“Getting Access to Your Cancer Treatment" (Chris Beardmore) [#73]

Brad Power and Vanessa Hugo
October 18, 2023

“I would generally argue that a lot of therapies that are out there today may have been developed in the old traditional approach where you've run a trial, and you've basically said this therapy is more effective in, let's say, greater than 50% of the population. And as a result, it may not necessarily be as effective as pursuing something which is more targeted.” – Chris Beardmore

“The biggest problem we face right now, as GBM patients, even if we can get xCures, Cancer Commons, Anova, or whatever other organization to recommend these combination therapies for us to try, whether they're still investigational or off label, is just the access. It's unreal, the barriers we face in trying to get access.” – Vanessa Hugo

“We're really good if a tumor board or a group of professionals has come back and said, ‘Hey, if you can find an MDM2 targeted drug, that would really help John Doe. Please get out here and help us do that.’ We can get those on clinical trials or in compassionate use in 60-70% of the cases we request.” – Chris Beardmore

“What we should be probably moving to is something we call ‘n of 1’ – get large volumes of patients moving through their journey, and then look for the signals of where they're finding success and double down on those areas.” – Chris Beardmore

Meeting Summary

Advanced cancer patients and their caregivers who are highly engaged in finding ways to treat their disease can get special tests done (like “functional testing” where drugs are tried on live tumor tissue) or get drug combination suggestions (from services like Cancer Commons or CureMatch). They can decide which treatment recommendations are the best for them and attempt to pursue them, but they are often confronted with the challenge of getting access to treatment if it is “off label” (FDA-approved drugs that have not been approved for that application).

Chris Beardmore, CEO and Co-Founder, Anova Enterprises, Inc., is uniquely qualified to provide valuable insights and practical tips to help navigate the healthcare system. His background in the regulatory system and clinical trials has allowed him to run down all the paths that can get patients and caregivers the drugs they want. Anova is operationalizing treatment access, especially to treatments outside the standard of care.

Why might patients want to get access to drugs outside the standard of care (off label)?

- The standard of care guidelines are out of date.

- The standard therapy may have been developed in a traditional clinical trial approach which has shown that the therapy is effective in greater than than 50% of the population, but may not necessarily be as effective as pursuing something which is more targeted.
- Novel tests point to a therapy that is personalized, but it has never been run in a clinical trial to bring that therapy into the standard of care. For example, for patients with a brain cancer like glioblastoma (GBM), there are some patients who may not respond well to the FDA-approved first line standard of care chemotherapy temozolomide, based on their “MGMT methylation status”. (MGMT is an enzyme which causes resistance to chemotherapy by compromising a DNA repair mechanism.) For those who may not respond to temozolomide, targeted therapy may be worthwhile.
- The prospects with the standard of care treatment (e.g., a 20% success rate) are not good enough for the patient and caregivers.

What are typical barriers patients and caregivers face in accessing personalized treatments outside the standard of care (off label)?

- Regulators won’t approve them due to safety concerns.
- Physicians won’t prescribe them due to safety and liability concerns.
- Insurance companies won’t reimburse them due to cost concerns.
- Pharmaceutical companies won’t provide the drugs due to profit concerns.

How can patients and caregivers access non-standard treatments they think are best for them?

- Pursue patient assistance programs from manufacturers – pharmaceutical companies have protocols for providing access to a therapy, especially if a patient needs financial help.
- Find and enroll in clinical trials
- Take advantage of “compassionate use” or “expanded access” (a process provided by regulators for a patient with a serious or immediately life-threatening disease or condition to gain access to an investigational medical product for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available)
- Negotiate with insurance companies

How does Anova help patients and caregivers (and physicians) access non-standard treatments that they believe are best?

- **Patient Assistance Programs:** An example Anova has seen is patients getting access to pembrolizumab (Keytruda) through Merck’s patient assistance program when their insurance company has refused to authorize it. A billing professional can reach out to the patient assistance program and ask for the drug.
- **Clinical trials**: Anova is running three clinical trials for patients with newly diagnosed glioblastoma (brain cancer): a cell-based therapy, an immunotherapy, and a small molecule that crosses the blood-brain barrier. They are also helping non-small cell lung cancer patients with a unique biomarker (an EGFR exon 20 insertion mutation) access a targeted treatment made by a Chinese pharmaceutical company (Dizal Pharma). Anova works with contract research organizations and Dizal to open up study sites within 5-10 working days. Dizal provides robust funding because they see value; while a trial may

cost a half million dollars to run, they're losing a million dollars per day that the drugs are not on the market.

- **Compassionate use**: Anova has operationalized compassionate use opportunities with companies like Kintara Therapeutics, which is developing novel solid tumor cancer therapies; Epitopoietic Research Corporation, a Belgian pharmaceutical company; and NeOnc Technologies, developing intranasal inhalation dosing therapies for the treatment of brain and lung cancers. A patient newly diagnosed with a Grade 3 astrocytoma (a growth of cells that starts in the brain or spinal cord; there's no cure for grade 3 and grade 4 astrocytomas, as they grow and spread quickly.) underwent standard of care treatment but wanted to also pursue a therapy targeted at a genetic mutation (IDH1). Anova got her compassionate use access to a targeted treatment made by NeOnc Technologies - an inhalable version of perillyl alcohol. She has been receiving that therapy now for 10 months with no evidence of progression.
- **Negotiation with insurance companies**: The physician of a cancer patient with glioblastoma recommended bevacizumab as a second line therapy. Bevacizumab costs about $14,000 per month and doesn’t confer a survival benefit. Anova requested that the insurance instead cover a different targeted drug that matched the patient’s particular tumor mutation. The targeted drug costs $2,000 per month (vs. $14,000), so the insurance company agreed.

Anova occasionally works with individual patients through agreements with navigation groups (e.g., Private Health) or pro bono, ad hoc.

Call to Action: How can patients and caregivers make access to personalized treatments easier in the future?

1. Lobby politicians and regulators to ease access to personalized treatment options.
2. Create and join “basket trials” (designs in which a targeted therapy is evaluated on multiple diseases that have common molecular alterations), “virtual trials”, or “learning systems” to track real world experience of what is working and not working for each patient. For example, the Musella Foundation has been running a virtual trial learning system, a registry of brain tumor patients where the treatments they do and the outcomes are tracked.
3. Take advantage of existing programs, like the FDA’s Project Facilitate, set up to expand access to investigational cancer products. Anova’s compassionate use requests can be approved in as little as two hours. Rather than investing millions more into finding new therapeutic targets, patient assistance groups (e.g., Anova, xCures, Cancer Commons) should join together in funding more compassionate use programs for the targeted therapies that already exist.
4. Develop a guide to physicians willing to treat patients off label. For example, Glenn Sabin and colleagues are developing a list of “pioneering prescribers” who are open minded about providing access to compassionate use drugs and combination therapies.
5. Don’t participate in a clinical trial from a pharmaceutical company that doesn't have a compassionate use program. As long as they are getting enough patients to fill their trial, they should be able to make extra doses available to those who ask.

6. Grade academic medical centers on how many clinical trials they offer for all patients for all lines of therapy. They should offer a minimum of 40 phase one clinical trials and 200 trial offerings.

