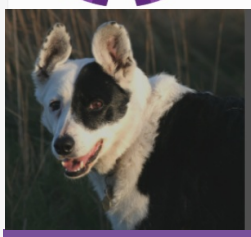
ONCOALESCE



Monograph

#6 April 2023

Greetings!

Dear Shah,

The teenage years

Welcome to the sixth edition of the Oncoalesce Monograph.

Juniper is sometimes a cat and sometimes a kitten! So, a teenager. Sometimes predictable and sensible but sometimes there are still random surprises and unexpected bursts of contrary behaviors. You can see where this analogy is going? So often in my conversations with oncologists who have tried out these new products, services and devices - sometimes they provide great results and make complete sense, sometimes the results are less expected. Time, patience and experience (and ongoing data collection) will overcome these early teenage quirks, both for Juniper and for oncology. It is my aim that Oncoalesce help this process. The monographs provide support for the individual oncologist who wants to expand their toolbox but need to feel more comfortable with the new offerings.

This edition introduces oncology to ONC Care: a new diet by Hills Pet Nutrition. I know everyone has questions about this, and Dr. Catherine Ruggiero, MS, DVM, DACVIM (nutrition) answers all of your queries.

LIFEPULSE BIO goes into far more detail on the safety and efficacy benefits of real time feedback through measuring impedance when applying ECT.

ImpriMed provide more data to improve the outcomes of those difficult T-cell lymphomas

Vidium publish data on the diagnostic and prognostic value of Searchlight DNA as well as the benefit of using the technology to find more treatments for MCT

Canalevia-CA1 contemplates more convenient packaging and is now available to the owners direct through Chewy and Stokes/Epicur.

Elias looks at new applications for immunotherapy and describes the final stages of their huge prospective trial.

I always try to keep this short. I failed! This is a long one, but the answers are very practical and relevant. I hope you find it useful.

I look forward to catching up with friends in Cancun - safe travels,

Warmest regards,

Tariq

Email me!

Download previous editions

Disclaimer and stuff

The following notes have been taken directly from data presented to the panel of oncologists in the Oncoalesce meeting #6. They then contain direct quotes and questions from the panel as well as the answers provided to them by the companies.

It is important to note some views presented here are made by individual oncologists but are not necessarily representative of the whole group. Whilst the panel comments are direct quotes, they are anonymized.

Conflict of Interest: All members of the panel were paid for their time by Oncoalesce at an industry acceptable hourly rate. They were not paid any other monies and act independently from the companies represented.
I am a paid consultant for the 6 companies represented in these monographs through Oncologize but I do not receive extra fees for publishing the Oncoalesce Monographs or for any content herein.

Panel (not all are present at every meeting):
- Dr. Jeff Bryan - University of Missouri
- Dr. Kim Cronin - MA Veterinary referral hospital
- Dr. Pamela Jones - QBiotics
- Dr. Kendra Lyons - Locum
- Dr. Melissa Parsons-Doherty – Pearland Animal Cancer and Referral Center
- Dr. Erin Roof – Animal Cancer Care Clinic
- Dr. Aarti Sabhlok – San Francisco Animal Medical Center.
- Dr. Andrew Vaughan – Las Vegas Veterinary Specialty Center
- Dr. Rachel Venable - Pet Cancer Care Consulting
- Dr. Carissa Wood - Locum
- Dr. Rachel Kovac - VCA Animal Diagnostic Clinic

Companies
- Elias Animal Health
- ImpriMed
- Vidium Animal Health
- Jaguar Animal Health
- Nutramax Laboratories
- LifePulse Bio
- Hills

There are at least 24 companies with an active presence within veterinary oncology. I hope over time more companies will be represented through Oncoalesce and will use this platform to provide clinically relevant information for you to be able to trust and adopt.

The Discussions

Hill's

Transforming Lives

NEW - ONC Care Nutritional support for pets fighting cancer

In keeping with our mission to help enrich and lengthen the special relationships between people and their pets, Hill's is excited to announce our newest product innovation: **Hill's Prescription Diet ONC Care**. This unique therapeutic food has exceptional taste and is designed to nourish and support pets living with cancer. This food offers nutritional support for the patient and is not a form of cancer therapy or treatment.

ONC Care provides complete and balanced nutrition and is appropriate for cats and dogs with all types of cancer (malignant or benign), whether they are receiving conventional cancer treatments (chemotherapy, radiotherapy, immunotherapy, etc.) or not.

Key features include:

- **Exceptional taste** clinically tested to promote food intake
- **High energy density** to meet requirements in smaller meals and help during times of decreased appetite
- **High protein digestibility** for easy assimilation of essential amino acids
- **Increased essential amino acids** (>180% AAFCO minimum) to help with natural ability to maintain muscle mass daily
- **Increased L-Carnitine** to help improve utilization of fat to avoid muscle breakdown for energy
- **High omega-3 fatty acids** to help manage inflammation
- **ActivBiome+ proprietary blend of prebiotic fibers** to help maintain consistent stool quality

Prescription Diet ONC Care is now available for cats and dogs. The feline product comes in 7 lb bags and 2.9 oz stew cans. The canine product includes 6 lb and 15 lb bags and 12.5 oz stew cans.

The first ONC Care clinical study was recently published:

Anthony RM, Amundson MD, Brejda J, Becvarova I. Acceptance of a novel, highly palatable, calorically dense, and nutritionally complete diet in dogs with benign and malignant tumors. Vet Sci 2023;10(2):148 (https://doi.org/10.3390/vetsci10020148).

Abstract: Diminished appetite and poor eating behavior accompanied by weight loss or cachexia are often reported in dogs living with cancer. This study was conducted to determine the acceptance and eating enthusiasm in dogs with cancer for a new therapeutic, nutritionally balanced, and calorically dense food designed for dogs with cancer. Adult dogs with diagnosis of cancer were recruited from general and oncology practices and were fed the study food for 28 days. Evaluations included physical examination, body weight, food intake, caloric intake, hematology and serum biochemistry,

and owner assessments, namely food evaluation, quality of life, and stool scores. The dogs transitioned smoothly and tolerated the food very well. The results showed high food acceptance within the first day, with continued eating enthusiasm over the 28 days. Significant increases in food and caloric intake were observed, with the study food having a positive impact on body weight in dogs that were losing weight and helping to maintain a high quality of life. Blood laboratory parameters remained within reference ranges. Thus, the therapeutic study food was well accepted and efficacious in supporting continued eating and required caloric intake, promoting a healthy weight gain and maintaining a high quality of life in dogs with cancer.

I would like to introduce **Dr. Catherine Ruggiero, MS, DVM, DACVIM (Nutrition)**, Manager of Scientific Communications with Hills Pet Nutrition.
Dr. Ruggiero provides the answers to the panel's questions on this new diet for our patients.

Panel's Thoughts on the presentation

Pet owners will love this. I get asked all the time about what to feed my pet with cancer.

It is nice to see Hills come out with a palatable diet for cancer patients.

It's awesome to have another option to offer pet owners; definitely the number 1 question I get asked! I love that it's high energy and they specifically mention smaller meals /decreased appetite, as I frequently recommend calorie-dense meals in my patients but clients always ask for a specific food name /label. Also very good to see a diet with some published science behind it!

I'm surprised the evaluation was only over 28 days. That seems like a short time to evaluate the impact of a food. Many of our canine cancer patients are not cachexic and often the opposite- overweight so it will be interesting to see if there is even more weight gain on this diet.

Many other diets have had poor palatability and are worthless because the patients don't eat them so it is nice to see the high palatability in the initial study.

This is a very common interest for owners and having options for them is always a positive addition to the conversation as it helps them feel engaged in their animal's care.
Having another tool to help manage poor appetite or stubborn diarrhea in our patient population is great.

Questions (concerns and clarifications)

I am always worried about strong antioxidants having a negative effect on chemotherapy drug activity. What is the level of omega-3 and what is Hills opinion on this as it is variable amongst oncologists? I work with a lot of pet owners who are employed by Mayo and none of them use antioxidants while their pet is on chemotherapy (just FYI).

The amounts of antioxidants (AOX) contained in ONC Care are appropriate for adult cats and dogs, including those with cancer, and are in the middle of the ranges for all Hill's foods. A certain level of AOX inclusion is critical in pet foods for both nutritional purposes and to help preserve the fatty acids in the food and this was our goal when formulating ONC Care.

There is not an agreed upon amount of AOX that is considered high or that has been shown to cause negative effects in dogs/cats with cancer. When concerns are expressed, they are related to use of concentrated AOX supplements, and not the amount of AOX included in a food like ONC Care. We do not recommend AOX supplements when feeding ONC Care to cats and dogs because they are not necessary, have no proven benefits, and have the potential to interfere with efficacy of common cancer treatments.

