“Bipolar Androgen Therapy for Prostate Cancer" (Emmanuel Antonarakis) [#56]

Russ Hollyer and Brad Power
May 12, 2023

“It's a paradox, right? Because we're giving high doses of testosterone, the thing that we have known for 60 years is the fuel for prostate cancer. How is it possible that giving the cancer its fuel in super high doses can kill the cancer?” – Emmanuel Antonarakis

“A lot of the genetic markers that often predict inferior prognosis, by the same token, predict superior response to BAT, which again is a paradox.” - Emmanuel Antonarakis

“What are the different types of responses, or lack of responses, that patients can have? And how common are these scenarios? … Each of these three scenarios occurs roughly in about 1/3 of patients that we treat with this approach.” – Emmanuel Antonarakis

“It's also the only type of therapy that I've ever seen when the patients come with their spouses. The spouse or the wife would have a big smile on her face after many, many years of frowning. And it's because yes, the sex drive can come back.” – Emmanuel Antonarakis

Meeting Summary

In a previous session, 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. Super patient Russ Hollyer has been self-administering BAT and has written a book about it.

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 who is willing to support it.

An Update on Bipolar Androgen Therapy (BAT) for Prostate Cancer from Dr. Emmanuel Antonarakis

Emmanuel Antonarakis, MD, is uniquely qualified to update us on bipolar androgen therapy for advanced prostate cancer. He is the Clark Endowed Professor of Medicine and Associate Director of Translational Research, Masonic Cancer Center, at the University of Minnesota Medical School. Dr. Antonarakis is a genitourinary medical oncologist with a particular focus on recurrent and advanced prostate cancer. He conducts clinical and translational studies to bring new therapies to patients with prostate cancer. In particular, he is interested in developing novel

androgen-directed therapies, genetically-targeted therapies, and immunotherapies for men with recurrent or advanced prostate cancer, and using germline and tumor genomics to inform precision oncology approaches for these patients. He also has an interest in liquid biomarker development, including the clinical validation of the AR-V7 marker as well as DNA repair markers and their therapeutic implications.

How is bipolar androgen therapy administered?

Bipolar androgen therapy (BAT) consists of cycling testosterone (a male hormone in the class of androgens, responsible for many normal functions, including growth and development of the genitals, muscles, and bones) levels from supraphysiological (greater than normally present in the body, >1500 ng/dl) to low (<150 ng/dl). It can be accomplished by injecting 400 mg of testosterone cypionate once a month. There is no reason that testosterone propionate could not be used instead of testosterone cypionate.

We do not know if administering testosterone once every four weeks is optimum. Six weeks might be better as it allows cypionate to decay to a lower value.

Some variations on BAT that have been considered include combining it with an immune checkpoint blockade. In the COMBAT trial, BAT was combined with an immune checkpoint blockade (nivolumab) and the PSA50 response rate (a decrease > 50% compared to baseline) was 40%, and the RECIST (Response Evaluation Criteria in Solid Tumors, the percentage of patients whose cancer shrank or disappeared after treatment) rate was 24%. The use of darolutamide interleaved with BAT might reduce the potential for future use of darolutamide monotherapy. The ExBAT clinical trial is using darolutamide interleaved with BAT. BAT has been used with etoposide. This combination should work well. However, it was found that etoposide therapy has many side effects and the benefit was deemed to be less than the harm.

How do people typically respond to bipolar androgen therapy?

Responses are roughly divided into thirds: one third will see a marked improvement in their PSA and a reduction in cancer, one third will see a PSA plateau (no progression = a benefit), and one third will see an increase in PSA and in cancer growth.

PSA is a rough marker. Scans and genetic tests should be performed to monitor therapeutic action. Sometimes PSA will increase but cancer scans show no growth or even regression. Along those lines, sometimes increased bone metastasis activity appears to occur for about 2-3 months before drastic reductions in activity are seen. It is reasonable to have a liquid biopsy prior to starting BAT and once in a while during BAT. However, PSA, scans, and clinical symptoms are preferred.

If PSA increases for 1-2 cycles, do not panic. PSA often increases before it starts going down. Sometimes PSA decreases yet scans get worse for a few months. What makes decisions difficult is sometimes PSA increases AND scans progress for a few months prior to receding.

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AR panels (10, 20, 50 genes) in RNA signature analysis can be used to determine AR activity.

Pain, especially bone pain, can occur, usually from inflammation. You can use 600-800 mg of Ibuprofen, Motrin, or another NSAID to control it.

Besides reducing cancer, what are the other benefits of bipolar androgen therapy?

BAT can substantially down-regulate androgen receptors (ARs) and despite this can continue to work. Someone who has become castrate resistant (not responding to androgen deprivation drugs, like Lupron or abiraterone) can become hormone sensitive again (will respond).

BAT can improve the effectiveness of some drugs. For example, in the TRANSFORMER study, 78% of men had a response to Xtandi if BAT was performed first, triple the conventional rate.

In addition to controlling the disease as well as many therapies, quality of life is usually markedly improved, particularly libido and energy.

When should you consider getting bipolar androgen therapy?

The ideal time to get BAT is when you start to show that you are becoming castrate resistant, i.e., when your PSA (prostate specific antigen, a biomarker of prostate cancer activity) rises indicating you are not responding to your androgen deprivation therapy.

How can you predict if you might get a good response from bipolar androgen therapy?

Paradoxically, the markers for BAT response are the same markers that usually signal an aggressive cancer. The following genetic mutations have been displayed by extreme BAT responders:

- BRCA2
- TP53
- TP53/BRCA2
- TP53/ BARD1
- BRCA2/ATM
- ARID1A
- ATM/RB1
- CDK12 has some response.
- Men with HRR mutations had a 68% PSA response rate (any PSA reduction). Men without an HRR mutation had a 37% PSA response rate.
- Men with tumor suppressor loss (TP53/PTEN, PTEN/RB1, TP53/RB1) exhibited a 54% PSA response rate.

Contraindications (don’t consider BAT if you have):

- Symptomatic bone pain. You could make the pain worse.

- Bone mets that are close to the spine or are threatening a fracture. You could wind up with spinal cord compression or a fracture.
- If the prostate gland is bulky or a pelvic lymph node is close to obstructing your urinary tract, you could develop a renal obstruction or possibly even kidney failure.

BAT does not seem to work well if you have AR-V7 splice variant but in general the higher the AR activity the better for BAT.

Proteomics has not been explored in relation to BAT response prediction. However, it is possible that if you have higher AR activity or HR mutation (e.g. BRCA2) you might have a higher likelihood of responding to BAT.

What if you are still responding to androgen deprivation therapy?

According to the standard of care, BAT is not recommended if you are still responding to androgen deprivation therapy. However, some men try BAT anyway. Men with hormone-sensitive prostate cancer who have PSA/cancer regression from BAT therapy should publicize their results in conjunction with their medical oncologists.

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Meeting Notes

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SUMMARY KEYWORDS

patients, psa, mutation, response, testosterone, study, question, cancer, bat, called, therapy, high, responding, proteomic, lupron, showed, ar, weeks, bipolar, heterogeneity

SPEAKERS

Dr. Antonarakis (42:36), Russ Hollyer (5:14), Brian McCloskey (1:46), Robert Ellis (1:43), Ken Anderson (1:42), Amit Gattani (0:49), Robert Gurmankin (0:27), Mike Yancey (0:23), Brad Power (0:17)

Session Outline

1. Dr. Antonarakis’s background. (0:00)
2. Dr. Sam Denmead’s background. (1:02)
3. Lhrh and PSA graph. (6:22)
4. What are the different types of responses and frequency of responses? (10:42)
5. What do people prefer? BAT or Abiraterone? (17:03)
6. Technical slide on p53 mutations. (22:48)
7. Cypionate vs. Propionate for the treatment of prostate cancer. (29:17)
8. PSA and cancer. (34:19)
9. The ideal time to start treatment with CDK12. (39:40)
10. How to screen for heterogeneity? (43:56)
11. Germline genetic testing for testosterone. (49:06)

Russ Hollyer 0:00
Dr. Antonarakis, I personally want to thank you. He's one of the premier BAT experts in the country, knows a lot about bipolar androgen therapy and has done a lot of really good and interesting research. I want to thank you personally, I was on an ADT about four and a half years ago, and I didn't see a way out and I wanted a way out. And I was willing to just gamble on anything. And I stumbled upon high testosterone and then your theories of BAT.I feel that it saved my life and extended my life, at least as being a strong person or being a person who could do things and was active in my life. So thank you very much. With that, would you like to know a little about myself, my background? If not, I'll turn it over to you. And if you can present maybe three to five slides, I'm sure we have lots of questions if that's okay with you.

Dr. Emmanuel Antonarakis 1:02
Yeah, if you want to give a background of yourself that's beyond what you just said, you can.

