What's New in Oncology? Cutting Edge Treatments Improving Patient Outcomes

Amy Back, DVM, MS, DACVIM (Oncology)

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Leading Specialty Healthcare for Pets

Hot Topics in Oncology

- Personalized medicine
- Precision medicine
- Immunotherapy
- Targeted therapy
- Biomarker testing
- Intralesional treatments
- New chemotherapies
- Cancer screening

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Why Do We Care?

- Of the 65 million dogs and 32 million cats in the US, approximately 6 million cancer diagnoses are made in each species each year
- Study: 58% of owners would not pursue chemotherapy due to risks, but 72% felt it would extend survival times
  - 72% overestimated survival times

*Factors Which Influence Owners When Deciding to Use Chemotherapy in Terminally Ill Pets: Williams, et al. *Animals* 2017

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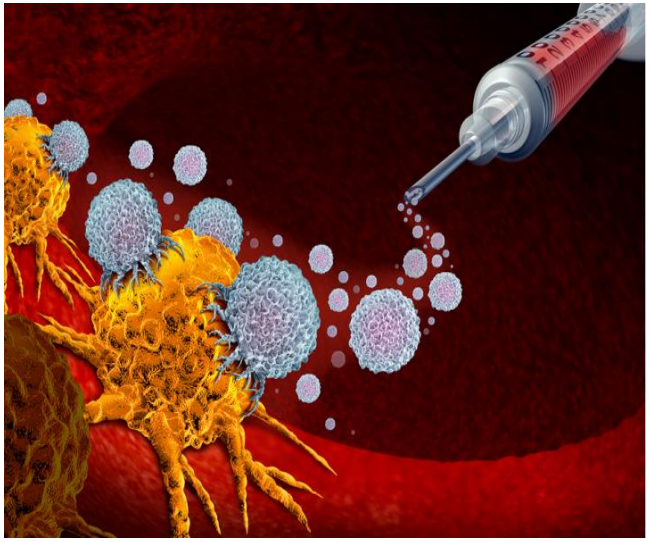
Hot Topics in Oncology

- Immunotherapy
  - Cancer treatment that helps the immune system fight the cancer
  - Immune checkpoint inhibitors, T-cell transfer therapy, Monoclonal antibodies, and tumor vaccines

- What's available in veterinary oncology?
  - Check Point inhibitors: Monoclonal antibodies for PD-1
  - Merial Oncept IL-2
  - T-cell transfer therapy: Elias Autologous cancer cell vaccination with adoptive T-cell transfer and IL-2
  - Monoclonal antibodies: Blontress® and Tactress®
  - Vaccines: **Torigen autologous cancer vaccines**, Melanoma Vaccine, Telomerase vaccines



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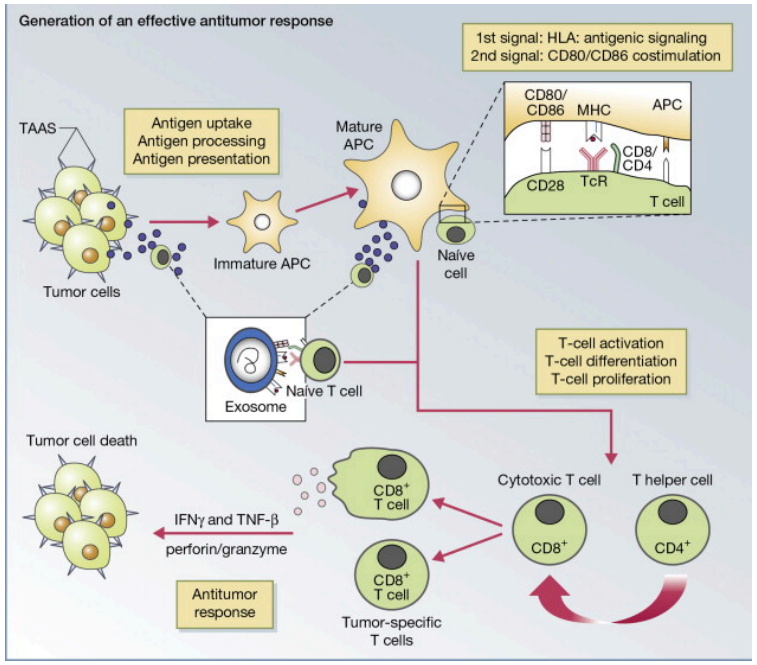
Torigen - Autologous Cancer Vaccines

- Whole tissue vaccines include both the mutated tumor cells and the associated extracellular matrix
- Historical ACV methods used *in vitro* expansion or enzymatic dissociation of cells
  - Alter or destroy Tumor Associated Antigens (TAA)
  - Lengthens the process
  - Possibility of microbial contamination
- The autologous cancer vaccine technology used by **Torigen Pharmaceuticals, Inc.** uses the patient's tumor tissue, with no *in vitro* culture, nor enzymatic treatment, and includes the tumor extracellular matrix

Why Autologous Cancer Vaccines?

- Contains relevant tumor antigens
- Vaccine can be produced without knowledge of specific antigens
- Well-tolerated
- Efficacious in people
- Less expensive than chemotherapy
- Option for treatment in those that don't want to pursue chemotherapy
- No special PPE required for handling or administration



Neil L. Berinstein, Jeffrey A. Berinstein, Therapeutic cancer vaccines. In: *Vaccines* (Sixth Edition), 2013.

Goal: Increase presentation of TAA to increase activation of tumor-specific T-cells

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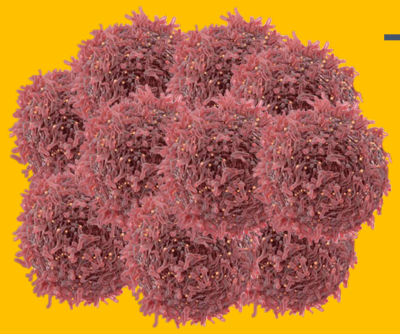
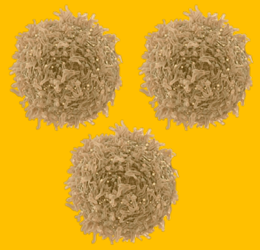
Torigen Process

1 Tumor is surgically excised

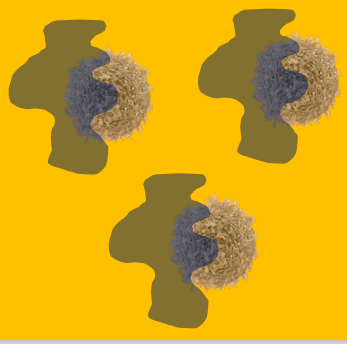


2 Single Cell Suspension of deactivated tumor cells

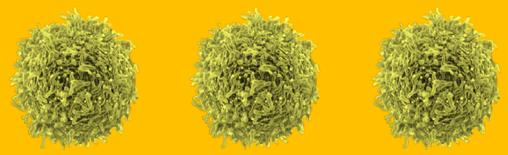


3 MIM is added

4 Individual tumor cells attached to MIM



5 MIM simulates T_h1 response and APC and cytotoxic T cell recruitment to injection site



6 Abundant and active circulating T cells target and destroy cancer cells throughout the body

Autologous Prescription Products created by Torigen Pharmaceuticals, Inc. are regulated by the USDA Center for Veterinary Biologics.
For use under supervision/prescription of a licensed veterinarian.
Safety and efficacy have not been established.

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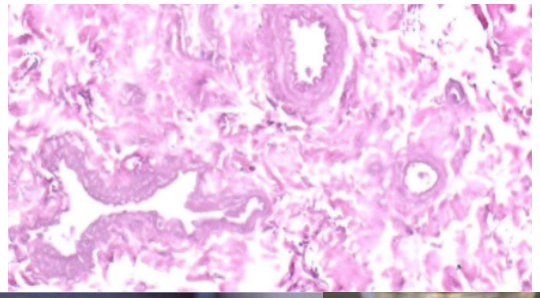
Adjuvant: Matrix Immune Modulator (MIM)

