

How Do Research Ideas Make It Into the Clinic?

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Dr. Dunbar: Hello again. I have the privilege and the pleasure to introduce one of my colleagues in the country. Dr. Tim Cloughesy is going to be speaking to us about how research ideas actually get into the clinic.

So a little bit about him. Dr. Cloughesy is a professor of neurology at the David Geffen School of Medicine in the University of California, Los Angeles. A member of the UCLA Brain Research Institute and Jonsson Comprehensive Cancer Center. He also serves as director of UCLA's neuro-oncology program and co-director of the Brain Tumor Center. Lastly, he directs the Henry Singleton Brain Tumor Research Program. But that's just a drop in the bucket of all the ways he helps brain tumor patients. With no further ado, come on up, Tim.

[Applause.]

Dr. Cloughesy: Thank you, Erin, so much. Thank you, Jeff, as both of you setting this up as co-chairs for the ABTA. Ralph and Emily and Nadia and Nicole. It's a great privilege to be here; thank you all for showing up. I know that it's a Friday and tomorrow's a Saturday and yet, you guys are here which is really amazing. So I hope there are some things that we can share with you.

I didn't come up with this title, but it's a really good title and it made me think a little bit about what I needed to present here to you all. And I hope what I present makes sense. I try not

to pull and soften any of the science. I want you to hear it, I want you to try and digest it as best you can, because I think it's really important to understand it as best we can.

Okay, so with that will move forward, good. So these are my disclosures; they're always good to share in case I'm saying something, you say oh look, you (inaudible 00:53:19) from this group, I don't like that. But anyway.

So this is the development process. When we think of how drugs -- how do we choose drugs, how are we thinking about drugs, we have to start with a process that we have a target of interest. And that target sometimes is druggable, sometimes it's not. But if we can create a drug for it, we then can move forward and find out with some of the models that we have; whether or not these models are showing the benefit with the drug that we're using. And if they are, then we go through this process where we try to make sure the drug is safe for patients.

And in doing that, we go through what we call an IND Enabling Process, where we give it to animals, make sure their organs don't fall apart in any particular way and make sure that we know what doses we can give. And it meets all the criteria for us to start giving it in humans. And then we start this process in humans where we do a Phase One study, increasing doses, trying to understand how much drug we can get in. We also get information about -- not only is it getting in, how long does it stay in there for, what are the interactions it might have? And then what are some of the side effects that it might have as we're getting drug [sic] into the patients.

We hope that we find some early evidence of some effect and then we usually like to transition into the later stage, which is going to be the Phase Two or Phase Three evaluations.

Where we're trying to find out is does the drug do something of value to the patient? And eventually, is it better than the standard of care.

And that's then where it enters and gets to you guys. So our goal is to try to find good things, bring it through that process as quickly as possible. And part of the problem is; it's expensive. This process takes a lot of money. In particular, the last part of this -- the Phase Two, Phase Three -- can easily cost over \$300 million dollars to do.

If you're a company and you've been looking at brain cancer saying, "You know, they haven't done as well as we'd like them to do." That's a big risk to go in. So somehow, we have to change that, we have to alter that in some way.

I want to present to you one; an example of a setting where science helped to find a unique target and that a drug was made and moving forward as an example of how do drugs get into the clinic.

And then I want to provide for you after that, once we identify these, what are going to be ways that we can make it cheaper? That we can make and allow for more opportunities for companies to want to get into brain cancer and evaluate brain cancer.

This was the scientific finding. We had never known about this before. In 2008 a discovery was made where they were sequencing and they identified this IDH mutation. And the IDH mutation ended up being that is was somatic; it wasn't in our body; it was only in the tumor.

It -- there was a common version of this mutation. It was involved in one allele; so it had a normal allele and then a mutated allele. And then there were some initial, early things that

were found; such that -- as that it was common in secondary glioblastomas but not in primary glioblastoma and also seen in a lot of lower grade tumors.

Some of the details that followed was [sic] -- so normally, this gene takes isocitric -- because it's isocitric dehydrogenase -- and metabolizes into alpha-ketoglutarate. This is a normal metabolite in the Krebs cycle. So then the mutated allele now takes out the ketoglutarate and creates something called 2-hydroxyglutarate.

