>> Yes. I am Jeff White. I am from the Division of Cancer Treatment and Diagnosis at the NCI, and I'm one of the co-chairs for this session. And it's my pleasure to introduce you to the other co-chair, which is Dr. Donald Abrams. He's a professor emeritus of medicine at the University of California at San Francisco. And you may remember him from day one. He gave a talk there in one of the sessions. He's also going to participate tomorrow. He has an integrated oncology consultation practice at the University of California, San Francisco, and he is probably known to many of you for his work in cannabis, but also in HIV over many years when he was the Chief of Hematology and Oncology at San Francisco General Hospital. He conducted clinical trials of cannabinoids in HIV infection and as well as in cancer and sickle-cell disease. And he's also one of the members of the PDQ Editorial Board at NCI and the Integrative Alterative and Complementary Therapies Board, which we have a summary on complementary cannabis therapy. And he's a former member of the National Academy of Sciences, Engineering and Medicines Committee on Health Effects of Cannabis. So he will be joining me at the end of this session when we begin the panel. So our speakers are listed there. They'll go in order as presented on the slide. Guillermo Velasco will be the first presenter. He's from Complutense University of Madrid, and he will speak on the title "Towards the Utilization of Cannabinoids as Anti-Cancer Agents." And then Ramesh Ganju from Ohio State University will present on novel signaling of cannabinoids, mechanisms in cancer and that will be followed by Chris Twelves from United Kingdom on Phase 1B randomized placebo controlled trial of the mixture of THC and CBD called Nabiximols along with Temozolomide in recurrent glioblastoma. And then finally Gil Bar-Sela from Israel will talk about interesting finding of the use of chronic cannabis by patients undergoing immunotherapy and the potential adverse effects of that. So let's go ahead and get underway with Dr. Velasco to start us off. Guillermo.

>> Thank you so much for the introduction and for giving me the opportunity to be in this meeting that is very interesting. So what I'm going to do is follow-up a little bit on what was explained before and more on the preclinical limit on what are the advances that we have made on trying to set the basis for the (unint.) of clinical studies and also explaining a bit on the clinical study that our lab was involved in. But before doing that, next slide, I would like to mention the potential conflict of interest. We had previously funding by GW Pharma and also (unint.) with cannabinoids (unint.) I will explain a bit later. It's the potential biomarker of CCTV to kind of protection and currently, we have collaborations with Neuron Consulting and also with Tilray. And I have also worked for specific projects for GW Pharma. The next slide, please. So as has been discussed in the previous session, cannabinoids exhibit anti-cancer activity in animal models of cancer, in many different types of tumors. As Manuel pointed out, we had to learn how to work on (unint.), but also on other tumor types. But in general, there is a wide consensus that cannabinoids, AC or CBD is another (unint.) of cannabinoid receptors in animal models of cancer can in general product anti-cancer activity. That's quite well established. Next slide, please. As Manuel also discussed, the reasons for this anti-cancer activity has to do with the different levels of control of cancer cell growth by inducing (unint.) cell death, by normalizing tumor angiogenesis and also by affecting tumor metastases. We know quite well the mechanism by which cannabinoids produce this effect, although still there is a lot to be learned yet, and there is a lot of additional studies that need to be conducted in order to clarify completely what's going on in every different type of tumor. In any case, and this is quite clear at the moment and also the fact that cannabinoids have sensitivity, high-grade sensitivity for cancer cells, but they don't produce (unint.) cells, and this could be also potentially interesting. So next slide, please. So after all these preclinical findings, they have continued by different labs, by our group, but many other groups, and some of them are present here. Obviously, the main question is, is there a potential for clinical application? Probably that's the question we would like to answer, and we don't have a clear answer yet, but we can explain a little bit what has been done at least, what we have been trying to do in the past year, trying to clarify disease. So the potential clinical application as Manuel also discussed is very limited at the moment, and the evidence for (unint.) activity in tumors, but there are a few studies that have been conducted. I will explain very shortly one, and then obviously Chris Twelves will explain later another one. So, please, next slide. So the first pilot clinical trial was conducted really some time ago. It was a pilot clinical trial, so only nine patients. And glioblastoma was selected because obviously this is a tumor type where there are very little therapeutic options, but also because there are many preclinical findings that were forming in this tumor type. So it was a good candidate. I think still it's a good candidate to perform clinical studies and see whether cannabis could add something, some additional value on the therapy that's currently being used for the management of this tumor. In this particular study, nine patients were recruited. These patients had been diagnosed with glioblastoma and then at that time they were undergoing the standard of care. It was not the same one that is currently used today, because this was a study that is the standard of care today had not been around yet. In any case, these patients were obviously undergoing surgery and radiotherapy and chemotherapy. And, unfortunately, glioblastoma patients in 100% of the cases, basically they have a relapse. So after their relapse, the patients, these patients were offered a possibility to enter the clinical study. This clinical study was for the intracranial administration of THC through a tunnel that was inserted in the cavity left by the tumor once it was removed from the brain. So THC was directly administered to these patients intracranially and then they, obviously because it was a pilot clinical trial, they were following the potential toxicity observed in the patients and then trying to obtain as many data as possible. Only with nine patient it's impossible to make a statistical analysis, so I will discuss now they were only trends, but trends doesn't mean anything. Just to point that the patients of this study, none of them had very significant side effects. When the doses were increased, some of them experienced relatively mild effects of THC. But for the regular doses that were used, there were not overt psycho activity, so it was very well tolerated. That would be one of main conclusions of this study. Then it's worth to mention that it was possible to take two samples in two specific patients before and after treatment with THC, and these samples were very valuable to try to analyze whether some of the mechanisms that we found in cells or in animal models could be also verified and confirmed in samples derived from humans. Obviously, this has to be interpreted with a lot of care, because there is not real control here and also time passed from the first sample that was taken after the operation, the second operation of the patients, and then their operation that was after treatment with THC. But in any case, this rendered interesting information. Next slide, please. So in this slide, this is a summary of some of the results that we obtained in analysis of these samples. So previous to treatment with THC and after treatment with THC. We could analyze the effects of proliferation, markers of angiogenesis, markers of cell data where three of the main mechanisms that we had seen at least in animal models could be activated by THC. And in our cases, in this sample from the patient, we observed a decreased proliferation, decreased number of base cells that more normalized and also an increase number of apoptotic cells upon analysis of the different markers, KI67 as a marker of proliferation, CD31 as a marker of (unint.) cells and caspase 3 as a marker of the apoptosis. So this suggested that the mechanism that we have found in cells and we have also found in animal models could be also potentially activated in patients, although as I said, this needs to be interpreted with care. I think it's a good proof of concept that cannabis could also have anti-cancer activity, at least in terms of the mechanism of action. Next slide, please. However, in terms of patient survival, as I said, it's not possible to extract any statistical conclusion only with nine patients. Obviously, there were not two arms in this study. And basically, what we could say is that there were (unint.) responses in a significant part of the patients in terms of magnetic resonance imaging showing decreasing tumor size after the initial treatment with THC. However, in terms of survival, although there were two patients that lived longer than expected for that code of patients in the hospital where the (unint.) was performed was (unint.) Spain. Obviously, there was not a striking effect on the survival of the patients. It was similar to the effects that the (unint.) drugs were producing in patients from that hospital that were suffering this type of tumor. So that's it. The conclusion is very encouraging rules, other encouraging results in terms of good tolerability by the patients in terms also of the existence of the activation of the mechanism of (unint.) also in the patients and also with some patients showing evidence of potential response. Obviously, we were not going to cure cancer. That's why you see THC with these patients. None of them was cured, or the survival was not extended for many months after treatment. So that indicated that it was necessarily probably to optimize the way that cannabis was administered, or the combination. So take different strategies to try to optimize the potential development of anti-cancer therapies based on the use of cannabis. Next slide, please. So then I think it has already been delineated somewhat in the previews discussed by the previous panels, but obviously there are different strategies that can be used to optimize the potential use of cannabinoids in cancer. And we think that some of them are first strength to know as much as possible what is the mechanism of action of cannabinoids, because that could probably tell us more how can we really play with the (unint.) the anti-cancer action of cannabinoids. But, obviously, also trying to identify the practice of resistance. This is something that has also been discussed by the previous panel, but I will go into some more details not. And there is also the combination of therapies, because (unint.) oncology is thinking of mono-therapy or even therapy. Yes, we want to extract to treat any kind of cancer. It's not what is used. And normally, one is going for a cocktail of different compounds, even different approaches. That could include (unint.) therapy. It could include surgery in combination with different types of (unint.). So probably we need to see whether cannabis can be included in that cocktail, but that would be the -- so next slide, please. So with respect to the mechanism of action, this has been already discussed by Manuel, so I just wanted to mention that we did a lot of work during the last 15 years to try to clarify the mechanism mainly in glioma, but also in some other tumor types. And as Manuel was pointing, we know that there is an important pathway in which cannabis (unint.) receptors, CB1 or CB2 depending on the type of tumor they can treat here. This cascade of (unint.) and mainly the activation (unint.) and mechanism that relates to apoptosis (unint.). We know quite a lot about the mechanism by which cannabinoids can trigger changes in the single composition, and this seems to be critical in order to activate cell death autophagy and then inducing apoptosis and promoting cell death. I will not go into details in this talk, because it's a little bit out of the scope of this panel. But just to point, we know quite a lot about that. And this also -- there is the possibility to really design potential combination of therapies based on the interference with some of these elements. For instance, we did a study combining with an inhibitor that enhances the combination of one of the single (unint.) that we believe could produce -- could trigger this effect downstream of cannabinoid receptors, and we were able to enhance the activity by combining THC with this compound. So this opened obviously the possibility to also use inhibitors of (unint.) all the activities for autophagy or potential mechanisms that could help to (unint.) cannabinoids that (unint.) cannabinoid receptors to stimulate this path. Next slide, please. And just to point that when we identity autophagy as one of the mechanisms that seems to be involved at least in animal models, in the mechanism of action of THC, we also went to (unint.) that we had obtained from the clinical study. And then we also found that actually autophagy was also activated after treatment with THC in these patients. So that was also something supporting the idea that this pathway is probably also activated in patients that was potentially (unint.). Next slide, please. So the second strategy for the optimization of cannabinoid anti-cancer activity would be identifying the factors for resistance to cannabinoid anti-cancer action. Next slide, please. Obviously, this is a very complex issue, and probably this needs to be run in many different tumor types and also not only as we have done in cancer cell lines of primary cancer of, in this case, glioma cells, but also the most important would be to do it in clinical trials. We mentioned that at the end of the talk. However, (unint.) approach, what we did is tried to compare cells that have different sensitivity to THC use cell death. Firstly with cell lines. Secondly with primary cultures derived from glioblastoma patients, and then we did an analysis of the gene expression profile. So (unint.) slide, but it doesn't matter, because one can see clearly that the cell lines that were more resistant also had the high grade expression of different genes and on these genes, we found several growth factors and specifically, we did a lot of work with midkine. As Manuel mentioned, we were able to show that it was associated to the resistance to THC anti-cancer. Interestingly, and next slide, please, midkine seems to be actually a factor of bad prognosis in general in glioma. Well, this is a story that we have been able to develop after these observations that actually led to a clinical study by Bloki (ph.), one of the pilots through which midkine would be working. So probably this is relevant not only in the context of anti-cancer activity, but in general in the context of resistance of glioma to different (unint.). In these graphs what is shown that patients with glioblastoma that have high grade expression of midkine, they have a lower survival and even for a tumor with a prognosis like glioblastoma, there seems to be a correlation between high expression and lower survival of the patient. So this led to the work on the role of midkine. But specifically in the context of glioblastoma and cannabinoids, we proposed this model. Next slide, please. In which enhanced expression of this factor, midkine, through binding to one (unint.) receptor is possibly from a kinase or ALK. So midkine is acting through what was able to interfere with the mechanism by which THC and cannabinoids, through cannabinoid receptors were able to induce autophagy and cell death. And let's say that enhancing (unint.) the midkine accumulation was able to prevent the action of (unint.). And therefore, a potential option was trying to interfere with midkine signaling to sensitive the cells (unint.). I'll show it now in the next slides. So next slide, please. So let's say like the third aim we'll be trying to design a combination of therapies, including enhanced THC or cannabinoids in general anti-cancer activity. And for that, obviously there could be different approaches. Next slide, please. But one of the approaches would be this one. We're trying to interfere with some of these mechanisms that promote resistance to THC anti-cancer. For instance, midkine is active throughout, so then we could interfere with midkine using midkine neutralizing antibodies or knocking down midkine expression or trying to block (unint.) by using, for instance, ALK inhibitors. Similar and like what we do for eGF receptors, those are very important in the context of glioma and many other cancer types. So next slide, please. So, for instance, in this experiment, we used tumors derived from glioma cells that have high levels of midkine. So they were particularly resistance to THC anti-cancer activity. For example, in this curve that is showing the growth of the tumors, one can see that THC is not able to reduce tumor growth, and this was due to the fact that midkine was enhanced in these tumors. So actually, when we knock down midkine expression, we would sensitive these tumors to THC anti-cancer. However, in terms of using something that could be potentially applied (unint.) therapy, we saw that inhibitors of ALK could be potentially interesting. So we used this inhibitor of ALK, and when we combine the inhibition of ALK with THC, the yellow line, then we found that there was a decrease in tumor growth. The tumors were (unint.) to THC anti-cancer activity. So this is like a proof of concept that by interfering with the mechanism of resistance to THC anti-cancer action, we do (unint.) the tumor and therefore produce an anti-cancer activity of THC. So this is something that could be potentially (unint.) in the future. Next slide, please. Also as Manuel also was discussing, cancer is very complex and contains very different types of cells. For instance, in the context of glioma, it's known that there are -- most of recurrences are probably due to the fact that there are cells with stain-like properties that look at everything in the tumor. So when one is doing the initial therapy, most of the different tumor cells are removed from the tumor, but the population of cell with the stain-like properties are still retained within the tumor. So afterwards, one has a relapse due to the fact that these cells are dividing and are able to replicate the tumor. And then probably in glioblastoma, this is one of the reasons because the patients relapse. So one thing that would be important is to see whether we can actually act not only on the different (unint.) cells, but also on the cells that are having stain-like properties that have the capability to regenerate new tumors afterwards. So we found, to make a very long story short, we found out that midkine seems to be very important for these populations. But interfering with midkine, we could also target this population, but also sensitize this population to THC anti-cancer activity. So that could be potentially an interesting approach that one could follow in order to enhance THC anti-cancer activity. Next slide, please. Actually, these graphs, I don't want to go into a lot of details, but basically they are showing the capacity of the population of cancerous stem cells that are from glioma or glioma (unint.) cells to divide and generate new glioma stem cells after different passages. What we see here is that by interfering with midkine signaling or with (unint.) signaling by using (unint.) antibody that was midkine from the medium, we produced an effect, but this effect is enhanced when we combine with THC. Therefore, we can actually eliminate completely the population of glioma (unint.) at least in these conditions. So this is probably relevant, and this could be something that could make potentially interesting to combine with certain drugs that may sensitize not in general tumor cells, but also cells that could potentially produce relapses in tumors, could be responsible for metastases, etc. And this is probably an avenue. Obviously, it's that we have initiated, but obviously it needs to be followed in other cancer types and also in tumors. Next slide, please. So as I mentioned, midkine could be a proof of concept for the (unint.) of tumors that could be potentially resistant to THC by interfering with midkine, by blocking using neutralizing antibodies, by blocking the receptor and their resistance to the cells. So this opens two possibilities, that midkine could be a biomarker, in this case, resistant to THC in gliomas, but also that there could be a resistance or other biomarkers are resistant in other tumor types that could be worth to explore. Obviously, this is something that needs to be explored in the future. And also that this could open the possibility of doing combination of therapies based on the blockage of the signaling (unint.) which promote resistance to THC or cannabinoids, it depends. And next slide, please. So to end the talk, I would like to also mention the other study. It would be trying to see whether there are some room for combination of cannabinoids and more classic chemotherapy so that at the end of the day (unint.) in most patients with cancer unless they have like a specific target that could be used for therapy. And then we thought that in the case of glioma, (unint.) could be a very good option. So next slide, please. So as Manuel also mentioned briefly, the standard therapy for the management of glioblastoma currently is still, unfortunately, the treatment with radiotherapy in combination with Temozolomide. This type of regime was actually -- the components of this study actually showed that adding Temozolomide to the treatment with radiotherapy was increasing slightly the survival of the patients and also most important was increasing the number of patients that were long-time survival. (Unint.) at least for this patient population. So that's the reason why we selected Temozolomide as a potential drug to investigation in combination with THC. Next slide, please. And this is a slide that Manuel showed in his presentation. It actually shows that the combination of THC and Temozolomide produce a very striking and a strong anti-cancer activity, leading to complete elimination of the tumor in (unint.) half of the animals and stronger the tumor size (unint.). So this was a very interesting observation. We saw that it could potentially lead to clinical development on investigation that could improve what we have found by using only THC (unint.) study. And next slide, please. So obviously it needs the reflection. The previous panel has already discussed that. What should we use in terms of really moving forward with clinical studies, well, moving forward with clinical studies that could be useful for the patient? Probably, as has been discussed, THC is probably the component that has the most potent anti-cancer activity, although in different tumor types that could be different, and CBD is clearly also having anti-cancer activity. There could be other options with CB1, CB2 agonists or inhibitors of the degradation of endocannabinoids, other pheytocannabiniods. Probably today, in my opinion, but we can discuss that later, combination of THC and CBD could be a very good option for the tolerability for the patients, because both compounds have anti-cancer activity and because there is already evidence that actually both compounds can act in not completely the same. Basically, at least take good -- improve the performance of each other because the (unint.) THC could be decreased. And the concentration of THC could be decreased. (Unint.) use of many things that contain THC or CBD in other applications. So that's why we need a lot of preclinical work to try to understand whether THC and CBD in combination with Temozolomide may have a potential anti-cancer activity, but trying to do all the preclinical work necessarily to unite the data could support a clinical (unint.). So next slide, please.

