Transcript of the KOL Webinar presented by Dr. Frank Giordano on June 10, 2022

GLORIA TOP-LINE RESULTS OF NOX-A12 & RADIOTHERAPY COMBINATION IN FIRST-LINE GLIOBLASTOMA PRESENTED AT ASCO 2022

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Introduction

Dr. Aram Mangasarian, NOXXON CEO

Thank you to all of the attendees for joining us today. My name is Aram Mangasarian, I am the CEO of NOXXON Pharma. We're very happy to have Dr. Giordano with us today to take us through the research he presented over the weekend at ASCO in Chicago. I'll give you some more details on his views on what this means. I'm just going to do a very brief introduction that summarizes some of the things that Dr. Giordano has laid out in his earlier webcast about the therapeutic landscape in glioblastoma. You all know this is a very aggressive disease. 5-year survival, very low around 4%. Median overall survival for the full population is 12 to 15 months. Within that already pretty dire prognostic, there are some high unmet need groups, and these are the groups we are actually targeting in this trial.

So, there's a biomarker for the methylation status of a gene called MGMT, and when this is unmethylated, and you can test this before you start treatment, which is what we've done in our study, then you know that chemotherapy, the standard of care, will be ineffective. And if you look at the graph on the bottom right, you'll see the difference in the survival curves between the methylated (in blue) and unmethylated (in orange) population. And, you'll appreciate, these are significant divergences between these two groups. The other group of patients that have a poor prognosis are those where surgeons are unable to fully remove the tumor. And so, these patients also have, because they have a larger starting massive tumor grows back more quickly. And we're actually, in our trial, including both of these poor prognostic factors into a patient population.

So, that's just to give you a brief overview. And with that, I will turn it over to Dr. Giordano. Thanks, Frank, for taking the time to present to the people interested in our program. We really appreciate it.

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Presentation of ASCO 2022 Poster Data

Dr. Frank A. Giordano, MD

Thanks, Aram. It's a great pleasure for me to present these data and I'll give you a bit more background data over the poster, walking through the poster, but I'll also give you a bit of background information and a bit of an audio track that you usually don't see and hear once you are at the poster at these conferences.

I'm very excited to lead this trial. We have been developing this idea based on a longstanding pre-clinical evidence that was generated with NOX-A12 and autochthonous models or in orthotopic models. And, also that based on that, I can just walk you through where we are with the clinical trial right now.

So, what I can basically now summarize and what Aram touched upon is already that we have started a clinical trial with radiotherapy and combined infusion of Olaptesed (OLA) at three dose levels. Here the recruitment is completed at this stage here and that's basically what I've presented at ASCO, and that's what I am going to present to you. What I can briefly touch upon is 2 cohorts that are now actively recruiting, its expansion cohort with bevacizumab (BEV) and one expansion cohort with pembrolizumab (PEM). And I probably will dive into that later and add more information.

Basically, both of these cohorts allow also completely resected GBM. We are talking about ASCO and a poster that we presented on ASCO. I'll walk you through it, we numbered it, so you can basically download that poster also from the NOXXON website. But it's a bit of a walk-through here and basically, the background very brief is depicted here. Radiotherapy causes hypoxia. That in turn leads to CXCL12 up-regulation. That's the major molecule you want to target. And because that is basically mediating vasculogenesis and immunosuppressive tumor microenvironment through recruitment of these CXCR4 positive cells. These cells are attracted by CXCL12 and we're capturing CXCL12 with Olaptesed pegol. I'm going to refer to it throughout the presentation as NOX-A12. That substance NOX-A12, binds and neutralizes CXCL12.

I already touched on the background and study design, so I'll briefly walk over that. It's a dose-escalation part of the trial where we combine radiotherapy, which was chosen by our investigator. By the way, we chose to include the true glioblastoma that WHO grade 4. The unmethylated, Aram has already told you that this is a cohort where we have a high unmet need, and where we know that we need a new therapy, because chemotherapy doesn't work. We looked at safety as a primary endpoint. We got a lot of secondary endpoints, which I'm going to walk you through all over the poster. What I'm really happy is at right at the start, we had a strong translational exploratory endpoint where we tried really to explore and to correlate these things we see also with histology, and with biomarker imaging that were generated from advanced MRIs.

