“How Proteomics and RNA Sequencing Are Guiding My Treatment” (Mike Yancey) [#51]

Mike Yancey and Brad Power
April 5, 2023

“The oncologist said that if it wasn't for this non-PSMA producing lesion or cancer on my spine, I could actually be a “poster boy” for successful Pluvicto treatment.” – Mike Yancey

“The open question is ‘why is my hip, pelvis, and femur cancer growing?’” – Mike Yancey

“How long is my body going to be capable of withstanding multiple treatments?” – Mike Yancey

Meeting Summary

When cancer treatments work for only a few months, patients, their caregivers, and their medical teams need to continuously identify new treatment options. One of the ways to find new treatments is to pursue cutting edge tests which can identify unique characteristics of a patient’s cancer that can be matched with new options.

Consider the case of Mike Yancey. Mike has an aggressive cancer and runs quickly through treatments. He responds to new treatments, but for an unusually short time, on average a few months. In his search for more treatments, Mike learned about proteomics, a cutting edge analysis of cancer expression, and a proteomics service provider (mProbe), from his participation in the Prostate Cancer Lab. He decided to pursue their test. The proteomic analysis of his tumor identified a new mutation which could be targeted by a chemotherapy which was normally used for lung cancer. It gave him another treatment option.

As Mike’s case shows, patients who are actively engaged in their care are more likely to get better outcomes. They need specific, personalized information about testing and treatment options, which can come from a community of fellow patients and hackathons. They need to find clinicians with whom they can partner to aggressively consider cutting edge tests and treatments.

In this session, Mike reviewed his recent experience and looked for feedback on what he should do next. This is a sequel to a previous session (meeting #27 in September 2022), where Mike described his medical history to that point. (You can see the notes from that session here.) Mike was diagnosed with prostate cancer in July 2021. In May 2022 tests revealed that he had mutations in three key “tumor suppressor genes” (PTEN loss, and RB1 and TP53 mutations). If someone has mutations in any two of these three genes, then the cancer is designated as “Aggressive Variant Prostate Cancer”. In his case, he had mutations in all three, which only 1% of prostate cancer patients have. Patients with this profile do not respond as well to many of the standard prostate cancer drugs. Usually the cancer is held back for up to two years following a treatment, but in his case it was only four months. He also learned that his cancer does not express much prostate specific antigen (PSA).

An Update on Mike’s Story: Successes Quickly Followed by Failures

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1. **Pluvicto Success**: In August of 2022 Mike started taking a relatively new drug for the treatment of prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer: “Pluvicto” (Lutetium vipivotide tetraxetan), which latches onto prostate-specific membrane antigen (PSMA) and delivers targeted radiation. Things initially seemed to be going quite well. Then around October he had a lesion show up on his spine, and they determined that it was not producing PSMA, so the Pluvicto was not working on that particular lesion. Mike had radiation on that lesion, hoping that would take care of it. The oncologist said that if it wasn't for this non-PSMA-producing cancer on his spine, he would be a “poster boy” for a successful Pluvicto treatment.
2. **Pluvicto Failure**: In late December Mike ended up in the hospital due to severe pain in his right hip and right shoulder. The pain was so severe that he was unable to stand unassisted. He had additional aggressive spine lesions growing on his spine, and they were pressing on his spinal cord. Once again, the cancer in his spine was not producing PSMA. Therefore, Pluvicto was not going to touch it and was not going to be of any benefit. He needed to stop Pluvicto since adding another drug would have high toxicity. He stopped Pluvicto after his fourth treatment in mid-December.
3. **Next Treatment Identification**: An October biopsy of Mike’s spine lesion had been sent to a proteomics diagnostic firm (mProbe), and they reported no androgen receptor expression, which meant that his cancer would not respond to drugs that attack androgen. Mike needed to find other treatment options quickly. mProbe further reported that Mike had high levels of a protein (“TOP2A”), for which there was a chemotherapy drug (Etoposide), a chemotherapy usually used for lung cancer, as opposed to the typical chemotherapy combination for prostate cancer (Cabazitaxel and Carboplatin). His oncologist also wanted to include Carboplatin, so he started taking Etoposide and Carboplatin in January 2023.
4. **A Qualified Success**: The chemotherapy worked quite well, except for the cancer on his hip, pelvis, and femur (the PSMA-producing cancer). The lesions on his spine were not growing, and at this point, no additional lesions had been identified. But the question remained: why was the cancer on his hip, pelvis, and femur growing?
5. **Flare up**: In January Mike’s hip pain increased, so in January and February he had radiation on it, which relieved the pain during those two months, allowing him to be mobile.
6. **More Trouble**: On March 5 Mike’s right hip and pelvis pain began again, and on March 6 scans showed renewed cancer growth from the PSMA-expressing cancer in his pelvis, hip, and femur, and he had his first PSA increase in four months. During January and February his PSA had continued to decrease to a low point of 0.14, but on March 6 his PSA jumped to 0.37, and his testosterone rose from non-detectable in January to 28 in February and 128 in March. The PSA increase was probably due to an experiment Mike had run to see what would happen if he stopped androgen deprivation therapy, which he had done in December, with the agreement of his oncologist. Normally an oncologist would not stop ADT just to see what happens, but Mike wanted to see if his testosterone increased whether it would cause his cancer to begin growing. It took three months for the testosterone to begin to rise. So it was pretty obvious that a lot of the reason for the

renewed pain around March 5 was due to the cancer growing because it now had lots of testosterone to feed off of.

7. **Treatment Restart**: Mike restarted ADT on March 6, using the oral drug Orgovyx. Mike had to stop taking a heartburn drug which interacts with Orgovyx since it slowed the Orgovyx effect.

What’s up next for Mike?

Mike has many treatment options in his portfolio. He received an RNA seq interpretation from SHEPHERD Bio that identified ten potential drugs plus one multi-drug combination, which he needs to review with his oncologist. He also has a 3-drug combination option that he got from CureMatch. Mike has plans for a bone biopsy on his right hip on April 18 that will enable more testing, including another proteomics analysis by mProbe, another RNA sequencing analysis by Tempus, RNA seq interpretation by SHEPHERD Bio, and possibly sequencing and analysis by Foundation Medicine.

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Meeting Notes

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Discussion Outline

1. Intro and welcome.- Brian McCloskey
2. Sharing with you my journey - Mike Yancey (1:16)
3. Blood counts (7:24)
4. Why did I have right hip pain? (12:28)
5. Did testosterone increase cause the cancer to begin growing? (16:52)
6. Protonix vs. Orgovix. (22:07)
7. SHEPHERD Bio’s report. (32:29)
8. Why not radiate the spine lesion? (36:44)
9. Treatment options for prostate cancer. (43:22)
10. What would a CureMatch report look like with the new data? (47:34)
11. What is the value of Xtiva? (54:52)
12. Mike’s AR expression (58:04)

SUMMARY KEYWORDS

lesions, bone, treatment, cancer, question, point, drug, psa, oncologist, spine, biopsy, scans, march, chemo, analysis, testosterone, mike, report, ar, liquid biopsy

SPEAKERS

Mike Yancey (63%), Gitte Pedersen (9%), Brian McCloskey (8%), Rick Stanton (6%), Ally Perlina (4%), Amit Gattani (3%), Russ Holyer (3%), Kevin Fordney (1%)

Brian McCloskey

Today, we have a very special guest, one of our own, Mike Yancey. And as you all are familiar, Mike has really been trailblazing the use of diagnostics in his treatment. And he's going to share with us his story of where he's been, and how he's doing and where he's going. We are super excited to have Mike present today and also want to thank him for doing this. We also want to thank him for just being a leader amongst us. He's done some things that many of us haven't had a chance to do. I'm honored to have him be part of the group and present his story.

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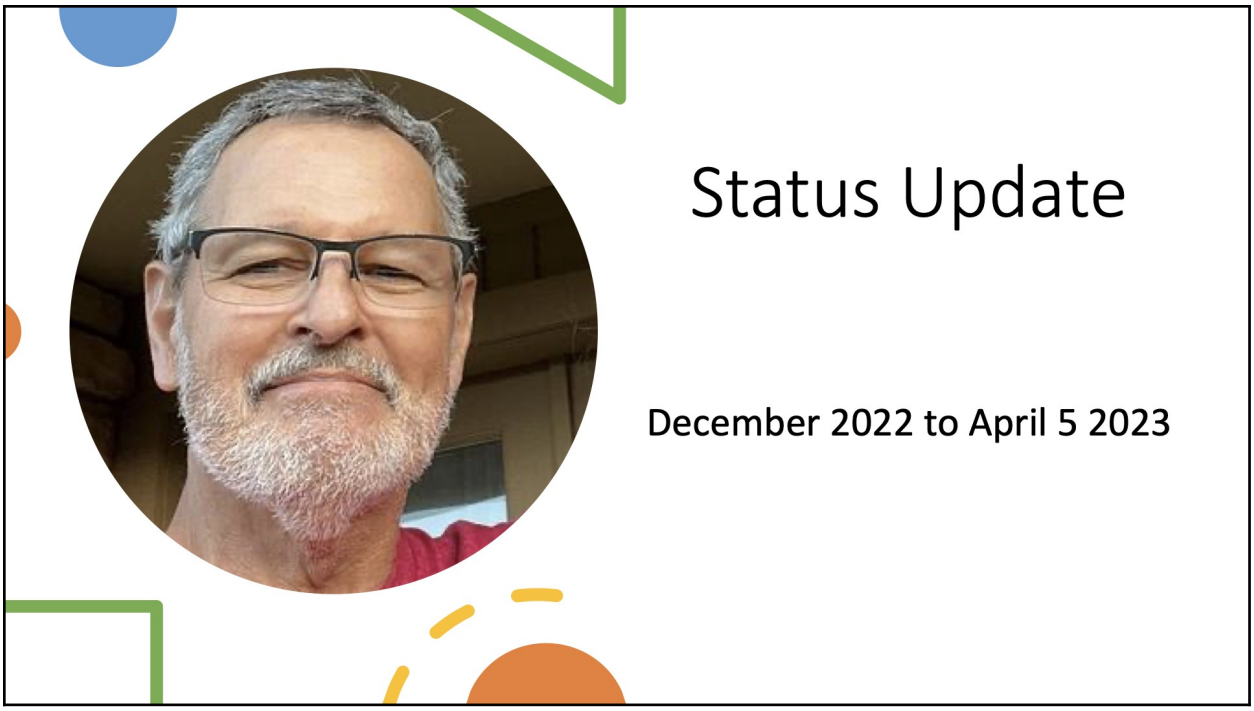