>> Guillermo, you'll need to wrap up in the next minute.

>> Okay. Yes. I'm finishing. So let's say that we need a lot of preclinical work to try to confirm that this was really relevant from the point of view in animal models. So using different ways of administration, different doses, and then we prove that this was really worth to re-explore in clinical study. Next slide, please. This is just a confirmation that, for instance, in intracranial models, by oral administration, using THC and CBD in combination with Temozolomide, we would decrease tumor size, also increase the survival of the animal. So let's say this was a confirmation that using doses that were appropriate and in an animal model that we're assembling more closely (unint.) now glioblastoma, we could have promising results. Next slide, please. So this led to the study that actually Chris Twelves will discuss later. So I will not go into details, because he will explain obviously with a lot of detail, but it was a second line study where the combination of THC and CBD (unit.) with Temozolomide was really tested in patients with glioblastoma. So Chris will explain that in detail later. So last slide, please. So just my final comment would be, we obviously need a lot of additional work, preclinical work, but also to develop clinical studies. Much more clinical studies are required to really clarify the anti-cancer activity of cannabinoids in glioma, but also in many other cancer types that, as one will discuss, (unint.) combination in certain types of tumors, in certain patients with certain biomarkers in combination with certain drugs could potentially be very useful. And that something I wanted to clarify for the good of the patients and (unint.). And thank you for your attention. That's all.

>> Great. Thank you, Guillermo. So next we'll hear from Ramesh Ganju from Ohio State. Ramesh.

