“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and **Vidula Sukhatme, MS**) [#147]

Brad Power and Kayla Yup
June 11, 2025

“We came to the realization that there are many potential interventions that we refer to as ‘financial orphans’, that are implementable today and for which there is no real unified advocate.” – Vikas Sukhatme, MD, ScD

“You are probably familiar with checkpoint blockade. This is clearly one of the biggest developments of the last 10 years or so. Durable responses have now been seen in many different solid tumor types. That's the good news. The bad news is these are very expensive, and there are serious immune related adverse events that do occur at fairly high frequency. The efficacy typically ranges around 20% to 40% depending on tumor type, but for the most part, it's on the lower side of that number. The question that we asked ourselves is: ‘Can we do better? Can we do better now? Can we do better now with inexpensive treatments?’ And the answer I'd like to posit to you is ‘Possibly. Yes.’” – Vikas Sukhatme, MD, ScD

Meeting Summary

Cancer patients and caregivers face challenges with immune checkpoint inhibitors. Immune checkpoint inhibitors are some of the most widely prescribed cancer drugs, representing over $40 billion in annual sales. While immune checkpoint inhibitors have revolutionized the treatment of many cancers, a significant portion of patients do not respond -- roughly 20% to 40% respond. Increasing the effectiveness of immune checkpoint inhibitors can have significant impacts.

Vikas Sukhatme, MD, ScD, professor of medicine at Emory University and the founding director of the Morningside Center for Innovative and Affordable Medicine at Emory University, and his wife, Vidula Sukhatme, MS, co-founder and CEO of GlobalCures, are uniquely qualified to lead a discussion about complementary therapies that can increase the effectiveness of immune checkpoint inhibitors. The Morningside Center was created to address the lack of financial incentives that inhibit the promotion of potentially effective and affordable medical treatments -- "financial orphans". Dr. Sukhatme completed a bachelor's degree and then a doctorate (ScD) in theoretical physics at Massachusetts Institute of Technology, and he received an MD from Harvard Medical School in the Harvard-MIT program in Health Sciences and Technology. He spent two years at Stanford in immunology research. Vidula Sukhatme is an Instructor in the Rollins School of Public Health, Emory University. She is a co-founder of the Morningside Center and is the founding CEO of GlobalCures, which searches published scientific papers to identify and prioritize generic existing drugs that could be repurposed for cancer use, as well as nutritional products and lifestyles that may be of value to cancer patients.

How have immune checkpoint inhibitors revolutionized cancer treatment?

Immune checkpoint inhibitors have been one of the biggest developments in cancer treatment in the last 10 years. They enable durable responses across multiple solid tumor types, which was

not previously possible. However, their effectiveness is still limited - ranging typically from 20-40% depending on tumor type, with most outcomes on the lower end of that range. The key advantages are:

- Ability to create long-lasting immune responses against cancer
- Potential for treatment across different cancer types
- Mechanism of "unleashing" T-cell responses against tumors

The main challenges remain:

- High cost
- Serious immune-related adverse events
- Relatively low overall efficacy rates

Should you consider getting an immune checkpoint inhibitor?

Checkpoint inhibitors are most often used in advanced (metastatic) cancer settings and in specific cancer types where durable responses have been observed. There is also increasing usage prior to surgical removal of tumors.

How might you increase the effectiveness of immune checkpoint inhibitors?

- Correct magnesium deficiencies
- Ensure adequate vitamin D levels
- Maintain a high-fiber diet (>20g/day)
- Time your infusions in the morning, if possible, at least for the first four infusions
- Delay immunotherapy 3-4 days after chemotherapy when both are being used concurrently
- Use antihistamines (specifically histamine 1 receptor blockers) if you have high histamine levels
- Correct vitamin deficiencies
- Avoid medications that might antagonize checkpoint inhibitors (steroids, antibiotics, proton pump inhibitors, histamine 2 receptor blockers, acetaminophen)
- Avoid off-the-shelf probiotics (but consider clostridium butyricum)

How can you access these complementary therapies?

- Over-the-counter options: vitamin D supplements, magnesium supplements, antihistamines (such as loratadine), high-fiber diet, probiotic clostridium butyricum
- Prescription-required interventions: time-of-day infusion scheduling and 3-4 day delay of immunotherapy after chemotherapy
- Get appropriate testing (such as plasma histamine, magnesium, and vitamin D levels)
- Always consult with your medical team regarding any of these interventions

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and **Vidula Sukhatme, MS**) [#147]

How can you learn more about complementary therapies for immune checkpoint inhibitors?

- Visit the Morningside Center's website for ongoing research and information and join their patient cancer registry to contribute and learn about emerging therapies
- Consult with oncologists who are open to exploring complementary approaches
- Review the scientific literature
- If you are going to get immune checkpoint inhibitors, talk with your medical team about the complementary interventions discussed.
- Contact Vidula Sukhatme at Vidula@Global-cures.org or Vikas Sukhatme at vsukhatme@emory.edu
- See other discussions that touch on complementary therapies and immune checkpoint inhibitors:
    - "Personalized Cancer Vaccines" (Willy Hoos) [#29]
    - “Update on Immunotherapies for Metastatic Castrate Resistant Prostate Cancer” (Sumit Subudhi) [#66]
    - “Update on Prostate Cancer Treatments, Especially Radiopharmaceuticals” (Oliver Sartor, MD) [#122]
    - “Finding Personalized Cancer Treatments Beyond the Standard through a Unique Test” (Travera) [#77]
    - “How I Help Patients Access New Diagnostics” (Joanne Weidhaas, MD, PhD, MSM) [#138]

The information and opinions expressed on this website or platform, or during discussions and presentations (both verbal and written) are not intended as health care recommendations or medical advice by Cancer Patient Lab, its principals, presenters, participants, or representatives for any medical treatment, product, or course of action. You should always consult a doctor about your specific situation before pursuing any health care program, treatment, product or other course of action that might affect your health.

For the video recording of this conversation, please see here.

For a transcript of the conversation, please see here.

For the slides, please see here.

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

Meeting Notes

KEYWORDS

Immune checkpoint inhibitors, complementary therapies, Morningside Center, financial orphans, cancer registry, magnesium deficiency, vitamin D, dietary fiber, histamine blockade, time of day effect, low dose chemotherapy, patient advocacy, clinical trials, repurposed drugs, cancer immunity cycle.

SPEAKERS

Vikas Sukhatme (47%), Vidula Sukhatme (29%), Chris Apfel (9%), Roger Royse (7%), Richard Anders (4%), Allen Morris (2%), Russ Hollyer (2%)

CHAT CONTRIBUTORS

Richard Anders, Roger Royse, David Plunkett, Russ Hollyer, Rick Davis, Chris Apfel, Allen Morris, Vidula Sukhatme

SUMMARY

Vikas Sukhatme and Vidula Sukhatme discussed complementary therapies to enhance the effectiveness of immune checkpoint inhibitors (ICIs). They highlighted the Morningside Center's efforts to create a database of financial orphans, focusing on optimizing dosing, scheduling, and efficacy. Key interventions include correcting magnesium and vitamin D deficiencies, using antihistamines, beta blockers, and delaying ICIs by 3-4 days post-chemo. They presented data showing improved outcomes with early morning infusions and specific dietary interventions. The Sukhatmes emphasized the need for a national patient cancer registry to collect and analyze outcomes data, aiming to improve ICI efficacy and reduce adverse events.

OUTLINE

Introductions and Overview of the Morningside Center

- Vikas Sukhatme introduced the Morningside Center's mission to bring new treatment options to patients, focusing on financial orphans like off-patent drugs, nutraceuticals, and lifestyle modifications.
- The center aims to create a clinical impact through a database of financial opportunities, sponsor trials, and create a cancer registry, with a focus on optimizing dosing and scheduling and increasing the efficacy of checkpoint blocking.
- The three major buckets of financial orphans are: off-patent FDA-approved drugs, nutraceuticals, and lifestyle modifications.
- Increasing the efficacy of checkpoint blocking is expensive and associated with serious immune-related adverse events.
- Various studies show the impact of magnesium, vitamin D, dietary fiber, histamine blockade, and time of day on the efficacy of checkpoint blocking.

Specific Interventions and Evidence

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

- Magnesium has a role in enhancing immunotherapy, according to a paper in Cell that outlines its mechanism.
- Patients with normal magnesium levels had better outcomes than those with hypomagnesemia.
- Vitamin D has a role in increasing PD-1 blockade efficacy, citing a paper in Melanoma.
- Data on dietary fiber intake show that patients with high fiber intake had better outcomes in a study from MD Anderson.

Histamine Blockade and Time of Day Effects

- Histamine blockade improves checkpoint blockade efficacy, according to studies in non-small cell lung cancer.
- Data show that patients on H1 blockers had better outcomes than those on H2 blockers or without blockers.
- Morning infusions are better, according to a review paper showing a two- to threefold-effect on overall survival.
- Data from a randomized control trial show that early time of day infusions led to better progression-free survival and overall response rates.

Delaying Immunotherapy and Combination Studies

- Delaying immunotherapy is better for patients receiving concurrent therapy, according to animal data and a retrospective study.
- Data show that delaying immunotherapy led to a 50% increase in progression-free survival and disease control.
- Combining interventions is better.
- A clinical trial to test the hypothesis that simultaneous interventions increase efficacy is needed.
- These interventions can improve the efficacy of chemotherapy and other treatments.

Adverse Events and Mechanisms

- Research is being done on reducing side effects and toxicity of checkpoint inhibitors and monitoring adverse events.
- H1 and H2 blockers have different mechanisms.
- Probiotics can potentially enhance checkpoint inhibitor efficacy.

Patient Registry and Advocacy Efforts

- A patient cancer registry to collect data on interventions and outcomes is needed.
- There are ongoing efforts to convince physicians to adopt these interventions and the need for legal protection for physicians.
- Conducting clinical trials presents challenges; a separate infrastructure to repurpose approved drugs is needed.

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

TRANSCRIPT

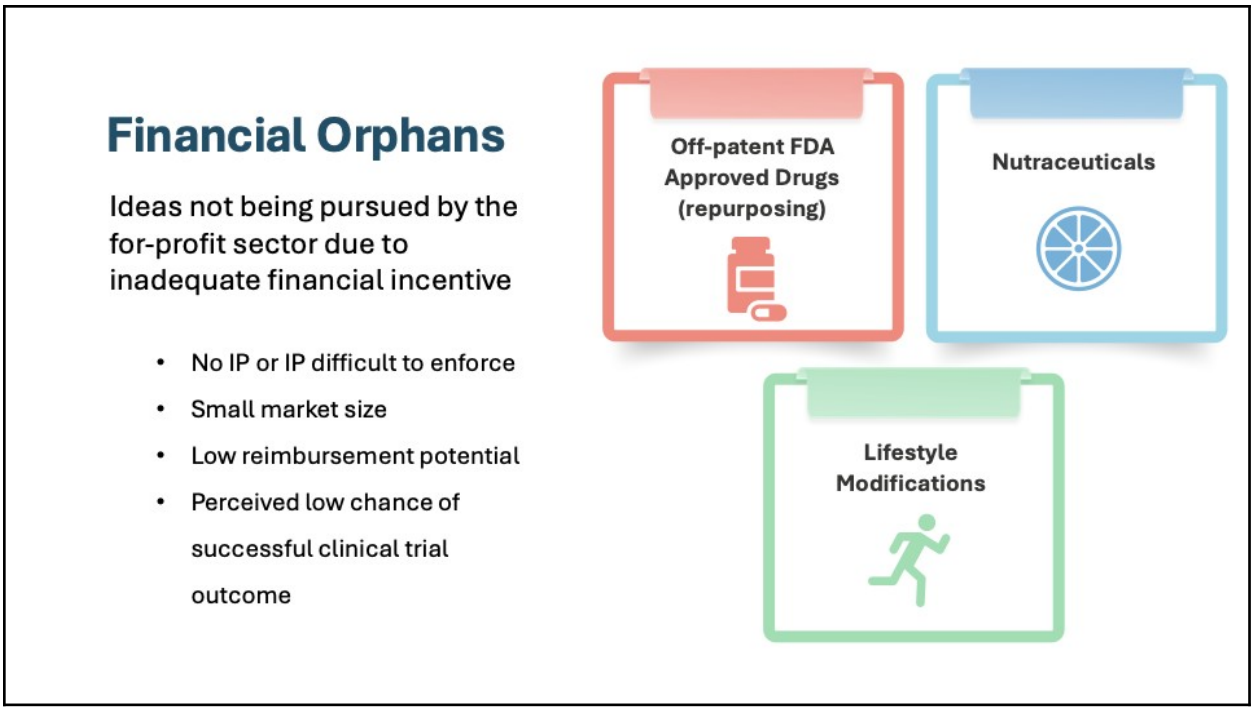
Roger Royse
Welcome to the Cancer Patient Lab webinar.

We're going to talk about how to increase the effectiveness of immune checkpoint inhibitors. Our speakers today are Vikas and Vidula Sukhatme. Vikas is a professor of medicine at Emory and a founding director of the Morningside Center for Innovative and affordable medicine at Emory University. And Vidula, who is his wife, is a co-founder and CEO of Global Cures. They are going to lead a discussion about complementary therapies that can increase the effectiveness of immune checkpoint inhibitors.