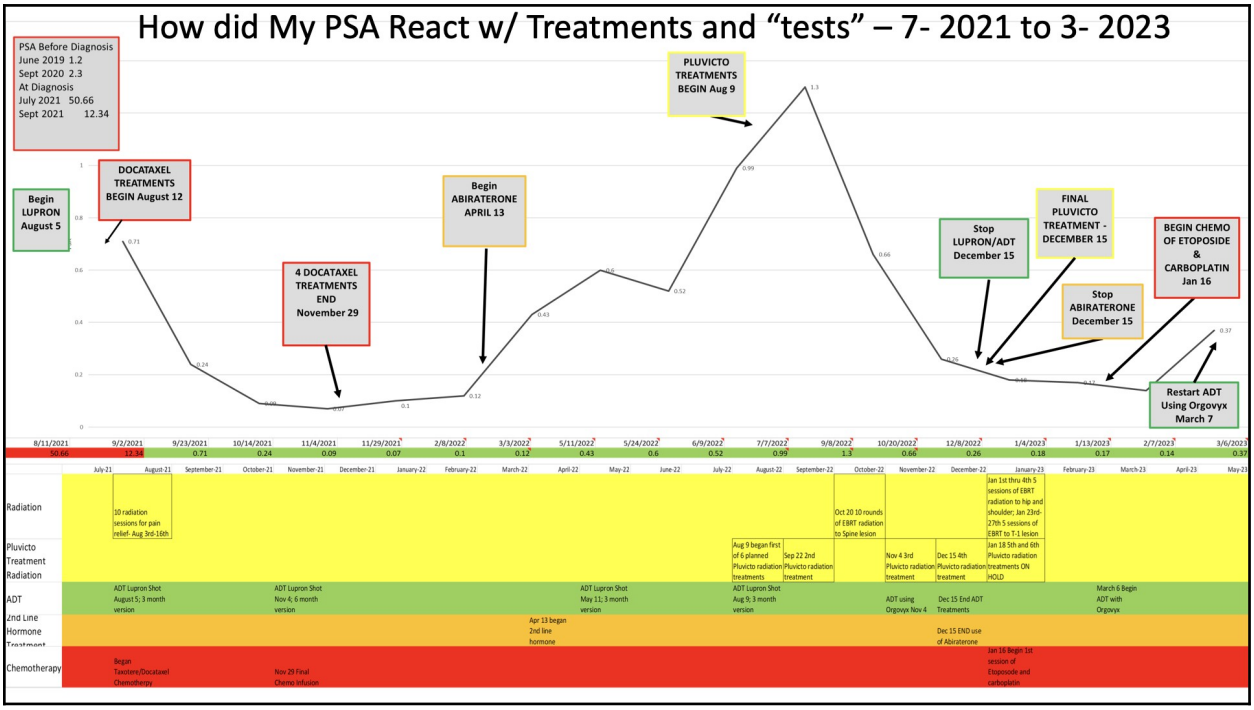

Mike Yancey
1:16
I'm going to share my journey. I'm going to be focused on bringing you up to date from the December timeframe to the present and provide a little bit of background to hopefully make it provide some continuity as we go forward here. Working with my oncologist,

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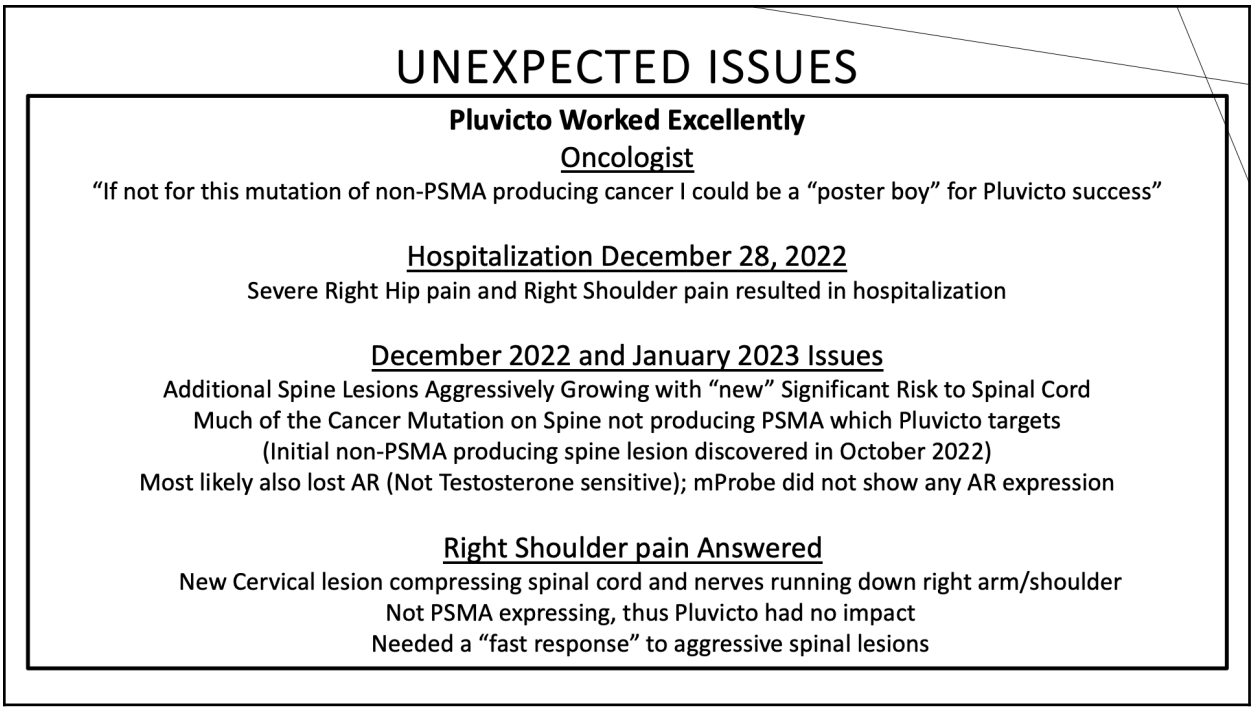

I had been on Pluvicto starting back in August of last year, and things seemed to be going quite well. And then, in the October timeframe, I had a lesion show up on my spine and we determined that it was not producing PSMA, so due to that, the Pluvicto was not working on that particular lesion. We did radiation on that lesion and hopefully took care of that. The oncologist said that if it wasn't for this non-PSMA producing lesion or cancer on my spine, I could actually be a “poster boy” for successful Pluvicto treatment.

So that was setting the base, as to how well Pluvicto was working for me at that point in time. But unfortunately, as our cancers often do, mutations occur and cause problems. We had radiated that one lesion on my spine back in the October timeframe, and thought we had things pretty much taken care of. But then on December 28, I ended up in the hospital due to severe pain in my right hip and my right shoulder and in fact the pain was so severe that I was unable to stand unassisted. Long story short, what we found is that I had additional aggressive spine lesions growing on my spine, and they were also pressing on my spinal cord. Once again, that particular cancer in my spine, for whatever reason, was not producing PSMA. Therefore, Pluvicto was not going to touch it and was not going to be of any benefit to me. Also, it was very likely that this cancer on my spine had lost all AR (androgen receptor) function. In other words, it was not testosterone sensitive. Additionally, the October biopsy I had done of the spine lesion was sent to mProbe that did some analysis and the report did not show any AR expression. It was very interesting, when Brian did share his mProbe report with me that of course his report did show AR expression. So in my case, I've lost that particular function in this set of cancer lesions.

Russ Holyer
7:00

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Could I ask a quick question about the AR? Does it show AR activity as digital (i.e. on or off) or does it show an analog measurement of AR activity?

Mike Yancey
7:18
No. I didn't show any AR at all, whereas in Brian’s report, he did show AR activity.

Russ Holyer
7:24
So it is digital. Okay.

Mike Yancey
7:30
That's my understanding. Yes.

At that point in time late last year and earlier this year, we were able to find the reason for the pain in my right shoulder: I had new lesions that were growing on my spinal cord and they happened to be pressing on the spinal cord as well as the nerves that exited and ran down my shoulder and my right arm creating some significant pain in that area. Therefore, we also found that not only did I have this new lesion pressing on my spinal cord and causing the shoulder pain, we also discovered additional lesions.

Therefore, we had to start looking at options for treatment in a “fast response” mode. I finished my fourth and last Pluvicto treatment on December 15, 2022. At this point in time, in early January, because of the number of lesions that were growing on my spine, it wasn't just one or two anymore. but it was multiples, we were not going to be able to continue Pluvicto. This was due mainly to the fact that I couldn't necessarily take two treatments simultaneously. So, therefore, we chose to stop Pluvicto and move to chemo because using them both would cause mylo-suppression issues that would be difficult to overcome. And in fact, I will confess that my blood counts have been very low from the time of finishing up the fourth Pluvicto and starting the chemo. We have had some challenges with my blood counts where we have had to give me some shots to promote my bone marrow to better produce.

Amit Gattani
9:17
Mike, when you started Pluvicto what were your blood counts? And when you finished Pluvicto do you remember how much of an impact Pluvicto had on your bone marrow?

