal patient management specific for each tumor type and at the discretion of the clinician. Complete blood count, biochemical profile and urinalysis will be obtained prior to and at the end of the study.

Blood Collection Procedures for Analysis:

Blood will be taken at times noted in Appendix 1 for a biochemical profile, urinalysis and hemogram along with other tumor specific analyses. A minimum of 3 ml of venous blood via jugular vein, or other acceptable location, into a heparinized and a non-heparinized serum collection tube. Centrifuged within 15 minutes and transfer of plasma and serum (approximately 1.5 ml each) into each of two (2) pre-labeled (using permanent marker; Patient's Name / Case Number / Date) cryofuge tubes. At Angel Care Cancer Center, all samples will be accumulated and forwarded to the CVS laboratory for analysis.

11.7 Tissue Collection and Preparation:

11.7.1 Supplies Needed

- IV catheter
- Freezer (cryo) vials, 2 ml
- Scissors and/or scalpel blades
- Para-film
- Freezer bags (for storage)
- Formalyn or Z fix
- Permanent markers (Sharpies®)

11.7.2 Procedure Flow Chart

Misc Sampling
Tissue Collection in the Operating Room
($\geq 1cm^3$ samples, of both tumor tissue)
↓
Place each sample in labeled cryovials
($1cm^3$ sample / vial)
↓
Record Information in Logbook

11.7.3 Tissue Collection in Operating Room

At east 1, 1cm^3 samples of tumor tissue is collected aseptically just after tumor removal. Tissue samples are aseptically placed into a pre-labeled (tumor or stromal) containers (specimen containers) as described below.

11.7.3.1 Fixation: Label 1 specimen containers with Z-fix or formalyn as follows

- "Tumor, Patient's Name, Case Number, Date"
- "Stromal, Patient's Name, Case Number, Date"

11.7.4 Records

Record the tumor type and location, case number, date collected, dates harvested and shipped, along with any other pertinent information in a designated lab notebook.

11.7.5 Shipping of Tissue Samples

Ship all samples overnight delivery, to the attention of the Diagnostic Laboratory, Attn: BE Powers

Colorado State University
Comparative Oncology Unit
Department of Clinical Sciences
College of Veterinary Medicine
Fort Collins, Colorado 80523-1620
Phone: 970-491-4527
Fax: 970-491-4437

11.8 Treatment Administration:

11.8.1 Dosing:

The PolyMVA or PLACEBO medication will be administred at 0.5 mls/kg BID.

Route of treatment : Oral

11.8.2 Frequency and duration of Dosing:

Twice Daily. (BID)

11.8.3 Documentation of treatment:

The medical records (history, gelcap count) at each checkup visit will serve as documentation of PolyMVA administration.

11.8.4 PolyMVA use accountability:

The principal investigator will ultimately be responsible for all treatment.

11.9 Concurrent/Concomitant Medication Restrictions:

With the exception of treatments which could interfere with the assessment of the PolyMVA , normal use of concomitant medications associated with cancer therapy will be allowed (e.g., NSAIDs, anti-emetics). All medications will be documented (Appendix 7).

11.10 Removal of Test Animal(s) from Study (Appendix 4):

11.10.1 Criteria for removal

Patient dies or develops a severe deterioration that is not acceptable to the clients or the investigator, or for which required but forbidden concomitant

treatments are necessary . Also included are Protocol deviations which could potentially bias the results.

11.10.2 Procedures for removal

The investigator will notify the monitor immediately of a protocol deviation, either real or perceived. The monitor will make a decision after gathering the appropriate facts as to the fate of the study participant, the data collected to date and make the investigator aware of the decision both through normal notification channels and in writing. Documentation will be maintained on all such procedures. One of three possible decisions will be the result of such action:

1. Patient will be removed from the study and the data from that patient will be excluded in its entirety.
2. Patient will be removed from the study and the data from the time of infraction will be excluded.
3. Patient will not be removed from the study and all the data is maintained. A complete report on the incident will be filed.

When a patient is removed from study for any reason :

- all the tests that are planned at the end of the study (Day 64) have to be performed.
- a "Final Disposition Form" needs to be completed and distributed as per any data form.

12 Specification of Study Observations/Variables and Data Analysis Procedures:

12.1 Variable(s) to be Measured (primary variables):

12.1.1 Time and duration (days) of progression free survival (PFS), survival time, partial or complete remission

12.1.2 Patient status at time of interim and final analysis (Quality of Life)

12.1.2.1 Modified Karnofsky's Criterion

12.1.2.2 Quality of life Parameters (VCOG)

12.1.2.3 Cellular energetics

12.1.2.4 ***Oxidative status***

12.1.3 Size and number of neoplastic lesions

12.2 Other Variables/Observations to be Recorded During Study (secondary, ancillary variables): e.g.,

12.2.1 Clinical Pathology data

12.2.2 Urinalysis data (when available)

12.2.3 CBC data

12.2.4 Quality of life indices

12.2.5 Physical exam results

12.3 Sample size Calculations

The double blind, randomized, placebo controlled clinical trial will be monitored regularly, and the actual situation may be different from the projected one. This study is exploratory and considered a pilot study to direct future research, with respect to a controlled multi-institutional double blind, randomized, placebo controlled study.

12.4 Data Analyses

If the PolyMVA displays a significant benefit for dogs with cancer, under the procedures outlined below, then the sponsor will be notified immediately.

Graphs and descriptive measures will be generated for each outcome. Various factors will be used to breakdown the measures. These include treatment group, stage, tumor site, and individual factors such as age, weight, sex, breed, and biochemical analyses in the blood.

The influence of these factors on outcome will be examined after the descriptions are made. Interactions of each factor with treatment will be investigated as well.

Disease-free interval will be analyzed with survival methods. Each factor will be tested for influence. For each factor of interest Kaplan-Meier curves will be created, and the curves will be compared using the log-rank test.

