“Adaptive Therapy” (Brad Power) [#10]

May 25, 2022
Brad Power

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Meeting Summary

In this meeting we discussed adaptive therapy, the approach described by Bob Gatenby based on evolutionary and game theory, which rests on four pillars:

- Low dose
- Drug combinations
- Sequencing (not a combination cocktail)
- Mathematical simulation models

Please see the notes from the last meeting for details.

Discussion

- **Drug combinations**: Everyone agreed that drug combinations that have a greater fit with identified biomarkers are preferred, but it is difficult to get oncologists to prescribe them. There should be trials that offer a couple of drugs, including investigational drugs. However, even if you want a combination of two approved drugs, they're considered a new drug (thereby lacking evidence) if you offer them together.
- **Sequencing**: While sequencing drugs makes sense in theory, there is little evidence to support it from traditional clinical trials, while there is evidence that combination drug cocktails provide better patient outcomes.
- **Mathematical simulation models**: Saed Sayad pointed out that the models that Bob Gatenby was using were very simple, and that models today are taking more variables into account, such as DNA, mRNA, and proteomics.
- **Obstacles**: Emma Shtivelman noted that physicians won’t prescribe drug combinations because there are few trials that have tested drug combinations. Even if each of two indicated approved drugs would provide a better outcome, physicians won’t prescribe the combination without clinical trial evidence. There should be clinical trials of drug combinations, including investigational drugs, but the obstacles are almost insurmountable. The combinatorics of a personalized treatment using multiple drugs at

multiple doses and different sequencing choices make it nearly impossible to use a randomized clinical trial to derive supporting evidence.

Requests

- Do you have any comments on adaptive therapy?
- This adaptive strategy seems intuitive, yet it’s not widely practiced. What are the barriers or objections to it?

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Meeting Notes

Brad Power: Today we're going to be talking about the presentation that Bob Gatenby made a week ago on adaptive therapy – using evolutionary and game theory to strategize about how to manage treatments. For those of you who weren't there, or didn't see the notes of the meeting, there are basically four pillars: drug combinations, low doses, sequencing, and mathematical models.

Saed Sayad: We were talking about old fashioned modeling, which is using mathematical equations to measure the change of the concentration of drugs in our system, in our blood. Based on that model, we can decide that when we reach 50% of the concentration, we can increase the dosage. This is kinetic modeling. This type of model is very limited because we now have huge amounts of data which are mixed data. We should be able to use those data and find the interaction between proteins and genes. And then instead of the simple mechanical mathematical model, we can use machine learning, data science, and predictive modeling to include many more factors in our equations.

Brad Power: In “The Signal and the Noise”, they talk about weather forecasting, and how the models get more sophisticated and the data gets more sophisticated. What I hear you're saying is that the standard of modeling today is to have many more variables in the model, instead of just a handful?

Saed Sayad: It’s the variety of elements in the model. It means it's not just a simple concentration of a drug; rather, it is about the interaction between different components of the cell, like the DNA, mRNA, and proteins.

Brad Power: Integrating all the different kinds of information you could be bringing together, such as different kinds of -omics, as well as medical history, has been a big theme for Brian. Emma Shtivelman, you put something in the chat last week about bipolar?

Emma Shtivelman: I asked about bipolar androgen treatment. It's sort of taking the evolutionary approach that has been proposed to an extreme. Not only do you do short time treatment in this case with androgen deprivation, you then flood the patient and the tumor cells with testosterone, hoping that this will prevent the development of resistance. The cells that were kind of responding to androgen deprivation will now flourish and the resistant clones will be pushed out of the picture.

Dr. Emmanuel Antonarakis is a big proponent of this approach. He reported some successes, particularly in patients who have mutations in the DNA damage repair pathway. It's literally case reports, not big studies, and after bad deprivation. He reported that patients in several cases responded well to immune checkpoint drugs. The first report was maybe nine years ago or so.

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Brad Power: Pete Kane, do you have any resources or people you've run into that might be able to help us with simulation models?

Pete Kane: Possibly. I'll give it some thought and see if I can make some introductions. Certainly there's been a wide cast of characters that we've encountered.

Brad Power: Ally Perlina, we have been having a conversation on drug combinations. We agree on that pillar of Bob Gatenby’s approach. But you challenged the notion of administering the drugs in sequence, rather than as a cocktail combination all at once. That's a very valid question.

