“Latest Insights from Applying Evolutionary Theory to the Treatment Strategies of Cancer Patients” (Bob Gatenby, MD) [#154]

Brad Power
July 30, 2025

“Typically, the design of clinical trials is ‘seat of the pants’. It's intuitive. One of the things that we know about complex dynamic systems, which is a mathematical description of cancer, is that there are nonlinear dynamics. Human intuition, which is linear, is not really good at those kinds of things. I want to emphasize the need to have formal mathematical modeling to make any of these decisions, especially if you're going to do something that's really far from conventional treatment.” – Bob Gatenby, MD

“If you think about cancer as a game between the oncologist who plays the game by applying a therapy, and the cancer which plays the game by evolving a resistance, the oncologist has two major advantages. One is that he or she always plays first because the cancer cannot make its move until the oncologist has applied a treatment. That's the equivalent of playing the white pieces in chess. It's called a Stackelberg game, and it gives an inherent advantage to the person who's leading the game. More importantly, is that the oncologist is sentient. The oncologist can anticipate what the cancer is going to do and plan for that; whereas, like any evolving population, the cancer cells can never anticipate the future. They can never adapt to something they have not seen before. The problem is that when we use the standard approach, which is maximum tolerated continuously until progression, with some adjustments only for toxicity, the oncologist is playing the same move at each cycle, so the cancer cells can simply respond as they have before. There's no additional burden placed on them. Because the oncologist changes treatment only when the cancer progresses, the oncologist has ceded control of the game to the cancer. What we want to do is have the oncologist playing a far more active and informed kind of game.” – Bob Gatenby, MD

Meeting Summary

Cancer patients and their caregivers face an explosion of testing and treatment options that is increasing the complexity of decision-making. For some patients, there are too many options, while other patients are faced with very few good treatment options. The typical approach is to look to the evidence-based standard of care and find your best treatment option. A drug is selected, often a chemotherapy or targeted therapy, and it is applied at the maximum tolerable dose until it fails, and you move on to your next treatment.

A more complex approach is to look long-term and strategically. This approach considers combining therapies, personalized (often low) doses, and sequencing treatments. For example, should you start with chemotherapy to eradicate or shrink your cancer, or get immunotherapy as a first line of treatment while your immune system is strong? If you have several possible treatment options, should you consider combining them?

Bob Gatenby, MD, Moffitt Cancer Center, Co-Director, Center of Excellence for Evolutionary Therapy, and Department Chair, Diagnostic Imaging, is uniquely qualified to lead a discussion on the big picture strategy you should use to manage your cancer treatment. He applies

mathematical simulation, mechanistic mathematical models, evolutionary and game theory, and experimental models to treatment decisions. Bob advocates using “adaptive therapy”: rather than continuously applying the maximum tolerable dose until resistance: you treat enough to knock the tumor back a little bit, and then pull the treatment away, allowing the tumor to grow back. But since the sensitive cells do not have the burden of the resistance mechanisms that the resistant cells have, the sensitive cells have a fitness advantage in the absence of therapy, and outcompete the resistant cells. The strategy is to use the sensitive cells that you can control to control the resistant cells that you cannot control. Other principles:

- **Combinations** (first strike second strike): This strategy emerges from investigations of Anthropogenic (human-induced) extinctions. Generally, we think about species extinctions in terms of the dinosaurs - a single massive application of evolutionary force. Arguably, the high dose density therapy in cancer is built upon this conceptual model. However, because our species is consistently causing extinction of other species, we have had an opportunity to observe species extinctions in real time. It turns out that most extinctions are not the result of a single event but rather a series of different perturbations none of which, in itself, could cause extinction. This has potential lessons for cancer therapy which, since the pioneering work of Ehrlich, focused on drug development to find “magic bullets” which are drugs that kill cancer cells but do not harm normal cells. The lessons from Anthropocene extinctions is that, lacking magic bullets, metastatic cancers can still theoretically be cured through a strategic combination of pretty good bullets. None of these bullets could by themselves cure the cancer, but a sequence of strategically timed perturbations can generate synergistic dynamics (termed an “extinction vortex”) that can result in extinction. Interestingly, the current sequence of treatments that are curative in childhood leukemia represent a real world example of this treatment strategy.
- **Sequencing** (not a combination cocktail): If you have a combination cocktail, especially as a first strike, you're applying the therapy to the largest possible population. The heterogeneity is such that almost certainly you will find tumor cells that can be resistant to the combination. It is better to hit the cancer with therapies in sequence, as each knocks the population down and can drive it to an extinction. Ideally, the sequence should generate an “evolutionary double bind”. In this strategy, a treatment is applied that kills cancer cells but also results in predictable evolution of a specific adaptive mechanism. The second therapy induces cytotoxicity by specifically targeting the mechanism of resistance. An analogy is control of a rodent population in an agricultural setting. An effective “therapy” is the introduction of owls. However, the rodents can adapt by hiding under bushes. This can be countered by introducing snakes. So, adaptation to one predator makes them vulnerable to the other and vice-versa. Evolution has a difficult time solving this conundrum and the typical result is a small stable population or complete eradication. This can be found in cancer treatment. For example, we have found that cancer cells adapt to DNA damaging agents by upregulating DNA repair pathways and immunogenic cell stress pathways. The latter includes increased expression of membrane proteins recognized by Natural Killer cells.

If we add NK cells to prostate cancer cells that have adapted to radiation therapy, they are consistently eradicated.

- **Focus on the mechanism of resistance** by giving one therapy and anticipating the adaptive response, then following up with a treatment that specifically targets the evolved resistance mechanism.
- **On-off cycling of treatments** based on your response.

How can mathematical models and evolutionary and game theory help you understand your complex cancer dynamics and improve your treatment strategy?

- Predict cancer cell evolution and resistance mechanisms
- Simulate treatment responses before clinical trials
- Optimize treatment timing and dosing strategies
- Develop personalized treatment plans based on your data
- Identify gaps in current understanding
- Develop more nuanced treatment approaches
- Move beyond intuitive, linear thinking and create more sophisticated, dynamic treatment strategies that anticipate your cancer's evolutionary responses

What are the key considerations for individualizing dosing and monitoring strategies in the adaptive therapy approach, for example in prostate cancer?

- **Maintain a population of treatment-sensitive cells**: prevent the dominance of resistant cells
- **Test frequently**: get consistent labs (weekly or bi-weekly) to track testosterone and PSA levels, observing rates of increase and decrease
- **Track your cancer biomarker**: monitor your PSA levels closely, allowing it to rise to about 50% of the pre-treatment value before stopping treatment.
- **Track other markers (e.g., hormones)**: ensure a rapid testosterone upsweep (within a few days) when coming off androgen deprivation therapy (ADT). A slow recovery can allow cancer cells to adapt.
- **Monitor your symptoms**: consider your symptoms alongside lab results, not just focusing on achieving the lowest possible PSA
- **Personalize cycles**: adjust treatment cycles based on your response, using mathematical models to guide decision-making

Who should consider adaptive therapy and mathematical models to guide their treatment?