12.5 Interim analyses

Subjective interim analyses will be conducted half way through the study, to assess the progress of the trial. This is particularly important in view of the sensitivity of the projections to uncontrolled factors such as accrual rates and relapse rates. The analyses will follow the methods described in the preceding section.

13 Adverse Reactions (Appendix 6):

Any adverse reactions which could be related to the PolyMVA will be reported to the Study Monitor immediately. The investigator (or his/her designated representative) will record any unusual observations involving the PolyMVA or PLACEBO delivery, PolyMVA or PLACEBO product info, or any animal behavior, on the daily Observation Log form. A detailed description of such events will include the time of onset, duration of the event, relationship to the PolyMVA or the PLACEBO (see below), and what corrective measures, if any, were instituted.

13.1 The event will be graded as follows:

13.1.1 Mild:

The symptoms are usually transient, require no specific treatment and do not interfere with usual activities

13.1.2 Moderate:

The symptoms can be ameliorated by simple therapeutic measures but may interfere with usual activities

13.1.3 Severe/Serious:

The symptoms are life-threatening, require hospitalization and/or specific treatment. Discontinuation of the treatment with the PolyMVA is mandatory

13.2 The relationship to the PolyMVA or PLACEBO will be described as:

Using reasonable clinical judgement make an assessment of the relationship between treatment and response using the following categories:

13.2.1 Probable:

13.2.1.1 Follows a reasonable temporal sequence from PolyMVA or PLACEBO administration

13.2.1.2 Abates upon discontinuation of the PolyMVA or PLACEBO

13.2.1.3 Cannot be reasonably explained by known characteristics of the patient's clinical state

13.2.1.4 Known response pattern

13.2.2 Possible:

13.2.2.1 Follows a reasonable temporal sequence from PolyMVA or PLACEBO administration

13.2.2.2 Could have been produced by the patients clinical state or by other modes of therapy administered to the patient

13.2.3 <u>Unlikely</u>:

13.2.3.1 Temporal association is such that the PolyMVA or PLACEBO is not likely to have any reasonable association with the event

13.2.3.2 Any reaction that does not meet the criteria detailed above

13.2.4 <u>Not assessable:</u>

13.2.4.1 Data provided are not sufficient to allow the classification of a relationship

14 Procedures for Handling and Retaining Source (Raw) Data/Study Records/Reports/Statements:

14.1 Source (raw) Data:

All the source data will be either collected on the provided data collection forms or the original document received from the laboratory or consultant, which will be placed in the individual patient's notebook. Records normally maintained by some clinic facilities such as daily observations, procedures listing, etc. in electronic file format are allowed however a documented (signed, dated) print out of the electronic information is required to be placed in the patient's notebook when available.

14.1.1 Making data corrections (Appendix 6):

Corrections are allowed but must be accomplished in accordance with the applicable guidelines and regulations. Entries and corrections will be made with black ink only. A correction will be made with a single line drawn through the error, the correct entry made above the error, date of correction next to the correction, explanation of error next to the date, and the initials of the person making the correction. Error codes may be used in place of a written explanation. A complete description of data entry, corrections and allowable error codes appear in the attached document (Appendix 6, Recording and Correcting Data Entry). The error code may be expanded by the investigator, documentation is required.

14.1.2 Archival:

Upon study completion and acceptance of the final report by the sponsor/monitor, all original documents (patient notebooks, etc.) will be transferred to PolyMVA Inc for archiving. A certified copy of all the documentation will be left at each investigator site with the exact location of the originals and instructions for retrieval purposes.

14.2 Communication of Records:

14.2.1 Communications:

All communications concerning study conduct, patients, clients or other involved parties, will be documented and maintained in the investigator's notebook. Contact log forms are provided by the sponsor to be used if desired. The use of the form supplied is optional, however some appropriate means of documentation is required.

14.2.2 Transmission of Data summarized on forms

CVS Angel Care Cancer Center Team members have been employed to receive replicas of all data forms, including "Initial, "Treatment", "Staging", and "Final Disposition" forms. These data forms should be FAXed to PolyMVA Inc, in a timely manner, upon completion. At the time of receipt these data will be reviewed for protocol compliance and quality assurance. Information from each FAX will be entered into a database for summarization and reporting.

14.2.3 Communication of Protocol Deviations or Adverse effects

These occurrences should first be documented in the patient notebooks under daily logs (or elsewhere as appropriate).

Incidence of protocol deviations should be transmitted to the central office at CVS Angel Care Cancer Center.

14.3 Clinical Investigator Study Report:

The investigator at each clinical site is required to complete a study report when the study is declared complete. The report will have the following topics discussed as a minimum:

14.3.1 Adverse Reactions:

All adverse reactions noted by the investigator and documented per instructions in Section 14 will be listed.

14.3.2 Statement of protocol and regulatory compliance:

Deviations will be listed and actions taken with each.

14.3.3 Quality assurance statement:

An explanation of who and how data was collected, maintained and checked for accuracy will be included.

15 Protocol Changes and Deviations:

15.1 Protocol Amendment:

Any formal change to the protocol must have prior written approval by the monitor in the form of an amendment. The amendment must be signed and dated by both the monitor and the investigator prior to comprehensive initiation of the change.

15.2 Protocol Deviation:

Deviations from the protocol must be entered into the daily logs and brought to the attention of the study monitor and/or the staff at Angel Care Cancer Center (as noted above in 15.2) whenever they are recognized. Instructions for handling each will be given in writing and all incidents will be fully documented.

16 PolyMVA Accountability and Disposition:

Distribution and shipping of the PolyMVA will be conducted in accordance with appropriate PolyMVA internal Standard Operating Procedures (SOP). appropriate SOP's.