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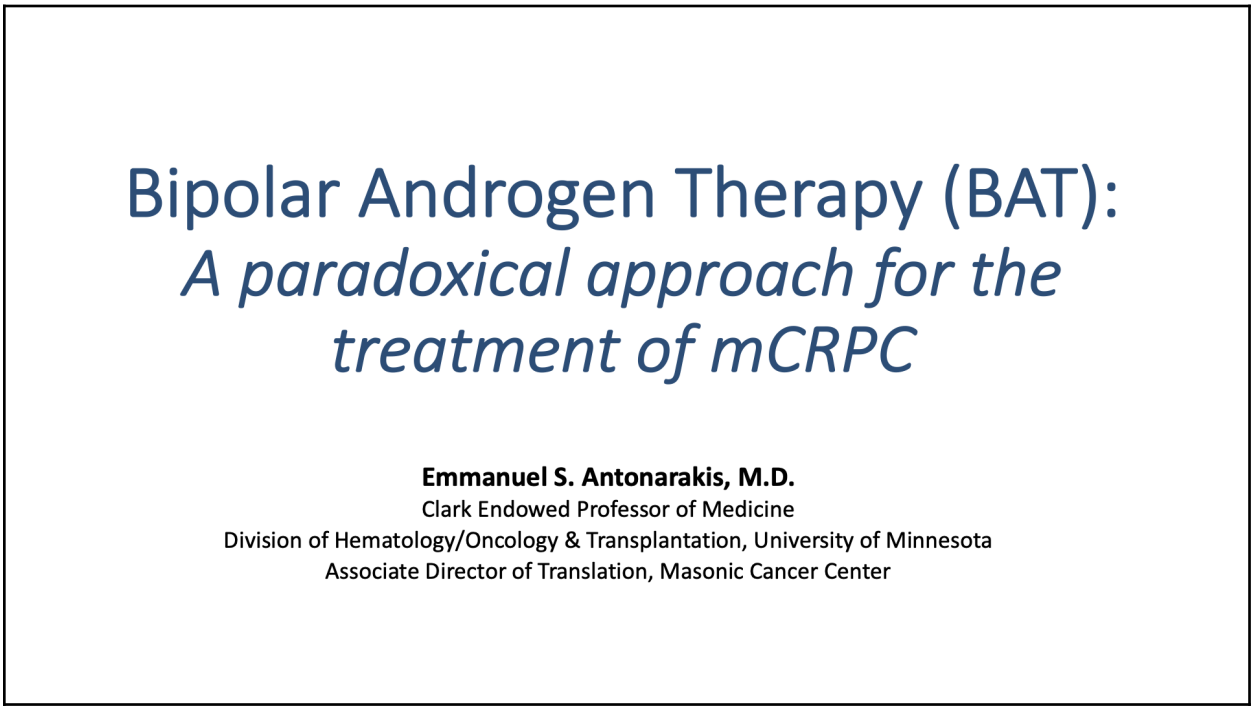
Russ Hollyer 1:08
I'm Gleason nine and a lot of these guys here are Gleason 8, 9, and 10. I had surgery back in 2018. And at that time, the Mayo Clinic gave me a 50/50 chance to get to two years and that was being on Lupron full time. I chose transdermal estrogen therapy, but after four and a half months I was looking in the mirror and kind of breaking down. I wanted to do something else.

Brad Power 1:56
Russ has the profile of a lot of people here.

Dr. Emmanuel Antonarakis 2:24
Well, thanks for that.



What I will do, because Brad didn't exactly tell me how many slides, I had 23 slides, but I don't have to go through all of them. I just want to give you guys a flavor of how this started and what we've learned so far, some pearls. Clearly this is not for everyone. And beyond that it can be dangerous if used indiscriminately. Russ mentioned it himself. He said, “I wanted to take a higher risk approach.” It can be a high risk for some people.

Let me just share what I've learned about this over the past 10 years. If I can summarize that in 20 minutes or 30 minutes, then we can leave time for questions. I might go through some of the more detailed scientific stuff a little bit faster.

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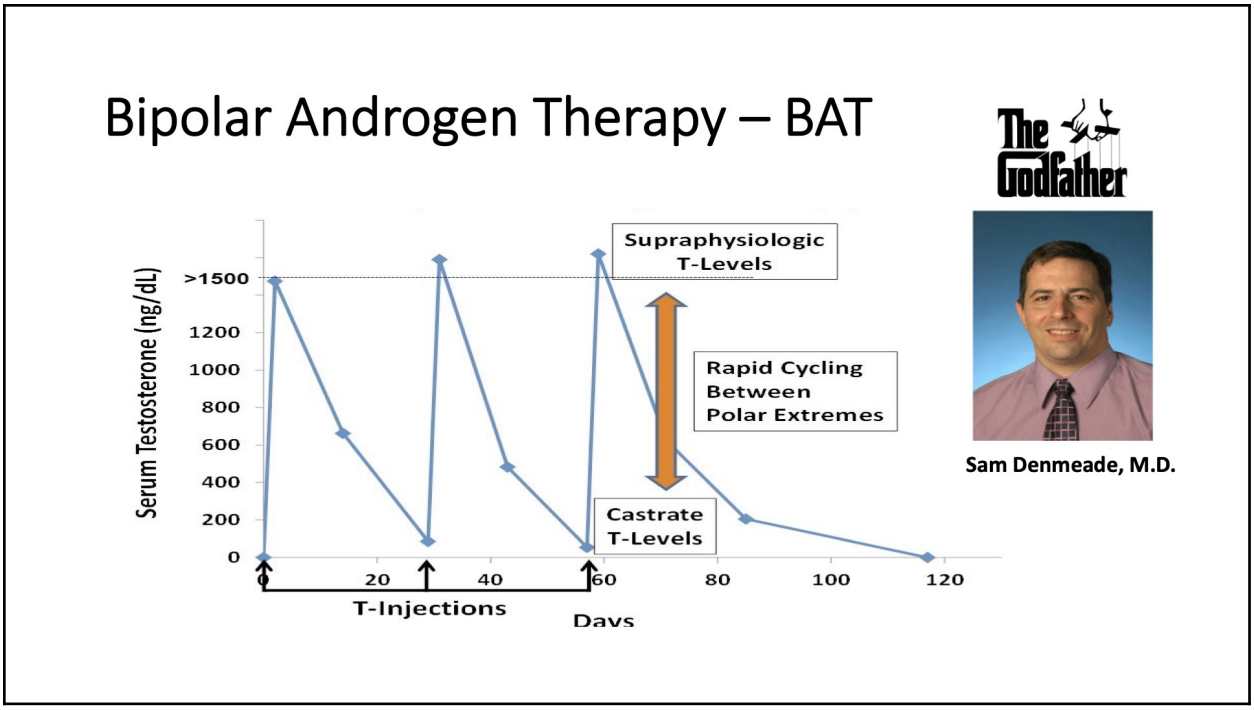
But of course, it's a paradox, right? Because we're giving high doses of testosterone, the thing that we have known for 60 years is the fuel for prostate cancer. How is it possible that giving the cancer its fuel in super high doses can kill the cancer? So that's why it's truly a paradox.

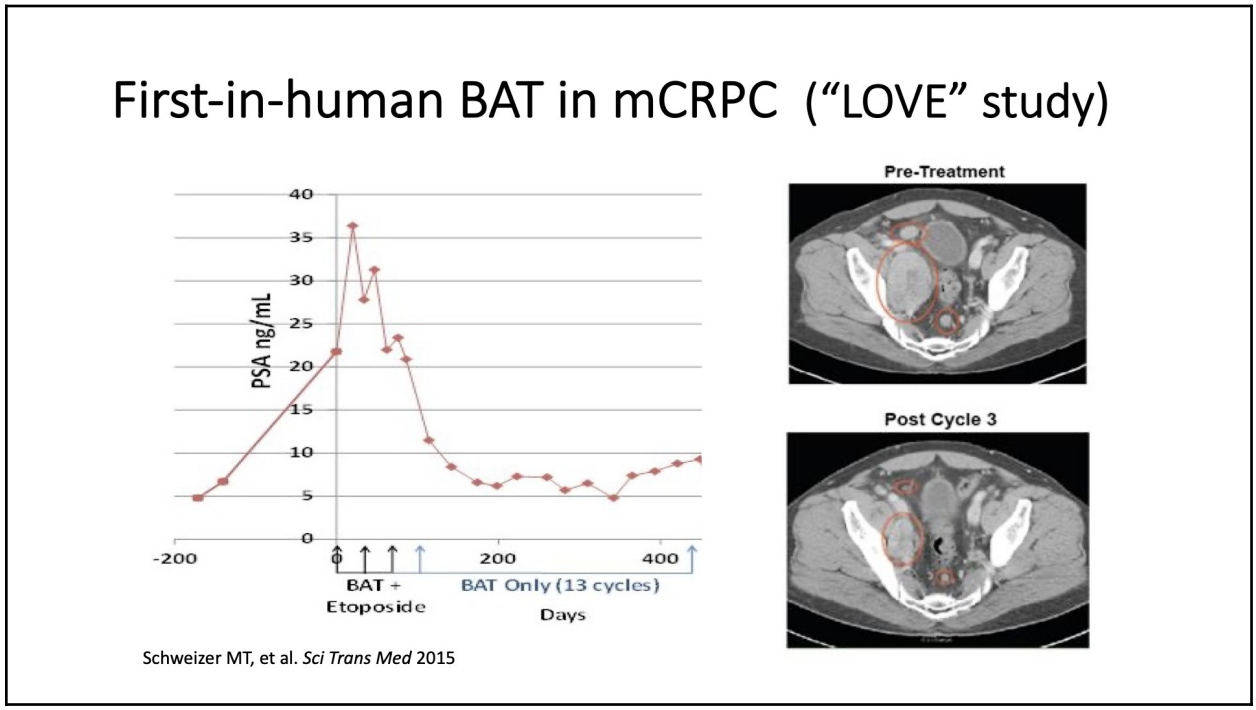


Before I get any further, I want to give absolute credit to who I consider to be the godfather of bipolar androgen therapy. As many of you may have seen the movie, I'm also a big fan of it. “The Godfather” of bipolar androgen therapy is Dr. Sam Denmead. He was the discoverer of it. And he designed many of the first clinical trials that I was privileged to be part of because I was working alongside him when I was at Johns Hopkins. I don't think any discussion of BAT can take place without showing a picture of Sam. He doesn't look quite this young anymore. This is a picture that is about 10 years old. But the concept of bipolar androgen therapy, we don't want to confuse this with bipolar disorder, we're not making people become bipolar, we are actually using opposite extremes of testosterone levels.

So as you can see, we're starting off with a castrate testosterone close to zero. And then we are giving men intramuscular injections of high dose testosterone such that they achieve Super physiologic levels, more than 1000 and sometimes more than 1500 nanograms per deciliter. Then over the course of 28 days (4 weeks), testosterone returns to zero or close to zero. And then another injection is given, and up it goes again, and then down again. And the key about bipolar androgen therapy, which many people don't fully understand, is that we always continue the Eligard, Lupron or Zoladex, that suppress testosterone. And that's another paradox. And while we're continuing that testosterone suppressing drugs, at the same time, we're also giving it once every four weeks. If we didn't do that, if we stopped the Eligard or the Lupron or those drugs completely, then over time the testosterone would continue to go up. And then over time, it would actually begin to feed the cancer again. So we need to do both simultaneously: keep

the testosterone suppressed by using drugs like Lupron and at the same time, give a once every four weeks high dose injection of testosterone.