So, this is a bit of a background that I was talking about. I'm going to deviate a bit. I'm going to tell you that we have been looking on 10 advanced MRIs of these 10 patients. And we also had the chance to look on pre- and post-matched samples of 2 patients. But then, we asked ourselves, what do we see there? What's different to what we see usually? And we thought it's a good idea to have a matched imaging control which is matched for histology and also matched with these unfavorable biomarker MGMT. And we needed to look into a CODEX reference just that we know that what we see there we can benchmark and if we see that in the regularly treated patient population.

Primary end-point, I think the most important endpoint, this was basically a safety study, a Phase 1/2 trial, basically looks at safety at first really primary end-point. And what I can say here is that of all, If

you look at the 158 AEs (adverse effects), most of them are not related to the therapy. Of those that are greater than or equal than (grade) 2 which were 77, only few were related to NOX-A12. You can look at those that are only NOX-A12 related only 1 time a G3 (grade 3), a GGT (gamma GT), and 2 times ALT increase but only grade 3 and grade 2. A really a mild tox profile if you compare that to the standard of care, that's absolutely a mild safety profile.

When we started the trial, we said 26 weeks of therapy is sufficient and enough, based on pre-clinical evidence. And then, we treated these patients for 26 weeks, and what we then saw is that we should have been keeping these patients on treatment longer. In some of these patients, that was just not enough. That we didn't know. And so, we're looking at the early-recurrence or recurrence here, once we stop treatment. In that patient, it turned out that this patient had a pseudo-progression here. So that, basically looks like tumor, was resected but was not a tumor inside. And that patient also stayed stable in the cavity, and you see once we discontinued the drug but later, the patient recurred. In that patient, we also had a chance to look into what's going on here, where we didn't see tumor of what's in there and we Multiplexed that, I am going to touch on that later. But the bottom line is that at that stage we amended the protocol and we then allowed to continue for a treatment as long as the investigators want, even beyond progression is possible. If you want to really figure out what progression is or not, in that case, we thought it was progression, but there was actually no tumor in it. So, our investigators are encouraged to give that drug as long as possible, as long as tolerated which for the time being is no problem at all.

Then let's go into the main points where everybody is looking at is how do people respond, how do patients respond to NOX-A12. What you can see here on the left side is radiographic response. You may even see that we have 9 patients, but we have 10 patients in the trial. But what we're looking at separately are target lesions, they are these two graphs here, and non-target lesions. So, we have both target lesions on the left side, and non-target lesions on the right side. And what do we look at: So, we take the some of the target lesions and we look at the diameters and we just add them up, and that's the left few images here. What you can see on the GLORIA patients, in NOX-A12 treated patients, 9 patients of all the 10 had a target lesion which we could then follow along the treatment, and you see that **4 out of 9 actually had a partial response (PR)**, something you rarely see in unmethylated glioblastoma. And **4 out of 9 had stable disease (SD)** as the best response. But what does that mean, stable disease? Stable disease means you're not really touching the 50% tumor reduction. But as you can see here, these tumors actually responded, but they just didn't touch that defined 50% which we would need to reach partial remission. But, the bottom line is almost all patients had 1 time point in which the tumor was shrinking and 4 out of 9 where we had measurable target lesions, even reached the threshold, which is necessary to define partial response (PR).

Now, looking at the reference cohort and I told you that once we look at the data we are interested in how does that look in our other cohorts and how do they match? You're going to see that here in that case, you don't see this image, you see it's a rather black and white image here. You see that few patients actually reach partial response (PR). We looked at 20. Few reach stable disease (SD), but the majority will just grow and grow further. And that we're talking about the best response under therapy. So, that at no time point, these patients were really having any sign of a response.

We also looked at non-target lesions and that is intriguing in that trial. Because you definitely see a better response of non-target lesions to therapy than even to the target lesions. So, what are non-target lesions? 9 patients had non-target lesions which we could follow. These are usually located a bit further distant to the cavity, they're not really resected and we can follow them, but they're not really getting surgery. They're not getting surgery resected, but they're also measured and they're also in the radiation field. And they also get the substance, or they are exposed to the substance. And what

you can see here, and of all the 9 patients with non-target lesions, 3 had a complete response (CR), 4 had a partial response (PR), and 1 has stable disease (SD) but also decreased in size.