Based on all available research to date, there is not an agreed-upon amount of n-3 fatty acids (EPA/DHA) for pets with cancer. In the process of creating ONC Care (which began in 2017), we solicited feedback and insights from pet parents and veterinary healthcare team members (including veterinary nutritionists & oncologists) and the single most important need they identified was a complete and balanced food with great taste that pets would eat consistently. Therefore, our primary goal was to formulate ONC Care with exceptional taste, to be complete & balanced for adult dogs/cats, to provide a caloric dense food with highly digestible macronutrients, support for muscle mass (high levels of essential amino acids & L-carnitine), and consistent stool quality (with our ActivBiome+). The amount of EPA/DHA included in ONC Care is there to help manage inflammation that may be present in pets with cancer. If there are concurrent conditions where higher amounts of EPA/DHA are needed, those could be supplemented. ONC Care Canine provides $224 \times BW(kg)^{0.75}$. There are no recommendations for EPA+DHA for a feline cancer patient.

How can this be promoted for pets with benign cancers? Isn't this reaching? Can you be more specific?

Benign cancers are not invasive but can influence the patient's well being either by producing tumor-associated toxins, by pressure on organs or creating mechanical barriers etc. In some pets they can cause or contribute to malnutrition. Because of its key feature/benefits, ONC Care is a good complete & balanced option for cats/dogs with benign cancer that do not have concurrent sensitivities to higher dietary fat, kidney disease, or are prone to being overweight/obese.

How does the level of fat affect patients with pancreatitis? And will the protein level be tolerated by patients with renal insufficiency?

Due to its fat content, it is not appropriate for pets with fat-sensitive conditions (e.g., pancreatitis, hyperlipidemia, lymphangiectasia). For pets that have not had pancreatitis or hyperlipidemia but are at risk (e.g., miniature schnauzers), it's a judgment call for the veterinarian to decide on whether to recommend ONC Care based on potential risks/benefits. Because of the amount of protein & phosphorus, ONC Care is not ideal for cats/dogs with kidney disease (especially advanced stages) or those with significant renal proteinuria.

Many patients ask about fish oil supplements for their pets. What is the level of omega-3-fatty acids? Would this address OA like j/d but not necessarily high enough for recommended cancer supplementation benefits? Should additional supplements be considered?

Although there are not agreed upon recommended doses of EPA+DHA for cancer management, many veterinarians default to 125 mg/kg$^{0.75}$ (metabolic weight) as the "anti-inflammatory" dose. We know that it's the EPA/DHA amounts (not the total omega-3 fatty acids) that are most important for biological effects such as helping manage inflammation. The doses of EPA+DHA in ONC Care Canine dry or canned foods are well above the Bauer 2011 recommended dose for inflammation. Bauer recommends 125xBW(kg)$^{0.75}$ while ONC Care Canine provides 224xBW(kg)$^{0.75}$. If a dog with cancer that is eating ONC Care needs additional EPA/DHA supplementation for managing a concurrent condition (e.g., arthritis), this can be added to the food. Careful consideration should be given to the safe upper limit for EPA+DHA (370xBW(kg)$^{0.75}$). Additionally, the calorie contribution of fish oil should be included in the treat allowance; limiting intake of any unbalanced food sources (including supplements) to < 10% of daily calorie intake is important for maintaining an overall complete and balanced diet.

What is the caloric content? Do we know the clinical condition of the patients in the study prior to starting on the food (eg. were they only mildly down in weight and still otherwise feeling fine, or were they end-stage cachexic and systemically ill? Were they in the middle of chemotherapy treatment or had they completed their protocols?)?

The Caloric Density chart is shown below.
The study by Anthony et al (2023) included patients with benign and malignant cancer in various stages of treatment or receiving no treatment at all. The goal of recruitment was to enroll dogs with a diverse group of tumor types, even those that have seemingly little influence on appetite, to evaluate nutritional intervention as a part of multimodal disease management and represent the typical population seen in clinical practice. Detailed inclusion and exclusion criteria for the study population are defined on page 4 (Section 2.3). Figure 3b illustrates body fat index (BFI), which was ~28% at enrollment for all tumor types. Ideal or lean BFI, consistent with BCS 4-5/9, is 20-25%; therefore, these patients on average were not underweight at the start of the study.

How does this diet compare to GI Biome for chronic diarrhea/ soft stool concerns?

Hill's Prescription Diet Gastrointestinal Biome is a high fiber food for pets with fiber-responsive large bowel diarrhea. Prescription Diet ONC Care is a highly digestible (low fiber) food. Although both foods contain ActivBiome+, a proprietary blend of prebiotic fibers, the fiber levels in Gastrointestinal Biome are significantly higher to address primary gastrointestinal disease. The levels of ActivBiome+ in ONC Care are lower, with the goal of promoting consistent stool quality. We have previously demonstrated in clinical studies at the Hill's Pet Nutrition Center that both dogs and cats showed improvements in markers of gastrointestinal microbiome health when the ActivBiome+ technology was added to other foods.

For the feline diet, is there a thought to a combination diet with k/d? Many of our feline patients are CKD patients and it would be amazing to have this option for them that try to provide a balance between readily available support for their cancer but also their phosphorous and protein levels.

The protein levels in ONC Care are too high for a pet with proteinuric kidney disease. The phosphorus levels, although not considered "high" relative to a typical

maintenance food, are still higher than recommended for pets with CKD (and higher than what is found in k/d). At the discretion of the veterinarian, ONC Care could potentially be considered for patients at risk of malnutrition and cachexia who also have non-proteinuric kidney disease after taking into account the goals of therapy and the current dietary phosphorus intake. Prescription Diet k/d is still the primary recommendation for pets with kidney disease and robust clinical studies support its use in these patients.

We do not recommend combining therapeutic foods, as it often dilutes out the benefits of each. For example, a combination of k/d and ONC Care would result in a moderate protein, moderate phosphorus diet that is not particularly good for kidney disease or cancer. Prioritizing one disease for nutritional therapy is often required in patients with comorbidities. We are always happy to discuss nutritional recommendations for these complex cases - please don't hesitate to call our veterinary consultation service (1-800-548-VETS).

Any experience of what was discussed.

Love this food so far. Very palatable as advertised.

I've tried it in a few patients so far. I've had a few dogs who would not eat it and others love it.

For a few canine patients. I have been relieved to not see the change to the stools as was potentially the issue with the Hill's former cancer diet. This was my primary concern with offering it to owners on its release. Having the study made me more comfortable to start moving forward.

I recently had a patient gain a significant amount of weight when transitioned to this diet.

Thoughts for the future

I find a lot of dogs gain too much weight on chemotherapy, but owners always want something specific like this to feed them.

Compare to Canine Biologics in quality vs cost vs outcome, or home prepared diet? I see convenience and the name as the main feature. (Sadly, the Canine Biologics diet is no longer available. Whilst it established itself as a premium product, the cost (with growing manufacturing costs thrown in) proved to be too high for sustainable use. Canine Biologics are now offering the NutriDapt range for critical patients, a flexible tailored liquid
diet: https://caninebiologics.com/collections/nutridapt-products - (Editor))

Will Hills consider using a base besides chicken?

This can certainly be considered for the future. The current products contain chicken as the primary protein source.

More information is coming out to show benefits in fecal microbiome - is there any indication that the diet is beneficial to gut microbiome which "may" enhance prognosis in cancer patients?

This is an early area of research in the veterinary profession which we are closely monitoring. Hill's has been actively conducting research on microbiome health, most notably through the development of Prescription Diet Gastrointestinal Biome and the ActivBiome+ technology. We are excited to include the ActivBiome+ prebiotic fiber blend in ONC Care to support consistent stool quality. We continue to look for opportunities to contribute to the growing body of research on the canine and feline microbiome.

I would love to see a larger /longer study stratifying the patients based on their cancer type and stage, and their overall clinical condition; I feel that we most need something like this towards the end of the disease process and over the course of months, and I'm not sure the study as-is really addresses that need.

I'd like to see a longer study evaluation on this diet, especially evaluating muscle mass and stool quality.

Agree that long-term study of effects on cachexia would be very beneficial to see.

It would be great if they could evaluate the diet's ability to help maintain weight and muscle mass through a treatment protocol.

Now that the food is commercially available, we look forward to supporting future studies and collaboration opportunities. There are current ongoing trials which we hope will answer some of these more specific questions.

Caloric density of ONC Care

	Feline Dry	Feline Wet	Canine Dry	Canine Wet
kcal/cup or can	581	77 (2.9 oz)	483	322 (12.5 oz)
kcal/kg as fed	4183	936	4158	909

Expanding on LifePulse Bio Electrochemotherapy

Impedance feedback has been proven to be the best indicator of cell permeability for both drug and gene delivery. While users of others systems have to guess maximum permeability, LifePulse VetPulse is the only device in the world to incorporate real time impedance feedback.

Why is this important? The ability to detect maximum permeability is important because it gives the practitioner assurance of delivery and makes it virtually impossible to either over, or equally important, under treat the targeted tissue. The importance of impedance was discovered with millions of dollars of NIH funded grants over many years of research. It is the most important evolution of the technology in 60 years and for the first time, allows the practitioner to feel confident of delivery before seeing results. In dozens of cases across the country since March of 2022, we have not seen a single case of burns or healthy tissue damage simply because real time impedance feedback will not allow it.

When combined with moderate heat, as our patented system does, the system allows reduction of the required voltage to less than half of the existing technology, with superior delivery. In fact, those with experience using the old technology have been astonished with the lack of violent reaction from the animal. It is such a drastic change that we've been able to treat horses standing for peri-anal melanoma. This will be discussed further in the next Monograph.

