“Personalized Drug Dosing” (Paul Van Camp and Jeff Krolick) [#68]

Paul Van Camp, Jeff Krolick, and Brad Power
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“Gatenby and his team said, ‘You only have three metastatic sites. You have a very low volume. Why don't we look at an extinction approach and do all three sites with SBRT, and then do a second strike. Then we'll look at a third strike after some genetic testing.’” – Jeff Krolick

Meeting Summary

The Problem and Opportunity

Advanced cancer patients want treatments that are uniquely tailored to them and their cancer for the best possible outcomes. The treatments that patients and their doctors consider are typically based on standard guidelines (e.g., the NCCN guidelines) derived from randomized clinical trials and population averages. The treatments are personalized to each patient to a limited extent, but treatment guidelines typically don’t extend to personalized drug dosing.

Getting the drug dose and schedule wrong can lead to the selection of a dose that:

- provides more toxicity without additional efficacy,
- causes severe toxicities that require a high rate of dose reductions,
- causes intolerable toxicities that lead to premature discontinuation,
- misses an opportunity for continued benefit from the drug,
- causes financial toxicity from overuse of an expensive drug,
- causes persistent or irreversible toxicities that limit the options for receiving benefit of subsequent therapies,
- can foster resistance mechanisms which may limit the effectiveness of the drug and subsequent therapies.

The guidelines for drug dosing are usually at the levels and frequency as established in the randomized clinical trial that got the drug approved, which is usually at the maximum tolerated dose. Phase I trials are dose finding trials done on a small number of patients at different, or escalating doses. This is to try to identify the maximum tolerated dose to be tested in Phase II larger pilot trials, and finally in larger and longer Phase III trials. They must show efficacy (“statistical significance”) that the drug has a positive outcome(s) result different from a placebo group randomly assigned. If this is demonstrated in the Phase III then the FDA may review it and grant approval for use in that specific patient population and stage of disease and at that specific dosing. It will be at the maximum tolerated dose, and not the minimum effective dose. This becomes incorporated into practice as the “standard of care”. Note that this is standard care and not necessarily the “gold-standard” or optimal care.

The conditions for drug approval are different from the conditions for a given patient. For example, they don’t consider body differences, such as the effective dose for a 250 lb.

bodybuilder vs. the effective dose for a 90 lb. person with sarcopenia (loss of muscle tissue as a natural part of the aging process).

Maximum tolerated continuous dosing of any cancer therapy that does not promptly and completely cure the cancer inevitably leads to its own failure by selecting for resistance. It is true for chemotherapies, and it is true of hormonal and immunotherapies.

Many drugs can be effective at lower doses with less side effects, such as the androgen deprivation drug abiraterone at 250 mg vs. 1000 mg daily when taken with a moderate fat breakfast (per the FDA). Other prostate cancer drugs, such as enzalutamide, can have terrible side effects such as severe fatigue for some, and have now demonstrated effectiveness at half the dosage (per many medical oncologists, including prostate cancer expert Dr. Oliver Sartor). The same may be true for other prostate cancer drugs, such as apalutamide and darolutamide. Indeed, preliminary evidence shows that the effective dose of darolutamide is not the maximum tolerated dose that is frequently used. Unfortunately we usually do not have adequate data for minimal effective dosages. This typically emerges slowly from real-world experiences.

Many drugs are administered without considering pharmacogenomics – that different people metabolize drugs at different rates. A diagnostic test may be able to personalize drug dosing.

The Solution - What You Should Do

To fully personalize cancer care, patients and their doctors must leverage patient data not only to identify the right therapy, but also to determine the precise dose that will maximize the patient’s benefit-to-risk ratio. Diagnostic technologies to personalize dosing can play a pivotal role in improving patient outcomes.

