Lung Cancer Mutations and Treatment Advances

Lung cancer, the most common cancer type with the highest mortality, can largely be categorized by the genetic mutations that cause it. By targeting the specific genetic mutation behind a patient's cancer, targeted therapies have enabled increasing numbers of patients to experience fewer toxic side effects and, often, live free of disease following their treatment.

KRAS mutations, which are found in about one-quarter of solid tumors and are the leading cause of lung cancer driving the growth of about 25,000 new lung cancers each year. However, in spite of being discovered four decades ago, they were deemed 'undruggable', until earlier this year when FDA approved the first targeted therapy for lung cancer caused due to the KRAS mutation.

We are talking to Dr. Kevan Shokat and Dr. Trever Bivona on lung cancer mutations, new treatments, trials and more. Lung cancer patient advocates Terri Conneran and Lisa Goldman joins the panel to bring in the patient perspectives.

Full Transcript:

Priya Menon: Hello and welcome to CureTalks I'm Priya Menon, your host. Today on CureTalks, we are discussing lung cancer mutations and treatment advances. We have with us Dr. Kevan Shokat, Professor in the Department of Cellular and Molecular Pharmacology, and Dr. Trever Bivona, Medical Oncologist, Professor of Medicine of Cellular and Molecular Pharmacology at UCSF Helen Diller Family Comprehensive Cancer Center. On the patient experts panel, we have lung cancer advocates Terri Conneran and Lisa Goldman. Welcome to CureTalks, everyone. I'm going to jump right in there is a new drug out there, it is Sotorasib, Sotorasib for G12C. Now I think people who follow the oncology drugs phase, will know that trying to drug KRAS has been the Holy Grail of oncology for a long time. Dr. Shokat, you're one of the frontline researchers, working on KRAS mutations, can you talk a bit about why it has been so hard to drug KRAS? And why is KRAS so interesting to lung cancer researchers?

Dr. Kevan Shokat: Sure, thank you Priya. Thanks for inviting me. Well, we've known about KRAS mutations in cancer since 1983. It was actually the first human oncogene to be identified and then it started as we are aware that it occurred as a driver oncogene in lung cancer, pancreatic cancer, etc. and so once you identify the mutation that is driving cancer that opens it up as a target for drug discovery. The problem with KRAS is that it's a very small protein that really has no pockets that we usually think of for binding to drugs, you could think of it as a bowling ball. And if a drug is like your fist, then you will just never be able to get it into a ball and that was the real limitation for everybody for the last 35 years. Then a number of years ago, my lab decided that maybe we shouldn't try to solve all of the KRAS mutant cancers, we should just focus on the one that's more frequent in lung cancer and that was caused by this G12C mutation or glycine 12 to cysteine and cysteine has a special chemical reactivity. So, it's like a little piece of super glue and so we identified a drug that could hold onto the glue even though it's on the surface of the bowling ball and that led to the identification of the pocket. And then it became a drug discovery effort and the drug you mentioned Sotorasib was just approved by binding to that pocket and turning off KRAS, and that's really a great benefit I think to lung cancer patients with this particular mutation.

Priya Menon: Dr. Bivona, you are no stranger to targeted therapies in lung cancer. When you think about targeted therapies, what are the drugs that you're using often? And what are some of the response rates

you're expecting to see?

Dr. Trever Bivona: Thank you for the invitation to be here. It's wonderful to be part of a panel. And so many of the drugs like Sotorasib that we're using in the clinic now are against other driver oncogenes as Dr. Shokat describes, that really caused cancer to grow and to spread. And these regimes like EGFR, the Epidermal Growth Factor Receptor, variants of ALK- Anaplastic lymphoma kinase that is Gene fusions. And so those are two of the more common ones and those are more well bound to the targets. And the drugs we're using against those are Sotorasib, in the sense, they're very potent and relatively specific especially, Olmutinib which is similar in that, it binds directly say EGFR in the same way, in a similar manner and as Sotorasib to KRAS and subsequent cysteine, and for ALK drugs like Alectinib which are again highly potent, and specific and very effective in patients and also very well tolerated, so very safe for patients which are as important. The response rates to EGFR or ALK inhibitors, these EGFR-ALK inhibitors specifically are actually quite high. They can be on the order for 80% or even higher in some cases. And so those inhibitors against EGFR and ALK are used in the first line of study, and they can provide benefit for sometimes years in patients.