I can represent Bob Gatenby's argument: He's saying that if you knock the population down successively, that's a way to get an extinction event. But if you hit the heterogeneous population all at once, up front, when there's a large population, you're going to get some resistant strains that are not going to respond. If you hit it with a combination, you'll get a better response. Progression free survival and the other metrics will look good, but you won't actually kill it off. There will be some resistant strains that are lurking there in the background, and they will eventually come back. When he talked about Brian's case, he said, “Brian, you have a low tumor burden. There's a low tumor population. You can go for an extinction, knockout blow if you take three drugs in succession.”

If Dr. Gatenby looked at the CureMatch drug combinations, I think he would want to do them in succession, not as a cocktail. I may be misrepresenting him, but I think that's the argument. Ally, you were saying there isn't any evidence to support that.

Ally Perlina: I didn't state that. I was asking because at a quick glance, we couldn't find any papers, but we may not have been thorough enough. I was asking if there's any clinical evidence to validate this theory.

Saed Sayad: I read the paper. They said that not only is sequencing the drugs important, but also the order. They were using doxorubicin and other CTL immunotherapy drugs. They showed that if you change the order, the effect is going to change. In many cases you can make a cancer cell uncomfortable, instead of killing it. Based on my research, this is a very new field. There are many questions, and few answers.

Brad Power: There's a specific example we've talked about. Rick schooled me on the notion of radiation turning a cold tumor hot, and then being responsive to immunotherapy. That would be a sequence of radiation followed by immunotherapy.

Rick Stanton: That's our hope. We looked at our immune deconvolution as assessed by Tempus RNA seq data, and we have very cold tumors. We have some evidence of cytotoxic T-cells in perforin and granzyme A (perforin and granzyme cooperatively induce target-cell death) that contradict that there's no CD8 T-cells. Nevertheless, it looks like we have pretty much no CD8 T-cells. Immune modulation without getting TILs into the tumor microenvironment is

probably not going to work. We need a prerequisite, which in our current thinking is radiation. It might be Pluvicto, which would come in and basically carpet bomb anything that has PSMA (prostate-specific membrane antigen) on it, and that would awaken or heat up the cold tumor. That would be perhaps the first step in what would be a great sequence. The second step would be immune modulators.

I'm very curious about what CureMatch and Ally bring to the table.

When I first saw the Tempus report with a super high BRAF expression for Brian, I took it with a grain of salt because I didn't get that section on overexpression in my Tempus report. Looking at the transcripts per million data that's coming out of Tempus for Brian, it was really apparent that his BRAF is off the charts. Either they made a mistake or that's very reportable.

That brings me into the whole concept of BRAF. Nobody is really hitting BRAF for prostate cancer. Why would this make sense? BRAF is a signaling molecule, or protein inside a cell cascade. It doesn't mean that you have activated or phosphorylated BRAF, it just means you have a ton of BRAF.

I make the analogy to a soccer game. At the cell surface an EGFR receptor kicks a soccer ball from the defense, to the midfield, to the strikers, down into the nucleus. Having a bunch of BRAF is like having a thousand midfielders, but it doesn't mean they have the ball. It doesn't mean that they're being phosphorylated and actively signaling. But Brian’s BRAF was not just a little high. It is like 10 times higher than anyone. It's off the chart.

Brian McCloskey: I’m something like number one out of 500 patients.

Rick Stanton: Yes. Brian is by far the highest of the 512 prostate adenocarcinoma patients (PRAD) in the Cancer Genome Atlas (TCGA) for BRAF. So you start thinking, maybe there must be some reason there are a thousand soccer midfielders there. That doesn't happen by chance. It made me very curious as to CureMatch bringing in BRAF inhibitors as potential therapies that I and the medical community would've never thought of. For Brian's case there could be a BRAF therapy in the sequence, if we kind of can adhere to Bob Gatenby's approach. In Brian’s case, maybe BRAF is a good idea.

Ally Perlina: Brian’s BRAF was overexpressed compared to the cancer cohort, and If it were compared to the normal tissue, it probably would be even more overexpressed. I can run another CureMatch pass with you with that data in mind.

We believe in molecular matching. Your molecular profile is an overall, mechanistic, biological picture of what's driving the cancer. You want to be able to interfere with that biological profile as a whole, as comprehensively as possible. If molecular matching is possible for BRAF, we know it's an oncogene, we know how to target it, and there are drugs available, then this would be a potential match, alongside other matches.