- If you are a prostate cancer patient, especially if you have metastatic castrate-sensitive disease, want to reduce treatment toxicity, are interested in maintaining a high quality of life, and with slow-progressing cancer

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- If you are willing to have frequent monitoring (PSA and testosterone), are comfortable with fluctuating biomarkers (PSA levels), want to reduce treatment costs, and are open to a more strategic, mathematically-guided treatment approach.
- If you have not responded well to standard continuous treatment

How can you learn more and get help in making strategic testing and treatment decisions using mathematical models?

- Consult with doctors familiar with adaptive therapy and who collaborate with mathematical modeling teams
- Consider consulting with teams that specialize in an evolutionary approach to cancer treatment, like Bob Gatenby (Robert.Gatenby@moffitt.org) and his team at Moffitt Cancer Center which includes oncologists, mathematicians, and evolutionary biologists
- Consider contacting Dr. Dawn Lemanne (doctor@oregonio.com) who works collaboratively with the Gatenby team to develop individualized treatment strategies
- See our previous conversations on adaptive therapy and using mathematical models for cancer treatment strategy:
    - An Evolutionary Treatment Strategy (Bob Gatenby) [#9]
    - Adaptive Therapy” [#10]
    - Personalized Drug Dosing (Paul Van Camp and Jeff Krolick) [#68]
    - The “Personalization Conundrum” (Brad Power) [#16]
    - "Modeling Disease" (Michael Liebman) [#24]
    - “Personalizing Treatments with Biosimulation" (Michael Castro, MD) [#88]
    - "Simulations for Predicting Treatment Response" (Marc Birtwistle) [#20]
    - "Bipolar Androgen Therapy" (Bryce Olson and Bob Gatenby) [#21]

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

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Meeting Notes

KEYWORDS

Cancer treatment, adaptive therapy, bipolar androgen therapy, prostate cancer, evolutionary biology, game theory, maximum tolerated dose, personalized dosing, testosterone levels, PSA ratio, mathematical models, oncology, resistance mechanisms, clinical trials, patient care.

SPEAKERS

Bob Gatenby (68%), Brad Power (9%), Chase (6%), Jeff Krolick (6%), Paul Van Camp (4%), Allen Morris (4%), Rick Davis (1%), Bill Paseman (1%), Chris Apfel (1%)

CHAT CONTRIBUTORS

Ari Akerstein, Chris Apfel, Rick Davis, Chase, Russ Hollyer, Allen Morris, Raj Aji, Richard Anders, David Plunkett, Steve R, Len Sierra, Bill Paseman

SUMMARY

Bob Gatenby discussed his adaptive therapy approach for prostate cancer, emphasizing the importance of maintaining treatment-sensitive cells. He highlighted a trial using Abiraterone, showing a 28-month overall survival difference and a $70,000 cost reduction per patient per year. The median time to progression exceeded 6 years, with patients receiving treatment only 46% of the time. He also introduced a directed evolution strategy using testosterone injections to target resistant cells. He noted that mathematical models guide treatment decisions, aiming to maintain a stable chronic disease state with reduced toxicity and cost.

OUTLINE

Introduction and Background of Bob Gatenby

- Bob Gatenby has joined for two previous sessions on evolutionary biology and game theory in cancer care.
- He is recognized for his leadership in adaptive therapy, particularly bipolar androgen therapy in prostate cancer.
- Bob's strategic approach to cancer treatment is unique, especially in contrast to the typical "maximum tolerated dose until failure" approach of most doctors.

Overview of Cancer Evolution and Treatment Strategies

- Cancer death is often due to evolution, with cancer cells rapidly evolving resistance to treatments.
- The typical scenario is a new targeted agent is effective initially but eventually leads to tumor progression.
- The concept is that an oncologist is playing a game with cancer cells, where the oncologist has the advantage of playing first and being sentient.
- The limitations of the standard approach of maximum tolerated dose until progression leads to competitive release and tumor progression.

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Adaptive Therapy Approach

- The adaptive therapy approach focuses on maintaining a significant population of sensitive cells to control resistant tumor cells.
- The cycling therapy is where treatment is applied to eliminate resistant cells, followed by a period without treatment to avoid selection for resistance.
- A trial using Abiraterone showed a 28-month difference in overall survival and a cost reduction of $70,000 per patient per year.
- Two patients are still cycling stably after eight years, highlighting the long-term effectiveness of the approach.

Latitude Trial and Current Findings

- The standard of care in castrate-sensitive disease is now based on the Latitude trial, which includes Abiraterone added to androgen deprivation therapy.
- New data shows that the median time to progression is not yet reached, with patients receiving no treatment 54% of the time.
- There is a significant reduction in toxicity and cost due to the adaptive therapy approach.
- The results are so good that they cannot be reported yet because the median time to progression has not been reached.

Directed Evolution and Future Trials

- The concept of directed evolution is where sudden increases in testosterone levels are used to kill resistant cancer cells.
- A case study of a patient who underwent a directed evolution approach showed a transition from resistant to sensitive cancer cells.
- A new trial that will explicitly test the directed evolution strategy in patients with prostate cancer.
- Mathematical models are important in guiding clinical cancer treatment and optimizing outcomes.

Patient Experiences and Practical Advice

- Bill Paseman asked about the application of the treatment regimen to other types of cancer, and Bob Gatenby mentoned ongoing trials in renal cancer.
- Chase asked for practical advice on dosing and monitoring, and Bob Gatenby explained the importance of PSA levels and testosterone upsweep.
- Jeff Krolick shared his personal experience with the adaptive therapy approach, emphasizing the importance of consistent monitoring and individualized treatment.
- Paul Van Camp asked about the cycling of androgen receptor activity and the effectiveness of Abiraterone, and Bob Gatenby explained the mathematical models and experimental data supporting the approach.

Final Thoughts and Emphasis on Mathematical Modeling

- Bob Gatenby emphasized the need for formal mathematical modeling to make informed decisions in cancer treatment.
- He highlighted the limitations of human intuition in dealing with complex dynamic systems like cancer.

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- Bob encouraged collaboration between experimentalists and mathematicians to develop better models and strategies for cancer treatment.

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TRANSCRIPT

Brad Power
This is the Cancer Patient Lab.

We're very honored today to have Bob Gatenby with us. This is the third time he's been gracious enough to spend time with us. In previous sessions, he shared his experience with evolutionary biology and game theory and the way that they use their models to develop a strategy for cancer care. I first heard of Bob, I think it was Marty Tenenbaum or someone pointed out he was he was interviewed with Peter Attia, and got a big coverage from that, but he was very useful in helping both Brian McCloskey and Bryce Olson through their approach to bipolar androgen therapy and their strategy generally. He's a leader in the adaptive therapy approach, which is manifest as bipolar androgen therapy in prostate cancer, which are the subjects of previous sessions we've had, and you can see those notes and video recordings for that background. Today I've asked him to focus on updates and things that he's learned over the last last year or two, and the insights that he's gotten with his approach. In my experience, Bob is the only person I know who's bringing a strategic approach to cancer treatment decisions. The default implicit premise of most doctors is maximum tolerated dose until failure. It's typically one thing. So the notion of combinations of sequencing, of personalized dosing, all those strategic things are things that Bob introduces that I see rarely, if at all anywhere else. He's a leader in that area.

Rick Davis 2:03
Not true. We frequently see doctors adjusting chemotherapy doses per responses. So if somebody responds badly, they may lower the dose. They may change the timing of the dose. They may go from three weeks to two weeks with a slighter dose. That's in academic practices. You make a good point, but it's not true to say we never see it.

