Dr Stefaan Van Gool:
Cancer is still a major cause of mortality worldwide that is well-known. And here, you see the International Agency of Research in Cancer map of 2022, the incidence and the mortality. But besides incidence and mortality, there is a third element that reflects the burden of cancer and that is the mean years of potential life lost due to cancer. And here we have to say, unfortunately, that brain cancers have in fact the highest mean years of potential life lost due to cancer. That means the cancer comes maybe at a little bit earlier age and the chance that you died due to this cancer is bigger as for instance with breast cancer or prostate cancers, which are much more frequent, but you can live much longer. And the most frequent malignant brain tumour is glioblastoma multiforme. And unfortunately, we have not been able to change the standard of care over the last 20 years. Here you see an example.
And the question is of course, why did we not be able to change this prognosis of this particular tumour? The reason is in fact very simple. It is a complex tumour. Why is it a complex tumour? Well, first of all, the constitution, how the tumour is built up is very heterogeneous. About half of the tumour cells are in fact not tumour cells, but cells from the body that are shaped in a way that they support the tumour. And, within the tumour, you have glioma cancer stem cells, you have different subclones of cell. So it's a very heterogeneous tumour that is always changing over time and that makes it so difficult. And within the tumour cells, you have a complex molecular biology with different mutations and signalling pathways that are disturbed and it makes it very, very, very difficult to make a good analysis of it.
But whatsoever, what we know already is that the MGMT promoter methylation status plays an important prognostic role. So if this enzyme is not translated into protein, that means that there is no MGMT expression. Then the prognosis is better, and that is the MGMT promoter methylated situation. While if the enzyme is produced, the gene is not locked down, then you have an MGMT unmethylated situation. And this MGMT enzyme can repair the effects of radiotherapy and chemotherapy, so the radiotherapy and the chemotherapy works less good. So that's already an extremely complex situation. But as I have said, this tumour changes over time. So there is a plasticity of the tumour, and the tumour after radiotherapy and the tumour after chemotherapy is absolutely not anymore the same tumour as at the time of operation.
Furthermore, if you want to analyse patients clinically, the clinical status of the patient plays also a very important role in the ultimate prognosis of the patients. Age plays a role, sex plays a role, extent of resection plays a role, the quality of radiotherapy plays a role, the Karnofsky Performance Index plays a role, the mini-mental status plays a role. These are all factors that influence the prognosis of the patient.
But meanwhile we know also that the interaction of the immune system with the tumour cells within the tumour can make also a prognostic categorization of patients as shown here. We will not go in detail of course. And once again, similar as the tumour cells can change over time, of course also the immune system changes over time and that all makes it a very complex situation to deal with a glioblastoma multiforme.
But whatsoever, if the tumour starts, it starts and it gives symptoms. At the same time, we know a glioblastoma can already suppress the immune system systemically and locally. So what has to be done? Symptoms have to be relieved, of course, as soon as possible and there the neurosurgeon comes in place and the neurosurgeon tries to reduce the tumour volume. The neurosurgeon never can completely operate the tumour out of the brain. There can be a macroscopic gross total resection, but there are always some tumour cells left. That's the reason why after the neurosurgery, radiochemotherapy and maintenance chemotherapy is included in the therapy to tackle the residual infiltrating tumour cells.

And that has been the standard of care. So there is an improvement with the median of the median overall survival with the addition of the chemotherapy. So there is an improvement of the median overall survival, by addition of the chemotherapy to the local therapy, surgery and radiotherapy. But look, in the MGMT unmethylated patients, look, this is an overall survival curve. So you start with 100 persons of the patients alive, you follow them over the years and as you can see, these curves fall down. So there are less and less surviving patients over time. The gain of the chemotherapy in this group is in median 27 days. That means if 100% of the patients take the temozolomide, half of them will live 27 days longer. In the MGMT methylated tumour, so radiotherapy and chemotherapy work better than you can already see in the red line that the curve with the radiotherapy alone is better than here, and the effect of chemotherapy is also. So half of the patients live 247 days longer.

