“Bipolar Androgen Therapy” (Bryce Olson and Bob Gatenby) [#21]

Brian McCloskey and Brad Power
August 10, 2022

“It's been all upside. I'm living my best life right now on this treatment. What guy wouldn't want testosterone?” Bryce Olson

“There's no reason to be optimistic about this result. As we design the future therapy, doing the same thing over and over again is simply going to give that population time to proliferate.” Bob Gatenby

Meeting Summary

Advanced prostate cancer patient Bryce Olson shared the story of his exceptional response to Bipolar Androgen Therapy (BAT), where high doses of testosterone are alternated with androgen deprivation therapy. Then Bob Gatenby, MD, commented on Bryce’s experience and strategy from his perspective as a leader in adaptive therapy -- using evolutionary and game theory to inform cancer treatment strategy.

Bryce’s Exceptional Response to BAT

Bryce Olson has been heavily treated for his prostate cancer since his diagnosis eight-and-a-half years ago. He has had 12 lines of therapy, including the standard therapy of androgen deprivation since 2014. Somewhat out of desperation, a few months ago Bryce took a flier with BAT, flooding his androgen-deprived cancer cells with testosterone, which normally fuels cancer growth. Six weeks after his first cycle of testosterone, his PSA dropped from 307 to 5, then after the next cycle from 5 to 1.79. It's been all upside. He’s living his best life – what guy wouldn't want testosterone? In addition, taking testosterone can restore sensitivity to hormone-blocking therapy again, creating the opportunity to cycle from providing testosterone to androgen deprivation therapy, an adaptive strategy.
It's criminal not to scale this.

What Does It Take to Choose BAT?

First, most patients and oncologists are not aware of or considering BAT as an option. Pharma won’t push this treatment that only costs $200.
Second, the patient has to be brave enough – taking testosterone can be like throwing gasoline on the fire, feeding cancer growth.
Third, the patient must find a doctor that's willing to support it.

The Good News

Bryce got the information and insights that predicted that this therapy would work. It has selected cancer cells sensitive to testosterone and done a great job of killing them. It's a wonderful example of precision medicine. He looked at the evolutionary status of the tumor in a way that revealed an Achilles heel, and he attacked it.

The Bad News

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Bryce's many treatments have made a mess of his tumor population, so no one knows what's in it, and that’s always a problem. What's almost certain is that there are cells that are resistant to what has been done. If there are still tumors, there is a small resistant population. Flooding with testosterone is punishing the adaptive strategy to low testosterone. At some point, it's going to go away. There's going to be a new strategy that's evolving. Even cycling between supplying testosterone and depriving androgen will be selecting for androgen-independent cancer growth. There's no reason to be optimistic in the longer term. Prostate cancer is hard to eradicate.

Strategy: What Should Bryce Do Next?

Humans think linearly, but cancer is a nonlinear system. It might seem that cycling on the hormone path will work, but it's very hard to predict. Bryce has put the tumor on the mat with BAT. He has a small cancer population, and small populations are vulnerable to extinction. But usually in evolution, the final nail in the coffin (extinction event) is not the same thing that drove the population down originally.
Should Bryce add a different therapy now when he has a small cancer population?

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Meeting Notes

SUMMARY KEYWORDS

testosterone, androgen receptor, psa, patients, therapy, cancer, tumor, population, cycle, androgen, resistant, oncologist, point, cells, bryce, kill, line, liquid biopsy, stop, people

SPEAKERS

Jonathan Starr, Saed Sayad, Emma Shtivelman, Brad Power, Brian McCloskey, Bryce Olson, Rick Stanton, Ryon Graf, Bob Gatenby, Jim Ward

Bryce Olson 00:03

Thanks for having me here. I want to talk a little bit about B.A.T., Bipolar Androgen Therapy. When we did the hackathon for me in February of 2021, we all knew about B.A.T., but it wasn't even in the top five things for us to consider, partially because I think it's perceived as so dangerous. Throwing a bunch of testosterone into a guy is like putting gasoline on a fire. We never considered it even though it was in the back of my mind. I want to tell you about my success story with this and then talk about why I think it deserves more attention and scale.

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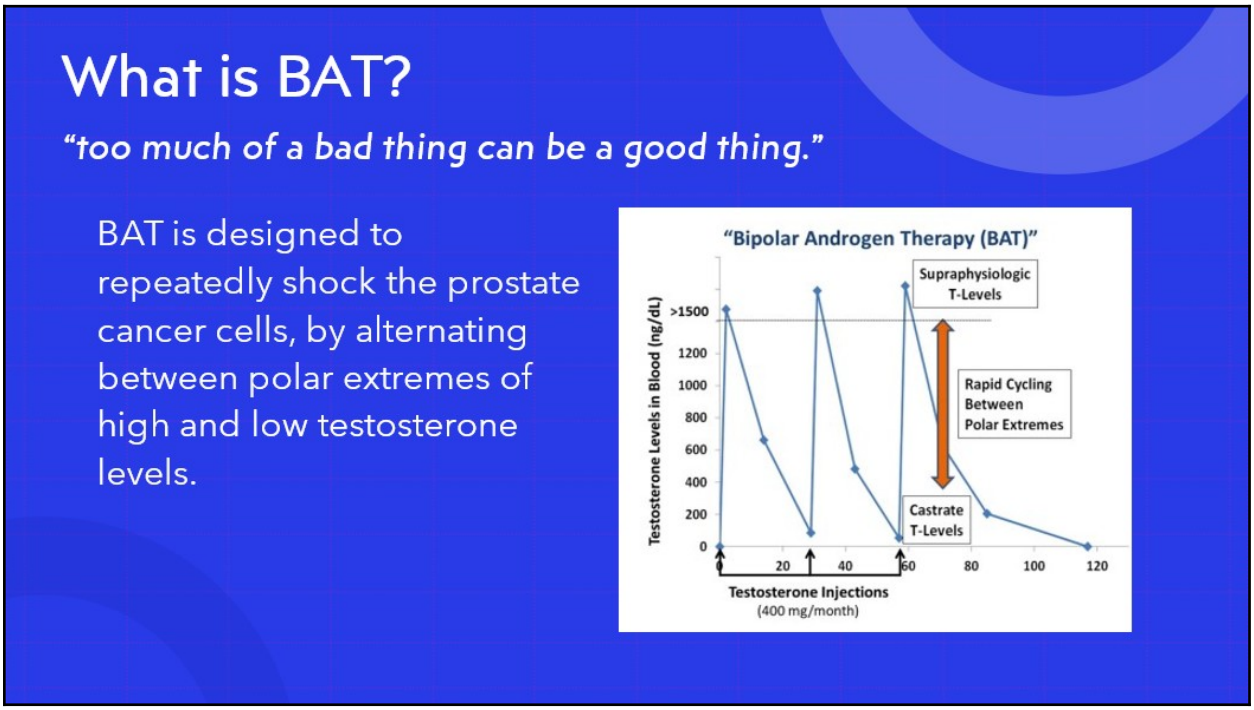

Bryce Olson 01:09

Is it a game changer? I think it could be. What is B.A.T.? It's bipolar androgen therapy. It's designed to repeatedly shock the prostate cancer cells. You're alternating between a polar extreme of high and low testosterone levels. As you can see on the graph on the right-hand side of this Johns Hopkins study, they were using 30-day cycles, or 28-day cycles. They would inject a patient with 400 milligrams of testosterone, and it would go up rapidly over the first two weeks or so, and then it would start to drop. This alternating pattern refers to supraphysiological T levels and then castrate levels. That's the gist of B.A.T.