To make clear how that looks like and why we look at it, I have an example. That's the exemplary case. In the baseline scan, there's some residual disease in the cavity, post-surgery, and here you see a non-target lesion which is a bit more medially located here, not an initial part of the cavity, not initially when we looked at in the target lesion setting. We treated these patients with radiotherapy and NOX-A12. You can see how that really disappears over the course of treatment. And then it is really intriguing. Because if you look at the image, it's even a much deeper and better response of non-target lesions than the target lesions. We're really intrigued by that and that's also huge problem for glioblastoma because these tumors tend to spread and invade. And at that stage, we actually have a surprising response of these non-target lesions, they even disappear.

So, when you look at the sum of non-target lesions, you might want to think of a dose-dependency. If you look at the course, here we plotted this with the Mean max change from baseline. We see that at highest dose it goes pretty well down. And also, if you look, you can dissect the tumor. In several aspects, in highly perfused, medium perfused, and low perfused aspects. That comes out of the advanced imaging that we did here as a secondary end-point. And what you can see, the fraction of tumor burden that's highly perfused. So, these parts of the tumor that are really highly proliferating, highly perfused. They got also go down with the dose. And then, we have to see also in cellularity, we looked at the diffusion that's also something you can measure. So, the more diffusion, the lower the cellularity of a tumor. That means that when it goes up it gets better. And then, you also see a slight dose-dependency. So, we basically see the things that we wanted to see. We see a bit of a dose-dependency in the target lesions in the tumor fraction, also in the cellularity.

Now I'm going to take you a bit outside of the poster because we have also seen things that help us to really understand also what's going on. I told you that we have done surgery on a patient where we found a pseudo-progression. What is a pseudo-progression, what's a true-progression? What we found out is that under NOX-A12, we have a nice imaging biomarker that helps us to figure out what is true-progression and what is pseudo-progression. Looking at that case, that patient here, underwent re-surgery. So, we have the ground truth. What was that here. And if you look at the rCBV, that means the profusion. You see that every time you measure, even here, if you can't even see it in one signal, profusion already goes up a bit, and here you see the tumor coming back. Here, didn't show his face, didn't really show hiding somewhere here, but already you see the biomarker going up. And also here, there's in the front lobe, tumor recurrence, and that was then basically confirmed with surgery.

So, let's look at the case that I mentioned before. The case where we thought we had progressive disease (PD). Look at what we see in the perfusion, no increased perfusion, even going further down along the path. And surgery confirmed that was no tumor. So, with rCBV, we have an imaging bio marker where we can basically also understand the kinetics of the tumor. It is a very handy tool to understand the response to radiotherapy and NOX-A12.

So, last not least, I told you about CODEX. Why did we do CODEX? Because, well, in pre-clinical data, we know that CXCL12 creates a really immune-suppressive tumor microenvironment, and that is basically repelling CD8 T cells from going into the tumor. This tumor microenvironment is really repelling these cells. And what we see under NOX-A12, which you can see here because we definitely looked at the CD 8 this is the T cell that, cytotoxic T cells. $GNZB^+$ means they are active. $K67^+$ means they are dividing. So, this is the fraction, if you want to wish, of the aggressive anti tumor T cells. You look at the baseline and you look at the NOX-A12, you really see that this nicely goes up, if you see the

images here. See that here, you don't really see that in that manner, but you see these clusters here. So, here you see T cell clusterings, that means here there's a proliferative and nest of T cells growing up. And also with the macrophages, we have seen things we have not seen before. For example, I wouldn't say that there's pretty much a change in macrophages, like from the numbers, but, what we have seen from the configuration of the microphages, this is a patient that just did not respond to therapy, and there we see some cuffing of macrophages. They really encapsulate T cells and keep them hostile somewhere here. Things we have not seen before, and they are not described essentially. And we're now deeper looking into that.

So, just to conclude, we think radiotherapy plus NOX-A12 in a population of chemotherapy-resistant or refractory population is safe. We did not see any DLT. I think we see a lot of clinical efficacy signals, more than expected, with target lesions, and non-target lesions even more. We see T cell recruitment and clustering. We even see what happens if macrophages encapsulate these T cells, things we have not seen before. And now, we even go deeper. And I've also mentioned in the previous slides that we're now combining it with bevacizumab and pembrolizumab and we are targeting VEGF also, and the PD-1 axis, as a consequence of what we have also seen in this set. With this, I hope I could make clear like what we have presented at ASCO, and also, figure out what we see in the imaging biomarkers and I'm happy to take your questions.

Q & A:

Q1) What the next steps are going to be with regards to the clinical development?