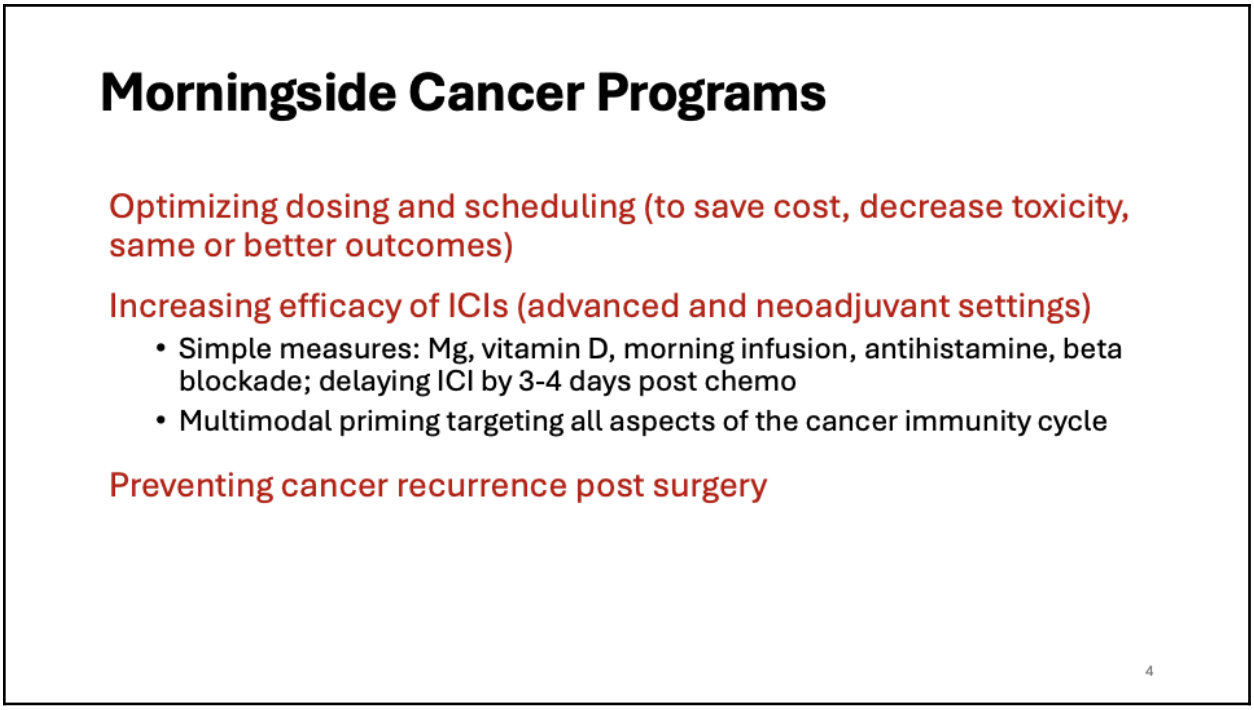
Vikas Sukhatme 0:43
This is a group of individuals that's one of the smartest groups I've ever met. I've been watching a number of your videos. I really appreciate what you're doing. Thank you again for this opportunity.

I want to say a few words first about the Morningside Center. This is a center within Emory University that we co-founded a few years ago, and we exist fundamentally to bring new treatment options to patients. In that sense, we are similar to pharma. We're not opposed to what pharma does, but we recognized a few years ago that when pharma tries to bring new drugs to the market, the underlying premise is that there is a financial incentive to do that. We came to the realization that there are many potential interventions that we refer to as “financial orphans”, that are implementable today and for which there is no unified advocate. We're creating a database of these financial opportunities, largely in the cancer field. We aim for clinical impact. We're sponsoring trials as well and have created a cancer registry, which we'll talk about very briefly, and we're involved in a number of advocacy efforts.

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]



Financial orphans fall into three major buckets: (1) off-patent, FDA-approved drugs that could be repurposed for other uses, (2) nutraceuticals, and (3) lifestyle modifications such as diet and exercise. The major reason that these are financial orphans is there's usually little intellectual property or no intellectual property, or an unenforceable intellectual property situation. There are other reasons here cited on the left hand side of the slide.

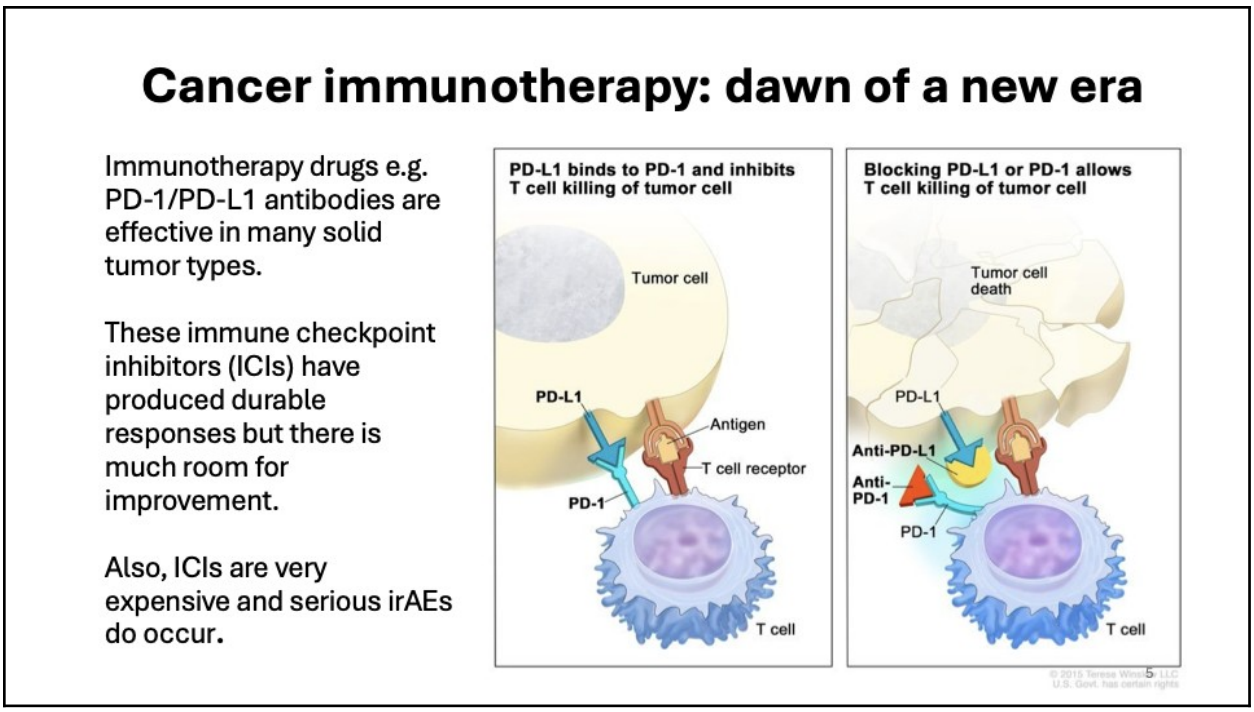


“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

The Morningside cancer programs are evolving. Our website doesn't have all of this yet on board. It has some of it. There are three major buckets that we are excited about:

1. The first is optimizing dosing and scheduling. This will not only save cost and decrease toxicity without we hope changing outcomes, or in some cases, we hope improving outcomes.
2. A second major bucket, which is the topic for today, is increasing the efficacy of checkpoint blocking. Many of the ideas here could be used both in the advanced setting and in the neoadjuvant setting, where I'm sure many of you know checkpoint blockade has now been adopted for a number of diseases. I'll talk primarily about simple measures listed here, such as correcting any magnesium or vitamin D deficiencies in getting infusions in the morning, potential use of antihistamines, beta blockers and delaying immune checkpoint blockade by three to four days after chemo, when the two are being given, quote, unquote together. I'll also tell you about an even broader landscape for what I refer to as multimodal priming, targeting, and all aspects of the cancer immunity cycle.
3. I'll be happy if we want to spend some time on preventing cancer recurrence. That's the third program.

But today I'm going to highlight the second of these programs.



You are probably familiar with checkpoint blockade. This is clearly one of the biggest developments of the last 10 years or so. Durable responses have now been seen in many different solid tumor types. That's the good news. The bad news is these are very expensive, and there are serious immune related adverse events that do occur at fairly high frequency. The

efficacy ranges between 15 or 20% to 50% depending on tumor type, but for the most part, it's on the lower side of that number.

Can we do better?

Can we do better **now**?

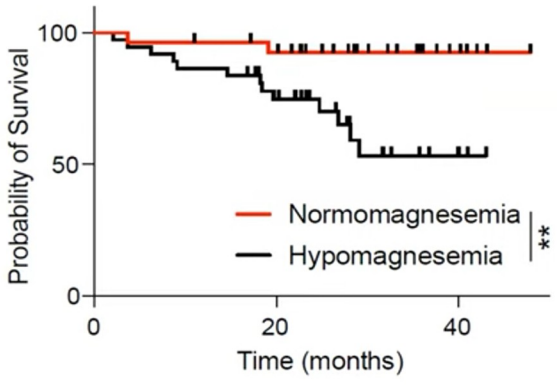
Can we do better **now** with **inexpensive treatments**?

Possibly yes, let’s take a look!

6

The question that we asked ourselves is: “Can we do better? Can we do better now? Can we do better now with inexpensive treatments?” And the answer I'd like to posit to you is “Possibly. Yes.” I'm going to show you some very quick evidence for many of the interventions I just talked to you about.

Maintaining normal magnesium levels in the blood enhances immunotherapy



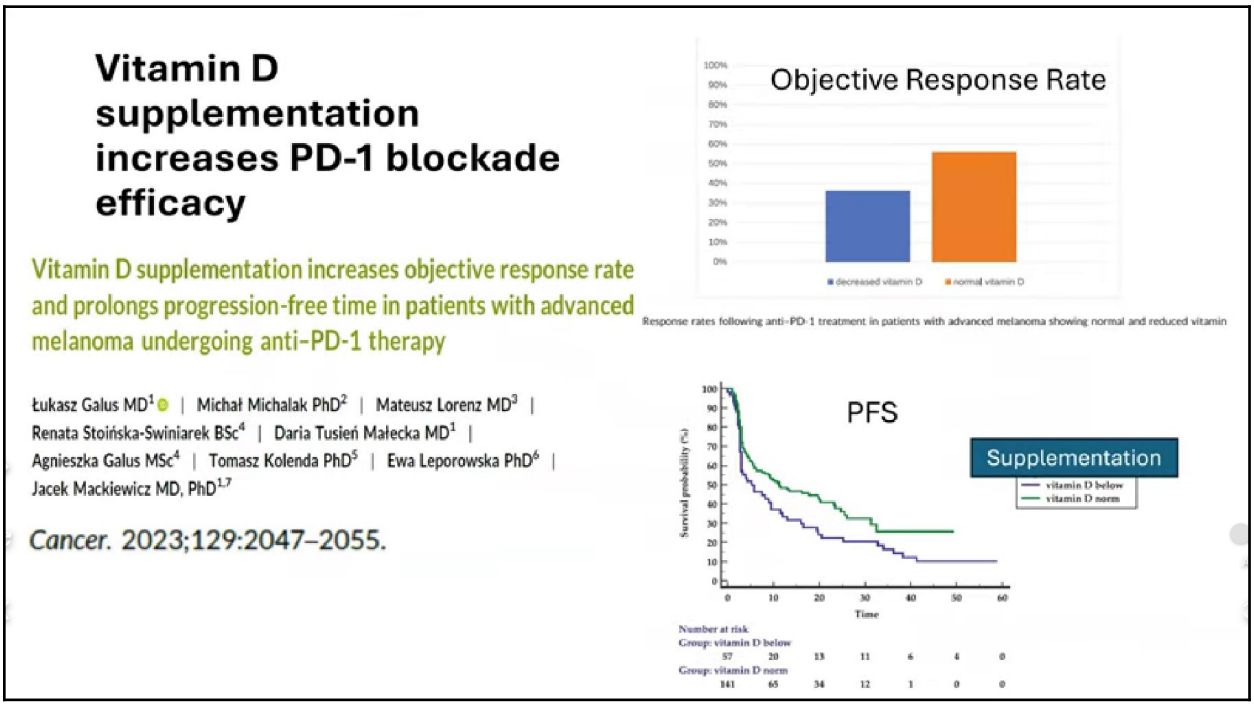
PD-L1 antibody treatment for NSCLC

Lötscher et al., Cell *185*, 585-602; 2022

7

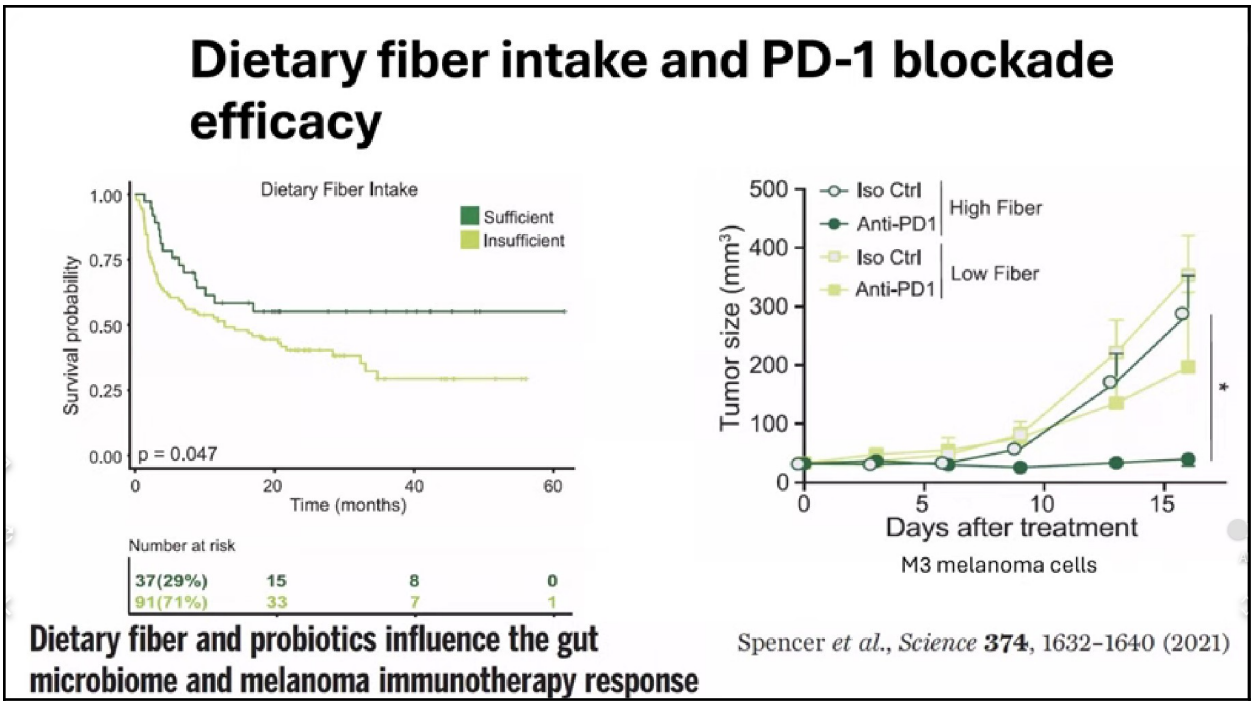
“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

