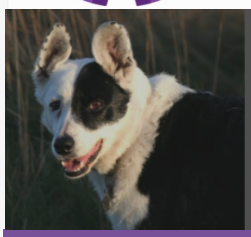
ONCOALESCE



Monograph

#2 August 2022

Greetings!

Dear Shah,

Cancer - Climbing the mountain together!

Welcome to the second edition of the Oncoalesce Monograph.

I hope you managed to read the first Monograph in June? If so, you know this is not a brief commercial summary. The OM takes an in-depth look at the new technologies within oncology, employs a panel of oncologists to challenge them, and finally provides the answers direct from the company to some of the questions you have been dying to ask.

This monograph will take time to read, but it is possibly one of the most comprehensive and useful documents available to you as a practicing oncologist. At least that is my aim.

Please grab a glass (or 2 - it is very very detailed), settle down and enjoy the read, as we start to climb the mountain together.

Tariq

Photo: Summit of Mount Toubkal 2022, Morocco. Highest mountain in North Africa, 36th in the world (by prominence). Summited July 21, 2022 together with my 14 yr old daughter Isabella. Scroll to the end for proof!

Email me!

Background (read this once - if you didn't read it last time)

Due to an increasingly hectic workday, Oncologists have difficulty keeping up with all of the new developments. They can struggle to reconcile what a company may be promoting when compared to the limited data available. They may want to try

something new but don't have the time to work out the logistics, or the specific benefits of adjusting their approach. "There is no data" is a common refrain when in actual fact there IS data, we just don't know it yet. Trust is a valuable thing and when looking for supportive information we tend to trust our friends and our peers the most.

Oncoalesce brings together oncology companies (pharma, diagnostics, and services) with a panel of oncologists. They will meet remotely on a regular basis every two months to discuss how the profession can best adopt and grow the new products that industry is increasingly introducing to the world of veterinary oncology. The panel consists of open-minded clinical oncologists who are prepared to ask: "How SHOULD we use this product?". The companies and the panel explore the claims, compare experiences, ask questions, and come to a consensus of how that product may best be utilized to benefit the patients in our care. Following the meeting, the minutes are transcribed into a succinct monograph that outlines the consensus and provides guidelines for your colleagues. Finally, they are shared freely with all oncologists in an easily digestible format to help guide your own clinical approach.

The aims of Oncoalesce:
1 Coalesce – to come together to form one body or whole: The coalition of veterinary oncology – working together in a partnership to achieve a common goal.
2 To improve the communication understanding and adoption of new technologies within veterinary oncology.
3 To accelerate the use of these technologies to improve the lives of our patients and to encourage the introduction of other companies into the oncology arena.

The following notes have been taken directly from data presented to the panel of oncologists in the Oncoalesce meeting #2. 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.

Panel:
- Dr. Jeff Bryan - University of Missouri
- Dr. Kim Cronin - MA Veterinary referral hospital
- Dr. Pamela Jones - QBiotics
- Dr. Kendra Lyons - In-between
- Dr. Melissa Parsons-Doherty – Pearland Animal Cancer and Referral Center
- Dr. Erin Roof – Animal Cancer Care Clinic
- Dr. Aarti Sabhlok – Ethos Pet Emergency and Specialty Ctr Marin
- Dr. Andrew Vaughan – Las Vegas Veterinary Specialty Center
- Dr. Rachel Venable - Pet Cancer Care Consulting

Companies
- Elias Animal Health
- ImpriMed
- Canine Biologics
- Elanco
- Vidium Animal Health
- Jaguar Animal Health
- Nutramax

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.

Elanco were not present for this meeting due to timing conflicts. However they are aware that oncologists are very keen to hear about supply updates and are happy to release the following:

As a valued Tanovea® (rabacfosadine for injection) customer, this communication is to inform you that Tanovea supply has normalized, allowing you to resume treating newly diagnosed dogs.

Thank you for your patience and understanding as our team worked diligently to manage limited inventory and normalize supply. Because of you, we were able to avoid a stock-out and ensure that all existing Tanovea patients could complete their course of treatment.
Additionally, Tanovea is currently going through a minor packaging change. This change removes the VetDC logo, reflecting Elanco's acquisition of Tanovea from VetDC in 2021. Tanovea 4-packs are currently shipping with the new packaging and 10-packs will follow in October.
I want to express gratitude for your support of Tanovea. As always, our specialty sales force and consulting veterinarians are available to support you. If you have any questions, please do not hesitate to reach out to your Elanco sales representative or contact Elanco customer service at 1-877-352-6261.
Sincerely,

Julia Loew
Senior Vice President Elanco Animal Health

The Discussions

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

Jaguar Animal Health

Antimicrobial Stewardship.

Jaguar Animal Health conducted a survey online in 2021 to gain understanding of the management of chemotherapy induced diarrhea from the clinicians' point of view. They found that 55% of GPs (n=87), and 62% of oncologists (n=15) prescribed metronidazole to treat CID. Now that Canaleivia CA-1 is an effective, well tolerated, conditionally licensed treatment for CID, Jaguar Animal Health presented some thoughts from the profession on antimicrobial stewardship.

The problem…
"As much as 50% of antibiotics prescribed by veterinarians for pets may not be needed, according to a 2015 report from an American Veterinary Medical Association task force on antimicrobial stewardship. At a veterinary teaching hospital, 38% of canine antibiotics prescribed over a 12-month period were for dogs with no infections, a study published in 2011 in the Journal of Small Animal Practice found. And in a study published this year in the Veterinary and Animal Science, almost 90% of students surveyed at a major veterinary medical center had not read or rarely read the antimicrobial resistance guidelines for judicious use created by the American Veterinary Medical Association and U.S. Food and Drug Administration"

Taken from the AVMA Policies:

Antimicrobial stewardship for veterinarians defined:
Antimicrobial stewardship refers to the actions that veterinarians take individually and as a profession to preserve the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public, and environmental health.
Core principles of antimicrobial stewardship in veterinary medicine:
Antimicrobial stewardship involves maintaining animal health and welfare by implementing a variety of preventive and management strategies to prevent common diseases; using an evidence-based approach in making decisions to use antimicrobial drugs; and then using antimicrobials judiciously, sparingly, and with continual evaluation of the outcomes of therapy, respecting the client's available resources.

Thoughts on the presentation:
I do think that antibiotic stewardship is important to consider given that we are now dealing with so many diseases that are becoming antibiotic resistant. However, while this is a good argument to use the Canalevia-CA1, it is only a small part to me of the reason to use this drug. I would want to use it if it is effective for diarrhea particularly in those dogs that are resistant to metronidazole.
Metronidazole and diarrhea is an easy target for antibiotic stewardship, but there are other equally common situations where the same issues arise (pyoderma, presumptive UTIs, snotty eyes and snotty noses). It's certainly a consideration for chemotherapy-induced diarrhea, and certainly based on the mechanism of action

could be a preferred agent for that subset of cases, but until we have more experience with the drug I'm not sure it's a driving force.

We certainly agree that antibiotic stewardship is a significant consideration when selecting a CID treatment but also understand that the safety and efficacy profile established in a clinical setting will be the main drivers of treatment selection. Based on our conditional approval, and the safety profiles of both drugs, we suggest prescribing Canalevia-CA1 as a first line treatment for CID in dogs, not limited to dogs refractory to metronidazole. The underlying cause of CID is non-infectious and an antiprotozoal/antibiotic may not be an ideal choice for treatment. Canalevia-CA1 has established safety and efficacy data in secretory diarrhea in dogs

I think antibiotic stewardship is an important topic and it has certainly been addressed by groups larger than us. I think its use for CID is good because of mode of action but not sure that antibiotic stewardship will change the thought of using a cheaper, historical use perspective.

Vets are bad about antibiotic stewardship. They are going to reach for what is cheap and effective. The drug is going to need to work really well for vets to change to it from metronidazole.

Cost can be an important consideration for treatment selection. However, our market research indicates that there is significant dissatisfaction among pet owners and vets with the success rate of metronidazole treatment in the CID population. There are also concerns with the side effects often seen with long term and/or high dose administration of metronidazole. The safety and tolerability of Canalevia-CA1 make it an excellent choice to manage CID in dogs without further complicating the host of symptoms a dog undergoing chemotherapy may experience.

Questions (concerns and clarification):
Do we have any reports of Canalevia being effective for more severe /hemorrhagic diarrhea as well?

The cause of hemorrhage should be addressed and resolved before a patient with CID is treated with Canalevia-CA1. There are no studies or reports evaluating the effectiveness of Canalevia-CA1 in patients with hemorrhagic diarrhea

The inability to get samples in veterinarians' hands is a big challenge given the price point.

We understand the importance of samples, however Canalevia-CA1 is only available in a 60-count dispensing size bottle. Smaller sample size packaging is not currently available. As a small company, it is not feasible to navigate all of the individual state pharmacy laws related to shipping a sample prescription product from state to state

Any Experiences with this or similar offerings:
I'm not even sure our hospital carries it yet...

It is available to order!

I tried my first case of a Dobie with chronic diarrhea and was optimistic. He is on metronomic chemotherapy for STS. Unfortunately, it did not work..... on to tylosin.