>> Yeah. My talk is going to focus (unint.), especially (unint.) modulating tumor micro environment, also in (unint.). Next slide, please. Basically, as you know, all of the models can have (unint.) cannabinoids. It's endocannabinoids, which are synthesized in our body and examples of AEA and 2AG and then we talk about cannabinoids such as CB1 and CB2. And then there are synthetic cannabinoids, which are synthesizable in lab, and then (unint.) synthetic cannabinoids, for example, (unint.) CB2 (unint.) CB1 and BC2. And then there are phytocoannabinoids that have been extracted from plant, cannabis sativa and an example would be THC as well as cannabidiol. Cannabidiol does not have any psychotropic activity and it comprises of 40% of this cannabis sativa plant, which has been approved by FDA for investigation of trials, but with (unint.) and it has also been shown to be safe and tolerated in clinical trials for (unint.). It certainly has been shown actually by electron microscope that CBD can bind to (unint.) known as transient receptor potential (unint.) CB2 receptor. And the CB2 receptor has been shown to be expressed in the brain, as well as the immune system. And my talk today is going to focus on CB2 as well as this with agonist (unint.) and the TRPV2 and agonist, Cannabidiol. Next slide, please. Next slide. And my focus of this enterprise is on two different types of cancers. One is breast and lung cancer. As we can see from this slide, the estimated new cancer cases among females, 30% are breast cancer and 12% are lung cancer. That's among female. About 42% new cases comprised of breast and lung cancer were most prevalent among females. And then among males also, lung cancer comprises about 13% of new cases. Both the cancers are (unint.) and (unint.) for these cancers. Next slide. And among breast cancer, there are different types of the subtypes of breast cancer depending upon what the receptors that are present on the surface of these breast cancers. Luminal A that are associated with (unint.), luminal B that has BR and HER2-positive, and then the HER2-enriched, which are positive for HER2 receptor, and there's one subtype, which comprise about 20% of the breast cancer, that's triple negative. They are negative for all (unint.) receptors. And among all these different subtypes of breast cancer, triple negative breast cancer, also known as basal-like, has less prognosis, has the least survival. And also there are limited treatment options available for this type of breast cancer, because there are no targeted therapies available, and most of the patients are treated only with phenotype. Next slide. We analyzed first the expression of these receptors. We analyzed the expression of the CB2 receptors (unint.). And to our surprise, what we found out that it was expressed a high amount of this CB2 receptor. And we also used publicly available data. So that also showed that these cancers show high CB2 receptors. But interestingly, what we found in the (unint.) that the breast cancer, that showed expression of CB2 and had better survival compared to the cancers that showed no expression of CB2 receptor. Next slide. Then we analyzed the effect of JWH, which has been shown to bind to the CB2 receptor. In (unint.) here we have used the triple negative breast cancer and the (unint.) positive. And what we found out that the JWH can inhibit the tumor growth and a lot of time, you can see it can reduce the metastasis. And to find out the effects specifically related to tumors, CB2 receptor, what we have used, we have used agonist of the CB2 receptor, which is one of the compounds, SR compound. And what we found out is SR compound, when we combined it with JWH, the effects were appropriated and we see there was less inhibition of growth and metastasis. Next slide, please. We have used also syngeneic mouse model. In this case, we have used mouse (unint.) cell line and (unint.) that shows actually spontaneous metastasis that you observed in human. And then what we found out actually here, when you treat the mice with JWH, you can inhibit tumor growth, as well as you can see on the bottom of the slide, you can inhibit significantly (unint.) metastasis in these mice. Next slide, please. We wanted to see what CB2 receptor does actually. And so far, we have shown the effect of (unint.), but we wanted to see what has gone on with the CB2 receptor itself. And we actually analyzed the effect of -- we used the CB2 receptor knockout mice and the wild type mice. We injected these with the mouse DMBC cell line and we were surprised what we found out. The CB2 knockout mice showed much enhanced growth compared to the wild type mice. Next slide, please. Then we wanted to see the effects on mediated (unint.) for the JWH effects on mediated to the CB2 receptor. In this case, what we did is we took the CB2 knockout mice, which were injected with this cell line, and then also the wild-type mice and then, again, treated them with JWH and analyzed the effect. What we found out, the CB2 knockout mice that we treated with JWH, it did not show any effect. It did not inhibit the growth. In case of wild type mice, we saw inhibition of the growth. And you can see over here that again, the wild type mice showed reduced growth compared to the knockout mice. And next slide. We, again, analyzed the effect on metastasis. You can see over here, again, the wild type mice showed reduced metastasis compared to the knockout mice with much higher metastasis. And again when we treated both knockout as well as wild type mice with JWH, there was no effect on (unint.) in the case of knockout mice (unint.) JWH (unint.) metastasis in the case of wild type mice. Next slide, please. We also analyzed the effect of JWH using the patient-derived tumor growth mouse models, and we found out actually (unint.) of these patients. These are DMBC activity, patients that had tumor growth. Next slide. And what we see is how this JWH mediates effect. And what we found out, actually, it can be inhibit the function. In fact, in one of the chemo (unint.), CXCL12. CXCL12 has been shown to play a part, a role in metastasis. I will show you in the next slide, and actually, it enhances the metastatic potential of the migration of the breast cancer cell as well as the (unint.) properties of the breast cancer cell. And here we analyze the fact that JWH (unint.) properties by measuring the wound healing or wound closed, ability of the (unint.) cells (unint.) contain (unint.) cells and then the cells were taken with CXCL12 alone or in combination with JWH. As you can see, CXCL12 use of enhanced (unint.), which was (unint.), which was (unint.). And the next slide shows the important -- next slide shows the important role of CXCL12 in metastasis. CXCL12, as is shown, can be produced by fibroblasts. We have generated a (unint.), CXCL12 (unint.), and when we cross (unint.) with the FSP3, FSP3 has been shown to (unint.) the genes from the fibroblast. And what we actually generated a CXCL12 (unint.), in which case, the CXCL12 was specifically created from the fibroblast. And you can see on here the middle panel that shows the (unint.). CXCL12 was specifically created from the fibroblast in case of the CXCL12 knockout mice compared with the (unint.) mice. And then the lower panel shows the activity of (unint.). And then you can see over here this fibroblast, the CXCL12 expressed in fibroblast. You can see by the green signal, which (unint.) in case of CXCL12 conditional (unint.). And when we crossed the CXCL12, the traditional knockout mice with (unint.) mice, but (unint.) mice actually developed breast cancers, or it goes through different progression, which is in both the (unint.) human breast cancers. And also it develops spontaneous metastasis. You can see on here these mice, CXCL12 related mice show a significantly low metastasis compared to the wild type mouse. The CXCL12 especially produced (unint.). Next slide. We also analyzed the effect of these cannabinoids on immune cells. And what we found out actually when we analyzed the immune cells, we actually -- that these tumors -- from either knockout or wild type mice that were analyzed for different immune cells. What we found out was in people -- knockout mice showed the (unint.) number of CB4 positive as well as CB8 (unint.). And in tumors, the JWH, we found enhanced presence of the CD3, the CD8 positive cells. Next slide. And in summary, I can say that CB2 is highly expressed in breast cancer tissue and its expression correlates with better prognosis in TNBC. And JWH has been shown to bind to CB2. It inhibits TNBC growth and metastasis in different mouse models, including (unint.) mouse model. And then JWH inhibits the CXCL12 induced functional effects and deletion of CB2 enhances TNBC growth and metastasis. And CB2 activation enhances recruitment of CD8 positive T cells. And (unint.) could be used to enhance the anti-tumor immune response by activating cytotoxic CD8 positive T cells. Next slide. Now my talk is going to focus on cannabidiol. Cannabidiol does not have any psychotropic activity. And recently, it has been shown to bind to (unint.) receptor. I will focus on (unint.) receptor. Next slide. We analyzed the effect of this cannabidiol on different TNBC cell lines. As here, 159 and MB231, which are the human (unint.) cell line and 4T1 is the mouse (unint.) cell line. We showed that CBD (unint.) of the cell in a dose-dependent manner. Next slide. We also analyzed the effect of CBD in syngeneic viral mouse models. And what we found out, it can inhibit the growth of (unint.) two different cell lines here. (Unint.) mouse (unint.) cell line with cannabidiol. And also (unint.) the response in metastasis of (unint.) significantly. Next slide. Again, we analyze the effect of CBD on the presence of different immune cells. What we found that actually these tumors that were taken with CBD does show the reduced presence of the (unint.) associated macrophages as analyzed by the presence of (unint.) markers. And we also found out actually by (unint.) with macrophages (unint.) by analyzing that expression for (unint.) macrophages. Next slide. Now, the monocytes have been shown to actually go to the tumors and essentially (unint.) macrophages, M1 macrophage or M2 macrophage. And M1 macrophages have been shown to actually inhibit tumor growth in (unint.). M1 macrophages have specific (unint.) tumors. M2 macrophages have been shown to enhance the tumor growth. That has shown discrete activity (unint.) growth factor that enhanced (unint.). And these M1 and M2 macrophages can be different genes based on different markers (unint.) or different chemo kinds that are present in these macrophages. Examples include like M1 macrophages expressed IN12 and it has also been shown (unint.) expression of INOS. That is M2 macrophages expressed -- and has high expression f (unint.) as well as diagnosis of CB206. Next slide. Now we analyzed the expression of these M1/M2 markers in these tumors, and what we found out actually is CBD (unint.) showed reduced presence of these M2 as analyzed by CD206 and F4/80 markers and as well as by ISC and as you can see, reduced expression (unint.). Basically, CBD (unint.) the preparation of the presence of these M2 macrophages in these tumors. Next slide, please. Now, we'll move onto see the mechanism by which CBD can inhibit these macrophages in the tumors. We analyzed the factor of CBD1 to (unint.) the cytokines reduced by these (unint.) cells. And what we found out actually (unint.) of GM-CSF, as well as (unint.), CXCL12 or also known as MIP-2. And both of these have been shown a very important role in the (unint.) of the macrophages to the tumors. Next slide. As I told you, recently, cannabidiol has been shown to be bind to this TRPV2 (unint.) expression of this TRPV2 receptor in different breast cancers. And what we found out is it was expressed in malignant, metastatic, as well as triple negative breast cancer. And the bottom slide shows the percent expression. We can see malignant as well as metastatic at least 60% (unint.) expression of the (unint.). We have (unint.) also expressed on different TNBC cell lines. (Unint.) human. That is SUM, MDAMB231 and SCP2 as well as the mouse (unint.) cell line. That's (unint.). Next slide. We have also analyzed expression in TNBC (unint.) in about 120 patient samples. And, again, we found most of this -- like there was a strong expression of like this TRPV2 shown -- there was high expression as well as moderate expression of TRPV2 was present in TNBC compared to (unint.). And then, next slide. (Unint.), so we wanted to look at the survival of these patients. It was a surprise, what we found out, that patients that expressed high TRPV2 showed much better survival compared to the patient that has no expression of TRPV2. And we are using a relevant data set. So what we found out that, again, high and moderate expression of TRPV2 showed much better survival compared to the low expression. Next slide. We also analyzed (unint.) expression in patients that were treated with chemotherapy or not treated with chemotherapy. And what we found out, the (unint.) breast cancer patients (unint.) that were not treated with chemotherapy, there was no difference in the survival between low or high expression TRPV2. However, we found significant difference in chemotherapy, chemotherapy treated patients (unint.) patients. The high TRPV2 expressed in patients showed much better survival compared to those (unint.) TRPV2 patients. Again, (unint.) breast cancer even if they are treated with chemotherapy or not treated with chemotherapy chemo type. Next slide. Then we wanted to see if it has an effect on, because TRPV2 as a (unint.) shown to (unint.) -- involved in uptake of (unint.) as well as different (unint.). We wanted to see if it has an effect on drug uptake. And we have used here a drug, Doxorubicin, formerly used for breast cancer patients, and it is the natural (unint.). And we measured the uptake of this drug (unint.) in presence or absence of cannabidiol. What we found out, as you can see, in case of control, there was more uptake whereas Doxorubicin (unint.) you can see that take up is in the cells. And then the presence of CBD was much higher uptake of (unint.). And then we also wanted to analyze the effect of this other CBD in combination with Doxorubicin on apoptosis. Here we have more amounts of CBD (unint.). It was 5 (unint.) of CBD as well as (unint.) analyzed the effect on (unint.) markers that is been in part (unint.). And then what we found out when we did the combination of the CBD and Doxorubicin, it showed enhanced (unint.) markers. And then we also analyzed apoptosis by (unint.), and then we found out this combination of CBD with Doxorubicin showed much higher apoptosis compared to CBD or Doxorubicin alone. Next slide. We wanted to see if these effects had mediated (unint.) TRPV2 (unint.) antagonist of the TRPV2 that is (unint.). And then, again, what we analyzed the effect of CBD on this Doxorubicin in presence of this transmitter. We found out that (unint.) uptake, which would enhance the presence of CBD, which is the green bar, and then, again, the presence of (unint.). Then we showed similar effects on the apoptotic markers (unint.) the effects of CBD (unint.). Next slide. We further confirmed that these effects are mediated by TRPV2 with double regulated TRPV2 (unint.) or non-targeted SIRNA. You can see on here the (unint.) expression was refused (unint.) SIRNA, especially for TRPV2. And then we used these cells for uptake of this Doxorubicin drug we can see in the lower panel in case of like the cells that were transferred to the non-SIRNA, that is the green bar, compared to the red bar (unint.) uptake. And, again, all of this uptake (unint.) the presence of CBD in case of non-specific (unint.). Again, (unint.). The CBD with Doxorubicin (unint.) formation only in the cells that (unint.) with non-specific SIRNA. Next slide. We further confirmed -- we have also over expressed TRPV2 in these cells. You can see the one here where SM blocked the TrPV2 that was expressed and the (unint.), again, analyze the effect of this TRPV2 over expression of (unint.) uptake (unint.) here. This is (unint.) that is a factor control is the green part and the red part is the TRPV2 (unint.) over expression cells. And you can see over here, the CBD enhances the Doxorubicin uptake (unint.) TRPV2 over expression (unint.). Next slide.

