“Feedback on My 17 Treatment Options?” (Brian McCloskey) [#15]

June 29, 2022
Brad Power

Meeting Summary

Advanced cancer patient Brian McCloskey shared the 17 treatment options that have been identified for him by various sources, including Cancer Commons/xCures, CureMatch, and Massive Bio, and solicited input on the complex decision he is facing in prioritizing among them. Brian had reviewed these options with his oncologist, Dr. Rana McKay, and he shared her opinions.

Rising to the top of his shortlist from the 17 options were four preferred treatments:

- An androgen receptor (AR) degrader (ARV-766) which destroys AR expression, not just inhibits it, available through a clinical trial from Arvinas identified by Massive Bio. (Prostate cancer is driven by the hormone androgen. Many treatments for prostate cancer inhibit androgen production. This drug attacks androgen reception.) Brian’s genomic analysis shows high AR expression.
- An Antibody Drug Conjugate (ADC) targeting B7-H3. This is available through a Daichi clinical trial. Brian’s primary and met tumor RNA seq analysis (done by Rick Stanton with Tempus data) shows very high expressions of B7-H3. An ADC is a monoclonal antibody chemically linked to a drug. The monoclonal antibody binds to specific proteins or receptors found on the cancer cells, and spares healthy cells.
- Pluvicto, the newly approved radioactive nanoparticle drug that binds to Prostate Specific Membrane Antigen. Rana McKay has seen very strong responses to this drug among her patients. There are challenges with access right now.
- Cabazitaxel, a standard of care drug for men with metastatic castration-resistant prostate cancer. It is a type of chemotherapy called a microtubule inhibitor.

Bipolar androgen therapy, a treatment tailored for a patient who has become “castration-resistant” (deprived of androgen through drugs, yet PSA is rising), is also something Brian is considering. It has been very effective for his friend, advanced prostate cancer patient Bryce Olson.

Emma Shtivelman, PhD, Cancer Commons Chief Scientist, a molecular biologist who has much experience in making treatment recommendations, weighed in with her opinions about Brian’s treatment strategy and tactics. She was attracted to pathways that are different from the androgen receptor pathway, which has been drugged for Brian several ways already. She feels that CAR-T is a potentially valuable treatment option, as is PSMA targeting (Pluvicto), but that they are farther off in Brian’s future. Therefore, she favored the Antibody Drug Conjugate attacking B7-H3. She also liked the trial sponsor, Daichi, which is a leader in the field of making good Antibody Drug Conjugates.

The drug combination options were a concern for Rana McKay, due to toxicity and quality of life risks. Brad Power and Saed Sayad recommended lower dosages for each of the drugs in a drug

combination. Brian wanted to see evidence for lower dosages. Brad said that is in the domain of experts (not clinical trial evidence), and suggested we tap a dosing expert.

Requests

- Do you know anyone who is an expert on dosing, especially as a way to reduce toxicity concerns in drug combinations?
- Would you like to join a group to talk about how we could create or find protocols (observational trials) that willing physicians could put their patients in to benefit them in real time, as opposed to 20 years from now, after you collect enough data?