Magnesium levels have been known to influence vaccination efficacy. In fact, this paper in *Cell* outlines how magnesium might be working to enhance immunotherapy. It appears to work both in helping T cells migrate into a tumor as well as the action of cytotoxic T cells as well. So here's one of the pictures from that article, looking at PD-L1 antibody treatment *[PD-L1 is a protein that acts like a “brake” for immune responses. It has been found in higher amounts on certain cancer cells, which use the protein to stop T cells from attacking them. PD-L1 antibody treatments bind to PD-L1 to block it, thereby allowing T cells to kill freely without threat of being stopped.]*
for non-small cell lung cancer. And as you can see, patients who had a normal level of magnesium ions in the blood did much better than those who are hypomagnesemic [a low level of magnesium in the blood]. And this is defined by a certain cutoff point in the paper. There's also lots of preclinical data in the paper that I'm not citing.



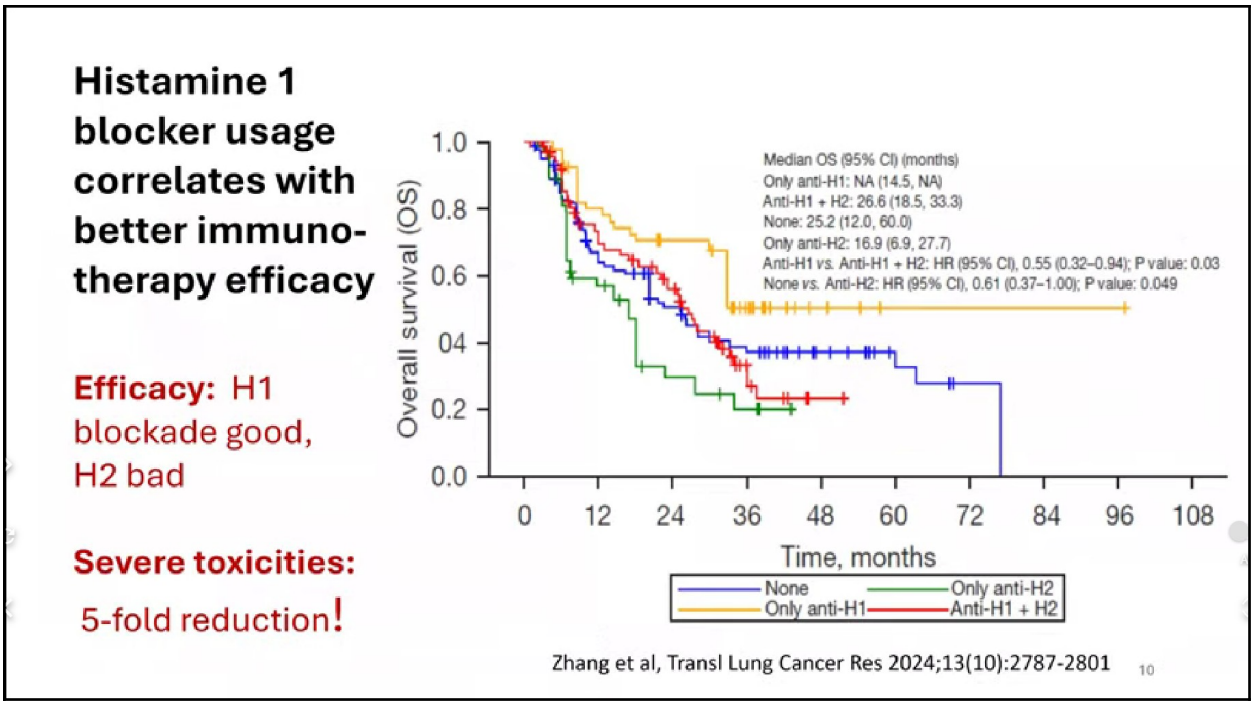
Here's a second intervention, vitamin D. There's a huge amount of literature on vitamin D, but this is one of the few papers where supplementation was actually noted to increase PD-1 blockade efficacy. This is in melanoma, it has not been tested in other tumor types. You can see some degree of efficacy here as well.

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

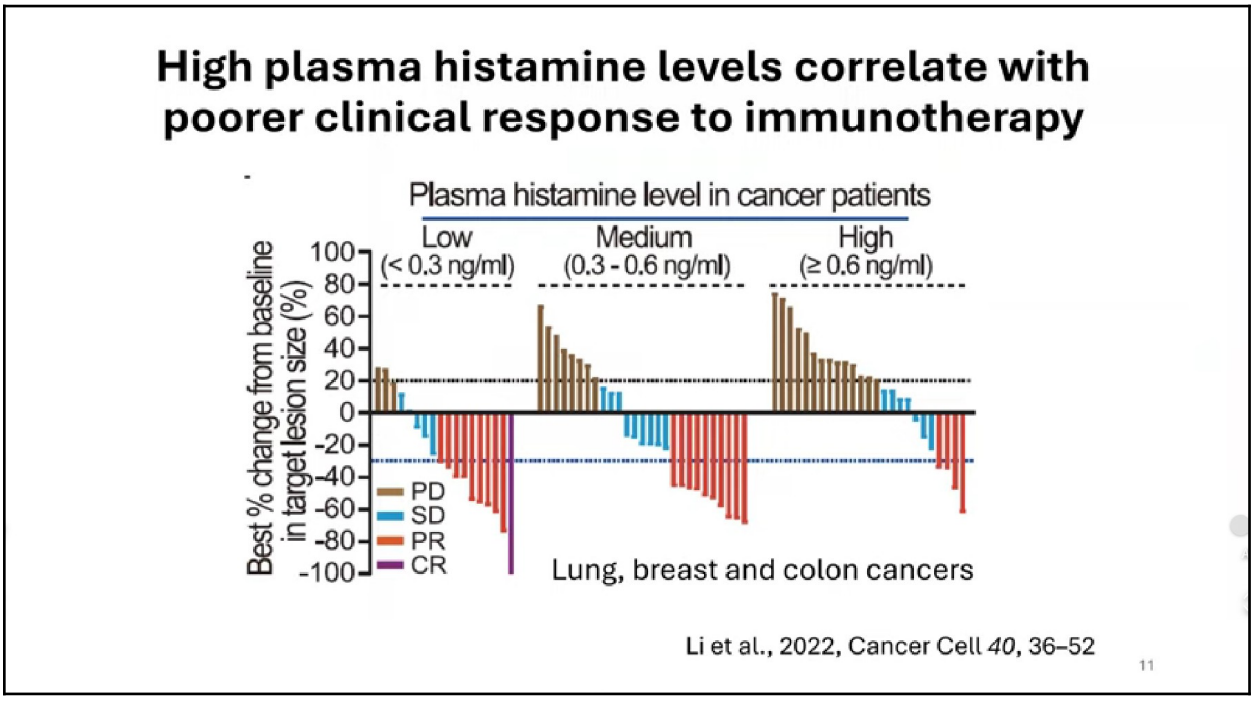


Here's dietary fiber intake. Here the cut off again. This is a melanoma paper with about 130 patients or so from MD Anderson, published in *Science*. They simply retrospectively looked back at those who had an intake above 20 grams a day versus those who didn't. On the left hand side, you can see how that works out. And on the right hand side is some animal experiments showing that anti PD-1 works much better in mice that are on a high fiber diet. I should mention to you that there is a mechanism of action here that's postulated, and that is, the microbiome is altered in the presence of dietary fiber. In particular, butyrate concentrations are thought to go up. And there is a whole literature on butyrate and T cells, which is quite complex. I won't belabor it right now, but that appears to be one of the major mechanisms of action.

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]



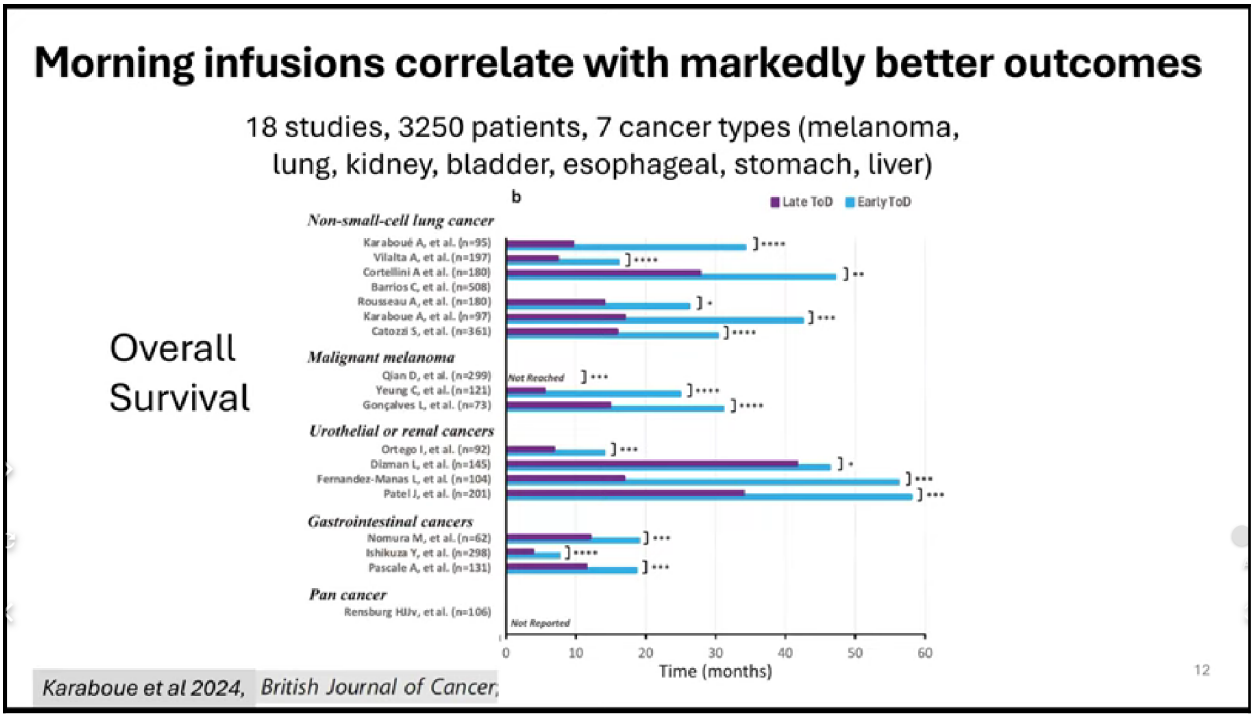
Here's data on histamine blockade. This is one of several papers out there looking at the effects of checkpoint blockade, in this case, in non-small cell lung cancer, on patients on either H1 blockers or H2 blockers or both. As you can see in the orange, the patients who received only H1 blockade were the ones who did the best. In fact, H2 blockade goes the wrong way, and is a cautionary note. This is one of several papers.