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The degree of matching has shown clinical correlation in prospective clinical trials.
The reason I have skepticism about delivering drugs sequentially is that the science says if you pick one target at a time from among multiple targets, you're doing a partial match. Partial matches correlate with poorer outcomes. When you just pick one, they may not live to try the next one. The sequential approach assumes that you can afford to try just one and there is no risk of giving a partial or a poor matching therapy. The data shows there is a lot of risk.

Brian McCloskey: I wonder if those clinical trials are not an exact match to Bob Gatenby's proposed process, because those patients probably did not progress to another drug until they completely failed the first drug in the treatment sequence. What he's looking at is you're not completely failing the first drug, you're waiting until you're progressing, like halfway down – whatever his mathematical model would be. You're progressing, but you haven't hit the nadir with that first drug. Then you're bringing in the second drug, and you're attacking that way. And then you maybe bring in a third drug. I don't know if that's what Bob's approach would be, but that's how I interpret it.

Ally Perlina: There are two points: (1) the types of therapy and (2) the number of lines of therapy.

On the types of therapy, the first line of therapy is usually going to be a broad action therapy, like chemotherapy or radiation, not a targeted therapy.

Brad Power: He's talking about advanced cancer, so people who are past the standard of care, so he's talking primarily about targeted therapies, not chemo.

Ally Perlina: The second point is that there was a publication with our approach applied to treatment naive patients with advanced cancers and complex profiles, but they did not have any prior treatments. It was published in Genome Medicine last October.
[Sicklick JK, Kato S, Okamura R, Patel H, Nikanjam M, Fanta PT, Hahn ME, De P, Williams C, Guido J, Solomon BM, McKay RR, Krie A, Boles SG, Ross JS, Lee JJ, Leyland-Jones B, Lippman SM, Kurzrock R. Molecular profiling of advanced malignancies guides first-line N-of-1 treatments in the I-PREDICT treatment-naïve study. Genome Med. 2021 Oct 4;13(1):155. doi: 10.1186/s13073-021-00969-w. PMID: 34607609; PMCID: PMC8491393.]

It shows an almost linear correlation. If you only partially address the molecular profile of the tumor then people do much worse. The progression-free survival and overall survival are poorer. And the more you match the profile, the better they do. It's not black and white. If you do a partial match, there's a worse outcome. If you do a semi-decent match, it's better. If you do a perfect match, it's a lot better. That's where the unexpectedly great results come from. That's why I was asking if the sequential theory has clinical trial results. We should be comparing on the same level, apples to apples.

Brian McCloskey: I don't think that data exists. I think that this would be a novel approach.

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I'm going to bring in the voice of Saul Priceman, who happened to attend Bob's presentation last week. Saul runs the Priceman Lab at City of Hope. He suggested a potential approach where I would take, say, Pluvicto to target PSMA, and then use some of the other data that I have about overexpression of certain genes to sequence in other targeted therapies. I know that there's a clinical trial that actually does this combination with Pluvicto and pembro. I've been on pembro, and I don't think that it is going to work for me, but potentially a combination of Pluvicto plus trametinib, which targets BRAF expression, and some of these other biomarkers. What do you think about that approach?

Ally Perlina: What markers do you have? it would make a lot of sense to take drugs which would target multiple biomarkers. The more of them the better.

Brian McCloskey: AR, FANCA, and BRAF showed up.

Rick Stanton: If you go into the immune modulators then, B7H3 is super high, and Brian's androgen receptor is also, wonderfully high and targetable. Those would pop off the top of the list. Even if it was cold.

Brian McCloskey: You suggested, for example, like Apalutamide to target that, which would make sense.

Ally Perlina: Then if you combine it with trametinib, it would be very analogous to some of our matched options.

Brian McCloskey: Let me push this just a little bit more. As far as I know, the only trial that Bob has done is the one that he presented last week, using abiraterone. There were only 19 patients. I thought that the outcomes were very compelling. But what we're talking about now is not monotherapy, we're talking about leveraging CureMatch’s combinatorial drug approach, looking at multiple targets. How can we build a proposal that would leverage CureMatch’s approach for targeted drugs? I would probably throw Pluvicito in there for me as well. I know that that was not part of your solution. The reason I would throw Pliuvicto in is because we do have this issue that I have a cold tumor, and potentially that would make it hot. How can we get some support to combine your approach with Bob's approach? Because intuitively both of your approaches make sense. And they seem very symbiotic.