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Meeting Notes

Discussion Outline

1. Access to cancer treatments off-label. (0:03)
2. Improving access to clinical trials and managing complex regulatory approvals. (3:23)
3. Access to therapies for aggressive diseases. (7:36)
4. Personalized cancer treatment options. (13:28)
5. Personalized medicine and patient empowerment. (18:21)
6. Personalized medicine and patient advocacy. (22:21)
7. Personalized medicine and patient advocacy. (28:17)
8. Personalized cancer treatment and collaboration opportunities. (32:53)
9. Improving access to cancer treatments through education and collaboration. (37:43)
10. Improving access to experimental treatments for life-threatening illnesses. (42:52)
11. Improving access to clinical trials for patients. (48:24)
12. Cancer treatment decision-making and progression. (53:14)

SUMMARY KEYWORDS

patients, GBM, work, drug, therapy, groups, compassionate, physicians, trial, biopharmaceutical companies, access, mutation, clinical trials, fda, disease, chris, approved, ucla, treatments, patient assistance programs

SPEAKERS

Chris Beardmore (77%), Brad Power (10%), Vanessa Hugo (4%), Brian McCloskey (3%), Glenn Sabin (3%), Rick Stanton (2%)

MEETING TRANSCRIPT

Brad Power

We're honored to have Chris Beardmore with us. Chris is the Co-founder and CEO of Anova Enterprises, which, among other things, helps patients get access to treatments. He works in clinical trials. He'll describe his background in greater detail, but it is a very important part of the process for us as advanced cancer patients.

I was introduced to Chris Beardmore by Chris Schuler, who has been very helpful with introductions for us and is working in brain cancer and fundraising. I was very taken by Anova’s services because early on in our journey, we worked closely with CureMatch, which recommends drug combinations that match patients’ biomarker profiles. Drug combinations offer, perhaps, a more durable response to patients. But most of the clinical trials that come up that get drugs approved are monotherapies where they are treated by themselves. When you're using the scientific method, you want to control everything else and just test for that one thing. The result is that most of the randomized clinical trials have approved the drug as a single therapy at maximum tolerated dose. Drug combinations actually are a good option, but there's limited randomized clinical trial evidence for many combinations. Increasingly, they're running

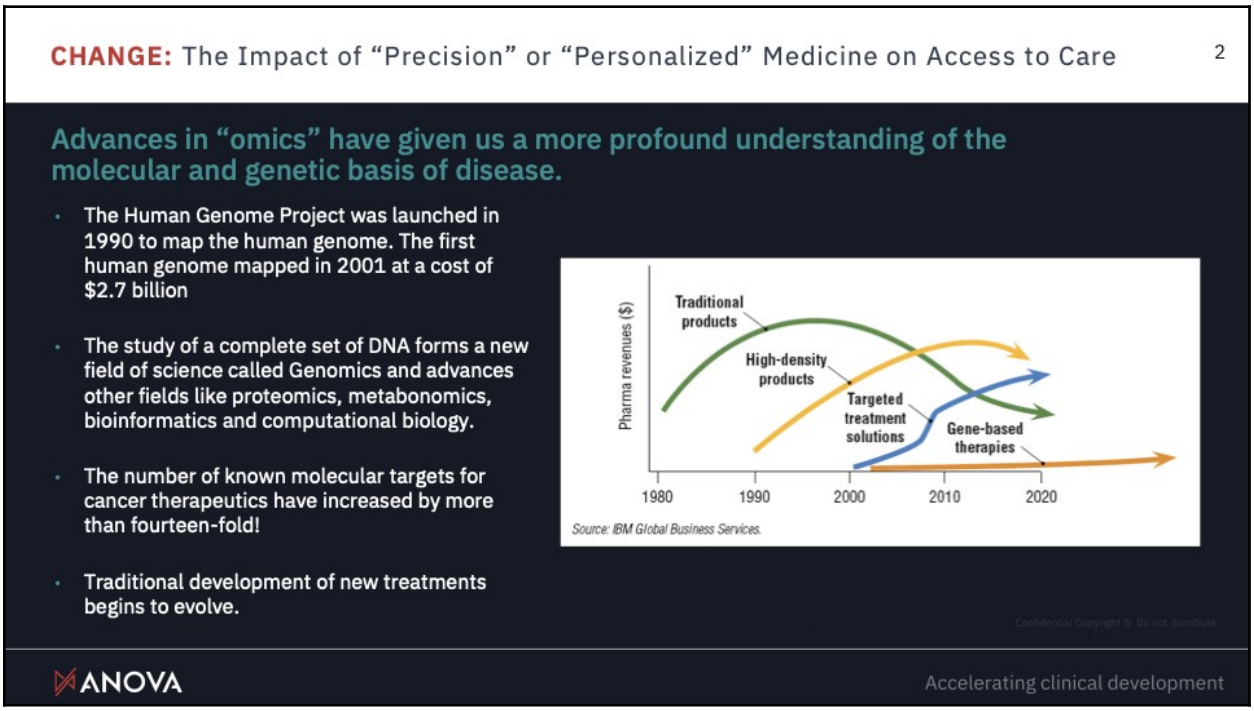
trials with immunotherapies plus something else, but many aren't. The CureMatch combinations are often what are called “off label.” There's no evidence that a clinician can use to prescribe them. So they will hesitate to prescribe that even though the patient may have decided that's really what they would like to use. The issue of access once you've decided what your best treatment option is, is a recurring one for our patients. I saw that Chris had some ideas on how to cut that Gordian knot and help people get access. His company does a lot of other things. He'll tell us about that.

The issue of interest to most of our patients would be, “How can Chris help us get access to whatever it is that we want, when it may be off label?”

Chris Beardmore 3:23

I'm a regulatory person by training. I started my career running IRBs (institutional review boards) Animal Care and Use (looking out for humane treatment of animals), radiation, and safety committees at the University of Maryland, at UCLA, and for the Department of Defense. A lot of that work early on was about access. At the University of Maryland, not only were we dealing with an AIDS epidemic, and what are you doing with combination therapies to try and address HIV, and what was creating individuals who were so immune-suppressed, but also emergency room research, tirilazad mesylate (a drug for the acute treatment of brain and spinal injuries and strokes), and a lot of work in the “golden hour” (the period of time immediately after a traumatic injury during which there is the highest likelihood that prompt medical and surgical treatment will prevent death) came out of that institution. At UCLA, a lot of the work was around new drugs like targeted therapies like Herceptin, Patrick Soon-Shiong working on islet cell transplants, artificial hearts, things like that. And compassionate use became something that we did quite a

bit of. For the Department of Defense we were working on biowarfare protective products – what you do when you have national emergencies and may need something like an anthrax vaccine or an emergency use authorization of a COVID vaccine. When I left academic medical centers, I started building cancer centers and was focused on how to improve access to clinical trials both with an idea that participation in studies probably improves outcomes. Some of that is probably related to improvements in technology and the precision medicine transformation and how products are probably hitting targets more effectively theoretically and resulting in better outcomes. But it also probably comes from the rigor that's applied to clinical research and compassionate use, that if you have to report adverse events, you have to deal and manage those adverse events.