Mike Yancey
9:29
I have that information, but I don't have it off the top of my head, but I keep all my labs. As I started Pluvicto, if I remember correctly, just in random numbers, my blood counts overall weren't too bad. What Pluvicto has really impacted me negatively is my platelets have dropped

down quite a bit and my white blood cell counts have dropped as have the red blood blood cell counts.

In fact, before I did my second chemo, my white blood cell count was actually below the minimum level where they normally will give you chemo. My number at the time was 1.9 and I had to be at 2. So basically we went ahead and went forward with chemo the next day. Since that point in time my blood counts have recovered a little bit before the third chemo. However, because they were still overall low, that's when I started the shots to try to get my bone marrow to help my blood counts get back up. And that was after my third chemo.

Amit Gattani
10:32
And what shots were you taking?

Mike Yancey
10:36
Neulasta.

Amit Gattani
10:50
Okay. The reason I'm asking is I'm in a similar, though maybe tougher situation, with my blood counts because of Pluvicto and then chemo. So just kind of trying to correlate some information.

Mike Yancey
11:05
Yeah, and since I just took my first Neulasta after my chemo last month I will be very interested in my upcoming labs this coming Monday to see how much benefit that shot has actually had on those counts. So stay tuned.

Kevin Fordney
11:28
How about your hemoglobin numbers?

Mike Yancey
11:32
It had dropped down quite a bit too. I don't remember off the top of my head what those numbers were but I'm more than glad to get with anybody and share all the numbers, so you can see how they've gone over time. The strange thing for me, I thought was unusual, is that even though my blood counts were not good, I felt great. In fact, during this time, I was walking three miles every other day, I was swimming 45 minutes per day non stop, and I was lifting weights. So I was surprised how some of those numbers were, especially with respect to the white blood and red blood counts. So anyway, even though I felt good, unfortunately, my body wasn't responding from my perspective accordingly.

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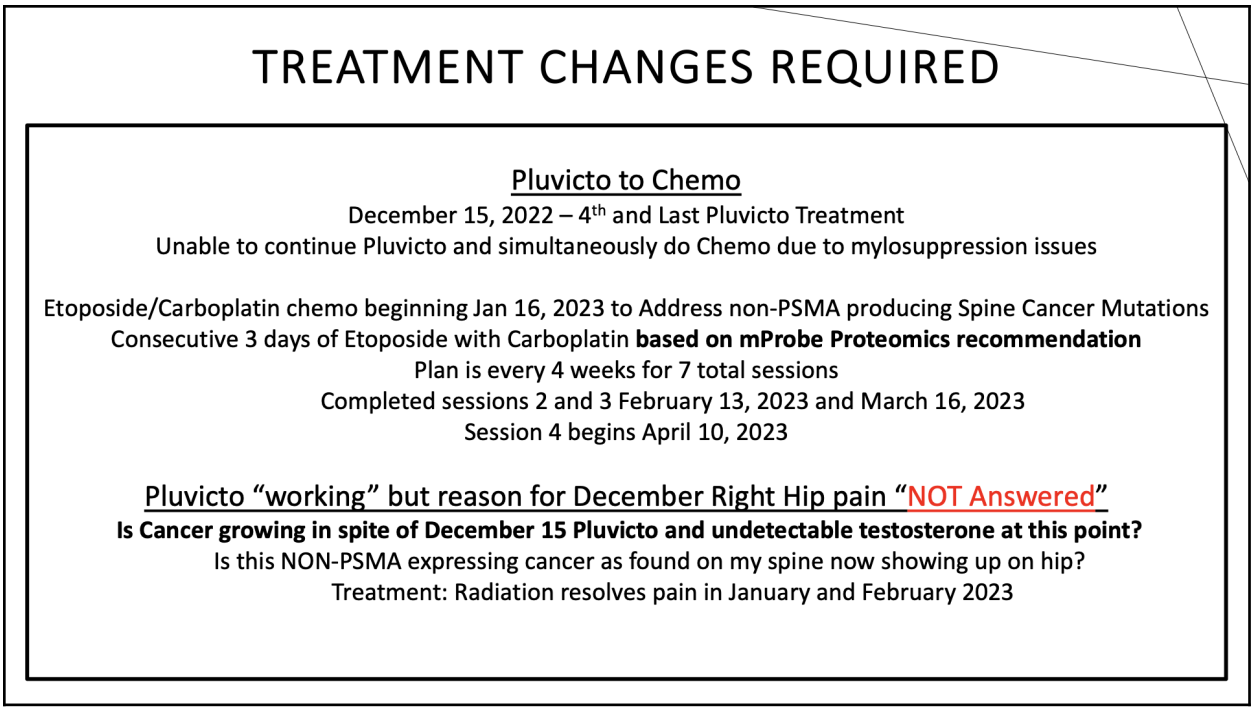

Mike Yancey
12:29
So, Pluvicto was working. But the one thing that was not answered for me is why I had the right hip pain. To differentiate that a little bit, as we know, the cancer in my hips, my femur, and my pelvis, pretty much were responding to Pluvicto and my cancer was reducing.

We know that the lesions on my spine were non-PSMA-producing. So the fact that my shoulder was being caused by a spine lesion answered that question of shoulder pain. But why did I have this pain in my right hip? We still didn't have that particular answer, and still don't to this point in time.

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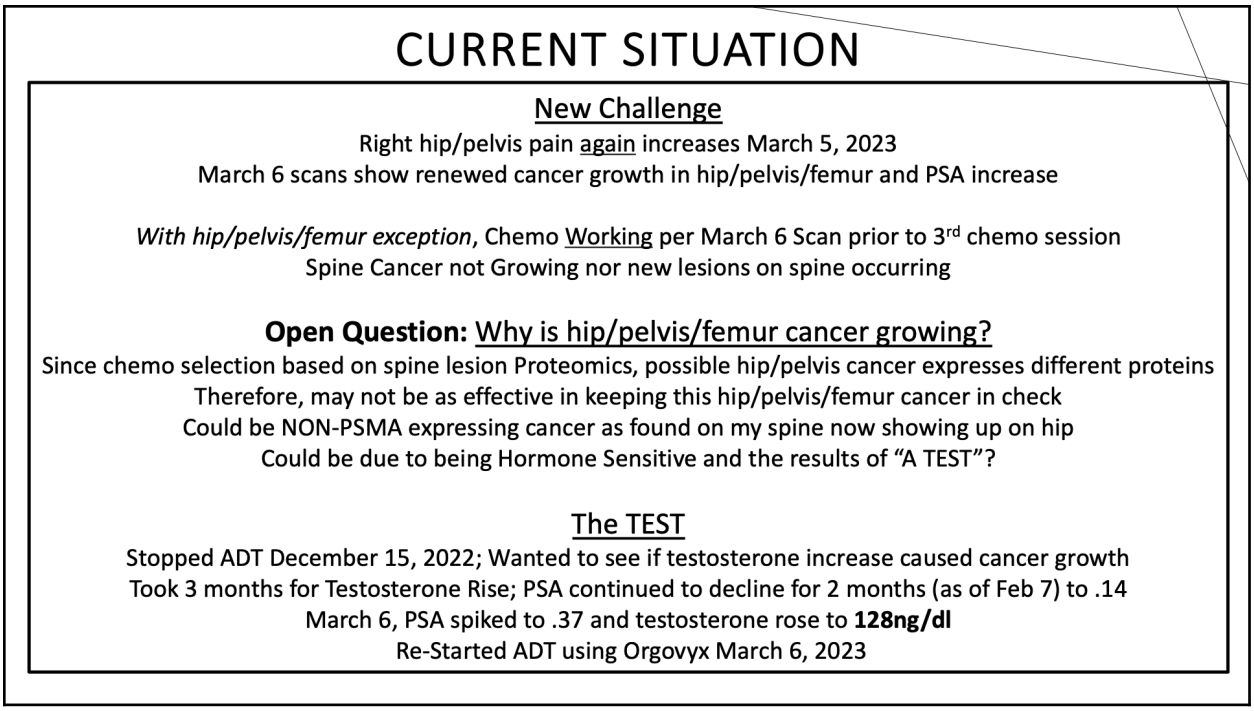


Is it possible that I now have a mixture of non-PSMA-expressing cancer like I've got on my spine now showing up on my hip? I don't know the answer yet. We're hoping to get that answer and I'll explain that in a moment. During the January/February timeframe, we went ahead and did radiation on this hip. That totally relieved the pain issue during those two months, allowing me to continue walking and things of that nature.

Pain was okay in my hip, but then on March 5, my right hip and pelvis pain began again. And on March 6, scans showed renewed cancer growth from the PSMA-expressing aspect in my pelvis, hip, and femur. Additionally, as of March 6, I had my first PSA increase. My PSA had continued to drop during December, January and February, but by March 6, it jumped up. I will explain part of the reason for that in a moment.

But overall, with the hip, pelvis, and femur exception, (the PSMA producing cancer), the chemo was working quite well. The lesions on my spine were not growing, and at this point, no additional lesions had been identified. So once again the open question is “why is my hip, pelvis, and femur cancer growing?”

Amit Gattani
15:07
What chemo agent were you given this time?

Mike Yancey
15:13
The chemo we chose was based on a biopsy I had done on one of the spine lesions. The biopsy was sent to mProbe for analysis and in their report, they found that I had high levels of a

protein called TOP2A. Based on this they recommended that we use Etoposide, as opposed to what normally would have been used which was Cabazataxel along with Carboplatin. Now I will admit that my oncologist was more than willing to utilize Etoposide but he also wanted to add to that Carboplatin. So I'm currently using Etoposide and Carboplatin.

That all seems to be working quite well. We're not quite sure of the reason for the hip issues that came up specifically in December.