“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

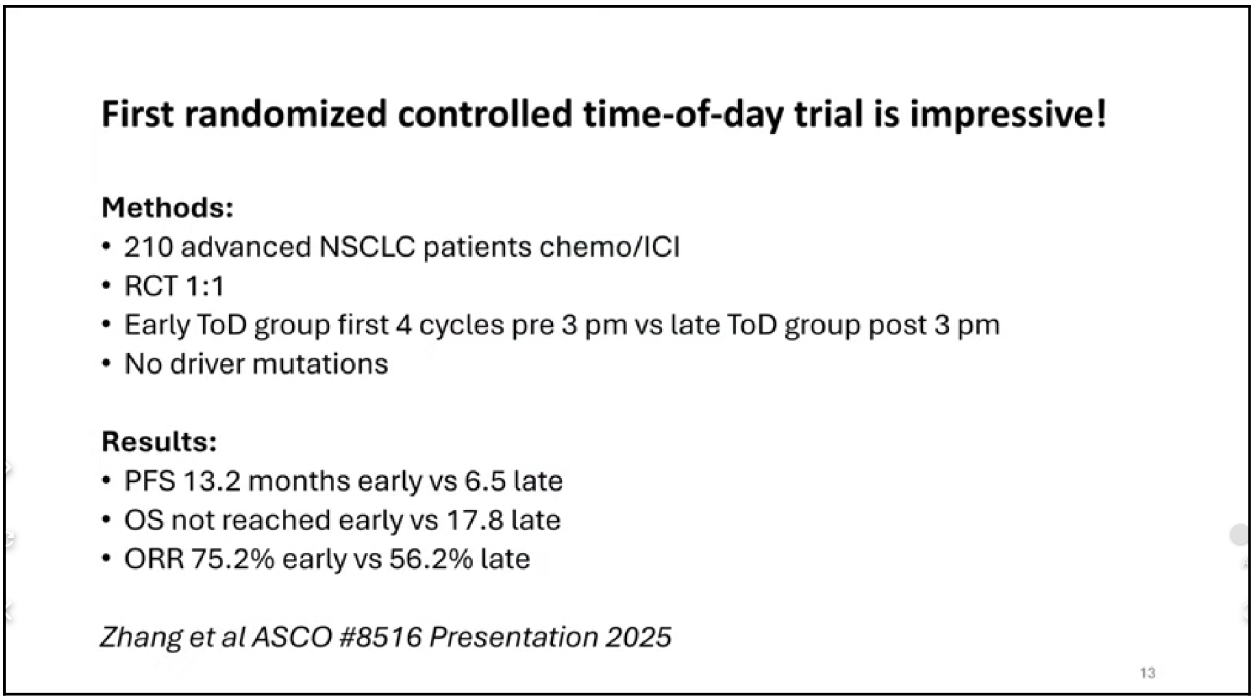
Here's another one published in *Cancer Cell* just a couple of years ago, looking at the baseline plasma histamine level and how that correlates with poor clinical response to immunotherapy.

Take a look at the right hand side. This is for about 70 patients drawn from a number of different cancer types. You can see those with high histamine levels, greater than 0.6 nanograms per ml, had quite a bit of progressive disease, compared to those who had less than 0.3 nanograms per ml. There is lots of mechanistic data in this paper as well. It appears that the H1 receptor on macrophages *[Macrophages are a type of immune cell that’s involved in the inflammatory response. They engulf and destroy bacteria, cancer cells, and damaged cells.]* is most critical in turning them into the M1 phenotype, which is thought to be the phenotype that's important in fighting cancer.



There are now 20 studies in over 6500 patients, in eight cancer types, correlating morning infusions with markedly better outcomes. This is from a review paper published about a year ago. It's very evident that time of day had a two to three fold effect on overall survival. *[Note: “Early time of day” was defined differently depending on the paper. Some of them defined it as before 12 o'clock, while others defined it as before three o'clock.]* But the bottom line is you can see] This is a stunning effect, to say the least.

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]



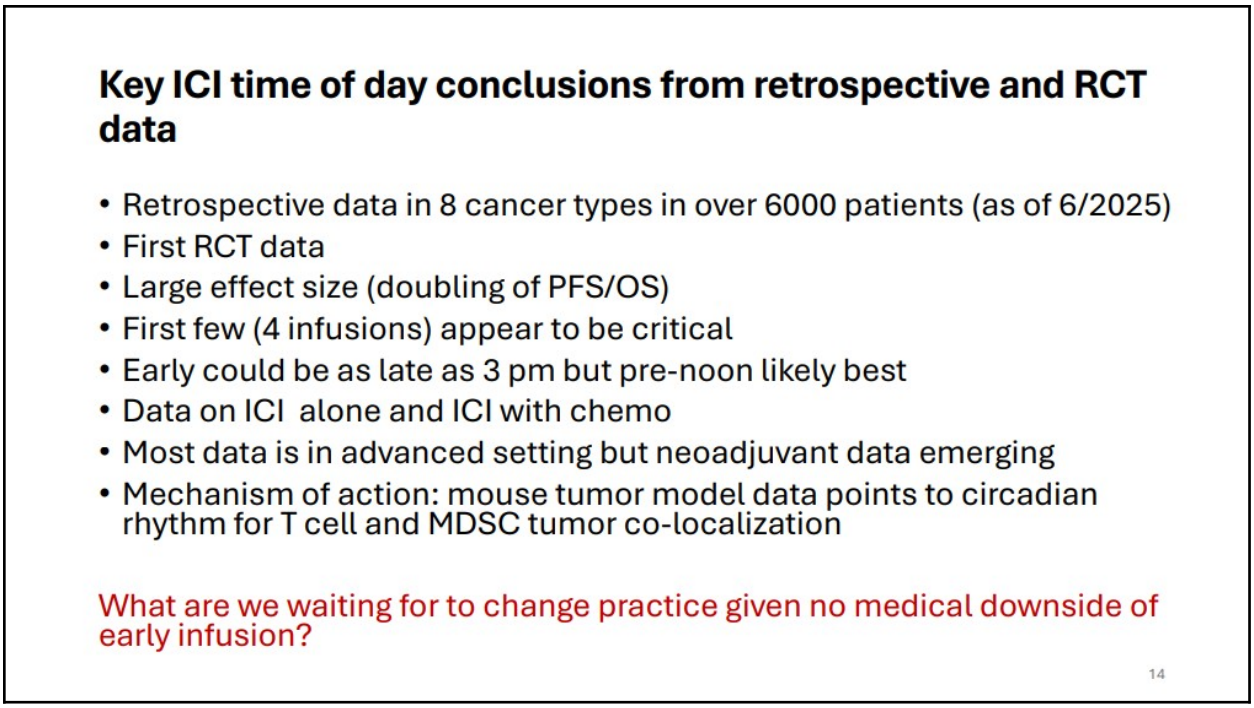
What is very exciting now is that just a few days ago, the first randomized controlled time-of-day trial data was published. This was in 210 patients with advanced false cell lung cancer getting both chemo and ICIs [ICI stands for immune checkpoint inhibitor].

The early time of day group was given the first four cycles before three o'clock, while the late group was given these first four cycles after three pm. Progression-free survival was (on average) 13.2 months for the early group and 6.5 months for the late group. Overall survival was not reached in the early group, while it was 17.8 months in the late group. And the overall response rate was 56.2% in the late group compared to 75.2% in the early group.

So the idea that the initial cycles are the important ones also came out of two retrospective analyses, which I have not mentioned over here.

This is extremely exciting, and is the first RCT data just fresh, hot off the press.

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

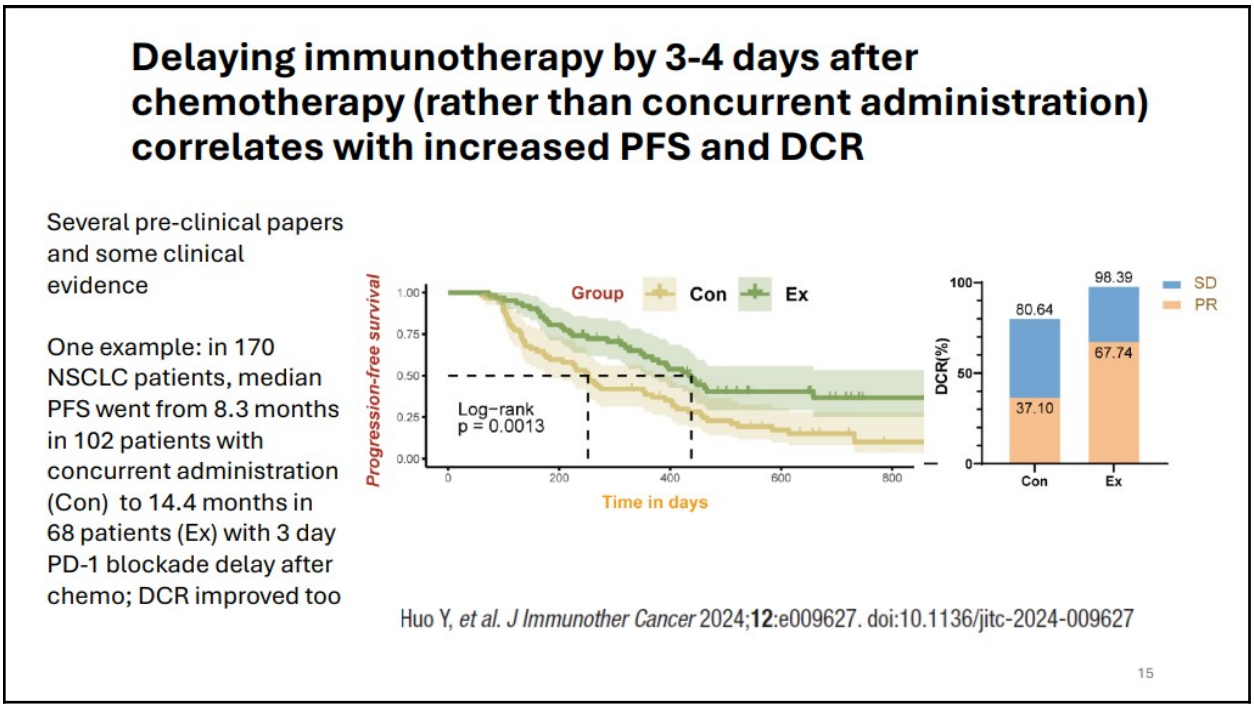


This summarizes what I said just a few minutes ago. This is a large effect size, and there's data on ICI alone and ICI with chemo. The ICI alone data is all retrospective, and this data is almost all in the advanced setting. Although, we know confidentially that here's some data in the neoadjuvant setting that's equally impressive. Here, the endpoints are looking at pathologic response rates.

Now there are three or four papers looking at the mechanism of action, and it points to circadian rhythm for both T cell and a suppressor cell population known as myeloid derived suppressor cells [immune cells that suppress T-cell responses] that are co-localizing in the tumor in the morning in patients.

The million dollar question that I'm just tossing out to the general group and any physicians who want to take this into account, what are we waiting for to change practice, given that there's no medical downside of early infusion, as far as we can tell?

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

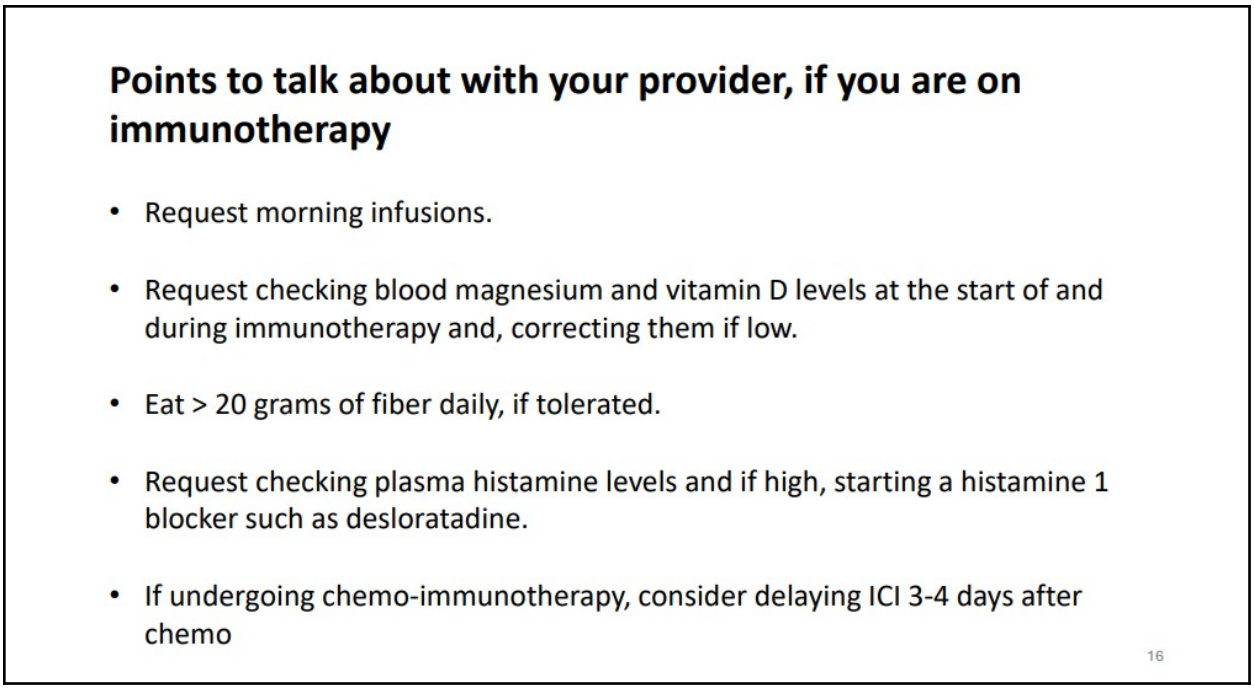


I also want to tell you about delaying immunotherapy in those patients who are getting concurrent therapy. It turns out there's plenty of animal data to back this up, all in the last two, three years.