Patients and their doctors must select effective alternatives to the “maximum tolerated dose until failure” model, including using Darwinian evolutionary dynamics to provide better clinical outcomes, avoid or slow resistance, slow progression of cancer through its developmental stages (“Hallmarks of Cancer”), reduce toxicity and harms of treatment, and improve quality of life while living with a cancer diagnosis. There are various strategies, but they all involve “switching things up” before the complete failure (resistance) of a treatment. Dosing should be personalized within a treatment strategy, such as mathematical models based on evolutionary biology, tying drug doses to diagnostic tests on drug response, rather than pre-defined doses and frequency. For example, Dr. Bob Gatenby described his adaptive therapy study which used evolution-based mathematical models to manage drug frequency, significantly prolonging drug response in metastatic castrate-resistant prostate cancer.

You should educate yourself about personalized dosing and adaptive therapy, and discuss personalized drug dosing with your doctors, checking to see if there is a possibility of a “minimum effective dose” vs. the standard “maximum tolerated dose”. Since pharmaceutical companies will not be motivated to run a randomized clinical trial to find a minimum effective dose, the way to find a minimum effective dose is to review the real world experience of other patients.

The US FDA’s Oncology Center of Excellence is leading an initiative, Project Optimus, to reform the dose optimization and dose selection paradigm in oncology drug development. It will also have implications for personalized drug dosing for patients in clinical delivery.

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Advanced prostate cancer patients Dr. Paul Van Camp and Jeff Krolick shared their insights and personal experiences with personalized drug dosing:

Patient Views and Cases

Dr. Paul Van Camp shared his views on the above issues, including how doses for FDA approval derive from clinical trials: Maximum Tolerated Dose vs. Minimum Effective Dose; the problem of continuous Maximum Tolerated Dose to failure, hormonal therapies (ADT +/- ARSI) until failure and progression to Castrate Resistant Prostate Cancer, how all Maximum Tolerated Dose administration continuously used will eventually fail (caused by resistance); combination treatments and sequencing strategies to overcome resistance; non-FDA dosing alternatives from real-world clinical experience (e.g., half dose enzalutamide or darolutamide; Abiraterone at 250mg with fatty breakfast as examples); remembering to check drug-drug interactions (and supplements, and effects on metabolizing enzymes (CYP450 - Human cytochrome P450 (CYP) enzymes, as membrane-bound hemoproteins, play important roles in the detoxification of drugs, cellular metabolism, and homeostasis). His regimen includes periodic senolytics (drugs that selectively clear senescent cells - which stop multiplying but don't die off when they should), for example, a three-day course every three months and especially after completing some other course of therapy such as radiation, radioligand, or chemotherapy.

Jeff Krolick has been microdosing various drugs and supplements to treat his cancer. He has been using Adaptive Therapy (and now SBRT for Oligometastatic prostate cancer) as directed by his medical oncologist, Dr. Lemanne, in collaboration with Drs.Gatenby, Brown and Anderson from the Integrated Mathematical Oncology team at Moffitt Cancer Center and Dr. Tran from the Radiation Oncology-Biology Integration Network Oligometastasis (ROBIN OligoMET) Center at the University of Maryland Medical Center, which is focused on understanding how radiation therapy can affect the metastatic process particularly in low-volume or oligometastatic prostate cancer.

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Meeting Notes

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Discussion Outline

1. Paul Van Camp introduction.
2. Dosing of drugs for prostate cancer. (2:49)
3. Effective dose vs. maximum tolerated dose. (6:43)
4. Is there a minimum tolerated dose for prostate cancer? (12:16)
5. Paul's response to questions. (17:01)
6. Jeff Krolick introduction. (26:09)
7. How do you make cancer extinct by using first and second strike strategies? (32:58)
8. Mushrooms (41:57)

SUMMARY KEYWORDS

drug, oncologist, dosing, dose, psa, patients, milligrams, toxicity, cancer, working, paul, regimen, prostate cancer, tolerate, overall survival, personalized, therapy, strike, cells, approved

SPEAKERS

Paul Van Camp (48%), Jeff Krolick (27%), Brad Power (13%), Amit Gattani (9%), Robert Gurmankin (3%), John Sandiford (<1%)

Meeting Transcript

Brad Power
Today we're going to talk about personalized dosing. This is a subject which we've covered once before with Mina Nikanjam. She was going to be joining us, but unfortunately is ill and will not be able to. We have two patients who will be talking about their experience with personalized dosing, Dr. Paul Van Camp and Jeff Krolick.