So this is the standard of care. This is significant. This is evidence-based medicine with the proper randomised clinical trial. This is the standard of care. But the reality is a little bit more dark to my view. With the radiotherapy and the chemotherapy we facilitate even the induction of new subclones. And with the radiotherapy and the chemotherapy, we weaken the immune system, and that is the situation where these new subclones have in fact a free highway to death, and that we do now for 20 years. So it's time to do something more, to do something different. It is indeed a complex tumour, but if we only rely on randomised control trials, which is the level one clinical evidence, then in fact, we use a system that has been developed in the UK by Sir Bradford Hill in 1948. So we should start to yield our evidence with other methods of clinical trials.

Because my question is, if we have now such complex dynamic tumours in complex dynamic environments, then the question is, is only surgery radiotherapy and one or two chemotherapies enough to deal with this tumour? That is a real question. But there comes even another question. If we have complex dynamic tumours in complex dynamic microenvironments, then the question is can we treat dynamic diseases with fixed protocols? This is driving a car without steering wheel in an old city. And even within the trial, the dynamics themselves are never controlled. So the methodology might absolutely not be appropriate to deal with this disease. So we have a need for innovative and dynamic combination treatments, and at least at this stage we have to sample real world data of treatments.

The community of the neuro-oncology becomes aware about the complexity of the tumour. And this is reflected in this publication in 2023 where for the first time it is mentioned that cell-based therapies for glioblastoma might be promising tools to tackle the tumour heterogeneity. And these are all immune cells. So in this review, people refer to the potentiality to tackle the heterogeneity with immunotherapy using different forms of immune cells. Curiously, because already 10 years before in 2013 cancer immunotherapy was called the breakthrough of the year. And even more curious, the use of dendritic cells to treat glioblastoma was already published for the first time about 20 years earlier. In 2004, we have the first case of glioblastoma treated with dendritic cell vaccines.

Immunotherapy is now spoken, but is misused and that is why we have re-summarised the different types of immunotherapy. So if doctors speak about immunotherapy, you have always to ask, what do you mean with immunotherapy? Restorative immunotherapy we don't do anymore. There are immunotherapies that take into account the particularities of the tumour and then we call them personalised immunotherapy like passive immunotherapy with antibodies, modulatory immunotherapies also with antibodies. Other types of immunotherapy not only take into account the particularity of the tumour but also the particularity of the individual patient. And that's why we then speak about individualised immunotherapy. And, if you combine these different modes of action, as you will see what we are doing; then you end up with the term individualised multimodal immunotherapy IMI.

I have said the tumour is heterogeneous and is changing over time, but I have also said half of the tumour volume are, in fact, not tumour cells. So this tumour microenvironment, these other cells that sustain the tumour should also be taken into account, and we rely on the cancer hallmarks published by Hanahan and Weinberg. There are several cancer hallmarks that play a role in the process of tumour formation. And we have made a theoretical design how that would fit into the process of tumour formation for glioblastoma. And we believe that there are five hallmarks. Really very important. These five hallmarks are the glioma stem cells, the hypoxia, the metabolic reprogramming, the immune response and inflammation, and the neuron-glioma interaction.

We should be aware again that this tumour microenvironment is within a tumour already very heterogeneous, that this tumour environment develops over the time and is prone to changes by the anti-cancer treatment. So both the tumour volume and the tumour microenvironment heterogeneity, and plasticity are making why it is so difficult to treat glioblastoma multiforme. But still, what can we do? Well, we have the standard of care, that's always the first step. But already within the standard of care we can add what we call immunogenic cell death immunotherapy. I come back to that ICD, immunogenic cell death immunotherapy because this is another mode of killing tumour cells in comparison to radiotherapy and chemotherapy. So then you have already more actions against the cancer.

But at the same time, it already changes the tumour microenvironment making the tumour more accessible for the immune cells, because after this first anti-cancer phase we believe the job is not done. But you should now prepare the body to block the free highway to death, because you should try to stimulate the immune system against the old tumour clones and the newly developing tumour clones. For that, we take particular antigens out of extracellular microvesicles. I come back to that later. So here in this immunisation phase, we actively stimulate immune system and we will also already modulate the immune system. And then it's not done because these tumours will try to escape the immune suppression with new clones. So you have further to act against also these new clones. You have to broaden your immunological umbrella so that if the tumour goes to the left or to the right, that it is covered by the immune blockage.