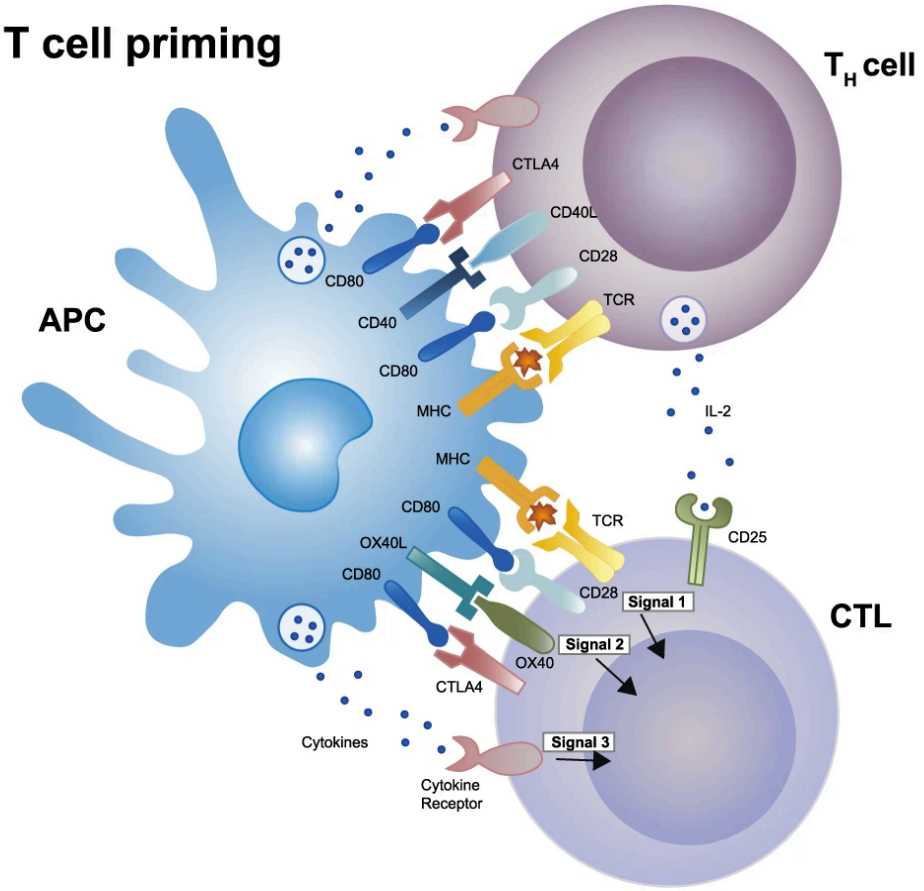
- Structural proteins
  - Collagen
  - Elastin
- Adhesion glycoproteins
  - Fibronectin
- Glycosaminoglycans (GAGs)
- Matricellular proteins



The addition of MIM to a tissue vaccine stimulates pro-inflammatory response and attraction of antigen presenting cells

Torigen: Does it stimulate the immune system? Antigen presentation assay

- Autologous cancer cell vaccines
  - From 13 unique dogs with HAS
  - MHC-II
    - Present on functional APC
    - Interacts with TCR
  - CD80
    - Costimulatory for T cell activation
    - Marker of activated APC



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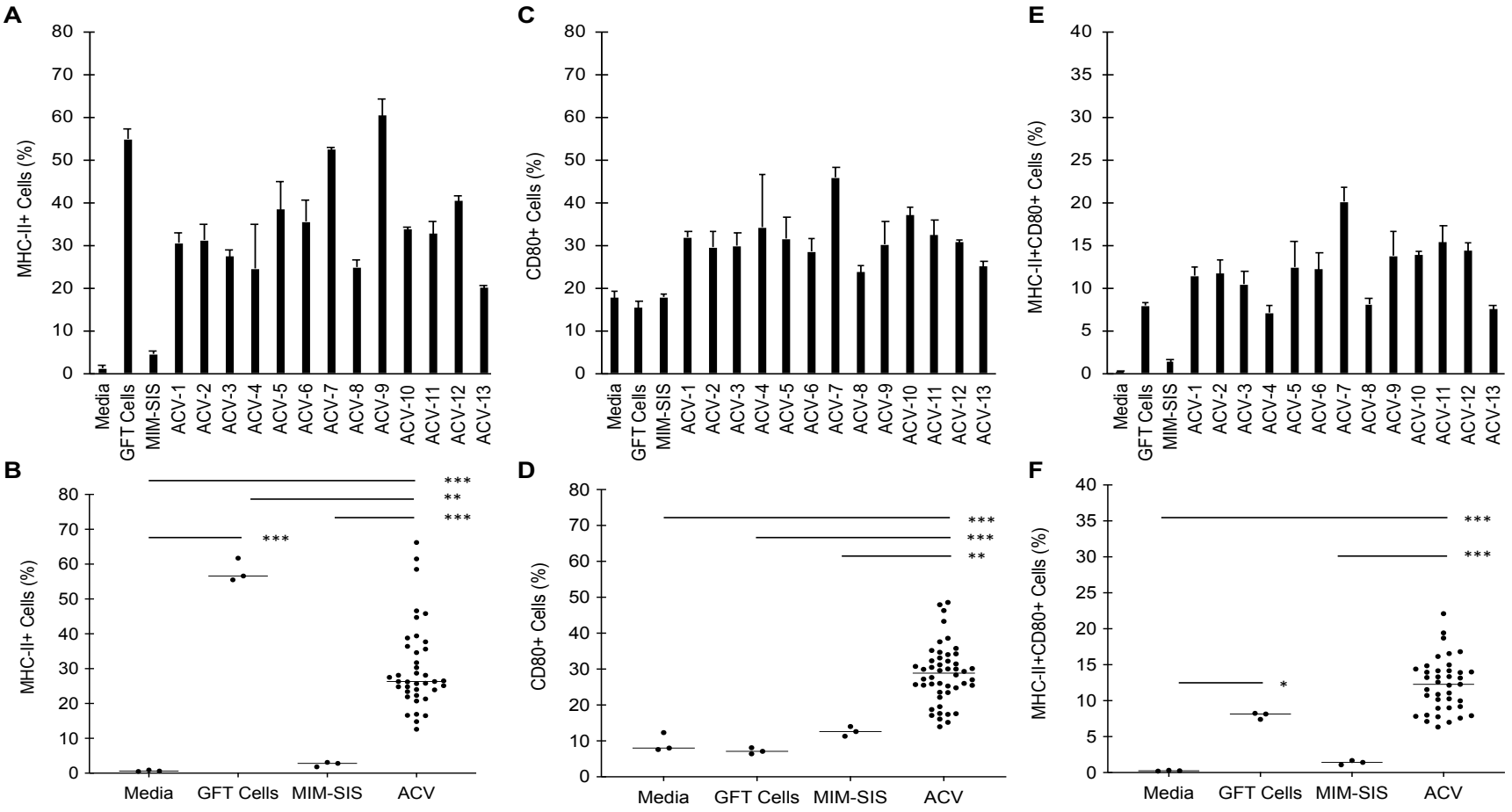
Torigen: Does it Stimulate the Immune System?

Canine HSA ACV upregulates CD80 and MHC-II in vitro



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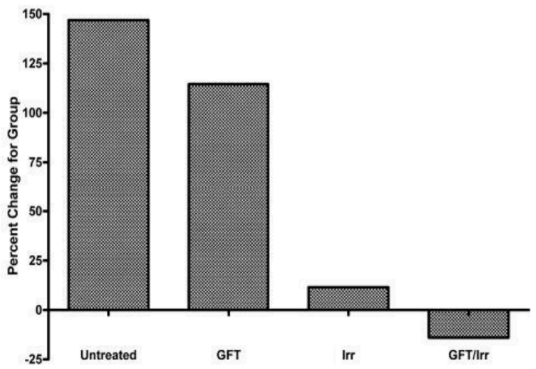
Torigen: The Rationale

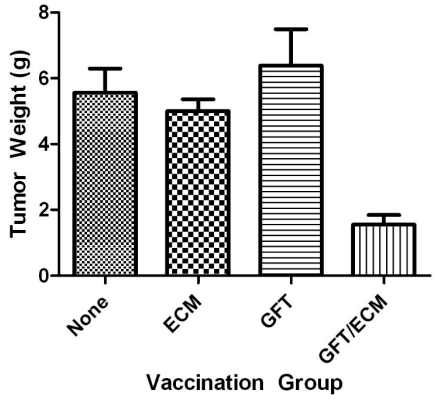
Multiple rodent models demonstrate efficacy

Tissue vaccine enhances effect of radiation therapy of prostate cancer in a rat model



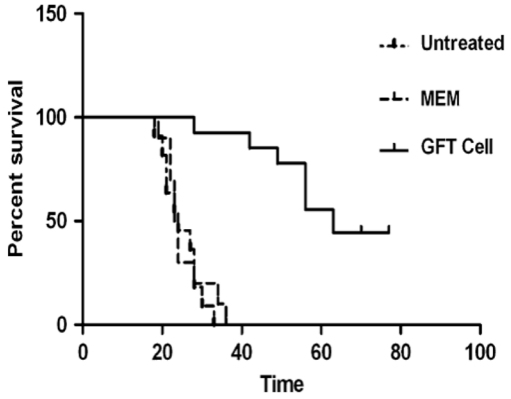
Suckow, MA, *et al.* Immunization with a tissue vaccine enhances the effect of irradiation on prostate tumors. *In vivo*. (2008) 22:171-178.

Melanoma regrowth significantly delayed with ECM adjuvanted tissue vaccine in mice



Mark A. Suckow, Rae Ritchie and Amy Overby (2011). Extracellular Matrix Adjuvant for Vaccines, In: Biomaterials Applications for Nanomedicine. Rosario Pignatello (Ed.),

Prevention of tumor metastasis to the lungs significantly improved survival in prostate cancer model



Suckow, MA, *et al.* Inhibition of prostate cancer metastasis by administration of tissue vaccine. *Clin Exp Metastasis.* (2008) 25:913-918.