Brad Power 1:19
To set this up, I'll try to give you a few highlights from the meeting description we sent out. Paul will pick up on these ideas as well. The dosing that you get is what the dosing was in the original clinical trial that approved the drug. And therefore the dosing is typically done at maximum tolerable dose. The way it's applied is typically maximum tolerable dose until failure. There's a possibility that people metabolize medicines differently, and that lower doses might be equally effective and have fewer side effects. So there's a discussion about how you can personalize dosing or reduce dosing based on an individual. And the solution is to do more testing to try and

figure out how you would personalize your dosing. You'll hear a couple of stories from our patients who've done that.

Brad Power 2:26
We'll start with Paul. Paul is both a trained medical doctor, as well as a prostate cancer survivor, and he is very knowledgeable and very helpful to other patients. So Paul, why don't you start on your views on drug dosing, personalized dosing, and actually how you've applied it to yourself?

Paul Van Camp 2:49
In considering dosing drugs for cancer, in general, and drugs for prostate cancer, specifically, we've seen several new and useful drugs come out into practice than in very recent years. These drugs are FDA approved, the requirement for FDA approval is that they go through stage one, two, and three clinical trials. Stage one, they take a few patients, and they do escalating doses. They keep pushing the doses and see how much they can get away with until there's an acceptable toxicity, then they take the level right below that, which is acceptable toxicity. And they test that and fit larger phase two trials to refine it to decide what dosage regimen and is going to go on to stage three, which leads to FDA approval based paths, just statistical analysis of the results over a period of time to an endpoint. And the endpoint usually is focused on the median patient, meaning if there's 100 patients in a trial that the 50th patient, either a progression free survival or overall survival, so it doesn't look at that bottom 20% or the top 20%. It looks at that theoretical median patient, which doesn't actually it's not actually a real person. It's a derivation, because for overall survival, they can't wait for the last patient to die. They wait for half the patients to die. pretty brutal. And that's the dose that gets approved. And like Brad said, it's a maximum tolerated dose meeting. Well, we think we can accept X percentage of patients having pretty severe side effects and maybe a few having extremely severe side effects, but what's not discussed but acknowledged within that is that there's a very wide variability of response, pretty much to any drug. And some people may live far, far, far longer than the median patient or, or, or, or have a delay in progression free survival much longer than the median patient. And then there's others for whom it's much more toxic, and they don't get anywhere near that. So we asked our own advocates, along with their oncologists, to be concerned with our personalized diagnosis. Where are we going? There are a variety of cell types within the ecosystem of cancer that work together? One quote, I always try to keep it top of mind, and I am sorry, but I can't even say which Prostate Cancer Research researcher said this was that “Cancer is a meadow and not a cornfield.” Meaning it's a diverse interacting ecosystem, and varies for all of us throughout the course of the disease. So all of our decisions have to be personalized. And in the end, we are experiments of one.

Paul Van Camp 6:43
The minimum effective dose is a different concept from maximum tolerated dose. And that's not elucidated in the clinical trials. And it does not correspond to the dose that the FDA finally approves, and for whom and approves it, which can be very narrowly defined. The trials are designed to maximize the chance of statistical success for the company who owns the drug, and try to try to do it with as few people as possible in as short a time frame as possible, so that they can show a statistical effect and get the thing approved.

So we need to be wary as individuals, that the maximum tolerated dose the FDA approved dose may not be the right dose for us individually. So where do we go? Where do we find out the minimum effective dose that's likely to be effective and less toxic? That comes out post approval in real world studies. When we find that people are not tolerating a drug well, their oncologist decides to lower their dose. And we've seen this happen. We've seen this happen with Enzalutamide. And this has led to the understanding that half dose Enzalutamide, half the approved dose seems to be very effective and may be equally effective as the full dose for many, Even if that's not proven, it certainly lowers the adverse side effects, and may have similar efficacy for many. So these are all personal considerations to be taken in and discussed with their oncologist. If we're on a regimen and we find unacceptable toxicity, I would be aggressive, I would be even bold about bringing this up to my oncologist saying, “No, It's toxic for me as an individual. And I would like to try a lower dose because it's been shown to be effective for some in the medical community.”