And on top of that, we have to treat the tumour microenvironment against all these hallmarks that I have mentioned. Let us make that a little bit more concrete. ICD immunotherapy, immunogenic cell death immunotherapy. This is a novel concept in oncology. And I participated here into a big group of researchers worldwide, where we have learned that you can kill tumour cells in a way that the immune system experiences it as a dangerous situation so that an immune response can start because cells, dendritic cells will pick up the antigens, will move to the lymph nodes, will stimulate immune cells, and these stimulated immune cells will then fight against the cancer. This is the working mechanism of immunogenic cell death.

And now so many years later, we know some types of radiotherapy can cause immunogenic cell death. Even some types of chemotherapy can cause immunogenic cell death. Maybe known by the patient community, the Tumour Treating Fields, OPTUNE. This is in fact a type of immunogenic cell death. The modulated electro-hyperthermia that we use, these are also electromagnetic waves, but in the megahertz instead of the kilohertz domain, it is immunogenic cell death. The oncolytic viruses that we use it is immunogenic cell death. So there are several modes that we can use as immunogenic cell death. You kill cancer cells and at the same time, you induce danger signals within the body so that the immune system becomes alarmed.

Dendritic cell vaccine. Then we take blood of the patient, we culture the cells in the laboratory, you get immature dendritic cells. Or we get then the tumour from the neurosurgeon, or we get antigenic extracellular microvesicles that we induce with this immunogenic cell death

immunotherapy. These are the source of the antigens that we put on our dendritic cells. We give a maturation signal and then you get a mature dendritic cell, a cell from the patient that presents the tumour antigens and the viral antigens on its surface. We inject these dendritic cells into the skin. The dendritic cells will move to the lymph nodes and in the lymph nodes they will stimulate the immune cells and the immune cells will fight against the cancer . Eventually helped by checkpoint inhibitors that block blocking mechanisms, and de-block the immune activation.
This is the general principle of the dendritic cell vaccine that we also use. I have learned that myself by the Nobel Prize winner Ralph Steinman, who was at Rockefeller University and who won the Nobel Prize for the discovery of dendritic cells. The idea to use these extracellular microvesicles, so these tumour fragments that we have in the blood, because we give the modulated electro-hyperthermia and we give the oncolytic viruses that as source of antigen to load our dendritic cells. This is in fact work developed at the IOZK together with Dr. Stücker and Professor Volker Schirrmacher.
So now we have our treatment concept combination treatments in three phases. I have said there are several types of immunotherapy, immunogenic cell death immunotherapy in all phases. Active specific immunotherapy with vaccines. But also modulatory immunotherapy that are the checkpoint inhibitors, but not only the checkpoint inhibitors. There again comes a whole strategy. First of all, this inflammation cells in the tumour that block the anti-cancer immune response should really be tackled. And we do that with several drugs and several mechanisms. There was in the beginning of 2024 a breakthrough publication that shows that you should also use an anti-PD-L1 checkpoint inhibitor to tackle the M2 macrophages. And then we also use other types of checkpoint inhibitors to block the T-cell exhaustion because these T-cells becomes tired, so you have to sustain them in the third phase. So even the modulatory immunotherapy is already a complex strategy.
But besides that, to tackle all these other hallmarks against cancer, we have developed a whole strategy to block stem cell axis, to change the metabolic dysregulation in the tumour cells, to tackle the neuron-glioma axis with anti-epileptic drugs to tackle the psychoneuroendocrinoimmunology axis, and then of course the gut-brain axis is also very important. This complex therapy has been developed over time and now we can look what are the results? Here you see a table. There are five randomised controlled trials published in the last years. Publications are here below.
Linda Liau from Northwest Biotherapeutics, so the dendritic cell vaccine company, which has its seat in Cambridge I think, they have used the control arms of these randomised controlled trials as an external control arm in their trial. And then we have published the first 50 patients from our data. We have expanded the group to 71 patients in a publication this year. And I present for the first time now the results of 90 patients. So this is the same patients but more and more bigger group of patients. I have said the clinical profile of the patients plays an important role in the prognosis.
Here you see the age of the patient. Our patients are maybe a little bit younger. This would be a better prognostic factor. Our patients have maybe a little bit more females than in the studies. This is better for immunotherapy. But, our patients have a clinical performance, Karnofsky Performance Index, which is lower as in the clinical trials. This is a real bad prognostic marker and our patients have a higher proportion of tumours that are not completely resected as compared to the control arm in the clinical trials.
So people always say there is somewhere a selection bias. It might be. The selection bias is that the clinical trial patients have a better profile than the real world data. And this is one of the comments that the selection with the inclusion and the exclusion criteria in the clinical trials is so hard, that they in fact do not represent the normal real world