Chris Apfel 2:45
The general principle is really to do the maximum tolerated dose, as Brad Power said, and most of those adjustments are usually as a result of side effects, often due to bone marrow suppression. What Brad said was actually quite true.

Brad Power 3:05
Okay, I don't want to start the conversation here. I was just trying to set the stage.

There are typical things we say at the front here. This is for information purposes only. We try to bring information to patients and caregivers so they can take it to their medical team. This is not medical advice. We are a nonprofit 501(c)(3), and we depend on the kindness of donors who help us keep our operations going so that we can bring you webinars like this.

Bob Gatenby 5:16
This is just an update, and what I'll try to do is just do a brief overview, and then get into what we've learned recently.

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The basic premise here is that increasingly, the cancer death is the proximate cause of cancer is evolution. When I first started working in oncology, a long time ago, there weren't that many drugs available. But what's happened in the in the meantime is that there have been many, many drugs that have been developed, but the death rates from cancer have not changed very much. The reason is because cancer cells have access to the whole human genome, and in a process, can evolve resistance rather quickly, or often very quickly and very effectively.

So this is a typical example. This is one of the new targeted agents that's treated for EGFR mutant lung cancer. It's very effective. And then what do we do? Well, we keep giving erlotinib, and eventually that you know the tumor progresses\.

If you think about cancer as a game between the oncologist who plays the game by applying a therapy, and the cancer which plays the game by evolving a resistance, the oncologist has two major advantages. One is that he or she always plays first. That's the equivalent of playing the white pieces in chess. It's called the Stackelberg game, and it gives an inherent advantage to the to the person who's leading the game. More importantly, is that the oncologist is sentient. The oncologist can anticipate what the cancer is going to do and plan for that; whereas, like any evolving population, the cancer cells can never anticipate the future. They can never adapt to something they have not seen before. The problem is that when we use the standard approach, which is maximum tolerated continuously until progression, with some adjustments for toxicity, the oncologist is playing the same move over and over again each cycle. It's the same thing that cancer cells can simply respond as they have before, there's no additional burden placed on them. And because the oncologist changes treatment only when the cancer progresses, the oncologist has ceded control of the of the game to the cancer. What we want to do is have the oncologist playing a far more active and informed kind of game.

This is just the evolutionary kind of demonstration of the what happens in maximum tolerated dose. You start with a population, perhaps a small number of them, have some ability to be resistant, either inherently, or they can develop resistance quickly. You give maximum tolerated dose and you get a great response. It's very, very impressive. By the process, you're sowing the seeds of your failure, because what you've done is that you've put intense pressure for resistance and who have eliminated all of the their potential competitors and and so they you can just keep repeating this, but all you're getting is sort of steady tumor progression. This actually has a name this. This is actually well a well known dynamic and evolution is called competitive release. And to be honest, it's hard to do something worse than this. This is a from an evolutionary point of view, nearly always unwise. So our approach is, and again, there are many types of evolutionary treatments, but this is the one that we used in prostate cancer. Here we apply a treatment instead of just, you know, with the goal of eliminating all of the cancer cells, our approach shifts from the cells that are sensitive to the treatment to the cells that are resistant, because those are the ones that ultimately dictate the outcomes. And so our goal here is not to kill as many cancer cells as possible, but to, in fact, maintain a significant population of sensitive cells with the goal of using them to control the resistant tumor cells. So here we apply a treatment, but rather than Maxim to reduce, rather than trying to kill as many cancer cells as possible, we deliberately leave behind a significant population of cells that are sensitive. Of and

then we stop treatment. During this period of time when there's no no treatment, there's also no selection for resistance. And in general, the there is a cost of resistance now, as they have to develop the molecular machinery necessary for that. That is that cost is exceeded by the benefit in the presence of treatment, but in the absence of treatment represents a cost with no benefit. And so in this case, the sensitive cells have a fitness advantage in the and so what you do then is allow them to sort of grow back. And what you do is sort of recapitulate the the population distribution that you started with originally, you can treat again. It will restore. You just keep and so this is this a kind of a cycling therapy. There's a this is the idea here is not passive. It's to use the the the treatment as a forcing function, and if you apply it at the correct time, you can induce oscillation, generating a near steady state. Our first trial was an Abiraterone i this. We've presented this before the about a 28 month difference in overall survival in the adaptive therapy group. The adaptive therapy group did not receive any treatment at all, 46% of the time. Percent of the time on trial, and that resulted in a cost, on average, a cost reduction of $70,000 per patient per year. Two of these patients are still of our adaptive therapy. Patients are still cycling stably after about eight years. So this actually was not what we predicted in model, and I was we did not think they could do that many cycles. And so again, points it points to the fact that these, our models are good, but they're not perfect, and we need to keep working on them. Now, since that original trial, the standard of care in castrate sensitive disease has changed because now it's based on the latitude trial. It's now Abiraterone added to androgen deprivation therapy in both in this case, however, it's continuous administration at maximum tolerated dose. The initial trial, New England Journal had median progression free survival of 33 months and a median overall survival of 53 months. We have not reached the median time to progression. So again, this is that kind of adaptive therapy, on, off, switching the effect three more patients have to progress to get to a median time to progression. None of them have had had PSA Progression, and they have to have radiographic progression to be off cycle. So it cannot be less than 68 months, and that's median time progression. So we will more than double the median time to progression of the standard of care. And importantly, these patients receive no treatment at all. 54% of the time on treatment, so more than half the time these men have normal testosterone levels, which significantly improves the toxicity. And since they receive Abiraterone, less than a quarter of the time. Aberrant was a very expensive drug that significantly reduces the cost. So this is where we are with this right now. It's sort of a weird situation because the results are so good that we can't report it because we haven't reached a median time to regression yet. So, but that said, we've tried to use what we want to know now is, what about these guys? What about the men that progressed early? Can we understand those dynamics, and can we intervene in those the and this, I will, I will, I'm sorry. I will point out one more thing, and that is, this is not terribly surprising. This is a man who has developed his own androgen deprivation therapy adaptive process, who's now 13 years into this, with a with a with a Gleason in the morning, metastatic prostate cancer. So this is the fact that we're seeing very long term stable diseases. Is not necessarily that surprising, but we still don't know exactly how common it is.

