

What's next in treatment of brain cancer patients? Testing NOX-A12 with Radiotherapy in a Phase 1/2 Clinical Trial.

September 23, 2019 Webinar

DRAFT Script

Panelist

Dr. Frank A. Giordano, MD, Interim Chair & Associate Professor, Dept. of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg

Introduction by *Aram Mangasarian, CEO of NOXXON:*

SLIDE 1

To those of you joining us live on this call today, welcome on behalf of NOXXON Pharma. This is Aram Mangasarian, CEO of NOXXON Pharma. I am very pleased to be joined by Dr. Frank Giordano, Interim Chair and Associate Professor at the Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg. Welcome Frank and thank you for joining us!

SLIDE 2

Before we get started, I've been asked to note to all listeners that this presentation contains forward looking statements and that listeners should consult NOXXON's prospectus as well as our most recent annual report and other disclosures for full information on the company and associated risks. Today is 23 September 2019 and this webcast is being recorded, and so if you are listening to it at a later date, please note that NOXXON will not be updating any information herein after the recording.

SLIDE 3

Dr. Giordano is the coordinating clinician for the trial testing the combination of NOX-A12 (NOXXON's CXCL12 inhibitor) + radiotherapy that has just started recruiting 1st line glioblastoma patients. Dr. Giordano is a radiation oncologist and translational scientist who has dedicated himself to developing better treatments for his patients and has led many clinical trials that tested potential therapies for brain cancer including INTRAGO I and II, Gamma-GBM and Imatinib in GBM which was published two weeks ago.

SLIDE 4

Aram Mangasarian: I know that many of our listeners are short on time and would like to hear the key messages summarized, so Dr Giordano and I will provide a Quick version of the presentation right now based on the agenda. We're also recording this presentation so you can come back and listen to it later on our website:

Aram: Dr Giordano – one sentence on glioblastoma:

Frank: The most malignant brain tumor in adults with extremely limited treatment strategies.

Aram: What's the current standard of care?

Frank: Since the early 2000s the first line setting consists of surgery, followed by radiotherapy and chemotherapy. There is no standard of care for recurrent disease.

Aram: What are the medical needs?

Frank: In first line 60% of the patients derive little to no benefit from standard chemotherapy, and we can identify these patients with a biomarker present in the tumor. This diagnostic marker in patients that will not derive benefit is called "MGMT". Patients that will benefit have a MGMT methylated promoter status in tumor tissue. Patients that will not benefit have an unmethylated MGMT promoter status.

Aram: Please give us a brief summary of various approaches that have been tested recently in glioblastoma

Frank: Despite many different approaches being tested we haven't seen a really positive glioblastoma trial in the last 14 years besides one that used electric alternating fields and one in which Martin Glas and Ulrich Herrlinger (both are also participating in the NOX-A12 trial, by the way) showed that adding a second chemotherapy agent to standard of care gives a better effect and prolonged survival, but only in the smaller subgroup of MGMT promoter methylated patients which represent about 40% overall front-line population.

Aram: What attracted you to the NOX-A12 mechanism of action?

Frank: The preclinical data suggests that we can strongly increase the efficacy of radiotherapy by blocking the ability of the tumor to send out a "help me, I need new blood vessels" signal via the target of NOX-A12, CXCL12. The process of repairing the damaged tumors via CXCL12 is called Vasculogenesis.

Aram: Tell us about the NOX-A12 + radiotherapy trial

Frank: We are planning to test three doses of NOX-A12 + radiotherapy in newly diagnosed glioblastoma patients. These will all be patients that are MGMT unmethylated, so we know that they would not derive benefit from standard chemotherapy. These are also patients that have tumor mass remaining that could not be surgically removed.

Aram: What are the objectives of the trial?

Frank: First, establishing the safety and tolerability of NOX-A12 + radiotherapy in these patients, and defining a recommended Phase 2 dose. We will also look at efficacy parameters, such as the ability of the tumor to rebuild blood vessels destroyed by radiotherapy, progression free survival and overall survival.

Aram: Thanks – in terms of timelines we target having top-line data from the first dose group mid-2020 and the other two other dose groups around of the end of 2020 if the trial and recruitment proceed smoothly. I hope that this gives some of you who are short on time a good overview.

SLIDE 5

I'd like to take a moment to put this trial into the context of the NOXXON pipeline.