It is unfortunate your experience in this dog was not positive. We are confident your clinical experience will be more positive as the number of cases treated for CID with Canalevia-CA1 grows

I've used it now in 4 patients- 2 worked very well, 1 of which the client did not want to utilize any antibiotics for diarrhea cases. One was refractory but the patient was refractory to all the other drugs as well (metro/ tylosin/Imodium/propectalin/ proviable/rx clay etc.)

We are pleased you had a positive experience in these early days and with a relatively small population. We look forward to your ongoing feedback as your clinical experience grows. Refractory cases across a wide range of treatment approaches, while disappointing, are not unexpected

Thoughts for the future
I would like to get more experience with this drug so that I can see if it works in my patients and what the client experience is using this drug.
The only drawback is that this is likely going to be a drug that is going to be available only through specialty practices due to the fact that it is conditionally licensed for chemotherapy induced diarrhea and that it may be difficult for clients to keep returning to our practice to get more of the drug. I know that you can script it out before they need it but given the cost that you would likely only want to send home smaller supplies.

Canalevia-CA1 is available to all licensed veterinarians in the US from multiple National and Regional distributors. There is no restriction to just specialty

practices. Clinics that refer patients to a specialty clinic can order Canalevia-CA1 for the dog with CID diarrhea that returns to them for treatment of CID

The cost is a pretty big barrier, especially if we're using it as a prophylactic. I usually send my clients home with a small supply of metronidazole for use "as needed" in case there's diarrhea at 2 AM on a Sunday and all the ERs are on diversion; not sure I can justify the cost for the same doses of Canalevia

Canalevia-CA1 is not approved for prophylactic use. Canalevia-CA1 should be prescribed "as needed" should CID develop. We understand that the cost may push some patients/clients away from filling a prescription, however we would like to encourage the vet to explain that there is an alternative to an antibiotic/antiprotozoal for dogs with CID

I use metronidazole like other panel members and so the cost is going to be a barrier until we know it really works and client are willing to pay more for it like cerenia for vomiting

I hope this works just as well as metronidazole and would consider a switch to sending this home on initial chemotherapy day if it proves effective.

The general feedback we are getting from Oncologists and GPs is that they do not expect the price point to be a barrier to prescribing Canalevia-CA1. Due in part to the low relative cost of Canalevia-CA1 to the overall chemotherapy treatment expense and the potential added cost of supportive care (i.e. rehydration therapy, ER visit, return visit to the hospital, mishap clean up, etc.

Sulforaphane content within broccoli is also limited by age, cultivation, growing conditions, and cooking[3,4].
The level of sulforaphane in sprouts and mature plants varies, and consuming mature broccoli or sprouts would require excessive quantities to receive the benefits of its oncological activity.
Broccoli seed contains the most significant amount of glucoraphanin; however, it also contains erucic acid, which is toxic in cattle and rats[5]. Therefore, direct seed consumption is not viable. Instead, sulforaphane is most efficiently delivered through seed extraction and produced as supplements, and depending on the quality of the product utilized in the production of the supplement, it can ensure a stabilized, consistent source[6].

Mode of Action

Sulforaphane is an unstable molecule that typically degrades within several hours after initiation. Glucoraphanin, a precursor of sulforaphane, is found in broccoli and other cruciferous plants in addition to myrosinase, a ß-thioglucosidase enzyme. Glucoraphanin and myrosinase are sequestered within different plant tissue structures preventing interaction[7].
Through crushing the plant tissues, such as chewing or chopping, the myrosinase acts on the glucoraphanin, converting it, through a hydrolysis reaction, into sulforaphane[3]. Without myrosinase, glucoraphanin remains inactive; however, humans and canines may possess gut microflora capable of producing some myrosinase[8].
Once released within the body, Sulforaphane elevates cytoprotective enzymes[9]. Sulforaphane's primary cytoprotective effect occurs through activating the nuclear factor erythroid-derived 2-like 2 (Nrf2) protein into triggering the production of Phase-2 detoxification enzymes, thereby reducing oxidative stress[9,10].
Oxidative stress is responsible for destroying large biomolecules, such as lipids, proteins, and DNA, leading to poor health outcomes throughout the body[3,11]. Research on sulforaphane has shown it as the most cited natural product activator of Nrf2, which reduces oxidative stress[3].
Sulforaphane fosters detoxification of environmental toxins, which can be ingested orally, through the skin, or by breathing[12]. Research studies have specifically demonstrated the reduction of benzene, a known carcinogen often found in herbicides and air pollution, after introducing sulforaphane into the diet[12,13].
Following a decade of research, Nutramax Laboratories developed Avmacol® and Avmacol® Extra Strength (with maitake mushroom extract), a stable source of sulforaphane. Upon its release, the Avmacol® brand has been used extensively in sulforaphane human clinical trials. More recently, Nutramax Laboratories has launched Avmaquin™ to promote sulforaphane production in dogs. Compared to adding broccoli to a pets' diet, Avmaquin provides a stable, consistent, convenient and palatable source of sulforaphane, using a reliable process using a validated processing method supported by continual batch analysis.
Sulforaphane Research
Sulforaphane has been the topic of extensive global research. Over 2,600 published papers have been indexed on The National Institutes of Health, Library of Medicine repository website, https://pubmed.ncbi.nlm.nih.gov/. Currently, 90 in-progress sulforaphane clinical trials are featured on https://clinicaltrials.gov/.

Bioavailability in Canines

Although canine research is limited there are studies showing sulforaphane's bioavailability in healthy dogs[14]. In addition, pharmacodynamic and pharmacokinetic properties were demonstrated in oral administration of Avmaquin™—which contains glucoraphanin and active myrosinase enzyme—through increased sulforaphane plasma levels in dogs, and by inducing the expression of Phase 2 detoxifying enzymes[15]. Results from this Avmaquin™ study show a higher total peak plasma compared to studies of other sulforaphane supplements[16].

Transitional Cell Carcinoma

After releasing in the body, sulforaphane has been shown to elevate cytoprotective enzymes by activating the Nrf2 protein, thereby reducing oxidative stress[3,9,10]. In addition, research has demonstrated sulforaphane's effect on carcinogen reduction of environmental toxins, such as benzene and herbicides, which have shown to be a factor in transitional cell carcinoma (TCC) in both humans and dogs[13,14,17,18].
Studies in human cells and rats have shown that sulforaphane can potentially improve or prevent instances of TCC[19-24]. TCC is the most common cancer of the canine urinary tract[25,26]. Although there have been no specific sulforaphane studies in dogs, a study of Scottish Terriers demonstrated that consuming vegetables at least three times per week reduced bladder disease by at least 70%[12]. However, research on healthy dogs showed that sulforaphane was related to a decrease in histone deacetylase activity[14].

Oncology Studies in Canines

In a study of dogs diagnosed with multicentric lymphoma, treatment with sulforaphane was associated with major changes in the proteome of neoplastic lymphocytes[27]. In other canine research, *in vitro,* and *in vivo* studies indicated modest protection against osteosarcoma and, when used with doxorubicin,

provided a significant protective effect against cancer and the stress caused by doxorubicin[10].

Oncology and Allergy Studies in Humans

Oncology research utilizing sulforaphane has studied breast cancer[1,4,28], and head and neck squamous cell carcinoma[13]. Avmacol® has been used in studies on tobacco-related cancer and detoxification of benzene[29], autism spectrum disorder[30,31], and allergic rhinitis[32].

Conclusion

Avmacol® is the most widely used sulforaphane supplement in clinical trial research. In addition, human and canine researchers continue to explore the potential benefits of sulforaphane related to various health conditions beyond those examined here.

Currently, there are 18 NIH clinical trials registered using Avmacol®. Eleven have been completed, and seven are still active. These studies have included the following topics:

- Schizophrenia (3)
- Autism (6)
- Toxins and Chemoprotection (5)
- Frontal Lobe Injury
- Fragile X Tremor/Ataxia
- Allergic Rhinitis
- H. Pylori/Stomach

When faced with today's environmental threats, a clinically researched sulforaphane supplement is strategic in supporting overall health in humans and their pets. As sulforaphane research continues to become more prevalent in canine oncology medicine, additional studies to assess the potential benefits of sulforaphane are highly warranted.

The references from the Nutramax presentation are available on request - just too many to put into this document.

Thoughts on the presentation:

I thought that the presentation was concise and laid out the science behind using this type of a product as well as the research that has been done in humans. It appears as this supplement can be used to prevent certain types of cancer, improve the response to therapy for certain type of cancer and also alleviate secondary effects if doxorubicin.

Very interesting, and the biologic basis is there, but studies to demonstrate efficacy for preventing cancer require massive enrollment and lifetime monitoring essentially unheard of in veterinary medicine. I worry that this product will be associated with big claims and we won't ever see the data to back those claims up. Given the original cruciferous vegetable link was in TCC, I would consider using this in TCC patients but hesitant in other tumor types.

Interesting science behind the drug and certainly good demonstration of use in humans. Preventative studies were mentioned and I am not sure a claim of efficacy for preventing cancer this large can be made as of yet.

Interesting presentation

I had attended the presentation at ACVIM. Interesting. Anything we can do to support the patient, especially if it is a supplement that can help with chemo side effects? some clients will appreciate the option.

Same thoughts as above.