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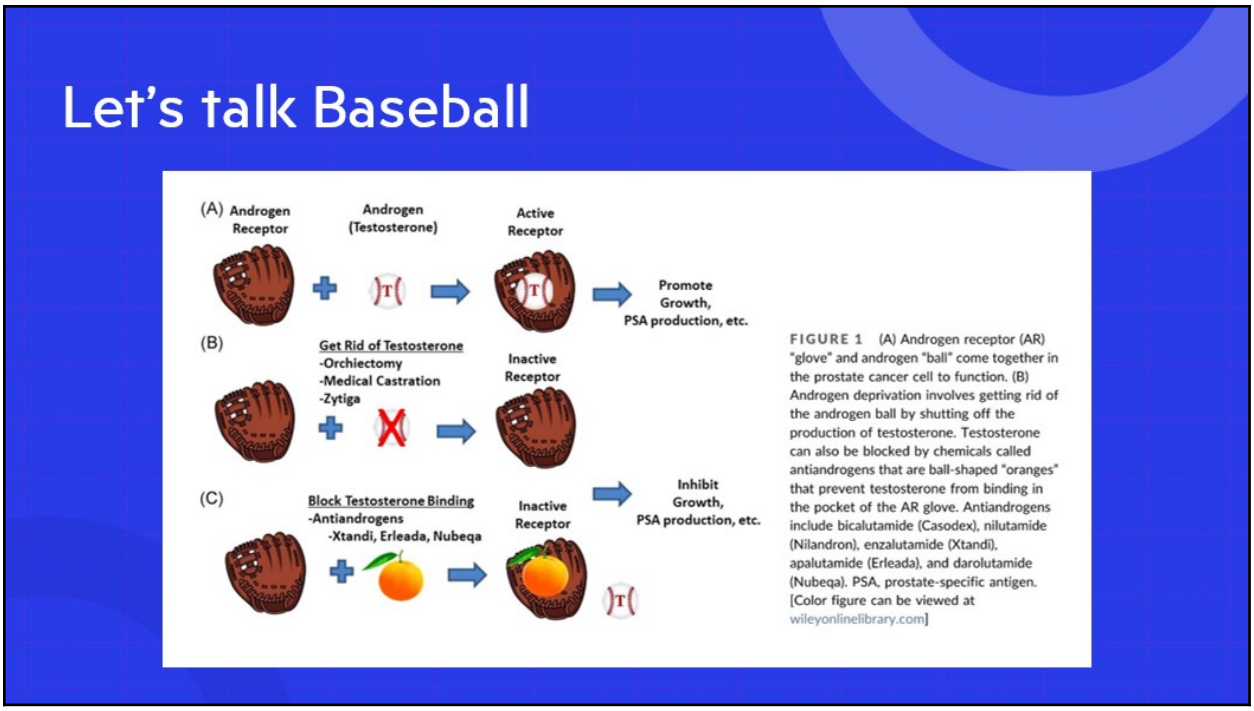


Bryce Olson

To more easily understand this, I want to talk a little bit about baseball. Using analogies is always an easy way to think about things. Let's talk a little bit about the androgen receptor and androgens in general, and we'll use a baseball analogy. Think of the androgen receptor which is on the cell surface of the prostate cancer cell. Your prostate cancer cells have androgen receptors on them, and they bind to androgens. Think of androgens as baseballs and androgen receptors as gloves. When you get an actual binding, that's when it folds in the nucleus and starts to rapidly divide. That's what generates prostate cancer growth and PSA production. If you take away testosterone, which is what we do with anybody who's in stage four, you give them Lupron or Eligard, and you're taking away the baseballs, so essentially the gloves don't have anything to bind to initially. It usually works for everybody for a little while and then cancer figures out how to grow despite having low levels of testosterone. The other way you can gum this up is using an anti-androgen like darolutamide, apalutamide, enzalutamide. Think of that as maybe throwing an orange into the glove. You gum up the receptor. That way a baseball can't bind into it. I'll say this again. Think of androgen receptors as gloves and testosterone, essentially androgens, as baseballs because I'm going to use this analogy when I tell you about my story.