17 Appendices:

17.1 Appendix 1: Flow Chart of Events

17.2 Appendix 2: Initial Inclusion Visit

17.3 Appendix 3: Staging Visit

17.4 Appendix 4: Final Disposition Form

17.5 Appendix 5: Client Consent Form

17.6 Appendix 6: Adverse Effects

17.7 Appendix 7: Concomittant Treatments

Quality of Life Evaluation
COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (VCOG-CTCAE) FOLLOWING CHEMOTHERAPY OR BIOLOGICAL ANTINEOPLASTIC THERAPY IN DOGS AND CATS v1.0
A consensus document from the Veterinary Cooperative Oncology Group (VCOG)

Modified with permission from: Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS

Quick Reference: The VCOG-CTCAE is a descriptive terminology which can be used for Adverse Event (AE) reporting in dogs and cats. A grading (severity) scale is provided for each AE term.

Components and Organization:

AE and grades apply to both cats and dogs unless otherwise stated.

CATEGORY
A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms
An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), clinical sign, or disease temporally associated with the use of a medical treatment that may or may *not* be considered related to the medical treatment. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. AEs are listed alphabetically within CATEGORIES.

17.7.1.1 Grades

Grade refers to the severity of the AE. The VCOG-CTCAE displays Grades 1 through 5 with unique clinical description of severity for each AE based on this general guideline:
Grade 1 – Mild AE, **Grade 2** – Moderate AE, **Grade 3** – Severe AE, **Grade 4** – Life-threatening or disabling AE, **Grade 5** – death related to AE.

Further comments

- A Semi-colon indicates 'or' within the description of the grade. When items within the description of the grade are separated by a comma, the "," means "and". All items separated by a comma are necessary to establish that grade level.
- An '---' indicates a grade is not available.
- Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.
- Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Abbreviations used.

- ADL = activities of daily living (eating, sleeping, defecating and urinating)
- CHF = congestive heart failure
- LLN = lower limit of normal
- ULN = upper limit of normal

18 ALLERGIC/IMMUNOLOGIC EVENT					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Allergic reaction/hypersensitivity	Transient urticaria	Rash; urticaria; dyspnea	Symptomatic hypotension, with or without urticaria; parenteral medications necessary; edema	Anaphylaxis requiring parenteral medications	Death
Autoimmune reaction	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated.	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
Vasculitis (Not including perivascular injection of drug)	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation or surgical debridement indicated	Death
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

19 BLOOD/BONE MARROW					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Bone marrow cellularity	Mildly hypocellular; < 25% reduction from normal cellularity for age	Moderately hypocellular; >25 - < 50% reduction from normal cellularity for age	Severely hypocellular; >50% reduction of cellularity from normal for age	---	---
Hemoglobin	Dog: 10 g/dl - <LLN Cat: 8.0 g/dl - <LLN	Dog: <10 – 8.0 g/dl Cat: <8.0 – 6.5 g/dl	Dog: < 8.0 – 6.5 g/dl Cat: <6.5 – 5.0	Dog: < 6.5 g/dl Cat: <5.0	---
Neutropenia	1,500/µL – <LLN	1,000 - 1,499/µL	500 - 999/µL	< 500/µL	---
Thrombocytopenia	100,000/µL – <LLN	50,000 – 99,000/µL	25,000 – 49,000/µL	<25,000	---
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

LLN = lower limit of normal

20 CARDIAC ARRYTHMIA					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Conduction abnormality/atrioventricular heart block. *Select:* -Asystole -AV block-First degree -AV block-second degree Mobitz I -AV block-second degree Mobitz II -AV block-third degree (complete) -Sick sinus syndromes -Other (specify_____)	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Supraventricular and nodal arrhythmia. *Select:* -Atrial fibrillation -Atrial flutter -Atrial tachycardia/Paroxysmal -Atrial tachycardia -Nodal/junctional -Sinus tachycardia -Supraventricular extrasystoles -Supraventricular tachycardia -Other (specify, _____)	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death

Cont'd next page.

21 CARDIAC ARRYTHMIA CONT'D					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Ventricular arrhythmia. *Select:* -Bigeminy	Asymptomatic, intervention not indicated	Non-urgent medical intervention	Symptomatic and incompletely	Life-threatening (e.g.,	Death

-Idioventricular rhythm -PVCs -Torsade de pointes -Trigeminy -Ventricular fibrillation -Ventricular flutter -Ventricular tachycardia -Other (specify, _____)		indicated	controlled medically or controlled with device (e.g., pacemaker)	arrhythmia associated with CHF, hypotension, syncope, shock)	
Other Cardiac Arrhythmia (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

22 CARDIAC GENERAL

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Cardiopulmonary arrest	-	-	-	Life-threatening	Death
Hypertension	Asymptomatic, transient (<24 hrs) increase; intervention not indicated	Recurrent or persistent (>24 hrs) or symptomatic increase; monotherapy may be indicated	Requiring more than one drug or more intensive therapy	Life-threatening consequences (e.g., hypertensive crisis)	Death
Hypotension	Asymptomatic; intervention not indicated	Brief (<24 hrs) fluid replacement or other therapy; no physiologic consequences	Sustained (> 24 hrs) therapy, resolves without persisting physiologic consequences	Shock (e.g., impairment of vital organ function)	Death
Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding; intervention not indicated	Asymptomatic, intervention indicated	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled with intervention	Death
Left ventricular systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60 – 50%; Fractional shortening (FS) 20 –25%	Asymptomatic, resting EF <50 – 40%; FS 15 – 20%	Symptomatic CHF responsive to intervention; EF < 40 – 20%, FS <15%	Refractory CHF or poorly controlled; EF < 20%	Death
Myocarditis	---	---	CHF responsive to intervention	Severe or refractory CHF	Death

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23 CARDIAC GENERAL CONT'D

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pericardial effusion	Asymptomatic	---	Physiologic	Life-	Death

(non-malignant)	effusion		consequences	threatening; emergency intervention indicated	
Right ventricular dysfunction (cor pulmonale)	Asymptomatic without therapy	Asymptomatic, therapy indicated	Symptomatic cor pulmonale, responsive to intervention	Symptomatic cor pulmonale, poorly controlled	Death
Valvular heart disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis. Treatment not indicated	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical therapy	Life-threatening; disabling; poorly responsive to medical therapy	Death
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