>> Excuse me, Ramesh. This is Jeff White. We are having some problem hearing you. Your sound is horrible.

>> Oh, okay. Can you hear me?

>> That sounds a little better now. And so when your voice volume drops it becomes worse. So if you can keep the voice up --

>> Oh, okay. Can you hear me now?

>> I think it's -- let's try it.

>> (Unint.) Yeah, can you hear me now?

>> I think it's better.

>> Okay. All right. Yeah. This shows the structure of the TRPV2. It contains six trans-membrane domain and overload, which has been shown actually more in uptake of these (unint.). We wanted to see if this is important in Doxorubicin uptake. And we have generated a new (unint.) receptor. Next slide. And using this mutant, we, again, analyzed the effect on Doxorubicin uptake. As you can see over here, this is the -- there is a TNBC cell line here, again. We over expressed this mutant part, this TRPV2, that (unint.) and then, again, analyzed the effect on Doxorubicin uptake. And you can see over here this red part that shows over expression of TRPV2 mutant with should reduce the uptake of Doxorubicin. Again, in the presence of CBD in case of (unint.), you can see enhanced uptake, which was, again, not seen in the case of the cells that over expressed this mutant TRPV2. Next slide. We also analyzed the effect of CBD on the cisplatin resistant lung cancer cell lines. And we (unint.) lung cancer cell lines. Here we used 468 as well as A549 to analyze the effect of CBD on following formation and analyze sphere formation. (Unint.) cisplatin slightly increases the growth of this cell, but CBD (unint.) both the colony formation and the sphere formation of both these cisplatin resistant drug cancer cell lines. Next slide. Now, cancer stem cells have been shown to play an important role in enhancing drug resistance. We analyzed the effect of this cannabidiol on cancer stem cells. And these cancer stem cells were analyzed by biomarkers like CD44 and CD133. You can see there was a significant inhibition of the cancer stem cells in the cells that were treated with cannabidiol. Next slide. We also found out actually CBD significant inhibited the migration of the drug -- the cisplatin resistant lung cancer cell, both H460 as well as 549. Next slide. Next slide.

>> And Ramesh, you'll need to wrap up in the next minute or so.

>> Okay. Yeah. I'm just finishing up. And then we have also analyzed the effect of this CBD (unint.) on this cisplatin resistant lung cancer cell line. And you can see over here, it significantly inhibited the growth. Cisplatin showed slight inhibition, but CBD significantly inhibited the growth of these cells. And then we also found out (unint.) metastasis as you can see in the lower panel of the cisplatin resistant cell lines. Next slide. Our initial data -- I mean preliminary data, it showed that there was actually enhanced presence of these anti-cells in these tumors that were treated with CBD. Next slide. Okay. I'll go to the next slide. Today I presented the data which shows that these cannabidiols may have an effect on modulating the tumor micro environment (unint.) by tumor (unint.) that can contain different (unint.) cells. That includes fibroblasts, as well as immune cells and anti-tumor cells (unint.) as well as the (unint.) play an important role in growth and metastasis of tumors and actually targeting this tumor environment is an important area of research for inhibiting the growth of tumors. And what we believe is that these (unint.) play an important role in modulating the tumor environment, what I have showed you today, activity. This JWH, it can inhibit the CXCL12 functional effect. CXCL12 has been shown to be produced by the fibroblasts and this CXCL12 are produced by fibroblasts, actually acts on the endothelial cells and changes the permeability of endothelial cells that enhances the metastasis. And that way, JWH can inhibit the metastasis. We have also shown that the JWH actually increases the presences of the cytotoxin T cells, which can inhibit the growth of tumors and also decreases (unint.), which has been shown (unint.) immune responses. And in case of CBD, we have shown that as we can innovate from the (unint.) GMCSS, again, that has been shown to play an important role in the improvement of macrophages. And we also agreed that the CBD may play an important role in this M1 and M2. It's very important, this M1 and M2 macrophages (unint.) M2 macrophages enhance the tumor growth. And it has been shown (unint.) and CBD may enhance actually M1 type of macrophages compared with the M2 (unint.). And, again, there is some data that indicates that it may also enhance the (unint.). There's a lot of studies that need to be done (unint.) cannabinoids in the immune system, especially in the (unint.) and to enhance the anti-tumor immunity or enhance the immune response of (unint.). Next slide. I would like to thank the lab members that did all the work to prepare for today, and the study was supported by (unint.).

>> Ramesh, we're going to need to move onto the next presentation.

>> Thank you. And our next speaker will be Chris Twelves from the University of Leeds in the United Kingdom.