The nutraceutical position is enviable because the barrier to broad use is lower.

Questions (concerns and clarification)

Given that this is somewhat of a chemopreventative agent, it this something that we should be considering to start all patients on early in life or possibly just breeds at high risk?

Do we know if there are any interactions that may occur with other supplements that would chance the efficacy of this supplement?

Avmaquin is a very good option to use on high-risk breeds and early on as a preventative. We are not aware of any interactions with other supplements that would negatively impact the efficacy of Avmaquin.

Does Avmacol guarantee the level of sulforaphane in the supplement? There is little to no regulation in the US on supplements and studies have found many are mostly rice protein, so it would be beneficial to know how much of the active ingredient is in the supplement and if that is regulated by the company. Also, what is the recommended use for Avmacol? They cite many studies on sulforaphane and ongoing studies, but never really say when to use it in dogs.

Nutramax guarantees the level of sulforaphane (and all other ingredients in Avmaquin and all Nutramax products) Please visit nutramaxlabs.com to learn more about our quality standards. Avmaquin is positioned to be used in combination with traditional modalities in dogs with TCC. In addition oncologists are looking at using

Avmaquin for dogs when the pet owners decide not to pursue traditional treatment protocols.

Negative interactions (chemoprotection from chemotherapy) is a concern and any data that can be highlighted would be appreciated.

Any Experiences with this or similar offerings
I will say I sent a client to their website for more information on this product yesterday. This is a particular client who evaluates every food substance that her dog ingests.

I was aware of this early on and the potential appears substantial

Thoughts for the future
Looking at chemopreventative strategies for canine (and human) patients is something that is worthwhile particularly if we can give it early and avoid having to treat for cancer. It would be nice to ultimately have these types of supplements incorporated into a diet if it is possible so that clients do not have to remember to give a separate supplement particularly if it is for chemoprevention.

I agree re: the diet, is this something that Canine Biologics have considered /already incorporated in their product?

I'd really like a prospective trial (similar to the Denamarin- CCNU hepatotox study) that showed some level of reduced oxidative stress in patients on chemotherapy (maybe with vinblastine and TCC).

It would be great to have a study showing Avmacol improved outcome in dogs with cancer specifically TCC, LSA, and OSA (mentions sulforaphane has some effect on these cancers).

ELIAS®
ANIMAL HEALTH

ELIAS Animal Health – How do we know Elias Adoptive T-cell therapy is working?

Dr. Noe Reyes reported on a study conducted to confirm ECI's mechanism of action in canines undergoing the ELIAS Cancer Immunotherapy (ECI) for appendicular osteosarcoma. The cytokine expression and cytotoxicity data was presented at the 2022 ACVIM conference in Austin, TX. The study was conducted at Charles River Discovery Research Services, Freiburg, Germany.

ECI adoptive T cell therapy is potentially a "platform technology" able to treat a variety of cancer types. This has been evidenced in pre-clinical rodent studies (melanoma), human clinical trials (renal cell carcinoma, malignant glioma), and in canines (osteosarcoma). Given ECI's good safety profile to date in over 100 treated dogs, ELIAS will support clinicians' who may wish to apply this therapy to other cancer types where a suitable sample of cancer tissue can be obtained.

The data presented for Oncoalesce was accepted by USDA-CVB as confirming ECI's MOA in canines. Specifically, that through the use of autologous cancer cell vaccines derived from source cancer tissue, host mononuclear cells could be conditioned to the cancer antigen(s). These conditioned cells are then harvested via apheresis, ex vivo activated and expanded, and reinfused into the patient.

Fig. E1 provides the level of "activation" typically seen in our process. As can be seen, post-activated mononuclear cells are highly activated as noted using the CD25 marker.

Live cell imaging of host cancer cells in culture alone and with host cancer cells plus T cells harvested after the vaccination series demonstrates cancer cells appear undisturbed and unchanged. However, after 48 hours incubation with **activated T-cells** there is significant disruption of cancer cell integrity; cancer cells loose normal spindle shape and there is significant proliferation of T-cells observed.

Fig. E2: Fluorescent color image of host cancer cells and activated T cells at T=43h of assay. Note reduction in red cancer cell. Also note that T cells have migrated to the T cells and are clustering around them (yellow circles).

Fig. E3: Fluorescent images: On top row: images taken at T=0 of assay, while lower row is the same culture at T = 43. From left to right: first column is of host cancer cells alone, second column is positive control (staurosporine), and last column is respective host cancer cells with activated T cells. Note proliferation and

clustering of T cells around host cancer cells at T = 43h.

The presentation demonstrated the cytokine analysis of all 4 dogs evaluated. Only activated T cells generated significant amounts of the desired proinflammatory cytokines desired (IFN-g, TNF-a, IL-6). Immunotherapies are dependent on a good host immune system and its response to therapy for best efficacy. The data showed variability between patient responses.

Fig. E4: Measurement of viable cancer cells through the use of red fluorescence staining. Positive control (staurosporine) significantly reduced red fluorescence indicating cancer cell death. Only post-activated T cells (green) demonstrated cytotoxic activity in the presence of the host cancer cells.

Summary of observations
Only ex-vivo activated T-cells migrated to and clustered around target cancer cells.
There was confirmed activated T-cell generation of desired proinflammatory and immunostimulatory cytokines (IFNy, TNFa and IL-6)
Validated canine ECI process can generate cancer-antigen specific T-cells. These were shown to proliferate and in the presence of target cancer cells, exhibit cytotoxic activity.
Finally there was a teaser introduction to Elias portfolio – ELI352 – a novel oncolytic virotherapy.
ELI352 drives immune activation by invading tumor cells enhancing tumor specific neoantigen presentation, turning the tumor microenvironment from “cold” to “hot”.
Clinical evaluation is to start early 2023.

Thoughts on the presentation
This presentation gave a different type of data than the last one and was more focused on assays that help to provide proof of principle i.e. measures of immune activation and in vivo assays that show decreases in malignant cells when cultured with activated T cells. It is helpful to have these presentations available along with the ones that data from clinical patients.

I appreciated the focus on graphic /assay results demonstrating the biologic basis behind the clinical data reported; I particularly thought the emphasis on the difference between using normal T-cell after vaccination vs. Activated T-cells was important as many of the vets I’ve spoken with about this immunotherapy put it on the same (low) level as autologous tumor vaccines and miss the critical CAR-T cell component.

As you correctly state, the T cell infusion is a critical component of ECI and the combination of the vaccines and T cell infusion is an important differentiator. The ECI vaccine is designed to do what vaccines have been shown to do in so many other diseases such as rabies, parvovirus, etc. – prime the immune system to recognize the pathogen (i.e., neoantigen in the case of cancer). The T cell infusion is designed to convert large numbers of neoantigen-primed T cells (collected by apheresis) into large numbers of activated T cells which includes a mixed population of Helper T cells (CD4+) and Cytotoxic T cells (CD8+). These activated T cells play a critical role in providing the immune system the ability to fight the cancer.

A comparison to the Tumor Infiltrating Lymphocyte (TIL) work being done by Dr. Stephen Rosenberg, Chief Surgeon at the NCI is a useful analogy. A key difference between TIL and ECI is the way we source the neoantigen-primed T cells. In TIL, they isolate from the tumor the lymphocytes that have infiltrated that tumor because those lymphocytes have been primed to the cancer neoantigens by the tumor itself. In ECI, the vaccines to do the priming of the lymphocytes to the cancer neoantigens.

Helper T cells (CD4+) play a central role in normal immune responses by producing factors that activate virtually all the other immune system cells. These cells include B cells, which produce antibodies needed to fight infection; cytotoxic T cells, which kill cells carrying infectious agents; and macrophages and other effector cells, which attack invading pathogens (disease-causing agents). Cytotoxic T cells (CD8+) bind to and kill cancer cells. However, we do believe that the use of vaccines to prime the lymphocytes is more efficient than the TIL process in harvesting T cells via apheresis. After the apheresis step, TIL and ECI are almost identical in that the T cells are ex vivo expanded and activated and then infused into the patient. Again, similar to TIL, a series of low dose IL-2 injections are provided to further stimulation post T cell infusion.

The background science helps solidify and provides excellent evidence for the use of Activated T-cell therapy. The assays help support clinical data. I agree that this is good evidence why autologous vaccines are not all the same.

I agree with what has already been said, and I think people really want to know response and survival times with therapy which were not listed in this presentation. I wish they would have given more information on the new therapy they plan to release next year.

Exciting to see how this application can be used in other diseases. Hopefully wider use will allow access for more centers.

I was excited to see the preliminary cytotoxicity data.

Elias continues to validate and expand their science and open avenues for further immunotherapy.

Questions (concerns and clarification)
What oncolytic virus is going to be used for the second study?

ELI352 is a genetically characterized, replication-competent oncolytic vaccinia virus that is a naturally attenuated isolate which utilizes a triple mode of action: it directly kills cancer cells, stimulates a tumor-specific immune response and converts the tumor microenvironment from an immunosuppressive (cold state) to an immunoreactive (hot state). Virus-mediated oncolysis results in immunogenic cell death and triggers immune activation and memory for long-term immunotherapy against cancer. The technology was licensed from Genelux Corporation (www.genelux.com) who has studied a similar oncolytic product candidate (Olvi-Vec) in multiple early- and mid-phase clinical trials via regional and systemic deliveries, as a monotherapy and in combination with other therapies, in approximately 150 patients with a variety of cancer types which have shown that Olvi-Vec is well tolerated with documented clinical benefits. A more robust discussion of ELI352 is planned for the next meeting.