24 COAGULATION					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
DIC (disseminated intravascular coagulation)	---	Laboratory findings with no bleeding	Laboratory findings and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage, or hemodynamically significant blood loss)	Death
PT (prothrombin time)	>1 – 1.5 x ULN	>1.5 - 2 x ULN	>2 x ULN	---	
PTT (partial thromboplastin time)	>1 – 1.5 x ULN	>1.5 - 2 x ULN	>2 x ULN	---	
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ULN = upper limit of normal

25 CONSTITUTIONAL SYMPTOMS					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Lethargy/fatigue	Mild lethargy over baseline	Moderate lethargy causing some difficulty with performing ADL	Compromised, severely restricted in ADL, ambulatory only to the point of performing ADL	Disabled, must be force fed and helped to perform ADL	Death
Fever (in the absence of grade 3 or 4 neutropenia)	1^{o} C above ULN	1 - 2^{o} C above ULN	2 - 3^{o} C above ULN	>3^{o} C above ULN	Death
Hypothermia	---	36 – >33^{o} C	33 - >28^{o} C	<28^{o} C or life-threatening consequences (e.g., coma, hypotension, pulmonary edema)	Death
Weight loss	5 – 10% from baseline; intervention not indicated	>10 - 20% from baseline; nutritional support indicated	> 20% of baseline	---	Death
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ADL = activities of daily living (eating, sleeping, defecating and urinating)

26 DERMATOLOGIC/SKIN					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Alopecia	Sparse thinning or denuding of hair at localized site	Sparse generalized thinning of hair coat	Generalized denuded hair coat	---	---
Bruising (in absence of Grade 3 or 4 thrombocytopenia)	Localized or in a dependent area	Generalized.	---	---	---
Erythema	Limited to localized site	Generalized, but noticeable only upon close examination	Generalized and easily visible upon examination.	---	---
Hyperpigmentation	Slight or localized	Marked or generalized	---	---	---
Hypopigmentation	Slight or localized	Marked or generalized	---	---	---
Injection site reaction/extravasation changes	Pain; itching; erythema	Pain or swelling with inflammation or phlebitis	Ulceration or necrosis not requiring operative intervention	Ulceration or necrosis that requires operative intervention	---
Nail/Claw	Discoloration, pitting	Weakening	Partial or complete loss of nail(s)/Claw(s); pain	Interfering with ADL	---
Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritis	Mild or localized	Intense or widespread	Intense, widespread and interfering with ADL	---	---

Cont'd next page

27 DERMATOLOGIC/SKIN CONT'D

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Rash/desquamation	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering < 50% of body surface area	Severe generalized erythroderma or macular, papular or vesicular eruption; desquamation covering > 50% body surface area	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
Rash:acne/acneiform	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	---	---
Rash: erythema muliforme	---	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, nutritional support indicated	Life-threatening; disabling	Death
Rash: "Palmar-plantar erythrodysesthesia syndrome"	Minimal changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	---	---

Continued next page

28 DERMATOLOGIC/SKIN CONT'D

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Scaling	Fine scaling, noticeable only upon close examination	Scaling easily visible but not exfoliation in clumps; minimal crusting	Easily visible scaling and crusting with exfoliation upon examination	---	---
Urticaria (hives, welts, wheals)	---	Transient	Intervention indicated < 24 hrs	Intervention indicated > 24 hrs	---
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

29 ENDOCRINE					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	Hospitalization	Life-threatening; disabling	Death
Pancreatic endocrine: glucose intolerance	Asymptomatic, intervention not indicated	Symptomatic, dietary modification or oral agent indicated	Symptoms interfering with ADL; insulin indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar)	Death
Parathyroid function (hypoparathyroidism)	Asymptomatic, intervention not indicated	Symptomatic, intervention indicated	---	---	Death
Thyroid function, low	Asymptomatic, intervention not indicated	Symptomatic, not interfering with ADL, thyroid replacement indicated	Symptoms interfering with ADL; hospitalization indicated	Life-threatening myxedema coma	Death
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

30 GASTROINTESTINAL					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anorexia	Coaxing or dietary change required to maintain appetite	Oral intake altered (<3d) without significant weight loss; oral nutritional supplements indicated	Of 3 – 5 days duration; Associated with significant weight loss or malnutrition; IV fluids, tube feeding or TPN indicated	Life-threatening consequences; >5 days duration.	Death
Colitis	Asymptomatic, pathologic or radiographic findings only	Abdominal cramping/pain; mucus or blood in stool	Abdominal pain, fever, change in bowel habits, ileus, peritoneal signs	Life-threatening consequences (e.g., perforation, bleeding, ischemia, necrosis)	Death
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, megacolon)	Death
Dehydration	Increased oral fluids indicated; dry mucous membranes; < skin turgor	Parenteral (IV or SC) fluids indicated <24 hrs	IV fluids indicated > 24 hrs	Life-threatening (e.g., hemodynamic collapse)	Death

Continued next page

31 GASTROINTESTINAL CONT'D					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of > 2 stools per day over baseline	Increase of 2 – 6 stools per day over baseline; Parenteral (IV or SC) fluids indicated < 24 hrs; not interfering with ADL	Increase of >6 stools per day over baseline; incontinence; IV fluids > 24hrs; hospitalization; interfering with ADL	Life-threatening (e.g., hemodynamic collapse)	Death
Dysphagia	Symptomatic but able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, food consistency); Parenteral (IV or SC) fluids indicated < 24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids >24hrs, tube feeding or PPN/TPN indicated	Life-threatening (e.g., obstruction, perforation)	Death
Enteritis (inflammation of the small bowel)	Asymptomatic, pathologic or radiographic findings only	Abdominal pain/cramping; mucus or blood in stool)	Abdominal pain/cramping, fever, change in bowel habits with ileus; peritoneal signs	Life-threatening (e.g., perforation, bleeding, ischemia, necrosis)	Death
Flatulence	Mild	Moderate	---	---	---