Priya Menon: Well, thank you. Dr. Shokat, quite an exciting story as I said, I think the past few months for lung cancer have been this KRAS G12C story and we've got multiple drugs that have been evaluated and an FDA approval for this one as of June. Can you talk briefly at a high level about this data?

Dr. Kevan Shokat: Yeah, I think when a molecule first is able to target an oncogene and we put it into the clinic and patients that all have that driver oncogene then we get to see well what happens when we shut it off and if the response rates are in the 35 to 40 percent range so interestingly much lower than the EGFR response rates that Trever described. So, we're all trying to understand is that some distribution of other mutations that occur or whether combination therapies, which I think will talk about, have a much better chance here, to expand the response rates and the depth of responses, or whether this is just the first drug that the one that Trever mentioned Alectinib is a so-called third-generation EGFR inhibitor. Whereas Sotorasib is just the first generation KRAS inhibitor. So, I think it certainly will improve but there's still a long way to go to sort of really get to the maximum benefits we can achieve through this mechanism.

Priya Menon: So, finally, I mean, I think the last line here is that we have a drug that targets, something we could never target before. And that's very exciting for lung cancer. Dr. Bivona, where do we go with these drugs? Are they single agents? Are they in combinations? Do we use it combinations and if yes, so what do we use it with? Is it the first line? Are we planning it for reserve in the second line? And how do we move forward with these?

Dr. Trever Bivona: This is a very important question and I think in many different directions. One is building upon the tremendous success of Sotorasib and Inhibitors like it. And as Dr. Shokat mentioned, developing perhaps even, better forms of those types of drugs like Bosutinib is a third-generation inhibitor which is better than the first- and second-generation EGFR inhibitor that's certainly one area in terms of drug development and clinical development. And then what you're alluding to what are the rational combination of approaches that can be used to enhance the effects of Sotorasib and these are common themes across EGFR and ALK and other driver oncogenes and we are trying to enhance response to these agents through combination therapies. In order for combination therapies to be successful in the clinic, they must be grounded in a sort of a mechanistic basis. And so, I think one of the first important avenues that researchers try to understand is what limits response to current Inhibitors against D12C inhibitors and other inhibitors. And so, some of the combinations that are being explored are targeting other proteins that help turn the KRAS on either upstream or that help mediate the effects of KRAS down the street and cause cancer cells to grow. And so, there are upstream receptors, like, EGFR, there are proteins such as SHP2, which helps to promote, RAS signaling in cancer growth. And then there are downstream targets such as MYC and ERK that mediate the effects of RAS and cause the cancer cells to grow. So, a lot of those combination therapies are being explored. And then, I think secondly combinations with other important treatments in lung cancer and other cancers such as checkpoint inhibitors, immunotherapy, so there is some mechanistic and support combinations of G12C inhibitors, and RAS pathway Inhibitors in general, with checkpoint Inhibitors, so immunotherapy, and those

are very exciting because that potentially leverages the immune system in the interactions between the RAS signals in the cancer cells and the immune system being able to effectively help eliminate the cancer cells in the body. And then, where do we go from here? I think it is certainly moving towards first-line therapies for G12C inhibitors alone and also some of this combination therapy should they prove effective in later lines of therapy. That certainly have the EGFR or ALK. Lung cancer sometimes has cases where Alectinib is the first-line treatment for EGFR mutations and elective or other agents like it ALK. So, I think that certainly is the way forward in terms of what line of therapy, hopefully, the first one.

Priya Menon: Okay. Thank you. So, I'm going to hand it over to the patient panel now. Our first panelist is Terri Conneran. Since 2017, Terri has been battling KRAS stage 3, lung cancer. She found a KRAS kicker in 2019 to create a network for patients and families in search of KRAS information and support. Terri over to you for your questions.

Terri Conneran: Hey. I got to say thank you for inviting me and it's a great honor to be able to speak with everybody this evening about this. I'm just kind of wanted to start off with a fun question. All right, we've heard about undruggable and KRAS whatever. What is the best metaphor that you've heard as far as getting into that pocket?

Dr. Kevan Shokat: Yeah. I think of it as climbing Mount Everest. There are many paths' people take before you reach the summit. Everybody knew it was there as I said for 40 years and even as we were taking our approach along the way, we had many hurdles a lot of the early indications we found a pocket people, good friends, and experts told to me, that it wouldn't work because the pocket was too shallow or it was in the wrong form of the protein, but we didn't have any other trail to go on. So, we just kept going, and luckily along the way things came our way, and the opportunity and the weather cleared that we want. And we got there. And the other thing about the Mount Everest metaphor is that now, there are so many people going there, and there are so many other approaches and trails and so, I'm really excited about that. Ten years ago, I don't think that was this sort of momentum to go after this important oncogene.