This is not normally in our body and this begins to accumulate in a cell where it normally shouldn't. So we're kind of hijacking what is part of this process of the Krebs cycle and shunting some of this into this accumulation of this metabolite. And what happens is, this metabolite causes a number of secondary changes. It changes the way the chromosomes and the chromatin come together. It changes a number of other abnormalities that occur in the cell that include having increase stress in the cell. It leads to changes with something called hypoxia inducible factor, and then it leads to a change where we're seeing changes from NADPH to NAP.

All of these are involved and now forming a tumor. So this is the first step of forming this particular tumor, which is really interesting. So all this science is coming forward, we're beginning to understand what's going on. And then we find out where does this exist in the field of gliomas?

If we find out that it's mostly in lower grade tumors, the primary GBM, that's only 5% of the cases where that occurs. 60 -- 80% of lower grade tumors and there's other types of mutations of IDH that may occur secondarily as well, but these are really rare.

We have IDH-1 that is really very common and ends up being 40% of the gliomas and before 2008 we didn't even know it existed. So it provides a real [sic] interesting opportunity to make drugs, but it also helped us better understand the disease.

Because now we have low grade tumors -- and we always have this problem with low grade tumors and maybe this will -- no. So over here what we see is how we used to grade tumors before we understood the IDH. And we looked at, under the microscope, we said, those look astrocytic, those look oligodendroglial, and these look like kind of a combination of oligodendroglial astrocytic and there was Grade II and Grade III and eventually Grade IV.

And what you see, is all of these -- let's go back. Can you go back one slide? We have all of these survival curves and they're all crossing over. So now we integrate the IDH information and now we break it down into a molecular classification. And this molecular classification really now includes; yep, how does it look under the microscope? Is it Grade II, Grade III or Grade IV? But then is it IDH mutated and is 1P19Q co-deleted or not co-deleted? And now that takes and changes the survival curves and they look very nice, so we have a low grade, Grade II or Grade III, IDH mutated, 1P19Q co-deleted. No 1P19Q co-deletion and then we have a glioblastoma that is IDH mutated in blue.

In red, we have low grade tumors that are not IDH mutated and then in this kind of yellowish and gold looking, we have non-IDH mutated or IDH-well type glioblastoma. So this helped us better understand what was going on much better than what we had over here.

This finding helped us create a molecular and histopathologic way that we could subdivide these tumors and it had prognostic information. Well, not only did it have prognostic

information, it had predictive information. And so this is an example of a study that was done back -- started in 1994 -- and as the data came out and we began to apply information about this new knowledge, we showed that those that were IDH mutated and 1P19Q co-deleted live longer. Those that were IDH mutated but were not 1P19Q co-deleted had an intermediate amount of survival, and those that were IDH wild type did not live very long.

But this study is looking at the difference between radiation and chemotherapy versus radiation alone; and there's a benefit that's occurring in each of these subgroups except for the IDH wild type. So it also gave us information to say radiation plus chemotherapy compared to radiation alone is beneficial in particular in these groups that are IDH wild type.

And in some of these settings we have some very nice, long timer survival, going out greater than 12 years. But we still need a lot of improvement here, even though we see a benefit to chemotherapy and over here in the IDH wild type we need a lot of benefit.

We kept learning more and more about IDH and like I said, it provided an opportunity for us to think about what should we be doing to try to create a drug that inhibits some aspect of process of increasing 2HG and the secondary changes that occur from that.

Well one of the most obvious one is to take out the mutant enzyme. So if you took out the mutant enzyme and you blocked it, so you're blocking the mutant enzyme, you won't get an accumulation of 2HG. All of these things will hopefully -- over time -- decrease and there may be an opportunity to kill the tumor, if we could do that successfully.

A company went ahead, identified this target, worked on how to make a drug to fit appropriately into the abnormal, mutant part of this enzyme and then they started to push it forward into this IND enabling studies and then into a Phase One study.

The Phase One study is just as we would normally do. You have different cohorts; we start with low doses of the drug; you then increase to higher and higher doses. And as we increase to higher and higher doses, we try to find a dose that we feel comfortable staying with to move forward with in our later evaluation.

Well, you can learn something as you're going through this process and one thing that we learned as we were doing this, is we had patients who had recurrence that had IDH mutated tumors and we had patients who had started in their newly diagnosed setting.