31.1 Continued next page

32 GASTROINTESTINAL CONT'D					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Asymptomatic, radiographic finding only	Symptomatic; altered GI function (e.g., altered dietary	Symptomatic and severely altered GI function; IV fluids, tube feedings, or	Life-threatening consequences	Death

		habits); Parenteral (IV or SC) fluids indicated < 24 hrs	PPN/TPN indicated > 24 hrs		
Incontinence, anal	Occasional	Daily	Interfering with ADL; operative intervention indicated	Permanent	Death
Mucositis/stomatitis	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening	Death
Nausea	Loss of appetite without alteration in eating habits	Salivation or "smacking of lips" < 12 hrs	Salivation or "smacking of lips" > 12 – 24 hrs	Salivation or "smacking of lips" > 24 hrs	---
Vomiting	<3 episode in 24 hours	3 – 5 episodes in 24 hours; < 3 episodes/d for > 2 days but < 5days; Parenteral (IV or SC) indicated < 24 hrs	>5 episodes in 24 hours; vomiting > 4 days; IV fluids or PPN/TPN indicated > 24 hrs	Life-threatening (e.g., hemodynamic collapse)	Death
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening	Death

33 HEMORRHAGE/BLEEDING					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hematoma	Minimal signs, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion or operative intervention indicated	Life-threatening; major urgent intervention indicated	Death
Hemorrhage/bleeding associated with surgery, intraoperative or postoperative	---	---	Requiring transfusion(s) beyond what is 'normal' for that procedure;	Life-threatening	Death

			operative intervention		
Hemorrhage/bleeding, spontaneous *Specify site*: _____	Mild or microscopic, intervention not indicated	Symptomatic, medical or minor operative intervention indicated	Transfusion, operative intervention indicated	Life-threatening; major urgent intervention indicated	Death
Petechiae/purpura (skin or mucosa)	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura	---	Death
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

34 HEPATOBILIARY/PANCREAS					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Cholecystitis	Asymptomatic, radiologic findings only	Symptomatic, medical intervention indicated	Operative or endoscopic intervention required	Life-threatening (e.g., sepsis or perforation)	Death
Liver dysfunction/failure (**clinical**)	---	---	Jaundice	Encephalopathy or coma	Death
Pancreatic exocrine insufficiency	---	Increase in stool frequency, bulk or odor; steatorrhea	Sequelae of absorption deficiency (e.g., weight loss)	Life-threatening	Death
Pancreatitis	Asymptomatic, enzyme elevation and/or radiographic findings	Symptomatic, medical intervention indicated	Endoscopic or operative Intervention indicated	Life-threatening (e.g., circulatory failure, hemorrhage, sepsis)	Death
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

35 METABOLIC/LABORATORY					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Albumin, low	<LLN - 2.0 g/dl	<2.0 – 1.5 g/dl	< 1.5 g/dl	---	---
Alkaline phosphatase	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20 x ULN	>20 x ULN	---
ALT	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 10 x ULN	>10 x ULN	---
Amylase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5 x ULN	>5 x ULN	---
AST	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 10 x ULN	>10 x ULN	---
Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10 x ULN	>10 x ULN	---
Calcium, low	<LLN – 8.0 mg/dL Ionized Dog: <LLN – 1.1 nmol/L Ionized Cat: <LLN – 0.9 nmol/L	<8.0 – 7.0 mg/dL Ionized Dog: <1.1 – 1.0 nmol/L Ionized Cat: <0.9- 0.8 nmol/L	<7.0 – 6.0 mg/dL Ionized Dog: <1.0 – 0.9 nmol/L Ionized Cat: <0.8 – 0.7 nmol/L	< 6.0 mg/dL Ionized Dog: <0.9 nmol/L Ionized Cat: <0.7 nmol/L	Death
CPK	>ULN – 2.5 x ULN	>2.5– 5 x ULN	>5 - 10 x ULN	>10 x ULN	Death
Creatinine	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 6 x ULN	>6 x ULN	Death
Glucose, high	Dog: >ULN – 160 mg/dL Cat: >ULN – 200 mg/dL	Dog: >160 - 250 mg/dL Cat: >200 – 250 mg/dL	Dog: >250 - 500 mg/dL Cat: >250 - 500 mg/dL	Dog: >500 mg/dL Cat: >500 mg/dL	Death
Glucose, low	<LLN – 55 mg/dL	<55 - 40 mg/dL	<40 - 30 mg/dL	<30 mg/dL	Death
Hemoglobinuria	Present	---	---	---	
Lipase	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5 x ULN	>5 x ULN	
Potassium, high	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	Death
Potassium, low	<LLN – 3.0	---	<3.0 – 2.5	<2.5	Death

	mmol/L				
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

36 MUSCULOSKELETAL/SOFT TISSUE					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Arthritis, non-septic	Mild pain with inflammation or joint swelling, but not interfering with function	Moderate pain with inflammation or joint swelling interfering with function, but not interfering with ADL	Severe pain with inflammation or joint swelling and interfering with ADL	Disabling	---
Extremity (gait/ambulation)	Limp evident only to trained observer	Noticeable limp, or limitation of limb function, but able to walk > 0.1 kilometer (1 city block)	Severe limp with stride modified, occasionally weight bears on involved limb	Non-weight bearing lame	---
Muscle weakness, generalized or specific area	Asymptomatic, weakness on physical exam	Symptomatic and interfering with function, but not interfering with ADL	Symptomatic and interfering with ADL	Life-threatening; disabling	Death
Myositis (inflammation of muscle)	Mild pain, not interfering with function	Pain interfering with function, but not interfering with ADL	Pain interfering with ADL	Disabling	Death
Soft tissue necrosis	---	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated	Life-threatening; major invasive intervention indicated (e.g., reconstruction, graft)	Death
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