Terri Conneran: Its a good analogy, how about you Dr Bivona? Would you care for one?

Dr. Trever Bivona: I would think of it as sort of a traffic jam and Dr. Shokat in college so found through the offer to get around it. And so, I mean, I think that really has them explore it, the field, I think it in many ways and Dr. Shokat can speak to this, perhaps better than I can. But there was sort of a bit 10 years ago there may be some fatigue around that we are just throwing the towel against KRAS. And so I think another transformative work by Dr. Shokat and others is really again, just completely alleviated this traffic jam.

Terri Conneran: It's a valid point that you need to keep poking through the trailblazing, even though you are getting very fatigued. So, I for one very happy that you guys kept going through it making the trail continue on. Okay so since this is taking more than one path to get there. Do you anticipate Dr. Shokat if it is going to be upstream/downstream or is just going to be some version of a combo that's really going to take it to really make the next level approach?

Dr. Kevan Shokat: Yeah, to be one of the most exciting conversations is actually one that Dr found which is a protein he mentioned SHP2 and that is upstream, and you normally think if the problem is downstream and you should work low, you shouldn't really work upstream but I think his studies showed that actually the upstream signal did sort of impact how the oncogene worked. So, and it just so happened that a couple of years before that G12C drugs came out, that upstream protein was drugged. It's own undruggable and that was very fortuitous that we have a fantastic option there to combine an SHP2 inhibitor with a KRAS inhibitor. So, I think once that plays out, we will really get a big movement on the needle. Personally, I think the next sort of layer of combination we need is that we've been talking about KRAS as the oncogene, the flip side of that in cancer genetics is the tumor suppressors, which we lose. And we think we know we sort of, by the numbers, it looks like about 50 % of lung cancer, KRAS patients also have lost p53. So, I think if we could sort of reactivating, the tumor-suppressive effect that has been lost, that we genetically and in models, we know would be a huge anti-cancer benefit. So, there are some drugs that kind of manic apart p53 the so-

called CDC46 Inhibitors. I think there are some next ideas coming around so that I think will if we can start to engage in tumor-suppressive activities, this will be a real, big step.

Terri Conneran: So, it's not just turning off the mutant, it's keeping what's wild and healthy until we were doing part 2 right? Okay. I just want to make sure I understand, I am not a scientist. Dr. Bivona, can you elaborate a little bit on the SHP2?

Dr. Trever Bivona: Yes, as Dr. Shokat alluded to we were studying in a collaboration with a biotech company in the Bay Area here SHP2 is a target in its own right independence of G12C necessarily. The take-home message was that what we found was those certain cancers, even if they had RAS mutations, like this G12C mutation still require some push from upstream and I think that the Dogma in the field had been for decades that if there was a RAS mutation be it G12C or another form of RAS mutations that causes cancer, it doesn't really need any push from proteins upstream. So, that it was just sort of an autonomous, is digitally active as what we call it, switch and so there was no, it was essentially like flipping a light switch as opposed to being sort of on a dimmer. And so, what we found I think by analogy was that G12C actually functions a little bit more like a dimmer than a strict light switch on or off and that it therefore SHP2 is actually turning up the brightness of the light of it, in terms of the G12C. So was turning it on even more by analogy. And so, therefore blocking SHP2 which as Dr. Shokat mentioned was also undruggable until recent developments by many drug developers in the field. Blocking it with a small molecule actually suppress the activity of G12C, even on its own independent gene cytokine network and so that became the basis for testing SHP2 Inhibitors in KRAS G12C cancers. But I think the real powerful approach, I agree with Dr. Shokat is the combination where you really turn cameras off and then you really clamp down under by also turning off the SHP2 protein that again is giving KRAS a little bit of an extra push.

Terri Conneran: And how do you think we're going to be able to apply this to some of the other KRAS mutations?