As for the reason for the pain and the problems I have had in early March, it is very probably due to the cancer being hormone sensitive and a result of which I'm going to refer to as a “test”. What was that test? I like to try things to see what happens when you do things that are different from what historically has been used in the medical community.
For example, my type of cancer, or “our " type of cancer I should say, being very aggressive, normally no oncologist would stop ADT just to see what happens. But my oncologist works with me quite well. I like him, we get along great. So I stopped ADT on December 15. I wanted to see if my testosterone increased, and if in fact that would cause the cancer to begin growing. It took three months for the testosterone to even begin to rise. Like I said, during January and February my PSA continued to decrease. It got down to a low point of 0.14, but on March 6, my labs at that time showed my PSA, in one month, had spiked to 0.37 and my testosterone had risen from basically non detectable in January to 28 in February, to 128 in March. So it was pretty obvious that a lot of the reason for the renewed pain around the March 5 timeframe was due to the fact that that cancer began growing because it now had lots of testosterone to feed off of and being aggressive began growing. So basically, I restarted ADT on March 6, using the oral drug Orgovyx.

Russ Holyer
18:01
First of all, Orgovyx is a really awesome drug. I wanted to do it but my insurance company denied that. So I'm using Lupron. Second comment, so testosterone rising up, first of all it's going to be a while for recovery; so three months. So that's pretty typical. Testosterone itself is going to overexpress PSA, and it's going to cause some inflammatory factors, which can result in pain, especially if you have any kind of bone Mets.

Did you happen to get a scan at that time? If you got a scan, then did things change dramatically? That is why they do scans as part of the BAT therapy. We know that PSA is overexpressed, like 5x, 7x, or 10x, whatever with increasing testosterone, and we know that inflammation can cause bone mets to cause pain. So that's not a good indicator either, but the scans are a better indicator of what's happening. So did you happen to get a scan?

Mike Yancey
19:13
Yeah, I actually had scans done in March, and it showed SUV increases for a lot of my cancer in my hips, my pelvis, etc. So indeed, not only had the PSA risen but the PSMA/PET Gallium 68 scans that I had done clearly showed that I did have increased SUV. The SUVs had been

decreasing pretty much since back in August when I began Pluvicto, but by March 6, the cancer was growing again and of course SUVs were increasing, whereas previously it had been declining.

Brian McCloskey
19:53
Just to back up a little bit. You did this combination of Etoposide plus Carboplatin. You said that your doctor was pretty adamant about adding Carboplatin. Can you explain why he was so adamant about it? And was there anything in the mProbe report that would indicate that the Carboplatin would work or that it wouldn't work? Because, you know, the mProbe report does advise on particular chemos that don't work.

Mike Yancey
20:22
There was really no reference in the mProbe report specific to Carboplatin. Now let me give a little bit of background as to the most likely reason for interest in Carboplatin. One of the things in my biopsy in October is that the pathologist said that if he did not know that it was prostate cancer that he was looking at, he couldn't have defined it. And that is oftentimes true when your cancer begins to mutate and migrate towards Neuroendocrine cells. I'm not there yet at this point in time. I did not have all of the biomarkers of true Neuroendocrine cancer cells.

But then a concern that I and my oncologist have had is that my particular type of aggressive cancer has a very strong tendency to move towards small-cell or Neuroendocrine cancer cells. So with Neuroendocrine, the platinum based chemos are some of the best options. When we say best option, no option is really good with Neuroendocrine, but the platinum-based chemo seems to at least have some impact.

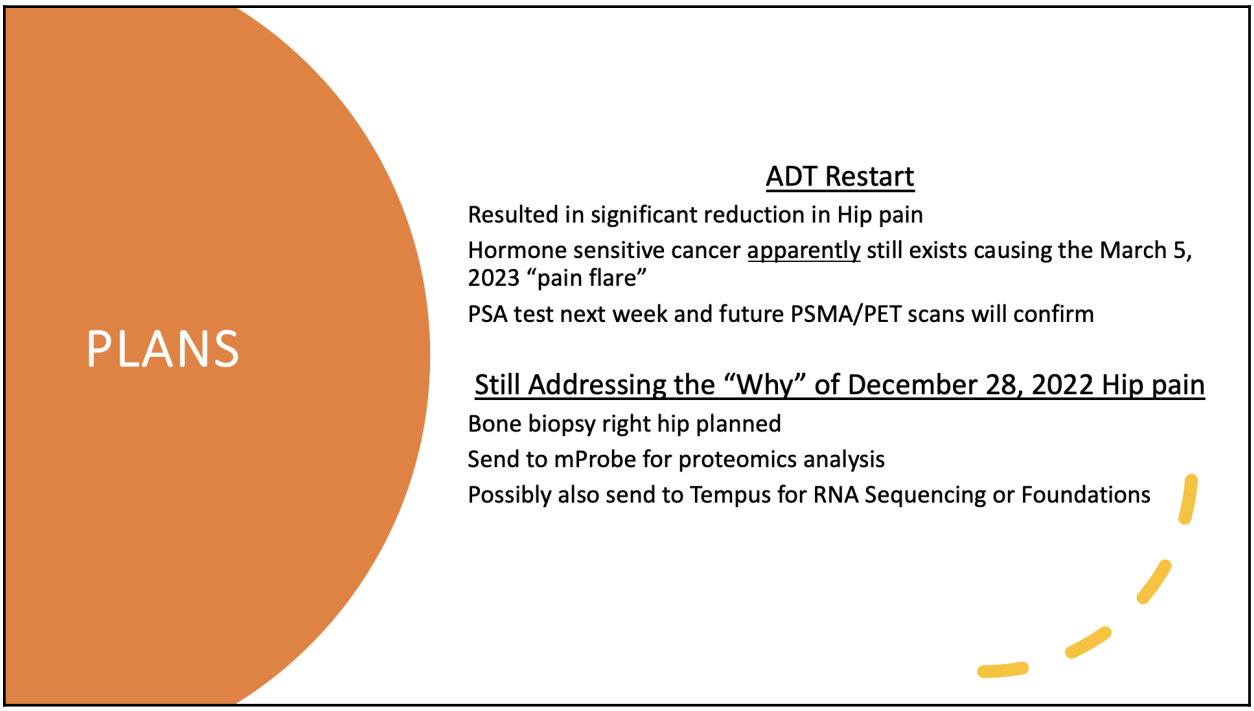
Mike Yancey
22:00
The overview slide provides a quick reference showing how my PSA has gone. Towards the end of the slide on the right side my PSA had declined to 0.14, then jumped up very quickly between February and March to 0.37. As you can see, I actually began my Pluvicto on August 9th. You can see my PSA was as high as it's been since I was diagnosed. We also know that based on the amount of cancerous lesions that I have, I don't put out a lot of PSA. So it's really a reference point. So for me, a 10th or a couple of tenths of a point movement is a lot where with other people they may see movement to the magnitude of 10, 20, or 30. So we just have to use it as a reference point. But as you can see here, I started Pluvicto and shortly after reached my peak PSA and have been dropping ever since until I stopped ADT and my PSA kicked back up in March.

So as I've already mentioned, we restarted ADT. As a background comment, prior to beginning Orgovyx, I had been on Lupron. My first attempt to try Orgovyx was in November of last year. However, I discovered an issue with some heartburn drugs I have been taking for about 5 years. I take a drug called Protonix which happens to be what they refer to as a PGP inhibitor. At that

time, the manufacturer of Orgovyx didn't highlight those types of drug conflicts; information wasn't on their website at that point in time.

Because of my identifying the issue with the PGP inhibitor, what was happening is the Orgovyx was getting into my system, but it was not being metabolized as fast as it should be. Therefore it was building up. So I was having extreme pain in my joints and muscles, as well as significant fatigue; probably the worst fatigue I've had. And so when I discovered this, we actually got with the manufacturer and made them aware of it. On another call that I'm on with other prostate cancer patients, we found a couple of other guys that also had issues with Orgovyx and in discussion found they were taking similar PGP inhibitor heartburn drugs.

So therefore, I stopped Orgovyx in November but didn't stop it completely until December 15 as I mentioned earlier. So in summary I had been using Lupron up until November and then used Orgovyx off and on until December then restarted it here in March. Of course I had to stop the particular heartburn drug that I had been using and move to a different type that does not have that same conflict.



Mike Yancey
25:27
Next week as I have already mentioned, I am looking forward to seeing what my PSA has done. We feel like Orgovyx works pretty quickly normally, so my PSA most likely will have dropped. I will also be interested in another month to see what the latest update on PSMA/PET scans show now that we seem to have some of the hip, femur, pelvis cancer under control.

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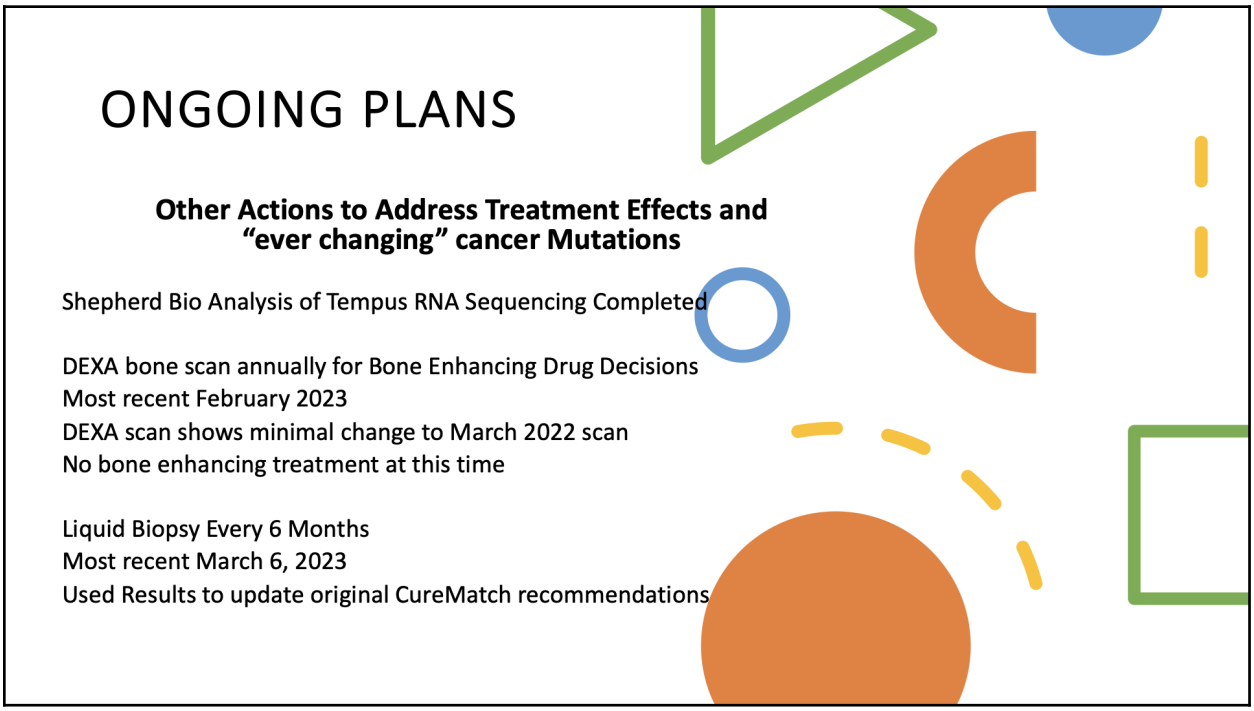
Since I've restarted ADT, and because of the chemo, we're continuing to have really good success with keeping the lesions in my spine on hold. Getting back to my original question, we're still trying to address the “why” of the December 28 hip pain because I had been off ADT just a few days at that point in time. So that really wasn't or could not have been a factor. As we're trying to understand what caused this flare in December, knowing that most likely the flare in March was due to the testosterone rise.