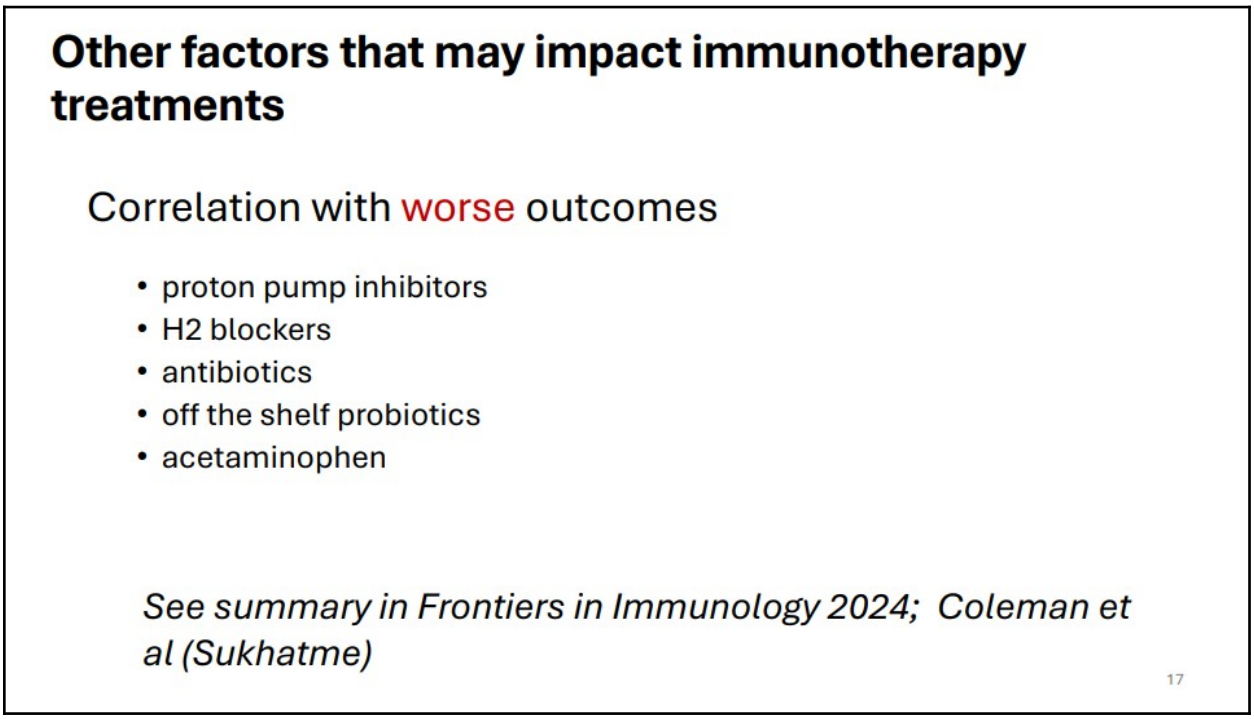
This is the largest single retrospective study, 170 patients. Median progression-free survival went from 8.3 months to about 14.4 months. Quite impressive. This is a more than 50% increase in progression-free survival. The disease control rate improved as well, so quite impressive data.

This makes a lot of biological sense. There are at least two major mechanisms to explain this. One is that steroids are often given with chemotherapy, and that, of course, is not what you want to do when you're about to go on checkpoint blockade. And secondly, we believe that following checkpoint blockade, as many people believe, there is an unleashing of a proliferative T cell response. And the wrong thing to do is to have chemo given on the same day, because there's enough level of chemo probably to mitigate that expansion of T cells. So these are at least two mechanisms. There are probably others that have to do with more effective suppression of various suppressor cell populations. Again, we can talk about this a little later, if you'd like.
This is waiting to be enacted in full force, and is not yet accepted by the oncology community.

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]



These are just pointers to take to your provider if you're on immunotherapy. I've just quickly summarized those here. These are from the slides that I presented.



What I haven't shown you is that there's also correlation with worse outcomes [when the following treatments are used concurrently with immunotherapy]. There is some mechanistic understanding of interventions that seem antagonistic to ICI use.

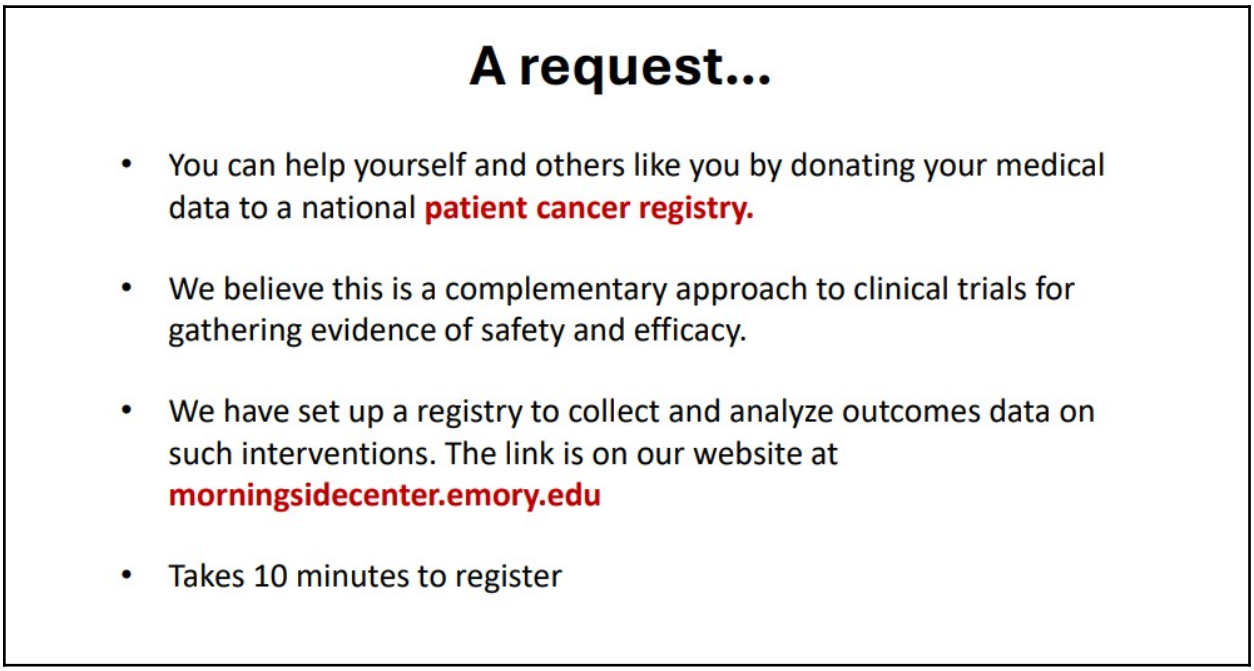
“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

We've mentioned steroids briefly. We've mentioned H2 blockers. There's data on PPIs, and very strong data on antibiotics and off the shelf probiotics.

There is one particular probiotic for which there's interventional, exciting data. It's called CBM 588 (a probiotic strain of the bacterium Clostridium butyricum), and again, we can spend more time on that. [Note: CBM558 could potentially increase the effectiveness of immunotherapy treatments. Read more here and here.]

And then there's some data on acetaminophen.

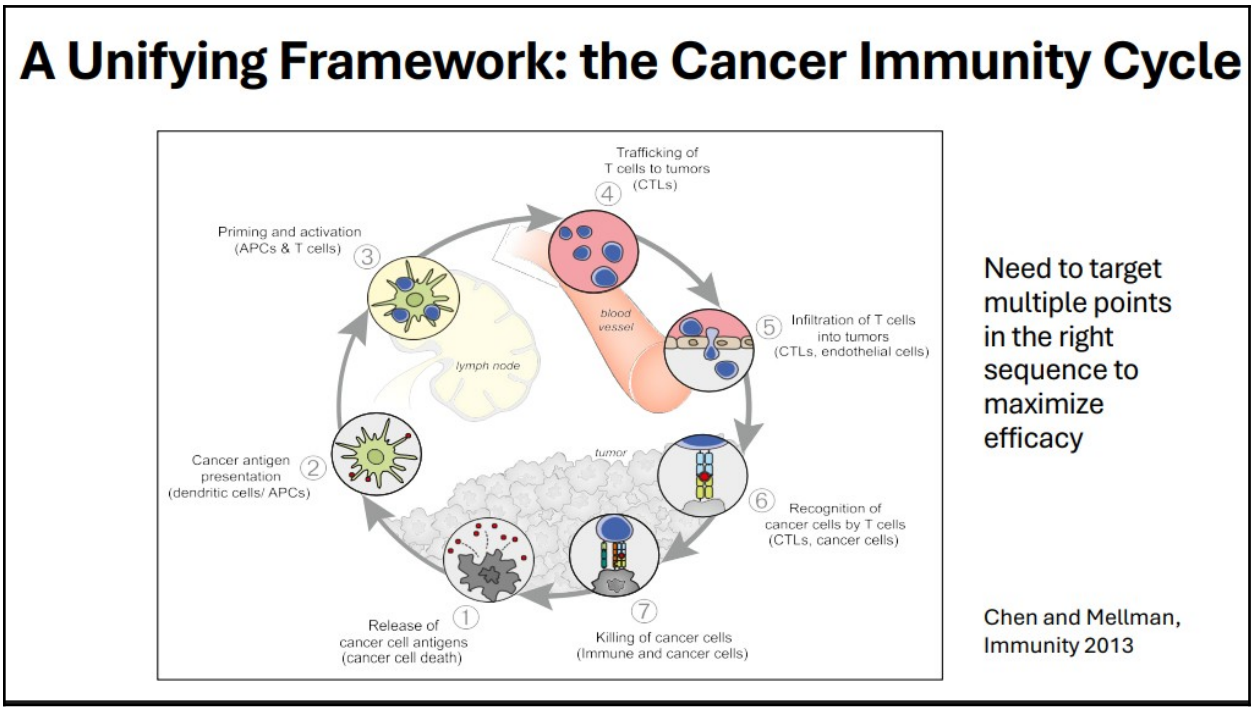
The mechanisms of how these antagonize PD-1 blockade are also not perfect, but there are more than a few hints as to how that might occur, and we've summarized that in a recent paper [read here].



We believe that clinical trials, as much as they are needed, cannot exhaust the extensive space and applications of some of these financial orphans, so we've created a national patient cancer registry and a collaboration with a company called xCures. This allows patients to register in just a few minutes. We’re hoping to convince more physicians to do one or more of these interventions, and to be able to collect and analyze that kind of outcomes data.

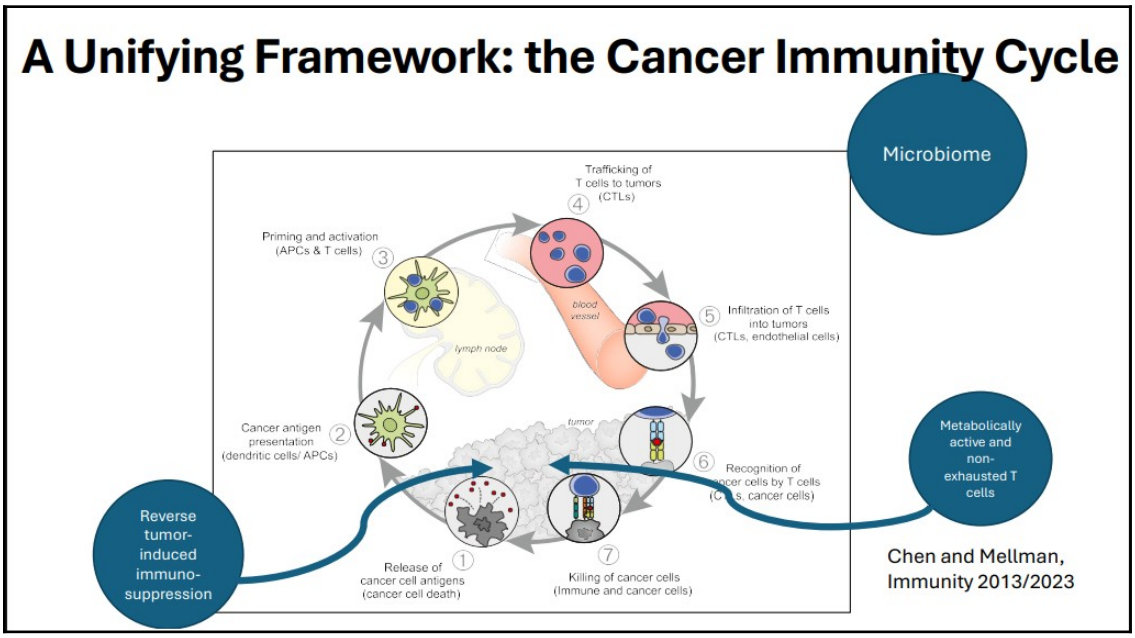
“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

I'm going to close by simply mentioning this. This is probably the only slide you'll remember out of everything I've shown you. These are two pictures of a woman who is a three-time Olympic champion in the heptathlon. A heptathlon is like the decathlon, but it has seven events instead of 10. It's only a women's event in the Olympics. The bottom line is this overlays very nicely with what I've talked about several times already: the cancer immunity cycle.

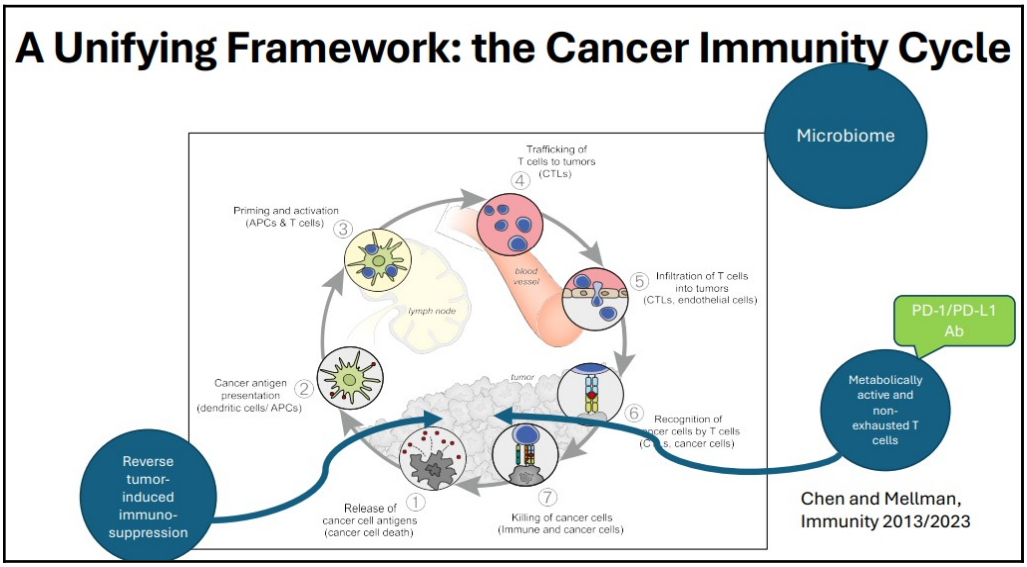


“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

This is a framework advanced by Chen and Melman in their classic paper in 2013 [read here]. This paper emphasizes the need to hit multiple points in this cascade, and to sequence them in the right way to maximize efficacy.