The approach the brain cancer trial is testing is a distinct one from the NOX-A12 + immunotherapy approach used in our pancreas and colorectal cancer trial. We won't discuss that trial today, but I will note that we are presenting an update on the pancreatic and colorectal cancer trial at the Congress of the European Society for Medical Oncology or ESMO in one week in Barcelona and that our Chief Medical Officer, Dr. Jarl Ulf Jungnelius and I will present another webinar for listeners to take them through the poster on Monday September 30 2019. This trial is a scientific collaboration with Merck & Co. /MSD as they are called in Europe, who kindly provided us with the Keytruda and we continue to interact with them as patient follow-up data emerges from this study.

Moving back to brain cancer...One of the most interesting sets of preclinical data that the company has seen was from the combination of NOX-A12 with radiotherapy. The initial work was done by Professor Martin Brown at Stanford University who did pioneering work in this area – Dr. Giordano will speak more about this later. Prof. Brown published very intriguing data with NOX-A12 showing 100% complete response rate, of which 2/3rd was durable, in a very difficult to treat brain cancer model. Prof. Brown's work generated a lot of interest in the clinical community around the CXCL12 target especially in the brain cancer area. Because of this extraordinary pull, we've really fought to find the resources to test this promising approach in this extremely challenging orphan disease with very limited to no efficient treatment options.

Moving to the next line - As you know we also have a preclinical agreement with an undisclosed top-10 Pharma that is evaluating NOX-A12 in a new indication that NOXXON is not developing in the clinic. We think that this should be seen as a new line in the pipe since the big Pharma is investing in this indication and could go rapidly into a large clinical trial if they decide to move forward given NOXXON previous clinical experience.

Both this and the Merck collaboration have built relationships with big pharmas and it's important to understand that building relationships like these are important for downstream collaborations.

NOX-E36 at the bottom is also a drug which has plenty of clinical experience outside of oncology and for the moment we are strengthening the preclinical studies in oncology where we have seen monotherapy activity in two different models of solid tumors: pancreas and liver cancer.

Coming back to our glioblastoma trial...

We've asked Dr. Giordano to give a brief description of glioblastoma, where it fits in the landscape of brain tumors and to describe the standard of care for these patients. He'll then provide his views on the industry pipeline and where the NOX-A12 approach fits. We'll then take you through the design of the upcoming trial.

As a reminder, NOXXON announced on September 12th, 2019 that we had initiated recruitment of a Phase 1/2 trial that aims to evaluate NOX-A12 + standard course radiotherapy in newly diagnosed (1st line) patients with glioblastoma who have residual tumor following surgical resection and who won't benefit from standard chemotherapy (no chemotherapy will be given).

SLIDE 6

Dr. Frank A. Giordano

Glioblastoma: an unsolved problem

Thank you for the introduction. I will provide you with some basic information about the disease, glioblastoma. First of all, it's important to know that treating glioblastoma patients still is an unsolved problem. The patients have very poor prognosis and we have extremely limited treatment strategies on the market. Glioblastoma is the most malignant brain tumor in adults and it's one of the most malignant cancers overall. Patients have poor prognosis despite the combination of surgery, radiotherapy, chemotherapy, electric field therapy, or systemic therapy. Depending on the patient profile, they will survive on average between 10-25 months.

Origins of Disease and Epidemiology

Etiology is still unknown, so the origin of this disease is not clearly identified at the moment. Median age at diagnosis is in the mid-60s and we see approximately 3,000 newly diagnosed patients with glioblastoma in Germany each year. In the US, we can count approximately 10,000 new patients per year.

Glioblastoma Treatment

How do we treat these patients? It's important to distinguish different treatment scenarios: treatment for newly diagnosed patients and tumor relapse, or recurrence of disease. The situation of newly diagnosed glioblastoma patients or the first-line scenario is clearly defined with a standard of care:

- a combination of tumor resection, if possible, then a macroscopic complete resection, microscopic complete resection is not possible because it's an invasive infiltrating disease, which means tumor cells migrate away from the point of origin in the normal brain tissue and become present in the whole brain,
- this treatment is followed by radiotherapy in combination with chemotherapy. And it's important to know that the standard chemotherapy is an alkylating compound called Temozolomide.

I should also mention that there is a novel treatment approach: We are also able to treat these tumors with so called alternating electric fields, which could influence cell division, cell proliferation and lead to cell apoptosis. And you should know that there is a controversial discussion whether we should include this approach in the standard treatment of care, but there is no consensus at the moment. There is a positive randomized phase 3 trial recently published and so this is another option in combination with Temozolomide.