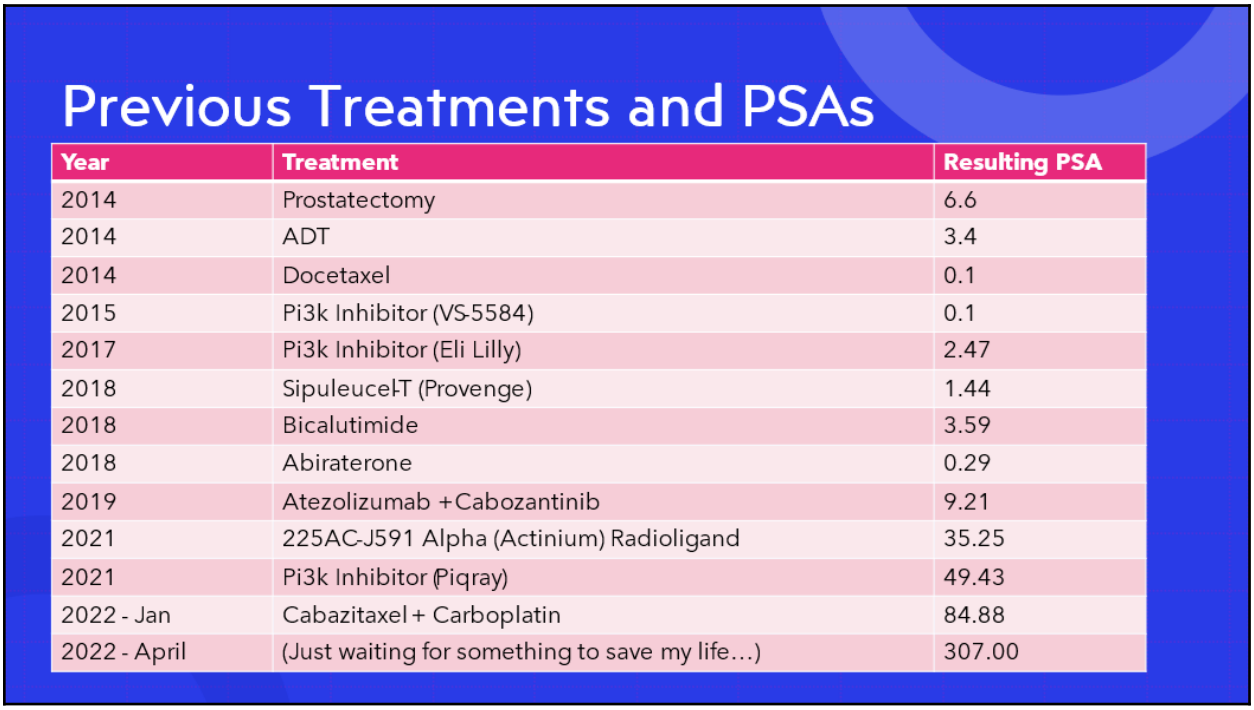
Bryce Olson 04:54

Why was I a good candidate for this? I was heavily pretreated. This is my 13th line of therapy over the last eight and a half years. I've seen ADT since 2014, and I failed abiraterone. I've already been on first line and second line hormonal therapies, and I'm castrate resistant. From a genomics perspective, you can see that I have AR copy number gain, so I have high levels of baseball gloves. When we took away the testosterone and then added abiraterone, that's when I saw the AR copy number gain show up. My cancer evolved, and it said, "Okay, not very much testosterone here, so we're going to add a ton of baseball gloves and try to scoop up any kind of baseballs that we can find." I have high levels of AR. I also have a P53 alteration. In a Johns Hopkins study, there's a hypothesis that people with BRCA DNA damage alterations, P53 alterations, and AR copy number gain probably do better on B.A.T.

I also shared ownership with my oncologist. Dr. Rana McKay hadn't done this before with anybody. She wasn't going to do this unless I came in and said I wanted to do it. It was going to have to be a shared ownership between the patient and the oncologist because this is not being scaled right now. Johns Hopkins did it, Oliver Sartor has done a little bit of it, and maybe a couple of doctors across the country have done a little bit of this, but it's not being widely used. It's going to require that the patient be brave enough. With testosterone in the equation, it can be like throwing gasoline on the fire. You must be brave enough to try it, and you must have a doctor that's willing to support it.

I have a couple other quick notes that show how my treatment is different from the Johns Hopkins study. I'm doing this every six weeks, so I'm not cycling on 30 days. I'm cycling on 45 days, every six weeks, and I'm adding pembrolizumab to it. The theory is that when you add testosterone in this type of a supra-physiological high-level way, you are turning on some of the immune function on the prostate cancer cell. I honestly don't know how much of my success is attributed to pembrolizumab versus testosterone, but I am using both. The other note is that I

did have a major pain flare after the first dose. As I have talked about this, it's been all upsides. I'm living my best life right now on this treatment. What guy wouldn't want testosterone? I'm loving this therapy, but I did have a major pain flare up that was excruciatingly painful for about three or four days after the first cycle. When you read the Johns Hopkins patient guide about this, they talk about it. They say if you have bone pain from cancer, they don't really want people with bone pain to do this. They consider you symptomatic, and they don't really want you to do it because they think it's going to be really painful. And it was super painful, but it went away. I did a high dose of steroids for five days, and then it went away. I haven't had it come back in the second and third rounds. I just want to throw that little note of caution up there. Go to the next slide.



Year	Treatment	Resulting PSA
2014	Prostatectomy	6.6
2014	ADT	3.4
2014	Docetaxel	0.1
2015	Pi3k Inhibitor (VS-5584)	0.1
2017	Pi3k Inhibitor (Eli Lilly)	2.47
2018	Sipuleucel-T (Provenge)	1.44
2018	Bicalutimide	3.59
2018	Abiraterone	0.29
2019	Atezolizumab +Cabozantinib	9.21
2021	225AC-J591 Alpha (Actinium) Radioligand	35.25
2021	Pi3k Inhibitor (Piqray)	49.43
2022 - Jan	Cabazitaxel + Carboplatin	84.88
2022 - April	(Just waiting for something to save my life…)	307.00

Bryce Olson 08:48

You can see a dramatic drop in my PSA from B.A.T. These are all the different treatments that I've done and my resulting PSA afterwards. Everything from ADT, to chemo, to multiple PI3k inhibitors, Provenge, abiraterone, actinium in New York City, another PI3K inhibitor, and cabozantinib with carboplatin. I got to the point in April 2022, when my PSA was at 300 PSA and I thought, "I'm in trouble." I was just waiting for something that could potentially save my life.

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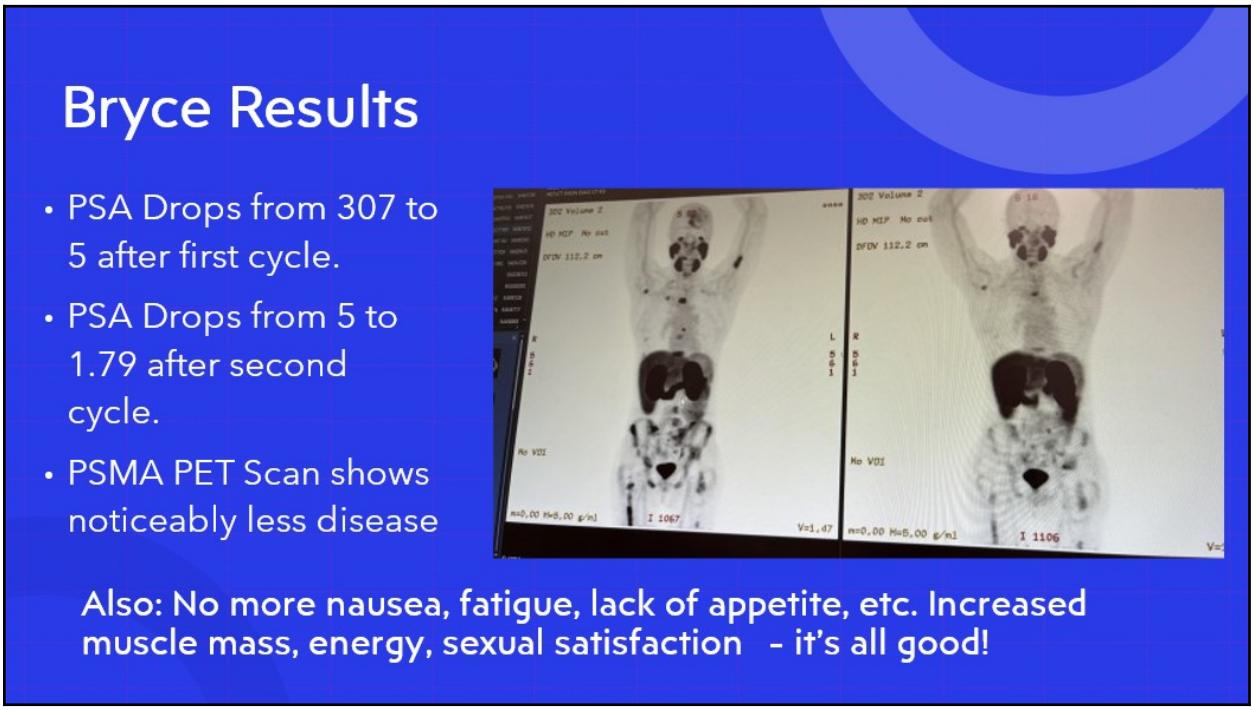