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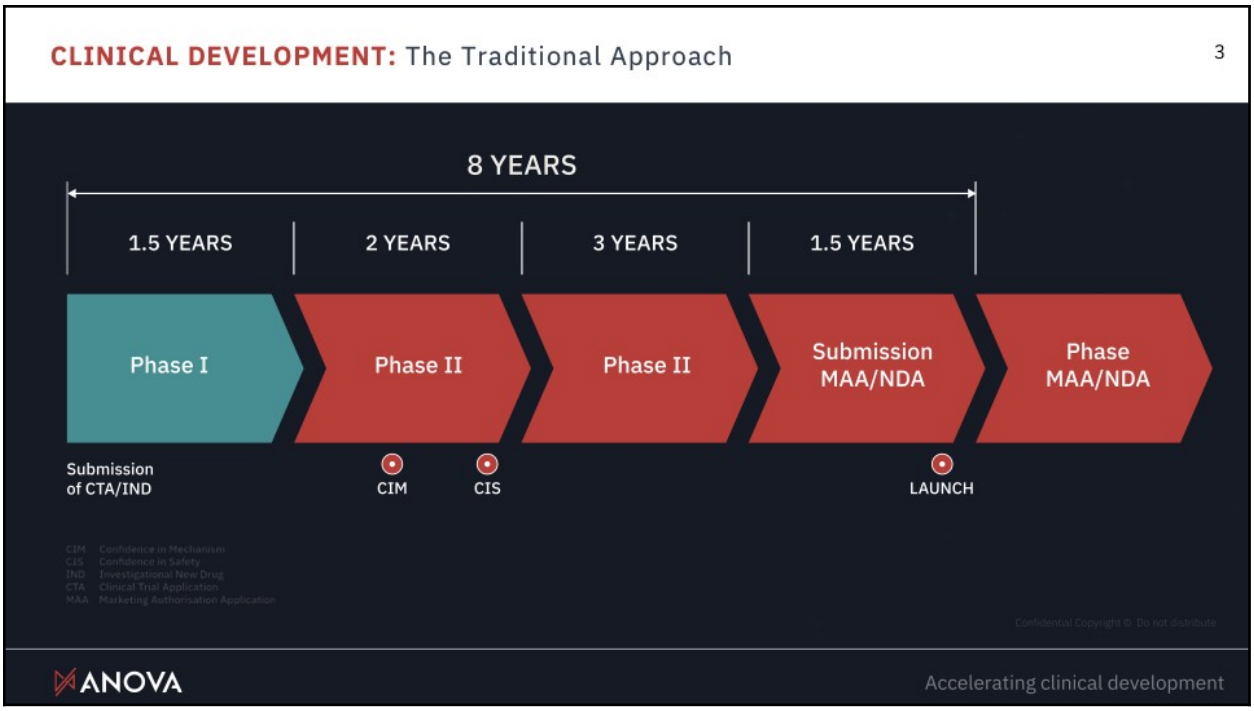

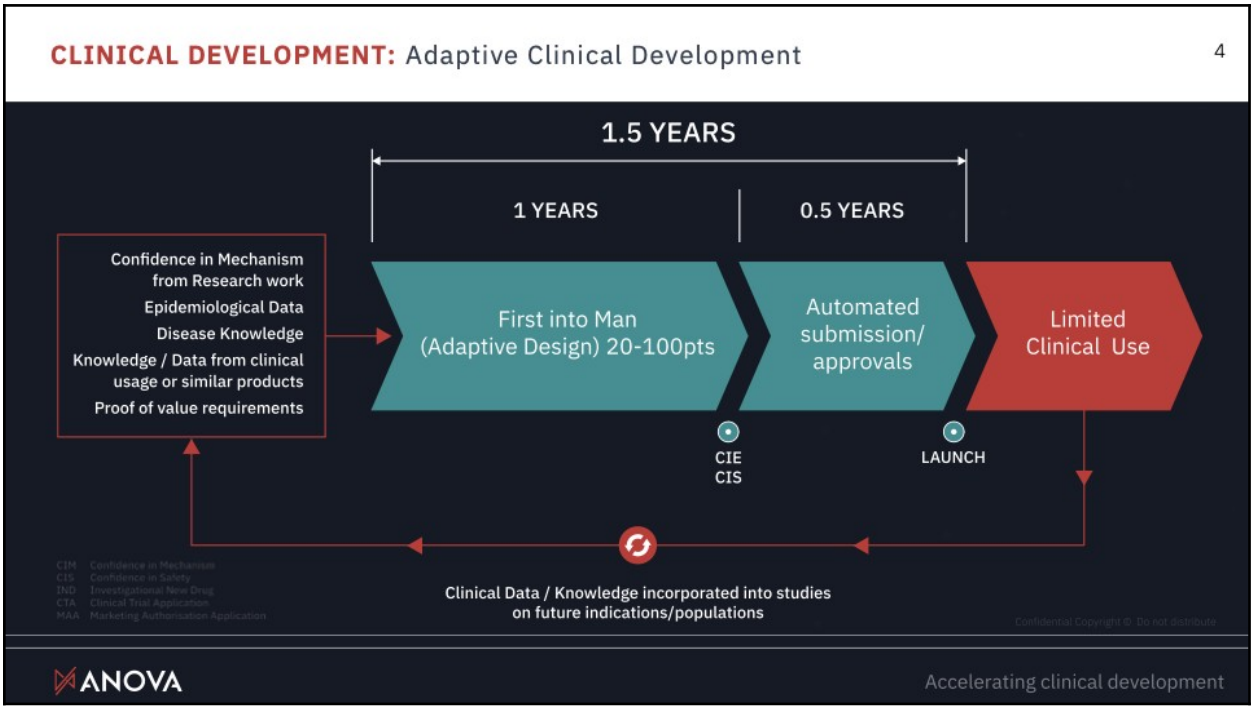

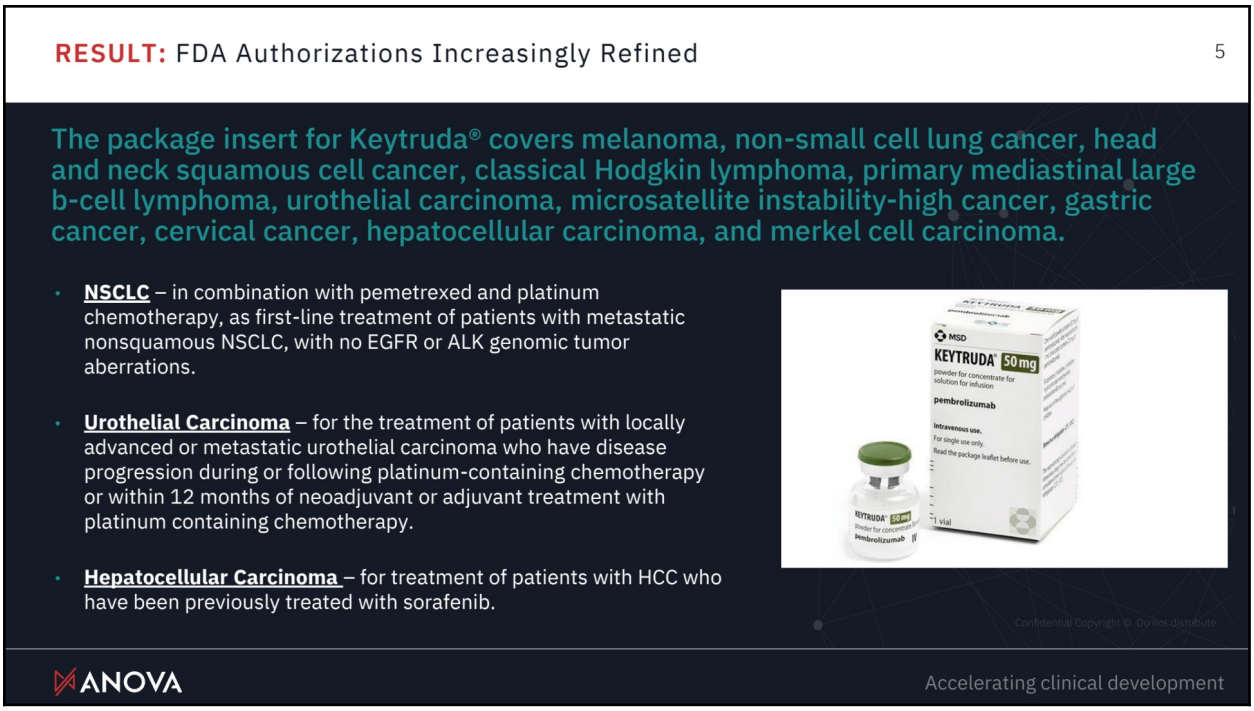

I think everybody understands that, ultimately, precision medicine has created a world where we are looking at therapies that have increasingly refined FDA approvals. I'd like to point to this one – the approval of Keytruda. Right now, the package insert, which is the document that's inserted into each vial of Keytruda, has all of the approved indications for the therapy. What you used to see would be an approval of a drug for a wide target population. You might see something like approval of a drug like sunitinib (Sutent) for, say, second line colorectal cancer. What you're seeing in these targeted therapies are package inserts that cover a large number of diseases. Here, you've got Keytruda already approved for melanoma, non-small cell lung cancer, head and neck, squamous cell cancers, liver cancers, and cervical cancers. Each of those individual treatment patient populations have very specific lines of therapy and other requirements. In non-small cell lung cancer, one of I think, three approvals is in combination with Pemetrexed, a platinum-based chemotherapy, as first line treatment, so long as you don't have an EGFR or an ALK mutation. So what a patient needs to do in order to become informed, or a physician to ultimately keep all of this straight, is becoming more complex. I would argue that at some point, we're going to be past the ability of the human brain to really manage this.

