ONCOALESCE

Monograph

#7 August 2023 (Part 4)

Greetings!

Dear Shah,

Welcome to part 4 of "July's Oncoalesce #7"
You can download previous versions as PDFs or audio files following the link below.

Imprimed have worked very hard over the last few years to provide data to support their Personal Prediction Profile. This week we explore data on relapsed B-cell lymphoma in a clinical trial in 60 dogs.

Enjoy,

Tariq

Email me!

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The Discussion

IMPRIMED

Increased survival and remission rates in canine relapsed B-cell lymphoma patients with treatments matching ImpriMed's artificial intelligence (AI) predictions

Introduction
While 80% of B-cell lymphomas can be driven into complete remission (CR) using a CHOP protocol in canine patients, the success rate for reinduction of CR after relapse is much lower. This indicates that tumor evolution processes change the drug sensitivity profile of the primary cancer in ways that make choosing a reinduction therapy more

challenging. ImpriMed's Personalized Prediction Profile (PPP) gives a real-time update on a patient's tumor drug sensitivity profile that may be taken into consideration by oncologists when choosing a reinduction therapy. The PPP includes clinical outcome predictions for 12 drugs commonly used to treat canine lymphoma. Predictions are generated by AI models trained to predict real-world clinical outcomes data from comprehensive tumor profiling data and patient information. To determine if utilization of ImpriMed's AI predictions leads to improved clinical outcomes, we conducted a prospective clinical trial using a matching score analysis that has been employed in a number of human precision oncology trials[1–3].

Trial results

All canine patients from ImpriMed's user database were selected who 1) were diagnosed with B-cell lymphoma and 2) had relapsed from prior therapy before their oncologist ordered ImpriMed's PPP to help guide future treatments. We requested medical records for each patient and received replies for 60 patients who met these criteria and who had also been treated with one or more anticancer drug(s). A matching score was calculated to quantify the degree to which each patient's treatment matched recommendations from the precision oncology platform as described previously[1–3]. For this calculation, recommended drugs were defined as those drugs with AI prediction scores above 0.5 (PPP scores range between 0.0 and 1.0, with higher values indicating a higher likelihood of partial or complete remission). Matching score for a patient was calculated by dividing the number of administered drugs that matched the PPP recommendations by the total number of drug administrations for that patient.

The 60 relapsed B-cell lymphoma patients were separated into two groups of equal size based on their matching scores: a high matching group and a low matching group (n = 30 each). For the high matching group, both complete remission rate (CRR) and overall response rate (ORR) were substantially higher than for the low matching group (53 % high vs. 4 % low for CRR with $p < 0.001$; 69% high vs. 42 % low for ORR with $p = 0.06$). In addition, patients in the high matching group experienced significantly longer overall survival ($p < 0.001$ for log rank test). After controlling for several potentially confounding variables (grade, stage, substage, age, and date of biopsy) using multivariate Cox proportional hazards modeling, the matching score was found to be the second most impactful predictor of patient survival (after substage), with a hazard ratio of 0.26 (95% CI 0.12 - 0.56). Thus, relapsed B-cell lymphoma patients who received treatments that matched those predicted to be effective by ImpriMed AI models experienced substantially better health outcomes by three different outcome metrics and after correction for confounding variables in a prospective study of patient outcomes.

1. Fountzilas, E., Tsimberidou, A. M., Vo, H. H. & Kurzrock, R. Clinical trial design in the era of precision medicine. *Genome Med.* **14**, 101 (2022).
2. Rodon, J. *et al.* Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. *Nat. Med.* **25**, 751–758 (2019).
3. Sicklick, J. K. *et al.* Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. *Nat. Med.* **25**, 744–750 (2019).