A more robust discussion of ELI352 is planned for the next meeting. We look forward to testing this and other immunotherapeutics in the coming year.

Does Elias have an up-to-date list of hospitals currently offering this treatment /who have access to the apheresis portion? (That is easily accessible for referring oncologists?) That would be very helpful when giving clients options – right now, I rarely talk about this option because I don't know where my clients can go to get it. Also, do we have data reporting the incidence of cytokine storms in veterinary patients (with this therapy or other immunotherapies)?
I would like more information on ELI352 if at all feasible – nice teaser slide!

There is a list of hospitals offering ECI and those offering apheresis as of July 14, 2022. This is an ever-changing list as we expand access to more hospitals. For the most up to date listing, please refer to the Locations tab on our website (https://eliasanimalhealth.com/available-locations/).

With regards to cytokine storm incidence, we cannot speak to other therapies but for our osteosarcoma patients undergoing ECI, cytokine release syndrome (CRS) has been rare with fewer than 5 out of more than 100 dogs treated requiring therapeutic intervention. The use of iv steroids has been very successful in controlling CRS in our patients. Steroid use in immunotherapy patients, including ECI, is contraindicated and its use is discouraged unless the patient is unresponsive to supportive care and CRS-like signs are progressing.

There are a lot of steps involved with this therapy and difficult to get it all done (I have never been able to get all the pieces together). I agree that a list of hospitals currently doing this therapy and apheresis sites would be very helpful.

We understand your concern regarding the protocol, and clinicians report that after treating 3 patients it doesn't seem so difficult. Our staff is very willing to help clinicians at every step of the process at any time. To help hospitals get started, our staff works closely with the hospital to identify the nearest apheresis referral center, identify a nearby surgeon (if needed), provide training for both oncology and surgical teams, and provide material for you to share with your referral network. When evaluating and treating patients, please text or call us – at any point – and we will assist you in resolving questions or concerns. We can usually get back to you within 15 minutes.

ELIAS will need to show where virolytic therapy has shown real promise to convince the community to use this new virus.

Yes, we plan too!

Any Experiences with this or similar offerings
Have not been able to use offer this treatment due to lack of availability of pheresis sites.
I have had experience with another clinical trial that was looking at using a virus that could be used to lyse tumor cells and expose multiple tumor antigens to get a broader immune response and was well tolerated by never got far enough into the project to look at efficacy

We routinely offer the ECI to clients on a commercial basis after participating in the clinical trials.

I treated 2 cases in Texas and we are now ready for cases in Orlando, FL but no takers as of yet

Thoughts for the future
It will be interesting to use this in combination with chemotherapy. In many cases, clients want the standard of care therapy to ensure a response but are willing to do

more to see if that response can be increased.

I want to be able to provide this as an option for all my osteosarcoma patients, but accessibility is a big issue. Does Elias have any thoughts on how using chemo beforehand /afterwards might impact the immune response, especially since the T-cells are activated ex vivo?

Questions often arise about using SOC chemotherapy and then follow with immunotherapy. Does Elias have any thoughts or evidence on the potential pros and cons of these approaches?

I asked about chemotherapy and ECI quite a bit and their current thought is if you are going to do chemotherapy- start it right away after amputation and before immunotherapy to maximize the future T cell expansion and response.

We do get this question regarding the use of chemotherapy often and our human health collaborator will be studying this in their FDA Fast Track designated glioblastoma study. There is scientific literature suggesting that the combination of chemotherapy with immunotherapy may have synergistic effects.

TIL plus chemotherapy in humans:
https://www.futuremedicine.com/doi/10.2217/imt-2020-0107

CAR-T plus chemotherapy in humans:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6036511/#:~:text=In%20conclusion%2C%20the%20combination%20of,the%20treatment%20of%20solid%20tumors

In our commercial patients, we have examples where clinicians dosed 1-3 rounds of carboplatin prior to initiation of the immunotherapy. The most common rationale provided is that the use of carboplatin will further reduce the cancer burden and improve conditions for the immunotherapy to be administered subsequently.

For now, we do not have a sufficient number of these cases to discuss with any certainty if this is helping or not, though we are monitoring the data. Our longest-lived combo-therapy survivor, a Newfoundland, has now been cancer free for 23+ months at last check. This dog received only 1 round of carboplatin prior to ECI.

At this time, we strongly discourage use of chemotherapy following the T cell infusion unless there is clear disease progression after two radiographs performed 30 days apart. Chemotherapeutics given after the T cell infusion may have a detrimental effect on the T cell population and possibly negate their ability to perform their cancer-cell killing function.

However, the use of chemotherapy (or potentially radiation) before the T cell infusion may not have the same detrimental effect on the immunotherapy.

Further research on this and other combinations may provide the data that is needed to answer this question more definitively. We welcome discussions with clinicians on this topic.

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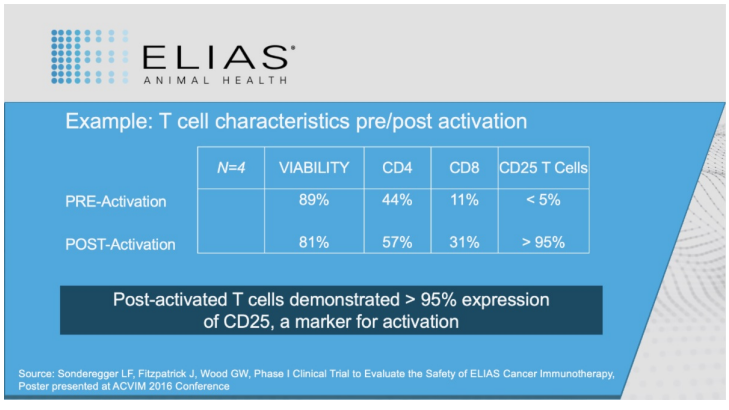
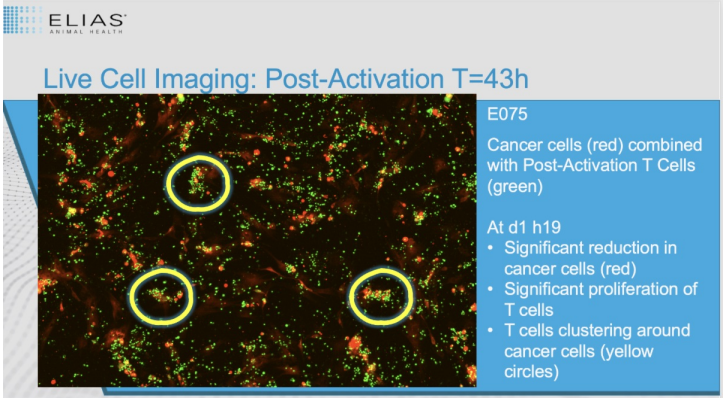
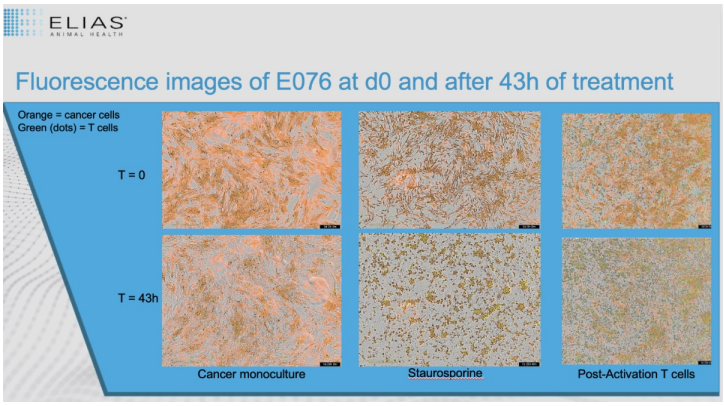
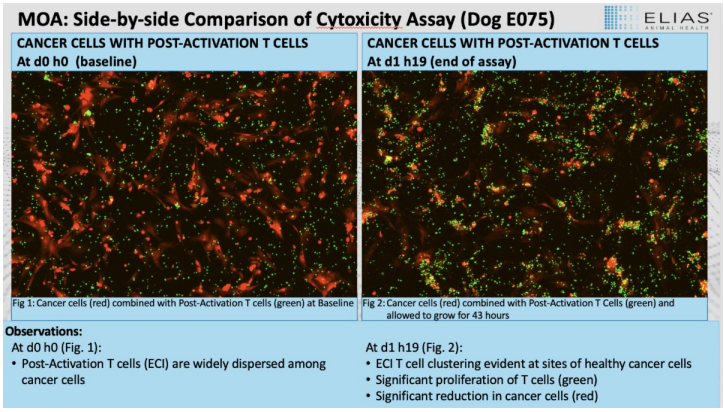








Learn more about Elias

vidium ANIMAL HEALTH a TGen subsidiary

A more In-depth Review of SearchLight DNA

SearchLight DNA is a targeted sequencing panel that utilizes next-generation sequencing to identify many mutation types in 120 cancer genes.
See Fig. V1 for sample types

SearchLight DNA gives meaning to identified mutations by providing BIOMARKER ASSOCIATIONS for each mutation, annotating each mutation as a biomarker of DIAGNOSIS, PROGNOSIS, and/or THERAPY, for EACH report:

These biomarker associations are made from HIGH EVIDENCE LEVELS and are based on PUBLISHED, PEER-REVIEWED LITERATURE.