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Torigen: Initial Safety Study in Dogs

- 93 client-owned dogs with spontaneous tumors
  - Written informed owner consent
  - Surgical resection of tumor
  - Torigen's autologous cancer vaccine
- Monitored for adverse events (VCOG-CTCAE)
  - 12% had grade I adverse events
  - Fever, swelling at injection site, lethargy
  - All resolved without intervention

Crossley RA, *et al.* Safety evaluation of autologous tissue vaccine cancer immunotherapy in a canine model. *Anticancer Res*. **39**: 1699-1703 (2019)

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Torigen: Follow-Up Safety Study

- 265 dogs treated 2018-2019
  - *909 doses of vaccine*
  - 52/48% M:F
- AE rate remains low
  - 5.3% of dogs had AE
  - 1.8% of administered doses was associated with an AE
  - 0.1% of administered doses were associated with a severe AE
- Review of 117 feline cases suggests similar low AE rate

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Torigen: Stage III Hemangiosarcoma in Dogs

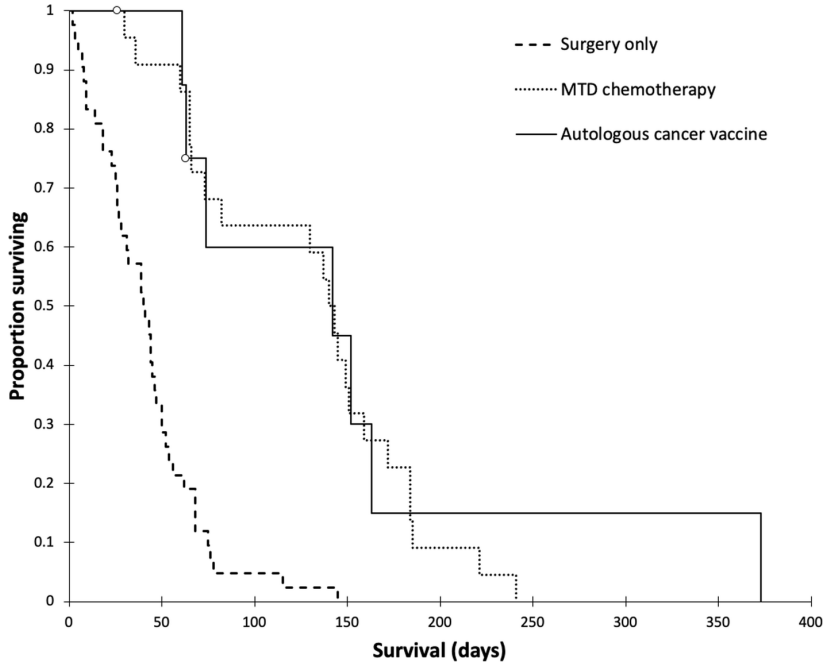
- Torigen database queried – 8 dogs
- Histologically confirmed HSA
  - Evidence of metastatic disease on presentation
  - Completed ACV protocol
  - No additional treatment
  - Compared to historical control groups*
    - Surgery alone (n=42)
    - Surgery + MTD chemotherapy (n=23)

Lucroy, M.D., *et al.* Evaluation of an autologous cancer vaccine for the treatment of metastatic canine hemangiosarcoma: a preliminary study. *BMC Vet Res* **16,** 447 (2020). https://doi.org/10.1186/s12917-020-02675-y

*Marconato L, *et al*: Adjuvant anthracycline-based vs metronomic chemotherapy vs no medical treatment for dogs with metastatic splenic hemangiosarcoma: A multi-institutional retrospective study of the Italian Society of Veterinary Oncology. *Vet Comp Oncol* 2019, 17(4):537-544.

Torigen Data:

Stage III Gemangiosarcoma in Dogs



Lucroy, M.D., *et al.* Evaluation of an autologous cancer vaccine for the treatment of metastatic canine hemangiosarcoma: a preliminary study. *BMC Vet Res* **16,** 447 (2020). https://doi.org/10.1186/s12917-020-02675-y

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Torigen:

Summary data from 73 dogs with Stage III HSA

	Surgery alone (n = 42)	Surgery plus MTD (n = 23)	Surgery plus ACV (n = 8)
Age, y (mean ± SD)	10.3 ± 2.00	10.0 ± 2.21	7.6 ± 1.71
Weight, kg (mean ± SD)	30.2 ± 5.96	31.6 ± 9.84	39.5 ± 11.83
Adverse events (%)	0	43	**0**
Hospitalizations (%)	0	17	**0**
Median survival time, d	41	142	142
Survival range, days	2 to 145	26 to 241	61 to 373
Alive at 1 year (%)	0	0	**12.5**

Lucroy, M.D., Clauson, R.M., Suckow, M.A. *et al.* Evaluation of an autologous cancer vaccine for the treatment of metastatic canine hemangiosarcoma: a preliminary study. *BMC Vet Res* **16,** 447 (2020). https://doi.org/10.1186/s12917-020-02675-y

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Torigen Preliminary Data

- Transitional cell carcinoma of the urinary bladder
  - Completed ATV protocol with Piroxicam
  - n = 13
  - MST = 438 days (66-580 days)
  - Piroxicam only MST 244 days
- Oral SCC in dogs
  - Completed ATV protocol – used as 2nd or 3rd line Tx
  - n = 9 (2 tonsillar, 2 metastatic)
  - MST = 150 days (112-351 days)
  - Hard to compare to historic controls
- Oral melanoma in dogs
  - Completed ATV protocol – used as 2nd or 3rd line Tx
  - n = 14
  - 10 stage III: MST = 83 d (26-215 d)
  - 4 stage IV: MST = 67 d (45-82 d)
  - Hard to compare to historic controls
- MCT
  - Data collection underway

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Torigen – How It's Done!

- Sample collection
  - Tumor is surgically excised or biopsied
  - 2-5 grams of tissue (1-5 cm3) of non-necrotic tissue
  - NOT formalin fixed
  - Torigen provides kit to ship the sample
  - Can select to have histopath performed via third party
    - Specialty Vet Path, IDEXX, Antech, Zoetis, VDx, VetPath - New York, SOPA
  - Please call before submission of OSA and LSA
  - Ready in 72 hours
- Tumors
  - Anal Sac Adenocarcinoma
  - Hemangiosarcoma
  - Fibrosarcoma
  - Mast Cell Tumors
  - Melanoma
  - Soft Tissue Sarcoma
  - Hepatocellular Carcinoma
  - Nasal Carcinoma
  - Squamous Cell Carcinoma
  - Transitional Cell Carcinoma

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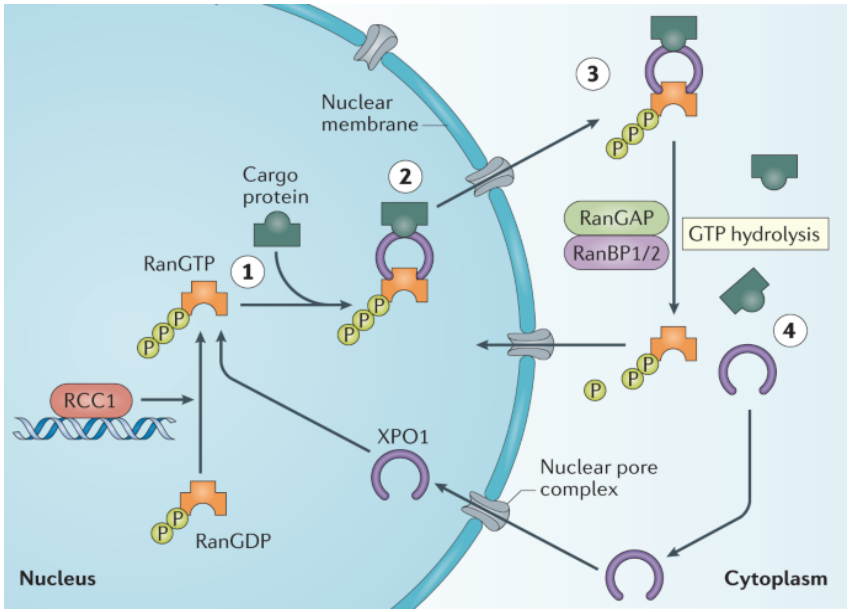
Hot Topics in Oncology

- Targeted Therapy
  - Targets changes in cancer cells that help them grow, divide, and spread
  - Small molecule drugs and monoclonal antibodies
- What's available in Veterinary Oncology?
  - **Laverdia-CA1**
  - Palladia



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Laverdia-CA1 (Verdinexor)

Sadowski *et al. BMC Veterinary Research* (2018) 14:250
https://doi.org/10.1186/s12917-018-1587-9

BMC Veterinary Research

RESEARCH ARTICLE Open Access

Phase II study of the oral selective inhibitor of nuclear export (SINE) KPT-335 (verdinexor) in dogs with lymphoma

Abbey R. Sadowski[1†], Heather L. Gardner[2†], Antonella Borgatti[3], Heather Wilson[4], David M. Vail[5], Joshua Lachowicz[6], Christina Manley[7], Avenelle Turner[8], Mary K. Klein[9], Angharad Waite[10], Alexandra Sahora[11] and Cheryl A. London[1,12*]