Bob Gatenby 14:42
And looking at this, what we found is that the that we have a biomarker for tumor progression, and that is the ratio of PSA to testosterone in this trial, unlike our first trial with Abiraterone, we

we have two general lines of data over time. One is. Testosterone level when the others PSA, they're always drawn together. And so what we've been looking at is that what we find is a predictor, is that the PSA to testosterone ratio begins to increase as the men develop, as the men develop more and more resistant disease. And so that's our biomarker, but it also suggests a different dynamic. And this is the model that we used to start with with the Abiraterone trial and for the antigen deprivation trial. But I think we made a mistake here, and that's this. We assume three populations all based on their interactions with with testosterone, t plus cells are the ones that require endogenous testosterone, and these ones sensitive to ADT. The TP cells are the ones that produce testosterone, and so are sensitive to Abiraterone. The T minus cells, we thought were going to be entirely independent of testosterone, that these would be just there would be no antigen dependence at all. What we've learned, what the what the PSA to testosterone ratio suggests to us, is that these cells are actually able to proliferate in lower and lower levels of testosterone, castrate levels of this testosterone. And so this goes to a kind of a different mechanism of at least initial progression, and that is that you are seeing high expression of antigen of antigen receptors. And you can see here, this is a example on the right of that kind of dynamic and how you can see it tremendously upregulated. What's interesting about these, about this mechanism, is that what we know about it is that the while they're very good at continuing to proliferate in low testosterone concentrations, sudden increases in testosterone cause a hyper stimulatory state which induces apoptosis. So this kind of gave us some suggestions that maybe we can engage in in what's called directed evolution. So for centuries, humans have have used directed evolution to promote desired traits in domesticated animals. Can we do this type of approach in cast it in the in the prostate cancer, as they transition from castrate sensitive to castrate resistant? And so we have the models to do deal with this. This is our the first patient that we've tried this on. I'm just going to go left to right here. So this is a person who had, had been on standard dose of ADT, went on to an adaptive cycle, and it went through several cycles. But you can see that as the as the testosterone is off, you start to see this increasing level of PSA. So we see it in two cycles. So for us, that's PSA Progression. What we then did was kind of a modified bat in that we injected testosterone here that the specific purpose is to kill the resistant population. Because we're we have this sudden increase in testosterone levels, which induces apoptosis and at the same time promote the population that is what we call the T plus cells, the ones that require sort of physiological levels of testosterone. So the goal here now being to change the dominant population so that we can bring it back to a cancer population that is sensitive to androgen deprivation therapy. In this case, this individual had had a variety of neurologic underlying diseases and could not tolerate any of the standard therapy for castrate resistant cells. He could not stand he could not even tolerate Abiraterone, none of the none of the chemotherapies. So we felt that this patient had the only thing we could do is essentially try to do a directed evolution approach so that we could restore sensitivity to androgen wet patients every so. So now here are four cycles in which we injected the testosterone. Unlike bat therapy, in which the the injection of testosterone, or the administration of testosterone is timed, is rigidly, kind of kept according to, you know, a couple of months here, each of these was based on the subsequent of the response. So we we had an initial tremendous increase in PSA with the injection came down, and then as soon as it went back to kind of baseline, we did another injection. Notice the PSA went up again, but much less than this. Right, and then third cycle, much less than this. We interpreted this to mean that the

hyperexpressing antigen receptor prostate cancer cells were initially responding tremendously, but also dying, so that that population then grew smaller and smaller. And you see on the fourth one, the the PSA went up slightly at its peak. We interpreted that to mean that we are now essentially stimulating the stem, you know, the T plus cells, the ones that require physiologic testosterone. And we felt that we probably had then transitioned his population, the populations, and so we went back on to cycling ADT. He's now gone through, I think, six cycles of this, and we're now sort of back to the adaptive ADT. So we sort of restored that castrate sensitivity level. And this is our so we've, this is our third generation trial, which has already crewed, I think, six patients. It just opened recently, and this, this is kind of a when, when we initially talked about using mathematics to guide clinical cancer treatment, this was kind of our goal. In this trial, every patient is going to go through an initial cycle, and that's going to be used to parameterize the models. And from then on, the mathematical models will be used by the oncologist to optimize outcome at each new treatment step. And so with that, I will stop sharing, and I'm happy to have a discussion.

Brad Power 21:46
Wow. So

Brad Power 21:49
Bob, can you start with what you just shared? How is that different than what you would have shared a year or two ago? What's what's new?

Bob Gatenby 21:58
The what we've, we've, you know, a year ago, we were so 12 months before this, we knew that the median time progression was in our second generation trial was pretty good, but now it's way above anything that's been done before, and we know that It's going to be at least six years, and probably probably seven. So some of these very long term survivors on adaptive therapy in androgen deprivation therapy, it's now looking like they were not as unusual as we thought. And the second thing is that we've learned that the mechanism resistance at least early on. And I don't, we're not quite sure how often this is, but I think it's pretty common. Is an epigenetic state in which they've upregulated the androgen receptor so that they're they're highly up regulated. It's not a genetic thing. It's an epigenetic thing. But what we've learned then, I think, is that we can kill those guys and that we have this kind of directed evolution strategy that is working. And so we actually have a trial, which is about to open, where we explicitly are going to try to to do this conversion therapy. I think that if we can, if we can use this sort of initial adaptive therapy approach, and get, you know, seven, eight years of of control, and then when there's progression, have the ability to move them back to the beginning, I think We can effectively eliminate prostate cancer's cause of death, and so it's a chronic disease at this point. But because the patients have normal testosterone more than half the time on treatment, the level of toxicity is significantly reduced, and because Abiraterone, which is a very expensive drug, is only given less than a quarter of the time on on treatment, they're, they're, they're, the expenses are going to be greatly reduced. So anyway that so that's kind of one of these that we've we're exploring a couple of of ideas, such that, for example, in the adaptive androgen deprivation therapy, the on off, we rely on the patient's own testosterone levels to come back

up. What we've learned is that that can be in some man a very slow process, and that's that's probably a mistake, because it's in that as it's coming back up, there's a prolonged period where it's still pretty low, and that's that's actually promoting the hyperandrogen receptor population. So what we're doing now, and I think what we'll do in the future, is that if the upbringing. Situation, if the upsweep of testosterone is not rapid, which is what we really need, we're going to have to do it on our own. We're going to have to use a patch, or something like that, so that we have a rigid control of the testosterone concentrations. I think that we've we've developed that. I think it's been a little too passive in the way we've been doing it in the past. But of course, we didn't realize that that sudden up sweet it was, was really important. And when we go back and look at the patients that were very that have been very prolonged response, that they all had this rapid up sweep at the beginning. So we we know that much about it. So I think we've learned quite a bit. And, I mean, I I'm reasonably confident that we can, we can maintain even, even terrible metastatic prostate cancer, you know, as a stable chronic disease with a very high quality of life. I mean, not, not perfect, because you're, you're not on, you know, the testosterone levels are still going to be very low, you know, not, not quite half the time, but, but, you know, but still, I think on the whole, this will, this gives us an opportunity to really say, this, this disease. We can, we can end, we can end this disease as a cause of death. I believe we're at that point.

Brad Power 26:26
Okay, we've got some folks who've raised their hand. Let me just ask one more question, clarifying question, before we go to the raised hands. And then, as Bob, you've several times referenced we. Could you describe your team and the resources you're bringing to bear to do your analysis,

Bob Gatenby 26:41
sure. So yes, thank you for mentioning that. I usually have a thank you slide at the end, and I forgot to do that. So Jin Zhang is the oncologist, prostate oncologist, who has run these trials and will run our the conversion trial. Sandy Anderson is the mathematician who has been working on this project, and he has a number of junior faculty members that were with him. Joel Brown is an evolutionary biologist who has worked with with us. So the the team is oncology plus math plus evolution. The and you I'm not sure I mentioned this, but at Moffitt has the largest Mathematics Department of any cancer center. We actually have 13 faculty mathematicians. We also have two faculty evolutionary biologists, and so that multidisciplinary kind of approach is built into the infrastructure. Now we have a cancer biology and evolution program. We have a center of excellence for evolution based clinical trials. And we have an evolution tumor board, which will which includes mathematicians and evolutionary biologists, although it's run by an oncologist with the idea that we can for individual patients, provide some guidance to the oncologist about how to optimize therapy.