Our approach to each case is INTERDISCIPLINARY, drawing expertise from medical oncology, pathology, and genomic science.
See Fig. V2 for interdisciplinary approach

How can SearchLight DNA be useful for diagnostically challenging cases?

Objective: Determine the clinical utility of SearchLight DNA in providing diagnostic,

prognostic, and therapeutic information for cases with ambiguous diagnoses, since ambiguous diagnoses hinder clinical management (unclear therapeutic options and prognoses).

Methods: Clinical cases with an ambiguous diagnosis that were submitted for SearchLight DNA analysis between September 2020 and May 2022 were selected to determine the utility of SearchLight DNA in providing diagnostic guidance, prognostic information, and targeted therapeutic options. Diagnostic ambiguity was determined from pathology reports containing any of the following descriptors:

- "Poorly differentiated…", "Anaplastic…", "Probable…", "Possible…", "Suspect…", "Suggestive…", "Atypical…", "Malignant…"

- "Neoplasm" or "Round cell tumor" without any further descriptors

Results:

52 samples were identified to have an ambiguous diagnosis
Almost half (46%) had at least 1 other, diagnostically unfruitful test performed prior to SearchLight DNA. Other diagnostic tests included PCR for antigen receptor rearrangement (PARR), flow cytometry, additional pathology opinion, immunohistochemistry (IHC)/immunocytochemistry (ICC)/special stains:
See Fig. V3 for results breakdown

Submitted sample types included the following: Aspirate- 29%, Biopsy- 71%
This shows that clinicians are starting to leverage the ease of FNA sampling for genomic analysis (nearly 30% of samples were aspirates).
Note 5 FFPE slides and one paraffin block were available for microdissection. Macrodissection allows us to increase tumor content and therefore have that much more confidence in our genomic results (sequencing data analysis is done in light of the tumor content).

Through qualitative analysis of biomarker associations, 83% of these 52 diagnostically challenging cases had diagnostic guidance, prognostic insight, and/or therapeutic options.
See Fig. V4 for results overview

Conclusions:
MOST (>80%) diagnostically ambiguous cases can benefit from at least one of the arms of SearchLight DNA utility - diagnosis, prognosis, and therapy - based on high evidence level biomarker associations from peer-reviewed, published literature.

Clinicians should strongly consider genomic analysis for any cancer, but especially those for which diagnoses, and therefore prognoses and therapeutic options, are ambiguous.

Thoughts on the presentation:
This presentation was very clear and concise about what the predicted uses of for this diagnostic. The data behind the diagnostics was well outlined and understandable. This presentation would definitely make me want to use this product.

Thank you for the lovely comment. We hope all clinicians can appreciate the multiple utilities of SearchLight DNA.

I appreciate the emphasis on using Searchlight as a diagnostic tool as well as prognostication /determining therapy; I definitely think they need to leverage their ability to do the profiling on aspirates as it's a HUGE advantage over similar panels at other companies.

Thank you for this comment. We think so too and hope other clinicians start to see these benefits.

I see the biggest advantage of this product as the accuracy of profiling on FNA samples – easy to obtain. I would definitely use on ambiguous cases.
Thank you for this comment. We hope other clinicians do the same.

I agree that the biggest selling point is that this can be done with an aspirate/cytology and the presentation highlighted this well.

I appreciate the number of mutations searched and that these can be assessed on aspirates.

We do cover many genes and mutation types, and we can give the same high-quality information from an easy aspirate sample.

I'm still excited about the pathology team at this group for those difficult to diagnose cases.

We do have a stellar pathology team and work well together to give the best information for the clinician.

Questions (concerns and clarification):
When can we expect this to be available for cats? I have a case currently and was

disappointed to find that cat samples cannot be tested.

We, too, hope to develop genomic tools for cats, as soon as science allows it. Unfortunately, the amount of information available about the genetics of feline cancer is nowhere near that of the dog. When that information is available, we will develop an assay for cats.

Does the company offer support in clinical decision-making after mutations are identified?

Absolutely. Vidium offers complimentary consultations (via email, phone, or virtual meeting) with clinicians to review reports and/or answer specific questions regarding genomic findings, drug information, and other pertinent information that could be used for clinical decision-making.

Any Experiences with this or similar offerings:
I did try to use this for an aspirate once and there were not enough cells to run the test. I think Vidium is now letting people know that the aspirates have to be very cellular.

Experiences with Other genomic companies have not been positive. Excited about the presentation Vidium offered.

Thoughts for the future:
I thought that it was very interesting to think about using this type of a genetic analysis not only to help determine what targeted therapy may be an option but also for use in predicting prognosis and also for use in making a diagnosis in cases when histopathology and IHC is not able to do so.

We agree, and thank you for the comment! One of our goals is to emphasize the diagnostic and prognostic utility of SearchLight DNA, which other companies cannot offer. And these utilities are on top of the therapeutic utility, which means all three are offered in each report.

The fact that this is possible to be done on a cytology slide is a huge advantage since there are many cases where it is not possible to obtain a biopsy due to tumor location and risks to patient.

Agreed! We are finding more and more clinicians leveraging this sample type. We hope the word continues to get out to all clinicians so that we can provide the same high-quality information with less morbidity (and cost) associated with sample collection.

Although from a science /ethical standpoint I think Vidium has would be my preferred diagnostic, most of my clients who come looking for genomic profiling come to me with a specific company already in mind, because that company is accessibly to clients, has a great marketing team, and makes dramatic claims about efficacy and cure rates. It's sometimes very difficult to shift the clients' focus away from other companies.

We've heard this from various oncologists and have provided some tools to re-direct the focus to Vidium. Many clinicians have found the pamphlets on SearchLight DNA a valuable tool, since it gives the owner something to physically hold and read, and gives the clinician a chance to highlight the different aspects of SearchLight DNA. If you'd like pamphlets sent to you, we are happy to do so. We also have these, as well as other resources, available on our website in the Clinic Support section.

Building capability in remote media will be helpful, similar to what PetDx is doing.

The great thing about SearchLight DNA is that special media is not necessary (if I am understanding "remote media" correctly). FNA samples can be submitted on slides as you would for any cytology analysis. We also accept a variety of histopath sample types and will work directly with the reference lab to obtain them. We always request FFPE slides or the block (so as to have macrodissection as an option), but what they send us will depend on the lab's ability/willingness to send us those vs. other (FFPE scrolls) types.

I think the triangulated idea of diagnostic, therapeutic and prognostic is intriguing. As more PK/PD data becomes available, it could find an important upfront space for other less ambiguous tumors.

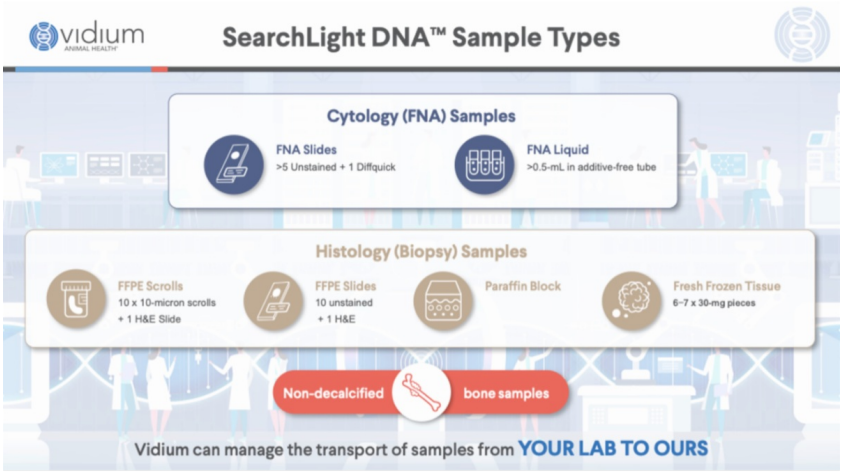
Agreed, and we hope that all of us (veterinary community at large) can work together to get the data that we want for effective use of these targeted therapies.

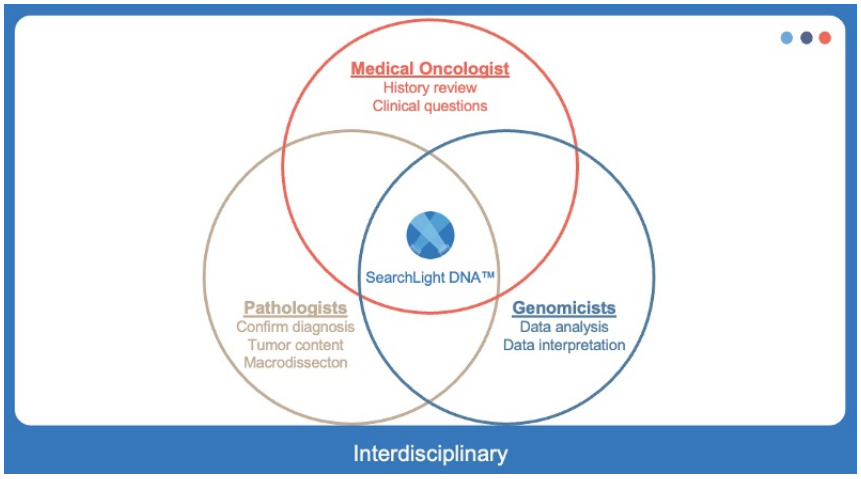
I'm struggling to get other oncologists who have their favorite pathologists/ ways of doing things to try a different group for difficult cases. The genomic profiling and database will have a huge impact on future therapy options. And yes, when can we get the cats involved?