A1) (Aram Mangasarian) As Frank outlined, we're going to complete these extension arms, and I think the data emerging from those are going be quite important in determining the next steps and what we actually take forward. And so, our goal now is to give an update on that and the strategy for developing it in the next few weeks. So, I think I'm going to have to push the final response to that question off a little bit.

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Q2) Why not extend the treatment beyond 6 months with a low dosage of NOX-A12? Why not combine NOX-A12 and NOX-E36 in patients resistant to basic treatment? When are the interim and final results expected for the expansion of the GLORIA study (referring to the combo with avastin and with PD1)?

A2) (AM) We are thinking a lot about those very combinations. I think for the moment we're focused on getting the data on the bevacizumab, the anti-VEGF arm in the anti-PD1 arm. The anti-bevacizumab arm is moving more quickly. It's just got slightly easier to fulfill the inclusion criteria than the other arm. And I hope to be able to give a high-level update on where we are again in a few weeks, because that's going to influence the path forward.

A2) (Frank Giordano) I think they are brilliant ideas. Maybe I can add that we started the trial with the idea of what came out of the pre-clinical model system. We have them like anti-vasculogenic effect, and I think I can say that we're stunned about the things we see on the CODEX. On the histology level, because that opens many other avenues and also what we see in the advanced imaging. Thanks to NOXXON, you went that way with us. We really put a lot of efforts in the imaging just to understand that the various aspects of these tumors, and I think I'm not telling too much that we have good ideas coming out of that very helpful Phase 1/2 trial.

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Q3) What MRI sequences did you use for rCBV?

A3) (FG) Dynamic Susceptibility Weighted Imaging. It is a T1 star weighted sequence. You inject the contrast agent and then you do frequent scanning with T1 star sequences. And then, you just look at the susceptibility curve and you see if you normalize that to the healthy brain on the other side, you can see that you can basically have a grade relative perfusion number, rCBV is the number, it is the term that we are looking at. Then you resect the tumor in rCBV values and then you can dissect the tumor in high, medium, and low perfused aspects.

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Q4a) Do you plan on using rCBV as a surrogate end-point in your pivotal trial to allow the trial to continue in case of pseudo-progression? And why this phenomenon of rCBV repeated in all the pseudo-progression that you observed?

A4a) (FG I don't know how many active substances in this world were on the market that were not successful because they were too early discontinued. Imagine you have active substance and you have a lot of pseudo-progression, you are going to discontinue active therapy, because of a false friend information. And the patients are going to die, and then the end, you are going to say: "*Well, yeah, there was a progressive disease (PD) anyway, because the patient then subsequently died*". But the

patient died because you discontinued the therapy too early. I don't really want to imagine how many patients have really not been benefiting from active therapies, because we did not have really good tools. We are now in a situation where we have a quite good biomarker to understand where we have a chance, or where we see early progression. We also have a patient, I have shown you that, (who) has not really responded to therapy. So, we are not like 100% winning hands down. But we now have a biomarker that we can maybe use. If it's the pivotal biomarker, I don't think so. For pivotal trial, you need hard end-points. But you have got to make sure that to get to that hard end-point you don't discontinue an active therapy too early, and there, rCBV is pretty helpful.

A4a) (AM) Now, we want to make sure that in the in the pivotal trial, and this is one of the things that we have been discussing with Dr. Giordano, is that the centers know to look at this perfusion value before they discontinue therapy. Because that is going to be key to make sure we reveal the true efficacy of the substance.

Q4b) Any medical center in the pivotal trial will be able to use such a tool, is that correct?

A4b) (FG) Every center that is participating here is a certified brain tumor (center), they run through various certifications, and they have neuro-radiologists or radiologists that are qualified to look at that. And to be fair, we didn't invent the wheel. Perfusion imaging is in 90% of brain tumor treating centers as standard sequence that's run to help distinguishing pseudo-progression from true-progression. And because you can also use it as a response-classifier in, for example, in brain mets that are where patients are under immunotherapy, you have the same situation. These brain mets initially tend to get larger after radiotherapy and then they shrink. And there rCBV is pretty much established.

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Q5) What were the criteria used to the matched cohort (WF plot)?