Ally Perlina: Here's how: you try one drug, and then you add another one in a week, and another one in another week. Therefore it's sequential. Problem solved.

Brian McCloskey: I like the math – every seven days.

Ally Perlina: We do our own mathematical modeling on the fly here.

Brian McCloskey: Have you ever encountered this sequencing approach, rather than the all in one?

Ally Perlina: Our approach basically doesn't agree. It's not that symbiotic to what we see as the approach that is having more reception and adoption in the field. It is a wave that is coming up. It's not easy in the medical system to get two or three drugs right away for any patient. And it takes some hoops to jump through. The drug acquisition specialist can make the molecular justification case for molecular indication of combinations of drugs, but it is doable. Our reality seems so different from the sequential approach.

Brad Power: One of the examples that Bob pointed to was pediatric leukemia, where the standard of care is 12 sequential therapies over a one year period, and it's curative. That was one evidence point that he cited.
Emma, since you've seen so many patients over the years, what do you think about this question of combinations and sequencing?

Emma Shtivelman: I'm in absolute agreement with Ally about the advantage of using combination treatments right away. But most of the time it's not possible. Sometimes it's like pulling teeth. Once in a while, I would see a patient that has two targetable mutations, and I will search for trials. And I will find a trial that miraculously offers two drugs.
For example, I worked with a patient who had an EDID1 mutation, which responds in that type of cancer very well to an ATR inhibitor. And there was also HER2 amplification present. And there was one trial that offered both drugs, which was ideal. I was so excited. She couldn't get into this trial, no matter what she tried. So she is receiving one of the drugs in a trial. She's doing well so far, but it is very frustrating. None of her oncologists would prescribe both drugs. The ATR inhibitor is not approved. It's very unfortunate, in my opinion.
The CureMatch approach is correct, but it depends on the oncologist to prescribe. And that often doesn't happen.

Brad Power: One of the key questions Brian has raised is: the adaptive therapy approach makes intuitive sense, yet we don't see it in practice. Why?
Whether it's combinations, sequencing, or low dose, they all seem to make sense from an evolutionary and game theory perspective, but getting them into actual use seems to meet with resistance. It's like cancer resistance: most of the doctors and the system are resistant.
Emma, when you look for a clinical trial with two drugs and you can't find one, what's going on, why is that? Even though it looks like it would be best for the patient.

Emma Shtivelman: There are not that many trials that would offer two drugs based on the presence of two mutations. The old NCI-MATCH Trial (Molecular Analysis for Therapy Choice trial), and there are others (e.g., PUR), offer one drug starting seven or eight years ago. It was huge progress because suddenly there was a realization that if there is a targetable mutation, we can hit it with one drug. You give the patient some respite from progression, and sometimes with the best targeted drugs you get a pretty good response that lasts. If a patient is lucky, it is maybe two years, but usually it is much less. Usually it's a month.

Can you devise trials considering that, as we mentioned, that oncologists are reluctant to prescribe two drugs? Can we devise trials that will offer drugs, including investigational drugs, combinations based on the presence of more than one mutation? What do you do with the patients who don't have more than one targetable mutation? It's not trivial. And the trial system is so slow and inadequate that it is mind boggling, but there should be trials that offer a couple of drugs, including investigational drugs. The obstacles are almost insurmountable because even if you offer two approved drugs, they're considered a new drug if you offer them together.

Rick Stanton: I chose a clinical trial of a three-drug combination (PD1, an, adenine inhibitor, and, docetaxel, which is chemo) because my doctors all said I should get on a clinical trial with a docetaxel backbone, and I personally knew the company, Arcus, running the clinical trial. But it's randomized, and it's not double blind. I got randomized to the docetaxel arm only, just because I was unlucky. Even if you find a combination that makes sense and you meet all the eligibility requirements, you may get randomized to the other arm.