- Novel, orally available chemotherapy that selectively inhibits nuclear transport
  - Administered orally at home twice weekly (72 hours apart)
- Anti-tumor activity for lymphoma

Laverdia-CA1 (Verdinexor)

- Neoplastic cells utilize the process of nucleo-cytoplasmic transport to export known tumor suppressor proteins and growth regulator proteins outside of the nucleus → cancer can overcome the normal cell cycle and genomic instability checkpoints
  - Depends on the activity of transport proteins called exportins
  - Exportin-1, also known as XPO1, is the main mediator of nuclear export
  - XPO1 inhibition forces nuclear retention of key tumor suppressor proteins and growth regulator proteins
- XPO1 is overexpressed in many hematologic and nonhematologic malignancies in humans and is associated with a poor prognosis in aggressive diseases

ANIVIVE

LAVERDIA

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Laverdia-CA1 (Verdinexor)

- Evaluated in naïve lymphoma or after a single relapse
- 58 dogs → 35 naïve and 23 first relapse
  - 28 dogs with B-cell and 7 with T-cell
- Overall Response rate: Naïve 39% for 34 days vs. Relapsed 38% for 19 days
- Time to progression of disease for T-cell lymphoma was 43 days
  - TTP was 73 days if started prednisone at the time of chemotherapy vs. 24 days if on it prior to treatment vs. 22 days without prednisone
- Bioavailability and absorption dependent on feeding → prednisone may help keep them eating
- Adverse events: anorexia (45%), weight loss (31%), vomiting (26%), lethargy (17%), and diarrhea (12%) → most minor
  - Serious: weight loss, weakness, hepatopathy, and PLN

Laverdia-CA1 (Verdinexor)

- Dosing: 1.25mg/kg-1.5mg/kg two times weekly (72 hours apart)
  - Give with food
  - 2.5mg, 10mg, and 50mg
- Monitoring – once monthly?
  - CBC, Chemistry Panel, Urinalysis?
- Benefits?
  - Not a first line therapy?
  - Reverse resistance
  - Increase chemotherapy sensitivity
  - In combination with other?
  - Other tumor types?
  - Cheaper option than chemotherapy?

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Laverdia-CA1 (Verdinexor)

- Client/Administration Safety
  - Gloves tested for chemotherapy administration should always be worn when handling Laverdia-CA1
  - Wear gloves when cleaning up after a dog undergoing treatment for three days following the last treatment
    - This includes handling the dog's food and water bowls, as well as feces, urine, vomit or saliva from the dog.
    - Laverdia-CA1 also comes with a client information sheet for prescribing veterinarians to give to their clients.

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Hot Topics in Oncology

- Precision Medicine
  - Helps oncologist select treatments that are most likely to help the patient based on genetic understanding of their disease
  - “Personalized medicine”
- What’s available in Veterinary Oncology?
  - **Fidocure**
  - **ImpriMed, Inc.**

Fidocure

How it Works

1. Sequence DNA

Your veterinarian submits a tissue sample to FidoCure® for DNA sequencing.

2. Identify Mutations

FidoCure® creates a personalized DNA report that helps identify genetic mutations that may affect treatment.

3. Targeted Therapy

Informed by FidoCure®, your veterinarian may prescribe targeted therapies (administered orally at home).

- Can be formalin fixed
- Can use previous histopathology sample

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Fidocure

FidoCure

Final Report Summary for Veterinarian

151-19_Toby Warwar

Referring Veterinarian: **Amy Back**
Biopsy Date: 3/8/2019
Report Date: 6/17/2019
Owner Name: [redacted]

Pet Name: [redacted]
Birth Date: 1/9/2009
Sex: Male Altered
Breed: Shetland Sheepdog

Questions?
Call (650) 350-9006

ABOUT THE TEST FidoCure uses next-generation sequencing-based assays and RNA diagnostics to identify changes in cancer related genes. For help interpreting the genetic results on this report, please call us at (650) 350-9006.

Histopathology **Hepatocellular carcinoma**
Fidocure's histology and gene expression profile are consistent with a diagnosis of hepatocellular carcinoma.

DNA Sequencing Findings

1 Actionable Finding:
SETD2

1 Additional Finding of Importance:
KMT2C

Therapeutic Implications
1. Vorinostat (HDAC inhibitor) - 45 mg/kg/every other day PO
2. Commonly altered gene family in human malignancies (KMT).

RNA Expression Findings

5 Actionable Findings:
KDR, MEK1/2, MET, MYC

11 Additional Findings of Importance:
BCL-XL, COX2, HIF1a MDM2, PGP, PROX1, RAS/RAF, MGMT, RRM1/2

Therapeutic Implications
1. Trametinib (MEK inhibitor) - 0.02 mg/kg/day PO
2. Imatinib (KDR inhibitor) - 10 mg/kg/day PO
3. Vorinostat (HDAC inhibitor) - 45 mg/kg/every other day PO
4. Crizotinib (MET inhibitor) - 1 mg/kg/day PO
5. Potential therapeutic benefit from NSAIDs.
6. Biomarkers associated with generalized chemoresistance including doxorubicin and the small molecule inhibitor, Sorafenib.
7. Potential tumor sensitivity to gemcitabine and/or alkylating agents.
8. Intracellular signaling via MAPK/ERK pathway.

For additional details on these alterations, please see pages 2-4.

Potential Initial Clinical Approach

Your patient's wellbeing is and always will be our top concern. All listed therapies are FDA approved for humans with meaningful canine toxicity information (from the FDA submission and when able scientific literature). Every drug has a No Observed Adverse Effect Level (NOAEL). We exclude therapies that have shown severe toxicity and adverse events. We aim for manageable side effects, and to date we have observed: diarrhea, vomiting, nausea, inappetance, lethargy, and anemia. To report an adverse effect please call us.

Combination therapy

Trametinib (MEK inhibitor) - 0.02 mg/kg/day PO
Rapamycin (mTOR inhibitor) - 0.1 mg/kg/day PO

FidoCure

Pet Name: [redacted]
Tumor Type: **Hepatocellular carcinoma**

Report Date: 6/17/2019

Gene Alterations Observed in RNA Expression

ACTIONABLE TRANSCRIPTOMIC ALTERATIONS

KDR: Overexpressed	Imatinib - 10 mg/kg/day PO · KDR is one of the subtypes of the family of vascular endothelial growth factor receptors (VEGFR). · These receptors primarily bind vascular endothelial growth factor (VEGF) leading to an intracellular signal via pathways such as MAPK/ERK and/or PI3K/AKT. · Overexpression of both VEGF and KDR can lead to increased celllular signaling resulting in proliferation, cell survial, and angiogenesis. (Millanta et al.) · Inhibition of KDR may reduce these potential tumorigenic effects.
MEK1/2: Overexpressed	Trametinib - 0.02 mg/kg/day PO · MEK is a gene that codes for the protein MEK1 or "mitogen-activated protein kinase". · MEK2 or MAP2K2 is a gene that codes for the identically named protein (MEK2). · MEK2 is highly homologous with MEK/MEK1. · These are downstream proteins that belong to the MAPK/ERK signaling pathway. · Overexpression of these genes may result in tumor cell growth, proliferation, and survival. · Inhibition of MEK1 and/or MEK2 may reduce effects that these genetic alterations have as drivers of canine cancer.
MET: Overexpressed	Crizotinib - 1-2 mg/kg/day PO · MET is a receptor tyrosine kinase (RTK) with its normal ligand being hepatocyte growth factor (HGF). · MET has numerous downstream effects inside the cell including cross-talk activation of MAPK and STAT signaling pathways. · MET overactivity can lead to cell growth, proliferation, and invasion. (Feng et al., McCleese et al.) · Inhibition of MET with targeted agents can help reduce the effects of this genetic alteration.
MYC: Overexpressed	Vorinostat - 45 mg/kg/every other day PO · MYC describes a number of genes which code for intranuclear transcription factors. · As such, these proteins are responsible for regulation of various other pathways and processes. · These processes include cellular growth and proliferation as well as celullar metabolism. · Increased MYC activity has been implicated in the genesis of numerous cancers in humans and dogs. · MYC, particularly c-MYC, has been shown as a substrate for histone deacetylase inhibitors (HDACi), such as Vorinostat, which have shown promising efficacy in reducing the effects of MYC as a potential cancer driver.(Kerr et al.)