data patient with glioblastoma. So our patient cohort that we describe here is at least comparable with the clinical trials and is also comparable with external control arm in the Linda Liau trial of Northwest Biotherapeutics. What are the results? I have said we should also take into account this molecular marker, the MGMT promoter methylation status. I have said if the tumour is unmethylated, MGMT is present, then the radiotherapy and the chemotherapy work less good than if the tumour is methylated. Here you see the median overall survival, that means the months when half of the patients have died: 14.6 months. In the methylated patients: 21 months. The percentage two year overall survival, 21% to 42%. So this is, in fact, the survival of the external control arm of all these trials and we can say this is in fact the current prognosis of the patients with the standard of care.

If we now look to our patients, the 50 patients, the bigger group of 71 patients, the bigger group of 90 patients, then we see if we add individualised multimodal immunotherapy within and after the standard of care in these three phases, then we see a major jump of the median overall survival in both the MGMT unmethylated and methylated group. And we see almost a doubling of the percentage two-year overall survival as compared to what you can accept as the standard of care prognosis. Almost a doubling. I do not need a statistician for that. If you look more into detail, then we have the survival curves. These are the data published by Linda Liau, the Northwest Biotherapeutics, so the DCVax brain. MGMT promoter methylated, MGMT promoter unmethylated. DCVax brain does not give a shift of the green curve compared to the black line. As you see here, the median overall survival is equal. In the MGMT promoter methylated patients, the green line is shifted as compared to the external control arm as you can see here as well. So DCVax brain was significant for the MGMT promoter methylated patients.

If you look to the OPTUNE Tumour Treating Fields, the Schtubb trial from 2017, this is here the publication, then you can see their control arm and in blue the experimental arm with OPTUNE for the MGMT promoter methylated patients, the MGMT promoter unmethylated patients. Then you can see in both there is a significant shift of the median overall survival, and also the percentage two-year overall survival is increased in both of these groups. Now I show for the first time our results on 90 patients, of course without control because we only have real world data, but here you see then how it can be compared. Our median overall survival has further improved in the good direction in both the MGMT promoter methylated and unmethylated patients, and the percentage two-year overall survival, as I have said, is almost doubled in both subgroups. So this is really with bigger group of patients, a confirmation of what we have already published with smaller group of patients. And sometimes you'll see extremely spectacular results as you can see here from this young Ukrainian lady.

Now, to my vision, if you have this data, for me it is important to continue because it is my vision that every day the patient lives longer with a good quality of life as such is invaluable. But of course a lot of people ask: "and now the randomised controlled trial?". Well, I say, if you see these results, then I do not believe that a lot of patients wants to participate in the standard control arm anymore, they all want the novel therapy. And in these randomised control trials, my other questions remain. So our strategy had to be a little bit different and you can criticise or not criticise, but it's the reality as we do it right now. So we have a cumulative number of patients that come into our centre over the years, and as you can see here, there is an enormous increase in the brain cancer patients.

So we simply try to convince the community by building up as much as possible real world experience. So that we avoid in fact clinical trials with all the issues that are mentioned here. And this is possible in Germany. This is also published, this figure. It is possible in Germany because we have here a particular legislation that allows individualised

treatment, Individueller Heilversuch. In the US they speak now about the Right to Try act. This is a little bit different as compared to Individuller Heilversuch, but these are in fact approaches that allows doctors to treat patients outside the guidelines and the standard of care if there is no treatment solution available. And I fear with the standard of care, we have to say that indeed a treatment solution is not yet available.