Russ Hollyer 6:22
I think that's a super good point. And it's something that a lot of people don't quite understand. What you're doing is, with the LHRH drug (luteinizing hormone-releasing hormone, causes the pituitary gland in the brain to make and secrete the hormones which cause the testicles to make testosterone), you're getting rid of the endogenous testosterone so that you can control it exogenously, correct?



Dr. Emmanuel Antonarakis 6:39
Exactly. I want to give you guys a bit of history. We treated our first patient in 2013, and then published our paper in 2015. So we've had a decade of experience. This PSA graph here, it was from the very, very first patient that we treated. Dr. Denmead had a great sense of humor. And he designed acronyms for all of his studies. The first study was called the LOVE study and it was a play on words. And the joke was that patients get their love life back, and their sex life back. And many of them actually did, so that we called it the LOVE study. It's also the only type of therapy that I've ever seen when the patients come with their spouses. The spouse or the wife would have a big smile on her face after many, many years of frowning. And it's because yes, the sex drive can come back.

The instructive thing about this very first patient was that you can see that his PSA initially went up before it went down. So there was a PSA of about 22 when he enrolled, and it went up to about 37. And then it kind of had this zigzag pattern. And then eventually by the third month dropped. And this patient had a response lasting 13 months. It's not the best response we've

ever seen, we've seen much, much longer, of course. But the thing that was gratifying to us was that he had a very large pelvic mass here that you can see. And even after three cycles, it decreased in size. And then by 12 cycles, it had disappeared. So lesson number one is, do not panic, do not freak out, if your PSA goes up in the first one or even two cycles, because it may go up prior to going down.

Clinical Trials with BAT (2013–2023)

TRIAL NAME	PATIENTS
1. Phase 1 BAT (“LOVE”)	16
2. BATMAN – mHSPC	34
3. RESTORE – Cohort A (post-Enza)	30
4. RESTORE – Cohort B (post-Abi)	30
5. RESTORE – Cohort C (pre-Enza/Abi)	30
6. RESTORE – Cohort D (*TP53/PTEN/RB1* mut)	22
7. TRANSFORMER – Enza vs. BAT	195
8. COMBAT – BAT + Nivolumab	45
TOTAL	***402***

This table shows the eight BAT studies that we've done over the decade between 2013 and 2023. And each one has an acronym. And over the course of those 10 years, we have treated 402 patients in these studies. And also countless other patients that were treated outside of a study either because they weren't eligible, or because they chose to not participate in the study but still asked us to administer and oversee that therapy, which we did after, you know, clearly outlining all the caveats and the risks with those patients.

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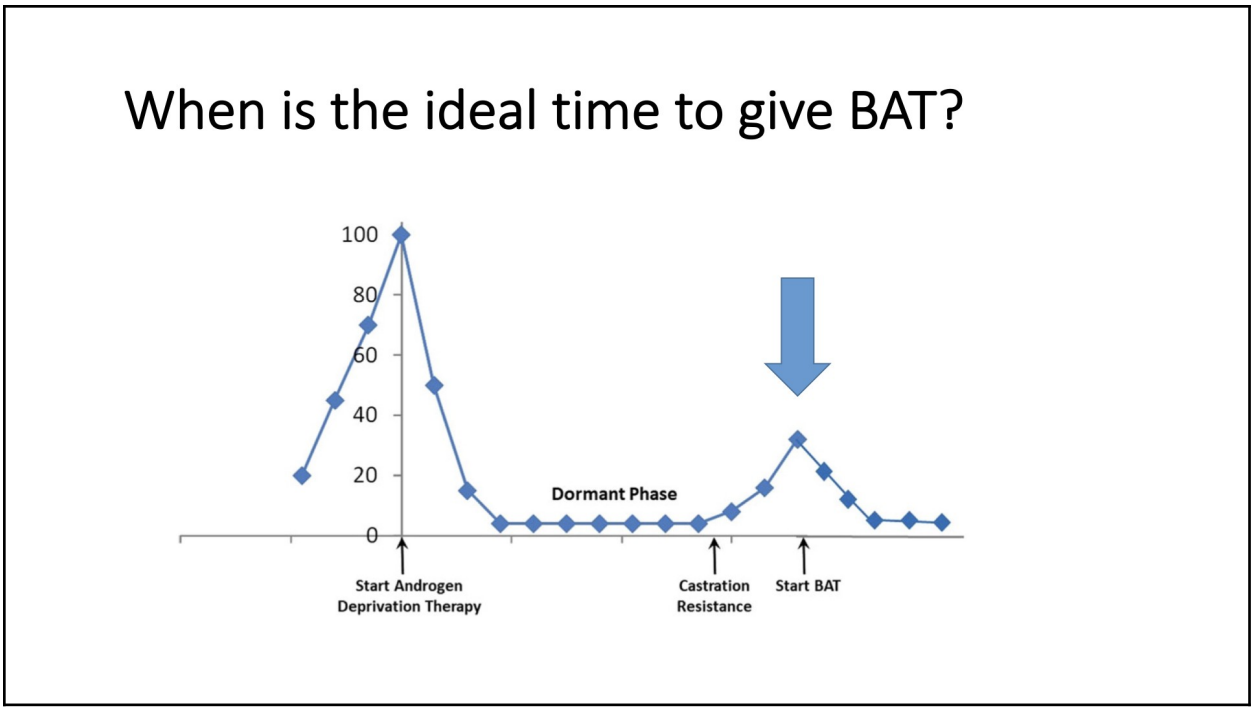

I want to go through a couple pearls. One is, “when is the ideal time to give BAT?” The counter to that is when you should not give BAT. And we have learned that we should not be giving BAT in patients that have hormone sensitive prostate cancer. This is not something that you want to do in the initial phases of the disease. As an alternative to androgen deprivation therapy in those patients, it will make the cancer worse. It will stimulate the cancer. So in other words, this is not a treatment for hormone sensitive prostate cancer. It's a treatment for castration resistant prostate cancer, and this graph shows it well. This is a hypothetical patient, and his PSA is 100. He begins androgen deprivation therapy, the cancer goes into a dormant phase where the PSA becomes undetectable or close to undetectable. And then over the course of time, the cancer becomes resistant to androgen ablation and is called castration resistant, and the PSA begins to go up despite testosterone being suppressed. And this is the phase of the disease, what I call “the early castration resistant phase”, ideally, before the patient gets chemotherapy, or other therapy, where BAT is most beneficial in our experience.

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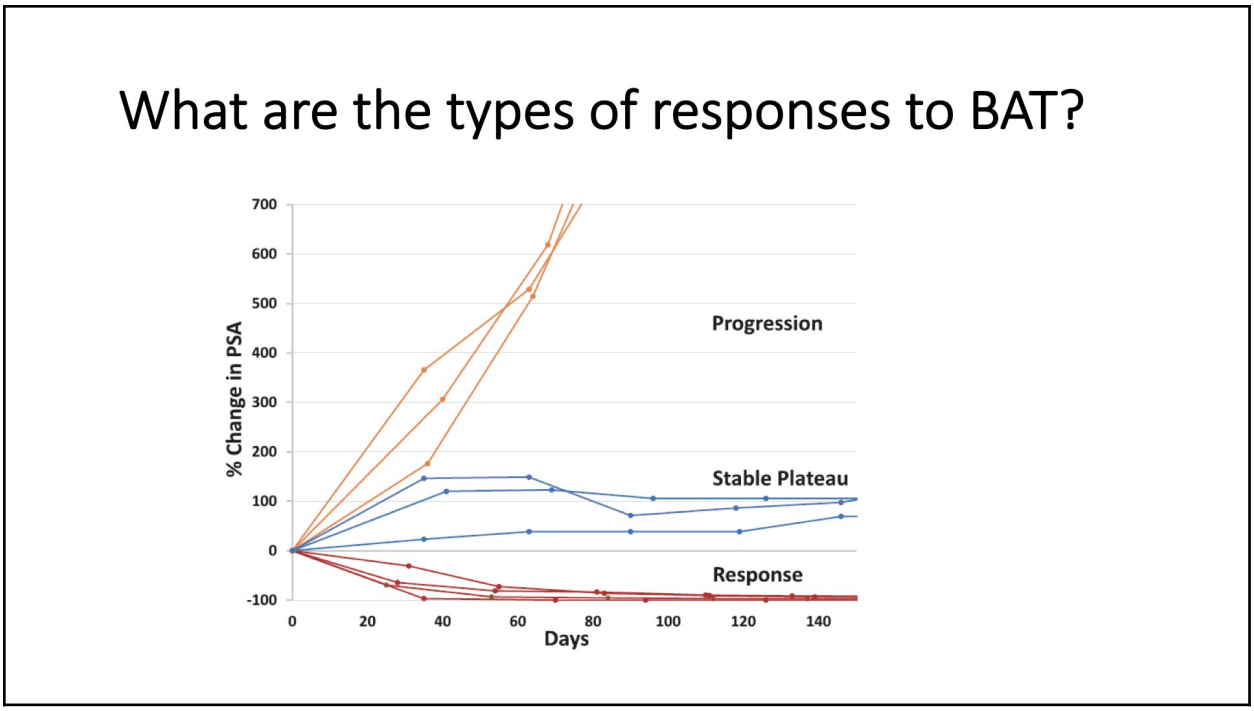