A5) (FG) So, we tried for the imaging, to look at matched cohort in terms of, and we cannot compare MGMT methylated and all respond to temozolomide with an MGMT non-responding population. So, the key point where we matched it was that it's unmethylated MGMT. These tumors that do not respond to any of the therapy we offer the patient. So, that was the key matching parameter. I must also say we also had a positive selected. So, the imaging cohort had to have at least two or more scans in the follow-up. That means of all the patients we look through, all those that died early, after maybe surgery, radiotherapy and did not even reach the first scan. We didn't look at that, because we needed some scans at least to figure out what the best response are based on 2-3 scans. So, the matched control cohort, if you wish, is a bit of a positively selected group of not-so-well-performing patients.

A5 (AM) You are actually excluding the worst-performing patients. You got the patients who survive long enough to have multiple follow-up scans. It's a slightly better performing cohort than you would expect from simply applying the recruitment criteria of our trial.

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Q6) Have you seen any interesting quality of life (QoL) improvements in treated patients?

A6) (FG) We are measuring the quality of life (QoL) with the standard questionnaires. But so far, what I can say is that if a patient is diagnosed with GBM, you don't really try to improve quality of life (QoL), you try to maintain quality of life (QoL) at the level of baseline and there we didn't see it decrease under NOX-A12. You definitely see a decrease in quality of life (QoL) in the moment that there's tumor progression, or there's anything coming along the path that's tumor-related. But considering the

therapy, I can say even like with a needle and like with replacing the substance needs to be 24/7 infused via a pump. I have not seen any or 1 patient that would have had a decrease in quality of life (QoL) because of the circumstance of the application of the drug. People are definitely willing to do that. Because it may be a bit unhandy to carry a bag with the pump, but people are willing to do that. And I have not seen a decrease in quality of life (QoL) so far under therapy.

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Q7) Does NOXXON intend to explore to participate to a platform trial for the Phase 2/3, like the GBM AGILE study?

A7) (AM) Yes, that's one of the platform trials that we are indeed looking at. That's one of the options. We haven't made a final decision yet. I think we need to see how the data shape up. For those of you who do not know what GBM AGILE is, it's a cooperative platform trial where there's a shared control arm. And then, multiple active agents are tested experimentally. And it's nice in a few ways, (but) it comes with some limitations, which I'll get into in a minute. But, it's nice because it's up and running. It allows you to join a trial that's running in the US, Canada, Europe, and soon Australia, and China. That would lead to approval. So, you can be up and running quickly. Limitation is that you have to adhere to the standard protocol, you have to adhere to the standard imaging. You can add some and that's one of the things we are exploring with them, whether we can add these important parameters that we've understood through this very important early work that we are doing, in that it is important to keep treating patients when they are actually responding, but the imaging looks like it might be a progression.

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Q8) Why did you choose to go for BEV (bevacizumab) and PEM (pembrolizumab)?

A8) (FG) When you look at all the pre-clinical data we had, the BEV (bevacizumab) combo is a logical next step because hypoxia leads to HIF-1-alpha (Hypoxia-Inducible Factor 1 alpha) mediated upregulation of CXCL12 and VEGF. So, that is well known and established for a long time. And, one is the salvage pathway of the other. That means if you inhibit one, you may want to circumvent that effect with VEGF. And it was shown that the VEGF blockade could be circumvented with CXCL12. So, inhibition of both has already been assessed in a murine model, and that was seen to be synergistic, but we had to start somewhere. First of all, we wanted to see if there's dose-dependency if we can establish that, if we can make that work, and if that's toxic at all, combine it with radiotherapy. But, the BEV (bevacizumab) combo was definitely there, a logical step from all that's known in pre-clinical models.

The motivation to include pembrolizumab (PEM), that was not on our watch when we started the trial. But when we looked at it with CODEX, and there with CODEX you can look at 50 biomarkers at a time, at the same slice that you look at, we saw T cell clusters, we saw massive influx of CD 8 positive effector T cells. And that was great. And that was not only seen in 2 patients that I mentioned, but it was also seen in another trial of NOXXON, it's called the OPERA trial, where NOX-A12 was given in metastatic colorectal and pancreatic cancers. So, there was accumulating evidence from the studies that are ongoing. It definitely makes sense to combine it with immunotherapy. But, to be fair and honest, I think we all didn't have that on our list. And it's something where I'm really happy that we had a strong translational component up and running in that trial.

A8) (AM) I'll just add that the images if you look in the publication of the OPERA study, are really very similar to these clusters that Frank and his colleagues found in the brain cancer tumor tissue. You see

these T cells going from sort of dispersed all throughout the tumor to these clusters that are very close to the cancer cells. And actually, in the pancreas and colorectal cancer tissue, that was one of the statistically significant outcomes was that the T cells actually moved closer to the cancer cells in the tissue, in patients who had this tissue response. So, it's a very interesting phenomenon. Looks like it's NOX-A12 driven, because in that earlier trial and pancreas and colorectal cancer, there was no radiation, and this before and after samples were only after 2 weeks of NOX-A12 monotherapy.