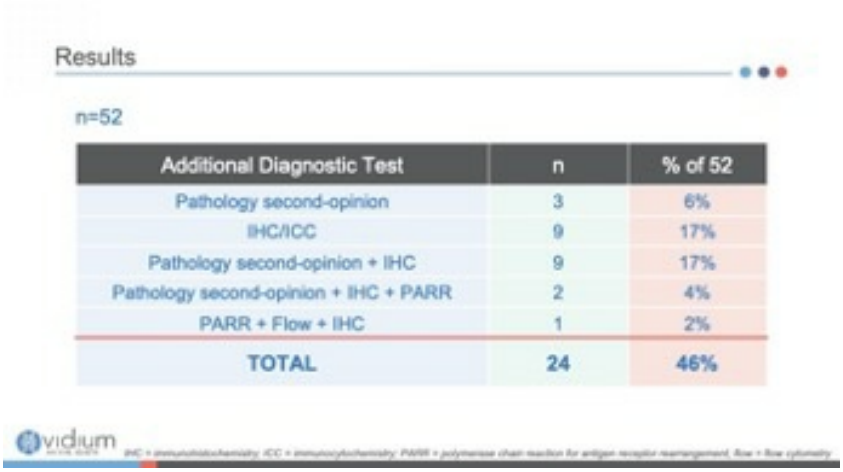
Yes, we have met the same kind of resistance with some clinicians, which is why we need this great group of oncologists to effectively spread the word to our colleagues about the benefits of this technology and what our company can offer for our patients. Please let us know if you would like Vidium to reach out to any

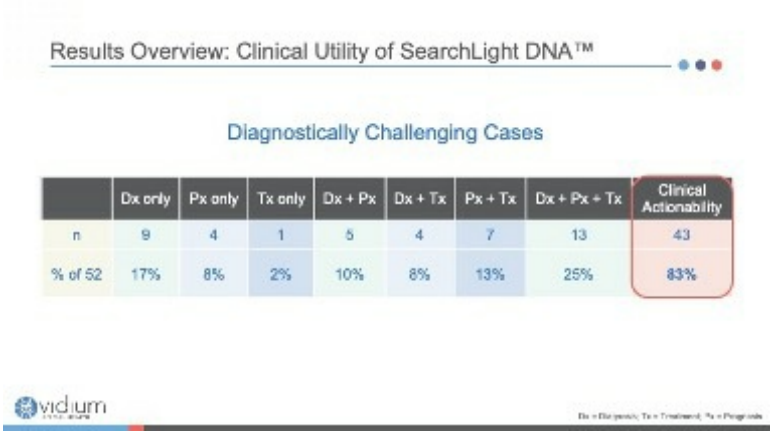
oncologists in particular. We are happy to have virtual meetings with them to introduce SearchLight DNA and our Specialty Pathology Services. You can have the pathologists email me directly at echon@vidiumah.com or Dr. Derick Whitley at dwhitley@vidiumah.com.

Following images - Fig. V1-4









Learn more about Vidium's Searchlight DNA

IMPRI
MEDI

Imprimed presented the data recently published in *Veterinary Sciences, Koo; 81(12):301 (2021):*

Predicting dynamic clinical outcomes of (L-)CHOP chemotherapy for canine lymphoma patients using an artificial intelligence model.

(This data is in addition to the published data "Predicting likelihood of in-vivo chemotherapy response in canine lymphoma using ex-vivo drug sensitivity and immunophenotyping data in a machine learning model" VCO, October 2020)

Rational:
CHOP protocols result in a clinical remission rate of 73-96%. However, median duration of PFS is 244 days for the B-cell and 108 days for the T-cell subtype, and median survival times are often 1 year or less for high grade lymphomas. Unfortunately, rescue protocols typically result in lower response rates and shorter remission durations than first-line protocols. The significant variance in treatment responses in various clinical scenarios implies a critical need to predict treatment response accurately, especially in patients with rare lymphoma subtypes, subtypes with low remission rates and relapsed patients.

It is important to appreciate that previous trials provide this data for a given population. By utilizing a prediction model such as the one demonstrated, we are more able to understand the response of an INDIVIDUAL patient which is of far more use to the client than a statistical median. *See Fig. I1*

In-vivo clinical outcomes were collected 90+ days after drug sensitivity, immunophenotyping and patient information (33 parameters) were generated; these were used in the machine learning models for (L-) CHOP chemotherapy response prediction. Combining these 3 sets of data significantly improved the prediction accuracy.

In addition to predicting which patients will achieve a complete remission and when this will happen, the assay also accurately predicts the probability of remission and can be used to provide insights on the survival of each case. *See Fig. I2, I3 and I4*

The presentation then explained how doctors use the prediction report, either continuing with CHOP if the report predicts a good response or deciding on a different protocol using the single drug response prediction model which provides information on up to 13 chemotherapy drugs. *See Fig. I5*

"Predictive models of treatment outcomes will empower veterinarians to make personalized therapy plans for canine lymphoma, which can lead to reduced treatment burden and increased survival".

Thoughts on the presentation:
The presentation was clear and concise and it presented data that showed that the process of predicting whether or not a lymphoma is going to respond to a particular drug.

One of the better Imprimed presentations I've seen, with a good balance between the explaining probabalistic details and drawing in clinical examples /clinical information. (Several of the panel agreed with this)

The information provided about time to achieve remission was interesting, since often we accept stable disease, or if complete remission is not obtained after one cycle, maybe 2 then we tend to believe that it will not be obtained.

I appreciate that the company has done most of its R and D using investor money, not client money. However, in the case presentations, I have yet to see one that the algorithm suggested a different course than I would have elected clinically.

Thanks for your time for the separate meeting we had with your team. I am glad that you liked Ellie's case where the 11.5-year-old patient was treated in a non-typical way using chlorambucil for her high-grade T-cell lymphoma treatment based on the ImpriMed prediction report.

Questions (concerns and clarification)
To me, it seemed as though the ability to predict a B cell lymphoma's response to CHOP was not significantly different from the data that is available from the literature based on immunophenotyping so it does not appear as though there is a clear advantage to using it in the situation. I would consider this to be better looking at T cell forms of lymphoma and also atypical presentations of lymphoma where it is harder to decide what to use and that CHOP is still often used as the default.

Among the 3,000+ patients who requested ImpriMed services, about 600 patients received the CHOP prediction reports so far. The likelihood of CR and the likelihood of relapse for a CHOP protocol were different for each patient regardless of the patient's immunophenotype (B or T), which confirms that we need a personalized approach even for CHOP protocols. *See examples in Fig. I6:*

My biggest concern remains that nobody has made this work on the human side. It leaves me skeptical that chemosensitivity prediction will ever be valid in dogs or cats.

As you pointed out, chemosensitivity 'alone' is not sufficient to provide accurate prediction for in vivo drug efficacies in the patient's body. This has been shown historically in many scientific papers especially in 1990s, and this is why none of the human insurance companies has given a reimbursement code for a chemosensitivity assay. In addition, it is not trivial to keep a patient's cancer cells alive once they are removed from the body. However, after we realized that genetic sequencing-based precision medicine shows clear limitations to correlate in vivo clinical outcomes, cell-based functional precision medicine approaches are being more and more highlighted these days. In the human oncology space, there are several functional precision medicine companies including Xilis, Notable Labs, and Cellworks, in addition to ImpriMed. You can look at The Society for Functional Precision Medicine (https://www.sfpm.io/) for more academic institutions and private companies in this field. What makes ImpriMed unique from the other companies is that we combine the most comprehensive information from a patient's cancer to provide the best prediction by using proprietary artificial intelligence algorithms.

Any Experiences with this or similar offerings
I still think the greatest utility of this assay is for atypical presentations (aberrant immunophenotypes, unusual organ involvement, etc.) or relapsed patients.

Yes, we provide great value to atypical or relapsed patients. However, most (77%) of our serviced patients are naive lymphoma patients. We have received great feedback from doctors regarding the utility of our single drug response predictions and our CHOP response and prognosis predictions, immediately after a patient is diagnosed with lymphoma or leukemia. Doctors also like that we provide comprehensive and accurate immunophenotyping results (PARR and flow cytometry) along with drug efficacy predictions for naive patients.

I have adjusted therapy based on the drug probabilities and have seen better than expected responses.

This is wonderful to hear!

Having the information that doxorubicin and Tanovea rated high for a specific patient, enabled me to feel more confident to use alternating protocol in place of single agent Tanovea for example when a patient is in remission.