>> Thank you. I hope you can all hear me. I'd much rather be in Washington, (unint.) in the United Kingdom at the moment not only to see the city, but also to meet and discuss with such a varied group of people. One of the disadvantages of these meetings is that today I've not been able to join you, because I've been tied up with COVID-19 vaccine issues and clinical trials in Leeds. So what I will be discussing now is what you see on the slide there, a Phase 1b, so an early clinical trial of a cannabinoid in patients with recurrent glioblastoma. So thank you very much to Guillermo for introducing the topic in the context of glioblastoma. Thank you, Ramesh, because one of my day jobs is as a breast cancer medical oncologist, so thank you for orientating me in that particular area. But what I suppose I'm looking to do now is to look at testing, if you'd like, a lot of the science that you've heard about and seen what exactly this may translate into in the real world of patients with cancer. Next slide, please. So here are my disclosures. I did do some advisory work with GW several years ago. There are some others there. But in addition to the disclosures, I suppose I've got a bit of a disclaimer, because my background is originally in clinical pharmacology. I'm a medical oncologist. I've been involved in the development of a few drugs that have come into routine practice in cancer, but I'm not a cannabinoid person. So I come at this from the perspective of a cancer drug developer rather than a cannabinoid focused person. So my take on this is perhaps a little bit different, and I come at this as somebody who has seen a range of different, very promising preclinical candidates, some of which have made it to the clinic and some of which have not. Next slide, please. So you've heard already from Guillermo about glioblastoma multiforme. It's an uncommon cancer, but it's the most common primary brain cancer in adults. It's incurable, and that doesn't quite do justice. What a dreadful disease this is. Most cancers or many cancers, I should say, are curable if you catch them early enough, if you give additional treatment. Some cancers, the hematological cancers and pediatric cancers can be curable even if diagnosed at an advanced stage. But GBM, glioblastoma multiforme is almost unique in that it is essentially incurable at whatever stage it is diagnosed. About one in 20 patients will live five years. And while many of these are patients in their middle life with families, they're in the very productive period of life, and it's a devastating illness, because not only is it cancer with all the implications that that carries, but because it's in the brain, it changes who the person is. Their personality, their physical and social interactions are ruined by this disease. And I'm not a neuro-oncologist, but I was able, or I had the duty to treat patients with this disease 35 years ago when I was training, and it really made a deep impression on me just how much worse, if you like, this disease is than most other cancers because of where it is and just how badly the prognosis is. We do have treatments for these unfortunate patients. That was with expensive surgery, I say, which means debulking, removing as much of the cancer as is possible. Unfortunately, we know that even if you remove as much of the cancer as possible, there will still be cancer left behind and of course removing a substantial part of the brain raises issues in itself. These patients are then treated with high-dose radiotherapy, which does add something to their short-term/medium-term survival with side effects in itself and we give them Temozolomide chemotherapy, which adds something, again, to the short-term/medium-term survival. But these are often young adults, middle age adults, and the average overall survival from the initial diagnosis is quoted as being about 14 to 18 months. And those figures, those quotes are for patients who are well enough to get into tertiary cancer referral centers and well enough to undergo treatment. So the average patient in the street probably has a worse prognosis than that. Those patients who do well enough to have their cancer resected have high-dose radiotherapy and chemotherapy with all the side effects, unfortunately, that involves. Those patients, their disease is usually controlled for about six to nine months, after which the cancer almost always comes back. And after the cancer comes back, some patients die within a few weeks, some within a few months, but their prognosis is really very, very poor. And for those patients whose cancer has come back, there really is no standard effective treatment. But one of the disheartening things about glioblastoma is -- a little background of my career as an oncologist, in most cancer types, we've made substantial advances. But for patients with glioblastoma multiforme, the treatment of surgery, radiotherapy, they've refined themselves in the last 30 years, but they've not made a major impact on the natural history of this disease. And the chemotherapy that we give after that initial treatment to delay the cancer coming back has improved a bit, but not a lot. Even in recent years with all the focus on molecular biology, we've learned that certain molecular phenotypes, such as methyl binding DNA, methyltransferases promoter methylation status may tell us something about the natural history of the disease or sensitivity to chemotherapy, but it doesn't actually lead to long-term survival. We've seen very few advances therapeutically. There is the use of a drug called Bevacizumab, who some of you will be aware of, which targets the vasculature of tumors, which in patients with glioblastoma certainly can improve the appearances of the MRI scans or the imaging, but it's not clear if it has any effect on survival. And there is another unusual treatment where patients have electrodes placed on their scalp to generate electric currents that does appear to have a modest impact on progression-free survival and overall survival. But the bottom line is that things are not a great deal different as I end my career in oncology compared to how they were when I started it 30-35 years ago. So the cannabinoids, I'm very pleased that you've been -- you're much more familiar with these than I am. As I said, this isn't my specialist area, but there is a rationale for looking at cannabinoids in patients with glioblastoma. These tumors do expressed CB1 and CB2, and high-grade tumors in particular express high levels of CB2. And on the right hand side of the slide, you see a representative panel of some of the preclinical data that has already been presented. At the top there, you see three different glioblastoma cell lines. I apologize if this isn't legible, but basically, THC and Temozolomide, the cytotoxy, have a bit of effect on the cells lines. And if you give the two together, the histograms or bars on the right of the (unint.) slide, they appear to have additional activity. On the bottom left there, you see similar data, looking at the increase in volume. The curve that's going up most steadily is the untreated one. The two in the middle are in the animal models where the treatments were with either THC or Temozololmide, but some benefits in the bottom is the combination. And on the right hand side of that slide, you see essentially the same data presented in different ways. So the preclinical data are indeed there, but the only clinical data comes from the trial that was referred to earlier by Guillermo, the Guzman trial, which was a pilot study of essentially instilling a cannabinoid into the cavity where the brain tumor had been resected where there was a suggestion of biological effect in terms of tumor proliferation in two of the patients who were treated. But all of this preclinical data really I think we have to view as being hypothesis generating. It could help us design clinical trials. But as an external observer, I would still say that the proof of principle that cannabinoids are effective in glioblastoma multiforme we have yet to demonstrate that definitively. Next slide, please. So the drug that we're talking about, the Sativex, the molecule you already heard about, Nabiximols has been developed by GW Research. It combines a combination of THC and CBD along with other ingredients. It's administered as an oral mucosal spray, and it has been used in a variety of other settings. There was a paper you'll be familiar with from a couple of years ago from Dr. Palen (ph.) and colleagues looking at pain symptom management, which was intriguing, because clearly the Nabiximols had an effect in terms of altering pain in these patients with cancer, but it didn't satisfy its primary endpoint. So a halfway house result, but clearly there was an effect. Next slide, please. So the trial that we carried out was looking at Nabiximols given as a spray in patients with glioblastoma. And what we were looking to do was primarily to establish whether we could administer the drug safely in patients with glioblastoma that had recurred after the initial treatment, and I repeat myself. This treatment at first presentation is limited, one that the cancer comes back, that there isn't standard effective treatments. We wanted to see whether you could combine this new intervention with a dose-intense retreatment with Temozolomide chemotherapy. The patients who we treated were adult patients. Their cancer, their tumor would come back after standard first-line treatment. The KPS over 60 means that they were relatively fit. They were fairly stable, and they were on either no steroids at all or a steady dose of steroids, and their organ function was satisfactory. We did an initial dose escalation or dose finding phase of the trial, which I'll describe in a minute, and then expanded this across a number of sites between the U.K. and Germany when we did this trial a few years ago. It will be published, I should say, very shortly in the British Journal of Cancer, and will become the second clinical trial in this context following the Guzman trial published in that journal, the first randomized trial. The patients took the Nabiximols or in the second part of the trial, placebo at a dose that was individualized, which I can explain in just a second. So they didn't all receive the same number of sprays of the placebo or of the therapeutic agent. What happened was the individuals started taking one spray a day on the first day. If they tolerated that, they then escalated that dose in the first part of the study, the dose finding part of the study where they were just taking the Nabiximols. It escalated that by one spray per day until they experienced side effects, at which point they stopped increasing the dose and if necessary had a brief break. But in this way what we sought to do was to individualize the dose in each patient, so quite different from the convention dose escalation of Phase 1 trial. There was a cap on the total number of sprays that patients would receive, delivering the doses of CBD and THC that you see there. And the plan was that patients would remain on treatment for a year or until they discontinued the trial. The patients received this alongside DIT, is dose-intense Temozolomide, so this is standard chemotherapy. I say "standard," but it was given in a slightly more aggressive or more intense dose than usual, because these were patients who cancers had relapsed. Next slide. During the first part of the study, we really were focusing on how feasible it was to do this dose escalation in individual patients. This has been done in other studies. The study in pain, the (unint.) study in pain did adopt this approach, but clearly these patients with glioblastoma are a different patient population, so we treated half a dozen patients to see how feasible this dose escalation was. Having established that that was feasible, the plan was that we would then randomize a second group of patients to receive -- all of them receiving the dose-intense Temozolomide chemotherapy, half of them to the cannabinoid and half to the placebo. It's an early phase clinical trial, so the toxicity was our primary endpoint, but we also wanted to get some sense of any hints of efficacy by looking at progression-free survival, how long until the cancer again became active by complex MRI scanning and survival and look at the pharmacokinetics of the cytotoxin, because we didn't want the cannabinoid to interfere with the pharmacokinetics. We also did some post-hoc evaluations on the basis of what we saw in the initial analysis that I'll describe later. Next slide. So here you see the patients part one is the cohort of six patients where we looked at how feasible it was to dose escalate in individual patients. We had the age. The performance status is the KPS, so these were basically patients who were fit, notwithstanding the fact that they had recurrent glioblastoma, and we have there the data as to how long their initial diagnosis to relapse. Similarly on the right hand panel or part of the panel we have the part two phase where the patients were randomized either to Nabiximols or to placebo. Again, they were very similar ages, similar fitness levels, and you see there for the first time that we see a slight difference in the slight characteristics. If you look at the time from the initial diagnosis to the patients who are relapsing and entering the trial, the patients who were randomized in the second part, the Nabiximols, had a rather longer period before they relapsed than those on the placebo arm. I don't think there's any enormous significance to that except that this was a small trial and in small trials, you do get imbalances in randomization. Next slide, please. So this is the first part. We don't need to go through all of this, but we assessed seven patients. Six of them were eligible in two cohorts of three patients. They underwent the dose escalation procedure. It worked. They ended up taking between 3 and 12 sprays a day. They continued on treatment for many weeks, and they were able to receive a good dose of chemotherapy alongside the Nabiximol. So that appeared to be effective. We did see some toxicity. It wasn't severe in the sense of being alarming or life-threatening, but it was unpleasant for the patients who might experience lethargy, dizziness, tiredness, some diarrhea or sickness. But we demonstrated this within patient dose escalation was feasible in this quite challenging group of patients. Next slide. In the second part of the study, we were looking at randomizing patients, so we started with 26 patients were assessed. Twenty-one were randomized. And as luck would have it, 12 received the chemotherapy plus the cannabinoid. Nine received the chemotherapy alone. If you look on the right hand side of the slide, you see that in terms of the cannabinoid, the patients randomized to the cannabinoid rather than the placebo received an average, a mean of 9.5 sprays per day. If you look towards the bottom, the placebo group, they received a few more sprays per day, clearly indicating that there were some side effects from the cannabinoid. The dose of chemotherapy that the patients received between the two arms though was very similar. So administering the cannabinoid wasn't significantly affecting the dose of the chemotherapy that could also be given. Next slide, please. If we look at the tolerability, and in an early phase trial that is absolutely key. If we look at the text on the left hand side of the slide, TEAEs are treatment emergent adverse events. So the toxicities that we saw in the trial were similar in both arms. We saw some vomiting, dizziness, nausea and fatigue. But when we looked at the part two bit where patients were randomly allocated either to the chemotherapy alone or the chemotherapy and the cannabinoid, we saw that there was rather more in the weight of side effects with the cannabinoid, and that those side effects were rather greater. I don't want to belabor this, because it's trial methodology, but you see the middle column there, the CTCAE grade. And if you compare that in the Nabiximols arm to the placebo arm, there was more toxicity and the numbers were a bit higher. But the toxicity was still by conventional standards of cancer drugs relatively modest. Next slide, please. So now we come onto the efficacy, and I would emphasize that the primary endpoint of the study was to show that this was feasible, that this was tolerable, but we did incorporate -- in the expansion phase of the trial, we did incorporate randomization between chemotherapy alone and chemotherapy plus the cannabinoid. And that was because we were concerned that patients with brain tumors who have had extensive previous treatment, it would be quite or could be quite difficult to tease out side effects that were due to the underlying disease as opposed to the treatment, but also to look for some hints as to regards to efficacy. So if we look at the efficacy data, then what we see on this slide is the -- on the right hand panel is the progression-free survival. So this is our data showing the time to which -- until the patients' glioblastoma progressed, usually on the basis of brain scan. And here you see that on the top in the blue are the patients who received the cannabinoid with the chemotherapy. The red line, the dotted line is the patients who received the chemotherapy alone. And if we just focus on that randomized element of the slide, we see that in both arms of the trial, patients progressed, 4 out of 12 on the Nabiximols arm, 3 out of 9 on the placebo arm. But if we look at overall survival at 12 months, there was a striking difference, which we'll see in the next slide. And that's a little bit -- sorry, what you see on the right hand panel. I apologize. And that's a little bit surprising, because there wasn't a big difference in terms of when the patients' cancers progressed. But in terms of when the patients died, if you look at the right hand part of this slide, and I apologize for my early confusion, you see that on the blue curve, the patients who were receiving the combination, they have apparently superior survival. And the previous find endpoint was survival at 12 months, and the proportion survival at 12 months in the Nabiximols arm was 80% compared to just over 40% in the placebo arm. Now this wasn't an efficacy study. It wasn't statistically powered, but if you indulge yourself and do a statistical comparison, that appears to be nominally sophistically significant. Next slide. Because of those data, we looked and did some post-hoc analyses. We went back and looked at two-year survival, which hadn't originally been planned. Under two-year survival for the interventional group, if you like, the Nabiximols arms was about 50% compared to 20% for the placebo arm. When we estimated median overall survival, again, that appeared to favor the cannabinoid arm. And as a way of trying to -- which is interesting and encouraging, but I guess you're taking the same data set and slicing and dicing it in different ways and coming up with the same answer. So what we also did was look at the EORTC prognostic indicator, which looks at a range of different prognostic indices to identify what a patient's median survival or (unint.) survival rather would be expected to be. What we saw in that analysis was that this group of patients overall in both arms of the study did a bit better than you might usually expect, and I think that's not surprising. These are clinical trial patients. But if you broke it down by the treatment arms, and I'd draw your attention to the bottom left of the slide, in the randomized element of the trial, ten of the patients treated with the Nabiximols did better than predicted by the EORTC calculator compared to just three of the patients on the placebo arm. So I accept and appreciate that this was a selective group of patients who were well enough to go onto the experimental trial, but there does seem to be a difference between the two arms. Next slide, please.