Chris Beardmore 7:59
If you look at the different ways that people can gain access to therapies, I largely think of them in these four categories.

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Certainly there are **FDA-authorized or approved products** that are out there. Patients should be discussing treatment options with their physicians all the time to figure out what's approved or what's about to be approved. However, having said that, I would generally argue that a lot of therapies that are out there today may have been developed in the old traditional approach where you've run a trial and you've basically said this therapy is more effective in, let's say, greater than than 50% of the population. As a result, it may not necessarily be as effective as pursuing something which is more targeted.

For example, I've been talking quite a bit with people in the glioblastoma space. If you look at the Stupp protocol, which is the regimen they use for all patients with newly diagnosed high grade brain tumors, gliomas, they will resect the tumor if they can, and they will administer radiation and temozolomide (a chemotherapy) based upon a study that was issued nearly 20 years ago. In the end, more patients will do better with that regimen than not. What is clear now that we're in this era of precision medicine is that a lot of things impact whether or not a patient is going to respond to temozolomide. Methylation status of the MGMT promoter is a big condition there, or whether or not the tumor can be impacted through radio sensitization, that sort of thing. You're beginning to see other mutations leading folks to believe that maybe it would be worthwhile to pursue targeted therapy in a world where effective first line therapy is pretty limited.

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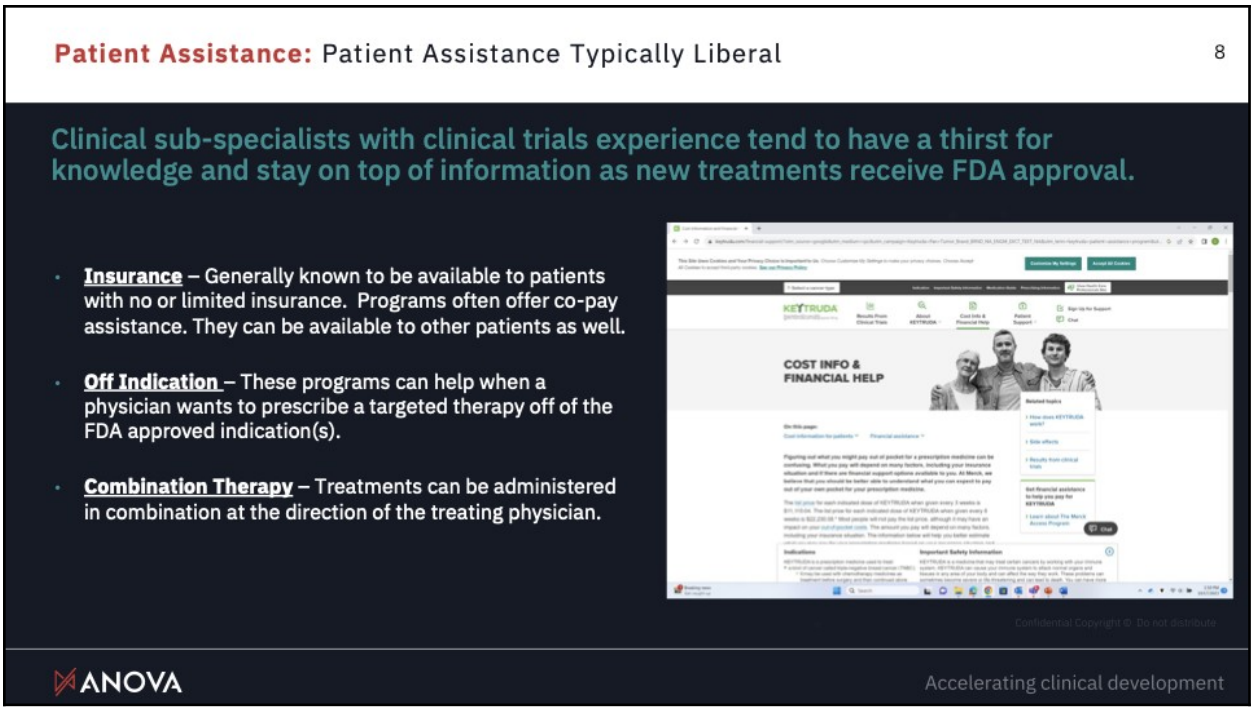

Just because the therapy is out there doesn't necessarily mean an insurance company or a physician is going to be eager to go find it and prescribe it. One of the things we often do is look towards **patient assistance programs**. There are a lot of times where biopharmaceutical companies will provide relatively easy access to a therapy, especially if a patient isn't making millions and millions of dollars. So a good example of that would be Merck and Keytruda. We've seen a number of patients with glioblastoma who have been able to get pembrolizumab (Keytruda) through these patient assistance programs when their insurance companies have refused to authorize it.

Of course, **clinical trials** are a good way to access care.

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Clinical Trials: Access vs. Suitability

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Patients who participate in clinical trials do better than those who receive standard of care. This is likely due to the rigor/oversight of clinical trials and improvements in treatments.

- **Access** – Clinical trials are mostly activated in the traditional fashion. The right clinical trial may or may not be available where a patient receives care. Plan ahead and be comfortable transferring care for a trial when appropriate.
- **Plan for Trials** – Clinical trials have inclusion/exclusion criteria. Getting the order right is important. Patients who wait until end of standard of care often miss out on trial opportunities. Patients who participate in clinical trials can still receive standard of care treatments.
- **Combination Therapy** – Insight can be gained as to use of treatments in combination. Review clinical trial opportunities to guide standard of care therapy.

Compassionate use is a good way to access care.

Compassionate Use: Access for patients with serious or life-threatening disease

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Compassionate use can go by many names globally: expanded access, compassionate use, ministry of health approval, named patient program, right-to-try, special access scheme.

- **Insurance** – Insurance companies love a good deal. Sometimes arguments can be made for cost effective compassionate use over expensive standard of care therapy.
- **Not for FDA Approved Treatments** – Once FDA approves a treatment access is typically through patient assistance rather than compassionate use.
- **Plan Ahead** – Office of Inspector General says 120 hours spent by clinical team and biopharmaceutical company to deliver compassionate use. Need 30-45 days to deliver product and time for treatment to work.

As Anova works with sites, physicians, biopharmaceutical companies, and patients, we tend to focus our efforts on those three areas of patient assistance, clinical trials, and compassionate use.