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Q9) How should we consider NOX-A12: as an agent that optimize radiotherapy anticancer effect, or rather like an inhibitor of the later effects of radiotherapy known to be pro-cancer?

A9) (FG) Radiotherapy has been used in glioblastoma for decades. And we have tried to dose escalate, we have tried to concentrate on the cavity. We have tried everything, hypo-fractionation, hyper-fractionated accelerated (radiotherapy). We've tried everything. What I think what we have learned so far is that we can be quite effective with radiotherapy, but we need to make sure that after we are done with the radiotherapy, this tumor microenvironment will recover quite quickly. And what I think what we've learned over the past 5 to 7 years is that radiotherapy might be beneficial in depleting tumor cells, but it also depletes small vessels. And the response of the tumor microenvironment is something you don't want to have. And over the past years, we have understood that we have to block certain pathways or we have to modulate the post-radiogenic tumor microenvironment. So, NOX-A12 is, to my understanding, not a radiosensitizer. But rather like an effect stabilizer, if you wish. Like you deplete the vessels and you kind of conserve or preserve the status quo that you have here after radiotherapy.

A9) (AM) Yes, I think that this blocking of repair of the destroyed vessels is one of the key effects and that the earliest pre-clinical work done at Stanford on this effect really focused on the vessel depletion. And I think, what Frank mentioned earlier, we weren't focused so much on the immune response, which is the other aspect we're now seeing in these tumors. That's quite interesting is that it wasn't analyzed as part of these early studies, which were very much focused on the vasculature. This came out of work we did in pancreas cancer. And we weren't sure to be honest, that we were going to get this influx of immune cells into the brain, because it's an immune-privileged side. But we saw it and indeed we saw it at the lowest dose already in a pretty dramatic fashion. So, it looks like we have two effects: one is this blockage of repair of the damaged blood vessels, and the other is this enhanced influx of the active arms of the immune system.

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Q10a) For now, the GLORIA treatment paradigm is radiation followed by continuous NOX-A12. Should the patient progressed after, let's say, 6 months, how would you expect this patient to be treated? Would that be by additional radiation and starting NOX-A12 again? (How do you see treatment post-progression?)

A10a) (FG) So, first of all, we have to make sure that it's a true-progression. I think we have touched on that pretty extensively. But, if we find out it's a true-progression, we are, so to speak mechanistically, all the investigators are tempted to give bevacizumab (BEV). Because, you feel that maybe that was the backup pathway that was activated. And we all know, I've seen and I've showed the patient. We all know that salvage temozolomide in the unmethylated patient will essentially lead to nothing. These patients will not respond to temozolomide, so you have got to have a better idea. And based on pre-clinical evidence, and based on everything we know from these models, we are tempted to give bevacizumab (BEV). But, to make that clear, I could also imagine recurrent

radiotherapy and continuing NOX-A12. Because you didn't back-deplete the vessels and sort of delay that again, but that's all speculative. And, in the recurrent setting, we don't really know what's going on. And if one or the other way, it may be beneficial, I can't really (tell). But, I could think of a re-radiation definitely, and trying to tackle that again, maybe like with a combination.

Q10b) Would you expect a total new cycle with resection, radiation, NOX-A12 plus or minus with bevacizumab (BEV)?

A10b) (FG) Well, that is highly speculative. I mean, we are not so far that I could really give a quite fundamental scientifically-based answer to that. I mean if a patient is able to be re-resected, I would always prefer re-resection, because you get the ground truth. Based on the experience we made, I would even think of low threshold for stereotactic biopsy to really nail that down. If you are dealing with a true-progression or a pseudo-progression, because these are two totally different ways of treating, and two totally different consequences for the patients.

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Q11) In your slide, we can see that one patient has GGT increased and two have ALT increased, only NOX-A12 related. Can you say when these increases occurred (early or late in the treatment), and if there were any correlation between these liver elevations and poorer outcome in these patients?