Another example would be with Abiraterone (plus prednisone), which was approved for at 1200 milligrams per day, once a day in the morning on an empty stomach. Now it turns out, that one quarter of that dose 250 milligrams taken with a food that includes some modest amount of fat produces the same effect and levels of Abiraterone as the full dose. That certainly saves financial toxicity. Even though the blood levels the actual circulating Abiraterone may be equivalent to the higher dose taken without food. Toxicity for the taxol chemotherapies. They're very toxic. They're designed to be poisonous to dividing cancer cells. These include Docetaxel. Cabazitaxel, Paclitaxel and many people who are advancing their disease cannot tolerate the full dose. The standard docetaxel dose is 75 milligrams per square meter body surface area. Well. So many oncologists are using lower doses and changing the frequency and extending the number of cycles, modifying the regimen to make it more tolerable. I keep remembering that I don't know of a single patient who was cured of prostate cancer, by Taxol chemotherapies, it does not lead to cure, it only leads to suppression of growth and progression, which is a good thing, and they can add to survival. But how much toxicity is accepted for that as an individual? Okay, so we have this balance of both toxicity versus efficacy.

Amit Gattani 11:27
In the examples that you're talking about, such as in the first example, you took half the dose as shown to be equally effective. Are these examples coming out of some controlled studies that have been done, or are these just anecdotal evidence? Because I'm actually going through a low dosage of Cabazitaxel and carboplatin right now, for the past three or four months, and I've been dealing with this dilemma of is it working, or not working? In the examples that you're talking about, are they maybe not called trials? But are these controlled studies, or these are just individual?

Paul Van Camp 12:14
Thank you for your question. And the answer is no. As I indicated briefly, this comes from real world clinical practice in the community post FDA approval. The drug company is not going to go back and do another clinical trial for a different dosage. But sometimes they acknowledge

that, “Oh, yes, this seems to be effective.” Because of the weight of experience of oncologists and patients in the community, who have tried lower limited doses due to intolerable side effects. And found that it seems like my response based upon my scans, and my PSA seems to be just as good. So enough of these reports come in, and then it gets acknowledged, and also gets published. So it's, it is ultimately reported in the literature, but they're not randomized controlled trials, because that's just not going to happen. Again, the company already has the drug approved. So this has to be gleaned from experience, and tested and those who don't tolerate the standard dose and choose a modified dose out of their own choice in consultation with their oncologist.

Amit Gattani 13:30
So somebody is systematically aggregating that data to be able to make that statement as opposed to all in one patient or by patients. I found this by one oncologist. Right. There's some systematic gathering and aggregation of this data.

Paul Van Camp 13:47
Well, I don't know that there's a formal process to aggregate and compile information on modified dosages. There is a formal process to aggregate information about post-approval toxicity on an ongoing basis. But these reports do get published, maybe some some years after the initial approval of a drug. And you can do a search on Medline or even on Google on a reduced dose and efficacy, and pull up published reports or a patient series that supports this. The weight of evidence is slow to accumulate in this manner. I'm just trying to raise awareness of the possibility of finding a possible minimum effective dose (MED). That is a moving (variable) target and you're looking in the dark for it. But the maximum tolerated dose (MTD) may not be best for everybody. It may not be appropriate or even tolerable for many.