We've got a bone biopsy planned for April 18. I had hoped to have already had that done, so that I would have had more information for you today. We're going to also send that to mProbe for another proteomics analysis. Very interested to see how this biopsy is going to be either similar or different to the results of the biopsy that mProbe looked at back in October. I feel there will be some differences and will be very interested to see what potential treatment recommendations come out of this particular analysis. Also, much like last time, we'll probably send some of the biopsy to Tempus for RNA sequencing. I'm also going to have some discussion about also sending it to Foundation Medicine since I've had several different blood biopsies as well as my original bone biopsy from July of 2021 analyzed by this company.



27:53
Other actions that I'm taking to address treatment effects and ever changing cancer mutations, is that I also sent my Tempus RNA sequencing to SHEPHERD Bio, who we'd had a presentation from several weeks ago.
They will do a deeper dive on the information that Tempus had from my biopsy in October.
And I'll share a few more points about that here in just a moment.

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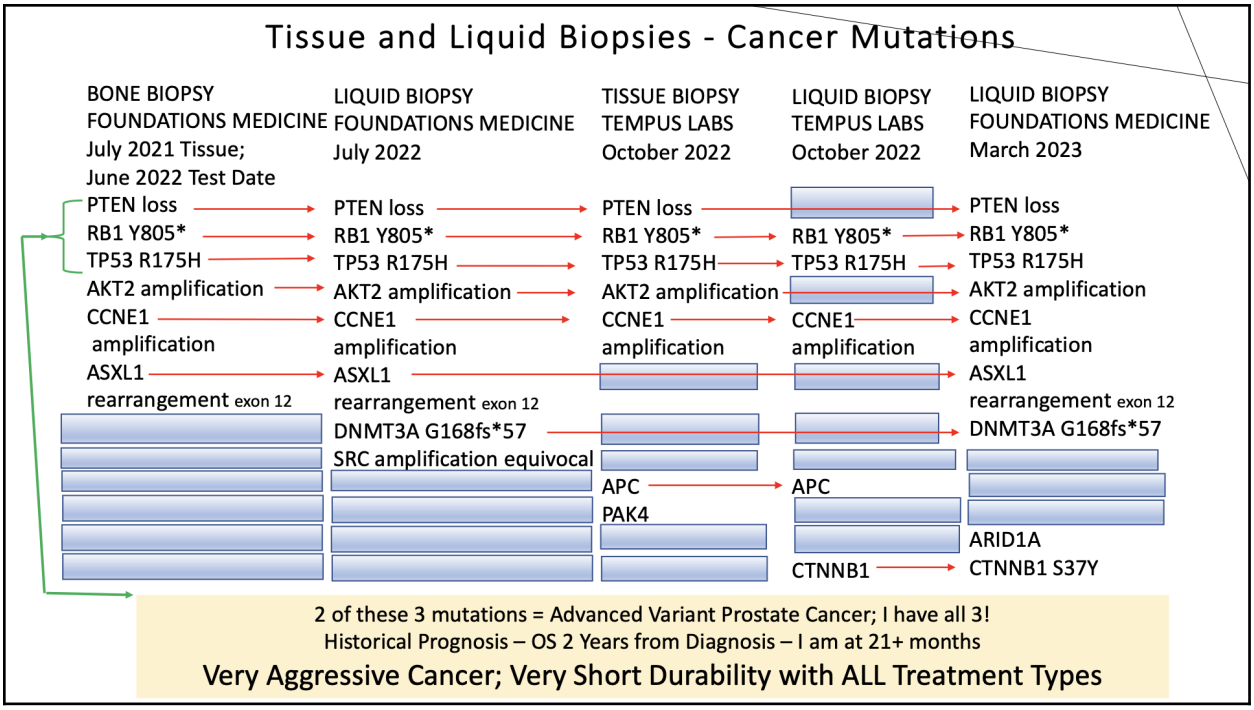
Another thing that I do annually is I have a DEXA bone scan for purposes of trying to keep track of the potential to experience significant osteoporosis in my bone due to treatments and ADT. My original bone scan was done back in 2017, which is our baseline. Since then I have had another DEXA scan a year ago which showed that things had not changed significantly from the 2017 scan. Now in February of 2023, I’ve had another scan that showed some changes but not any significant at this point in time. So my bones seem to be holding up pretty well. We're not moving forward to the utilization of any bone enhancing treatments at this point in time. Keeping it in our back pocket for use at the right time. When I do start showing some potential for Osteoporosis we can begin to use it at that point in time.

The last thing I am doing is liquid biopsies every six months. I'll show you a slide here in a moment and compare how things change over time. Also based upon this latest liquid biopsy I’ve kept CureMatch updated. They basically took the recommendations they had provided to me last year based upon my biopsies that I had available at that point in time, and they updated it with this most recent liquid biopsy. With their three drug combo, they basically retained two of the drug recommendations and just exchanged one drug out of three. And so I'm still keeping that as a potential treatment in the future.

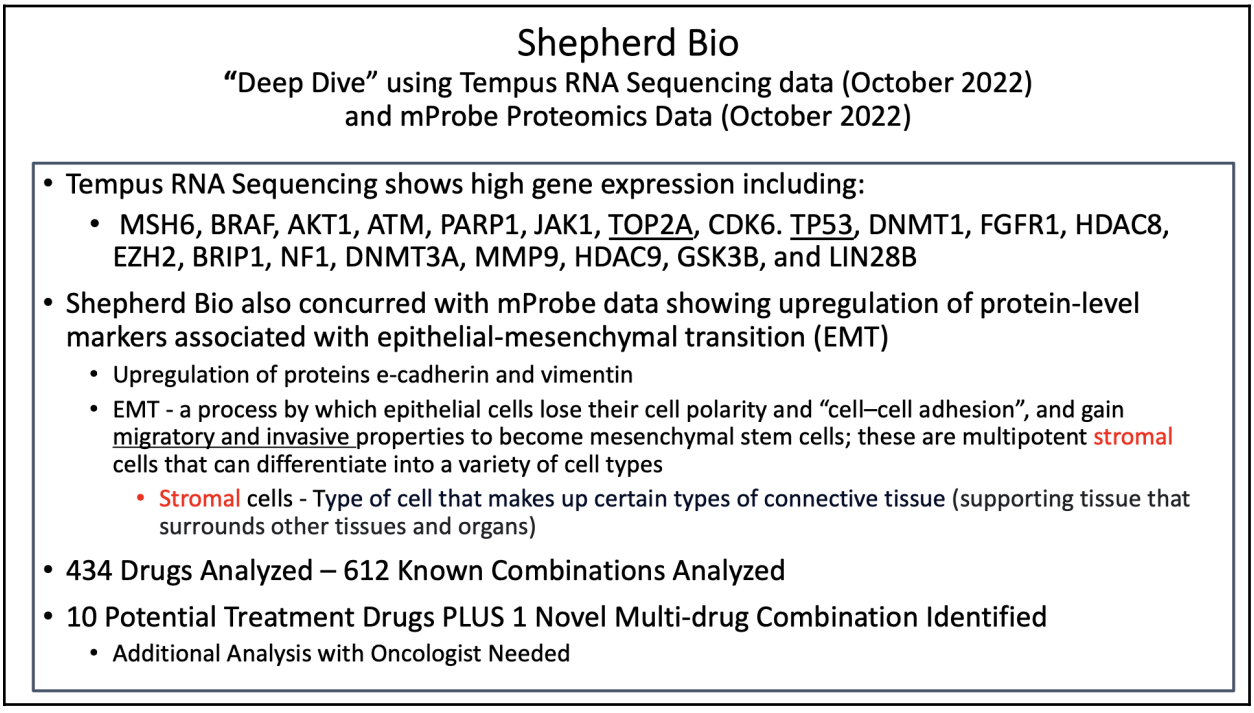


This slide I wanted to show you so that you can begin to see the results of both my liquid biopsies as well as tissue biopsies and see what's changed and what hasn't. The little blue boxes depict where things that showed up elsewhere didn't show up in that particular vendor’s analysis.