Bryce Olson 09:39

This is what happened to me. I started the B.A.T. with pembro and we measured it. After the first cycle six weeks later, my PSA drops from 307 to five. We do it again and the PSA drops from five to 1.79. I do imaging after my second cycle leading into my third cycle. This is on the right-hand side. This is a PSM-PET scan. I want you to look on the left. Look at my legs, pelvis, and hip area. Look at my sternum and chest area and then look at my head on the left-hand side. Now look at the right-hand side. The lesions on the head are gone. The lesions on the chest are going away - it's lighter. Look at the pelvis and the legs. Look how light it is. That's PSMA uptake. It's literally starting to erase from my body. I used to have pain in this area, I was even a little bit wobbly when getting up off the couch. It's all gone. All that's gone. I don't feel any pain. I don't feel anything bad. From chemo and actinium, I had nearly permanent nausea and fatigue. I had no appetite. I lost 20 pounds; I went from 170 to 150. I was really going into a bad spot. I got rid of all that. I have no more nausea. I have no more fatigue. I have an appetite now. I have more muscle mass. I got to 170 again. I'm not even exercising but still gaining muscle mass just from testosterone. Sex is better. It's all upside. Please go to the next slide.

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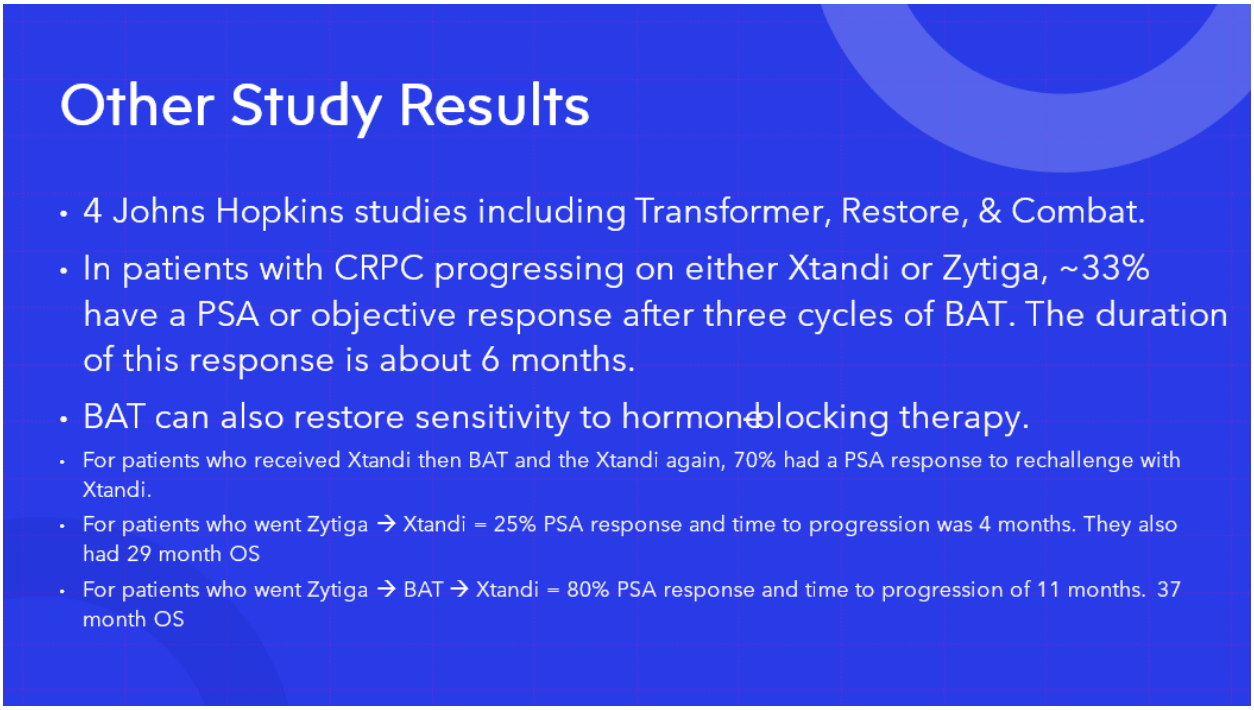

Bryce Olson 11:45

Here are some other study results. I took a picture of the actual patient guide. If you want to Google it you can download it and read it. Brad, I could send you the .PDF and put it in the notes too for people that want to read about it. There were four Johns Hopkins studies on this. What they show in the studies is that patients fell into three categories. They either had a PSA response, and that response was usually a 50% drop. They saw on scans that some of the cancer was going away which lasted for months. There was a PSA-stable cohort as well. Patients that had a little bump in their PSA, but then it flattened out, and they didn't progress. They just kept them on that as well. There was also a cohort of folks that progressed. Their PSA went up right away. It didn't work at all. But in patients with CRPC that were progressing on Xtandi or Zytiga, about 33% had a PSA or an objective response after three cycles. That duration, on average, was about six months. The other thing that's interesting about this is that B.A.T. can restore sensitivity to hormone blocking therapy again. It's a twofer. You get the B.A.T., which in my case, had this dramatic response. I'm re-sensitizing myself to hormone therapy again so I could redo this. That's what's cool about this. Not only do I B.A.T right now, but if I start to get a rise in PSA and start to progress on imaging, I can go back to Zytiga or Xtandi and get some more mileage out of this. You can read about some examples in the report. You can see patients who received Xtandi and then they went to B.A.T., and then they went to Xtandi again. This should never work right? Once you build up resistance to Xtandi, it shouldn't work. But if you go to Xtandi then B.A.T., and then Xtandi again, 70% of these people had a PSA response with the rechallenge. For patients who went on Zytiga and then Xtandi without B.A.T., 25% would have a PSA response and the time to progression was four months with their overall survival at 29 months. For those patients, if you went on Zytiga and then before Xtandi you did B.A.T. and then did Xtandi, 80% had a PSA response, and time to progression was 11 months. They had a 37-month OS. That's super cool. You get B.A.T., and you get re-sensitized to some of these second line hormonal drugs, so you just get extra mileage.