In the case of tumor recurrence there is no standard of care at the moment. In the clinical community we discuss additional surgery, repeating radiotherapy and mainly these strategies consist of pharmacological approaches which means off-label chemotherapy or off-label systemic therapies.

SLIDE 7

You can see here in a summary from a paper published by the German Glioma Network the effects of two key tumor-related parameters on progression free survival and overall survival in glioblastoma patients. First – if the tumor mass can be completely removed by surgery, this provides benefit for the patient. However, another important parameter is the sensitivity of the tumor cells to the standard chemotherapy, temozolomide. There is a particular gene whose expression is turned on or off, and when it is present (MGMT unmethylated) we know that there will be little to no survival benefit from the chemotherapy.

The population highlighted in yellow is the target population for the NOX-A12 + radiotherapy clinical trial. These patients have residual tumor and will not benefit from chemotherapy. They have an average progression free survival of 6 months and overall survival of 10 months.

SLIDE 8

Medical Need & Market for New Treatments

So how about medical need and what about the market for new treatments?

In the first line setting there is only a single approved drug, temozolomide, an alkylating drug. As you saw from the table, we just showed you, in the first line patient population the highest medical need is amongst patients where the MGMT promoter is “unmethylated” (as opposed to “methylated” who have a better prognosis). It’s important to remember that these patients with an unmethylated MGMT promoter did not show any significant benefit from Temozolomide, from the standard of care therapy.

This situation of having only a single approved drug has been the case since 2005 and now we are in 2019 and we haven’t seen a really positive glioblastoma trials besides one that used electric alternating fields and another in which Martin Glas and Ulrich Herrlinger (also participating in the NOX-A12 trial, by the way) performed showing that if you add another alkylating agent, Lomustine, to Temozolomide you get a better effect and prolonged survival. But it’s important to note that this has only been seen in the smaller subgroup of MGMT methylated patients.

Aram Mangasarian

I’ll say a few words about the glioblastoma market – which is an interesting one for an orphan disease. We know that worldwide sales of temozolomide peaked at over \$1b. The success in glioblastoma drove development in other indications and the serious nature of glioblastoma and the unmet treatment needs mean that you know relatively quickly (on the pharmaceutical drug development time-scale) whether you have activity in this indication.

SLIDE 9

Dr. Giordano

This covers the current status of chemotherapy focusing on the overall pipeline for glioblastoma.

SLIDE 10

A few words on radiotherapy - We had these dose escalation trials done by Walker et al. (Walker, Int J Radiat Oncol Biol Phys, 1979) in London that established 60 Gy of radiation or 6,000 cGy in the US terminology, as a standard of care and we combine this with Temozolomide during the radiotherapy course of 6 weeks and then add some cycles of Temozolomide afterwards.

There have been some improvements in the technology of how we apply radiotherapy in order to decrease the side effects and in this aspect, there has really been some progress. Side effects went down but the efficacy is still on the same level as years ago. Basically, everything else that we have had from a technology point of view in radiotherapy; gamma knife, stereotactic radiotherapy whatever – nothing has really worked better until now, but there is now a truly novel approach that we apply some of our radiation dose as early as possible during surgery. And the idea behind this is that the surgical wound creates a microenvironment that is stimulatory. If you get a cut, the body secretes and produces cytokines that stimulate cell proliferation (cell growth), angiogenesis (blood vessel growth), wound healing, fibroblast migration, everything, and this cocktail of stimulatory cytokines also unfortunately stimulates any remaining tumor cells. A phase 2 trial tPI showed some promising data that adding intraoperative radiotherapy notably changes the tumor microenvironment and adds efficacy to the 60 Gray.

SLIDE 11

The third important therapeutic class to discuss is immunotherapy. We can summarize relatively quickly here that for the moment, we don't have any good signals of efficacy, and indeed some recent failures of checkpoint inhibition combined with radiotherapy.

SLIDE 12

What's making these glioblastoma tumors so difficult to treat? The tumor microenvironment.