Atkins, R.M., Fawcett, T.J., Gilbert, R.A., Hoff, A.M., Connolly, R., Brown, D.W., and **Jaroszeski, M.J**. (2021) **Real Time Impedance Feedback Data for Enhanced Cutaneous Gene Electrotransfer in a Murine Model.** Bioelectrochemistry, 2021, 107885, ISSN 1567-5394, https://doi.org/10.1016/j.bioelechem.2021.107885. (https://www.sciencedirect.com/science/article/pii/S1567539421001481)

This paper describes the application of impedance to measure effectiveness of increasing cell permeability through the use of an electric field. In this paper the aim is to increase the uptake of gene therapy. In oncology this is the same methodology to increase update of large chemotherapy molecules, hence we use the term Electro Chemo Therapy (ECT). The principal of measuring impedance therefor applies to both ECT and Gene Electro Transfer (GET). For this reason, LifePulse Bio often refers to the broader application for this technology – Enhanced Molecular Delivery (EMD).
This is not a research paper to demonstrate the efficacy of ECT, that has been done many times over the last 40 years. This is to demonstrate the efficacy of measuring impedance to improve ECT – the technology now introduced by LifePulse Bio.

The following is key text from the paper regarding impedance.

Permeabilizing electric fields are established by applicators containing electrodes in direct contact with the target tissue. These electric fields generated in the skin cause ions in the local extracellular space and within cells to collect on the inner and outer leaflets of cell membranes like the charging of a capacitor. As the ions

accumulate, the trans- membrane potential eventually reaches a breakdown voltage of the insulating phospholipid bilayer resulting in current flow through the membrane and permeabilization.
Rearrangements in cell membrane structure following permeabilization provide new pathways for current resulting in measurable changes in electrical conductivity. Changes in conductivity can therefore be used to indicate when changes in membrane permeability occur. Such changes in tissue conductivity and capacitance allow impedance spectroscopy to be used as a tool for quantifying changes in the electrical characteristics of cells and tissue.
Current in vivo electro transfer treatment protocols typically apply a fixed set of pulses to the tissue to obtain gene delivery. The pulse characteristics (field strength, pulse duration, number of pulses, etc.) are typically empirically derived based upon mean responses from preclinical studies. When determining these optimal parameters, there is currently no method available to account for differences between individuals with respect to chemical environment and tissue architecture. Similarly, empirical approaches do not permit the ability of real time alterations of pulse parameters in response to any measured parameter (such as impedance or conductivity changes in the tissue) during electrical treatment nor do they provide any indication of successful gene delivery. Thus, any differences in chemical environment and/or tissue architecture will result in large variations in gene delivery thereby decreasing the reliability and clinical relevance of this gene delivery method.
This paper reports on research efforts to identify impedance spectra characteristics of tissue that correlate with successful gene delivery. Experimental results showed a strong relationship between the change in impedance magnitude with both field strength and biological response indicating that tissue impedance is an excellent indicator of membrane permeabilization and subsequent transfection.
Real time use of tissue impedance measurements can be used to decide whether more electric field pulses are required to maximize gene delivery, and in the same way, arrest any further pulsing once maximum permeability is achieved.

Thoughts on the presentation

Very interesting to see this requires less voltage so it is better tolerated. Also interesting that it tells you in real time how to treat.

I could consider ECT if there was less reaction by patient under anesthesia or if they could be treated with sedation only! Also the administration of less voltage and less side effects are more likely to make us consider ECT when response/ efficacy is not yet guaranteed.

I look forward to trying this therapy.

Interesting use of measuring effectiveness in real time. The approach towards accuracy vs over treatment and tissue necrosis is attractive.

Interesting approach to determining efficacy and reducing side effects. An improvement in previous ECT recommendations which didn't seem to be based on any real data.

Interesting but the mouse data are unconvincing to consider abandoning our current unit to buy another unit. It also isn't clear that the hyperthermia portion of this unit is equally good across tumor types. Are there some that might be harmed using this?
There is far more data available than is included here (including a range of tumors). The heat is only 43 degrees, and for a short period of time, so it does not cause long term harm.

The improvement in potential side effects is very nice.

If this technology can be used to reduce discomfort, ECT could be made even more cost effective if only minimal sedation is required.

Questions (concerns and clarifications)

Are these results with impedance the same for any tissue? Meaning subcutaneous tumors or even organs with tumors?

All cells respond to electric fields in a similar manner (ie permeabilized). Therefore, the impedance of all tissues will be reduced as electric fields are applied. We have observed this in animal models for skin (published), several tumor types, and muscle.

Is there a shorter/ longer treatment time? less efficacy? more treatments needed overall?

It is the same or shorter treatment time because the electrode does not have to be relocated from to ajcacent areas because we have large electrode arrays. It has higher efficacy because there is a measure of successful electrical

treatment. Since there is a measure of complete electrical treatment the practitioner is far less likely to undertreat. Therefore, fewer treatments would be needed.

Are there limitations to which tumor types or body locations can be treated. Does the type of chemotherapy used in conjunction with treatment change impedance?

No limitations to location. And the type of chemotherapy agent does not appear to impact the measured impedance. Every tissue has a baseline impedance (pretretment) that is measured. It is measured after injection but before any pulses are applied so impedance is measured after each pulse and compared to the post injection values.

Have they evaluated for differences in their protocol vs. a more traditional ECT delivery with regards to long-term outcome?

Long term data is being gathered. The biggest differences are seen immediately in the almost complete lack of muscle jerking. Traditional ECT delivery should also "work", since the basic technology is the same, so the long term differences are going to be more towards the fewer treatments required and less tissue damage.

The paper discusses that changes in tissue architecture lead to large variations in delivery. Since ECT is frequently used in the post-operative setting, would those challenges translate to significant variations in delivery with post-operative patients?

It is possible that there can be some effect based upon the architecture changes; however, the basic concepts of the therapeutic approach would not be affected.

Any experience of what was discussed.

No one had experience of LifePulse Bio, and not surprisingly, very little direct experience with ECT in general.

Thoughts for the future

It would be great to see how the use with impedance for treatment is still as effective or more than other forms of ECT.

Agreed, a side by side will be a good study.

Seems like they are on the right track. Don't feel that I know enough about practically administering ECT to know if this will improve overall SOP.

The machine and software are very user-friendly and guide the user through the process.

Ongoing evaluation of effectiveness with impedance feedback and heat over other ECT. Side-by-side comparison of the discomfort aspect.

We agree that this should be done. However, we do have murine data that shows increased effectiveness.

ECT is more commonly in use with linear accelerators being so expensive and overprogrammed. Clearly ECT is here to stay, but clinical trials must be conducted and published. Not just retrospective series.

There are about 80 human clinical ECT trials published in multiple tumor types. These data might be useful to the veterinary market

Evaluating this technique in patients who have undergone previous surgery and whether or not that impacts response would be great.

True!

Canalevia®-CA1
(crofelemer delayed-release tablets)
Jaguar Animal Health

epicur® PHARMA

Canalevia CA-1 Thoughts on different presentations and availablilty

We are pleased to announce that Canalevia-CA1 is now available through Chewy. You can see the product page here:https://www.chewy.com/canalevia-ca1-tablets-dogs/dp/741982

As of April 14th Stokes/Epicur will offer Canalevia (within 24 hours) to owners direct. One of the issues raised by oncologists is that Canalevia is too expensive to give 6 tablets to everyone, but too essential to not have available immediately if needed. With the help of Stokes, this enables the protocol of sending home an affordable TWO tablets with all chemo clients, who can then order the remaining FOUR direct from Stokes if they have a need. Ideally, they won't use the 2 tablets during the course of chemo and if this is the case they only paid for two tablets. BUT if they do need it, this system would work.
Canalevia is available to be ordered by veterinarians via the on-line system – iFill, or they can call the script into the pharmacy.

Questions for the Panel:

- Do you think this will be helpful in making it more convenient for vets and pet owners to access Canalevia-CA1?
- What other online pharmacies would you prefer to see carry Canalevia-CA1?

We are also considering offering Canalevia-CA1 in a smaller count bottle. If you could order a bottle of 6 tablets rather than the current 60 tablets, would that be helpful? The dosage of Canalevia-CA1 is two tablets per day for three days so that each new bottle would correspond to a typical course of therapy for each presentation of diarrhea.

- What are your thoughts on offering a 6 count bottle in addition to the 60 count bottle?

WHAT IS Canalevia-CA1?
A NON-ANTIMICROBIAL OPTION FOR THE TREATMENT OF CHEMOTHERAPY-INDUCED DIARRHEA (CID) IN DOGS.
Canalevia-CA1 normalizes fluid flow to reinstate normal function in the GI tract and

is an antidiarrheal, enteric-coated tablet for oral administration. It acts locally and it is not absorbed into the blood stream, resulting in a well tolerated and non-opioid drug product. It is naturally and sustainably harvested from the sap of a medicinal tropical plant, the *Croton lechleri* tree.
Canalevia-CA1 is well tolerated with only a three-day course of treatment for dogs under 140 lbs.

Thoughts on the presentation

I like the idea of having more options to get the pills. I have found the large bottle count to be a deterrent for many vets and pet owners. I think the low count will be very helpful as people are trying out the product. Cerenia only comes in a pack of 4 because that is how it is prescribed too. The large bottle is more expensive and not all clinics know yet if they want to buy that much.