You can see my original bone biopsy from July 2021, there on the far left done by Foundation Medicine. Then you can see all of the different mutations that were identified at that point in

time. I will comment, from a clinical perspective, Aggressive Variant cancer is usually defined by having at least two of three mutations either in PTEN, RB1, or TP53. I'm the lucky guy that has all three. I have PTEN loss, mutations in RB1, as well as in TP53. So that's why I have this very aggressive cancer, as well as the other mutations. I had a liquid biopsy done in July of 2022, a year after my original tissue biopsy there in the hospital. You can see not a lot changed; had DNMT3A show up in that particular Foundation Medicine result.
Then I had Tempus. Two different analyses that show some significant differences from Foundation Medicine as you can see there by the blank sections that are listed by the blue box. Of course, then my latest Foundation Medicine liquid biopsy in March of 2023 is the most current information that I have. It has several different additional mutations. You can see towards the bottom, the AR1DA and CTNNB1

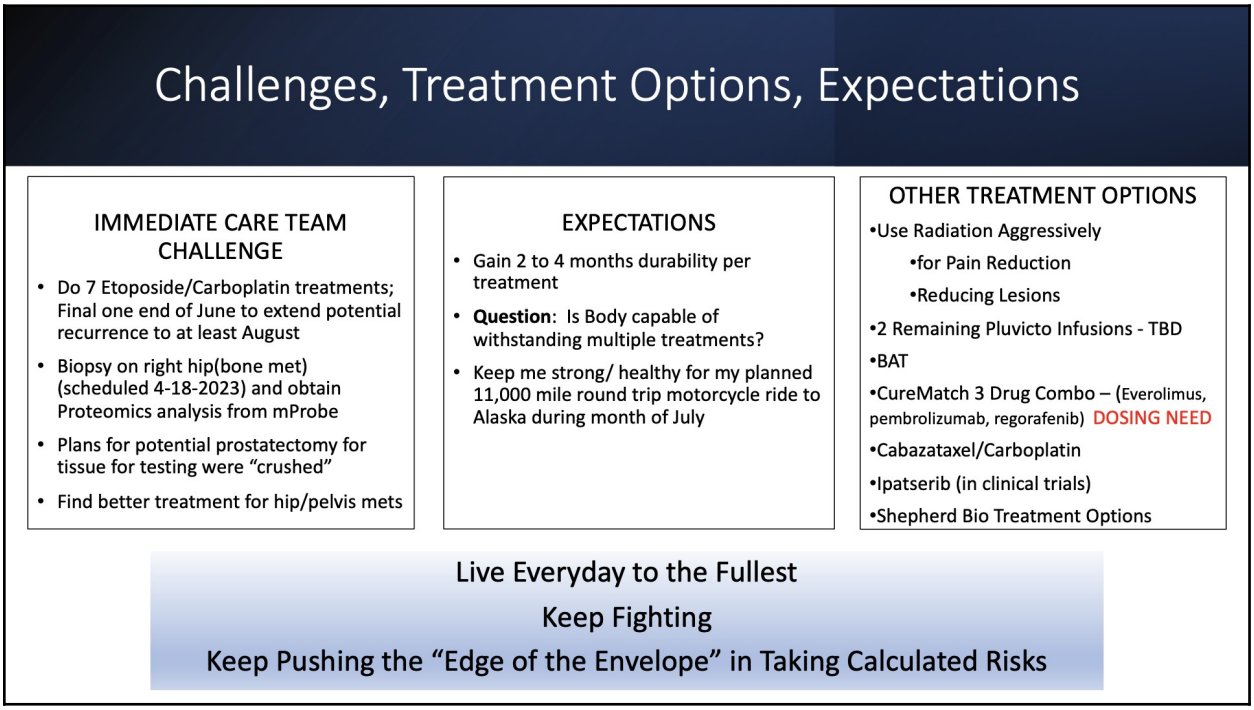
All these mutations I haven't gotten educated enough to know all the details and specifics around them. I really continue to stay really focused on the PTEN, RB1 and TP53 and things like AKT2 amplification and things of that nature.



Here's the SHEPHERD Bio information that I received. They did a deep dive on the Tempus information. I'll have to admit the Tempus report on the RNA sequencing was basic. It did not give me a lot of in depth detail that we've seen from people like Rick Stanton and Brian where they've gotten into the actual data in the background and then been able to do some analysis on it. So that's basically what I think Shepherd Bio was doing. As you see here, high gene expression on a large number of things here that are listed across the top. They also concurred with the data that mProbe provided showing significant upregulation of some protein level markers associated with, and I'll butcher this, but epithelial-mesenchymal transition or EMT. That's due to the fact that I have protein upregulation of e-cadherin and vimentin.

“How Proteomics and RNA Sequencing Are Guiding My Treatment” (Mike Yancey) [#51]

Basically we're starting to see some cell migration to stromal cells. Once again, I'm not fully educated on all this, but I think part of this, if I understand correctly, is part of the migration towards small cell/Neuroendocrine. Net result of Shepherd Bio was the identification of 10 potential treatment drugs plus one multi drug combination. And so I haven't had a chance yet to discuss this report with my oncologist. That's still on the “to do” list,



So where do we go from here?
The immediate care team challenge, of course, is if we're going to do seven of the Etoposide and Carboplatin treatments, assuming they continue to work, particularly on the non-PSMA producing lesions on my spine. The final one will be towards the end of June. Because of my history of having very short durations with any treatment, we're hoping to extend the benefit after we complete the planned sessions to at least the end of August, hopefully, longer. And of course, as I have already mentioned, I'll get the biopsy coming up on my right hip, on the 18th and we'll get the proteomics analysis from mProbe and see what it tells us.

And one thing I was planning on doing, and I've mentioned on this call before, I'm one of the few strange people that still have their prostate. My plan had been to, at some point, potentially do a prostatectomy. Not aggressively but do one nevertheless to get more tissue to potentially send to companies such as SEngine or some of these other places that require much greater amounts of tissue who will do testing. I talked with the urologist here a few weeks ago, and he kind of crushed my hopes. He said that there have been so few surgeries done on people that have done Pluvicto and still have their prostate, that he was very reluctant to ever try to do it because he did not know what we'd run into. Knowing full well that my intent was not to be curative, we wanted to minimize things such as minimal margins, having incontinence issues,

etc. He was very concerned that even being very conservative, not knowing what we might run into, that we could create those issues resulting in a bad quality of life. So he did not recommend it. So that's pretty much off my radar at this point in time as an option for getting significant tissue for analysis.

The immediate care team challenge also includes finding better treatment for hip and pelvis mets. Hopefully in another few weeks, we'll have some good information there.

What's my expectations? Once again, gain at least two to four months durability for every treatment we try. That's kind of been my average, so we'll keep pushing for that.

Amit Gattani
36:48
So with your spine lesion that you're trying to take care of with the carboplatin and etoposide, why not radiate that since it is kind of a contained lesion and you know exactly where it's at? Why not radiate it?

Mike Yancey
37:03
Well, it was. Initially it was a small number of lesions, one or two initially. We did radiate the initial one. The problem now is they were popping up so fast, that radiation was not really an option, it was going to be too much radiation on too many lesions that continued to pop up from time to time. So that's why we chose to go towards the chemo route.

Amit Gattani
37:25
Carboplatin is pretty high in mylosuppression, so I'd love to understand how your graph of cell counts is progressing. I'm on Carboplatin and after a couple of doses being given I'm basically on hold now from treatment because of my cell count; mylosuppression is too high. But I also have disease in the bone marrow. So my bone marrow capacity has gone down. But I would love to see a chart on your cell counts and stuff with each of the chemos.

Mike Yancey
38:01
I'll send that to you. And then also put it out there on Circle. So anybody else who has some interest can see my spreadsheet. It's pretty detailed, so it will all be there. Not the prettiest format, but at least the numbers are there. So you'll see those.

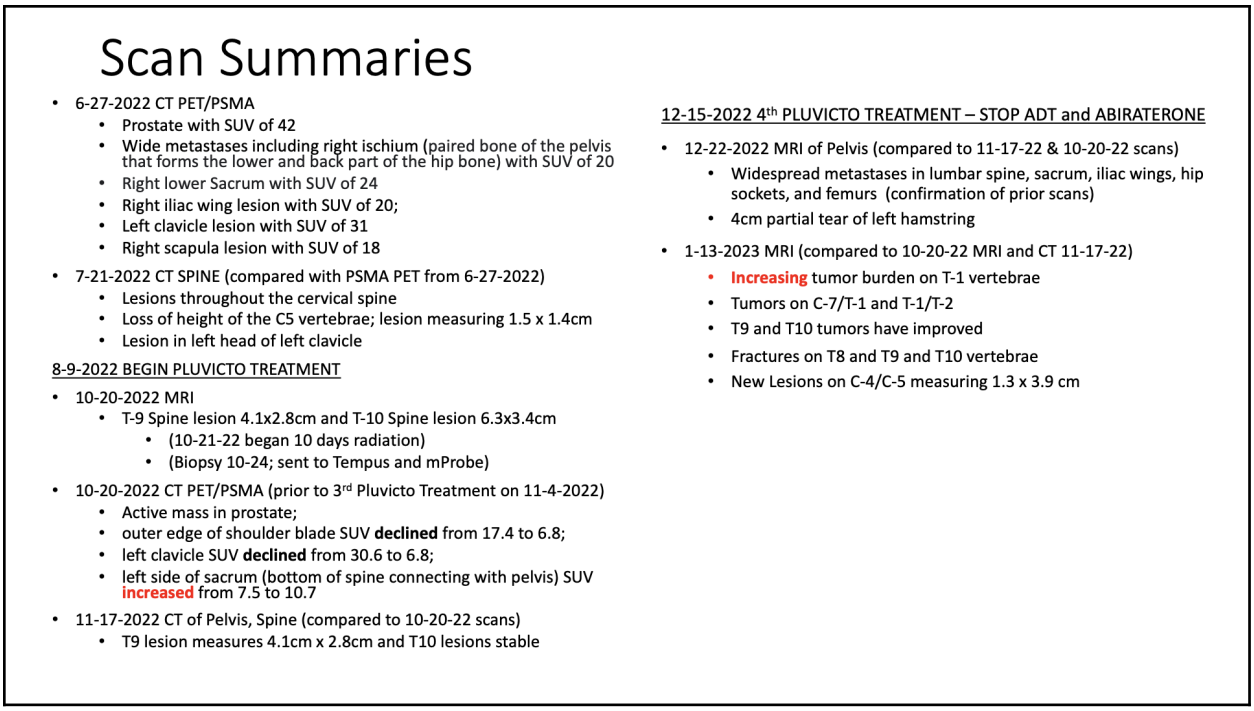
Mike Yancey
38:20
Much to your point Amit, the question is “how long is my body going to be capable of withstanding multiple treatments”? Even if I change to different treatments, how long before I may run into problems where suppression or something else comes up to where we put a hold on things. So that's always an outstanding question. The other thing as far as expectations go,

all my doctors, my Palliative Care doctor, my Medical Oncologist, and my Radiation Oncologist, they all have the priority understanding that they have to keep me healthy enough for my planned 11,000 mile round trip motorcycle ride to Alaska during the month of July. So I think everybody's on board with that. In fact, my Palliative care doctor said, “Can you do a short ride before then?” I said, sure we can make that happen. And so April 21, I'm taking off on about a 1500 mile to 2000 mile ride. I just met with her this week, and she was glad to hear that I was doing that in advance of the long ride.