>> And Chris, you have about a minute to wrap up.

>> Yeah. Thank you. Pharmacokinetics are easy to roll through (unint.) pharmacokinetics, but I'm pleased to say that the cannabinoid didn't affect the chemotherapy pharmacokinetics. Next slide. So strengths and weaknesses. Well, I'll be bullish about this. It's a clinical trial. We tested it to the patients. We introduced the element of randomization. So we're in the real world and we're trying to do the best that we can. And it is the first systematic reevaluation of this type of agents in cancer in a randomized trial. The individual dosing appears to work. And by having the randomization at least we've posed the questions to whether there is an efficacy effect. But at the same time, of course I recognize the weaknesses. There's a small number of patients across a range of different centers, so there is real potential for heterogeneity in practice and bias in patient selection. The balance between the patient allocations wasn't equal, and so there are inevitably flaws. You either come at this as a cup half full or a cup half empty. And for me, the randomization is a strength, not a weakness. We didn't have a pre-specified power calculation, because it wasn't an efficacy study, but the chemo regimen isn't routine or generally used, and some of the analyses are post-hoc. At the time as I'm trying to look at my slides had raised a question. I hope to (unint.) something similar. They did the MGMT methylation status. So the answer is I know it, but the company don't because it wasn't part of the predefined study protocol. So we don't have those data, which I apologize. So finally if we move to the last slide, the spray, the Nabiximol spray is tolerable. We can do personalized dosing in this patient population. No new safety concerns. No evidence and in fact, a negative effect on the PK of the chemotherapy, and how you interpret the outcome data, I don't know for sure, but I think that we've seen so few positive signs in glioblastoma that these differences are at least worthy of discussion and evaluation. Thank you.

>> Thank you, Professor. Our final talk before the panel is from Gil Bar-Sela from the Emek Medical Center in Israel. Gil.

>> Hi, everybody. I'm Gil Bar-Sela, professor for oncology (unint.) from the Emek Medical Center. It's in the northeast of Israel. My topic will be the use of cannabis during immunotherapy. Do we really know what we are doing? And of course, I'm very happy to take part in this conference, and thank you for inviting me. Those are my disclosures. So in the last (unint.) at least, we have both things coming together, the use of cannabis by many, many patients during treatments, during oncology treatments. And, of course, the interest of immunotherapy to almost any kind of cancer disease. So if we are taking both direction, we should note that patients are taking it together, and of course we need to know what we are doing. So if we are -- just take a look on several publications that were published in different aspects of diseases. We see that there is improvement of autoimmune diseases by using cannabis. Of course, it doesn't mean that it's inside mechanism of the disease, but it may be. We can see a better progression or better improvement of symptoms in inflammatory bowel disease. In Graft-versus-Host-Disease there are many -- not many, but some studies, not just one, that showed really improvement even if you started earlier in the treatment. And also in multiple sclerosis, we're all familiar with it, but also in the diabetic type I in a study with animals. So it's different aspects, but you can say that it influences autoimmune response of surviving and it may interfere with the immunotherapy. We're all familiar with the complicity of the immune system and the immune response to immunotherapy. We know that we have some activators and some inhibitors, different T cells and different cells in the tissue, so it's really hard to understand the (unint.) immunotherapy, but at the end, we have as end results the response rates of the patients. So we need to keep it mind and try to understand it, but we need first to get the answers of what happened. So the first of the mission of the study was actually retrospective analysis with patients who to Nivolumab in a different cancer diagnosis. And we just looked back what's happened with them. It was published in 2019, but we first reported in 2017 in ESMO where we saw that the response rate was very low if patient had background cannabis when starting immunotherapy. We separated groups for lung cancer and non-lung cancer. That's mainly melanoma (unint.). We know that the melanoma, it's the first line in dose use. Nivolumab was second or third line in the lung cancer. But anyway, the cannabis users had lower response rate also in lung cancer, but also of course in melanoma and rental (unint.). And if we took out those patients who died two months after starting immunotherapy, because we know those patients are not responding, so the gap just became larger. So I think it's really something that we should be aware of it. In this study, we didn't find correlation to a survivor or progression-free survivors. It was different in survivor for one month in the median. But, of course, the groups are too small for such a study and retrospectively, we have a lot of things that influence. Mainly it was brain metastasis, performance status and so on, very basic characteristic. So in the second study, we tried to collect some data prospectively, but also add some direction of mechanism. We want to go deeper into the endocannabinoid system. We thought that it may be the one that influenced the immune system. So we measured the level of the endocannabinoids before starting the immunotherapy and after it. And the patients in observation and (unint.), you can see that there was two-thirds who were using immunotherapy without cannabis and one-third had cannabis in the background. Those were the characteristics of the patient. There was one difference, but I think it's very important. More patients on the cannabis group were in their second or third line of treatment and not in the first line. It's important, but we correct the results regarding survival and progression-free survival to these characteristics. So it seems the results are true, but it's an important issue to keep in mind. One interesting observation, both the count of lymphocytes is really reduced in the cannabis users. It maybe gives us some hint to see in what direction we need to go, but it was very interesting to find. You can see that there was a big difference in the time to tumor progression. It was 3.4 months instead of 13 months in the non-users of cannabis, and of course it's a huge difference in time to tumor progression. But, of course, also in the survival, you can see it's half a year instead of over two years when we are comparing the groups and when we corrected to the line of treatment. So it's a true difference. Observational, of course, but a true difference. There were also differences in response mainly in the complete remission. It was 21% instead of 9%, and, of course, the progression disease was also more than 20% difference for the non-users of cannabis. With this slide, we saw less autoimmune side effects in the group of cannabis. I think it's very important to see the difference in the colitis, but no patients who used cannabis has grade three or four colitis. And 9% of the group without cannabis has this side effect. But also you can see that we didn't reach a significance. It was just new, but we also enrolled one patient with edema and one patient with general deterioration. So it may be related to the immune side effects, and also they were in the cannabis group. So without those two patients, this probably would reach a significant difference. What happened regarding the endocannabinoids? Well, I think that was very interesting. You can see the use of cannabis did not change the levels of the endocannabinoids. There was no difference between the users and the non-user in each one of the cannabinoids. Here we have a line, which is 27, and it was not different. What really changed the level of the endocannabinoids was the use of immunotherapy. You can see that the level is really changed after using immunotherapy in each one of the endocannabinoid. And what we further found that four cannabinoids influenced the survival. Reduction of three of them, those specific endocannabinoids were with better survival, and this one was elevated and had a prognostic, positive prognostic value. So we can build some kind of prognosis index while using the endocannabinoid system. Of course, it's just a beginning of direction to be -- that needs to be deeper in other studies that we are doing right now, but I think it's very important to be aware of all those differences. So what we have in the study, we saw that there was a reduction in the immune adverse event by using cannabis in the background so that the use of cannabis really (unint.) of survival and decreasing time to tumor progression. And we find that (unint.) the cannabinoids influenced the endocannabinoids level in the body, but in immunotherapy (unint.) different in dose and endocannabinoids. And so the difference in the overall survival and time to tumor progression actually has (unint.) around two for both of them, and, of course, with the adjustment to the line of treatment. So my conclusion for this study is that we should be cautious with starting immunotherapy under cannabis use at the baseline. That's what I'm advising my patients, trying to stop the cannabis or to see if they're really needed once they are starting the immunotherapy. Maybe they can add it a little bit later, after the creation of the immune response in the body. We were surprised with what the dose results were. If we go back 35 years ago to the studies that were done when cannabis was used for HIV patients to reduce the side effects of the treatments back in the'80s, we can see that the THC really suppressed cytotoxic T cells and along the use, we have other studies that are showing the same actually also for the CBD. So we should not be so surprised that the use of cannabis influences the results of immunotherapy. So what we are doing now, we are now going deeper into the mechanism, trying to understand what actually happened when those two modalities of cannabis and immunotherapy are combined, what happened in the body and specifically, what happened to the different T cells. So we are taking blood samples from patients who are on chemotherapy or immunotherapy and starting the cannabis before they are starting the treatment and after, they were using cannabis in several points and still what happens to the T cell population. We think that we will find differences between the groups because every patient is actually analyzing his own results. So the difference will be very specific, and we don't need very huge groups of patients. And I think we find differences when we are starting cannabis on chemotherapy or on immunotherapy. Of course, we still don't have those results. So thank you very much for the opportunity to give this topic, and I hope you find it interesting. Of course, it is open to discussion in the coming minutes.