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Meeting Notes

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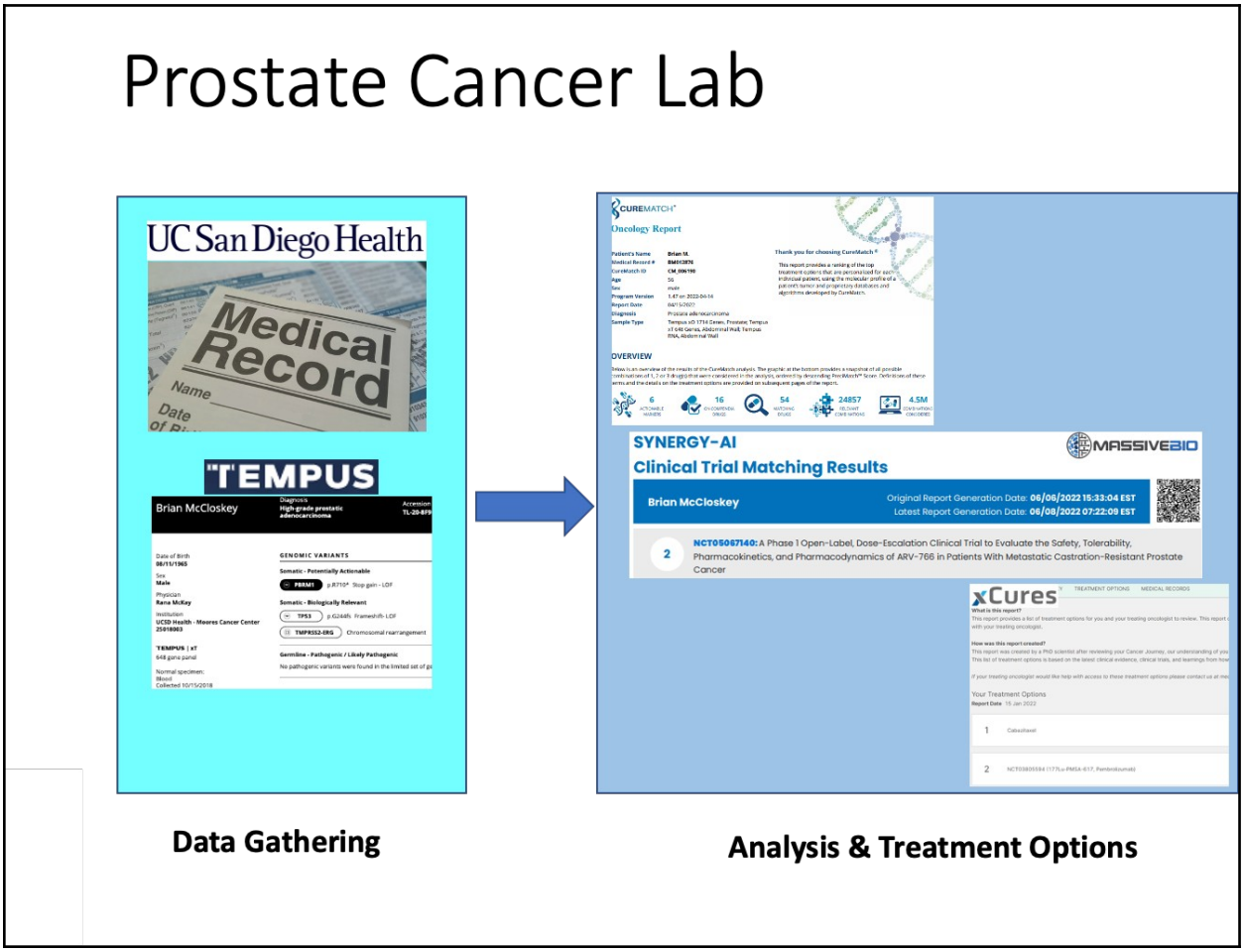
Brian McCloskey: I'm going to be speaking to you about the process that I've gone through to identify treatment options. Many of you have been part of that journey in helping me along the way. I first want to thank all those that have contributed to this. This is an inflection point in terms of how the Prostate Cancer Lab is benefiting me and Rick, and other patients, such as Ken and Mike who are teed up in the process as well.



Over the past several months I have had the great pleasure of working with three companies to help me identify potential targeted therapies for me to consider and to take to my doctor. The process has been really straightforward and very simple. It consists of two components.
One is data gathering. As many of you know, I'm being treated primarily at UC San Diego Health. I'm also at The City of Hope and the Larry Ellison Institute for Transformative Medicine. Over the course of the past six years, I have a pretty long rap sheet in terms of my medical records. My medical records from UC San Diego are long and illustrious. The other data input is my genomic profile. I have five separate genomic reports. Some relate to my primary tumor,

some relate to my metastatic tumors, and then liquid biopsies along the way. In total, there were nine different documents that went into the analysis that I've shared with three different companies.

The first is CureMatch. Ally Pearlina has provided concierge, white glove service to me in terms of taking in all of my information and integrating that into their treatment matching process.
The second company is Massive Bio. Their process is a little bit different, and similar to xCure’s, where all of those nine different documents were uploaded into their portal. Then they reached back out to me to make sure that they had everything. They worked directly with UCSD to capture all of my medical record information, imaging, et cetera. That was basically the same for xCures – a combination of online document uploading and white glove service where they worked directly with the healthcare provider, and then made sure that they had all of the information.

Once those three companies have all of the information, they then run it through their matching algorithms. Depending upon their focus, they provide treatment options. For example, CureMatch is very focused on combinatorial approaches that are targeting my specific molecular targets.

Massive Bio does something similar, but they're really not focused so much on drug combinations, although that is part of their solution. They focus on clinical trials.
How do you find the right treatments?

Based upon the profile of the patient, their history, medical records, molecular profile genomics, et cetera, and then find those trials.

xCures is similar to Massive Bio in that they are using the same information for their matching. They consider clinical trials as well as standard of care and some off-label drugs as well.
Across all three vendors, you have a pretty rich group of different options to choose from.
It's interesting that across each of these three vendors, I received 17 different treatment options, and there was no overlap in any of them. That's kind of nice because they were complementary, I have more options. But on the other hand, it raises the question: can we do better in terms of having the right information upfront to have more precise treatment options?