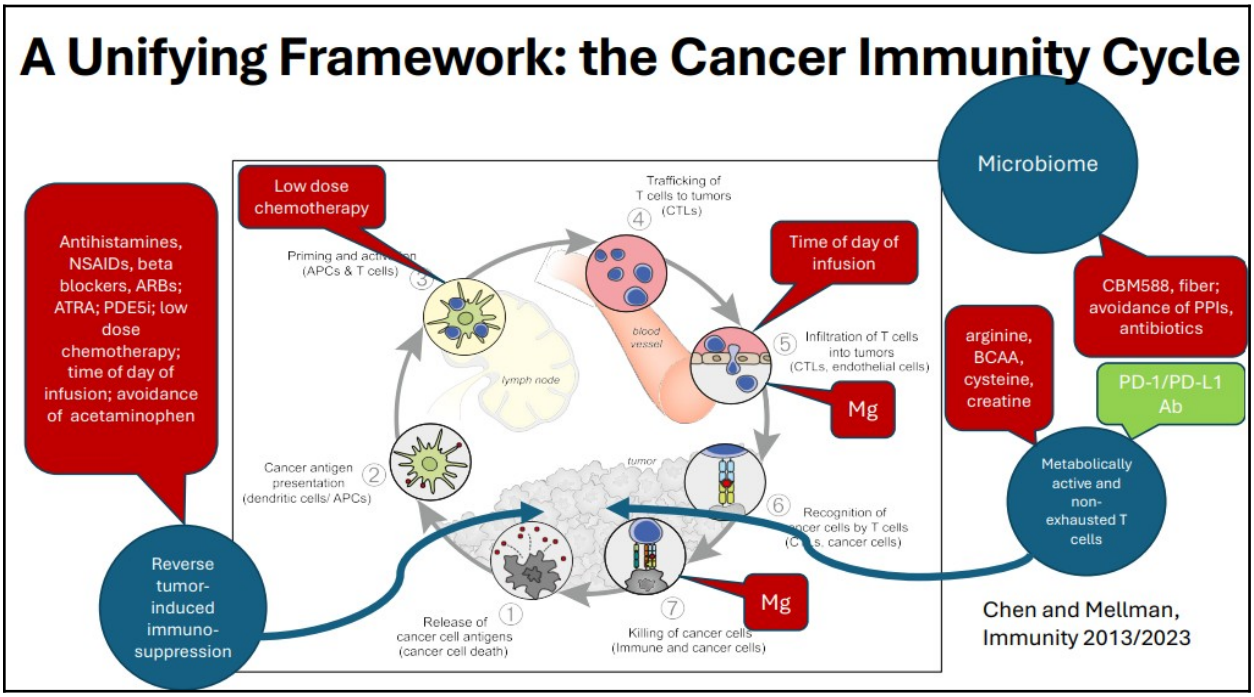


What the paper did not do in 2013 is talk about the microbiome. It did not talk about on the left hand side here, reversing tumor induced immunosuppression. And it did not really talk a lot about metabolically active and non-exhausted T cells as being critical for an immune response. So they modified the paper, and there's a new figure in their paper that came out in 2023 [see here].



“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

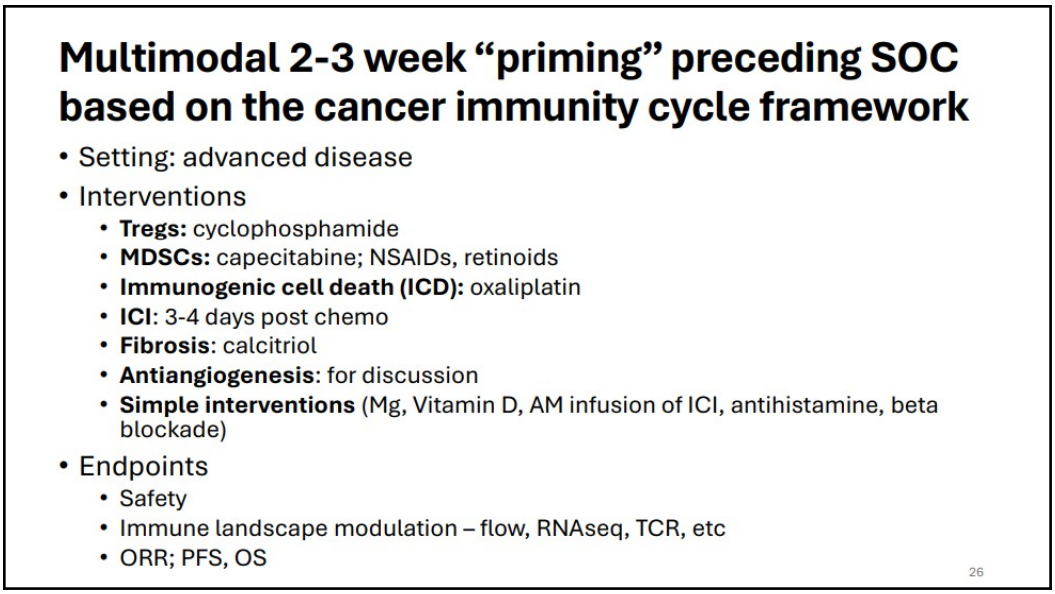
All I want to point out here now is that a PD-1 blockade, or PD-L1 blockade, acts at only one major point in this cycle. It shouldn't be a surprise at all that this is not going to have 100% efficacy.



Here, overlaid, are some of the interventions that I mentioned to you. For example, magnesium. Also, the time of day is mentioned here, as it has to do with infiltration of T cells and trafficking. We have not talked yet about low dose chemotherapy, which can affect a number of parameters, both in priming and activation of dendritic and T cells.

On the left hand side here, you'll see there are a whole number of ways of reducing the tumor induced immunosuppression. There are key cell types: T regulatory cells, the myeloid-derived suppressor cells, the M2 macrophages. All of these can be addressed with one or more of the interventions mentioned on the left hand side.

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]



I'm going to stop at this point to just again point out that if we could convince people to actually prime prior to standard of care therapy, based on the cancer immunity cycle, this would not only improve checkpoint blockade efficacy, but also potentially change the efficacy of chemotherapy. I'm speculating now, but there is data that chemotherapy works best actually in an immune intact environment, which sounds a little ironical, but there is some data to support that. And so some of these interventions that focus on this, on this cancer immunity cycle, may well work outside of immunotherapy as well.

Roger Royse 18:22
Have you also done any research into what actually not only increases the effectiveness of the checkpoint inhibitors, but maybe decreases some of the side effects and toxicity? Is that something that's been part of your study?

Vikas Sukhatme 19:12
Vidula and I just came from a meeting at Duke University a few days ago, and the entire meeting was focused on immune related adverse events. I may have mentioned one of the interventions here had some very significant effects on immune-related events. There's little doubt that some of these events may actually increase as we increase efficacy. There is a correlation of those two, but it may turn out that they don't. We don't yet know where we're on the curve of efficacy versus adverse events. We're just starting to pay some more attention to that. Roger, this is a very active area of interest. We'll be watching that very carefully.

Vidula Sukhatme 20:08
There's only a little bit of data suggesting that some of the adverse events are much lower in patients who have high vitamin D levels. That's the only thing they have found so far. There are a couple of treatments, but the group that is just forming, whose conference we attended, I think there's going to be a lot of people looking into those things, so we will make sure that we post them on our website as we find those ideas.

Vikas Sukhatme 20:41
That was the slide I presented. There was a five-fold decrease in the major adverse events bucket.

Roger Royse 20:48
Before we leave [this topic], it's not trivial, the statistics I've seen say that 20% of patients will have an adverse event from one inhibitor. But usually they stack them so there's more than one drug, and most patients have more, so that raises it to over 50%. So, I'm glad people are looking at that.

Why don't you go ahead, Russ?

Russ Hollyer 21:16
I actually don't know what H1 and H2 are? Can you explain those?

Vikas Sukhatme 21:26
The H stands for histamine. There are four receptors for histamine. The H1 blockers and H2 blockers are the most popular. The H2 blockers are drugs that basically are used for gastric acidity and H1 blockers are typically used as allergy medications.

Vidula Sukhatme 21:53
Cetirizine and loratadine are the h1 blockers, and famotidine is a h2 blocker. These are the commonly used drugs that people use.

Russ Hollyer 22:05
Thank you. And can we measure histamine commercially?

Vikas Sukhatme 22:09
Yes, there is a CLIA-approved test.

Vidula Sukhatme 22:14
It is usually used for mast cell activation syndrome. That community is what gets this test. We are trying to convince people to offer that to cancer patients. We haven't succeeded so far, but we are trying to do that.

Vikas Sukhatme 22:31
So in our report, they just measure one time baseline plasma histamine.

Russ Hollyer 22:40
Okay, can you estimate the cost? What's the test cost?

Vikas Sukhatme 22:46
I do not know.

Vidula Sukhatme 22:47
I don't think it's more than $500 but we are hoping we can get it for a lot less because we may have to do it a couple of times during a clinical trial with antihistamines. As part of the trial, we'll figure out these tests and all the costs involved. We may have to negotiate the costs with some of the laboratories who offer them because, as mentioned, magnesium is not routinely measured in cancer patients unless they're getting a particular chemotherapy. We find that a lot more oncologists are now actually checking vitamin D levels, but not everybody is doing it, so we are trying to put together three, four, five tests. We also didn't present the data, but there's some data to suggest that if you have high thromboxane levels in the blood, you may not be able to have your immune system work properly. So we are trying to collect all these agents to see if we can actually put together a panel of tests that people can routinely do. And all of these have actionable drugs that we have identified, so if you have high thromboxane levels, you could use aspirin. If you have high histamine levels, you can use antihistamines and so on.

Russ Hollyer 24:04
Do you have a survival study? You had interesting graphs on magnesium, vitamin D, et cetera. Do you have combination studies like, let's say somebody had high magnesium and high vitamin D and also was taking lots of fiber. What's their survival?

Vikas Sukhatme 24:26
That's one reason we're setting up the registry. The answer is that nobody's looked. Numbers kind of wither out. First of all, not everybody has done enough of these interventions, and that's what we're trying to encourage by going to patient advocacy groups to take this kind of information to your physician. But Russ, you hit it right on the head. I would love to know the answers to those questions. One thing we are doing is we're in the middle of a scientific review right now, going on with two different IRBs at two different institutions where we're putting in the vast majority of the interventions I just mentioned as one group. In other words, it is testing the hypothesis that if you do one or more of these things simultaneously, you are going to increase efficacy. So it's a safety tolerability study and a biomarker heavy study. It's not really powered for outcomes, but we want to sort of take the more conservative route first.

Vidula Sukhatme 25:26
And the conservative route that we are trying to take is because it could actually increase autoimmunity, and therefore, the adverse events, so we want to get a handle on it. I personally don't think that will happen. I think it's going to work for different people, so that the efficacy will be improved. But we don't know that until we have a small group where we try all the interventions at once. And so we will do the pilot study first, and then do the next step.

Roger Royse 25:58
There's a question related to that in the chat, it's, “Are the H1 blockers highly specific, or are they sloppy? And if they're sloppy, are there more or less H1 specific drugs?

Vikas Sukhatme 26:12

The prototype for H1 blockers was Benadryl (diphenhydramine) but that is relatively a little sloppier. It also penetrates the blood brain barrier, so it has more drowsiness as a side effect. The next generations, including cetirizine, loratadine, etc, have less side effects in the central nervous system. Desloratadine has some of the best data, I would say. If I had to suggest one, it would be that. There's also a more complicated issue around what is called “cationic amphiphilic” [a property where a molecule has both a water-attracting and water-repelling portion]. It’s a whole discussion in itself. Those H1 blockers that have that property seem to do the best, and that's where desloratadine appears to have an advantage.

Richard Anders 27:01
I guess what might have been studied is the fact that loratadine works, as opposed to a tight binder, a tight and exclusive binder works. Has the question of exclusive, highly specific binders to H1 worked, in contrast to just loratadine or whatever drugs they've studied? And if so, just out of curiosity, are there super specific H1 antihistamines or not really?

Vidula Sukhatme 27:47
We don't know the answer. A lot of people are trying to do it in animals, and I'm sure somebody, if they find a specific one that is not available, could then go through a new drug development route. What we are looking at is existing data. The way we have come up with all these things is through retrospective studies, which means it includes patients who are already on a drug, which means that drug has to be an approved agent. They have looked at whole other classes of drugs as well. But as Vikas was saying, that particular class in which desloratadine falls was the most effective. Now a caveat there is, if you have brain metastases, some of these may not reach and go through the blood brain barrier. There may be other drugs that you would have to look at. And there are people looking at those studies, but these whole H1 blocker studies are fairly recent in the last five years, and you will find that a lot more people are beginning to actually study that particular class of drugs. I'm anticipating that in the next two, three years, we'll see a whole bunch of papers being published. At least I'm hoping that that would be the case.