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Bob Gatenby 15:22

Congratulations on a very thoughtful and well-designed strategy. It illustrates the point that if we understand the underlying dynamics of cancer, we can develop therapies that are based on that even far into the disease.

We have a protocol with patients just presenting metastatic prostate cancer. We do androgen deprivation therapy, but we do it with cycling. We cycle based on the PSA. Basically, when the PSA goes below 50% of its pretreatment value, we stop and then let it come back. What we've learned from that is that the body begins to produce testosterone very quickly after that and continues to do so. We have patients who continue that for nine years. They are still on it after nine years. That's fairly simple, on-off, on-off, but guided by the dynamics of the patient. We don't force it arbitrarily, just on-off at three months or four months. We're watching. We're letting the tumor tell us when to do it. You're far into this process. You've been on androgen deprivation therapy for a long time, and we know that if you stop androgen deprivation therapy, you will not get testosterone coming back immediately. It takes a fairly long time, perhaps a year or more. With B.A.T. you're using testosterone as a driver, and it has worked very well at this point. The fact that you had the duplication of the androgen receptor means that the androgen level, your testosterone level, was low because of the ADT, but not zero. There's some around, and they're going to up regulate their receptors to get the signal so that they can proliferate. When you suddenly give them a whole bunch of testosterone they seem to die. It's probably because you're forcing them into proliferating when the environment is not up to it.

We can do the same thing with estrogen. If we put the breast cancer in a low oxygen concentration, for example, it will down regulate the estrogen receptors. The reason is because it can't survive proliferation at that point. If we force it to upregulate the estrogen receptors, and give them estrogen, they all die because they're trying to proliferate in an environment that they can't. It may be more complicated than that, but you're getting a certain amount of cell kill

probably from the testosterone itself. You're also getting some effect from the decline so it's very good.

Unfortunately, I don't think most people get that response. Very correctly, you got the information that you needed to predict that this would work. It's a great example of precision medicine. We often talk about precision medicine within a very narrow definition of it. You find a mutated gene or something, and that's a target that you can treat. But you really looked at the evolutionary status of the tumor. It has responded to the various things that have occurred, and in a very complex way. But it's done so in a way that reveals an Achilles heel and attacks it. It uses evolution to understand what's going on, and then treat it from there.

One of the strategies that we've used is what's called the double-blind therapy, where you push the tumor in one way, but that way adapts, and it makes it more vulnerable to a second line therapy. An example that we've seen is immunotherapy given against P53 in small cell lung cancer. They developed a very good immune response to p53, but they didn't have a clinical effect. When you follow that with chemotherapy, when historically the response rate is 5% or less, we got a 65% response. What happened was that the adaptive strategy to the immunotherapy made it vulnerable to chemotherapy. Those are the kinds of things that we want to do.

The question for me is, "what do you do now"? If you keep cycling, are you going to drop the PSA lower and lower so that the population of tumor cells is smaller and smaller? But one of things we know with prostate cancer is that it's hard to eradicate it. The ADT that's typically given at the beginning of treatment will normalize the PSA, and sometimes make it undetectable in 90% plus of men, and yet it's never cured. You've put the tumor on the mat with this. Could this be a curative maneuver? I think it's unlikely, but it's possible. You want to treat for cure, which in this case might be to add an extinction therapy. You've got a small population and small populations are vulnerable to extinction. But usually, the final nail in the coffin is not the same thing that drove it down originally. Do you want to add something to this at this point when you've got a small population?

An alternative is to stop what you're doing now and just let everything kind of come back and then start the therapy again. The only thing I would just caution you about is that as good as this result is, you should be aware of this concept of evolutionary rescue. When your tumor is probably pretty diverse, and even if there's a small population that's resistant, at some point it's going to come back to bite you. Think about what to do next with an expectation that there will be evolutionary rescue. There will be a small population that's resistant, and it's very small compared to what it was at the beginning. You have the sensitive cells, in the absence of treatment, that have a tremendous fitness advantage. That's because they were, by far, the dominant population before you started therapy. But there probably is a small population that's resistant, and then the question is, "how do you want to manage this in a way that you can go down the road for years and maintain control of the tumors"?

Bryce Olson 24:01

Exactly. That's fascinating. There are a couple things to add to that. I did another liquid biopsy after the first cycle, which was six weeks into this treatment plan. What was really interesting was that the genomics had changed in two ways. My AR copy number gain was gone when I flooded it with testosterone.

Both Foundation Medicine and Tempus liquid biopsies showed this. What's happening is that I introduced a large amount of testosterone, and it started shedding the AR copy number gain alteration. Guess what else? It shed, crazily enough, my PI3k alteration.

These alterations I used to have I don't see on the liquid biopsy. Both FMI and Tempus are showing that the only thing I still have is P53. All these other alterations are okay.

Bob Gatenby 26:57

Let me be clear, there's no reason to be optimistic about that result. I'm pessimistic about that result because it's exactly what you've said. Your therapy has selected those cells with bulk copy numbers, and you've done a great job of killing them. But if you're still detecting tumors, you're detecting a small resistant population.

So we know it's there, but we have to take that into account. As we design the future therapy, doing the same thing over and over again, is simply going to give that population time to proliferate.

Bryce Olson 27:47

That's where you could get into an adaptive therapy, and Johns Hopkins is starting to look at this with future studies. I've seen this rapid PSA decline, treatment over treatment, 300, to five, to 1.5. Radiographically, you can see that I've had improvement. At some point, if I just keep doing this every six weeks, we're going to see the PSA start to rise. When that happens, I could just introduce darolutamide, or Xtandi, and bring it back down again. And then once I get to that point, I could reintroduce B.A.T., so I can essentially cycle between B.A.T. and second line hormone therapy. I could keep cycling that way.

Bob Gatenby 28:44

It's possible. We would have to think about it. This is where evolutionary models are very helpful to work through that in computer simulations and see if that would work.

Bryce Olson 29:05

I like the extinction event idea that you have. My only concern is that I've already seen carboplatin. I've seen cabazitaxel. I've seen docetaxel and those things. My cancer has figured out a way to become somewhat resistant to it. I don't know what the extinction event drug would be if we were to go down that path.

Bob Gatenby 29:54

Remember that tumor cells have to deploy resistance mechanisms to be resistant and that's going to cost them energy. They have to divert energy from some other source because they're in a tumor environment that's got very poor resources. You could add an anti-androgen which is not terribly effective in a large tumor population in prostate cancer, but there is some evidence that it's effective in smaller populations. Keep in mind that the goal is to exploit this small population vulnerability. You've made a mess of this tumor population so God knows what's in it and that’s always the problem. But what's almost certainly in it are cells that are resistant to what you've done.