Brian McCloskey’s 17 Treatment Options

	Therapy Option	Targets	Rationale and Expert Input	Source	Drug Access
1	Antibody Drug Conjugate	CD276 (B7-H3)	Primary and met tumor RNAseq analysis shows very high expressions of B7-H3 relative to pan cancer and prostate cancer cohorts.	Tempus/ Stanton Biosciences	Daichi
2	Cabazitaxel	Unspecified	SOC	xCures/ Cancer Commons	N/A
3	177Lu-PSMA-617, Pembrolizum	PSMA	If eligible for a clinical trial, consider the combination of 177Lu-PMSA-617 and the immune checkpoint inhibitor	xCures/ Cancer Commons	https:// www.clinicaltrials.gov/

	ab		pembrolizumab. Trial located at UCSF. The Phase 3 VISION study reported a 38% reduction in risk of death and 60% reduction in risk of radiographic disease progression or death in men with PMSA-positive mCRPC who received 177 Lu-PMSA-617 plus best standard of care as compared with standard of care alone. (https://www.globenewswire.com/news-release/2021/06/03/2241602/0/en/Novartis-177Lu-PSMA-617-significantly-improves-overall-survival-and-radiographic-progression-free-survival-for-men-with-metastatic-castration-resistant-prostate-cancer-in-Phase-III.html).		ct2/show/NCT03805594
4	Cabozantinib, Atezolizumab	Unspecified	If eligible for a clinical trial, consider the combination of cabozantinib and atezolizumab. Trial has multiple locations in CA. A Phase 1b trial of cabozantinib and atezolizumab in advanced solid tumor patients reported, in 132 patients with mCRPC, a partial response rate of 15% and a median overall survival time of 18.4 months (https://www.targetedonc.com/view/atezolizumab-combined-with-cabozantinib-shows-efficacy-in-high-risk-mcrpc)	xCures/ Cancer Commons	https://clinicaltrials.gov/ct2/show/NCT03170960
5	Degarelix, Enzalutamide, Trametinib	BRAF, AR, MAP2K2 over expression	Consider the combination of AR inhibition with the MEK inhibitor trametinib. Targets the BRAF, AR, and MAP2K2 overexpression. Mimics part of ongoing NCT01990196. A study in a mCRPC patient reported a decrease in PSA of 85% and 93% at 3- and 5-months following treatment with trametinib, and no radiologic or clinical progression for 18 months (https://www.nature.com/articles/s41391-019-0134-5)	xCures/ Cancer Commons	Off Label
6	1)Apalutamide, 2) olaparib,	1)AR,2) FANCA via PARP1,	CM_006190 BM CureMatch Report 20220418.pdf	CureMatch	1) FDA approved 2) FDA

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	3)trametinib	PARP2, 3) BRAF via MAP2K1, MAP2K2 MAP2K2			approved 3) Off label
7	1) Carboplatin 2) regorafinib 3) trametinib	1) FANCA via DNA damage 2) BRAF TP53 via FLT1, KDR 3) BRAF via MAP2K1, MAP2K2 MAP2K2	CM_006190 BM CureMatch Report 20220418.pdf	CureMatch	1) FDA approved 2) Off label 3) Off label
8	1) palbociclib 2) regorafinib 3) trametinib	1) CDK4 2) BRAF TP53 via FLT1, KDR 3) BRAF via MAP2K1, MAP2K2 MAP2K2	CM_006190 BM CureMatch Report 20220418.pdf	CureMatch	1) FDA approved 2) Off label 3) Off label
9	1)Apalutamide, 2) olaparib	1)AR, 2) FANCA via PARP1, PARP2	CM_006190 BM CureMatch Report 20220418.pdf	CureMatch	1) FDA approved 2) FDA approved
10	1) Carboplatin 2) trametinib	1) FANCA via DNA damage 2) BRAF via MAP2K1, MAP2K2 MAP2K2	CM_006190 BM CureMatch Report 20220418.pdf	CureMatch	1) FDA approved 2) Off label
11	1) Olaparib 2) regorafinib	1) FANCA via PARP1, PARP2 2) BRAF TP53 via FLT1, KDR	CM_006190 BM CureMatch Report 20220418.pdf	CureMatch	1) FDA approved 2) Off label
12	Olaparib	FANCA via PARP1, PARP2	CM_006190 BM CureMatch Report 20220418.pdf	CureMatch	FDA approved
13	Carboplatin	FANCA via DNA damage	CM_006190 BM CureMatch Report 20220418.pdf	CureMatch	FDA approved

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14	Trametinib	BRAF via MAP2K1, MAP2K2 MAP2K2	CM_006190 BM CureMatch Report 20220418.pdf	CureMatch	Off label
15	CCW702	PSMA	CCW702 is an investigational immunotherapy for prostate cancer	Massive Bio	Clinical Trial - Phase 1
16	ARV-766	AR	AR degrader designed to destroy AR expression, not just inhibit	Massive Bio	Clinical Trial - Phase 1
17	Abiraterone + Abemaciclib	AR + CD4/6 inhibitor	Adding an targeted to my existing drug, Abiraterone	Massive Bio	Clinical Trial - Phase 2/3

I'm not going to go through all of these in detail, but I'm going to hit some of the highlights. First, just a little bit about the transition from getting all 17 different treatment options into the conversation that I had with my oncologist, Dr. Rana McKay, on Monday. I sent Rana this spreadsheet, which you see here. This is a summary of the different reports that I got from each of the three different providers. I also sent her all of the backup documentation from the three providers. She had all of that information prior to our meeting, and she reviewed it in detail. We spent about an hour in the clinical office visit.

We spoke first about the particulars of where I am with my health. I'm currently on abiraterone. I've hit nadir with my PSA. I hit that probably about three months ago, I'd say March. My PSA has gone from 0.45 to 0.49. It's now at 0.54. It's gradually moving upwards. We both think that there's mileage to be gotten from my existing drug.