Let's lay out the facts: In glioblastoma, we have a tumor microenvironment that is 1) poorly immunogenic, 2) does not allow T-cells to come in and 3) is extremely hypoxic (oxygen-deprived). Now, hypoxia creates a strong attraction for cells from the bone marrow. These bone marrow cells want to come in, they want to build new blood vessels in there and make this tumor oxygenated again. Unfortunately, these cells come along with a lot of bad guys: myeloid cells which turn on the brakes of all other immunologically active cells in the area. So, basically it is these myeloid cells you want to keep out of the tumor. But will T cells home in brain tumors – or even in the brain at all? Are there mechanisms that we can use to make these tumors more susceptible to therapy? We think there are.

SLIDE 13

We put together a chain of events on the left side of slide 13 – showing some of the things that happen after radiotherapy. On the right is a figure from an editorial in the Journal of Clinical Investigation in 2010 (Greenfield et al) prompted by a paper from Prof. Martin Brown's group (Kioi, 2010) because his findings were so novel in 2010 that we needed a new way of thinking. At that time, radiation oncologists concentrated on the radio-sensitivity of tumors and we almost neglected the microenvironment. We focused on the seed and not the soil. What we forgot is that with radiotherapy, we are depleting all the microscopic vessels in the tumor, which in turn is getting hypoxic. A hypoxic tumor, and that's true for all the other tumors in body, will classically respond with up-regulation of SDF-1 (CXCL12) – a sort of "help me, I need new blood vessels" signal. SDF-1 then recruits myeloid cells in the tumors that then build new vessels. Most are CD34 positive, which, for all of those that are a bit deeper in the biology, is a common progenitor marker of the bone marrow.

The bottom line of this JCI editorial image is that you have a tumor that nourishes itself by angiogenesis at first but then switches to vasculogenesis. Both angiogenesis and vasculogenesis create blood vessels but get there by very different means. This is why Avastin – an angiogenesis inhibitor tested in glioblastoma - failed. Digging a bit deeper you can also get an idea why angiogenesis inhibitors as a class failed: the tumor simply switched to vasculogenesis after radiotherapy, shut down the VEGF pathway and up-regulated SDF-1 / CXCL12. This VEGF bypass concept was later fully supported by a workup of the aflibercept study in the paper from John de Groot from Harvard (Clin Cancer Res, 2011), where angiogenesis was immediately bypassed by vasculogenesis, leading to lack of efficacy of the VEGF-blocking agent in the phase II trial (JCO 2011).

So, what we think is really needed after radiotherapy is an inhibitor of vasculogenesis – that is to say an inhibitor of SDF-1 / CXCL12. Now SDF-1 has two receptors, CXCR4 and CXCR7 and a number of people, have done work with CXCR4 receptor antagonists (including Prof. Martin Brown who started developing the concept with the CXCR4 antagonist AMD3100/plerixafor), but we think that the second receptor also plays a role, so blocking SDF-1/CXCL12 itself is likely to be a better approach.

SLIDE 14

Aram Mangasarian

Thank you, Frank – let me show one of the key experiments that Prof. Brown published using NOX-A12 in an animal model that is thought to be relevant for the human condition and also produces multiple different types of tumor to challenge therapeutics that are being tested. Pregnant rats are treated with a carcinogen called ENU during a particular period in development of the offspring. This reliably results in fatal brain tumors arising in the children of the treated rats with the mortality starting around 100 days after birth and reaching 100% around 250 days (rat age 100-250 days equivalent to approx. 10 – 25 human years, - Ref: Pallav Sengupta, Int J Prev Med. 2013 Jun; 4(6): 624–630 The Laboratory Rat: Relating Its Age With Human's)

Now remember that what we are doing with NOX-A12 is preventing replacement of blood vessels feeding the tumor that were destroyed by radiotherapy. The graph shows tumor volume. So, you can see that the black line, NOX-A12 alone without radiotherapy does nothing. This is as we expect since there is not damage to tumor blood vessels to repair. Radiotherapy (red) and Radiotherapy plus temozolomide (green) are similar slowing tumor growth for a time, but never really shrinking it significantly. When we add NOX-A12 after radiotherapy – the blue line -, all the tumors in all the animals shrink rapidly until they are below the detection limit of the MRI. Just as interesting, once we stop treatment with NOX-A12 after 10 weeks, tumors recur only in 1/3rd of the animals. So 66% of the complete responses we see are durable.