The 6 count bottle is a good idea, less of investment on the shelf. I am not so thrilled that Chewy et al have access, we spend enough time approving chewy prescriptions with no revenue for our time. Cost still limiting to make Canalevia the initial "just in case" medication vs others.

I like having more options/ways to dispense this medication. Smaller bottles may be easier to stock/lower overhead.

I like that Jaguar is looking at ways to make Canalevia-CA1 more convenient and affordable for pet owners.

I think having smaller bottles available AND having alternative sources to obtain the drug are super helpful. That said, for patients who are actively having diarrhea I think having 24 hour ordering through Stokes is going to be more helpful than ordering through Chewy as my experience with prescription approval and turnaround times for Chewy has been very poor.

Chewy would be convenient for some owners but we are treating so many cases of recurrent diarrhea that the 3 day dosing is often not enough. I'm not sure a 6 count bottle would change my practice much on sending it home but it may be better for inventory.

I do think that a 6 count bottle would be useful. I have been impressed with the benefit of Canalevia recently in a few cases. We also need to strongly consider leaving antimicrobial treatment of diarrheas in the past, and this drug breaks that barrier.

I would very much like to see the option for 1800-pet meds as many of my clients utilize them instead of Chewy as well as the options for Stokes. A 6 count bottle would be a better option in situations for owners ordering direct.

A 6 count bottle would be extremely convenient for dispensing. In my opinion, that's more helpful than having it on Chewy. I would imagine that would make it more feasible for smaller oncology practices to carry it as well.

Questions (concerns and clarifications)

I also like the idea of having other pharmacy options. But a lot of vets do not like Chewy and see them as competition. As an oncologist, I do not mind Chewy, but I know a lot of GPs really dislike them.
I would dispense all 6 tabs. 2 seems less helpful if they then have to get the remaining 4 tablets and is inconvenient when treating diarrhea.

This is only an option if providing all 6 to all owners becomes cost prohibitive. They would request the remaining 4 tablets as soon as they have a need to administer the first one.

Would it be possible for Costco to carry this medication (as they carry a number of other veterinary medications)?

Canalevia-CA1 is not currently carried by Costco but is something we will explore in the future.

For those that have indicated cost is a factor – what is the cost difference between dispensing a 2 vs 6 tablet treatment? While a 6-tablet bottle is attractive for dispensing, is the benefit that the clinic doesn't have the large inventory on the shelf? What is the shelf-life of the drug? What is the cost difference per tablet between 6 vs 60 tablet bottle? My point is that I am surprised that makes a difference for most oncologists – it may make a difference for primary care practice availability or those emergency practices that may see patient afterhours for CID.

The anticipated cost for a 6-count bottle would be same on a per pill basis as the 60-count bottle.

It may be beneficial as a prophylaxis, but I don't think it will benefit patients who are already in the process of having diarrhea. Additionally, I know we've discussed cost and shelf-life before, but it would be helpful to have a quick refresher!

The shelf life would be the same, around 2 years.

We had a problem with receiving a very short-dated bottle. That is a huge issue given the cost of the drug and that we aren't using it as our dominant drug yet.

Sorry – all bottles going out now have a far longer shelf life. Please work with your distributor to get a credit for your short- dated bottle.

I find the process of utilizing Chewy very frustrating at times due to the process for approval.

To me a 6 count bottle with a long shelf-life would negate most of the concerns regarding cost of keeping too much inventory.

Any experience of what was discussed.

Yes - worked in several refractory cases but have not yet it my first line. We have it available and a nice option.
I don't think I would ever send home 2 tablets with scripts to get more- just get the 6 tablets at the same time. If they are already in the same bottle, great.

Yes, this is the only thing that has stopped diarrhea in two dogs on oral paclitaxel. Impressive responses in both dogs very quickly. It will be exciting when the use scope is broader, as I think the utility will be high. The drug isn't expensive compared to a rug cleaner!

We also dispense it often enough a 6 count vs. 60 count doesn't change things much overall.

Since I work at a practice with 3 other oncologists, we go through the drug quickly enough that a 60 count bottle is fine. However, the time save of having the medication essentially ready to hand to the client (with the 6 count bottle) would be great.

Thoughts for the future

I think it is going to take time for people to try the product and see how they like it. I have not seen much advertising to vets and when I mention to GPs most have not heard of it. It looks like there are opportunities to get the word out about it to general vets and ER who may not do a lot of chemotherapy but see the pets for any side effects like diarrhea.

3 days of therapy is nice way to promote it if it will work completely since some dogs are on metronidazole or Imodium long term. Also, natural product promotion is a way to differentiate the drug. Cost is not as much a deal if dealing with diarrhea, but for "just in case" med to go home a little expensive.

Would this help if the diarrhea was multi-factorial? I.e. chemo, dietary indiscretion, stress colitis?

Canalevia-CA1 is currently only indicated for Chemotherapy-Induced Diarrhea. It is at the Oncologist's discretion to determine that the main cause of diarrhea is caused by chemotherapy.

What is the status of trials directly evaluating its effectiveness for CID? Is it variably effective on CID depending on the type of chemotherapy? May be variable effectiveness based on the multifactorial pathophysiology.
I agree with what's already been expressed: very interested to know if there's any follow up studies planned evaluating for various causes of diarrhea, effect of dietary indiscretion vs. chemo vs. targeted therapy, etc!

Jaguar Animal Health is currently working with the CVM to get protocol concurrence on the Full Effectiveness Trial for Canalevia-CA1. Chemotherapy types are a variable that will be explored during the study.

We see diarrhea in chemotherapy patients frequently but I'm not convinced the chemotherapy drug is always the culprit as clients are feeding their pets more home cooked and boutique diets. Has there been any evaluation in dogs with chronic diarrhea from other sources? Any information on giving it once a day for more than 3 days?

Canalevia-CA1 was previously evaluated in cases of non-infectious diarrhea in shelter dogs. However, due to its current FDA conditional approval, Canalevia-CA1 can only be prescribed for dogs with CID at the label recommended dosage.

Will they be assessing this for targeted therapy induced diarrhea vs. traditional chemotherapy induced? I find there to be a big difference between the two treatment categories as far as the drugs ability to improve the patient's diarrhea. I also would interested same as ER if they have evaluated it in a a more chronic setting.

Canalevia-CA1 is currently approved to treat diarrhea caused by both targeted and traditional chemotherapy. The Full Effectiveness Trial will cover both chemotherapy types.

Has this medication been evaluated for diarrhea suspected to be related to acute radiation side effects?

No.

vidium ANIMAL HEALTH a TGen subsidiary

Vidium recently published a manuscript explaining the benefit of SearchLight DNA in difficult-to-diagnose tumors. Here are the major findings:

In a cohort of 69 diagnostically challenging cases, SearchLight DNA provided clinically useful (diagnostic, prognostic, and/or therapeutic) information in 86% of cases.

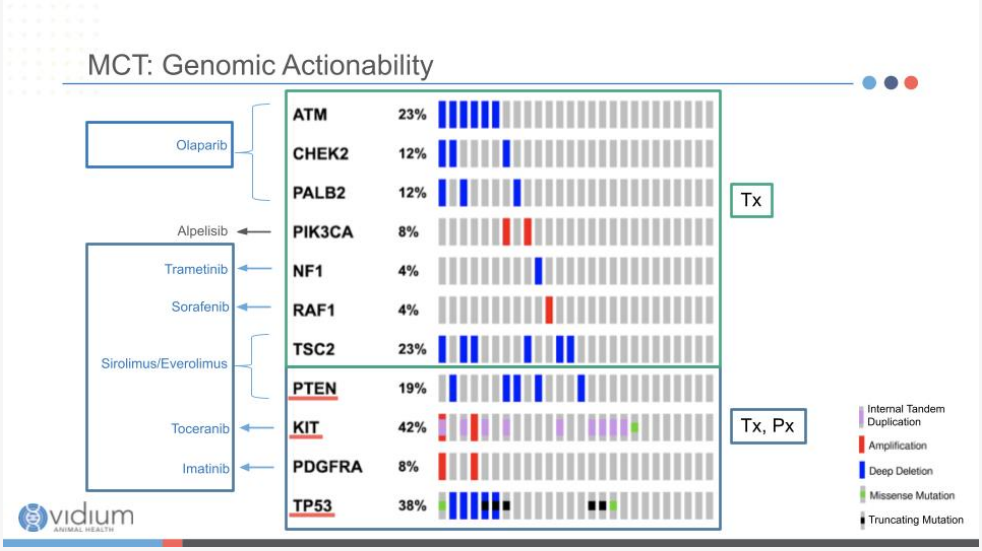
SearchLight DNA provided diagnostic clarity in 54% of cases and therapeutic and/or prognostic information in 69% of the remaining cases for which the diagnosis remained elusive.

MAST CELL TUMORS: Why would you think of SearchLight DNA for these cases?

In a cohort of canine mast cell tumor cases that were evaluated by SearchLight DNA, there was clinical actionability in the majority (84%) of cases. For therapeutic actionability specifically, >50% of cases matched to a targeted therapy, including many drugs *aside from Palladia*.