We are going to go after imaging, get some baselining, and understand the extent to which my disease is progressing or stable. It's been maybe nine months or so since I've had CT scans, so we're going to do that. And I'm going to have a PSMA PET, which I have not had since June of 2020.

Those are just some of the basics in terms of what we talked about relative to my health. Then we got into the various treatment options as we started to plan for my imminent failure of abiraterone.

The first one that we talked about was option #1: the antibody drug conjugate which is targeting B7H3. This option came from work that Rick Stanton did with Tempus and myself to identify a target through some transcriptomics, an RNA seq analysis. There is a trial that Daichi is running and Rana feels that this is a possibility. I would mark this green. This is something that we are going to keep on the menu.

Option #2 is cabazitaxel. This is a standard of care treatment. It's certainly a possibility. It came from xCures.

Option #3 is Pluvicto plus pembro, which is a clinical trial that's being run out of UCSF. The commentary on this option was that it is very interesting. She said that she has seen two patients that early in the cycles have seen complete remission on Pluvicto alone, a radioligand. She likes the idea of combining it with something like pembro. I would not qualify for this trial, because I've already seen pembro in my care. But she is pretty enthusiastic about Pluvicto.

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Option #4 is cabozantinib and atezolizumab. She thinks that this is a possibility, but a little bit less confident about the response.
For some of the other options she has some concerns about toxicity.

Jeff Waldron: Going back to Pluvicto, option #3, in addition to getting access through trials, you could consider getting a compassionate use, expanded access program to receive that therapy.

Brian McCloskey: Pluvicto is FDA approved. To get access to it is not an issue; rather, the challenge is supply. She said forget about a combination with pembro or any other drug. If you wanted to get this drug in December, we would have to start the process right now. It's a very, very slow process. They've had supply issues, et cetera. But right now, I don't think we're leaning towards that as a next option.

Rick Stanton: What is the target in your option #4 of cabozantinib and atezolizumab?

Brian McCloskey: This came from xCures, and the target was unspecified.

Emma Shtivelman: Cabozantinib is a very powerful drug. It's an inhibitor of multiple tyrosine kinases, and also angiogenesis. Atezolizumab is a PDL1 drug. You are not eligible for this trial, Brian.

Brian McCloskey: I’m not eligible because …?

Emma Shtivelman: xCures didn't look into your previous treatments.

Brian McCloskey: Option #5, degarelix, enzalutamide, and trametinib: Rana was concerned about toxicity.

Option #6, apalutamide, olaparib, and trametinib,was provided by CureMatch. The commentary on this was that I've seen apalutamide and so not sure it's a fit. I could potentially retry apalutamide, but it was not clear why I would go after that as opposed to other options.

Options #7 and 8, Rana was concerned about toxicity. We talked a lot about toxicity. I've been treated now for six years. I'm currently on abiraterone. Abiraterone is generally viewed as a very tolerable drug. Mike and I spent some time yesterday talking about it. And Mike, you can correct me if I'm wrong, but it seems to be very well tolerated for him. I know somebody else has been on it and they thought it was super easy. For me, it has been a problem. I've seen my anemia has gotten worse. I don't know if it's because of this drug or just simply because I've been on these drugs for such a long time that I'm just much more susceptible to anemia. But in general, she's concerned about combining all of these drugs and the toxicity that it will have on me. I know that that would be mitigated through lower dosing, but still where is the data that would actually show that toxicity would not be a factor when you combine all three of these drugs? We've not really talked about the element of toxicity significantly. We've talked about the scientific approach of using combinatorials to go after multiple targets, as opposed to a single target. And that sounds great on paper, but this is the first time that I've had a conversation about combinatorials and quality of life.
One thing that I appreciate about Rena is that I've seen her now for 5 and a half years, and she's always been really good about trying to balance drugs along with quality of life. As we think about these drug combinations, that's something that we have to keep in the back of our minds.

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Anonymous Caregiver: That makes me think about known or knowable adverse events. How many of these therapy options in your column B have actually been used before versus someone's algorithm thought, “try this”, and be the first one who did?
With all the uncertainties that a patient like you is sitting with, some of these things are quantifiable, even if it's small N and not large N yet.
My question would be, how can you add another column or put something in where we know, what is the evidence base to date for that particular therapy?

Brian McCloskey: And when you say “therapy”, you’re speaking about the drug combination?

Anonymous Caregiver: Yes. Whatever that combination is and that protocol. If you're talking about a particular protocol, like in the case of Massive Bio matching you to clinical trials, there's a particular dosing sequence and what have you

Brian McCloskey: I wish Ally Perlina was on the phone. I'm sure she could provide a lot of great insight into that. I can't. Point taken.