And the scans looked different there. You can have non-enhancing tumor for the low grades; but if the low grades go and progress later on, they can have changes that look like this contrast enhancement here. And when these patients were treated with the IDH inhibitor, their tumors continued to grow. So that didn't seem to be a great fit for the use of the IDH inhibitor. And maybe because, you know, IDH is no longer driving that tumor. Maybe there are other molecular changes that are going on that allow now for this to not be inhibited by an IDH inhibitor.

This is another group of patients. These are patients who have low-grade tumors. Now, I was supposed to have a different set up here for my computer to show you this, but what you see on the left-hand side, is you see that there's a number of different dates of scans of the patient. And that [sic] first three scans are all kind of historic scans before starting.

So just -- let's see if we can just go through these, because I don't think I can go backwards. What you can see is the tumor increased in size -- am I going to be able to go backwards? No. Okay, go forward one. I got it now, I got it. So follow an area like right in here. And as I go forward, you'll see that it's getting bigger, coming into the study. Everybody can probably see this, I hope. If not, I apologize.

And then they go on the inhibitor and what happens when they go on the inhibitor -- and again, let's just focus like on this area right here -- when they go on the inhibitor, you'll see that it's decreasing over time. And that gives you a lot of confidence that something is happening with this drug.

I saw it growing coming in and now I see it shrinking, going down. But it's taking it a long time for it to shrink. So long that, you know, that it's hard to do this with our traditional measurements. But now we've identified a population that we think may benefit from this therapy.

What we normally do for these tumors is we usually have surgery and if there's residual tumor, or not residual tumor, we'd watch and wait. And then we may watch and wait to see if this grows over time.

Now, surgery has its problems. You can see this is a patient who had a very aggressive surgery and when you take out good and bad tissue, because it's intermixed, there are problems associated with it. So this is one way we go about treating but it's not a perfect way of treating.

The other way that we have of treating this is using radiation and chemotherapy. I showed you those survival curves that radiation and chemotherapy provide an additional benefit.

But over time there can be complications associated with giving radiation and chemotherapy. Those complications can affect patients such that, in a case where of the patients that had not progressed after greater than five years, only 41% were employed and 30% had severe cognitive impairment.

Again, it's better than not being alive, but if there are other therapies that we have, there is an opportunity for treating this early on and getting in and potentially using a drug that doesn't have negative effects.

There was an expansion group that was done, after identifying this, of the low-grade patients, the patients that had non enhancing tumors. There were other patients that showed evidence of some increase in growth before treatment and then decrease after treatment. This provided the confidence to move forward with the later stage study. The later stage study, or I should say, there was one other thing that was done that we always like to do, is we like to show whether or not the drug got into the brain.

Now, if you see tumor [sic] shrinking you pretty much feel pretty good, that something must have gotten in there. Nevertheless, it's still nice to have this additional information. And so, what we have here are two different drugs that were being evaluated. This is what was in the plasma, this is what was in the tumor and you have a brain to blood ratio of 1.59 in this setting. So this has good brain penetrance, it gets in.

This one, over here has a blood to brain ratio of 0.31, so much lower. However, the total amount of drug that's getting in, it's pretty equal between these two. So it doesn't matter

necessarily what the blood/brain barrier ratio is or the brain to plasma ratio, sometimes what matters is how much drug is actually getting there.

This type of information can be very helpful and help us understand, again, what drug should we move forward with when we're evaluating this. And the second part that I told you is that we have to hit the mutant enzyme. So we have to decrease 2-hydroxyglutarate. Well, are we decreasing it? Again, we saw the tumor shrinking and a couple of these cases we're pretty happy about that.

What this shows is that these are patients at the level of 2-hydroxyglutarate in the tumor who did not receive drug, and then these are the levels of the patients who did receive drug. And there's a nice decrease of around 92 to 93%. So with that, that's actually really interesting and helpful and I think it gives the confidence to be able to now move forward in a later stage study.

And the later stage studies -- especially in the setting of trying to go after a single target in a group of patients where we think this is an important target we're going after -- we could use response rate or we could do randomized studies to evaluate for change in survival and progression free survival.

Well turns out that only when I provided you with those MRI scans to show how it was shrinking was it easy to see, but it's actually really hard to measure this and determine whether or not there's actually been tumor shrinkage. And to show regulators whether that's the case.