Great to hear this. In fact, there are many doctors who treat patients more confidently when their original plans/expectations are well aligned with the results in the ImpriMed report.

Thoughts for the future:
I would like to see more of the flow cytometry data that has been generated particularly the less common subtypes of B and T cell forms of lymphoma. I think that this data would provide a stronger argument for using this type of an assay.

So far, we've provided our flow cytometry results to 2,300+ canine hematologic cancer patients, and we were able to cover less common immune subtypes as shown in *Fig. I7:*

Given that cancer resistance mutates rapidly, are there any plans for reduced pricing for patients who go through multiple assays (ie. At diagnosis, at relapse, at 2nd relapse, etc.)?

We've been giving a 50% discount to any patient who used our full service in the past.

RV- It would be interesting to see how dogs responded to the recommended rescue protocols compared to historic controls.

To answer this exact question, we evaluated drug responses in relapsed B-cell lymphoma patients by comparing a higher concordance group (the patients who received 2 or 3 drugs in the top three of ImpriMed's AI predictions) vs. a lower concordance group (0 or 1 drug used in the top three). The high concordance group doubled the overall response rate compared to the low concordance group. This result was presented at the VCS Mid-Year 2022 in Mexico this April.
Please see *Fig. I8*

As we know lymphoma changes and is heterogenous - Could it be that a future approach may be to figure out how to use this diagnostic throughout a patient's lymphoma treatment whether it be to predict the next step when patient relapses or to define the transition of lymphoma to a different variant or resistance profile?

I love the idea of serial testing on a single patient over their treatment and relapse, can we do better for these patients over time?

Among the 3,000+ canine lymphoma patients we've served so far, there were many cases where we were able to track how a patient's cancer cells evolved when they were naive vs. relapsed since the patient used our Personalized Prediction Profile service when newly diagnosed and used it again when relapsed. Usually, the antigen receptor profile of relapsed patients' cancer cells are almost identical (or very similar) to that of the naive status, but sometimes we observed cases where the naive patient's immunophenotype was mixed between B- and T-cells, and it seemed that the first chemotherapy effectively killed the T-cell but not the B-cell lymphoma cells. According to this change in immune subtype, the drug response prediction results also changed.
If you want to look at more clinical cases in detail, please see Yoki and Samson's treatment courses and their ImpriMed test results in Dr. Choy's recent presentation: https://youtu.be/ssgMmeyUYrs

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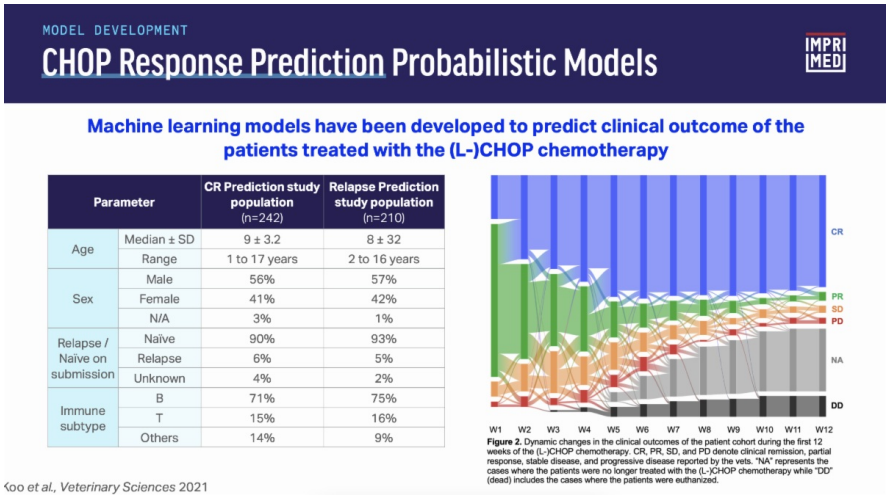
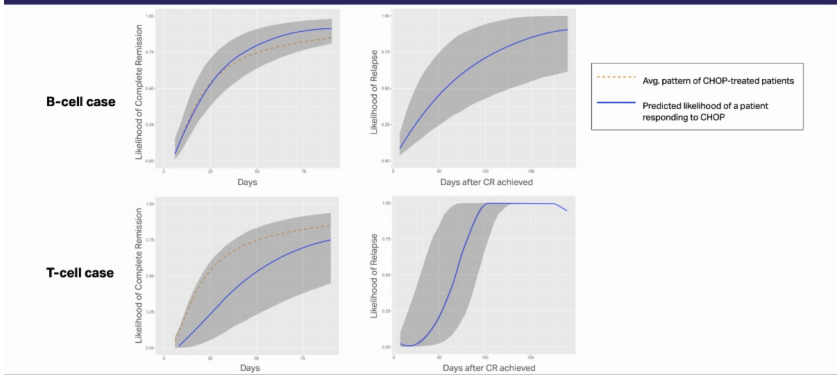


THE PRODUCT

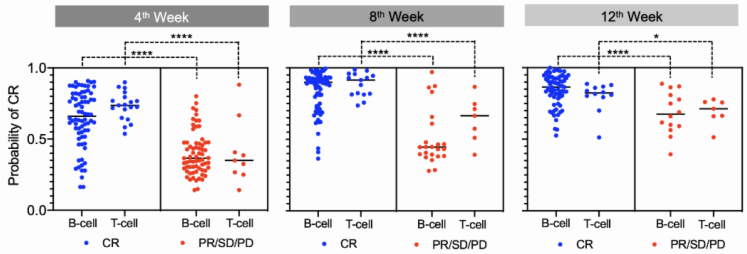
CHOP Response Prediction Probabilistic Models



RESULTS

CHOP Response Prediction Probabilistic Models

Our CHOP response predictive model accurately predicts probability of achieving CR and distinguishes between CR and non-CR populations on Week 4, 8, and 12



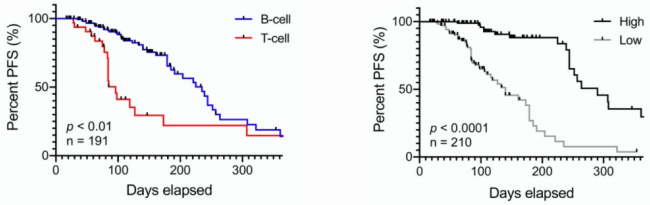
Koo *et al., Veterinary Sciences* 2021

RESULTS

CHOP Response Prediction Probabilistic Models

Our models also predict accurately the probability of relapse after remission and can be used to provide insights on the survival