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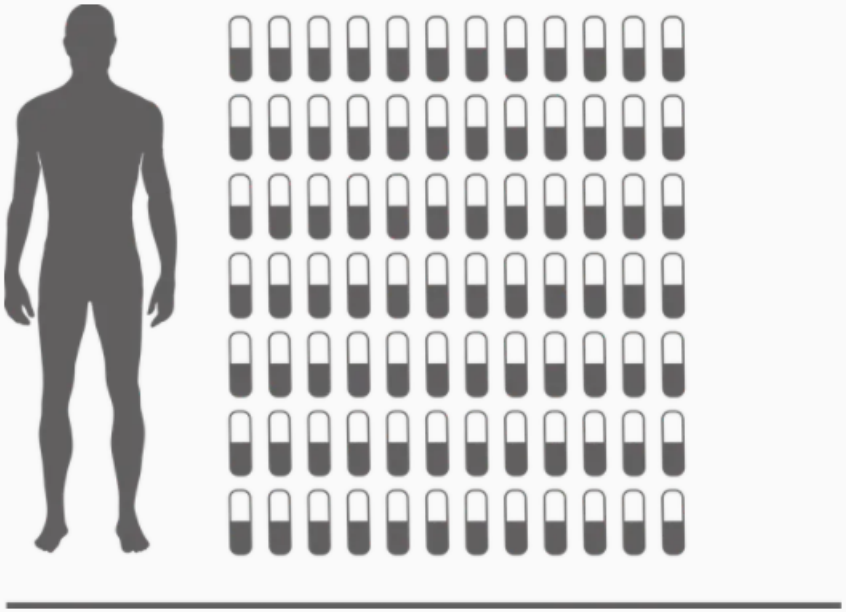
Fidocure: Another goal?

Human Oncology

1.6M New Annual Cases

84+ Targeted Therapies in use



Veterinary Oncology

6M New Annual Cases

1 Targeted Therapy

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Fidocure

DNA SEQUENCING & TARGETED THERAPY	THERAPY ONLY SERVICE
• DNA sequencing helps identify the cancer's mutations to better inform the diagnosis. • Veterinarians receive a DNA Report and targeted therapy treatment plan. • FidoCure facilitates access to recommended oral targeted therapies. • Recommended therapies are FDA-approved and easy to administer at home. • Offers alternatives to more invasive treatment or a new option when traditional therapies fail.	• Veterinarians receive a Data-Based Report with information about the diagnosis and recommended therapies. • In cases such as MCT and TCC/UC that already have widely adopted therapies, veterinarians can choose to receive expedited access to therapy. • Because many MCTs are c-Kit driven and TCCs are BRAF+, FidoCure facilitates access to a c-Kit targeted therapy or EGFR/HER2 and/or MEK targeted therapy. • Oral therapies are FDA-approved, easy to administer at home and offer an alternative to more invasive treatment or a new option when traditional therapies fail.

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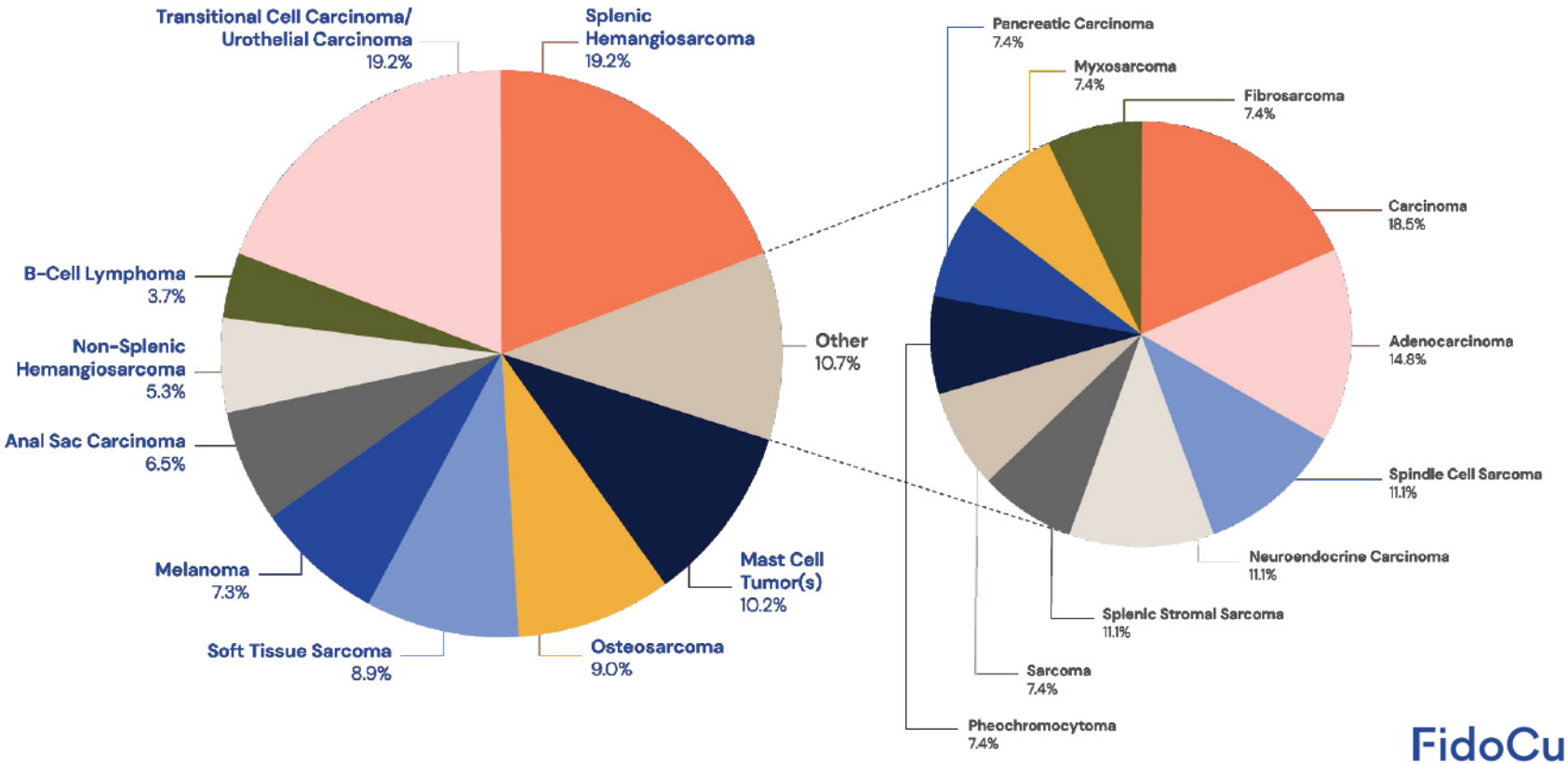
FidoCure® is Available for all Tumor Types



FidoCure®

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Fidocure

Veterinary Cancer Society 2020 Poster

Safety and Toxicity of Small Molecule Inhibitors in Dogs with Spontaneously Occurring Malignancies — The Use of Real World Data

- FidoCure® therapies have been evaluated in over 400 tumor-bearing dogs
- The adverse event profile is similar to Palladia®
- The most common adverse events are hyporexia diarrhea, anemia and neutropenia

FidoCure®

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Fidocure

FidoCure®

Safety and Toxicity of Small Molecule Inhibitors in Dogs with Spontaneously Occurring Malignancies — The Use of Real World Data

G. Harvey[1], L. Lambert[1], L. Rodrigues[1], B. Lewis[1], C. Lopes[1], G. Post
[1]FidoCure®, Palo Alto, CA 94301

INTRODUCTION

The FidoCure® platform integrates canine tumor genomics with access to small molecules, targeted therapeutics. Small molecule inhibitors (SMIs) target specific proteins involved in processes critical for cancer cell growth and survival. There are over 125 of these therapies that are FDA-approved for people and they have shown clinical efficacy in a wide-array of human cancers. Given the similarity in cancer types and molecular targets between humans and dogs, the application of SMIs has been identified as an attractive novel therapeutic approach in canine cancer. For many of these anti-cancer drugs, there is extensive safety data on their use in normal dogs available in the IND packets submitted to the FDA or EMA. The purpose of this investigation was to evaluate the adverse event profile of 8 SMIs (trametinib, rapamycin, lapatinib, dasatinib, imatinib, vorinostat, toceranib and crizotinib) in tumor-bearing canine patients enrolled through FidoCure®.

A. Preliminary Adverse Effects Patient Data

TOTAL Patients on Therapy	TOTAL Patients with Clinician Reported Outcomes	TOTAL Patients with Reported Adverse Effects	TOTAL % of Patients with Reported Outcomes with AE
455 ∴	390	130	33%

	Patients on Therapy *	Patients with Clinician Reported Outcomes	Patients with Reported Adverse Effects **	% of Mild, Moderate and Severe Adverse Events Per Therapy		
Trametinib	240	215	47	13%	9%	0.4%
Rapamycin ⁘	166	147	29	12%	7.5%	0.6%
Lapatinib	131	120	27	18%	7.5%	0%
Dasatinib	86	76	25	18%	15%	0%
Imatinib	78	62	15	21%	5%	1.5%
Vorinostat ⁞	62	54	18	11%	22%	1.9%
Toceranib	49	39	10	33%	7.6%	0%
Crizotinib	7	6	3	50%	17%	0%

* Patients on combination therapies are counted more than once. They are counted for each particular drug

** In 25% of reported AEs, patients were on combination targeted therapies making it difficult to determine which single therapy caused the AE or if the AE was due to the combination. In these cases, the AE was counted for all drugs. It is also unknown what percentage of patients were on additional chemotherapy in combination with targeted therapy.