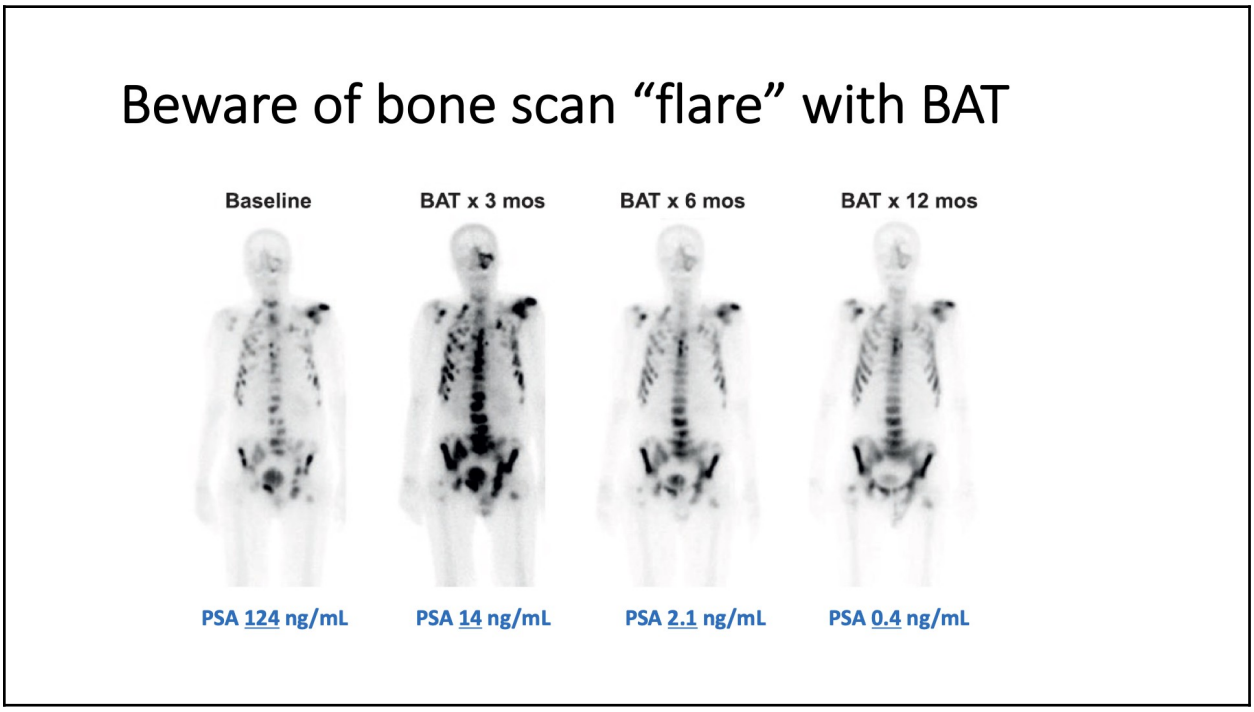
The second question is, “What are the different types of responses, or lack of responses, that patients can have?” And “how common are these scenarios?” We have summarized it as three potential scenarios that we have seen in our clinic. Each of these three scenarios occurs roughly in about 1/3 of patients that we treat with this approach. The best case scenario, which is shown in the red are what we call the responders and this is the no brainer. These are the patients who take bipolar androgen therapy, and their PSA goes down immediately. And they remain suppressed, and their disease shrinks on their scans. This happens in about 1/3 of patients. When we see this, there's really no dilemma or no question, you know that the patients know that they're responding, we know that they're responding. And it's, as I said, it's a no brainer. And this occurs in about 1/3 of patients. I'm going to show you a slide later to try to determine what are the genetic predictors of those patients, are there any genetic mutations or other things that can help us to predict who these responders are going to be. And we haven't completely solved that, but we have some clues.

The second group are these people that we call the stable plateau where their PSA level was previously rising very, very steeply. They are placed on the BAT therapy. And even though their PSA doesn't drop, it levels off and it creates this plateau. And sometimes this plateau can last for months or even years. And if you were a patient whose PSA was going up very sharply, and you can make it plateau, and by the way, your quality of life improves during that time as well. That's a “win win”, even though you're not getting a reduction response, so to speak. The plateau, as long as the quality of life improves during that period of time, is also beneficial. This happens in about 1/3 of patients.

And then in about 1/3 of patients, the treatment is not working at all. And it may even accelerate the disease. And that's depicted here in these orange lines. So when I discuss this with my

patients, I basically tell them, there's a two out of three chance that you're going to have some benefit, a benefit being defined as either a stabilization of your disease, or a remission of your disease. So if you add the remission category, plus the stable disease category, you get to about two thirds, 67%.

And that leaves again the 1/3 of patients who unfortunately will have no benefit whatsoever and in some you may actually make the disease worse.

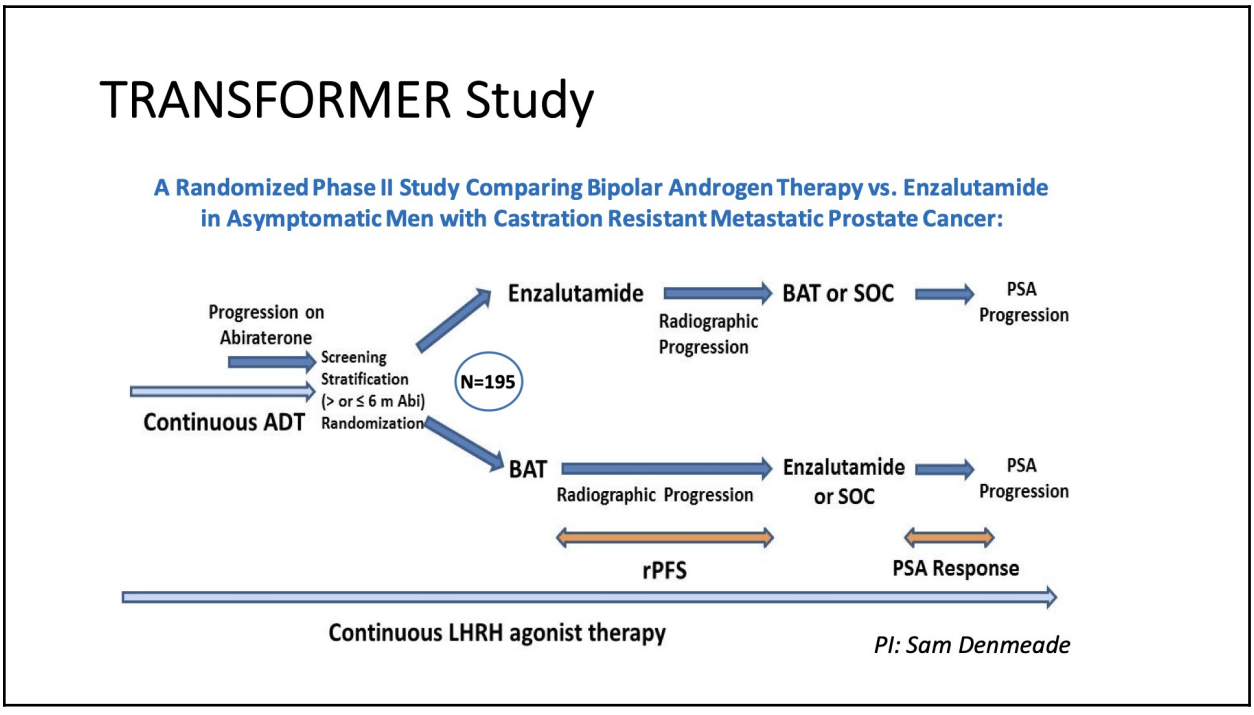


Here's a caveat from my own clinic. This is a real patient. This has been de-identified of course. I want to caution everyone about the possibility of what we call “a bone scan flare". You might have heard about bone scan flare in the context of other treatments. This treatment can also, in some patients, cause a bone scan flare. What does that mean? It means that in the short term, the bone scan could look worse before it begins to look better. This is an actual patient, this is his real bone scan. At time zero when he enrolled in one of our BAT studies, his PSA was 124 and it was rising. You can see after three months, all the spots in the bone scan look darker and there's even some new ones that weren't there before. However, his PSA has now dropped down to 14. So when a patient sees this type of scan, or when a physician sees this type of scan, especially if it's an oncologist who's not comfortable with or is not used to BAT, he might have abandoned the treatment here, which is obviously the wrong thing to do. And the hint you know in this case was the fact that his PSA dropped, and then by six months and 12 months, those lesions are actually beginning to disappear. And the PSA is continuing to decline. The challenge is, at three months here, this bone scan could look this way if the patient was progressing as well. So it's very hard to distinguish unless you have a lot of clinical experience, the true progressors. In this case, we were aided by the PSA, which was the hint. But sometimes the PSA doesn't go down initially, as I mentioned before, it might go up. And so if

you had a patient who's PSA went up, and he had a scan like this, there would be a huge dilemma in my mind and in the patient's mind, “Am I benefiting from this or not?” And so that can sometimes be very, very tricky to resolve.