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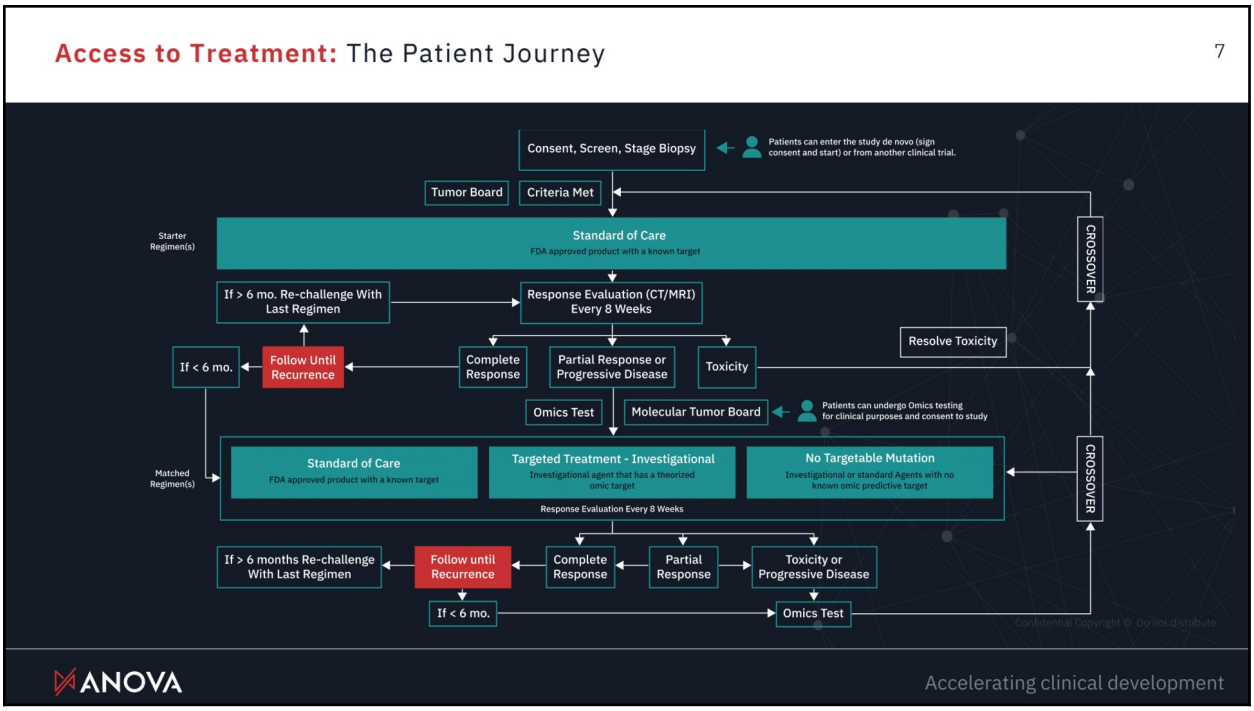

I tend to view the world in this way, particularly in the diseases that are aggressive or are metastatic in the way of cancer, or let's call it those that are serious or life threatening.

Patients are going to enter a world where they should have, at this point, some sort of multidisciplinary team talking about what it is that they should think of doing. For patients who have things like breast cancer, or prostate cancer, where there's been a lot of money, a lot of traditional research done, and a lot of therapeutic options, the idea that **multiple experts** will come together and help inform where to start with standard of care becomes important.

The second thing that I get into with folks is to make sure that there's a really strong and disciplined approach to **measuring progression** of disease. The number of patients we talked to who say, “Oh, I get scanned, you know, twice a year,” even though they know they have metastatic breast cancer. I go, ‘Why are you waiting?’ If a disease is progressing, and getting larger or metastasizing, the number of times you can turn the engine and try other therapies is limited. In the clinical setting, one of the things that's a bit surprising to me is that - to use cancer as an example - radiologists don't always use very precise measurements to try and assess progression. So in clinical trials, you'll get RECIST or you'll get RANO measurements that are very explicit, they track X number of lesions and X number of origin groups and they ultimately come back and say, “Okay. Your disease has gotten 5% larger or 10% larger, let's switch therapy.” Whereas in the clinical setting, a lot of times we see a pathology or radiology report that looks a whole lot more like a lot is happening, but I'm not quite sure. Maybe you should talk to your doctor about what to do next, which is less helpful. But anyway, my point here then is once you get into this world of standard of care and a group of people, or yourself, are inform your physicians what you want to do, the question then becomes, as you progress, can you move in a directed fashion from the things that are approved that we know have a high

likelihood of working. If you're going to get a first or second line therapy, and that therapy has an 80% chance of working for you, by all means go with the standard of care. It's got a high likelihood of being successful. If that doesn't happen, then I would argue that targeted therapies, even if they're investigational or used off indication, is a way to think about addressing a progressive disease. If not, then go to the things that are more non-targeted in their approach.

You can run through these loops in a very systematic way and attempt to land on those therapies that are most likely to generate a complete response or a partial response or move away from toxicity to those things that work.

Brian McCloskey 15:23
I really like your last slide. Thanks for putting that together. It's a really succinct way of looking at a patient's decision-making process.

How do you model that? For example, if a patient were to come to you and say, “Hey. I've had these six or seven lines of therapy, some are standard of care, some are targeted, etc.” Then they also provide you with targets that are based upon DNA alterations, RNA alterations, RNA expressions, proteomic expressions, or other data. Could you model for the patient what is the next best treatment option for him or her?

Chris Beardmore 16:09
The short answer is I think that's the Holy Grail. That's the brass ring. The short answer is that we can't at the moment, although we are moving in those directions.

Two areas where Anova has been focusing our efforts are in the adult high grade glioma environment, the glioblastomas (brain cancer), and in Lou Gehrig's disease, ALS. I would add a couple other ones, such as pancreatic cancer, where you can do the same sort of thing. It's much, much harder when you're looking at breast cancer, prostate cancer, or colorectal cancer these days due to just the sheer volume of therapies that are out there.

But the short answer is right now we've been trying to load the system in those areas where we've been focusing with a large number of opportunities so that when patients hit these inflection points, that we can meaningfully help.

As an example, in the GBM (glioblastoma, brain cancer) space, we're running three clinical trials for patients with newly diagnosed glioblastoma. One is a cell-based therapy. One is an immunotherapy. One is a small molecule that crosses the blood-brain barrier. We then have pursued second and third line opportunities, as well as relationships with companies like Kintara Therapeutics, which is developing novel solid tumor cancer therapies; Epitopoietic Research Corporation, a Belgian pharmaceutical company; and NeOnc Technologies, on their compassionate use opportunities to sit back and say, “Look. Eventually the standard of care is limited in this area.” Beyond the Stupp protocol, probably Bevacizumab, which doesn't change survival, it just kind of improves symptomology and maybe CCNU/ lomustine, these kinds of chemotherapy drugs are relatively toxic. There's not a lot for a patient with GBM. So you almost

want to consider clinical trials early. You want to try and do things like look at biopsies and look at the mutation burden and H3k27 and IDH1 mutations, and then try and come back to people and go, “Well, here are your options. Which ones of these do we think are most likely to be effective?” In the end, I think that's going to be essentially a learning system.

I guess the question is, “Who controls and manages and works within that learning system?” From discussions we've had with Tempus, Foundation Medicine, Caris, and other kinds of proteomic and omics providers, whether that's DNA, RNA or quantitative proteomics, in some way they believe that it will be them. But I'm not positive that's the case.

What we should be probably moving to is something we call “n of 1” – get large volumes of patients moving through their journey, and then look for the signals of where they're finding success and double down on those areas. Yes, some of that will certainly be genomic, but some of that may be the order of therapy. Some of that may be anatomical and access. In GBM, maybe what treatments can you really deliver across the blood brain barrier? the short answer is, that's where we all should be running towards. In the meantime, patients are stuck in this environment where the best they can probably get is a multidisciplinary team that says, “I think the next best thing for you is x.” How can Anova provide access to those therapies via whatever, by hook or crook, so to speak?

Brian McCloskey 19:50
What you're saying is very consistent with our philosophy and what we're trying to do, but it is very complicated. It's a real challenge to build a real world evidence database that can provide the foundation to build models, which can then be used for decision analytics and to help patients. We’re not there.

Chris Beardmore 20:14
Correct. And the FDA is shying away.

Brian McCloskey 20:17
There are a lot of barriers, even when a patient such as myself brings a ton of data to the table with recommended treatment options. There is still this preference almost, or bias, towards the standard of care, towards chemotherapy, as opposed to a targeted immunotherapy or something like that. There are a lot of dynamics at play, but empowering patients to make these decisions is really, really important.