∴ Totals are not a sum of all events but total number of patients affected.

⁘ In 83% of reported Rapamycin AEs, the therapy was used in combination with other targeted therapies

⁞ Vorinostat: Early Vorinostat recommendations were at a higher dosage but have since been reduced due to a high rate of adverse events.Following this dose decrease, the number and percentage of AEs has dropped dramatically.

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B. Number and Type of Preliminary Adverse Effects Reported

	Diarrhea	Vomiting	Inappetance	Lethargy	Skin Lesions
Trametinib					
Mild	7%	3%	4%	3%	0.5%
Moderate	4%	1%	5%	3%	1%
Severe	0%	0%	0%	0%	0%
Other less common effects – Anemia, Hemorrhagic Gastroenteritis					
Rapamycin					
	7%	5%	5%	3%	0%
	5%	1%	2%	2%	0%
	0%	0%	0%	0%	0%
Other less common effects: Anemia					
Lapatinib					
	9%	3%	5%	3%	0%
	3%	1%	3%	3%	0%
	0%	0%	0%	0%	0%
Other less common effects: Progressive Liver Enzyme Elevations, Oral ulcer					
Dasatinib					
	8%	8%	9%	4%	0%
	7%	7%	3%	1%	3%
	0%	0%	0%	0%	0%
Other less common effects: Elevated Kidney Values					
Imatinib					
	10%	6%	3%	5%	0%
	0%	0%	0%	2%	0%
	2%	2%	0%	2%	0%
Other less common effects: Anemia, Increased Cardiac Toxicity					
Vorinostat					
	9%	4%	4%	0%	0%
	17%	17%	7%	4%	0%
	0%	0%	0%	0%	0%
Other less common effects: Aeizure, Oral ulcer					
Toceranib					
	21%	0%	13%	3%	0%
	3%	5%	8%	3%	0%
	0%	0%	0%	0%	0%
Crizotinib					
	0%	0%	33%	17%	0%
	0%	17%	0%	0%	0%
	0%	0%	0%	0%	0%

RESULTS

Of 390 patients with clinician reported outcomes, 130 patients (33%) reported a suspected adverse event. Across all agents, AEs were predominantly mild (61%) with only 4 AEs graded as severe. Many of these pets were treated with a combination of cytotoxic chemotherapy and SMIs. The most commonly reported adverse events included lethargy, anorexia, vomiting, diarrhea, anemia, and/or liver enzyme elevation. Crizotinib was the only drug with a higher percentage of adverse events than toceranib.

Of 201 patients with clinicopathologic data, 131 patients (65.17%) had an AE. Of those patients with a clinicopathologic AE, 68.70% (90/131) were grade 1, 9.92% (13/131) were grade 2, 19.09% (25/131) were grade 3 and 2.29% (3/131) were grade 4. Many of these pets were treated with a combination of cytotoxic chemotherapy and SMIs. The most common clinicopathologic AEs were anemia, neutropenia, thrombocytopenia, elevations in creatinine, alkaline phosphatase (ALP) and alanine aminotransferase (ALT), and blood glucose abnormalities.

A. Clinical Adverse Events grouped by targeted therapy. For patients with Clinical Adverse Events, 61% of these AEs were mild, 36% were moderate and 3% were severe.

B. Type of Clinical Adverse Event for each targeted therapy. Diarrhea and Anorexia were the most commonly reported clinical AEs.

C. Laboratory Adverse Events grouped by targeted therapy. For patients with Laboratory Adverse Events, 68.70% were grade 1, 9.92% were grade 2, 19.09% were grade 3 and 2.29% were grade 4.

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CONCLUSIONS

The adverse event profiles of the SMIs enabled by FidoCure® are comparable to previously published reports of the safety of Palladia® (6) used alone or in combination with cytotoxic chemotherapy (7). Studies categorizing all AEs according to the VCOG-CTCAE criteria and research evaluating the PK and PD of these drugs are underway.

FUTURE

We have partnered with CSU for a study evaluating the efficacy of targeted therapies selected by FidoCure® on cell lines from 10 types of canine cancers. This informatioin will help inform the most effective dosages and identify potential biomarkers that make certain cancers more responsive to these drugs.

- More and more information regarding targeted therapies based on specific mutations noted in the tumor sequence is being gathered
  - Studies documenting mutations and tolerability

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ImpriMed

Received: 20 July 2020 | Revised: 24 September 2020 | Accepted: 2 October 2020

DOI: 10.1111/vco.12656

ORIGINAL ARTICLE

Veterinary and Comparative Oncology WILEY

Predicting likelihood of in vivo chemotherapy response in canine lymphoma using ex vivo drug sensitivity and immunophenotyping data in a machine learning model

Zach Bohannan[1] | Raghavendra Sumanth Pudupakam[1] | Jamin Koo[1,2,3] | Harrison Horwitz[1] | Josephine Tsang[1] | Amanda Polley[1] | Enyang James Han[1] | Elmer Fernandez[1] | Stanley Park[1] | Deanna Swartzfager[1] | Nicholas Seah Xi Qi[1] | Chantal Tu[4] | Wendi Velando Rankin[4] | Douglas H. Thamm[5] | Hye-Ryeon Lee[1,2] | Sungwon Lim[1,2]

- A precision medicine platform that evaluates the probability of chemotherapy drug efficacy for canine lymphoma by combining ex vivo chemosensitivity and immunophenotyping assays with computational modelling.
  - Tests: Doxorubicin, vincristine, cyclophosphamide, Tanovea, and CCNU

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ImpriMed: Rationale

- Cell-based ex vivo drug sensitivity assays have been studied as a precision medicine tool to mimic the tumor microenvironment in vitro and predict in vivo responses in human lymphoproliferative disorders → now in VetMed
  - A direct measurement of drug response in primary cancer cells is a potential predictor of actual response in the body
- Individualized patient outcome modelling is another core feature of precision medicine. In human oncology, personalized predictive modelling has many clinical applications, especially related to diagnostic and prognostic decision making
  - Machine learning is a particularly popular modern approach for predicting patient outcomes in human oncology and machine learning strategies have been successfully applied to a variety of human cancers and treatment regimens to predict drug response → rarely used in VetMed

ImpriMed: Complications?

- Strengths: including the ability to informatively predict the likelihood of positive treatment response and close association with improved time to complete response in patients with positive predictions.
  - It is difficult to fully determine the role of individual drugs when used in a multi-agent protocol
- Hypothesis: Direct measurements of treatment response in primary tumor samples are relevant to treatment response in patients
  - Ex vivo assessments of chemosensitivity may not fully capture the behavior of drugs or cells in vivo → insufficient to fully predict individual treatment responses alone
- Conclusions:
  - Drug sensitivity parameters were highly important for doxorubicin, vincristine, and rabacfosadine
  - Flow cytometry variables were more important in the prediction of response for cyclophosphamide and CCNU
  - In summary, it is an option → efficacy is truly unknown

Hot Topics in Oncology

- Intralesional therapy
  - Injection of a substance or chemotherapy into the tumor or scar
- What's available in Veterinary Oncology?
  - **Tigilanol tiglate (TT) = Stelfonta**
  - **5-Fluorouracil for STS**
  - Triamcinolone for MCT

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Stelfonta (Tigilanol tiglate)

- A novel diterpene ester is approved as a simple-to-administer, intratumoral treatment for a range of cancers in humans and companion animals
  - Derived from the fruit of the tropical blushwood tree
- Potent cellular signaling molecule → activation of protein kinase C
- Intratumoral injection elicits a rapid but highly localized inflammatory response, disruption of tumor vasculature, and induction of tumor cell death by oncosis → leads to hemorrhagic necrosis and destruction of the tumor mass within 2 to 7 days

Results: resolution of the wound with good cosmetic and functional outcomes between 28 and 84 days after treatment

- Activates immune system to promote healing

Stelfonta

Received: 29 October 2019 | Accepted: 6 May 2020
DOI: 10.1111/jvim.15806

Check for updates

STANDARD ARTICLE

Journal of Veterinary Internal Medicine Open Access ACVIM American College of Veterinary Internal Medicine

Randomized controlled clinical study evaluating the efficacy and safety of intratumoral treatment of canine mast cell tumors with tigilanol tiglate (EBC-46)

Thomas R. De Ridder[1] | Justine E. Campbell[1] | Cheryl Burke-Schwarz[2] | David Clegg[3] | Emily L. Elliot[4] | Samuel Geller[5] | Wendy Kozak[6] | Stephen T. Pittenger[7] | Jennifer B. Pruitt[8] | Jocelyn Riehl[2] | Julie White[9] | Melissa L. Wiest[10] | Chad M. Johannes[11] | John Morton[12] | Pamela D. Jones[1] | Peter F. Schmidt[1] | Victoria Gordon[1] | Paul Reddell[1]

- 81 dogs treated with Stelfonta with 42 receiving placebo
- Stage Ia-IIIa MCT → complete staging not performed
- Scarpa system of cytological grading at time of screening
  - Antech and University of Georgia