What is going forward is taking patients that are IDH mutated that have low grade tumors that have received a surgery, have some residual tumor and then their randomized to either receive the inhibitor or placebo. Now, people may think that's not very nice to do that and to

some degree, that's true. As it turns out with this disease, that this is a time when we would normally perform watchful waiting to see whether or not there was progression. So the progression could go on the inhibitor and we can see how long does it take for the tumor to come back and the same with the placebo, see how long it takes for the tumor to come back. And if they show progression they can now go on the inhibitor or the patient could decide to go on to standard of care which is going to be radiation and chemotherapy.

There's an opportunity to evaluate this drug through doing -- through evaluating progression free survival in this way but then also in this group if we developed a growth curve and see that this is increasing as we go on it -- as we're on the placebo -- and then on the inhibitor if it decreases, we also get this understanding of a change in grade and how many patients are responding in that way.

We get a lot of data when we do this, and we think we're not putting patients at risk, but I think there's an opportunity to understand how to best use one of these drugs. So I gave an example, and it's a really nice, cool example of how a drug was developed and how from 2008 and here we are in 2019 and there's a Phase Three study. From initial discovery to drug getting in and moving forward, it's moving pretty good. I mean, we get pretty happy about that.

But there are lots of other drugs that are moving forward and where they're doing Phase One evaluations and they have to hit this late stage as whether or not it's providing some evidence of effect and whether it's better than standard of care. So we have to think about how we do this better. I told you already, this is expensive, that we haven't had successes. So we have to change this in some way.

We got [sic] to be better at selecting the drugs that come in, and we got [sic] to have a better way of evaluating that. To some degree what we've done because of that, is we've taken shortcuts. When you take a shortcut you end up with bad data for making decisions upon. This is a series of Phase Three studies that were done and I think there's are a couple of points to take from this. This is the time from Phase Two to Phase Three and you can see that time frame is long.

Two; these are the number of patients used in the Phase Three setting and that will come back in the Phase Two setting. And remember, there's always controls in there; so half the patients are basically going to be controls. And then, this is the reason -- hold on, I'll do it. Oh boy. This is the reason that they went forward with the Phase Three study. But it was a single arm study; it wasn't comparing to a control.

And that creates a problem and I want to kind of explain a little bit why that creates a problem. There we go. So it creates a problem, because when we use a single arm study, we never really know how we've selected that patient population before they come in. And this is just an example of number of months of survival and these are some characteristics that could push a patient population -- any patient population -- to have a better overall survival. And this over here is a group of characteristics that could push a group of patients to not have a good survival.

When you randomize you pretty much are going to have balance because patients will get the drug and not get the drug and you'll have that randomization. But when you do single arm

studies, which I'm telling you what we did, because we're trying to save money and trying to make it easier for companies to want to come in, you make mistakes.

The first is -- now this is a randomized study against an immunotherapy versus Bevacizumab and there's no difference in the outcome. But if these were taken as single arm settings, single arm evaluations in a recurrent setting, a survival of nine months to ten months is pretty good. What you don't know, is before the patients came on the study, the investigators were asked, you know, make sure it's a small tumor size, make sure there's not a lot of edema, make sure that the patients are on a low dose of steroids, because we're worried about there being an inflammatory change. So that just pushes this entire survival curve over this way.

Again, if this was taken as a single agent, as a single arm evaluation, we would have said this has a high likelihood of being a positive study. Yet here's the randomized study and it's a negative study.

This is an overestimation of the effect and this is the group that goes on to get studied later on. The group that doesn't go on to get studied later on, is a group that where we would underestimate the effect and this is a group where maybe there would be more selection of larger tumor size, larger steroid doses, etcetera.

This is a randomized study and you can see both of these arms; you can see we have 5.6 in this arm and we have 7.4 in this arm. Both of those are much lower than 10. Yet taken as single arms, these would not be effective therapies. So what we have, is we have this randomized study that says this is a beneficial therapy. It's being compared, it's randomized, we have equal -- a balanced group here and so, we have to realize that we have to do randomization.

If we have to do randomization and half the patients are controls and it's more expensive, who's going to come in and want to evaluate drugs in glioblastoma? And that's kind of where our problem is.

We hope that there can be a solution. One is, we've got to try a number of drugs and if we don't try a number of drugs, we're not going to have the ability to find out what's going on.