37 NEUROLOGY					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Apnea	---	---	Present	Intubation indicated	Death
Ataxia	Asymptomatic	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Disabling	Death
Encephalopathy	---	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death
Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	---	---
Laryngeal nerve dysfunction	Asymptomatic; clinical exam finding	Symptomatic, but not interfering with ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated	Life-threatening; tracheostomy indicated	Death
Neuropathy : Cranial Nerve *Select*: CNI CNVII CNIII CNIV CNV CNVI CNVII CNVIII CNIX CNX CNXI CNXII	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL	Life-threatening; disabling	Death

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38 NEUROLOGY CONT'D					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Neuropathy: Motor	Asymptomatic; weakness on exam/testing only	Symptomatic weakness interfering with function but not ADL	Weakness interfering with ADL	Life-threatening; disabling (e.g., Paralysis)	Death
Neuropathy: Sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia but not interfering with function	Sensory alteration or paresthesia, interfering with function but not ADL	Sensory alteration or paresthesia interfering with ADL	Disabling	Death
Personality/behavior	Change noticed but not adversely affecting patient or family	Change, adversely affecting patient or family	Change is harmful to others or self	---	---
Seizure	---	One brief generalized seizure; well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder with breakthrough seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death

Continued next page

39 NEUROLOGY CONT'D					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Somnolence/depressed level of consciousness	----	Somnolence or sedation interfering with function but not ADL	Obtundation or stupor; difficult to arouse; interfering with ADL	Coma	Death
Syncope (fainting)	---	---	Present	Life-threatening	Death
Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADL	Severe tremor interfering with ADL	Disabling	---
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

40 OCULAR/VISUAL					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Cataract	Asymptomatic, detected on exam only	Symptomatic with moderate decrease in visual acuity	Symptomatic with marked decrease in visual acuity; operative intervention indicated	---	---
Dry eye syndrome	Mild, intervention not indicated	Symptomatic, interfering with function but not ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL	---	---
Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual deficit	EIOP causing early visual field deficit; multiple topical or oral agents indicated	EIOP causing marked visual deficits; operative intervention indicated	EIOP resulting in blindness; enucleation indicated	---
Keratitis (corneal inflammation/corneal ulceration)	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness.	---

Continued on next page

41 OCULAR/VISUAL CONTINUTED					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, interfering with function but not ADL; topical antibiotics or other topical intervention indicated	Symptomatic and interfering with ADL; operative intervention indicated	---	---
Optic disc edema	Asymptomatic	Decreased visual acuity	Blindness	---	---
Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and some visual acuity loss but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness	---
Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity	Blindness	---	---
Scleral necrosis/melt	Asymptomatic or symptomatic but not interfering with function	Symptomatic, interfering with function but not ADL; moderate decrease in visual acuity; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	Blindness; painful eye with enucliation indicated	---

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42 OCULAR/VISUAL CONTINUTED					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Uveitis	Asymptomatic	Anterior uveitis;	Posterior or	Blindness	---

		medical intervention indicated	pan-uveitis; operative intervention indicated		
Vitreous hemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function but not ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated	---	---
Epiphora	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not ADL	Symptomatic, interfering with ADL	---	---
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

43 PAIN					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pain *Specify site*: _____	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function but not ADL	Severe pain; pain or analgesics severely interfering with ADL	Disabling	---
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

44 PULMONARY/RESPIRATORY					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Respiratory Distress Syndrome (ARDS)	---	---	Present, intubation not indicated	Present, intubation indicated	Death
Aspiration	Asymptomatic; radiographic findings	Symptomatic; medical intervention indicated	Clinical or radiographic signs of pneumonia or pneumonitis	Life-threatening	Death
Bronchospasm, wheezing	Asymptomatic	Symptomatic, not interfering with function	Symptomatic, interfering with function	Life-threatening	Death
Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic indicated	Symptomatic and interfering with sleep or ADL	---	---
Dyspnea	Dyspnea on exertion, but can walk without tiring	Dyspnea on exertion and tires upon ambulating	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death
Edema, larynx	Asymptomatic edema by exam only	Symptomatic edema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening; tracheotomy, intubation, indicated	Death
Hypoxia	---	< O_2 saturation with exercise	< O_2 saturation at rest; continuous O_2 supplementation required	Life-threatening; intubation or ventilation required	Death

Continued next page

45 PULMONARY/RESPIRATORY CONT'D					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pleural effusion (non-	Asymptomatic	Symptomatic,	Symptomatic and	Life-	Death

malignant)		intervention with diuretics or up to 2 thoracenteses indicated	supplemental oxygen, >2 thoracenteses, tube drainage, or pleurodesis indicated	threatening (e.g., hemodynamic instability or ventilatory support)	
Pneumonitis/pulmonary infiltrates	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O_2 indicated	Life-threatening; ventilatory support indicated	Death
Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic; non-operative intervention indicated	Sclerosis and/or operative intervention indicated	Life-threatening, hemodynamic instability; ventilatory support	Death
Pulmonary fibrosis (radiographic)	Minimal, estimated lung volume involved < 25%	Patchy or bilateral changes with estimated lung volume 25 – 50%	Dense or widespread infiltrates/consolidation with estimated involved lung volume 50 – 75%	Estimated involved lung volume >75%	Death
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

46 RENAL/GENITOURINARY					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Cystitis	Asymptomatic; microscopic hematuria/pyuria	Pollakuria with dysuria; macroscopic hematuria	Transfusion indicated; pain or antispasmodic medication; bladder irrigation indicated	Catastrophic bleeding; non-elective intervention indicated	Death
Incontinence, urinary	Occasional (e.g., with coughing, sneezing, etc)	Spontaneous	Interfering with ADL; medical intervention indicated	Operative intervention indicated	---
Obstruction, urinary	Asymptomatic; radiographic or endoscopic finding	Symptomatic without hydronephrosis or renal dysfunction	Symptomatic, altered organ function; hydronephrosis; operative intervention indicated	Life-threatening; organ failure	Death
Renal failure	---	---	Chronic; dialysis not indicated	Chronic dialysis or renal transplant indicated	Death
Urinary frequency	> in frequency or nocturia up to 2 x normal	> 2 x normal but < hourly	> or = 1 x/hour	---	---