Dr. Trever Bivona: Well, I think I'll bug different from Dr. Shokat kind of this in terms of the drug development, but there are very creative approaches I think to target RAS in different ways. So, there are other pockets that have been identified again, on the heels of the breakthrough work by Dr. Shokat. There are other approaches to take advantage of interactions between RAS and certain protein in cells to create a sort of glue to dock small molecules that can block KRAS. And so, I think the next frontier is developing small molecule drugs that go beyond G12C and can target some of the other important forms. Dr. Shokat mentioned pancreatic cancer and other forms of KRAS like B12D that are more common in the G12C and pancreatic cancer, for example. And even in lung cancer, there are other forms beyond G12C like G12D and G12V and all these are oncogenes, they all cause cancer but can't be targeted in exactly the same way as the G12C can and so these other approaches I think are the next frontier there.

Terri Conneran: Would you elaborate a little bit Dr. Shokat?

Dr. Kevan Shokat: Sure. Yeah, I think Dr. Bivona summarized it well and these other mutations that drive cancer they don't have that superglue of the cystine, the glycine 12 to aspartate which occurs in lung cancer and very frequently in pancreatic. It's sort of like the glue that's on a postes note. It's much weaker and we don't have all the right tools to make that a permanent sort of attachment, but there are a lot of creative approaches going on and I think we'll see that in the next sort of six to nine months in the literature. And I bet in the clinic, we will see those molecules enter in probably the second half of 2022. So, I think there's really that sort of groundswell and the rush to the G12C has really motivated everybody. And now basically, every approach is on the table and some of them have… I wouldn't have thought they would have worked as well as they have. And so, we're getting a lot of it, really exciting data. A lot of it is in companies now, so we don't get to see it except in sort of press releases, but real science will come out soon, I think.

Terri Conneran: I'm hopeful. I know that's huge. I'm also on a G12C but there's a huge population and I recently saw I don't know the exact number but something like G12D and G12V makes up all the largest portion of all cancer and under KRAS, is that right?

Dr. Kevan Shokat: Yeah. That's right.

Terri Conneran: Yeah.

Dr. Kevan Shokat: Yeah, it's sort of like 45% of G12D. It's maybe 30% G12V and then like 25% C and then a few others. Yeah.

Terri Conneran: Yeah, because proportionately I think it was chemistry12C represents about the same number of people in lung cancer as having EGFR lung cancer. And so, once you start winding it up, who has KRAS, I mean, so I'm asking. I'm not telling you I'm asking, is that correct?

Dr. Kevan Shokat: Yeah, Trevor probably knows the distribution better than I do.

Dr. Trever Bivona: Yes, I just start the comparison. It depends a little bit on the demographics and the patient population, but I would say here in the United States that's a bit accurate.

Terri Conneran: It's a huge number of people who will thank you guys both so much for everything that you're doing climbing in getting us to climb Mount Everest without and being able to trailblaze. My favorite metaphor that they used was the star breaking down the death star of cancer, that was my favorite. So, I'm going to hand it over to Lisa Goldman, who has I'm sure some fantastic questions, much more technical.

Dr. Trever Bivona: Thank you, Terri for all you do with the KRAS kickers. It's great seeing them on Twitter. Thanks.

Terri Conneran: Well thanks. Yeah, and we might be able to hook you up with up a pen and a copy for both. Yeah.

Priya Menon: Next on the panel we have Lisa Goldman. Lisa is one of the founders and the president of ROS wonders Inc. a non-profit corporation representing the largest collection of ROS1 patients in the world. She was diagnosed with stage 4 and CLC, in Jan 2014 at the age of 41. Lisa, you can ask your questions.

Lisa Goldman: Yes. So, since I'm a ROS1 patient, I'm going to shift the conversation a little more general, away from the focus on KRAS, and ask just some questions that I often hear, because I get a lot of questions from ROS1 when patients are other lung cancer patients, not necessarily ROS1 and just has an active advocate in the lung cancer space. So, one question that's been coming up a lot and I don't know if either of you has thoughts on this is, people are starting to ask me, what is crisper technology. And can it be used to treat gnomically driven cancers? I guess. I'll ask you first, Trever, and then shift.

Dr. Trever Bivona: Sure. It's nice to see you Lisa and thanks for having us. Crispr is a very very powerful approach to our genome anatomy. So, it's a way to sort of edit DNA in cells in the laboratory and now more recently even potentially in patients and so this is a different approach to treating disease. It's not using molecules and drugs, but it's using a sort of basically certain instruction manual that allows basically wanted to go in and getting rewire the DNA of a cell. And so, this technology actually was awarded the Nobel Prize a couple of years ago as you may have heard and it's one approach to say, for example, going to fix or correct mutations that are an oncogenic mutation and there are experiments going on that are testing that in academics and in industry and they're slowly moving towards the clinic. You can imagine it's quite technical and there's a host of sort of safety issues to think about when tinkering with the human beings DNA and also getting powerful ways. But this is something that is sort of potentially an expert is here. Although I think a bit out from kind of clinical practice, in terms of oncology at it, or, at least, in terms of oncogenes in lung cancer space.