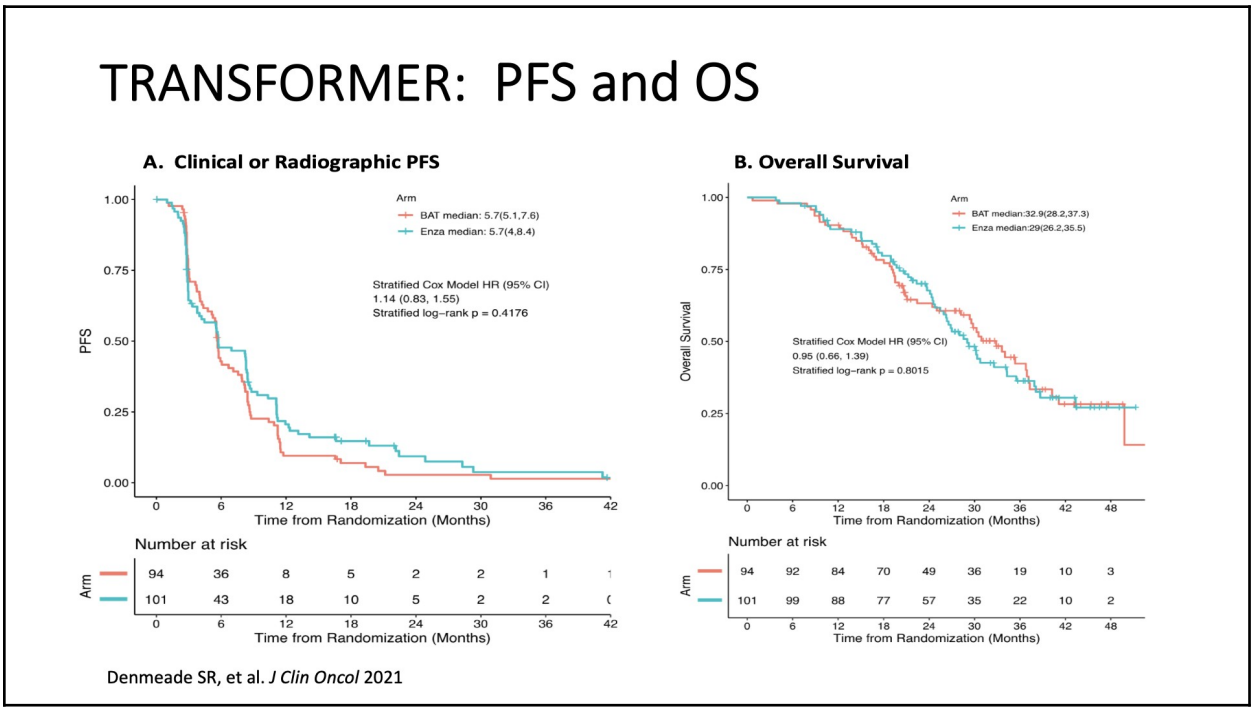
And that's where the very open conversation with the patient is really the key because you might have to look the patient in the eye and say, I, as the expert, really don't know, whether you're responding or not, are you willing to stick with it? In other words, are you willing to continue to take the risk? Or do you feel that you've had enough, and you want to abandon this and try something else. One of the things that helps when making that decision is the symptoms of the patient. If the patient is having an increase in his bone pain, probably it's not a good idea to continue. But on the other hand, if the bone scan looks like this, and the pain is not worse, or if the pain has gotten better, that can often help us to determine whether to proceed, even though the scan looks ugly, rather than to abandon. I have some other slides about the TRANSFORMER study, which was a randomized study where we compared that against Enzalutamide. I could go through those or I could stop there and take questions. What do people prefer?

Brian McCloskey 17:06
I'd like to see it.



Dr. Emmanuel Antonarakis 17:18
Okay, I'll just go to that quickly. One of the things that the FDA kept asking us is to do a randomized trial because they said, okay, the single arm studies are good, and they look promising. But how do you know that you're doing something that's better than the existing agents that are out there? We decided to do a randomized study in patients that had previously

received standard ADT, as well as Abiraterone, so these were all patients that also received Abiraterone. And then we randomized about 200 patients under 95. Receiving Enzalutamide or bipolar androgen therapy. And when we designed a study, we were so ambitious, and we were so pumped that this was going to be better than enzalutamide. So we said we're going to go for the home run, we're going to design a trial that looks for superiority against enzalutamide. And at the time, we honestly believed that we would achieve that. And ultimately, what happened was that we did not show superiority.

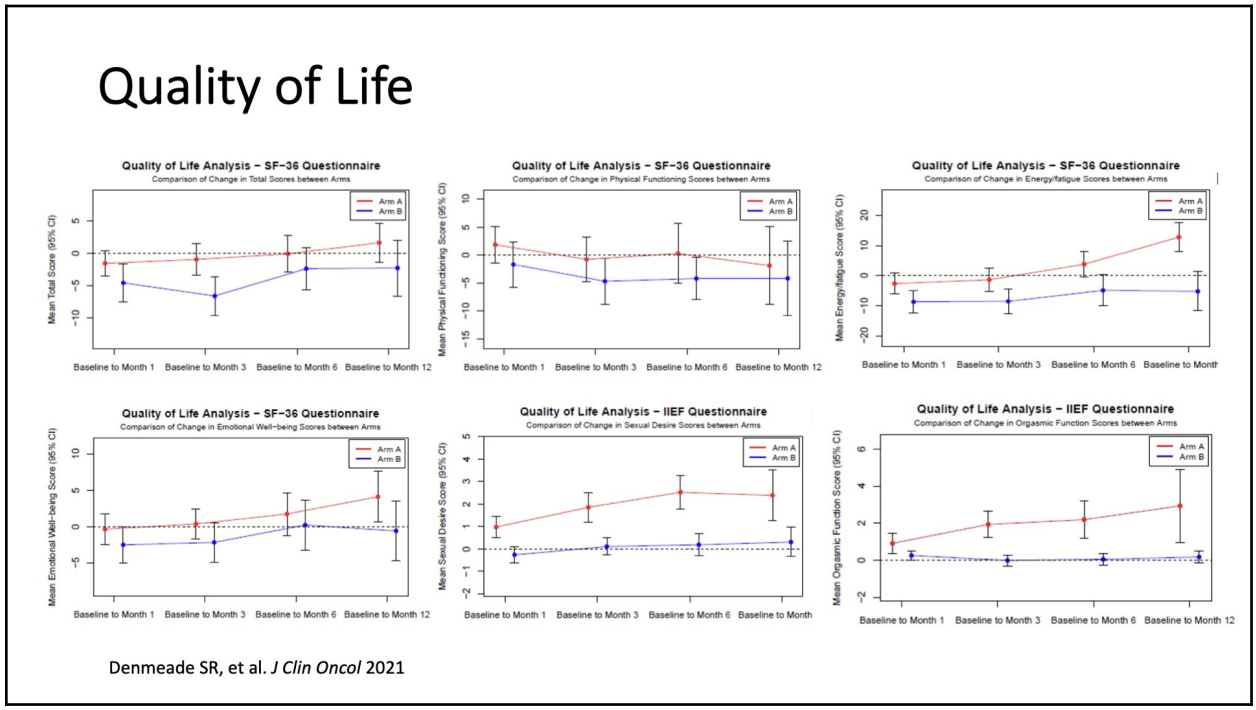


So the blue curve here shows enzalutamide, or maybe it looks green to you. And the red curve is BAT. This is the progression free survival. How long does it take until the cancer gets worse? And then this is the overall survival, also not showing a statistical difference. So when we presented this to the FDA, they said, “This is not enough for us to approve that as an FDA approved medication for prostate cancer, because even though you showed equivalence to enzalutamide, you did not show superiority.” Our pushback was, “Shouldn't equivalence be good enough? Because the quality of life in these patients is way better than the quality of life on enzalutamide.” And they said, “Thanks, but no thanks, because you designed this as a superiority study, and you did not show superiority.” So if we had to go back, we would have designed this as an equivalence study. But of course, hindsight is 20/20. One of the things that was the most striking about this study was that we were eventually re-sensitizing patients in the future to other hormone therapies. So what this shows here is that in the clinical trial itself, the chance of responding to BAT was 28%. If you use the 50% decline as your metric versus 25% with Enzalutamide, so numerically a greater chance of having a PSA response with BAT. It's not breathtaking. But the breathtaking part, and I'll skip these slides for a second. The breathtaking part was this: in patients who got BAT, and then down the line in the future, got subsequently treated with enzalutamide, about 78% responded. Whereas if they got enzalutamide, without

ever having previously received BAT, as shown on the previous slide, the response was about 25%. So what this suggests is that by giving BAT prior to enzalutamide, you're tripling the chance of enzalutamide working down the line.

Russ Hollyer 20:53
Is that being followed up with the STEP UP trial? Are you looking at the sequential treatment to prove efficacy and get it ingrained in the standard of care? Are you looking at the sequential opportunities instead of just one or the other?

Dr. Emmanuel Antonarakis 21:08
We are, and I have a slide about that. But yes, this was the data that motivated us to design the STEP UP study, which I'll show at the end.



The quality of life piece is important. What these six graphs here show are different ways of measuring the patient's quality of life, the red ones are the patients receiving BAT, and the blue ones are the patients receiving Enzalutamide, and this is the total quality of life score, which was better, but if you look at the individual components, the one on the top middle is the physical functioning. The physical functioning of patients receiving that was better than as a randomized, the one on the top right is the energy and fatigue scale. And this was better with the BAT, the one on the bottom left is emotional well being, the one in the bottom middle is sexual desire, and the one on the bottom right is orgasmic function. So, basically, across the board, whether we looked at overall quality of life, whether we honed in on energy, whether we honed in on sexual desire, whether we honed in on orgasms, in each of these six categories, the BAT therapy outperformed Enzalutamide. And in the case of sexual and orgasmic function, outperformed it by a longshot. So, these patients, not only are they having cancer control, which

is of course the goal. But more importantly, they're doing that while at the same time having improvements in their quality of life.

BAT: Effect of HRR and/or *TP53* mutations

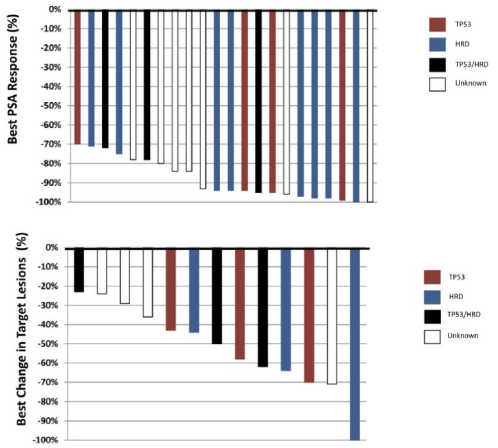
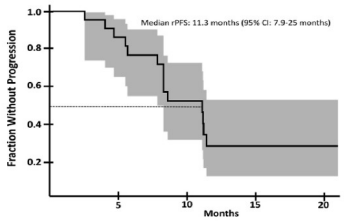


Table 2 List of observed mutated genes in extreme responder cohort.