Brad Power 28:16
Thank you. Okay. Bill Passman, you have your hand raised, yeah.

Bill Paseman 28:21

So first off, I want to congratulate you on such great work. I mean, I've very seldom seen a treatment regimen based on a solid mathematical and biological basis. Is this so that I want to you know you should be congratulated on that that said I don't have prostate cancer. I've got kidney cancer. And I was wondering what other kinds of cancers this thing is being applied to.

Bob Gatenby 28:43
We have actually two trials in renal cancer going going on. One has been just a there. So what I what I showed you here, was we sort of have a dual treatment in the in the case of prostate cancer, we've largely focused on the cost of resistance. An alternative is to focus on the mechanism of resistance. And so in that case, you give one therapy, and you anticipate the evolution the adaptive response, and then you give a follow on therapy that specifically targets the evolution, the evolved mechanism of resistance. And so that's what we've been doing in renal cancer, and we have one set of patients who have had prolonged responses to a single sequence of treatments and a second trial, which is just about to begin, is more of an adaptive therapy trial, similar to what I've shown you before. If you I'm happy to just offline speak about this, if you want to hear more,

Bill Paseman 29:57
great, I'll send you your email to. Us, I guess, is available from Brad, yes, thank you very much. Yeah,

Brad Power 30:03
sure. Thanks. Phil Chase, you're up next.

Chase 30:10
Dr gamby, just want to thank you for your work. It's I just thank you a couple of small things. Abirateron is now available as a generic. So you can get for like $26 a month. Okay,

Bob Gatenby 30:23
that's good that that was that haunted us in the in that first trial, the cost was tremendous.

Chase 30:29
Yeah, yeah. So I, I'm working with Dr Jang John. You pronounce like a J, John, so his, you know, I live in Washington State, but you are the only guys who have any hope for me, other than just like, well, take this till doesn't work anymore. So I've been seeing Dr John. The piece that is, is is difficult for me is to determining what is my actual dosing. Like. I understand the concept? I want to keep some sensitive cells around, and I want to, but how, how do I actually figure out I'm been using erlita and dutasteride, and do I go for like, do I take it for three days, or do I take it for one month? Do I take you know? How is that determined? We

Bob Gatenby 31:24
try to use the metric of response, in the case of prostate cancer, PSA as as as our kind of guideline. Now, as I said, we've added testosterone to that, which I think has been very helpful. But, and there's two ways to approach this. One is what I showed is that the adaptive therapy

on off. You you give a treatment, you wait till the PSA goes to about 50% of the pre treatment value, and then you stop, and you just let it come back. When it goes back to the pre treatment value, start again. So you just keep going on, on and on with that. That's pretty much everything that I've showed you so far. There's an alternative approach, which in our preclinical experiments were, was more expensive, was more successful. And that is that as you start to see the PSA or the whatever the tumor marker was going up, you apply a therapy at one point with the goal of plateauing it, making it just just not, not not necessarily pushing it down, but just keeping it flat there and then. From then on, you, you, you can increase or decrease the dose of drug, each, at each at each decision point based on what had happened before that. So if the PSA goes down a little bit, you you reduce. The dose, goes up a little bit, you increase the dose, and that's called the dose adjustment strategy. That was actually the better strategy of the two, again, in preclinical experiments, but it's very hard to do in a clinical setting because it requires constant decision making, and oncologists don't terribly like to do that. That said, Michelle Lockley is a oncologist in the UK who is doing this with ovarian cancer, and she, you know, repeated our experiments, and now she has a very active trial going on where she's using that dose adjustment strategy to to maintain a tumor control. And so we'll see how that plays out clinically. It's probably not necessary in prostate cancer, because the the the problem in the pre clinical setting was that if you had a very aggressive cancer, like a triple negative breast cancer, in these on off cycles, you ran the risk of losing control of the tumor. It could, it could, it could blow up so quickly that it was, you know, sudden, it just got too big to do anything about. So, so that was, that was why we, we use that project. Cancer is probably not that in most cases, not that aggressive, where that's really a huge problem, does that is that, what did I answer your question? Yeah,

Chase 34:07
that it that is the, that is the question, you know, like, so I don't want to turn this into a into a treatment for me, but just like, my PSA doubles every week. So I've been taking the, I've been taking my PSA, and I let it get up to, like, say, 50, and then I take a few days of medicine. And if I go, like, three or four days of medicine, it'll come all the way back down to, say, five or six, and then I can be off it for three weeks or something like, this is essentially the the, yeah,

Bob Gatenby 34:37
that's what we see. There's the there's two things to think about. One is the maximum. There's there's no particular evolutionary problem letting the maximum number go up higher. You don't I mean, you could stay with that, but as long as you're not having. The symptoms you could you can let it go up higher. The reason is that the more time you give the treatment, sensitive cells to grow, the more they're suppressing the resistant guys. The tendency, though, the biggest tendency, is to over treat. And we, as we analyzed our first trial, that's what we found, is that you really, you remember the treatment sensitive cells are your friends, and you want them to take care of your enemies for you. You don't want to eliminate that population. So if you push it too hard, though, you know, the more you the lower that population is at that at the beginning of the next cycle, the bigger problem you have in maintaining control so you don't want to go down too far. Now there's a there's a there's a caveat to that. And that is what we think is. And didn't realize at the beginning was that the is that the upshoot of the of the testosterone is very

important. You can, you can tolerate going lower. If the upshoot of the testosterone is very rapid, if it's not very rapid, then you we need, either need to cut off the the dose at a higher PSA level, or you need to start taking testosterone at that at the trough, so that you get the sudden surge. It doesn't have any injection. There are patches that can be used. The point is that we want to go. We want to get to physiological levels as quickly as possible when we decide to stop the ADT.

Chase 36:37
And what is rapid is that, like, a week, or is that a month?

Bob Gatenby 36:43
That's a couple of days? And so if, if, and this is, this is what we're finding is very high, highly variable. Yeah, testosterone does not go up really quickly. And I but I mean, like overnight, kind of quickly. The problem is that, because the resistance mechanism, up regulation of the androgen receptors is a is an epigenetic mechanism. It means it's not hardwired in the genome. It's the expression piece of it. If you give those guys time, they can down regulate the as the testosterone level is going up, and if it's going up slowly, they have time to down regulate the expression of of the androgen receptors. And so you're not getting that killing effect that you want, because our the goal with this is to boost it, you know, just overwhelmingly simulate all of their androgen receptors at the same time, which which then induces apoptosis, so that that that timing seems to be very important.

Chase 37:46
So just to restate, you want the test you're following testosterone levels and at the ADT, the testosterone comes down, but you want it to recover quickly within now a normal, normal testosterone level is like 250 or something, so you wanted to come back up to normal within a few days. Yes,

Bob Gatenby 38:06
now, if you Okay, and again, it's, you know, it's, it's, it's surprisingly how it's surprisingly variable and but, yeah, yes, the

Chase 38:15
Yeah, I mean that, but that's the whole point of what you're doing is to try to figure out, on individual level, like, what you need to do. So you're taking the you're following the ADT for just whatever time it needed, to bring it down and then come back up in two or three days. Okay, yes, yes, I don't, I don't want to monopolize I have one last question, which is, you know, finding I have, I've watched your every YouTube you got, and I've I'm trying to find you on the web as much as possible, etc. Do you have, like, a most of the things I've seen you are presenting to a new group of people for like, one hour? Do you have like, a five hour thing? Or do you have something where you have worked with your team and you're recording something that, like gives the whole where can I find the most information about what you're doing?