Lisa Goldman: Okay.

Dr. Kevan Shokat: I agree with all of that. I think it's fantastic technology. It's mind-boggling to think the

hurdles that have to be overcome to make it apply in cancer. But like we've been talking about overcoming hurdles you really don't know until you try. So, it's great to see so many people working on it.

Lisa Goldman: Great, thanks.

Dr. Trever Bivona: It has been used successfully just in on a side note recently in some other as mother human diseases such as sickle cell disease, for example, and again, not cancer different context, but so there is to agree with Dr. Shokat's optimism, I think that there are significant obstacles, but it essentially could work over the longer term.

Lisa Goldman: Great. Dr. Bivona, I think you touched on a few minutes ago about combining different types of treatments like immunotherapy and targeted therapy. Another question that comes up a lot especially to me personally because I was diagnosed back in 2014, I started on chemotherapy before my biomarker was discovered and I shifted to targeted therapy, but a lot of people wonder if my longevity on the targeted therapy has something to do with my taking chemotherapy first. And so, patients often ask me should I do chemotherapy at some point before I started targeted therapy or alongside my targeted therapy. Do either of you have thoughts on combining chemotherapy or patients with oncogene-driven cancers, I should say should incorporate traditional chemotherapy.

Dr. Trever Bivona: I think from the clinical standpoint that's an excellent question. I think that the jury is still out and across most examples like EGFR and ROS and others. What the data has shown is that if you compare saying EGFR inhibitor or ROS1 inhibitor to conventional chemotherapy not together, but side by side, we know that the targeted therapy is superior, and it's also generally better tolerated for most examples of that. There are certain clinical trial studies, that have shown that in some cases there can be a benefit to combining them in certain situations, although again EGFR is an example there. But again, those are not approved regimens and I think it's still an area of ongoing research. So, I would say for the most part in a situation where you have a biomarker where there's an approved therapy like ROS1 or G12C now or EGFR, now still that the best option in terms of efficacy and safety is the targeted therapy alone. I would say the one area that's again whether could be rationale in utility is in the drug resistance setting. So once the cancer has become resistant to ROS1 inhibitor or an ALK inhibitor or EGFR inhibitor, there in some cases chemotherapy can help particularly where there's no sort of the next ALK inhibitor or the next ROS inhibitor or the next combination therapy immediately available.

Lisa Goldman: That makes sense. A question, maybe Dr. Shokat can fill this one first. Another question I get is, if targeted therapy is targeted why am I still experiencing side effects? So, I agree with you that targeted therapy is a lot more tolerable than chemotherapy. However, people still do have struggles with it. So, can you explain a little bit about why people are experiencing that?

Dr. Kevan Shokat: That is a fantastic question. And it is a targeted therapy because it hits one protein usually, and rather than chemotherapy which sort of puts a lot of damage around for the cells and less than usual, it will die but that happens to normal tissue as well. The targeted therapy, even though it hits one protein, it hits the protein as its mutated in a tumor cell, but it also inhibits the original wild-type normal form of the protein in the rest of the body. And so, when we talk about the therapeutic index, we hope that the tumor is much more sensitive than the normal cells, but that toxicity is because it inhibits the target in the normal tissues. Now, what's great about the third-generation EGFR inhibitor of Sunitinib we talked about earlier is it has a wild-type sparing effect. So, it does a little bit more on the tumor cell than it does on the rest of the body, but it's not exclusive. The KRAS drug is really exciting because it is exclusive to the tumor. So, as we get more and more, I think of these as more, third-generation targeted therapies where they should work the way you exactly, hopefully, wanted all targeted therapy to work. So now, we're really working to get that. And that's it. A drug design challenge, but we're doing that.

Lisa Goldman: Great. Priya. I have endless questions, but I'm not sure how long you want me to keep going here. So, I just want to check-in.

Priya Menon: You can ask one more I can give you a couple of minutes more Lisa.

Lisa Goldman: Okay. I'll go back to a basic one that I get a lot. So, people get confused and ask me, what's the difference between getting genome testing or genetic testing, how do I know? Do I already know my biomarker I already got tested for, for example, BRCA or something like that? Maybe, Dr. Bivona, you can take this one?