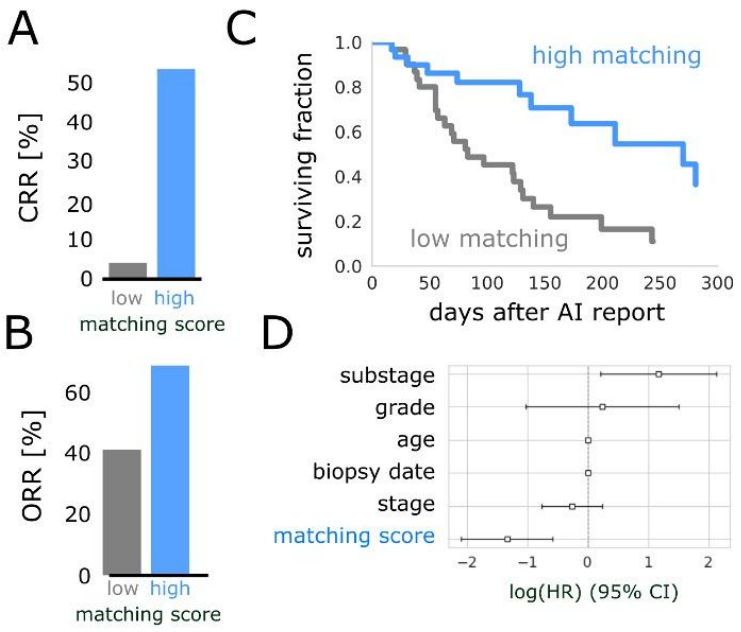

Figure 1. Canine patients with relapsed B-cell lymphoma experienced better clinical outcomes when treatments matched drugs that were predicted to be effective in their ImpriMed Personalized Prediction Profile. **A.** Complete remission rate is higher in the high matching group (53% high vs. 4% low, $p < 0.001$). **B.** Overall response rate is higher in the high matching group (69% high vs. 42% low, $p = 0.06$). **C.** Overall survival is higher in the high matching group (log rank test $p < 0.001$). **D.** High matching score is associated with reduced hazard of mortality in a multivariate Cox proportional hazards model. The hazard ratio for matching score group is 0.26 (0.12 - 0.56 CI).

Thoughts on the presentation

Exciting to see dogs with high drug matching rates have higher ORR and CRR then dogs with low.

This information may encourage me to start using the assay more than I have been. I will definitely take this into consideration.

Very exciting to see that AI can help improve outcome!

Nice match with the T-cell paper from last time; I also appreciate that this is all in the relapsed setting as this is primarily where I use the assay.

This is exciting to see and useful when speaking with clients.

I think this helps provide evidence to show clients the utility of this type of diagnostic.

I was very interested to see that we could more accurately pick drugs for a second remission with the assay. It has been more guesswork picking a second treatment based on clinical experience and patient information in order to achieve a second remission.

Questions (concerns and clarifications)

Does “low matching” and “high matching” mean the test found drugs that were low or high match or that the high is what the test found would be effective and pets were treated with those drugs and low is what the clinician used but the test did not find the drugs to match well?

The latter. Matching refers to the match between recommended drugs and administered drugs, not the match between the drug and the particular patient/tumor. Recommended drugs are defined as those with prediction scores above 0.5 for this study.

Were all of these patients first-relapse? Did all of the patients get treated with standard CHOP as first-line therapy?

With this cohort, our records don't go all the way back to the beginning of treatment for every patient. So we can't systematically answer this question yet. Within the next few months we expect to have our records uniformly backfilled to the start of treatment and have the ability to answer these questions. In previous analyses, most of our B-cell patients received (L)CHOP as the first-line therapy so we expect that this was also the case for this set of relapsed patients.

We know that response to treatment is a predictor of outcome for lymphoma in general; is there any correlation between which protocols were recommended and the patients who had low agreement? Were the recommended drugs difficult to obtain or administer? Were they associated with an increased risk of side effects?

This analysis is for our single drug predictions, so there were no protocol recommendations on which to base an answer to your first question.

All of the drugs in the study are known to have side-effects. Doxorubicin, which can lead to adverse events, was recommended less frequently in the low-matching group. Lomustine, which is also associated with some adverse events, was recommended with a similar frequency in the low-matching and high-matching groups.

None of the drugs in this study are considered difficult for an oncology practice to administer.

The study spanned the pandemic during which drug shortages were intermittent. We don't have enough data to determine how drug shortages may have impacted clinical behavior, but we expect that they would equally affect the low-matching and high-matching groups given that both groups were evenly distribution over time.

Should we be making a combination of the top drugs for relapsed patients? Does it matter if it's a combination of 2 or 3 of the top drugs?

For this cohort, we analyzed the clinical outcomes of the patients who received drugs with Prediction Scores above 0.5 rather than the ones who received the top 2 or 3 drugs at a higher frequency. Based on the limited prospective data, the way to achieve the best outcomes seems to be to avoid drugs with prediction scores below 0.5 when possible and to choose from the drugs with predictions scores above 0.5 that you believe would be most effective for your patient.

While no one likes to think about these things in terms of dollars and cents, have you ever considered looking at the “return” of the test? Could there be some level of cost savings for these dogs’ care because finances weren’t wasted on less effective drugs?

We haven't done this type of economic analysis yet, but we appreciate that cost is a major factor for our pet parents so this is a great idea for a future study. For instance, we could estimate months of survival per dollar spent for the low-matching and high-matching groups.

The only concern that I would have is that it can up to 7-10 days to get the analysis back. Does it make a difference if you choose another therapy first to get you to the point where the analysis is available and you can go off the recommendations? I would expect that is not the case but I’m not sure what the company recommends until that time.