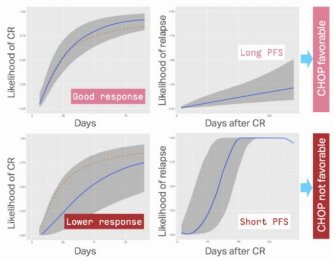
Lymphoma patients treated with CHOP



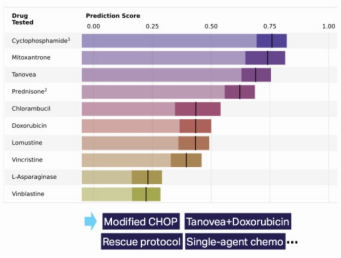
oo *et al., Veterinary Sciences* 2021

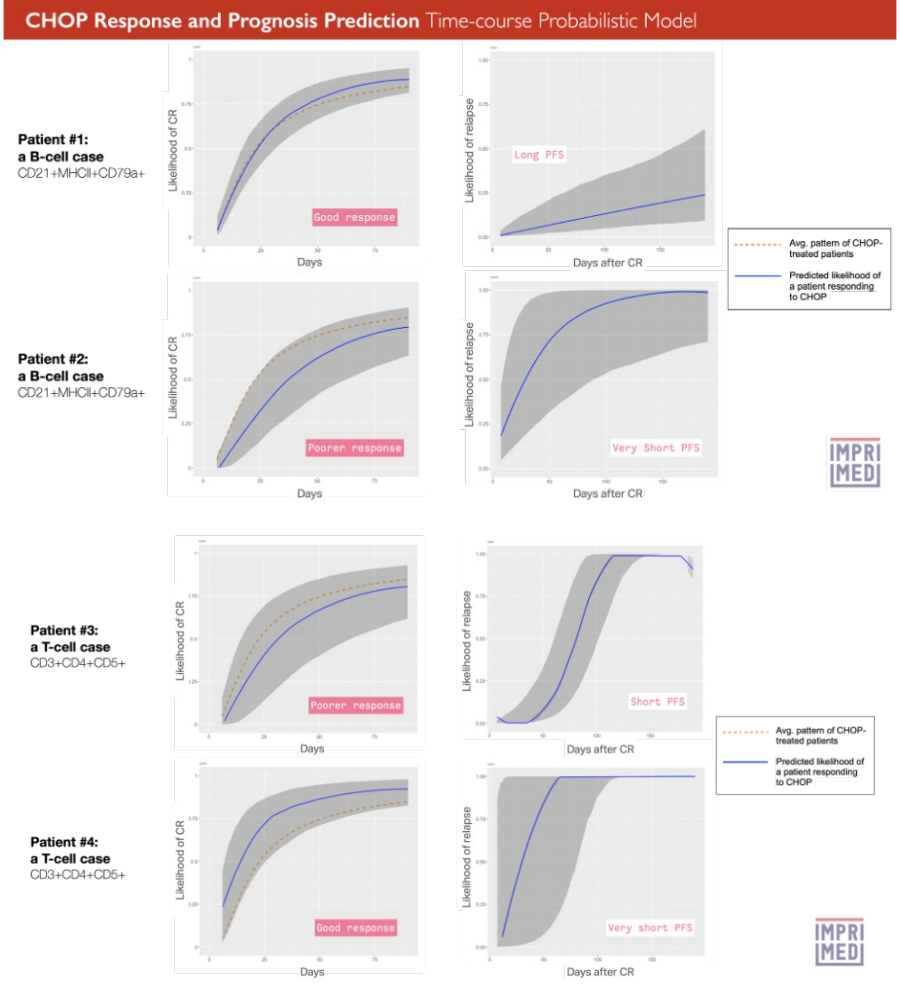
How doctors use our prediction report

CHOP response predictions for naive lymphoma

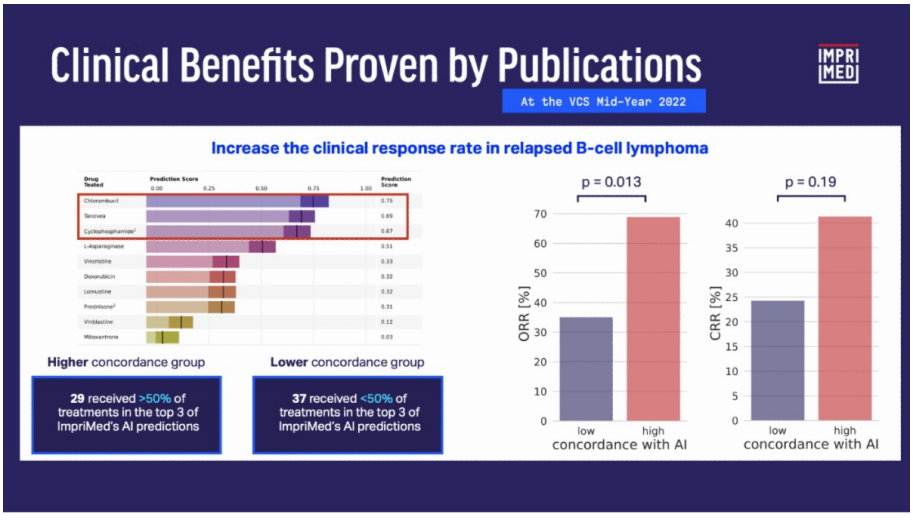


Single drug response predictions for naïve or relapsed lymphoma





TYPE	count	%
B	1739	73.34
T	357	15.06
T-zonal	108	4.56
Inconclusive	57	2.40
Mixed	41	1.73
ALL	20	0.84
CD45+CD34- Non-B Non-T	12	0.51
B-CLL	8	0.34
T-ALL	7	0.30
T-CLL	6	0.25
AML	6	0.25
Immature B- cell	6	0.25
Non/lymphoid/Normal	2	0.08
Chronic myelomonocyte leukemia	1	0.04
DP T - cells	1	0.04
TOTAL	2371	100



Learn more about
Imprimed

CANINE BIOLOGICS

Canine Biologics

We need to adjust the mindset about the role nutrition plays in veterinary cancer. The notion that any diet, including prescription diets, will help provide the best result for dogs with this disease is not true. Veterinary nutritionists understand the unique needs of dogs with this disease. Cancer-appropriate nutrition should be incorporated into every case to improve patient outcomes.
Cancer permanently alters the way a dog's body metabolizes proteins, fats and carbohydrates, and significantly changes a dog's nutritional requirements. Feeding a maintenance or veterinary diet to a dog with this disease deprives them of the nutrition needed to battle their disease effectively and may even be detrimental to their health.
Dogs with cancer need a diet with 25-40% fat, 35-50% protein, fewer than 20% complex carbs and a very specific amount and ratio of n6 to n3 fatty acids. Only two options are suited for these dogs: the Canine Biologics Integrated Nutrition System or a veterinary-nutritionist guided, home-cooked diet. While the latter is only food, the Canine Biologics three-part system also incorporates supplements including mushroom (cordyceps) and omega-3 fatty acids shown to offer specific physiologic benefits for these patients.
We invite the oncology community to learn why dogs with cancer need a different diet. What clients should feed your patients is not a lifestyle choice, it is crucial for best outcomes.
Canine Biologics have prepared a client hand out which provides more details. To read or download a copy of this document, please follow the link below. (example also below!)

Thoughts on the presentation:
I thought that the presentation was well organized and gave me a better idea about the how and why of using this product. It appears to be a more complete product for clients to use instead of a home cooked diet and it is nutritionally balanced.

I think the handout is great for clients and certainly it's an easy way to pacify a client who wants to feed a cancer-specific diet. That said, I think it would be better if the information for oncologists could include references to (1) studies demonstrating how the indicated metabolic alterations differ between different types of cancer, because a low grade soft tissue sarcoma is not going to be the same as a disseminated histiocytic sarcoma or a stage IV lymphoma; and (2) studies demonstrating that altering the balance of a diet also alters the metabolic changes in vivo, particularly with regards to carbohydrates as that's a common thing for clients to see on the internet and get very focused on. I recommend it to any client who asks about a cancer-specific diet, but I remain skeptical of the science behind it.

We appreciate the feedback and continue to do nutritional research in conjunction with our formulation consultant who is a DVM/PhD, full professor of clinical nutrition with over three decades focus on oxidative stress diets.

Client brochure is good and explains the information succinctly and clearly. The integrated product seems like an easy "fix" for a complex problem.

I agree with the above

The presentation was great and the brochure is easy to follow.

Questions (concerns and clarification)
Do we know that the metabolic alterations that are reported occur in all types of cancer? For example, I would not likely consider this diet for a lifetime diet for a dog with a soft tissue sarcoma that was completely excised since it was a more localized tumor and surgery is curative. If I had a patient with a systemic form of neoplasia such as lymphoma, I would be more likely to consider this diet for life.

Have there been palatability studies done with this diet? Many of our patients that are undergoing chemotherapy and other therapies are sometimes very selective about the food that they will eat so is this a diet that has a high palatability?

The Integrated Nutrition System has at its core, palatability. This is one reason why 100% human grade/human edible ingredients are used which includes wild caught salmon oil. The Supplement component relies on pork liver to further enhance palatability. As noted below, not every dog loves this nutrition system but hundreds of dogs (and a few people including a vet tech who recently spoke of having it for lunch – minus the salmon oil and supplement) can speak to its palatability. Of

course, there has yet to be a diet created that every dog enjoys.

What is the shelf life of this product? There were no expiration dates on the samples that I had received and I suspect that the expiration dates are shortly given the ingredients that are used.

The shelf life easily exceeds two years for the oil and supplement components and the food component is safe for up to 25 years depending on storage.

I see thorough products such as this as a treatment for systemic forms of cancer, agreeing with above comments. I have not seen conclusive evidence that dogs with a solitary low grade form of neoplasia have altered metabolic needs. One of my concerns is that this is a "one-size fits all" and we know that many patients have other comorbidities such as CRF, Cushing's disease or susceptibility to pancreatitis. Have they evaluated those concerns?

Canine Biologics makes no claim as being a 'treatment'. In addition to vitamins and minerals, the compounds in our Supplement component – chosen by a practicing DVM/PhD in Tumor Immunology – have shown positive action across a range of studies and trials on their own. In addition, since we do provide the system's major components separately, conditions such as pancreatitis can, to a point, be accommodated since the use of wild caught salmon oil – making up 40% of the total fat – can be modulated, Further, this component can be employed at reduced levels during periods of chemotherapy or in cases with higher risk of hemorrhage.

I think this is a great option for a client that wants some control and wants to feel like they are helping with their pets cancer diagnosis and outcome. While the science may not be complete, and we may not think it will change outcome, how is it any worse than the other prescribed diets or foods picked up at the pet stores? At the end of the day, nutrition is not always possible to control when your pet's appetite is not there so parents end up offering multiple options.

Any Experiences with this or similar offerings

I have tried it in my own dogs and they didn't like the taste – we home cook and use commercial diets routinely. Also, cost for a large breed dog can be prohibitive. I like the diet, but it would be better to have several options as eating one food daily must be a disappointment in dogs that enjoy food overall.

Canine Biologics does have additional options (beef and fish as the primary protein source) on our product roadmap

My dogs also did not find it palatable.

I've seen your dogs, Dr. Bryan, and whilst they are exquisitely beautiful creatures, they are not known for their voracious appetites. (Tariq's comments :-)

I recommend this diet any time a client asks about diet. I ask them to read all the literature listed on the Canine Biologics website- there are links to abstracts/ papers and the research that helped formulate this diet so they understand how it was prepared AND how little we actually know about canine cancer diets. It drives home how most of the general internet information out there is just opinion.

Thoughts for the future

Continuing to emphasize that this is an option guided by a nutritionist is an important message to make ubiquitous.

Thank you for the comment – please see above regarding our consulting nutritionist – we do try and make it clear that DVMs who are either Board Certified in Veterinary Nutrition or hold a PhD in Tumor Immunology guide the selection of all ingredients

Cancer Diet Handout link

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