Can you walk me through what you would suggest if it progresses?

Bryce Olson 31:09

Johns Hopkins would say let the PSA progress up to where it started before you started therapy. They would let it get up there. Then once it progressed beyond that, then they would introduce Xtandi, or darolutamide, or some anti-androgen to stop it from going further. I went from 307 down to one. I don't know if we should wait to get up to 307. We don't need that much progression.

Bob Gatenby 31:49

When would you introduce the B.A.T.?

Bryce Olson 31:54

I would go back to B.A.T. when it goes up to half of that, say around 150. When there's a clear signal that the hormone sensitive cancer is really starting to get stronger. Right?

Bob Gatenby 32:17

Why not stop the cycling, stop the B.A.T. right now?

Bryce Olson 32:26

Yes, that's what we would do. Sorry, to be clear, the plan is that if we see a lot of progression of PSA or radio graphical progression, we stop B.A.T and we introduce an anti-androgen...

Bob Gatenby 32:39

...But why not stop it now and then start it again when the PSA goes up?

Bryce Olson 32:50

This is what I am seeing because I did some mid-course PSA checks. What's happening to me right now is that the spike in testosterone is very good for me. When I start to drop, you can see it dropping in week four and a half, or five, by six, I'm starting to get towards castrate levels. My PSA does start to inch up a little bit. When I get down to castrate levels my cancer loves that environment. It knows how to exist and thrive in a low testosterone environment. I am seeing it slightly bump up now. But then when we introduce B.A.T. again, it just slams it right back down.

Bob Gatenby 33:38

You're punishing its adaptive strategy to low testosterone. At some point, you're punishing that strategy so it's going to go away. There's going to be a new strategy that's evolving. The population that has up regulated receptors are presumably what you're punishing, and you've just done a serum marker that suggested that that has declined, and that makes sense. You punished it enough that you've reduced it. Before you started all that, as soon as you get testosterone, these guys die like dogs, which means that that population, in the absence of your therapy, is fitter than the resistant cells. If there's a small population weapon, then stop. That's

going to come back up again. You could have let it come back up again. In the process, it's going to be suppressing the growth of the resistant guys, and then to start B.A.T. again.

Bryce Olson 35:05

That's interesting. We could try that. I don't know if I have the cojones to do that.

Bob Gatenby 35:12

I'm sorry. Walk me through what you think. If you continue the B.A.T.s and you then get resistance and the PSA goes up, what do you think is going to be the properties of the resistant cells?

Bryce Olson 35:27

They're going to be not so much castrate resistant, but they're going to be hormone sensitive. The original cancer cells that love testosterone are going to become the herd boss again. This is what I think. Every six weeks, I'm introducing testosterone again. Up until now, when I introduced testosterone, it kills all these castrate resistant cancer cells, which are the herd bosses today. But at some point, the hormone sensitive original cancer cells will start to take over because they want to introduce testosterone. I can see it in the genomics already. I know Ryon and I were just chatting about this. On the liquid biopsies, at least the cancer that's coming up in the liquid biopsies, doesn't have AR copy number gain anymore. Those cancer cells love testosterone, and they will eventually learn how to bind. What's happening is the bipolar nature of this treatment is that it sees testosterone, then it sheds the androgen receptor and says, "It's too busy." It's shedding all these alterations that it had, and by the time it figures out what to do, the testosterone is dropping already. It's really confusing it. But at some point, it'll learn how to not be confused, and it'll start growing again. If it does, then these are kind of hormone sensitive cells that I could stop with darolutamide or Xtandi. Once I'm effectively stopping it with a second line hormone drug, like I said in the presentation, you can re-sensitize the cancer to the second line hormonal drugs again. I would introduce Xtandi or darolutamide and then reintroduce B.A.T again. I'm thinking of cycling between B.A.T. and second line hormonal drug, B.A.T. and second line hormonal drug, etc. That could be my adaptive strategy if I don't have an extinction event.

Bob Gatenby 37:41

My concern is that you will be selecting for androgen independent growth. I don't know. I hope you're right. Just to be clear, these are very complex dynamics right now. Let's characterize the cell populations. There's one that's got a lot of androgen receptors on its surface, and it's vulnerable to increasing testosterone levels. Perhaps there's another population that has a normal amount of androgen on its androgen receptor. I guess what you would say is that when you give testosterone, does that population proliferate?

Bryce Olson 38:34

Eventually? I think it will.

Bob Gatenby 38:39

As you're killing off this pulse-up of androgen that you get, you're killing off the cells with a lot of androgen receptors. Then, do you think you're causing the ones with a normal amount of androgen receptors to proliferate at that point?

Bryce Olson 39:06

I don't think they are yet. But that is the natural evolution. Those will go back to being the ones that proliferate. When that happens then I can introduce a second line hormonal drug again and get a bunch of mileage.

Bob Gatenby 39:20

I have just one concern and I could be wrong. These are very complicated things. If you see the PSA rising when the androgen levels go down, I think you interpret that as being a proliferation of cells that have sort of a normal amount of androgen receptors. Is that it?

Bryce Olson 39:48

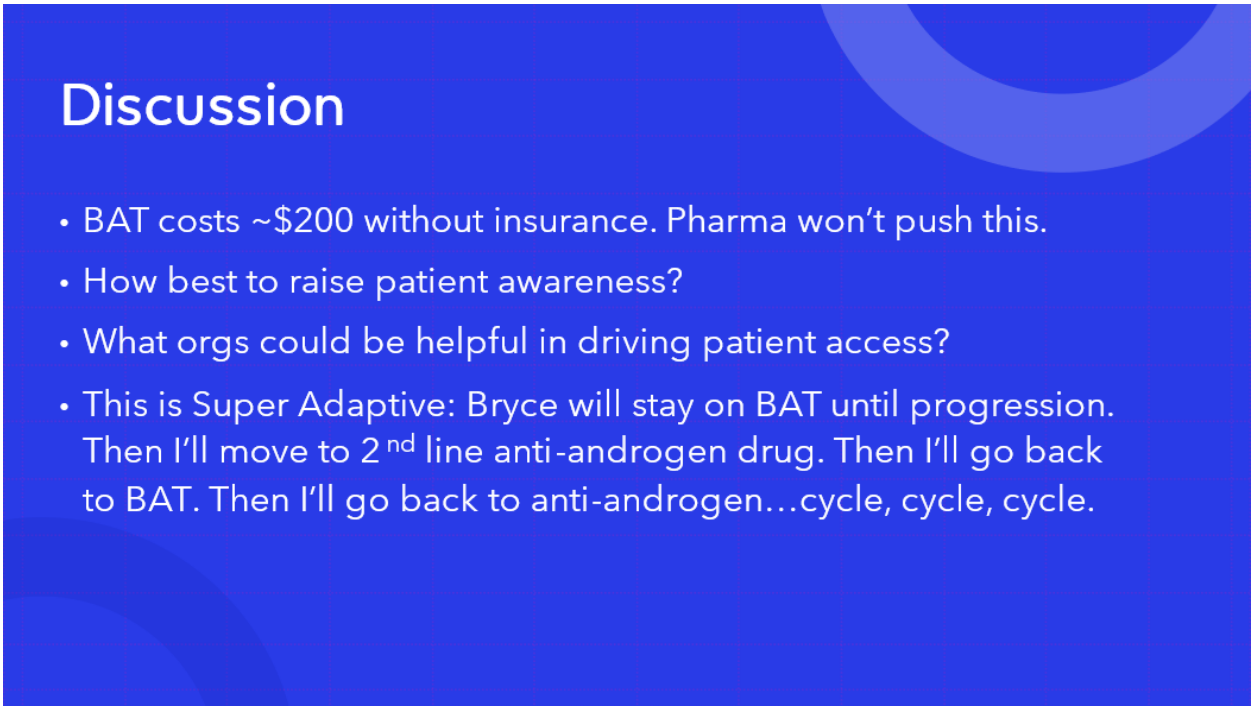
No - I don't think so.