SLIDE 15

Frank Giordano

After he did this work, Martin Brown then went around the corner to his neurologist colleague at Stanford, Lawrence Recht, and they designed a Phase I/II trial exploring the concept (NCT01977677). The first data of this trial was presented last year at ASCO - summarized here on slide 14. You see they enrolled 29 patients and treated them with a 4-week continuous intravenous infusion of AMD3100 starting one week before radiotherapy. They saw that the out-of-field recurrence rate was increasing to 60% (it is usually <10%) and thus showed that they can improve control the tumor control within the radiation therapy field. And that's a really a major step for glioblastoma – and a first clear clinical signal that blocking SDF-1/CXCL12 signaling during radiotherapy is an interesting approach for glioblastoma.

There were some limitations to this study – they could not treat with AMD3100 for more than 4 weeks, and this is a really short half-life compound – so not the most convenient to use.

After seeing all of this develop, we approached NOXXON and said we want to have that compound, NOX-A12, for our patients, simply because you already have clinical experience and you have orphan drug status. We then together developed the clinical trial concept, and we built a consortium of influential people that are interested and involved. So here is the design of the trial...

SLIDE 16

The patient population eligible to participate in this study are those with the highest unmet medical need in glioblastoma: we could not surgically remove the entire tumor mass and their tumor is MGMT unmethylated, so we know that they will not benefit from temozolomide, the standard of care chemotherapy. These patients have an average PFS of 6 months and overall survival of 10 months.

They will get the standard of care radiotherapy (60 Gray over 6 weeks) and in parallel get NOX-A12 during the six weeks of radiotherapy and the NOX-A12 will continue to be given continuously up to six

months. We plan to test up to three doses of NOX-A12. Increasing the dose after each three patients. We are working on recruiting the first patient now and expect to be able to give news on that soon. We'll watch the first patient on therapy for some time before recruiting additional patients to be sure there are no unexpected safety signals.

The primary objective of this study is to demonstrate that NOX-A12 + radiotherapy is safe and well tolerated and to define a recommended Phase 2 dose. We are also interested in determining whether NOX-A12 prevents revascularization of the tumor and will follow this via MRI as this will confirm our predicted mechanism of action in the human setting. Finally, we want to see whether there is some benefit for the patients in the form of progression-free and overall survival.

Aram

I'll just note in addition that we have orphan drug status for NOX-A12 +RT in this indication in the US and Europe. This facilitates interactions with regulatory agencies and if approved provides for minimum exclusivity periods.

We'll now open up for questions – if you have any please type them into the webinar interface.

Q&A

Aram Mangasarian: I'll start with one while we get questions in from the audience. There has been a lot of work done in brain tumor models with NOX-A12 combined with radiotherapy. I'm curious what you think the potential is of NOX-A12's plus radiotherapy in other tumors. Do you see potential for more general application?

Dr. Giordano: Most -if not all- cancers will respond to radiotherapy in the same way. Usually you think radiotherapy is something that controls tumor cells. Actually, it is not only that. You only get the full job done by also depleting the small blood vessels in the tumor. So, we are actually destroying the blood lines that nourish these tumors. We think that roughly 20 to 40% of the efficiency of the primary radiotherapy is due to depletion of these small vessels. But many tumors are not entirely depleted and they start expressing SDF-1 (CXCL12) to attract myeloid cells and to finally build up new vessels with this "help from the outside". Then all you have left are tumor cells that have survived the first course of radiotherapy getting re-nourished by new vessels built by myeloid cells. I really think that blocking the invasion of myeloid cells has the potential to be a universal anti-tumor principle, completely independent of tumor type, so to speak.

Question from the Analyst: Glioblastoma is known for its high rate of failures in clinical trials, what reasons do you have to believe that NOX-A12 + radiotherapy is a more de-risked approach than others?

Aram: Multiple factors lead us to believe that this is a de-risked approach relative to prior trials:

- The analysis and learning from previous failures have pointed to the TME and the use of by glioblastoma of CXCL12 to drive growth or replacement blood vessels– both aspects are addressed by the NOX-A12 + RT approach
- In contrast to many molecules/inhibitors that failed, our approach does not target a single receptor. When using small molecules, cells bearing the targeted receptors are mended-out and rapid niche replacement by receptor negative cells occurs. Our approach is targeting hypoxia, which is occurring in any rapidly growing tumor.
- We have strong animal data from using the NOX-A12 + RT approach and the MoA does not appear to rely on brain penetration (an issue for many other approaches)– but rather on stopping "repair" cells from getting to the tumor
- There is clinical validation from Dr. Recht's group at Stanford University that blocking part of CXCL12 signaling through CXCR4 improves with local tumor control in the radiation field

END