Chris Beardmore 21:01
100%. You're absolutely right. Look at those incentives. Do I blame a physician at Duke or Hopkins or UCLA – I'm just randomly throwing names out – not that any of them have behaved well or poorly. They are faced daily with clinic schedules that are going to be 20 or 30 patients. Let's say that they buy off on all the literature you bring in. You haven't brought them, “Let's grind up peach pits because the arsenic in there will help us all out.” You brought in something that's truly evidence-based. Now you're going to ask them to begin doing work. In the patient

assistance world, that means getting a billing professional to reach out to that patient assistance program and ask for the drug.

A lot of them are doing it effectively. There's a client group we have in Los Angeles, called OPN, and they take on financial risks. They're working with insurance companies, and they're just responsible. If you get cancer in these insurance programs in Southern California, you may land in one of their practices. They will sit down when a drug is requested off indication by their physicians, by patients, whatever and say, “Look, is it reasonable? Is there any evidence that this would work?” If it meets NCCN Guidelines, all the better. If it doesn't, then the question is, “Is there anything known that's better out there?” If you can make the argument, then they're totally willing to go to an insurance or to a biopharmaceutical company and say, “Hey. Can I have access to a PI3 kinase inhibitor? Because we see that target here, and we've looked at the Caris result, and the active driver this tumor appears to be this PI3 kinase mutated variant of the disease.”

Similarly, we were surprised we had a very large insurance company, where the standard of care for this brain tumor patient, this GBM patient, second line was Bevacizumab. The cost of Bevacizumab was $14,000 or $15,000 a month, something like that. And it doesn't change survival. We wrote a note to the insurance company and said, “Look, I can get compassionate use of this drug from this other company for this particular mutation. They want to cover the cost of their drug; it's $2,000 a month versus $14,500 on average. Would you be willing to cover that cost?” And they said, “Yes.” That's a shocking development, but a shocking good development. We're going to see more and more of that happening.

Compassionate use right now is still incredibly burdensome on everybody. A compassionate use request takes around 120 hours on the site side and a similar amount on the sponsor side. At Anova, when we got out of the gates, we sat back and said, “Well, we'd love to have a learning system. We'd really love to help patients make better decisions on what's the next thing in their journey.” But you can't solve the operational issue of every study being available at every site. You don't have to have a patient move from site to site. For example, in LA moving from UCLA to USC to Cedars Sinai is not an easy exercise for a patient or their family or their caregivers. You've got to solve the operational issues first and then you can start building the other pieces.

That's where we are in our particular journey at the moment, which is we're really good if a tumor board or a group of professionals has come back and said, “Hey, if you can find an MDM2 targeted drug, that would really help John Doe, please get out here and help us do that.” We can get those on clinical trials or in compassionate use in 60-70% of the cases we request. We've been doing that ad hoc pro bono, as we learn and try to bring to the world a transformative way of working.

In the end, this is all going to work very similarly to, let's use Uber, the car driving service, as an example. When they were early on, they set up a black car service in New York and San Francisco. You could get a relatively wealthy person who needed to get around the city a ride.

But eventually, they had enough cars and enough whatever, that the path of least resistance was hopping in an Uber versus a taxi cab. Eventually, that's going to be happening in our field.

The genomics or the omics providers are not going to be able to keep carving up the landscape the way they have. They're going to have to come together and provide an informative report to physicians and patients that lets them know what they could consider acting on. Then there will have to be other groups like Anova, who are in the mix here, at the site and the sponsor level, delivering those trials in real time. We're getting there. A year and a half ago, it was all wonderful theory. Now we're doing a lot of this.

Brian McCloskey 26:17
You got your finger on the pulse. Thank you for all that you're doing. You're heading in the right direction.

Chris Beardmore 26:24
I'm not entirely certain that you can make wrong decisions if you're a patient. If you look back at MD Anderson, MD Anderson ran a trial about 10 years ago where they had a phase one program, and they randomly assigned patients to whatever was the next phase one study that had an open slot versus one where they had a tumor board sit down and make an informed decision as to what it was that would would best help the patient. It wasn’t all that surprising to find out that if you had a tumor board, who said, “Oh, this person has an ALK mutation, this person has an EGFR mutation, let's put them on the new EGFR-targeted phase one study”, they did better. They did better, like 30 or 40% above the other population. Patients should be constantly doing this.

I'm doing it today with my mother who has a fairly rare mantle cell lymphoma with blastoid characteristics. It is a very aggressive, very terminal disease. They're all talking about, “Let’s rechallenge with the BTK inhibitor that we tried before,” that didn't work. Well, she won’t be at that facility much longer. I will transfer her to a place where we can try something else. It may be CAR-T therapy, it may be another targeted agent, but I believe we will get a better outcome than trying the same old stuff because it's just the easiest thing to pull off the shelf.

Vanessa Hugo 27:56
Of your patient population now, can you break down the percentage of what type of cancers you are addressing? You named a few that you're focused on.

And as a practical matter, how do patients engage Anova? And what's the associated cost?

Chris Beardmore 28:19
Right now about 30% of what we're doing is in the GBM space, and then the rest of it is going to break down following through the diseases of cancer that are bad. Pancreatic cancer would be next, colorectal, and non-small cell lung cancer. About 10 to 15% of what we're doing is in the neuro space.

Weirdly, when we launched the platform, it was about a month before COVID. Originally, we were almost 99% patients who had COVID infections that were on ventilators delivering Risperidone (a drug for schizophrenia, bipolar disorder, and irritability caused by autism). Celularity had a program with natural killer cells that was very interesting.

The short answer is: we don't do a lot of marketing, and we tend to drive towards, again, those diseases that have limited outcomes.

On our side, we care very much about what the drivers are, and we think that the drivers, like that Uber analogy I was giving you earlier, are going to be the drug companies who have the resources to develop their products and are looking for more efficient ways to find out whether their treatments are safe or effective. Sites and site networks, where we have a number of customers, are doing that; that includes groups like Mary Crowley in Texas where we have all of their phase one studies available for patients. It includes groups like QCCA and Exigent, which are networks of community practices, and then academic medical centers and hospitals like Hackensack Meridian Health in Jersey or UC Irvine, where we have a good relationship with Daniela Bota and others there.

Lastly, we have the patient thing. We have two types of patients that get to us. We have agreements with groups like Private Health, which are patient navigators. They're groups that sit down and say, “We're going to go out and get all of the omic testing we possibly can, and we're going to use that information to make some recommendations with patients and their care providers.” They hire us to go find those therapies for them.

We also do pro bono stuff for patients as well. We probably have between five and ten at any one time.

The short answer for you is: “I don't know exactly who it is in your family or what you're dealing with, but if you send a summary to me via email, I'm happy to provide some options and do that to try and help out.” We're making plenty of cash on the GBM studies we're running for sponsors that are helping us to learn and do more of this.

Eventually, our goal in the next year or two is to have what we call our “ENPI” operating, which would be a place for patients to be able to come in and say, “Hey, look, this is my situation, where would be a good doctor for me to go? Because my physician has said, they're just not interested in anything other than standard of care.” We didn't think we needed that originally, but unfortunately, we're finding that some physicians are not movable. Giving patients the ability to get to a like-minded treatment provider seems to be of need. We hope to have that up in Q1 of next year.

Brad Power 31:44
That's been an interest of ours. We may have talked about it. I know Glenn Sabin has been interested in pulling something like that together as well. A common problem is, “We know what we want, but we can't get a doctor to prescribe it.”

Chris Beardmore 31:57
Totally agree. I'm in public here, so I should be a little cautious with my language. But we have run into physicians who will lean into this. I believe Daniela Bota at UC Irvine in the GBM space. Sam Singer, who's actually at Northwell Health is an amazing individual. Frances Chow and Tom Chen at USC. There are a lot of places that I think are willing to help. It's just, how do you make those connections?

Brad Power 32:33
You have referenced a few case examples. Would you mind taking one or two patient stories from “soup to nuts”, so that people here can imagine what that journey looks like and working with you?