Bob Gatenby 39:10

If you send me, I we had a article in Nature review oncology that is a fairly long and was meant to be fairly comprehensive review. I do have an article coming out on cancer research, just as this a much shorter review, but was is a commentary on Michelle lockley's papers. So, yeah, okay, so one hours my limit,

Chase 39:39
yeah, well, I mean, what you're doing is super interesting, and, you know, I'm just trying to, I can't find anybody who will help me, like, figure out what my individual thing is, aside from Dr John, who's wonderful, but a long ways away from me,

Bob Gatenby 39:56
sure, I, you know, we, we're. With a physician in on the West Coast who is a private practice physician, but works with people and and our group does sort of an informal collaboration with her. So if that, if that does, you know her name is Don Lamont, L, E, M, a, n, n, e,

Brad Power 40:20
and that's If I could interject here, that's a good segue to Jeff Krolik, who is a patient of Dr Lamont and Dr gatby. So Jeff, could you maybe share a little bit for Chase's benefit and others benefit, what your experience has been from a patient's point of view adopting these methods? You're on mute, Jeff,

Jeff Krolick 40:42
yeah, After some consideration and discussion, I work with Dr Dawn Lamon. She strongly recommended using an adaptive approach so we have she consults regularly with the team at Moffitt Cancer Center. Occasionally we do, I guess you would call it like a tumor board via zoom. To discuss, I would say the for me, the the most important part that I had to make an adjustment to is the very consistently getting almost weekly testosterone and PSA labs, so the rate of increase in both of those and decrease and symptoms that I'm experiencing or not experiencing can be taken into account. Now my insurance will pay for that. I have a lab very close to me, so it's easy to do. And sure, sometimes I might go two weeks without a lab, but that seems to be a key in the individualizing the treatment based on my rates of increase and decrease and symptoms that I'm experiencing or not experiencing, but I like it because it does give me, at least periodically, a testosterone boost I did have to get used to a higher PSA. You know, the goal is not to squelch your PSA to point 001, you know, at certain points, you know, my PSA is up over 100 Now it may go down to 50, but as long as, from my perspective, I'm not experiencing more symptoms, and occasionally we throw in a PSMA or an MRI scan just to see what's going on. This is the treatment that I feel is the best path for me going forward, and we have rolled in some super physiological testosterone along the way, when it looked like I was starting to have more of A or less of a hormone sensitive population, and that seemed to be able to do a reset. So anyway, that's my experience. I like it, and I will continue with it for as long as it seems to work.

Paul Van Camp 43:37
Just for Jason, I throw in a couple of questions,

Brad Power 43:40
yeah, yeah. Let me just comment that Don Lemon is physically in Oregon, and Jeff's in Oregon, so she's practicing, and I think she can also practice in maybe New York and California, or something like I'm in Washington

Chase 43:55
State. Is there a limit to the high PSA, or is that high

Paul Van Camp 43:59
point? Go back. Can I throw in a couple of questions that are applicable to more people before we do focus just on cases? Right? Paul, Hi, I just want to get a couple of questions. Is that it's not an individual focused on my treatment, but about the concepts behind this. Robert, the cycling of androgen receptor number and activity, of course, is central to this, with low on ADT or abidron or both, androgen receptor increase in activity in number, and that makes it primed for the next dose of high testosterone cycling on that but then after a few weeks, I believe the androgen Re. Receptors get down regulated. And so the cycling is actually necessary to cycle high and low androgen level receptor activities. And along with that, cmyc, the the big driver of of cancer, is also cycled high and low, which is interesting question is, how long does it actually take? I've been guessing three to four weeks of ADT or androgen block is sufficient to restore high androgen level activities to prime for my next cycle of high testosterone. And by the way, I use very high testosterone. I use 300 milligrams of T sip tcipionate every week until I'm five weeks out. For my ADT cycle, I switch to T propionate. Thanks Russ for that information on that so that I can have a rapid drop going into ADT, that's one second. Last question would be, Abiraterone is sometimes used without ADHD, because it's very effective all by itself. It's suppressing testosterone levels. Is there ain't really any need to have an luteinizing hormone drug in addition to Abiraterone. Thank you, sir.

Bob Gatenby 46:24
Sure. In my opinion, Abiraterone is not necessary, as in ADT we had it in our protocol only because that's become common practice in the United States. I doubt that it's necessary, but it's hard to deviate too far from common practice in these dosing schemes. We it's what we don't know is, you know, could fill volumes and so how quickly cells can move back and forth from, you know, in terms of their androgen receptor regulation, go from very small to very large. Is not something we know what one of the things so physics, for centuries has has had empirical data and and mathematical theory together, and one can inform the other. We don't tend to do that in oncology or medicine, but this is an example of where the the the Math Model is telling you. We really don't need to know this. So you guys in the experimental world need to measure it. And so so far, I have not seen that, but, but you get the i But, but you're exactly right. The this is what the one thing should be informing, you know, the goal is to work together with the experimentalists so that we can work things out, as opposed to the current strategy, which is to kind of throw everything at the wall experimentally. You know, we get, we get, you know, mutations and this and this and that. And I think that's without underlying theory, you know, we

that's where AI we need that doesn't, you know, you get so much data, you can't deal with it. So, so that's that connection is something we try to

Brad Power 48:20
do. Okay, Paul, you're good. Just picking up a couple of questions in the chat. Alan Morris, you've posted a few things there. Do you want to choose one and raise it here?

Allen Morris 48:34
You know, can you just read them? Because I was slammed at the last learning session for suggesting that physicians know about liquid biopsies in the minimal residual disease state. I know that's off topic. This group, this prostate cancer advocacy group, which is a patient advocacy group, is incredibly pro the concept of super physiologic bat testosterone therapy, and then seguing that with the concept in cancer that the earlier is the better, which is true for many cancer treatments, they have gone off the guard rails of mainstream medicine and have done n of one experiments on themselves, including in the biochemical recurrence phase. You know, I'm going to go, you know what? You started me on a long diatribe, and I'm going to get crushed by everybody, because everybody's Pro, super physiologic bat on this, this thing. But I will say, I will try to ask a question. It it turns out da Mead, who's the leader in Super physiologic bat, actually indicates a subset of patients that are most responsive. Admittedly, it's for re sensitization to testosterone, and those are the ones that are the most advanced, not only in the advanced state of metastatic cast. Resistant prostate cancer, but those that have advanced genomic biomarkers, specifically, you know, tumor mutational burden, Brad positive, all these things that are incredibly advanced. And so the danger, I mean, the conventional wisdom historically was that testosterone was gasoline for prostate cancer. Like you shouldn't do it right? Don't you think there's a danger in doing super physiologic testosterone on a cancer that I'm going to characterize is genomically indolent, which I believe most early biochemical recurrence of patients are, especially if their PSA doubling time is greater than either nine months or 15 months, or whatever the cut point is for low risk. BCR, I know that's a complicated question. I'm sorry for jumping in because I'm going to get slammed, so I'm ready for the onslaught.