Richard Anders 29:02
Because I paid some attention to antihistamines a number of years ago. I read a book by a Canadian drug developer. I don't remember the drug. I think he was at Bayer, and he was a good scientist. I don't know if his drug ever actually got approved. I could probably find the name. But one of the things that he suggested in his book was a paradoxical increase in cancer in lab animals that were given anti histamines, which I kind of remembered. So I have no idea if there's been any validation of that, and certainly that might not have anything to do with this effect, but it was an interesting thing I noted.

Vikas Sukhatme 29:44
We’d be happy to take a look. Always send them along.

Vidula Sukhatme 29:47

If you find it, let us know. We do believe that a lot of the drugs that we are talking about are repurposed drugs, and they're working on some of the common homeostatic processes that happen in our body. So we have beta blockers, we have antihistamines. We are looking at statins, Metformin, these are commonly used drugs for a reason. A lot of people have issues where their homeostatic mechanisms are out of fact. So if your blood sugar is out of fact, you are given Metformin. But when you take Metformin, the blood sugar has increased for a reason, and the body homeostatically tries to go back to that set point that it was trying to go back to before. And so a lot of the drugs that we are looking at there are, I personally believe—and again, we don't have data to prove all this—but it's going to be in a particular range that that drug is going to be effective. Too little or too much, and it may not work. When we are planning the antihistamine trial, we don't want people to blindly take antihistamines. We want them to actually check their histamine levels, and only if they are high, we want them to take the antihistamines. Same thing with vitamin D. If you take too much of vitamin D, it could actually be immunosuppressive, so you want to be in that middle range of normal for the system to work perfectly. But as you can see, trying to do clinical trials with ranges is a different ball game, and it's not going to be that easy, which is why, again, we are going through this registry concept so that we can actually gather the data and see if this is making sense, theoretically.

Richard Anders 31:33
So you're measuring H1 and H2 antihistamines in the body, or just H1?

Vidula Sukhatme 31:39
We are measuring total histamine levels, which can then go both against H1 as well as H2.

Chris Apfel 31:48
Histamine is a molecule. It's one molecule and H1, H2 are different receptors. So you're measuring histamine.

Richard Anders 31:57
I see. So they're not different variants of histamine. They're all just receptors on the histamine, got it.

Vidula Sukhatme 32:05
So histamine is a molecule that is secreted by mast cells in the body. It has major responses for wound healing, and if there are very high histamine levels, it is immunosuppressive. So that's why we want to give antihistamines to stop the immunosuppressive effect.

Richard Anders 32:25
I mean, but that is difficult to reconcile with the fact that H1 and H2 have [different] effects. I mean, if you're still neutralizing histamine with H1 or H2 you would think that the effect would be similar, unless they're located differently. I mean, H2 tends to be in the stomach, I guess. But then that does sort of indicate you might be looking at locations of histamines, or, you know, maybe some histamines have more H2 or more H1 or something. I mean, it's a complicated question, obviously.

Vidula Sukhatme 33:00
Yes, absolutely.

Vikas Sukhatme 33:03
I mean the backdrop for this is that there is data on mast cells and cancer, and generally, the data points to the fact that having mast cells in a tumor is deleterious from a patient's standpoint. And one of the major things that mast cells can have in them when they degranulate, is release of histamine. And histamine has all kinds of important effects as part of a wound healing response. So this is again, part of a larger discussion we can have. This framework of wound healing is a very interesting framework in which to think about cancer therapy. Cancer is a wound that doesn't heal. All the events that occur — from platelet degranulation to mass cell degranulation to release of various growth factors — all of those promote any tumor cells that might be left behind after surgery. So that’s one reason why we believe in beta blockers. We believe in antihistamines, we believe in antiplatelet agents, etc, etc. And it's not just we believe, there's data to back these things up.

Richard Anders 34:16
Wow, amazing, really interesting,

Vidula Sukhatme 34:19
We have spent a lot of time on this wound healing response. Basically, when you have an infection in the body, the first job of the immune system is to make sure that it controls whatever microbes are invading the body once the wound has been sterilized. The next job is there is some destruction that has happened, and so the body has to rebuild it, and at the time the rebuild process takes over, you really don't want to have all these grenades going off that were going off before in order to kill the microbes. You want a stable environment. So the wound healing response in the later stages after the infection has been controlled, is actually immunosuppressive. It doesn't want the T cells. It doesn't want the macrophages coming there and throwing all the hand grenades that they were throwing before. That is my layman's explanation. But in the beginning of a wound, the body has to make sure that it is not infected. Once it's assured that there's no infection, then it's immunosuppressive. And cancer is in that second bucket. There is no infection there, as far as we know, and therefore it is continuously in an immunosuppressive mode. So the cancer itself is growing and causing injury, as you know, it breaks the membranes around it. And all the therapies for cancer we give are also injurious to the tissue, so the wound healing response is continuously in place and it is immunosuppressive.

In order to really make headway, we have to be paying attention to that piece, and these simple molecules like beta blockers, antihistamines, and COX-2 inhibitors (which is aspirin), can actually help reenergize the immune system. We just don't know in what combination and what order we need to do that.

Richard Anders 36:13
Have you tested the COX-1 inhibitor as opposed to the COX-1 and 2 inhibitors?

Vikas Sukhatme 36:22
Well, there's all kinds of data on COX-2, which hasn't quite borne out. It seems like COX-1 may be just as important. We have some data that we published on that in these surgical resection models that COX-1 blockade may play a more important role. There is, however, some positive data on relatively selective COX-2 inhibitors as well. It's a guy in Israel by the name of Ben-Eliyahu who's done a lot of work on this using beta blockade and selective COX-2 blockade. You may want to look at some of those papers, all in the surgical context.

Vidula Sukhatme 37:01
That is that third category that Vikas had mentioned, where we have ideas of how to prevent recurrence if you have been able to go through surgery. That's the space in which Ben-Eliyahu has published the beta blocker and COX-2 inhibitor data.

Roger Royse 37:18
We got some other questions in the chat. So you mentioned that you do this additional treatment three or four days after chemo, and the suggestion is, how about 10 to 14? Since it's about that long before a person feels a little better. And the second question David had is, what about the idea that vitamin K improves uptake of vitamin D?

Vikas Sukhatme 37:48
There is one retrospective analysis paper in which 10 to 14 days was looked at. That was not as good as the three to five day bucket in that paper. That was the best, the three to five day bucket. I could just cite you that as one retrospective analysis. I am quite sure there's at least one preclinical paper looking at an increase in that delay that found it was not as effective as well. So at the moment, three to four days seems to be the magic time by which chemotherapy levels in the blood have gone down, and the T cells can now wake up. It’s the magic time for the chemotherapy to act on the immunosuppressive populations, and time for the steroids to have worn off. That seems to be the magical sort of time.

Vidula Sukhatme 38:47
Three to six days seems to be the magic number, based on a whole bunch of other studies.

Your second question (about vitamin K) is a good question, because we do know that when we take vitamin D ourselves, the magnesium, vitamin D and Vitamin K in our bodies work together in biological processes. Again, going back to that homeostatic process, you don't want to undo too much of the balance in the body, so it would probably make sense to have some vitamin K on board, especially if you're going to take higher amounts of vitamin D. But I don't think we have actual data on that.

Roger Royse 39:38
Yeah, and also calcium, probably.

Vidula Sukhatme 39:40

Also calcium, but most people do have calcium in their diets. It’s the vitamin K that seems to be variable.

Roger Royse 39:48
Okay, there's a question about, what about akkermansia for enhancing the check one inhibitor? What about probiotics, generally, especially akkermansia?

Vikas Sukhatme 39:59
The CBM 588, that I mentioned, for which there is some randomized study data in kidney cancer, is a Clostridium butyricum. It actually generates butyrate in the gastrointestinal tract. So that's the one I mentioned. There is some data on akkermansia as well, as well as a number of others. I cannot quote you chapter and verse on that off the bat, but it is an evolving literature that should be looked at.

Roger Royse 40:46
Russ asked if someone is not doing chemo, but has cancer, have any of these things been investigated?

Vidula Sukhatme 40:59
You mean they are getting no cancer treatments, or just not chemo?

Russ Hollyer 41:03
They're not getting chemo. Like, let's say they're doing ADT if they have prostate cancer.

Vidula Sukhatme 41:11
Targeted therapies in particular?

Russ Hollyer 41:14
Yeah, SBRT [Stereotactic Body Radiation Therapy], or some kind of immunogenic therapy

Vidula Sukhatme 41:21
We have not seen any data for the things that we told you about today, but we don't think that that's going to be an issue. This is a general immunity cycle that is activated by magnesium, vitamin D, fiber, etc. I think it's going to help with any cancer treatment you get. But I don't know if people have looked at the data.

Again, if we can get enough patients in the registry, then we would have a chance to look at all these things. We are hoping that a lot of cancer patients will join the registry and offer to share their medical records with us. There are some very highly motivated cancer patients who are also willing to share data of other treatments that they're taking that may not be in their medical records. For example, if you're taking a high fiber diet, or if you're taking one of these probiotics, the chances are very high that that data is not in your medical records. And if that's the case, we can't do a retrospective analysis. We are hoping that we can get data on cases of people experimenting with all kinds of things.

Roger Royse 42:37
What is the hypothesis as to why ICI is so much more effective earlier?

Vikas Sukhatme 42:46
The hypothesis is based largely on animal studies, and as I mentioned minutes ago, there appears to be the highest level of suppression with myeloid suppressor cells in the morning hours. These are the guys who are going to express PD-L1 on their surface and interact with PD-1 on T cells and create an exhausted T cell. There also appears to be the highest level of cytolytic T cell migration into a tumor in the morning hours as well. It's as if the battle is ready to go, and you come in at that time with PD-1 blockade. That's at least one of the ongoing theories. It's basically a circadian rhythm of T cell and suppressor cell arrival into the tumor bed itself. There are other theories. There are different times of day in which dendritic cells get activated and migrate and so on so forth. So this is a complicated subject, but there are three papers on time of day in animal models that support this.

Vidula Sukhatme 44:00
It is a little bit difficult to figure out because people may have slightly different circadian rhythms. The interesting part was that the retrospective studies were done in different parts of the world, so obviously the day and night could have been all off, and yet they all showed the same thing. So there is something there, we just don't know exactly what it is.

Vikas Sukhatme 44:54
Thank you. This has been exciting, and I particularly wanted to thank Brad for introducing us to a number of folks who've been on this presentation before. There have been some nice interactions.

Vidula Sukhatme 45:13
We all have to work together because the drug companies are doing their thing. The physicians are doing their things, but the patients have actually a lot to contribute. I'm a patient advocate. I started on this journey because a close friend of mine was diagnosed with breast cancer, and when her doctors said they had nothing to offer, we had to go through and look through the data ourselves. This is what started our journey, and I believe all of you are basically doing the same thing. By sharing that information with each other, I think we can add that third leg to the stool. Thank you.

Allen Morris 45:59
Almost all of the agents you were talking about are over-the-counter which patients have access to. And I recognize the noble idea of the registry to try to collect data because that's lost. Stated another way — Everybody's experimenting on themselves with the over the counter products and we're not benefiting from those ‘n of one’ experiments. A registry to collect the data is a noble quest.

That said, one of the things that I saw is not over the counter was low dose cyclophosphamide, which some of our citizen-scientists are very enthusiastic about. Low dose cyclophosphamide is not going to be accessible by patients as far as doing self experimentation. So, let's say I really believed low dose cyclophosphamide was helpful in some sort of immune way (e.g. eliminating the immunosuppressive T cells, the Tregs) so much so that I was willing to experiment on myself. I don't have access to low dose cyclophosphamide, and I don't think any patient does. Am I wrong?

Vikas Sukhatme 47:07
You're absolutely correct. Those interventions would need oversight and prescription from a physician.

Chris Apfel 47:15
But you could prescribe it to yourself, Allen, right? I mean, legally, you can.

Allen Morris 47:21
Yes. [But I would not want to play doctor on myself with a prescription drug I have no experience with - especially a chemotherapeutic drug - as the saying goes “a physician who treats himself has a fool for a patient”]

Vikas Sukhatme 47:24
A lot of those interventions on the last slide are very systematically looking at agents that deplete T regs, that deplete myeloid derived suppressor cells, that convert macrophages to M1 macrophages, and that heighten antigen presentation. Most of those will require a physician to prescribe. But we're designing some trials now where we are starting to combine these agents together. That's the goal, to really do some sophisticated serial measurements in a given patient as to what happens to these immune cell subsets and so on so forth.

Vidula Sukhatme 48:05
Allen, you bring a very good point. You will see we have tons and tons of ideas in that particular field — how to get the immune system to work better. We haven't posted a lot of those on our blog because of this issue (it might be frustrating for patients to see the data and not be able to get a physician to act on it for them.) If any one of you know physicians who are willing to act on the kind of data that we are showing you, we would love to talk with them. Because we need at least a few people to try these therapies out. We are hoping that once the registry gets going and we have enough patients, we are going to try to write consent forms on behalf of patients, saying, ‘I as a Patient, consent to this treatment, knowing that this is a promising but not proven therapy.’ Because physicians are afraid to offer it to you without some legal protection. We are trying to actually work out, ‘how can we protect the physicians?’