Matching targeted therapies included olaparib, sirolimus, sorafenib, imatinib, toceranib, and trametinib, all of which are available through compounding pharmacies. Below is an oncoprint of some of the frequently mutated genes found in this cohort of mast cell tumors. Matching targeted therapies are to the left; biomarker associations are to the right.

Benefits of Searchlight Paper link



- *Px = Prognostic biomarker, Tx = Therapeutic biomarker*
- Red-underlined genes are diagnostic biomarkers
- Blue font within blue box on left indicates drugs *available* to vets from compounding pharmacies
- Gray font indicates that it is *not yet accessible* by vets from compounding pharmacies

Thoughts on the presentation

It is good to see numbers to help get an idea how often this test can help with diagnosis and therapy options.

Surprising to see the number of lymphoma cases in the publication. I would welcome targeted therapies to use when dealing with a resistant cell population. I expected sarcoma and melanoma to be included. I am enjoying seeing the targeted therapies available overall in compounding pharmacies and have started using these more and more.

I appreciate that Vidium can provide both diagnostic and prognostic information in a variety of tumors. The fact that it can be done on aspirates has been quite helpful in a number of tumors.

It is important that in the recent publication, 38% (26/69) of samples were easily obtained aspirates. This is still one of the key aspects to Vidium's SearchLight DNA.
We are glad that more and more veterinarians are leveraging this sample type.

I think emphasizing that they've published on the utility of Searchlight is important; I know when we were reviewing articles with the interns /residents, they had a tendency to skip over this article because of the title but it's actually really important information! Having it reiterated in an abbreviated form in this presentation is super helpful to highlight the benefits of Searchlight over other genomic profiling services. I'm also impressed that every time I hear from Vidium re: Searchlight, they're able to give me a "lightbulb" moment and help me think about genomic profiling for tumors that I don't normally consider targeted therapy for (eg. lymphoma during the last session, and non-Palladia MCT this session).

I am glad you find the value of SearchLight DNA for its other aspects (not just the therapeutic ones) and for stressing its importance in your residents and interns. And we're so glad that we can provide those lightbulb moments for you.

Having SOME information on these difficult to diagnose tumors is always helpful and if this can give you therapeutic or prognostic information, all the better.

Vidium continues to produce solid data on their platform. I particularly appreciate that they are free with the sequencing results that can matter in diagnosis, prognosis or therapy. These techniques are important in human medicine both diagnostically and therapeutically. Our data on therapy response remains thin.

We agree that therapy response data could be more robust, and I am so glad to see that our veterinary oncology community is working towards producing that data.

For MCT the ability to better direct additional targeted therapy is a very welcome addition

We wanted to highlight that Palladia is not the only targeted therapy for mast cell

tumors, so thank you for picking that up.

A diagnostic and therapeutic option that can be obtained by just an FNA is exciting. The therapeutic information is the most intriguing because even when you can name a tumor, sometimes it doesn't help guide the treatment plan.

Questions (concerns and clarifications)

How often does immunohistochemistry get a diagnosis? Just wondering if the numbers for immunohistochemistry getting an answer is higher than 54%.

Immunohistochemistry has a strong track record historically in characterizing neoplasia, however, we all know that there are diagnostically challenging cases in which IHC is not helpful. SDNA should not replace IHC in the diagnostic process, but our hope is to create awareness that genomic testing can provide diagnostic support and can be a helpful next diagnostic step when pathology and IHC have been unable to characterize a neoplasm.

On the oncoprint for MCT, do dogs often have multiple mutations which could have various therapeutic options or usually just one? How do we know which drug would be the most effective if there are multiple mutations?

Yes, some dogs can have multiple mutations with multiple associated targeted therapeutic options; some dogs may have only 1 mutation/targeted therapeutic option; and some may have no targeted therapeutic option. For those that have multiple therapeutic options, we will prioritize the drugs based on mutation-level evidence and report them in the SearchLight DNA Summary (bottom of the first page of the report).

Cytology is a nice feature but sometimes limited by cellularity of the sample. I've tried to get an answer for possible plasma cell vs melanoma and the test has provided me with few options. How about the cats?

We do not yet have a panel available for cats. Since our assay is based on published literature, there will need to be sufficient published genomic information with clinically useful biomarker associations before we can have a panel that can be useful for the veterinarian. But cats are on the top of our list of species to help next, so they are definitely not forgotten.

It has been previously reported that DNA analysis provides actionable information in 75-80% of cases. Is there information on what percentage of patients respond to the recommended treatment? Would we expect this test to provide prognostic information on MCTs?

We are currently collecting outcome data that should give insight into the prognostic value of SearchLight DNA for many cancers, including mast cell tumors. Please stay tuned!

The report mentions clinical actionability – what about simple prognostics looking at low vs high grade to predict behavior? Do low grade tumours have these targets or are the targets absent?

Your question about correlating genomics with grade is a great one, and we too are interested in genomics as a predictor of grade. Please stay tuned!

Regarding the utility of SearchLight, for those cases in which it provided diagnostic clarity, is any information available about what other diagnostics were attempted? Was SearchLight an preliminary test or a test of last resort after failure of histopath and IHC? Regarding the MCT oncoprint, was there any evaluation of correlation with grade or other prognostic factors eg. Ki67?

Yes! We have that information in Table 2, under "Prior diagnostic tests performed", and Group 1 included those cases for which SearchLight DNA provided diagnostic clarity.
Only a minority of cases (29%) in Group 1 had other diagnostics performed prior to SearchLight DNA, while the majority of cases (71%) in Group 1 did not have other prior diagnostics performed.
We did not specifically look for any correlations between genomic mutations and other established prognostic factors (such as grade) for this mast cell tumor cohort, since this would have necessitated outcome analysis, which was outside the scope of this study.

What has been the response rates in the dogs treated with predicted drugs? We know that they vary widely in human medicine across histologies with the same mutations. What will we see in our patients? Would love to see those reported.

We share your curiosity and are currently working on collecting and evaluating outcome data.

For the mast cell tumors with metastatic lymph nodes. Would they want both

samples in the event that they have different mutations and potential therapeutic targets and if so would they be looking at combination therapy in those cases.

Currently, there is no hard-and-fast rule about primary vs. metastatic lesion (met) for genomic analysis, since there are several considerations such as accessibility, quality of the sample, metastatic disease burden, degree of progression, etc. If all considerations are equal, we would lean towards the primary tumor because it is the most representative of truncal mutations shared across all mets whereas it's possible that unique mutations may have arisen distinctly in different mets. Some scenarios where we would consider a met over a primary are if we have only one large met; if the primary was resected months ago with no recurrence and the mets are the most recent; the met is the sole progressive lesion after therapy; if there is a stable primary while mets have been rapidly progressing. Ultimately, we would/could accept either primary or met (or both, if you or the pet parent are interested at looking at how they may differ, although this does mean that they will be considered 2 separate sites and therefore charged as such), and we would prioritize the most recent available sample in order to capture the various aspects of tumor evolution; having the highest quality sample (highest tumor content, high DNA quality, etc.); and having a sample that is most representative of disease burden if possible. Generally, preference would be towards the primary more than towards the met if all considerations are equal.

For OSA cases that we have no control on them undergoing decalcification prior to submission for Vidium, is there any potential direction to make these samples possible or any thoughts on how to best approach these cases when there is not a new lesion to sample?

It's good to be aware that labs do not usually decalcify the entire neoplasm, and usually retain formalin fixed, non-decalcified tissue in the lab anywhere between 2-4 weeks. If running SearchLight DNA is a consideration at all for a bone tumor, we recommend contacting the pathology lab immediately and asking them to hold the wet tissue so that it's not discarded. If there is still wet tissue on hand, Vidium can work with the lab to obtain a non-decalcified sample for genomic analysis. Alternatively, you can send the pathology straight to Vidium from the beginning where we attempt to take soft tissue sections of all bone tumors in order to have non-decalcified FFPE blocks on hand for genomic analysis. If a tumor has been completely decalcified and all wet tissue discarded, unfortunately there are not any options for pursuing genomic analysis on the case unless there is a metastatic lesion to sample.

For the mast cell tumors, were they confirmed high grade? Have they looked at whether or not this test could be used to evaluate whether or not mast cells in a draining lymph node are metastatic? For the difficult to diagnose tumors, were you able to collect more follow up data with regards to treatments and outcomes?

The mast cell tumors were a mixture of various grades, although many were intermediate to high grade.
It would be awesome if genomics could evaluate mast cells in draining lymph nodes to discern neoplastic vs. resident/reactive mast cells. However, our validation studies require a minimum threshold of atypical cells which, if met, would already be high enough for cytologic confirmation of metastasis.
Outcomes were outside the scope of the study, but we are separately collecting and evaluating outcome data. Pleast stay tuned!

Any experience of what was discussed.

I had a confusing case which was a round cell tumor that we did Vidium to help with diagnosis, but unfortunately it was one that it was unable to help.

Thank you for using SearchLight DNA to obtain diagnostic clarity. As with any test, it is not 100%, but I hope it was able to give you other clinically useful information, such as prognostic data and treatment options.