A11) (FG) No. So, both patients we have included have pre-existing diseases. Both patients with liver enzyme elevations had pre-existing diseases that may proceed because these liver enzyme elevations. For example, one had chronic diverticulitis and the other had idiopathically elevated baseline liver enzyme level. So, we understand from earlier Phase 1 trials on NOX-A12 that they were liver signals coming up, but these trials had much higher exposure doses, but there were definitely paying attention. But these previous trials with the liver enzyme signals, had much higher doses.

A11) (AM) I think it's one of the reasons that the investigators are so sensitive to seeing liver enzyme elevations and, you know, by precaution, want to flag it as probably NOX-A12 related even if there is a pre-existing condition. There's something we are keeping a careful eye on as a company, I know the investigators and treating clinicians are keeping very careful eye on the patients.

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Q12) How challenging the recruitment of these patients was and if the data are confirmed in Phase 3? How likely it is for NOX-A12 to become standard of care in this patient population? And maybe actually, can you remind how big this patient population is?

A12) (FG) So, GBM has an incidence of 3 to 4 in 100,000. 60% are unmethylated. You do the math. And, I would say it doesn't matter If you have a resectable or unresectable tumor, I mean it's both the same. In the first few patients, we include unresectable. In the first, those levels were included unresectable and then we now open the trial for fully resected. I think recruitment is always an issue with glioblastoma, because only half of the patients are operable and with those that are then unmethylated, you only get a subfraction of a subfraction of a very rare disease. I think the point is that in high volume, tumor centers, like we have in Bonn, or all the sites that are participating, that is not really the issue. The issue is to find a patient that is not so bothered by the initial status. But you really have the chance to help these patients with a therapy. I'm making an example of patients that is under a permanent seizure with a tumor in a very delicate location. These tumors, they even may develop pseudo-progression and die then from a pseudo-progression or have any complication that you cannot control. In all the clinical trials with glioblastoma, patient selection is absolutely key to find,

or to even have the chance that you can really figure out an effect from like an unspecific background noise that this disease really creates.

And the second part of the question, I mean that's the sort of jackpot question. If you have a positive Phase 3 trial, you're water falls on dry ground. I mean there's nothing been changing this therapy for 20 years. So, if you come up with a positive signal in the Phase 3 trial, then you can basically can check the guidelines all over the world, that's going to be standard of care immediately.

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Q12) The proportion of drugs developed in GBM with positive Phase 2 but failing to demonstrate clinical benefit in Phase 3 is very long. How would you position the robustness of the NOX-A12 clinical data generated to date with the other Phase 2 generated by other compounds, and what do you think makes NOX-A12 so different?

A12) (FG) Well, that's a very good question, and actually, if you go to a pharmaceutical company and try to convince them for going into glioblastoma, you will have to face this question. You definitely have to be prepared, because this question is the key question. If you want to get in touch with the pharmaceutical company. But, the key is that you have to implement an elaborated and sophisticated imaging protocol, and in all earlier trials, that I know, this was not really implemented. I already mentioned I don't know how many active substances are really burning in the fire of pseudo-progression. And when the therapies get discontinued despite having an efficacy signal, which you don't see because you don't measure the right thing. So, in other words, we, now and today, know better if we deal with pseudo-response or pseudo-progression and can figure out how we deal with one or the other. And one very, very important point in that trial is that we looked into the samples with massive parallel immunoplexing. That is looking at 50 markers at a time just to make sure that these things we see with the imaging correlate to a kind of histology and that is actually the case in that trial. So, the plan was not to go in a naked Phase 1 trial and see what happens. The plan was to go in a Phase 1 trial established as many as possible translational components to get the wider picture. That is definitely necessary to decide whether or not we move on in the clinical development or not. And that's where we right now are.

A12) (AM) It's a really important point and I think that the work that the group that Frank has assembled around the trial, not just the clinicians in the clinic, but also the scientists looking at the tissue has been really extremely important in advancing our understanding of how NOX-A12 works.

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Q13a) Based on your experience, what kind of median OS we could expect based on the ORR that you are achieving in the GLORIA study?

A13a) (FG) I can not really comment on that because follow-up is not mature yet. There is 2 out of 10 patients that are still on drug or in follow-up. But, what I can say, and I don't know if I can say that, but 50% of patients achieved to live already now longer than a year. And there's one patient on trial that is now close to a year. So, we are going to be exceeding 50%. But, these efficacy parameters will take a bit more time. Also, I have to mention, be careful if you look at classical efficacy parameters, because I showed you an image of a patient that we discontinued, or 2 patients that we discontinued too early. And there was a steep learning curve we all took in the GLORIA trial. These patients probably could have lived much longer if we would have kept them on the drug for longer than 26 weeks. So, we're looking at the learning curve, we're looking at the 'not-mature follow-up', and all these things come

down together. And, believe me, I'm having a hard time with putting that together, putting that down in words in a manuscript that describes all that.