The next options are all from CureMatch, and they're two-drug and monotherapies, the subsets of option #3. We have the same issue with apalutamide, and the concern around toxicity. For the monotherapies, we didn't really dig into those significantly. She was interested to see what was happening with trametinib, option #14. She thinks that that is something that we should keep on the radar. Of the options #12 - 14, those three monotherapies from CureMatch down at the bottom, trametinib is one for us to watch.
Then we moved into the Massive Bio set, and she's actually the principal investigator for this first one, option #15. This is a BiTE (bispecific T-cell engager – a targeted immuno-oncology platform that connects patients' T cells to malignant cells). Unfortunately this trial is on hold. They're working through some dosing changes, et cetera.
Option #17, same thing, the trial stopped, so that one's off the table.

However, the one that we really gravitated towards was Option #16, ARV-766. This is a trial from Arvinas. This is one that Massive Bio recommended. Arvinas has a newer drug, which is ARV-110, and that may be better. Maybe it would be great to talk to Massive Bio about this a little bit more, but she recommended going with ARV-766 because I would be guaranteed to get the drug, the trial with ARV-110 has a control arm. And so it's possible that I wouldn't actually see the drug.

If we look at all of these different options, this one, option #16, is a strong contender.
Option #1, the ADC, is a strong contender.
We like Pluvicto, but this combination probably won't work. And I've got challenges with access right now.
Those are the more promising drugs or therapies.

To transition to how this process worked and what the benefits and the pros and cons of it are, I would start off with: having this menu was really helpful to guide the conversation.
It was helpful for her to think about maybe drugs or therapies that she may not have been thinking about. There's a rationale behind all of these. She doesn't necessarily agree or would need more data with some of these recommendations. We would expect that. I applaud her too, because this was a lot of information, and I could tell that she had spent enough time to actually digest this. Kudos to her.

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While I had 17 options, this is far from comprehensive. There are many different treatment options. And one in particular that did not show up on any of these recommendations was bipolar androgen therapy. We have a friend who is an advanced prostate cancer patient. He recently went on bipolar androgen therapy. He's an eight year survivor, so he has seen a lot of drugs, and his PSA went from like 300 to five on BAT. It is risky because you are integrating testosterone into the equation, which can either make it go wildly right, or wildly wrong.
Rana posed the question back to me: “What do you think about it?” I thought, “Here we are in this situation where I have to make the decision.” I don't know if I'm ready to go after bipolar androgen therapy. Maybe. It's certainly something for me to consider. I've seen how it can work, and it's pretty impressive. I don't know all the negative cases, but I'm sure they're there.

The thing that I wanted to do with this conversation was not only to look at these different options, 17 of them, but also how we could get better insight to differentiate across the 17. We got into diagnostics: proteomics, spatial phenotyping, and a few other things. And when it comes to some of these other testing mechanisms, I felt that she was more conservative. So on spatial phenotyping, for example, we talked about how Akoya Biosciences, who's one of the leaders in this area, is just instantiating their machines at UCSD. She was aware of it. She was excited about it, but she also said that she wasn't really ready to make any treatment recommendations based upon the data that it would provide. We talked a little bit about proteomics. Karin Rodland had a really, really amazing presentation a couple weeks ago. Rana needs to see a bit more evidence in terms of how it can work in treating cancer patients. She's not willing to jump out on a limb, to say these are the additional tests that are really going to make a difference. We talked a little bit about mRNA. There might be some more stuff to do there, but if I had not brought up additional testing to make a better decision across these 17 or others, I'm not sure it would've been part of the conversation.

Obviously, in an hour-long conversation, we were covering a lot of territory. I covered maybe 80% of the things that need to be covered, not everything. I'm super thankful that I got 60 minutes with her.

The short story is I have 17 different treatment options, and four that are contenders.
My next step is to get some baseline imaging done. I'm going to have CT scans and PSMA PET. We'll see what's happening with my PSA relative to the drug amount right now. I think we agree that we're going to try to get the most mileage out of abiraterone as possible. And then I'm going to have to make a decision across these four, or five if you throw in BAT, and maybe something else that might come up between now and the time I have to make the decision.

Emma Shtivelman: There are two classes of drugs that didn't make it into that list. One is the bispecifics that target CD3 and PSMA. There are some others, and of course, CAR-T targeting PSMA and PSCA. For you, I completely understand that CAR-T should be saved for later. From that point of view, bispecifics tied to PSMA should not be considered now because there is a danger that they will deplete PSMA, probably not a real danger, but a consideration.
You've been on endocrine treatment for a while. There was almost always something targeting the androgen receptor. My suggestion would be to lay off targeting this pathway and go with something different. So in your case, the real opportunity is the antibody drug conjugate from Daichi as the first option. B7-H3. If it kills cancer cells, it will be based on just something that's more or less randomly present on them.

Brian McCloskey: That's really helpful. I had that same concern, although I couldn't articulate it. I've been pounding AR. If I did an AR degrader, that’s more of the same. Is that a layman's translation of what you're saying?