Bob Gatenby 50:54
Well, let me say I would never have thought to give testosterone had it not been for the bat therapy literature, I would have just not thought that was just incredibly dumb. So so I appreciate that, and I think I I'm with you on that one and and it was only the fact that the there was good literature to suggest that we won't kill somebody with with increasing the testosterone level, and again, that the the the this is a very controlled kind of process. The math models tell us this is when we want to give the testosterone we are. We are at a point that the PSA to testosterone ratio is telling us that this is the this is a significant population that's increasing in size. This is the basis for progression on ADT. And so in this case, we what we want to do is a limited sequence of testosterone, not, not, not three months. You'll notice that what we did was that when the testosterone, testosterone went up and it came down, exactly when it came down is when we gave another dose. We're not it's not a timing thing. It's a single dose. And it's a

sequence of four doses given in, you know, consistent with the underlying mathematical models.

Allen Morris 52:13
Which would you ever consider? I'll state it a different way. Would you ever consider giving super physiologic testosterone, whether in the form of that or any other way, in a patient whose PSA doubling time is greater than 15 months,

Bob Gatenby 52:30
you'd have to look at the models. I mean that that's what we do. That's why, that's why God made mathematicians, as far as I'm concerned. So every one of you know all of these patients have models associated with them, and they're followed, we look at the rate of rise as one of the things we'd have to I'd be interested in knowing what the testosterone looks like. We can estimate the underlying evolution dynamics mathematically and then simulate the, you know, the activity of a testosterone injection to see if that would be beneficial or not. I do think that whether we're able to do this in a large number or not, I think will remain to be seen, which is why we have a why we're starting a clinical trial on it. And I that's all, all I could say I wouldn't given the hypothesis, I wouldn't touch that person unless we had mathematical models showing us what we need to do.

Jeff Krolick 53:33
Just add that my PSA doubling time is quite a bit less than 15 months, and it's been quite successful for me. So it's really individualized in not a, okay, here's what we do for everybody. And so far so good.

Bob Gatenby 53:49
Yeah, Mr. Mr. Has a has his own math model and and so that's that's always sort of simulated at every kind of meeting. We don't, we come with that, but we don't actually do it in front of him, but behind the scenes is, you know, fairly quantitative approach, and that kind of precision is, you know, what we think we need in this. But, and Mr. Koch has a very complicated story. I mean, he was on ATT for a long time. I think it was like 18 months continuous. So, so he's a good example of how that continuous, high dose treatment will tend to eliminate the treatment sensitive population, which we need to maintain it. So he, he didn't have a lot of cycles before we start to see progression. Which is, which is what we expected. The the fact that we could not go with, really anything that was typically used for castrate resistant, made him, we felt, ethically, that we were okay. And of course, he was extensively consulted. Started on this, that the approach, although we had not tried it before, was reasonable.

Brad Power 55:08
We're coming up to the hour, and I know you're, you're on vacation, so I don't want to, I want to respect your time. I have a

Bob Gatenby 55:14
DR Lamont has a patient to discuss in in one minute. So

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Brad Power 55:20
I like to allow the discussion leader to wrap up by having any final words of wisdom or any major key messages you want to leave with us.

Bob Gatenby 55:36
The typical cancer therapy is seat of the pants. It's intuitive. One of the things that we know about complex dynamic systems, which is a mathematical description of cancer, is that there are nonlinear dynamics. Human intuition, which is linear, is not really good at those kinds of things. I want to emphasize the need to have formal mathematical modeling to make any of these decisions, especially if you're going to do something that's really far from the the conventional treatment.

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CHAT DISCUSSION

00:15:56 ari akerstein: We are a fiery group - because it matters!
00:16:12 Dr. Chris Apfel: Yes, I agree.
00:16:19 ari akerstein: Reacted to "Yes, I agree." with ❤️
00:16:49 Rick Davis: Chris - what Brad said ws that we never see HCPs changing dose. He made no reference to your qualifier.
00:17:09 Chase: Will we have time for questions?
00:17:29 Chase: Fantastic!
00:17:49 Rick Davis: Like I told our AnCan Group last night, bad information must be addressed.
00:18:17 Russ: Perhaps what Brad should have said that HCPs do not adapt the dose/therapy proactively based on predicted PCa response.
00:20:03 Dr. Chris Apfel: Replying to "Chris - what Brad sa..."

O.k. might have been sub-optimally phrased.
Dosing is generally according to protocols aiming for the maximal tolerated dose and adjustments are usually only done when side-effects become intolerable.
00:20:53 Russ: Replying to "Chris - what Brad sa..."

👍
00:22:19 Rick Davis: Replying to "Chris - what Brad sa..."

Generally agreed, although we've seen GU MOs adjust dose upfront based on the patients' co-morbidities.
00:22:35 Allen Morris: What are your thoughts on using supraphysiologic Bipolar Androgen Therapy (sBAT) in the Biochemical Recurrence (BCR) phase of Prostate Cancer? including directed by a citizen scientist as an N of 1 experiment?
00:23:01 Rick Davis: Replying to "Chris - what Brad sa..."

In most cases we'd agree that MOs dive in with max dose - but not always
00:24:53 Allen Morris: What are your PSA triggers for your on and off cycles on abiraterone?
00:25:07 Raj Aji: Is this applicable to all kinds of treatments- broad based chemotherapy, inhibitors, immunotherapy etc ?
00:25:20 Rick Davis: Re. abiraterone.... we now see IHT frequently, and sometime with monotherapy abi. IHT = intermittent hormone therapy
00:26:14 Dr. Chris Apfel: Replying to "Chris - what Brad sa..."

Agreed, though it is less common. But again, it aims at the maximal tolerated dosage.
We see significant differences in sensitivity/resistance profiles from patient to patient, but there is no way to talk about dosages or combinations that are not in the guidelines...
00:27:07 bill: Which cancers -doesn’t- this approach work on and why?
00:27:30 ari akerstein: Reacted to "Which cancers -doesn..." with 👍

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00:28:21 Rick Davis: PSA to T ratio is tricky. ADT drives T to zero - how is that taken into account?
00:29:16 Russ: Replying to "Chris - what Brad sa..."

Aims at MTD and I have rarely heard of a HCP that uses true adaptive therapy. Base the drug/therapy on predicted response.
00:29:31 Russ: Replying to "Chris - what Brad sa..."

In other words, we typically do not use game theory.
00:30:00 Russ: Replying to "Chris - what Brad sa..."

Are there updates on the adaptive abiraterone (Zytiga) or adaptive enzalutamide (Xtandi) clinical trials? If not, do you anticipate new data releases?
00:30:19 Rick Davis: Replying to "Chris - what Brad sa..."

Russ - you do not work with a GU MO. Amongst our GU MO"s we do see it as appropriate.
00:30:31 Russ: Replying to "Chris - what Brad sa..."

I work with 12.
00:30:44 Russ: Replying to "Chris - what Brad sa..."

None of them use game theory Rick.
00:31:01 David Plunkett: Reacted to "Are there updates on..." with 👍
00:31:13 Russ: Replying to "Chris - what Brad sa..."