>> Yes. Thank you. So now we'd like to ask all the speakers to turn on your cameras and unmute yourselves so we can have our panel presentation. I want to thank everyone for giving outstanding presentations, and we are certainly looking forward to having a lively discussion. We have several questions that have come through, and I believe Donald is going to start off with a few questions for the speakers.

>> Yeah. First of all, thank you, Gil, for that excellent presentation and for all the work Israel colleagues have done advancing the field for us. My question with regards to the study, as we know, PDL1 status is a great predictor of outcomes. And my concern about the data that we just saw was, as you point out, the statistically significant difference between those patients who were receiving immunotherapy as first line versus second or third. And my concern is that PDL1 status or the line of therapy or in fact even though it wasn't statistically significant, the amount of liver metastases being 67% versus 19% may have been confounders in this data. And it's important to know because this for me has been practice-changing, as we say in oncology. I inform all of my patients on immunotherapy about these results and caution them about the use, but I wonder if there are other confounders.

>> Of course there are confounders. As you mentioned -- we know that there are people with more advanced disease are reaching the cannabis in larger groups in the first line, and by itself is a confounder. I think we can see also the differences in the response rates that are in two studies, in the retrospective and also in the prospective. And also the reduce of the side effects by using immunotherapy underlying cannabis, that all means that it actually changed the immune response in the body. So we don't have the mechanism, but it's just in the States. I'm not saying the patients don't take cannabis if helps you to sleep, against pain, and all the symptoms, but you should be aware that it can be influenced, the results, and I don't think it's the last answer for this conflict of using both of them. But it's really going to give us direction in what we should be looking for in the near future actually and also to give the information to the patient. I think that's important.

>> It would be interesting if you could retrospectively check the PDL1 status of the two different groups and see if that might be a predictor as well as the cannabis products used, whether they're inhaled versus highly concentrated oil. So something to think about. Chris, tomorrow I'm going to talk about some barriers to enrolling cancer patients in clinical trials, and I noticed in two and a half years at ten centers that 27 patients were enrolled in the Nabiximol study. Can you comment on that?

>> Part of that slowness was due to the fact that this is a difficult group of patients to include. As you'll be familiar with, the standard requirements for early trials are that basically patients are pretty stable, reasonably fit, and have got a few months to live. So this was a challenge. So I don't think that's an inherent obstacle. I'd rather turn that on its head, because even in the U.K. we have a study, a trickle of patients who ask about or are using cannabinoids. So I think we should use that to encourage the rational evaluation of such patients. So I think it's the patient population, not issues around the use of cannabinoids.

>> Just one final question for everybody is, you know, CBD certainly has jumped to the top of the most favorite cannabinoid list and sort of agreeing with Mark Wallace's comments yesterday that that's in the absence of a lot of information. I appreciate THC, particularly for glioblastomas, may have good agonist activity with the CB1 receptor. CBD actually, in my understanding, is a negative allosteric modulator, which changes the shape of the receptors. So, you know, when my patients ask me what is the right ratio I should use, I tell them all we know in the literature is one-to-one THC-to-CBD. But I wonder, does CBD detract? I know in vitro it's synergistic, but is one-to-one the right ratio that we should be evaluating in cancer? Anybody.

>> You articulated the question very clearly. The conventional way to evaluate this in drug development would be to do randomized phase two trial with the different ratios looking for either clinical or pharmacodynamic endpoints. There is a temptation because this is a slightly novel, some might say off the wall approach to try and be overly innovative. But, you know, we have models for not being clear about what the relative contributions are throughout the study we can fall back on.

>> I can comment on the question. I think it is very interesting. Obviously, as Chris said, I mean, the only way to really solve the question is doing clinical trials comparing different ratios. In terms of preclinical studies, I mean, we did quite a lot of work on that. Initially, we saw that the one-to-one ratio was good and then one of the comments on the potential interference between CBD acting as an antagonist of CB1 receptor and then kind of competing with THC. We never found it at least in vitro or even in vivo models. And (unint.) also did some work on that. But in general, we found that actually you can enhance or even decrease the dosage of THC that you need in order to get a good result when you combine also CBD. So then we went and tried different combinations with different ratios. So we also went to 1:5, even 1:9. And in general, (unint.) models, including in vivo models, we found a good response, even increasing CBD if we kept at this minimum dose of THC that was active. So we didn't find that interference, but that it is something to take into account. So probably there is room at least considering other ratios, keeping with certain amount of THC, at least in gliomas. Obviously, other tumor types may require different ratios. But one of the key points here is we need to do more trials, because that's the only way of really solving the question, because we can do preclinical work. But at the end, the only way to answering the question if it really matters for patients is doing larger studies and maybe doing comparison studies. And that's critical.

>> No, I very much support that. As I said, I'm not a born again convert, but there clearly is -- you know, the preclinical data across the board in cancer (unint.) sufficient to get you into the clinic and give you some hints as to how you might design your studies. But there is a limit to how much you can do in the preclinical arena. You then need to find smart ways of getting into the clinic and neither killing your compound inappropriately, you know, nor keeping it alive indefinitely, but actually doing that in an iterative way with the preclinical work. And for me, I don't in any way view our study as definitive. What I do think is if I look back five years ago, what would I have been happy with? I would have been happy with what we've seen. That gives me a rationale for us to look into this in more detail. And it is -- you guys are the experts, but I think this is the first randomized comparison. I always get nervous, not just in the cannabinoids sphere, but in any area where as a clinician, I look into a new agent and they're either -- 95% of the PubMed article are preclinical, or 95 of them are reviews rather than original data. Cannabinoids are a little bit in that camp where there's lots of information, and we need to start intelligently interrogating that preclinical data in patients.

>> I just want to add -- it's not answering your question, Donald, but we just published a paper three or four weeks ago concerning the symptom control, because now in Israel we have up to prescribe levels the THC and CBD in the different cannabis. So we saw less symptom control with the combination equally of THC and CBD. It was less effective regarding the control of the cancer symptoms or treatment-related symptoms. And we have a better response regarding the patients' report in CBD high levels and the THC more in terms of sleep disturbance and not the other symptoms. So I don't know regarding the cancer control itself, but symptom control, the equal amount of CBD and THC was less effective according to several hundred patients who report us their result.

>> Yeah, that's supported by the large relief study that I mentioned in my presentation two days ago, yeah. THC is what works. Well, the question is, we're focusing on CBD. Maybe it's CBN or THCV or, you know, CBG, or maybe it's the whole plant. I don't know.

>> Yeah.

>> Jeff, do we have other questions? You're on mute, Jeff. You're on mute.

>> Thank you. Yeah. Yeah, we do have some other questions. I guess a little bit on that same theme though for Dr. Bar-Sela, one of the questions is about the amount of cannabis usage that is being reported in your study. Do you have a quantification about the users, of how much they're using and for what situations or what conditions they're using it for? For palliative care? So what kind of product, amount, and for what purpose?

>> Ours was 30 grams. Thirty to 40, but the median was the 30 grams each (unint.). And in the year that we follow the patient, but we still don't have the exact prescription in Israel. It was (unint.) free. So Our patients changed what they took every month, and there was no use to collect the data, because the difference was so big in the patients. Each patients, they try different things in different months, so it was not without volume. We could not report it systematically to get to any conclusion. So the amount was 30 grams and most of the patients, around 60% get most of the cannabis in health, but they also change and try the oil, the different oil. So we decided to keep it as one group and not get into subgroups, because it was no trace to any specific amount of this. So it's a general answer about starting immunotherapy while you are using cannabis (unint.) for -- we start from two weeks and, of course, more starting the immunotherapy. So it was two weeks before starting immunotherapy at least, and it was one year and more in the other side of the patients on the long run with the cannabis.

>> Were all these patients non-smokers?

>> No. There are also lung cancers. And, of course, some of them were smokers, but the smoking was no difference between the two groups.

>> Why did they take the cannabis if they didn't smoke?

>> Ah. The cannabis? Around 32% -- most of the use of the cannabis was in smoking or inhalers. We have several inhalers that are used in (unint.). (Unint.) also in 2018-2019, patients can change what they are taking every month. It was not -- the prescription was very just the amount of the cannabis and it was controlled only by the patient. So it's really changed for one patient to another every one or two months.

>> Okay. All right. Here's a question for Dr. Ganju. The question is, "Are there any interactions relative to -- any known interactions relative to cancer from different substances acting on different GPCRs such as capsaicin relative to the cannabinoids?"

>> What was the question?

>> Yeah. It's about interactions between other substances that (unint.) on the GPCRs and specifically they're asking about the capsaicin. Is there any known interaction between capsaicin and cannabinoids through that system?

>> I don't that. I don't know that there are any drug interactions. We haven't done those studies with other GPCR parts.

>> As a general comment as a clinician, I'd just say without one (unint.) interactions, give us something that (unint.) a phase 2 work or a phase 3 trial, and we'll work with the interactions if you'd like. You know, cancer and chemotherapy has a long history of drugs that work, but are difficult to use. And then we spend five years, ten years learning how to deliver them safely to patients. So show the (unint.) first, and then we'll live with it.

>> Yeah. Exactly.

>> In these days with personalized cancer care, does anybody think that it would be worthwhile to routinely look for CB1 and CB2 receptors on patients' tumors to see if we can get a better understanding of how that correlates with outcomes perhaps in use of cannabis? Guillermo.