Separately, we analyzed the treatments given during the time before the AI report

arrived. Only 1 treatment in the entire cohort of 60 patients led to a positive clinical response observable at the subsequent visit to the oncologist. This was a partial remission induced by a combination of mitoxantrone and prednisone. If we look at patient survival rather than overall response rate, the patients who received vincristine (with or without prednisone) before arrival of the AI report lived the longest. However, this survival duration is likely due to treatments given after the AI report was received rather than to the initial dose of vincristine. In a univariate Cox regression model, usage of vincristine before receipt of the AI report is associated with a mortality hazard ratio of 0.66 relative to baseline risk of 1.0 (95% CI 0.29 to 1.5). Here mortality hazard refers to the interval between biopsy and death.

Any experience of what was discussed.

I have used Imprimed especially when I locum for an oncologist in Phoenix. I have noticed the predict remission rate/response has been very similar to what I am seeing clinically in an individual dog.

Since we have limited drugs for relapse, we end up using them all eventually, but this may help us use the best one first. I have used Imprimed in the past but got away from it when the predictions were not validated in the patient.

I've used it in several patients with either unusual presentations or in the relapse setting; I feel like the predictions match the initial response, but response durations seem highly variable. I've also had a couple results where the predicted responses were very low for all drugs, which clients were a little disappointed by (those definitely matched the predicted response rates when we tried something anyways!).

Thanks for sharing your experience with the ImpriMed service. As you noted, our current AI models predict initial responses to drugs but not response durations. We are working on time-series analyses to improve our AI models to predict duration of a drug response. We do recognize there were a few cases where all the Prediction Scores showed below 0.5. As we understand this kind of result may be disappointing to clients, we offer running our assays again to confirm the result, at no additional cost.

I've used this in the naive and relapsed setting for guidance with therapy and prediction through CHOP.

I have not yet had any clients with the resources and desire for this testing, but this additional data may help push more clients to consider it.

I have used it on a few clients for relapsed lymphoma but have not had any success probably due to the fact that I have used it in late stages when most drugs are not going to be effective.

Yes, please try our services at an earlier time point of treating relapsed or naive lymphoma patients.

Thoughts for the future

Can you look at T cell lymphoma and drug prediction similar to this study?

We previously shared results from a prospective study of canine T-cell lymphoma patients. The results and conclusions were quite similar to the ones from this relapsed B-cell lymphoma study. We plan to publish both the T-cell and relapsed B-cell studies this year. (See Oncoalesce Monograph #6)

I'm looking forward to the Mast cell tumor work that is coming up!
There has been a resurgence of scientific abstracts presenting Caninized CD20 MAb for DBCL - any thoughts as to how this may fit into Imprimed's AI algorithm modeling?

If CD20 mAbs start to see regular clinical use, we would definitely be interested in developing AI models to discriminate between mAb responders and non-responders. Because antibody therapeutics can be costly, ImpriMed's drug response predictions could become an integral part of the decision-making process for pet parents. We are also open to collaborators who are interested in developing AI-based companion diagnostics for CD20 mAbs or other promising drugs.

I appreciate that we now have evidence supporting Imprimed's use in both T-cell and B-cell lymphoma; I'd really like to see if there's a difference in benefit for relapsed vs. naïve lyphoma
Excited about the mast cell tumor information as well.

That is a good suggestion. We can study the benefits of our service in relapsed vs. naive lymphoma treatment. As you already know, we have been collecting clinical samples and treatment outcome data for canine mast cell tumor to develop an AI-based prediction service similar to canine lymphoma. Please participate!

Has there been any consideration of evaluating the benefit of AI for TCC/UC? Similar to lymphoma, it's a disease where we are frequently cycling through quite a few drugs hoping for a sustained response.

We haven't discussed TCC/UC much internally, but we're excited for new suggestions like these and will investigate the potential for ImpriMed decision support here.

As it has been suggested, It would be nice to know more about T cells forms of lymphoma given that they are so much more difficult to predict in regards to first remissions and also rescue therapy.

Please see response above, or refer back to the Oncoalesce monograph # 6.

Isabella with a Welsh cat...

...And Isabella with a Thai cat!

Disclaimer and stuff

The following notes have been taken directly from data presented to the panel of oncologists in the Oncoalesce meeting #7. 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 Animal Cancer Care Specialists
- Dr. Pamela Jones - QBiotics
- Dr. Kendra Lyons - Locum
- Dr. Melissa Parsons-Doherty – Pearland Animal Cancer and Referral Center
- Dr. Erin Roof – FL Animal Cancer Care Clinic
- Dr. Aarti Sabhlok – San Francisco Animal Medical Center.
- Dr. Rachel Venable - Pet Cancer Care Consulting
- Dr. Carissa Wood - FL Animal Cancer Care Clinic
- Dr. Rachel Kovac - TX 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.

NOMV
NOT ONE MORE VET
Inc.

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