MEDVET

Stelfonta

- Cutaneous tumors can be anywhere on the body
  - Subcutaneous needs to be below the elbow or hock
- MCT was measured using digital calipers to estimate length, width, and thickness
  - Tumor volume then was calculated using a modified ellipsoid formula (tumor volume [Tvol] in cm3 = ½ [length × width × thickness]).
- Exclusion criteria were: (1) locoregional LN metastasis confirmed on FNA or signs of systemic MCT disease, (2) tumor ulceration, (3) tumor recurrence at a previous biopsy or surgical site, and (4) radiotherapy, chemotherapy, or other anticancer treatment within the previous 2 months.
  - Also excluded if calculated dose for treatment was >0.25 mg/kg body weight, tumor volume was >10 cm3, or tumor diameter was <1 cm

Stelfonta

- Treatment group received a single intratumoral injection of Stelfonta (1mg/ml) with the dose dependent on tumor volume.
  - The dose rate was 0.5 mg (0.5 mL) per cm3 of tumor volume
  - Exception: estimated tumor volume was <0.2 cm3 in which instance a minimum fixed dose of 0.1 mL was injected
  - Max dose of 5mg
  - Cannot be used in cats → propylene glycol
- Protocol: two days prior to treatment: Prednisone, Diphenhydramine, and Omeprazole
    - Prednisone 0.5mg/kg PO BID x 7 days, then SID x 3 days, then discontinue
    - Prescribed 7 days of Gabapentin post injection
  - Typically degranulate 3-4 days post injection
- Stelfonta was administered intratumorally using a 23-gauge needle on a Luer-lock syringe at a single injection point (where possible) and the solution "fanned" throughout the tumor to evenly distribute the drug.
  - Leave in the needle and hold pressure

Stelfonta

- Wounds formed at the treatment site after tumor slough are left to heal by secondary intention without bandaging or other interventions.
  - Normal exercise
  - Allow the dog to lick the wound → use e-collar if excessive, but not recommended
  - Can wash with water and pat dry
  - No antibiotics required
- Recheck on day 7 and 28 post treatment
- All wounds healed by 3 months post treatment

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Stelfonta

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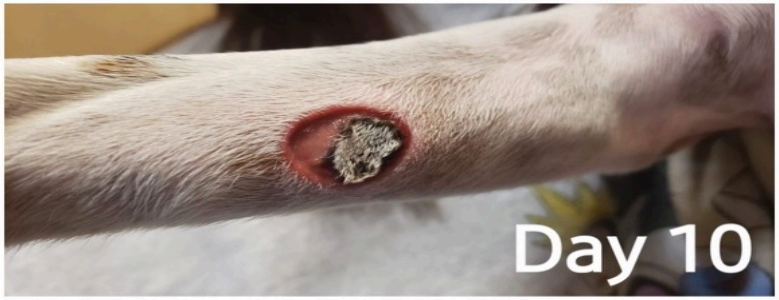
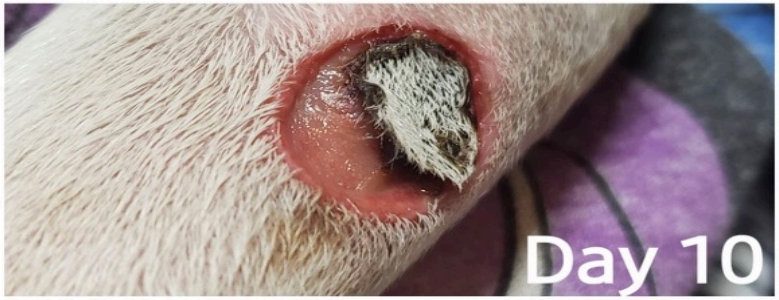
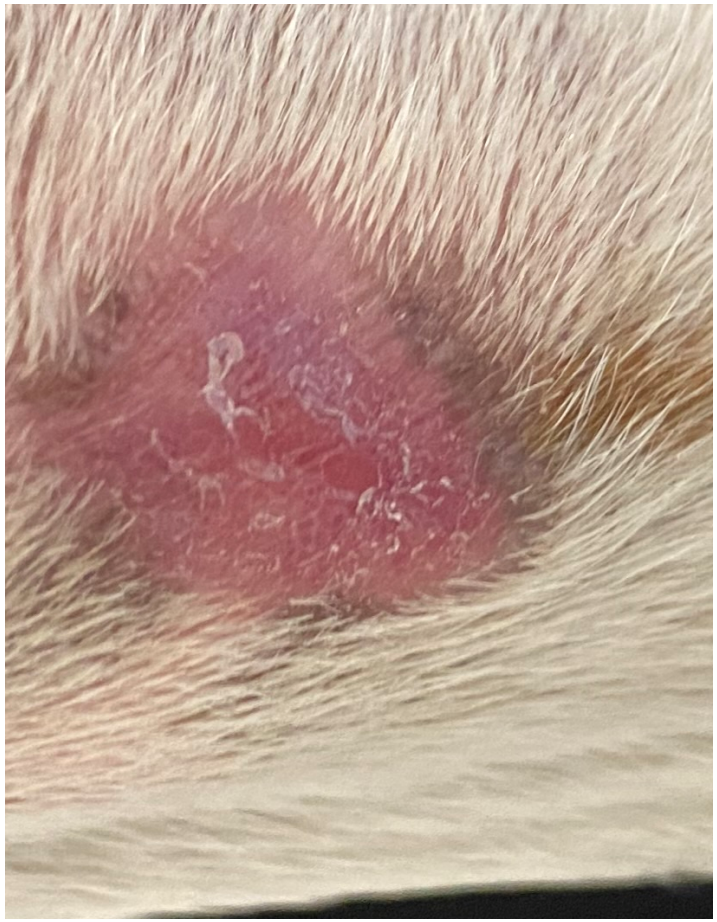
Stelfonta







Courtesy of Karina Valerius, DVM, MS, DACVIM (oncology)

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Stelfonta

- 73% of dog had a CR 28 days after a single TT treatment
  - 94% of the CR dogs had no local recurrence at 84 days
- 18 dogs that did not achieve CR after their first treatment
  - Received a second treatment at 28 days post first infection
  - 44% of these retreated dogs achieved CR 28 days later
- Combined data: overall CR for this group at 28 days was 88%
  - 93% of the CR dogs having no local recurrence 84 days after their last treatment
- In all dogs that achieved CR, a consistent pattern of clinical response at the treatment site was observed:
    - Development of bruising and edema at the treatment site within 15 minutes to 24 hours post-treatment
    - Onset of hemorrhagic necrosis of the mass followed by tumor slough within 3 to 10 days resulting in exposure of a well granulated underlying wound bed that healed by secondary intention
- CR determinants: (1) the formation of a wound after slough of the treated tumor, (2) the maximum surface area of that wound relative to initial tumor volume, and (3) tumor cytological grade (CR: 72% vs. 38%)
  - No difference between SQ and cutaneous

Stelfonta

- Adverse events
  - Edema, erythemia, pain, and bruising at the site
  - Hypoalbuminemia – two dogs with large wounds >100cm2 → unlikely related to the treatment itself?
  - Bacterial infection → hospitalization and antibiotics for 28 days
  - Recurrence of the tumor
  - Other forms of neoplasia – unlikely due to Stelfonta treatment
- Overall, owners felt that the QOL was good with most adverse events not requiring veterinary intervention

Stelfonta Uses

- Pros
  - A site not amendable to surgery
  - Pet is not a good candidate for surgery
  - Owner doesn't want surgery
  - Dogs that develop multiple mast cell tumors
- Cons
  - Won't know the grade or margins

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Intralesional 5-FU

- 5-Fluoruracil (5-FU) is an antimetabolite that acts as a false pyrimidine base that inhibits nucleic acid synthesis
- 5-FU can be administered either systemically or topically
- 5-FU has been used as single agent or in combination regimens to treat a variety of canine cancers
  - Malignant mammary tumours, gastrointestinal adenocarcinoma, anal sac adenocarcinoma, nasal adenocarcinoma, and sun-induced squamous cell carcinoma
- Side-effects are rare
  - Neurotoxicity and bone marrow suppression
- **CANNOT be administered in cats**

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Intralesional 5-FU

- Use: Incompletely excised soft tissue sarcomas
- Dosing: 150mg/m2
  - Mix with Sesame oil at a ratio of 1:2 oil:5-FU
  - Use 3-way stop cock to mix and create a milky emulsion
  - Inject into the subcutaneous tissue under the scar
    - Single injection site using 22 gauge needle
  - Weekly for 4-6 treatments
- Chemotherapy Safety
  - Face shield, chemo gown, and gloves
- Side effects
  - Ulceration at the site – typically week 3
    - Treatment: NSAIDS, antibiotics, treatment delay
    - Prevent self trauma

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Intralesional 5-FU

Postsurgical intra-incisional 5-fluorouracil in dogs with incompletely resected, extremity malignant spindle cell tumours: a pilot study

L. Marconato[1], S. Comastri[1], M. R. Lorenzo[1], F. Abramo[2] and G. Bettini[3]

[1]Clinica Veterinaria L'Arca, Naples, Italy
[2]Department of Animal Pathology, University of Pisa, Pisa, Italy
[3]Department of Veterinary Public Health and Animal Pathology, University of Bologna, Ozzano Emilia, Italy