Continued next page

47 RENAL/GENITOURINARY CONT'D					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Urinary retention (including neurogenic bladder)	Hesitancy or dribbling, no significant residual	Bladder atony requiring indwelling	More than daily catheterization indicated;	Life-threatening consequences; organ failure	Death

	volume	catheter for < 2 weeks	operative intervention indicated		
Urine color change	Present	---	---	---	---
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

48 SECONDARY MALIGNANCY					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Secondary Malignancy – possibly related to cancer treatment (*Specify*, _____)	---	---	Non-life threatening benign tumor or malignancy	Malignant solid tumor, leukemia or lymphoma	Death
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

49 SEXUAL/REPRODUCTIVE FUNCTION					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Mammary gland function/lactation	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	---	---	---
Gynecomastia	---	Asymptomatic breast enlargement	Symptomatic breast enlargement	---	---
Infertility/sterility	---	Male: oligospermia/low sperm count Female: Diminished fertility/estrus	Male: Sterile/azoospermia Female: infertile/anestrous	---	---
Vaginal discharge (non-infectious)	Mild	Moderate to heavy	---	---	---
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	---

50 VASCULAR					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Acute vascular leak syndrome	---	Symptomatic, fluid support not indicated	Respiratory compromise or fluids indicated	Life-threatening; pressor support or ventilatory support indicated	Death
Peripheral arterial ischemia	---	Brief (<24 hrs) episode of ischemia managed nonsurgically and without permanent deficit	Recurring or prolonged (>24 hr) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end-organ damage (e.g., limb loss)	Death
Phlebitis	---	Present	---	---	---
Thrombosis/thrombus/embolism	---	Deep vein thrombosis or cardiac thrombosis; intervention not indicated	Deep vein thrombosis or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, invasive procedure)	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Visceral arterial ischemia	---	Brief (<24 hr) episode of ischemia managed medically and without permanent deficit	Prolonged (>24 hr) or recurring symptoms and/or invasive intervention indicated	Life-threatening; disabling; evidence of end- organ damage	Death
Other (Specify, _____)	Mild	Moderate	Severe	Life-threatening; disabling	Death

TOXICITY AND EFFICACY OF A LIPOIC ACID-PALLADIUM COMPLEX FOR THE TREATMENT OF DOGS WITH OSTEOSARCOMA:
A Descriptive Statistical Analysis Using Kaplan-Meier Survival Curves

51 Executive Summary

Introduction: Osteosarcoma (OSA) accounts for approximately 85% of malignant bone tumors in dogs (1). It occurs primarily in the appendicular skeleton, and is a common cancer of large to giant breed dogs (1.). Even with the removal of the primary bone tumor before the spread of the cancer is clinically detectable, metastases to lung, bone, or other sites eventually develop in a majority of dogs. Due to the high mortality rate from distant metastatic disease, targeted adjuvant therapies are needed to prolong currently achievable survival times.

Poly MVA is a dietary supplement based on the nontoxic chemotherapeutic lipoid acid-palladium complex (LAPd). LAPd complexes have demonstrated anecdotal effectiveness thus far in over 20 different types of cancer. LAPd is reported to benefit cancer patients in part by transferring excess electrons from membrane fatty acids in cancer cells to DNA via the mitochondria (2). LAPd can both quench free radicals as well as provide energy to the mitochondria (2). It also facilitates the activation of an apoptotic complex that contributes to cancer cell death. James Forsythe, MD reported a 70% complete and partial response rate in stage IV human cancer patients treated with LAPd. Concrete data about poly MVA's function in prolonging survival time of cancer patients is lacking. The purpose of the present study was to identify and evaluate whether a relationship exists between poly MVA administration and clinicopathologic outcome among different treatment modalities.

Methods: The study group comprised 57 dogs with histologically confirmed osteosarcoma that were entered into this prospective study to test the hypothesis that LAPd is safe and effective when used alone or in combination with surgery, chemotherapy, and/or radiation therapy. Clients were educated about the potential risks and benefits of all of their treatment options before deciding on a definitive course of action. Twenty of these dogs received palliative therapy (35%), 11 underwent surgery (19%), 17 underwent surgery and received chemotherapy (30%), and 9 received all other treatment options (16%). Other treatment options included the following: (a) chemotherapy only, (b) radiation only, (c) chemotherapy and radiation, (d) surgery and radiation, (e) surgery, chemotherapy, and pamidronate, (f) chemotherapy, radiation, and pamidronate, and (g) pamidronate only. All 57 patients were administered poly MVA, 48 patients were administered docosahexaenoic acid (DHA) (84%), 44 patients were administered piroxicam (77%), and 38 patients received all three medications (66%): poly MVA, DHA, and piroxicam. The 57 dogs in the experimental group were then compared with a control group of 162 dogs with histologically confirmed osteosarcoma who received only amputation and no poly MVA. Information on additional medications (i.e. DHA and piroxicam) was not available for analysis.

Results: Kaplan-Meier survival curves were generated, and the influences of treatment on outcome were evaluated via log-rank analysis. The median survival times (MST) for the different treatment groups were as follows: control (n=162) 165 days; palliative therapy (n=20) 66 days;

surgery (n=11) 268 days; surgery and chemotherapy (n=17) 367 days; and for all other therapy options (n=9) 208 days. In this study, 116 cases who were in the control group (n=162), 17 cases who received palliative treatment (n=20), 8 cases who had surgery performed (n=11), 12 cases who had surgery performed and chemotherapy administered (n=17), and 9 cases who received all other treatment options (n=9) presented the outcome of interest, which was death. The chi-square statistic was 11.61, with an associated p-value of 0.02.