I think there's a little bit of them that still haven't been killed off, and those guys are very comfortable growing in a low testosterone environment. In the six-week cycle when my testosterone levels drop, I'm seeing that my lowest PSA is probably in week three and a half to four. At week six, when I get ready for the next cycle, the PSA bumps up a little bit. What's happening is that I'm at this low level of testosterone, and there are still some cells that are like, "I love that. We know how to grow on that." But then when I slam more testosterone into my system, those get killed even further down because I saw that go from 300 to five, and then to 1.5. I'm slowly killing them. I might see my next cycle that I'm down to zero point something. It might just continue to kill them. But eventually, whether it's a year or six months from now, the cancer will start growing in a high testosterone environment. It will learn how to do that. But if it does that, then I can just introduce a second line hormonal drug and slam it back down again because that's the cycling that I can do.

What frustrates me is that there are a ton of people out there with stage four metastatic prostate cancer who have been highly treated like me and would probably have similar dynamics with the androgen receptor who could really benefit from this. But nobody is getting it.

Bob Gatenby 40:00

This is so fascinating. In our paper we published last year in European Urology, we detected androgen receptor amplifications in about 20% of men who are going to first line CRPC, and about 30 to 40% by second line there. If this is actually something that can be used in these men, this is potentially transformative, but I don't need to be the one telling you that.



Bryce Olson 42:15

This ridiculously amazing treatment costs 200 bucks tops, somewhere between $50 and $200 to get 400 milligrams of testosterone every six weeks. Xtandi costs $10,000 a month, right? No pharma company is going to push this because they're not making any money off it. This isn't something they newly developed. A lot of oncologists are incentivized to push FDA-approved drugs. They're incentivized to drive the new clinical trials. I don't know what the best way to raise patient awareness for this is. I don't know if we should find some organizations that are helpful at driving patient access. There's a ton of patients out there that don't have good insurance and don't have great money that could benefit from something like this. I'd love to get the team's feedback on the best way to scale something like this and build more awareness, so more patients like me can benefit because it is criminal to hide this.

Brian McCloskey 43:33

I can just jump in here for a second because we've been talking a lot about it. It's incredible what your response is. As I looked at my options, B.A.T. was one of them. I talked to Rana McKay, (Bryce and I share the same doctor) and she was resistant to pursue it because she said that I had just moved into a castration resistant setting. She felt that it was too soon to go after it. I think that we need to identify who are the best patients that will respond to this. Bryce, you said AR copy number gain and TP53 are markers, but how long do you have to be castration resistant before this therapy will work? What are the other dynamics that we need to consider? Before more patients can respond, I think that we need a little bit of due diligence on that.

Bryce Olson 44:40

Yeah, or it could be that every oncologist has that set of patients that have exhausted a ton of drugs who are running out of options and the oncologist is scratching his or her head and doesn't know what to do. They've probably failed ADT and second line hormonal therapy a long time ago and should be given this as an option. Why not try this? I don't know if this is a mass educational effort that the oncologists need to get more aware of. Perhaps go through zero cancer.org and push it through them because they have a large set of patients that pay attention to their message.

Jim Ward 45:33

A question for Brian McCloskey: I'm learning a lot about B.A.T. I'm a little bit lower on the learning curve than certainly a lot of you, but it seems odd to me that you're saying your shared oncologist told you that she's hesitant to do B.A.T. because you've just recently gone castrate resistant. I guess I don't really understand what the rationale is behind that.

Brian McCloskey 46:05

Her perspective was that Bryce has been castration resistant for several years. She felt that I'm still a little bit hormone sensitive and that I could get a little more mileage with abiraterone right now. She wants me to stay the course on abiraterone right now before we get into this type of therapy.

Bryce Olson 46:36

I kind of think that she might be onto something there. It would be different if Brian was showing resistance to abiraterone. For example, on imaging you can see cancer was growing, and his PSA was rising, then he's really CRPC. ADT doesn't work, and second line hormonal therapy doesn't work. Then he's entered the same kind of realm as me, but right now he's responding. You could make an argument that maybe it's not the right time.

Brian McCloskey 47:08

One more quick thing on this. Bob, you and I had a little offline conversation about this yesterday. ARV 766 is one of the treatments that is in line for me. How would an AR degrader work with B.A.T. down the line? How do we think about a strategy for how those work together? It seems to me that if I went on ARV 766, I would degrade my AR, and I would have less mitts to catch the androgens. True or not?