Mutated Gene	N (%)
BRCA2	5 (33.3%)
TP53	4 (26.6%)
TP53, BRCA2	2 (13.3%)
TP53, BARD1	1 (6.7%)
BRCA2, ATM	1 (6.7%)
ARID1A	1 (6.7%)
ATM, RB1	1 (6.7%)



Markowski MC …. Antonarakis ES. *Clin Genitourin Cancer* 2021

BAT: Effect of HRR mutations (e.g. *BRCA2*)

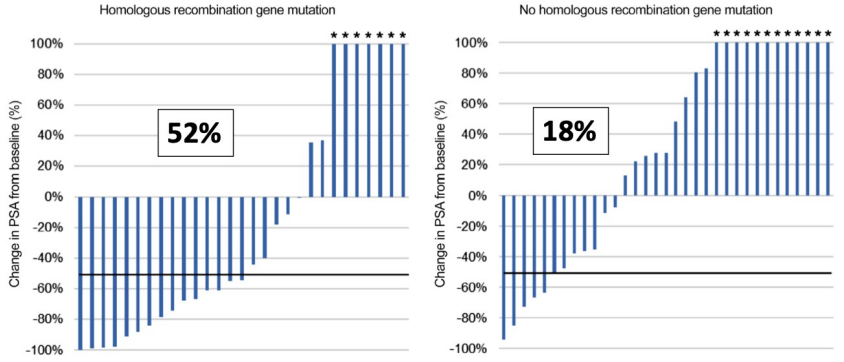


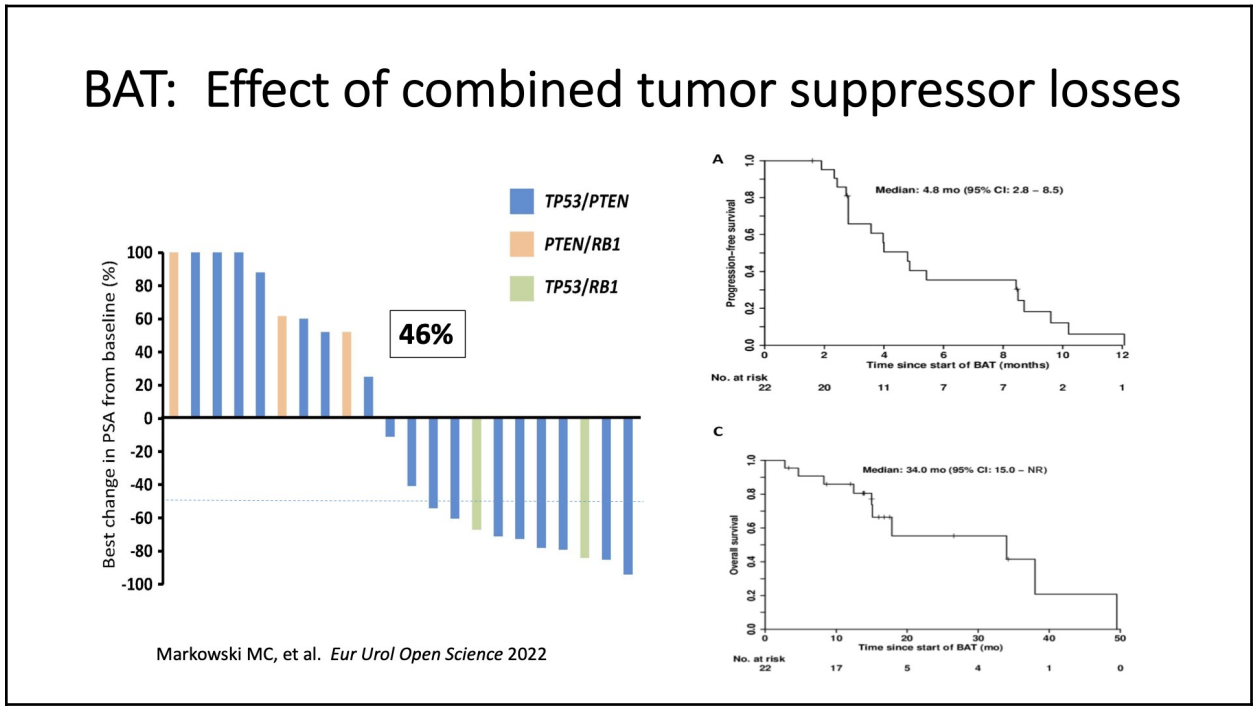
Figure 6. Clinical response to supraphysiological T treatment is associated with mutations in homologous recombination DNA repair genes. PSA waterfall plot for patients receiving BAT as part of 2 ongoing phase II trials. Data are presented for patients with and without pathogenic germline or somatic mutations in HR DNA repair pathway genes (i.e., HRD). PSA declines of greater than or equal to 50% (PSA_{50} response) were more frequent in patients with HRD compared with those without HRD (PSA_{50} response: 15/29 [52%] vs. 6/33 [18%]; χ^2 $P = 0.005$). *Percent change in PSA truncated at 100%.

Chatterjee, Schweizer, et al. *J Clin Invest* 2019

I want to talk about a little bit of a technical slide here. One of the things that we noticed was early on was that patients that had cancers that had either homologous recombination repair mutations like BRCA2, for patients that have TP53 mutations, which was known for a long time to be a bad prognostic factor, those patients appeared to paradoxically have better responses to

“Bipolar Androgen Therapy for Prostate Cancer" (Emmanuel Antonarakis) [#56]

BAT. So we made this observation that has been replicated by others that, paradoxically, again, there's a lot of paradoxes with that, paradoxically, if your cancer has a BRCA2 mutation or similar mutations to that, or if it has a TP53 mutation, your chance of responding to that. It's not 100%, but it's probably markedly increased. And our colleagues and other institutions, for example, in this study, showed the same thing. So if you look at the waterfall plot on the left, it shows a 52% chance of responding to BAT if you have a homologous recombination mutation like BRCA2, versus if you don't, the chance of responding is only 18%. Again, not a perfect biomarker, but it enriches our responses. And then the other thing that was paradoxical was, there are these genes that are called tumor suppressors.



And the tumor suppressor genes are TP53, PTEN, and RB1. And the worst of the worst cancers, unfortunately, are the ones that have mutations in two or more of these three genes. So in other words, the TP53 plus PTEN mutation or the TP53 plus RB1 mutation. What we showed with BAT is that these patients that have the double tumor suppressor losses, which are the worst of the worst, so to speak, were also the ones that have the best response to BAT. So a lot of the genetic markers that often predict inferior prognosis, by the same token, predict superior response to BAT, which again is a paradox.

Russ Hollyer 25:09
So that would seem like it might possibly lead to FDA approval. Also, if you can show vast superiority among a subgroup of men versus existing therapies, wouldn't that be possible?

Dr. Emmanuel Antonarakis 25:23

It would be, and, of course, that would have to have a control. You would have to have the three mutations and compare against either chemotherapy or lutetium, or something else that would be acceptable to patients.

Russ Hollyer 25:37
Is that being planned now?

Dr. Emmanuel Antonarakis 25:42
It's not being planned at the moment. You know, what we're trying to do is to try to use the data from the TRANSFORMER study to see whether that hypothesis is true.

Brian McCloskey 26:08
Are there other markers such as AR copy number gain? Have you looked at RNA seq expressions that helped to identify patients that respond better than others, or even proteomics, because some of the patients here actually have the full gamut of DNA, RNA and proteomic analyses?

Dr. Emmanuel Antonarakis 26:41
That's a good question. Yes, and that gets a bit complicated, which is why I chose not to show that the higher the addiction to the androgen receptor, the greater the chance of this cancer responding. There is one exception. And the exception is patients with predominant ARV7 are not responding. So what you need, the perfect storm, would be a very high AR, either amplified AR, mutated AR, but not ARV7 splice variants. And that can be analyzed in two different ways, as you pointed out, Brian, one is it can be analyzed just by doing a DNA-based next generation sequencing to look for AR mutation or amplification. But the second, which is actually much more elegant, but not widely available to many men, maybe outside of this call is RNA based, transcriptome analysis, in which there are signatures of androgen receptor response, there are 20 gene signatures and 30 gene and 15 depending on how complex you want to get. The proteomic stuff I have to say is uncharted territory. Proteomics is such a novel field. I have not seen any publications yet, including from our group, linking any proteomic marker with response to BAT, but my prediction would be that if you had a proteomic marker of antigen receptor activity, or if you had a proteomic marker of perhaps BRCA2 or other homologous recombination deficiency, then you would, in theory be able to predict response. We have published our RNA predictive signature in the Journal of Clinical Investigation. The first author was Dr. Laura Sena. And the signature is in that paper, and the data from that paper is actually has been deposited in this publicly available. So perhaps after this call, I can send it to Brad, and then you can share it with you because somebody on the chat asked about the signature. Rick asked about cypionate versus propionate. The vast vast majority of our studies have been with testosterone cypionate; there is no reason to think that propionate would not work. The dose might be slightly different. But where we have used testosterone cypionate 400 milligram intramuscular injection once every four weeks, other people are using that once every six weeks. The time interval is probably not that critical. But it probably shouldn't be more often than once every four weeks.

Russ Hollyer 29:55
The dose will be different. You're getting quite a bit more of a peak with propionate. Along those lines, do you think that a castrate level of going down about 150 nanograms is optimal? Or do you think that we should possibly go lower like 20 nanograms per deciliter, or shoot for lower? What would your theoretical thoughts be? (It hasn't been trialed of course.)

Dr. Emmanuel Antonarakis 30:24
Russ brings up a point that every reviewer mentions when we submit our papers or our grants, and that is, you picked four weeks in your first study, that you stuck with four weeks. And they're absolutely right. The four week time point was empirically chosen. And it may not be the optimal biological time point. And one reason that it may not be the optimal biological time point is that very few men drop down to testosterone less than 50 or even less than 100 after four weeks. But many men do drop down to less than 100, at least after six weeks. So we have been rethinking the optimal interval. And it's possible that the optimal interval may, in fact, be six weeks. The challenge with doing a study with six weeks is when you have a track record of 10 prior studies, with every four weeks, and the ethics committee looks at that they say, “Okay, why are you switching now to six weeks, all of a sudden? You've been doing four weeks for your last parameter definitions.”