>> Yeah, no, I mean, following on what you are saying, but also what Chris was mentioning, I think it's definitely very important to understand very well. If we consider any anti-cancer radiant, there are always patients that develop resistance. There are always patients that are more or less sensitive. If we take the example, for instance, immunotherapy, (unint.) in cancer therapy. But if one looks at the data, only 20%-30% of the patients with metastatic melanoma or with lung cancer are responding to the therapy. So actually, even if it's really a complete change in the therapy, still there are a lot of patients that are not responding and (unint.) in the case of immunotherapy maybe it has (unint.) or not. So I think for cannabis it is the same thing. Clearly, there would be reasons that explain why some patients could be or not responding. Obviously, we need to demonstrate it, but there are probably patients that are responding very well. Some others are not, and we need to probably investigate not only cannabinoid receptors, but any other potential markers. I think from the clinical trials, we will not only learn about the effectivity of cannabis, but we also learn which patients are responding better or worse, what are the molecular (unint.) associated. So I think we need to take advantage of these trials when they take place to extract as much as possible information, because that could lead us also to understand better what's going on. So that would be interesting, just particularly looking at cannabis receptors (unint.). I think we have to go beyond that point if we want to really understand better.

>> I think the receptors can (unint.) biomarkers as our data is definitely suggesting. In the case of breast cancer, the CB2 receptor and the patient that you have expression of CB2 receptor, they have better survival. Both patients could be used for personalized treatment using cannabinoids, especially synthetic cannabinoids, which is specifically CB2. And in case of TNBC, we have shown that it highly expresses TRVP2 again. Cannabidiol has been shown to bind to TRVP2, to active the TRVP2 and those patients could be used also for -- can be like used for developing these combination therapies. That's what I showed in my layout, that if you use combination of Doxorubicin with cannabidiol, that may have much better effect than using Doxorubicin alone or actually using much lower concentration of Doxorubicin. That will also reduce toxicity associated with this chemotherapy, because chemotherapy drugs are mostly toxic. And if you can reduce their concentration but increase their efficacy, you can have much better effects. Therefore, again, looking for those receptors and then trying to see those patients which could be more -- these drugs will have more of an effect on (unint.) patients.

>> I think it's a very interesting question. Actually, we can have the data. We can try to look for biomarkers in the tissue, because we know to whom we give cannabis. And, actually, we can do wonderful studies retrospectively, try to see if something, kind of maybe CB1, CB2, but maybe other receptors interact and really influence the prognosis of patients who are taking cannabis, because we know to whom we are giving cannabis. It's not hard to take 50 patients with glioblastoma and to see if the use of cannabis and the level who use cannabis and the level of the CB1, for example, influence the survival. It's interesting, and it's not very hard to do.

>> I think this can be hypothesis-generating, but they carry inherent biases in terms of being seen as definitive. But certainly they can help point us in certain directions.

>> Okay. I think we'll do a few more questions, and then we're at 2:45. But since we do still have some more questions here, for Dr. Twelves about the side effects that were noted in your study. The question is, "It seems paradoxical that cannabis is -- well, the way it's normally administered is associated with relief of chemotherapy-induced nausea and vomiting, but you saw higher amounts of nausea and vomiting in your cannabis patients. Do you have any thoughts about what's the reason for that?"

>> It's an interesting perspective, not one that I had myself or have myself. I guess as a -- I was going to say elderly, but as an established researcher, you don't usually get anything for nothing in cancer research. So it's an unusual for you to get extra biological activity without it being at some kind of price. And the challenge usually for us is to make that price manageable and acceptable. We did have patients drop out of the study because of toxicity. You know, these were patients in a difficult place with multiple other problems. So that -- very subjectively, this didn't feel to me like something that was unduly toxic or difficult to manage. But as I said in an earlier comment, there's a long history of cancer. You show something (unint.) and then you find a way to make it deliverable and doable. I think the purpose, the situation where you make the patient's bad side effects go away and everything else is wonderful. (Unint.) a realistic goal. The other thing is that you kind of (unint.) on two different pathways. Patients with later stage disease with specific symptoms, such as pain (unint.) cannabinoids are different from those with less advanced disease having the cannabinoid as an anti-cancer drug. So I agree it's an interesting contrast. I'm not (unint.) that they're mutually compatible.

>> Okay. So then I think as a final question, if I could just ask each of the speakers just to give maybe one comment about an obstacle to research that you encountered that you think more effort needs to be made to push through, or a specific opportunity that you see for future research that you think we need to jump on to move the field forward. So we can maybe go in the sequence of the presentations or however so. I guess that's Guillermo first.

>> Well, it's obviously a good question. I think that definitely we need to -- I mean, everything needs to, if possible, get us (unint.) to clinical study, because in terms of solving the problems of the patients, and really answer the question of whether this could be useful for the patients or not, we need to run more clinical studies, because there is a lot of preclinical research already done, but only in certain tumor types. At the preclinical level, really we have a lot of work maybe done on glioma, maybe breast cancer, but definitely there are many potential combinations with different drugs all in these tumors, but also in many other tumor types. So I think we should definitely go for studies that really determine whether there is a good combination, there are potential toxicities or not, because in terms of even going to a clinical trial where there's drug combination, at the end, you need to see where there are toxicities or not. Having like a good idea in preclinical models could really help to push to something specifically. Let's say metastatic melanoma that there's no responding to therapy or breast cancer that is metastasizing because it becomes resistant to inhibitors. But there are always rooms for cannabis to be applied in cancer patients, but I think we need to preclinical research (unint.) in combination with other drugs that may help to really move into the direction. Obviously, we could do a lot of things mechanistically that are very interesting, but we think in patients, probably that would be the key step.

>> Great. Thanks. Ramesh, that's you next.

>> Yeah. I agree a lot with (unint.) analyzing the effect of these cannabinoids on immune system, because some of this stuff, especially CB2, is present mostly on immune cells. And currently, these cannabinoids have effect on immune system and not much is (unint.) modulate the immune system, how they modulate the tumor micro environment. And that update would be used to boost the immune response. I know there are some studies. They showed that the cannabis use and dampen the immune system, but I still believe a lot more studies need to be done to see how you can use these compounds -- if you can use the (unint.) compounds. I don't know if you use the whole cannabis and (unint.) compounds. But if you use (unint.) compounds like cannabidiol or (unint.) agonist, JWH, which I showed, that it can enhance the immune response, it might have much more better immune like (unint.) effects, or you can combine with other immunotherapeutic, or combining these cannabinoids with other drugs, especially as shown (unint.) could be used in combination with chemotherapy, but that's -- it can enhance the efficacy of chemotherapy, because this -- combination studies need to be done a lot more. Maybe alone itself it may not be much more effective. But if you combine with other drugs, this can have much better effect.

>> Great. Thank you. Chris, obstacles or opportunities?

>> Okay. So before you cut me out, I've been doing this for 40 years with patients. And this isn't a slam dunk. I've not listened to all your meetings, which I apologize, but the evidence is not greatly, I might say, any more convincing than for a number of targets that we've seen come and go in many years. So I do think, and I've just been looking at the questions and comments. Because I'm a clinical doctor, I want this to work, but that does mean you, as a community, we as a community, need to convince not the believers, but the skeptics and those that are hesitant. And the unmet needs are real, but, you know, we really need to get into the clinic and test the hypotheses. You know, if there's something in this, it's too important to miss. If there isn't, we need to be looking elsewhere. And I don't think that would be -- I don't see major obstacles to, you know, properly design clinical trials evaluating cannabinoids. At some point in any agent or class of agents, you have to say, we're not going to stop the preclinical work, but we kind of say this is the best we've got at the moment, and we test that and we go for it. I'd encourage us to go down that route. The need is there. I think the appetite is there from patients, but we/you have got to bring the community along, because it's not a slam dunk.

>> Thanks. So just to push a little bit on the obstacle issue for you, based on Donald's earlier question about the length of time for your study, yes, it's certainly in a difficult population to work in, but did you find no resistance to -- were there other competing studies that just were more attractive biologically or scientifically, or what do you think?

>> Historically, we don't like to, as a community, do studies in JVM for the most part progressively. Patients with brain metastases who might also talk about would be a bigger population, but anyway that's a different discussion, are specifically excluded from those trials. So there are a number of issues. I, as any clinician, I get asked on a weekly basis about cannabinoids. So there is a groundswell around them that could be I was going to say manipulated is the wrong term, but could be developed to see if there is something in this.

>> Great.

>> We need things.

>> Agreed. Thanks. And so, Gil, you're the last one on this.

>> Yeah, Jeff, just to add, because things were already said, but I think we have a lot of interesting stories from the Internet. And I myself, I must say that I have a few patients who are taking high does cannabis oil, and some of them respond, but more what I see is stabilization of the disease as a result than any other oncology kind of drugs. So I think there is something in the cannabis, and mostly in the high doses of cannabis that really can act clinically as anti-cancer, not just in the laboratory studies. And it's really good if we have Phase 1 study, like it's done with other drugs, and it's just the companies. I've tried several years to write this up and still didn't succeed, because the companies are not so interesting. And from my point of view, doing such a study -- and I think it's fitting. And if we have some evidence from this direction, we can continue with other studies of combination and so on. From my point of view, it's the most important thing.

>> If I can add on, obviously, there is a big hurdle there. When we do the clinical trials, we do it with Nabiximols. We do it with generic, and many companies have been interested on (unint.). But definitely we need to find a formula and, I don't know, maybe comparative studies, maybe something that really provides, because I think there are many oncologies that are interested in clinical trials. In Spain, we have even a group of new oncologists that are really keen on doing clinical trials, including cannabinoids. But doing it without the support clearly of pharmaceutical companies complicate it and really that’s the key point, because the standard clinical trials are with molecules. There are new molecules that are (unint.) to move forward and (unint.). But for something like this (unint.) compound is more complicated. I think we need to think carefully how everybody can get a benefit, how we can really have a product that we can use widely to do clinical trials and then obviously the people can get also benefit afterwards. And that's really critical, because that's the main reason why we are not able to do clinical trials, I think.

>> (Unint.) on its head, and one of the drugs we use most widely in cancer -- well, many of the drugs we use most widely in cancer cytotoxics are plant derivatives like the (unint.) or the mixtures of extraction from the original source with chemical manipulation have worked. So in discuss with pharma, you know, there is a roadmap for that.

>> Sure. Yeah. Most of those are (unint.) natural products as opposed to the straight extracted product like Sativex or Nabiximol. Thank you so much. I guess we're going to have to close it here. I think we've had a great session. There are other questions that perhaps -- I know you’ve answered some of them in the chat section, but if you spend some more time with that, that would be appreciated. And so I think we can wrap up for the day. But, again, thanks to everyone, and we look forward to a further discussion about this.

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