Another topic I want to raise before my time runs out here is drug-drug interactions that have to be considered anytime we start a new medication. A lot of that drug interactions are due to how the drugs are metabolized. And there's a group of enzymes called cytochrome P 450. enzymes, which live on the endoplasmic reticulum inside cells, and on the inner mitochondrial membranes, and they metabolize the majority of drugs and other substances and do other metabolic activities. And these have a limited capacity. So if you take a drug that is metabolized by cytochrome 3A4, for example, and then you introduce another drug that’s metabolized by the same one. The drug levels may be altered dramatically, depending upon whether the drug induces more of that enzyme, or inhibits it or competes for it. So you can look this up very easily. I won't go into many examples but there are powerful examples within the prostate cancer drugs where they interact significantly. Including Enzalutamide and Abiraterone for examples. And this is where the effect of grapefruit juice on cytochrome 3A4 comes in. So these need to be checked online by doing a drug-drug interaction check on your computer. It is very quick and easy to do whenever you add a new medication to your regimen.

Brad Power 17:01
I was watching a new Netflix series called “Painkiller”. It's the story of OxyContin, Purdue Pharma, and the opioid epidemic. And in it the drug salespeople are being paid on commission

on the amount of milligrams sold. And so they're asking all the doctors to increase the dosage to prescribe more so they can sell more drugs and get reimbursed more. So you would think that maybe this system is designed to serve the pharmaceutical companies a little bit if you're of a suspicious nature.

George Lundberg put out a post today about a group in Canada that's looking at the right kinds of measures for drugs and measuring overall survival and quality of life to a greater extent and progression free survival, because progression free survival encourages more drug consumption, so that pharmaceutical companies are optimizing for that, which may be not taking into account fully quality of life and overall survival as much.

> *It's really not about the doctor, the "Cancer Center", the researcher, the NCI, the VCs, or Big Pharma. Many imagine "it" as being about the robust thriving of the "Oncology Industrial Complex".*
> *No.*
> *It is about the outcomes that matter....for the patient. Overall survival (OS), not Progression-free survival (PFS); quality of life whilst weathering adverse effects and uncertainty; hope, not false hope; economic viability of family, after the ordeal of advanced cancer; reaching realistic shared goals.*
> *Read here about a new group called "Common Sense Oncology" begun at Kingston, Ontario. Their message rings true and is timely.*
> *https://cancercommons.org/latest-insights/common-sense-oncology-moving-back-towards-outcomes-that-matter/*
> *I suggest that you sign on to this new effort. Help to make it a movement. It is time.*
> *george*

Paul Van Camp 18:36
Very good point. Thank you for bringing that up. Yes. and quality of life needs to be front and center along with duration of life and progression and overall survival, even though both are very important. And yes, the drug companies, executives have financial motivations that need to be considered. I want to show one other example. This one's more moving to enter the adaptive therapy realm. The recent study published on adaptive use of Abiraterone. This was by Gatenby, the adoptive therapy guru. And this is a cohort study. It's not a randomized, placebo controlled clinical. A comparison trial where patients are starting on Abiraterone for advanced prostate cancer. Half of them elected to do a program where, when their PSA dropped to half of their starting baseline PSA, a PSA drop by 50%. They would then stop the Abiraterone and discontinue it until the PSA returned up to that baseline level. Then they would restart it again. This was compared to a cohort that started Abiraterone with similar disease states, but stayed on it continuously. And what they found was very interesting that those who did the adaptive approach stopping and starting from 50% drop back up to baseline. And they were off the abrupt run for almost half the time by 46%. And the time to progression was 33.5 months in the adaptive protocol versus 14 months on continuous dosing. And overall survival was 58.5 in the adaptive approach, versus 31.3 months on the continuous Abirterone. This shows clearly a powerful advantage for the adoptive regimen. This is not using some computer algorithm. This

was a very simple individualization. Stopping the drug when one hits the 50% level was selected arbitrarily. And then re-start when you get back to your baseline. So you're using half the drug, you're off the drug half the time, and you live over over twice as long and over twice as long to progression.

So it shows that the “continuous drug to failure” approach, which always selects for the resistance strain within the “meadow” (diiverse ecosystem) of our prostate cancers, are sub optimal and the continuous maximum tolerated dose to failure always selects for its own failure. Any drug that started to treat cancer that does not immediately result in cure ultimately leads to its own failure by selection for resistance strains. So that's our catch 22. So why then does combining ADT with a second generation androgen receptor drug increases survival? We know that these combined regimens do increase survival, even while it's selecting for its own failure. Why is that? What's the paradox? The paradox is that the combined AR + ADT drugs actually slows down replication. So it slows down accumulation of mutations that lead to failure. So even though it's making it inevitable, it's giving a survival advantage of some variable duration. Well, that makes our decision making in selecting drug regimens very, very difficult. And I don't do not have the answer for it. So I'll stop there. There's any other questions or move on to the next presenter?