Dr. Trever Bivona: Sure. So, the biomarkers that we've been talking about today in lung cancer and certain other cancer types, be on lung cancer are exclusive to the cancer cells. So, there's been processing the DNA in the cancer cells that give rise to these mutations. They are not present in the normal cells in your body. And so those are acquired, we call them somatic mutations. So, these are ROS1, ALK, KRAS, G12C, EGFR mutations, right? So, those would be sort of tumor genomic mutations specifically to the tumor cells, right? There are different classes of mutations that can be inherited from one generation to another someone's parents to children, and those are hereditary mutations. And those are often in the tumor suppressor genes. So, an example is the breast cancer, susceptibility gene called BRCA that you've heard about that's inherited from one's ancestors. So, the genetic testing that's done would be if there's a familiar pattern of cancer pathogenesis in the family. In lung cancer, there are no examples of that or are very rare examples that I should say. There's one prominent one that's actually in EGFR called T790M mutation, which is a mutation that causes resistance in the first-generation EGFR Inhibitors. Very rarely, one percent or less of the population contains that mutation as hereditary and that can be passed down. But that is by far not the rule, that's by far, the exception, right? So by and large we're talking about lung cancer biomarkers. We are talking about tumor genomic testing and not the hereditary mutations that are inherited.

Lisa Goldman: So, patients won't have the ability to test for that prior to a diagnosis. So, any kind of genetic testing that they may have done is inapplicable here and they still need to go for biomarker testing. I just wanted to clarify that for people.

Dr. Trever Bivona: Yes, absolutely. So, if you've had genetic testing for whatever reason, for some reason in past, if you're diagnosed with cancer then it's imperative to have the tumor biomarker testing done in addition. I will say there's an area, an emerging area in research that is trying to detect cancerous growth using DNA sequencing technology, for example, liquid biopsies, where we take a blood sample and sequence DNA, that's in the blood circulation. And so again, not ready for prime time yet, but there are efforts to try to detect cancers early by essentially screening. So, pre-diagnostic assays of high-risk inpatients for individuals, for example, but again, as it stands today, this is biomarker testing that we need to be done after diagnosis of a cancer independent of any biogenetic condition that one has had.

Lisa Goldman: Thank you so much.

Priya Menon: Thank you, Lisa, thanks for all those questions. I'm going to circle back to KRAS here. Dr. Shokat, the drug has been found to be responsive against other cancers too like colon, ovarian and other solid KRAS tumors. So, definitely, there's more to come from this group of drugs. Can you talk a little bit about that?

Dr. Kevan Shokat: Yeah, when the mutation occurs in any tissue, that Sotorasib would be a very very viable molecule drug to try to get a response. It's very interesting and its area of really deep current research why the response rates are different in lung cancer, and colon cancer of the same drug when the same mutation is there and that's because other mutations come along that are different in colon and lung. And so that to say that it will always respond doesn't look to be true, but it certainly will probably be one of the drugs people use that probably need to be different drugs combined to go after the other tissues. And then the next level is something I think we spoke with Terri about other KRAS drugs that are on their way.

Priya Menon: Dr. Bivona can you talk a little bit about the eligibility for this drug and the time period that we're looking at and have you started administering this in your clinics right now?

Dr. Trever Bivona: Yes, absolutely. Sotorasib yes, I think is now in clinical use. So, we treat patients with G12C lung cancer with Sotorasib. There is another G12C inhibitor called Adagrasib that is also coming along and will probably be FDA approved soon, don't know the exact time. So, there will be multiple G12C inhibitors that are available through for G12C, inhibitor patients. That's very exciting. And we're seeing excellent effects in patients. So, I think the clinical trial data are playing out in the real-world service team.

Priya Menon: That's good. So, there's a lot of enthusiasm here and I think I'm curious to see as we move these drugs upfront, whether the response rates will increase. So, it's quite exciting for the oncology field. With that, I would be wrapping up today's discussion and Dr. Shokat, Dr. Bivona thank you so very much for taking time today to join us on CureTalks. Terri, I hope this discussion will be useful for the KRAS Community. Terri and Lisa thank you for joining and asking great questions and bringing in the patient's perspective here. We thank also UCSF Helen Diller Family Comprehensive Cancer Center. The talk will be available on curetalks.com. Thank you, everyone. Thanks for joining.