Additional Kaplan-Meier survival curves were generated comparing each of the treatment modalities against each other. Hazard ratios, along with their 95% confidence intervals were also calculated. See Table 1. The log-rank test comparing the palliative treatment and surgery survival curves produced a chi-square statistic of 2.94, with an associated p-value of 0.08 and a hazard ratio of 2.02 (95% CI 0.90-4.49). When comparing the palliative treatment and surgery/chemotherapy survival curves, the chi-square statistic was 6.28, with an associated p-value of 0.01 and a hazard ratio of 2.42 (95% CI 1.24-5.88). When comparing the palliative treatment and all other therapy options survival curves, the chi-square statistic was 0.50, with an associated p-value of 0.47 and a hazard ratio of 1.33 (95% CI 0.60-2.92). The logrank test comparing the surgery and surgery/chemotherapy survival curves produced a chi-square statistic of 1.05, with an associated p-value of 0.30 and a hazard ratio of 1.56 (95% CI 0.62-4.51). When comparing surgery and all other therapy options survival curves, the chi-square statistic was 1.14, with an associated p-value of 0.28 and a hazard ratio of 0.61 (95% CI 0.20-1.59). When comparing the surgery/chemotherapy and all other therapy options survival curves, the chi-square statistic was 5.56, with an associated p-value of 0.01 and a hazard ratio of 0.37 (95% CI 0.09-0.80).

Conclusions & Recommendations: In the current investigation, we observed that the five survival curves differed significantly. In other words, the grouping variable (treatment modality) has a statistically significant influence on survival time. When analyzed individually against one another, it was found that dogs treated with palliative therapy did not have a significantly different survival time than dogs treated with surgery (p=0.08). Likewise, dogs treated with surgery did not have a significantly different survival time than dogs treated with surgery/chemotherapy (p=0.30). There was also no significant difference in survival time between dogs treated with surgery and dogs treated with all other therapy options (p=0.28), or between dogs treated with palliative therapy and all other options (p=0.47). Survival times were significantly different between dogs treated with palliative therapy and dogs treated with surgery/chemotherapy ($p<0.01$), as well as between dogs treated with surgery/chemotherapy and dogs treated with all other therapy options ($p<0.01$). When comparing these treatment modalities against the control group, there was no significant difference between the control versus palliative therapy, control versus surgery, and control versus all other therapy options (p=014; p=01.1; p=0.90 respectively). There was a significant difference in survival times seen between the control group and dogs treated with surgery/chemotherapy ($p<0.004$).

Because there are 7 options grouped together in the "all other therapies" category, it is difficult to discern which, if any, of these treatments are more effective than others. Additionally, the

differences seen between treatment groups could be attributed solely to the varying effectiveness of each treatment modality against the others, with the effect of poly MVA being negligible. Based on the median survival times reported by other studies (3-15), longer median survival times were reported in this preliminary study with those groups treated with poly MVA. The median survival time (MST) of dogs treated with surgery was reported to be 129 days in other studies (3), while the current study found a MST of 268 days. The MST of dogs treated with surgery and either single agent or combination chemotherapy was reported to be between 234 to 330 days (4-15), while the current study found a MST of 367 days. Moreover, the MST of the control group (amputation only, no Poly MVA) was 165 days, which is similar to the MST of 129 days reported in additional studies for dogs treated with surgery. These findings suggest that there are other variables besides the treatments themselves that affect median survival times. What cannot be conclusively determined from this investigation is whether it is the poly MVA or other medications/supplements such as piroxicam and DHA (or a combination of these drugs) that are affecting the MST.

The present study utilized descriptive statistics using Kaplan-Meier survival curves and log-rank tests to analyze the effect of poly MVA on clinicopathologic outcome. Because there were potentially confounding variables (i.e. DHA and piroxicam) that were controlled for, these results do not conclusively show that poly MVA has a correlation with survival time. Additional studies need to be conducted in a double-blind randomized trial while controlling for all variables. Moreover, we cannot rule out the possible effects if a larger sample size were to be analyzed. In addition to comparing objective quality of life parameters, subjective measures can also be quantified through distribution of a quality of life survey to the patient's owners. Further investigation of this population is warranted in order to evaluate the potential beneficial effects of poly MVA, and survival effects associated with its use in each treatment modality.

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TITLE: A Case Study:

Changes in *quality of life* outcomes for dogs receiving PolyMVA

ABSTRACT:

The objective of this study was to assess changes in quality of life outcomes over time for dogs with cancer (n=169) as evaluated by the primary caregiver with treatment protocols including PolyMVA for all individuals. Quality of life outcomes were measured both on a visual analog scale (VAS; 0="bad" and 100="excellent") and on a categorical scale (0 to 3). The VAS outcomes included overall quality of life, appetite, upset stomach and degree of comfort before onset of cancer, at initial diagnosis, during the first two weeks of PolyMVA administration, and between administration of PolyMVA and study end. Categorical outcomes included quality of life, activity, mood, hygiene, pain, appetite, tiredness, difficulty sleeping, vomiting, intestinal function, ability to position for defecation/urination, family attention, and 3 composite outcomes. These were recorded at diagnosis, at 2 and 4 weeks, and over the entire study period. Analysis of VAS outcomes showed significant improvement in comfort levels over all post-diagnosis time periods. Analysis of categorical quality of life outcomes indicated significant improvement in quality of life, mood, and pain at 4 weeks and over the entire study period. Significant improvement in difficulty sleeping at 4 weeks was also found. The only significant decrease in score was for intestinal function at 2 weeks. The VAS and the categorical outcomes, taken together, would seem to indicate a potential beneficial effect of PolyMVA treatment. However, without appropriate control individuals, the cause/effect relationship can not be determined. Future research should be undertaken to fully evaluate the potential benefits of PolyMVA treatment for cancerous dogs.