Chris Beardmore 32:53
There's a patient MB who lives in Portland. She was diagnosed with a Grade 3 astrocytoma (an aggressive brain cancer). She went ahead and did her surgical resection and treatment with temozolomide (a chemotherapy). She approached us and asked if we could help her. She worked with that group I mentioned, Private Health. Private Health came back and said, “We think these are the following most optimistic targets for her.” One of those in her case was a mutation called IDH1. One of our clients is a group called NeOnc Technologies. They have an inhalable version of perillyl alcohol. Her physicians up there in Oregon and Northern California were not supportive of the request. She ended up with a physician in Southern California named Jose Corrillo, who works with a guy named Santosh Kesari at St. Joe's Hospital in Orange County, and they put in a compassionate use request, which we approved, and she's been receiving that therapy now for 10 months with no evidence of progression. I'm not sure how long she'll receive benefits, but it's been going swimmingly for her as best I can tell.

Another example, on the other side, we've done quite a bit of work for companies that have drugs that are targeting EGFR and HER2 mutations, in particular exon 20 insertions. One of the things that we're doing right now for a Chinese company called Dizal is working with sites to identify in a just-in-time fashion those patients who have non-small cell lung cancer, who are newly diagnosed for one of their trials, or are in the second line therapy, who share that EGFR exon 20 insertion mutation. We've now identified and enrolled patients at five sites over the last two months. We don't do genomic testing. They're getting a report from Caris or something through their physicians, but when the physician cares enough for the patient to say, “Hey, look, how can I get access to this?”, we've set up with the CROs (contract research organizations) and Dizal a mechanism to have that study open within five to ten working days. We use private IRBs (institutional review boards), which tend to be faster. We have an accelerated clinical trial agreement template that we use, so that we don't have to go back and forth and negotiate nonsense and contracts. We have a robust budget so that the sites don't have to complain at all, we just need to get this done. The company (Dizal) seems to care and see value because, they might spend an extra half a million dollars running the trial on site startup fees, but they're going to lose a million dollars a day if the drug is not on the market, frankly. So let's get the thing done and identify the patients as quickly as we can.

Brad Power 36:19
I would like to migrate this conversation into how we might collaborate. Vanessa Hugo is a personal instantiation of the expansion we at the Cancer Patient Lab have into GBM, which you've mentioned is your primary area. We're setting up a discussion forum on our online discussion platform, where GBM patients can come together and share announcements of things they've seen that are going on in the world, advice as you are just giving, for example, about who are the good doctors, which might be the good facilities, what are the good tests, what are the good treatments, or whatever it might be. We are working with Cancer Commons and the Musella Foundation. They are advising people on molecular biology and treatment options. We're putting together a suite of services, and it would seem that yours would be complementary. There's some overlap on some points, but then the way that you're getting into access is unique and distinctive to our group.

Any thoughts on how we might work together?

Chris Beardmore 37:38
We're seeing a lot of folks wanting to have something happen. I think Chris Schuler is one of them. Obviously, that's how we got connected. We've met amazing people who are now the survivors of family members who've passed from, say, GBM, such as Barb Crowell in Orange County. Her husband had a GBM, and they were probably the most informed and aggressive in pursuing therapies. He lived for quite a long time, due to their impressive efforts. Tarek Hallal, who lost his son in San Diego, who's somebody who's gone on into Congress, and is looking for funding and all of that. My point is, we've already begun trying to bring those groups together. I'd be happy to hand them to you all.

One of the pieces is: is there an information and education source for patients that ultimately can help them get an idea of the landscape? While some of those resources exist, certainly there's clinicaltrials.gov, and cancer.gov at the NCI, it's not quite what people are looking for. So that needs to happen.

The second thing I was getting at is: we should all be working together to find a way to do some sort of “basket trial” or “learning system”. There's no reason at all why we should be exposing hundreds of patients to standard of care arms that they don't want anyway, and that are really slowing down these trials. The FDA is being very subtle in their language. We have to work pretty cautiously through this. Because the FDA views, for example, real world evidence as unreliable data. That they equal the same thing because nobody's checking it. Nobody's filling gaps in the data. Nobody's monitoring it. Nobody's querying it. If you talk to FDA and say, “Let's build an external control group, that is in fact monitored,” and that we could use to advance all of these therapies in a bad area – pancreatic cancer is one, GBM would be another – then you could create an acceleration in learning that would be pretty darn impressive.

The short answer is, for those who want to do education and websites, that's not what Anova does. We've just been trying to fill the gap because so many patients come to us, and they're just frankly confused about what to do, from the beginning to the end of that journey.

But when it comes to those adaptive trials and going back to groups like Tim Cloughesy and the group at UCLA that put together an adaptive GBM thing that's been running for seven years, we haven't seen an actual protocol yet. Let's get those things done. If we can help them in any of those ways, we're eager to, and I did send an email last night. I'm happy to share with Vanessa, if she'd like to join the group, or you guys want to. We just want to jumpstart that discussion and get them going while we try to figure out the operationalizing of access. Because that is what will come crashing into each other over the next year or so.

Vanessa Hugo 41:13
I’m trying to bite my tongue over here because all that really resonates with me. If you haven't met Al Musella, you definitely need to connect with him. Because your learning trial and the learning system that you discussed is something that he has. He had his own brain tumor virtual trial that he ran through his website for years, and that amassed thousands of patients. He came to the point where he realized, “This is bigger than just GBM. This requires advanced AI, to match those omics with those combination therapies.” He helped spin off xCures, if you're familiar with xCures, and he's a consultant for them now. That's what they're trying to do. I don't know how much I can share about it, because not all of it is public. But that very much is the future, whether it's through xCures or through another company.

The biggest problem we face right now, as GBM patients, even if we can get xCures, Cancer Commons, Anova, or whatever other organization to recommend these combination therapies for us to try, whether they're still investigational or off label, is just the access. It's unreal, the barriers we face in trying to get access. My husband flew to UCLA today. We're in Florida, and he's flying to UCLA just to establish patient care to see if he potentially could enroll in a trial at recurrence.

Chris Beardmore 42:51
It is frustrating. It’s part of why I was saying we've been doing a little bit of work on the ALS side. These serious and life threatening illnesses tend to do something which is somewhat unique, and that is they’re horrific experiences for people. But the second thing is, until now most of those patients pass away. When they pass away, people don't necessarily want to dedicate the rest of their lives to the suffering they just went through. So they lose their voice. And that voice is hard to convey going forward, but is important.

I would never – and I mean this as a hard statement, I'm going to say it as a “never” but I probably don't believe this – participate, if I got a GBM, in a clinical trial of a company that didn't have a compassionate use program. You don't get my benefit, I'll go pass away quietly, somewhere. Because the obligations need to be there. You can see a lot of this behavior. Biogen did this. It's well documented in the press. I'm not giving away anything. We worked with a woman named Lisa Mauriello, who had a SOD1-mutated ALS, and they wouldn't give her

compassionate use. Their trial was fully enrolled. They claimed there were all kinds of unfair reasons why she should get access to the drug while there were people in a standard of care arm that was “watch and wait”. My point was, nobody wanted to deny her a chance for a good outcome. It's hard, but the GBM community, the pancreatic cancer community, the ALS community, the Duchenne muscular dystrophy community, these groups are going to get to a place where they say, “No longer. You can make an extra 5,000 doses and so long as we're accruing the trials, so that you get your answers as quickly as you can, and we get these drugs approved as quickly as we can. You owe us something slightly in return.” We'll see. I believe that'll get there.

Vanessa Hugo 45:06
One thing, which we've experienced firsthand, is getting expanded access to investigational treatments. For example, for a drug we wanted to access in a phase two trial, we reached out to the manufacturer and said, “Can you create an expanded access program for those that don't qualify for the trial?” The response we got was, “We don't even have enough money to complete our phase two trial at this time. So we definitely don't have money for expanded access.”