To make that concrete for the patients, what should be done? Well, there is neurosurgery of course. And then the patient can already contact us over the email or over the telephone, radiochemotherapy has to happen. This is the first step in the standard of care to reduce the cancer volume. I strongly suggest to keep the steroids as low as possible. This is a general rule. And then the doctor will start the maintenance chemotherapy that are five days temozolomide each four weeks, or six days temozolomide plus lomustine each six weeks. At that time we need to see the patient because we then can do our immunodiagnostic procedures and we can already start the first ICD immunotherapy. And these ICD immunotherapies are then connected into each cycle of chemotherapy. That is really workable, with several colleagues in the UK, this is meanwhile happening. So good collaboration is feasible for the doctors and for the patients.

Basic requirements of course are there. The Karnofsky Performance Index should be more than 60 to 70. If the patient is too diseased, the immune system is also too diseased, and then it will not be possible to do the whole effort to stimulate the immune system against the cancer. And of course, for whatever reason, repetitive travelling to Köln and staying in Köln for ambulance therapy should be safe and feasible. I know that there are also questions related to the costs. The costs are here in this way calculated as a nonprofit situation because we rely on the German law for ambulant therapy. So the costs are created by the concrete medical activities that are performed. And these concrete medical activities are dependent on the individualised treatment plan that we have to design for each patient, and to which the patient has to consent of course. And payments are step-by-step.

What I did not include in the presentation here, but was a question from Helen, also to deal with CeGaTs. So CeGaT is another way of vaccination. So let's say the nose goes completely into the same direction, but there are still some differences. And to explain that in a very simple way, for a vaccine, you need always three elements. First element is the carrier, second element is the antigen, third element is the danger signal. The carrier at IOZK are the dendritic cells. They are taken and produced out of the blood of the patient. The carrier in CeGaT is sodium chloride solution, simply sodium chloride solution. The antigen, the antigen in CeGaTs are short fragments of amino acid sequences, which we call peptides. And they are very specific for each tumour because CeGaT asks the tumour tissue, asks blood and they look what is the difference between the tumour and the blood. And based on that they predict which antigens could be different in the tumour as compared to the healthy tissue. So they predict the tumour neoepitopes based on the tumour tissue that they receive for this analysis. At the IOZK I have explained that we kill at a certain time point the tumours with ICD immunotherapy, oncolytic virus and modulated electro-hyperthermia, and we take out the antigens that are released at that time out of the blood to load our dendritic cells. And I think this is a major difference because CeGaT relies on the tumour that has been operated before the radiochemotherapy and before the maintenance chemotherapy. So this is in fact old data tumour, I have explained that this tumour, these subclones change always over time. So there is the risk that you do not cover with the panel of CeGaT peptides, that you do not cover the novel subclones that are developing in the presence of radiotherapy and chemotherapy. While in our vaccines we take really the antigens that are at that moment in the brain, the advantage of CeGaT is they can monitor everything very well. The

disadvantage of our system is we cannot monitor, we have only the overall survival curves, but they're very attractive.
The last element I have said, the carrier, the antigen, the danger signal, the danger signal that CeGaT is using is Aldara cream imiquimod and the short dose of GM-CSF, which is a pro-inflammatory cytokine, which we do not like that much. While in our vaccine we give the danger signal in the laboratory to the dendritic cells. So they are forced to experience the danger signal and to be alarmed as never before. So that is the difference between CeGaT and IOZK. You can combine both types of vaccine, there's no problem at all because the ultimate goal is exactly the same, stimulate your immune system against cancer. So that is the difference with CeGaT. And I have explained the difference with the Northwest Biotherapeutics DC vaccines.
So in conclusion, if we see what we now have, we have neurosurgery, radiotherapy, chemotherapy. This is the standard of care. This is anti-cancer activity. Targeted therapies, targeted immunotherapies like CAR T-cells, CAR-NK cells, sometimes passive immunotherapies with antibodies. They are all in fact aimed to kill cancer cells. Immunogenic cell death immunotherapy with biological treatment, oncolytic viruses, or physics treatments, OPTUNE modulated electro-hyperthermia, they are aimed to kill the cancer cells, but I have explained they all can eventually already induce a little bit immunogenic cell death immunotherapy, which would mean a treatment-induced anti-cancer immunisation. I have explained that this is not enough. You need a second layer, a second phase to give an active stimulation of the immune system to fight against the cancer and to modulate that as good as possible.
Curiously, for this second layer, for this second phase, two Nobel Prizes have been given showing how important it might be, but people simply neglect it. And I have explained it's not done with that. You have to continue because the tumour will try to escape the immune system. So you have to include a third phase, a maintenance and expansion phase to expand the immune protection. I have said that tumours and hosts are dynamic processes. I've explained that we need to repurpose drugs to act against the cancer hallmark because half of the tumour mass are in fact not tumour cells but cells that stimulate the tumour. And then at the end I have shown that real world data can have their own scientific and clinical value besides data from randomised control trials. And that is in fact what I hope that is now translated to the community in England. I thank you for your attention.