We sent in repeated cytology for hepatocellular carcinoma, ultimately no sequencing possible due to cellularity, so ended up with cytology of HCC; went with sorafenib.
I LOVE the option of more therapies for MCT.

I remember this HCC case, and I am sorry cellularity was not sufficient to move forward with sequencing. We don't want to waste your client's money by sequencing a sample that doesn't meet our validated DNA quantity/quality criteria and therefore has little chance of producing reliable information. To be confident in our results, we do need to make sure not only tumor content is sufficient, but that ultimately DNA quantity and quality have met our thresholds before sequencing is even begun.

I have found Vidium to be helpful in some poorly differentiated tumors and in tumors where there is no consensus on therapy.

I like the idea of using genomics to diagnose and provide therapeutic targets but

predicting prognosis is particularly important when looking at equivocal diagnosis.

We agree, and that was our thought too with this study.

I had a difficult time obtaining samples on a presumptive metastatic HSA case with lung/ kidney involvement- many slides obtained without enough DNA for SearchLight. We were able to get the initial histopath sent over for analysis and the report was helpful.

I have not used this clinically yet, but in discussions with Vidium about collaborating on a grant. The company is very accessible.

Unfortunately at this time the samples I have submitted have not provided therapeutic targets for my patients. That said it is a low number and it will take time to fully understand the information they are obtaining and how it applies best to clinical practice. I have found the turn around time for samples submitted to labs by the rDVM can be a bit delayed. But from my follow up this appears to be on the rDVMs part in not providing the required release needed.

We do our best to expedite the transfer of tumor sample from a reference laboratory to ours. Unfortunately, we can't control how quickly the outside reference laboratories send us the sample; likewise for the authorization for sample release by the rDVM. However, we do our best to get their cooperation in getting the sample to Vidium as quickly as possible. This is one of the advantages of having our own histopathology services, though. Since the sample is already with us, there is no additional time spent to have the sample shipped to us. If you haven't already, please consider using our pathology services for a more streamlined process. We have world-class pathologists (like Dr. Barb Powers!) with a quick turn-around time for histopath and cytopathy, and adding on SearchLight DNA is rapid and painless if that is the route you want to take for your patient.

I have found Vidium to be helpful for tumor types for which there are no known effective therapies. The biggest challenge is getting the histopath sample from the lab to Vidium in a timely manner.

I am glad you have found Vidium helpful for those cases with no known effective therapies.
If the pathology will be ordered initially by you, please consider using Vidium's pathology services for a more streamlined process.

Thoughts for the future

It would be great to know how these mutations affect prognosis. Meaning if the tumor has mutation X then this is associated with a survival or progression free interval of Y. Currently, the results of mutation X is associated with a more aggressive cancer which is not overly helpful in dogs with known aggressive cancers like hemangiosarcoma.

Yes, that is our hope for the future too.

I think even more clients would pursue this diagnostic/therapeutic tool if the time from submission to results were shorter.

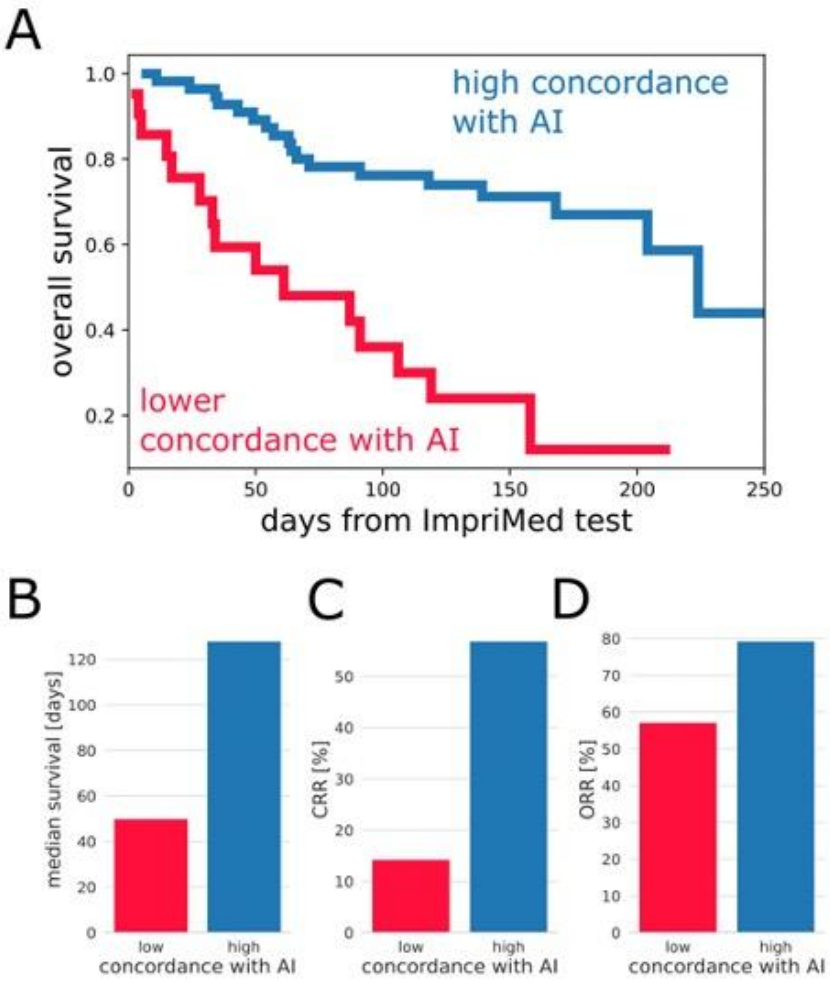
To shorten the overall time for you, the quickest way is to have had the initial pathology performed by Vidium, since the sample will already be in our possession, and there will be no time spent to get the sample sent from another reference laboratory. Once the sample reaches our lab, the time to report generation is 9-12 calendar days. We utilize every bit of this time to ensure that you get the highest quality and most clinically useful information as possible.

Have you looked at any of these MCTs in the naive versus treated setting and do the genetic profiles change post therapy?

This is another great aspect to evaluate. We have not done this yet but welcome collaborations to look at this and other comparisons.

These methods are clearly the way of the future. Hopefully indications will continue to grow.

We hope so too, and if genomics in human medicine is any indication, veterinary medicine is heading in the right direction.



Canine T-cell lymphoma patients have better outcomes when treated in concordance with drugs predicted to be effective using ImpriMed's AI and cancer-profiling platform. **A.** Kaplan-Meier curves are plotted for high and low concordance groups as a function of the number of days after oncologists ordered ImpriMed's AI predictions. **B-D.** Median survival, complete remission rate (CRR), and overall response rate (ORR) are higher for patients that received treatments highly concordant with ImpriMed's AI predictions.

Post-market assessment of ImpriMed's AI-based clinical decision support suggests potential for dramatic improvement in canine peripheral T-cell lymphoma outcomes

Introduction

Canine patients with peripheral T-cell lymphoma do not respond well to chemotherapy and have shorter survival times than most lymphoma patients. Remissions induced in these patients by CHOP therapy tend to be of short duration, which has led clinicians to explore a number of alternatives such as MOPP and LOPP. In 2021, ImpriMed launched an innovative commercial service that provides clinical outcome predictions for different anticancer drug treatment options. The outcome predictions are generated by artificial intelligence (AI) algorithms trained to predict real-world clinical outcomes data using patient information and tumor profiling results as inputs. ImpriMed's lab generates comprehensive tumor profiles using a number of technologies, including a high-

throughput live-cell drug sensitivity assay, immunophenotyping by flow cytometry, and PCR-based clonality testing. ImpriMed's platform is designed to provide oncologists with evidence-based clinical decision support that is personalized to individual patients. This support is likely to be particularly useful when caring for patients with cancers like peripheral T-cell lymphoma where there is not a strong consensus on an optimal treatment. Here we report the results of a post-market analysis designed to assess the impact of our AI predictions on the health outcomes of peripheral T-cell lymphoma patients.

Analysis of post-market clinical performance

ImpriMed continuously collects medical records from our oncologist users to accumulate more clinical evidence for our AI algorithms. These records also enable us to periodically assess the impact of our technology on the outcomes of our patients. Using our database of patient information and clinical outcomes, we defined a study group of 79 peripheral T-cell lymphoma patients. The oncologists treating these patients had each received our AI prediction report prior to or during treatment.

To ask if our predictions were associated with better clinical outcomes, we divided the patients into two groups based on how well their treatments subsequent to the AI report date agreed with the predictions found in those reports. A high concordance group (n = 58) was defined as those patients for whom the top drug in our prediction report made up at least 25% of the drug treatments they received. This definition was designed so that patients who received our top drug as part of a 4-drug combination therapy cycle would be considered to have received treatment in concordance with our predictions. A lower concordance group (n = 21) was defined as those patients who were not treated with the top drug from our prediction report or for whom our top drug made up less than 25% of the drug treatments they received. We found striking differences between complete remission rate (CRR), overall response rate (ORR), and median survival in the two concordance groups (57 % high vs. 14 % low for CRR with $p < 0.001$; 79% high vs. 57 % low for ORR with $p = 0.08$; 128 days high vs. 50 days low for median survival with $p < 0.001$; 224 days high vs. 50 days low for median survival adjusted for censoring with $p < 0.001$). Thus, peripheral T-cell lymphoma patients who received drugs predicted to be highly effective by our AI algorithms experienced dramatically better clinical outcomes than those who did not. This difference indicates that our predictive AI models are successfully identifying effective drugs and are therefore likely to be contributing to better outcomes in T-cell lymphoma patients.