We could do one thing where we could just say, okay we're just going to do more trials. Who's going to pay for them? How are we going to get that done? That will get us there faster because at least we'll do evaluations of all these drugs and if one of them works; we're great. We're changing the field.

There's this opportunity to do something called a Master Protocol and a Master Protocol has one control arm and many treatment arms. And with these many treatment arms, if you have harmonization of endpoints overall survival and they have the same balance of inclusion, exclusion criterias [sic], all these things across, there's a real opportunity to save on the number of controls and to be more efficient in the setting. Which means it would be cheaper as well.

This is why GBM AGILE was created and I want to just walk you through what GBM AGILE tries to do. So GBM AGILE is a platform trial; many therapies being considered against a common control. There are different populations that could be evaluated by each therapy. We could have first line -- yeah, let me stick with that.

We have first line methylated, first line unmethylated and recurrent. And these are what we call subtypes. These are the populations that are coming in to be randomized and they'll be randomized to one of these specific arms, based upon a couple features that I'll tell you about.

The primary endpoint for this is overall survival, so regardless of whether its first line methylated, unmethylated or recurrent, it's going by hazard ratio and overall survival.

The second part of this, because that's how they're coming into the study to get randomized. I'll tell you the deficiencies that come with that, but then within each of these arms, there are evaluations based upon each of these individual subtypes.

How is this doing compared to the control of first line methylated? How is this doing compared to the control of first line unmethylated and recurrent? But it also takes into account what if we begin to group these populations and say how is all first line doing compared to all first line in the control? Or how is the entire group doing? So you have the opportunity not to just evaluate one population, but many populations and groups of populations. And this is part of the benefit of using the Avazian approach.

The other thing that exists in GBM AGILE, is the ability to take on what is the equivalent of a companion diagnostic or a predictive biomarker. It may not be known that that's the one, but you get to choose one in any particular therapy.

Now you break it down to first line methylated, biomarker positive/negative. Same thing with first line unmethylated and then in recurrence. And again, as these subtypes come in, they get randomized based upon that into the arms, but then as they're being evaluated within the arms these signatures come about. And again they can be all of the individual subtypes or these clusters as they come together. And you can build groups out of them; that might include for instance, all biomarker positive.

The way that this ends up working is there's two stages because we want to have efficiency. Our first stage that we would typically bring a drug in here for, is to determine whether or not we think there's a signal of meaning. And I again, I told you that it needs to be done in a controlled setting.

We have these two stages. The first stage where we're evaluating the therapy to see whether there's some kind of benefit that we're beginning to see. And then if we see a benefit, we go onto the second stage where there's this fixed randomization. And in the second stage, if that hits, that goes on and moves to a New Drug Application.

It all happens seamlessly and these evaluations are done through a simulation process where all of the data are [sic] collected and can be used in the end. The entire data from the stage one and stage two for that New Drug Application.

What happens first is there's fixed randomization and if there's one control -- the control gets about 20% of the patients. You have a one in four chance -- a one in five chance of getting the control. Then the rest of the 80% are divided equally between the different drugs and we have this initial enrollment that occurs in this fixed randomization, so we gather data.

As we're gathering data, we now are looking at -- through a machine learning type environment, Avazian evaluation -- which patients and which subgroups are doing better and performing better. So then as a new patient comes along -- they'll come along.

[Laughter.]

That one there is first line methylated, biomarker positive so the question is how are the rest of the first line methylated, biomarker positive groups doing within each of those arms?

And the answer is --

Audience: The right screen does not flicker.

Dr. Cloughesy: Oh, is that right? I'm going over here.

[Laughter.]

Dr. Cloughesy: See how that works there. So what you can see is this is now the revised probability randomization based upon the data for that particular subgroup. And so the patients -- this patient has a higher likelihood of going into this group because they're performing better in that group.

Patients that are enrolled again, we continue. A new patient comes on; this is recurrent first line -- or recurrent with biomarker positive. These are the groups that are being evaluated within each of those arms. The probability for randomization occurs again and we see these changes and we have an increased likelihood that they're going to be randomized into this group.

So as this goes on there's now -- what is the fate of the arms? I've told you what the fate is of each patient coming in; how they come in, how that decision gets made, but what's the fate of each of these arms?

Well there's three possible outcomes. The first one is futility and futility occurs if all of the signatures that are possibly -- could be evaluated within that arm are performing so poorly -- all of them -- that there's no sense in going forward. So you fail early.