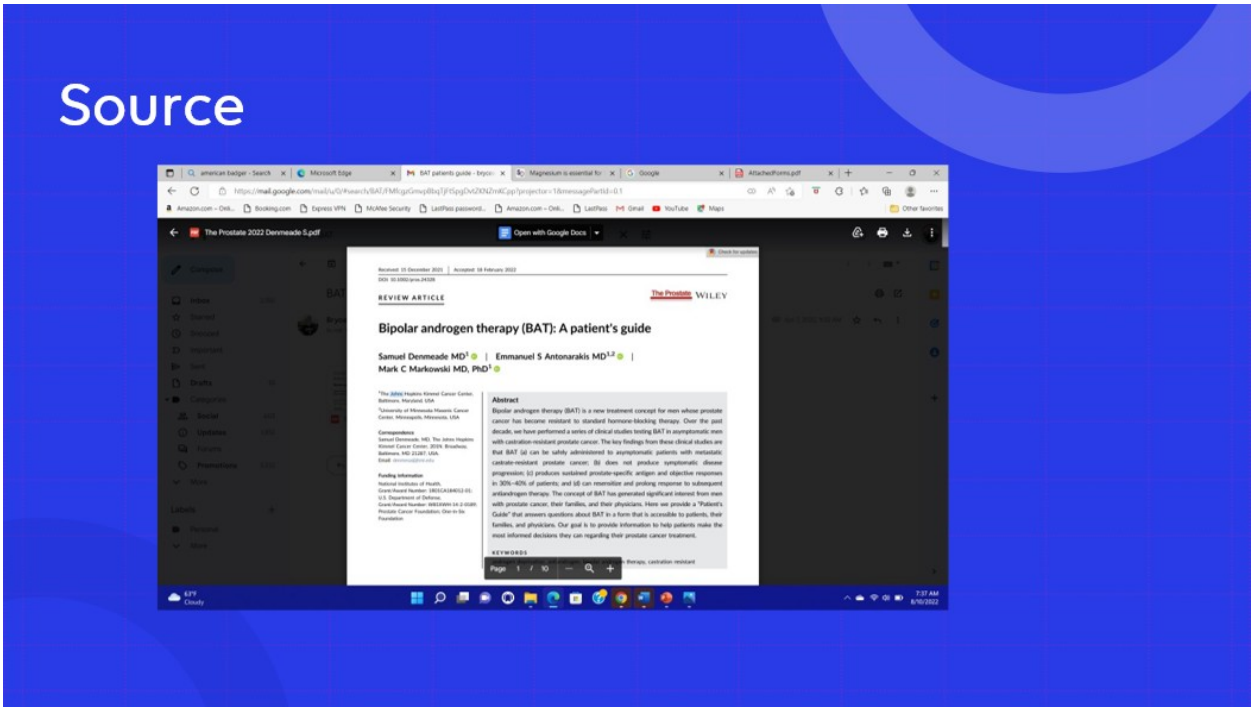
Bob Gatenby 47:42

These are nonlinear dynamics. The human brain is very good at linear dynamics. For example, if x gives you two y, 2x gives you four y - that's linear. But cancer is a nonlinear system. It's very hard to intuit what's going on with it. I think that Bryce showed this example beautifully that he got information on the intra tumor or evolutionary state of cells, and the treatment was appropriate for that state. I guess this is obvious, but we need better biomarkers to understand how evolution is going on and what cells are selected. We can debate whether the B.A.T therapy is going to select for cancer cells with the normal amount of receptor, or whether it's going to select for androgen-independent growth. But we need to know that in planning treatment. When you get into these very complex situations where people have been treated with multiple things, it's hard to anticipate what's going on with it or to accurately predict the results of a perturbation applied to this nonlinear system.

“Bipolar Androgen Therapy” (Bryce Olson and Bob Gatenby) [#21]

Emma Shtivelman 50:19

The problem was B.A.T. is that there are no predictive markers of response. It's difficult to say who might benefit - we're all guessing. There are a couple of reports that patients who have mutations in the HRD pathway, like BRCA1, and those with TP53, tend to respond, but people who administer B.A.T., like Johns Hopkins, should probably start collecting data and looking at them systematically after they conducted for trials and probably patients who were treated off trials as well.



Bryce Olson 51:06

On the patient guide, they talk a little bit about that.

Emma Shtivelman 51:11

I saw the patient guide.

Bryce Olson 51:15

Their early hypothesis is that DNA damage repair BRCA and TP53 might be synergistic. AR copy number gain looks like it's really synergistic. I know that Rana is sharing my response information with the Johns Hopkins team because maybe one to three people max out of that 300 or so that were in it had dramatic responses to me. I'm very rare in the precipitous drop of PSA.

Jonathan Starr 52:05

Bryce, thanks for this talk and I'm happy to see these fantastic results for you. One small point I want to bring up is that you're talking about your plan going forward. There are several other drugs in the pipeline, some of which are looking quite promising. Brian mentioned ARV766 as one of them and others like Veru111. There are others. Instead of having to plan your entire future going forward, you could look at this as potentially a bridge to when other things become available.

Bryce Olson 52:51

I agree. I think I'm buying a tremendous amount of time with this. I was a little bit worried that I wouldn't see my way out of 2022, honestly, before I started this treatment. I'm just ecstatic that I'm buying at least a year of time, if not more, for these new drugs to come onboard when I need it. You're right. There are new drugs and tomorrow's better than today when you're fighting this disease.

Saed Sayad 53:32

These are very interesting results. Actually, I believe the purity behind that testosterone effect on prostate cancer is wrong, or was wrong and was based on some limited knowledge.

This is the simulation of public data related to prostate cancer. I used 20 genes here. This is a model and I have testosterone and doxorubicin, which is docetaxel. I just showed the effect of testosterone on this data. I added one unit, 1%. I applied this on down-regulated genes. We have 1234567 upregulated genes by testosterone. Now I changed testosterone to doxorubicin with the same amount. I reset it and apply ACC 12345678910; it easily shows the effect of testosterone can be close to doxorubicin. I believe we have a problem with knowledge.

Brad Power 55:23

That is worth a follow-on conversation. That looks pretty intriguing.

Rick Stanton 55:35

I've just read this book, "How to Starve Cancer." Thanks to Robert Ellis. The author goes into how to starve it, and then how to kill it with ferroptosis. I wanted to mention this to Bob. I'd never heard of ferroptosis. Some of the kills that are being described in the book are along the lines of Bob’s ideas – which is that you push towards extinction. You introduce a bolus of free radicals via intravenous vitamin C, which is surprising. They're saying that the remaining cancer cells cannot tolerate what is normally thought of as bad with the abundance of free radicals. Evidently, according to this author, the cancer cells are more sensitive, and you can go for a kill shot. We can go further into this, but I just wanted to mention a metabolic axis. I'm frustrated that everyone is reaching the end of the genomic and gene expression way to kill cancer. I'm so happy with Bryce, but I'm trying to add another dimension from a different angle to be synergistic. For another day, but I want to introduce that.

Brad Power 57:09

Bryce and Bob, how do you react to the ideas that it's not all on the androgen vector, but it's something else? Would a metabolic approach possibly be useful?

Bob Gatenby 57:26

I think so. I would encourage people to look at the website from Christopher Gregg, who is a neuroscientist at the University of Utah. He's also a cancer patient and has done extensive research in exactly this kind of thing, the use of various metabolic approaches. I think when you're trying to kill something, it's not the time to be selective. If you find something you didn't hit it with, then you do it. I think metabolic strategies are perfectly valid and should be integrated into the more classic set of toxic options. Chris Gregg has done a great job of looking into this. He's a scientist himself and has presented data that's available on different strategies. I would encourage people to look at that.