Speaker 2:
Thank you so much. I'm so glad we recorded it and have your slides because I think there's a lot to process on there and everybody will be coming at this at different levels, for some all of this is quite new and for others they'll be quite well versed in it. So what I think we should do, and we are a small group, there's only 22 and I would like people to feel they have a voice. If I just run through the questions first that have been posted and then if you want to put your hands up after we've been through theirs and ask any more questions, that would be really, really good. Also, some of the people couldn't access the slides on their screen, so I think it'll be helpful for them to have the recording. So there was quite a few actually about the same thing. The presentation is about the glioblastoma, but some of the people on the group today have got a grade 4 astrocytoma. Does it still apply? Do you still work with patients with an anaplastic astro?

Dr Stefaan Van Gool:
Yes. So this type of immunotherapy is in fact what we call an agnostic treatment strategy. That means it does not take into account from which source of tissue the malignancy is created as long as you have an antigen and an immune system, you can get that fixed together. So indeed for other

types of brain cancer, also the IDH1 mutated grade 4 astrocytoma or also the anaplastic astrocytoma grade 3 or oligoastrocytoma grade 3 or oligodendroglioma grade 3, it's in fact the same principle. Sometimes we connect with other types of drugs, for instance like in the oligodendroglioma, but the same idea to get the cancer small, to stimulate the immune system and to keep the system going on. That is for all the same.

Speaker 2:
Thank you. And another question is, a simple question, what are the side effects?

Dr Stefaan Van Gool:
Well, the less the cancer volume, the less the side effects. That's one rule. And the second rule is immunotherapy is not an external poison that is given into the body, but immunotherapy stimulates the immune system to clean the job in the body. So the side effects are much, much, much less. And sometimes I say the biggest side effect is coming to Köln because I cannot imagine that I would go with my family to the UK to a foreign doctor to do something new. I think that is already a major stress for the patients, which we try to resolve with this webinar, but I think that is still a major burden. But that's sometimes the only thing that is... Toxicity is in fact coming to Köln.
Of course, there are also some things to mention. What is a side effect? So you have an adverse event and you have an adverse reaction. That's a difference. I mean in this way if there is some immune response, there might be some edoema, for instance, there might be an epileptic attack induced even. So at that time point, the question is, is that now an adverse event, an adverse reaction, or is this in fact an effect of the treatment? So that is also sometimes starting to be a matter of definition. But we cover that in global and I said, the patients are in fact mostly if not always ambulant. So that is in fact the goal that we have no major issues. So immunotherapy is not an external toxicity that the body is forced to receive.

Speaker 2:
Thank you. And how long does the treatment go on for?

Dr Stefaan Van Gool:
Well, I always say starting treatment is easier than stopping treatment. So phases, some patients that are already long runners together with us and so we fade out this third phase. We try to fade that out. But I experienced that most patients want to come two times, three times a year because they feel well, they say, "That's good for me" and they simply persist in coming. I even had now a patient from Australia, I think we have treated her in 2018. She phoned me or mailed me and she said, "Next year I'm in Europe, I want to come." I've said, "What should I treat?" But yeah, patients feel good with that. So stopping therapy is sometimes more difficult than starting. But to make it in another way, we aim to give treatment for several years in frequency that goes slowly down over the years. Somewhere you have also to take into account the risk periods, so and that you see on the progression survival curves, the risk period for GBM. Yeah, once you are several years further, the risk that you relapse then is maybe a little bit less, although I have seen that.

Speaker 2:
Thank you. There's quite a few cluster of questions around timing of this treatment. So somebody's had eight cycles of temozolomide, somebody's been on temozolomide for a year, but somebody else where it stopped working and they're discussing the option of going on to lomustine. But your

presentation mentioned just going in after the first cycle. Is this a treatment that could be taken at any point in the clinical pathway?