The second consideration is you've reached your maximum number of patients that have enrolled and it's been set up in a way so that that maximum number is a number whereby you're not having a huge effect; you might be having a relatively small effect but there's still a potential benefit. And what happens is these patients go on, they complete enrollment, they wait for a year and then all of the data about all the signatures are provided back to the company.

Then they have a decision about whether they want to move forward, because there's some effect. It may not be a very strong effect and they can also now power their study because they understand what the expected effect should be. How many patients should be in this Phase Two study?

Well the one that we all want to have come out of this is moving onto Stage Two because there was a particular signature that showed a very strong effect before the enrollment was completed in the first stage. So then it moved forward into the second stage and now it's being compared against the control population that has been gathered over time. And as this is a fixed randomization so we get data quickly, that this -- if it turns out to be positive -- moves to a New Drug Application.

And within that New Drug Application, this is not only going to be in that particular population, with maybe a biomarker so it identifies throughout all of this, who's going to do the best, what the highest impact is and with this information we can move forward faster into patients. Because that's where we have to have the drug as soon as we get a benefit.

This is going to be an international trial so that means it's in the U.S., it's in Europe, and it's in China. So when it hits in all of those -- in all of those regulatory jurisdictions -- it will have approval.

There's a number of different benefits that exist for doing this. I think we got into this faster, cheaper. I think the idea that we have -- can integrate a biomarker, that we can use this seamless process to get through to a New Drug Application. I think the thing I want to concentrate more is what is the value to patients and advocates?

One is, there's multiple therapies evaluated -- available. Two, it would be offered at a multitude of sites and be available. This is a continuous trial so as we drop off different arms, we bring in new arms. So it's a perpetual trial as that's going.

In a sense the trial should become the standard of care because that's how we're going to learn, that's how we're going to move this forward. It helps with precision medicine because, as I showed you, as a patient comes in, they're going to be placed in -- at least have a higher probability of being placed in -- to the therapy that is performing best for them.

It's disease centric and not drug centric. We care about not which arm is being evaluated, but that the patients are being evaluated and they get the opportunity to be in the most appropriate arm for them. The idea that there's a shared control group, I think everybody feels comfortable about. And I think then, that the idea that it's faster to fail, faster to market. Those are the things we want; to fail early and win early with this.

This kind of puts everything into perspective as you go through what's the difference between doing a randomized study or doing parallel randomized studies, compared to doing a

platform study. And the reality is it's faster, cheaper, there's less patients. Hopefully lower development costs and hopefully lower consumer costs as well.

As we're bringing up and identifying new therapies and they're going through that Phase One process and we're trying to figure out how to move on to that Phase Two setting, we think that GBM AGILE provides that opportunity. So that more companies are going to be coming in because it's not that \$300 million to do the evaluation. That it's a fair and quick evaluation and that I think that patients will want to drive the therapy towards this as well.

This is just the structure of how GBM AGILE goes forward. There's a sponsor which is the Global Coalition for Adaptive Research is a 501(c3). They're the sponsor. Different drug companies interact with the sponsor and then there's CROs, vendors, and of course the sponsor along with the pharmaceutical partner interacts with the FDA.

I'm going to stop here and thank you all for listening. I hope that our technical difficulties -- that we made it through. And I guess time for questions. Any questions?

Q: I was wondering how much collaboration there is between yourselves and UCSF?

A: Oh. Well I think at different times, we have SPOREs. So this is a special aide program of Oncology Research Excellence. Part of what we have to do for this SPORE is collaborate.

Q: Can I back up?

A: Yeah.

Q: I'm always afraid when I say UCSF that some people won't know what UCSF is.

A: Oh.

Q: You know, because UCLA is pretty well known but UCSF --

A: Oh, really? Must be that football team that we have that UCSF doesn't.

[Laughter.]

Q: -- but UCSF doesn't have a football team.

A: I know, but they could probably at least put up a good fight with UCLA these days.

Trip Kelly hasn't come through yet.

Q: Well, to explain that, UCSF is University of California, San Francisco.

A: Yes. That was my understanding. I don't think I answered your question, did I?

Q: No, I answered myself.

Q: It's pretty compelling; this approach makes a lot of sense and there's a lot of benefits that I can see. What are the challenges or why isn't this being done, kind of, uniformly?