Emma Shtivelman: Yes. Change the strategy entirely. Lay off targeting AR with whatever it is. There are several options here that do just that: apalutamide and the protech drugs, the IV drugs, of which one is on the list, and one is not. That's why I would like to have a break from this approach. And by the same reasoning, I don't think that targeting PSMA is very useful now because ultimately, and hopefully, you will be in a CAR-T trial, because there is some promise. PSMA is not a good target now because you might sort of eliminate it or reduce the levels by using Pluvicto or other combinations. There is a trial that combines Pluvicto with a different radionuclide that targets PSMA, but it's a different isotope. Actinium I believe it's called. It offers both at once, which is probably rough.

Brian McCloskey: Bryce was on actinium and that was really hard for him to tolerate.

Emma Shtivelman: That would be my logic: lay off the androgen receptor and lay off PSMA for now, which leaves something. In my mind, the Daichi ADC to B7H3 is a good option. Assuming that the data you got from Tempus on overexpression of RNA will be confirmed by immunohistochemistry.

Anonymous Caregiver: Another thought along the lines of getting more information of where you've already been treated: You may know that typically FDG (fluorodeoxyglucose) scans are not so recommended for prostate cancer, because they're not so revelatory of anything early. But after there's been a lot of treatment, FDG can be useful. The standard of care will take a newly diagnosed patient, and if their PSA is high enough, they'll get a CT scan and a conventional bone scan. We know that that's less likely to show things at least at lower PSAs. FDG is similar. It’s a glucose uptake, something that prostate cancer doesn't tend to do, at least initially, but I've heard that later after accumulating a lot of treatments, at some point FDG can become a useful scan to prostate cancer patients.I don't know if that's on your list of scan intentions, but you could discuss that with someone.

Emma Shtivelman: It's a common die used for PET scans in other cancers. It's basically fluorescent glucose that's taken up by cancer cells because they consume more glucose.

Saed Sayad: What is your main question for this session? Is it your next best treatment?

Brian McCloskey: Yes. The objective here is to get your feedback on these treatment options, within the context of the conversation I had with my oncologist.

Saed Sayad: And you are currently under some treatment?

Brian McCloskey: Yes. I’m on abiraterone. My PSA has hit nadir, and it's increasing very gradually.

Saed Sayad: How many next step options do you have?

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Brian McCloskey: 17 treatments. I'm on a treatment now. For the next, let's say I take one, that might last six months. Are you asking what my treatment will be after that? Are you talking about treatment strategy?

Saed Sayad: Based on your existing situation, the first question is why do you want to go to the next best treatment?

Brian McCloskey: It's because I'm in the process of failing abiraterone.

Saed Sayad: 17. For each of those 17 treatments, do we have some data to support them based on experience? Or are we going to judge them just based on our educated guesses? I want to know why one, why two, why three?

Brian McCloskey: I appreciate the mathematical thinking that you're applying to this.
Emma, maybe you can chime in here a little bit in terms of how xCures or Cancer Commons makes their treatment recommendations and what evidence they have that would support each of the four different treatment options provided. I know you removed one of them.

Saed Sayad: The reason I'm asking is because I'm seeing a lot of research in this field, and they just try to explain something. But we have a question which we need to answer. We don't want to just explore it. Exploration is good. We increase our knowledge. But the point here is that the goal here is to find the answer to our question. Out of one to 17, why should I go for each one? There should be a good reason based on data, reason, or biology, the biology behind good guesses.

Emma Shtivelman: I cannot really comment on how xCures do their treatment recommendations to trial recommendations. I can guess, but we are very separate in this regard. I also should mention that I never composed the official looking trial option report for you, Brian. I don't know why I didn't. It never happened. It was always like informal email communication like this. I don't like that.
But for myself, and for other scientists at Cancer Commons, the way we work is we review trials that are suitable, of course geographically. We carefully review the inclusion and exclusion criteria, because they're very important. For example, because of previous tests, you are not eligible for a couple of trials with fairly promising ADC that targets new antigens on prostate cancer, like CD46. In general, when I see a trial a lot of the time, I know a little bit about the drug, and I try to find evidence of clinical activity. If it's available. It's not always available. If I think the drug is promising, based on very strong preclinical data, I will include this trial, but I don't do that often. I mostly look for preliminary evidence of clinical activity. Usually in the reports that I compose for patients, I include this supporting data, trying of course to choose publications that are more easily accessible.

Saed Sayad: That means we can just use a random number and go through and select one of them, and see what happens. I just want to have some organized way to approach our problem. Otherwise it's going to be analysis paralysis.

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Emma Shtivelman: In my head, it's organized to solve the main problem of trying to convince both the patient and the oncologist that it makes sense. Oftentimes, I actually rank clinical trials. I say the best trials, the most relevant ones, the most promising guy at the top, number one, two, et cetera. I'm talking about the process. I never did it for Brian, which is pretty clear. He has the file. He has the spreadsheet. And I expressed my preference for targeting B7-H3 because it's outside of the treatments he’s been having. It could be any cancer. I believe there are some preliminary clinical results with the antibody. And also because Daichi is the leader in the field of making good ADCs, for example, in breast cancer, the drug that really revolutionized the field of treatment of HER2 low breast cancers.
It was discussed at one of these meetings that these cancers were previously considered to be just like HER2 negative. And they made a new antibody drug conjugate that works amazingly well in HER2 and in HER2 high. There are a number of other antibodies. They have new antibody conjugates for TROP2 and HER3. They know how to make good antibody drug conjugates.