Tony Crispino: The development of clinical trials have control arms for a reason. We have to have those control arms, and, unfortunately, we can't select being on an active arm of a clinical trial because that's simply just not the way it's done. We have to have the control arm to go ahead and make sure that we're following the same criteria for both (a) the control arm and (b) the experimental arm. It's very important that this randomization takes place to bring the integrity of the trial to where it can be practice changing. It's very difficult to tell a patient who got onto a clinical trial, but they ended up in a control arm, that they ended up in a good spot. Technically you did, because there's another side of this trial: it can fail, and the drug isn't effective, in which case you were receiving comorbidities and side effects from a drug which isn't going to help you. It's important just to know that the purpose of a clinical trial is not to provide treatment, but to provide an answer to a question. In this case the particular question is: can we combine this drug with this drug, and compare it with the standard of care, which is based on docetaxel? That's the question, then what are you comparing that question to?

I don't know if you guys are familiar with PICO or PECO or Picos (the Population, Intervention, Comparison, and Outcomes). This is how scientific questions are asked, and it's how we develop questions. Every time we do a clinical trial, those questions are the key for you to look at. It’s not, “Is this trial going to provide this drug and this drug, and that's how I get those drugs?” You have to look at the question that's being asked for that clinical trial to understand. Rick, as bad as it is that you think that you got onto the control arm, you're actually playing just as important a role as the active arm. I know that that's not something to cheer about, but it's very important that we have you there.

Brad Power: You responded to Rick's specific frustration.
There was a more general question that prefaced that, which is that there is resistance to drug combinations. Let's take Emma's example. We have a patient who has two mutations, and we'd like to be able to have that patient get access to two drugs, but there's no oncologist that will prescribe it. There's no clinical trial because those two drugs have never been combined before. Any thoughts about why the system systematically won’t allow that, when it seems like it's

common sense from the patient's point of view? There's another good on the other side that's going on. Do you have any comments on what's going on there?

Tony Cripsino: The reason why clinicians are negative about going forward and just doing it is a question of ethics. The negative effects have not been explored. A clinician is going out on a limb and prescribing something that's outside of protocols or guidelines. Anytime you step outside of a guideline, you're stepping into a higher risk situation for both the physician and the patient. The safest thing to do is to keep them within the guidelines of what's proven. When we write the guidelines, we talk about the insertion of trials because there's no real general benefit to picking and choosing which patients you're going to be doing this with if we're not trying to do it in research. Typically our statements in the guidelines will say, if you're going to do something different here, do it within a clinical trial.

That is in the guidelines for physicians to follow. Any physician can add onto this, but this has been a tried-and-true methodology that we follow now. Does this mean that every time we get into a circumstance of a new experimental drug, we're near the end of life for a patient that we might give that a shot? That's entirely up to the stakeholders. That would be the clinician and the patient themselves to try something like that. But in almost every instance, it's going to be to try to develop the hypothesis, put the question to it, put it into a trial, and give the equal arms an equipoise within the trial to try to arrive at something that can change practice.

That's changing practice. What you're asking for is can we change the direction of an individual anecdotally? That's very difficult.

Brad Power: What we're facing here is that if you take a personalized approach of multiple drugs at multiple doses and different sequencing choices, the combinatorials that creates would make it difficult to use a randomized clinical trial to derive supporting evidence. The number of patients you would need in a sample to make it valid and achieve evidence over a multi-year horizon would mean that it's not going to happen in that patient's lifetime. It's like a clash of strategies.

Emma Shtivelman: Logistically it's very difficult to run a big trial like that. The MATCH trial is run by NCI, which obviously has some power, and they offer single drugs. They have agreements with the manufacturers to offer these drugs in the trial that may or may not produce some meaningful results. But if you are talking about combinations, the trial will have difficulties to accrue patients because they will have a list of say 30 targeted drugs and patients who have mutations in two of the targets for which there are drugs. It is not a very high probability that patients can be found with that profile to be directed to the trial. The problems are tremendous.

Brian McCloskey: Ally, I'm sure this is a problem that you have come across. Your whole business is based upon combinatorial approaches. How is CureMatch thinking about increasing the penetration rate of its solutions with patients and with physicians?

Ally Perlina: We're trying to help or empower the system from different angles. One is, of course, physicians. We help them make the case to get the drugs. It does work; it is just more difficult. It's challenging to get many drugs at the same time. Let's just say at least for your case, for Rick's case, for these cases, just because something is challenging, doesn't mean we're not going to try it.
From the company perspective we're approaching this more from a medical institution level. We're talking to different centers, showing our evidence. It's not just anecdotal. We point to the evidence and see if there could be a bigger partnership for adoption through the NGS companies. Some of them put us on their test acquisition form. They take care of the actual journey from when the physician orders NGS, and we're the next bus stop.
In tandem, if there's anything to CureMatch, then we will produce a report. That just makes it a little bit more habitual and seamless for the patient and the doctor.