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Intralesional 5-FU

- Six dogs
- Intralesional 5-FU at 150mg/m2 – no sesame oil
- Started median 14 days post surgery
  - One into open wound and five into scar
  - No delay in wound healing
- Median follow-up for all the patients was 546 days (297 – 1207)
  - 1- and 2-year percent survival rate: 83.3% and 66.7% respectively
  - 1- and 2-year percent tumor control rate was 100% and 83.3% respectively
- Dogs number 3, 4, 5 and 6 are still alive in CR at 753, 364, 1207 and 689 days respectively

Hot Topics in Oncology

- New chemotherapy drugs
  - **Tanovea (rabacfosadine)**

Tanovea®-CA1 (rabacfosadine)

- Pro-drug preferentially taken up by lymphocytes
  - Inhibits proliferation via disruption of DNA synthesis – guanine analog
- Administered at 1mg/kg IV q21 days x 5 treatments
- Dose limiting toxicity: dermatopathy, neutropenia, and GI signs
  - Pulmonary fibrosis
  - Monitoring: CBC/Chemistry panel/thoracic radiographs before the first and fourth treatments
  - CBC prior to each treatment
- Response rate of 79% with 45% achieved a complete response
  - Response duration of approximately 194 days
  - Cutaneous T-cell lymphoma had an overall response rate of 45%

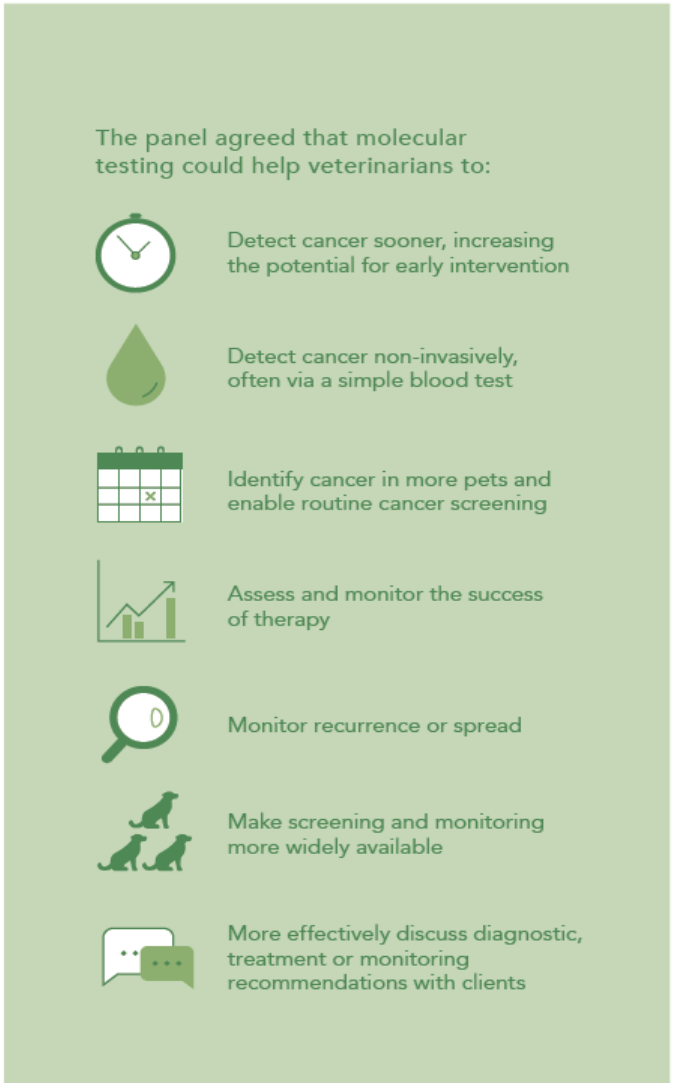
Hot Topics in Oncology

- Cancer Screening Tests
  - Checking the body for cancer before symptoms
  - Molecular tests
- What's available in VetMed?
  - Nu.Q

MedVet

Nu.Q

- Molecular test for cancer using blood
- Non-invasive test for monitoring of response to treatment in lymphoma
- Detects nucleosomes
  - Epigenetics control nucleosomes – before DNA mutations
  - Cancer nucleosomes are higher in number than normal
    - Overactivation of genes that control proliferation
  - Released as cancer cells die
    - Prognostic and diagnostic



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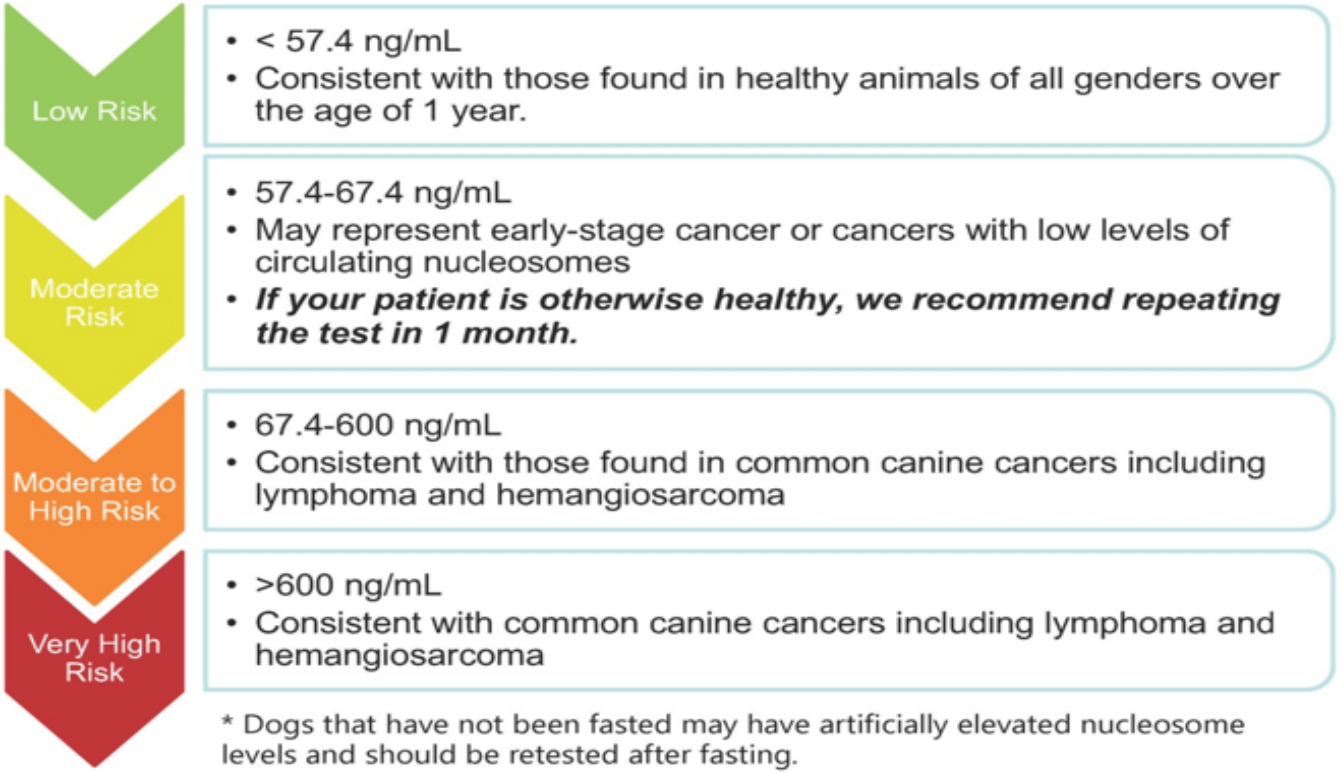
Nu.Q

- When to Use
  - The test is available to veterinarians in North America for use during annual wellness checks of older dogs, for cases where there is a suspicion of cancer, or for younger dogs from breeds with a high risk for developing cancer in their lifetimes.
    - The Nu.Q Vet Cancer Screening test may not be able to differentiate between significant systemic inflammation and cancer. If you are unsure if this test is appropriate for your patient, please contact us at AskNuQVet@volition.com or call 979.862.2861.
- Dogs that have not been fasted may have artificially elevated nucleosome levels and should be retested after fasting. If your patient has not been fasted, please indicate on the submission form.

Nu.Q

How to interpret Nu.Q™ Vet Cancer Screening Test



* Dogs that have not been fasted may have artificially elevated nucleosome levels and should be retested after fasting.
** This test may not be able to differentiate severe inflammation from cancer therefore ***if clinically indicated***, additional tests may be needed to confirm or deny the suspicion of cancer in your patient.

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Nu.Q

- At a recommended cut off of 67.4ng/mL the results for Nu.Q™Vet Cancer Screening Test gave an Area Under the Curve (AUC) of 87.3% and 97.6% respectively for lymphoma and hemangiosarcoma.
- At 100% specificity this provides 74% detection of lymphoma and 89% of hemangiosarcoma.

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Questions?

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