Brad Power 22:57
We have had discussions with Dr. Gatenby twice. If you're interested in exploring those topics further, those are out there and published.

John Sandiford 23:15
Part of Paul's comments was about senescence, clearing out the senescence cells. Can you speak on that a little bit more?

Paul Van Camp 23:25
Yes. Cancer treatments for radiation, chemotherapies, radioligand pharmaceuticals and others are very toxic to cancer cells. However, despite killing a large number of the cancer cells by various mechanisms, it also results in creating a population of cells called senescent cells that no longer reproduce, but they do produce and secrete cofactors that promote the expansion of other surviving cells and their spread including being able to create metastases. This is called the senescence associated secretory phenotype, SASP. And these are induced by cancer therapies and so are called treatment-emergent senescent cells. Even though this is not yet of proven benefit in prostate cancer.

Every four months or so, I do a three day regimen of substances that are known to clear senescence cells to cause them to undergo autophagy and die.I suspect that this is a good thing. And this has not been proven, this is outside of standard of care. But I take a three day regimen, which is all that is needed, including two natural substances Quercetin and Fisetin, two phytochemicals that are very safe and well tolerated. You can buy them on Amazon. I combine this with one medication called Dasatinib, which is also a powerful senolytic drug. And my personal regimen is 100 milligrams of Dasatinib daily for three days, combined with 1000

milligrams each of Quercetin and Fisetin. The Dasatinib at that level has very low toxicity, and Fisetin and Quercetin have zero toxicity. And one could do a regimen without the Dasatinib one if you wanted to keep it completely natural.

Brad Power 25:54
Jeff Krolick is going to tell us about some of the ways that he's personalized his dosing, working with his medical team.

Jeff Krolick 26:09
I have been working with Moffitt Cancer Center (Bob Gatenby), and with my oncologist, Dr. Lemanne, and we've been following an adaptive protocol using Orgovyx. We were graphing out the PSA results. I would start and stop based on that. Orgovyx, for me, has a very, very quick reduction in testosterone. And there's also a very quick testosterone rebound. And so we were bouncing back and forth between a low PSA of about six or seven and a high of up to 30. And we kind of settled into about a two week cycle, although it was always based on how quickly the PSA went up in their calculations.. What changed the approach for me was I was having some hip pain, which corresponded to a metastatic lesion in my left hip socket, the acetabulum. So, we thought SBRT treatment, stereotactic body radiation therapy, would be a good solution. And while we were preparing for that, Gatenby and his team said, “You only have three metastatic sites. You have a very low volume. Why don't we look at an extinction approach and do all three sites with SBRT, and then do a second strike. Then we'll look at a third strike after some genetic testing.” So that's where I am currently. I'm in the second strike, which is Orgovyx and Abiraterone, at least for prescribed medication that seems to be going fine. So that's for me the personalized piece, with the usual prostate cancer medications.

However, there are some other things that I do for myself. One of which is I take some over the counter supplements, for example, Arabinoxylan, which is a fermented rice bran. I found that doing some NK cell (natural killer cell) activity tests that the activity increased. Natural killer cells are part of the innate immune system. And natural killer cells, there are a variety of them, can be quite cytotoxic to a variety of viruses and cancer. As you know, cancer cells and their microenvironment are very good at inhibiting many of the signaling pathways that tell natural killer cells and other adaptive immune system components, “Hey, don't go here”. So Quest Diagnostics, at least on the West Coast, used to have an NK cell activity test available. They don't any longer, although I believe they have this available on the East Coast, or maybe the mid states, you would have to check. But when it was available, I was actually able to test NK cell activity. And in general, my NK cell activity fell below the threshold that Quest Diagnostics determined was basically not not active at all. So working with my oncologist, Dawn Lemanne, in a kind of roundabout way, what we found was certain over the counter supplements when taken in combination with Valacyclovir, which can inhibit DNA replication in viruses, there is some evidence that it can do it for Epstein Barr, and Herpes, both of which have mechanisms to tamp down the immune system by themselves. So what I found is taking one gram of valacyclovir daily, and 3 grams 1 time per week all the while taking the Arabinoxylan actually could increase my NK cell activity from no activity to low normal. And I was able to do this for I think, three months in a row with monthly testing. So it's a leap to say that that translates into