Saed Sayad: When you have 17 options, you need a way to score them. We have two options, search and research. I like the research part. Research means first we do search – we go through our data, public data, private data, and see if we can find an answer and score them, score those 17 options. If you don't have the research, then search.

Emma Shtivelman: For clinical trials, first we do a search. Then I click on each individual clinical trial. I research the information available about this drug, preferably clinical information, not some studies in mice or even in cells in culture. That part is research and also other not obvious things like, as I mentioned, what do you think about the company that produces this drug? What do you think about the type of drug in general, et cetera.

Saed Sayad: I suggest for the future, it's going to be much more productive if we are focused on one question. This is the question. Let's try to find the answer. Finding that answer should follow some process. Is there somebody else? Do we have some public data about this one, some trial, something? If not, then we need to bring in an expert and get the expert opinion based on their expert guessing. They are the best people to guess, because we don't have any data to support finding our answer. Then we need a good guesser. A good guesser is one of the experts in this field. Ask the expert to put a weight score on this list. This way we can help each other. Otherwise it's going to be just, as I said, analysis paralysis.

Emma Shtivelman: I think that Brian is already at this point.

Saed Sayad: Then we need to see their score.

Brad Power: He is effectively scoring them, but it's not numeric.

Saed Sayad: We can use fuzzy numbers. Say, high, or low.

“Feedback on My 17 Treatment Options?” (Brian McCloskey) [#15]

Brad Power: He's saying, here are the high rated ones of the 17. Here are the four that I think are most attractive.

Saed Sayad: That's also good. Human beings are all about fuzzy numbers.

Brad Power: I really like the way that you are asking these questions. We're behaving like a virtual molecular tumor board, reviewing these treatment options, and then uncovering the principles that are guiding some of these decisions. You're going to uncover the root level principles behind the decisions. It was great to hear Emma say, these are the considerations I make to arrive at the prioritization that I come up with.

I want to add a shout out to Bob Gatenby, because he would also ask why Brian is looking at another drug. Because Brian is on an existing drug and he's reached resistance. And the implicit principle behind everything that happens in prostate care is you take a drug until resistance. Then another drug, then another drug, and you take each until resistance. And then you go on to the next one. That's interesting because it's breeding resistance in a heterogeneous population.

The second thing that Emma said is, “I like B7-H3, because it's a different pathway.” There may be resistance to AR, but there’s potentially no resistance to B7-H3. That is another implicit principle that you have uncovered. And I think we could uncover others, for example, as she said, the credibility of the company, the success they've had previously, et cetera.
A question I want to ask you is actually a step back. I was thinking back to your previous session in which you shared analysis of publicly available datasets that indicated certain drugs or treatments that would be appropriate for prostate cancer. Do any of those from your recollection of that analysis, which as I recall, there were a half dozen or 12, and they were based on population level data. They're not personalized to Brian, but would there be any of those that came from your recollection of that analysis, that Brian should add to his 17, that should be maybe number 18? I'm just doing a completeness test on his 17 treatment options, given the fact that each of the three sources came up with treatment options, none of which overlapped?

Saed Sayad: Based on a single cell analysis of resistance, cyclosporin A is one example, which is a completely different mode. For every drug we use, there are a thousand different effects in our system.
What I found overall is better outcomes from less concentration and more drugs simultaneously. For example, if we give 10 units, give 10 drugs with one unit each, but this is just a guess.

Brad Power: That's confirmed by Bob Gatenby and by CureMatch. That's the issue that Brian ran head on into, which is talking about dosing, and reducing the toxicity risk by virtue of reducing the dosing, as Saed is just reinforcing. That's a viable option to consider, particularly when you have B7-H3, that's on a different wavelength than others.

“Feedback on My 17 Treatment Options?” (Brian McCloskey) [#15]

Brian McCloskey: I'll need to follow up with Rana regarding dosing and toxicity. We did not get into that. I'd also like to have recommendations in terms of what the doses are for each of the different recommended treatment options, because that tells me that they have evidence, which suggests that those drug combinations actually work because they've been tried at various dosing levels together.

Brad Power: My 2 cents would be that, just as Saed was pointing out, that's going to be the zone of experts, not of evidence, because once you get into combinations and dosing, you can have principles, but you can't have randomized controlled trials that will have tested all of those options because the permutations are so many that it will be impossible to have randomized clinical trials evidence. We should think about dosing. I know Kristine Ashcraft at Invitae, who's an expert in pharmacogenomics, and maybe she’s the kind of person that you need to ask. There must be dosing experts we can tap.

Saed Sayad: I want to give you one example, which we did a few years ago on psoriasis. The skin disorder. We analyzed one of the best public data sets on the genomics. We found an antibiotic Metronidazole will affect this disease. That drug is usually just for infections. We used it in some real practice and it had a good effect, as good as many very expensive drugs. Again, there are tons of opportunities for everyday drugs, such as aspirin. The biggest problem is we cannot test it. It's difficult, it's costly, and nobody has any interest in testing it. We need to find the doctors. We need to find the group to try it. But I believe there are tons of opportunities for existing drugs, and in combinations. I can show you real cases for it.