A: You know I think some of the challenges are -- if we go back one slide -- that the sponsor is not the pharmaceutical company. So as we've gone through and spoke [sic]¹ with

¹ [sic] is used to denote the typed material was transcribed exactly as spoken.

different pharmaceutical companies that was one of the things that was a concern. Control; pharmaceutical companies like control.

But it's interesting that the FDA -- our interactions with the FDA have been really great. And our meetings with the FDA -- when we bring a sponsor to the meeting, they find it a completely different interaction. Because the FDA used to sponsor someone who may be trying to pull something over on them, may be trying to do things differently. But when you have an independent group that comes in and is going to be evaluating this fairly across the board, not looking for some angle, not trying to do things differently, there's real opportunities that come out of that. And that's what actually helps us drop the cost as well, because the level of monitoring that's required is much less.

That discussion though, it just takes a while to get there with the company because they're just not used to this. This is the first registration study that is going forward. Most of the other kind of platform studies were not registration studies, so this is where there's a little bit of difference with this.

We, you know, had difficulties raising the money for the build of this. Initially, that's always a task but I think, you know, now that we're up and running it's just going to be about adding different partners. We have one partner that we have right now and we have three other partners that we're evaluating. And we hope that they'll be joining by the end of the year.

And as I said, you know, with the FDA there was a challenge. So we started with the FDA around 2017. We had to have a five-hour meeting with the statisticians at the FDA to convince them that this is what we want to do.

When we initially went to the FDA this was a one stage evaluation. Meaning we were just going to do a screening evaluation and in our discussions with the FDA, they said what happens if you have a big hit and we can't approve it because it wasn't set up to be a registration study and you've lost equipoise because you've shown a big difference?

And that's where the two-stage component came from. Really as a suggestion and a response to -- from what the FDA was asking of us. So we made it through the FDA and we're working with the EMA.

Each time you go to a different jurisdiction you have to kind of deal with their concerns about using a Frequentist verses Avazian statistic approach. And so that's always a little bit of a challenge but again, it's just time. So we get there but it takes some time. Those were some of the challenges anyway.

Q: I was just curious as to what your thoughts were on the pharmacist students in Ohio, with their discovery of the drug that was killing the tumor?

A: I don't know that specific one, so if you have more detail on it that would be great. I'm just not sure which one you're referring to, but I like that students came up with it.

Q: Yeah, me too. We just need it to hurry up.

A: We're ready to put it into GBM AGILE, by the way. Whatever it is.

Q: I have a few interrelated questions. The first is, is this the first time that that model, GBM AGILE, has been used? The second was is that only going to be for GBMs, no low grades? And the third is what is a reg -- maybe I missed it -- but what is a registration study?

A: That means, you know, how you get it approved. It has to be something that's going to allow for marketing -- for us to market it in the United States as a drug. So the FDA has that ability; they call those studies registration studies. And then they evaluate the data and if it goes forward than it receives a New Drug Application and the indication and it's available and marketed.

Dawn Berry and the Berry Group is the one that develops these studies. In terms of -- and they work with key opinion leaders to define how to develop them in different groups. With different diseases like glioblastoma. There's one in pancreatic cancer that is not yet opened but the design is very similar to this.

EyeSpy Three, I think, is getting ready to go but is not quite ready. And there's other groups that want to do this as well. Wherever there's kind of an orphan disease I think there's opportunity to do something along these lines. This is not currently for low grade tumors. It's hard developing drugs for low grade tumors because it takes such a long period of time that you have to really work and identify a unique kind of endpoint. Which is what happened with this IDH inhibitor drug. That's really where that came out of.

Otherwise, if you have to do radiation plus chemotherapy in a lower grade and add a drug onto it, you know, that's a ten-year study. And that makes it really hard for companies to maintain interest in it.

A: I'm scared.

Q: I have an interesting dilemma or something. I have macular degeneration and I've been getting Avastin as an ocular --

A: Yeah.

Q: -- thing and I just wondered, because there's some controversy a couple years ago. Genentech produces Avastin and they also produce Lucentis. And essentially, I think they do the same thing.

A: Yeah.

Q: The thing was that Avastin was first approved by the FDA for stomach cancer, I guess. I don't know exactly which one it was because I was only introduced to it because of my eyes. So if they can get FDA approval for one thing and then somebody finds out that it can be used for a different function in the body, that they can go ahead and use it and that's why my optometrist is doing.