Russ Hollyer 31:33
Yeah, they make data really messy and hard to use.

Dr. Emmanuel Antonarakis 31:40
But my belief is that six weeks might actually be more ideal than four weeks, it also makes the visits less frequent to the doctor.

Mike Yancey 31:55
In your first slide with the LOVE studies, I noticed that it showed BAT wit etoposide. And I just wondered if there's any commentary on that. And my question is, on the type of person who puts out very little PSA, since we're experienced with low PSA producers.

Dr. Emmanuel Antonarakis 32:20
Yeah, two questions there. The first was about etoposide, when we designed it in our first study. Our best hypothesis at the time was how this worked was we thought that it caused double stranded DNA breaks in the cancer cell. Etoposide is a drug that prevents the repair of those DNA breaks through an enzyme called topoisomerase2. So it seemed like the perfect rationale. What we found out actually was etoposide has quite a few side effects that patients didn't like. And unfortunately, in that first study of 16 patients, we had one patient who died of a neutropenic infection that we thought was caused by the etoposide. So after that happened, we got very, very scared and worried about etoposide. And even in the 15 patients who didn't die, they did not like the way they felt. There was hair loss with the etoposide, there was nausea. So we pretty quickly abandoned that.

Your second question was about the low PSA producers. And probably, this may not be the first choice of therapy for a low PSA producing castration resistant prostate cancer, and the reason for that goes back to something we've talked about before, which is that we think that high androgen receptor level is probably necessary for this to work or at least high androgen receptor level increases the odds of this being successful. PSA is an output of AR activity. So, if your PSA is low, it probably means that your prostate cancer is not as androgen receptor addicted or dependent as many others. So, it may not be the ideal scenario for a PSA low patient. Have we ever done a PSA low patient? Yes. Have I ever seen a very striking or long term response? With a PSA? You know, when it's less than five, let's say to begin with, probably not.

Russ Hollyer 34:27
Along those lines, my PSA goes up as far as 1.49 drops down to 0.15 after one day castrate. So talking to my MO I mean, obviously that can't be cancer regression and massive growth. It seems that it is not only androgen receptor dependent but androgen dependent too. So is it over expressed by testosterone and DHT in your opinion?

Dr. Emmanuel Antonarakis 35:12
Actually, we've seen the opposite. And because what we've seen is because you're giving exogenous testosterone, then the body thinks that the natural level is very, very high. So it decreases the endogenous production, at least. That's what we believe.

Russ Hollyer 35:31
The endogenous production of testosterone, but what about PSA, though, would PSA possibly be increased, overexpressed?

Dr. Emmanuel Antonarakis 35:41
In our study that I mentioned with the RNA signature, one of the transcripts that we measured was PSA, which is the KLK3 transcript. And we saw that in the patients who had a clinical response, the KLK3 transcript over the course of 12 weeks, in tumor biopsies went down.

Russ Hollyer 36:06
Okay, over time, though. But if you look at it during the highs and the lows, are you looking at it continuously? An example is that my PSA has dropped over time from 0.17 two years ago to about 0.02 today. So it's dropped over time, but it has these massive peaks, and then quick reductions.

Dr. Emmanuel Antonarakis 36:32
That is a very important lesson that should be, you know, publicized and published restlessness. For the moment, one of the things that we're typically doing is we are generally discouraging patients that have high Gleason scores and low PSAs from doing that. And if your experience can be published together with your oncologist, I think that might dispel the myth that even I myself might be propagating, which is that the low PSA producers maybe shouldn't be getting BAT, but you are a clear exception to that.

Russ Hollyer 37:08
I'd be more than happy to converse with you. And about a month ago, my MO talked to me about being a case study because I'm a poster boy, if you will, for HSPC BAT.

Robert Gurmankin 37:31
Two questions.
You've talked about BRCA. Will that also be effective, as far as responding, if it's in somatic versus germline?

Dr. Emmanuel Antonarakis 37:46
Yes, that's what we have found. But by the way, if you had a BRCA mutation, and it's somatic, the first thing I would do is probably not BAT. I would probably do the PARP inhibitor first. But putting that aside, yes, we have not seen better responses in the germline BRCAs versus the somatic BRCAs. We've seen about 60% or 70% responses in both types,

Russ Hollyer 38:12
Potentially do both BAT and olaparib - COMBAT?

Dr. Emmanuel Antonarakis 38:23
No, it was a study by Michael Schweitzer at the University of Washington, in Seattle. And he's published that, he didn't show synergy when doing that. And it was very surprising. So I'm not quite sure why there wasn't synergy. One explanation is that it's possible that when you have a BRCA mutation, olaparib by itself works well enough, and that adding BAT doesn't further improve the response.

Russ Hollyer 38:52
Oh, okay.

Robert Gurmankin 38:55
So that might cover my second question, and that is, “have you seen any, or done anybody with MMR mutations on BAT?

Dr. Emmanuel Antonarakis 39:05
We've treated less than five patients. I think the mismatch repair patients are 3 to 4% of the total.

Robert Gurmankin 39:17
I'm one of those 3 or 4%. So, okay, that was my question.

Dr. Emmanuel Antonarakis 39:23
We have not of course, we have seen responses with BRCA as you're aware. I have not seen any anecdotes of responses with mismatch repair.

Amit Gattani 39:42

You showed a very good graph of the ideal time for BAT to be inserted in the treatment roadmap. Many of us are fairly advanced and have been through a lot more treatments. Are there any fence posts that you have determined where BAT is not a good idea? Like if you have gone through this, this, and this, it doesn’t point to BAT.

Dr. Emmanuel Antonarakis 40:20
That's a challenge because a lot of the patients that think about BAT are the ones that have received 5-8 prior systemic therapies. So it's so good to say you should do it early. But the truth is, in many patients, they've already had all these treatments. There's no absolute warning sign, as long as you have an informed conversation with your physician, and you don't go into it with your eyes closed, if you go into it with your eyes open. Oncology is always about discussion between risks and benefits. And sometimes the risks might be very, very high. But sometimes, the risks of untreated cancer, if you have no options, are even higher. So some of the general recommendations against that are, if you have symptomatic bone pain already, we generally don't recommend it because the bone pain can become worse. If you have a bone metastasis in an area that is threatening a fracture, for example, a fracture of the femur, or a fracture of the spine. We also don't recommend that to those patients because if we get it wrong, and we accelerate the cancer, we can cause a spinal cord compression, or a femur fracture. And then the third one is if you have a very bulky prostate gland, or pelvic lymph node that is threatening to obstruct your urinary tract, or your kidneys. We don't recommend that because you could develop renal obstruction or kidney failure even. So those are sort of the three greatest contraindications, although none of them are absolute contraindications.

Amit Gattani 42:16
That's very helpful. Just one quick follow up. Some of us have a CDK12 mutation, I'm pretty high CDK12 mutation, any data on that with that?

Dr. Emmanuel Antonarakis 42:31
You know, CDK12 mutations are tricky. A few years ago, we were all enthused that they might perhaps respond to PD-1 inhibitors. There were some anecdotes, and there was a high profile publications that suggested that we have not really seen such dramatic responses, at least not in my hands, with PD-1 inhibitors with the CDK12 mutations. I have seen favorable responses with BAT with CDK12 mutations, not as dramatic as with the BRCA2 mutations. So as you may know, CDK12 is thought to perhaps be one of the homologous recombination genes. There's some controversy about that. So the long story short is we have seen responses with CDK12. It's probably less than the BRCA2 to patients in the P53 patients. But unfortunately, as many of you know, CDK12 is a risk factor for poor prognosis overall. Those patients typically develop castration resistance faster; they also can have chemo resistance faster.

Brian McCloskey 43:58
Along the lines of what Amit was talking about on screening for heterogeneity. We may have some cancer that expresses a lot of AR, for example, but then we may have others that could be hormone sensitive and could take off. I think some of us know a patient where that

happened. Is there any way to screen for that right now to look for the risk of heterogeneity where we could kill some but really fuel to file for fuel and fire for others?

Dr. Emmanuel Antonarakis 44:36
There isn't a good clinical way to do that. You know, there's a lot of emphasis about heterogeneity because we've known for a long time that different patients are heterogeneous from each other. We've also known that a single patient his tumor can be heterogeneous depending on which metastatic site you biopsy for example, and if course if you do a liquid biopsy a circulating tumor DNA biopsy, you will get to see all the heterogeneity, even though you may not know exactly where it's coming from. The best ways currently, which is still not a perfect way of knowing what to target first, is to look at the so called mutant allele fraction, also called variant allele fraction, VHF or MAF. And that'll tell you that percentage of the cancer cells that have a particular mutation. Not all of the commercial NGS platforms report the VHF or the MAF. But if you have, let's say, a different mutation from a biopsy, and one of them is that you know, 45%, mutation allele frequency, and one is a 2%, you should target the one that's at 45%. First, it makes sense, right? Because that's the one that's most abundant. And then you go down the list. So that's kind of the way that I do it. It's not perfect. And it only gives you a snapshot at one particular moment in time. And that may change. Because there might be one particular therapy that wipes out a particular clone with the P53 mutation, let's say but leaves the BRCA2 alone or the opposite.

Brian McCloskey 46:23
Great. And then related to that. What, what type of diagnostics would you recommend? And what's the frequency? So I'm assuming like, a liquid biopsy, while you're getting bat? Is that standard practice for you? Does it provide any insight that helps determine direction?

Dr. Emmanuel Antonarakis 46:48
it's not necessarily standard practice. For me, I like to get a liquid biopsy, you know, before we start, do I check it every three months? Or every six months? Probably not? Do I check it every month? No, you know, there are problems with getting that reimbursed. A lot of insurance companies unfortunately, will not allow you to get monthly and pay for it. Or even every three months. I think it would be reasonable to check a liquid biopsy, you know, before you start the BAT and then at the point that you decide to stop it.