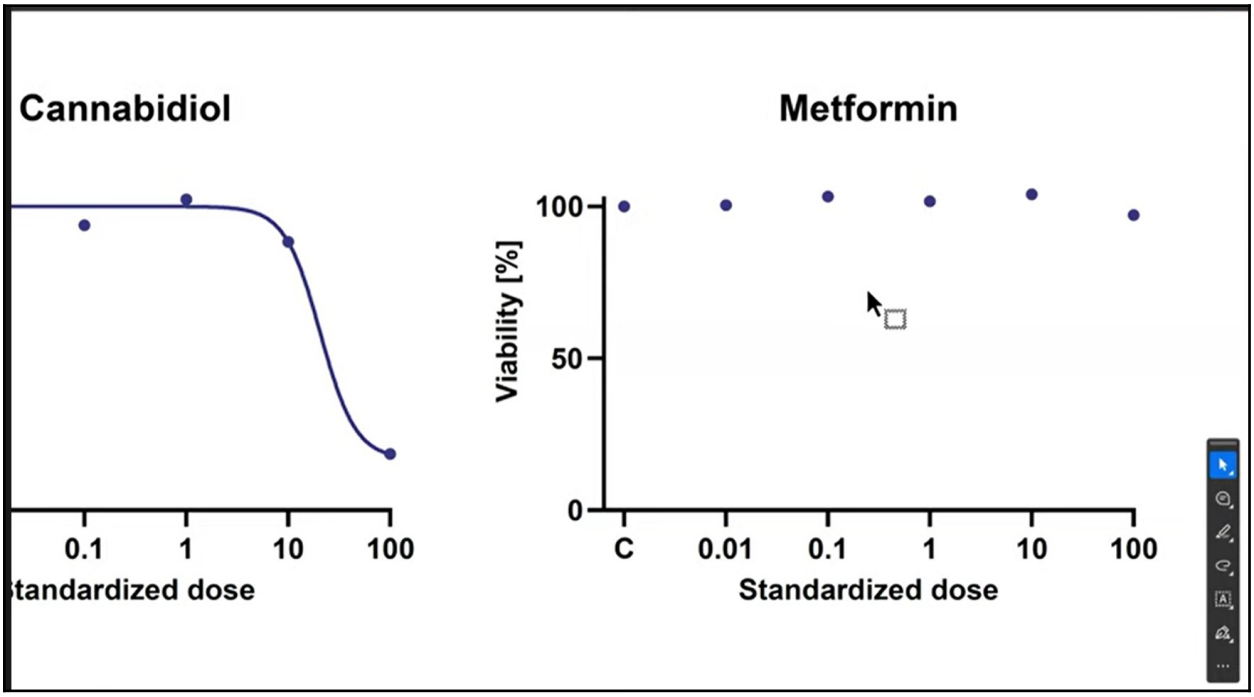
A lot of people we have talked to, including oncologists, have said low dose cyclophosphamide is another drug that we want to experiment with. There is calcitriol that we can add to that group. Physicians may be willing to do it, but not individually. They need a group of people. They need a group of doctors to talk to who have given the cyclophosphamide and can share what

happened to their patient. A clinical trial is what provides them that education. When they treat one patient at a time, they are on their own, and which is why they don't do it. It took us a while to figure it out, but we have to actually help physicians to offer you the treatment. If you have any thoughts on how we can collect this group of physicians to help patients, please give us a call or send us an email, and we'd be happy to brainstorm that idea. We are in the process of trying to collect those names right now.

Chris Apfel 50:22
I have a question and a comment. I'm really excited to see how you have taken this to the next level. I also have a medical background, I'm an MD/PhD.

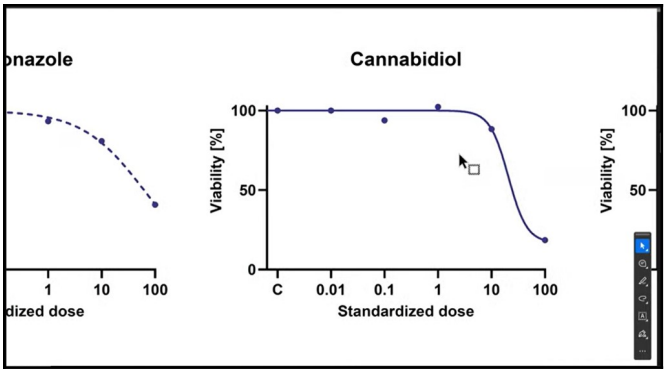
When my father had lung cancer, he basically refused chemotherapy because he suffered through this when my mother had ovarian cancer. Treatment actually made her only worse. So he basically refused, and he said to me, ‘unless you can promise to me, son, that it’s going to work, I don't want it.’ That was, for me, a real wake up call. I've published extensively in my field, anesthesia and curative care medicine, over 100 papers, etc. I was shocked to realize that, even though we talk about precision oncology and precision medicine, cancer treatment is still largely trial and error. That's actually why I looked into functional precision oncology methods, functional profiling, which we developed further at SageMedic Corp (Dr. Chris Apfel’s company). I then left the clinical department at UCSF.

We developed a functional precision oncology platform in order to really test those drugs. We can actually create those microtumors within one day, so that we have a result within one to two weeks for the patient. We can test both targeted therapies as well as repurposed therapies. We have a repurposed drug panel, which is usually 12 drugs.

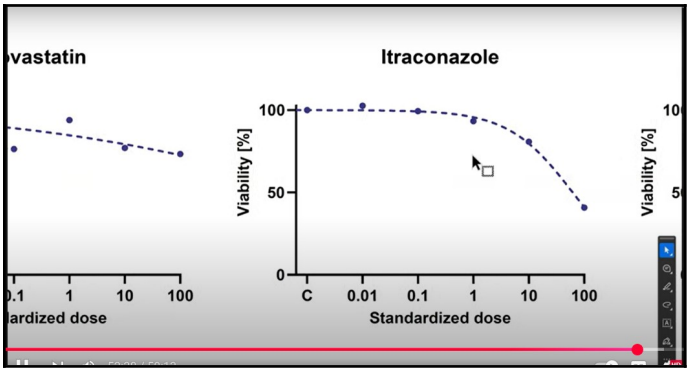


“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

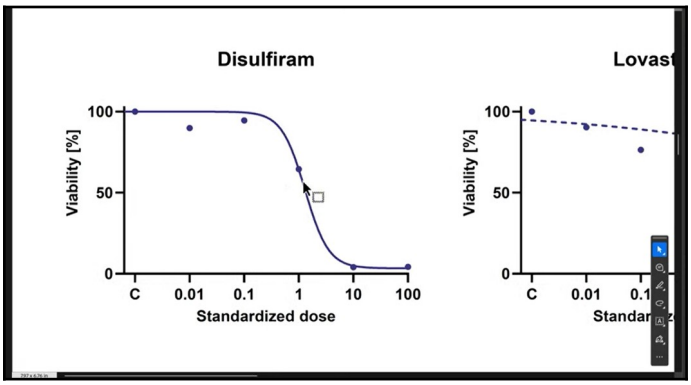
Do you see the Metformin data that I'm currently projecting? So normally we have a 12 drug panel. In this case, this was a lobular stage four breast cancer in a woman who is a physician herself. I'll just show you a couple of dose responses.



This is cannabidiol, we just added it to the panel.



Itraconazole, I have always been very excited about. But this didn't show much.



We had other samples where lovastatin has gotten wonderful dose response curves. And then disulfiram. This is actually very promising, and she's going to start on that alone. This is the

cytotoxicity assay. We actually have an antiproliferation assay. And it's very interesting. There are certain drugs where you have antiproliferative effects within one to 10 orders of magnitude lower than the cytotoxic effects.

It really varies from patient to patient, and so I would love to continue the conversation with you and see how we can really understand who will benefit from what, because all those mechanisms of the repurposed drugs are well described and well known. But until we have really tested the tumor, we actually don't know whether it's going to work. If we can perhaps combine forces in one way or the other to establish this, this would be great.
And then my second comment on this is how to provide legal protection. What we try to do is we stay within standard of care guidelines, within the NCCN guidelines. But even then you get resistance, and if you have anything that's outside of guidelines, the patients are encountering the challenges that you mentioned. I think there are two angles. Number one, a patient should have a right of self determination. With a prognosis that is at stage four, with a very poor prognosis when other treatments have failed, I think there is a way the patient should be able to demand to get this treatment. Otherwise it would be kind of abandonment. That's a hard line approach. The other approach, and we can probably discuss how we organize it, is to design a a registry trial, and have this with IRB approval and that should provide the oncologist with the legal protection. The second one is probably the easier path, at least at this point forward.

Vidula Sukhatme 55:13
It is easier, but it is a long path, and it's an expensive path. That's what we are finding. We have trials that have been written, and the process takes about nine months to get them approved.

Chris Apfel 55:29
Sorry, no, you go to Western IRB or to Advarra, and that should not take that long.

Vidula Sukhatme 55:36
At least the institution we are working on, even when you go to the Western IRB, they require there to be their own IRB approval to go to the Western IRB, so that itself takes time. And then the other thing we have been quoted, and maybe you guys can help us with this, we wanted to do a very simple time of day trial. There was no new drug involved. We wanted to do the morning versus the afternoon. We don't need to do that trial anymore, because I think we have enough data, but in the early days, the budget for that trial came to around $15,000 a patient. We are a nonprofit within a university, so there's no way we can fund that trial to be a definitive trial. We could fund it for 10 people, 20 people, but not a lot more than that. So when we go the route of the clinical trial, that is where we are experiencing issues. For me as a patient advocate, that is very frustrating, because I started this entity because I wanted immediate help for patients like my friend who didn't have time to wait. The trials are just taking way too long. It's really a catch 22, if we could do the trial.

I did mention in the very beginning that we are trying to do some advocacy with agencies that may have a for profit way of developing new drugs [and that wouldn’t otherwise be able to explore new uses for their already approved drugs]. To get the last ounce of usefulness from

that drug, maybe we should consider having a separate infrastructure. It could be a government infrastructure. We are looking into something called FFRDC, a federally funded research and development center that we can set up where private and public folks could work together, and the sole purpose of that agency could be to take every approved drug and see if it can be repurposed or used better. So doing studies on factors like the time of the day, lower dosage or different scheduling. The pharmaceutical companies, they don't have incentives. We haven't given them incentives to do their studies, so we need a parallel agency to kind of do all these studies. Europe is way ahead of us. They are the ones who are actually a lot of the studies we find. They are coming from Europe and China.

Roger Royse 58:28
Could you, Vikas and Vidula, drop your contact information in the chat, because I think some people might want to follow up with you and continue the conversation.

Vikas Sukhatme 58:40
Yeah, sure, we will. Brad has it as well. So again, we wanted to thank you very much.

Roger Royse 58:56
Thank you for being here.

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

CHAT CONVERSATION

00:21:38 Richard Anders: Were the patients treated to be normal magnesia or was that just a correlation?
00:31:25 Roger Royse: here is the patient study site https://patient.xcures.com/signup?program=morningside
00:35:07 Richard Anders: What were the p values of these various studies?
00:35:46 David Plunkett: Can you point us to any studies supporting or refuting the idea that Vit. K improves uptake of Vit. D ?
00:37:27 Richard Anders: Are the H1 blockers highly H1 specific, or are they somewhat sloppy? If sloppy, are there some more or less H1 specific drugs
00:39:43 David Plunkett: Re: 3 to 4 days after chemo for additional treatment -- any information about doing it 10 to 14 days after chemo instead? 3 to 4 days after each chemo infusion was when I felt worst, I would not have wanted to get out and about at that time. Second week after chemo I felt much better.
00:49:02 Russ: Replying to "Brad - did our/AnCan..."

Inc in rats H1 ... https://pubmed.ncbi.nlm.nih.gov/7909571/
00:50:59 Russ: https://academic.oup.com/jnci/article-abstract/86/10/770/910362
00:52:15 Brad Power: What about akkermansia for enhancing the ICI?
00:52:15 Rick Davis: What is the hypothesis as to why ICI is so much more effective early in the day?
00:54:18 Russ: Say, someone isn't doing chemo/ICIs but has cancer, have any of these things been investigated?
00:54:38 Russ: optimum vitamin d ? 25-45 ng/ml?
00:57:02 Rick Davis: There's a bunch of studies on PrCa and Vit D.... suggest you do a search, Russ
00:57:26 Rick Davis: 25 is low - 40-80
00:57:50 Russ: Thanks. I have looked into Vd. Wondering about the fiber, etc. Correlating with treatment outcomes?
00:58:03 David Plunkett: Replying to "Can you point us to ..."

I haven't found anything other than this 2017 report: The Synergistic Interplay between Vitamins D and K for Bone and Cardiovascular Health: A Narrative Review - PMC
00:58:59 Russ: Replying to "Can you point us to ..."

might be some stuff in here
:
00:59:26 Russ: Replying to "Can you point us to ..."

too long David. i'll post on CPL. D3 and lots of PCa metrics
00:59:45 Russ: Replying to "Can you point us to ..."

Trials, etc. DO-HEALTH is a good one.

“Increasing the Effectiveness of Immune Checkpoint Inhibitors” (Vikas Sukhatme, MD, ScD, and Vidula Sukhatme, MS) [#147]

00:59:48 Dr. Chris Apfel: Vikas and Vidula, what an impressive presentation. At SAGE we're also seeing direct cytotoxic or antiproliferative effectiveness of such repurposed drugs in our functional precision oncology platform, but the efficacy depends really on the patient's tumor.
01:02:24 Richard Anders: You would need to find a doctor who would do it and perhaps a compounder
01:04:17 Richard Anders: It might be hard to run by an IRB as well.
01:13:23 Richard Anders: Sometimes you can do things around orphan drug indications in such drugs
01:13:31 Richard Anders: Or use patents also
01:13:39 allen morris: what dose/schedule do you recommend for low dose cyclophosphamide?
01:14:00 Vidula Sukhatme: Vidula@Global-cures.org