Chris Beardmore 45:34
That's exactly the sort of thing that we could fix. I don't want to be hard on people, because groups like PanCAN and ASCO do amazing work. But could those groups come together with a pool of money that helps biopharmaceutical companies to manufacture enough drugs for a compassionate use program? If we did have an expanded access IND, could we talk to the FDA about how to make all of those products available when patients have run out of options? I don't think that the FDA would want to turn any of that off. I go to friendly social events, and people say, “We'd have a cure for stuff if companies really wanted it.” And I go, “No, you guys are insane. If I could make the cure for GBM today and have it approved, I'd be one of the richest people around. Trust me, I would love to do it if I could.”

The FDA is not looking to say, “No,” either. Richard Pazdur set up Project Facilitate. They review and approve compassionate use requests that we give them in usually around two hours. That's how fast the FDA can move. And they do. They don't disapprove hardly anything. We do very, very informed requests. I would have the experience of them approving everything we submit, because we're really good. But my point is it's not the experience where they just tell us to shove it, and a patient should go off to hospice.

These groups should come together and say, “Look, I'm not going to invest another $3 million into basic science work to find a new target, when I've got 40 companies who have drugs, and they just can't get them to patients, because we have a manufacturing issue here. Let's get that run done, and let's get those products out.” Or let's put, I don't know what it's going to cost, you know, $300,000 into a compassionate use program, and three administrators who process those cases for those companies and collect data, so that we know in real patients how they do.

In the end, xCures, Cancer Commons, and Anova should all come together in one big solution, because we do a better job of getting treatments to patients in real time. They're doing amazing

things in their journey, work, and their data work. The stuff that xCures is doing around children with diffuse midline gliomas is important, and the academic medical centers haven't solved those issues.

Glenn Sabin 48:24
We are trying to develop a list of what we call either “pioneering prescribers” or “n-of-1 prescribers” that are open minded to providing access, not only through compassionate use, but also combinations, etc., whether these are academics, or more likely community providers. You mentioned a few names, and if you'd be willing to share any additional names maybe offline via email, or what have you, that would be wonderful, because that really is a challenge.

Then you have the challenge of the reality of the economics when the community provider, who is typically even more stressed than the academics when they're investing the unbillable time to go after these agents or combinations, and discuss it internally through tumor board meetings to feel somewhat comfortable, or comfortable enough to pursue this. They also don't get reimbursed or paid for the drugs. There's no way to mark that up based on how they get the drugs.

These are some of the rate limiting factors, but I think that starting with a list of prescribers would get us further along the way to then being able to address these other factors.

Chris Beardmore 49:58
I agree, and I'm happy to help. In the end, that's the sort of transparency that we're hoping that we'll see. In a world where you have drug companies on one side, or medical device manufacturers, you've got sites and physicians on another, and you've got patients and maybe regulators. Those four groups. The question is: in a world where you don't know anything about what's going on, who's responsible for what doesn't happen? Right now, they all point at each other.

The “right to try” debate was mostly about pharmaceutical companies saying, “If it wasn't for that darn FDA, I'd have a compassionate use program.” Now we've got “right to try” and “single patient expanded access” and all kinds of mechanisms that would work. Now it's about, “I don't have any drugs”, or “I don't have a person who can process that request.” I see everybody being graded.

Is an academic medical center a leading academic medical center if they don't have a robust offering of clinical trials for all patients down all lines of therapy? You can't open 20 studies a year and think you're going to be great. I was shocked. I had a call with an academic medical center in the, let's call it, mid-south of the United States. And they said, “We have a wonderful phase one program here for our cancer patients. We have three open and accruing phase one trials.” And I said, “I have no idea what you're talking about. That's not success. How many people are going into three trials with three patient cohorts? Six a year? You're an academic medical center covering a state. You need 40 phase one clinical trials and 200 trial offerings.”

And we're fighting over governing law in a contract. We're fighting over a study startup fee of $15,000 versus $10,000.

If every patient could go into a clinical trial, first of all, you would probably have a lot more free drugs provided. So you would have a decrease in cost to the healthcare system overall. A lot of those sites are exposed to risk. They buy that drug from Cardinal Health, or AmerisourceBergen, or whatever. If they don't get reimbursed, they pay for it. So they've got to collect 11 times, let's say, for every patient that does not pay them. And then the studies are robust. A phase one trial in cancer might pay $40,000 or $50,000 a patient who's on trial. So if you sat down and said, “All the people that we gave an off indication drug to went on a clinical trial with that drug”, instead, you would get a research payment, you would get free drugs, and you would get all the clinical billing for all the scans and laboratory and doctor stuff that you normally do. That's a much better financial picture for a site than where they are today.

Rick Stanton 53:28
I really liked your flowchart. That was really cool. I've done flowcharts similarly. I saw the ability to overlay something like a Napoleon war where the width of the line was the number of soldiers in the battle, big at the beginning, and small at the end. You could maybe show rather than all the same width lines, the paths the patients tend to go down, like this is one patient, this is 100 patients.

Chris Beardmore 54:32
That’s a really cool idea. I agree. That's in Tufte’s book (The Visual Display of Quantitative Information). I'll take a look at it because in the early part of a disease, by definition, in theory, you should be pursuing probably more standard of care options than not, although I would argue that those standard of cares plus or minus a research drug would be helpful, particularly if your chance of efficacy starts dropping below 60%. That would be, that would be great. I'm going to try and get that Tufte book.

Rick Stanton 55:19
That would be one part that would be handy. The other would be the decision criteria to move left or right, to make a decision. Which path? That's what we were all talking about.

Chris Beardmore 55:40
That's a hard one. I would love to talk more about it. There was a guy at the FDA, whose name is going to escape me, but who eventually I think went over to Flatiron Health, who had a very decent program where they were trying to look at decision-making in medical record data. Flatiron had a large source of data from community oncology practices. One of the things that they were trying to do was, say the imaging occurs, and then the patient does something. Either they stay on the therapy they were on before, or they transfer over to some other therapy. Long story short is that in the medical record data, they said it was pretty hard to figure out why a decision was made, because there were a lot of cases where scans would show progression, but a physician decided to keep treating. I would bet that the reason why is that a medical oncologist will make a decision sometimes that slow progression is better than unfettered

disease progression. Though they're making some of those decisions, I'm not positive those communications are always with patients where they sat down and said, in the most binary sense, “If I can prove that you've got a new site of disease, or you've got progression of any tumor by 10%, do you want to switch therapy?” Patients would probably almost always say, “Yes, or keep what I'm on and add something to try and target that new thing.”

I want to put some time to your thoughts there because it's a very smart one. I'm just not quite sure how you define the lines when patients might have different opinions as to what they want.

Glenn Sabin 57:40
But does slow progression always equate to failed treatment these days?

Chris Beardmore 57:46
Correct. It's like a slow progression of disease in children with diffuse midline gliomas that have recurred where their chance of survival past five months is near zero. Getting to a year or two years is quite meaningful, even if it never stops. There's a lot to happen in how you evaluate how disease is progressing. You may have noticed that there's a new RECIST version 2.0 that just came out, I believe, or RANO 2.0. My point is they still consider stable disease to be not a response. We're going to have to figure that out. Because it's an equivalent of what my dad said when I was a kid: if I can get somebody to give me a loan today for a billion dollars, and I have to pay it back $1 a month, it's a great loan. If I could get my disease to stop spreading, one day, I'll die of a heart attack or get hit by a bus. That seems like a pretty good option.

It was just published by Patrick Wen at Harvard:

> *RANO 2.0: Update to the Response Assessment in Neuro-Oncology Criteria for High- and Low-Grade Gliomas in Adults*

“Getting Access to Your Cancer Treatment" (Chris Beardmore) [#73]