Nik Schork: It might be good to get a smaller team together to talk about how one could put protocols together that willing physicians could participate in. Resourcing that and paying for that of course are questions, but we can cross that bridge when we get to it. I’m happy to have further conversations on designing protocols that can address these questions that have the dual purpose of vetting something scientifically and advancing insights, that'll benefit the patients in real time, as opposed to 20 years from now, after you collect enough data.

Rick Stanton: Adding another couple columns would be useful to your excellent spreadsheet. A column for rank immediately comes to mind. They should be ordered. They're kind of loosely ordered, but should be clearly ordered.

The second needed column is for evidence. Why are these 17 on the list at all? It's going to be a combination of population statistics or personalized medicine.

The B7-H3 is indicated for both population and personalized as we have RNA seq indicating population B7-H3 is highly expressed in advanced prostate cancer patients statistically. We also have your RNA seq data, which shows that we have a super high expression of B7-H3.
I love Emma's idea to go to a different axis, and just adding those columns, especially the molecular evidence or population evidence would be very illuminating.

“Feedback on My 17 Treatment Options?” (Brian McCloskey) [#15]

The fact that there's no overlap between what these three vendors are recommending is not surprising because CureMatch only deals in FDA-approved drugs, which is not the focus of the other two. Massive Bio is highly focused on clinical trials. So you're not going to get a whole lot of overlap there.

I'm wondering about this for myself as well. It seems like you're failing an AR blockade. Why is that? We know we are developing resistance.

What is changing? How is the heterogeneity of the tumor changed, such that we're no longer responsive? Can we detect it and can we steer around it?

At such a low PSA, your liquid biopsy may not be illuminating, but I hope we would be able to identify an AR mutation that might be able to be steered around. It would also give you some insight as to whether you should be doing BAT, or an approach like Bob Gatenby would recommend: “Go on something else.” Which definitely agrees with Emma to get off that AR axis and let the AR heterogeneity and sensitive cells blossom, and then hit it again – the strategy that Bob might recommend to go off of everything for a while.

Spatial phenotyping is pretty out there for most physicians to pay attention to, but IHC is not. Emma’s comment of staining for B7-H3 via IHC, and of course you would want to stain for CD3, which is very basic. That's a multiplex of one spatial phenotype. When I progress and I can have a biopsy, I want to have IHC and spatial analysis because I'm looking for concordance – my RNA tells me this, do I see it in the spatial? Do I see it in the IHC?

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Addendum from Emma Shtivelman
Via Email
July 5, 2022

I have mentioned that I have not yet put together a list of treatment options for you. You have several lists already (CureMatch, MassiveBio, Xcures – I have nothing to do with the latter, BTW), and obviously you made a “summary” list yourself. I have reviewed the 17 options in your Excel file, and transferred them to a google spreadsheet for easier editing (this would be the first sheet in the spreadsheet I just shared with you:
https://docs.google.com/spreadsheets/d/1sUI1ys0keKFXWJ_RtsgBYa32CNEayQZT4wwXiL5tKk4/edit#gid=1919647396

I added some comments to the existing 17 options. Obviously, I am not in favor of most, sorry. I do like the approach of CureMatch a lot, but I have serious doubts for these reasons: 1. elevated levels of BRAF RNA are not a strong good rationale for MEK inhibitor (trametinib). 2. Copy loss of FANCA is not a solid rationale for PARP inhibitors (PARPi are effective in prostate cancer with BRCA1/2 and PALB2 mutations, not with other mutations in the HRD pathway). Of course, drug combinations, as CureMatch always suggests, may have a synergistic effect, but what about side effects? Especially with triplets…

“Feedback on My 17 Treatment Options?” (Brian McCloskey) [#15]

The second sheet has trials that I have found in addition to my “favorite” Ds-7300. No matter how diligently I looked for options other than targeting AR pathway, there are a very few, and if not AR targeting, then it is PSMA targeting. So, I have listed what could be promising (best at the top), even including a couple of trials for which I do not think you are eligible, just in case (shaded in grey), and some trials with new drugs that have no clinical results. I do not think that the last category trials are worth considering now.

My theoretical problem with targeting PSMA now is that it is possible that once you try one more treatment option, you may choose CAR-T, and if it is PSMA targeting, it is not a good idea to engage the same target twice. On the other hand, there are two more targets currently for CAR-T in CRPC: PSCA and KLK2.

Mainly I am concerned that there is a small chance that NCT03888612 will not find high enough expression of B7-H3 protein in a tumor biopsy, and other options will be needed urgently.

I also would suggest to consider seriously testing with Sengine, if a biopsy is at all possible, of course. (Not sure about this, because I have not seen your imaging results for 2022 at all…) Sengine will throw all the targeted drugs identified by CureMatch, for example, at your cancer organoids, and this will provide meaningful answers.

I would welcome any questions, of course.