Dr Stefaan Van Gool:
Yes, absolutely. So let's go to the basic schedule because that is maybe for the community, the best. So if you are already busy with maintenance chemotherapy or you just have finished the maintenance chemotherapy or you are starting with your second line chemotherapy, as long as this chemotherapy is running, we can easily connect at one point the ICD immunotherapy. And then after chemotherapy is finished, we start with the second phase, the immunisation phase with the antigens that are present at that moment. So even if the patient has already taken four or five temozolomides, we easily can jump in. I always say a treatment that is given might work, a treatment that is not given certainly does not work. And this is something which is simply on top of the standard of care. So if patients want to use this on top of standard of care treatment, that can be started at any time point, and we help of course in each patient to get that realised given their own condition.

Speaker 2:
Okay, thank you. I'm just scrolling down the questions. Yes, contraindicated. Are there any medicines that are not compatible with treatment such as Avastin?

Dr Stefaan Van Gool:
No, Avastin is absolutely good. It's even better. Avastin also changes the tumour microenvironment and the hypoxia situation. So Avastin is certainly good. There are some people now and certainly in the diffuse midline glioma situation where everolimus is presented to the patient. Everolimus is a targeted therapy, so it's the fourth pillar in my last schedule, but everolimus is really an extreme strong blocker of immune activation. So then we simply have to say, "Don't start to embark on the immunotherapy route because already a priori you block everything in your immune system." Everolimus is, for instance, one of these drugs where we really recommend not to start immunotherapy because that's really contra-productive. Patients on dexamethasone, yeah. If a patient is on dexamethasone, we work with real world patients in the real world situation. And if dexamethasone has to be used, we still believe that the immunogenic cell death immunotherapy, at least in part the dendritic cell vaccination might help in getting some immune reactivity against the cancer. Of course,we like the dexamethasone as low as possible. We do not recommend to go below two milligrammes per day because sometimes the body really needs a little bit dexamethasone to get it done. So if we somewhere land in two milligrammes at time of the immunisation, that's really acceptable. But being in real world, you cannot change the real world. And if there is more dexamethasone needed, then it is so, have something to do with safety of the patient. Also the travelling should be safe. Of course, if patients come from the UK or from the US or from Australia or South Africa, travelling is a safety issue, as such, that should be somewhere thought about.

Speaker 2:
Thank you. And Tommy's asking, can you have it after lomustine as well?

Dr Stefaan Van Gool:
Yes. So lomustine is each six weeks. Lomustine is in fact the father of temozolomide. It's an alkylating agent. It does exactly the same. It has a little bit more toxicity certainly on the platelets, but it's in fact same mode of action. So what has been said for temozolomide is exactly the same as what can be said for lomustine, and also the combination lomustine temozolomide, this is six days chemotherapy in cycles of six weeks. That's all the same principle.

Speaker 2:
Right, thank you. I'm just going through the questions. There's quite a few pragmatic ones. People just would like a ballpark figure. If you could say like is it under 100,000, over 100,000?

Dr Stefaan Van Gool:
Yeah. So if you have the full package as is exemplified here, you end a little bit above the 100,000 euros. That we have to say. And that is extremely frustrating. It gives also a particular stress to the patients. The point is not it's so much, the point is in fact who has to pay? And there unfortunately the solidarity of the community fails because, and that's a discussion that we really have with insurance companies, the insurance companies, they rely on this level one clinical evidence in randomised control trials. But I have explained in my presentation that randomised control trials, first of all, this is a methodology that does not work in GBM. That's why we do not make progress in GBM. And second, now that we have this data, who wants to be in the placebo? It will be almost unethical to do a proper randomised, eventually double-blind placebo-controlled clinical trial.
That's the only thing that the insurance companies claim before they move on to reimbursement. And that's why I have said we need novel methodologies to yield evidence. My evidence runs around the street, but nobody believes that they run around the street. You know this problem likely from several discussions.

Speaker 2:
Yes. Oh, absolutely. And it ties in with a question that Emma Louise is asking. She says, "I notice, of course, based on the individual situation and difficult, almost impossible I would say to measure, but what are your indicators so far as to estimates of how life extending it is and what are the time periods you work with versus actually curing tumour development?"