cytotoxicity for some cancers, but it may very well. I don't have any side effects from the valacyclovir, which is an antiviral, and you have to get a prescription for it. But I did find, again, through my evidence of the Quest Diagnostics NK cell activity test, that this actually worked, and it worked quite well.

Paul Van Camp 33:07
I just want to comment on that. Thank you for that. Since you've talked about extinction dynamics, how do you make cancer extinct by using first strike second strike strategies, and I've done this myself, but I want to point out one difficulty. Personally, I did SBRT to all of my identifiable lymph nodes, the only cancer sites I had last year on a PSMA scan. I followed it one month later with radioligand therapy Lutetium177-J591, a monoclonal antibody, in Perth Australia. Additionally I'm on a long-cycle BAT regimen, my own program, and I won't comment on that because we have Russ here now. I just want to say that Gatenby points out that a second-strike treatment should be at exactly the point where you reach no evidence of disease (NED). When that first strike is maximally effective is when PSA goes to nadir or undetectable. That's exactly when you need to apply the next strike, let's say, too. I recently went to an undetectable PSA for the first time. If I was to do a proper second-strike, I might ask my oncologist for a few rounds of chemo right then. However this is really hard to undertake. It's really difficult emotionally to go for an additional toxic treatment at the exact moment when everything seems to be going so well. But that's what the extinction dynamics calls for. So it's very much a challenge. And I have not opted to request chemo at this particular time. Because I know I don't tolerate it well at all. But subsequent strikes need to be given right when things seem to be working so well. That is what produced extinction (= cure). And that's exactly when most oncologists also want to say, “Oh, it's working. So let's just keep going until it fails.” And then you're not doing extinction dynamics, but rather following in the old model.

Jeff Krolick 35:23
This was Bob Gatenby’s recommendation that we were doing this. It is different than the published results for this, he will say, “I'm doing this on a very strong hunch.” Taxanes are not possible for me because I have some pre-existing neuropathy, and I do not want that to worsen. And my radiation oncologist was also involved in this discussion. So anyway, this is what we are aiming for. If we don't get the results, we're hoping in the third strike. Based on when we get some genetic testing back, there's some indication that a PARP inhibitor might be the third strike. That's where we are with that.

The other thing that I wanted to talk about, because it was of some interest before, is not really related to my cancer dynamics, per se. It is related to my emotional response to cancer dynamics. I've been following a psilocybin microdosing protocol for pretty close to a year now. My subjective experience is, it does help, and I also am a meditator. But what I found is with the psilocybin microdosing, is that it helps with my mood and it helps with my mental energy level. I can't say if it does or doesn't with my physical energy level. And also, again, subjectively, I find that my mental focus is better

Jeff Krolick 38:31

So again, my experience is I haven't really experienced mental fog that androgen deprivation therapy can cause or exacerbate, and, again, not even so much the physical fatigue. Also at my age, I'm 71, there's some natural neurological cognitive decline. And there's some pretty good evidence that microdosing in particular for seniors seems to slow down or even reverse some aspects of cognitive decline. So those are the things that I do. Those of you who are interested, I grow my own psilocybin so I know its source. Microdosing is taking maybe a 10th to a 20th of what would be considered a full dose. So if anybody is interested in such a thing, Paul Stamets was one of the researchers and developers and promoters of micro dosing. If you want to look up Paul Stamets, in the Stamets stack, you'll find information about the research that's been done and the possible benefits. If people are interested in going farther, there is a place where I get psilocybin spores. And there's another place where I get growth medium. And it's not that complicated to do. So if anybody is interested in more information about that, you can certainly contact me. I'd be happy to give you the link to the website for the spore provider, and also for the company that provides a growth medium for a variety of different mushrooms. So that's what I have to say about my personalized medicine.