Finally, and very importantly, we're in the process of getting our CPT code to help with reimbursement, which also helps with credibility.

And we have a new type of solution, a value calculator, where for any ranked number of options it can rank the value, which is a combination of the money it's going to cost for the score for any given option. If two options are extremely close, we provide alternative drugs. I've shown that before, but if all things are almost equal, or equal in terms of the molecular match, what would be the most realistic sort of affordable option to get?

The overall value is the financial value plus the clinical value, and the calculator will offer the best balance.

We're going to be approaching payers more. We already had some presentations and early evaluations from independent parties that say that this might actually be very promising.
One more point about the evolutionary perspective, which comes from a study that is not published because it was confidential: there was longitudinal data, like I've never seen before. We saw six, seven samples for some of the patients, and we had no patients with less than four longitudinal samples, with treatments in between. It was about half a year to a year apart when the samples were taken. We saw that there are mutations that appeared in the beginning that disappeared for the two next rounds, then reappeared for the two final rounds. We saw the treatment history, and it was very clear that they saw this one and a few others, but they only picked the EGFR inhibitor, and nothing else. EGFR markers or related markers went away, did not get detected, or maybe just barely passed the limit of QC for the clinical lab sequencing detection, and didn't get reported. Then it came back, and that happened in a whole cohort. It was solid tumors with clinical data collected from a medical institution. And at CureMatch. A lot of times we get Tempus reports that summarize things more conveniently. We don't get six longitudinal samples there, but it's quite frequent that we see three. And when we see three, we see that some mutations from the first round disappeared on a second round of testing and reappeared again. And sometimes there is a little fraction that really varies, like it barely passes. That leads us to believe that when there's some population of a tumor with a driver, even if that driver is targeted, I don't think there's any evidence to believe that you completely extinguish

that cancer population. And in the meantime, while you're targeting that driver, other ones completely take over because you're ignoring the other drivers. That is also shown in longitudinal data. Even though that is not published, I can point out that it's from real data.

Brian McCloskey: I want to see if we can get to some action here because I see some opportunities, and I don't want them to be obscured. First off, do we all agree that a combinatorial approach makes sense, and going after one target is not the answer?

[Group raises hands in agreement.]

Brian McCloskey: Ally, how do we work with you to create a virtual tumor board where we can have your entire team or the appropriate people work with, I'll just say for now, Rana McKay at UCSD, my doctor and Rick's doctor, to go through and have a conversation about what this approach is, and how we can put it into action for me, or for Rick, or for whomever. How do we create a success story, and how do we get focus around creating a success story for your solution?

Ally Perlina: We're creating our success story just fine. I worry more about creating a success story for your and Rick's cases. That's really why we're here. If we can help, and it's successful, the rest will take care of itself. If it's really something that makes a difference, it will only be a matter of time until more and more people are convinced. It can happen sooner, or later; more publicity now, less publicity later. I really don't want to put that as an objective. For you guys, before we solve all the world's problems, it's just getting more precision-oncology-minded physicians to the table discussing your next treatment strategies.

It could be some of the physicians from UCSD, if they're available. If you look at the papers that I just shared this morning, some of the co-authors or the lead PIs on the trial are actually practicing oncologists that are very much focused on precision oncology, as opposed to being focused on one type of cancer.

If you can get these clinical minds in the same room, their word will go much farther than mine or my team’s, because it's more peer-to-peer, oncologist to oncologist. I'll be happy to participate if there's a tumor board discussion. That's where you'll see what they're willing or not willing to suggest and what your doctor is willing or not willing to do.

Brian McCloskey: Obviously creating solutions for Rick and for me are paramount. Maybe I need to chat with Rana about how we convene some sort of virtual tumor board.

Brad Power: Regarding access to custom treatments, there’s expanded access, compassionate use, and N-of-1 clinical trials. If a doctor, like Rana McKay, was willing to go to bat for something, she can essentially create a personalized clinical trial for you. There's a bureaucracy that surrounds that, but it's doable. Then you could be the success story role model that others could emulate.