Q13b) Can you remind us, what is the 1-year survival rate of the unmethylated population?

A13b) (AM) It's not just unmethylated, because we're taking unmethylated and incompletely resected. And, when you put those two together, you're getting the worst half. And then you're taking the worst of that. I think the best publication we have found, the one we always cite, is the study that broke it down the best and then came to around 10 months OS for that population. Frank, I think from your clinical experience, you should say whatever you think.

A13b) (FG) A benchmark from the trial where you showed overall survival data, Aram, this was the EORTC trial where MGMT was also established as a biomarker and where temozolomide was established as a therapeutical drugs. But where you have to be sure that those per today's definition were not really all true glioblastoma. At that time, there was also a huge fraction of IDH mutated tumors that would not be qualified as glioblastoma. And there the 12-month survival was about 40%, that 80% resection rate. So, we're looking at, like out of the blue, I would say we're looking at 25 to 35 something percent, 40% 1-year survival, if we would match the whole population. But since our trial is not randomized, and we can only make up some numbers, but I would say, we are not so bad, even though we had a learning curve and we had discontinued many patients too early.

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Q14) How do you explain the NOX-A12 effect non-target lesions (recruitment of immune or inhibition of vasculogenesis)?

A14) (FG) I think the point is that where we have a low tumor volume, exactly that, I think the question goes right in the right direction, and we discussed that many times. Where you have these low tumor volumes where actually the immune system can win. If you look at all the immunotherapy trials, they want to have low tumor burden to start. So, that you can basically win. We also have a good idea why these non-target lesions really can be disappearing. But at that time, I have no proof that it may be immune-related, or we don't really have the proof for that. But it's really making us wonder why this small lesions would then disappear. It may well be that they're small enough to be defeated, so to speak.

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Q15) NOX-A12 is a permanent infusion. So, did any patient discontinue had convenience-related issues leading to some not optimal treatments? Is there a way to formulate NOX-A12 as a more convenient formulation that will not require pumps such as a weekly subcutaneous injection? (in an optimal manner where the dose of NOX-A12 surely is flat and stable?)

A15) (FG) So, when it comes to convenience, I would say these patients get a deadly diagnosis and they basically try to do everything to come into the trial, because the alternative is definitely to have no therapy option at all. So, for the time being, I have not experienced these patients to be protesting against the pump. Rather to the contrary, the patients, when we discontinued after 26 weeks before we amend the protocol, I think they were pretty close to coming to Berlin and to protest that we take away the pump, but we were simply not allowed to make that infusion longer. When it comes to convenience, I see that this can be solved in the future. I mean, for GCP (good clinical practice) reasons, trained staff has to replace the needle and the pump. It's just for study and GCP (good clinical practice) reasons. I don't see where this could be a problem that the patient just disconnects it and connects it. I mean, many cancer patients do that themselves and replace the cassette themselves, so they won't

even have to come into hospital to do that. You give them the pump on stock. I don't know if there's an issue with how stable the substance is, but to my notion it is very stable in room temperature or even in warmer environments. I see no problem why the patient cannot change everything once weekly. But with the formulation, I don't know. Aram, that's up to you to comment on that.

A15) (AM) Maybe I'll make a few comments. You're correct on the stability. Indeed, we don't have any issues with stability at room temperature. And now, we've even thought about loading the pump with enough drug for longer times between refilling. The reason we use the pump is really to have a completely flat PK curve because that's what was seen in the early models in the rats when you give a subcutaneous administration. We may explore something we're thinking about other dosing regimens that involve IV bolus administration. That way the patient won't have to carry anything around between. But at the moment, that would have to be more frequent. And we're also looking at formulations where you would have a delayed-release. So, essentially the goal of that research would be to get a formulation where you have a subcutaneous or intramuscular injection, and then the drug is released and you get a similar curve to the pump. But again, that's something that would have to come later. We are looking at various formulation options that are available and that's something we would definitely think about.

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Useful Resources:

1) The KOL Webinar presentation slidedeck
2) ASCO Poster
3) ASCO Poster presentation video with Dr. Giordano's commentary