Please let me know the names of the ones who do.
00:31:39 Russ: Replying to "Chris - what Brad sa..."

Denmeade is the closest and even he does not use true game theory.
00:31:55 Rick Davis: Replying to "Chris - what Brad sa..."

We can refer you to several who adapt dose. IT may not be based on Game Theory - rather patient condition and response.
00:32:33 Russ: Replying to "Chris - what Brad sa..."

Thanks but I'm interested in game theory. Not blunt changes mostly based on side effects.
00:33:04 Rick Davis: Replying to "Chris - what Brad sa..."

Efstathiou, Szmulowitz, Rathkopf, Aggarwal to name a few.
00:33:37 Russ: Replying to "Chris - what Brad sa..."

Thanks. I'll contact them. I'd be interested in their game theory and evolutionary theory approaches.
00:35:00 Russ: Replying to "Chris - what Brad sa..."

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While game theory, which analyzes strategic decision-making in interactive situations, has been increasingly applied in various medical contexts to understand interactions between patients, providers, and even cellular populations, it's crucial to acknowledge the distinction between its use in the context of cancer treatment strategies and its connection to Dr. Efstathiou's work. Game theory models can explore treatment as a strategic contest between the physician's therapy and cancer cells' resistance mechanisms, aiming to optimize treatment protocols by considering tumor adaptation and evolution.
00:35:24 Rick Davis: Replying to "Chris - what Brad sa..."

As stated, bear in mind it may not be based on Game Theory - rather patient condition and response. From the outset I have made that clear.
00:36:01 Russ: Replying to "Chris - what Brad sa..."

Ok.... So I asked about game theory/
00:36:17 Russ: Replying to "Chris - what Brad sa..."

I made that clear. Please scroll up and read.
00:36:31 Allen Morris: Do you view intermittent hormone (testosterone lowering) treatment as adaptive therapy and/or bipolar therapy? And if so, have you considered comparing the off cycles between normal physiologic and super high levels of testosterone levels.
00:36:45 Rick Davis: Replying to "Chris - what Brad sa..."

We have seen men use IHT effectively for many years. Isn't this just a refinement?
00:37:45 David Plunkett: Abiraterone is considered expensive?
00:37:51 Rick Davis: Replying to "Chris - what Brad sa..."

Abiraterone today is not such an expensive drug. It is generic and can be obtained quite cheaply. Secondly, it can be taken at 25% dose with food. Important to get our facts straight.
00:38:17 Chase: Replying to "Abiraterone is consi..."

It is now available cheaply. www.costplusdrugs.com $26/month
00:38:40 Russ: It was David. Now a generic is available. It was once like Nubeqa.
00:38:55 Richard Anders: Are there TWO Efstathious who study evolutionary cancer treatments?
00:39:16 Russ: It appears that none of the individuals you listed—Efstathiou, Szmulowitz, Rathkopf, or Aggarwal—are prominently associated with applying game theory to cancer research.
00:41:23 Rick Davis: Replying to "It appears that none..."

Russ - you are putting words in my mouth. I have twice posted... "As stated, bear in mind it may not be based on Game Theory - rather patient condition and response. From the outset I have made that clear." What part of that am I not making clear.?

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00:41:57 Russ: Replying to "It appears that none..."

I asked about game theory. You did not read what I wrote. No problem.
00:42:31 Russ: Replying to "It appears that none..."

Please re-read what I wrote and explain how I failed to communicate.
00:44:08 Rick Davis: Replying to "Are there TWO Efstat..."

There are two Efstathious - one is a GU MO, the other is a RO. I don't know if either study game theory. My point is that Dr. Eleni Efstathiou and the other docs mentioned adjust dose.
00:45:37 Allen Morris: Intermittent hormone theory, though theoretically adaptive theory in phase 3 Stage 4 Prostate cancer trials have not been shown to be superior to constant lowering? Can you comment on why you think there was no difference?
00:47:18 Rick Davis: Replying to "It appears that none..."

Clearly there is cross communication. I just went back and read the thread. I have been referring from the outset to doctors who adjust dose ex- game theory.
00:48:10 Russ: Good Rick.
00:48:15 Rick Davis: Replying to "Intermittent hormone..."

They have been shown to be non-inferior.
00:49:17 Russ: Replying to "Intermittent hormone..."

Did you read the Moffitt study? Median time to progression in this adaptive protocol was ~25.8 months, compared to 12.1 months in continuous dosing benchmarks—a significant delay in cancer progression
00:50:05 Allen Morris: Now, there are 7 classes of Prostate Cancer treatment. ---- Concerning your extinction theory, have you considered looking into sequencing the various treatments to maximize the possibility of extinction?
00:51:09 Russ: Replying to "Intermittent hormone..."

Alan, IADT has not been shown to be superior to ADT. QoL is superior and costs are lower. But overall results are not superior.
00:51:28 Russ: Reacted to "Now, there are 7 cla..." with 👍
00:51:44 Russ: How can adaptive protocols incorporate multiple drug classes — ADT, ARSIs, Zytiga, supraphysiologic testosterone (SPA), MDT, RLT, and PARP inhibitors?
00:52:14 Allen Morris: Replying to "Intermittent hormone..."

Yes Rick you are correct. Non-inferior.
00:52:31 Steve R: By using intermittent ARSI monotherapy, T should remain high to immediately re-sensitize the cells without injecting T. By avoiding LHRH agonists and antagonists, T should never fall.
00:53:31 Steve R: to lower than normal levels.
00:54:41 Russ: Steve, a trial is in progress for adaptive ARSI (Xtandi).

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00:56:04 Len Sierra: Reacted to "By using intermitten..." with 👍
00:56:41 Steve R: Russ, I have been using apalutamide and I hope the Xtandi trial confirms this protocol.
00:57:06 Chase: Question: is there a PSA level above which you would prefer not to go?
00:57:35 Russ: Steve, I hope so and let me know. I have that on my backup plans (Zytiga and Nubeqa - with occasional SPT)
00:59:35 Russ: Paul, yes... I wondered the same but it's not just Zytiga. It's a d4a metabolite. d4a impairs the 5ar isoenzymes.
01:00:05 Russ: I did an experiment once and verified by measuring DHT that this does indeed happen.
01:00:14 Russ: Serum DHT is not PCa DHT but....
01:00:32 Chase: I am doing this method with apalutamide and dutastaride only, no other ADT.
01:01:45 Richard Anders: Do you know if there are cells which can change their Androgen Receptor expression profile (and presumably their responses to androgen therapy, accordingly) depending on the local environent? If so are these cells widely expressed in certain tumor populations or generally rare? And finally, do you know if their cycle time (assuming they exist) is fast or relatively slow.
01:02:47 Russ: Richard, I assume the question was aimed at Bob. I think we know that and it is conventional. I can post the rough cell types and what they do if you want.
01:03:29 Richard Anders: It was directed to Bob, but if you have those insights, that would be great.
01:03:52 Russ: Ok. I'll post. CPL.
01:07:04 Russ: Replying to "It was directed to B..."

https://community.cancerpatientlab.org/c/bipolar-androgen-therapy/cell-types-and-response-development
01:08:37 Richard Anders: Thanks Russ. A lot to digest but I'll look at with interest.