A: Yeah.

Q: Is he's using it for my -- and the difference in price is well, roughly, it's \$200 for the Avastin treatment for the eye and Lucentis was \$2,000 for one treatment.

A: So I'm going to change your question a little bit to say --

Q: That's approved.

A: -- to say what are the options for trying drugs that are already FDA approved or are maybe now generic and people want to look at repurposing them in some way? So as long as they are still FDA approved and under patent the company still has to go through and prove that there is benefit in the following way that I just described.

It's also true, even if there's a generic drug, that the company usually would pay for that process. Going through that process if they still have the patent and they're able to push that forward. A drug that no longer -- that is a generic drug, somebody else has to do that.

And there are different 501(c)(3)s that are evaluating, looking at generic drugs and repurposing them for different reasons. You still have to go through this process. One could just simply use them, but we want evidence and we want good evidence. So you have to go through some kind of randomized evaluation to understand whether that's true. So this could take on a repurposed drug. Certainly in a company that's trying to extend an indication, that's very common. But somebody would have to work on paying for -- if this was just a generic drug that we wanted to put in, because it costs money to do that evaluation.

Q: My question is related to overall strategy and I'm not a medical professional -- I'm an attorney by trade -- but sometimes I have difficulty understanding what the benefit is of each individual cancer organization working independently to speed up the overall FDA process, versus collaborating as a whole and retaining those dollars?

And secondary [sic²] -- so if you could explain that overall strategy, you know, specializing in GBMs versus the entire organization or the entire cancer community?

And secondly, although I selfishly -- and probably everybody in this room -- feels passionately about GBMs, I have to wonder if part of the reason why -- all cancers are horrible and they should be eradicated. However, GBM does have, you know, an overall lower survival rate. So there's also that need for faster outcomes and faster timeline for this. So could you help me just understand the overall strategy of this entire process and why benefit a specific cancer type or everybody overall? And really how that aligns with the overall grades of GBM, specifically?

A: I'm not going to address about all the advocacy groups coming together; I'm going to let advocacy groups do that. But, yeah, sounds like a good thing to do. I think, obviously, the move with the Brain Tumor Funders Collaborative is very much along that line, at least what ABTA is doing.

So the overall strategy -- everybody wants to take a shot in a different way. In the end, we're not going to be able to do anything to a patient unless we have a way of clinically evaluating them. So one way of improving that strategy in the late stage is this. But there's discovery. There's then coming up with drugs. Then there's that early phase; how do we pick that out?

² [sic] is used to denote the typed material was transcribed exactly as spoken.

There isn't really -- there hasn't been a uniform way of doing that. The NCI had a task force that was supposed to put together a group of recommendations so that their funding would be more focused in this way and trying to make sure that the different assets -- the drugs that were coming through were evaluated in a similar way, through the same types of models, the same type of process in that way.

I hope that's coming. They have the report, they've submitted the report, now they're supposed to be writing some RFAs. So we hope that that will translate into a strategy rather than more of a haphazard approach. Everybody taking a shot, not having enough money. So I hope that happens.

Dr. Dunbar: So thank you, Dr. Cloughesy for a wonderful talk. I want to congratulate you and thank you for your hard work on making medicines come to patients faster. I did have one final question for you. We have some exciting talks coming up; Dr. Lesser talking about what things excite your doctor. We have Dr. Butowski in to talk about medical cannabis; help or hype.

So in framing those upcoming talks, I wanted to ask you, does the AGILE platform -- do you envision that any of the drugs incorporated over the next numerous years may be what a lot of us are excited about in clinic and our patients? Which might be candidates for tumors or other herbs or supplements? Do you envision this ever going into medicines that are not biochemistry driven? You know, the Novo drug from (inaudible 01:43:42).

Dr. Cloughesy: I think they can. I think the same thing occurs which is how do we pay for a good evaluation? And maybe that's something we just need to separately raise money for; to have the opportunity to have those shots. It's really about create -- doing good studies. As we use those -- and we have the ability to use many of the things that you just described -- and we kind of collect them and the results that occur with patients, and we try to make sense of it. But it's very hard to make sense of it. So the studies need to be, you know, well designed and well conducted in order for us to understand what's going on. Thank you.

[Applause.]