Oh, and one other thing, I do take a variety of supplements, many of them mushroom supplements, which seem to have some immune stimulating properties. But I will cycle through all of those. So I won't take any one supplement for longer than maybe a couple of months. And then I'll stop, and then I'll switch to another one.

Brad Power 41:41
As you just mentioned, in case you don't know that Oregon is unique in being open to psychedelic therapy. And Jeff lives in Oregon, so that helps.

Amit Gattani 41:57
More of a comment, I wanted to share, close to Jeff's last conversation about mushrooms, I've done the same thing, based on UCSF integrative oncologist recommendations. I cycle through the Turkey Tail and assignment seven (a blend of reishi, himematsutake, maitake, lion's mane, shiitake, fu ling, and turkey tail mushrooms), on an every six week basis. So that was the recommendation I also got.

Different topic: I'm on a sort of an adaptive therapy of carboplatin plus Cabazitaxel chemo. The reason for that is the limitations of my bone marrow, which is highly impacted, and hence my platelet counts, and hemoglobin, and all of those things are very, very margina, to get the full dosage. So for the past almost four months, since March 1, we have been trying to reduce those. Every week I get tested. And based on that, on a call, we sit down and make a decision. What's the next dose I can tolerate? Can I get the dual agents or not? Even if I am getting a single agent, like for cabazitaxel, a full dose is 20 milligrams per meter square, and I've started with 7, 10, 15, just depending on what it is and how many weeks cadence. Everything is decided on a weekly basis. It has kept me stable in this timeframe. The difficulty that I see, and I'm curious if anybody has anything to say to that, as my oncologists don't know, really, because there is no data to say whether this is being effective or not effective, because there's no data. We are doing this because we don't have any other option right now on the table. And this is the

best option to deal with my disease. We are continuing to do this and just look at progression, both on scans and PSA. But how effective is it? They just don't know. How many times have they said that, “We don't know if it's really being effective or not.”? So that's the difficulty with adaptive therapy, and designing dosing. I got into this situation because there was just no choice. I cannot tolerate full doses and this is kind of after five or six consults around the country. Everybody was like, “Yeah, this is what you need to do, and just see what you can tolerate and not shoot your bone marrow any further. So that's what I wanted to share about my situation and adaptability experience.

Robert Gurmankin 45:17
Real quick, just getting back to what Paul said about, you know, maximum dose versus when anytime, when I was on Abiraterone, anytime I hit 1000, my bilirubin would shoot up. And they put me back to 750. And it was fine. 1000 No way. And, you know, both my oncologist and I went for a second opinion, both felt that 750 works just as well, even though you know, the trials are at 1000 Is it? And they don't know, but 500 might work just as well, too. But like Ahmed was saying, nobody knows because the trials just aren't done that way. So

Paul Van Camp 46:04
There's quite a body of evidence accumulated in the community that 250 milligrams in the morning with a fatty fat containing breakfast works just as well as 1000 milligrams on an empty stomach. And that's due to absorption issues. One way if you wanted to test that would be to take it without ADT. And see if Abiraterone itself takes your testosterone to castrate level which it is capable of doing in some but probably not all individuals. That has also been demonstrated and reported in the community. And since there's no blood assay for Abiraterone, you can't measure drug levels that I've seen in community hospitals, or even major medical centers. Taking it without ADT would be one way to see how well it works for an individual by its effect on blocking testosterone production in the body.

Robert Gurmankin 47:10
I'm awkward now but it was just like I said they both felt the lower dose and they also asked about the 250 and they said with the meal like that you're gonna get blood levels that are going to approach what would be if you took 1000 with no food so that it just felt stick to what is keeping my liver happy. But ultimately Abiraterone failed for me so that was it.