Thoughts on the presentation

Exciting to see that there is a difference in overall survival if you use the recommended drugs vs not using those drugs

I had not had this experience otherwise I would be excited about this data. Maybe I need to just keep using Imprimed to see the difference in more patients.

I am hoping showing the difference between dogs treated with recommended drug vs historical treatment will influence more owners and clinicians to use this tool.

The evaluation of T-cell lymphoma is very important and certainly makes ImpriMed's AI very attractive for patients diagnosed with T-cell LSA.

This is the number 1 question I get when discussing Imprimed's assay with one of the groups I locum at, so it's exciting to finally be able to see statistical support for a change in outcome based on Imprimed results. I do think that it would be interesting to know if the response rates and survival times differed in naive vs. refractory patients, or whether receiving additional rescue therapy afterwards made any difference.

The T cell evaluation is very interesting and should prompt us to use this test more in the naive setting.

Really interesting. This is exactly what we would hope for from a well functioning AI program like this. Exciting start!

Further supports utilizing in naive setting to help with initial drug selection to allow for a potentially improved clinical outcome.

Questions (concerns and clarifications)

The lower concordance group has a very low survival time even for T cell. Did those dogs have more aggressive features of their lymphoma on flow? Did both groups have similar flow characteristics?

Encouraging data provided but need details regarding populations to see if similar stage, flow etc. or naive vs resistant

Can you provide more stage /immunophenotyping information for the two groups? Is there any suggestion that one of the groups could have had different prognostic factors at baseline, aside from the Imprimed assay results /drug selection? Could that have impacted the clinician's decision to use or not use the recommended drug?

I agree with all the questions. What other associations are present that could also explain the difference in survival? Those will be need to be carefully considered. What about clinical stage. Ie were they GI (stage 5), or 3,4 and were they substage a or b.

An analysis of the factors that differ between our low concordance and high concordance groups is in progress. We are compiling extensive data on the patients for the analysis including stage, substage, grade, flow cytometry, breed, and clinical history (naive, resistant, relapsed, etc.). Look for more results at the VCS Mid-Year Conference and likely in a publication within a few months.

I also think that looking at the absolute numbers, the survival times for both groups are surprisingly short (even for T-cell).

Yes, the survival of the low concordance group is clearly low, and we're excited to find explanatory factors that could help improve future care. This analysis is in progress. The median survival of the high concordance group is 224 days from our Kaplan-Meier analysis which is within the ballpark of values reported in the literature. This value is higher than the value of 204 days for all patients we analyzed. The median survival in this study is not tightly constrained because of relatively short follow-up times: there is a median observation duration of 150 days for censored patients. We also have a small number of patients who began treatment before time zero in our Kaplan-Meier analysis, and this will cause the median survival to go down to some extent.

It may be a small cohort that did not achieve significance but was there a difference between the patients that had drug predictions prior to treatment and those that received predictions during treatment? In other words, did prior treatment predict potential response and is there evidence that using the predicted model recommendations leads to better outcomes?

Most of our oncologists ordered predictions prior to treatment, so we probably won't have enough patients in this study to compare outcomes in those with predictions before treatment and those with predictions during the course of treatment, although we will conduct this analysis.

Not exactly pertaining to this information but… We noticed that drugs that we do not commonly use for lymphoma (mitoxantrone) frequently are the highest listed predicted drug for a relapsed lymphoma patient. Is there any correlation with the number of dogs receiving this drug and the predicted responses for another patient?

We have not found a correlation between a low number of dogs receiving a particular treatment in our training set and a preponderance of high prediction scores. We train our models to have balanced sensitivity and specificity, and, generally speaking, this training process tends to prevent one of the models from dominating the report with high prediction scores. Thank you for flagging high mitoxantrone prediction scores in relapsed patients. We will look for statistical support of this phenomenon to see if this presents a performance issue.

Did there seem to be a supportive pattern for front line drug choice in T-cell lymphomas that can be used to support therapy options for when owners choose not to submit?

In further studying these results, we may find general patterns that would enable you to rationally optimize first-line therapy without the need for an ImpriMed test. Whether or not that would be revealed publicly is a commercial decision, but at ImpriMed we love to give back to the oncology community that supports us.

What was the reason for why the low concordance group didn't follow the AI recommendations? Could this have introduced bias?

Although we cannot fully analyze doctors' decision-making process, we are currently doing a more detailed analysis to determine factors that may have caused low concordance.

Any experience of what was discussed.

I have recommended and used Imprimed several times as a locum or recommended to vets so I have not seen many dogs finish the protocols, but overall I have seen dogs respond to the drugs similar to what is predicted on the report.

Initially used imprimed a lot and was excited to get away from CHOP but in the end,

no improvement and cycled through all the typical drugs. I am not seeing differences in outcomes. Considering using it in refractory cases to see if previously used drugs could be considered and if that profile has changed? We did perform flow on a patient initially and then after several therapies and there were differences in profile and type of lymphoma (was still B cell, initially cd21 + and then cd79a+ primarily).

I discuss Imprimed with every newly diagnosed lymphoma and relapsed lymphoma. Finances tend to be the limiting factor

This is convincing enough that I would use this for T-cell LSA diagnosed patients if clients could afford the expense. We need all the help we can get with better outcomes for T-cell patients.

I've recommended it several times (although it seems few clients have the money /really understand how it can help them) and feel that it's very helpful in making treatment decisions for atypical cases or those where we don't have any great options. It's nice to have more evidence for recommending it in T-cell cases!

I discuss it with every new lymphoma and it seems to just come down to money available for diagnostics/ prognostic information.

We have used Imprimed recently and found results that were surprising and useful in managing a couple of refractory cases.

I have been discussing it with every new lymphoma and strongly recommending it for those that do not achieve remission early in protocol or that fail the protocol if they declined in the naive setting for both my B and T-cells. I have found at times, roughly 1/4 of my patients, that the drugs predicted fail quickly or do not work. Though it does appear to be predominately in those that I have utilized in the rescue/relapse setting.

I haven't used this yet, but would be intrigued to use it with a motivated client.

Thoughts for the future
Can you look further into the results to give predictions for LOPP or MOPP like you do for CHOP? It would be great especially for T cell if we knew which protocol to pick at the beginning.

I would love to see multi-drug prediction models vs single agent predictions

The general consensus for lymphoma chemotherapy (at least for first line therapy) is that multidrug protocols are more effective than single agent therapy. Is there a way to use the AI modeling to evaluate combination therapy?

For our T-cell patients, small sample sizes have precluded the creation of multiple different combination therapy models in the past but our dataset is growing rapidly and we will be able to release these kinds of models soon.

Naive vs resistant comparison? can we go back to previously used drugs since there are so few?

The question of whether our AI recommended previously administered drugs with a positive subsequent outcome in this T-cell lymphoma study population hasn't been investigated yet, but now we know that you are interested we will study this! With our canine lymphoma service, we have seen patients who have benefitted from drugs predicted to be effective in the future that had already been used in the past.

I think it has been brought up before but is ImpriMed gaining evidence that this model is better for deciding treatment for the typical DLBCL? For relapse only? Both naïve and relapse cases?

In cross validation studies, we've found that patients in our database (mostly DLBCL patients) who received our top drug prediction exhibited a positive clinical response 20% more frequently than the population as a whole. This effect was seen in both naive and relapsed patients. We've also done a treatment concordance study similar the one just presented for T-cell lymphoma but for relapsed B-cell lymphoma patients. The results, which were impressive, were presented at last year's VCS Mid-Year Conference. In this study, the predictions were generated retrospectively using our most accurate AI models, so it did not have the potential to measure the interaction between the clinician and the AI. We are repeating this relapsed BCL study now with predictions that were generated prospectively during the course of cancer care.

A prospective study would be so useful here. It would be exciting to see a group of practitioners partner with you in a grant application to understand the real impact here.

Yes, we agree. Even though our current study collected concordance and clinical outcome data prospectively and analyzed it retrospectively, a controlled prospective

clinical trial will be more impactful. We are investigating several opportunities to partner with an oncology team to conduct such a prospective clinical trial.

Have they looked at how their prediction models changed between presentation and relapse for these patients (or B-cell patients)?

We have these data and currently working on a systematic study. Thanks for the suggestion!

Updates on the Trials and lookin ahead to future applications of ECI

ELIAS is wrapping up the final details of the ECI-OSA-04 clinical trial and expects to make its regulatory submission this month. As a next step, we are continuing to evaluate the ECI treatment in other disease settings through collaborations with veterinary oncologists. A pilot study is currently underway to evaluate safety and progression-free survival in canine lymphoma patients who achieve remission using a combination chemotherapy followed by ECI. A second pilot study will begin in mid-2023 to evaluate safety and progression-free survival in canine appendicular osteosarcoma where limb-sparing surgery is medically indicated. These single-site pilot studies are designed to enroll a minimum of 10 patients and the data collected in these studies will be used to inform the design of future clinical trials and product development.
Finally, ELIAS has formally launched its long-term patient registry which will collect both long-term survival and quality of life data on dogs who participated in our clinical trials (treatment and control arms) or received the ECI treatment outside of clinical trials. Enrollment in the registry is done through informed consent and data collection begins after completion of trial participation or completion of treatment if not enrolled in a clinical trial. Early response rates from pet owners has been high, with very few pet owners opting out. We urge practitioners to encourage pet owners to participate in the registry.