Dr Stefaan Van Gool:
Well, so the only thing that we rely is overall survival. Whatsoever at the end for each patient, overall survival with good quality of life is the only thing that counts. It's also still a very objective readout, overall survival. And I think we have developed our strategy that we see a clear shift in the overall survival curve. And that's in fact my only read out of success. Of course, this is important for me and also for our authorities because we get regular audits by the German authorities. Also, our GMP laboratory has regular controls audits by the authorities.
I think these overall survival curves are important for us to know the road that we walk is okay. It's worthwhile to continue, it's worthwhile to present that to the patient community, but also to the scientific community next week in the SNO in Houston. But for an individual patient, it has less importance because for an individual patient, the only thing that counts is do my body respond to the treatment, yes or no? And that we cannot predict. There is no biomarker, no information that will say this patient will do it and this patient will not do it. And that's why I have said a treatment that you give might work, a treatment that you do not give never works. But at the end it is like it is, and so I think we should make stepwise approaches. We have multiple phases, it's on the screen and we should see together with each patient, is that a good direction for this body, yes or no? And if it is not, we have to say it's not, it does not work. And then we have to stop, of course. So you can stop this treatment each day of the year.

Speaker 2:
Okay. Right, I've got three more quick questions. I'm going to call it a day because I'm aware of your very precious time. So the first one is,

would you ever use this treatment on an inoperable grade two tumour before it transforms?

Dr Stefaan Van Gool:
If the tumour is already quite long after first line radiotherapy or second line radiotherapy I would consider it because of the fact that we know early or late such type of tumour will go into malignancy, and then it starts to become more and more mutated and then it starts to have more and more tumour antigens. But in a short period, if there is a diagnosis of a grade two and they ask me for immunotherapy, I would always say no at that moment because we need different enough distinction between the tumour with tumour antigens and the healthy tissue.

Speaker 2:
Yeah, which you only get with a transformed one. Okay.

Dr Stefaan Van Gool:
Exactly, yeah.

Speaker 2:
Then two basic, quite easy questions I think for you. Is there a wait list? We're so used to on the NHS having to wait for treatments.

Dr Stefaan Van Gool:
I have discovered that the tumours do not take holiday. So that means that we also do not take holiday and we try to get everything planned as good as possible. So the waiting list should be minimal, but that's our whole organisation and the responsibility of our organisation. We try to manage each patient in time.

Speaker 2:
Thank you. And I don't think you'll be able to answer this question because I think it's specific to the UK, but somebody has raised the issue of what will it take for health insurers to cover this treatment? I don't know what the situation is in Germany, whether you get private healthcare funding this treatment or not.

Dr Stefaan Van Gool:
At the moment in Germany, so we have also a private insurance system, which is 10 to 15% of the medical activities and the medical patients versus the Krankenkasse Medicine that's the more the NHS situation. So for the private insurances, sometimes blood samplings and all are covered. And for the Krankenkasse Medicine, so the NHS type, there are some patients who really go to court to get the insurance companies forced. And sometimes with children for instance, that helps. I think there, and that's really good that Brainstrust has this sort of activities. I think ultimately, as I have said, my strategy is to build up this experience as fast and as big as possible to present this real world data. And then I think the patient communities have to come into action and have to say, as it was with the HIV community at a certain time point, as it was with the COVID at a certain time point, the community has to say, "Now it's enough, should be payback."

Speaker 2:
Yeah, thank you very much. And I know that there is a groundswell of evidence about using real world data and turning into evidence, and it is becoming more validated amongst the clinical research community. So I have fingers crossed. And you know anybody on this call this afternoon, I do have patients that are... They go to Stefaan's clinic and they're doing really well. And if you want to talk to a patient about their experience, they will be more than willing to do that. And the thank-yous are beginning

to pour in, Stefaan. It was a fabulous presentation. Thank you so much. I will definitely be in touch. All right. So everybody's got Stefaan's email if you need to contact him. Are you happy for me to share the presentation as well?

Dr Stefaan Van Gool:
Yes, no problem. No problem.

Speaker 2:
Okay, so I'll ask your team to send that to me then. So I will email out the presentation and the video. The recording as well. Thank you very much. Have a good evening everybody.

Dr Stefaan Van Gool:
Okay. Bye-bye.

Speaker 2:
Bye. Bye.