So as far as other treatment options, just to kind of summarize, we want to use radiation when we can very aggressively for both pain reduction and reducing lesions when it makes sense. As my doctor often says, even though there are Pluvicto production issues that have become a problem, in his mind, we still have those two remaining doses (number 5 and 6) for future use. On the issue of BAT, I know that the intent of BAT is the introduction of very high testosterone volumes into your system and then let it decline over a month period. But I'm going to admit that I was very interested in doing BAT treatment, but have backed off on that only due to what we have found with my stopping ADT “test”. True, in that case, I never had super, super high testosterone, but just the fact as to how quickly my cancer responded to a little bit of testosterone has me thinking that may not be the best treatment option for me. Looking further into the future, I am keeping the CureMatch three-drug combo on the forefront. I'm going to have to pick that conversation back up with my oncologist just to make sure he understands that though I've gotten a drug mix revision based on this latest liquid biopsy from Foundation Medicine, I'm going to be reaching out soon to people like Brian and Brad because I'm going to need to get assistance from Mina or someone she recommends to get some dosing assistance. with this multiple drug treatment. I still have the “Standard of Care" using Cabazitaxel and Carboplatin that will continue to be on the list. Additionally Ipatserib has been in clinical trials, it's had a lot of press recently and there does seem to be some benefits utilizing Ipatasertib with some other treatments simultaneously. Then I've got the list of Shepherd Bio treatment options.

So, “Live every day to the fullest, keep fighting, and keep pushing the “edge of the envelope” and taking calculated risks. I've told my oncologist that I'm willing to be a lab rat, I'm willing to “push the edge of the envelope” and try things that might have some very negative interactions with my body and its capability. At this point, we really haven't pushed that hard that far toward anything that really caused me significant issues. I've been very fortunate in all my treatments that the side effects have been very manageable. I've been able to stay very active in spite of those treatments.

“How Proteomics and RNA Sequencing Are Guiding My Treatment” (Mike Yancey) [#51]



Scan Summaries

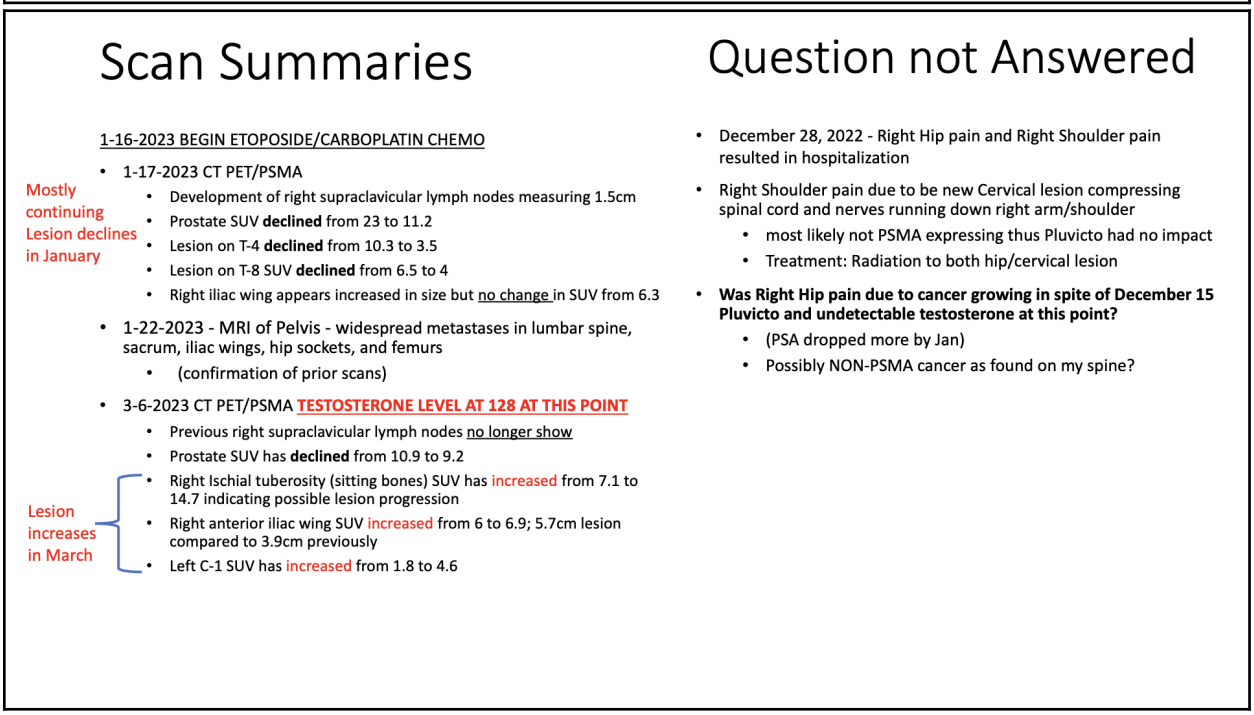
- 6-27-2022 CT PET/PSMA
  - Prostate with SUV of 42
  - Wide metastases including right ischium (paired bone of the pelvis that forms the lower and back part of the hip bone) with SUV of 20
  - Right lower Sacrum with SUV of 24
  - Right iliac wing lesion with SUV of 20;
  - Left clavicle lesion with SUV of 31
  - Right scapula lesion with SUV of 18
- 7-21-2022 CT SPINE (compared with PSMA PET from 6-27-2022)
  - Lesions throughout the cervical spine
  - Loss of height of the C5 vertebrae; lesion measuring 1.5 x 1.4cm
  - Lesion in left head of left clavicle

8-9-2022 BEGIN PLUVICTO TREATMENT

- 10-20-2022 MRI
  - T-9 Spine lesion 4.1x2.8cm and T-10 Spine lesion 6.3x3.4cm
    - (10-21-22 began 10 days radiation)
    - (Biopsy 10-24; sent to Tempus and mProbe)
- 10-20-2022 CT PET/PSMA (prior to 3rd Pluvicto Treatment on 11-4-2022)
  - Active mass in prostate;
  - outer edge of shoulder blade SUV **declined** from 17.4 to 6.8;
  - left clavicle SUV **declined** from 30.6 to 6.8;
  - left side of sacrum (bottom of spine connecting with pelvis) SUV **increased** from 7.5 to 10.7
- 11-17-2022 CT of Pelvis, Spine (compared to 10-20-22 scans)
  - T9 lesion measures 4.1cm x 2.8cm and T10 lesions stable

12-15-2022 4th PLUVICTO TREATMENT – STOP ADT and ABIRATERONE

- 12-22-2022 MRI of Pelvis (compared to 11-17-22 & 10-20-22 scans)
  - Widespread metastases in lumbar spine, sacrum, iliac wings, hip sockets, and femurs (confirmation of prior scans)
  - 4cm partial tear of left hamstring
- 1-13-2023 MRI (compared to 10-20-22 MRI and CT 11-17-22)
  - **Increasing** tumor burden on T-1 vertebrae
  - Tumors on C-7/T-1 and T-1/T-2
  - T9 and T10 tumors have improved
  - Fractures on T8 and T9 and T10 vertebrae
  - New Lesions on C-4/C-5 measuring 1.3 x 3.9 cm



Scan Summaries

1-16-2023 BEGIN ETOPOSIDE/CARBOPLATIN CHEMO

- 1-17-2023 CT PET/PSMA
  - Development of right supraclavicular lymph nodes measuring 1.5cm
  - Prostate SUV **declined** from 23 to 11.2
  - Lesion on T-4 **declined** from 10.3 to 3.5
  - Lesion on T-8 SUV **declined** from 6.5 to 4
  - Right iliac wing appears increased in size but no change in SUV from 6.3

Mostly continuing Lesion declines in January

- 1-22-2023 - MRI of Pelvis - widespread metastases in lumbar spine, sacrum, iliac wings, hip sockets, and femurs
  - (confirmation of prior scans)
- 3-6-2023 CT PET/PSMA **TESTOSTERONE LEVEL AT 128 AT THIS POINT**
  - Previous right supraclavicular lymph nodes no longer show
  - Prostate SUV has **declined** from 10.9 to 9.2
  - Right Ischial tuberosity (sitting bones) SUV has increased from 7.1 to 14.7 indicating possible lesion progression
  - Right anterior iliac wing SUV increased from 6 to 6.9; 5.7cm lesion compared to 3.9cm previously
  - Left C-1 SUV has increased from 1.8 to 4.6

Lesion increases in March

Question not Answered

- December 28, 2022 - Right Hip pain and Right Shoulder pain resulted in hospitalization
- Right Shoulder pain due to be new Cervical lesion compressing spinal cord and nerves running down right arm/shoulder
  - most likely not PSMA expressing thus Pluvicto had no impact
  - Treatment: Radiation to both hip/cervical lesion
- **Was Right Hip pain due to cancer growing in spite of December 15 Pluvicto and undetectable testosterone at this point?**
  - (PSA dropped more by Jan)
  - Possibly NON-PSMA cancer as found on my spine?