Thoughts on the presentation

Excited to see more uses for ECI technology and interested to see how pet owners believed their dog did with the treatment.

Broader application for more diseases and more patients is encouraging that we may have another therapy available to us and hopefully the availability to clients will be improved over the few centers in the south. Data will help us get behind the treatment and as a result we are more likely to encourage clients to pursue this therapy.

I am curious to know which cancers are going to be investigated? Are they going to collect data for individual tumors before moving on to the next? Where are the clinical trial sites?

We are looking at OSA limb spare and after chemo in lymphoma at the University of Missouri. We also have interest HSA and TCC. TCC in particular looks interesting as it is a less aggressive cancer and surgical removal of the tumor is standard of care. For more aggressive tumors (eg, HSA) where time is of the essence, a combination approach may be needed. Some ideas being considered would be ECI after doxorubicin or paired with another immunotherapy.

I like that Elias is taking a measured approach to pilot trials in other types of cancer. Ongoing database collection will also help to shore up the evidence behind ECI treatments.

Of all the novel therapies /immunotherapies that have come out in the past decade, I do feel that Elias has taken the most rigorous approach with regards to data collection and publishing their results. I've been eagerly anticipating the results of this trial and I'm glad to hear they're planning on pursuing additional pilot studies with different tumor types; I'd heard of a few isolated non-OSA tumors being treated with their protocol and I was concerned about the difficulties discussing n=1 cases with clients so it's nice to see a company preempt that concern for once!

We try hard to "follow the science path". The data is the data and we try and work with that like it or not.

The pilot trials will be very interesting but limb spare still seems a rare procedure even if medically indicated. We are doing much more stereotactic radiation therapy for these patients at multiple locations if that is an avenue worth looking into.

I agree that limb spare is less common, however, the need for the tissue for the vaccines presents a challenge in the radiation setting. The limb spare approach makes sense (trial is at Missouri in full disclosure). Appreciate ELIAS' openness with their data and their responsiveness to the community. Interested to hear more about the oncolytic virus they were pursuing.

Initial studies on the oncolytic virus are still ~12 months away. In the meantime, we are looking at other possible combinations in the limb spare study. We are also looking at a variety of potential therapeutic combinations that could be expected to increase the number of immunotherapy responders.

I agree that it would be good to consider ECI with stereotactic RT. I would find this avenue much more applicable given that limb spare surgery is a treatment that is offered at so few facilities.

Limb spare aside, SRT and ECI can be a potential combination and has been used in human medicine to improve outcomes and responses. The timing of these therapies and collection of tissue are the keys.

The patient registry is intriguing as it could help to gain insight into who the long term responders are and potentially help us identify why.

Questions (concerns and clarifications)

Has Elias published more data on the OSA trial? I heard it wrapped up a while ago but have not seen the article and am very interested to read it.
For the long-term survival data, I would recommend asking the pet owners questions which help tease out what QOL looks like to them because it seems so different between different pet owners. It would also be interesting to see how many dogs died from the disease vs euthanized. Basically, I would be interested to see when most of these pet owners euthanized the dog. Was it when the disease metastasized or when the dog could no longer walk, or something like that. I think some of the trouble with veterinary studies is that pet owners euthanize at different time points vs in people you die naturally from the disease.

It has taken an unexpected amount of time to "herd all the cats" for the final study report. ELIAS has not completed their regulatory submission and is planning to submit the report for evaluation at USDA this month (April 2023). Study results will be released after the USDA's review.
"I think some of the trouble with veterinary studies is that pet owners euthanize at different time points vs in people you die naturally from the disease."
Regarding the comment above: We agree. We found this to be one of the more challenging issues dealt with during our trial. At times, the clinician may have felt (or the owner) that euthanasia at first sign of progressive disease was the best course or similarly administering contraindicated glucocorticoids out of caution as opposed to in response to concerning CRS-like signs. ELIAS is making every effort to further educate and discuss with veterinarians how these immunotherapies manifest themselves, their particular signs, and the management of treated animals to achieve the best outcomes possible.

The idea of less tissue is a great one, or even cytology? aspirate? The registry is a great initiative by the company to provide the end user, the client, an opportunity to provide feedback . It's their opinion, combined with the data that will give the best outcome / results of the treatment.

The collection of source antigen cancer tissue is obviously paramount for vaccine manufacturing. Tissue aspirate may not provide sufficient cells to start the process. ELIAS' has successfully grown out small samples, but this creates a delay in the start of therapy which may be problematic with aggressive cancers.

Are there new statistics on the percentage of patients that respond? Will there be a separate arm looking at the combination of chemotherapy with immunotherapy? Is the company looking at ways to create the vaccine with a smaller amount of tissue so that we may treat patients that elect to pursue SRT vs amputation?

In our first clinical trial, about 30% of dog had a clinically relevant response (i.e., improved longevity, cancer in prolonged remission). This percentage is very similar to what has been seen in humans using this therapy (Sloan 2000, Chang 2003). However, this "hit rate" will vary as personal variables (genetics, health, immune system, etc) for each patient can have a significant influence of success. We have also found that while the procedures followed to administer ECI are straight forward (e.g., intradermal injections), the technical skill or technique used by medical professional is important.
We have demonstrated ECI's MOA in a prior study and have confidence that our

adoptive T cell therapy is biologically doing what is intended. However as noted, what we are striving for is a jump in the responder rate. This is an area of great interest to us and combination therapies are and will be looked at. We have 2 studies planned: 1) ECI after L-CHO chemotherapy, and 2) limb spare where a novel adjuvant may be included to improve the immune response rate to ECI.
In some non trial cases, veterinarians have combined chemotherapy with ECI. Radiotherapy combinations can similarly be done if appropriate and directed by the clinician. The way it has been used is to first surgically harvest the cancer tissue, then vaccines are manufactured and stored in -80C until needed over a period not to exceed 4 months. During that period, the clinician may elect to do SRT or chemotherapy and afterwards initiate the ECI protocol. We only have anecdotal stories of results with these combinations ranging from long term success (complete remission) to limited response. As only a few of these cases have occurred to date, information regarding differences in responder rates is not available.

Who is providing the data for the long-term follow up for the database? Does this come directly from the owner or from the clinicians?

This data comes from the owners. On the informed consent forms, pet owners opt-in to participate in the Long Term Patient Registry, which is in the form of an online survey. After completion of treatment, the survey is sent to each pet owner every six months while the dog is living.

Depending on what kind of detail is being collected, I am a little concerned over the potential accuracy if pet owners are supplying the information. What about if the patients have received other medical therapies following ECI – is there collection of this information as this may influence outcomes?

The registry survey asks pet owners for information on disease progression, additional diagnoses (cancer and otherwise), and quality-of-life using a condensed version of the HHHHHMM Quality of Life Scale. We use the HHHHHMM Quality of Life Scale form throughout treatment, so pet owners are familiar with the type of information we're looking for prior to responding to the registry. Finally, we request permission from the pet owner to contact the treating veterinarian in the event of death/euthanasia so that we may obtain more information about the circumstances. We acknowledge there will be subjectivity in the responses from pet owners, but we have taken great care in developing the questions to reduce this as much as possible. We also believe that when combined with other objective data, such as breed, age, tumor location and grade, we will be able to identify trends that will support future development of our therapies.

Maybe just some clarity on the goals of the registry- Is this (thought to be) clinically objective data and who is reporting?

We do not expect the information to be clinically objective since pet owners are providing the information, but we have developed the survey questions using industry best practices to reduce bias as much as possible. The primary goals of the registry are pharmacovigilance and to obtain a general understanding of the quality of life and ultimate fate of these patients after treatment. Our hope is that we will also be able to identify characteristics of those patients which fully respond to the therapy.

I would be interested regarding what parameters the are using that medically indicate a limb sparing procedure. If data on follow up therapy is also collected, would they work to include information such as dosing amount, frequency, etc. This can be important in practice when deciding on treatment protocols as few studies really give this information when the patients are from multiple facilities.

We are working closely with Dr. Jeff Bryan (DACVIM-O) and surgical oncologist Dr. Megan Mickelson (DACVIM-SA) to implement a clear set of limb sparing parameters in this study protocol. The final study materials will clearly describe these requirements and will be shared.
Other treatments the veterinarian deems appropriate are allowed starting 30 days after the final ECI protocol visit. During the protocol, immunosuppressants are not allowed and ELIAS recommends avoiding the use of immunosuppressive drugs for as long as feasible afterwards. To your point, it would be of value to collect information on any follow-on treatments provided to patients, however those dogs are seen off trial privately and not required to be reported to us. Although data collection from pet owners in a long term patient registry is not as rigorous as that collected from veterinarians in a randomized controlled clinical trial, it can provide useful insights into the real-world uses and experiences associated with this therapy.

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