Dr. Emmanuel Antonarakis 47:26
In other words, to help you decide the next therapy, but as a measure of response to BAT I think you have other clues, which are probably easier to interpret and more established and cheaper. So of course, you know, PSA is one, you know, clinical symptoms is one. And the scans are the other. So I embraced liquid biopsy. But there's another person who's going to be giving a talk to you guys. In a few months. Oliver Sartor. If you asked Oliver, there he gets liquid biopsies in his patients, I think monthly. I don't know how he was paying for that data. I don't know whether he's gonna keep doing that now that he's at the Mayo Clinic, but I don't use it as much as he does.

Robert Ellis 48:27

I just got the results of my Tempus xF+ yesterday, and there are some markers here that I don't know the significance of. Other people may have them so I just wonder if you could comment. I do have the BRCA2 mutation at 50.3% variant allele fraction. I have CHEK2 at 0.3%, I have AR p.T878A at 1.6% and APC at 1%. Median variant allele fraction at 1.3%. Is any of that significant or predictive of how I might respond? I’m scheduled to start BAT next week.

Dr. Emmanuel Antonarakis 49:14
The disclaimer is that I'm not providing direct medical advice to any one given patient, but I'm just going to make some broad comments. If one's variant allele frequency of BRCA2 is 52%, that means that it's a germline variant. That individual should have a germline test to confirm that. The reason that you know that is because if you have a germline mutation, and the pivot the bracket to Gene obviously has two copies, you get one copy from each parent mutation is only going to be one of the two copies. So if you have the mutation in every single cell in your body, and you inherited it from one parent, that VAF is going to be between 48% and 52%. So that type of patient should immediately undergo germline testing, then that's got implications for his offspring, of course, male and female offspring. That's number one.

And then number two, is that in that particular patient, obviously, we're not talking about you, AR of 1.6%, becomes much, much, much less relevant, because that mutation has a tiny fraction of all the cells that haven't any; 1.6% is absolutely fine. And the CHK2 is 0.3%, if I remember correctly, from what you said, that's even smaller. So the moment a patient like that, we're not talking about you, ignore everything else, and all the rags in the brackets to basket for the moment. That patient should also get germline genetic testing right away. That would have a high chance of working.

Robert Ellis 51:01
Okay, great. I'm curious, too. So it lists some variants of unknown significance. There's a KMT2C at 47.5%. Is any of that significant?I'm just noticing there's a couple here that are above 40%. And I think you said something earlier…

Dr. Emmanuel Antonarakis 51:25
The most likely explanation for that is again, germline inherited variants that you were born with that dominate. Okay, but yes, whenever you see VAF above the 45% level, you should be thinking that these are probably inherited, and in the case of those particular genes, there are no genetic syndromes that are caused by a germline KMT2C mutation, for example. So the assumption is that those are just benign variants.

Robert Ellis 51:52
Two quick questions. One is: Is there any preference in terms of ADT? I'm on Orgovyx now. I used to be on Lupron. Does it matter what ADT I'm on during BAT? Is one preferable to another? No, no preference? Okay. And then how about shutting down T? You know, more completely when I'm cycling at low testosterone days? You said my T could be at 100 or something? Is there anything I could do to shut it down more?

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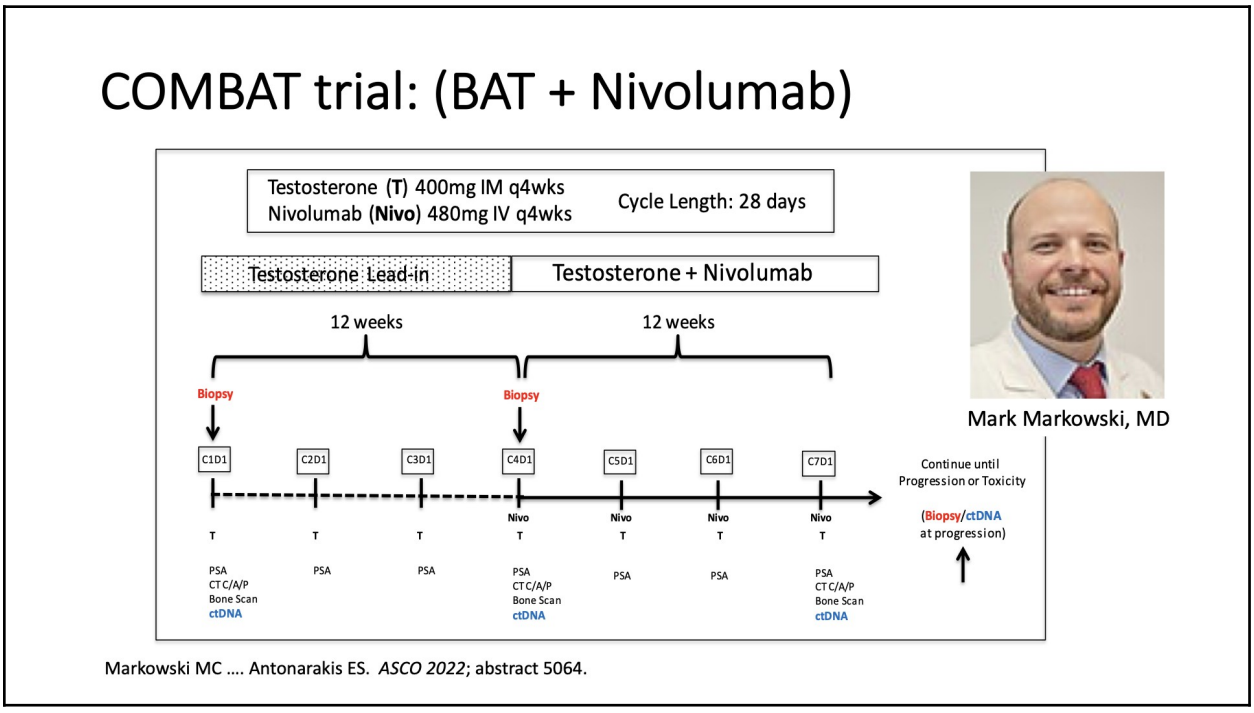
Dr. Emmanuel Antonarakis 52:27
I mean, you could add enzalutamide, but I don't typically recommend that. Orgovyx is going to be as good as any of the LHRH agonists. It's actually going to be a little bit better because it's an antagonist. So I would not do anything further.

Russ Hollyer 52:43
Could he possibly add darolutamide with a very short half life? Could he possibly do that for like a week or something? I know, it has not been trialed. It's in trials right now that I think interleave but so the possibility,

Dr. Emmanuel Antonarakis 52:55
I wouldn't do that. Darolutamide is effective at prolonging survival when given as a monotherapy. Why combine something you know at this time when you can save it for later? I don't typically do that.

Ken Anderson 53:27
I don't want to make it personal. I have been through four cycles in four months. I had a number of adverse events, mostly related to lower body muscular pain. Could you touch on what someone might anticipate when starting bipolar enemy therapy, as far as the adverse events?



Dr. Emmanuel Antonarakis 54:00
One of the things that happens when you give bipolar androgen therapy – and it was one of the reasons that we decided to combine it with nivolumab in another study called COMBAT – that I've been talking about, is that we do think it increases the anti tumor immune response, but it also increases inflammation. And a lot of patients who take that, about 15%, I would say of all of

them have a very significant muscular and joint inflammatory response, which manifests as muscle pains or joint pains. And it's interesting because it's not bone pain, per se. It's not pain in the bone metastasis, but it's pain in the muscles and the joints. And that can be treated relatively effectively, not perfectly, but relatively effectively with anti inflammatory drugs, like ibuprofen or Motrin, Aleve. If you don't have a contraindication for those drugs, but you have to use relatively high doses. So for example, if you're using ibuprofen, you have to use 600 to 800 milligrams. And that's what we've often recommended to people that get the muscle pains or the or the joint pains. The other thing that can happen is you can get fluid retention, especially in the feet and ankles. The high dose testosterone makes the blood vessels in the feet and legs more leaky. So that fluid can leak into the tissues and cause edema. And that is something that is difficult to reverse if it occurs, but we will usually warn people about as well.

Ken Anderson 55:38
I can honestly say I do take high dose ibuprofen and it does work. It's something you have to do repeatedly throughout the day, but it does work.

The next question was, okay, I finished the four cycles. I'm on darolutamide. In fact, my PSA has continuously gone up, though. It hasn't gone down. I'm making it personal, unfortunately. And right now, my PSA is like 3000. My ALK Phos (alkaline phosphatase, used to diagnose liver damage or bone disorders), though, is like 58. So I'm like, “Okay, I've had a scan at the three month mark, and I showed a little more clip from, like the November mark, but with low ALK Phos and a super high PSA.” So what's the overexpression element with PSA? No, PSA is a terrible marker in general for prostate cancer, but it's the one we all use.

Dr. Emmanuel Antonarakis 56:42
Your cancer might have a combination of high AR but also maybe some AR splice variants in there. So AR splice variants like ARV7 are also going to cause high PSA expression and may not respond to that. Whereas, you know, amplified AR might respond or you might have, speaking of heterogeneity, a bit of both. And the short answer is without a clear worsening of the scans, you may want to stick with it in consultation with the bad that is in consultation with your oncologist.

Ken Anderson 57:20
Yeah, I'm doing that with Paul at MD Anderson. So I think I'm good. I just was more interested in adverse events.

“Bipolar Androgen Therapy for Prostate Cancer" (Emmanuel Antonarakis) [#56]

BAT Clinical Pearls

- BAT should only be given to patients with castrate-resistant (NOT hormone-sensitive) prostate cancer.
- BAT should NOT be given to prostate cancer patients with cancer-related bone pain.
- BAT should not be given to patients with urinary obstruction due to enlarged prostate or prostate cancer.
- BAT should be given together with ongoing ADT or surgical castration.
- BAT may be continued despite PSA elevation, if there is clinical benefit and stable scans showing no progression.
- BAT should not be combined with Zytiga, Xtandi, Erleada, or Nubeqa (or with taxane chemotherapy).
- BAT may render CRPC patients sensitive to Zytiga or Xtandi after ADT or after prior progression on these drugs

Denmeade SR, et al. *The Prostate* 2022; 82: 753-762.