I've got a couple of slides here that show some of my scan summaries and show where we saw SUVs increasing or decreasing as well as insight from CT scans where they were actually looking at the lesions on my spine that did not show up in the PSMA/PET scans.

Brian McCloskey
42:28

“How Proteomics and RNA Sequencing Are Guiding My Treatment” (Mike Yancey) [#51]

Mike, thank you so much. I appreciate you putting in the work to put this presentation together. I want to go back to the beginning of this conversation.

Gitte Pedersen
43:22
First of all, Mike, thank you so much for sharing that personal story. And you're absolutely right, hang in there and you're doing all the right things with testing new ways to find better treatments. In the Shepherd Bio list, there were several options that I found very, very interesting. So one of them was upregulated kinase inhibitors, CDK6, where there's a drug approved for metastatic breast cancer. There's also some convergence between PTEN loss and upregulation of some other biomarkers, that could mean that you could be responsive to PARP inhibitors. PARP inhibitors are, I believe, either in late clinical stage or approved in prostate cancer. So what I want to say is that you should definitely take this data and have a conversation with your oncologist and consider maybe combining treatments.

Also there were some suggestions from CureMatch. I saw the immunotherapy Pembrolizumab/Keytruda. I don't know if you have the tumor mutation burden from the Foundation Medicine analysis, because a lot of prostate cancers have very low tumor mutational burden, which is quite low. You're quite low. I would talk with CureMatch about that, because unless you do something, and you have tumor antigens that are expressed, and you can ask maybe SHEPHERD if there's any tumor antigens expressed, then you just unleash your immune system.

Gitte Pedersen
45:56
The last one: your tumor definitely has multiple variations at this point. One is not expressing the endocrine receptor anymore. I'm pretty convinced that it's the normal resistance mechanism. Tumors are very smart and in that regard you put drug pressure on and it just changed. So you may have more than one type of tumor at this point and the metastatic lesions may be a little different from the original tumor. So hang in there, and have that discussion with your oncologist because you have some options.

Brian McCloskey
46:43
Ally, I know you had a question in the chat and now might be a good time to ask your question in terms of what are the new treatment options that SHEPHERD has provided. Mike, can you share that, again, what the recommendations were?

Mike Yancey
47:07
I don't have the specific recommendations in front of me. But they basically offered 10 different recommendations that point out which mutation each recommendation would be target. They offered one four-drug combination. As I said, I haven't really dived into that report at a detailed level; awaiting some time to discuss that with my oncologist.

“How Proteomics and RNA Sequencing Are Guiding My Treatment” (Mike Yancey) [#51]

Ally Perlina
47:34
May I suggest that when you get these reports that you give it to us, so we can at least present what this would look like together, if we took that information together with the information that you gave us for the last CureMatch report, because the CureMatch report is meant to be like the “catch all”, sort of last step, after all the data is in report.

So it's not necessarily to rerun somebody's drug recommendations themselves, but to rebrand biomarkers. So if there were genes expressed, which we didn't get before, or proteins, or any new data, basically, which was used by anyone for drug matching, then maybe this would be a good attempt to see, at least from our perspective, of course, if we were to reconcile it and say, from previous DNA inputs and all the levels, with the new data, what would be the top three-drug combinations, top two-drug combinations, how we usually do, but then taking in an integrated approach. So then if a doctor is pressed for time, or just overwhelmed by different options, it could give a more condensed view, and we can discuss it all together here, too. I'm completely open to say why this one and something else didn't go in, if that's what happens, or if there are any questions, but I'm just suggesting if there's still time, maybe we can quickly reconsider it.

Mike Yancey
49:03
Absolutely, because at this point, my best guess about utilizing the CureMatch multi-drug combo is probably going to be sometime around August, September of this year, depending upon how things occur and expand as far as cancer growth after I get back off my trip in July.

Ally Perlina
49:24
For the question that Gitte raised. We went with I think there was PDL-1 expression, and I double checked which inputs should we consider for matching. Should we still consider all of these? Some tests were done a couple of years ago, I believe. And because it was part of the package to be considered for matching, it was one of the inputs. I believe it was outdated. And I asked Mike several times, he knows, was there any more testing done for immune profiling, and I don't think we had any so, on the side of anything that can be matched will be matched, we took that in and took it seriously (PDL-1) But if you think that it's no longer relevant if you get new immune profiling data, it's possible that maybe Pembrolizumab/Keytruda does not need to be there, maybe some other drugs could be in our top three drug combo. So let's say if it's a CDK inhibitor, it could be possibly considered as the third drug instead of Pembrolizumab.

Mike Yancey
50:30
I know that some of the upcoming data that I will get I'll be sharing with you. Specifically it will be off the biopsy that I have planned on the 18th of April so hopefully stay tuned.

Ally Perlina
50:42
Sounds good. Thank you for sharing everything. It's well organized, and presented. Thanks a lot.

Brian McCloskey
50:51
Thanks, Ally, for your support, and Gitte as well.
Rick, you had some questions about Xgeva and personalized vaccines.

Rick Stanton
51:21
I wonder if Xgeva may make sense when you say you have a tendency to get new bone mets that are popping up all over the place. And even with perhaps a bone density of above threshold, where you would normally give Xgeva, you've got an experiment that's being proven out that you're getting bone Mets so that's what Xgeva was designed to prevent. Why wouldn't Xgeva make sense?

Mike Yancey
51:59
What Xgeva really works on is helping your bone rebuild itself. So therefore the cancer and the Mets that are eating up the bone Xgeva is meant to kind of achieve reconstruction. One of the things that I am looking at that I didn't have on my list that I want to keep on the list because I do have a large number of bone mats of course is Radium 223.
It definitely is one treatment I want to have on the table. But I have to be very careful with it if we're needing to also do chemo because taking them simultaneously is likely not going to work because of the blood issue.

Rick Stanton
52:55
So you're saying that you've been told, and I don't know so I'm not challenging, I'm asking that if you already are getting a bunch of bone Mets Xgeva doesn't work because it will reinforce those bone Mets rather than prevent. I mean, it would probably help stop the spread of new bone mets but it would enhance the existing rationale?

Mike Yancey
53:24
My understanding is Xgeva is not going to really do it but I haven't asked the question quite like you're asking it. My understanding is that Xgeva is really not going to do anything with respect to the creation of new bone Mets or addressing an existing bone met, but my understanding is it is mainly just meant to help your bones overcome the damage that the bone Mets are doing.

Rick Stanton
53:46

No, no.

Kevin Fordney
53:51
That's my understanding too Mike. I'm on Zometa. My understanding is that when things are getting bad it is to try to prevent fractures and to strengthen bones but it's not treatment related at all. It's a preventative to keep the bones strong.

Amit Gattani
54:17
That's my understanding as well. These things have nothing to do with the spread of bone mets or preventing bone mets from happening. That's a different process. This is just when once through treatment a bone met is gone, bone is decalcifying, and it's helping bone have its strength. So it's kind of helping the bone retain its strength and get better. So it's a healing thing not a preventative thing for the bone mets.

Rick Stanton
54:52
That's not my understanding.

Brian McCloskey
55:05
I mean, Rick, you would probably know, right? Rick was involved in the development of Xgeva.

Rick Stanton
55:21
Yeah, and you think that I would know more, and I know some things, but it's crazy that I don't know more, but I don't. But my understanding is Xgeva is of value to bone cancer to prevent or minimize new metastases. ~~A bone in the bone from the fertile soil theory, which is, I~~if you have weak bones, or an~~y~~ old fracture, or any weakness in the bone, that is where you are going to most likely get new metastases. And by strengthening the bones, you're making it difficult for cancer to spread to strong bones. I did help discover the RANK ligand which is the basis of Prolia Xgeva. But embarrassingly, I don't know all that much about it. But that was my understanding while I was at Amgen. I'm getting mets spread to my bone, so I'm going to be asking that and I'll be happy to report back what my oncologists think.

Do you have a high expression of AR?

Mike Yancey
56:58
My understanding is “no”. I answer that way, but I really haven't dived into that question specifically, but to my knowledge, I seem to still have some AR in the hip, pelvis, etc. But none in the lesions on my spine.

“How Proteomics and RNA Sequencing Are Guiding My Treatment” (Mike Yancey) [#51]

Rick Stanton
57:24
I would recommend looking at that number. Do you have a normalized number? Numbers that are considered super high, kind of high. That would be a direct question leading to how you might respond to BAT.

Mike Yancey
57:47
The level of reports that I have don't show anything with respect to AR so I can't answer that question.

Rick Stanton
57:57
Gitte, can you follow up on that? Or is that easy for your company?
Can you comment on Mike's AR expression? Either off the cuff or later?

Gitte Pedersen
58:23
Yeah, off the cuff, I actually had a question about the numbers not because of when he showed the graph. But that was his PSA. So you are asking about his AR expression. We will be able to see that in our assay. I didn't see that listed on SHEPHERD Bio. And that could be because I don't know what data was sent to SHEPHERD that you lost that expression. That is a typical resistance mechanism when you are targeting that particular biomarker.

Brian McCloskey
59:21
I think you'd need the raw file Gitte. You don't have his raw files. If you had his raw files from Tempus, then, you…….. Rick is shaking his head no.

Gitte Pedersen
59:33
Yeah, so we would be concerned about how because there's a lot of math in the back end of the platform. We validated that without chemistry, and we have not used Exon panels, which is what Tempus is using. The few panels we use have not been very effective. We haven't used Tempus panels, so I can't speak to that. But for our platform, it's not just to take the data and you run it through the bioinformatics back end. It will require that we get this slide sent, and we'd be happy to do that. Yeah, so that's tougher to get every biopsy or whatever material you have in store from all the biopsies.